EPA and CV outcome
Insights from recent clinical trials

林口長庚醫院 心臟內科
吳家棟 醫師

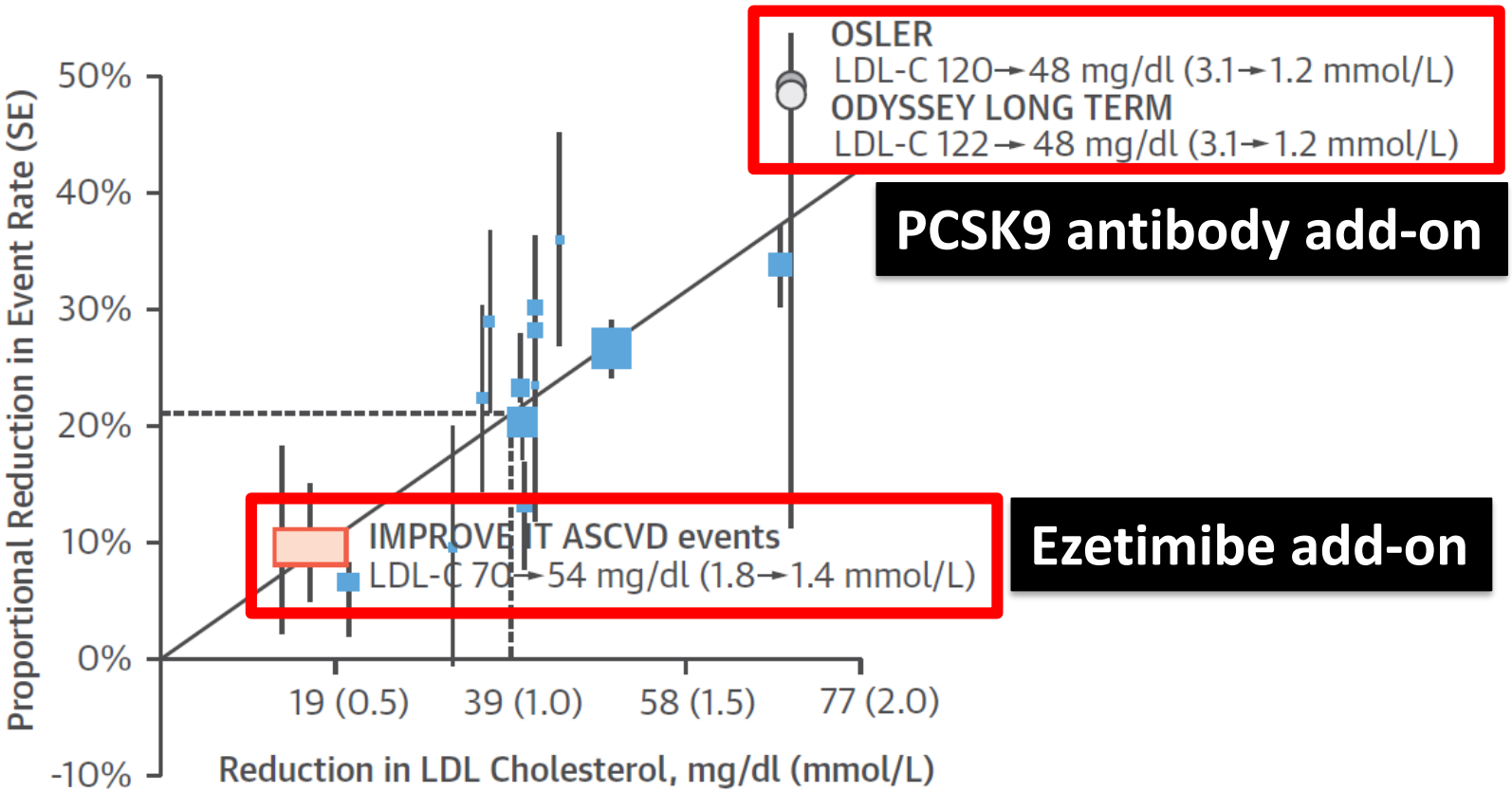
Managing dyslipidemia,
From past to present

Determining When to Add Nonstatin Therapy

A Quantitative Approach

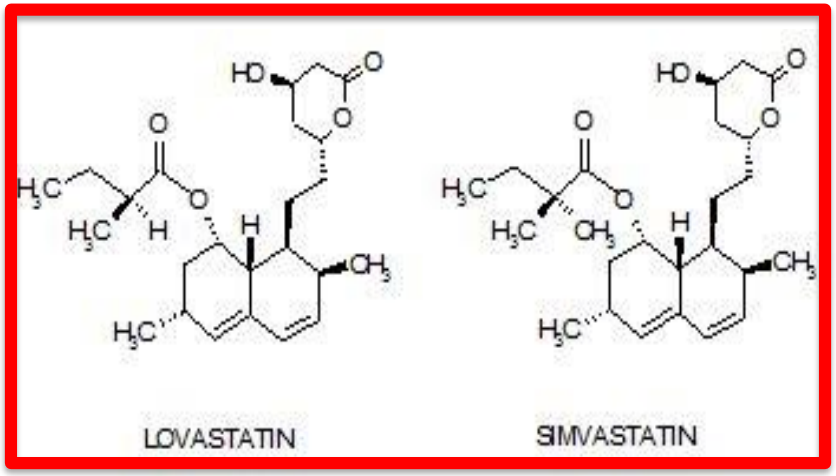
Post-statin era

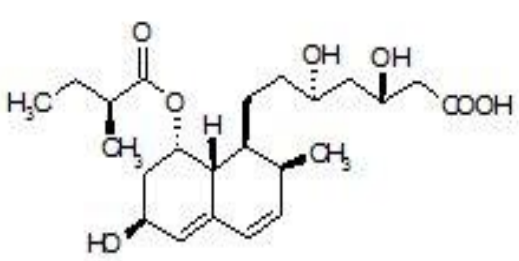
Jennifer G. Robinson, MD, MPH,[a] Roeland Huijgen, MD, PhD,[b] Kausik Ray, MBChB, MD, MPhil,[c] Jane Persons, PhD,[a] John J.P. Kastelein, MD, PhD,[b] Michael J. Pencina, PhD[d]

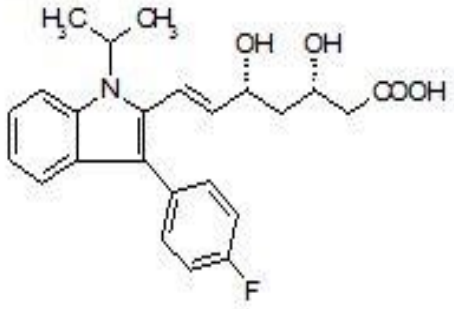


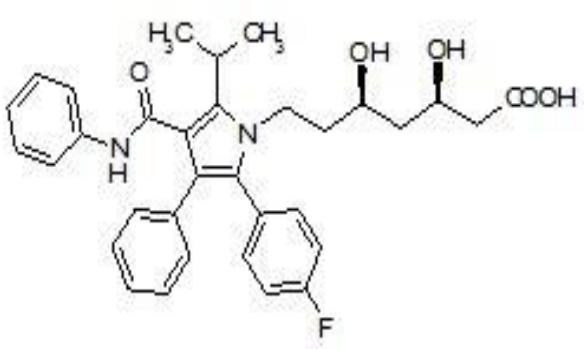
J Am Coll Cardiol 2016;68:2412–21

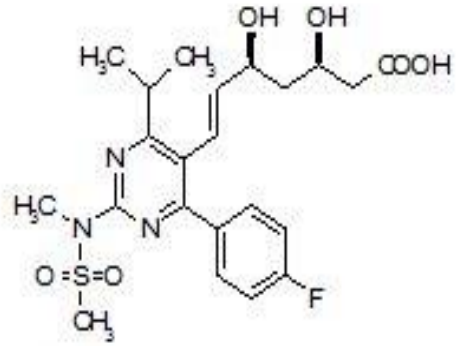
Structure of statin

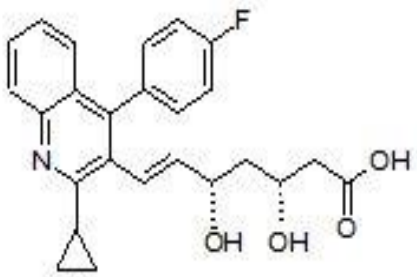












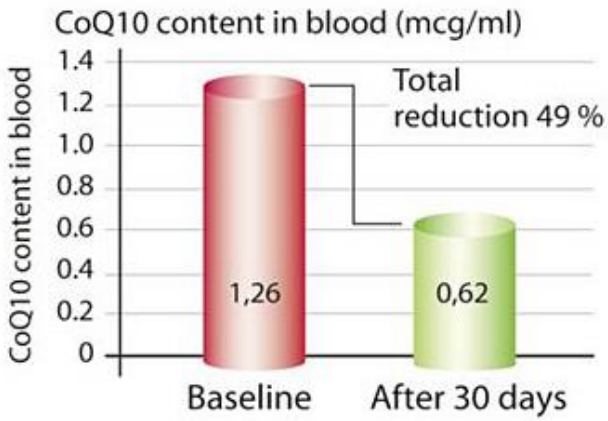
STATINS

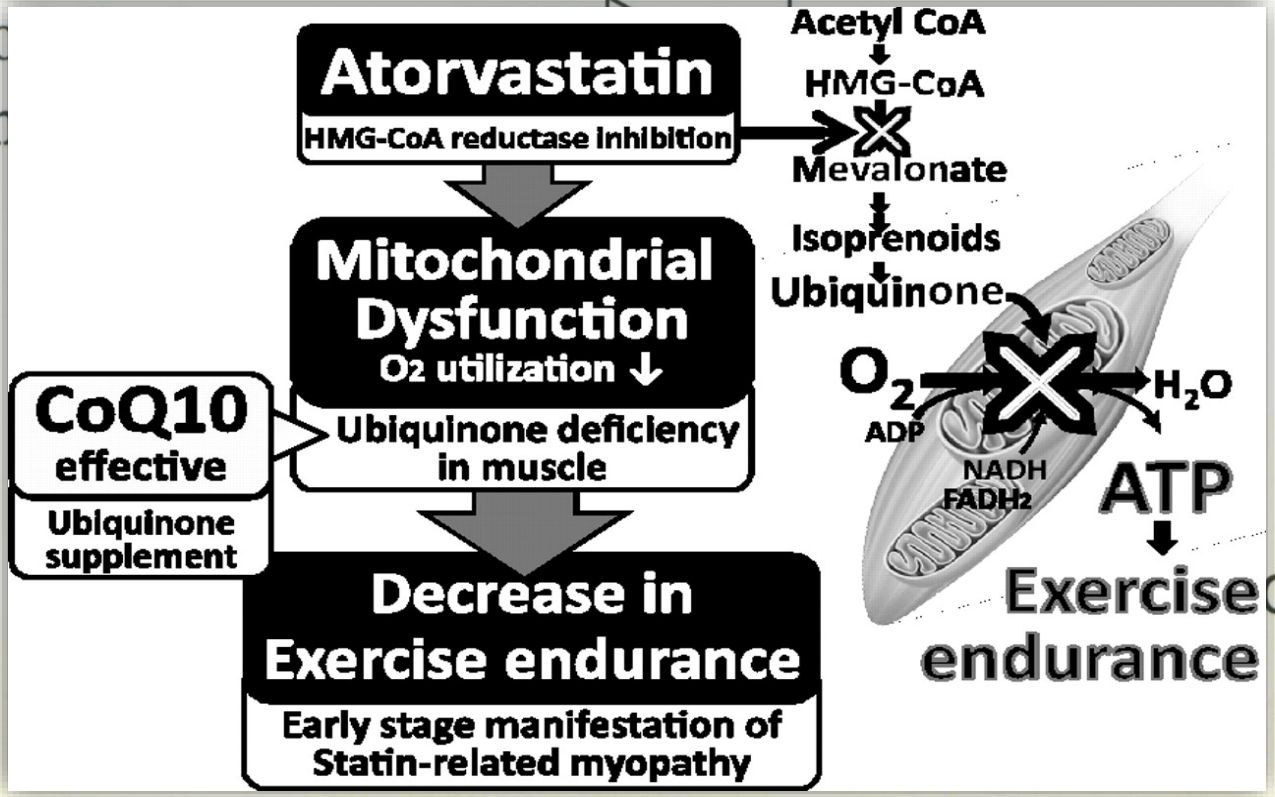
HMG-Co
(en

1-CoA)

CoQ10 reduction and statin use

Atorvastatin decreases the coenzyme Q10 level in the blood of patients. Ref. Arch. Neurol. 2004 Jun;61(6): 889-92.

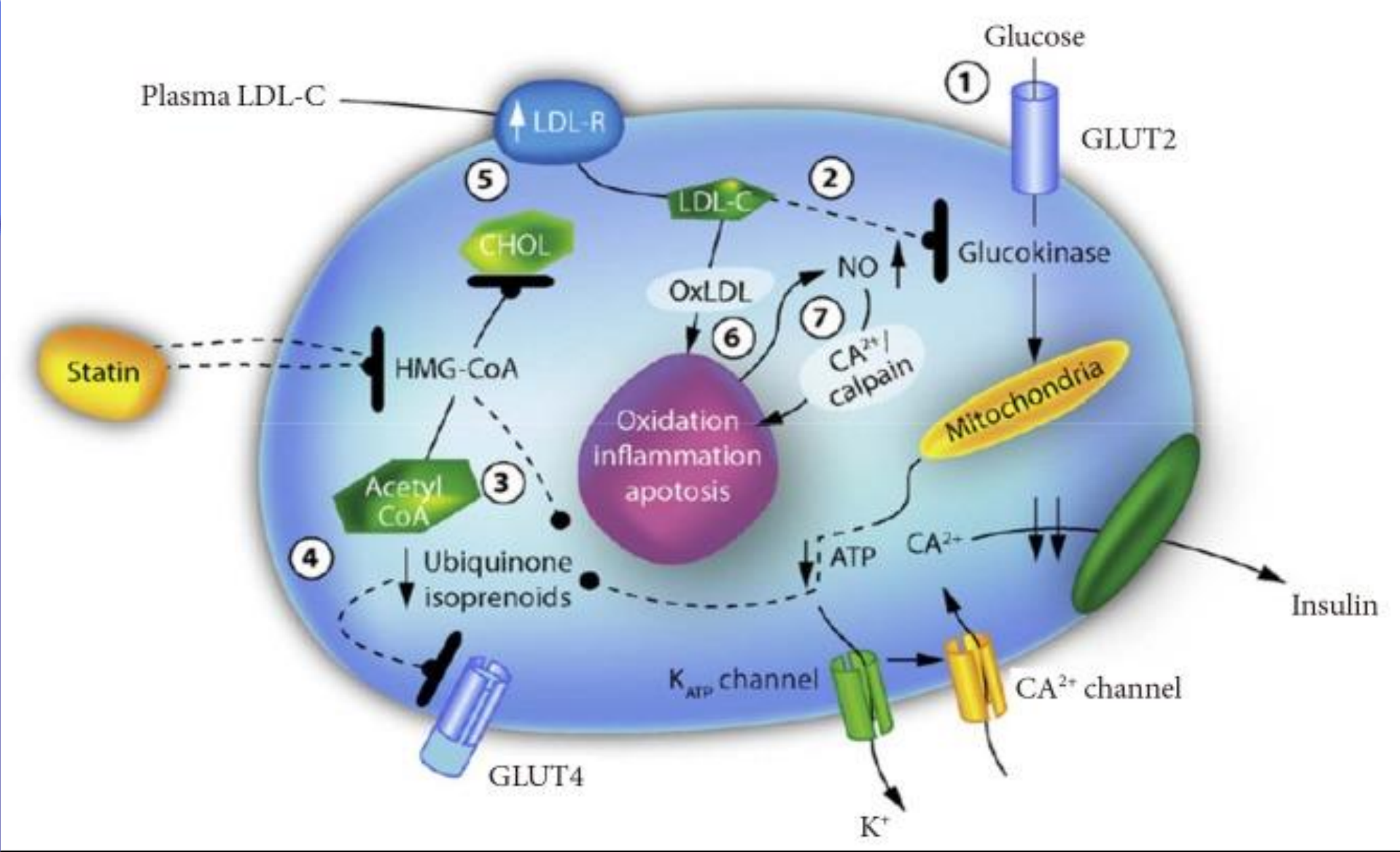




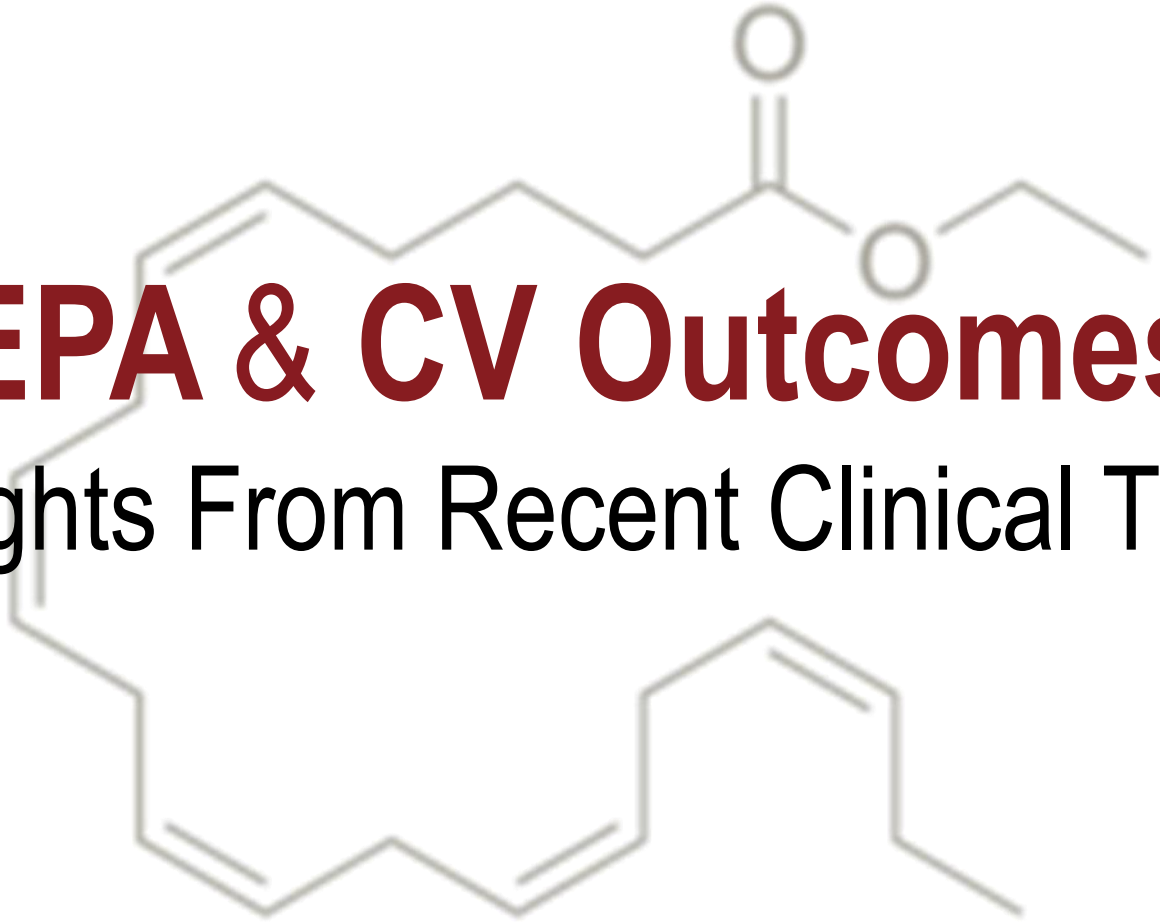
Safety of Atorvastatin 80 mg in Clinical Trials

	Follow-up	Patients	↑ALT/AST >3x ULN	↑CK >10x ULN
Newman et al[+]	variable	4,798	26 (0.6%)	2 (0.06%)
PROVE-IT	2 years	2,099	69 (3.3%)	NA
TNT	4.9 years	4,995	60 (1.2%)	0
IDEAL	4.8 years	4,439	61 (1.38%)	0
SPARCL	4.9 years	2,365	51 (2.2%)	2 (0.08%)
Total	variable	**18,696**	**267 (1.43%)**	**4 (0.021%)**

[+] Am J Cardiol 2006;97:61-67



Possible mechanisms of statin-related blood sugar elevation



EPA & CV Outcomes

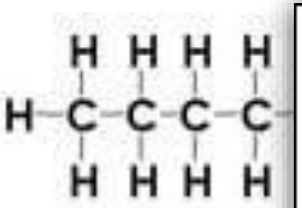
Insights From Recent Clinical Trials

Outlines

- What is EPA ?
- EPA/DHA for secondary prevention
- EPA/DHA for primary prevention
- Why is EPA not DHA effective for *1st* prevention ?

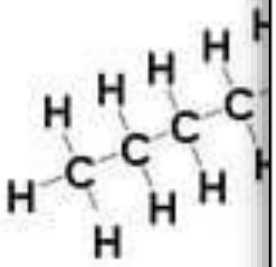
Structure of fatty acid

SATURATED
Stearic acid
(found in butter)



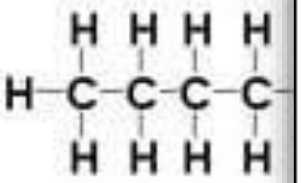
飽和脂肪酸

UNSATURATED
Linoleic acid
(found in vegetable oil)



不飽和脂肪酸
順式 vs. 反式

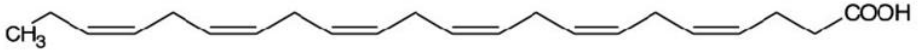
TRANS
***trans*-Linoleic acid**
(found in some margarine)



Omega-3 fatty acids

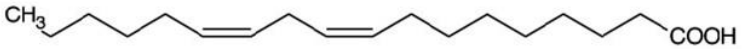
ALA: α-Linolenic acid C18:3 n-3

EPA: Eicosapentanoic acid C20:5 n-3

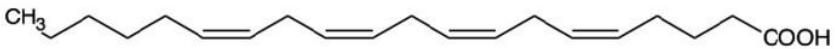


DHA: Docosahexanoic acid C22:6 n-3

Omega-6 fatty acids



LA: Linoleic acid C18:2 n-6

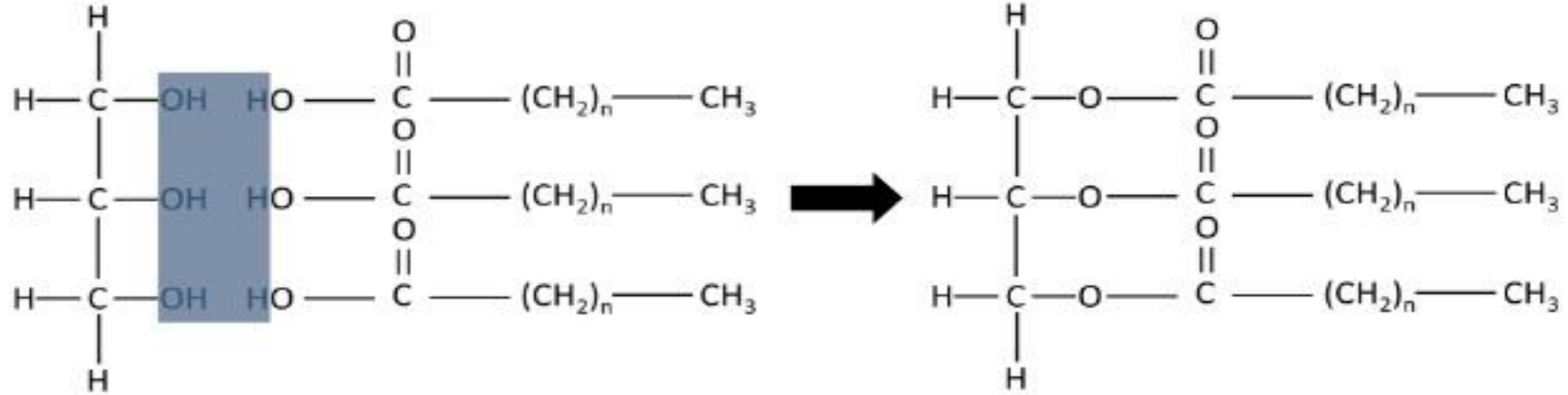


AA: Arachidonic acid C20:4 n-6

DPA: Docosapentanoic acid C22:5 n-6

TG and fatty acids

Condensation reaction between glycerol and fatty acids



Hydrolysis is the reverse of this process, catalysed by lipase

+ $3H_2O$

Lipids are glycerol combined with 1, 2 or 3 fatty acids, therefore **triglycerides are lipids**

American Heart Association. life is why™ | Healthy For Good™

THE FACTS ON FAT

The American Heart Association recommends replacing bad (saturated) fats with good (unsaturated) fats as part of a healthy eating pattern.

