台灣血脂衛教協會
南部學術研討會

Icosapent Ethyl EPA & Cardiovascular Outcomes

Insights From Recent Clinical Trials

高雄市立大同醫院（高醫）
心臟血管內科
朱志生 主治醫師
Chih-Sheng Chu, MD, PhD

2020-07-12 (Sun)

Contents

- **Omega-3 in TG lowering**
- **What is EPA ?**
- **EPA/DHA & *2nd* prevention in clinical ASCVD**
- **EPA/DHA & *1st* prevention**
- **Why is EPA not DHA effective for *1st* prevention ?**
- **How to choice EPA product ?**
- **Conclusions**

三酸甘油酯 200-499要小心

三酸甘油酯濃度如果偏高

糖尿病患者必須特別注意!!

除了血糖高，多數亦有三酸甘油酯偏高

美國糖尿病協會及國家膽固醇教育計畫成人治療第三版建議，至少需控制在 **200mg/dl** 以內

三酸甘油酯 >500要著急

增加罹患

冠狀動脈心臟病的風險

罹患 **急性胰臟炎**

什麼是急性胰臟炎？
會有左上腹痛、背痛、嘔吐、噁心、便秘、發燒畏寒等症狀，嚴重還會併發急性腎衰竭、呼吸衰竭，甚至有生命危險

館長洗油

可靠洗腎儀器治療 平時少吃炸物甜食

顏宗海表示，三酸甘油脂指數若超過500 mg/dL，就得注意患急性胰臟炎的風險，造成急性胰臟炎原因大多是膽道系統結石、酒精過量引起，會出現腹痛、嘔吐、意識不清，是得住院治療的大病。少數三酸甘油脂過高患者，透過飲食調整、藥物控制，指數仍居高不下，可請專科醫師評估，申請使用血漿置換術，透過洗腎儀器讓血液在體外循環，能快速有效控制。而像糖尿病、甲狀腺疾病、腎病症候群等續發性的患者，則建議除了得控制三酸甘油脂，也得找出根本原因一起治療，避免血脂暴衝。

輔大醫院研究副院長盧國城表示，一般需要做血漿置換術的患者大多是先天血脂代謝能力不良者，且已對心臟、胰臟出現影響，緊急做血漿置換術可快速舒緩症狀。而平日大吃大喝、睡眠不夠等造成的高血脂患者，通常不建議做血漿置換術，避免感染風險。

盧國誠表示，不一定肥胖者才容易有高血脂，建議民眾趁例行健檢，抽血檢查有無三酸甘油脂過高。如有高血脂，平時不要暴飲暴食，少吃甜食和炸物，養成運動習慣，控制體重，使用降血脂藥物效果也會較好。

2.6.1 全民健康保險降血脂藥物給付規定 (2)

（86/1/1、87/4/1、87/7/1、91/9/1、93/9/1、97/7/1、102/8/1）

全民健康保險降三酸甘油酯藥物給付規定表				
	非藥物治療	起始藥物治療三酸甘油酯值	三酸甘油酯目標值	處方規定
心血管疾病或糖尿病病人	與藥物治療可並行	TG≧200mg/dL且(TC/HDL-C>5或HDL-C<40mg/dL)	TG < 200mg/dL	第一年應每3-6個月抽血檢查一次，第二年以後應至少每6-12個月抽血檢查一次，同時請注意副作用之產生如肝功能異常，橫紋肌溶解症。
無心血管疾病病人	給藥前應有3-6個月非藥物治療	TG≧200mg/dL且(TC/HDL-C>5或HDL-C<40mg/dL)	TG < 200mg/dL	
無心血管疾病病人	與藥物治療可並行	TG≧500mg/dL	TG < 500mg/dL	

心血管疾病定義：

(一) 冠狀動脈粥狀硬化病人：心絞痛病人，有心導管證實或缺氧性心電圖變化或負荷性試驗陽性反應者(附檢查報告)

(二) 缺血型腦血管疾病病人包含：

1.腦梗塞。

2.暫時性腦缺血患者(TIA)。（診斷須由神經科醫師確立）

3.有症狀之頸動脈狹窄。（診斷須由神經科醫師確立）

OMEGA-3 VS 現行降TG藥物
療效差不多

Table 12. Effect of Lipid-Lowering Therapies on Triglyceride Reduction[504,480a–480d]

Drug	% Triglyceride Reduction
Fibrates	30–50
Immediate-release niacin	20–50
Omega-3	20–50
Extended-release niacin	10–30
Statins	10–30
Ezetimibe	5–10

降三酸甘油脂為主藥物

降膽固醇為主藥物

Circulation. 2011;123:2292-2333.

別再每天吃一堆保健食品 美研究：只有2樣值得買

2019-08-09 10:22 世界日報 編譯陳韻涵／綜合報導

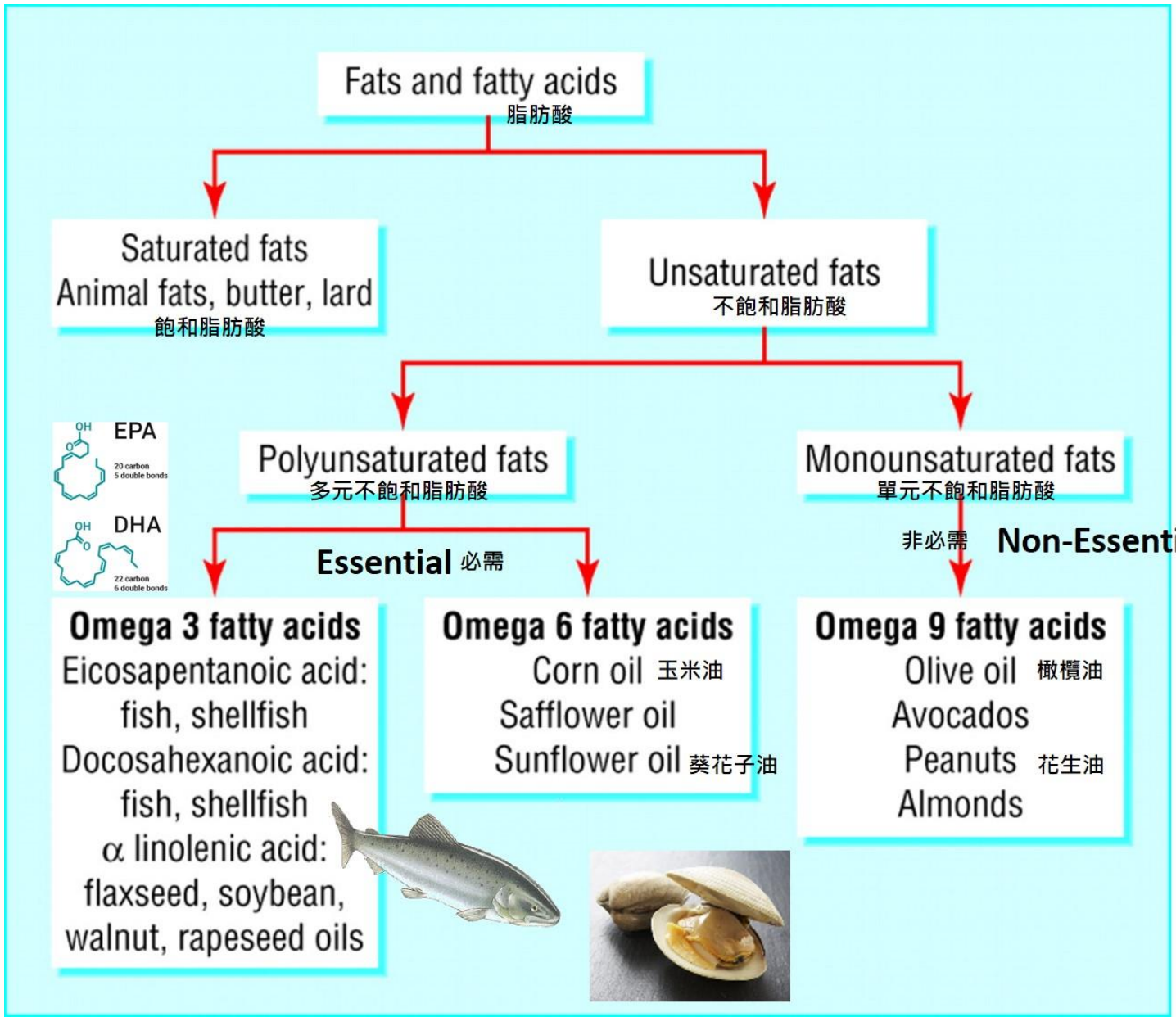
美國骨科協會表示，86%的美國人服用至少一種維他命保健，但發表於「內科醫學年刊」的研究指出，多數維他命和營養食品在維護心臟健康和延長壽命方面，不如人們想得這麼有幫助，只有**葉酸**(folate)和**魚油**值得買。

研究團隊分析227項臨床實驗計畫和15種營養品，包括抗氧化劑、β-胡蘿蔔素、維他命B複合物、多種維他命、維他命A、維他命B3(菸鹼酸，niacin)、維他命B6、維他命C、維他命E、**維他命D**、鈣、「鈣與維他命D複合物」、葉酸、鐵和ω-3脂肪酸。

結果顯示，幾乎所有接受測試的營養品與延長使用者壽命或維護心臟健康都沒有顯著關係；事實上，部分營養品，尤其是「鈣與維他命D複合物」可能增加中風的機率。

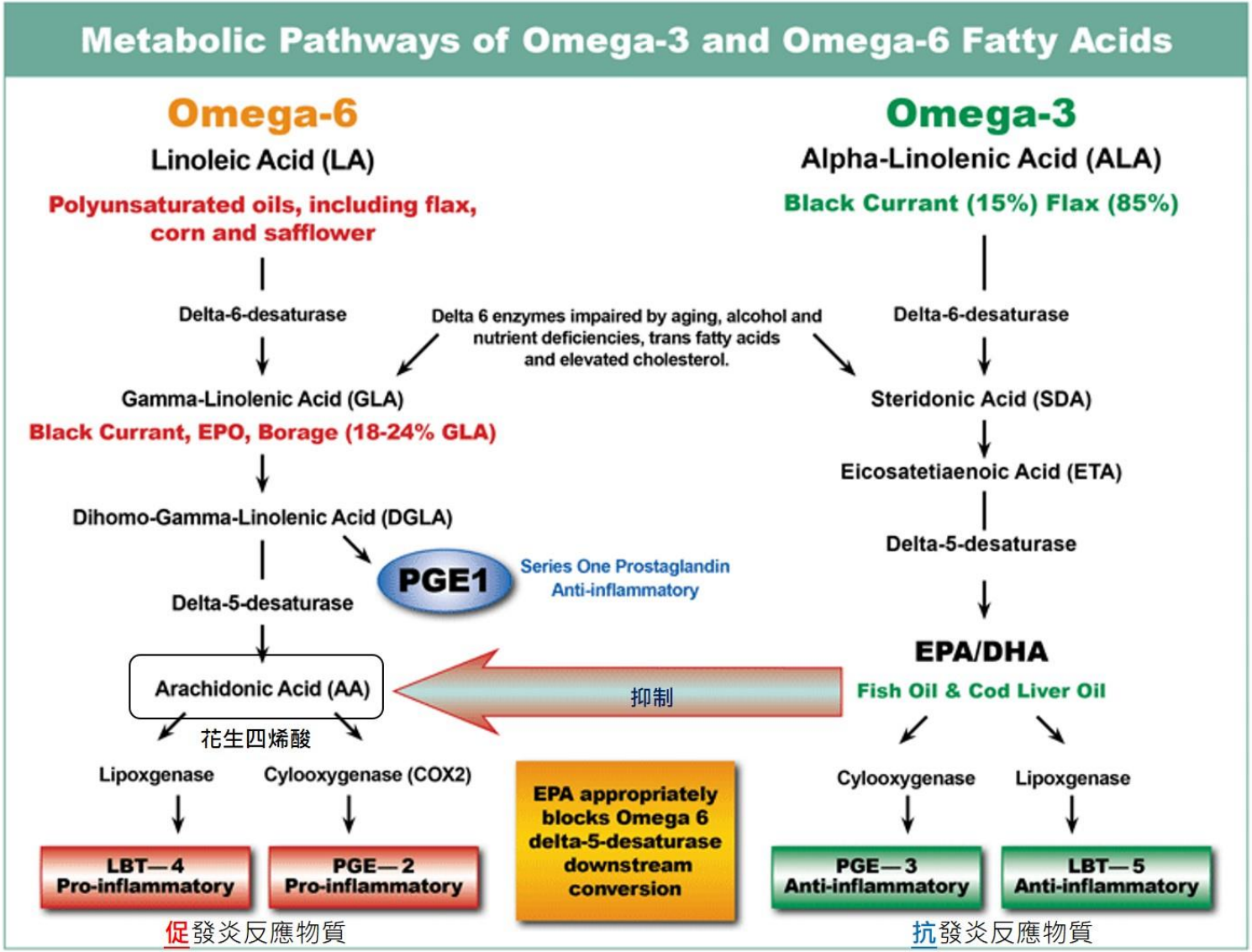
只有兩項營養品例外：葉酸和魚油 。

EPA is the member of omega-3 PUFA

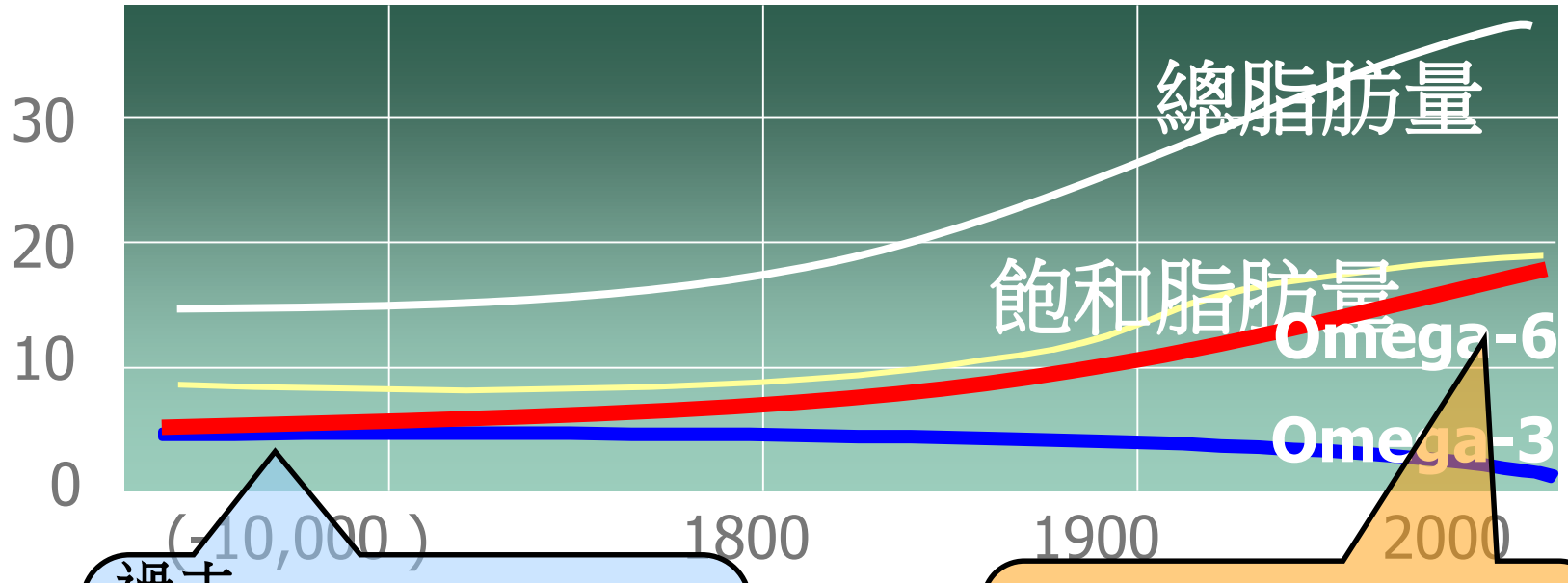


亞麻籽
黃豆
核桃
油菜籽

OMEGA-3抗發炎；OMEGA-6促發炎



人類攝取OMEGA3比例的逐漸失衡



過去
omega-6:omega-3
攝取均衡比率約為**1:1**

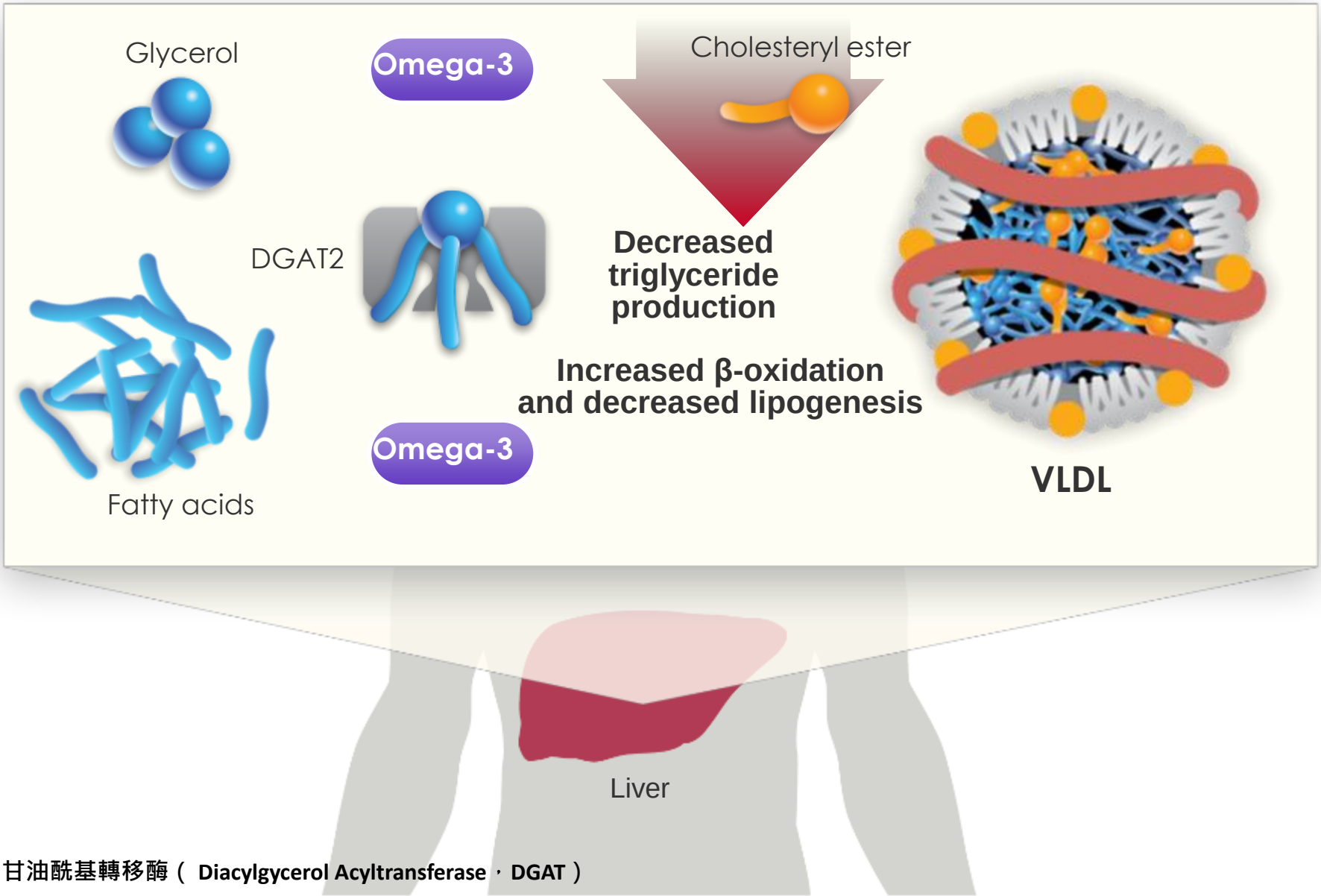
如今
omega-6:omega-3
已偏離將近至**20:1**

觀察型研究顯示：Omega-3攝取不足，與心血管疾病致死率呈正相關

Omega-3/Omega-6攝食比例不平衡的結果
Differences in concentration of FA in thrombocyte phospholipids

