[연수강좌]

Current Trend of LDL Lowering Management

한 기 훈

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A. Identification of High Risk and Setting LDL Goal

4 Categories of Risk That Modify LDL Cholesterol Goals

	Risk Category	LDL Goal (mg/dL)
Very High	ACS CHD Hx (+) with other RFs	< 70
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.

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

- 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 non HDL-C ≥ 130 with low HDL-C ≤ 40)
  4. with ACS

" CHD " or " CHD equivalents "

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

CHD ; coronary heart disease

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 빼 줌.

고혈압

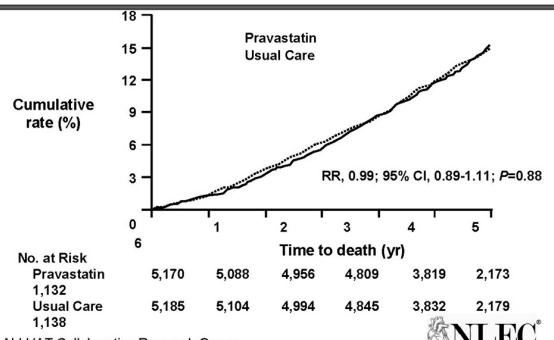
ALLHAT-LLT

10355 with moderate risks including older, hypertensive with one more RF
> 55 yrs, LDL-C 120-189 mg/dl, TG < 350 mg/dl
pravastatin, for 4.8 yrs – LDL-C reduction; 17% vs. 8 % placebo

- Failed to observe benefits of lipid lowering tx
  - Maybe LDL-C did not reach lower than 100 mg/dl.

LDL-C levels of subjects with moderate risk, i.e. elderly and hypertensive, should be lower than 100 mg/dl.

ALLHAT-LLT: All-Cause Mortality



ALLHAT Collaborative Research Group.
JAMA. 2002;288:2998-3007.

ALLHAT-LLT: Comparison to Other Large, Long-term Statin Trials

Trial	Sample Size	% Change in TC	Odds Ratio (95% CI) All-Cause Mortality	Odds Ratio (95% CI) CHD Events
Prior trials*	54,381	20.2	0.83 (0.78-0.88)	0.70 (0.67-0.74)
ALLHAT-LLT	10,355	9.6	0.99 (0.89-1.11)	0.91 (0.79-1.04)
All Trials	64,736	18.5	0.86 (0.82-0.90)	0.73 (0.69-0.77)

*Includes 4S, LIPS, HPS, WOSCOPS, CARE, AFCAPS/TexCAPS, LIPID, PostCABG

ALLHAT Collaborative Research Group.
JAMA. 2002;288:2998-3007.

고혈압

ASCOT-LLA

19342 with hypertension with at least 3 other RFs
40 - 79 yrs, LDL-C 132 mg/dl
Atorvastatin 10 mg, for 3.3 yrs – LDL-C reduction; 29 % 42 mg/dl

- Benefits – reducing
  - Stroke by 27 %
  - Total cardiovascular events by 21 %
  - Total coronary events by 29 %

고령

PROSPER

5804 with hx. of vascular disease or CVD RFs
70-82 yrs, TC 150-350 mg/dl
Pravastatin 40 mg, for 3.2 yrs, LDL-C reduction by 34 %

- Benefits – reducing
  - Coronary death, MI, stroke by 15 %
  - Nonfatal MI + coronary death by 19 %
  - CHD death by 24 %
  - TIA by 25 %

LDL reduction is good to elderly people

Age, y	Points
20-34	−9
35-39	−4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

	Points				
	Age 20-39 y	Age 40-49 y	Age 50-59 y	Age 60-69 y	Age 70-79 y
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

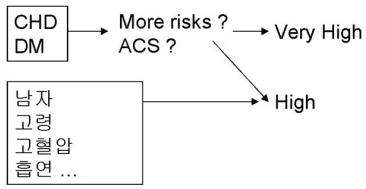
HDL, mg/dL	Points
≥60	−1
50-59	0
40-49	1
<40	2

