Risk Evaluation 의 시작

위험군의 발견

A man over 60

66세 남성
당뇨 (−)
고혈압 (+) ; 약 2가지, 120/85 mmHg
흡연 (+)
가족력 (−)

식이 운동 요법 권장 후 6주 후의 공복시 지질수치
       TC = 232 mg/dl
       TG = 220 mg/dl
       HDL−C = 38 mg/dl
   (LDL−C = 150 mg/dl, non−HDL = 194 mg/dl)

a. 고혈압약도 드시니까 고지혈증 치료는 좀 기다려보죠.
b. 많이 높지는 않으신데.. 그래도 약은 드셔야겠는데요.
c. 현재 위험한 상태이니 꼭 약을 드셔서라도 조절하셔야 합니다.

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 빼 줌.

What does he have right now ?

	major RF	MS
• Smoking	o	-
• High blood pressure	o	X
• Low HDL-C	o	o
• High TG	-	o
• Family history	X	-
• Old age	o	-
• High glucose	X	o
• Obesity	-	o

NCEP-III 에 의한
10-year-risk는 얼마로 계산될까요 ?

Scoring system in NCEP-III

Men

Point Total	10-Year Risk, %
<0	<1
0	1
1	1
2	1
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

Women

Point Total	10-Year Risk, %
<9	<1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	≥30

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

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

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

	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

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

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

Age, y	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

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
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140-159	3	5
≥160	4	6

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21	14
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23	22
24	27
≥25	≥30

16 points = 25 % !!!
= like CHD EQ !!!

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3	1
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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

Before = 16 points

Now = 12 points

4 points down make 60 % reduction !!!

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	20 / 10			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.

Risk Stratification 의 진화

'최고'위험군의 등장

ACS ; atherogenesis + inflammation

Plaque Rupture
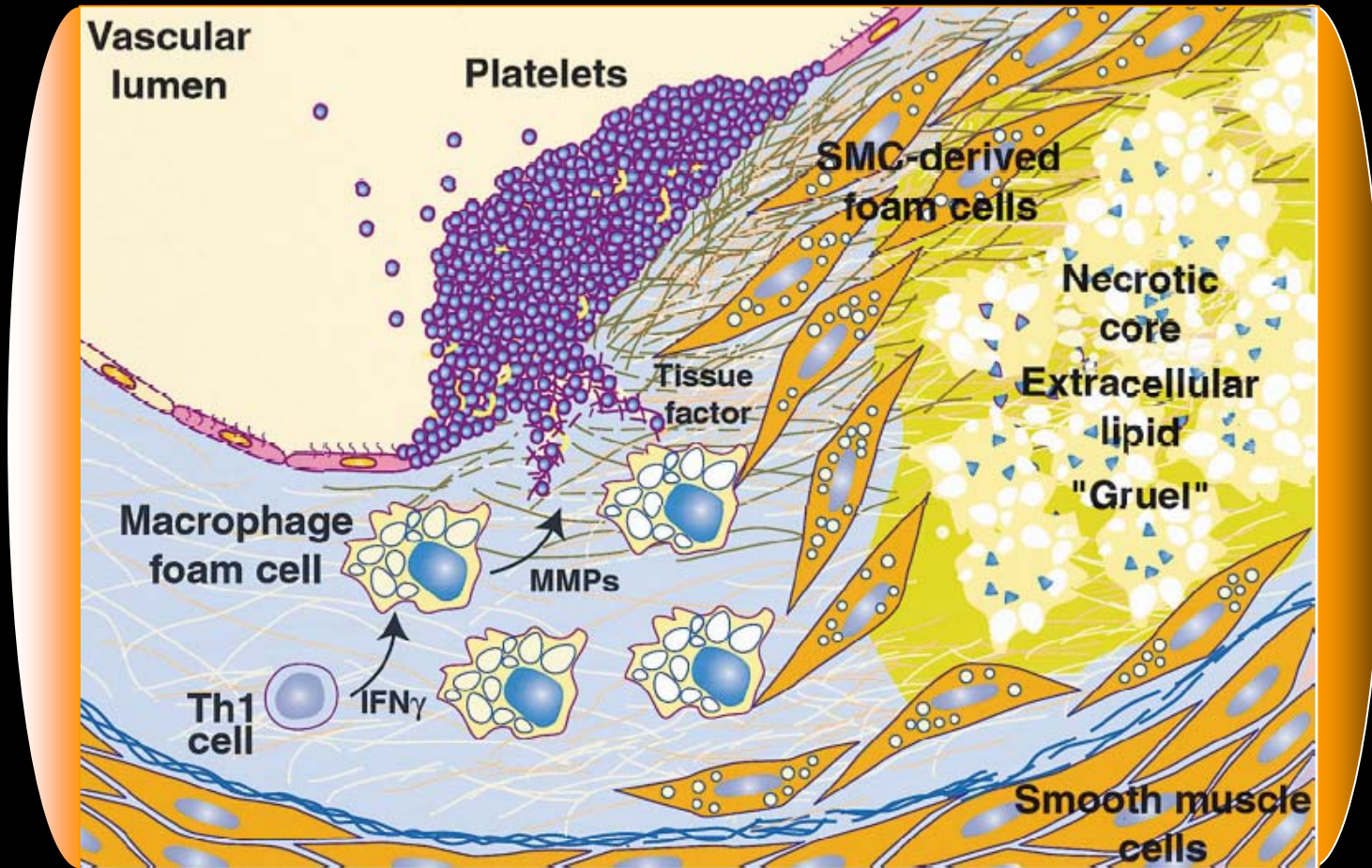
Metabolic Pathways Blocked By Statins

Acetyl-CoA + Acetoacetyl-CoA

↓

HMG-CoA

Statins → **Block** ↓

Mevalonate

↓

Isopentanyl PP

↓

Geranyl PP

↓

Farnesyl PP — **Geranyl Geranyl PP** → **Rho**

↓

Squalene

↓

Cholesterol

Slower Late Benefit

Related to Hepatic LDL Reduction

Early/Rapid and Later Benefit (pleiotropic effect)

Important in Vascular Cellular Responses

Prenylation

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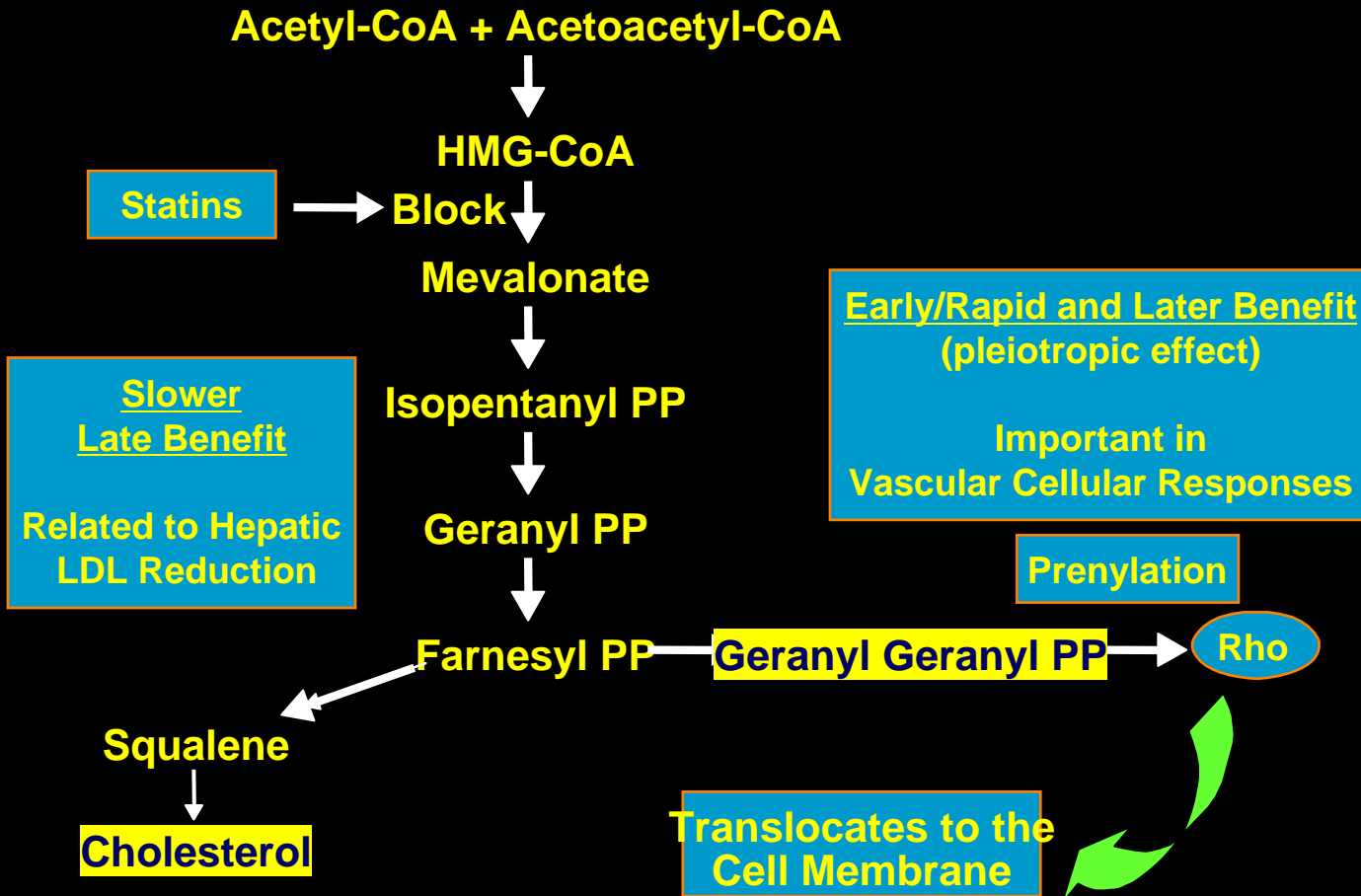
PP = pyrophosphate.
Reproduced from Ray and Cannon. *Curr Opin Lipidol.* 2004;15:637, with permission.
Ray and Cannon. *Am J Cardiol.* 2005;96(suppl):54F.

PROVE-IT Proves Intensive Treatment

PROVE IT Examined Intensive Lipid Lowering vs Moderate Lipid Lowering in Patients with ACS

4S (N=4444)

CARE (N=4159)

LIPID (N=9014)

AVERT (N=341)

MIRACL (N=3086)

PROVE IT (N=4162)

TNT, IDEAL ...

1 2 3 4 5 6

Time from coronary event (months)

Time of index coronary event
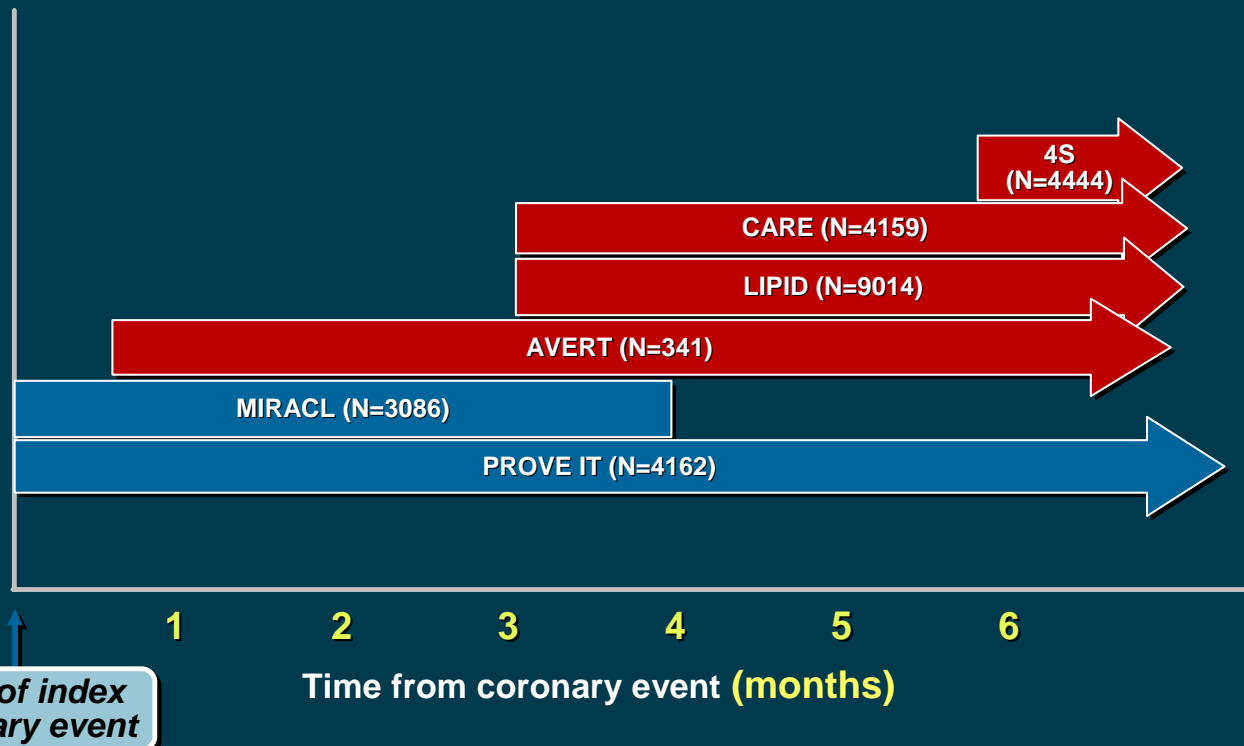
PROVE IT=Pravastatin or Atorvastatin Evaluation and Infection Therapy trial.
Scandinavian Simvastatin Survival Study Group. *Lancet.* 1994;344:1383-1389; Lewis SJ et al. *Ann Intern Med.* 1998;129:681-689; LIPID Study Group. *N Engl J Med.* 1998;339:1349-1357; Pitt B et al. *N Engl J Med.* 1999;341:70-76; Schwartz GG et al. *JAMA.* 2001,285:1711-1718; Cannon CP et al. *N Engl J Med.* 2004;350:1495-1504.

24

PROVE –IT

4162 Acute coronary syndrome
Atorva 80 mg vs. prava 40 mg, for 2 yrs
LDL-C in atorva 80 mg/d; **67** mg/dl
LDL-C, in prava 40mg/d; 97 mg/dl

TNT

15464 Stable chronic angina
Atorva 80 mg vs. 10 mg, for 4.9 yrs
LDL-C 130-250mg/dl, TG<600 mg/dl
LDL-C in atorva 80 mg/d; **70** mg/dl, in 10mg/d ; 100 mg/dl

IDEAL

8888 Old myocardial infarction
Atorva 80 mg vs. simva 20 mg, for 4.8 yrs
Age <80 yrs. LDL-C 130-250mg/dl, TG<600 mg/dl
LDL-C in atorva 80 mg/d; **80** mg/dl, in simva 20mg/d ; 99.8 mg/dl

PROVE-IT | Significant reduction in all-cause mortality, MI, unstable angina, revascularization ≥30 days, and stroke

TNT | Significant reduction in MI and stroke

IDEAL | Significant reduction in nonfatal MI and PVD
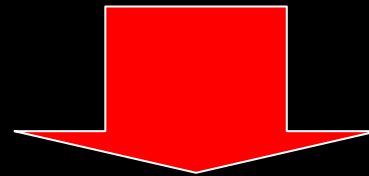
LDL-C < 70 mg/dl

PROVE IT–TIMI 22: Prognostic Value Of 30-Day Achieved LDL And CRP On Recurrent MI Or Death From Cardiovascular Causes
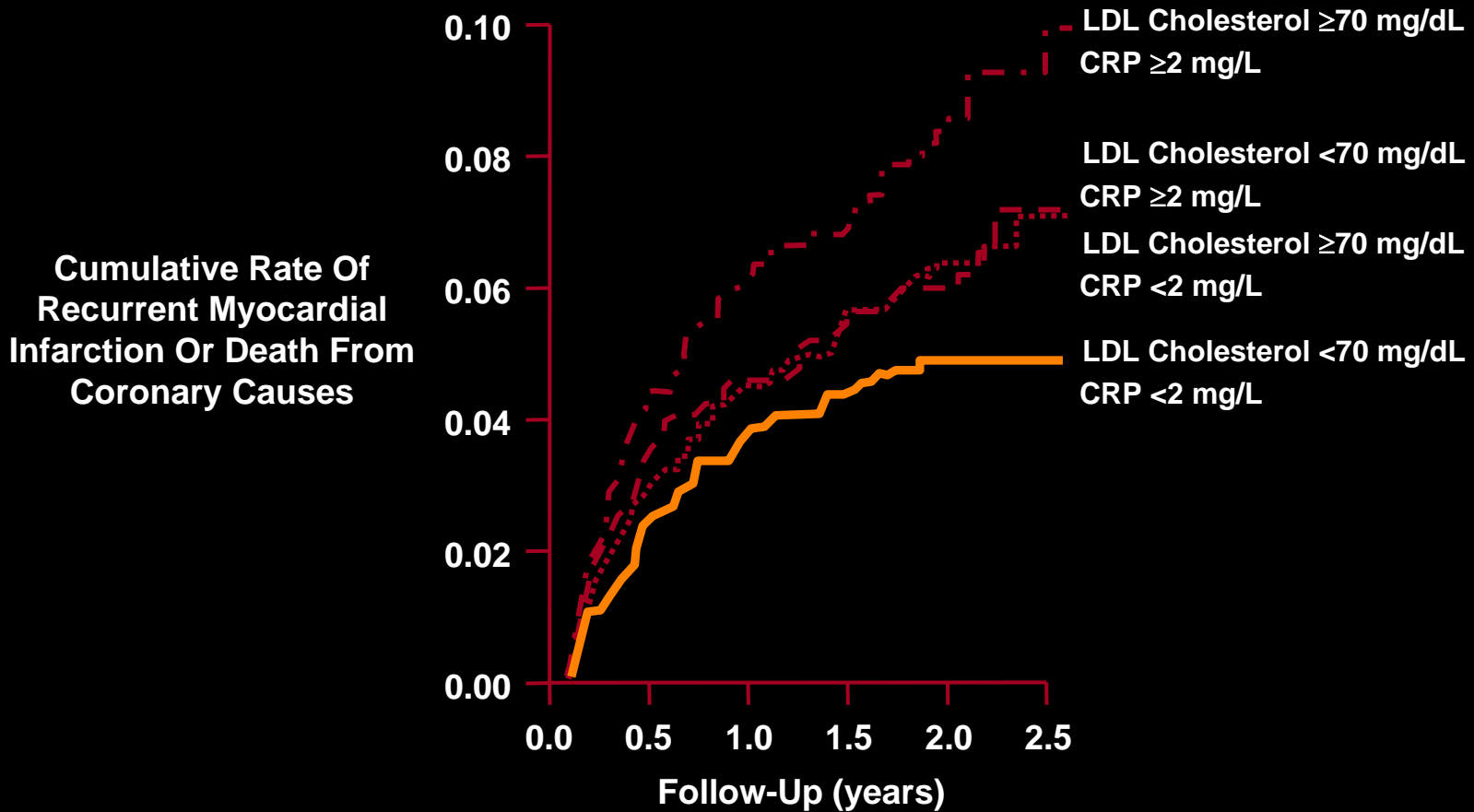
Reproduced from Ridker et al. *N Engl J Med.* 2005;352:20, with permission.
Ray and Cannon. *Am J Cardiol.* 2005;96(suppl):54F.

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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 ; <u>CVD with</u>

     1. multiple RFs (esp. DM)

     2. poorly controlled RFs (esp. smoking)

     3. multiple factors of the Metabolic syndrome

        (high TG $\geq$ 200 plus nonHDL-C $\geq$ 130 with low HDL-C $\leq$ 40)

     4. with ACS

'Very High' is replacing Just 'High'

ACS

Angina

Hx of MI

> 50 % stenosis

High CRP ?

Diabetes ?

Hypertension ?

You can expect statin effects even more in Higher risk patients

- <u>Earlier</u> is better
- <u>Lower</u> is better

- ACS ; MIRACL, PROVE-IT

- High atherosclerotic burden ; REVERSAL, ASTEROID, TNT, IDEAL

- Diabetes ; CARDS

- Hypertension with many RFs ; ASCOT-LLA

Risk <u>Modification</u> 의 진화

보다 높은 목표의 등장

Way to Win

Defense

Offense

Retard the plaque growth

↓
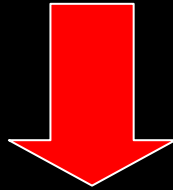
Regress the plaque

REVERSAL
ASTEROID

The IVUS technique can detect angiographically 'silent' atheroma

< Angiogram >

No evidence of disease

< IVUS >

Little evidence of disease
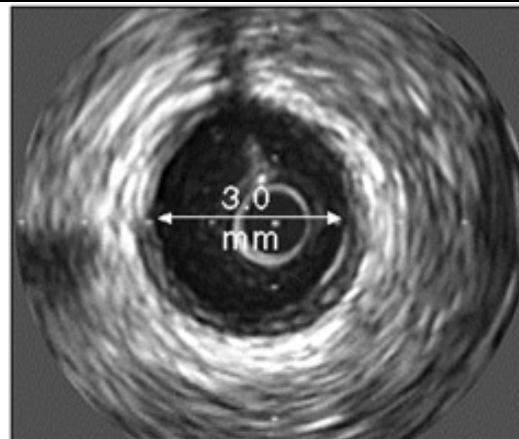
Atheroma
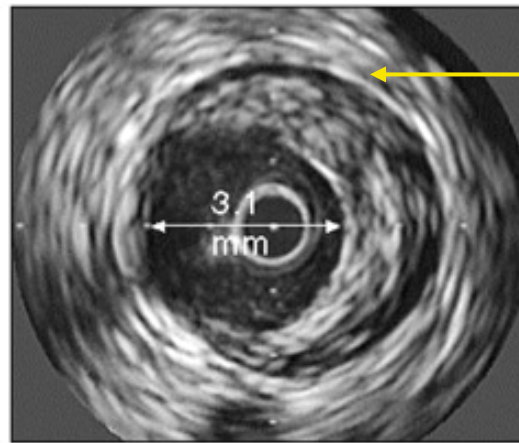
IVUS=intravascular
Nissen S, Yock P. C

Example of regression of atherosclerosis with statin, measured by IVUS

Baseline IVUS
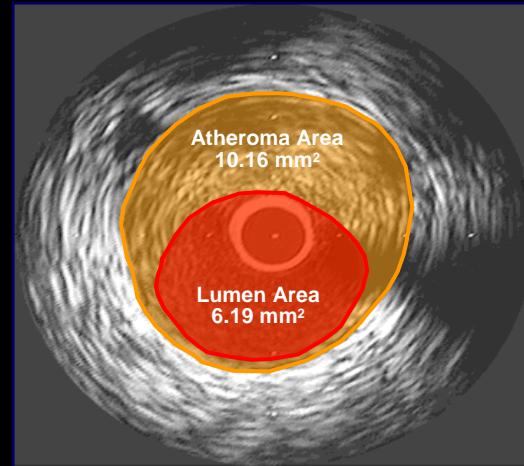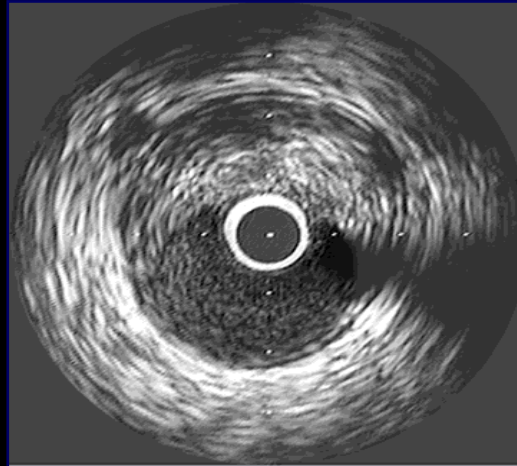
Follow-up IVUS 24 months rosuvastatin

