Omega 3 FA: A Review of its use in Secondary and Primary Prevention and the Treatment of Hyper-triglycemia

主講人: 吳建興醫師

Date:

01.Sep.2019

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長庚醫療財團法人
CHANG GUNG MEDICAL FOUNDATION

Speaker disclosures

- I hereby disclose that I am an invited speaker for Excelsior Biopharma Inc Taiwan.

OUTLINE

1. Introduction of Omega-3 FA
2. Common Myths About Omega-3
3. Triglycerides and CAD
4. What is the Eeurope and American guideline for omega-3 FA supplements in high risks patients.
5. Present meta-analysis provide no support for omega-3 FA supplements the recommendations, why?
6. How about the higher dose of omega-3 FA supplements.
7. Conclusion

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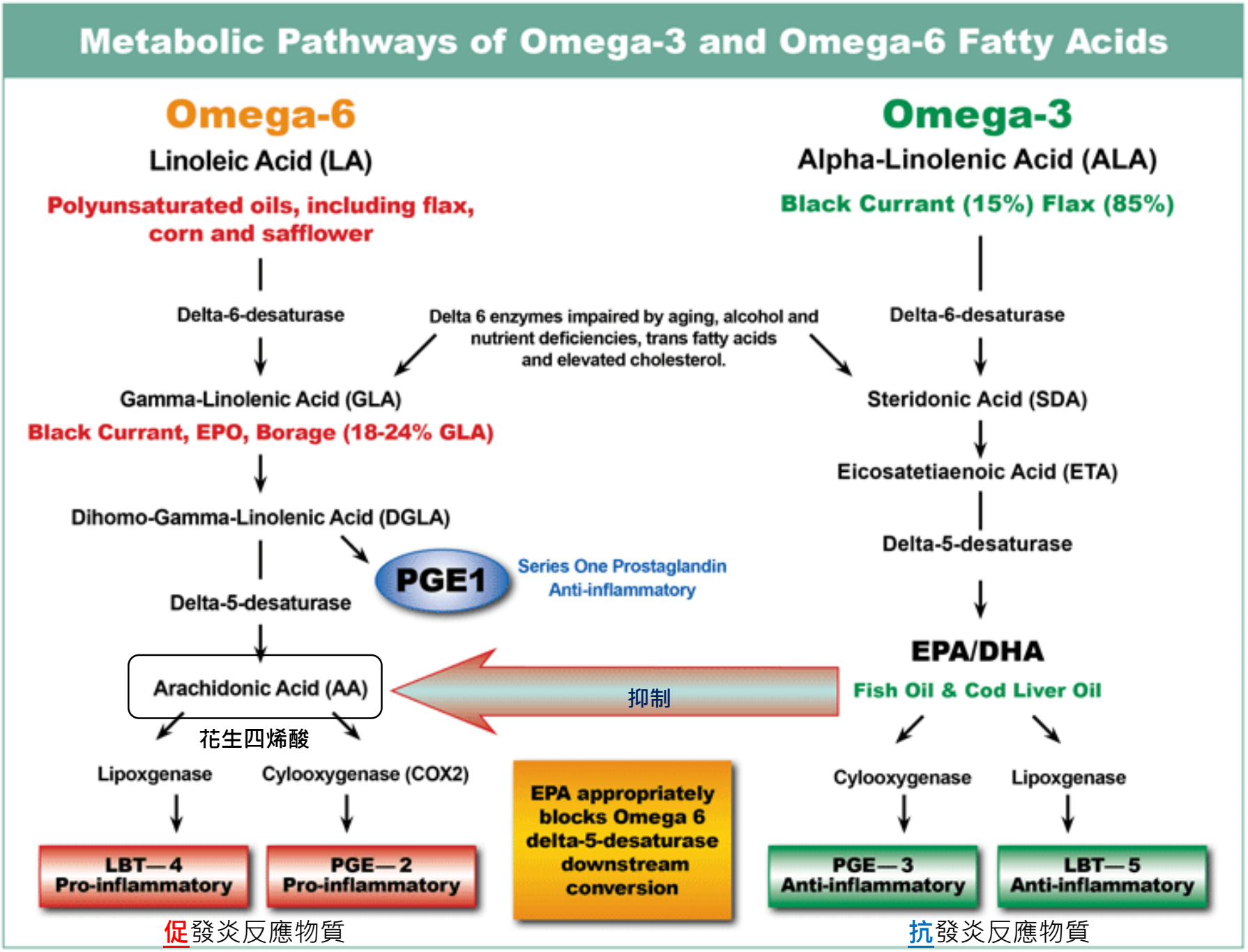
油脂分成飽和脂肪酸及不飽和脂肪酸

1. 飽和脂肪酸: 主要來自動物油，像豬油、牛油，穩定度雖高，但攝取過多可能對健康造成影響。
2. 不飽和脂肪酸: 具健康價值，對身體有益

	多元不飽和脂肪酸		單元不飽和脂肪酸	飽和脂肪
	Omega-3	Omega-6	Omega-9	飽和脂肪
健康影響	改善發炎 清除血栓 腦部發育 保護眼睛	容易發炎	降低膽固醇 改善發炎	形成膽固醇
發煙點	最不耐高溫	不耐高溫	耐高溫	耐高溫
食物來源	深海魚 亞麻仁籽 堅果種子	大部分植物油	高油酸葵花油 苦茶油 橄欖油 酪梨	大部分動物油 椰子油 棕櫚油


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)
Delta-5-desaturase
PGE1
Series One Prostaglandin
Anti-inflammatory
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
抑制
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
Cylooxygenase
Lipoxgenase
PGE—3
Anti-inflammatory
LBT—5
Anti-inflammatory
促發炎反應物質
抗發炎反應物質

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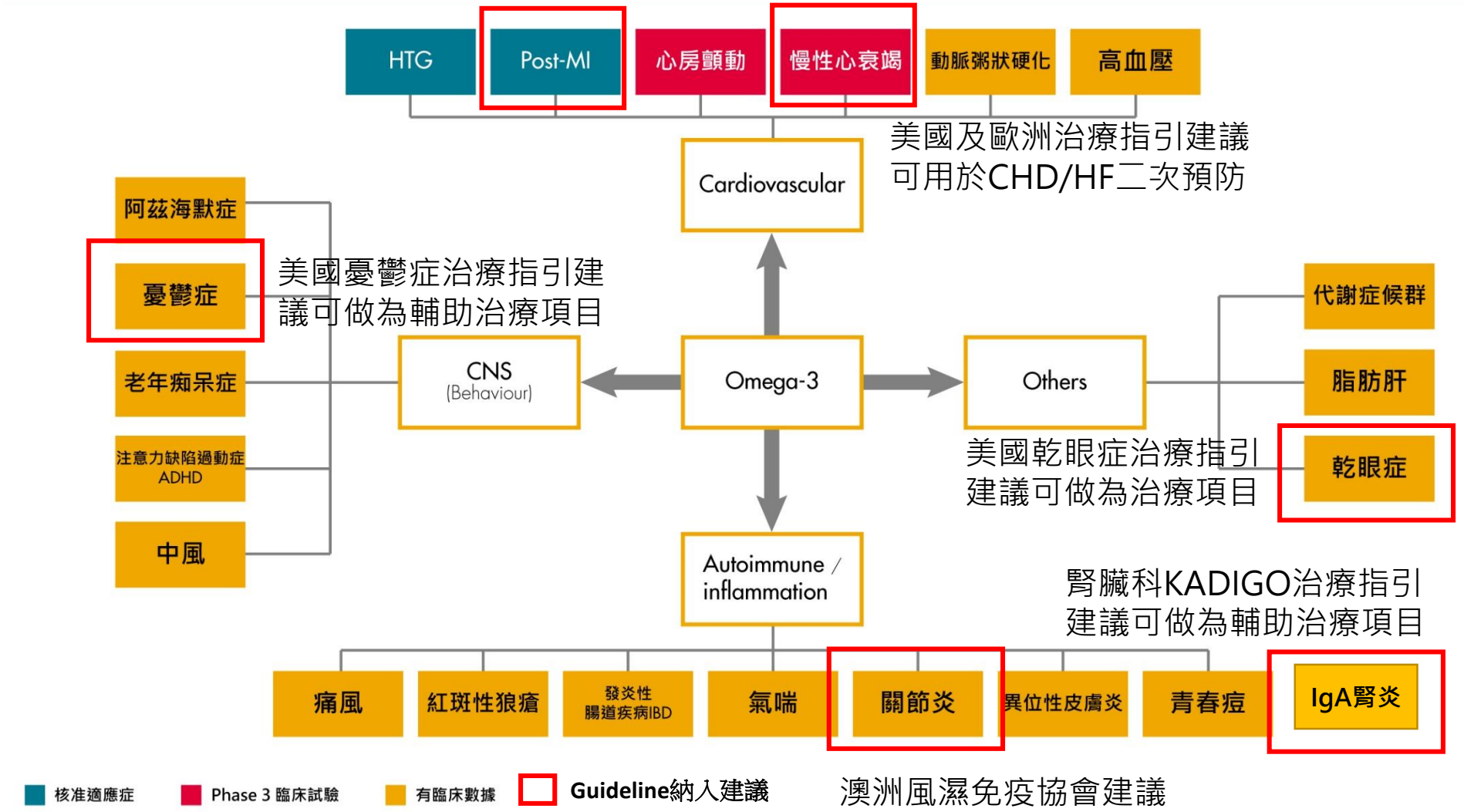
Common Myths About Omega-3

- Myth 1: Omega-3s are fats and therefore make us fat
- Myth 2: Omega-3 only benefits the heart
- Myth 3: I eat fish, so I don't need omega-3/fish oil supplements
- Myth 4: All fish oil supplements are the same
- Myth 5: All fish are equally nutritious

Potential for Omega-3 derived pharmaceuticals



差很大！謝震武代言葡萄糖胺飲　成分含量僅6成

時間： 2016/08/03 17:36

點評:登愣！！！

ET健康雲

說這專頁讚 1.5 萬 按讚次數

誰 221

台灣版 > 新聞 > 台灣

電視購物葉黃素濃度少50倍　生技公司涉詐欺

2016年03月04日(五) 16:30 推薦 55 Tweet G+1 0 分享

電視購物頻道所賣的葉黃素，濃度竟與標示差50倍，被檢警會同衛生單位查獲。（保七總隊圖片）

1/4

抽查10件8件不符合標示內容

頭條要聞 〉 8款進口魚油 虛報營養量

分享到FB 分享到g+ 分享到Plurk 分享到Twitter

8款進口魚油 虛報營養量

疑混沙拉油 DHA和EPA只含一兩成

2015年03月24日 傳送 讚 1.3萬 G+1 8 更多專欄文章

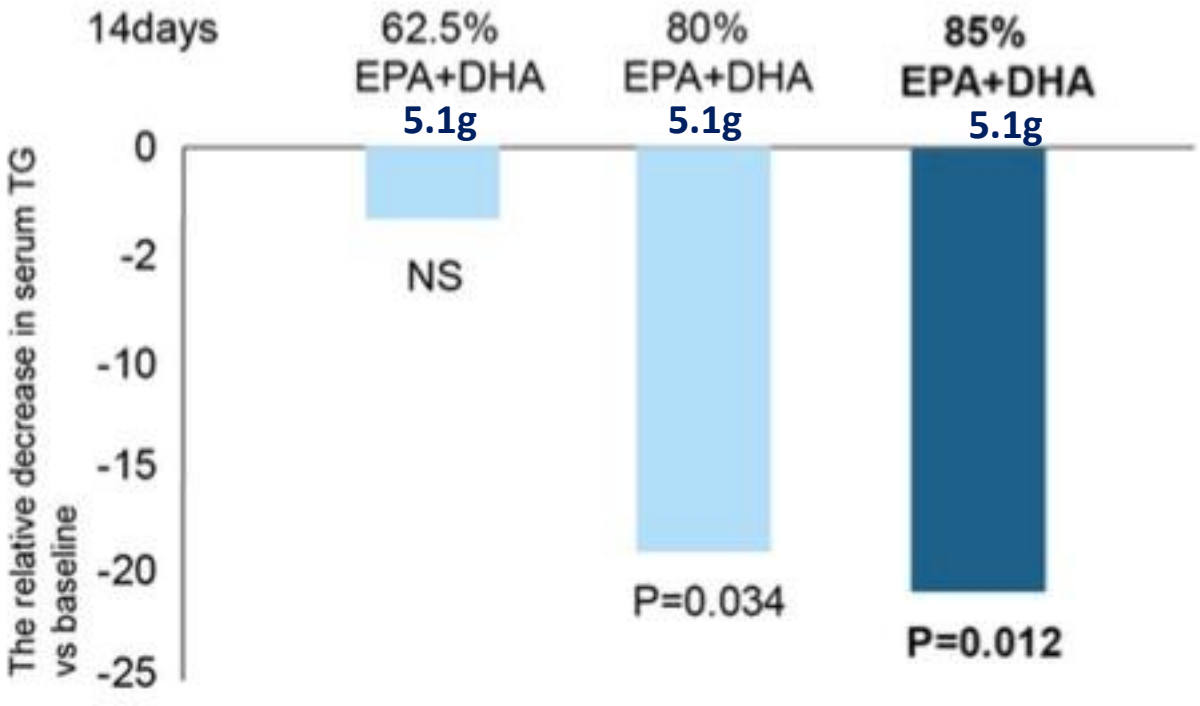
不合格魚油

【鄧惠珍／彰化報導】彰化縣衛生局昨抽驗十件市售魚油產品，八件進口魚油ＤＨＡ及ＥＰＡ實際含量低於標示含量。衛生局稱若涉假冒擾偽，可依《食品安全衛生管理法》重罰兩億元，並涉詐欺刑責。已通知所屬縣市衛生局查處；醫師說，魚油若混摻其他油脂，恐傷害心血管健康！

具高營養價值的魚油富含ＥＰＡ（Eicosapentaenoic Acid，二十碳五烯酸）以及ＤＨＡ（Docosahexaenoic Acid，二十二碳六烯酸），是熱門保健食品；最近有民眾向彰化縣衛生局檢舉，買的魚油有沙拉油味，懷疑混充。

臨床實驗證明80%以上EPA/DHA濃度才有降血脂能力

N=111



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 – 可能為低濃度魚油無療效之因

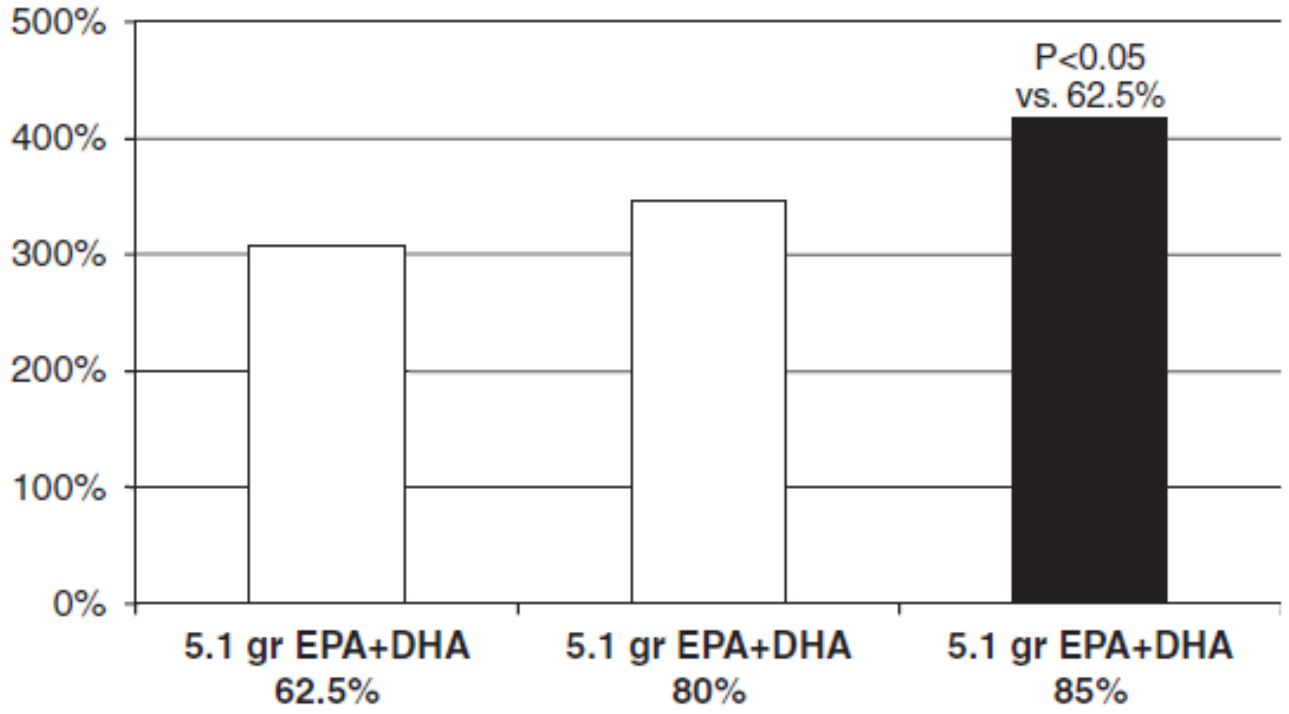


Fig. 1. Relative increase in EPA serum phospholipids versus baseline from day 0 to 14.

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

107年元月1日起
保健食品強制標示”不具醫療效能”

衛生福利部食品藥物管理署
Food and Drug Administration

請輸入關鍵字 站內 站外 搜尋 進階搜尋

熱門關鍵字： 食品添加物 營養標示 非登不可 基因改造

公告資訊 機關介紹 業務專區 法規資訊 便民服務 出版品 政府資訊公開 個人化服務

::: 目前位置：首頁 > 公告資訊 > 本署新聞

公告資訊

本署公告
本署新聞
本署徵才
維護公告
活動訊息
食藥闢謠專區
預告法規沿革區
重大政策
科技計畫
招標資訊
科研採購

本署新聞

預告訂定「健康食品應加標示事項」【發布日期：2017-08-30】

衛生福利部(下稱衛福部)於8月30日預告訂定「健康食品應加標示事項」。該規定重點為，依健康食品產品型態不同，應分別標示與「藥品」或「療效」區隔之醒語，及產品均應標示「用量提醒」之醒語。

衛福部表示，為提供消費者清楚資訊，避免誤解健康食品保健功效是藥品療效，依健康食品管理法第13條第1項第10款公告「健康食品應加標示事項」(草案)，預定自107年1月1日起，健康食品產品應於「注意事項」加標2項內容：

一、 針對與藥品或療效區隔之醒語：

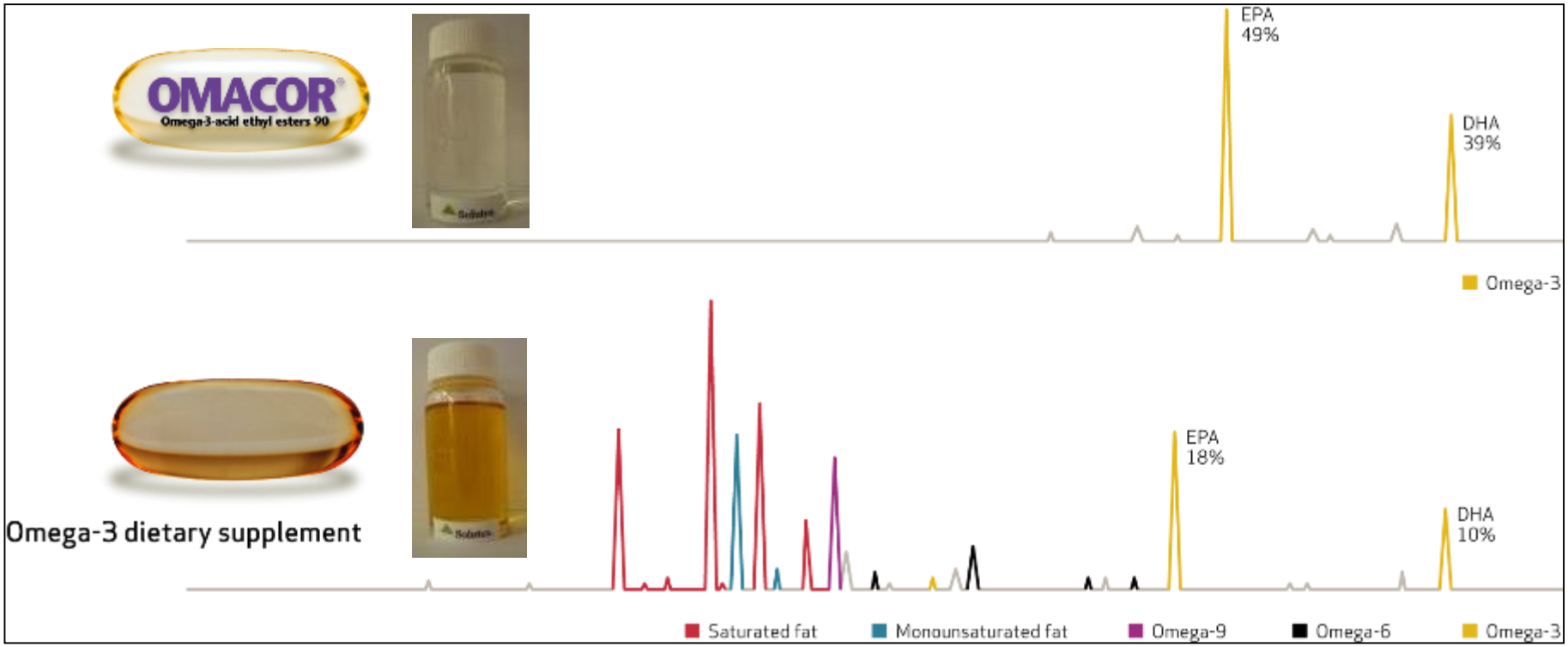
(一) 膠囊及錠狀產品，係考量產品型態與藥品較為類似，應標示「本產品非藥品，僅供保健用，罹病者仍需就醫。」字樣。

