What do we learn from "REDUCE-IT"?

- The role of omega-3 fatty acid in the dyslipidemia management

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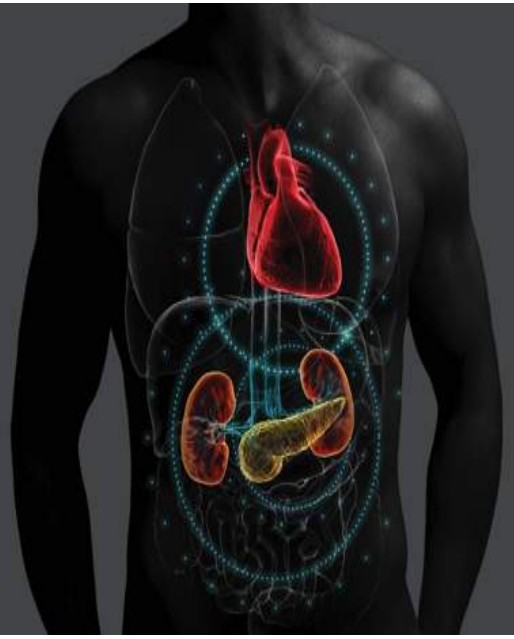
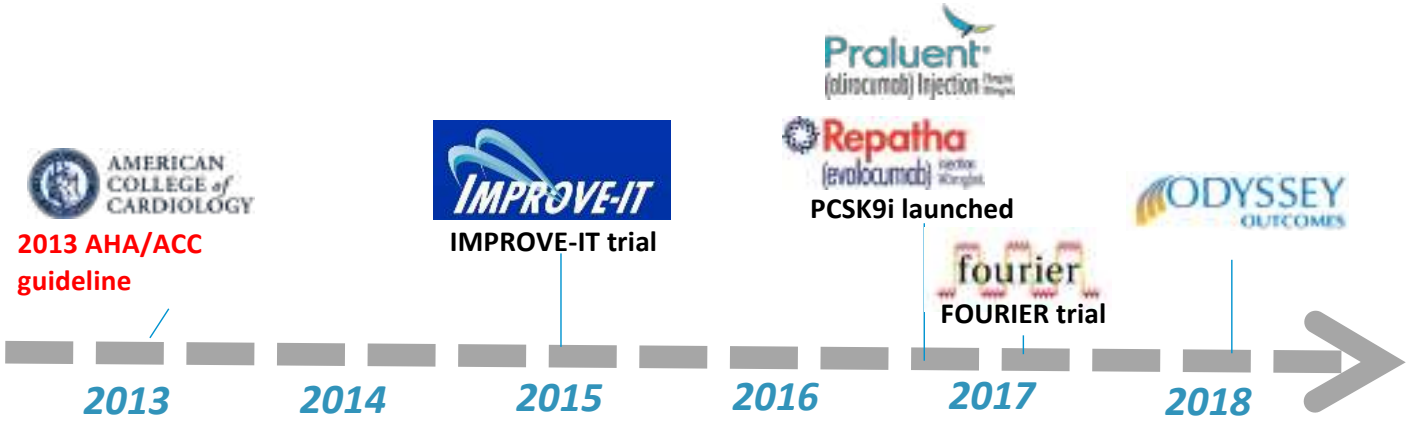


2019-03-10

Guideline Update

- Since 2013, new clinical evidence has emerged demonstrating the benefits of adding non-statin drugs to statin therapy in reducing ACSVD risk.



The 2018 guideline provides updated guidance for the management of dyslipidaemia with non-statin agents while continuing to emphasize the importance of a healthy lifestyle and the benefits of statin therapy.

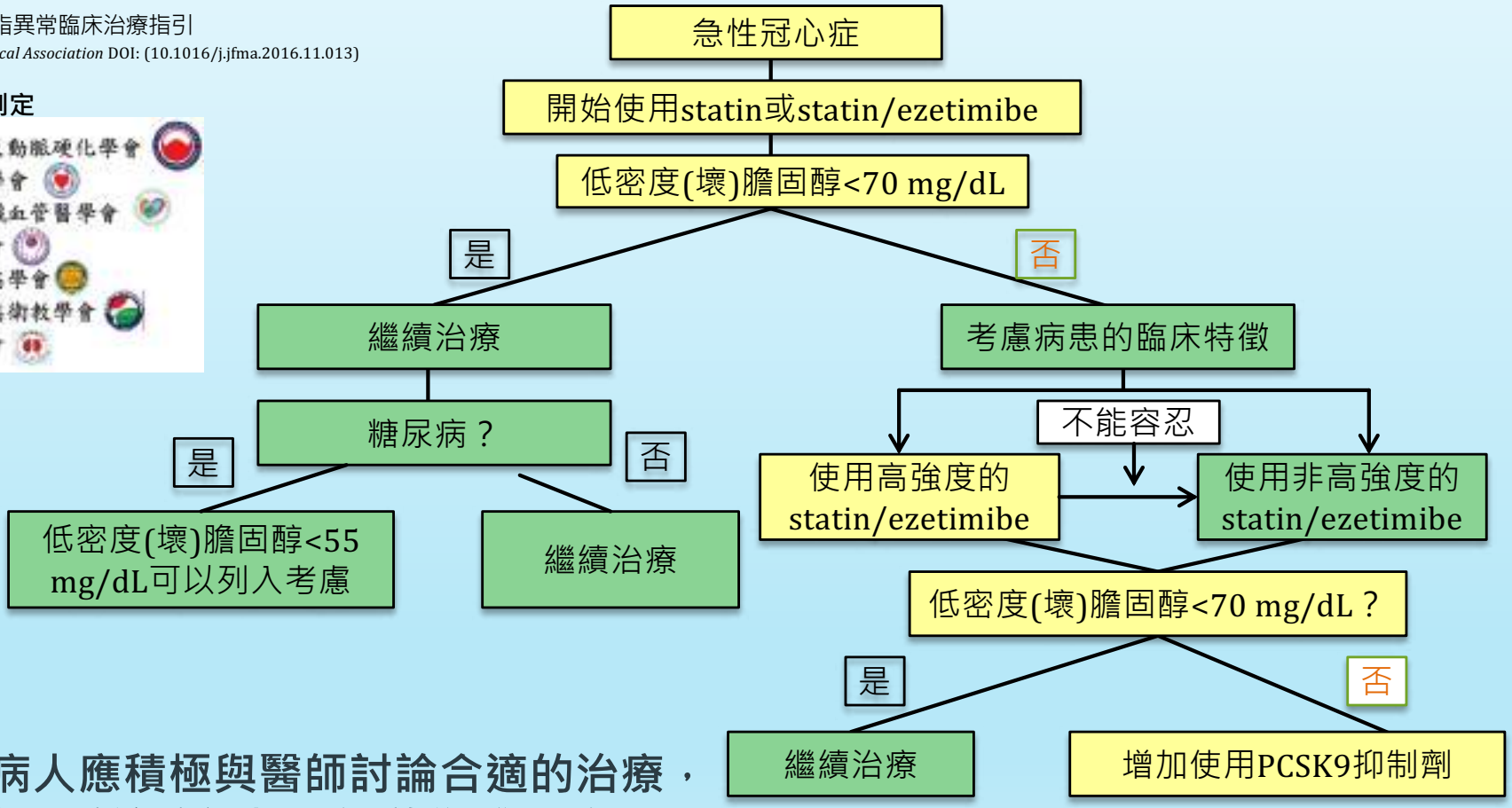
Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.
Gundy SM et al. J Am Coll Cardiol. 2018 Nov 8. [Epub ahead of print]

台灣七大學會共同制定
2017年台灣高風險病人血脂異常臨床治療指引建議：

台灣高風險病人血脂異常臨床治療指引
Journal of the Formosan Medical Association DOI: (10.1016/j.jfma.2016.11.013)

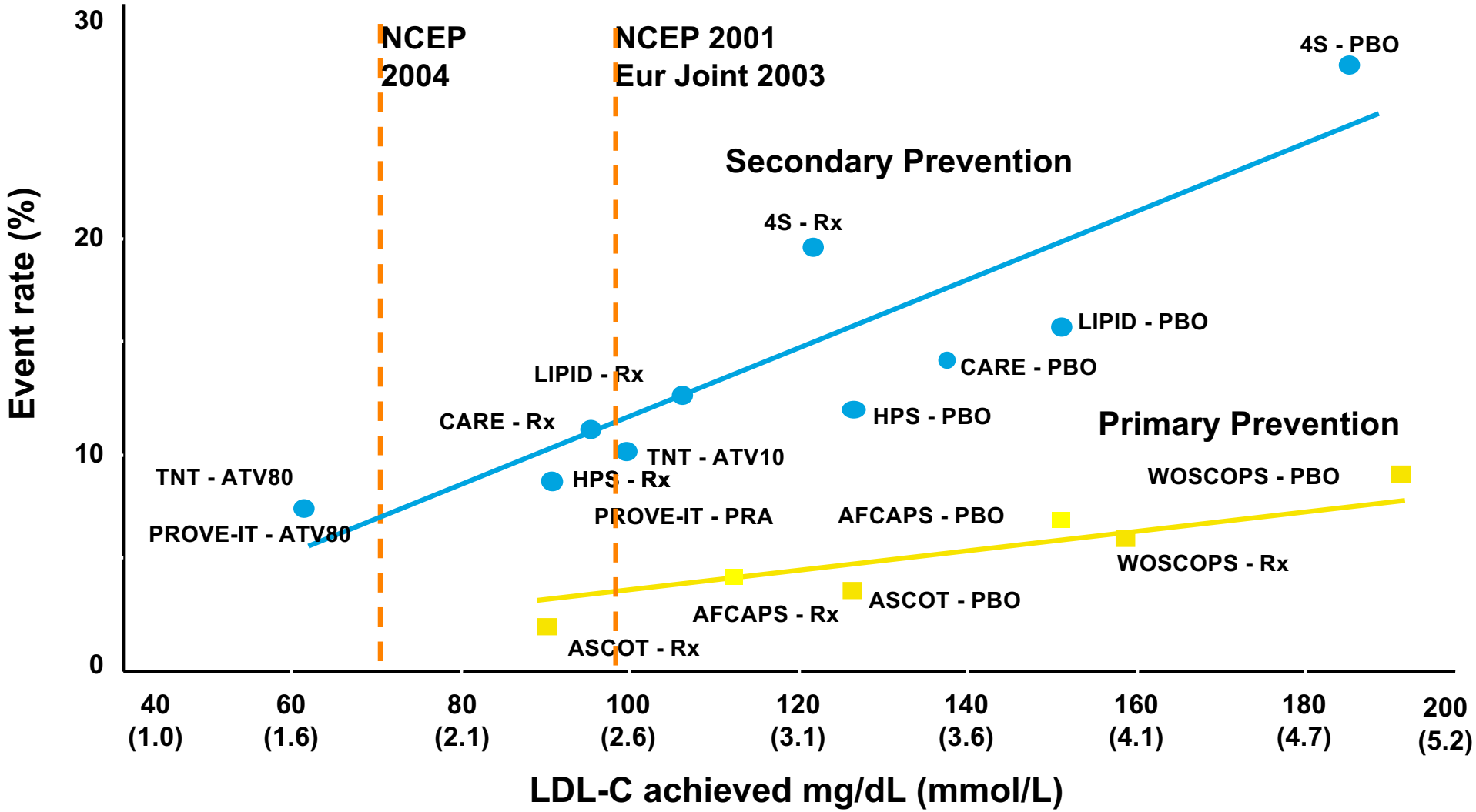
七大學會共同制定

- 中華民國血脂及動脈硬化學會
- 中華民國心臟學會
- 臺灣介入性心臟血管醫學會
- 台灣腦中風學會
- 中華民國糖尿病學會
- 中華民國糖尿病衛教學會
- 台灣腎臟醫學會



呼籲高風險病人應積極與醫師討論合適的治療，
追求壞膽固醇治療達標，遠離復發風險!

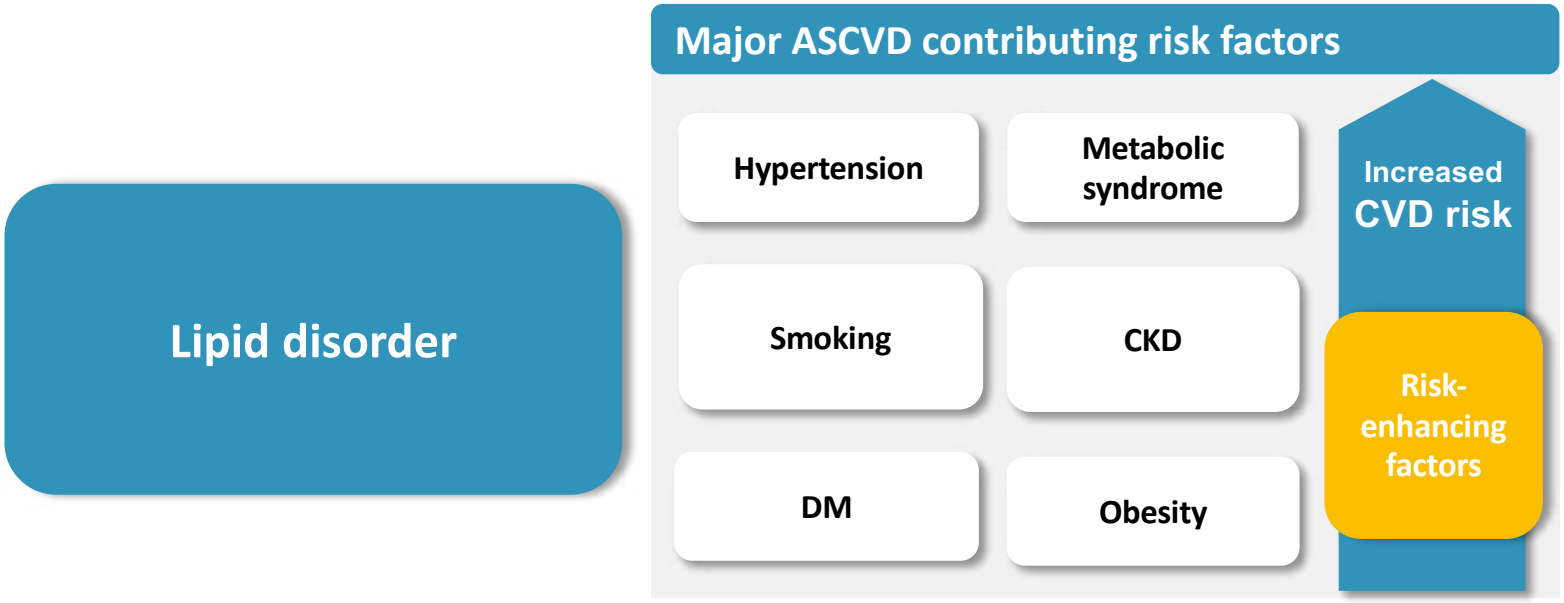
LDL是降血脂首要目標



Adapted from Rosensen, Exp Opin Emerg Drugs 2004;9:269;
LaRosa J et al, N Engl J Med, 2005;352:1425

Principle in 2018 guideline for ASCVD risk reduction is unchanged from 2013[1,2]

LDL-C is the primary target and "lower is better"



LDL-C measurements are important for initial ASCVD risk assessment and monitoring adherence and response to LDL-C lowering medications and lifestyle therapies.

A reduction in LDL-C levels of 1% gives an approximate 1% reduction in ASCVD risk.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol.

1. Stone NJ et al. J Am Coll Cardiol. 2014;63:2889-934; 2. Gundy SM et al. J Am Coll Cardiol. 2018 Nov 8. [Epub ahead of print]

PP-LIP-TWN-0232-201901

2018 ACC/AHA: First line therapy: Statins

AHA/ACC divides statin therapies into 3 intensity categories[1]:

	High-intensity	Moderate-intensity	Low-intensity
Average LDL-C reducing effect	**≥ 50%**	**30%-49%**	**< 30%**
Daily doses	**Atorvastatin 40-80 mg** **Rosuvastatin 20 mg (40 mg)** *Rosuvastatin is only approved at 20 mg in Taiwan unless for familial hypercholesterolemia[2]*	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40-80 mg Pitavastatin 1-4 mg Fluvastatin 40 mg BID/80 mg *Rosuvastatin 5 mg starting dose is recommended in Asians with caution taken when titrating[2]*	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; BID, twice daily; LDL-C: low-density lipoprotein cholesterol; RCT, randomized controlled trial.

Boldface *type indicates Boldface type indicates specific statins and doses that were evaluated in RCTs, and the Cholesterol Treatmen meta-analysis. All these RCTs demonstrated a reduction in major cardiovascular events.*

1. Gundy SM et al. J Am Coll Cardiol. 2018 Nov 8. [Epub ahead of print]
2. Crestor® 中文仿單

Second line therapy: Ezetimibe

- **Indicated for combination therapy with statins in patients with elevated LDL-C despite maximally tolerated statin therapy or whom experience statin-associated side effects.**[1]

Treatment regime	LDL-C lowering effects[2]
Ezetimibe Monotherapy (12W)	
Ezetimibe 10 mg	↓ LDL-C 13%-20%
Ezetimibe + Statin vs. Statin Monotherapy (12W)	
Ezetimibe 10 mg + Atorvastatin 10-80 mg	↓ LDL-C 53%-61%
Atorvastatin 10-80 mg	↓ LDL-C 37%-54%
Ezetimibe 10 mg + Simvastatin 10-80 mg	↓ LDL-C 46%-58%
Simvastatin 10-80 mg	↓ LDL-C 27%-45%
Ezetimibe 10 mg + Pravastatin 10-40 mg	↓ LDL-C 34%-42%
Pravastatin 10-40 mg	↓ LDL-C 21%-31%
Ezetimibe 10 mg + Lovastatin 10-40 mg	↓ LDL-C 34%-46%
Lovastatin 10-40 mg	↓ LDL-C 20%-30%

IMPROVE-IT demonstrated ezetimibe add-on to statin therapy can lower LDL-C by about 24% and further reduce the absolute risk of ASCVD by 2%.[3]

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol.

1. Gundy SM et al. J Am Coll Cardiol. 2018 Nov 8. [Epub ahead of print]
2. ZETIA Prescribing Information. Accessed date: 13 Dec 2018
3. Cannon CP et al. N Engl J Med. 2015;373:2387-97

PP-LIP-TWN-0232-201901

Second/third line therapy: PCSK9i

- **Indicated as add-on therapy for patients with significant ASCVD risk or with FH after maximally tolerated statin therapy + ezetimibe.**[1]

Treatment	LDL-C reducing effect	ASCVD risk reduction
Alirocumab: 75 mg Q2W + **Statin:** High-intensity dose or maximum tolerated dose	↓ LDL-C 54.7% vs. placebo[2]	15% risk reduction in major adverse cardiac events compared with placebo*[2]
Evolocumab: 140 mg Q2W / 420 mg once monthly + **Statin:** High-intensity dose ± ezetimibe	↓ LDL-C 59% vs. placebo[3]	15% risk reduction of composite of CV death, MI, stroke, UA requiring hospitalization, or coronary revascularization[3]

*composite of CHD death, nonfatal MI, ischemic stroke, or UA requiring hospitalization

Cons: (1) Requires subcutaneous injection; (2) Limited long-term safety data; (3) High cost

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CV, cardiovascular; FH, familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol; MI, myocardial infarction; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; UA, unstable angina; Q2W, every 2 weeks.

1. Gundy SM et al. J Am Coll Cardiol. 2018 Nov 8. [Epub ahead of print]
2. Schwartz GG et al. N Engl J Med. 2018;379:2097-107; 3. Sabatine MS et al. N Engl J Med. 2017;376:1713-22

PP-LIP-TWN-0232-201901

Other LDL-C lowering/triglyceride lowering agents

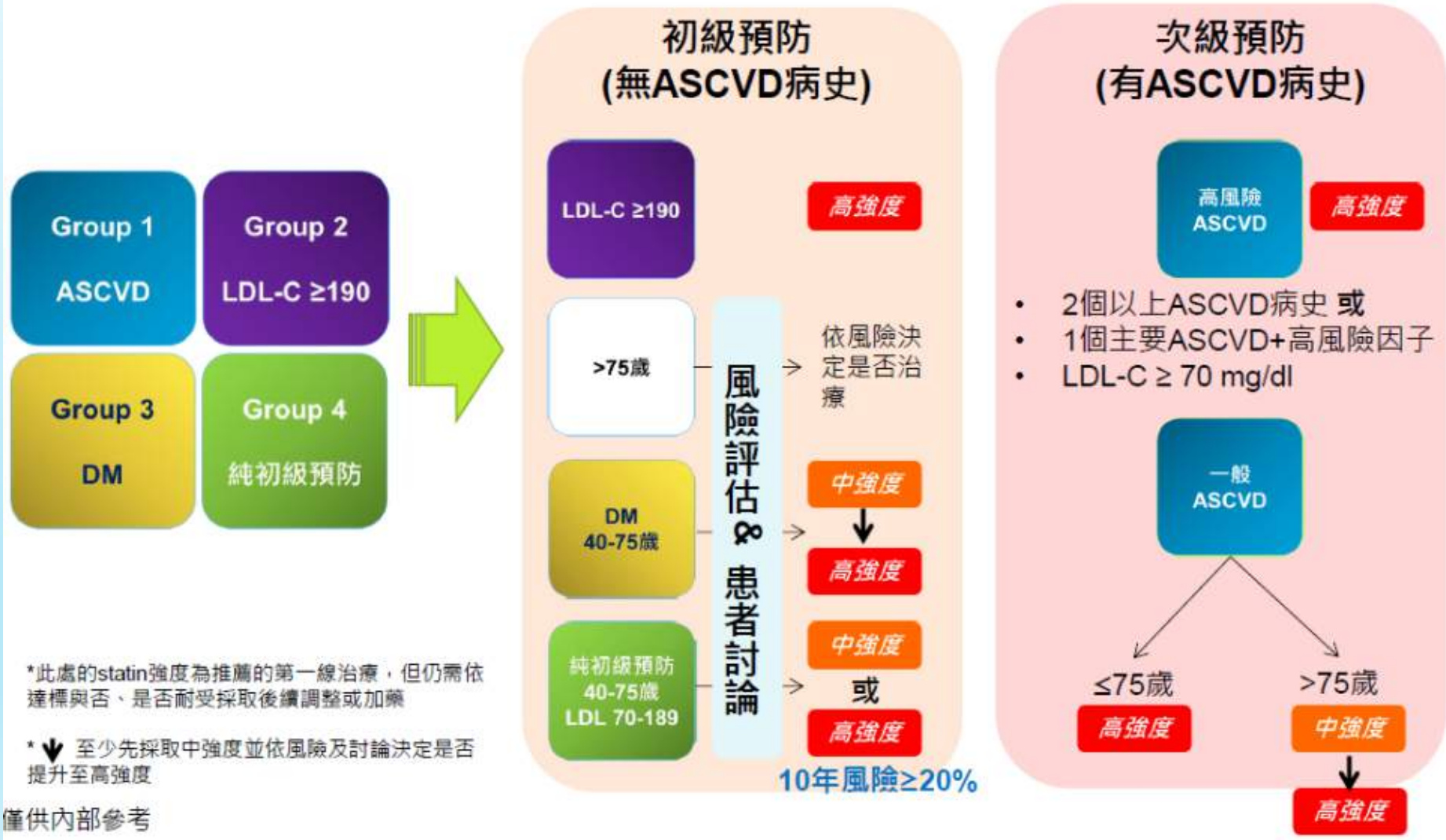
	Agents	Clinical consideration
Bile acid sequestrants[1]	• **Cholestyramine** • **Colesevelam** • **Colestipol**	• Lowers LDL-C 15%-30% • Add-on to statin therapy or use in patients with statin-associated side effects supported by RCT • Avoided if TG ≥ 300 mg/dL • Associated with GI side effects
Fibrates[1,2]	• **Gemfibrozil** • **Fenofibrate** • **Fenofibric acid**	• Lowers TG 20-35% • Myopathy/rhabdomyolysis when used with statin
Niacins[1,2]	• **Nicotinic acid**	• Lowers TG 20-30%; LDL-C 10-25%
Omega-3 fatty acids[2]	• **Icosapent ethyl, omega-3-acid ethyl esters**	• Lowers TG 27-45% • Effect of cardiovascular morbidity and mortality unknown in patients with severe hypertriglyceridemia

Abbreviations: GI, gastrointestinal; LDL-C: low-density lipoprotein cholesterol; RCT, randomized clinical trial; TG, triglycerides.

