Strategic Approach for Management of Dyslipidemia in Cardiometabolic Patients

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Agenda

I. LDL-C, a causal factor for ASCVD

II. Unmet needs of current lipid management

III. Strategic approach for management of dyslipidemia in cardiometabolic patients

IV. Direction of alternative option in lipid guideline

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I. **LDL-C, a causal factor for ASCVD**

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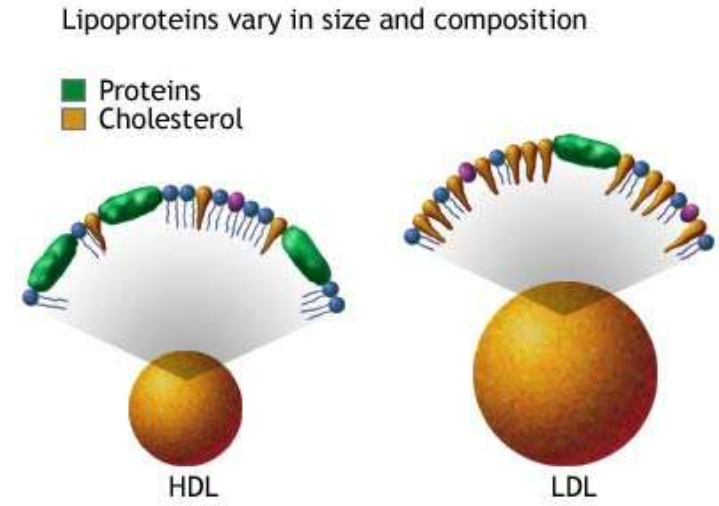
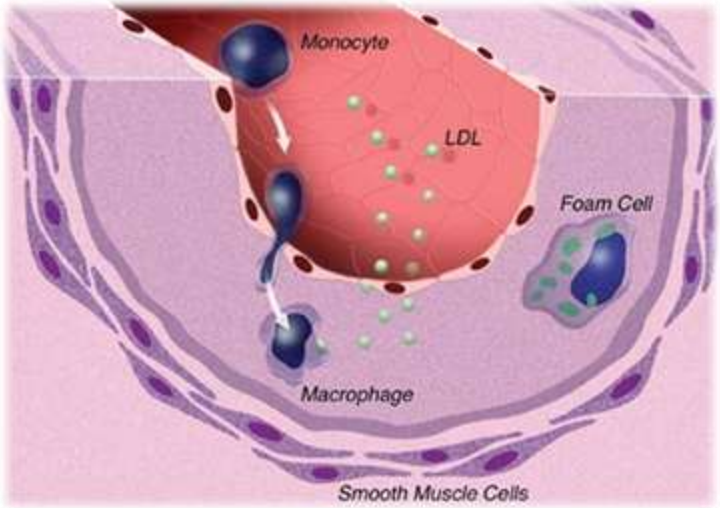
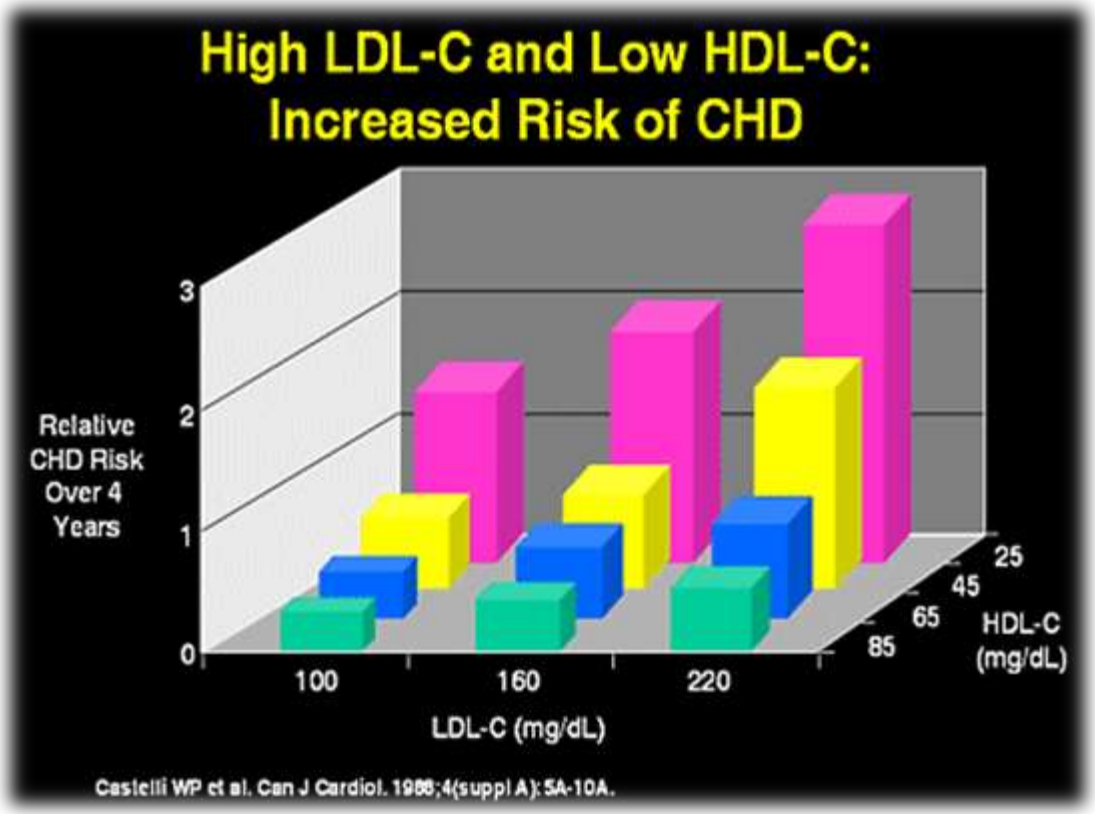
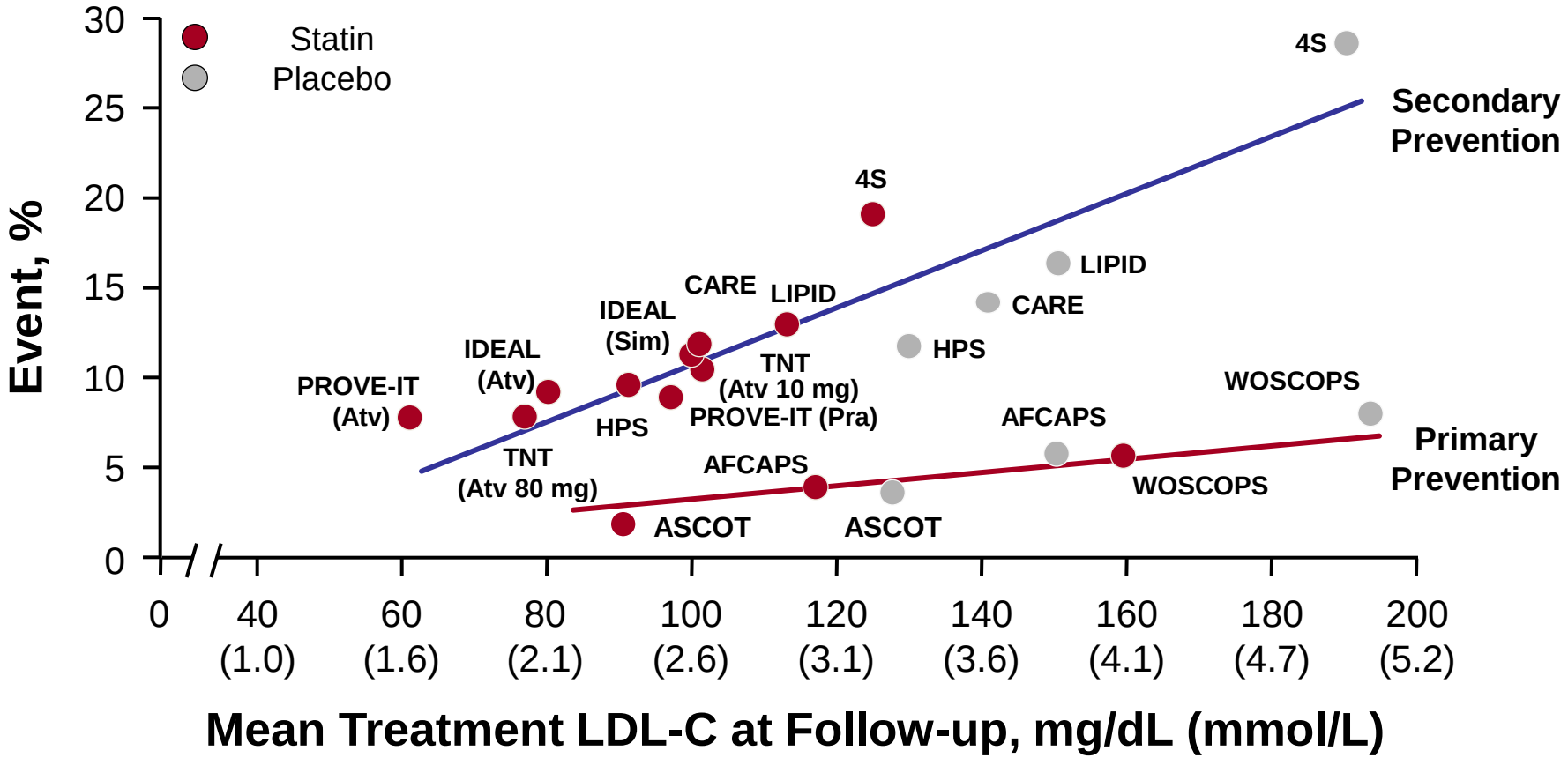
LDL-C, a causal factor for ASCVD





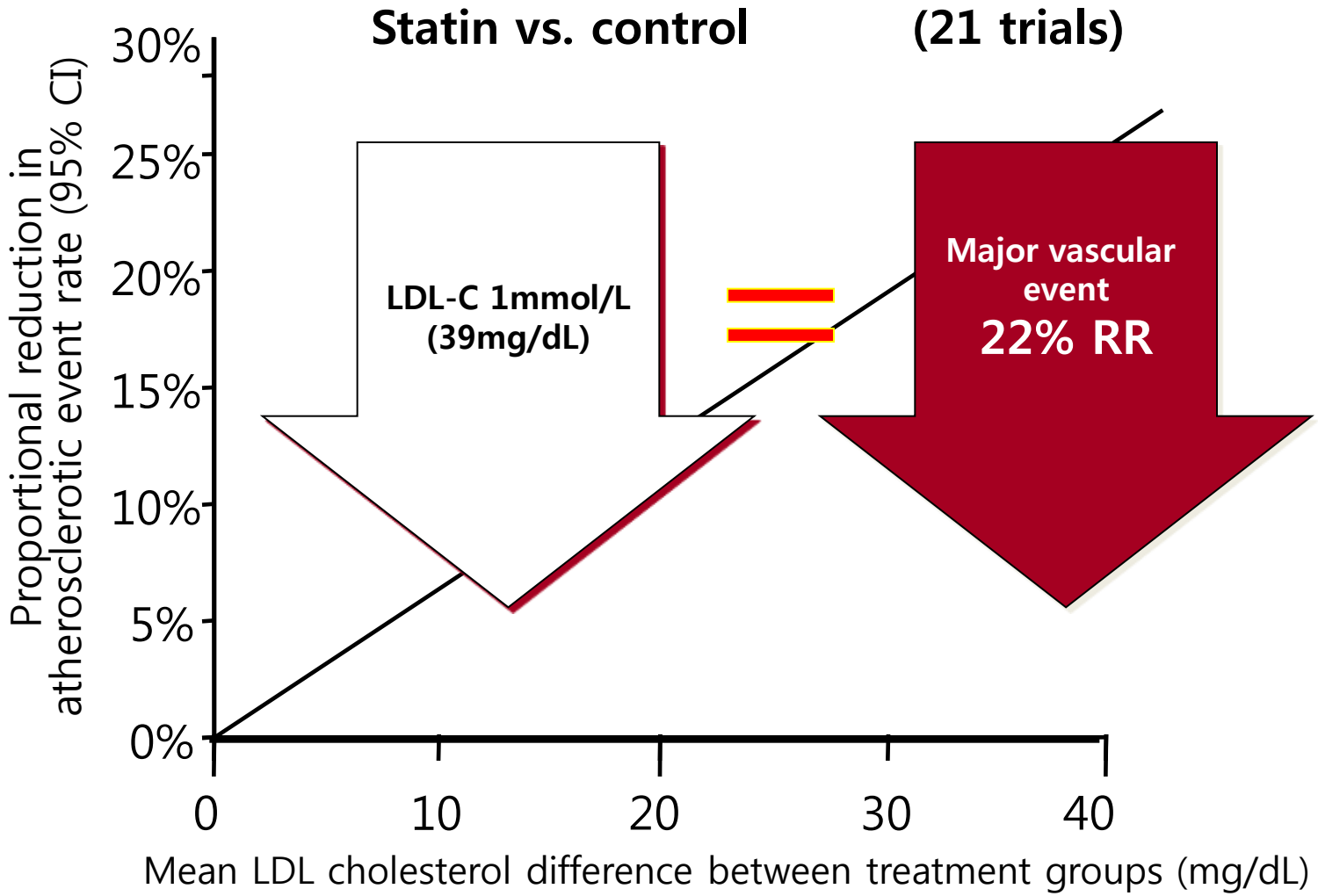


Relationship Between LDL-C and CV Incidence



Adapted from Rosenson RS. *Expert Opin Emerg Drugs*. 2004;9:269–279; LaRosa JC, et al. *N Engl J Med.* 2005;352:1425–1435; Pedersen TR, et al. *JAMA*. 2005;294:2437–2445.

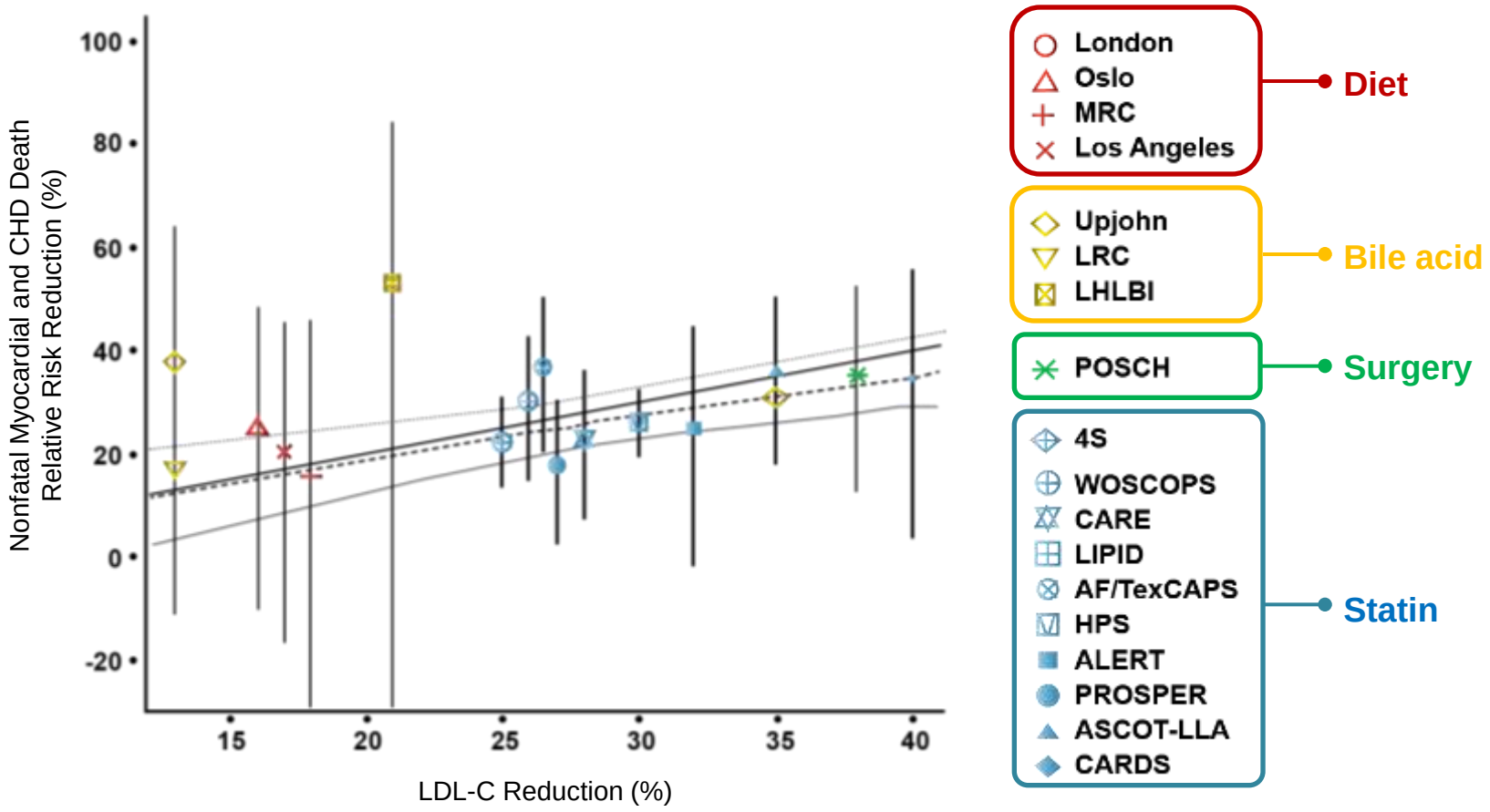
LDL-C is still strong indicator of ASCVD



Cholesterol Treatment Trialists

Statin is a mainstream of LDL-C reduction

Treatment studies involving statins, resins, diet, and ileal bypass surgery have shown a relationship between LDL-C



Robinson JR, et al. *J Am Coll Cardiol* 2005;46:1855.

