

[연수강좌]

고지혈증의 조절

한 기 훈

울산의대

“생애 전환기”

본인의 건강상태가 갈리는 시기

From ICEBERG

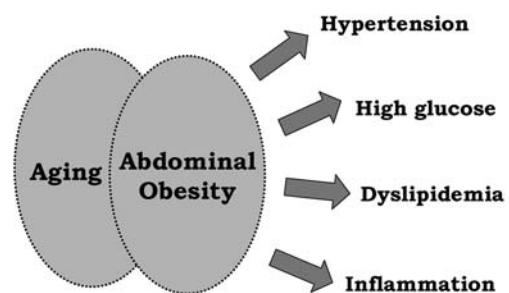


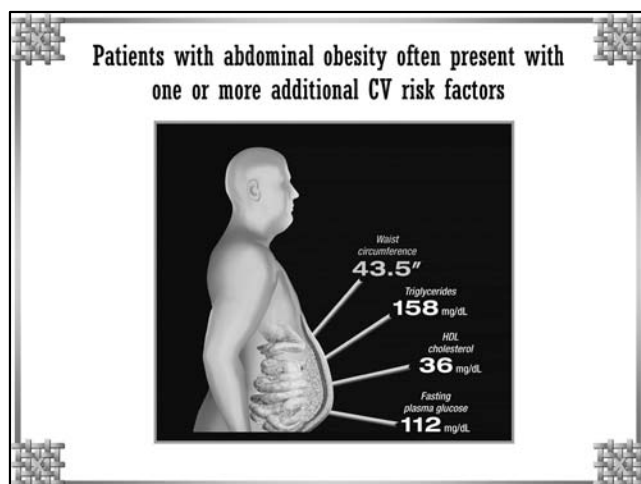
To Volcano



Photo taken on August 27, 2005 @ 8h50 pm ©Arenal.net

Strong Comorbidities in Obese/Aging Conditions !





知彼知己百戰不殆

Know your Risk !

Identification of Cardiovascular Risk Factors

More than 200 factors had been described in the articles so far.

" CHD " or " CHD equivalents "

- 확진된 CHD
- 증상이 있는 기타혈관질환 (symptomatic carotid disease, aortic aneurysm, peripheral arterial disease)
- 당뇨병

CHD ; coronary heart disease

심장질환의 주 위험인자 * (LDL Cholesterol 수치 불포함)

