Omega-3 FA: A Review of its Use in Secondary & Primary Prevention and the Treatment of Hypertriglyceridemia

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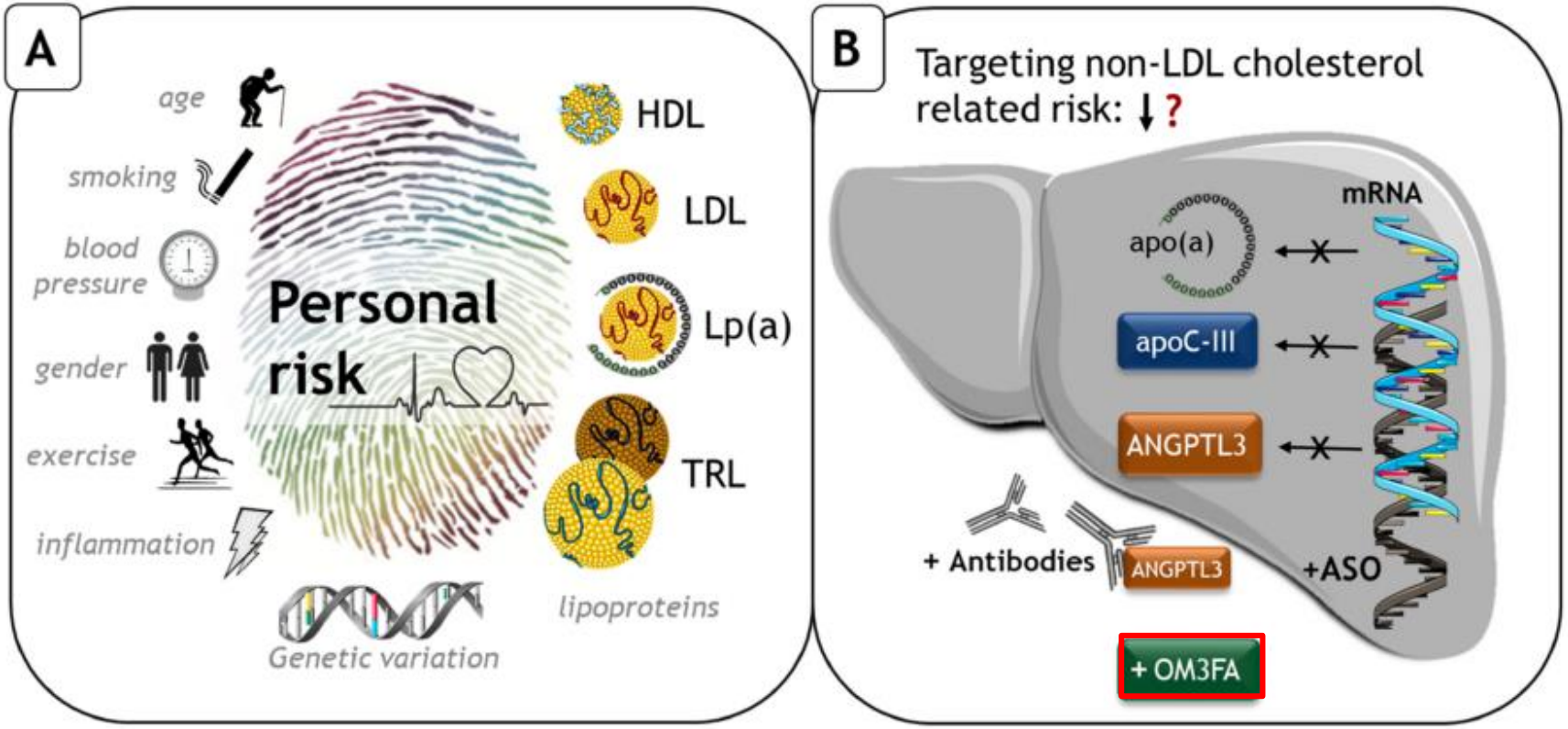
Outline

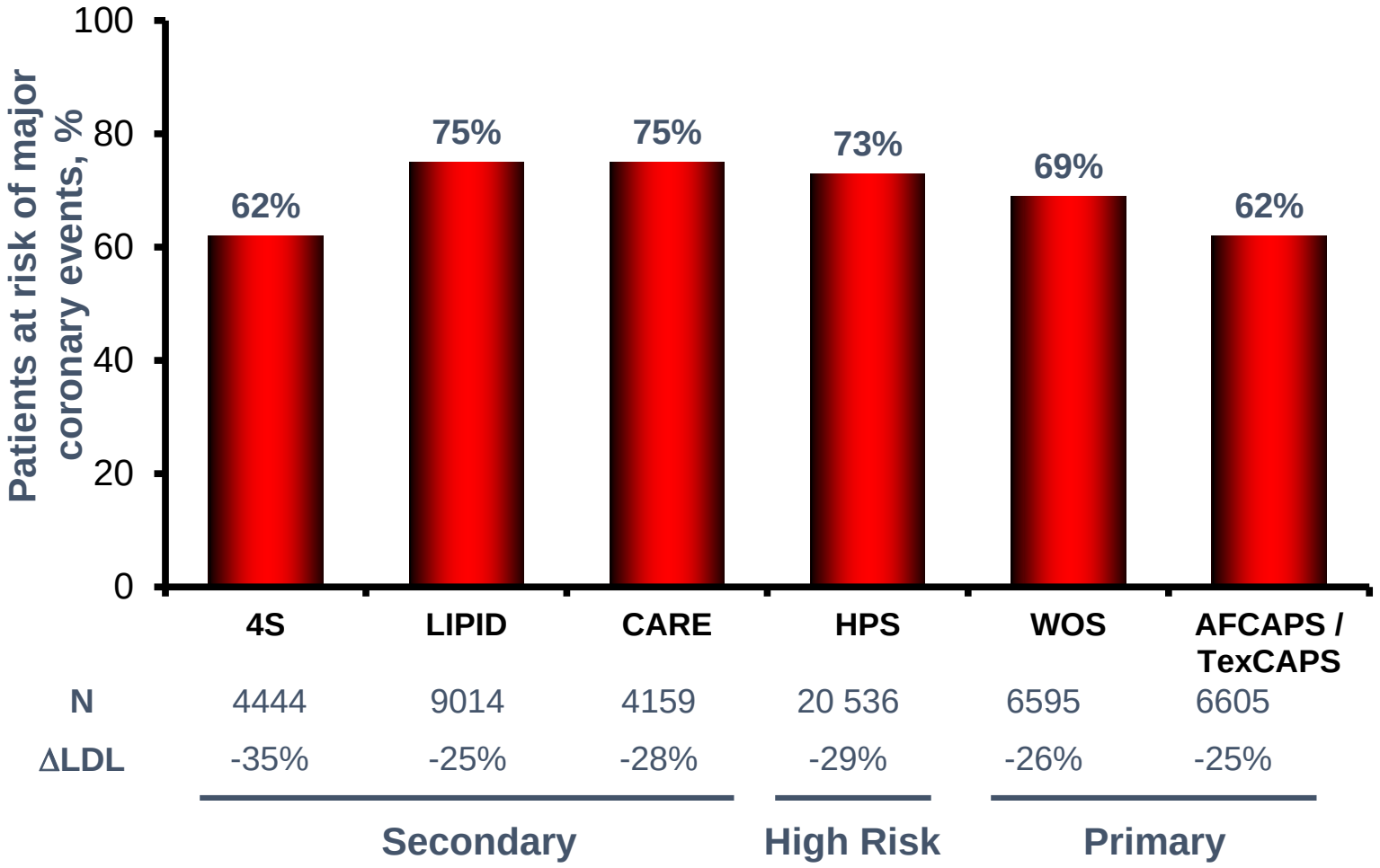
- Residual cardiovascular risk
- Role of triglyceride in cardiovascular diseases
- Diabetic dyslipidemia
- Role of Omega-3 FA in treatment of cardiovascular diseases
- Clinical trials –Primary and Secondary Prevention
- Guidelines recommendation

Risk Factors Associated with Atherosclerotic Cardiovascular Disease and Reduce the Risk beyond Low-density Lipoprotein (LDL)



Zwol Wv, et al. J. Clin. Med. 2019, 8, 1085

Residual Cardiovascular Risk in Major Statin Trials



Adapted from Libby PJ, et al. J Am Coll Cardiol 2005:46:1225-28

PROCAM Substudy

Residual Risk-R3i

Probability (OR) of MI

	TG>150	HDL<45	HDL<45 y/o TG>150
LDL<100	2,6	3,4	5,0
LDL 100-129	1,9	2,6	2,9
LDL 130-159	1,1	2,8	2,4
LDL>160	1,0	2,0	2,0

Assmann G, et al. Diab Vasc Dis Res 2010;7:204

Residual Atherosclerotic Cardiovascular Disease Risk

- Whether optimal LDL-C control varies from person to person rather than according to overall clinical subgroup.
- Whether residual ASCVD risk could be prevented by even more aggressive LDL-C lowering using more stringent statin regimens or additional LDL-C–lowering strategies, such as inhibitors of PCSK9, which has some effects distinct from those of statins on non–LDL-C risk factors.
- What extent non–LDL-C risk factors explain the residual risk.

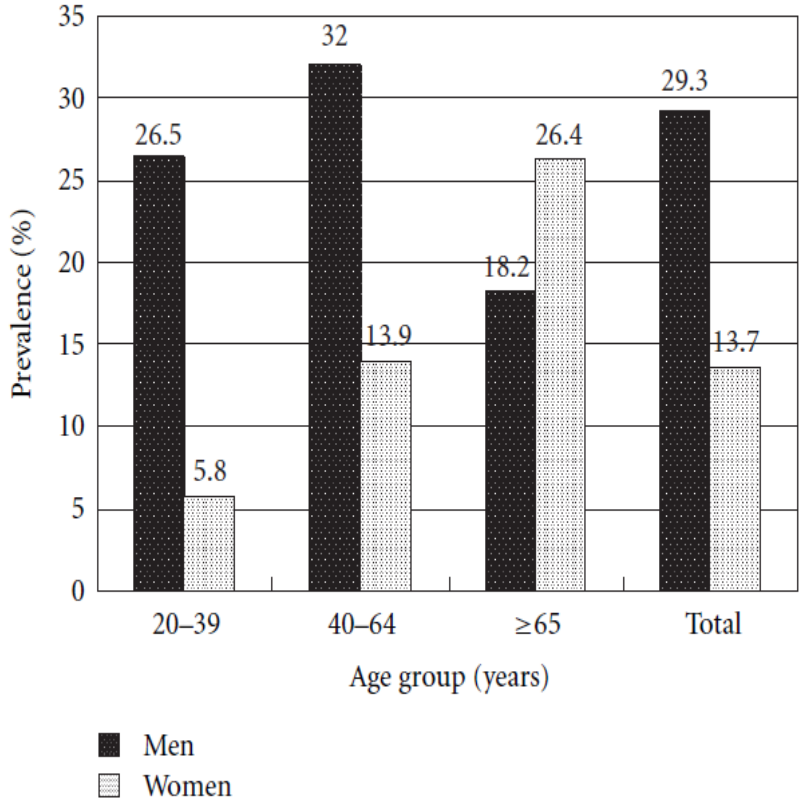
Targeting Risk of Plasma Lipid-driven Atherosclerotic Cardiovascular Disease beyond LDL Cholesterol

Target	Name of the Drug	Mechanism of Action	Lipid Effect		Stage of Development	Comments*
Lp(a)	1. IONIS-APO(a) RX 2. IONIS-APO(a)-LRX	ASO to block apo(a) synthesis and thereby Lp(a) formation	1. Lp(a) ↓ 72% Lp(a) ↓ 92%	[13] [14]	Phase 2–3	Lp(a) levels are not measured in the clinic
APOC-III	Volanesorsen (AKCEA-APOCIIIRX)	ASO to block ApoC-III synthesis	TG ↓ 73%	[15]	Phase 3	Increases LDL cholesterol, thrombocytopenia risk
	AKCEA-APOCIII-LRX	ASO to block ApoC-III synthesis	TG ↓ 71%	[16]	Phase 2	
ANGPTL3	Evinacumab	Monoclonal antibodies target ANGPTL3 in plasma	TG ↓ 50%	[17]	Phase 3	Reduces HDL cholesterol
	IONIS-ANGPTL3-LRX	ASO to block ANGPTL3 synthesis	TG ↓ 50%	[18]	Phase 2	Reduces HDL cholesterol
OM3FA	1. OM3FA-EE/Lovaza 2. OM3FA-CA/Epanova 3. OM3FA-IPE/Vascepa	Reduced TG levels, inflammation, oxidative properties of atherogenic lipoproteins and increases plaque instability	1. TG ↓ 45% 2. TG ↓ 31% 3. TG ↓ 18–27%	[19, 20]	Approved for HTG-patients	Inconclusive results on cardiovascular outcomes

* Potential drawbacks for all ASOs and monoclonal antibodies include discomfort and injection site reactions. Abbreviations: APO, apolipoprotein; ASO, antisense oligonucleotide; mRNA, messenger RNA; OM3FA, omega-3 fatty acid; EE, ethyl esters; CA, carboxylic acid; IPE, icosapent ethyl; HTG, hypertriglyceridemia.

Zwol Wv, et al. J. Clin. Med. 2019, 8, 1085

Hospital-based Study of Prevalence of Dyslipidemia in Taiwan

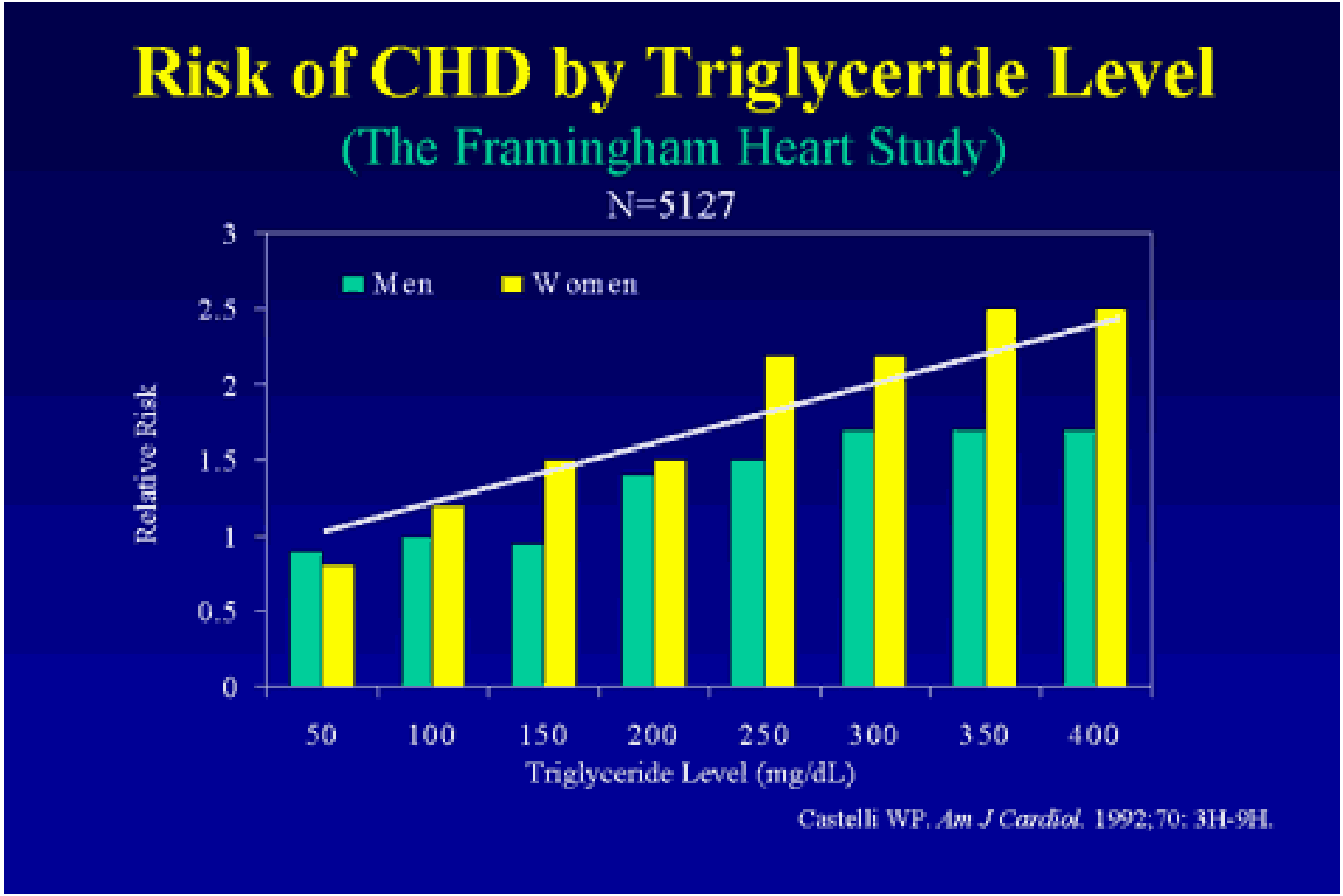


- Prevalence of hypertriglyceridemia in gender and three age groups.

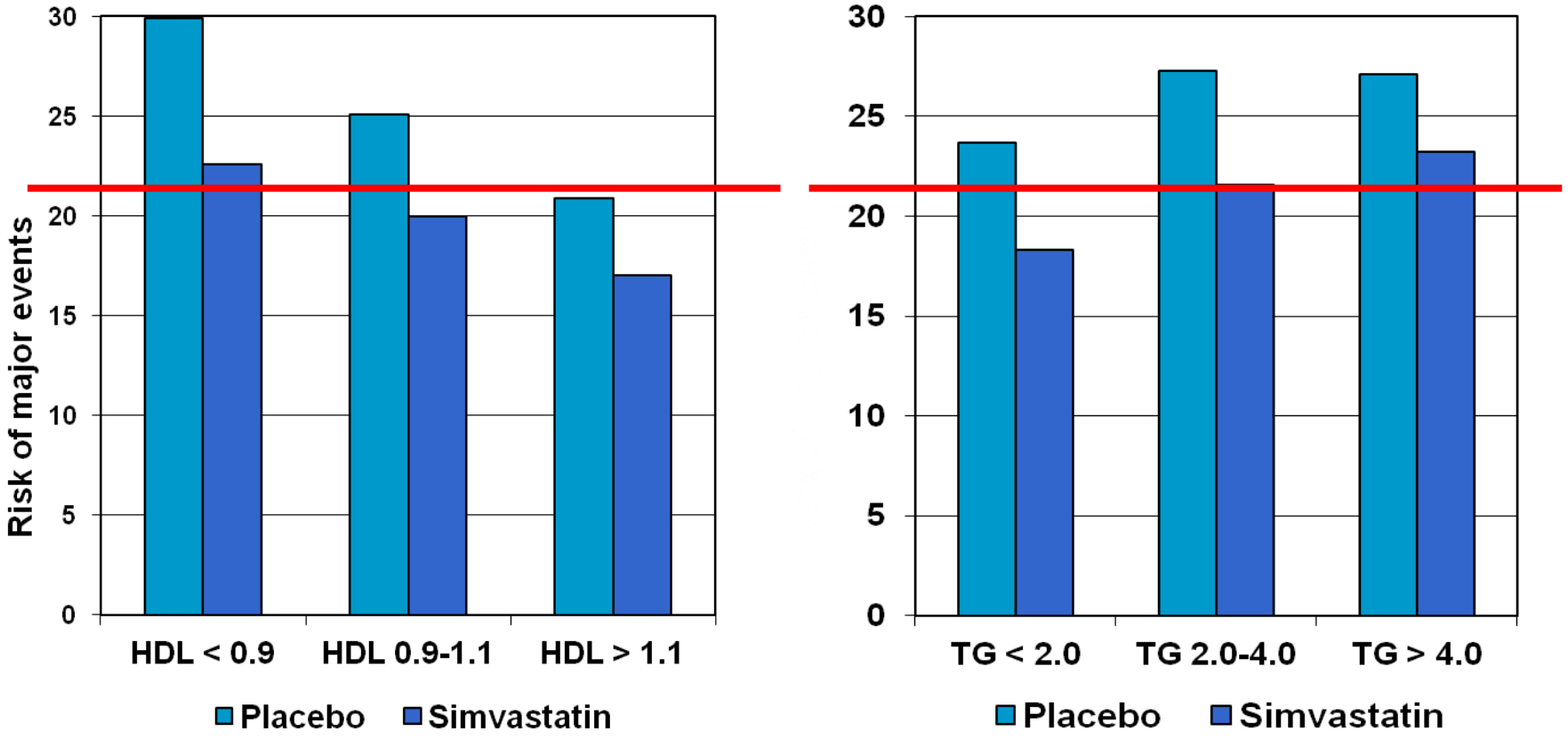
- 22.5 % overall
- 29.3 % in men
- 13.7 % in women
- Increasing with age in women

Cheng KC, et al. Cholesterol 2011;2011:314234.

Triglyceride Level and Risk of CHD



Risk Associated with TG and Low HDL-C not Eliminated in the HPS Study

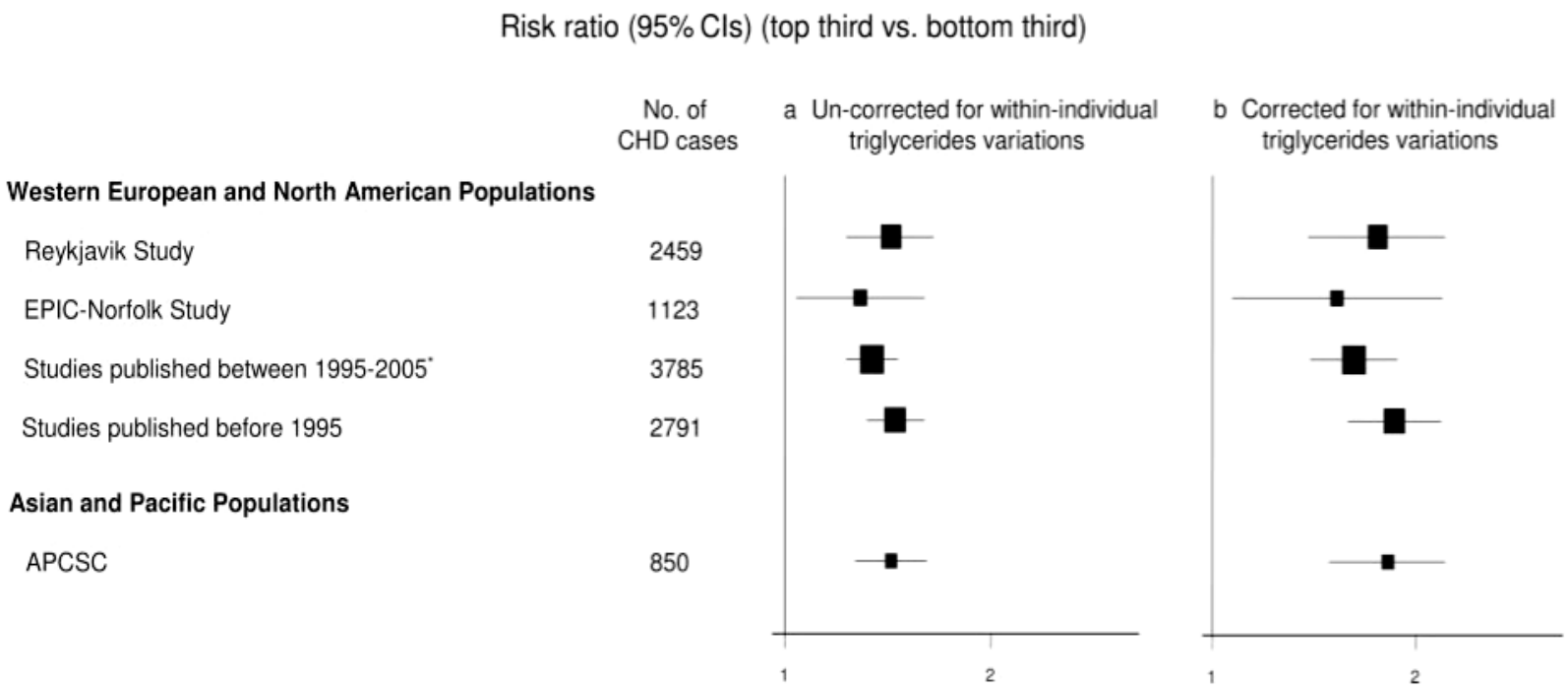


Lipids in mmol/L

Collins R, et al. Lancet 2003:361:2005-16

Triglycerides and Coronary Risk

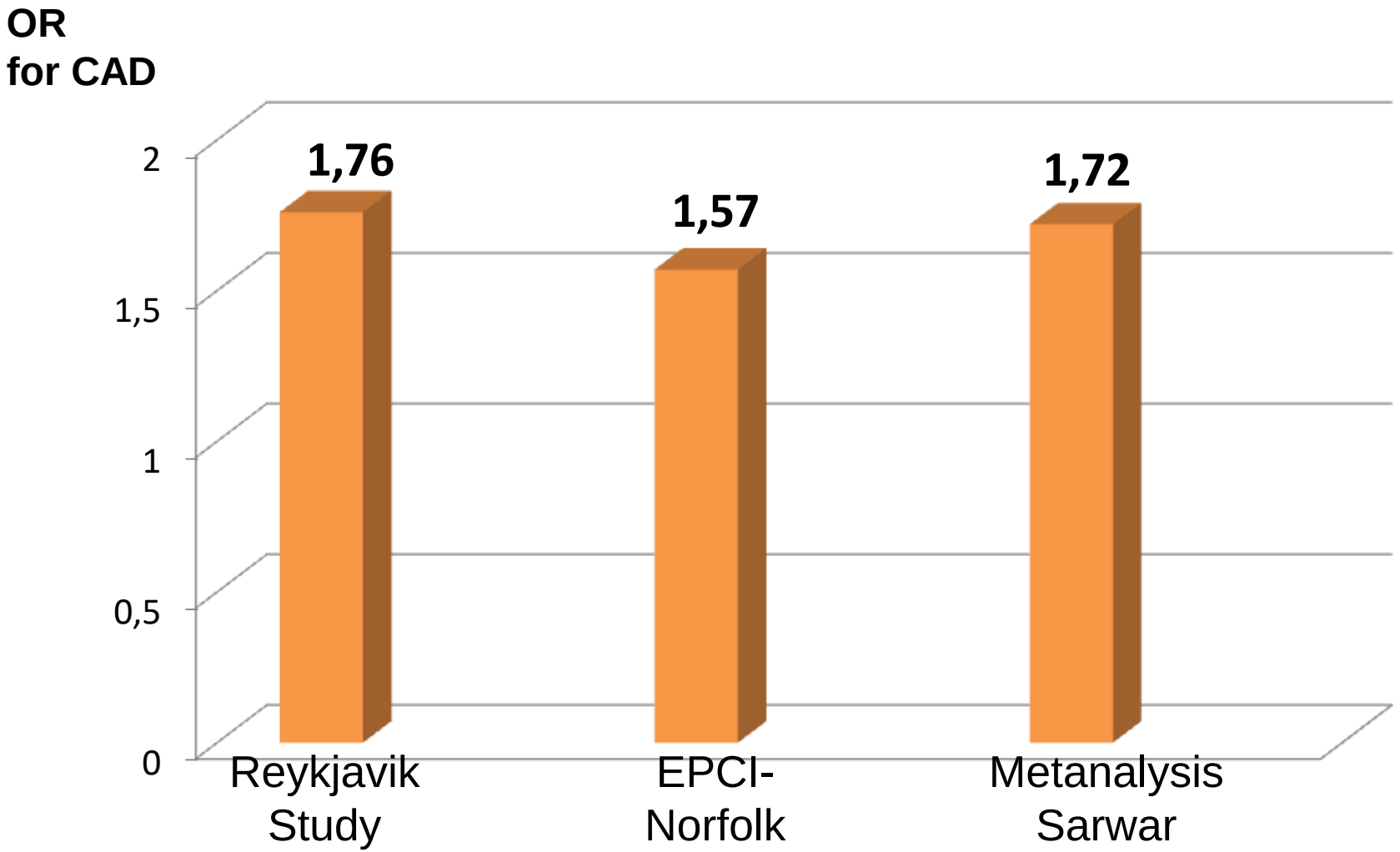
Metanalysis with > 260.000 participants and over 10.000 cases of CHD



Available prospective studies of triglycerides and CHD in essentially general populations. APCSC indicates Asian and Pacific Cohort Studies Collaboration. *Includes 3 studies that were published before 1995 but were not included in the previous review.

