Omega-3 Fatty Acids: A Review of its Use in Secondary Prevention and the Treatment of Hypertriglyceridemia

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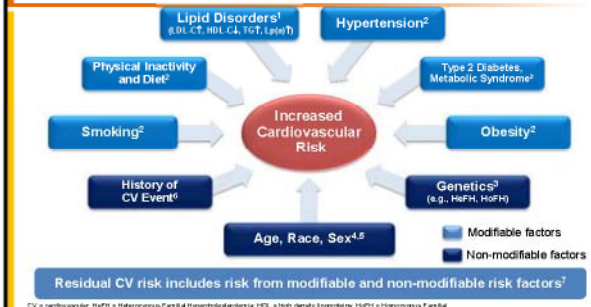
Outlines

- Hypertriglyceridemia and CV risk
  - Residual Risk
  - Treatment of Hypertriglyceridemia
- Omega-3 Fatty Acids
  - Brief introduction
  - Review in Secondary Prevention
- Conclusions

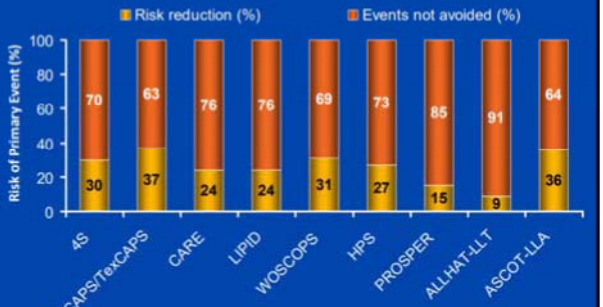
Multiple Modifiable and Non-modifiable Factors May Contribute to Cardiovascular Risk



CV = cardiovascular; HeFH = Heterozygous Familial Hypercholesterolemia; HDL = high density lipoproteins; HoFH = Homozygous Familial Hypercholesterolemia; LDL = low-density lipoproteins; Lp(a) = lipoprotein(a); TG = triglycerides.

1. Keenan TE, et al. *Curr Cardiol Rep.* 2013;15(6):366. 2. WHO. 2011. *Global atlas on cardiovascular disease prevention and control.* Geneva: World Health Organization in collaboration with the World Heart Federation and the World Stroke Organization. 3. Ehret M, et al. *Heart.* 2015;102(15):1000-1006. 4. Jellinger PS, et al. *Endocr Pract.* 2012;18(suppl 1):1-78. 5. Roger VL, et al. *Circulation.* 2012;125:e2-e220. 6. Stone NJ, et al. *J Am Coll Cardiol.* 2014;63:2889-2934. 7. Vanuzzo D. *Intern Emerg Med.* 2011;6 Suppl 1:45-51.

Residual risk after statin therapy



Kastelein et al. *Eur Heart J.* 2005;7(suppl F):F27-F33.

Major Atherosclerotic Cardiovascular Disease Risk Factors

Major risk factors	Additional risk factors	Nontraditional risk factors
Advancing age	Obesity, abdominal obesity	⇧ Lipoprotein (a)
⇧ Total serum cholesterol level	Family history of hyperlipidemia	⇧ Clotting factors
⇧ Non–HDL-C	⇧ Small, dense LDL-C	⇧ Inflammation markers (hsCRP; Lp-PLA_2)
⇧ LDL-C	⇧ Apo B	⇧ Homocysteine levels
Low HDL-C	⇧ LDL particle concentration	Apo E4 isoform
Diabetes mellitus	Fasting/postprandial hypertriglyceridemia	⇧ Uric acid
Hypertension	PCOS	⇧ TG-rich remnants
Stage 3 or 4 chronic kidney disease	Dyslipidemic triad	
Cigarette smoking		
Family history of ASCVD		

Abbreviations: apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; hsCRP, highly sensitive C-reactive protein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lp-PLA_2, lipoprotein-associated phospholipase; PCOS, polycystic ovary syndrome.

AACE PDSWC. *Endocr Pract.* 2005;11:126-134; ADA. *Diabetes Care.* 2017;40(Suppl 1):S1-S135; Brunzell JD, et al. *Diabetes Care.* 2008;31:811-822; Cromwell WC, et al. *J Clin Lipidol.* 2007;1:583-592; Einhorn D, et al. *Endocr Pract.* 2003;9:237-252; Brundy SM, et al. *Circulation.* 1998;97:1876-1887; Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice.* 2017;23(4):479-497.; Kastelein JJ, et al. *Circulation.* 2008;117:3002-3009; NCEP. NIH Publication No. 02-5215. September 2002; Pearson TO, et al. *Arch Intern Med.* 1992;152:1490-1500; NHLBI. NIH Publication No. 04-5230. August 2004; Stamler J, et al. *JAMA.* 1986;256:2823-2828; Weiner DE, et al. *J Am Soc Nephrol.* 2004;15(5):1307-1315; Yusuf S, et al. *Lancet.* 2004;364(9438):937-952.

Residual CVD Risk Despite OMT

- FOURIER evaluated PCSK9 inhibitor (evolocumab) vs placebo in statin-treated patients
  - ASCVD (N = 27,564)
  - Optimized statin therapy with or without ezetimibe
  - LDL-C level ≥ 70 mg/dL
- In-trial LDL-C levels of 30 mg/dL
- Residual CVD risk despite OMT
- Potential factors in residual risk beyond LDL-C
  - Inflammation
  - Triglyceride-rich lipoproteins (TGRLP)
    - Lab slip TG measurement is a biomarker of a class of atherogenic lipoproteins

Sabatine MS, et al. *N Engl J Med.* 2017;376:1713-1722.

Triglycerides

- The body converts excess calories, sugar, and alcohol into triglycerides, a type of fat that is carried in the blood and stored in fat cells throughout the body.
- People who are overweight, inactive, smokers, or heavy drinkers and those who eat a very high carbohydrate diet tend to have high triglycerides
- A triglycerides score of 150 or higher puts you at risk for metabolic syndrome, which is linked to heart disease and diabetes.

