Clinical Implications from Recent Lipid Guideline for High-risk Patients

Chang-Wook NAM, MD, PhD

Keimyung University Dongsan Medical Center

- **I have nothing to disclosure for this presentation.**
- **The view expressed herein represents those of the speaker and not necessarily those of the MSD Korea.**

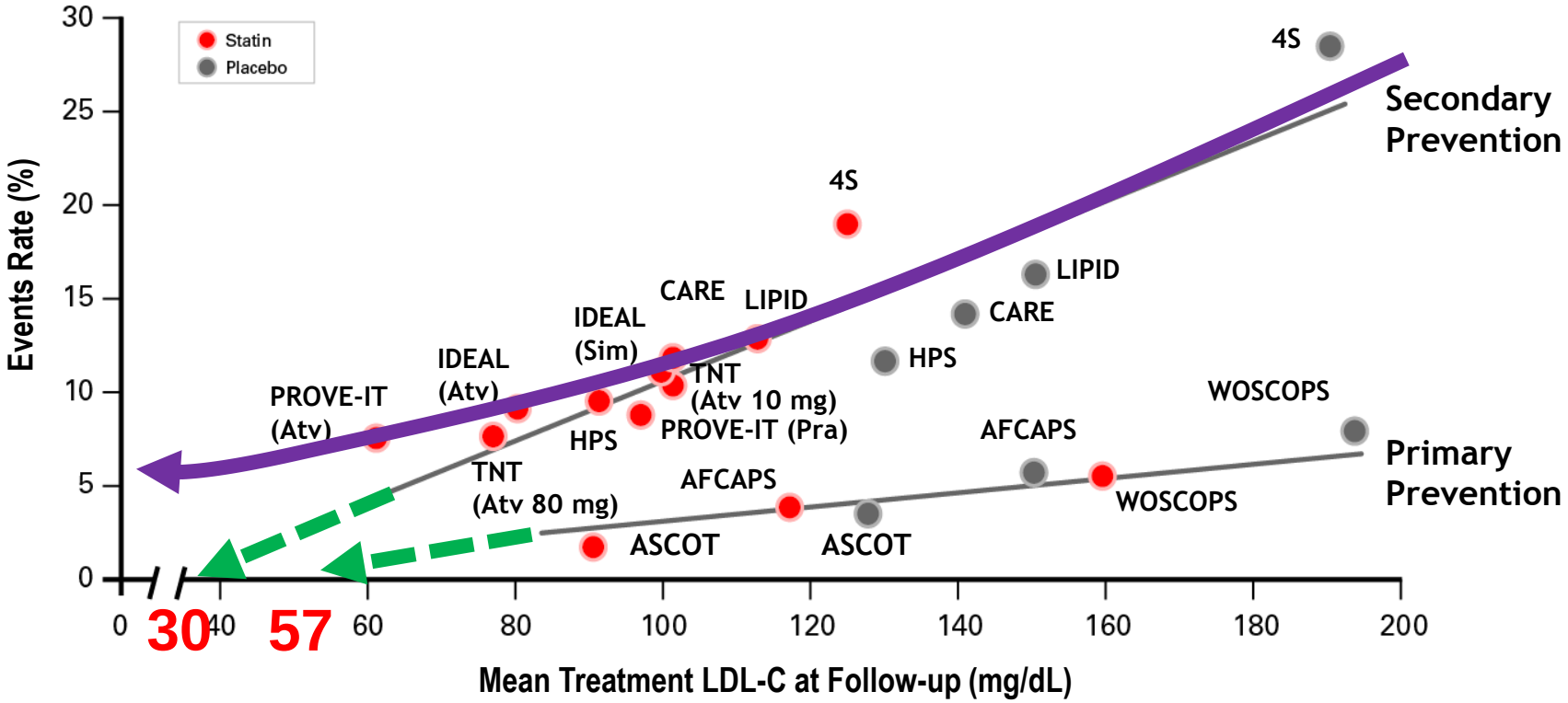
Agenda

1. **Benefits of combination therapy aligned with recent update guidelines**
   - Recent update guideline and Implications
   - Benefits of ezetimibe/statin combination therapy for LDL-C reduction

2. **New considering point of view for preventing Atherosclerosis**
   - CRP
   - Chylomicron and ApoB in atherosclerosis
   - Further clinical outcomes of combination therapy

1. **Benefits of combination therapy aligned with recent update guidelines**
   - Recent update guideline and Implications
   - Benefits of ezetimibe/statin combination therapy for LDL-C reduction

Relationship Between LDL-C on Treatment and Clinical Event Rates in Major Trial

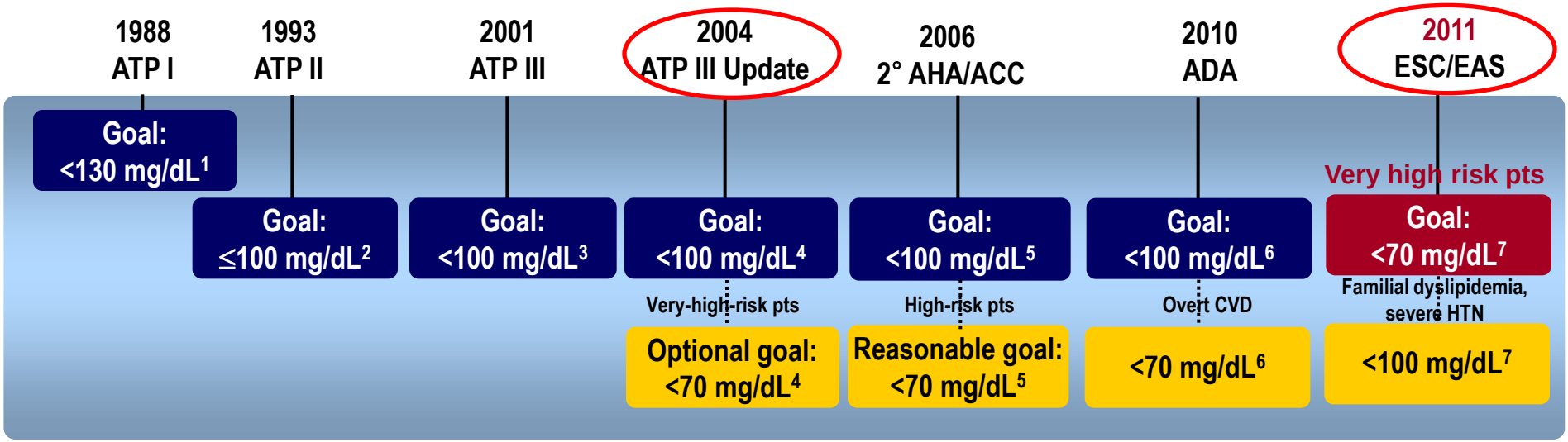


Atv = atorvastatin; Pra = pravastatin; Sim = simvastatin; PROVE-IT = Pravastatin or AtorVastatin Evaluation and Infection Therapy; IDEAL = Incremental Decrease in Endpoints through Aggressive Lipid Lowering; ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; AFCAPS = Air Force Coronary Atherosclerosis Prevention Study; WOSCOPS = West of Scotland Coronary Prevention Study

1. Rosenson RS. *Expert Opin Emerg Drugs*. 2004;9:269–279. 2. LaRosa JC, et al. *N Engl J Med*. 2005;352:1425–1435.

LDL-C Goals for High-Risk Patients Have Become More Intensive

- As part of therapeutic lifestyle changes, including diet, LDL-C treatment goals for high-risk patients have been lowered over time



Definition of high-risk / highest-risk or very high patient:

- ATP I: definite CHD or 2 other CHD risk factors[1]
- ATP II: existing CHD or other atherosclerotic disease[2]
- ATP III and the 2004 update: CHD or CHD risk equivalents[3,4]
- 2° AHA/ACC 2006: established coronary and other atherosclerotic disease[5]
- ADA 2010: overt CVD[6]
- ESC/EAS 2011: CVD (MI, ACS, revascularization), ischemic stroke, type 2 DM, moderate to severe CKD, or SCORE ≥10%[7]

CHD: coronary heart disease, CVD: cardiovascular disease, MI: myocardial infarction, ACS: acute coronary syndrome, CKD: chronic kidney disease, HTN: hypertension

1. NCEP ATP I. *Arch Intern Med*. 1988;148:36–69; **2.** NCEP ATP II. *JAMA*. 1993;269:3015–3023; **3.** NCEP ATP III. *JAMA*. 2001;285:2486–2497; **4.** Grundy SM et al. *Circulation*. 2004;110:227–239; **5.** Smith SC Jr et al. *Circulation*. 2006;113:2363–2372; **6.** ADA. *Diabetes Care*. 2010;33(suppl 1):S11–S61. 7. Reiner Z. et al. *European Heart Journal* 2011;32:1769-1818

Very high risk in updated ATPIII

- Established CVD plus
  - ✓ Multiple major risk factors (especially DM)
  - ✓ Severe and poorly controlled risk factors (especially continued smoking)
  - ✓ Multiple risk factors of MetS (especially Tg≥200, Non-HDL-c ≥130, and HDL-c <40)
  - ✓ Acute coronary syndrome

→ LDL-c goal <70mg/dL

- In high risk persons (10yr CHD risk >20%), LDL-c goal <100 mg/dL
  - ✓ **if LDL-c ≥100mg/dL, LDL-c lowering drug is indicated**
  - ✓ if LDL-c <100mg/dL, LDL-c lowering drug is an option
  - ✓ **When TG ≥200mg/dL, non-HDL-c is secondary target of therapy, with a goal 30mg/dL higher than LDL-c goal**

When LDL-c lowering drugs are used,
LDL-c levels should be reduced at least 30-40%

Current status of NCEP ATP IV (As of Feb.13)

The following table reflects the status of each report and progress through the remaining stages of the review process before the guidelines are released.

	Draft Finished	Federal Review	Expert Review	Advisory Council	Public Comment	HHS Clearance	Release
Lifestyle	Completed	Completed	Completed	In Progress			
Risk Assessment	Completed	Completed	Completed	In Progress			
Cholesterol	Completed	Completed	Completed	In Progress			
Blood Pressure	In Progress						
Obesity	In Progress						

- **Draft Completed**: Expert panelists have completed a full draft of the systematic review and recommendations.
- **Federal Review**: Federal agency representatives of the NHLBI's National Program to Reduce Cardiovascular Risk (NPRCR) coordinating committee provide review and comment.
- **Expert Review**: External peer reviewers with expertise in the relevant risk factors provide review and comment.
- **Advisory Council**: The National Heart, Lung, and Blood Advisory Council provides review and comment and recommends approval.
- **Public Comment**: The draft is offered publicly for review and comment.
- **HHS Clearance**: The U.S. Department of Health and Human Services provides editorial review, comment, and approval.

ESC/EAS 2011 Guidelines : Very High– and High CV Risk Level Classification[1]

- **Very High Risk includes subjects with any of the following:**

✓ Documented CVD, previous MI, ACS, coronary revascularization, other revascularization procedure, ischemic stroke, PAD

✓ Type 2 diabetes or type 1 diabetes with target organ damage (such as microalbuminuria)

✓ Moderate to severe CKD (GFR <60 mL/min/1.73 m^2)

✓ A calculated 10-year risk SCORE ≥10%

- **High Risk includes subjects with any of the following:**

✓ Markedly elevated single-risk factors (eg, familial dyslipidemias or severe hypertension)

✓ A calculated 10-year risk SCORE ≥5% and <10% for fatal CVD

Patients with VERY HIGH or HIGH total CV risk need active management of all risk factors.

For all other people, the use of a risk estimation system such as SCORE is recommended to estimated total CV risk.

CVD = cardiovascular disease; MI = myocardial infarction; ACS = acute coronary syndrome; PAD = peripheral artery disease; CKD = chronic kidney disease; GFR = glomerular filtration rate; SCORE = Systematic Coronary Risk Estimation.

1. Reiner Z et al. Eur Heart J. 2011;32:1769–1818.

ESC/EAS 2011 Guidelines: Lipid Targets[1]

More aggressive target for high-risk patients

	LDL-C	Non–HDL-C	Apo B
	Primary Target	**Secondary Targets**	
Very high risk Documented **CVD**, previous **MI**, ACS, coronary or other arterial revascularization, ischemic **stroke**, PAD, **type 2 diabetes** or type 1 diabetes with target organ damage, **moderate to severe CKD**, or a calculated 10 year risk SCORE ≥10%	<1.8 mmol/L **(~70 mg/dL)** And/or **≥50% reduction from baseline**	<2.6 mmol/L (~100 mg/dL)	<80 mg/dL
High risk Markedly elevated single risk factors such as familial dyslipidemia and **severe hypertension**, or a calculated SCORE ≥5% and <10% for 10 year risk of fatal CVD	<2.5 mmol/L (~100 mg/dL)	<3.3 mmol/L (~130 mg/dL)	<100 mg/dL
Moderate risk SCORE is ≥1% and <5% at 10 years	<3.0 mmol/L (~115 mg/dL)	<3.8 mmol/L (~145 mg/dL)	Not defined

ESC/EAS = European Society of Cardiology/European Atherosclerosis Society; apo = apolipoprotein; CVD = cardiovascular disease; MI = myocardial infarction; ACS = acute coronary syndromes; PAD = peripheral artery disease; CKD = chronic kidney disease; SCORE = Systematic Coronary Risk Estimation.

1. Reiner Z et al. Eur Heart J. 2011;32:1769–1818.

ESC/EAS 2011 Guidelines:
Management of Dyslipidemia in Acute Coronary Syndrome[1]

- High dose statin therapy be initiated during the first 1–4 days of hospitalization for the index ACS; if basal LDL-C values are known, the dose should aim at reaching the LDL-C target of <1.8 mmol/L (less than ~70 mg/dL).
- The use of lower intensity statin therapy should be considered in patients at increased risk of side effects with high doses of statin (e.g. the elderly, hepatic impairment, renal impairment, or potential for interaction with essential concomitant therapy).
- Lipids should be re-evaluated 4–6 weeks after the ACS to determine whether target levels have been reached and regarding safety issues; the statin dose can then be adapted accordingly.

ESC/EAS = European Society of Cardiology/European Atherosclerosis Society.

1. Reiner Z et al. Eur Heart J. 2011;32:1769–1818.

ESC/EAS 2011 Guidelines:

Management of Acute myocardial infarction with ST-segment elevation[1]

- **Statins should be given to all patients with acute myocardial infarction, irrespective of cholesterol concentration.**
- **The use of lower-intensity statin therapy should be considered in patients at increased risk of side-effects from statins.**
  - ✓ e.g. the elderly, patients with hepatic or renal impairment, with previous side-effects of statins or the potential for interaction with essential concomitant therapy
- **In patients known to be intolerant of any dose of statin, treatment with ezetimibe should be considered**

1. Steg European Heart Journal 2012;33 2569–2619

ESC/EAS 2011 Guidelines:
Management of Dyslipidemia in the Elderly[1]

- Statins are recommended for elderly patients with established CVD in the same way as for younger patients [Class I, Level B].
- Since elderly patients often have comorbidities and have altered pharmacokinetics, it is recommended to start lipid-lowering medication at a low dose and then titrate with caution to target lipid levels, which are the same as in younger subjects [Class I, Level C].
- Statin therapy may be considered in elderly subjects without CVD, particularly in the presence of at least 1 other CV risk factor aside from age [Class IIb, Level B].

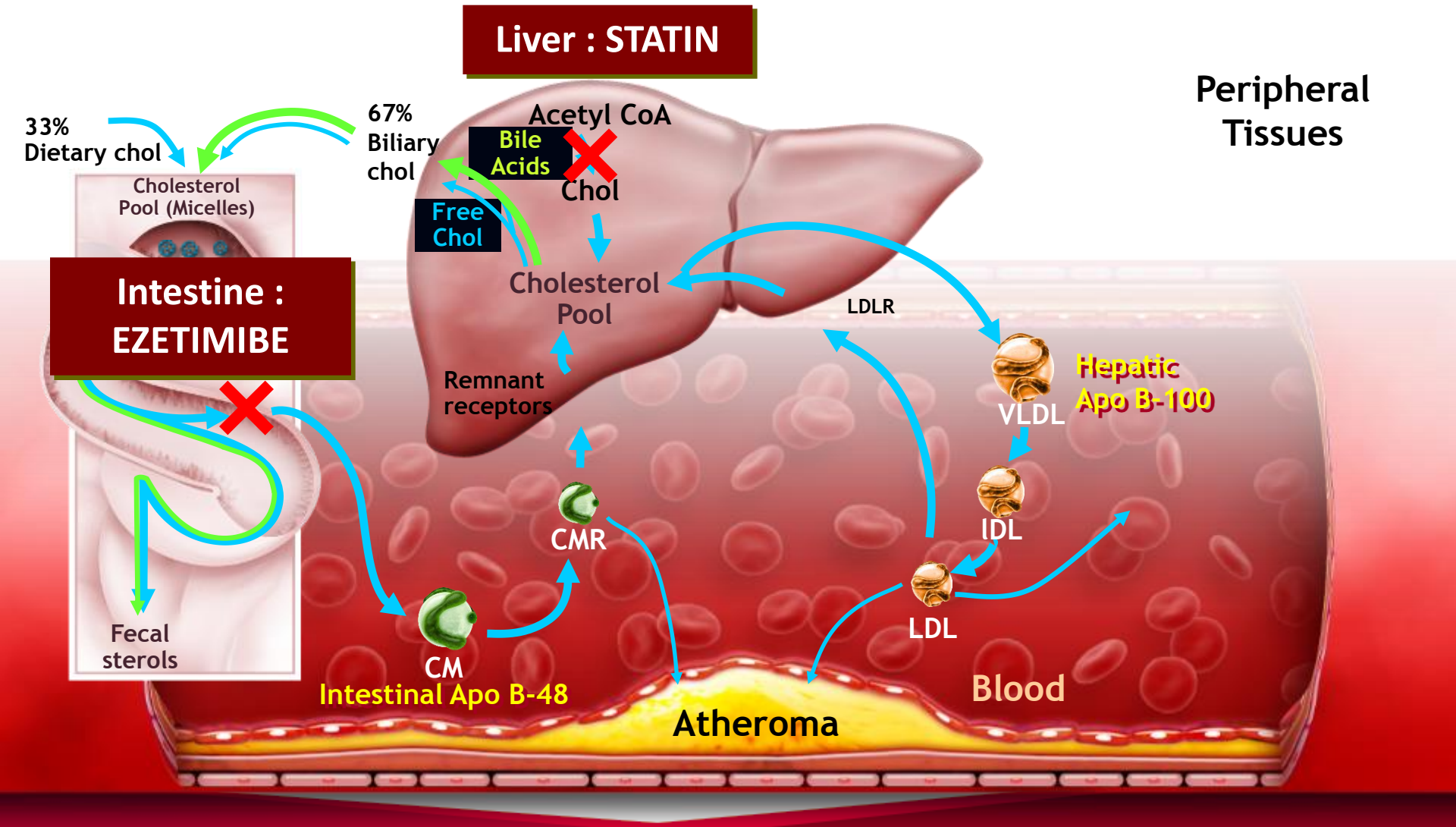
Class: Class of recommendation, Level: Level of evidence, CV: cardiovascular

ESC/EAS = European Society of Cardiology/European Atherosclerosis Society.

1. Reiner Z et al. *Eur Heart J.* 2011;32:1769–1818.

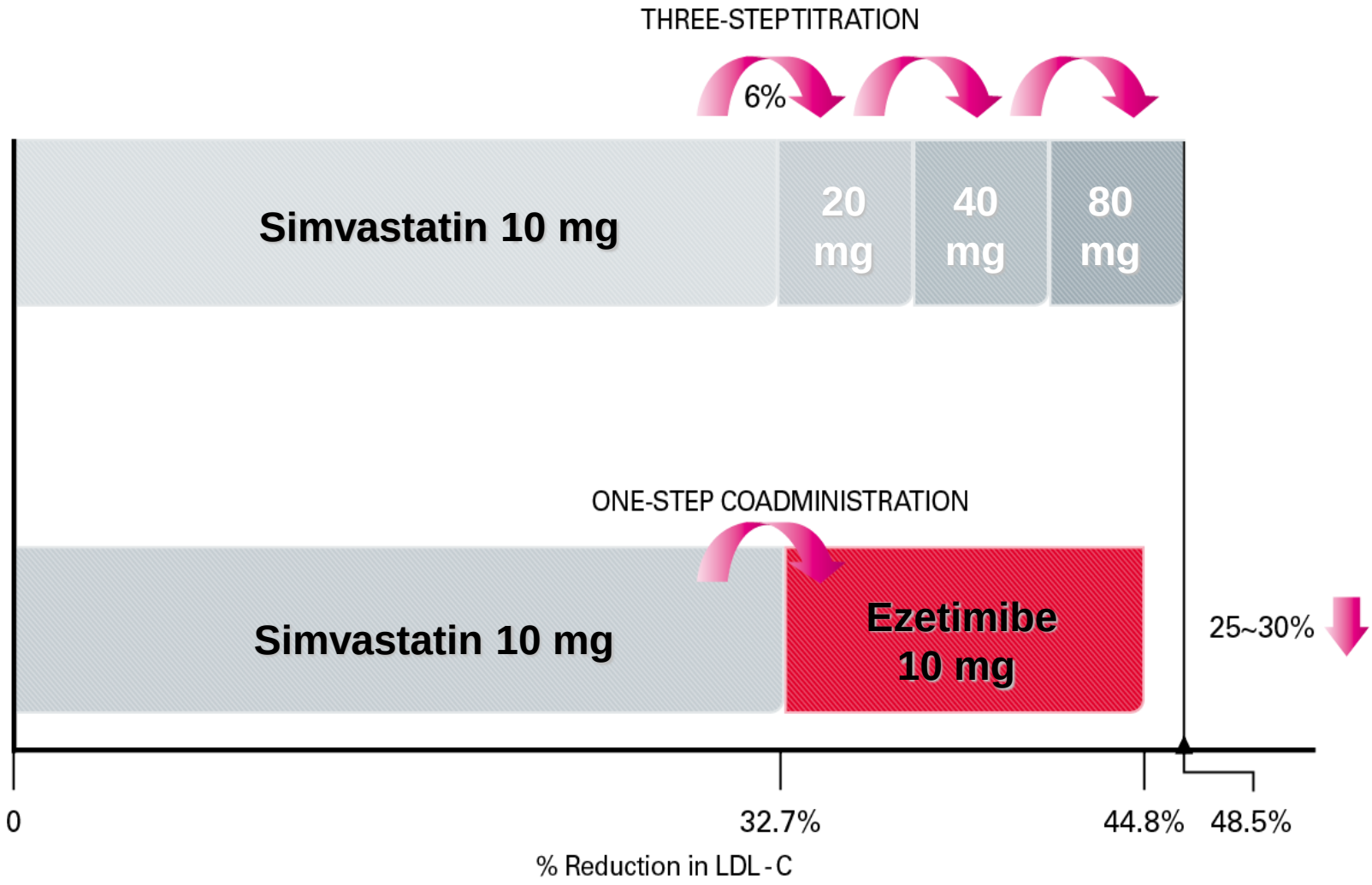
VYTORIN (ezetimibe/simvastatin):

Dual Action in Cholesterol Metabolism



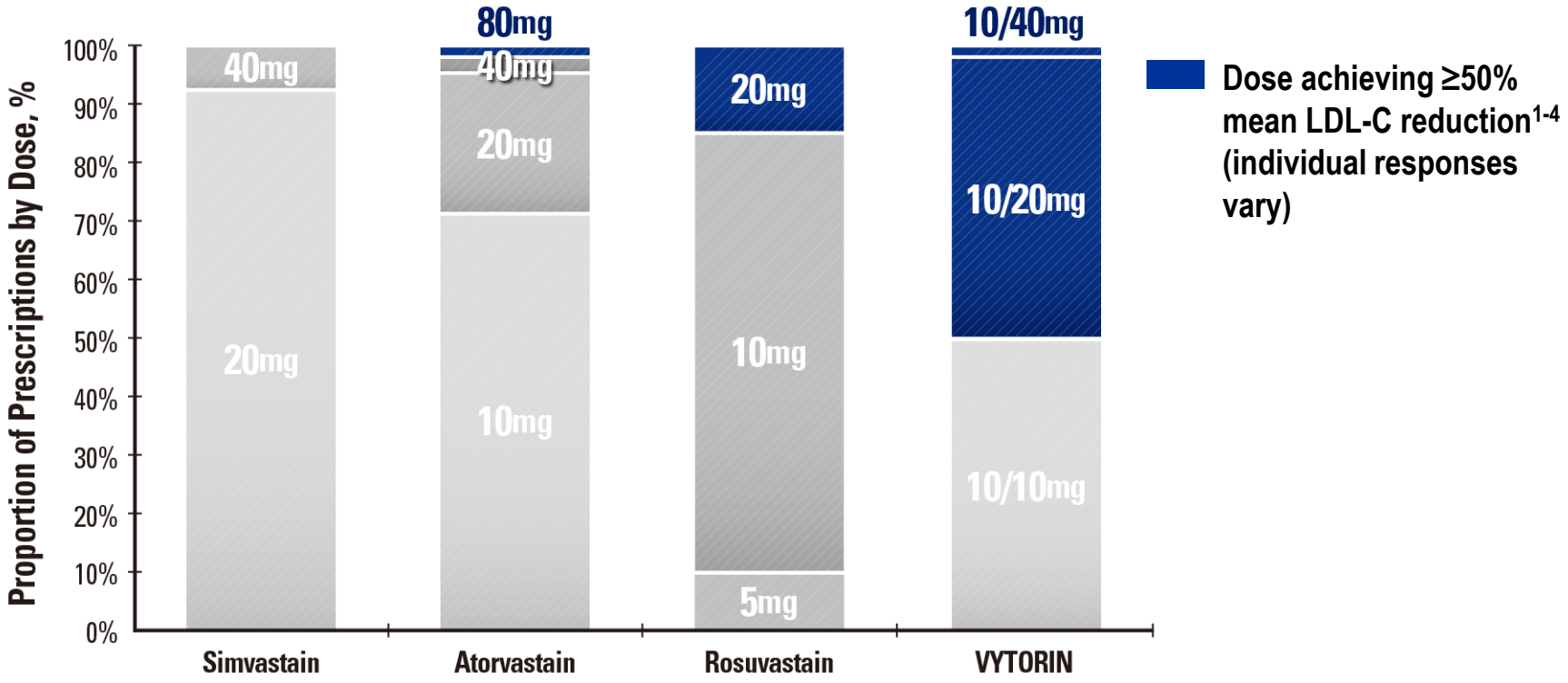
Cohen DE, Armstrong EJ. In: *Principles of pharmacology: The pathophysiologic Basis of Drug Therapy.* 2nd ed. Philadelphiak PA:Lippincott, Williams & Wilkins; 2007:417-438; Wang DQH. *Annu Rev Physiol.* 2007;69:221-248.

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



1. Bays et al. *Clin ther*. 2004;26:1758-1773; 2. Bays H, Dujovne C. Expert Opin Pharmacother 2003;4:779-790.

Based on 3 Separate Clinical Studies, More Dosing Options of VYTORIN (ezetimibe/simvastatin) Provided ≥50% Mean LDL-C Reduction vs Other Selected LDL-C–Lowering Drugs



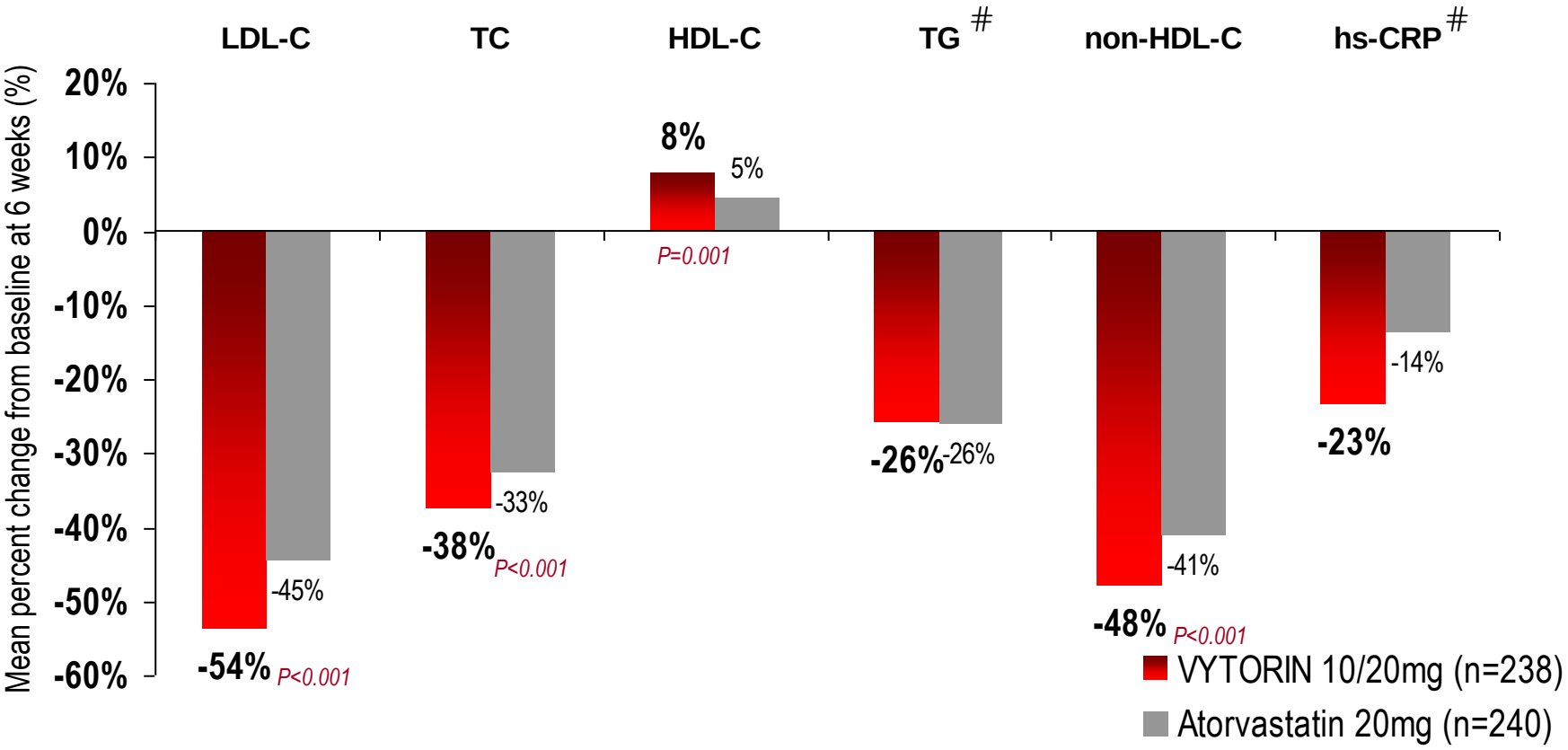
- The above comparisons do not establish that the products have the same indications, safety profiles, or dosing regimens.

1. 2012 4Q Korea IMS 2011 4Q; **2.** Bays HE et al. *Clin Ther*. 2004;26:1758–1773;
3. Ballantyne CM et al. *Am Heart J*. 2005;149:464–473; **4.** Catapano AL et al. *Curr Med Res Opin*. 2006;22:2041–2053.

