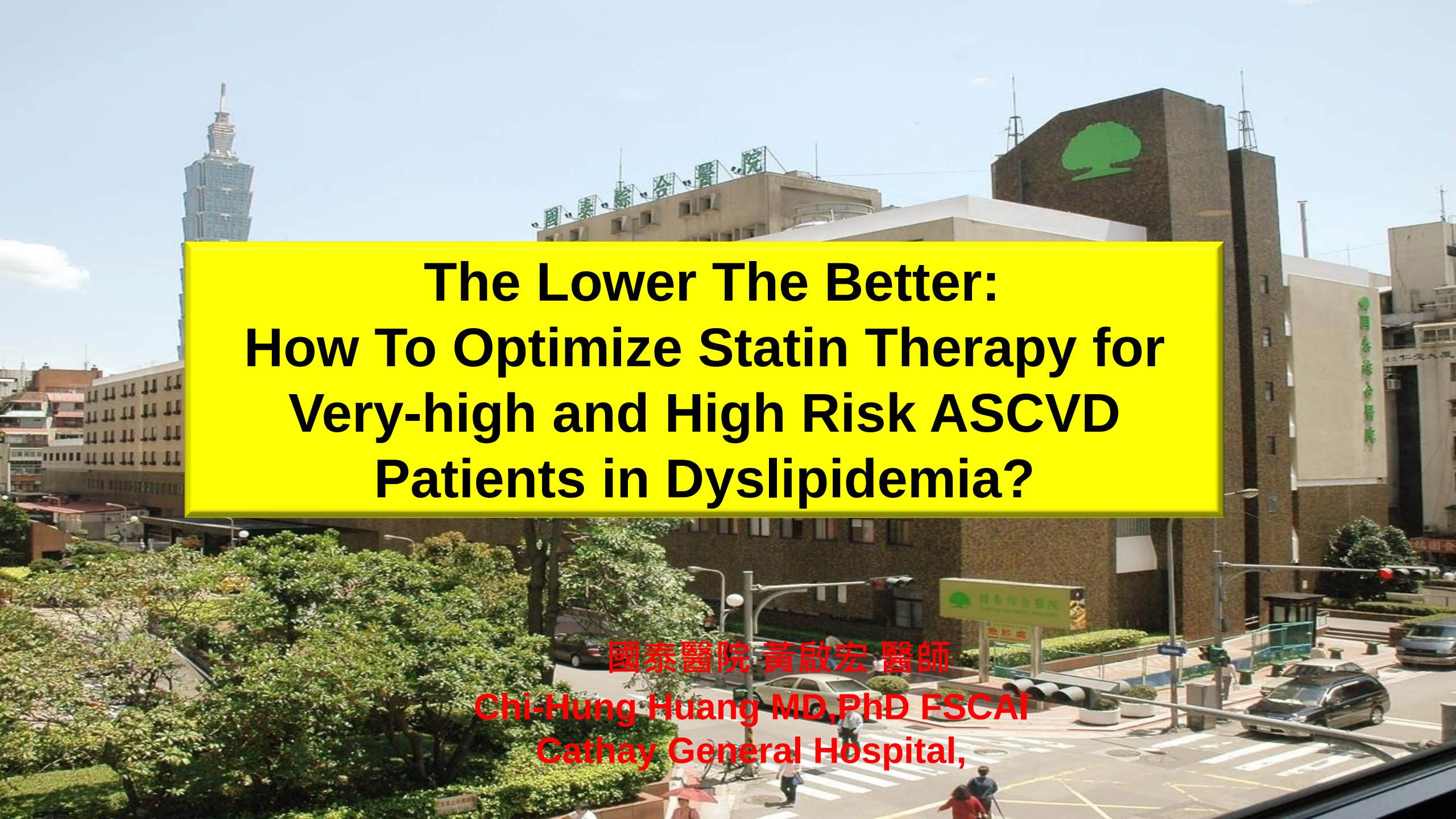


The Lower The Better: How To Optimize Statin Therapy for Very-high and High Risk ASCVD Patients in Dyslipidemia?

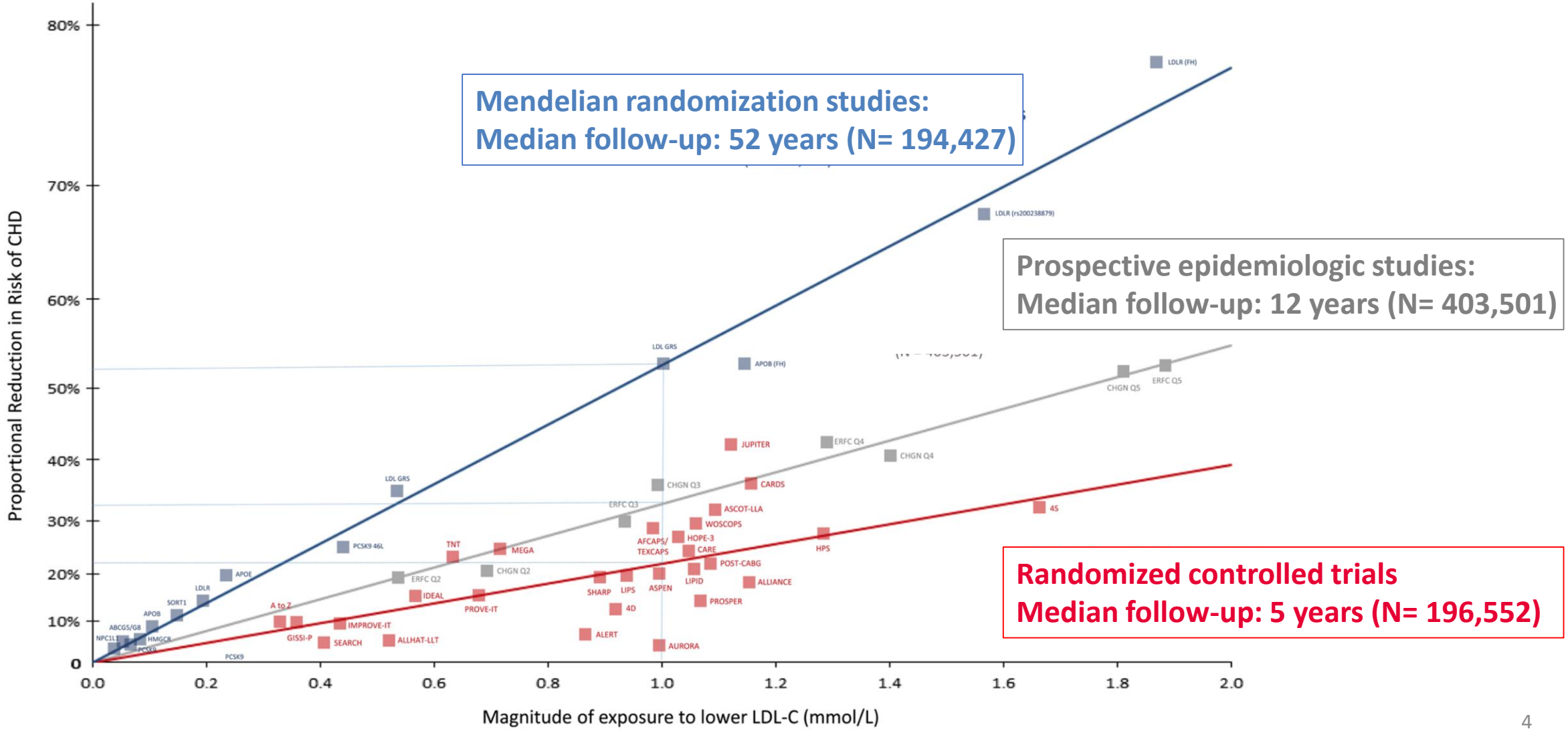
國泰醫院 黃啟宏 醫師
Chi-Hung Huang MD,PhD FSCAI
Cathay General Hospital,

Outline

- Unmet Need in Hyperlipidemia
- Guidelines Recommendation
- Clinical Guideline vs Real World Practice
- WHY High-Intensity

Unmet Need in Hyperlipidemia

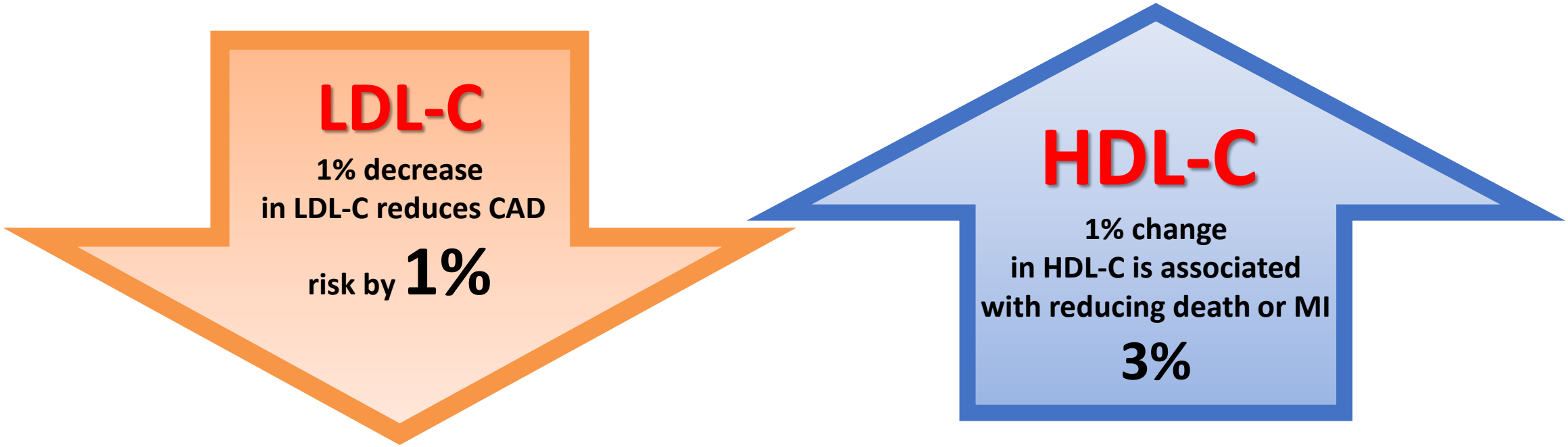
LDL cause atherosclerotic cardiovascular disease (ASCVD) : Evidence from genetic, epidemiologic, and clinical studies



Eur Heart J. 2017 Aug 21;38(32):2459-2472.

The Lower the better

- Reduce CAD risk by the additive benefit of concomitant reduction of LDL-C and raising of HDL-C

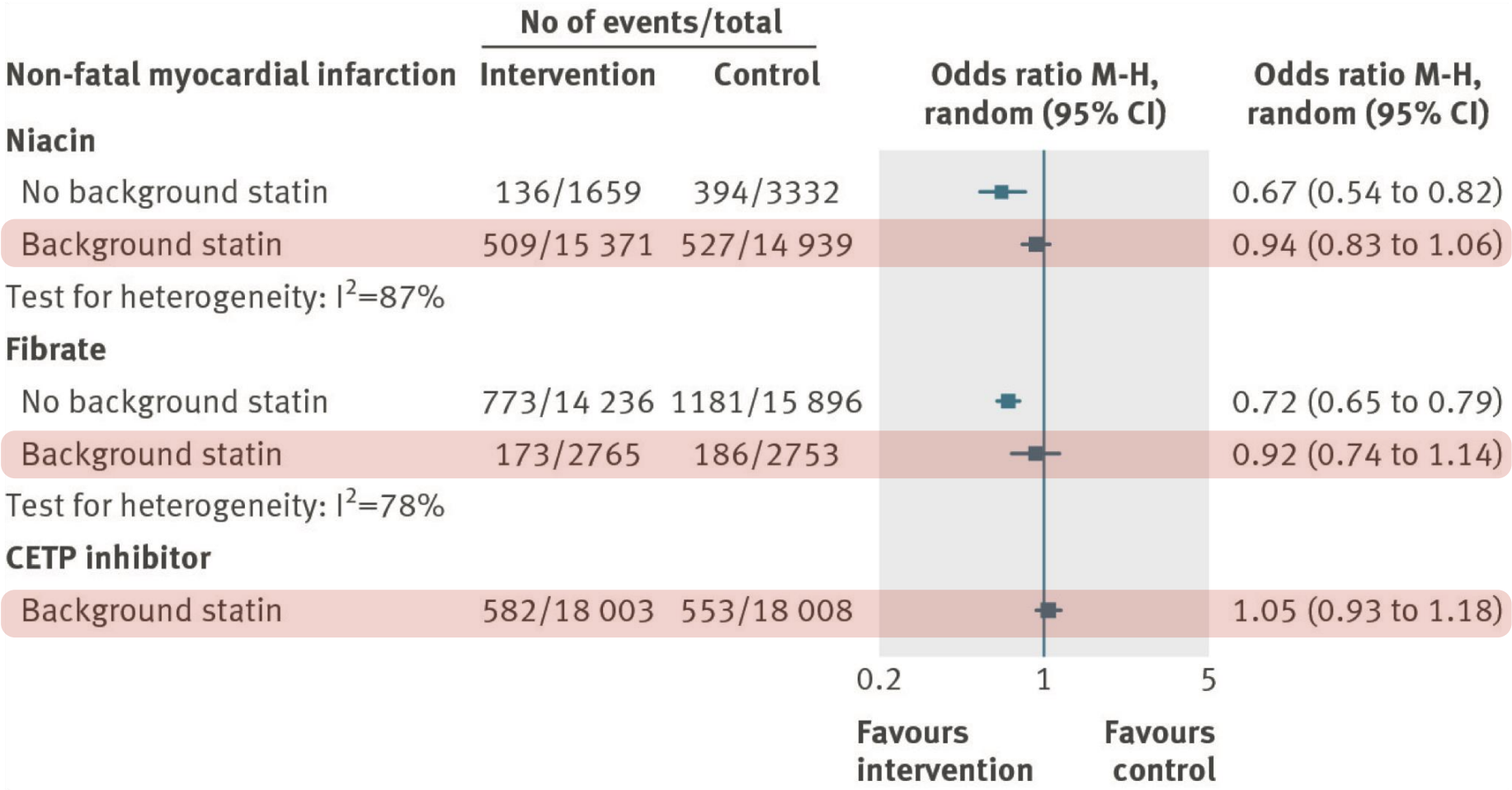


CAD = coronary artery diseases; HDL-C = high density lipoprotein-cholesterol; LDL-C = low density lipoprotein-cholesterol; MI = myocardial infarction

Circulation. 2004;110(2):227-239.
Circulation. 1989;79(1):8-15.
Am J Cardiol. 2000;86(12A): 19L-22L.
JAMA. 1988;260(5):641-651.

TG/HDL-targeted drugs had no effect on CV outcomes

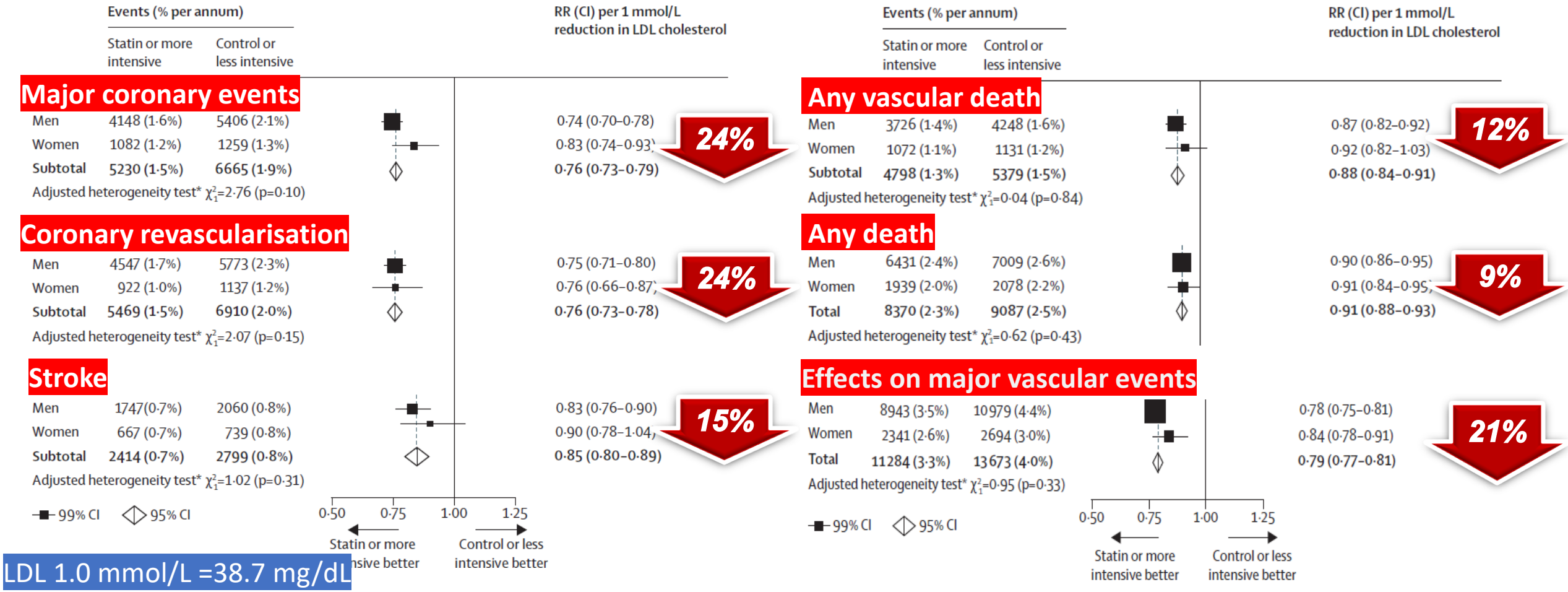
meta-analysis of RCT including 117,411 patients



BMJ 2014;349:g4379

Reduce 1 mmol/L LDL by statin: reduce 21% risk of major vascular events

- 174 000 participants, meta-analysis, **27 randomized trials**

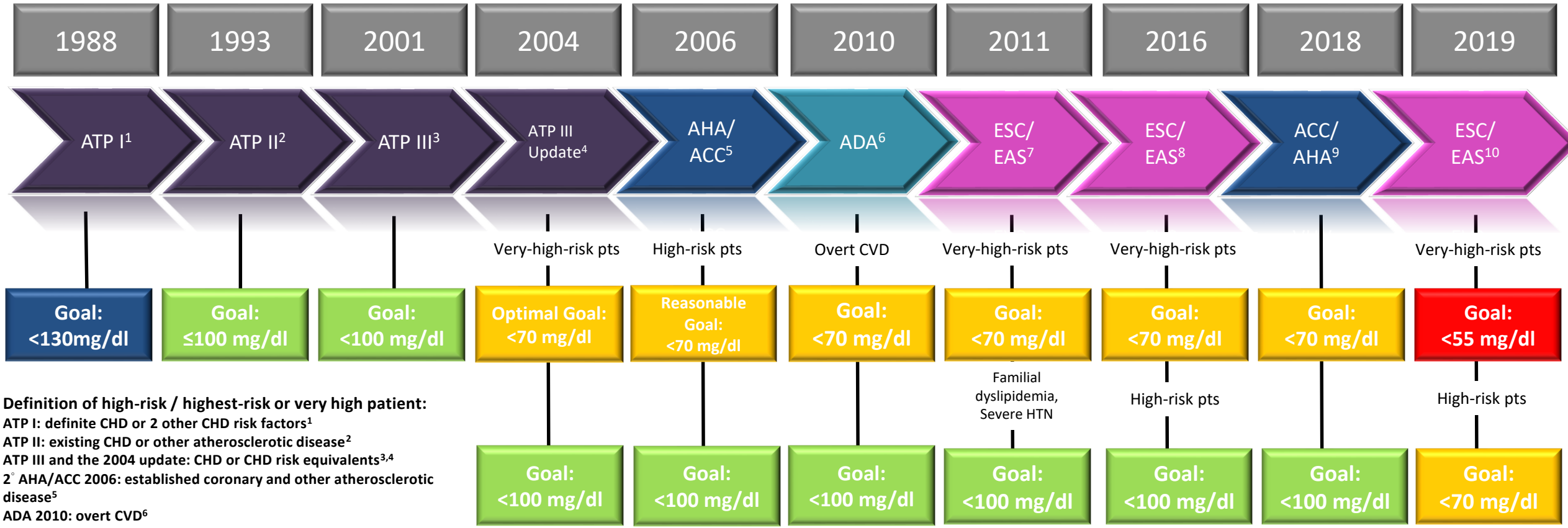


LDL 1.0 mmol/L =38.7 mg/dL

Lancet. 2015 Apr 11;385(9976):1397-405

Guidelines Recommendation

Guideline continued to recommend lower LDL-C target



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; 8. European Heart Journal (2016) 37, 2999–3058; 9. Circulation. 2018 Nov 10:CIR0000000000000625; 10. 2019 ESC/EAS Guidelines for the management of dyslipidemias