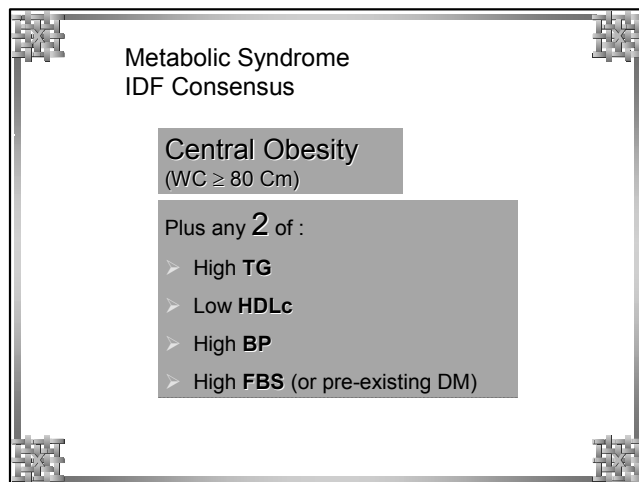
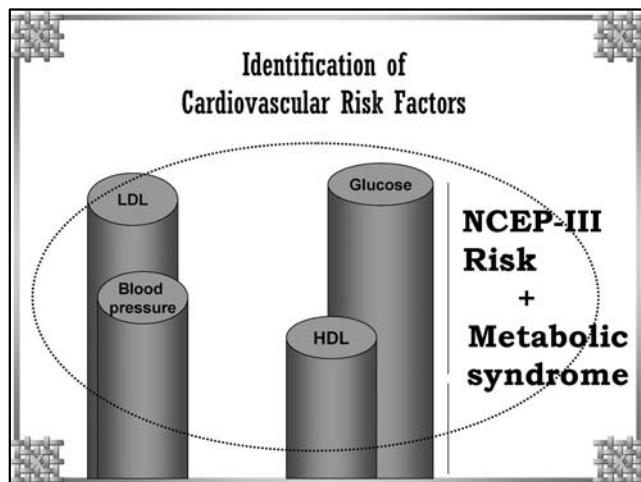
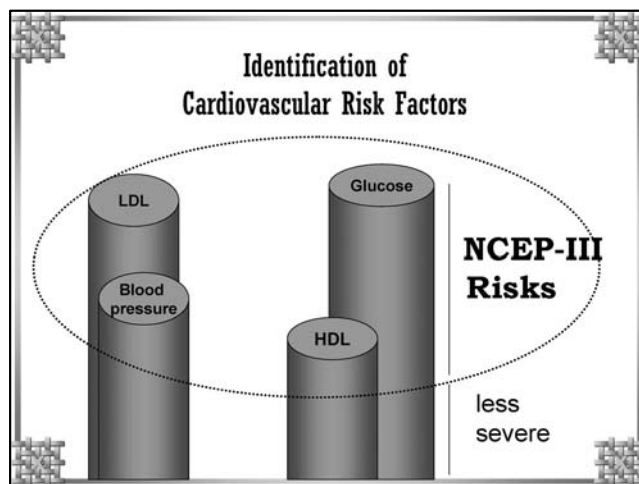
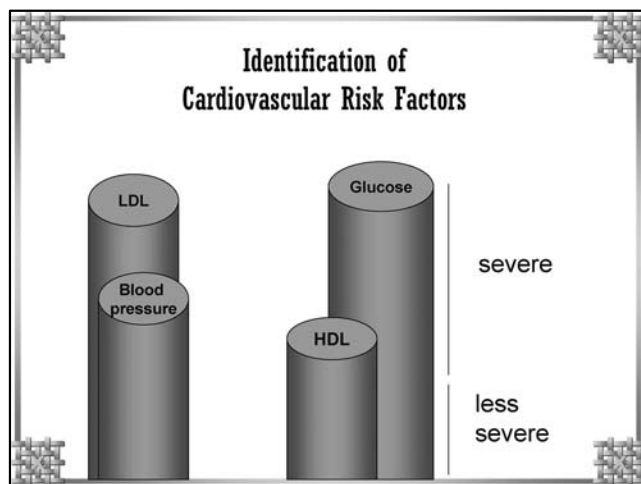
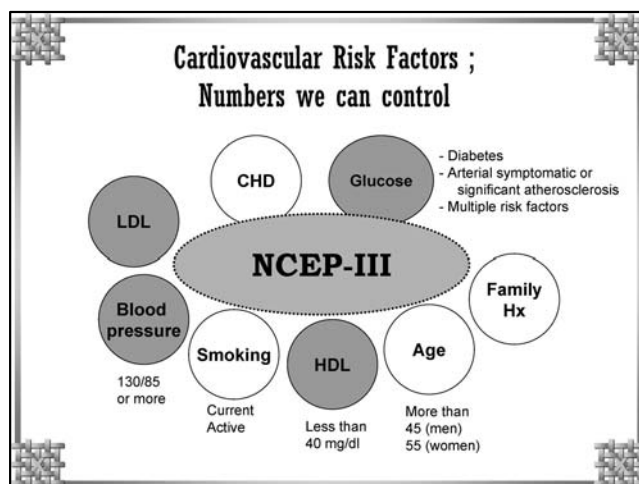
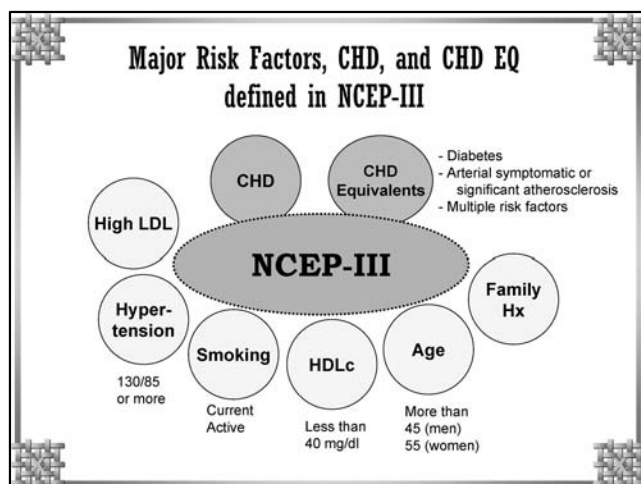
- 흡연
- 고혈압 ($\geq 140/90$ mmHg 또는 약물치료중)
- 낮은 HDL cholesterol 수치 (< 40 mg/dL)†
- 심질환의 가족력 (CHD in male first-degree relative < 55 years ; CHD in female first-degree relative < 65 years)
- 연령 (남 ≥ 45 ; 여 ≥ 55 세)

*당뇨는 coronary heart disease (CHD) risk equivalent로 승진.
†HDL cholesterol ≥ 60 mg/dL이면 하나를 빼줌.

Identification of Cardiovascular Risk Factors ; NCEP-III Guideline

Diagram illustrating the NCEP-III Guideline for identifying cardiovascular risk factors. The central oval is labeled "NCEP-III". Surrounding it are circles representing risk factors:

- High LDL
- Hyper-tension (130/85 or more)
- Smoking (Current Active)
- HDLc (Less than 40 mg/dl)
- Age (More than 45 (men) 55 (women))
- Family Hx

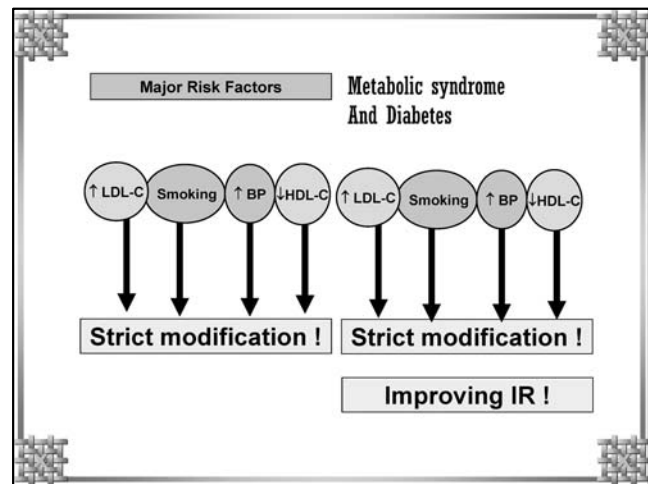
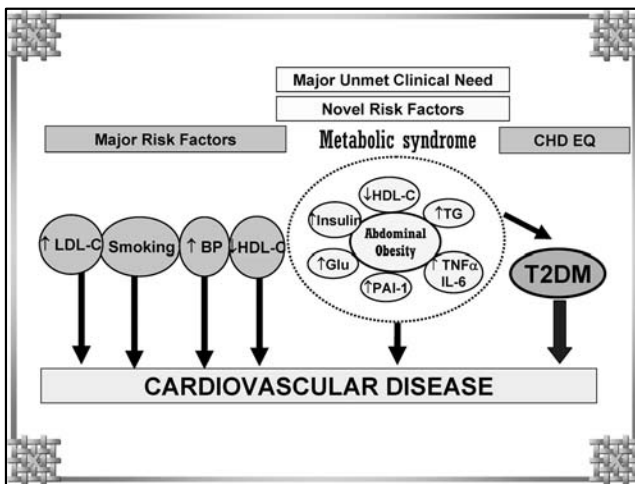


