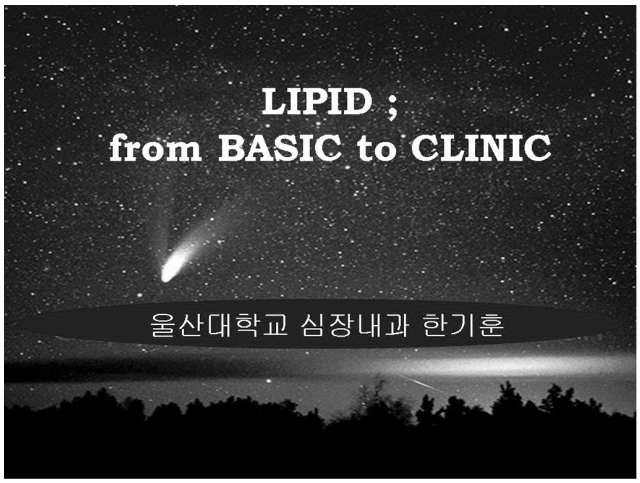
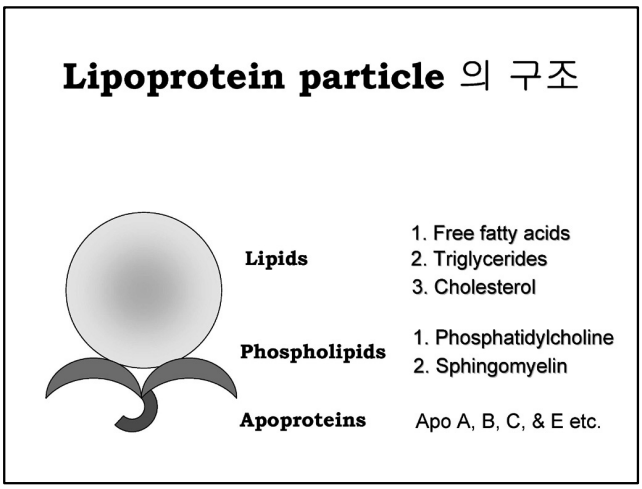
[연수강좌]