In hypercholesterolemia patients

VYTORIN 10/20mg provided ≥50% reduction in LDL-C[1]

In a clinical study of patients with hypercholesterolemia and type 2 DM (VYTAL study)

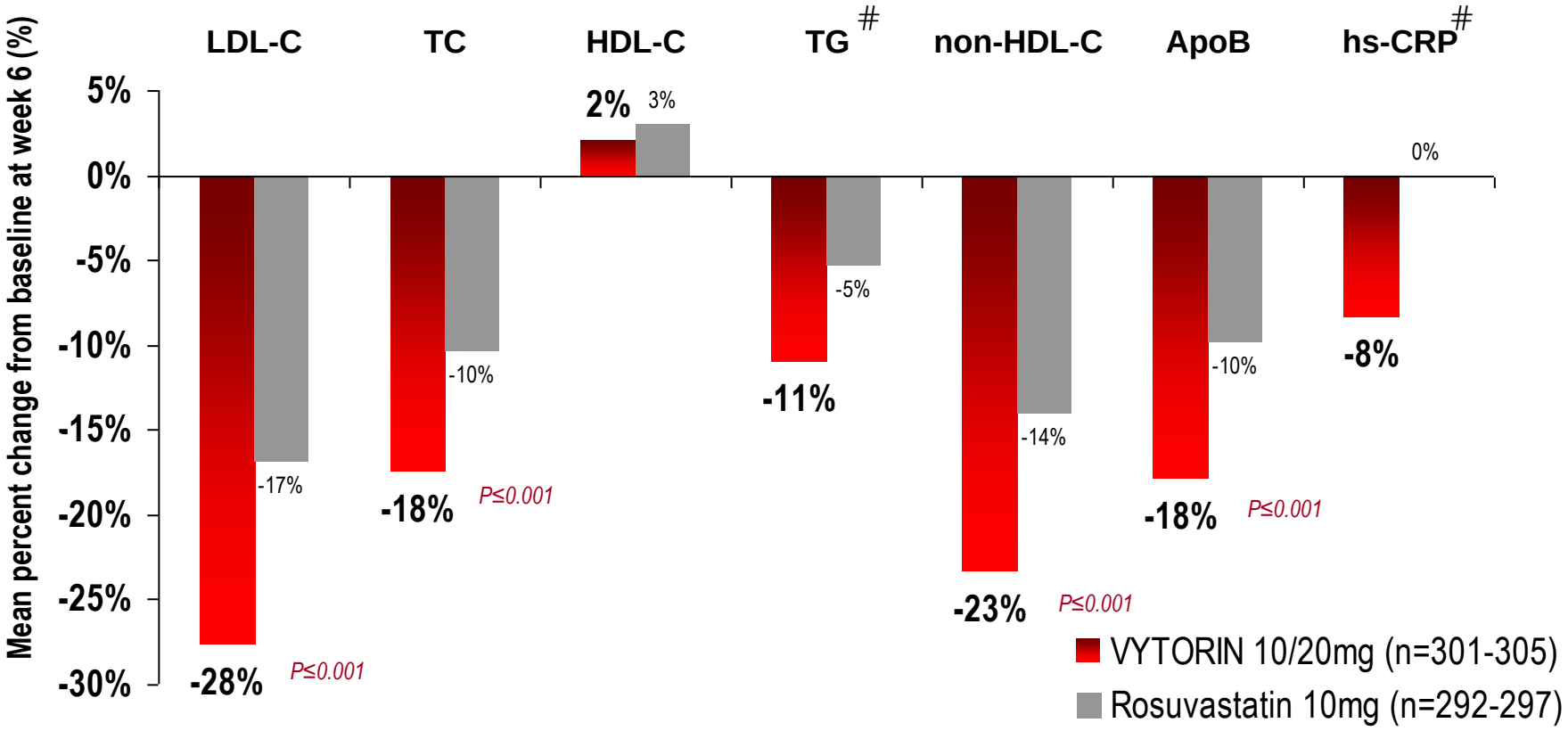


HDL-C: high-density lipoprotein cholesterol, hs-CRP: high-sensitivity C-reactive protein,
LDL-C: low-density lipoprotein cholesterol, TC: total cholesterol, TG: triglycerides
#: median

1. Goldberg RB, et al. *Mayo Clin Proc.* 2006;81(12):1579–1588

Statin treated, but Not at LDL-C goal,

Switching to VYTORIN 10/20mg provided ≥ 25% reduction in LDL-C[1]



Apo: apolipoprotein, HDL-C:high-density lipoprotein cholesterol, hs-CRP: high-sensitivity C-reactive protein, LDL-C: low-density lipoprotein cholesterol, TC: total cholesterol, TG: triglycerides

#: median

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

VYTORIN was Generally Well Tolerated[1,2]

Adverse Events	Statin untreated [1]		Statin treated, not at goal [2]	
	All VYTORIN 10/20, 10/40mg/day (n=485-494)	All atorvastatin 10, 20, 40mg/day (n=723-732)	VYTORIN 10/20 mg/day (n=314)	Rosuvastatin 10 mg/day (n=304)
≥1 Clinical event	19.8%	22.7%	7.1%	11.2%
Drug-related clinical event	4.0%	4.1%	2.6%	3.3%
Discontinuation due to drug-related clinical event	0.2%	1.0%	2.2%	1.0%
ALT and/or AST ≥3 × ULN (consecutive)	0	0.4%	0.7%	0
CK ≥ 10X ULN	0	0		
CK ≥ 5X ULN			0	0

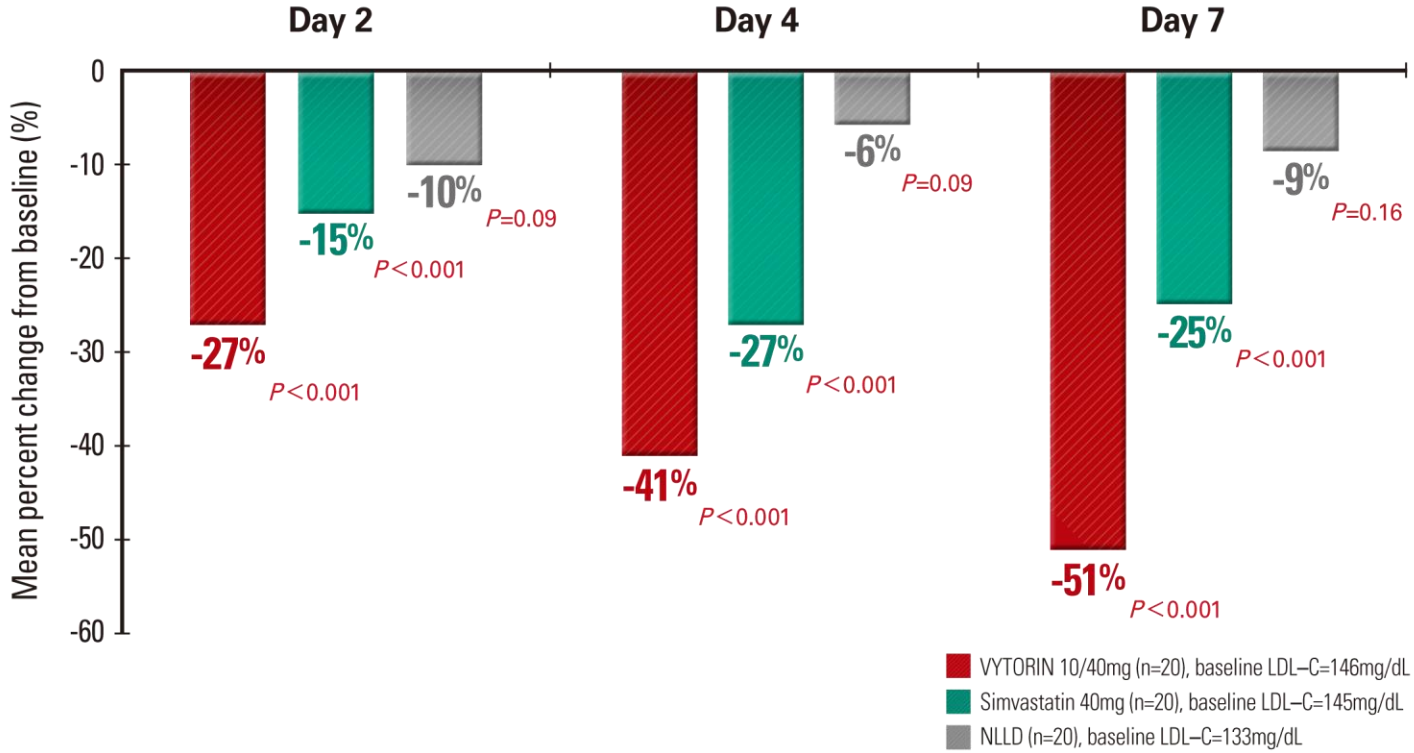
Adapted from Goldberg RB,et a and Farnier M. et al

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal; CK=creatine kinase.

1. Goldberg RB, et al. *Mayo Clin Proc*. 2006;81(12):1579–1588 / 2. Farnier M, et al. *Int J Clin Pract*. 2009;63(4):547-559

Rapid LDL-C reduction with VYTORIN
in hyperlipidemia patients with AMI

- **60 admitted AMI patients** were randomized to simvastatin 40 mg, VYTORIN(ezetimibe/simvastatin) 10/40mg or NLLD and had their lipid levels assessed 2, 4 and 7 days later.

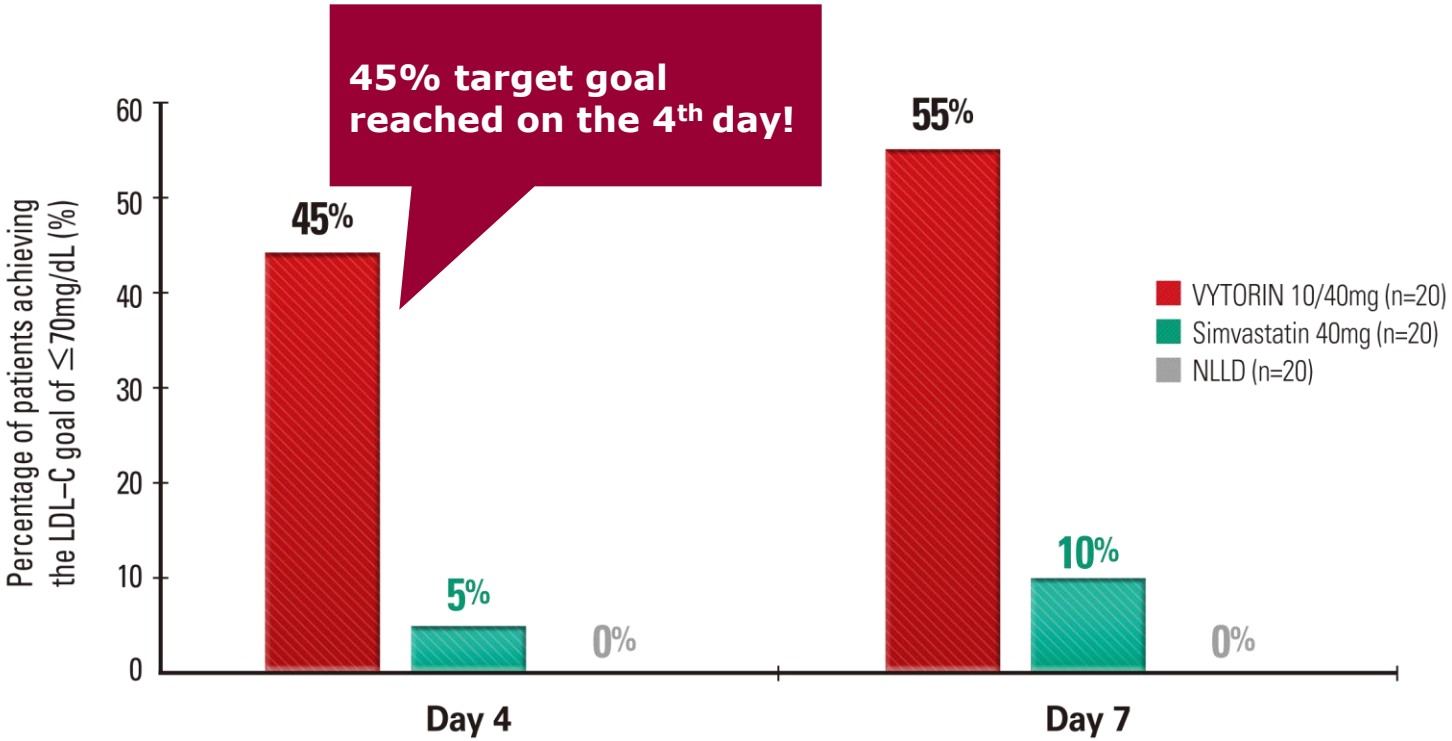


AMI= acute myocardial infarction; NLLD= no lipid-lowering drugs; LDL-C= low density lipoprotein-cholesterol.

1. Chenot F, et al. *Eur J Clin Invest 2007; 37 (5): 357–363*

Benefit of Early Start of VYTORIN

Rapid LDL-C target goal achievement with VYTORIN in AMI patients.

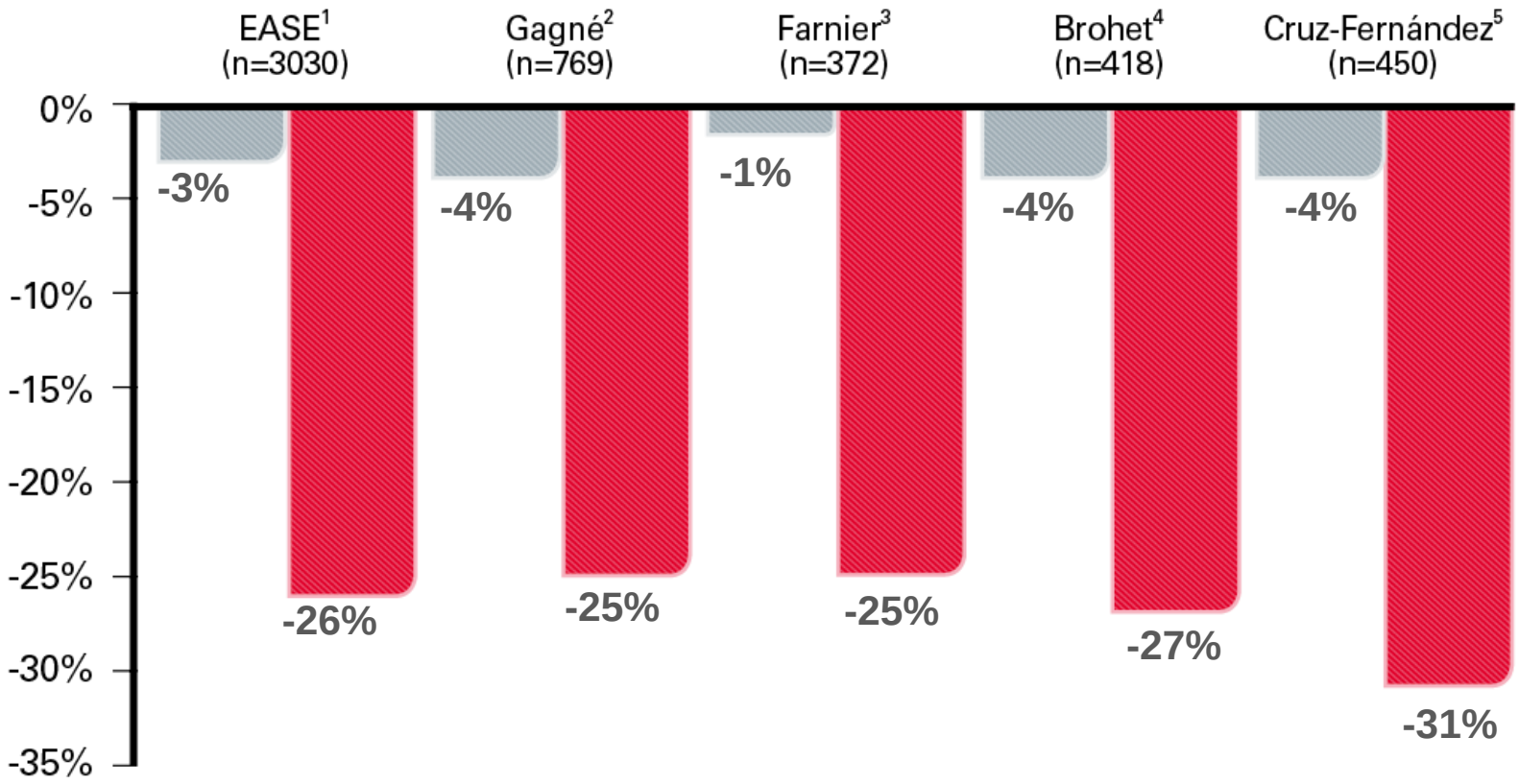


Percentage of patients achieving a goal LDL-C level of < 70 mg dL−1 during treatment with NLLD(n=20), simvastatin 40 mg/day(n=20), or ezetimibe 10 mg/day co-administered with simvastatin 40 mg/day(EZE/SIMVA, n=20) after an AMI.

AMI= acute myocardial infarction; NLLD= no lipid-lowering drugs; LDL-C= low density lipoprotein-cholesterol.

1. Chenot F, et al. *Eur J Clin Invest 2007; 37 (5): 357–363*

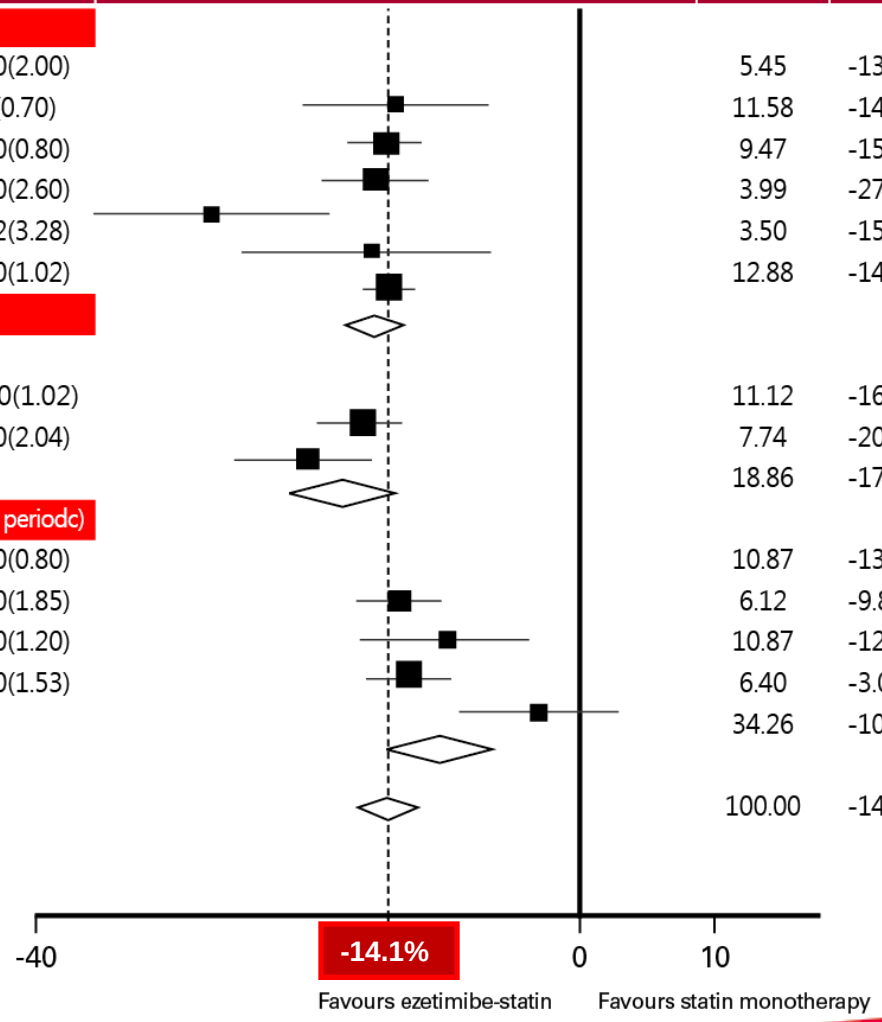
Ezetimibe add-on to any statin provided additional 25-31% reduction of LDL-C in diabetes



1. Pearson TA et al. *Mayo Clin Proc* 2005;80:587-95; 2. Gagné C et al. *Am J Cardiol* 2002;90:1084-91; 3. Farnier M et al. *Int J Cardiol* 2005;102:327-32; 4. Brohet C et al. *Curr Med Res Opin* 2005;20:571-8; 5. Cruz-Fernández JM et al. *Int J Clin Pract* 2005;59:619-27

LDL-C lowering with initial statin dose Ezetimibe/Statin vs. monostatin

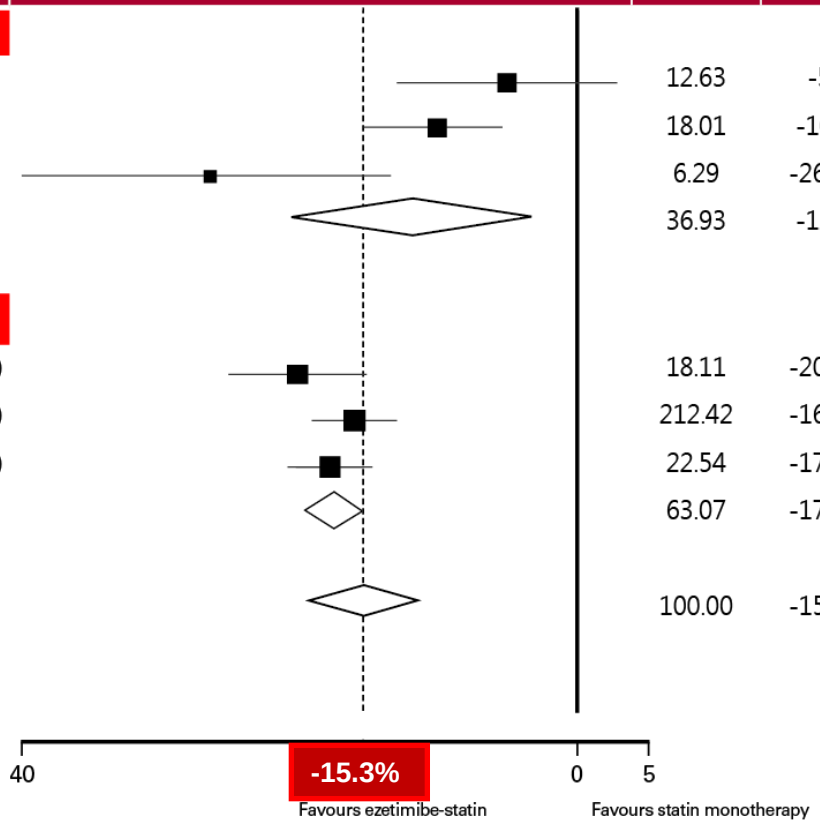
Study type or sub category	N	Ezetimibe-statin%(SD)	N	Statin% (SD)	Weight %	Odds ratio (95% CI)
Goal (1st treatment perioda or study endpointb						
Dobs, 2003	66	-24.50(1.50)	34	-11.10(2.00)	5.45	-13.40(-20.26, -6.45)
Stein, 2004a[33]	293	-22.80(0.70)	303	-8.60(0.70)	11.58	-14.20(-16.94, -11.46)
Feldman, 2004[a43]	108	-53.00(1.20)	246	-38.00(0.80)	9.47	-15.00(-18.92, -11.08)
Masana, 2005[a36]	355	-23.70(1.80)	78	3.30(2.60)	3.99	-27.00(-35.62, -18.38)
Strony, 2008[b39]	87	-44.40(1.52)	22	-29.12(3.28)	3.50	-15.28(-24.69, -5.87)
Zieve, 2010[a44]	515	-27.00(1.02)	515	-13.00(1.02)	12.88	-14.00(-16.00, -12.00)
Test for heterogeneity I-squared=41.5%, p=0.19						
Single treatment period (endpoint)						
Leiter 2008[a42]	277	-27.00(1.20)	279	-11.00(1.02)	11.12	-16.00(-19.00, -13.00)
Conard, 2008[41]	92	-31.00	92	-11.00(2.04)	7.74	-20.00(-25.00, -15.00)
Test for heterogeneity I-squared=44.7%, *p*=0.179					18.86	-17.48(-21.26, -13.69)
Forced titration (1st treatment perioda, endpoint b , or 2nd treatment periodc)						
Ballantyne, 2004[a45]	263	-50.30(0.80)	262	-37.20(0.80)	10.87	-13.10(-16.24, -9.96)
Ballantyne, 2004[a40]	45	-48.40(1.33)	201	-38.60(1.85)	6.12	-9.80(-16.03, -3.57)
Barrios, 2005[a46]	221	-32.80(1.20)	214	-20.30(1.20)	10.87	-12.50(-15.64, -9.36)
McKenney, 2007[c15]	73	-53.00(1.53	72	-50.00(1.53)	6.40	-3.00(-9.00, 3.00)
Test for heterogeneity=68.0%, *p*=0.001					34.26	-10.30(-14.10, -6.49)
Total	2395	-35.90	2318	-21.8	100.00	-14.11(-16.13, -12.10)
Test for heterogeneity I-squared=68.5%, *p*=0.001						
Test for overall effect Z statistic=13.71, *p*<0.001						



1. Mikhailidis Curr Med Res Opin 2011; 27 1191–1210

LDL-C lowering with initial dose failure Ezetimibe add on vs. doubling statin

Study typeor sub category	N	(Ez + St) - St (P_1)(SD)	N	St - (Ez + St) (P_2)(SD)	Weight %	WMD (95% CI)
Multiple treatment periods						
Zieve, 2010[44]	516	-14.00 (1.79)	509	-9.00 (2.19)	12.63	-5.00 (-12.81, 2.81)
Ballantyne, 2004[45]	263	-13.10 (1.25)	262	-3.10 (1.33)	18.01	-10.00 (-15.04, -4.96)
Masana, 2005[36]	355	-27.00 (3.43)	78	-0.70 (3.43)	6.29	-26.30 (-39.75, -12.85)
Test for heterogeneity: I-squared = 72.30%, p=0.027					36.93	-12.00 (-20.97, -3.03)
Single treatment period						
Conard, 2008[41]	92	-31.00 (2.04)	92	-11.00 (2.04)	18.11	-20.00 (-25.00, -15.00)
Leiter, 2008[42]	277	-27.00 (1.28)	279	-11.00 (1.02)	212.42	-16.00 (-19.00, -13.00)
Roeters van Lennep, 2008[38]	178	-29.10 (1.40)	189	-11.50 (1.50)	22.54	-17.60 (-20.54, -14.66)
Test for heterogeneity: I-squared = 0.00%, p=0.390					63.07	-17.29 (-19.23, -15.36)
Total	1681	-24.05	1409	8.79	100.00	-15.26 (-19.14, -11.38)
Test for heterogeneity: I-squared = 72.50%, p=0.002						
Test for overall effect Z statistic = 7.71, p<0.001						

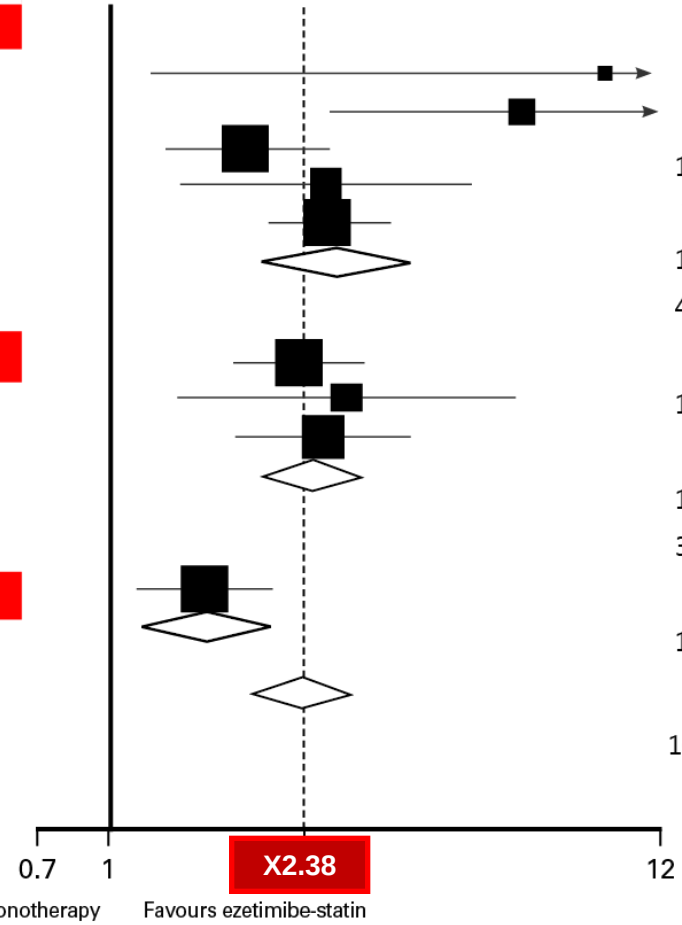


1. Mikhailidis Curr Med Res Opin 2011; 27 1191–1210

LDL-C goal attainment with initial statin dose Ezetimibe/Statin vs. monostatin

Eze/Simva combination therapy was better than mono statin in achieving LDL-C goal attainment

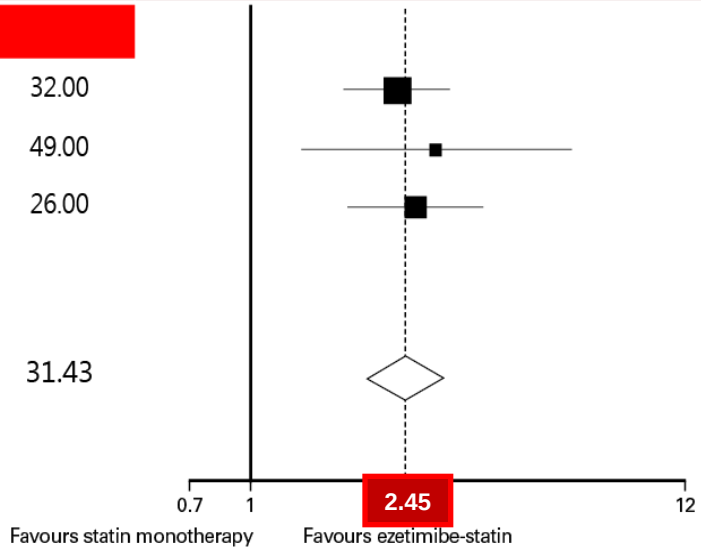
Study typeor sub category	N	Ezetimibe-statin%	N	Statin%	Weight %	Odds ratio (95% CI)
Goal (1st treatment period)						
Dobs, 2003[33]	66	27.27	34	2.94	1.15	9.27 (1.19, 72.44)
Stein, 2004[43]	293	12.00	303	2.00	5.19	6.39 (2.66, 15.35)
Feldman, 2004[35]	108	83.00	246	46.00	14.83	1.83 (1.28, 2.62)
Masana, 2005[36]	355	59.60	53	22.60	7.84	2.63 (1.36, 5.09)
Zieve, 2010[44]	515	47.40	515	17.90	17.69	2.65 (2.03, 3.47)
Test for heterogeneity: I-squared = 72.30%, p=0.027					46.71	2.76 (1.89, 4.02)
Single treatment period						
Leiter, 2008[42]	277	74.00	279	32.00	16.70	2.32 (1.72, 3.13)
Conard, 2008[41]	92	84.00	92	49.00	6.27	2.90 (1.34, 6.29)
Roeters van Lennep, 2008[38]	178	67.00	189	26.00	13.85	2.58 (1.74, 3.81)
Test for heterogeneity: I-squared = 0.00%, p=0.390					36.82	2.45 (1.95, 3.08)
Single treatment period						
Barrios, 2005[46]	221	78.00	214	52.00	16.47	1.50 (1.10, 2.04)
Total	2215	66.05	1925	32.42	100.00	2.38 (1.89, 2.98)
Test for heterogeneity: I-squared = 72.50%, p=0.002						
Test for overall effect Z statistic = 7.71, p<0.001						



