2012 춘계 대한심장학회 산학학술세션

VYTORIN (ezetimibe/simvastatin) DUAL POWER!

- **Date: 2012. Apr. 21 (Sat)**
- **Venue:** 부산 벡스코

Solution to Reduce CV risk:

Exploring the latest pathway to treat Hypertension & Dyslipidemia

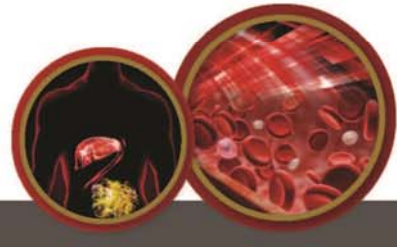
- **Reducing cardiovascular risk in high-risk patients**

: How we would apply new treatment guideline in a real practice?

(연세의대 최동훈 교수님)

- **The Significance of Uric acid for Hypertension treatment**

(연세의대 강석민 교수님)



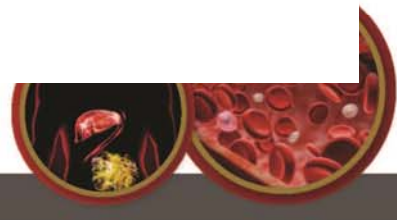
Reducing cardiovascular risk in high-risk patients
: How we would apply new treatment guideline in a real practice?

1. Global treatment guideline changes to more aggressive treatment.

- Three points of updates in 2011 ESC/EAS guideline are
  a. It is importance to get to LDL-C <70mg/dL or 50% reduction from baseline for high-risk patients.
  b. CKD is also CHD equivalent risk factor
  c. Management of atherogenic particle number is valuable approach for Metabolic syndrome and DM patients (non-HDL and ApoB is secondary target)

2. 80% of CHD patients are not at LDL-C goal(<70mg/dL) with statin in Korea

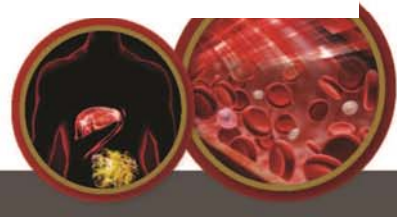
- Because, Statin mono therapy has some limitation to get to target goal at once.
  a. Safety concern of high dose statin: hepatic and muscle injury
  b. Lack of additional value of doubling or switching: Rule of six
  c. (Risk of incident diabetes (FDA warning, 2012))



3. VYTORIN is the smart option to be aligned with guideline change.

- VYTORIN proved superior efficacy vs. statin therapy (mono, doubling or switching)
  a. 9 out of 10 patients are getting to goal at once with initial dose of VYTORIN.
  b. Initial dose of VYTORIN cut off 50% reduction LDL-C at once.
     (EZT add-on to any statin provided additional 25% reduction of LDL-C.)
  c. EZT/VYTORIN attained triple target goal for managing atherogenic particle vs. statin mono therapy.

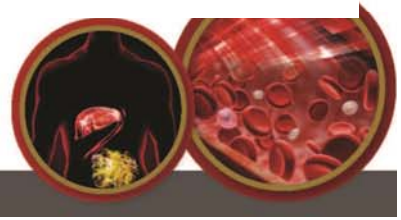
- VYTORIN proved long-term clinical benefits for high-risk patients safely.
  a. Initial dose of VYTORIN (10/20mg) proved 17% risk reduction of atherosclerotic event (coronary death, non-fatal MI, non-hemorrhagic stroke and any revascularization) in patients with high-risk patients.
  b. VYTORIN had proved safety profile for highest risk patient such as CKD in 5 years.



4. EZT / VYT provide additional benefits beyond LDL-C

- EZT / VYTORIN is better option for minimizing concern of increasing DM vs. statin.
  a. Based on RCT and meta analysis, statin (rosuvastatin, atorvastatin) seems to be associated with development of DM (meta-analysis data)
  b. In animal and human data, EZT / VYTORIN proved no deleterious effect on insulin resistance
  c. In SHARP, no report on DM incidence vs. placebo.

- EZT / VYTORIN improved endothelial function.
  a. Low dose Simvastatin and Eze preserved post-fat load endothelial function in male MS patients.
  b. Ezetimibe improves postprandial induced endothelial dysfunction.
  c. Impact of Ezetimibe therapy on Endothelial Dysfunction in patients on statin therapy with CAD and hyperTG.

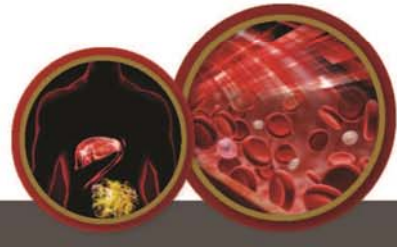


Reducing cardiovascular risk in high-risk patients : How we would apply new treatment guideline in a real practice?

[Take Home Message]

VYTORIN is the smart option to be aligned with guideline change.

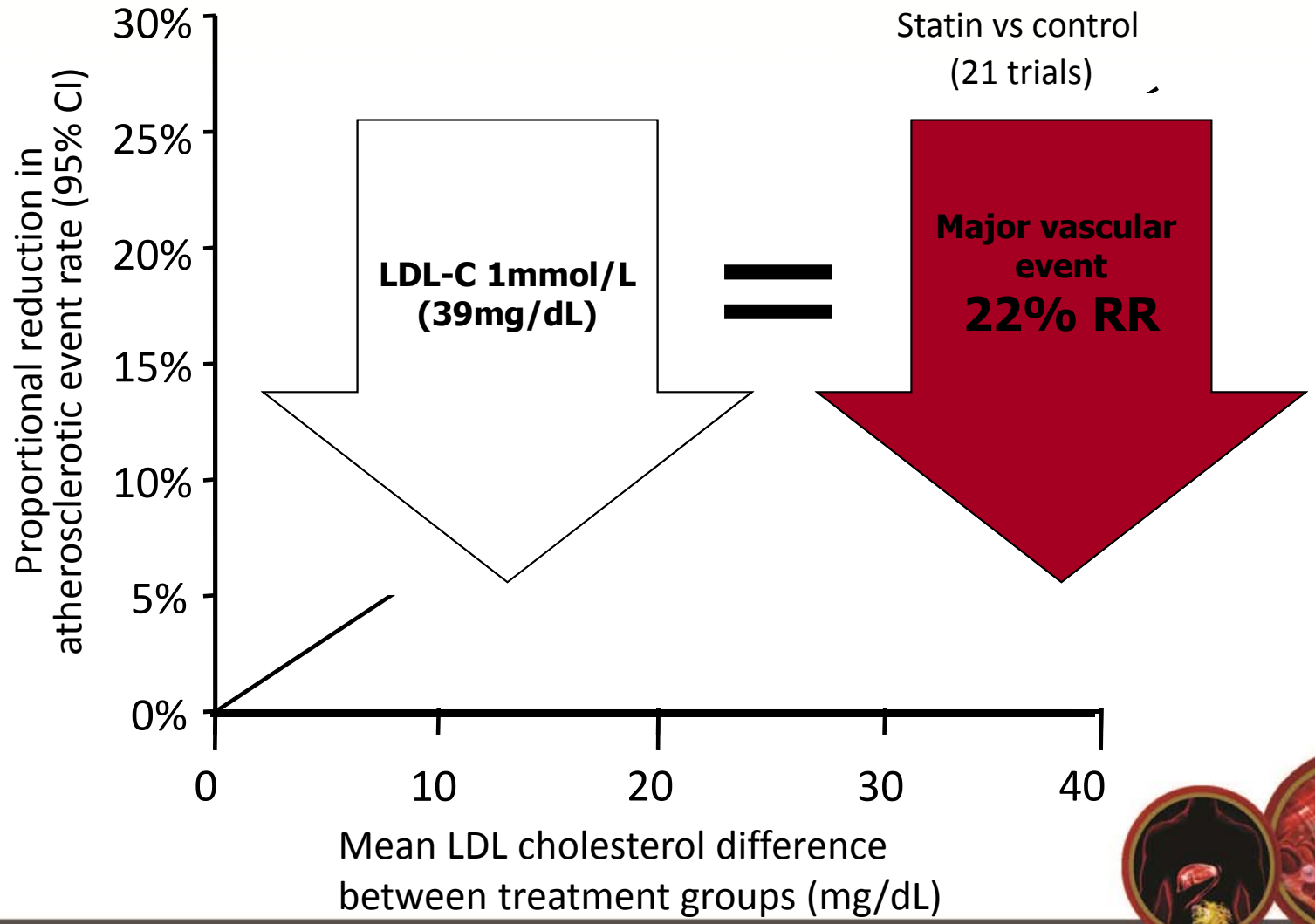
1. For better goal achievement, VYTORIN 10/20mg cut off 50% LDL-C reduction safely at once.
2. VYTORIN attained triple target goal for managing atherogenic particle vs. statin mono therapy
3. Reduction of LDL cholesterol with VYTORIN 10/20mg safely reduced the incidence of major atherosclerotic events in high-risk patients.

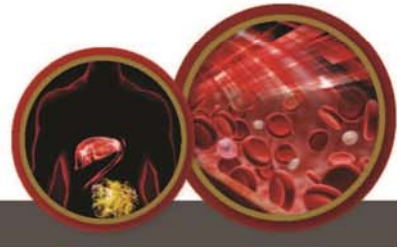


Reducing cardiovascular risk in high-risk patients

: How we would apply new treatment guideline in a real practice?

Lower Is Better : Cholesterol Treatment Trialists





1. Cholesterol Treatment Trialists' (CTT) Collaboration. *Lance*t 2010; 376: 1670–81

2004 NCEP ATP III guideline

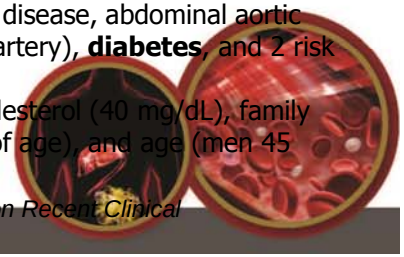
Risk Category	LDL-C Goal	Initiate TLC	Consider Drug Therapy
High risk: **CHD or CHD risk equivalents** (10-year risk 20%)	**<100 mg/dL (optional goal: <70 mg/dL)**	≥100 mg/dL	≥ 100 mg/dL (100 mg/dL: consider drug options)
Moderately high risk: 2 risk factors (10-year risk 10% to 20%)	<130 mg/dL (optional goal: <100mg/dL)	≥ 130 mg/dL	≥ 130 mg/dL (100–129 mg/dL; consider drug options)
Moderate risk: 2 risk factors‡ (10-year risk 10%)	<130 mg/dL	≥130 mg/dL	≥ 160 mg/dL
Lower risk: 0–1 risk factor§	<160 mg/dL	≥160 mg/dL	≥ 190 mg/dL (160–189 mg/dL: LDL-lowering drug optional)

*CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.

†**CHD risk equivalents** include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease transient ischemic attacks or stroke of carotid origin or 50% obstruction of a carotid artery), **diabetes**, and 2 risk factors with 10-year risk for hard CHD 20%.

‡Risk factors include cigarette smoking, hypertension (BP 140/90 mm Hg or on antihypertensive medication), low HDL cholesterol (40 mg/dL), family history of premature CHD (CHD in male first-degree relative 55 years of age; CHD in female first-degree relative 65 years of age), and age (men 45 years; women 55 years)

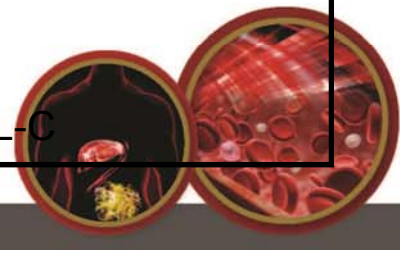
*TABLE 2. ATP III LDL-C Goals and Cutpoints for TLC and Drug Therapy in Different Risk Categories and Proposed Modifications Based on Recent Clinical Trial Evidence (**Circulation**. 2004;110:227-239.)*



2011 ESC Update :
Updated recommendations for Very high risk

- Very high risk
  - **Documented CVD, previous MI, ACS, coronary revascularization** (PCI, CABG) and other arterial revascularization procedures, ischemic stroke, PAD
  - Patients with **type 2 diabetes**, patients with type 1 diabetes with target organ damage (such as microalbumiuria) (1)
  - **Patients with moderate to severe CKD (GFR < 60mL/min/1.73m^2)**
  - A calculated 10 year risk SCORE ≥ 10%

- Treatment targets
  - Primary target – LDL-C (2)
    - In patients at VERY HIGH CV risk **the LDL-C goal is < 70mg/dL and/or ≥ 50% LDL-C reduction** when target level cannot be reached
  - Secondary target (3)
    - Specific target for **non-HDL-C** should be 30mg/dL higher than the corresponding LDL-C target.
    - **Apo B** appears to be a risk factor at least as good as LDL-C and a better index of the adequacy of LDL-lowering therapy than LDL-C



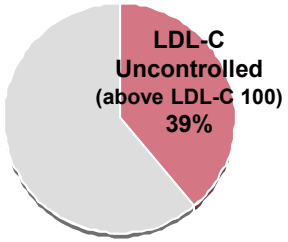
1. Zeljko Reiner et al. *European Heart J.* (2011)32;1769-1818

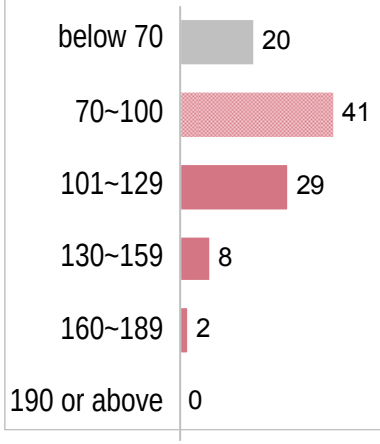
Therefore, 80% of CHD patients are not at the goal even with Statin Rx in Korea

LDL-C distribution

❖ LDL-C Uncontrolled after Statin Rx.