Triglycerides

Risk Classification of Serum Triglycerides

Normal <150 mg/dL
Borderline high 150–199 mg/dL
High 200–499 mg/dL
Very high ≥500 mg/dL

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

Triglycerides

- Publication of meta-analyses have shown that elevated triglycerides are in fact an ***independent risk factor*** for CHD
- This suggests that some triglyceride-rich lipoproteins (TGRLP) are atherogenic.

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

Triglycerides

- If triglycerides are very high (≥500 mg/dL), attention turns first to prevention of acute pancreatitis, which is more likely to occur when triglycerides are >1000 mg/dL.
- Triglyceride-lowering drugs (fibrate or nicotinic acid) become first line therapy; although statins can be used to lower LDL cholesterol to reach the LDL goal, in these patients

NCEP ATPIII. Chapter IV *Circulation December 2002 pp 3247*

Treatment Approach for TG ≥ 500 mg/dL to Reduce Risk of Pancreatitis

- Dual treatment approach
  - Lifestyle changes
    - Low carb, low saturated fat diet
    - Exercise
    - No alcohol
  - Pharmacotherapy can lower TG by up to 50% but may also increase LDL-C levels
    - Omega-3 fatty acids (EPA or EPA/DHA): 20% to 50%
    - Fibrates: 30% to 50%
- Other potential causes of very high TG levels
  - Medications, including estrogens, tretinoin, protease inhibitors, beta-blockers
  - Hypothyroidism

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

Question: How are different drugs used to treat dyslipidemia?

Statins, Fibrates

Recommendations associated with this question:

- **R55.** In individuals at risk for ASCVD, aggressive lipid-modifying therapy is recommended to achieve appropriate LDL-C goals **(Grade A, BEL 1).**

Statins

- **R56.** Statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials **(Grade A; BEL 1).**
- **R57.** For clinical decision making, mild elevations in blood glucose levels and/or an increased risk of new-onset T2DM associated with intensive statin therapy do not outweigh the benefits of statin therapy for ASCVD risk reduction **(Grade A, BEL 1).**
- **R58.** In individuals within **high-risk and very high-risk** categories, further lowering of LDL-C beyond established targets with statins results in additional ASCVD event reduction and may be considered **(Grade A, BEL 1).**
- **R59. Very high-risk** individuals with established coronary, carotid, and peripheral vascular disease, or diabetes, who also have at least 1 additional risk factor, should be treated with statins to target a reduced LDL-C treatment goal of <70 mg/dL **(Grade A, BEL 1).**
- **R60. Extreme risk** individuals should be treated with statins or with combination therapy to target an even lower LDL-C treatment goal of <55 mg/dL **(Grade A, BEL 1).**

Fibrates

- **R61.** Fibrates should be used to treat severe hypertriglyceridemia (TG >500 mg/dL) **(Grade A; BEL 1).**
- **R62.** Fibrates may improve ASCVD outcomes in primary and secondary prevention when TG concentrations are ≥200 mg/dL and HDL-C concentrations <40 mg/dL **(Grade A; BEL 1).**

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

Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497.

Question: How are different drugs used to treat dyslipidemia?
Bile acid sequestrants, omega-3 fish oil, combination therapy

Recommendations associated with this question:

Bile Acid Sequestrants

- **R66.** Bile acid sequestrants may be considered for reducing LDL-C and apo B and modestly increasing HDL-C, but they may increase TG **(Grade A; BEL 1)**.

Omega-3 Fish Oil

- **R63.** Prescription omega-3 oil, 2 to 4 g daily, should be used to treat severe hypertriglyceridemia (TG >500 mg/dL). Dietary supplements are not FDA-approved for treatment of hypertriglyceridemia and generally are not recommended for this purpose **(Grade A, BEL 1)**.

Combination Therapy

- **R71.** Combination therapy of lipid-lowering agents should be considered when the LDL-C/non-HDL-C level is markedly increased and monotherapy (usually with a statin) does not achieve the therapeutic goal **(Grade A; BEL 1)**.

Abbreviations: apo, apolipoprotein; FDA, Food and Drug Administration; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Jellinger P, Handelsman Y, Rosenblit P, et al. Endocr Pract. 2017;23(4):479-497.

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.

J Formos Med Assoc. 2017 Apr;116(4):217-248.

Risk Difference vs Placebo of HTG Subgroups
Primary and Secondary CVD Prevention Trials

	Trial (drug)	Entire Cohort Primary Endpoint, % (P)	Lipid Subgroup Criterion	Subgroup Post-Hoc Primary Endpoint, % (P)
Fibrates	HHS[a] (gemfibrozil)	-34 (< .02)	TG > 204 mg/dL LDL-C/HDL-C ratio > 5.0	-72 (.005)
	BIP[a] (bezafibrate)	-9 (NS)	TG ≥ 200 mg/dL	-39.5 (.02)
	VA-HIT[a] (gemfibrozil)	-22 (.006)	TG ≥ 150 mg/dL	-27 (.01)
	FIELD[b] (fenofibrate)	-11 (.16)	TG ≥ 204 mg/dL HDL-C < 40 mg/dL (men) or < 50 mg/dL (women)	-27 (.005)
	ACCORD[b] (fenofibrate)	-8 (.32)	TG ≥ 204 mg/dL HDL-C ≤ 34 mg/dL	Prespecified -31 (< .05)
EPA	JELIS[a] (EPA)	-19 (.011)	TG ≥ 150 mg/dL HDL-C < 40 mg/dL	-53 (.043)
Niacin	AIM-HIGH[a,b] (niacin)	+2 (.79)	TG ≥ 200 mg/dL HDL-C <32 mg/dL	-36 (.032)

a. Maki KC, et al. *J Clin Lipidol.* 2012;6:413-426.
b. Guyton JR, et al. *J Am Coll Cardiol.* 2013;62:1580-1584.