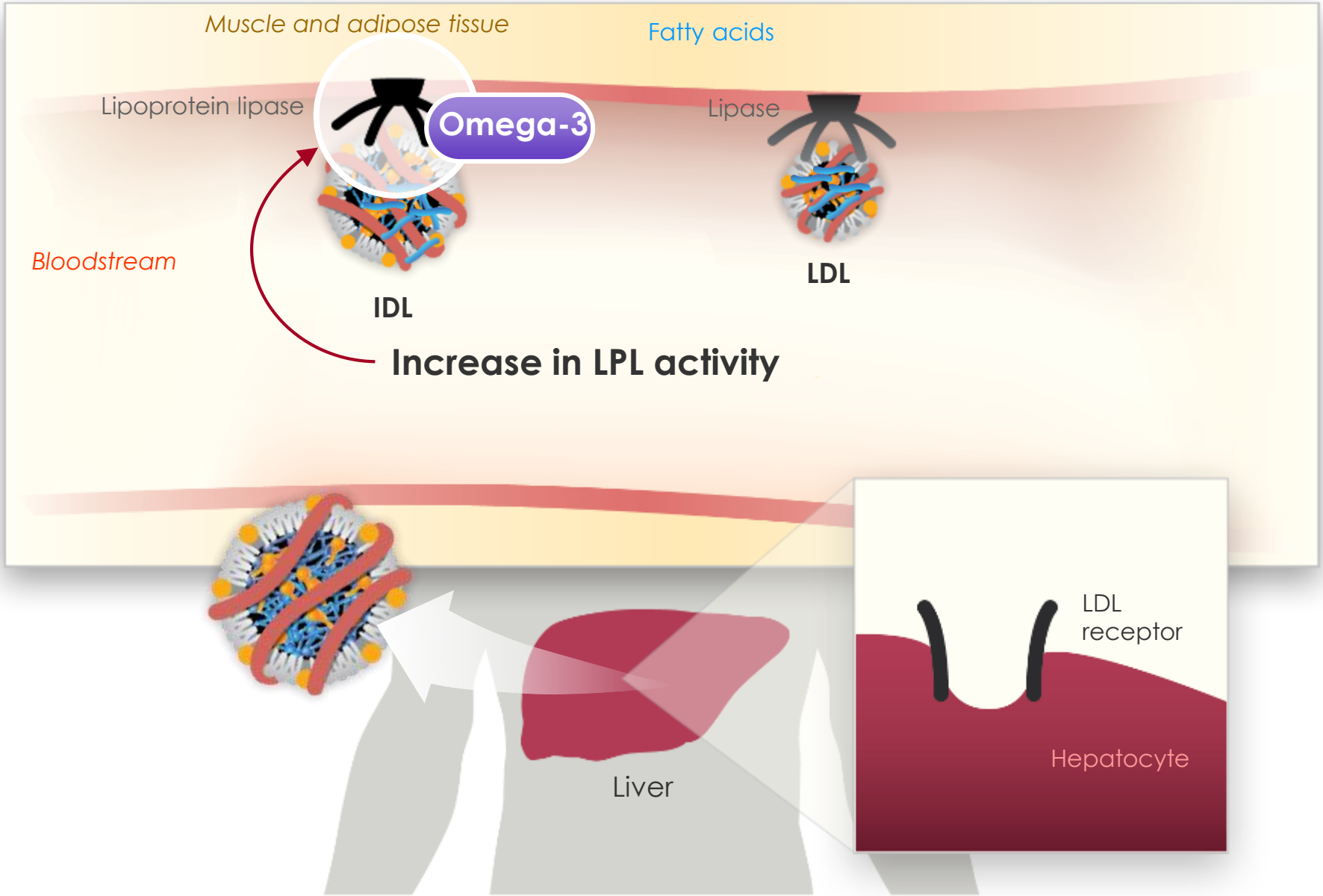
	歐美%	日本 %	愛斯基摩 格陵蘭島%
飲食中的Omega 6 Omega 6 in diet	26	21	8.3
飲食中的EPA EPA in diet	0.5	1.6	8.0
Omega-6/Omega-3 攝食比例	**50**	**12**	**1**
因心血管致死率 **CV Mortality rate**	**45**	**12**	**7**

Omega-3 PUFA: Proposed Intrahepatic Mechanisms of Action

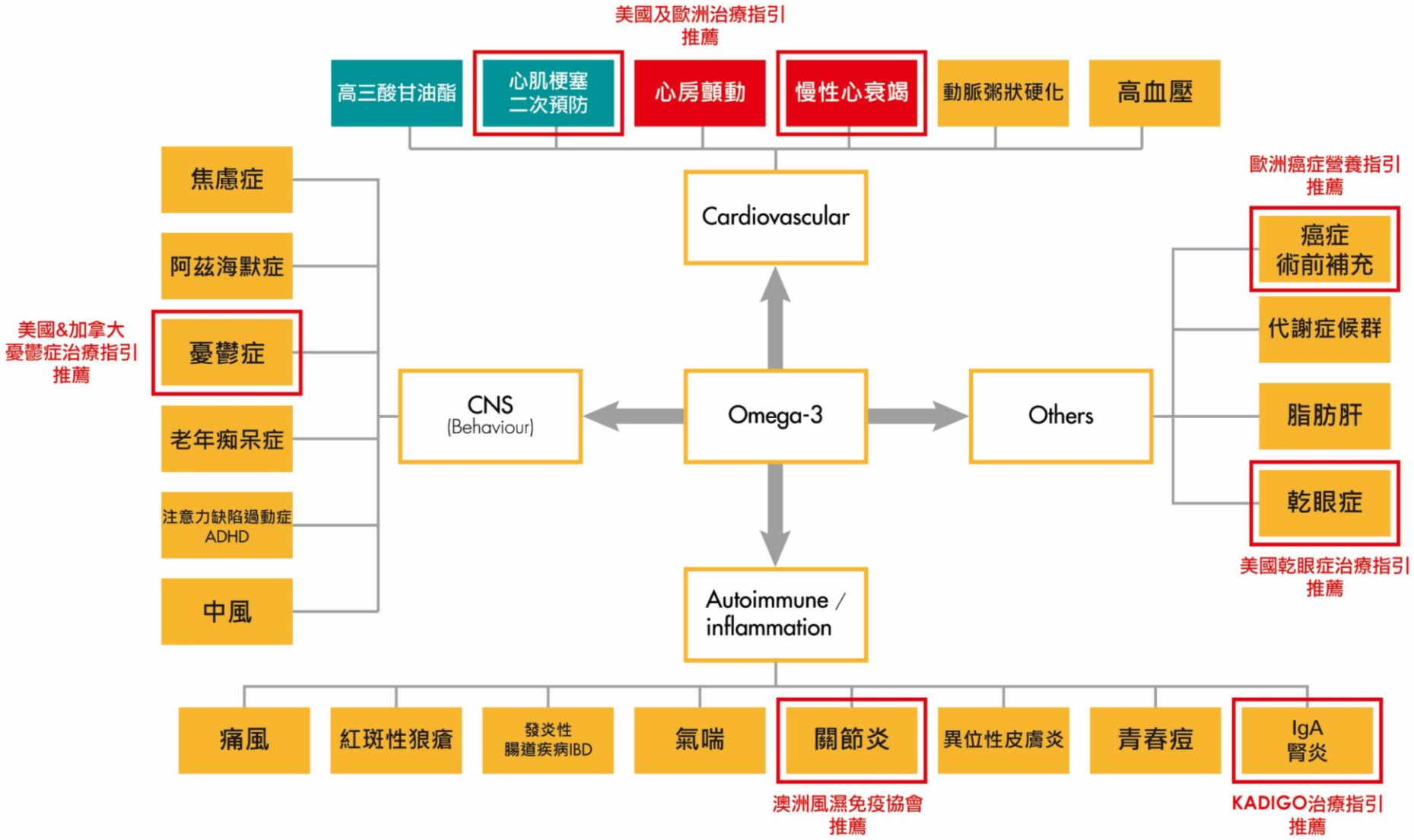


甘油酰基轉移酶（ Diacylgycerol Acyltransferase，DGAT ）

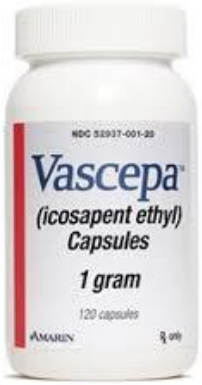
Omega-3 PUFA: Proposed **Extra**hepatic Mechanism of Action



OMEGA-3已獲得
兩個適應症/五個治療指引建議



What difference between pure EPA & mix-type Omega-3 in CVD prevention ?



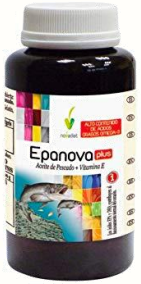


Table 1 Prescription Omega-3 Fatty Acid Product Information and Associated Trials

Product	Lovaza[a] =Omacor (Omega-3-Acid Ethyl Esters)[1]	Vascepa 純EPA (Icosapent Ethyl)[4]	Epanova (Omega-3-Carboxylic Acids)[3,19]
FDA approval	2004	2012	2014
Indication	Indicated as an adjunct to diet to reduce TG levels in adult patients with severe hypertriglyce		
Description	• 1-g transparent, soft-gelatin capsules filled with light-yellow oil • Inactive ingredients include α-tocopherol, gelatin, glycerol, and purified water	• 1-g amber-colored, soft-gelatin capsules • Inactive ingredients include tocopherol, gelatin, glycerin, maltitol, sorbitol, and purified water	• 1-g red/brown coated, soft-gelatin capsules • Inactive ingredients include α-tocopherol, porcine Type A gelatin, glycerol, sorbitol, and purified water
Dosage	Total dose: 4 g/day, taken as: • Single 4-g dose (4 capsules) • Two 2-g doses (2 capsules BID)	Total dose: 4 g/day, taken as: • Two 2-g doses (2 capsules BID)	Total dose: 2 g/day or 4 g/day, taken as: • Single 2-g dose (2 capsules) • Single 4-g dose (4 capsules)
Omega-3 content	Contains at least 0.9 g of OM3FA ethyl esters from fish oils: • EPA ~0.465 g • DHA ~0.375 g	Contains 1 g of IPE: • EPA 1 g	Contains 1 g of fish-oil-derived free FAs with at least 0.85 g of polyunsaturated FAs, including multiple OM3FAs from fish oils: • EPA 0.550 g • DHA 0.2 g

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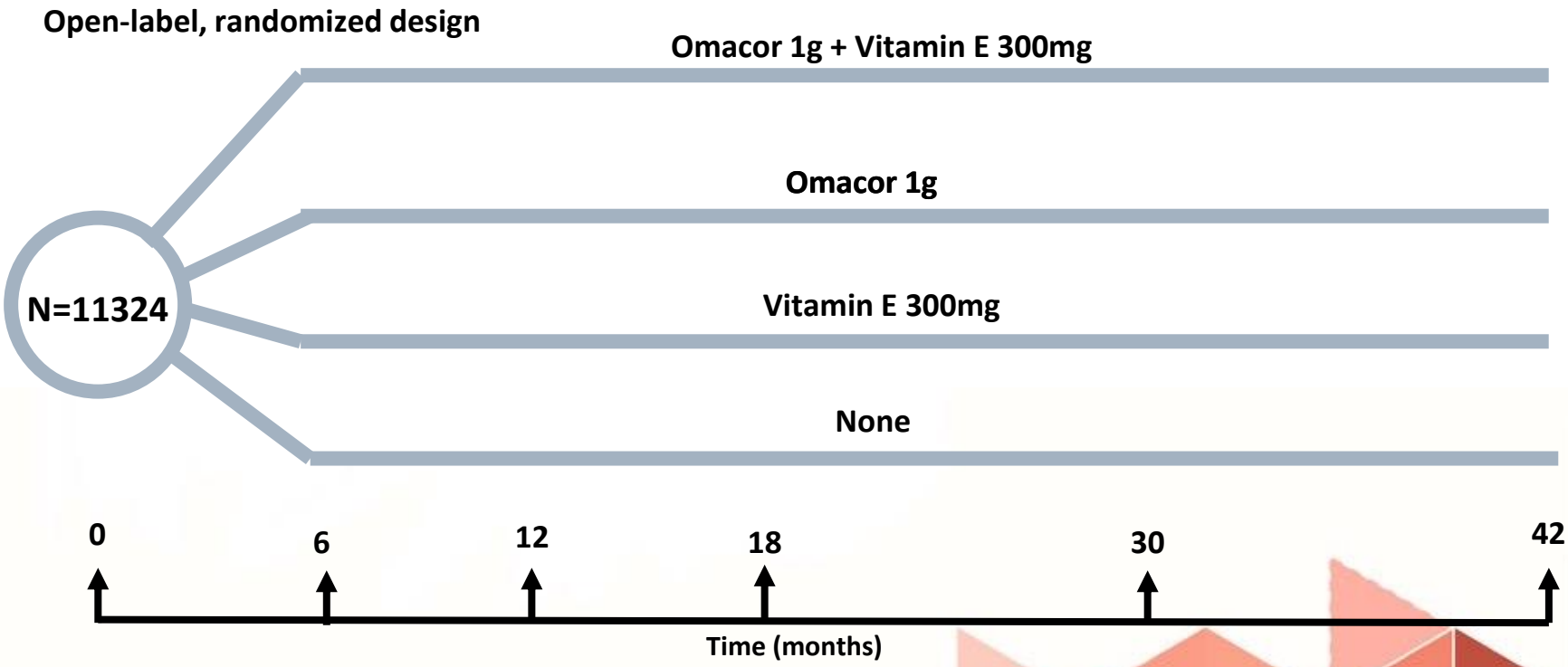
GISSI-Prevention trial



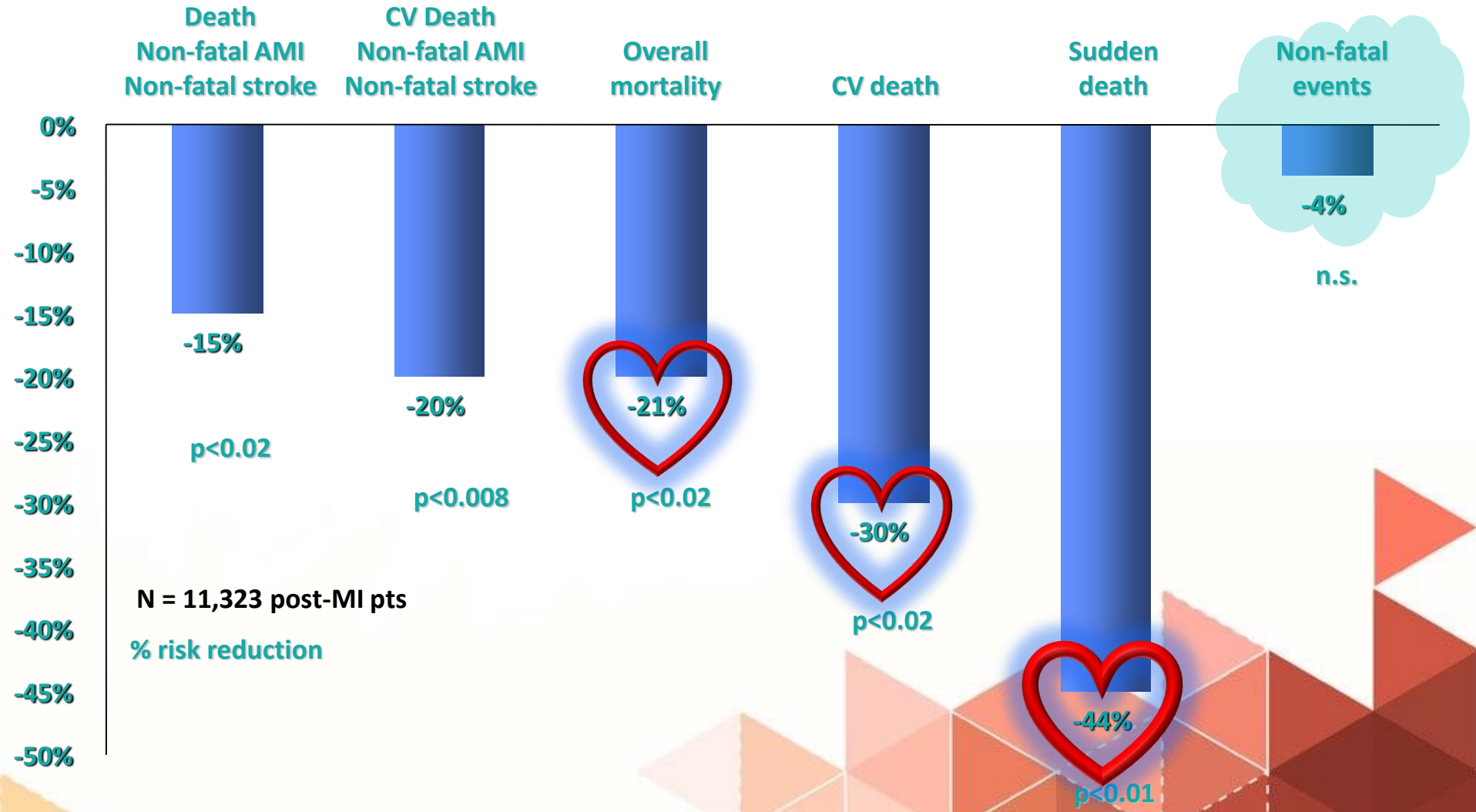
Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E **after myocardial infarction**: results of the GISSI-Prevenzione trial

Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico

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

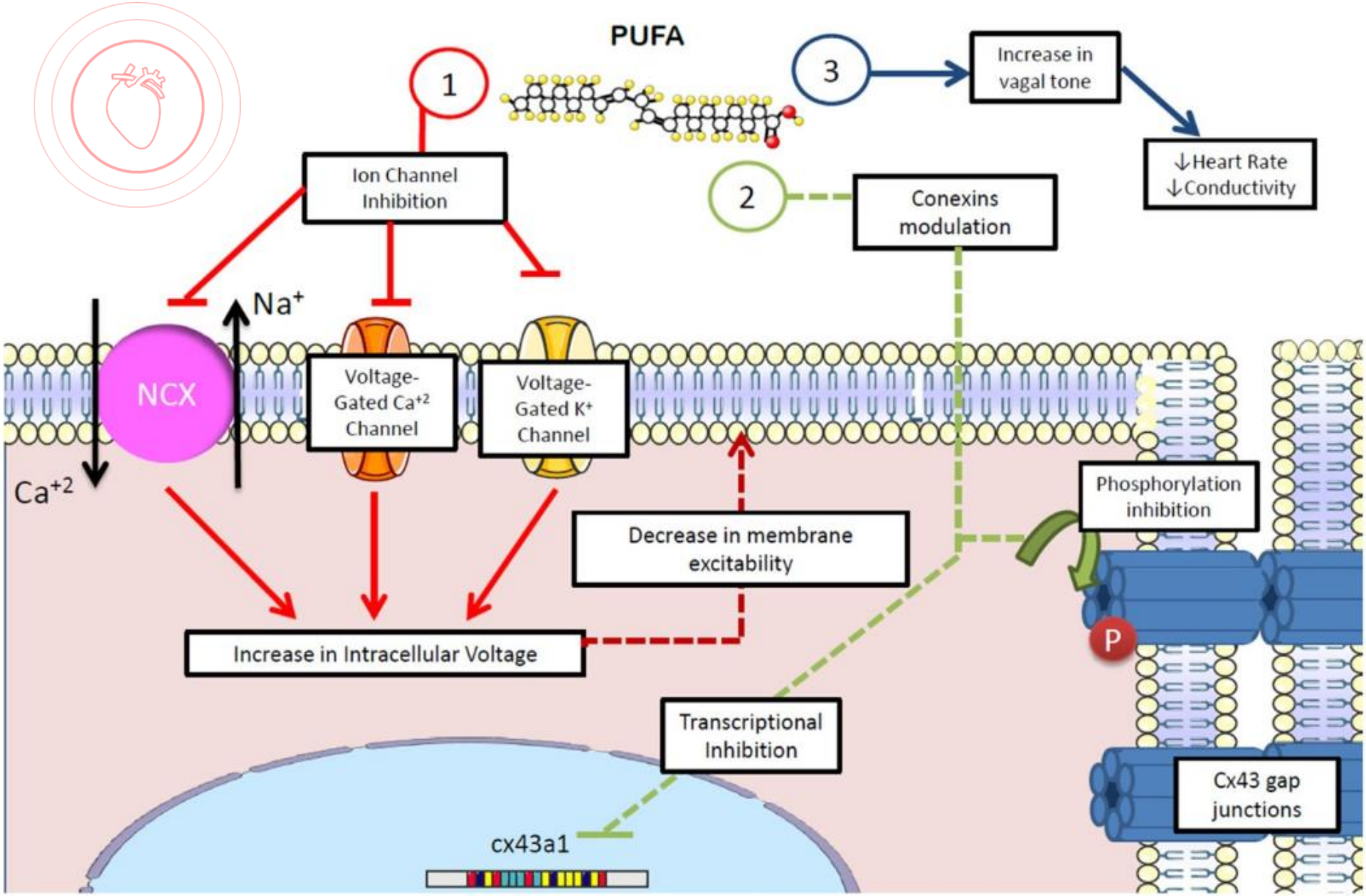
1999 GISSI-P Study

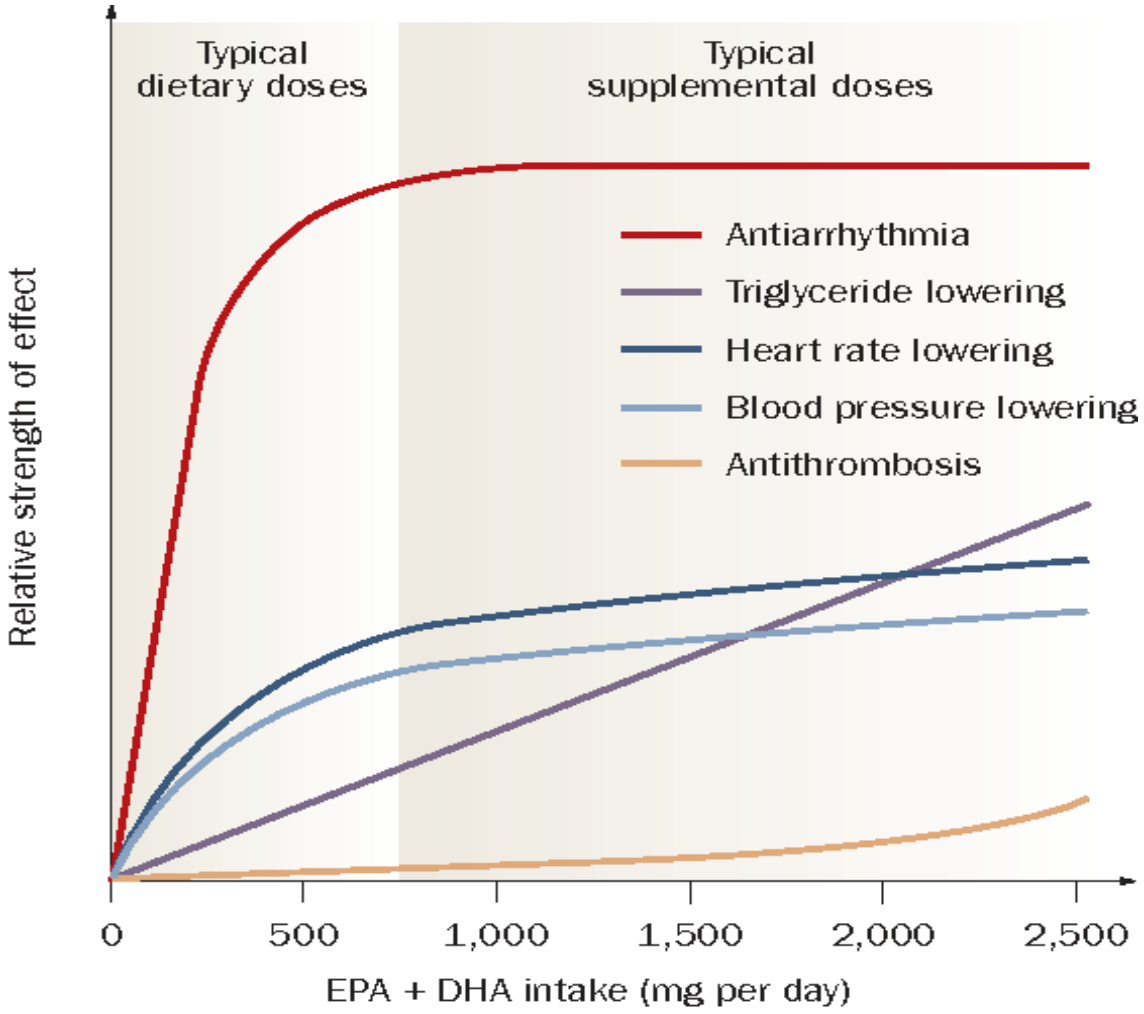
1g Omacor reduced total mortality by 21 % in MI patients



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

Anti-arrhythmia effect of Omega-3 Fish Oil



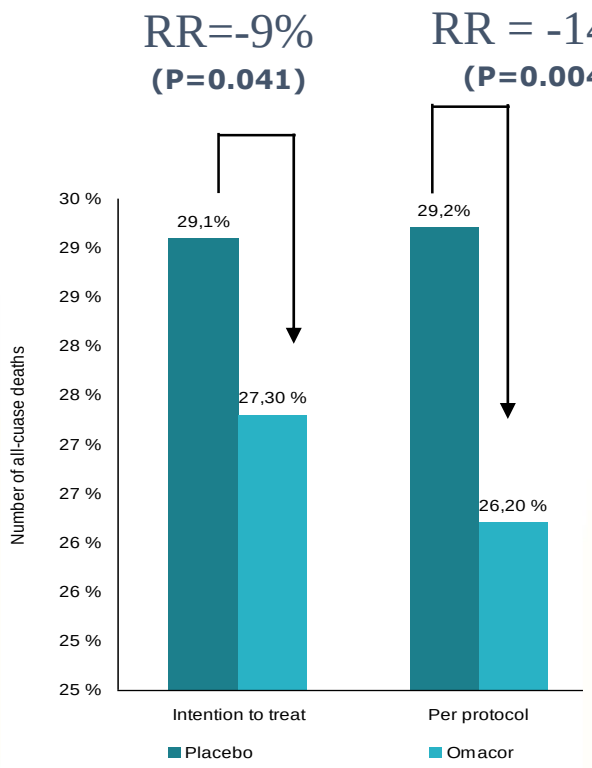


Clinical effect	Time course to alter clinical events
Antiarrhythmia	Weeks
Triglyceride lowering	Months to years
Heart rate lowering	Months
BP lowering	Months to years
Antithrombosis	Weeks

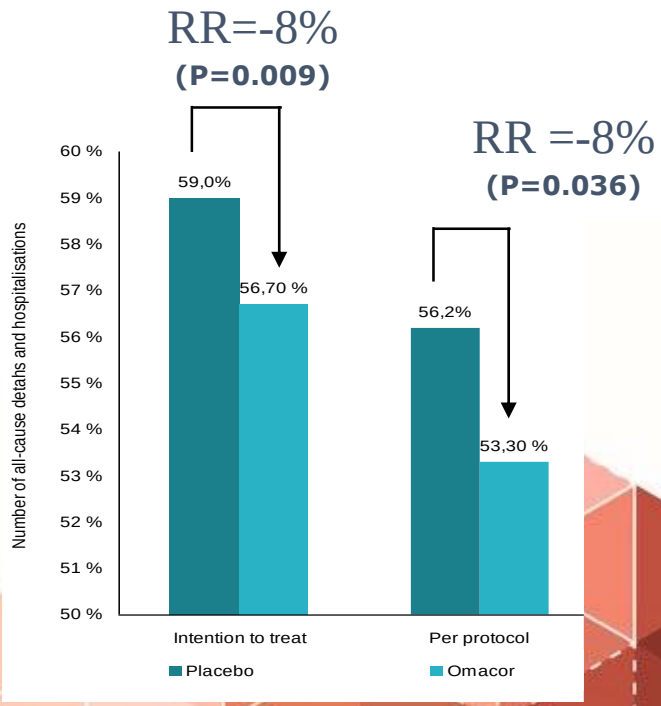
Figure 1 | Schematic of potential dose–response curves that indicate the beneficial physiological effects for intake of long-chain omega-3 fatty acids. Antiarrhythmic and antithrombotic effects can be clinically beneficial within weeks. Beneficial clinical effects of heart-rate lowering can be achieved over a period of months, and those for triglyceride and blood-pressure lowering over a period of months to years. Abbreviations: DHA, docosahexaenoic acid; ePA, eicosapentaenoic acid. Reproduced with permission from Mozaffarian, D. & Rimm, e. B. JAMA 296, 1885–1899

2008 GISSI-HF Study
1g Omacor reduced mortality by 9 % in HF patients

Number of all-cause death



Number of all-cause death & hospitalisations



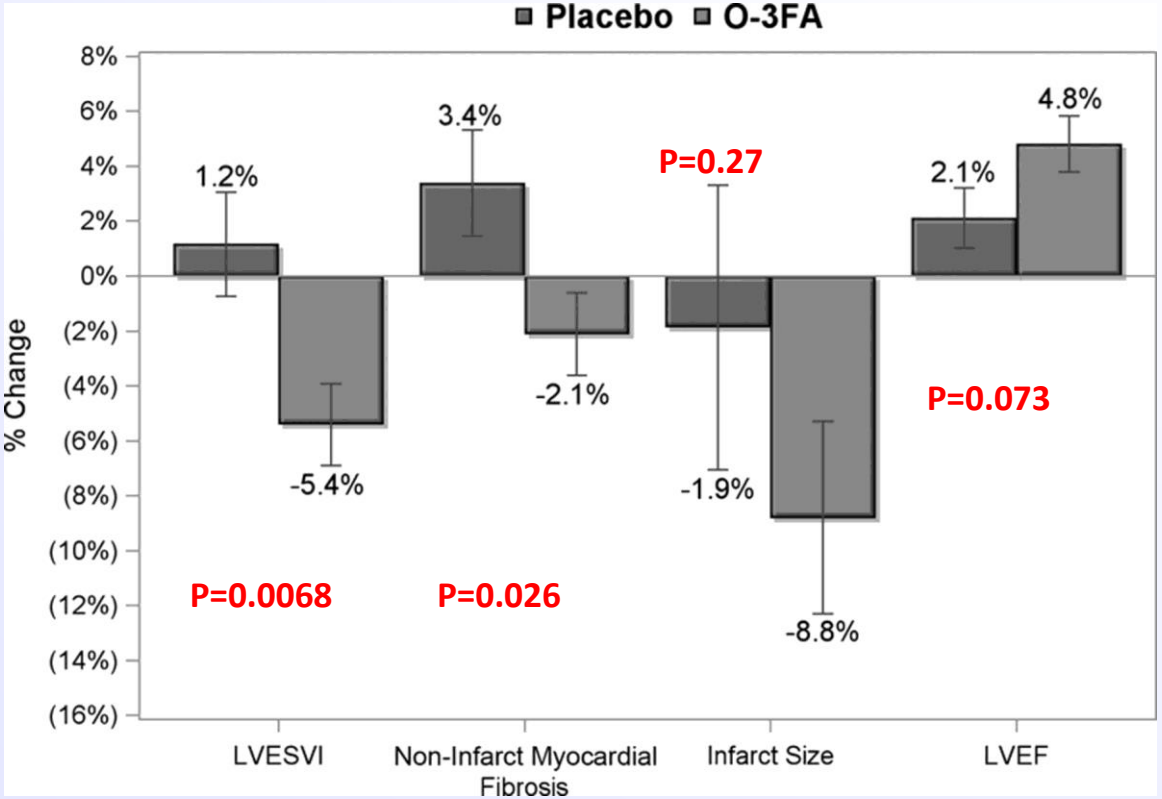
Lancet. 2008 Oct 4;372(9645):1223-30.

Effect of Omega-3 Acid Ethyl Esters on Left Ventricular Remodeling After Acute Myocardial Infarction

The OMEGA-REMODEL Randomized Clinical Trial

4g of O-3FA(Omacor)

(1) N=180
(2)Omacor : 4g/天
(3)投藥時間 : 6 months



Circulation. 2016;134:378–391

高劑量Omega-3脂肪酸魚油 可救心

台灣新生報 作者【記者蘇湘雲／綜合外電報導】｜台灣新生報－2016年8月3日 上午12:00

心臟病患者吃魚油，或許可以幫助心臟復原。美國最新研究發現，心臟病患者若在心臟病發作後攝取高劑量含Omega-3脂肪酸魚油，持續六個月，可幫助改善心臟功能，減少疤痕組織生成。

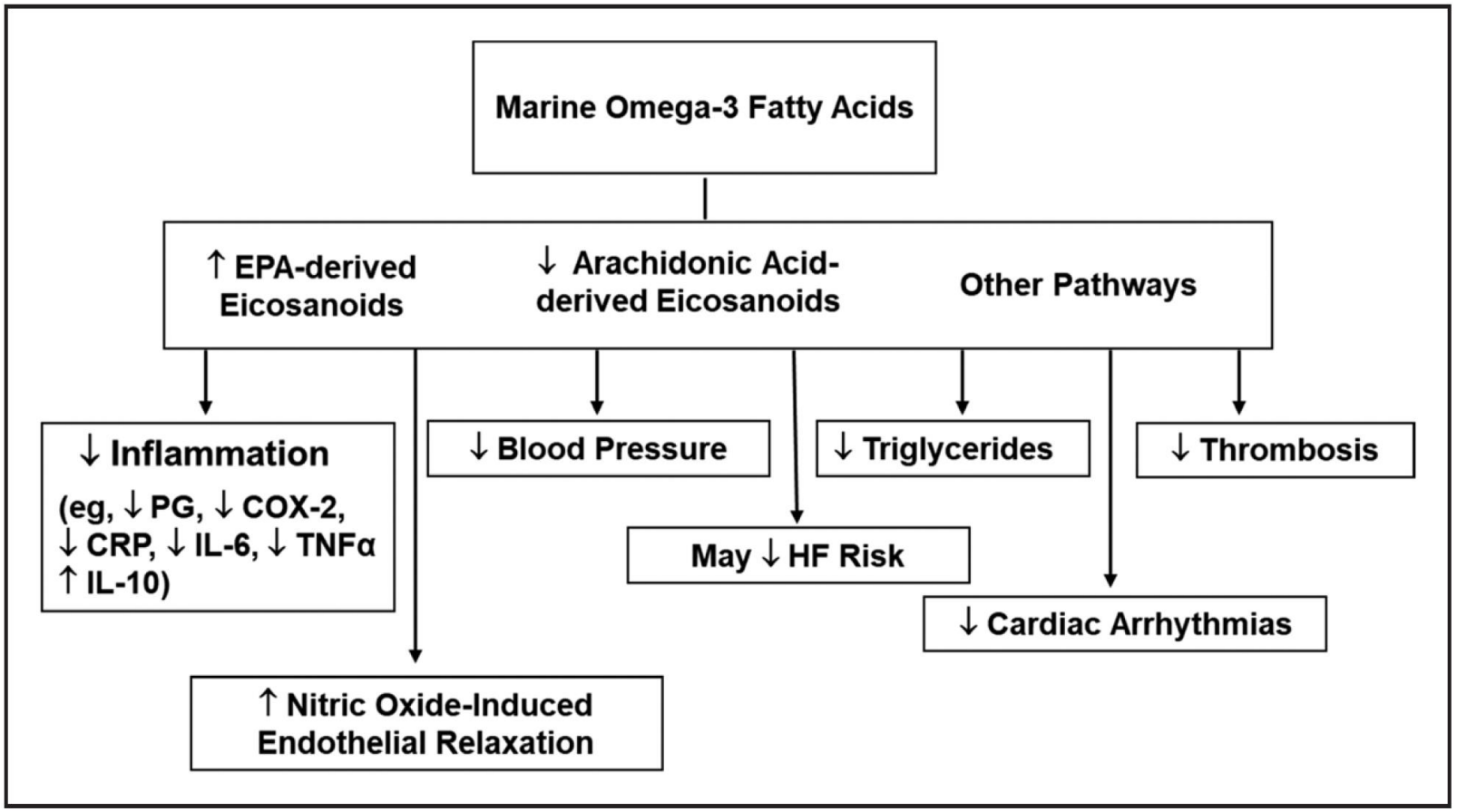
上述研究成果已發表於美國心臟協會所出版的〈循環〉期刊。

研究作者分析，心臟病發作後，患者的心臟形狀、心臟功能都可能出現變化，這種變化稱為「心臟病後重塑」現象，一旦心臟出現這些改變，患者不但復原情況較差，甚至可能引起心臟衰竭，醫界多希望心臟復原更順利，或防止這類現象發生。

過去研究顯示，魚油中的Omega-3脂肪酸可以提升心臟病患者存活率，但醫界、學界並不瞭解Omega-3脂肪酸如何改善患者心臟構造、心臟組織。在這次研究當中，研究人員透過隨機臨床實驗發現，與服用安慰劑的患者相比，心臟病患者每天服用四公克Omega-3脂肪酸，持續六個月，結果「左心室收縮容積指數」降低百分之五點八，心臟肌肉纖維化情況也減緩百分之五點六。醫師多半透過「左心室收縮容積指數」預測患者心臟病發作後的復原狀況。

研究資深作者美國布萊根婦女醫院心臟核磁共振攝影科主任、美國哈佛大學醫學副教授雷曼德・鄺（RaymondY.Kwong）表示，對於心臟病發作患者來說，即使患者接受所有治療、照顧，還是得面對心臟衰竭問題。這項研究顯示，Omega-3脂肪酸或許可以改善心臟重塑現象，且這種方法安全又有效。這種輔助治療方式往後說不定可以減少心臟衰竭發生率、心臟病死亡風險。

Mechanisms by which omega-3 may lower cardiovascular disease risk



Circulation Research. 2020;126:112–128.

2017美國心臟學會建議Omega-3可用於CHD/HF二次預防

Table 8. Omega-3 PUFA Supplementation for Prevention of Cardiovascular Events: Recommendations for Clinical Use by Indication and Population

Indication (Population)	Recommendation	Class (Strength of Recommendation)		
Primary prevention of CHD (general population [without CHD])	No recommendation	…		
Prevention of CVD mortality in diabetes mellitus/prediabetes	Treatment is not indicated	III*		
Prevention of CHD among patients at high CVD risk (mixed populations with and without CHD)	Treatment is not indicated	III*†		
Secondary prevention of CHD and SCD among patients with prevalent CHD	Treatment is reasonable	IIa†		
Primary prevention of stroke (high CVD risk [with or without prevalent CHD])	Treatment is not indicated	III*		
Secondary prevention of stroke	No recommendation	…		
Primary prevention of heart failure	No recommendation	…		
Secondary prevention of outcomes in patients with heart failure	Treatment is reasonable	IIa		
Primary prevention of AF	No recommendation	…		
Secondary prevention of AF in patients with prior AF	Treatment is not indicated	III*	A	Based on several RCTs.
AF after cardiac surgery	Treatment is not indicated	III*	A	Based on 1 large RCT (OPERA) and a meta-analysis of all existing RCTs.