1. Gundy SM et al. J Am Coll Cardiol. 2018 Nov 8. [Epub ahead of print]
2. Jellinger PS et al. Endocr Pract. 2017;23(Suppl 2):1-87

風險族群如何改變?(那些患者應該要治療?)

- 初級預防(Non-ASCVD)及次級預防(ASCVD)為最大架構，並將風險族群進一步分群以決定是否採取高強度治療(詳見附錄)。



*此處的statin強度為推薦的第一線治療，但仍需依達標與否、是否耐受採取後續調整或加藥

* ↓ 至少先採取中強度並依風險及討論決定是否提升至高強度

僅供內部參考

大陸政協談「民主協商」 陸委會：台灣民眾絕不會上當 21:20

聯合新聞網

降血脂藥健保標準降低 造福3萬患者

2019-02-27 10:56 聯合報 記者簡浩正／即時報導

高血脂治療健保資源更充足，今年2月1日起健保下修部分高危險族群的治療藥物給付條件至LDL-C（低密度脂蛋白膽固醇、壞膽固醇）小於 70mg/dL，助全台逾3萬名患者，避免血脂回升，抑制心血管疾病發生。醫師提醒，LDL-C即使達標，患者仍要持續治療，勿擅自停藥導致回升，暴露於疾病風險中。

健保署自2月1日起，放寬高危險群病人（如有急性冠狀動脈症候群病史、心導管介入治療，冠狀動脈粥狀硬化等）藥物治療給付條件，從LDL-C 100mg/dL下修至70mg/dL。中華民國血脂及動脈硬化學會理事長李貽恒表示，冠心症為冠狀動脈狹窄或阻塞造成的心臟疾病，而高血脂、糖尿病等易使內皮細胞功能異常，是造成動脈粥狀硬化、冠心病等疾病的高危險群。

李貽恒說，過往健保給付條件為LDL-C超過100mg/dL以上才合乎標準，介於100mg/dL與70mg/dL間患者只能自費用藥；據近年來流行病學研究顯示，有超過8成冠心症等心血管疾病患者，LDL-C未控制小於70mg/dL，隨時有發作可能。所幸健保給付規定修訂後，解決了這個治療斷層，嘉惠超過3萬名患者。

馬偕醫院副院長葉宏一則表示，許多民眾以為採清淡飲食以及控制達標即能降低血脂，但血液中的膽固醇（包含LDL-C）只有約15%來自飲食；另有研究顯示，若高危險群患者在血脂降到標準值後停藥，血脂便會在3至4個月內回升至服藥前狀況，仍有心血管疾病再發及死亡風險，還是得持續服用藥物才有成效。

李貽恒指出，LDL-C若超過70 mg/dL，疾病發生率高達25%；若LDL-C每降低39 mg/dL，就可減少2成心肌梗塞與中風的風險，不過也得看患者的身體狀況而定；他曾收治過LDL-C高達400mg/dL的患者，但也收治過患者按時服藥[illegible]上運動，LDL-C降到非常低的例子，希望病人都能做好血脂控制，遠離疾病威脅。

高危險群病人（如有急性冠狀動脈症候群病史、心導管介入治療，冠狀動脈粥狀硬化等）藥物治療給付條件，從LDL-C 100mg/dL下修至70mg/dL

降血脂藥品給付規定修訂對照

民國108年2月1日生效

中央健保署網站公告

「藥品給付規定」修訂對照表　　附件

第2節 心臟血管及腎臟藥物 Cardiovascular-renal drugs

修訂後給付規定

2.6.1. 全民健康保險降血脂藥物給付規定表（86/1/1、87/4/1、87/7/1、91/9/1、93/9/1、97/7/1、102/8/1、108/2/1）

	非藥物治療	起始藥物治療血脂值	血脂目標值	處方規定
1. 有急性冠狀動脈症候群病史 2. 曾接受心導管介入治療或外科冠動脈搭橋手術之冠狀動脈粥狀硬化患者（108/2/1）	與藥物治療可並行	LDL-C≧70mg/dL	LDL-C＜70mg/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。
心血管疾病或糖尿病患者	與藥物治療可並行	TC≧160mg/dL 或 LDL-C≧100mg/dL	TC＜160mg/dL 或 LDL-C＜100mg/dL	
2個危險因子或以上	給藥前應有3-6個月非藥物治療	TC≧200mg/dL 或 LDL-C≧130mg/dL	TC＜200mg/dL 或 LDL-C＜130mg/dL	
1個危險因子	給藥前應有3-6	TC≧240mg/dL 或	TC＜240mg/dL 或	

原給付規定

2.6.1. 全民健康保險降血脂藥物給付規定表（86/1/1、87/4/1、87/7/1、91/9/1、93/9/1、97/7/1、102/8/1）

	非藥物治療	起始藥物治療血脂值	血脂目標值	處方規定
無	無	無	無	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。
心血管疾病或糖尿病患者	與藥物治療可並行	TC≧160mg/dL 或 LDL-C≧100mg/dL	TC＜160mg/dL 或 LDL-C＜100mg/dL	
2個危險因子或以上	給藥前應有3-6個月非藥物治療	TC≧200mg/dL 或 LDL-C≧130mg/dL	TC＜200mg/dL 或 LDL-C＜130mg/dL	
1個危險因子	給藥前應有3-6個月非藥物治療	TC≧240mg/dL 或 LDL-C≧160mg/dL	TC＜240mg/dL 或 LDL-C＜160mg/dL	

同意
放寬!

冠心病的次級預防
LDL-C 起始治療值與治療目標降為 70 mg/dl

自2019年2月1起，健保給付將針對以下患者放寬規定[1]

急性冠狀動脈症候群
病史

或

曾接受心導管介入治療

或

外科冠動脈搭橋手術之
冠狀動脈粥狀硬化患者

降血脂藥物修訂後給付規定[1]

1. 有急性冠狀動脈症候群病史
2. 曾接受心導管介入治療
3. 外科冠動脈搭橋手術之冠狀動脈粥狀硬化患者

起始藥物治療血脂值：LDL-C ≥ 70 mg/dL

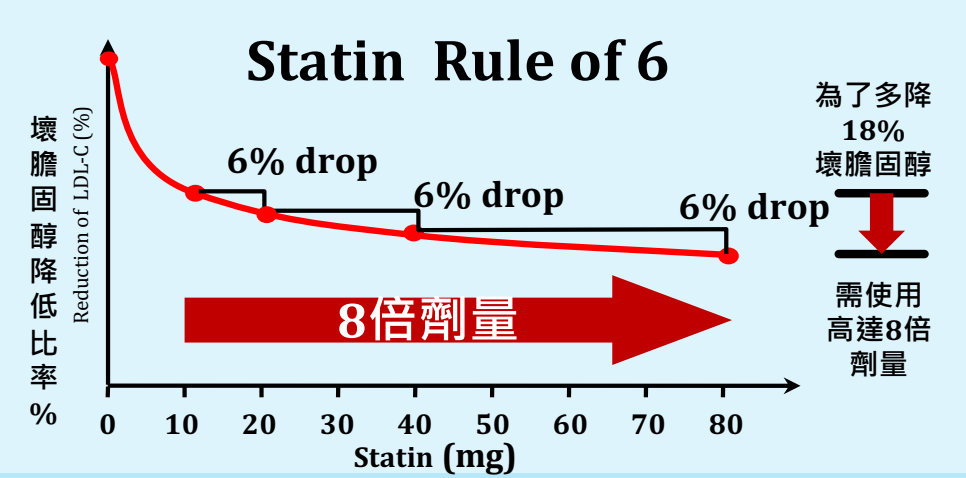
血脂目標值：LDL-C < 70 mg/dL

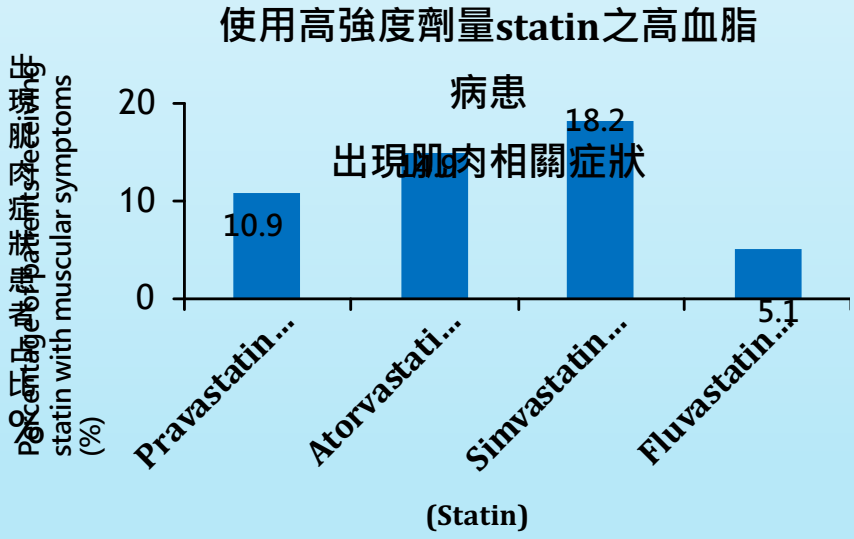
Statins 擔心的事

偏限一： “Rule of 6”
增加Statins劑量只能多降6%壞膽固醇

偏限二：病患無法耐受
使用高強度劑量病患表示出現肌肉疼痛

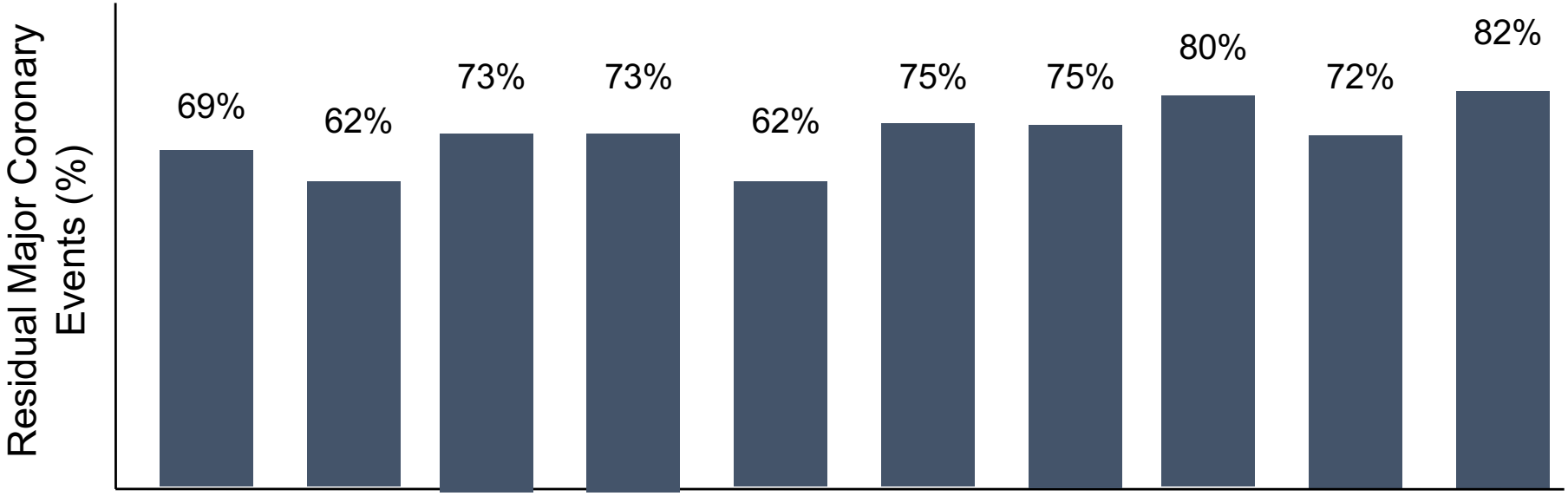
偏限三：患者害怕高強度Statin會影響肝功能
最常見的不良反應之一





The combination of Ezetimibe and Statin: a new treatment for hypercholesterolemia ; doi: 10.4081/hi.2007.12
Leitersdorf E. Cholesterol absorption inhibition: filling an unmet need in lipid-lowering management. Eur Heart J Suppl. 2001;3(suppl E):E17–23
Bruckert E. et al. *Cardiovascular Drugs and Therapy* 2005;19:403-14.
Statins and its hepatic effects: Newer data, implications, and changing recommendations
J Pharm Bioallied Sci. 2016 Jan-Mar; 8(1): 23–28.
doi: 10.4103/0975-7406.171699

服用Statin後仍有
6~7成心血管殘餘風險



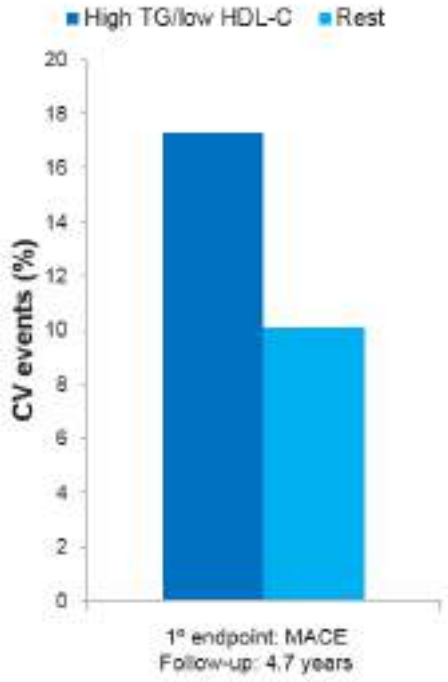
Trial	WOSCOPS	AFCAPS/ TexCAPS	HPS	ASPEN	4S	LIPID	CARE	TNT Total	TNT Met S	TNT Diabetes
N	6.595	6.505	20.536	2.410	4.444	9.014	4.159	10.001	5.584	1.501
∆ LDL-C	-26%	-27%	-29%	-29%	-36%	-25%	-28%	-21%	-24%	-20%

Adapted from Libby P, J Am Coll Cardiol 2005;46:1225-1228

高風險族群，就算接受Statin治療，TG過高仍會明顯增加心血管疾病風險

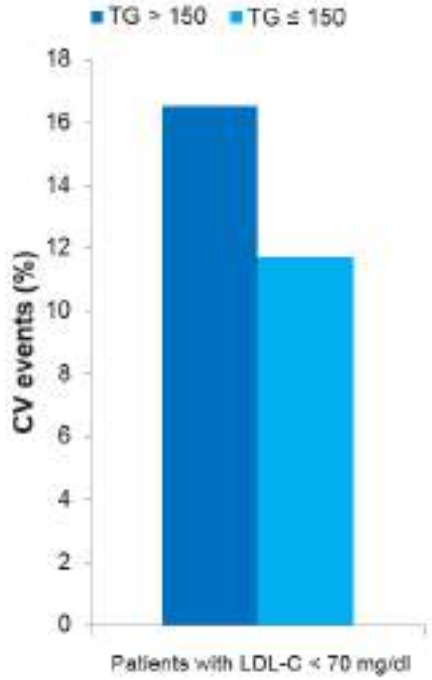
ACCORD-Lipid trial

- 5518 patients with T2DM
- All patients treated with simvastatin

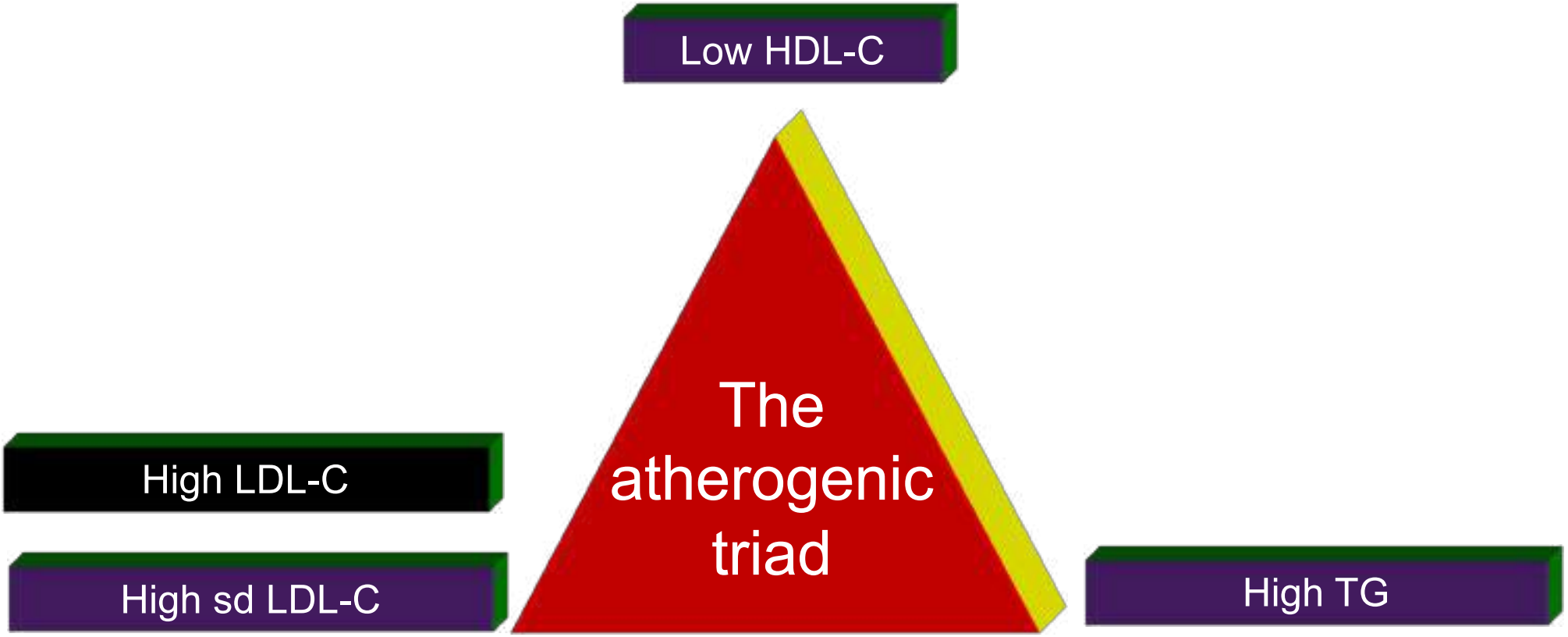


PROVE-IT TIMI

- Post ACS trial
- All patients treated with atorvastatin 80 mg or pravastatin 40 mg

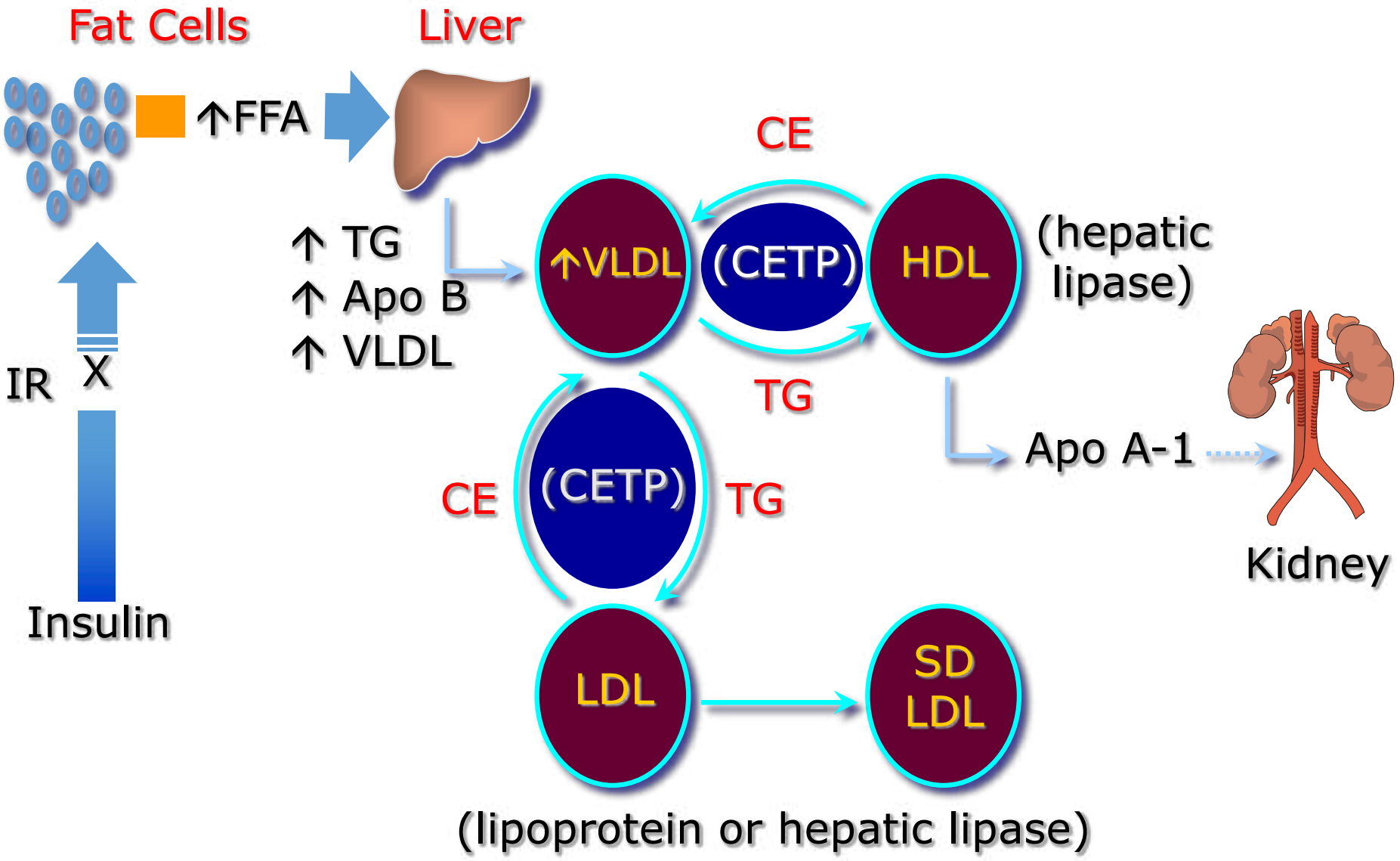


sd-LDL過高、HDL-C過低及TG過高是粥狀動脈硬化患者血脂異常特徵



Expert Panel on Detection, Evaluation,and Treatment of High Blood Cholesterol in Adults JAMA 2001;285:2486-2497

