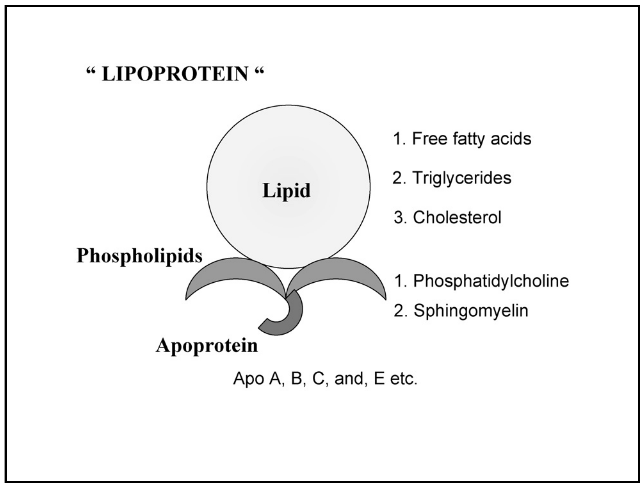
[연수강좌]

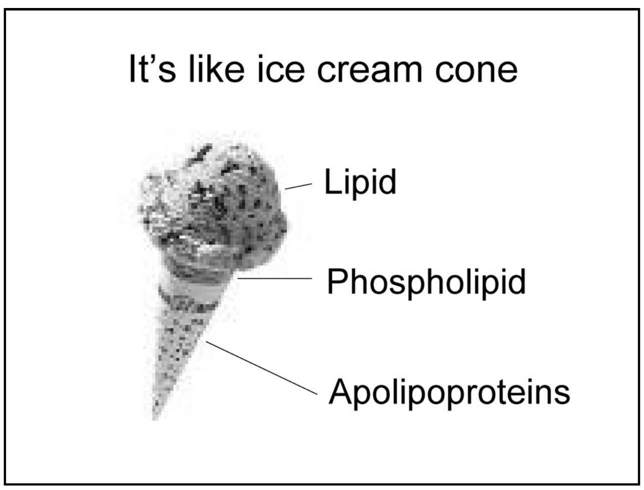
TG and HDL

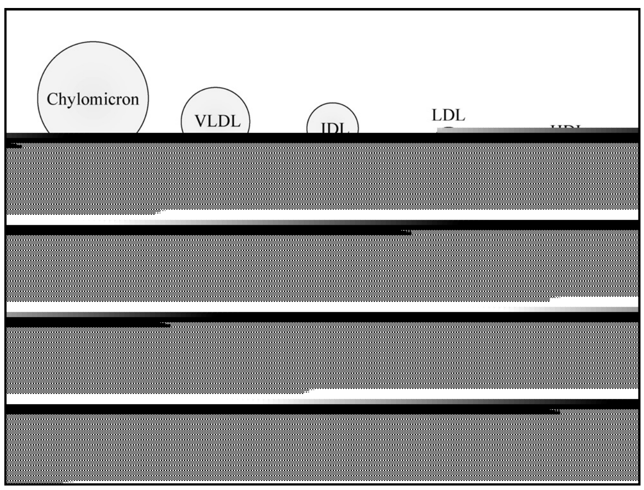
한 기 훈

울산의대 심장내과

What is lipid particles ?







" 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

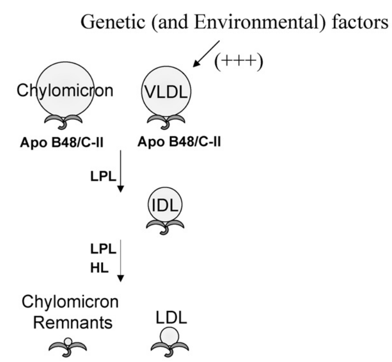
↓

Friedewald formula
LDLc = TC - TG/5 - HDLc

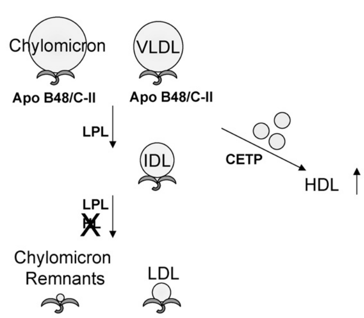
TC	LDLc	TG
↑	normal to dec	↑
↑	↑	normal
↑	↑	↑

What is hyper-TG ?