Secondary prevention of CHD and SCD among patients with prevalent CHD	Treatment is reasonable	IIa†
Primary prevention of stroke (high CVD risk [with or without prevalent CHD])	Treatment is not indicated	III*
Secondary prevention of stroke	No recommendation	…
Primary prevention of heart failure	No recommendation	…
Secondary prevention of outcomes in patients with heart failure	Treatment is reasonable	IIa

Circulation. 2017;135

1g Omega-3(460mg EPA/ 380mgDHA) is useful for prevent 2ed CHD/HF,

how about 1st prevention ???

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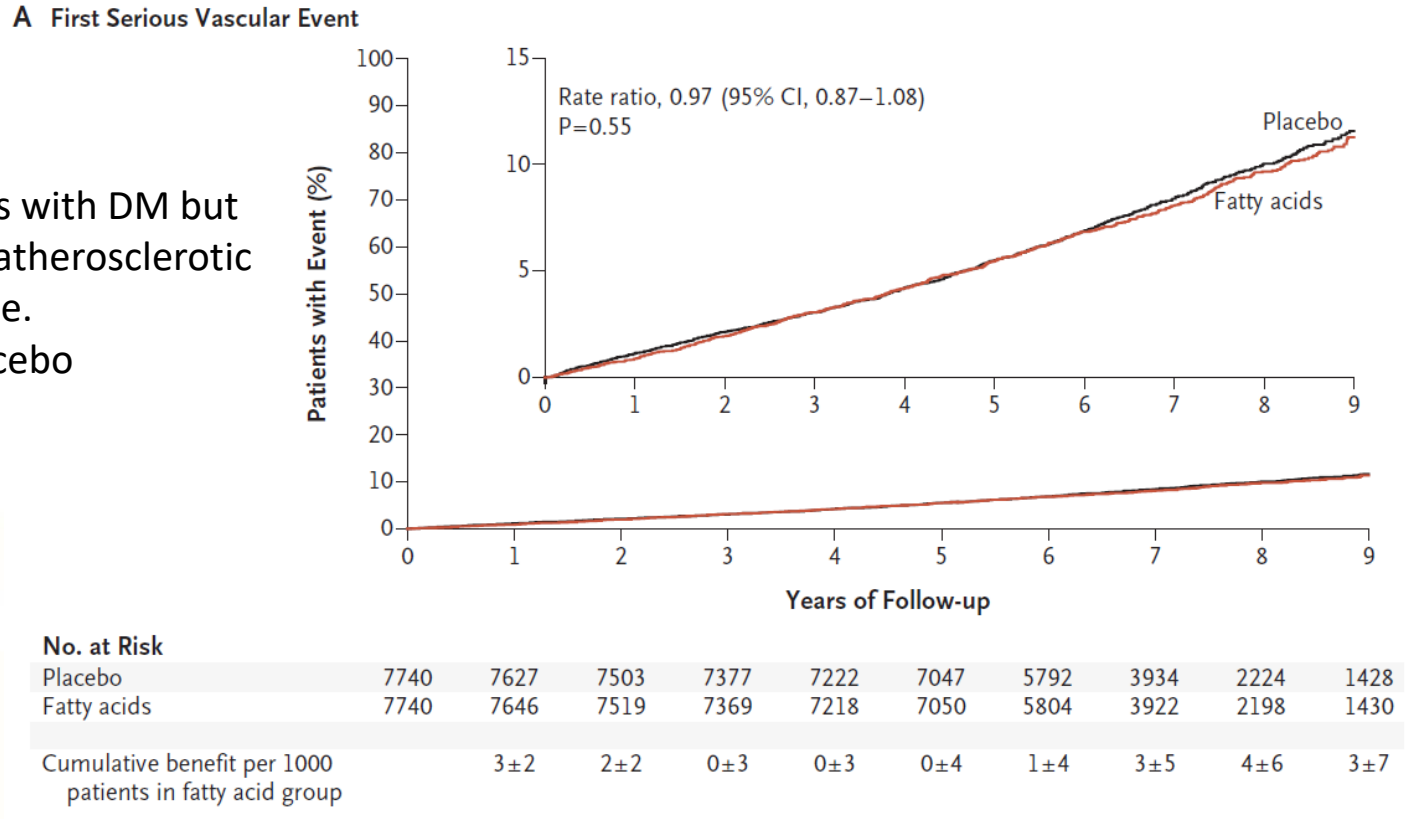
2018 ASCEND Study
發現1g Omacor (EPA460mg+DHA380mg)
對於糖尿病患者之初次預防無效

(1) RCT
(2) N=15,480 patients with DM but without evidence of atherosclerotic cardiovascular disease.
(3) 1g Omacor vs Placebo

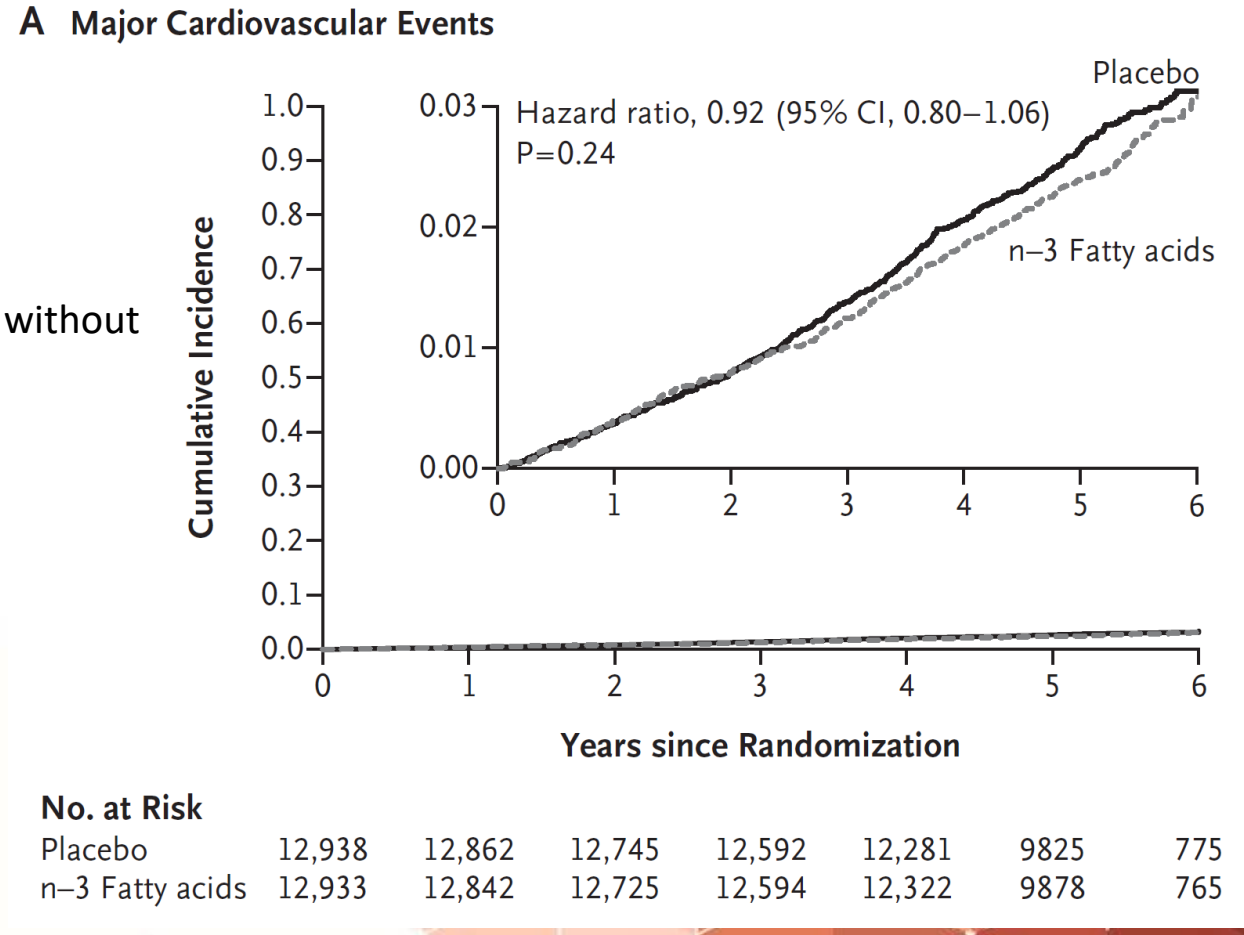


No. at Risk										
Placebo	7740	7627	7503	7377	7222	7047	5792	3934	2224	1428
Fatty acids	7740	7646	7519	7369	7218	7050	5804	3922	2198	1430
Cumulative benefit per 1000 patients in fatty acid group		3±2	2±2	0±3	0±3	0±4	1±4	3±5	4±6	3±7

N Engl J Med. 2018 Oct 18;379(16):1540-1550.

2019年Vital Trail
發現1g Omacor (EPA460mg+DHA380mg)
對於老年患者之初次預防無效

(1)RCT
(2)N=25,871 older adults without history of CVD or cancer
(3)1g Omacor vs Placebo

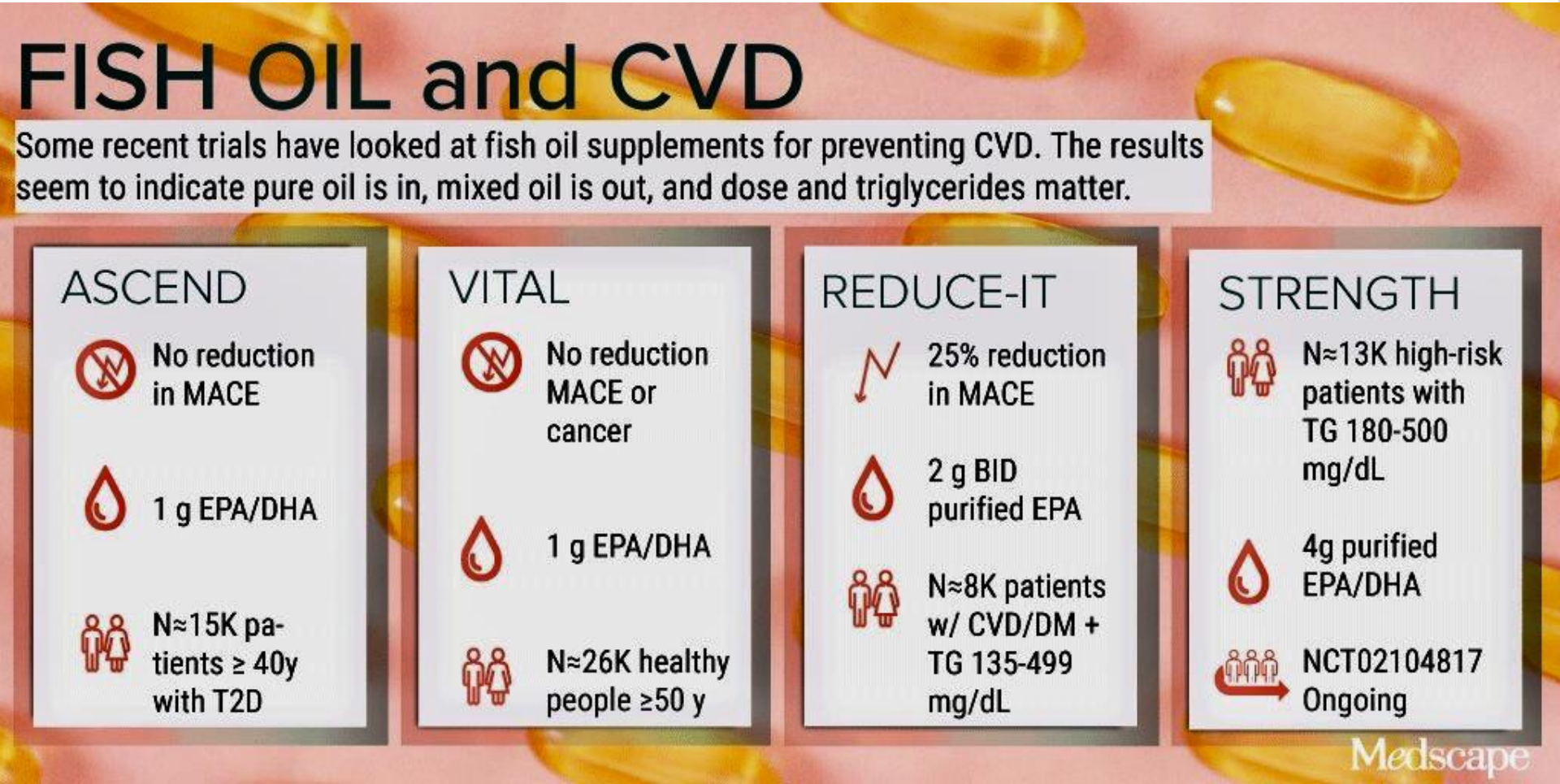


N Engl J Med. 2019 Jan 3;380(1):33-44.

1g Omacor沒效(460mg EPA + 380mgDHA)

那提高混合型Omega-3劑量呢？

℞ omega-3臨床試驗一覽及分析



Received: 6 May 2018 | Revised: 14 August 2018 | Accepted: 15 August 2018 Clinical Cardiology. 2018;41:1281–1288.
DOI: 10.1002/clc.23055

PREVENTION WILEY CLINICAL CARDIOLOGY

TRIAL DESIGNS

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

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

2.2g EPA + 0.8g DHA一樣對初次預防無效

阿斯利康终止Epanova鱼油衍生物的三期临床试验

2020年01月15日 14:00 界面

Epanova是阿斯利康2013年收购Omthera Pharmaceuticals制药公司是的时候获得的，当时该药正在接受FDA获批用于治疗高甘油三酸酯的决定。

在2014年获批之后，紧接着，阿斯利康就开启了药物的三期临床试验STRENGTH，寄希望能通过该试验佐证Epanova在治疗心血管事件上的有效性，但五年过去了，试验结果却令人失望。

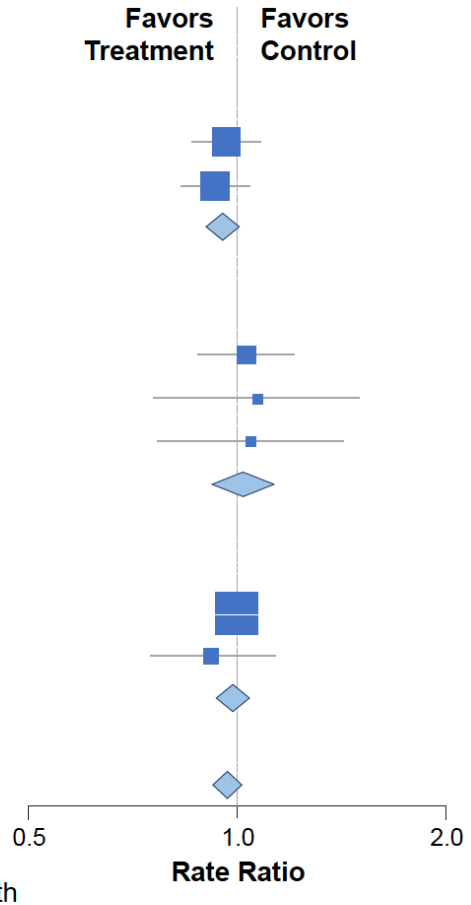
“对于这样的结果，我们很是失望。但我们会继续满足患者在心血管治疗方面的需求。”阿斯利

1g Omacor = 0.46g EPA + 0.38g DHA

4g Epanova = 2.2g EPA + 0.8g DHA

Low Dose Omega-3 Mixtures Show No Significant Cardiovascular Benefit

Source	No. of Events (%) Treatment	Control	Rate Ratios (CI)
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




NOT
THE
END

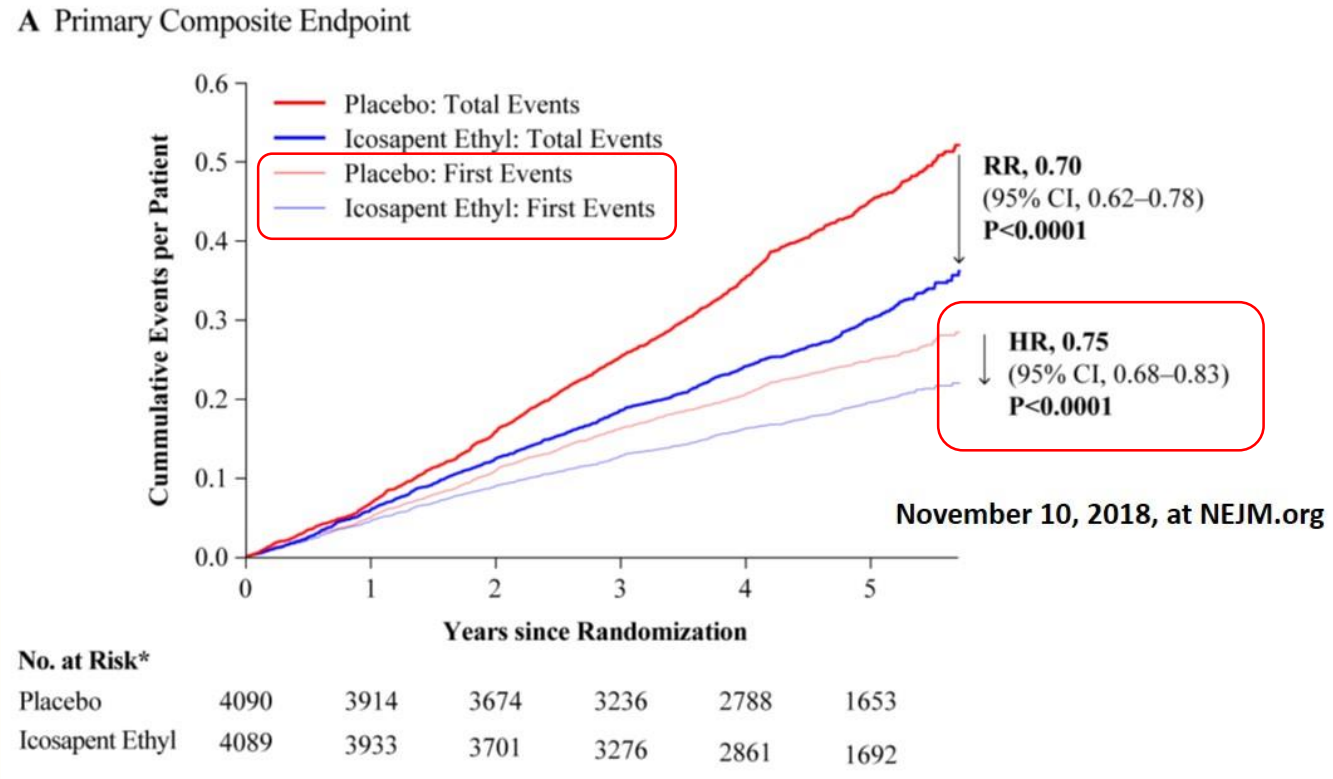
《第 68 屆美國心臟病學學院年會》

純化魚油衍生物新藥 可降低 30%心血管疾病風險

2019.03.19 環球生技雜誌記者/李林璦 編譯

2019年Reduce-it證實，add on **4g EPA**於已服用statin之患者(CVD or DM)能再**額外降低25%初次心血管事件**發生率

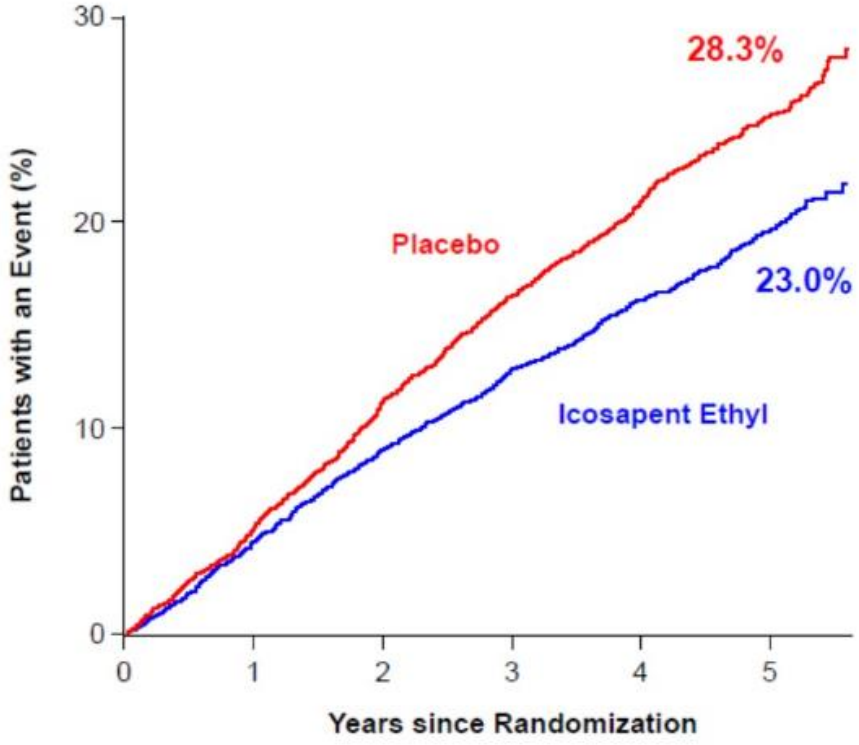
(1)N=8,179
(2)Patient type : w/ CVD(70.7%) or DM receiving statin & TG 135 ~ 499 mg/dl(Median TG 216 mg/dl)
(3)Treat EPA 4g/day 4.9years



N Engl J Med. 2019 Jan 3;380(1):11-22.

