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

中醫大附醫 智能糖尿病暨代謝運動中心

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50克的鯷魚(祕魯近海小型鯷魚)

首頁 » 歐洲食品 » 義大利Delicius—油漬鯷魚罐頭

P G+1

義大利Delicius—油漬鯷魚罐頭

價格：NT$165元

重量：46g
保存方式：陰涼處存放，開封後冷藏

數量：1 放入購物車

- 《livescience》報導，然而今年到目前為止，有紀錄以來的死亡數字就已達到73隻，包含3隻在阿拉斯加州、5隻在加拿大（Canada）卑詩省、25隻在華盛頓州、3隻於奧勒岡州與37隻於加州。
- 明顯營養不良真正死亡量還有很多

- 科學家發現，在這些死亡的灰鯨屍體中，大部分都已缺乏脂肪、消瘦、明顯營養不良，這代表前一年在北極的覓食季節中，很可能因為糧食短缺而吃得不夠—箇中關鍵在於北極海域嚴重暖化、人類過度捕撈商業用之磷蝦，導致灰鯨因食物不足而死亡。

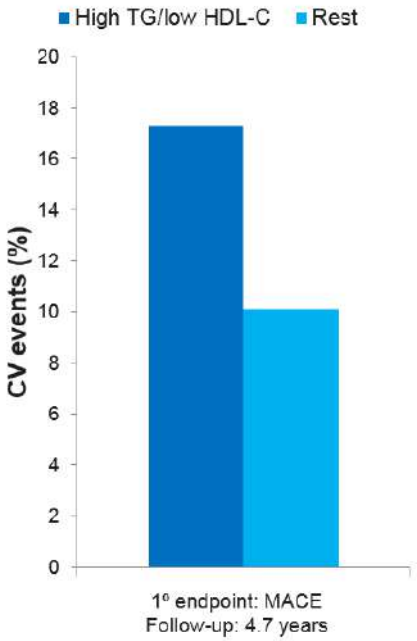
- 酒駕也將啟用「連坐罰」，若酒駕者酒精濃度超過0.25毫克以上，同車只要年滿18歲以上的乘客都將受罰，可處罰鍰6百元至3千元，其中，年滿18歲、未滿20歲的乘客可罰600元至900元；乘客20歲以上，日間開罰2200元至3000元，夜間則開罰1500元至1900元。
- 酒駕累犯或拒絕酒測者，若致人重傷或死亡，將直接沒入車輛，交通部說明，若駕駛人本身為車輛所有人，將直接沒入；但若駕駛人並非車輛所有人，不過，車輛所有人借用車輛給該駕駛人時，已知其有喝酒、吸毒或者即將有類似情節時，也會直接沒入。

in cardiovascular disease

高風險族群，就算有在接受Statin治療，TG過高仍會明顯增加心血管疾病風險

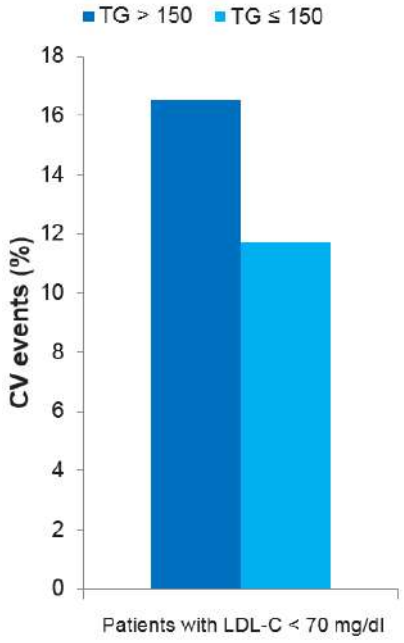
ACCORD-Lipid trial

- 5518 patients with T2DM
- All patients treated with simvastatin



PROVE-IT TIMI

- Post ACS trial
  急性冠心症(acute coronary syndrome, ACS)
- All patients treated with atorvastatin 80 mg or pravastatin 40 mg



將OMACOR與Statin並用是安全的

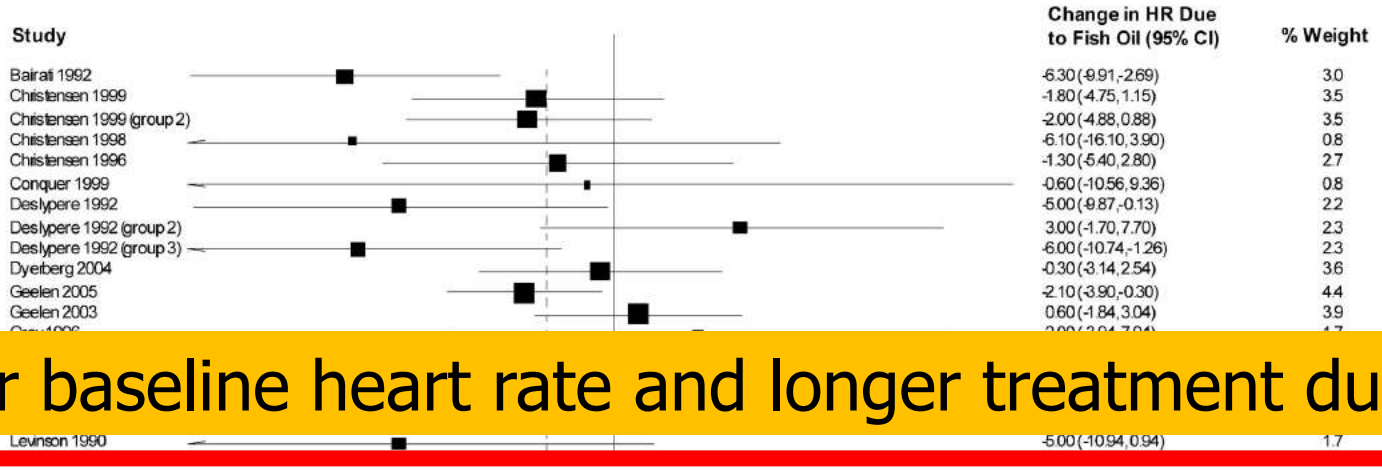
Treatment-Emergent Adverse Event (AE): Overview

	Omacor + Atorvastatin (N=122)	Placebo + Atorvastatin (N=122)
Subjects with any AE	79 (64.8%)	72 (59.0%)
Subjects discontinuing for AE	8 (6.6%)	6 (4.9%)
Subjects with drug-related AE	16 (13.1%)	16 (13.1%)
Subjects with SAE	4 (3.3%)	2 (1.6%)
Subjects with drug-related SAE	0	0

SAE=serious adverse event

Maki K et al presented at ATVB meeting April 29, 2009

Omega-3 reduced heart rate



Higher baseline heart rate and longer treatment duration

- Direct effects on cardiac electrophysiological pathway
- Improving left ventricular diastolic filling
- Augmenting vagal tone

Mozaffarian D et al., Circulation 2005;112:1945-1952

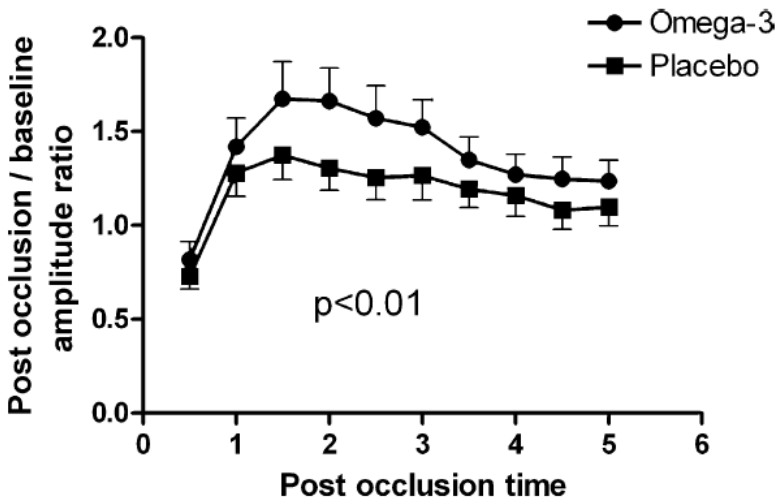
Omega-3 reduce blood pressure

- Increase NO production
- Mitigate vasoconstriction response to norepinephrine and angiotensin II
- Enhance vasodilatory responses
- Improve arterial compliance

	(mmHg)
Overall	2.27, −0.62)
Age	
⩽ 45 years	1.93, 0.01)
> 45 years	3.65, −1.03)
	0.089
Gender*	
Male/female	3.03, −0.91)
Male only	1.97, 0.52)
	0.13
Hypertension†	
No	1.61, 0.27)
Yes	3.95, −1.52)
	0.010
Body mass index	
⩽ 26.8 kg/m^2	2.58, −0.10)
> 26.8 kg/m^2	2.34, −0.17)
	0.93

Geleijnse JM et al., J Hypertens 2002;20:1493-1499

Omega-3 improves endothelial function



Subjects: obese adolescents
Intervention: Omega-3 1.2 g/days for 3 months
Measurement: Flow-mediated dilation (FMD)

	Omega-3	Placebo	*p*
SBP (mmHg)	111 ± 11	110 ± 11	0.67
DBP (mmHg)	64 ± 7	64 ± 6	0.61
HR (bpm)	67 ± 11	68 ± 8	0.62
PWV (m/s)	7.0 ± 0.9	7.0 ± 0.9	0.76
AI (%)	−15.0 ± 7.6	−11.4 ± 11.2	0.05
Intima thickness (mm)	0.055 ± 0.007	0.056 ± 0.009	0.73
Media thickness (mm)	0.20 ± 0.05	0.18 ± 0.04	0.29
Intima-media thickness (mm)	0.25 ± 0.05	0.24 ± 0.04	0.39
Diameter (mm)	1.9 ± 0.2	2.0 ± 0.4	0.05
RHI	1.8 ± 0.4	2.0 ± 0.6	0.07
F-RHI	0.21 ± 0.16	0.23 ± 0.16	0.61
RH_{max} (% of baseline at max dil)	1.9 ± 0.9	1.6 ± 0.7	0.095
RH_{60s} (% of baseline at 60 s post-occlusion)	1.7 ± 1.0	1.3 ± 0.6	0.056
$AUC_{0-1\,min}$	0.6 ± 0.3	0.5 ± 0.2	0.23
$AUC_{0-3\,min}$	3.8 ± 1.9	3.2 ± 1.4	0.07
$AUC_{0-5\,min}$	6.5 ± 2.9	5.5 ± 2.3	0.11

Dangardt F et al., Atherosclerosis 2010;212:580-585

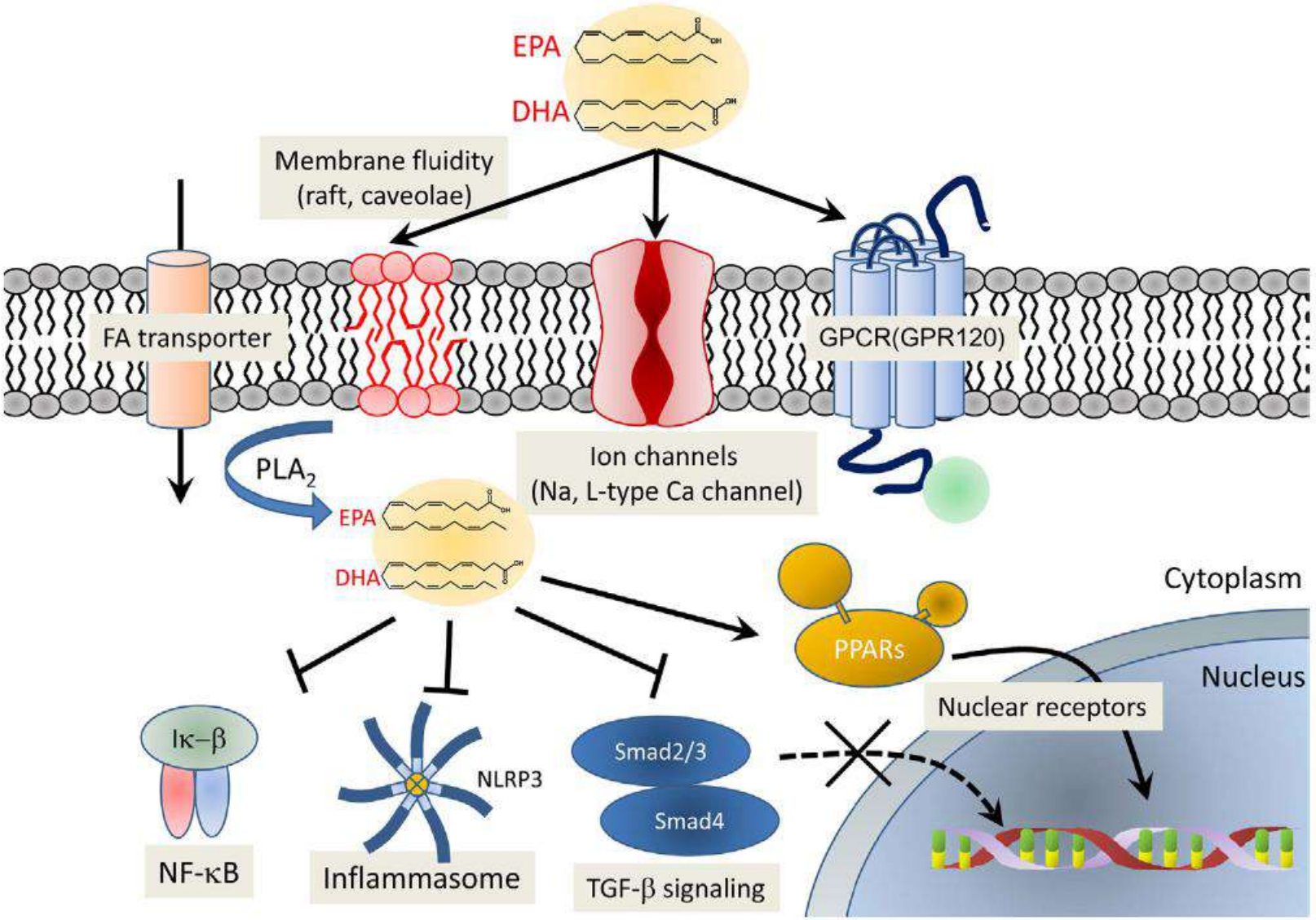
Omega-3 has anti-inflammatory effects

高血脂讓硬漢「館長」都倒下 小心你的身體正在發炎

2019年8月16日

Dangardt F et al., Atherosclerosis 2010;212:580-585

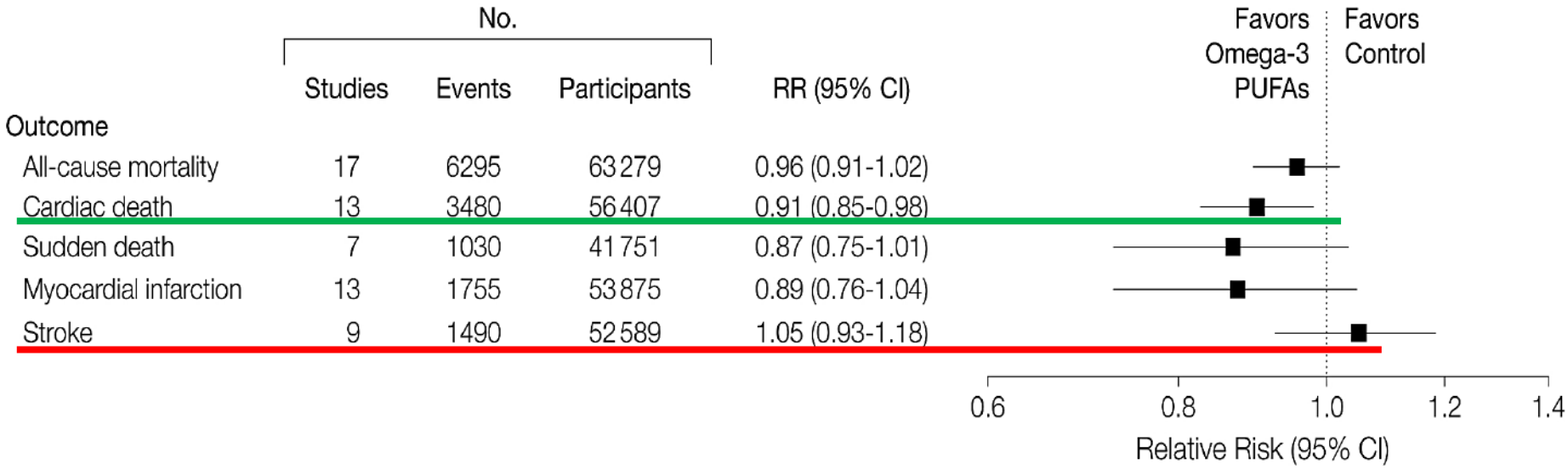
Molecular mechanisms of cardioprotection of Omega-3



Endo J et al., J Cardiol 2016;67:22-27

Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis

20 studies of 68,680 patients were included, reporting 7044 deaths, 3993 cardiac deaths, 1150 sudden deaths, 1837 myocardial infarctions, and 1490 strokes.