Metabolic Syndrome NCEP ATP-III, 2001	
Clinical identification (≥3 risk determinants)	
Risk Factor	Definition Level
Waist circumference	
Men (cm)	> 102 (90)
Women (cm)	> 88 (80)
Triglyceride (mg/dL)	≥ 150
HDL-C	
Men (mg/dL)	< 40
Women (mg/dL)	< 50
Blood pressure (mmHg)	≥ 130 / ≥85
Fasting glucose (mg/dL)	≥ 110

JAMA 285:2486, 2001

Abdominal obesity: required for diagnosing the metabolic syndrome			
IDF criteria of the metabolic syndrome		NCEP III criteria of the Risk factors	
⊕ High waist circumference			
Plus any two of			
⊕ ↑ Triglycerides	≥ 150 ‡	NA	(mg/dl)
⊕ ↓ HDL cholesterol			
■ Men	< 40 ‡	< 40	(mg/dl)
■ Women	< 50 ‡		
⊕ ↑ Blood pressure	≥ 130/85 ‡	≥ 140/90 ‡	(mmHg)
⊕ ↑ FPG	≥ 100 ‡	Diabetes	(mg/dl)

‡for specific treatment for these conditions
International Diabetes Federation (2005)



한모씨 ; “ 지방수치가 높아요 ”

46세 / 남자
가족력 ; 아버지가 62세 때 관동맥 우회로술 받음
어머니가 62세 때 당뇨병 진단
흡연 ; 1갑/일 5년

46세 ? O
남자 ? O (with age)
가족력 ? X
흡연 ? X

More to know ?

- Blood pressure
- Glucose
- Lipid battery

한모씨 ; “ 지방수치가 높아요 ”

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46세 ? O
남자 ? O (with age)
가족력 ? X
흡연 ? X

More to know ?

- Blood pressure
- Glucose
- Lipid battery
- Obesity (abdominal)

< 4-6 주간의 식이요법 및 생활요법 이후 >

- Blood pressure
140/85 mmHg, taking calcium channel blocker
- Glucose
115 mg/dl
- Lipid battery
total cholesterol : 252 mg/dl
triglyceride : 320 mg/dl
HDL cholesterol : 36 mg/dl
LDL = $252 - 320/5 - 36 = 152$ mg/dl
- 허리둘레 : 36 인치 BMI : 32.5 (BMI = Bwt/Ht²)

Risk stratification ;

Major Risk Factors

- 연령 ? O
가족력 ? X
흡연 ? O
고혈압 ? O
HDL ? O
- 4 개
- 당뇨 ? X
죽상경화증 ? X

Metabolic syndrome

- (복부)비만 ? O
중성지방 ? O
HDL ? O
고혈압 ? O
혈당치 ? O
- 5 개

18점 ;
고위험군 !

Table B1. Estimate of 10-Year Risk for Men (Framingham Point Scores)

Age, y	Points
20-24	-2
25-29	0
30-34	1
35-39	2
40-44	3
45-49	4
50-54	5
55-59	6
60-64	7
65-69	8
70-74	9
75-79	10

Total Cholesterol, mg/dL	Points
<160	0
160-199	1
200-239	2
240-279	3
≥280	4

Systolic BP, mm Hg	Points
<110	0
110-119	1
120-129	2
130-139	3
140-159	4
≥160	5

Table B2. Estimate of 10-Year Risk for Women (Framingham Point Scores)

Age, y	Points
20-24	-2
25-29	0
30-34	1
35-39	2
40-44	3
45-49	4
50-54	5
55-59	6
60-64	7
65-69	8
70-74	9
75-79	10

Total Cholesterol, mg/dL	Points
<160	0
160-199	1
200-239	2
240-279	3
≥280	4

Systolic BP, mm Hg	Points
<110	0
110-119	1
120-129	2
130-139	3
140-159	4
≥160	5

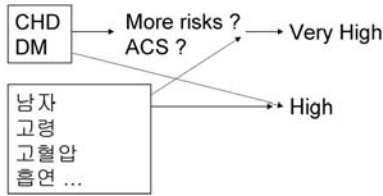
Age, y	Points
20-24	-9
25-29	-4
30-34	0
35-39	1
40-44	2
45-49	3
50-54	4
55-59	5
60-64	6
65-69	7
70-74	8
75-79	9

Total Cholesterol, mg/dL	Points
<160	0
160-199	1
200-239	2
240-279	3
≥280	4

Systolic BP, mm Hg	Points
<120	0
120-129	1
130-139	2
140-159	3
≥160	4

Points	10-Yr-Risk %
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
17	30

Identification of High Risk Groups



< 4 주간의 식이요법 및 생활요법 이후 >

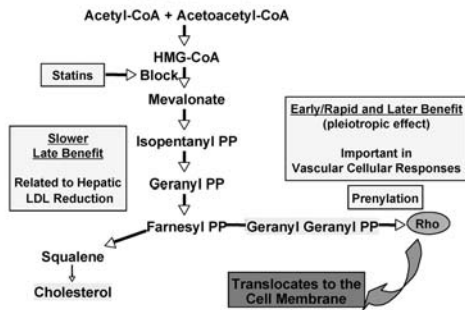
- Lipid battery
total cholesterol : 252 mg/dl
triglyceride : 320 mg/dl
HDLc : 36 mg/dl
LDLc = $252 - 320/5 - 36 = 152$ mg/dl
nonHDLc = $252 - 36 = 216$ mg/dl
- 목표치
LDLc = 130 mg/dl 이하 ; 차이는 22 mg/dl
nonHDL = 160 mg/dl 이하 ; 차이는 56 mg/dl