Sarwar N, et al. Circulation 2007;115:450–58

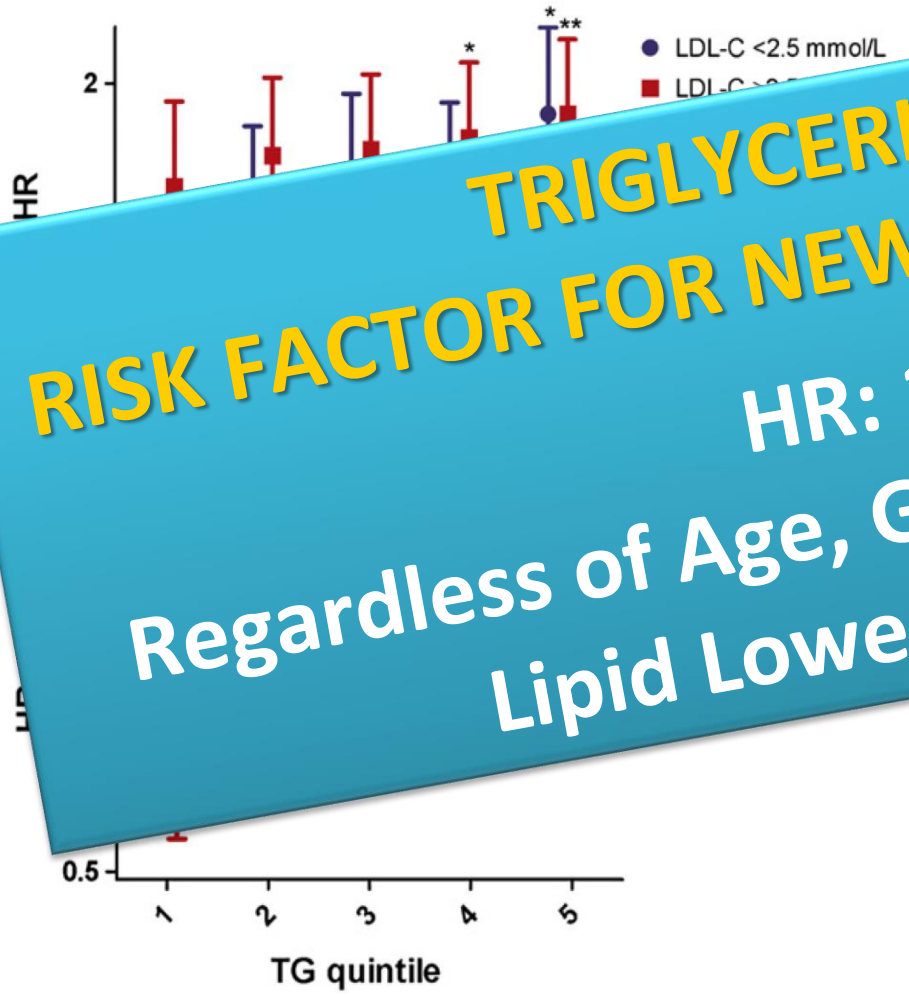
Coronary Risk in Hypertriglyceridemia

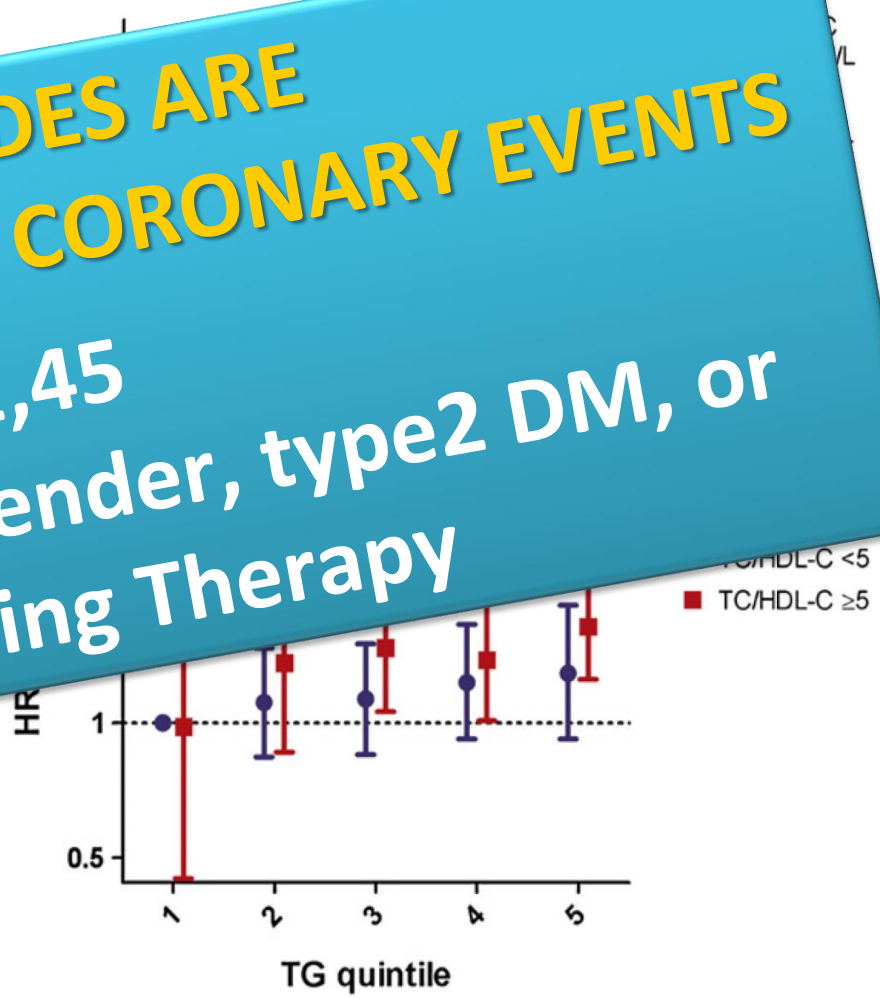


TG Risk factor of Recurrent Vascular Events Independent of LDL or Non-HDL

n=5.731 pts with CVD, followed 5 yrs

*** p<0.05; ** p<0.01**





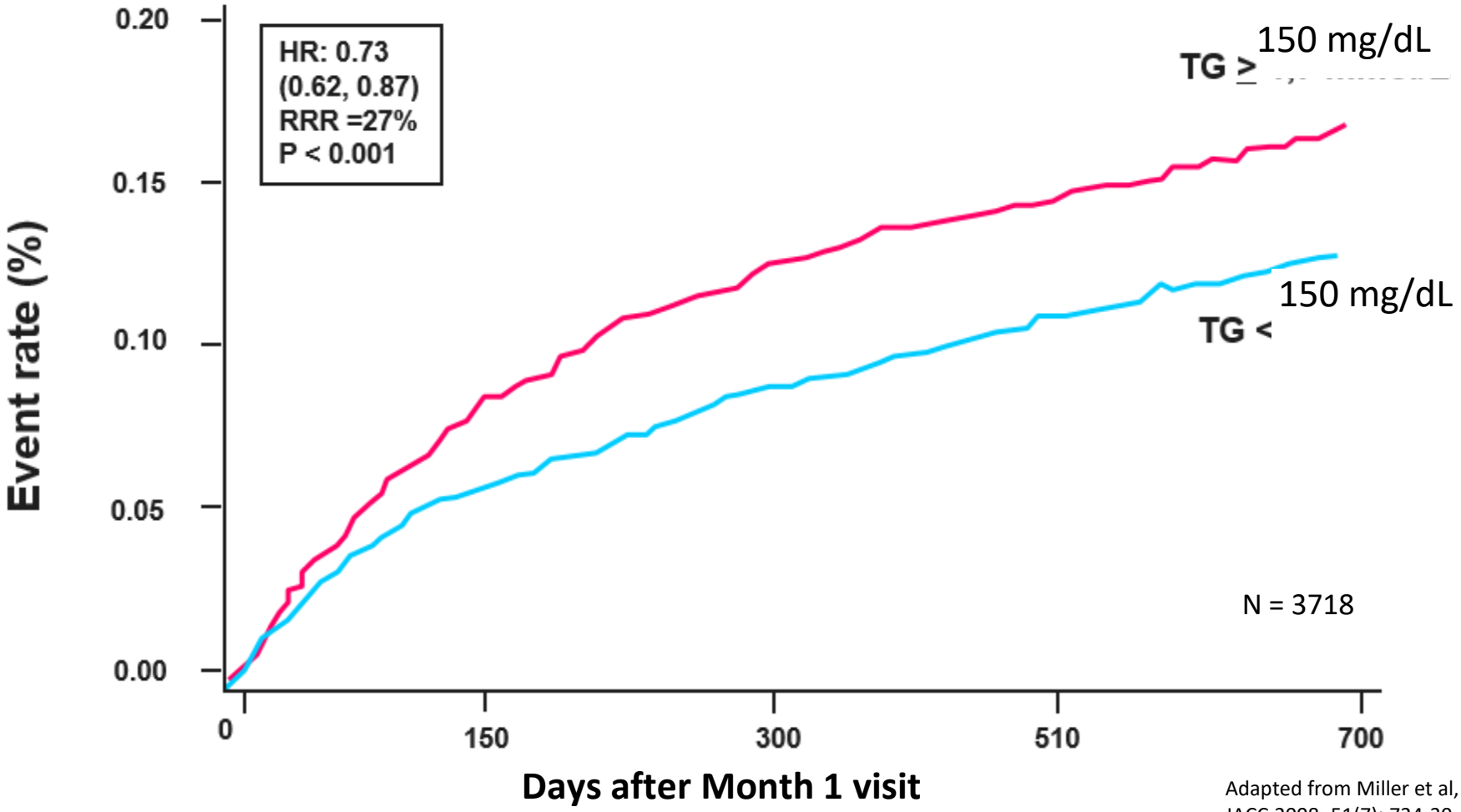
TRIGLYCERIDES ARE RISK FACTOR FOR NEW CORONARY EVENTS

HR: 1,45

Regardless of Age, Gender, type2 DM, or Lipid Lowering Therapy

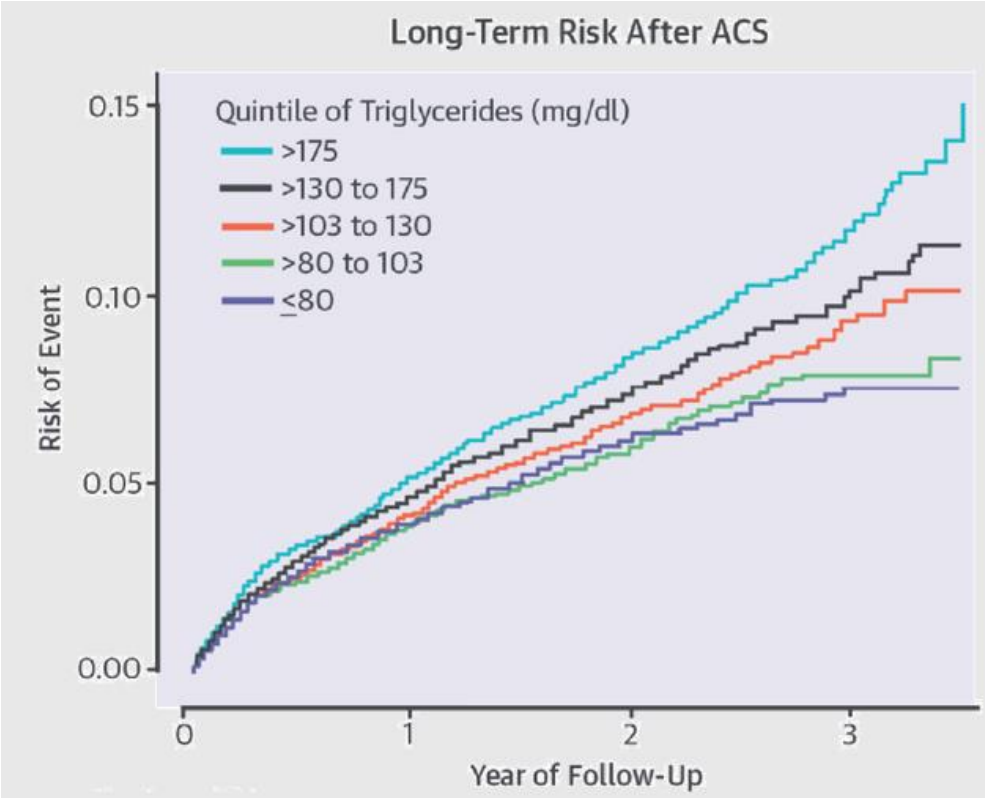
van de Woestijne AP, et al. Int J Cardiol 2013 Jul 31;167:403-08

Triglyceride Level and CHD Risk after Acute Coronary Syndrome



Adapted from Miller et al, JACC 2008; 51(7): 724-30

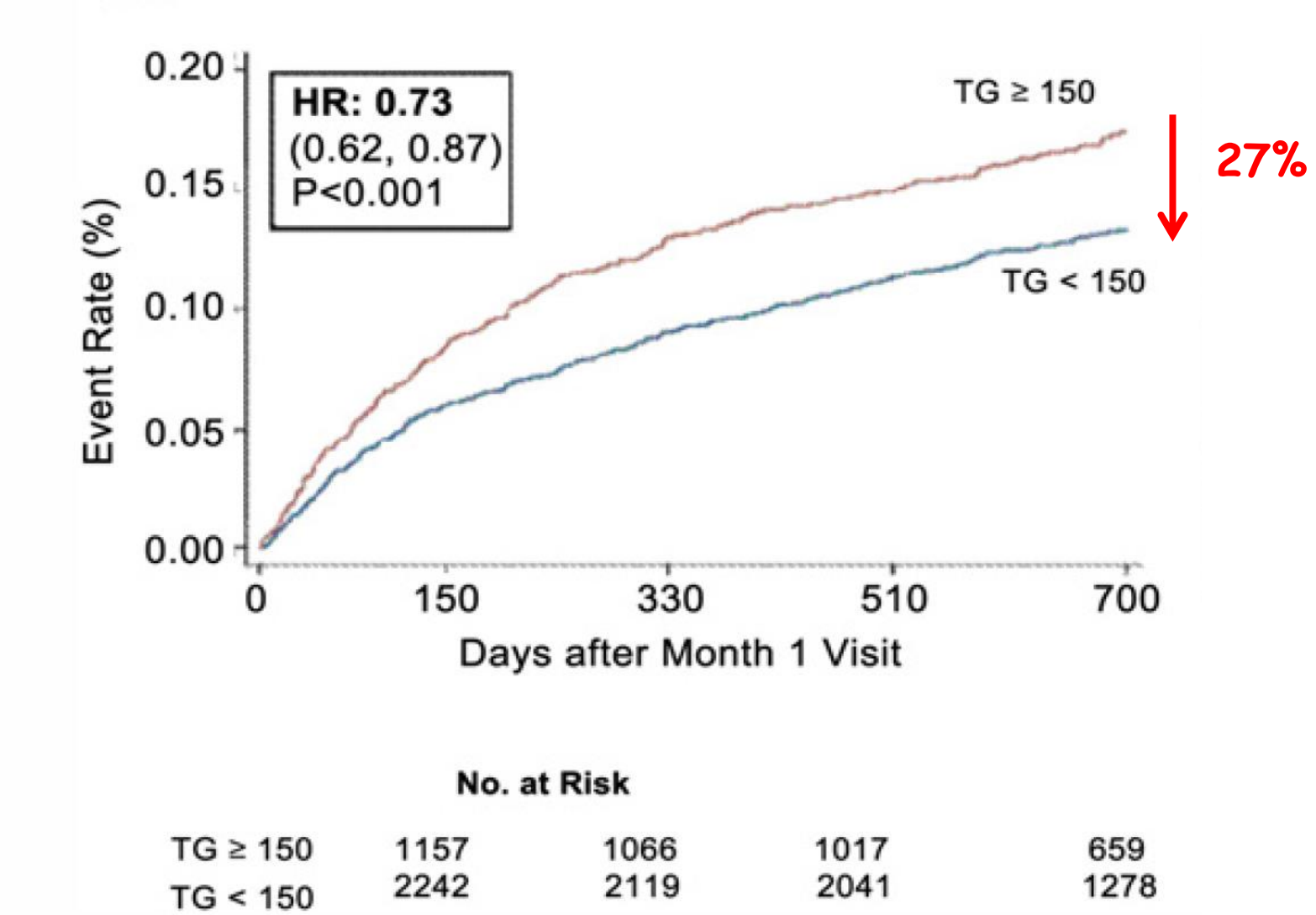
Triglyceride Level and Long Term Risk after Acute Coronary Syndrome



		Year of Follow-up			
		0	1	2	3
Number at Risk		3124	2874	2525	653
		3171	2952	2592	657
		3142	2931	2595	691
		3135	2942	2619	730
		3245	3028	2869	729

Triglycerides and Coronary Events

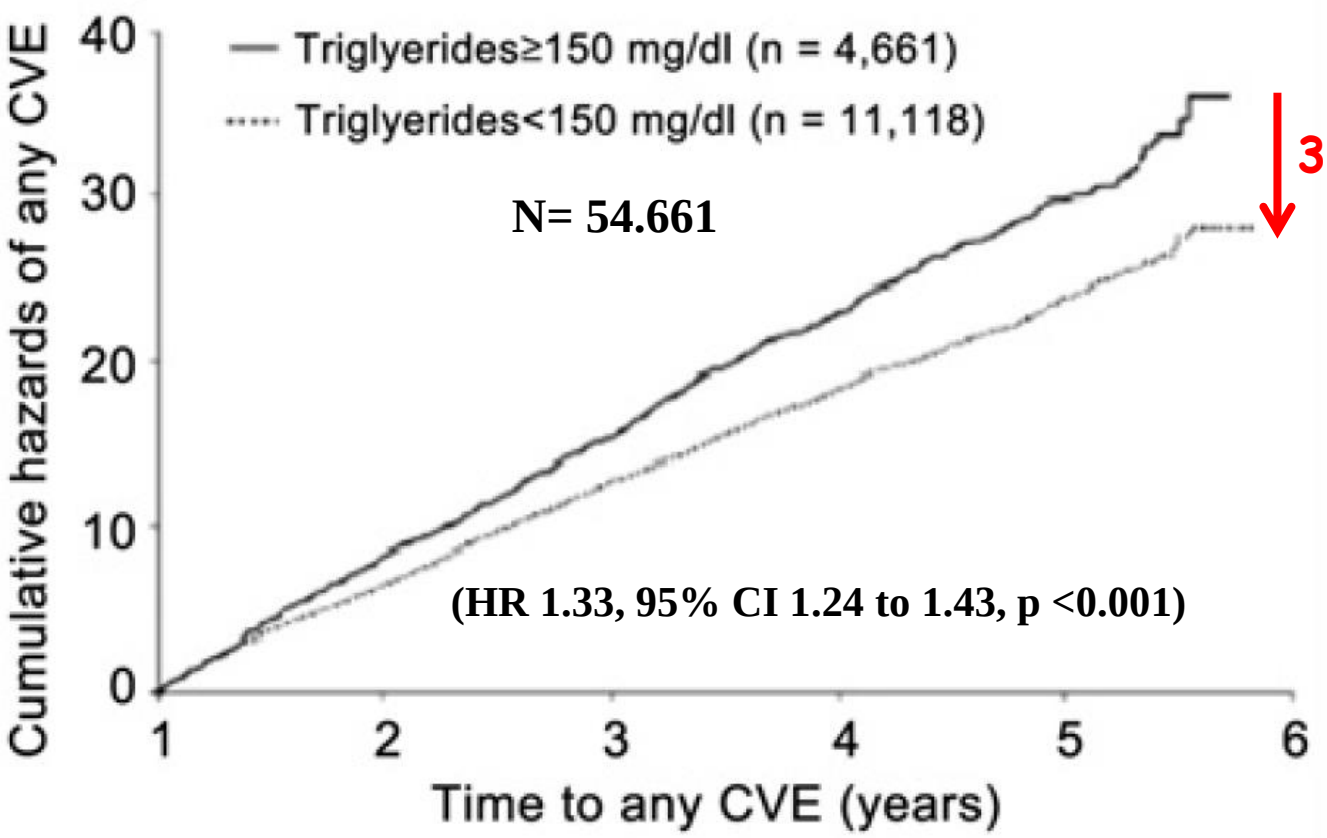
PROVE IT-TIMI 22 Trial



Miller M, et al. PROVE IT-TIMI 22 trial. J Am Coll Cardiol 2008;51:724-30

Triglycerides and Coronary Events

TNT & IDEAL Trials

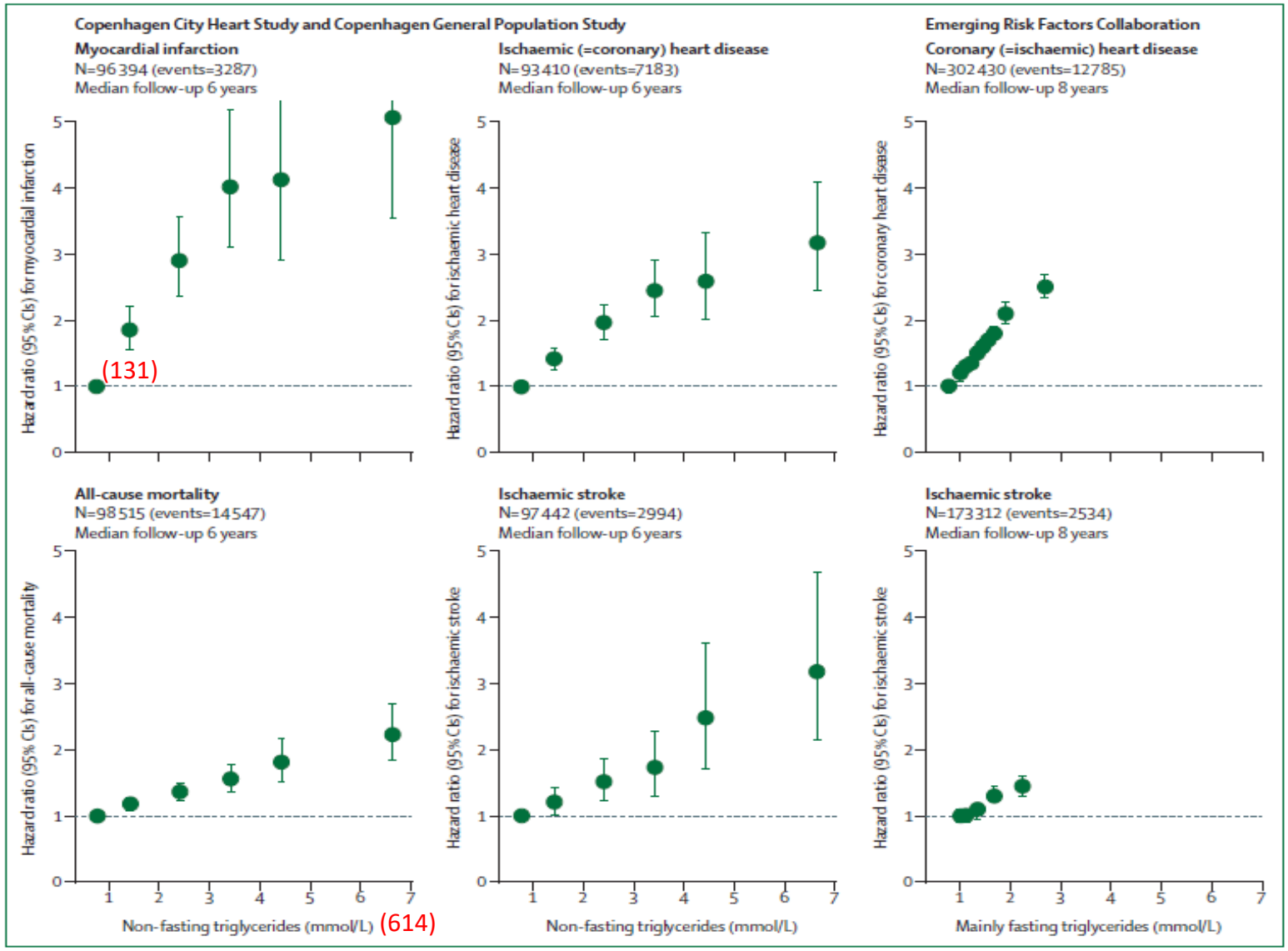


TG comparing
1° vs 5° quintiles
RRR: 63%

Predictive value reduces after HDL adjustment and disappears in multivariant analysis

Faergeman O, et al. Am J Cardiol 2009;104:459–63

Associations between Concentrations of TG, and Cardiovascular Disease and All-cause Mortality



(from mmol/L to mg/dL: multiply by x 88.6)

Nordestgaard BG, et al. Lancet 2014;384(9943):626-635.

