Maximizing statin benefit of treating patients with dyslipidemia for primary prevention

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Outline

1. Importance of primary prevention in dyslipidemia

2. Variation of statin efficacy between Asian and Western dyslipidemia

3. Tailored lipid control in Asian primary prevention

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2. **Variation of statin efficacy between Asian and Western dyslipidemia**
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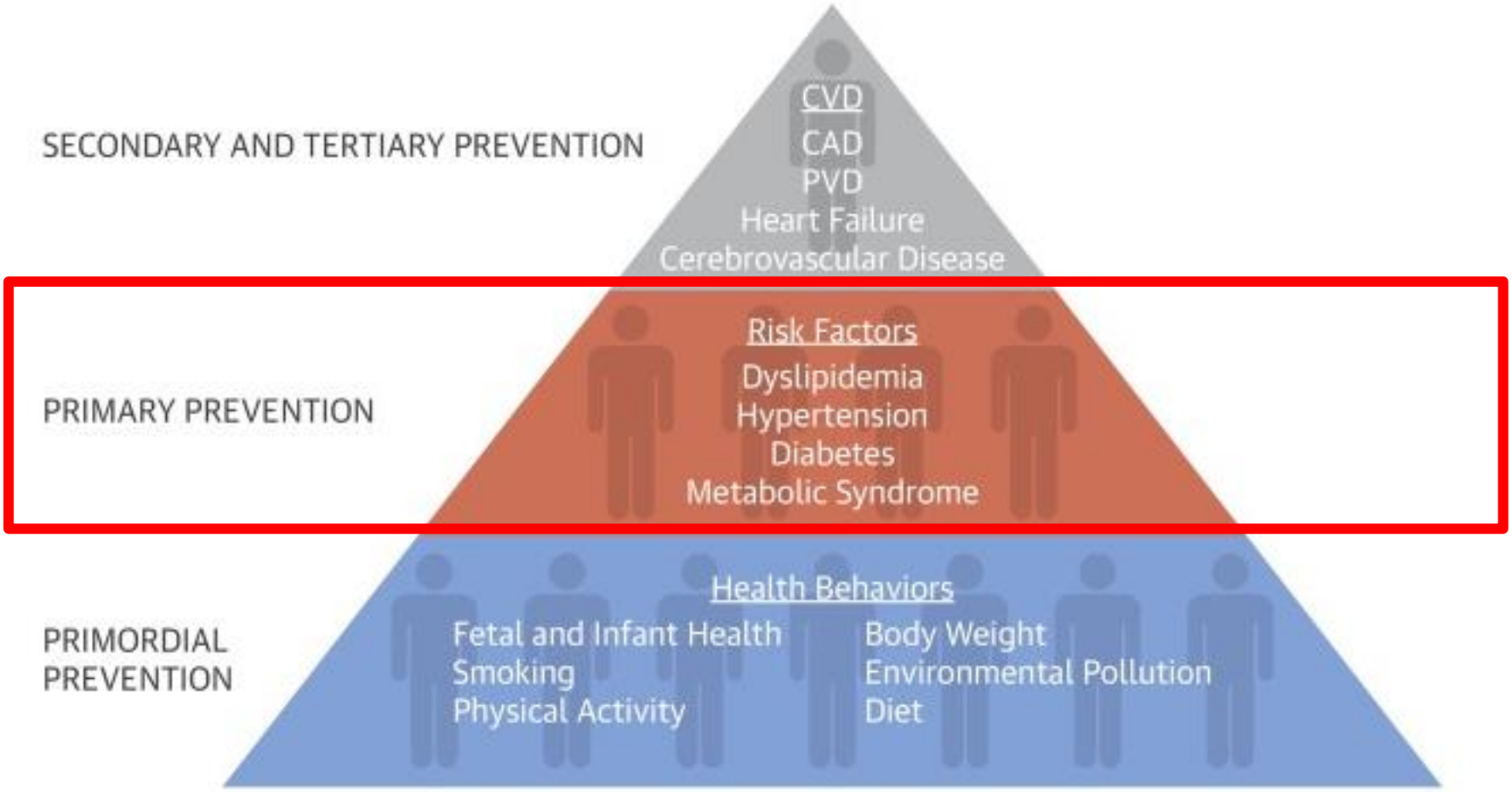
Cardiovascular disease prevention



J Am Coll Cardiol. 2017; 70 (17): 2171-85

HMG-CoA reductase inhibitor evidence: Degree of Benefit in Prevention Types

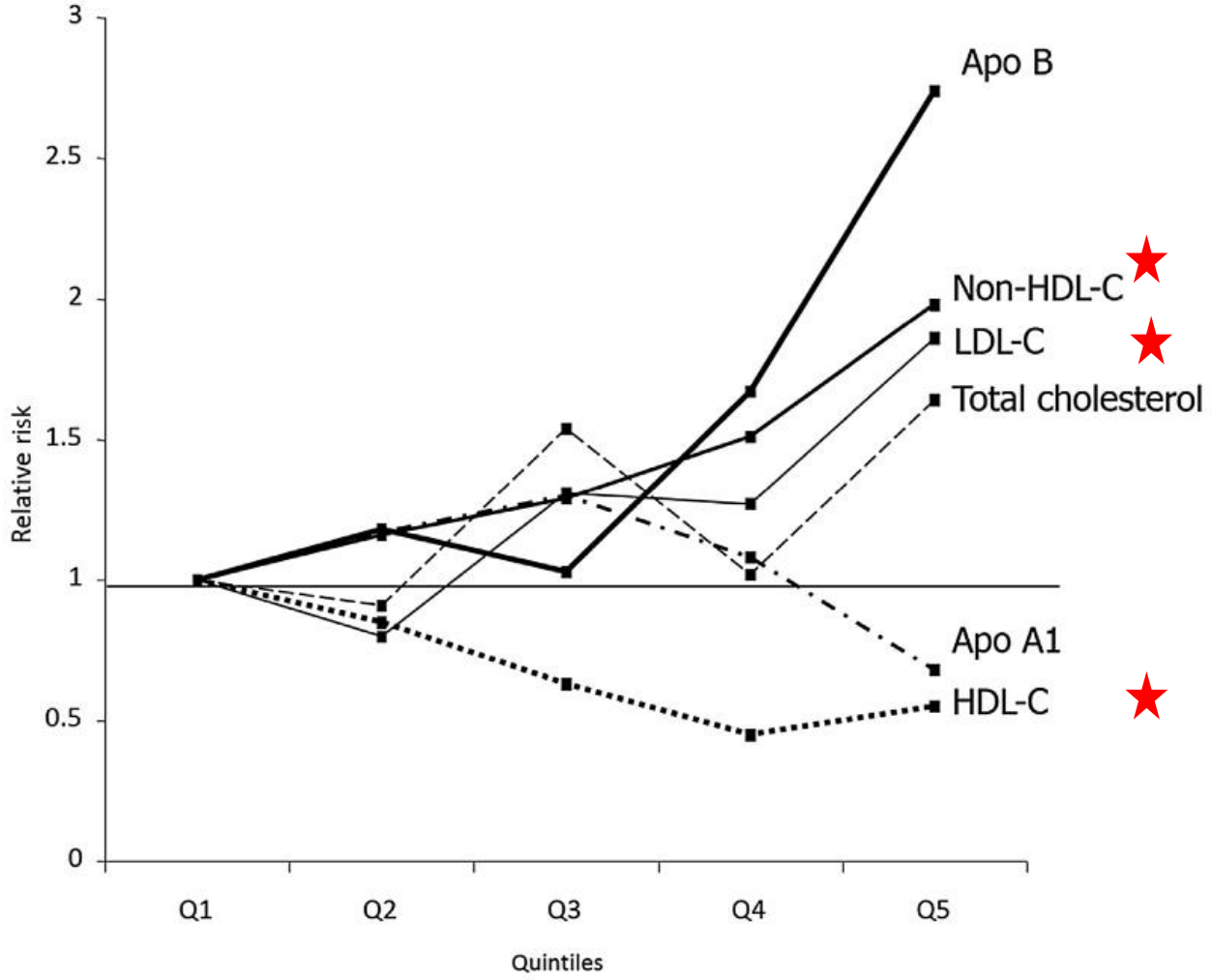
Meta-analysis of randomized controlled trials comparing risk reductions between primary and secondary prevention patients

	Relative Risk Reduction		Absolute Risk Reduction		Number Needed To Treat	
	Primary	Secondary	Primary	Secondary	Primary	Secondary
Major CHD events	29.2	20.8	1.66	2.4	60	33
Major CV events	14.4	17.8	0.37	0.8	268	125
Nonfatal MI	31.7	NA	1.65	NA	61	NA
PCI or CABG	33.8	20.3	1.08	2.7	93	37

CABG=Coronary artery bypass graft surgery, CHD=Coronary heart disease, CV=Cardiovascular, MI=Myocardial infarction, PCI=Percutaneous coronary intervention

Source: Thavendiranathan P et al. *Arch Intern Med* 2006;166:2307-2313

Relative risks of lipid profiles for the risk of CHD



Journal of the Formosan Medical Association (2017) 116, 217e248

2019 American Diabetes Association

2018 American Heart Association's

2017 Taiwan lipid guideline

2019 European Society of Cardiology

2018 ACC/AHA Guideline

Group 1

Secondary ASCVD Prevention

ACS, MI, angina, coronary arterial revascularization, stroke, TIA or PAD

Group 2

Severe Hypercholesterolemia

LDL-C ≥190 mg/dL(4.9 mmol/L)

Group 3

Diabetes mellitus in Adults

+ age of 40–75 years
+ LDL-C 70–189 mg/dL

Group 4

Primary Prevention

+ age of 40–75 years & LDL-C 70–189 mg/dL + 10-year ASCVD risk≥7.5% (intermediate-risk)

Group 5

Other Populations at Risk

Ethnicity, Hypertriglyceridemia, Women, CKD & Chronic Inflammatory Disorders and HIV