Three Categories of Risk That Modify LDL Cholesterol Goals

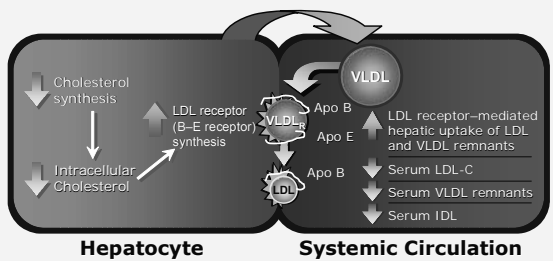
Risk Category	LDL Goal	non-HDL Goal(mg/dL)
CHD and CHD risk equivalents Multiple (2+) major risk factors with 10-year risk > 20 %	< 100	≤ 130
Multiple (2+) major risk factors with 10-year risk ≤ 20 %	< 130	≤ 160
0-1 risk factor	< 160	≤ 190

cf. CHD indicates coronary heart disease.

Statins



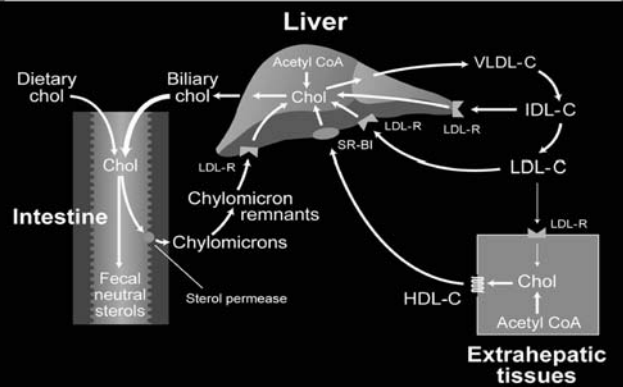
Statins: Mechanism of Action



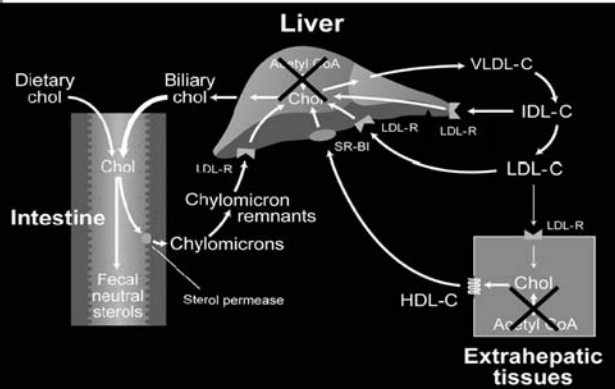
Reduce hepatic cholesterol synthesis, lowering intracellular cholesterol, which stimulates upregulation of LDL receptor and increases the uptake of non-HDL particles from the systemic circulation.

