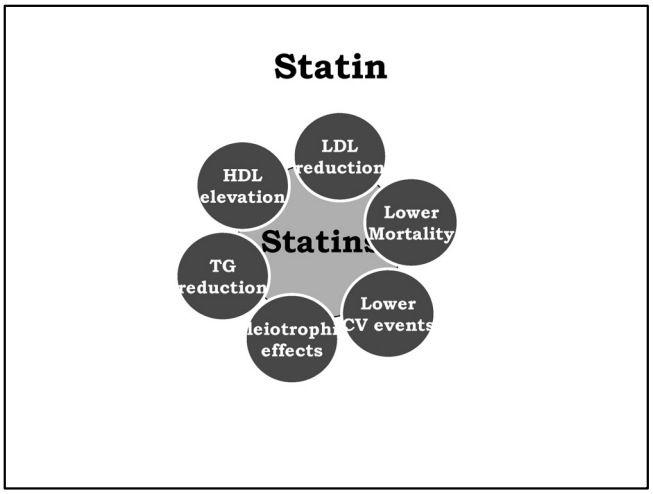
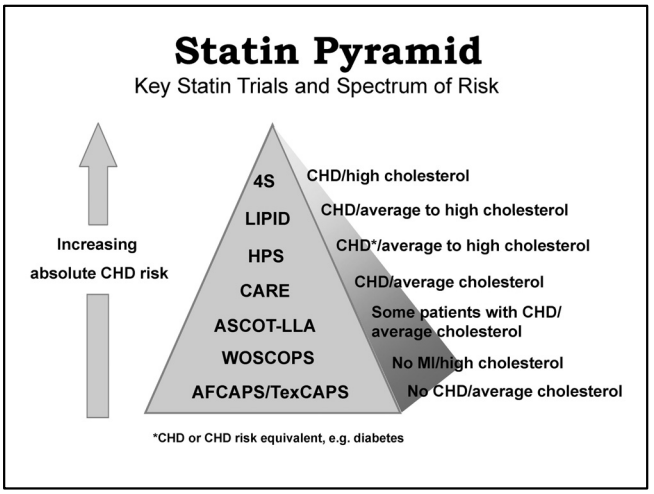
[연수강좌]

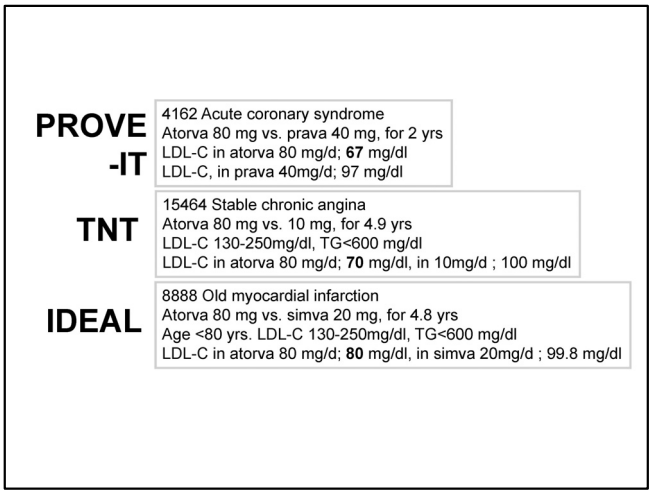
Triglyceride-HDL LDL; Is that enough?

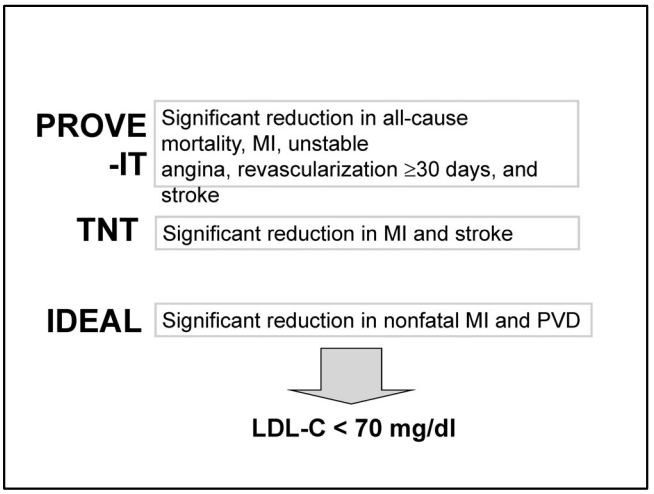
한 기 훈

울산의대





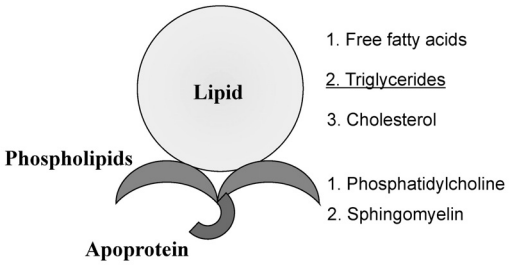




“What if LDL-C less than 40 mg/dl ?”

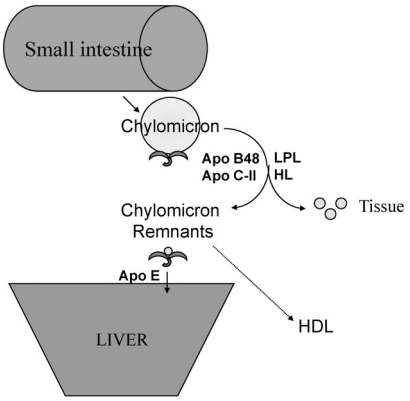
- JACC 2005, 46(8); 1411-1416 ; PROVE-IT subgroup analysis
- HR = 0.61 when compared to LDL 80-100mg/dl
- No further AE

“ LIPOPROTEIN “

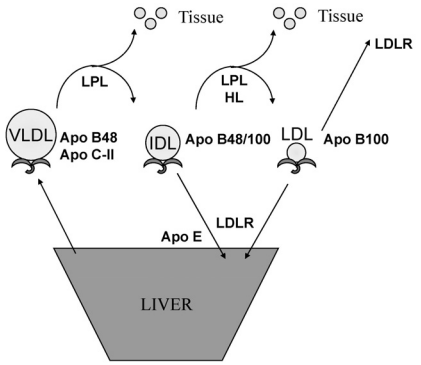


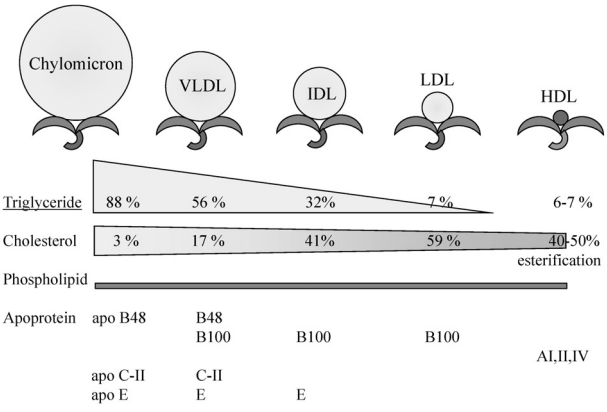
Apo A, B, C, and, E etc.