LOVE IT

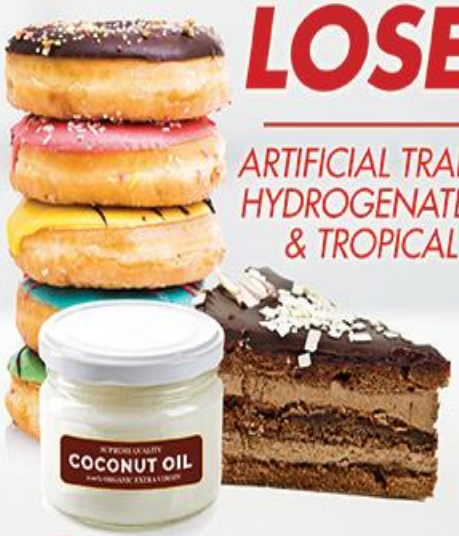
UNSATURATED (POLY & MONO)

- Lowers rates of cardiovascular and all-cause mortality
- Lowers bad cholesterol & triglyceride levels
- Provides essential fats your body needs but can't produce itself

LIMIT IT

SATURATED

- Increases risk of cardiovascular disease
- Raises bad cholesterol levels



LOSE IT

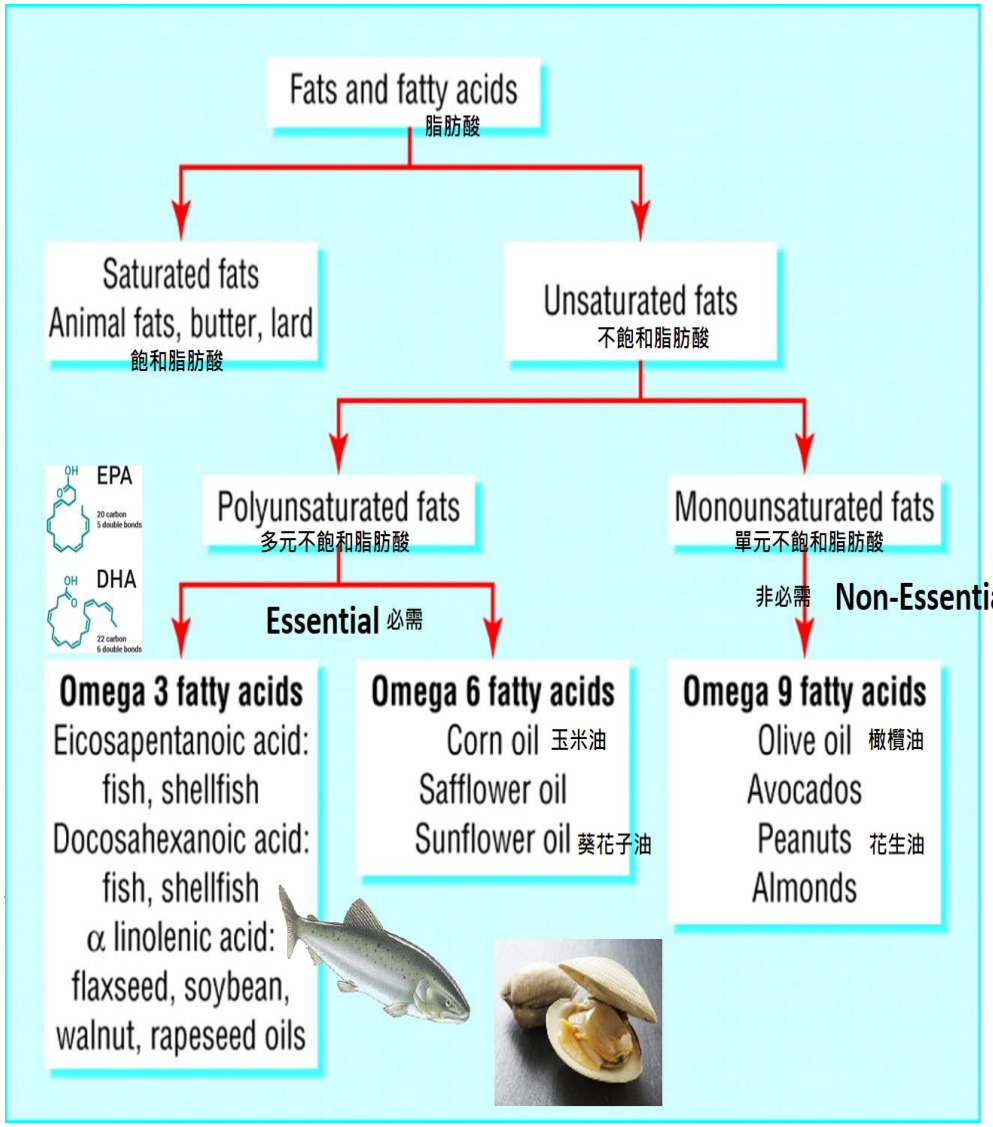
ARTIFICIAL TRANS FAT, HYDROGENATED OILS & TROPICAL OILS

- Increases risk of heart disease
- Raises bad cholesterol levels

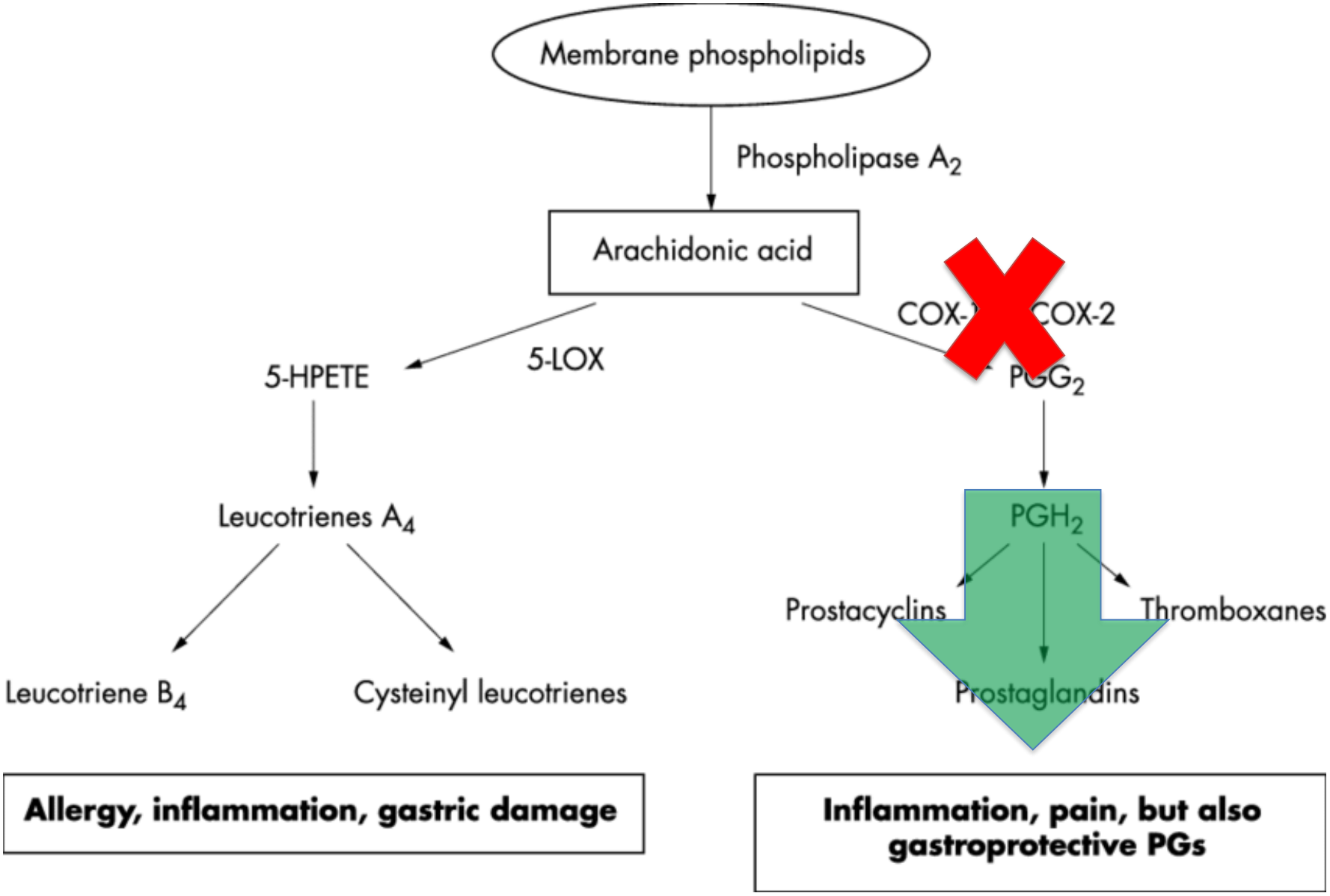
EPA is a member of omega-3 PUFA

脂肪的種類、特徵及代表食品

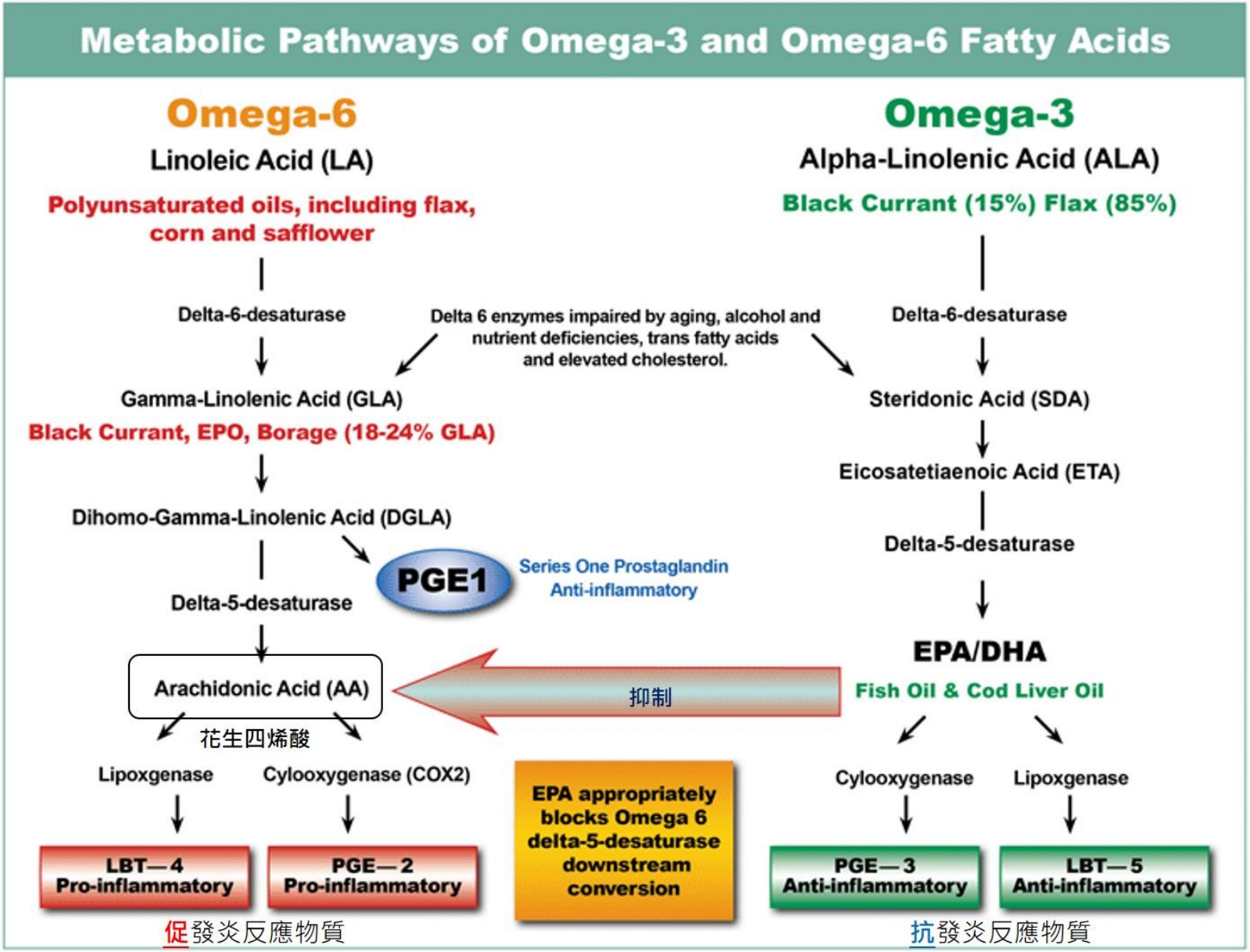
脂肪種類		主要含有食品
不飽和脂肪	單元不飽和脂肪酸 例: Omega-9	肉類、乳製品、酪梨、橄欖等
	多元不飽和脂肪酸 例: Omega-3 Omega-6	Omega-3: 鮭魚、青色的魚、核桃、亞麻籽等 Omega-6: 植物性油、穀類、雞蛋、堅果類等
	反式脂肪	冰淇淋、起酥油、乳製品、加工肉類 炸物等速食食品、糕點類等
飽和脂肪酸		奶油、起司、牛油等動物性油、 肥肉類、巧克力、椰子油等

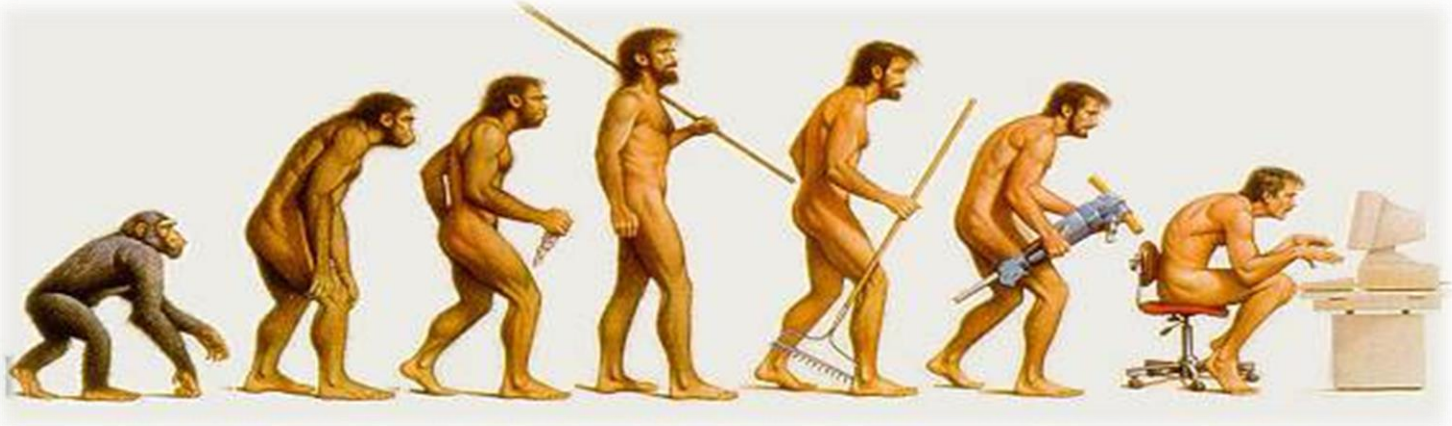


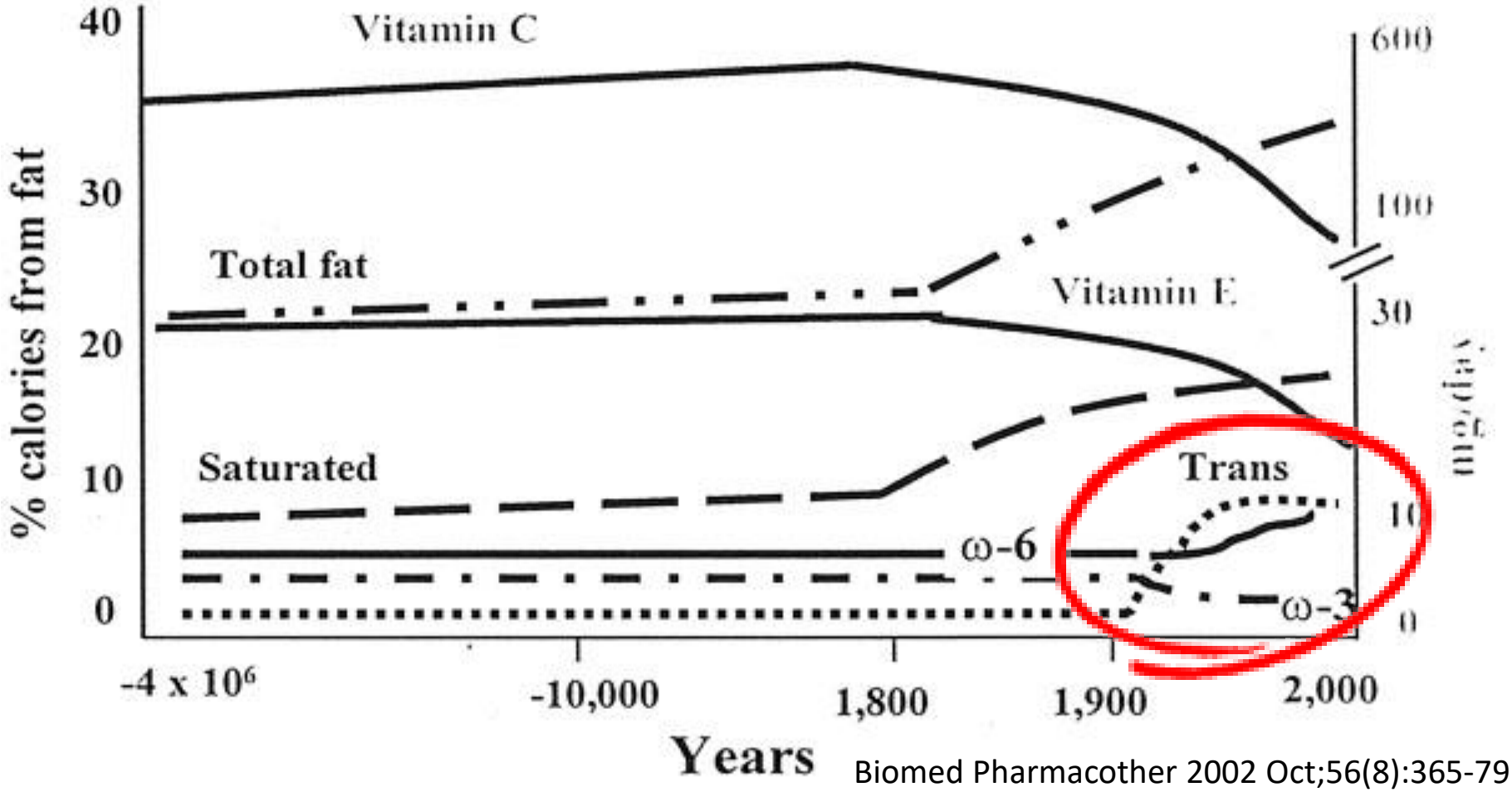
Omega 6 代謝産物：Arachidonic acid



OMEGA-6促發炎；OMEGA-3抗發炎

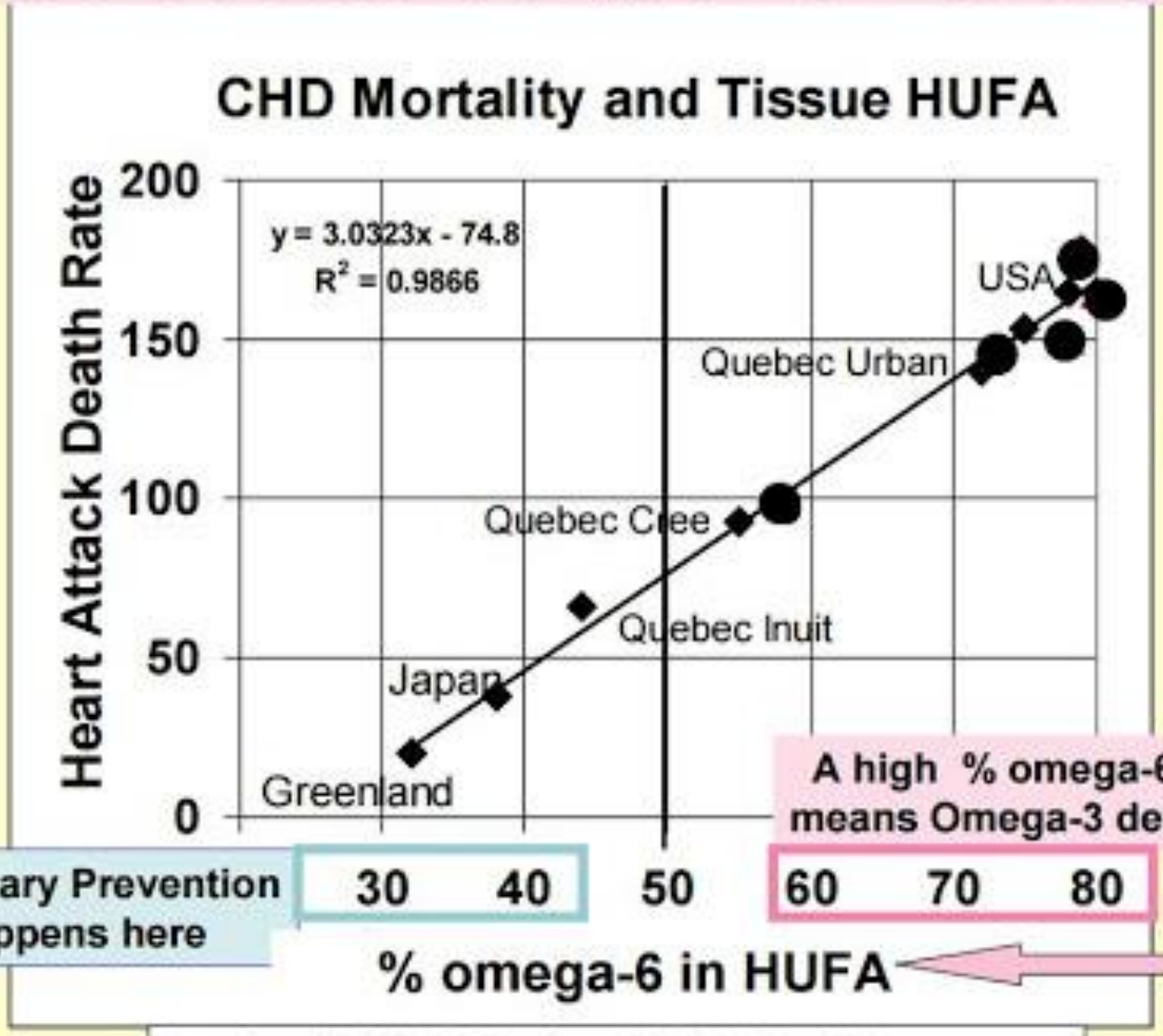






Biomed Pharmacother 2002 Oct;56(8):365-79

Americans have excessive omega-6 in HUFA & an omega-3 deficit



Lands, Lipids 2003 (Apr.); 38: 317–321
http://efaeducation.nih.gov/sig/personal.html

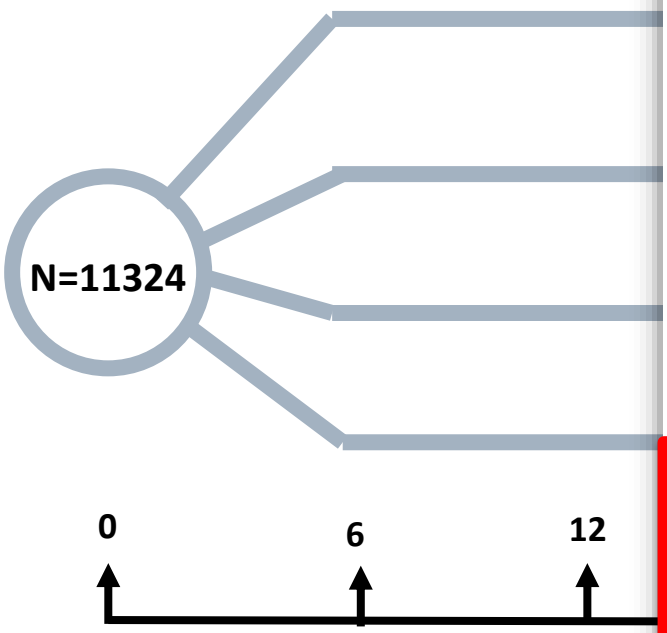
Outlines

- What is EPA ?
- **EPA/DHA for secondary prevention**
- EPA/DHA for primary prevention
- Why is EPA not DHA effective for *1st* prevention ?

Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial

11 324 patients surviving recer
assigned supplements of n-3 P
n=2830), both (n=2830), or no

Open-label, randomized design



Pharmacological therapy	
Antiplatelet drugs	
Baseline	2601 (92·2%)
6 months	2308 (88·2%)
42 months	1707 (83·4%)
Angiotensin-converting-enzyme inhibitors	
Baseline	1298 (46·0%)
6 months	1033 (39·5%)
42 months	788 (38·5%)
β-blockers	
Baseline	1237 (43·9%)
6 months	1092 (41·7%)
42 months	807 (39·4%)
Cholesterol-lowering drugs	
Baseline	124 (4·4%)
6 months	782 (28·6%)
42 months	1003 (46·0%)

1g Omacor 包含 460 mg EPA及380 mg DHA

Lancet. 1999 Aug 7;354(9177):447-55

Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial

Baseline TC 210 mg/dL, LDL-C 137 mg/dL, TG 162 mg/dL

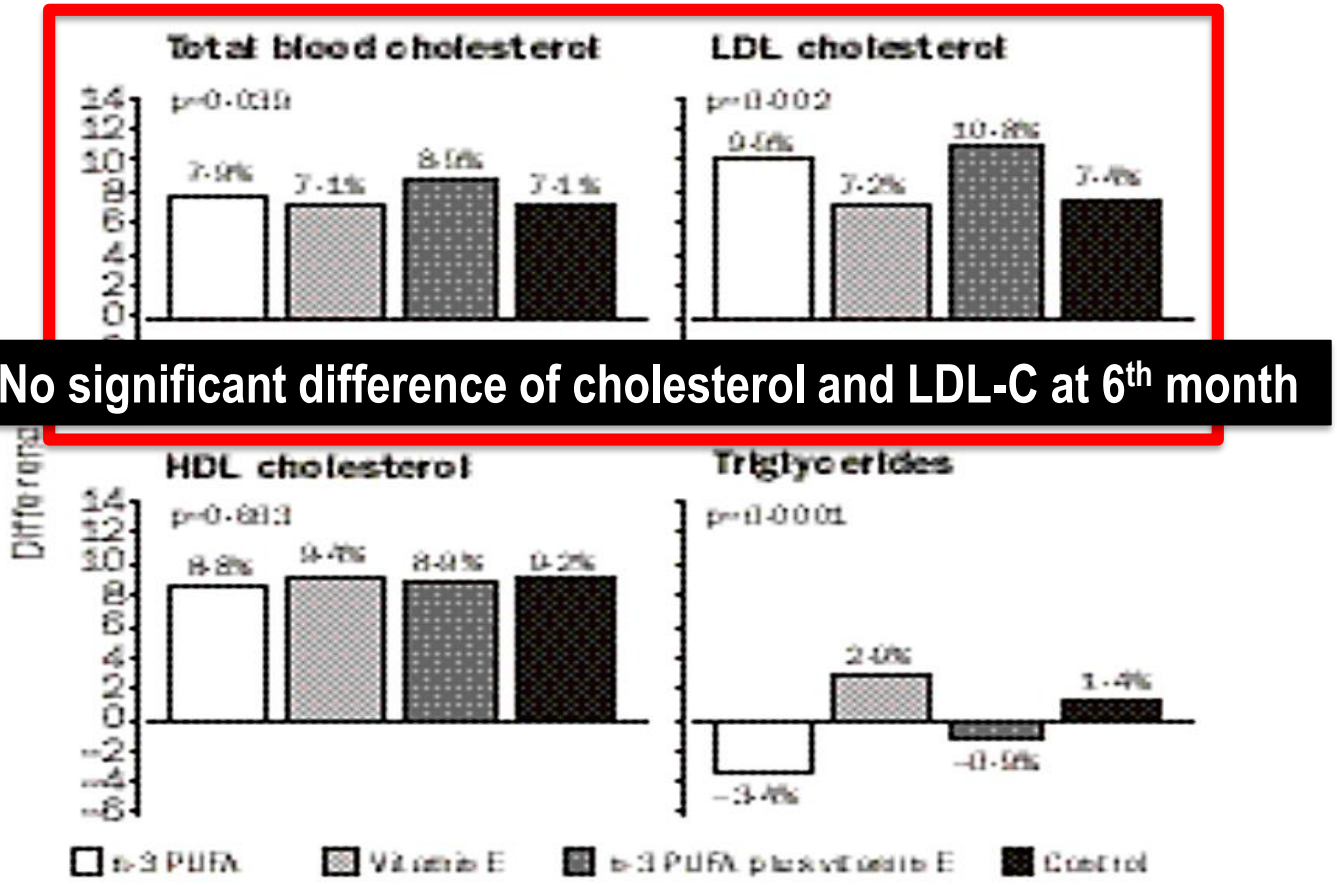
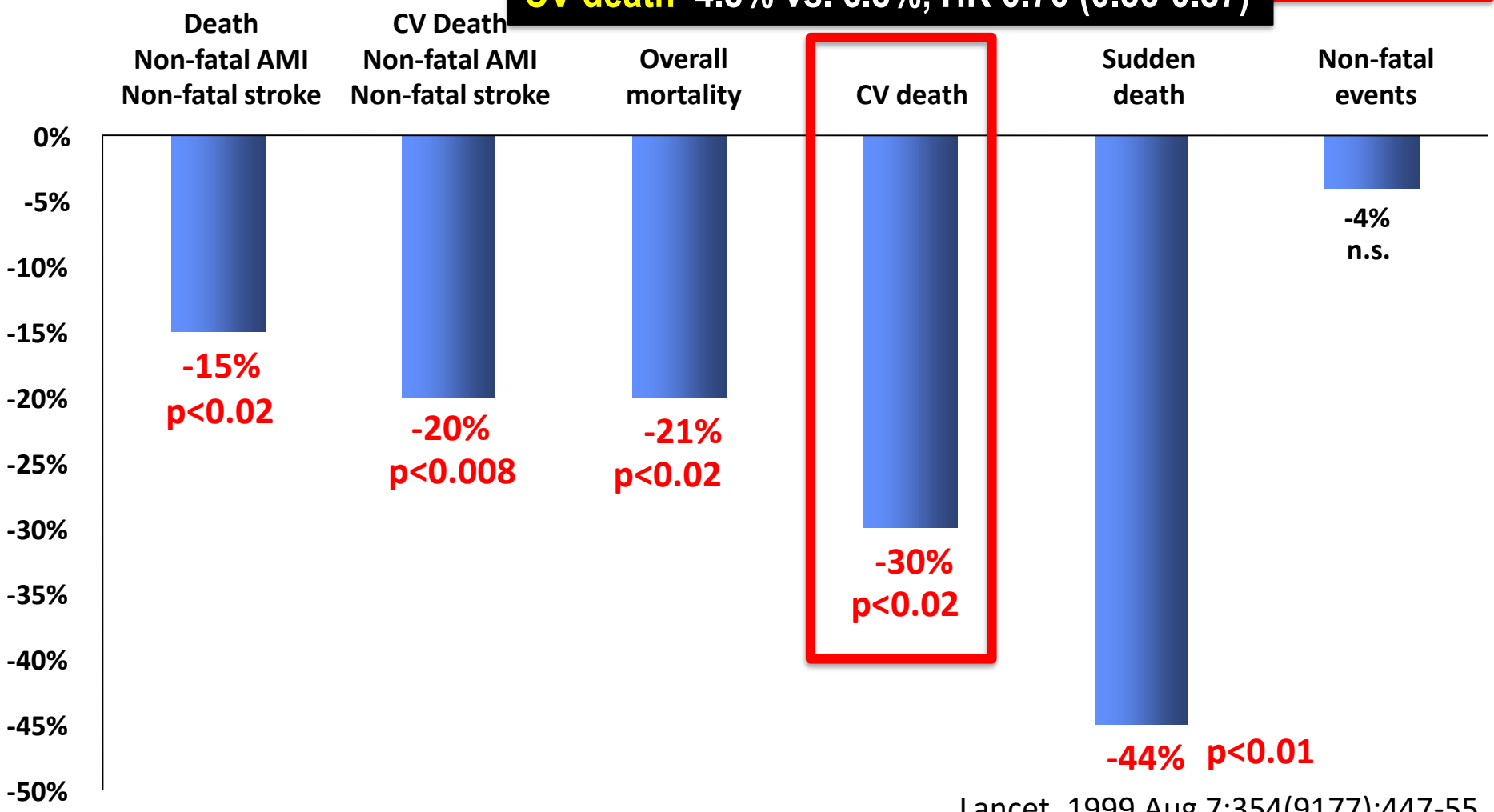


Figure 2: **Percentage differences in blood lipid concentrations at 6 months**

Lancet. 1999 Aug 7;354(9177):447-55

	All (n=11 324)	Two-way analysis			Four-way analysis		
		n-3 PUFA (n=5666)	Control (n=5668)	Relative risk (95% CI)	n-3 PUFA (n=2836)	Control (n=2828)	Relative risk (95% CI)
Main endpoints							
Death, non-fatal MI, and non-fatal stroke	1500 (13·3%)	715 (12·6%)	785 (13·9%)	0·90 (0·82–0·99)	356 (12·3%)	414 (14·6%)	0·85 (0·74–0·98)
Cardiovascular death, non-fatal MI, and non-fatal stroke	1155 (10·2%)	547 (9·7%)	608 (10·8%)	0·89 (0·80–1·01)	262 (9·2%)	322 (11·4%)	0·80 (0·68–0·95)
Secondary analyses							
All fatal events	1017 (9·0%)	472 (8·3%)	545 (9·6%)	0·86 (0·76–0·97)	236 (8·3%)	293 (10·4%)	0·80 (0·67–0·94)
Cardiovascular deaths	639 (5·6%)	291 (5·1%)	348 (6·2%)	0·83 (0·71–0·97)	136 (4·8%)	193 (6·8%)	0·70 (0·56–0·87)
Cardiac death	520 (4·6%)	228 (4·0%)	292 (5·2%)	0·78 (0·65–0·92)	108 (3·8%)	165 (5·8%)	0·65 (0·51–0·82)
Coronary death	479 (4·2%)	214 (3·8%)	265 (4·7%)	0·80 (0·67–0·96)	100 (3·5%)	151 (5·3%)	0·65 (0·51–0·84)
Sudden death	286 (2·5%)	122 (2·2%)	164 (2·9%)	0·74 (0·58–0·93)	55 (1·9%)	99 (3·5%)	0·55 (0·40–0·76)
Other deaths	378 (3·3%)	181 (3·2%)	197 (3·5%)	0·91 (0·74–1·11)	100 (3·5%)	100 (3·5%)	0·99 (0·75–1·30)
Non-fatal cardiovascular events	578 (5·1%)	287 (5·1%)	291 (5·1%)	0·98 (0·83–1·15)	140 (4·9%)	144 (5·1%)	0·96 (0·76–1·21)
Other analyses							
CHD death and non-fatal MI	909 (8						0·75 (0·62–0·90)
Fatal and non-fatal stroke	178 (1						1·30 (0·87–1·96)

CV death 4.8% vs. 6.8%, HR 0.70 (0.56-0.87)

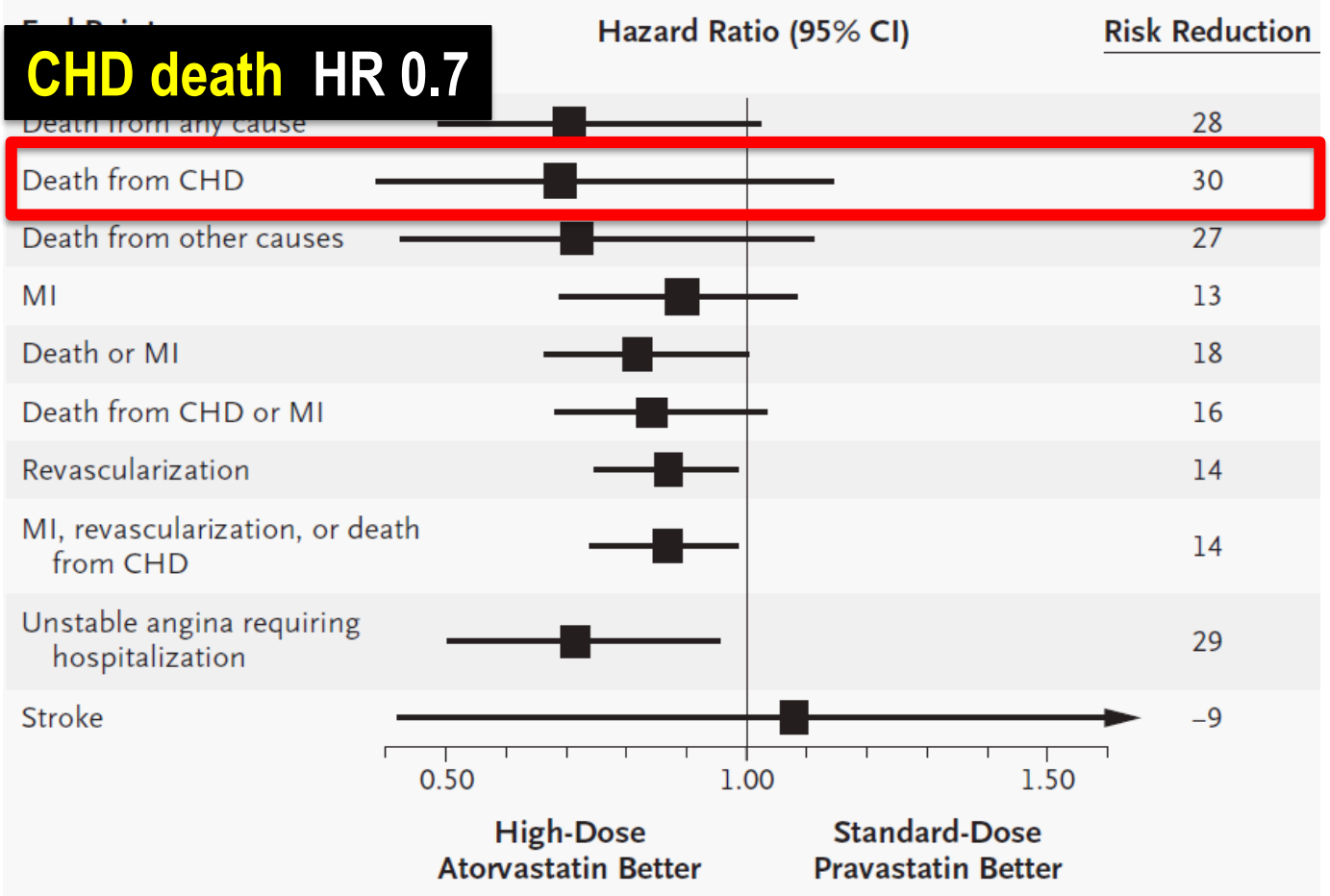


Lancet. 1999 Aug 7;354(9177):447-55

Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes

Christopher P. Cannor… iel J. Rader, M.D.,
Jean L. Rouleau, M.D., Re… Pfeffer, M.D., Ph.D.,
and Allan M. Skene, Ph.D… erapy–Thrombolysis

2004 NEJM PROVE-IT
Atorvastatin 80mg vs. Pravastatin 40mg



N Engl J Med 2004;350:1495-504

Omega-3 Polyunsaturated Fatty Acid (Fish Oil) Supplementation and the Prevention of Clinical Cardiovascular Disease

A Science Advisory From the American Heart Association

SECONDARY PREVENTION OF CHD AND SCD AMONG PATIENTS WITH PREVALENT CHD

.... the majority of co-authors concluded that treatment with omega-3 PUFA supplements is reasonable for the secondary prevention of CHD death (*Class IIa Recommendation*); a minority of coauthors preferred a slightly lower strength of recommendation for treatment of patients with this indication (*Class IIb Recommendation*).

Circulation. 2017;135:e867–e884

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'

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)

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

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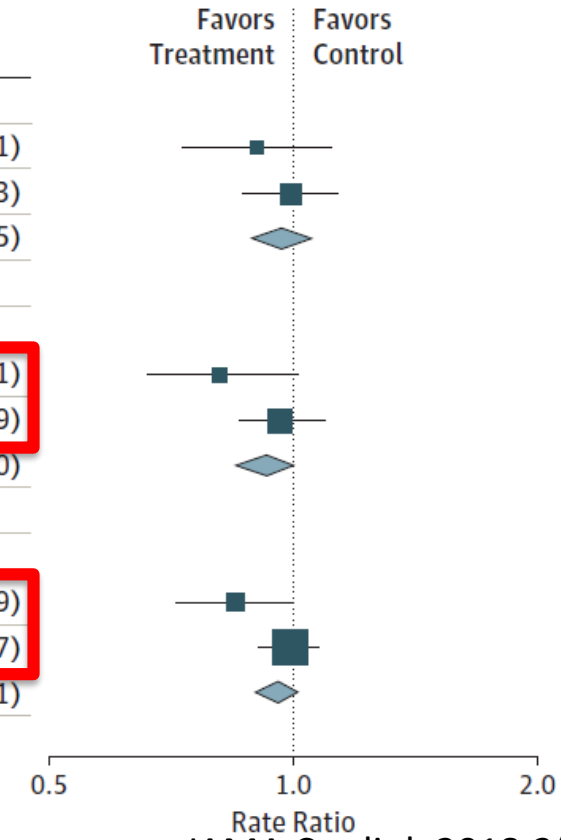
Source	No. of Events (%) Treatment	Control	Rate Ratios (CI)
Nonfatal myocardial infarction			
Open	285 (1.9)	316 (2.1)	0.90 (0.73-1.11)
Blind	836 (3.5)	839 (3.5)	0.99 (0.87-1.13)
All	1121 (2.9)	1155 (3.0)	0.97 (0.89-1.05)
			P = .40
Coronary heart disease death			
Open	276 (1.8)	337 (2.2)	0.81 (0.66-1.01)
Blind	1025 (4.3)	1057 (4.4)	0.96 (0.86-1.09)
All	1301 (3.3)	1394 (3.6)	0.93 (0.85-1.00)
			P = .05
Any coronary heart disease			
Open	512 (3.4)	598 (4.0)	0.85 (0.72-0.99)
Blind	2573 (10.7)	2590 (10.8)	0.99 (0.91-1.07)
All	3085 (7.9)	3188 (8.2)	0.96 (0.90-1.01)
			P = .12



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

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

New York Heart Association class II–IV, irrespective of cause and left ventricular ejection fraction, and randomly assigned them to n-3 PUFA 1 g daily (n=3494) or placebo (n=3481)

	n-3 PUFA (n=3494)	Placebo (n=3481)
Patients' characteristics		
Age (years)	67 (11)	67 (11)
Age >70 years	1465 (41·9%)	1482 (42·6%)
Women	777 (22·2%)	739 (21·2%)
Heart disease risk factors		
BMI (kg/m²)	27 (5)	27 (5)
SBP (mm Hg)	126 (18)	126 (18)
DBP (mm Hg)	77 (10)	77 (10)
Heart rate (beats per min)	72 (13)	73 (14)
Current smoking	502 (14·4%)	485 (13·9%)
History of hypertension	1886 (54·0%)	1923 (55·2%)
NYHA class		
IV	90 (2·6%)	95 (2·7%)
LVEF (%)	33·0% (8·5)	33·2% (8·5)
LVEF >40%	333 (9·5%)	320 (9·2%)