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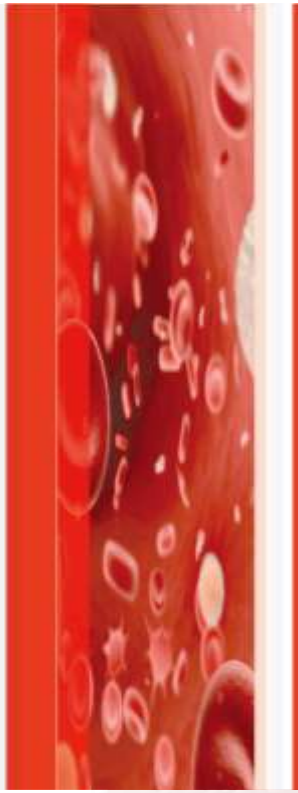
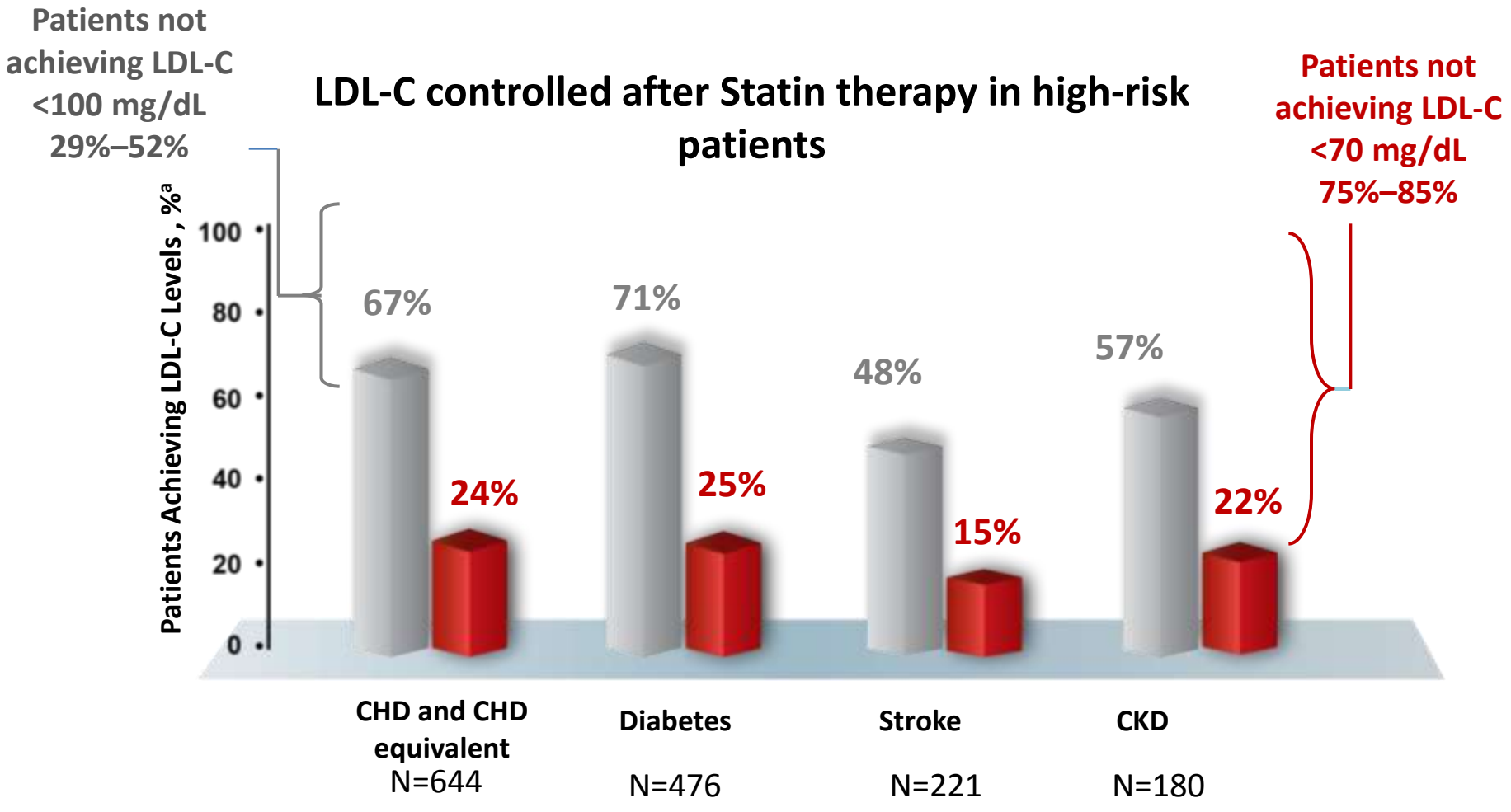
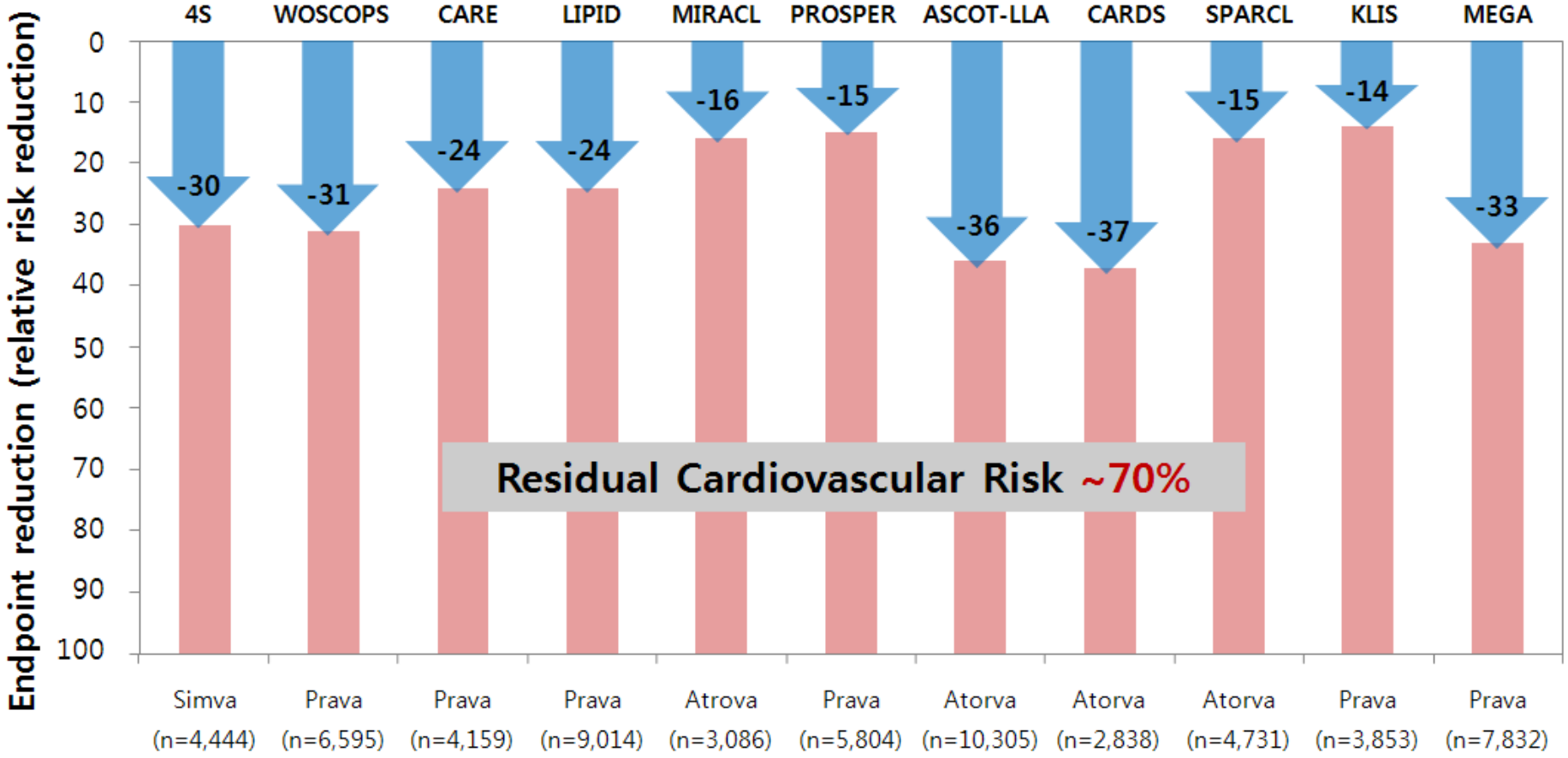


Many High-Risk Patients Did Not Achieve LDL-C <100 mg/dL or <70 mg/dL in Korea



Data on file, MSD Korea (Market Research for understanding CKD risk and LDL-C control level of statin Rx. Patients by Ipsos, 2011)

Statin Effects on CV Event Reduction and Residual Risk



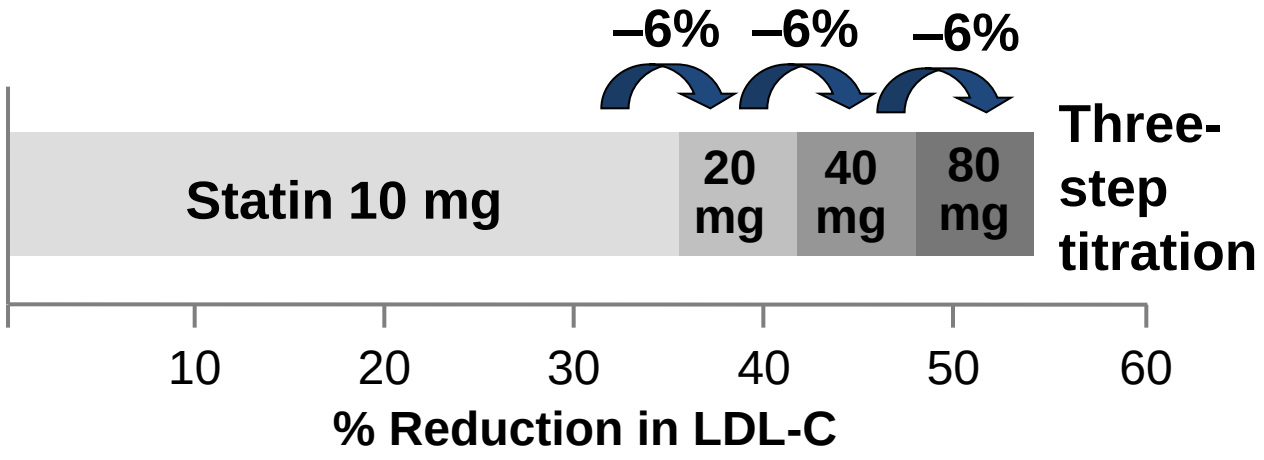
Lancet 2005;366:1267-1278

Statin up-titration has efficacy limitations

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

NCEP ATP III Final Report

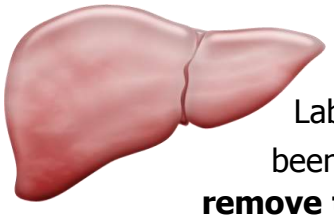
Effect of statin therapy on LDL-C levels: "The Rule of 6"



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

FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs: Feb. 28. 2012

Monitoring Liver Enzymes

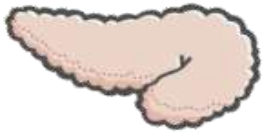


Labels have been revised to **remove the need for routine periodic monitoring of liver enzymes in patients taking statins**. The labels now recommend that **liver enzyme tests should be performed before starting statin therapy and as clinically indicated thereafter**.

FDA has concluded that serious liver injury with statins is rare and unpredictable in individual patients, and that routine periodic monitoring of liver enzymes does not appear to be effective in detecting or preventing serious liver injury.

Adverse Event Information

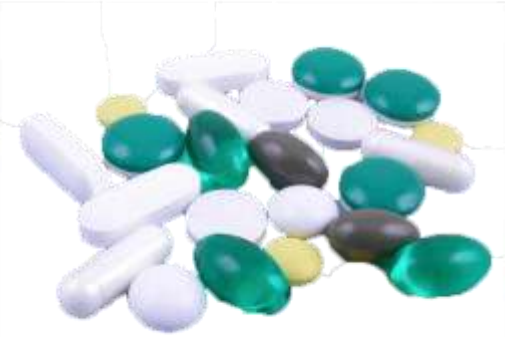
Information about the **potential for generally non-serious and reversible cognitive side effects** (memory loss, confusion, etc.) and reports of **increased blood sugar and glycosylated hemoglobin (HbA1c) levels has been added to the statin labels**.



FDA continues to believe that the cardiovascular benefits of statins outweigh these small increased risks.

Drug Interactions

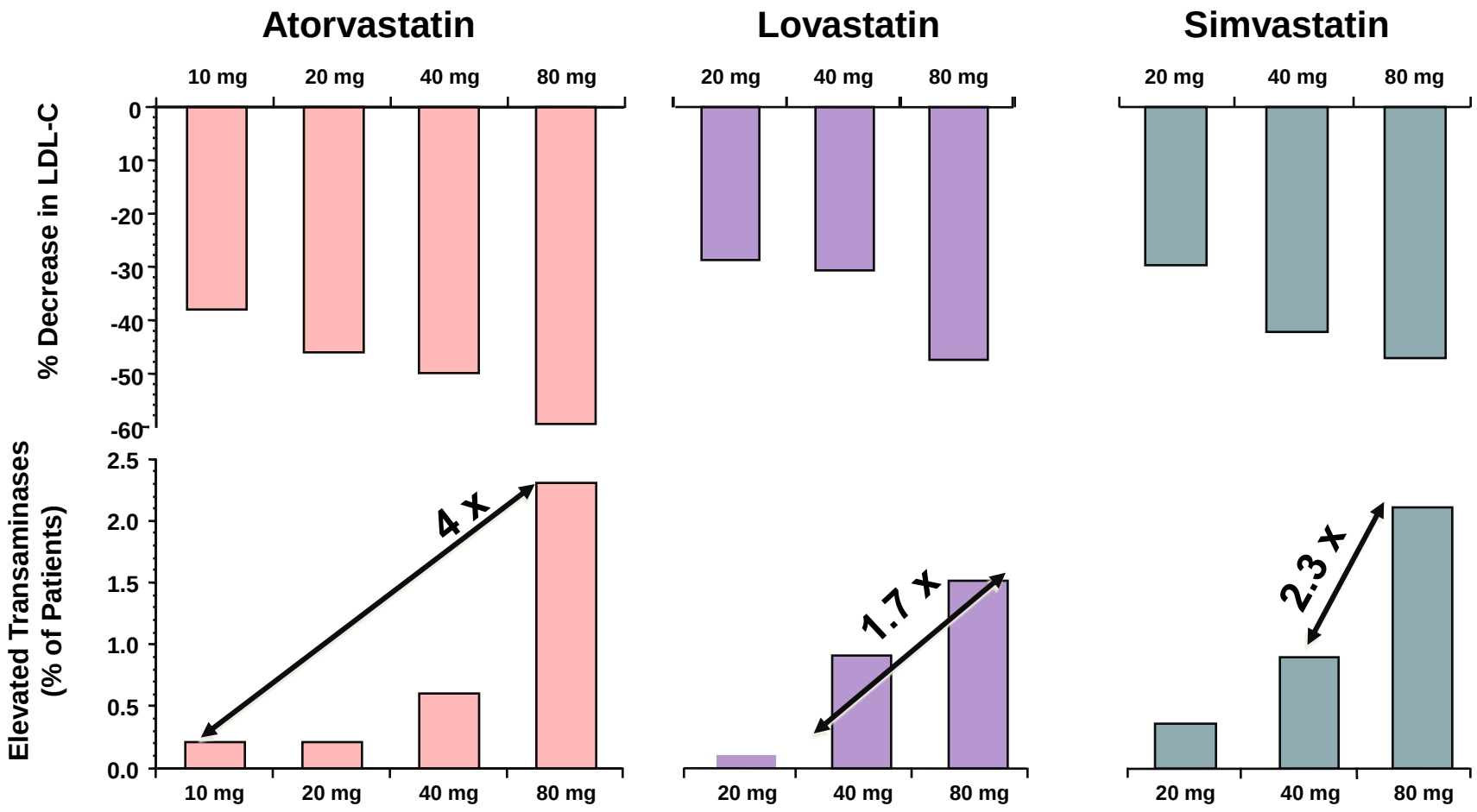
The lovastatin label has been extensively updated with new contraindications (situations when the drug should not be used) and dose limitations when it is taken with certain medicines that can increase the risk for muscle injury.



FDA, Food and Drug Administration.

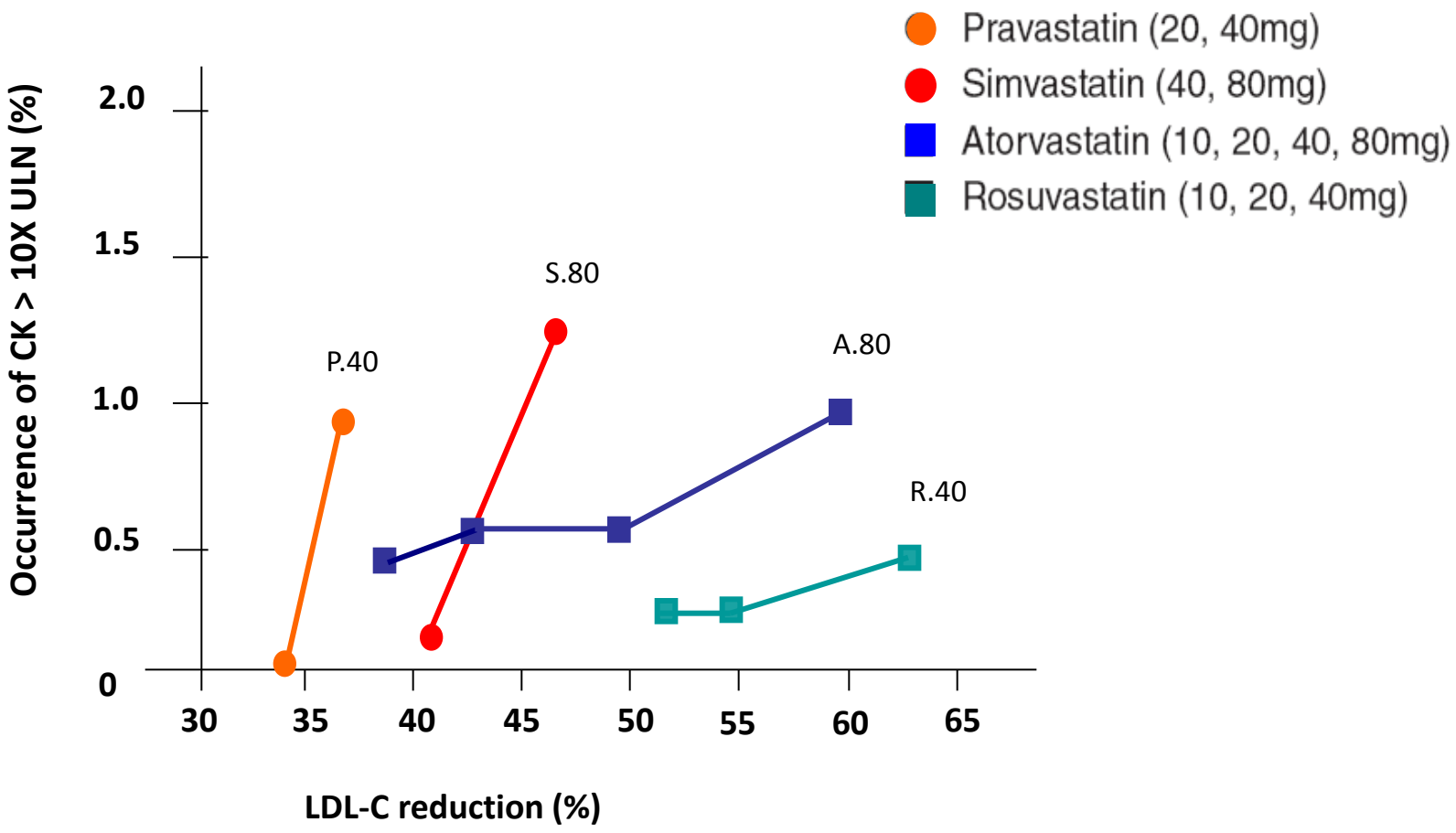
1. FDA Drug Safety Communication. Available at http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm Accessed May 31, 2012

Higher doses associated with increased hepatic toxicity



Data from prescribing information for atorvastatin, lovastatin, simvastatin – *20 mg includes pts on 40 mg (37%). This does not represent data from a comparative study.