TG過高亦會降低HDL及增加sdLDL



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**

Fats and fatty acids
脂肪酸

Saturated fats
Animal fats, butter, lard
飽和脂肪酸

Unsaturated fats
不飽和脂肪酸

Polyunsaturated fats
多元不飽和脂肪酸

Essential 必需

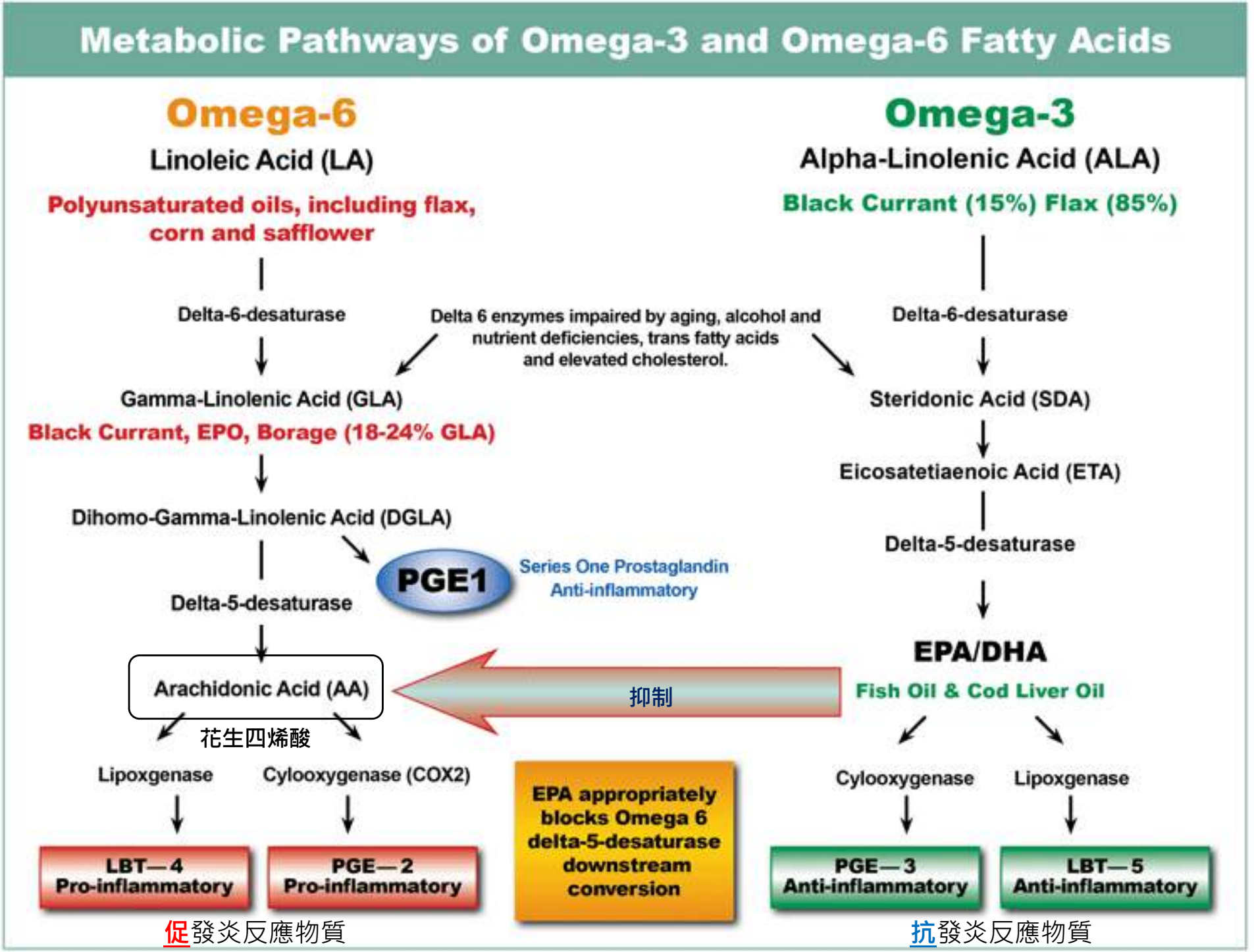
Omega 3 fatty acids
Eicosapentanoic acid:
fish, shellfish
Docosahexanoic acid:
fish, shellfish
α linolenic acid:
flaxseed, soybean,
walnut, rapeseed oils

Omega 6 fatty acids
Corn oil 玉米油
Safflower oil
Sunflower oil 葵花子油

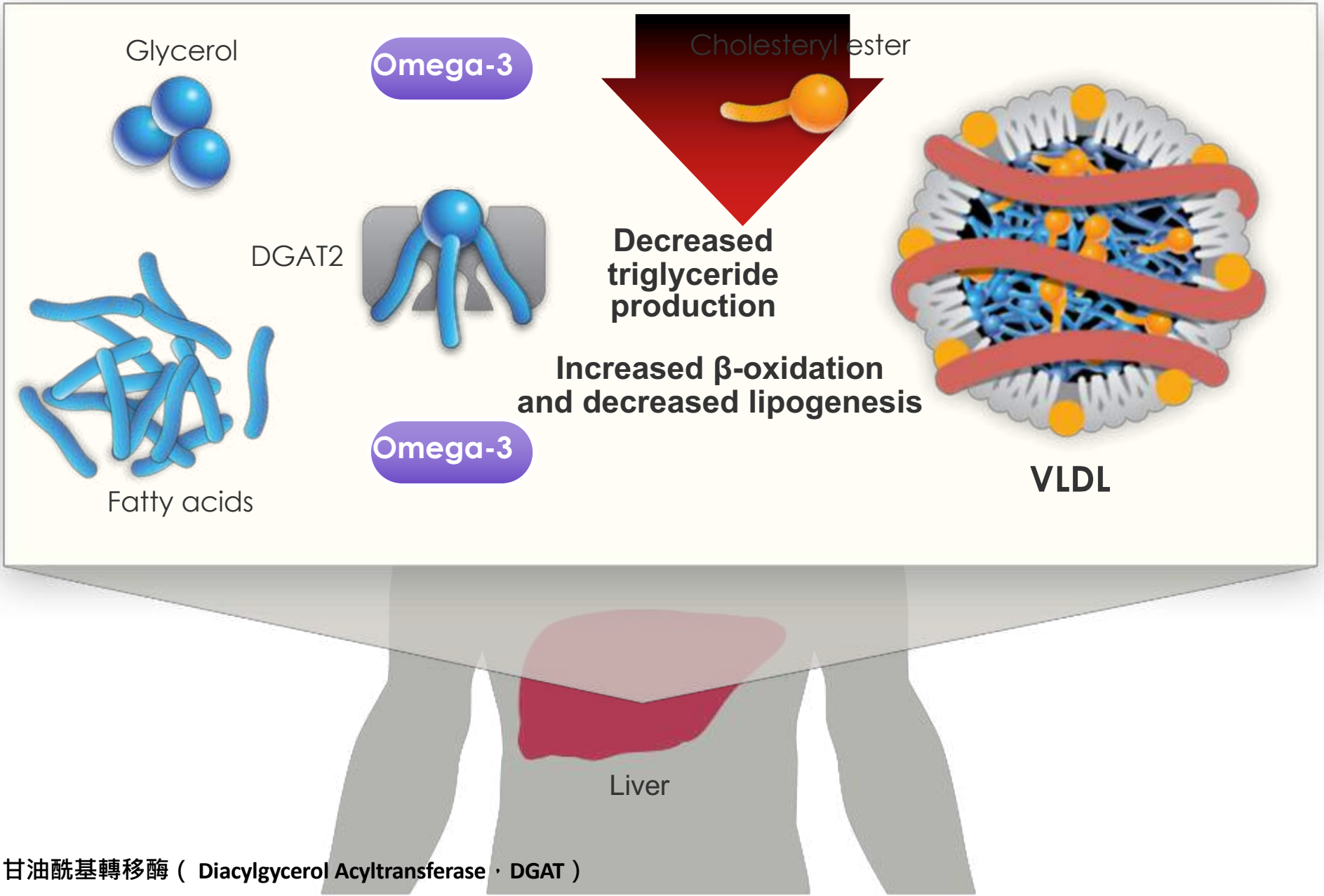
Monounsaturated fats
單元不飽和脂肪酸

非必需 **Non-Essential**

Omega 9 fatty acids
Olive oil 橄欖油
Avocados
Peanuts 花生油
Almonds

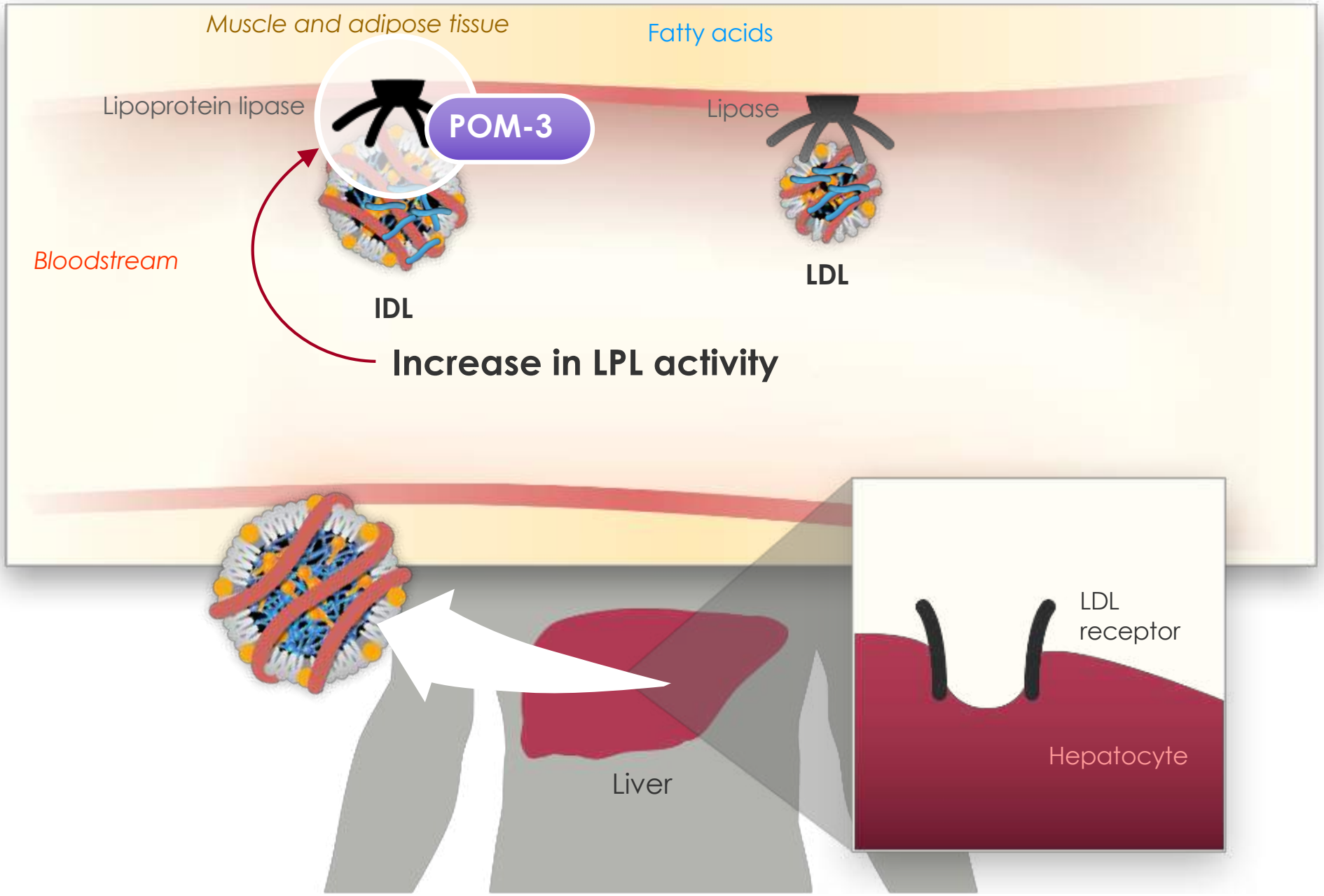

Metabolic Pathways of Omega-3 and Omega-6 Fatty Acids
Omega-6
Linoleic Acid (LA)
Polyunsaturated oils, including flax, corn and safflower
Delta-6-desaturase
Gamma-Linolenic Acid (GLA)
Black Currant, EPO, Borage (18-24% GLA)
Dihomo-Gamma-Linolenic Acid (DGLA)
PGE1
Series One Prostaglandin
Anti-inflammatory
Delta-5-desaturase
Arachidonic Acid (AA)
花生四烯酸
Lipoxgenase
Cylooxygenase (COX2)
LBT—4
Pro-inflammatory
PGE—2
Pro-inflammatory
Delta 6 enzymes impaired by aging, alcohol and nutrient deficiencies, trans fatty acids and elevated cholesterol.
EPA appropriately blocks Omega 6 delta-5-desaturase downstream conversion
Omega-3
Alpha-Linolenic Acid (ALA)
Black Currant (15%) Flax (85%)
Delta-6-desaturase
Steridonic Acid (SDA)
Eicosatetiaenoic Acid (ETA)
Delta-5-desaturase
EPA/DHA
Fish Oil & Cod Liver Oil
抑制
Cylooxygenase
Lipoxgenase
PGE—3
Anti-inflammatory
LBT—5
Anti-inflammatory
促發炎反應物質
抗發炎反應物質

Proposed Intrahepatic Mechanisms of Action

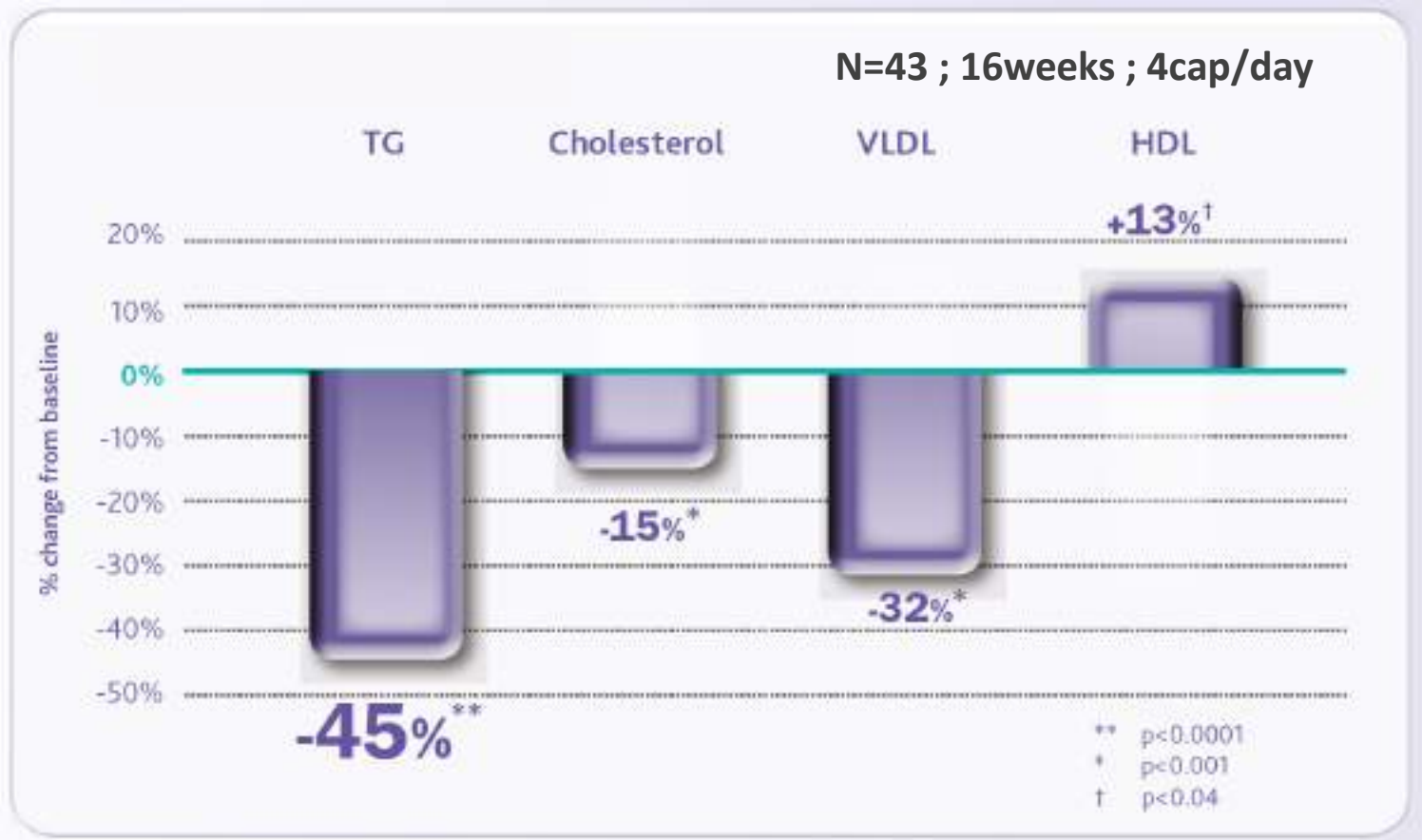


甘油酰基轉移酶（ Diacylgycerol Acyltransferase，DGAT ）

Proposed Extrahepatic Mechanism of Action



N-3可明顯降低TG達45%



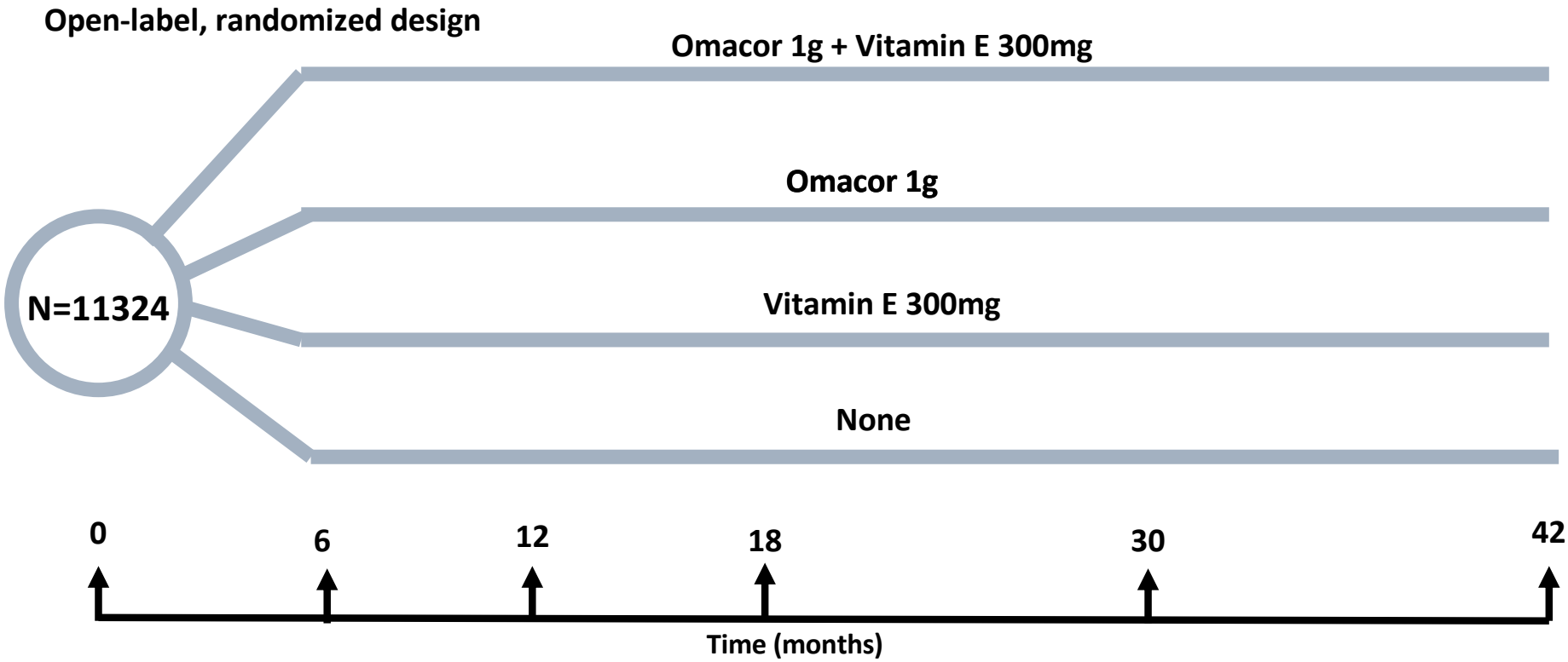
Patient characteristics:

- Plasma triglycerides 5,65-22,60 mmol/l (**500-2000mg/dl**)

Harris WS et al. J Cardiovascular Risk 1997; 4: 385-91

CV OUTCOMES

GISSI-Prevention trial

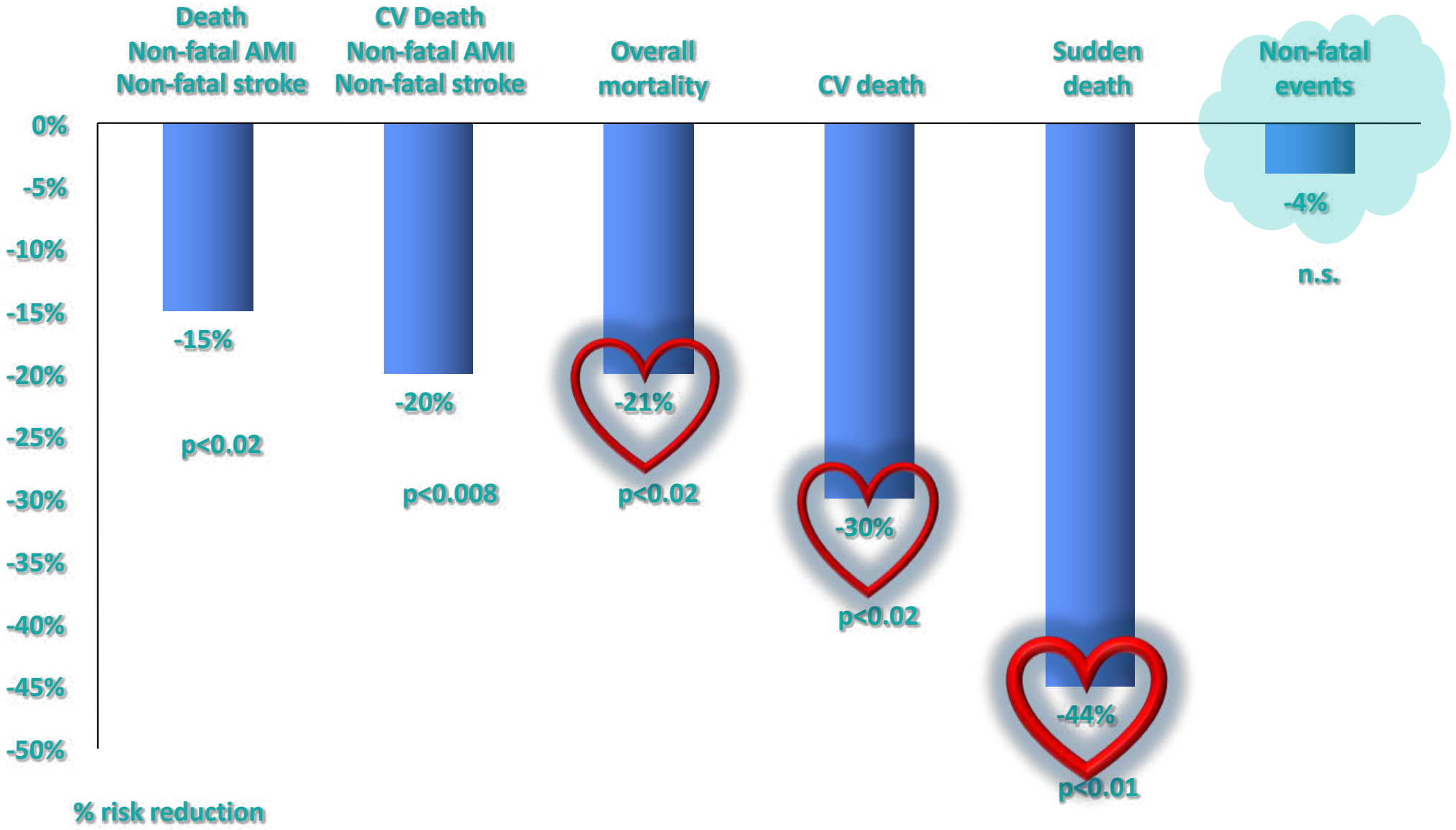


Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E **after myocardial infarction**: results of the GISSI-Prevenzione trial

Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico

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

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



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

Circulation. 2016;134:378–391.