JAMA 2012 Sep 12;308(10):1024-33. doi: 10.1001/2012.jama.11374.

結果與安慰劑組相比無差異

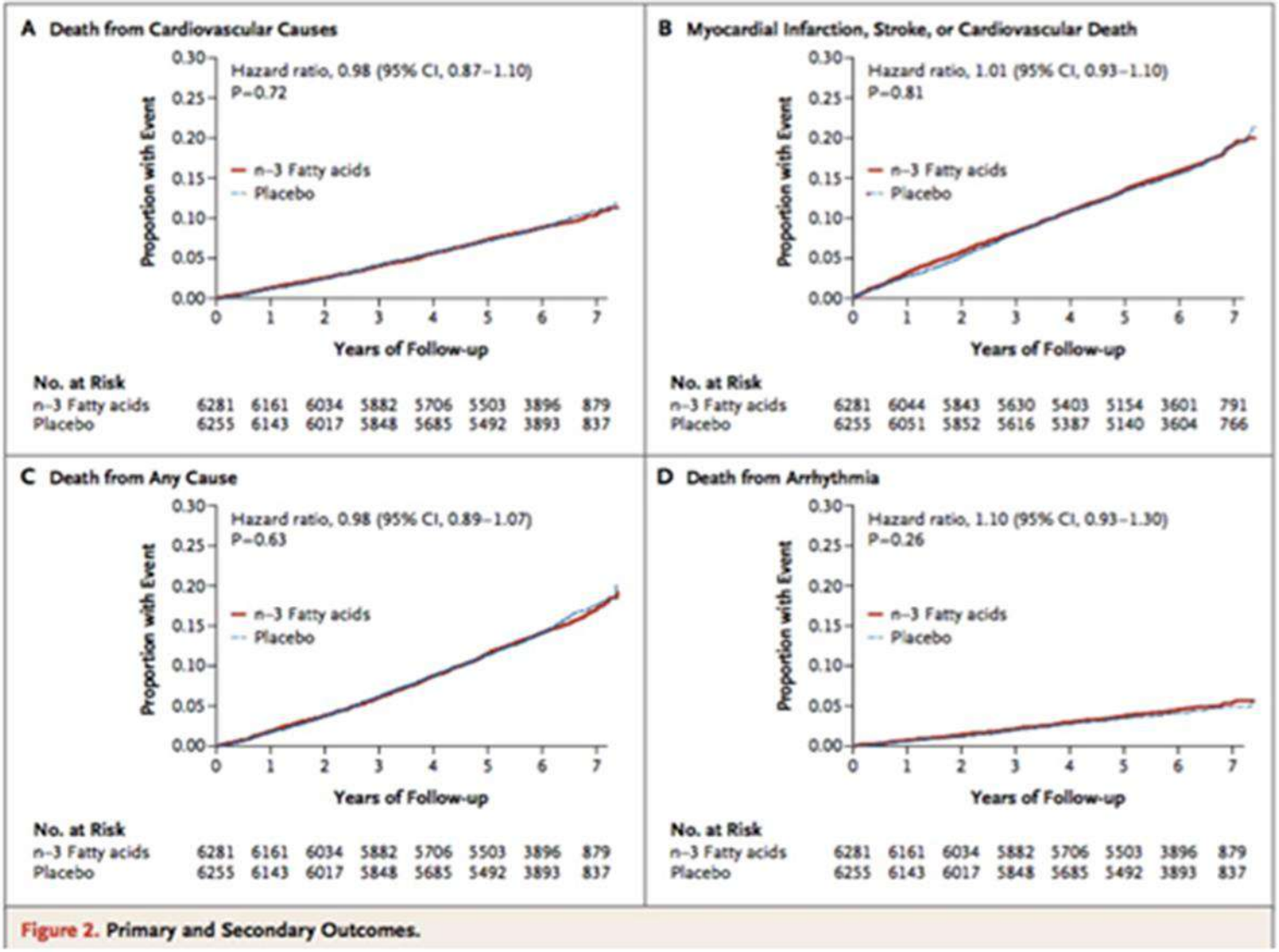
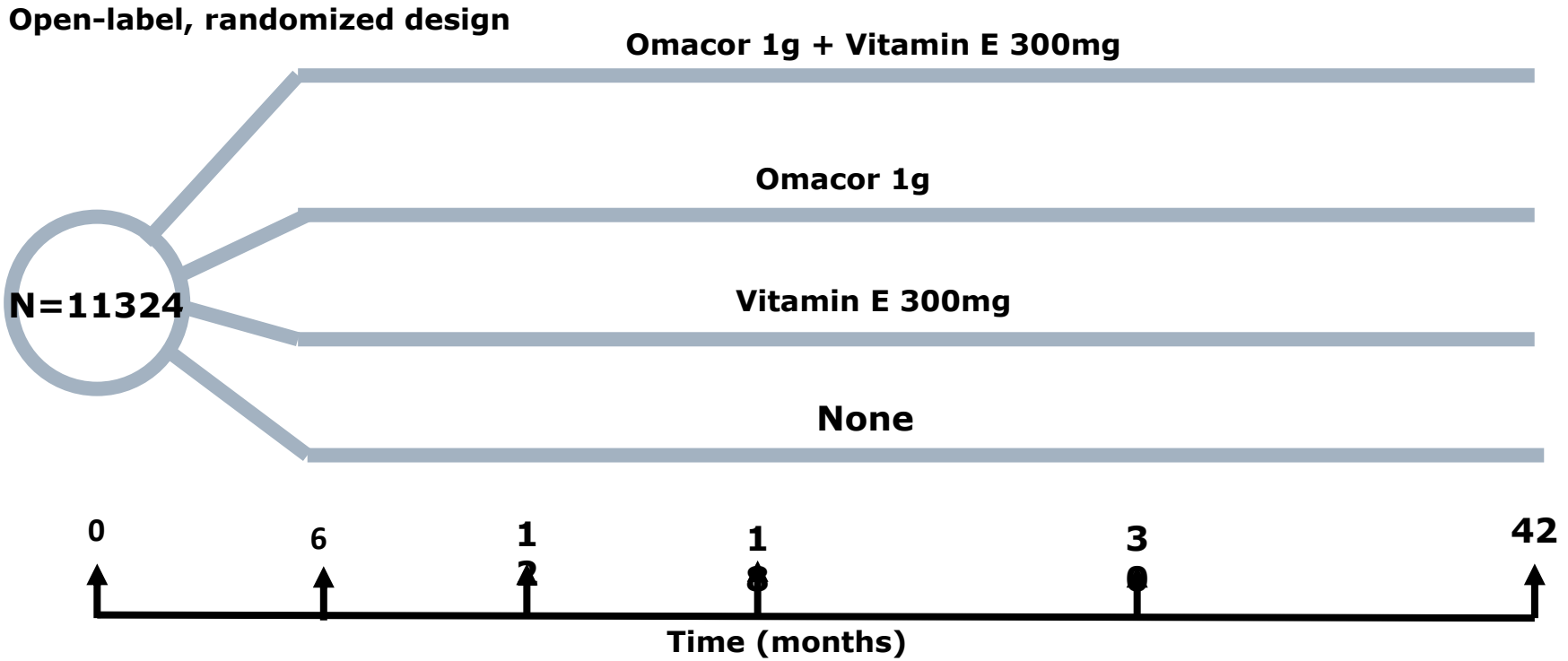


Figure 2. Primary and Secondary Outcomes.

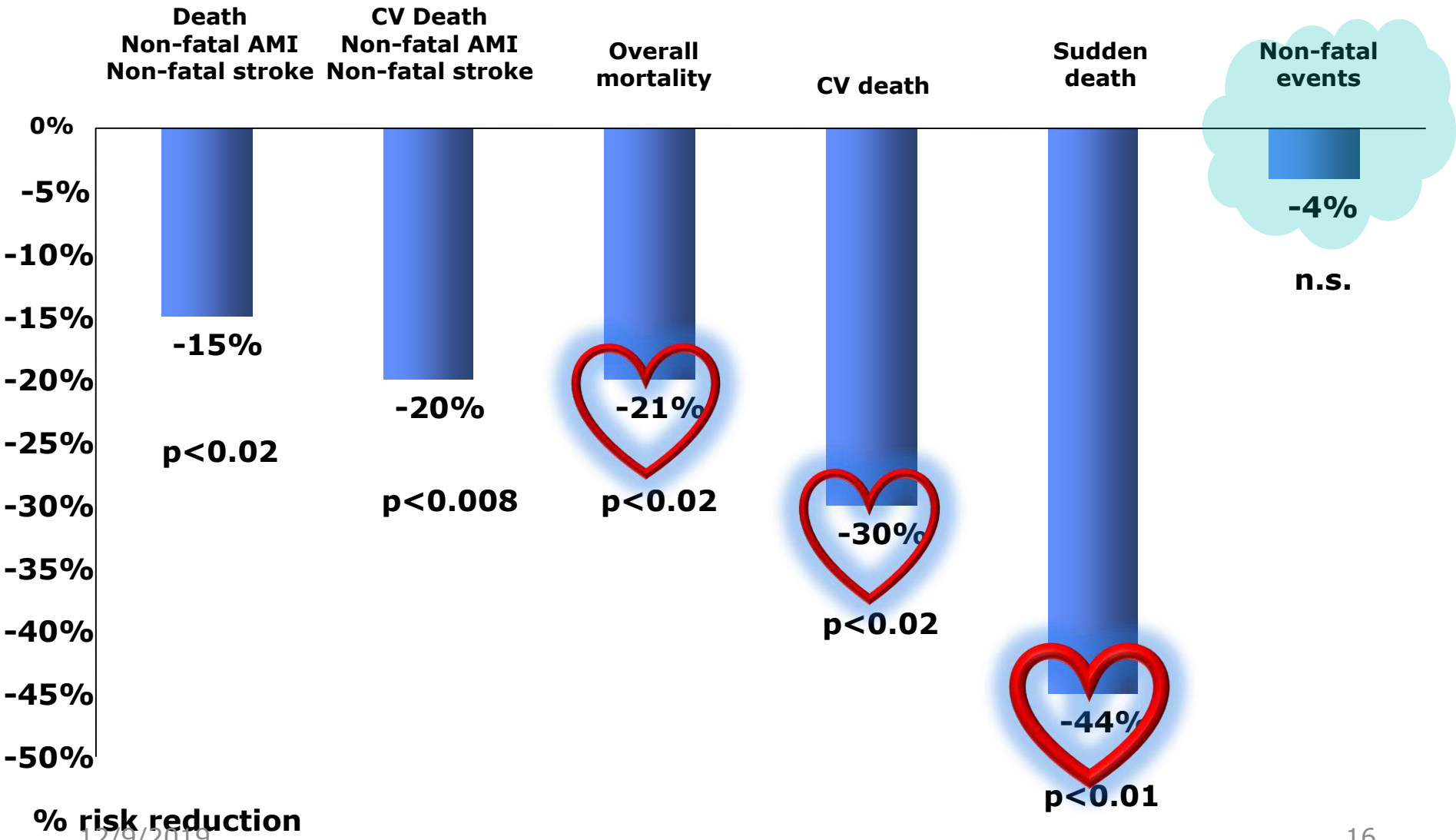
GISSI-Preventione trial

Recent MI (≤ 3 mo; median, 16d)



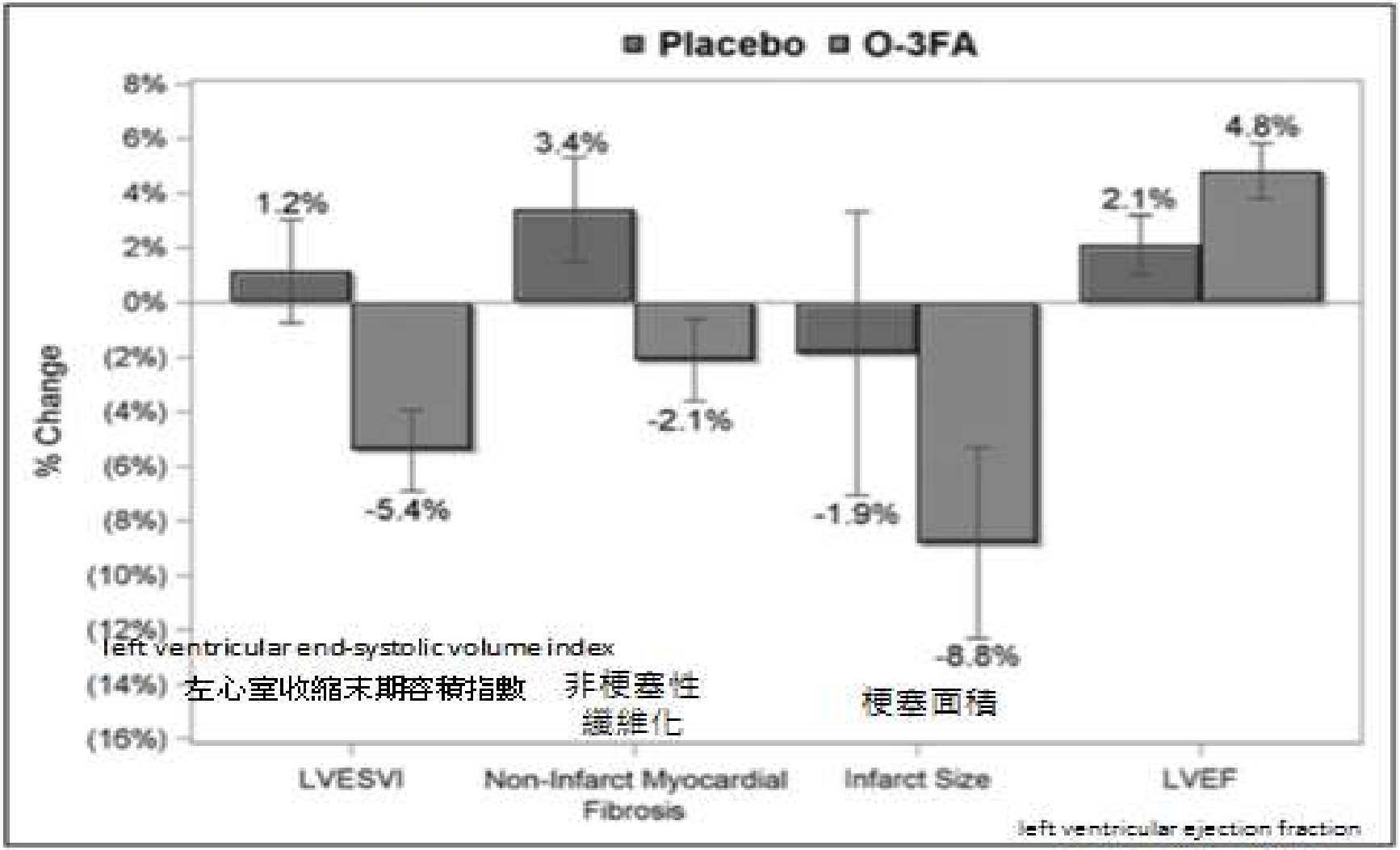
Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E **after myocardial infarction**: results of the GISSI-Prevenzione trial
Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico
Lancet. 1999 Aug 7;354(9177):447-55

Effect of n-3 PUFA treatment in GISSI-Prevenzione (11,323 post-MI pts)



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

此篇研究發現Omacor能讓急性心肌梗塞患者避免心臟結構惡化及無力！！！



Circulation. 2016;134:378–391.