Total
(n=925)

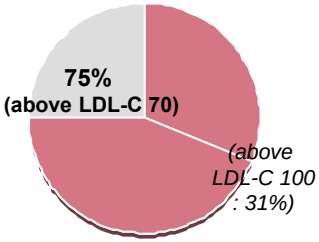




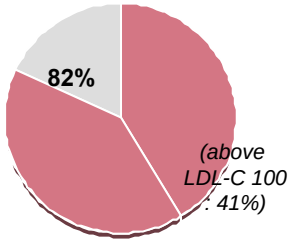
LDL-C distribution by CV disease

[Base: Pts have LDL-C after Statin Rx., Unit: %]

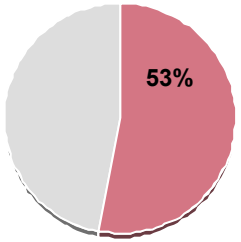
CHD
(n=526)



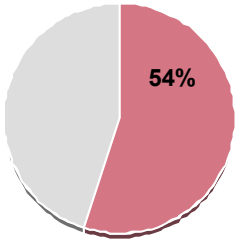
CHD equivalent (=DM)
(n=118)

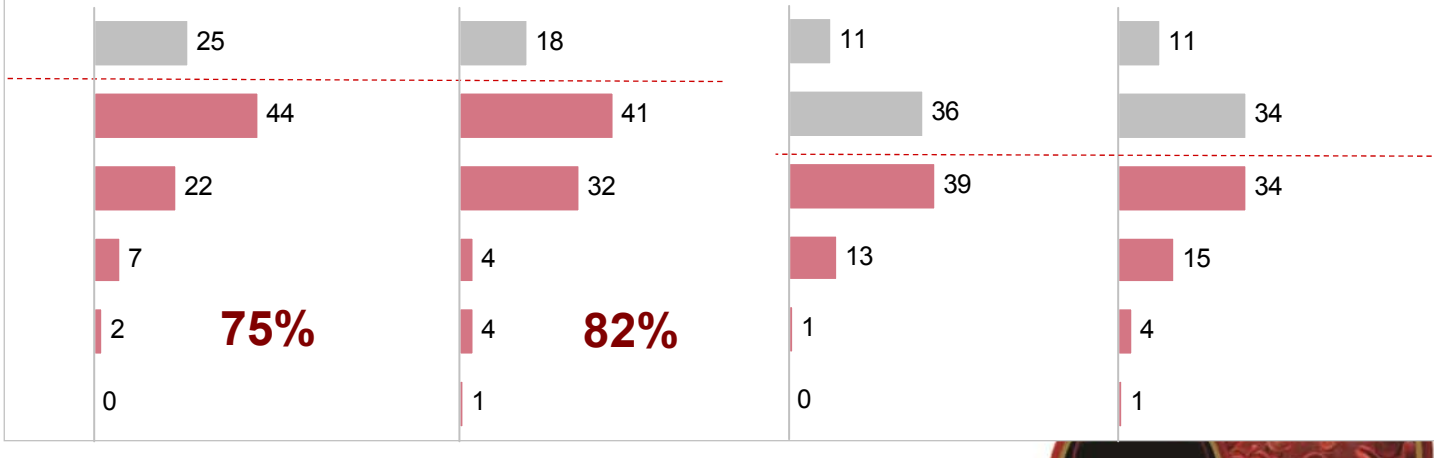


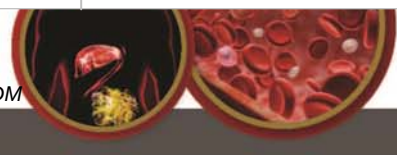
HTN with 2 more risk*
(n=201)



No Risk
(n=80)



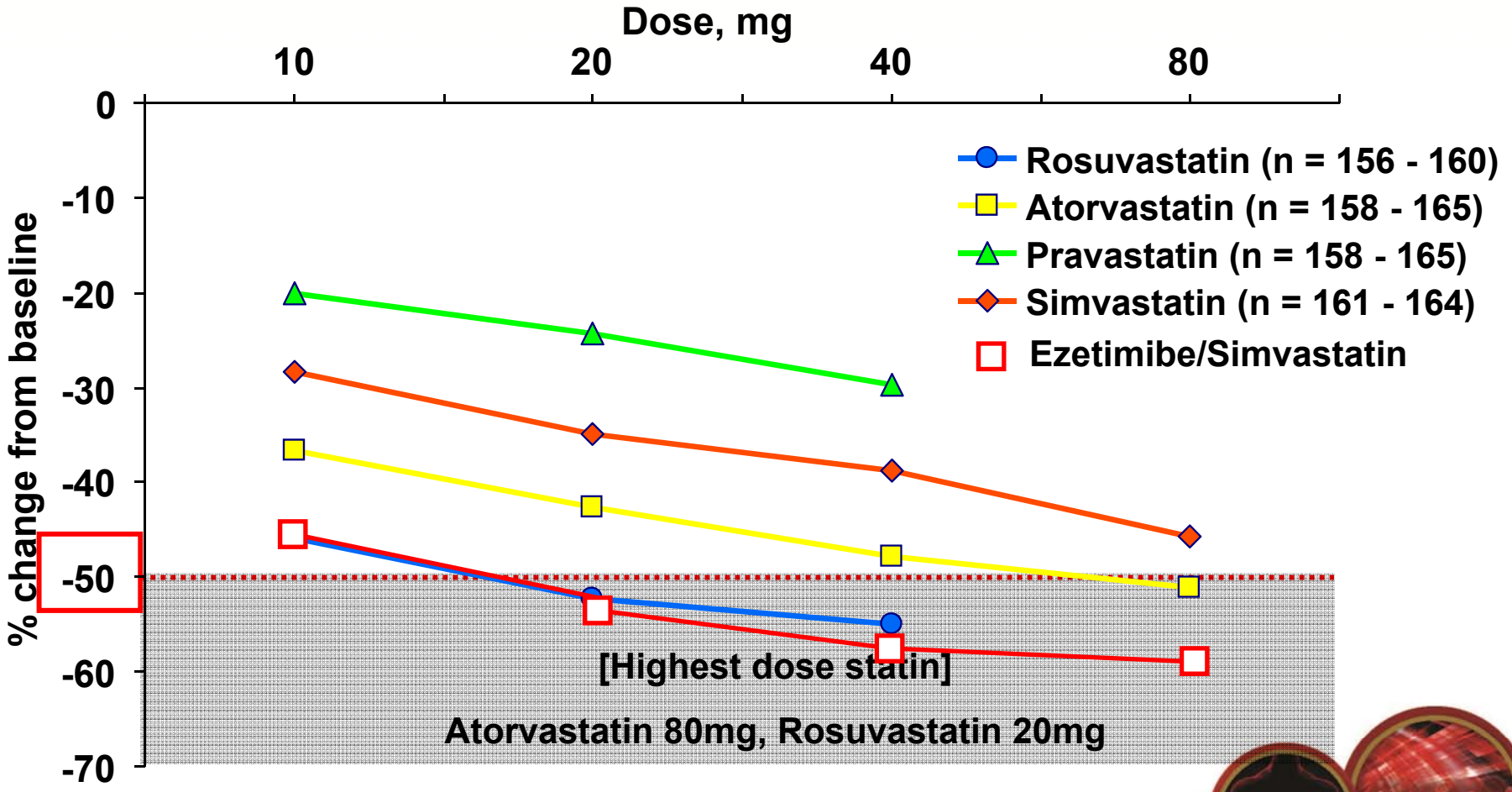




*HTN with 2more risks: HTN patients with 45+y/o (Male) or 55+y/o(Female) but who do not have CHD or DM

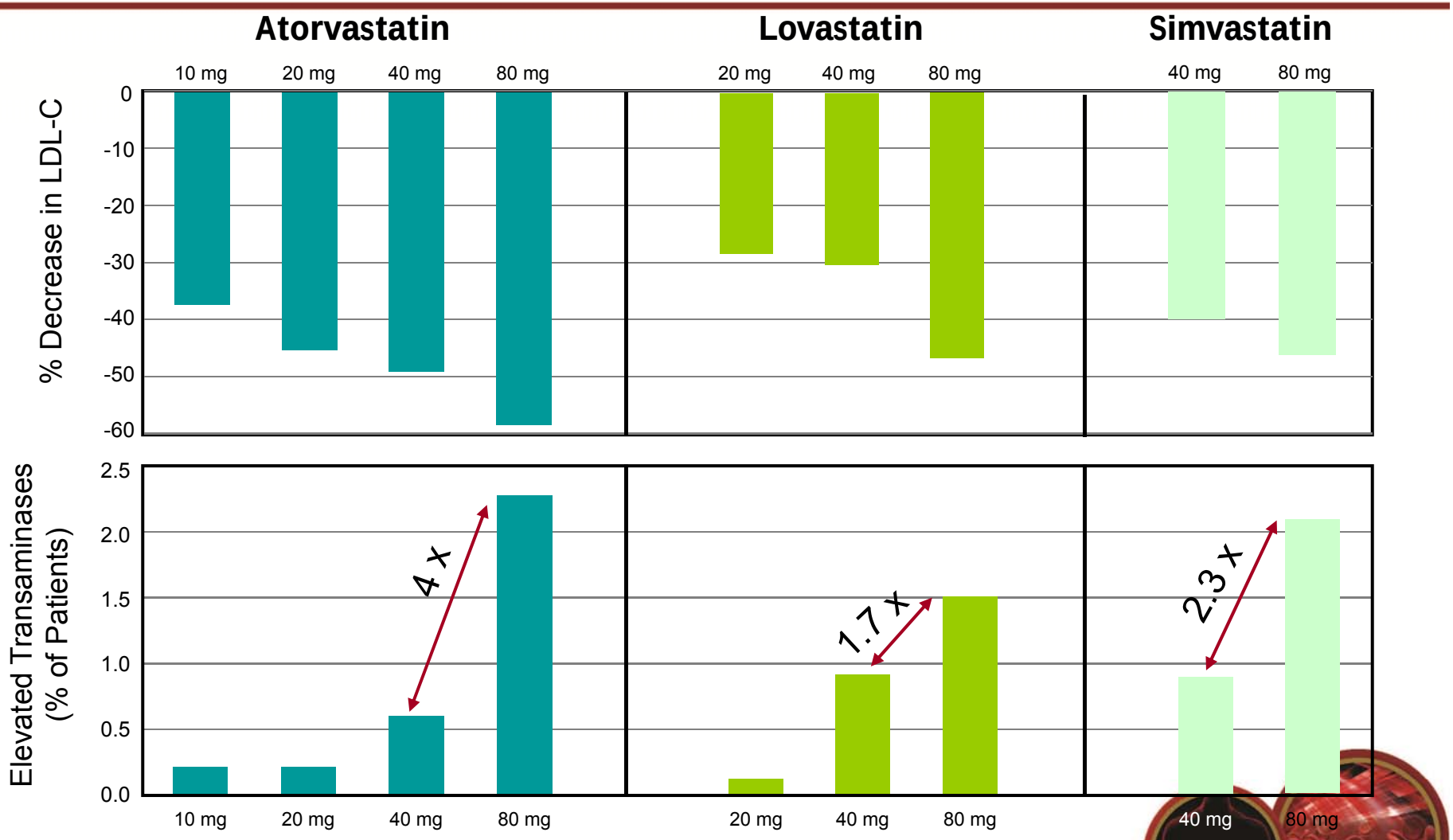
2011 한국 고지혈증 치료현황 조사 (IPSOS)

Only highest dose of statins can achieve 50% LDL-C reduction



Am J Cardiol. 2003 Jul 15;92(2):152-60

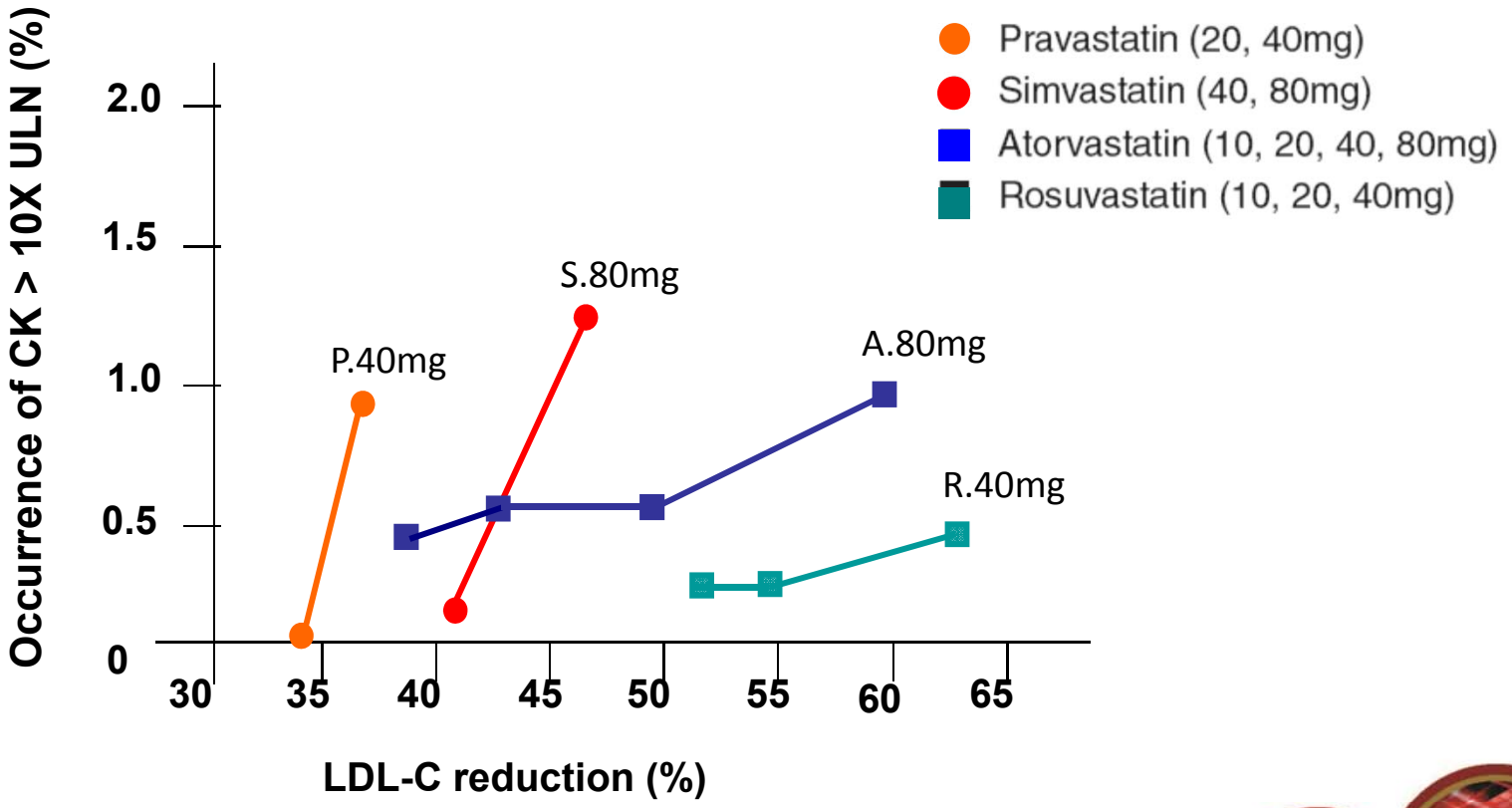
Highest doses associated with increased hepatic toxicity

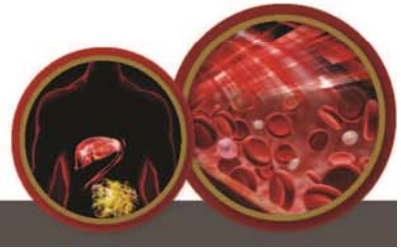


Data from prescribing information for atorvastatin, lovastatin, simvastatin.
This does not represent data from a comparative study.