Slide Source:
Lipid Science
www.lipidscience.org

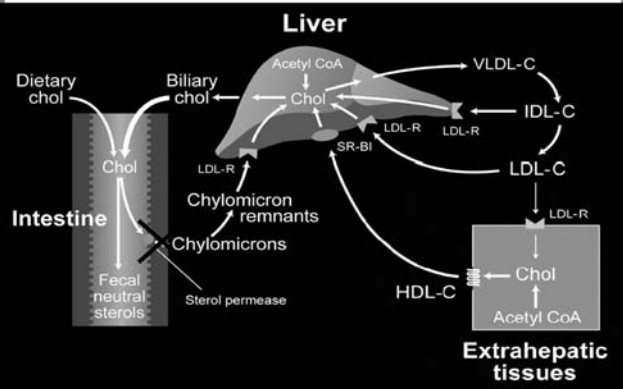
Overview of Cholesterol Transport

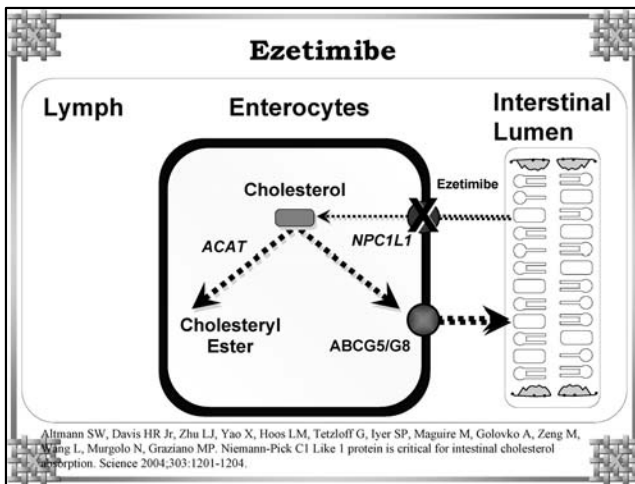


Action of Statins



Action of Ezetimibe



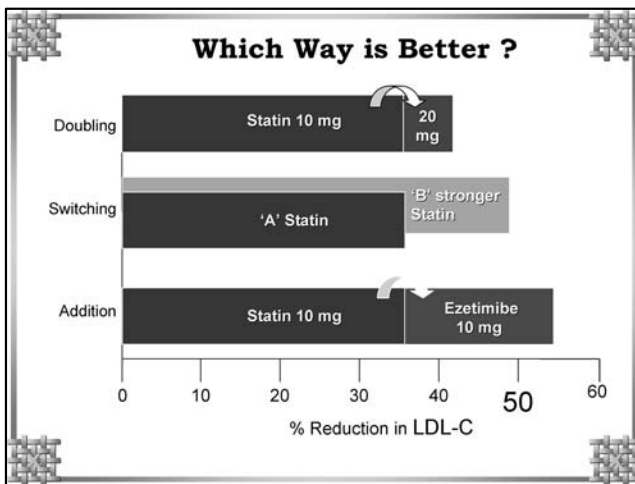


Comparative Efficacy of the Statins

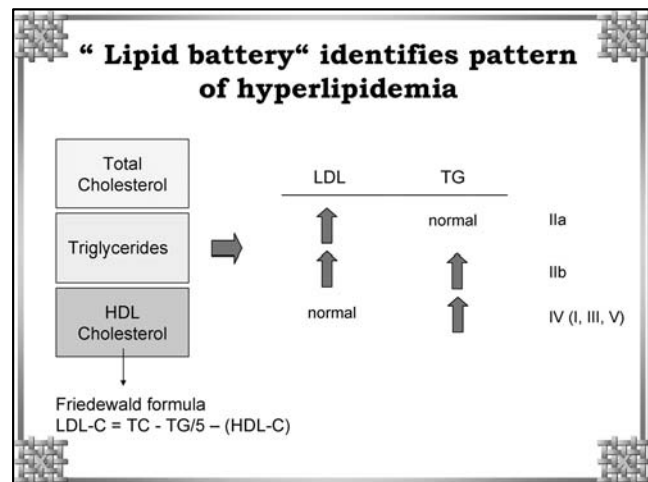
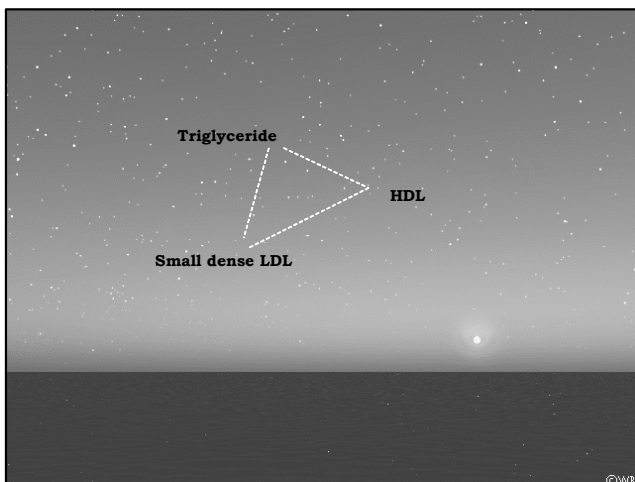
	Statin Drug(mg)					Cholesterol levels	
	Atorva	Simva	Lova	Prava	Fluva	TC	LDL
		10	20	20	40	-22%	-27%
10	20	40	40	80		-27%	-34%
20	40	80				-32%	-41%
40	80					-37%	-48%
80						-42%	-55%

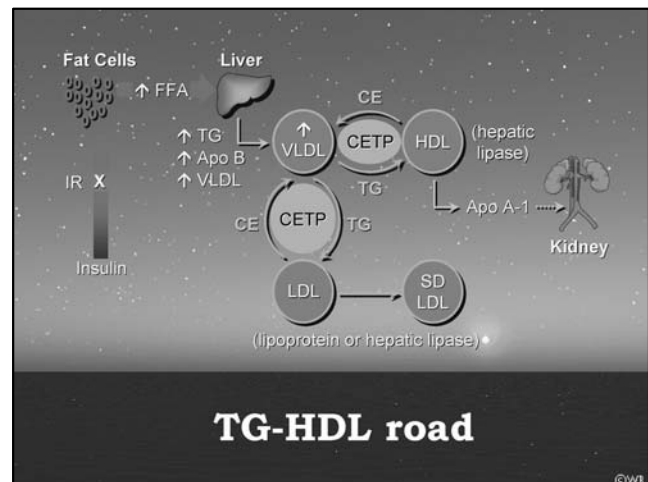
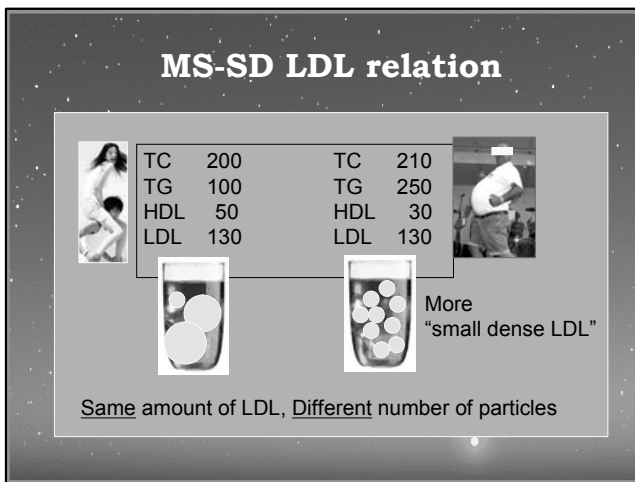
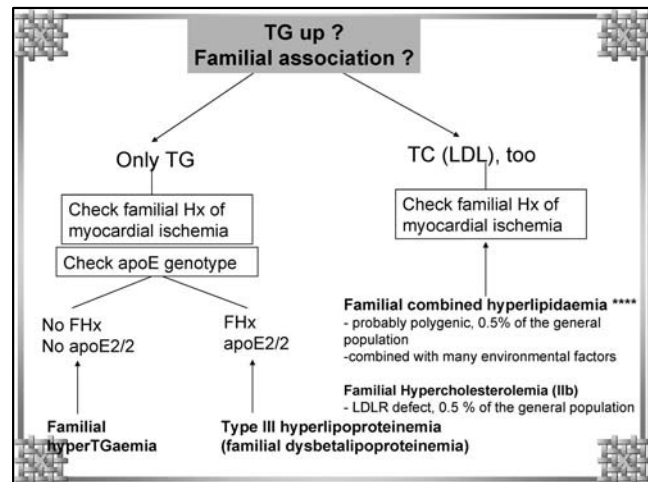
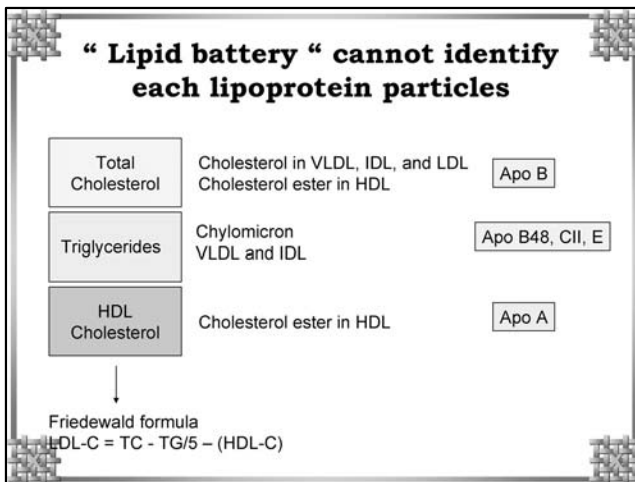
The rule of 5 and the rule of 7 in lipid-lowering by statin drugs