“ Chylomicron “



“ VLDL - IDL - LDL “





Liver controls lipoprotein synthesis

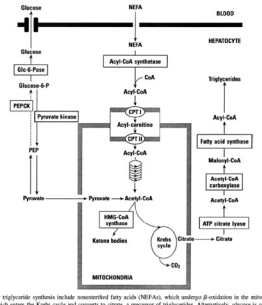


Figure 1. Substrates for triglyceride synthesis include nonesterified fatty acids (NEFAs), which undergo β-oxidation in the mitochondria to form acetyl coenzyme A (CoA), which enters the Krebs cycle and converts to citrate, a precursor of triglycerides. Alternatively, glucose is converted to pyruvate by pyruvate kinase, which is also converted in the mitochondria to acetyl-CoA and then enters the Krebs cycle to form citrate. Therefore, both glucose and NEFAs are substrates for triglyceride synthesis. ATP = adenosine triphosphate; CO_2 = carbon dioxide; CPT = carnitine palmitoyltransferase; Glc-6-P = glucose-6-phosphate; HMG = 3-hydroxy-3-methylglutaryl; Pase = phosphatase; PEP = phosphenol pyruvate; PEPCK = phosphoenolpyruvate carboxykinase. (Adapted from *J Nutr.*[7])

Am J Cardiol 2006;98[suppl]:27i–33i

Liver controls lipoprotein synthesis(2)

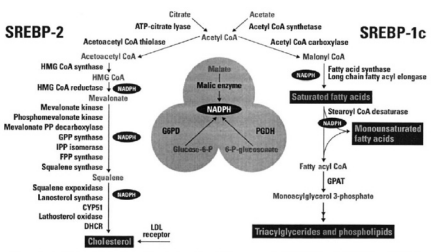
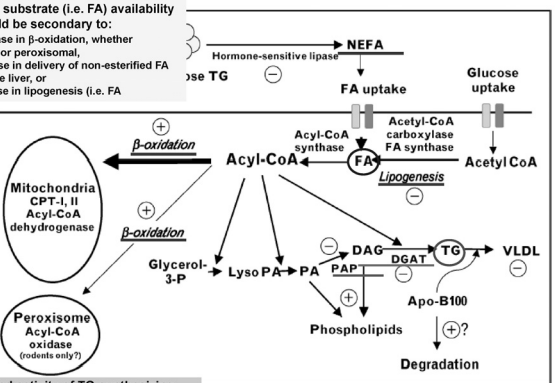


Figure 2. The liver X receptor (LXR) controls both sterol regulatory element binding protein (SREBP)-2 and SREBP-1c. SREBP-2 regulates the genes involved in cholesterol synthesis, whereas SREBP1-c stimulates the production of genes involved with the lipogenic enzymes. Inhibition of LXR would result in 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

Potential TG-Lowering Mechanisms

1. reduced substrate (i.e. FA) availability which could be secondary to:
(a) an increase in β-oxidation, whether microsomal or peroxisomal,
(b) a decrease in delivery of non-esterified FA (NEFA) to the liver, or
(c) a decrease in lipogenesis (i.e. FA synthesis);



2. decreased activity of TG-synthesizing enzymes, such as diacylglycerol acyltranferase (DGAT) or phosphatidic acid phosphohydrolase (PAP);

3. increased phospholipid synthesis [which could drain diacylglycerol (DAG) away from DGAT].

Impact of Triglyceride Levels Beyond Low-Density Lipoprotein Cholesterol After Acute Coronary Syndrome in the PROVE IT-TIMI 22 Trial

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Jie Qin, MS,† Kausik K. Ray, MD, MRCP,‡ Eugene Braunwald, MD, MACC,†
for the PROVE IT-TIMI 22 Investigators
Baltimore, Maryland; Boston, Massachusetts; and Cambridge, United Kingdom

JACC 2008,51;724-30

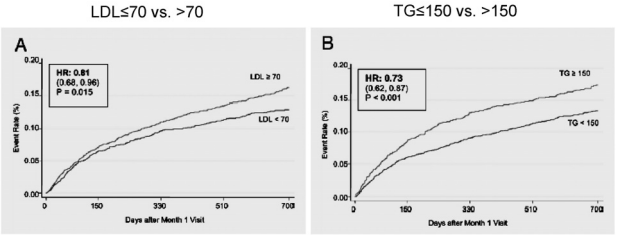
Table 1 Baseline Characteristics by TG Quintile at 30 Days After an ACS

Characteristic	TG Quintile 1 (n = 763)	2 (n = 753)	3 (n = 737)	4 (n = 732)	5 (n = 733)	Total (n = 3,718)
General						Mean
Mean age, yrs	59.7	59.2	58.8	57.5	55.3	58.1
Men, %	81.9	78.9	76.0	74.0	82.0	78.6
Coronary risk factors, %						
Current smoker	30.0	34.0	33.7	41.3	42.4	36.2
Hypertension	46.7	45.3	51.7	51.8	51.6	49.4
Obesity (BMI >30 kg/m^2)	28.4	34.8	39.2	43.8	51.3	39.4
Diabetes	13.8	16.1	16.4	19.1	20.6	17.2
Prior ACS	22.4	23.5	28.1	28.3	34.8	27.4
Prior statin use	20.3	21.9	26.5	27.1	31.8	25.5
Peripheral vascular disease	4.6	6.1	5.4	5.5	6.6	5.6
Lipids and lipoproteins, median (IQR)						
TG, mg/dl	69 (59–77)	97 (90–102)	123 (116–130)	162 (150–177)	254 (218–317)	
Total cholesterol, mg/dl	120 (100–146)	130 (112–153)	138 (118–160)	152 (127–178)	170 (147–193)	
LDL-C, mg/dl	63 (47–82)	68 (53–88)	73 (54–92)	78.5 (57–102)	81 (59–101)	
HDL-C, mg/dl	42 (36–50)	41 (35–47)	40 (34–47)	38 (32–45)	35 (30–42)	
High-sensitivity CRP, mg/l	1.41 (0.66–3.31)	1.90 (0.87–4.26)	1.93 (0.95–4.36)	2.15 (1.02–4.43)	2.36 (1.14–4.43)	