Lipid-Lowering Drug Therapies, Starting Dosages, and Dosage Ranges
Omega-3 Fatty Acids

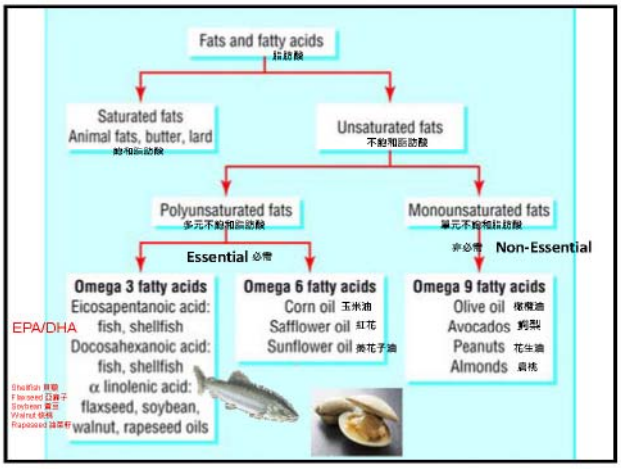
Agent	Usual recommended starting daily dosage	Dosage range	Method of administration
Omega-3-acid ethyl esters (Lovaza)	4 g per day	4 g per day	Oral
Icosapent ethyl (Vascepa)	4 g per day	4 g per day	Oral

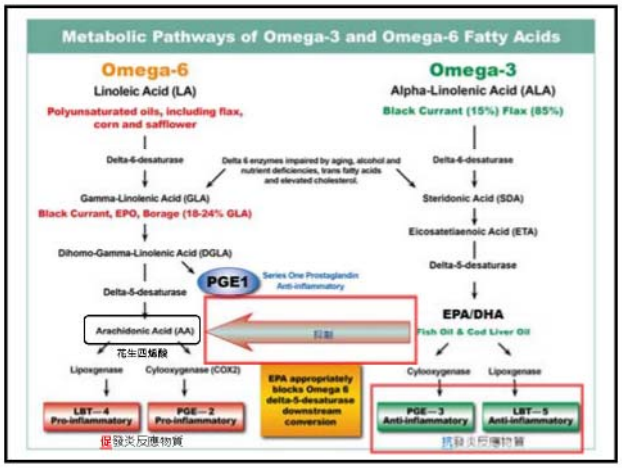
Metabolic Effects:

- ↓ TG 27%-45%, TC 7%-10%, VLDL-C 20%-42%, apo B 4%, and non-HDL-C 8%-14% in individuals with severe hypertriglyceridemia most likely by reducing hepatic VLDL-TG synthesis and/or secretion and enhancing TG clearance from circulating VLDL particles. Other potential mechanisms of action include: increased ß-oxidation; inhibition of acyl-CoA; 1,2-diacylglyceral acyltransferase; decreased hepatic lipogenesis; and increased plasma lipoprotein activity.

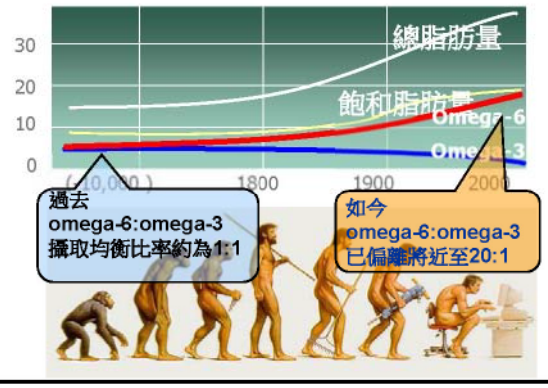
Abbreviations: apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; VLDL, very low-density lipoprotein.

Jellinger P, Handelsman Y, Rosenblit P, et al. Endocr Pract. 2017;23(4):479-497; Lovaza (omega-3-acid ethyl esters) [PI]. 2015; Vascepa (icosapent ethyl) [PI]. 2019.





人類攝取脂肪酸比例的逐漸失衡



2015-2020 Dietary Guidelines for Americans

Recommendations

- Nutritional needs should be met primarily from foods
- Consume about 8 oz/wk of a variety of seafood
  - Average of 250 mg of omega-3 PUFA daily

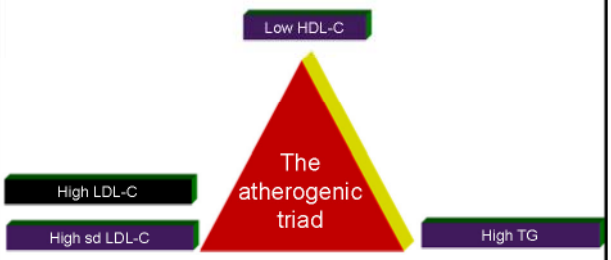
US Department of Health and Human Services, US Department of Agriculture. December 2015.

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

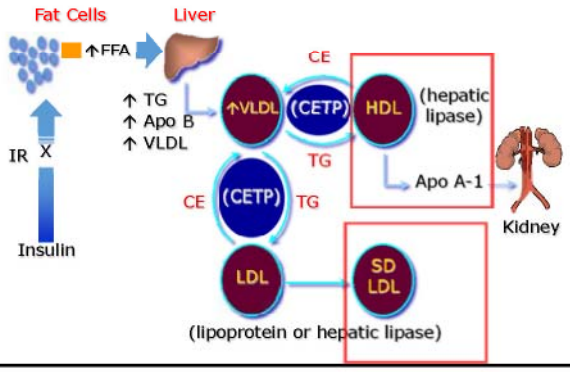
	歐美%	日本 %	愛斯基摩格陵蘭島%
飲食中的Omega 6 Omega 6 in diet	26	21	8.3
飲食中的EPA EPA in diet	0.5	1.6	8.0
Omega-6/Omega-3 攝食比例	**50**	**12**	**1**
因心血管致死率 CV Mortality rate	**45**	**12**	**7**

粥狀動脈硬化患者血脂異常特徵



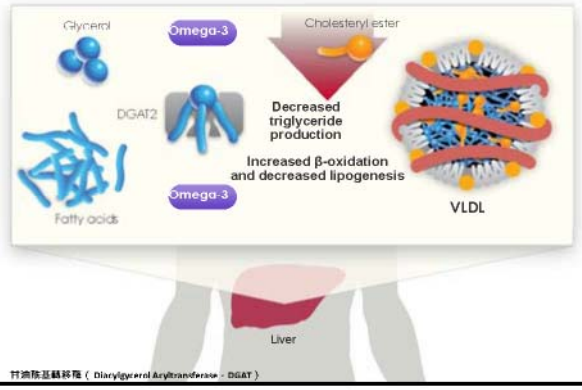
Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults JAMA 2001;285:2486-2497