Total Cholesterol, mg/dL	Points				
	Age 20-39 y	Age 40-49 y	Age 50-59 y	Age 60-69 y	Age 70-79 y
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

Systolic BP, mm Hg	If Untreated	If Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

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

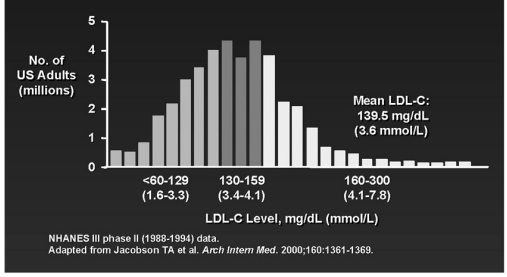


B. How to get to LDL Goal ?

얼마나 낮추어야 하는가 ?
: LDL-C Goal

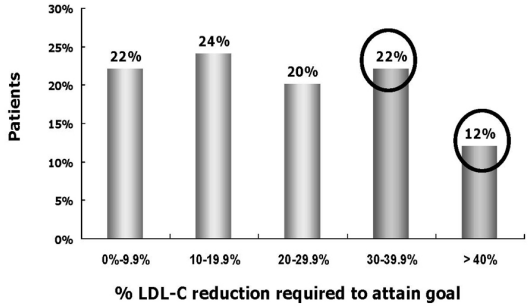
- Very High Risk ; 70 mg/dl
- High Risk ; 100 mg/dl
- Intermediate Risk ; 130 mg/dl

Distribution of LDL-C Levels in Patients With 2 or More CHD Risk Factors



NHANES III phase II (1988-1994) data.
Adapted from Jacobson TA et al. *Arch Intern Med.* 2000;160:1361-1369.

REALITY: LDL-C Reduction Required at Study End for Patients not at Goal



Adapted from HS Kim et al. *EAS, 2004*

보험기준이 스타틴의 투여에 제한을 가하고 있다.

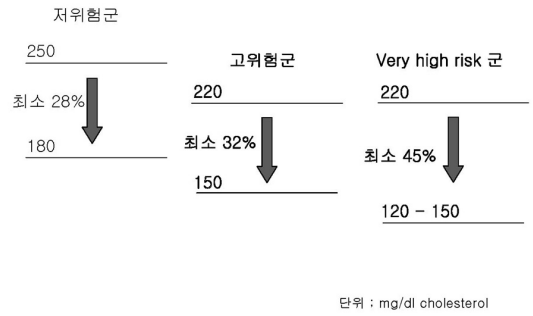
한국의 보험 급여 기준 및 약제 선정 지침

(1) 순수 고콜레스테롤혈증

가. 위험요인 (-) ;
TC 250mg/dl 이상일 때 부터 투약
나. 위험요인 (+) ; **심근경색의 기왕력, 허혈성 심질환, 고혈압, 당뇨병**
TC 220 mg/dl 이상일 때 부터 투약하되, **가능한 저용량 투여**를 원칙
다. 약제종류: HMG-CoA환원효소저해제 (statin류), 담즙산제거제

; 스타틴의 경우 유지 용량을 **1일 0.5 – 1 정으로** 권장

How much should We lower TC levels ?