ACS = acute coronary syndrome; BMI = body mass index; CRP = C-reactive protein; HDL-C = high-density lipoprotein cholesterol; IQR = interquartile range; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

JACC 2008,51;724-30

Estimates of death, myocardial infarction, and recurrent acute coronary syndrome between 30 days and 2 years of follow-up



JACC 2008,51;724-30

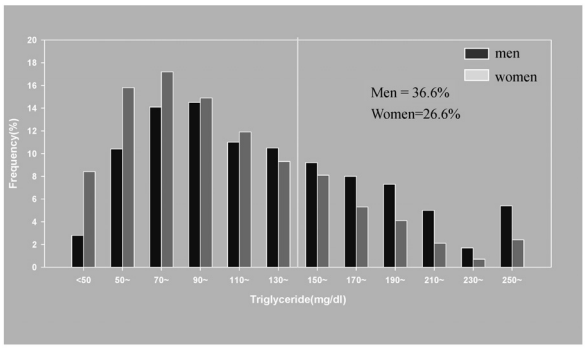
Table 3 Risk of Death, MI, or Recurrent ACS With LDL-C <70 mg/dl and Selected On-Treatment TG or Non–HDL-C Cut-Points 30 Days After ACS

LDL-C <70 mg/dl + Variable	Patients, n	Rate, %	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)*	p Value, Adjusted Analysis
TG ≥200 mg/dl	603	20.3	1.00	0.76 (0.52–1.12)	0.170
TG <200 mg/dl	2,796	13.5	0.64 (0.53–0.78)	0.60 (0.45–0.81)	0.001
TG ≥100 mg/dl	2,259	15.4	1.00	0.90 (0.71–1.14)	0.368
TG <100 mg/dl	1,140	13.4	0.85 (0.71–1.03)	0.82 (0.61–1.10)	0.189
Non–HDL-C ≥130 mg/dl	741	17.9	1.00	0.83 (0.26–2.63)	0.755
Non–HDL-C <130 mg/dl	2,652	13.9	0.77 (0.63–0.93)	0.79 (0.61–1.02)	0.067
Non–HDL-C ≥100 mg/dl	1,676	16.5	1.00	1.07 (0.73–1.56)	0.722
Non–HDL-C <100 mg/dl	1,718	13.1	0.79 (0.66–0.94)	0.83 (0.66–1.05)	0.123

*Adjusted for age, gender, low HDL-C, smoking, hypertension, obesity, diabetes, prior statin therapy, prior ACS, peripheral vascular disease, and treatment effect compared with higher levels of LDL-C and TG or non–HDL-C.
Abbreviations as in Tables 1 and 2.

JACC 2008,51;724-30

TG distribution in Korean population

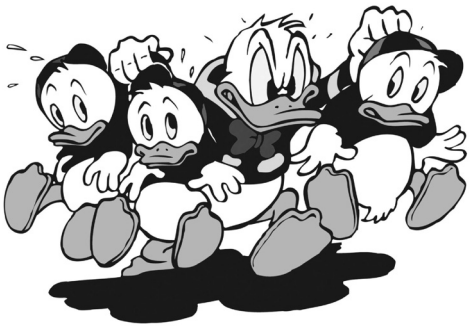


What is the meaning of high TG ?

TG itself ?

Low HDL?

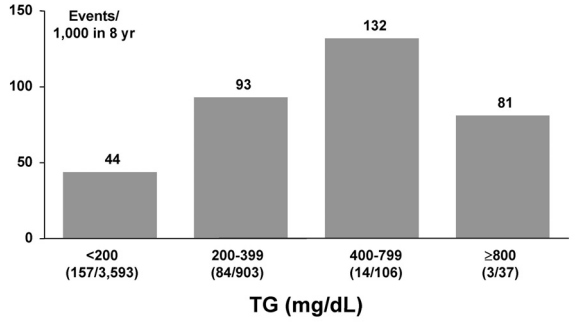
Bad LDL?



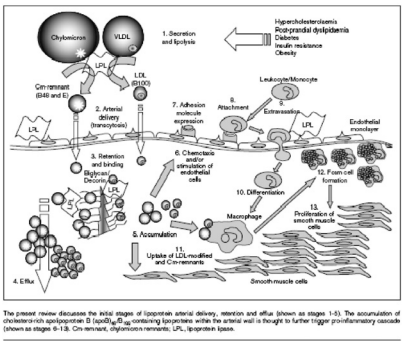
Is that TG ?

- Pros ;
  HyperTG particles can act like LDL particles
- Cons ;
  Familial hyperTGemia or hyperchylomicronemia do not develop premature atherosclerosis

Hypertriglyceridemia—An Independent Risk Factor for CHD: PROCAM Study



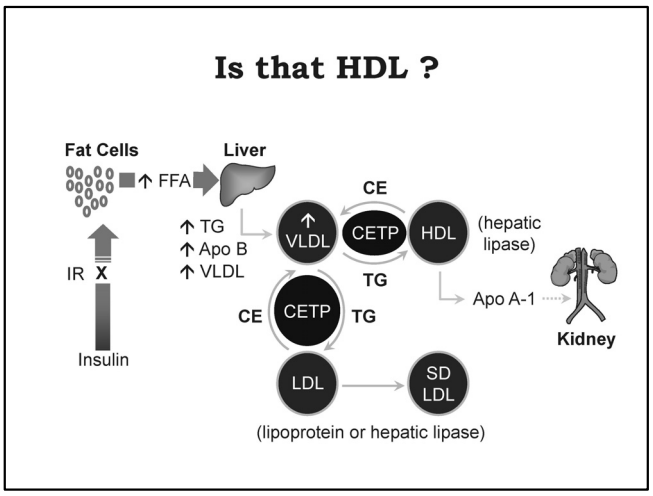
Assmann G et al. *Am J Cardiol.* 1992;70:733-737.