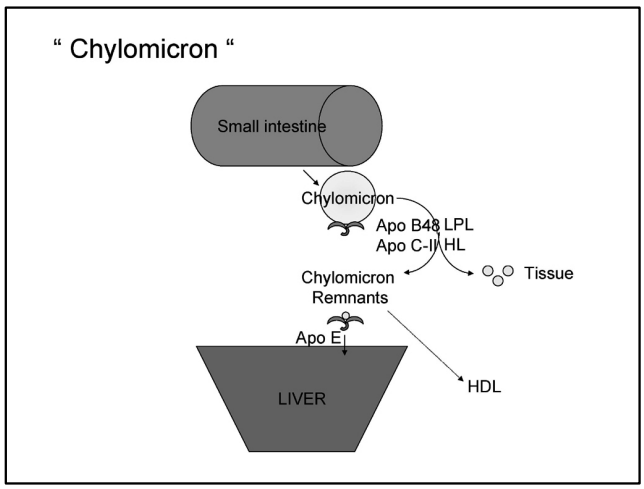
고지혈증치료제의 최신 지견

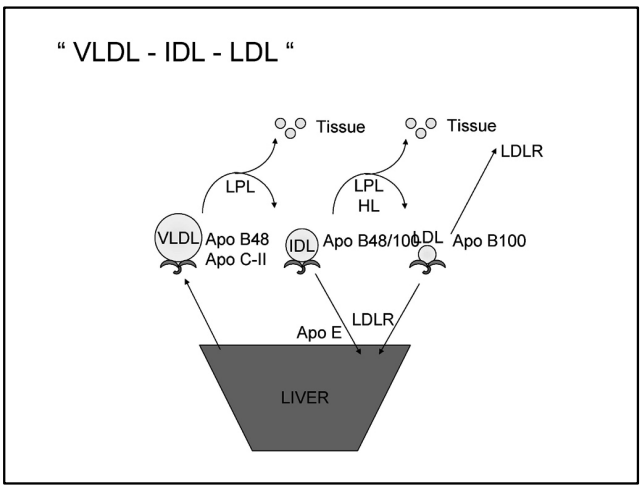
한 기 훈

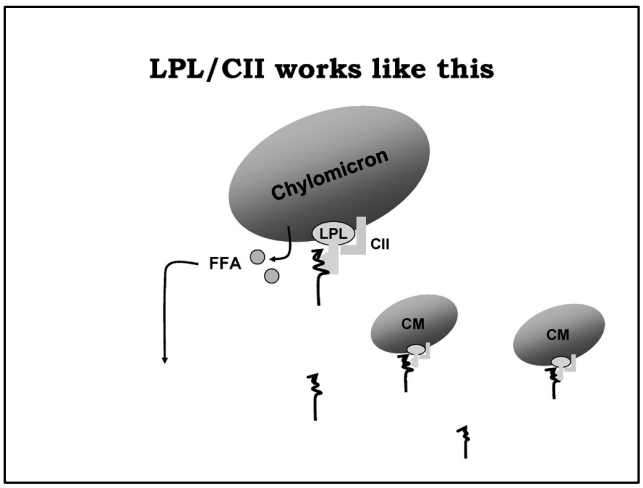
울산대학 서울아산병원 심장내과

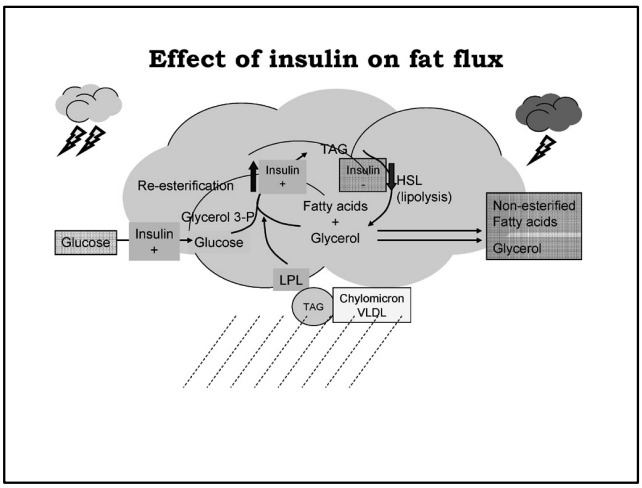


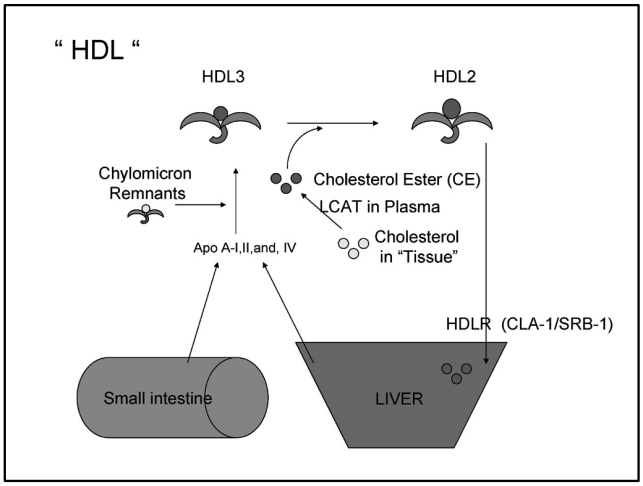


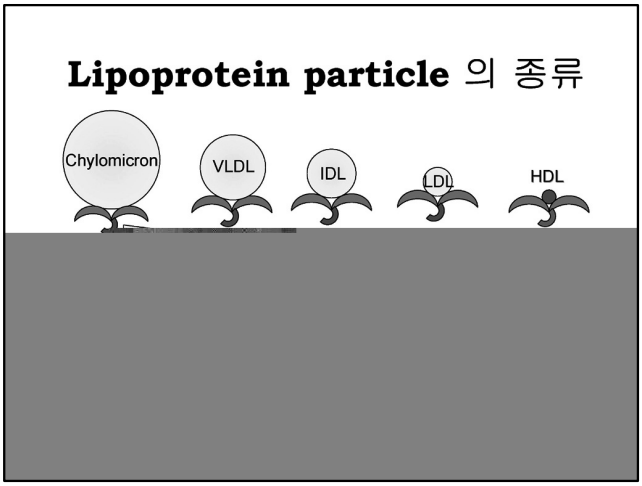




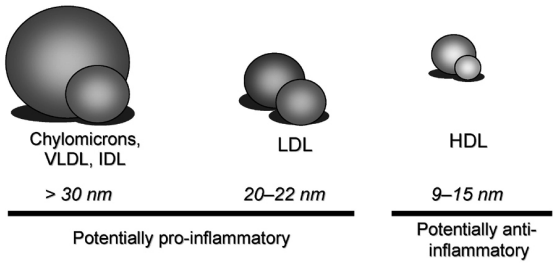

LPL/CII works like this
Chylomicron
LPL
CII
FFA
CM
CM


Effect of insulin on fat flux
TAG
Re-esterification
Insulin
+
Insulin
-
HSL
(lipolysis)
Glycerol 3-P
Fatty acids
+
Glycerol
Non-esterified
Fatty acids
Glycerol
Glucose
Insulin
+
Glucose
LPL
TAG
Chylomicron
VLDL


“ HDL “
HDL3
HDL2
Chylomicron
Remnants
Cholesterol Ester (CE)
LCAT in Plasma
Cholesterol
in “Tissue”
Apo A-I,II,and, IV
HDLR (CLA-1/SRB-1)
Small intestine
LIVER


Lipoprotein particle 의 종류
Chylomicron
VLDL
IDL
LDL
HDL

Lipoprotein Classes and Inflammation



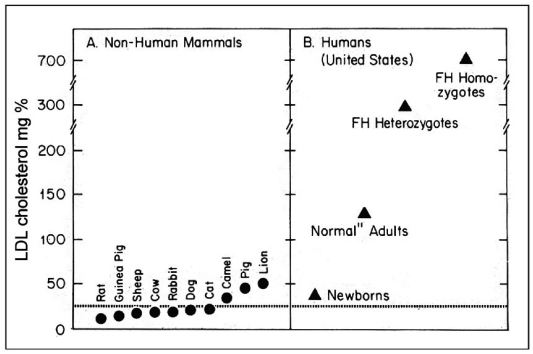