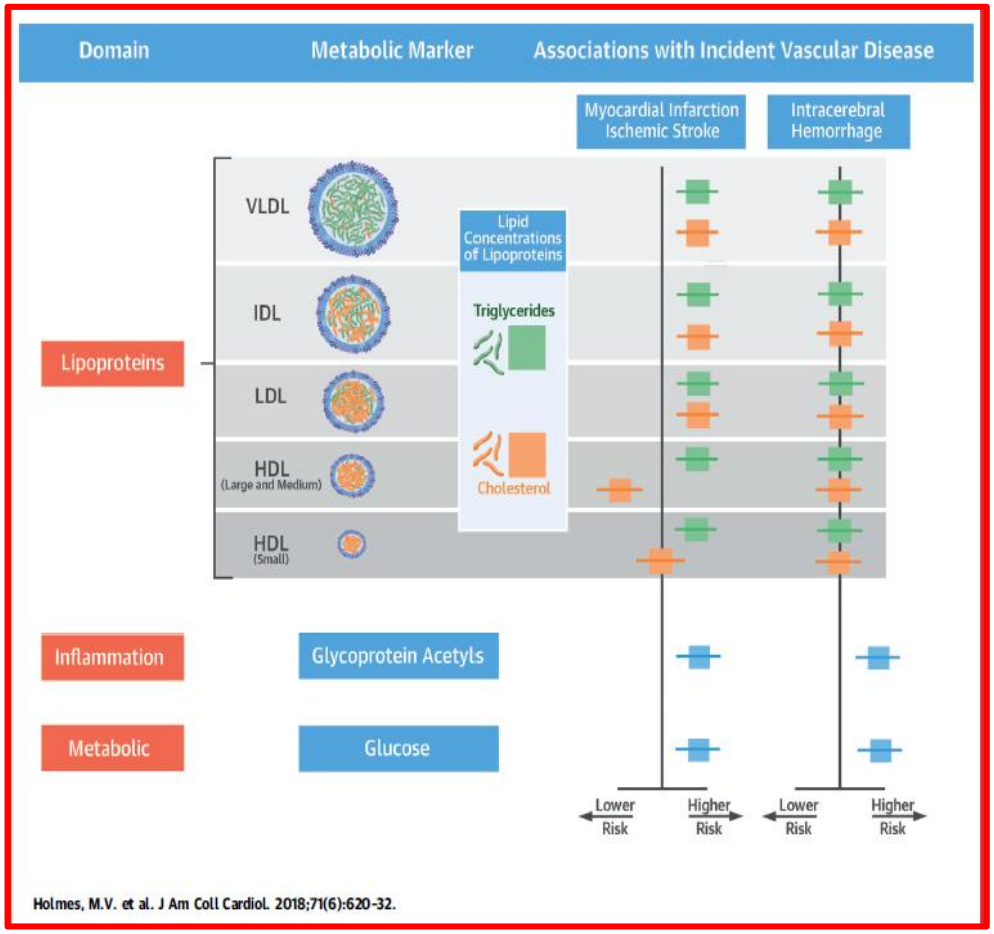
Elevated Triglycerides

Normal <150 mg/dL

- Borderline high 150–199 mg/dL
- High 200–499 mg/dL
- Very high >500 mg/dL

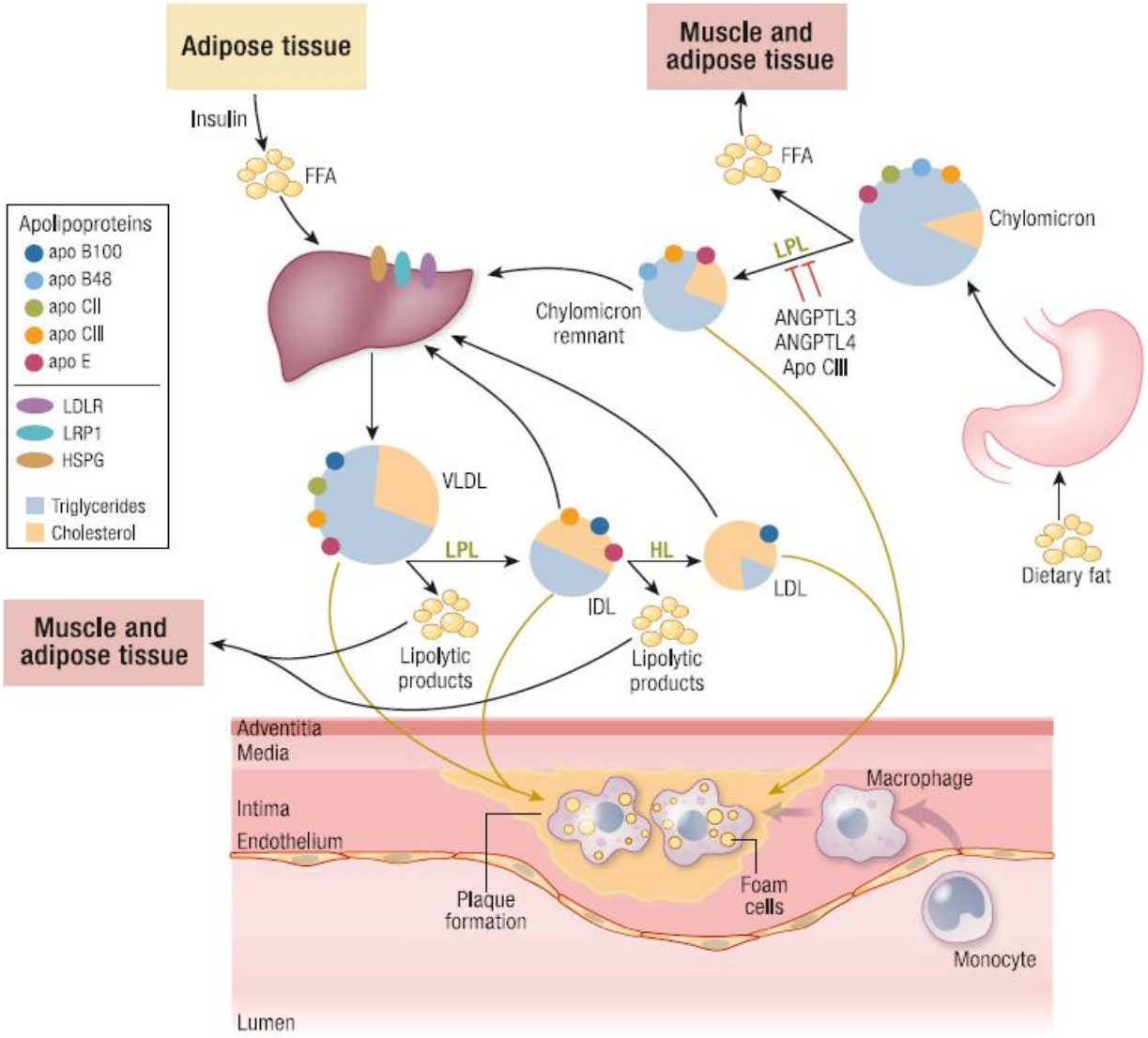
Lipoprotein Lipids and Other Metabolic Markers With Risk of Incident MI, IS, and ICH

- OBJECTIVES: This study sought to investigate the associations of plasma metabolic markers with risks of incidence of MI,IS, and ICH.
- METHODS: In a nested case-control study (2004-2008, 912 MI, 1,146 IS, and 1,138 ICH cases, and 1,466 common control subjects) 30 to 79 years of age in China Kadoorie Biobank, nuclear magnetic resonance spectroscopy measured 225 metabolic markers in baseline plasma samples.



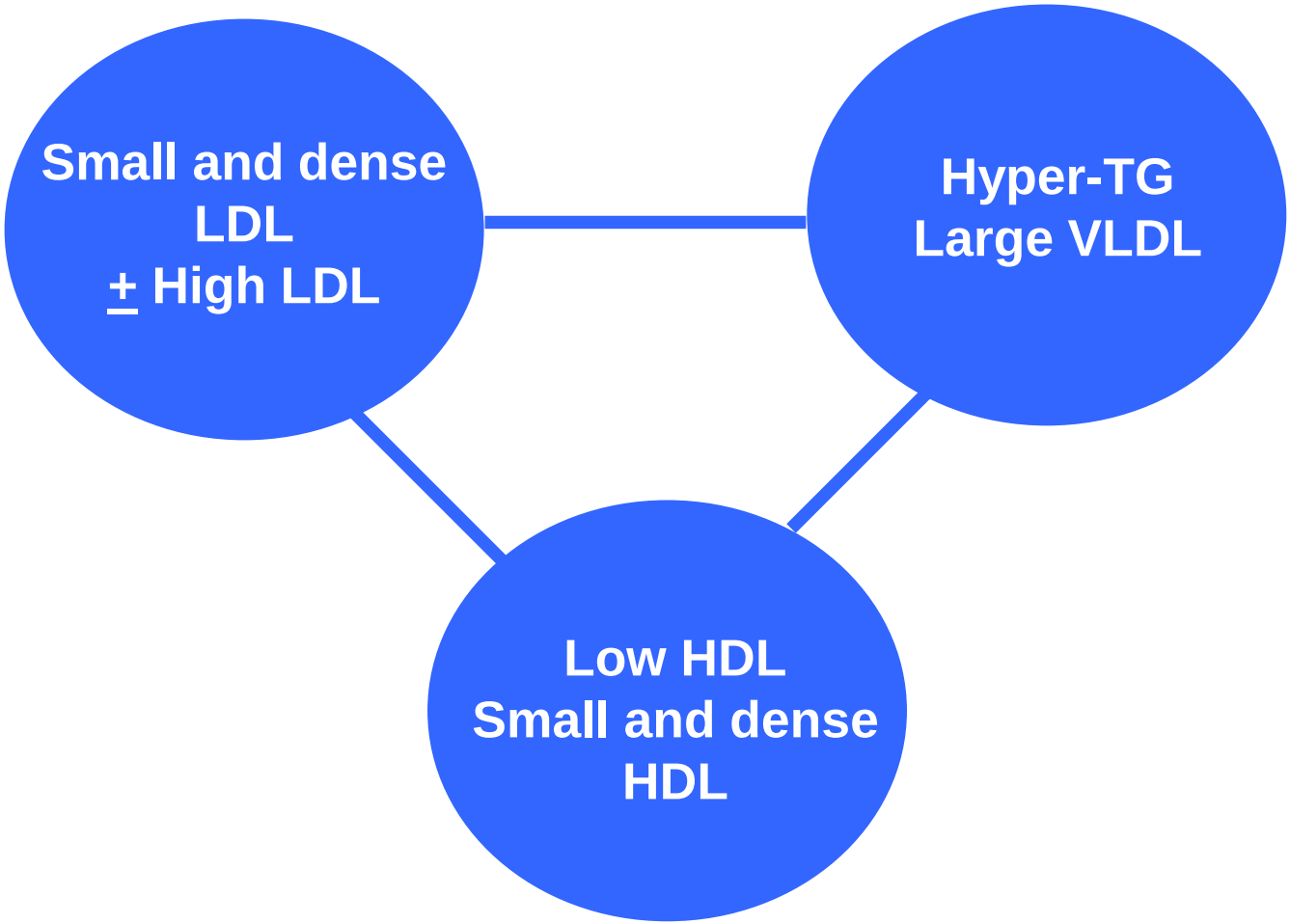
Holmes, M.V. et al. J Am Coll Cardiol. 2018;71(6):620–32.

Triglyceride-rich Lipoprotein Metabolism and Mechanism of Atherosclerosis



Sandesara PH, et al. Endocr Rev. 2019;40(2):537-557.

Dyslipidemia in Diabetes Mellitus (60% of cases)

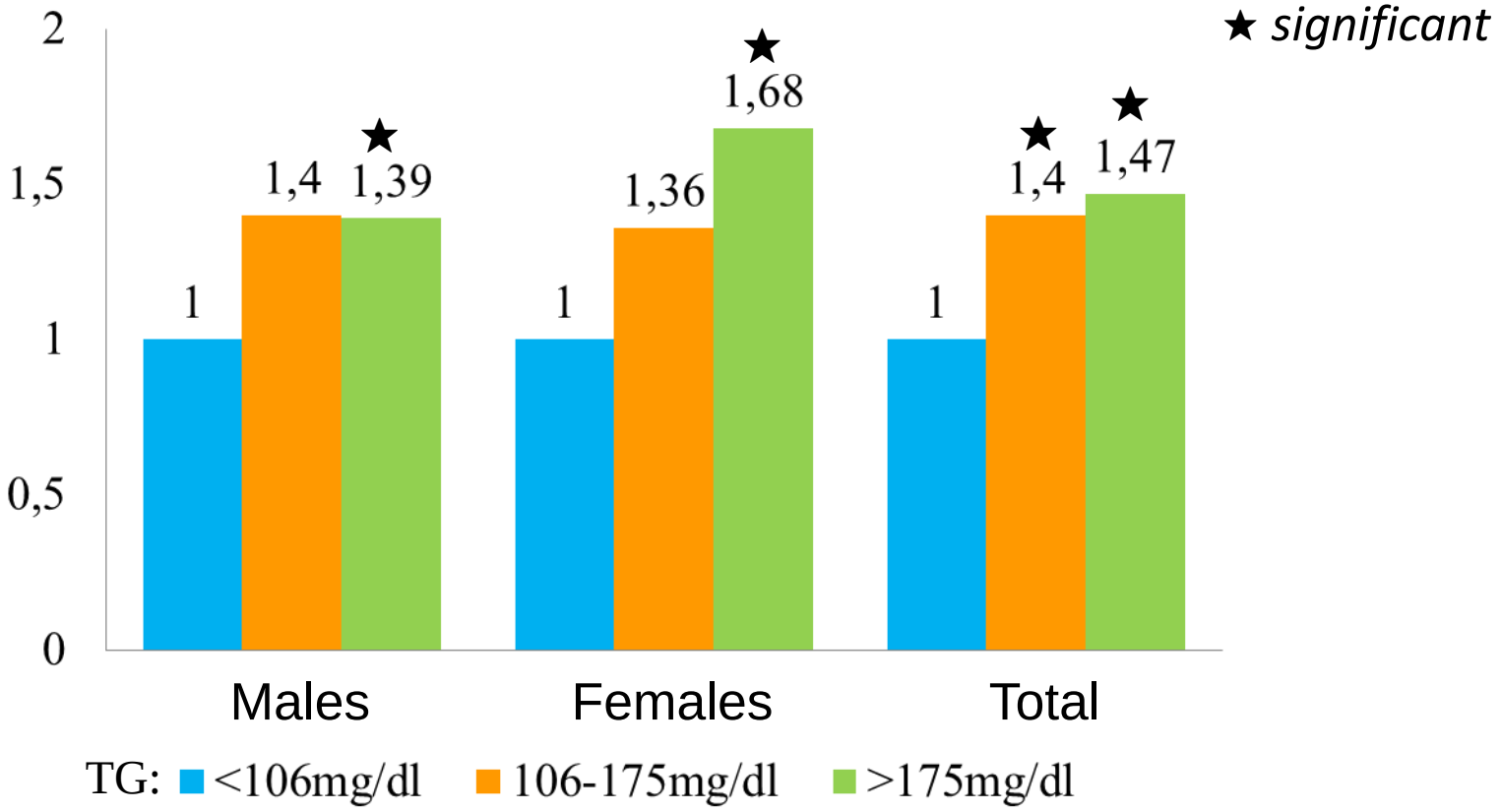


Triglycerides in Type 2 Diabetes Mellitus

Strong Heart Study

2.108 DM
vs
2.060 Ctrls

Flw-up: 9 yrs

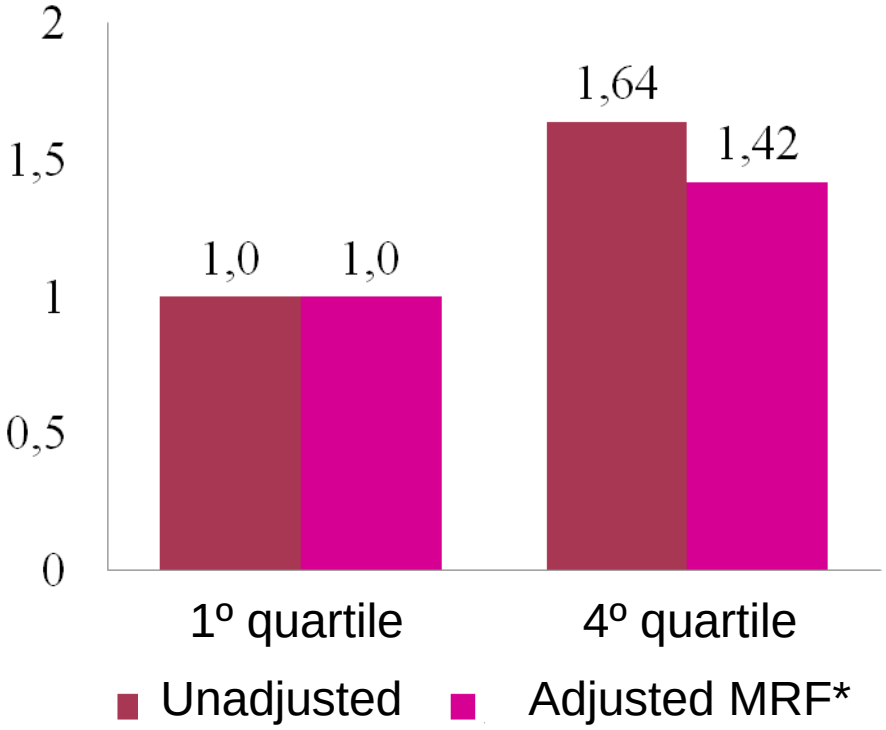


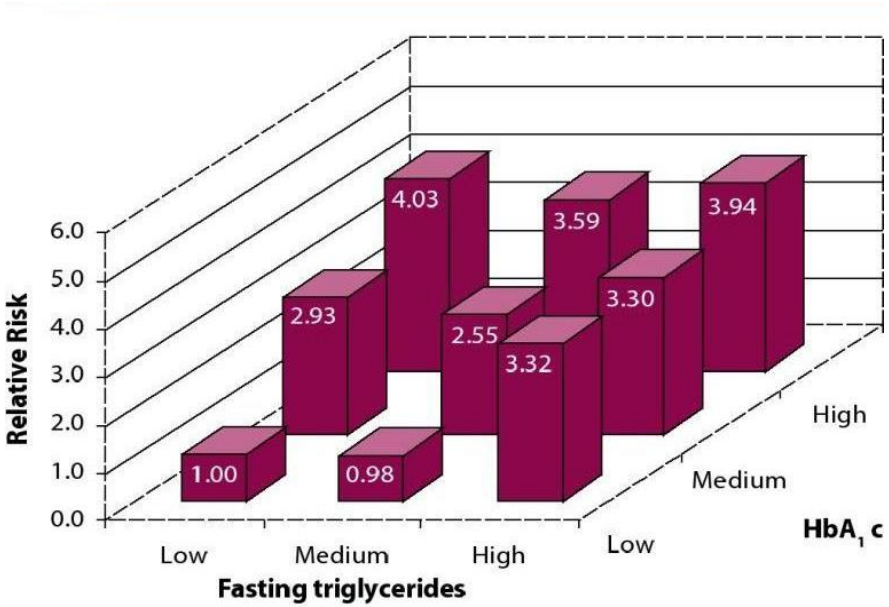
Adjusted by age, BMI, smoking, SBP, HbA1c, fibrinogen, insulin & albumin/creat ratio

Lu W, et al. Diabetes Care 2003;26:16-23

Triglycerides are Risk Factor for CAD in type2 Diabetes Mellitus

921 ♀; mean age:60 years; follow up:10 years





* MRF: Age, HBP, BMI and use of ASA

Schulze MB, et al. Diabetologia 2004;47:2129–36

Postprandial TG in type2 DM

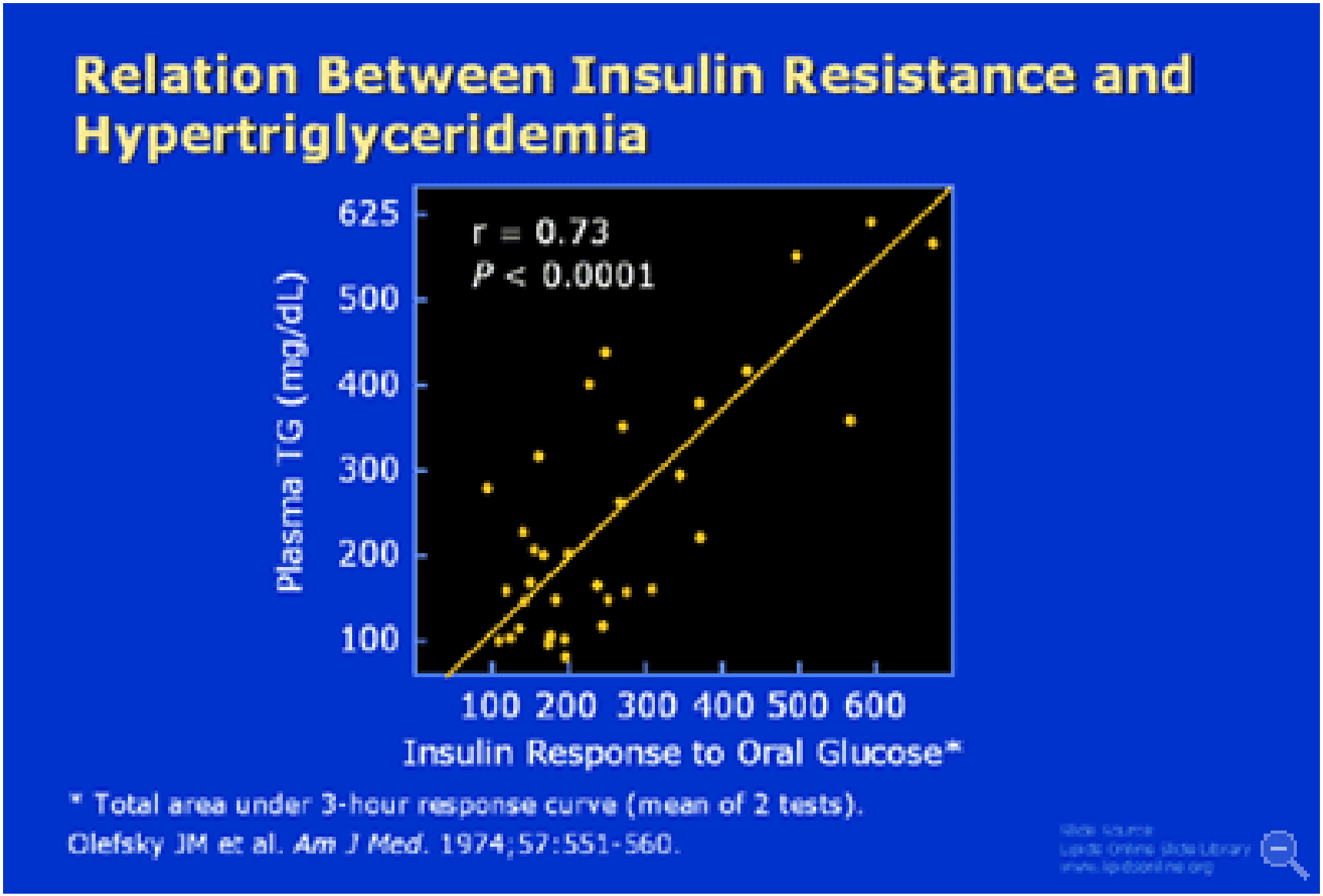
1.337 type2 DM patients followed 8 yrs

Variable	Cases/*n*	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Triacylglycerols			
Tertile 1 (0.22–1.36)	25/444	1.00	1.00
Tertile 2 (1.37–2.24)	33/446	1.09 (0.64, 1.87)	1.11 (0.65, 1.90)
Tertile 3 (2.25–11.91)	58/447	1.73 (1.04, 2.87)	1.79 (1.07, 2.98)
p value for trend		0.01	0.01
HDL-cholesterol			
Tertile 1 (0.40–0.91)	53/445	1.00	1.00
Tertile 2 (0.92–1.14)	44/438	0.96 (0.63, 1.45)	0.95 (0.62, 1.45)
Tertile 3 (1.14–2.56)	19/454	0.41 (0.23, 0.72)	0.41 (0.23, 0.72)
p value for trend		0.002	0.002
LDL-cholesterol			
Tertile 1 (0.54–2.48)	37/459	1.00	1.00
Tertile 2 (2.49–3.18)	34/437	0.79 (0.49, 1.28)	0.79 (0.49, 1.28)
Tertile 3 (3.19–6.62)	45/441	0.89 (0.55, 1.42)	0.87 (0.55, 1.40)
p value for trend		0.65	0.61

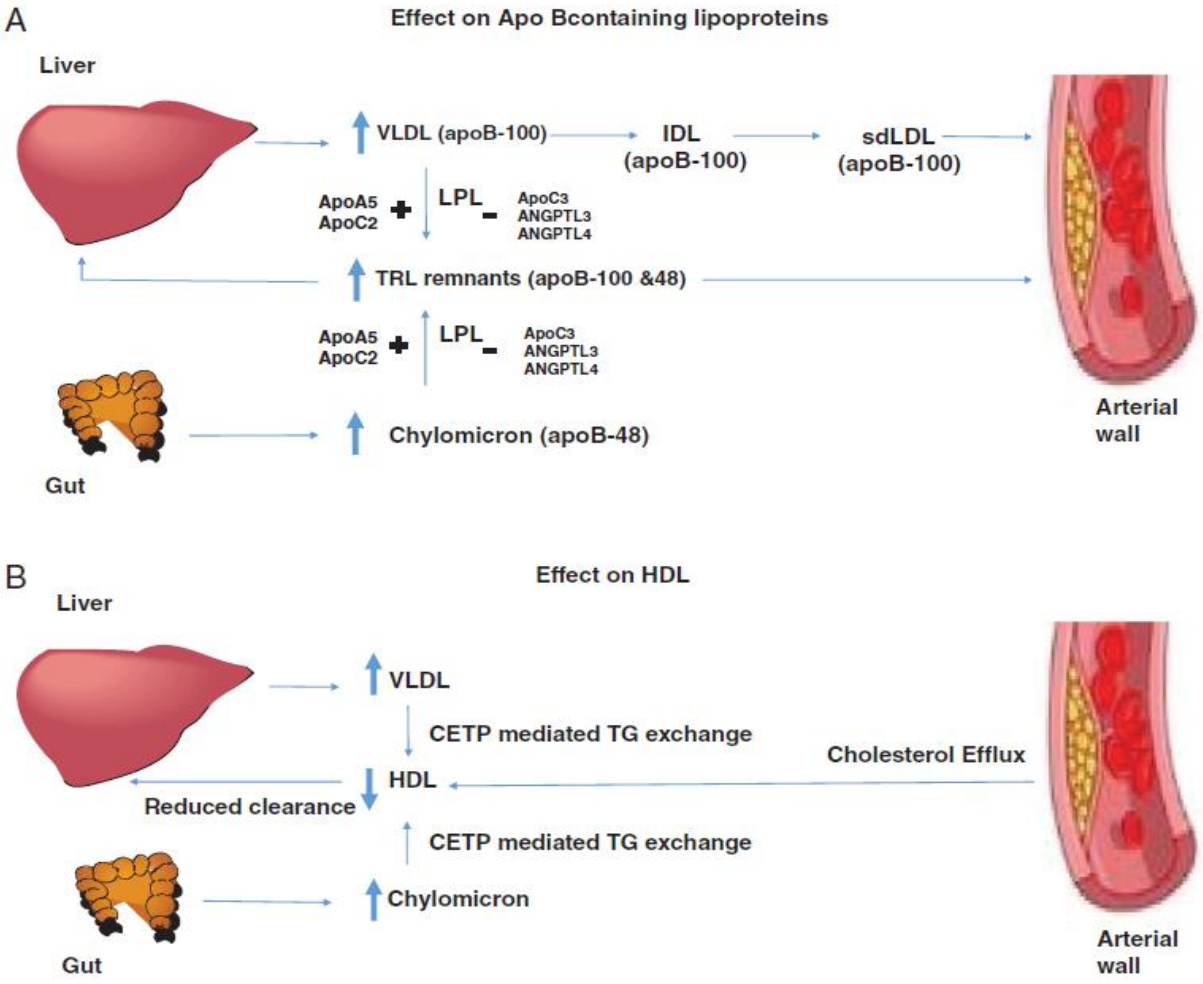
Model 1, adjusted: age, BMI, Smoking, SPB, HbAic, ethilism, DM duration , Kcal intake, DM Rx, physical activityy.
Model 2: 1 + postprandial time

Van Dieren S, et al. Diabetologia 2011;54:73–77

Triglycerides & Insulin Resistance



Insulin Resistance and Type II Diabetes Associated with Production of Triglyceride-rich Lipoproteins



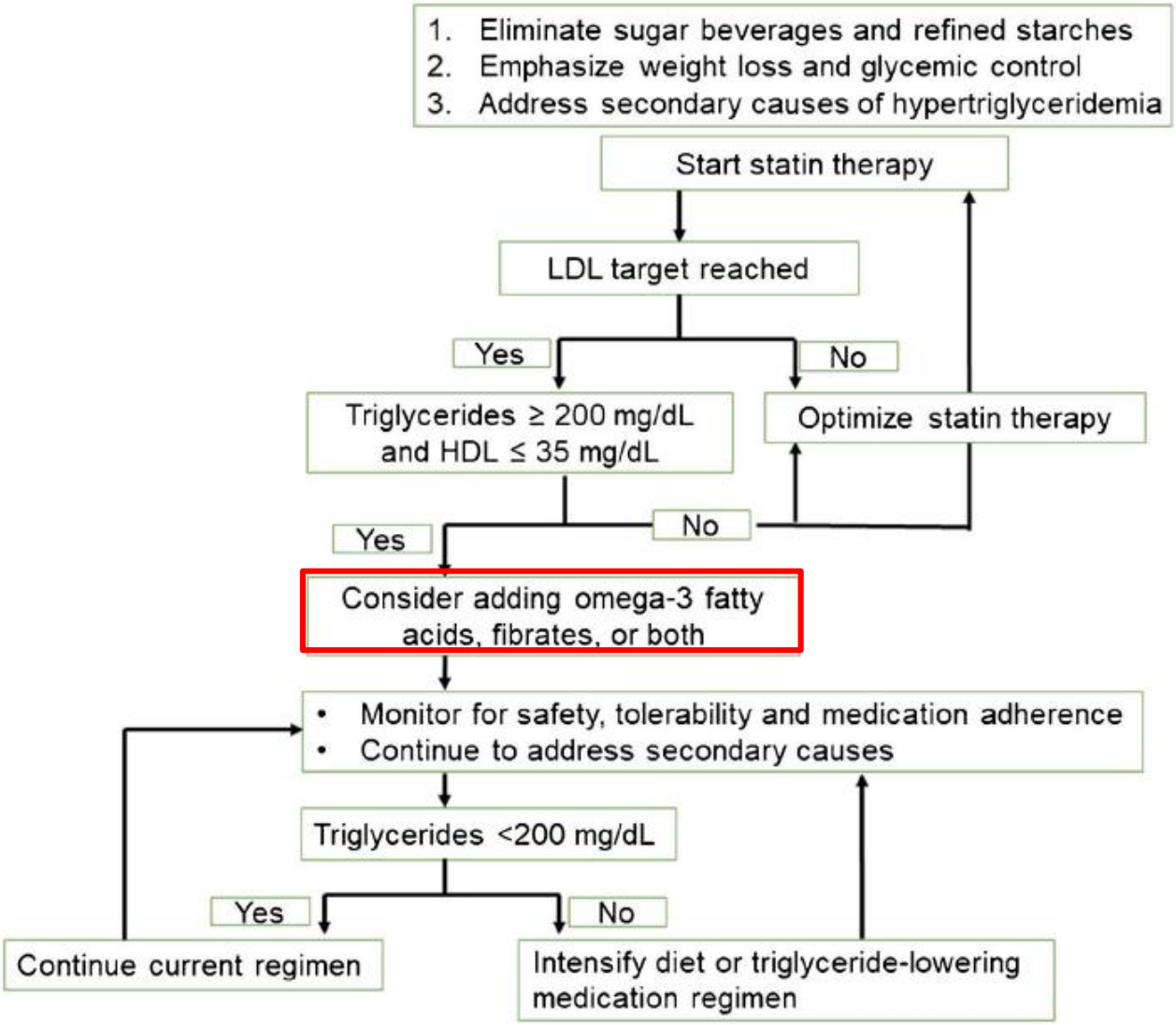
Dash S, et al. Diabetes Obes Metab. 2019;21 Suppl 1:28-38.