Roberts WC. *Excerpta Medica* 1997;106-107



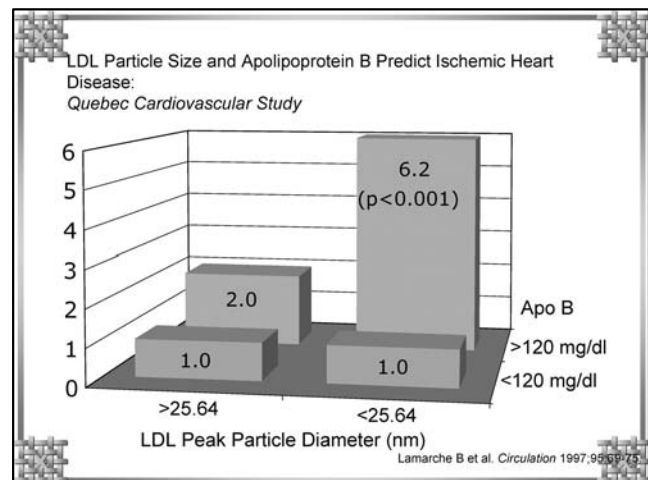
- ### Knowing New Drugs ; Getting More information
- ⊕ **Rosuvastatin**
 - 장점 ; 10 mg 으로 LDL-C 50 % 하강
중성지방 강하효과 HDL-C 상승효과 보전
가격대비 효과
 - 단점 ; CHD prevention의 evidence 가 필요
 - ⊕ **Pitavastatin**
 - 장점 ; 가격대비효과 (?)
HDL-C 상승효과 보전
 - 단점 ; CHD prevention의 evidence 가 필요
 - ⊕ **Ezetimibe**
 - 장점 ; 새로운 기전, 빠른 작용시간
안정성
낮은 스타틴 용량을 유지
스타틴과의 병용시 LDL, CRP 강하효과 극대화
 - 단점 ; CHD prevention의 evidence 가 필요





Small Dense LDL

- ⊕ LDL < 25.5nm
- ⊕ Easy oxidation
- ⊕ Easy attachment to proteoglycan
- ⊕ Highly associated with metabolic syndrome and other risk factors



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						P for Trend
	0	1	2	3	4	5	
Women	n=562	n=464	n=298	n=134	n=102	n=29	
NMR-derived lipoprotein measures							
Total LDL particle No., nmol/L	1169±6	1344±17	1496±22	1600±32	1678±37	1663±69	<0.0001
Small LDL particles, nmol/L	429±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	1249±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

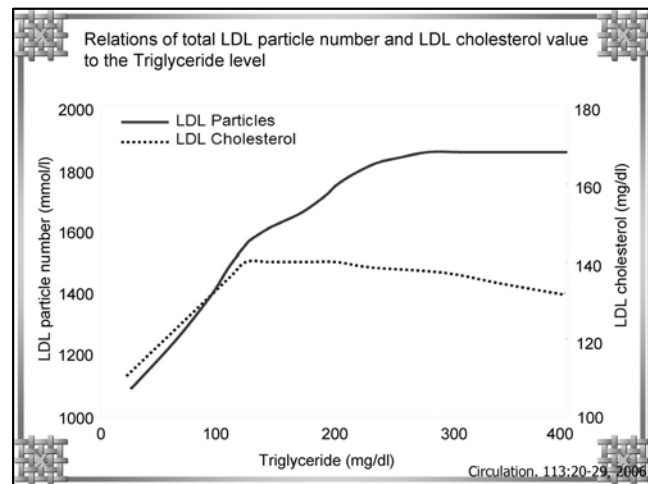
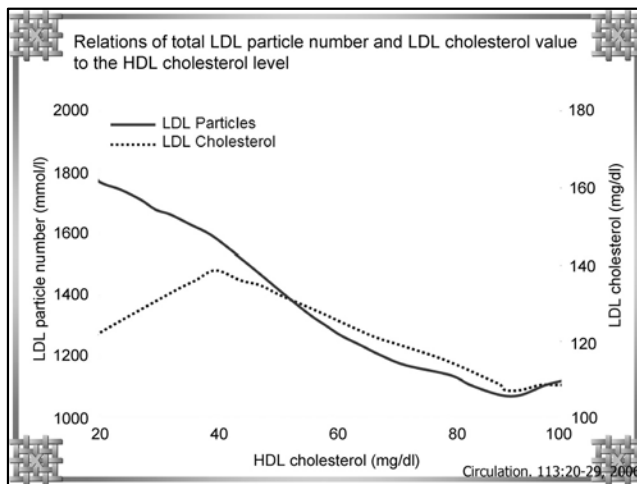
Small LDL Particle Number vs. Others
A Prominent Feature of the Metabolic Syndrome in the Framingham Heart Study