GISSI–HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Heart Failure)

- GISSI–HF project:

  A large-scale, randomized, double-blind study designed to investigate the effects of omega-3 fatty acids and statin therapy on mortality and morbidity in patients with CHF (NYHA class 2–4 regardless of cause and LVEF)

- Treatments in the two separate substudies:

GISSI–HF, PUFA study	GISSI–HF statin
n-3 PUFA 1 g daily or placebo	Rosuvastatin 10 mg or placebo

- Co–primary end points:

  Death and death or admission to the hospital for CV reasons

GISSI–HF: Results

At follow-up of 3.9 years

L Tavazzi (Fondazione IRCCS Policlinico San Matteo, Pavia, Italy)
European Society of Cardiology 2008 Congress

GISSI–HF PUFA: Primary and secondary outcomes[a]

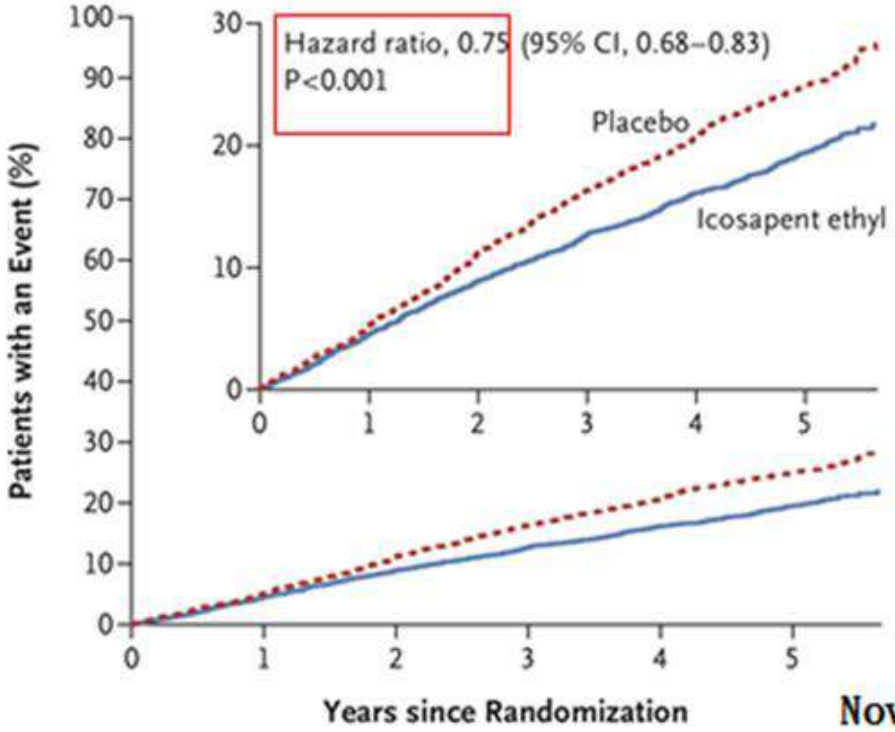
End point	Omega-3 fatty acids (n=3494), %	Placebo (n=3481), %	Adjusted hazard ratio (95% CI)
Primary end points			
Mortality	27.3	29.1	0.91 (0.833–0.998)
All-cause mortality or hospitalization for CV causes	56.7	59.0	0.92 (0.849–0.999)
Secondary end points			
Death from CV causes	20.4	22.0	0.90 (0.81–0.99)
Sudden cardiac death	8.8	9.3	0.93 (0.79–1.08)
Patients admitted for CV causes	46.8	48.5	0.93 (0.87–0.99)
Patients with fatal and nonfatal MI	3.1	3.7	0.82 (0.63–1.06)
Patients with fatal and nonfatal stroke	3.5	3.0	1.16 (0.91–1.53)

Lancet 2008; 372: 1223–30

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%心血管事件發生率

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

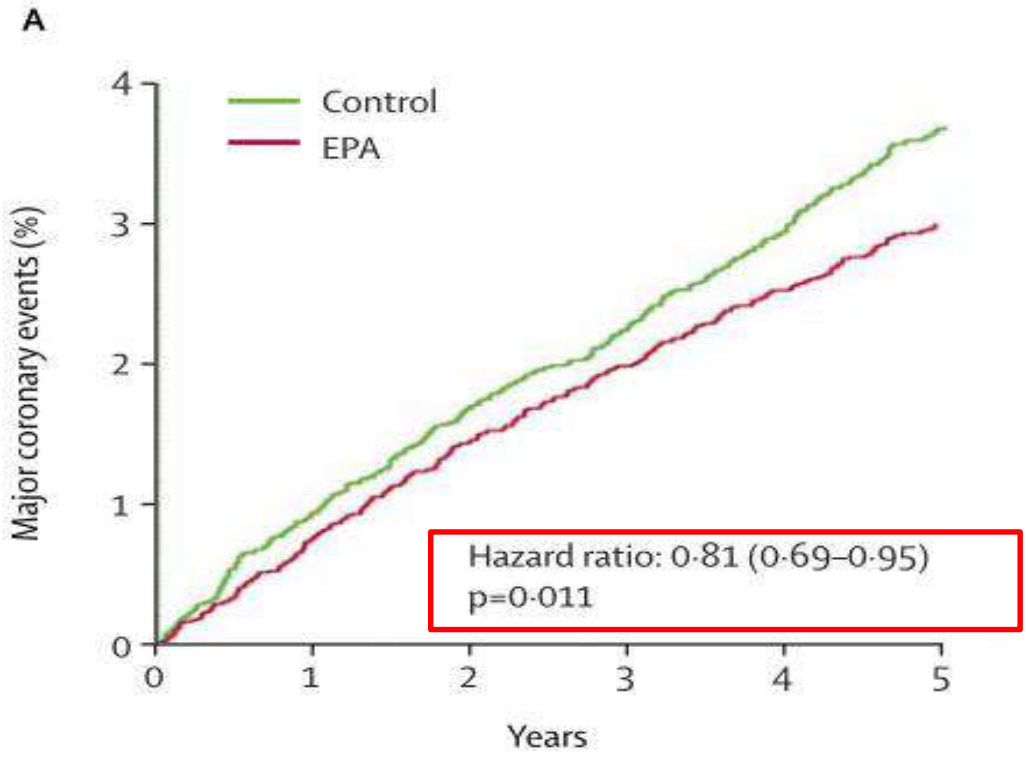
A Primary End Point



November 10, 2018, at NEJM.org

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

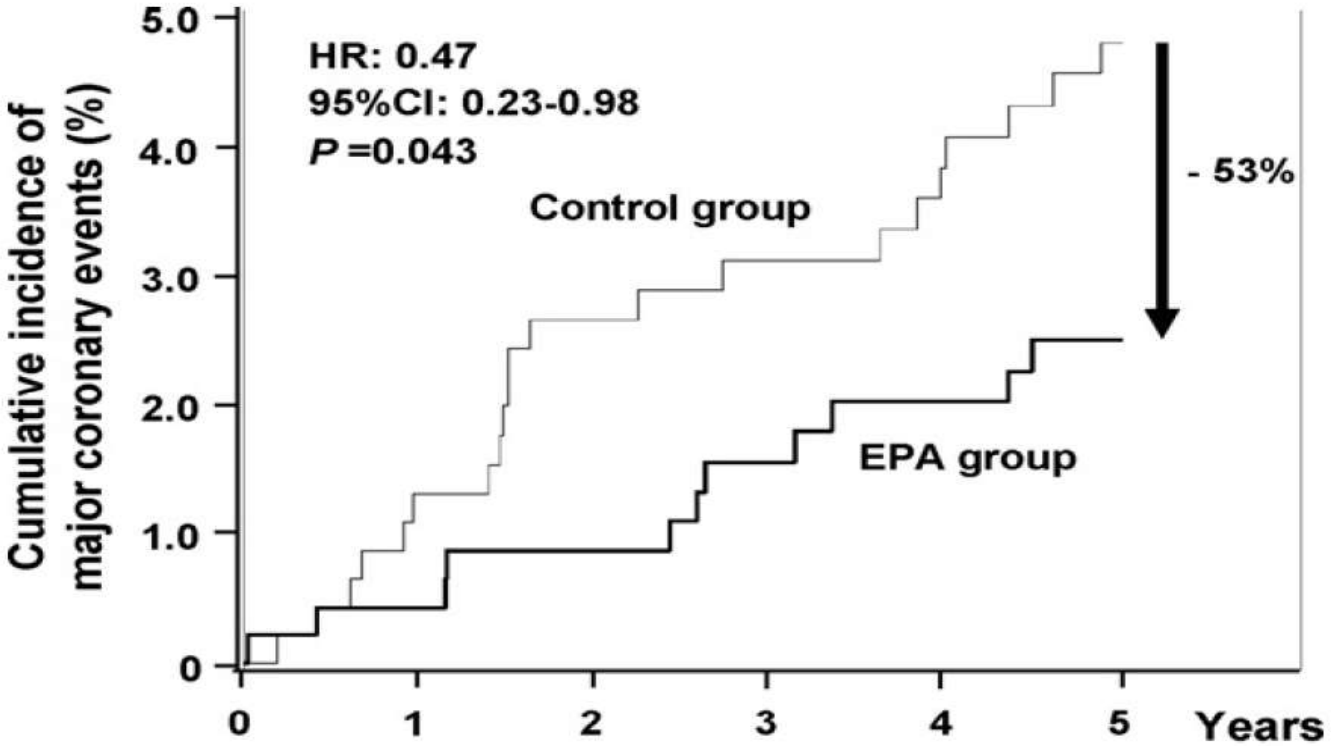
80% 1st primary prevention



- **EPA ethyl ester 1.8 g/day** plus low-dose pravastatin or simvastatin versus statin alone in hypercholesterolemic patients with or without CHD
- A total of 18,645 patients (**primary prevention cohort, 14,981 patients; secondary prevention cohort, 3,664 patients**).

Lancet 2007; 369: 1090–98

Effects of EPA on the incidence of MCE for the TG >150 and HDL-C <40 in (JELIS)



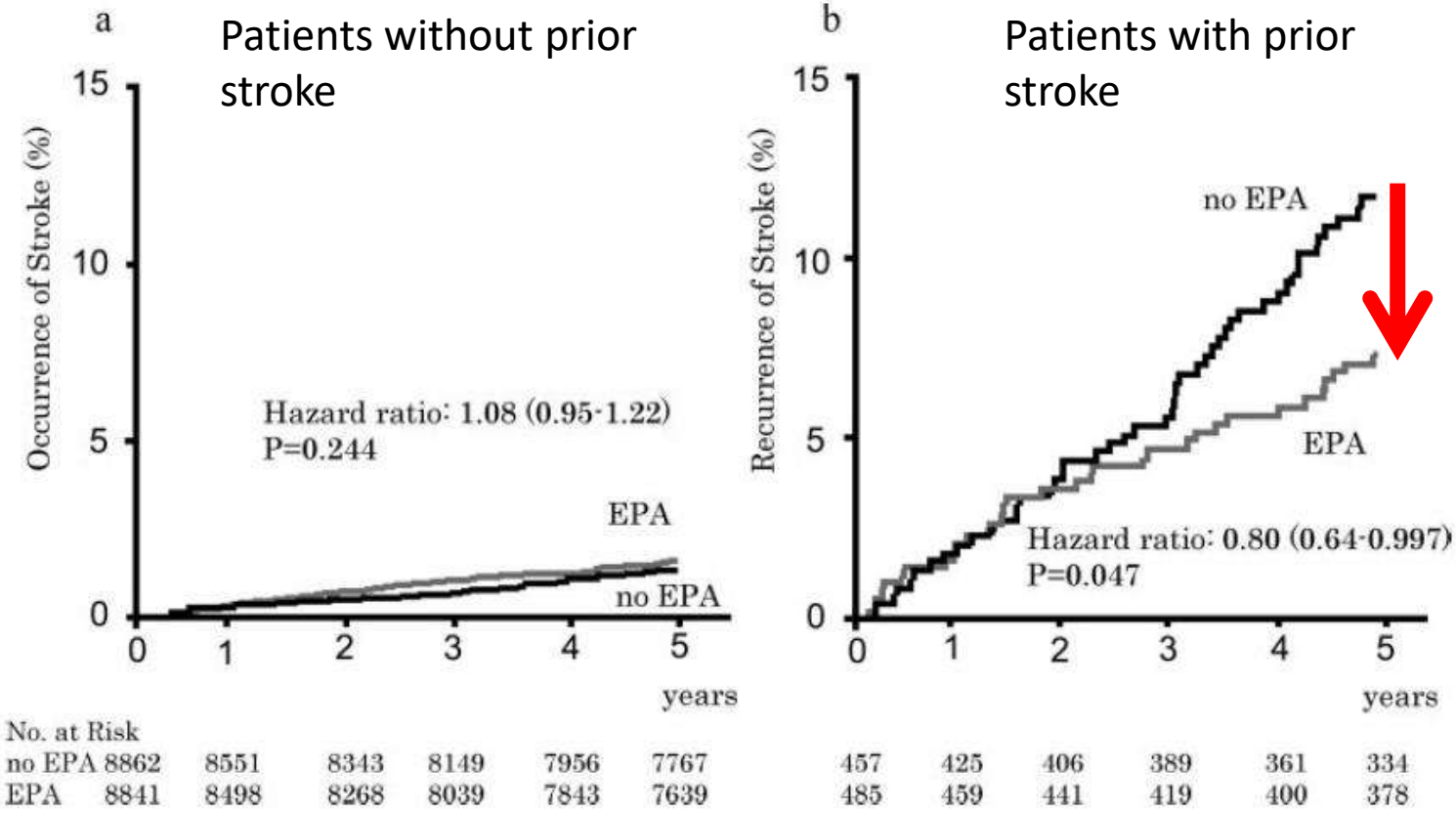
Number of patients

Control	475	444	432	414	400	392
EPA	482	455	443	427	413	403

Atherosclerosis 200 (2008) 135–140

In patients with ischemic stroke

Post hoc analysis of JELIS trial



Tanak K et al., Stroke 2008;39:2052-2058

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

A Science Advisory From the American Heart Association

Indication (Population)	Recommendation	Class (Strength) of Recommendation	Level (Quality) of Evidence	Comments
Primary prevention of CHD (general population [without CHD])	No recommendation	…	…	One RCT in participants from the general population (VITAL) is ongoing.
Prevention of CVD mortality in diabetes mellitus/prediabetes	Treatment is not indicated	III*	B-R	Based on 1 large RCT (ORIGIN) in patients with diabetes mellitus or prediabetes. One RCT in diabetic patients (ASCEND) is ongoing.
Prevention of CHD among patients at high CVD risk (mixed populations with and without CHD)	Treatment is not indicated	III*†	B-R	Of 4 large RCTs, 3 (ORIGIN, R & P, AREDS2) did not show benefit (although they were individually underpowered to show differences in cardiac death), and 1 open-label RCT (JELIS) showed a benefit in total CVD events resulting from reduction in nonhard cardiovascular end points (angina, revascularizations).

Circulation. 2017;135:00–00. DOI: 10.1161/CIR.0000000000000482

Secondary prevention of CHD and SCD among patients with prevalent CHD	Treatment is reasonable	IIa†	A	Of 2 large RCTs, 1 (GISSI-Prevenzione) showed benefit and 1 (Alpha Omega) did not. Of 3 small RCTs, 1 (DART) showed benefit and 2 (OMEGA, SU.FOL.OM3) did not. Meta-analysis (Rizos et al[11]) yields a significant risk ratio for cardiac death of 0.9.
Primary prevention of stroke (high CVD risk [with or without prevalent CHD])	Treatment is not indicated	III*	B-R	Based on meta-analysis of RCTs with stroke as a secondary outcome (Rizos et al[11]). No RCTs have been performed with stroke as primary outcome.
Secondary prevention of stroke	No recommendation	…	…	No RCTs performed.
Primary prevention of heart failure	No recommendation	…	…	No RCTs performed.
Secondary prevention of outcomes in patients with heart failure	Treatment is reasonable	IIa	B-R	Based on 1 large RCT (GISSI-HF) in patients receiving current state-of-the-art heart failure care.
Primary prevention of AF	No recommendation	…	…	No RCTs performed.
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.