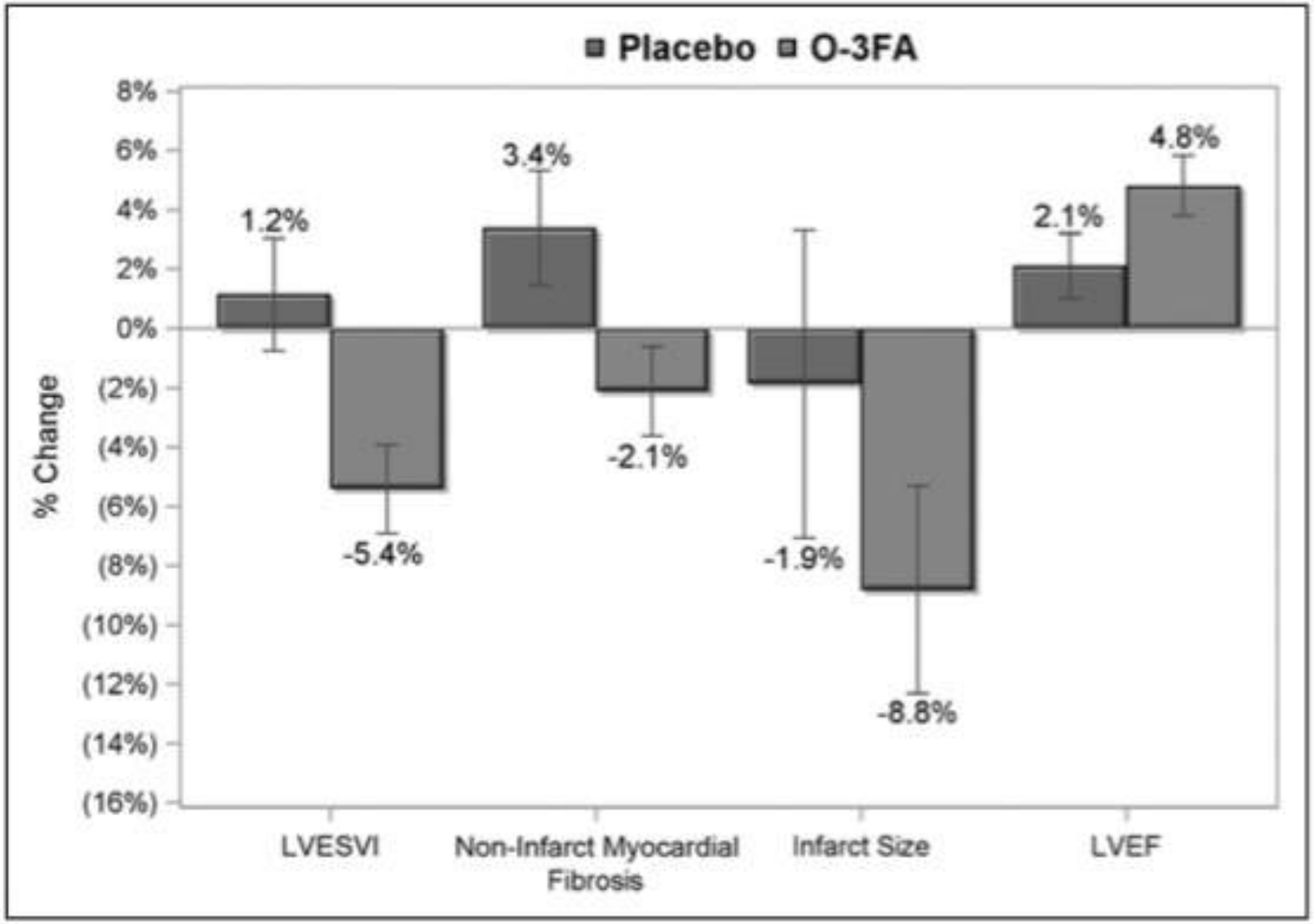
ORIGINAL RESEARCH ARTICLE

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

The OMEGA-REMODEL Randomized Clinical Trial

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

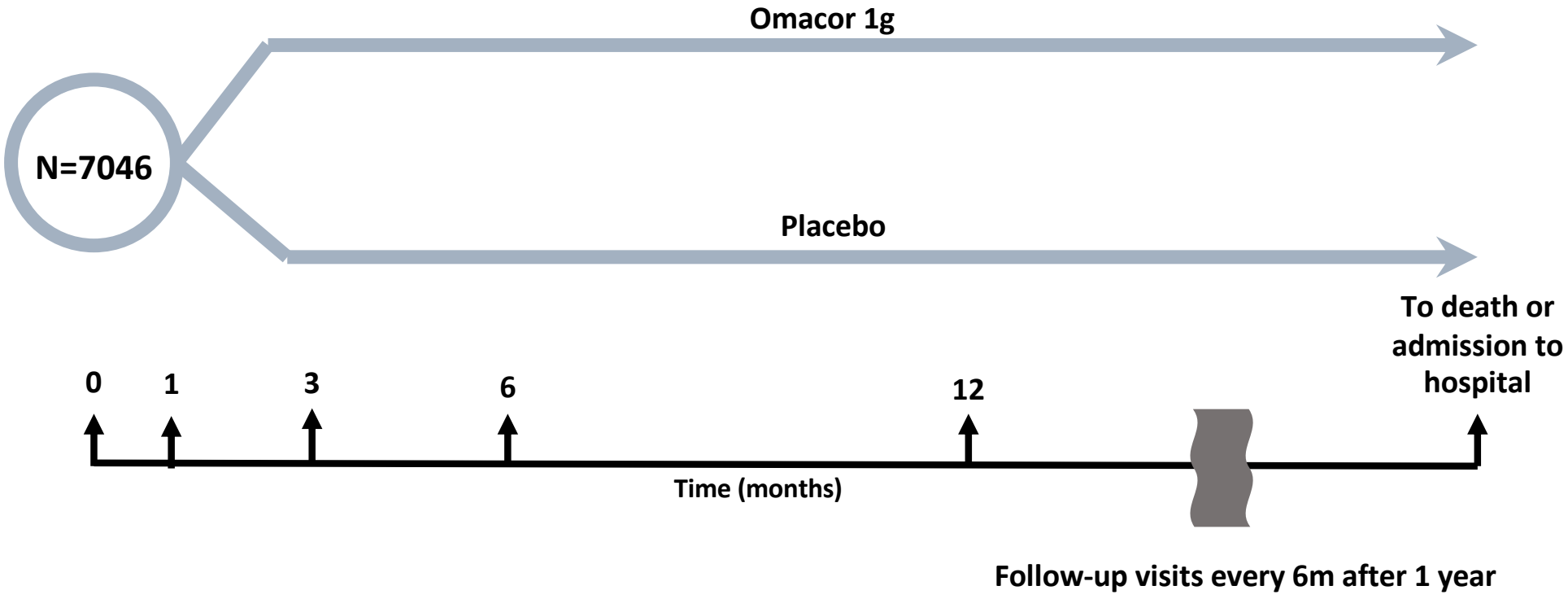
AMI後對心臟具保護效果



Circulation. 2016;134:378–391.

GISSI-HF trial

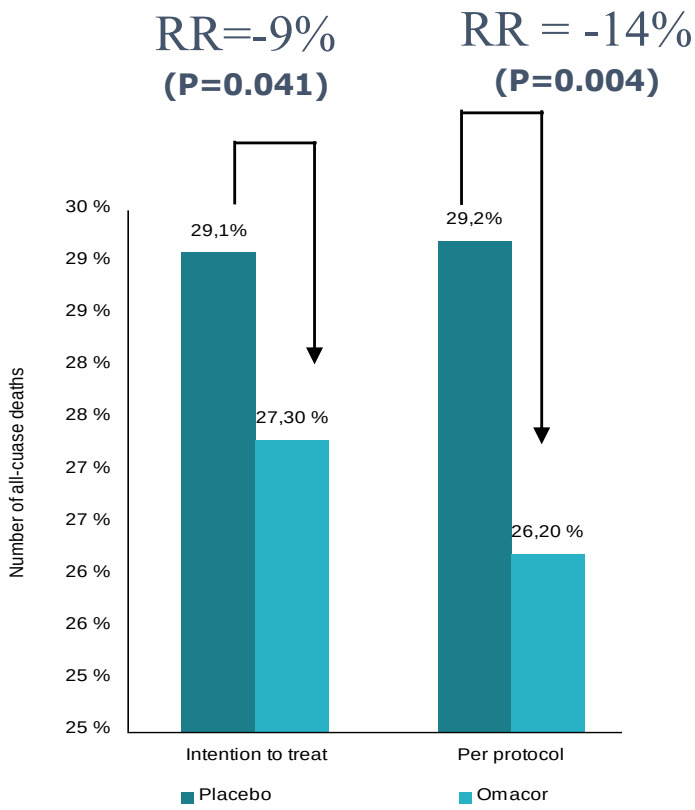
Effect of n-3 polyunsaturated fatty acids in patients with **chronic heart failure** (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial.



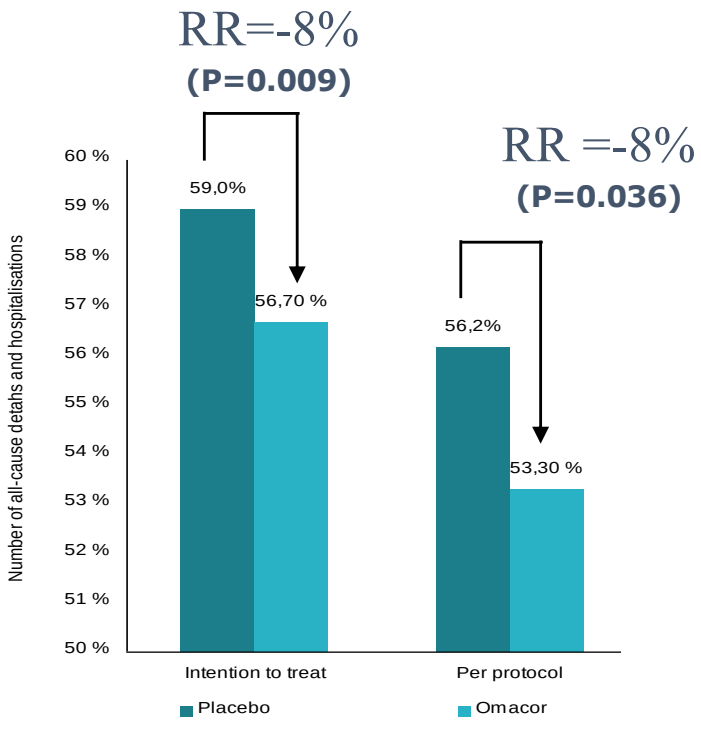
Lancet. 2008 Oct 4;372(9645):1223-30.

GISSI-HF 臨床實驗發現:可降低HF約9%死亡率

Number of all-cause death

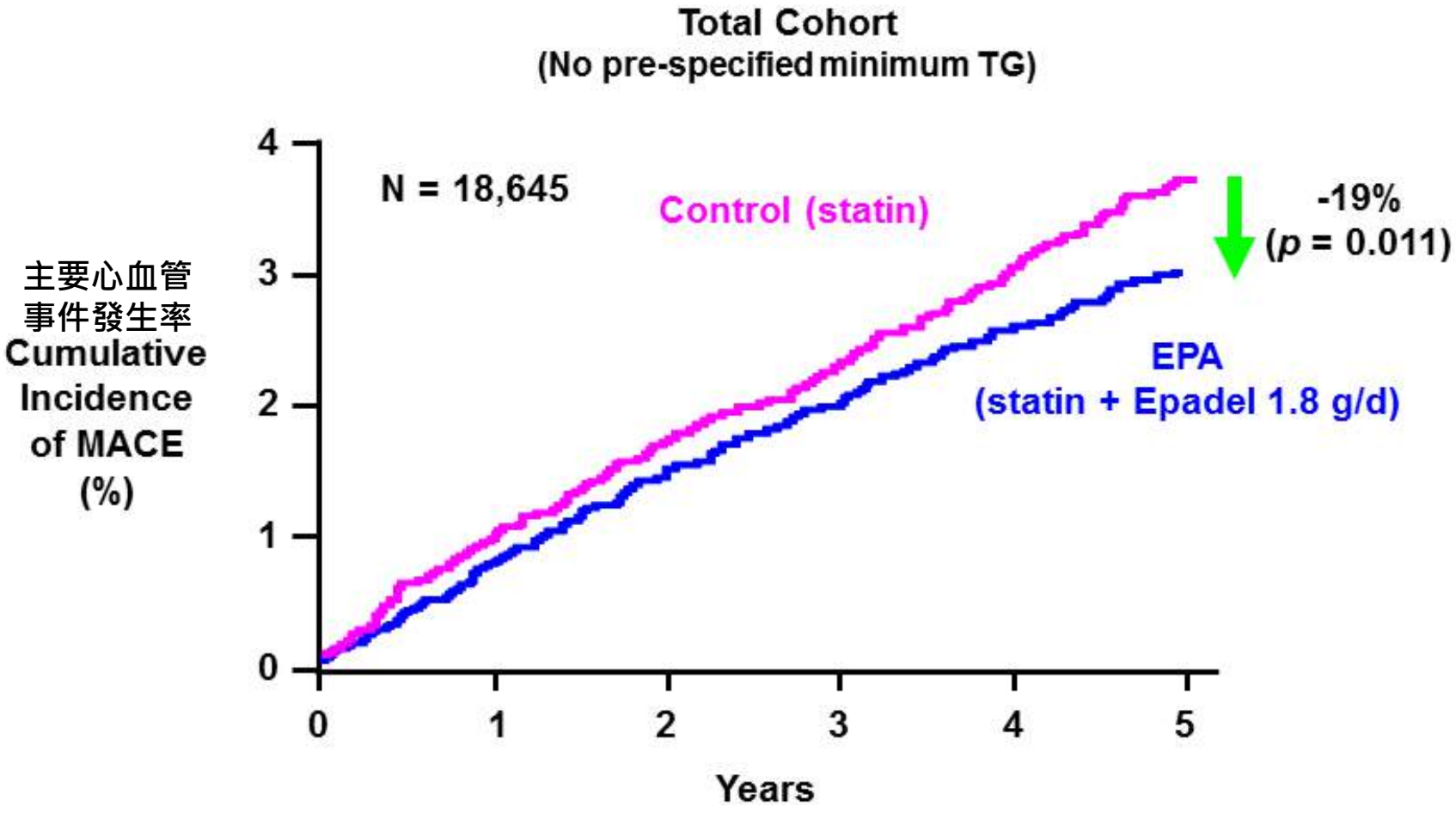


Number of all-cause death & hospitalisations



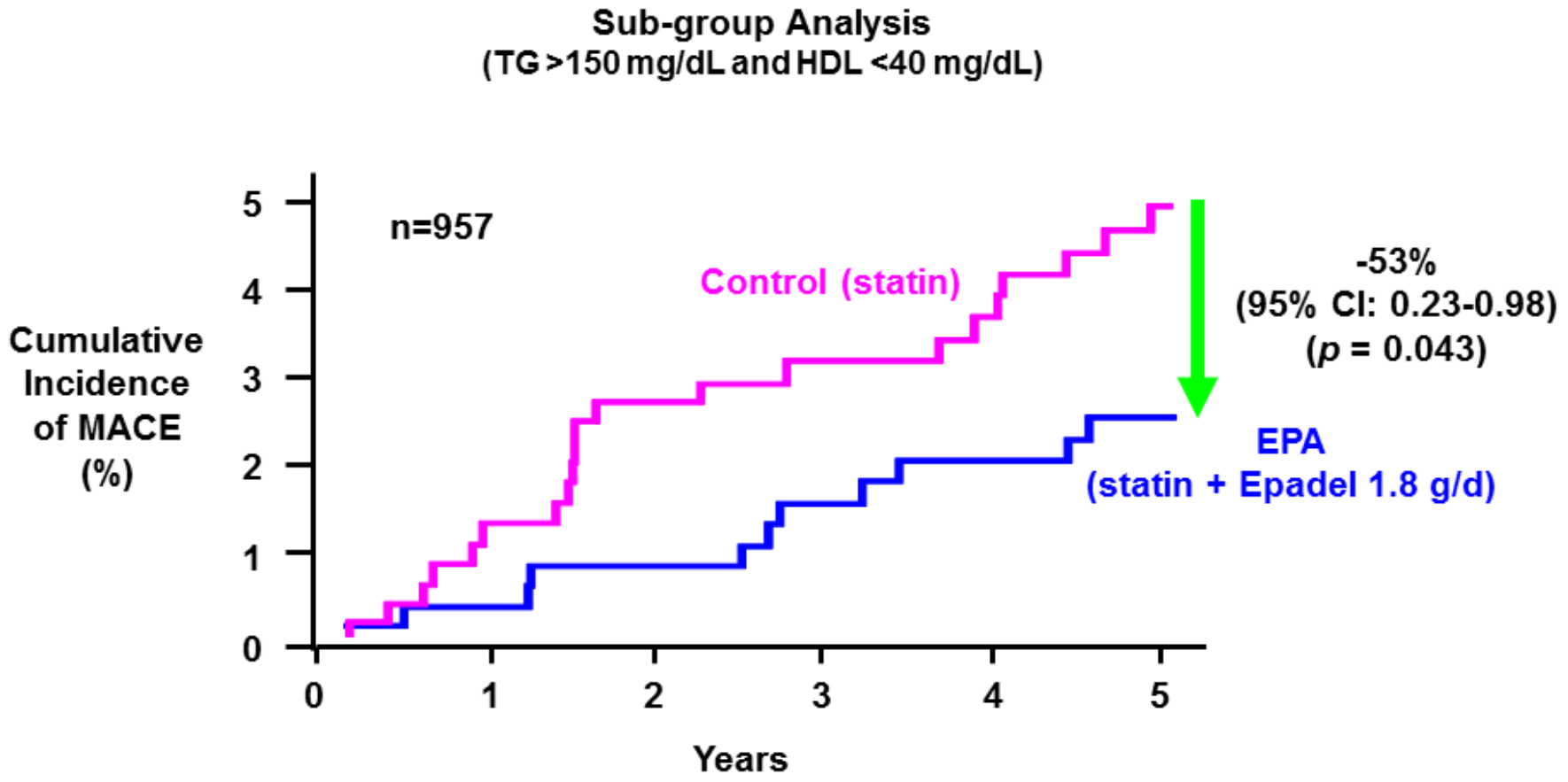
Lancet. 2008 Oct 4;372(9645):1223-30.

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



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

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



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

AHA 2018 - CHICAGO

What's new and what's more in 2018 AHA?

Hotlines form Daily News #AHA18

- **REDUCE-IT finds medication *added to statins* reduced risks among patients with high triglyceride**
- **VITAL trial consider *omega-3 fatty acids*, vitamin D in CV protection and cancer mortality**
- Diagnose and treat "residual inflammatory risk" aggressively (CANTOS, CIRT)
- Results from DECLARE trials show drug may reduce CV death or hospitalization for HF patients with Type 2 diabetes
- Yoga may have potential for cardiac rehab in low- and middle-income settings
- POINEER-HF: from "*chronically stable HF*" to "*stabilized after acute HF*", from *"post-discharge"* to *"in-hospital"* setting

REDUCT-IT (Nov 2018)

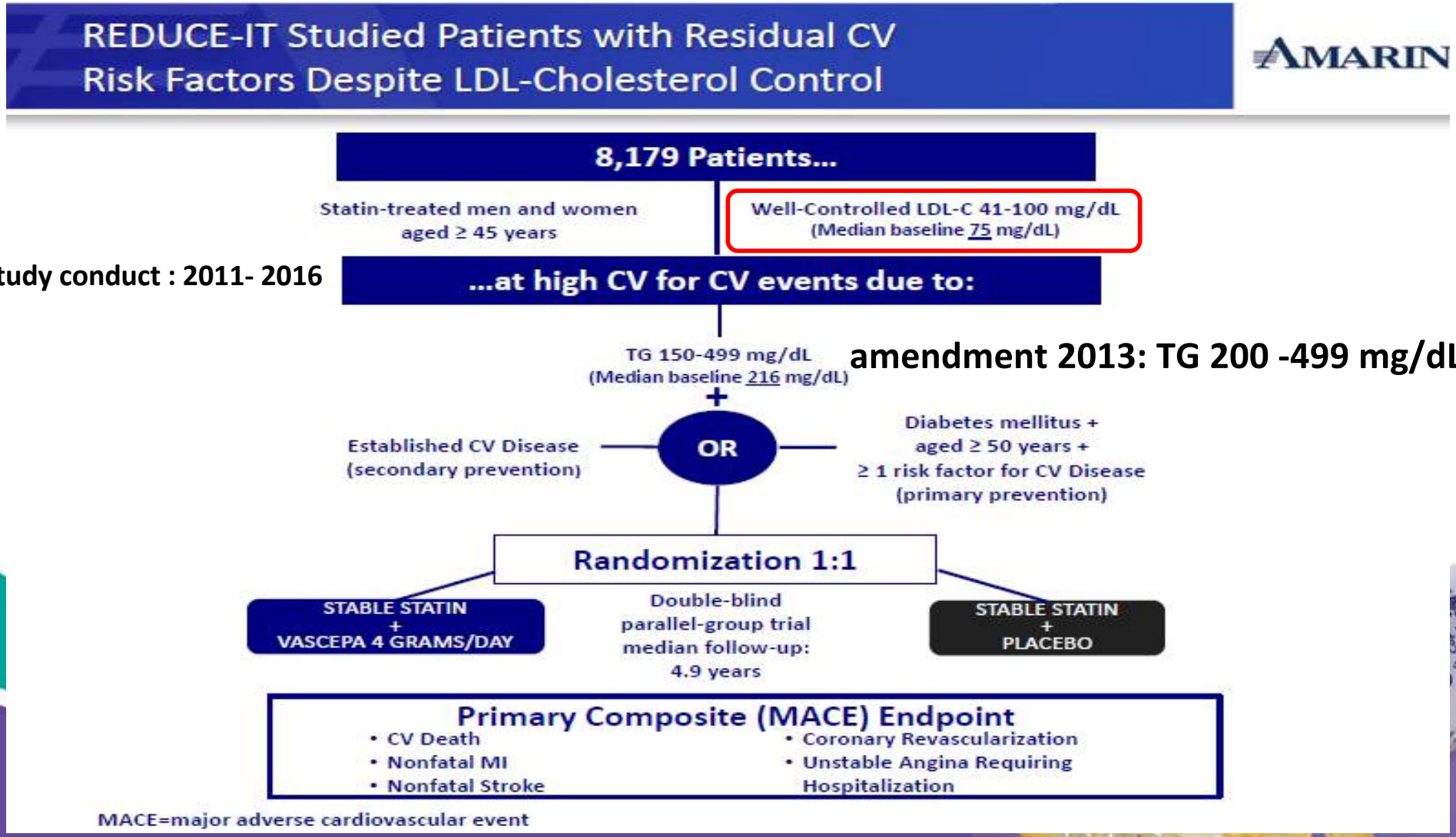
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. 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*

REDUCE-IT Study Design



Study conduct : 2011- 2016

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

Vascepa® (icosapent ethyl) capsules

Vascepa (icosapent ethyl) is an Omega-3 acid known as EPA in ethyl-ester form, not fish oil, but derived from fish

Single active ingredient EPA (eicosapentaenoic acid)

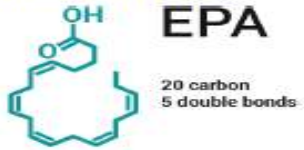
- Unique omega-3 molecule[1] derived from nature
  - New chemical entity designation by FDA for Vascepa as pure EPA
  - Purity achieved while overcoming the fragility and stability issues associated with omega-3s
- Excludes saturated fats, omega-6s and other components in fish oil
- No known drug-drug interactions[1]

EPA is smaller than DHA in length and number of double bonds that influence activities

- Small molecule capable of entering and improving function of endothelial cells
- Doesn't inhibit clearance of LDL-C like DHA (docosahexaenoic acid)

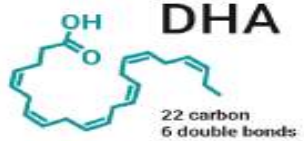
Omega-3s are easily oxidized or otherwise damaged

- Vascepa is expertly manufactured and encapsulated
- Demonstrated multi-year stability with consistent reproducibility



EPA

20 carbon
5 double bonds



DHA

22 carbon
6 double bonds

Vascepa differs from other omega 3 products: it is a pure form of EPA and does not contain docosahexanoic acid (DHA), whereas other fish oil products are combination of EPA/DHA. DHA can cause LDL-C levels to increase

US PI : Vascepa® (icosapent ethyl)

Approved in 2012 (FDA) , indicated as adjunct to diet to reduce TG levels in adult pats with severe (≥500 mg/dL) hypertriglyceridemia (sHTG)

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

----------INDICATIONS AND USAGE----------
VASCEPA is an ethyl ester of eicosapentaenoic acid (EPA) indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia. (1)

Limitations of Use:
•The effect of VASCEPA on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined. (1)

•The effect of VASCEPA on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined. (1)

----------DOSAGE AND ADMINISTRATION----------
The daily dose of VASCEPA is 4 grams per day taken as 2 capsules twice daily with food. (2)
Patients should be advised to swallow VASCEPA capsules whole. Do not break open, crush, dissolve, or chew VASCEPA. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 1 gram (3)

----------CONTRAINDICATIONS----------
VASCEPA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to VASCEPA or any of its components. (4)

----------WARNINGS and PRECAUTIONS----------
In patients with hepatic impairment, monitor ALT and AST levels periodically during therapy. (5.1)

Use with caution in patients with known hypersensitivity to fish and/or shellfish. (5.2)

----------ADVERSE REACTIONS----------
The most common reported adverse reaction (incidence >2% and greater than placebo) was arthralgia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amarin Pharma Inc. at 1-855-VASCEPA (1-855-827-2372) or contact the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Omega-3 acids may prolong bleeding time. Patients receiving treatment with VASCEPA and other drugs affecting coagulation (e.g., anti-platelet agents) should be monitored periodically. (7)