Higher doses associated with increased muscle injury



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

About 10% of hyperlipidemic patients suffer from muscular symptoms with high dose statin

PRIMO study: mild to moderate muscular symptoms with high dosage statin therapy in hyperlipidemic patients

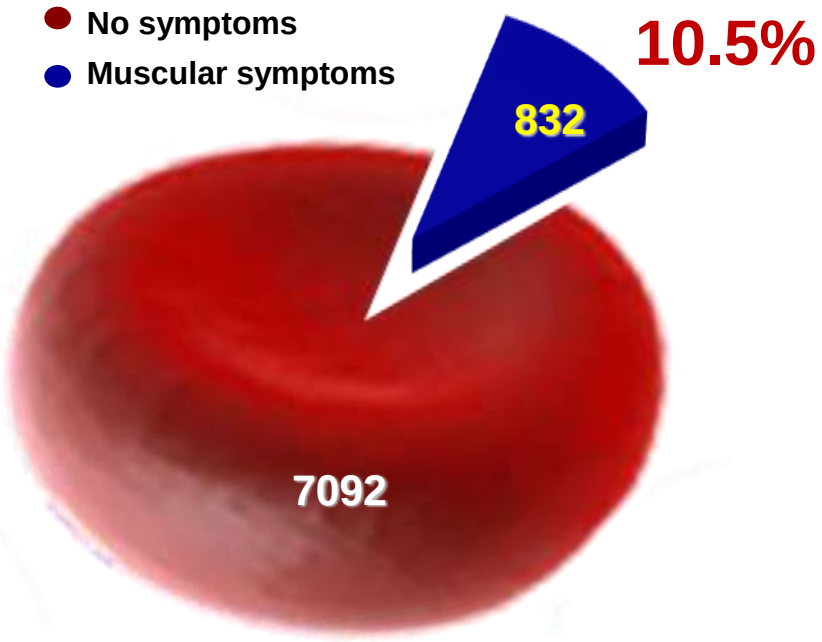
Objective: To characterization the risk factors, rate of occurrence, onset, nature and impact of mild to moderate muscular symptoms with high dose statin.

Design: Observational survey, 7924 hyperlipidemic pts.

Risk factors of muscle pain

- **Unexplained cramps (OR 4.14)**
- **History of CK (OR 2.04)**
- **Hypothyroidism (OR 1.71)**
- **Duration of statin treatment more than 3 month (OR 0.28)**

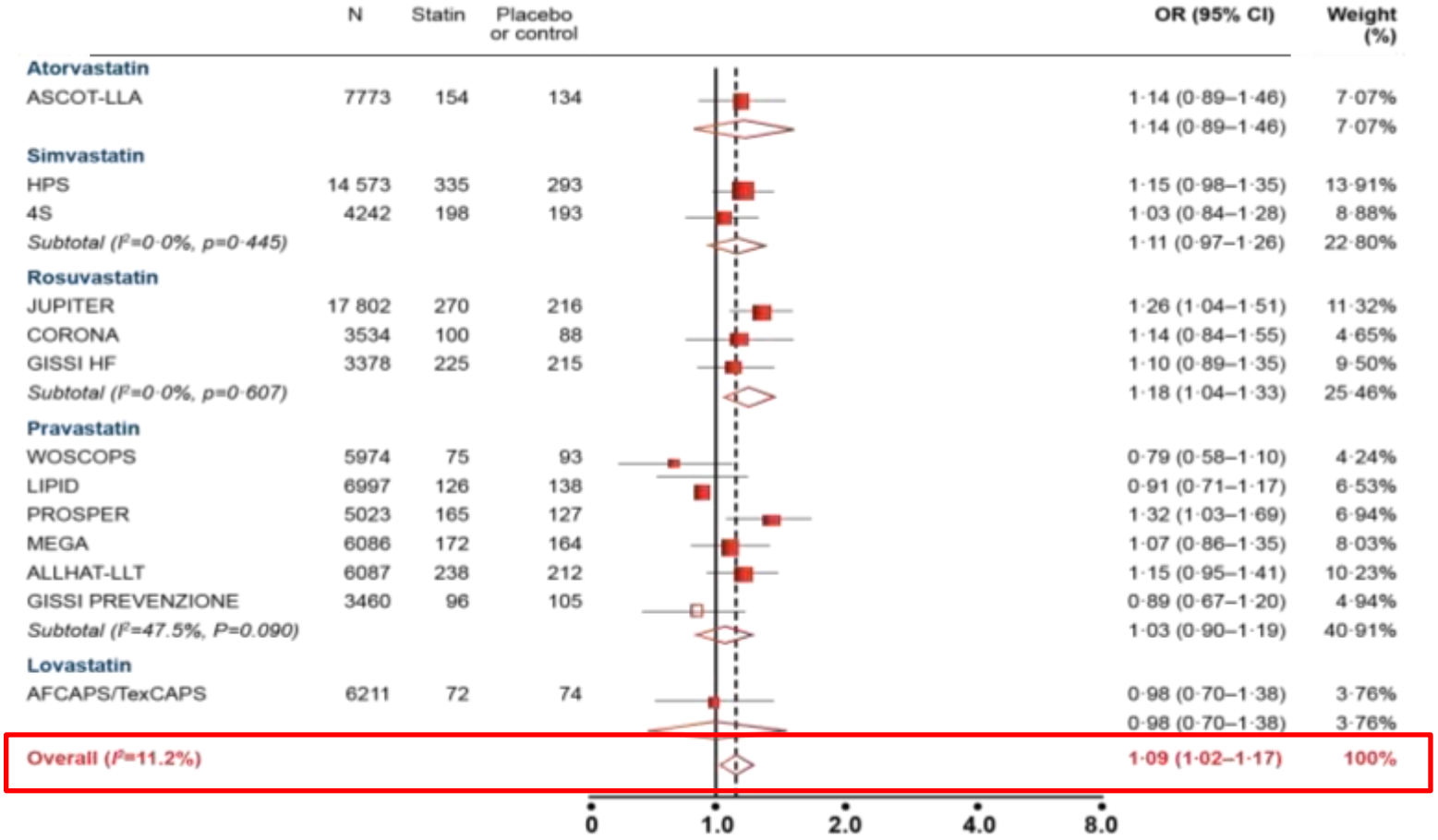
1 month following initiation of statin therapy



. Bruckert et. al, Cardiovascular Drugs and Therapy, 2005;19:403-414

Statin therapy was associated with a 9% increased risk for incident diabetes

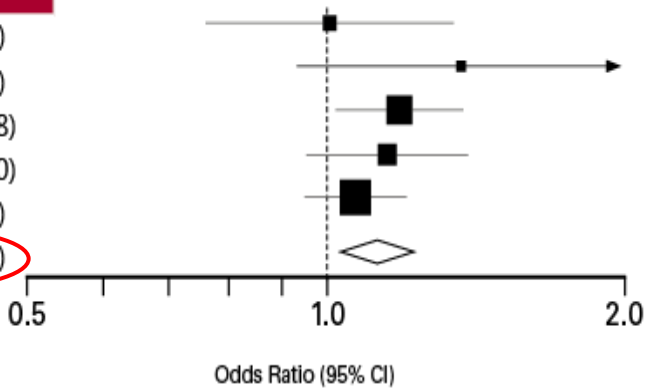
In meta-analysis of 13 major trials with 91,140 participants, Statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio [OR] 1.09;95% CI 1.02-1.17), with little heterogeneity between trials.



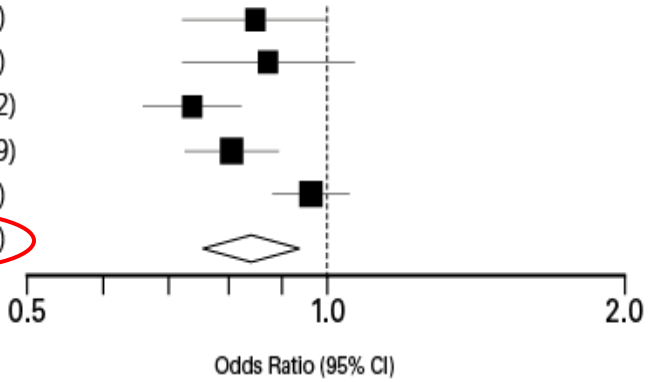
1. Sattar N, et al. *Lancet* 2010;375:735-742.

Intensive-dose statin therapy: a 12% increased risk for NOD compared with moderate-dose statin therapy

Incident Diabetes	Statin Dose Comparison	OR (95% CI)
PROVE IT-TIMI 22, 2004	Atorvastatin 80mg vs. Pravastatin 40mg	1.01 (0.76-1.34)
A to Z, 2004	Simvastatin 80mg vs. Simvastatin 20mg	1.37 (0.94-2.01)
TNT, 2005	Simvastatin 80mg vs. Simvastatin 10mg	1.19 (1.02-1.38)
IDEAL, 2005	Atorvastatin 80mg vs. Simvastatin 20 or 40mg	1.15 (0.95-1.40)
SEARCH, 2010	Simvastatin 80mg vs. Simvastatin 20mg	1.07 (0.95-1.21)
Pooled odds ratio		1.12 (1.04-1.22)
Heterogeneity: I^2 =0%, P=0.60		



Incident CVD	Statin Dose Comparison	OR (95% CI)
PROVE IT-TIMI 22, 2004	Atorvastatin 80mg vs. Pravastatin 40mg	0.85 (0.72-1.01)
A to Z, 2004	Simvastatin 80mg vs. Simvastatin 20mg	0.87 (0.72-1.07)
TNT, 2005	Simvastatin 80mg vs. Simvastatin 10mg	0.73 (0.65-0.82)
IDEAL, 2005	Atorvastatin 80mg vs. Simvastatin 20 or 40mg	0.80 (0.72-0.89)
SEARCH, 2010	Simvastatin 80mg vs. Simvastatin 20mg	0.97 (0.88-1.06)
Pooled odds ratio		0.84 (0.75-0.94)
Heterogeneity: I^2 =0%, P=0.60		



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

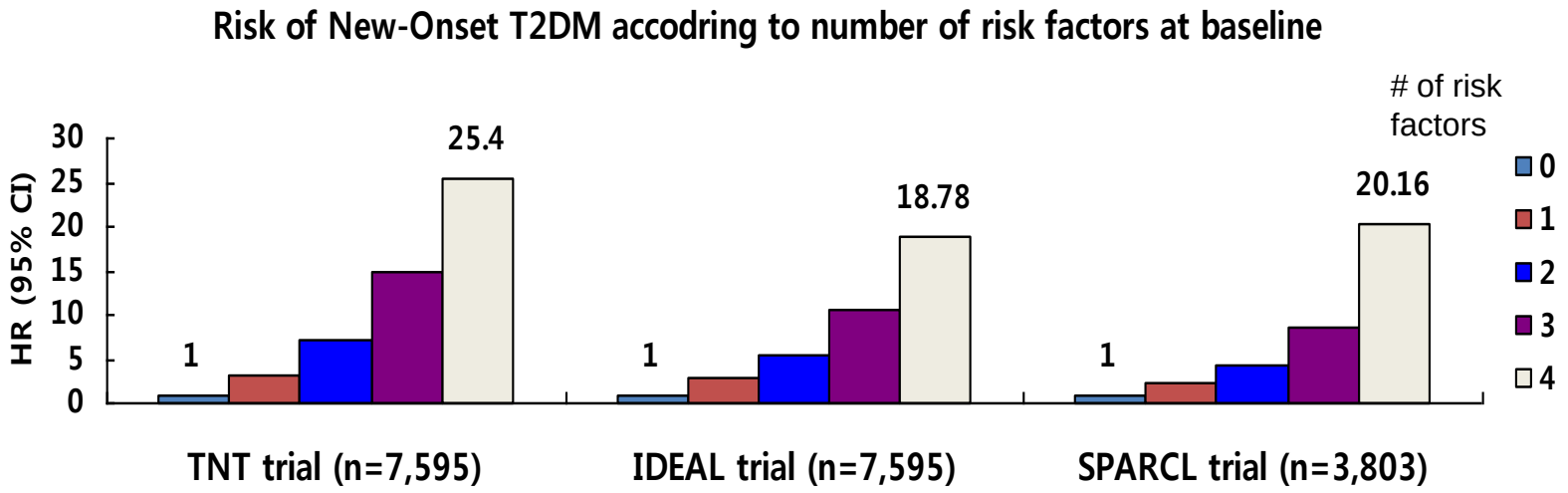
Baseline fasting glucose level and features of the metabolic syndrome are predictive of NOD

Prediction of new-onset T2DM across the 3 trials

- **Objective**: to examine the incidence and clinical predictors of new-onset T2DM within 3 large randomized trials with atorvastatin.

Risk Factors:

1) baseline fasting glucose > 100 mg/dl
2) fasting triglycerides > 150 mg/dl
3) BMI >30 kg/m^2
4) History of hypertension



Waters DD. et al. *J Am Coll Cardiol*. 2011;57(14):1535-1545.

Definition of Metabolic Syndrome

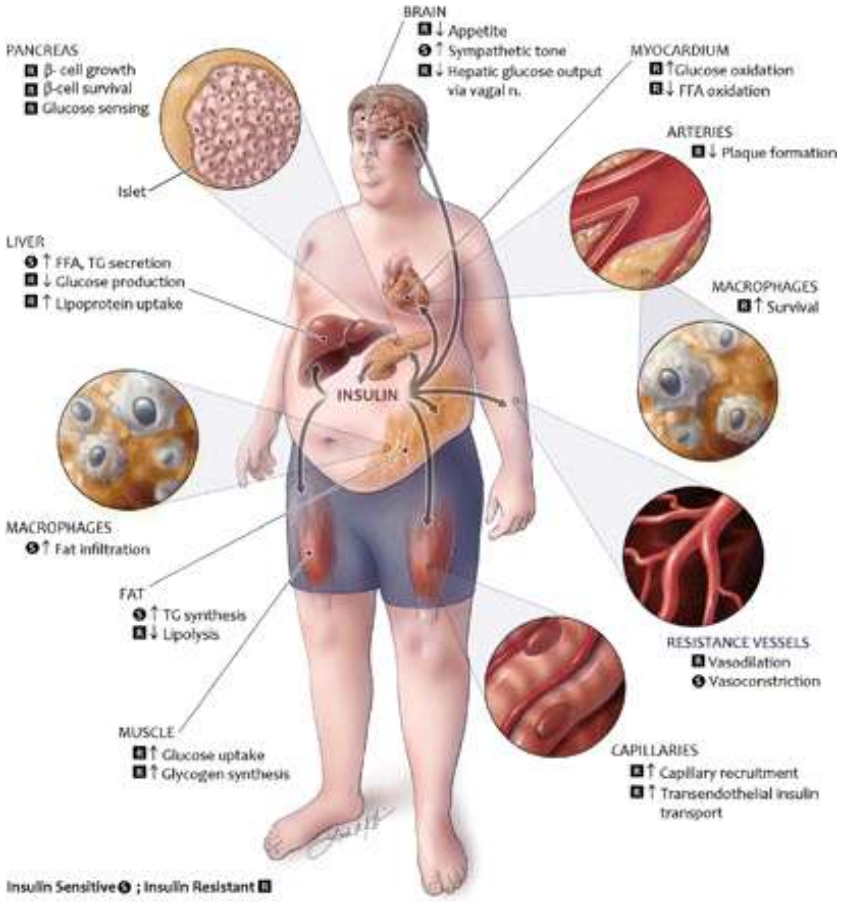


Table 3: ATP III Definition of the Metabolic Syndrome[11]

≥3 of the following:

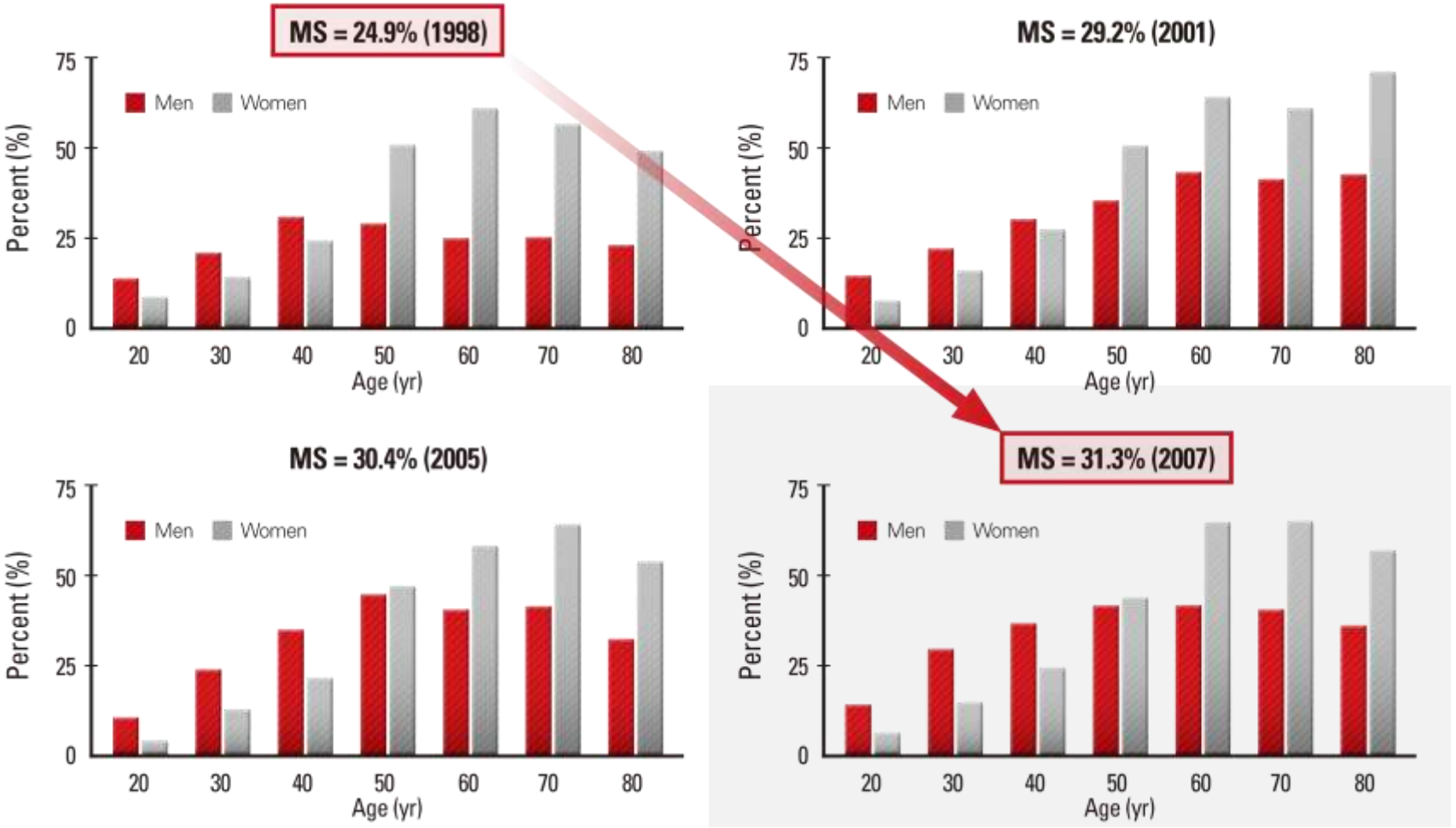
- **Waist circumference**
  - >35" (>88 cm) women and >40" (102 cm) men
  - 37-40" (94-102 cm) for men predisposed to insulin resistance
- **Triglycerides:** ≥150 mg/dL
- **HDL**
  - <50 mg/dL in women
  - <40 mg/dL in men
- **Blood Pressure:** ≥130/85 mm Hg
- **Fasting glucose:** ≥110 mg/dL*

*New ADA recommendations suggest that this should be 100 mg/dL.[14]

Adapted from *JAMA*. 2001; and National Institutes of Health. NIH Publication No. 02-5215. September 2002.