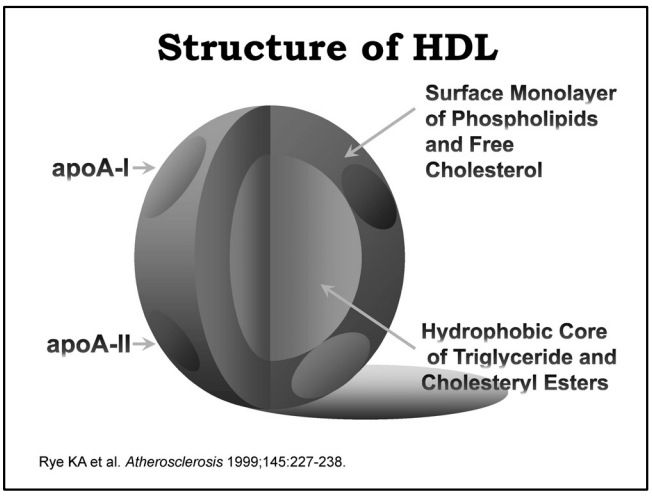


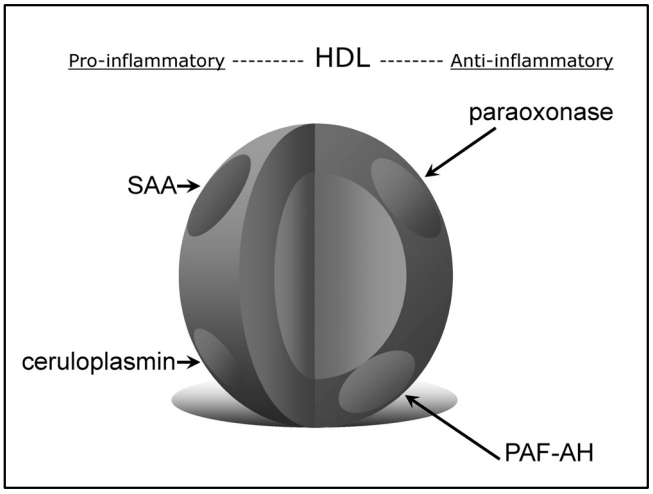
The present review discusses the initial stages of lipoprotein arterial delivery, retention and efflux (shown as stages 1-5). The accumulation of cholesterol-rich apolipoprotein B ($apoB_{100}$/$apoB_{48}$ containing lipoproteins within the arterial wall is thought to further trigger proinflammatory cascade (shown as stages 6-13). Cm-remnant, chylomicron remnants; LPL, lipoprotein lipase.

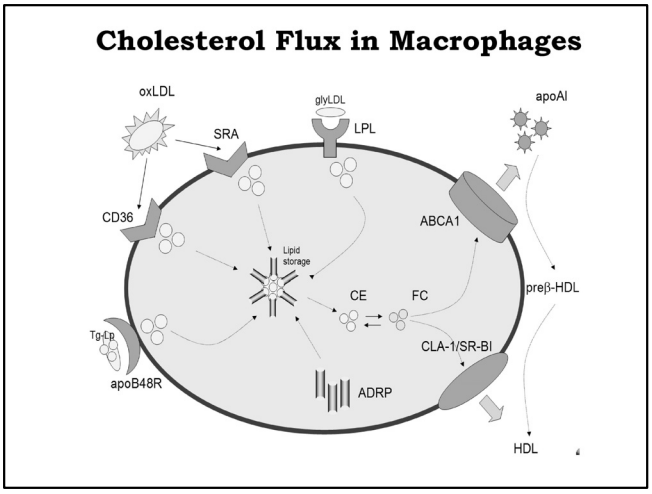
The consequence of postprandial cholesterol flux, high plasma concentrations of apoB48, evidence of arterial retention, and proinflammatory properties of apoB48-containing chylomicron remnants suggest that this lipoprotein may be an underestimated risk factor for CVD.

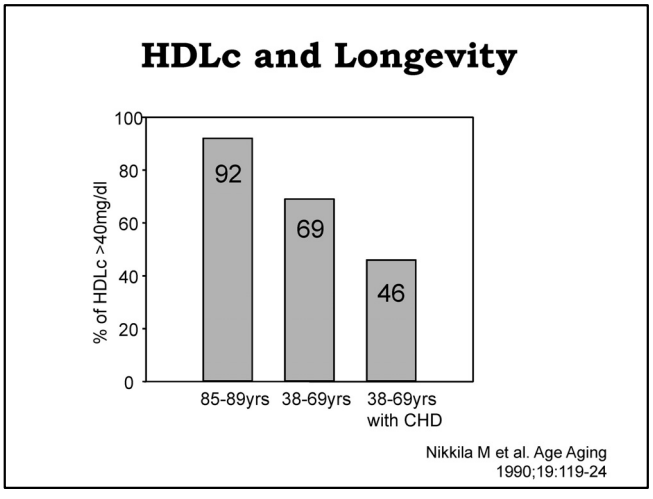
Proctor, S. *Current opinion in lipidology* 2002, 13:461-470

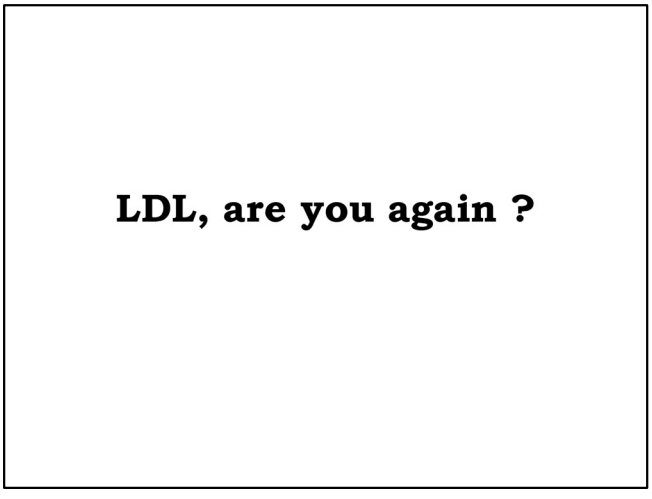

Is that HDL ?
Fat Cells
Liver
↑ FFA
↑ TG
↑ Apo B
↑ VLDL
IR X
Insulin
CE
VLDL
CETP
HDL
(hepatic lipase)
TG
Apo A-1
Kidney
CE
CETP
TG
LDL
SD LDL
(lipoprotein or hepatic lipase)

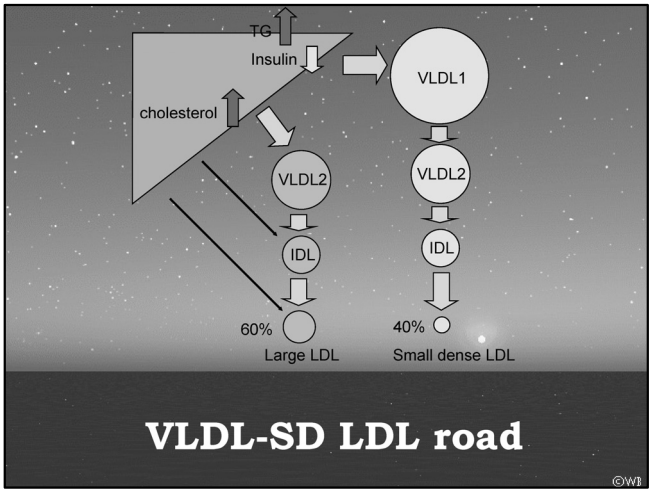

Structure of HDL
Surface Monolayer of Phospholipids and Free Cholesterol
apoA-I
apoA-II
Hydrophobic Core of Triglyceride and Cholesteryl Esters
Rye KA et al. Atherosclerosis 1999;145:227-238.