Atheroma Area 10.16 mm²
Lumen Area 6.19 mm²

Atheroma Area 5.81 mm²
Lumen Area 5.96 mm²

Ref: Nissen S *et al.* JAMA 2006; **295**
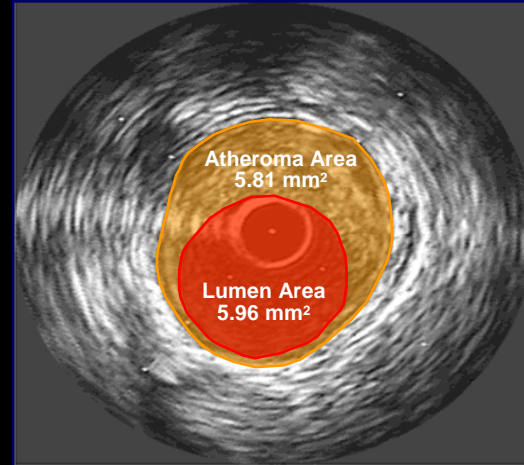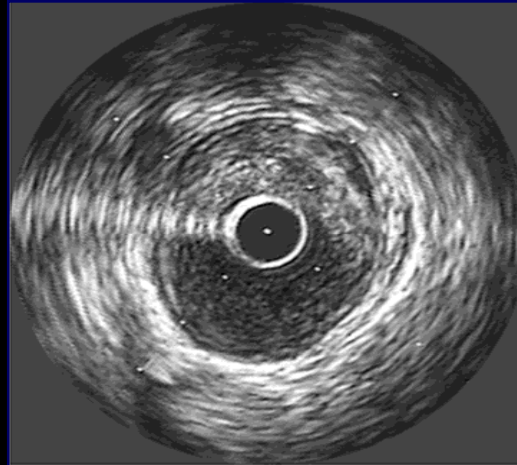
Atheroslerosis Regression Studies

- <u>**REVERSAL**</u>

- Atorva 80 mg/d

- Basal LDLc 150

- LDLc down to 80

- CRP down by 30 %

<u>**ASTERIOD**</u>

Rosuva 40 mg/d

130 mg/dl

60-70 mg/dl

HDL up by 15 %

Relationship between LDL-C levels and change in percent atheroma volume for several IVUS trials

$R^2 = 0.97$
$P < 0.001$

REVERSAL
pravastatin

CAMELOT
placebo

Median change in Percent Atheroma Volume (%)

1.8

1.2

0.6

0

-0.6

-1.2

REVERSAL
atorvastatin

A-Plus
placebo

ASTEROID
rosuvastatin

Progression

Regression

50   60   70   80   90   100   110   120

Mean LDL-C (mg/dL)
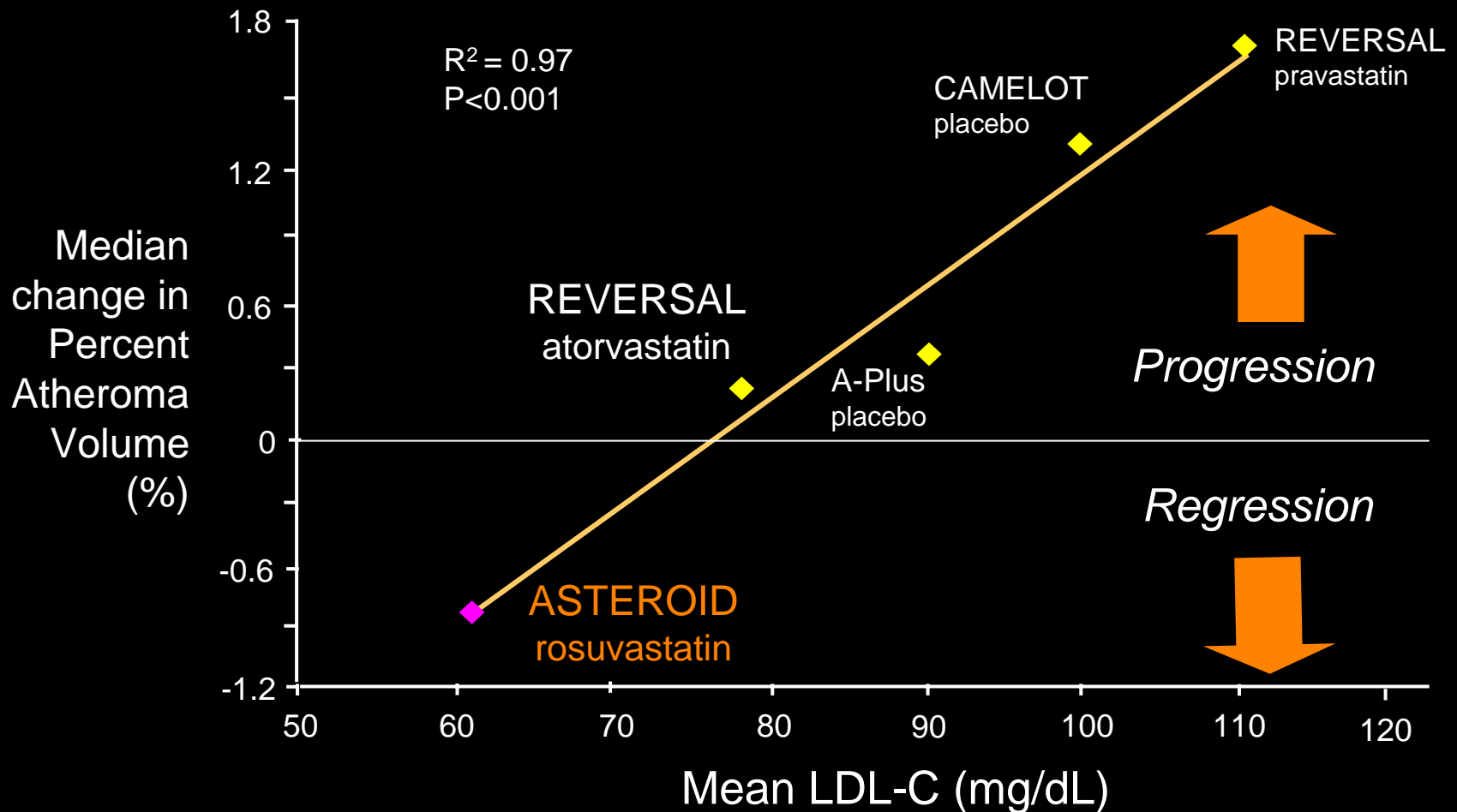
3 + 1 Categories of Risk That Modify LDL Cholesterol Goals

Risk Category	LDL Goal (mg/dL)
Very High	< 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 $\leq$ 20 %	< 130
Low ; 0-1 risk factor	< 160

cf. CHD indicates coronary heart disease.

Risk Modification
through
Lipid Modification

절반의 성공

Cholesterol Awareness in Korea

Awareness over the Normal/standard level	Health Index	Self-level Awareness
52.3%	Blood Pressure	67.1%
5.4%	Glucose Level	6.2%
1.8%	Cholesterol	5.5%

•Source: Gallup Korea, "Awareness on heart and coronary heart disease in Korea"
n=1,585 aged 30~65, conducted in Aug., 2005

Lipid management to high risk patients ;
10 center study (2003)
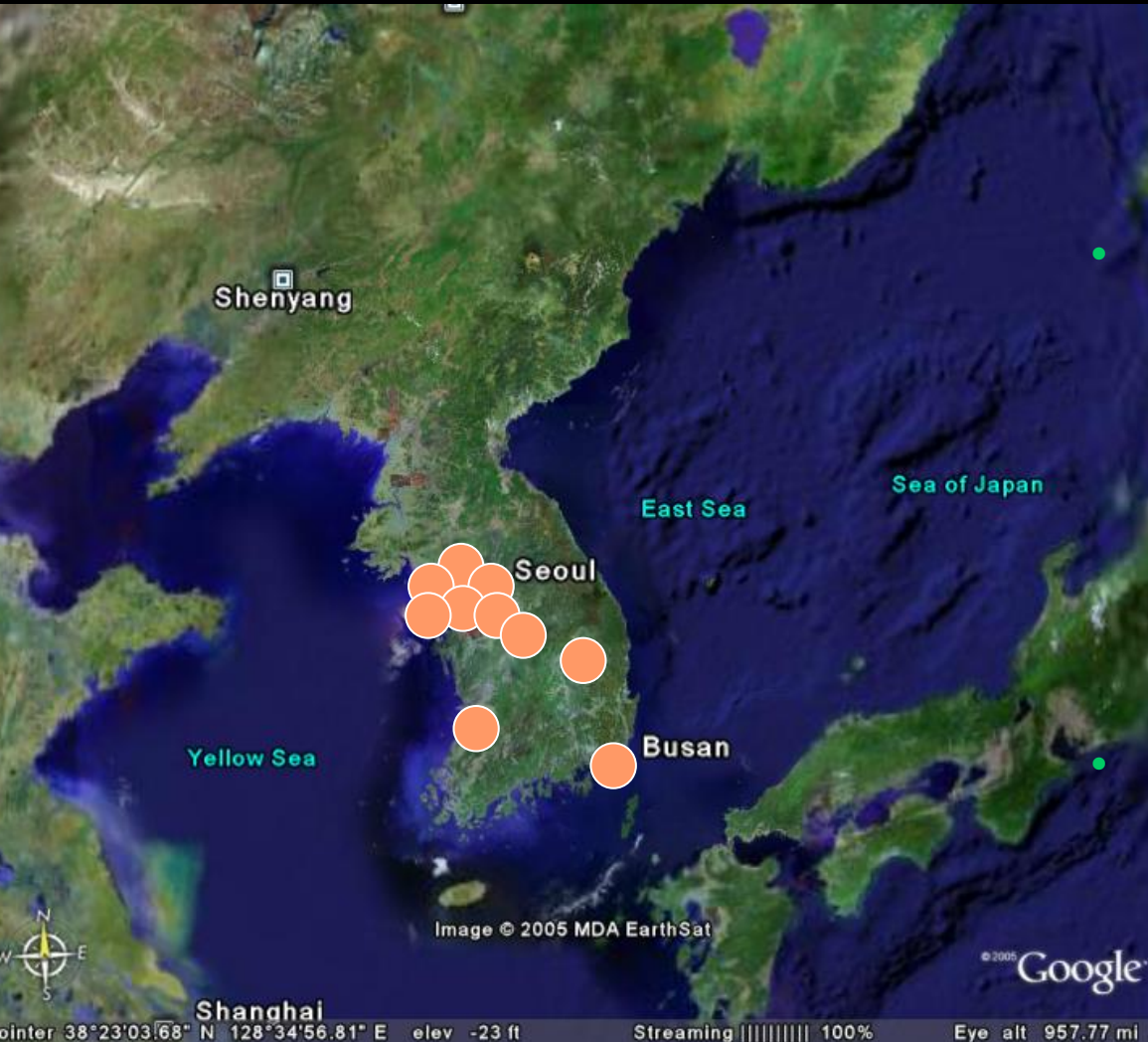
- 1,000 Patients with CAD
  (10 centers, >100 pts per center)
  confirmed by
  - CAG ; stenosis more than 50% or
  - Stress test ; positive or
  - Medical record ; s/p PTCA(PCI), s/p CABG
- & OPD F/U within recent 6 months

Change of Lipid Profile in Whole Patients at Initial & F/U Point

HAN KH copyright
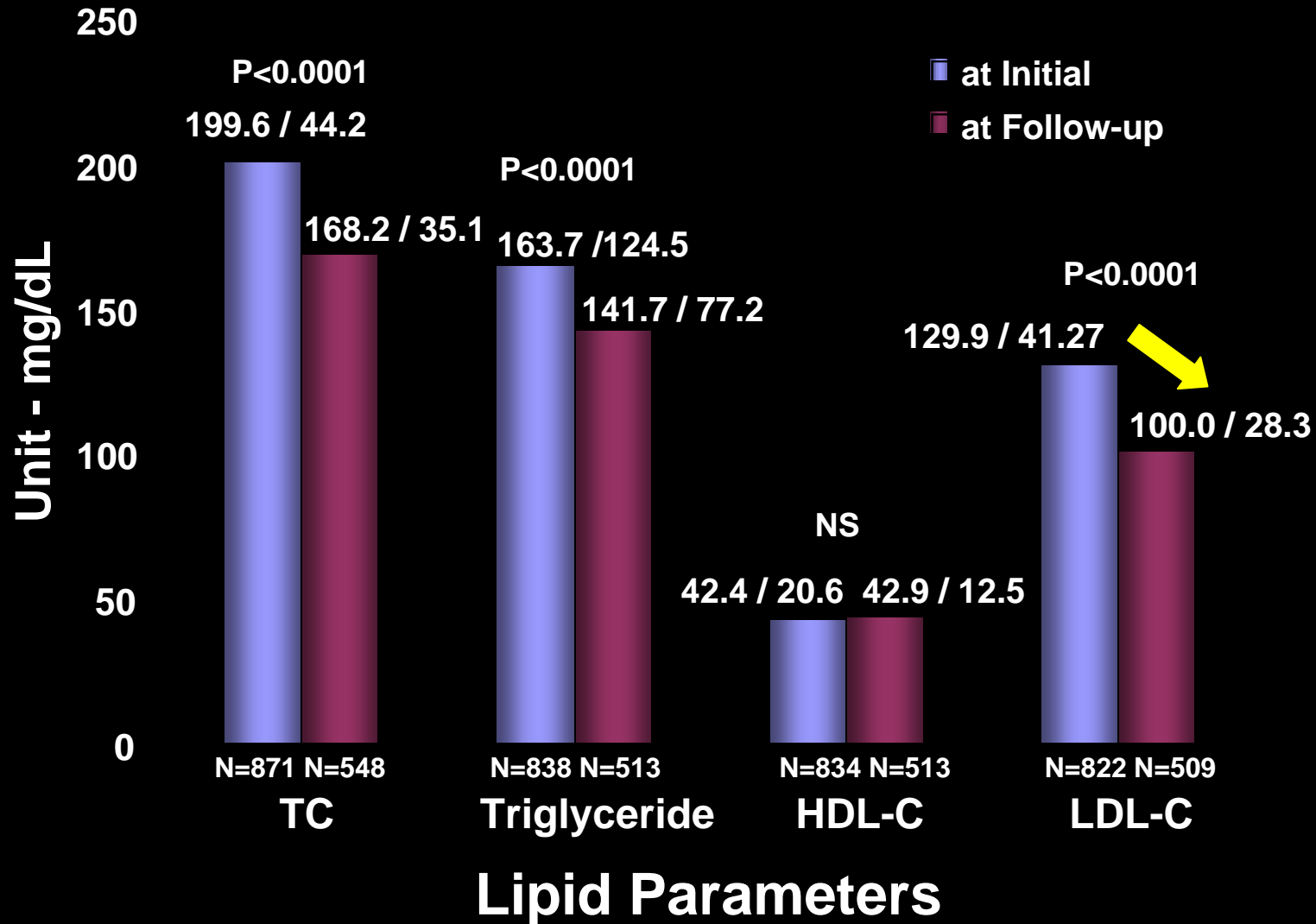
at Initial & F/U Point

HAN KH copyright
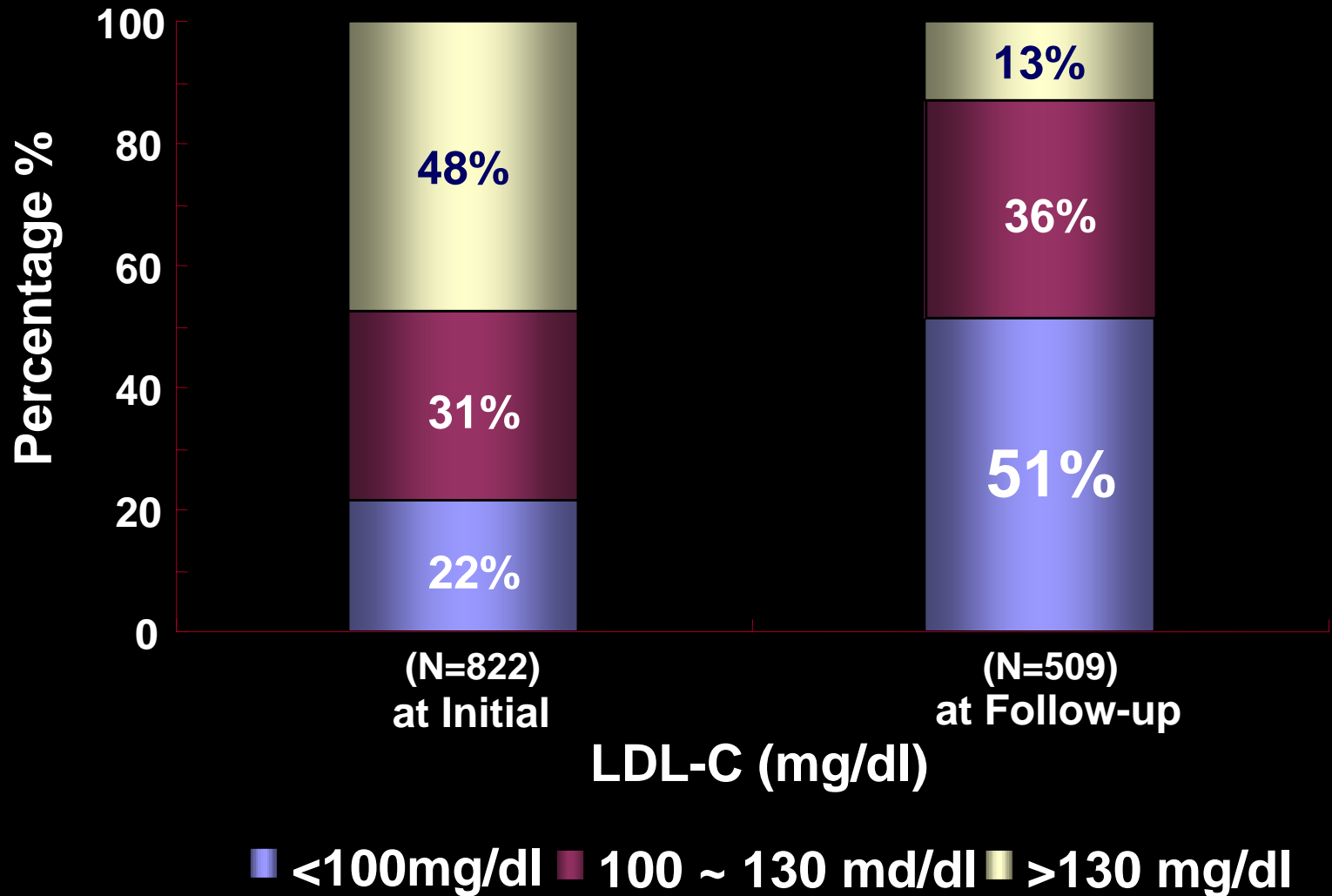
Lipid management in Real World ;

REALITY study (2003)

Return on Expenditure Achieved for LIpid TherapY

- From private clinic to general hospital

- 100 investigators across Korea

- 5 patients / investigator

Common statin doses in Korea

- Most of the patients are either started with

  - medium (66%) potency statin

  - low (28%) potency statin

- Medium potency statins are the most commonly used initial drugs

  - Atorvastatin 10 mg : 34.8%

  - Simvastatin 20 mg : 24.4%

Percentage of Patients reaching to LDL−C Target Goal
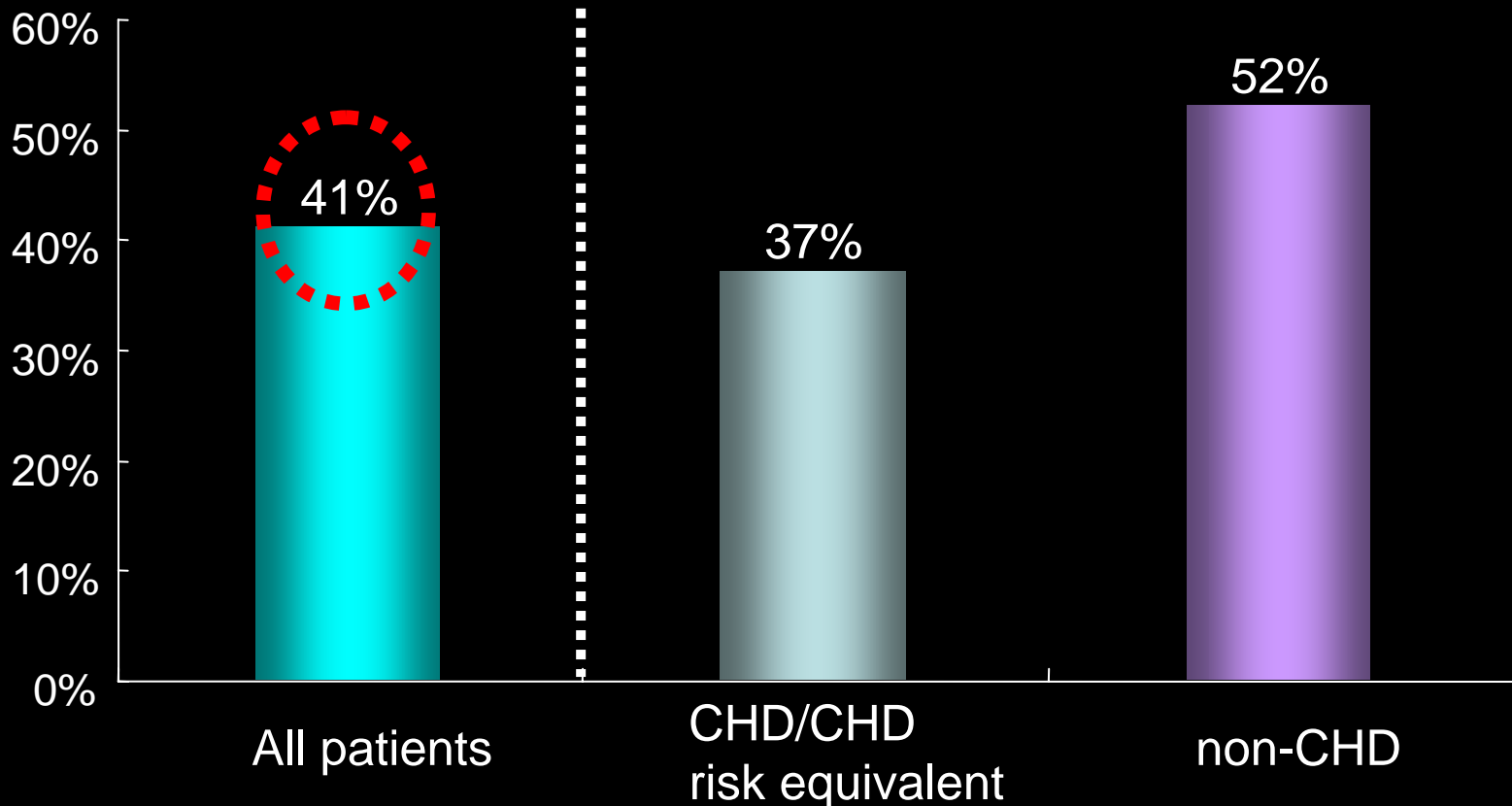
% of Patients attaining a treatment goal

Design: Multi-center retrospective review of medical records, 100 investigators across Korea, total 500 patients included. Minimum 1 year follow-up

Adapted from HS Kim et al. Presented at *EAS, 2005*

Additional Percentage of LDL−C reduction to reach Target Goal

Patients

30%
25%
20%
15%
10%
5%
0%

| 0- 9.9% | 10-19.9% | 20-29.9% | 30-39.9% | > 40% |

22% 24% 20% 22% 12%

% LDL-C reduction required to attain goal

Adapted from HS Kim et al. Presented at *EAS, 2005*
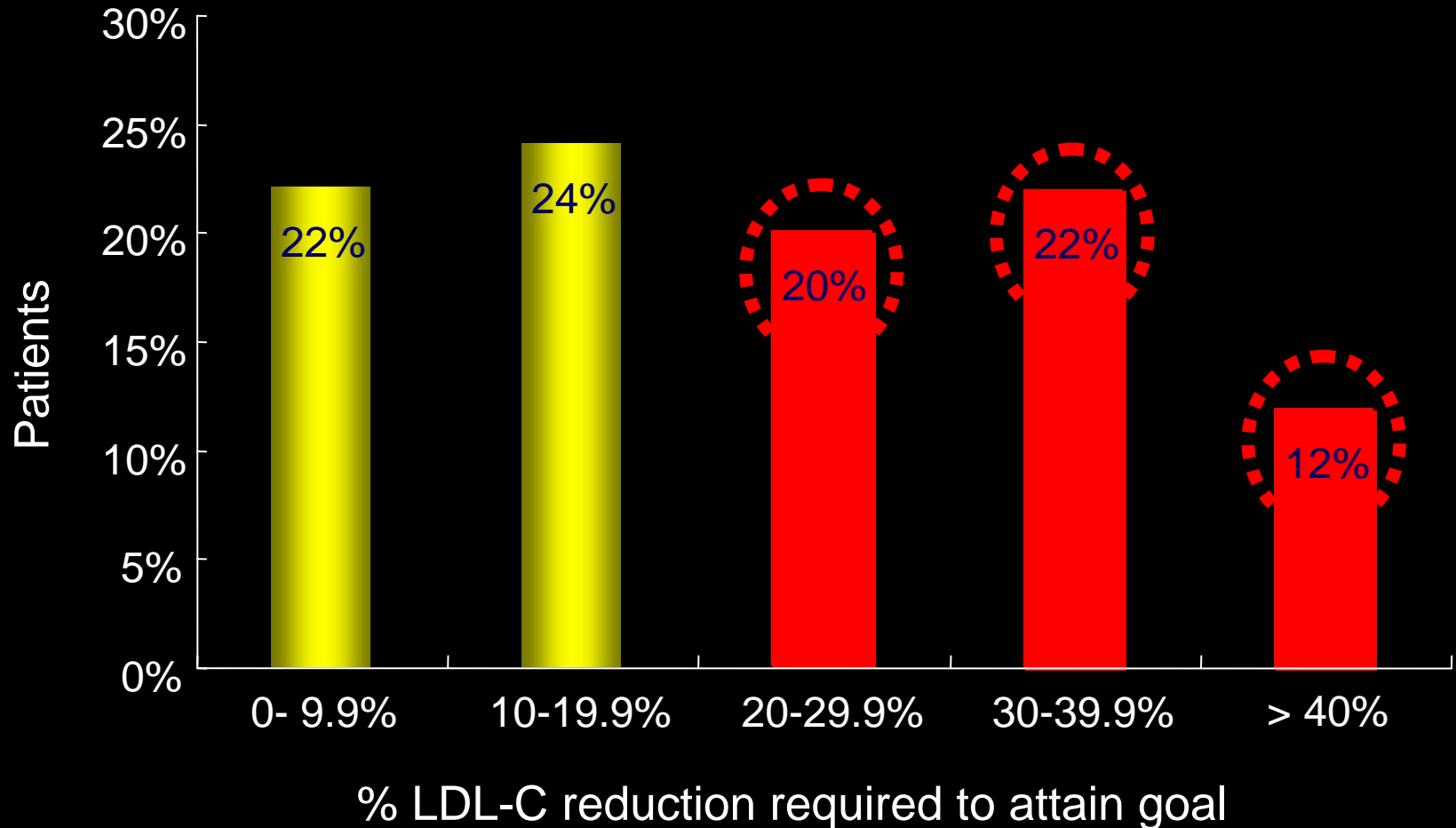
LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories *

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.