Drug safety 2006;29(5):421-448

Highest doses associated with increased muscle injury(> 10X CK)





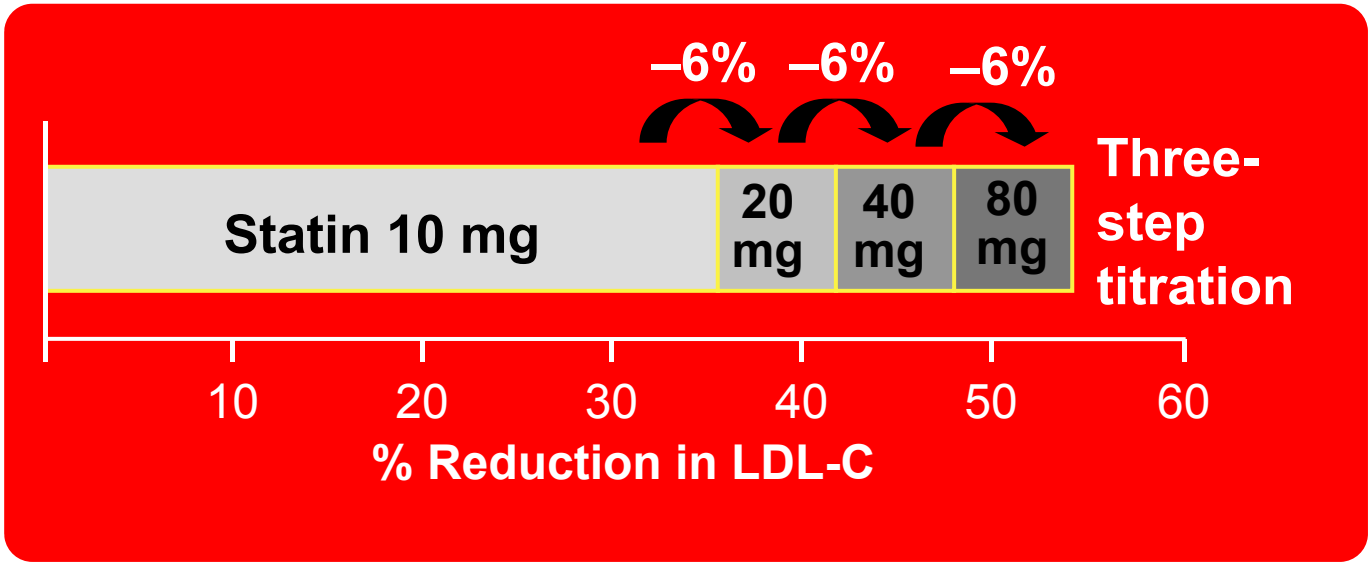
Drug safety 2006;29(5):421-448

Statin up-titration has limitation on LDL-C reduction

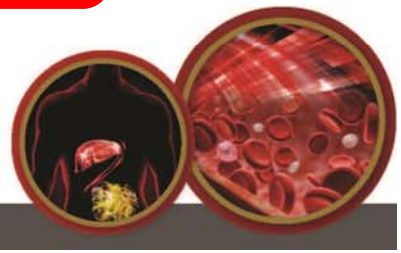
"…With each doubling of the dose of statin, LDL-C levels fall by about 6 percent."

NCEP ATP III Final Report

Effect of statin therapy on LDL–C levels: "The Rule of 6"



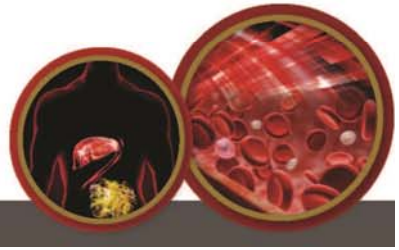
1. Bays H, Dujovne C. *Expert Opin Pharmacother* 2003;4:779-790.
2. NCEP ATP III guideline 2002



What is your option to reach target goals (LDL-C<70mg/dL or ≥50% reduction)?

1. Escalation of Statin dose ?

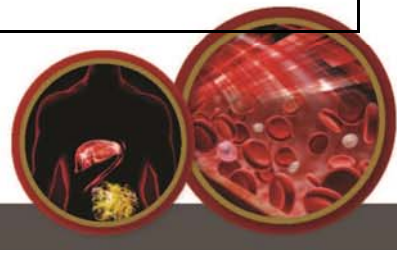
2. Utilization of dual action mechanism?



Ezetimibe :
The 1st cholesterol absorption inhibitor

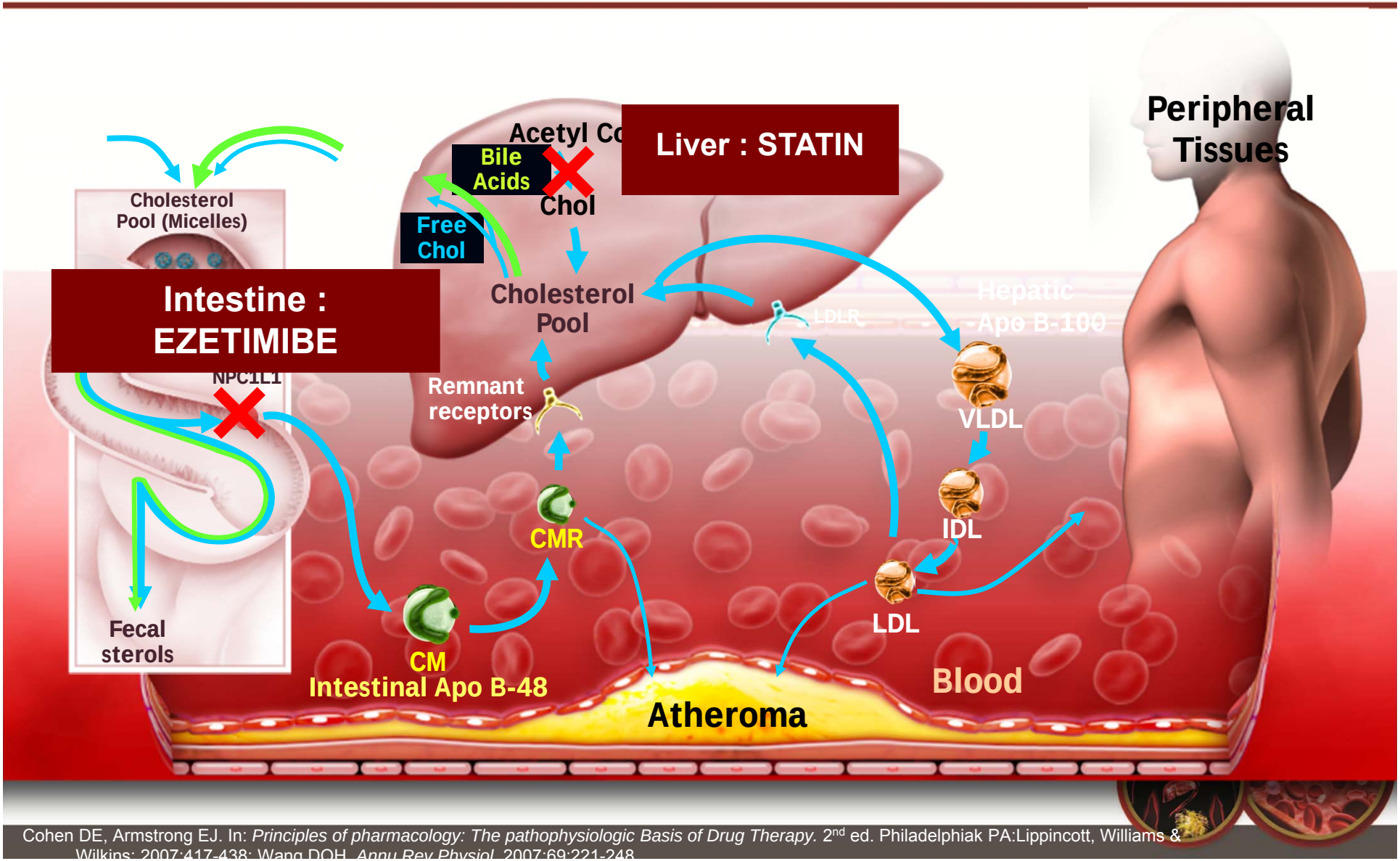
Adverse events	Placebo (%) N=205	Ezetimibe10mg(%) N=622
Most common treatment-emergent AEs	65	61
Headache	11	4
Upper respiratory infection	7	8
Back pain	4	4
Musculoskeletal pain	4	3
Constipation	4	2
Laboratory tests assessing liver and muscle function		
Liver function tests(≥3XULN)		
Alanine aminotransferase	0	<1
Aspartate aminotransferase	0	<1
R-Glutamyltransferase	3	2
Creatine phosphokinase ≥10XULN	0	0

- Half-life: **22 hours**



1. Altmann SW, et al. *Science.* 2004;303:1201-1204;
2. VYTORIN US prescribing Information
3. Knopp RH et al. *Eur Heart J.* 2003 Apr;24(8):729-41.

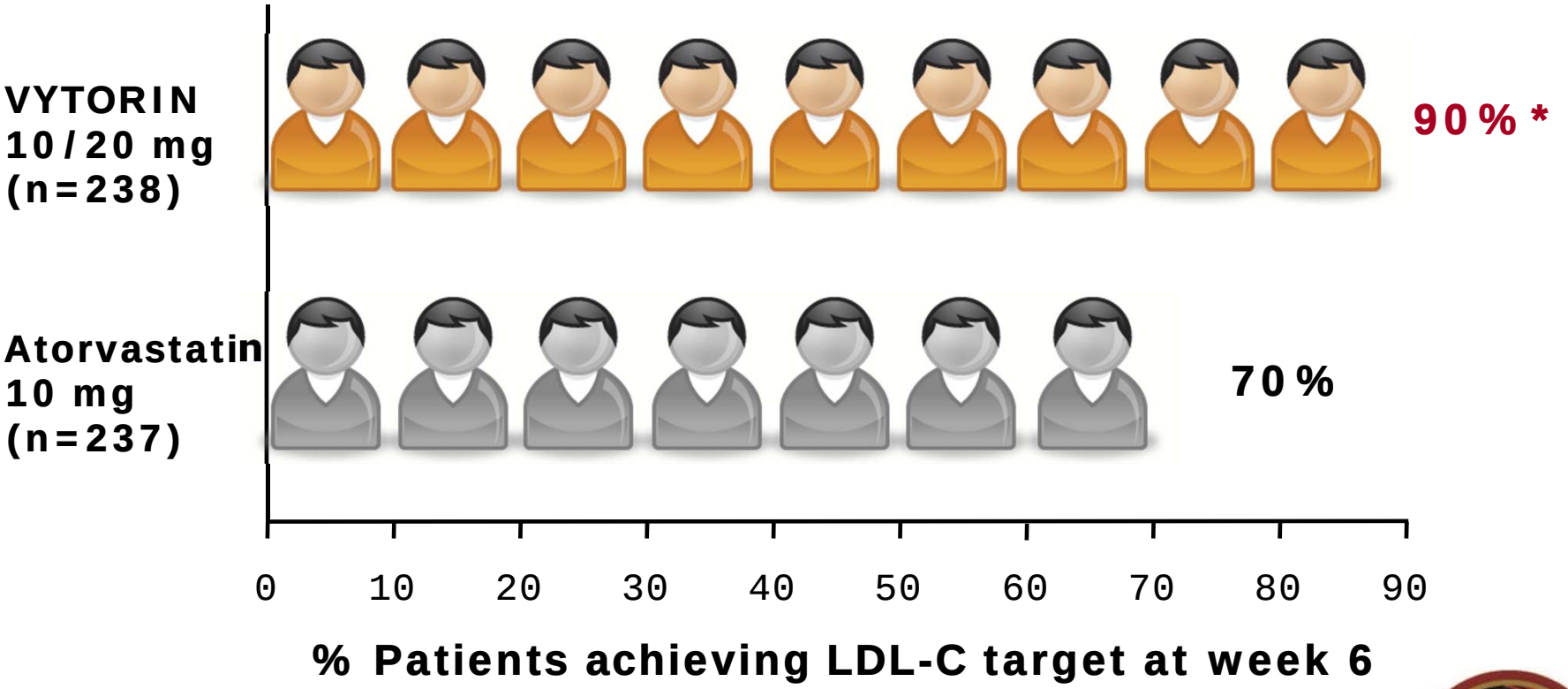
Vytorin:
DUAL INHIBITION in cholesterol



Cohen DE, Armstrong EJ. In: *Principles of pharmacology: The pathophysiologic Basis of Drug Therapy.* 2nd ed. Philadelphiak PA:Lippincott, Williams & Wilkins; 2007:417-438; Wang DQH. *Annu Rev Physiol.* 2007;69:221-248.