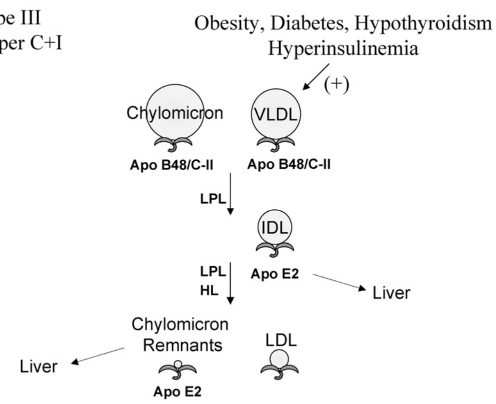
Type IV
Hyper VLDL



Type III
Hyper C+I



Type III
Hyper C+I



<u>Type III hyperlipoproteinemia (familial dysbetalipoproteinemia) *</u>**

- apo E2 homozygotes (mostly) or heterozygotes. 1 : 5000 prevalence
- combined with obesity, diabetes, hypothyroidism and other genetic disorders
- chylomicron and VLDL remnants up, usually normal LDL
  TG and C up ; up to 10 mmol/l
- corneal arcus, xanthelasma, tubero-eruptive xanthomata (knees and elbows),
  palmar striae, **<u>myocardial ischemia</u>** (more than 50% of patients)
- Dx (indirect) ; plasma lipoprotein EP, and, apo E genotyping
- Tx ;
  1. Correction of precipitating factors
  2. Fibrates (+ nicotinic acid)

Mixed - unclassified

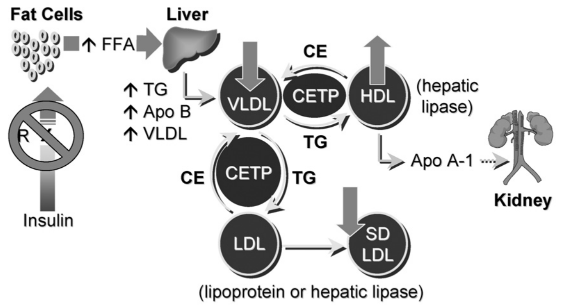
<u>Familial combined hyperlipidaemia **</u>**

- probably polygenic, 0.5% of the general population
- combined with many environmental factors
- increased VLDL production - VLDL up
  VLDL catabolism may or may not be impaired
- no definite clinical features except **<u>myocardial ischemia</u>**
- Tx ;
  1. Correction of precipitating factors
  2. Nicotinic acid (+ fibrates)

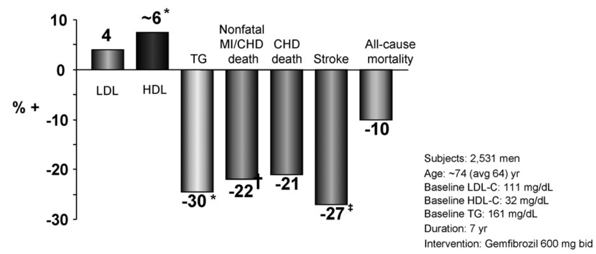
<u>Familial hypercholesterolemia (FH) ***</u>**

- AD inheritance, 0.2% of general populations
- LDLR defect or deficient, LDL up (IIa), but sometimes TG up, too (IIb)
- homozygote ; child onset, severe coronary atherosclerosis
- heterozygote ; premature atherosclerosis
  characteristic tendon xanthoma
- diagnosis ; <u>tendon xanthoma</u> is clinical hall mark of FH
- treatment ; HMG Co-A reductase inhibitors in heterozygotes
  consider LDL apheresis/liver transplantation in homozygotes

Fibrates activates PPARα



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



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

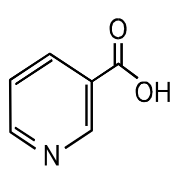
Myopathy, 간기능이나 신기능 이상시 금기

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)