보험기준

A. Without risk factor :
　　　총콜레스테롤 ≥ **250 mg/dl**

B. With risk factor :
　　　History of MI or IHD, 고혈압, 당뇨
　　　총콜레스테롤 ≥ **220 mg/dl**

≥2 risk factors and
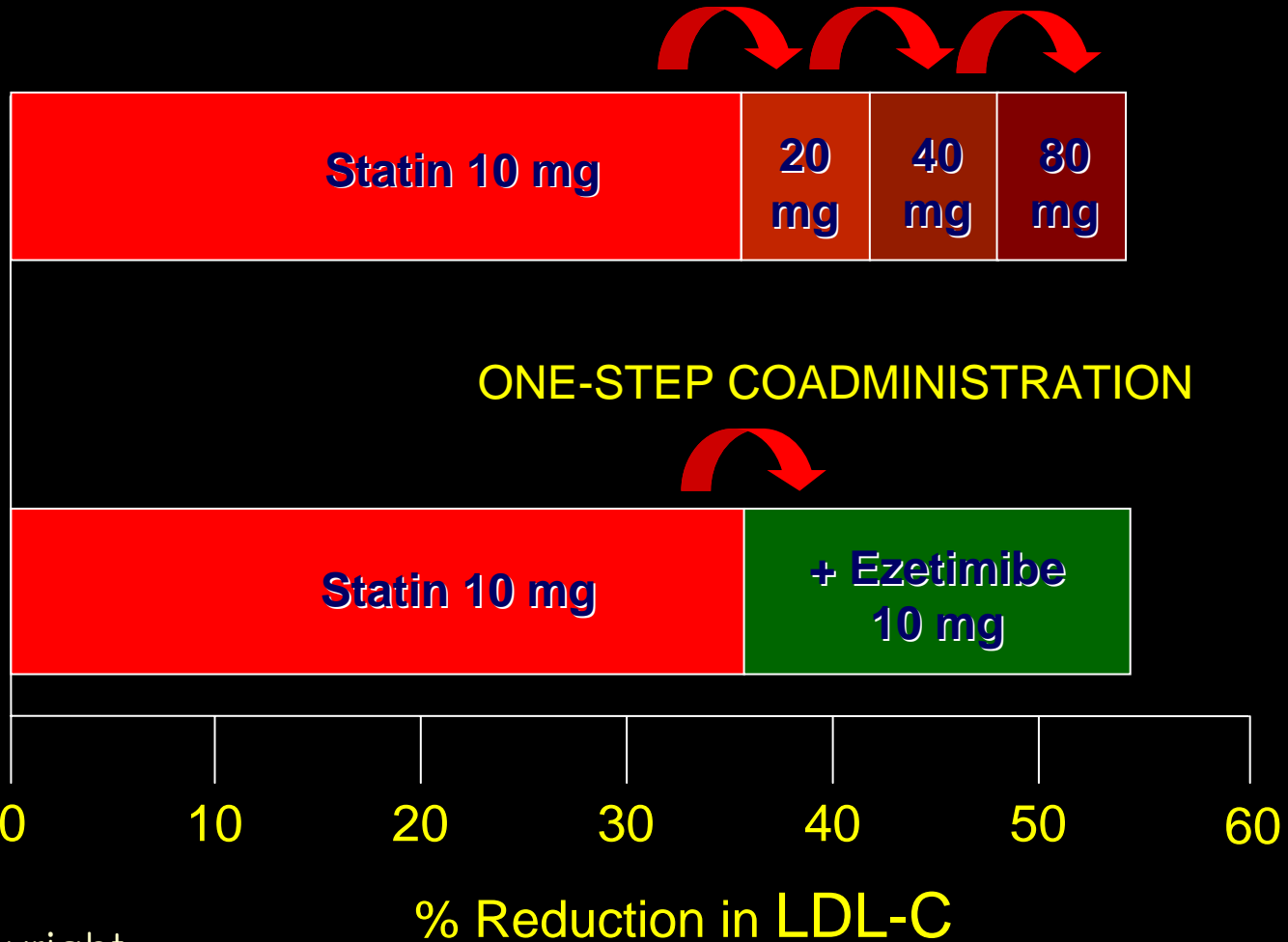≥10 year risk ≥ 10 %

220

400

LDL-C

300

Ideal Zone

Under-treatment

200

130

100

130

100

0

0   100   200   300   400   500

TC

Over-treatment

HAN KH copyright
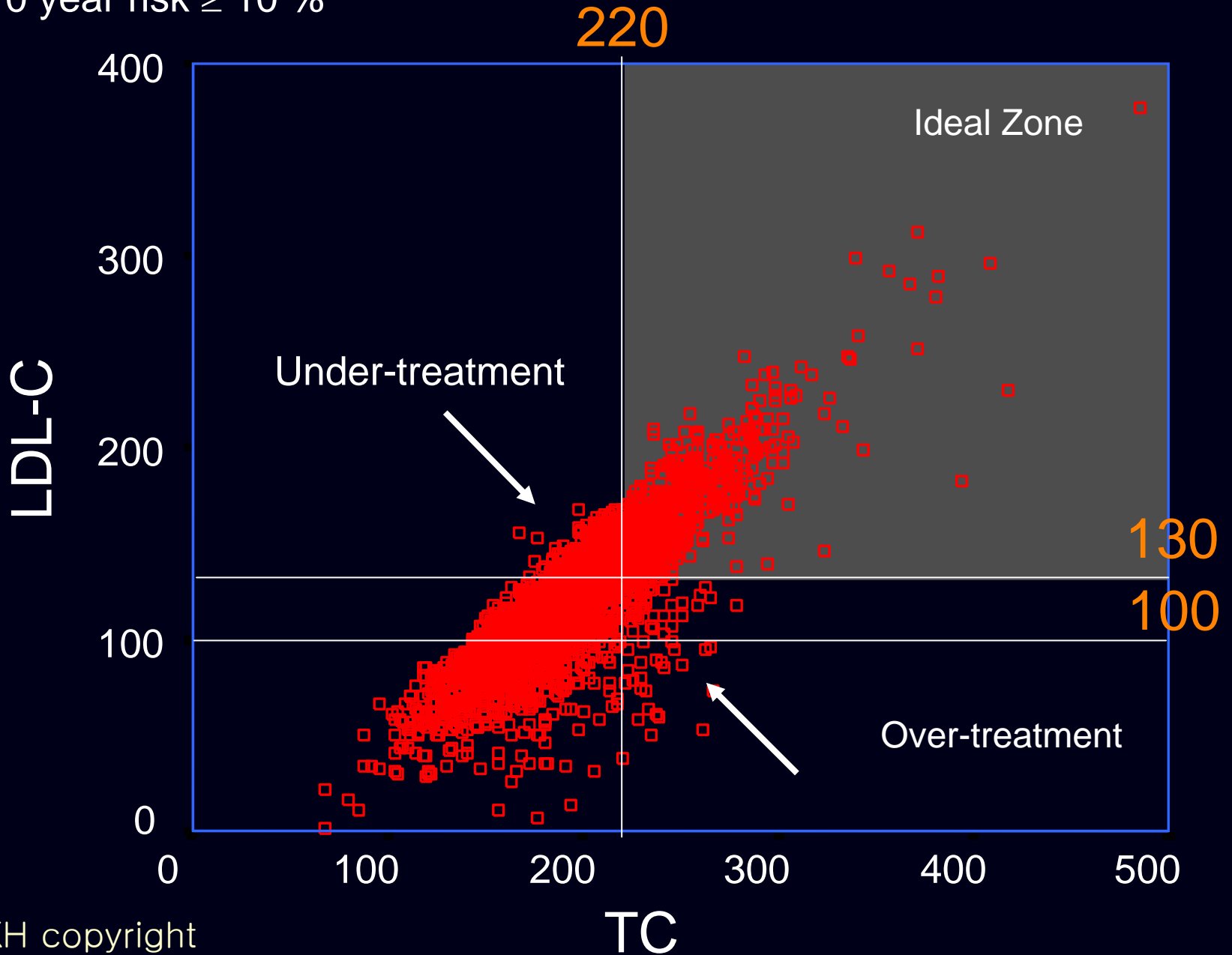
한국보험기준으로 인한 고지혈증 치료의 특징

- 고위험군일수록 약물투여가 불가능한 경우가 많이 발생한다.

- 많은 분들이 고위험군으로 인정받지 못한다.

- 지질저하 약물중 강한효과를 가진 약물이 선호된다.

Choice of ideal drugs to correct dyslipidemia

LDL

HIGH

+ ezetimibe
+ colesevelam
Dose up
switch to stronger ones

STATINS

statins + fibrates
statins + niacin
ezetimibe + fibrates

STATINS to
lower
inflammation

FIBRATES
Niacin SR

combination
+ omega 3-fatty acid

LOW

LOW   **HIGH**

TG

HAN KH copyright
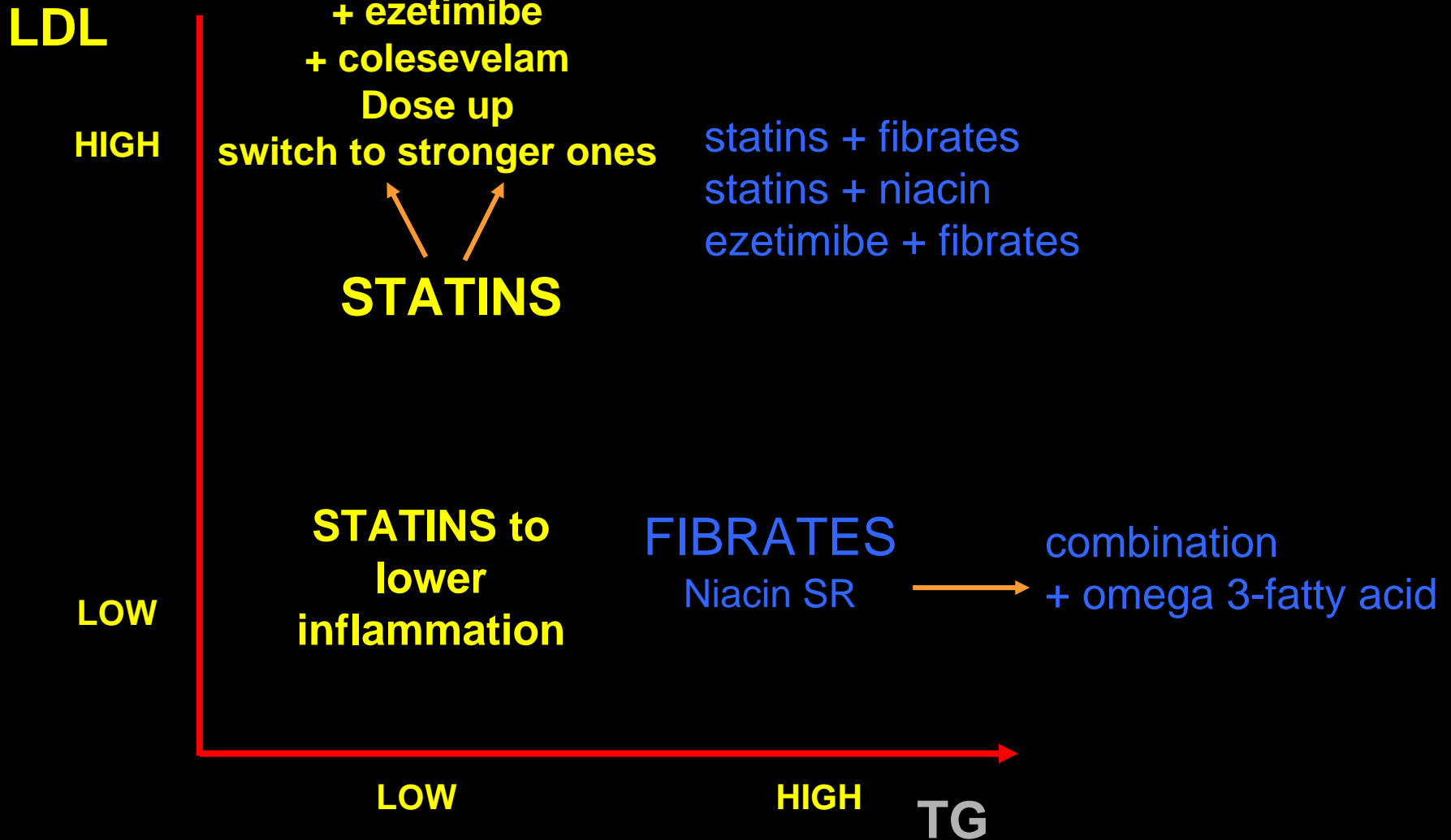
스타틴을 올리는 것이 좋은 경우

- 스타틴의 pleiotropic effects에 대한 강한 믿음
- 고위험군으로 높은 염증성 상태로 판단되는 경우
- 특히 당뇨성 상태/ 최근에 심혈관질환을 경험한 경우

" 당뇨 " ; CARD Study

2838 with NIDDM 40-75 years
atorvastatin 10 mg/day, LDL-C reduction by 40 %, 4 yrs

	No. of patients with an event (%)		Hazard ratio (95% CI)	P value
	Placebo	Atorvastatin 10 mg		
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.

HAN KH copyright

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

Median baseline lipids	No. of patients with an event (%)		Hazard ratio (95% CI)	P value
	Placebo	Atorvastatin		
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
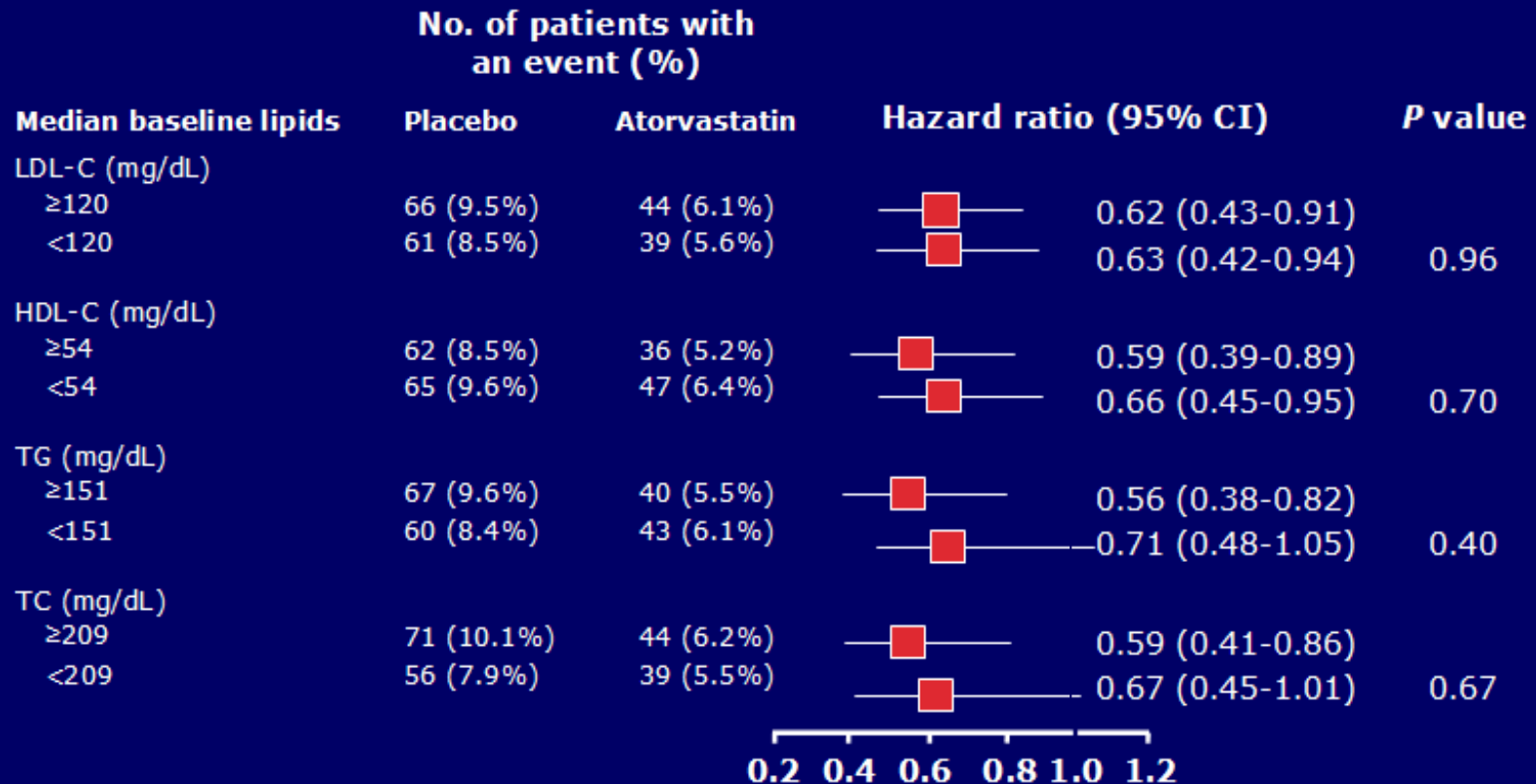
Symbol size is proportional to amount of statistical information.
P values are for test of heterogeneity.

CARDS=Collaborative Atorvastatin Diabetes Study.

Colhoun HM et al. *Lancet*. 2004;364:685-696.
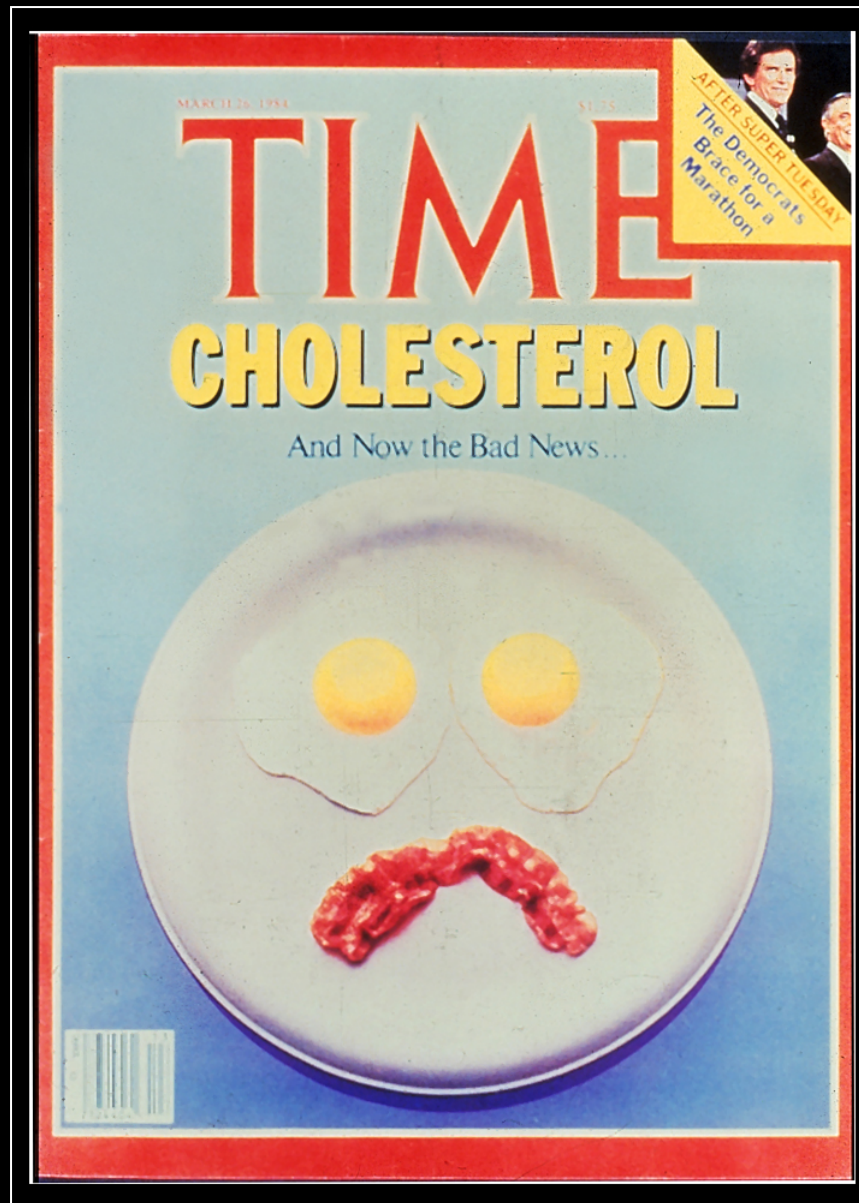
LDLc or Statin ?