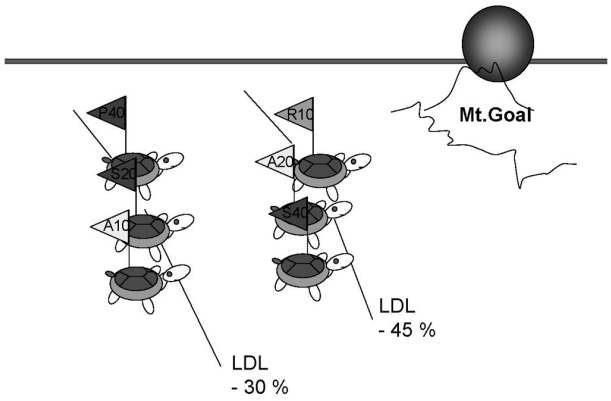
단위 : mg/dl cholesterol

Comparative Efficacy of Available Statins

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

Rule of 5s & 7s

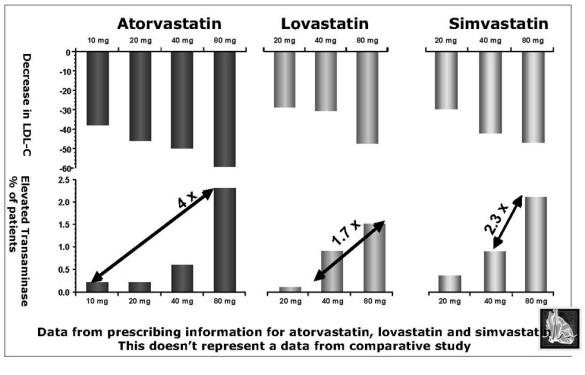
Roberts WC. *Am J Cardiol.* 1997;80:106-107.
Stein E et al. *J Cardiovasc Pharmacol Therapeut.* 1997;2:7-16.



스타틴의 고용량에서의 주의점

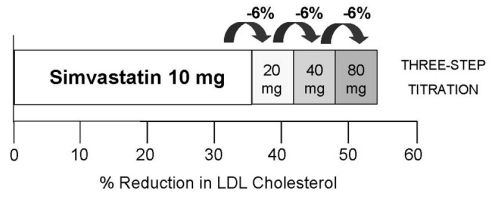
- Myopathy 의 발생이 높은 집단을 감별 !
- 고령 (주로 80세 이상)
- 몸집이 작은 사람
- 당뇨성 신증등 다기관의 질병
- 약물병용
- 알코올 의존 경향

스타틴 : 간독성

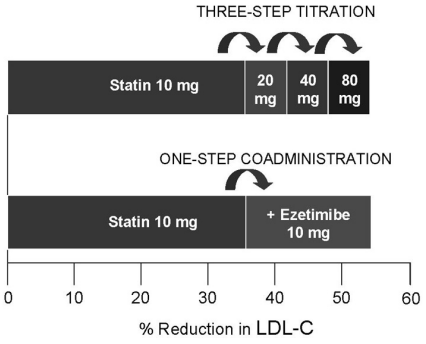


스타틴의 용량조절

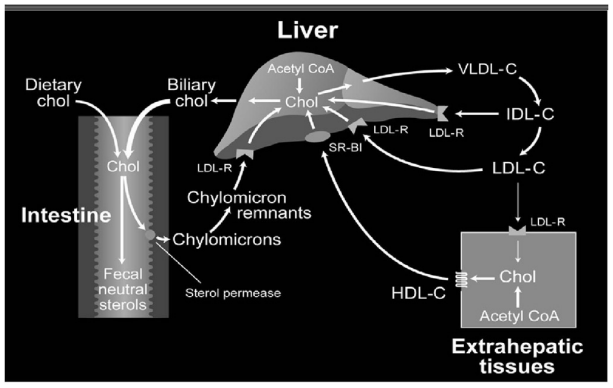
Effect of Statin Therapy on LDL-C Levels: "The Rule of 6"