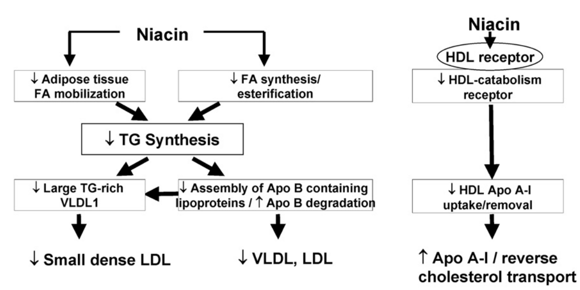
Niacin



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

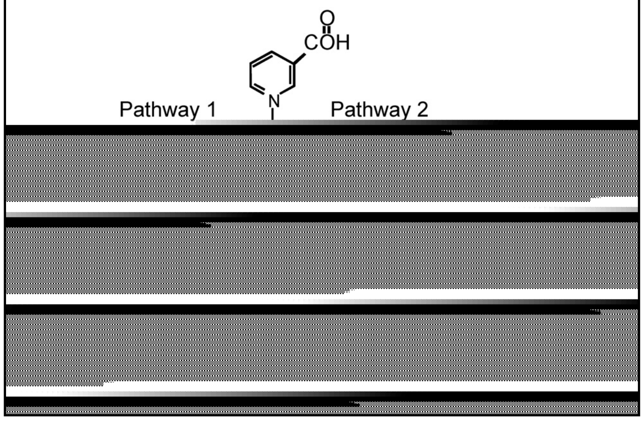
(National Cholesterol Education Program Adult Treatment Panel III Report) **Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *Circulation.* 2002;106:3143**

Mechanism of Action of Niacin on Lipoprotein Metabolism



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

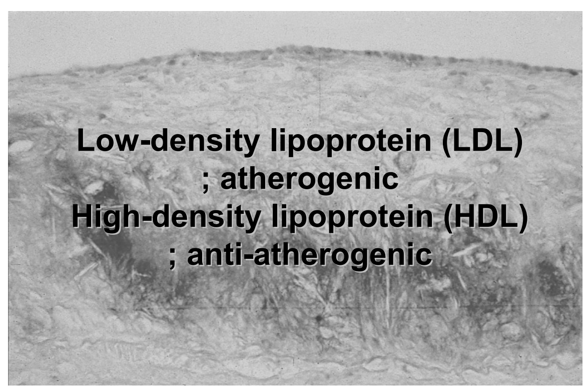
Niacin Metabolism



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

HDL



HDL and atherosclerosis

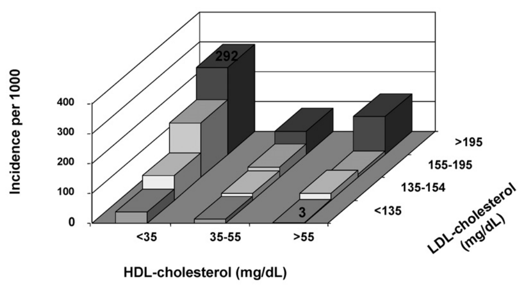
- 2-4 % reduction of cardiovascular disease (CVD) in every 1 mg/dl elevation ; more powerful than LDL reduction
- Low serum HDL-C level (<40mg/dl) is recognized as an major risk factor of CVD (NCEP-III guideline, 2001)

HDL-raising in human studies

Trial	Drug	HDL-cholesterol		LDL	Relative	Absolute
		Base	After Tx	After Tx	RR (%)	RR (%)
AFCAPS	Lovastatin	36	+ 6 %	- 25%	- 37	- 0.7
4S	Simvastatin	46	+ 8 %	- 35%	- 34	- 3
CARE	Pravastatin	39	+ 5 %	- 28%	- 24	- 2.3
LIPID	Pravastatin	37	+ 5 %	- 25%	- 24	- 2
VA-HIT	Gemfibrozil	32	+ 6 %	0%	- 22	- 2

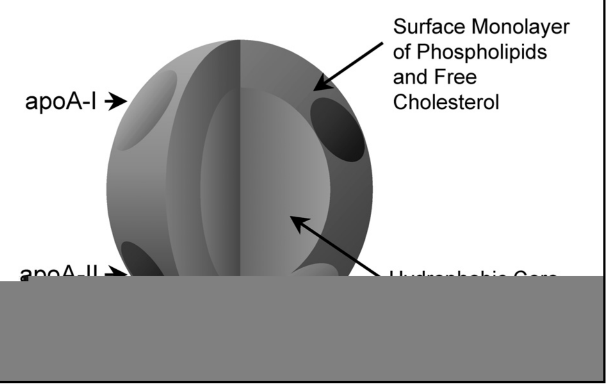
LDL and HDL Impact on CHD Risk

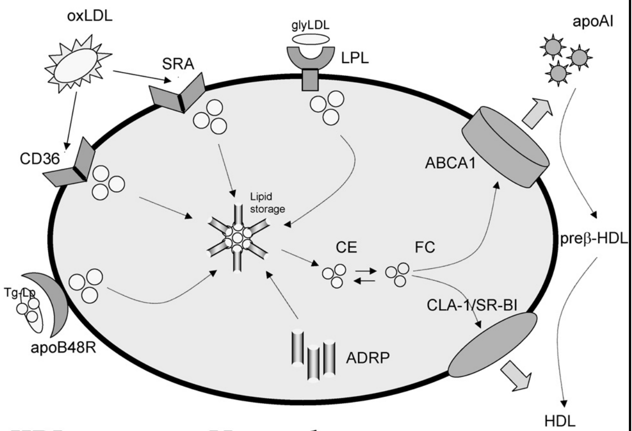
(PROCAM study) N=4559, 6 yrs F/U



Assmann G, et al. Atherosclerosis. 1996;124(suppl):S11-S20.