Primary End Point:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina

reduce-it



Hazard Ratio, 0.75
(95% CI, 0.68–0.83)
RRR = 24.8%
ARR = 4.8%
NNT = 21 (95% CI, 15–33)
P=0.00000001

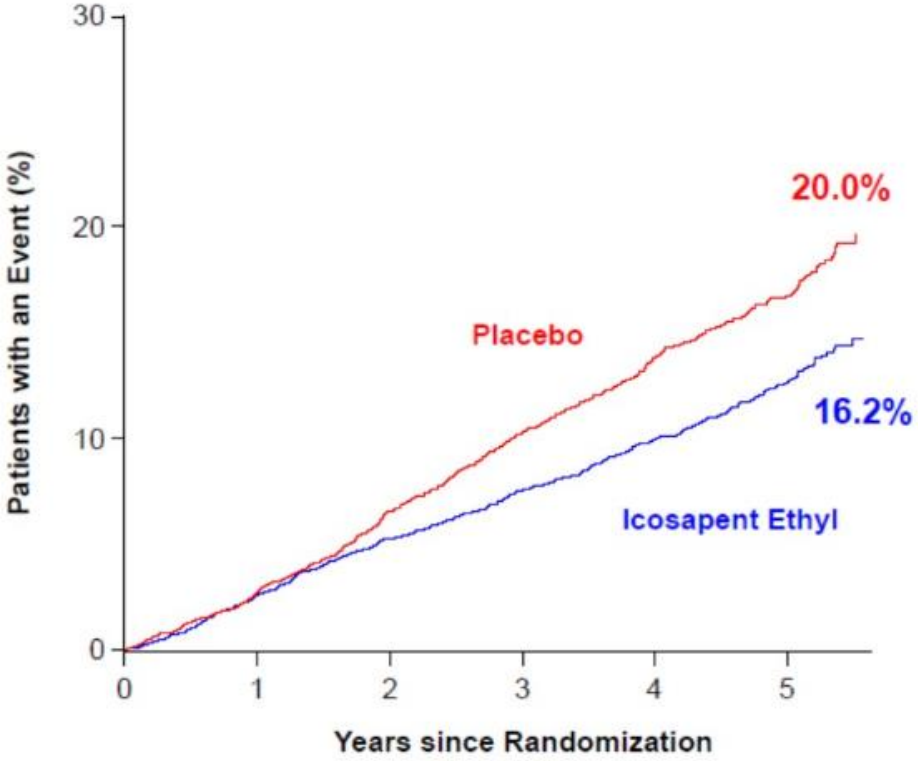
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018. Bhatt DL. AHA 2018, Chicago.

AMARIN

Pure EPA
Vascepa
(icosapent ethyl)

Key Secondary End Point:
CV Death, MI, Stroke

reduce-it



Hazard Ratio, 0.74
(95% CI, 0.65–0.83)

RRR = 26.5%

ARR = 3.6%

NNT = 28 (95% CI, 20–47)

P=0.0000006

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018. Bhatt DL. AHA 2018, Chicago.

AMARIN

Pure EPA
Vascepa
(icosapent ethyl)

魚油證實對心臟有益　美國小藥廠股價飆三倍

　出版時間：2018/09/25 16:56

Amarin藥廠股價飆升。翻攝Amarin官網

美國紐澤西生物製藥廠Amarin生產製造的魚油，經臨床證實對心臟病患者有明顯好處，藥廠周一收市股盤價，較上週飆升314%。藥廠表示，不會將目前的魚油售價往上調。

1.8g EPA + 0g DHA

JELIS Suggests CV Risk Reduction with EPA in Japanese Hypercholesterolemic Patients

(1)RCT

(2)N=18,645 patients w or w/ coronary artery disease, all under statin treatment

(3)1.8g EPA vs Placebo

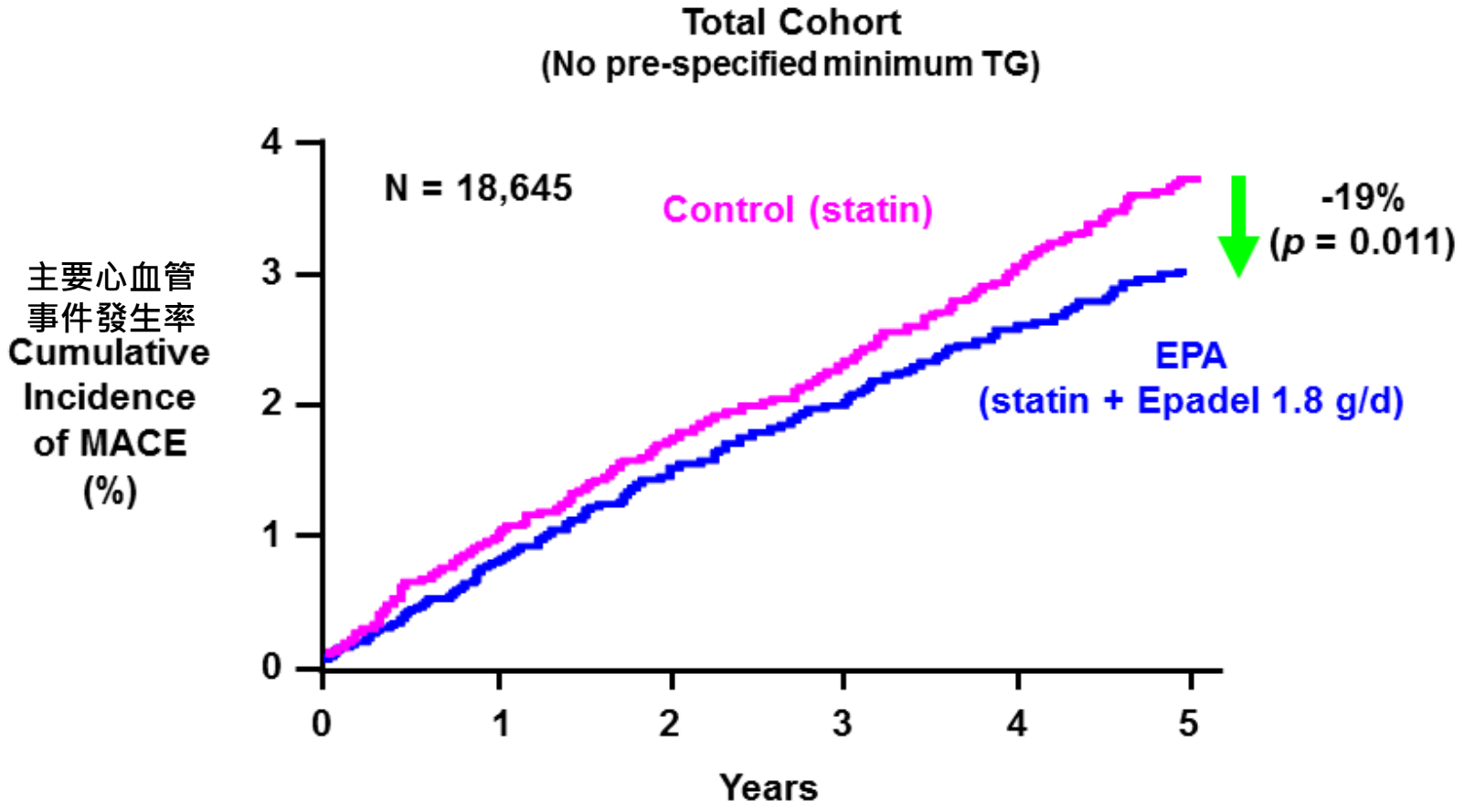
Table 2 Effect of Epadel on Risk of Major Coronary Events[a] in JELIS and JELIS Substudies

Analysis Group	Cohort	N	HR (95% CI)	*P* Value	Reference
JELIS	All patients	18,645	0.81 (0.69–0.95)	0.011	Yokoyama, 2007 [36]
Impaired glucose metabolism[b]	All patients	4565	0.78 (0.60–0.998)	0.048	Oikawa, 2009 [46]
Peripheral artery disease	All patients	223	0.44 (0.19–0.97)	0.041	Ishikawa, 2010 [47]
JELIS	1° prevention	14,981	0.82 (0.63–1.06)	0.132	Yokoyama, 2007 [36]
TG ≥150 mg/dL and/or HDL-C <40 mg/dL	1° prevention	957	0.47 (0.23–0.98)	0.043	Saito, 2008 [45]
Patients not achieving LDL-C and non-HDL-C goals[c]	1° prevention	6592	0.62 (0.43–0.88)	0.007	Sasaki, 2012 [48]
JELIS	2° prevention	3664	0.81 (0.657–0.998)	0.048	Yokoyama, 2007 [36]
Prior myocardial infarction	2° prevention	1050	0.73 (0.54–0.98)	0.033	Matsuzaki, 2009 [49]
Prior coronary intervention	2° prevention	895	0.65 (0.48–0.89)	0.007	Matsuzaki, 2009 [49]

Brinton and Mason Lipids in Health and Disease (2017)

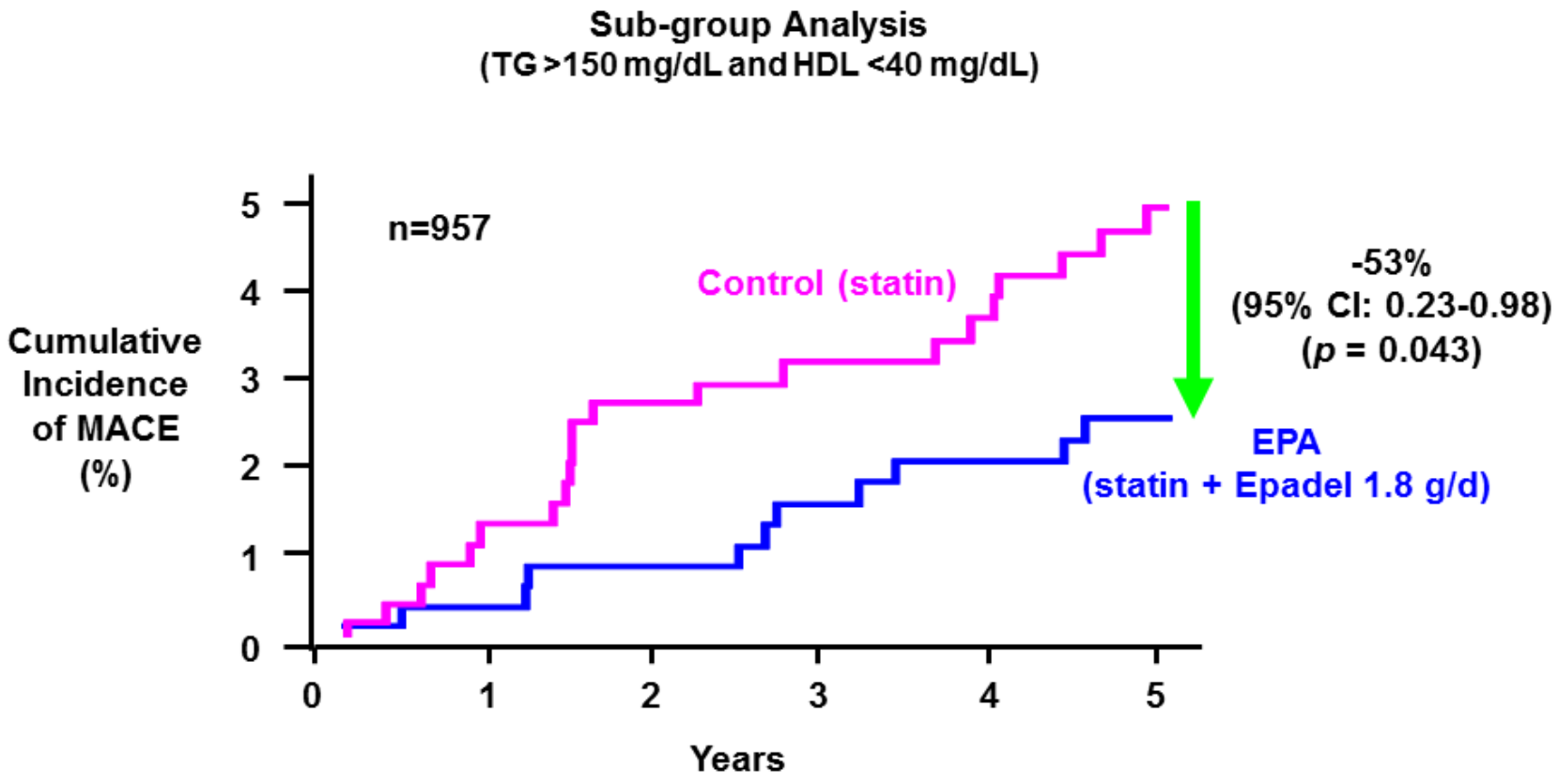
***Lancet* 2007; 369: 1090–98**

2007年JELIS study發現 , add-on 1.8g EPA於服用statin之初級預防患者，能再降低19%心血管發生率 (Primary prevention)



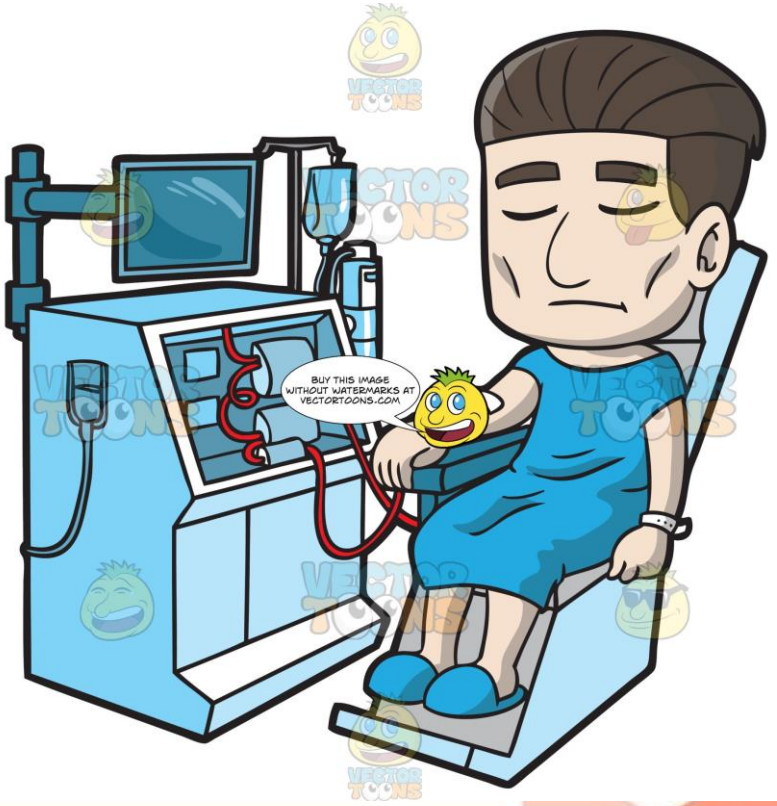
p-value adjusted for age, gender, smoking, diabetes, and hypertension
Yokoyama. *Lancet* (2007)

EPA對於TG>150mg/dl & HDL<40mg/dl患者，預防心血管發生率效力更大(降低53%)



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

對於洗腎透析的病人有一樣好處？



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)

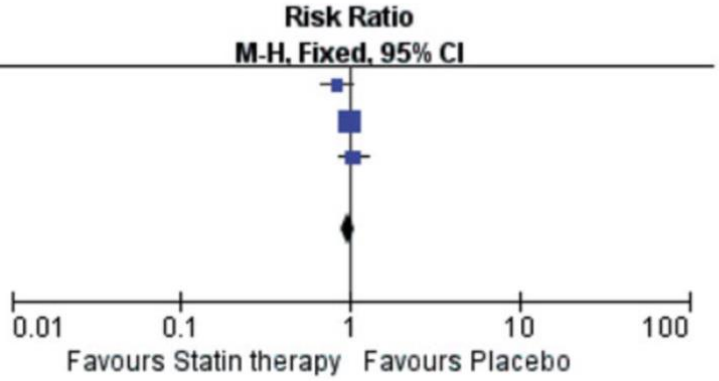


Figure 8. Forest plot of comparison for cardiovascular deaths: statin therapy versus placebo.

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)

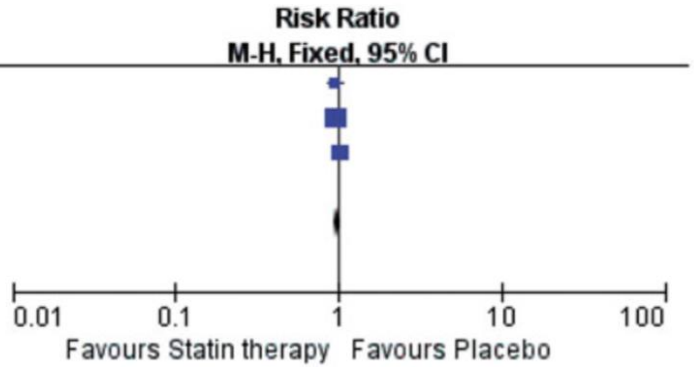


Figure 9. Forest plot of comparison for all-cause mortality: statin therapy versus placebo.

每日2顆Omacor(0.92gEPA+0.76gDHA)
無法降低洗腎患者死亡率及CV Event

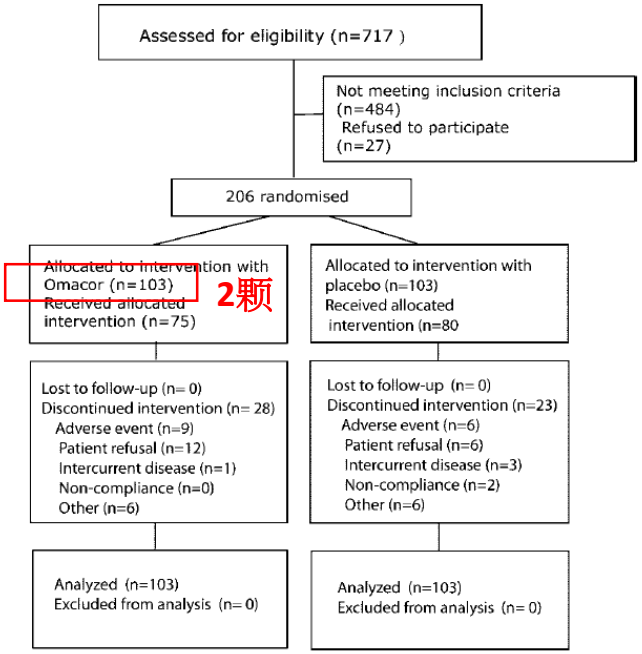


Figure 1. Flowchart illustrating trial profile.