Circulation. 2017;135:00–00. DOI: 10.1161/CIR.0000000000000482

美研究：阿斯匹靈無助預防心臟病

〔本報綜合外電報導〕以往認爲每天服用低劑量的阿斯匹靈，可以降低心臟病與中風等機率。根據美聯社報導，一項美國研究發現，阿斯匹靈無法預防中度風險者發生第一次中風或心臟病。另一項英國研究測試阿斯匹靈針對糖尿病患者的影響，發現阿斯匹靈的好處被出血風險給抵消。另外，英國研究中也測試了補充omega-3脂肪酸的成效，結果也發現沒有助益。

一項由美國波士頓布里翰婦女醫院（Brigham and Women's Hospital）領導的研究，讓一萬二千五百四十六人分爲二組，分別服用阿斯匹靈以及安慰劑，這些民衆有中度心臟病或中風的風險，可能在十年內病發。

服用五年後，兩組人都各有百分之四出現心臟問題，差異遠低於預期。領導這項研究的醫師嘉基安諾（C. Michael Gaziano）說，阿斯匹靈沒有什麼機會幫上忙。

另外，研究發現服用阿斯匹靈的一組，有百分之一出現腸胃出血，比率是服用安慰劑組的二倍。服用阿斯匹靈服者也有較多鼻出血、消化不良、胃食道逆流或腹痛問題。

研究成果發表於英國醫學期刊《刺胳針》（Lancet）。

另一項英國的研究，牛津大學人員，將一萬五千四百八十名第一型或第二型糖尿病患者，隨機分配成四組，按組別每天服用阿斯匹靈、一公克魚油（omega-3脂肪酸）、阿斯匹靈與魚油兩種都吃、安慰劑四種方式。

七年半後，阿斯匹靈服用者出現心臟問題的案例減少，但卻出現較多的嚴重出血病例，因此大致上只是把一個風險換成另一個。這項研究也測試了omega-3脂肪酸，補充劑攝取者的與服用安慰劑者接近，每組人各有百分之九有心臟問題。研究結果發表於《新英格蘭醫學期刊》（New England Journal of Medicine）。

英國牛津大學研究領導人鮑曼（Louise Bowman）醫師說：「我們很有信心認爲，魚油補充劑似乎無法預防心臟病。」

Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Table 3 New recommendations, and new and revised concepts

New recommendations	
2016	**2019**
Lipid analyses for CVD risk estimation	**Lipid analyses for CVD risk estimation**
ApoB should be considered as an alternative risk marker whenever available, especially in individuals with high TG.	ApoB analysis is recommended for risk assessment, particularly in people with high TG, DM, obesity or metabolic syndrome, or very low LDL-C. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG, DM, obesity, or very low LDL-C.
Drug treatments of hypertriglyceridaemia	**Drug treatments of hypertriglyceridaemia**
Statin treatment may be considered as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia.	Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia [TG >2.3 mmol/L (200 mg/dL)].
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.	

Very-high-risk	People with any of the following: Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. DM with target organ damage,[a] or at least three major risk factors, or early onset of T1DM of long duration (>20 years). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.

Table 7 Treatment targets and goals for cardiovascular disease prevention

Table 8 Impact of specific lifestyle changes on lipid levels

	Magnitude of the effect	Level	Reference
Lifestyle interventions to reduce TC and LDL-C levels			
Avoid dietary trans fats	++	A	129,138
Reduce dietary saturated fats	++	A	129,139
Increase dietary fibre	++	A	140,141
Use functional foods enriched with phytosterols	++	A	142,143
Use red yeast rice nutraceuticals	++	A	144–146
Reduce excessive body weight	++	A	147,148
Reduce dietary cholesterol	+	B	149,150
Increase habitual physical activity	+	B	151
Lifestyle interventions to reduce TG-rich lipoprotein levels			
Reduce excessive body weight	+	A	147,148
Reduce alcohol intake	+++	A	152,153
Increase habitual physical activity	++	A	151,154
Reduce total amount of dietary carbohydrates	++	A	147,155
Use supplements of n-3 polyunsaturated fats	++	A	156,157
Reduce intake of mono- and disaccharides	++	B	158,159
Replace saturated fats with mono- or polyunsaturated fats	+	B	129,137

7.5.6 n-3 unsaturated fatty acids

Observational evidence indicates that consumption of fish (at least twice a week) and vegetable foods rich in n-3 fatty acids (α-linoleic acid is present in walnuts, some vegetables, and some seed oils) is associated with lower risk of CV death and stroke, but has no major

194. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT Jr, Juliano RA, Jiao L, Granowitz C, Tardif JC, Ballantyne CM; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med* 2019;**380**:11–22.

risk of ischaemic events, including CV death, was observed in patients with elevated TG levels despite the use of statins treated with 2 g of icosapent ethyl b.i.d. [twice a day].[194]

Other features of a healthy diet contributing to CVD prevention are presented in the *Supplementary Data*.

ASCVD outcomes in people with elevated serum TGs; the trial enrolled ~8000 patients on statin therapy, with LDL-C levels between 1.0—2.6 mmol/L (41—100 mg/dL) and various CV risk fac-

8.8 n-3 fatty acids

8.8.1 Mechanism of action

The n-3 (or omega-3) fatty acids [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] can be used at pharmacological doses to lower TGs. n-3 fatty acids (2—4 g/day) affect serum lipids and lipoproteins, in particular VLDL concentrations. The underlying mechanism is poorly understood, although it may be related, at least in part, to their ability to interact with PPARs and to decreased secretion of ApoB.

including 460 mg of EPA and 380 mg of DHA) vs. matching placebo. It showed that supplementation with either n-3 fatty acids at a dose of 1 g/day, or vitamin D3 at a dose of 2000 IU/day, was not effective for primary prevention of CV or cancer events among healthy middle-aged men and women over 5 years of follow-up.[333]

Lipid analyses for CVD risk estimation		
TC is to be used for the estimation of total CV risk by means of the SCORE system.	I	C
HDL-C analysis is recommended to further refine risk estimation using the online SCORE system.	I	C
LDL-C analysis is recommended as the primary lipid analysis method for screening, diagnosis, and management.	I	C
TG analysis is recommended as a part of the routine lipid analysis approach.	I	C
Non-HDL-C evaluation is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C
ApoB analysis is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, or MetS, or very low LDL-C levels. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C

Drug treatment of patients with HTG		
Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with HTG [TGs >2.3 mmol/L (>200 mg/dL)].	I	B

AHA SCIENTIFIC STATEMENT

when used as monotherapy or in combination with a statin. In the largest trials of 4 g/d prescription n-3 FA, non–high-density lipoprotein cholesterol and apolipoprotein B were modestly decreased, indicating reductions in total atherogenic lipoproteins. The use of n-3 FA (4 g/d) for improving atherosclerotic cardiovascular disease risk in patients with hypertriglyceridemia is supported by a 25% reduction in major adverse cardiovascular events in REDUCE-IT (Reduction of Cardiovascular Events With EPA Intervention Trial), a randomized placebo-controlled trial of EPA-only in high-risk patients treated with a statin. The results of a trial of 4 g/d prescription EPA+DHA in hypertriglyceridemia are anticipated in 2020. We conclude that prescription n-3 FAs (EPA+DHA or EPA-only) at a dose of 4 g/d (>3 g/d total EPA+DHA) are an effective and safe option for reducing triglycerides as monotherapy or as an adjunct to other lipid-lowering agents.

*This update was prepared in part by Dr Engler in her personal capacity. The opinions expressed in this article are the author's own and do not reflect the view of the National Institutes of Health, the US Department of Health and Human Services, the US Department of Defense, the US government, or the Uniformed Services University of the Health Sciences.

Key Words: AHA Scientific Statements ■ docosahexaenoic acid ■ eicosapentaenoic acid ■ fatty acids, omega-3 ■ hypertriglyceridemia ■ hypolipidemic agents ■ lipoproteins ■ triglycerides

Circulation. 2011;123:2292-2333

KEY FINDINGS

Vitamin D supplementation

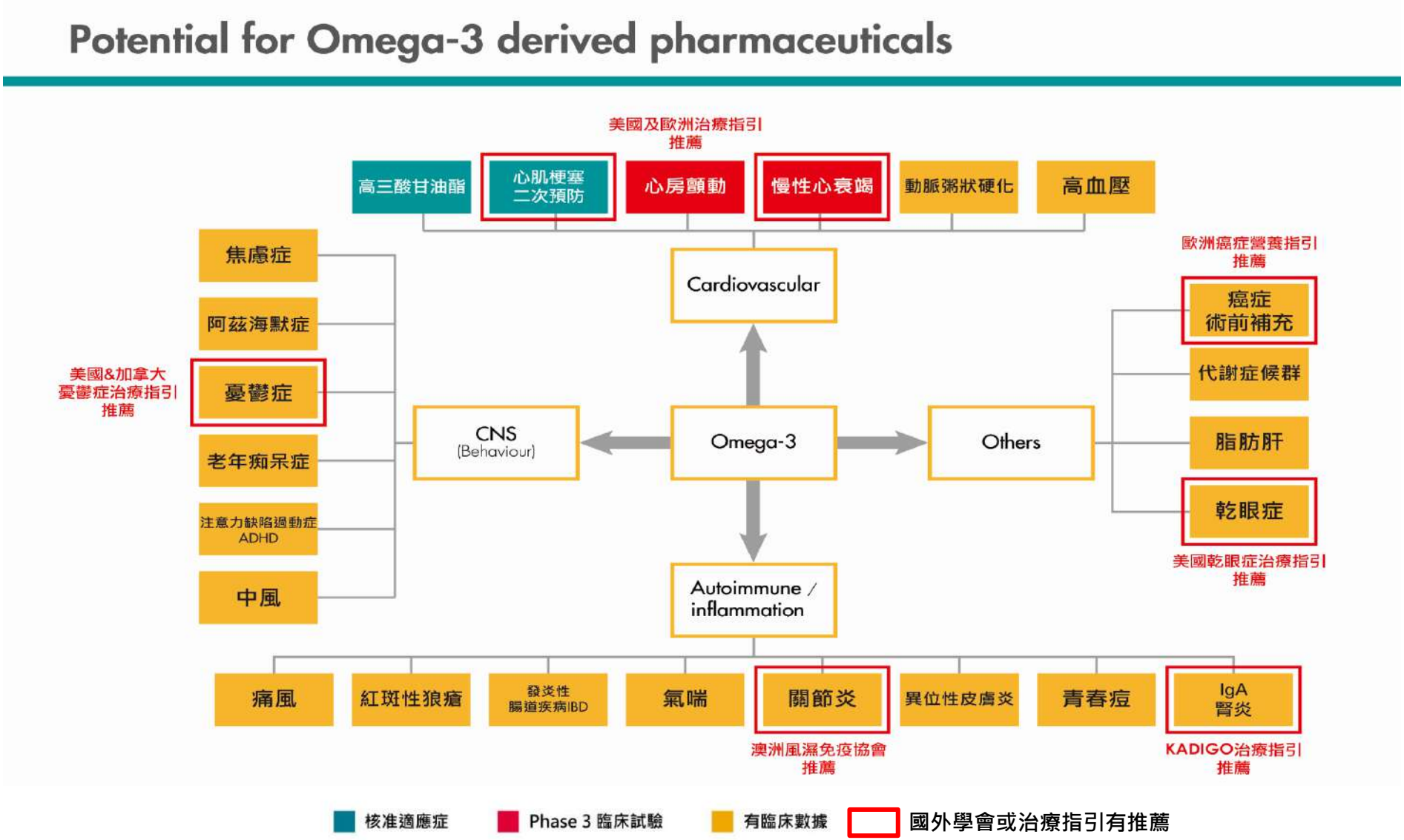
- Did not reduce risk of cancer
- Did not reduce risk of major cardiovascular events (heart attack, stroke, or cardiovascular death considered together)
- Appeared to reduce risk of cancer-related death

Omega-3 fatty acid supplementation

- Did not reduce risk of cancer
- Did not reduce risk of major cardiovascular events in the overall study population, but did reduce risk of these events by 19% in people with low fish intake
- Reduced risk of heart attack by 28%, when heart attack was considered separately from other cardiovascular events; the benefit appeared strongest in African Americans

- VITAL, a randomized, double-blind, placebo-controlled trial, enrolled 25,871 men and women age 50 and older from across the U.S., including 5,106 African Americans. Eligible participants had no history of cancer, heart attack, stroke, or other forms of cardiovascular disease at the time of enrollment.
- While earlier trials have examined whether fish oil or other supplements may prevent heart attack or stroke in patients with a history of heart disease or at very high risk of such disease, VITAL is the first large trial of omega-3 fatty acids for **primary prevention**—that is, preventing the first occurrence—of heart disease in a general population.

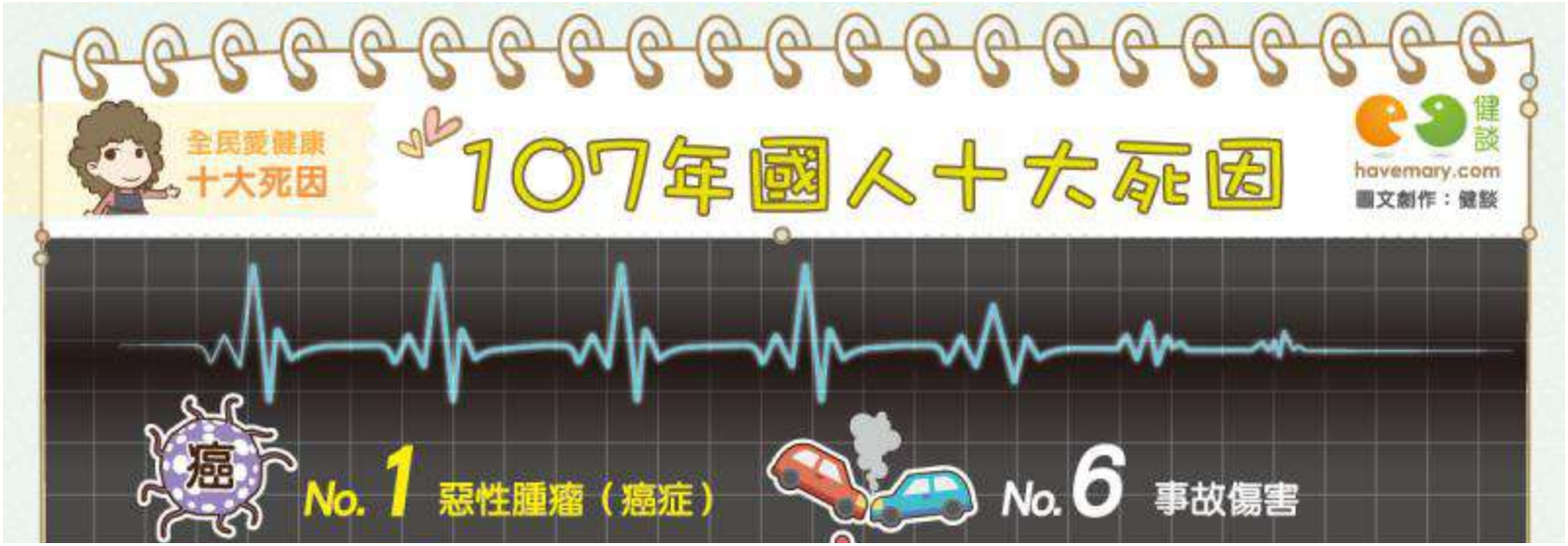
下圖為Omega-3目前於人體臨床實驗有正向結果之相關疾病



- 健保開辦之初，85年健保費用才2229億元，近日國發會才核今年健保費用成長率為3.708%至5.5%，估計109年健保總額應會落在7400億至7500億。短短廿多年間，總額增加3.3倍，就算政府開徵補充保費，但整體健保收入成長率卻遠落後健保總額成長率，我國健保從106年起，年年虧損百億元，去年虧266億元，預估今年破洞更大，恐達虧損逾400億元。