ACS ; atherogenesis + inflammation
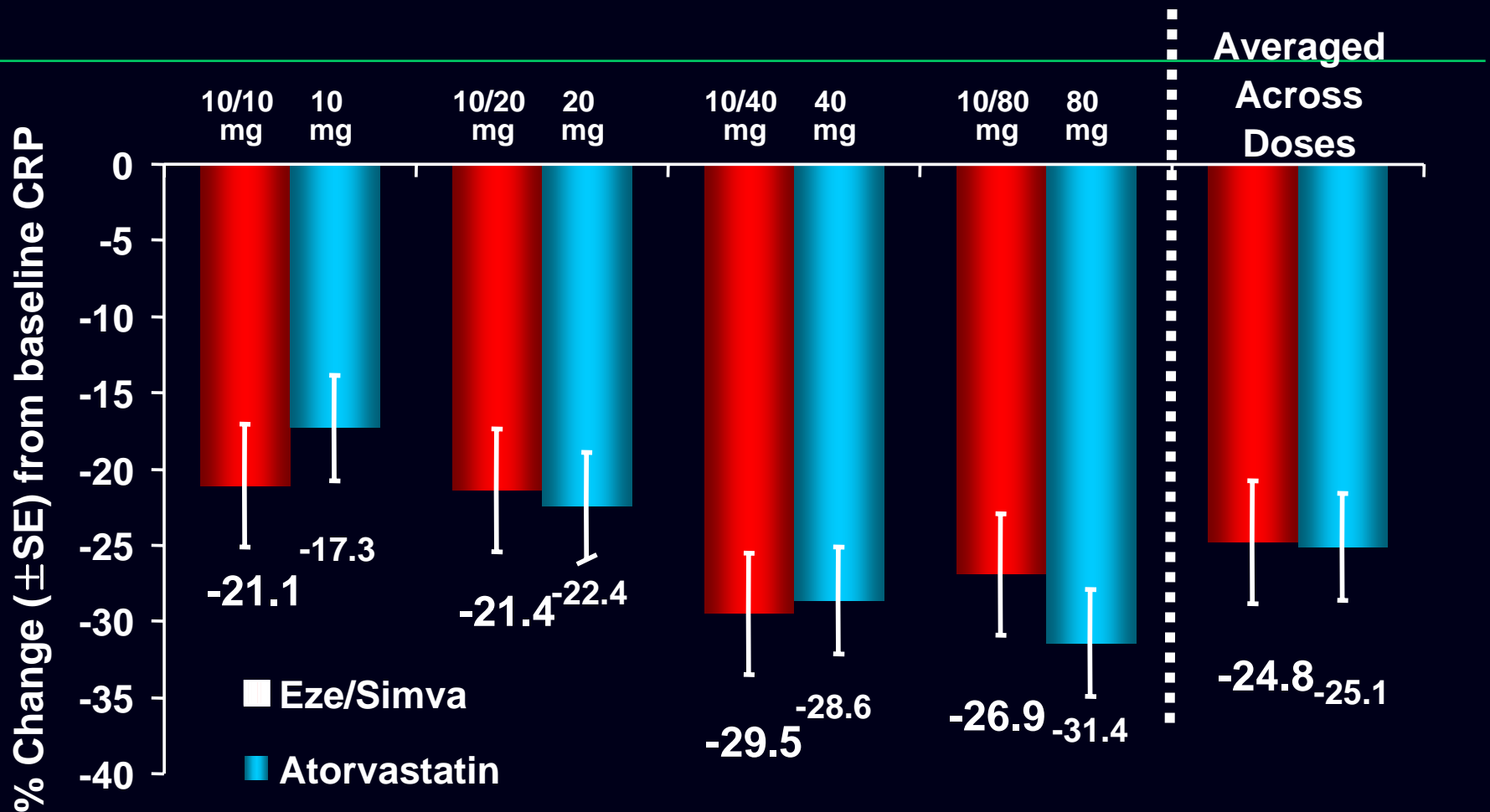
Plaque Rupture
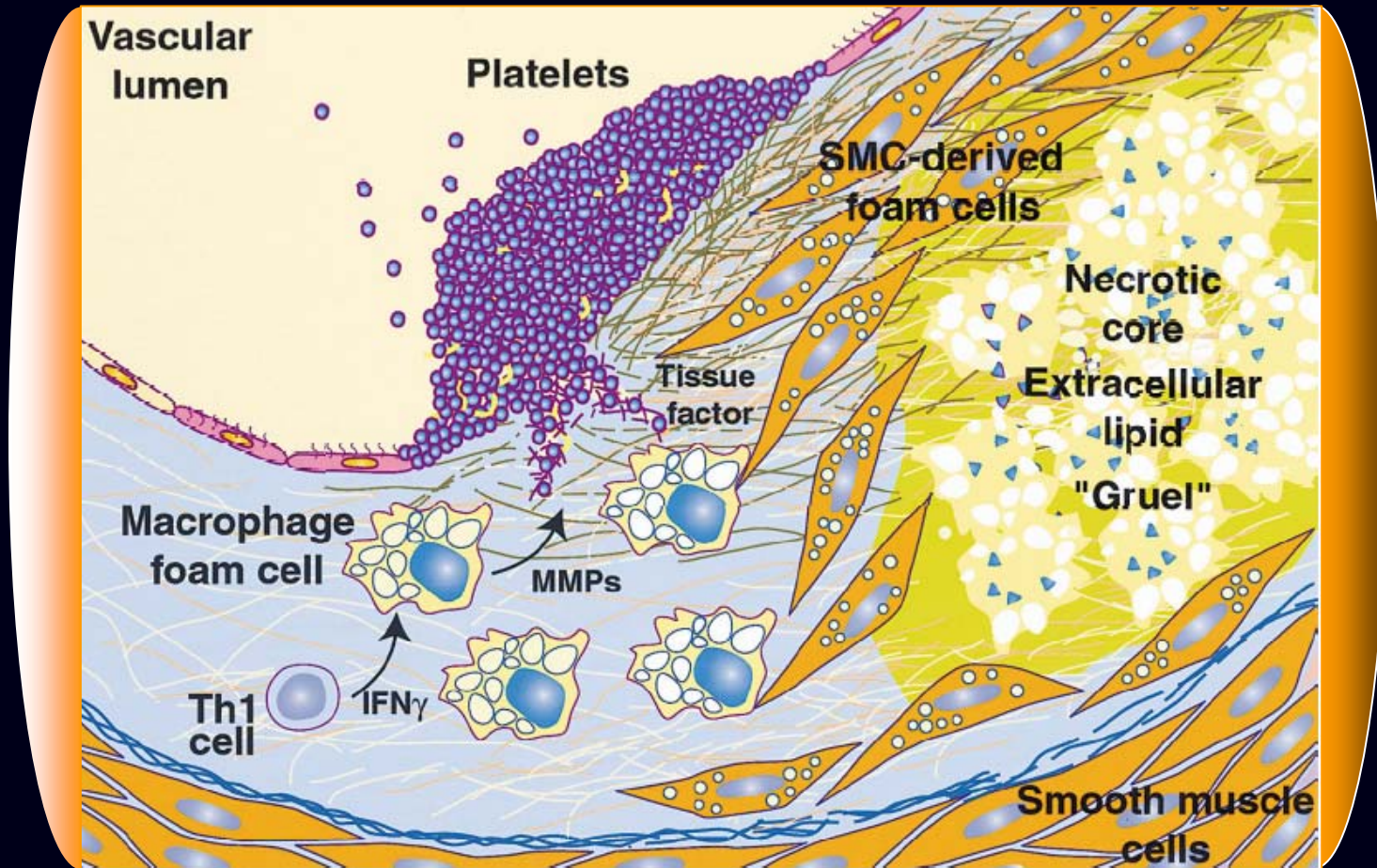
Anti-inflammatory effects of simvastatin 20 mg/d

-Eur Heart J. 2006 May;27(10):1182-90.

           Ez 10 mg + Simva 20 mg

                FBF elevation (+)

-J Cardiovasc Pharmacol. 2006 Jan;47(1):30-6.

          Simva 20, 40 mg

              serum VEGF reduction

-Arterioscler Thromb Vasc Biol. 2005 Sep;25(9):1952-9.

          Simva 20 mg

              inc. production of long chanin PUFA

- J Biol Regul Homeost Agents. 2004 Jul-Dec;18(3-4):295-301.

          Simva 20 mg

              dec. IL-2 production

Simvastatin reduces CCR2/MCP-1 concentration
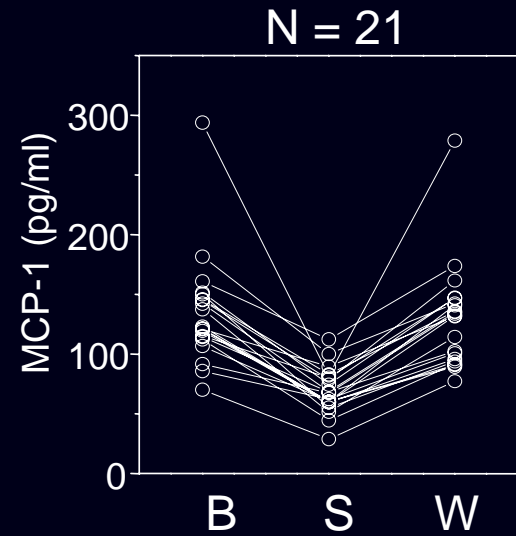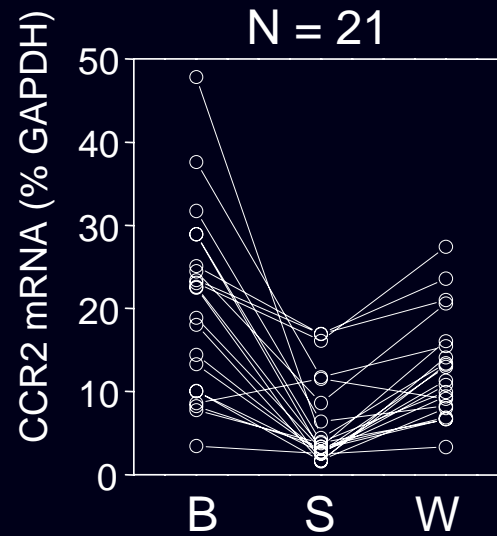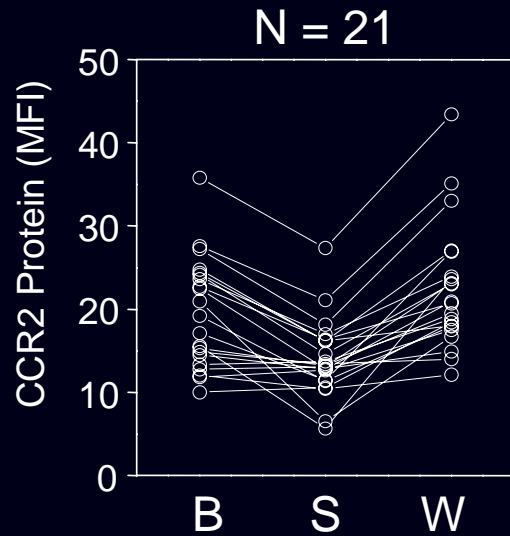
hs-CRP Reduction
VYTORIN vs. atorvastatin

Treatment Comparison at Each Dose and Averaged Across Doses

Ballantyne CM et al. *Am Heart J* 2005;149:464–473

Ezetimibe (바이토린) 의 장점
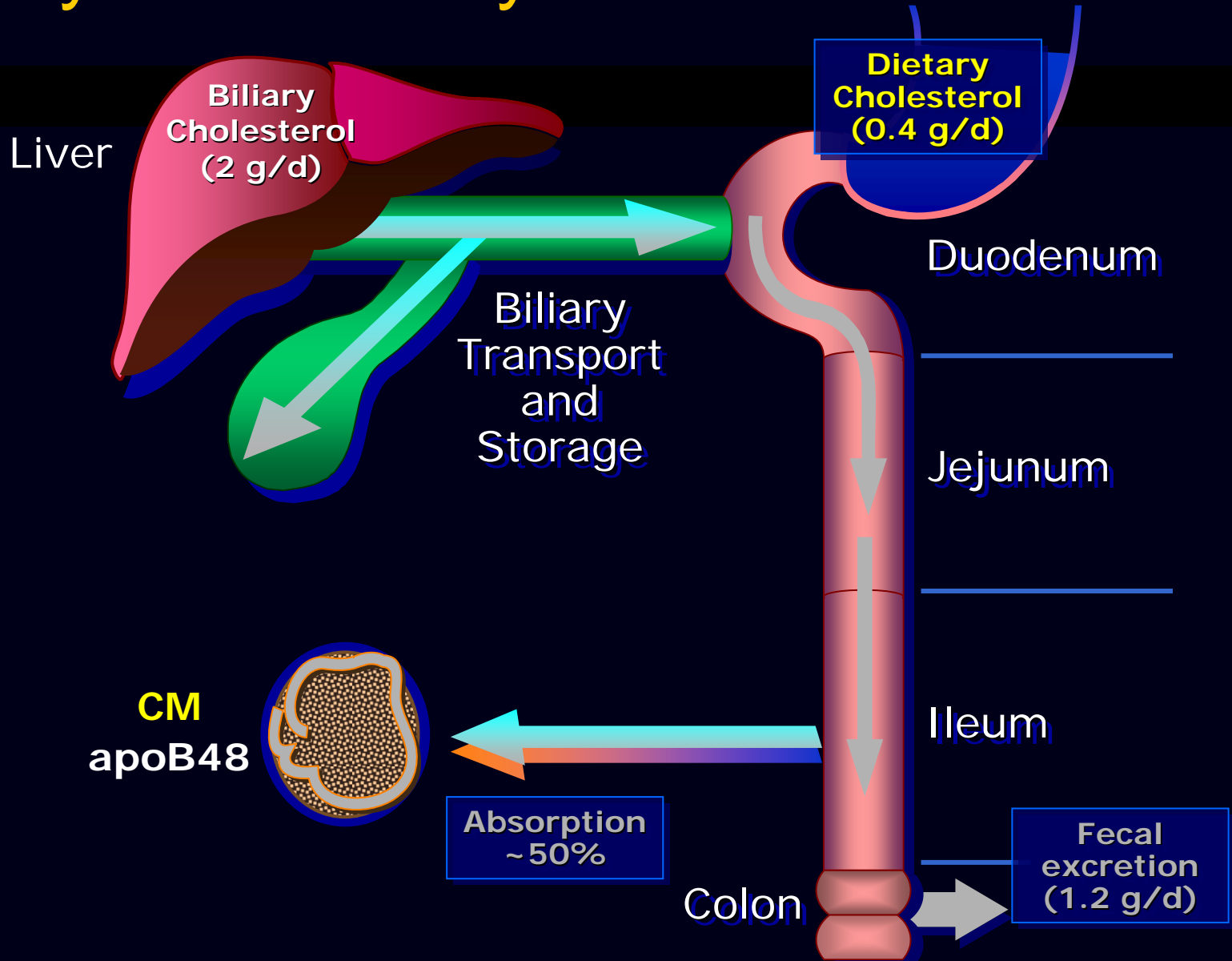
- High Efficacy & Safety profile ;

  Excellent Numbers !

Overview of Cholesterol Transport
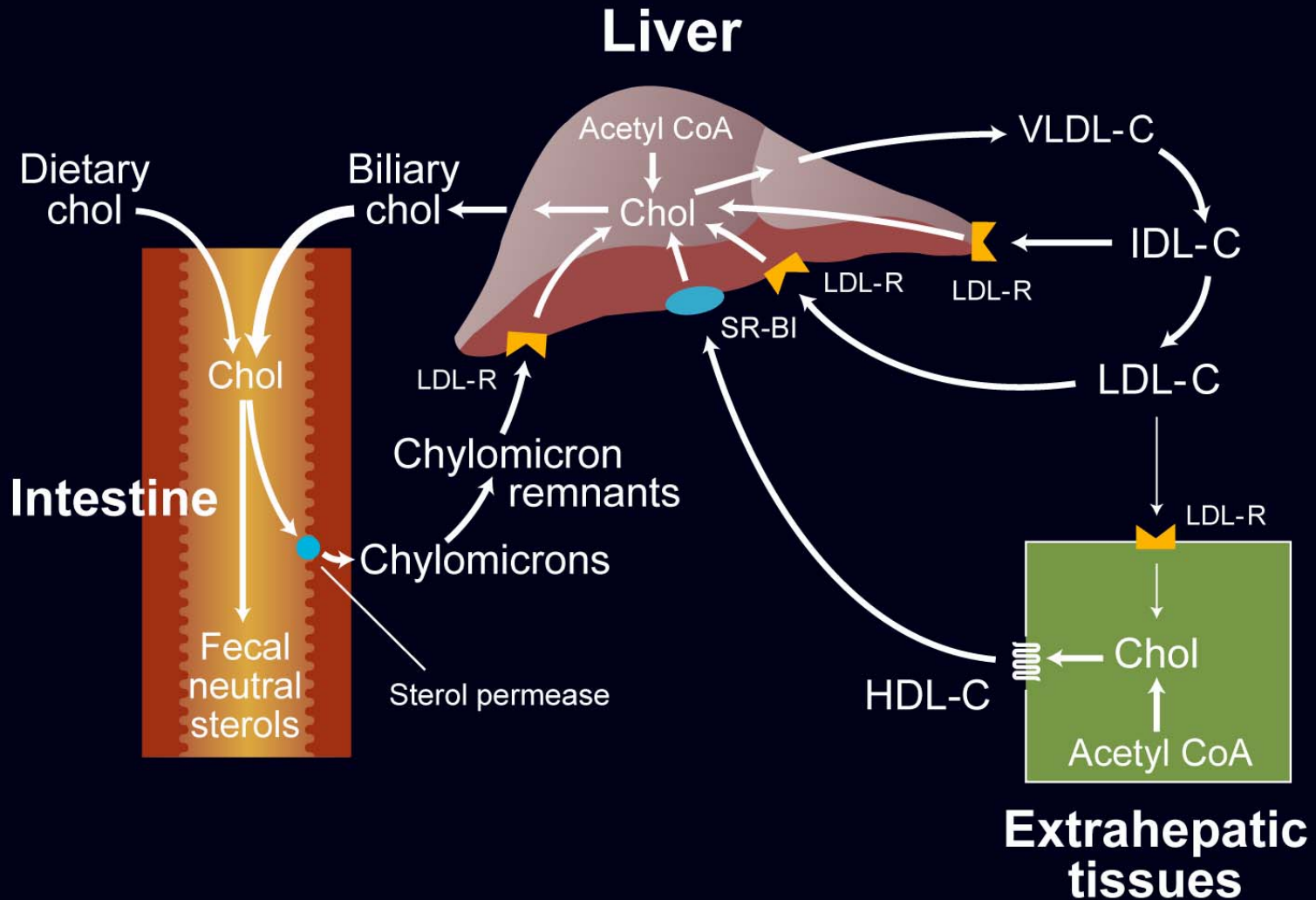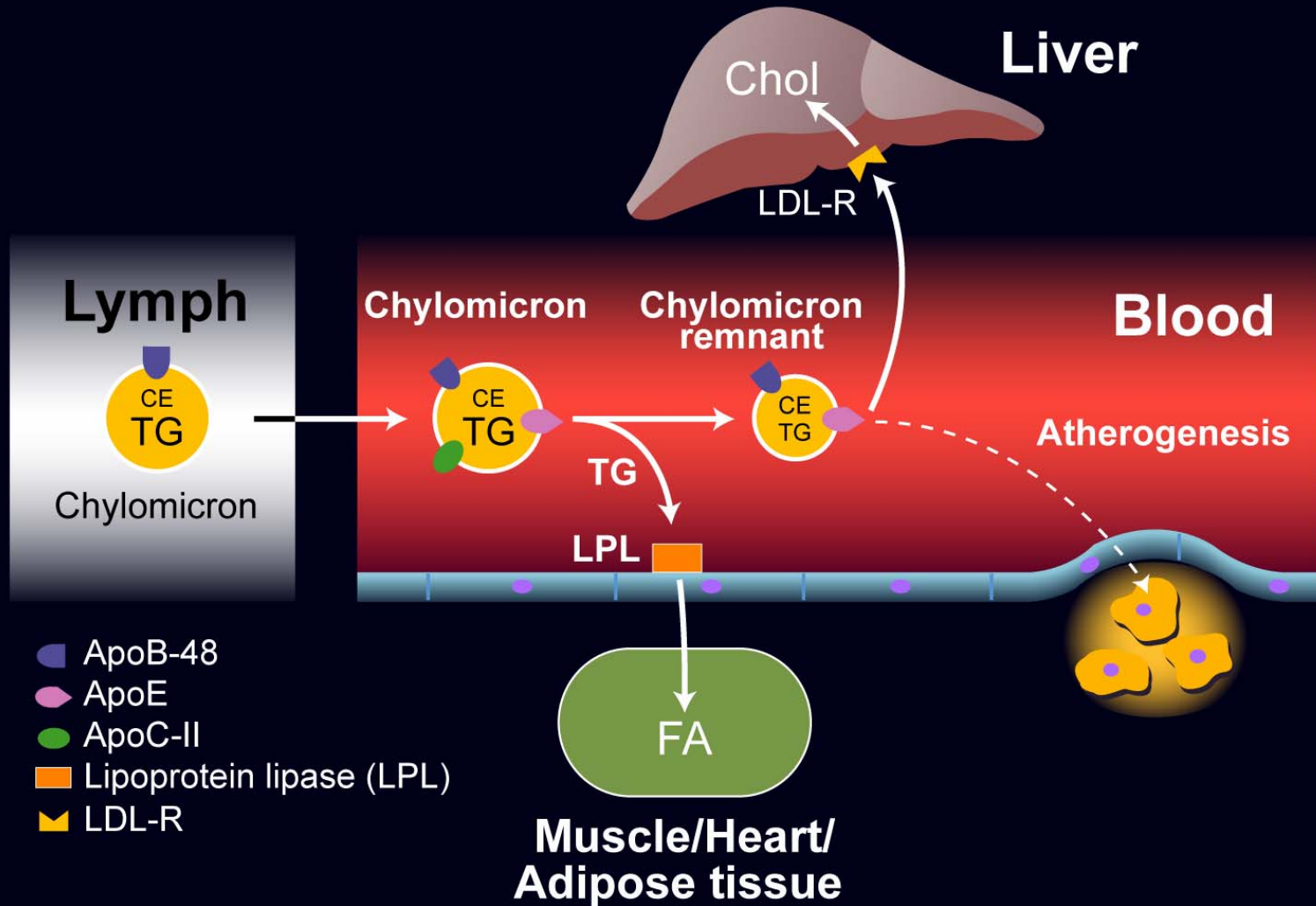
Enterohepatic Circulation of Bile Salts

Liver

Synthesis
0.4 g/d

Secretion
24 g/d

Biliary Transport and Storage

Duodenum

Jejunum

Ileum

Portal Venous Return (>95% of Biliary Secretion)

