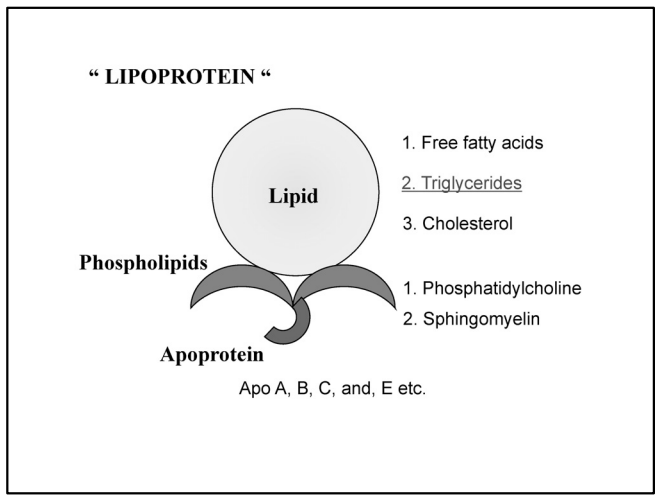
[연수강좌]

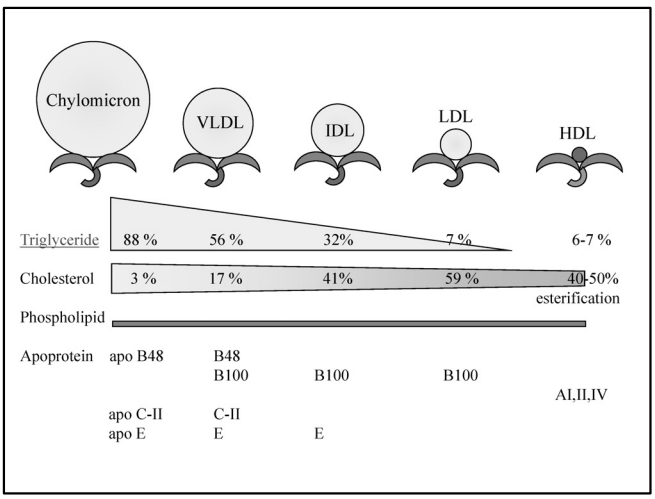
고중성지방혈증 치료의 새로운 근거

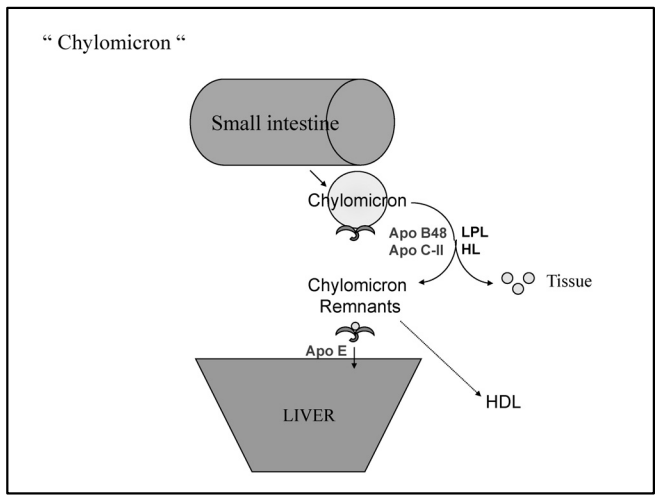
한 기 훈

울산의대

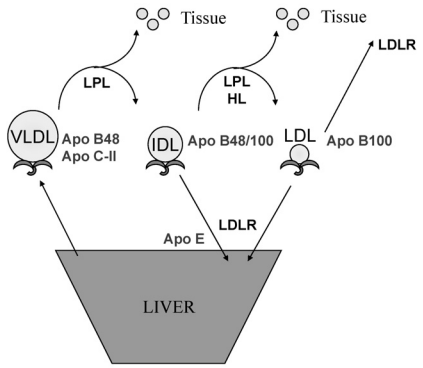
Lipid particle 에는 중성지방이 많다.





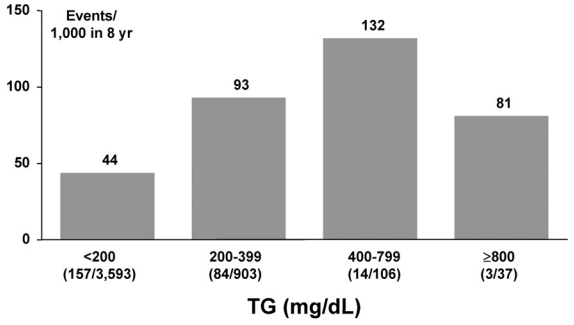


" VLDL - IDL - LDL "

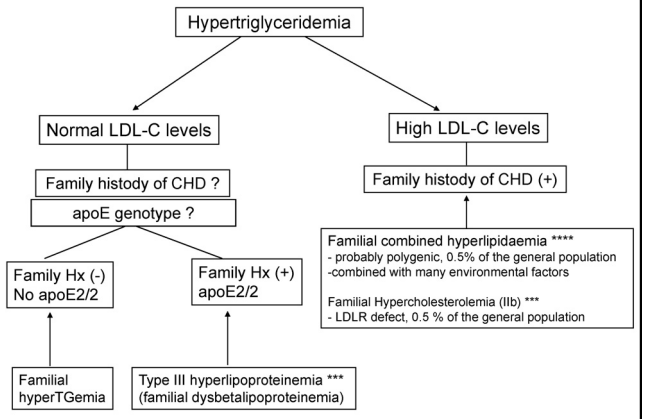


What is hyper-TG ?

Hypertriglyceridemia—An Independent Risk Factor for CHD: PROCAM Study



Assmann G et al. *Am J Cardiol.* 1992;70:733-737.



What is lipid battery ?

" Lipid battery "

Total Cholesterol	Free fatty acids Cholesterol in VLDL, IDL, and LDL Cholesterol ester in HDL	Apo B (esp. 100)
Triglycerides	**Chylomicron** **VLDL and IDL**	Apo B48, CII, E
HDLc	Cholesterol ester	Apo A

Friedewald formula

LDLc = TC - TG/5 - HDLc

TC	LDLc	TG
↑	normal to dec	↑
↑	↑	normal
↑	↑	↑

Behind the curtain

Metabolic syndrome
& Small dense LDL

MS; NCEP-ATP III, 2001

Clinical identification (≥3 risk determinants)

Risk Factor	Definition Level
Waist circumference	
Men (cm)	> 102 (90)
Women (cm)	> 88 (80)
Triglyceride (mg/dL)	≥ 150
HDL-C	
Men (mg/dL)	< 40
Women (mg/dL)	< 50
Blood pressure (mmHg)	≥ 130 / ≥85
Fasting glucose (mg/dL)	≥ 110