Reduction in Plasma TG Levels with Lifestyle and Pharmacological Interventions

Intervention	Approximate Reduction in Plasma TG Level
Lifestyle	
Weight loss (38, 132, 133)	0.27 mg/dL per kg weight loss
	5%–10% reduction in initial body weight reduces TG levels by 25%
Dietary modification (38, 134, 135)	0.18 mmol/L (15.7 mg/dL) reduction in plasma TG levels with a plant-based protein and unsaturated fat–enriched diet
	10%–15% reduction in plasma TG levels with Mediterranean diet
Exercise (38)	≤20% reduction in plasma TG levels with moderate to intense aerobic exercise
	~5% reduction in plasma TG levels with resistance training
Pharmacotherapy	
Statins (131)	Dose-dependent reductions in TG of 22%–45% in individuals with baseline TG >250 mg/dL
	Minimal reduction in TG in individuals with baseline TG <150 mg/dL
Fibrates (15)	30%–50%
Niacin (15)	≤30%
OM3FAs (15)	30%–50%

Sandesara PH, et al. Endocr Rev. 2019;40(2):537-557.

Management of Triglycerides in Diabetic Dyslipidemia



Alexopoulos AS, et al. Curr Diab Rep2019;19(4):13.

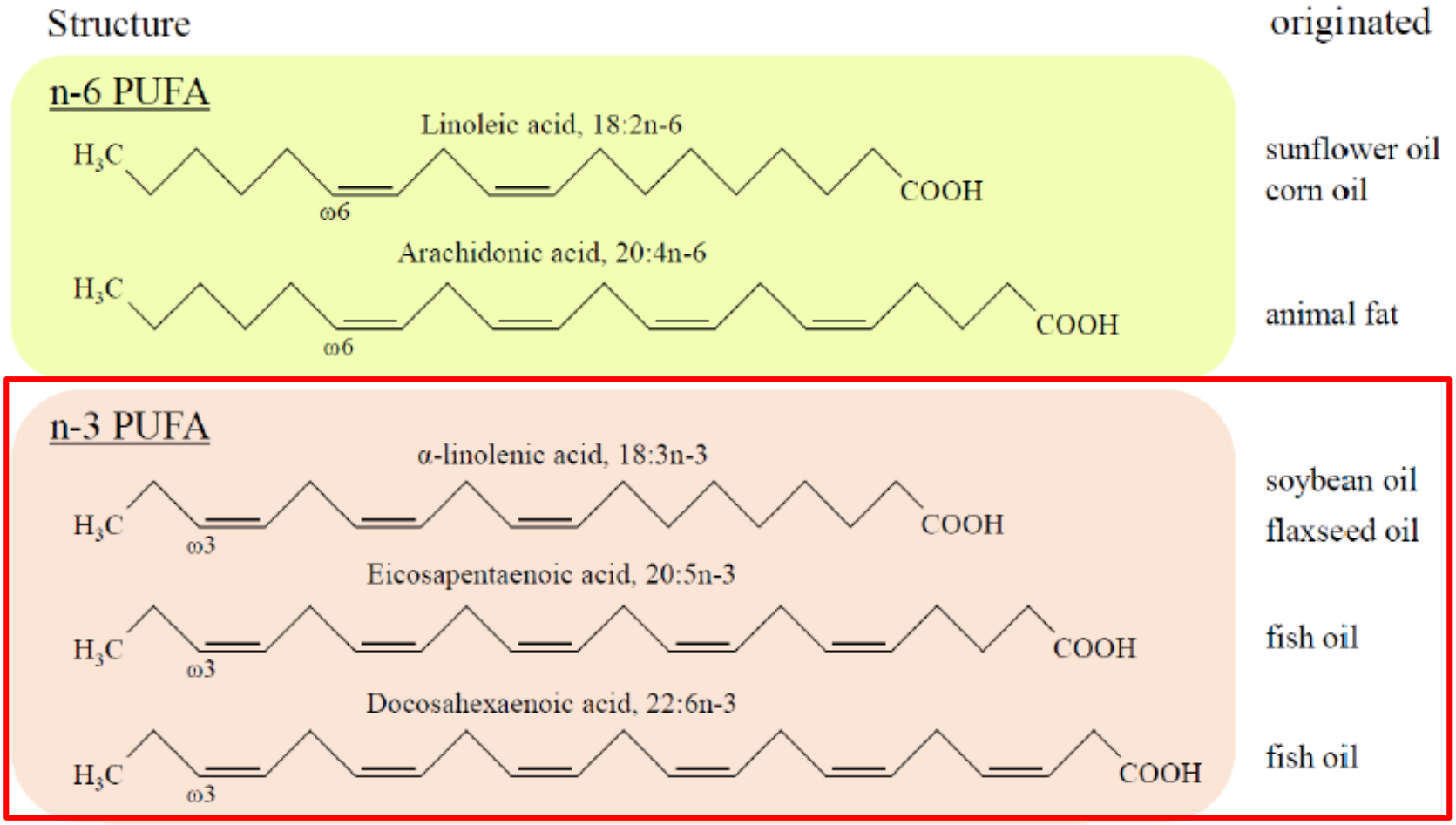
Summary of CVD Trials with TG Lowering Drugs

Trial	Drug	Patient population	Statin use	HDL	TG	LDL	CVD outcomes
HHS	Gemfibrozil	Non-HDL-C >5.2 mmol/L. Asymptomatic with no prior CVD	No	19.4% increase	52% decrease	8.4% decrease	34% reduction in CVD, no mortality benefit
VA-HIT	Gemfibrozil	Established CVD, HDL <1 mmol/L, LDL <3.6 mmol/L	No	6% increase	31% lower	No significant difference	24% reduction MACE
BIP	Bezafibrate	Coronary artery disease	No	18% increase	21% decrease	6.5% decline	Neutral
FIELD	Fenofibrate	Type 2 diabetes with and without CVD	Not at baseline	1.2% increase	22% decrease	5.8% decrease	24% reduction non-fatal MI, 11% decrease on CVD events
ACCORD	Fenofibrate	Type 2 diabetes with and without CVD	Yes	No significant change vs placebo	25% decrease	No significant difference vs placebo	Neutral
JELIS	Eicosapentaenoic acid (EPA)	Hypercholesterolaemic patients on low dose statin	Yes	No significant change	5% decrease vs placebo	25% decrease	19% decrease
REDUCE-IT	Icosapent ethyl	High risk CVD	Yes	No significant change	18.3% reduction	3.1% increase vs 10.2% increase in placebo	25% reduction

Dash S, et al. Diabetes Obes Metab. 2019;21 Suppl 1:28-38.

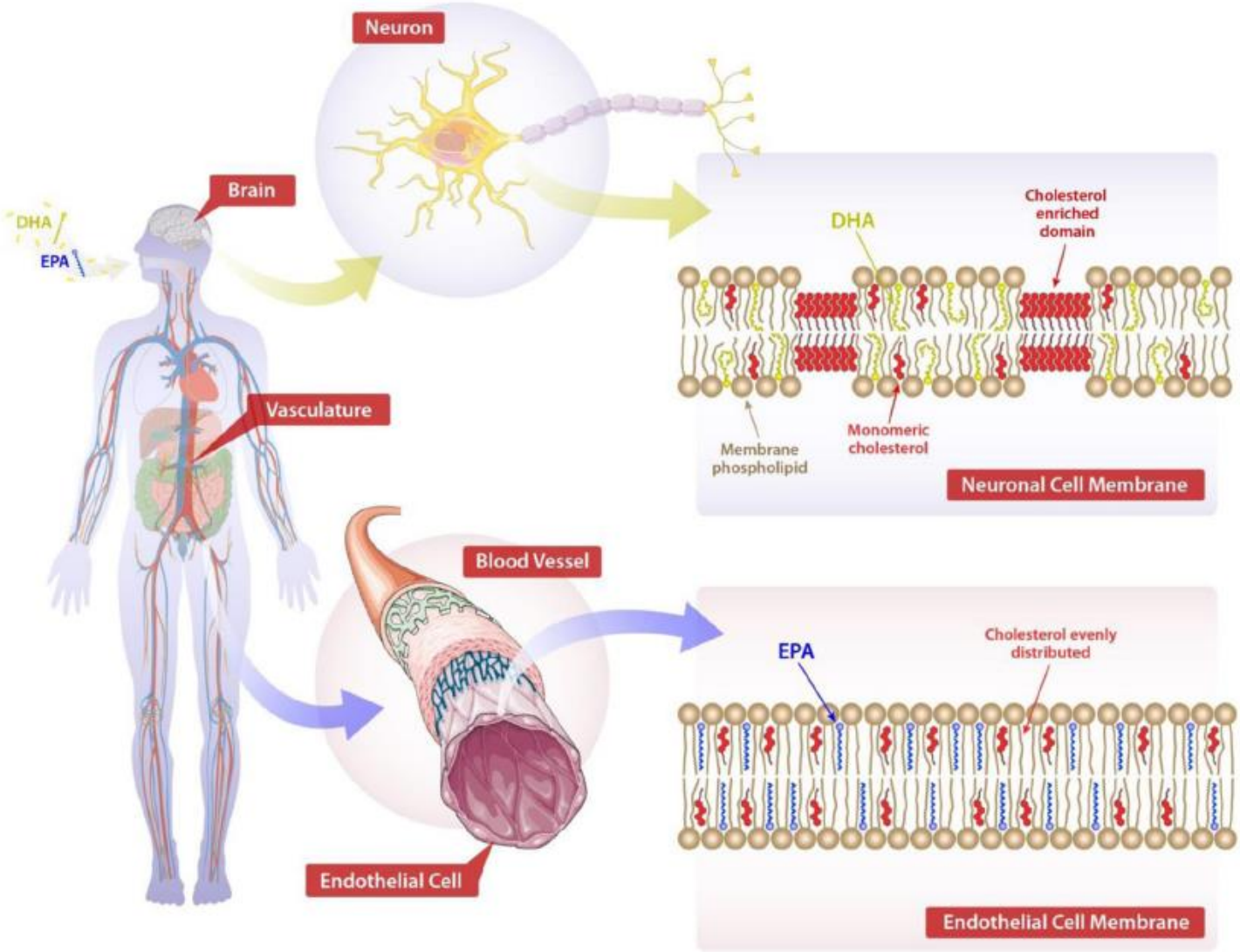
Structure of Polyunsaturated Fatty Acids (PUFAs) and Originated Oils

The major OM3 include alpha-linolenic acid (ALA, primarily in plants), eicosapentaenoic acid and docosahexaenoic acid (EPA and DHA), and others such as stearidonic acid (SDA) and docosapentaenoic acid (DPA) are present in very low amounts in the diet.



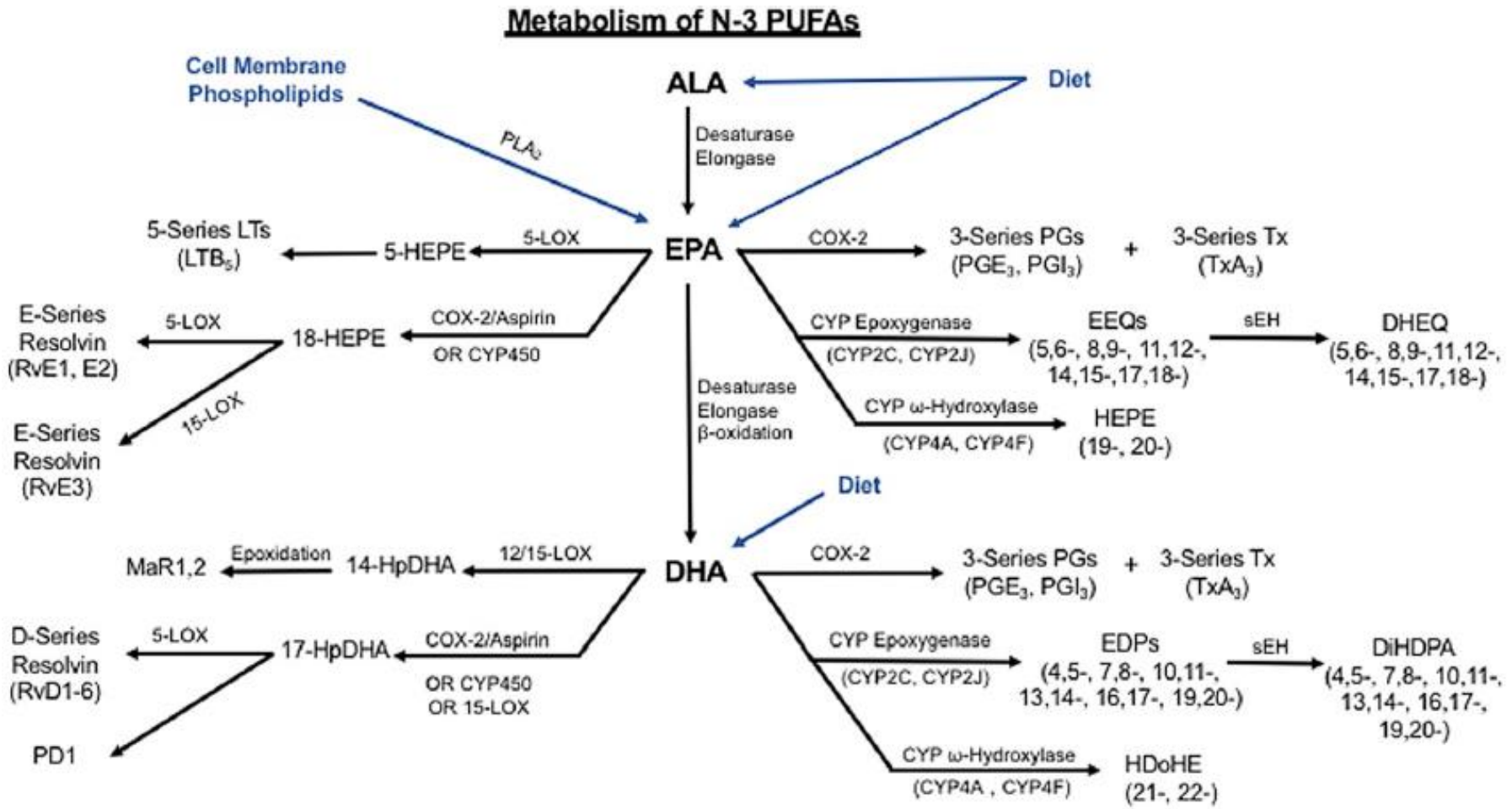
Sakamoto A, et al. Int J Mol Sci. 2019;20(16). pii: E4025.

The Effects of EPA and DHA on Endothelial and Neuronal Cell Membrane



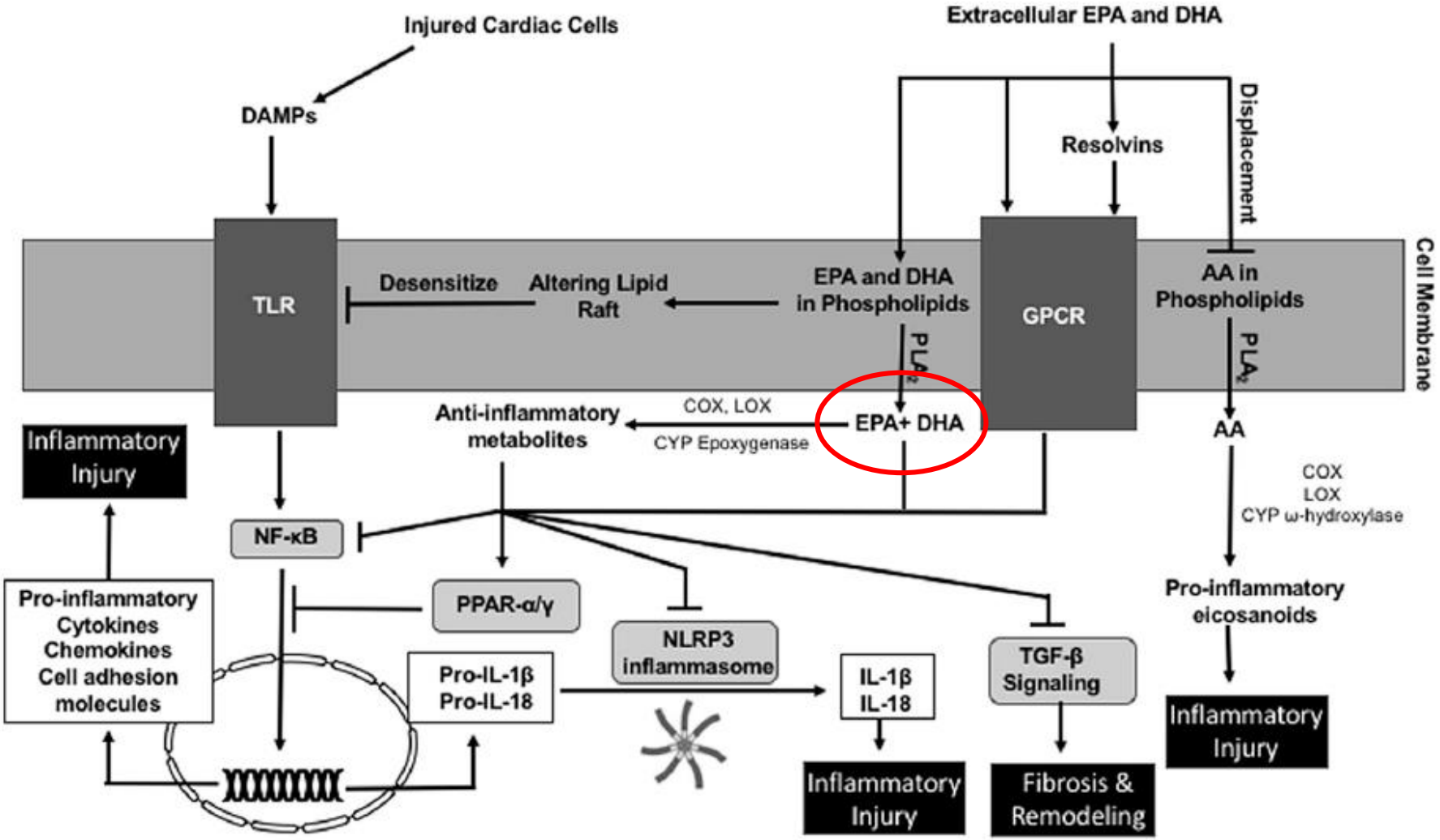
Preston Mason R. Curr Atheroscler Rep 2019;21:2.

Metabolism of Omega-3



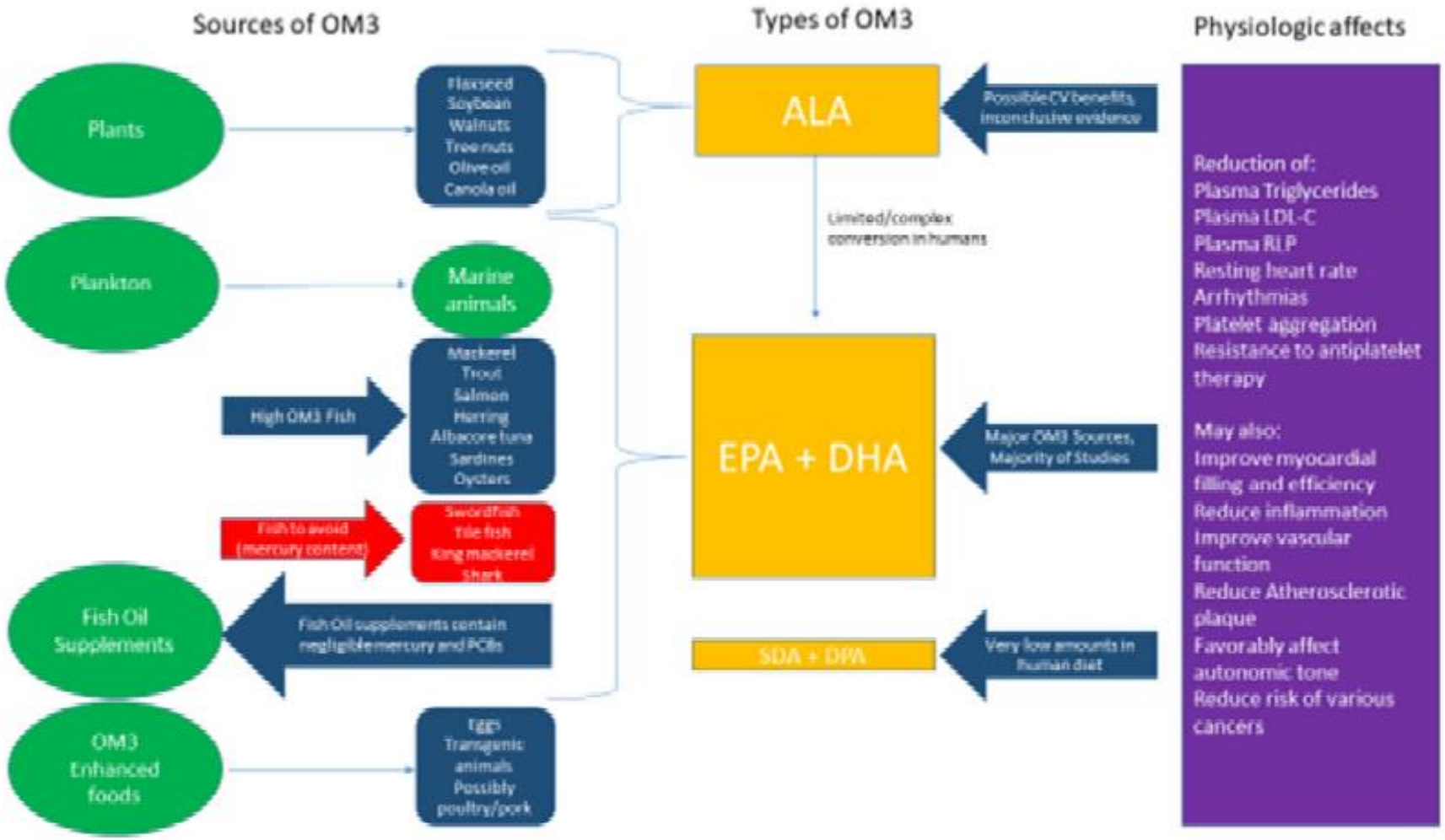
Darwesh AM, et al. Chem Biol Interact 2019;308:20-44.

The Immuno-modulatory Effects of Omega-3



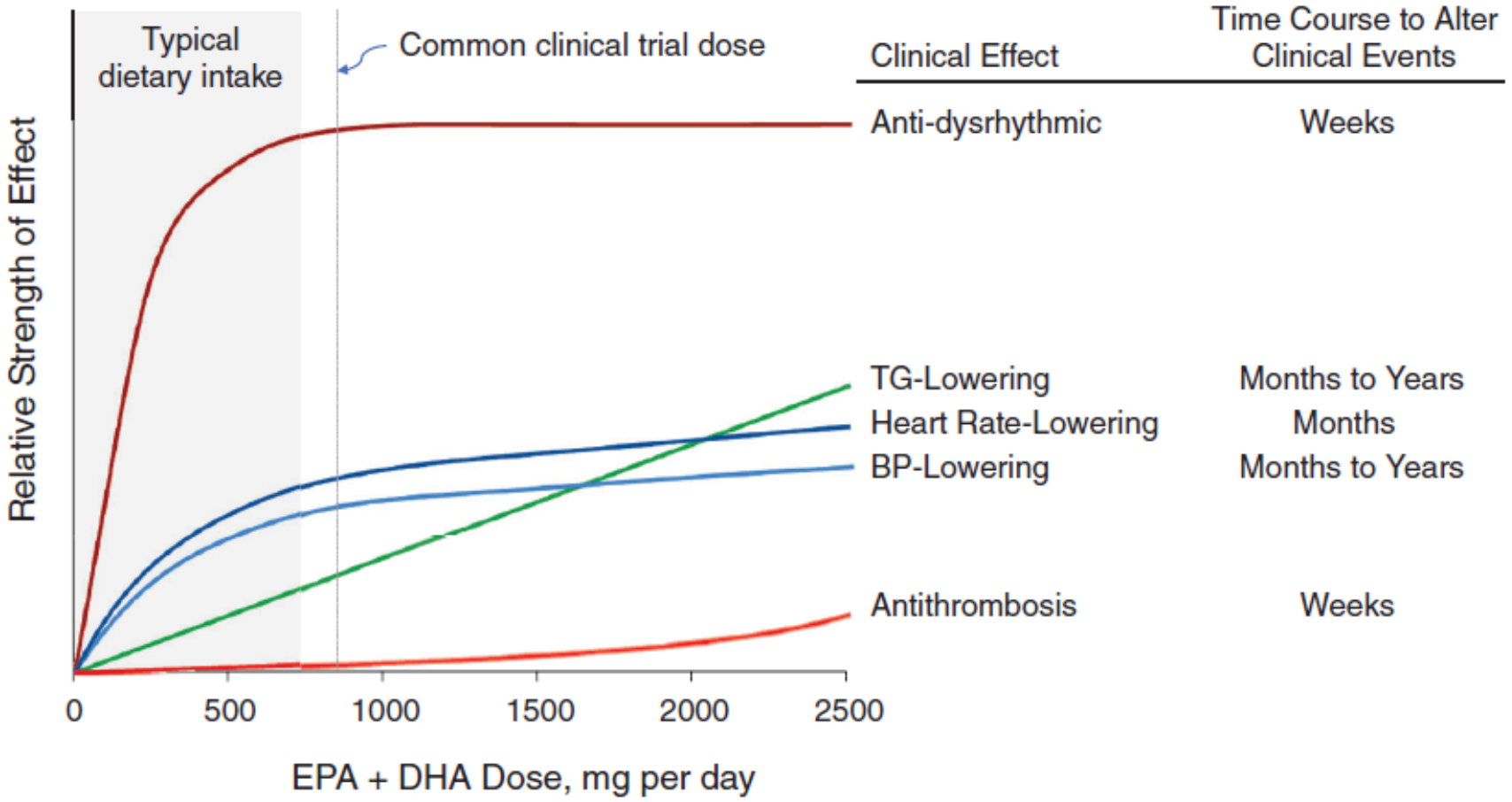
Darwesh AM, et al. Chem Biol Interact 2019;308:20-44.

OM3 types, Sources and Physiologic Effects



Elagizi A, et al.Prog Cardiovasc Dis. 2018 ;61(1):76-85.

The Effect of EPA+DHA on Cardiovascular Risk



Baum SJ, et al. Clin Cardiol. 2019 Jun 29

Effects of EPA on Plaque Progression

Under conditions of…	EPA increases…	EPA decreases…
Endothelial dysfunction and oxidative stress	• Endothelial function • NO bioavailability	• Cholesterol crystalline domains • oxLDL • RLP-C • Adhesion of monocytes • Macrophages • Foam cells
Inflammation and plaque growth	• EPA/AA ratio • IL-10	• IL-6 • ICAM-1 • hsCRP • Lp-PLA_2
Unstable plaque	• Fibrous cap thickness • Lumen diameter • Plaque stability	• Plaque volume • Arterial stiffness • Plaque vulnerability • Thrombosis • Platelet activation

Preston Mason R. Curr Atheroscler Rep 2019;21:2.