Colon

Fecal excretion (0.4 g/d)
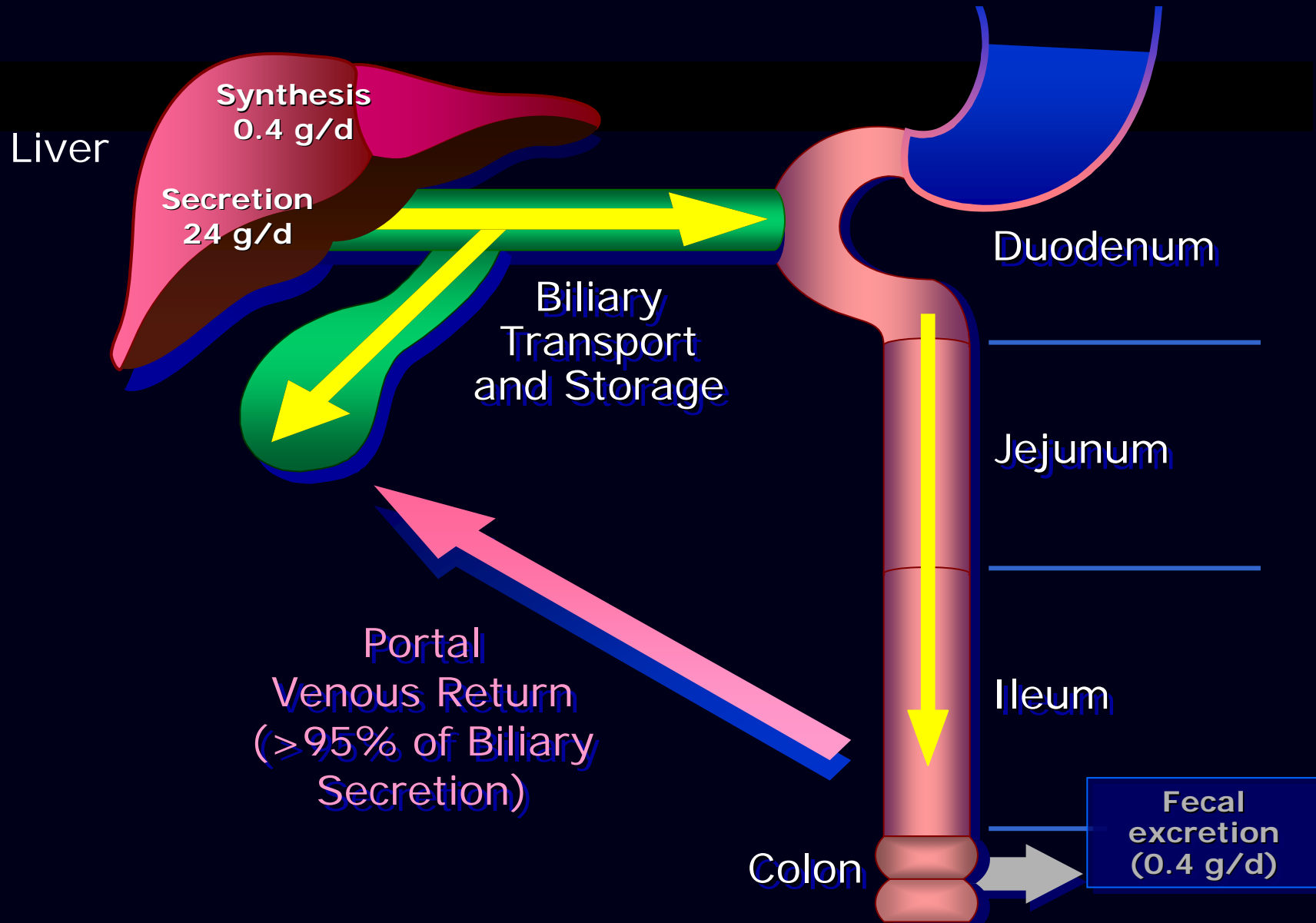
Biliary and Dietary Cholesterol

Liver

Biliary Cholesterol (2 g/d)

Dietary Cholesterol (0.4 g/d)

Biliary Transport and Storage

Duodenum

Jejunum

Ileum

CM apoB48

Absorption ~50%

Colon

Fecal excretion (1.2 g/d)

Cholesterol Balance

Liver

Synthesis (1.2 g/d)

Loss (1.6 g/d) — Dietary Cholesterol (0.4 g/d)

Cholesterol

Bile salts

Biliary Transport and Storage

Dietary Cholesterol (0.4 g/d)

Duodenum

Jejunum

Ileum

Loss (1.6 g/d)

Cholesterol (1.2 g/d) + Bile Salts (0.4 g/d)

Colon
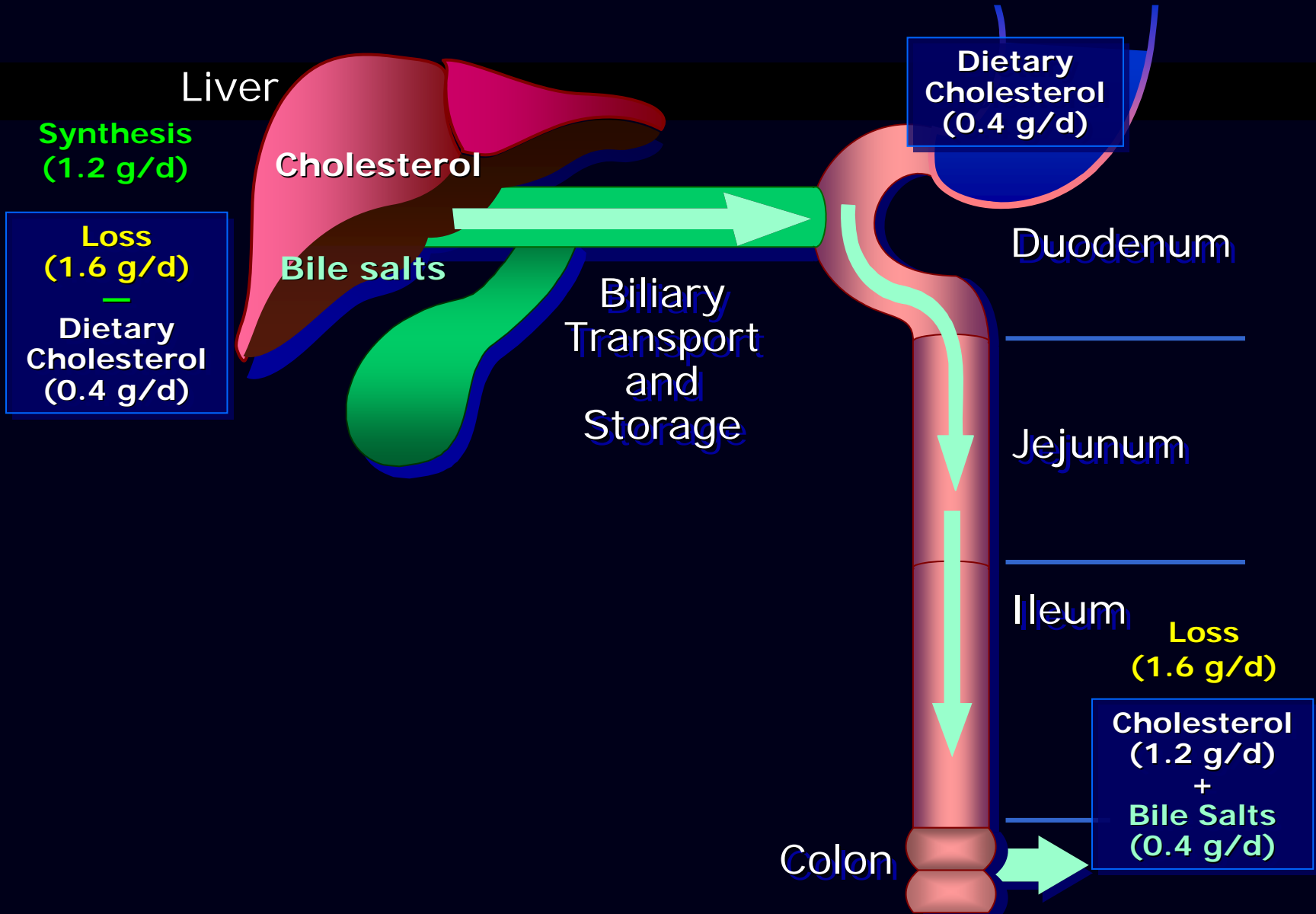
Transport of Intestinal Cholesterol

The Characteristics of Ezetimibe
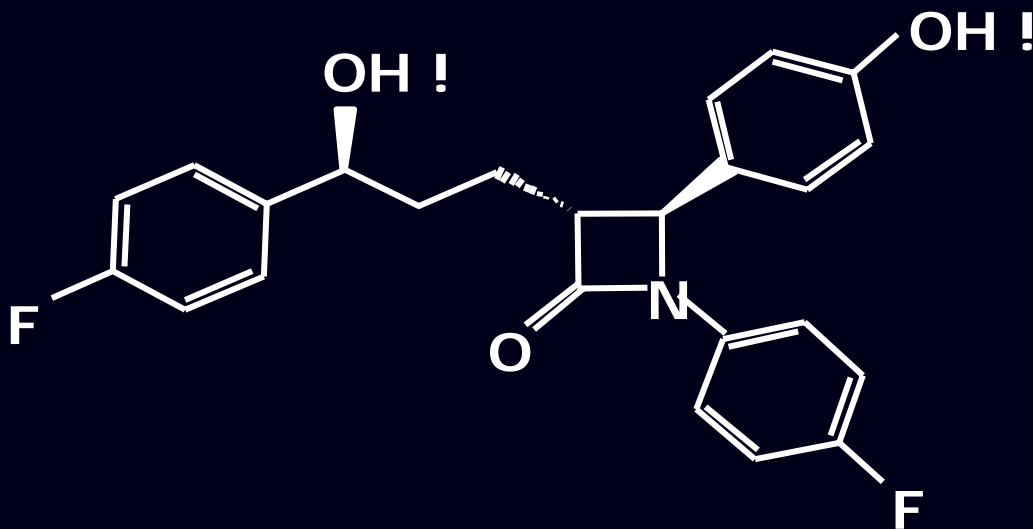
Intestinal Cholesterol Absorption
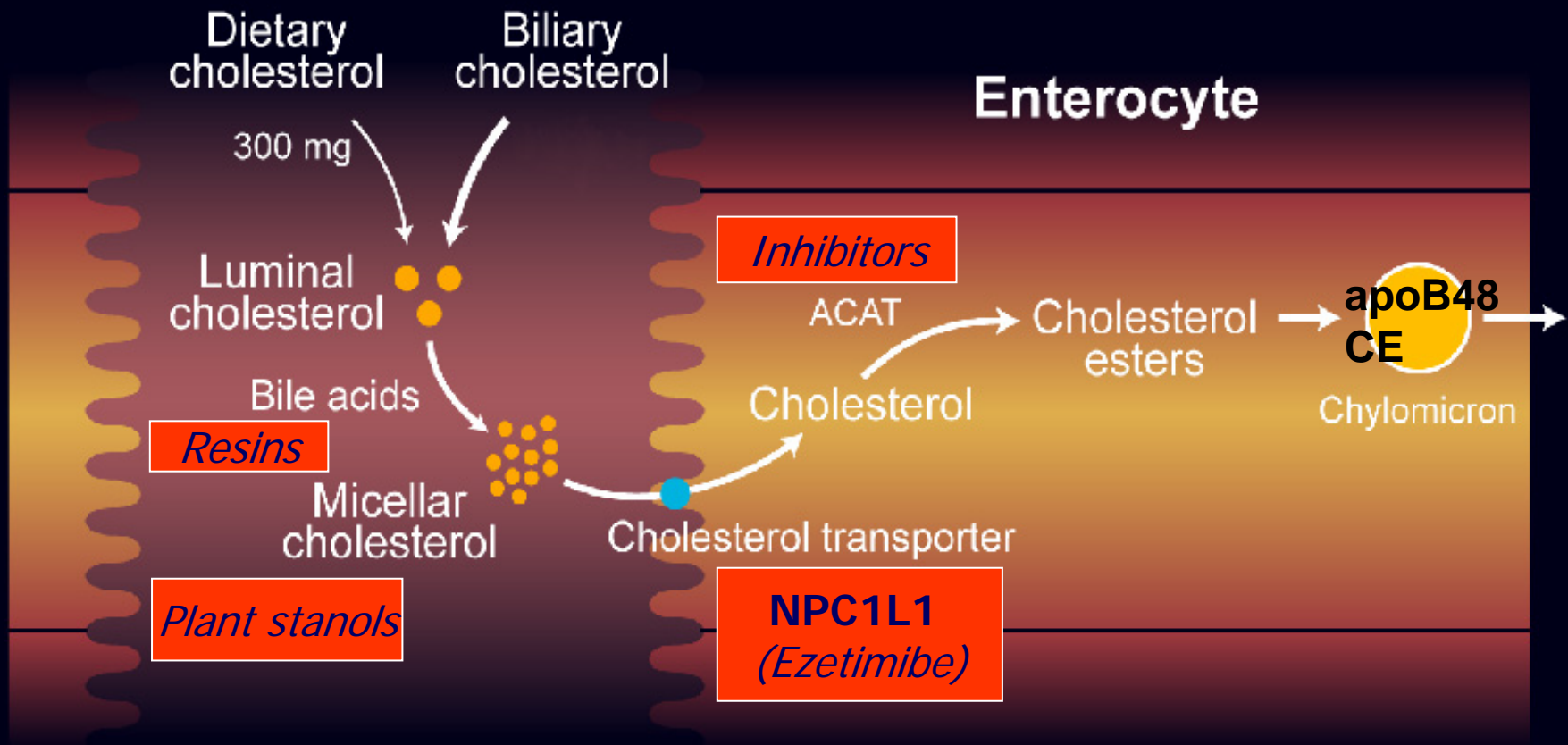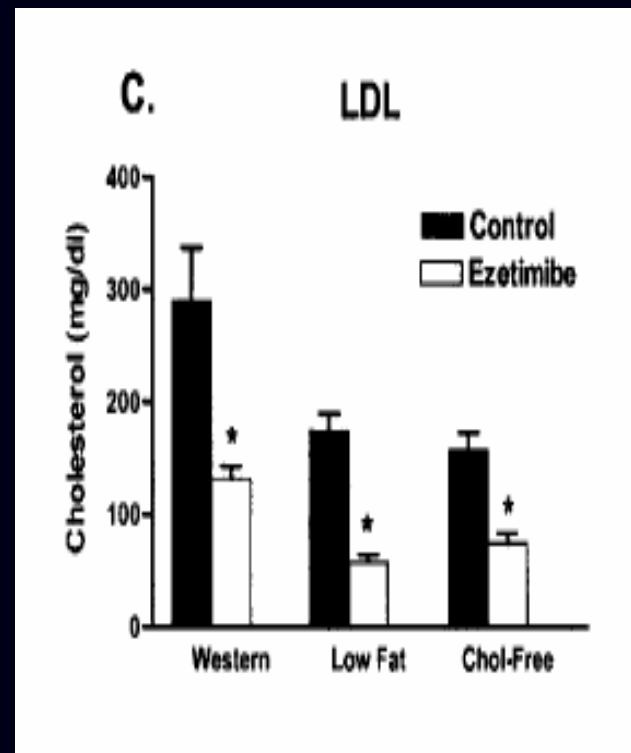

Altmann et al. *Science* 2004; 303: 1201-1204

Effect of Ezetimibe on Cholesterol Absorption in Humans

Mean = -54%
Range: 0 to -94%

Sudhop et al. *Circulation* 2002; 106;1943
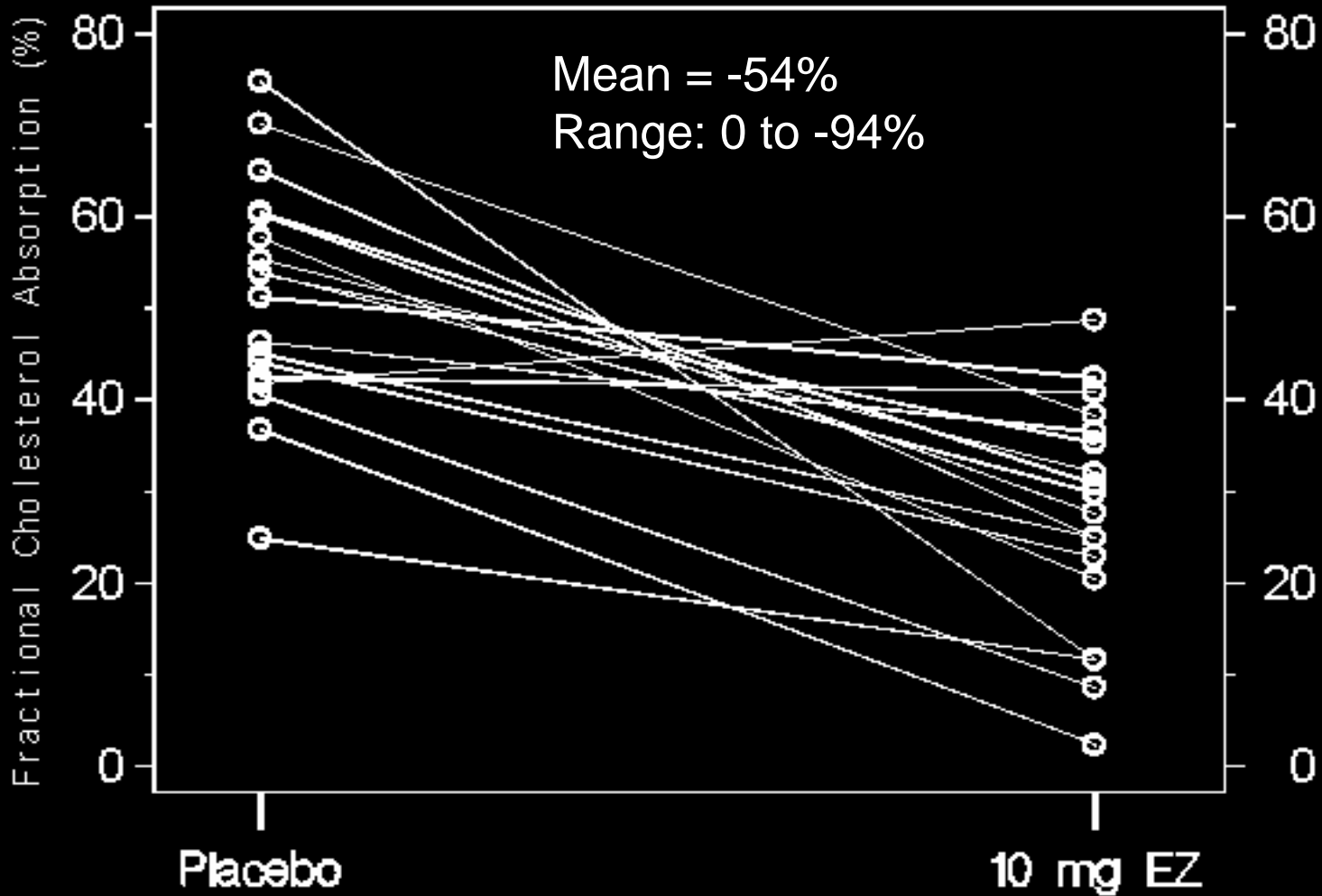
Effect of Ezetimibe in Apolipoprotein E Knockout Mice with Different Cholesterol Consumption
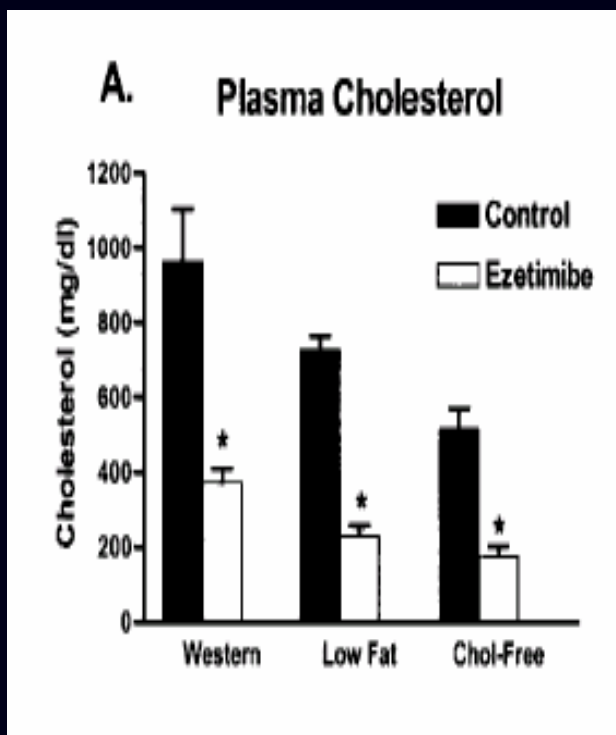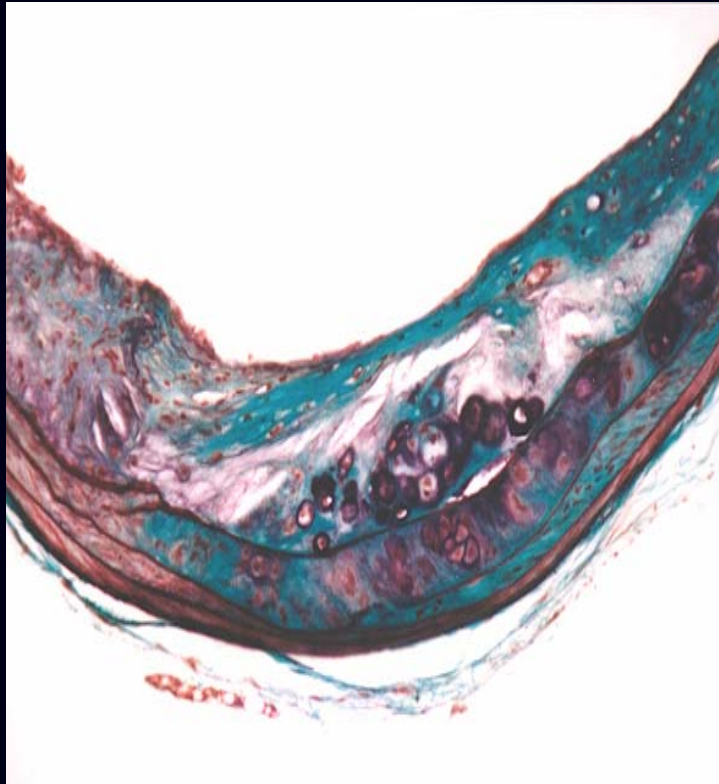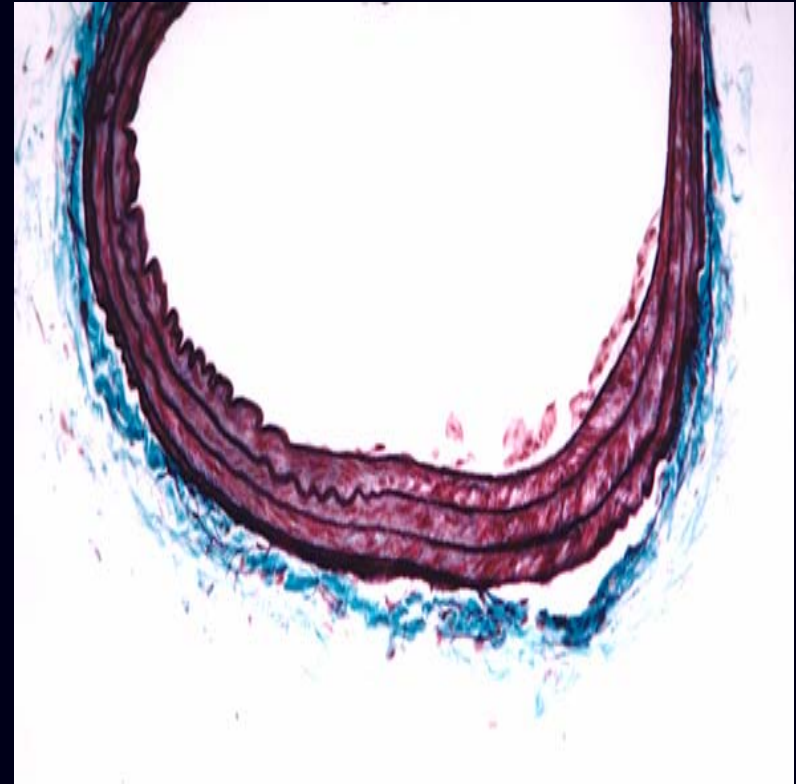

Plasma Cholesterol

LDL-C

*Mice fed 0.15% cholesterol diet for six months

Adapted from Davis HR Jr et al *Arterioscler Thromb Vasc Biol* 2001;21:2032–2038.

Ezetimibe Reduces Carotid Artery Atherosclerosis in ApoE Knockout Mice*

Control

Ezetimibe 5 mg/kg/d

* Mice fed 0.15% cholesterol diet for 6 months

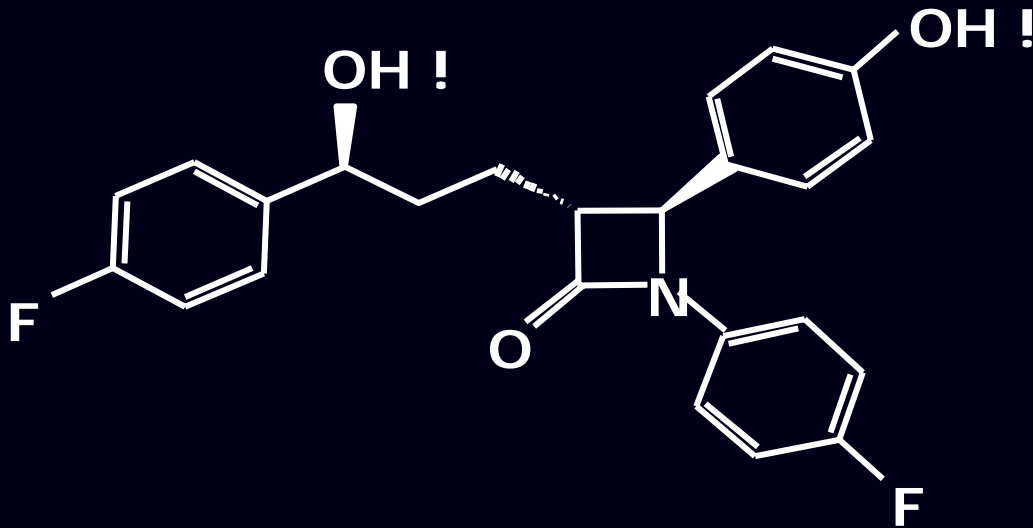Davis et al. *Atherosclerosis.* 2000; 151:133 (Abs).