1. Mikhailidis Curr Med Res Opin 2011; 27 1191–1210

LDL-C goal attainment with initial dose failure Ezetimibe add on vs. doubling statin

Study typeor sub category	N	Ezetimibe-statin%	N	Statin%	Odds ratio 95% CI	Weight %	Odds ratio (95% CI)
Multiple treatment periods							
Zieve, 2010[44]	277	74.00	279	32.00		57.60	2.32 (1.72, 3.13)
Ballantyne, 2004[45]	92	84.00	92	49.00		8.59	2.90 (1.34, 6.29)
Masana, 2005[36]	178	67.00	189	26.00		33.80	2.58 (1.74, 3.81)
Test for heterogeneity: I-squared = 72.30%, p=0.027							
Total	547	72.49	560	31.43		100.00	2.45 (1.95, 3.08)
Test for heterogeneity: I-squared = 72.50%, p=0.002							
Test for overall effect Z statistic = 7.71, p<0.001							

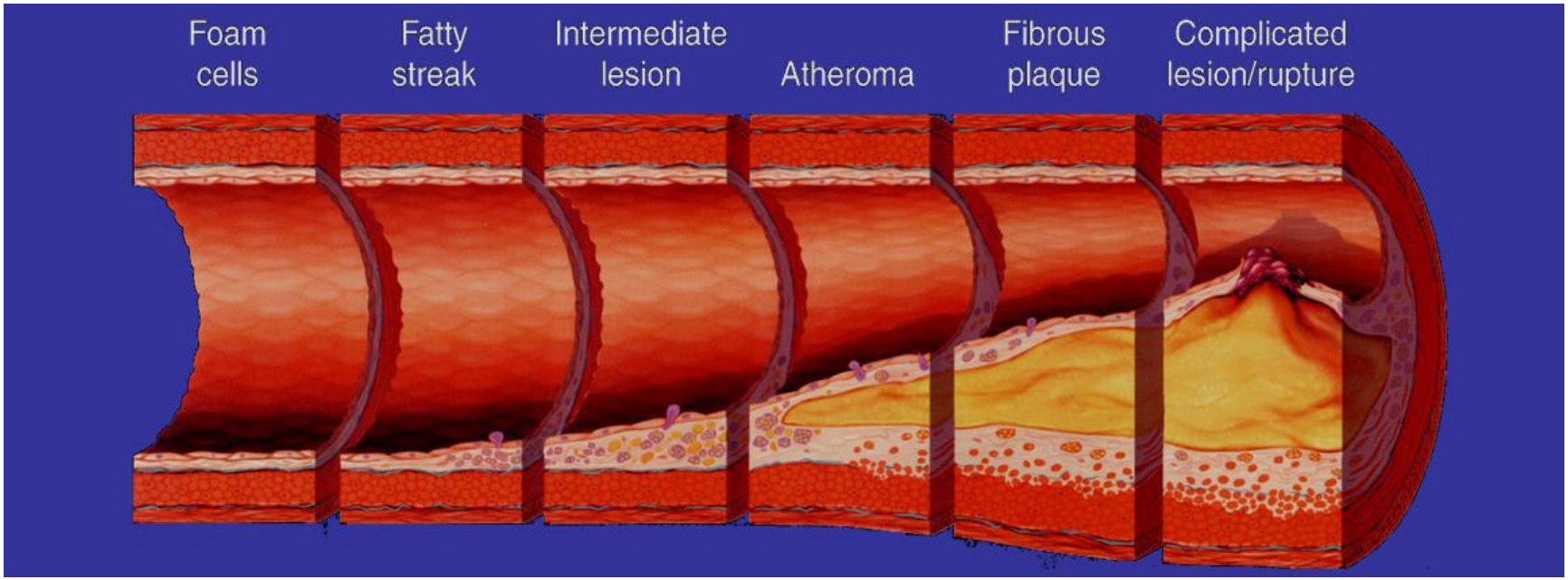


1. Mikhailidis Curr Med Res Opin 2011; 27 1191–1210

2. New considering point of view for preventing Atherosclerosis

- CRP
- Chylomicron and ApoB in atherosclerosis
- Further clinical outcomes of combination therapy

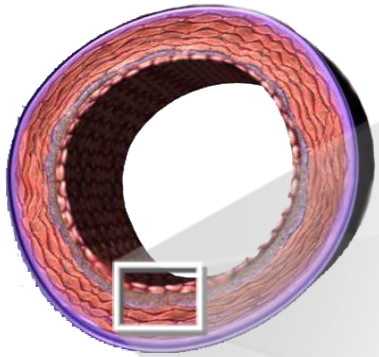
Atherosclerosis is the Most Common Pathologic Condition Leading to Cardiovascular Disease[1]



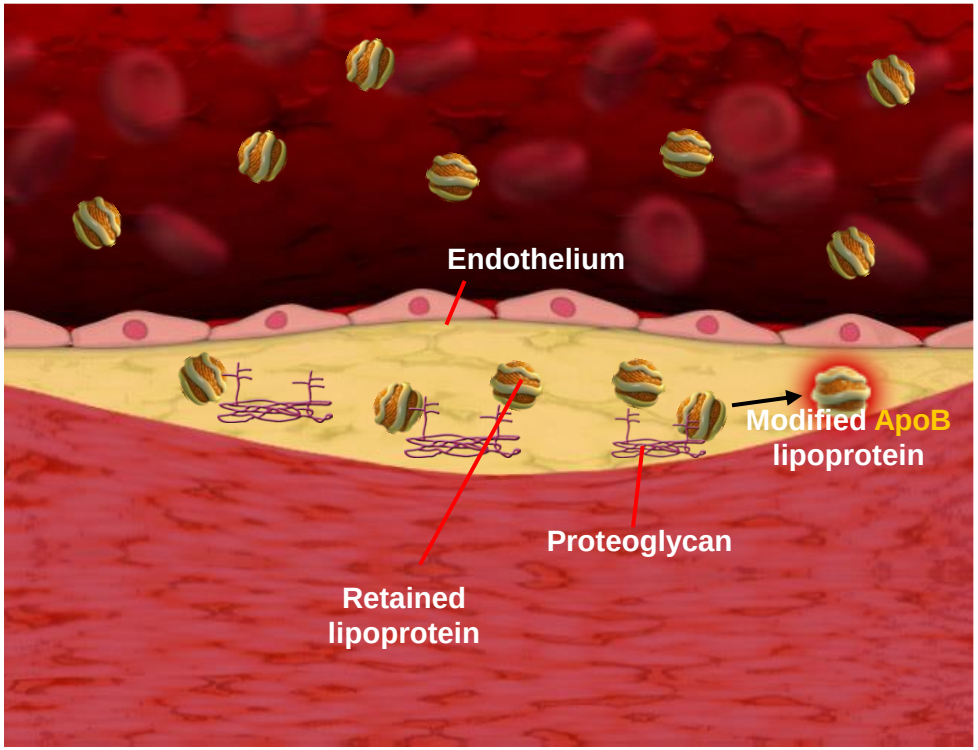
- A dynamic disease process clinically characterized by narrowing of the arterial lumen due to accumulation of atherogenic lipoproteins
- Mainly due to a complex interaction of lipoproteins, inflammation, and the arterial wall

1. Sherer Y et al. *Nat Clin Pract Rheumatol*. 2006;2:99–106.

Prolonged retention leads to ApoB modification



- Interaction between lipoproteins and subendothelial matrix molecules promotes retention[1]
- Prolonged retention leads to LDL modification (eg, oxidation,[a] lipolysis, aggregation)[2]

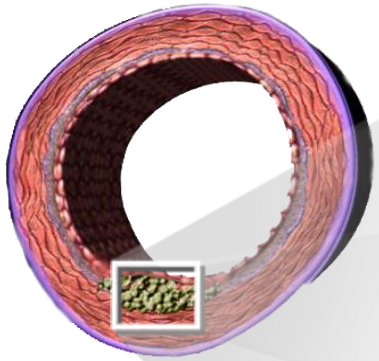


ApoB = apolipoprotein B.

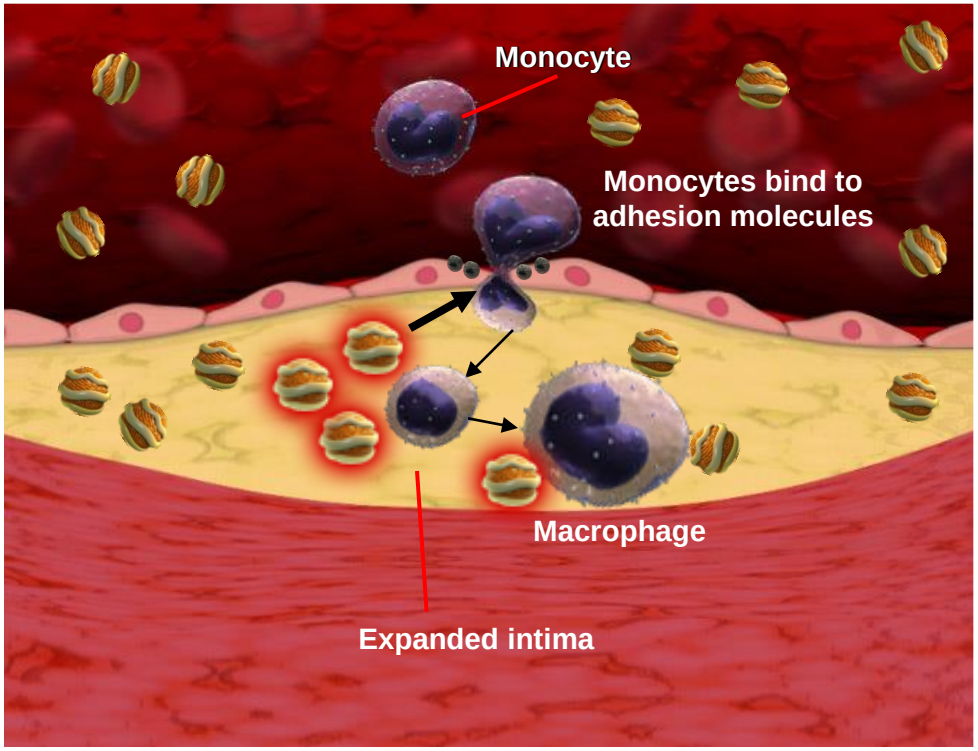
[a]Results from prospective clinical trials do not show a benefit of antioxidants in treating atherosclerosis.[3]

1. Tabas I et al. *Circulation*. 2007;116:1832–1844. **2.** Khalil MF et al. *Arterioscler Thromb Vasc Biol*. 2004;24:2211–2218. **3.** Jialal I et al. *Circulation*. 2003;107:926–928.

Modified ApoB triggers a series of maladaptive inflammatory response

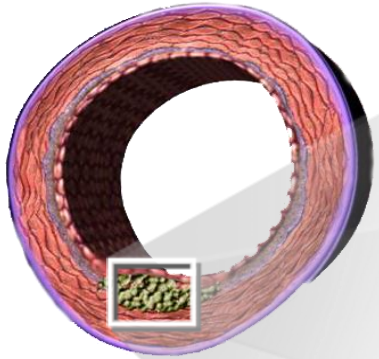


- Attracts circulating monocytes, which differentiate into macrophages
- Inhibits macrophage egress and enhances macrophage uptake of ApoB lipoproteins
- Causes endothelial activation

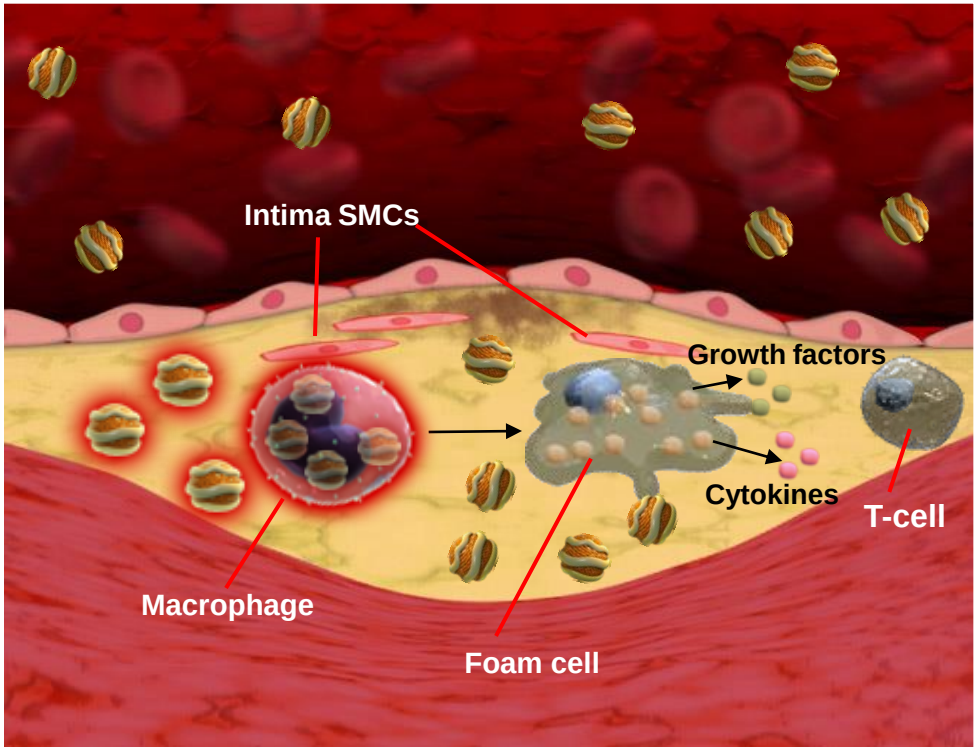


1. Tabas I et al. *Circulation*. 2007;116:1832–1844. **2.** Steinberg D et al. *N Engl J Med*. 1989;320:915–924; **3.** Hansson GK. *J Thromb Haemost*. 2009;7(Suppl 1):328-331.

Lipoprotein retention accelerates maladaptive inflammatory response



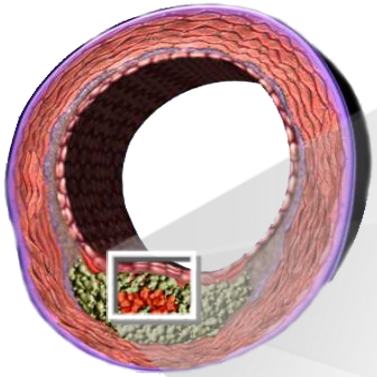
- Macrophages ingesting modified lipoproteins and forming foam cells[1]
- Other immune cells entering lesion[1]
- Release of growth factors and cytokines from foam cells[2]



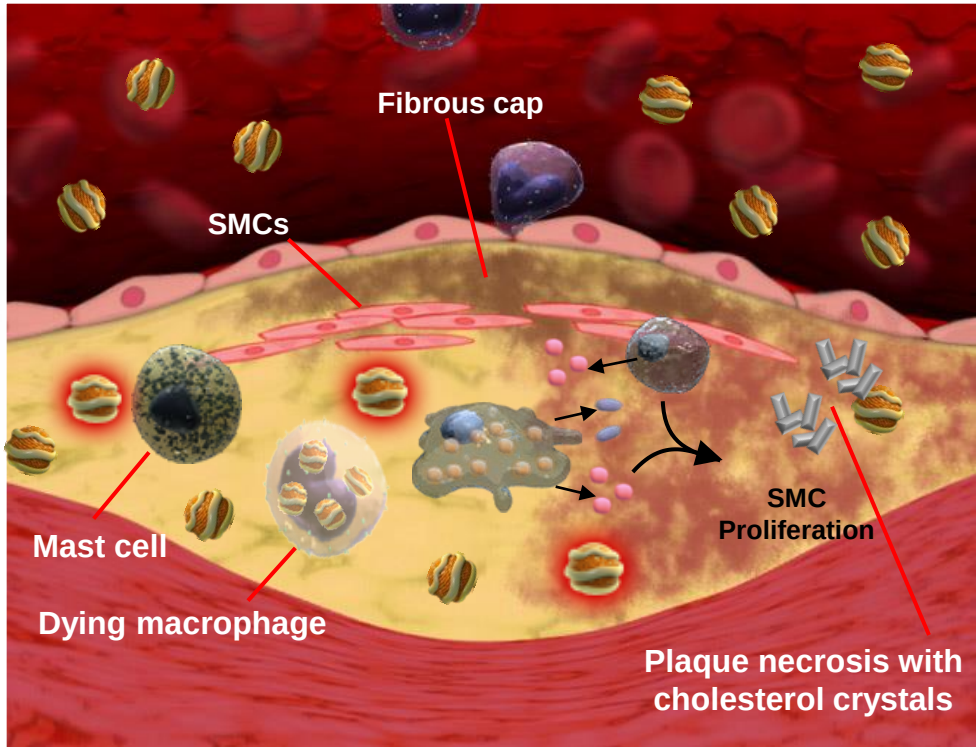
SMC = smooth muscle cell

1. Tabas I et al. *Circulation.* 2007;116:1832–1844. **2.** Sherer Y et al. *Nat Clin Pract Rheumatol.* 2006;2:99–106.

Lesion progresses give rise to necrotic areas



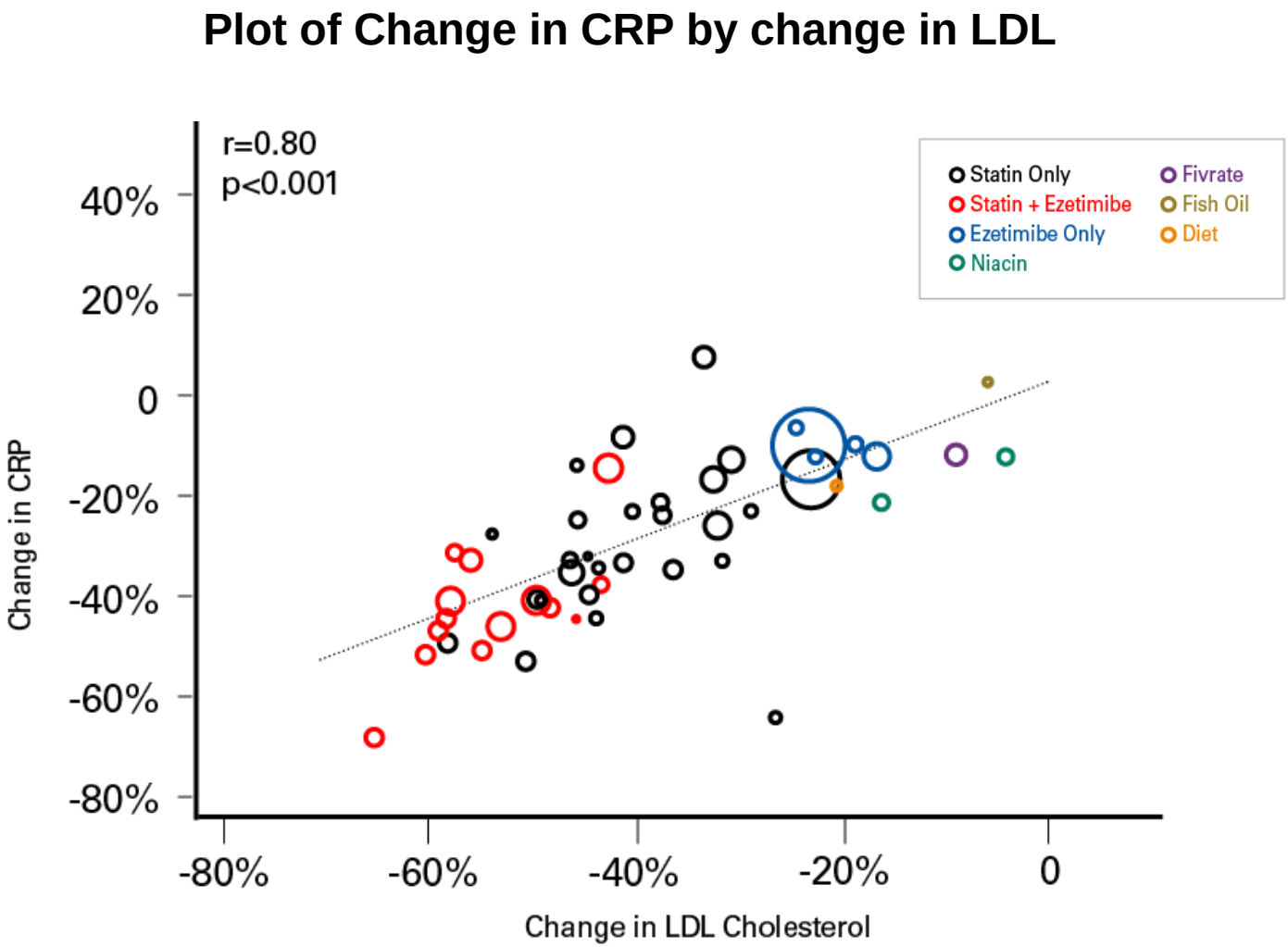
- Immune cells further contribute to inflammatory response
- SMCs migrate into intima
- Fibrous cap forms
- Macrophages begin to die and give rise to necrotic areas



SMC = smooth muscle cell.

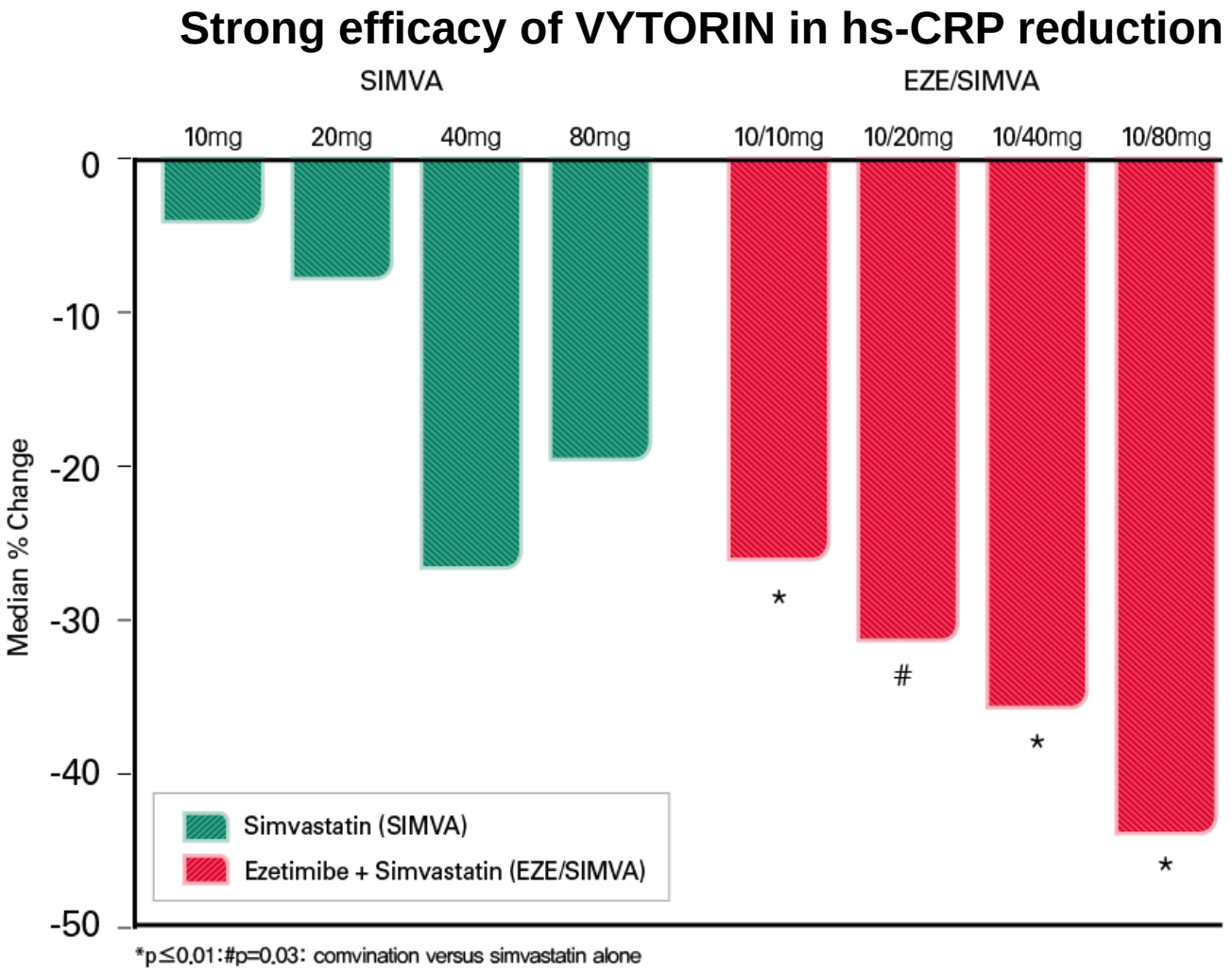
1. Tabas I et al. *Circulation*. 2007;116:1832–1844.

hs-CRP lowering was related to LDL-C lowering



1. Kinlay J Am Coll Cardiol 2007;49 2003–2009,

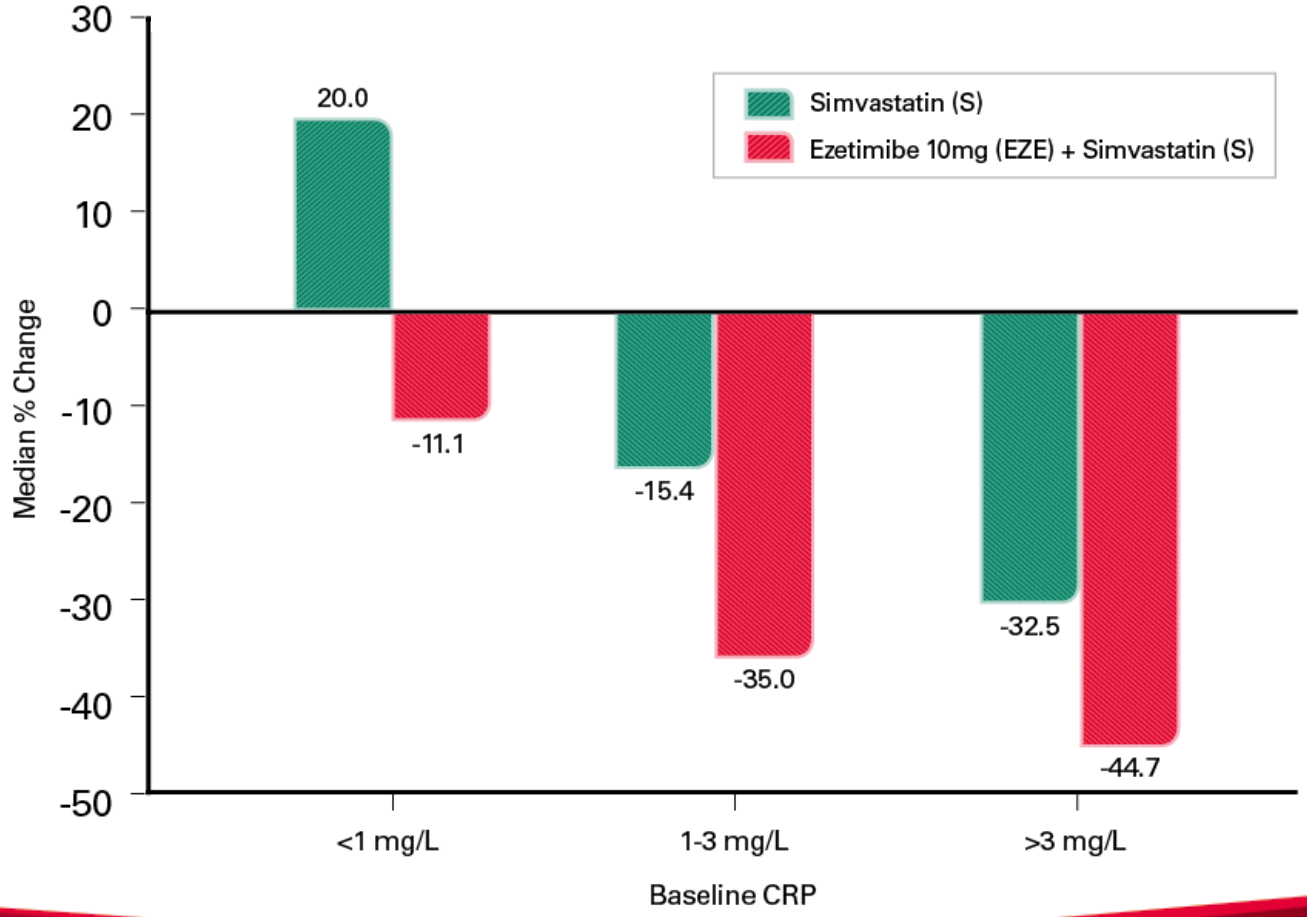
hs-CRP lowering was related to LDL-C lowering



1. Sager PT et al. Atherosclerosis 2005;179:361–367

Strong efficacy in hs-CRP reduction

- Effect of baseline hs-CRP levels at clinically meaningful strata on the hs-CRP response to treatment with simvastatin monotherapy(pooled across doses), and ezetimibe 10mg+simvastatin(pooled across doses).