Grundy SM, et al. 2018 AHA Cholesterol Clinical Practice Guidelines

2018 ACC/AHA Guideline

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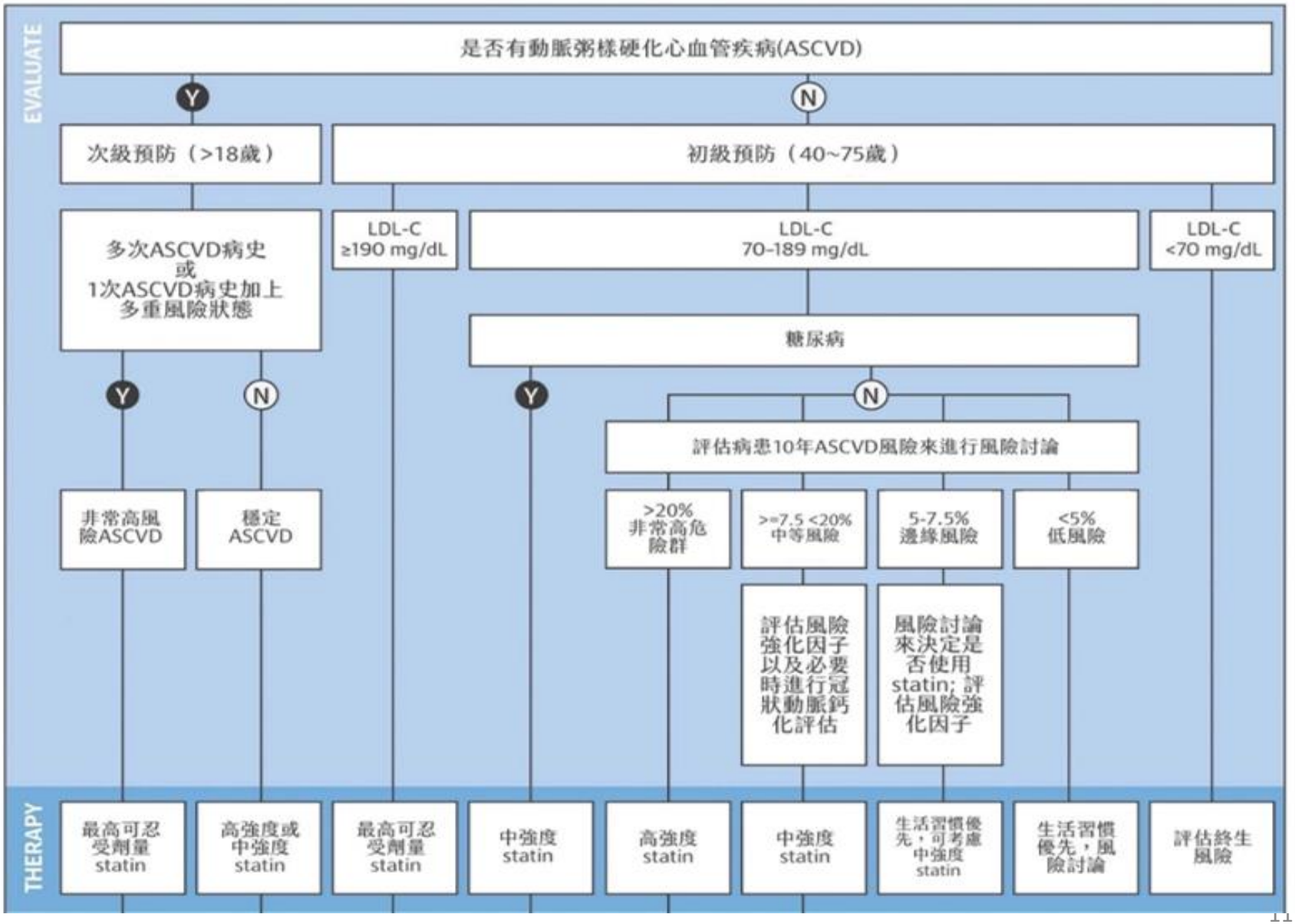
High- Moderate- and Low-intensity statin therapy

	High Intensity	Moderate Intensity	Low Intensity
LDL-C lowering†	≥50%	30%–49%	<30%
Statins	**Atorvastatin (40 mg‡) 80 mg** **Rosuvastatin 20 mg (*40 mg***	**Atorvastatin 10 mg** (20 mg) **Rosuvastatin** (5 mg) **10 mg** **Simvastatin 20–40 mg§**	Simvastatin 10 mg
	…	**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

Grundy SM, et al. 2018 AHA Cholesterol Clinical Practice Guidelines

CENTRAL ILLUSTRATION: 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol



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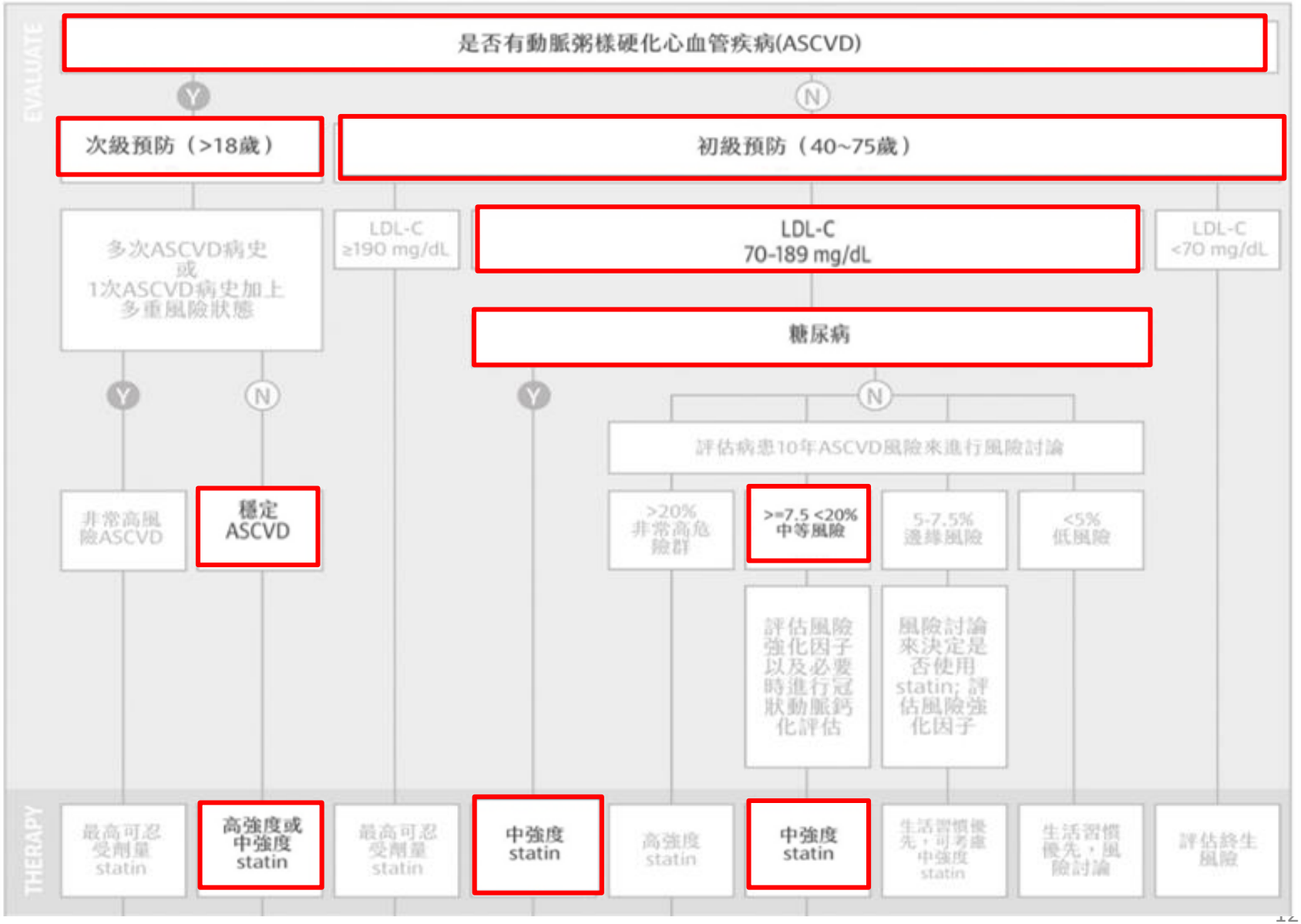

Grundy SM, et al. 2018 AHA Cholesterol Clinical Practice Guidelines

2019 ADA : Recommendations for statin and combination treatment in adults with diabetes

Age	ASCVD	Recommended statin intensity^ and combination treatment*
<40 years	No	None†
	Yes	High • If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)#
≥40 years	No	Moderate‡
	Yes	High • If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

1. ≥40 years : Moderate intensity statin

2. ASCVD : High intensity statin

2017台灣高風險病人血脂異常臨床治療指引

疾病 / 狀態	低密度膽固醇 (LDL-C) 之目標
急性冠心症候群	< 70 mg/dL
急性冠心症候群+ 糖尿病	< 55 mg/dL 可以考慮
穩定冠狀動脈疾病	< 70 mg/dL
缺血性腦中風或暫時性腦部缺氧	< 100 mg/dL
糖尿病	<100 mg/dL
糖尿病+心血管疾病	< 70 mg/dL
慢性腎臟病(階段 3a–5, eGFR < 60)	> 100 mg/dL 時開始治療
家族性高膽固醇血症	成人: < 100 mg/dL 小孩: < 135 mg/dL 有心血管疾病: < 70 mg/dL

中華民國血脂及動脈硬化學會
Taiwan Society of Lipids & Atherosclerosis

2019 ESC dyslipidemia guideline: Risk stratification

Very-high-risk	People with any of the following: 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,[a] 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 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.

High-risk	People with: Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage,[a] with DM duration ≥10 years or another additional risk factor. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

2019 ESC dyslipidemia guideline

Recommendations	Class[a]	Level[b]
In secondary prevention for patients at very-high risk,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.[33–35,119,120]	I	A
In primary prevention for individuals at very-high risk but without FH,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.[34–36]	I	C
In primary prevention for individuals with FH at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.	IIa	C
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.[119,120]	IIb	B
In patients at high risk,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.[34,35]	I	A
In individuals at moderate risk,[c] an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered.[34]	IIa	A
In individuals at low risk,[c] an LDL-C goal <3.0 mmol/L (<116 mg/dL) may be considered.[36]	IIb	A

1. **Very high risk: LDL-C <55 mg/dL**
2. **High risk: LDL-C <70 mg/dL**
3. **Moderate risk: LDL-C <100 mg/dL**
4. **Moderate risk: LDL-C <116 mg/dL**