Doi H et al. *Circulation* 2000;102:670-676; Colome C et al. *Atherosclerosis* 2000; 149:295-302; Cockerill GW et al. *Arterioscler Thromb Vasc Biol* 1995;15:1987-1994.

Ideal balance of lipid particles

- VLDL, IDL, LDL; Lower, the better
- HDL ; Higher, the better

Be like bear !

"사람의 콜레스테롤 수치가 가장 높아"



" Lipid battery (L3007)" identifies each lipoprotein particles

Total Cholesterol	Cholesterol in VLDL, IDL, and LDL Cholesterol ester in HDL	Apo B
Triglycerides	Chylomicron VLDL and IDL	Apo B48, CII, E
HDL Cholesterol	Cholesterol ester in HDL	Apo A

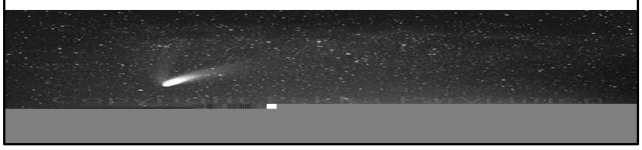
Friedewald formula
LDL-C = TC - TG/5 – (HDL-C)

" Lipid battery (L3007)" identifies pattern of hyperlipidemia

	LDL	TG	
Total Cholesterol			
Triglycerides	↑	normal	IIa
	↑	↑	IIb
HDL Cholesterol	normal	↑	IV (I, III, V)

Friedewald formula
LDL-C = TC - TG/5 – (HDL-C)