Pro-inflammatory --------- HDL -------- Anti-inflammatory
paraoxonase
SAA
ceruloplasmin
PAF-AH


Cholesterol Flux in Macrophages
oxLDL
glyLDL
apoAI
SRA
LPL
CD36
ABCA1
Lipid storage
CE
FC
preβ-HDL
Tg-Lp
apoB48R
CLA-1/SR-BI
ADRP
HDL


HDLc and Longevity
% of HDLc >40mg/dl
100
80
60
40
20
0
92
69
46
85-89yrs
38-69yrs
38-69yrs with CHD
Nikkila M et al. Age Aging 1990;19:119-24


LDL, are you again ?



Lipoproteins vs. Severity of Metabolic Syndrome

A Prominent Feature of the Metabolic Syndrome in the Framingham Heart Study

TABLE 4. Plasma Levels of NMR-Determined Lipoprotein Measures and Biochemical Lipid Measures With Increasing Number of MetSyn Features*

	No. of Components of MetSyn						
	0	1	2	3	4	5	*P* for Trend
Women	n=562	n=464	n=298	n=134	n=102	n=29	
NMR-derived lipoprotein measures							
Total LDL particle No., nmol/L	1169±16	1344±17	1496±22	1600±32	1678±37	1663±69	<0.0001
Small LDL particles, nmol/L	428±15	591±16	756±20	918±30	1090±34	1187±64	<0.0001
Large LDL particles, nmol/L	714±12	716±13	697±17	618±25	529±28	419±53	<0.0001
Biochemical lipid measures							
LDL-C, mg/dL	117±1	128±2	135±2	137±3	138±3	133±6	<0.0001
ApoB, mg/dL	84±1	92±1	101±1	110±2	111±2	113±4	<0.0001
Triglycerides, mg/dL	71±2	84±2	121±2	154±4	188±4	211±8	<0.0001
HDL-C, mg/dL	66±1	57±1	51±1	45±1	40±1	36±2	<0.0001
Men	n=286	n=407	n=335	n=233	n=113	n=30	
NMR-derived lipoprotein measures							
Total LDL particle No., nmol/L	1290±23	1485±19	1554±21	1690±25	1783±36	1767±69	<0.0001
Small LDL particles, nmol/L	574±26	813±21	991±24	1232±29	1396±41	1361±79	<0.0001
Large LDL particles, nmol/L	684±17	630±14	520±16	411±19	336±27	362±52	<0.0001
Biochemical lipid measures							
LDL-C, mg/dL	127±2	137±2	135±2	137±2	135±3	136±6	0.01
ApoB, mg/dL	90±1	99±1	103±1	111±1	115±2	115±4	<0.0001
Triglycerides, mg/dL	71±3	96±3	133±3	178±4	214±5	231±10	<0.0001
HDL-C, mg/dL	52±1	48±1	43±1	37±1	33±1	32±2	<0.0001

Circulation. 113:20-29, 2006

Small LDL Particle Number vs.Others

A Prominent Feature of the Metabolic Syndrome in the Framingham Heart Study

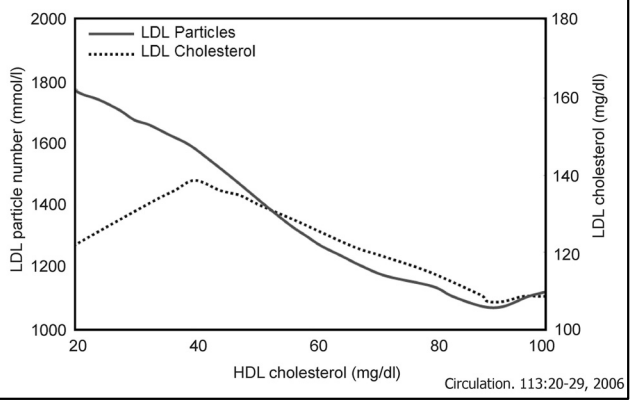
TABLE 3. Correlations Among Small LDL Particle Number and Components of the MetSyn

	ApoB	SBP	DBP	Waist Circumference	Fasting Glucose	HDL-C	Triglycerides
Small LDL particle No.	0.61	0.19	0.20	0.30	0.20	−0.55	0.61
ApoB	…	0.18	0.20	0.28	0.16	−0.34	0.55
SBP	…	…	0.73	0.29	0.23	−0.06	0.23
DBP	…	…	…	0.32	0.17	−0.07	0.25
Waist circumference	…	…	…	…	0.28	−0.35	0.41
Fasting glucose	…	…	…	…	…	−0.14	0.18
HDL-C	…	…	…	…	…	…	−0.52
Triglycerides	…	…	…	…	…	…	…

See the footnote to Table 1 and text for explanation of abbreviations.
Data are Pearson partial correlations adjusted for age and sex.

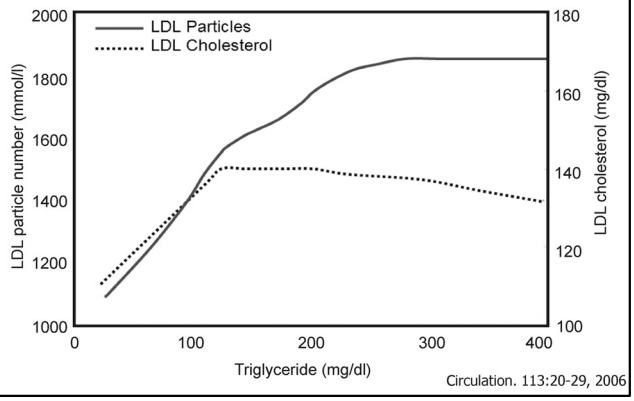
Circulation. 113:20-29, 2006

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



Circulation. 113:20-29, 2006

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



Circulation. 113:20-29, 2006

LDL, is that enough ?