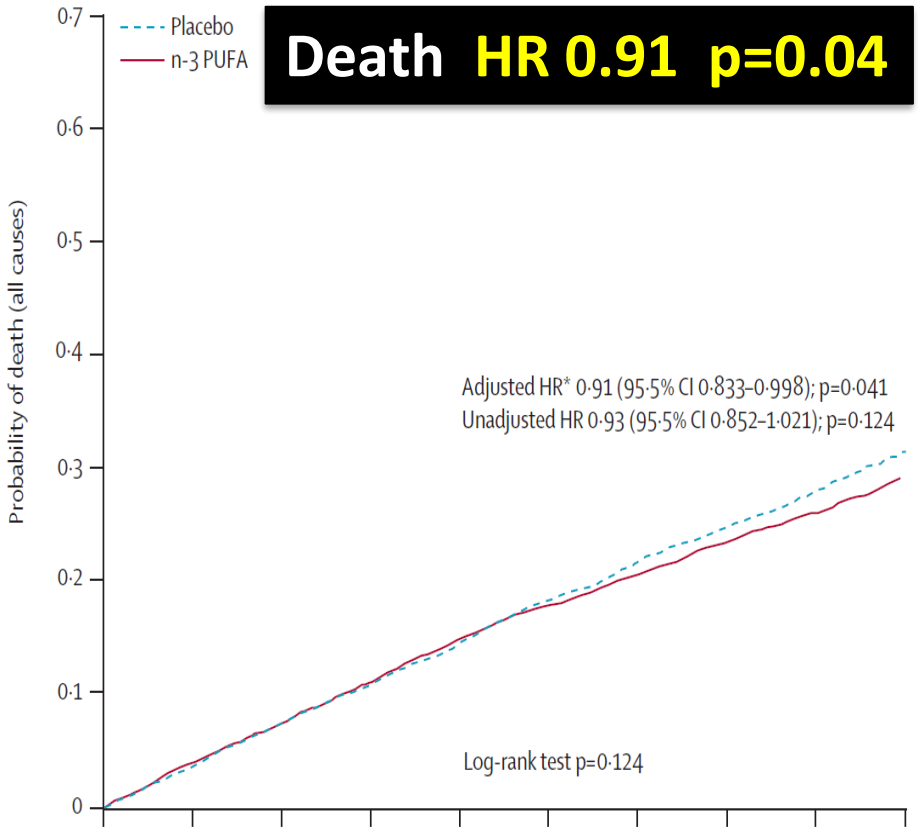
Average LVEF 33.1%, NYHA Fc II 63.5%

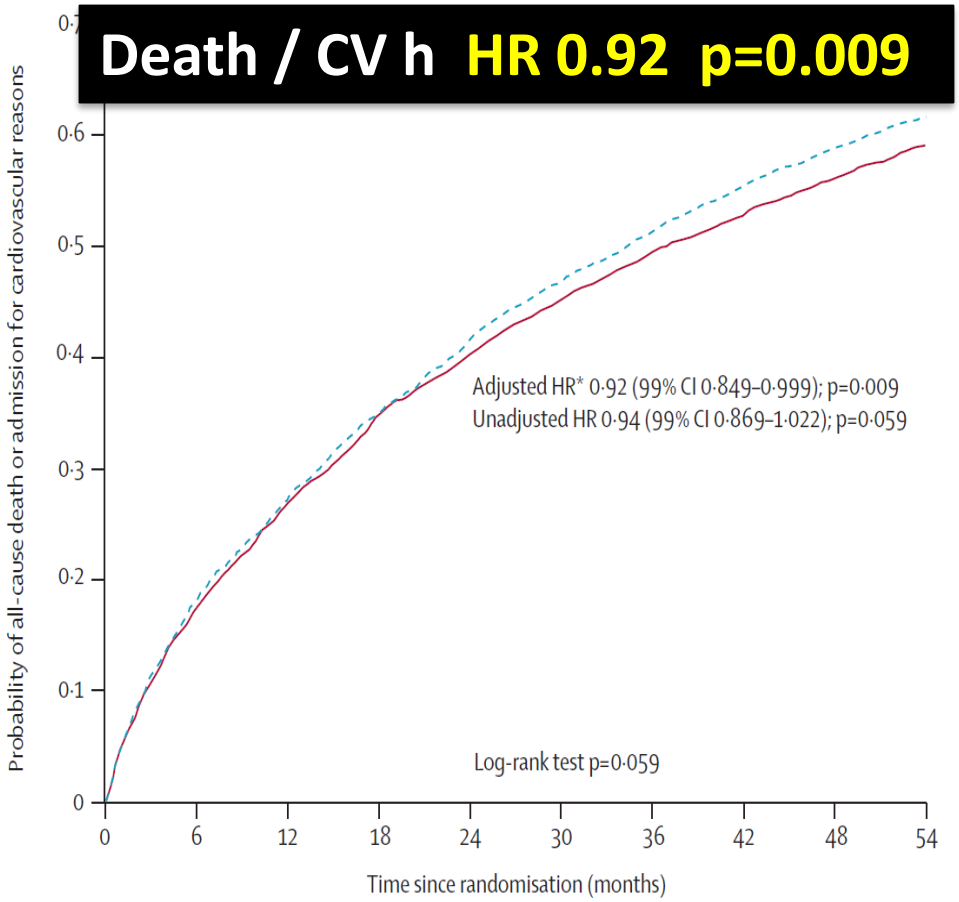
Medical treatment		
ACE inhibitors	2696 (77·2%)	2678 (76·9%)
ARBs	673 (19·3%)	648 (18·6%)
ACE inhibitors/ARBs	3268 (93·5%)	3252 (93·4%)
β blockers	2275 (65·1%)	2247 (64·6%)
Spironolactone	1347 (38·6%)	1393 (40·0%)
Diuretic drugs	3127 (89·5%)	3133 (90·0%)
Digitalis	1296 (37·1%)	1292 (37·1%)
Oral anticoagulant drugs	1027 (29·4%)	982 (28·2%)
Aspirin	1673 (47·9%)	1685 (48·4%)
Other antiplatelet agents	345 (9·9%)	371 (10·7%)
itrates	1236 (35·4%)	1236 (35·5%)
alcium-channel blockers	343 (9·8%)	366 (10·5%)
Amiodarone	668 (19·1%)	690 (19·8%)
Statin (open)	778 (22·3%)	801 (23·0%)

1g Omacor 包含 460 mg EPA及380 mg DHA

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

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.

2013 ACCF/AHA Guideline for the Management of Heart Failure

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

Developed in Collaboration With the American College of Chest Physicians, Heart Rhythm Society and International Society for Heart and Lung Transplantation

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation

Omega-3 polyunsaturated fatty acid (PUFA) supplementation is reasonable to use as adjunctive therapy in patients with NYHA class II–IV symptoms and HF*r*EF or HF*p*EF, unless contraindicated, to reduce mortality and cardiovascular hospitalizations.[539,540] ***(Level of Evidence: B)***

Macchia A, et al. Left ventricular systolic dysfunction, total mortality, and sudden death in patients with myocardial infarction treated with n-3 polyunsaturated fatty acids. Eur J Heart Fail. 2005;7:904–9.
Tavazzi L et al. 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;372:1223–30.

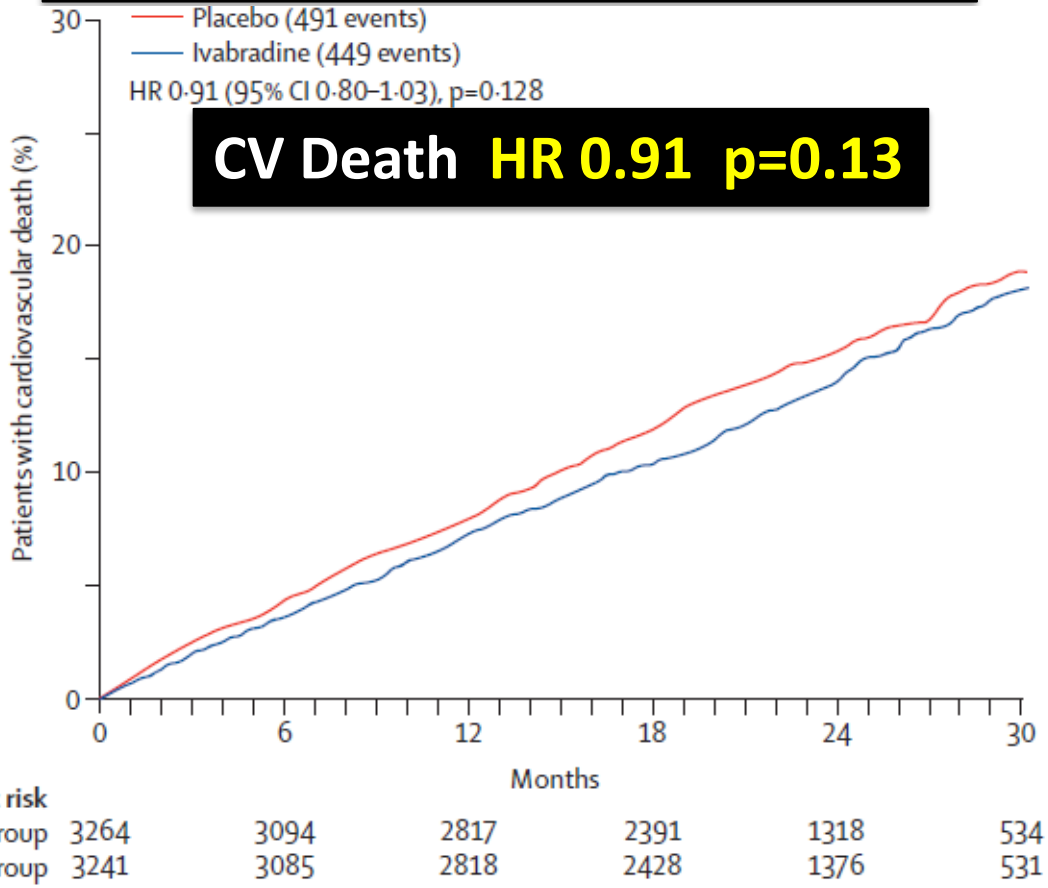
Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

*Karl Swedberg, Michel Komajda, Mi… urs, Luigi Tavazzi, on behalf of the SHIFT Investigators**

2010 LANCET SHIFT

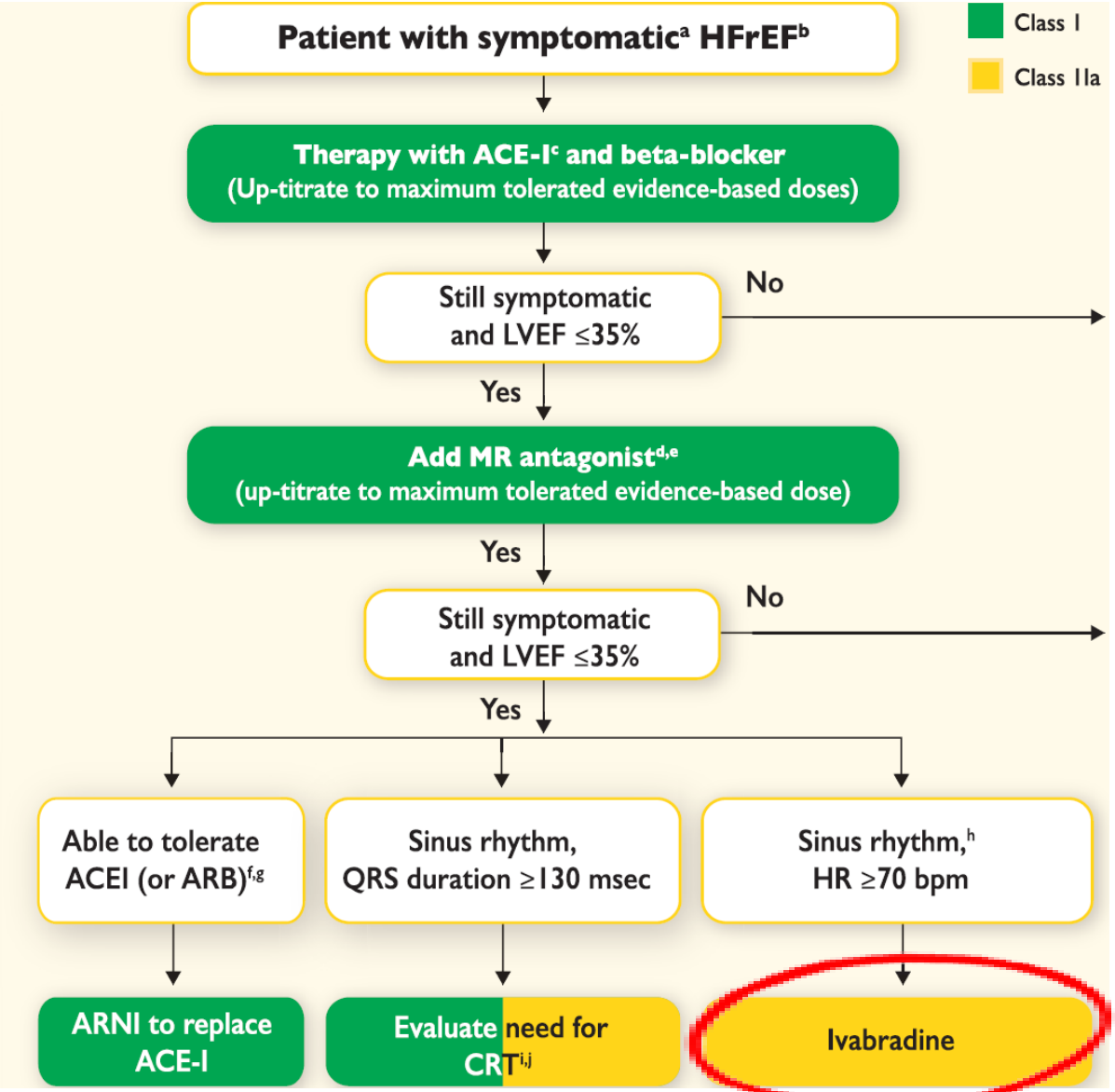
Ivabradine vs. placebo for CHF

Average LVEF 29%, NYHA Fc II 49%



Lancet 2010; 376: 875–85

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure



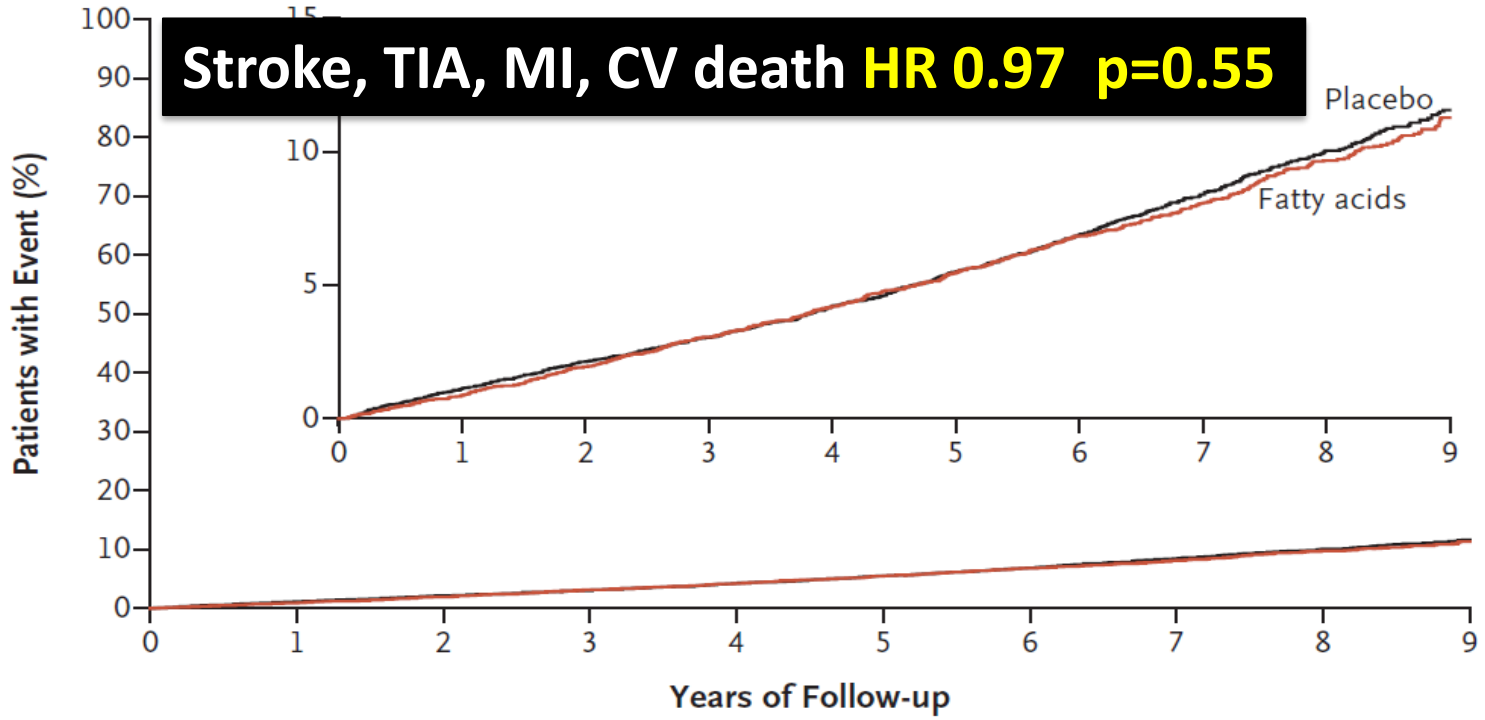
Outlines

- What is EPA ?
- EPA/DHA for secondary prevention
- **EPA/DHA for primary prevention**
- Why is EPA not DHA effective for *1st* prevention ?

Effects of n–3 Fatty Acid Supplements in Diabetes Mellitus

The A **2018 NEJM ASCEND** roup*

15,480 patients, average 63y/o, with diabetes but without evidence of ASCVD to receive 1-g capsules containing either n–3 fatty acids (fatty acid group) or matching placebo (olive oil) daily.

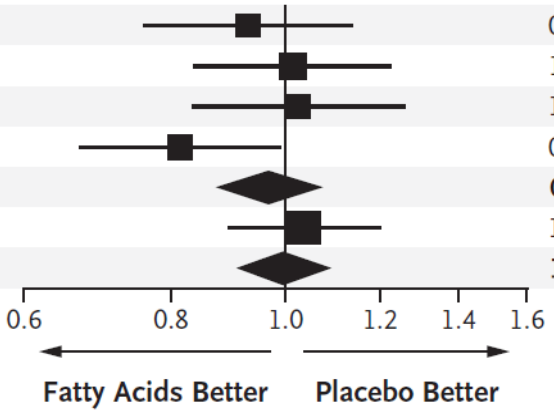


1g Omacor 包含 460 mg EPA及380 mg DHA

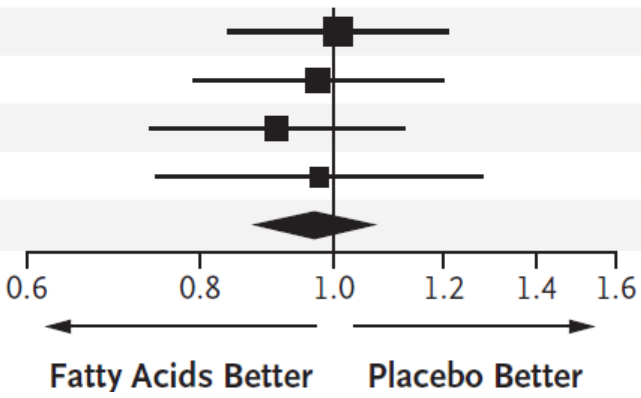
DOI: 10.1056/NEJMoa1804989

Effects of n–3 Fatty Acid Supplements in Diabetes Mellitus

Type of Event	Fatty Acids (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of patients with event (%)			
Nonfatal myocardial infarction	186 (2.4)	200 (2.6)	0.93 (0.76–1.14)	
Nonfatal ischemic stroke	217 (2.8)	214 (2.8)	1.01 (0.84–1.22)	
Transient ischemic attack	185 (2.4)	180 (2.3)	1.03 (0.84–1.26)	
Vascular death	186 (2.4)	228 (2.9)	0.81 (0.67–0.99)	
Serious vascular event	**689 (8.9)**	**712 (9.2)**	**0.97 (0.87–1.08)**	**0.55**
Any revascularization	368 (4.8)	356 (4.6)	1.04 (0.90–1.20)	
Serious vascular event or revascularization	**882 (11.4)**	**887 (11.5)**	**1.00 (0.91–1.09)**	



Year of First Event	Fatty Acids (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of patients with event (%)			
<3	236 (3.0)	234 (3.0)	1.01 (0.84–1.21)	
3 to <5	181 (2.5)	186 (2.5)	0.97 (0.79–1.20)	
5 to <7	167 (2.4)	184 (2.6)	0.91 (0.74–1.12)	
≥7	105 (2.7)	108 (2.7)	0.98 (0.75–1.28)	
All	**689 (8.9)**	**712 (9.2)**	**0.97 (0.87–1.08)**	**0.55**
Test for trend across years χ^2=0.22 (P=0.64)				

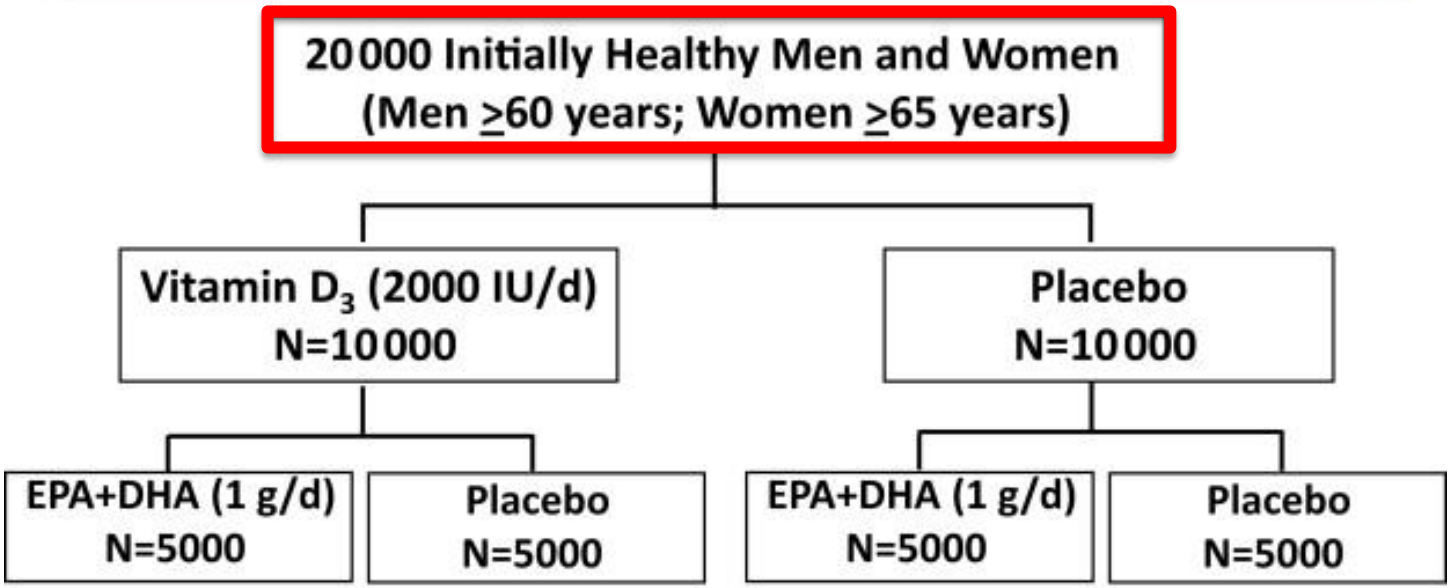


DOI: 10.1056/NEJMoa1804989

Marine n–3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer

2018 NEJM VITAL

The *VIT*amin D and Omeg*A*-3 Tria*L* (*VITAL*): Design



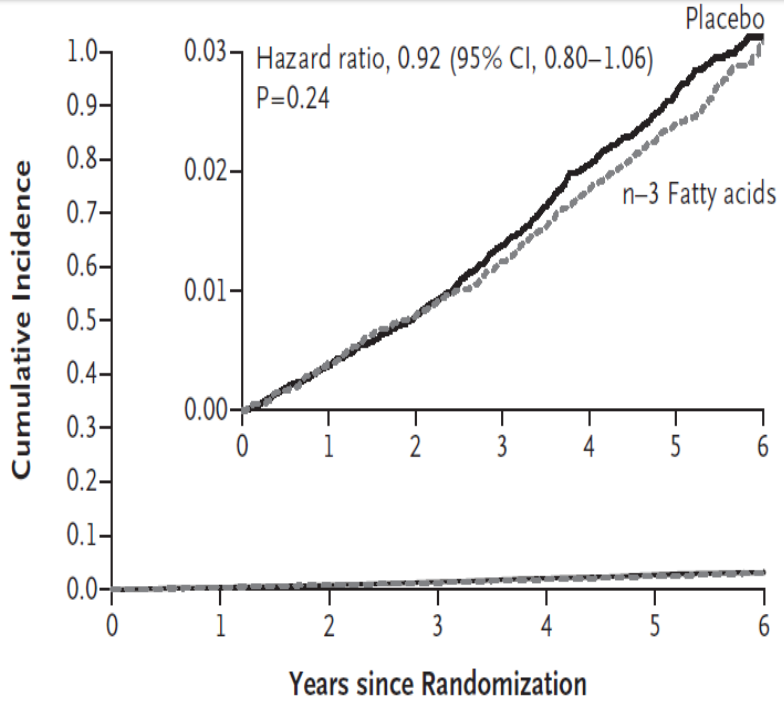
Mean Treatment Period = 5.0 years
Blood collection in ~12000; follow-up bloods in 2000
Primary Outcomes: Cancer (total) and CVD (MI, stroke, CVD death)