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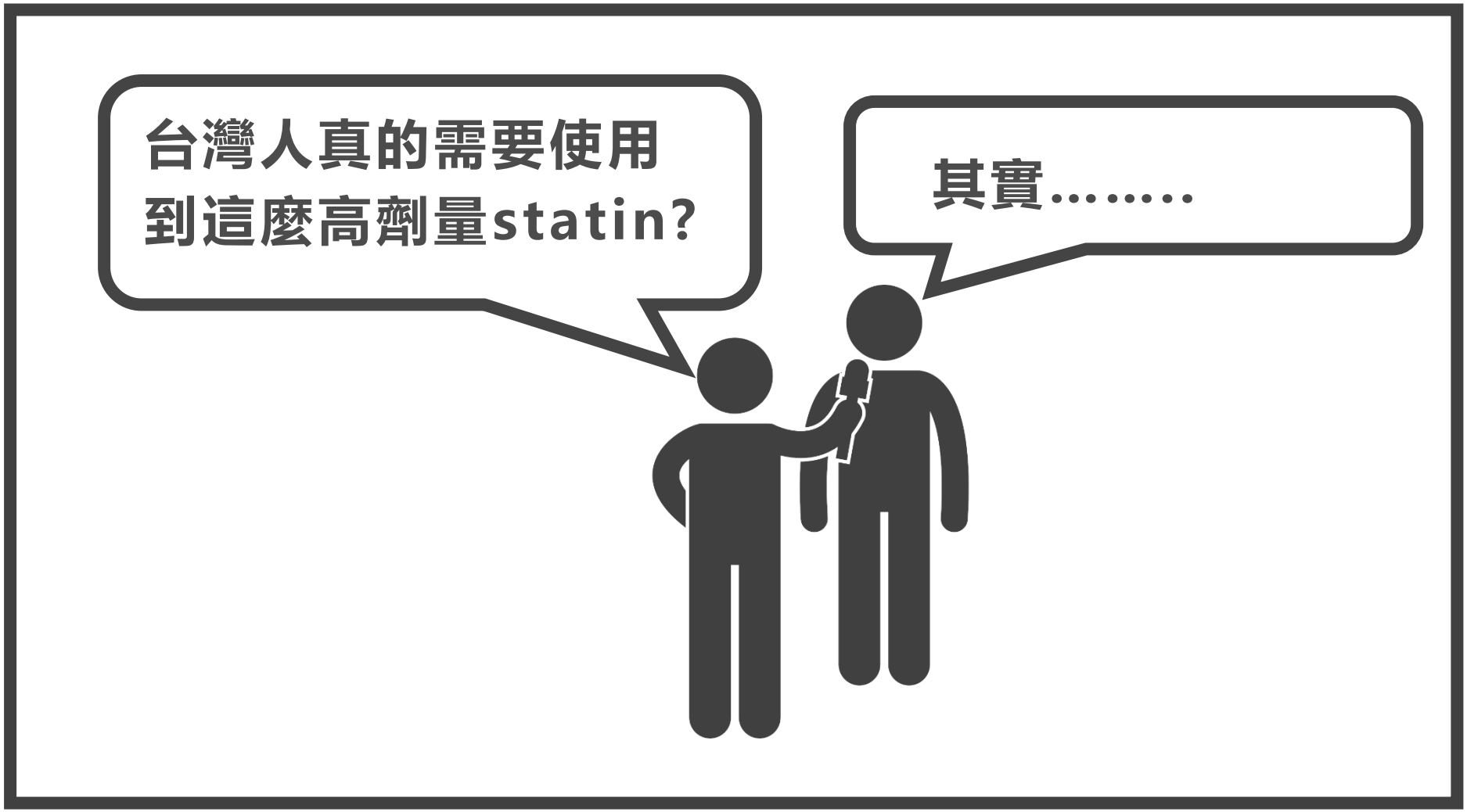

台灣人真的需要使用
到這麼高劑量statin?
其實……

Asian patients are more sensitive in statin therapy

Table 2. Variant allele frequency (percentage) of polymorphisms having effects on statin pharmacokinetics in different ethnic groups

SNP	Chinese	Japanese		Caucasian	Indian[a]
SLCO1B1 521T>C	14.6-15.1	11.0		15.0	2.3
SLCO1B1 388A>G	81.7-83.7	65.1	>	40.3	55.7
ABCG2 421C>A	28.9-29.3	31.1-34.3		11.1-11.7	6.2

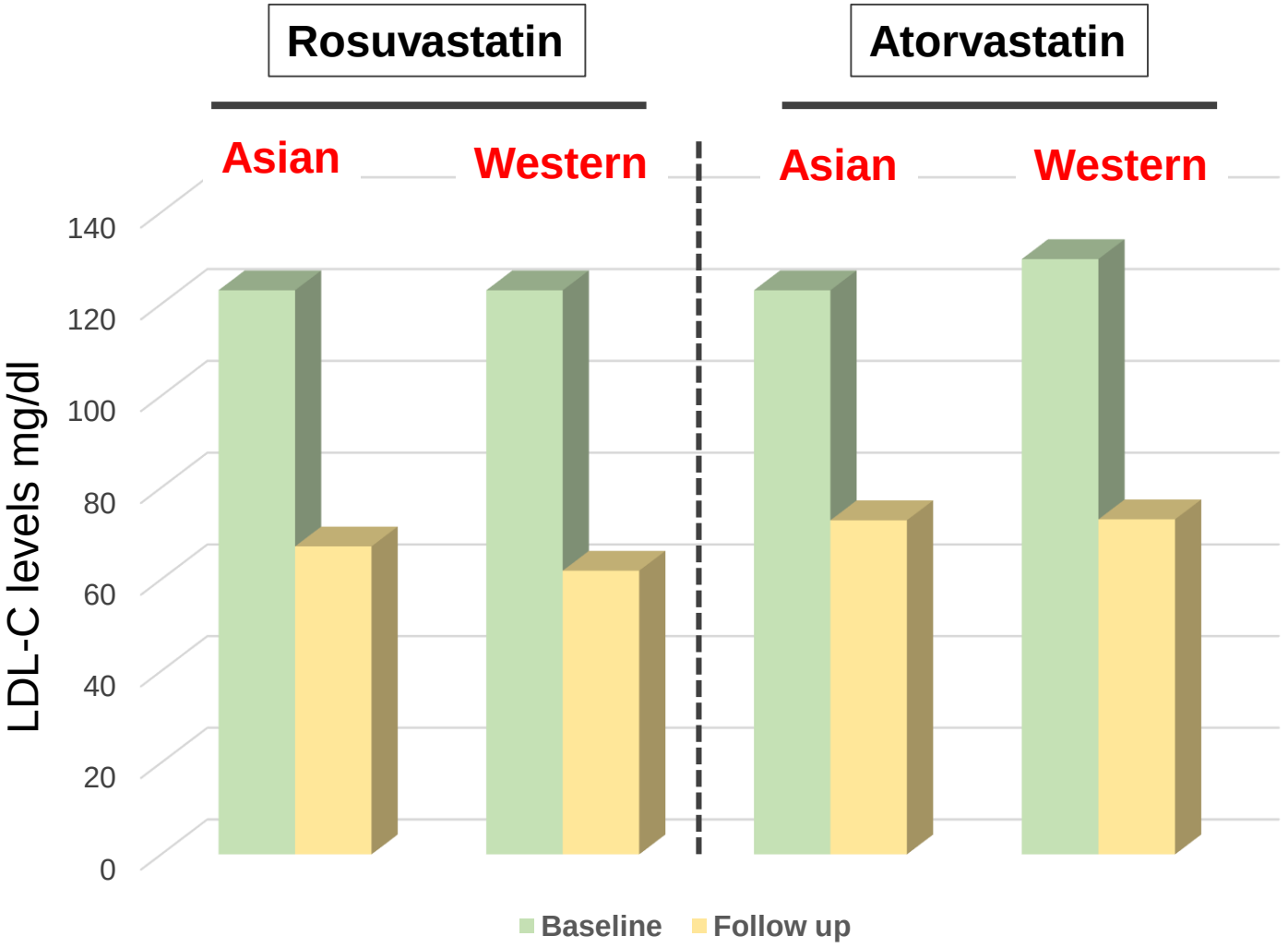
The *SLCO1B1* 521C allele results in the *SLCO1B1**5, *15 and *17 haplotypes.
Data from HapMap. [a]Gujarati Indians in Houston, Texas.

SLCO1B1: is expressed on the basolateral membrane of hepatocytes and can facilitate hepatic uptake of statins except for fluvastatin.

ABCG2: drug efflux transporter ATP-binding cassette G2 gene. Subjects with the variant allele have plasma rosuvastatin concentration twice as high as those with the wild-type genotype

J Atheroscler Thromb, 2017; 24: 00-00

Asian patients are more sensitive in statin therapy



J Atheroscler Thromb, 2017; 24: 19-25

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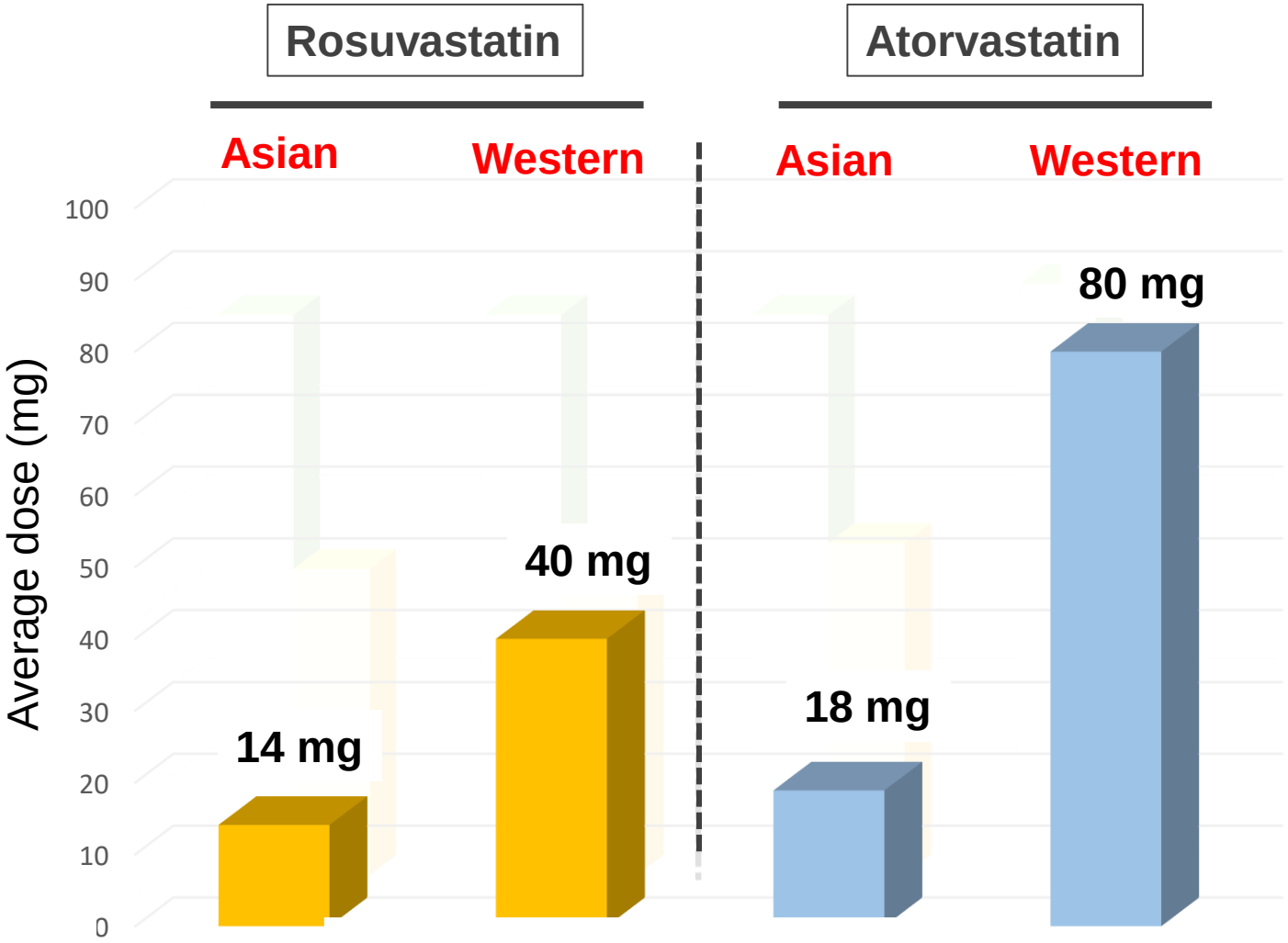
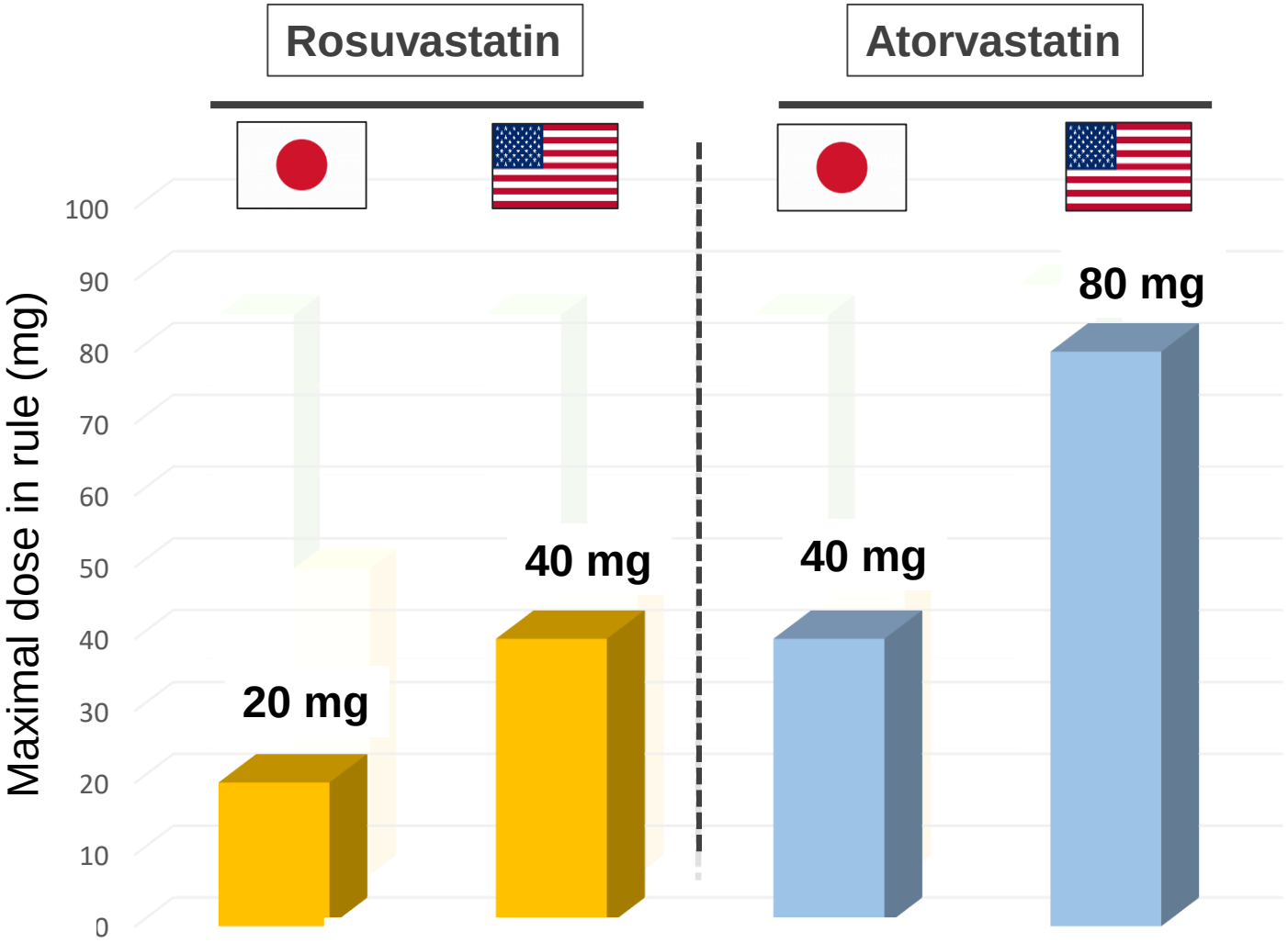