Structure of HDL



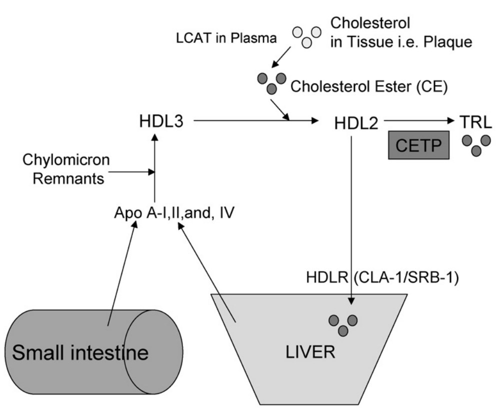


HDL squeezes Macrophages

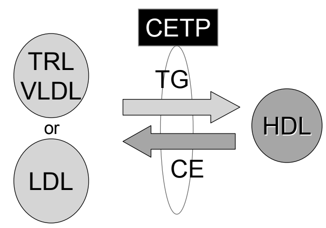
Therapeutic modalities to enhance cholesterol efflux from atheroma

- Agents that increase functionally active HDL
  - Niacin, Statins, Fibrates
- Apo A-1 recombinant protein or agents that upregulate Apo A-1
- Agents that upregulate ABCA1 ; PPARs agonists
- Mutants of Apo A-1 ; Apo A-1 milano or paris

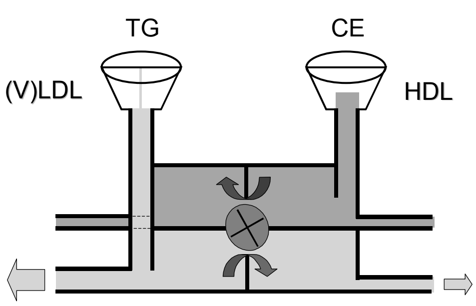
" HDL in reverse cholesterol transport "



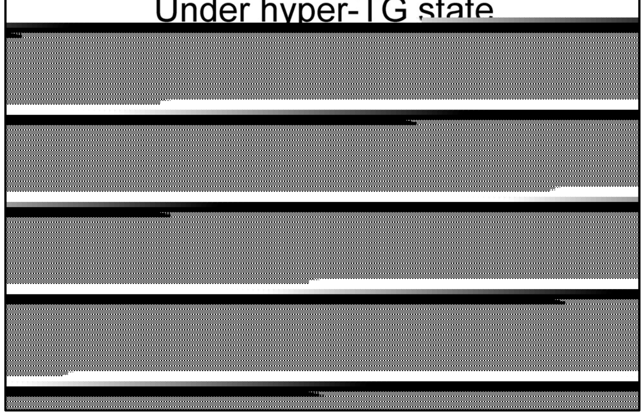
Cholesterol Ester Transport Protein (CETP)