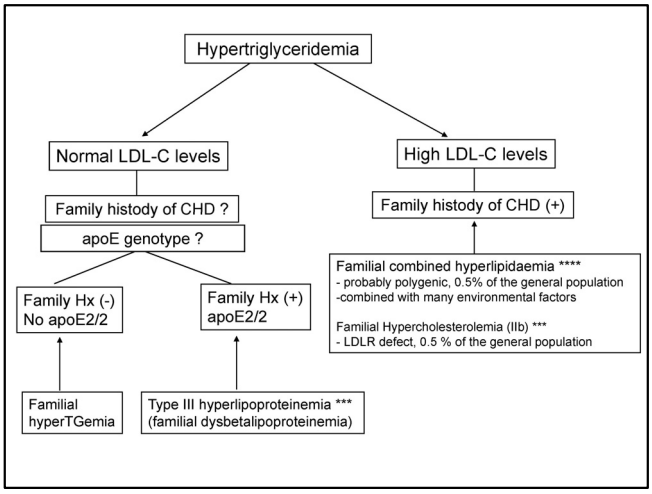
- Lower is better, but earlier is better in high risk patients.
- Lowering LDLc is not enough, especially when the patient shows the feature of metabolic syndrome/diabetes.
- Consider TG and HDL as a next target for the prevention of CVD.
- Towards era of combination ; still needs lots of evidence to come.

Guidelines for Controlling TG

Management of High TG

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

• 가장 채식을 즐기는 나라는 ?



New Features of ATP III

⇒ Modifications of Lipid Targets:
- MAIN TARGET: LDL <100 mg/dL
- HDL <40 mg/dL considered low (instead of 35 mg/dL)
- Triglycerides >200 mg/dL considered to be high

⇒ Focus on Multiple Risk Factors:
- Diabetes (without CHD) raised to the level of CHD equivalent

⇒ Support for Implementation:
- Recommends complete lipoprotein profile (TC, LDL, HDL & TG) as preferred initial test

NCEP-ATP III = National Cholesterol Education Program-Adult Treatment Panel III

Expert Panel *JAMA* 2001;285(19):2486-2497; Wood D et al *Atherosclerosis* 1998;140:199-270; Sempos CT et al *JAMA* 1993;269(23):3009-3014; Pearson TA et al *Arch Intern Med* 2000;160:459-467

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		

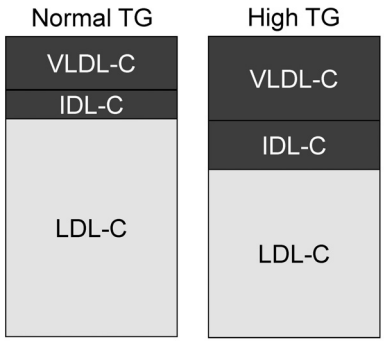
New Features of ATP III

- 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



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

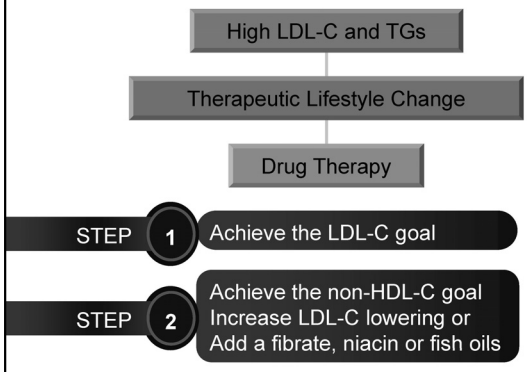
Adult Treatment Panel III (2004 Update)

	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

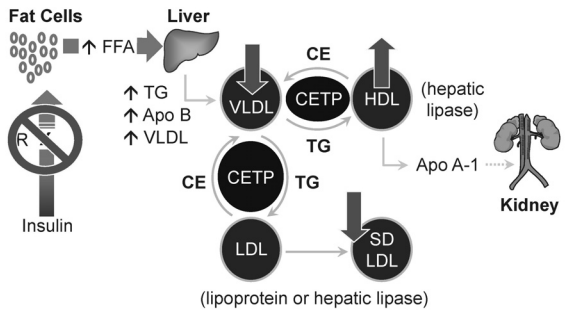
Treatment of Mixed Hyperlipidemia



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

Fibrates

Fibrates are PPAR-alpha activators



Physiologic effect

PPAR alpha activator – TRL 의 **catabolism**을 증가시킴
insulin resistance 를 호전시킴
apo A의 합성을 증가시킴

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

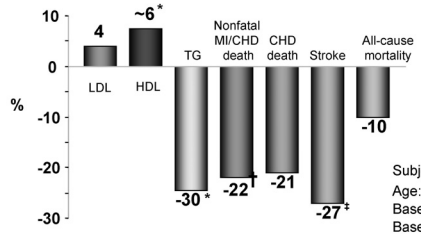
Myopathy, 간기능이나 신기능 이상시 금기
cholesterol gall stone (biliary tract dz시 금기**)**

Fibrate-Statin combination

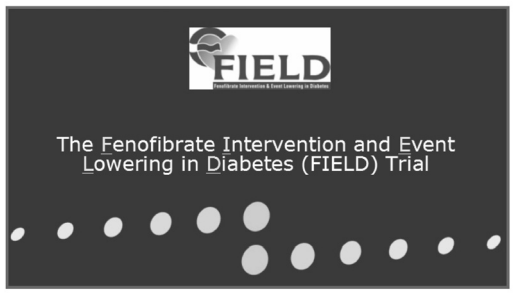
- Increase in LDL level after fibrate tx.
  - mainly due to increase in lipolysis by LPL
- Gemfibrozil – No
  Fenofibrate – Yes (pending ACCORD study)

- Bezafibrate ; BIPS
  - pan PPAR activator
  - 9.4 % reduction of MI and sudden death
- Gemfibrozil ; VA-HIT study
  - 20-30 % reduction of CVD in lowHDL subjects
- Fenofibrate ; FIELD study

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



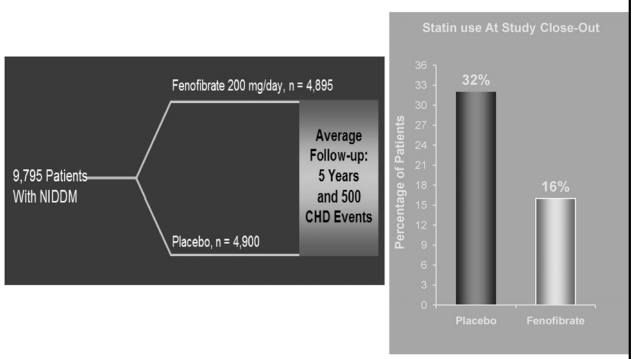
Subjects: 2,531 men
Age: ~74 (avg 64) yr
Baseline LDL-C: 111 mg/dL
Baseline HDL-C: 32 mg/dL
Baseline TG: 161 mg/dL
Duration: 7 yr
Intervention: Gemfibrozil 600 mg bid