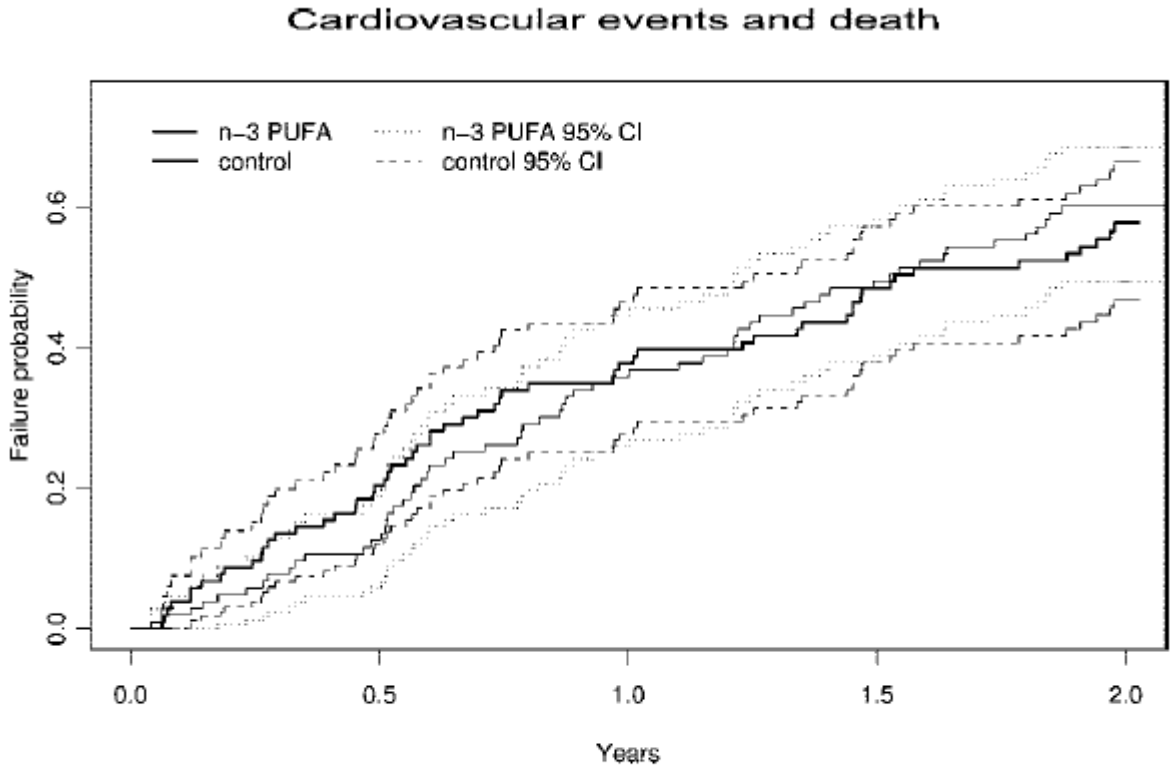


*Figure 2.*Kaplan-Meier survival curve showing the total number of cardiovascular events and death in the two treatment groups.

Clin J Am Soc Nephrol 1: 780–786, 2006. doi: 10.2215/CJN.00630206

每日1.8g純EPA *可能*可降低透析患者心血管死亡率及總死亡率

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

用純EPA處理殘餘風險，比PCSK9效果更好且CP值更高!

Class	CVOT	Relative Risk Reduction (RRR)	Positive CVOT	Peak Net Sales in U.S.
STATIN THERAPY				
Statins	Various	**25-35%**	√	健保給付
OTHER LDL-CHOLESTEROL LOWERING DRUGS ON TOP OF STATIN THERAPY				
Cholesterol Absorption Inhibitors	IMPROVE-IT	6%	√	健保給付
PCSK9 Inhibitors	FOURIER ODYSSEY	15% 15%	√	台灣自費1.7萬/月
OTHER DRUGS ON TOP OF STATIN THERAPY				
Anti-Inflammatory	CANTOS	15%	√	
Omega-3 Mixture (Lovaza 1g/d) =Omacor	ASCEND/VITAL	Not Significant	X	
EPA (Epadel) **EPA=1.8g**	JELIS	19%	√	台灣自費 0.3~0.6萬/月
EPA (Vascepa) EPA=4.0g	**REDUCE-IT**	**25%**	√	

2019年ADA(美國糖尿病協會)最新治療指引已將純EPA納入建議

ADA Guideline原文：

Based on findings from the Reduction of Cardiovascular Event with Icosapent Ethyl(EPA)-Intervention Trial (REDUCE-IT), an additional recommendation has been officially added to the section "Treatment of Other Lipoprotein Fractions or Targets." The new recommendation reads as follows:

In patients with ASCVD or other cardiac risk factors on a statin with controlled LDL-C, but **elevated triglycerides (135-499)**, the addition of **icosapent ethyl(EPA)** should be considered to reduce cardiovascular risk. (Level : A)

Ref. Diabetes Care Volume 42, Supplement 1, January 2019

2019 歐洲最新血脂指引
亦將EPA納入建議

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.
Treatment of dyslipidaemias in older people
Treatment with statins is recommended for primary prevention, according to the level of risk, in older people aged ≤75.
Treatment of dyslipidaemias in older people
Initiation of statin treatment for primary prevention in older people aged >75 may be considered, if at high risk or above.
Treatment of dyslipidaemias in DM
In patients with T2DM at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55mg/dL) is recommended. In patients with T2DM at high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended. Statins are recommended in patients with T1DM who are at high or very-high risk.

European Heart Journal (2019) 00, 178

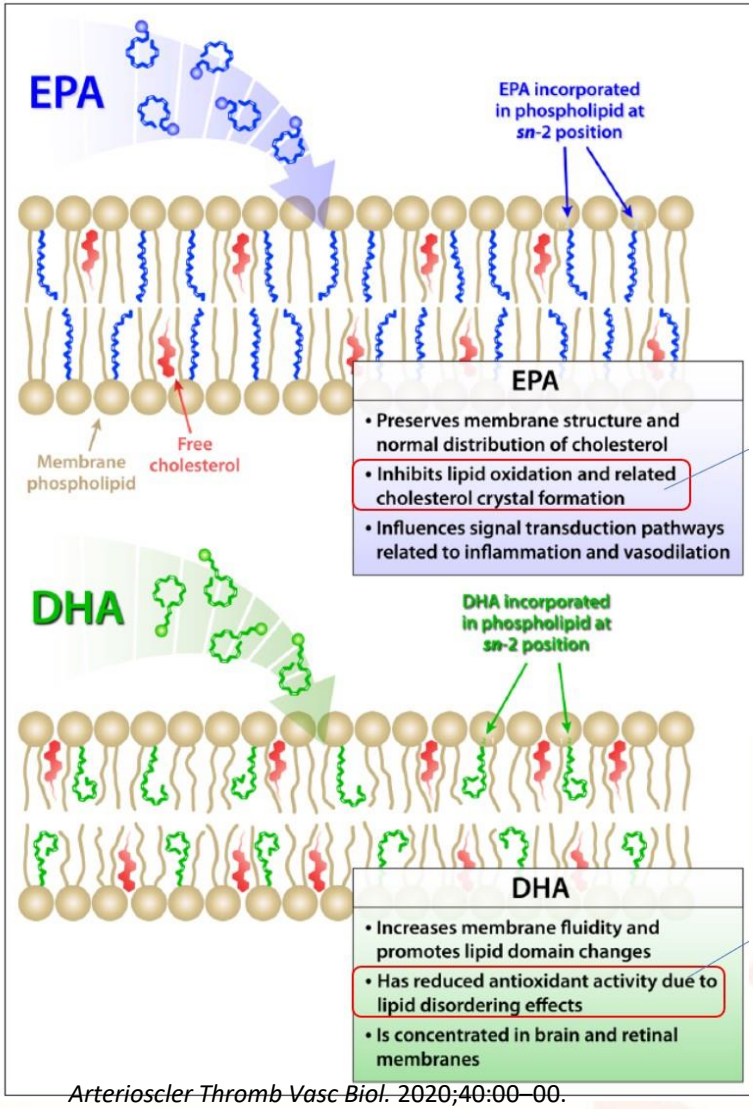

Omega-3
PCSK9i
Niacin
Statin
Ezetrol
Fenofibrate

Contents

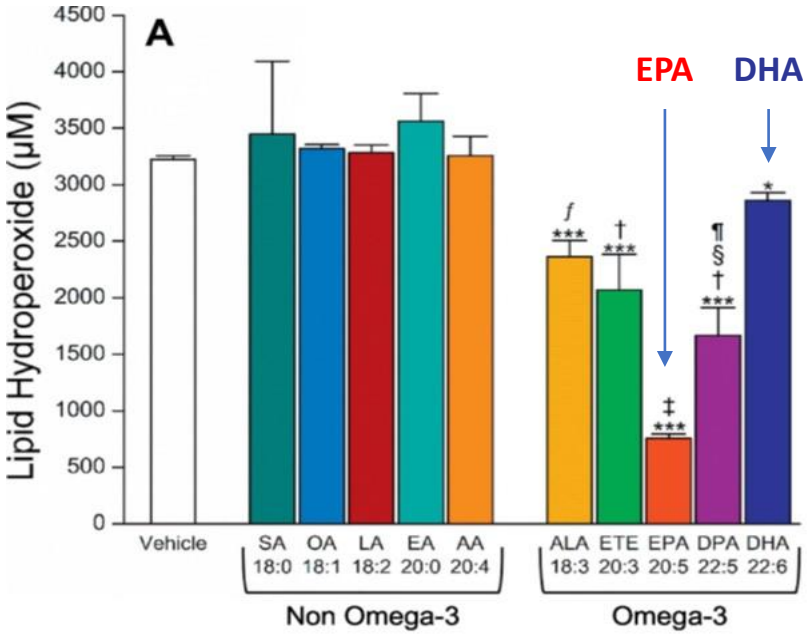
- What is EPA ?
- EPA/DHA & *2ed* prevention
- EPA/DHA & *1st* prevention
- **Why is EPA not DHA effective for *1st* prevention ?**
- How to choice EPA product ?
- Conclusions

Reason(1) :

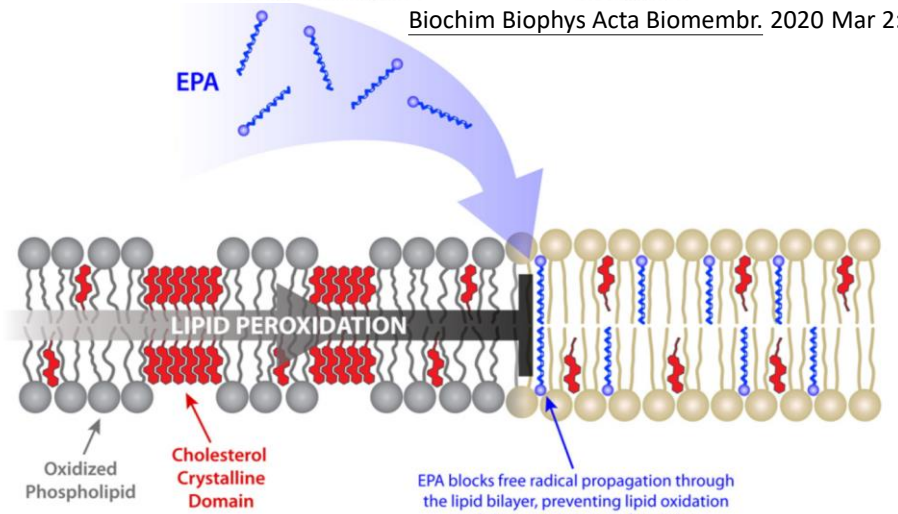
EPA has potent **antioxidant** effects in various apolipoprotein B-containing lipoprotein particles (LDL, VLDL, and small dense LDL) and in model membranes.



Arterioscler Thromb Vasc Biol. 2020;40:00–00.

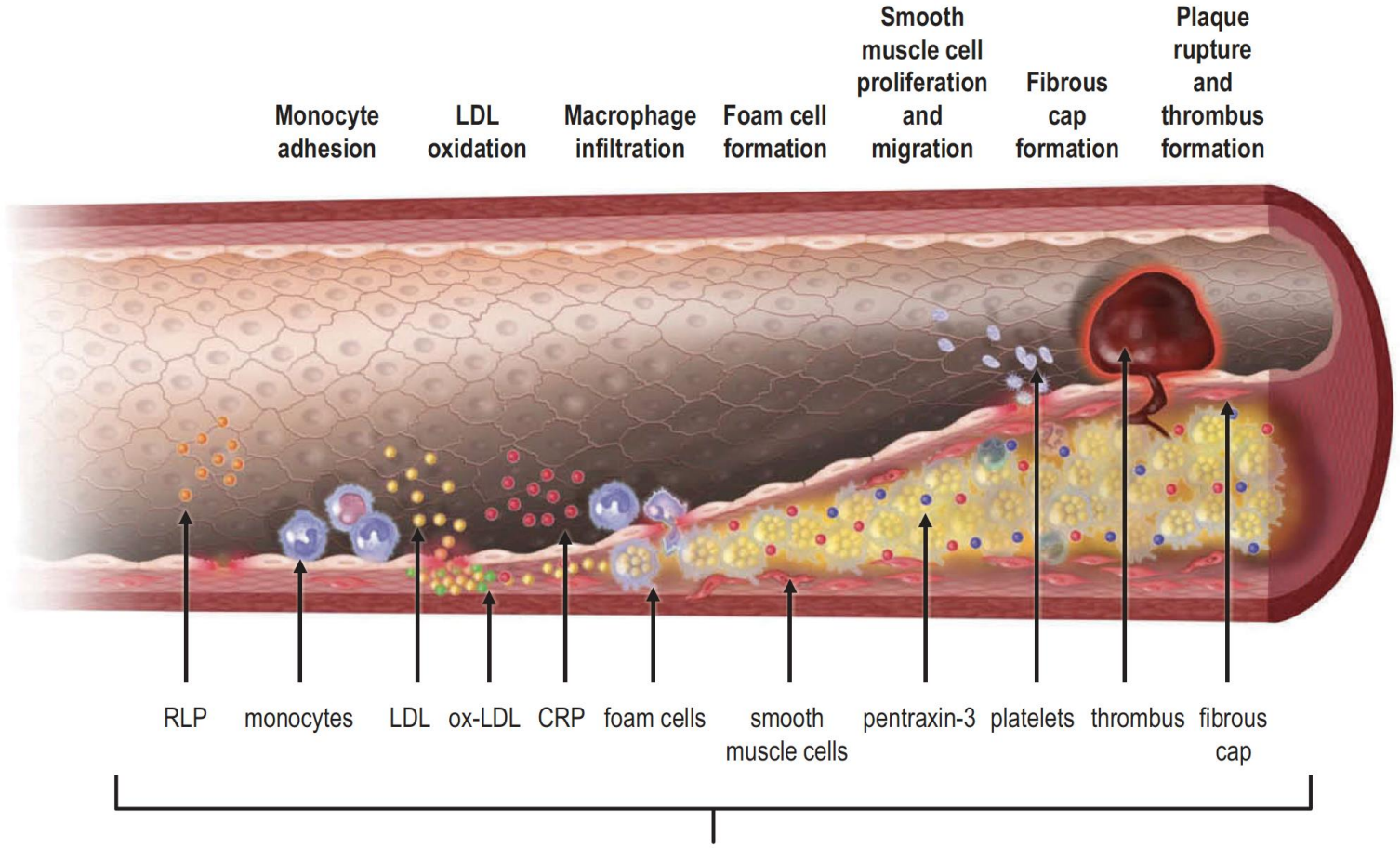


Biochim Biophys Acta Biomembr. 2020 Mar 2:183254.



Current Atherosclerosis Reports (2019) 21: 2

EPA reported to exert beneficial effects at multiple steps in the atherogenic pathway



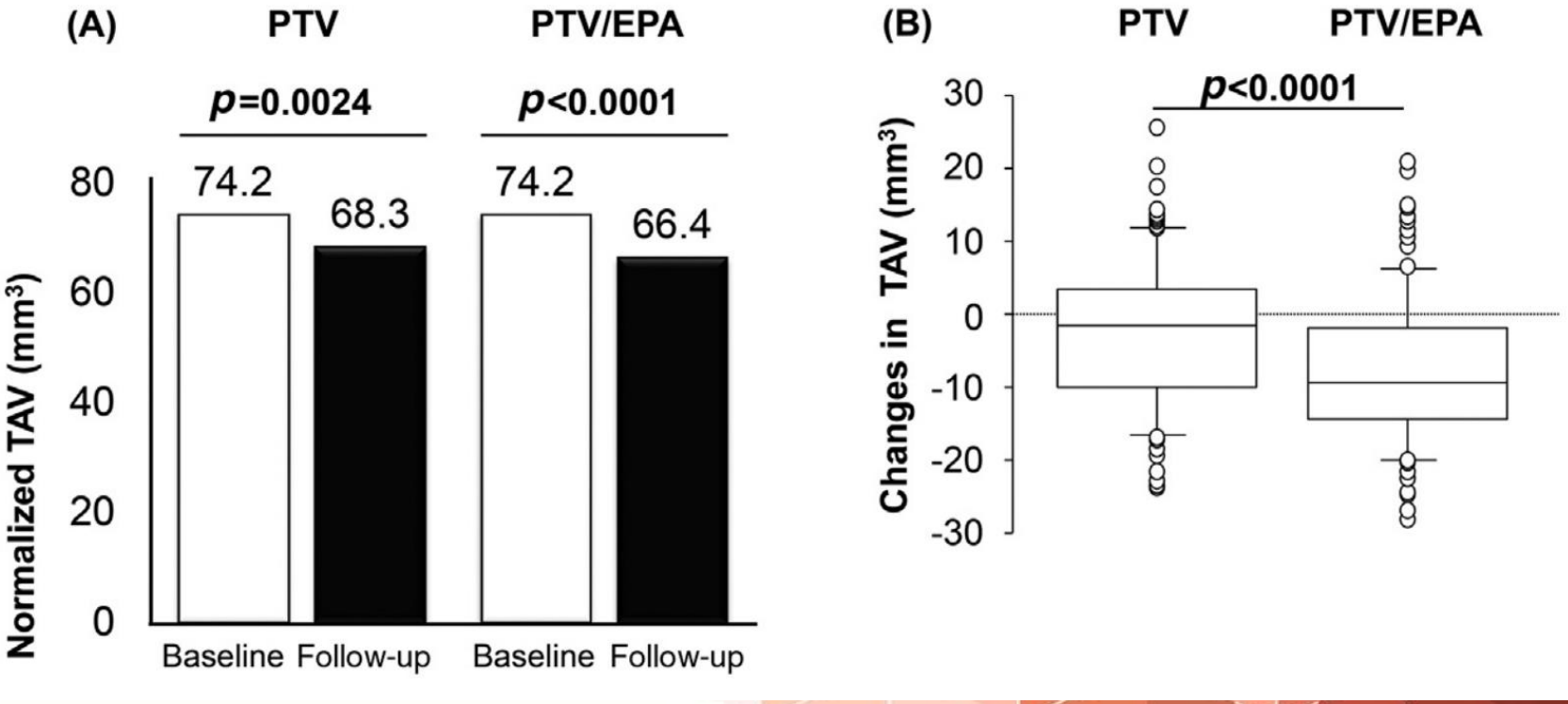
EPA reported to exert beneficial effects at multiple steps in the atherogenic pathway

POSTGRADUATE MEDICINE 2019, VOL. 131, NO. 4, 268–277

Combination EPA/statin therapy significantly reduced coronary plaque volume compared to statin therapy alone

Methods: We enrolled 193 CHD patients who underwent percutaneous coronary intervention (PCI) in six hospitals. Patients were randomly allocated to the PTV(pitavastatin) 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).