JAMA 285:2486, 2001

Metabolic Syndrome
IDF Consensus

Central Obesity
(WC ≥ 80 Cm)

Plus any 2 of :
- High **TG**
- Low **HDLc**
- High **BP**
- High **FBS** (or pre-existing DM)

MS-SD LDL relation

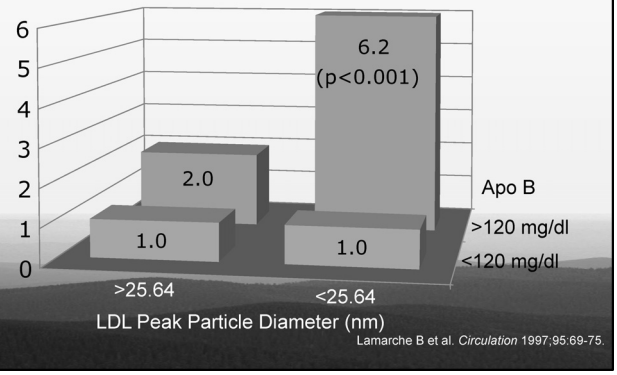
TC 200
TG 100
HDL 50
LDL 130

TC 210
TG 250
HDL 30
LDL 130

More
"small dense LDL"

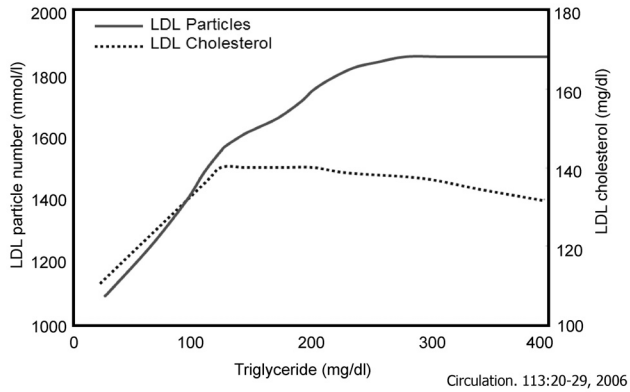
Same amount of LDL, Different number of particles

LDL Particle Size and Apolipoprotein B Predict Ischemic Heart Disease:
Quebec Cardiovascular Study



Lamarche B et al. *Circulation* 1997;95:69-75.

Relations of total LDL particle number and LDL cholesterol value to the Triglyceride level



Circulation. 113:20-29, 2006

Guidelines for Controlling TG

ATP III
Lipid and Lipoprotein Classification

Serum Triglycerides		**HDL Cholesterol**	
• Normal	<150	Low	<40
• Borderline high	150–199	High	≥60
• High	200–499		
• Very high	≥500		

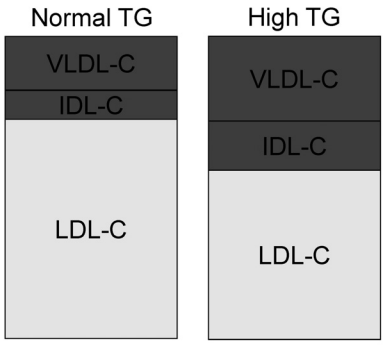
New Features of ATP III

- For patients with triglycerides 200-500 mg/dL
  - LDL cholesterol: primary target of therapy
  - Non-HDL cholesterol: secondary target of therapy

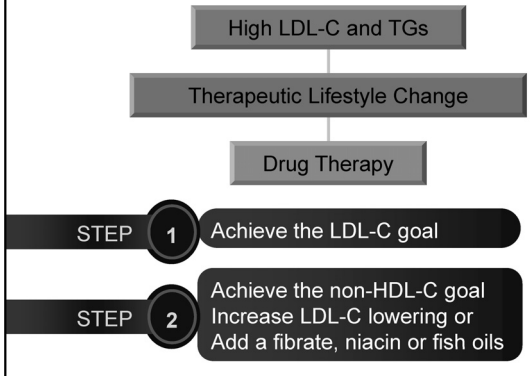
Non HDL-C = total cholesterol – HDL cholesterol
= VLDL-C + IDL-C +LDL-C

- Therapeutic approaches to elevated non-HDL cholesterol
  - Intensify therapeutic lifestyle changes
  - Intensify LDL-lowering drug therapy
  - Nicotinic acid or fibrate therapy to lower VLDL

NonHDL Cholesterol



Treatment of Mixed Hyperlipidemia



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

Adult Treatment Panel III (2004 Update)

	10 Y CHD RIsk	LDL-C (mg/dL)	nonHDL-C (mg/dL)
Very High Risk*	>20%	<70 (optional)	<100
High Risk*	>20%	<100	<130
Moderately High Risk	10-20%	<130	<160
Moderate Risk	<10%	<130	<160
Lower risk	<10%	<160	<190

* CHD or CHD risk equivalents

Grundy et al. Circulation 2004; 110; 227-39

고위험군 - " big blow "

" CHD " or " CHD equivalents "

- 확진된 **CHD**
- 증상이 있는 기타혈관질환
(symptomatic carotid disease, aortic aneurysm, peripheral arterial disease)
- 당뇨
- 많은 위험인자 **(10yr risk 20 %** 이상**)**

CHD ; coronary heart disease

고위험군 - " 가랑비에 옷 젖듯이 "

심장질환의 주 위험인자 *
(LDL Cholesterol 수치 불포함)

- 흡연
- 고혈압
  (≥ 140/90 mmHg 또는 약물치료중)
- 낮은 **HDL cholesterol** 수치
  (< 40 mg/dL)†
- 심질환의 가족력
  (CHD in male first-degree relative < 55 years
  ; CHD in female first-degree relative < 65 years)
- 연령 (남 ≥ **45** ; 여 ≥ **55** 세)

*당뇨 는 coronary heart disease (CHD) risk equivalent 로 승진.
†**HDL cholesterol** ≥ 60 mg/dL 이면 하나를 뺌 줌.