(二) 其他類型產品，即非膠囊及非錠狀產品，應標示「本產品僅供保健用，不具醫療效能。」字樣。

二、 針對用量提醒之醒語：考量健康食品係核可安全又有效的建議攝取量，即使是傳統食品，亦應適量飲食，爰規定產品均應標示「請依建議攝取量食用，多食無益。」字樣。

衛福部提醒業者應注意本規定實施日期，把握緩衝時間及早因應準備。對於法規生效日(107年1月1日)以後才取得健康食品許可證者，均應依規定標示，並無緩衝期；而法規生效日(107年1月1日)以前已取得健康食品許可證者，緩衝期為期半年，即產品於107年7月1日起製造者，均應依規定標示。

EPA/DHA濃度越低代表"雜油"越多



Data on file, Pronova BioPharma

製造/原料/檢驗/大型臨床試驗

	Omacor	一般魚油
製造廠	PIC/S GMP	GMP
原料	DMF	食用原料
檢驗規格	逐批檢驗	備查即可
經大型臨床試驗證明安全有效	有	無

(1) 政府未強制要求檢驗保健食品，所以保健食品廠商用SGS檢驗取信消費者

(2)保健食品廠商SGS檢驗未標批號與製造日期 *(消費者拿到的跟檢驗的是否同一批???)*

(3)SGS檢驗零/未檢出不代表是0，只要重金屬低於2ppm就可列零/未檢出

SGS

食品實驗室-台北
FOOD LAB-TAIPEI
初 示 報 告
Initial Report

北極熊國際食品有限公司
台北市內湖區民權東路六段264號5樓

報告編號： FA/2015/34087
日期： 2015/04/08
頁數： 1 of 2

以下測試之樣品係由申請廠商所提供並確認資料如下：

產品名稱: 挪威北極熊魚油添加磷蝦油膠囊
樣品狀態: 市售完整包裝
產品型號/批號: —
申請廠商： 北極熊國際食品有限公司
生產或供應廠商： Pharmatech AS
製造日期： —
有效日期： —
原產地(國)： 挪威
收樣日期： 2015/03/26
測試日期： 2015/03/26

測試結果：

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

備註：1.測試報告僅就委託測試者之委託事項提供測試結果，至若本產品之合法性，仍應由主管機關依法判斷。
2.本報告不得分離或擷線使用。
3.若該測試項目屬於定量分析則以「定量極限」表示；若該測試項目屬於定性分析則以「偵測極限」表示。
4.依於定量極限/偵測極限之測定值以 "未檢出"或" 陰性 " 表示。
5.本次委託測試項目(EPA及DHA)由SGS食品實驗室-高雄執行。

- END -

Chengchia Tsai Manager
Signed for and on behalf of

特別註明：
本初示報告係作為通知之用，詳細測試結果

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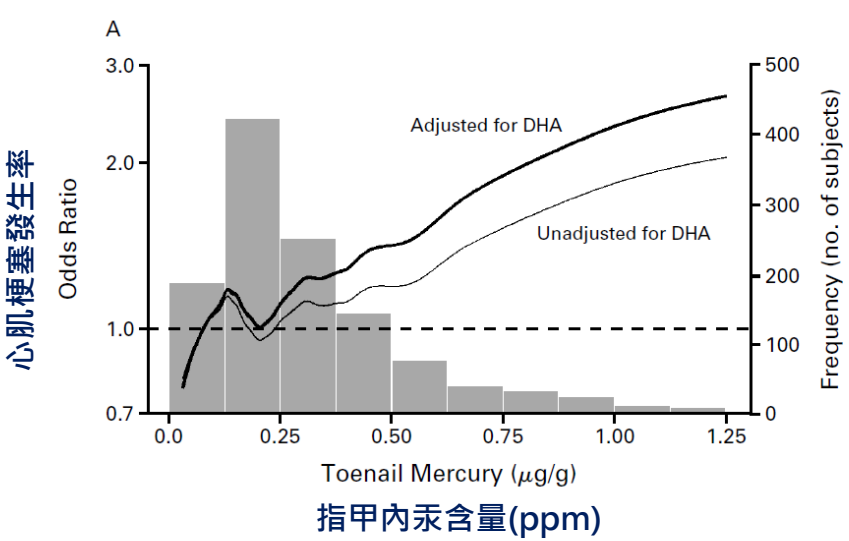
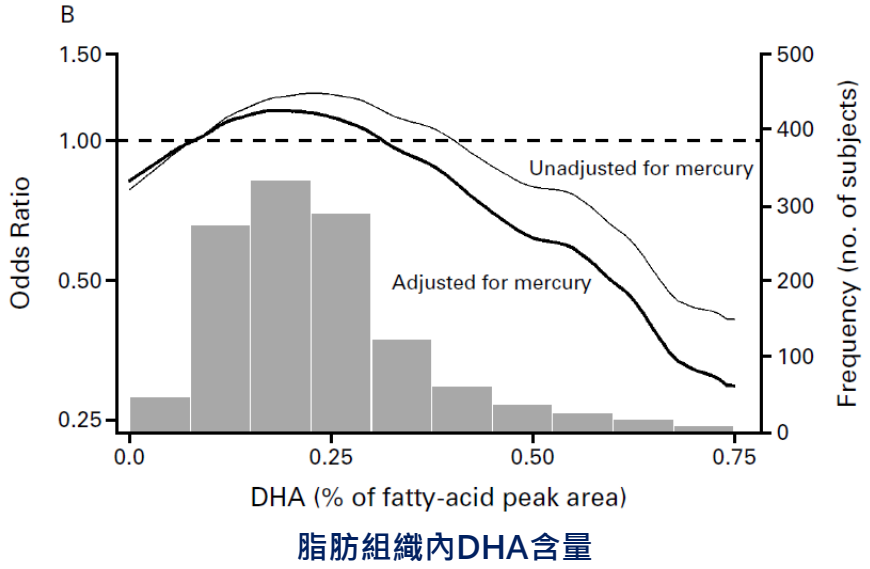
國家品質標章廠商　進口磷蝦油含砷量竟超標92倍

　出版時間：2018/06/26 20:37

2002 NEJM研究發現：重金屬可能會抵銷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!!!)





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

TABLE 1

Omega-3 oil levels in various fish and seafoods*

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

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

					
產品	三得利 魚油DHA&EPA	NU SKIN 深海賦活魚油	NU SKIN 華茂精選魚油	倍健 天然高濃縮魚油	OMACOR
等級	食品級				藥品級
EPA含量(mg)	25	150	150	300	460
DHA含量(mg)	75	100	100	200	380
魚油總量(mg)	400	1000	1000	1000	1000
EPA/DHA濃度	25%	25%	25%	50%	84%
包裝	120顆/瓶	120顆/瓶	60顆/瓶	60顆/瓶	28顆/瓶
市售價	1600元	2000元	830元	2000元	1680
單價/顆	13元	17元	14元	33元	60
1000mg EPA/DHA總價	130元	68元	56元	66元	60元

不考慮生體可用率
也不考慮濃度是否為真的成本計算

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

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降血脂藥物之「合理用法」

台北榮總心臟內科 主治醫師
陳肇文

血脂升高的原因可 分兩大方面

- 原發性的體質因素:「家 族性高血脂症」
- 次發性的高血脂症

1.**疾病因素:**有些疾病會使脂肪代謝 異常，而引發高血脂，如，糖尿病、甲狀 腺機能低下、庫欣氏症候群(Cushing's syndrome)、及某些腎衰竭的患者。

2.**飲食因素:**喜好高脂肪飲食、肥胖、喝酒過量。

3.**藥物因素:**有些藥物的長期使用會使血 脂肪昇高，如:類固醇、口服避孕藥、利 尿劑、乙型神經阻斷劑

台北榮總心臟內科 主治醫師
陳肇文

心血管疾病的「一級預防」(Primary prevention)

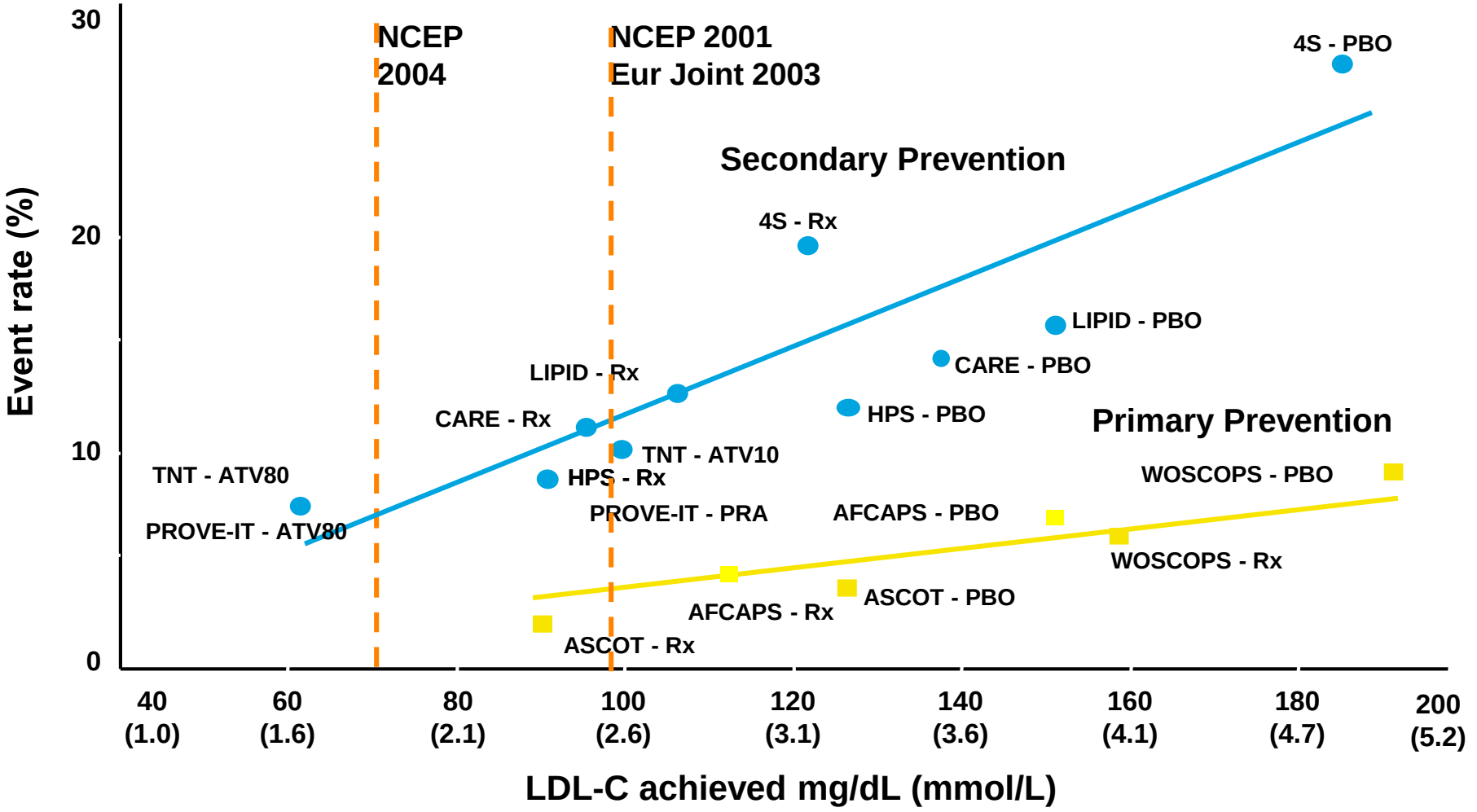
- 目前對一般沒有其他危險因子的單純高血脂症的患者，強調先以飲食控制及經常運動等積極的修正生活型態，追蹤3到6個月後若血脂值仍未降至標準值，才給予藥物治療。此所謂心血管疾病的「一級預防」(Primary prevention)。

台北榮總心臟內科 主治醫師
陳肇文

心血管疾病 的「二級預防」 (Secondary prevention)

- 動脈硬化性心血管疾病的高危險 群(如糖尿病患者)或已經有動脈硬化性 心血管疾病病史者，目前臨床證據建議其 血脂值必須盡快降至比一般人標準值更低 之合理目標值，才能有效預防心血管疾病 再發。因此，這類病人只要血脂值高於合 理目標值，就應立即修正生活型態及同時 給予降血脂藥物治療。此所謂心血管疾病 的「二級預防」(Secondary prevention)。

LDL仍是降血脂首要目標



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

2019健保署新降血脂藥物給付規定

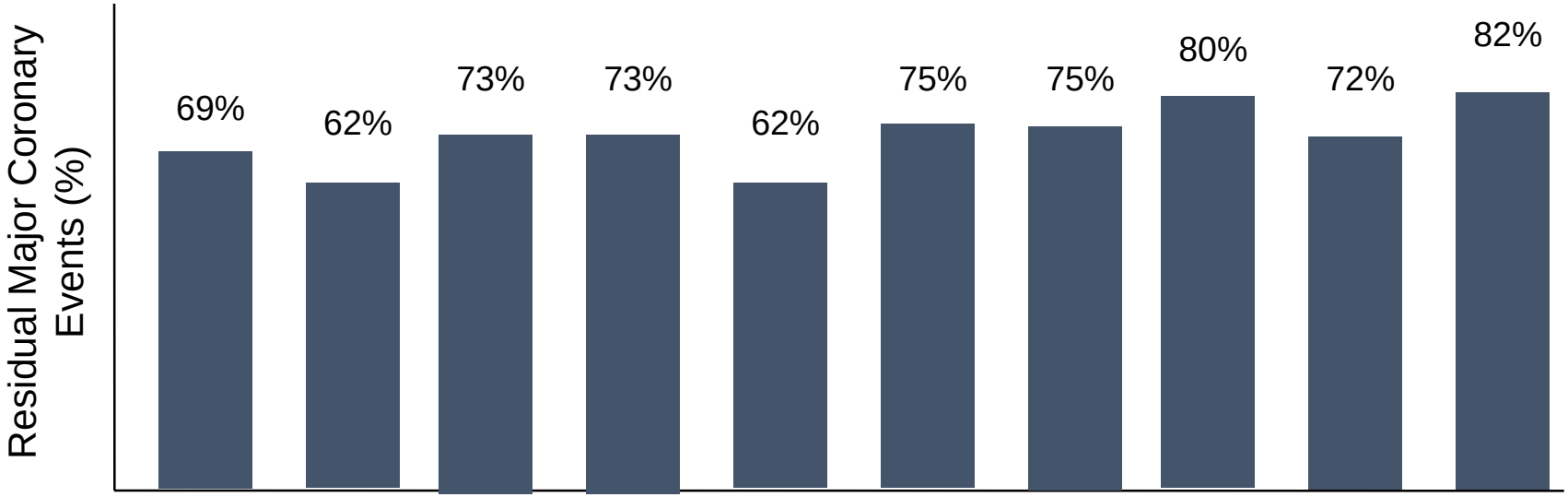
	非藥物治療	起始藥物治療血脂值
1.有急性冠狀動脈症候群病史 2.曾接受心導管介入治療或外科冠動脈搭橋手術之冠狀動脈粥狀硬化患者(108/2/1)	與藥物治療可並行	LDL-C ≥70mg/dL
心血管疾病或糖尿病患者	與藥物治療可並行	TC≧160mg/dL或LDL-C≧100mg/dL
2個危險因子或以上	給藥前應有3-6個月非藥物治療	TC≧200mg/dL或LDL-C≧130mg/dL
1個危險因子	給藥前應有3-6個月非藥物治療	TC≧240mg/dL或LDL-C≧160mg/dL
0個危險因子	給藥前應有3-6個月非藥物治療	LDL-C≧190mg/dL

危險因子

1.高血壓
2.男性≧45歲，女性≧55歲或停經者
3.有早發性冠心病家族史(男性≦55歲，女性≦65歲)
4.HDL-C<40mg/dL
5.吸菸(因吸菸而符合起步治療準則之個案

心血管疾病定義:
(一)冠狀動脈粥狀硬化病人:心絞痛病人，有心導管證實或缺氧性心電圖變化或負荷性試驗陽性反應者(附檢查報告)
(二)缺血型腦血管疾病病人:
1.腦梗塞。
2.腦內出血(不含其他顱內出血)。
3.陣發性腦缺血(TIA)
4.有症狀之頸動脈狹窄。

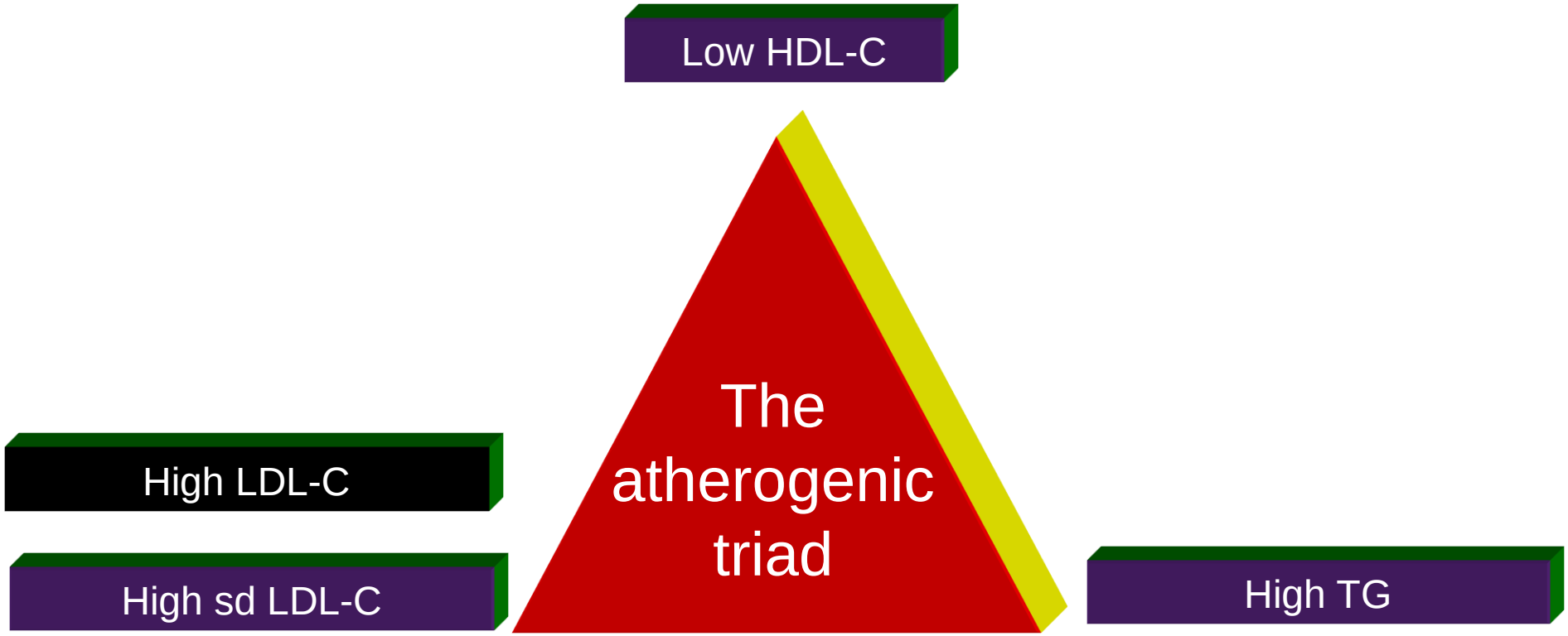
服用Statin後仍有 6~7成心血管殘餘風險



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
Δ LDL-C	-26%	-27%	-29%	-29%	-36%	-25%	-28%	-21%	-24%	-20%