I. LDL cholesterol

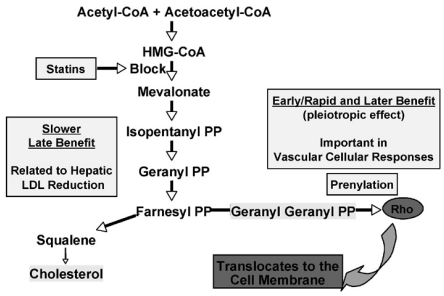


3 Categories of Risk That Modify LDL Cholesterol Goals

Risk Category	LDL Goal (mg/dL)
High ; CHD and CHD risk equivalents Multiple (2+) major risk factors with 10-year risk > 20 %	< 100
Medium ; Multiple (2+) major risk factors with 10-year risk ≤ 20 %	< 130
Low ; 0-1 risk factor	< 160

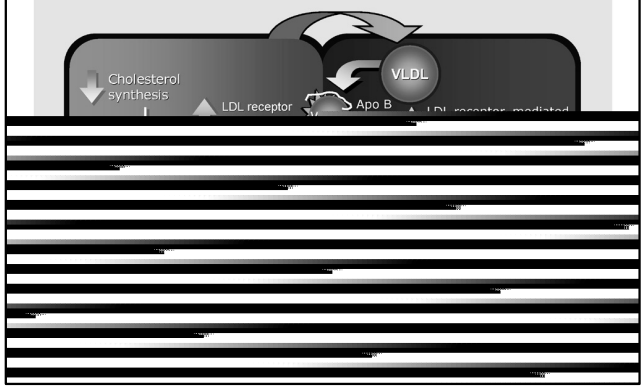
cf. CHD indicates coronary heart disease.

Statins

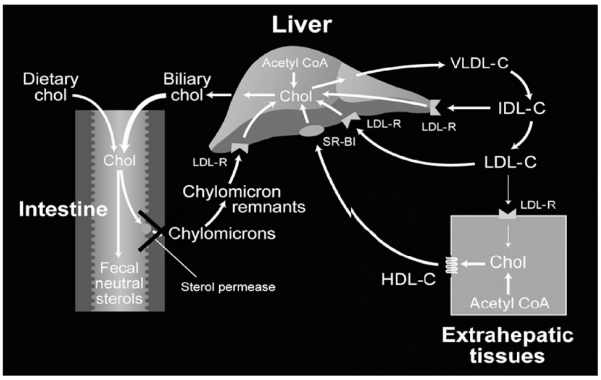


PP = pyrophosphate.
Reproduced from Ray and Cannon. *Curr Opin Lipidol.* 2004;15:637, with permission.
Ray and Cannon. *Am J Cardiol.* 2005;96(suppl):54F.

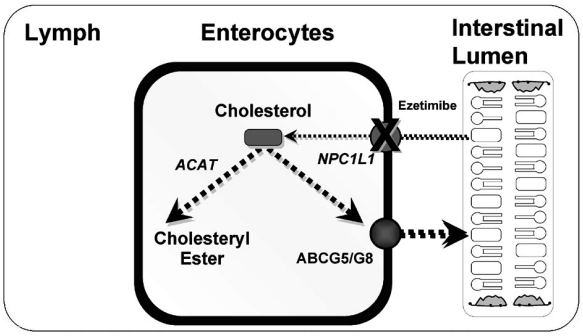
Statins: *Mechanism of Action*



Action of Ezetimibe



Ezetimibe



Altmann SW, Davis HR Jr, Zhu LJ, Yao X, Hoos LM, Tetzloff G, Iyer SP, Maguire M, Golovko A, Zeng M, Wang L, Murgolo N, Graziano MP. Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. Science 2004;303:1201-1204.