ATP-III update (2004)
Modified LDL Goal ; absolute LDL-C levels

- **High risk patients ;**
  <100 mg/dl as a 'minimal' goal with 'standard' statin dose
- **"Very" high risk patients ;**
  <70 mg/dl is favored (and CRP <2 mg/L)

  - very high ; CVD with
    1. multiple RFs (esp. DM)
    2. poorly controlled RFs (esp. smoking)
    3. multiple factors of the **Metabolic syndrome**
       (high TG ≥ 200 plus nonHDL-C ≥ 130 with low HDL-C ≤ 40)
    4. with ACS

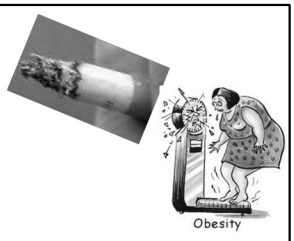
Management of High TG

- Intensify therapeutic lifestyle changes
- Treat secondary causes
- Intensify LDL-lowering drug therapy
- Nicotinic acid or fibrate therapy to lower VLDL

Non-Drug Management for Lowering TG

Hypertriglyceridemia
- environmental causes

- Obesity and overweight
- Physical inactivity
- Cigarette smoking
- Excess alcohol intake
- High carbohydrate diets
- Several diseases
  - type 2 diabetes, chronic renal failure
  - nephrotic syndrome



Hypertriglyceridemia
- Iatrogenic

- Atypical anti-psychotics
- Beta blockers
- Thiazides
- Estrogen (in higher dose oral contraceptives and unopposed oral estrogen)
- Glucocorticoids
- Immunosuppressants
- Isotretinoin
- Protease inhibitors
- Tamoxifen

Alcohol

- Daily intake: <1 drink/d for women and <2 drinks/d for men
- To avoid hypoglycemia consume with food
- Raises TG and blood pressure
- Contributes to obesity

Dietary Fiber
Foods Rich in Soluble Fiber

Fruits:	Vegetables:	Beans:
Apricots	Green peas	Chickpeas
Cantaloupe	Okra	Lima beans
Cherries	Sweet potato	Navy beans
Grapefruit	Winter squash	Split peas
Orange	Zucchini	
Papaya		
Peaches	Cereal:	
Plums		
Prunes	Granola	
Raisins	Oat Bran	
	Oatmeal	

Dietary recommendations for TLC

Table 6. Nutrient Composition of the Therapeutic Lifestyle Changes (TLC) Diet

Nutrient	Recommended Intake
Saturated fat*	<7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25%-35% of total calories
Carbohydrate†	50%-60% of total calories
Fiber	20-30 g/d
Protein	Approximately 15% of total calories
Cholesterol	<200 mg/d
Total calories‡	Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain

Trans fatty acids are another LDL-raising fat that should be kept at a low intake.
†Carbohydrates should be derived predominantly from foods rich in complex carbohydrates including grains, especially whole grains, fruits, and vegetables.
‡Daily energy expenditure should include at least moderate physical activity (contributing approximately 200 kcal/d).

Dietary Fats

- Saturated
  - Short, Medium, Long chain
- Mono-unsaturated
  - *cis*, *trans*
- Poly-unsaturated
  - ω-3, ω-6

Saturated Fats

- Long chain saturates except stearic acid [18:0] raise LDL cholesterol
- Main sources: Ghee, Butter, Palm Oil
- Medium chain saturates also raise LDL cholesterol
- Main sources: Coconut oil

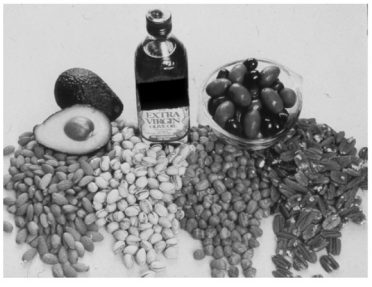
Trans-Monounsaturated Fats

- Trans fatty acids like elaidic acid (18:1 *trans*) raise LDL cholesterol and lower HDL cholesterol
- Main sources: Hydrogenated fats
  – Margarines, Shortenings, Frying oils
- Butter, milk fat (traces)

cis-Monounsaturated vs. Polyunsaturated fats

- Both reduce LDL cholesterol equally
- High intakes of n-6 polyunsaturated fats may reduce HDL cholesterol

Sources of *cis*-monounsaturated Fats



Mustard oil contains erucic acid (C20:1)
Canola Oil contains oleic acid (C18:1)

N-3 polyunsaturated Fats

- N-3 Fatty acids (EPA (20:5)/DHA (22:6) from fish oils) lower triglycerides
- Main sources: Fish
- Sources of α-linolenic acid (18:3): Vegetables, Flaxseed oil (No TG reduction) May raise LDL cholesterol
- Can adversely affect glycemia

Secondary dyslipidaemia

Antihypertensives
- thiazides
  - TC & TG (VLDL & LDL) up, no HDL change
  - maybe related to glucose intolerance
  - especially in obese males and postmenopausal women
- beta blockers
  - especially in beta blockers without ISA
  - TG up (15-30%), and HDL down (6-8%)
  - maybe due to decreased LPL activity

Immunosupressives
- corticosteroids
  - impaired glucose tolerance & insulin resistence
  - maybe VLDL synthesis up, too
  - TG up and HDL down

Hormonal Influences

Pregnancy
- TC, TG (VLDL & LDL) and HDL mildly up d/t physiologic change

Estrogen
- VLDL and LDL up in premenopausal women
- HDL up, LDL down in postmenopausal women
- could be useful as a primary prevention
  on hyperlipidaemic postmenopausal women ?

Hypothyroidism
- usually Type IIa, IIb type d/t decreased LDL catabolism
- TFT (T4 and TSH) should be regarded in hyperlipidaemic patients whose lipid profiles do not respond to therapy

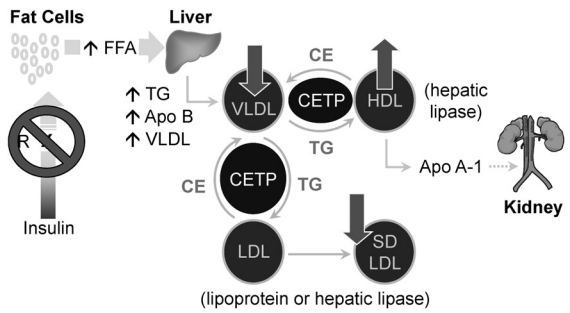
Diabetes Mellitus (NIDDM)
- Type IV most common d/t VLDL production up (may combine the decreased LPL activity)
- usually LDL is normal d/t decreased LPL activity
- usually HDL is down d/t decreased LPL activity

Obesity
- insulin resistence
- mimic the situations of NIDDM

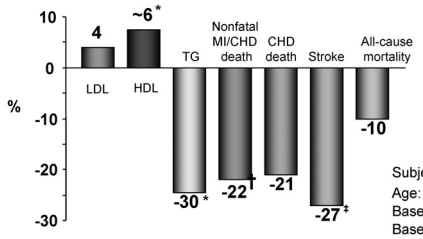
Others
- Nephrotic syndrome - usu. type II
- CRF - usu. type IV and HDL down
- Alcohol - usu. type IV or V

TG lowering drugs
except omega-3 FA

Fibrates activate PPARα



VA-HIT: Fibrate decreases CVD Events in CHD Patients With Isolated Low HDL-C



Subjects: 2,531 men
Age: ~74 (avg 64) yr
Baseline LDL-C: 111 mg/dL
Baseline HDL-C: 32 mg/dL
Baseline TG: 161 mg/dL
Duration: 7 yr
Intervention: Gemfibrozil 600 mg bid