TG過高亦會降低HDL及增加sdLDL

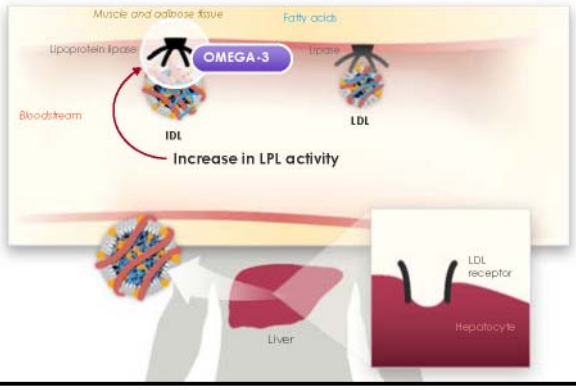


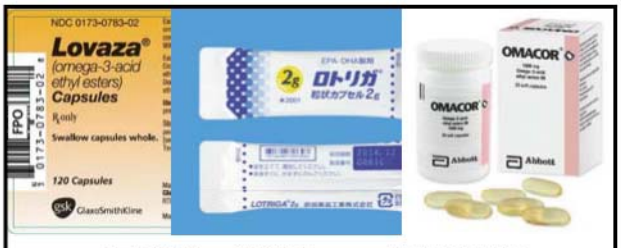
Omega-3降TG機轉

Omacor®: Proposed Intrahepatic Mechanisms of Action



Omacor®: Proposed Extrahepatic Mechanism of Action



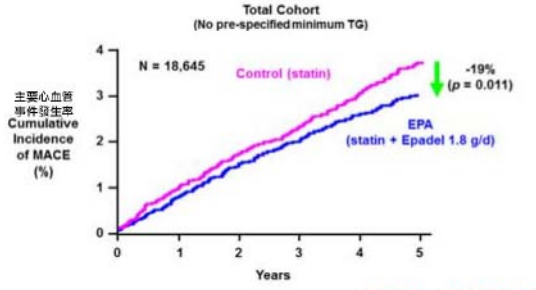


在歐洲，他叫Omacor(亞培經銷)
在美國，他叫Lovaza(GSK經銷)
在日本，他叫Lotriga(武田經銷)

原開發藥廠: 挪威Pronova藥廠，只生產原料

EPA Benefit on CHD Risk Suggested by JELIS Study

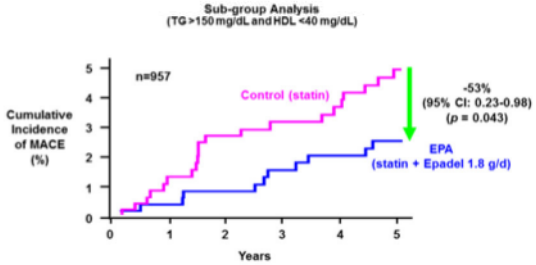
Primary prevention



1.8克EPA = OMACOR 4#

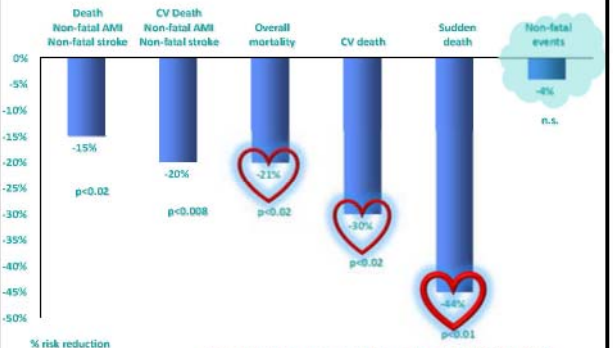
p-value adjusted for age, gender, smoking, diabetes, and hypertension
Yokoyama. *Lancet* (2007)

Mixed Dyslipidemia Subgroup Analysis in JELIS Study



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

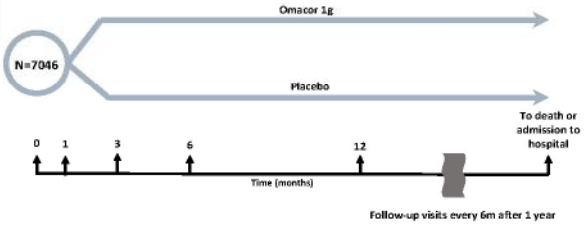
Effect of n-3 PUFA treatment in GISSI-Prevenzione (11,323 post-MI pts)



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

GISSI-HF trial

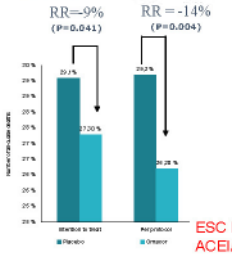
Effect of n-3 polyunsaturated fatty acids in patients with **chronic heart failure** (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial.



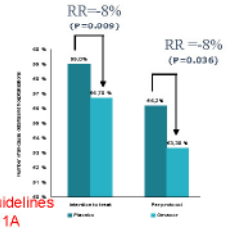
Lancet. 2008 Oct 4;372(9645):1223-30.

GISSI-HF: OMACOR可降低慢性心衰竭患者約9%死亡率

Number of all-cause death



Number of all-cause death & hospitalisations

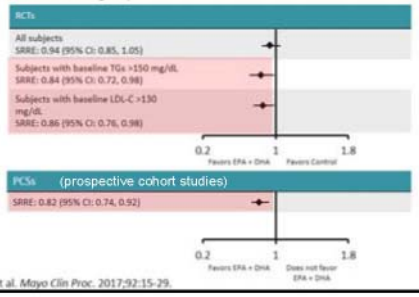


ESC HF Guidelines
ACEI/ARB: 1A
Omega-3: 2B

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

Meta-Analysis of RCTs and PCSs
Omega-3 PUFA and CHD Risk

- Included 18 RCTs (n = 93,000 subjects) and 16 PCSs (n = 732,000 subjects) examining EPA + DHA from foods or supplements and any CHD event (MI, SCD, coronary death, and angina)



Alexander DD, et al. *Mayo Clin Proc.* 2017;92:15-29.