2017 Taiwan lipid guidelines for high risk patients

Disease category	LDL-C target (mg/dL)
ACS	< 70
ACS+DM	< 55 can be considered
Stable CAD	< 70
PAD	< 100
PAD +CAD	< 70
Stroke or TIA	< 100
DM	< 100*
DM+ CV disease	< 70
CKD(stage 3a-5，GFR<60 mL/min/1.73m^2)#	≥ 100 should be initiated with statin
Familial hypercholesterolemia	Adult：< 100 <18 y：<135 CAD：< 70

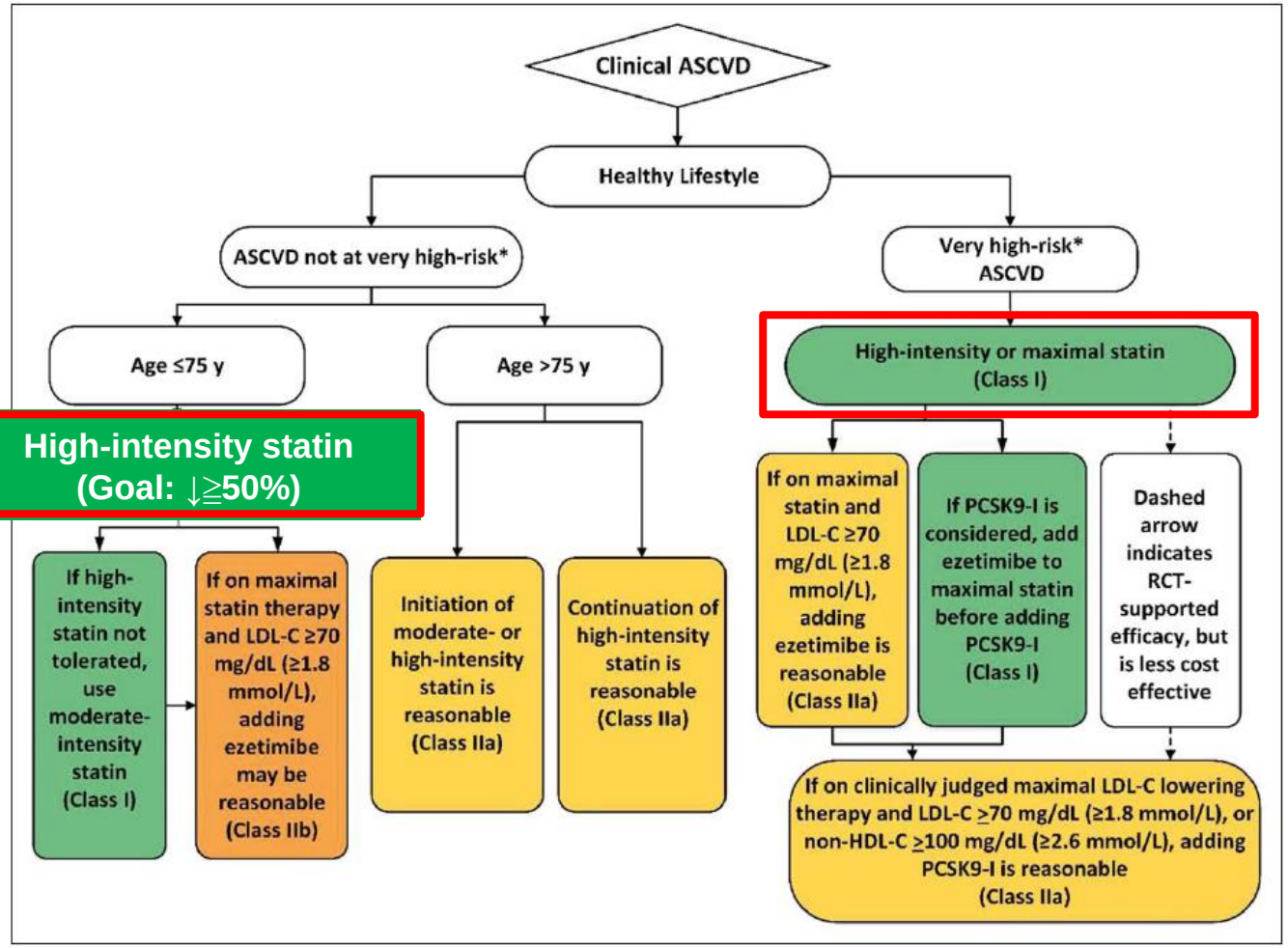
* For diabetic patients who are 40 years of age, or who are < 40 years of age but have additional CV risk factors

For dialysis patients, randomized controlled trials indicated that statin or statin/ezetimibe initiated during chronic dialysis provided no benefits in CV events reduction

J Formos Med Assoc. 2017 Apr;116(4):217-248.

2018 ACC/AHA Guideline: reduce LDL-C with high-intensity statins or maximally tolerated statins to decrease ASCVD risk

Secondary Prevention in Patients with Clinical ASCVD



Very High-Risk* for Future ASCVD Events

Major ASCVD Events
Recent acute coronary syndrome (within the past 12 months)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation[S4.1-40])
High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2)[S4.1-15,S4.1-17]
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

*Very high-risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions.

Circulation. 2019 Jun 18;139(25):e1082-e1143.

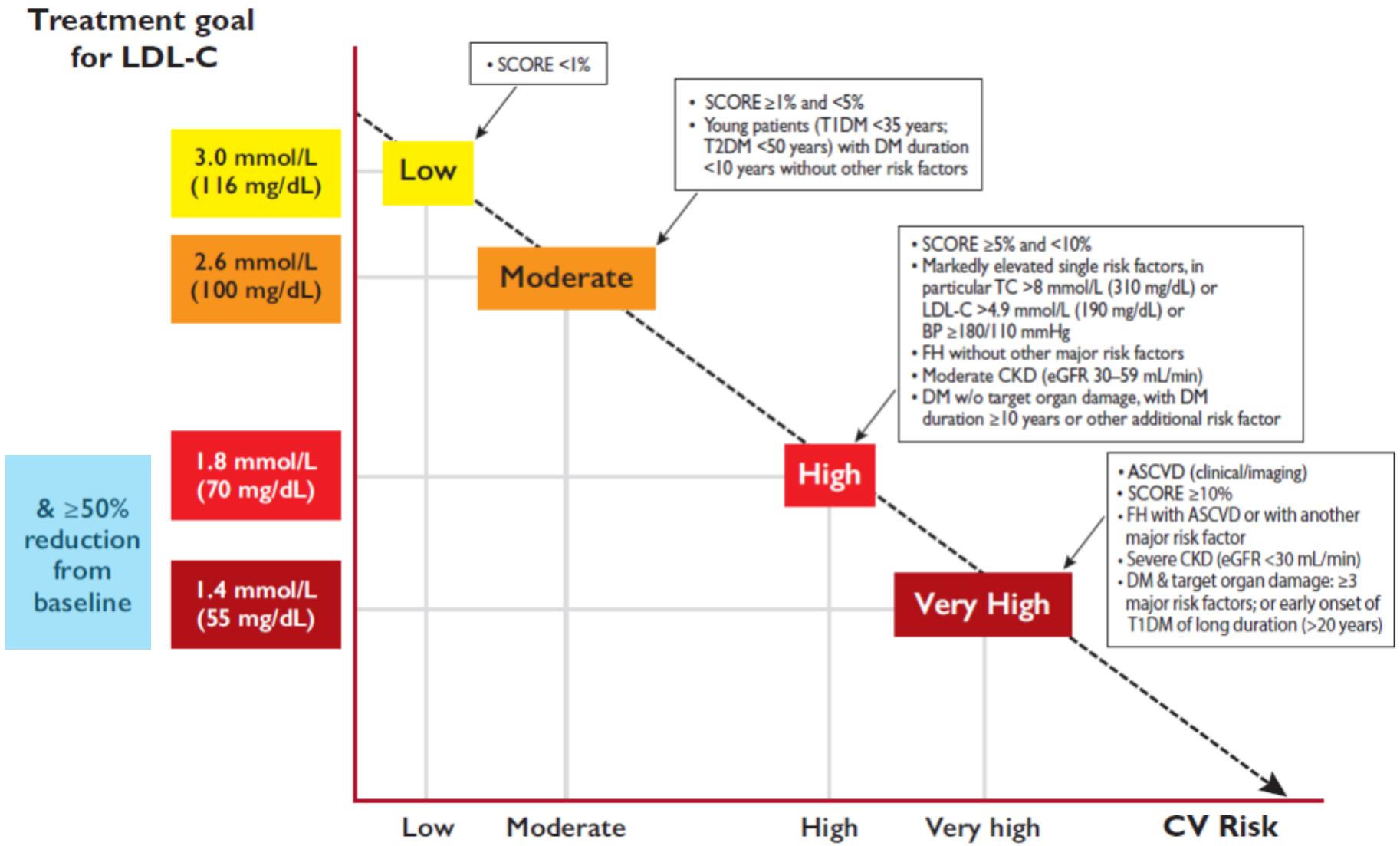
2018 ACC/AHA Guideline Recommendations for Statin Therapy

Intensity of statin therapy			
	High-Intensity	**Moderate-Intensity**	**Low-Intensity**
LDL-C+ Lowering	≥50%	30%–49%	<30%
Primary Statins	Rosuvastatin **20mg** (40mg) Atorvastatin (40 mg‡) 80 mg	Rosuvastatin **(5 mg) 10 mg** Atorvastatin 10 mg (20 mg) Simvastatin 20–40 mg§	Simvastatin 10mg
Other Statins		Pravastatin 40 mg (80 mg) Lovastatin 40 mg (80 mg) Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 1–4 mg	Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg

*Percent reductions are estimates from data across large populations. Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice.S3.2.1-2
†LDL-C lowering that should occur with the dosage listed below each intensity.
‡Evidence from 1 RCT only: down titration if unable to tolerate atorvastatin 80 mg in the IDEAL (Incremental Decrease through Aggressive Lipid Lowering) study.S3.2.1-3
§Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA because of the increased risk of myopathy, including rhabdomyolysis.

Circulation. 2019 Jun 18;139(25):e1082-e1143.

2019 ESC/EAS guideline LDL treatment goal



European Heart Journal (2019) 00, 1-78

2019 ESC/EAS guideline:
For very-high risk patients, LDL-C target has changed from 70 mg/dL to 55 mg/dL

Recommendations	Class	Level
In secondary prevention for patients at **very-high risk**, an **LDL-C reduction of ≥50%** from baselined **and** an **LDL-C goal of <1.4 mmol/L (<55 mg/dL)** are recommended.	I	A
For patients with ASCVD who **experience a second vascular event within 2 years** (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, an **LDL-C goal of <1.0 mmol/L (<40 mg/dL)** may be considered.	IIb	B

The rationale for the revised, lower LDL-C goals across CV risk categories is discussed, based on a critical synthesis of available evidence from lipid-modifying interventions resulting in reductions in CV risk.

Very-high risk definition

- Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes **previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease.** Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as **significant plaque** on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound.
- **DM with target organ damage***, or at least three major risk factors, or early onset of T1DM of long duration (>20 years).
- **Severe CKD (eGFR <30 mL/min/1.73 m2)**.
- A calculated SCORE ≥10% for 10-year risk of fatal CVD.
- FH with ASCVD or with another major risk factor.

* Target organ damage is defined as microalbuminuria, retinopathy, or neuropathy

European Heart Journal (2019) 00, 1-78

2019 ESC/EAS guideline:
All ACS patients should start with high-dose statin regardless of LDL-C baseline

Management of patients with ACS	Class	Level
In **all ACS patients** without any contraindication or definite history of intolerance, it is recommended that **high-dose statin therapy** is initiated or continued as early as possible, **regardless of initial LDL-C values**.	I	A
If the LDL-C goal is not achieved after 4-6 weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended.	I	B
If the LDL-C goal is not achieved after 4-6 weeks despite maximal tolerated statin therapy and ezetimibe, adding a PCSK9 inhibitor is recommended.	I	B
Recommendations for lipid-lowering therapy in very-high risk patients undergoing PCI	**Class**	**Level**
Routine **pre-treatment or loading** (on a background of chronic therapy) with a **high-dose statin** should be considered in patients **undergoing PCI for an ACS or elective PCI**	IIa	B

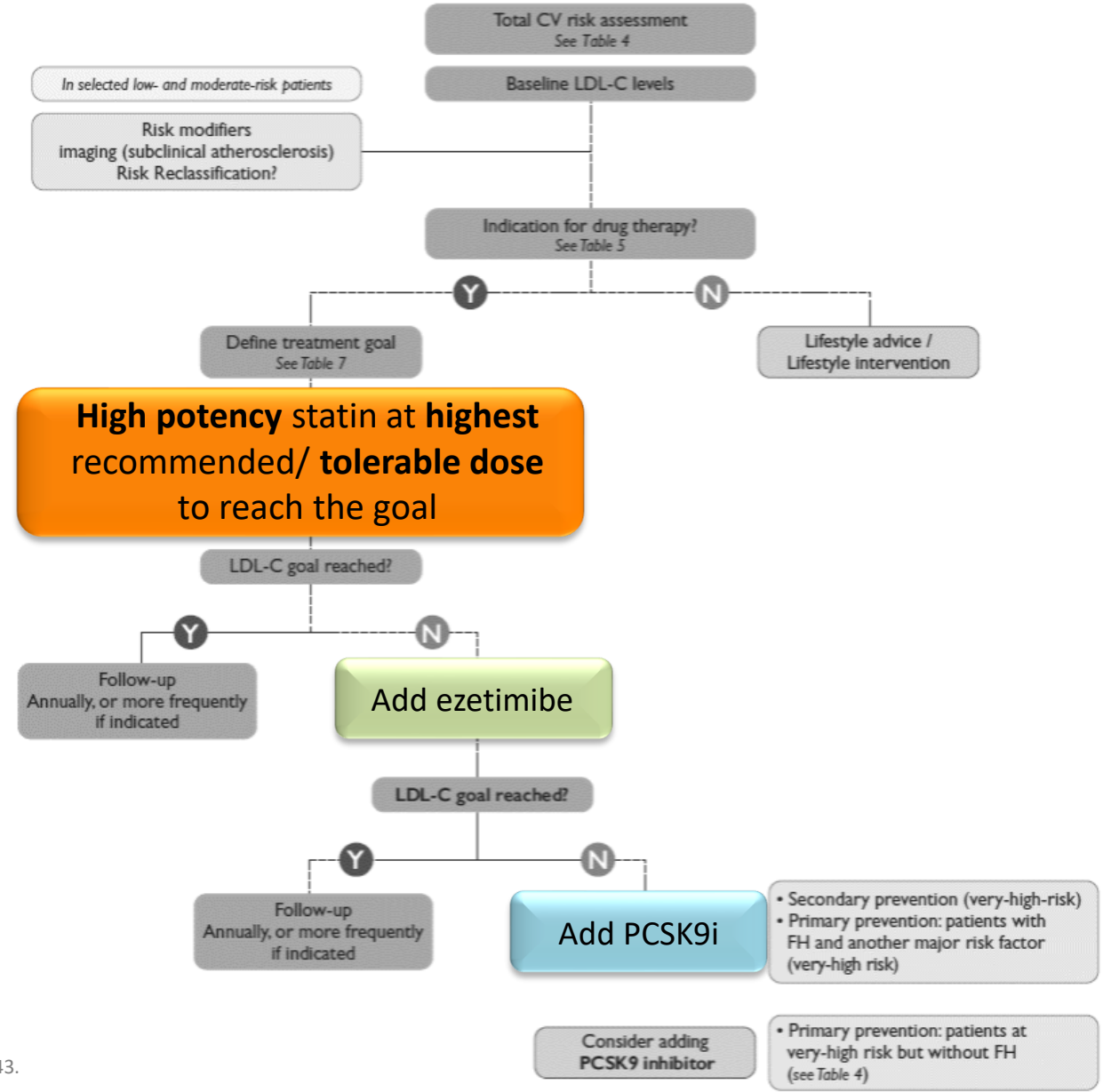
European Heart Journal (2019) 00, 1-78

2019 ESC/EAS guideline treatment algorithm: statin as first line treatment

2018 ACC/AHA Intensity of statin therapy:

	High-Intensity statin
LDL-C Lowering	≥50%
Primary Statins	Rosuvastatin **20mg** Atorvastatin (40 mg‡)

‡Evidence from 1 RCT only: down titration if unable to tolerate atorvastatin 80 mg in the IDEAL (Incremental Decrease through Aggressive Lipid Lowering) study.S3.2.1-3



European Heart Journal (2019) 00, 1-78; Circulation. 2019 Jun 18;139(25):e1082-e1143.

“

Furthermore, **these clinical trials have clearly indicated that the lower the achieved LDL-C values, the lower the risk of future cardiovascular (CV) events**, with **no lower limit for LDL-C values, or ‘J’-curve effect….**

there is no longer an 'LDL-C hypothesis', but established facts that increased LDL-C values are causally related to ASCVD [atherosclerotic cardiovascular disease], and that lowering LDL particles and other ApoB-containing lipoproteins as much as possible reduces CV event.

”

— Quote from ESC 2019 guidelines on dyslipidemia..