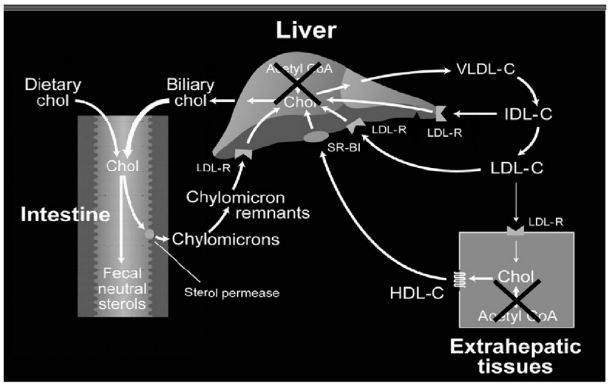
새로운 LDL 강하방법 ; Ezetimibe



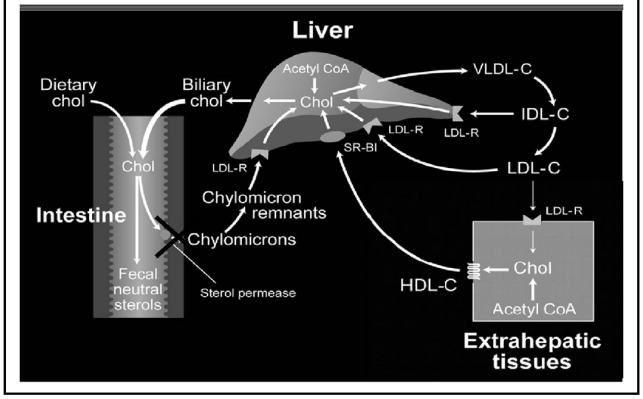
Overview of Cholesterol Transport



Action of Statins



Action of Ezetimibe



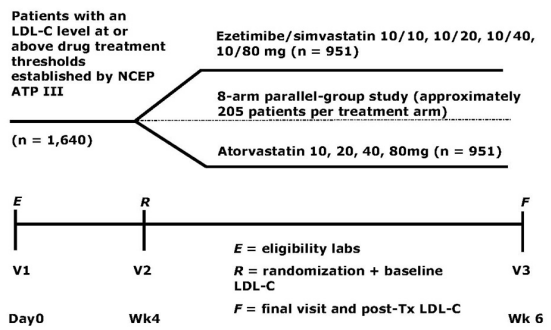
VYVA trial

VYtorin Versus Atorvastatin study

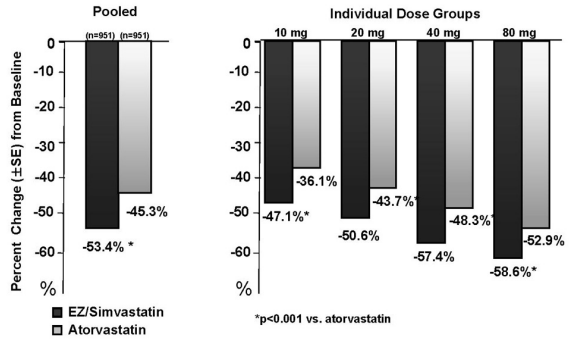
Multicenter, Double-blind, Randomized, Active-controlled trial of ezetimibe and simvastatin (VYTORIN) versus atorvastatin in patients with hypercholesterolemia

Christie M. Ballantyne et al.
***America Heart Journal*, 2005, Vol. 149, No. 3, 464~473**

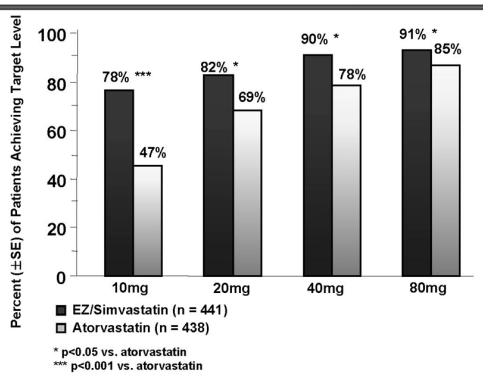
Trial Design



Efficacy of Dual Inhibition on LDL-C Lowering



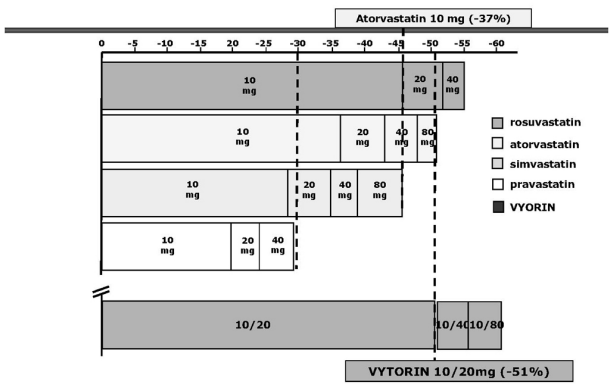
Attainment of LDL- C target of < 100 mg/dL in patients with CHD or CHD risk equivalents