1. Sager PT et al. *Atherosclerosis* 2005;179:361–367

Inflammation markers were significantly improved by VYTORIN

- Arms : 10 mg/d of ezetimibe , 20 mg/d of simvastatin , 40 mg/d of simvastatin and 10 mg/d of ezetimibe
- Duration : 12 wks
- Pts: 178 pts with hypercholesterolemia

	Placebo	Ezetimibe(10 mg)	Simvastatin(40 mg)	Ezetimibe + simvastatin(10/40 mg)
High-sensitivity C-reactive protein (mg L^{-1})				
Baseline	3.2 ± 0.4	3.4 ± 0.4	3.3 ± 0.4	3.5 ± 0.4
After 4 weeks	3.3 ± 0.3(3)	2.8 ± 0.3(-18)	2.5 ± 0.2(-22)[a,d]	2.0 ± 0.4(-43)[c,f]
After 12 weeks	3.4 ± 0.5(6)	2.7 ± 0.4(-19)	1.9 ± 0.2(-42)[c,f,h,l]	1.1 ± 0.2(-69)[c,f,i,k,n]
Intercellular adhesion molecule 1 (ng mL^{-1})				
Baseline	302 ± 32	305 ± 46	307 ± 31	299 ± 35
After 4 weeks	306 ± 24(1)	253 ± 31(-17)	236 ± 18(-23)[a,d]	202 ± 24(-32)[c,f]
After 12 weeks	308 ± 26(2)	247 ± 23(-19)	196 ± 15(-36)[c,f,g,l]	147 ± 16(-51)[e,f,i,j,m]
TNF-α release (ng mL^{-1})				
Baseline	348 ± 31	361 ± 26	364 ± 34	359 ± 38
After 4 weeks	361 ± 33(4)	305 ± 28(-16)	280 ± 25(-23)[a,d]	241 ± 22(-33)[b,f]
After 12 weeks	365 ± 31(5)	298 ± 32(-17)	220 ± 21(-40)[c,f,g,l]	175 ± 23(-51)[c,f,i,j,m]
IFN-γ release (ng mL^{-1})				
Baseline	53.2 ± 6.0	54.2 ± 7.1	54.4 ± 5.2	52.9 ± 6.4
After 4 weeks	52.8 ± 7.4(-1)	45.6 ± 3.7(-16)	41.6 ± 3.5(-24)[a,e]	36.7 ± 5.1(-31)[b,f]
After 12 weeks	52.4 ± 4.4(-2)	44.5 ± 4.5(-18)	32.7 ± 3.2(-40)[c,f,h,l]	24.8 ± 2.2(-53)[c,f,i,j,m]
IL-2 release (ng mL^{-1})				
Baseline	5.5 ± 0.6	5.6 ± 0.6	5.8 ± 0.5	5.7 ± 0.5
After 4 weeks	5.5 ± 0.5(0)	4.6 ± 0.5(-18)	4.5 ± 0.3(-22)[a,d]	3.9 ± 0.4(-32)[c,f]
After 12 weeks	5.7 ± 0.5(4)	4.5 ± 0.5(-19)	3.7 ± 0.2(-36)[c,f,g,l]	2.9 ± 0.3(-49)[c,f,i,j,m]

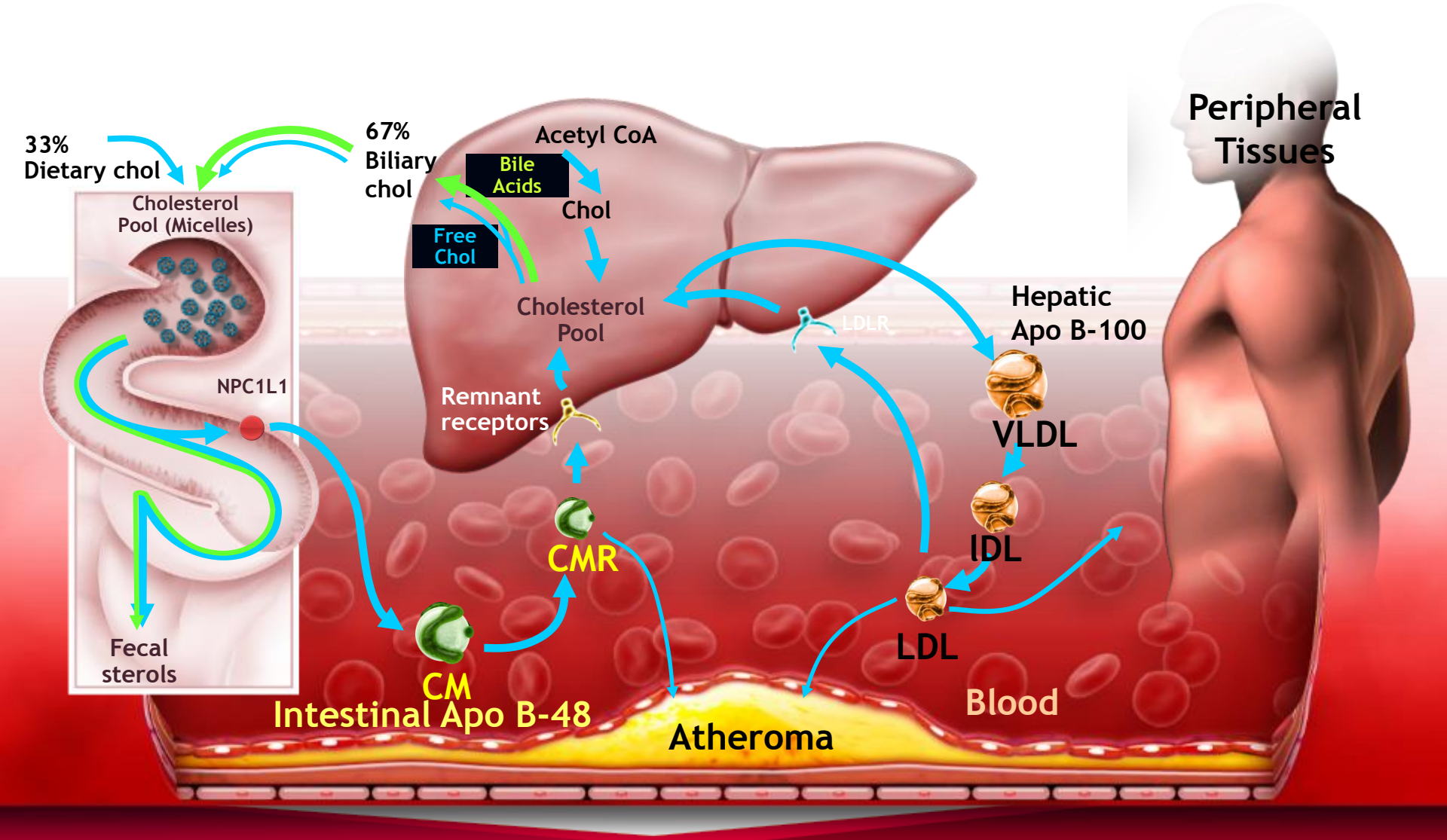
Data represent the mean ± SD. Values in parentheses represent percentage changes from baseline values. [a]P<0.05, [b]P<0.01, [c]P<0.001 vs. control group. [d]P<0.05, [e]P<0.01, [f]P<0.001 vs. pretreatment values. [g]P<0.05, [h]P<.001, [i]P<0.001 vs. ezetimibe-treated patients. [j]P<0.05, [k]P<0.001 vs. simvastatin-treated patients. [l]P<0.05, [m]P<0.01, [n]P<0.001 vs. the effect after 4 weeks of treatment.

*Only data from subjects who completed the study were included in the final analyses.

1. Krysiak R Journal of InternalMedicine 2012;271 32–42

2. **New considering point of view for preventing Atherosclerosis**
   - CRP
   - Chylomicron and ApoB in atherosclerosis
   - Further clinical outcomes of combination therapy

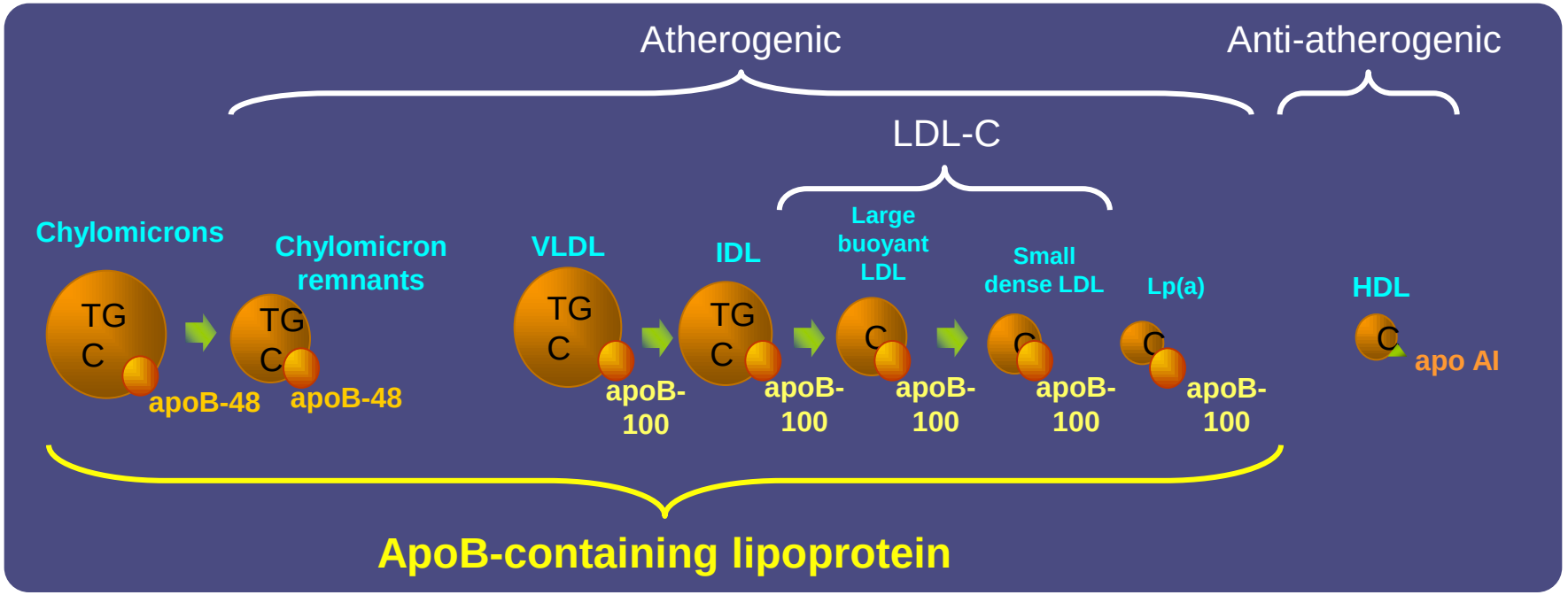
Cholesterol homeostasis



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

ApoB-containing lipoproteins are atherogenic

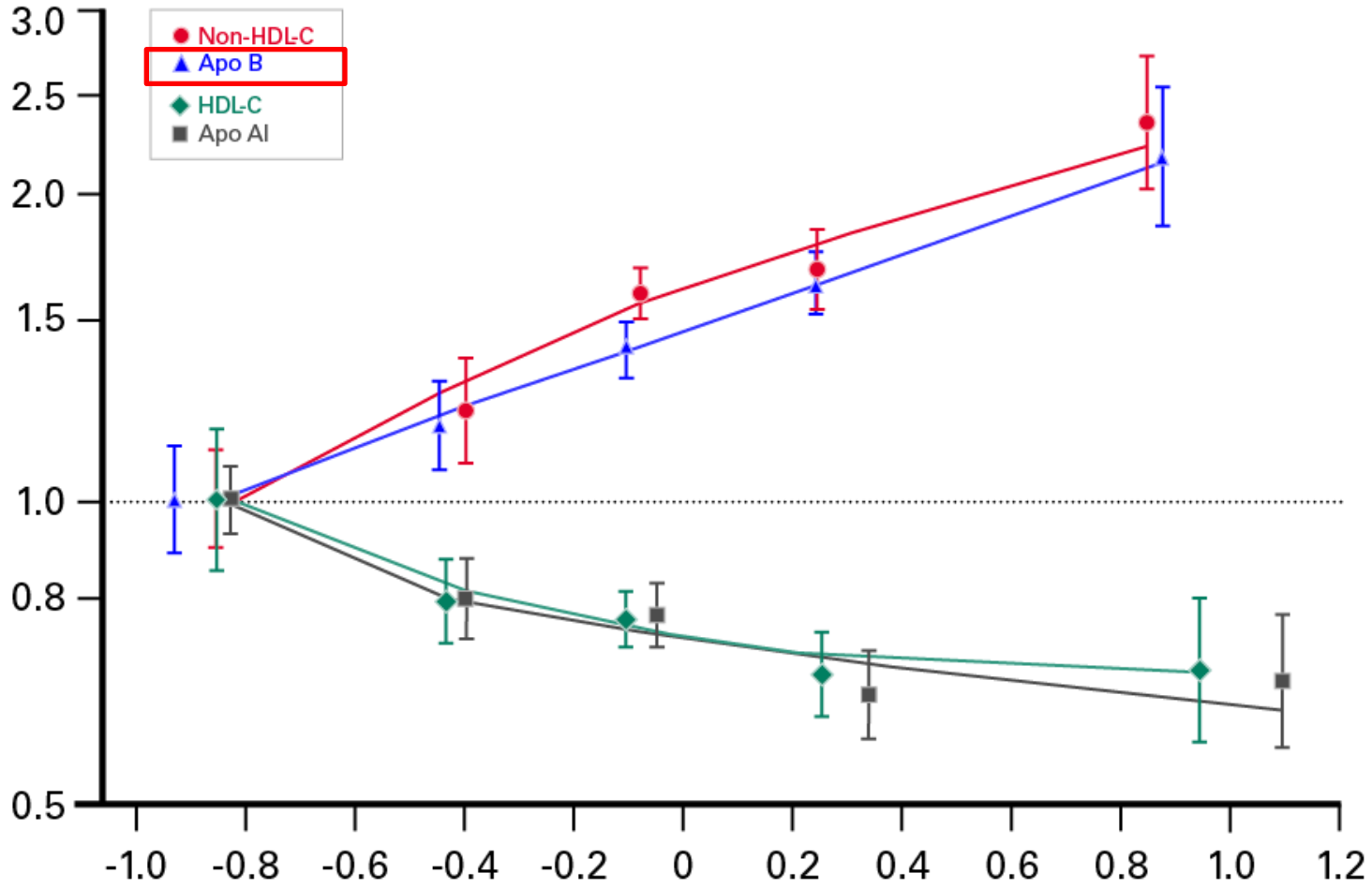
- ApoB-containing lipoproteins (chylomicron, chylomicron remnants, VLDL, VLDL remnants, IDL, large buoyant LDL, and small, dense LDL) are atherogenic[3]



Apo = apolipoprotein; VLDL = very low-density lipoprotein; IDL = intermediate-density lipoprotein; TG = triglyceride; C = cholesterol.
[a]Except in the presence of insulin resistance and/or metabolic syndrome.[5]

1. Kastelein JJ et al. *Circulation*. 2008;117:3002–3009. **2**. Walldius G et al. *J Intern Med*. 2004;255:188–205. **3.** Robinson JG. *J Am Coll Cardiol*. 2009;55:42–44. **4.** Mudd JO et al. *J Am Coll Cardiol*. 2007;50:1735–1741. **5.** Kinoshita M et al. *J Atheroscler Thromb*. 2009;16:517–522.

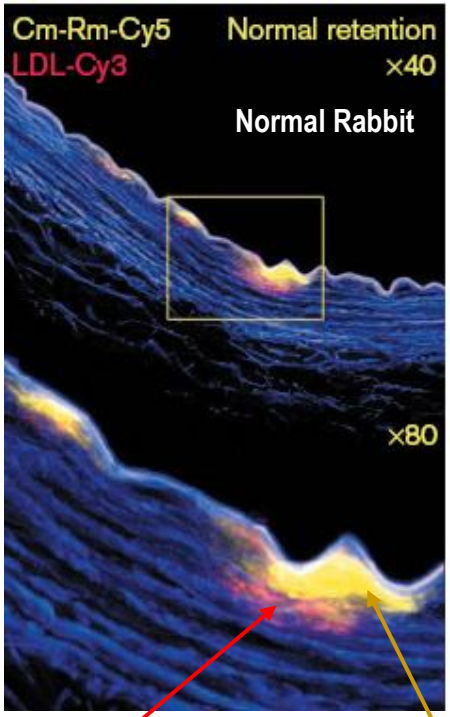
ApoB concentration is in positive correlation with CVD



1. Emerging Risk Factors Collaboration JAMA. 2009;302(18)1993-2000

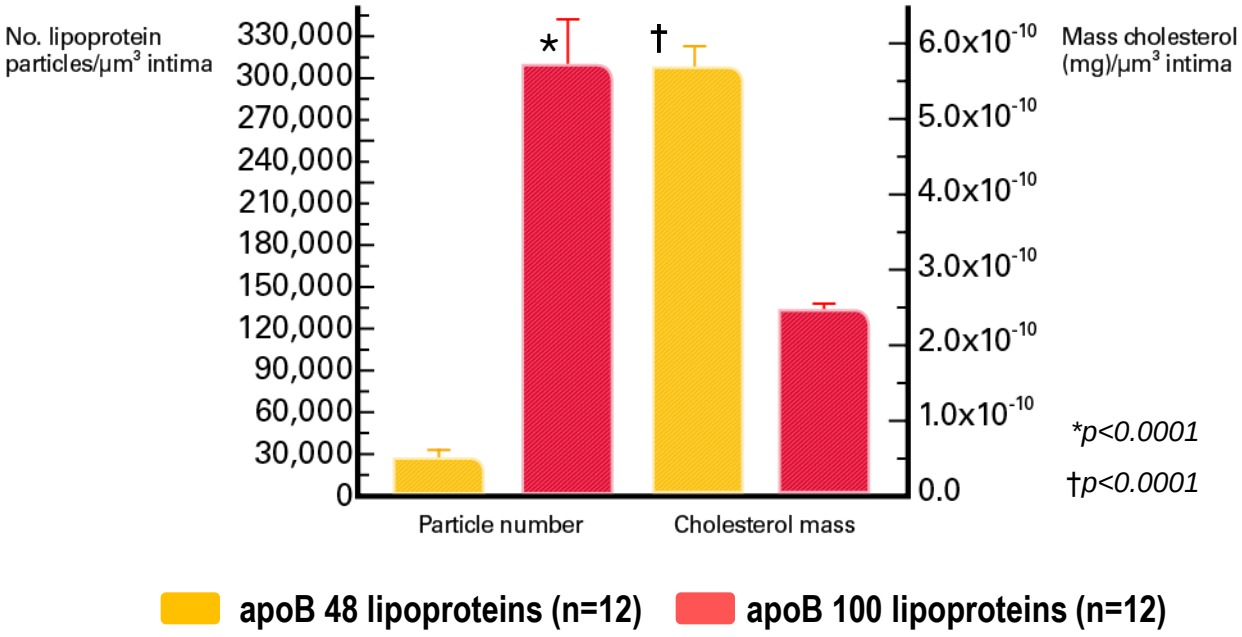
ApoB 48-containing lipoprotein, Possible significant atherogenic risk factor

- Fewer numbers of ApoB 48-containing particles are retained within the intima relative to ApoB 100-containing particles (Approximately 10-fold less)
- In human, ApoB 48-contatining chylomicron remnants contain approximately 40 times more cholesterol per particle than do ApoB 100-containing LDL particles



ApoB 100 – containing LDL in red

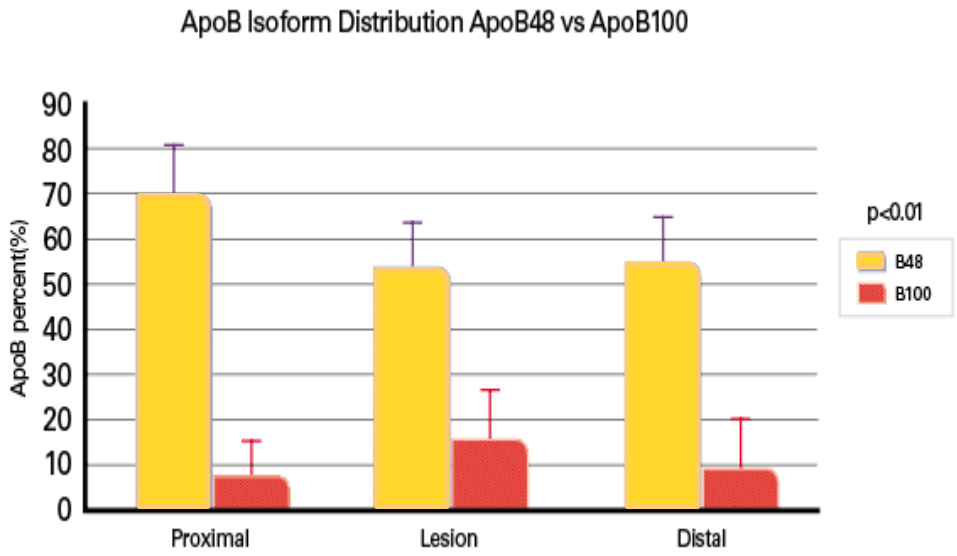
ApoB 48 – containing Chylomicron remnant in yellow

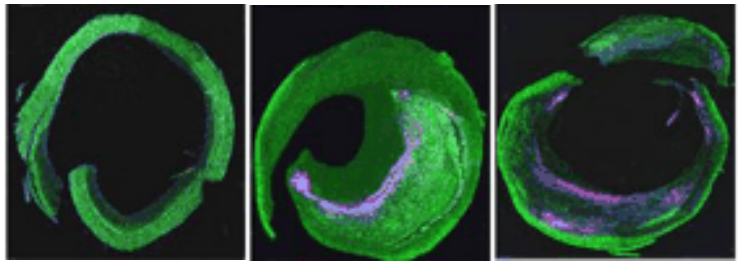


1. Proctor et al. *Current Opinion in Lipidology* 2002, 13:461-470

Chylomicron (apoB48) occupied significantly larger area of human carotid atherosclerotic plaques, compared to hepatic apoB100

- **Objective** : To evaluate relative quantification of apoB100 and apoB48 in plaque.
- **Design** : DS-IF for apoB100 and apoB48 was performed on 4 human carotid plaques from the lesion and proximal and distal regions
- **Results** : Compared to apoB100, **ApoB48-positive area was significantly larger in proximal, mid and distal sections** (70% vs 5%, 53.4% vs 16.2% and 55% vs 9.3%, respectively; p<0.001 for all)

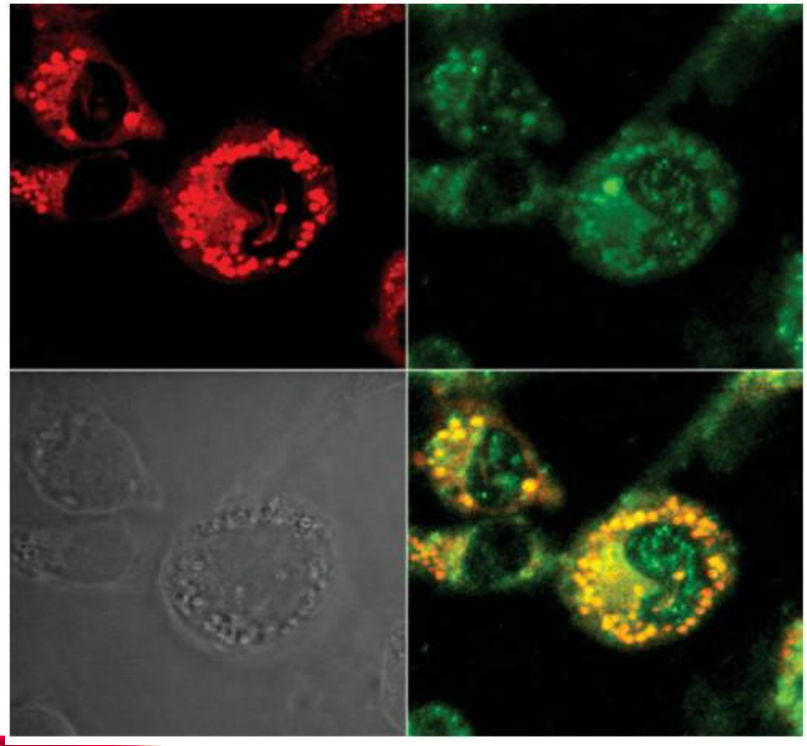




1. Vazquez-Figueroa Circulation. 2010;122 A16886.

Macrophage change to foam cell formation by CM remnant

- Lipid taken up from CMRs, regardless of their oxidative state, is not readily cleared from the cells by efflux (cholesterol) or metabolism (TAG)
- This may be due to the sequestration of the lipid in lysosomes after their uptake by the cells.
- This resistance of the lipid to removal from macrophages, therefore, is another factor which is likely to contribute to the atherogenicity of CMRs.



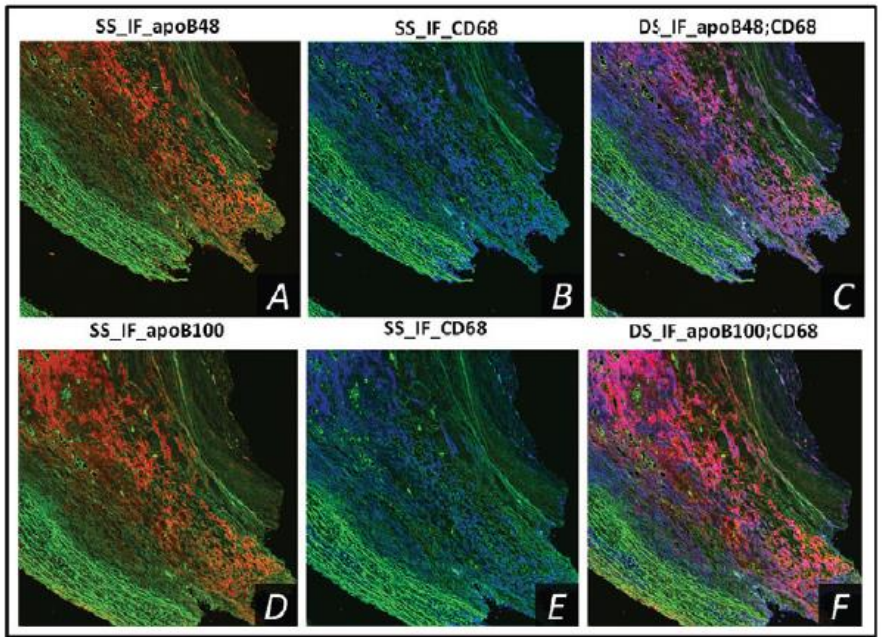
✓ The bottom left panel shows the cells only, the top left shows the DiI fluorescence, the top right the FITC fluorescence and the bottom right the DiI and FITC fluorescence merged. The yellow color indicates co-localization of LAMP-1 and CRLP-derived lipid.

CRLPs : Chylimicron remnant lipoproteins
LAMP-2 : lysosomalassociated membrane protein-1

1. Botham K.M et al. Biochemical Society Transactions 2007;35:454-458

Both hepatic apoB100 and intestinal apoB48 co-localize with macrophages in human carotid atherosclerotic plaques

- **Objective** : To evaluate co-localization of apoB48 and apoB100 with macrophages.
- **Design** : In 3 patients undergoing carotid endarterectomy (CEA), plaques were stained for apoB100/CD68 and apoB48/CD68 dual stain (DS)-IF
- **Results** : (A,D) Both apoB100 and apoB48 are present in plaques. (C,F) while CD68 staining is present throughout the plaque and in areas independent of apoB100 and apoB48, both apoB100 and apoB48 are always co-localized with CD68.

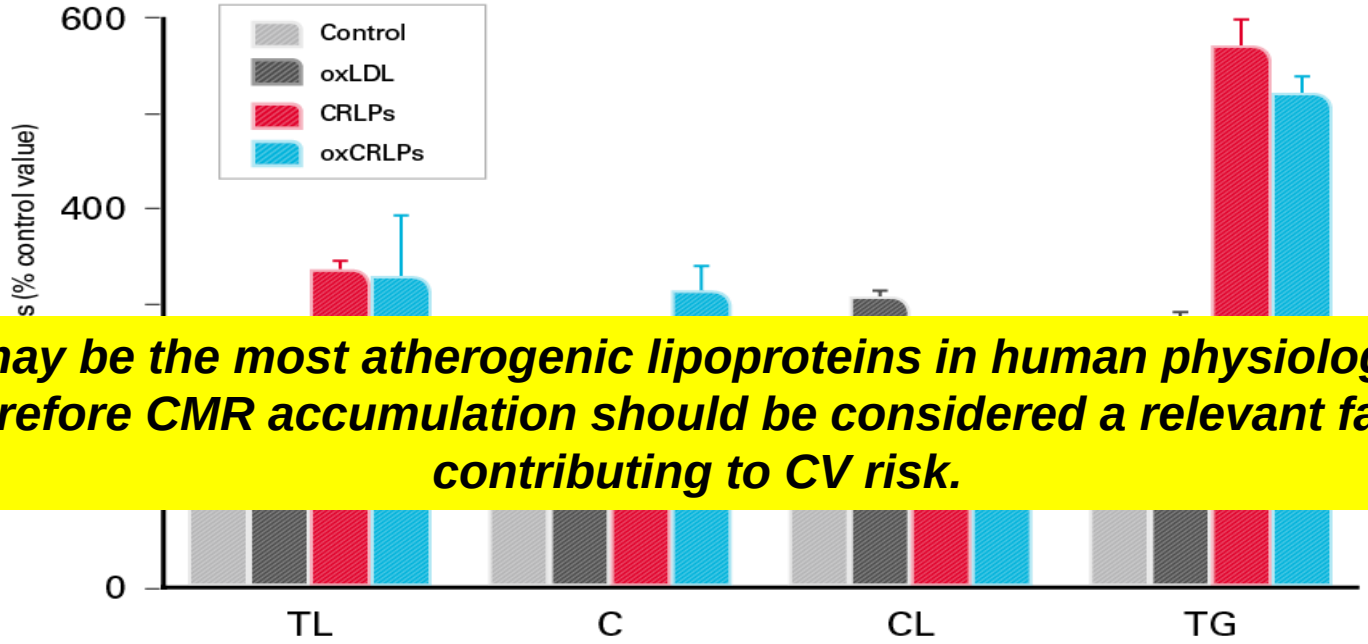


Single stain immunofluorescence(SS-IF) demonstrates the distribution of intestinal apoB48; Hepatic-apoB100(red)(A, D) and macrophages-CD68(blue)(B, E); Dual stain immunofluorescence(DS-IF) showing co-localization of apoB48 and apoB100 with macrophages(purple) in human carotid artery(C, F)

1. Vazquez-Figueroa E542 JACC 2012;59

Chylomicron remnant can induce form cell formation without the need to become modified, in contrast to native LDL

- Chylomicron remnants have multiple direct effects on three major cell types of the arterial wall which are likely to promote the development of atherosclerotic lesions
- These effects may be modulated by various lipids carried by the particles, including the type of fat (saturated or unsaturated or oxidized fat)



CM may be the most atherogenic lipoproteins in human physiology and therefore CMR accumulation should be considered a relevant factor contributing to CV risk.

THP-1 macrophages were incubated with or without oxLDL, CRLPs or oxCRLPs (30mg cholesterol/ml) for 48 h and the cholesterol (C), cholesteryl ester (CE), triacylglycerol (TG) and total lipid (TL = C + CE + TG) content of the cells was determined.
($P<0.01$ three lipoprotein types vs. control cells)

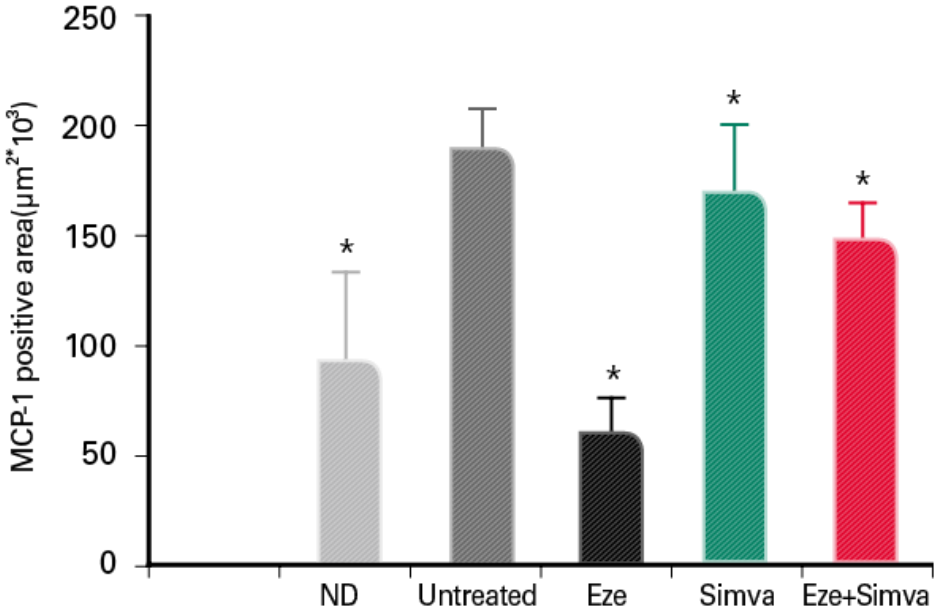
LDL, low density lipoprotien, CV, cardiovascular.