J Atheroscler Thromb, 2017; 24: 19-25

Maximal dose of statins in Japan and U.S



J Atheroscler Thromb, 2017; 24: 19-25

2018 ACC/AHA Guideline on the Management of Blood Cholesterol

Racial/ethnic issues in intensity of statin therapy & response to LDL-C lowering

- Japanese patients may be sensitive to statin dosing. In an open-label, randomized primary- prevention trial, Japanese participants had a reduction in CVD events with low-intensity doses of pravastatin as compared with placebo (S4.5.1- 33)

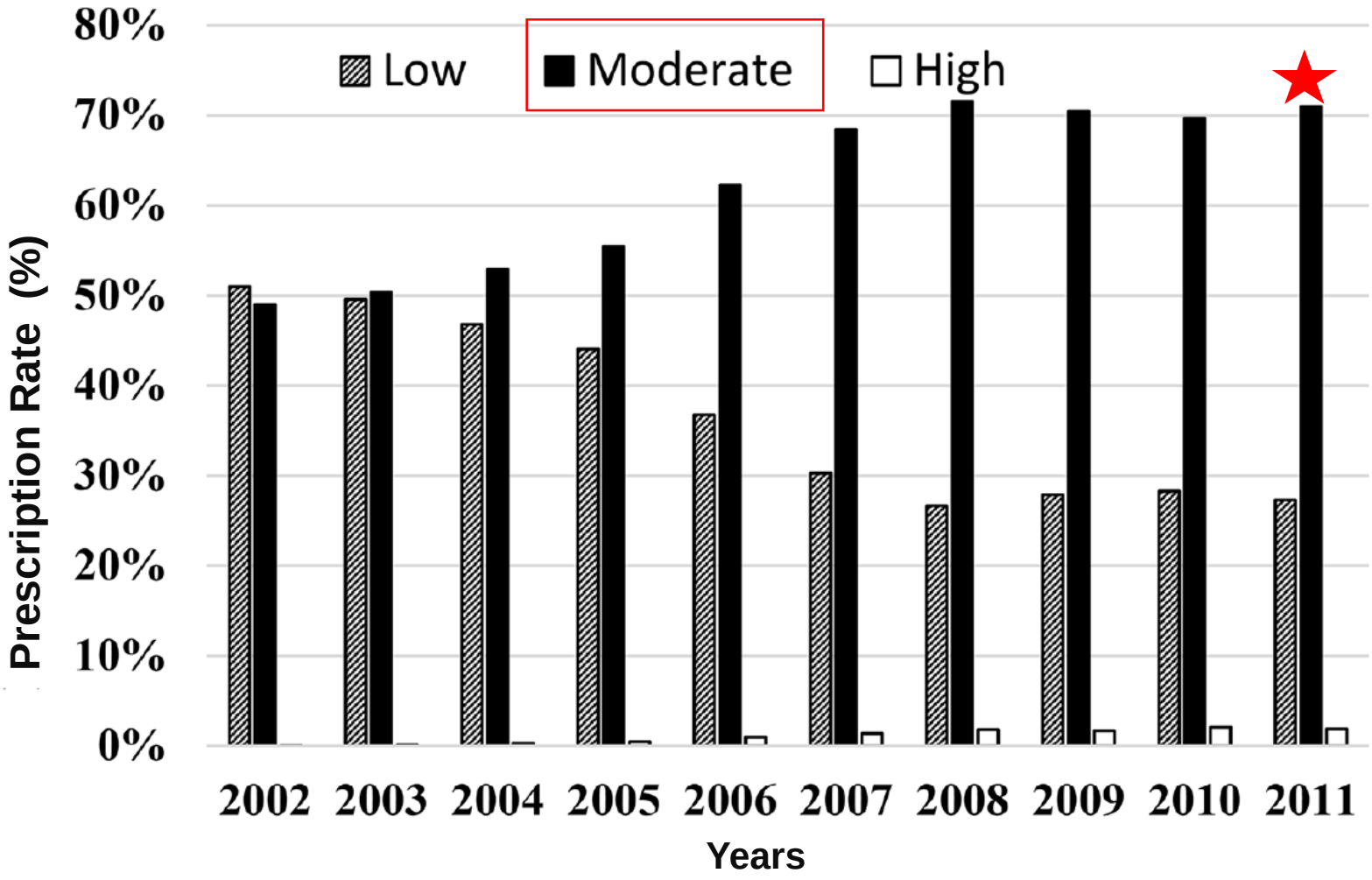
- In a secondary prevention trial, Japanese participants with CAD benefitted from a [moderate-intensity] dose of pitavastatin (S4.5.1-34)

- **Using a lower statin intensity in Japanese patients may give results similar to those seen with higher intensities in non-Japanese patients**

2019 ESC dyslipidemia guideline: Recommendation for aged >65y/o

Recommendations	Class[a]	Level[b]
Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients.[217]	I	A
Treatment with statins is recommended for primary prevention, according to the level of risk, in older people aged ≤75 years.[217]	I	A
Initiation of statin treatment for primary prevention in older people aged >75 years may be considered, if at high-risk or above.[217]	IIb	B
It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals.	I	C

Moderate intensity statin is more popular in TW



BMJ Open 2017;7:e014150

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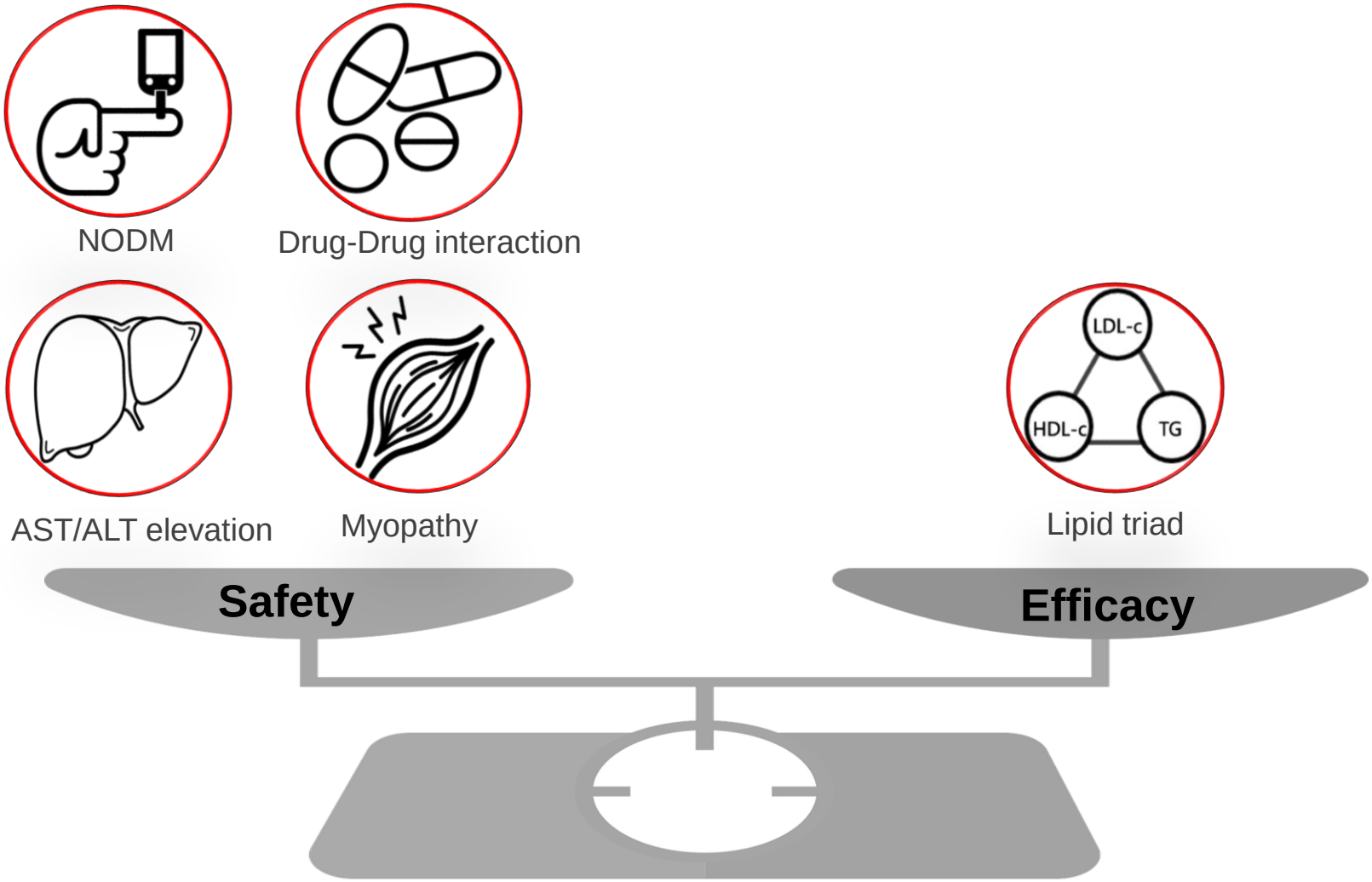
Which patient can get maximal benefit from pitavastatin?