Ezetimibe: PK -Absorption

- 투여 후 ezetimibe는 신속히 흡수되어 glucuronide conjugation(포합)을 통해 광범위하게 대사, active metabolite 인 ezetimibe-glucuronide를 형성

- 약물의 흡수는 음식물의 투여에 영향을 받지 않음

- T_{max}(혈중 최고 농도에 도달하는 시간)
  – ezetimibe-glucuronide: 1~2 hrs
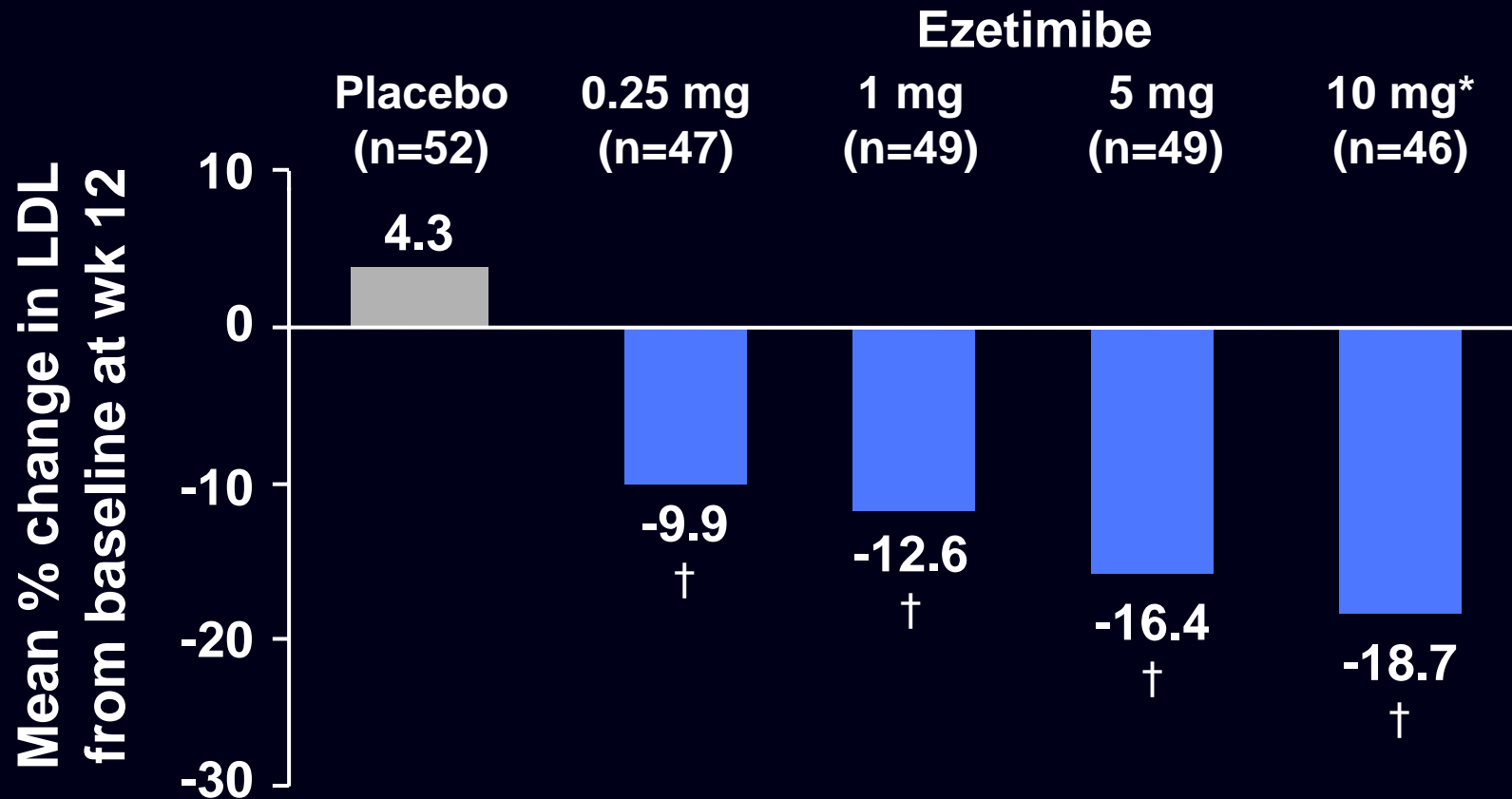 – ezetimibe: 4~12 hrs

VYTORIN WPC, USPC 참조

EZETIMIBE: PK –Elimination (배설)

- Primary elimination route – feces (after extensive enterohepatic recirculation)
- ^{14}C-ezetimibe (20 mg)를 투여한 임상 시험에서,
  - 혈장에서는 total radioactivity의 약 93%가 detect
  - 투여 48 후, 혈장 중 radioactivity 검출되지 않음
  - 10일간의 collection 결과, feces에서 약 78%, urine에서 약 11% 검출됨
- Half-life(반감기): 약 22 hrs

Why Ezetimibe and Statins ?

Ezetimibe Phase IIb Dose-Response Study

Ezetimibe

Placebo (n=52)	0.25 mg (n=47)	1 mg (n=49)	5 mg (n=49)	10 mg* (n=46)
4.3	-9.9 †	-12.6 †	-16.4 †	-18.7 †

Mean % change in LDL from baseline at wk 12
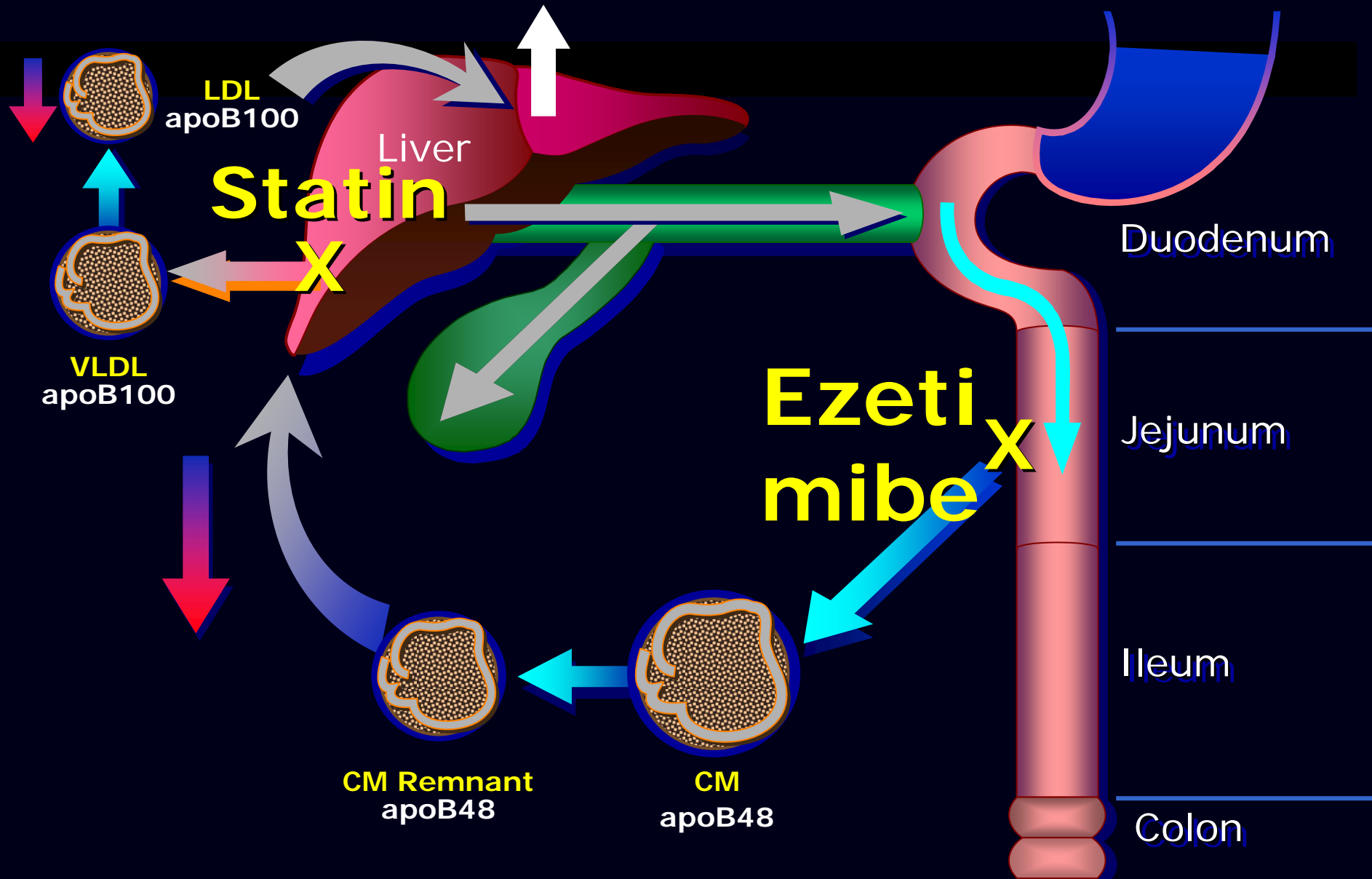
†*P*<0.05 vs placebo.

Bays et al. *Clin Ther*. 2001;23:1209.

Cholesterol Absorption Study

Indices of Cholesterol Synthesis After 2 Weeks of Treatment (geometric mean values)

Cholesterol Synthesis Rates (mg/day) — PBO and EZE bar chart

Plasma Lathosterol/Cholesterol Ratio — PBO and EZE bar chart

Sudhop et al. *Circulation* 2002; 106;1943

**Between treatment *P* value <0.001.
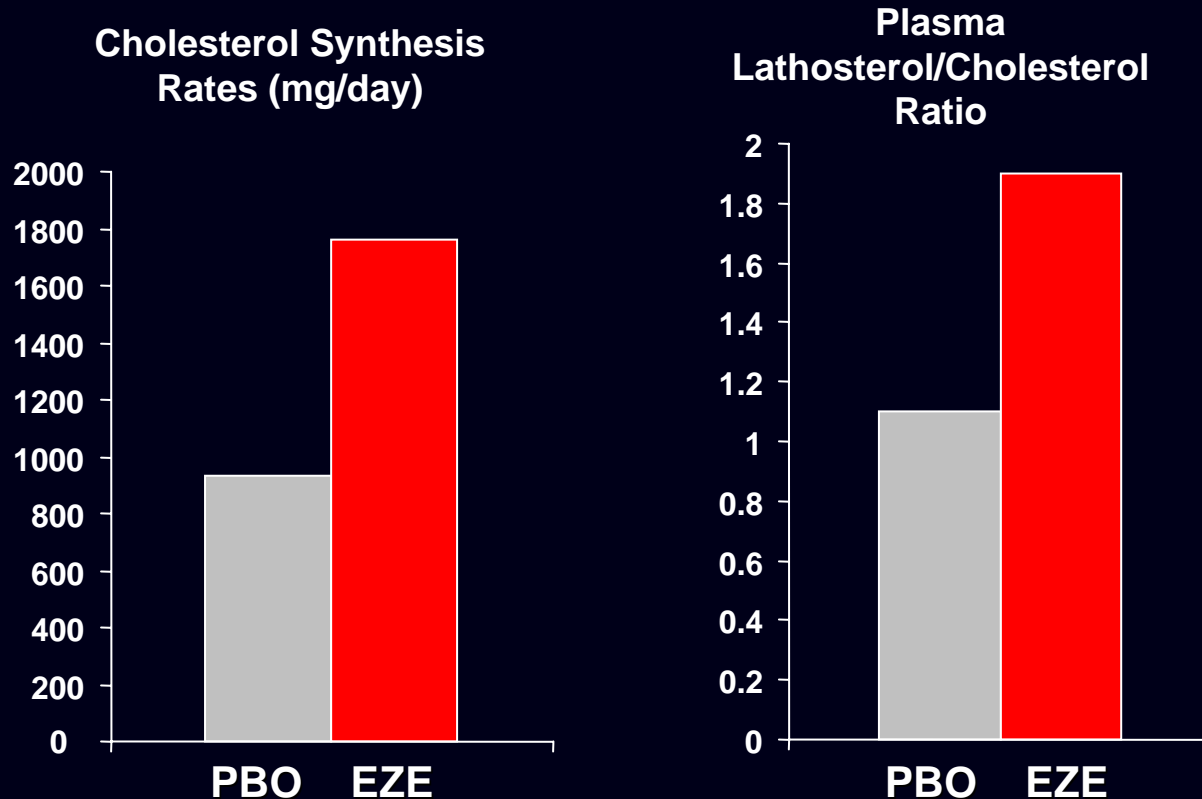
Dual Inhibition of cholesterol metabolism

LDL
apoB100

Liver

Statin
X

VLDL
apoB100

Duodenum

Jejunum

Ezeti
mibe **X**

Ileum

CM Remnant
apoB48

CM
apoB48
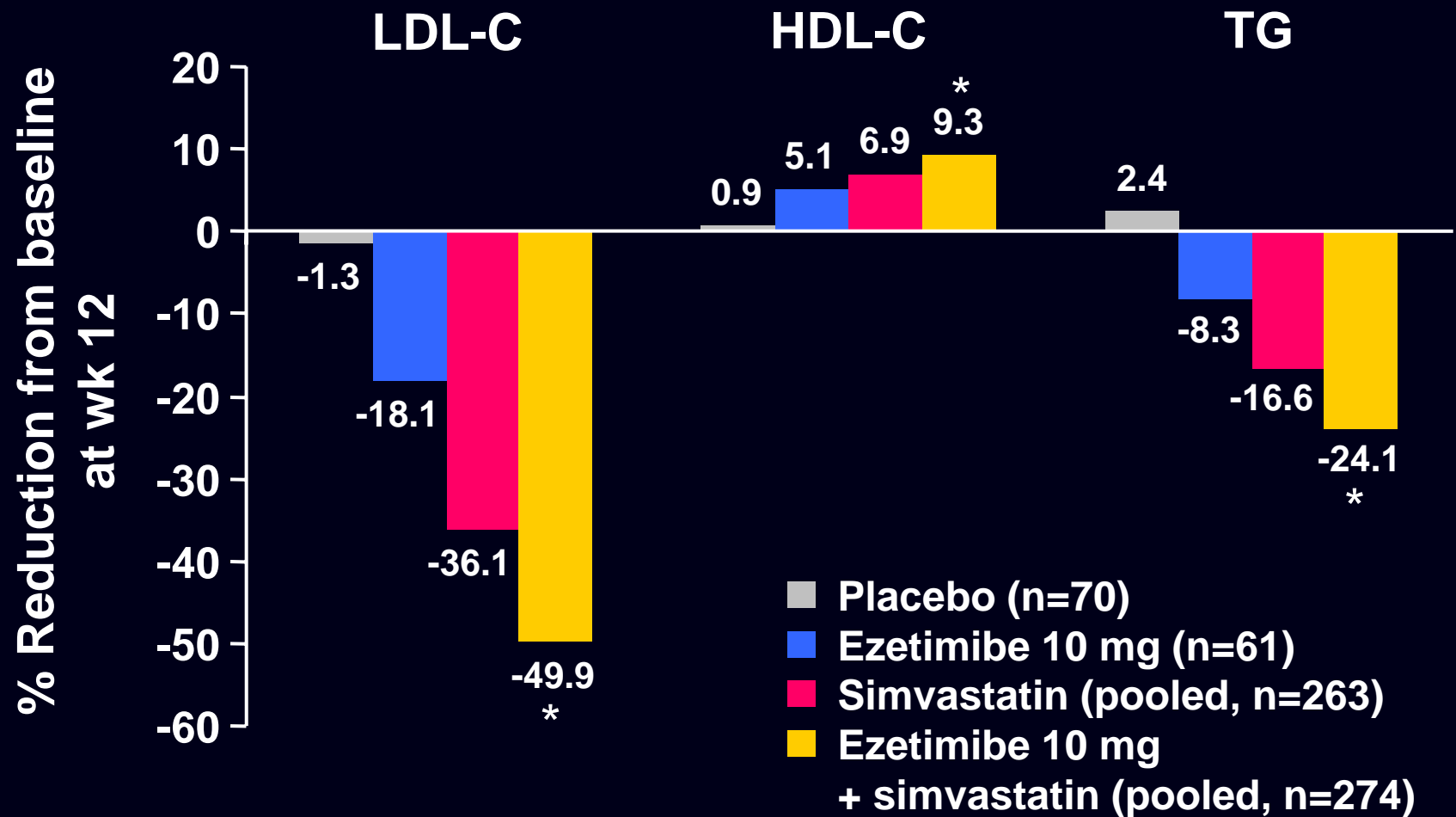
Colon

Theoretical Basis for Combination Therapy
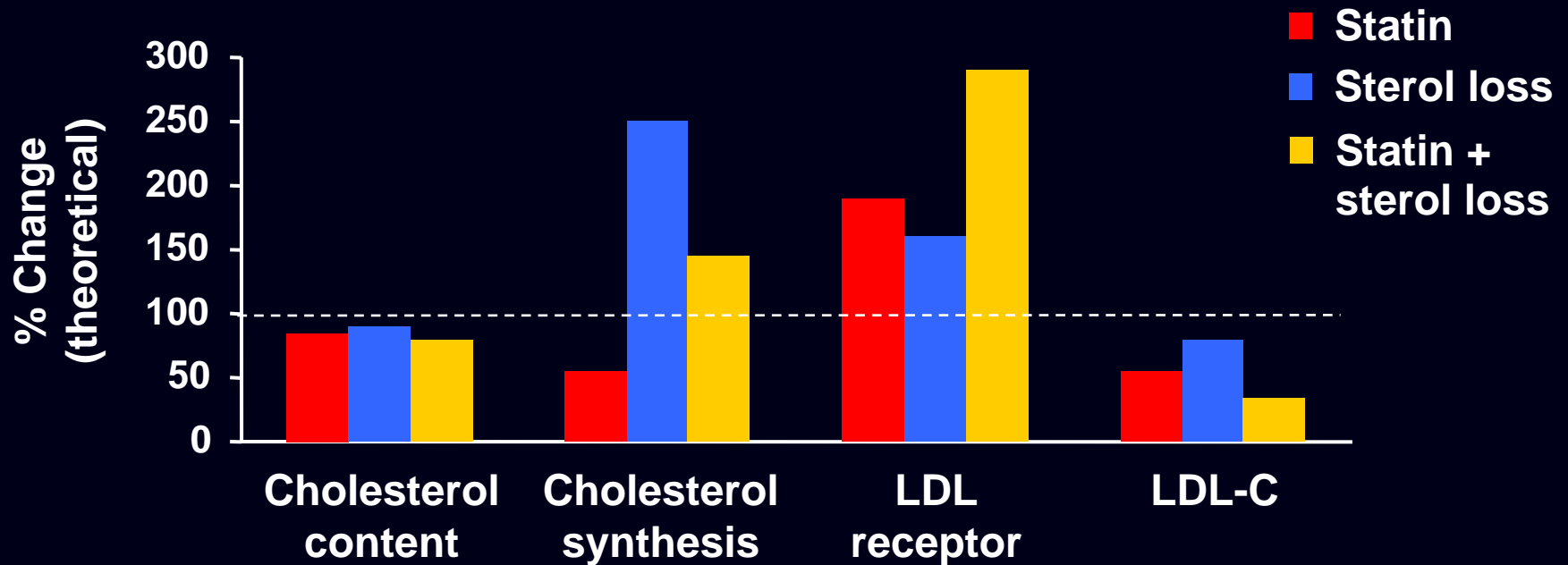
Phase III Combination Therapy: Ezetimibe Plus Simvastatin—Efficacy

% Reduction from baseline at wk 12

LDL-C
- -1.3
- -18.1
- -36.1
- -49.9 *

HDL-C
- 0.9
- 5.1
- 6.9
- 9.3 *

TG
- 2.4
- -8.3
- -16.6
- -24.1 *

Legend:
- ■ Placebo (n=70)
- ■ Ezetimibe 10 mg (n=61)
- ■ Simvastatin (pooled, n=263)
- ■ Ezetimibe 10 mg + simvastatin (pooled, n=274)

*$P<0.03$ vs simvastatin.

Davidson et al. *J Am Coll Cardiol*. 2002;39(suppl A):Abstract 1084-90.

Comparison to Atorvastatin

Comparison to Rosuvastatin

VYtorin (Eze/Simva) Vs. Atorvastatin (VYVA)
- Study Design -

Patients with an LDL-C level at or above drug treatment thresholds established by NCEP ATP III

N = 1,902

(at 216 study sites)

EZE/Simva 10/10	**n = 238**
EZE/Simva 10/20	**n = 238**
EZE/Simva 10/40	**n = 238**
EZE/Simva 10/80	**n = 237**
Atorva 10 mg	**n = 238**
Atorva 20 mg	**n = 237**
Atorva 40 mg	**n = 237**
Atorva 80 mg	**n = 239**

Week -9/-7	Week -4	Week -1	Week 0 R		Week 6

← Washout → ← Active Treatment →

V1   V2   V3   V4

← PBO lead in →

Ballantyne CM et al. *Am Heart J* 2005;149:464–473.