Physiologic effect

TG ↓: 40%

HDL ↑: 10%

LDL 감소효과는 적다

Use

Gemfibrozil (Lopid®) 600 mg, 식전 **30, 1~2** 회**,** 매일
Fenofibrate (Lipidil®) 200 mg, 식후 즉시 **1**회**,** 매일

Toxicity

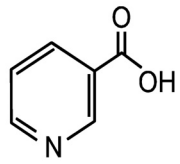
Myopathy, 간기능이나 신기능 이상시 금기

cholesterol gall stone (biliary tract dz시 금기**)**

Fibrate-Statin combination

- Increase in LDL level after fibrate tx.
  - mainly due to increase in lipolysis by LPL
- Gemfibrozil – No
  Fenofibrate – Yes (pending ACCORD study)

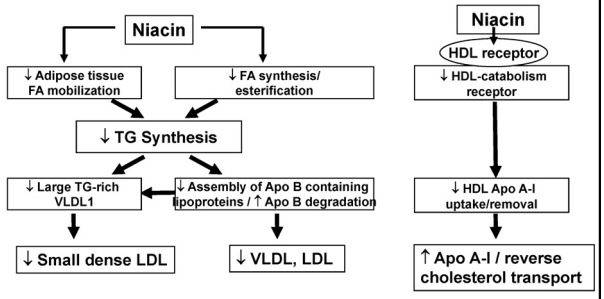
Niacin



"Among lipid-lowering agents, nicotinic acid appears to be the most effective for favorably modifying all of the lipoprotein abnormalities associated with atherogenic dyslipidemia."

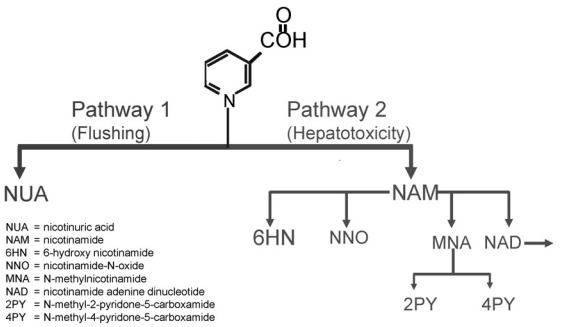
(National Cholesterol Education Program Adult Treatment Panel III Report) Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *Circulation.* 2002;106:3143

Mechanism of Action of Niacin on Lipoprotein Metabolism



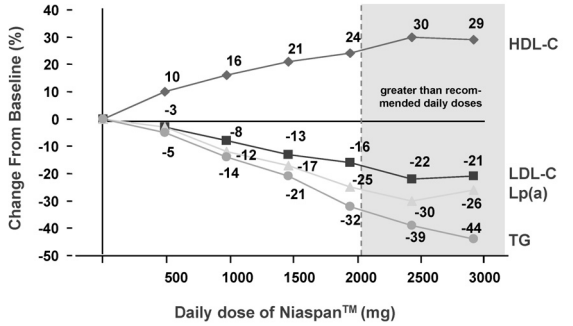
Adapted from Kamanna VS, Kashyap ML. *Curr Atheroscler Rep.* 2000;2:36-46

Niacin Metabolism



Piepho RW. *Am J Cardiol.* 2000;86(suppl):35L

Efficacy of Niaspan™



Niacin and Cardiovascular Protection: Secondary Prevention Studies

Study	Treatment(s)	Duration (years)	Efficacy results
Coronary Drug Project (CDP)[1,2]	Nicotinic acid	5 15	Non fatal MI ↓ 27% Stroke/TIA ↓ 24% Total mortality ↓ 11%
Stockholm Ischemic HeartDisease Study (IHD)[3]	Nicotinic acid + clofibrate	5	Total mortality ↓ 26% CHD mortality ↓ 36%
HDL Atherosclerosis Treatment Study (HATS[4])	Nicotinic acid + simvastatin ± antioxidant vitamins, vs placebo	3	CHD mortality/Non fatal MI or revascularization procedure ↓ 60% to 90%

1. **The CDP Research Group. *JAMA*. 1975;231:360** 2. **Canner PL et al, for the CDP Research Group. *J Am Coll Cardiol*. 1986;8:1245** 3. **Carlson LA, Rosenhamer G. *Acta Med Scand*. 1988;223:405**
4. **Brown BG et al. *New Engl J Med*. 2001;345:1583**

Side Effects of Niacin

Skin	**Flushing, dry skin, pruritus**
Eyes	**Conjunctivitis, cystoid macular edema, retinal detachment**
Respiratory tract	**Nasal stuffiness**
Heart	**Supraventricular arrhythmias**
GI tract	**Heartburn, loose bowel movements or diarrhea**
Liver	**Mild increase in serum aminotransferases, hepatitis**
Muscles	**Myositis**
Metabolic system	**Hyperglycemia, increase of uric acid**

TG lowering drugs ; omega-3 FA

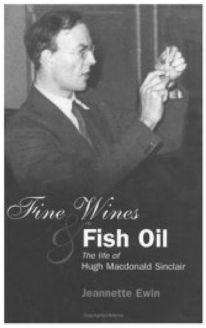
Myth ; Omega-3 Fatty Acids

Eskimo <<< Inuit
‘ the people ‘

Seal oil ; 8-9 grams/day

Photo taken in 1907

Hugh Macdonald Sinclair (1910-1990)



His self-experimentation, including the infamous 100 day seal-meat diet, were the subject of widespread ridicule and professional ruin.

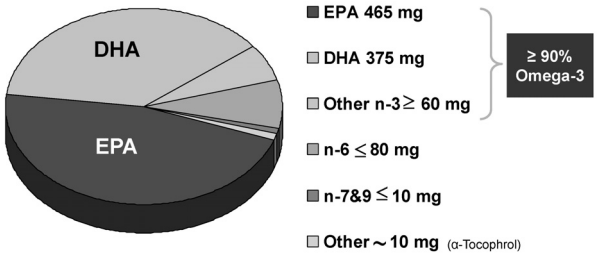
omega-3 fatty acids

marine-derived ;
eicosapentaenoic acid, C20:5n-3 [EPA]
docosahexaenoic acid, C22:6n-3 [DHA].

plant-derived ;
alpha-linolenic acid, C18:3n-3

Omega-3 Ethyl Esters (Omacor®) FA Composition

Omega-3 fatty acid-derived prescription pharmaceutical product



Source: FDA www.fda.gov/cder/foi/label/2004/32654lbl.pdf

Marine omega-3 fatty acids

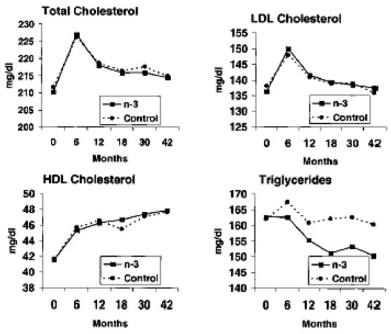
- Diet And Reinfarction Trial (DART)

  - a 29% reduction in all-cause mortality over a 2-year period in male MI survivors advised to increase their intake of oily fish (200 to 400 g of fatty fish per week, which provided an additional 500 to 800 mg/d of omega-3 fatty acids).