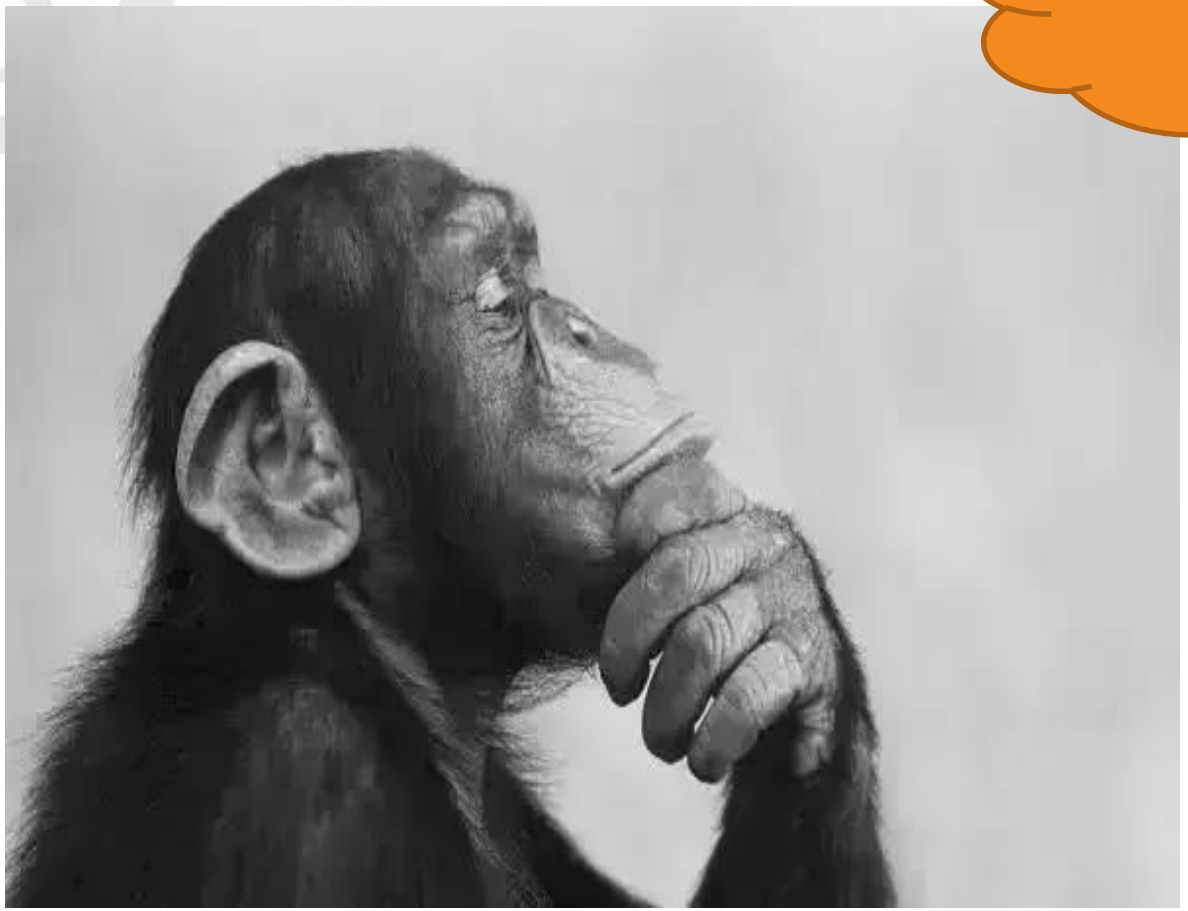
Adapted from Libby P, J Am Coll Cardiol 2005;46:1225-1228

sd-LDL過高、HDL-C過低及TG過高
也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的重要性

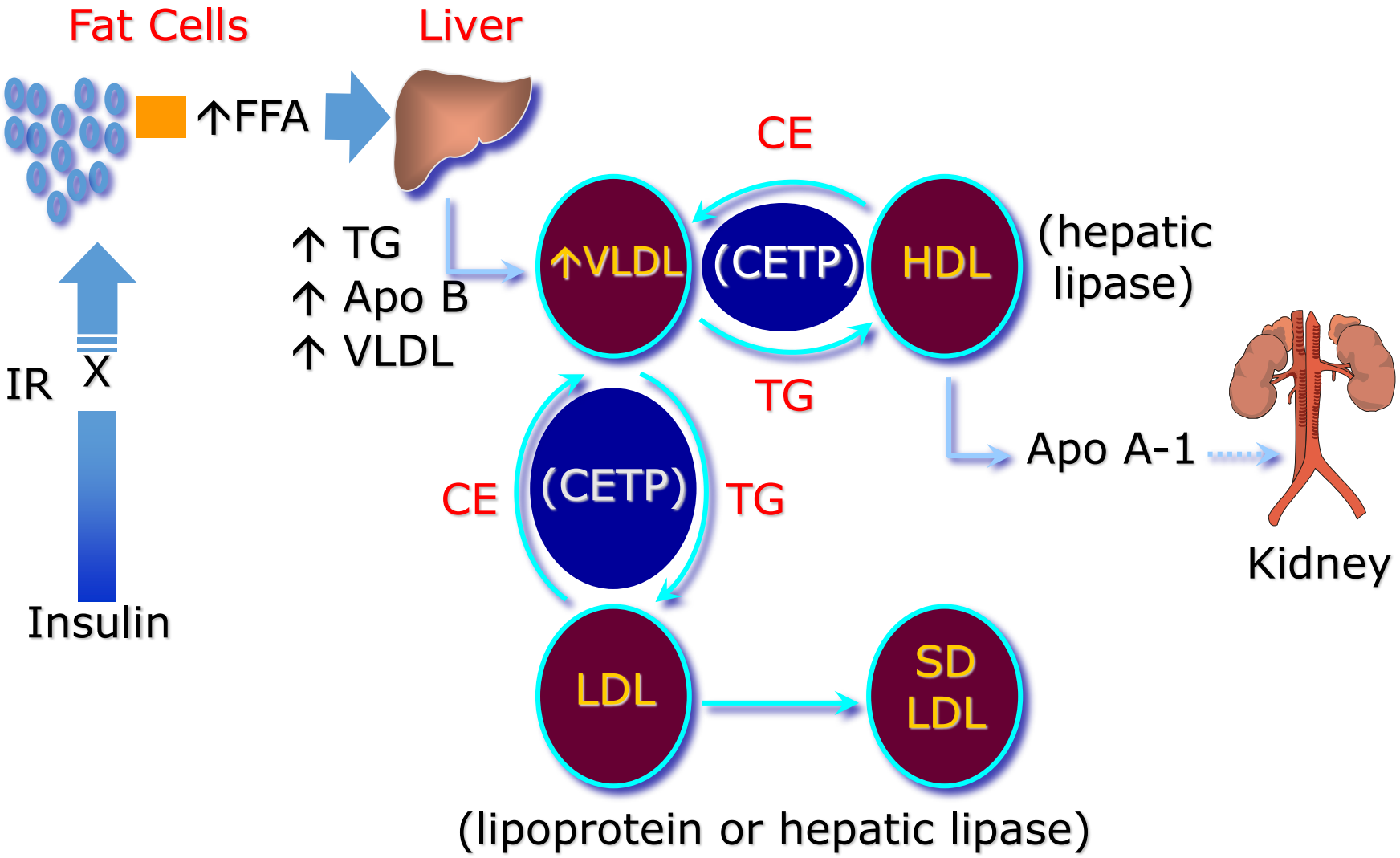


Definition of Raising Serum Triglycerides

Normal <150 mg/dL

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

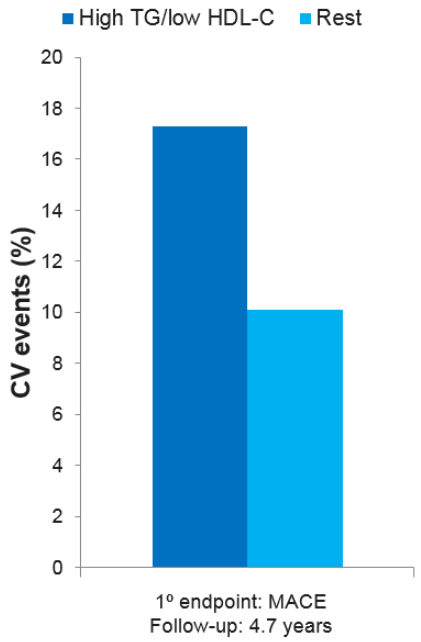
TG過高亦會降低HDL及增加sdLDL



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

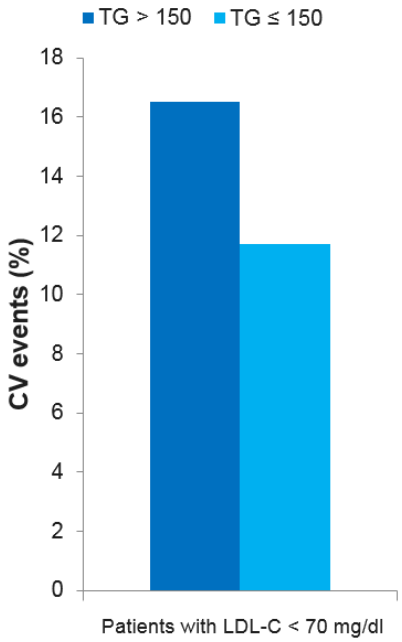
ACCORD-Lipid trial

- 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



Prevalence of HTG in Taiwan

- Hospital-based study of prevalence of dyslipidemia in Taiwan
  - 22.5 % overall
  - 29.3 % in men
  - 13.7 % in women
  - Increasing with age in women

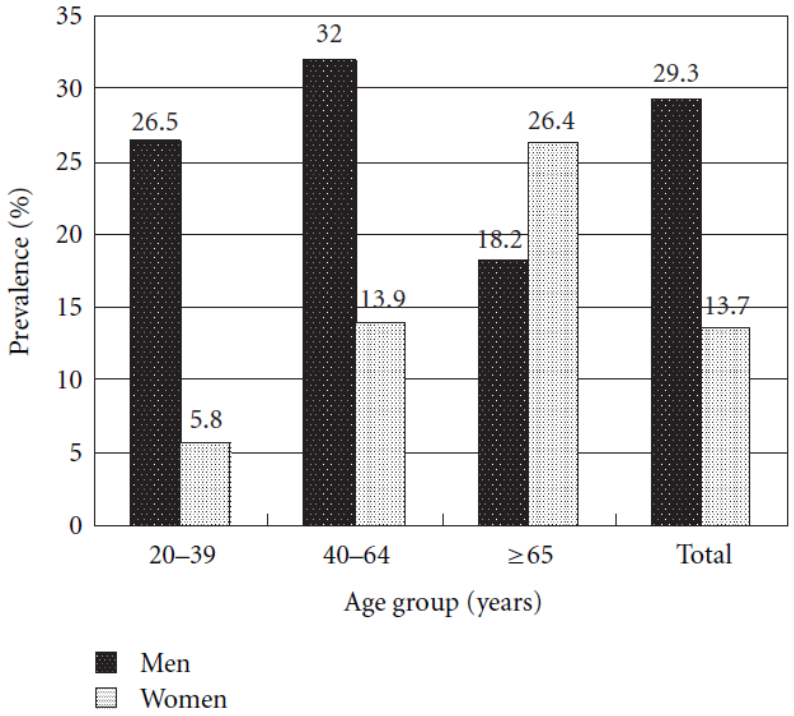
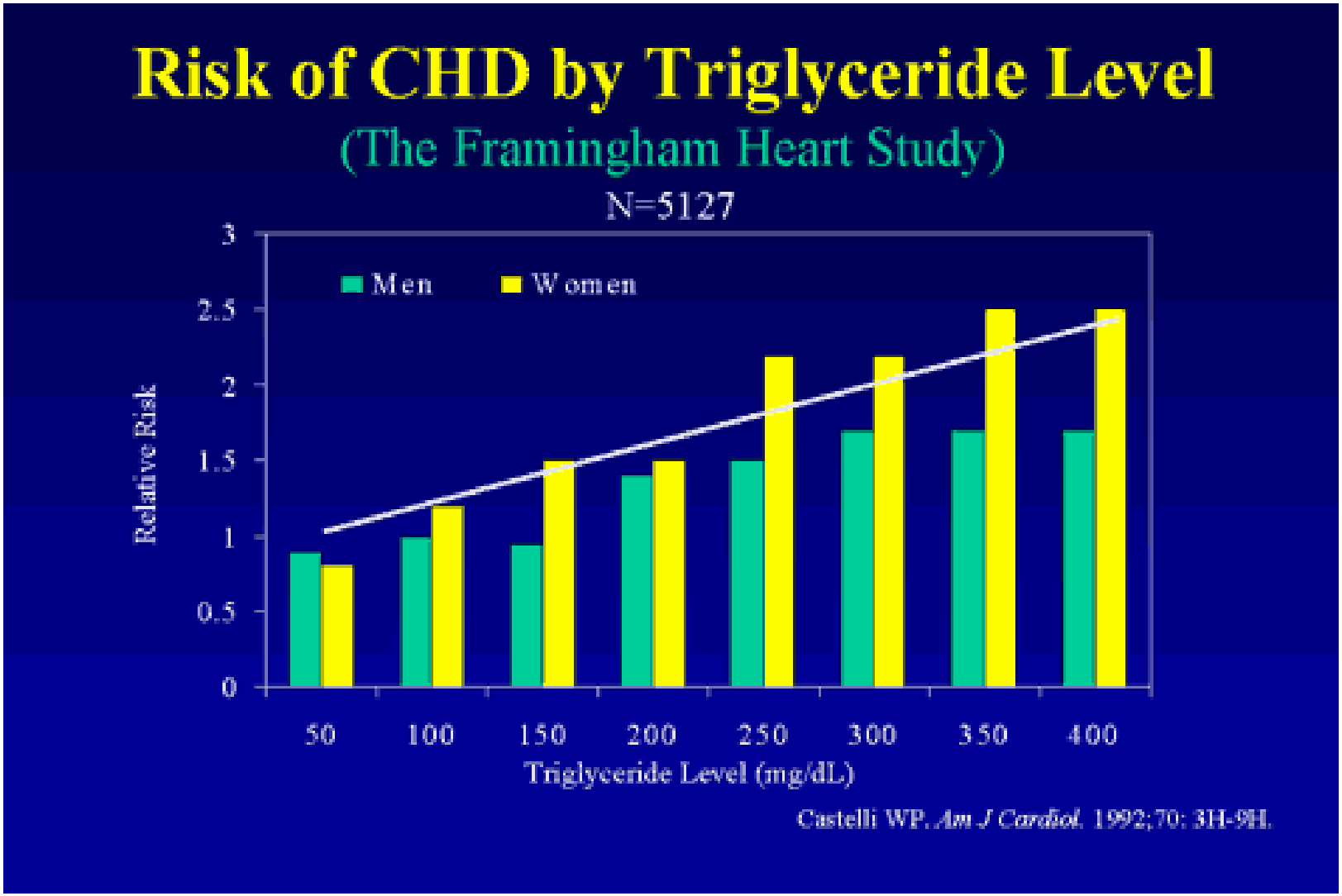


FIGURE 2: Prevalence of hypertriglyceridemia in gender and three age groups.

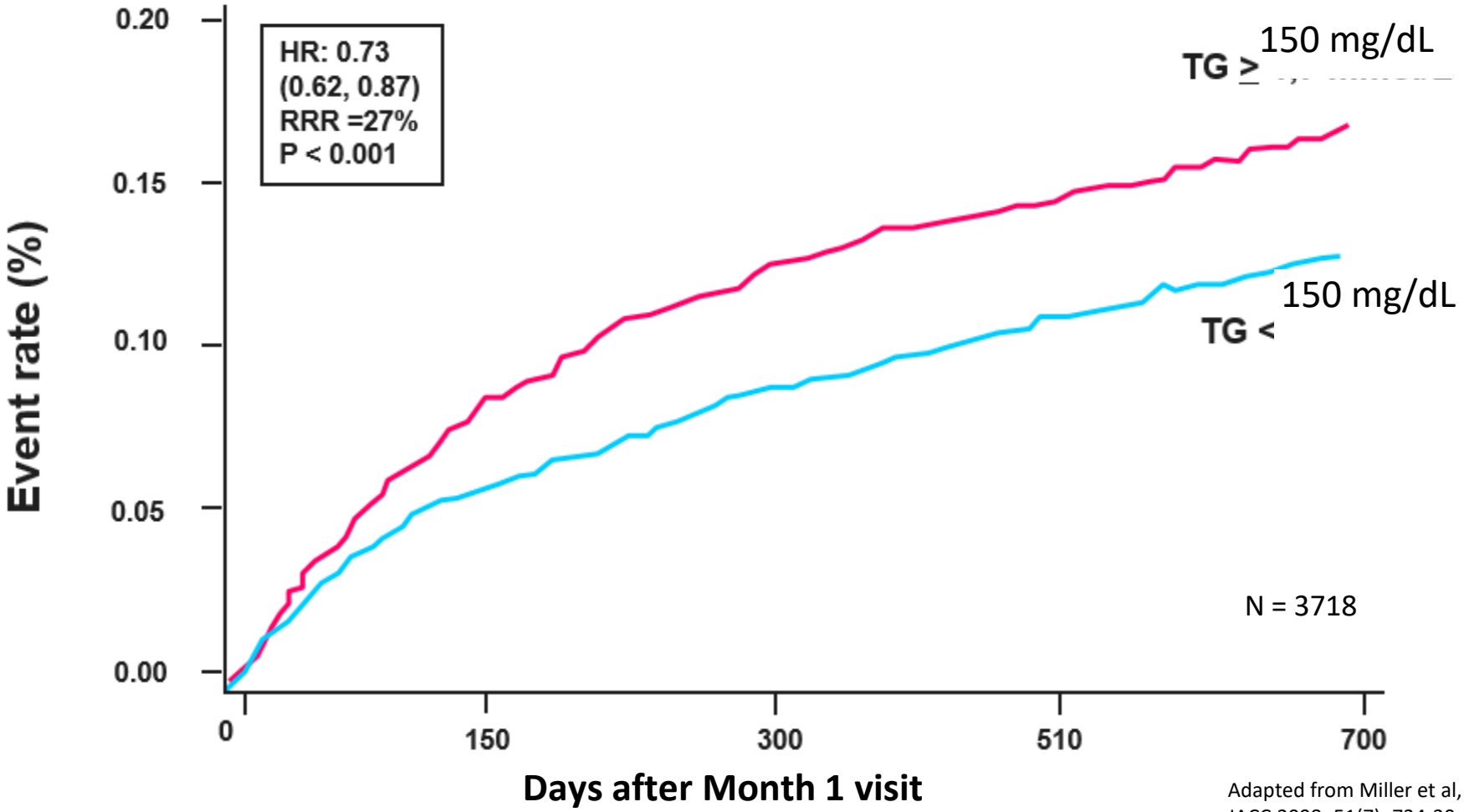
Adapted from Cheng et al, Cholesterol 2011, doi: 10.1155/2011/314234

HYPERTRIGLYCERIDEMIA

Triglyceride level and risk of CHD



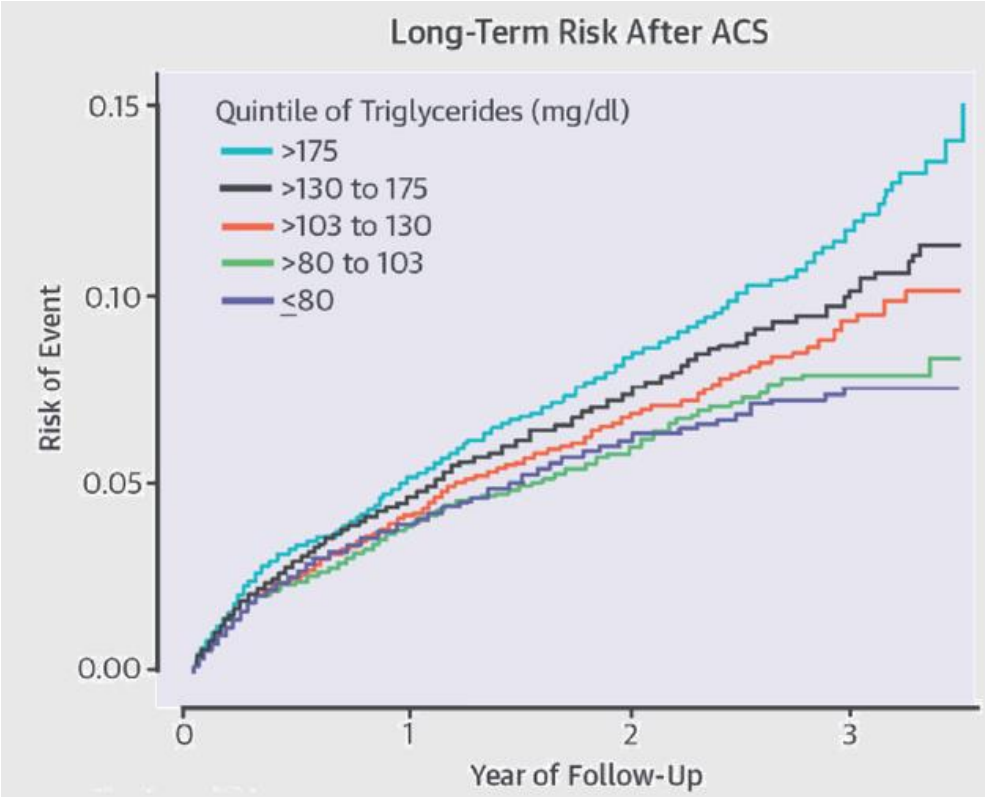
Triglyceride level and coronary heart disease risk after acute coronary syndrome



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

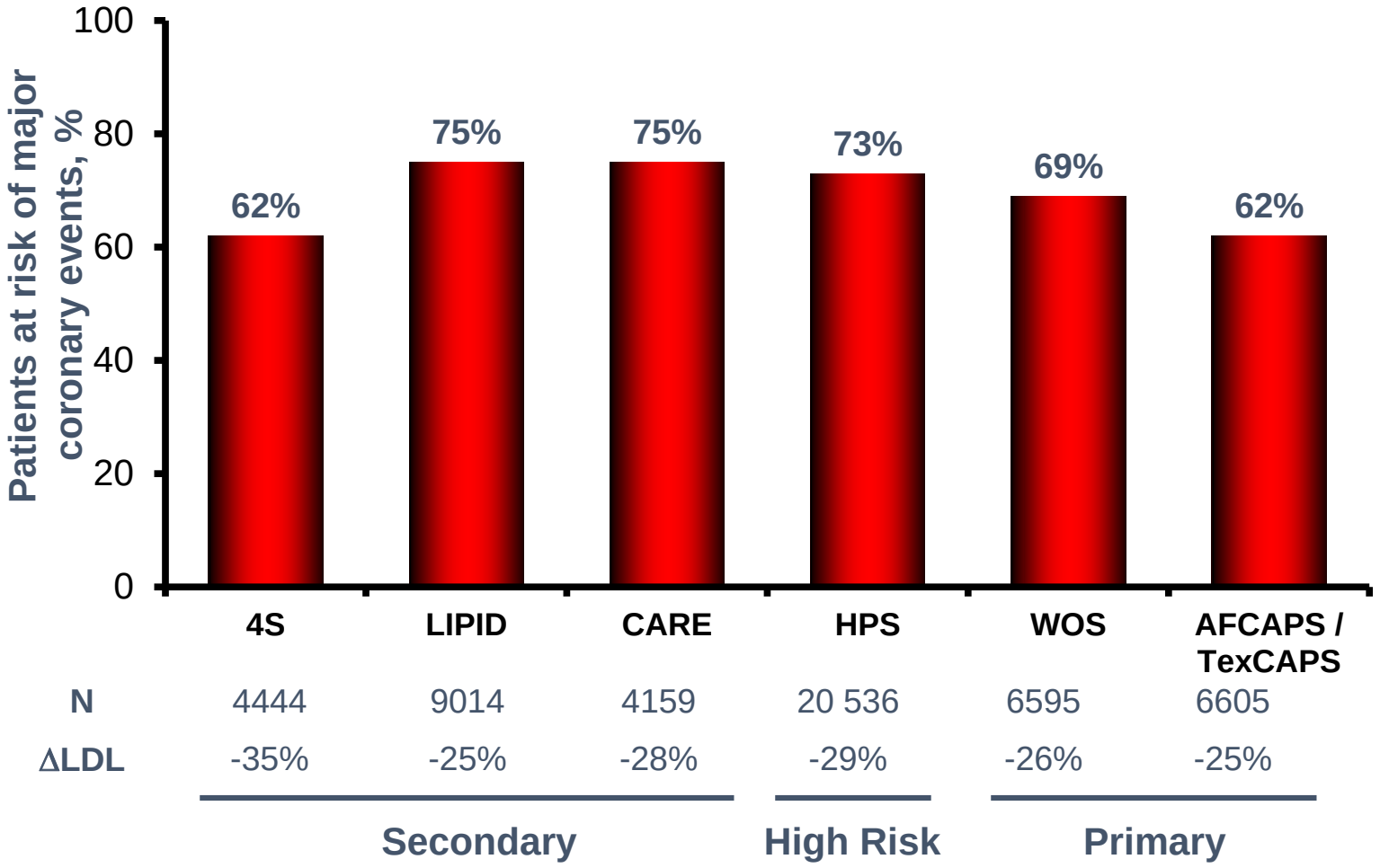
HYPERTRIGLYCERIDEMIA

Triglyceride level and long term risk after acute coronary syndrome



		Year of Follow-up			
		0	1	2	3
Number at Risk	>175	3124	2874	2525	653
	>130 to 175	3171	2952	2592	657
	>103 to 130	3142	2931	2595	691
	>80 to 103	3135	2942	2619	730
	≤80	3245	3028	2869	729

Residual Cardiovascular Risk in Major Statin Trials



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

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.