TAV = total atheroma volume



Journal of Cardiology 70 (2017) 537–544

EPA has been shown to associate with atherosclerotic plaque membranes in blood vessels where it interferes with lipid oxidation and various signal transduction pathways linked to inflammation and endothelial dysfunction.

Table 2 Effects of EPA on plaque progression [2•, 45]

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

AA arachidonic acid, *EPA* eicosapentaenoic acid, *hsCRP* high-sensitivity C-reactive protein, *ICAM-1* intercellular adhesion molecule 1, *IL-6* interleukin 6, *IL-10* interleukin 10, *Lp-PLA_2* lipoprotein-associated phospholipase A, *MMPs* matrix metalloproteinases, *oxLDL* oxidized low-density lipoprotein, *RLP-C* remnant lipoprotein cholesterol

Reason(2) :

Metabolic data provide evidence that pure-EPA do **not** raise LDL cholesterol levels, whereas DHA-based formulations do

Table 2 Prescription *n*-3FA products indicated as an adjunct to diet to reduce TG levels in adults with severe hypertriglyceridemia (TG ≥ 500 mg/dL) according to FDA-approved product package inserts [18–21]

	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 with meals	2 caps twice daily or 4 caps daily with or without meals
% Lipid/LP change Rx vs placebo (per PI)			
TG	− 51.6	− 33[b]	− 21[b]
LDL-C	+ 49.3	− 2	+ 15
non-HDL-C	− 10.2	− 18	− 10[b]
TC	− 8.0	− 16	− 9
HDL-C	+ 9.1	− 4	+ 4
VLDL-C	− 40.8	− 29[b]	− 21
apoB	Not reported	− 9[b]	+ 2

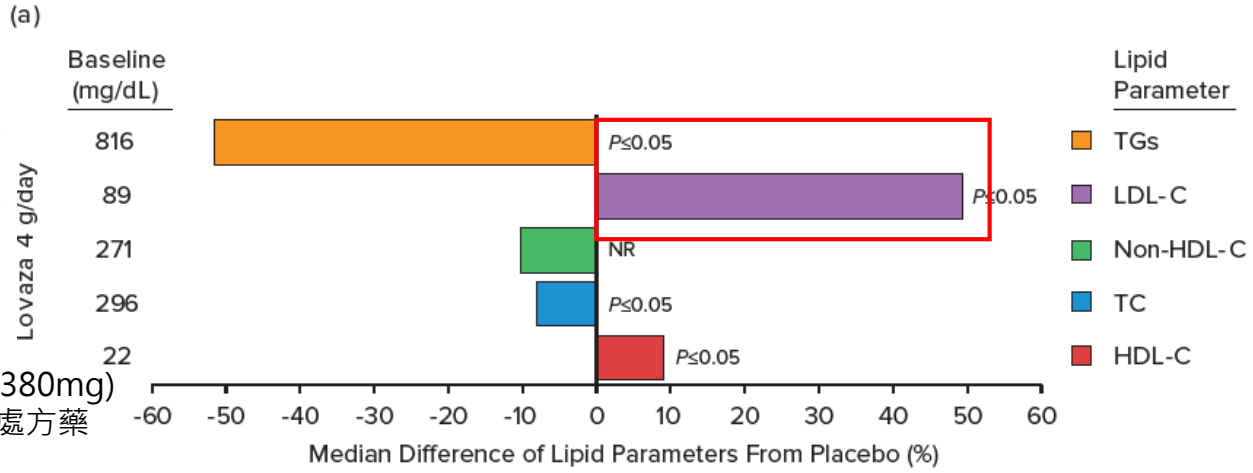
Table 3 Lipid/lipoprotein effects of *n*-3FA

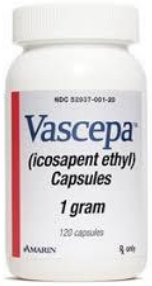
Mean response to *n*-3FA	EPA (% change)	DHA (% change)
LDL-C	− 0.7	+ 2.6
TG	− 15.6 (− 4.4 to 40.5)	− 22.4 (− 8.9 to 30.3)
HDL-C	+ 1.4 (± 3.5%)	+ 7.3% (± 6.1%)
non-HDL-C	− 2.9 (± 3.3%)	− 1.2 (± 2.9%)

Curr Atheroscler Rep (2017) 19:60

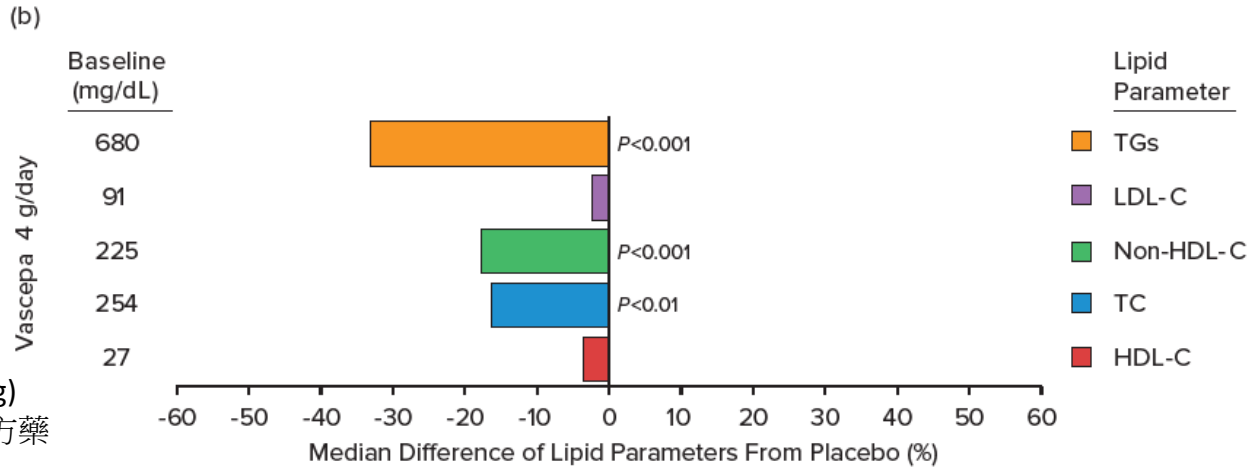
臨床觀察到混合型魚油(DHA/EPA)會導致LDL-C反竄，但純EPA魚油不會

(EPA460mg/DHA380mg)
美國混合型魚油處方藥





(EPA1000mg)
美國純EPA處方藥



X2 a day

Take two 1-gram capsules twice a day with food.

X2 a day

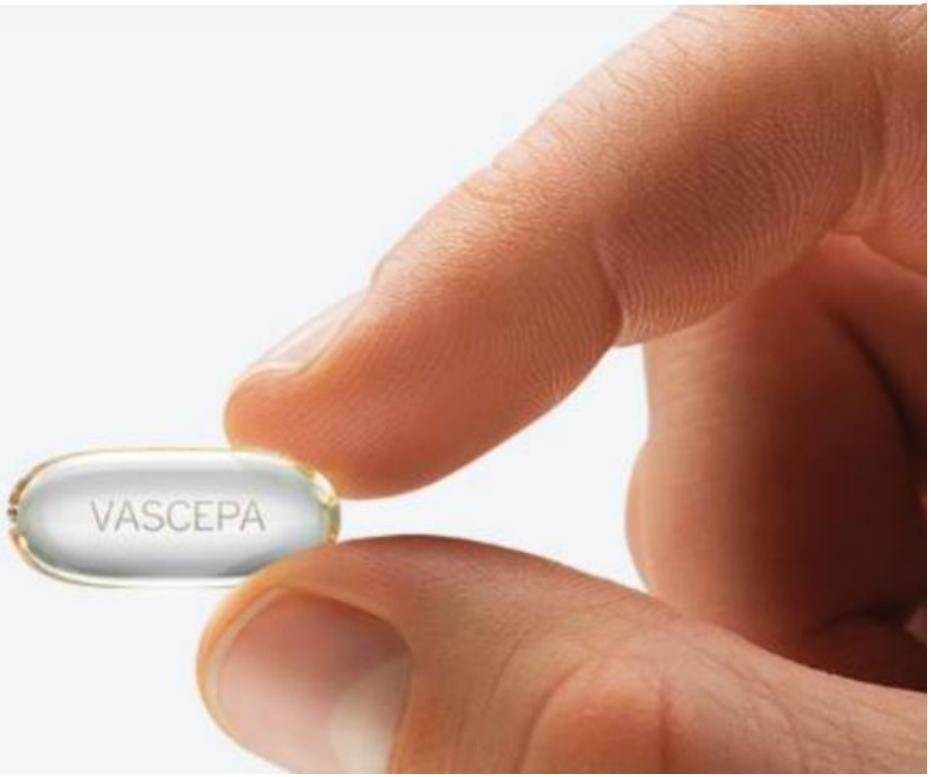
Take four 0.5-gram capsules twice a day with food.

VASCEPA is the first and only prescription EPA treatment clinically proven, along with diet, to lower very high triglycerides in adults by

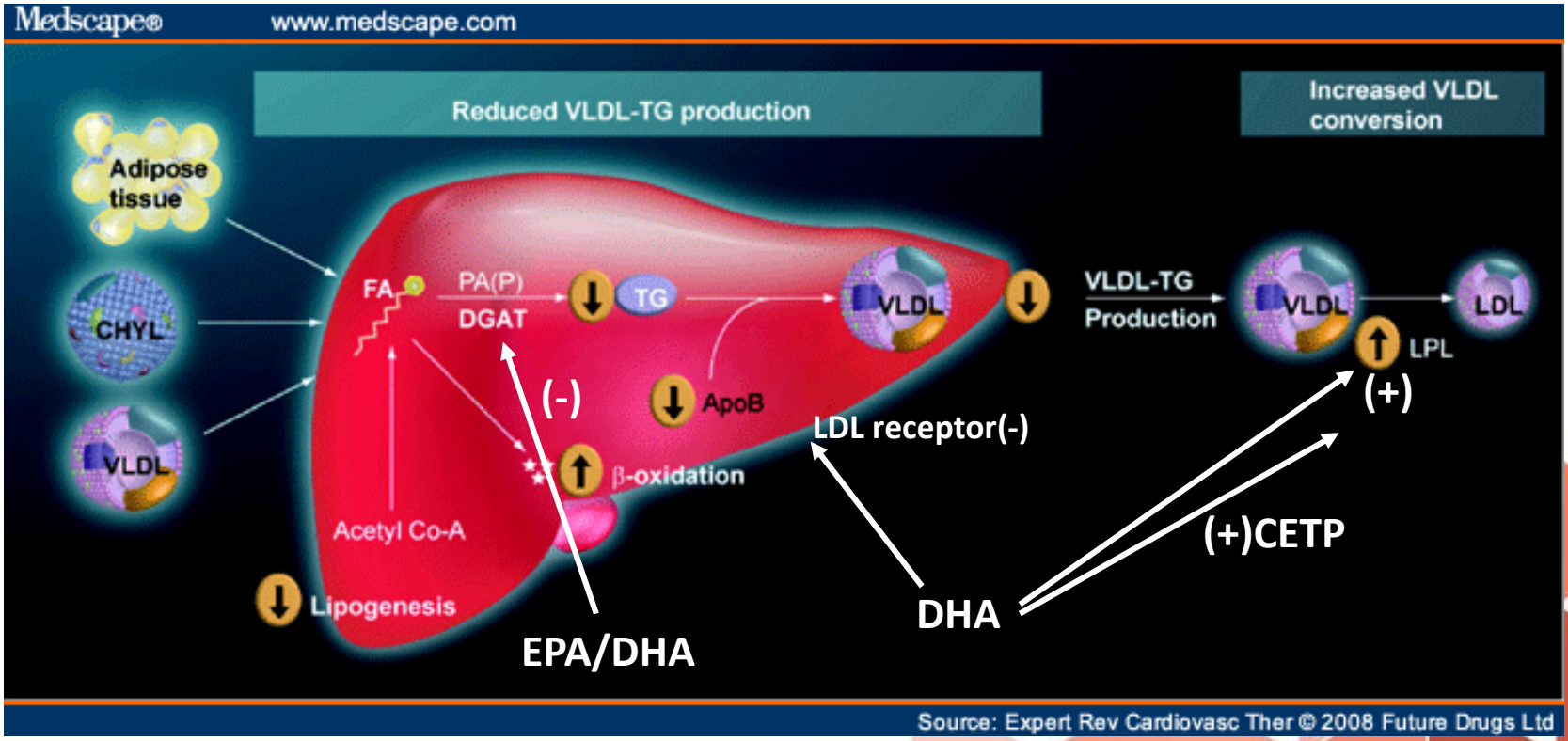
↓33%

without raising bad cholesterol (LDL-C).†

Download your Savings Card now and talk to your doctor about VASCEPA today!

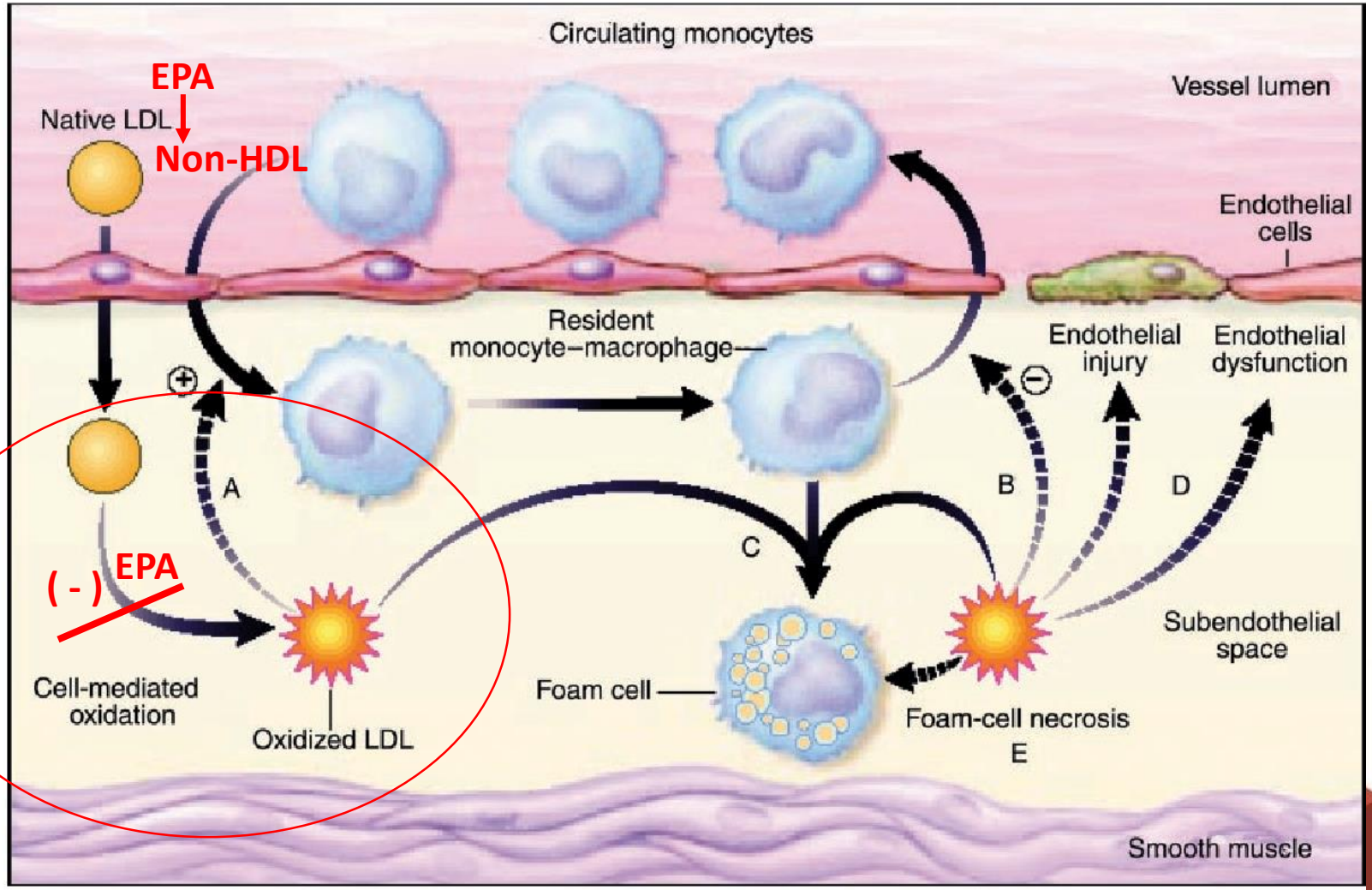


DHA一共透過三個機轉
讓LDL-C上升!



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

結論：EPA不只降低non-HDL-c，更能抑制脂蛋白(VLDL/LDL)的氧化!!!



EVAPORATE: Early Mechanistic Clues to *Vascepa's* CV Benefits

American Heart Association. Scientific Sessions
NOV. 16-18, 2019 | PHILADELPHIA, PA

Patrice Wendling

November 19, 2019

PHILADELPHIA — Interim results from a study designed to explain the striking results from the REDUCE-IT trial with icosapent ethyl (*Vascepa*, Amarin) show that the high-dose eicosapentaenoic acid (EPA) therapy slows, but does not reverse, coronary plaque progression.

Among 67 statin-treated patients with high triglycerides, there was no significant difference in the primary endpoint — change in low attenuated plaque — between those treated with icosapent ethyl or placebo in the EVAPORATE study.

There was significantly less progression, however, in total, noncalcified, fibrous, and calcified plaque in the icosapent ethyl group on interim CT angiography at 9 months, Matthew Budoff, MD, UCLA School of Medicine, Torrance, California, reported here at the American Heart Association (AHA) Scientific Sessions 2019.