Primary prevention:

Balance of efficacy and safety



全民健康保險降血脂藥物給付規定表

	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	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	

- 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：

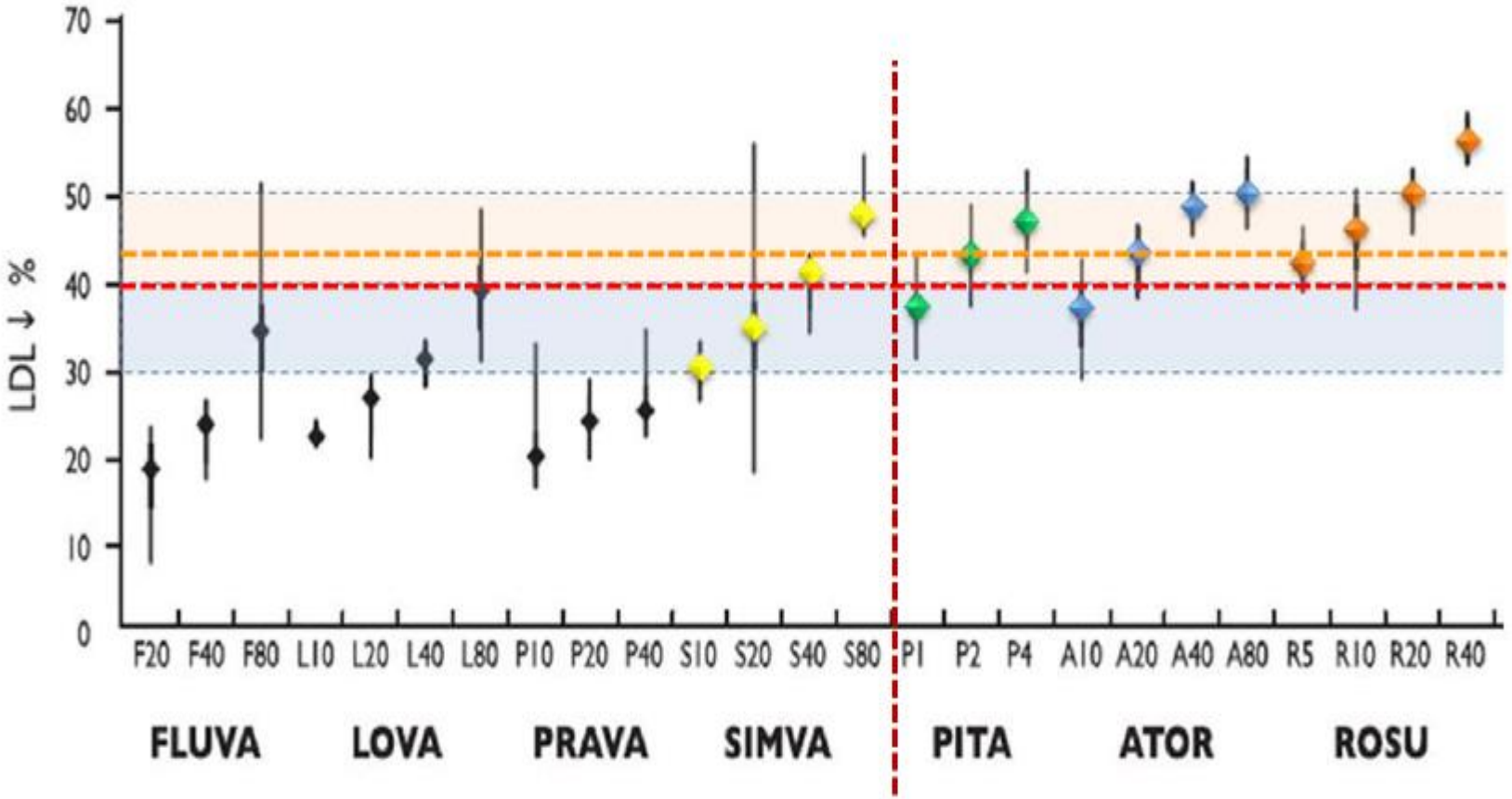
1. 腦梗塞。
2. 暫時性腦缺血患者(TIA)。（診斷須由神經科醫師確立）
3. 有症狀之頸動脈狹窄。（診斷須由神經科醫師確立）

- **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)。

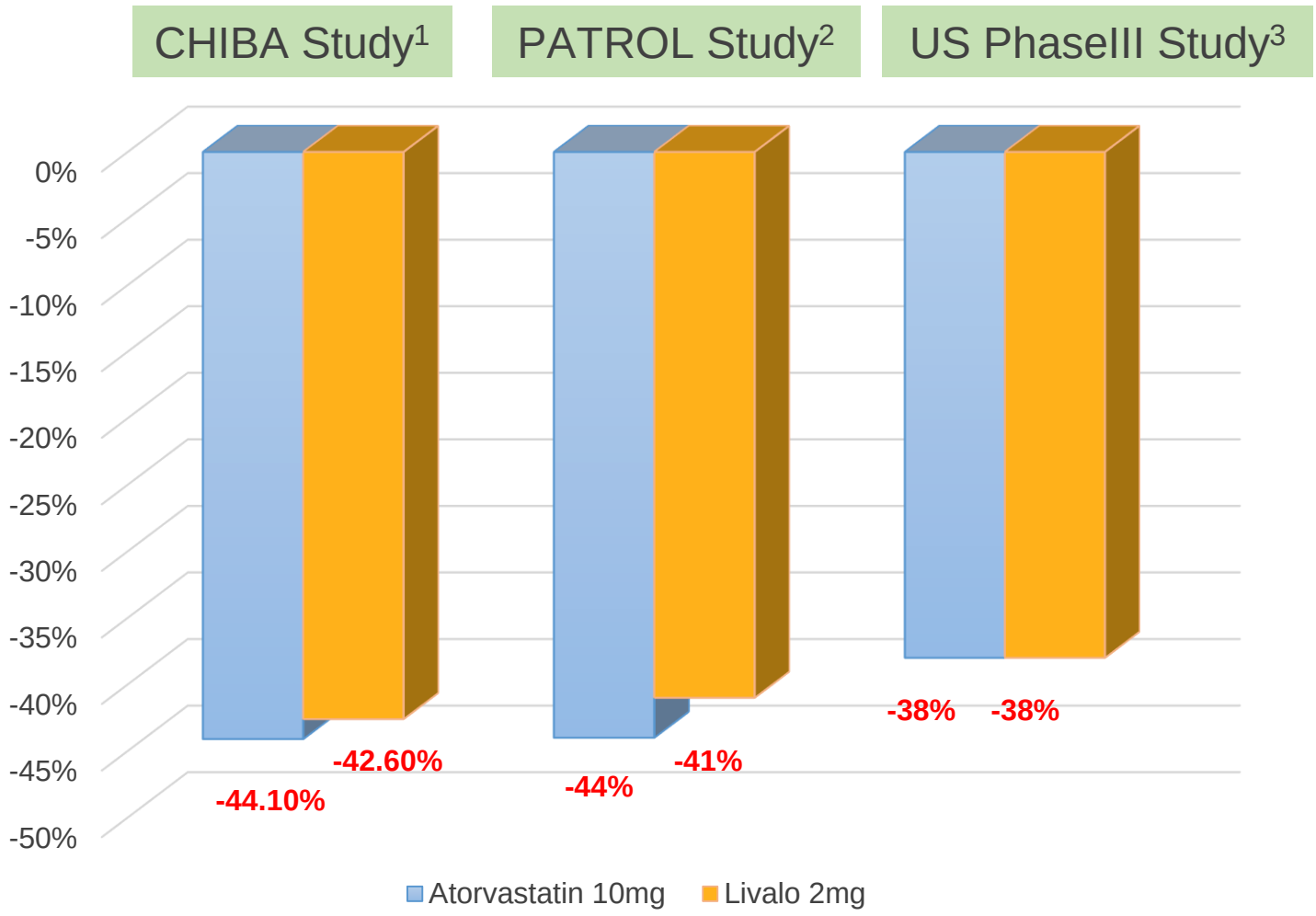
2016 ESC/EAS Guidelines

PITA, ATOR, ROSU all can reduce LDL > 40%



Weng TC, et al. J Clin Pharm Ther . 2010;35:139-151
Mukhtar RY, et Al. Int J Clin Pract . 2055;59(2):239-252