Triglyceride Reduction藥物一覽

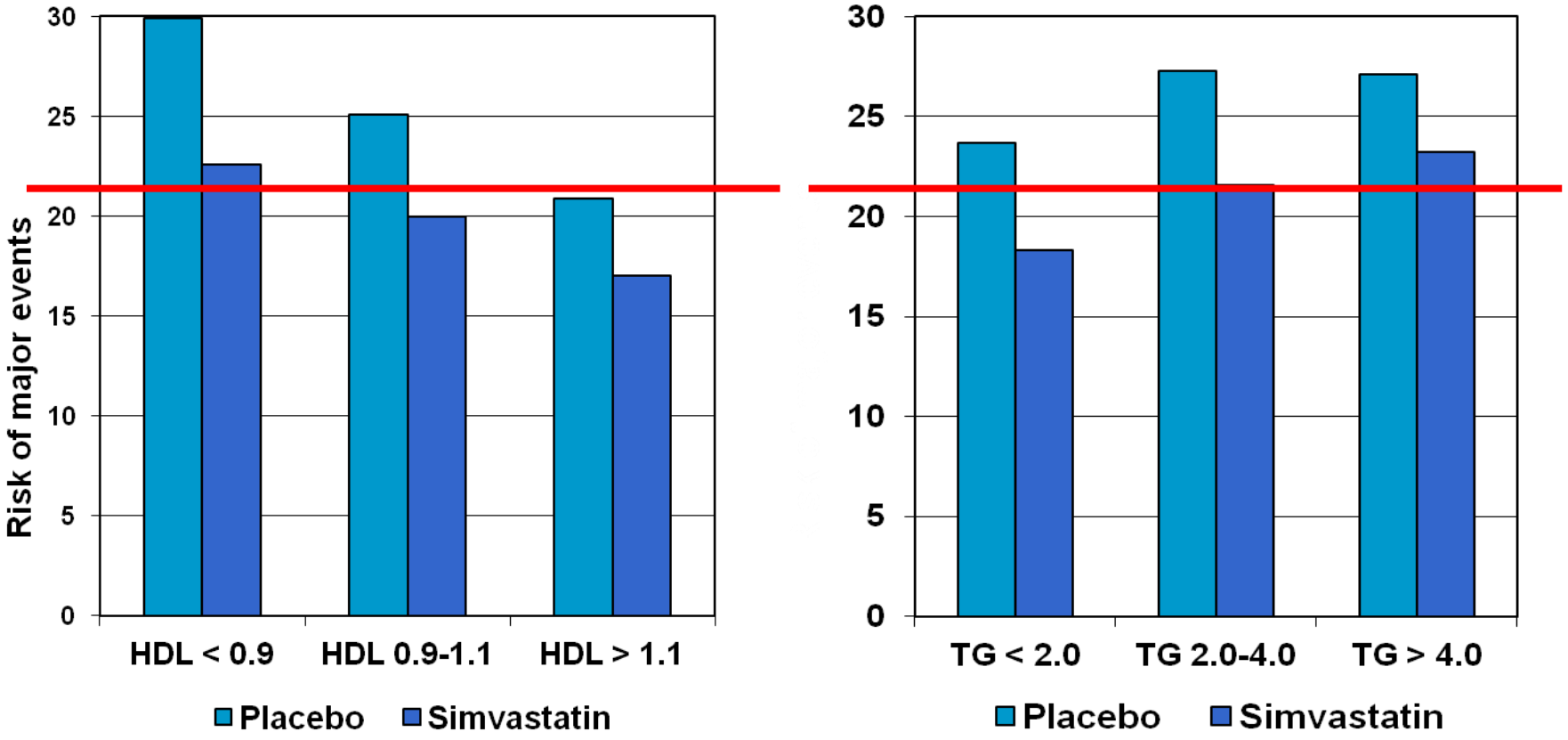
Table 12. Effect of Lipid-Lowering Therapies on Triglyceride Reduction[504,480a–480d]

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

不能用Fibrate
or
Fibrate不夠用

Circulation. 2011;123:2292-2333.

Risk associated with TG and low HDL-C not eliminated in the HPS study



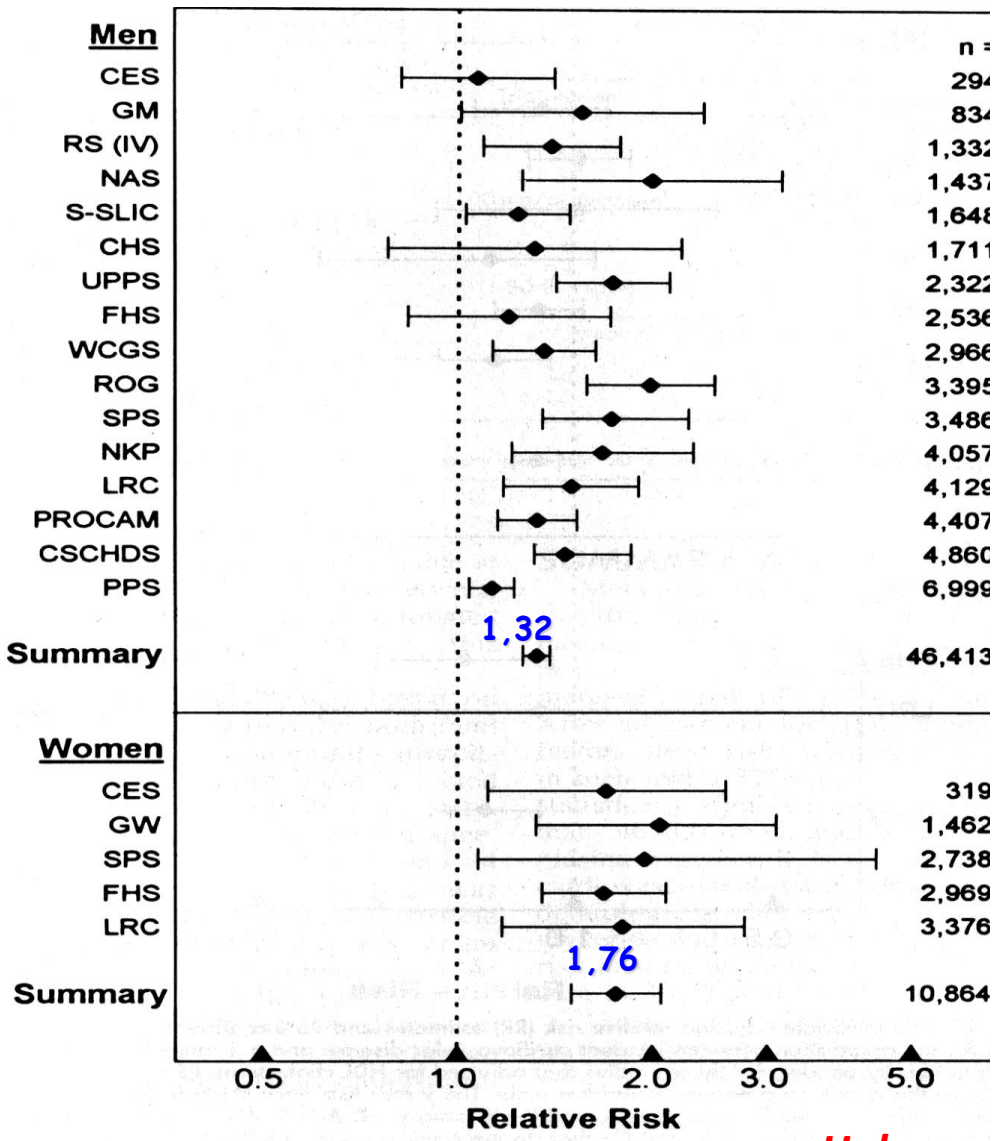
Lipids in mmol/L

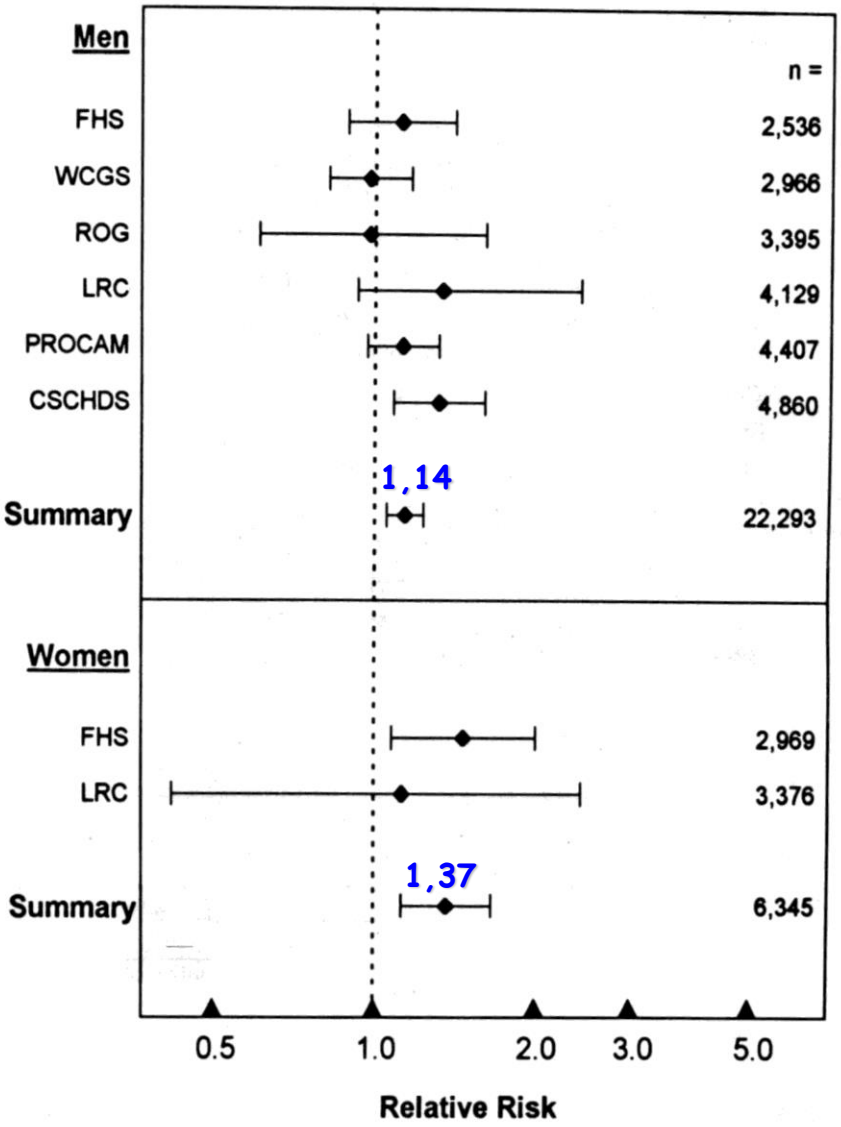
Collins R, et al. Lancet 2003:361:2005-16

Triglycerides and CAD

- Residual Risk after Statins
- **Triglycerides, risk factor for CAD & death**
- Associated abnormalities
- Diabetes: a special case

Triglycerides and Coronary Risk





Hokanson JE, et al. J Cardiovasc Risk 1996;3:213-19

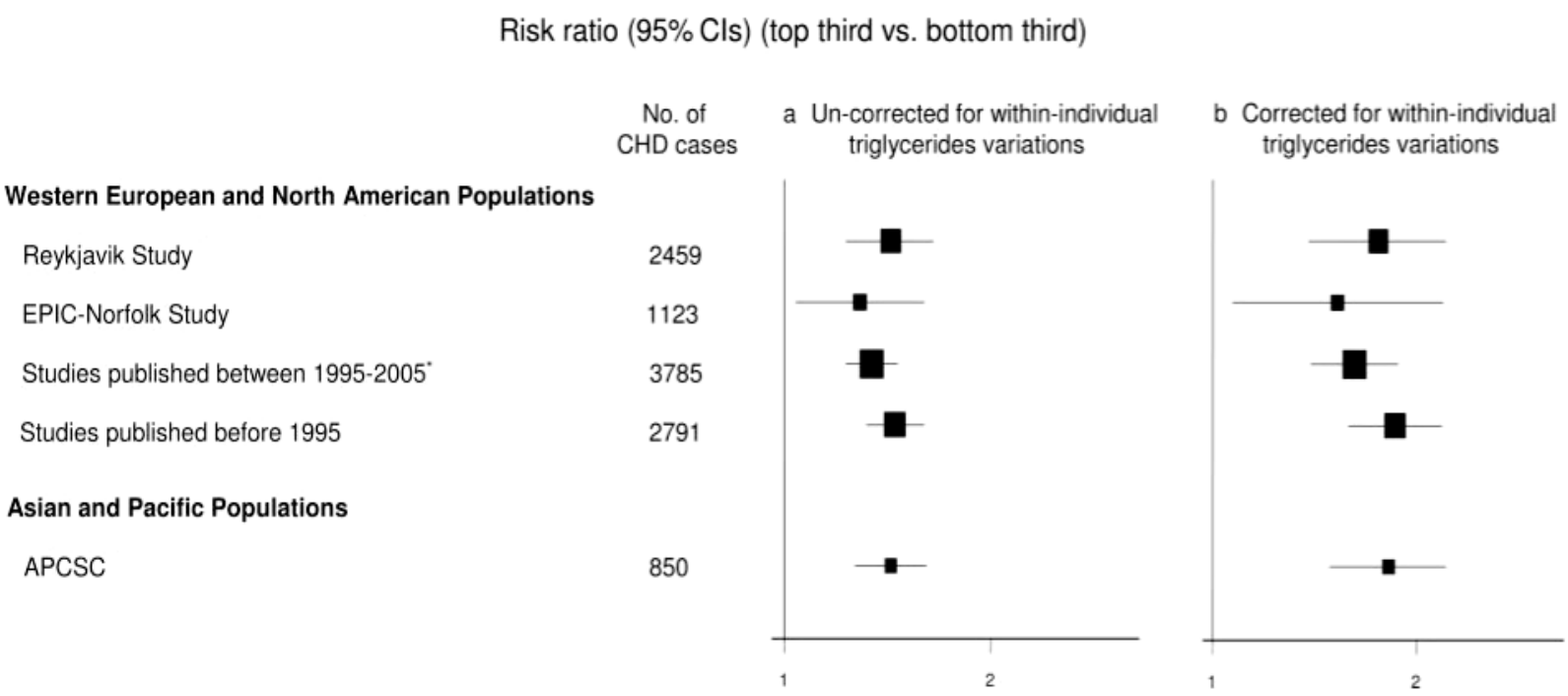
TG, Risk Factor for Coronary Heart Disease?

- Hokanson and Austins meta-analysis of prospective population-based studies
  - ❖ pooled analysis of 46,413 men enrolled in 16 studies
  - ❖ association between the serum triglyceride concentration and cardiovascular disease
  - ❖ univariate risk ratio (RR) for triglyceride of 1.32 (95 percent CI 1.26 to 1.39) for men
  - ❖ five studies of nearly 10,800 women were associated with a univariate RR of 1.76 (95 percent CI 1.50 to 2.07).
  - ❖ with adjustment for HDL and other risk factors, correlation was still significant

Hokanson JE, et al. J Cardiovasc Risk 1996;3:213-19

Triglycerides and Coronary Risk

Metanalysis with > 260.000 participants and over 10.000 cases of CHD



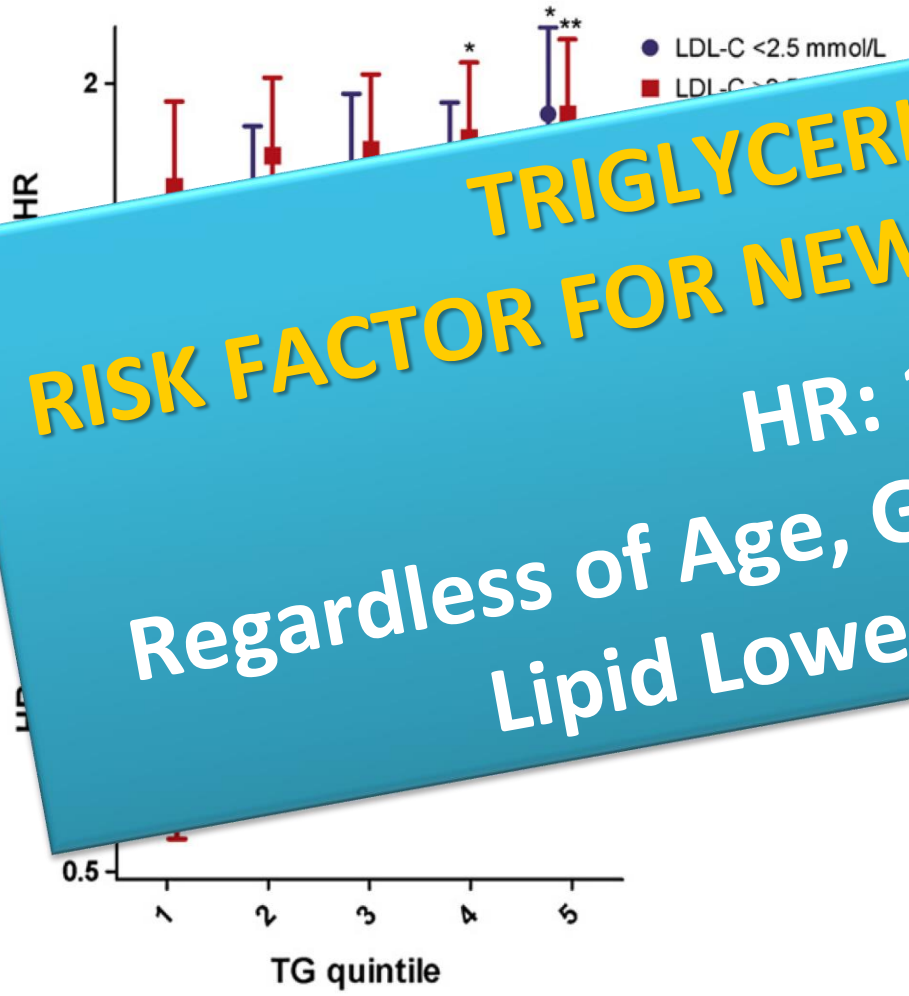
Available prospective studies of triglycerides and CHD in essentially general populations. APCSC indicates Asian and Pacific Cohort Studies Collaboration. *Includes 3 studies that were published before 1995 but were not included in the previous review.