1g Omacor 包含 460 mg EPA及380 mg DHA

DOI: 10.1056/NEJMoa1811403

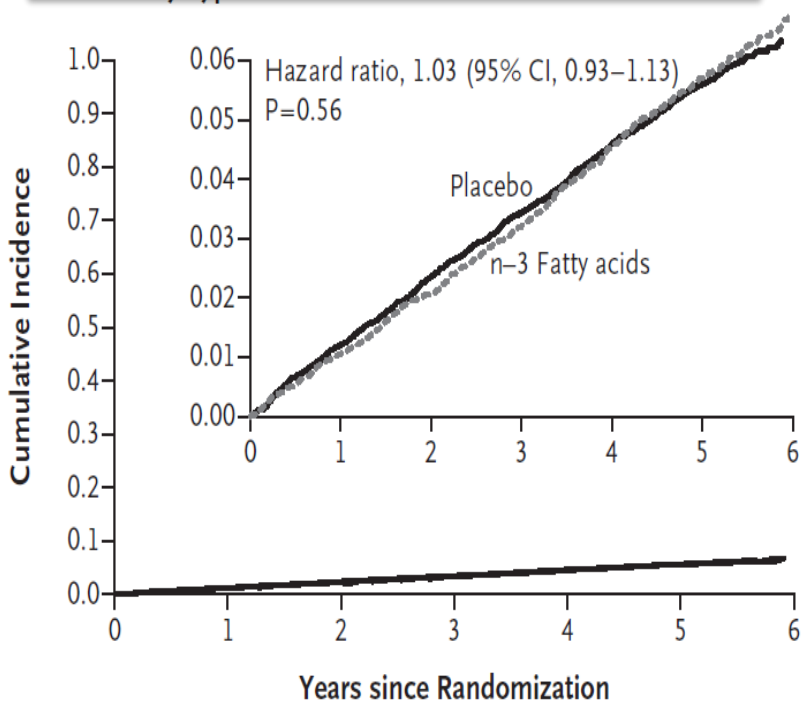
Marine n–3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer

Major CV events HR 0.92 p=0.24



No. at Risk							
Placebo	12,938	12,862	12,745	12,592	12,281	9825	775
n–3 Fatty acids	12,933	12,842	12,725	12,594	12,322	9878	765

Any cancer HR 1.03 p=0.56



No. at Risk							
Placebo	12,938	12,747	12,544	12,330	11,981	9543	756
n–3 Fatty acids	12,933	12,756	12,566	12,356	11,996	9557	734

DOI: 10.1056/NEJMoa1811403

Marine n–3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer

End Point	n–3 Group (N = 12,933)	Placebo Group (N = 12,938)	Hazard Ratio (95% CI)
	no. of participants with event		
Cardiovascular disease			
Primary end point: major cardiovascular event†	386	419	0.92 (0.80–1.06)
		567	0.93 (0.82–1.04)
Total myocardial infarction	145	200	0.72 (0.59–0.90)
Total stroke	148	142	1.04 (0.83–1.31)
Death from cardiovascular causes	142	148	0.96 (0.76–1.21)

All myocardial infarction HR 0.72 (0.59-0.9)

DOI: 10.1056/NEJMoa1811403

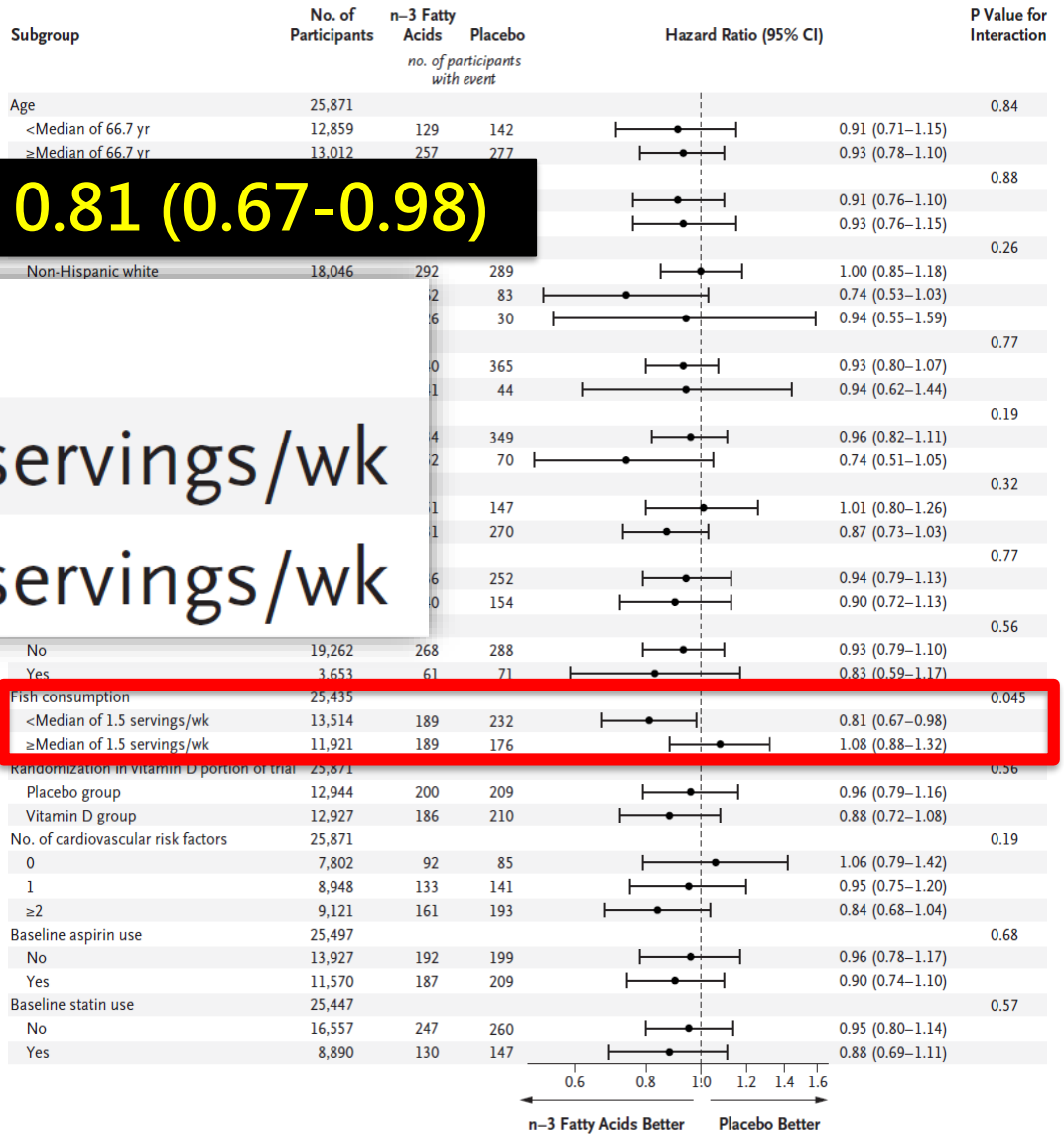
Marine n–3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer

少吃魚的人比較有效, HR 0.81 (0.67-0.98)

Fish consumption

<Median of 1.5 servings/wk

≥Median of 1.5 servings/wk



Subgroup	No. of Participants	n–3 Fatty Acids	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
		no. of participants with event			
Age	25,871				0.84
<Median of 66.7 yr	12,859	129	142	0.91 (0.71–1.15)	
≥Median of 66.7 yr	13,012	257	277	0.93 (0.78–1.10)	
					0.88
				0.91 (0.76–1.10)	
				0.93 (0.76–1.15)	
					0.26
Non-Hispanic white	18,046	292	289	1.00 (0.85–1.18)	
		2	83	0.74 (0.53–1.03)	
		6	30	0.94 (0.55–1.59)	
					0.77
		0	365	0.93 (0.80–1.07)	
		1	44	0.94 (0.62–1.44)	
					0.19
		4	349	0.96 (0.82–1.11)	
		2	70	0.74 (0.51–1.05)	
					0.32
		1	147	1.01 (0.80–1.26)	
		1	270	0.87 (0.73–1.03)	
					0.77
		6	252	0.94 (0.79–1.13)	
		0	154	0.90 (0.72–1.13)	
					0.56
No	19,262	268	288	0.93 (0.79–1.10)	
Yes	3,653	61	71	0.83 (0.59–1.17)	
Fish consumption	25,435				0.045
<Median of 1.5 servings/wk	13,514	189	232	0.81 (0.67–0.98)	
≥Median of 1.5 servings/wk	11,921	189	176	1.08 (0.88–1.32)	
Randomization in vitamin D portion of trial	25,871				0.56
Placebo group	12,944	200	209	0.96 (0.79–1.16)	
Vitamin D group	12,927	186	210	0.88 (0.72–1.08)	
No. of cardiovascular risk factors	25,871				0.19
0	7,802	92	85	1.06 (0.79–1.42)	
1	8,948	133	141	0.95 (0.75–1.20)	
≥2	9,121	161	193	0.84 (0.68–1.04)	
Baseline aspirin use	25,497				0.68
No	13,927	192	199	0.96 (0.78–1.17)	
Yes	11,570	187	209	0.90 (0.74–1.10)	
Baseline statin use	25,447				0.57
No	16,557	247	260	0.95 (0.80–1.14)	
Yes	8,890	130	147	0.88 (0.69–1.11)	

為何 n-3 Fatty acid 對初級預防看不出好處？

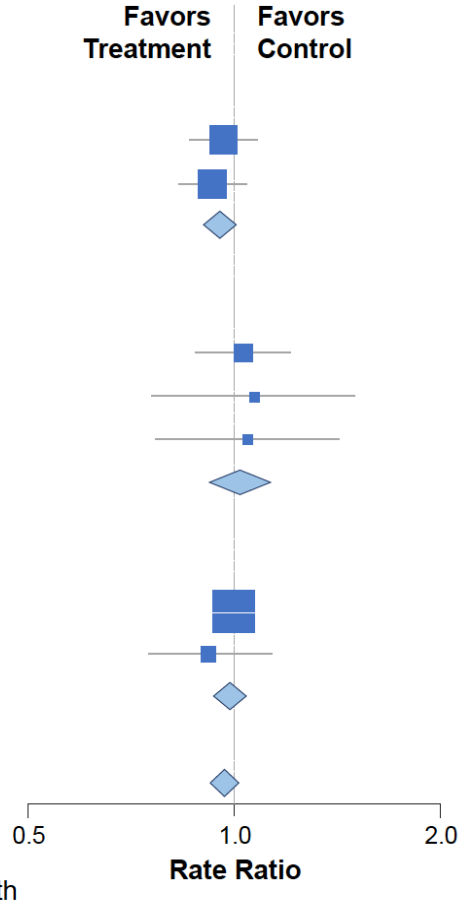
Less effect on low risk patient ?

Dose of n-3 fatty acid?

Component of n-3 fatty acid ?

Low Dose Omega-3 Mixtures Show No Significant Cardiovascular Benefit

Source	No. of Events (%)		Rate Ratios (CI)
	Treatment	Control	
Coronary heart disease			
Nonfatal myocardial infarction	1121 (2.9)	1155 (3.0)	0.97 (0.87–1.08)
Coronary heart disease	1301 (3.3)	1394 (3.6)	0.93 (0.83–1.03)
Any	3085 (7.9)	3188 (8.2)	0.96 (0.90–1.01)
			P=.12
Stroke			
Ischemic	574 (1.9)	554 (1.8)	1.03 (0.88–1.21)
Hemorrhagic	117 (0.4)	109 (0.4)	1.07 (0.76–1.51)
Unclassified/other	142 (0.4)	135 (0.3)	1.05 (0.77–1.43)
Any	870 (2.2)	843 (2.2)	1.03 (0.93–1.13)
			P=.60
Revascularization			
Coronary	3044 (9.3)	3040 (9.3)	1.00 (0.93–1.07)
Noncoronary	305 (2.7)	330 (2.9)	0.92 (0.75–1.13)
Any	3290 (10.0)	3313 (10.2)	0.99 (0.94–1.04)
			P=.60
Any major vascular event	5930 (15.2)	6071 (15.6)	0.97 (0.93–1.01)
			P=.10



1g Omacor 沒效 (460mg EPA + 380mgDHA)

那提高混合型Omega-3劑量呢？

Meta-Analysis > J Hum Nutr Diet. 2018 Feb;31(1):67-84. doi: 10.1111/jhn.12493. Epub 2017 Jul 4.

Eicosapentaenoic acid and docosahexaenoic acid containing supplements modulate risk factors for cardiovascular disease: a meta-analysis of randomised placebo-control human clinical trials

Methods: An analysis was carried on 171 clinical trials with acceptable quality (Jadad score ≥3) that were identified from a comprehensive electronic search strategy of two databases (Pubmed and Cochrane Library). A random effect model was used to obtain an overall estimate on outcomes of interest. Heterogeneity between trial results was tested for using a standard chi-squared test.

Results: Compared with control, EPA and DHA supplements produced significant reductions of triglycerides of 0.368 mmol L^{-1} [95% confidence interval (CI) = -0.427 to -0.309], systolic blood pressure of 2.195 mmHg (95% CI = -3.172 to -1.217), diastolic blood pressure of 1.08 mmHg (95% CI = -1.716 to -0.444), heart rate of 1.37 bpm (95% CI = -2.41 to -0.325) and C-reactive protein of 0.343 mg L^{-1} (95% CI = -0.454 to -0.232). This analysis indicates an increase in both low-density lipoprotein cholesterol (mean difference = 0.150 mmol L^{-1} ; 95% CI = 0.058-0.243) and high-density lipoprotein cholesterol (mean difference = 0.039 mmol L^{-1} ; 95% CI = 0.024-0.054). The triglyceride-lowering effect was dose-dependent.

Conclusions: The lipid-lowering, hypotensive, anti-arrhythmic and anti-inflammatory actions of EPA and DHA supplements were confirmed in this analysis of randomised placebo-control blinded clinical trials.

Assessment of omega-3 carboxylic acids in statin-treated patients with high levels of triglycerides and low levels of high-density lipoprotein cholesterol: Rationale and design of the STRENGTH trial

Primary + secondary prevention

High cardiovascular Risk patients (1. established atherosclerotic cardiovascular disease, 2. diabetes with an additional risk factor or 3. high-risk primary prevention) on optimal statin therapy with triglycerides ≥180 to <500 mg/dL and high-density lipoprotein cholesterol <42 mg/dL (men) or <47 mg/dL (women)

Screening and Lipid Stabilization Period

4-8 weeks

- Epanova 4 g daily (n=6,543) — **2.2g EPA + 0.8g DHA**
- Corn Oil 4 g daily (n=6,543)

Treat until 1,600 primary endpoints with a projected median duration of therapy of 3 years

Primary endpoint: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization or hospitalization for unstable angina

Clinical Cardiology. 2018;41:1281–1288.

January 14, 2020 | 2 min read

SAVE

STRENGTH CV outcomes trial of omega-3 fatty acid stopped for futility

ADD TOPIC TO EMAIL ALERTS

Steven E. Nissen

Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis

Steven E. Nissen, M.D., Neville D. Yeomans, M.D., Daniel H. Solomon, M.D., M.P.H., Thomas F. Lüscher, M.D., Peter Libby, M.D., M. Elaine Husni, M.D., David Y. Graham, M.D., Jeffrey S. Borer, M.D., Lisa M. Wisniewski, R.N., Katherine E. Wolski, M.P.H., Qiuqing Wang, M.S., Venu Menon, M.D., Frank Ruschitzka, M.D., Michael Gaffney, Ph.D., Bruce Beckerman, M.D., Manuela F. Berger, M.D., Weihang Bao, Ph.D., and A. Michael Lincoff, M.D., for the PRECISION Trial Investigators*

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

closed because of a low likelihood of omega-3 carboxylic acids (Epanova) demonstrating a benefit in the trial population.


NOT
THE
END

為何 n-3 Fatty acid 對初級預防看不出好處？

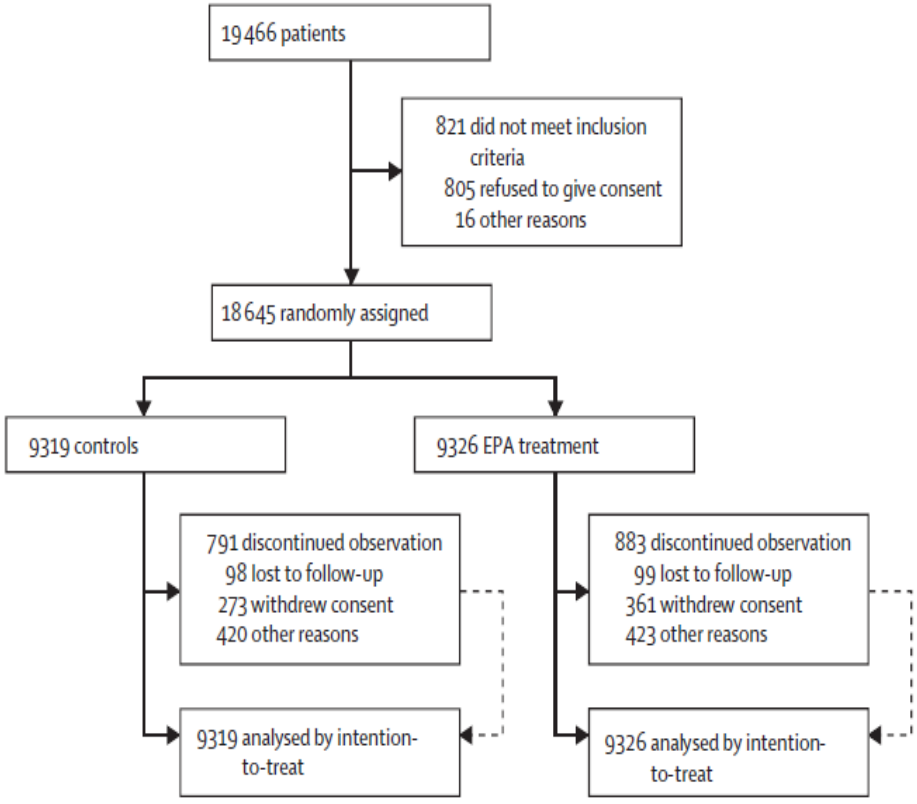
Less effect on low risk patient ?

Dose of n-3 fatty acid?

Component of n-3 fatty acid ?

Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis

MitsuhiroYokoyama, Hideki Origasa, Masunori Matsuzaki, Yuji Matsuzawa, Yasushi Saito, Yuichi Ishikawa, Shinichi Oikawa, Jun Sasaki, Hitoshi Hishida, Hiroshige Itakura, Toru Kita, Akira Kitabatake, Noriaki Nakaya, Toshiie Sakata, Kazuyuki Shimada, Kunio Shirato, for the Japan EPA lipid intervention study (JELIS) Investigators



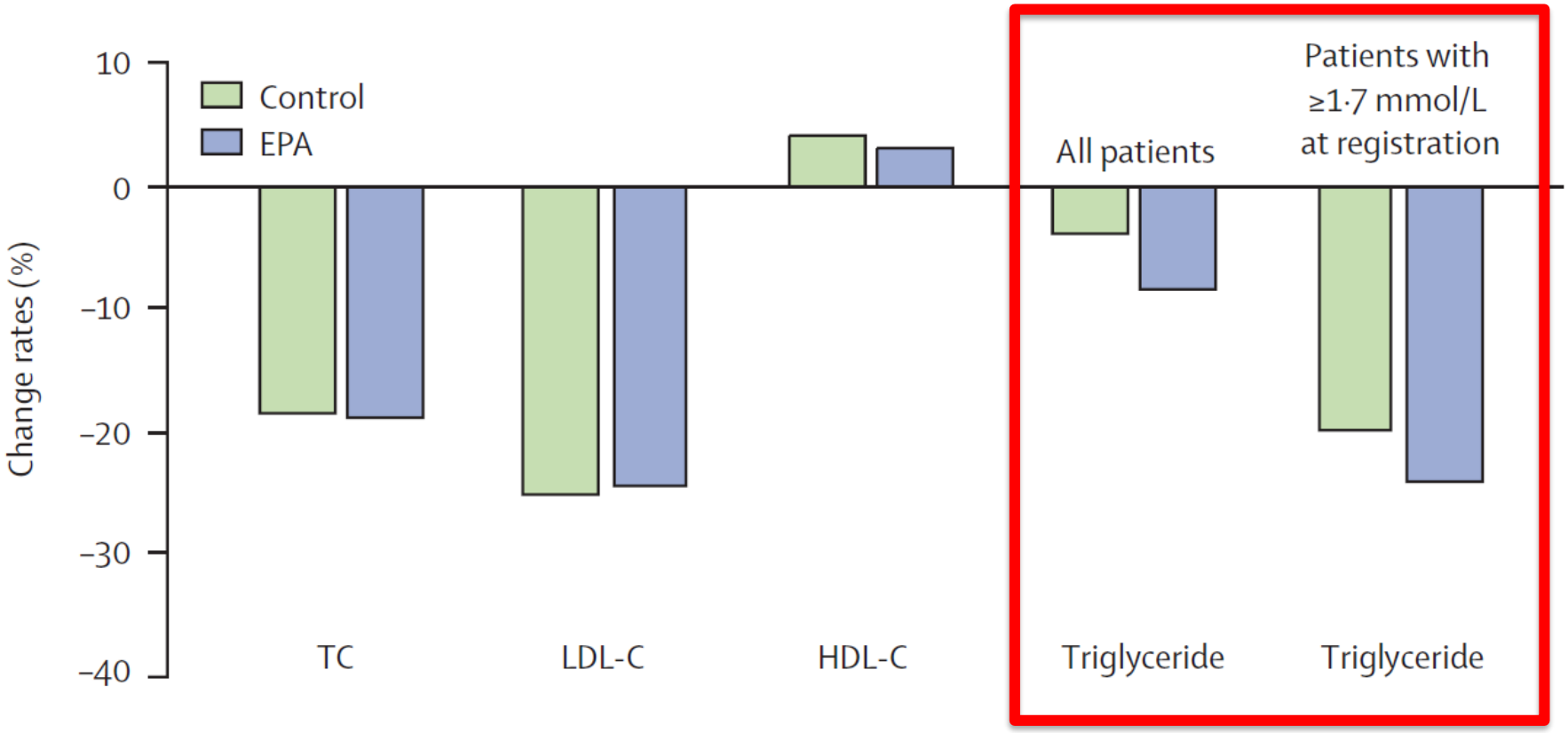
18 645 patients in Japan with a **total cholesterol of 6·5 mmol/L or greater** randomly assigned to receive either **1800 mg of EPA daily with statin (EPA group; n=9326) or statin only (controls; n=9319) with a 5-year follow-up**.