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.

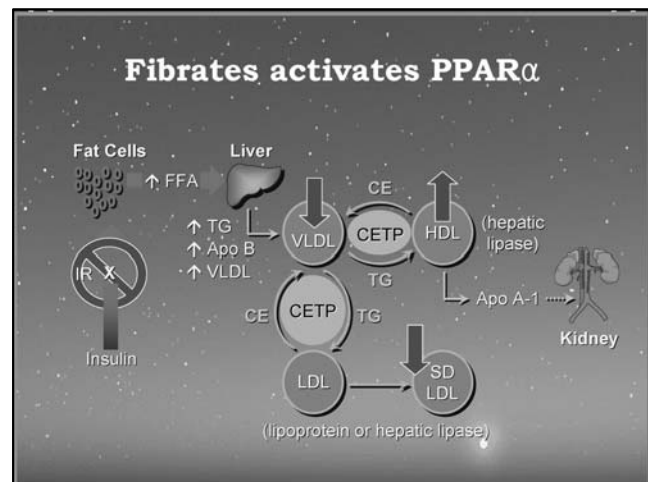
Circulation. 113:20-29, 2006

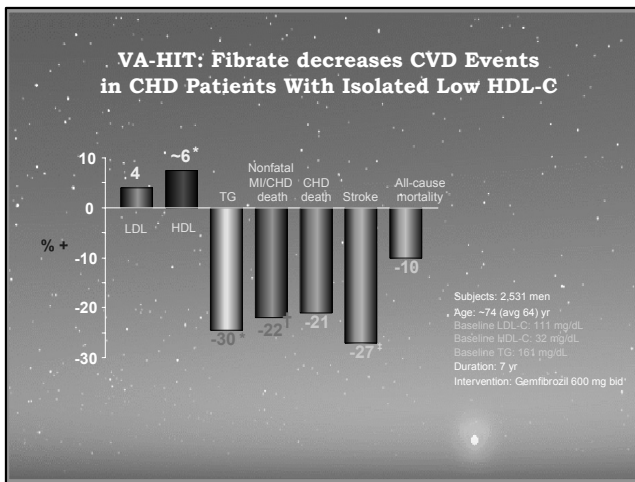


Currently Available Fibrates

Drug	Maximum Dose	Usual Toxicity	Contraindications
Clofibrate	2000 mg/d	Myalgias; sporadically, rhabdomyolysis (may be aggravated by combination with statins); elevated transaminases (ASAT, ALAT); gallstone formation	Liver and renal insufficiency
Gemfibrozil	1200 mg/d	Same as for clofibrate	Same as for clofibrate
Bezafibrate	600 mg/d	Same as for clofibrate	Same as for clofibrate
Fenofibrate	200 mg/d	Same as for clofibrate	Same as for clofibrate
Ciprofibrate	100 mg/d	Same as for clofibrate	Same as for clofibrate

Staels B, et al. Circulation 1998;98:2088





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

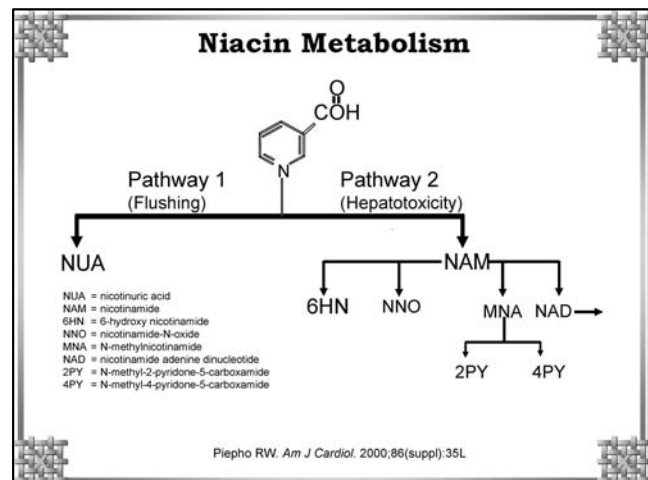
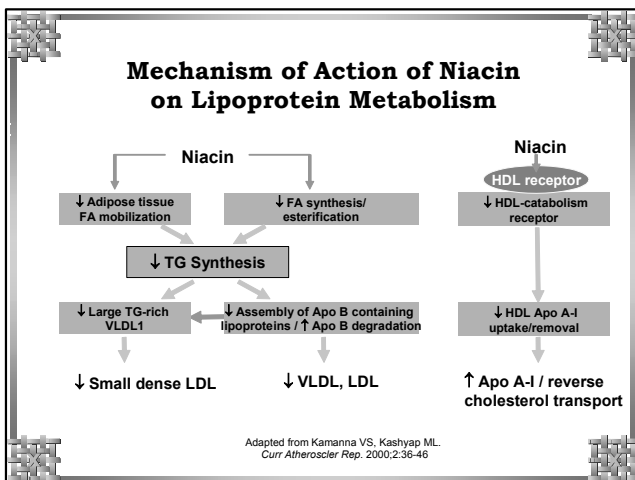
- ⊕ Increase in LDL level after fibrate tx.
- mainly due to increase in lipolysis by LPL
- ⊕ Gemfibrozil – No
Fenofibrate – Yes (pending ACCORD study)