VYTORIN: 9 out of 10 patients achieved LDL-C Goal Attainment to <100 mg/dL

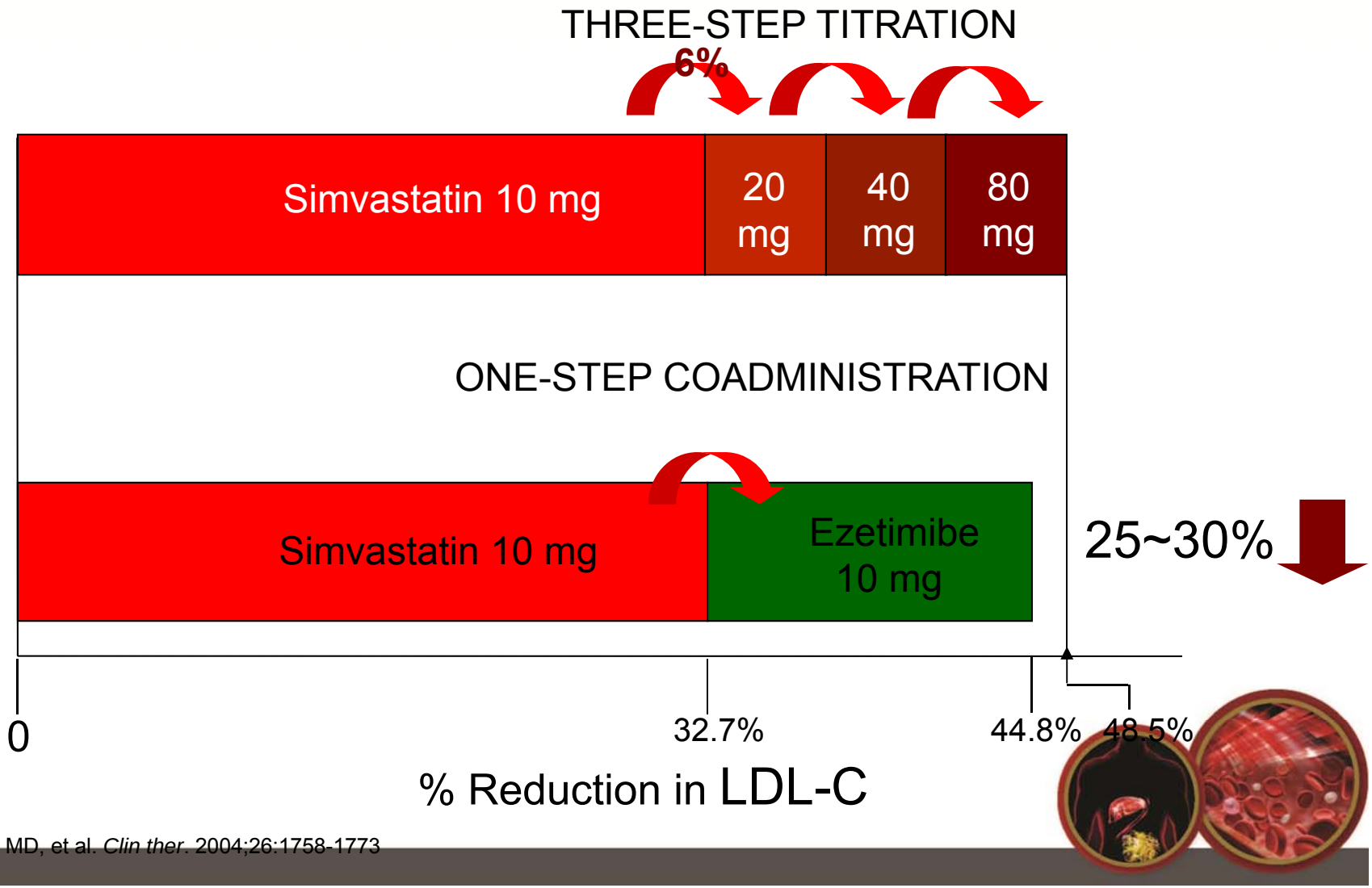
Percentage of Patients Who Achieved LDL-C 100mg/dL with Starting Dose



* p<0.001 vs. atorvastatin

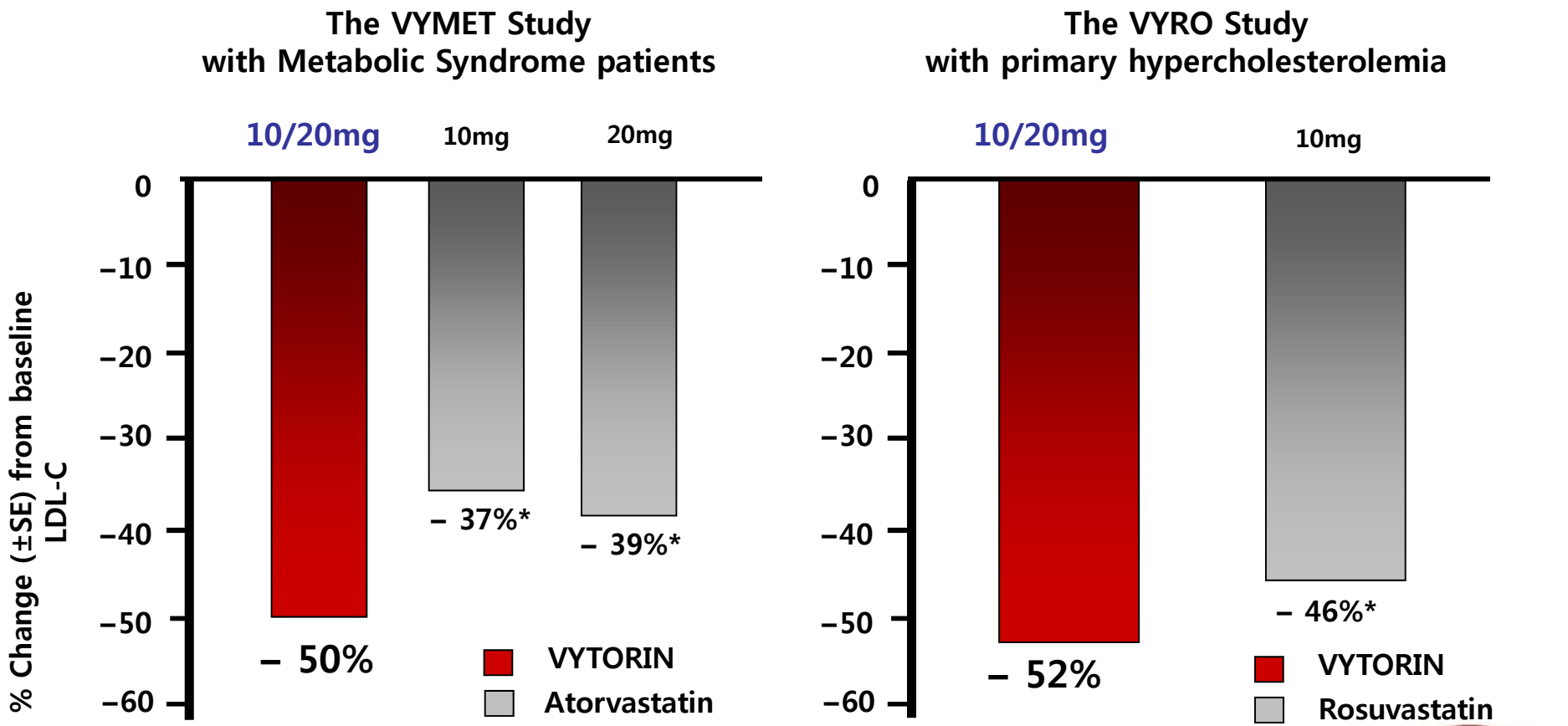
Mayo Clin Proc. 2006;81(12):1579–1588

Ezetimibe add-on vs. Statin doubling in LDL-C lowering

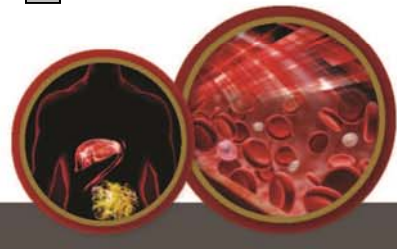


Harold E. Bays, MD, et al. *Clin ther*. 2004;26:1758-1773

VYTORIN :
Superior LDL-C reduction at Starting Dose



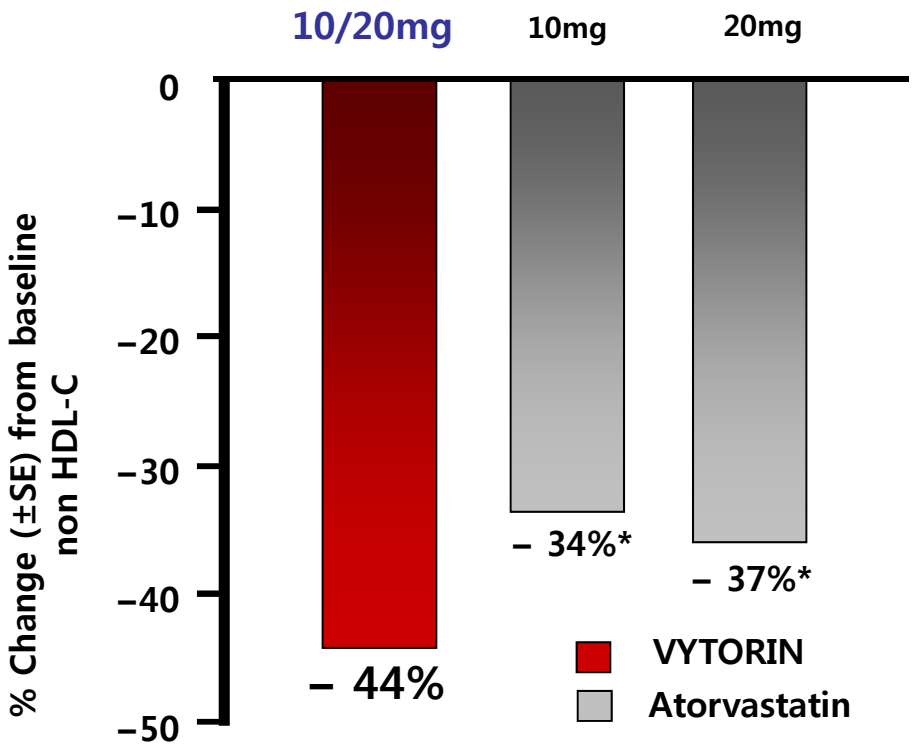
* p<0.001 vs. statin



Am J Cardiol 2009;103:1694-1702 / *Mayo Clin Proc.* 2006;81(12):1579–1588.

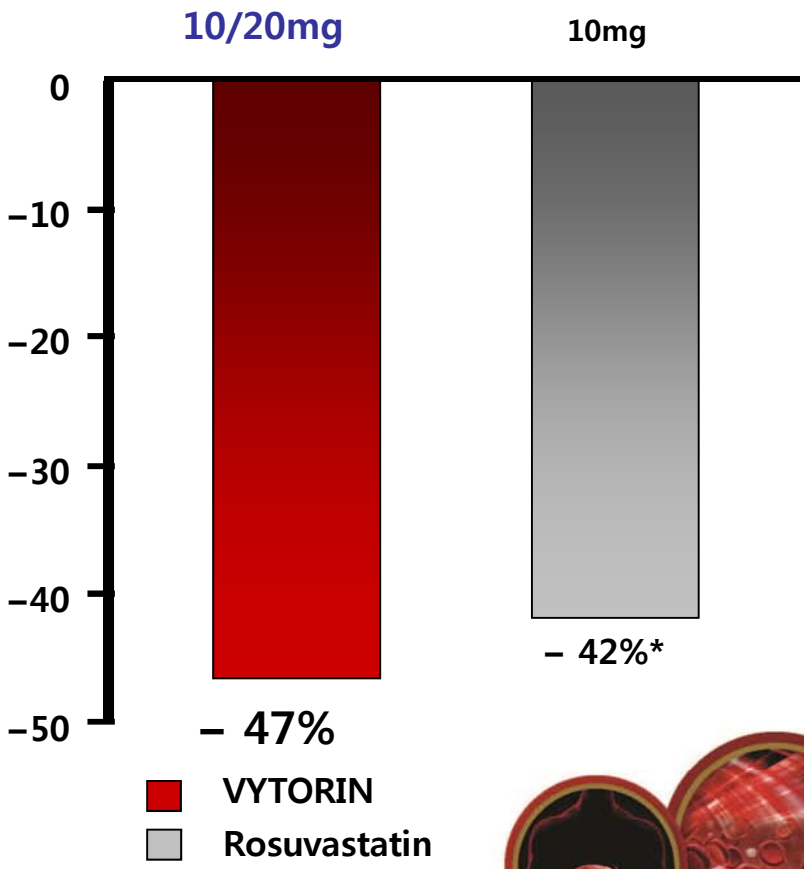
VYTORIN :
Superior non HDL-C reduction at Starting Dose

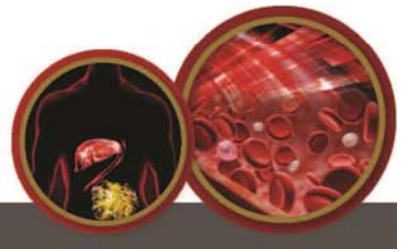
The VYMET Study
with Metabolic Syndrome patients



* p<0.001 vs. statin

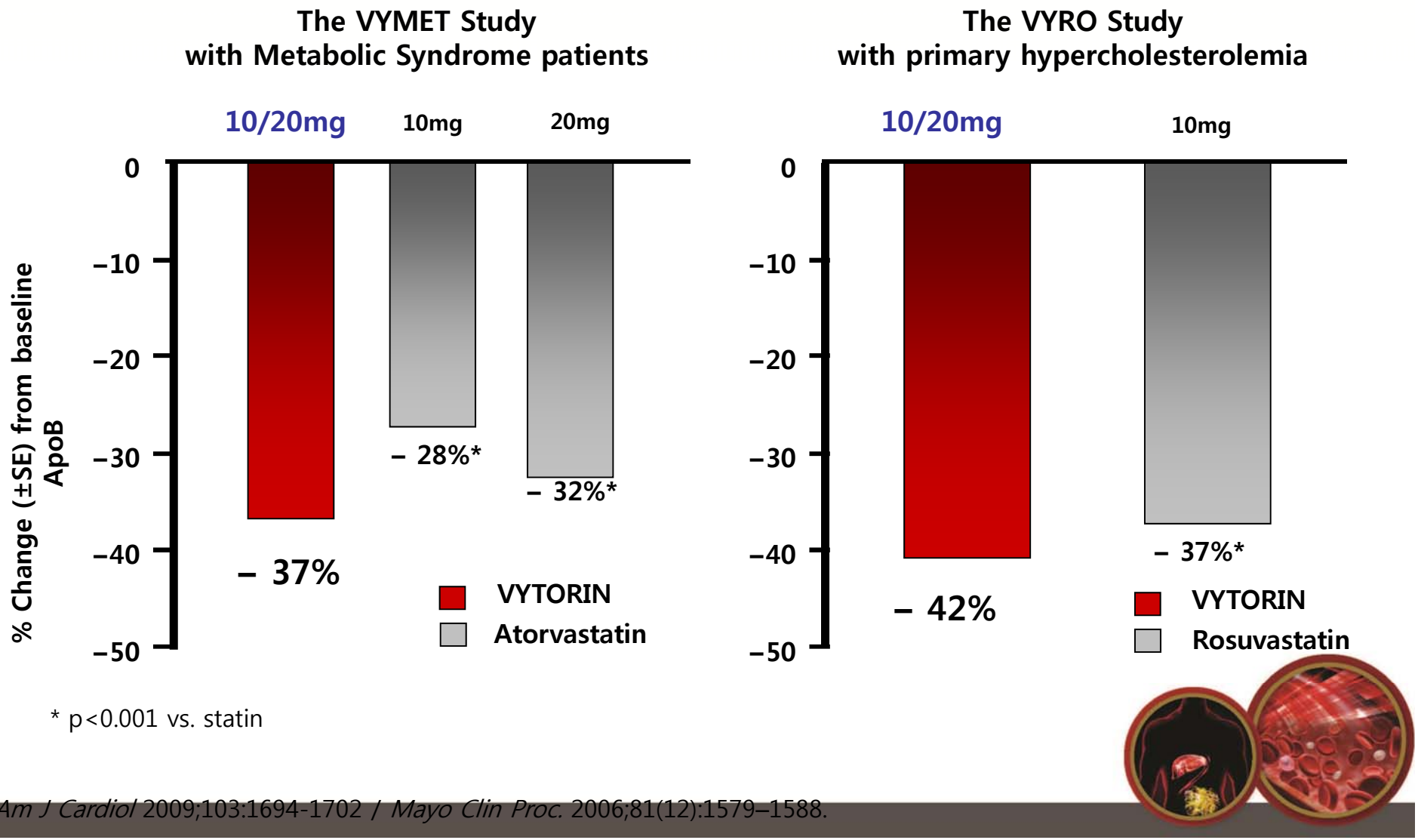
The VYRO Study
with primary hypercholesterolemia





Am J Cardiol 2009;103:1694-1702 / *Mayo Clin Proc.* 2006;81(12):1579–1588.