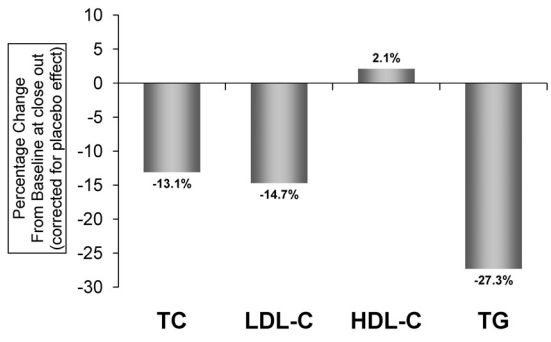
Baseline Characteristics

	Total Population (n = 9,795)
Male/Female, %	**62.7/37.3**
No Prior CVD, %	**78.3**
Diabetes management with diet plus one oral hypoglycemic agent %	**59.5**
Median duration of diabetes, years	**5**
Median HbA1c, %	**6.9**
Diabetic complications	
Retinopathy, %	**8.3**
Nephropathy, %	**2.8**
Lipid parameters, mg/dl	
TC (mean)	**194**
LDL-C (mean)	**119**
HDL-C (mean)	**42**
TG (median)	**153**
Dyslipidemic*, %	**37**

*TG > 150 mg/dL and HDL < 40 mg/dL for men or < 50 mg/dL for women



Lipid Effects of Fenofibrate At Study Close (patients without statins)

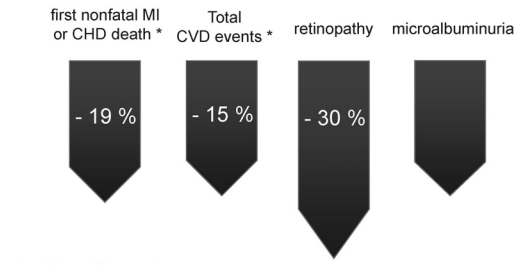


Benefit on the Primary End Point

Fenofibrate Treatment Effect	Relative Risk Reduction (95% CI)	P
CHD Events		
Unadjusted	11% (-5 to 25)	0.16
Adjusted for statin use*	19% (4 to 32)	0.01
Total CVD Events		
Unadjusted	11% (1 to 20)	0.035
Adjusted for statin use*	15% (5 to 24)	0.004

* Non-randomised comparison adjusting for on-study statin use

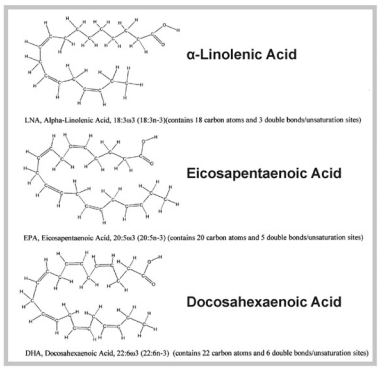
FIbrate as a shiELD



- * ; Adjusted for statin use
- Fenofiibrate shows more effect to the patients without prior cardiovascular event

Omega-3-fatty acid

Structure (n-3 PUFA)



Holub DJ and Holub BJ. Mol Cell Biochem 2004;263:217

Effect of ω-3 Fatty Acids

	Baseline triacylglycerol < 2.0 mmol/L	Baseline triacylglycerol ≥ 2.0 mmol/L
Number of data sets	16	16
Number of subjects		
Placebo	410	750
Fish oil	393	790
Duration (wk)	7.5 (3–16)	18.8 (4–52)
n−3 Fatty acids (g/d)	3.5 (1.5–6.4)	3.7 (1.1–7)
Cholesterol: percentage Δ (%)		
With placebo	1.7	1.6
With fish oil	4.1	4.2
Net placebo–fish oil	2.5	2.5
Triacylglycerol: percentage Δ (%)		
With placebo	5.0	−1.3
With fish oil	−20.4	−26.5
Net placebo–fish oil	−25.4	−25.2
LDL cholesterol: percentage Δ (%)		
With placebo	1.3	2.4
With fish oil	5.8	7.4
Net placebo–fish oil	4.5	5.2
HDL cholesterol: percentage Δ (%)		
With placebo	2.4	5.3
With fish oil	5.1	5.1
Net placebo–fish oil	2.8	−0.1

Harris WS. AJCN 1997;65:1645S

GISSI-Prevenzione trial

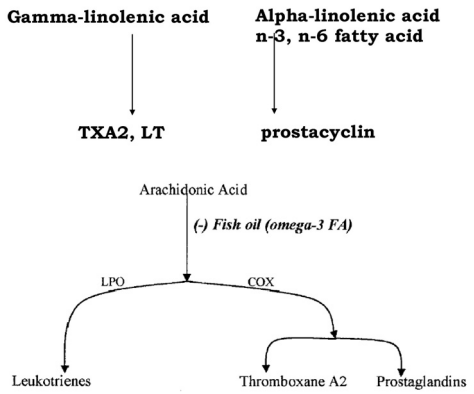
	All (n=11 324)	Two-way analysis			Four-way analysis		
		n-3 PUFA (n=5666)	Control (n=5668)	Relative risk (95% CI)	n-3 PUFA (n=2836)	Control (n=2828)	Relative risk (95% CI)
Main endpoints							
Death, non-fatal MI, and non-fatal stroke	1500 (13·3%)	715 (12·6%)	785 (13·9%)	0·90 (0·82–0·99)	356 (12·3%)	414 (14·6%)	0·85 (0·74–0·98)
Cardiovascular death, non-fatal MI, and non-fatal stroke	1155 (10·2%)	547 (9·7%)	608 (10·8%)	0·89 (0·80–1·01)	262 (9·2%)	322 (11·4%)	0·80 (0·68–0·95)
Secondary analyses							
All fatal events	1017 (9·0%)	472 (8·3%)	545 (9·6%)	0·86 (0·76–0·97)	236 (8·3%)	293 (10·4%)	0·80 (0·67–0·94)
Cardiovascular deaths	639 (5·6%)	291 (5·1%)	348 (6·2%)	0·83 (0·71–0·97)	136 (4·8%)	193 (6·8%)	0·70 (0·56–0·87)
Cardiac death	520 (4·6%)	228 (4·0%)	292 (5·2%)	0·78 (0·65–0·92)	108 (3·8%)	165 (5·8%)	0·65 (0·51–0·82)
Coronary death	479 (4·2%)	214 (3·8%)	265 (4·7%)	0·80 (0·67–0·96)	100 (3·5%)	151 (5·3%)	0·65 (0·51–0·84)
Sudden death	286 (2·5%)	122 (2·2%)	164 (2·9%)	0·74 (0·58–0·93)	55 (1·9%)	99 (3·5%)	0·55 (0·40–0·76)
Other deaths	378 (3·3%)	181 (3·2%)	197 (3·5%)	0·91 (0·74–1·11)	100 (3·5%)	100 (3·5%)	0·99 (0·75–1·30)
Non-fatal cardiovascular events	578 (5·1%)	287 (5·1%)	291 (5·1%)	0·98 (0·83–1·15)	140 (4·9%)	144 (5·1%)	0·96 (0·76–1·21)
Other analyses							
CHD death and non-fatal MI	909 (8·0%)	424 (7·5%)	485 (8·6%)	0·87 (0·76–0·99)	196 (6·9%)	259 (9·2%)	0·75 (0·62–0·90)
Fatal and non-fatal stroke	178 (1·6%)	98 (1·7%)	80 (1·4%)	1·21 (0·91–1·63)	54 (1·9%)	41 (1·5%)	1·30 (0·87–1·96)