European Heart Journal (2020) 41, 111188

2019 健保給付更新: ACS, PCI & CABG病人血脂目標值LDL-C< 70 mg/dL

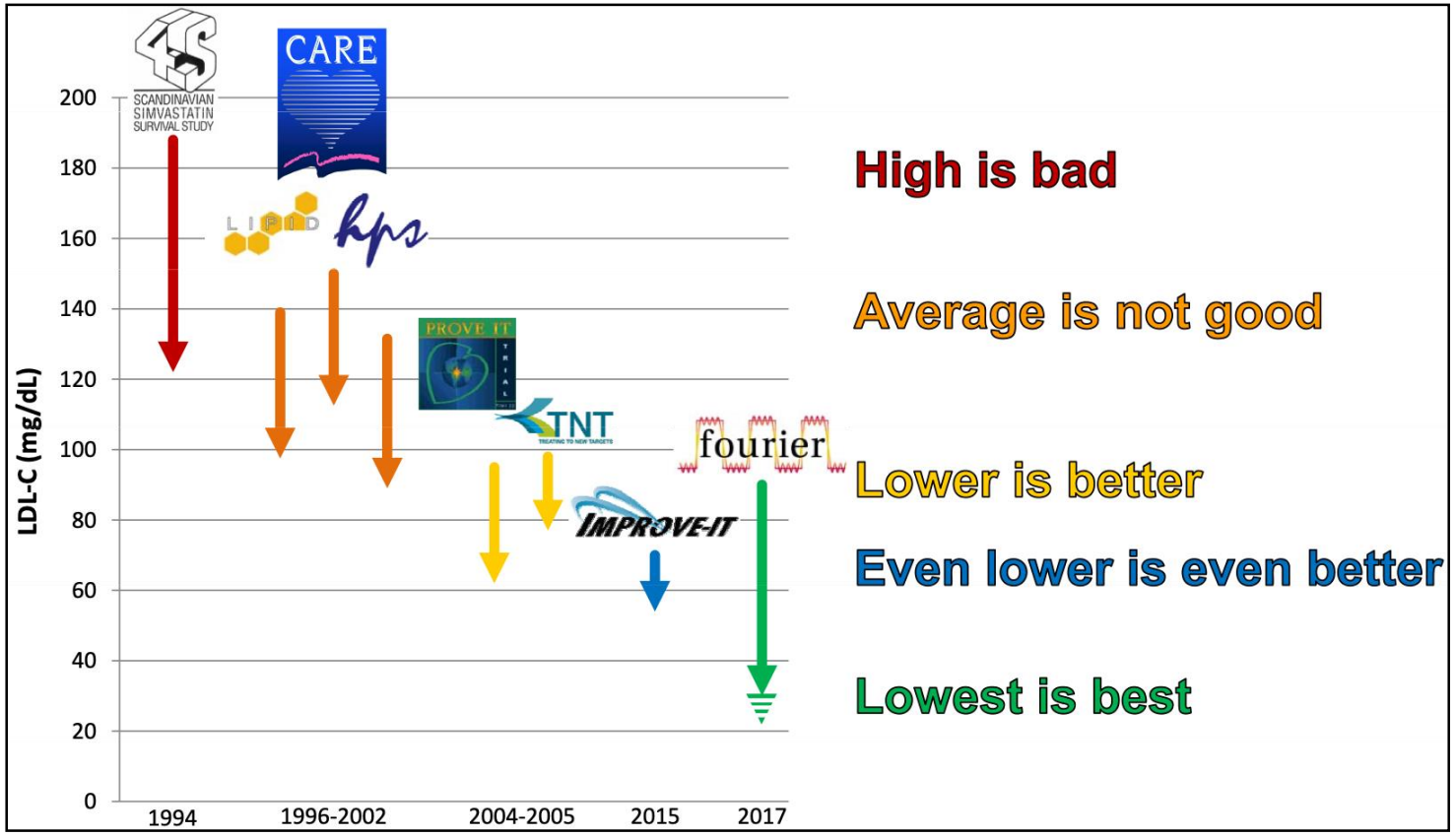
	非藥物治療	起始藥物治療血脂值	血脂目標值	處方規定
1. 有**急性冠狀動脈症候群**病史 2. 曾接受**心導管介入治療**或**外科冠動脈搭橋手術**之冠狀動脈粥狀硬化患者 (108/02/01)	與藥物治療可並行	LDL-C≧70mg/dL	LDL-C < **70mg/dL**	第一年應每3-6個月抽血檢查一次，第二年以後應至少每6-12個月抽血檢查一次，同時請注意副作用之產生如肝功能異常，橫紋肌溶解症。
心血管疾病或**糖尿病**患者	與藥物治療可並行	TC≧160mg/dL或 LDL-C≧100mg/dL	TC < 160mg/dL或 LDL-C < **100mg/dL**	
2個危險因子或以上	給藥前應有3-6個月非藥物治療	TC≧200mg/dL或 LDL-C≧130mg/dL	TC < 200mg/dL或 LDL-C < 130mg/dL	
1個危險因子	給藥前應有3-6個月非藥物治療	TC≧240mg/dL或 LDL-C≧160mg/dL	TC < 240mg/dL或 LDL-C < 160mg/dL	
0個危險因子	給藥前應有3-6個月非藥物治療	LDL-C≧190mg/dL	LDL-C < 190mg/dL	

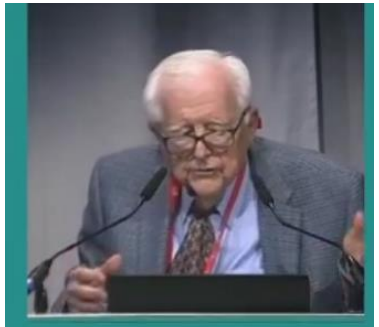
102/08/01 移除字眼: 如已達治療目標得考慮減量至最低有效劑量，並持續衛教

- 心血管疾病定義：
  (一)冠狀動脈粥狀硬化患者包含：心絞痛病人，有心導管證實或缺氧性心電圖變化或負荷性試驗陽性反應者(附檢查報告)
  (二)缺血型腦血管疾病患者包含：1.腦梗塞。2.暫時性腦缺血患者(TIA)。（診斷須由神經科醫師確立）3.有症狀之頸動脈狹窄。（診斷須由神經科醫師確立）
- 危險因子定義： 1.高血壓2.男性≧45 歲，女性≧55 歲或停經者 3.有早發性冠心病家族史(男性≦55 歲，女性≦65 歲) 4.HDL-C<40mg/dL 5.吸菸(因吸菸而符合起步治療準則之個案，若未戒菸而要求藥物治療，應以自費治療)。

Prof Eugene Braunwald:

we should strive to achieve very low levels of LDL-C early in individuals to maximize cardiovascular benefit



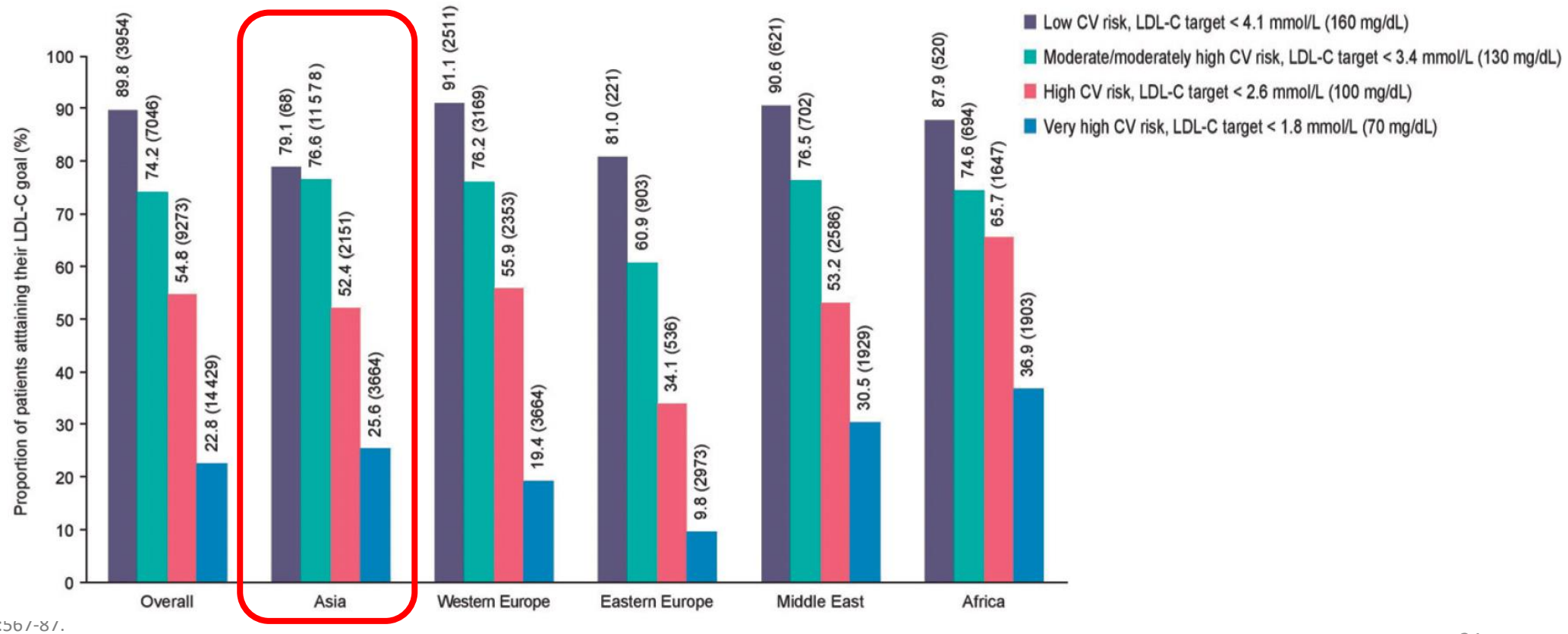


ESC
European Society of Cardiology

Clinical guideline vs Real world practice

By 2004 NCEP ATP III : Overall only 49.4% reach LDL-C goal, 54.8% and 22.8% at high and very high cardiovascular risk

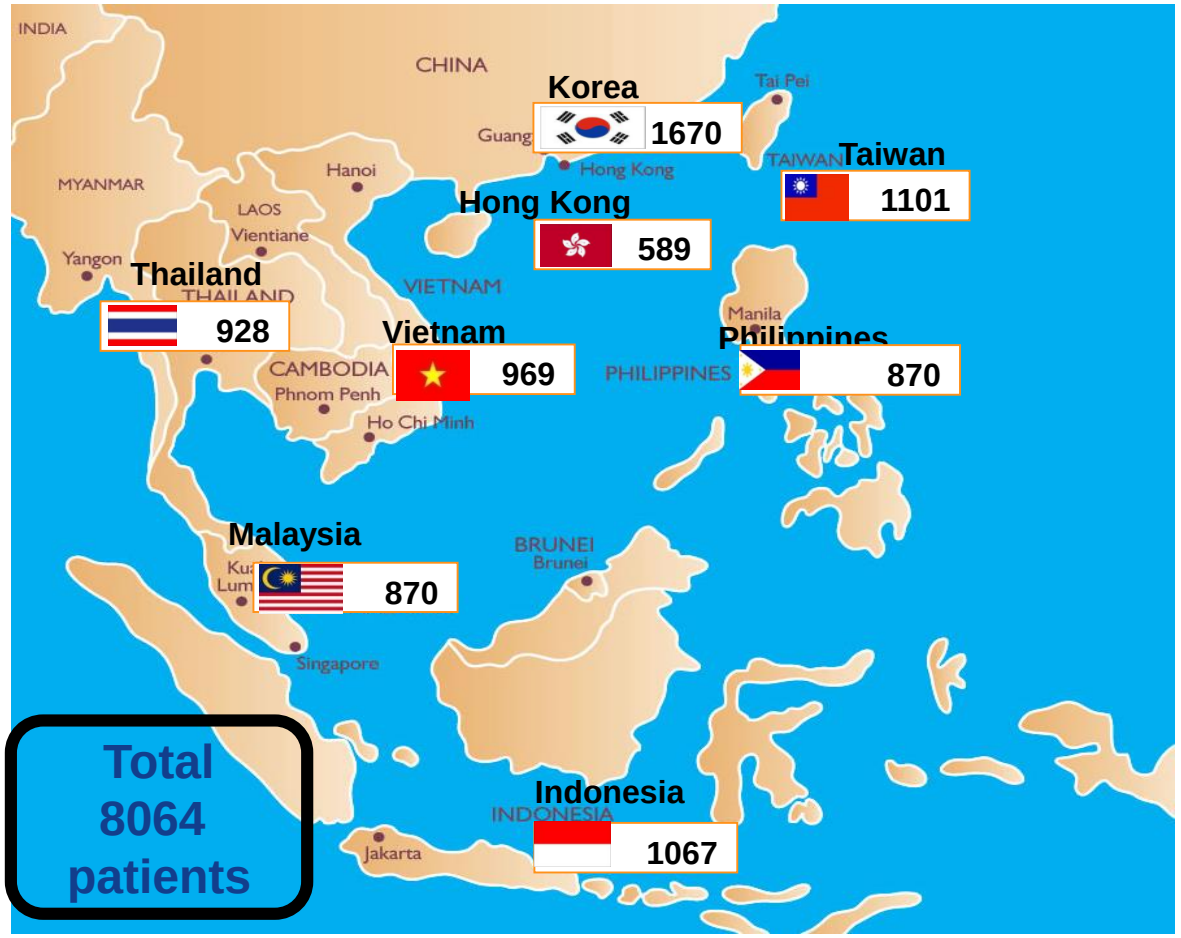
- 2006-2010, 5 multicenter, cross-sectional Centralized Pan-Regional Surveys on the Undertreatment of Hypercholesterolemia (CEPHEUS) study
- In total: 35,121 patients (mean age: 60.4 years), and 90.3% statin monotherapy

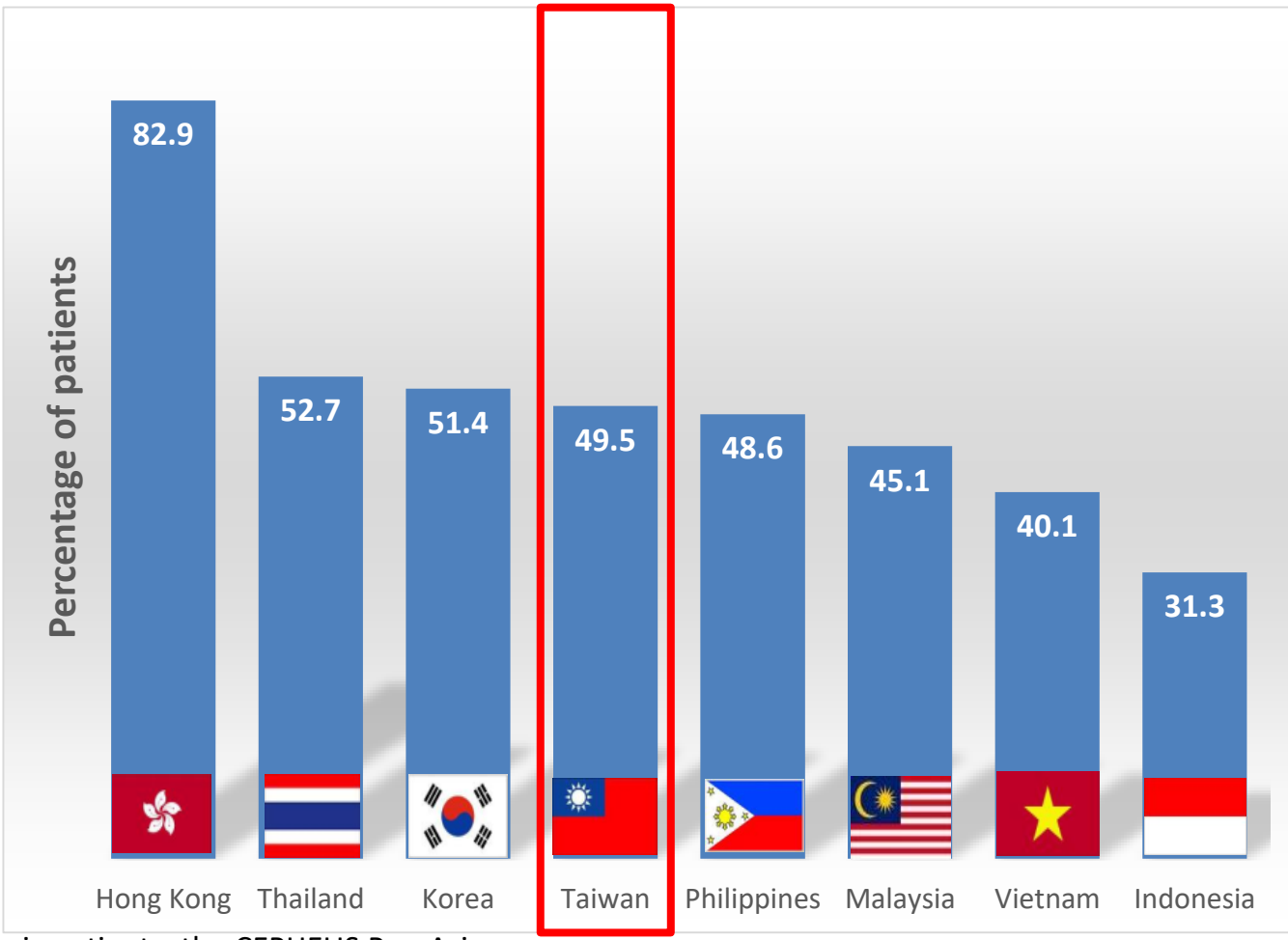


J Atheroscler Thromb. 2016 May 2;23(5):567-87.

Only 49.5% of Taiwan patients attain LDL-C target goal

Pan-Asian CEPHEUS was the Largest Survey conducted in 8 Asian Countries





Park JE, Chiang CE, Munawar M, et al. Lipid-lowering treatment in hypercholesterolaemic patients: the CEPHEUS Pan-Asian survey.

Eur J Prev Cardiol. 2012;19(4):781-794.

Cholesterol Goal Attainment in the Real World: Comparison of Overall Goal Attainment in Asia

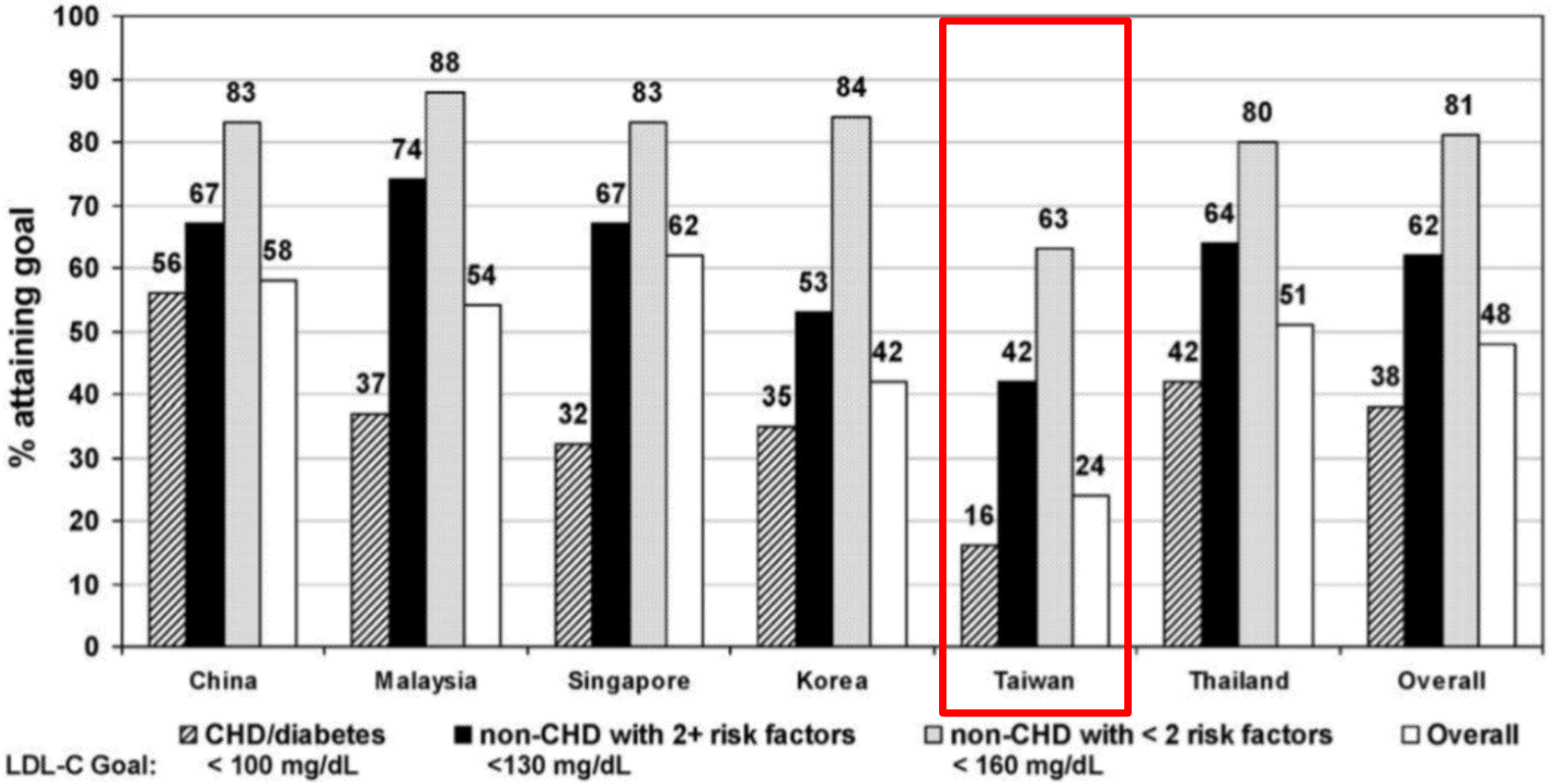
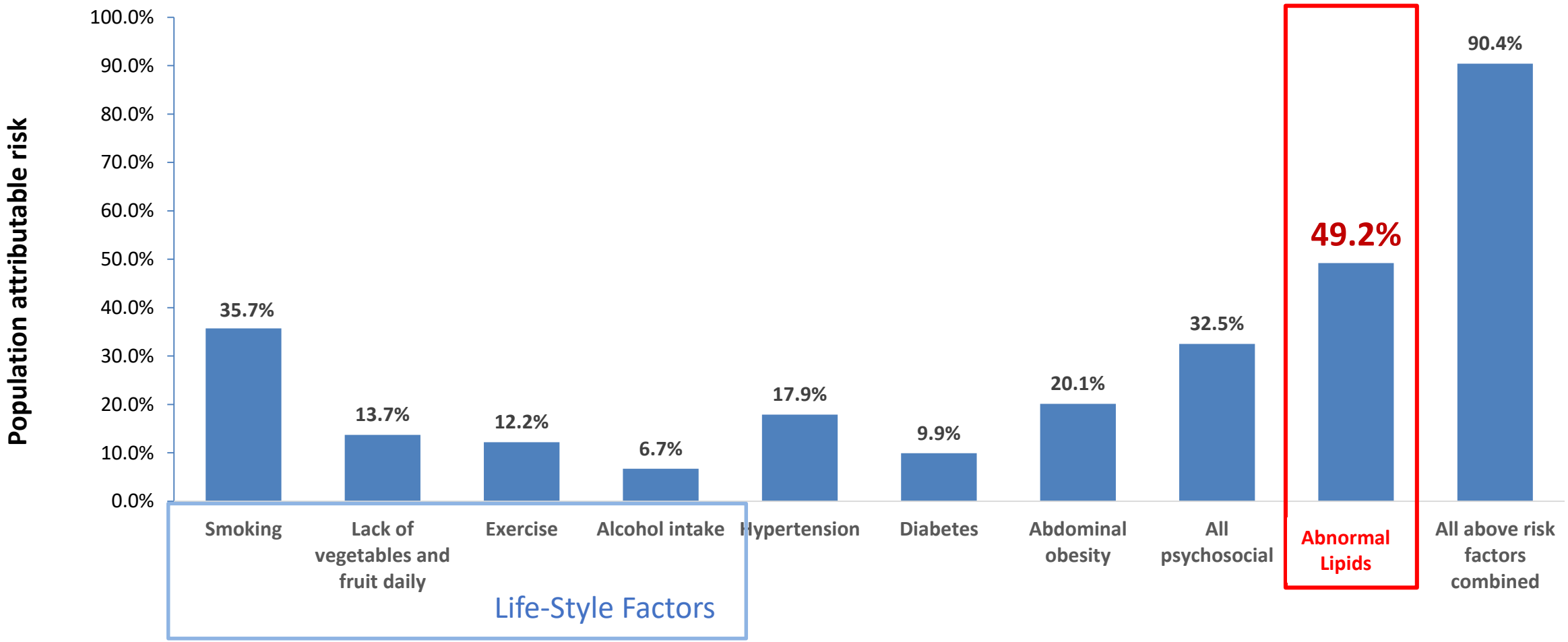