Regulatory Role of CETP ( ) Under usual state



Regulatory Role of CETP ( ) Under hyper-TG state



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

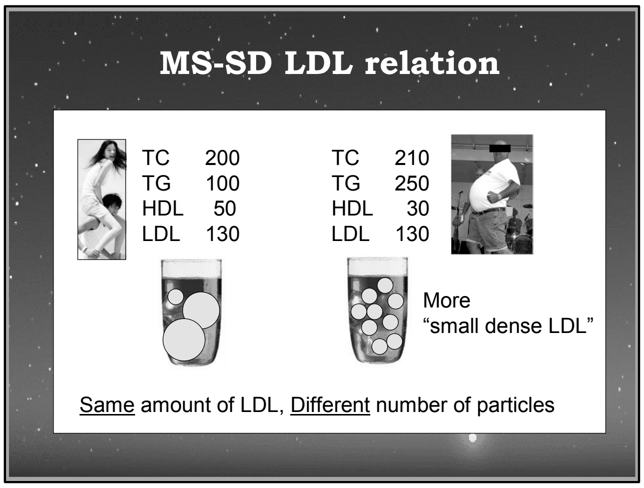
JAMA 285:2486, 2001

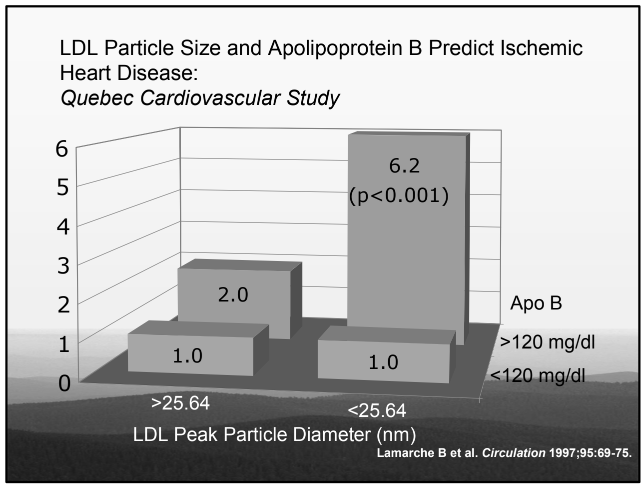
Metabolic Syndrome
IDF Consensus

Central Obesity
(WC ≥ 80 Cm)

Plus any 2 of :

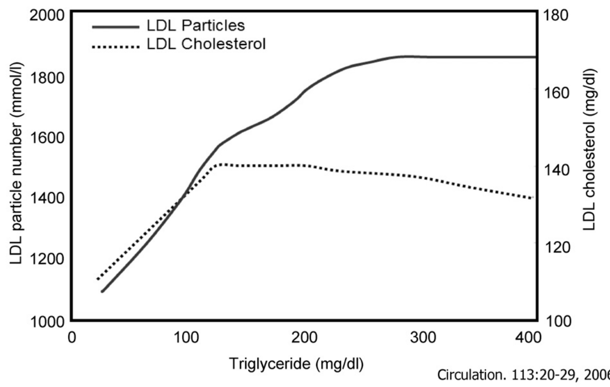
- High **TG**
- Low **HDLc**
- High **BP**
- High **FBS** (or pre-existing DM)





Lipoproteins vs. Severity of Metabolic Syndrome
A Prominent Feature of the Metabolic Syndrome in the Framingham Heart Study

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



Circulation. 113:20-29, 2006

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)

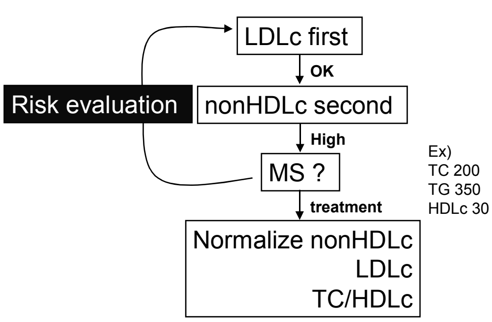
***당뇨** 는 coronary heart disease (CHD) risk equivalent로 승진.
†**HDL cholesterol**≥60 mg/dL 이면 하나를 빼 줌.

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

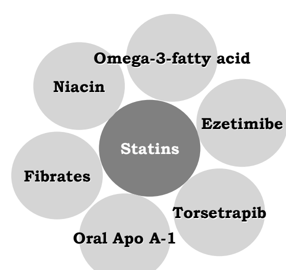
- **High risk patients ;**
  <100 mg/dl as a ‘minimal’ goal with ‘standard’ statin dose
- **“Very” high risk patients ;**
  <70 mg/dl is favored (and CRP <2 mg/L)

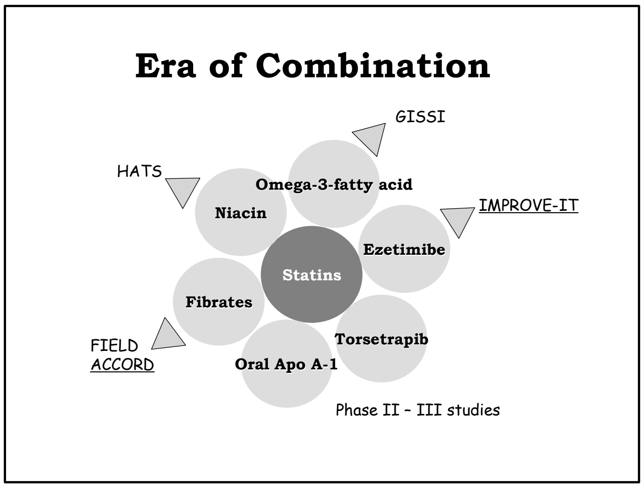
- very high ; CVD with

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



Statin is like Salt




Era of Combination
GISSI
HATS
Omega-3-fatty acid
Niacin
IMPROVE-IT
Ezetimibe
Statins
Fibrates
Torsetrapib
FIELD
ACCORD
Oral Apo A-1
Phase II – III studies