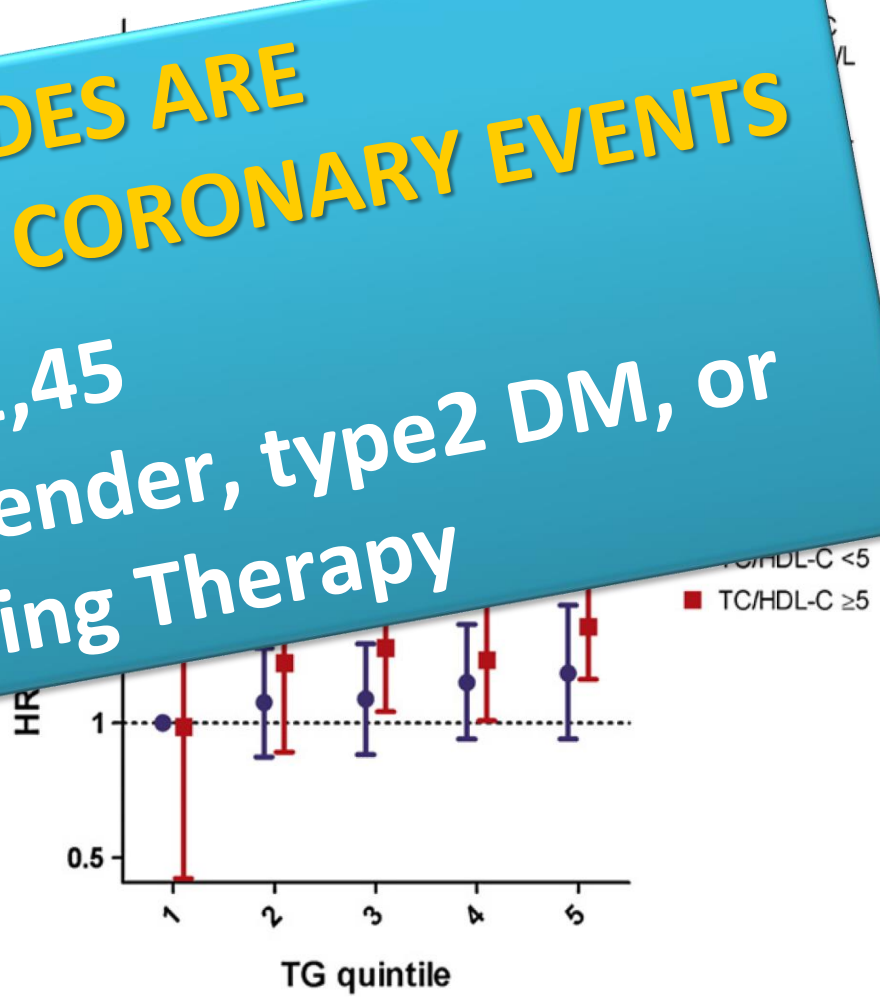
Sarwar N, et al. Circulation 2007;115:450–58

TG risk factor of recurrent vascular events independent of LDL or Non-HDL

n=5.731 pts with CVD, followed 5 yrs

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





TRIGLYCERIDES ARE RISK FACTOR FOR NEW CORONARY EVENTS

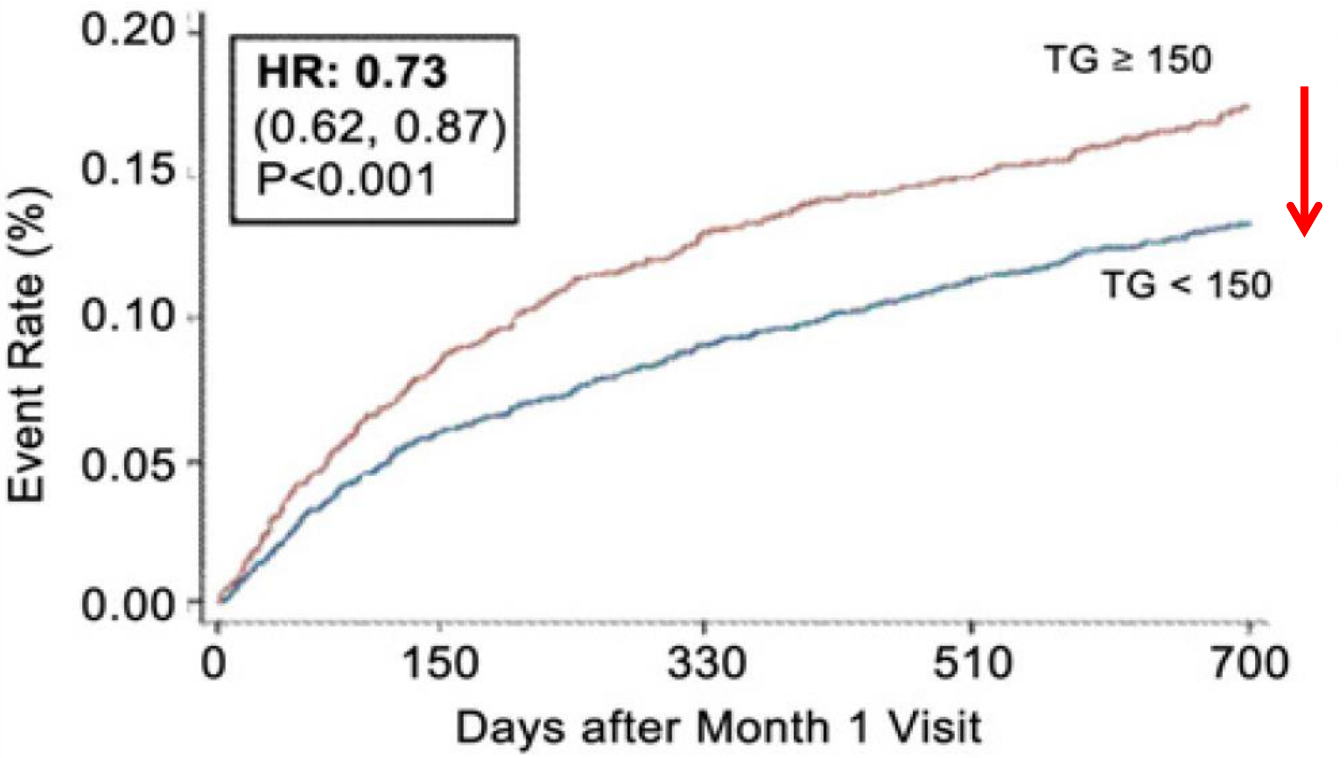
HR: 1,45

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

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

Triglycerides and Coronary Events

PROVE IT-TIMI 22 Trial



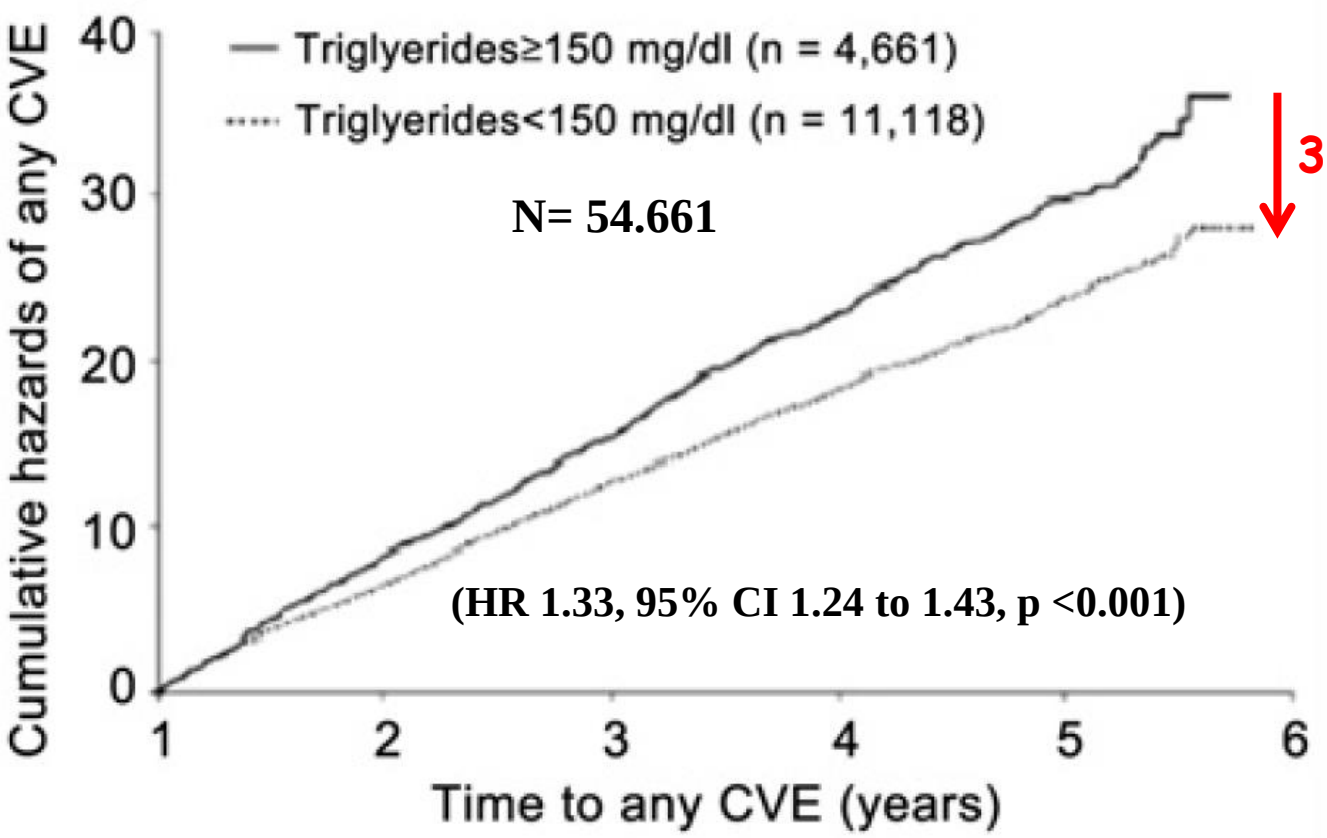
No. at Risk

TG ≥ 150	1157	1066	1017	659
TG < 150	2242	2119	2041	1278

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

Triglycerides and Coronary Events

TNT & IDEAL Trials



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

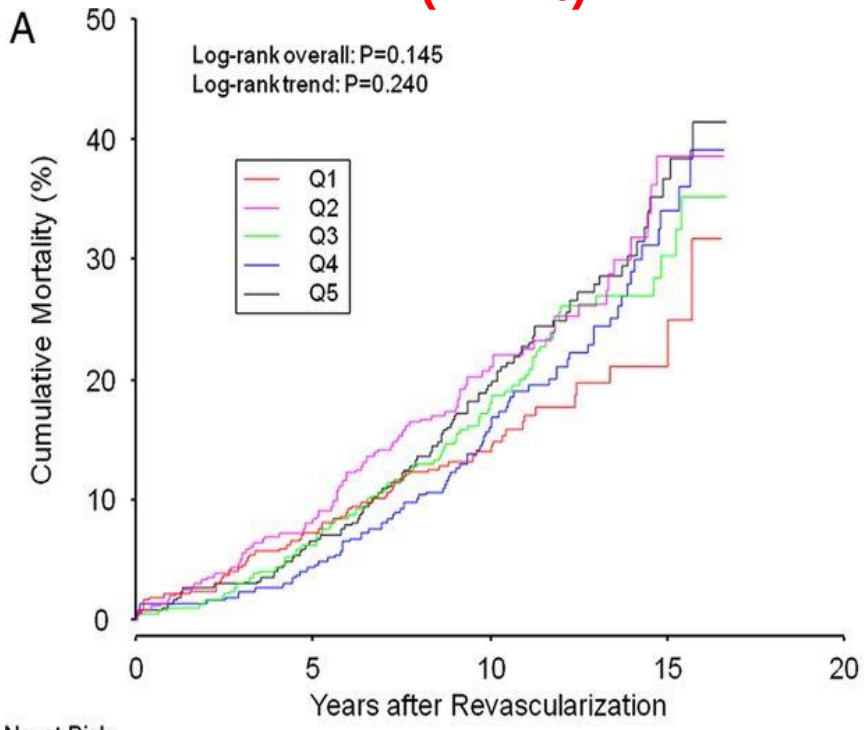
Predictive value reduces after HDL adjustment and disappears in multivariant analysis

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

Triglycerides and Mortality in CAD

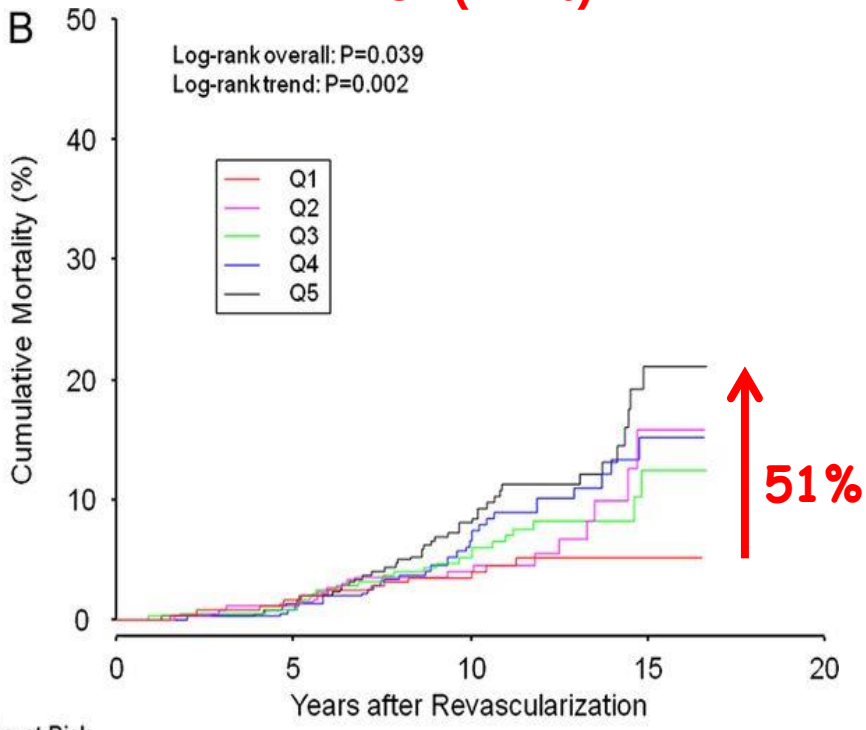
n = 1.836 pts with CAD after PTCA, followed >10 yrs

All cause Mortality
412 (22.4%)



No. at Risk				
Q1	369	340	183	20
Q2	359	327	176	17
Q3	369	343	220	33
Q4	370	351	207	38
Q5	369	341	225	38

Mortality due to Heart Disease
131 (7.2%)

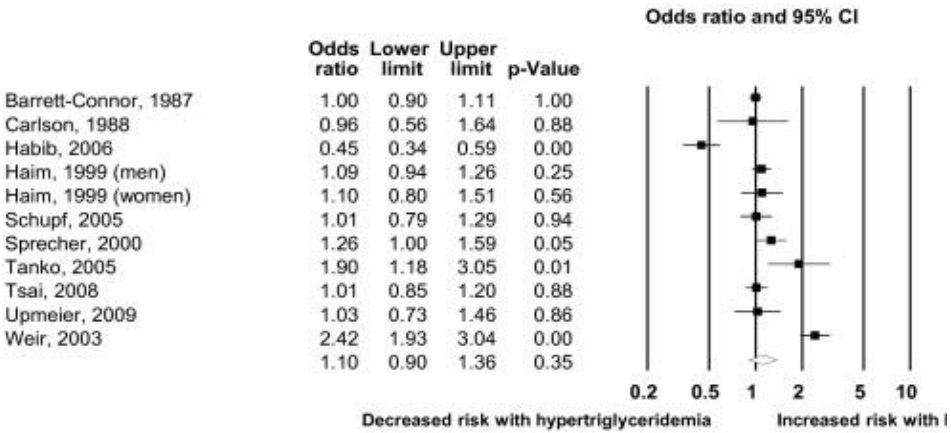


No. at Risk				
Q1	369	340	183	20
Q2	359	327	176	17
Q3	369	343	220	33
Q4	370	351	207	38
Q5	369	341	225	38

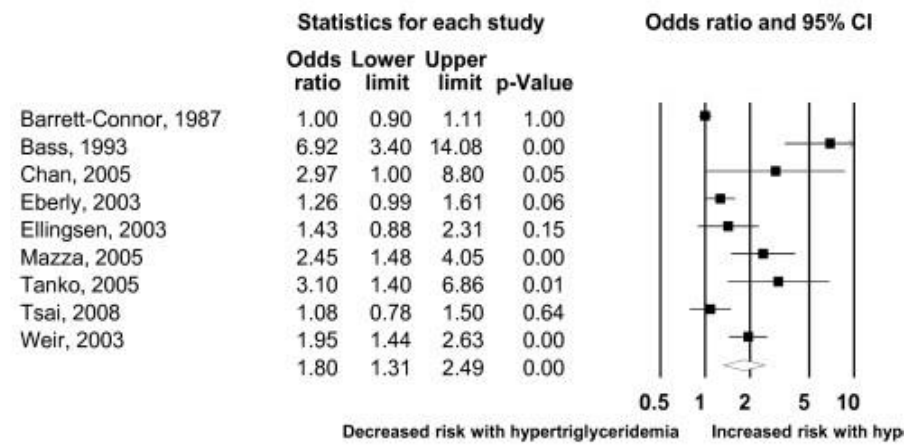
Kasai T et al. Heart 2013;99:22-29

Triglycerides, CVD and Pancreatitis

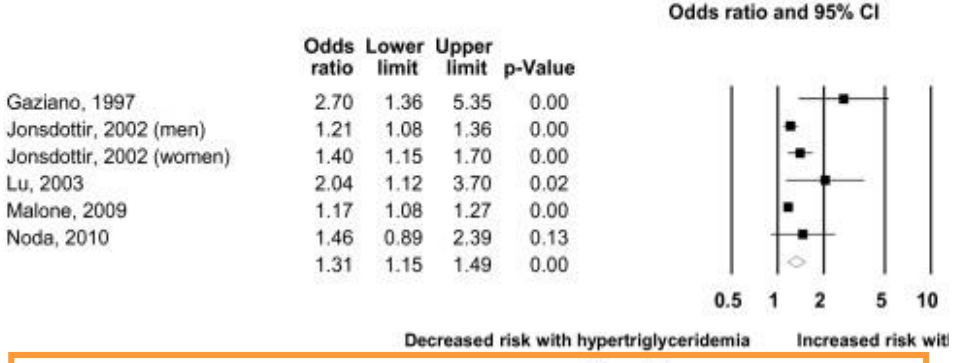
All-cause mortality



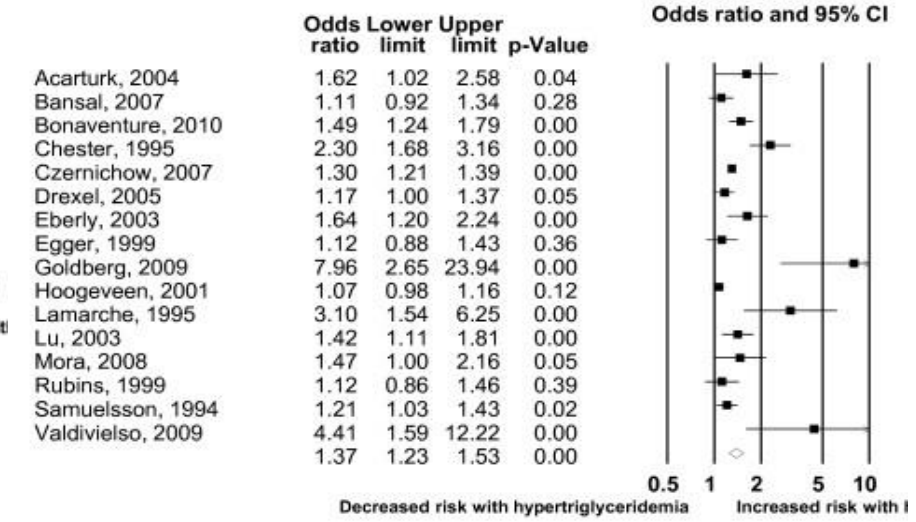
Cardiovascular death



Myocardial Infarction



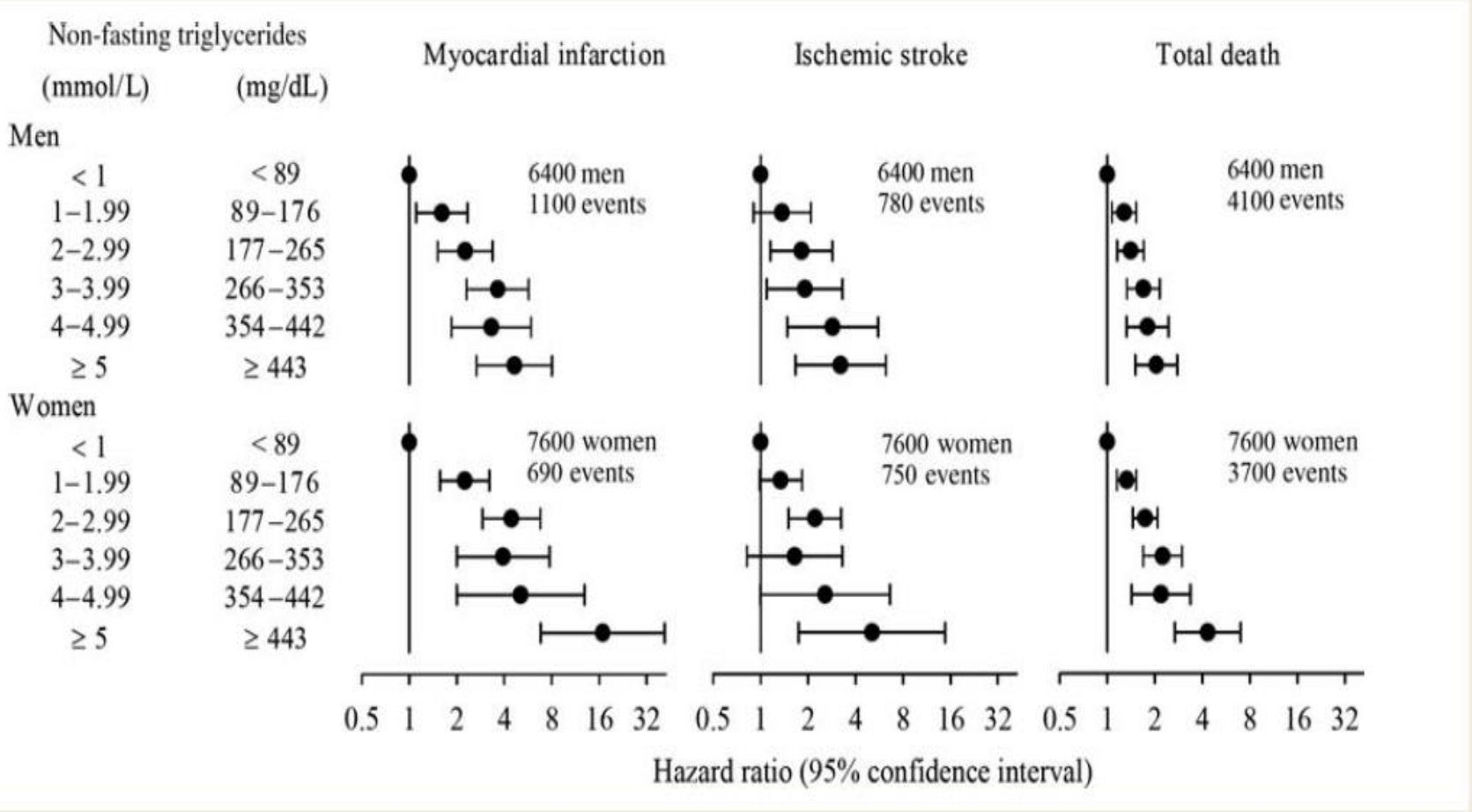
Cardiovascular events



Fasting hypertriglyceridemia was significantly associated with pancreatitis (OR: 3.96; 95% CI: 1.27-12.34)