Figure 3. *Cholesterol goal attainment (percent of patients attaining goal) by risk status in the overall population and by country/region, including coronary heart disease (CHD) and/or diabetes mellitus (DM), ≥2 risk factors without CHD/DM, or <2 risk factors without CHD/DM at baseline*

Curr Med Res Opin. 2008 Jul;24(7):1951-63.

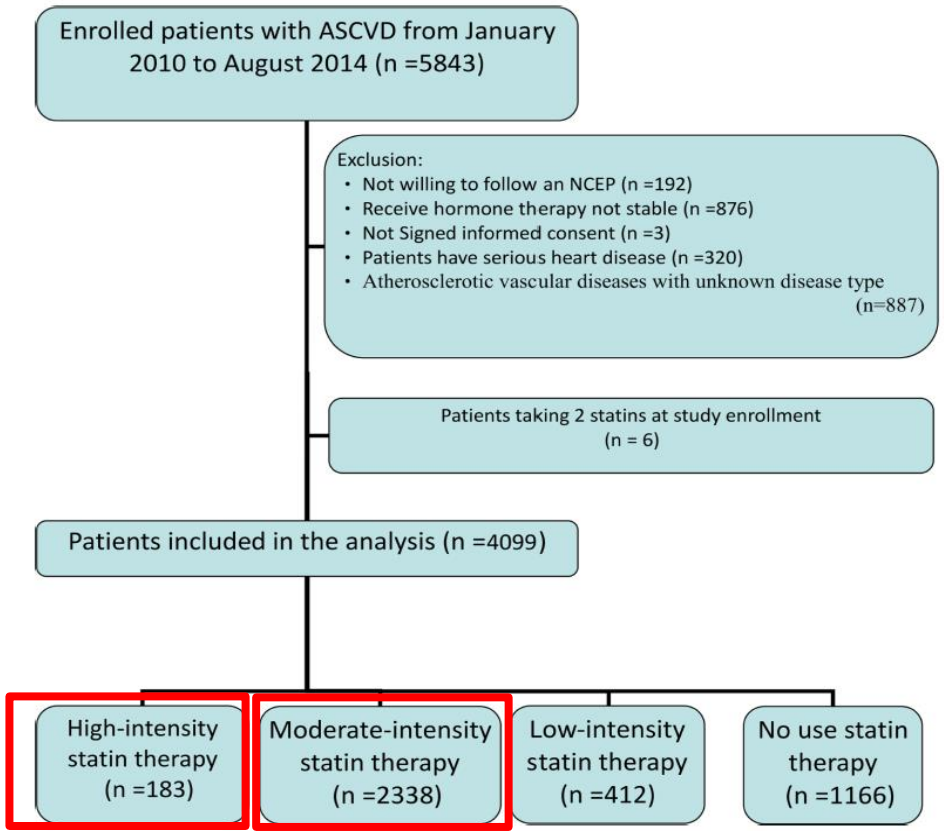
Abnormal lipids : the most risk factor for myocardial infarction

- **INTERHEART Study** :15,152 patients**,** case-control study**,** 52 countries in Asia, Europe, the Middle East, Africa, Australia, North America, and South America



Journal of Clinical Lipidology (2016) 10, 472–489

Taiwan Secondary Prevention for patients with AtheRosCLErotic disease (T-SPARCLE) Study : 44% failed to achieve LDL-C < 100 mg/dL



- Failure to achieve an LDL-C (100 mg/dL): increased risk of MACEs in ASCVDs
- Importance of keeping LDL-C at goal levels

Table 3. Multivariate Cox regression model for MACE by joint distribution of statin use status and LDL-C level.

Category	n	Hazard ratio†	95% CI	*p*-value
Under statin LDL-C < 100 mg/dL	1747	1.00	(as reference)	
Not under statin & LDL < 100 mg/dL	571	1.42	0.77–2.63	0.26
Under statin & LDL ≥ 100 mg/dL	1186	1.66	1.04–2.63	0.03
Not under statin & LDL ≥ 100 mg/dL	595	2.04	1.06–3.94	0.03

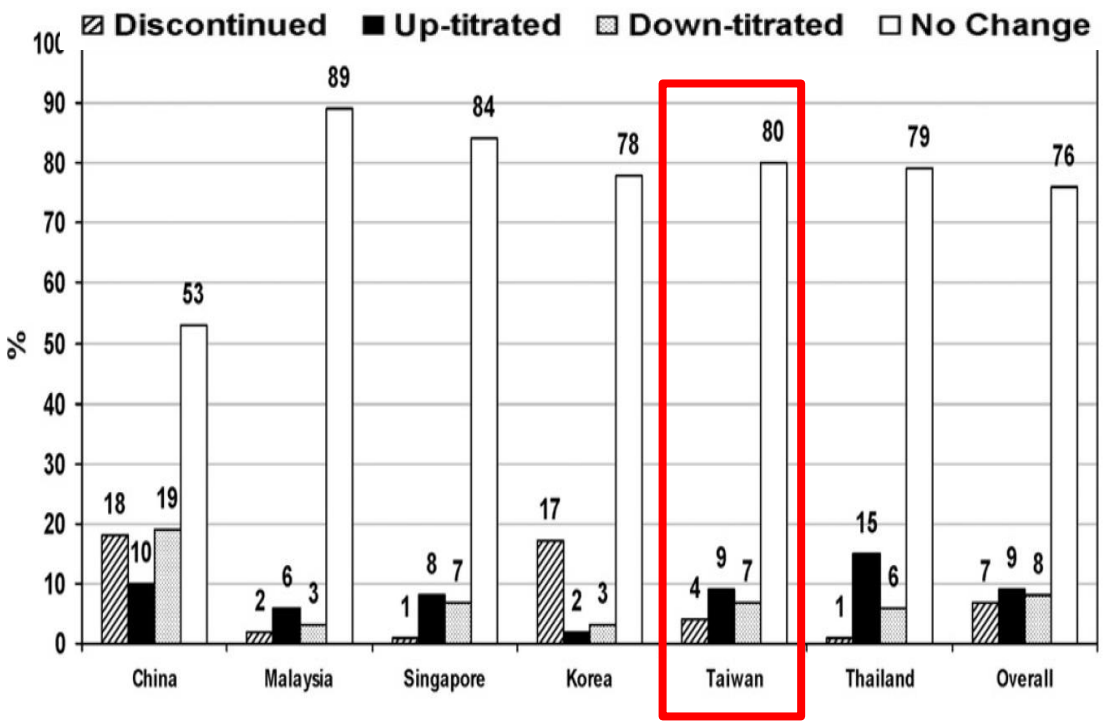
†Adjusted for age, gender, body mass index (BMI) level, cigarette smoking history, fibrate use, history of hypertension, heart failure, diabetes, myocardial infarction, ischemic stroke or transient ischemic attack, previous coronary or lower extremity arterial disease (LEAD) intervention and levels of estimated glomerular filtration rate (eGFR) at baseline.

- Multicenter prospective observational study,
- Jan.2010-Aug.2014, follow-up data as of March 2015
- > 18 years old with stable symptomatic atherosclerotic diseases

PLoS One. 2017 Oct 26;12(10):e0186861.

LDL-C goal attainment of Taiwan is lower: why ?

Changes in lipid-modifying regimens during follow-up in the overall population



From Physicians

- Inertia to increase the dose or move to a combination[1]
- Starting dose : non-effective potency[2]
- 80% fixed prescriptions[5]
- Limitation of National health Insurance(NHI)[4]

From Patients

- Compliance[1]
- Inertia, as well[1]

1. Atherosclerosis 236 (2014) 142e143
2. J Atheroscler Thromb. 2016 May 2;23(5):567-87.
3. Curr Med Res Opin. 2008 Jul;24(7):1951-63.
4. 心血管病患之合理血脂治療- Optimal Lipid Lowering Treatment for Patients with Cardiovascular Disease
5. Curr Med Res Opin. 2008 Jul; 24(7): 1951-63

WHY Rosuvastatin : Low Dose, High Potency

FDA: CRESTOR 10mg/20mg reduce 47%/55% LDL-C

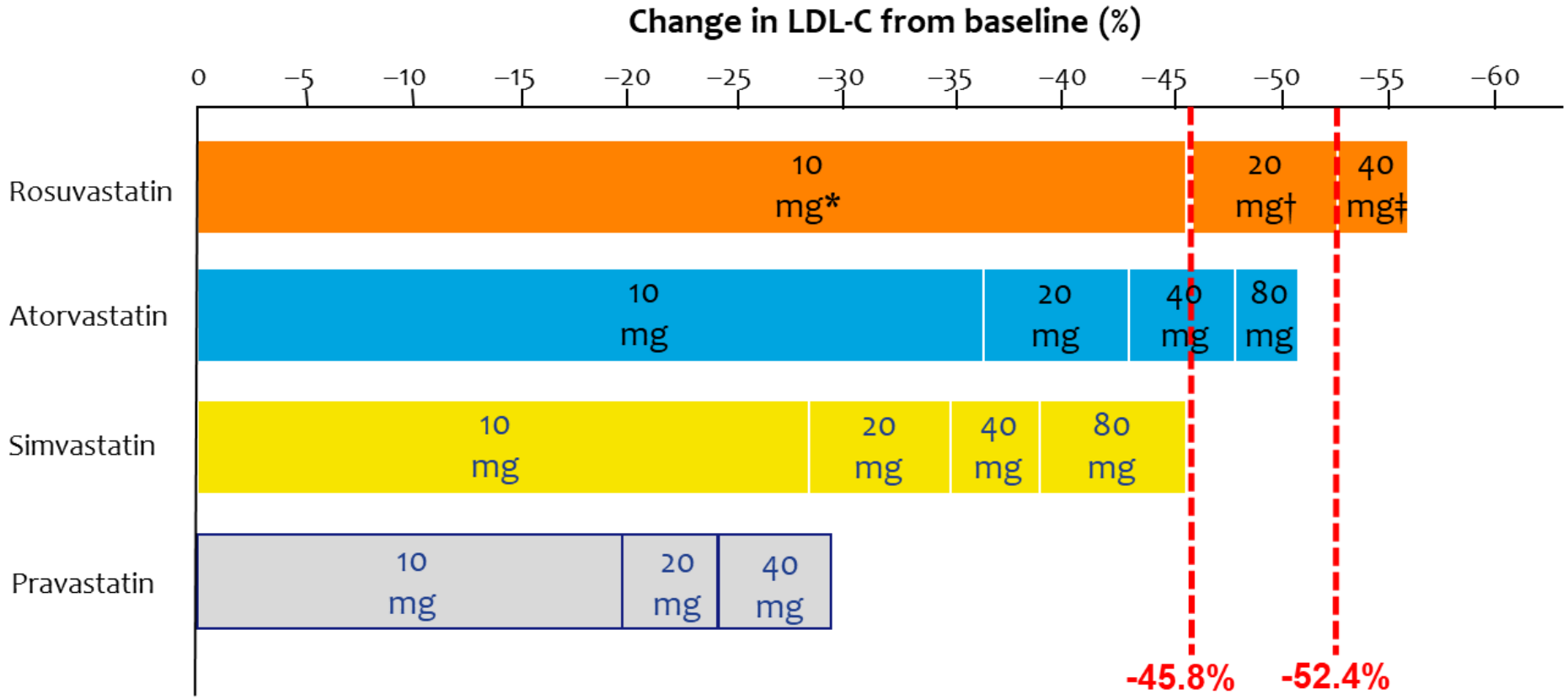
U.S Food and Drug Administration

Rosuvastatin	Atorva.	Fluva.	Pitava.	Lova.	Prava.	Ezetimibe /Simva.	Simva.	%↓ LDL-C
		40 mg	1 mg	20 mg	20 mg		10 mg	30%
	10 mg	80 mg	2 mg	40 mg or 80 mg	40 mg		20 mg	38%
5 mg	20 mg		4 mg	80 mg	80 mg	10/10 mg	40 mg	41%
10 mg	40 mg					10/20 mg	80 mg	47%
20 mg	80 mg					10/40 mg		55%
40 mg						10/80 mg		63%

Atorva=Atorvastatin; Fluva=Fluvastatin; Pitava=Pitavastatin; Lova=Lovastatin; Prava=Pravastatin; Simva=Simvastatin; LDL-C: Low-density lipoprotein cholesterol.
* Based on individual statin efficacy data, not head to head comparisons between statins.
1. Adapted from FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. U.S. Food and Drug Administration. Updated 2016. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm Last accessed: 19.12.2016.

http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm#aihp

H2H: CRESTOR 10mg/20mg is better than Atorvastatin 20mg/40mg in LDL-C reduction

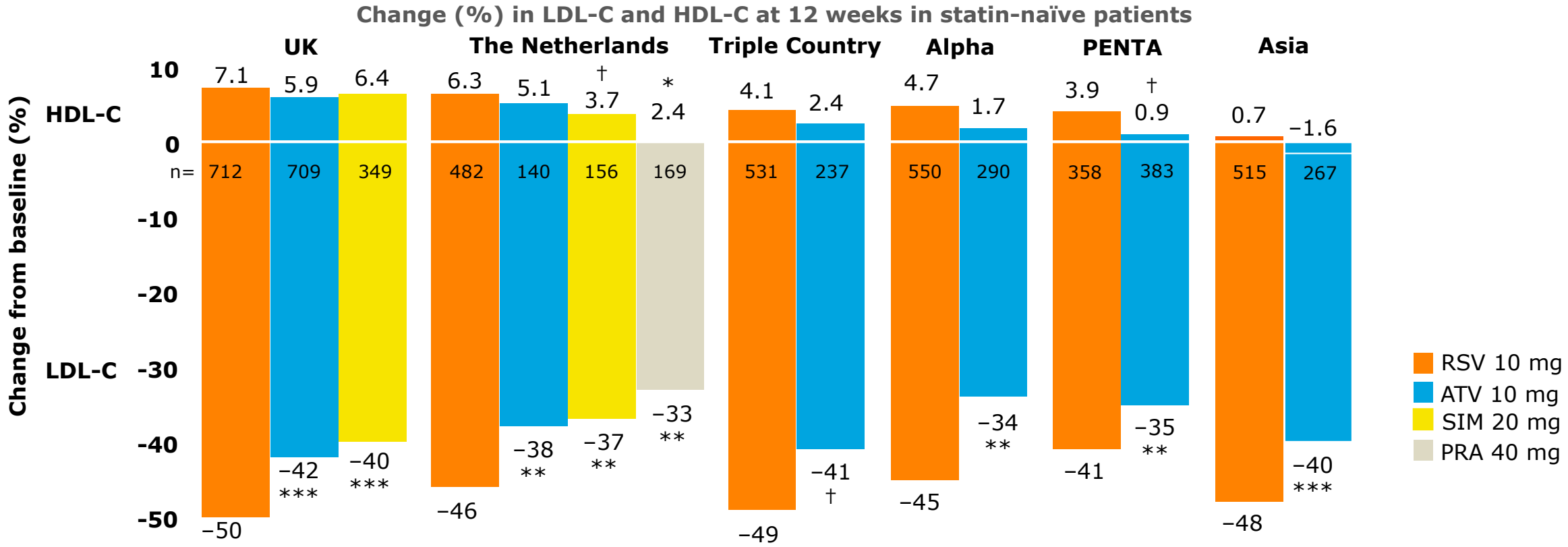


- Study design: The primary objective of this 6-week, parallel-group, open-label, randomized, multicenter trial was to compare rosuvastatin with atorvastatin, pravastatin, and simvastatin across dose ranges for reduction of low density lipoprotein (LDL) cholesterol.