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 6/2015

Population Summary

Enrolled patients with CV risk factors beyond elevated LDL-C

8179 statin-treated patients with well-controlled LDL-C (41-100 mg/dL; median baseline 75 mg/dL)

TG 135-499 mg/dL (median baseline 216 mg/dL)

Stratified by risk into either secondary prevention or primary prevention cohort

- 71% — patients with established CVD and ≥45 years (secondary prevention cohort)
- 29% — patients with diabetes mellitus, ≥50 years, and one additional CV risk factor (primary prevention cohort)

Randomized to VASCEPA 4 g/d + stable statin or placebo + stable statin

Patients were on background lipid-lowering therapy with a median baseline LDL-C of 75 mg/dL

Baseline characteristics

Table 1. Characteristics of the Patients at Baseline.*

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

Baseline Lipids Levels

Table 1. Characteristics of the Patients at Baseline.*

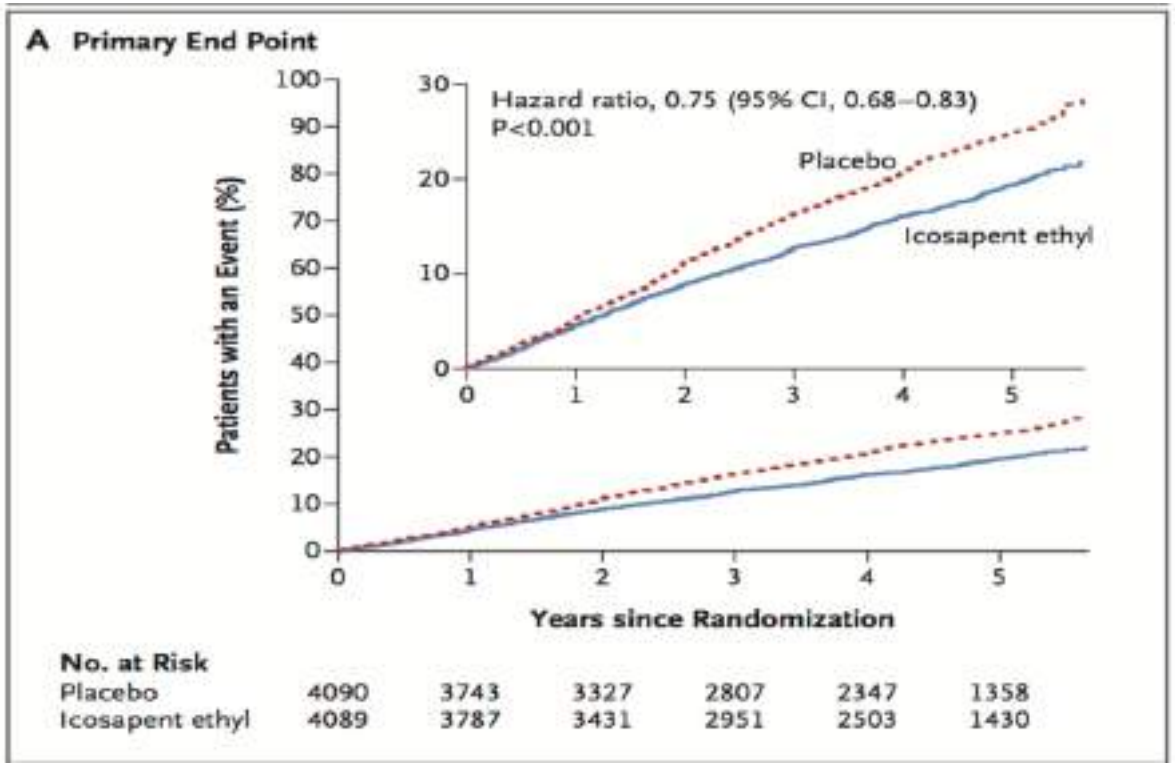
Characteristic	Icosapent Ethyl (N = 4089)	Placebo (N = 4090)
Median high-sensitivity CRP level (IQR) — mg/liter	2.2 (1.1–4.5)	2.1 (1.1–4.5)
Median triglyceride level (IQR) — mg/dl	216.5 (176.5–272.0)	216.0 (175.5–274.0)
Median HDL cholesterol level (IQR) — mg/dl	40.0 (34.5–46.0)	40.0 (35.0–46.0)
Median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

Biomarkers changes (from baseline to year 1)

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

*Apo B and hsCRP were measured at Year 2.

Primary endpoint

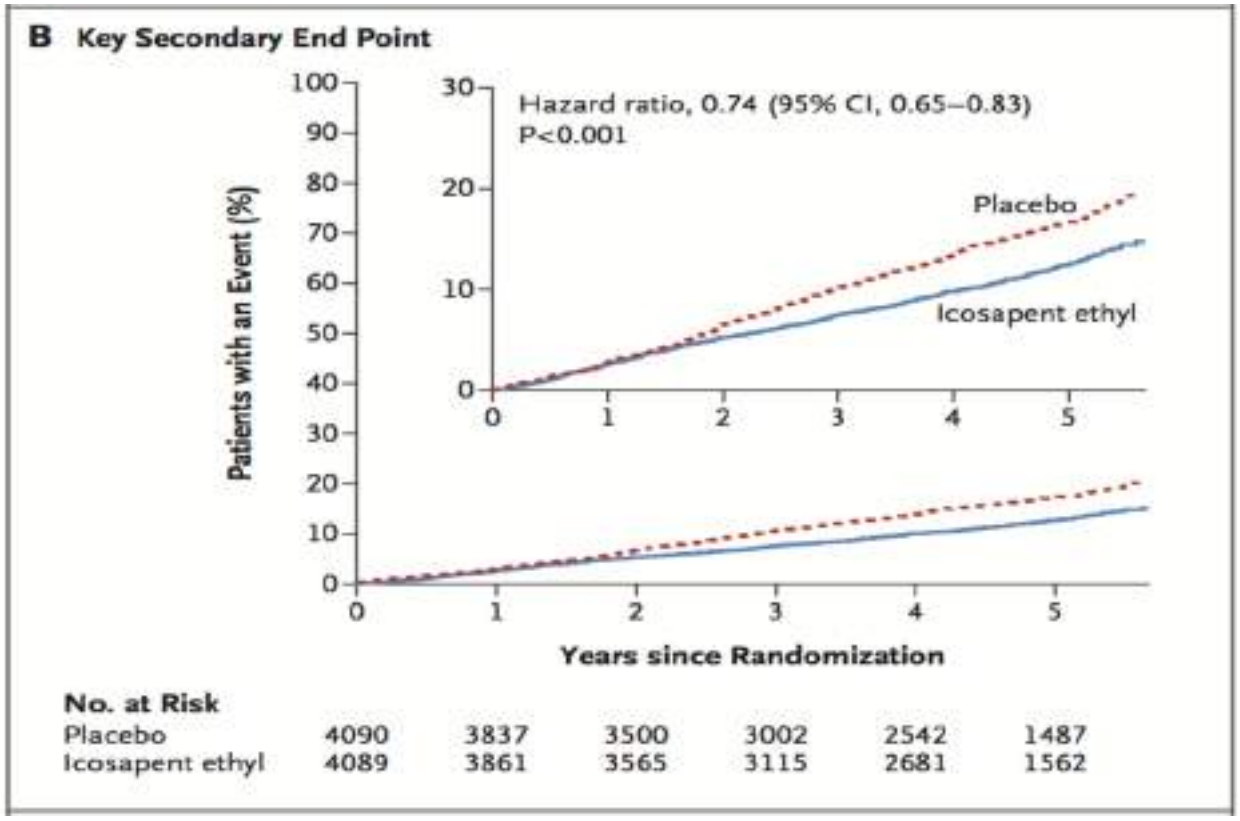


Primary EP: CV Death, nonfatal MI, nonfatal stroke, coronary revascularization or unstable angina (5 point MACE)

Median follow-up 4.9 years

- Primary (5-MACE): RRR=24.8%; ARR=4.8%; NNT 21
- **CV event curve for VASCEPA visually separated from the placebo event curve at approximately 1 year and remained separated throughout follow-up period**

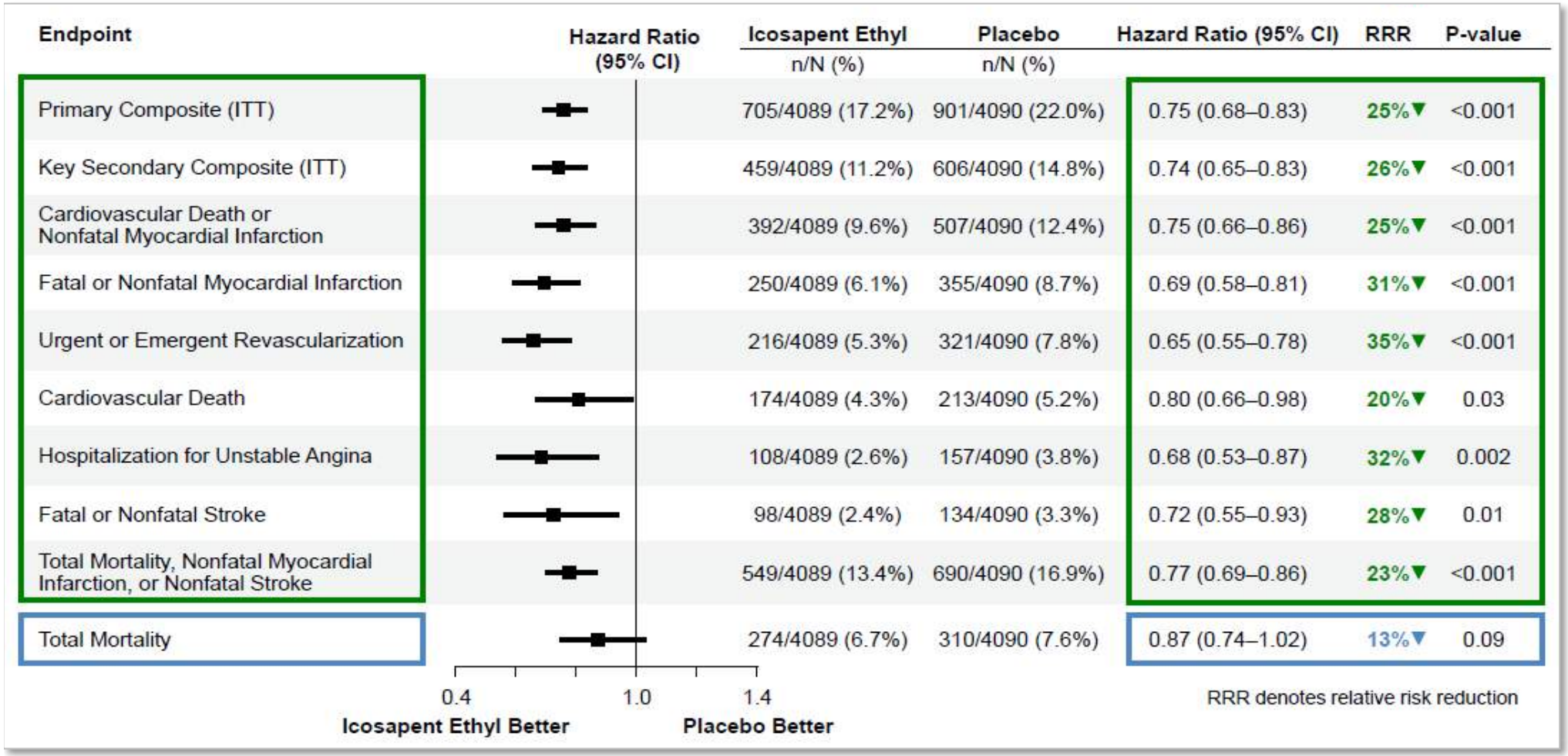
Secondary endpoint



Key secondary EP: CV Death, nonfatal MI or nonfatal stroke

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

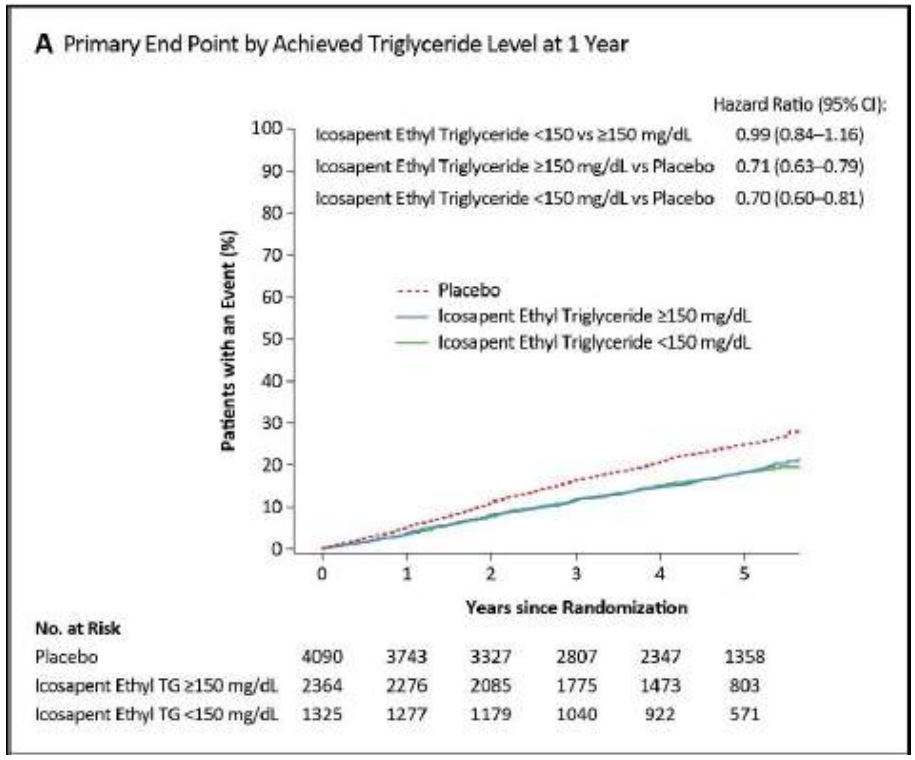
Pre-specified Hierarchical testing

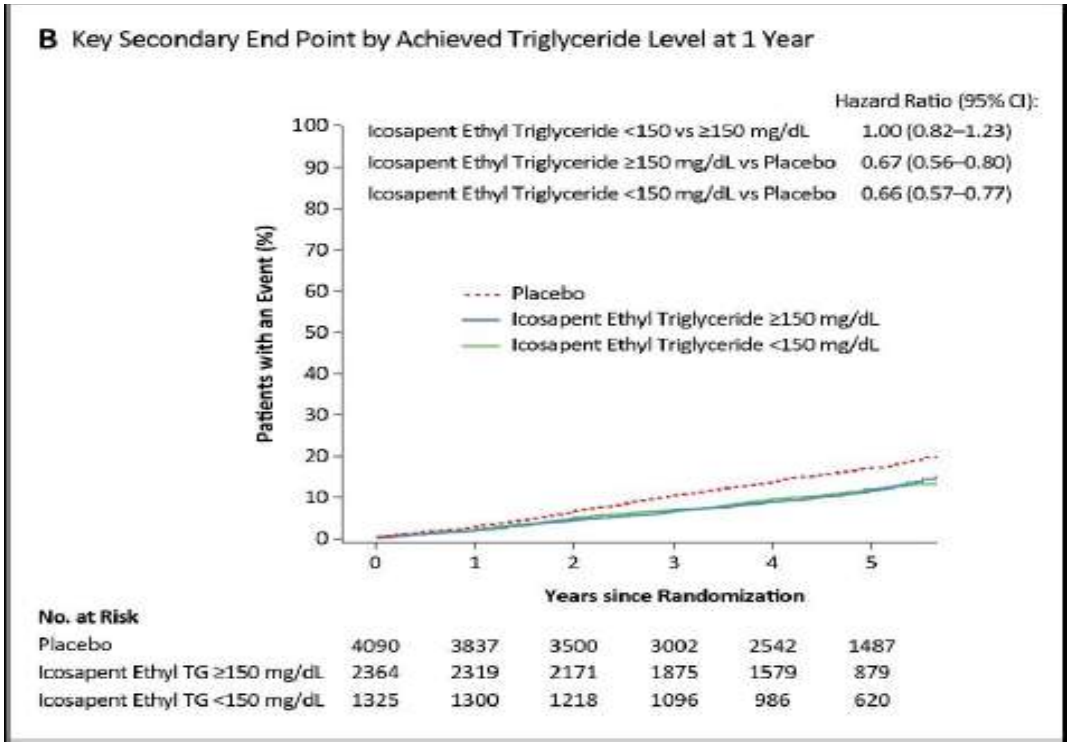


Endpoint	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)		705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)		459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction		392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%▼	<0.001
Fatal or Nonfatal Myocardial Infarction		250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%▼	<0.001
Urgent or Emergent Revascularization		216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%▼	<0.001
Cardiovascular Death		174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)	20%▼	0.03
Hospitalization for Unstable Angina		108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53–0.87)	32%▼	0.002
Fatal or Nonfatal Stroke		98/4089 (2.4%)	134/4090 (3.3%)	0.72 (0.55–0.93)	28%▼	0.01
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke		549/4089 (13.4%)	690/4090 (16.9%)	0.77 (0.69–0.86)	23%▼	<0.001
Total Mortality		274/4089 (6.7%)	310/4090 (7.6%)	0.87 (0.74–1.02)	13%▼	0.09

RRR denotes relative risk reduction

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





Safety

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P value[1]
Patients with at Least One TEAE,[2] n (%)	3343 (81.8%)	3326 (81.3%)	0.63
Serious TEAE	1252 (30.6%)	1254 (30.7%)	0.98
TEAE Leading to Withdrawal of Study Drug[3]	321 (7.9%)	335 (8.2%)	0.60
Serious TEAE Leading to Withdrawal of Study Drug[3]	88 (2.2%)	88 (2.2%)	1.00
Serious TEAE Leading to Death[4]	94 (2.3%)	102 (2.5%)	0.61

Overall TEAES rates similar in Vascepa and placebo groups

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

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

Comments

- First trial to show a CV benefit in a specific population of patients with hyper TG
- Previous negative trials with n–3 fatty acid supplementation. A higher dose of EPA (4 g/day) was tested vs previous trials. Other trials with moderate to high doses of EPA are ongoing.
- Differences in baseline lipid profiles and statin use in REDUCE-IT (TGs 216 mg/dL; LDL-C 75 mg/dL; HIS use 30%) vs ODYSSEY OUTCOMES LDL-C (TGs 129 mg/dL; LDL-C 87 mg/dL; HIS use 89%)
- Questions remains on the mode of action and the role of the (mineral oil) placebo on the observed CV benefit
- Amarin plans to submit to the FDA a sNDA in early 2019 (standard review)

What's the message from the PI of "REDUCE-IT"?

"We hope REDUCE-IT will transform the care of millions of patients worldwide" . "That side effect might have worried about me, but we saw a 28% reduction in stroke, which is the worst thing that Afib could do. I wouldn't *not* use it in a REDUCE-IT population because of the risk of Afib" said Depak I.

What is a REDUCE-IT population? Well-controlled LDL-c on statins for secondary or primary prevention who had TG between 135-500mg/dL

Treatment Duration: Avg. FU 5 years

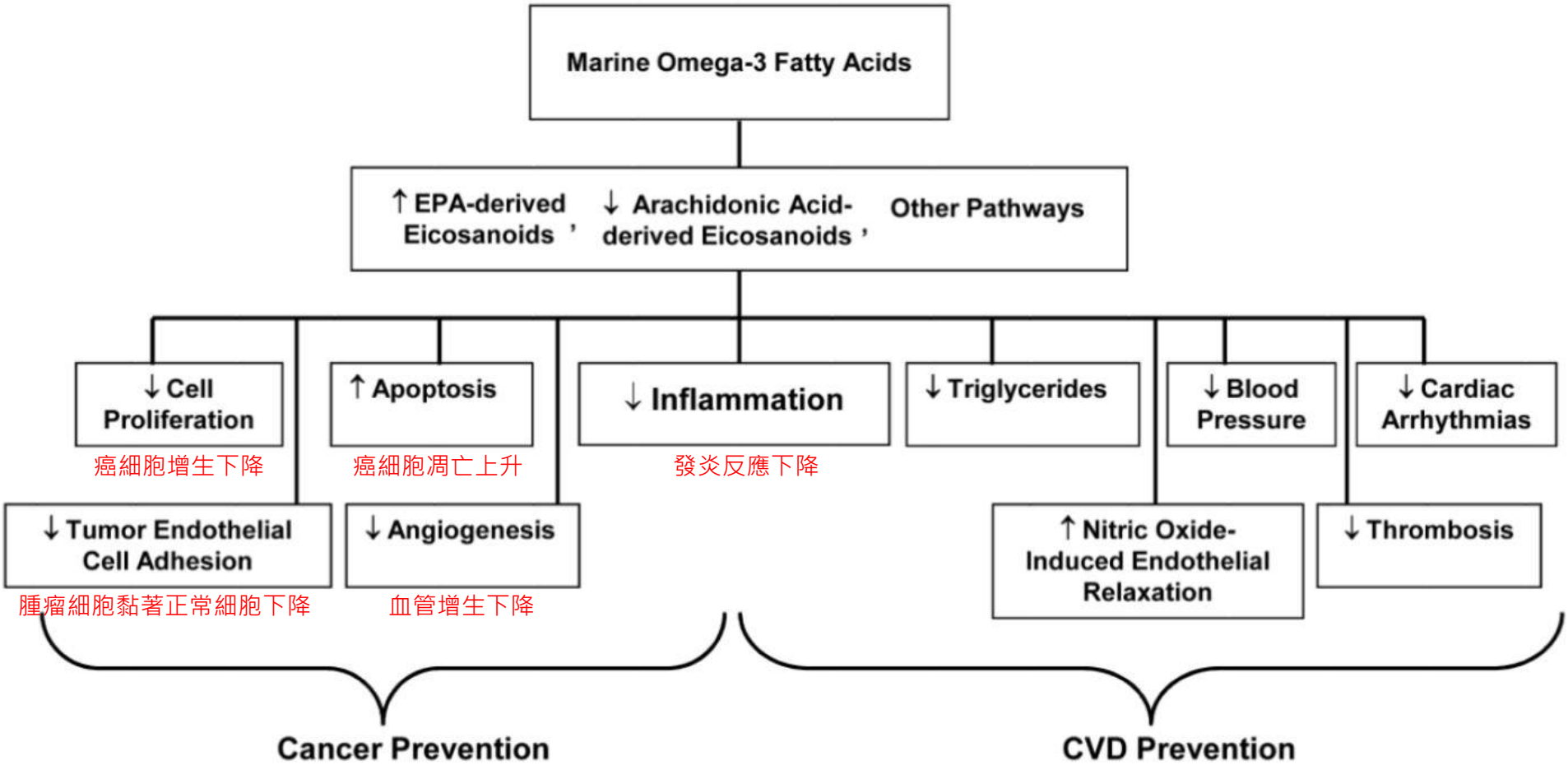
Vital Trial

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

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

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

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 *VIT*amin D and Omeg*A*-3 Tria*L* (VITAL)) Contemp Clin Trials. 2012 January ; 33(1): 159–171.