	Controls (n=9319)	**EPA treatment** (n=9326)
Age (years)	61 (9)	61 (8)
Male	2908 (31%)	2951 (32%)
BMI (kg/m²)	24 (3)	24 (3)
Cardiovascular history		
Myocardial infarction	502 (5%)	548 (6%)
Angina	1484 (16%)	1419 (15%)
CABG or PTCA	433 (5%)	462 (5%)

Lancet 2007; 369: 1090–98

Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis

MitsuhiroYokoyama, Hideki Origasa, Masunori Matsuzaki, Yuji Matsuzawa, Yasushi Saito, Yuichi Ishikawa, Shinichi Oikawa, Jun Sasaki, Hitoshi Hishida, Hiroshige Itakura, Toru Kita, Akira Kitabatake, Noriaki Nakaya, Toshiie Sakata, Kazuyuki Shimada, Kunio Shirato, for the Japan EPA lipid intervention study (JELIS) Investigators



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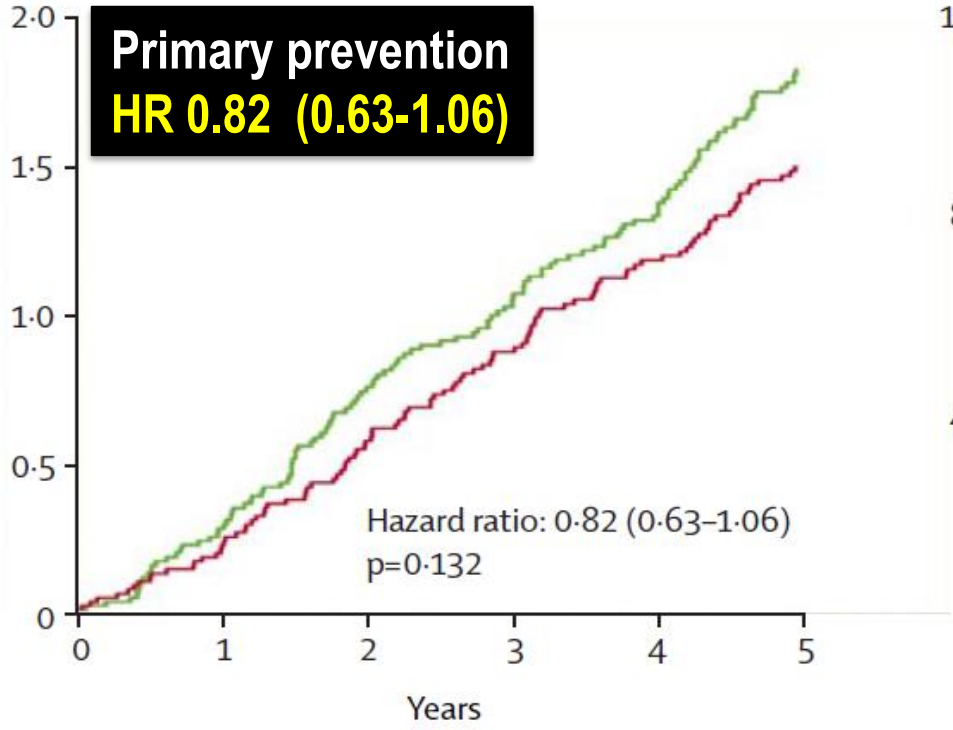
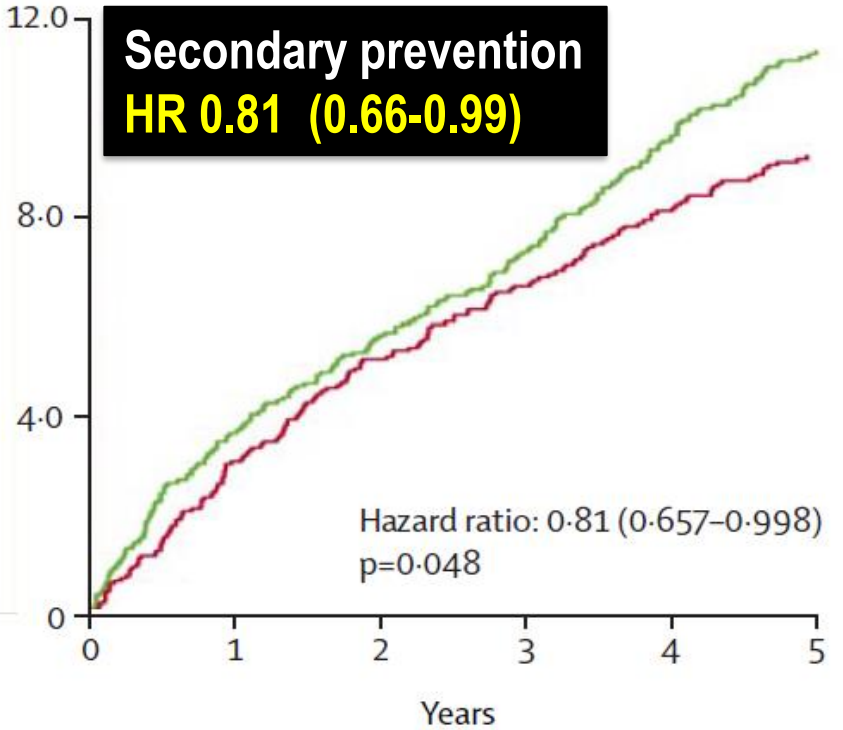
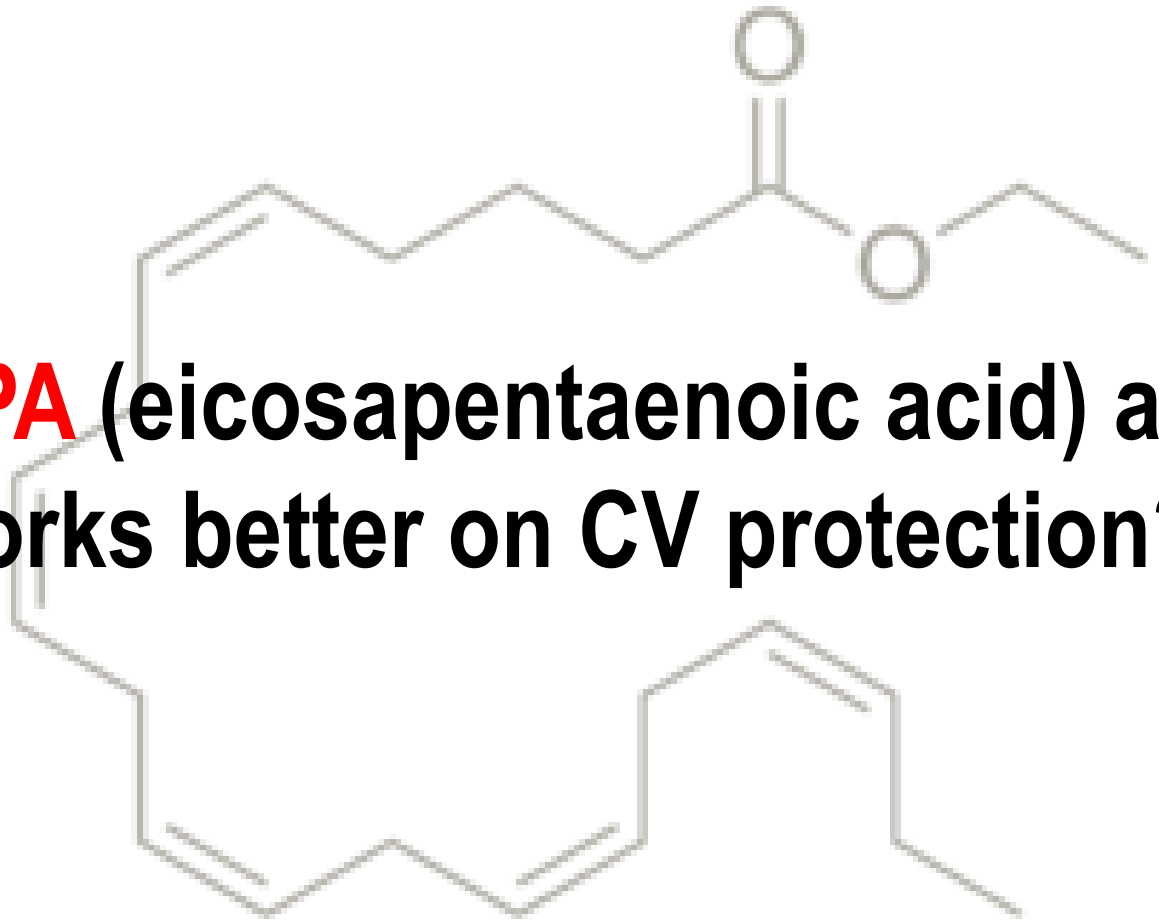




7478	7204	7103	6841	6678	6508
7503	7210	7020	6823	6649	6482

1841	1727	1658	1592	1514	1450
1823	1719	1638	1566	1504	1442

Lancet 2007; 369: 1090–98



EPA (eicosapentaenoic acid) alone works better on CV protection?

Vascepa獲FDA批准後，Amarin調整了收入指導（revenue guidance），將其淨收益總額提高到4.1億至4.25億美元之間，同時也預計2020年的淨收益總額將在6.5億到7億美元之間，主要收益來自Vascepa在美國的銷售額。

羅仕資本合夥人(Roth Capital Partners)金融分析師Yasmeen Rahimi預期，2030年Vascepa的銷售將可上看32億美元，並在下一個十年達到12.1%的市占率。

Share Tweet Linkedin Email Print

For Immediate Release: December 13, 2019

Español

The U.S. Food and Drug Administration today approved the use of Vascepa (icosapent ethyl) as an adjunctive (secondary) therapy to reduce the risk of cardiovascular events among adults with elevated triglyceride levels (a type of fat in the blood) of 150 milligrams per deciliter or higher. Patients must also have either established cardiovascular disease or diabetes and two or more additional risk factors for cardiovascular disease. Patients are advised to continue physical activity and maintain a healthy diet.

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M… …hael Miller, M.D.,
Eliot A. Brinton, M… …Ketchum, Ph.D.,
Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D.,
Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and
Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

2019 NEJM REDUCE-IT

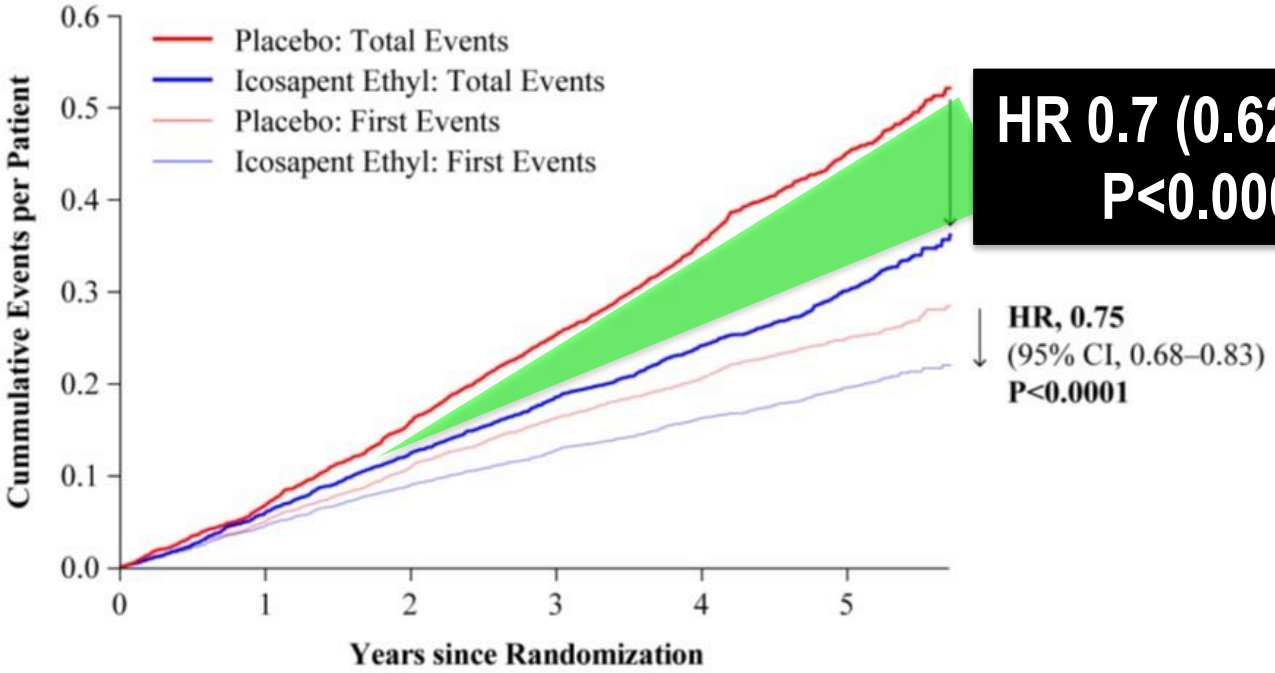
Characteristic	Icosapent Ethyl (N = 4089)	Placebo (N = 4090)
Age		
Median (IQR) — yr	64.0 (57.0–69.0)	64.0 (57.0–69.0)
≥65 yr — no. (%)	1857 (45.4)	1906 (46.6)
Male sex — no. (%)	2927 (71.6)	2895 (70.8)
White race — no. (%)†	3691 (90.3)	3688 (90.2)
Body-mass index‡		
Median (IQR)	30.8 (27.8–34.5)	30.8 (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)

DOI: 10.1056/NEJMoa1812792

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

N=8,179, median TG 216 mg/dl, treat EPA 4g/day 4.9years

A Primary Composite Endpoint

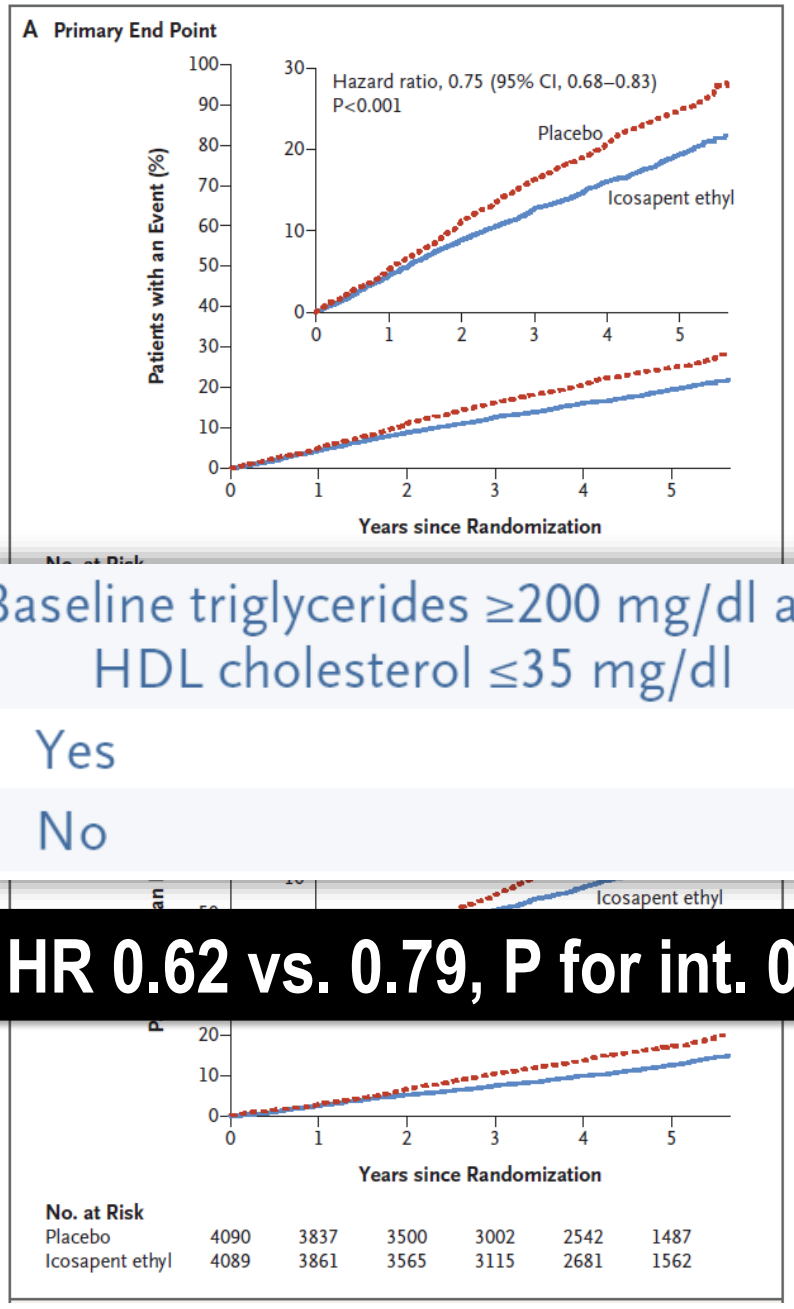


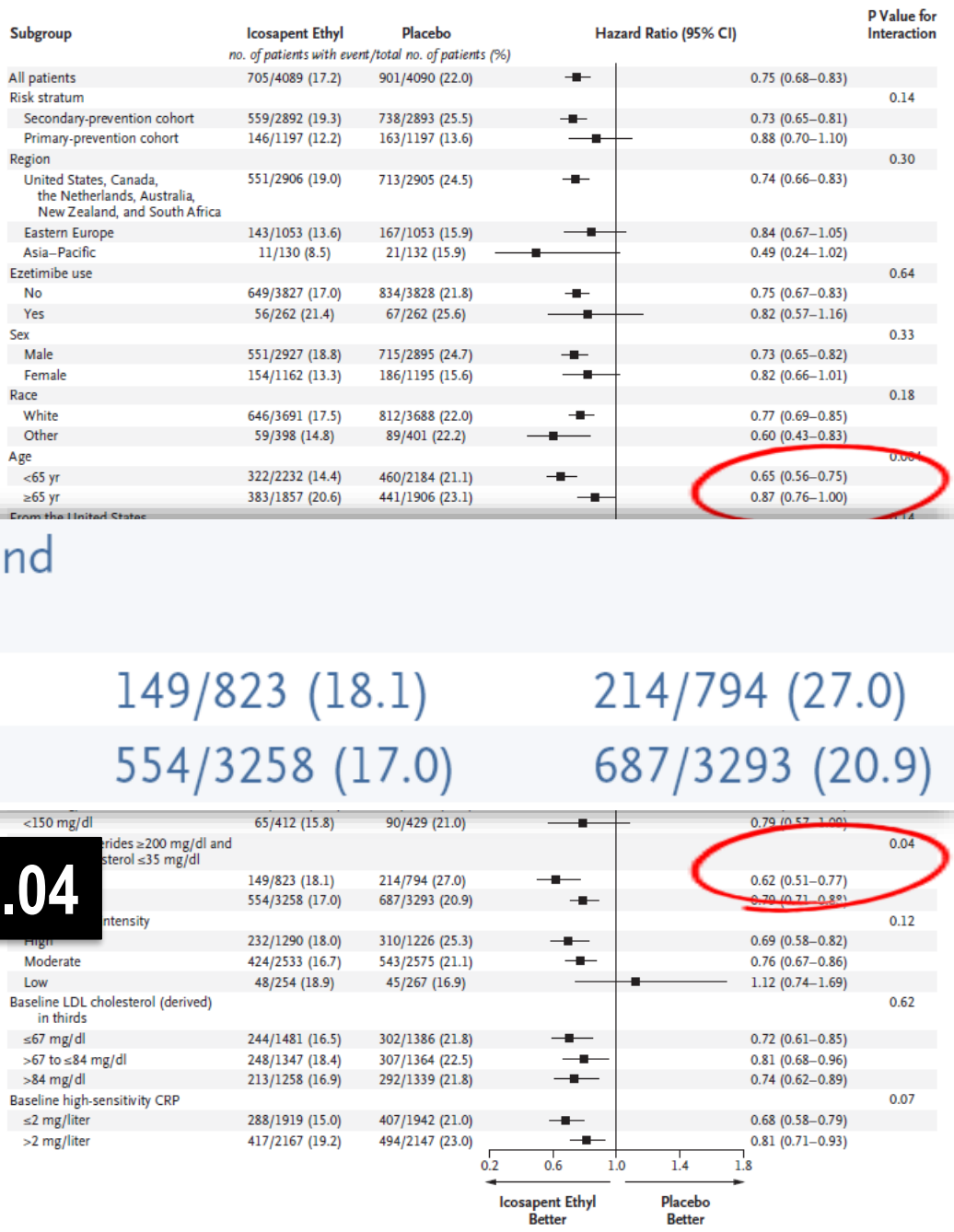
No. at Risk*

Placebo	4090	3914	3674	3236	2788	1653
Icosapent Ethyl	4089	3933	3701	3276	2861	1692

The primary efficacy end point was a composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina

DOI: 10.1056/NEJMoa1812792





Baseline triglycerides ≥200 mg/dl and HDL cholesterol ≤35 mg/dl

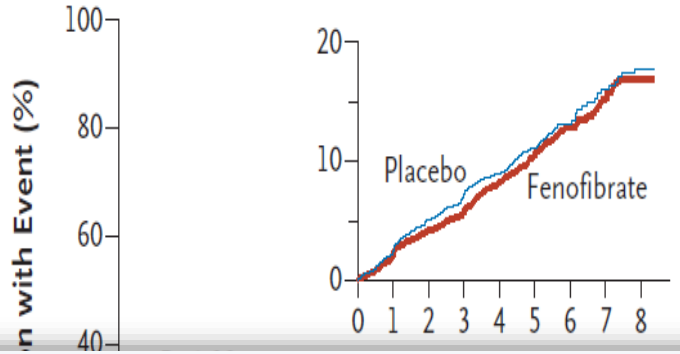
Yes	149/823 (18.1)	214/794 (27.0)
No	554/3258 (17.0)	687/3293 (20.9)