VYTORIN :
Superior ApoB reduction at Starting Dose

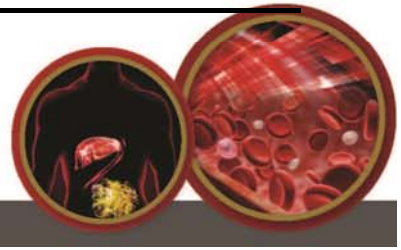


* p<0.001 vs. statin

Am J Cardiol 2009;103:1694-1702 / *Mayo Clin Proc.* 2006;81(12):1579–1588.

VYTORIN was Generally Well Tolerated

Adverse Events	VYTORIN 10/20 mg/day (n=314)	Rosuvastatin 10 mg/day (n=304)
≥1 Clinical event	7.1%	11.2%
Drug-related clinical event	2.6%	3.3%
Discontinuation due to drug-related clinical event	2.2%	1.0%
ALT and/or AST ≥3 × ULN (consecutive)	0.7%	0
CK ≥5 × ULN	0	0

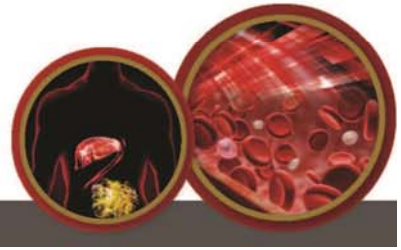


Adapted from Farnier M. et al
ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal; CK=creatine kinase.

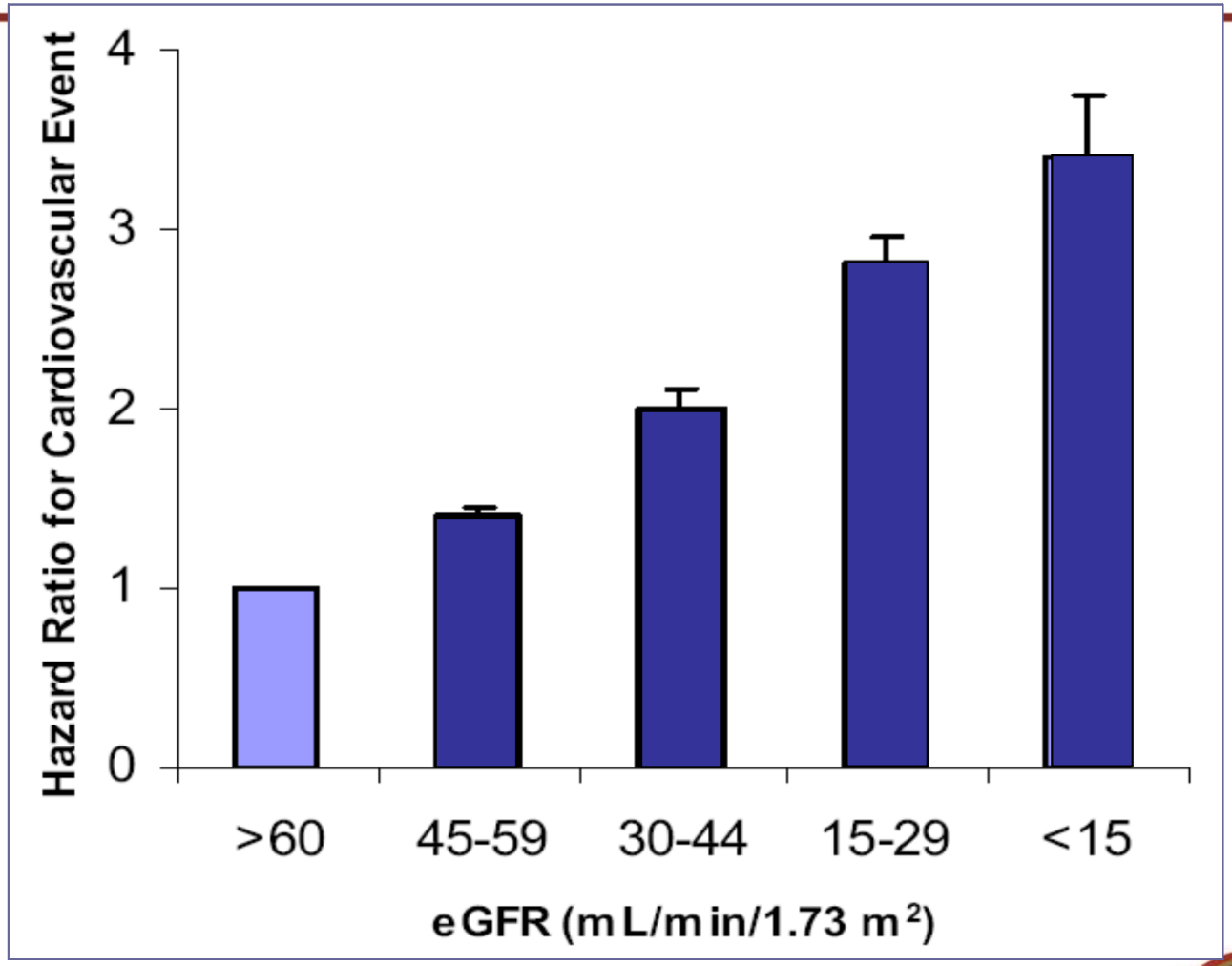
1. Farnier M, et al. *Int J Clin Pract*. 2009;63(4):547-559

The effects of lowering LDL cholesterol with Simvastatin plus Ezetimibe in patients with chronic kidney disease

(Study of Heart And Renal Protection : SHARP)



Hazard ratios for cardiovascular events



*Adjusted for baseline age, sex, income, education, coronary disease, chronic heart failure, stroke or transient ischemic attack, peripheral artery disease, diabetes, hypertension, dyslipidemia, cancer, hypoalbuminemia, dementia, liver disease, proteinuria, prior hospitalizations, and subsequent dialysis requirement.

Cardiovascular Disease and CKD: Core Curriculum 2010. American Journal of Kidney Diseases, 2010(56); 2: 399-417

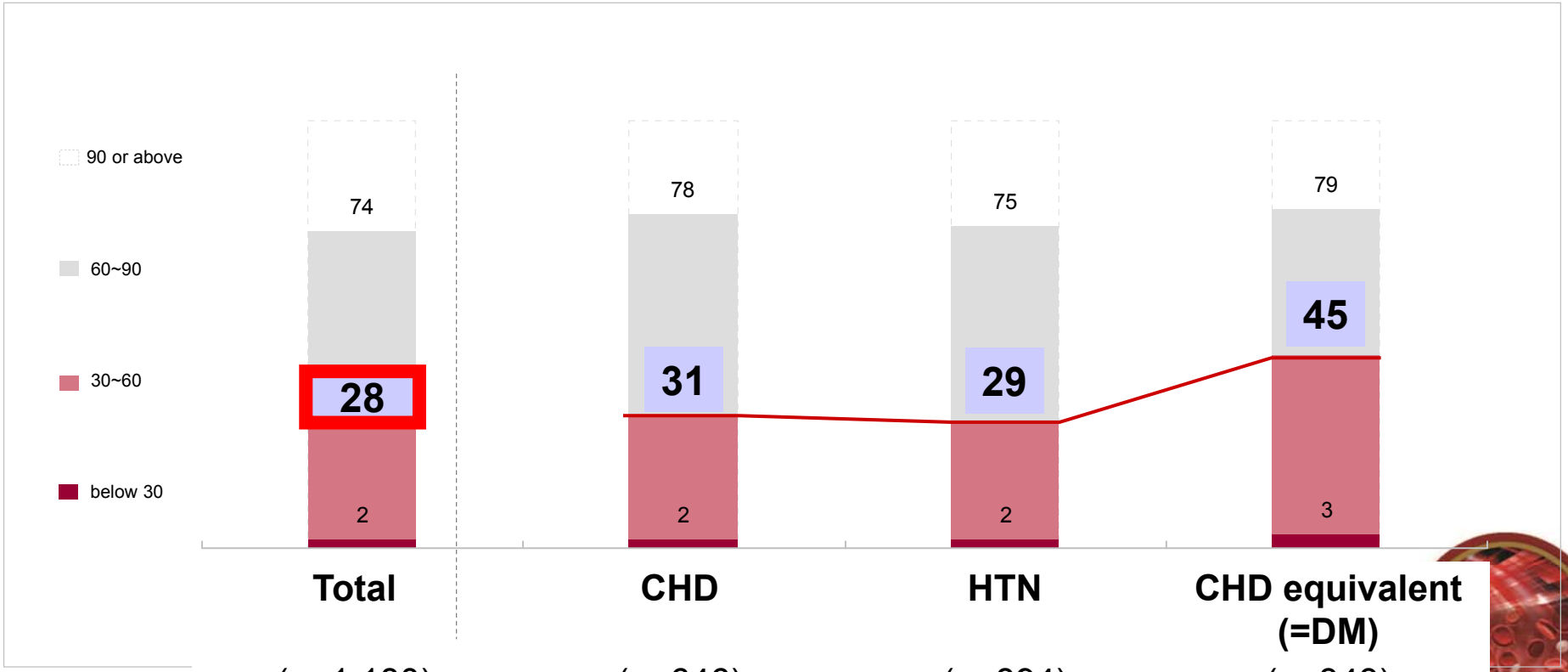
Cardio

CKD risk patients (below GFR 60) are 28%

By CV disease, Patient with DM shows higher portion of CKD risk patients as 45% compared to other CV disease.

GFR Score by MDRD II (Tally-Results) by CV disease

[Base: Pts who have Scr record (n=1,180), Unit: %]



Deficiency of Renal function in patient with NSTEMI
(from the Korea Acute Myocardial Infarction Registry)

Baseline clinical characteristics according to renal function and management

Variable	Renal Function	EI Group	DI Group	Conservative Group	p Value	
					Invasive vs Conservative	EI vs DI
	Overall	1,154 (32%)	1,663 (46%)	799 (22%)		
	Normal	58 (33%)	74 (43%)	42 (24%)		
	Mild	464 (36%)	628 (48%)	224 (17%)		
	Moderate	562 (33%)	814 (47%)	353 (20%)		
	Severe	68 (18%)	143 (37%)	174 (45%)		
Age (years)		63 (53–71)	65 (56–73)	69 (59–77)	<0.001	<0.001
Men		826 (72%)	1,110 (67%)	459 (58%)	<0.001	0.007
Body mass index (kg/m^2)		24 (22–26)	24 (22–26)	23 (21–25)	<0.001	<0.001
Hypertension		601 (52%)	893 (54%)	437 (55%)	0.333	0.420
Diabetes mellitus		314 (27%)	565 (34%)	265 (33%)	0.262	<0.001
Hyperlipidemia		148 (13%)	221 (13%)	97 (12%)	0.549	0.777
Previous coronary artery disease		224 (19%)	331 (20%)	241 (30%)	<0.001	0.736
Previous stroke		63 (5.5%)	146 (8.8%)	105 (13.1%)	<0.001	0.001
Previous heart failure		11 (1.0%)	53 (3.2%)	72 (9.0%)	<0.001	<0.001
Smoker		677 (59%)	881 (53%)	350 (44%)	<0.001	0.002
Heart rate >100 beats/min		93 (8.1%)	182 (11%)	155 (20%)	<0.001	0.012
Killip class >I		165 (15%)	383 (24%)	313 (40%)	<0.001	<0.001
Presence of chest symptom on admission		950 (83%)	1,323 (81%)	549 (71%)	<0.001	0.070
Presence of dyspnea on admission		228 (20%)	461 (29%)	312 (41%)	<0.001	<0.001
Angina before admission		660 (57%)	878 (52%)	353 (45%)	<0.001	0.037
ST-T change on admission		645 (56%)	990 (60%)	482 (60%)	0.272	0.043
Atrial fibrillation/atrial flutter		41 (3.6%)	63 (3.9%)	61 (7.8%)	<0.001	0.762
Left ventricular ejection fraction ≤35%		63 (5.9%)	156 (9.9%)	131 (18.4%)	<0.001	<0.001
Estimated glomerular filtration rate (ml/min/1.73 m^2)		58 (47–69)	57 (46–68)	52 (34–66)	<0.001	0.017
Thrombolysis In Myocardial Infarction risk score ≥5		140 (12%)	236 (14%)	160 (20%)	<0.001	0.114
Modified Global Registry of Acute Coronary Events score ≥140		310 (27%)	563 (33%)	434 (54%)	<0.001	<0.001

68%

1. Daisuke Hachinohe et al. *Am J Cardiol* 2011;108:206–213)

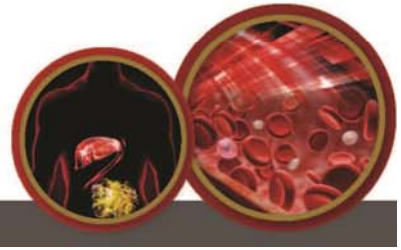
SHARP: Eligibility and Key outcome

- History of chronic kidney disease
  - not on dialysis: elevated creatinine on 2 occasions
    - Men: ≥1.7 mg/dL (150 µmol/L)
    - Women: ≥1.5 mg/dL (130 µmol/L)
  - on dialysis: haemodialysis or peritoneal dialysis
- No history of myocardial infarction or coronary revascularization