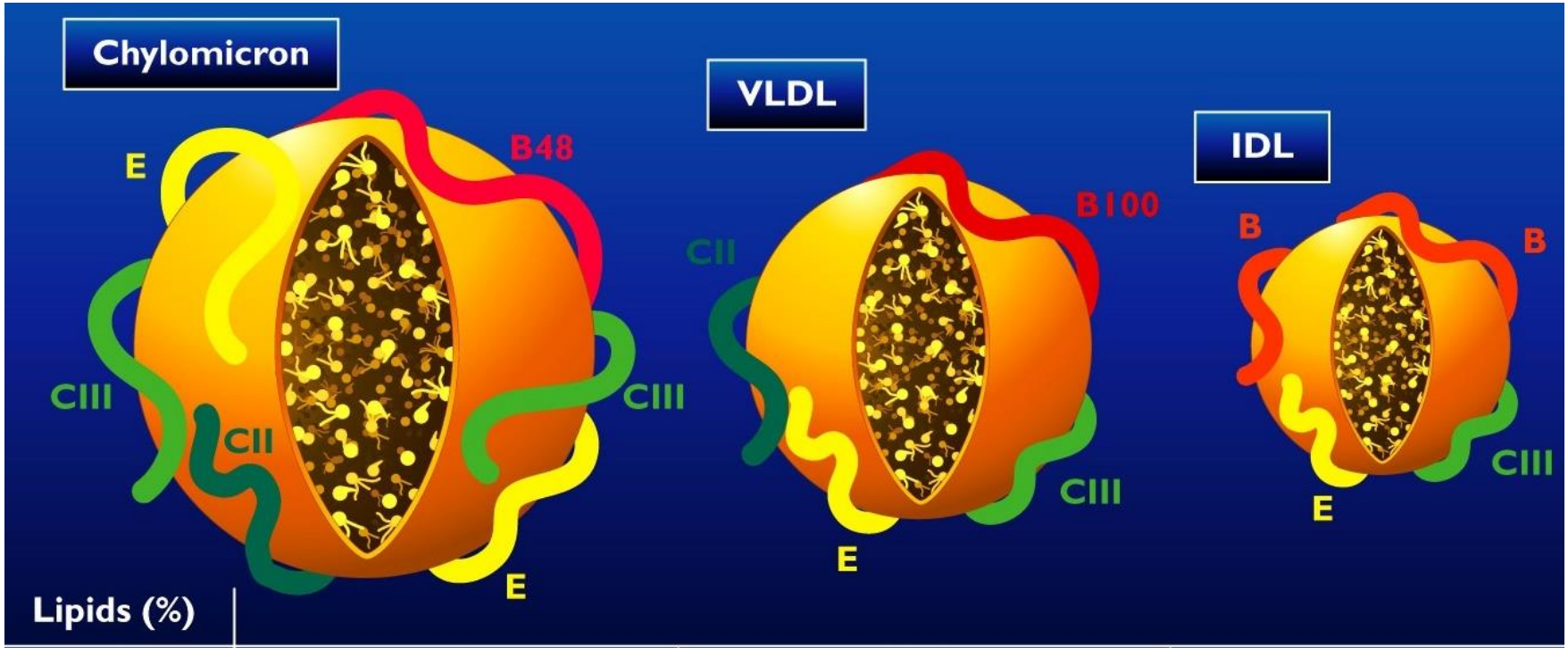
Murad MH, et al. BMC Endocr Disord 2012;12:2

Non-fasting Triglycerides, risk factor for CAD, CVD & Death



Evidences on TG and HDLc. Eur Heart J 2011;32:1345-61

Triglyceride-rich Lipoproteins



Lipids (%)			
TG	85–90	50–60	18–25
Cholesterol	2–6	14–22	30–38
Phospholipid	6–9	12–20	20–28
Size (Å)	800–5000	300–800	200–350

Triglyceride and Small and Dense LDLc

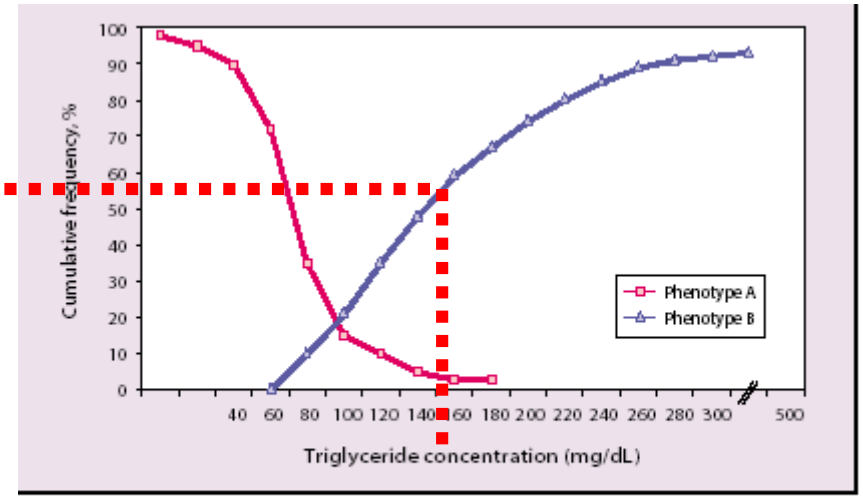
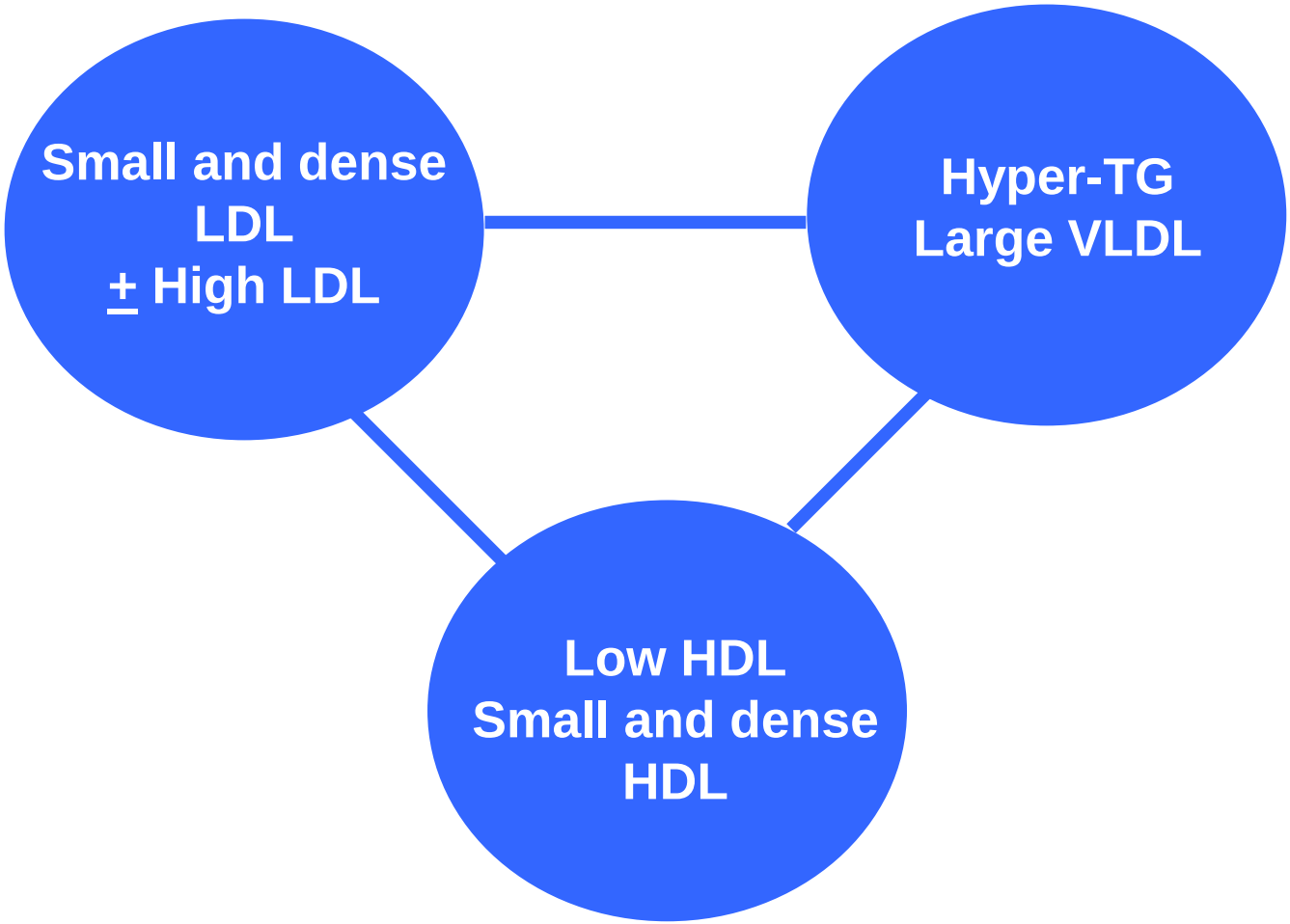


Figure 7. *Low-density lipoprotein (LDL) phenotype can often be determined by knowing the triglyceride concentration. With triglyceride levels less than approximately 70 mg/dL, nearly all individuals have large, buoyant LDL (phenotype A), but with triglyceride levels greater than approximately 150 mg/dL, small, dense LDL particles (phenotype B) predominate. Adapted with permission from Austin et al.*[19]

Austin M, et al. Circulation. 1990;82:495-506.

Dyslipidemia in Diabetes Mellitus
(60% of cases)

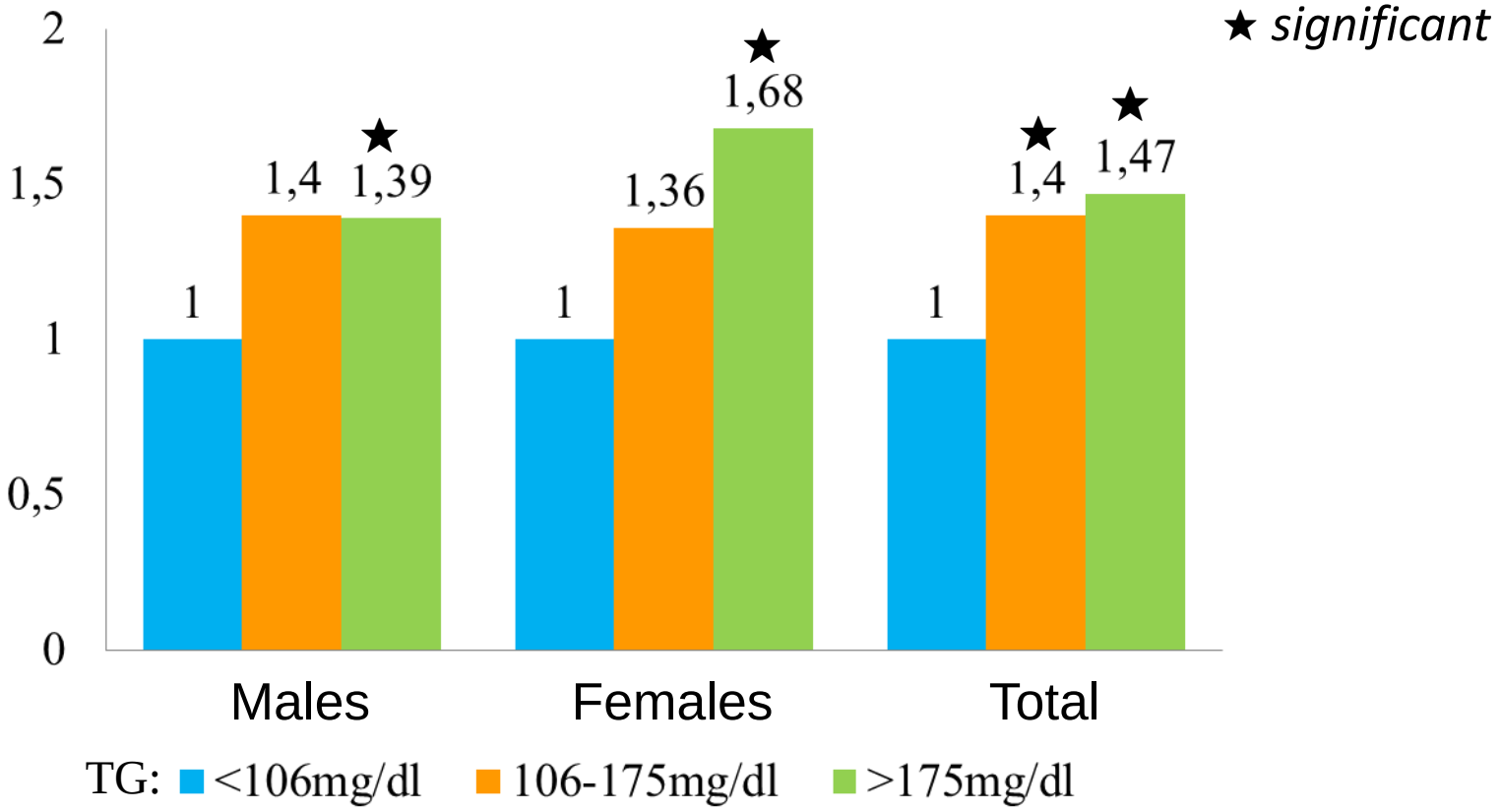


Triglycerides in type 2 Diabetes Mellitus

Strong Heart Study

2.108 DM
vs
2.060 Ctrls

Flw-up: 9 yrs

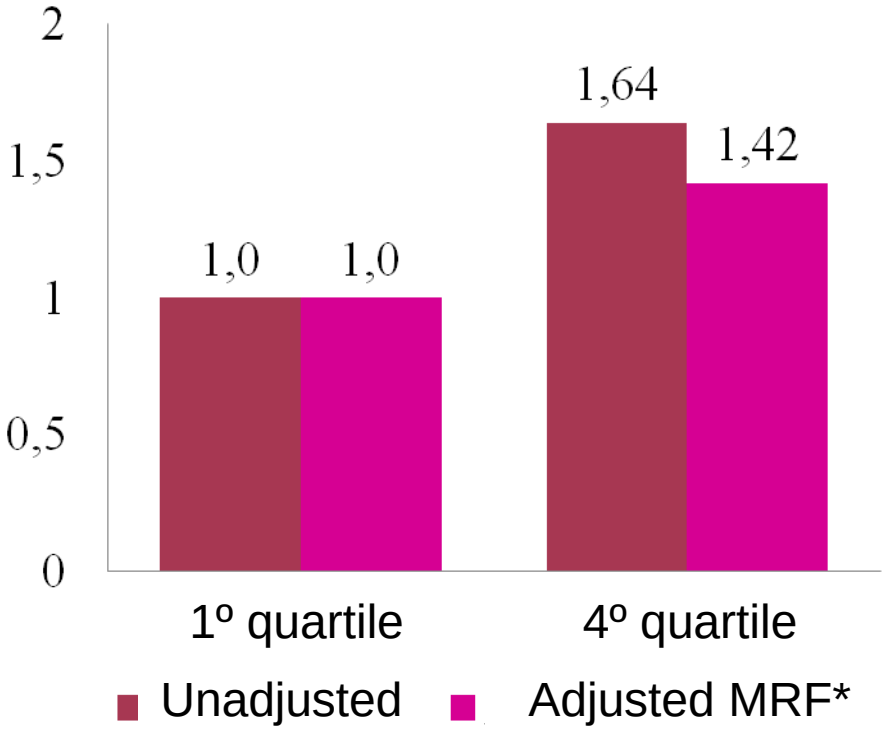


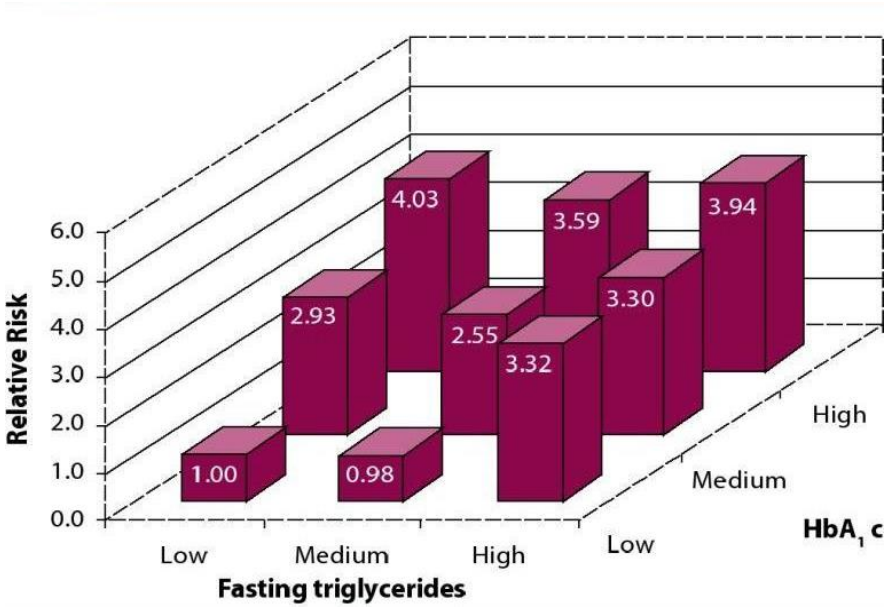
Adjusted by age, BMI, smoking, SBP, HbA1c, fibrinogen, insulin & albumin/creat ratio

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

Triglycerides are risk factor for CAD in type2 Diabetes Mellitus

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





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

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

Postprandial TG in type2 DM

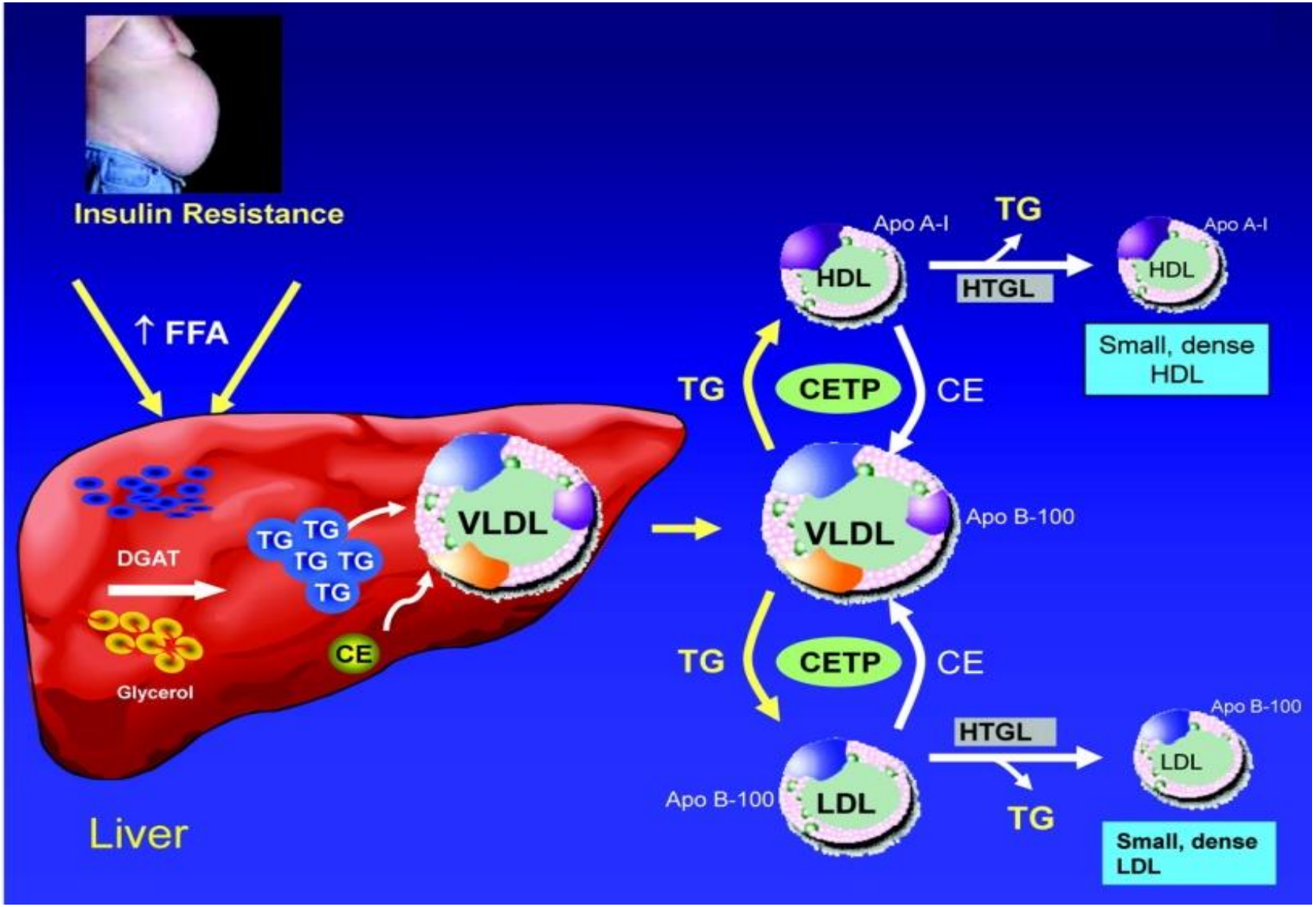
1.337 type2 DM patients followed 8 yrs

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

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

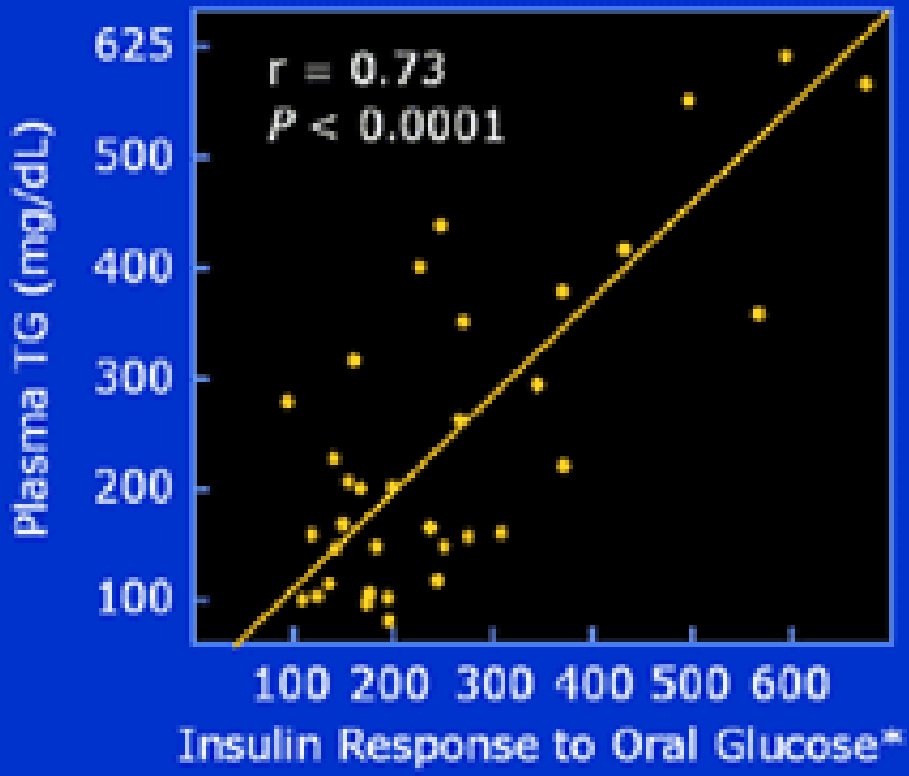
Van Dieren S, et al. Diabetologia 2011;54:73–77

Triglycerides & Insulin Resistance



Triglycerides & Insulin Resistance

Relation Between Insulin Resistance and Hypertriglyceridemia



* Total area under 3-hour response curve (mean of 2 tests).