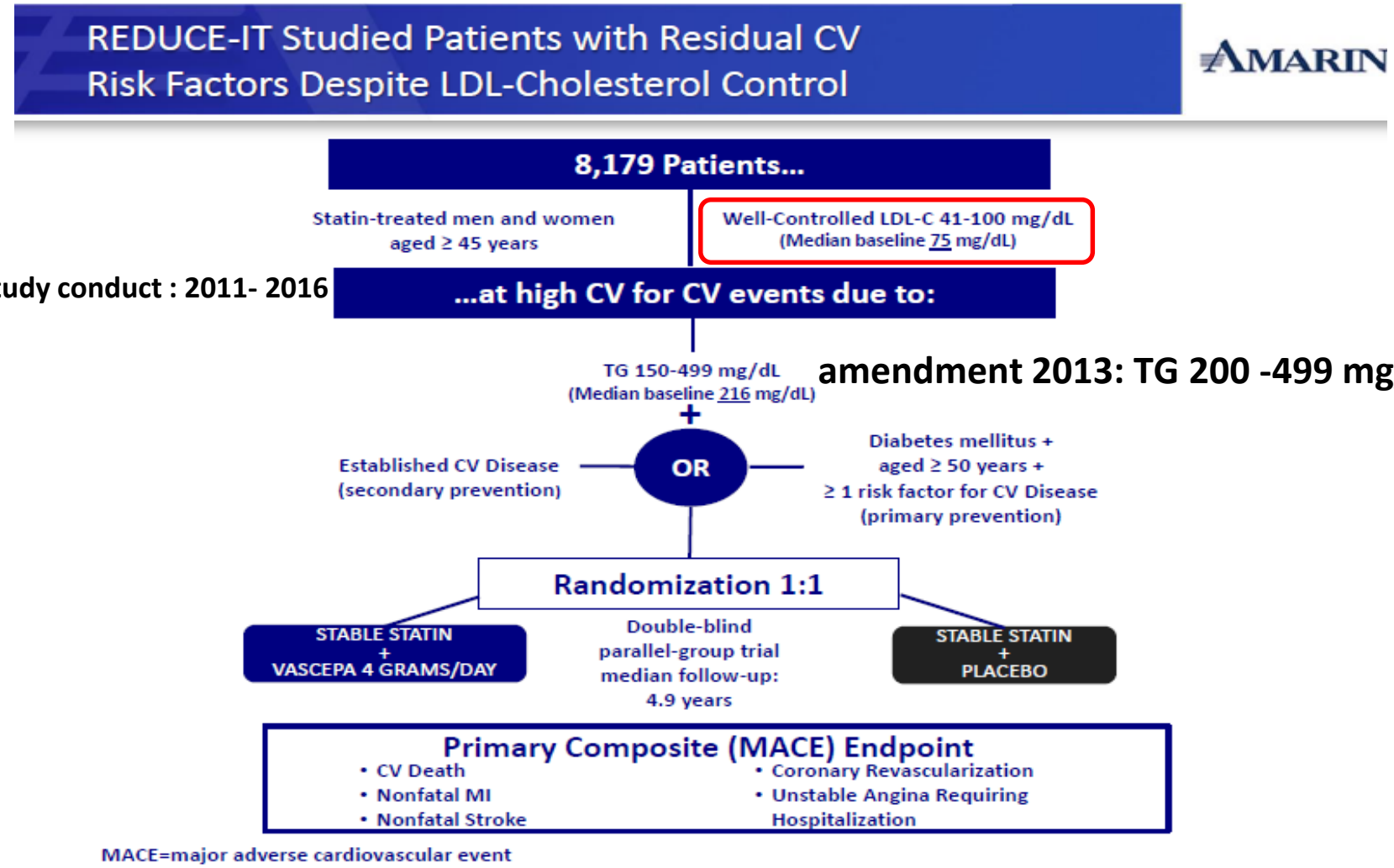
Efficacy of Pitavastatin on LDL-C



1.Atherosclerosis vol.201(2008) : 345-352
2.Circ. J. 2011 vol.73, NO.6 : 1493-1505
3.Clin. Lipidol. 2009, vol.4, NO.3 : 291-302

The NEW ENGLAND JOURNAL of MEDICINE

REDUCE-IT Study Design



Study conduct : 2011- 2016

amendment 2013: TG 200 -499 mg/dL

Design and rationale published in 2017 in Clinical Cardiology (Bhatt et Al. Clinical Cardiology.2017;40:138–148): 90% power to measure a 15% reduction in MACE primary endpoint.

Bhatt, et al,N Engl J Med 2019; 380:11-22

Baseline Lipids Levels

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Icosapent Ethyl (N = 4089)	Placebo (N = 4090)
Median high-sensitivity CRP level (IQR) — mg/liter	2.2 (1.1–4.5)	2.1 (1.1–4.5)
Median triglyceride level (IQR) — mg/dl	216.5 (176.5–272.0)	216.0 (175.5–274.0)
Median HDL cholesterol level (IQR) — mg/dl	40.0 (34.5–46.0)	40.0 (35.0–46.0)
Median LDL cholesterol level (IQR) — mg/dl	74.0 (61.5–88.0)	76.0 (63.0–89.0)
Distribution of triglyceride levels — no./total no. (%)		
<150 mg/dl	412/4086 (10.1)	429/4089 (10.5)
≥150 to <200 mg/dl	1193/4086 (29.2)	1191/4089 (29.1)
≥200 mg/dl	2481/4086 (60.7)	2469/4089 (60.4)
Triglyceride level ≥200 mg/dl and HDL cholesterol level ≤35 mg/dl — no. (%)	823 (20.1)	794 (19.4)
Median eicosapentaenoic acid level (IQR) — μg/ml	26.1 (17.1–40.1)	26.1 (17.1–39.9)

Bhatt, et al,N Engl J Med 2019; 380:11-22

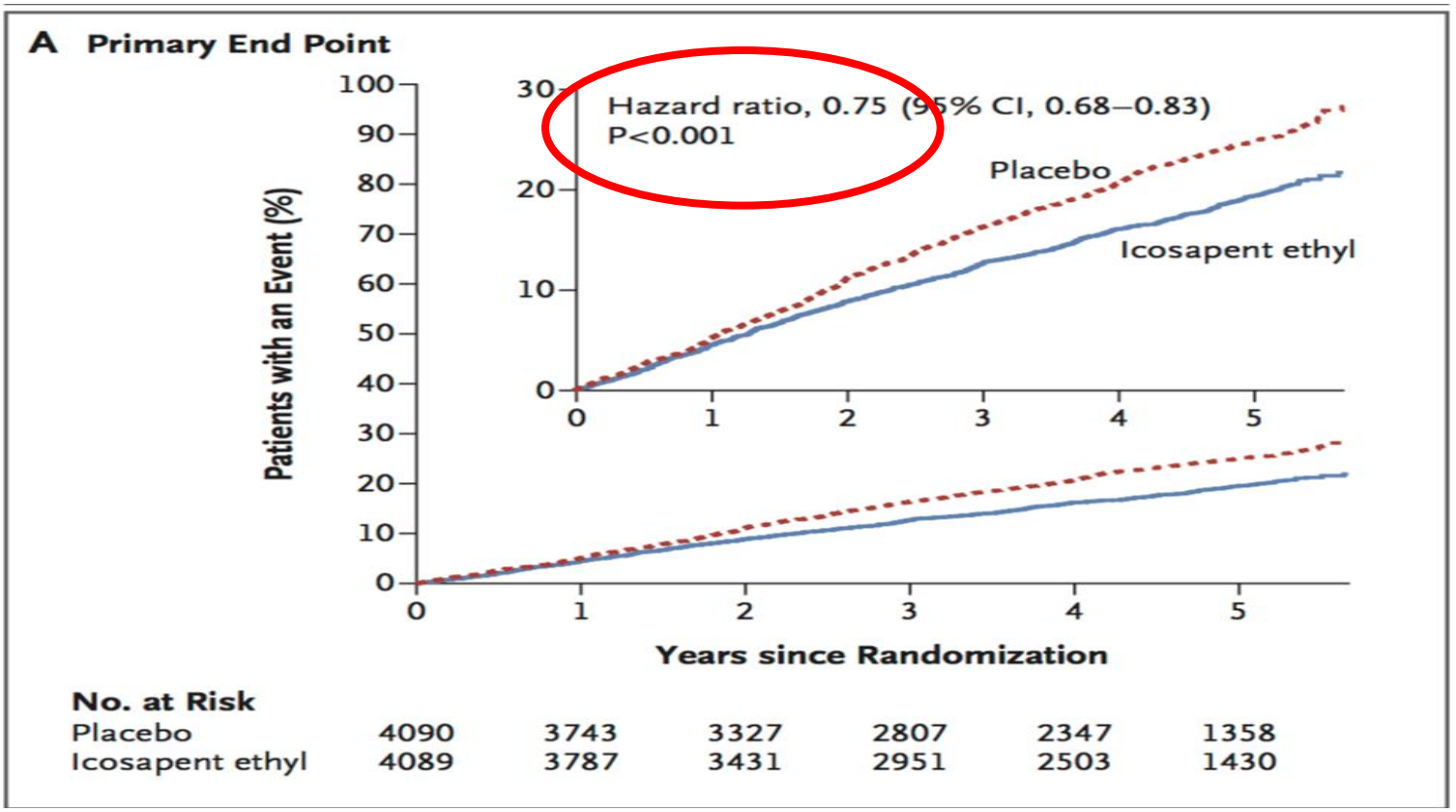
Biomarkers changes (from baseline to year 1)

	Icosapent Ethyl (N=4089) Median		Placebo (N=4090) Median		Median Between Group Difference at Year 1		
Biomarker*	Baseline	Year 1	Baseline	Year 1	Absolute Change from Baseline	% Change from Baseline	% Change P-value
Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7	<0.0001
Non-HDL-C (mg/dL)	118.0	113.0	118.5	130.0	-15.5	-13.1	<0.0001
LDL-C (mg/dL)	74.0	77.0	76.0	84.0	-5.0	-6.6	<0.0001
HDL-C (mg/dL)	40.0	39.0	40.0	42.0	-2.5	-6.3	<0.0001
Apo B (mg/dL)	82.0	80.0	83.0	89.0	-8.0	-9.7	<0.0001
hsCRP (mg/L)	2.2	1.8	2.1	2.8	-0.9	-39.9	<0.0001
Log hsCRP (mg/L)	0.8	0.6	0.8	1.0	-0.4	-22.5	<0.0001
EPA (µg/mL)	26.1	144.0	26.1	23.3	+114.9	+358.8	<0.0001

*Apo B and hsCRP were measured at Year 2.