LDL-C Efficacy
VYTORIN vs. atorvastatin

% Change (±SE) from baseline LDL-Cholesterol

| | 10/10 mg | 10 mg | 10/20 mg | 20 mg | 10/40 mg | 40 mg | 10/80 mg | 80 mg | Averaged Across Doses |

- -47* (Eze/Simva, 10/10 mg)
- -36 (Atorvastatin, 10 mg)
- -51* (Eze/Simva, 10/20 mg)
- -44 (Atorvastatin, 20 mg)
- -57* (Eze/Simva, 10/40 mg)
- -48 (Atorvastatin, 40 mg)
- -59* (Eze/Simva, 10/80 mg)
- -53 (Atorvastatin, 80 mg)
- -53* (Eze/Simva, Averaged Across Doses)
- -45 (Atorvastatin, Averaged Across Doses)

■ Eze/Simva ■ Atorvastatin

*p < 0.001 for all pairwise comparisons

Treatment comparison at each dose and averaged across doses

Ballantyne CM et al. *Am Heart J* 2005;149:464–473

HDL-C Efficacy
VYTORIN vs. atorvastatin

Ballantyne CM et al. *Am Heart J* 2005;149:464–473

Vytorin
Safety & Tolerability Profile

Predefined Limits of Change	All Atorva n (%)	All Vytorin™ n (%)	P value
ALT $\geq$ 3 x ULN, consecutive	10/939 (1.1)	0/933 (0.0)	0.002
AST $\geq$ 3 x ULN, consecutive	7/939 (0.7)	1/933 (0.1)	0.070
ALT and/or AST* $\geq$ 3 x ULN, consecutive	11/939 (1.2)	1/933 (0.1)	0.006
CPK $\geq$ 10 x ULN CPK $\geq$ 10 x ULN with muscle symptoms	1/939 (0.1) 0/939 (0.0)	0/933 (0.0) 0/933 (0.0)	1.000 -

One patient randomized to 80 mg had ALT and AST elevations $\geq$ 3 X ULN at baseline. Sensitivity analysis minus this patient confirmatory of the statistically significant difference.
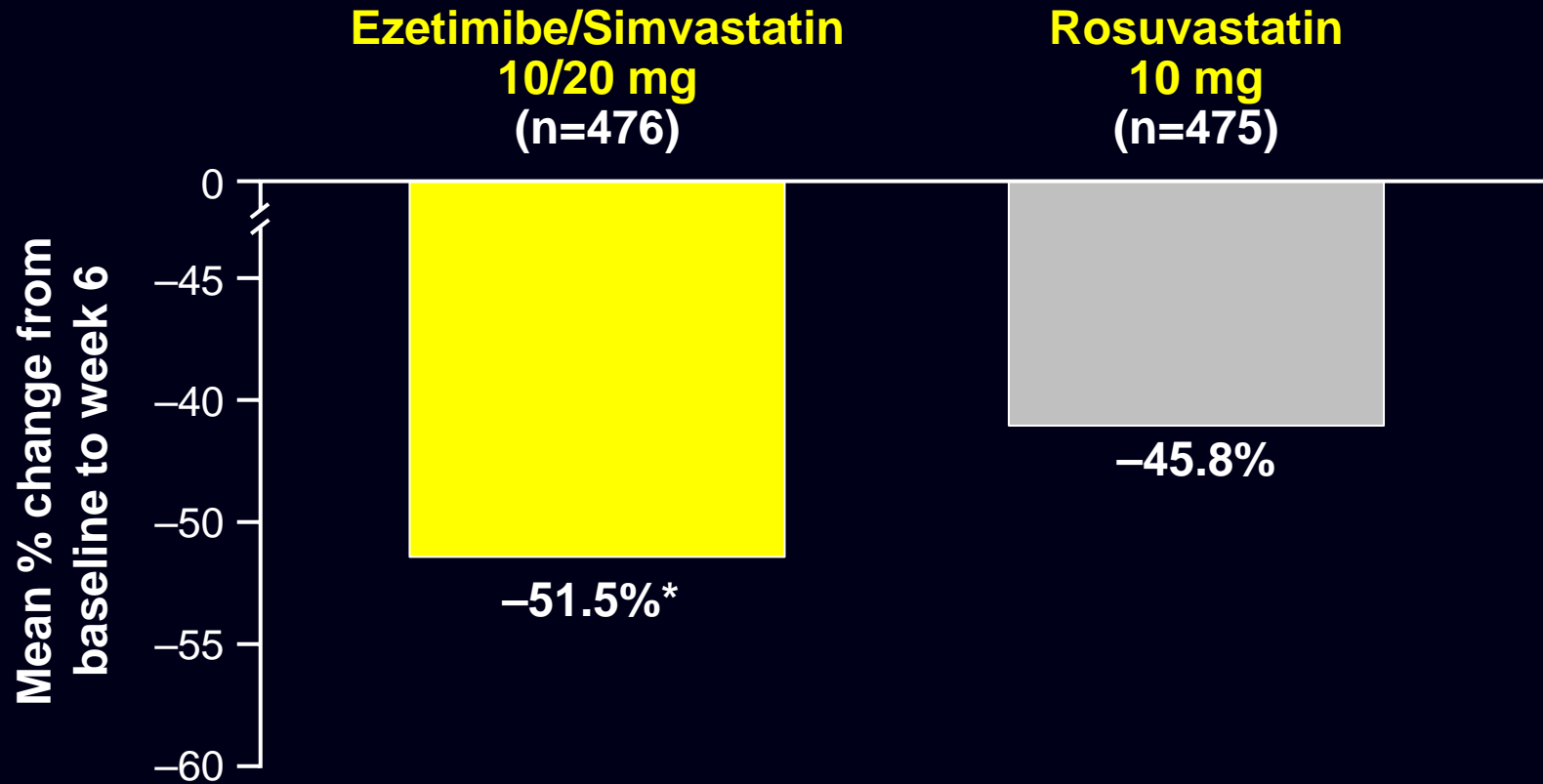
Ballantyne CM et al. *Am Heart J* 2005;149:464–473

Comparison to Atorvastatin

Comparison to Rosuvastatin

Study Design

- Design
  - Multicenter, double-blind, randomized, parallel-group, 10-week study (four-week placebo run-in followed by six-week double-blind period)

- Selected entry criteria
  - LDL-C 3.7–6.5 mmol/L (145 – 250 mg/dL)
  - TG $\leqslant$ 4.0 mmol/L (350 mg/dL)

- Treatment groups
  - Ezetimibe/simvastatin 10/20 mg, 10/40 mg, or 10/80 mg
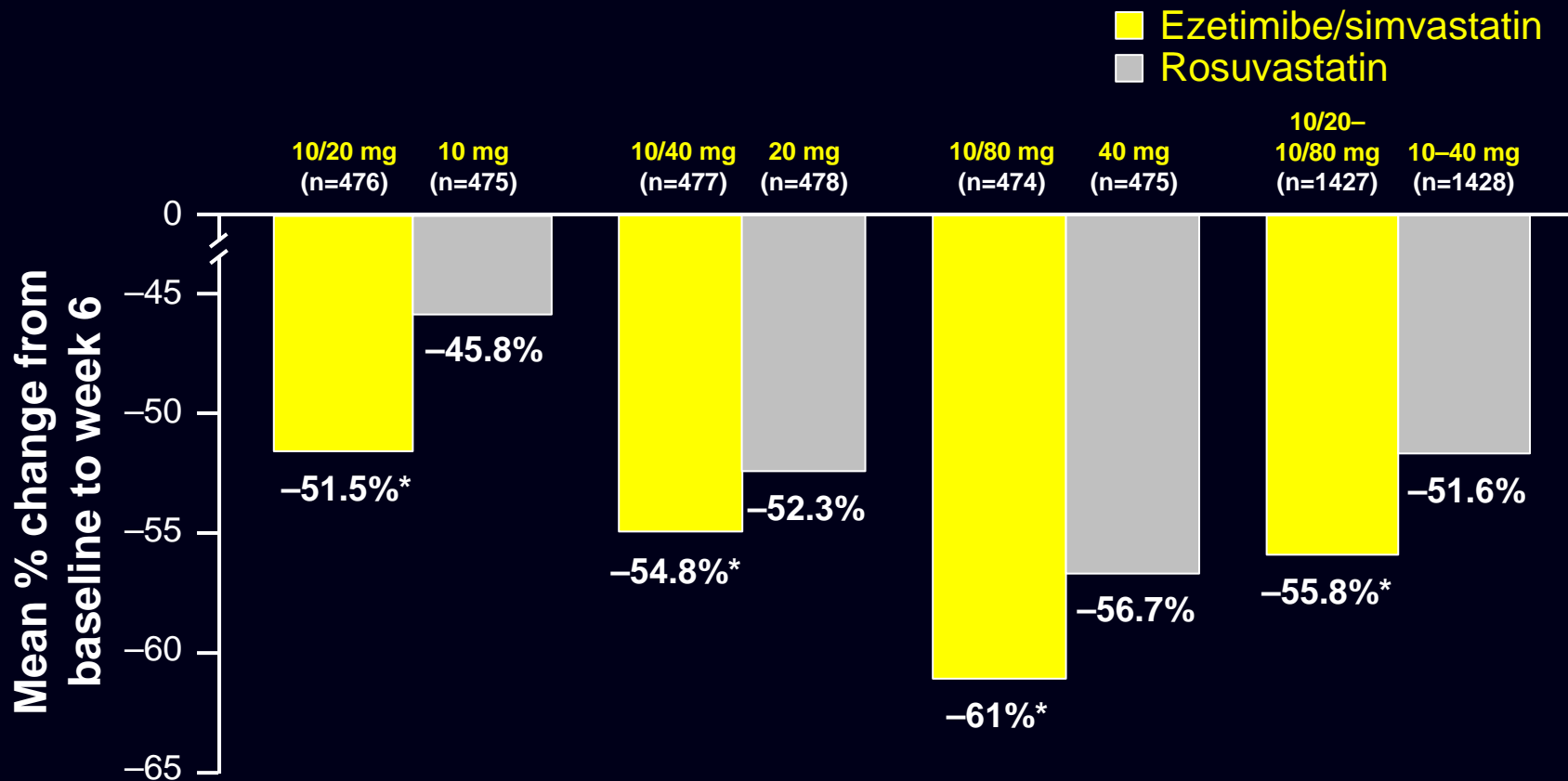 - Rosuvastatin 10 mg, 20 mg, or 40 mg

Ezetimibe/Simvastatin Significantly Reduced LDL-C at Starting Doses

Ezetimibe/Simvastatin 10/20 mg (n=476)

Rosuvastatin 10 mg (n=475)

Mean % change from baseline to week 6

0
−45
−40
−50
−55
−60

−51.5%*

−45.8%

Ezetimibe/Simvastatin Significantly Reduced LDL-C Across The Dose Range

■ Ezetimibe/simvastatin
■ Rosuvastatin

Mean % change from baseline to week 6

| | | | | |
| 10/20 mg (n=476) | 10 mg (n=475) | 10/40 mg (n=477) | 20 mg (n=478) | 10/80 mg (n=474) | 40 mg (n=475) | 10/20–10/80 mg (n=1427) | 10–40 mg (n=1428) |

−51.5%* −45.8% −54.8%* −52.3% −61%* −56.7% −55.8%* −51.6%

*p≤0.001

Adapted from M.H. Davidson et al. Poster presented at ISA 2006 & *Current Medical Opinion and Research* (in press)

Ezetimibe/Simvastatin Provided Superior Goal Attainment in High-Risk Patients (< 100mg/dl)
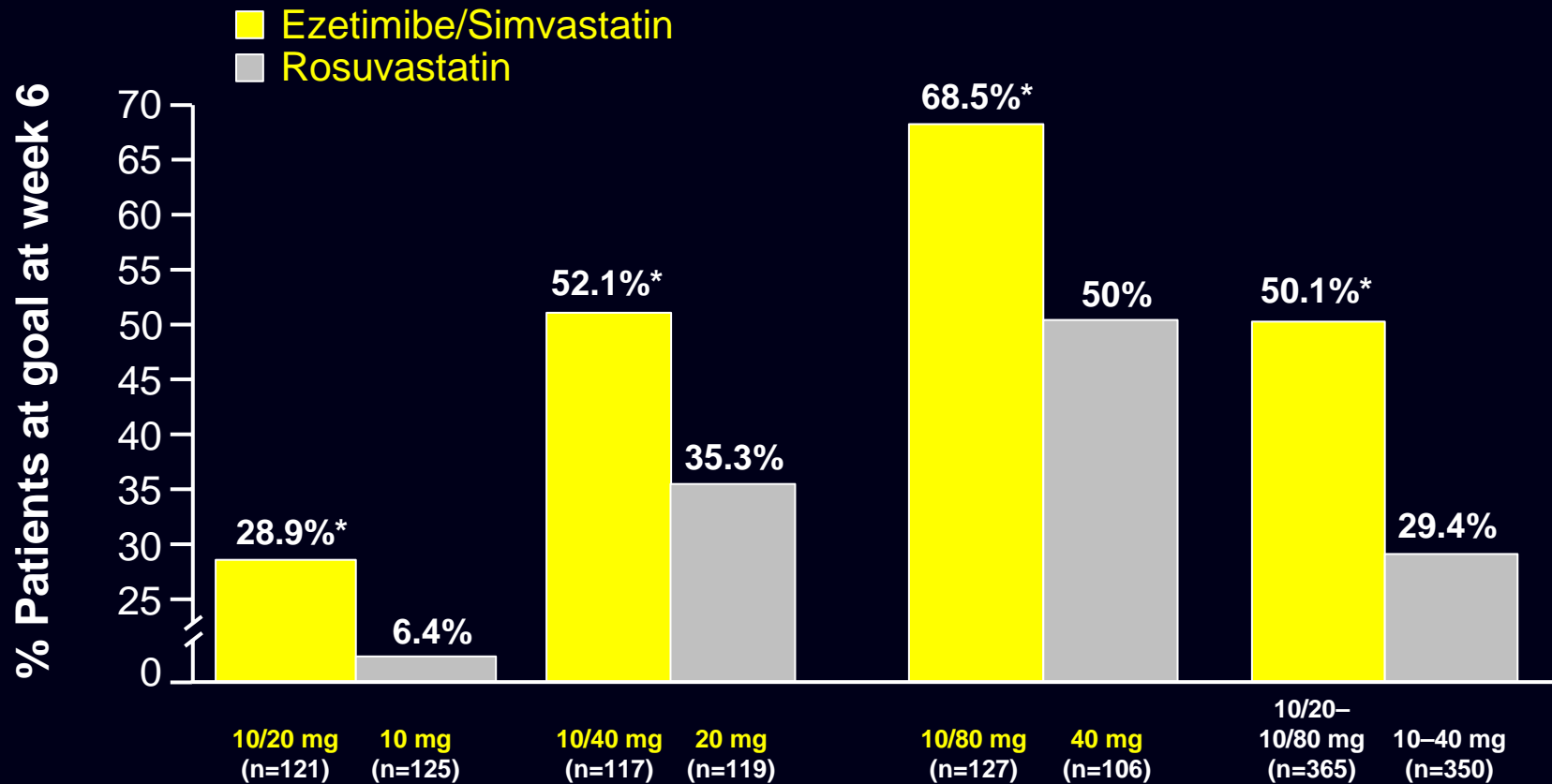

Legend: ■ Ezetimibe/Simvastatin ■ Rosuvastatin

Y-axis: % Patients at goal at week 6 (0, 70, 75, 80, 85, 90, 95, 100)

Bar values:
- 10/20 mg (n=121): 83.5%
- 10 mg (n=125): 72.8%
- 10/40 mg (n=117): 91.5%
- 20 mg (n=119): 84.0%
- 10/80 mg (n=127): 95.3%
- 40 mg (n=106): 90.6%
- 10/20–10/80 mg (n=365): 90.1%*
- 10–40 mg (n=350): 82%
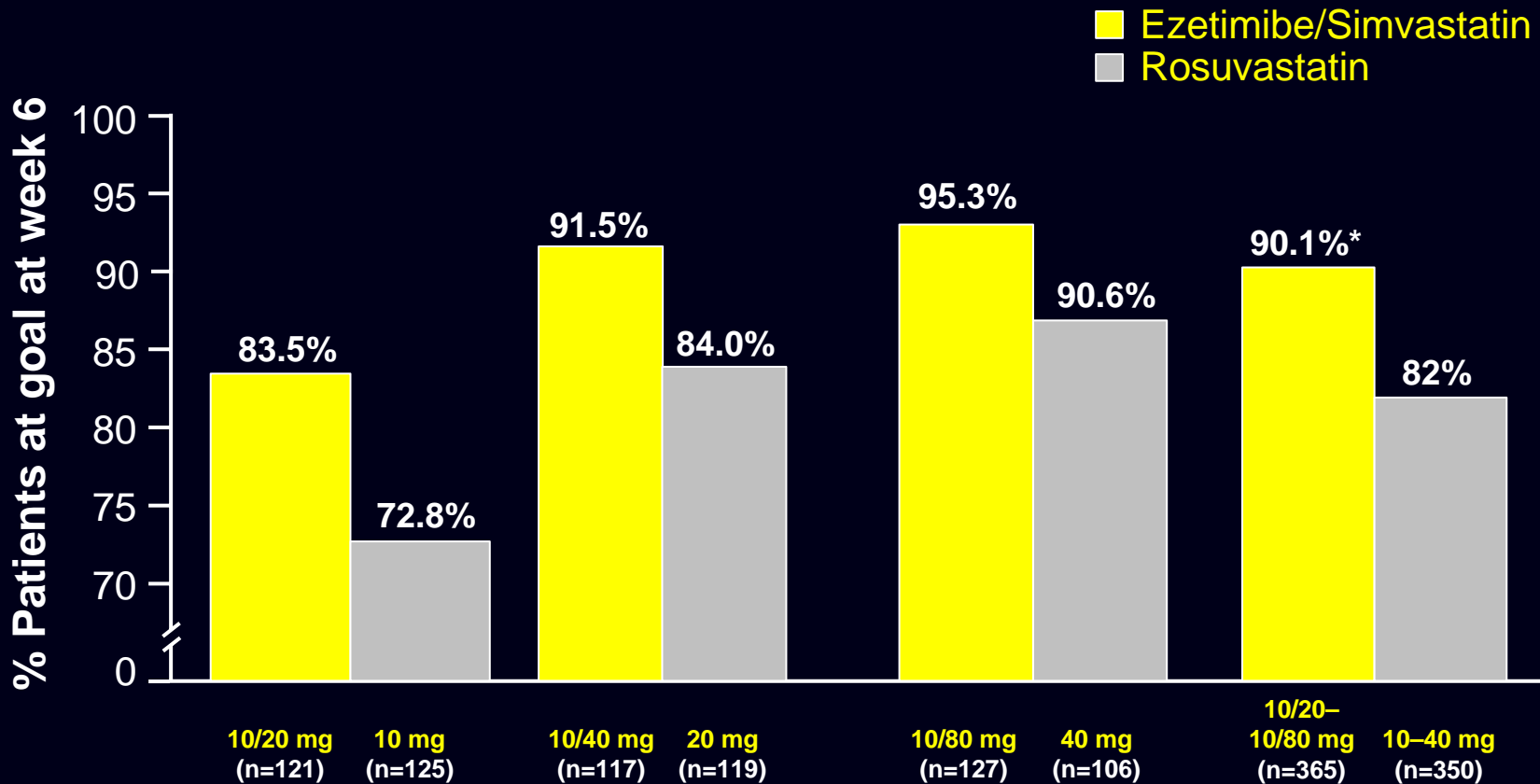
Target LDL-C (<100mg/dL)

*p<0.05 vs.. rosuvastatin 10–40 mg

Adapted from M.H. Davidson et al. Poster presented at ISA 2006 & *Current Medical Opinion and Research* (in press)

Ezetimibe/Simvastatin Provided Superior Goal Attainment in High-Risk Patients (< 70mg/dl)

■ Ezetimibe/Simvastatin
■ Rosuvastatin

% Patients at goal at week 6

Dose	Value
10/20 mg (n=121)	28.9%*
10 mg (n=125)	6.4%
10/40 mg (n=117)	52.1%*
20 mg (n=119)	35.3%
10/80 mg (n=127)	68.5%*
40 mg (n=106)	50%
10/20–10/80 mg (n=365)	50.1%*
10–40 mg (n=350)	29.4%

*p<0.05 vs.. rosuvastatin

Adapted from M.H. Davidson et al. Poster presented at ISA 2006 & *Current Medical Opinion and Research* (in press)

Ezetimibe/Simvastatin Provided Improvements in Other Lipid Parameters
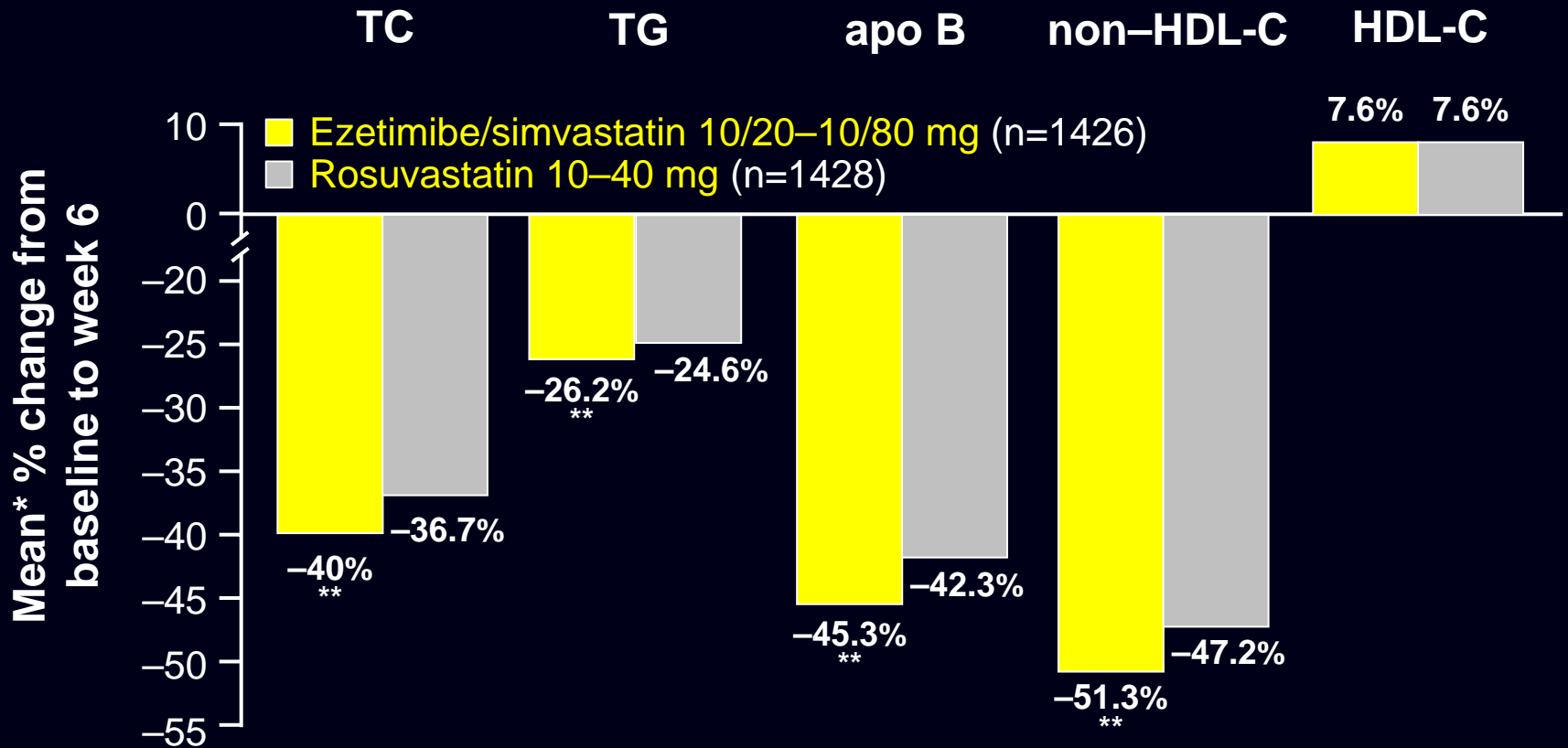
*Except for TG, for which median percent changes are shown; **p<0.05 vs. rosuvastatin

Adapted from M.H. Davidson et al. Poster presented at ISA 2006 & *Current Medical Opinion and Research* (in press)

VYTORIN provides superior LDL-C lowering efficacy vs. all major statins
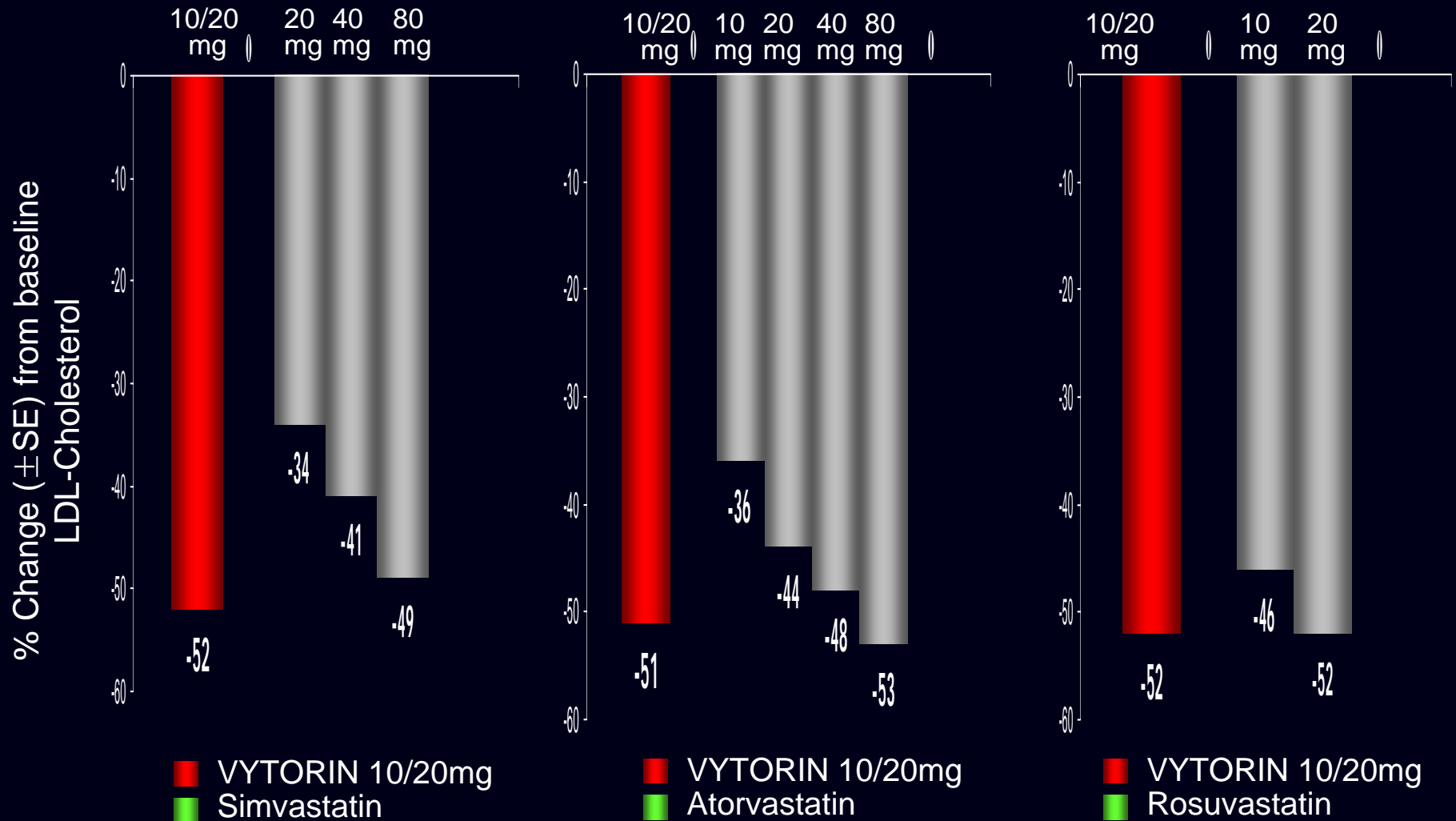
Bays H et al. *Clin Ther.* 2004;26:1758-1773
Ballantyne CM et al. Am Heart J. 2005;149:464-473
Adapted from M.H. Davidson et al. Poster presented at ISA 2006