Olefsky JM et al. *Am J Med*. 1974;57:551-560.

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Hypertriglyceridemia in AHA/ACC Guideline

Recommendations for Hypertriglyceridemia		
COR	**LOE**	**Recommendations**
I	B-NR	In adults 20 years of age or older with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175 to 499 mg/dL [1.9 to 5.6 mmol/L]), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides.
IIa	B-R	In adults 40 to 75 years of age with moderate or severe hypertriglyceridemia and ASCVD risk of 7.5% or higher, it is reasonable to reevaluate ASCVD risk after lifestyle and secondary factors are addressed and to consider a persistently elevated triglyceride level as a factor favoring initiation or intensification of statin therapy (see Section 4.4.2.).

Hypertriglyceridemia in AHA/ACC Guideline

Recommendations for Hypertriglyceridemia		
COR	**LOE**	**Recommendations**
IIa	**B-R**	**In adults 40 to 75 years of age with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.6 mmol/L]) and ASCVD risk of 7.5% or higher, it is reasonable to address reversible causes of high triglyceride and to initiate statin therapy.**
IIa	**B-NR**	**In adults with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.7 mmol/L]), and especially fasting triglycerides ≥1000 mg/dL (11.3 mmol/L)), it is reasonable to identify and address other causes of hypertriglyceridemia), and if triglycerides are persistently elevated or increasing, to further reduce triglycerides by implementation of a very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and, if necessary to prevent acute pancreatitis, fibrate therapy.**

AHA SCIENCE ADVISORY

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

A Science Advisory From the American Heart Association

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 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).
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.
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.

Table 9 Impact of specific lifestyle changes on lipid levels

	Magnitude of the effect	Level of evidence	References
Lifestyle interventions to reduce TC and LDL-C levels			
Reduce dietary saturated fat	+++	A	63
Reduce dietary trans fat	+++	A	64
Increase dietary fibre	++	A	65
Lifestyle interventions to reduce TG levels			
Reduce excessive body weight	+++	A	68
Reduce alcohol intake	+++	A	74
Reduce intake of mono- and disaccharides	+++	A	75, 76
Increase habitual physical activity	++	A	77
Reduce total amount of dietary carbohydrate	++	A	78
Utilize supplements of *n*-3 polyunsaturated fat	++	A	79
Replace saturated fat with mono- or polyunsaturated fat	+	B	63
Lifestyle interventions to increase HDL-C levels			
Reduce dietary trans fat	+++	A	64
Increase habitual physical activity	+++	A	77
Reduce excessive body weight	++	A	68
Reduce dietary carbohydrates and replace them with unsaturated fat	++	A	78
Use alcohol with moderation	++	B	80
Among carbohydrate-rich foods prefer those with low glycaemic index and high fibre content	+	C	-
Quit smoking	+	B	81
Reduce intake of mono- and disaccharides	+	C	-

Table 16 Recommendations for drug treatment of HTG

Recommendations	Class[a]	Level[b]	Ref[c]
In particular high risk patients (see above), lowering of HTG by using the following drugs:			
is recommended: fibrates	I	B	127
should be considered: nicotinic acid	IIa	B	131
nicotinic acid + laropiprant	IIa	C	-
n-3 fatty acids	IIa	B	135, 136
statin + nicotinic acid[d]	IIa	A	142, 145
statin + fibrate[d]	IIa	C	-
may be considered: combinations with *n*-3 fatty acids[e]	IIb	B	146

Table 18 Summary of the efficacy of drug combinations for the management of mixed dyslipidaemias

• In combined dyslipidaemia an increase of HDL-C and a decrease of TG, on top of the LDL-C reduction that can be achieved with a statin, may be considered. Therefore a combination of statin with nicotinic acid can be considered, but the adverse effect of flushing may affect compliance.
• A combination of statins with fibrates can also be considered while monitoring for myopathy, but the combination with gemfibrozil should be avoided.
• If TG are not controlled by statins or fibrates, prescription of *n*-3 fatty acids may be considered to decrease TG further, and these combinations are safe and well tolerated.

HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; TG = triglyceride.

Table 26 **Recommendations for treatment of dyslipidaemia in HF or valvular disease**

Recommendations	Class[a]	Level[b]	Ref[c]
n-3 PUFAs 1 g/day may be considered to be added to optimal treatment in patients with HF (NYHA classification II-IV).	IIb	B	184
Cholesterol-lowering therapy with statins is not indicated in patients with moderate to severe HF (NYHA classification III–IV).	III	A	36,39
Lipid-lowering treatment is not indicated in patients with valvular disease without CAD.	III	B	38

2017 Taiwan Lipid Guideline

Recommendation

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

However, under statin control of LDL-C, all clinical trials with add-on therapy of fibrate, niacin, or CETP inhibitor, that decreased TG and increased HDL-C could not further reduce cardiac risk compared with placebo.

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Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks

Meta-analysis of 10 Trials Involving 77 917 Individuals

JAMA Cardiol. 2018 Mar; 3(3): 14–22.

Question

補充海洋來源的Omega-3脂肪酸是否與心血管疾病高危人群中致死性或非致死性冠心病的減少有關？

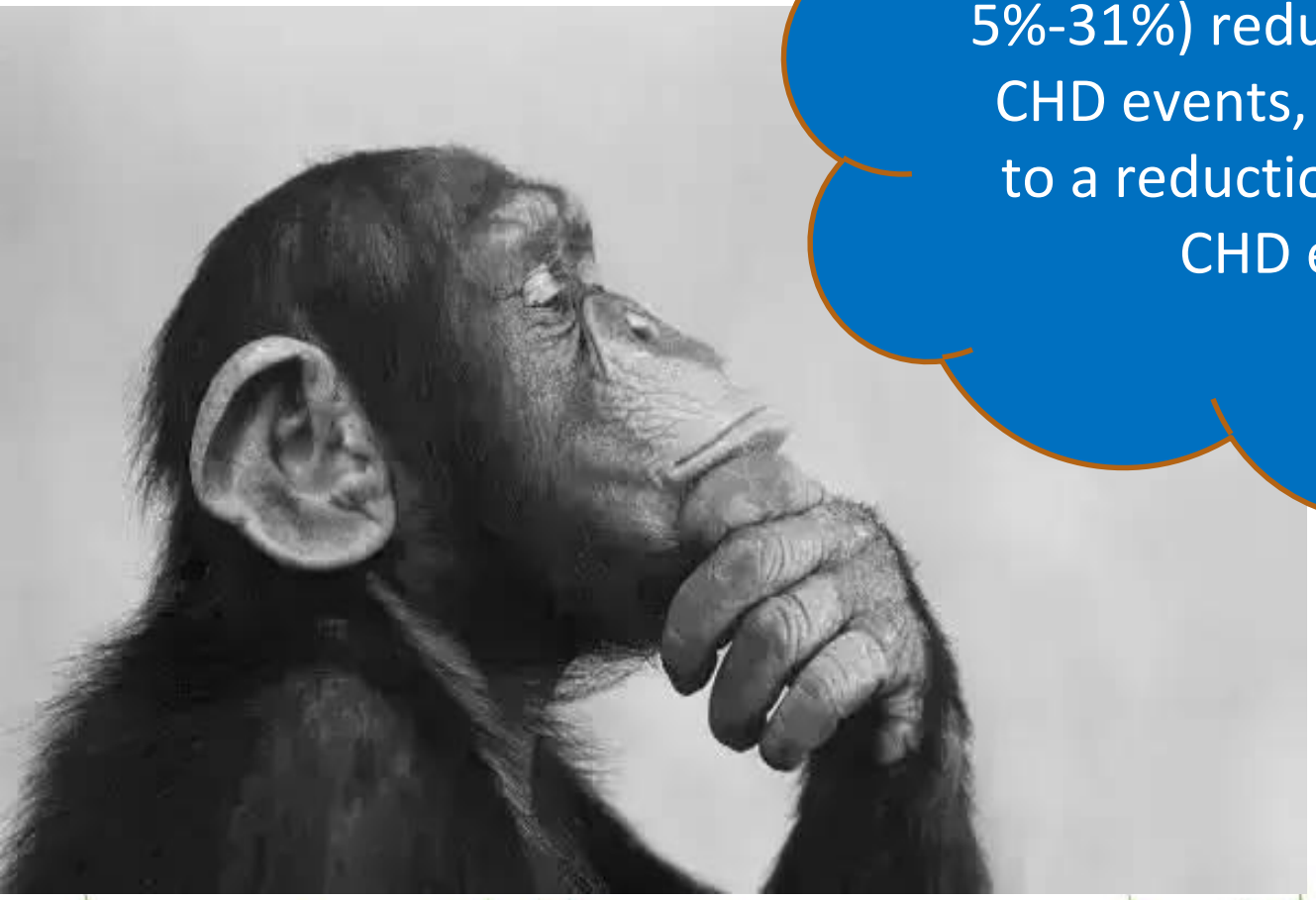
Findings

共77917名參與者的10項試驗的meta-analysis 分析，補充海洋來源的ω-3脂肪酸平均為4。4年與致死性或非致死性冠心病或任何主要血管事件的減少無顯著相關性。

GISSI-Prevenzione trial
reported a 14% reduction in major vascular events, chiefly owing to an 11% reduction in cardiac deaths.

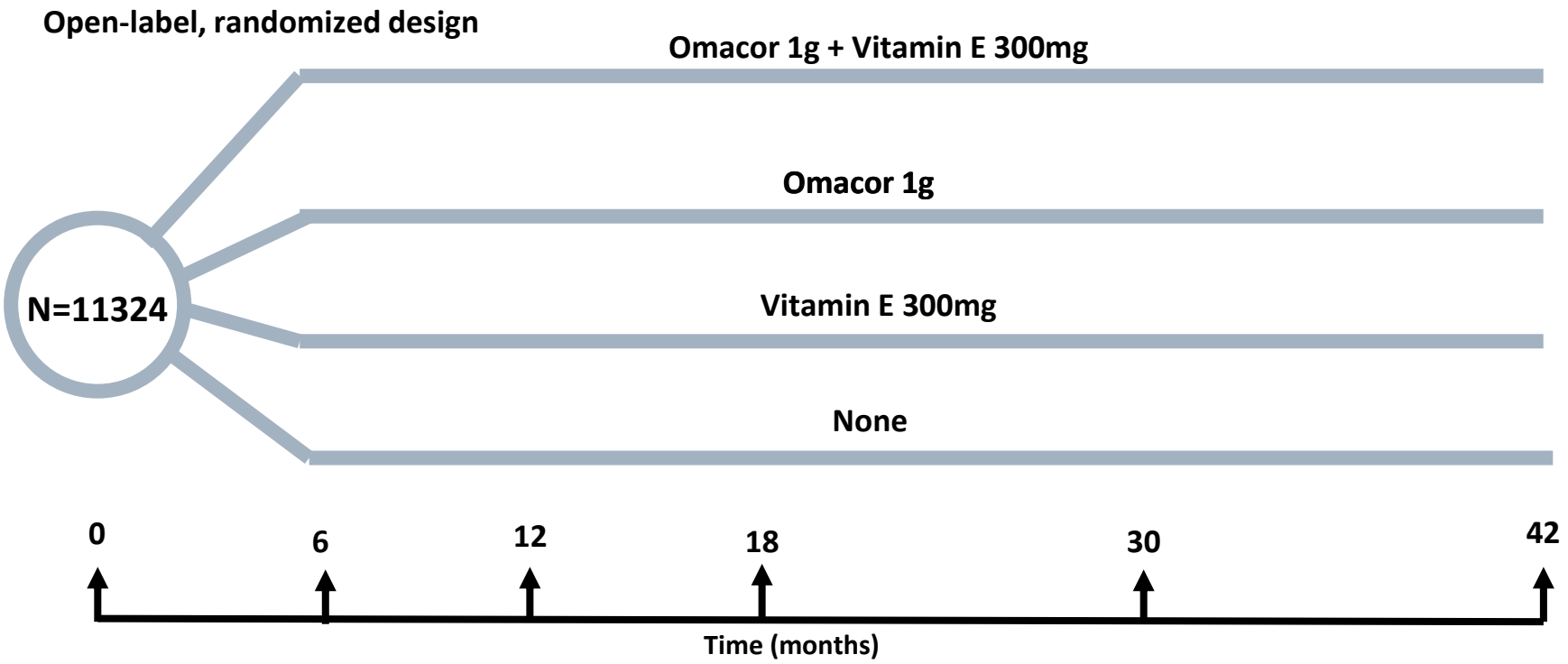
JELIS trial

reported a 19% (95% CI, 5%-31%) reduction in major CHD events, chiefly owing to a reduction in nonfatal CHD events



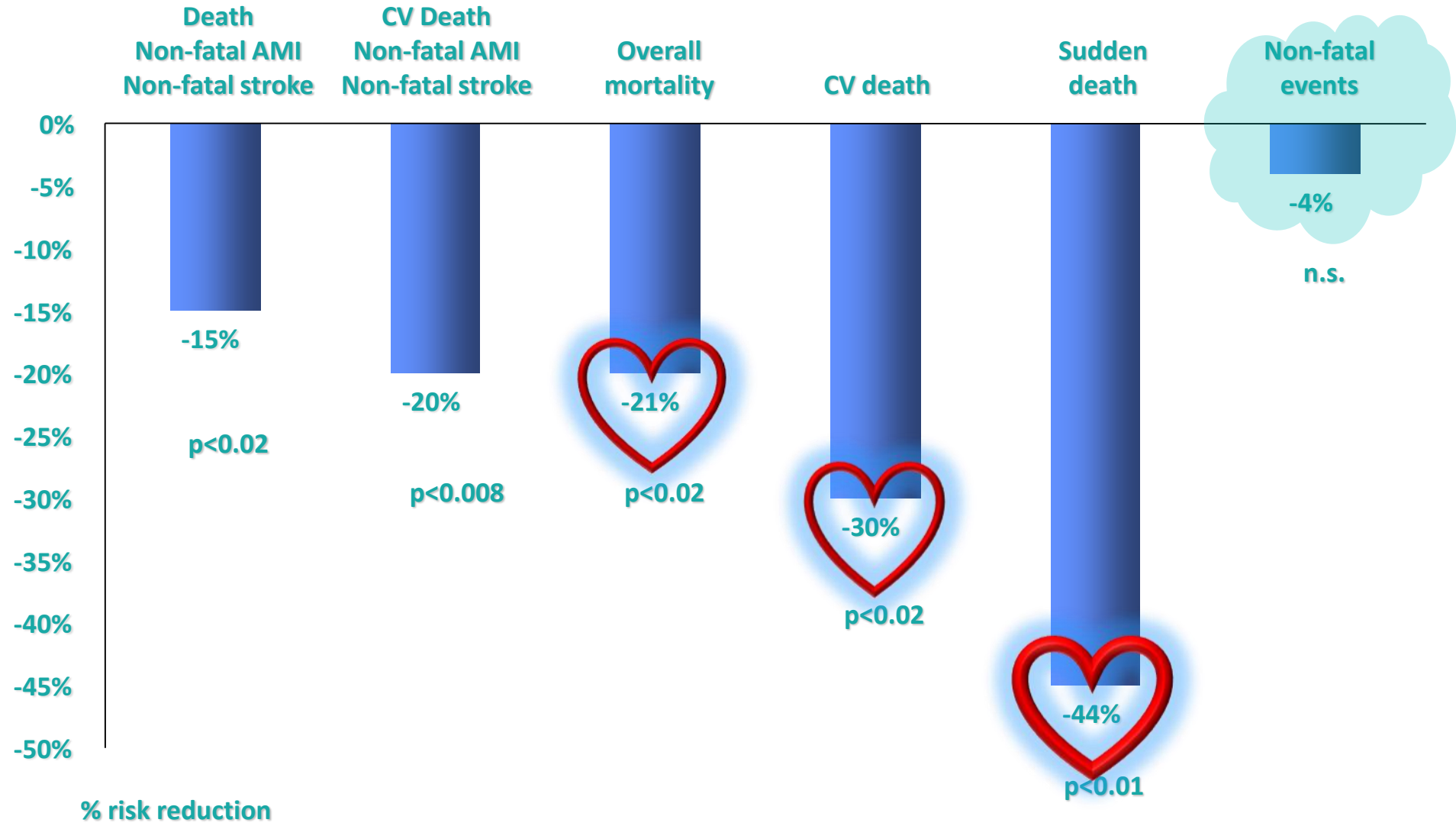
It is unclear whether differences in inclusion criteria for **prior diseases**, **concomitant use of statins**, or **other secondary prevention treatments** may explain some of the conflicting results of individual trials

GISSI-Prevention trial



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

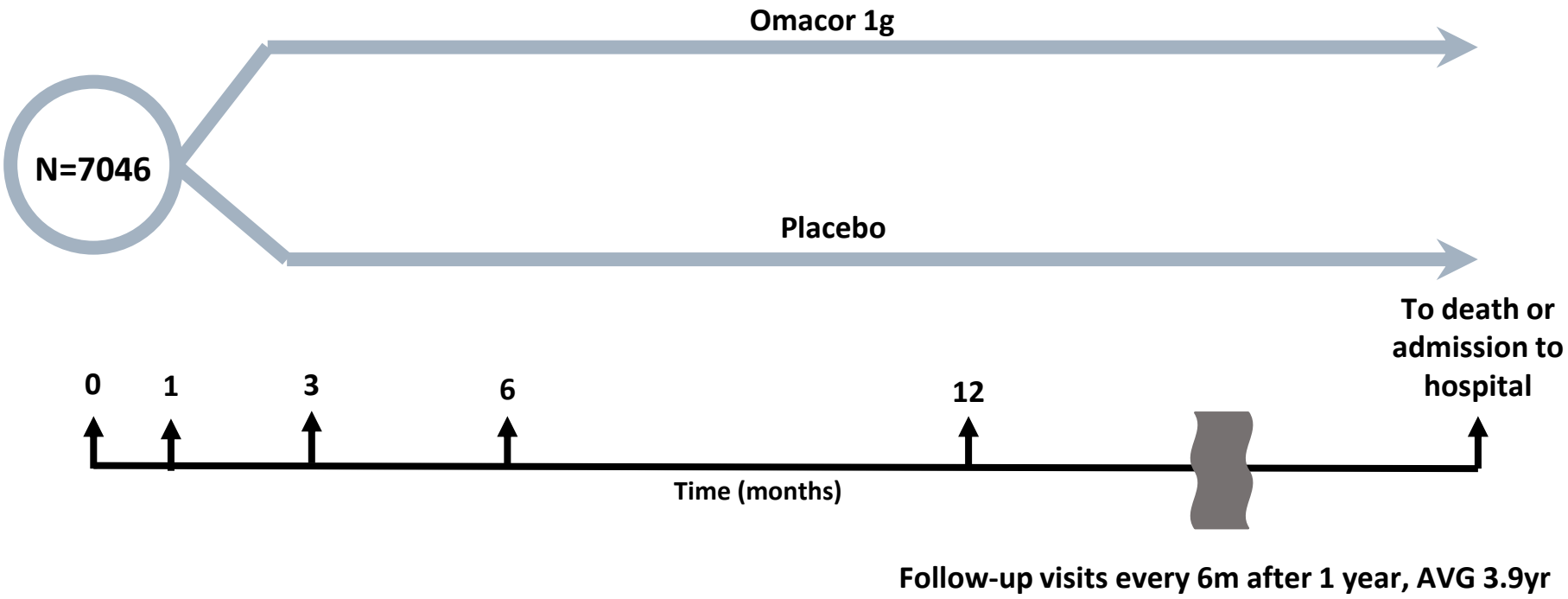
GISS-Preventation臨床實驗發現，心肌梗塞患者每天一顆Omacor能大幅降低死亡率



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

GISSI-HF trial

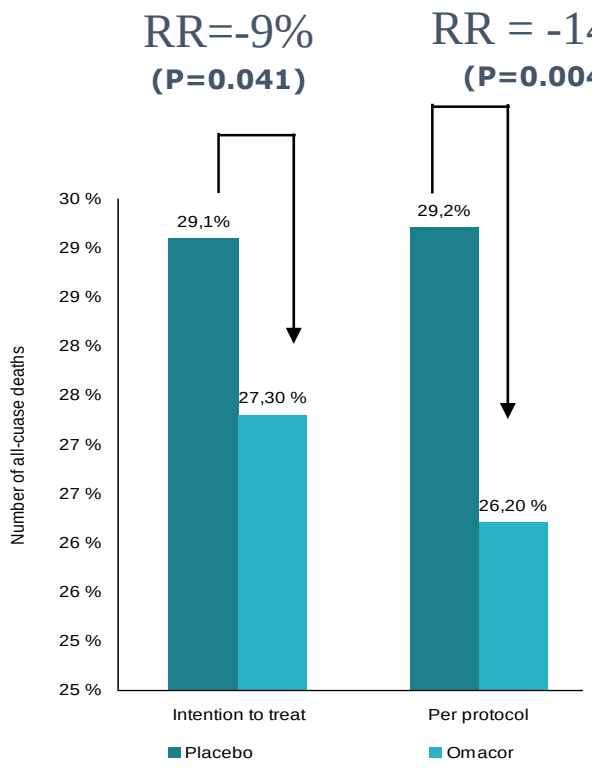
Effect of n-3 polyunsaturated fatty acids in patients with **chronic heart failure** (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial.