Meta-Analysis of RCTs
Omega-3 PUFAs and Risk of Cardiac Death

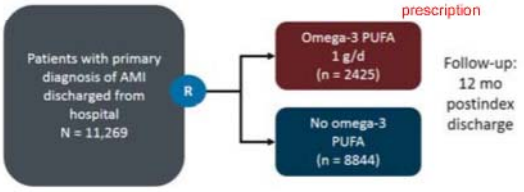
supplements or pharmaceuticals

- Primary analysis included 14 RCTs (n = 71,899 subjects)
- Primary analysis subsets included 7 to 10 RCTs (n = 20,418 to 27,111 subjects)

Analysis	RR	95% CI	*P* Value
Primary analysis RCTs	0.920	0.863, 0.981	.011
Primary analysis subsets			
> 1 g/d EPA + DHA	0.709	0.508, 0.990	.043
TGs ≥ 150 mg/dL	0.826	0.723, 0.944	.005
LDL-C ≥ 130 mg/dL	0.828	0.725, 0.946	.005
Secondary prevention	0.870	0.801, 0.945	< .001
Statin use < 40%	0.871	0.801, 0.948	.001

Maki KC, et al. *J Clin Lipidol.* 2017;11:1152-1160.e2.

Retrospective Observational Cohort Study
Design



Risk of all-cause mortality and repeat AMI compared between groups

reduced all-cause mortality (HR 0.76, 95% CI 0.59 to 0.97) and recurrent AMI (HR 0.65, 95% CI 0.49 to 0.87) through 12-month follow-up.

Greene SJ, et al. *Am J Cardiol.* 2016;117:340-346.

Circulation. 2016;134:378–391.

ORIGINAL RESEARCH ARTICLE

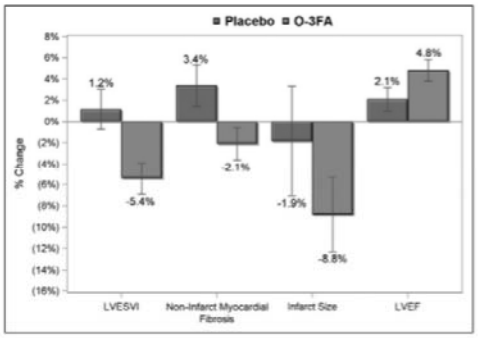
Effect of Omega-3 Acid Ethyl Esters on Left Ventricular Remodeling After Acute Myocardial Infarction

The OMEGA-REMODEL Randomized Clinical Trial

METHODS

- In a multicenter, double-blind, placebo-controlled trial, participants presenting with an acute myocardial infarction were randomly assigned 1:1 to 6 months of high-dose omega-3 fatty acids (n=180) or placebo (n=178).

Cardiac magnetic resonance imaging was used to assess cardiac structure and tissue characteristics at baseline and after study therapy. The primary study endpoint was change in left ventricular systolic volume index. Secondary endpoints included change in noninfarct myocardial fibrosis, left ventricular ejection fraction, and infarct size.



Circulation. 2016;134:378–391.

LVESVI: LV end-systolic volume index

JAMA Cardiology | Original Investigation

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

Meta-analysis of 10 Trials Involving 77 917 Individuals

CONCLUSIONS AND RELEVANCE This meta-analysis demonstrated that omega-3 fatty acids had no significant association with fatal or nonfatal coronary heart disease or any major vascular events. It provides no support for current recommendations for the use of such supplements in people with a history of coronary heart disease.

結論說Omega-3對於心血管疾病預防無效(包含次級預防)故引起話題及爭議!!!

JAMA Cardiol. 2018;3(3):225-234. doi:10.1001/jamacardio.2017.5205

此篇收錄的臨床試驗，有三大不同，
也許是造成統計出來無意義的原因

(1)病人Type不同：並非全部都是Secondary preventation患者
(2)Omega-3等級不同：並非都用處方藥等級的Omega-3(10篇只有5篇是用藥品級)
(3)Omega-3劑量不同：每日服用EPA/DHA差異很大!!!

Table. Characteristics of Included Trials

Study (Year)		Patients, No.	Dose of EPA/DHA (mg/d)	Male, No (%)	Mean Trial Duration, y	Mean (SD) Age, y	No (%) Prior CHD	Prior Stroke	Prior Diabetes	Statin Use
DOIT (2010)		563	1150/800	563 (100)	3	70 (3)	133 (23.6)	37 (6.6)	46 (8.2)	NA
AREDS-2 (2014)		4203	650/350	1816 (43.2)	4.5	74 (NA)	405 (9.7)	211 (5.0)	546 (13.0)	1866 (44.4)
SU.FOL.OM3 (2010)		2501	400/200	1987 (79.4)	4.7	61 (NA)	1863 (74.5)	638 (25.5)	440 (17.9)	2079 (83.1)
JELIS (2007)[a,b]	R	18 645	1800/NA	5859 (31.4)	4.6	61 (8)	NA	NA	3040 (16.3)	18 645 (100.0)
Alpha Omega (2010)		4837	226/150	3783 (78.2)	3.3	69 (6)	4837 (100.0)	345 (7.2)	1014 (21.0)	4122 (85.2)
OMEGA (2010)	R	3818	460/380	2841 (74.4)	1	64 (NA)	796 (22.5)	192 (5.5)	948 (27.0)	3566 (94.2)
R&P (2013)		12 505	500/500	7687 (61.5)	5	64 (NA)	Not stated (30)	594 (4.8)	7494 (59.9)	12 505 (100.0)
GISSI-HF (2008)	R	6975	850/950	5459 (78.3)	3.9	67 (11)	3614 (51.8)	346 (5.0)	1974 (28.3)	NA
ORIGIN (2012)	R	12 536	465/375	8150 (65.0)	6.2	64 (8)	8094 (64.6)	10 877 (86.8)	11 081 (88.4)	6739 (53.8)
GISSI-P[c] (1999)	R	11 334	850/1700	9658 (85.2)	3.5	59 (11)	11 334 (100.0)	NA	2139 (18.9)	NA
Total		77 917	NA	47 803 (61.4)	4.4	64	31 076/46 767 (66.4)	13 240/47 938 (27.6)	28 722 (36.9)	49 522 (83.4)