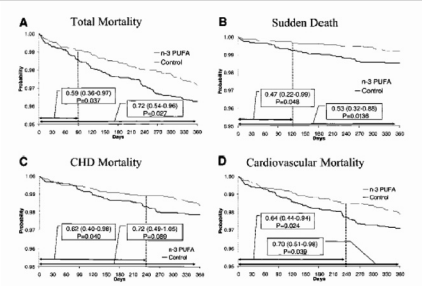
- GISSI-Prevention Study

  - 11,324 patients with preexisting CHD, 3.5 years of follow-up
  - either 300 mg of vitamin E, 850 mg of omega-3 fatty acid ethyl esters (as EPA and DHA), both, or neither
  - a 15% reduction in the primary end point of death, nonfatal MI, and nonfatal stroke (P<0.02), a 20% reduction in all-cause mortality (P=0.01) and a 45% reduction in sudden death (P<0.001) compared with the control group; vitamin E provided no additional benefit.

GISSI-Prevention Study ; Effects on lipid profile



GISSI-Prevention Study ; outcome



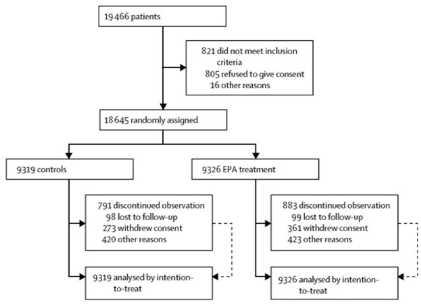
Survival curves diverged early after randomization. Total mortality was significantly lowered after 3 months of treatment (RR=0.59), and by 4 months, risk of sudden death was reduced (RR=0.47).

GISSI-Prevenzione Results

Outcome	Control (%)	Omega 3 (%)	RRR (%)	P
Death, MI, Stroke	14.8	12.6	16	0.02
CV Death, MI Stroke	11.7	9.4	20	0.006
Death	10.6	8.4	21	0.006
CV Death	7.2	5.1	30	< 0.001
Cardiac Death	6.1	4.0	35	< 0.001
Coronary Death	5.2	3.6	32	< 0.01
Sudden Death	3.3	1.8	44	< 0.001
Nonfatal CV Events	4.9	4.9	2	NS

Lancet **1999;354:447-455;** ***Eur Heart J Suppl*** **2001;3(Suppl D):D85-D97;** ***Circulation*** **2002;105:1897-1903**

JELIS study



Yokoyama et al, Lancet 2007, 369:1090

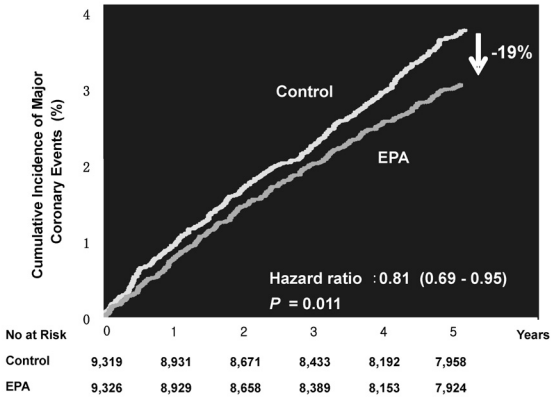
#0008

Baseline characteristics

	Control group n = 9,319	EPA group n = 9,326
Average age (yr)	61± 9	61± 9
Male (%)	2,908 (31)	2,951 (32)
Smoker (%)	1,700 (18)	1,830 (20)
BMI (kg/m^2)	24± 3	24± 3
Diabetes (%)	1,524 (16)	1,516 (16)
Hypertension (%)	3,282 (35)	3,329 (36)
Coronary artery disease (%)	1,841 (20)	1,823 (20)
Total cholesterol (mg/dl)	275± 26	275± 26
LDL-cholesterol (mg/dl)	182± 29	181± 30

#0010

Kaplan-Meier estimates of major coronary events



No at Risk						
Control	9,319	8,931	8,671	8,433	8,192	7,958
EPA	9,326	8,929	8,658	8,389	8,153	7,924

#0011

Major coronary events incidence

	No. of events (%) Control N=9,319	EPA N=9,326	P value	Hazard ratio (95%CI)
Major coronary events	324 (3.5)	262 (2.8)	0.011	0.81 (0.69 - 0.95)
Sudden cardiac death	17 (0.2)	18 (0.2)	0.854	1.06 (0.55 - 2.07)
Fatal MI	14 (0.2)	11 (0.1)	0.557	0.79 (0.36 - 1.74)
Nonfatal MI	83 (0.9)	62 (0.7)	0.086	0.75 (0.54 - 1.04)
Unstable angina	193 (2.1)	147 (1.6)	0.014	0.76 (0.62 - 0.95)
CABG or PTCA	222 (2.4)	191 (2.1)	0.135	0.86 (0.71 - 1.05)

#0012

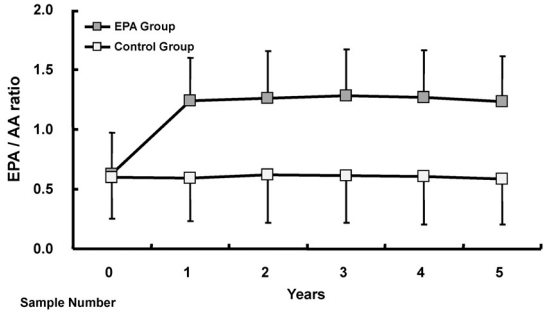
Combined endpoints

	No. of events (%) Control N=9,319	EPA N=9,326	P value	Hazard ratio (95%CI)
Major coronary events	324 (3.5)	262 (2.8)	0.011	0.81 (0.69 - 0.95)
Coronary death	31 (0.3)	29 (0.3)	0.812	0.94 (0.57 - 1.56)
Coronary death or MI	113 (1.2)	88 (0.9)	0.083	0.78 (0.59 - 1.03)
Fatal MI or nonfatal MI	93 (1.0)	71 (0.8)	0.091	0.77 (0.56 - 1.05)
Nonfatal coronary events	297 (3.2)	240 (2.6)	0.015	0.81 (0.68 – 0.96)
All-cause death	265 (2.8)	286 (3.1)	0.333	1.09 (0.92 – 1.28)

※ Coronary death = Sudden cardiac death or fatal MI

#0026

Plasma Eicosapentaenoic acid /Arachidonic acid ratio



Sample Number						
Control	8,321	6,967	6,326	5,875	5,386	4,970
EPA	8,076	6,772	6,114	5,668	5,196	4,854