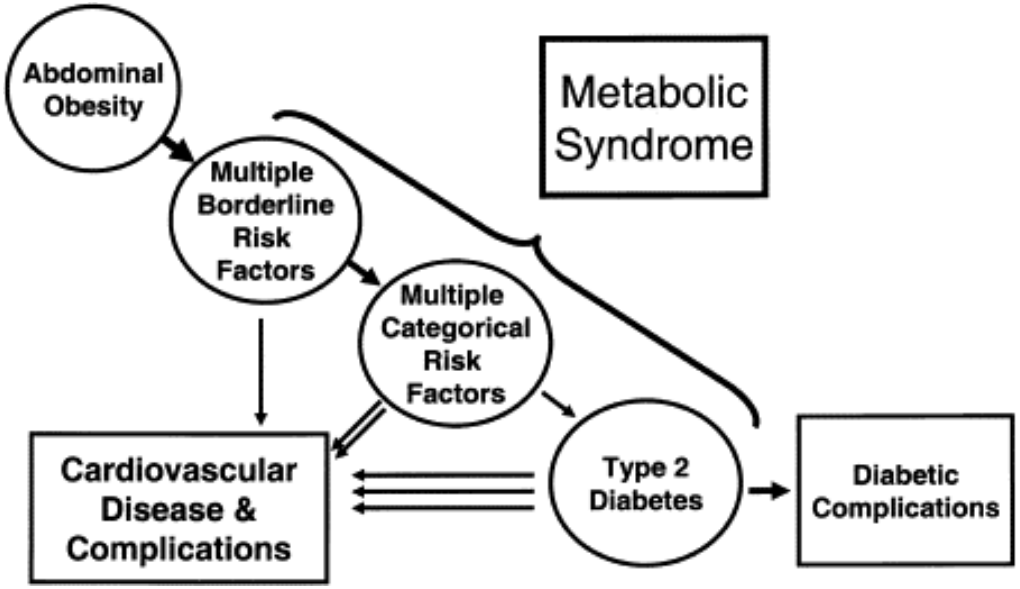
Increased Prevalence of MetS in Korea

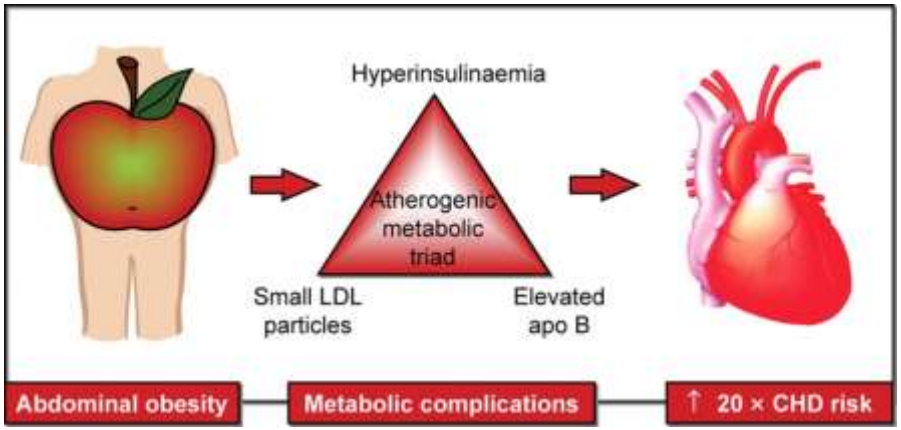
A total of 6,907(mean±SE age 45.0±0.2 years), 4,536 (45.5±0.2), 5,373 (47.1±0.22), and 2,890 (49.9±0.3) Koreans aged >20 years participated in the Korean National Health and Nutrition Examination Surveys in 1998, 2001, 2005, and 2007, respectively.[1]

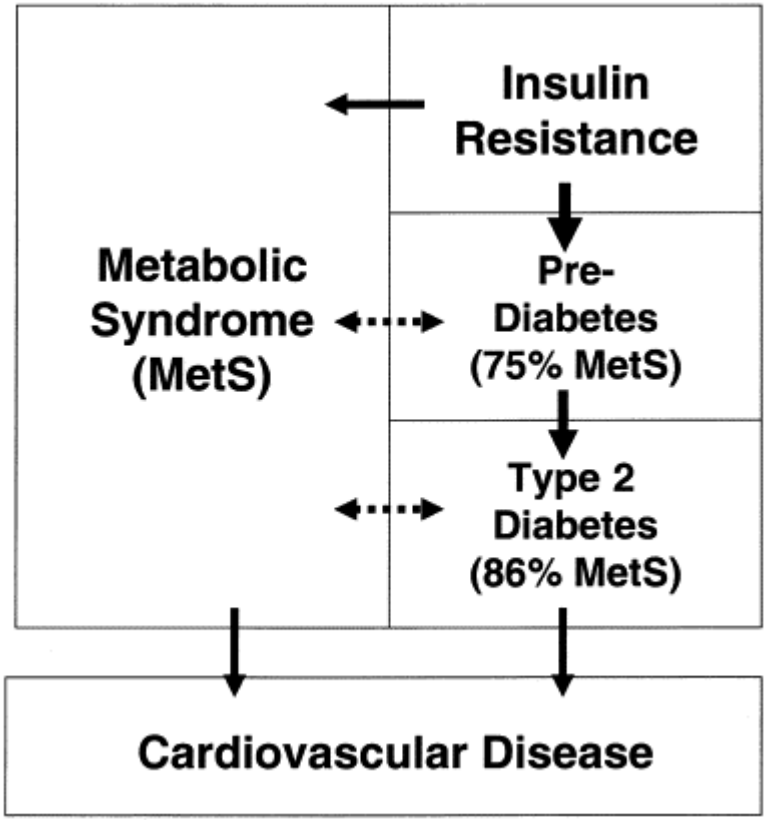


1. Lim S et al. *Diabetes Care* 2011;34:1323–1328.

Progression and Outcomes of MetS



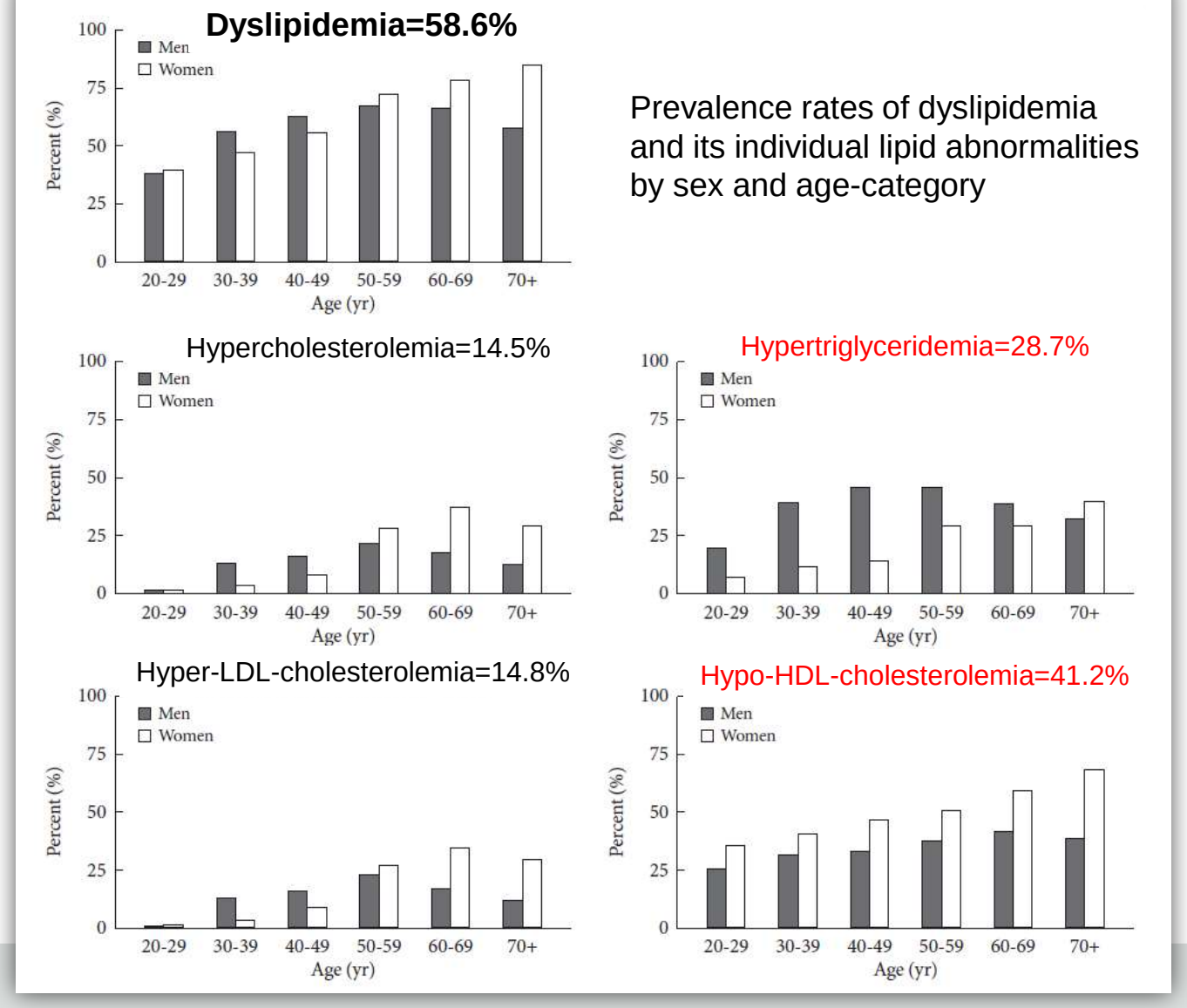




J Am Coll Cardiol. 2006;47(6):1093-1100

Prevalence of Dyslipidemia in Korea

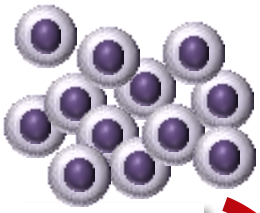
- adults aged ≥20 yrs
- data from the Korea National Health and Nutrition Surveys (KNHANES) 1998 to 2010



Prevalence rates of dyslipidemia and its individual lipid abnormalities by sex and age-category

Diabetes Metab J 2013;37:433

Mechanism of Dyslipidemia in the CardioMetS



Fat cells

↑FFA

Liver

Insulin resistance

↑ Hormone-sensitive lipase and lipoprotein lipase

↑ TG
↑ Apo B
↑ VLDL-C

↑ VLDL-C

TG

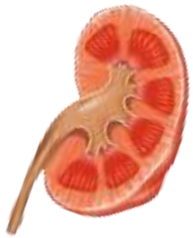
CETP

CE

LDL-C and HDL-C

SD LDL-C and SD HDL-C

SD LDL-C ↑ Atherosclerosis



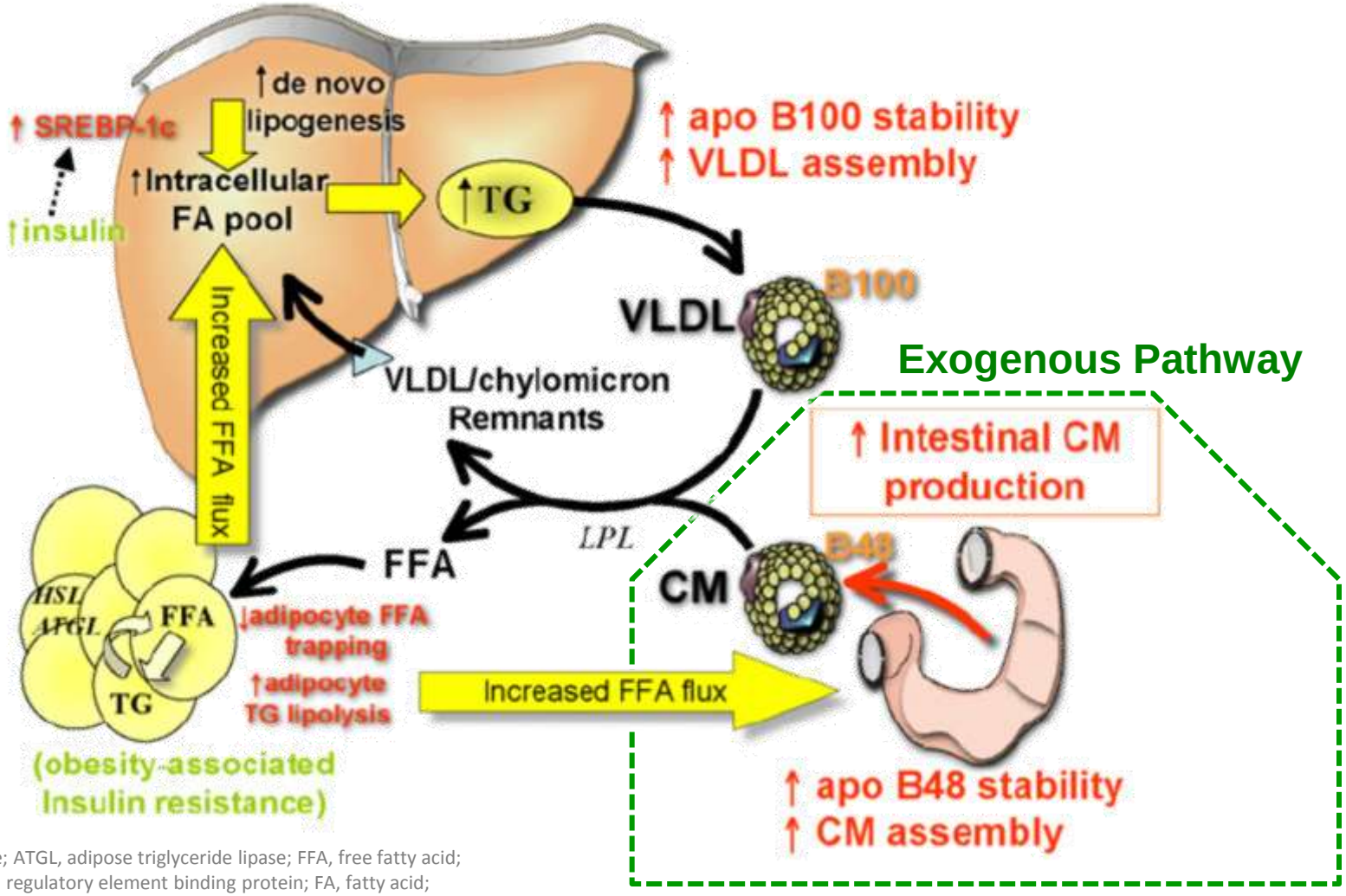
SD HDL-C ↑ Excretion

Loss of APO A_1

↑ = increased; FFA = free fatty acid; TG = triglycerides; Apo B = apolipoprotein B; VLDL-C = very low-density lipoprotein cholesterol; CETP = cholesterol ester transfer protein; CE = cholesterol ester; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; Apo A_1 = apolipoprotein A_1; SD LDL-C = small dense LDL-C; SD HDL-C = small dense HDL-C.

Govindarajan G et al., JCMS . 2006:153-155.

Mechanisms Relating Insulin Resistance and Dyslipidemia in Exogenous pathway

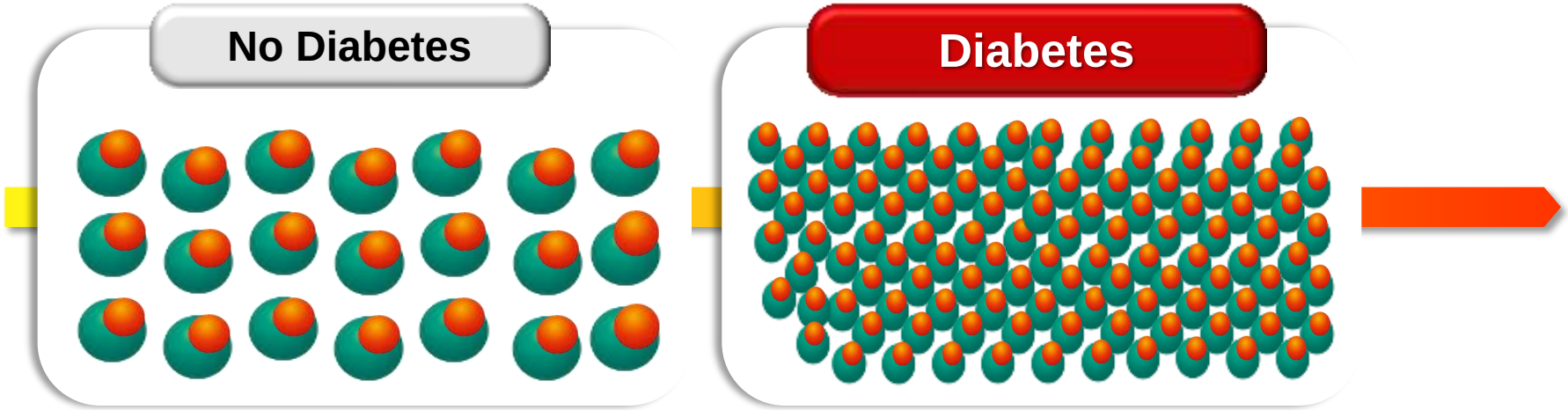


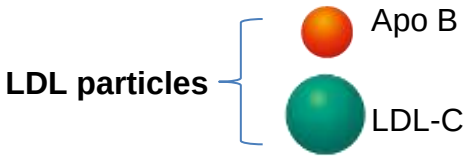
HSL, hormone sensitive lipase; ATGL, adipose triglyceride lipase; FFA, free fatty acid; TG, triglyceride; SREBP, sterol regulatory element binding protein; FA, fatty acid; VLDL, very low-density lipoprotein; apo, apolipoprotein; CM, chylomicron; LPL, lipoprotein lipase.