in dyslipidemia

TG的重要性



Received: 24 November 2018 | Revised: 4 March 2019 | Accepted: 25 March 2019

DOI: 10.1111/1753-0407.12926

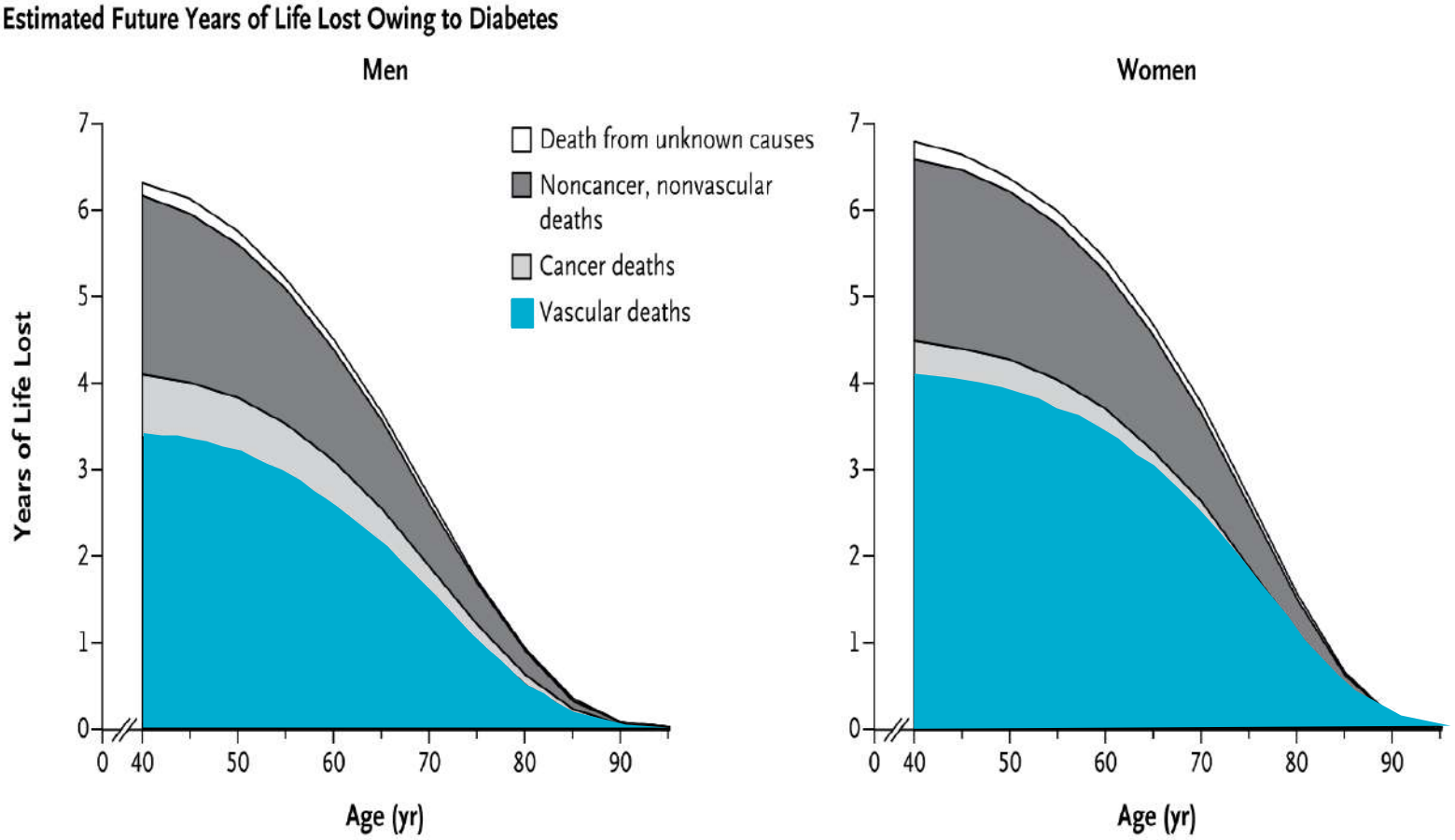
ORIGINAL ARTICLE

Journal of Diabetes WILEY

Cancer risk among patients with type 2 diabetes: A real-world study in Shanghai, China

Jiying Qi[1†] | Ping He[2†] | Huayi Yao[2] | Ruogang Song[1] | Chenglong Ma[1] | Min Cao[1] | Bin Cui[1] | Guang Ning[1]

Vascular diseases attribute 58% cause of death in diabetes



On average, middle-aged adults with diabetes would incur about 6 years of life lost than people without diabetes

Data were analyzed from individual-participant data on 123,205 deaths among **820,900 people** in 97 prospective studies.
Seshasai et al. N Engl J Med 2011;364:829-41

服用Statin後仍有
6~7成心血管殘餘風險

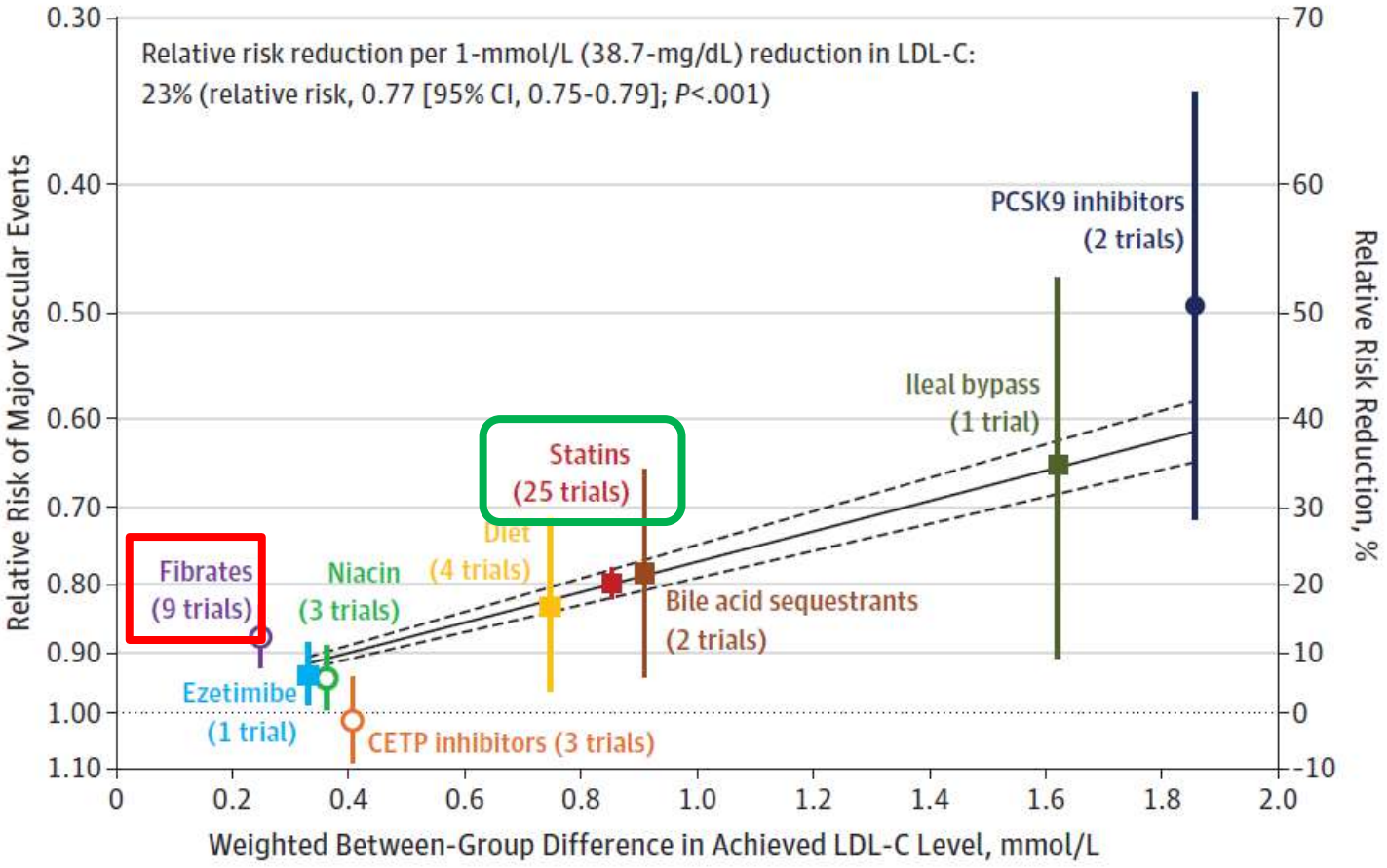
CARDIOVASCULAR RISK COMPONENTS OF THE METABOLIC SYNDROME

Increased waist circumference	High triglycerides	Low HDL-C (good cholesterol)	Elevated blood pressure	Elevated fasting glucose
>40 inches in men (>35 inches for Asian men); >35 inches in women (>31 inches for Asian women) or population- and country-specific definitions	≥150 mg/dL, or taking medication for high triglycerides	<40 mg/dL in men; <50 mg/dL in women, or taking medication for low HDL-C	≥130 mm Hg systolic ≥85 mm Hg diastolic, or taking antihypertensive medication in a patient with a history of hypertension	≥100 mg/dL or taking medication to control blood sugar

The metabolic syndrome is diagnosed when a person has ≥3 of these risk factors.

Statins reduce 20% CVRR

25 trials of statins with consistent relative risk reduction



5. 2016 JAMA 316 (12): 1289-1297

KEYWORDS:
Triglycerides variability;
Microalbuminuria;
Dyslipidemia;
Long-term exposure hypertriglyceridemia;
Type 2 diabetes

BACKGROUND: Experimental and clinical studies have shown a strong association between hypertriglyceridemia and diabetic nephropathy. A variability of triglyceride (TG) levels has been reported in diabetes.

OBJECTIVES: To investigate the relationship of TG variability with the incidence of microalbuminuria (albumin excretion rate > 20 μg/min), in patients with type 2 diabetes.

METHODS: A longitudinal, retrospective, observational study was performed on a consecutive series of 457 normoalbuminuric outpatients, with measurements of HbA_1c, lipids and microalbuminuria thrice per year with 6.8-year follow-up. TG variability, defined as standard deviation of TG (TG-SD) and TG-SD adjusted for the number of visits was calculated. A nested case-control sensitivity analysis was performed to validate the results of the primary cohort study.

RESULTS: Incident microalbuminuria (N = 124, 27.1%) was associated with higher median TG-SD (33.6 mg/dL vs 29.0 mg/dL, $P < .05$) and TG-SD adjusted for the number of visits (31.4 mg/dL vs 26.7 mg/dL, $P < .05$). At multivariate (Cox) analysis, logTG-SD and adj-logTG-SD were significant predictors of incident microalbuminuria (hazard ratio 2.1 [1.1–4.2], $P = .028$ and 1.5 [1.1–3.3], $P = .042$, respectively). In the case-control analysis, time spent with TG > 150 mg/dL during the follow-up was significantly higher in cases vs controls (27.2 ± 19 vs 16.7 ± 12.5 months, $P < .05$) with hazard ratio 2.0 (1.1–5.1), $P < .05$, for adj-logTG-SD.

CONCLUSIONS: A higher intraindividual TG variability is a predictor of incident microalbuminuria in type 2 diabetes. In addition, time of exposure to elevated TG levels (>150 mg/dL) predicts incident microalbuminuria.

Diabetic nephropathy (DN) is the most common cause of end-stage renal disease in people with diabetes.[1] Chronic

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Obesity

ABSTRACT

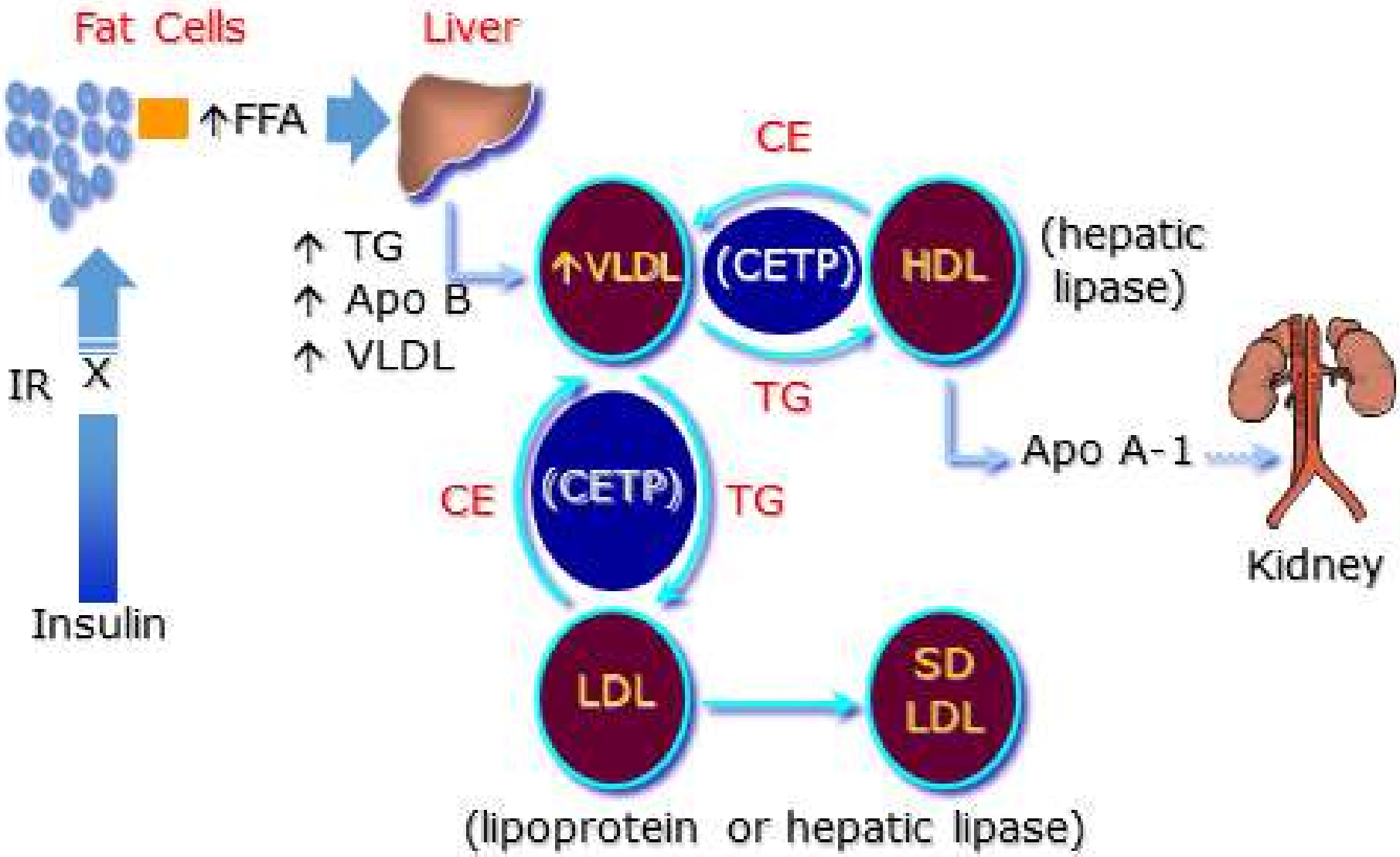
Background and aims: Non-LDL dyslipidemia (NLD) confers cardiovascular risk, and prevalence rates appear to be high in elderly populations. Small cohorts have identified several lifestyle, anthropometric, and medical factors associated with NLD. We aimed to assess sex- and age-specific prevalence of NLD in a contemporary population cohort (n = 167 729), and to identify independent determinants of NLD, focusing on lifestyle, anthropometric, and medical factors.

Methods: The prevalence of NLD was assessed per 10-year age intervals in adults without cardiovascular disease not using lipid-modifying drugs from the Dutch LifeLines cohort. NLD was defined as low HDL-cholesterol or high triglycerides or high remnant cholesterol as per guideline cut-off values. Multivariable regression was used to identify factors independently associated with NLD. Determinants included age, smoking, alcohol use, physical activity, diet, BMI, diabetes mellitus (DM), chronic kidney disease, and in women, menopausal state and oral contraceptive use.

Results: NLD occurred in 15–19% of women and 13–30% of men in this cohort, with the highest prevalence of 30% in 35–55 year old men. In most age groups, the prevalence in women was lower than in men. Obesity (both sexes: Odds ratio (OR) 5.3, 95% confidence interval (95%CI) 5.0–5.7), current smoking (men: OR 1.8, 95%CI 1.7–1.9; women OR 2.2, 95%CI 2.1–2.3), and DM (men: OR 2.2, 95%CI 1.8–2.6; women: OR 2.7, 95%CI 2.3–3.1) were strongly associated with NLD.

Conclusions: NLD already occurs frequently at an early age. Modifiable lifestyle choices, obesity, and DM were strong determinants of NLD. Public health efforts could substantially contribute to decrease NLD.

TG過高亦會降低HDL及增加sdLDL



進一步分析這群無肝炎的肝癌患者罹癌風險，研究團隊找出了三大風險因子，分別為脂肪肝糖尿病史、三酸甘油脂過高，若再把這三組病患分為有酒癮和沒有酒癮者，結果發現，沒有酒癮的無慢性病毒肝炎的肝癌患者中，三個代謝性疾病風險因[illegible]究成果刊登於4月美國肝[illegible]官方期刊

Triglyceride大於
160 mg/dL

黃秀芬指出，有酒癮[illegible]無肝炎、肝硬化，也可能罹患肝癌，女性的風險更高。她建議國健署，應該將脂肪肝、糖尿病史、三酸甘油脂過高等民眾，納入公費肝癌篩檢的對象。如果這項三項因子都有者，屬於肝癌高風險族群，應該定期回診，接受超音波檢查。

Back to Table of Contents

Prev **GUIDELINES MADE SIMPLE**

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

Top 10 Take-Home Messages for the Primary Prevention of Cardiovascular Disease

(1 of 3)

1 *The most important way to prevent atherosclerotic vascular disease, heart failure, and atrial fibrillation is to promote a healthy lifestyle throughout life.*

2 *A team-based care approach is an effective strategy for the prevention of cardiovascular disease. Clinicians should evaluate the social determinants of health that affect individuals to inform treatment decisions.*

Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol, Journal of the American College of Cardiology (2018), doi: https://doi.org/10.1016/j.jacc.2018.11.003.