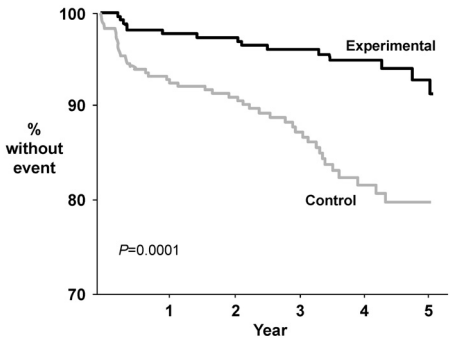
ADVERSE EXPERIENCE

#0028

	Control	EPA	P value
Total number of Incident (%)	2,004 (21.7%)	2,334 (25.3%)	<0.0001
Major adverse experience of account			
Haemorrhage	315 (3.4%)	350 (3.8%)	0.172
Abnormal laboratory data	322 (3.5%)	378 (4.1%)	0.032
Neoplasms	218 (2.4%)	242 (2.6%)	0.263
Joint pain,Lumbar pain,Muscle pain	180 (2.0%)	144 (1.6%)	0.043
Gastrointestinal disorder	155 (1.7%)	352 (3.8%)	<0.0001
Eruption,Itching,Exanthema,Eczema	64 (0.7%)	161 (1.7%)	<0.0001

(χ^2-test)

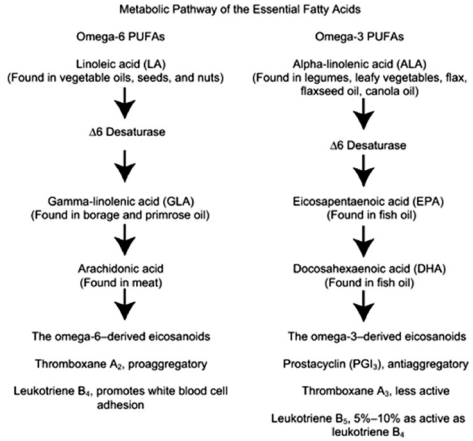
Lyon Diet Heart Study: Cumulative Survival Without Cardiac Death and Nonfatal MI



de Lorgeril M et al. *Circulation*. 1999;99:779-785.

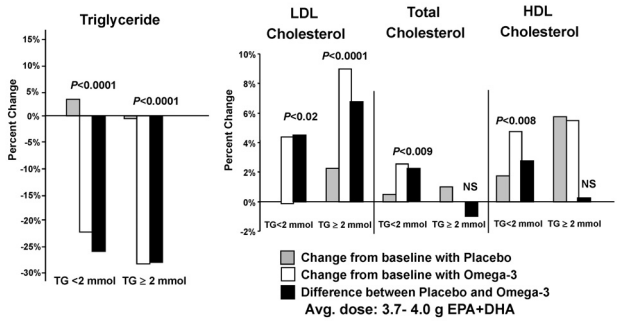
Omega-3 Polyunsaturated Fatty Acids

- Inhibit platelet aggregation
- Anti-inflammatory
- Decrease triglycerides and Lp (a)
- Anti-arrhythmic (direct myocyte effect) etc.



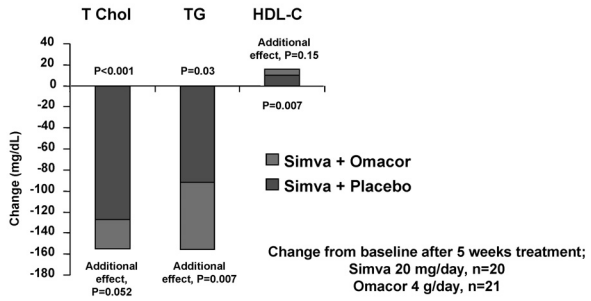
TG-lowering effects

Omega-3 FA and Lipids
Summary of 72 Placebo-controlled Studies



Harris WS. *Lipids*. 1996;31:243-252.

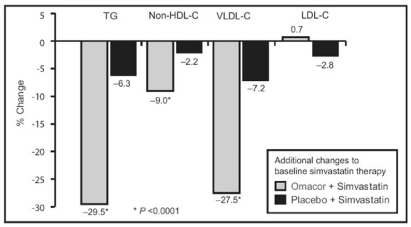
Effects of Omega-3 Ethyl Esters in Combination with Simvastatin



Nordoy A, et al. J Intern Med 1998;243:163-170

COMBOS study ; add-up effect

Figure 2. Median Percent Change in TG, Non-HDL-C, Calculated VLDL-C, and LDL-C from Baseline to End of Treatment in the ITT Population



N=122, OMACO 4g/day

Liver-tropic effects of Ω3FA (1)

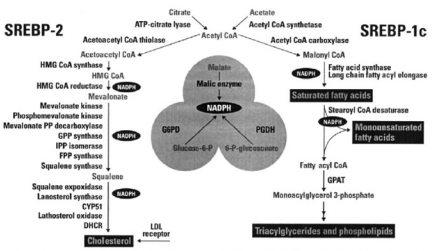


Figure 2. The liver X receptor (LXR) controls both sterol regulatory element binding protein (SREBP)-2 and SREBP-1c. SREBP-2 regulates the genes involved in cholesterol synthesis, whereas SREBP1-c stimulates the production of genes involved with the lipogenic enzymes. Inhibition of LXR would result in a decrease in both cholesterol and triglyceride synthesis. ATP = adenosine triphosphate; CoA = coenzyme A; CYP51 = cytochrome P450-51; DHCR = 7-dehydrocholesterol reductase; FPP = synthase-farnesyl diphosphate; Glucose-6-P = glucose-6 phosphate; GPAT = glycerol-3-phosphate acyltransferase; GPP = geranyl pyrophosphate; G6PD = glucose-6-phosphate dehydrogenase; HMG = 3-hydroxy-3-methylglutaryl; IPP = isopentenyl diphosphate; LDL = low-density lipoprotein; NADPH = reduced form of nicotinamide-adenine dinucleotide phosphate; PGDH = 6-phosphogluconate dehydrogenase.