Duez H, Pavlic M, Lewis GF. *Atheroscler Supple.* 2008;9(2):33-38.

Increased numbers of LDL particles, even when LDL-C levels are normal in DM

- Increased number of LDL particles (as denoted by a high apoB concentration) should be considered as a indicator of CHD risk in diabetes.





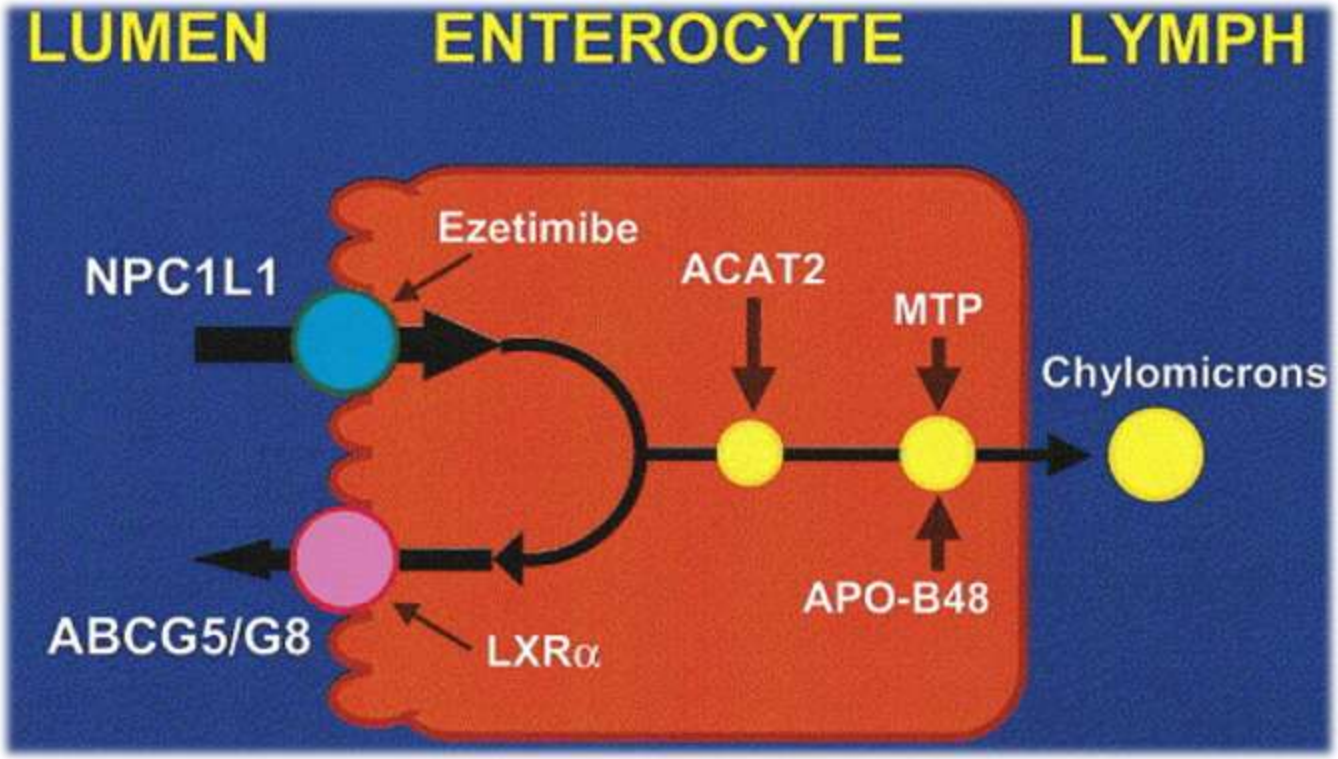
small dense LDL w/ more ApoB

↑ Number of LDL particles
↑ Concentration of apolipoprotein B

CHD, coronary heart disease; LDL-C, Low Density Lipoprotein-cholesterol; apoB, apolipoprotein B; LDL, Low Density Lipoprotein; sdLDL, small dense Low Density Lipoprotein

Buse JB et al. *Circulation.* 2007;115:114, Walldius G, et al. *Eur Heart J*. 2005;26:210, Chahil TJ, et al. *Endocrinol Metab Clin North Am*. 2006;35:491

Intestinal genes that regulate cholesterol absorption and chylomicron synthesis



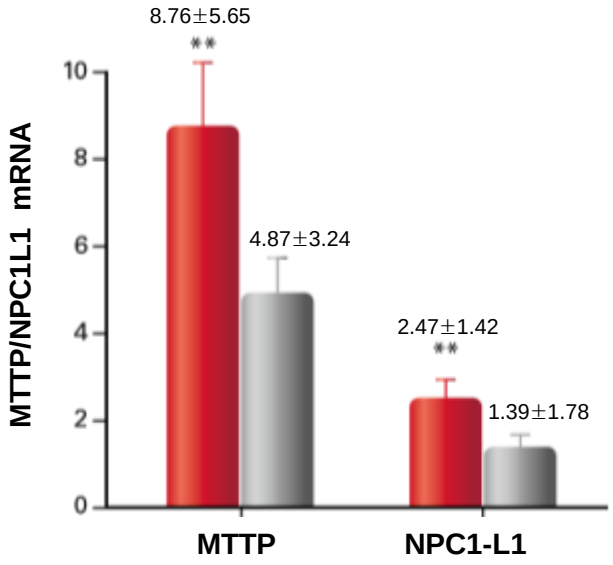
- Regulation of cholesterol absorption: NPC1-L1, MTTP
- Regulation of cholesterol excretion to intestinal lumen: ABCG5/G8

NPC1L1, Niemann–Pick C1 Like 1; ABCG5 and ABCG8, ATP-binding cassette transporters G5 and G8; MTTP, microsomal triglyceride transfer protein

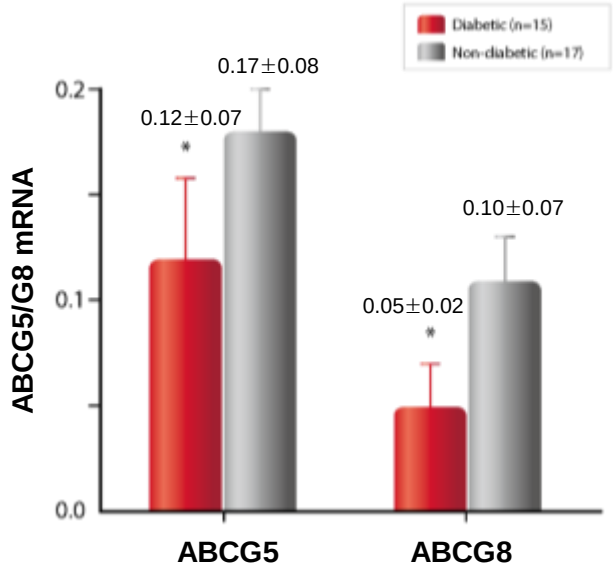
Alteration of expression of intestinal genes that regulate cholesterol absorption and chylomicron synthesis in DM

- Levels of NPC1L1, ABCG5 and ABCG8 and MTTP mRNA were measured in duodenal biopsies by real-time PCR. Lipoproteins were isolated by sequential ultracentrifugation.

Regulation of cholesterol absorption



Regulation of cholesterol excretion to intestinal lumen



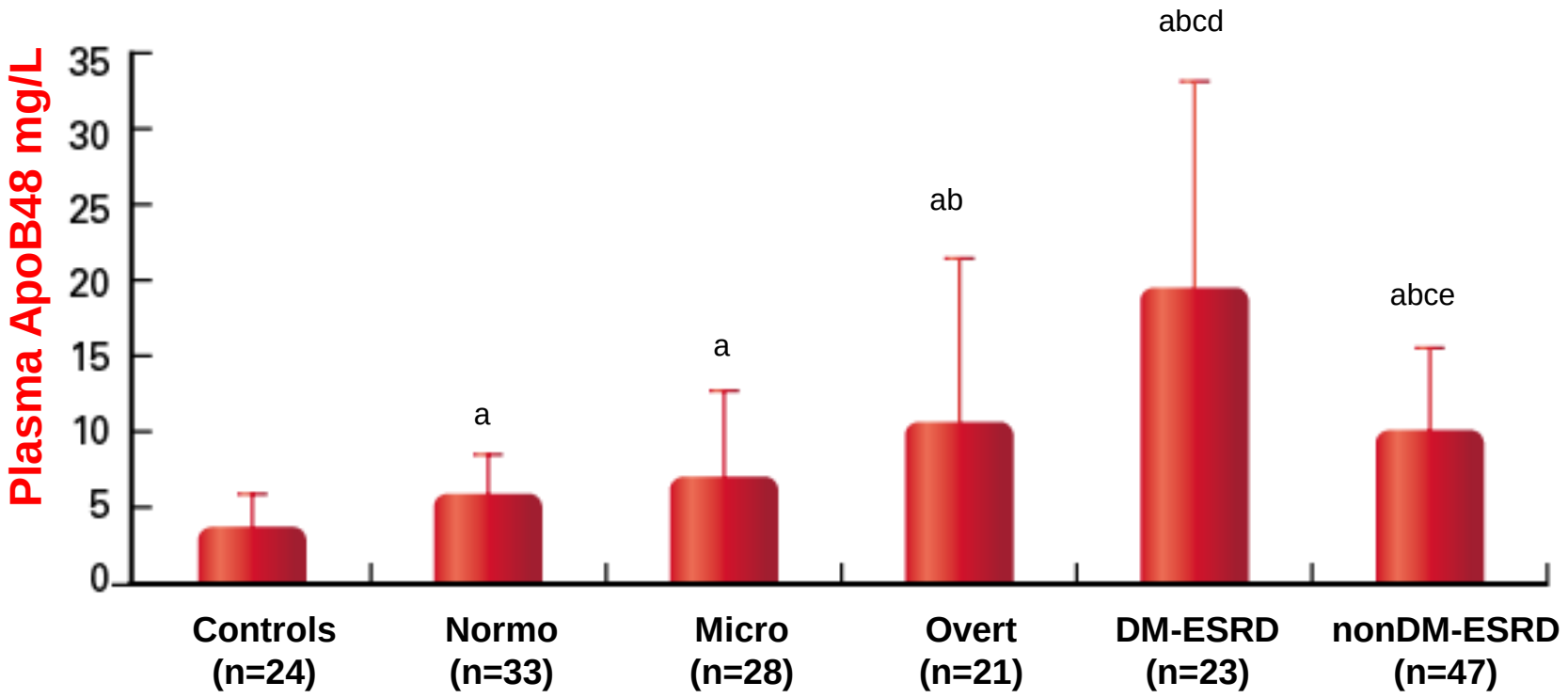
- In type 2 diabetes there are **important alterations to the expression of intestinal genes that regulate cholesterol absorption and chylomicron synthesis.**
- In diabetic patients **statin therapy** is associated **with reduced MTTP expression** and **increased ABCG5 and ABCG8 mRNA.**

ApoB48, apolipoprotein B48; DM, diabetes mellitus; NPC1L1, Niemann–Pick C1 Like 1; ABCG5 and ABCG8, ATP-binding cassette transporters G5 and G8; MTTP, microsomal triglyceride transfer protein; mRNA, messenger ribonucleic acid; PCR, polymerase chain reaction

1. Lally S, et al. *Diabetologia*. 2006;49:1008-1016.

Increased serum Apo B48 levels in T2DM patients: correlation bw plasma Apo B48 and DM w/ ESRD

- Serum concentration of **apoB48 level** is **higher** in **diabetic** patients and **peaked** in the patients with **diabetic ESRD**



Fasting plasma apoB48 level in non-diabetic control subjects, type 2 diabetic subjects with various stages of nephropathy and non-diabetic patients with end-stage renal disease (ESRD). Normo, normo-albuminuric diabetes; micro, micro-albuminuric diabetes; overt, overt-proteinuric diabetes. Significance ($P < 0.05$) was determined by ANOVA: (a) vs. control; (b) vs. normo; (c) vs. micro; (d) vs. overt; (e) vs. diabetic ESRD.

Hayashi T, et al. *Atherosclerosis*. 2008;197:154-158.

Rasing Question

What would be the better option to **minimize** the concern of **increasing DM** and **safety** issue especially in the **Cardiometabolic Patients**?

Agenda

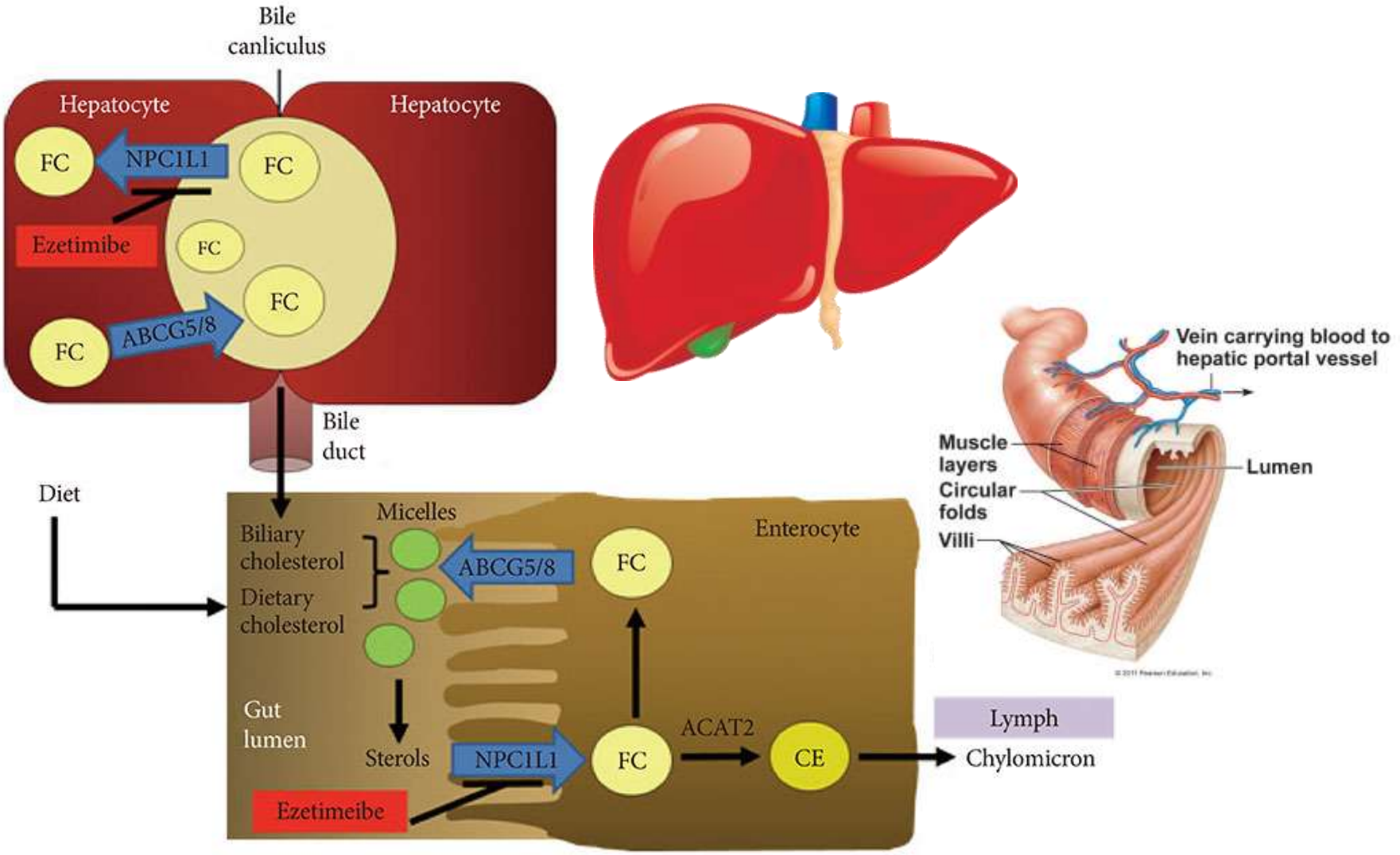
I. LDL-C, a causal factor for ASCVD

II. Unmet needs of current lipid management

III. Strategic approach for management of dyslipidemia in cardiometabolic patients

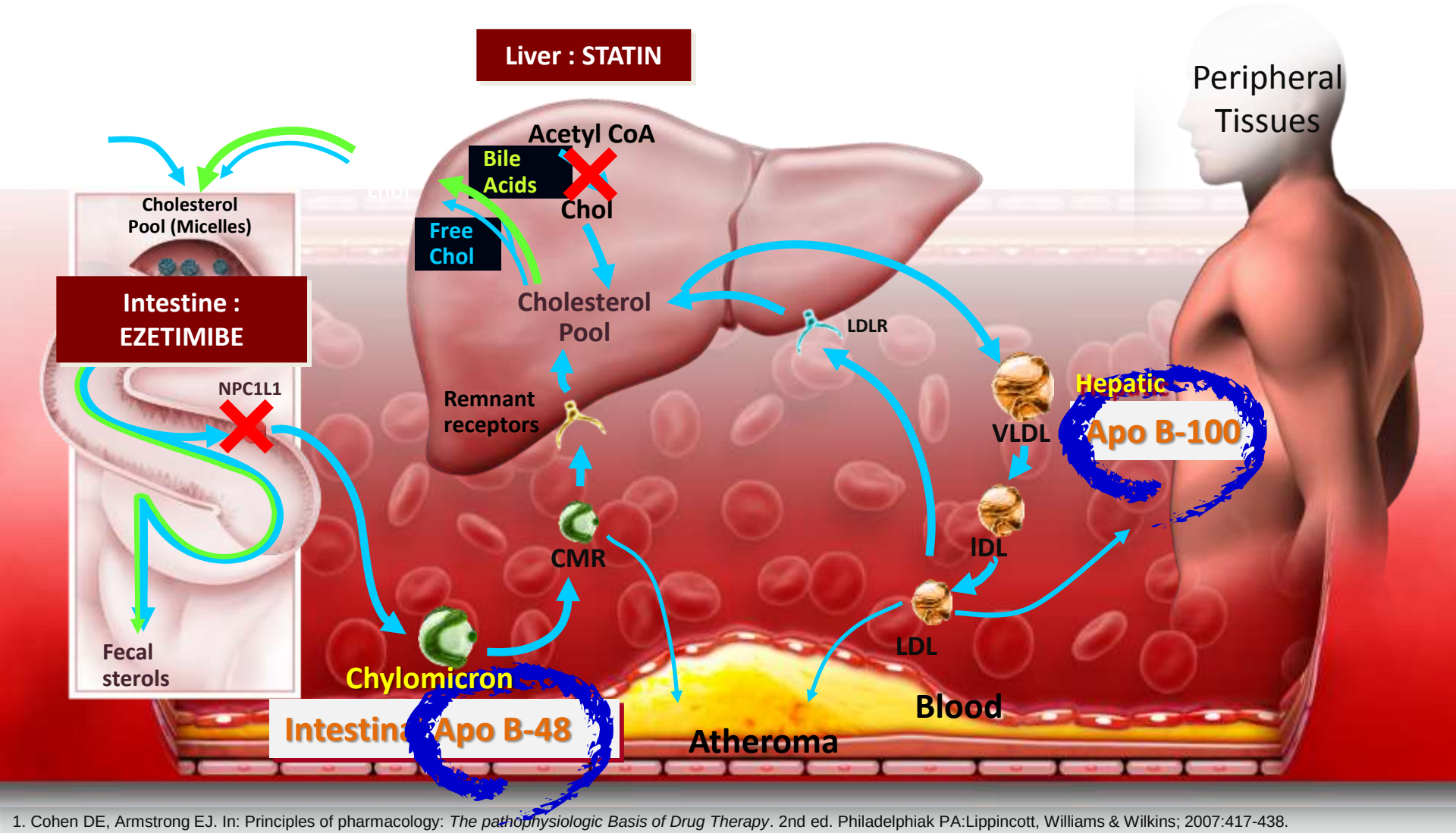
IV. Direction of alternative option in lipid guideline