1. Botham KM et al. Current Pharmaceutical Design 2005;11: 3681-3695

Ezetimibe/statin reduced migration of macrophage

Beneficial effects of ezetimibe

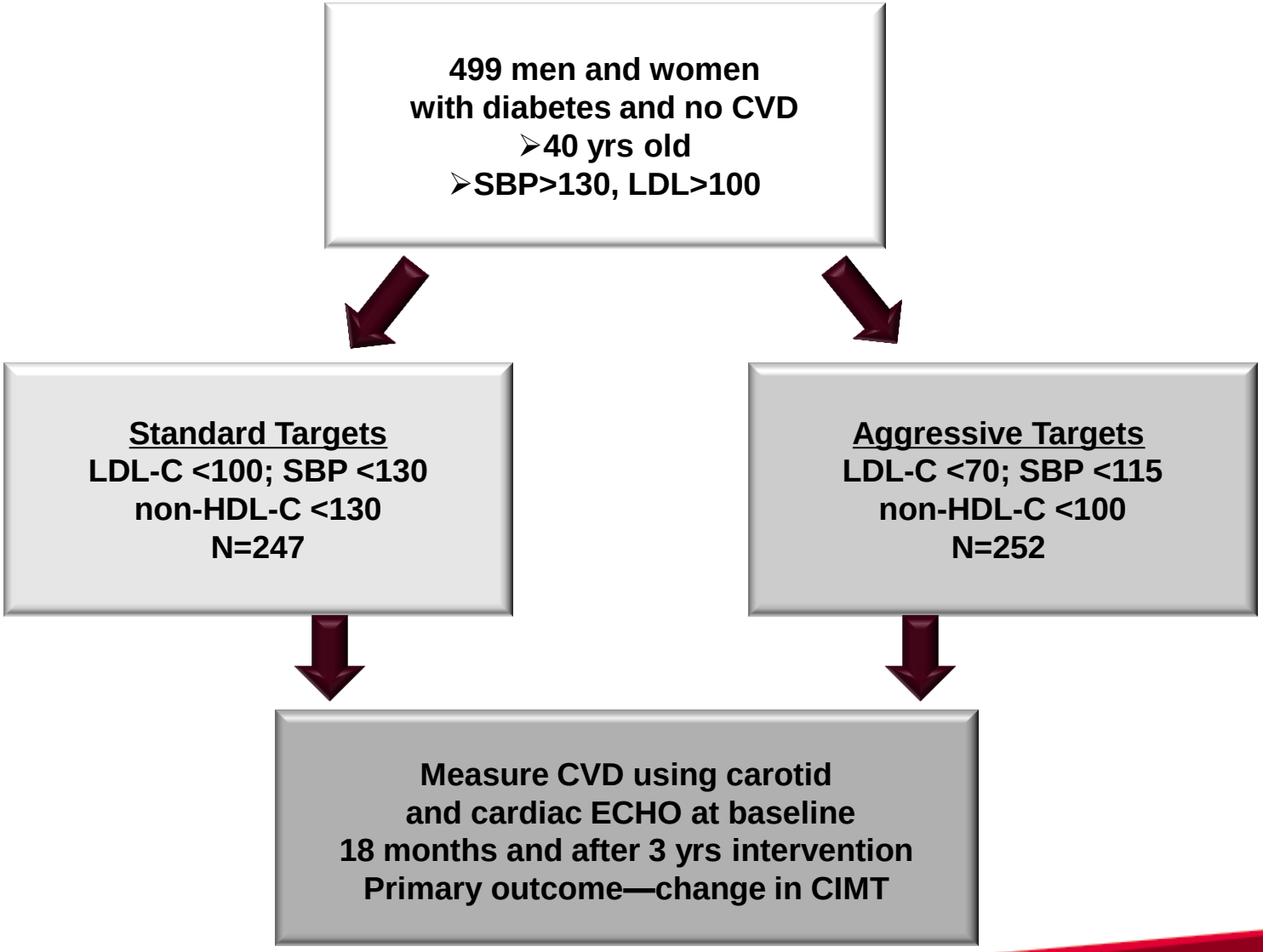
1. atherosclerosis progression
2. depletion of plaque lipid and macrophages & contributing to the plaque stabilization



Immunolocalization of monocyte chemoattractant protein-1 (MCP-1) on femoral arteries from normolipidemic diet (ND, A), untreated (B), ezetimibe-treated (Eze, C), simvastatin-treated (Simva, D) and ezetimibe + simvastatin-treated (Eze + Simva, E) rabbits. *P < 0.05 versus untreated rabbits.

1. Gómez-Garre British Journal of Pharmacology 2009;156 1218–1227

SANDS (Stop Atherosclerosis in Native Diabetics Study)



1. Howard et al. JAMA. 2008;299(14):1678-1689

SANDS (Stop Atherosclerosis in Native Diabetics Study) Trial

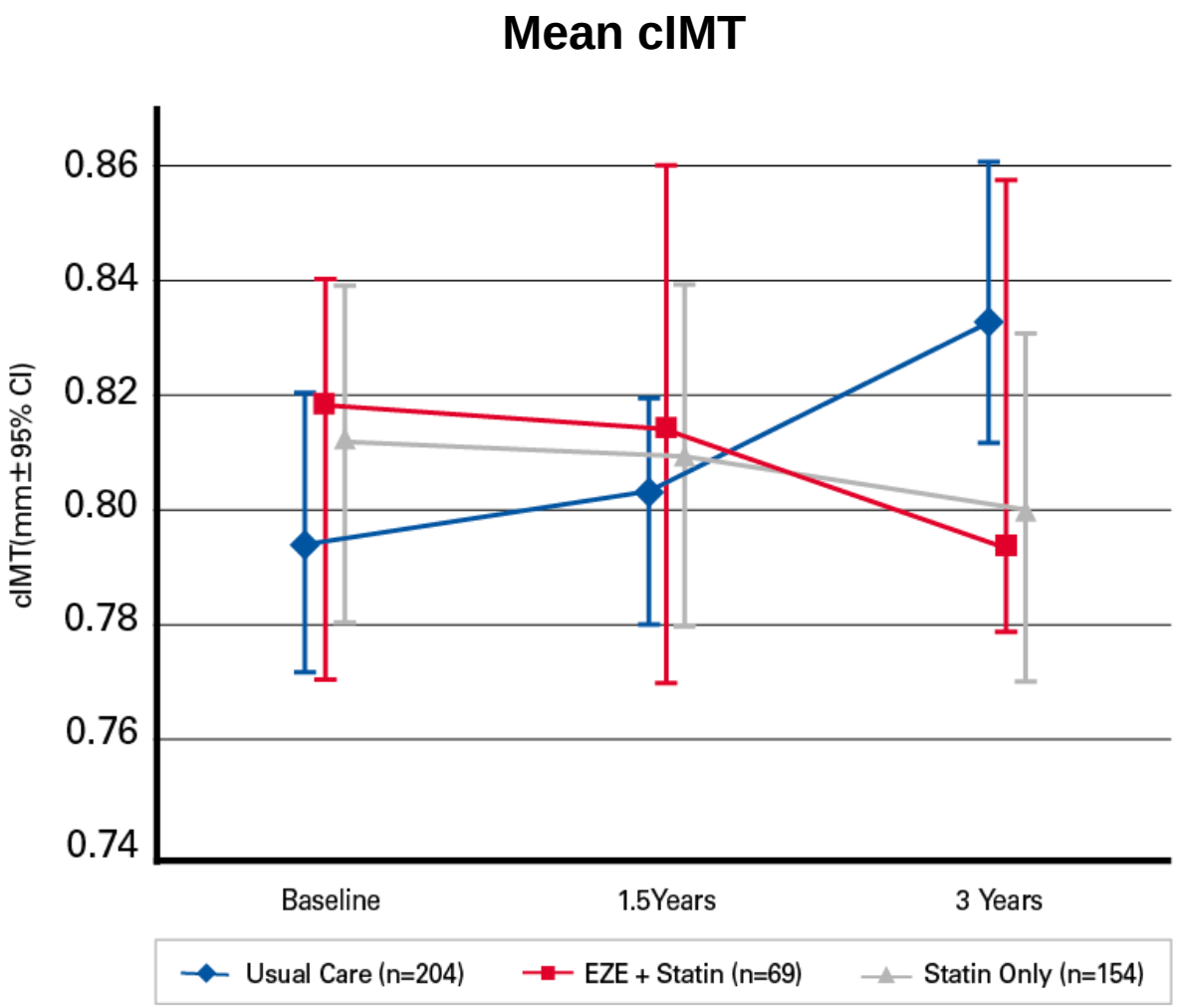
- Study population:
  - Native Americans (>40 years of age) with type 2 diabetes (N=499)
  - **Lipid lowering therapy at enrollment:**
    - **37% - 44% on statins**
    - **4% - 7% on fibrates**
    - **0 – 2% on niacin**
    - **0 – 2% on fish oil**
- Treatment duration: 3 years
- Primary endpoint: mean change in cIMT

Tx arm	Baseline LDL-C (mg/dL)	Endpoint LDL-C (mg/dL)	Change (%)
Usual care	102	**103**	+ 0.9
Aggressive Tx			
Statin only	101	**68**	– 32
EZE + statin	108	**78**	– 31

*P-value for change in cIMT for both active treatment arms vs usual care group

1. Fleg JL et al. *J Am Coll Cardiol.* 2008;52:2198.

SANDS (Stop Atherosclerosis in Native Diabetics Study) Trial



1. Fleg JL et al. *J Am Coll Cardiol.* 2008;52:2198.

VYCTOR (VYTORIN on cIMT and Overall Arterial Rigidity) Study

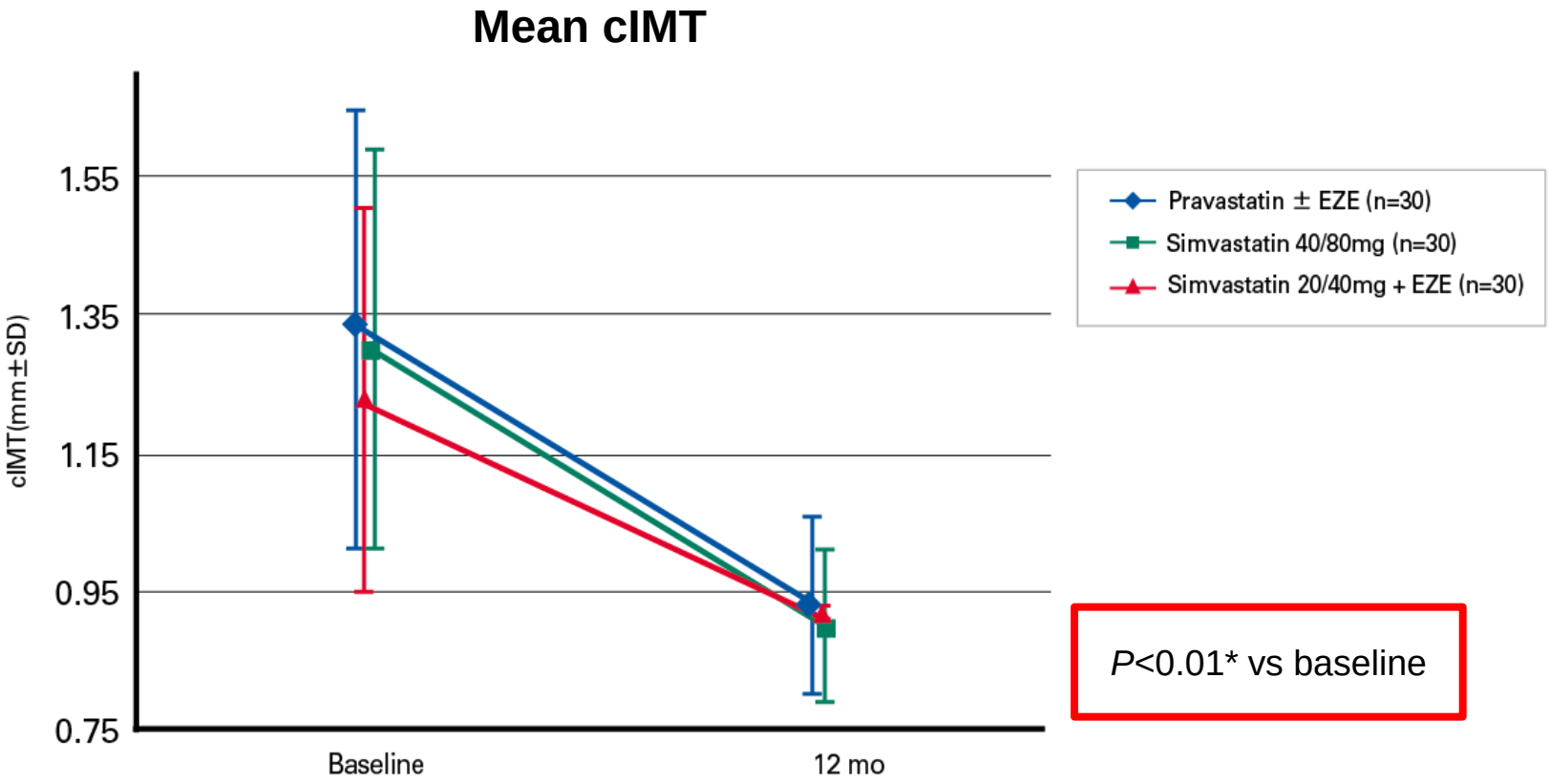
- Population:
  - Mexican patients 40 – 72 years of age with 10-year absolute risk for CD or MI >20% (N=90)
  - **Majority of patients on prior low-dose statins**
  - **No prior use of ezetimibe**
- Treatment Duration: 12 months
- Primary endpoint: change in mean cIMT

Tx arm	Baseline LDL-C (mg/dL)	Endpoint LDL-C (mg/dL)	Change (%)
Pravastatin 40 mg ± EZE 10 mg[A]	128	48	**– 62**
Simvastatin 40 mg or 80 mg[B]	130	45	**– 65**
Simvastatin 20 mg or 40 mg[C] + EZE 10 mg	131	48	**– 63**

A: EZE added in month 2 if goal was not attained
B. Simva titrated to 80mg in month 2 if goal was not attained
C. EZE/Simva titrated to 10/40mg in month 2 if goal was not attained

1. Meaney et al. Journal of Clinical Pharmacology, 2009;49:838-847

VYCTOR (VYTORIN on cIMT and Overall Arterial Rigidity) Study

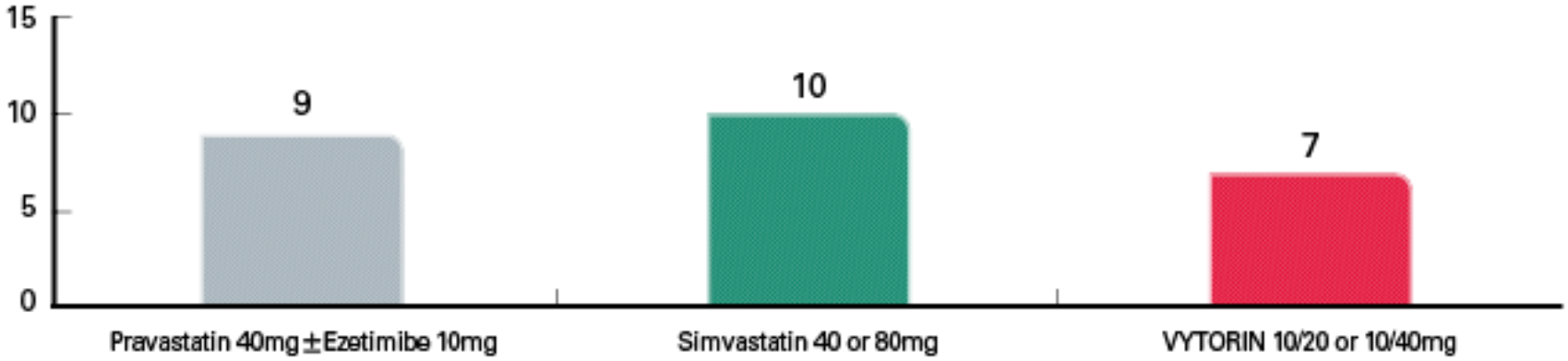


CD = Coronary death; MI = Myocardial infarction

*P–value for intragroup analysis for 12 month vs baseline cIMT for all groups

Meaney et al. *J Clin Pharmacol.* 2009;49:838-47.

Same cIMT regression, but low discontinuation



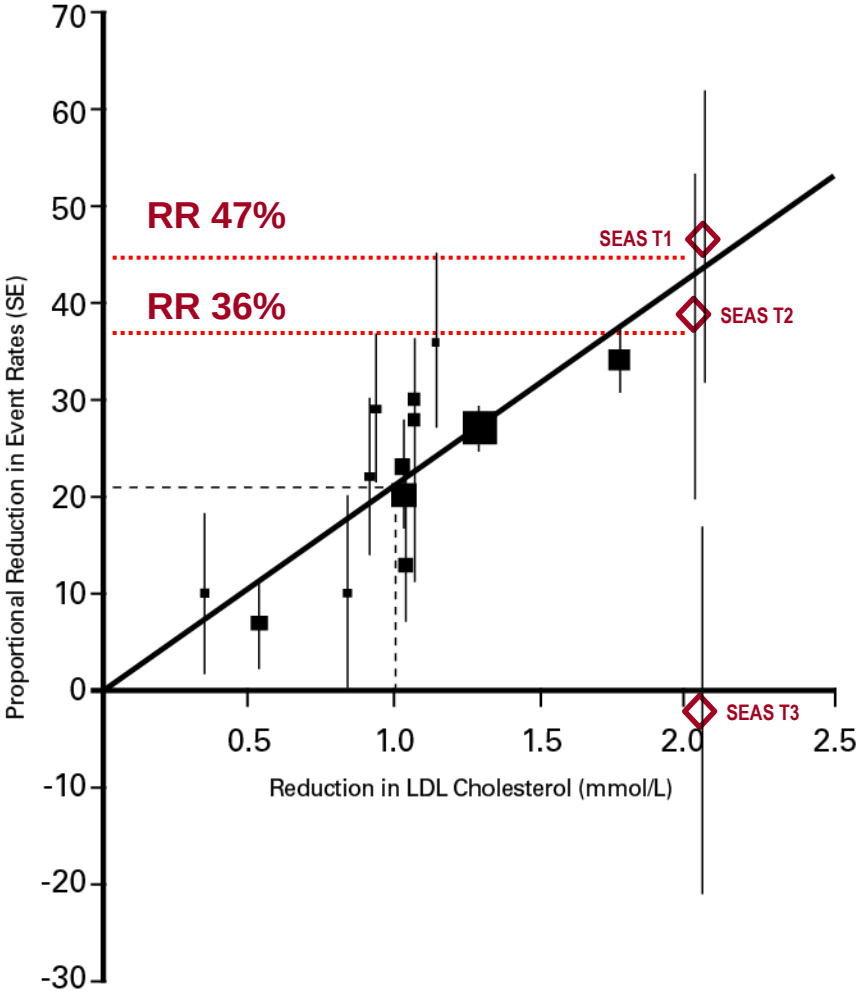
Group	No Goal Attainment	Raise of CPK	Abandonment	Rash	Myalgia	Total
Pravastatin 40 ±Ezetimibe 10mg	8[a]	0	1	0	0	9
Simvastatin 40 or 80mg	4[b]	3[c]	2	0	1	10
VYTORIN 10/20 or 10/40mg	4[d]	0	2	1[e]	0	7
Total	16	3	5	1	1	26

CPK, creatine phosphokinase, 5 times higher than normal reference values. All secondary effects in group B occurred with 80 mg of simvastatin.
a. Pravastatin 40 mg + ezetimibe 10 mg.
b. Simvastatin 80 mg.
c. Simvastatin 40 mg.
d. Simvastatin + ezetimibe 40/10 mg.
e. Simvastatin + ezetimibe 20/10 mg.

Meaney et al. *J Clin Pharmacol.* 2009;49:838-47.

2. **New considering point of view for preventing Atherosclerosis**
   - CRP
   - Chylomicron and ApoB in atherosclerosis
   - Further clinical outcomes of combination therapy

Reduction of Ischemic Cardiovascular Events in SEAS trial



- In the **Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial, combined ezetimibe (10 mg) and simvastatin (40 mg)** decreased low-density lipoprotein cholesterol levels by 50% and **ischemic cardiovascular event (ICE) risk** by 22% compared to placebo.
- In JV tertiles 1(baseline mean JV=2.5m/s) and 2(3.1m/s), **ICE risk decreased by 47% and 36%,** respectively, was reasonably well predicted by all LCs, and was consistent with findings from meta-regression analyses in other populations. (JV terriles 3: 3.7m/s)

1. Holme Am J Cardiol 2010;105 1802–1808

SHARP: Eligibility and Key outcome

- The effects of lowering LDL cholesterol with Simvastatin plus Ezetimibe in patients with chronic kidney disease (Study of Heart And Renal Protection : SHARP)
- 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

SHARP: Study of Heart And Renal Protection

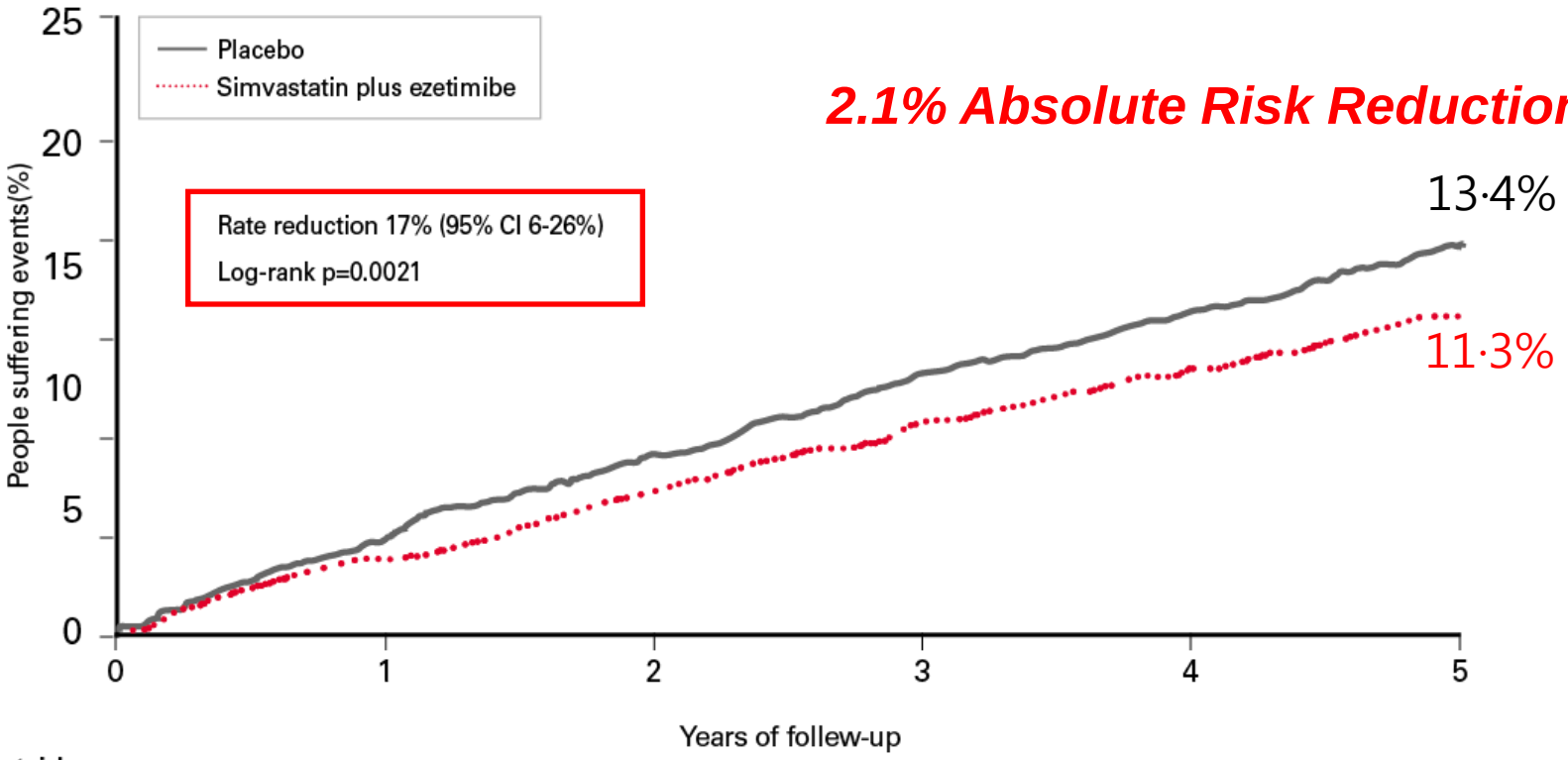
	Simvastatin + ezetimibe (n=4,650)		Placebo (n=4,620)
Previous vascular disease*	711 (15%)		682 (15%)
Diabetes*	1,054 (23%)		1,040 (23%)
Men	2,915 (63%)		2,885 (62%)
Age at randomisation (years)*	62 (12)		62 (12)
Total cholesterol (mmol/L)	4.88 (1.20)	**189 mg/dL**	4.90 (1.17)
LDL cholesterol (mmol/L)	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)
Renal status			
On dialysis	1,533 (33%)		1,490 (32%)
Haemodialysis	1,275 (27%)		1,252 (27%)
Peritoneal dialysis	258 (6%)		238 (5%)
Not on dialysis†	3,117 (67%)		3,130 (68%)

Data are n (%), mean (SD), or median (IQR). MDRD=Modifi ed Diet in Renal Disease.17 GFR=glomerular fi ltration rate. *Variables updated at 1 year for patients originally allocated simvastatin only who were rerandomised to simvastatin plus ezetimibe or placebo. †Five versus fi ve patients received a transplant before rerandomisation.

1. Colin Baigent Lancet 2011; 377 2181–2192

SHARP: Major Atherosclerotic Events composite endpoint

coronary death, non-fatal MI, non-hemorrhagic stroke and any revascularization



2.1% Absolute Risk Reduction

13·4%

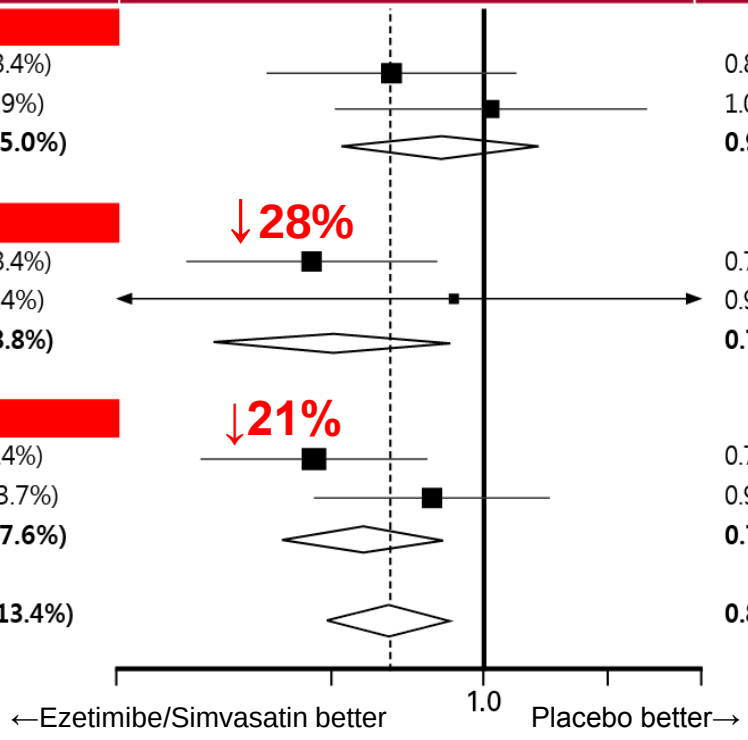
11·3%

Numver at risk						
Placebo	4620	4204	3849	3469	2566	1269
Simvastatin plus ezetimibe	4650	4271	3939	3469	2655	1265

1. Colin Baigent Lancet 2011; 377 2181–2192

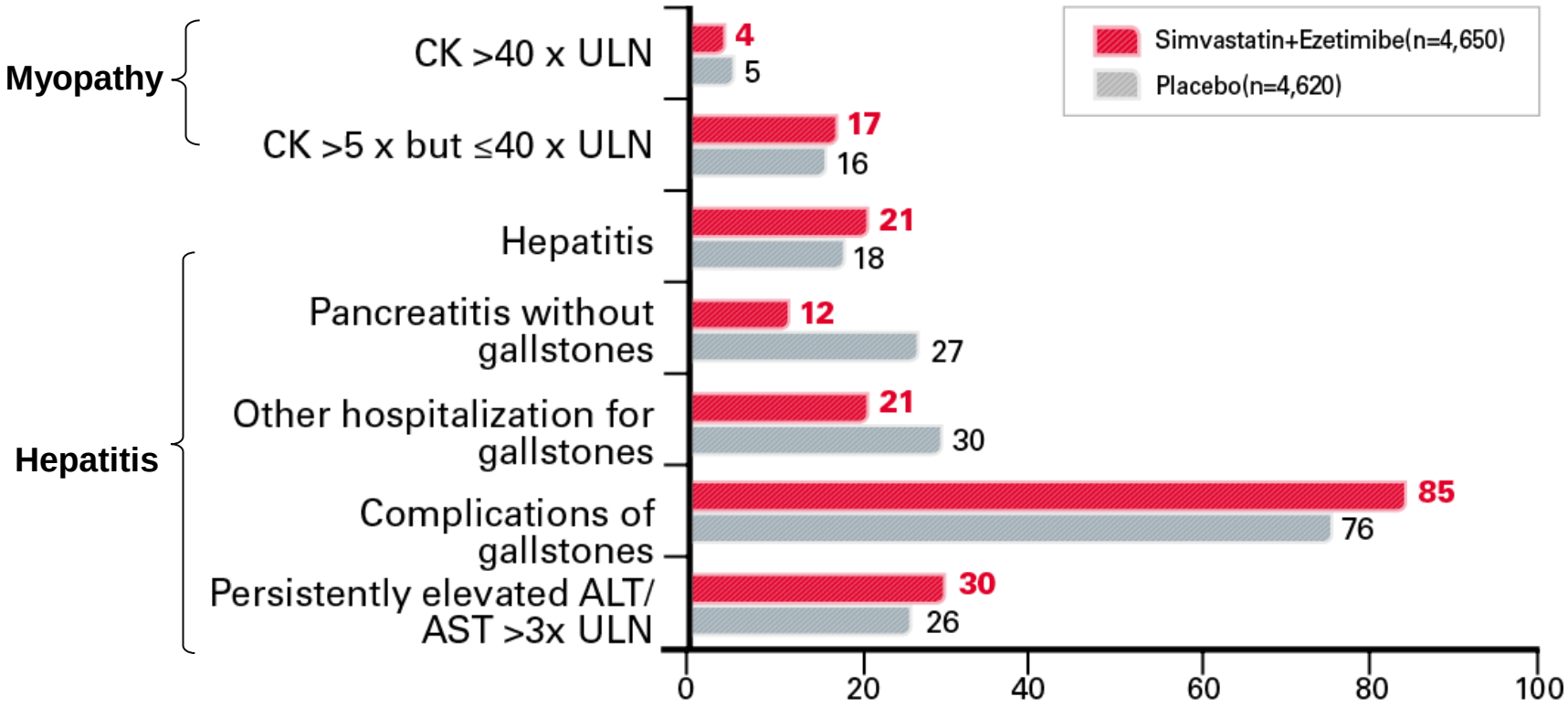
SHARP: Major Atherosclerotic Events composite endpoint