*p<0.002 vs atorvastatin 10 mg; simvastatin 10, 20, 40 mg; pravastatin 10, 20, 40 mg
†p<0.002 vs atorvastatin 20, 40 mg; simvastatin 20, 40, 80 mg; pravastatin 20, 40 mg
‡p<0.002 vs atorvastatin 40 mg; simvastatin 40, 80 mg; pravastatin 40 mg

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

CRESTOR 10 mg is more efficacious at lowering LDL-C and increase HDL-C

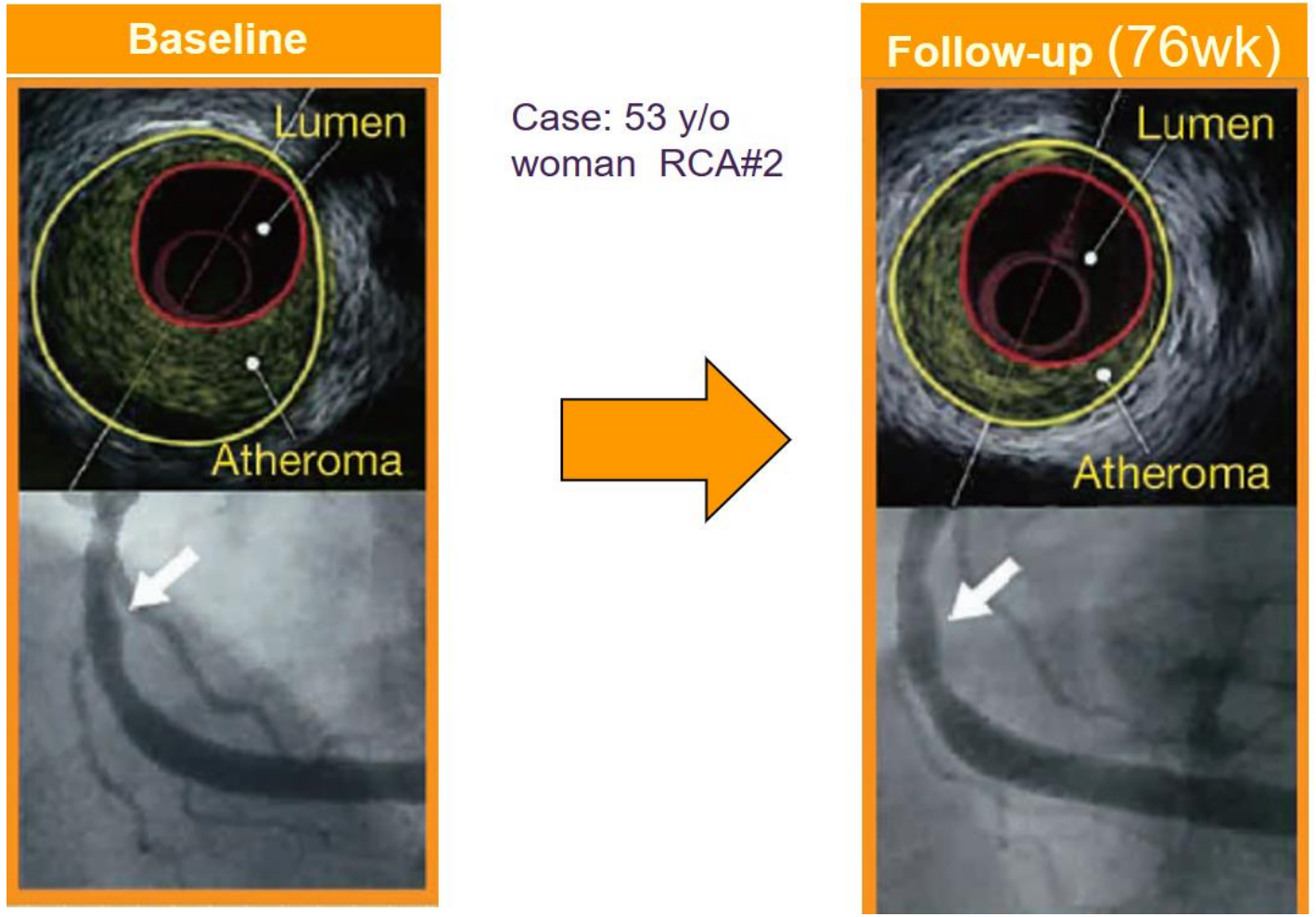


Curr Ther Res 2006; 67: 21–43.
Int J Clin Pract 2005; 59: 1387–1394.
Curr Med Res Opin 2005; 21: 1307–1315
Br J Cardiol 2006; 13: 72–76.
Clin Ther 2004; 26: 1821–1833.
Curr Med Res Opin 2007; 23: 3055–3068

LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; RSV=rosuvastatin; ATV=atorvastatin; SIM=simvastatin; PRA=pravastatin
†p<0.05 vs RSV 10 mg; *p<0.01 vs RSV 10 mg; **p<0.001 vs RSV 10 mg; ***p<0.0001 vs RSV 10 mg

Based on individual statin efficacy data, not head-to-head comparisons between statins.

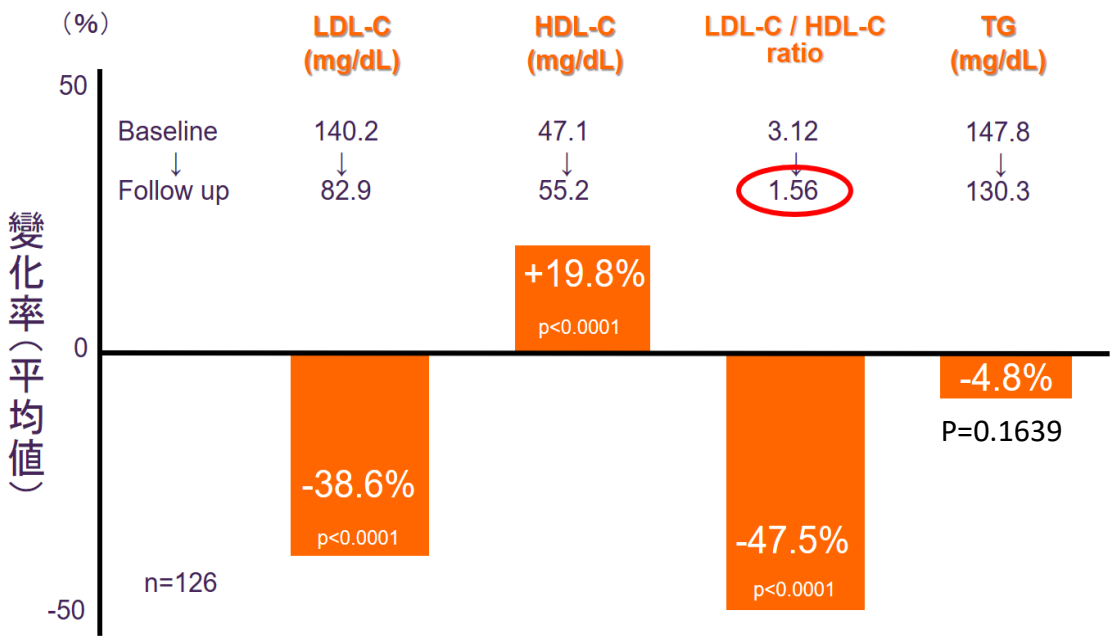
CRESTOR shows significant regression of coronary plaque volume in Japanese hyperlipidemia patients with stable CAD



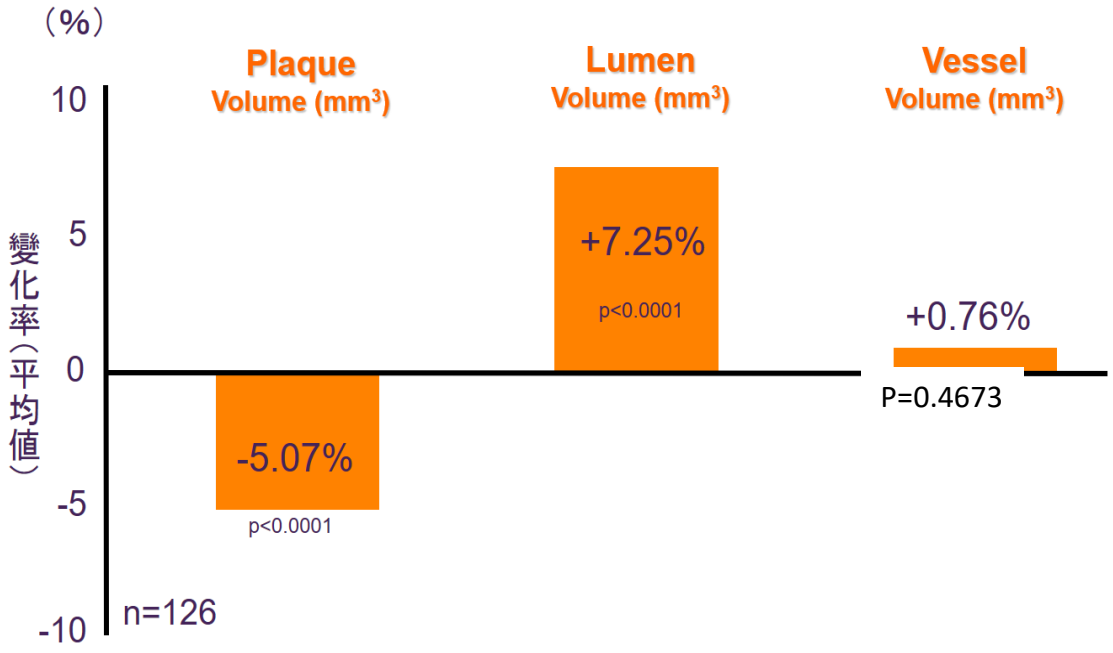
Circ J 2009; **73:** 2110 – 2117

CRESTOR shows significant regression of coronary plaque volume in Japanese hyperlipidemia patients with stable CAD

COSMOS Lipid Profiles



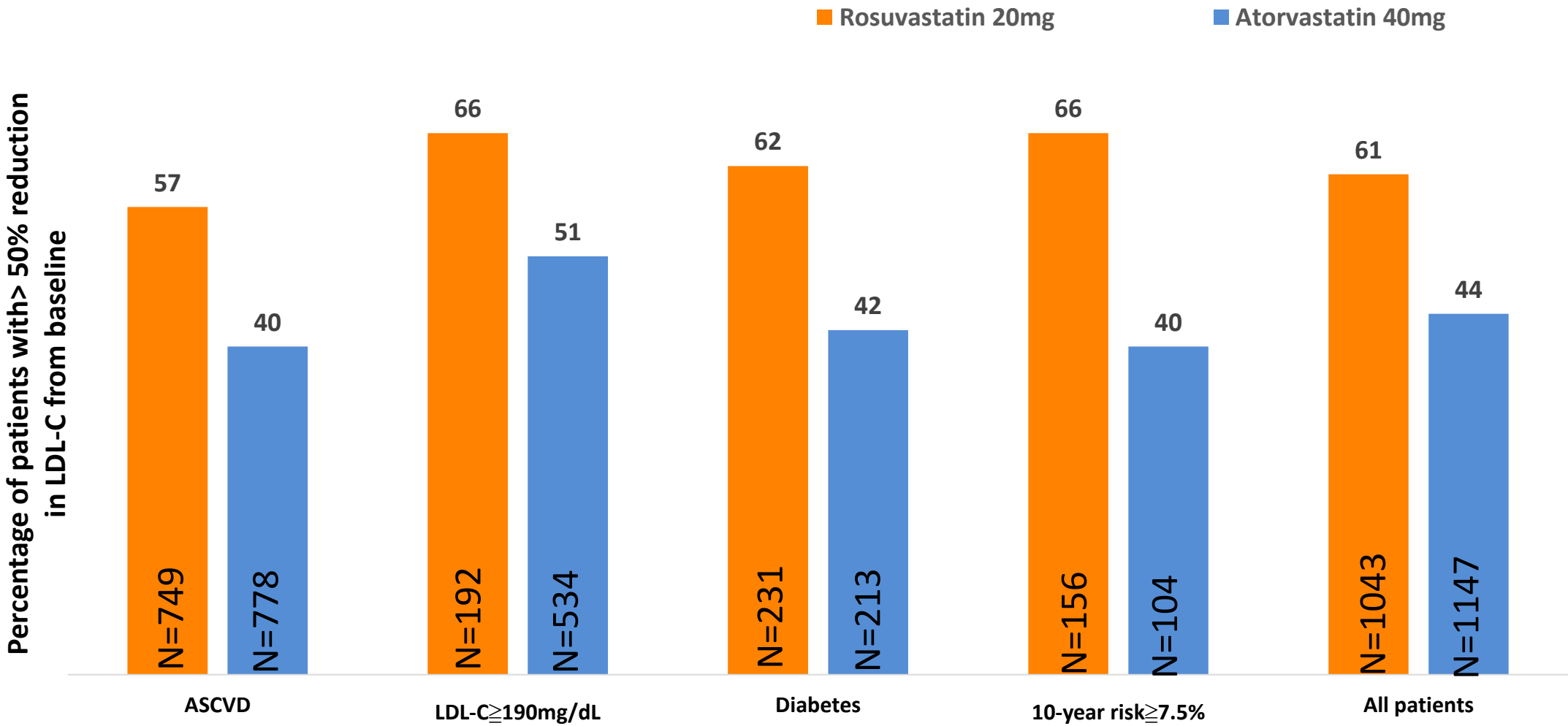
Reduction of Plaque Volume



- Study design: A 18 month, open-label, multicentre, single-arm study using intravascular ultrasound (IVUS) to evaluate the effect of CRESTOR 2.5mg-20mg on the progression of plaque volume in Japanese subjects with hypercholesterolaemia and coronary heart disease

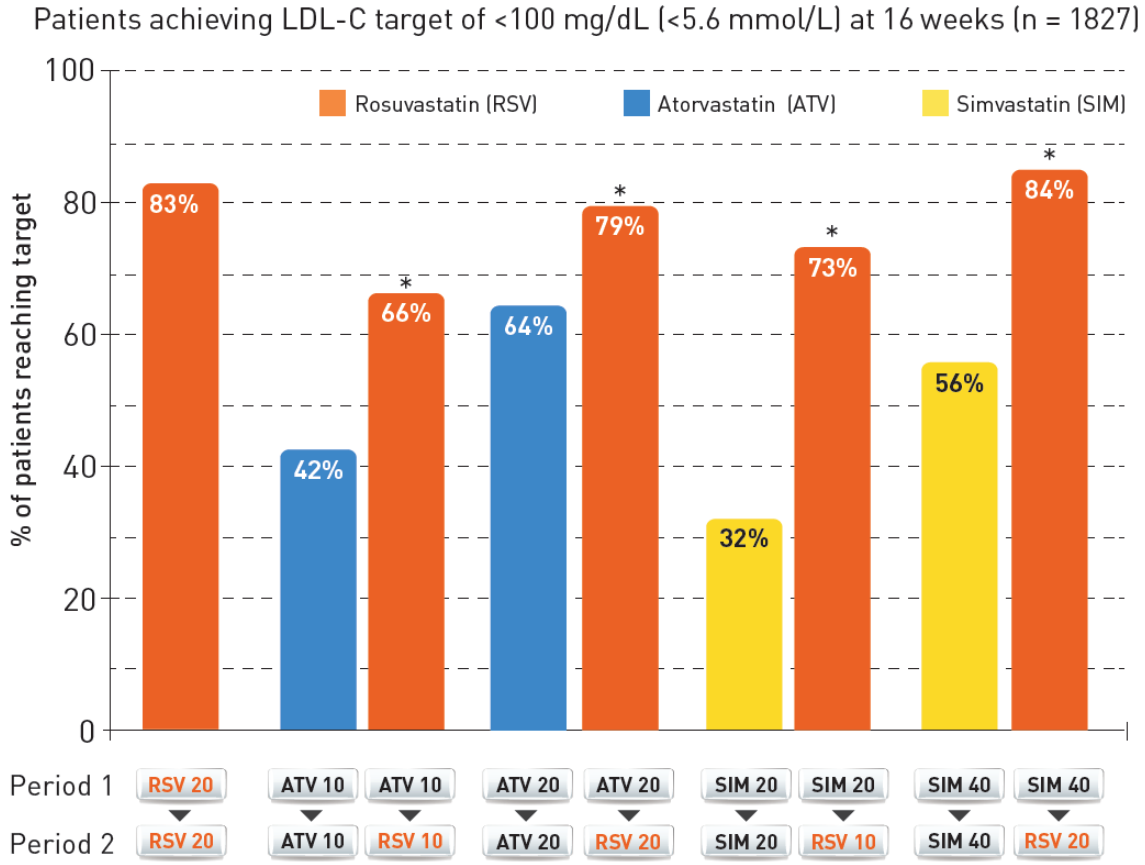
Circ J 2009; **73:** 2110 – 2117

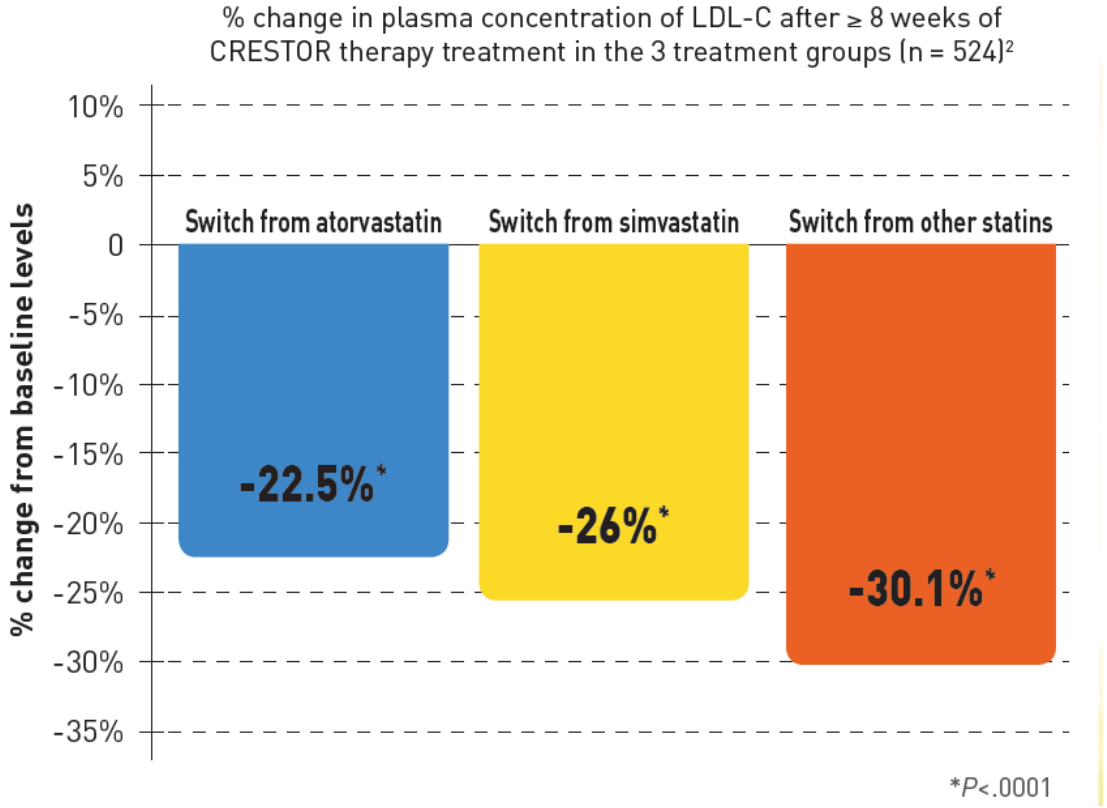
CRESTOR 20mg achieves ≧ 50% reduction LDL-C in high risk patients better than Atorvastatin 40mg



Adapted from Atherosclerosis 241 (2015) 450-454

Switching to Rosuvastatin
Significantly help more high-risk patient achieve LDL goal



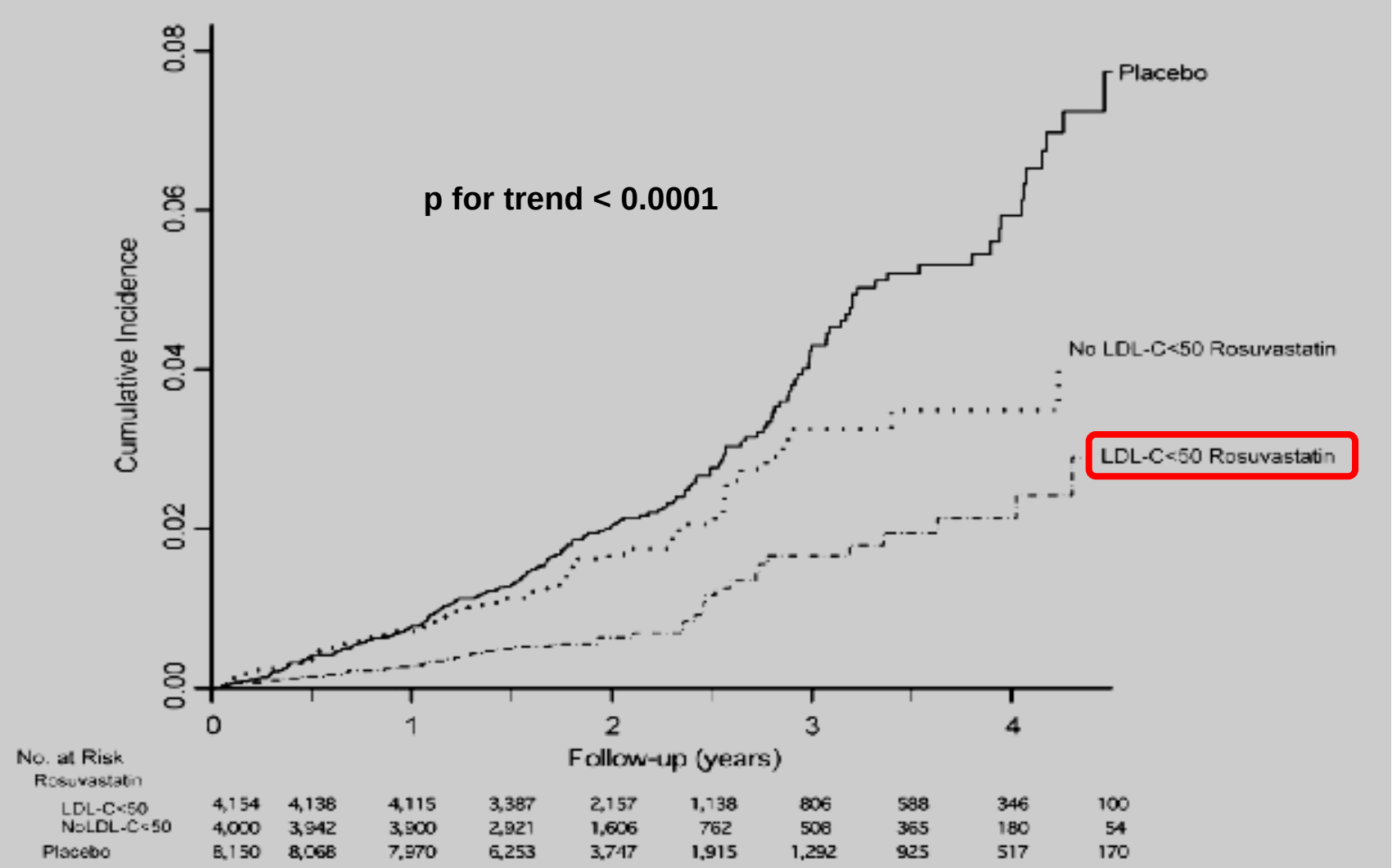


LDL-C goals were achieved in a greater proportion of high-risk patients (n = 1011) after switching to rosuvastatin compared to those remaining on atorvastatin or simvastatin[1]

- Study design: A completed 16-week, randomised, open-label study comparing efficacy (% patients reaching NCEP ATP III goal and other lipid parameters) and safety following a switch to the potential start doses of CRESTOR from the accepted/potential start doses of atorvastatin and simvastatin in high-risk subjects with primary hypercholesterolaemia

Am Heart J. 2006;151:975.e1-9; Atherosclerosis Thromb. 2009;16:509-516.