Niemann-Pick C1-Like 1 (NPC1L1) in cholesterol transport in the intestine and liver and Ezetemibe



Diabetes Metab J. 2013;37:240-24

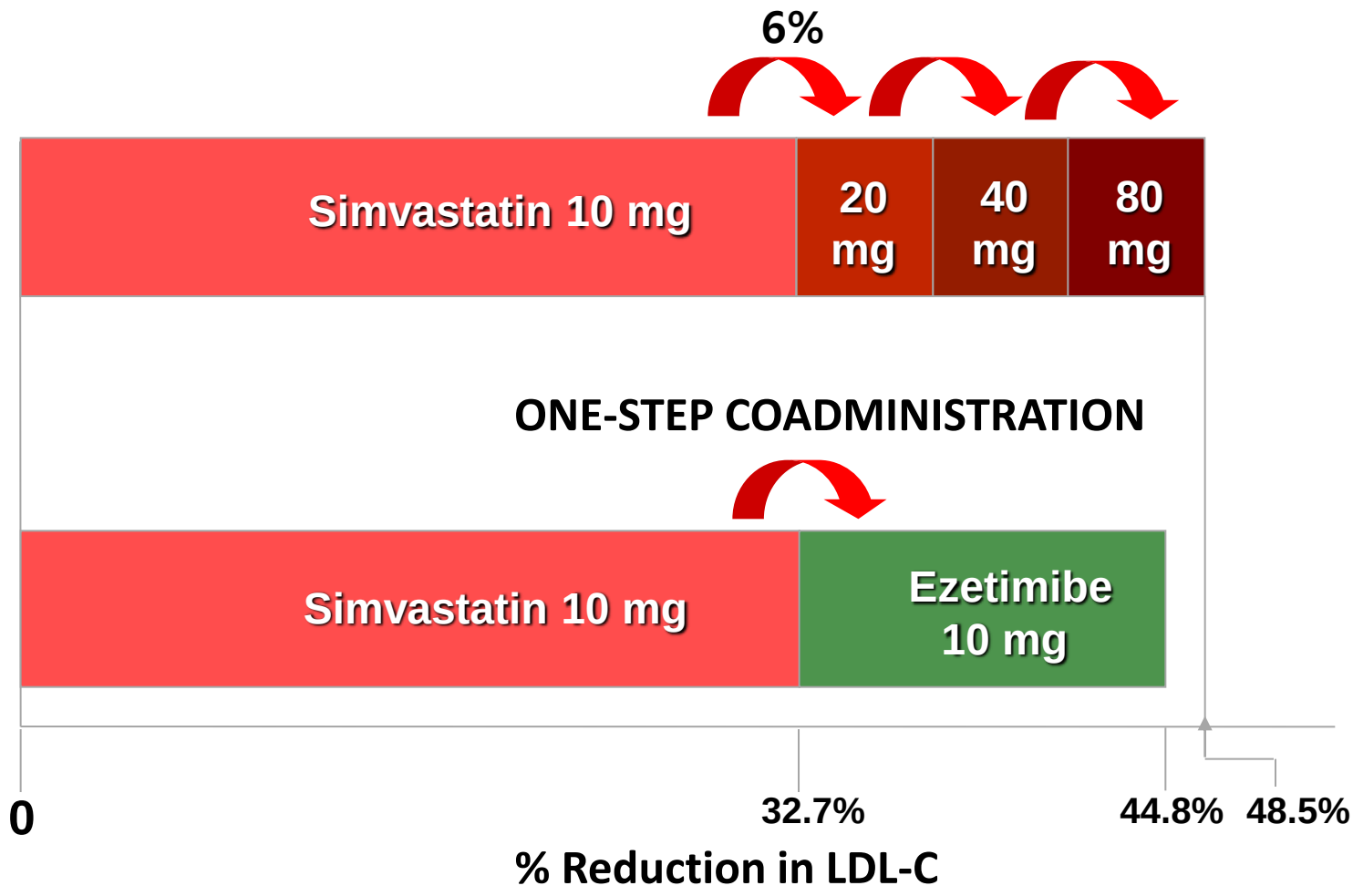
VYTORIN (ezetimibe/simvastatin): Dual Action in Cholesterol Metabolism



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.

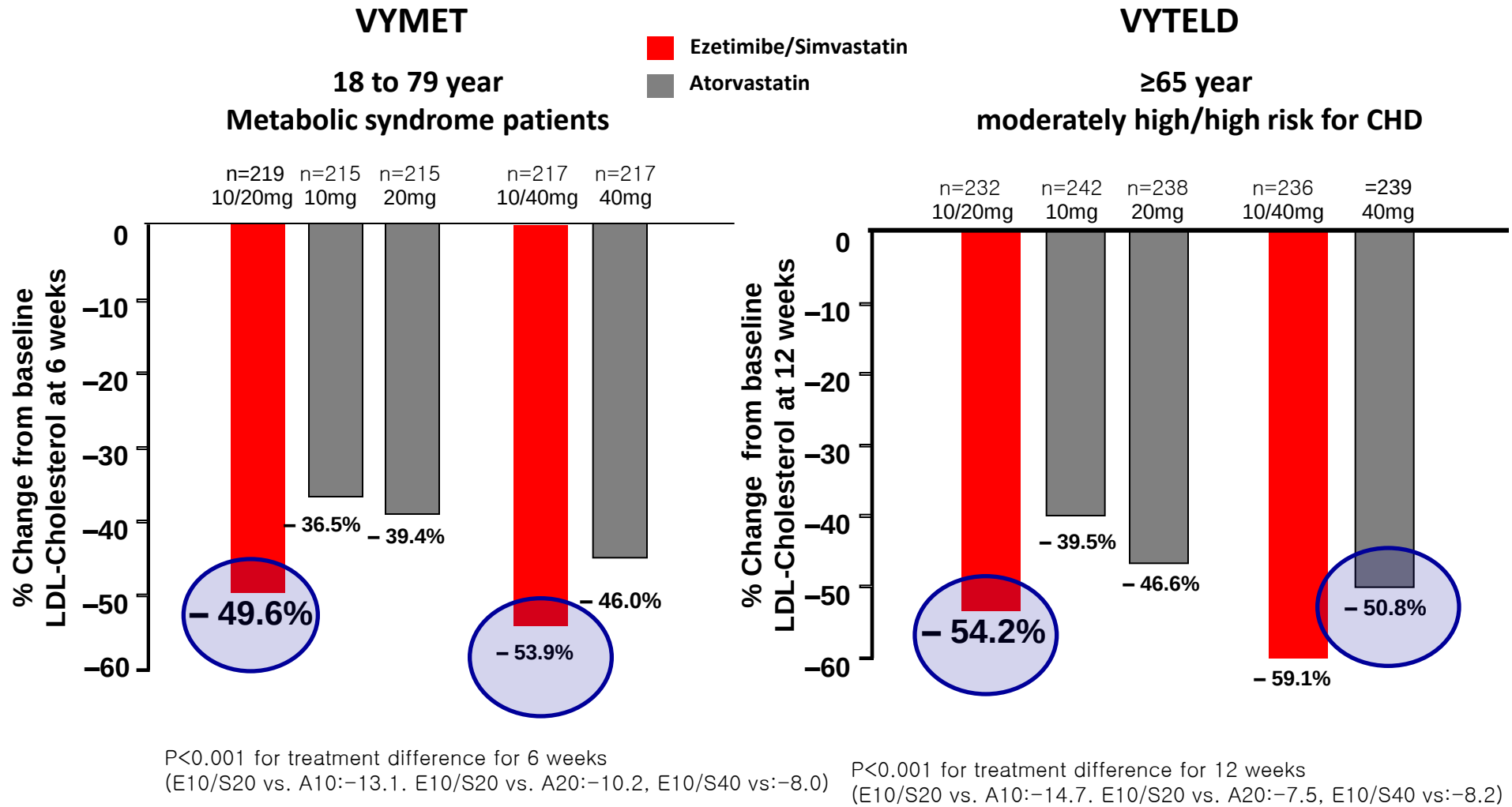
2. Wang DQ. *Annu Rev Physiol* 2007;69:221-248.

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



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

Ezetimibe + Simvastatin: Superior LDL-C reduction vs. Atorvastatin at Starting Dose

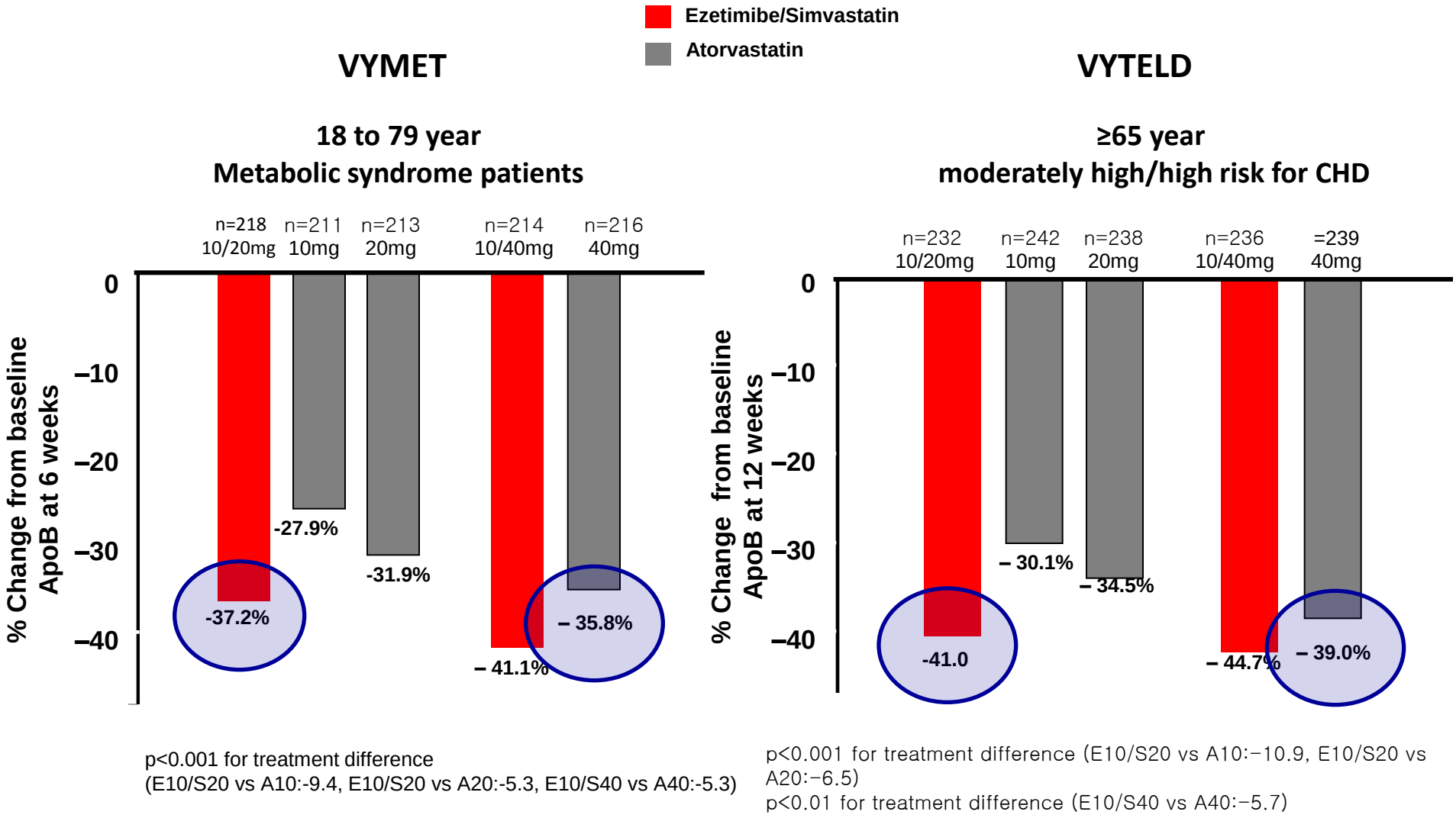


P<0.001 for treatment difference for 6 weeks
(E10/S20 vs. A10:−13.1. E10/S20 vs. A20:−10.2, E10/S40 vs:−8.0)

P<0.001 for treatment difference for 12 weeks
(E10/S20 vs. A10:−14.7. E10/S20 vs. A20:−7.5, E10/S40 vs:−8.2)

Robinson JG, et al. *Am J Cardiol* 2009;103:1694-1702;
Foody JM, et al. *Am J Cardio* 2010;106:1255-1263

Ezetimibe + Simvastatin: Superior ApoB reduction vs. Atorvastatin at Starting Dose



p<0.001 for treatment difference
(E10/S20 vs A10:-9.4, E10/S20 vs A20:-5.3, E10/S40 vs A40:-5.3)

p<0.001 for treatment difference (E10/S20 vs A10:−10.9, E10/S20 vs A20:−6.5)
p<0.01 for treatment difference (E10/S40 vs A40:−5.7)

Robinson JG, et al. *Am J Cardiol* 2009;103:1694-1702;
Foody JM, et al. *Am J Cardio* 2010;106:1255-1263

Effect of Ezetimibe on Insulin Resistance Improvement

Patients with primary hyperlipidemia and CHD or 10yrs CHD risk >20% included for treatment of pravastatin 40mg (n=50) or pravastatin 10mg + ezetimibe 10mg (n=50) for 6 months

Parameters	Group1 (n=50)	Prava 40mg	Group2 (n=50)	Prava 10mg + Eze 10mg	
	Before treatment	After treatment	Before treatment	After treatment	*P* Values
Glucose (mg/dl)	109.1±18.2	107.5±14.6	100.1±10.9	97.4±9.7	*P*=0.01
Total cholesterol (mg/dl)	231.1±83.5	211.3±37.2 *	250.9±51.8	187.9±34.9 *	*P*=0.04
Triglyceride (mg/dl)	243.5±96.8	190.9±55.2	270.3±158.9	154.6±60.7 **	*P*=0.05
LDL-cholesterol (mg/dl)	165.7±29.7	133.4±26.6 *	158.1±47.5*	116.9±26.4 **	*P*=0.003
HDL-cholesterol (mg/dl)	46.3±10.25	44.1±8.6	43.7±11	42.1±10	*P*=0.51
Insulin (U/ml)	15.1±7.5	11.6±5.7	11.5±5.4	7.6±2.6 **	*P*=0.08
Insulin resistance*	4.05±2.31	3.16±1.90	2.96±1.50	2.05±0.55 **	*P*=0.01
Hs-CRP (mg/l)	6.69±6.11	3.02±1.70*	6.36±2.06	2.68±1.79 **	*P*=0.04

*HOMA formula [HOMA 12 = fasting insulin (*m*u/mlt) X fasting blood sugar (mmol/lt)/22.5].

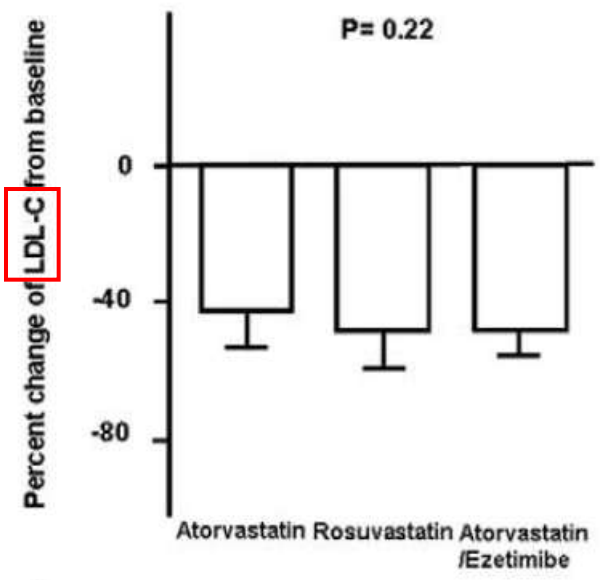
The Values are mean ± standard deviation (range)*p* Value compare of value before treatment and after 6 months treatment between groups; **p*<0.05, before treatment and after 6 months treatment in groups; meaningful as statistical; ***p*<0.01, before treatment and after 6 months treatment in groups

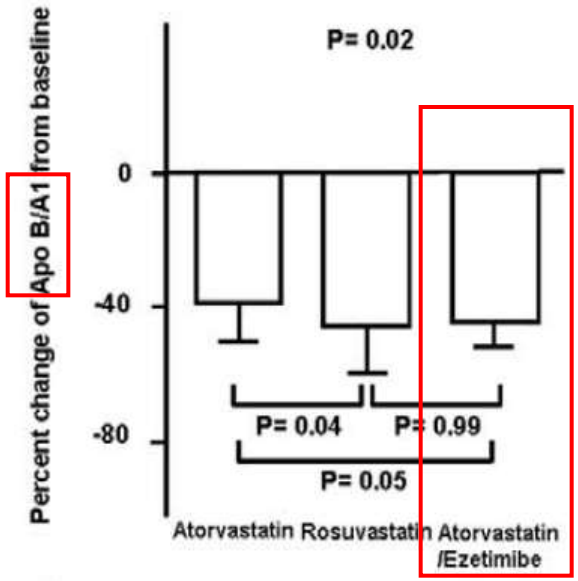
Inflammation. 2007;30:230-235.