表一、糖尿病人血脂目標

主要目標		說明
低密度脂蛋白膽固醇	所有病人 <100 mg/dl 已有心血管疾病 <70 mg/dl	建議使用中 / 強效果的 statins 為第一線藥物治療
高密度脂蛋白膽固醇	男 >40 mg/dl 女 >50 mg/dl	生活型態介入治療及血糖控制為優先
三酸甘油酯	<150 mg/dl	血糖控制及生活型態介入治療為優先。但三酸甘油酯 ≥500 mg/dl，需給 fibrates
次要目標		
非高密度脂蛋白膽固醇	所有病人 <130 mg/dl 已有心血管疾病 <100 mg/dl	當主要目標達成時，再評估次要目標

Omacor是CKD患者最好的選擇

Lipanthyl在CKD患者要調劑量非常麻煩

Lopid在CKD患者要注意不能並用Statin

表二　慢性腎臟病病人降血脂藥物治療建議應根據腎功能調整劑量

藥物品項	肌酸酐廓清率 (Ccr) 60-90 ml/min/1.73m^2	肌酸酐廓清率 (Ccr) 30-59 ml/min/1.73m^2	肌酸酐廓清率 (Ccr) 15-29 ml/min/1.73m^2	肌酸酐廓清率 (Ccr) < 15 ml/min/1.73m^2
Statin				
Atorvastatin	不需調整劑量			
Pravastatin	不需調整劑量			
Simvastatin	不需調整劑量		從 5 mg/day 起小心使用	
Fluvastatin	不需調整劑量	證據不明，Ccr<30 ml/min 考慮從低劑量起用		
Rosuvastatin	不需調整劑量		從 5 mg/day 起小心使用，最大劑量 10 mg/day	
Lovastatin	不需調整劑量	考慮減半劑量使用		
Nonstatin				
Cholestyramine	證據不明，腎功能不佳者考慮從低劑量開始使用			
Colesevelam	不需調整劑量			
Ezetimibe	不需調整劑量	→ CKD 3~5		
Fenofibrate	減半劑量使用	減成 1/4 劑量使用		禁忌使用
Gemfibrozil	不需調整劑量			
Nicotinic acid	證據不明，腎功能不佳者考慮從低劑量開始使用			
Omega-3 fatty acid	不需調整劑量			

* 以上乃依據最新藥物使用建議，根據腎功能調整劑量。

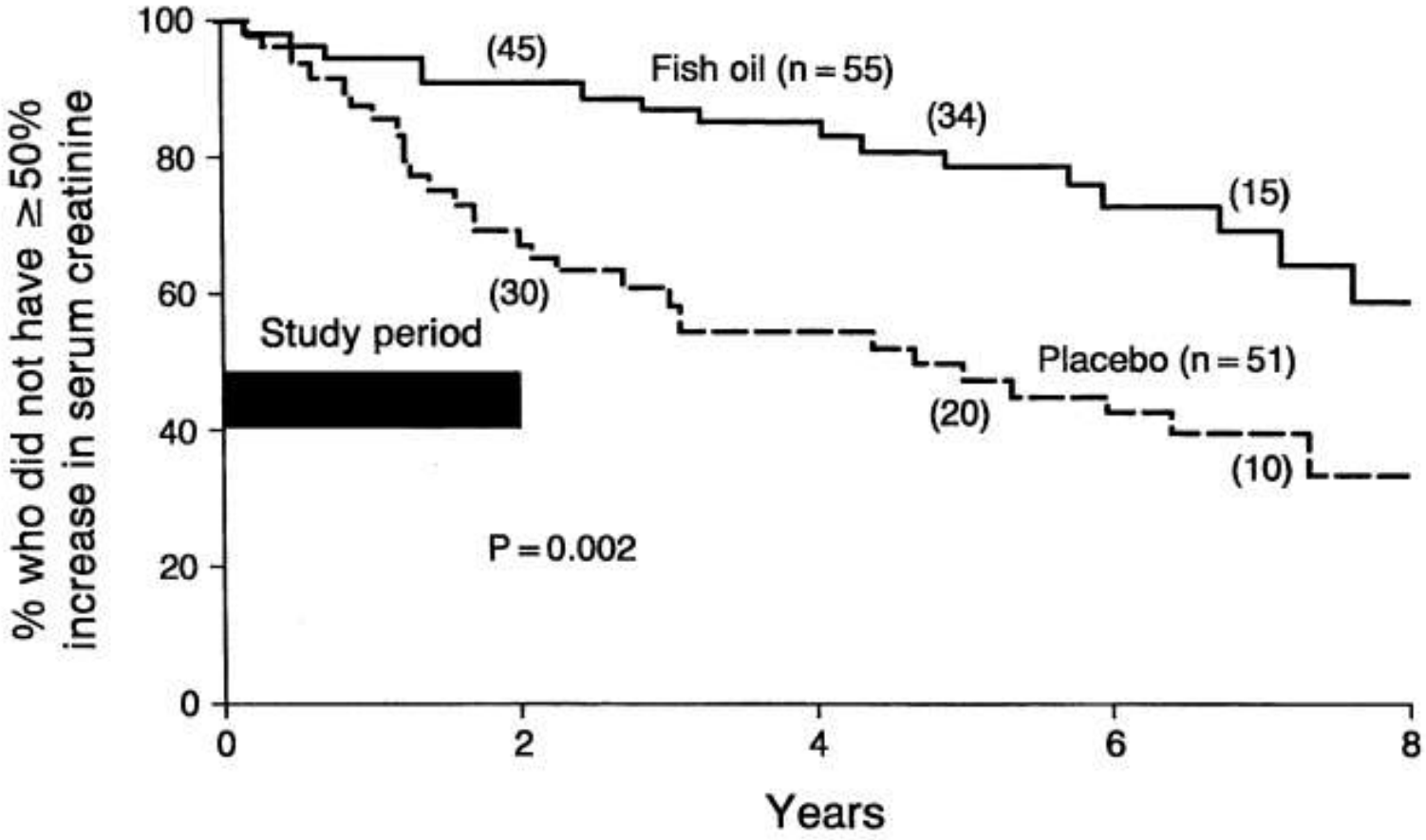
歐盟及臺灣已禁止Gemfibrozil與Statin並用

2015 臺灣慢性腎臟病臨床診療指引專書

Taiwan Chronic Kidney Disease Clinical Guidelines

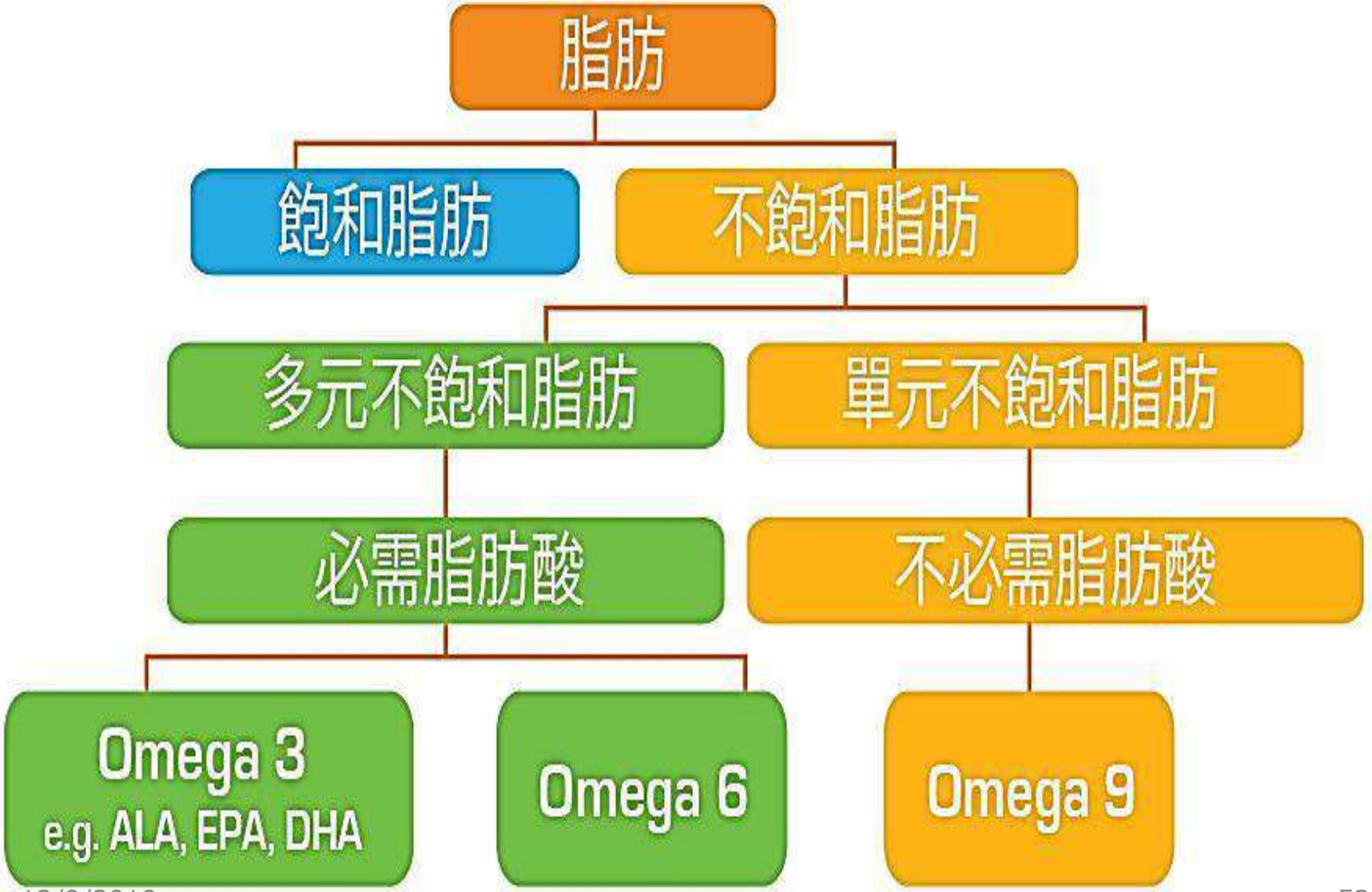
建議強度	建議（上）/ 實證內容（下）	證據等級	文獻編號
	國際建議中之 PUFA 與 MUFA 之比例並無實證基礎。	4	13,47-48
	國人常用烹飪用油 PUFA/MUFA 比值偏高。	4	40
A	CKD 病人補充 ω-3 多元不飽和脂肪酸可降低心血管疾病的風險。		
	CKD 病人以 ω-3 PUFAs 取代 MUFAs 或碳水化合物來補充熱量，可降低血清 TG 濃度及心血管疾病的風險。	2+ 1++	52 53
	非末期腎病的 CKD 病人補充二十二碳六烯酸（DHA）及二十碳五烯酸（EPA），可降低血清 TG 濃度及心血管疾病的風險。	2+ 1+	54-55,57 56

The long-term outcome of patients with IgA nephropathy treated with fish oil in a controlled trial



J Am Soc Nephrol 10:1772–1777, 1999. 2

脂肪分類


脂肪
飽和脂肪
不飽和脂肪
多元不飽和脂肪
單元不飽和脂肪
必需脂肪酸
不必需脂肪酸
Omega 3
e.g. ALA, EPA, DHA
Omega 6
Omega 9

thebmj Visual Abstract

Systematic review and meta-analysis

Fats fail to fight diabetes

Published effectiveness of polyunsaturated fats for prevention and treatment of type 2 diabetes mellitus

Summary

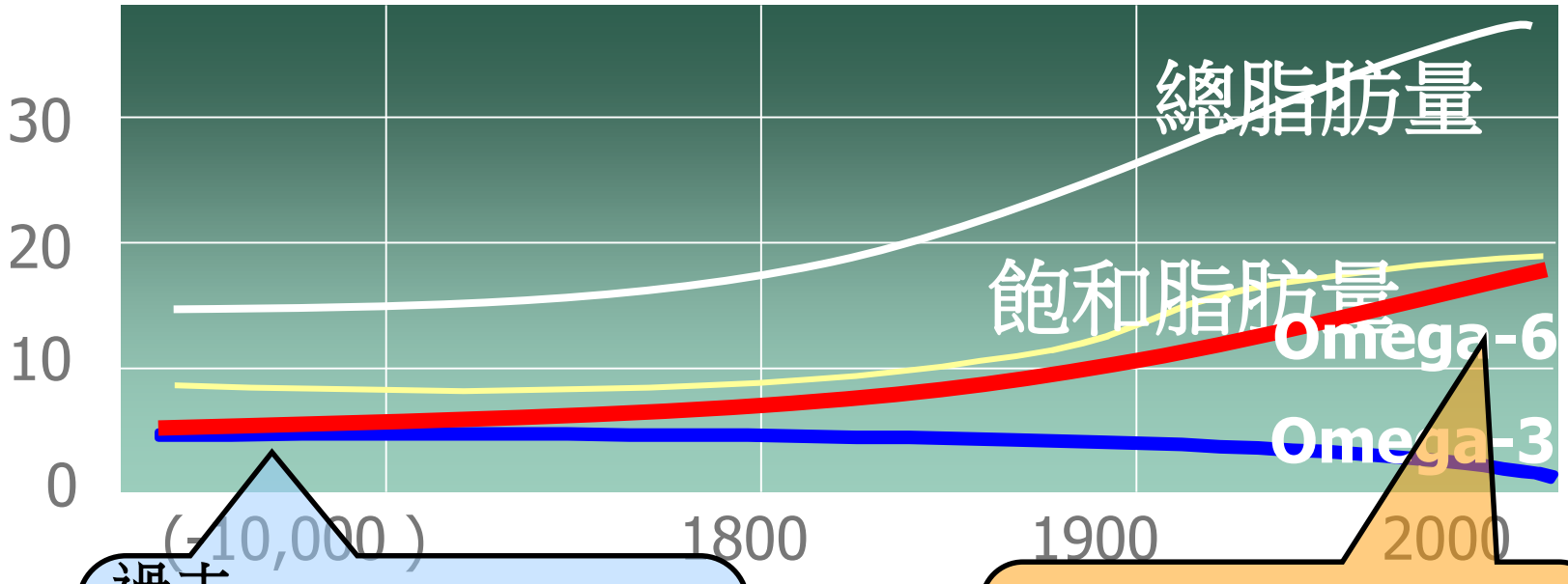
Increasing long chain omega-3 intake had little or no effect on diagnosis or glucose metabolism - there may be negative outcomes at high dose. Effects of other polyunsaturated fats were unclear

CONCLUSIONS

This is the most extensive systematic review of trials to date to assess effects of polyunsaturated fats on newly diagnosed diabetes and glucose metabolism, including previously unpublished data following contact with authors. Evidence suggests that increasing omega-3, omega-6, or total PUFA has little or no effect on prevention and treatment of type 2 diabetes mellitus.