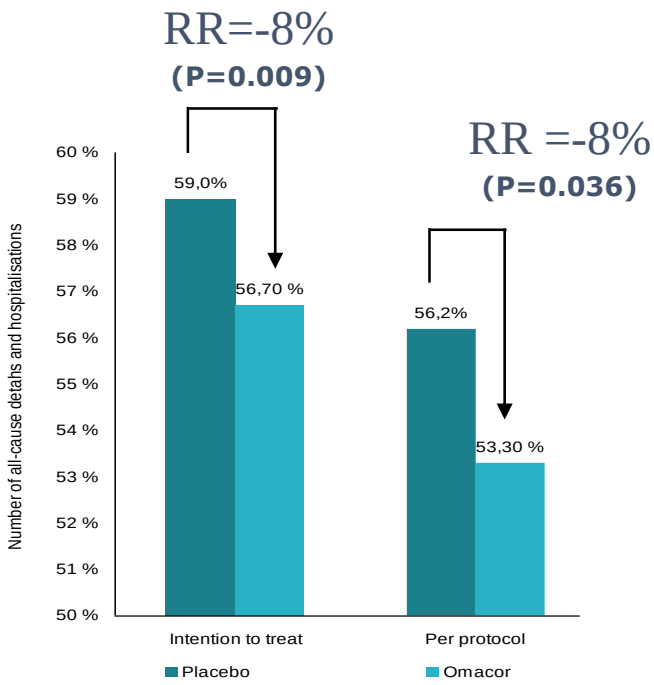
Lancet. 2008 Oct 4;372(9645):1223-30.

GISSI-HF 臨床實驗發現: OMACOR可降低CHF約9%死亡率

Number of all-cause death

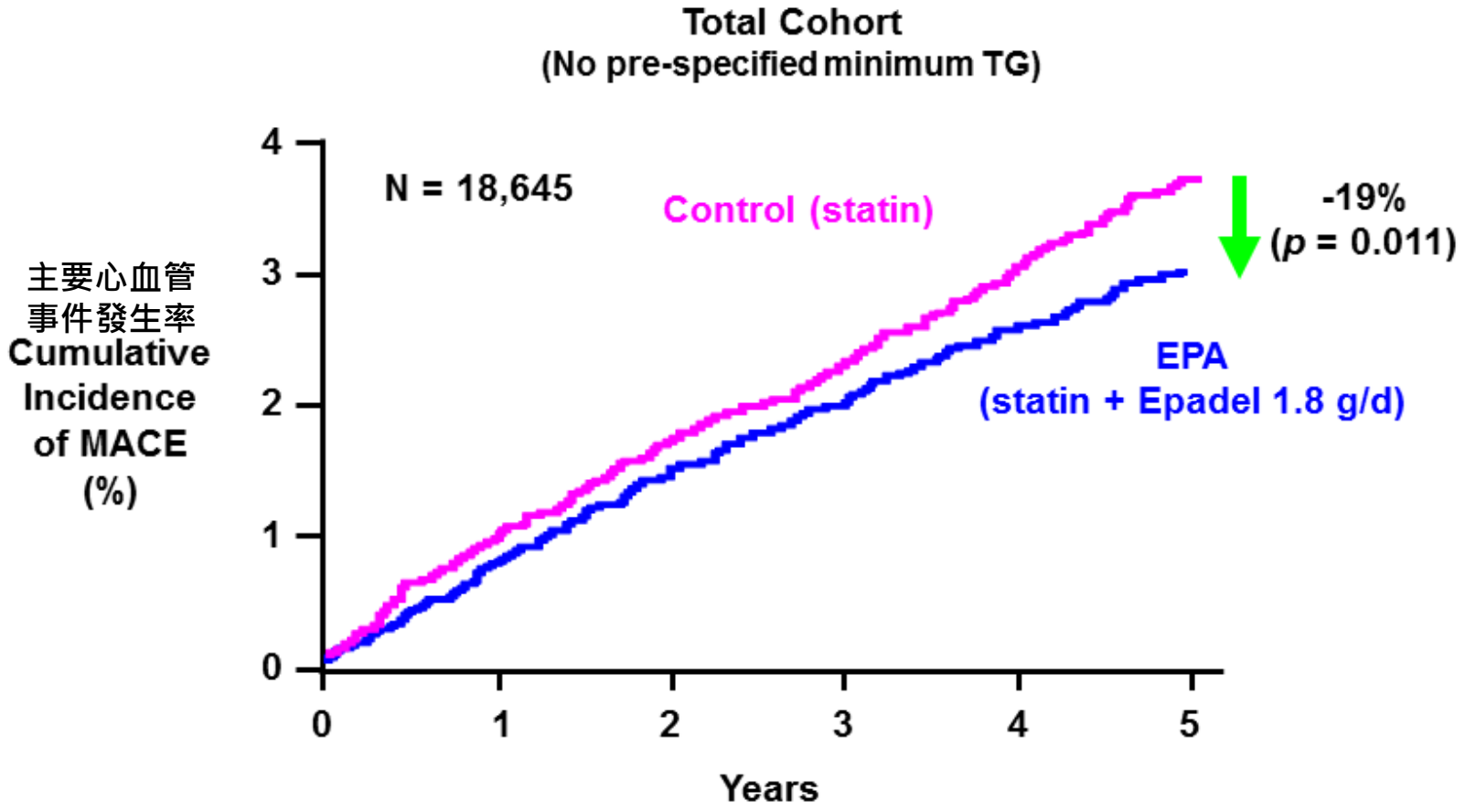


Number of all-cause death & hospitalisations



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

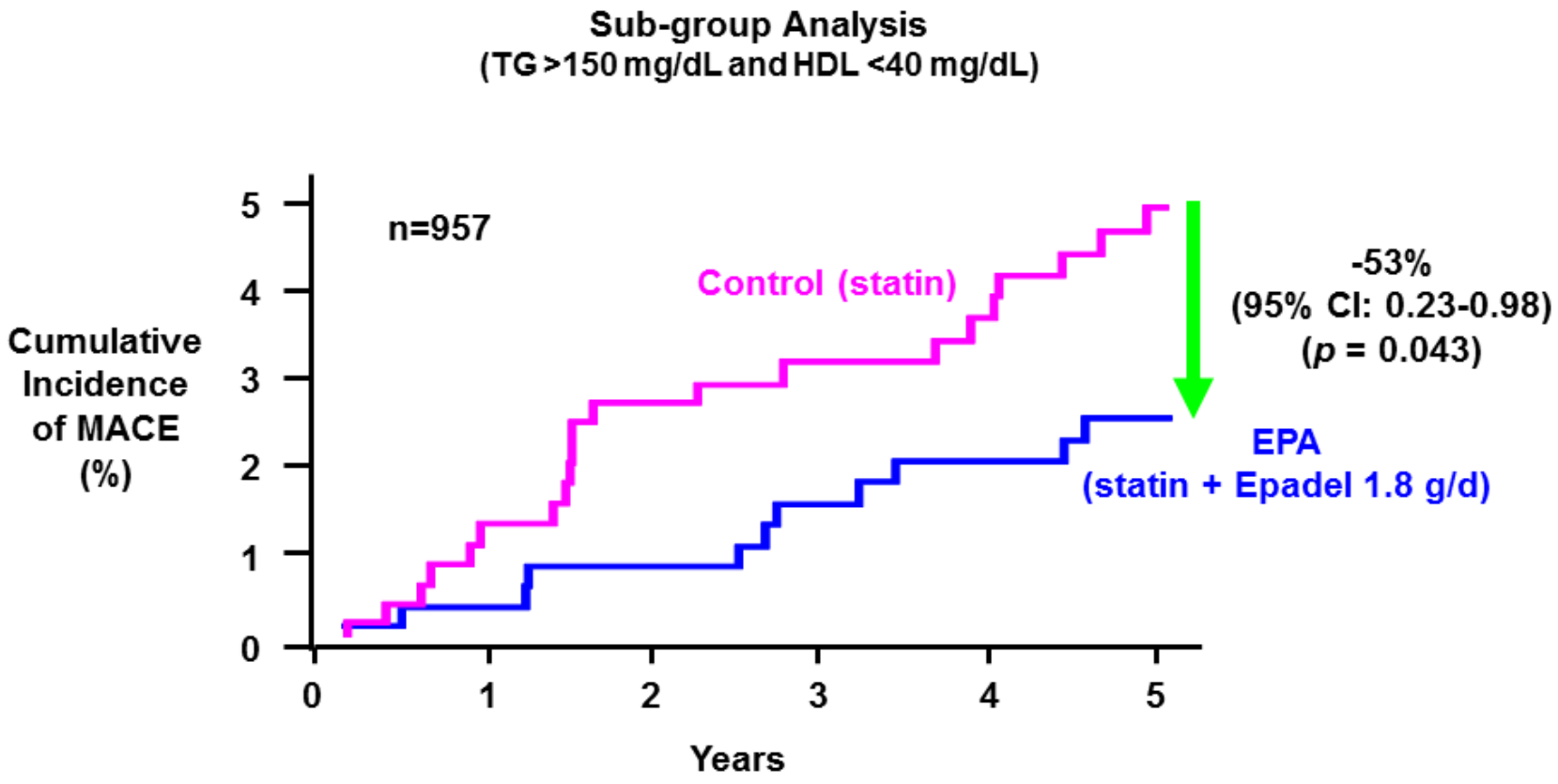
JELIS Study發現，EPA可能有預防心血管疾病的效果(Primary prevention)



AVG 4.6yr

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

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



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

REDUCT-IT (Nov 2018)

The NEW ENGLAND JOURNAL of MEDICINE

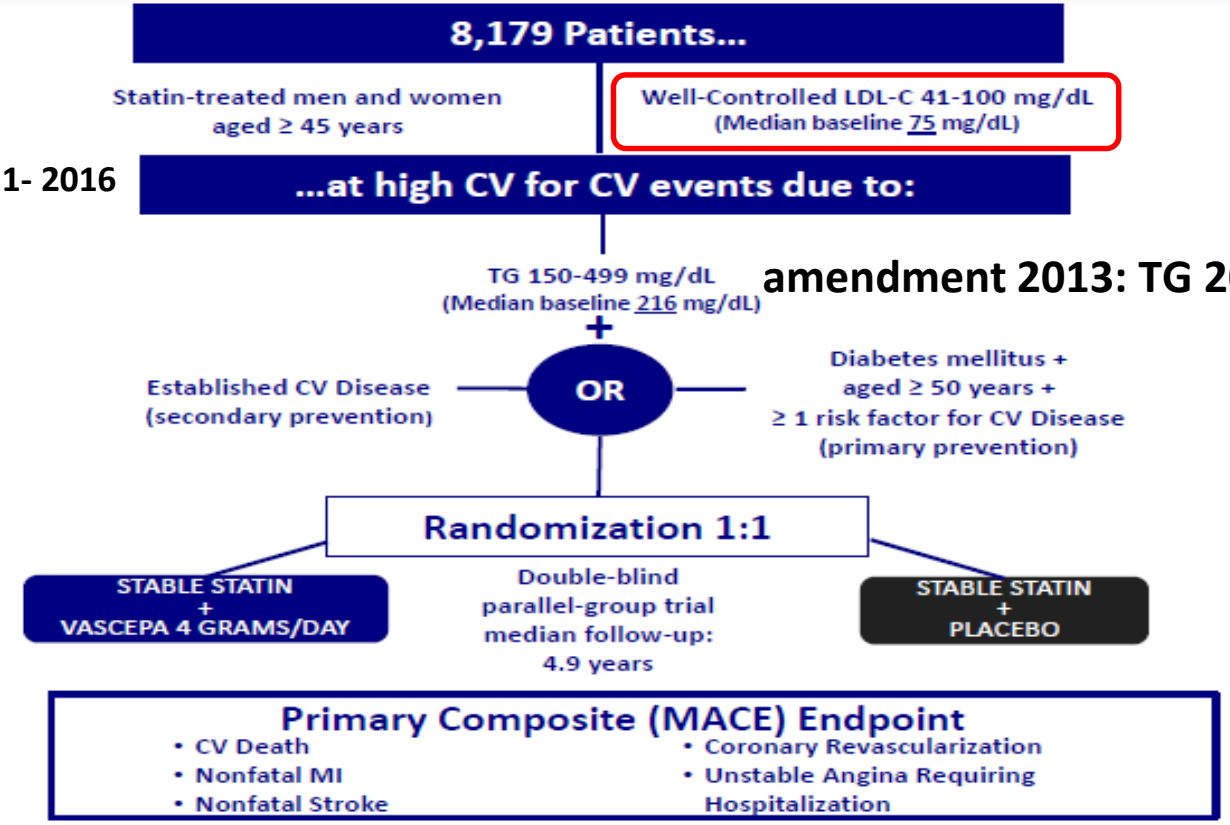
ORIGINAL ARTICLE

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

AMARIN



Study conduct : 2011- 2016

amendment 2013: TG 200 -499 mg/dL

MACE=major adverse cardiovascular event

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

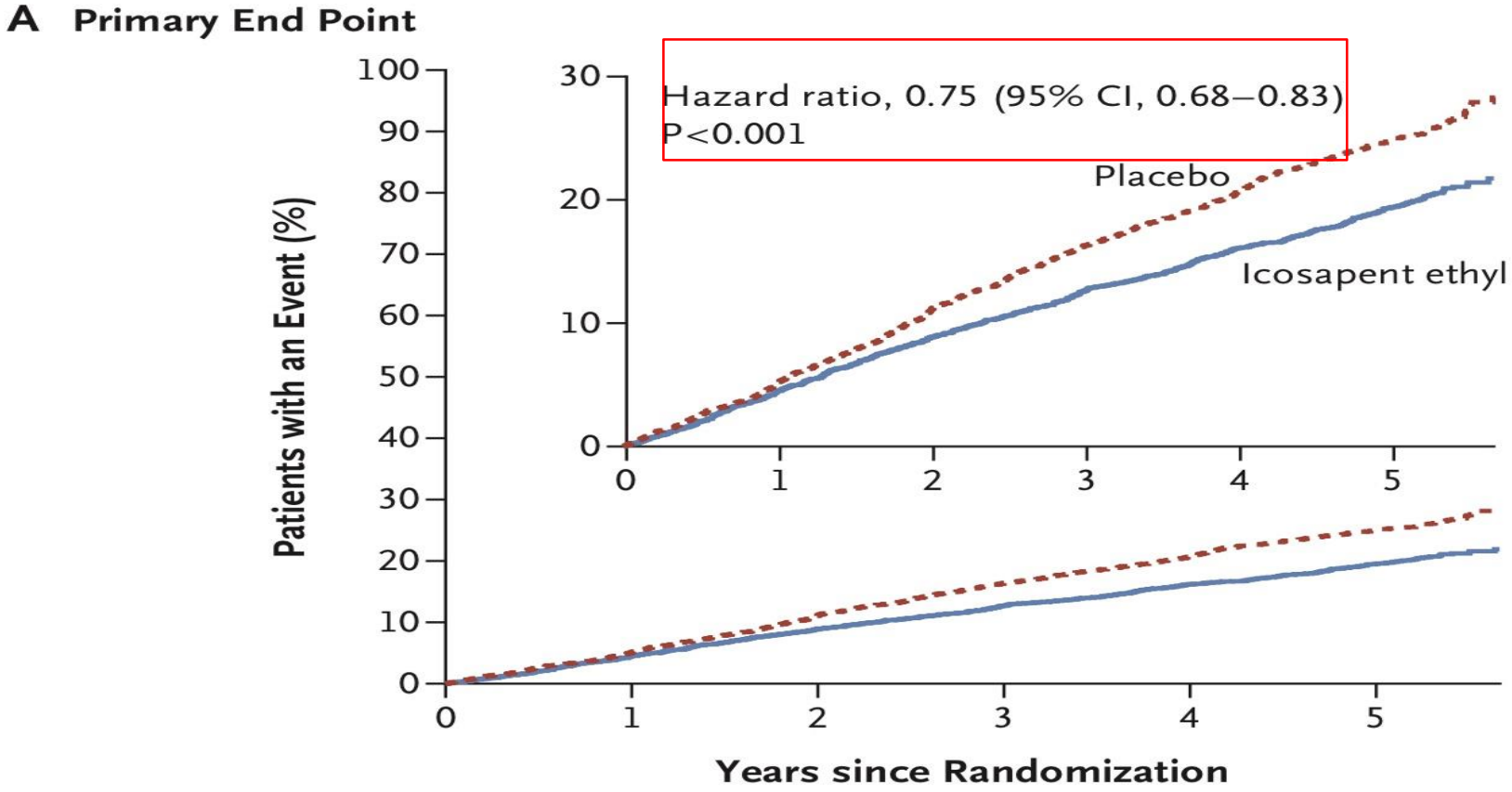
Comments

- 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)

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

November 10, 2018, at NEJM.org

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



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℞ Omega-3臨床試驗一覽及分析

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

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

當LDL達標後，該持續降低LDL還是處理殘餘風險？？？

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.


PLUS
Il Sole 24 ORE
GUIDA
I MERCATI • I FONDI • IL

結語

- 4g的n-3藥物可以有效降低TG，但須鑑別診斷其他致病原因(如甲狀腺功能低下或是糖尿病控制不佳)，且處方前應先改變生活型態
- 目前有EPA+DHA以及純EPA兩種n-3藥物，因缺乏直接比較的研究，目前無法建議何者為佳
- 民眾不應自行使用非藥物魚油來治療疾病，因為FDA從未審閱或是核准任何一種食品魚油

1841 Sir James Clark Ross discovers the Ross Sea on HMS Erebus and HMS Terror, along with Ross Island, the Ross Ice Barrier and Mt Erebus

1901 Captain Robert Falcon Scott leads the British National Antarctic Expedition on HMS Discovery, erecting the Discovery hut at Hut Point in McMurdo Sound

1902 Scott Island discovered and becomes a New Zealand territory, part of the Ross Dependency

1902 Scott makes first unsuccessful attempt to reach the South Pole, but achieves the 'farthest south' record at 82° south

1908 Ernest Henry Shackleton leads his first Antarctic Expedition on HMS Nimrod, building a hut at Cape Royds before his unsuccessful attempt to reach the South Pole

1911 December 14 – Scott's second expedition is beaten by Norwegian Explorer, Roald Amundsen

1912 January 18 – Scott comes second in the "race for the Pole" but perishes on the return journey just a few kilometers from base

1913 Memorial Cross is erected on Observation Hill in Scott's remembrance

1929 Admiral Richard E Byrd (US) makes the first historic flight over the South Pole

1946 The US launches Operation Highjump, the largest Antarctic Expedition ever mounted with over 4,000 men, 13 ships and 23 aircraft, to undertake extensive mapping of the coast and interior

1955-6 McMurdo Station was constructed by the US as part of the Operation Deepfreeze expeditions

1955 December 20 - First aircraft landing on the ice at McMurdo Ice Runway with 2 Neptunes P2V's and 2 Skymasters R5Ds

1956 December 14 - The famous 'Barber Shop' pole is erected

1957-8 The International Geophysical Year (IGY) results in increased scientific activities in Antarctica and the construction of over 40 bases, including Scott Base

1958 Sir Edmund Hillary leads the New Zealand Trans-Antarctic Expedition, the first overland journey to the Pole since Scott and is also the first to do so using motor vehicles - Massey Ferguson farm tractors

1959 The Antarctic Treaty is signed by the 12 IGY countries prohibiting all military activity and designating the continent as a place for scientific research and peaceful activities only - 45 countries have since signed the treaty

1960 US Navy C-130 Hercules equipped with skis are used for the first time in Antarctica

1977 QANTAS commences day excursion flights over Antarctica

1978 Air New Zealand commences DC-10 scenic flights over Antarctica

1979 28 November – an Air New Zealand DC-10 scenic flight (TE901) crashes into Mt Erebus, killing all 237 passengers and 20 crew members aboard

1991 The International Association of Antarctic Tour Operators (IAATO) is established marking the beginning of Antarctic tounsm

2005 The last flight by a USAF C-141 Starlifter was made from Christchurch having operated in the Antarctic since 1966