MI=myocardial infarction; CHD=coronary heart disease.
Patients with two or more events of different types appear more than once in columns but only once in rows.

Table 3: **Overall efficacy profile of n-3 PUFA treatment**

GISSI-HF trial

- 1g/day reduced mortality by 9% in HF patients



How to use Fish Oil

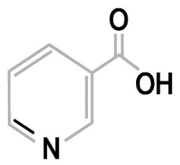
Table 2. Clinical Uses and Recommendations

Clinical Use	Dosage	Comments	Strength of Recommendation
Secondary prevention of cardiovascular disease	1–2 g/day	May encourage dietary intake, or fish oil supplementation	A[19,20]
Hypertriglyceridemia	Initial 2–4 g; up to 12 g	For doses greater than 3 g, consider monitoring for bleeding side effects, LDL, and glycemic response	A[23]
Rheumatoid arthritis	2.6–6 g may initiate at 90 mg/kg; maintenance dose 45 mg/kg	May take 8–12 weeks for clinical response; consider tapering NSAIDs; compliance may be an issue	A[29,30]
Infants (not breast-feeding)	0.35% of dietary fat as DHA	Consider Ω-3 and Ω-6 enriched infant formula	B[42,43]
Women (pregnant and of childbearing age)	2 fatty fish meals a week (up to 12 oz)	Avoid shark, tile fish, king mackerel, swordfish. Limit albacore tuna to 6 oz per week.	C[47,48,66]

How to use Fish Oil

Patient population	*Recommendation*
No documented history of CHD	Eat a variety of fish (preferably oily) at least twice per week. Include oils and foods rich in alpha-linolenic acid (flaxseed, canola, and soybean oils; flaxseeds and walnuts).
Documented history of CHD	Consume approximately 1 g of EPA plus DHA daily, preferably from oily fish. EPA plus DHA capsule supplements may be used in consultation with a physician.
Needs to lower triglyceride level	Consume 2 to 4 g of EPA plus DHA daily in capsules in consultation with a physician.

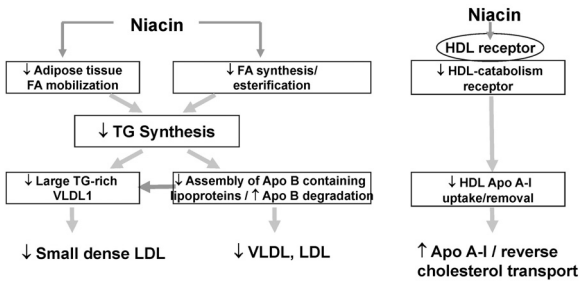
Niacin



"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

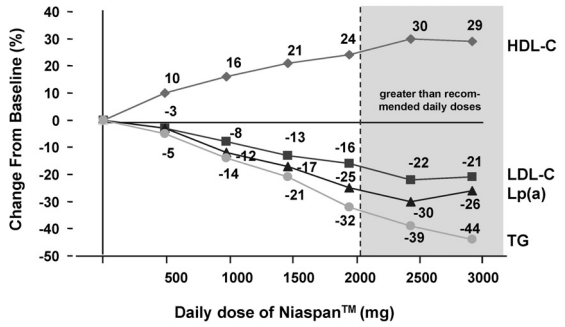


Adapted from Kamanna VS, Kashyap ML. *Curr Atheroscler Rep*. 2000;2:36-46

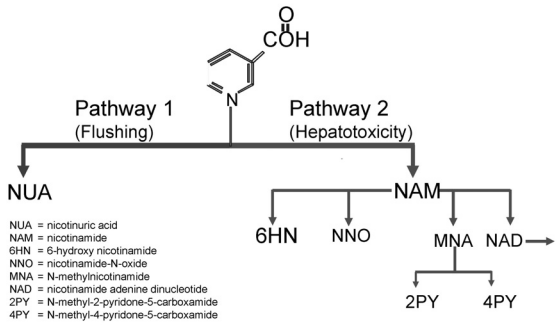
Molecular mechanisms of niacin ; niacin receptor GPR109A/PUMA-G/HM74A

- On adipocytes
  - dec. lipolysis (AMP/PKA pathway blocking)
- On plasma
  - Indirectly inhibits CETP
- On hepatocytes
  - dec. VLDL synthesis
- On macrophages (Biochem Pharmacol 67:411-9, 2004)
  - inc. ABCA1, PPARr, CD36
  - No change in LDLR

Efficacy of Niaspan™



Niacin Metabolism



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

Niacin and Cardiovascular Protection: Secondary Prevention Studies

Study	Treatment(s)	Duration (years)	Efficacy results
Coronary Drug Project (CDP)[1,2]	Nicotinic acid	5	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**

약물의 정리

- Fibrates ;
  - 당뇨가 있거나 대사증후군이 있는 경우
  - 매우 높은 중성지방 수치를 보이는 경우
  - 심혈관질환이 아직 없는 경우
  - HDL이 낮은 경우
- O3FA ;
  - 심혈관질환이 있는 경우
  - 스타틴과의 상호작용이 우려되는 경우
  - Gallstone이 있는 경우
  - 혈전이 문제가 되는 경우
- Niacin ;
  - HDL수치가 매우 낮은 경우

즐거운 한 주 되세요 !