Am J Cardiol 2006;98[suppl]:27i–33i

Liver-tropic effects of Ω3FA (2)

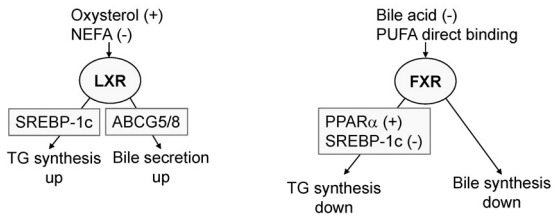


Table 1
Summary of effects of omega-3 fatty acids on nuclear receptors involved in regulation of lipogenesis

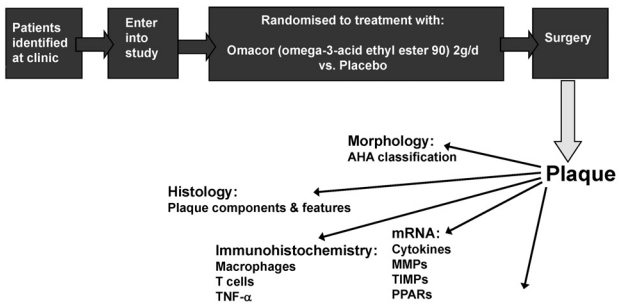
Metabolic Nuclear Receptor	Effects on Gene Regulation	Expected Changes		
		Triglycerides	HDL	LDL
PPAR-α	↑	↓ ↓	↑	↓
LXR	↓	↓ ↓	↓	↓
FXR	↑	↓ ↓	↑	↑
HNF-4α	↓	↓ ↓	↓	↔
Net effects		↓ ↓ ↓ ↓	↔	↔

FXR = farnesol X receptor; HDL = high-density lipoprotein; HNF-4α = hepatocyte nuclear factor–4α; LDL = low-density lipoprotein; LXR = liver X receptor; PPAR-α = peroxisome proliferator-activated receptor; ↑ = increase; ↓ = decrease; ↔ = neutral effect.

The OCEAN Study

Omacor Carotid EndArterectomy iNtervention

OCEAN Study outline

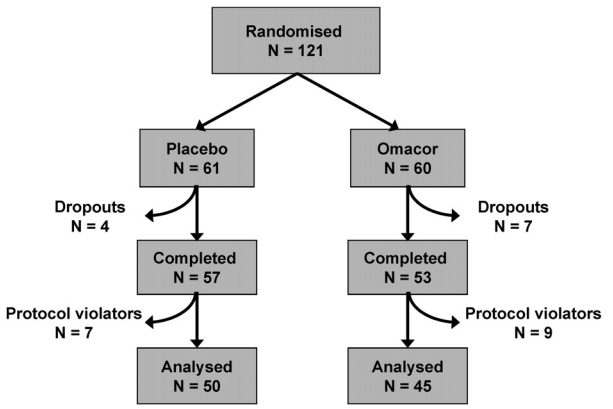


Multicenter (3), Double blind

Inclusion criteria:
- Awaiting carotid endarterectomy
- > 18 years of age
- Written informed consent

Exclusion criteria:
- Consumption of fish oil or evening primrose oil
- Consumption of > 2 oily fish meals/week
- Surgery in < 7 days
- Pregnancy or breastfeeding
- Participation in another trial

Flow of patients



Subject Characteristics

	Placebo	Omacor
Age (y)	74.1 ± 8.5	70.9 ± 8.7
Men (%)	66	63
BMI (kg/m^2)	26.9 ± 4.3	27.3 ± 5.2
Smoking history	64% ex	57% ex
	15% current	22% current
Right stenosis (%)	65 ± 30	70 ± 26
Left stenosis (%)	70 ± 23	72 ± 26
SBP (mmHg)	156 ± 23	156 ± 26
DBP (mmHg)	82 ± 13	81 ± 13
Hypertension (%)	87	85
Type 2 diabetes (%)	31	23
Angina (%)	26	23

Lipid Values
(baseline)

	Placebo	Omacor
Serum TG (mM)	1.6 ± 0.8	1.4 ± 0.6
Serum cholesterol (mM)	4.8 ± 1.2	4.8 ± 1.1
Serum LDL cholesterol (mM)	2.8 ± 1.0	2.7 ± 1.0
Serum CRP (mg/l)	5.5 ± 6.9	6.5 ± 9.3

Treatment Duration
(days)

	Placebo	Omacor
Range	8 - 102	7 - 71
Median*	21	21

* The observed median treatment duration was shorter than originally expected when planning the study

Histology Feature	Omacor Mean ± SE	Placebo Mean ± SE	P
Lipid Core	2.20 ± 0.13	2.30 ± 0.13	0.56
No. of Foam Cells	1.51 ± 0.12	1.87 ± 0.12	0.039
Haemorrhage	1.44 ± 0.10	1.39 ± 0.10	0.77
No. of Macrophages(plaque)	2.75 ± 0.14	3.00 ± 0.14	0.22
No. of Macrophages (cap)	2.48 ± 0.19	2.61 ± 0.19	0.62
Inflammation (plaque)	2.33 ± 0.14	2.57 ± 0.14	0.22
Inflammation (cap)	2.17 ± 0.19	2.38 ± 0.19	0.44
Mean Score	2.32 ± 0.11	2.52 ± 0.11	0.20

Plaque EPA level is negatively correlated with inflammation and plaque stability (primary endpoint)

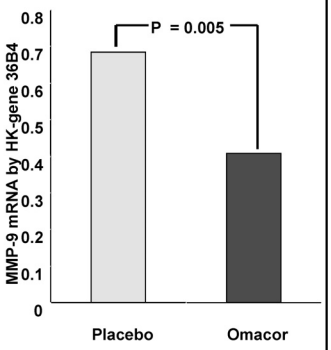
Histology Feature	Plaque EPA*	p-value
Mean Score	-0.21	0.043

⇒ The more EPA in the plaque the less inflamed and more stable it is

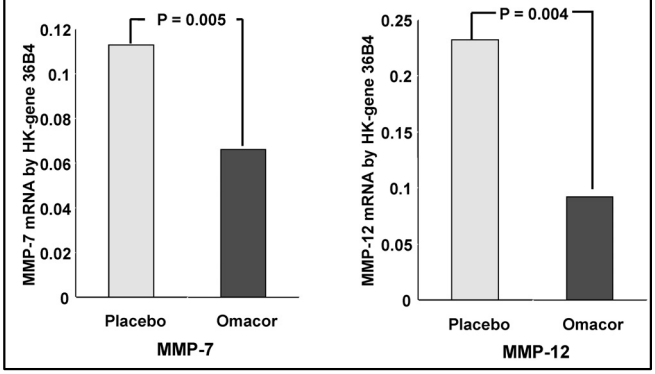
* Pearson Correlation Coefficient

Plaque MMP-9 mRNA expression was significantly lower in the Omacor group

- MMP-9 highly expressed in carotid plaques
- Involved in collagen breakdown and cap weakening
- MMP-9 regulated by PGE_2 pathway

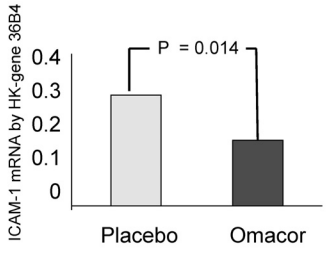


Plaque MMP-7 & MMP-12 mRNA expression lower in the Omacor group



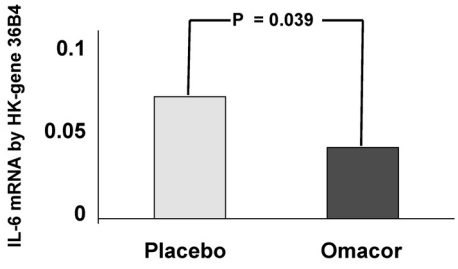
Plaque ICAM-1 mRNA expression was significantly lower in the Omacor group