CV Prevention Trials of Omega-3 (I)

	GISSI-P[80]	JELIS[81]	GISSI-HF[82]	OMEGA[83]	Alpha-Omega[2]
Publication date	1999	2007	2008	2010	2010
N	11 324	18 645	6975	3851	4837
Median follow-up, years	3.5	4.6	3.9	1 (treatment duration)	3.3
Enrollment Criteria					
Primary or secondary prevention	Secondary	Primary	Secondary	Secondary	Secondary
Enrollment criteria	Recent MI (≤3 months)	Total-C ≥ 251 mg/dL	Chronic HF, NYHA classes II-IV	Recent MI (≤14 days)	Prior MI
Baseline TG levels, mg/dL	No enrollment requirement				
Baseline LDL, mg/dL	No requirement	≥170	No enrollment requirement		
Baseline statin required	No				
Baseline lipid characteristics					
Median TG mg/dL	162-163	153-154	126	NR	144-150
Mean or median, HDL-C, mg/dL	41	58-59	NR	NR	~50
Mean or median, LDL-C mg/dL	137-138	182	NR	~49% had "hypercholesterolemia"	98-102
Lipid lowering therapy, %	~5	100%, added to both arms	22-23		86
Treatment					
Active treatment (daily dose)	850 mg, EPA + DHA	1800 mg Icosapent ethyl	850 mg, EPA + DHA	460 mg EPA + 380 mg DHA	Margarine containing ALA, EPA, and DHA (Avg 376 mg, EPA + DHA per day)

Results of CV Prevention Trials of Omega-3 (I)

	GISSI-P[80]	JELIS[81]	GISSI-HF[82]	OMEGA[83]	Alpha-Omega[2]
Primary endpoint					
Primary endpoint	Death, MI, or stroke	Cardiac death, MI, UA, PCI, CABG	Co-primary: Death, and Death or CV hospitalization	Sudden cardiac death	CV event (fatal or nonfatal), PCI, or CABG
Result, HR (95% CI)	0.85 (0.74-0.98) 4-way analysis	0.81 (0.69–0.95)	Death: 0.91 (0.833-0.998), death or CV Hosp: 0.92 (0.849-0.999)	0.95 (0.56-1.60)	1.01 (0.87-1.17)

Baum SJ, et al. Clin Cardiol. 2019 Jun 29

CV Prevention Trials of Omega-3 (II)

	SU.FOL.OM3[84]	ORIGIN[3]	Risk and Prevention[85]	VITAL[73]	ASCEND[4]	REDUCE-IT[1]
Publication date	2010	2012	2013	2018	2018	2018
N	2501	12 536	12 513	25 871	15 480	8179
Median follow-up, years	4.7	6.2	5	5.3	7.4	4.9
Enrollment Criteria						
Primary or secondary prevention	Secondary	Primary	Mixed	Primary	Primary	Mixed
Enrollment criteria	History of MI, UA, or ischemic stroke	High risk + impaired fasting glucose, impaired glucose tolerance, or diabetes	ASCVD but no MI, or multiple risk factors	Men ≥50 years; Women ≥55 years	Diabetes mellitus, no evidence of CV disease	• Established CV disease (at least 70% of participants) • DM + other risk factors
Baseline TG levels, mg/dL						135-499
Baseline LDL, mg/dL						41-100
Baseline statin required						Yes
Baseline lipid characteristics						
Median TG mg/dL	97-115	140-142	150	NR	NR	216
Mean or median, HDL-C, mg/dL	43	46	51	NR	49	40
Mean or median, LDL-C mg/dL	2.6-2.7	112	132-133	NR	112-113 (non-HDL-C)	75
Lipid lowering therapy, %	83-87	53-55	41	38	75-76	100
Treatment						
Active treatment (daily dose)	600 mg, EPA + DHA (2:1)	465 mg EPA 375 mg DHA	850 mg, EPA + DHA	460 mg EPA + 380 mg DHA (+/− vitamin D)	460 mg EPA + 380 mg DHA	4 g Icosapent ethyl

Results of CV Prevention Trials of Omega-3 (II)

SU.FOL.OM3[84]	ORIGIN[3]	Risk and Prevention[85]	VITAL[73]	ASCEND[4]	REDUCE-IT[1]
CV death, MI, stroke	CV death	CV death or CV hospitalization	MI, stroke or CV death	First MI, stroke, TIA, or vascular death (excluding intracranial hemorrhage)	CV death, MI, stroke, coronary revascularization, UA
1.08 (0.79-1.47)	0.98 (0.87-1.10)	0.97 (0.88-1.08)		0.97 (0.87-1.08)	0.75 (0.68–0.83)

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Primary Prevention of Heart Failure Clinical Trials

Study or Author/Reference	Year of Publication	Region	Follow Up (Years)	Study Population	HF Event	Incidence of HF
Cardiovascular Health study [8]	2005	USA	12	4.738 (male 42%, age > 65)	955	Boiled or baked fish intake was negatively associated
Woman's Health Initiative Observational study [9]	2011	USA	10	84.493 (all female, age 50–79)	1.858	Boiled or baked fish intake was negatively associated
Physicians' Health study [22]	2012	USA	14	18.968 (fish consumption analysis) 19.097 (dietary n-3 PUFA analysis, all male, age > 58.7)	695/703	Fish consumption greater than once per month was negatively associated
JACC study [23]	2008	Japan	12.7	57.972 (male 40%)	307	Fish and n3 PUFA intake were negatively associated
Rotterdam study [25]	2009	Nederland	11.4	5.299 (male 41%, age > 55)	669	Fish/n-3 PUFA intake was not associated
Levitan EB et. al. [26]	2009	Sweden	7	39.367 (all male, middle and old age)	597	Fish/n-3 PUFA intake was not associated
Levitan EB et. al. [27]	2010	Sweden	9	36.234 (all female, age 48–83)	651	Moderate consumption of fatty fish and n-3 PUFA were negatively associated

All trials were done with an observational cohort study. To date, no published randomized control trials (RCTs) have assessed the effect of dietary fish and n-3 PUFA intake on primary prevention of HF. Accordingly, the advisory form of the American Heart Association (AHA) has no recommendation of the n-3 PUFA intake for the purpose of HF primary prevention thus far [29].

Sakamoto A, et al. Int J Mol Sci. 2019;20(16). pii: E4025.

Secondary Prevention of Heart Failure Clinical Trials (I)

Study or Author/Reference	Year of Publication	Study Design	Number of Patients	Region	n-3 PUFA	Baseline Patient Background	Follow Up	Outcomes	Interpretation
GISSI-HF [10]	2008	MC, RDM, DB, PC	3494; n-3 PUFA 3481; placebo	Italy	1 g/day	Mean age; 67 y, male 78%, NYHA; II 63%, III 34%, IV 3%, Mean EF; 33%	3.9 years	All-cause death or admission to hospital for cardiovascular reasons; HR 0.92 (99% CI 0.849–0.999)	n-3 PUFA can provide a small benefit for mortality and hospitalization
Zhao et. al. [31]	2009	MC, RDM, DB, PC	38; n-3 PUFA 37; placebo	China	2 g/day	Mean age; 73 y, male 73%, NYHA; II 37%, III 63%, Mean EF; 31%	3 months	Reduced in serum NT-proBNP ($p < 0.001$), TNF-α ($p = 0.014$), IL-6 ($p = 0.003$), and ICAM-1 ($p = 0.023$)	n-3 PUFA can reduce levels of plasma inflammatory markers and NT-proBNP
GISSI-HF (Echo sub-study) [30]	2010	MC, RDM, DB, PC	312; n-3 PUFA 296; placebo	Italy	1 g/day	Mean age; 65 y, male 84%, NYHA; II 77%, III 22%, IV 1%, Mean EF; 31%	3 years	Increased in LVEF ($p = 0.005$)	n-3 PUFA can provide a small advantage in terms of LV function
Nodari et. al. [24]	2011	SC, RDM, DB, PC	67; n-3 PUFA 66; placebo (olive oil)	Italy	5 g/day for 1mon 2 g/day for 11mon	Mean age; 62 y (18 to 75), NYHA; I 14%, II 86% Mean EF 36%	1 years	Increased LVEF and Peak VO_2. Improved in exercise duration and NYHA. Reduced in Hospitalization. (all $p < 0.001$)	n-3 PUFA increased LV systolic function and functional capacity, and reduce HF hospitalizations
Mehra et. al. [32]	2006	SC, RDM, DB, PC	7; n-3 PUFA 7; placebo (corn oil)	USA	8 g/day	Mean age; 57 y, male 71%, NYHA; III 57%, IV 43%, Mean EF 17%	4.5 months	Decreased in TNF-α and IL-1	n-3 PUFA decreased TNF-α production in HF
Moertl et. al. [33]	2011	SC, RDM, DB, PC, 3-arm	14; n-3 PUFA (1g/d) 13; n-3 PUFA (4g/d) 16; placebo	Austria	1 g/day or 4 g/day	Mean age; 58 y, male 86%, NYHA; III 91%, IV 9%, Mean EF; 24%	3 months	Increased LVEF (4 g/day; +5%, 1 g/day; +3%). Reduced hs IL-6 by 2.3 pg/mL ($p = 0.01$ vs baseline)	n-3 PUFA dose dependently improved LVEF and decreased serum IL-6
Kojuri et. al. [34]	2013	SC, RDM, DB, PC	38; n-3 PUFA 32; placebo	Iran	2 g/day	Mean age; 57 y, male 60%, NYHA; II to III, Mean EF; 31%	6 months	Reduced late diastolic velocity index, Tei index and plasma BNP	n-3 PUFA slightly decreased plasma BNP levels and moderately improved ventricular diastolic function.
Kohashi et. al. [35]	2014	SC, OL, PRS	71; EPA 68; no EPA	Japan	EPA 1.8mg/day	Mean age; 70 y, male 86%, NYHA; II 91%, III 9%, Mean EF; 37.6%	1 year	Increased LVEF. Reduced MCP-1and ADMA. Suppressed cardiac death and HF readmission; HR 0.21 (95% CI 0.05–0.93)	EPA improved cardiac function and prognosis of HF

Sakamoto A, et al. Int J Mol Sci. 2019;20(16). pii: E4025.

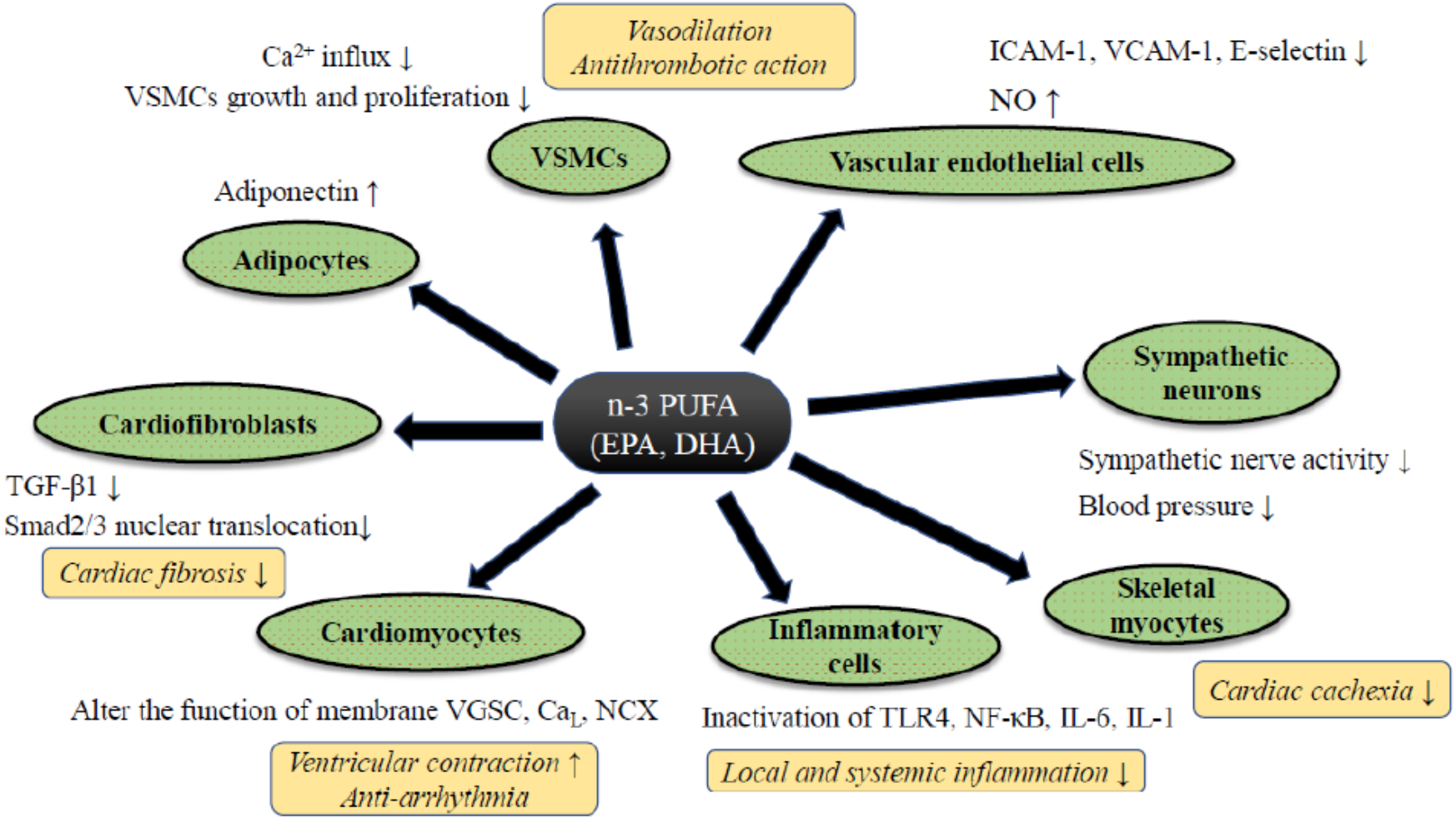
Secondary Prevention of Heart Failure Clinical Trials (II)

Study or Author/Reference	Year of Publication	Study Design	Number of Patients	Region	n-3 PUFA	Baseline Patient Background	Follow Up	Outcomes	Interpretation
OMEGA-REMODEL [36]	2016	MC, RDM, DB, PC	180; n-3 PUFA 178; placebo (corn oil)	USA	4 g/day	Mean age; 59 y, male 80%, NYHA; I 91%, II 8%, III 1%, Mean EF 54%	6 months	Reduced LVESVI and non-infarction myocardial fibrosis and ST2	High dose n-3 PUFA reduced LV remodeling, myocardial fibrosis, and inflammatory biomarkers in patients with post AMI.
Chrysohoou et. al. [37]	2016	SC, RDM, OL, PRS	101; n-3 PUFA 95; without n-3 PUFA (no placebo)	Greece	1 g/day	Mean age; 63y, male 83%, NYHA; I-III, Median EF; 28%	6 months	Reduce ESLVD, LAEF, TDI Etv/Atv and BNP	n-3 PUFA improved LV diastolic function and decreased BNP levels
Oikonomou et. al. [38]	2019	SC, DB, PC, cross over	15 vs 16; n-3 PUFA/placebo (olive oil, cross-over with 6 weeks wash-out period)	Greece	2 g/day	Mean age; 67 y (18 to 80), NYHA; II 65%, III 35%, Mean EF 29%,	2 months	Increased LVEF Reduced global longitudinal strain, E/e' ratio, hsCRP, ST2 levels, FMD % increase	n-3 PUFA improved inflammatory, fibrotic, and endothelial functional status as well as systolic and diastolic LV function.

Abbreviations: ADMA: Asymmetric Dimethylarginine, DB: Double blind trial, ESLVD: End-systolic left ventricle diameters, Etv/Atv: Early rapid right ventricular filling/late right ventricular filling, FMD: Flow-mediated dilatation, LAEF: Left atrial ejection fraction, LVESVI: Left ventricular end-systolic volume indexed to body surface area, MC: Multi-center trial, MCP-1: Monocyte chemoattractant protein 1, NYHA: New York Heart Association class, OL: Open label trial, PC: Placebo-control trial, PRSP: prospective trial, RDM: Randomized trial, SC: Single-center trial, ST2: Suppression of tumorigenicity 2, TDI: Tissue Doppler imaging.

Sakamoto A, et al. Int J Mol Sci. 2019;20(16). pii: E4025.

Putative Mechanism of Omega-3 mediated Cardiac Protection against Heart Failure



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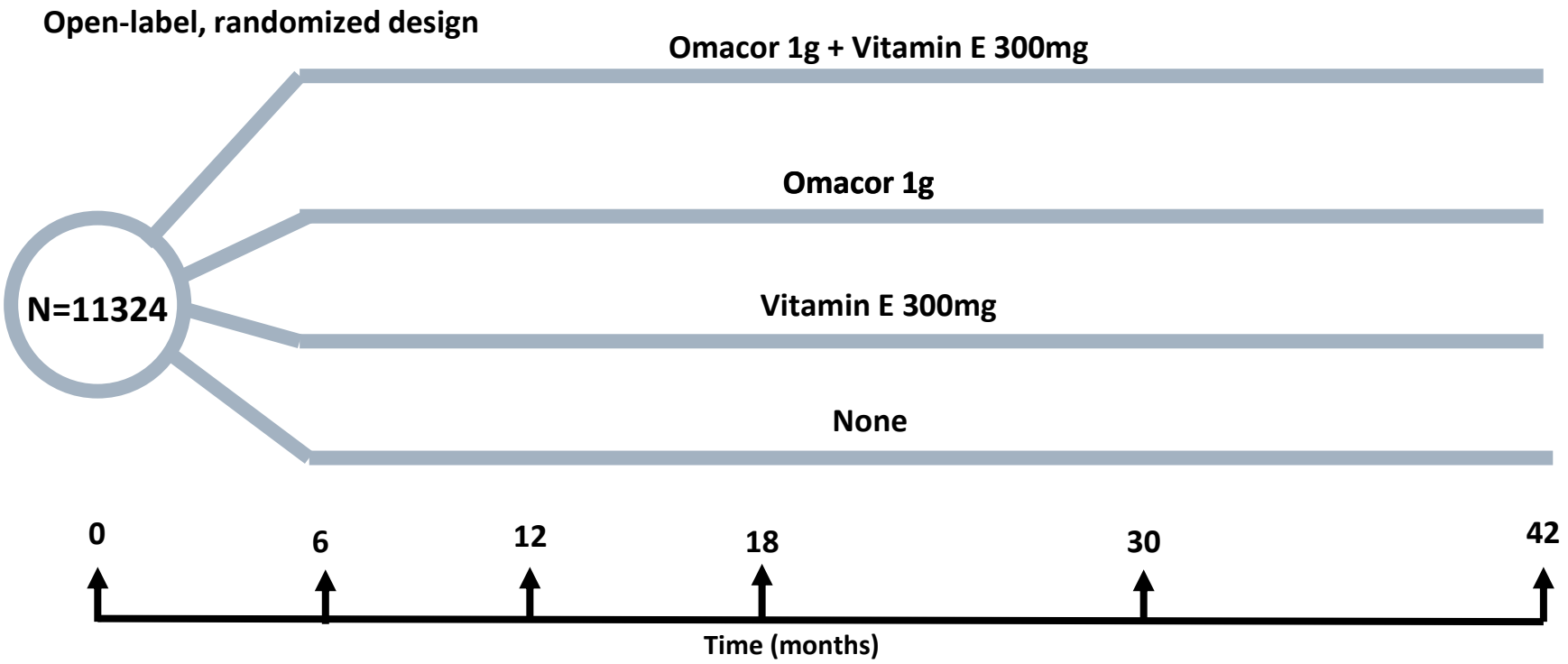
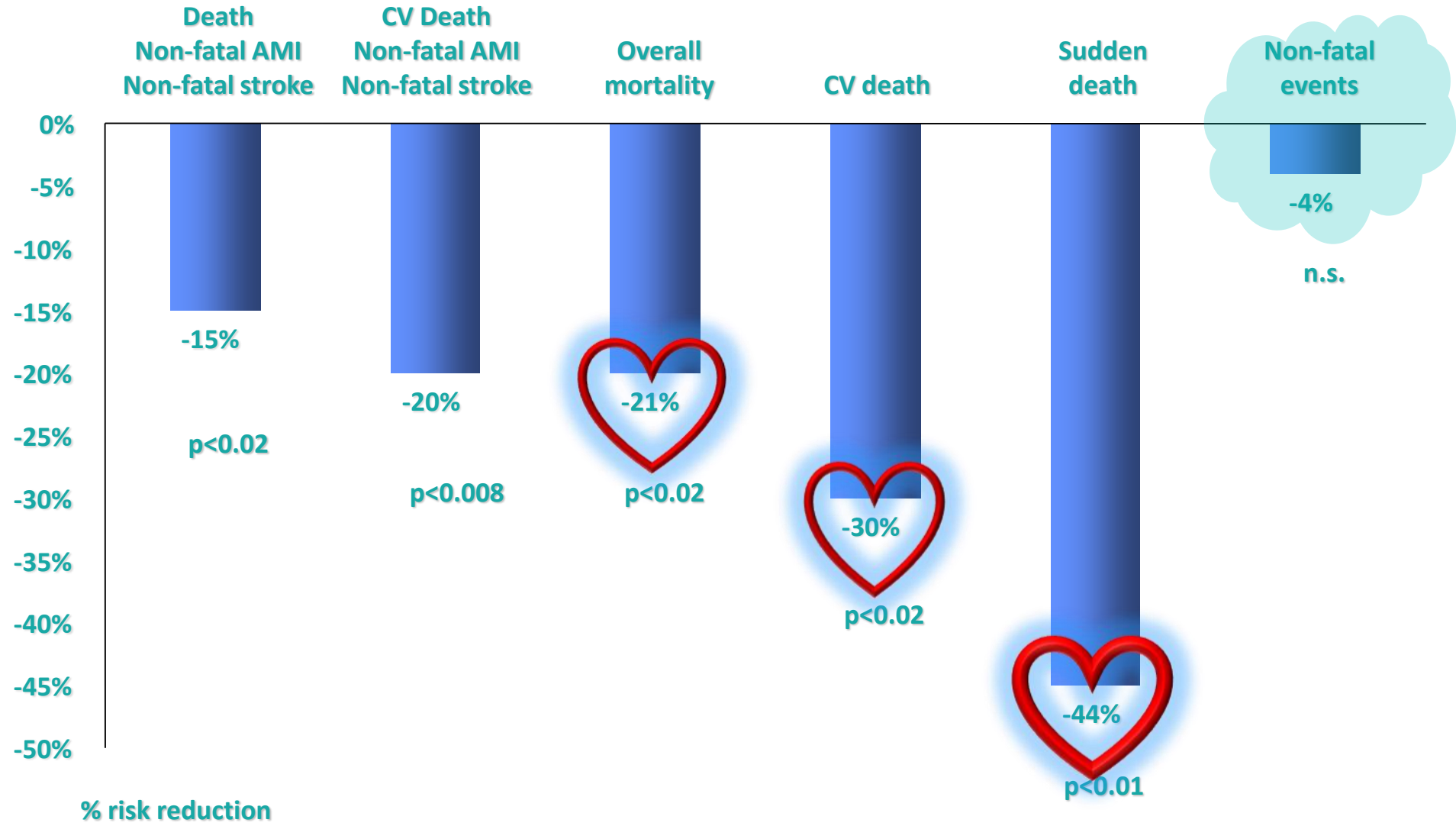
GISSI-Prevention trial



Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E **after myocardial infarction**: results of the GISSI-Prevenzione trial (AVG 3.5 yr)
Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico
Lancet. 1999 Aug 7;354(9177):447-55

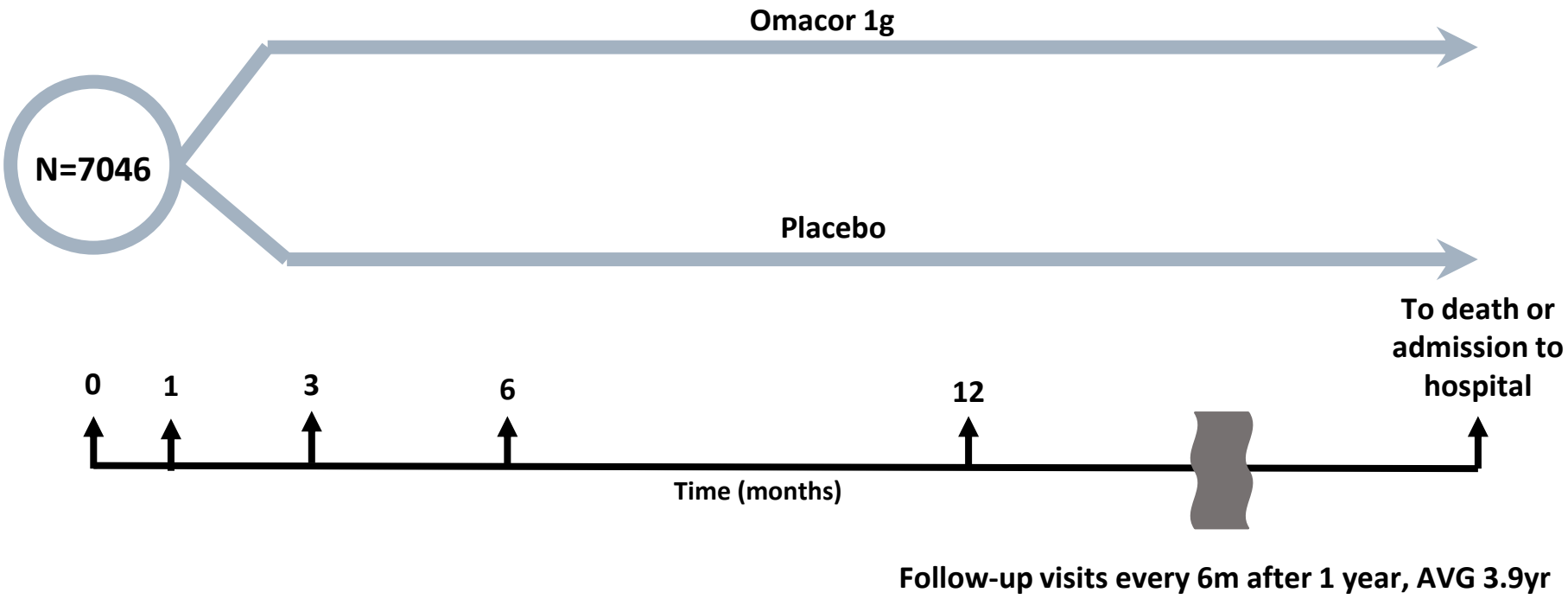
GISS-Preventation臨床實驗發現，心肌梗塞患者每天一顆Omacor能大幅降低死亡率



(GISSI-Prevenzione Investigators, Lancet 1999; 354:447)

GISSI-HF trial

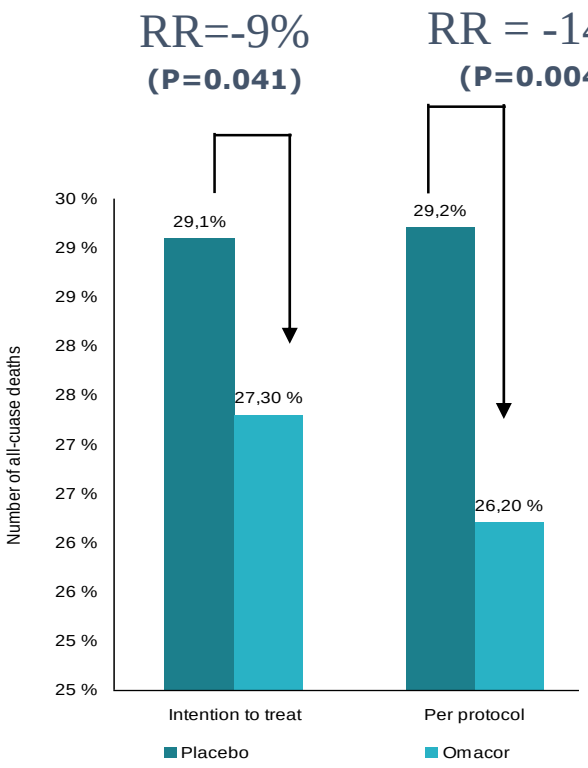
Effect of n-3 polyunsaturated fatty acids in patients with **chronic heart failure** (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial.