VITAL Trial

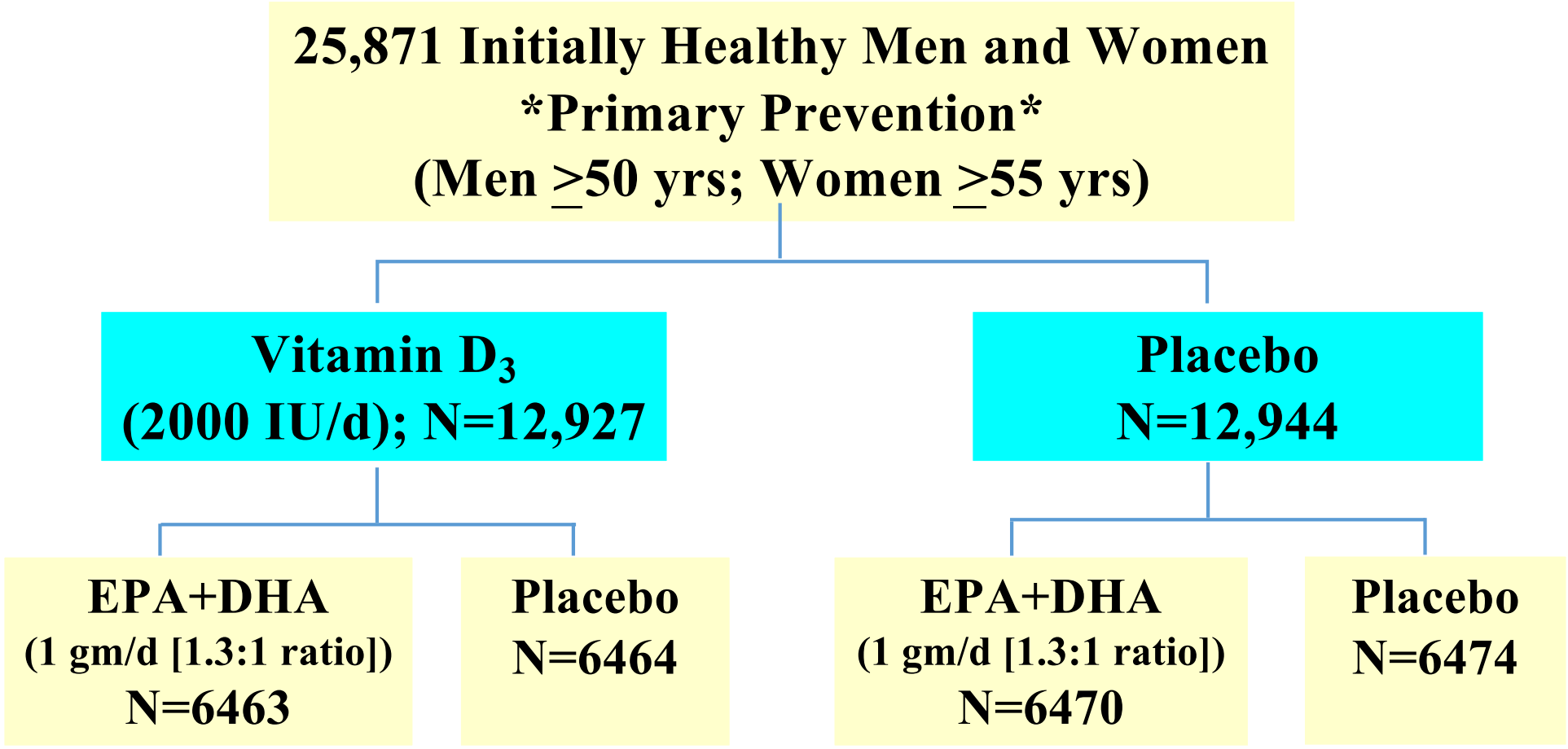
- The VITamin D and Omega-A 3 TriaL (VITAL) is an ongoing nationwide, randomized, double-blind, placebo-controlled clinical trial: evaluation for a role of supplemental vitamin D and marine omega-3 fatty acids in preventing cancer and cardiovascular disease (CVD).
- The study population consists of 25,874 U.S. adults without cancer or CVD at baseline, who were selected only on age (men aged ≥50 and women aged ≥55), with an oversampling of African Americans (n=5,107).
- 16,956 participants (65.5%) provided an optional blood sample.
- Baseline data disclosed in 2016 (Contemp Clin Trials. 2016 Mar;47:235-43)

VITAL用的Omega-3正是Omacor(1顆/天)

Abstract

Data from laboratory studies, observational research, and/or secondary prevention trials suggest that vitamin D and marine omega-3 fatty acids may reduce risk for cancer or cardiovascular disease (CVD), but primary prevention trials with adequate dosing in general populations (i.e., unselected for disease risk) are lacking. The ongoing ***VIT***amin D and Omeg***A***-3 Tria***L*** (VITAL) is a large randomized, double-blind, placebo-controlled, 2×2 factorial trial of vitamin D (in the form of vitamin D_3 [cholecalciferol], 2000 IU/day) and marine omega-3 fatty acid (Omacor® fish oil, eicosapentaenoic acid [EPA] + docosahexaenoic acid [DHA], 1 g/day) supplements in the primary prevention of cancer and CVD among a multi-ethnic population of 20,000 U.S. men aged ≥50 and women aged ≥55. The mean treatment period will be 5 years. Baseline blood samples will be collected in at least 16,000 participants, with follow-up blood collection in about 6000 participants. Yearly follow-up questionnaires will assess treatment compliance (plasma biomarker measures will also assess compliance in a random sample of participants), use of non-study drugs or supplements, occurence of endpoints, and cancer and vascular risk factors. Self-reported endpoints will be confirmed by medical record review by physicians blinded to treatment assignment, and deaths will be ascertained through national registries and other sources. Ancillary studies will investigate whether these agents affect risk for diabetes and glucose intolerance; hypertension; cognitive decline; depression; osteoporosis and fracture; physical disability and falls; asthma and other respiratory diseases; infections; rheumatoid arthritis, systemic lupus erythematosus, thyroid diseases, and other autoimmune disorders.

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



Median Treatment Period = 5.3 years.

5,106 African Americans.

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

Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease

- N Engl J Med. 2019 Jan 3;380(1):33-44. doi: 10.1056/NEJMoa1809944. Epub 2018 Nov 10.

- A total of 25,871 participants, including 5106 black participants, underwent randomization. During a median follow-up of 5.3 years, cancer was diagnosed in 1617 participants (793 in the vitamin D group and 824 in the placebo group; HR=0.96; 95% CI=0.88-1.06; P=0.47). **A major CV event occurred** in 805 participants (396 in the vitamin D group and 409 in the placebo group; HR=0.97; 95% CI=0.85-1.12; P=0.69).
- 2nd end points (HRs): for death from cancer (341 deaths), 0.83 (95% CI, 0.67 to 1.02); for breast cancer, 1.02 (95% CI, 0.79 to 1.31); for prostate cancer, 0.88 (95% CI, 0.72 to 1.07); for colorectal cancer, 1.09 (95% CI, 0.73 to 1.62); for the expanded composite end point of **major CV events plus coronary revascularization**, 0.96 (95% CI, 0.86 to 1.08); for MI, 0.96 (95% CI, 0.78 to 1.19); for stroke, 0.95 (95% CI, 0.76 to 1.20); and for death from CV causes, 1.11 (95% CI, 0.88 to 1.40). In the analysis of death from any cause (978 deaths), the HR was 0.99 (95% CI, 0.87 to 1.12).
- No excess risks of hypercalcemia or other adverse events were identified.

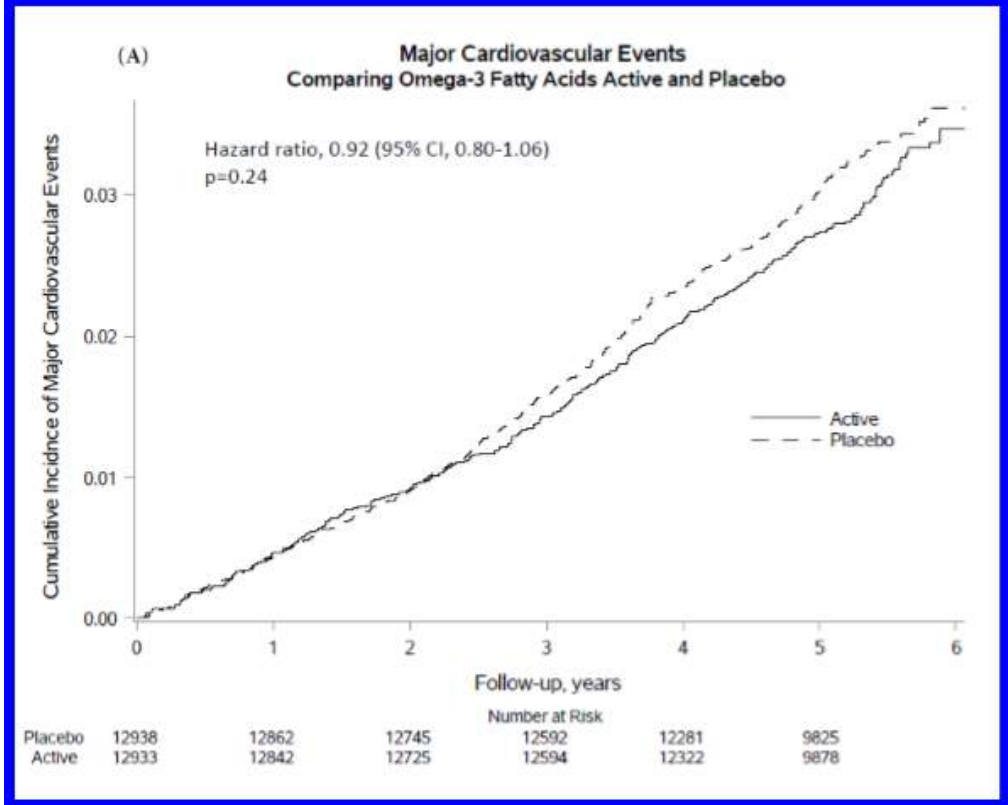
Marine n-3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer

- N Engl J Med. 2019 Jan 3;380(1):23-32. doi: 10.1056/NEJMoa1811403. Epub 2018 Nov 10.

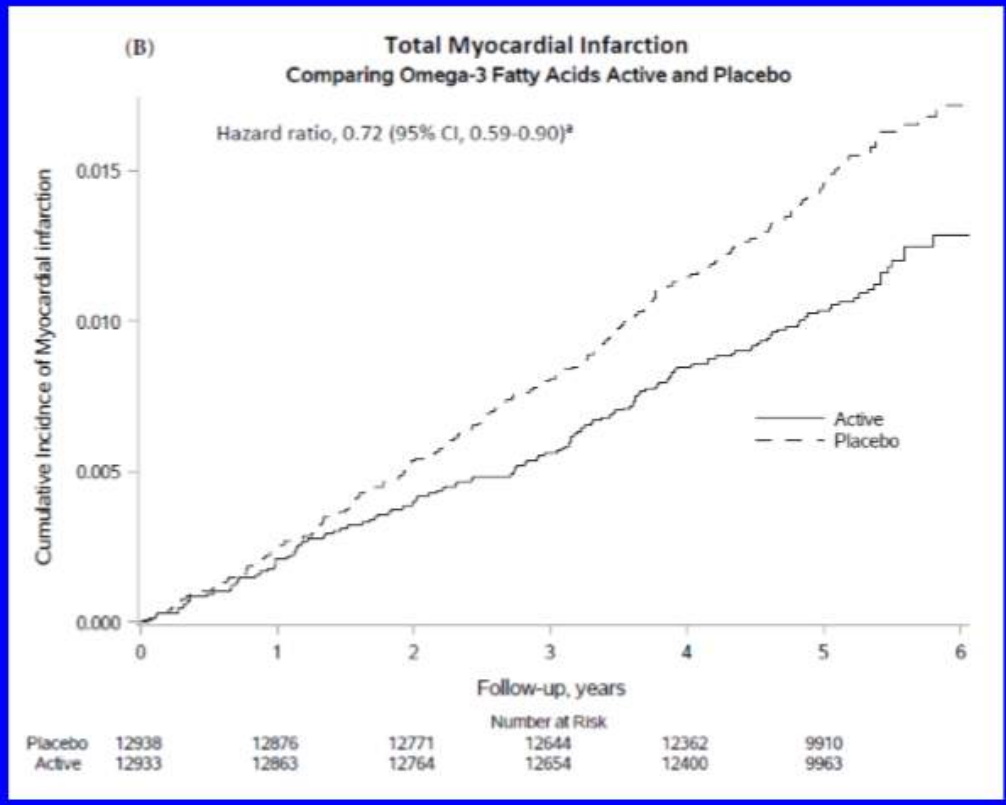
- A **major CV event** occurred in 386 participants in the n-3 group and in 419 in the placebo group (HR=0.92; 95% CI=0.80-1.06; P=0.24). Invasive cancer was diagnosed in 820 participants in the n-3 group and in 797 in the placebo group (HR=1.03; 95% CI=0.93-1.13; P=0.56).
- In the analyses of key secondary end points (HRs): for the expanded composite end point of CV events, 0.93 (95% CI, 0.82 to 1.04); **for total MI, 0.72 (95% CI, 0.59 to 0.90);** for total stroke, 1.04 (95% CI, 0.83 to 1.31); for death from CV causes, 0.96 (95% CI, 0.76 to 1.21); and for death from cancer (341 deaths from cancer), 0.97 (95% CI, 0.79 to 1.20). In the analysis of death from any cause (978 deaths overall), the hazard ratio was 1.02 (95% CI, 0.90 to 1.15).
- **No excess risks of bleeding or other serious adverse events were observed.**
- **CONCLUSIONS:** Supplementation with n-3 fatty acids did not result in a lower incidence of major cardiovascular events or cancer than placebo.

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

Major CVD Events



Total MI



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

VITAL顯示N-3無法降低MACE，但可預防MI

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

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

Conclusions

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

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

LDL的下一步?

Adding to statins? Notable outcome studies

Study	Drug/combination	Population	% reduction in risk of MACE	Trial ID
Reduce-IT	Vascepa (EPA plus statin)	High-risk patients with mixed dyslipidemia	25%	NCT01492361
Fourier	Repatha (PCSK9 plus statin)	High-risk patients with CV disease	15%	NCT01764633
Odyssey Outcomes	Praluent (PCSK9 plus statin)	High-risk ACS patients	15%	NCT01663402
Improve-IT	Vytorin (simvastatin plus ezetimibe)	High-risk ACS patients	6.4%	NCT00202878

Notes: CAD=coronary arterial disease. Source: company press releases, JAMA Cardiology.

~7千(by JELIS primary prevention劑量)
~2千(by GISSI secondary prevention劑量)
近2萬

AHA Recommendations for EPA/DHA Intake in 2002

Population	Recommendation
Patients without documented CHD	Eat a variety of (preferably oily) fish at least twice a week. Include oils and foods rich in α-linolenic acid (flaxseed, canola, and soybean oils; flaxseeds; and walnuts)
Patients with documented CHD	Consume ~1 g of EPA+DHA per day, preferably from oily fish. EPA+DHA supplements could be considered in consultation with the physician
Patients needing triglyceride lowering	2–4 grams of EPA+DHA per day provided as capsules under a physician's care

Kris-Etherton PM et al. *Circulation* 2002;106:2747-2757.

2017 ACC/AHA: 處方藥Omega-3可用於CHD及CHF的secondary prevention

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	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
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

2018 ACC/AHA Cholesterol Guideline: Other LDL-C lowering/triglyceride lowering agents

	Agents	Clinical consideration
Bile acid sequestrants[1]	• **Cholestyramine** • **Colesevelam** • **Colestipol**	• Lowers LDL-C 15%-30% • Add-on to statin therapy or use in patients with statin-associated side effects supported by RCT • Avoided if TG ≥ 300 mg/dL • Associated with GI side effects
Fibrates[1,2]	• **Gemfibrozil** • **Fenofibrate** • **Fenofibric acid**	• Lowers TG 20-35% • Myopathy/rhabdomyolysis when used with statin
Niacins[1,2]	• **Nicotinic acid**	• Lowers TG 20-30%; LDL-C 10-25%
Omega-3 fatty acids[2]	• **Icosapent ethyl, omega-3-acid ethyl esters**	• Lowers TG 27-45% • Effect of cardiovascular morbidity and mortality unknown in patients with severe hypertriglyceridemia

Abbreviations: GI, gastrointestinal; LDL-C: low-density lipoprotein cholesterol; RCT, randomized clinical trial; TG, triglycerides.

1. Gundy SM et al. J Am Coll Cardiol. 2018 Nov 8. [Epub ahead of print]
2. Jellinger PS et al. Endocr Pract. 2017;23(Suppl 2):1-87

2017台灣血脂治療指引建議

DM患者TG<150mg/dl

ACS/CAD患者應TG<200mg/dl

2017 Taiwan lipid guidelines for high risk patients☆

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

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

2017版台灣血脂治療指引

Table 5 Summary of lipid-lowering drugs.

Drug class	Agents and daily doses	Lipid effe		
Statins	Lovastatin (20–80 mg) Pravastatin (20–40 mg) Simvastatin (20–40 mg)	LDL HDL TG		
	Fluvastatin (20–80 mg) Atorvastatin (10–80 mg) Rosuvastatin (5–40 mg) Pitavastatin (1–4 mg)	Non		
Cholesterol absorption inhibitor	Ezetimibe 10 mg	LDL HDL ↑ 1–2% TG ↓ 5–10% Non-HDL↓ 14–19%	Muscle pain	with statin
PCSK9 inhibitors	Evolocumab (140 mg, s.c., Q2W)	LDL ↓ 50–70%	Injection site reaction (5%)	Not increased serum transaminases
	Alirocumab (75 mg, s.c., Q2W)	HDL ↑ 4–7% TG ↓ 6–19% Non-HDL ↓ 20–50%		Require subcutaneous injection
Nicotinic acid	IR nicotinic acid (1.5–3 g) ER nicotinic acid (1–2g)	LDL ↓ 15–18% HDL ↑ ~25%	Flushing Hyperglycemia	Glucose intolerance ER niacin more tolerable than IR
	SR nicotinic acid (1–2 g)	TG ↓ 20–40% Non-HDL ↓ 8–23%	Hyperuricemia GI distress Hepatotoxicity Excess infection	
Fibric acids	Gemfibrozil, 600 mg bid Bezafibrate, 200 mg bid/tid	LDL ↓ 10-15% HDL ↑10-20%	Dyspepsia Increased serum transaminases	May ↑ creatinine + homocysteine Do not combine gemfibrozil + statin
	Fenofibrate, 200 mg qd Fenofibric acid, 135 mg qd	TG ↓ 20-50% Non-HDL↓ 5-19%	Gallstones Myopathy	
Omega-3 fatty acids	Omega-3 fatty acids 2–4 g	LDL ↓6%–↑25% HDL ↓5%–↑7% TG ↓ 20–45% Non-HDL↓ 5–14%	Fishy smell Skin eruption	Combination with statin Improve postprandial TG level

ER = extended-release; HDL-C = high-density lipoprotein cholesterol; IR = immediate-release; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; SR = sustained-release; s.c. = subcutaneous; TG = triglyceride.

Recommendation

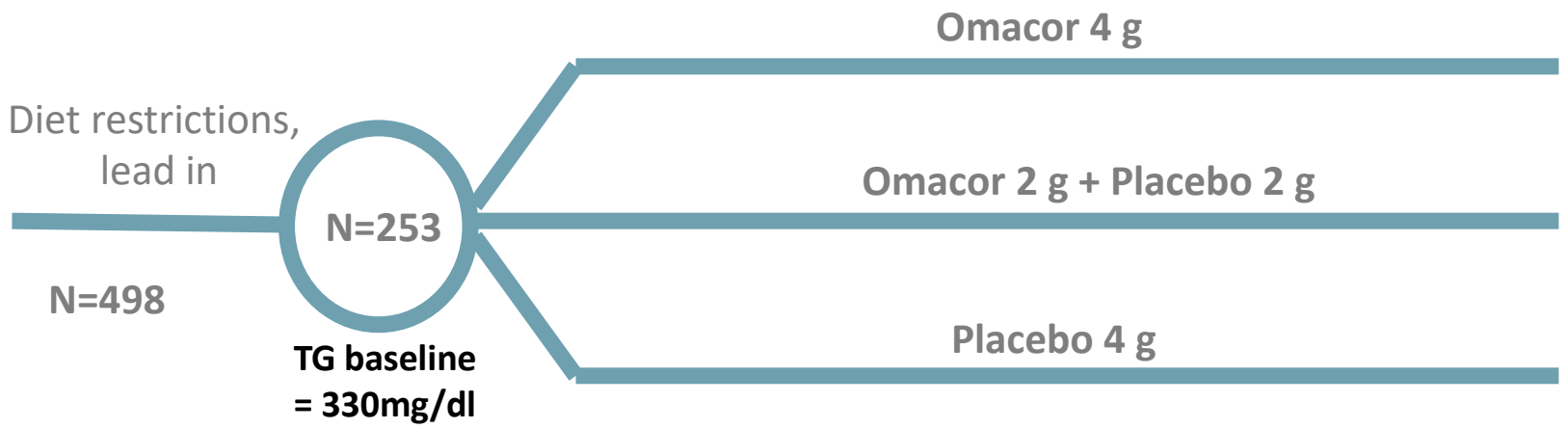
- Omega-3 fatty acid is indicated for the treatment of very high TG (≥500 mg/dL). (COR IIa, LOE B)
- EPA and DHA are recommended for patients with coronary heart disease and hypertriglyceridemia. (COR IIa, LOE B)

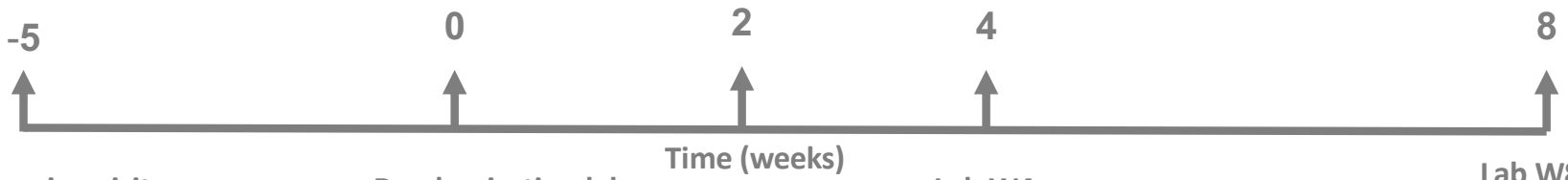
OMACOR TAIWAN TRIAL

A randomized, double-blinded, placebo-controlled study to assess the efficacy and safety of Omacor® in Taiwanese hypertriglyceridemia patients

台大/成大/北榮/中榮

Omacor® Taiwan Trial
- Method Design





Screening visit lab:
TG
LDL-C
HDL-C
Total-C
VLDL-C
LDL-C/HDL-C
Apo A1 & B

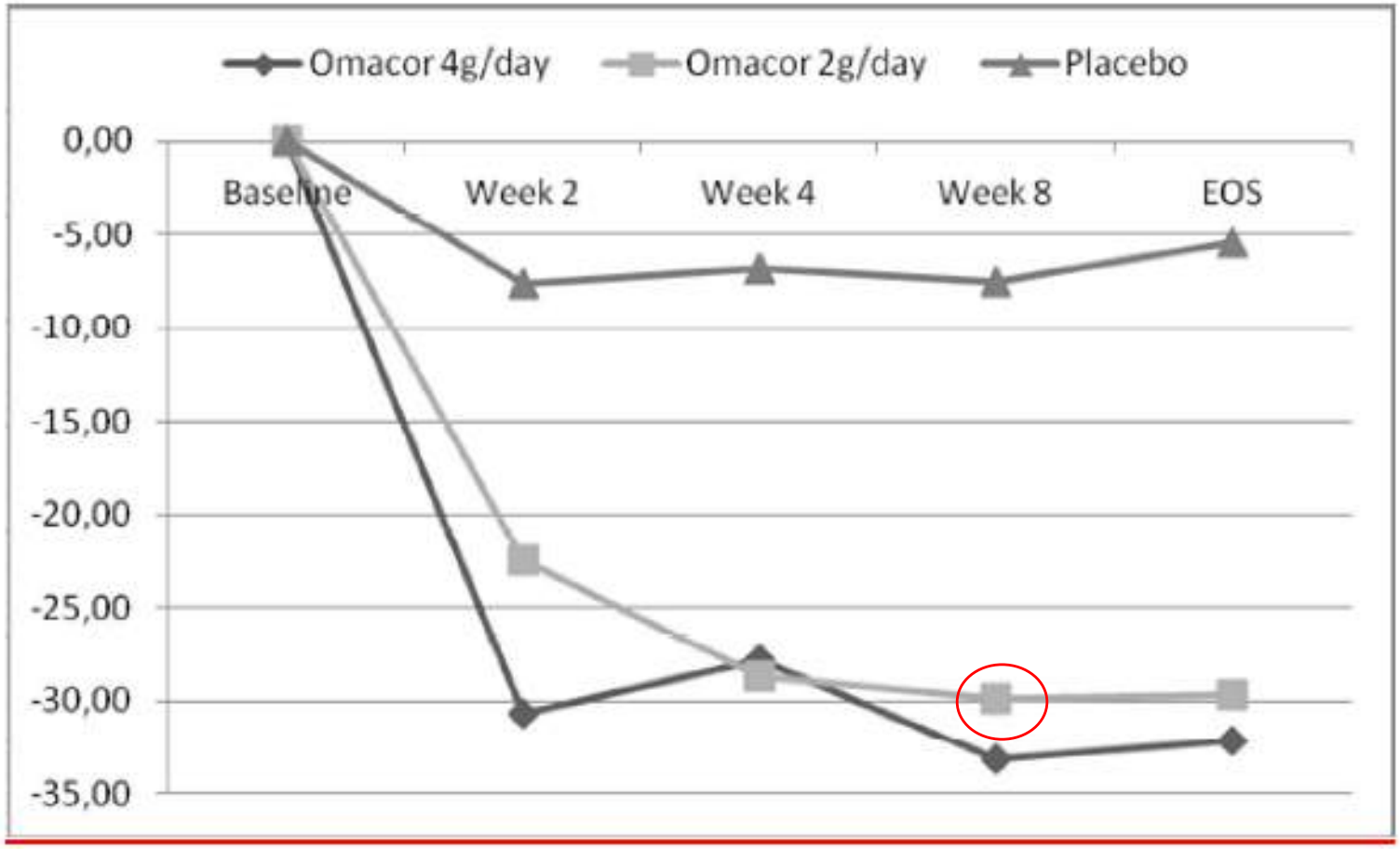
Randomization lab
TG
VLDL-C
LDL-C
HDL-C
Total-C
Apo A1 & B
LDL-C/HDL-C