HR 0.62 vs. 0.79, P for int. 0.04

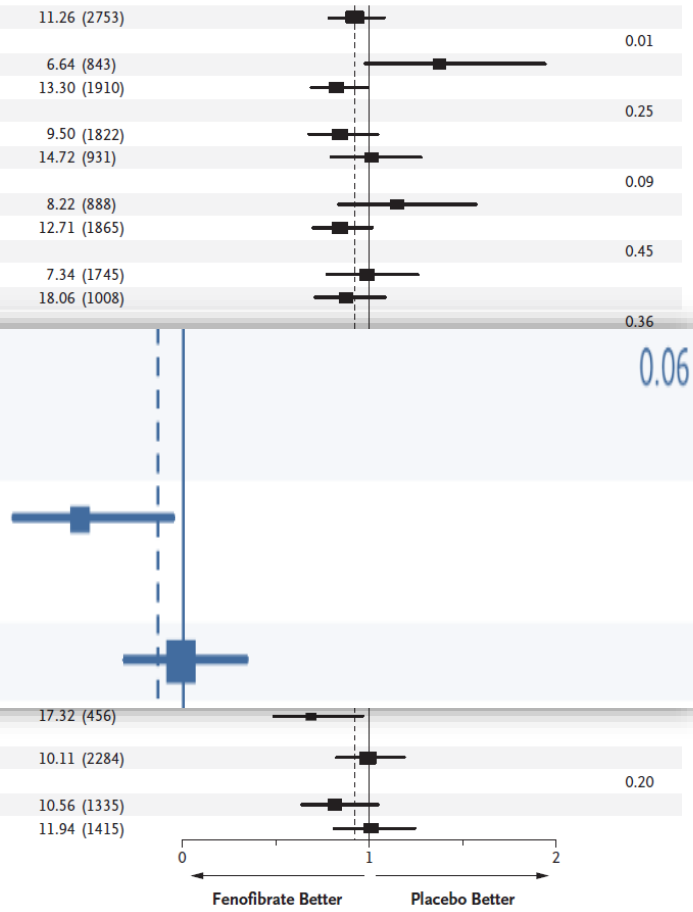
DOI: 10.1056/NEJMoa1812792

Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus

2010 NEJM ACCORD-lipid



Subgroup	Fenofibrate	Placebo	P Value for Interaction
	% of events (no. in group)		
Overall	10.52 (2765)	11.26 (2753)	
Sex			0.01
Female	9.05 (851)	6.64 (843)	
Male	11.18 (1914)	13.30 (1910)	
Age			0.25
<65 yr	8.11 (1838)	9.50 (1822)	
≥65 yr	15.32 (927)	14.72 (931)	
Race			0.09
Nonwhite	9.70 (856)	8.22 (888)	
White	10.90 (1909)	12.71 (1865)	
Previous cardiovascular disease			0.45
No	7.29 (1757)	7.34 (1745)	
Yes	16.17 (1008)	18.06 (1008)	
Glycemia group			0.36
Triglyceride–HDL cholesterol combination			0.06
Triglyceride ≥204 mg/dl and HDL ≤34 mg/dl	12.37 (485)	17.32 (456)	
All others	10.11 (2264)	10.11 (2284)	
Glycated hemoglobin			0.20
≤8.0%	8.69 (1324)	10.56 (1335)	
≥8.1%	12.20 (1435)	11.94 (1415)	



No. at Risk

Fenofibrate	2765	2644	2565	2485	1981	1160	412	249	137
Placebo	2753	2634	2528	2442	1979	1161	395	245	131

N Engl J Med 2010;362:1563-74.

EPA showed survival benefit on patients under hemodialysis in small RCT and cohort studies

Table 1. Effects of EPA on cardiovascular outcomes in hemodialysis patients

First author [Ref.], year	Study design	EPA dose, g/day	Follow-up, years	Clinical outcome (EPA vs. control)
Nasu [26][a], 2013	179 subjects (EPA [n = 89] vs. control [n = 90]); prospective, randomized, open-label trial	1.8	2	EPA decreased CV death by 80% (p = 0.037), CV events by 50% (p = 0.039), and CV death or events by 51% (p = 0.021)
Inoue [27], 2015	176 subjects (EPA [n = 51] vs. no EPA [n = 125]); longitudinal, observational cohort study	1.8	3	EPA decreased all-cause mortality by 58% (p = 0.034)
Umemoto [28][a], 2015	459 subjects (EPA [n = 106] vs. no EPA [n = 353]); both groups received standard therapy; longitudinal, observational study	0.9	3	EPA decreased all-cause mortality by 47% (p = 0.023) and CV mortality by 59% (p = 0.029)

CV, cardiovascular; EPA, eicosapentaenoic acid. [a] Preliminary evidence; data from European Society of Cardiology abstract.

Cardiorenal Med 2018;8:18–30

Statins had no impact on all cause or cardiovascular mortality in dialysis patients.

Study or Subgroup	Statin therapy Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4D2005	121	619	149	636	23.2%	0.83 [0.67, 1.03]
AURORA2009	324	1389	324	1384	51.1%	1.00 [0.87, 1.14]
SHARP2011	172	1533	161	1490	25.7%	1.04 [0.85, 1.27]
Total (95% CI)		**3541**		**3510**	**100.0%**	**0.97 [0.88, 1.07]**
Total events	617		634			

Heterogeneity: Chi² = 2.51, df = 2 (P = 0.29); I² = 20%
Test for overall effect: Z = 0.61 (P = 0.54)

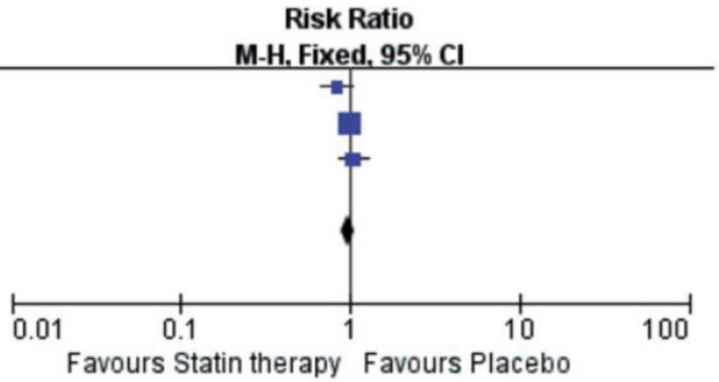


Figure 8. Forest plot of comparison for cardiovascular deaths: statin therapy versus placebo.

Study or Subgroup	Statin therapy Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4D2005	297	619	320	636	21.6%	0.95 [0.85, 1.07]
AURORA2009	636	1389	660	1384	45.2%	0.96 [0.89, 1.04]
SHARP2011	507	1533	480	1490	33.3%	1.03 [0.93, 1.14]
Total (95% CI)		**3541**		**3510**	**100.0%**	**0.98 [0.93, 1.04]**
Total events	1440		1460			

Heterogeneity: Chi² = 1.28, df = 2 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.69 (P = 0.49)

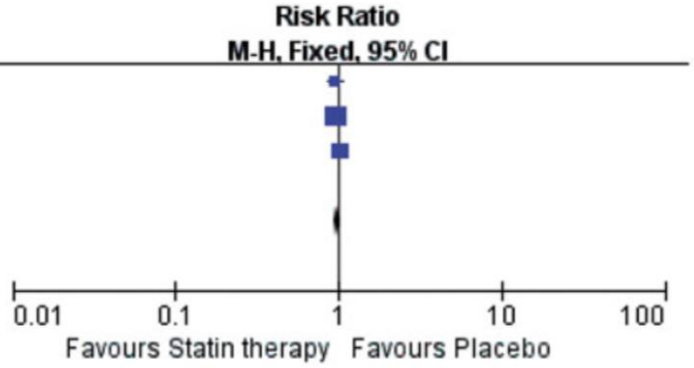


Figure 9. Forest plot of comparison for all-cause mortality: statin therapy versus placebo.

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk* 2019年歐洲心臟學會建議

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

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

In high-risk (or above) patients with TG between 135 - 499 mg/dL, despite statin treatment, n-3 PUFAs (icosapent ethyl 2 *2g/day) should be considered in combination with statins.

(> 190 mmol/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.

National Lipid Association Scientific Statement on Icosapent Ethyl

Dec 03, 2019 | Sherrie R. Webb, PA-C

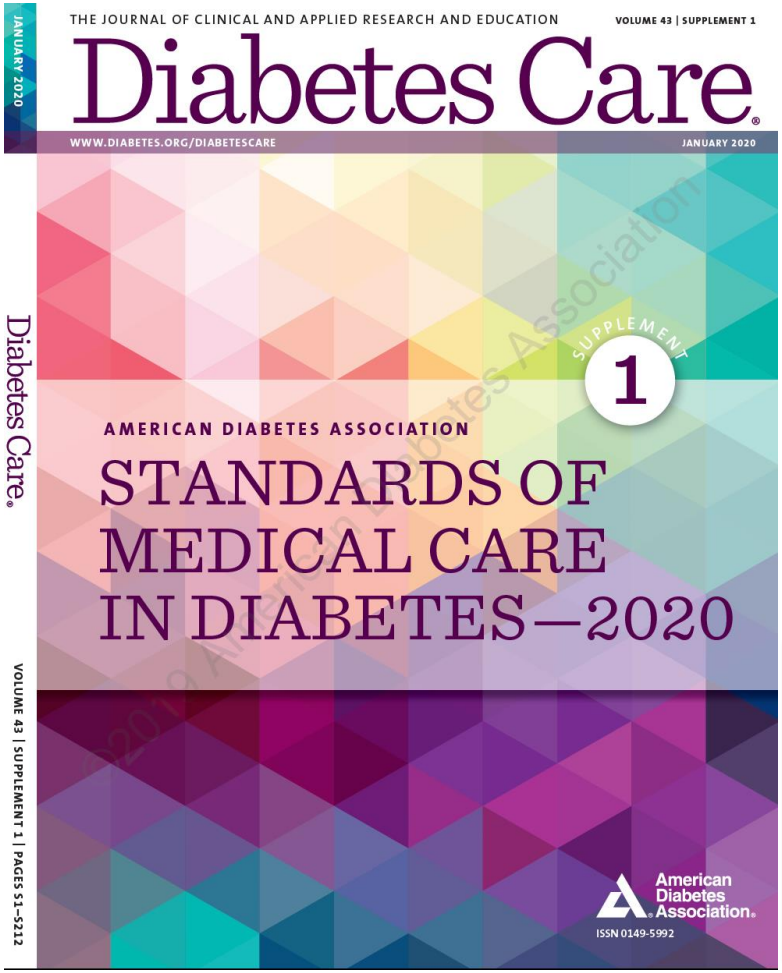
2019年美國心臟學會建議

The National Lipid Association now makes a Class I recommendation for use of IPE (4 g/d) to reduce cardiovascular risk in patients

- ≥45 years of age with clinical atherosclerotic cardiovascular disease (ASCVD) or
- ≥50 years of age with diabetes mellitus requiring medication and ≥1 additional risk factor;
- already on high-intensity or maximally tolerated statin therapy;
- with fasting triglycerides 135-499 mg/dL; and
- with or without ezetimibe.

https://www.acc.org/latest-in-cardiology/ten-points-to remember /2019/12/03/15/51/ national-lipid-association-scientific-statement-on-icosapent ethyl

2020年ADA (美國糖尿病學會)
治療指引也將純EPA納入建議

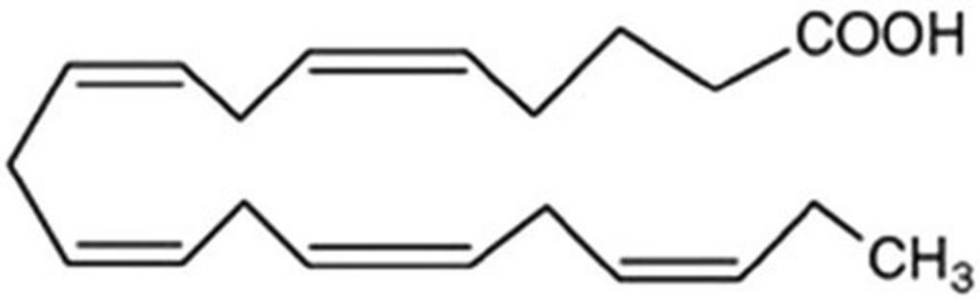


In patients with atherosclerotic cardiovascular disease or other cardiovascular risk factors on a statin with controlled LDL cholesterol but elevated triglycerides (135–499 mg/dL), the addition of icosapent ethyl can be considered to reduce cardiovascular risk. **A**

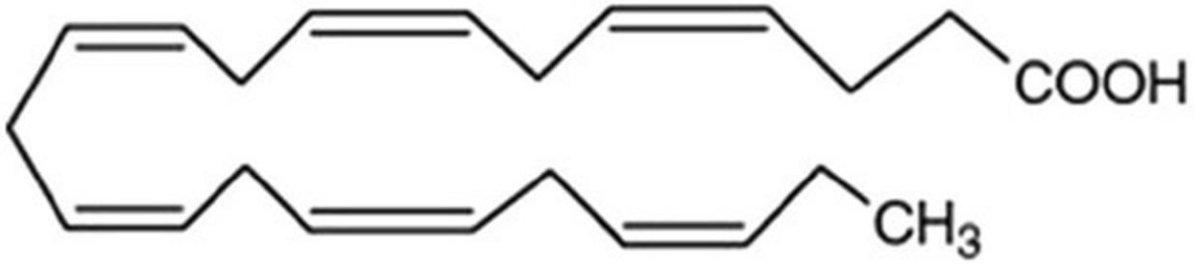
Outlines

- What is EPA ?
- EPA/DHA for secondary prevention
- EPA/DHA for primary prevention
- **Why is EPA not DHA effective for *1st* prevention ?**

EPA and DHA



Eicosapentaenoic acid



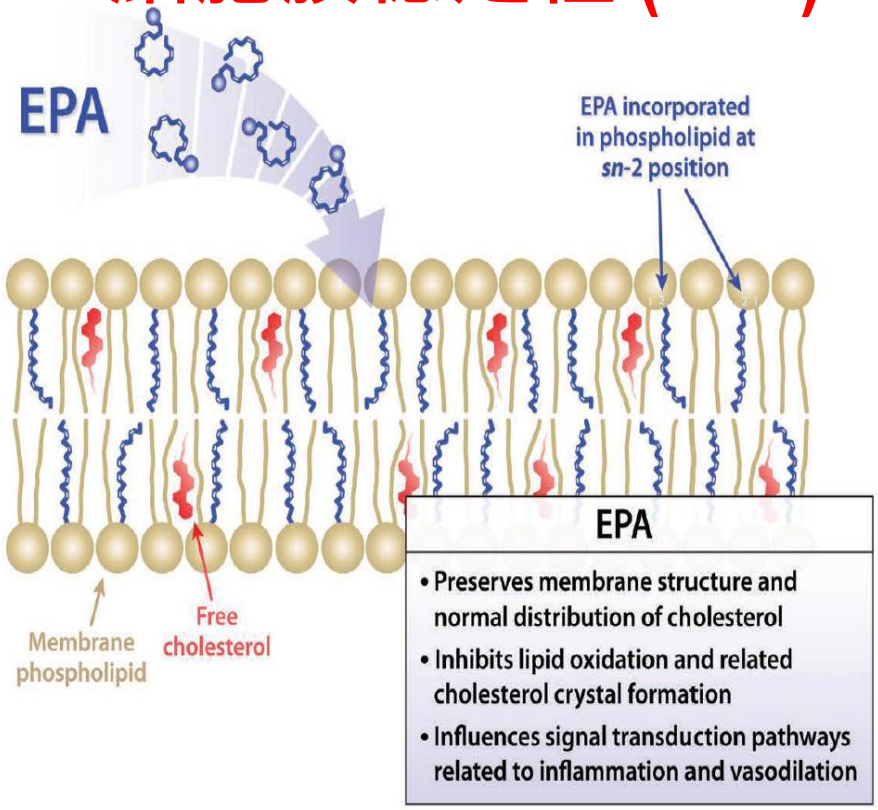
Docosahexaenoic acid

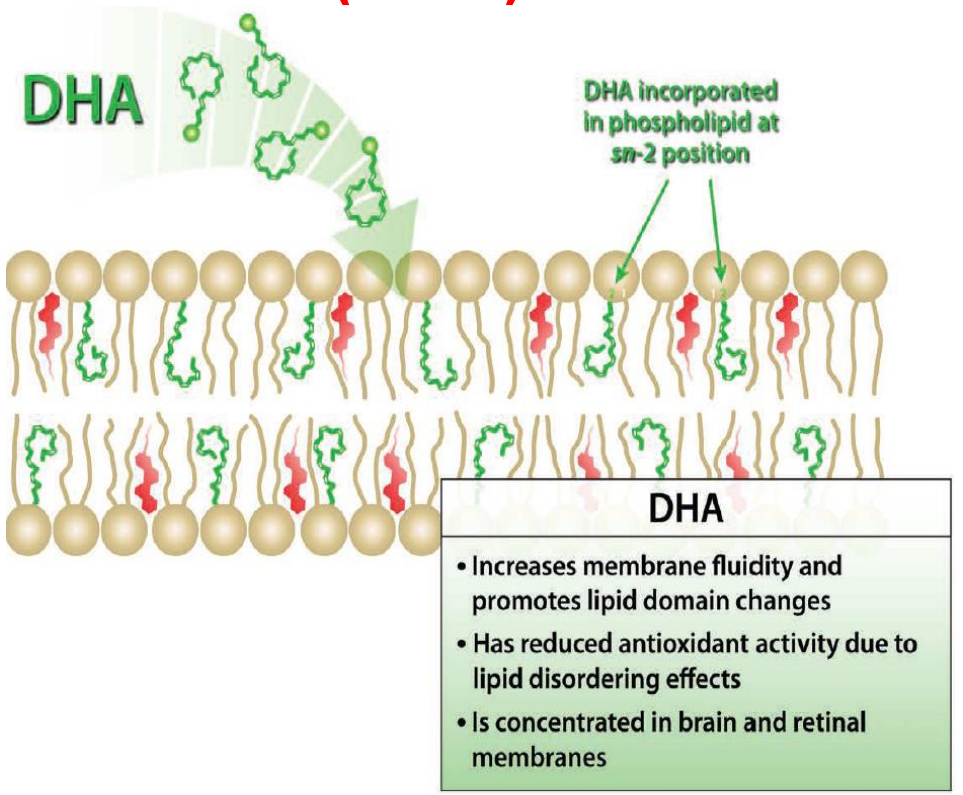
EPA / DHA and cell biology

Emerging Mechanisms of Cardiovascular Protection for the Omega-3 Fatty Acid Eicosapentaenoic Acid

R. Preston Mason, Peter Libby, Deepak L. Bhatt

細胞膜穩定性 (EPA) vs. 流動性 (DHA)

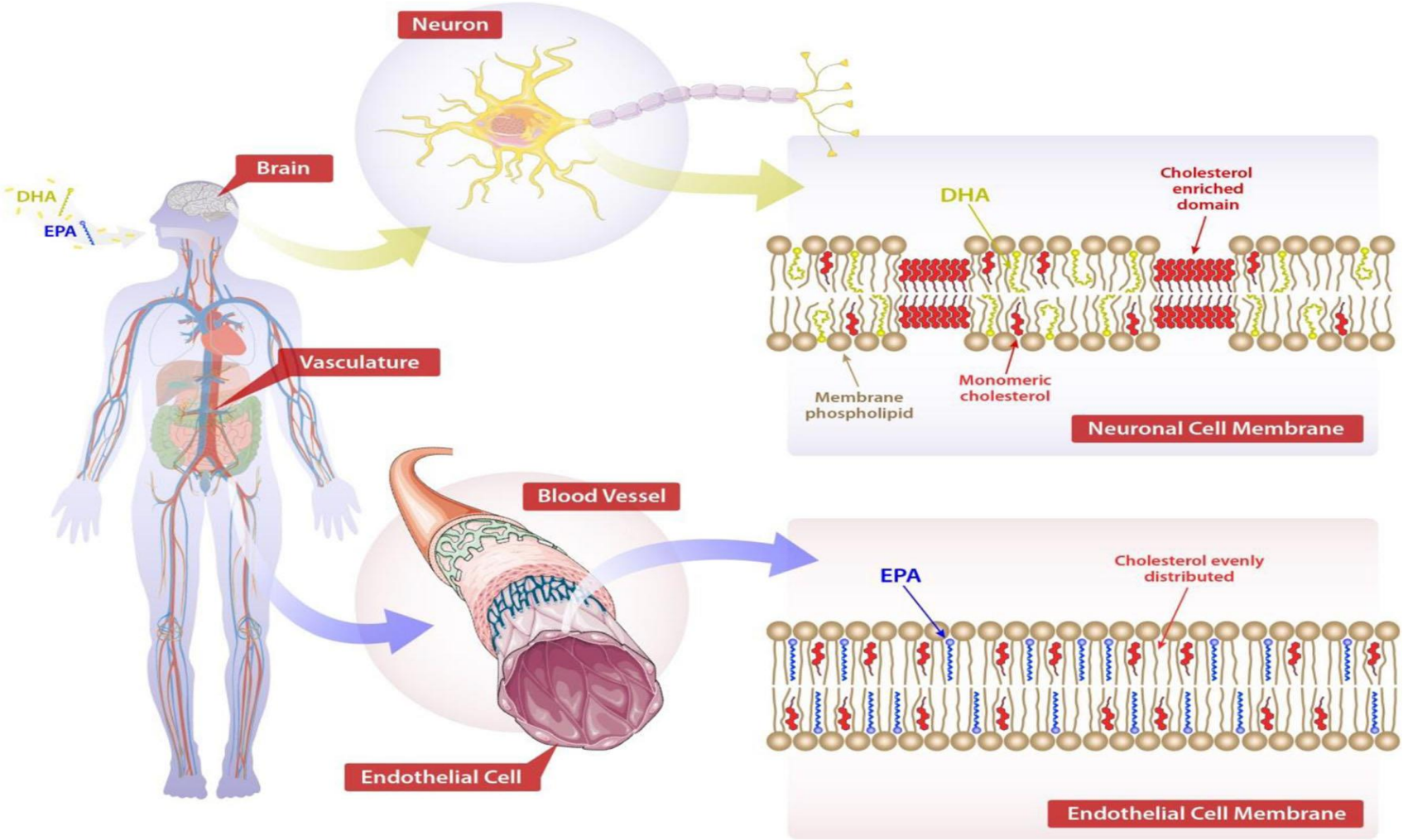




Arterioscler Thromb Vasc Biol 2020 May;40(5):1135-1147.