VYVA Trial: Safety & Tolerability Profile

Parameter	All Atorva (n = 939)	EZ/All Simva (n = 933)	P value
ALT ≥ 3 X ULN	10 (1.1%)	0 (0.0%)	.002
AST ≥ 3 X ULN	7 (0.7%)	1 (0.1%)	.070
ALT and/or AST ≥ 3 X ULN	11 (1.2%)	1 (0.1%)	.006
CK ≥ 10 X ULN	1 (0.1%)	0 (0.0)	1.000
CK ≥ 10 X ULN with muscle symptoms	0 (0.0)	0 (0.0)	-

LDL-C Reduction across Dose



Adapted from Goldberg AC et al *Mayo Clin Proc* 2004;79:620–629; Jones PH et al *Am J Cardiol* 2003;92:152–160

Ezetimibe 병용에 따른 LDL 강하효과

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.

Ezetimibe 병합요법의 장점

- Ezetimibe 와 statin의 병용으로 콜레스테롤의 흡수와 생합성을 동시에 저해시킬 수 있다.
- Ezetimibe 의 추가투여로 LDL 수치를 추가로 20% 감소시킬 수 있다.
- Ezetimibe 와 statin의 병용으로 부작용의 증가를 경험하지 않고도 LDL 의 목표치에 도달할 수 있다 (80% 이상)

C. Statin ; anti-atherogenic agent, not only a lipid lowering agent.

투여 시작점의 재고

LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories *

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to - Initiate TLC (mg/dL)	Consider Drug Therapy (mg/dL)
CHD or CHD risk equivalents (10-year risk >20%)	< 100	≥100	≥ 130 (100-129: drug optional †)
2+ Risk factors (10-year risk ≤ 20%)	< 130	≥130	10 - year risk 10% - 20%: ≥ 130 10 - year risk < 10%: ≥ 160
0-1 Risk factor ‡	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

* LDL indicates low-density lipoprotein; CHD, coronary heart disease.
† Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol level of < 100 mg/dLcannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, eg, nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
‡ Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

당뇨

Collaborative Atorvastatin Diabetes Study

2838 with type diabetes, baseline LDL 160 or less
atorvastatin 10 mg (n=1428) vs placebo (n=1410), LDL 40 % reduction

- Benefits – reducing
  - Cardiovascular-related events and death significantly
  - All-cause death margianlly

CARDS: Effect of Treatment on Primary and Secondary End Points

	No. of patients with an event (%) Placebo	Atorvastatin 10 mg	Hazard ratio (95% CI)	*P* value
Primary end point	127 (9.0%)	83 (5.8%)	0.63 (0.48-0.83)	0.001
Acute coronary events	77 (5.5%)	51 (3.6%)	0.64 (0.45-0.91)	
Coronary revascularization	34 (2.4%)	24 (1.7%)	0.69 (0.41-1.16)	
Stroke	39 (2.8%)	21 (1.5%)	0.52 (0.31-0.89)	
Secondary end point				
Death from any cause	82 (5.8%)	61 (4.3%)	0.73 (0.52-1.01)	0.059
Any acute CVD event	189 (13.4%)	134 (9.4%)	0.68 (0.55-0.85)	0.001

0.2 0.4 0.6 0.8 1.0 1.2

Note: Only the first acute coronary event, revascularization, or stroke is included in the primary end point.
Symbol size is proportional to amount of statistical information.
CARDS=Collaborative Atorvastatin Diabetes Study.
Colhoun HM et al. *Lancet*. 2004;364:685-696.