Lab W4
TG
VLDL-C
LDL-C
HDL-C
Total-C
Apo A1 & B
LDL-C/HDL-C

Lab W8
TG
VLDL-C
LDL-C
HDL-C
Total-C
Apo A1 & B
LDL-C/HDL-C

Omacor 1g BID，可降TG 29.7%

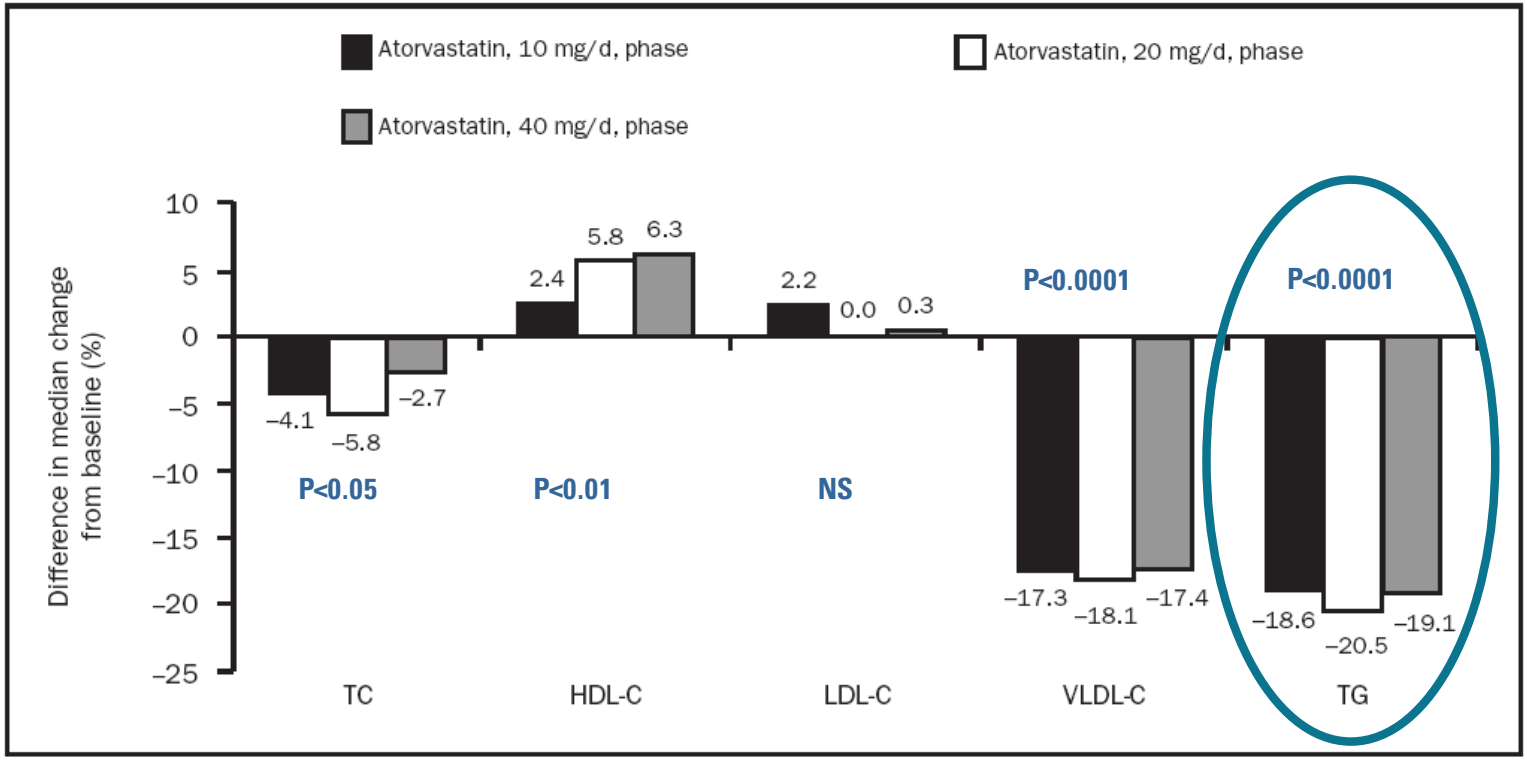
Figure 2. Time-course of Percent Change in Triglyceride Level (ITT population)



OMACOR Clinical Trial in Tawian

不論已使用高低劑量的statin 併用後皆能額外降低TG 20%

OMACOR maintains its potency providing an additional 20% reduction in TG levels independent of the statin dosage



Mayo Clin Proc 2010; 85(2): 122-128.

併用Statin是安全的

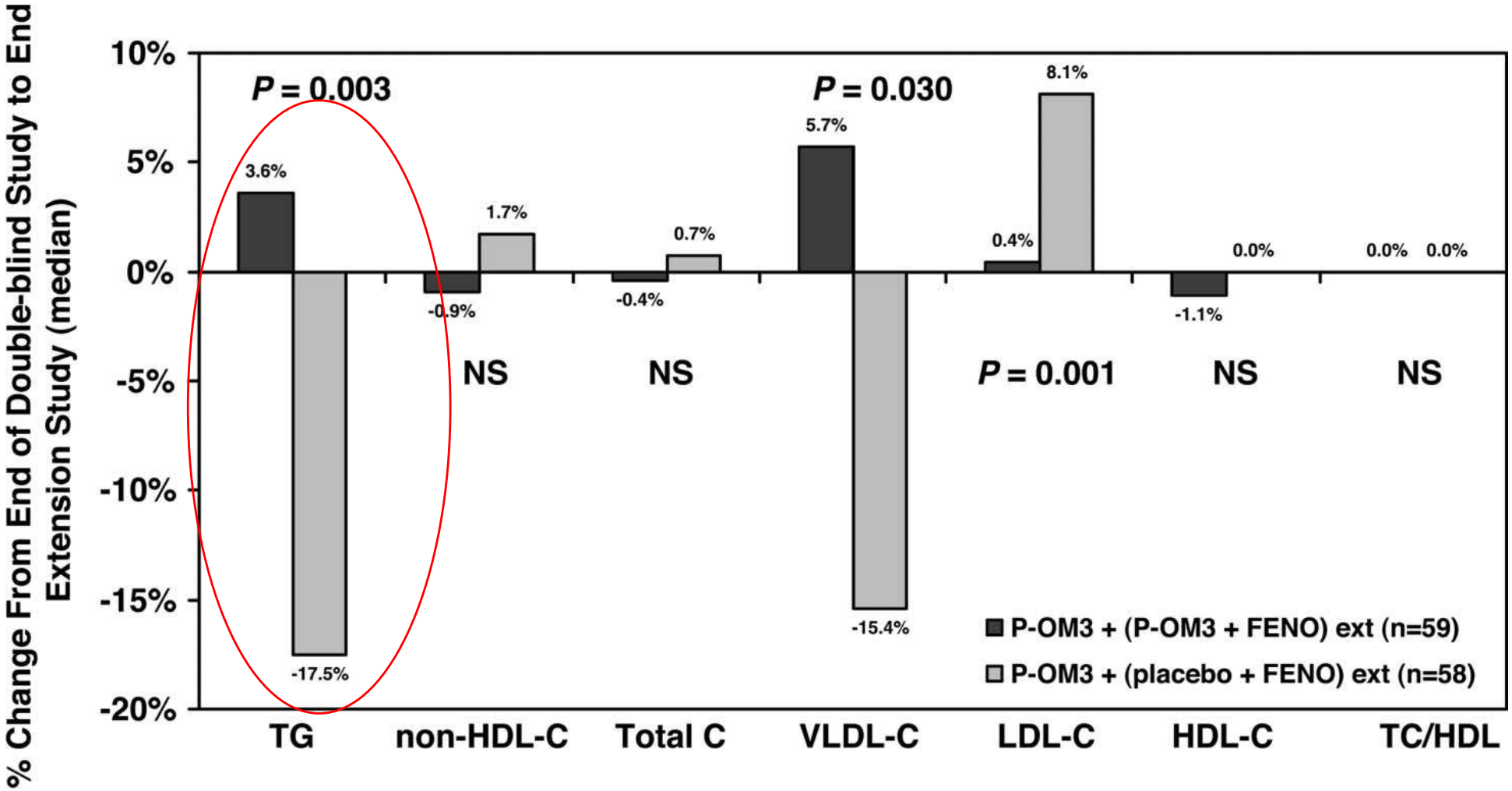
Treatment-Emergent Adverse Event (AE): Overview

	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

已使用Fenofibrate的患者，併用後可再降TG達17.5%



J Cardiovasc Pharmacol. 2009 Sep;54(3):196-203.

併用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)

Omacor適合用於CKD

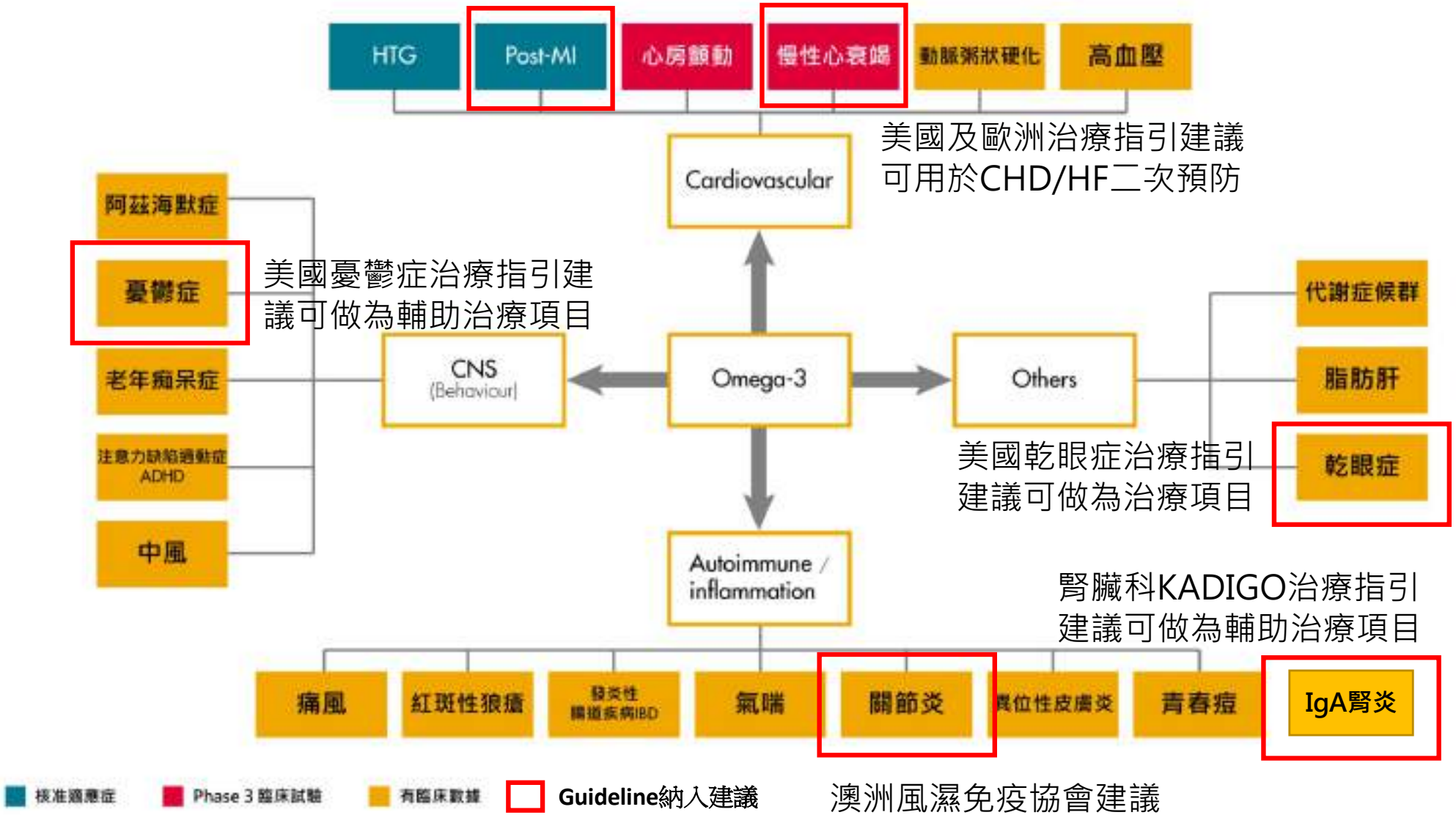
表二　慢性腎臟病病人降血脂藥物治療建議應根據腎功能調整劑量

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	歐盟及臺灣已禁止Gemfibrozil與Statin並用		
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。

OMEGA-3其餘臨床應用

Potential for Omega-3 derived pharmaceuticals



歐洲臨床營養與代謝學會(ESPEN)2017年癌症營養指南建議，術前7天補充N-3 fatty acids (1~2 g/day)更有利預後

B5 – 7	N-3 fatty acids to improve appetite and body weight
Strength of recommendation WEAK	*In patients with advanced cancer undergoing chemotherapy and at risk of weight loss or malnourished, we suggest to use supplementation with long-chain N-3 fatty acids or fish oil to stabilize or improve appetite, food intake, lean body mass and body weight.*
Level of evidence	Low
Questions for research	Effect of long chain N-3 fatty acids on body composition and clinical outcome in cancer patients undergoing antineoplastic treatment Effect of long chain N-3 fatty acids on quality of life and clinical outcome in patients with cancer cachexia

C1 – 4	Immunonutrition (arginine, N-3 fatty acids, nucleotides) in perioperative care
Strength of recommendation STRONG	*In upper GI cancer patients undergoing surgical resection in the context of traditional perioperative care we recommend oral/enteral immunonutrition.*
Level of evidence	High
Questions for research	Specifying the role of the individual constituents of immunonutrition regimens

澳洲風濕免疫學會建議
魚油可用於關節炎輔助治療

ARTHRITIS
INFORMATION SHEET

Fish oils

This sheet provides general information about the use of fish oil supplements as a treatment for arthritis. It includes information about who may benefit from taking fish oils, how much to take and where to find more information.

Arthritis AUSTRALIA

Australian Rheumatology Association

關節炎患者服用藥品級魚油的建議？

澳洲風濕免疫學會建議，每日2.7g Omega-3 (2顆以上藥品級魚油)能有效改善關節炎症狀!

How do omega-3 fats work for arthritis?

Certain types of omega-3 fats can reduce inflammation from arthritis. This may help to relieve joint pain and stiffness in a similar way to non-steroidal anti-inflammatory drugs (NSAIDs).

What types of arthritis benefit from omega-3 fats?

Omega-3 fats have not been studied in all forms of arthritis. Current research suggests omega-3 fats are helpful for people with inflammatory arthritis, such as rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. There is also evidence that fish oils can help control symptoms of lupus (systemic lupus erythematosus). Fish oils have not been thoroughly tested in other forms of arthritis, such as osteoarthritis, so it is unclear whether they are useful for these conditions.

What dose should I take for arthritis?

Research suggests the dose needed to reduce inflammation is 2.7 grams of omega-3 (EPA plus DHA) daily. This dose usually requires approximately either:

- nine to 14 standard 1000mg fish oil capsules or five to seven capsules of a fish oil concentrate per day, or
- 15mL of bottled fish oil or five to seven mL of concentrated bottled fish oil per day.

(Note, fish oil can benefit your heart and general health at lower doses. However these doses, generally, will not control symptoms of arthritis).

How long will it take to notice an effect?

You may need to take fish oil supplements regularly at the recommended arthritis dose for two to three months before you notice improvements in your arthritis symptoms. If there is no change by then, the supplements are probably not effective for your arthritis.

Arthritis AUSTRALIA

Australian Rheumatology Association

魚油對哪些關節炎有臨床證據：
風濕性關節炎/僵直性脊髓炎/乾癬性關節炎等
建議劑量：
2.7g omega-3/day

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美國乾眼症Guideline將Omega-3列為治療選項之一

Dry Eye Syndrome PPP: Management

TABLE 4 CATEGORIES OF DRY EYE TREATMENTS

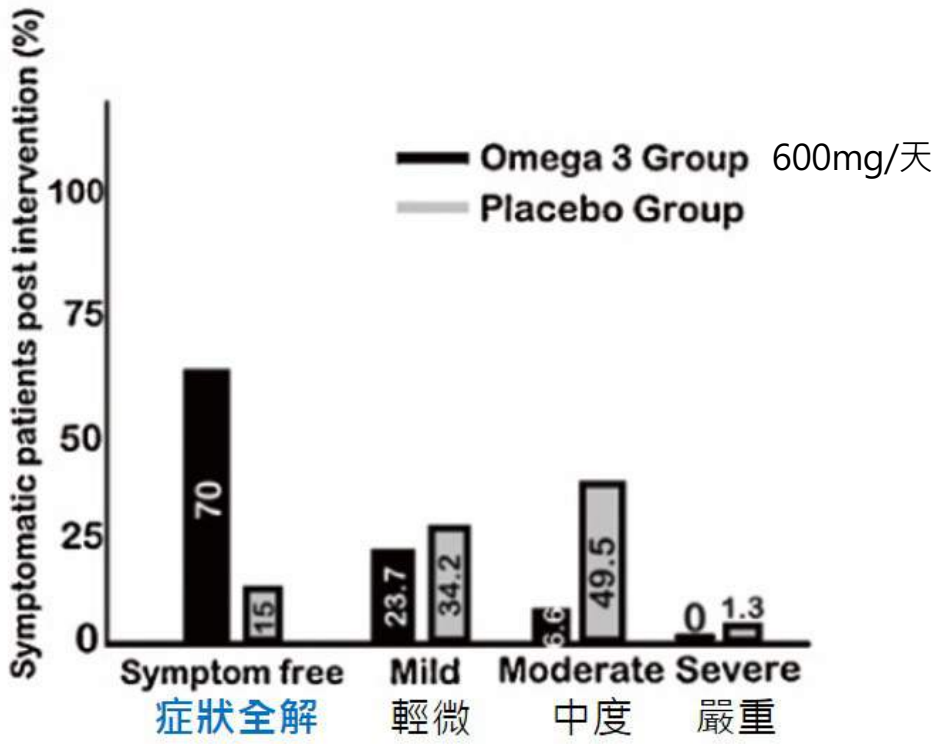
Type of Therapy	Treatment
Environmental/Exogenous	• Education and environmental modifications* (e.g., humidifier) • Elimination of offending topical or systemic medications
Medication	
Topical medication	• Artificial tear substitutes, gels/ointments* • Anti-inflammatory agents (topical cyclosporine and corticosteroids) • Mucolytic agents • Autologous serum tears
Systemic medication	• Omega-3 fatty acids • Tetracyclines* (for meibomian gland dysfunction, rosacea) • Systemic anti-inflammatory agents • Secretagogues
Surgical	• Punctal plugs • Permanent punctal occlusion • Tarsorrhaphy* • Repair of eyelid malpositions or exposure* • Mucous membrane, salivary gland, amniotic membrane transplantation
Other	• Eyelid therapy (warm compresses and eyelid hygiene)* • Contact lenses • Moisture chamber spectacles*

AMERICAN ACADEMY OF OPHTHALMOLOGY
The Eye M.D. Association

Dry Eye Syndrome

乾眼症患者服用藥品級魚油的建議？

國外臨床試驗顯示，每日600毫克 Omega-3
(1顆藥用魚油)能有效減緩乾眼症狀



美國憂鬱症Guideline將Omega-3列為治療輔助選項之一

PRACTICE GUIDELINE FOR THE

Treatment of Patients With Major Depressive Disorder

Third Edition

憂鬱症患者服用藥品級魚油的建議？

2016加拿大憂鬱症治療指引建議
每日EPA 1g(2顆以上藥品級魚)可輔助憂鬱症之治療

Table 3. Summary of Recommendations for Natural Health Products.