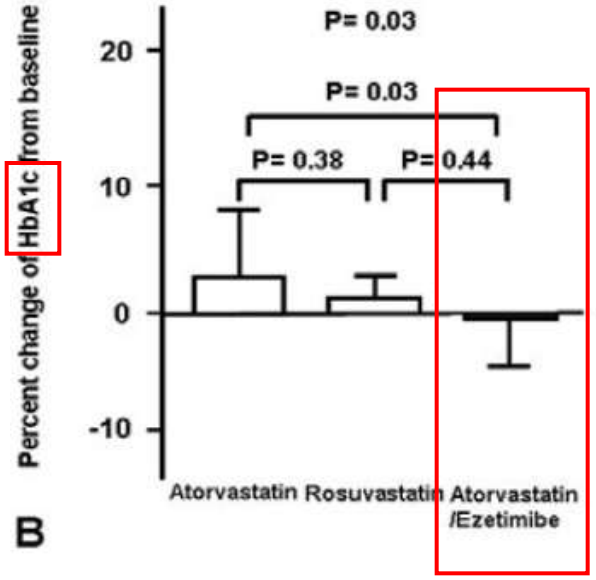
Effects of Atorva 20mg, Rosuva 10mg, and Atorva /Ezeimibe 5mg/5mg on lipoproteins and glucose metabolism

Ae-Young Her, MD,[1] Jong-Youn Kim, MD, PhD,[1] Seok-Min Kang, MD, PhD,[1]
Donghoon Choi, MD, PhD,[1] Yangsoo Jang, MD, PhD,[1] Namsik Chung, MD, PhD,[1]
Ichiro Manabe, MD, PhD,[2] and Sang-Hak Lee, MD, PhD[1]

- Purpose: to compare the effects of 3 different statin regimens that have equivalent LDL-C lowering efficacy on the apolipoprotein B/A1 ratio and glucose metabolism
- 90 hypercholeserolemic patients were randomly assigned to 1 of 3 treatment groups for 8 weeks: atorvastatin 20 mg, rosuvastatin 10 mg, or atorvastatin/ezetimibe 5 mg/5 mg.
- At drug treatment week 8, we compared the percentage changes in lipid parameters, apolipoprotein B/A1 ratio, hemoglobin A1c, and homeostasis model assessment-insulin resistance (HOMA-IR) from baseline.







J Cardiovascular Pharm and Therapeutics 2010;15:167–174

ApoB 48 and ApoB 100 in Plaque

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Available online at www.sciencedirect.com

ScienceDirect

Clinica Chimica Acta xx (2008) xxx – xxx

www.elsevier.com/locate/clinchim

Detection of apolipoproteins B-48 and B-100 carrying particles in lipoprotein fractions extracted from human aortic atherosclerotic plaques in sudden cardiac death cases

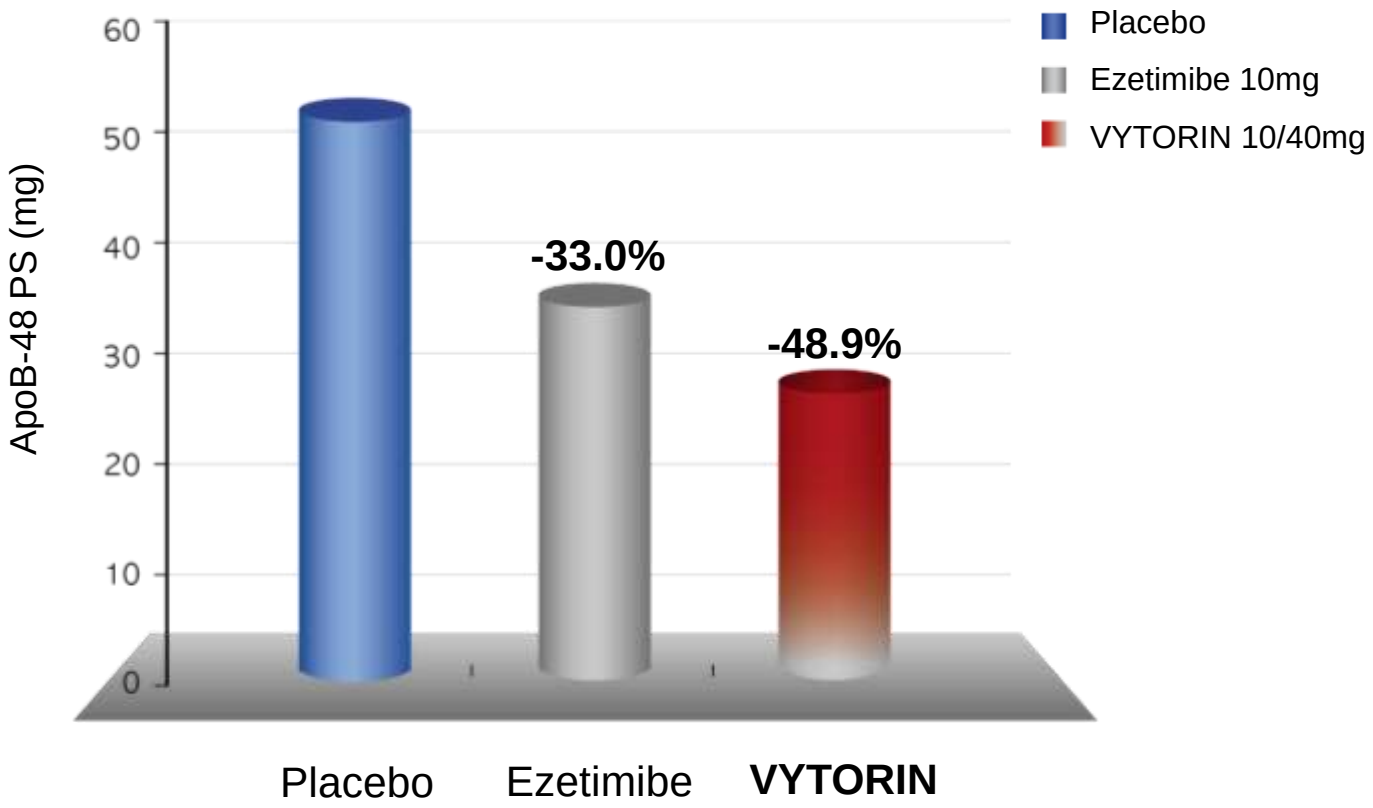
Takamitsu Nakano [a,*], Katsuyuki Nakajima [a,b], Manabu Niimi [a], Masaki Q. Fujita [b], Yasuhiro Nakajima [b], Sanae Takeichi [c], Makoto Kinoshita [d], Teruhiko Matsushima [e], Tamio Teramoto [d], Akira Tanaka [f]

[a] *JIMRO Laboratories, 351-1 Nishiyokote-cho, Takasaki, Gunma 370-0021, Japan*
[b] *Department of Legal Medicine, Keio University School of Medicine, Tokyo, Japan*
[c] *Department of Forensic Medicine, Tokai University School of Medicine, Isehara, Kanagawa, Japan*
[d] *Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan*
[e] *Internal Medicine, Tsukuba Memorial Hospital, Tsukuba, Ibaraki, Japan*
[f] *Laboratory of Clinical Nutrition and Medicine, Kagawa Nutrition University, Sakado, Saitama, Japan*

Received 13 August 2007; received in revised form 13 December 2007; accepted 13 December 2007

Nakano. *Clinica Chimica Acta*, 2008

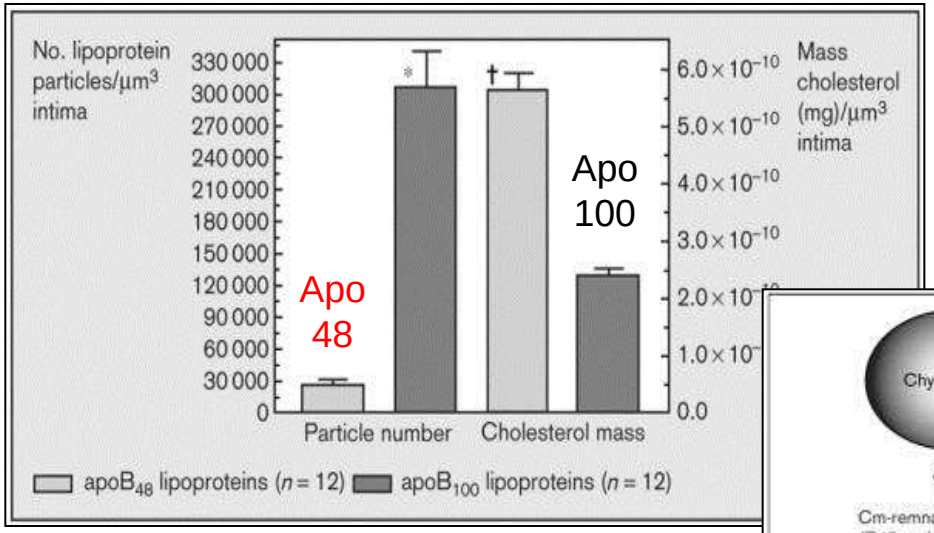
Ezetimbie strongly reduces ApoB48



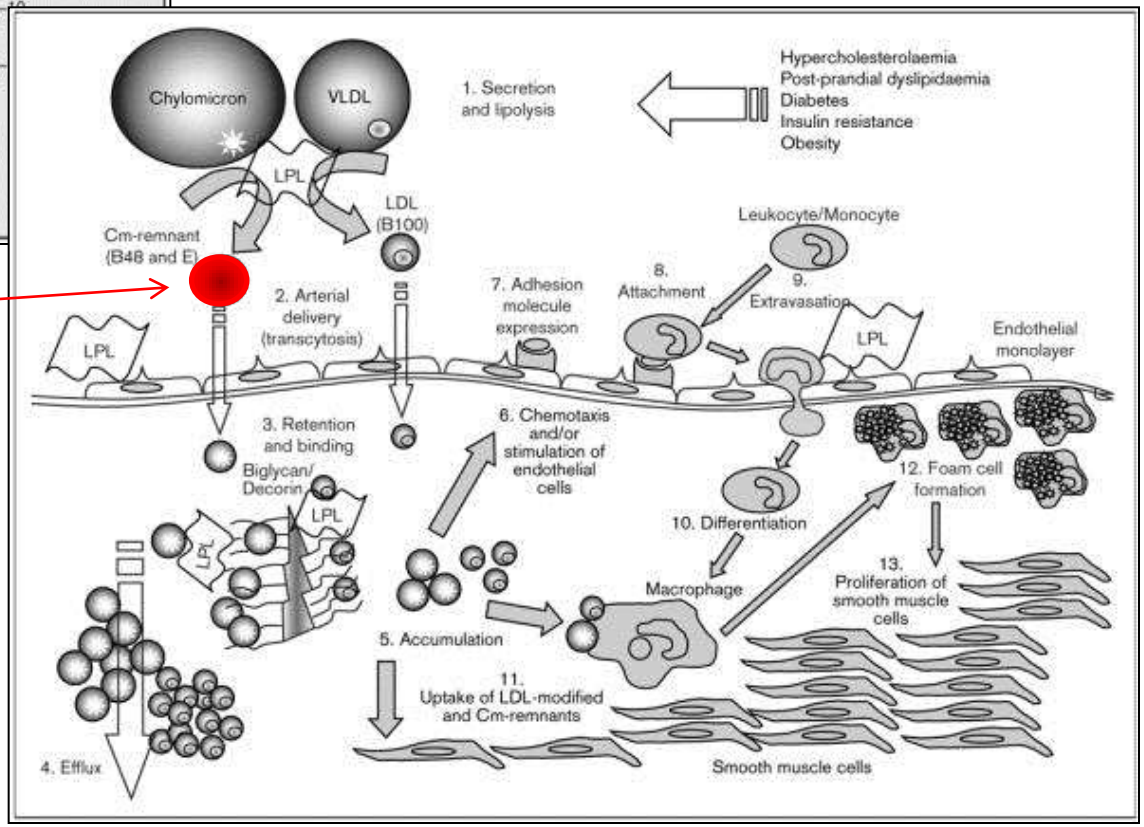
P < 0.05 for both ezetimibe and simvastatin vs. placebo

J Lipid Res. 2009 Jul;50(7):1463-71.

CMR w/ ApoB48 involves early atherosclerosis

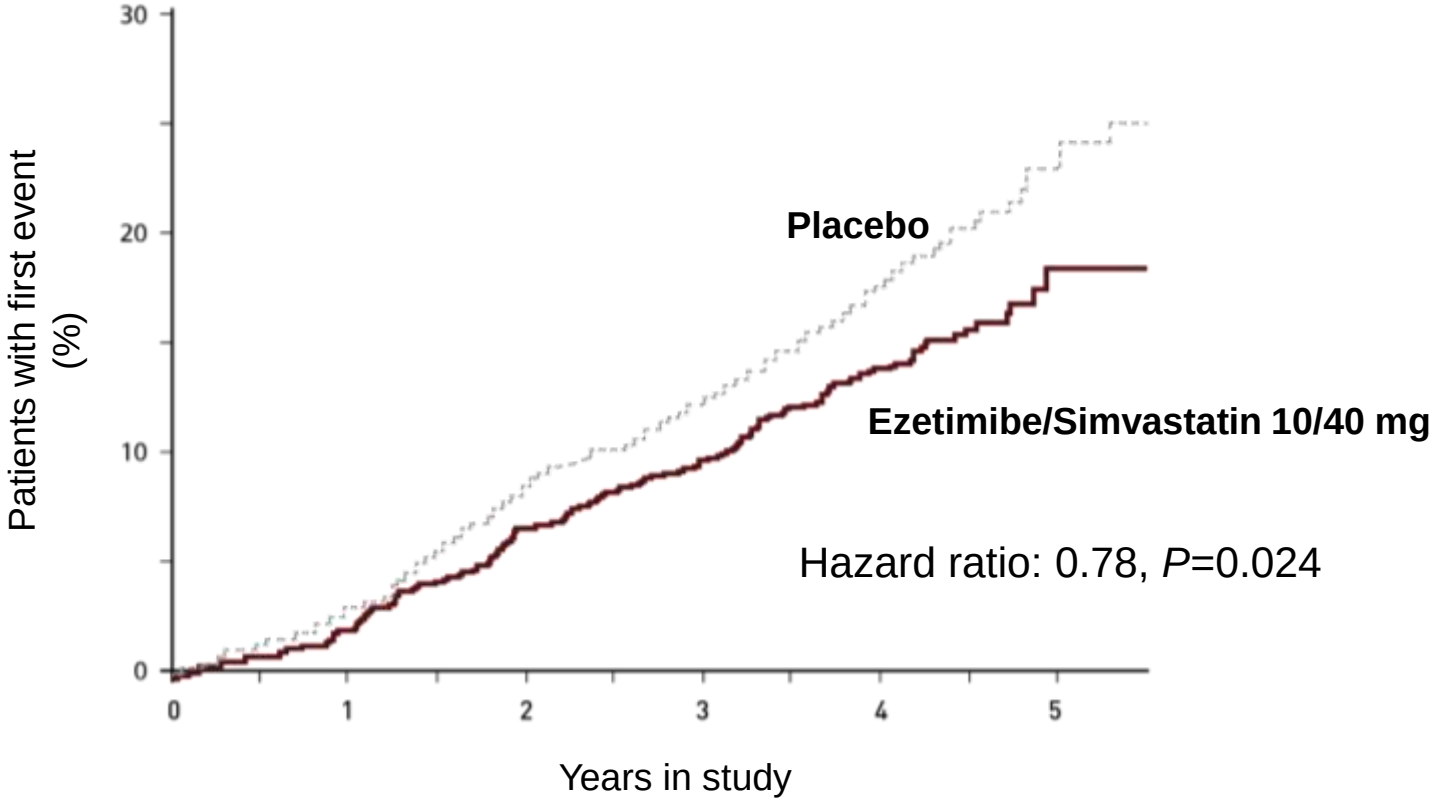


Chylomicron-Remnant (Apo B48 and E)



Current Opinion in Lipidology. 13:461-470,

SEAS: Ischemic Cardiovascular Event in AS



No. at risk

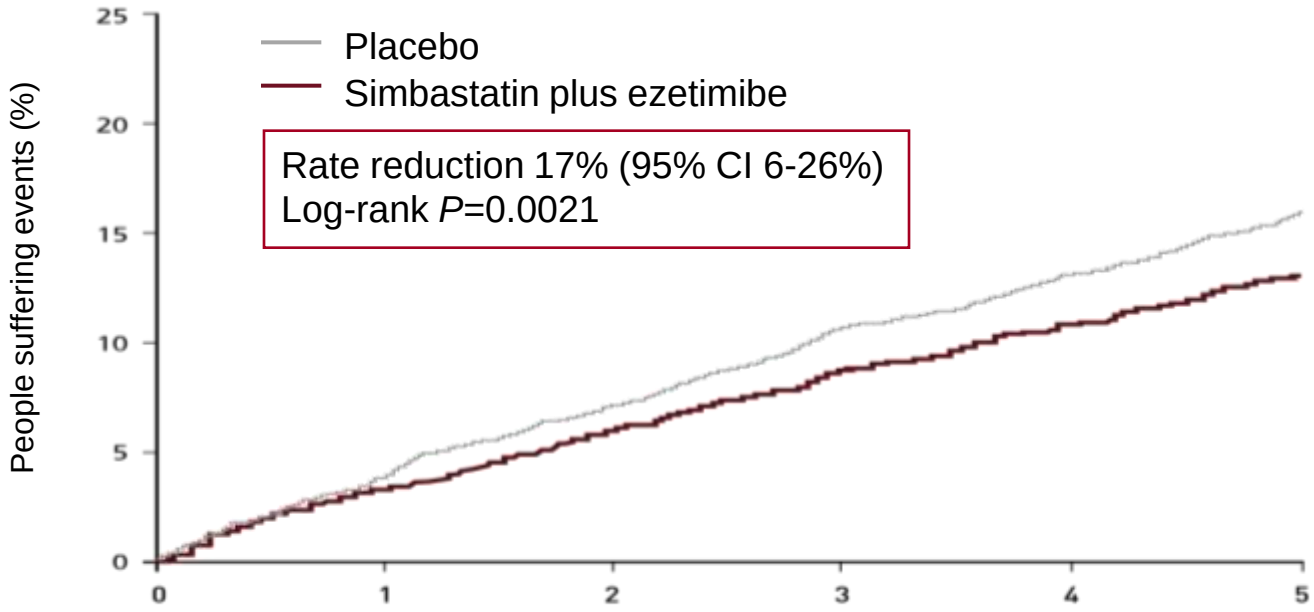
Ezetimibe/Simvastatin 10/40 mg	917	867	823	769	76
Placebo	898	838	788	729	76

Rossebø et al. *NEJM* 2008;359

SHARP: Major Atherosclerotic Events in CKD

(Composite endpoint: coronary death, non-fatal MI, non-hemorrhagic stroke and any revascularization)

- Randomized double-blind trial included 9270 patients with chronic kidney disease

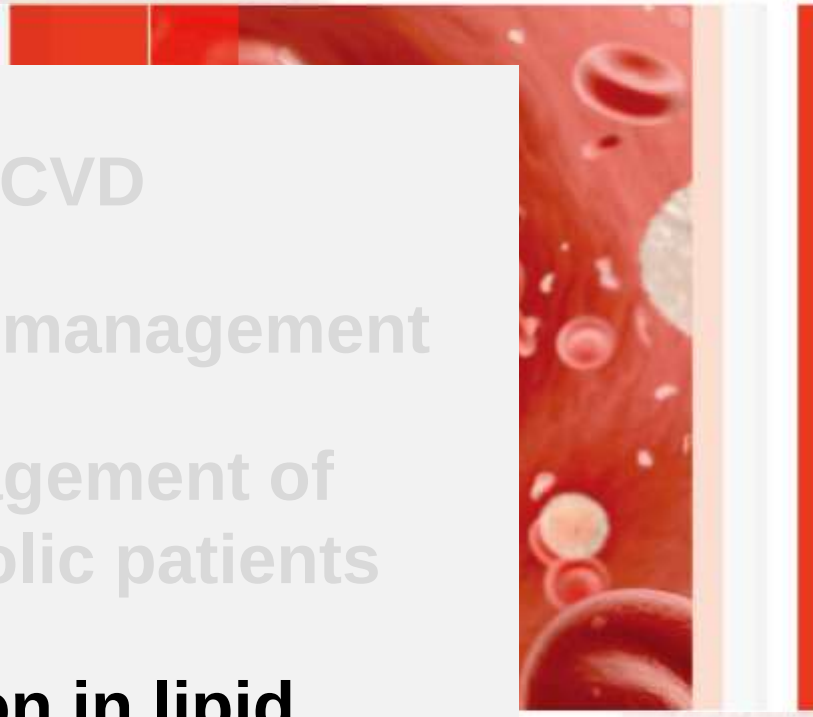


Number at risk						
Placebo	4,620	4,204	3,849	3,469	2,566	1,269
Simbastatin plus ezetimibe	4,650	4,271	3,939	3,546	2,655	1,265

Numbers remaining at risk of a first major atherosclerotic event ar the beginning of each year are shown for both treatment groups.