EVAPORATE: Effect of EPA on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy

Randomized, Double-Blind, Placebo-Controlled Trial

Patient Population (N=~80)

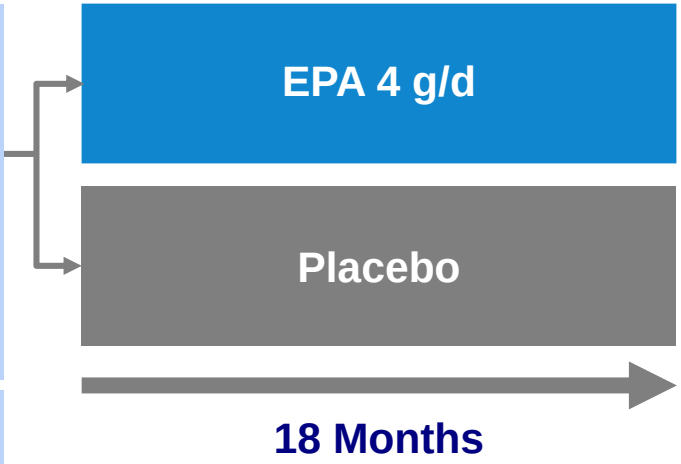
- 30–85 years of age
- TG: 135–499 mg/dL
- LDL-C >40 mg/dL and ≤115 mg/dL (on statin)
- ≥1 angiographic stenosis with ≥20% narrowing by CTA
- No history of MI, stroke, or life-threatening arrhythmia within the prior 6 months and no history of CABG

Primary endpoint

- Progression rates of low attenuation plaque

Secondary endpoints include

- Plaque morphology and composition
- (non-calcified, total, fibrous, fibrofatty, calcified)
- Markers of inflammation (Lp-PLA_2)
- LDL-C and HDL-C



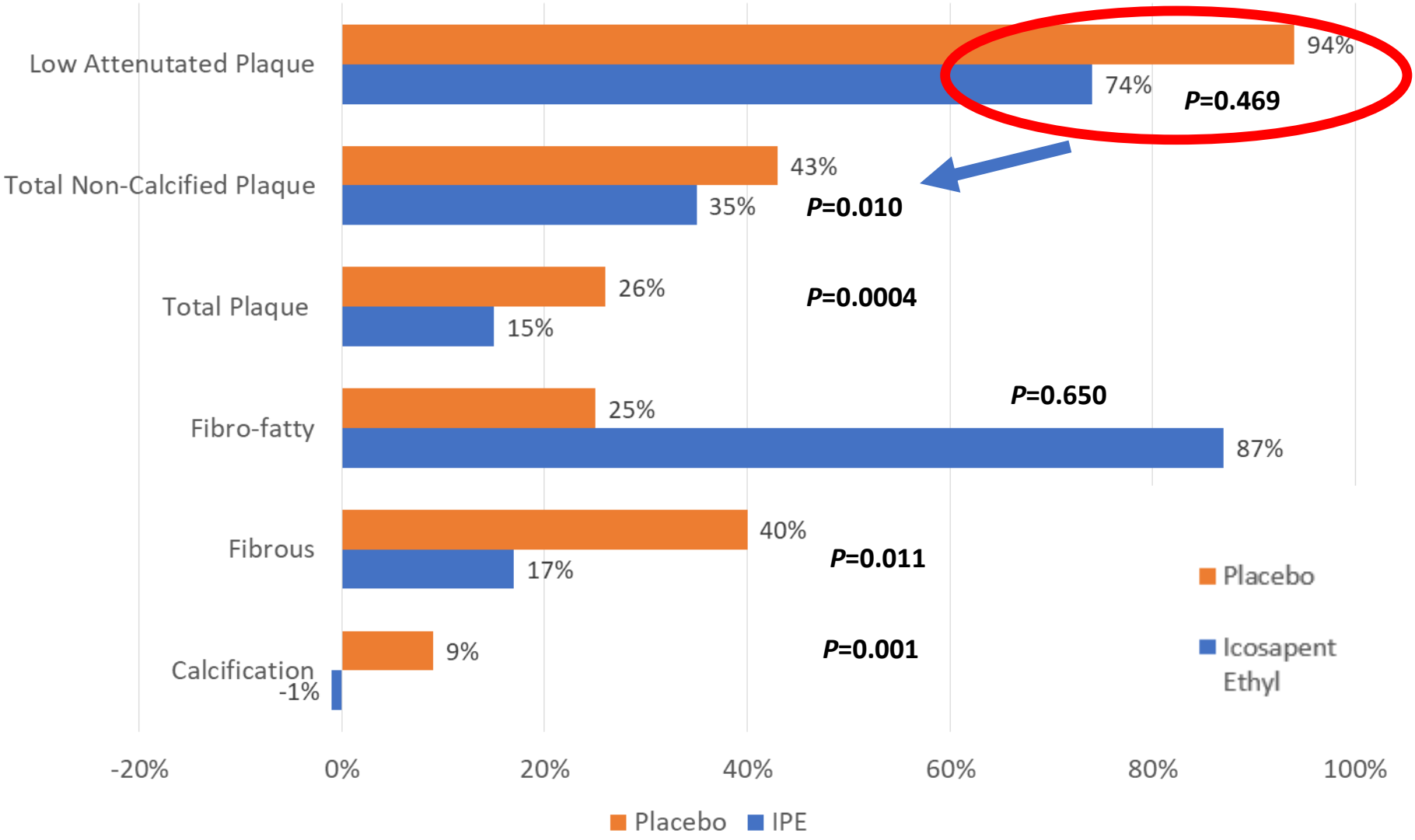
The EVAPORATE study seeks to determine whether IPE 4g/d will result in a greater change from baseline in plaque volume than placebo in statin-treated patients

Exclusion criteria:
Severe (NYHA class IV) heart failure ; Contrast Allergy;
Renal Insufficiency (eGFR <60) or Hypersensitivity to fish and/or shellfish

CABG=coronary artery bypass graft; CTA=computed tomography angiography.

EVAPORATE Clinical Trial. https://clinicaltrials.gov/ct2/show/NCT02926027. Updated February 08, 2018. Accessed June 19, 2018.

Fully adjusted median Plaque Progression at 9 months



EVAPORATE: Conclusions

- Mechanistic Study using Coronary CT Angiography demonstrated benefits of Icosapent Ethyl as adjunct to statin on plaque characteristics at 9 months, and study is continuing to 18 months as planned

- Demonstrated that placebo progression rates using mineral oil is similar to non-mineral oil (cellulose) using same methodology, scanner and laboratory in a matched cohort.

MDCT Coronary Imaging and CV Outcome Trials

Drug	CTA Progression	CVOT
Rosuvastatin	+++ (regression)	+++
Atorvastatin	+++ (regression)	+++
Estrogen	Neutral	Neutral
Rivaroxaban vs Warfarin	++ (slowed progression)	++
Fish Oil (EPA)	++ (slowed progression)	+++
Testosterone	Progression	Harmful
Apixaban vs Warfarin	+ (slowed progression)	+

Eicosapentaenoic Acid: Atheroprotective Properties and the Reduction of Atherosclerotic Cardiovascular Disease Events

These posters and oral presentations were presented from the 28th to 30th March as part of the American College of Cardiology (ACC) Together With World Congress of Cardiology (WCC) Virtual Congress

Speakers: Anthony David Pisaniello,[1] Stephen J. Nicholls,[2] Christie M. Ballantyne,[3] Deepak L. Bhatt,[4] Nathan D. Wong[5]

1. Johns Hopkins University, Baltimore, Maryland, USA
2. South Australian Health and Medical Research Institute, University of Adelaide, Adelaide, Australia
3. Center for Cardiometabolic Disease Prevention, Baylor College of Medicine, Houston, Texas, USA
4. Brigham and Women's Hospital Heart and Vascular Centre and Harvard Medical School, Boston, Massachusetts, USA
5. Heart Disease Prevention Program, Division of Cardiology, University of California, Irvine School of Medicine, Irvine, California, USA

Table 1: JELIS trial and REDUCE-IT characteristics.

JELIS trial characteristics	REDUCE-IT trial characteristics
Homogenous patient population from one country	Multinational study with different patient populations
Prospective, randomised, open-label study	Randomised, double-blind, placebo-controlled study
Patients were receiving low-efficacy statin	Patients were receiving high-efficacy statin therapy
EPA treatment of approximately 2 g/day	EPA treatment of 4 g/day
Baseline EPA 95–97 µg/mL	Baseline EPA 26 µg/mL
Greatest benefit in secondary prevention	Inclusion of mostly secondary prevention and high-risk individuals with diabetes and AGE
Greatest benefit found in patients with elevated triglycerides >150 mg/dL and low HDL cholesterol	Entry criteria included elevated triglycerides >150 mg/dL on statin therapy

Adapted from Yokoyama et al.[4] and Bhatt et al.[5]

AGE: advanced glycation end products; EPA: eicosapentaenoic acid; HDL: high-density lipoprotein.

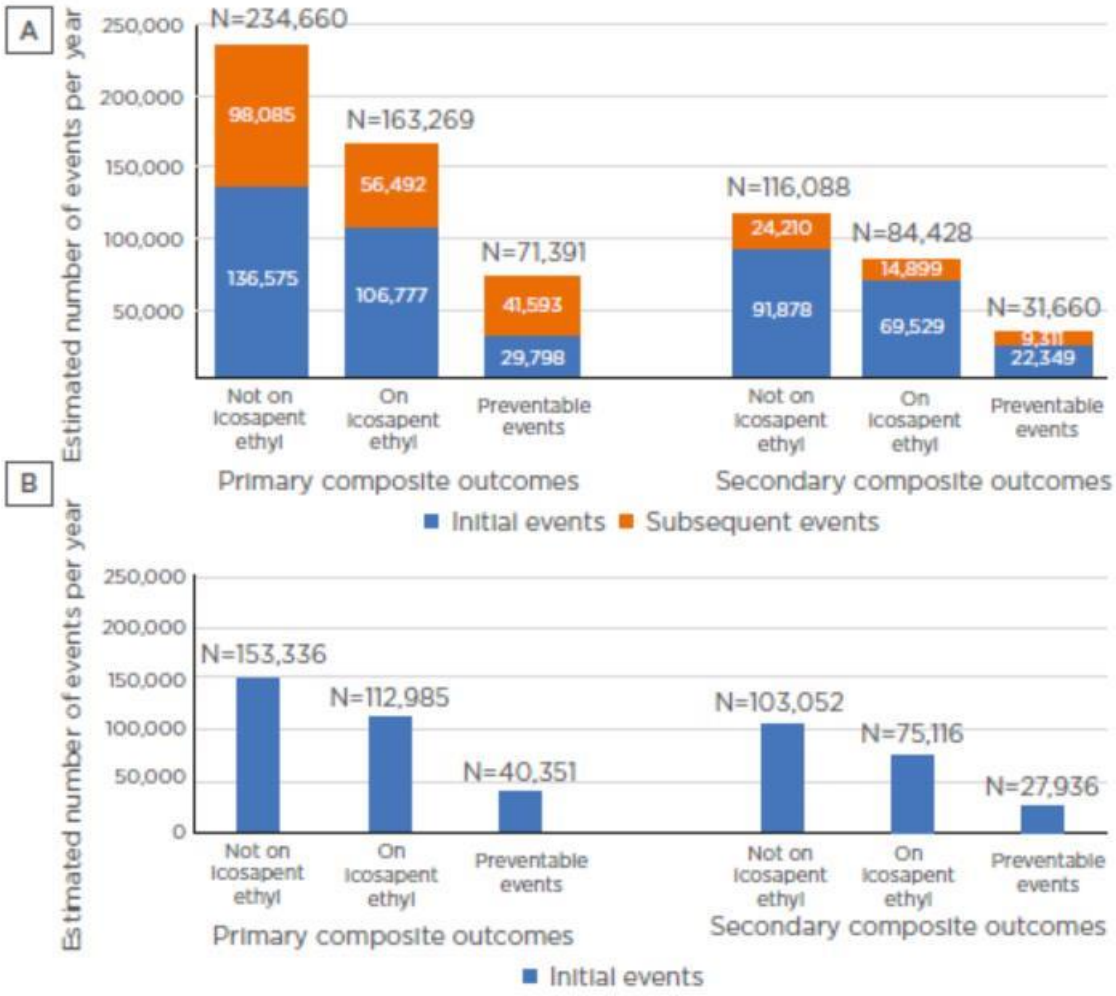


Figure 1: A) Distribution of annual projected initial and subsequent preventable primary and secondary composite endpoint events in the USA if eligible individuals were on icosapent ethyl (NHANES 1999–2016). **B)** Distribution of annual projected initial preventable primary and secondary composite endpoint events in the USA if eligible individuals were on icosapent ethyl based on REDUCE-IT USA results (NHANES 1999-2016).

NHANES: National Health and Nutrition Examination Survey.

Contents

- Omega-3 in TG lowering
- What is EPA ?
- EPA/DHA & *2ed* prevention
- EPA/DHA & *1st* prevention
- Why is EPA not DHA effective for *1st* prevention ?
- **How to choice EPA product ?**
- Conclusions

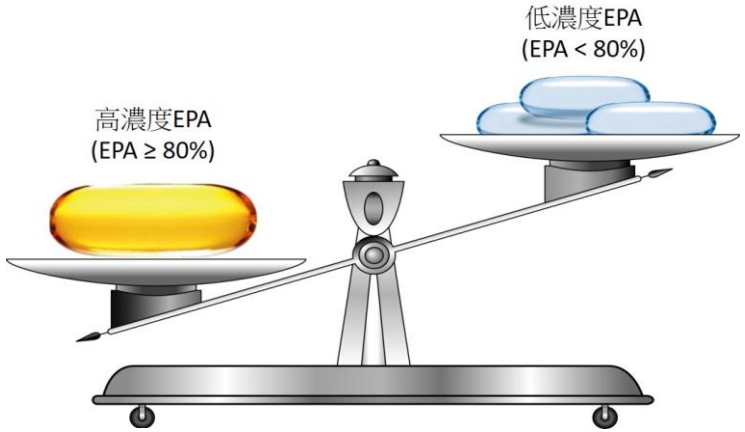
EPA產品挑選三大關鍵

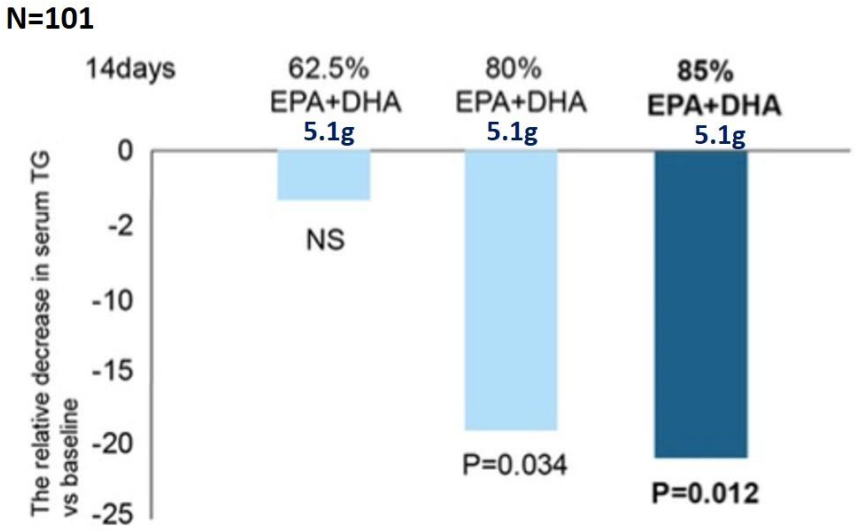
濃度(>80%)

純度(不含DHA)

重金屬(<0.1ppm)

EPA/DHA濃度與吸收率呈正比
建議選擇濃度80%以上EPA產品!





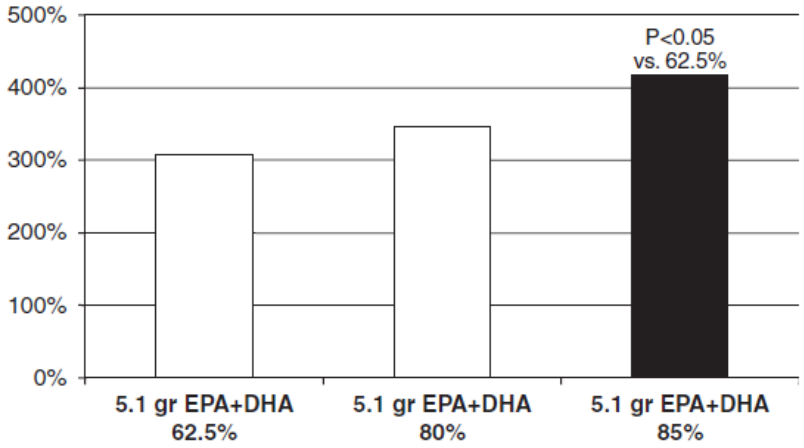


Fig. 1. Relative increase in EPA serum phospholipids versus baseline from day 0 to 14.

Prostaglandins, Leukotrienes and Essential Fatty Acids 75 (2006) 19–24

DHA會提升LDL-C
初級預防建議選擇不含DHA之純EPA產品

高濃、純度EPA能有效降低三酸甘油酯 (20%~50%)，且不提升壞的膽固醇 (LDL)。但含有DHA 的魚油會增加 20%~45% 的壞的膽固醇 (LDL)。

一般OMEGA-3產品僅要求驗到重金屬上限2ppm，藥品級是0.1ppm

	歐盟魚油規定	台灣規定
重金屬上限	0.1ppm	2ppm

測試項目	測試方法	測試結果	定量/偵測極限(註3)	單位
EPA (as FFA)	參考行政院衛生福利部102年9月6日部授食字第1021950329號公告修正魚油中二十碳五烯酸及二十二碳六烯酸之檢驗方法	14.11	0.05	g/100g
DHA (as FFA)		23.49	0.05	g/100g
砷 (As)	參考行政院衛生福利部 103 年8 月25 日部授食字第1031901169 號公告修正重金屬檢驗方法總則	未檢出	2.0	ppm(mg/kg)
鉛 (Pb)		未檢出	2.0	ppm(mg/kg)
鎘 (Cd)		未檢出	2.0	ppm(mg/kg)
汞 (Hg)		未檢出	2.0	ppm(mg/kg)
銅 (Cu)		未檢出	2.0	ppm(mg/kg)

備註：1.測試報告僅就委託測試者之委託事項提供測試結果，至若本產品之合法性，仍應由主管機關依法判斷。

2.本報告不得分離或擷錄使用。

3.若該測試項目屬於定量分析則以「定量極限」表示；若該測試項目屬於定性分析則以「偵測極限」表示。

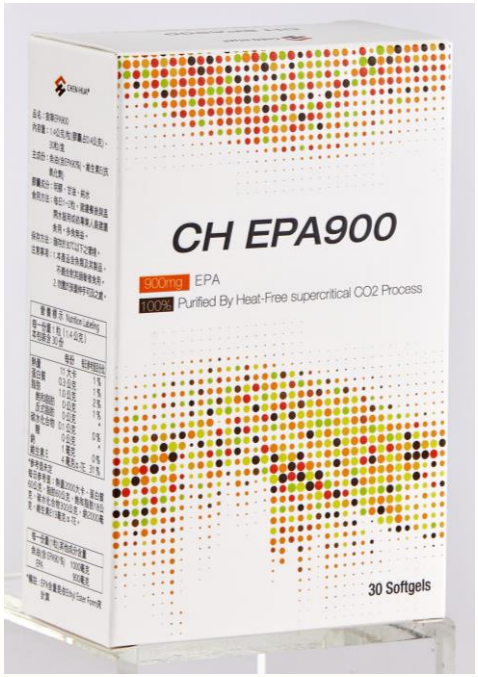
4.低於定量極限/偵測極限之測定值以 "未檢出"或" 陰性 " 表示。

5.本次委託測試項目(EPA及DHA)由SGS食品實驗室-高雄執行。

- END -

台灣唯一90%純EPA產品

更易達到有效EPA劑量！且負擔更低！



	宸華 EPA900	台灣 藥品級 魚油	一般 食品 魚油
EPA濃度	>90% (實際驗出94%)	46%	<15%
DHA濃度	0%	38%	<15%
重金屬檢驗上限	<0.1ppm (食品級最嚴格)	<0.1ppm	<2ppm
預防心血管疾病 (1.8~4gEPA/天)	NT 100~200 (2~4顆)	NT 240~480 (4~8顆)	-

混合型一無是處嗎！？

- 二次預防(歐盟是應證/美國心臟協會建議)
- IgA腎炎(KADIGO Guideline建議)
- 乾眼症(美國乾眼症Guideline建議)
- 關節炎(澳洲風濕免疫協會建議)
- 癌症術後補充(歐洲癌症Guideline建議)
- **上述病況，還是根據混合型的臨床實證及Guideline推薦**

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Take home messages

- 1g omega-3 mixture is effective for 2nd prevention but not for 1st prevention
- High dose of EPA(1.8~4g) has been proved effective for 1st prevention by recent clinical trials
- “In patients with ASCVD or other cardiac risk factors on top of statin with controlled LDL-C, but elevated TG (135-499 mg/dL), the addition of EPA should be considered to reduce cardiovascular risk” recommended by ADA & ESC/EAS
- High concentration(80%) , without DHA & heavy metal <0.1ppm are key points to choice EPA product

濃, 純, 淨

“顧心臟，顧心情，通血路，心臟不會碰碰秤”

感謝聆聽 敬請指教