Bhatt, et al,N Engl J Med 2019; 380:11-22

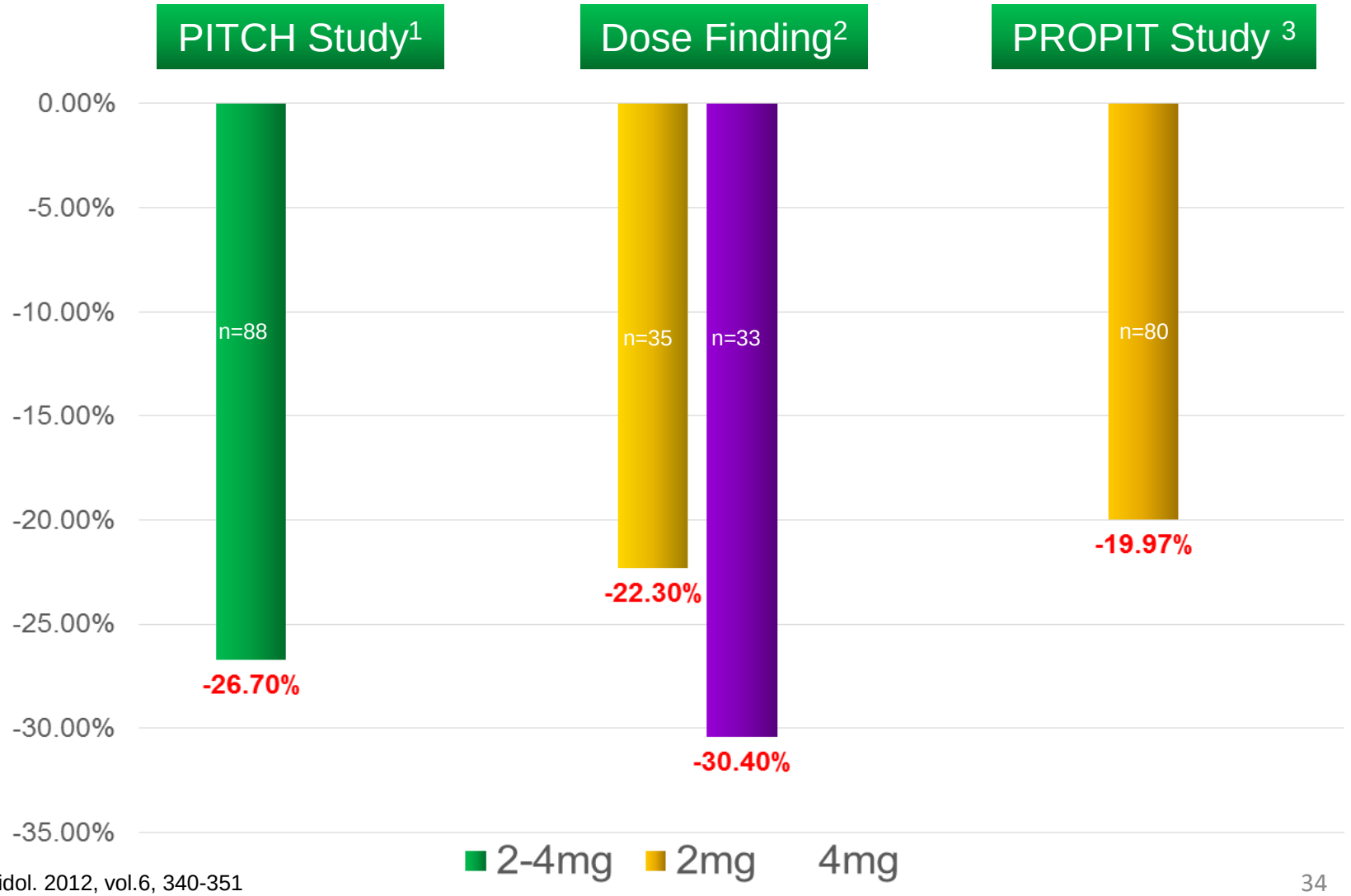
Primary endpoint



- **Primary EP: CV Death, nonfatal MI, nonfatal stroke, coronary revascularization or unstable angina (5 point MACE)**
- **Median follow-up 4.9 years**
- Primary (5-MACE): RRR=24.8%; ARR=4.8%; NNT 21
- **CV event curve for VASCEPA visually separated from the placebo event curve at approximately 1 year and remained separated throughout follow-up period**

Bhatt, et al,N Engl J Med 2019; 380:11-22

Efficacy of Pitavastatin on TG



1.J of Clin. Lipidol. 2012, vol.6, 340-351
2.Drug Res. 2002,vol.52,NO.4 : 251-255
3.Clin. Endo. 2014,vol.82,NO.5 : 670-677

European Heart Journal (2016) **37**, 2999–3058
doi:10.1093/eurheartj/ehw272

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

7.4 Statins

Since statins have significant effects on mortality as well as most CVD outcome parameters, these drugs are the first choice to reduce both total CVD risk and moderately elevated TG levels. More potent statins (atorvastatin, rosuvastatin and pitavastatin) demonstrate a robust lowering of TG levels, especially at high doses and in patients with elevated TGs. In subgroup analyses from statin trials, the risk reduction is the same in subjects with HTG as in normotriglyceridaemic subjects.

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European Heart Journal (2016) **37**, 2999–3058
doi:10.1093/eurheartj/ehw272

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

7.4 Statins

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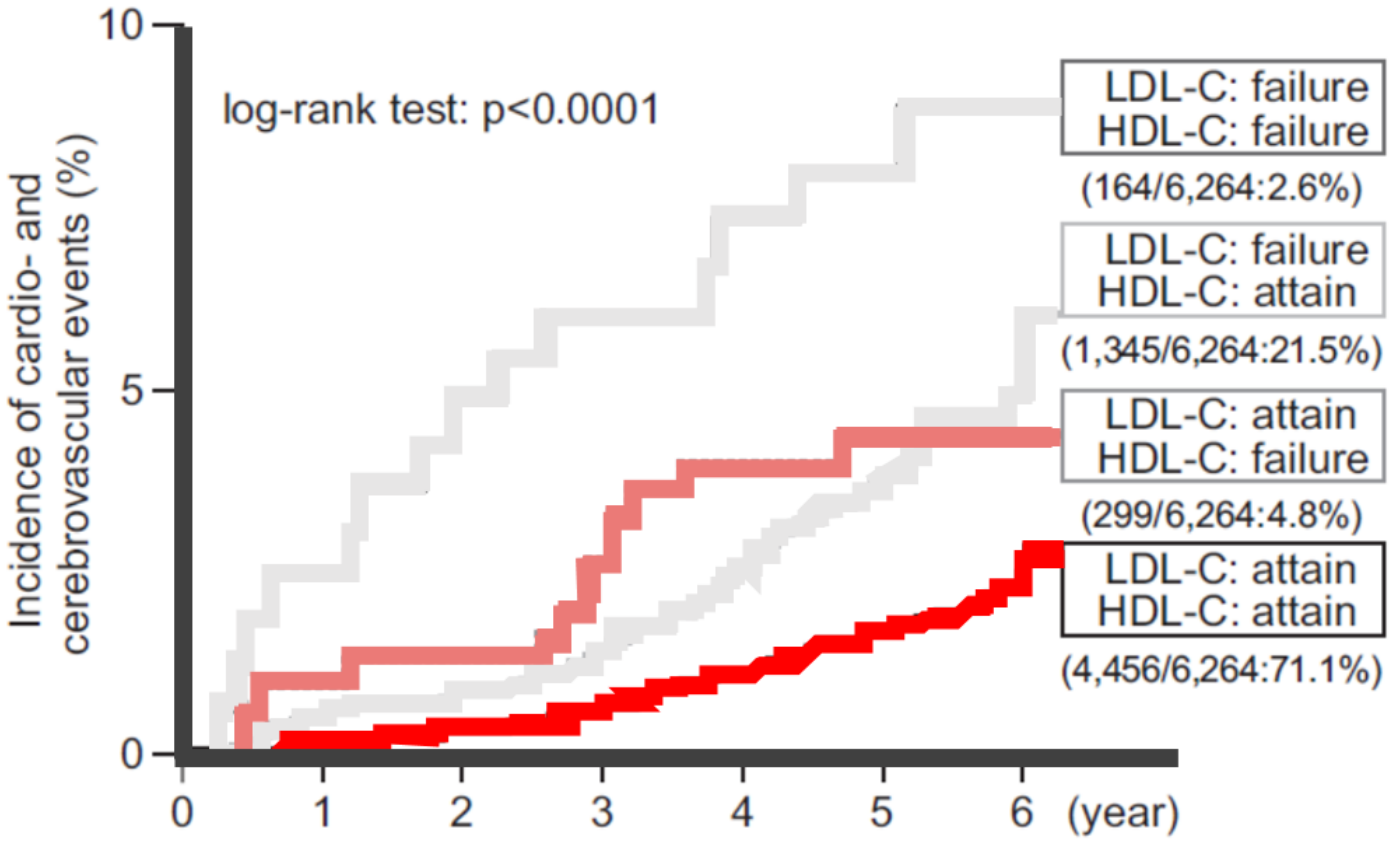
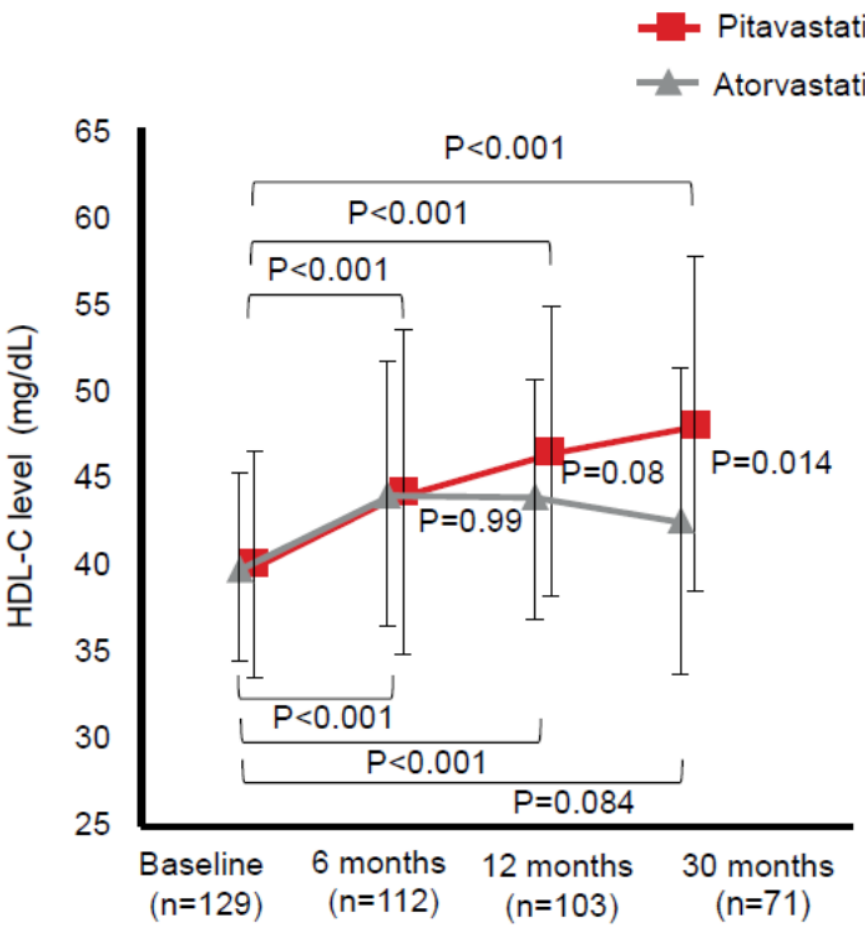
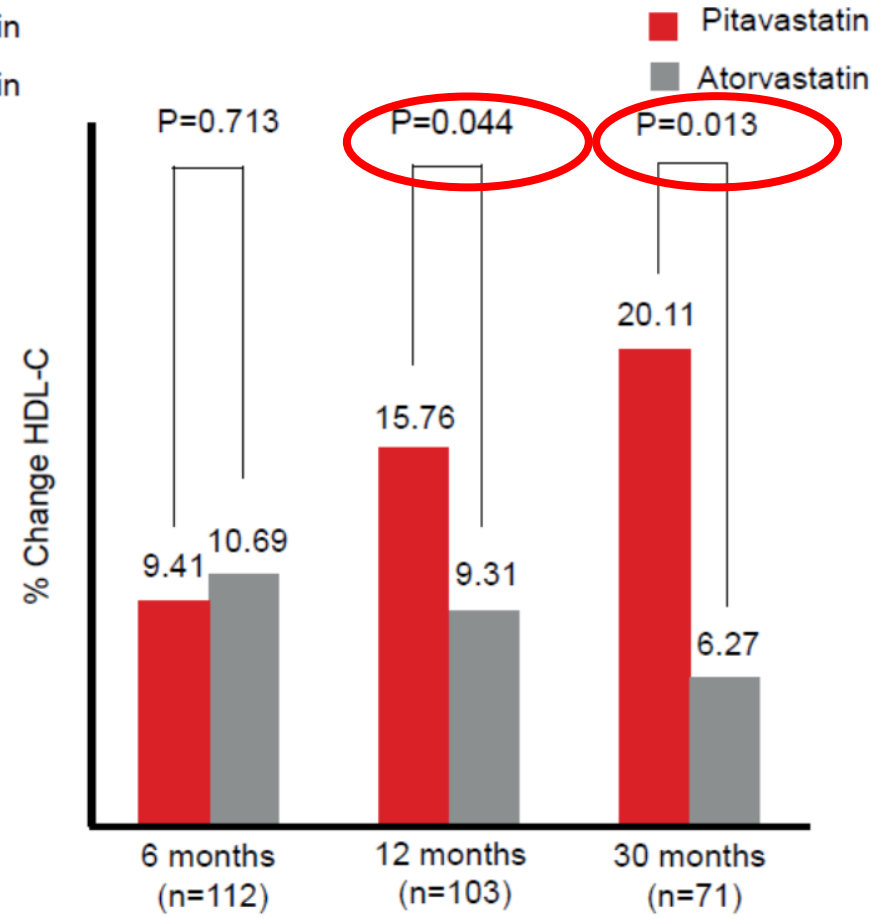
Both LDL & HDL are important for reducing cardiovascular events (Live study)



Teramoto T. Atherosclerosis Supplements 2011;12:285-8.