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

Agenda



I. LDL-C, a causal factor for ASCVD

II. Unmet needs of current lipid management

III. Strategic approach for management of dyslipidemia in cardiometabolic patients

IV. Direction of alternative option in lipid guideline

ESC/EAS 2011 Guidelines: the use of lower intensity statin therapy should be considered in some patients

In Acute Coronary Syndrome, Acute myocardial infarction with ST-segment elevation.[1]

- 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).

In the Elderly[1]

- 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].

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

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

Ezetimibe in ESC/EAS 2011 Guidelines

7.5.2 Statins and cholesterol absorption inhibitors

Combining ezetimibe with a statin reduces LDL-C by an additional 15–20%. The results of the **SEAS study** in patients with asymptomatic aortic stenosis showed that **ezetimibe** and **simvastatin** applied **concomitantly reduce the incidence of ischaemic CVD events (up to 46% in the patients with less severe aortic stenosis)** but not events related to aortic valve stenosis. Recently the data of the **SHARP trial** were presented with **positive results in CKD patients,**

For those with **dyslipidaemia** who are **unable to take statins, ezetimibe** could be considered as an alternative in those with high LDL-C

Intensity of statin therapy based on the efficacy of LDL-C lowering in ACC/AHA 2013 Guideline

Recommended more 50% of LDL-C lowering in very high risk patients.

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately **≥50%**	Daily dose lowers LDL–C on average, by approximately **30-50%**	Daily dose lowers LDL–C on average, **by <30%**
• **Atorvastatin (40†)–80 mg** **Rosuvastatin 20** *(40)* mg	• **Atorvastatin 10** *(20)* **mg** • **Rosuvastatin** *(5)* **10 mg** • **Simvastatin 20–40 mg**‡ • **Pravastatin 40** *(80)* **mg** • **Lovastatin 40 mg** • *Fluvastatin XL 80 mg* • **Fluvastatin 40 mg bid** • *Pitavastatin 2–4 mg*	• *Simvastatin 10 mg* • **Pravastatin 10–20 mg** • **Lovastatin 20 mg** • *Fluvastatin 20–40 mg* • *Pitavastatin 1 mg*

Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in *italics*.

LDL–C, low-density lipoprotein cholesterol; RCT, randomized controlled trial.

1. Stone NJ, et al. *JACC.* 2013 ACC/AHA Blood Cholesterol Guideline.

Minimum Drug Dose to Achieve 50% LDL-C Reduction

Drug	Dose,mg/d	LDL-C reduction, %
ATORVA	**80**	**51–54**
EZE/SIMVA	**10/20**	**50–51**
ROSUVA	**20**	**52**

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

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

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

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

ACC/AHA 2013 Guideline provides direction of Non-Statin cholesterol lowering therapy

6.3.2. Non-statins Added to Statins or in Statin Intolerant Individuals

Clinicians treating high-risk patients who have a less-than-anticipated response to statins, who are unable to tolerate a less-than-recommended intensity of a statin, or who are completely statin intolerant may consider the addition of a nonstatin cholesterol-lowering therapy.

ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; HF, heart failure.

1. Keaney JF Jr, et al. *N Engl J Med.* 2014;370:275-278.3.

Lipid Lowering Agents

	LDL- C	HDL-C	TG
Statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastain, imvastatin)	↓18-63%	↑5-15%	↓7-30%
Bile Acid Sequestrants (colesevelam,cholestrymine,colestipol)	↓15-30%	↑3-5%	0 or ↑
Nicotinic Acid	↓5-25%	↑15-35%	↓20-50%
Fibric Acid Derivatives (gemfiborozil, fenofibrate)	↓5-20 or ↑	↑ 10-20%	↓20-50%
Cholesterol Absorption Inhibitor (ezetimibe)	↓18%	↑ 1%	↓7%
Omega-3 fatty acids (prescription strength)	0 or ↑	0 or ↑	↓12-30%

Evaluation of non-statins for high risk pts of ASCVD

Annals of Internal Medicine | REVIEW

Effectiveness of Combination Therapy With Statin and Another Lipid-Modifying Agent Compared With Intensified Statin Monotherapy

A Systematic Review

Kimberly A. Gudzune, MD, MPH; Anne K. Monroe, MD, MSPH; Ritu Sharma, BSc; Padmini D. Ranasinghe, MD, MPH; Yohalakshmi Chelladurai, MBBS, MPH; and Karen A. Robinson, PhD

Background

1. Some patients do not tolerate or respond to high intensity statin monotherapy
2. **Lower-intensity statin combined with nonstatin medication** may be an alternative

Purpose

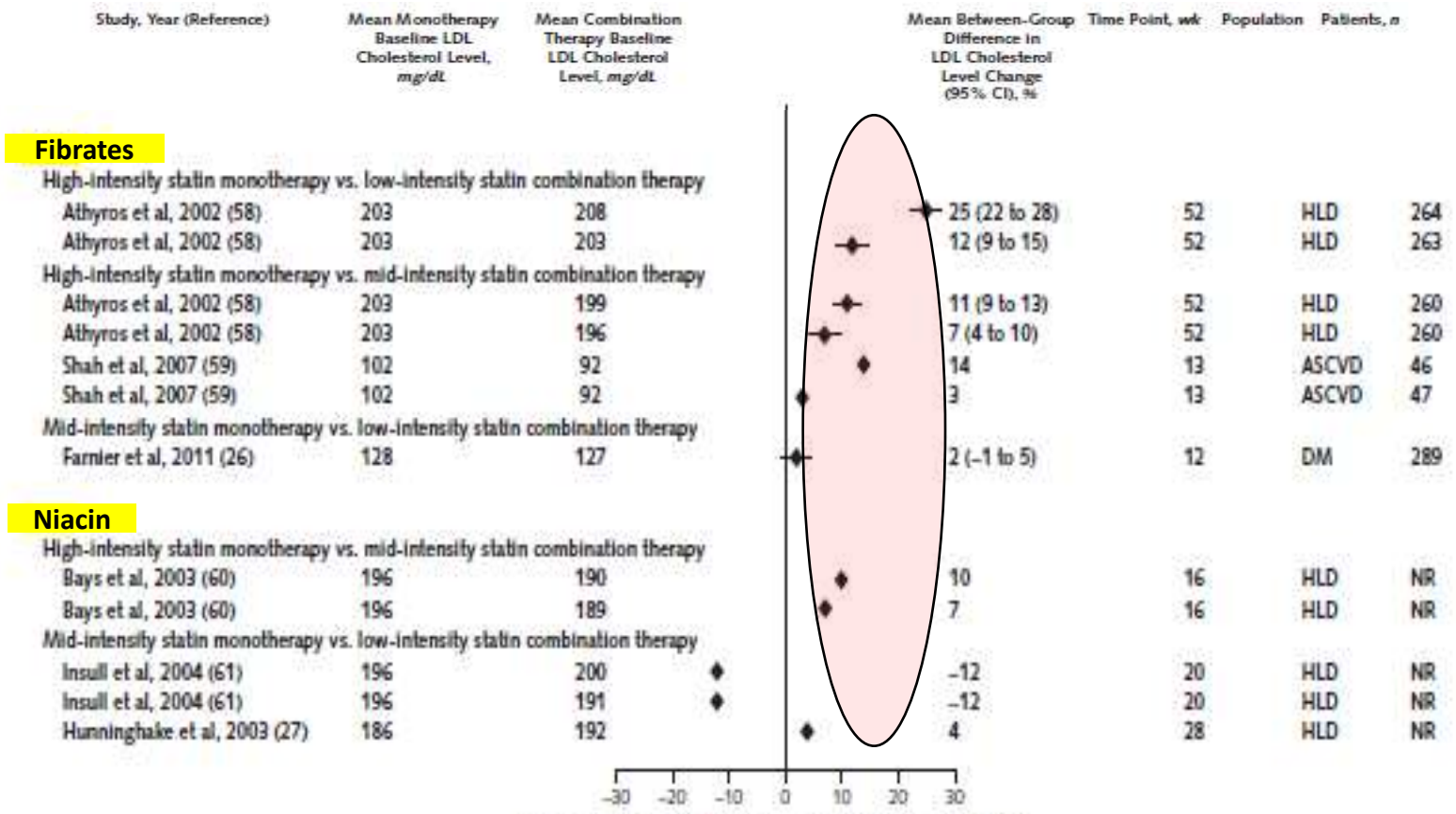
To compare the clinical benefits, adherence, and harms of lower-intensity statin combination therapy with those of higherintensity statin monotherapy among adults at high risk for atherosclerotic cardiovascular disease (ASCVD)

Method

Meta analysis of 36 randomized, controlled trials

Insufficient evidence to evaluate LDL cholesterol for fibrates, niacin, and ω-3 fatty acids

Figure 2. Difference in mean percentage change in LDL cholesterol among high-risk groups by nonstatin agent between higher-intensity statin monotherapy and lower-intensity statin combination therapy.

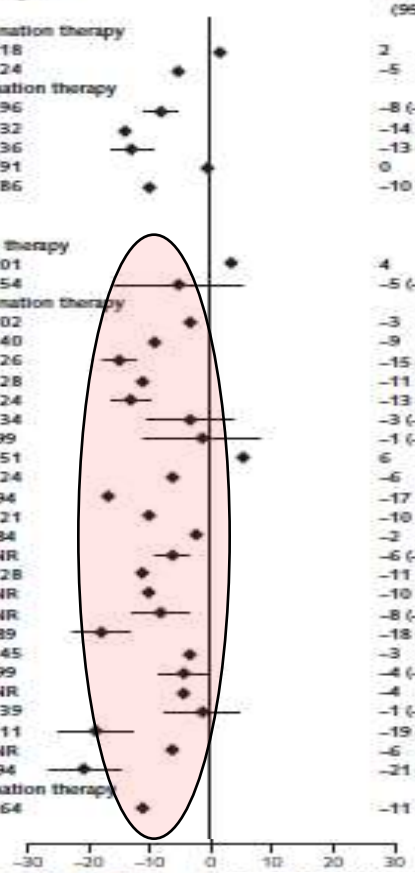


Ann Intern Med 2014

Could consider using lower-intensity statin combined with Ezetimibe or Bile acid sequestrant

Figure 2. Difference in mean percentage change in LDL cholesterol among high-risk groups by nonstatin agent between higher-intensity statin monotherapy and lower-intensity statin combination therapy.

Study, Year (Reference)	Mean Monotherapy Baseline LDL Cholesterol Level, mg/dL	Mean Combination Therapy Baseline LDL Cholesterol Level, mg/dL	Mean Between-Group Difference in LDL Cholesterol Level Change (95% CI), %	Time Point, wk	Population	Patients, n
Bile acid sequestransts						
High-intensity statin monotherapy vs. mid-intensity statin combination therapy						
Johansson, 1995 (28)	222	218	2	12	HLD	55
Johansson, 1995 (28)	222	224	–5	12	HLD	54
Mid-intensity statin monotherapy vs. low-intensity statin combination therapy						
Knapp et al, 2001 (29)	180	196	–8 (–11 to –5)	6	HLD	NR
Ismail et al, 1990* (30, 31)	224	232	–14	8	HLD	NR
PMSG II et al, 1993 (32)	236	236	–13 (–17 to –9)	8	HLD	NR
Schrott et al, 1995 (33)	195	191	0	12	HLD	NR
Schrott et al, 1995 (33)	195	186	–10	12	HLD	NR
Ezetimibe						
High-intensity statin monotherapy vs. low-intensity combination therapy						
Araujo et al, 2010 (34)	206	201	4	4	HLD	23
Rudofsky et al, 2012 (35)	151	154	–5 (–16 to 6)	8	DM	21
High-intensity statin monotherapy vs. mid-intensity statin combination therapy						
McKenney et al, 2007 (36)	198	202	–3	8	HLD	145
Plorkowski et al, 2007 (37)	135	140	–9	4	ASCVD	51
Averna et al, 2010 (19)	128	126	–15 (–18 to –12)	6	ASCVD	112
Bardini et al, 2010 (38)	124	128	–11	6	ASCVD	NR
Barrios et al, 2005 (39)	124	124	–13 (–16 to –10)	6	ASCVD	422
Cho et al, 2011 (40)	132	134	–3 (–10 to 4)	6	ASCVD	85
Pesaro et al, 2011* (41, 42)	101	99	–1 (–11 to 9)	6	ASCVD	78
Ostad et al, 2009 (20)	148	151	6	8	ASCVD	NR
Hamdan et al, 2011 (43)	131	124	–6	12	ASCVD	75
Matsuo et al, 2013 (44)	95	94	–17	12	ASCVD	243
Okada et al, 2011 (45)	120	121	–10	12	ASCVD	81
Yamazaki et al, 2013 (46)	89	84	–2	12	ASCVD	NR
Zieve et al, 2010* (47, 48)	NR	NR	–6 (–9 to –3)	12	ASCVD	891
Bardini et al, 2010 (38)	124	128	–11	6	DM	NR
Barrios et al, 2005 (39)	NR	NR	–10	6	DM	NR
Bays et al, 2013 (49)	NR	NR	–8 (–13 to –3)	6	DM	495
Constance et al, 2007 (22)	93	89	–18 (–23 to –13)	6	DM	423
Goldberg et al, 2006* (50–52)	146	145	–3	6	DM	479
Rosen et al, 2013* (23–25)	97	99	–4 (–8 to 0)	6	DM	629
Foody et al, 2010 (53)	NR	NR	–4	12	DM	NR
Lee et al, 2013 (54)	134	139	–1 (–7 to 6)	12	DM	125
Tonimoto et al, 2013 (55)	112	111	–19 (–26 to –12)	12	DM	75
Zieve et al, 2010* (47, 48)	NR	NR	–6	12	DM	216
Gaudiani et al, 2005 (56)	92	94	–21 (–27 to –15)	24	DM	210
Mid-intensity statin monotherapy vs. low-intensity statin combination therapy						
Kawagoe et al, 2011 (57)	154	164	–11	12	DM	24



Favors Combination therapy

Favors Statin monotherapy

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Direction of Non-Statins in NICE 2014 Guideline

98. Do not offer ***the combination of a bile acid sequestrant (anion exchange 11 resin), fibrate, nicotinic acid or omega-3 fatty acid compound with a statin*** for the prevention of CVD. [new 2014]

99. **People with primary hypercholesterolaemia should be considered for ezetimibe treatment in line with Ezetimibe** for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (NICE 16 technology appraisal guidance 132)

The population groups covered by the ezetimibe Technology Appraisal 132 (National Institute for Health and Clinical Excellence., 2007) are:

- Adults with primary (heterozygous familial and non-familial) hypercholesterolaemia who are candidates for treatment with statins on the basis of their CVD status or risk and;
- whose condition is not appropriately controlled with a statin alone or;
- in whom a statin is considered inappropriate or is not tolerated.

KDIGO 2013 Guideline recommends Statin/Ezetimibe combination with high evidence level

Chapter 2: Pharmacological cholesterol-lowering treatment in adults

2.1.1: In adults aged ≥50 years with eGFR<60 ml/min/1.73 m^2 but not treated with chronic dialysis or kidney transplantation (GFR categories G3a-G5), we recommend treatment with a statin or statin/ezetimibe combination. (1A)

2.1.2: In adults aged ≥50 years with CKD and eGFR≥60 ml/min/1.73m2 (GFR categories G1-G2) we recommend treatment with a statin. (1B)

2.2: In adults aged 18–49 years with CKD but not treated with chronic dialysis or kidney transplantation, we suggest statin treatment in people with one or more of the following (2A):

- known coronary disease (myocardial infarction or coronary revascularization)
- diabetes mellitus
- prior ischemic stroke
- estimated 10-year incidence of coronary death or non-fatal myocardial infarction 410%

2.3.1: In adults with dialysis-dependent CKD, we suggest that statins or statin/ezetimibe combination not be initiated. (2A)

2.3.2: In patients already receiving statins or statin/ezetimibe combination at the time of dialysis initiation, we suggest that these agents be continued. (2C)

2.4: In adult kidney transplant recipients, we suggest treatment with a statin. (2B)

Take Home Message

1. More intensive LDL-C reduction might be appropriate for patients with ASCVD including cardiometabolic patients.

2. Intensive-dose statin therapy has clinical limitations especially in cardiometabolic patients

3. VYTORIN (Ezetimibe+Simvastatin) is the practical option for more intensive LDL-C management

4. VYTORIN (Ezetimibe+Simvastatin) may be a better option for cardiometabolic patients with less side effect and additional clinical benefit from the unique mechanism


Thank You