R = 使用處方藥等級Omega-3

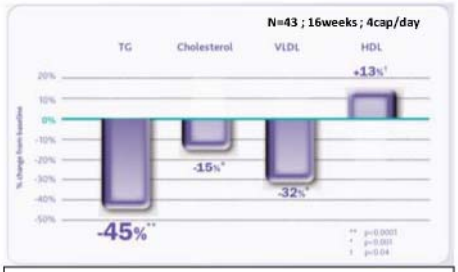
JAMA Cardiol. 2018;3(3):225-234. doi:10.1001/jamacardio.2017.5205

Study, Author, Year	Trial Design, No. of Subjects, Duration	Patient Population	Intervention and Control	End Point Results (Primary End Point)	Strengths and Limitations
Alpha Omega Kromhout et al[a] 2010 (6/10)	RCT n=4837 3.4 y	Inclusion criteria: Dutch patients age 60–80 y, history of MI (up to 10 y prior) Exclusion criteria: low intake of margarine (delivery vehicle), cancer, unintended weight loss	Intervention: 376 mg/d (226+150) EPA+DHA 1.9 g/d ALA Comparator: placebo (margarine)	Primary end point: major cardiovascular events (fatal and nonfatal CVD events plus coronary revascularizations): 675 events; RR, 1.01 (95% CI, 0.87–1.17); RR, 0.95 (95% CI, 0.68–1.32)	Strengths: moderate sample size, moderate duration of follow-up, large number of primary events Limitations: low dose of EPA+DHA, modest number of cardiac deaths (138 events), moderate to high background intake of fish (median, 1 serving/wk)
ORIGIN Bosch et al[a] 2012 (9/10)	Randomized double-blind, placebo-controlled clinical trial n=12 536 6.2 y	Inclusion criteria: multicountry patients age ≥50 y with diabetes mellitus treated with ≤1 oral agent, IGT, or IFG, and history of CVD, albuminuria, LVH, or PVD (59% had prior MI, stroke, or coronary revascularization) Exclusion criteria: HbA_{1c} ≥9%, history of CABG within past 4 y with no intervening CVD event, severe heart failure, or cancer that might affect survival	Intervention: n=6281 840 mg/d EPA+DHA (465+375) Comparator: n=6255 Placebo (olive oil)	Primary end point: CVD death; 1055 events; RR, 0.98 (95% CI, 0.87–1.10)	Strengths: large sample size, long duration of follow-up, large number of primary events, large number of arrhythmic deaths (547 events) Limitations: high background dietary EPA+DHA intake (median, 210 mg/d) at baseline

Safety and efficacy of Omacor in severe hypertriglyceridemia.

J Cardiovasc Risk. 1997 Oct-Dec;4(5-6):385-91.

Omega-3 PUFA Significantly Reduced Triglycerides Up to 45%



Patient characteristics:

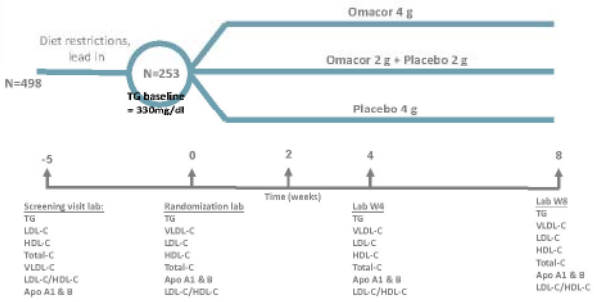
- Plasma triglycerides 5,65-22,60 mmol/l (500-2000mg/dl)

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

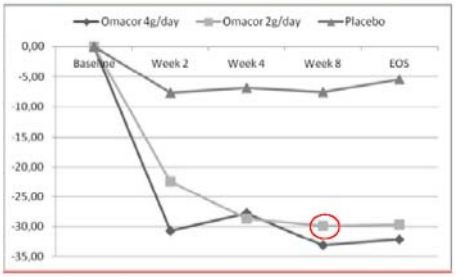
Omacor® Taiwan Trial - Method Design



Design: randomized, placebo controlled, double blind

每天服用Omacor兩顆，連續8周 可以降低三酸甘油脂 29.7%

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

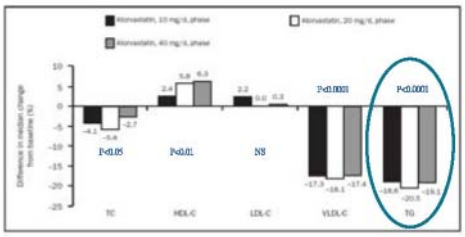


建議: TG < 500 , 2顆
TG > 500 , 4顆

OMACOR Clinical Trial in Tawian

不論高低劑量的statin 並用OMACOR後皆能額外多降TG 20%

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



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

並用OMACOR與Statin是安全的

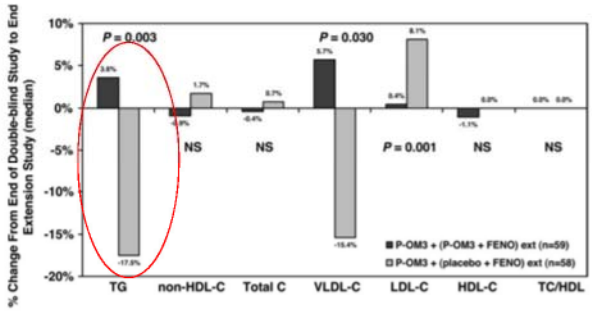
Treatment-Emergent Adverse Event (AE): Overview