Established evidence of “Lower is Better”



J Am Coll Cardiol 2011;57:1666–75

WHY Rosuvastatin : Safety

CRESTOR is hydrophilic statin with lower risk of some side effects*

Drug	Solubility	Metabolism	Clearance	$T_{1/2}$	Effect of food on bioavailability (%)
Rosuvastatin	**Hydrophilic**	**Non-CYP450 Limited CYP2C9/8**	**Hepatic and renal**	**20**	**No**
Atorvastatin	Lipophilic	CYP3A4	Hepatic	11-30	Yes (↓ 13)
Fluvastatin	Lipophilic	CYP2C9	Hepatic	0.5-2.3	Yes (↓ 15-25)
Lovastatin	Lipophilic	CYP3A4	Hepatic	2.5-3.0	Yes (↓ 50)
Pitavastatin	Lipophilic	Non-CYP450 Limited CYP2C9/19	Hepatic	11	No
Pravastatin	Hydrophilic	Non-CYP450	Hepatic and renal	0.8-3.0	Yes (↓ 30)
Simvastatin	Lipophilic	CYP3A4	Hepatic	1.9-3.0	No

Circ Res. 2019;124:328-350; Drug Des Devel Ther. 2011;5:283-97.

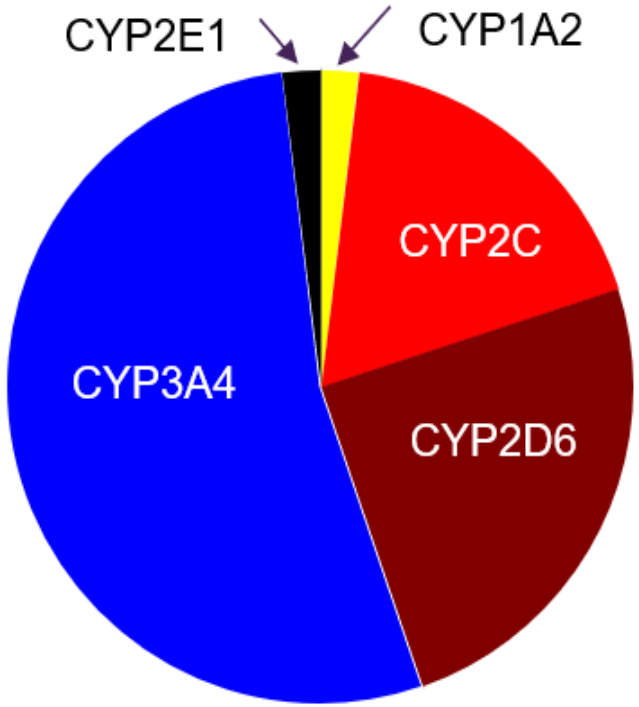
*Statin-associated muscle symptoms, renal toxicity and statin-induced hepatotoxicity

CRESTOR has less risk of drug-drug interaction as not dependent on CYP3A4

- Most of drugs are inhibitors or substrates of CYP450, especially the 3A4 isoenzyme: increase statin-associated myopathy

CYP 3A4

- Simvastatin
- Atorvastatin
- Lovastatin
- Diltiazem
- Clopidogrel
- Amiodarone
- Cimetidine
- Ery/Clarithromycin
- Ketoconazole
- Carbamazepine
- St John's wort
- Grapefruit juice



CYP 2C9

- Rosuvastatin
- Fluvastatin
- Phenytoin
- Fluconazole
- Warfarin

Shimada T et al. J Pharmacol Exp Ther 1994;270(1):414.; Journal of the Formosan Medical Association (2019) 118, 1385-1392

Drug-Drug Interaction: CYP3A4-metabolized Statins and Clopidogrel

European Heart Journal (2012) **33**, 2151–2162
doi:10.1093/eurheartj/ehs083

CLINICAL RESEARCH
Thrombosis/antithrombotic therapy

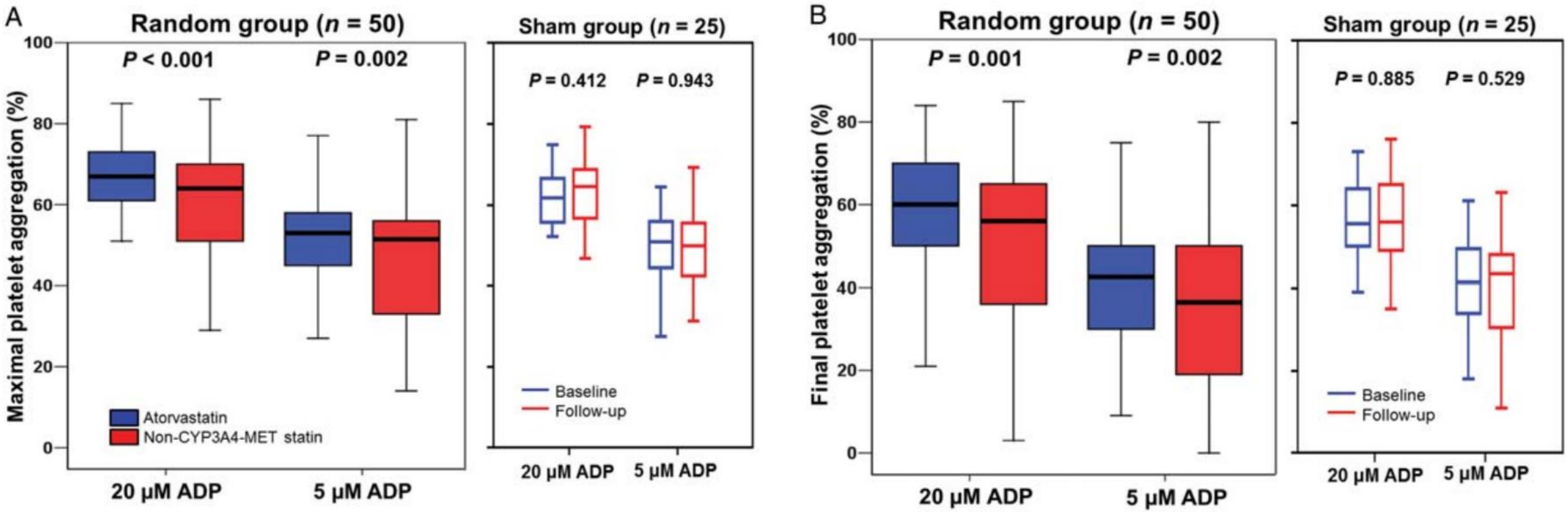
Accelerated platelet inhibition by switching from atorvastatin to a non-CYP3A4-metabolized statin in patients with high platelet reactivity (ACCEL-STATIN) study

Yongwhi Park[1], Young-Hoon Jeong[1,2]*, Udaya S. Tantry[2], Jong Hwa Ahn[1], Tae Jung Kwon[1], Jeong Rang Park[1], Seok-Jae Hwang[1], Eun-Ha Gho[3], Kevin P. Bliden[2], Choong Hwan Kwak[1], Jin-Yong Hwang[1], Sunjoo Kim[3], and Paul A. Gurbel[2]

[1]Division of Cardiology, Department of Internal Medicine, Gyeongsang National University Hospital, Jinju, Korea; [2]Sinai Center for Thrombosis Research, Cardiac Catheterization Laboratory, 2401 W. Belvedere Ave., Baltimore, MD 21215, USA; and [3]Department of Laboratory Medicine, Gyeongsang National University Hospital, Jinju, Korea

Received 3 February 2012; revised 24 February 2012; accepted 6 March 2012; online publish-ahead-of-print 16 April 2012

Interaction between Statins and Clopidogrel

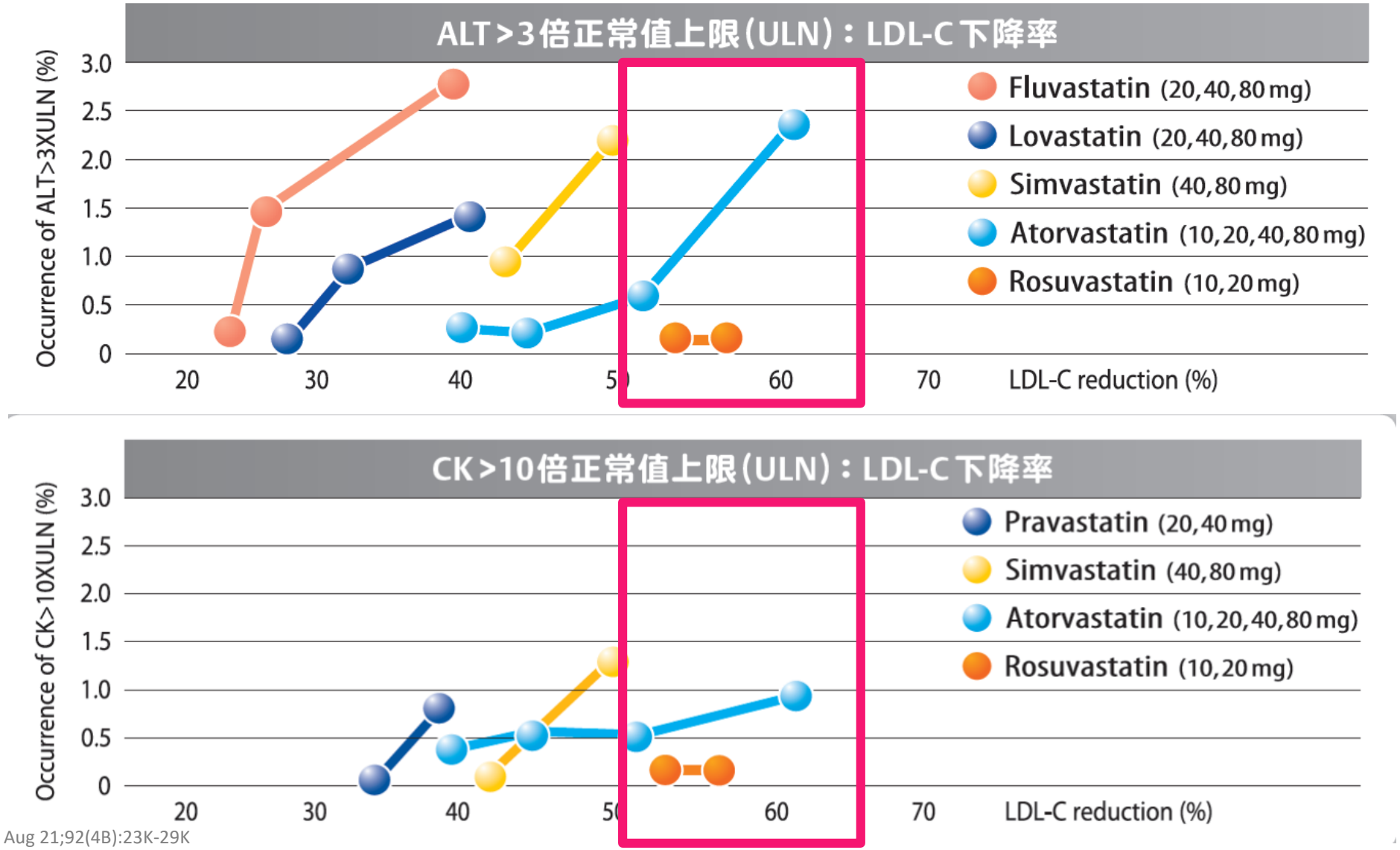


Non CYP3A4-MET statin : Rosuvastatin, Pravastatin

Figure 2 (*A* and *B*) Maximal and final platelet aggregations and (*C* and *D*) P2Y12 reaction units and percent inhibition during atorvastatin therapy vs. after switching to a non-CYP3A4-metabolized statin. The sham group represents patients without change of atorvastatin. The central box represents the values between the lower and upper quartiles, and the middle line is the median. The vertical line extends from the minimum to the maximum value, excluding outside values, which are displayed as separate points. ADP, adenosine diphosphate; CYP3A4-MET, cytochrome P450 3A4-metabolized.

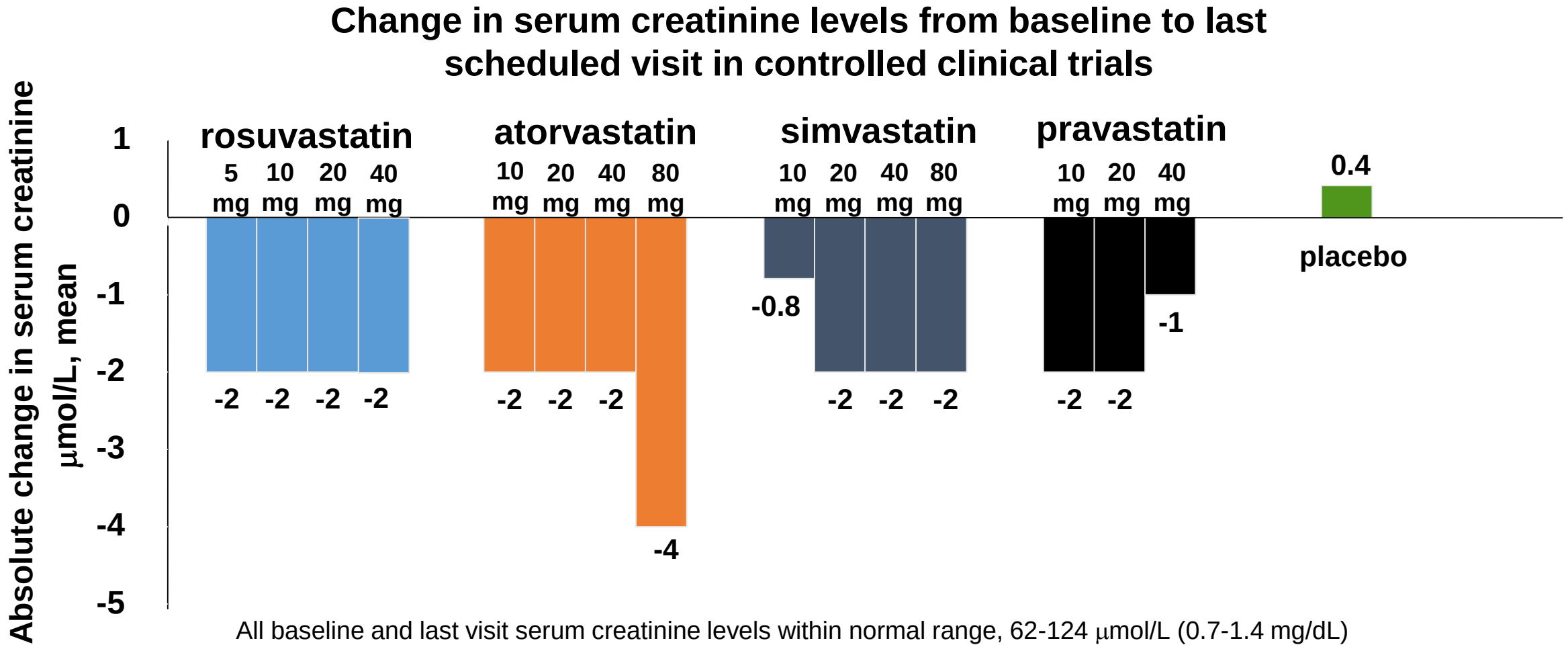
European Heart Journal (2012) 33, 2151–2162

Rosuvastatin : Low dose and high potency has a favorable safety profile and good tolerability



Adapted from: Am J Cardiol. 2003 Aug 21;92(4B):23K-29K

Rosuvastatin : maintenance of renal function assessed by serum creatinine



All baseline and last visit serum creatinine levels within normal range, 62-124 µmol/L (0.7-1.4 mg/dL)

Cardiology. 2004;102(1):52-60

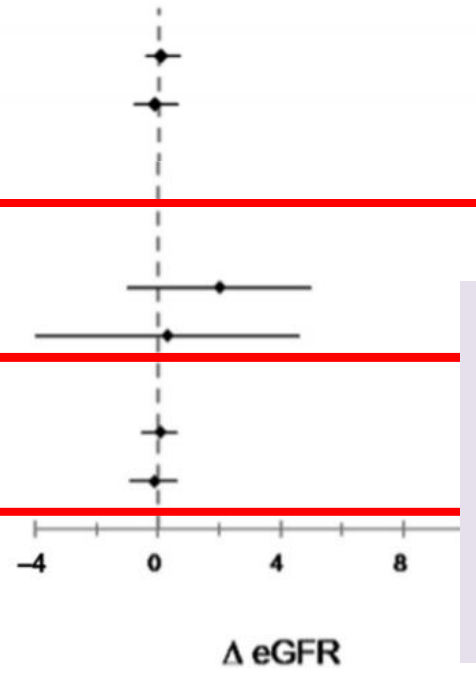
Taiwan RWE: Rosuvastatin and atorvastatin showed a similar phenomenon in eGFR

Effects of Atorvastatin and Rosuvastatin on Renal Function in Patients With Type 2 Diabetes Mellitus

Chao-Lun Lai, MD, PhD[a,b,c], Hsu-Wen Chou, PhD[c], K. Arnold Chan, MD, ScD[d,e], and Mei-Shu Lai, MD, PhD[c,f,*]

N= 5556

Subgroups	n	Δ eGFR	95% CI	p*
Total				0.27
Atorvastatin	3601	0.1 ,	–0.4 to 0.7	
Rosuvastatin	1968	–0.1 ,	–0.8 to 0.6	
Dose of statins				
High				0.54
Atorvastatin	170	2.0 ,	–1.0 to 5.0	
Rosuvastatin	65	0.3 ,	–4.1 to 4.6	
Low				
Atorvastatin	3431	0.1 ,	–0.5 to 0.6	
Rosuvastatin	1903	–0.1 ,	–0.9 to 0.6	