CARDS: Effect of Treatment on Primary End Point by Lipid Level

Median baseline lipids	No. of patients with an event (%) Placebo	Atorvastatin	Hazard ratio (95% CI)	*P* value
LDL-C (mg/dL)				
≥ 120	66 (9.5%)	44 (6.1%)	0.62 (0.43-0.91)	
<120	61 (8.5%)	39 (5.6%)	0.63 (0.42-0.94)	0.96
HDL-C (mg/dL)				
≥ 54	62 (8.5%)	36 (5.2%)	0.59 (0.39-0.89)	
<54	65 (9.6%)	47 (6.4%)	0.66 (0.45-0.95)	0.70
TG (mg/dL)				
≥ 151	67 (9.6%)	40 (5.5%)	0.56 (0.38-0.82)	
<151	60 (8.4%)	43 (6.1%)	0.71 (0.48-1.05)	0.40
TC (mg/dL)				
≥ 209	71 (10.1%)	44 (6.2%)	0.59 (0.41-0.86)	
<209	56 (7.9%)	39 (5.5%)	0.67 (0.45-1.01)	0.67

0.2 0.4 0.6 0.8 1.0 1.2

Symbol size is proportional to amount of statistical information.
P values are for test of heterogeneity.
CARDS=Collaborative Atorvastatin Diabetes Study. Colhoun HM et al. *Lancet*. 2004;364:685-696.

안정형 협심증

Treating New Targets (TNT)

- Stable angina
- Atorva 10 vs. 80 mg/day for 5 yrs
- 22 % reduction in CV events and the related death

ATP-III update (2004)
Modified LDL Goal ;
percentage LDL-C reduction

- 30 – 40 % LDL-C reduction can be achieved by standard statin doses.
- Minimal LDL goal should (can) be achieved esp. patients with high risk.

Beyond ATP-III

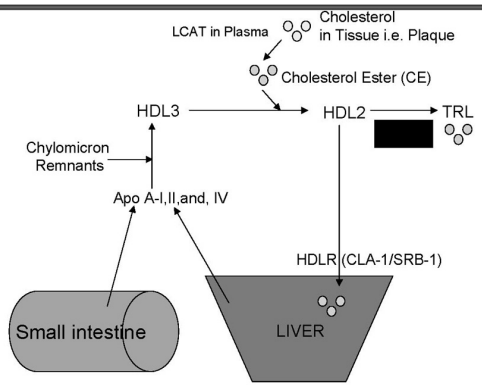
MIRACL
PROVE IT ; faster & lower, ACS
CARDS ; lower, diabetes
PROSPER ; lower, elderly
ASCOT ; lower, multiple RFs with HT
TNT ; lower, stable angina

C. HDL; Next Target

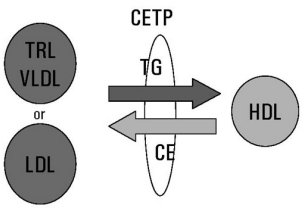
Anti-atherogenic Role of HDL

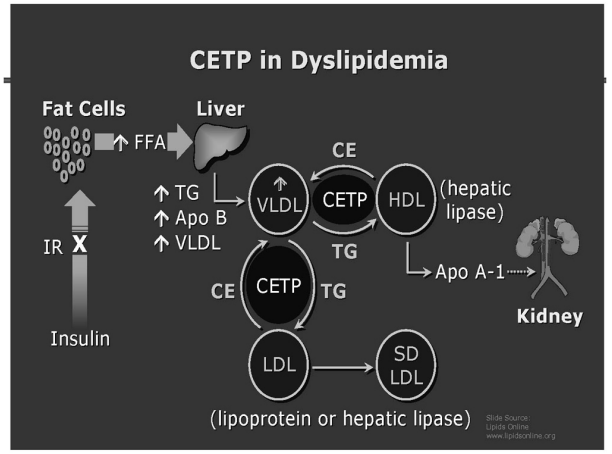
- Anti-inflammatory
- Anti-oxidative
- Reverse Cholesterol Transport

" HDL in reverse cholesterol transport "



Cholesterol Ester Transport Protein (CETP)





Potential Benefits of CETP inhibition

- May elevate HDL
- May reduce small dense LDL

C. Other Drugs are Coming Soon

Niacin
Omega-3 fatty-acid
colesevelam

Choice of ideal drugs to correct dyslipidemia