Read the full article online: http://bit.ly/BMJfffd

人類攝取脂肪酸比例的逐漸失衡



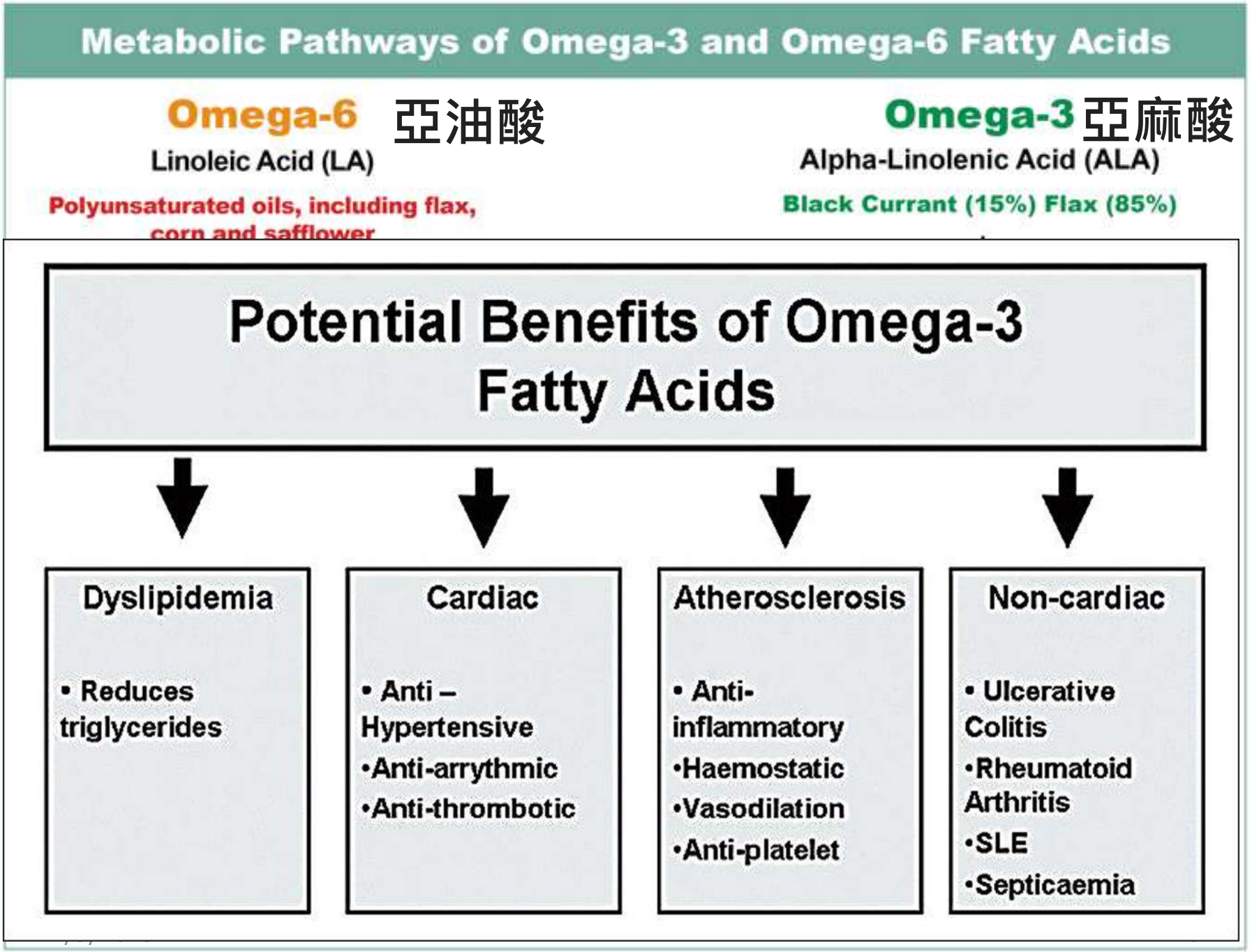
過去
omega-6:omega-3
攝取均衡比率約為**1:1**

如今
omega-6:omega-3
已偏離將近至**20:1**

Omega-6/Omega-3 Rations in Different Populations

Population	ω-6/ω-3
Paleolithic 旧石器時代	0.79
Greece prior to 1960	1.00–2.00
Current Japan	4.00
Current India, rural	5–6.1
Current UK and northern Europe	15.00
Current US	16.74
Current India, urban	38–50

Nutrients 2016, 8, 128

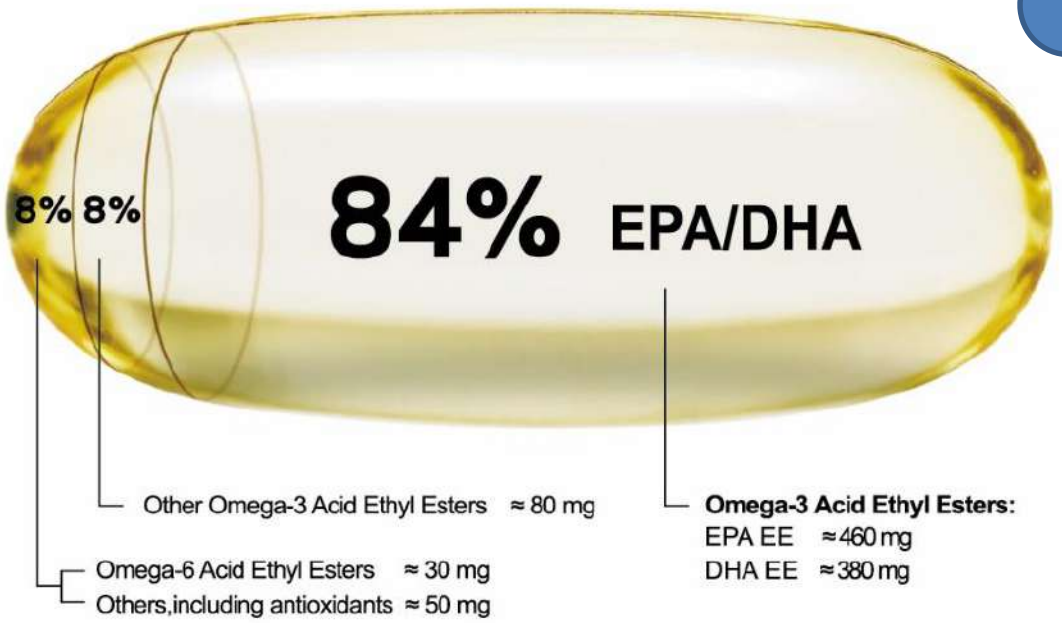

Metabolic Pathways of Omega-3 and Omega-6 Fatty Acids
Omega-6 亞油酸
Linoleic Acid (LA)
Polyunsaturated oils, including flax, corn and safflower
Omega-3 亞麻酸
Alpha-Linolenic Acid (ALA)
Black Currant (15%) Flax (85%)
Potential Benefits of Omega-3 Fatty Acids
Dyslipidemia
• Reduces triglycerides
Cardiac
• Anti – Hypertensive
•Anti-arrythmic
•Anti-thrombotic
Atherosclerosis
• Anti-inflammatory
•Haemostatic
•Vasodilation
•Anti-platelet
Non-cardiac
• Ulcerative Colitis
•Rheumatoid Arthritis
•SLE
•Septicaemia

OMACOR®中的

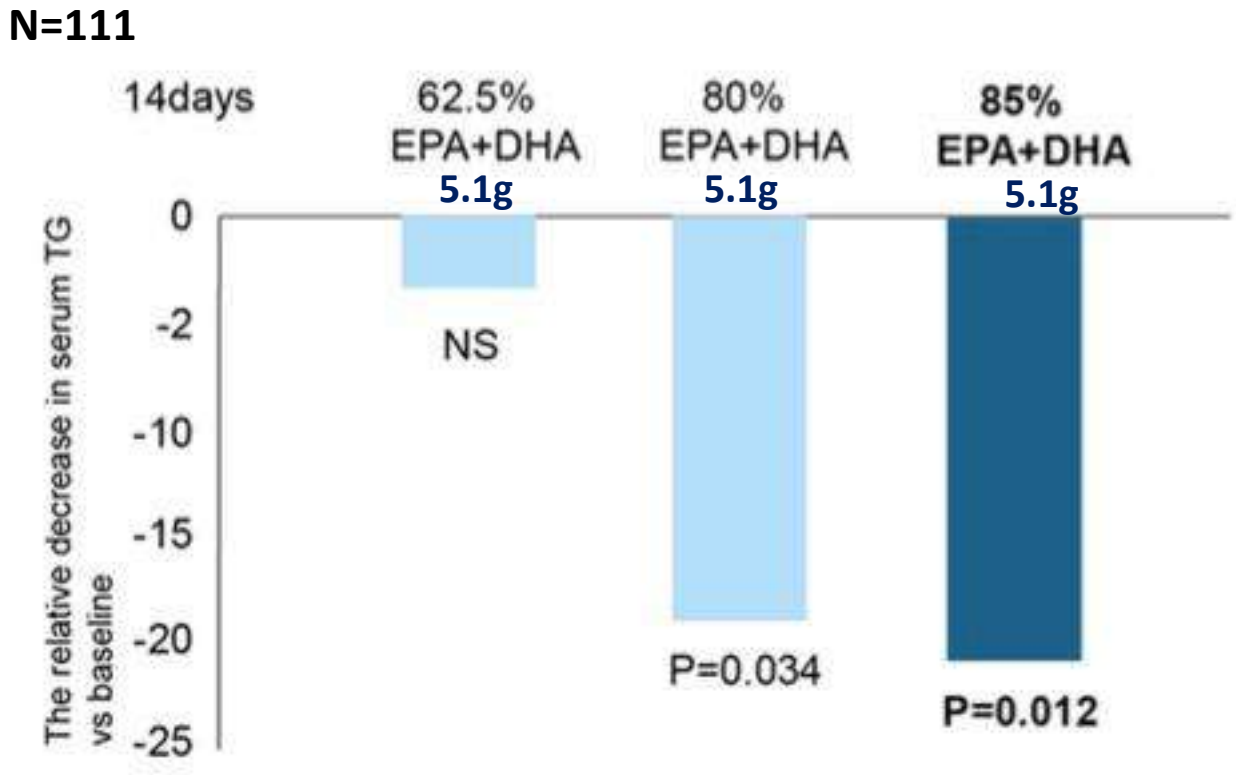
EPA/DHA濃度超過84%

omega-3 PUFA濃度超過90%

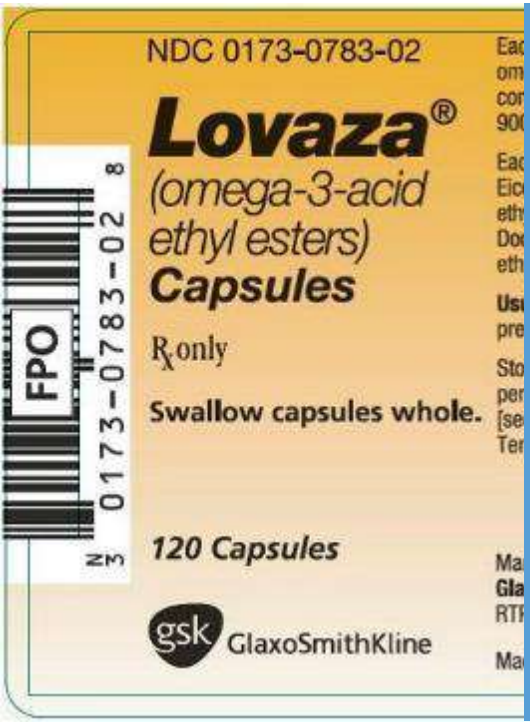
一般市售保健食品魚油濃度8成都低於30%



臨床實驗證明80%以上EPA/DHA濃度才有降血脂能力



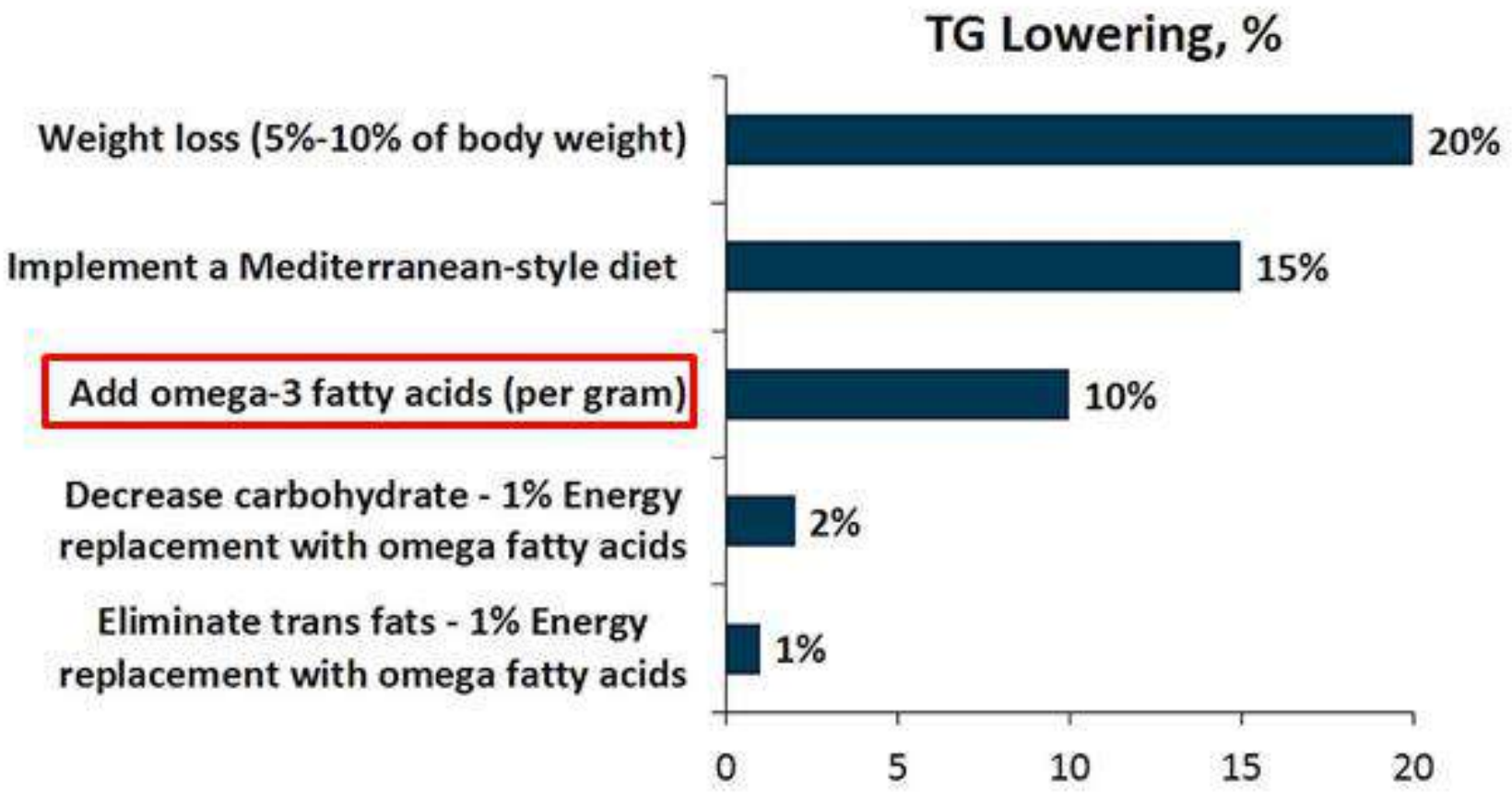
Prostaglandins, Leukotrienes and Essential Fatty Acids 75 (2006) 19–24



在歐洲，他叫Omacor
在美國，他叫Lovaza
在日本，他叫Lotriga

在台灣，我們稱他為Omacor(脂妙清膠囊)