- ICAM-1 is an adhesion molecule involved in recruitment of monocytes into the vessel wall
- Increased expression is associated with progression of atherosclerosis



Decreased macrophage numbers in the plaques could be related to lower ICAM-1 expression

Plaque IL-6 mRNA expression was significantly lower in the Omacor group



Cardiomyo-tropic effects of Ω3FA

PUFAs significant inhibit cardiac Na+ and Ca2+ channels

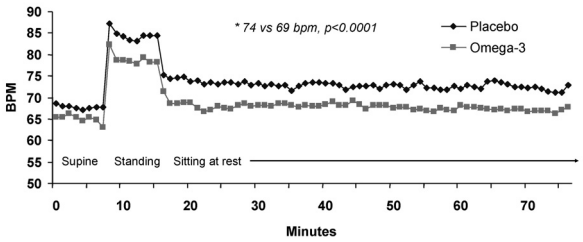
- d/t changing fluidity of cell membrane ?
- by alteration of stresses between channel and membrane when the hydrophobic length of the transmembrane channel protein does not match the hydrophobic thickness of the resting membrane phospholipid bilayers
- d/t direct interaction with specific channel proteins

PUFAs have no significant effects on *I*K1 and HCN channels

- IK1 ; critical for maintaining resting membrane potential in most cardiomyocytes
- HCN channels ; critical for pacemaker cells in the heart

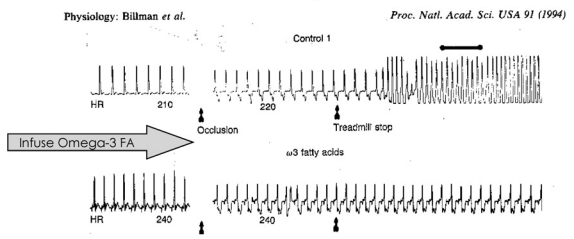
(J Membr Biol. 2005 Jul;206(2):141-54.)

Effect of EPA+DHA (810 mg/d x 4 mo) on Heart Rate in 18 CHD Patients



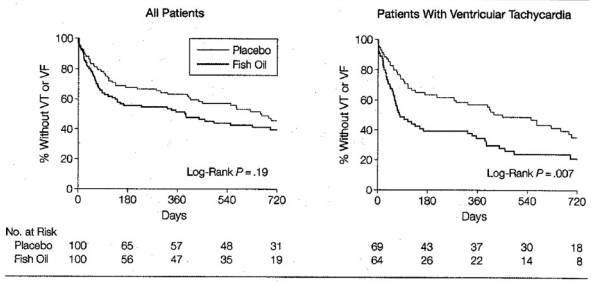
O'Keefe et al. Am J Cardiol 2006;97:1127-1130

Omega-3 FA Infusion Prevents Ventricular Tachyarrhythmias in Dogs



Omega-3 FA and Risk for VT/VF in Patients with ICD's

Figure 2. Survival Curves for Time to First Episode of ICD Therapy for VT or VF in All Patients and in VT Patients by Fish Oil vs Placebo Group



ICD indicates implantable cardioverter defibrillator; VT, ventricular tachycardia; and VF, ventricular fibrillation.

Raitt et al. JAMA 2005;293:2884.

Heart rate variability

	Mean (+SD) before	Mean (+SD) after
SDNN		
Omega-3	**115 (39)**	**124 (30)***
Control	**115 (45)**	**105 (36)**
Mean RR	**807 (104)**	**825 (95)**
	823 (187)	**827 (175)**

*** p=0.04**

Christensen et al, BMJ 1996; 312:677

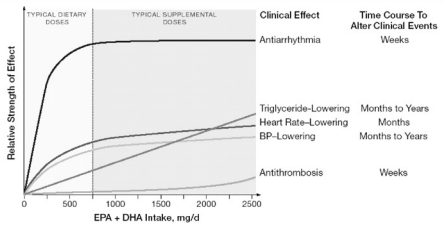
Neurotropic effects of Ω3FA ; Dementia

- Neurons and synapses are highly enriched in long chain unsaturated fatty acids (DHA)
- Aged Tg2576 APPsw transgene-positive mice with DHA depleting diet exhibited increased oxidative damage and transgene-dependent loss of CNS DHA and massive (70–95%) loss of postsynaptic proteins like the actin-regulatory drebrin etc.
- DHA partially suppressed p85α subunit loss, improved neuroprotective AKT, BAD and GSK3β phosphorylation

Ω3FA & Dementia

- Low serum DHA levels increased the development of dementia (Framingham study; Arch Neurol. 2006 Nov;63(11):1545-50.)
- Compared to normals, participants with dementia had significantly lower n-3 FA levels (2.9% vs 3.2%; p <.05), particularly alpha-linolenic acid levels (0.34% vs 0.39%; p <.05) (InCHIANTI study; J Gerontol A Biol Sci Med Sci. 2007 Oct;62(10):1120-6.

Figure 3. Schema of Potential Dose Responses and Time Courses for Altering Clinical Events of Physiologic Effects of Fish or Fish Oil Intake



The relative strength of effect is estimated from effects of eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) on each risk factor and on the corresponding impact on cardiovascular risk.[70-72,79-84] For example, dose response for antiarrhythmic effects is initially steep with a subsequent plateau, and clinical benefits may occur within weeks, while dose response for triglyceride effects is more gradual and monotonic, and clinical benefits may require years of intake. At typical Western levels of intake (eg, <750 mg/d EPA + DHA), the physiologic effects most likely to account for clinical cardiovascular benefits include (1) modulation of myocardial sodium and calcium ion channels, reducing susceptibility to ischemia-induced arrhythmia;[16,19] and (2) reduced left ventricular workload and improved myocardial efficiency as a result of reduced heart rate, lower systemic vascular resistance, and improved diastolic filling.[67-72,80] At higher levels of intake seen with fish oil supplementation or in Japanese populations[69,70] (>750 mg/d EPA + DHA), maximum antiarrhythmic effects have been achieved and clinically relevant effects occur on levels of serum triglycerides[79] and possibly, at very high doses, thrombosis.[78] Potentially important effects on endothelial,[72] autonomic,[74] and inflammatory[81] responses are not shown because dose responses and time courses of such effects on clinical risk are not well established. Effects are not necessarily exclusive: eg, antiarrhythmic effects may be partly mediated by effects on blood pressure (BP) or heart rate.

AHA Recommendations for Omega-3 Fatty Acid Intakes

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, Harris and Appel. *Circulation*. 2002; 106:2747-57

Era of Combination