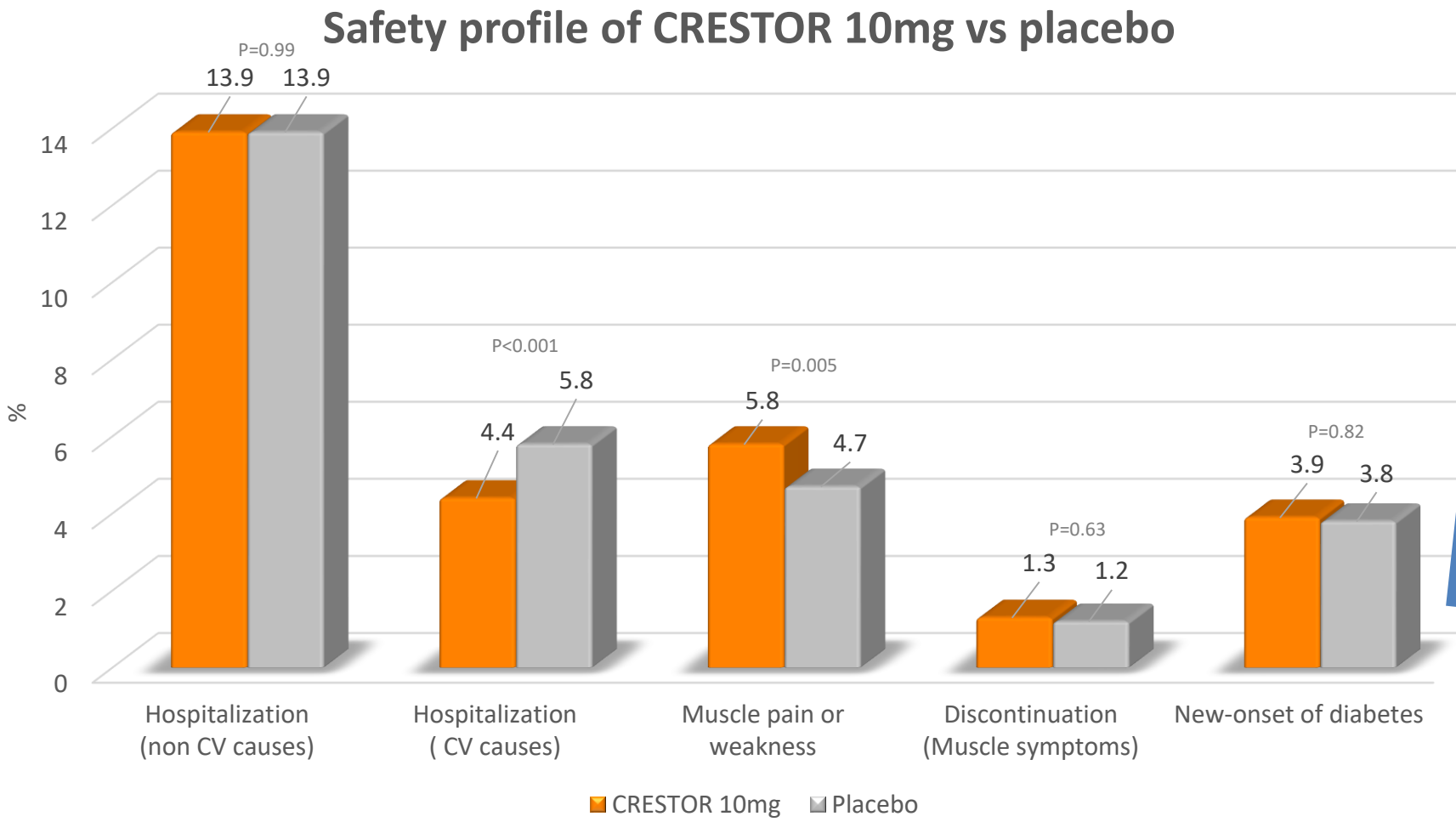


high-dose users mean daily dosage：
52.2 ± 26.3 mg in atorvastatin users
22.2 ±13.3 mg in rosuvastatin users

low-dose users mean daily dosage：
13.1 ± 9.7 mg in atorvastatin users
8.8 ± 4.5 mg in rosuvastatin users

Am J Cardiol. 2015 Mar 1;115(5):619-24.

Rosuvastatin demonstrated comparable safety profile with placebo



CRESTOR®
did not significant increase in new-onset of diabetes

N Engl J Med. 2016; 374:2021-2031

CRESTOR is associated with low risk of new-onset diabetes (NOD) in a retrospective cohort study

The risk estimate of new-onset diabetes for fluvastatin, lovastatin and **rosuvastatin** was lower than nonusers.

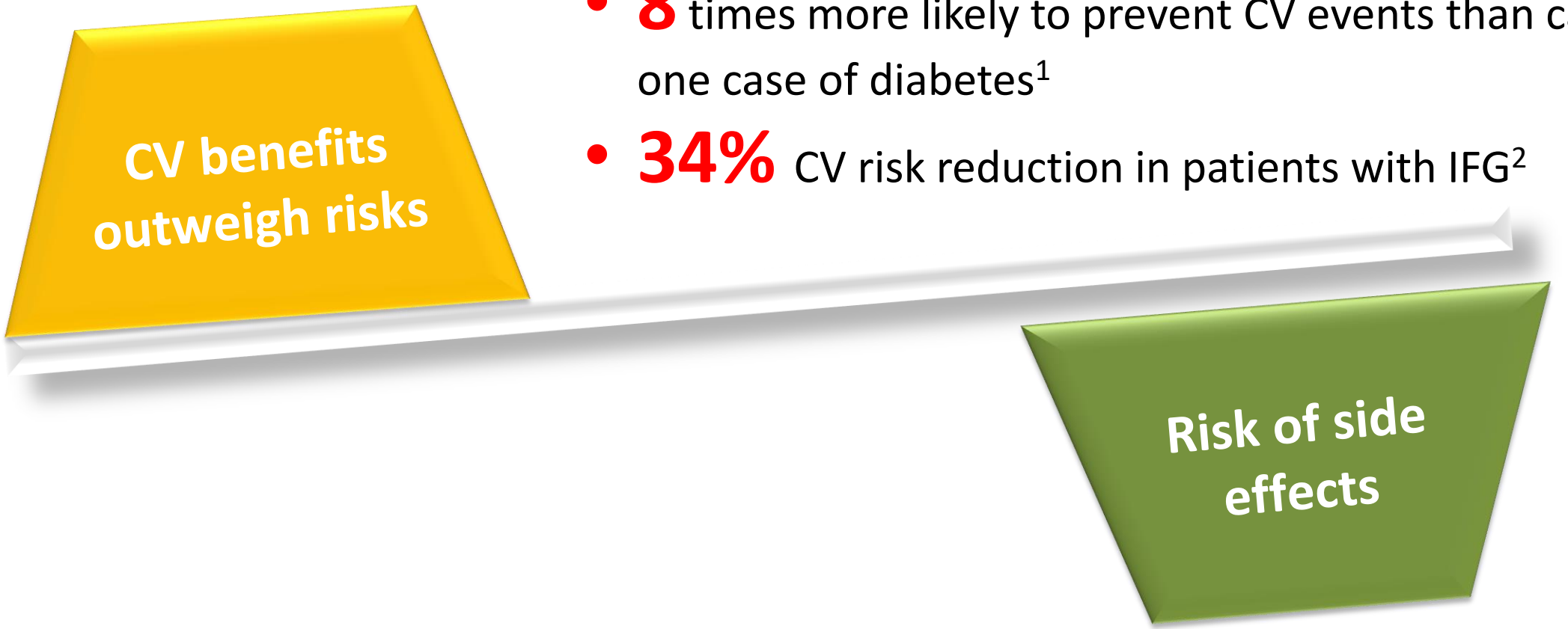
Cox univariate analysis of incidence of hazard ratios (HRs) with 95% CIs for patients with new-onset diabetes (NOD) according to prescriptions for statins compared with non-NOD subjects.

Drug class	HR	95% CI	p	HR*	95% CI*	p†
Pravastatin	1.40	1.20–1.62	<0.0001	1.34	1.15–1.55	0.0001
Fluvastatin	0.45	0.34–0.60	<0.0001	0.45	0.34–0.60	<0.0001
Lovastatin	0.66	0.57–0.78	<0.0001	0.71	0.61–0.84	<0.0001
Simvastatin	1.12	0.94–1.34	0.2068	1.10	0.92–1.31	0.3034
Atorvastatin	1.32	1.19–1.47	<0.0001	1.29	1.16–1.44	<0.0001
Rosuvastatin	0.53	0.38–0.74	0.0002	0.54	0.39–0.77	0.0005

*All variables were adjusted for age and sex. †P values between NOD and non-NOD subjects.

Clin Ther. 2012 Sep;34(9):1977-83.

Statin risk summary: CV benefits outweigh risks



- **8** times more likely to prevent CV events than cause one case of diabetes[1]
- **34%** CV risk reduction in patients with IFG[2]

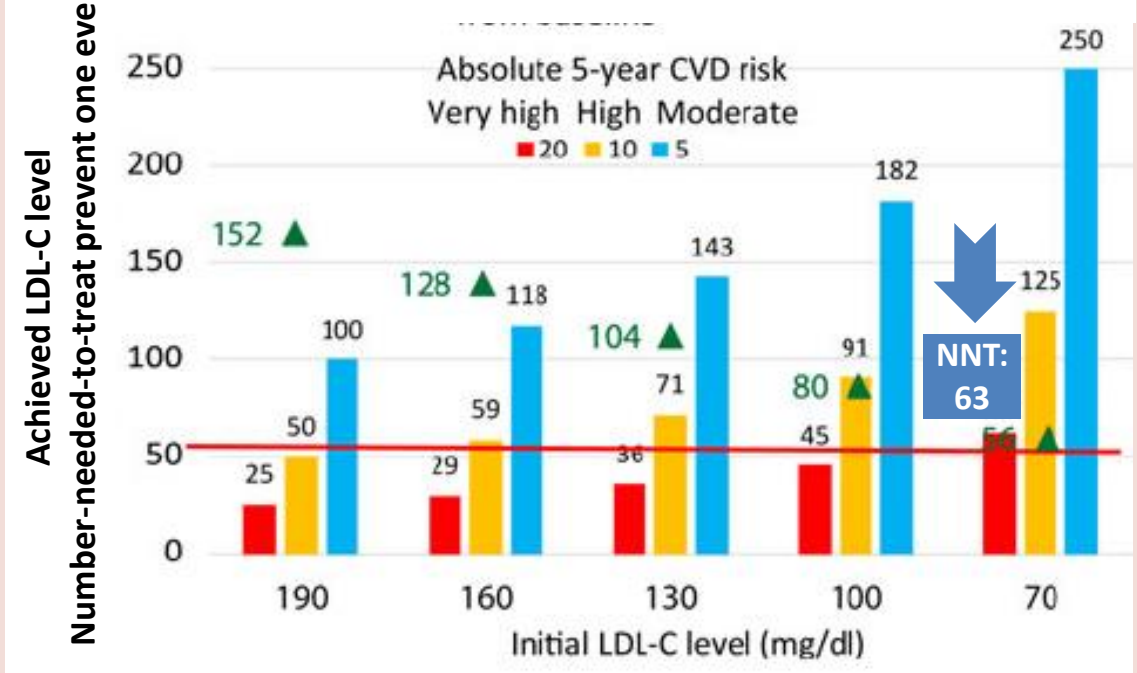
1. *Evidence-Based Med.* 2010;15(3):84–85.
2. *Curr Opin Cardiol.* 2011;26(4):342–347.

WHY Rosuvastatin : High Intensity Help

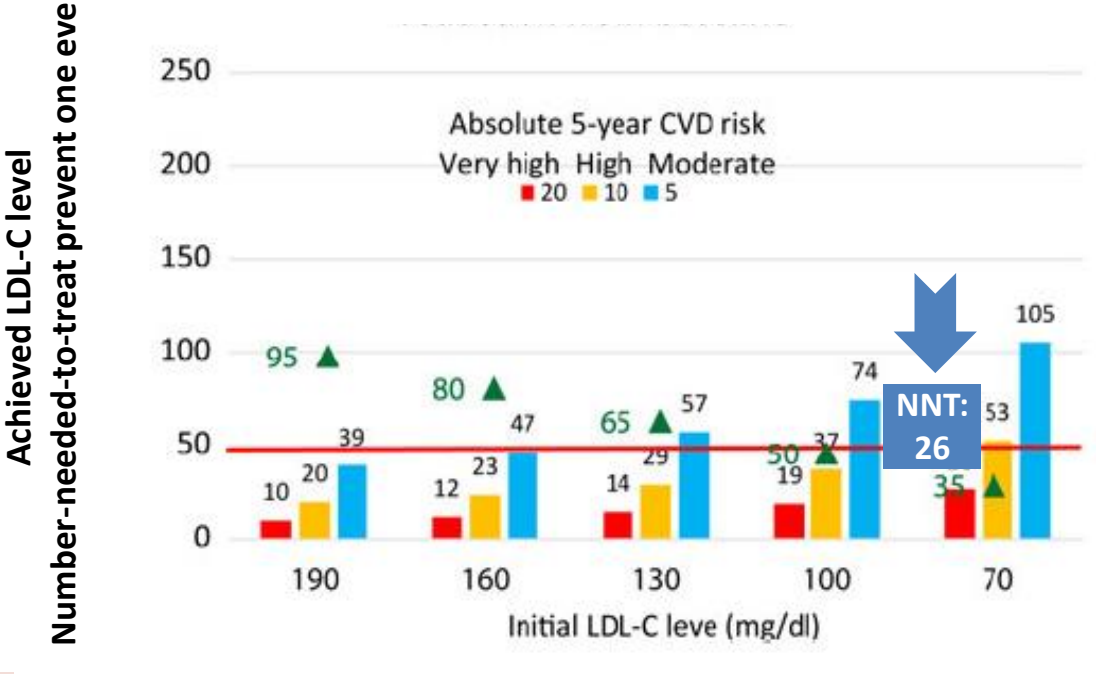
LDL-C ≥50% reduction results with lower NNT: Lower might be better

LDL-C decision-making could be based on net benefit as estimated by NNT

NNTs and achieved LDL-C for 20% reduction from baseline



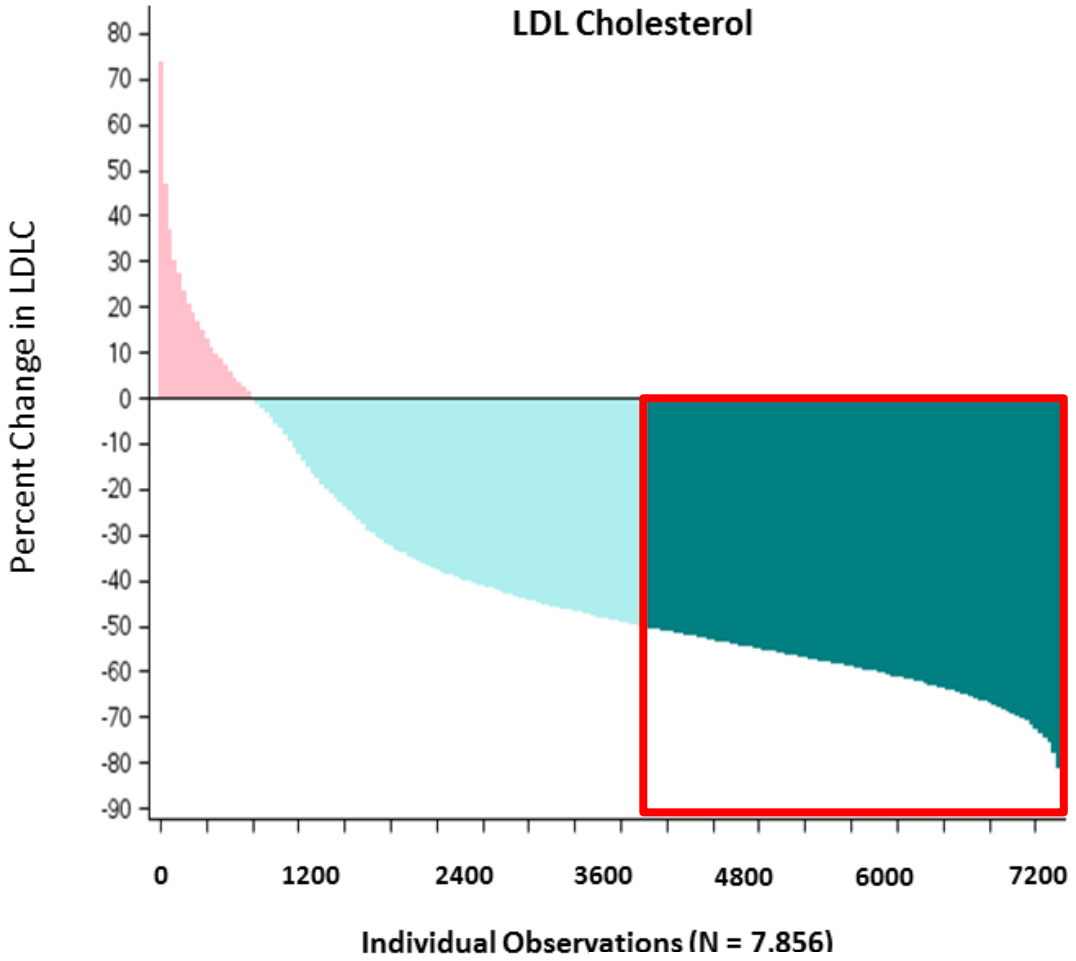
NNTs and achieved LDL-C for 50% reduction from baseline

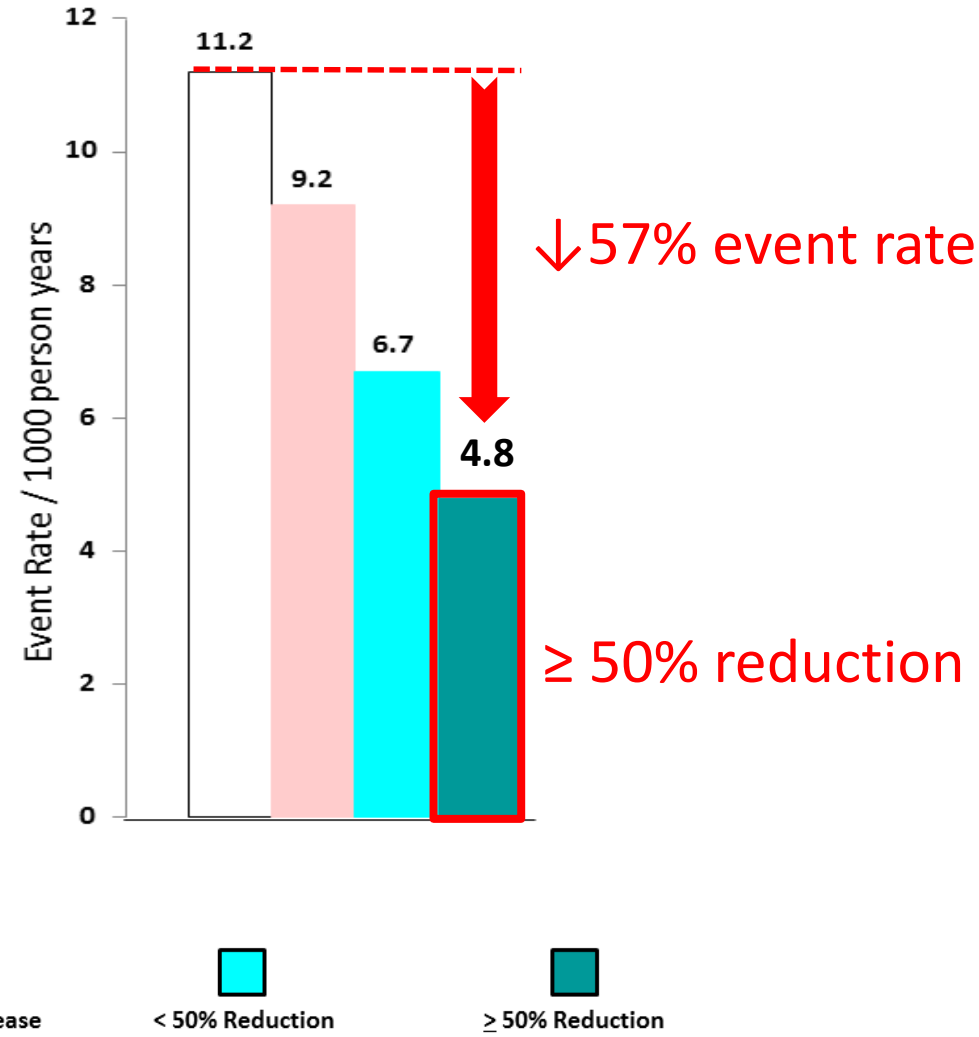


NNT= Number needed to treat

Eur Heart J. 2016;37(17):1380-1383.