Key outcome

Composite of major atherosclerotic events including

- Coronary death,
- Non-fatal MI
- Non-haemorrhagic stroke
- Any revascularization



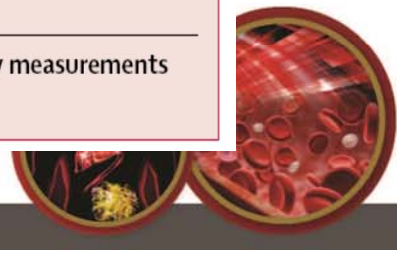
1. SHARP Collaborative Group *Am Heart* J 2010;0:1-10.e10
2. Colin Baigent et al. *Lancet* 2011 Published Online June 9, 2011 DOI:10.1016/S0140-6736(11)60739-3

SHARP:
Study of Heart And Renal Protection

	Simvastatin plus ezetimibe (n=4650)	Placebo (n=4620)
Previous vascular disease*	711 (15%)	682 (15%)
Diabetes*	1054 (23%)	1040 (23%)
Men	2915 (63%)	2885 (62%)
Age at randomisation (years)*	62 (12)	62 (12)
Current smoker	626 (13%)	608 (13%)
Diastolic blood pressure (mm Hg)*	79 (13)	79 (13)
Systolic blood pressure (mm Hg)*	139 (22)	139 (22)
Total cholesterol (mmol/L)	4·88 (1·20) **189 mg/dL**	4·90 (1·17)
LDL cholesterol (mmol/L)	2·77 (0·88) **107mg/dL**	2·78 (0·87)
HDL cholesterol (mmol/L)	1·12 (0·35) **43 mg/dL**	1·11 (0·34)
Triglycerides (mmol/L)	2·31 (1·76) **204 mg/dL**	2·34 (1·68)
Body-mass index (kg/m²)*	27·1 (5·7)	27·1 (5·6)
Renal status		
On dialysis	1533 (33%)	1490 (32%)
Haemodialysis	1275 (27%)	1252 (27%)
Peritoneal dialysis	258 (6%)	238 (5%)
Not on dialysis†	3117 (67%)	3130 (68%)
MDRD-estimated GFR (mL/min per 1·73 m²)*‡§		
Mean (SD)	26·6 (12·9)	26·6 (13·1)
≥60	44 (1%)	44 (1%)
≥30 to <60	1100 (37%)	1055 (35%)
≥15 to <30	1246 (41%)	1319 (44%)
<15	614 (20%)	607 (20%)
Not available	113	105
Urinary albumin:creatinine ratio (mg/g)‡§		
Median (IQR)	217 (44–788)	196 (43–748)
<30	545 (20%)	562 (20%)
≥30 to ≤300	1032 (37%)	1076 (39%)
>300	1203 (43%)	1156 (41%)
Not available	337	336

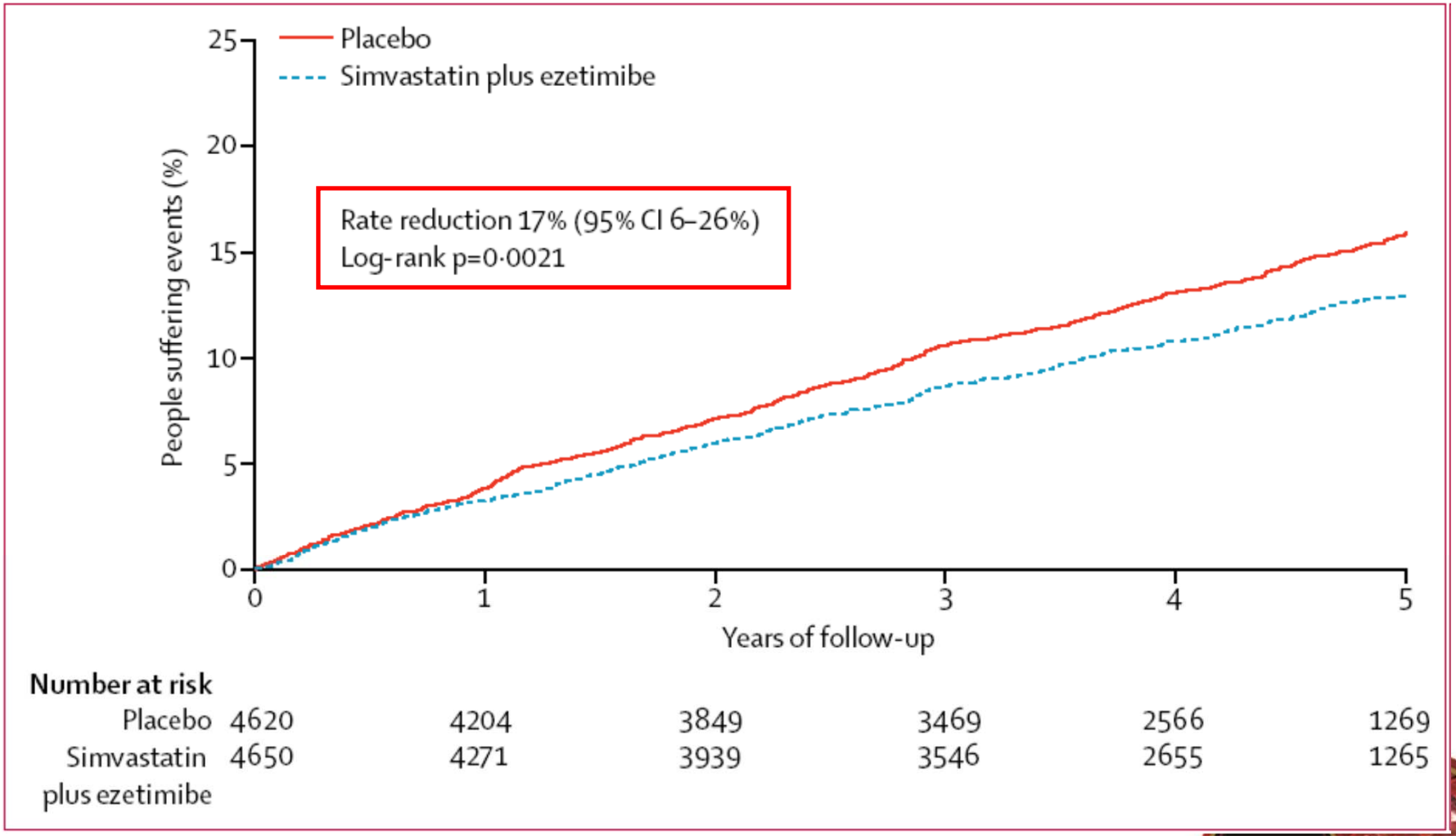
Data are n (%), mean (SD), or median (IQR). MDRD=Modified Diet in Renal Disease.[17] GFR=glomerular filtration rate. *Variables updated at 1 year for patients originally allocated simvastatin only who were rerandomised to simvastatin plus ezetimibe or placebo. †Five versus five patients received a transplant before rerandomisation. ‡Percentages exclude participants for whom data were not available for that category. §For patients not on dialysis.

Table 1: **Baseline demographic features and laboratory measurements by treatment allocation**



1. Colin Baigent et al. *Lancet* 2011 Published Online June 9, 2011 DOI:10.1016/S0140-6736(11)60739-3

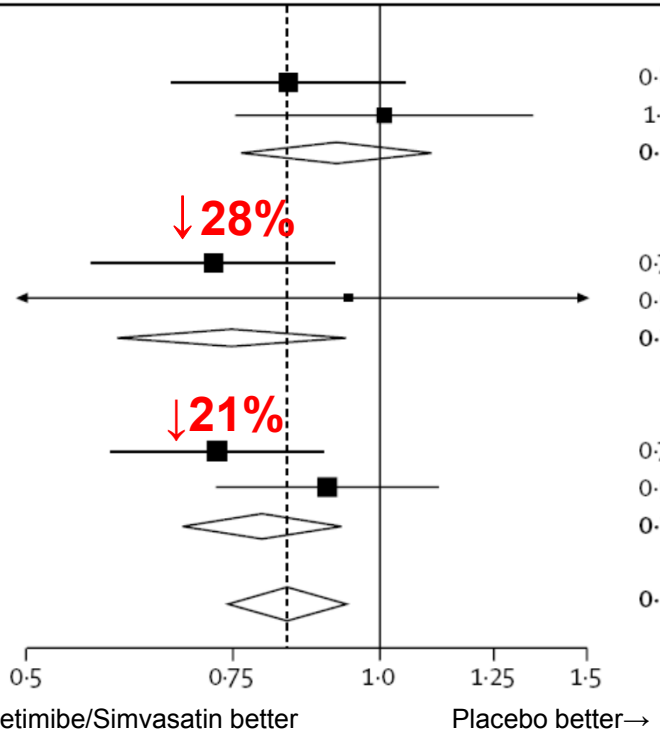
Major Atherosclerotic Events composite endpoint:
coronary death, non-fatal MI, non-hemorrhagic stroke and any revascularization

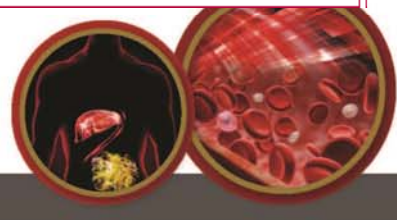


Colin Baigent et al. *Lancet* 2011 Published Online June 9, 2011 DOI:10.1016/S0140-6736(11)60739-3

Major atherosclerotic event subdivided type

	Simvastatin plus ezetimibe (n=4650)	Placebo (n=4620)	Risk ratio (95% CI)	p value
Coronary events				
Non-fatal MI	134 (2·9%)	159 (3·4%)	0·84 (0·66–1·05)	0·12
CHD death	91 (2·0%)	90 (1·9%)	1·01 (0·75–1·35)	0·95
Subtotal: any major coronary event	**213 (4·6%)**	**230 (5·0%)**	**0·92 (0·76–1·11)**	**0·37**
Non-haemorrhagic stroke				
Ischaemic	114 (2·5%)	157 (3·4%)	0·72 (0·57–0·92)	0·0073
Unknown type	18 (0·4%)	19 (0·4%)	0·94 (0·49–1·79)	0·85
Subtotal: any non-haemorrhagic	**131 (2·8%)**	**174 (3·8%)**	**0·75 (0·60–0·94)**	**0·01**
Revascularisation procedures				
Coronary	149 (3·2%)	203 (4·4%)	0·73 (0·59–0·90)	0·0027
Non-coronary	154 (3·3%)	169 (3·7%)	0·90 (0·73–1·12)	0·36
Subtotal: any revascularisation	**284 (6·1%)**	**352 (7·6%)**	**0·79 (0·68–0·93)**	**0·0036**
Total: any major atherosclerotic event	**526 (11·3%)**	**619 (13·4%)**	**0·83 (0·74–0·94)**	**0·0021**

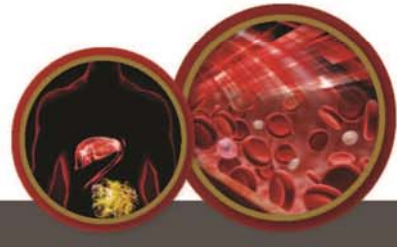




1. Colin Baigent et al. *Lancet* 2011 Published Online June 9, 2011 DOI:10.1016/S0140-6736(11)60739-3

SHARP: Safety

	Simv/Eze (n=4650)	Placebo (n=4620)
Myopathy		
CK >10 x but ≤40 x ULN	17 (0.4%)	16 (0.3%)
CK >40 x ULN	4 (0.1%)	5 (0.1%)
Hepatitis	21 (0.5%)	18 (0.4%)
Persistently elevated ALT/AST >3x ULN	30 (0.6%)	26 (0.6%)
Complications of gallstones	85 (1.8%)	76 (1.6%)
Other hospitalization for gallstones	21 (0.5%)	30 (0.6%)
Pancreatitis without gallstones	12 (0.3%)	27 (0.6%)

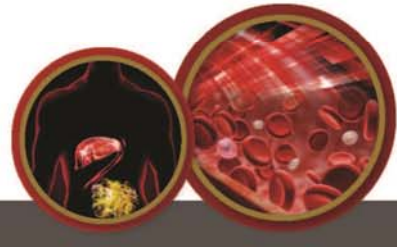


1. Colin Baigent et al. *Lancet* 2011 Published Online June 9, 2011 DOI:10.1016/S0140-6736(11)60739-3

Additional benefit of Ezetimibe beyond LDL-C

1. Better option for minimizing concerns of increasing DM

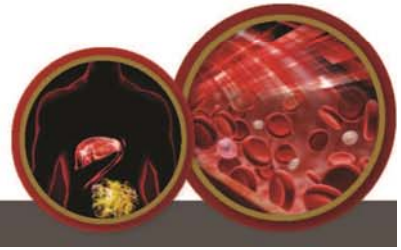
2. Improvement of endothelial dysfunction



FDA Expands Advice on **STATIN RISKS**

- Altoprev (lovastatin extended-release)
- Crestor (rosuvastatin)
- Lescol (fluvastatin)
- Lipitor (atorvastatin)
- Livalo (pitavastatin)
- Mevacor (lovastatin)
- Pravachol (pravastatin)
- Zocor (simvastatin).
- Advicor (lovastatin/niacin extended-release)
- Simcor (simvastatin/niacin extended-release)
- Vytorin (simvastatin/ezetimibe).

- A small increased risk of raised blood sugar levels and the developm ent of Type 2 diabetes have been reported with the use of statins.
- "Clearly we think that the heart benefit of statins outweighs this small increased risk," says Egan.
- But what this means for patients taking statins and the health care professionals prescribing them is that blood-sugar levels may need to be assessed after instituting statin therapy," she says.



www.fda.gov/ForConsumers/ConsumerUpdates/ucm293330.htm

Higher doses of statins are associated with new-onset Diabetes

DM

CLINICAL REVIEW

CLINICIAN'S CORNER

Risk of Incident Diabetes With Intensive-Dose Compared With Moderate-Dose Statin Therapy

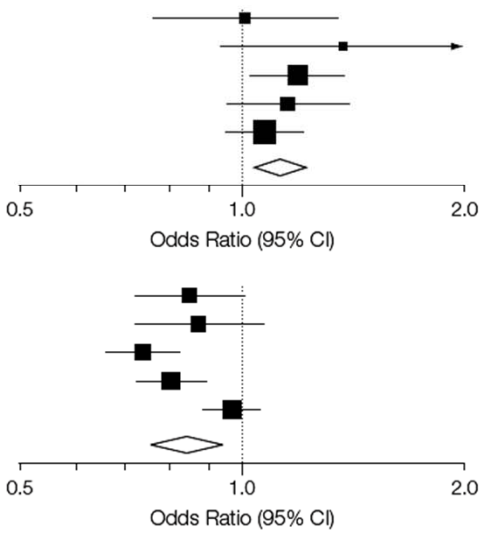
A Meta-analysis

In a pooled analysis, intensive-dose statin therapy was associated with an increased risk of new-onset diabetes compared with moderate-dose statin therapy.