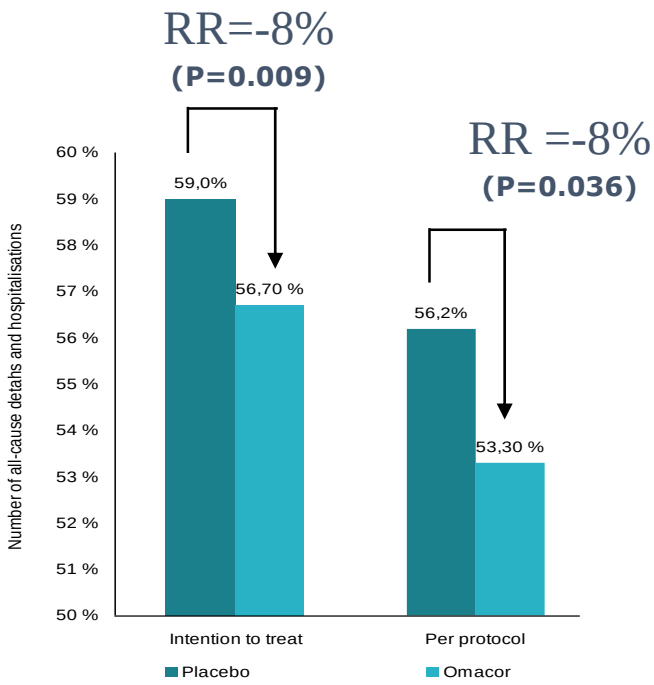
Lancet. 2008 Oct 4;372(9645):1223-30.

GISSI-HF 臨床實驗發現: OMACOR可降低CHF約9%死亡率

Number of all-cause death

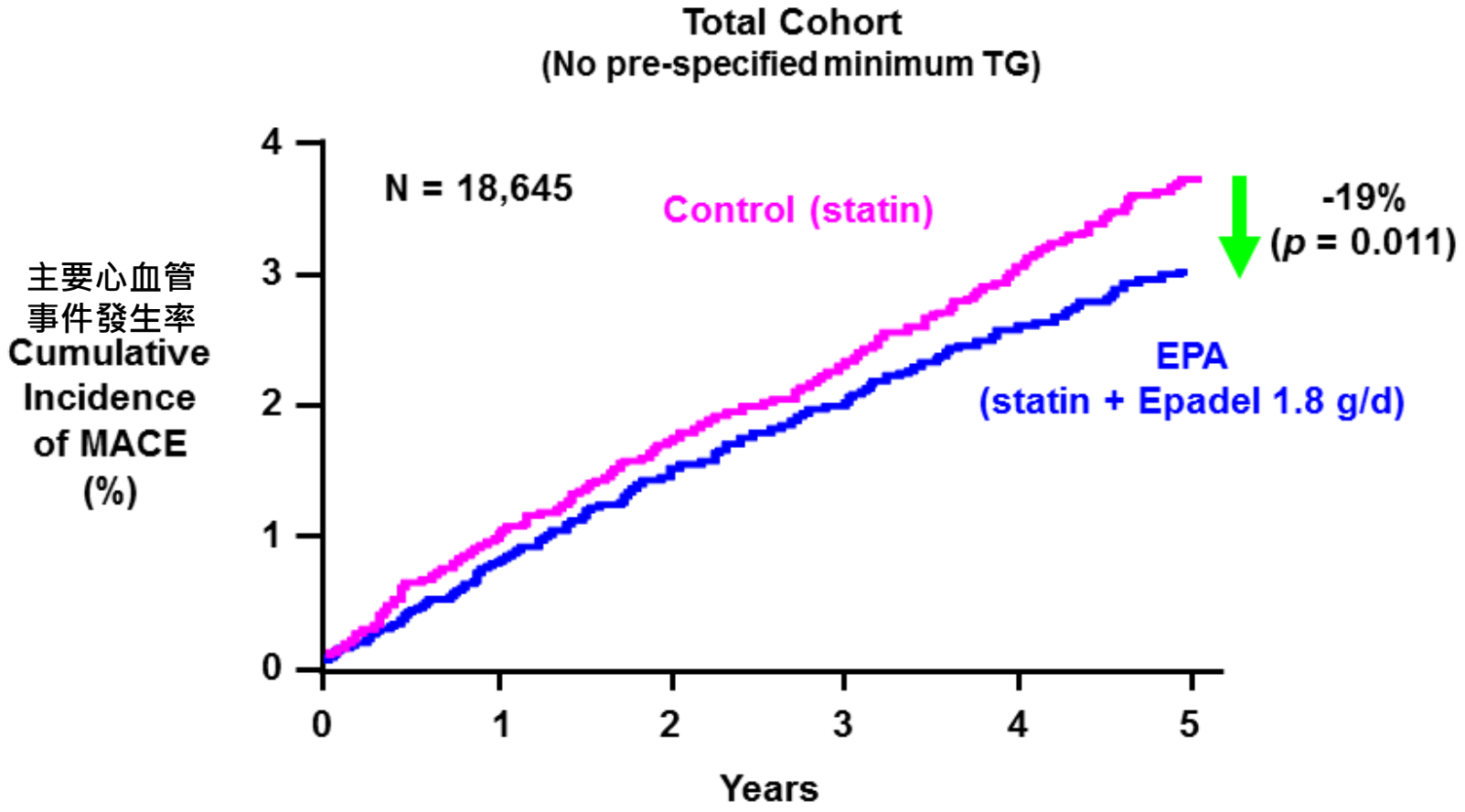


Number of all-cause death & hospitalisations



Lancet. 2008 Oct 4;372(9645):1223-30.

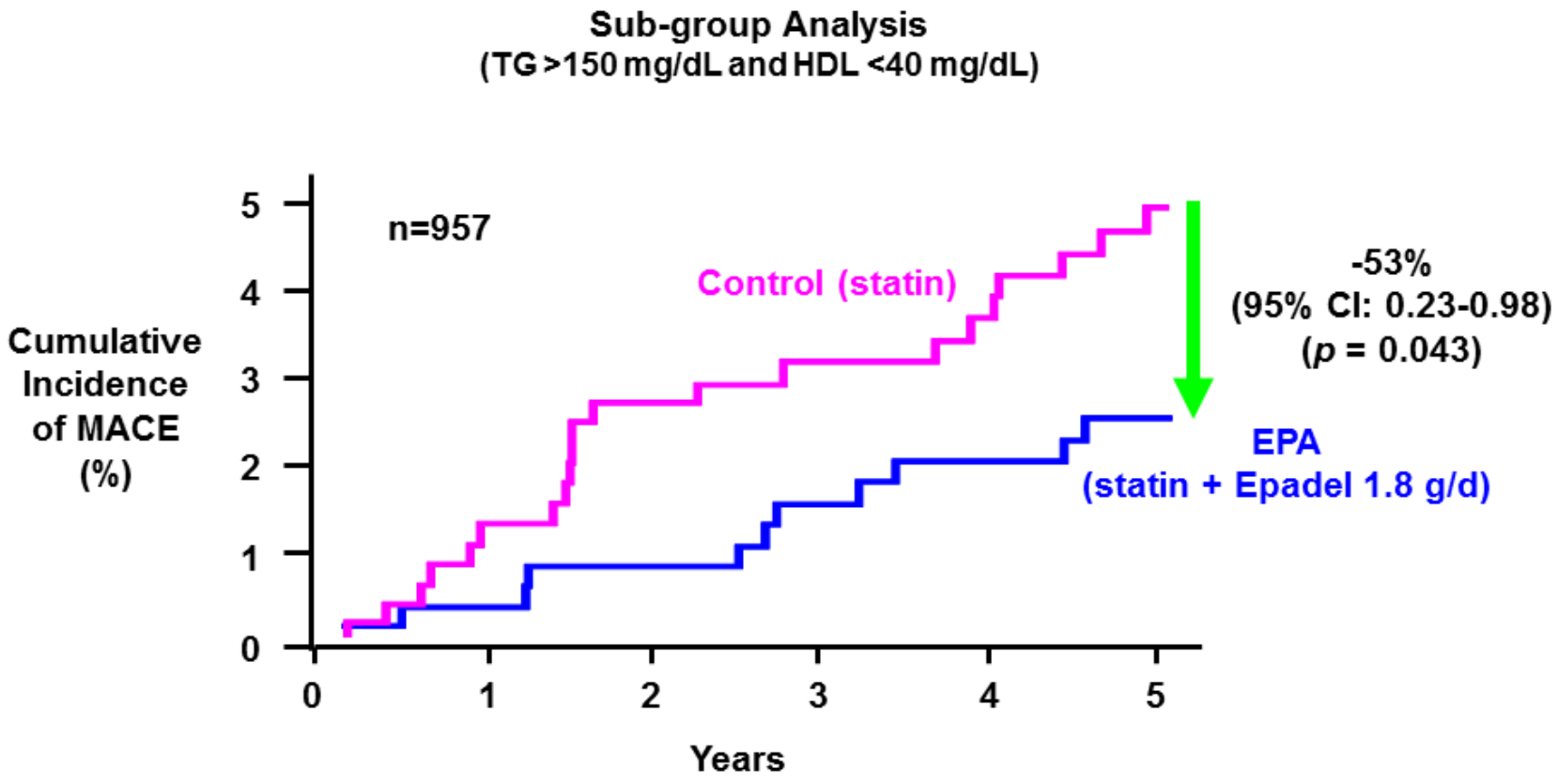
JELIS Study發現，EPA可能有預防心血管疾病的效果(Primary prevention)



AVG 4.6yr

p-value adjusted for age, gender, smoking, diabetes, and hypertension
Yokoyama. *Lancet* (2007)

若患者TG>150mg/dl & HDL<40mg/dl , 有無服用EPA對於心血管疾病初級預防差異更大



p-value adjusted for age, gender, smoking, diabetes, and hypertension.
Saito. *Atherosclerosis* (2008)

The NEW ENGLAND JOURNAL of MEDICINE

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Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia (REDUCE-IT Trial)

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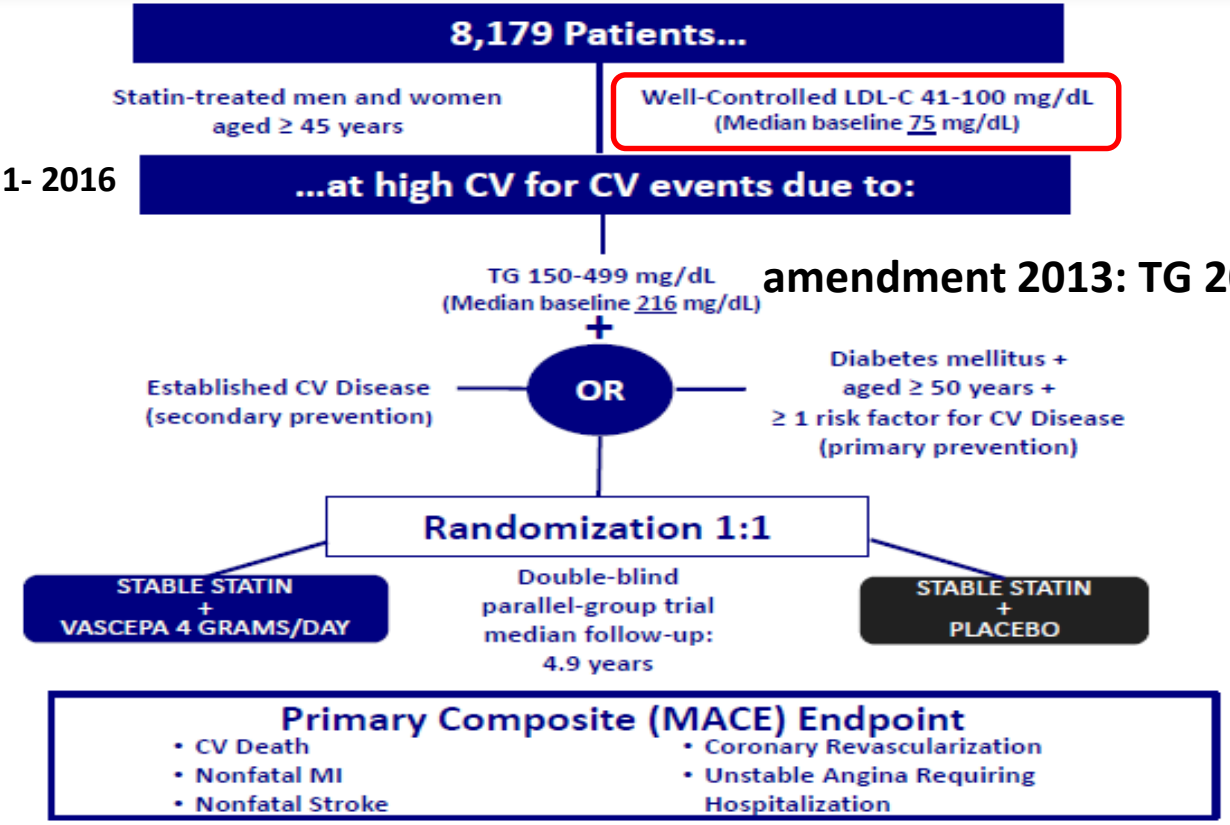
Bhatt DL, et al. N Engl J Med 2019;380;1.

REDUCE-IT Studied Patients with Residual CV Risk Factors Despite LDL-Cholesterol Control

AMARIN



Study conduct : 2011- 2016

amendment 2013: TG 200 -499 mg/dL

MACE=major adverse cardiovascular event

Design and rationale published in 2017 in Clinical Cardiology (Bhatt et Al. Clinical Cardiology.2017;40:138–148): 90% power to measure a 15% reduction in MACE primary endpoint.

Patient Population

- **Enrolled patients with CV risk factors beyond elevated LDL-C**
- 8179 statin-treated patients with well-controlled LDL-C (41-100 mg/dL; median baseline 75 mg/dL)
  - TG 135-499 mg/dL (median baseline 216 mg/dL)
  - Stratified by risk into either secondary prevention or primary prevention cohort
    - 71% — patients with established CVD and ≥45 years (secondary prevention cohort)
    - 29% — patients with diabetes mellitus, ≥50 years, and one additional CV risk factor (primary prevention cohort)
- Randomized to VASCEPA 4 g/d + stable statin or placebo + stable statin
- **Patients were on background lipid-lowering therapy with a median baseline LDL-C of 75 mg/dL**

Bhatt DL, et al. N Engl J Med 2019;380;1.

Baseline Characteristics

Characteristic	Icosapent Ethyl (N=4089)	Placebo (N=4090)
Age		
Median (IQR) — yr	64.0 (57.0–69.0)	64.0 (57.0–69.0)
≥65 yr — no. (%)	1857 (45.4)	1906 (46.6)
Male sex — no. (%)	2927 (71.6)	2895 (70.8)
White race — no. (%)†	3691 (90.3)	3688 (90.2)
Body-mass index‡		
Median (IQR)	30.8 (27.8–34.5)	30.8 (27.9–34.7)
≥30 — no. (%)	2331 (57.0)	2362 (57.8)
Geographic region — no. (%)§		
United States, Canada, the Netherlands, Australia, New Zealand, and South Africa	2906 (71.1)	2905 (71.0)
Eastern European	1053 (25.8)	1053 (25.7)
Asia–Pacific	130 (3.2)	132 (3.2)
Cardiovascular risk stratum — no. (%)		
Secondary-prevention cohort	2892 (70.7)	2893 (70.7)
Primary-prevention cohort	1197 (29.3)	1197 (29.3)
Ezetimibe use — no. (%)	262 (6.4)	262 (6.4)
Statin intensity — no. (%)		
Low	254 (6.2)	267 (6.5)
Moderate	2533 (61.9)	2575 (63.0)
High	1290 (31.5)	1226 (30.0)
Data missing	12 (0.3)	22 (0.5)
Diabetes — no. (%)		
Type 1	27 (0.7)	30 (0.7)
Type 2	2367 (57.9)	2363 (57.8)
No diabetes at baseline	1695 (41.5)	1694 (41.4)
Data missing	0	3 (0.1)

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Baseline Lipids Levels

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Icosapent Ethyl (N = 4089)	Placebo (N = 4090)
Median high-sensitivity CRP level (IQR) — mg/liter	2.2 (1.1–4.5)	2.1 (1.1–4.5)
Median triglyceride level (IQR) — mg/dl	216.5 (176.5–272.0)	216.0 (175.5–274.0)
Median HDL cholesterol level (IQR) — mg/dl	40.0 (34.5–46.0)	40.0 (35.0–46.0)
Median LDL cholesterol level (IQR) — mg/dl	74.0 (61.5–88.0)	76.0 (63.0–89.0)
Distribution of triglyceride levels — no./total no. (%)		
<150 mg/dl	412/4086 (10.1)	429/4089 (10.5)
≥150 to <200 mg/dl	1193/4086 (29.2)	1191/4089 (29.1)
≥200 mg/dl	2481/4086 (60.7)	2469/4089 (60.4)
Triglyceride level ≥200 mg/dl and HDL cholesterol level ≤35 mg/dl — no. (%)	823 (20.1)	794 (19.4)
Median eicosapentaenoic acid level (IQR) — μg/ml	26.1 (17.1–40.1)	26.1 (17.1–39.9)

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Biomarkers Changes (from baseline to year 1)

	Icosapent Ethyl (N=4089) Median		Placebo (N=4090) Median		Median Between Group Difference at Year 1		
Biomarker*	Baseline	Year 1	Baseline	Year 1	Absolute Change from Baseline	% Change from Baseline	% Change P-value
Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7	<0.0001
Non-HDL-C (mg/dL)	118.0	113.0	118.5	130.0	-15.5	-13.1	<0.0001
LDL-C (mg/dL)	74.0	77.0	76.0	84.0	-5.0	-6.6	<0.0001
HDL-C (mg/dL)	40.0	39.0	40.0	42.0	-2.5	-6.3	<0.0001
Apo B (mg/dL)	82.0	80.0	83.0	89.0	-8.0	-9.7	<0.0001
hsCRP (mg/L)	2.2	1.8	2.1	2.8	-0.9	-39.9	<0.0001
Log hsCRP (mg/L)	0.8	0.6	0.8	1.0	-0.4	-22.5	<0.0001
EPA (µg/mL)	26.1	144.0	26.1	23.3	+114.9	+358.8	<0.0001

*Apo B and hsCRP were measured at Year 2.

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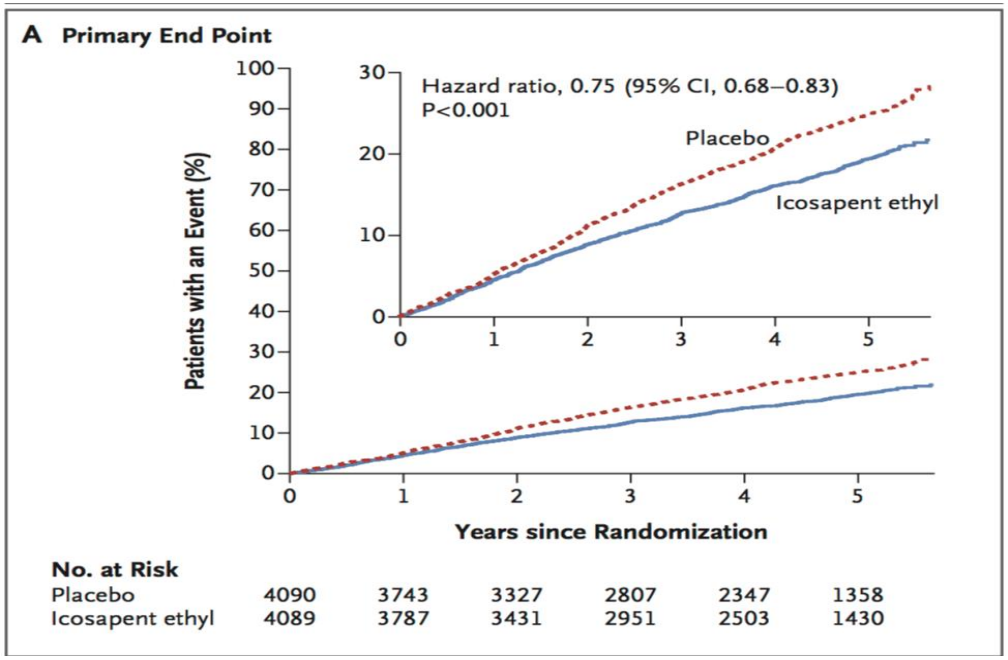
Primary Endpoint



- Primary EP: CV Death, nonfatal MI, nonfatal stroke, coronary revascularization or unstable angina (5 point MACE)
- Median follow-up 4.9 years
- Primary (5-MACE): RRR=24.8%; ARR=4.8%; NNT 21
- CV event curve for VASCEPA visually separated from the placebo event curve at approximately 1 year and remained separated throughout follow-up period

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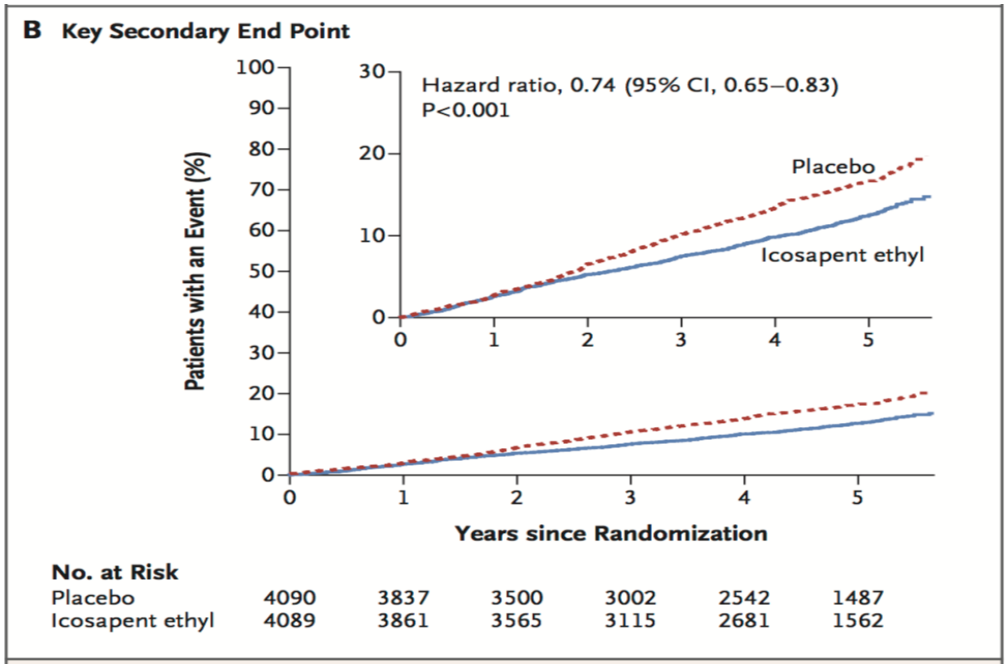
Secondary endpoint



Key secondary end point: CV Death, nonfatal MI or nonfatal stroke

- RRR=26%, NNT=28
- CV event curv visually separate from placebo event curv before 2 years and remained separated throughout follow up period

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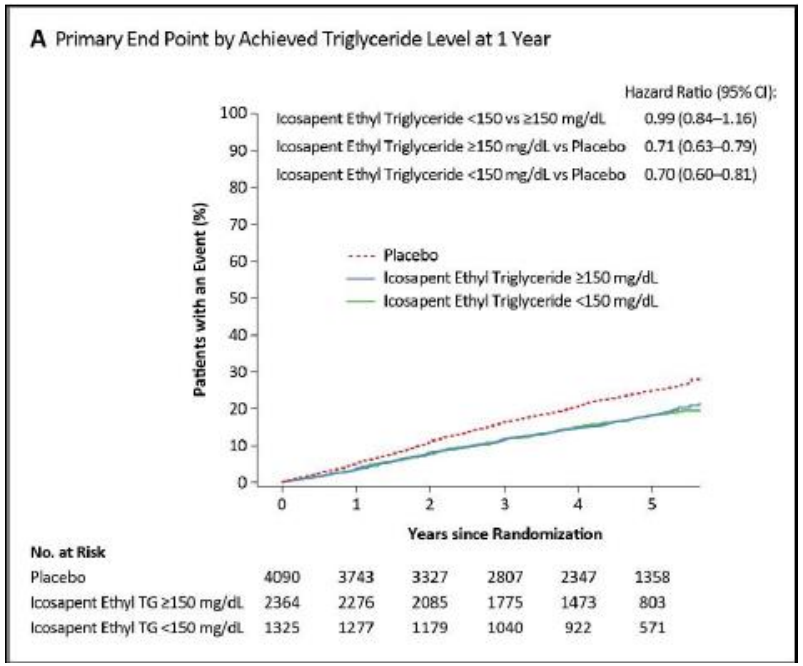
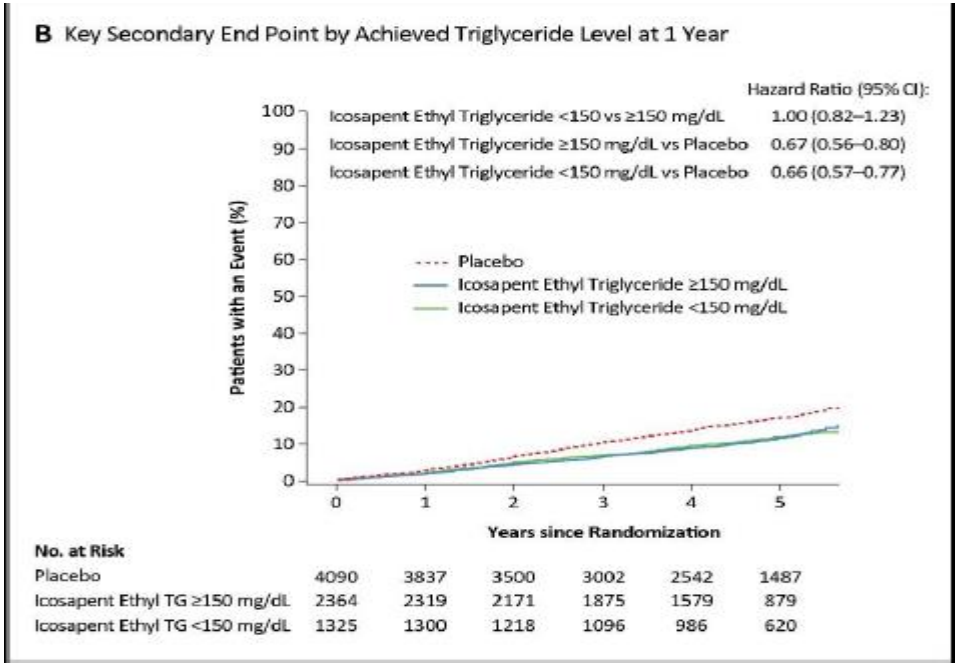
Endpoints by achieved TG level at 1 year
(<150 mg/dL or >=150 mg/dL)





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Safety

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P value[1]
Patients with at Least One TEAE,[2] 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[3]	321 (7.9%)	335 (8.2%)	0.60
Serious TEAE Leading to Withdrawal of Study Drug[3]	88 (2.2%)	88 (2.2%)	1.00
Serious TEAE Leading to Death[4]	94 (2.3%)	102 (2.5%)	0.61

- Overall TEAES rates similar in Vascepa and placebo groups
- **Higher in Vascepa vs PBO: Peripheral edema (6.5% vs 5.0% PBO, p= 0.02), constipation (5.4% vs 3.6% in PBO, p<0.001), atrial fibrillation/flutter (5.3% vs 3.9% , p=0.003)**
- **Higher in PO vs Vascepa : Diarrhea (11.9% vs 9.0% p=0.002)**

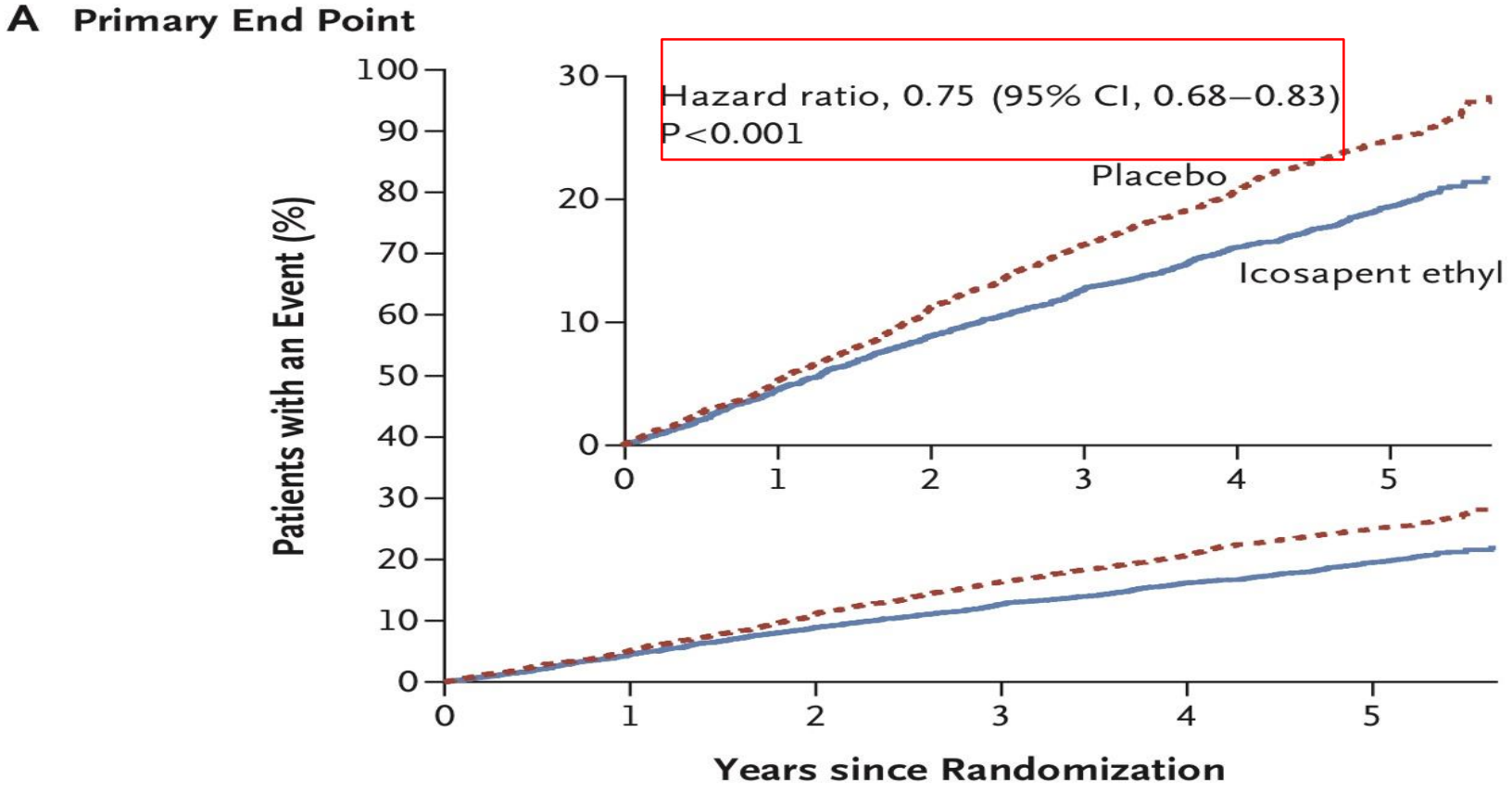
- A larger percentage of patients in Vascepa than in PBO hospitalized for atrial fibrillation or flutter (tertiary endpoint ; 3.1% vs. 2.1%, p = 0.004). Serious bleeding events in 2.7% in Vascepa vs 2.1% in the placebo group (P = 0.06).