	Simvastatin plus ezetimibe (n=4,650)	Placebo (n=4,620)	Risk ratio(95% CI)	P value
Coronary events				
Non-fatal MI	134 (2.9%)	159 (3.4%)	0.84 (0.66-1.05)	159 (3.4%)
CHD death	91 (2.0%)	90 (1.9%)	1.01 (0.75-1.35)	90 (1.9%)
Subtotal: hemorrhagic event	**213 (4.6%)**	**230 (5.0%)**	**0.92 (0.76-1.11)**	**230 (5.0%)**
Non-hemorrhaging stroke				
Ischemic	114 (2.5%)	157 (3.4%)	0.72 (0.57-0.92)	157 (3.4%)
Unknown type	18 (0.4%)	19 (0.4%)	0.94 (0.49-1.79)	19 (0.4%)
Subtotal: any non-hemorrhagic	**131 (2.8%)**	**174 (3.8%)**	**0.75 (0.60-0.94)**	**174 (3.8%)**
Revascularisation procedures				
Coronary	149 (3.2%)	203(4.4%)	0.73 (0.59-0.90)	203(4.4%)
Non-coronary	154 (3.3%)	169 (3.7%)	0.90 (0.73-1.12)	169 (3.7%)
Subtotal: any revascularisation	**284 (6.1%)**	**352 (7.6%)**	**0.79 (0.68-0.93)**	**352 (7.6%)**
Total: any major ahterosclerotic event	**526 (11.3%)**	**619 (13.4%)**	**0.83 (0.74-0.94)**	**619 (13.4%)**

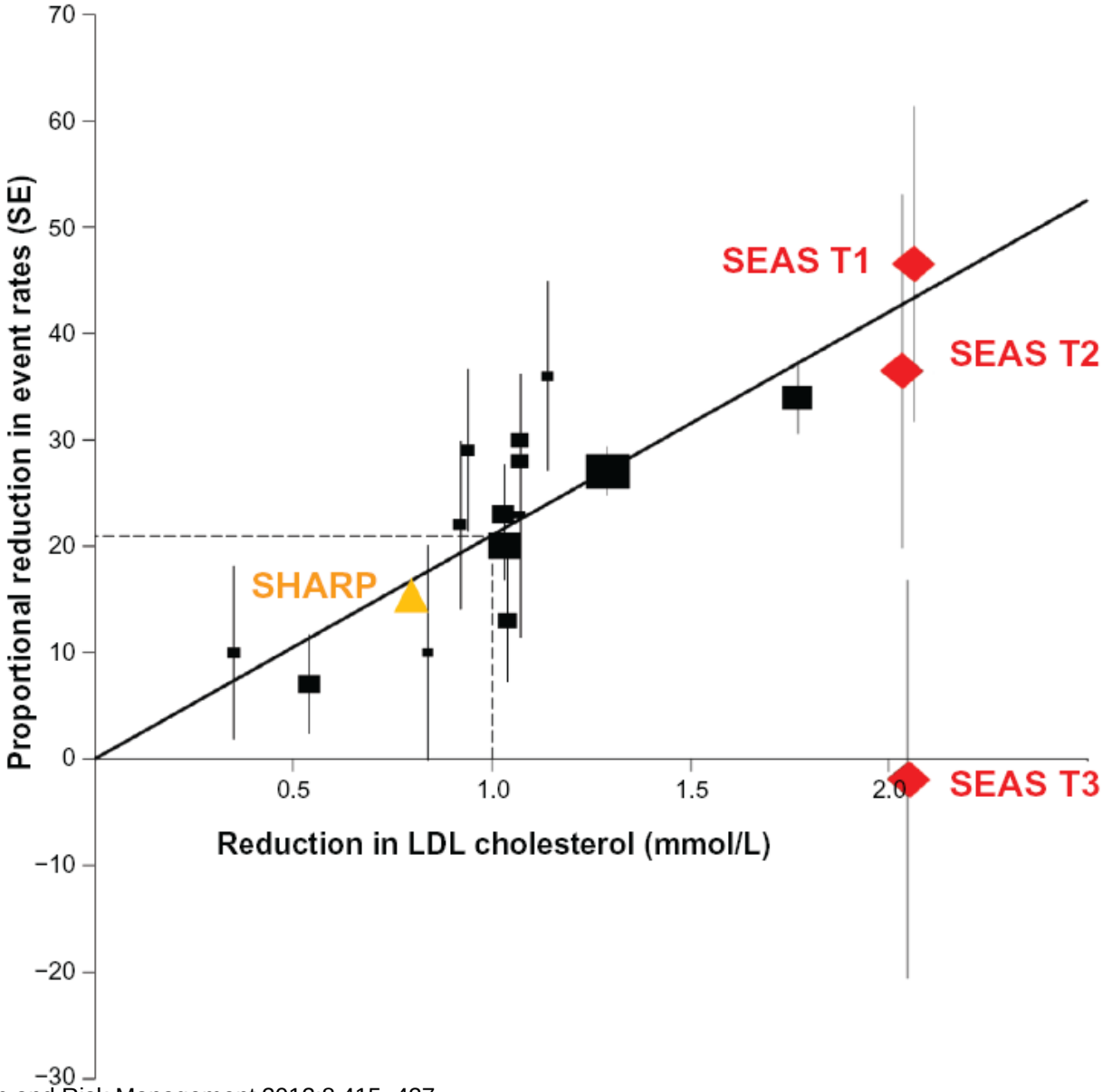


1. Colin Baigent Lancet 2011; 377 2181–2192

SHARP: Safety

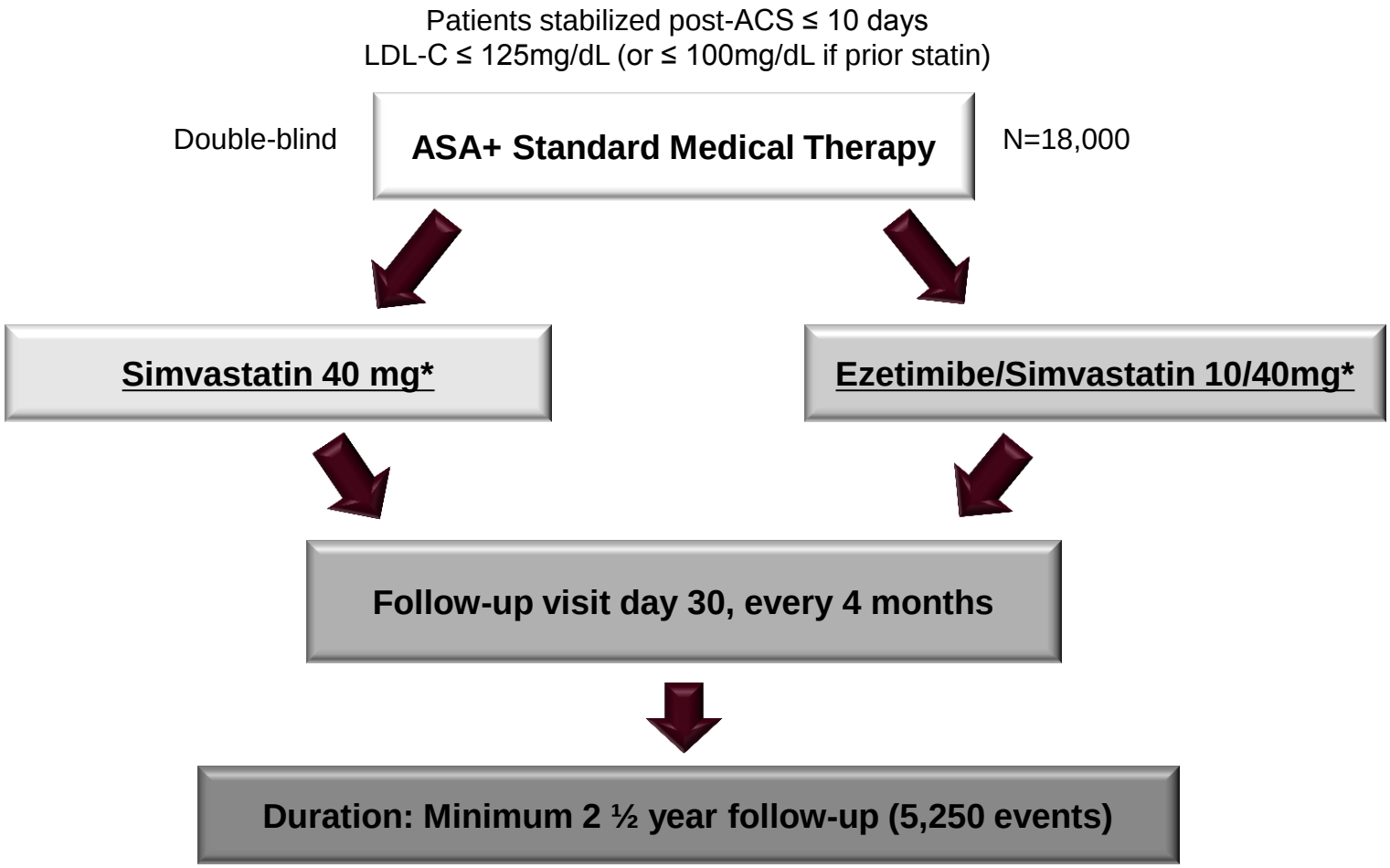


Event reduction based upon the level of LDL-C reduction of ezetimibe/statin and the Cholesterol Treatment Trialists'



Vascular Health and Risk Management 2012:8 415–427

IMPROVE-IT: IMProved Reduction of Outcomes: Vytorin Efficacy International Trial



Primary Endpoint: CV Death, MI, Hospital Admission for UA, Revascularization (>30 days after randomization), or Stroke

LDL-C, low density lipoprotein-cholesterol; CV, cardiovascular; MI, Myocardial infarction; UA, unstable angina

1. Cannon et al. American Heart Journal. 2008;156:826-832.

Take Home Messages

Ezetimibe and Statin Fixed dose combination might be smart option for managing dyslipidemia in high risk patients

1. Ezetimibe/Statin therapy may be useful for lowering LDL-C level, irrespective of baseline levels of cholesterol absorption and synthesis marker[1]
2. ESC/ESA 2011 recommends more aggressive lipid target for very high-risk patients [< 1.8 mmol/L(~70 mg/dL) And/or ≥ 50% reduction from baseline][2]
3. Combined ezetimibe (10mg) and simvastatin(40 mg) decreased LDL-C by 50% and ischemic cardiovascular event(ICE) risk by 22% compared to placebo[3]

1. Okada, et al. Circ J. 2011;75:2496-504, 2. Reiner Z et al. Eur Heart J. 2011;32:1769–1818, 3. Holme Am J Cardiol 2010;105 1802–1808.

STAR VYTORIN

STrong, sAfe, Rapid on target

MSD does not recommend the use of any product in any different manner than as described in the approved Prescribing information.

Physicians are advised to consult the prescribing information issued by the manufacturers before prescribing any drug discussed or described at this meeting.

VYTORIN Prescription Information

바이토린 정(에제티미브/심바스타틴) 10/10, 10/20, 10/40, 10/80 mg

[효능 효과] 원발성 고콜레스테롤혈증(이형접합 가족형 및 비가족형) 및 혼합형 고지혈증 환자의 상승된 총 콜레스테롤(total-C), LDL-콜레스테롤(LDL-C), 아포 B 단백(Apo B) 및 트리글리세라이드(TG)을 감소시키고, HDL-콜레스테롤(HDL-C)을 증가시키기 위한 식이요법의 보조제로서 투여합니다. 동형접합 가족형 고콜레스테롤혈증(HoFH) 환자의 상승된 총콜레스테롤 및 LDL-콜레스테롤을 감소시키기 위한 다른 지질저하 치료(예, LDL Apheresis)의 보조제로서, 또는 다른 지질 저하 치료가 유용하지 않은 경우 투여합니다.

[용법 용량] 바이토린을 투여전 및 투여중인 환자는 표준 콜레스테롤 저하식을 해야 하며, 투여량은 환자의 LDL-콜레스테롤의 기저치, 권장되는 치료목표치 및 환자의 반응에 따라 조절되어야 합니다. 바이토린은 식사와 관계없이 1일 1회 저녁에 투여합니다. 일반적으로 권장되는 초회용량은 1일 10/20mg이고, LDL-콜레스테롤 감소의 필요성이 적은 환자인 경우 1일 10/10mg으로 시작할 수 있습니다. 바이토린의 투여를 시작 후 또는 용량 적정 후, 4주 이상의 간격을 두고 혈중 지질치를 확인 한 후 용량을 조절합니다. 심바스타틴 80 mg 용량은 저용량 및 다른 스타틴계 약물에 비해 근육병증의 위험이 높기 때문에 10/80mg 용량은 중증의 고콜레스테롤혈증 환자 및 심혈관계 합병증의 위험이 높은 환자 중 저용량에서 치료목표에 이르지 못하고, 약물사용의 유익성이 잠재적인 위험성을 상회하는 경우에 한하여 제한적으로 투여합니다. 경증의 신장애(추정 사구체여과율(GFR) ≥ 60mL/min/1.73㎡) 환자의 경우 용량 조절이 필요하지 않습니다. 만성 신장 질환을 동반하고 추정 사구체 여과율 <60mL/min/1.73㎡인 환자의 경우, 바이토린10/20mg을 1일 1회 저녁에 투여합니다. 이러한 환자에게 더 높은 용량으로 투여할 때에는 신중히 투여하여야 하며 세심히 모니터링 해야 합니다. 경증의 간장애환자의 경우 용량 조절이 필요하지 않으나, 중등도 또는 중증의 간장애 환자의 경우 바이토린의 투여가 권장되지 않습니다.

[금기] 바이토린의 성분에 과민증인 환자 / 활동성 간질환 환자 또는 혈청 아미노전이효소 수치가 원인불명으로 지속적으로 높은 환자 / 임부 및 수유부 / 강력한 CYP3A4 억제제를 투여 중인 환자 / 겜피브로질, 사이클로스포린 또는 다나졸을 투여 중인 환자 / 갈락토오스 불내성(galactose intolerance), Lapp 유당분해효소 결핍증(Lapp lactase deficiency) 또는 포도당-갈락토오스 흡수장애(glucose-galactose malabsorption)등의 유전적인 문제가 있는 환자

VYTORIN Prescription Information

[경고]

1) 근육병증/횡문근융해: 근육병증/횡문근융해의 위험성은 심바스타틴 용량과 관련이 있습니다. 바이토린의 투여를 시작하는 모든 환자, 또는 용량을 증량한 모든 환자에게 근육병증의 위험성을 알려야 하며 설명되지 않는 근육통, 압통 또는 근육약화가 생기면 즉시 의사에게 보고해야 합니다. 만일 근육병증이 진단되거나 의심되면, 바이토린의 투여를 즉시 중지해야 합니다. 근육병증을 유발하는 요소로는 65세 이상의 고령자, 여성, 조절되지 않는 갑상선기능저하와 신기능 손상 등이 있습니다. 심바스타틴을 투여한 41,413 환자의 임상시험 데이터베이스 중 평균 추적조사 기간 4년 이상인 24,747명의 환자(약 60%)에서, 심바스타틴 20mg, 40mg, 80mg/일을 투여하였을 때 근육병증의 발현율은 각각 약 0.03%, 0.08% 및 0.61%였습니다. 이 임상시험들에서 환자는 주의깊게 모니터링 되었으며, 약물상호작용이 있는 몇몇 의약품들은 제외되었습니다. 심근경색증의 병력을 가진 환자에게 심바스타틴 80mg/일을 투여한 임상시험에서(평균 6.7년 동안 추적조사) 근육병증 발현율이 20mg 투여군에서 0.02%인 것에 비해, 80mg 투여군에서는 약 0.9%였습니다. 근육병증의 위험성은 유사한 LDL-콜레스테롤 감소 효능을 가진 다른 스타틴계 약물 치료에 비해 심바스타틴 80mg을 복용하는 환자군에서 더 높았습니다. 따라서 바이토린 10/80mg 용량은 심혈관계 합병증의 위험성이 높은 환자 중 저용량에서 치료목표에 이르지 못하고, 약물사용의 유익성이 잠재적인 위험성을 상회하는 경우에 한하여 제한적으로 투여합니다. 바이토린 10/80mg을 복용하는 환자가 바이토린과 상호작용하는 약물을 복용해야 하는 경우, 저용량의 심바스타틴을 함유한 이 약 또는 약물 상호작용 가능성이 보다 낮은 다른 스타틴-에제티미브 요법을 투여해야 합니다.

다음 약과의 병용투여시 근육병증/횡문근융해의 위험성이 증가됩니다:

- 바이토린의 용량은 아미오다론, 베라파밀 또는 딜티아젬을 병용투여하고 있는 환자에서 1일 10/20mg을 초과해서는 안 됩니다. 또한, 암로디핀을 병용투여하고 있는 환자에서 1일 10/40mg을 초과해서는 안 됩니다.
- 바이토린과 CYP3A4에 대한 중간 정도의 억제 효과를 가지는 것으로 알려져 있는 약물을 병용투여하는 경우, 근육병증의 위험성이 증가할 수 있습니다.
- 바이토린은 겜피브로질과 병용 투여하지 않습니다. 바이토린과 피브레이트계 약물과의 병용투여는 피해야 합니다.
- 바이토린과 푸시딘산을 병용투여하는 환자는 주의깊게 모니터링 되어야 하며,바이토린의 일시적인 투여 중단을 고려할 수 있습니다.
- 심바스타틴과 지질저하 용량(1일 1g 이상)의 니코틴산을 병용 투여하였을 때 근육병증/횡문근융해가 관찰되었습니다. 바이토린과 니코틴산 병용투여시 근육병증에 대한 위험성이 증가할 수 있으므로, 1일 10/20mg을 초과하는 용량과 지질저하 용량(1일 1g 이상)의 니코틴산을 병용 투여하지 않도록 합니다.

VYTORIN Prescription Information

2) 간기능 이상환자: 3개의 위약대조, 12주 임상시험 결과, 혈청 아미노전이효소(transaminase) 수치의 지속적 상승(정상상한치의 3배 이상)의 발현율은 바이토린을 투여한 전체 환자에서 1.7%였으나, 10/80mg을 투여한 환자에서는 2.6%로 용량과 관련 있게 나타났습니다. 바이토린을 투여 전 및 투여시작 후 임상적으로 필요한 시기에 간기능 검사를 실시하는 것이 바람직합니다. 바이토린 10/80mg으로 증량한 환자는 증량하기 전과 증량하고 3개월 후, 이후 치료의 첫 1년간 주기적인(예, 년2회) 간기능 검사를 추가 실시합니다. 혈청 아미노전이효소 수치가 상승된 환자의 경우 간기능검사를 다시 하여 모니터링 하며, 정상치로 돌아 올 때까지 간기능검사를 자주 실시해야 합니다. 만약, 혈청 아미노 전이효소(ALT 또는 AST)의 수치가 정상상한치의 3배 이상 상승할 경우 바이토린의 투여를 중지하는 것이 바람직합니다. 바이토린을 투여하는 동안 임상적 증상 및/또는 고빌리루빈혈증을 동반한 심각한 간손상이나 황달이 나타날 경우, 즉각 투여를 중단합니다. 다른 병인이 확인되지 않을 경우, 바이토린을 재투여하지 않습니다.

[이상반응] 바이토린 (또는 바이토린과 동등한 에제티미브와 심바스타틴의 병용투여)에 대한 안전성은 임상시험에 참여한 10,189명 이상의 환자에서 평가되었습니다. 바이토린은 일반적으로 내약성이 우수하였습니다. 유사하게 실시된 3개의 위약대조 임상시험(n=1,420)에서 투여약과의 관련성을 고려하지 않고 바이토린을 투여한 환자의 2% 이상에서 보고되었으며, 위약군에서의 발현율보다 높은 비율로 보고된 임상적 이상반응은 두통, 설사, 인플루엔자, 상기도 감염, 근육통 사지통 이었습니다.

[임부/수유부에 대한 투여] 임부에게 투여해서는 안 되며, 임신이 확인되면 즉시 투여를 중지해야 합니다.

[소아에 대한 투여] 소아 환자에 대한 안전성 및 유효성 자료는 불충분합니다.

[고령자에 대한 투여] 임상시험에서, 바이토린을 투여한 환자 중 792명이 65세 이상이었고(176명의 환자는 75세이상이였음) 안전성은 고령자 환자와 젊은 환자간에 유사하였으나, 일부 고령자 환자에서 보다 민감한 반응이 나타날 수 있음을 배제할 수 없습니다.

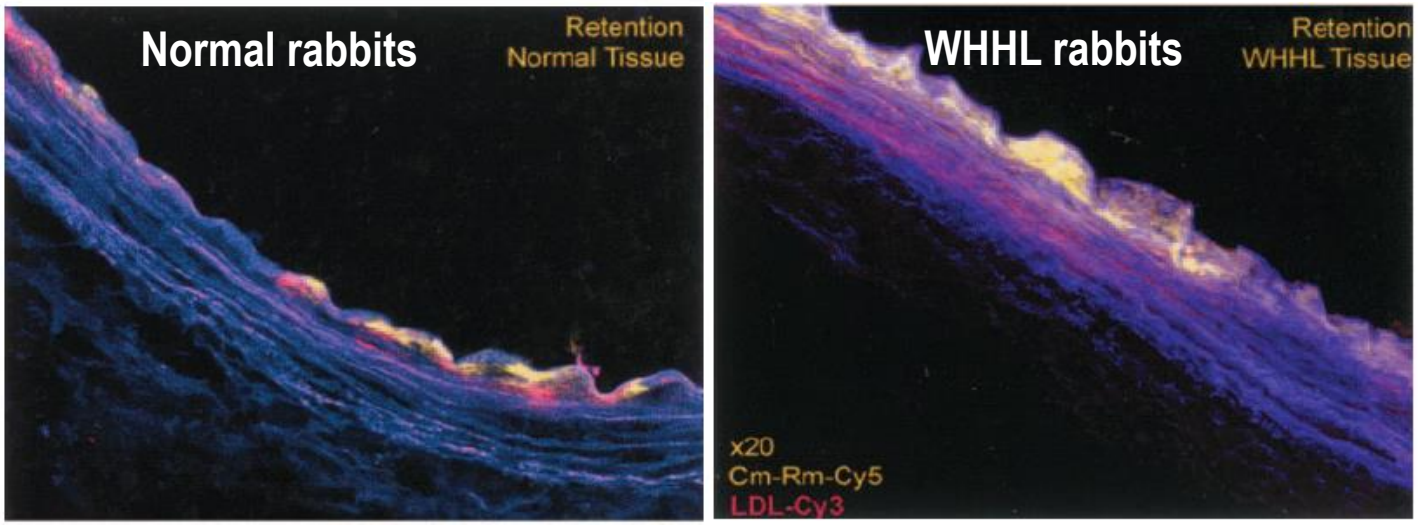
개정년월일 2012년 9월 18일

처방하시기 전에 각 항목에 대한 자세한 내용은 제품설명서 전문을 참조하시기 바랍니다.

Visual Comparison of the retention of LDL (red) and Chylomicron remnants (yellow) in carotid arteries from normalrabbits and WHHL rabbits

- Using 3D confocal microscopy to quantitatively determine arterial retention of ApoB 100 and ApoB48 lipoprotein
- Watanabe Heritable HyperLipidemic strain is primary model of human familial hypercholesterolemia. WHHL rabbits have mutation in the gene that encodes the ApoB100/ApoE LDLreceptor

⇒ The arterial retention of cholesterol derived from apoB48 and apoB100 lipoproteins was investigated in a rabbit carotid perfusion model under physiological conditions. We found that **the intimal retention of cholesterol derived from apoB48 lipoproteins was greater in WHHRs compared with controls** despite evidence that up to 90% of apoB48 lipoprotein internalization is mediated via the LDL receptor

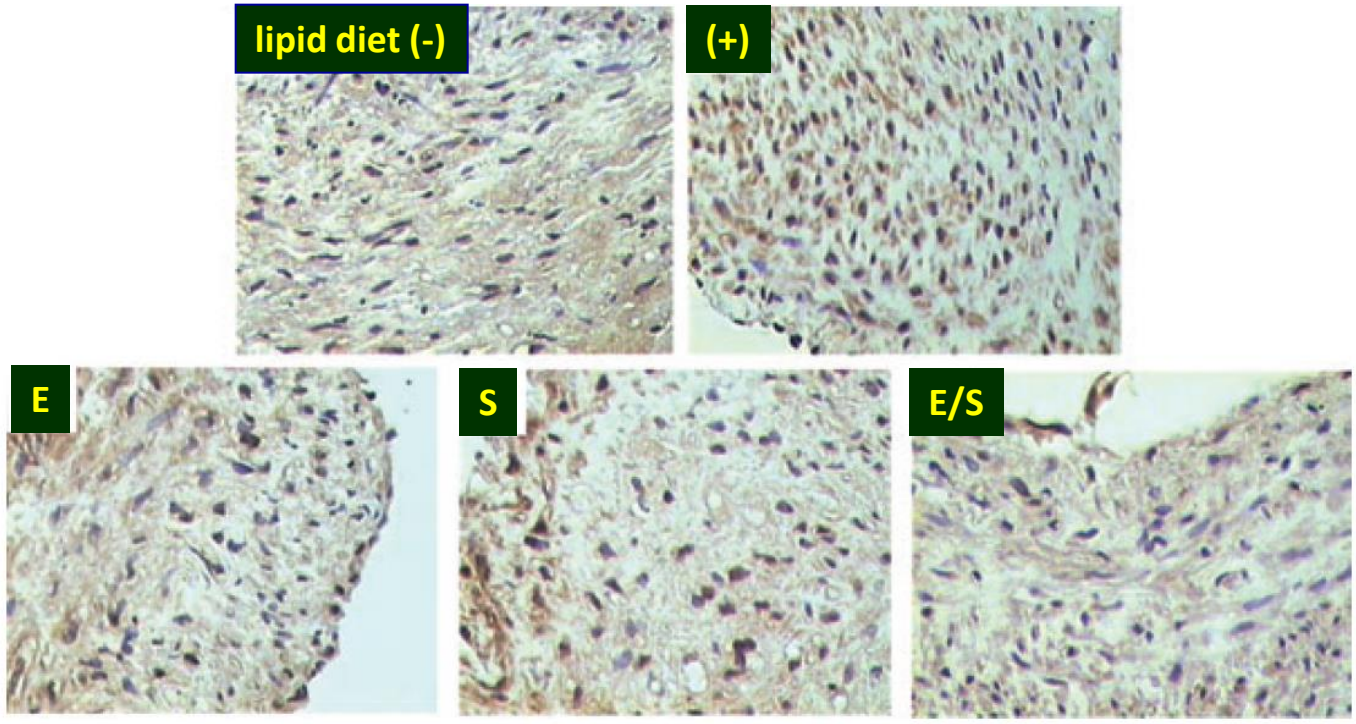


WHHL rabbits = watanabe heritable hyperlipidemic rabbits

1. Proctor, John C.L. Mamo. *Arterioscler Thromb Vasc Biol.* 2003;23:1595-1600

Ezetimibe/statin reduced migration of macrophage

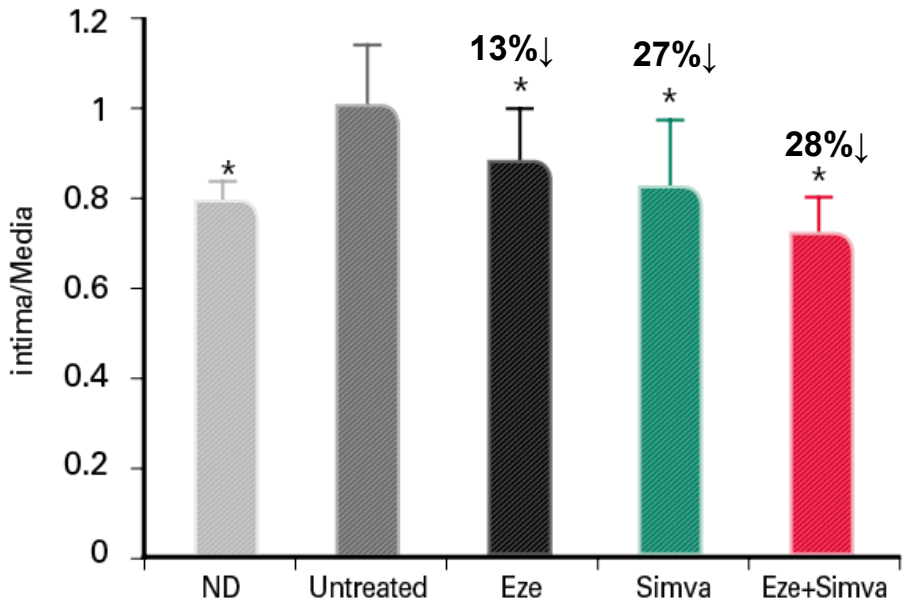
Immunolocalization of monocyte chemoattractant protein-1 (MCP-1)



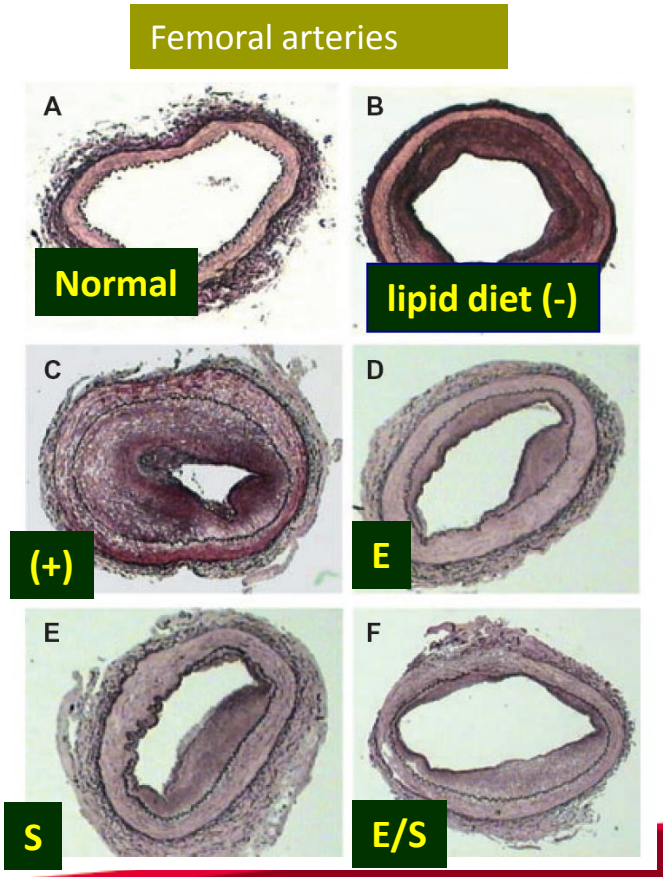
1. Gómez-Garre British Journal of Pharmacology 2009;156 1218–1227

Ezetimibe/statin might improves plaque stabilization (in rabbit model)

- Arms : ezetimibe, simvastatin, E/S
- Duration : 6 weeks
- Animal model : 34 Rabbits of accelerated atherosclerosis



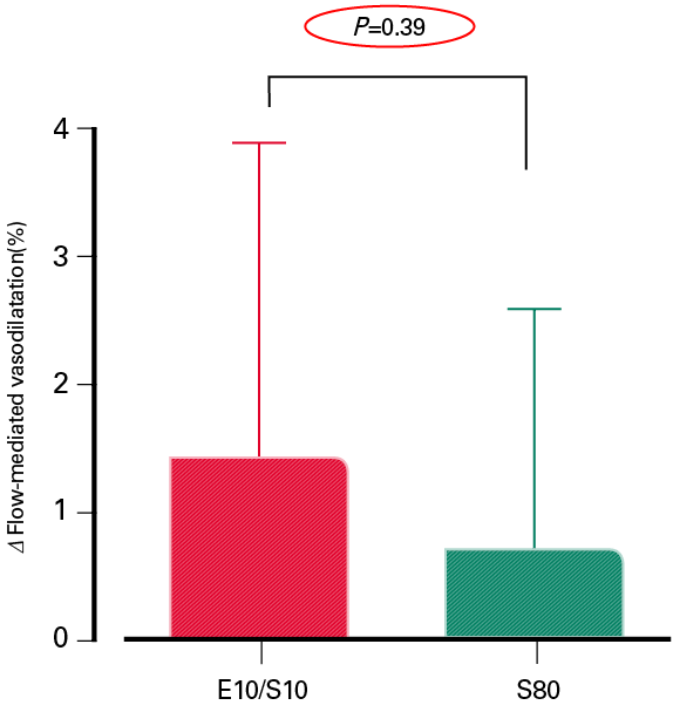
normolipidemic diet (ND, B), untreated (C), ezetimibe-treated (Eze, D), simvastatin-treated (Simva, E) and ezetimibe + simvastatin-treated (Eze + Simva, F) rabbits.
*$p < 0.05$ versus untreated rabbits.