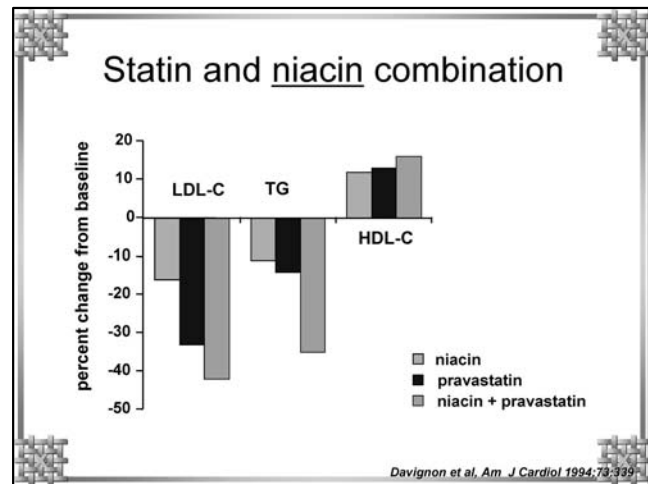
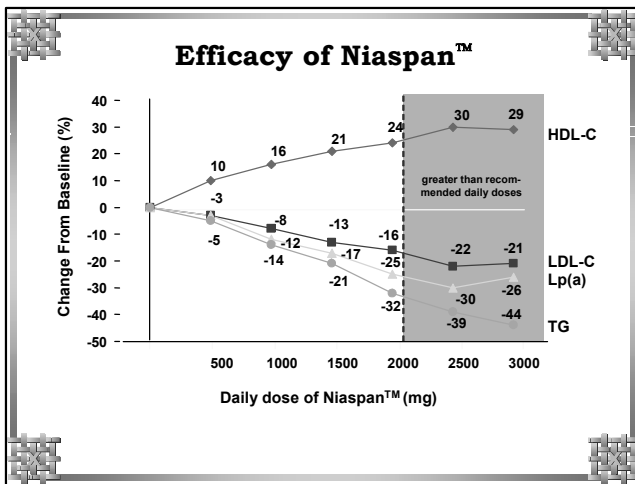
Niacin

OC(=O)c1cccnc1

“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





Side Effects of Niacin

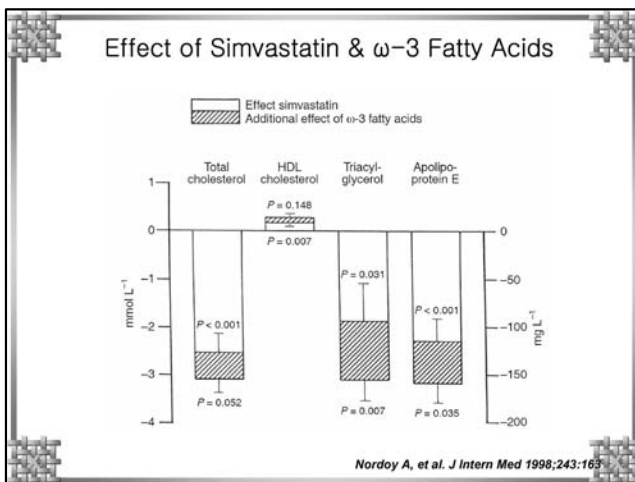
Skin	Flushing, dry skin, pruritus
Eyes	Conjunctivitis, cystoid macular edema, retinal detachment
Respiratory tract	Nasal stuffiness
Heart	Supraventricular arrhythmias
GI tract	Heartburn, loose bowel movements or diarrhea
Liver	Mild increase in serum aminotransferases, hepatitis
Muscles	Myositis
Metabolic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

Effect of ω -3 Fatty Acids

	Baseline triacylglycerol < 2.0 mmol/L	Baseline triacylglycerol \geq 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

Effect of n-3 fatty acids on serum lipids and lipoproteins in humans: placebo-controlled, parallel design studies

Harris WS, AJCN 1997;65:1645S



Missing something ?

- Hidden causes ?
- Family screening ?
- Other risk factors ?

Iatrogenic

Antihypertensives ; TC, TG up, HDL down
 - thiazides ; especially in obese males and postmenopausal women
 - beta blockers ; especially in beta blockers without ISA

Immunosuppressives ; TC, TG up, HDL down
 - corticosteroids ; impaired glucose tolerance & insulin resistance

Hormonal Influences

Pregnancy ; TC, TG and HDL mildly up

Estrogen

- VLDL and LDL up in premenopausal women
 - HDL up, LDL down in postmenopausal women

Hypothyroidism

; TC up
 - 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 resistance
 - mimic the situations of NIDDM

Others

Nephrotic syndrome - usu. type II

CRF - usu. type IV and HDL down

Alcohol - usu. type IV or V

Other Risk Factors

- Obesity
- Physical inactivity
- Atherosclerotic diet
- Impaired fasting glucose
- Evidence of subclinical atherosclerotic diseases
- Lipoprotein (a)
- Prothrombotic factors ; PAI-1, fibrinogen
- Proinflammatory factors ; CRP