% LDL-C reductions directly related to the risks of first CV events





European Heart Journal (2016) 37, 1373–1379

>50% LDL-C reduction with less risk of first cardiovascular events

Attained LDL≤70mg/dl

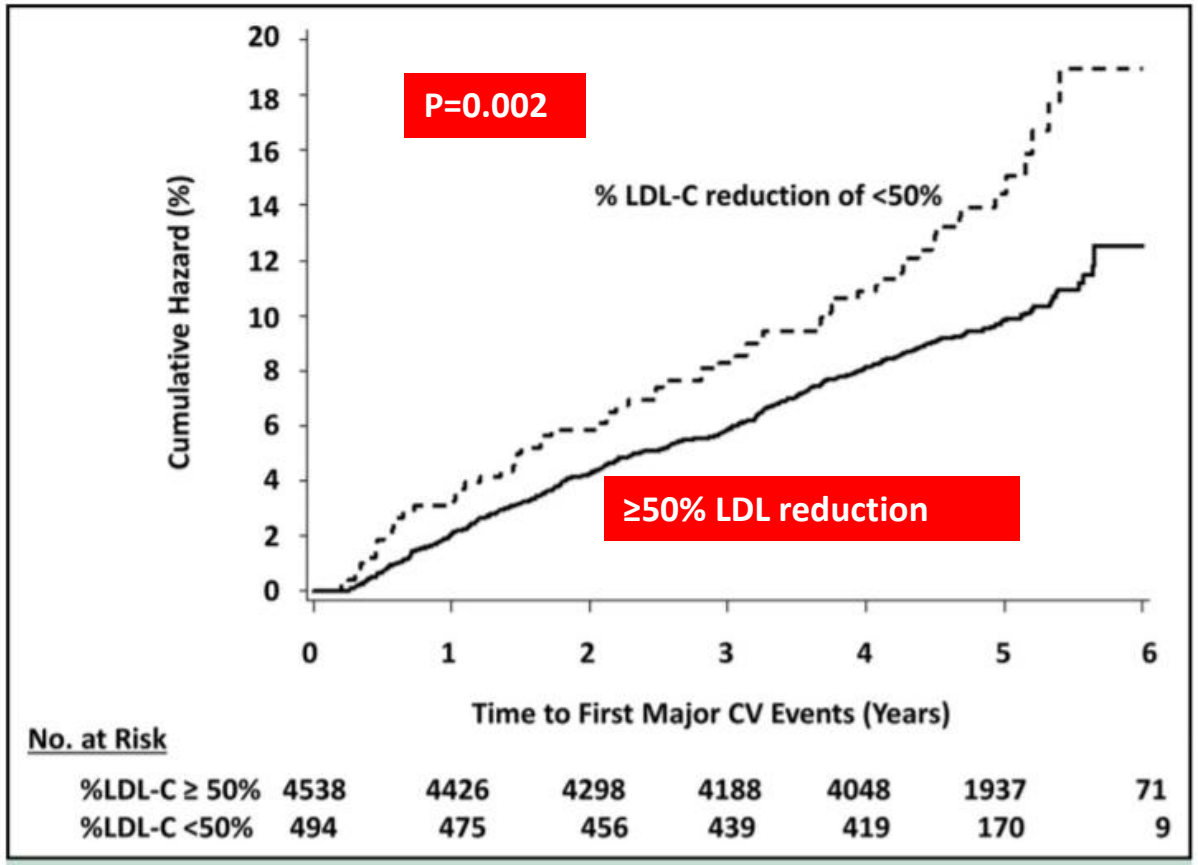


Figure 1 Major cardiovascular events in the cohort with attained LDL-C ≤70 mg/dL as a function of percent LDL-C reduction. LDL = low-density lipoprotein.

Attained LDL>70mg/dl

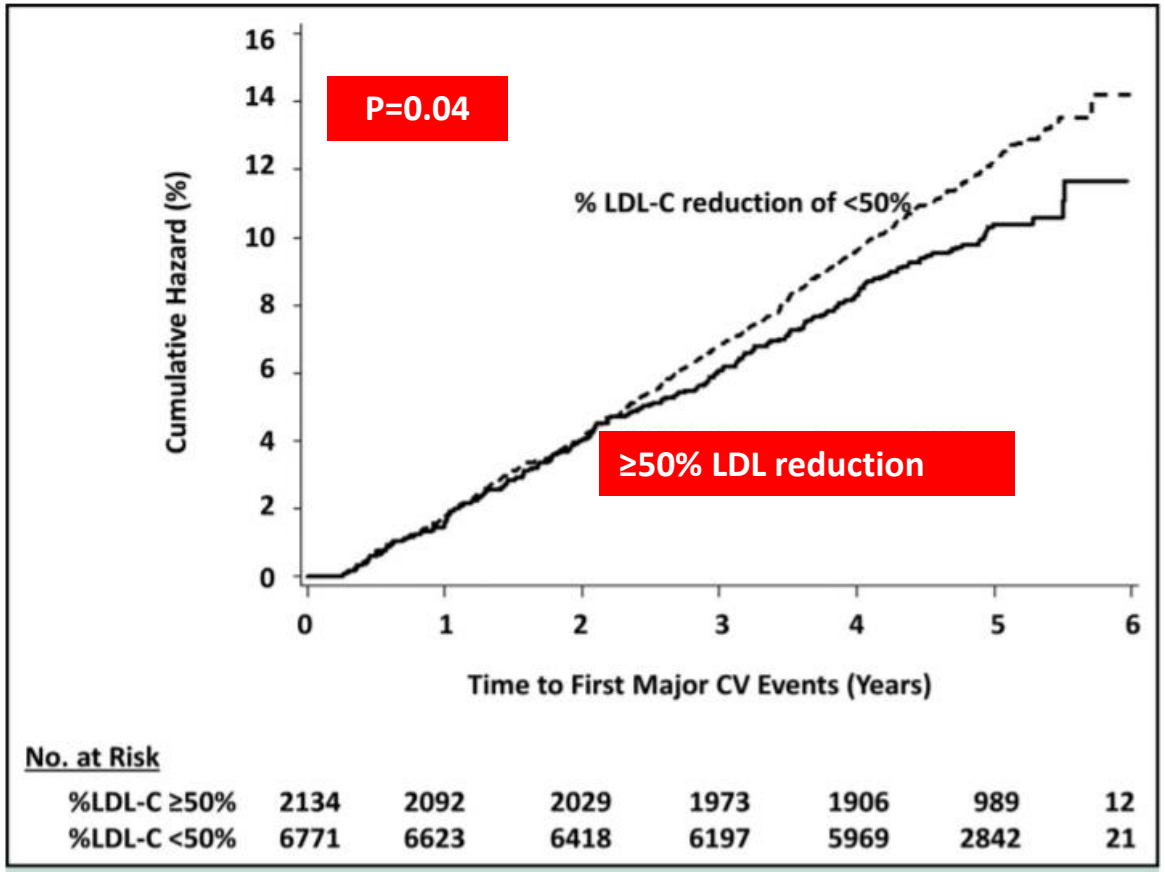
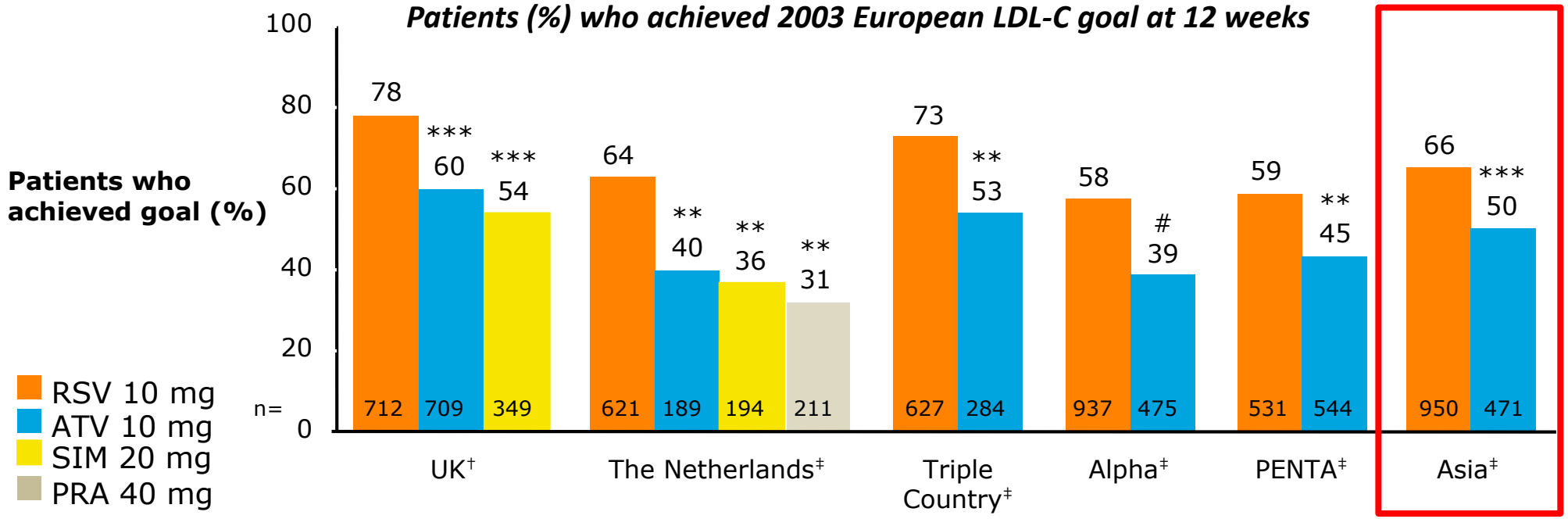


Figure 2 Major cardiovascular events in the cohort with attained LDL-C >70 mg/dL as a function of percent LDL-C reduction. LDL = low-density lipoprotein.

The American Journal of Medicine (2016) 129, 384-391c

WHY Rosuvastatin： In practice

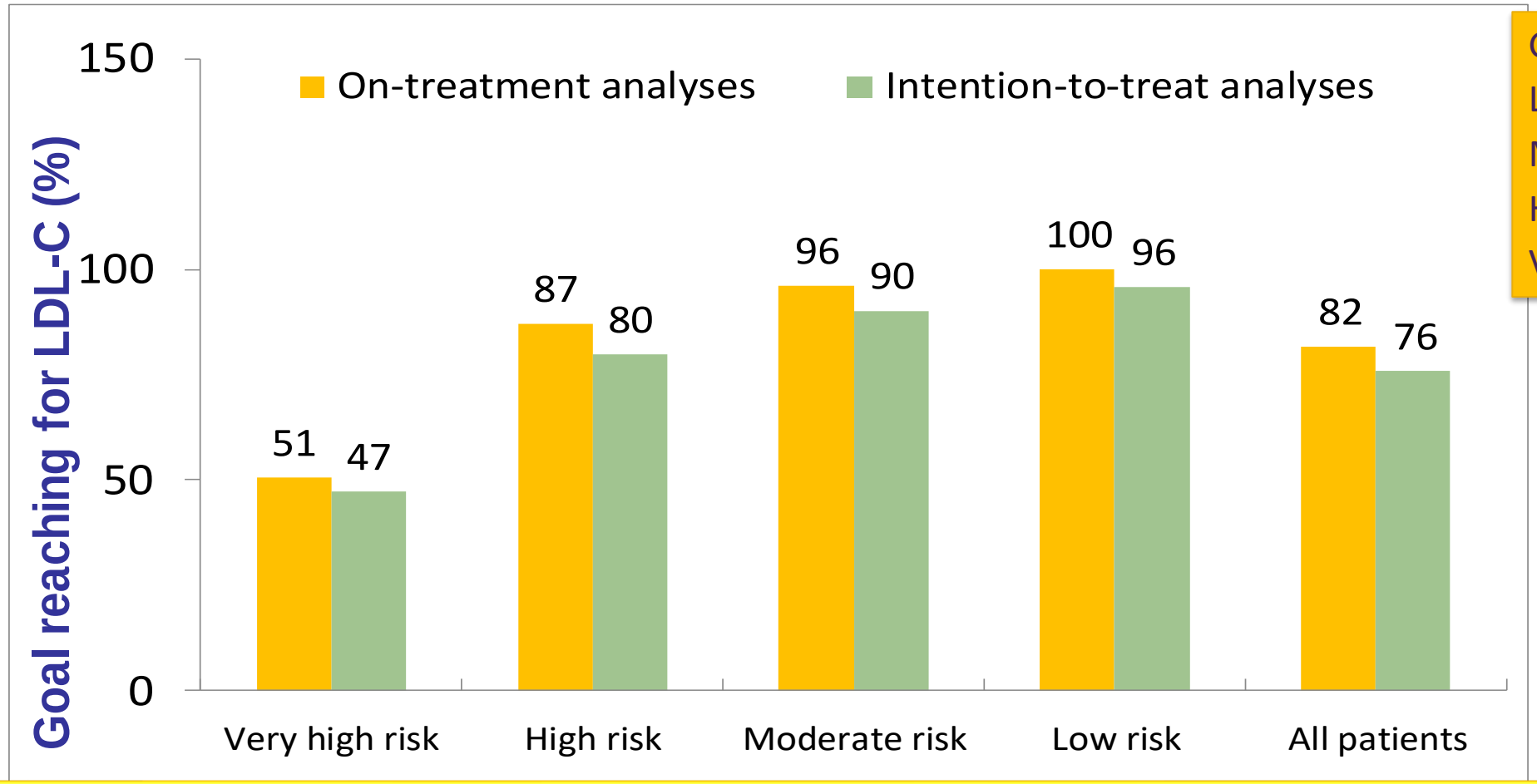
CRESTOR in Asia : more than 60% patients achieve goal



2003 European goal: LDL-C <2.5 or 3.0 mmol/L depending on CVD risk
LDL-C=low-density lipoprotein cholesterol; RSV=rosuvastatin; ATV=atorvastatin; SIM=simvastatin; PRA=pravastatin; CVD=cardiovascular disease
†Statin-naïve patients; ‡Statin-naïve and previously treated patients;**p<0.001 vs RSV 10 mg;***p<0.0001 vs RSV 10 mg;
#No statistical analysis was performed on these data

Curr Ther Res 2006; 67: 21–43.
Int J Clin Pract 2005; 59: 1387–1394.
Curr Med Res Opin 2005; 21: 1307–1315
Br J Cardiol 2006; 13: 72–76.
Clin Ther 2004; 26: 1821–1833.
Curr Med Res Opin 2007; 23: 3055–3068

CRESTOR 10mg helped more than 75% Taiwan patients reached their therapeutic goals



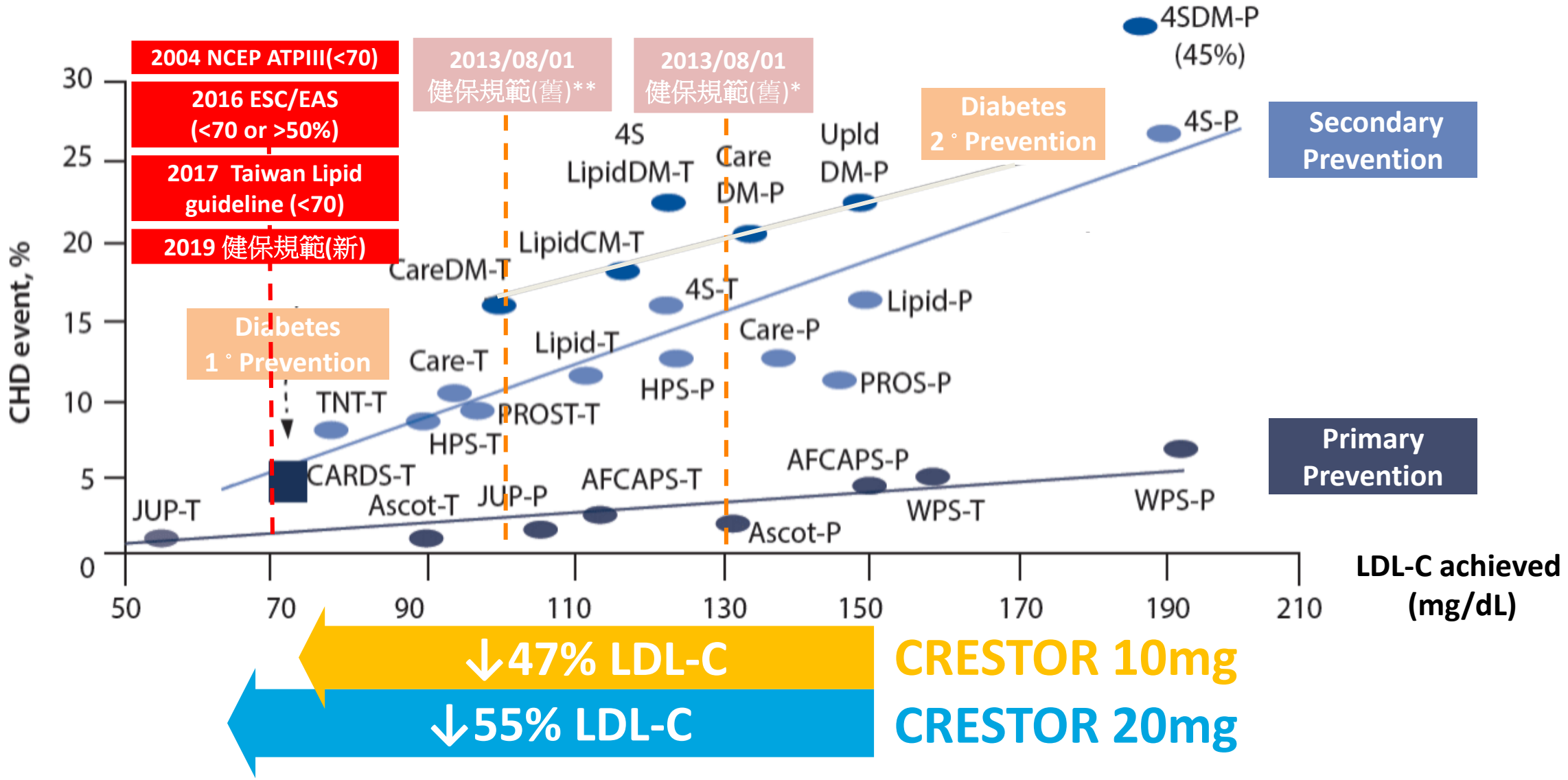
Goal (mg/dL)
Low risk < 160
Moderate risk < 130
High risk <100
Very high risk <70

Overall more than 75% of patients reached therapeutic goals with rosuvastatin therapy

Adapted from J Chin Med Assoc. 2008 Mar;71(3):113-8.

Established evidence of “Lower is Better”

: very-high risk
*兩個危險因子以上
**心血管疾病或糖尿病患者



↓47% LDL-C CRESTOR 10mg

↓55% LDL-C CRESTOR 20mg

S Afr Med J. 2014 Mar;104(3):168-73.

Take Home Messages

- **Rosuvastatin has greater LDL-C lowering efficacy[1] and superior HDL-C increasing efficacy[2]**
- **Rosuvastatin is efficacious in regressing coronary plaque volume in CAD patients with hyperlipidemia, and useful for secondary prevention[3]**
- **Rosuvastatin helped more than 75% Taiwan patients reached their therapeutic goals[4]**
- **Rosuvastatin has low potential for drug-drug interactions through non-CYP3A4 metabolism[5]**

1. Jones P et al. Am J Cardiol 2003;92:152–160. 2. McTaggart F and Jones P. *Cardiovasc Drugs Ther* 2008;22:321–38 3. Circ J. 2009 Nov;73(11):2110-7. 4. J Chin Med Assoc. 2008 Mar;71(3):113-8 5. Am J Cardiol 2001; 87 (Suppl): 28B-32B


Thanks for Your Attention
黑白分明的沉思者