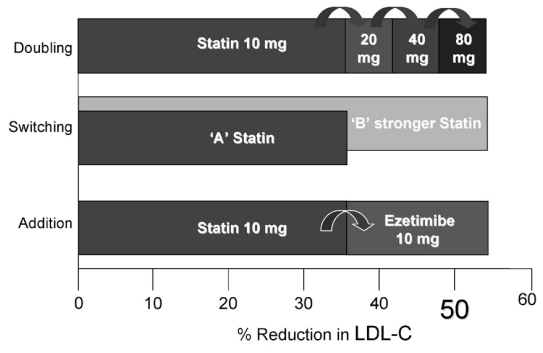
Relative potency of statins

Dose (mg) of agent					% Reduction	
Rosuva	Atorva	Simva+EZ	Simva	Lova / Prava	TC	LDL-C
	5		10	20	22	27
	10		20	40	27	34
10	20		40	80	32	41
20	40	10 / 10	80		37	48
40	80				42	55

Rule of 5s & 7s

Roberts WC. *Am J Cardiol.* 1997;80:106-107.
Stein E et al. *J Cardiovasc Pharmacol Therapeut.* 1997;2:7-16.

Which Way is Better ?



Drug Interactions with Statins

- Cytochrome P450
  simva- lova- atorva- (mainly 3A4)
  ceriva- (mainly 3A4 + 2C9)
  fluva- (mainly 2C9)
- Glucuronidation
  ceriva- simva- lova- atorva-
- P-Glycoprotein
  simva- lova- atorva- prava-

Cyclosporin *
Erythromycin*
Cimetidine*
Azole antifungals*
Lignocaine
Nifedipine
Verapamil
Felodipine
Quinidine
Triazolam
Amiodarone
Mibefradil

Drug Interactions with Statins

- Cytochrome P450
  simva- lova- atorva- (mainly 3A4)
  ceriva- (mainly 3A4 + 2C9)
  fluva- (mainly 2C9)
- Glucuronidation
  ceriva- simva- lova- atorva-
- P-Glycoprotein
  simva- lova- atorva- prava-

Absent in ~ 1% caucasian & black population

NSAIDs
s-Warfarin
Losartan
Amiodarone
SSRIs (some)
Metronidazole

Drug Interactions with Statins

- Cytochrome P450
  simva- lova- atorva- (mainly 3A4)
  ceriva- (mainly 3A4 + 2C9)
  fluva- (mainly 2C9)
- Glucuronidation

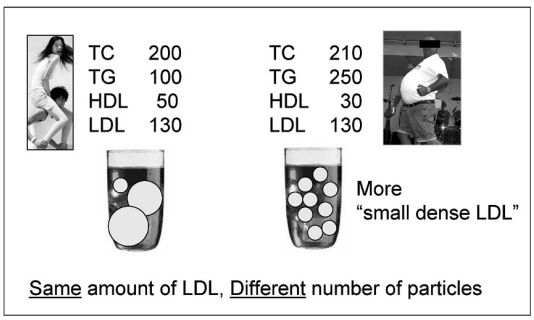
MS; NCEP-ATP III, 2001

Clinical identification (≥3 risk determinants)

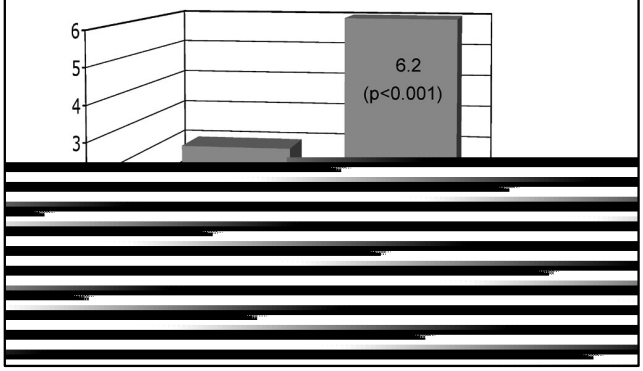
Risk Factor	Definition Level
Waist circumference	
Men (cm)	> 102 (90)
Women (cm)	> 88 (80)
Triglyceride (mg/dL)	≥ 150
HDL-C	
Men (mg/dL)	< 40
Women (mg/dL)	< 50
Blood pressure (mmHg)	≥ 130 / ≥85
Fasting glucose (mg/dL)	≥ 110