- As compared with moderate-dose statin, the number needed to harm per year for intensive-dose statin was **498 for new-onset DM** while the number needed to treat per year for intensive-dose statin was **155 for C-V events.**

Figure 2. Meta-analysis of New-Onset Diabetes and First Major Cardiovascular Events in 5 Large Trials Comparing Intensive-Dose to Moderate-Dose Statin Therapy

	Cases/Total, No. (%)		
	Intensive Dose	Moderate Dose	OR (95% CI)
Incident Diabetes			
PROVE IT–TIMI 22,[18] 2004	101/1707 (5.9)	99/1688 (5.9)	1.01 (0.76-1.34)
A to Z,[17] 2004	65/1768 (3.7)	47/1736 (2.7)	1.37 (0.94-2.01)
TNT,[15] 2005	418/3798 (11.0)	358/3797 (9.4)	1.19 (1.02-1.38)
IDEAL,[16] 2005	240/3737 (6.4)	209/3724 (5.6)	1.15 (0.95-1.40)
SEARCH,[5] 2010	625/5398 (11.6)	587/5399 (10.9)	1.07 (0.95-1.21)
Pooled odds ratio	1449/16408 (8.8)	1300/16344 (8.0)	1.12 (1.04-1.22)
Heterogeneity: $I^2=0\%$; $P=.60$			
Incident CVD			
PROVE IT–TIMI 22,[18] 2004	315/1707 (18.4)	355/1688 (21.0)	0.85 (0.72-1.01)
A to Z,[17] 2004	212/1768 (12.0)	234/1736 (13.5)	0.87 (0.72-1.07)
TNT,[15] 2005	647/3798 (17.0)	830/3797 (21.9)	0.73 (0.65-0.82)
IDEAL,[16] 2005	776/3737 (20.8)	917/3724 (24.6)	0.80 (0.72-0.89)
SEARCH,[5] 2010	1184/5398 (21.9)	1214/5399 (22.5)	0.97 (0.88-1.06)
Pooled odds ratio	3134/16408 (19.1)	3550/16344 (21.7)	0.84 (0.75-0.94)
Heterogeneity: $I^2=74\%$; $P=.004$			



Preiss D, JAMA. 2011;305:2556-2564

Data marker size indicates relative weight of the studies; OR, odds ratio; and CI, confidence interval.

DM

Ezetimibe might be good option for reducing risk of high dose statin on insulin resistance

In animal data

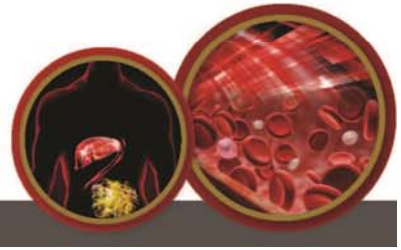
- Ezetimibe might decrease hepatic insulin resistance by reducing hepatic cholesterol

Am J Physiol Endocrinol Metab (2009) 297: E1030–E1038

In Human data

- Ezetimibe, inhibiting molecules of NPC1L1 improved HOMA-IR compared with baseline in NAFLD patients

J Gastroenterol (2011) 46:101–107



The mechanism of improved HOMA-IR might be related with inhibition of hepatic NPC1L1 by Ezetimibe

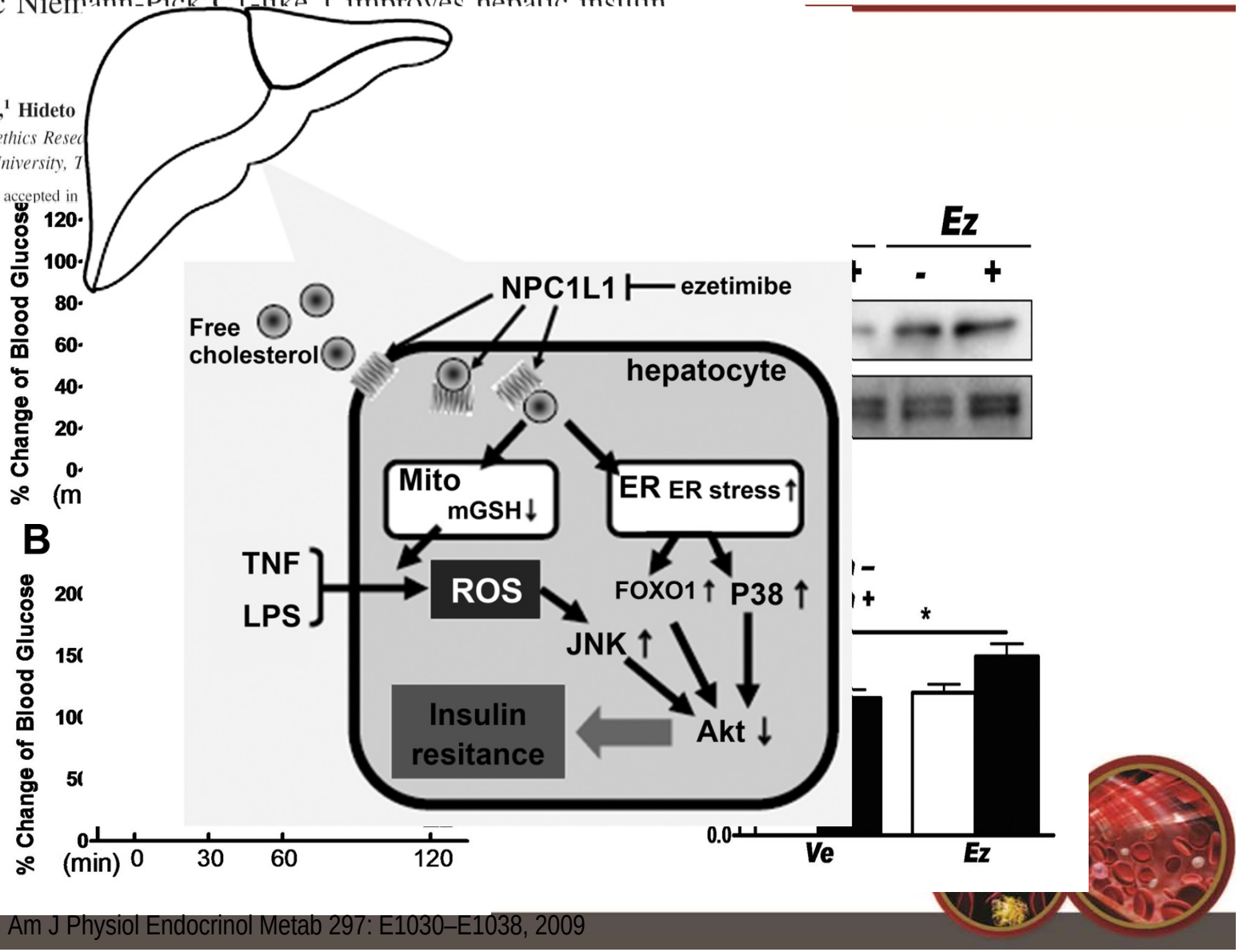
DM

Am J Physiol Endocrinol Metab 297: E1030–E1038, 2009.
First published August 4, 2009; doi:10.1152/ajpendo.00343.2009.

Inhibition of hepatic Niemann-Pick C1-like 1 improves hepatic insulin resistance

Mitsunori Nomura,[1] Hideto
[1]*Life Science and Bioethics Resea*
Medical and Dental University, T

Submitted 26 May 2009; accepted in



Ezetimibe, inhibiting molecules of NPC1L1 improved HOMA-IR compared with baseline in NAFLD patients

DM

J Gastroenterol (2011) 46:101–107
DOI 10.1007/s00535-010-0291-8

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Efficacy of long-term ezetimibe therapy in patients with nonalcoholic fatty liver disease

Hyohun Park · Toshihide Shima · Kanji Yamaguchi · Hironori Mitsuyoshi · Masahito Minami · Kohichiroh Yasui · Yoshito Itoh · Toshikazu Yoshikawa · Michiaki Fukui · Goji Hasegawa · Naoto Nakamura · Mitsuhiro Ohta · Hiroshi Obayashi · Takeshi Okanoue

Received: 8 May 2010 / Accepted: 6 July 2010 / Published online: 24 July 2010

Table 2 Clinical and laboratory parameters of baseline and after ezetimibe treatment

	Baseline	At 12 months	At 24 months
Body mass index (kg/m^2)	26.9 ± 3.3	26.0 ± 3.5	26.1 ± 3.2
Waist circumference (cm)	92.3 ± 5.7	90.5 ± 5.8	90.9 ± 6.0
Visceral fat area (cm^2)	155.9 ± 38.9	150.8 ± 33.6	146.5 ± 34.8*
Subcutaneous fat area (cm^2)	170.9 ± 51.3	166.4 ± 41.5	167.1 ± 41.5
HbA1c (%)	6.3 ± 0.8	6.5 ± 0.7	6.4 ± 0.9
Fasting glucose (mg/dl)	113 ± 24	112 ± 27	112 ± 28
Fasting insulin (μU/ml)	10.9 ± 5.6	9.2 ± 5.8*	9.4 ± 5.1*
HOMA-R	3.04 ± 1.17	2.60 ± 1.33*	2.62 ± 1.24*
Aspartate aminotransferase (IU/l)	40 ± 22	36 ± 16	36 ± 16
Alanine aminotransferase (IU/l)	62 ± 25	48 ± 25**	49 ± 23**
Triglycerides (mg/dl)	168 ± 94	136 ± 90*	138 ± 88*
Total cholesterol (mg/dl)	228 ± 44	193 ± 36**	194 ± 36**
HDL cholesterol (mg/dl)	49 ± 13	53 ± 15	52 ± 14
LDL cholesterol (mg/dl)	136 ± 33	117 ± 34*	114 ± 31*
Oxidative LDL (U/ml)	14.1 ± 6.9	13.6 ± 7.1	11.8 ± 5.5*
Electronegative charge modified-LDL (ecd)	6.4 ± 3.5	3.5 ± 3.6$^{\#}$	3.4 ± 3.2$^{\#}$
Type IV collagen 7S (ng/dl)	5.1 ± 2.9	4.7 ± 2.5	4.7 ± 2.5
Adiponectin (μg/ml)	5.8 ± 3.1	6.1 ± 3.4	6.1 ± 3.4
Leptin (ng/l)	4.0 ± 2.9	3.8 ± 3.1	3.8 ± 3.1
Resistin (ng/ml)	7.7 ± 3.1	7.4 ± 3.4	7.4 ± 3.4
High-sensitivity C-reactive protein (ng/ml)	883 ± 408	677 ± 392*	685 ± 377*

Data are the mean ± SD

ecd electronegative charge density

* $P < 0.05$, ** $P < 0.01$, and $^{\#}$ $P < 0.005$ versus baseline

Baseline characteristics

Hyperlipidemia, obesty, pre-DM, NAS >5

J Gastroenterol (2011) 46:101–107

Ezetimibe significantly diminished postprandial lipemia in obese patients

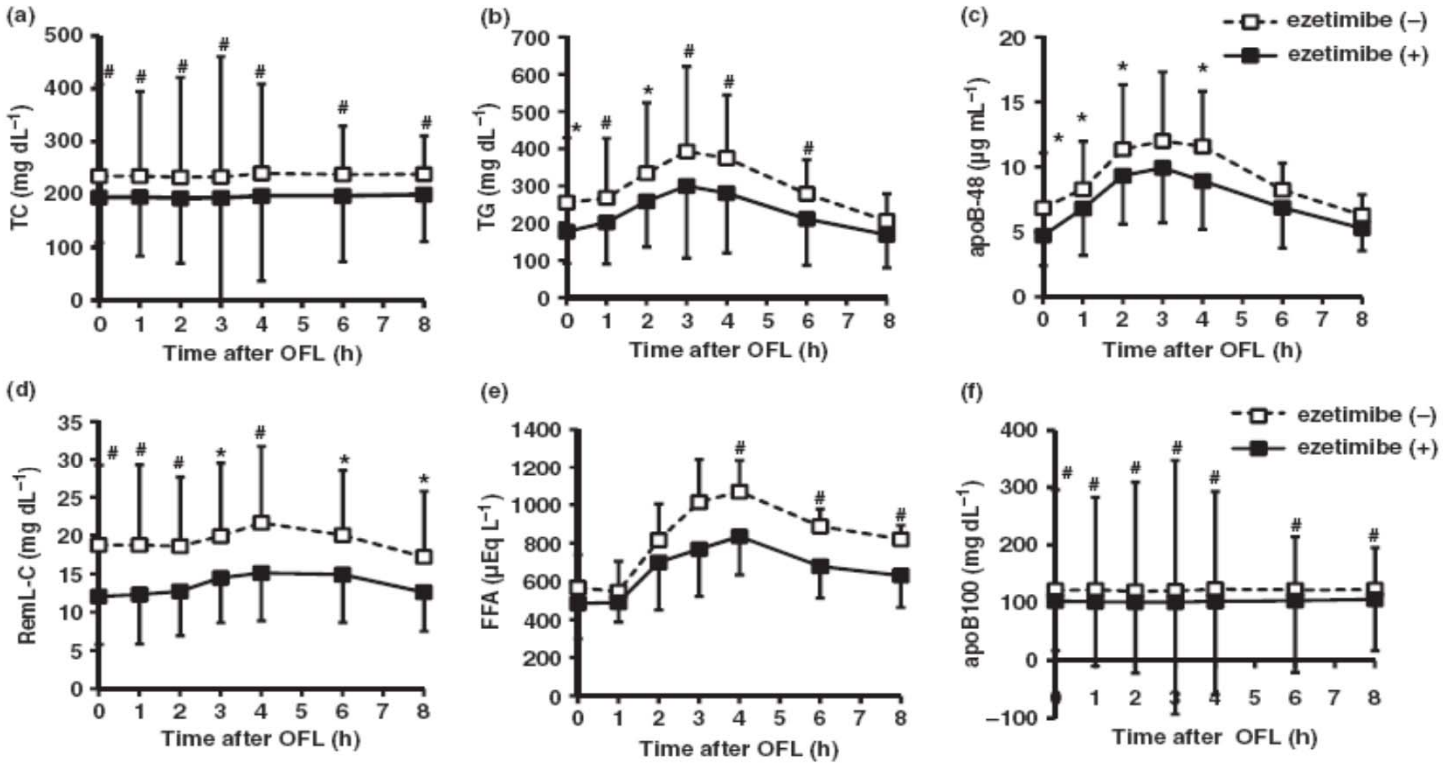
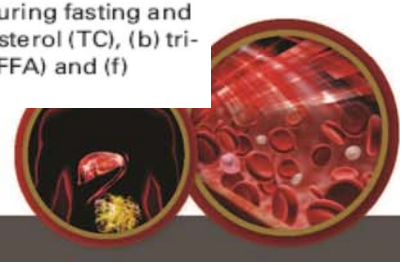


Figure 2 Oral fat loading (OFL) test before and after administration of ezetimibe. Patients with type IIb hyperlipidaemia (n = 10, two females and eight males) were given OFTT cream (containing 35% fat without sugar, 30 g fat m^{-2} body surface area) after overnight fasting before (open squares) and after (closed squares) administration of ezetimibe. Blood samples were drawn during fasting and 1, 2, 3, 4, 6 and 8 h after OFL, and serum and plasma were separated immediately. Concentrations of (a) total cholesterol (TC), (b) triglyceride (TG), (c) apolipoprotein B-48(apoB-48), (d) remnant lipoprotein cholesterol (RemL-C), (e) free fatty acids (FFA) and (f) apoB-100 were measured as described in Materials and methods. *P < 0·05, #P < 0·01.