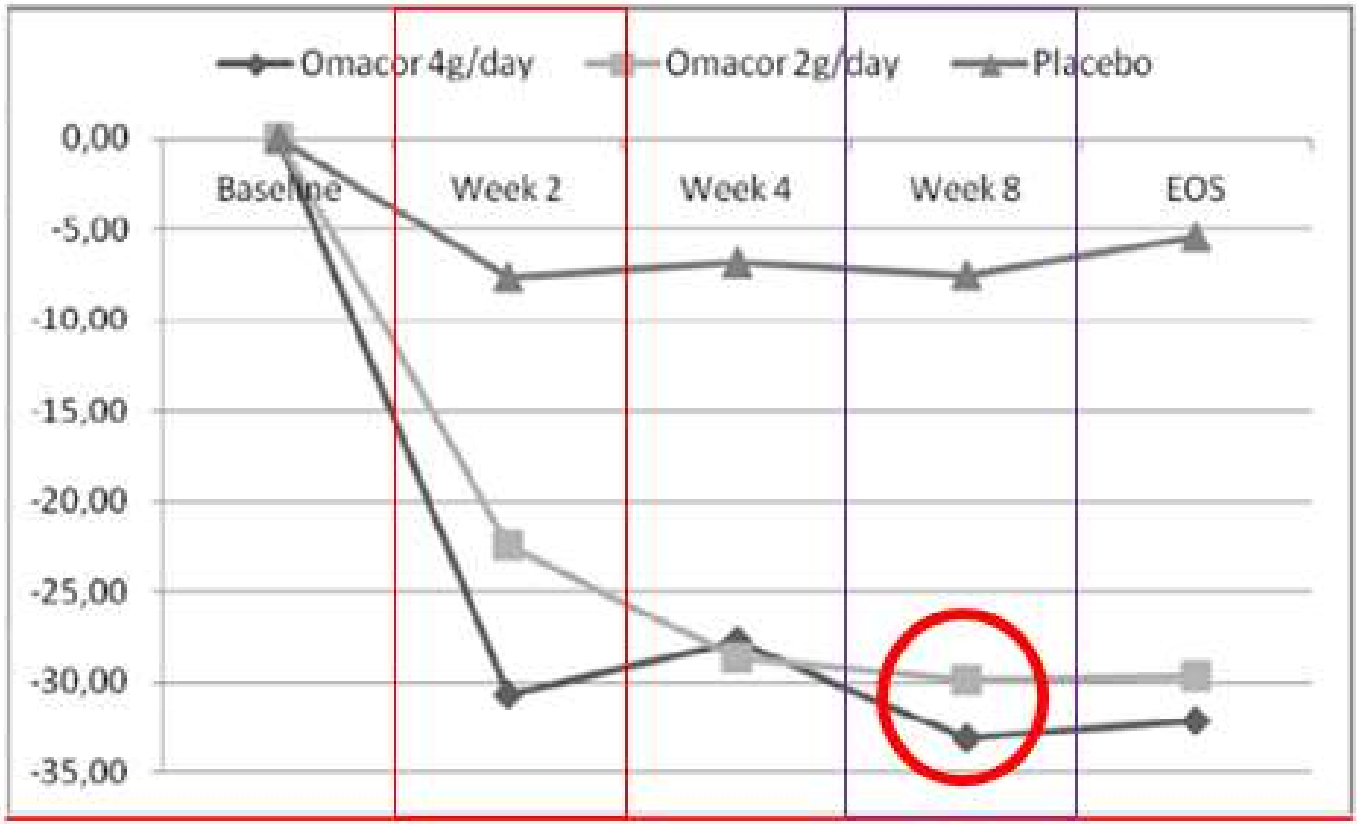
Effects of Nutrition Practices on TG Lowering



Miller M, et al. *Circulation.* 2011;123:2292-2333.[7]

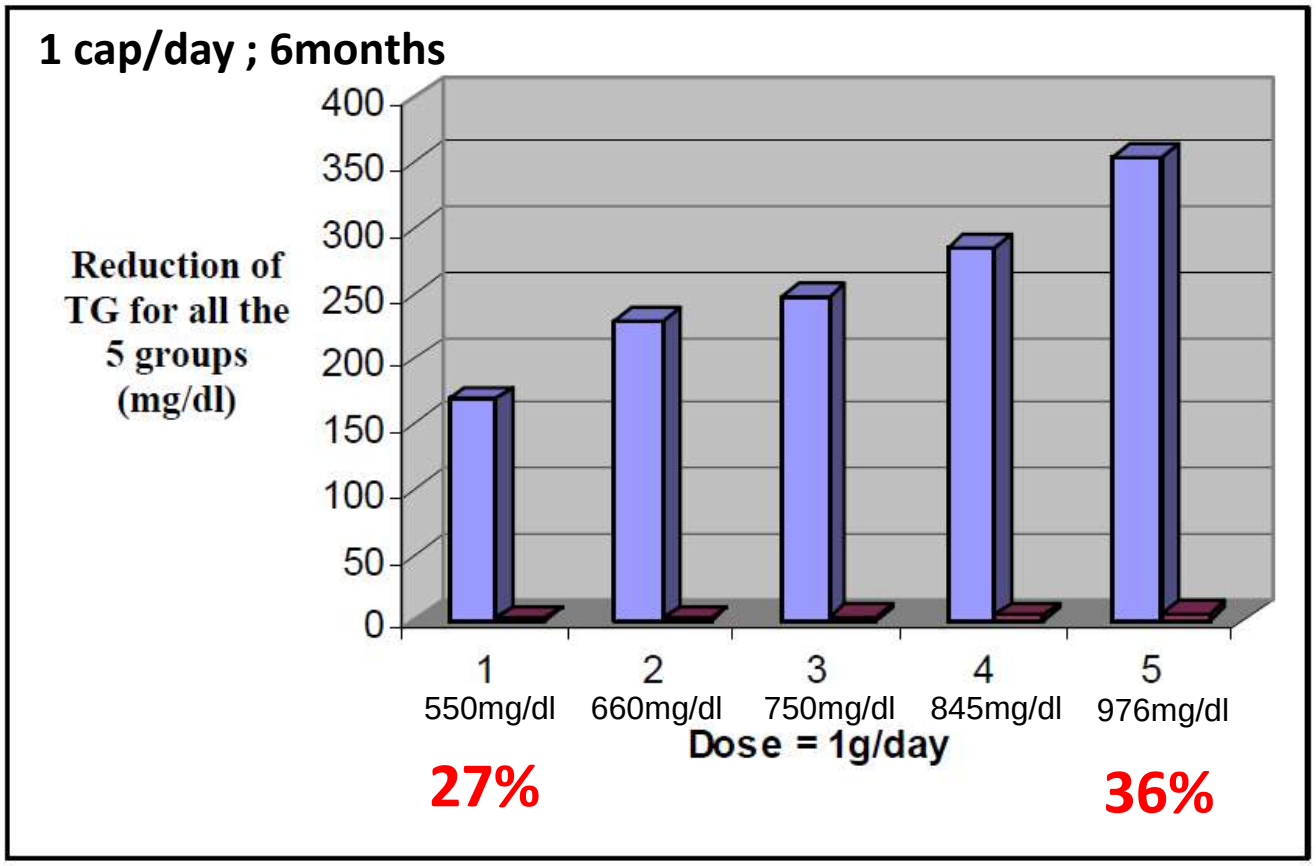
根據台灣臨床試驗，每天2顆
2週即有明顯療效，8週達最大療效

Figure 2. Time-course of Percent Change in Triglyceride Level (ITT population)



OMACOR Clinical Trial in Tawian

一天一顆仍有顯著療效



ROM. J. INTERN. MED., 2008, **46,** *1*, 81–86

已使用Fenofibrate的患者，併用OMACOR後可額外降TG達17.5%

並用OMACOR與Fibrate是安全的

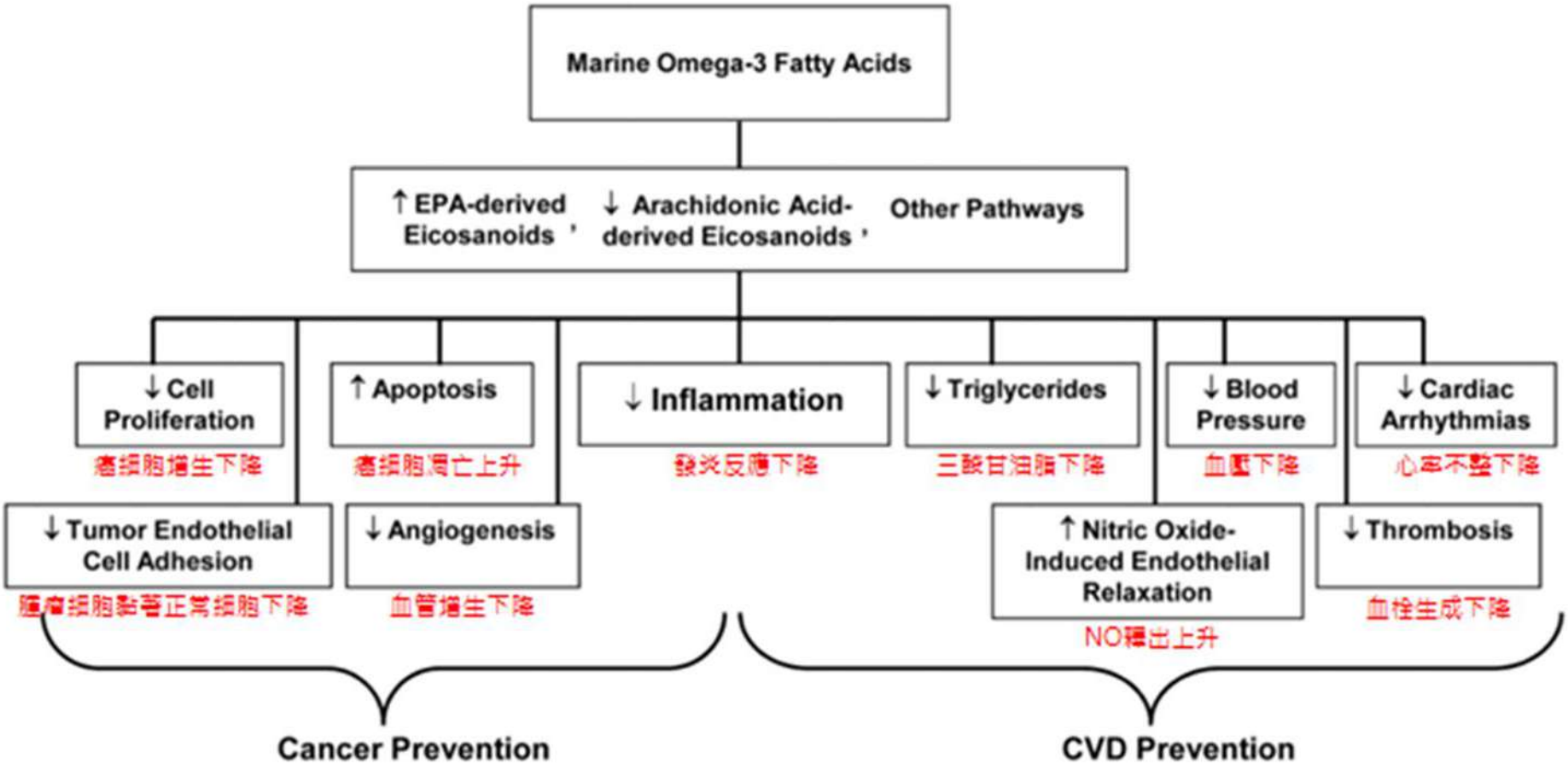
Treatment-Emergent Adverse Event (AE): Overview

TABLE 2. Incidence of Adverse Events (n [%] of Subjects)

	P-OM3 + FENO (n = 84)	Placebo + FENO (n = 83)	P-OM3 + FENO ext P-OM3 + FENO (n = 59)	Placebo + FENO ext P-OM3 + FENO (n = 58)	2nd Extension P-OM3 + FENO (n = 89)
Any adverse events	55 (65.5)	53 (63.9)	24 (40.7)	29 (50.0)	69 (77.5)
Serious adverse events	3 (3.6)	1 (1.2)	0 (0)	1 (1.7)	4 (4.5)
Related to study drug*	13 (15.5)	13 (15.7)	4 (6.8)	7 (12.1)	9 (10.1)

Take hOme message

Omega-3在過往動物實驗與小型臨床試驗已看到對於心血管疾病及癌症預防可能有幫助



Redf : NIH(The *VI*Tamin D and Omeg*A*-3 Tria*L* (VITAL)) Contemp Clin Trials. 2012 January ; 33(1): 159–171.

OMACOR適合推薦給哪些患者?

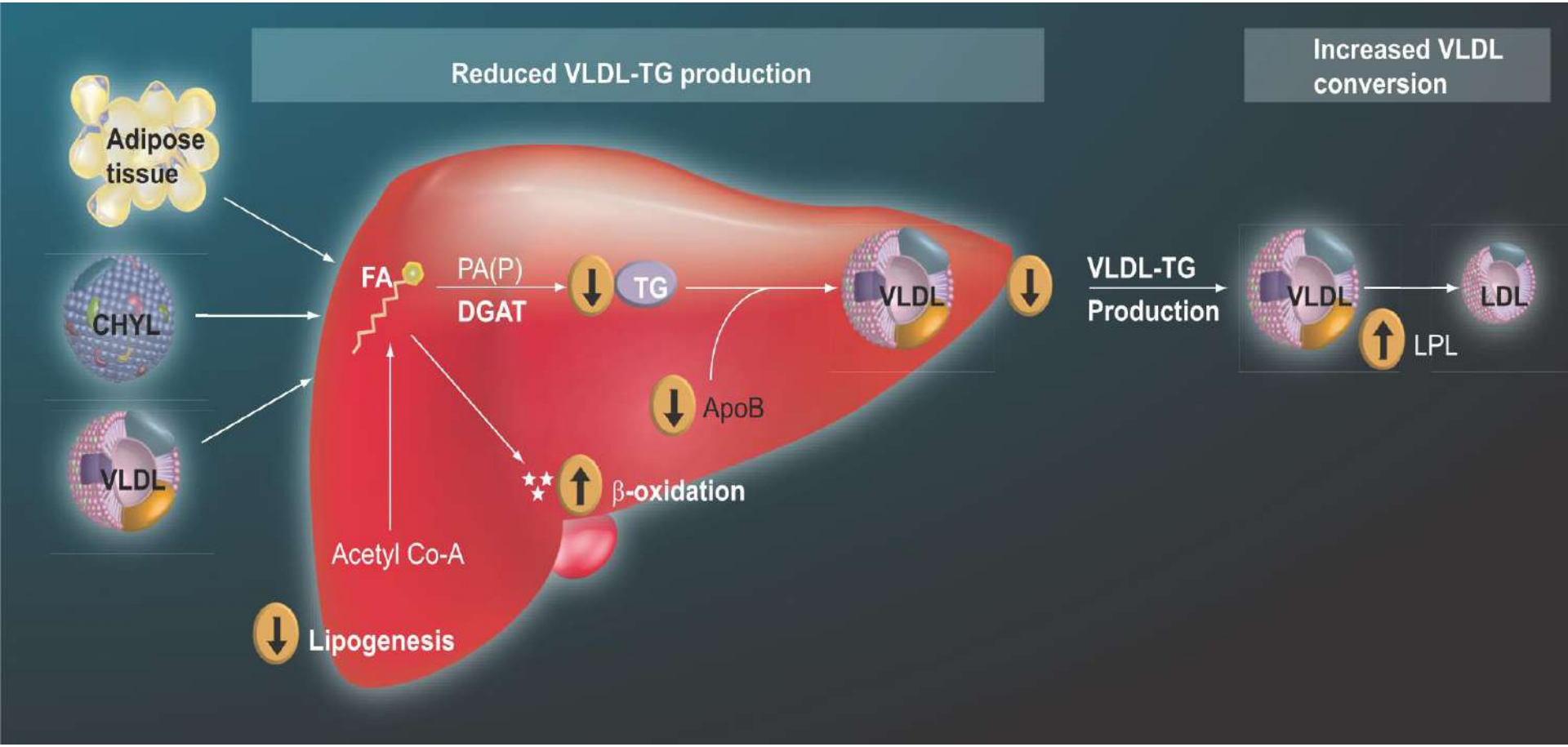
- 已經吃了Fibrate但TG仍超過500的患者
- 不能使用Fibrate的患者
- 高風險族群(已使用Statin但TG仍超過200的患者)
- 不符合健保規範或是不想吃傳統西藥來降TG的患者
- CHD/HF患者(國內外治療指引推薦)
- IGA腎炎(KADIGO治療指引推薦)
- 憂鬱症(美國治療指引建議)
- 乾眼症(美國治療指引推薦)
- 關節炎(澳洲風濕免疫協會建議)
- 亞健康患者，習慣購買食品魚油保養的患者(預防老人痴呆 ；CVD；癌症)


意如


北方館


猪
2019
YEAR OF THE PIG

Triglyceride-Lowering Mechanisms of Omega-3 FA



Expert Rev Cardiovasc Ther. 2008;6(3):391-409

Omega-3降TG機轉

- 第一,我們**肝臟**自己會合成三酸甘油脂,因為三酸甘油脂不只會從油脂來,也會從**糖分和酒精轉換**而來,怎麼轉化,主要就是透過肝臟裡面的甘油西基轉移酶,這個酶會將血液裡面的游離脂肪酸和甘油合成三酸甘油脂,再藉由VLDL帶到血液中,而**Omega-3**會阻斷掉甘油西基轉移酶的作用,降低肝臟的合成
- 第二,血液中，**Lipoprotein Lipase**會把滿載三酸甘油脂的VLDL降解成LDL，而LDL會再把剩餘的三酸甘油脂(也包含膽固醇但這裡不用提)送回肝臟。 而Omega-3會促進Lipoprotein Lipase作用，加速VLDL的分解。 **所以Omega-3一方面抑制TG的合成,二方面促進VLDL的代謝**