JAMA 285:2486, 2001

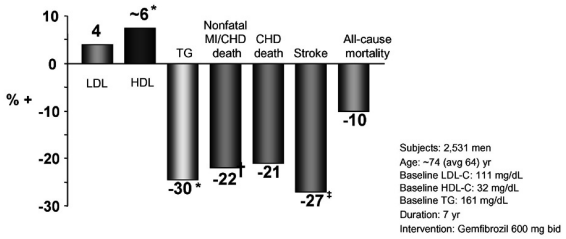
MS-SD LDL relation



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



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 1회, 매일

Toxicity

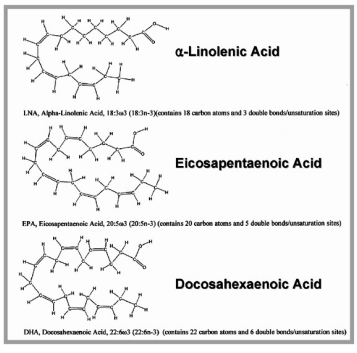
Myopathy, 간기능이나 신기능 이상시 금기
cholesterol gall stone (biliary tract dz시 금기)

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)

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

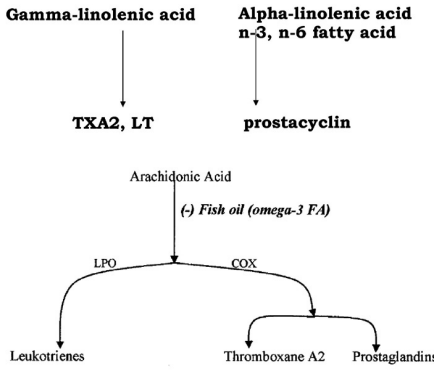
Harris WS. AJCN 1997;65:1645S

GISSI-Prevenzione trial

	All (n=11 324)	Two-way analysis			Four-way analysis		
		n-3 PUFA (n=5665)	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 (0·87–1·95)

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.

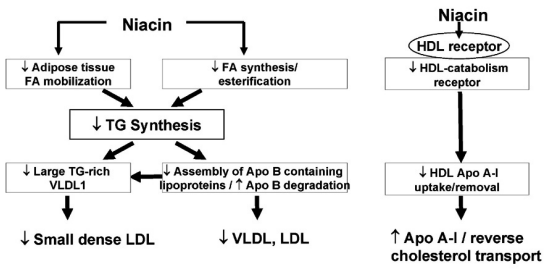
Table 3: **Overall efficacy profile of n-3 PUFA treatment**



How to use Fish Oil

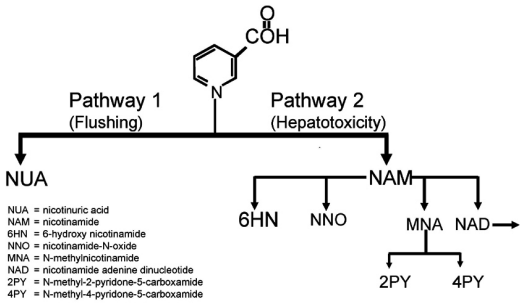
Patient population	Recommendation

Mechanism of Action of Niacin on Lipoprotein Metabolism



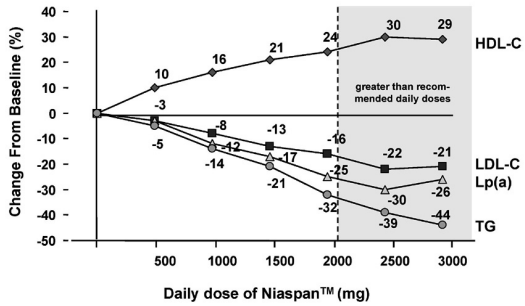
Adapted from Kamanna VS, Kashyap ML. *Curr Atheroscler Rep.* 2000;2:36-46

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**

정리 - 이해목록

- Lipoprotein의 구조를 이해
- LDL에 의한 동맥경화의 발생을 이해
- HDL의 동맥경화 방지기전을 이해
- Lipid battery의 의미를 이해
- LDL을 적극적으로 낮추어야 하는 '고위험군'을 이해
- 스타틴의 기전을 이해
- 중성지방을 낮추는 약제를 열거
- 각종 이상지질혈증의 상태에서 적합한 약제를 선택