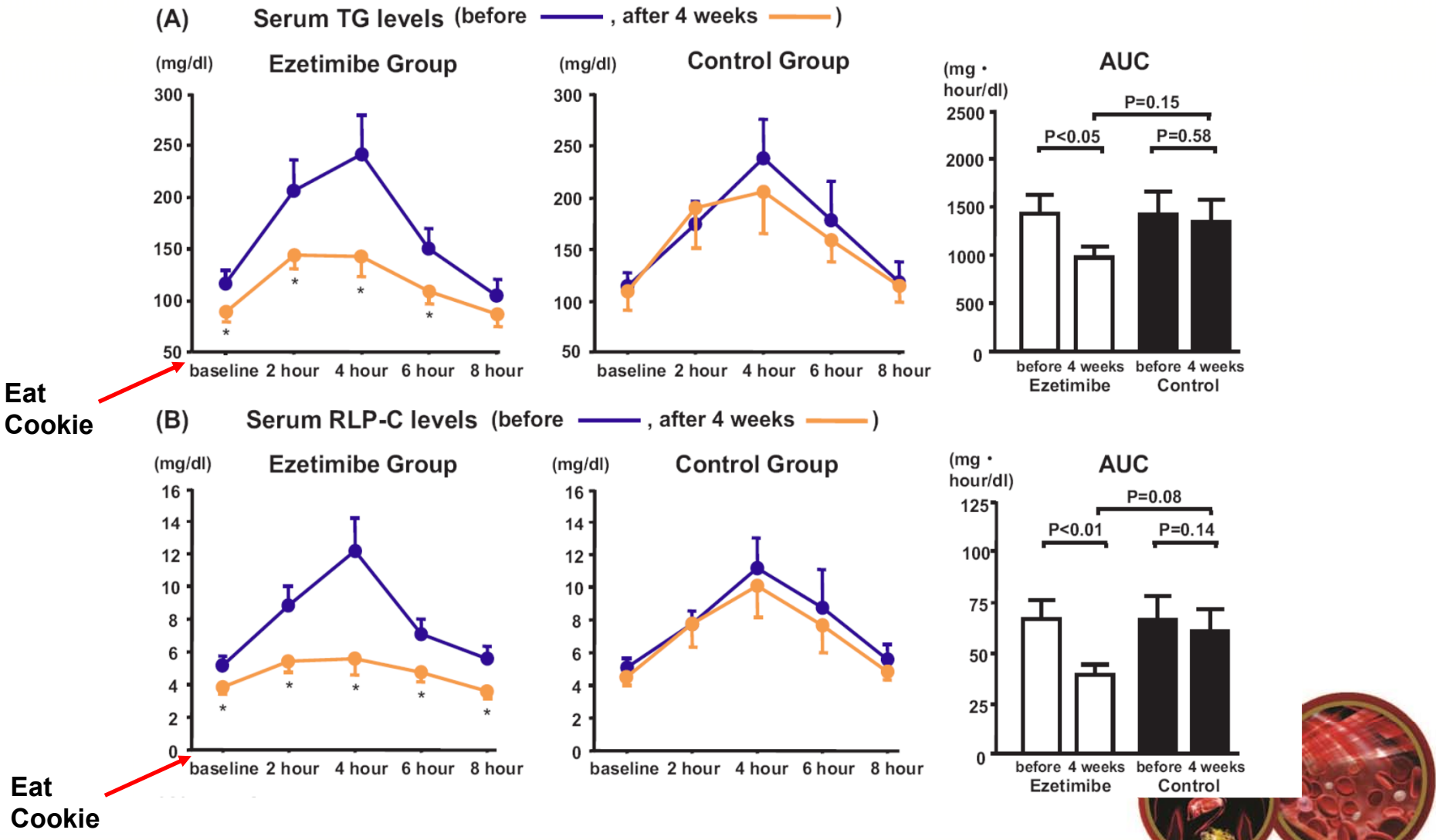


D. Masuda, et al. *European J. of Clinical Investgation* 2009;39(8):689-698

Yunoki Study **Ezetimibe 10mg vs. control**

Postprandial TG

Serum TG levels were reduced by Ezetimibe but did not different between Ezetimibe group and control group in non-fasting state



Kei Yunoki et al. *Atherosclerosis* 2011

Ezetimibe/statin affect on postprandial TG and lipoproteins

Prospective, randomized, double blind, crossover trial. Male obese metabolic syndrome patients (*n* = 19) were treated with simvastatin 80 mg and simvastatin/ezetimibe 10 mg/10 mg for 6 weeks.

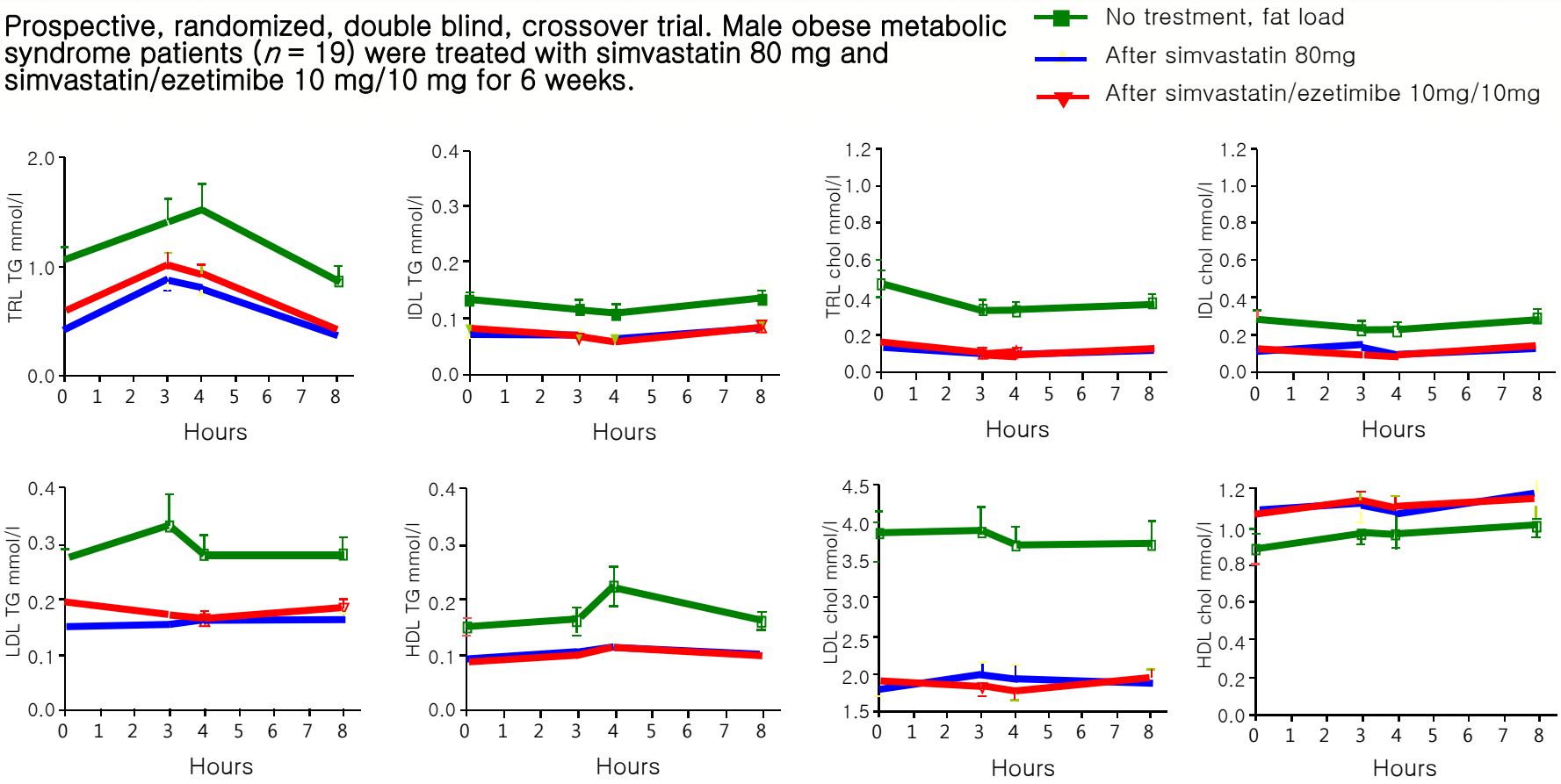
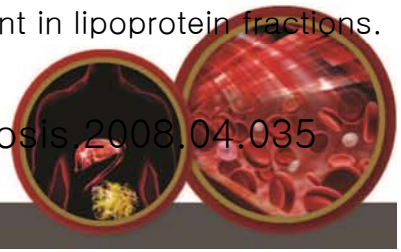


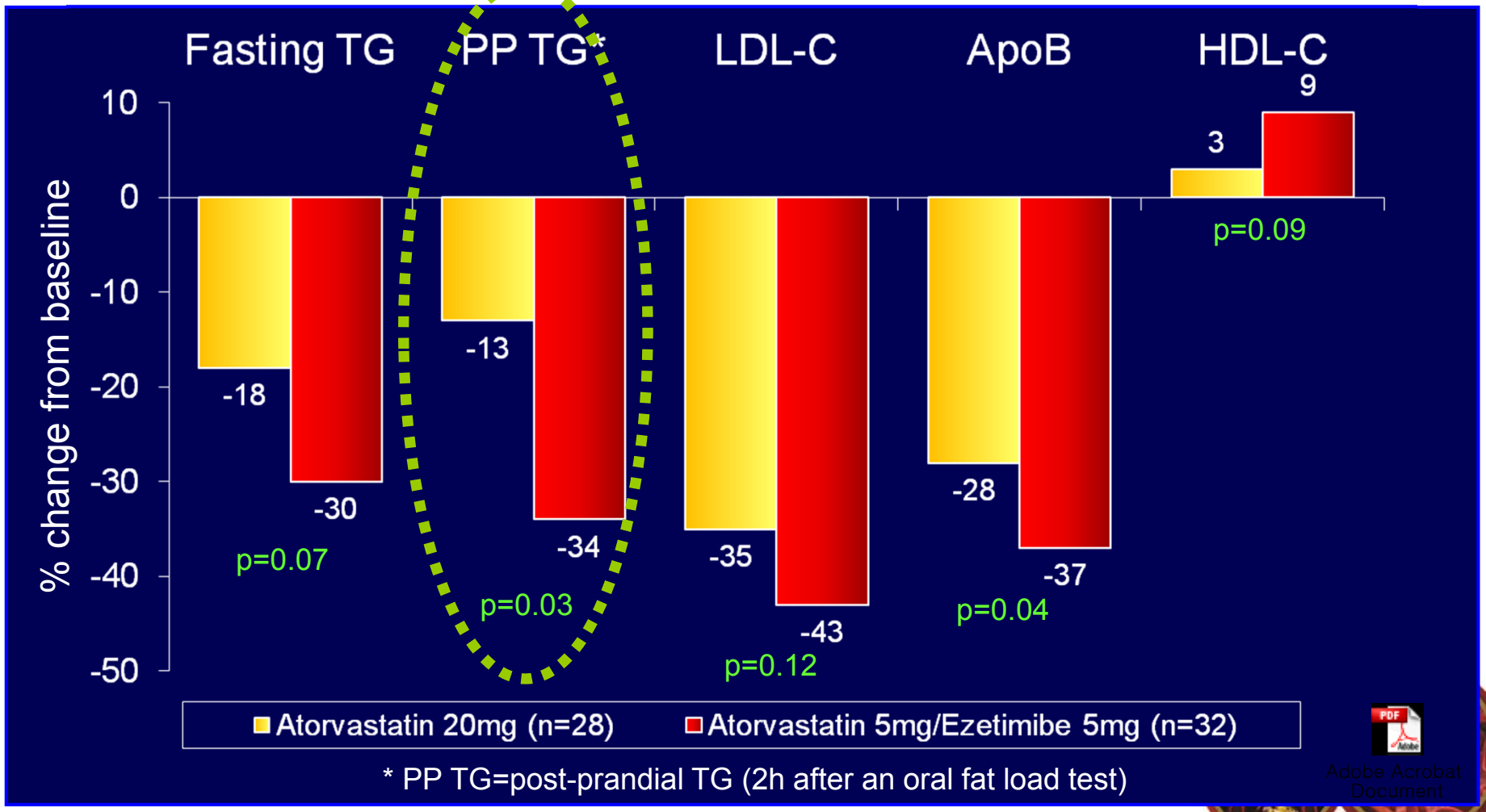
Fig. 1. Postprandial triglyceride content in lipoprotein fractions. Fig. 2. Postprandial cholesterol content in lipoprotein fractions.

Hajer. *Atherosclerosis*. 2008, doi:10.1016/j.atherosclerosis.2008.04.035



Ezetimibe combination therapy is reduced more postprandial TG than mono-statin after comparable LDL-C lowering.

- Randomized, open-label study, 8 weeks of treatment;
- 60 patients with LDL-C > 130 mg/dL and TG 150-499 mg/dL



Take home messages

- For better goal achievement, VYTORIN 10/20mg safely reduced 50% LDL-C from baseline safely at week 6
- VYTORIN achieved non-HDL-C & apo B target goals as well as LDL-C better than statin monotherapy
- VYTORIN 10/20mg reduced incidence of major atherosclerotic events in high risk patients