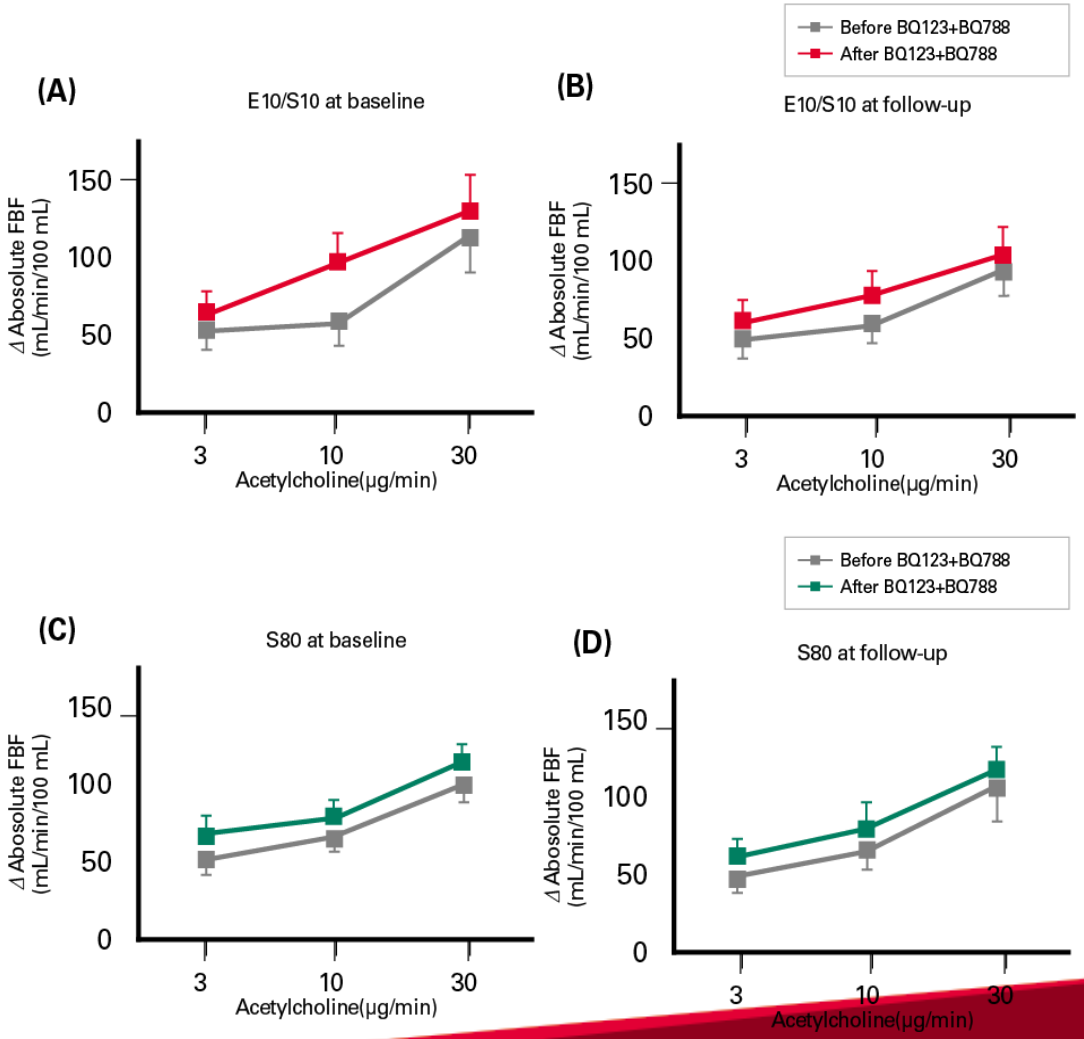
1. Gómez-Garre British Journal of Pharmacology 2009;156 1218–1227

Endothelial function marker was related with LDL-C lowering

- Arms : Simvastatin 80mg vs. Ezitimibe/Simvastatin(E/S) 10/10mg
- Duration : 6 wks
- Pts: 39 T2DM or IGT pts



Absolute changes in FMD



1. Settergren European Heart Journal 2008;29 1753–1760

ESC/EAS 2011 Guidelines:
Management of Dyslipidemia in Diabetes[1]

- **Type 1 Diabetes**
  - ✓ In all patients with type 1 diabetes and in the presence of microalbuminuria and renal disease, LDL-C lowering (≥30%) with statins as the first choice is recommended irrespective of the basal LDL-C concentration [Class I, Level C]

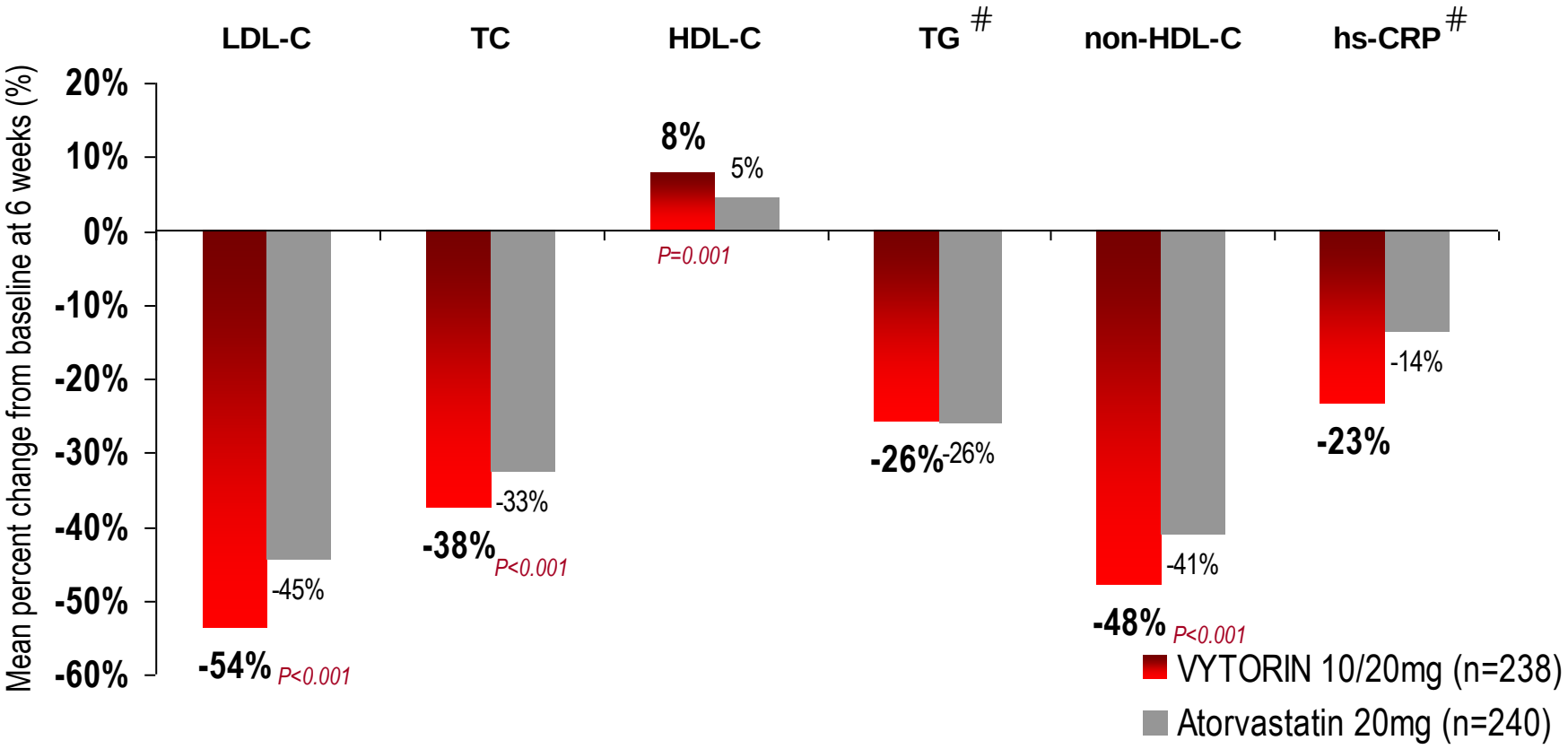
- **Type 2 Diabetes**
  - ✓ In patients with type 2 diabetes and CVD or CKD, and in those without CVD who are over the age of 40 years with 1 or more CVD risk factors or markers of target organ damage, the recommended goal for LDL-C is <1.8 mmol/L (~70 mg/dL) and the secondary goal for non-HDL-C is <2.6 mmol/L (100 mg/dL) and for apo B is <80 mg/dL [Class I, Level B]
  - ✓ In all people with type 2 diabetes, LDL-C goal <2.5 mmol/L (~100 mg/dL) is the primary target. Non-HDL-C <3.3 mmol/L (130 mg/dL) and apo B <100 mg/dL are the secondary targets. [Class I, Level B]

Class= Class of recommendation, Level= Level of evidence, CV= cardiovascular, ESC/EAS = European Society of Cardiology/European Atherosclerosis Society.

1. Reiner Z et al. Eur Heart J. 2011;32:1769–1818.

VYTORIN 10/20mg provided ≥50% LDL-C reduction in Type 2 Diabetes patients[1]

In a clinical study of patients with hypercholesterolemia and type 2 DM (VYTAL study)

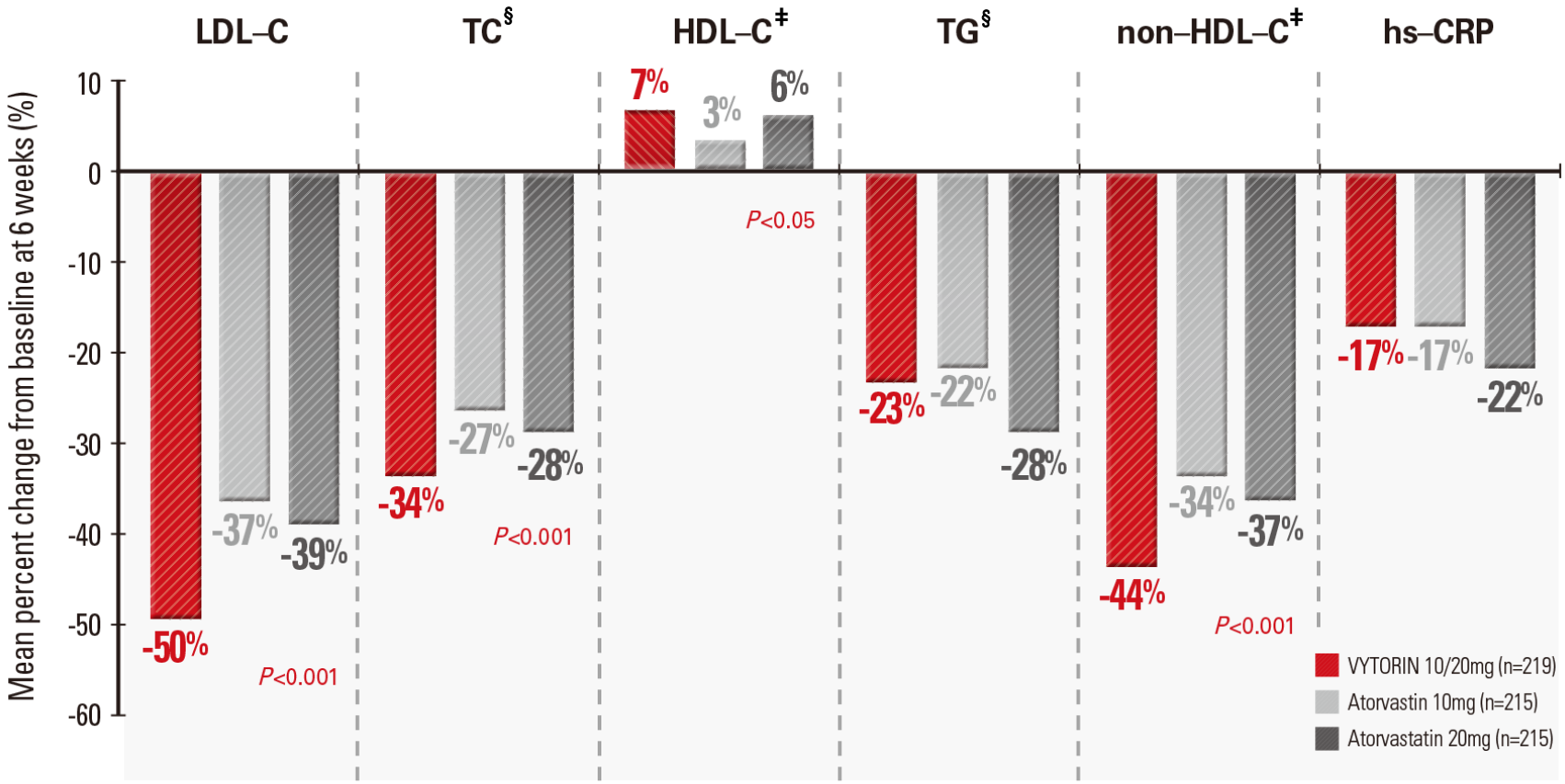


HDL-C: high-density lipoprotein cholesterol, hs-CRP: high-sensitivity C-reactive protein,
LDL-C: low-density lipoprotein cholesterol, TC: total cholesterol, TG: triglycerides
#: median

1. Goldberg RB, et al. *Mayo Clin Proc.* 2006;81(12):1579–1588

VYTORIN 10/20mg provided ≥50% reduction in LDL-C[1]

In a clinical study of patients with* hypercholesterolemia *and Metabolic Syndrome (VYMET study)

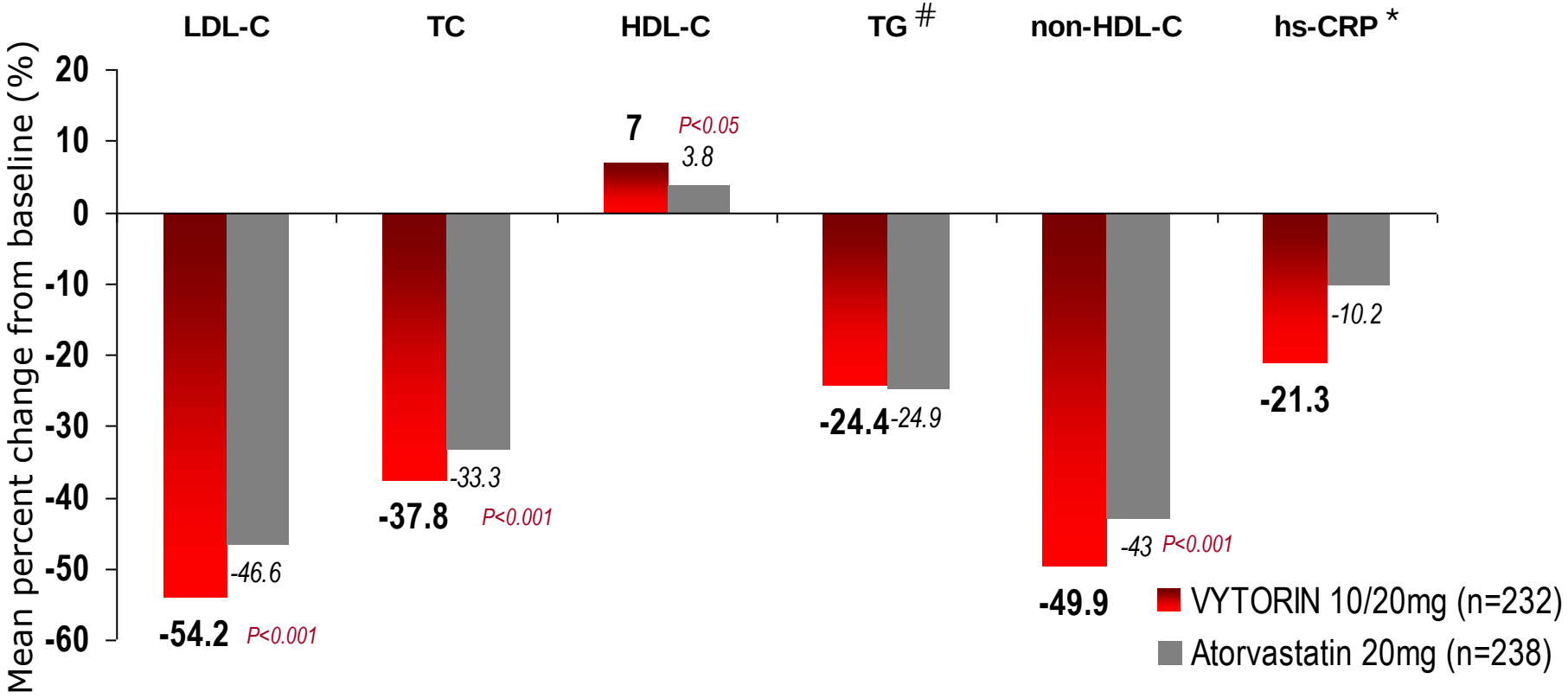


HDL-C= high-density lipoprotein cholesterol; hs-CRP= high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; TC= total cholesterol; TG= triglycerides.
§ Number of patients 220 for E/S 20 mg, 216 for A 20 mg.
‡Number of patients 216 for A 20 mg.

1. Robinson JG, et al. *Am J Cardiol* 2009;103:1694 –1702

VYTORIN 10/20mg: Greater improvements in key parameters than mono statin in elderly hyperlipidemia patients

In a clinical study of hypercholesterolemia patients ≥ 65 years of age with or without cardiovascular disease (VYTELD study)



HDL-C: high-density lipoprotein cholesterol, hs-CRP: high-sensitivity C-reactive protein,

LDL-C: low-density lipoprotein cholesterol, TC: total cholesterol, TG: triglycerides

#: Nonparametric results (medians) are presented for triglycerides

*: Longitudinal data analysis results are presented for high-sensitivity C-reactive protein.

Foody JM , et al, Am J Cardiol 2010;106:1255–1263

VYTORIN was Generally Well Tolerated[1]

Adverse Events	All VYTORIN 10/20, 10/40mg/day (n=513)	All atorvastatin 10, 20, 40mg/day (n=771)
≥1 Clinical event	28.3%	24.6%
Drug-related clinical event	4.1%	4.3%
Discontinuation due to drug-related clinical event	1.9%	1.2%
ALT or AST ≥3 × ULN (consecutive)	0.8%	0.5%
CK ≥ 10 X ULN with muscle symptoms	0%	0%

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal; CK=creatine kinase.

1. Foody JM , et al. *Am J Cardiol* 2010;106:1255–1263

Relationship of Atherosclerosis and Cardiovascular disease

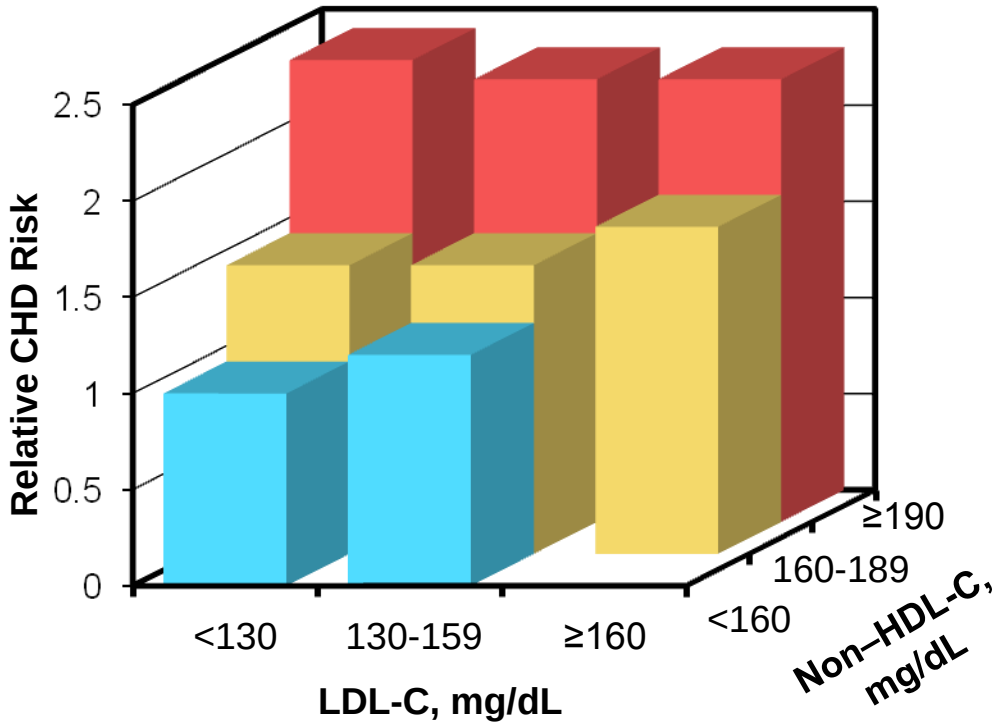
- Cardiovascular disease (CVD) due to atherosclerosis of the arterial vessel wall and to thrombosis is the foremost cause of premature mortality and of disability-adjusted life years (DALYs) .
- The management of dyslipidemias as an essential and integral part of CVD prevention.
- Dyslipidemias cover a broad spectrum of lipid abnormalities, some of which are of great importance in CVD prevention.

1. Reiner Z et al. *Eur Heart J.* 2011;32:1769–1818.

Non–HDL-C Is Superior to LDL-C in Predicting CHD Risk

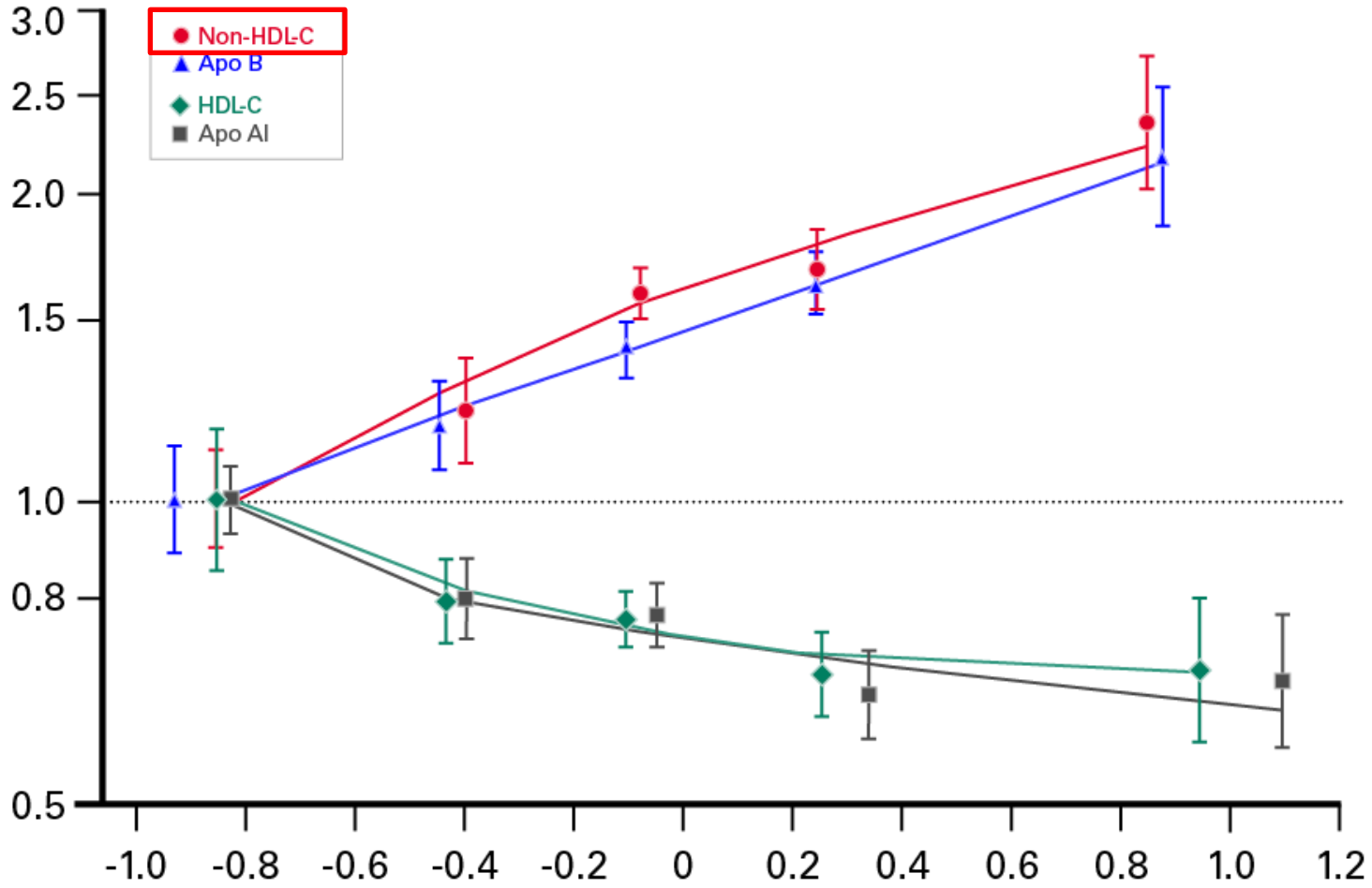
The Framingham Study

- Within non–HDL-C levels, no association was found between LDL-C and the risk for CHD
- In contrast, a strong positive and graded association between non–HDL-C and risk for CHD occurred within every level of LDL-C
- Non–HDL-C is a stronger predictor of CHD risk than LDL-C



1. Liu Am J Cardiol. 2006;98 1363-1368

Non-HDL-C concentration is in positive correlation with CVD



1. Emerging Risk Factors Collaboration JAMA. 2009;302(18)1993-2000

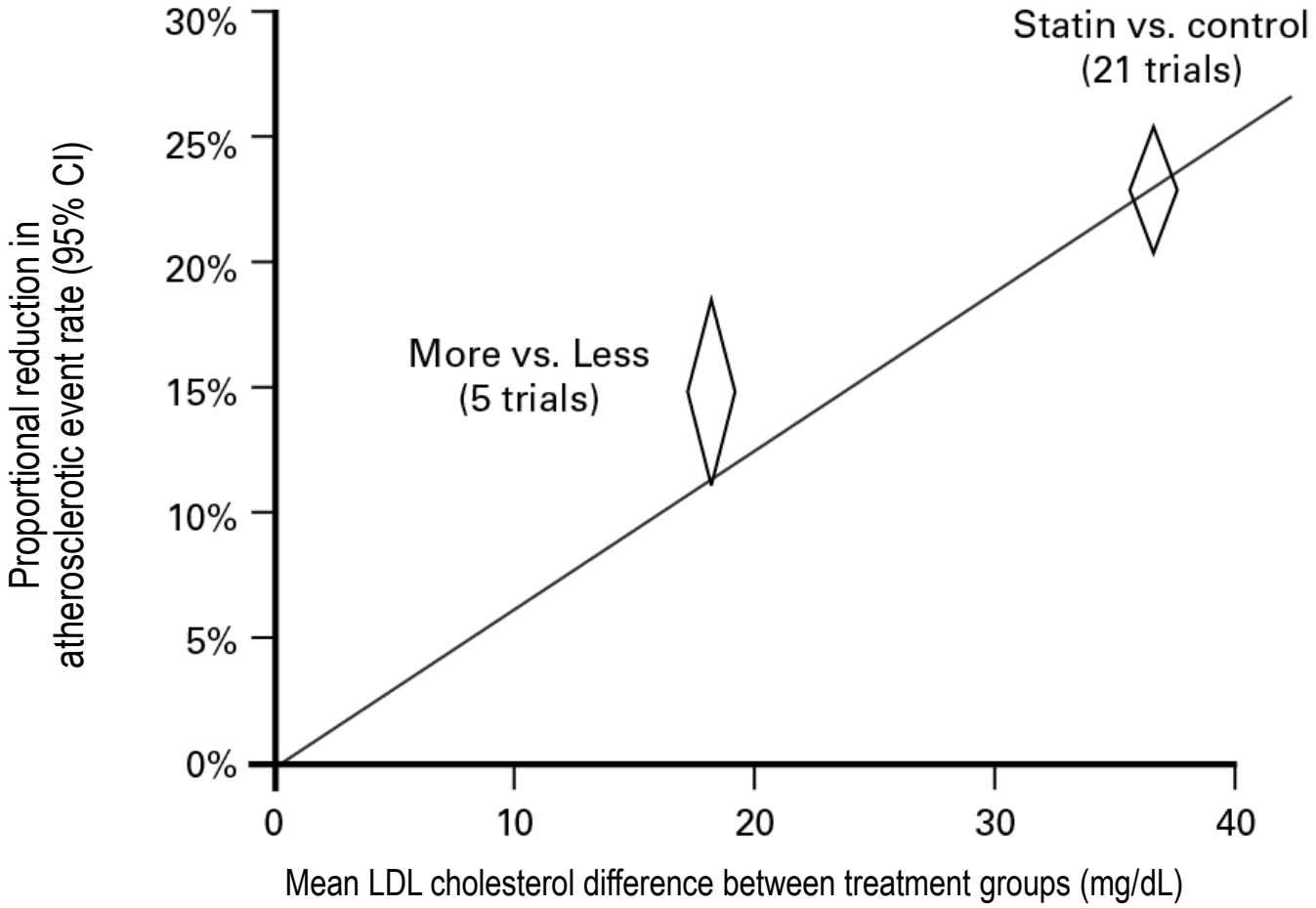
Non HDL-C: Secondary target of therapy

- Non-HDL-C = TC – HDL-C
- Apo B concentration represents total number of lipoprotein particles (LDL + IDL + VLDL + chylomicron)
- This may be called “non-HDL” cholesterol or “atherogenic cholesterol”
- If baseline triglycerides: ≥200 mg/dL,