New Insights into Mechanisms of Action for Omega-3 Fatty Acids in Atherothrombotic Cardiovascular Disease

不同細胞, 膽固醇在細胞膜的分布不同



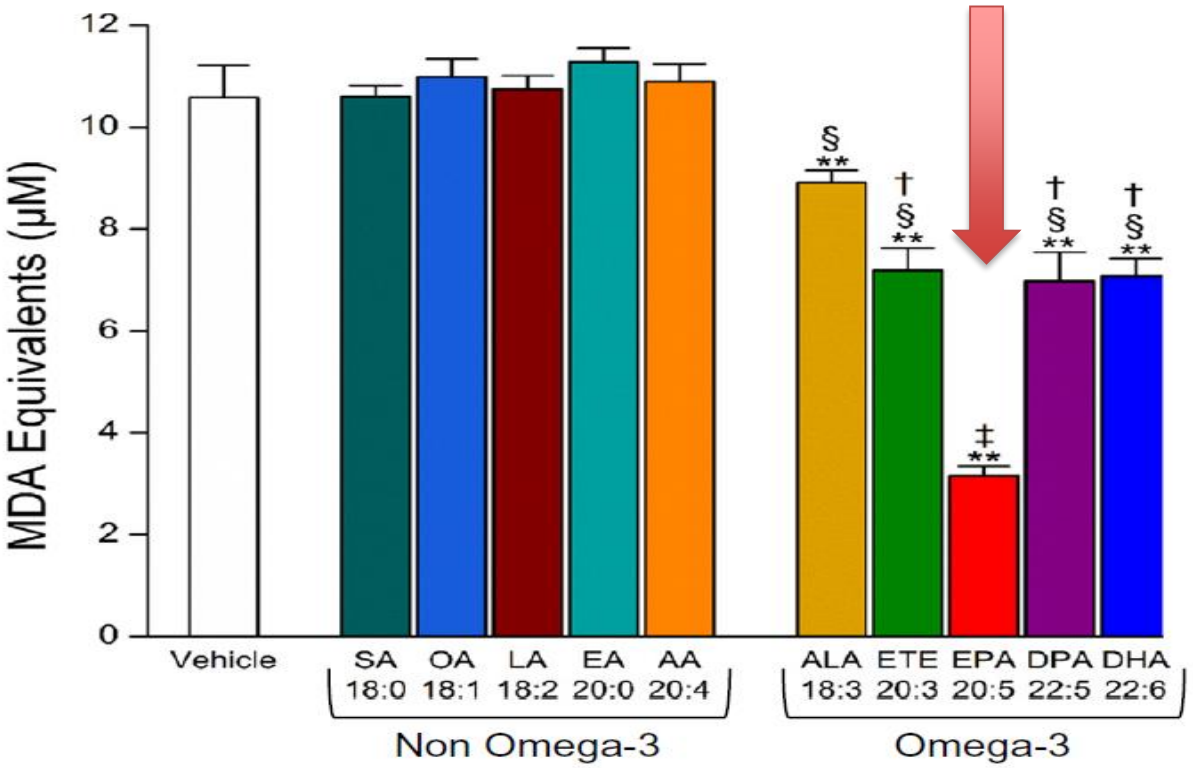
Curr Atheroscler Rep. 2019; 21(1): 2.

Eicosapentaenoic acid (EPA) has optimal chain length and degree of unsaturation to inhibit oxidation of small dense LDL and membrane cholesterol domains as compared to related fatty acids in vitro

Samuel C.R. Sherratt[a], Rebecca A. Juliano[b], R. Preston Mason[a,c,*]

[a] *Elucida Research LLC, Beverly, MA 01915-0091, USA*
[b] *Amarin Pharma, Inc., Bridgewater, NJ, USA*
[c] *Department of Medicine, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115-6110, USA*

EPA 較其他 fatty acid 減少氧化壓力



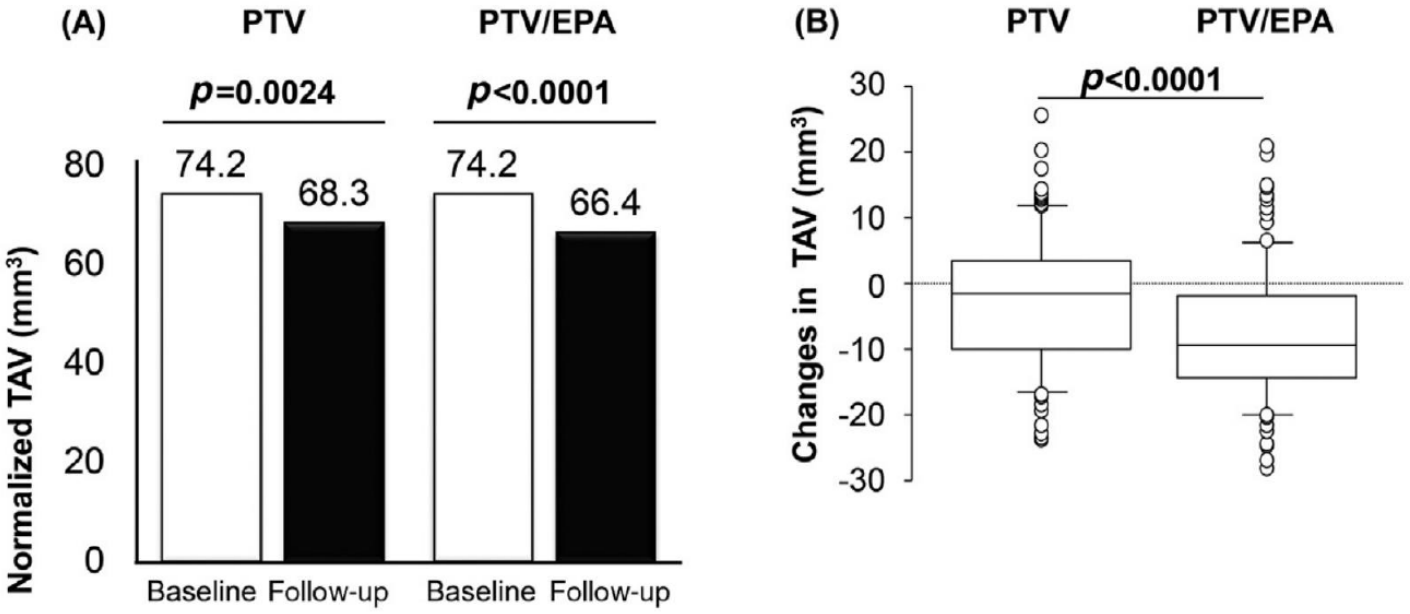
Malondialdehyde (MDA) is a marker for oxidative stress

Biochim Biophys Acta Biomembr 2020 Jul 1;1862(7):183254

Combination EPA/pitavastatin therapy significantly reduced coronary plaque volume compared to PTV therapy alone. Plaque stabilization was also reinforced by EPA/pitavastatin therapy.

Statin加上EPA 更減少冠狀動脈斑塊

EPA=1.8g/day



Methods: We enrolled **193 CHD patients** who underwent percutaneous coronary intervention (PCI) in six hospitals. Patients were randomly allocated to the PTV group (PTV 4 mg/day, n = 96) or PTV/EPA group (**PTV 4 mg/day** and **EPA 1800 mg/day**, n = 97), and prospectively followed for 6–8 months. **Coronary plaque volume** and composition in nonstenting lesions were analyzed by integrated backscatter intravascular ultrasound (IB-IVUS).

Journal of Cardiology 70 (2017) 537–544

New Insights into Mechanisms of Action for Omega-3 Fatty Acids in Atherothrombotic Cardiovascular Disease

EPA 增加.....

- Endothelial function
- NO bioavailability
- EPA/AA ratio
- IL-10
- Fibrous cap thickness
- Lumen diameter
- Plaque stability

EPA 減少.....

- Cholesterol crystalline domains
- oxLDL
- RLP-C
- Adhesion of monocytes
- Macrophages
- Foam cells
- IL-6
- ICAM-1
- hsCRP
- Lp-PLA_2
- Plaque volume
- Arterial stiffness
- Plaque vulnerability
- Thrombosis
- Platelet activation

Curr Atheroscler Rep. 2019; 21(1): 2.

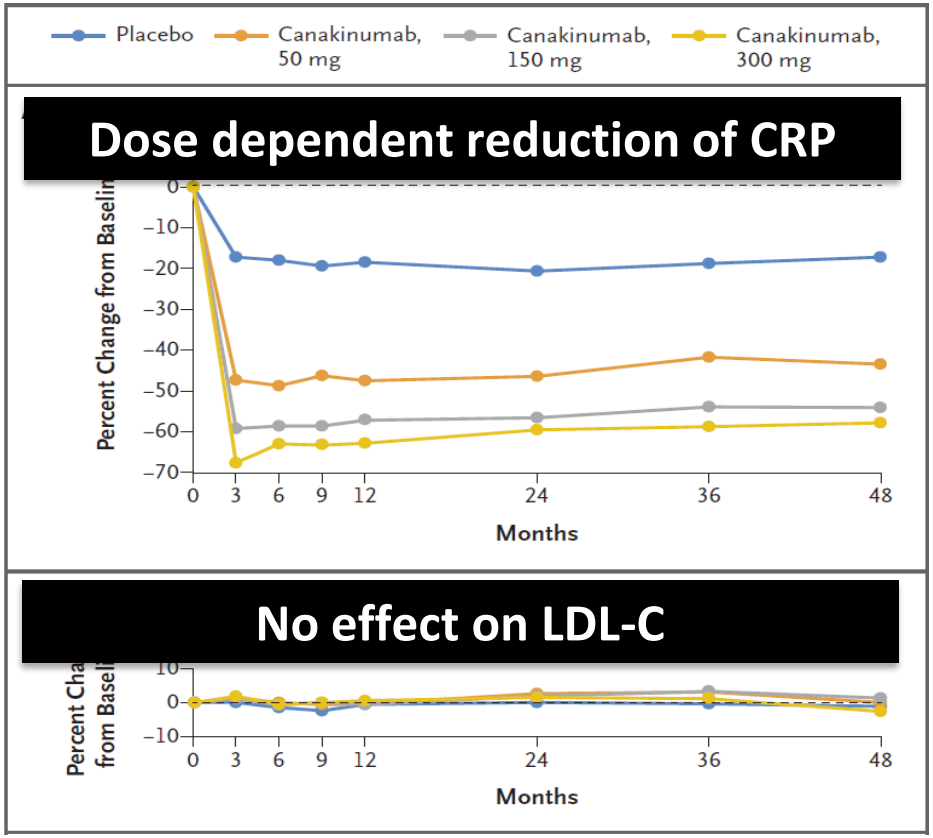
Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

P.M. Ridker, B.M. Everett, T. T… onseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H… enzatti, T. Forster, Z. Kobalava, L. Vida-Simiti, M. Flathe… R.P.T. Troquay, P. Libby, and R.J. Glynn, for the CANTOS Trial Group*

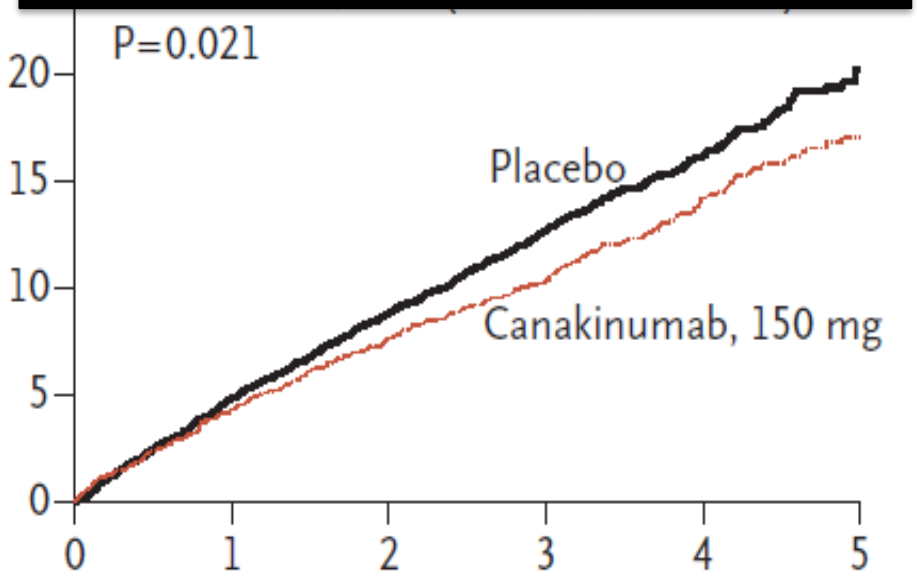
2017 NEJM CANTOS

Canakinumab: monoclonal antibody to interleukin-1β

10,061 patients with previous MI and CRP > 2 mg/dL



Non-fatal MI, stroke, and CV death
3.86 vs 4.5/100p-y, HR 0.85, p=0.021



N Engl J Med 2017;377:1119-31

EPA / DHA and lipid profile

Review of Cardiometabolic Effects of Prescription Omega-3 Fatty Acids

DHA + EPA 可能導致 LDL-C上升

Megan F. Burke [1] · Frances M. Burke [2] · Daniel E. Soffer [3]

	EPA + DHA EE	EPA-only EE	EPA + DHA FFA
Brand name	Lovaza®, Omtryg™[a]	Vascepa®	Epanova®
Generic available	Yes	No	No
EPA/DHA (%)	55/45	100/0	73/27
n-3FA g/capsule	EPA 0.465 g DHA 0.375 g	EPA 1 g	EPA 0.550 g DHA 0.20 g
Regimen, capsules	2 caps twice daily or 4 caps daily with meals	2 caps twice daily	2 caps twice daily or 4 caps daily with or without meals
TG	− 51.6	− 33[b]	− 21[b]
LDL-C	+ 49.3	− 2	+ 15
VLDL-C	− 40.8	− 29[b]	− 21
apoB	Not reported	− 9[b]	+ 2

TG -52% -33% -21%

LDL-C +49% -2% +15%

FDA仿單資料

Curr Atheroscler Rep (2017) 19: 60

HIGHLIGHTS OF PRESCRIBING INFORMATION

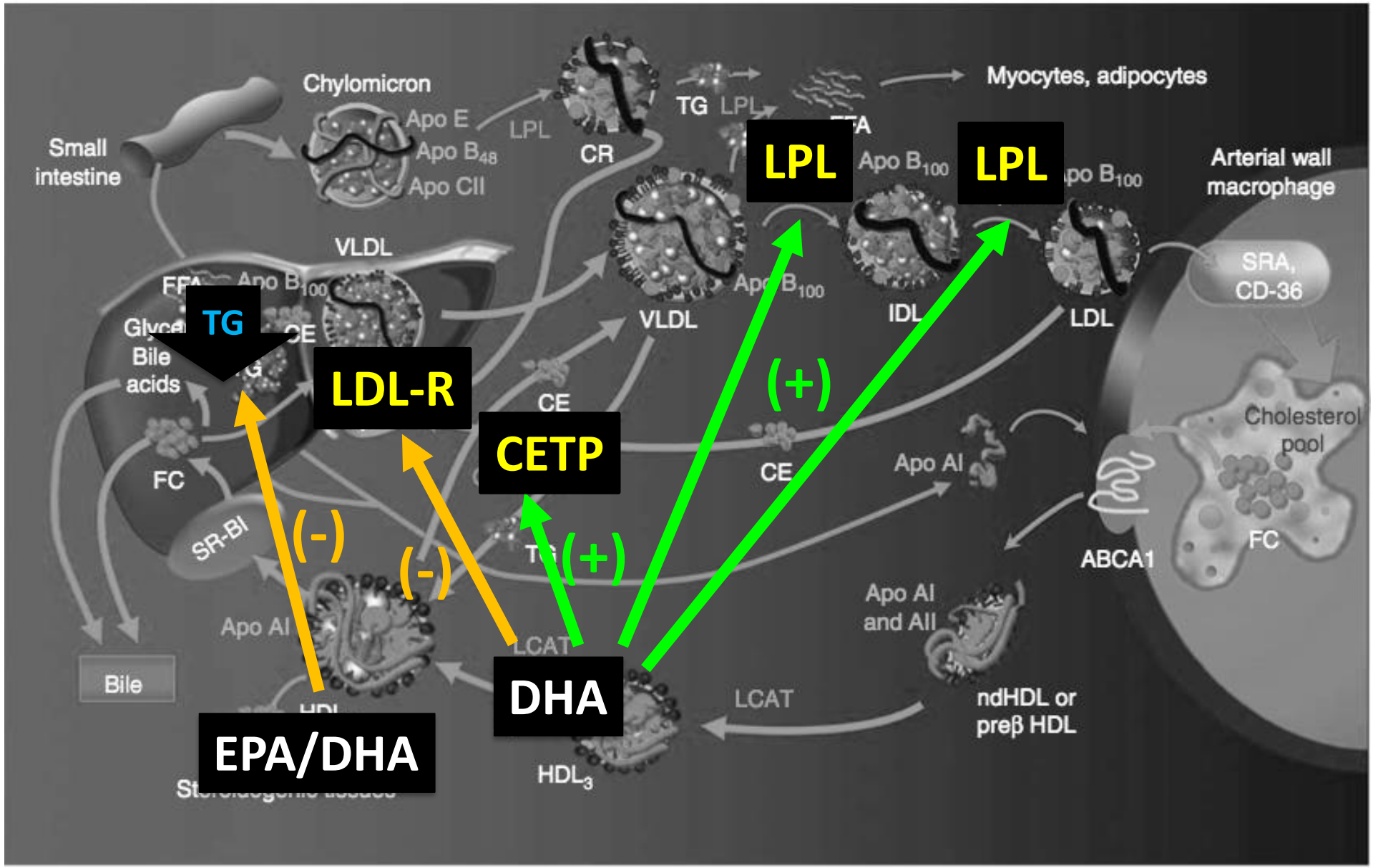
These highlights do not include all the information needed to use OMTRYG™ safely and effectively. See full prescribing information for OMTRYG.

OMTRYG (omega-3-acid ethyl esters A) capsules, for oral use
Initial U.S. Approval: 2004

Parameter	Omega-3-Acid Ethyl Esters* N = 42		Placebo N = 42		Difference
	BL	% Change	BL	% Change	
TG	816	-44.9	788	+6.7	-51.6

Parameter	Omega-3-Acid Ethyl Esters* N = 42		Placebo N = 42		Difference
	BL	% Change	BL	% Change	
Non-HDL-C	271	-13.8	292	-3.6	-10.2
TC	296	-9.7	314	-1.7	-8.0
VLDL-C	175	-41.7	175	-0.9	-40.8
HDL-C	22	+9.1	24	0.0	+9.1
LDL-C	89	+44.5	108	-4.8	+49.3

DHA讓LDL-C上升的可能機轉



Brinton and Mason Lipids in Health and Disease (2017) 16:23

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VASCEPA® safely and effectively. See full prescribing information for VASCEPA.

VASCEPA® (icosapent ethyl) capsules, for oral use
Initial U.S. Approval: 2012

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	12/2019
Warnings and Precautions, Atrial Fibrillation/Flutter (5.1)	12/2019
Warnings and Precautions, Bleeding (5.3)	12/2019

----------INDICATIONS AND USAGE----------

VASCEPA is an ethyl ester of eicosapentaenoic acid (EPA) indicated:

- 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
    - diabetes mellitus and 2 or more additional risk factors for cardiovascular disease. (1)
- as an adjunct to diet to reduce TG levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia. (1)

----------WARNINGS and PRECAUTIONS----------

May increase the risk of AF/AFL

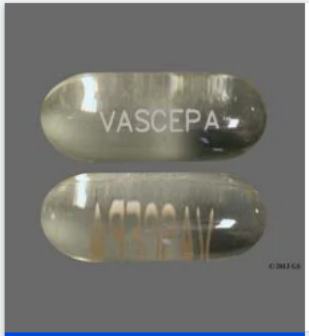
ed with an increased risk
lization in a double-blind,
placebo-controlled trial. The incidence of atrial fibrillation was greater in patients with a previous history of atrial fibrillation or atrial flutter. (5.1)

Potential allergic reaction in patients with fish allergy

obtained from the oil of fish. It is not known whether patients with allergies to fish and/or shellfish are at increased risk of an allergic reaction to VASCEPA. Inform patients with known hypersensitivity to fish and/or shellfish about the potential for allergic reactions and advise them to discontinue VASCEPA and

May increase the risk of bleeding
(serious bleeding 3% vs. 2% in REDUCED-IT)

ed risk of bleeding in a
of bleeding was greater in patients receiving concomitant antithrombotic medications, such as aspirin, clopidogrel, or warfarin. (5.3)



Vascepa Icosapent Ethyl

Vascepa (icosapent ethyl) is used to treat high triglyceride levels. It is more popular than other comparable drugs. There are currently no generic alternatives to Vascepa.

GoodRx has partnered with InsideRx and Amarin to reduce the price for this prescription. Check our savings tips for co-pay cards, assistance programs, and other ways to reduce your cost. Vascepa is covered by some Medicare and insurance plans.

Prescription Settings | brand | capsule | 1g | 120 capsules | SHARE

- Prices
- Medicare
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Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

2018 NEJM ODYSSEY OUTCOME

G.G. Schwartz, , S.G. Goodman, C. Hanotin, R.A. H Pordy, K. Quintero, M.T. Roe, W.J. Sasiela, J.-F. Tamby, P. Tricoci, H.D. White, and A.M. Zeiher, for the ODYSSEY OUTCOMES Committees and Investigators*

18,924 patients with ACS 1 to 12 months earlier, , LDL-C > 70mg/dL

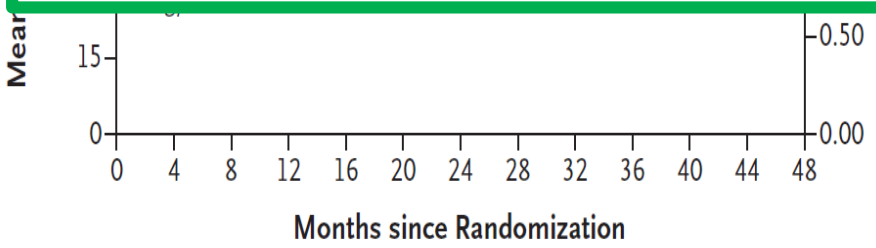
LDL-C 92 to 38 mg/dL

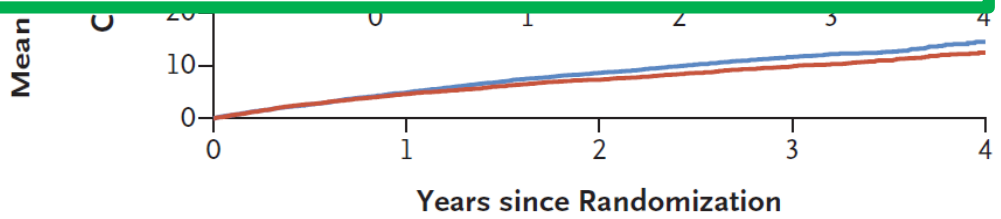
9.5% vs. 11.1%, RR 0.85

ODYSSEY: median f/u period 34m, LDL-C 92 vs. 38 mg/dL

Primary efficacy EP 9.5% vs. 11.1%, NNT = 62.5/event

Cost : 9,176 * 34 * 62.5 = 19,499,000 / event





N Engl J Med 2018;379:2097-107.

Take home messages

1g Omega-3 mixture is effective for secondary prevention but not for primary prevention.

High dose of EPA(1.8~4g) has been proved effective for both secondary and high risk primary prevention according recent clinical trials.

"In patients with ASCVD or other cardiac risk factors on a statin and elevated TG level, addition of EPA should be considered to reduce cardiovascular risk" recommended by ADA, ACC, and ESC.

健保的資源有限
人類的慾望無窮

The story never ends...