Bhatt DL, et al. N Engl J Med 2019;380;1.

REDUCE-IT證實，併用EPA+statin之患者(CVD or DM)，能再額外降低25%心血管事件發生率

November 10, 2018, at NEJM.org

(1)N=8,179
(2)Patient type : w/ CVD or DM receiving statin & TG 135 ~ 499 mg/dl(Median TG 216 mg/dl)
(3)Treat EPA 4g/day 4.9years



VITAL Trial

美國國家衛生研究院2012年開始進行Omega-3及D3對於Cancer/CVD和其他疾病的Primary Prevention研究

Published in final edited form as:
Contemp Clin Trials. 2012 January ; 33(1): 159–171. doi:10.1016/j.cct.2011.09.009.

The *VIT*amin D and Omeg*A*-3 Tria*L* (VITAL): Rationale and Design of a Large Randomized Controlled Trial of Vitamin D and Marine Omega-3 Fatty Acid Supplements for the Primary Prevention of Cancer and Cardiovascular Disease

VITAL Specific Aims

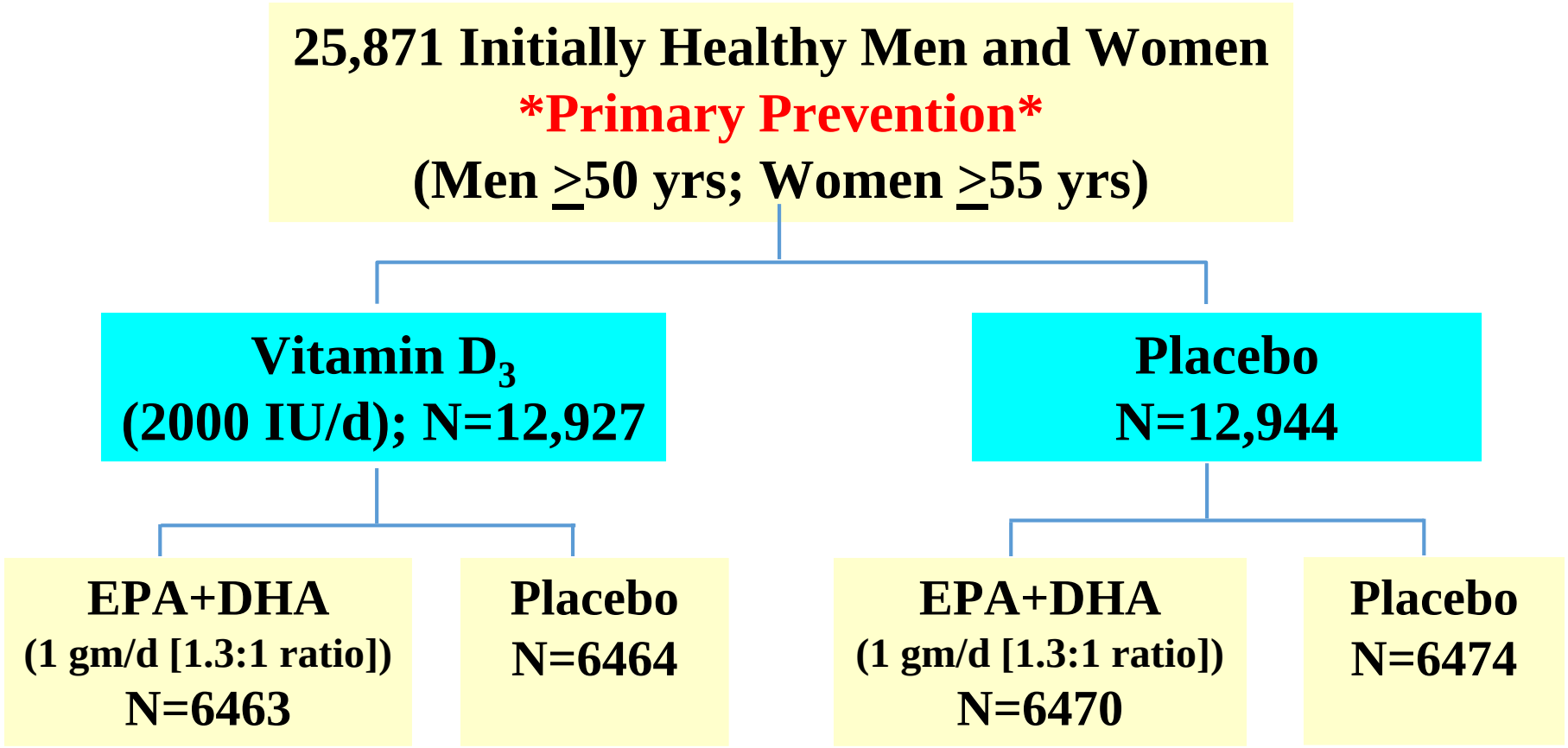
Primary Aims

1) To test whether vitamin D_3 and/or omega-3 fatty acids reduce risk of (a) major CVD events (composite of MI, stroke, CVD death), (b) total invasive cancer.

Secondary Aims

1) To test whether these agents lower risk of (a) MI/stroke/CVD death/PCI/CABG and (b) individual components of primary CVD outcome.
2) To test whether these agents lower risk of (a) site-specific cancer, (b) total cancer mortality.
3) Assess key subgroups, including age, sex, race/ethnicity, nutrient status at baseline.

The VITamin D and OmegA-3 TriaL (VITAL): Design



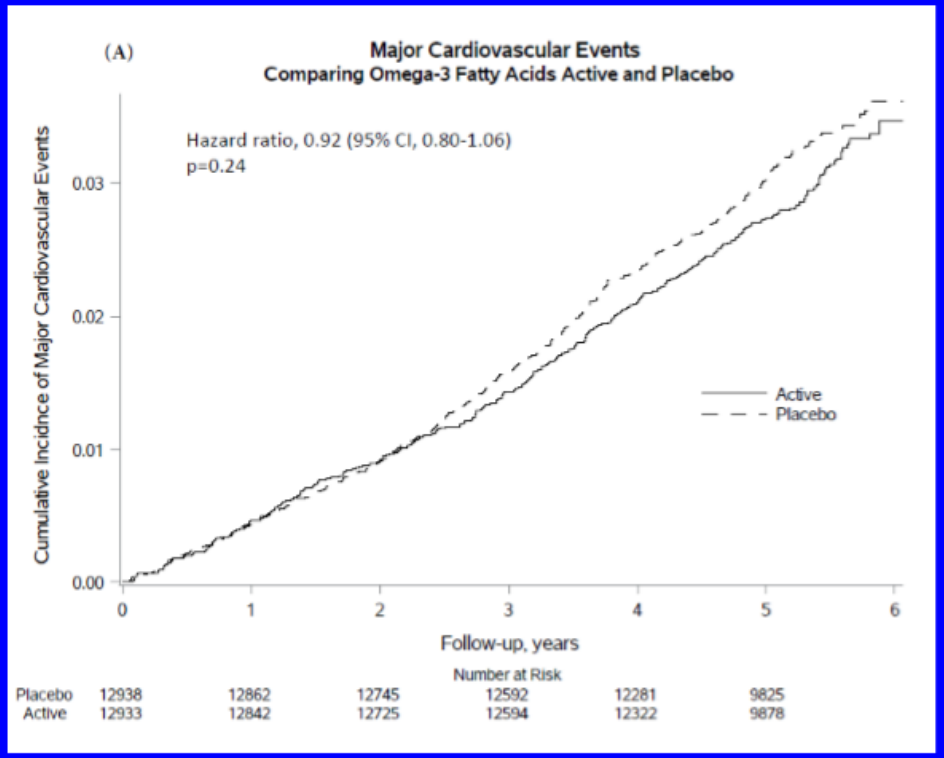
Median Treatment Period = 5.3 years.

5,106 African Americans.

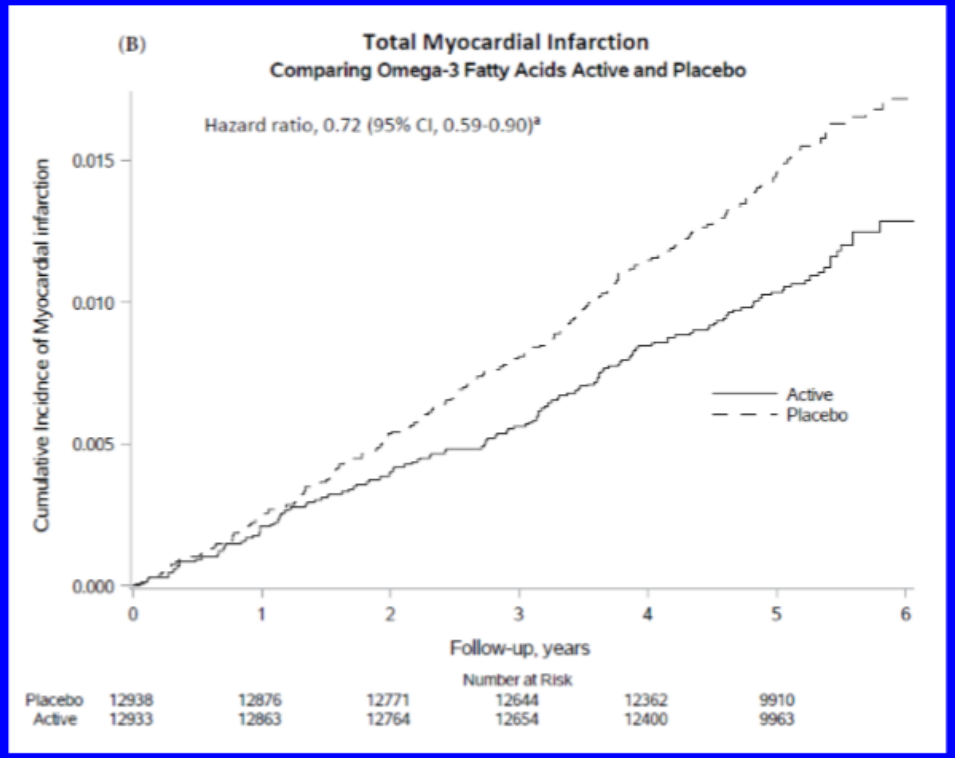
Blood collection in ~16,953 at baseline, follow-up bloods in ~6000.

Cumulative Incidence Rates of Major CVD Events and Total MI by Year of Follow-up: Omega-3s vs. Placebo

Major CVD Events



Total MI



For Major CVD Events: p-value = 0.24
For Total MI: nominal p-value = 0.003 and Bonferroni-adjusted p-value = 0.015.

VITAL Trial 顯示N-3無法降低MACE，但可預防MI

	Omega-3s (N=12,933)	Placebo (N=12,938)	HR	(95% CI)
	No. of Events			
Cardiovascular disease (1°and 2° outcomes)				
Major CVD events[a]	386	419	0.92	(0.80-1.06)
Major CVD + PCI/CABG[b]	527	567	0.93	(0.82-1.04)
Total MI	145	200	0.72	(0.59-0.90)*
Total stroke	148	142	1.04	(0.83-1.31)
CVD mortality	142	148	0.96	(0.76-1.21)
Other vascular outcomes[c]				
PCI	162	208	0.78	(0.63-0.95)*
CABG	85	86	0.99	(0.73-1.33)
Total CHD[d]	308	370	0.83	(0.71-0.97)*
CHD death	37	49	0.76	(0.49-1.16)
Fatal MI	13	26	0.50	(0.26-0.97)*

[a]Primary outcome. A composite of MI, stroke and CVD mortality. [b]Expanded CVD composite
[c]Not prespecified as primary or secondary outcomes. [d]A composite of MI, PCI/CABG, and CHD death.
All analyses are intention-to-treat. *Nominal p-value <0.05. For MI, the nominal p-value was 0.003.

Conclusions

- Neither omega-3s nor vitamin D significantly reduced the primary endpoints of major CVD events or total invasive cancer.
- Omega-3s reduced total MI by 28% (nominal p-value=0.003, Bonferroni-adjusted p-value=0.015), with greatest reductions in those with low dietary fish intake and in African Americans. PCI, fatal MI, total CHD (MI + coronary revasc + CHD death) were also reduced.
- Vitamin D reduced total cancer mortality in analyses excluding early follow up.

℞ Omega-3臨床試驗一覽及分析

- Secondary Prevention: ≥ 1g N-3 by GISS-P & GISS-HF, **4g N-3** by REDUCE-IT
- Primary Prevention: ≥ EPA 1.8g by JELIS
- 2018年 VITAL，每日1g omega-3無法有效降低MACE，但於能預防心肌梗塞達28% (secondary end-point)

Primary Prevention				Secondary Prevention			
Non-DM		DM		MI		HF	
Low does (1g N-3)	High dose (>1g N-3)	Low does (1g N-3)	High dose (>1g N-3)	Low does (1g N-3)	High dose (>1g N-3)	Low does (1g N-3)	High dose (>1g N-3)
2012 NEJM 2018 VITAL	2007 JELIS (1.8 g EPA)	2018 NEJM ASCEND 2018 VITAL	2007 JELIS (1.8g EPA) 2018 Reduce-it (4g EPA)	1999 GISSI-P	2018 Reduce-it	2008 GISSI-HF	-

Emerging Therapy for Hypertriglyceridemia

OM3FAs			
VASCEPA (icosapent ethyl) also known as AMR101 (Amarin Pharma)	Highly purified ethyl ester of EPA	REDUCE-IT (NCT01492361) (159)	RCT evaluating the efficacy of AMR101 vs placebo in reducing incident CV events in ~8000 participants
Treatment dose: 4 g/d			Inclusion criteria: individuals with established CVD or at high risk with hypertriglyceridemia and receiving statin therapy
Epanova (AstraZeneca)	Omega-3 carboxylic acids	STRENGTH (NCT02104817) (160)	RCT evaluating the efficacy of Epanova vs corn oil in reducing MACE in ~13,000 participants
			Inclusion criteria: patients at high risk for future CV events on stable diet and statin therapy with LDL-C <100 mg/dL and TG level ≥180 mg/dL and <500 mg/dL and HDL-C <42 mg/dL for men or HDL-C <47 mg/dL for women
Omacor	Marine OM3FAs (465 mg of EPA and 375 mg of DHA)	VITAL (NCT01169259) (161)	RCT in 25,871 participants evaluating daily dietary supplementation of 2000 units of vitamin D3 or OM3FAs for reducing the risk of developing cancer, heart disease, and stroke
Treatment dose: 1 capsule/d (840 mg of marine OM3FA)			
Icosabutate (162)	Potent, synthetically modified EPA molecule	No phase 3 outcomes trials underway	N/A

Sandesara PH, et al. Endocr Rev. 2019;40(2):537-557.

2017 updated AHA Science Advisory Regarding OM3 Supplementation

Cohort	Evidence	Recommendation	Comments
Primary prevention of CHD	No RCTs exclusively studying primary prevention of CHD	No recommendation	
Prevention of CVD mortality in DM or prediabetes	Overall, the current evidence from RCTs suggests no benefit of OM3 among patients with or at risk for DM to prevent CVD	Class III: No benefit	
Prevention of CHD in patients with high CVD risk	2/3 trials showed no benefit from OM3 supplementation on clinical CHD JELIS showed reduced risk of the composite outcome with OM3 use, but little evidence of risk reduction in hard endpoints (non-fatal MI, CHD death)	Majority: Class III: No benefit Minority: Class IIb: Treatment is reasonable	
Secondary prevention of CHD and SCD in CHD patients	OM3 supplements may reduce CHD death, possibly through a reduction in ischemia-induced SCD, among patients with prior CHD, but the treatment does not reduce the incidence of recurrent nonfatal MI	Majority: Class IIa: Treatment is reasonable Minority: Class IIb: Treatment is reasonable	
Primary prevention of Stroke	Overall, there is no proven benefit of OM3 to reduce risk of stroke among patients without a history of stroke	Class III: No benefit	Stroke was not a primary outcome in any RCT, and there is little evidence of reduction in stroke events with OM3 supplements from meta-analyses
Secondary prevention of Stroke	Overall, there is no evidence of OM3 supplementation to reduce risk of stroke or other CVDs in patients with prior stroke	No recommendation	Post hoc analysis of JELIS patients with a history of stroke had 6.8% stroke recurrence who received EPA vs 10.5% in controls, for risk reduction of recurrent stroke of 20% (RR 0.80; 95% CI 0.64–0.997), number needed to treat 27 These results should be considered for hypothesis generating
Primary prevention of HF	No RCTs to date	No recommendation	
Secondary prevention of outcomes in patients with HF	Based on a single, large RCT, in which 91% pts had EF < 40%	Class IIa: Treatment is reasonable among patients with HFrEF	OM3 may reduce HF-related hospitalizations and death in patients with HFrEF More RCTs are needed among patients with HFpEF
Primary prevention of AF	No data from large RCTs	No recommendation	
Secondary prevention of AF in patients with prior AF	Overall, high-quality evidence from multiple RCTs does not support OM3 supplementation to prevent recurrent AF	Class III: No benefit	
AF after cardiac surgery	6 RCTs did not find OM3 reduction of postoperative AF	Class III: No benefit	

Comment: The doses of OM3 (~1000 mg) used in the studies in this scientific statement (other than JELIS, 1800 mg) are generally too low to meaningfully lower TG levels.
AF = atrial fibrillation; CHD = coronary heart disease; CVD = cardiovascular disease; DM = diabetes mellitus; EF = ejection fraction; EPA = eicosapentaenoic acid; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; MI = myocardial infarction; OM3 = Omega-3 polyunsaturated fatty acid; RCT = randomized controlled trial; RR = relative risk; SCD = sudden cardiac death.

Elagizi A, et al.Prog Cardiovasc Dis. 2018 ;61(1):76-85.

Ongoing Randomized Controlled Trials with Omega-3 Fatty Acids and CV Disease

Trial (location)	*N*	Age (years)	Design	Formulation, dose	Duration (years)	Expected completion date	Inclusion criteria or cohort characteristics
STRENGTH (USA)	13,086	18–99 (> 40 if diabetes)	Secondary prevention of CVD; primary if diabetes with risk factors	EPA + DHA carboxylic acids, 4 g	5	2020	LDL-C < 100 mg/dL, on statin; TG 180–499 mg/dL; HDL-C < 42 mg/dL in men, < 47 mg/dL in women; patients with CVD or diabetes with risk factors
RESPECT-EPA (Japan)	3900	20–79	Stable CAD open-label	EPA, 1.8 g	5	2022	Statin treated; patients with stable CAD
OMEMI (Norway)	1400	70–82	Secondary prevention	EPA + DHA, 1.8 g	2–4	2020	Statin-treated patients with post-MI, stable

Preston Mason R. Curr Atheroscler Rep 2019;21:2.

CLINICAL PRACTICE GUIDELINE: EXECUTIVE SUMMARY

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

4.5.2. Hypertriglyceridemia

Recommendations for Hypertriglyceridemia
Referenced studies that support recommendations are summarized in Online Data Supplement 30 to 32.

COR	LOE	RECOMMENDATIONS
I	B-NR	1. In adults 20 years of age or older with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175-499 mg/dL [2.0-5.6 mmol/L]), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides (S4.5.2-1).
IIa	B-R	2. In adults 40 to 75 years of age with moderate or severe hypertriglyceridemia and ASCVD risk of 7.5% or higher, it is reasonable to reevaluate ASCVD risk after lifestyle and secondary factors are addressed and to consider a persistently elevated triglyceride level as a factor favoring initiation or intensification of statin therapy (see Section 4.4.2.) (S4.5.2-2–S4.5.2-6).
IIa	B-R	3. In adults 40 to 75 years of age with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.6 mmol/L])) and ASCVD risk of 7.5% or higher, it is reasonable to address reversible causes of high triglyceride and to initiate statin therapy (S4.5.2-3-5, S4.5.2-7, S4.5.2-8).
IIa	B-NR	4. In adults with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.7 mmol/L], and especially fasting triglycerides ≥1000 mg/dL [11.3 mmol/L]), it is reasonable to identify and address other causes of hypertriglyceridemia), and if triglycerides are persistently elevated or increasing, to further reduce triglycerides by implementation of a very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and, if necessary to prevent acute pancreatitis, fibrate therapy (S4.5.2-7, S4.5.2-9).

Grundy SM, et al. J Am Coll Cardiol. 2019;73(24):e285-e350.

Omega-3 Fatty Acids for the Management of Hypertriglyceridemia

A Science Advisory From the American Heart Association

Table 5. Summary Statements About the Effects of n-3 FA in Managing HTG

	Summary Statements
Triglycerides 200–499 mg/dL	≈20%–30% reduction in triglycerides and no LDL-C increase with 4 g/d prescription n-3 FA
Triglycerides ≥500 mg/dL	≥30% reduction in triglycerides with 4 g/d prescription n-3 FA, LDL-C increase with DHA-containing agents
Children/adolescents	Apparently safe but more research needed to further evaluate efficacy
Use with other lipid therapy	Safe and apparently additive triglyceride reduction with statin therapy; apparently safe with fibrates or niacin but more research needed to evaluate efficacy
Prescription n-3 FA agent	On the basis of available data, all prescription agents appear comparably effective, but head-to-head comparisons are lacking

Circulation 2019;140:00

ESC European Society of Cardiology
European Heart Journal (2019) **00**, 1–78
doi:10.1093/eurheartj/ehz455

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

Table 3 New recommendations, and new and revised concepts

New recommendations
Cardiovascular imaging for assessment of ASCVD risk
Assessment of arterial (carotid and/or femoral) plaque burden on arterial ultrasonography should be considered as a risk modifier in individuals at low or moderate risk.
Cardiovascular imaging for assessment of ASCVD risk
CAC score assessment with CT should be considered as a risk modifier in the CV risk assessment of asymptomatic individuals at low or moderate risk.
Lipid analyses for CVD risk estimation
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.
Drug treatments of patients with hypertriglyceridaemia
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 × 2g/day) should be considered in combination with statins.
Treatment of patients with heterozygous FH
In primary prevention, for individuals with FH at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.

2017台灣血脂治療指引建議

DM患者TG<150mg/dl

ACS/CAD患者應TG<200mg/dl

2017 Taiwan lipid guidelines for high risk patients☆

Acute coronary syndrome (ACS)
Stable coronary artery disease (CAD)
Non-HDL-C < 100 mg/dL can be the secondary target in patients with TG 200 mg/dL.

Diabetes mellitus (DM)
TG < 150 mg/dL and HDL-C > 40 mg/dL in men and >50 mg/dL in women should be the secondary target after the LDL-C target has been achieved.

2017 Taiwan Lipid Guideline for High Risk Patients

Recommendation

- Increased TG may be a risk factor of recurrent CV events after ACS. (COR IIa, LOE B)
- Non-HDL-C < 100 mg/dL can be the secondary target in patients with TG ≥ 200 mg/dL. (COR I, LOE B)
- TG-lowering therapy is necessary in patients with TG ≥ 500 mg/dL to prevent pancreatitis. (COR I, LOE B)

Recommendation

- Omega-3 fatty acid is indicated for the treatment of very high TG (≥500 mg/dL). (COR IIa, LOE B)
- EPA and DHA are recommended for patients with coronary heart disease and hypertriglyceridemia. (COR IIa, LOE B)

Li YH, et al. J Formos Med Assoc. 2017;116(4):217-248.

Patients Who May Benefit from Omega-3 FA

Those not meeting recommended dietary fish intake
CHD or other ASCVD
Secondary prevention of CHD death or SCD
Recent CHD event (e.g. post-MI)
Following PCI
HFrEF
Heart transplant
Aspirin resistance
Clopidogrel resistance
Hypertriglyceridemia (>150 mg/dl)
High LDL-C (>130 mg/dl)
Hypertension

ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease; HFrEF = heart failure with reduced ejection fraction; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; SCD = sudden cardiac death.

Elagizi A, et al.Prog Cardiovasc Dis. 2018 ;61(1):76-85.

Take Home Message

- The potential role of Omega-3 polyunsaturated fatty acids (OM3) in reducing cardiovascular (CV) disease (CVD) and CVD events has been studied for decades.
- Treatment with omega-3 PUFA supplements is reasonable for secondary prevention of the patients with previous CV disease and a potential modest reduction in CHD mortality (10%) in this clinical population with a relatively safe therapy.
- Omega-3 could be benefit for patients with reduced heart failure to reduce mortality and hospitalizations (9%) on the basis of a single, large RCT.
- Omega-3 should not be used for patients with diabetes mellitus and prediabetes to prevent CHD, there was a lack of consensus on the recommendation for patients at high CVD risk and to prevent incident stroke among patients at high CVD risk and recurrent AF.

Thank You for Your Attention!

攝取足夠的Omega-3的方法?

Ways to Get 1 g/d EPA+DHA

- Fish
  - 2–3 oz salmon, sardines, mackerel per day
- Dietary Supplements
  - *Low Potency:* 300 mg EPA+DHA/g
    (Typical drug store capsules; 3 g/d)
  - *Mid Potency:* 500–700 mg EPA+DHA/g
    (Mail-order, online, etc; 2 g/d)
- Drugs
  - ***High Potency:* 850 mg EPA+DHA/g**
    (Omega-3 acid ethyl esters; 1 g/d)
- Cod Liver Oil
  - 1 tsp (RDA for vitamin D; 2× RDA for vitamin A)

Omacor
是否能與抗凝血劑並用?