Minimum Drug Dose to Achieve ≥50% LDL-C Reduction

Drug	Dose mg/d	LDL-C reduction%
Atorvastatin	80	51–54
Ezetimibe/Simvastatin	10/20	50–51
Rosuvastatin	20	52

Jones PH et al. *Am J Cardiol* 1998;81:582–587

Jones PH et al. *Am J Cardiol* 2003;92:152–160

Ballantyne CM et al. Am J Cardiol 2004;93:1487–1494

Ballantyne CM et al. *Am Heart J* 2005;149:464–473
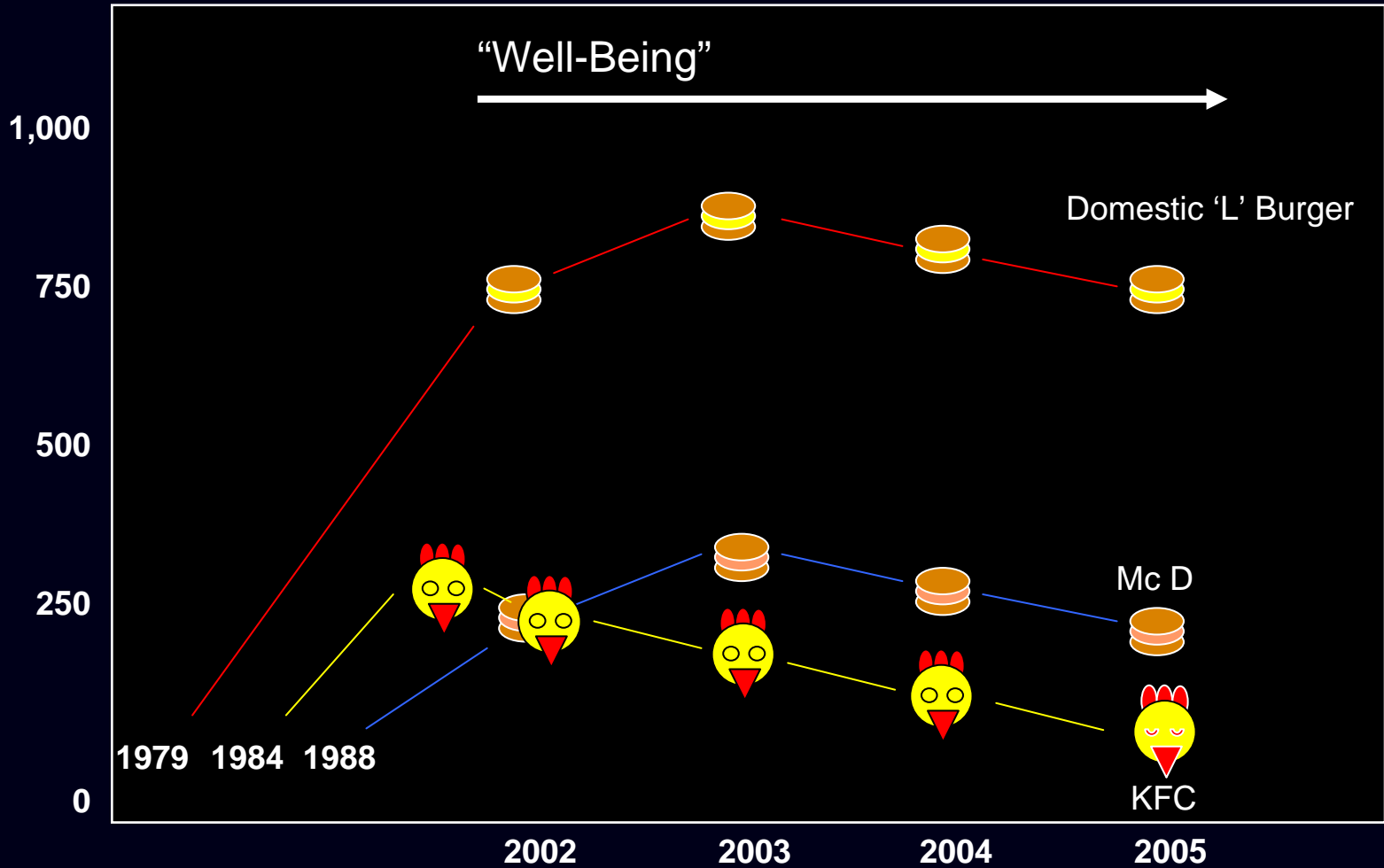
VYTORIN
Ongoing Clinical Outcome Programs

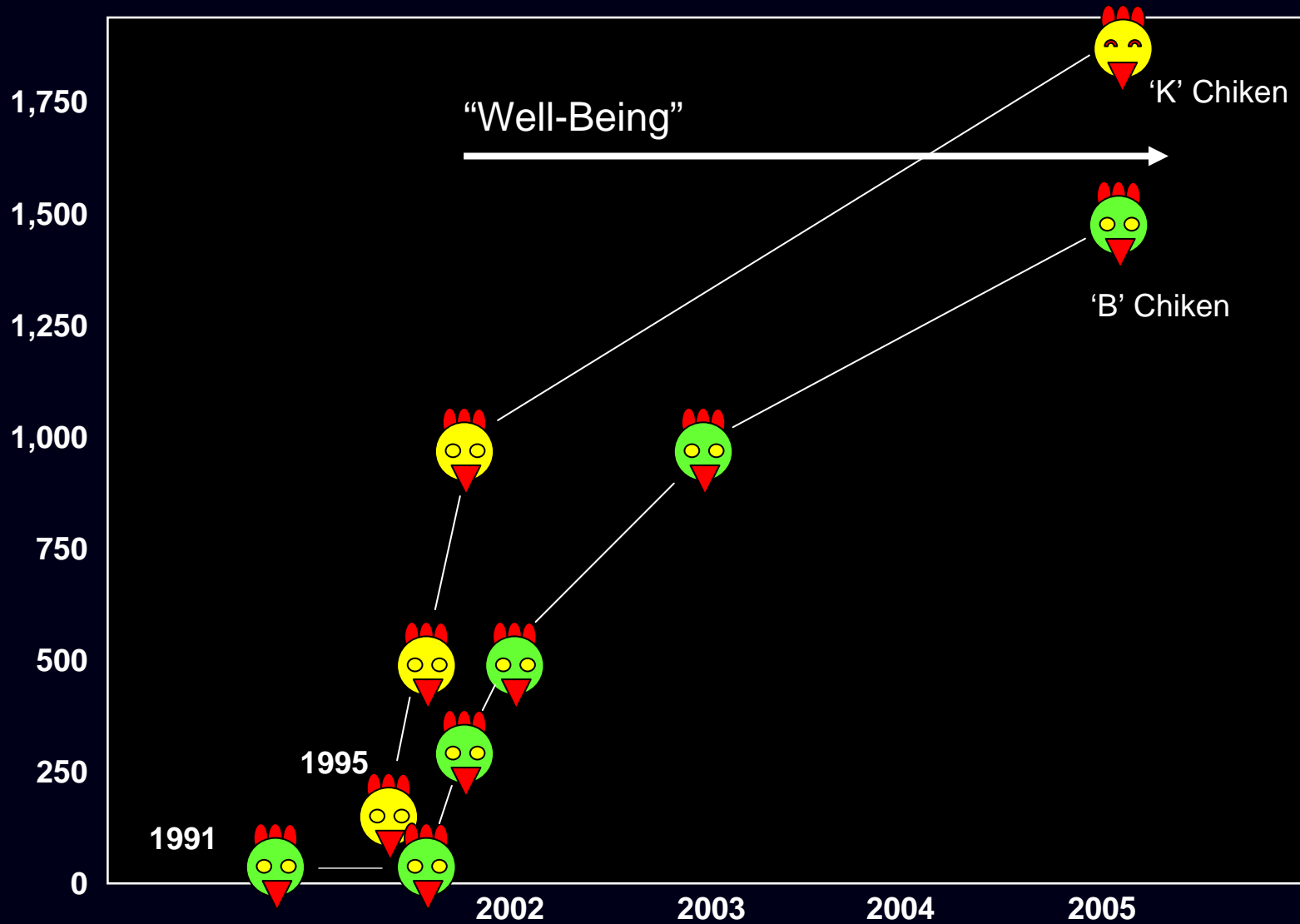| Trial	Population	Endpoint	Treatment
ENHANCE	HeFH (n = 720)	Carotid IMT	Vytorin 10/80 vs.. Simva 80
SEAS	Aortic Stenosis (n = 1800)	MACE	Vytorin 10/40 vs.. PBO
SHARP	Chronic Kidney Disease (n = 9000)	MACE	Vytorin 10/20 vs.. PBO vs. Simva 20
IMPROVE-IT	ACS (n = 10,000)	MACE	Vytorin 10/40 vs.. Simva 40
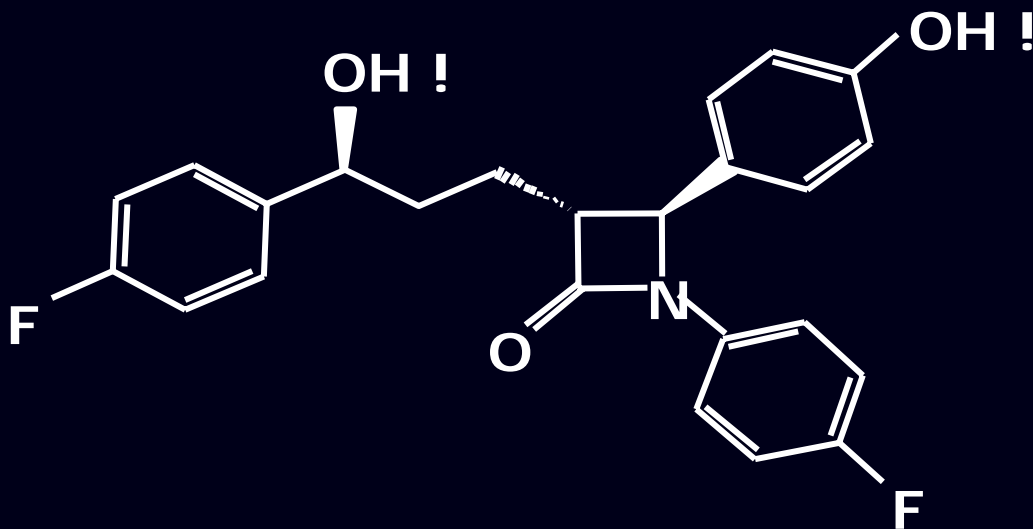
The Trend is Not Really Toward "Well-Being"

- Number of Stores Selling Fried Chicken with Korean Paste -
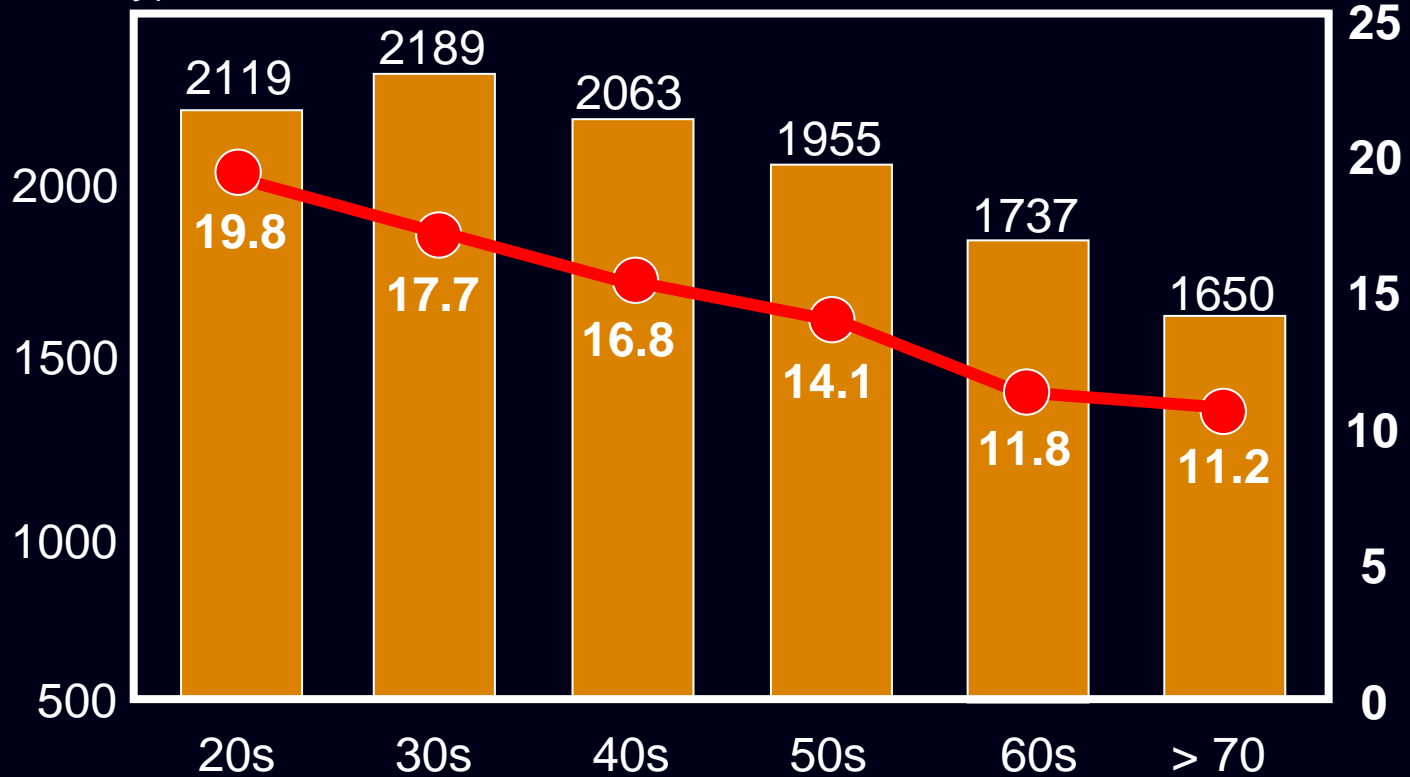
Korean Ezetimibe Trial

The first stage	The second stage
placebo + diet therapy	Randomization and life style modification

Visit	S	1	2	3	4	5	6
Week	≤-4	-4	0	4	8	12	Post visit

Simvastatin 10mg + Ezetimibe 10mg

Simvastatin 10mg + Placebo 10mg
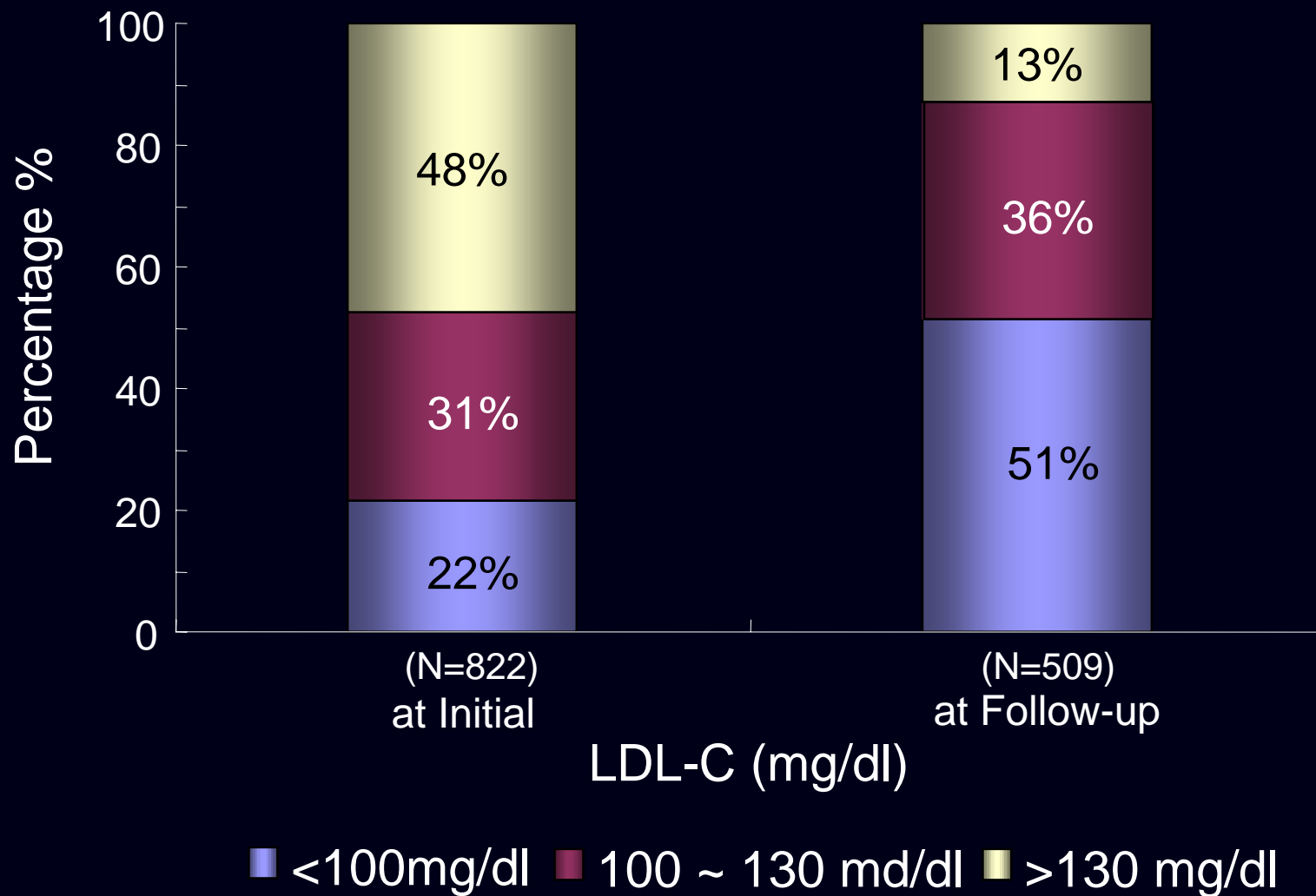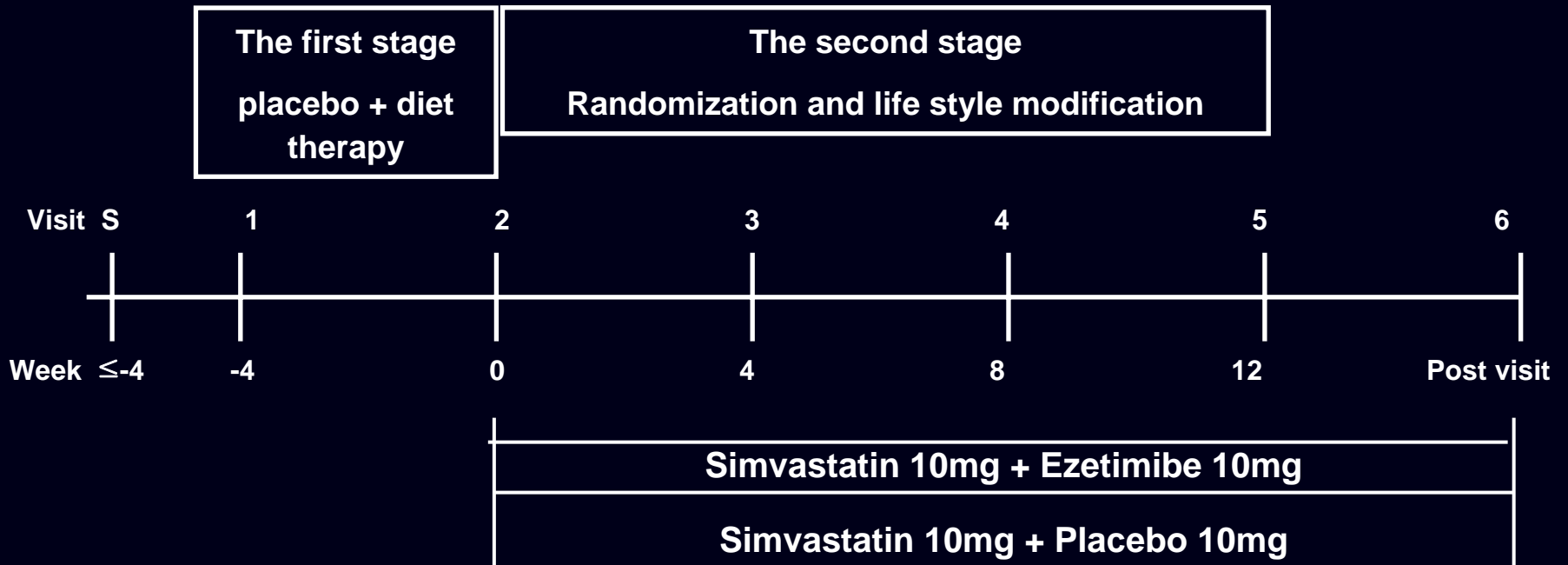
Lipid profile, safety monitoring*, uhCG : Visit 1, 2, 3, 4, 5, TFT : Visit 1, 5

Post visit : Safety monitoring

Exclusion from trial : lipid profile, safety monitoring, uhCG, TFT

*Safety monitoring : CBC, Chemistry, UA with microscopy

Bridging of Korean data with Foreign data

	Korean		Foreign			
	Simva (10mg)	Eze+simva (10mg)	Simva (10mg)	Eze+simva (10mg)	Simva (10mg)	Eze+simva (10mg)
Mean% change from baseline [95% CI]	-36.3 [-39.5, -33.1]	-50.9 [-54.1, -47.7]	-27.4 [-30.8, -24.0]	-44.4 [-47.8, -41.0]	-31.3 [-34.5. -28.1]	-46.2 [-49.2, -43.2]
Difference and 90% CI from simvastatin monotherapy	-14.6 (p<0.001) [-17.6, -11.8]		-17.0 (p<0.001)		-14.9 (p<0.001)	
			[-24.15, -8.05]			

- Further reduction in LDL-C achieved by co-administration of ezetimibe to simvastatin was similar between Korean and foreign (Caucasian) data.

Wrap-up

- Ezetimibe 의 기전을 이해

- Ezetimibe와 statin의 병용의 이점을 이해

- Ezetimibe와 statin 병용시 혈중지질치와 CRP수치의 개선효과를 이해

- Ezetimibe의 안정성을 이해