	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OMACOR後可額外降TG達17.5%



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

並用OMACOR與Fibrate是安全的

Treatment-Emergent Adverse Event (AE): Overview

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

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

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

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/1.73m²	肌酸酐廓清率 (Ccr) 30-59 ml/min/1.73m²	肌酸酐廓清率 (Ccr) 15-29 ml/min/1.73m²	肌酸酐廓清率 (Ccr) < 15 ml/min/1.73m²
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			
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			

→ CKD 3~5

*以上乃依據最新藥物使用建議，根據腎功能調整劑量。

美國心臟科學會最新建議 – Omega-3可用於CHD及HF的secondary prevention

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

Circulation

2017新版台灣血脂治療指引

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)

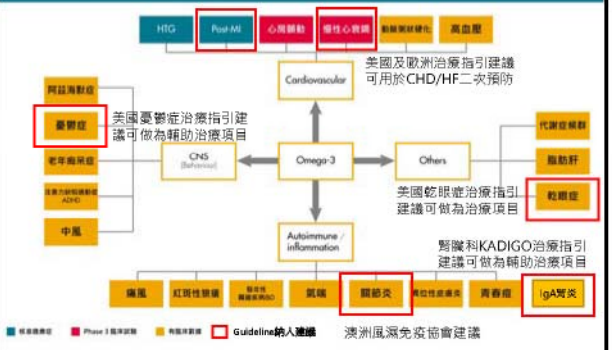
2015 臺灣慢性腎臟病臨床診療指引

Taiwan Chronic Kidney Disease Clinical Guidelines

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

OMEGA-3其餘臨床應用-Off-Label Use

Potential for Omega-3 derived pharmaceuticals



107年元月1日起 保健食品強制標示”不具醫療效能”

Cardiology Journal
2013, Vol. 20, No. 5, pp. 478–485
DOI: 10.5603/CJ.2013.0132
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ISSN 1897–5593

VIA MEDICA

ORIGINAL ARTICLE

N-3 polyunsaturated fatty acids do not influence the efficacy of dual antiplatelet therapy in stable angina pectoris patients after percutaneous coronary intervention

Katarzyna Mizia-Stec[1], Magdalena Mizia[1], Maciej Haberka[2], Bartosz Lasota[2], Klaudia Gieszczyk-Strózik[1], Artur Chmiel[2], Jacek Najda[3], Zbigniew Gąsior[2], Sławomira Kyrcz-Krzemień[3]

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[2]Department of Cardiology, Medical University of Silesia, Katowice, Poland
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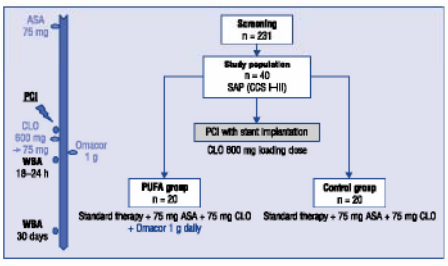


Figure 1. Participant flow; ASA — acetylsalicylic acid; CLO — clopidogrel; PCI — percutaneous coronary intervention; SAP — stable angina pectoris; WBA — whole blood impedance aggregometry.

研究顯示Omacor與Aspirin/Plavix並用不會延長出血時間

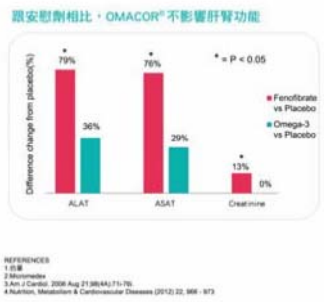
Table 5. Comparison of delta platelet test results (baseline and 1 month after percutaneous coronary intervention).

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)

和Fibrate一對一的比較中，Fibrate反而會明顯增加肝指數，而OMACOR不會



REFERENCES
1 [illegible]
2 Monomedex
3.Am J Cardiol. 2008 Aug 21;98(4A):71-76.
4.Nutrition, Metabolism & Cardiovascular Diseases (2012) 22, 966 - 973

懷孕分級C級

- FDA制定之懷孕五等級用藥安全分級：
- A級：沒有數劃形之感，為安全的藥物，在人體已做過對照組研究，證實藥物對胎兒傷害的可能性最微小，維他命即屬此類，證實藥物不多，因為很少研究會在孕婦身上做實驗。
- B級：動物實驗顯示對胎兒沒有危險性，但未對孕婦做過對照組研究。
  另外，動物實驗顯示對胎兒有不良影響，但對孕婦所做的對照組研究中，無法證實此類藥物對胎兒有害。
- 許多常用藥物即屬此類，例如乙醯胺酚（普拿疼成分）。
- C級：動物試驗顯示對胎兒有不良影響，但沒有對孕婦做過對照組研究。
  有些藥物並未做過動物試驗及人體試驗，
  屬於此一等級的藥物，只能以臨床利益明顯大於對胎兒的潛在利益之前提下使用。
- 某些抗精神症狀藥物如 Lorazepam、Haloperidol，在使用上就要小心謹慎。
- D級：有足夠的證據顯示對胎兒有危險性，但評估此類藥物對孕婦有益，例可不論其胎兒危險性。
- 例如抗癲癇藥物Carbamazepine及Phenytoin。
- X級：動物或人體試驗均顯示會造成胎兒異常，對胎兒有危險性，這類藥物對孕婦是絕對禁忌。

Arch Gynecol Obstet (2013) 287:839–843
DOI 10.1007/s00404-013-2786-z

MATERNAL-FETAL MEDICINE

Therapeutic apheresis for severe hypertriglyceridemia in pregnancy

Rafet Basar · Ayse Kubat Uzum · Bulent Canbaz · Sema Ciftci Dogansen · Sevgi Kalayoglu-Besisik · Senem Altay-Dadin · Ferihan Aral · Nese Colak Ozbey

國外Review paper說明TG>500mg/dl孕婦，Omega-3是最安全選項

Abstract

Introduction During pregnancy, a progressive increase in serum triglyceride (TG) and cholesterol levels is observed whereas TG levels mostly remain <300 mg/dl. In women with genetic forms of hypertriglyceridemia, pregnancy may cause extremely elevated TG levels leading to potentially life-threatening pancreatitis attacks and chylomicronemia syndrome. The only safe medical treatment option during pregnancy is ω-3 fatty acids, which have moderate TG lowering effects. Therapeutic apheresis could be used as primary treatment approach during pregnancy.