Intervention	Indication	Recommendation	Evidence	Monotherapy or Adjunctive Therapy
St. John's wort	Mild to moderate MDD	First line	Level 1	Monotherapy
	Moderate to severe MDD	Second line	Level 2	Adjunctive
Omega-3	Mild to moderate MDD	Second line	Level 1	Monotherapy or adjunctive
	Moderate to severe MDD	Second line	Level 2	Adjunctive
SAM-e	Mild to moderate MDD	Second line	Level 1	Adjunctive
	Moderate to severe MDD	Second line	Level 2	Adjunctive
Acetyl-L-carnitine	Mild to moderate MDD	Third line	Level 2	Monotherapy
Crocus sativus (saffron)	Mild to moderate MDD	Third line	Level 2	Monotherapy or adjunctive
DHEA	Mild to moderate MDD	Third line	Level 2	Monotherapy
Folate	Mild to moderate MDD	Third line	Level 2	Adjunctive
Lavandula (lavender)	Mild to moderate MDD	Third line	Level 3	Adjunctive
Inositol	Mild to moderate MDD	Not recommended	Level 2	
Tryptophan	Mild to moderate MDD	Not recommended	Level 2	
Rhodiola rosea (roseroot)	Mild to moderate MDD	Not recommended	Insufficient evidence	

DHEA, dehydroepiandrosterone; MDD, major depressive disorder; SAM-e, S-adenosyl-L-methionine.

studied, the most common being eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The typical dose range is 3 to 9 g/day of ω-3 or 1 to 2 g of EPA plus 1 to 2 g of DHA per day.[69] Duration of treatment ranges from 4 to 16 weeks.[30,71]

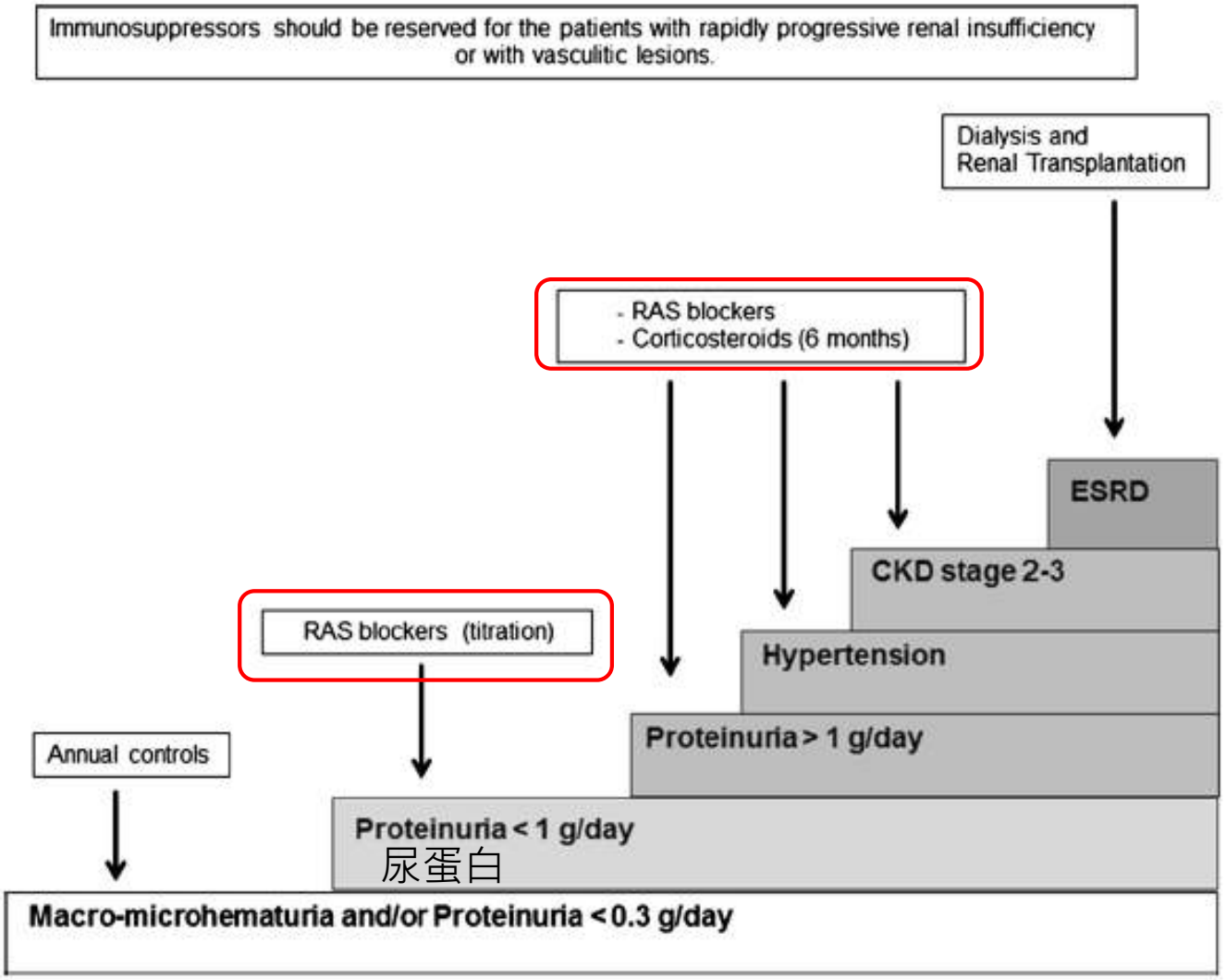
Four new meta-analyses[70-73] and 2 systematic reviews[69,74]

various physiological processes.[61] Proposed mechanisms of antidepressant action include modulation of monoaminergic neurotransmission.[79]

SAM-e is prescribed in Europe as an oral or parenteral treatment for several conditions, including MDD.[80] In the

Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines

IgA腎炎標準治療流程



J Nephrol (2016) 29:21–25

KADIGO Guideline建議:
當IgA患者尿蛋白超過1g/day，可以把魚油加到標準治療中

- 10.5.1.1: We suggest using fish oil in the treatment of IgAN with persistent proteinuria > 1 g/d, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control). (2D)

Kidney Int Suppl . 2012;2:209-217

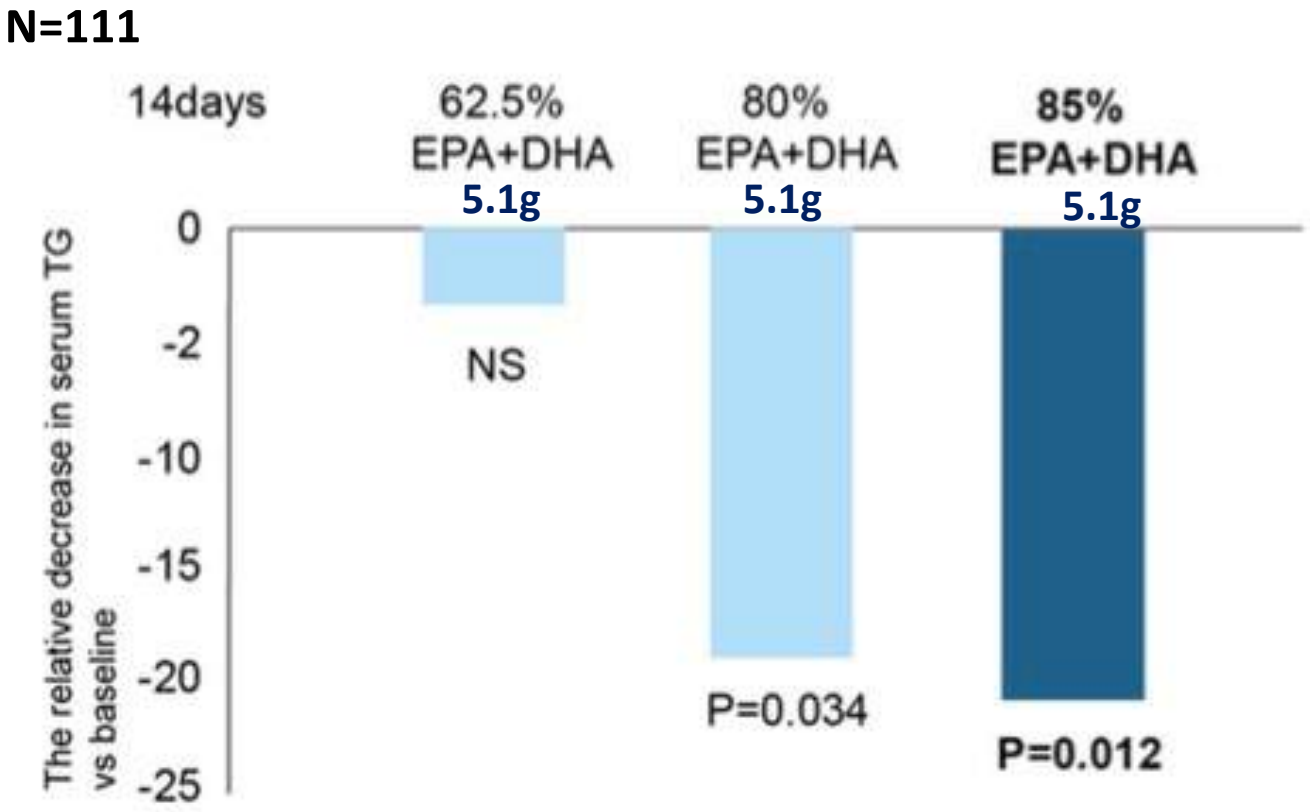
VITAL Extended Studies:

- **LUNG VITAL:** on acute exacerbations of chronic respiratory disease, asthma control, pneumonia and lung function in adults. (Contemp Clin Trials. 2018 Apr;67:56-67)
- Effects on **Bone** Structure and Architecture (Contemp Clin Trials. 2018 Apr;67:56-67)
- **Bone** health ancillary study (trabecular bone score) (Osteoporos Int. 2018 Nov;29(11):2505-2515)
- **VITAL-DEP**: for prevention of late-life depression. (Contemp Clin Trials. 2018 May;68:133-145)
- To prevent and treat **diabetic kidney disease** (Contemp Clin Trials. 2018 Nov;74:11-17)
- Assessing the effect of omega-3 fatty acid combined with vitamin D3 versus vitamin D3 alone on **estradiol** levels: a randomized, placebo-controlled trial in females with vitamin D deficiency. (Clin Pharmacol. 2019 Feb 4;11:25-37)

我最常被問的問題之一：

藥用魚油與保健食品有差嗎？

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

製劑EPA/DHA濃度越低，生體可用率越低

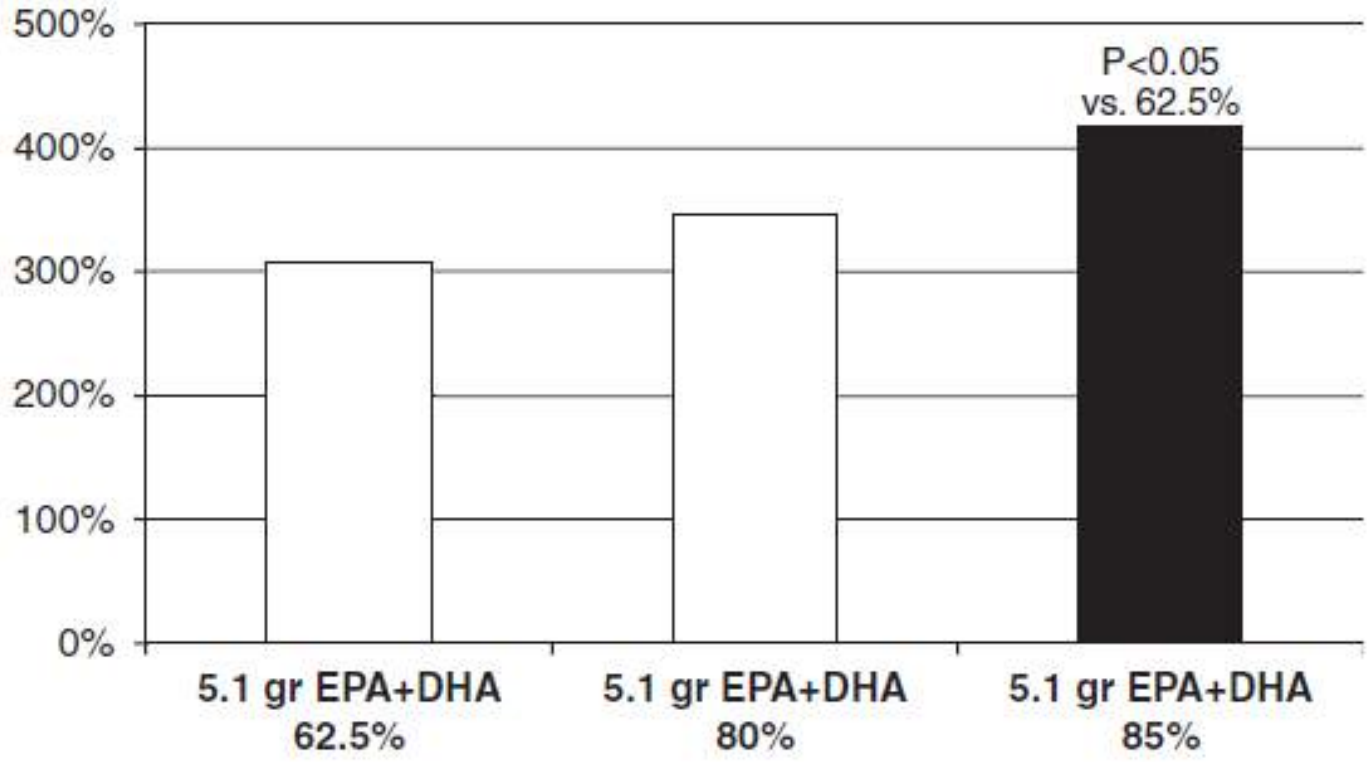
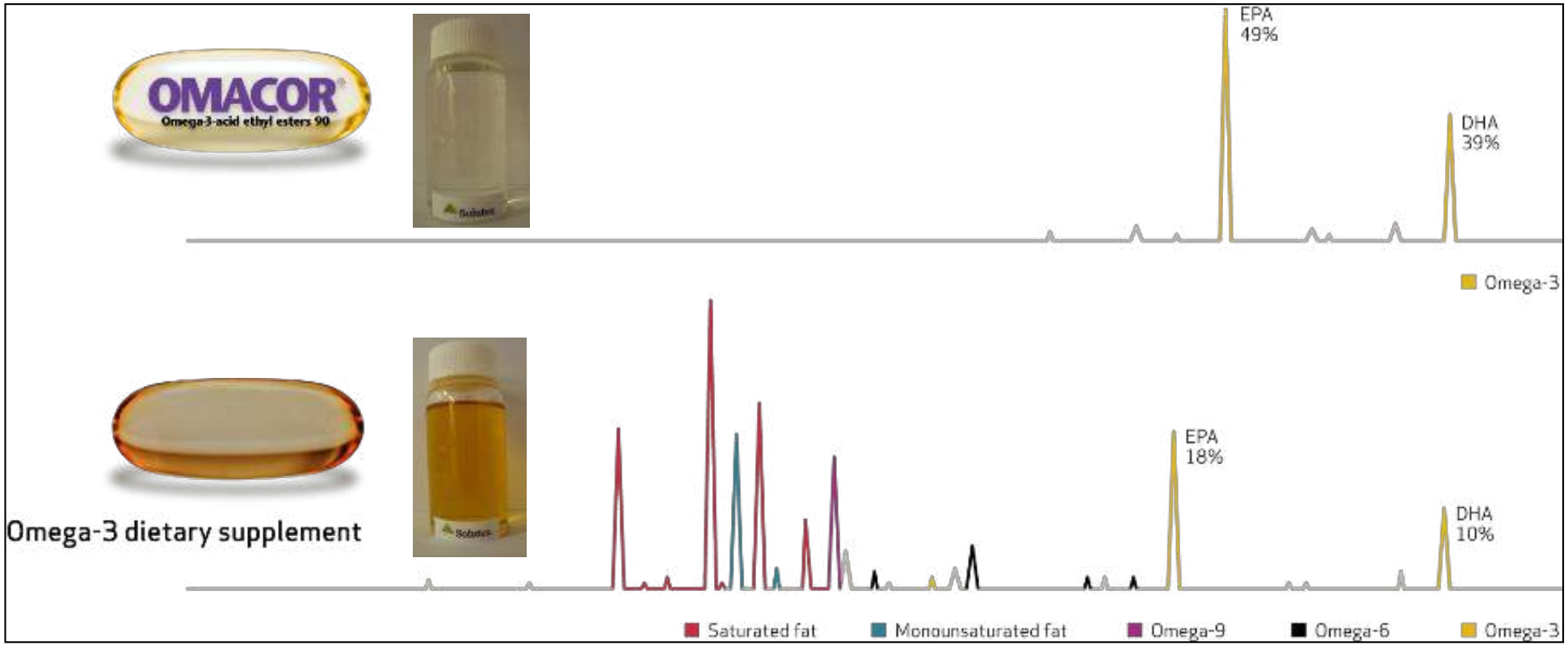


Fig. 1. Relative increase in EPA serum phospholipids versus baseline from day 0 to 14.

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

EPA/DHA濃度越低代表"雜油"越多

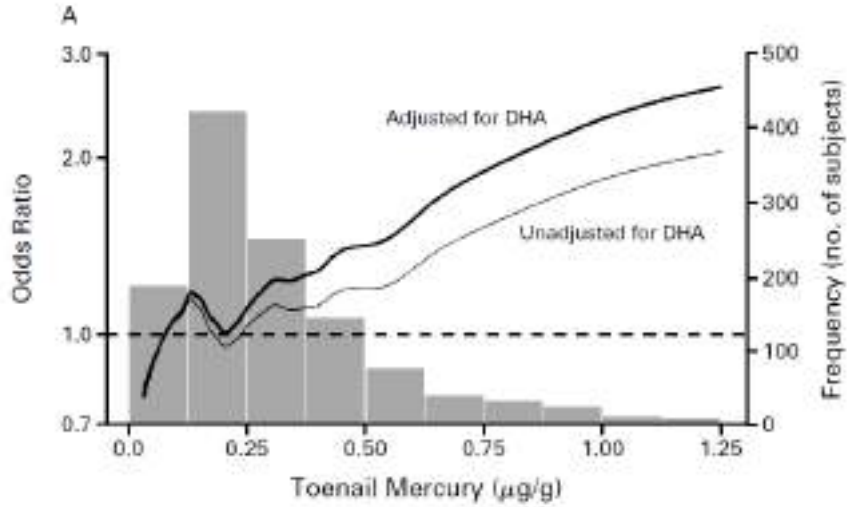


Data on file, Pronova BioPharma

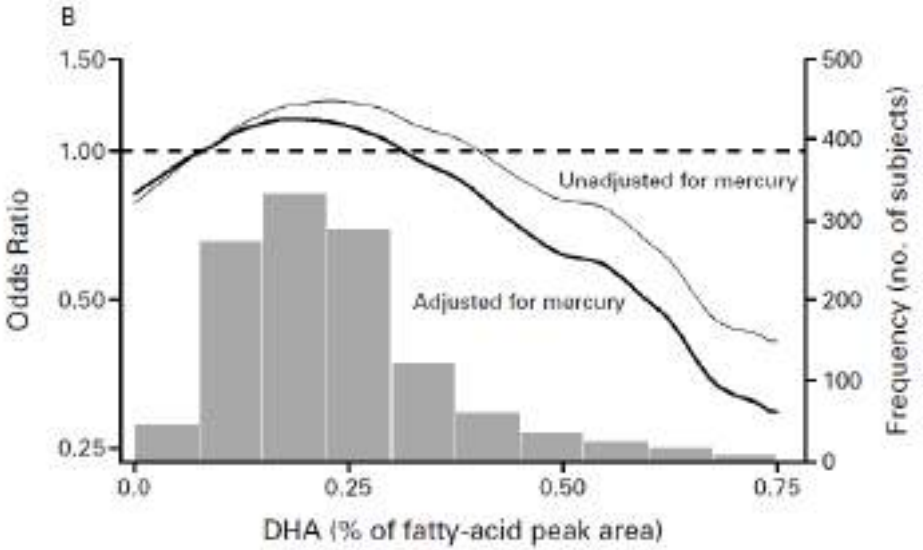
2002 NEJM研究發現：
重金屬會抵銷Omega-3的好處

Conclusions : The toenail mercury level was directly associated with the risk of myocardial infarction, and the adipose-tissue DHA level was inversely associated with the risk. High mercury content may diminish the cardio protective effect of fish intake.
(魚或魚油內的重金屬可能會抵銷**Omega-3**對心血管的好處**!!!**)

心肌梗塞發生率



指甲內汞含量(ppm)



脂肪組織內DHA含量

(N Engl J Med 2002;347:1747-54.)

藥品 vs. 保健食品

原料重金屬檢驗需低於0.01ppm *(比保健食品嚴格200倍)*

BASF
We create chemistry

CERTIFICATE OF ANALYSIS

Product: K85EE		Batch no: 0014680998
Manufacturing date: 01.02.16	Retest date: 31.01.18	Specification and Revision no: 50355290-11 Rev. 2

Test	Specification	Result	Unit	Method
Anisidine value	Max 15	2		PhEur 1250 / 2.5.36
Absorbance at 233 nm	Max 0,55	0,29	AU	PhEur 1250 / 2.2.25
Oligomers	Max 1,0	0,5	area %	PhEur 1250 / 2.2.30
Cholesterol	Max 3,0	0,2	mg/g	PhEur 2.4.32
Microbial limits				
TAMC *Total aerobic microbial count*	Max 1E3	<1E1	cfu/g	PhEur 2.6.12
TYMC *Total combined yeasts/moulds count*	Max 1E2	<1E1	cfu/g	PhEur 2.6.12
Bile-tolerant gram-negative bacteria	Max 1E2	<1E1	cfu/g	PhEur 2.6.13
E. coli	Absence in 1 g	Absence in 1 g		PhEur 2.6.13
S. aureus	Absence in 1 g	Absence in 1 g		PhEur 2.6.13
Salmonella	Absence in 10 g	Absence in 10 g		PhEur 2.6.13
Periodic analyses				
Periodic analyses tested		060116	ddmmyy	
The following parameters are tested after change of crude oil or at least once a year				
Inorganic impurities				
Hg, Mercury	Max 0,1	<0,01	mg/kg	611522
Pb, Lead	Max 0,1	<0,01	mg/kg	611522
Cd, Cadmium	Max 0,1	<0,01	mg/kg	611522
As, Arsenic	Max 0,1	<0,03	mg/kg	611522

Omega-3 Fatty Acid and Cardiovascular Outcomes: Insights From Recent Clinical Trials

- Data from the randomized, controlled trial REDUCE-IT, when viewed within the context of other recently published trials ASCEND and VITAL, add to a growing body of evidence on the use of ω-3 FA therapies in the treatment of atherosclerotic cardiovascular disease (ASCVD). Given the different formulations, dosages, and patient populations studied, CVOTs of ω-3 FA have provided valuable insight into the use of these agents in cardioprotection.
- Current data suggest that **higher dosages of pure eicosapentaenoic acid ω-3 FA formulations** provide additional benefit in reduction of ASCVD events.

Curr Atheroscler Rep. 2019 Jan 10;21(1):1. doi: 10.1007/s11883-019-0763-0.

我最常被問的問題之二：

能否與抗血小板或凝血劑並用?

仿單未列禁忌(表示可並用)

7. 藥物交互作用

7.1 抗凝血劑或影響凝血之其他藥物

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

2013：心血管裝支架患者並用的臨床試驗

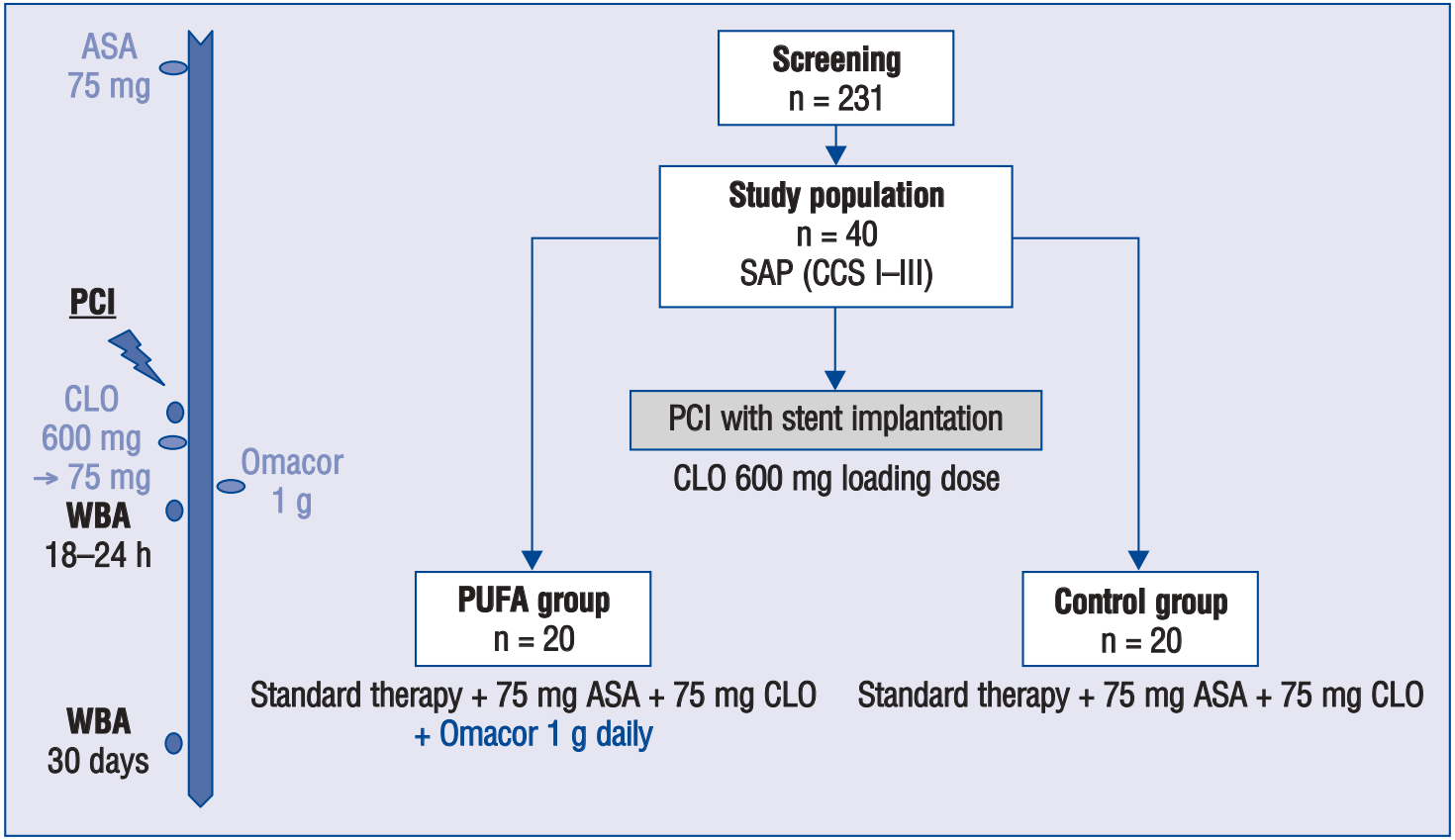


Figure 1. Participant flow; ASA — acetylsalicylic acid; CLO — clopidogrel; PCI — percutaneous coronary intervention; SAP — stable angina pectoris; WBA — whole blood impedance aggregometry.

研究顯示與Aspirin/Plavix並用不會延長出血時間

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

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

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

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

Reviews: 安全無虞

Safety and Tolerability of Omacor

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

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

Am J Cardiol 2006;98[suppl]:71i–76i

Thanks for your attention

wuyw0502@gmail.com