Non-HDL cholesterol: Secondary target of therapy

1. Grundy SM. *Circulation* 1997;95:1-4.

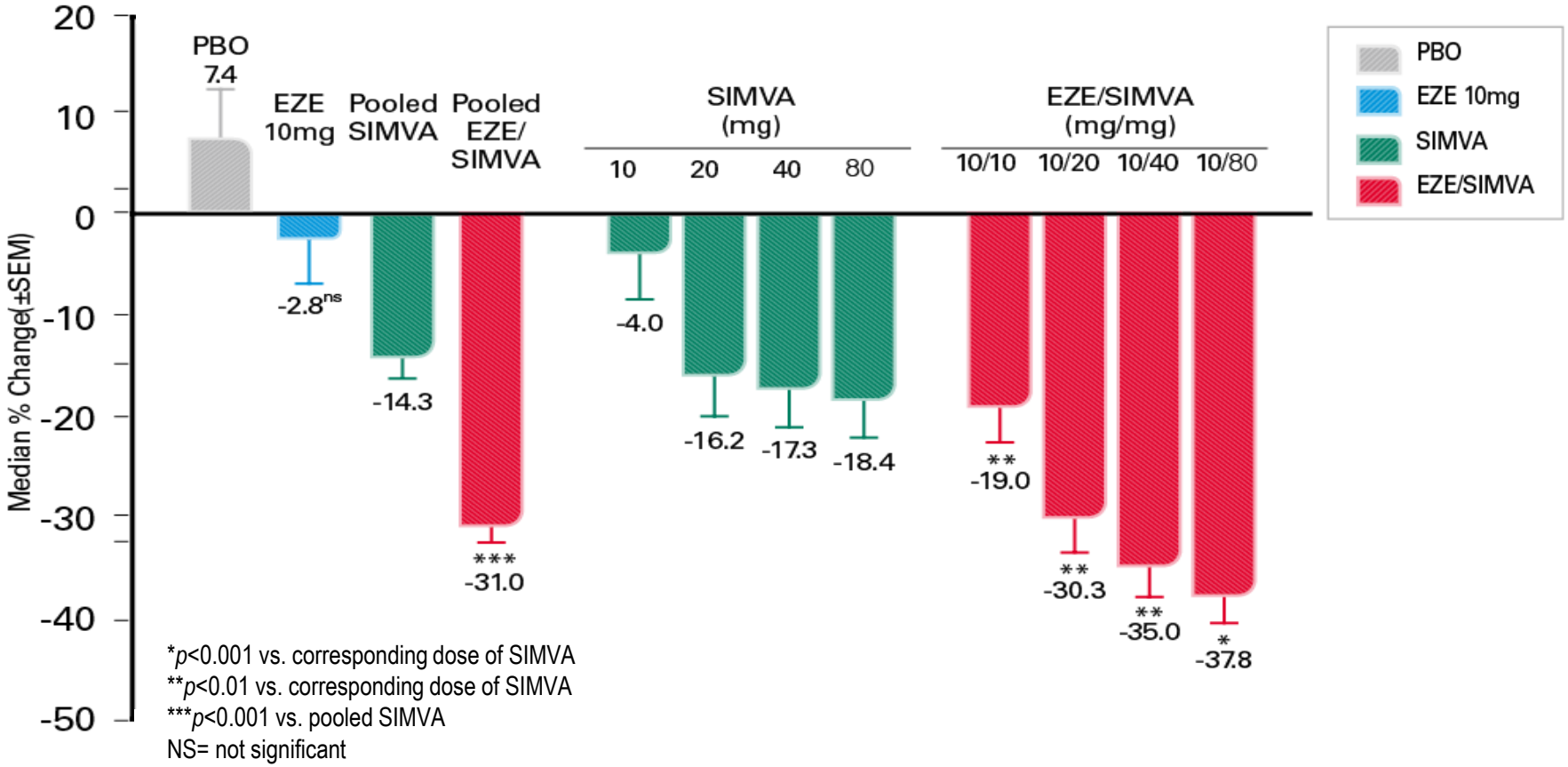
The LOWER, The BETTER : Cholesterol Treatment Trialists



1. Cholesterol Treatment Trialists' (CTT) Collaboration. *Lancet* 2010; 376: 1670–81

Significantly Greater % Reductions in CRP Were Achieved With Eze/Simva

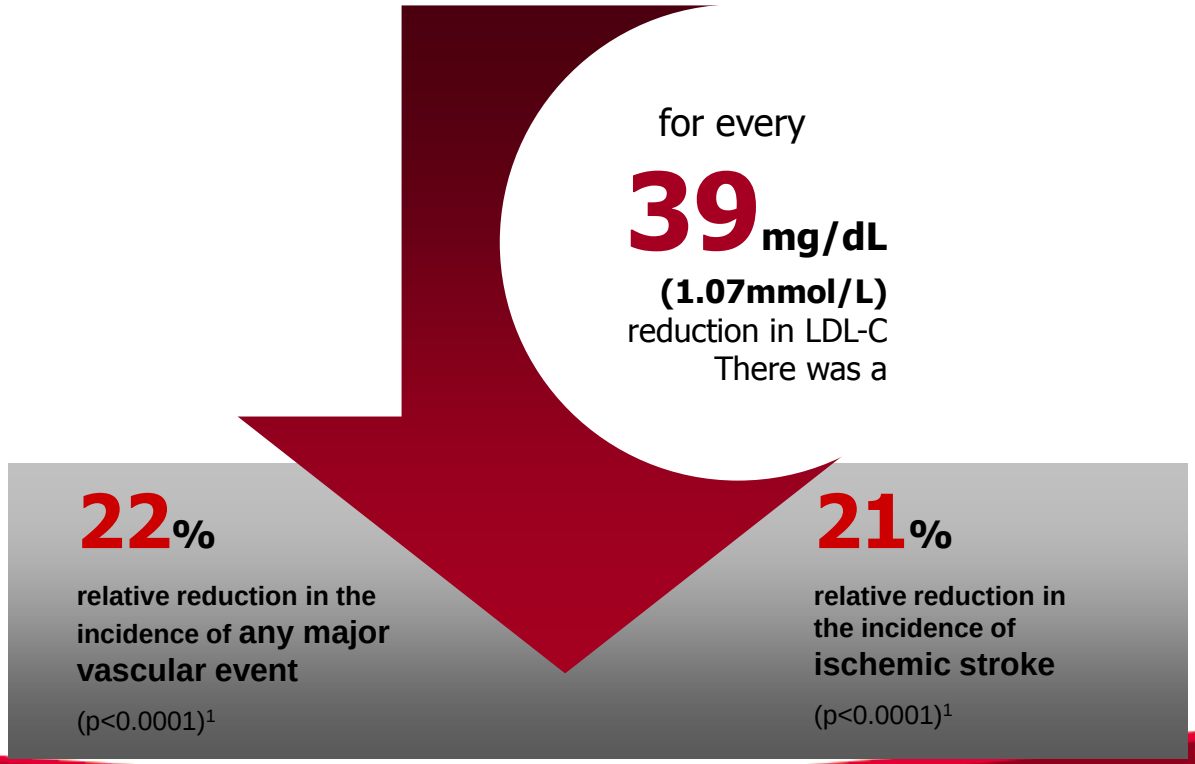
- Significantly Greater % Reductions in CRP Were Achieved With Eze/Simva Compared With Each Corresponding Dose of Simva Monotherapy



1. Pearson T et al. Am J Cardiol 2007;99:1706–1713

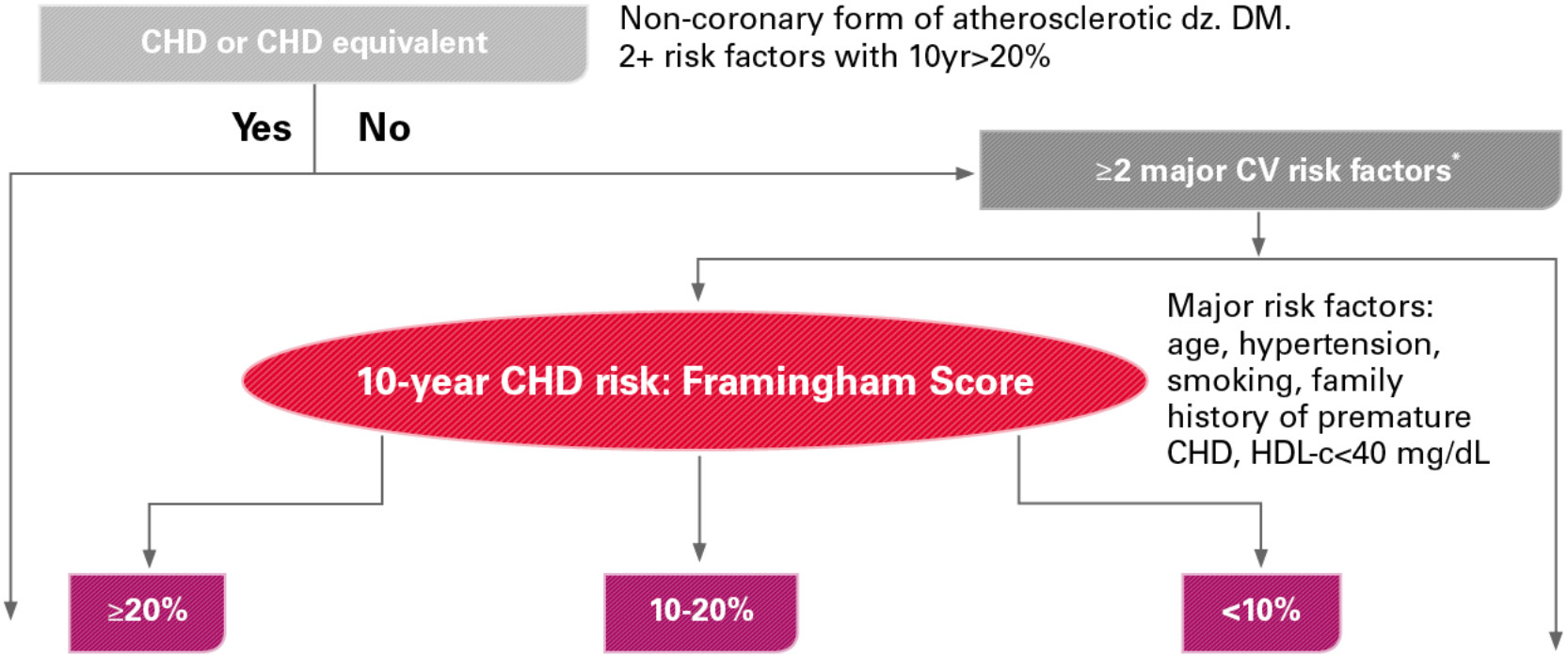
Lower LDL-C levels were correlated with reduced CV risk

- In a meta-analysis of more than 169,000 patients in 26 clinical trials with statins.
- There were 87,903 (52%) participants with preexisting CHD, 32,210 (19%) with a history of diabetes, and 25,920 (15%) with other vascular disease.[1]



1. Cholesterol Treatment Trialists' (CTT) Collaboration. *Lancet* 2010; 376: 1670–81

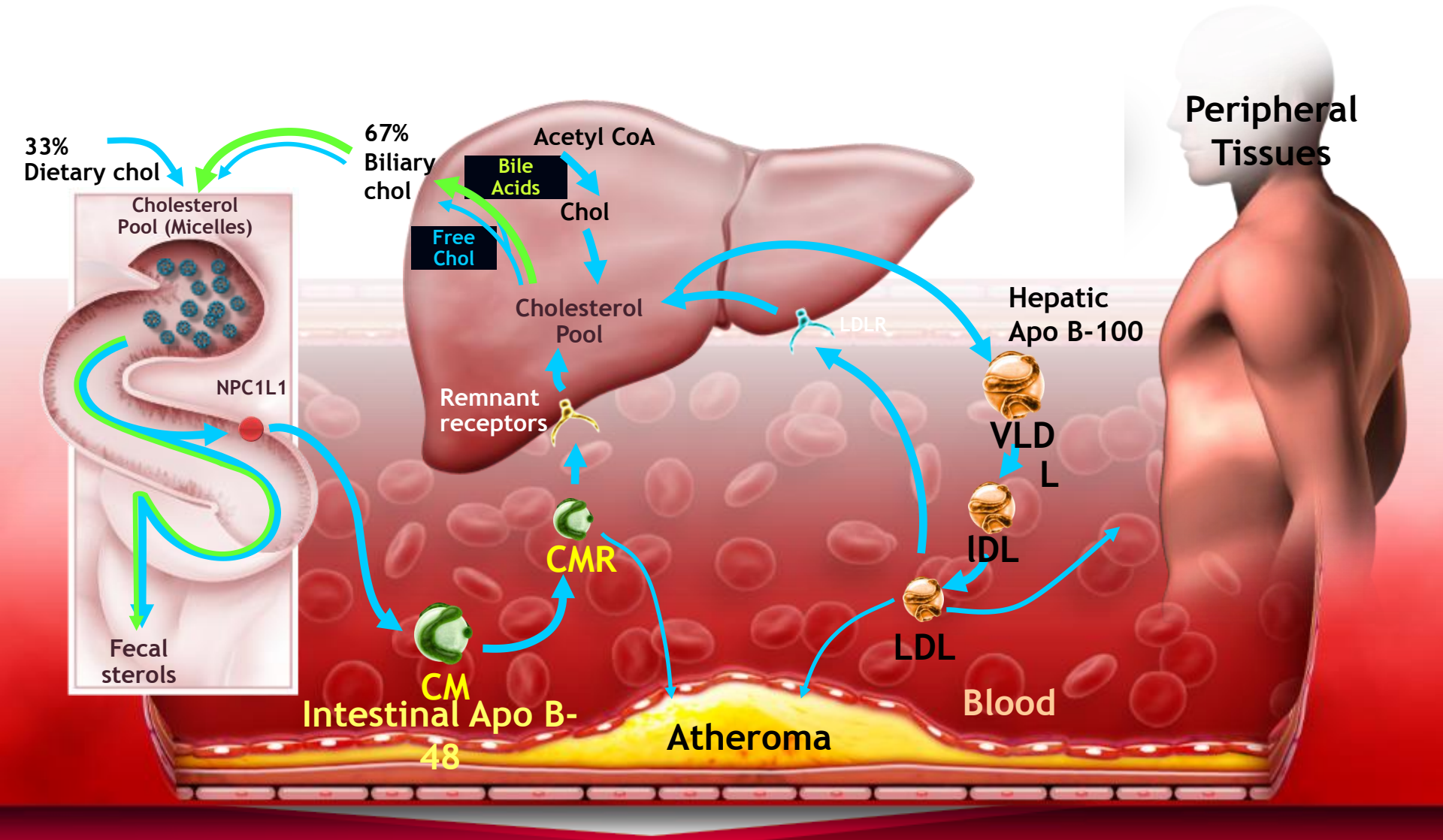
2001 NCEP ATP III: LDL-C goal value



Risk	High	Moderately high	Moderate	Low
LDL-c goal	<100	<130	<130	<160
Medication start	≥130 (100-129: optional)	≥130	≥160	≥190 (160-189: optional)

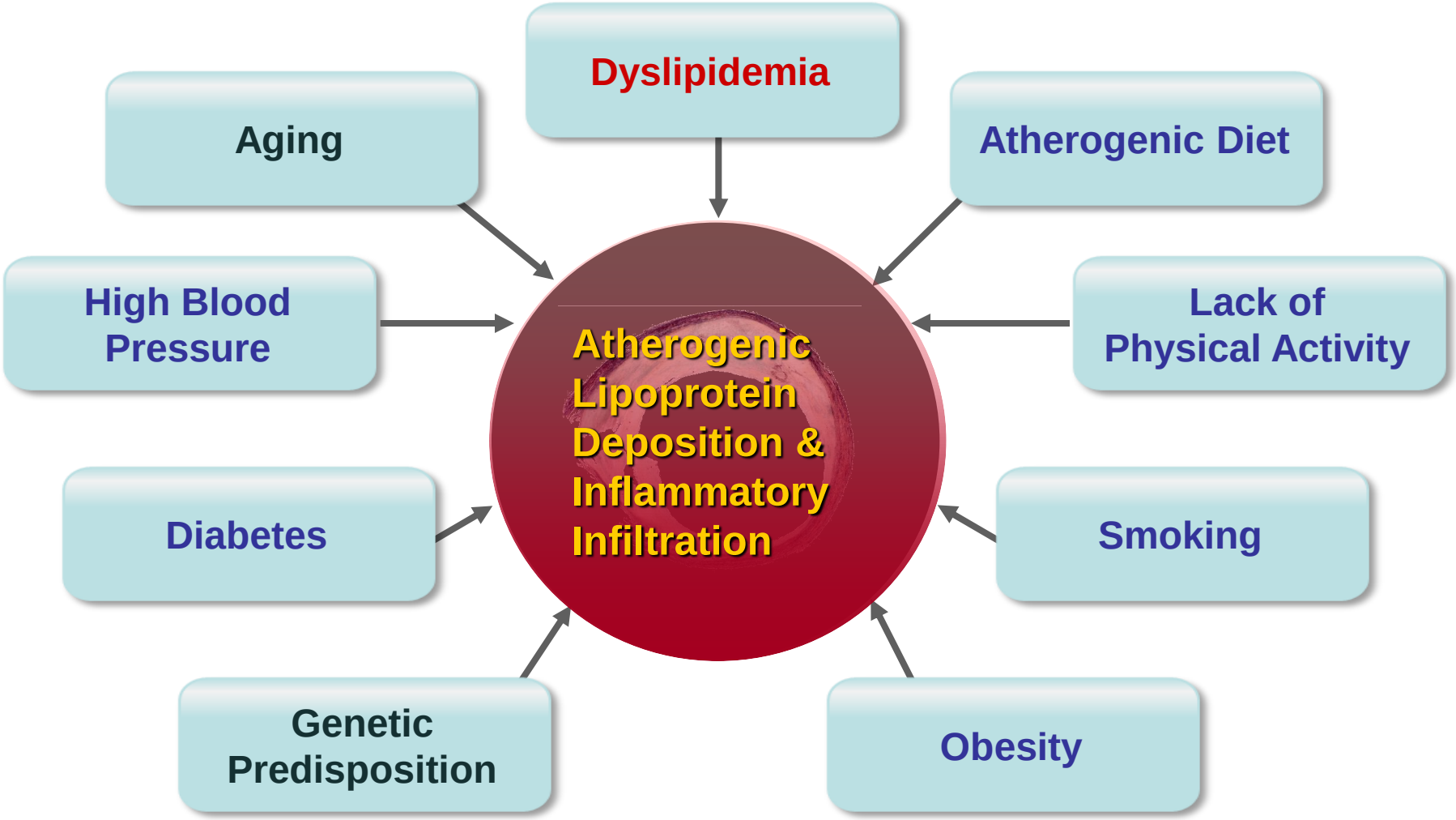
1. NCEP ATP III. *JAMA*. 2001;285:2486–2497

Cholesterol homeostasis



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

Biology of Atherosclerosis: Contributing Factors[1–3]



1. NCEP Circulation. 2002;106 3143–3421. **2.** Wilson PW et al. *Circulation*. 1998;97:1837–1847. **3.** Hubert HB et al. *Circulation*. 1983;67:968–977.

Ezetimibe/Statin Showed Complementary Effects on Cholesterol Absorption and Production

Statin had inverse effects on absorption and production

Ezetimibe had opposite effects vs. simvastatin

Ezetimibe/Statin had complementary effects

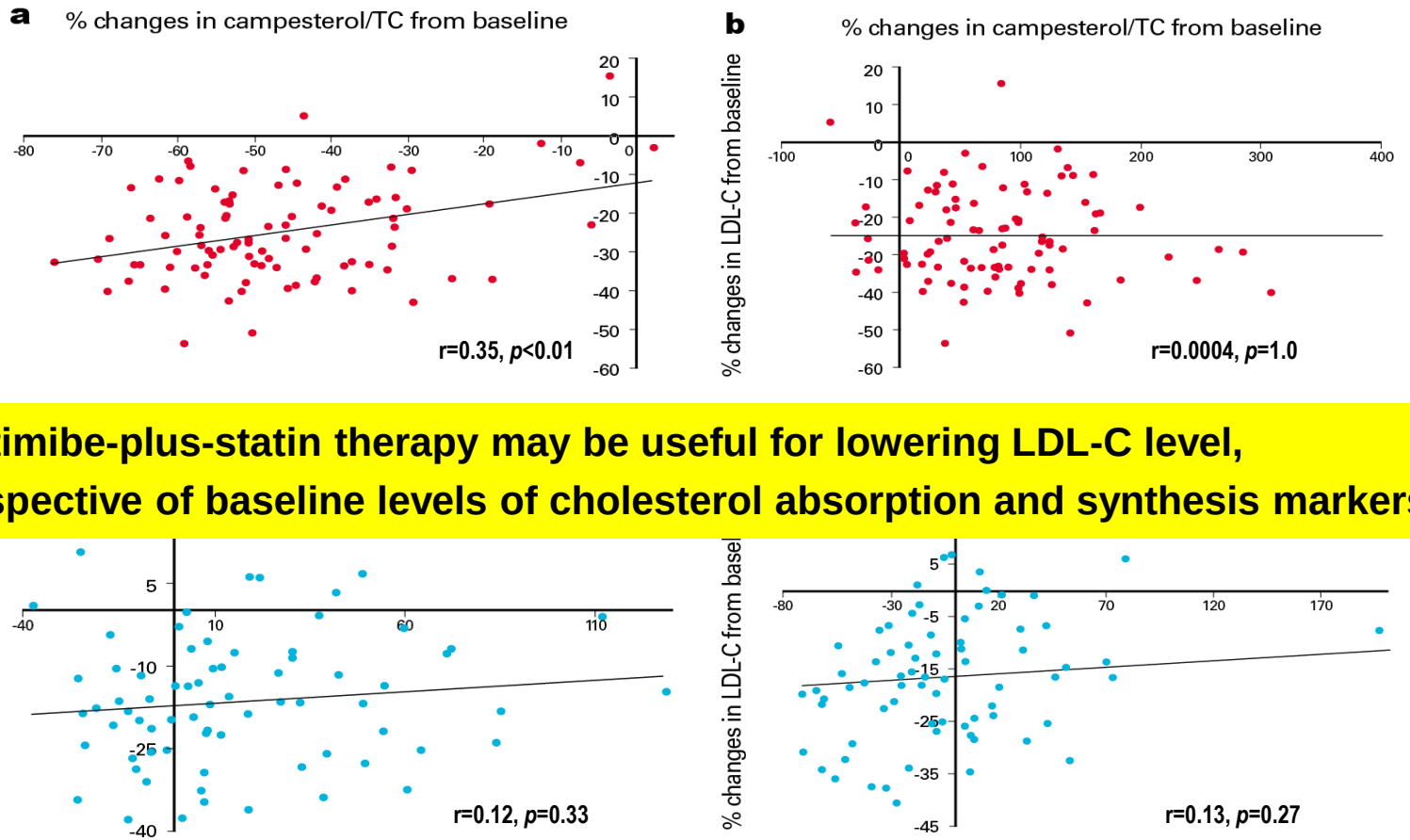
Production Marker:Total Cholesterol Ratio[a]	Absorption Marker:Total Cholesterol Ratio[b]
↓	↑
↑	↓
↓	↓

[a]Cholesterol production markers: lathosterol and desmosterol; [b]Cholesterol absorption markers: sitosterol and campesterol.

1. Assmann G, et al. *Curr Med Res Opin.* 2008;24(1):249–259.

Inhibition of cholesterol absorption may lower LDL-C levels effectively

- **Object :** To evaluate the relationship between LDL-C lowering effect and baseline cholesterol absorption and synthesis markers n patients with CAD
- **Arm** : ATV 20mg/day, RSV 5mg/day, ATV 10mg/EZE 10mg, RSV 2.5mg/EZE 10mg
- **Patients** : 171 patients with CAD



Ezetimibe-plus-statin therapy may be useful for lowering LDL-C level, irrespective of baseline levels of cholesterol absorption and synthesis markers.

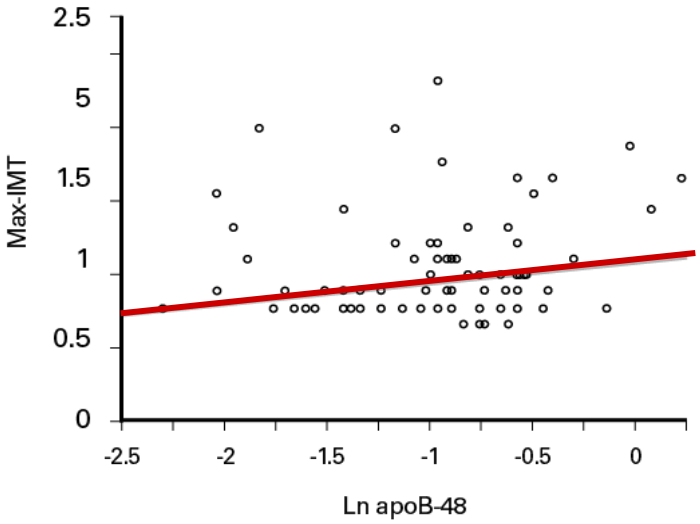
Campesterol/TC ratio: an index of cholesterol absorption; Lathosterol/TC ratio: an index of cholesterol synthesis

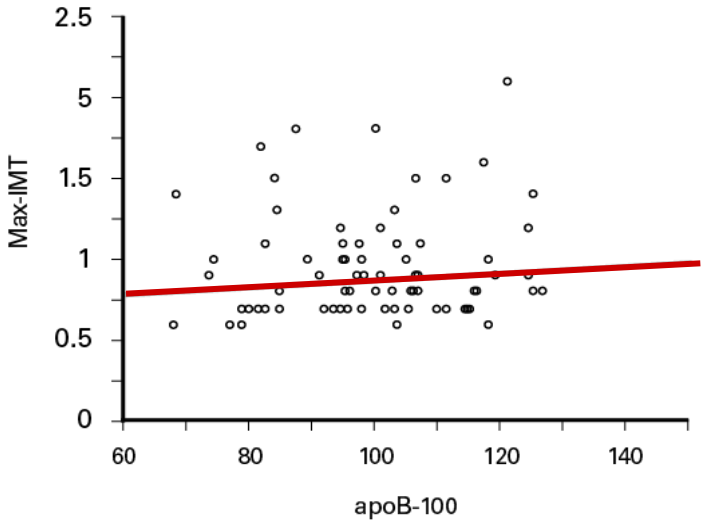
LDL-C, low density lipoprotein; CAD, coronary artery disease ; ATV, atorvastatin; RSV, rosuvastatin; EZE, ezitimibe

1. Okada Okada, et al. Circ J. 2011;75:2496-504

Serum apoB48 level might be a good marker for the detection of early atherosclerosis with normal-range levels of BP and TG

- **Objective:** To investigate the correlations between profiles of apoB48-containing lipoproteins and the progression of atherosclerosis in subjects with normal TG levels
- **Patients:** 164 osaka police hospital (annual health check)
- **Conclusion:**
  - ✓ **The accumulation of CMR might be an independent risk factor for the development of atherosclerosis among subjects with TG levels between 100 mg/dL-150 mg/dL.**
  - ✓ **The measurement of fasting apoB48 level is very useful for the detection of early onset of atherosclerotic plaques**





BP blood pressure; TG, tryglyceride;CMR, chylomicron remnants

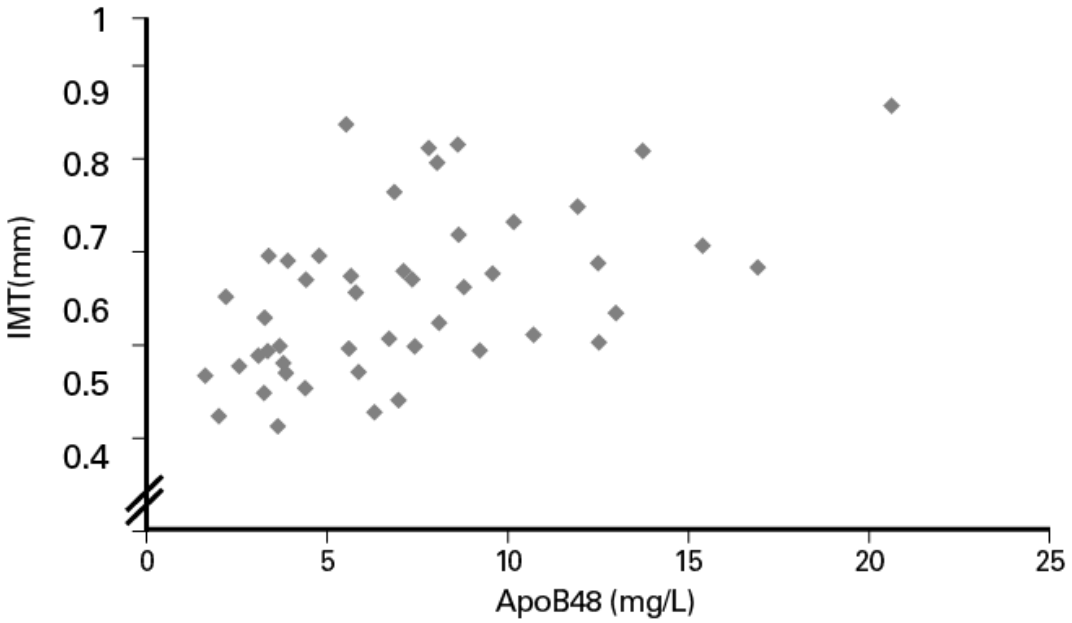
1. Nakatani, et al. Atherosclerosis 2011;218:226–232

In patients not using statin,
The surrogate atherosclerosis marker IMT correlated best with apoB48

- **Objective** : To investigate whether fasting plasma levels of apoB48 can help to differentiate subjects with different conditions with remnant accumulation [e.g. FCH, T2DM and CAD] from subjects without remnant accumulation. The relationship between apoB48 and IMT was also investigated
- **Method :** Patients-189 subject(FCH, FH, CAD, T2DM, Control, CAD+T2DM)
- **Conclusion :**

✓ **ApoB48 concentrations are highest in patients with FCH and in atherosclerotic subjects with T2DM.**

✓ **In patients not using statins, the surrogate atherosclerosis marker IMT correlates best with apoB48, suggesting that fasting apoB48 may help to detect subjects at risk.**



T2DM, type 2 diabetes mellitus; FCH, familial combined hyperlipidaemia ; FH, familial hypercholesterolaemia ; CAD, coronary artery disease ; IMT, Intima-media thickness

1. Alipour et al. Eur J Clin Invest 2012;42:702–708