仿單未列禁忌(表示可並用)

7. 藥物交互作用

7.1 抗凝血劑或影響凝血之其他藥物

一些使用 Omega-3-acids 之臨床試驗顯示會延長流血時間，在這些試驗中延長流血時間並未超過正常極限，也未發生臨床上顯著流血事件。徹底觀察併用 Omacor 與抗凝血劑效果之臨床試驗並未執行，患者接受Omacor及抗凝血劑或其他影響凝血之藥物治療時(如：抗血小板劑)，應定期的監測。

2013年有發表一篇關於心臟裝支架患者，拿Omacor並用抗凝血劑的臨床試驗

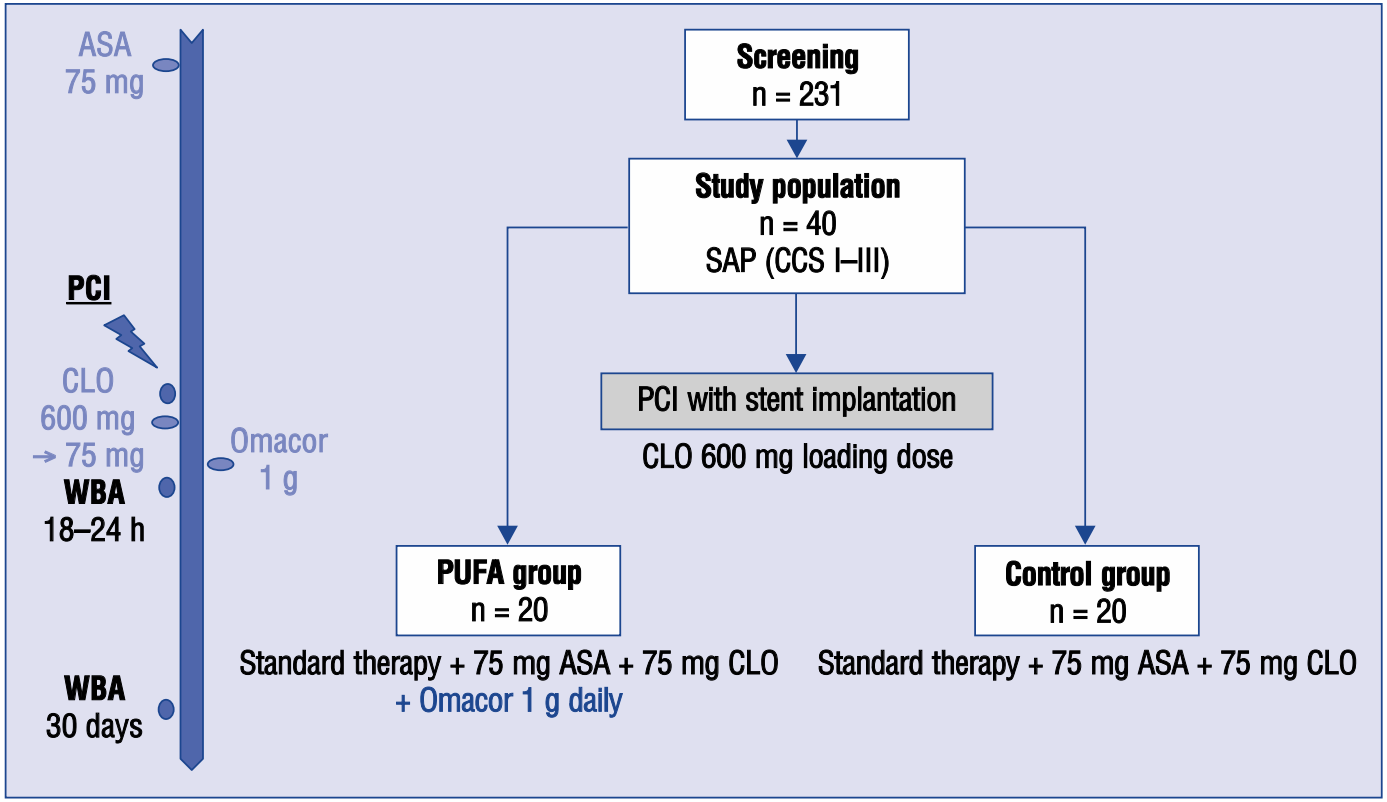


Figure 1. Participant flow; ASA — acetylsalicylic acid; CLO — clopidogrel; PCI — percutaneous coronary intervention; SAP — stable angina pectoris; WBA — whole blood impedance aggregometry.

研究顯示Omacor與Aspirin/Plavix並用不會延長出血時間

Table 5. Comparison of delta platelet test results (baseline and 1 month after percutaneous coronary intervention).

Test*	Group PUFA (n = 20)		Group C (n = 20)		P
	Mean ± SD	25–75 percentile	Mean ± SD	25–75 percentile	
Delta ADP	3.8 ± 12.0	–3.5/11	5.0 ± 10.4	–6/12	0.73
Delta ASPI	8.5 ± 25.0	–1/13.5	–3.9 ± 24.1	–4/13	0.12
Delta COL	2.7 ± 15.3	–4/11.5	2.8 ± 11.2	–5/10	0.98
Delta TRAP	14.3 ± 19.7	3/25.5	18.2 ± 31.0	–6/31	0.63

*Platelets activity tests with different activators: arachidonic acid (ASPI), adenosine diphosphate (ADP), thrombin receptor activating peptide-6 (TRAP), collagen (COL).

Conclusions: *N-3 PUFA supplementation does not affect the efficacy of dual antiplatelet therapy in patients with SAP after PCI.* (Cardiol J 2013; 20, 5: 478–485)

Review Paper載明
過往臨床試驗皆未發現有出血副作用

Safety and Tolerability of Omacor

Omacor has been shown in clinical trials to be generally well tolerated. Adverse experiences are rare; if they do occur, they usually involve belching or eructation or perhaps taste perversion. Omacor has not been shown in clinical trials to have an adverse effect on plasma glucose levels, bleeding, or levels of muscle or liver enzymes or to cause abnormalities in kidney or nerve function. No case of hypervitaminosis or illness due to exposure to environmental toxin (Table 6)[20] has been reported, likely because of Omacor's extensive purification and concentration process (Figure 1).[21] This production process results in a content of <90 mg of omega-6, -7, and -9 fatty acids; undetectable concentrations of heavy metals, halogenated polycarbons, and dioxins; and <0.05% of *trans* fatty acids.

With regard to tolerability, each 1-g capsule of Omacor contains 4 mg (6 IU) of vitamin E. The addition of this antioxidant, coupled with the extensive purification process, results in reduced "fishy" taste or belching, the most common tolerability issue in clinical practice.

Am J Cardiol 2006;98[suppl]:71i–76i

仿單有寫到肝指數上升？
所以會傷肝?

仿單講到的肝指數上升為在臨床實驗有出現的案例，但比例並未超過3%及高於安慰劑組

以 23 項臨床試驗匯總資料為基礎，將不良反應發生率至少 3%，及 Omacor 組發生率高於安慰劑組的各種不良反應列於下表一。

表一 Omacor 臨床試驗，不良反應發生率大於 3% 者及高於安慰劑組者

不良反應[a]	OMACOR (N=655)		安慰劑 (N=370)	
	N	%	N	%
打嗝異味	29	4	5	1
消化不良	22	3	6	2
味覺異常	27	4	1	<1

[a] 臨床試驗受試者包括高三酸甘油酯症 (HTG) 及嚴重高三酸甘油酯症

臨床試驗中額外的不良反應列於下方：

消化系統：便秘、腸胃不適及嘔吐

代謝及營養失調：ALT、AST 值增加

皮膚：搔癢、皮疹

Review Paper載明
過往臨床試驗皆未發現有肝副作用

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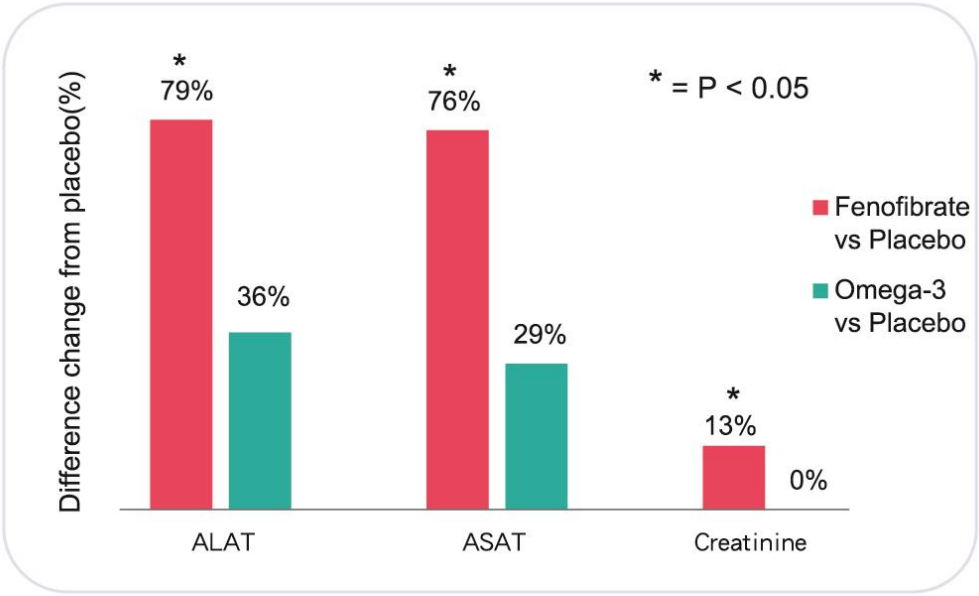
Am J Cardiol 2006;98[suppl]:71i–76i

和Fibrate一對一的比較中，Fibrate反而會明顯增加肝指數，而OMACOR不會

– 怕傷肝更應該以Omacor代Lipanthyl!!!

跟安慰劑相比，OMACOR® 不影響肝腎功能



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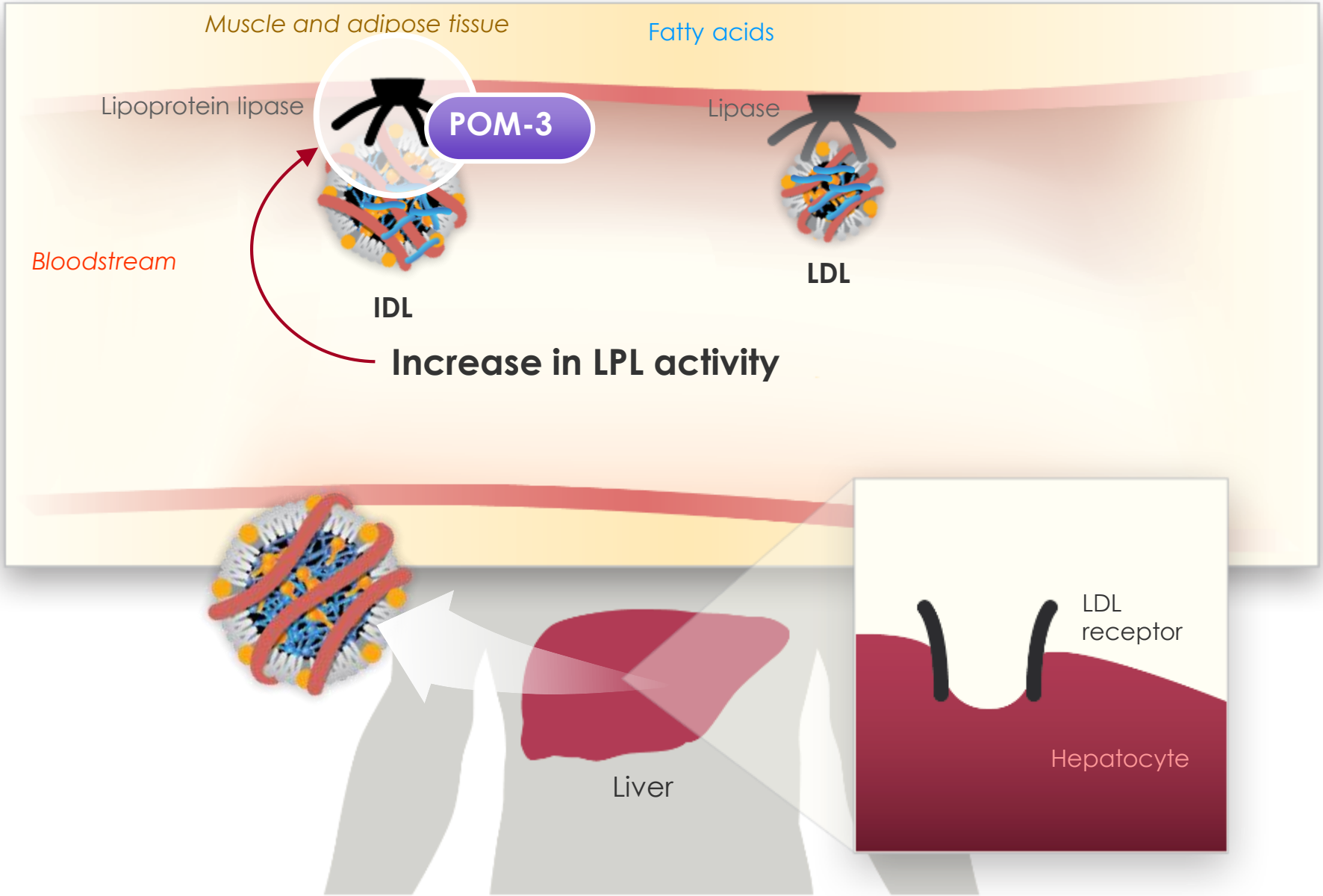
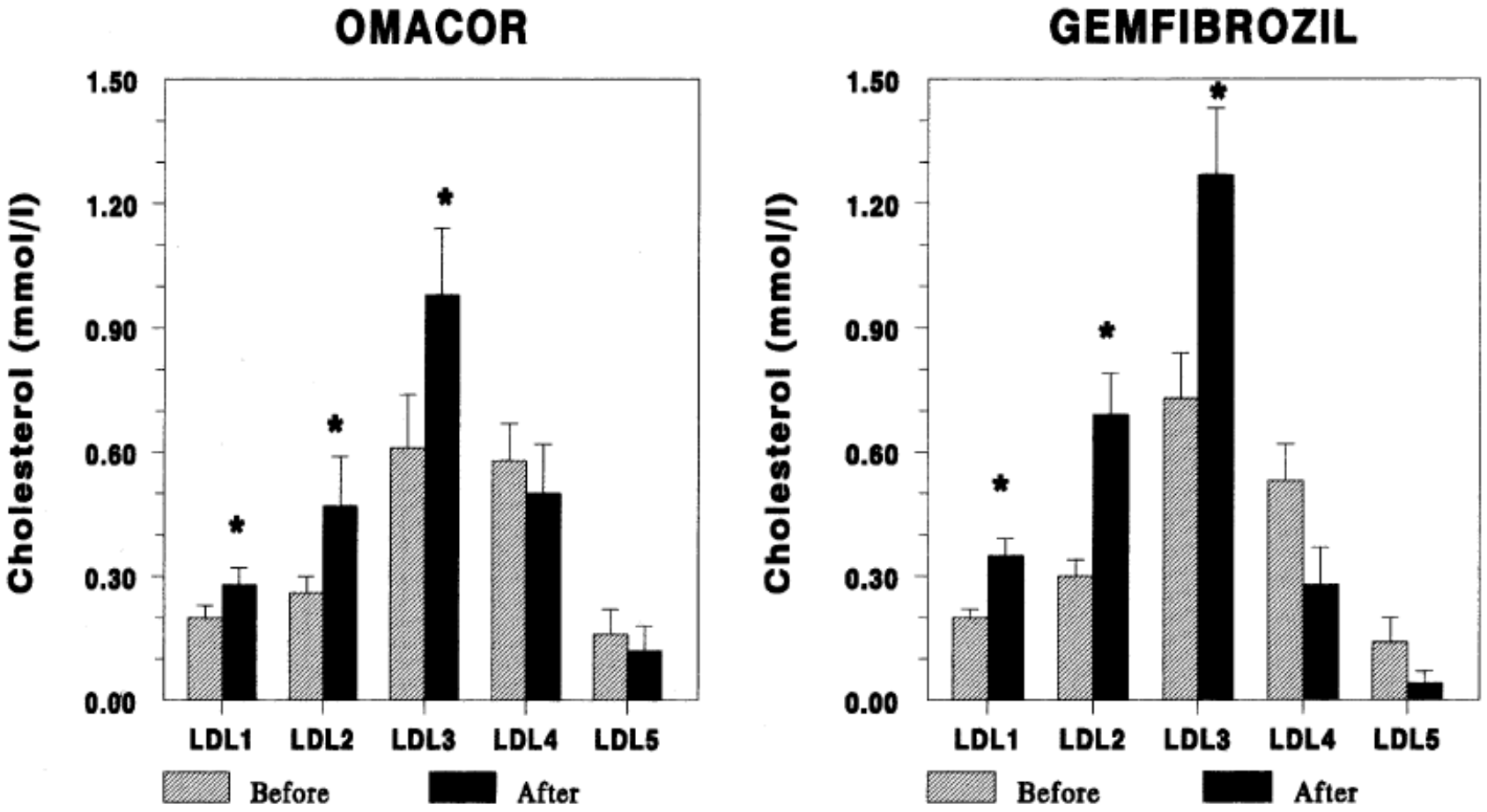
1.仿單
2.Micromedex
3.Am J Cardiol. 2006 Aug 21;98(4A):71i-76i.
4.Nutrition, Metabolism & Cardiovascular Diseases (2012) 22, 966 - 973

是否會增加LDL

Omega-3同Fibrate因會促進VLDL代謝成LDL，故會短暫增加LDL血中濃度



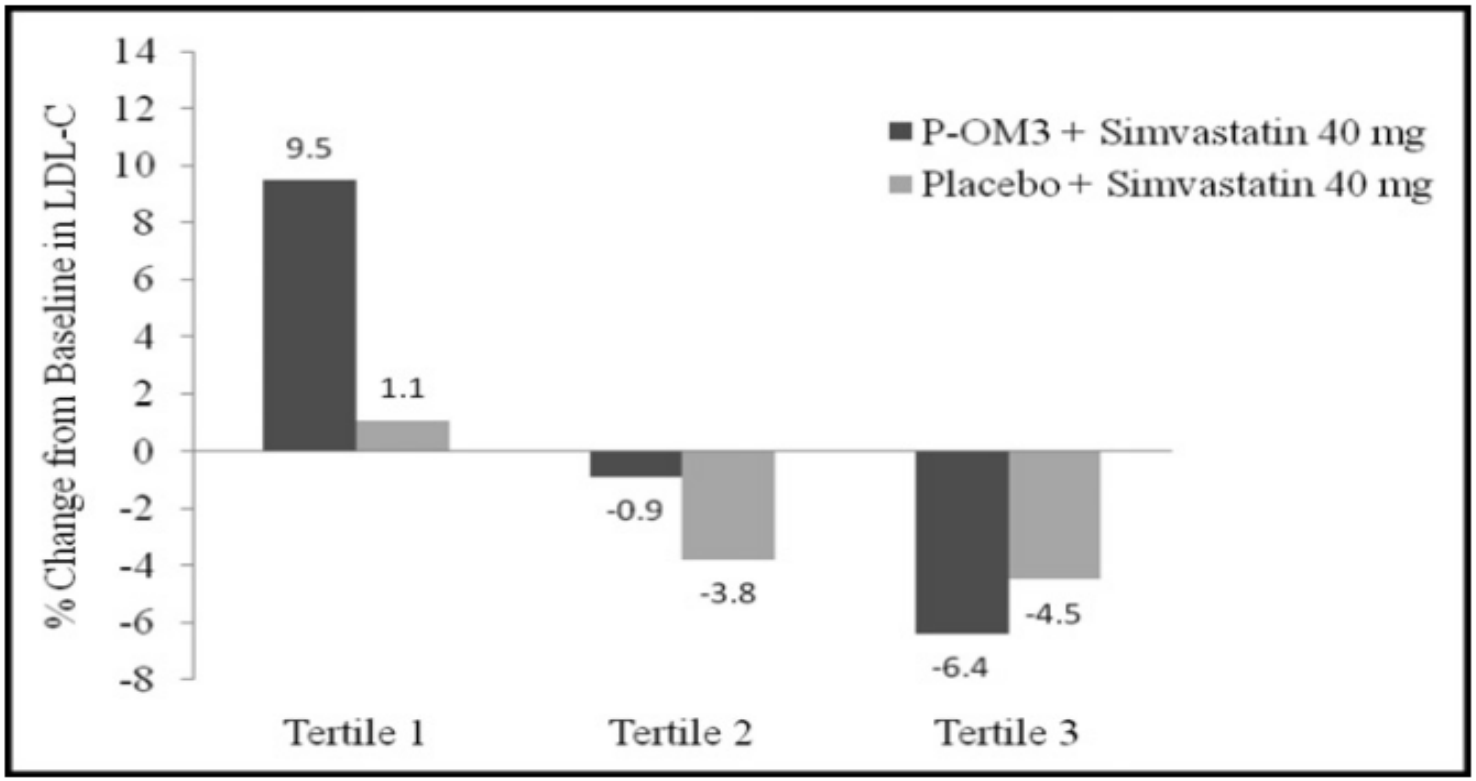
OMACOR和Fibrate都是上升大顆粒LDL；反而使較危險的sd-LDL下降



LDL 1~3是大顆粒；4~5是小顆粒

Atherosclerosis **153 (2000) 129–138**

對於已服用Statin之患者，Omacor只有在LDL低於80mg/dl，才會些微增加LDL，而LDL原本高於80mg/dl患者，並不會額外增加



<80.4 mg/dl

> or =99.0 mg/dl

Maki et al. Am J Cardiol 2010;105:1409 –1412

過往臨床試驗顯示，單純HTG患者服用OMACOR後，不會讓LDL超標(160mg/dl)

Table IV. Efficacy of oral omega-3 ethylester concentrate (omega-3 EEC) monotherapy in adult patients (pts) with hypertriglyceridaemia. Summary of two randomized, double-blind, multicentre studies comparing omega-3 EEC with placebo (PL)[85] or gemfibrozil (GEM).[46] Pts received omega-3 EEC 4000 mg once daily or a comparator (PL[85] or oral GEM 1200 mg/day[46]) for 12[46] or 16[85] weeks. Dietary advice/assessment was provided prior to and throughout the active therapy phase.[46,85] All baseline, endpoint and percentage change from baseline values are means. Where specified, data are reported for the per-protocol population[85]

Study	Treatment	No. of pts	TG (mmol/L)		TC (mmol/L)		VLDL-C (mmol/L)		LDL-C (mmol/L)		HDL-C (mmol/L)	
			baseline	endpoint [%Δ]	baseline	endpoint [%Δ]	baseline	endpoint [%Δ]	baseline	endpoint [%Δ]	baseline	endpoint [%Δ]
Comparison with PL												
Harris et al.[85]	Omega-3 EEC	22	10.38	5.71 [−45†††]	6.94	5.91 [−15††]	4.12	2.33 [−32††]	2.05	2.69 [+32]	0.78	0.88 [+13†]
	PL	20	9.91	11.38 [+16]	7.80	7.64	4.59	4.56	2.49	2.36 [NR‡‡‡]	0.73	0.73
Comparison with GEM												
van Dam et al.[46]	Omega-3 EEC	45	12.36	7.82**** [−29][a]	8.81	7.61**** [−10]	3.82	2.92** [−11]	3.28	3.66	0.81	0.75 [+1]
	GEM	44	11.55	5.22**** [−51‡‡][a]	8.41	6.82*** [−13]	3.55	2.07*** [−19]	3.59	4.60*	0.83	0.95 [+28‡]

79mg/dl➔103mg/dl

126mg/dl➔141mg/dl

138mg/dl➔177mg/dl

a Primary endpoint.

%Δ = percentage change from baseline; **HDL-C** = high-density lipoprotein cholesterol; **LDL-C** = low-density lipoprotein cholesterol; **NR** = not reported; **TC** = total cholesterol; **TG** = triglyceride; **VLDL-C** = very-low-density lipoprotein cholesterol; * $p<0.05$, ** $p<0.01$, *** $p\leq0.005$, **** $p<0.0001$ vs baseline; † $p<0.05$, †† $p\leq0.001$, ††† $p<0.0001$ vs PL; ‡ $p<0.05$, ‡‡ $p<0.01$, ‡‡‡ $p<0.005$ vs omega-3 EEC.

Ref : Drugs 2009; 69(8): 1077-1106

已服用Statin的患者
服用Omacor前後不會額外增加LDL

Study	Treatment (mg/day)	No. of pts	Timepoint (wk)	TG (mmol/L)		TC (mmol/L)		VLDL-C (mmol/L)		LDL-C (mmol/L)		HDL-C (mmol/L)		Non-HDL-C (mmol/L)	
				baseline	endpoint [%Δ]	baseline	endpoint [%Δ]	baseline	endpoint [%Δ]	baseline	endpoint [%Δ]	baseline	endpoint [%Δ]	baseline	endpoint [%Δ]
Davidson et al.[97]	Omega-3 EEC 4000 od + SIM 40	122	8	3.2	2.3 [−28.2††]	4.7	4.5 [−4.7††]	1.4	1.0 [−23.8††]	2.3	2.3 [+3.4]	1.2	1.3 [+4.1††]	3.5	3.2 [−7.9†† c]
	PL + SIM 40	132	8	3.2	3.1 [−3.5]	4.8	4.7 [−1.5]	1.4	1.3 [−4.8]	2.4	2.3 [−1.9]	1.2	1.1 [−1.1]	3.7	3.6 [−1.5c]
Durrington et al.[86]	Omega-3 EEC 2000 bid + SIM 10–40	30	12	4.6	3.3*** [−22.8†a]	5.6	4.9*b	1.0	0.6** [−34.2†a]	3.5	3.1b	1.1	1.2b		
	PL + SIM 10–40	27	12	3.8	3.9 [+12.8a]	6.2	6.3b	0.9	0.8 [−2.8a]	4.2	4.2b	1.1	1.2b		
	Omega-3 EEC 2000 bid + SIM 10–40	29	24	4.6	3.5*** [−18.6†a,c]	5.6	5.0*b	1.0	0.6** [−31.4†a,c]	3.5	3.3b	1.1	1.0b		
	PL + SIM 10–40	26	24	3.8	3.9 [+4.2c]	6.2	6.4b	0.9	0.8 [−10.0a,c]	4.2	4.4b	1.1	1.3b		

Ref : Drugs 2009; 69(8): 1077-1106

魚類EPA/DHA含量

TABLE 1

Omega-3 oil levels in various fish and seafoods*

FISH	GRAMS OF OMEGA-3 OIL PER 3-OZ SERVING	NO. OF OUNCES PER DAY TO EQUAL 1 G EPA/DHA
Tuna		
Light, canned in water, drained	0.26	12
White, canned in water, drained	0.73	4
Fresh	0.24-1.28	2.5-12
Sardines	0.98-1.70	2-3
Salmon		
Sockeye or pink	1.05	3
Chinook	1.48	2
Coho, farmed	1.09	3
Coho, wild	0.91	3
Atlantic, farmed	1.09-1.83	1.5-2.5
Atlantic, wild	0.9-1.56	2-3.5
Mackerel 鯖魚	0.34-1.57	2-8.5
Herring 鯡魚		
Pacific	1.81	1.5
Atlantic	1.71	2
Trout, rainbow 鱒魚		
Farmed	0.98	3
Wild	0.84	3.5
Cod 鱈魚		
Atlantic	0.13	23
Pacific	0.24	12.5
Catfish 鮰魚		
Farmed	0.15	20
Wild	0.2	15
Flounder/Sole 比目魚	0.42	7
Oyster 牡蠣		
Pacific	1.17	2.5
Eastern	0.47	6.5
Lobster 龍蝦	0.07–0.41	7.5–42.5
Crab, Alaskan king	0.35	8.5
Shrimp, mixed species	0.27	11
Clam	0.24	12.5
Scallop 扇貝	0.17	17.5

*Omega-3 fatty acid content varies widely with the season, the diet and age of the fish, and the storage and preparation methods. Values based on US Department of Agriculture Nutrient Data Laboratory, available on th Internet at **www.nalusda.gov/fnic/foodcomp/.** Accessed February 2, 2004.