Materials and methods We reported the effect of double filtration apheresis in one pregnant women with severe hypertriglyceridemia, therapeutic plasmapheresis and double filtration methods in the other severe hypertriglyceridemic pregnant woman; a 32-year-old pregnant woman (patient 1) with a history of hypertriglyceridemia-induced acute pancreatitis during pregnancy and a 30-year-old pregnant woman with extremely high TG levels (12,000 mg/dl) leading to chylomicronemia syndrome (patient 2). Medical nutrition therapy and ω-3 fatty acids were also provided. Double filtration apheresis (patient 1) and plasmapheresis + double filtration apheresis (patient 2) were used.

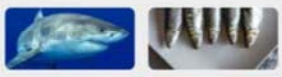
Result and conclusion When we calculated the TG levels before and after therapeutic apheresis, maximum decrease achieved with double filtration apheresis was 46.3 % for patient 1 and 37.3 % for patient 2. However, with plasmapheresis TG level declined by 72 % in patient 2. Plasmapheresis seemed to be more efficient to decrease TG levels. Iron deficiency anemia was the main complication apart from technical difficulties by lipemic obstruction of tubing system. Healthy babies were born. Delivery led to decreases in TG levels. It is concluded that during pregnancy therapeutic apheresis is an effective method to decrease extremely high TG levels and risks of its potentially life-threatening complications.

Keywords Hypertriglyceridemia · Pregnancy · Acute pancreatitis · Plasmapheresis · Double filtration apheresis

Fibrates with or without statins cannot be used during pregnancy, although fenofibrate has been used in some cases [4, 10]. The only safe preparation during pregnancy is ω-3 fatty acids with moderate TG lowering effect [1, 3, 4].

Safety of Omega-3 PUFA

- Prolonged bleeding[a]
  - Only with "hyper-Eskimo" doses (eg, >20 g/d)
  - No increased bleeding with up to 7 g omega-3 PUFA, even when taken with antiplatelet therapy or warfarin
- Concern over mercury and other contaminants in fish[a,b]
- AHA advises children and pregnant or nursing women to avoid fish with high mercury content[b]



Fish with high mercury content include[a]:	Fish with low mercury content include[a,b]:
swordfish, tilefish, king mackerel, and shark	salmon, anchovies, herring, shad, sardines, Pacific oysters, trout, and Atlantic and Pacific mackerel

a. Lavie CJ, et al. *J Am Coll Cardiol.* 2009;54:585-594; b. US Department of Health and Human Services, US Department of Agriculture. December 2015.

Allergies and Supplements

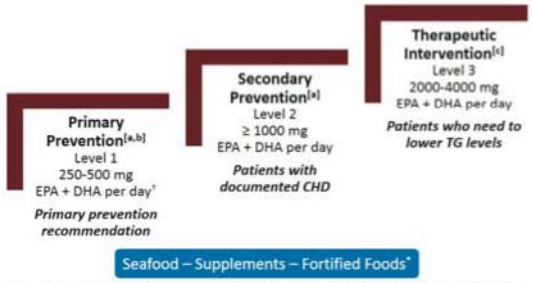
- Concern for patients who might have seafood allergies or iodine allergies
- True allergy is mostly coming from the protein and not from the actual oil of the fish
- Proceed cautiously, but that would not be a contraindication for a patient or the public to take omega-3 fatty acids for supplementation, even with a sensitivity

CVDs That May Benefit From Omega-3 PUFAs

- Post MI
- Hypercholesterolemia
- Heart failure
- Hypertriglyceridemia
- Atherosclerosis
- AF
- Complex ventricular arrhythmias
- Hypertension

Lavie CJ, et al. *J Am Coll Cardiol.* 2009;54:585-594.

EPA and DHA Intake
Continuum of Cardioprotection



*Everyone meets their EPA + DHA needs differently. *GOED recommendation is 500 mg; other scientific bodies recommend 250 mg.
a. GOED. April 2016; b. US Department of Health and Human Services, US Department of Agriculture. December 2015; c. Ito MK. *PT.* 2015;40:826-857.

CV Outcomes Trials in Patients With Hypertriglyceridemia

	REDUCE-IT[a]	STRENGTH[b]	PROMINENT[c]
Agent Dose	EPA (EE) 4 g/d	EPA+DHA (FFA) 4 g/d	SPPARMα – Pemafibrate 0.2 mg bid
Location	International	International	International
N	~8000	Estimated 13,000	Estimated 10,000
Age	≥ 45 years	≥ 18 years	≥ 18 years
Risk Profile	CVD (70%) or ↑ CVD risk (30%)	CVD (50%) or ↑ CVD risk (50%)	T2D only CVD (2/3) or ↑ CVD risk (1/3)
Follow-up	4–6 years (planned)	3–5 years (planned)	5 years (planned)
Statin Use	100% (at LDL-C goal)	100% (at LDL-C goal)	Moderate-/high-intensity or LDL-C < 70 mg/dL
Primary Endpoint	Expanded MACE	Expanded MACE	Expanded MACE
Statistical Power	Powered for 15% RRR	Powered for 15% RRR	Powered for 18% RRR
Entry TG Entry HDL-C	200–499 mg/dL N/A	200–499 mg/dL < 40 mg/dL M, < 45 mg/dL W	200–499 mg/dL ≤ 40 mg/dL

a. ClinicalTrials.gov. NCT01492361; b. ClinicalTrials.gov. NCT02104817; c. ClinicalTrials.gov. NCT03071692.

Summary

- HyperTG is still one of ASCVD risk factors
  - Interact with HDL, sdLDL
  - Population at risk
    TG > 150 in diabetic patients
    TG > 200 and HDL < 40, TG/HDL > 5
- Omega-3 Ethyl Ester (Omacor approval by TFDA)
  - The only prescription omega-3 Drug in Taiwan
  - ↓DGAT, ↑LPL
  - Beneficial in patients with TG>500, Post-MI, HF
  - No interaction with CKD
  - Single use or concomitant use with statin, fibrate