Efficacy of pitavastatin on HDL-C (COMPACT-CAD Study)

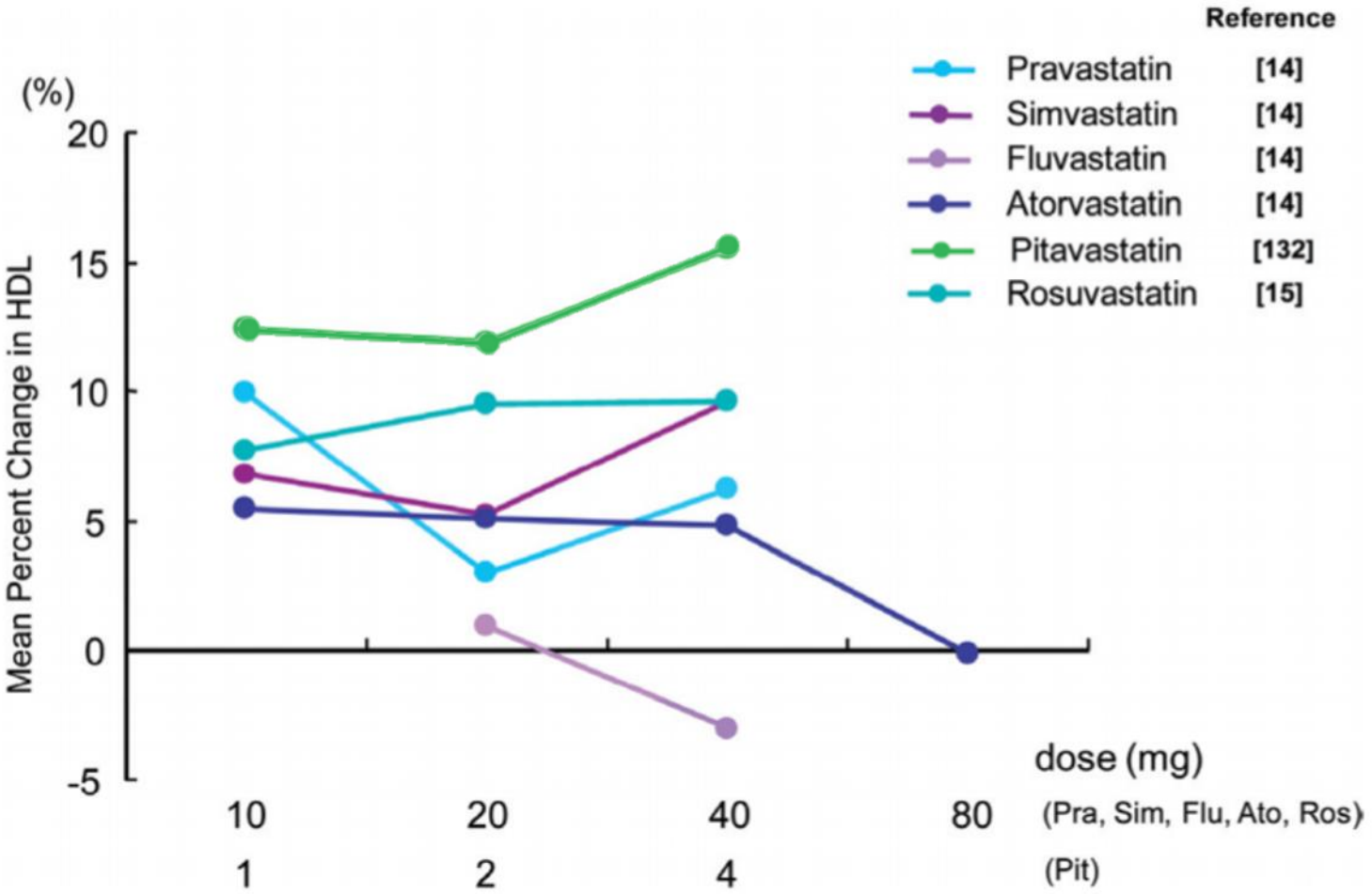




Baseline HDL-C (mg/dL):
Pitavastatin 39.9 ±6.5 Atorvastatin 40.1±5.5

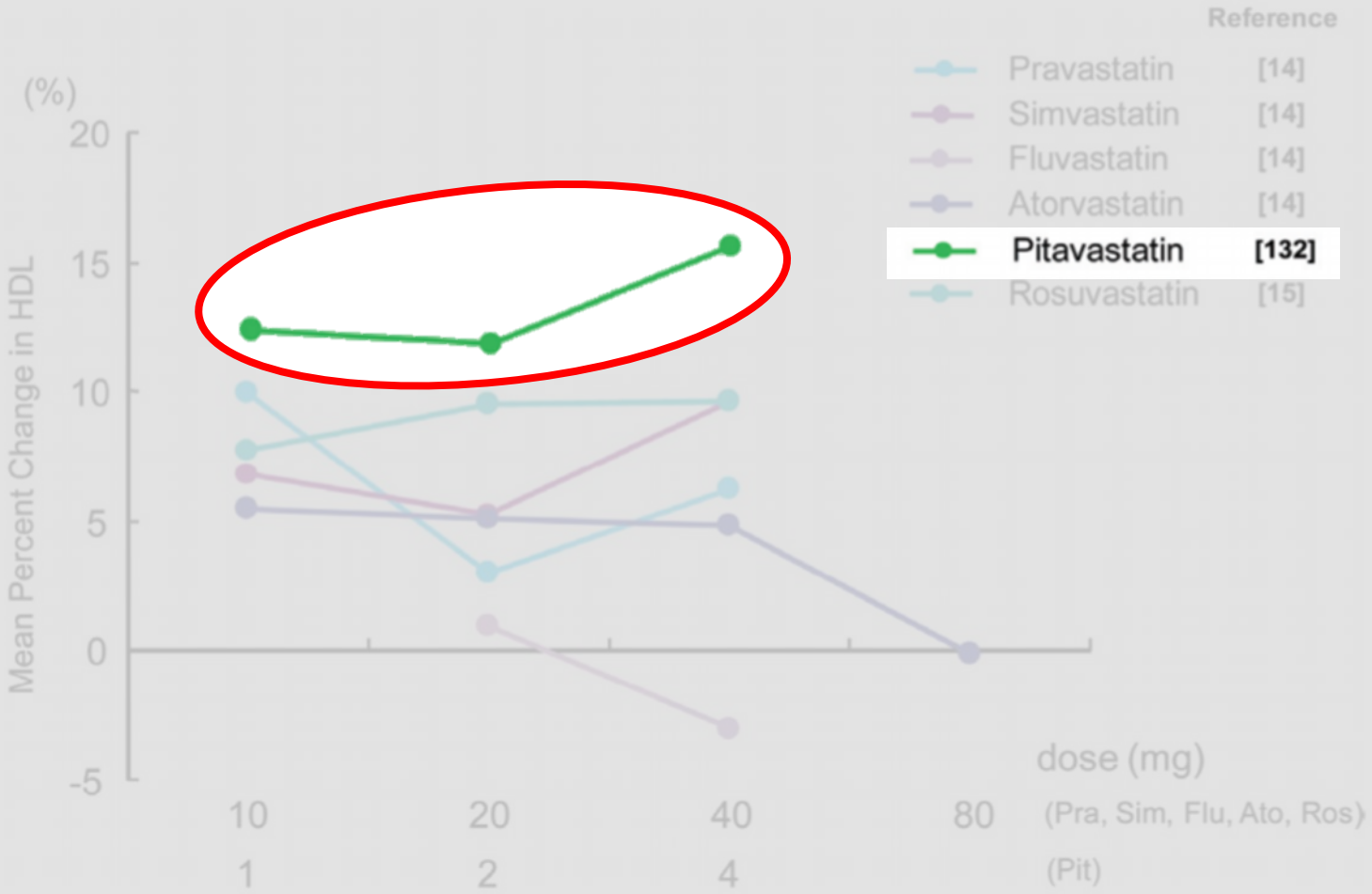
Journal of Cardiology 62 (2013) 87–94

Pitavastatin can elevate HDL effectively



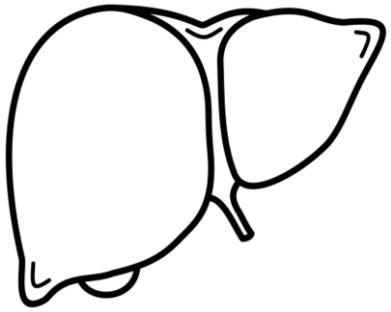
Am J Cardiol, 1998;81 582-587
Am J Cardiol, 2003;92 152-160
Por Med, 2004: 249-14

Pitavastatin can elevate HDL effectively



Am J Cardiol, 1998;81 582-587
Am J Cardiol, 2003;92 152-160
Por Med, 2004: 249-14

Glucose fluctuation & NODM



AST/ALT elevation

Drug-Drug interaction

Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials

Naveed Sattar, David Preiss, Heather M Murray, Paul Welsh, Brendan M Buckley, Anton J M de Craen, Sreenivasa Rao Kondapally Seshasai, John J McMurray, Dilys J Freeman, J Wouter Jukema, Peter W Macfarlane, Chris J Packard, David J Stott, Rudi G Westendorp, James Shepherd, Barry R Davis, Sara L Pressel, Roberto Marchioli, Rosa Maria Marfisi, Aldo P Maggioni, Luigi Tavazzi, Gianni Tognoni, John Kjekshus, Terje R Pedersen, Thomas J Cook, Antonio M Gotto, Michael B Clearfield, John R Downs, Haruo Nakamura, Yasuo Ohashi, Kyoichi Mizuno, Kausik K Ray, Ian Ford

用statin治療255 個病人4 年會額外增加1 個DM, 但可預防5.4 個心血管事件發生

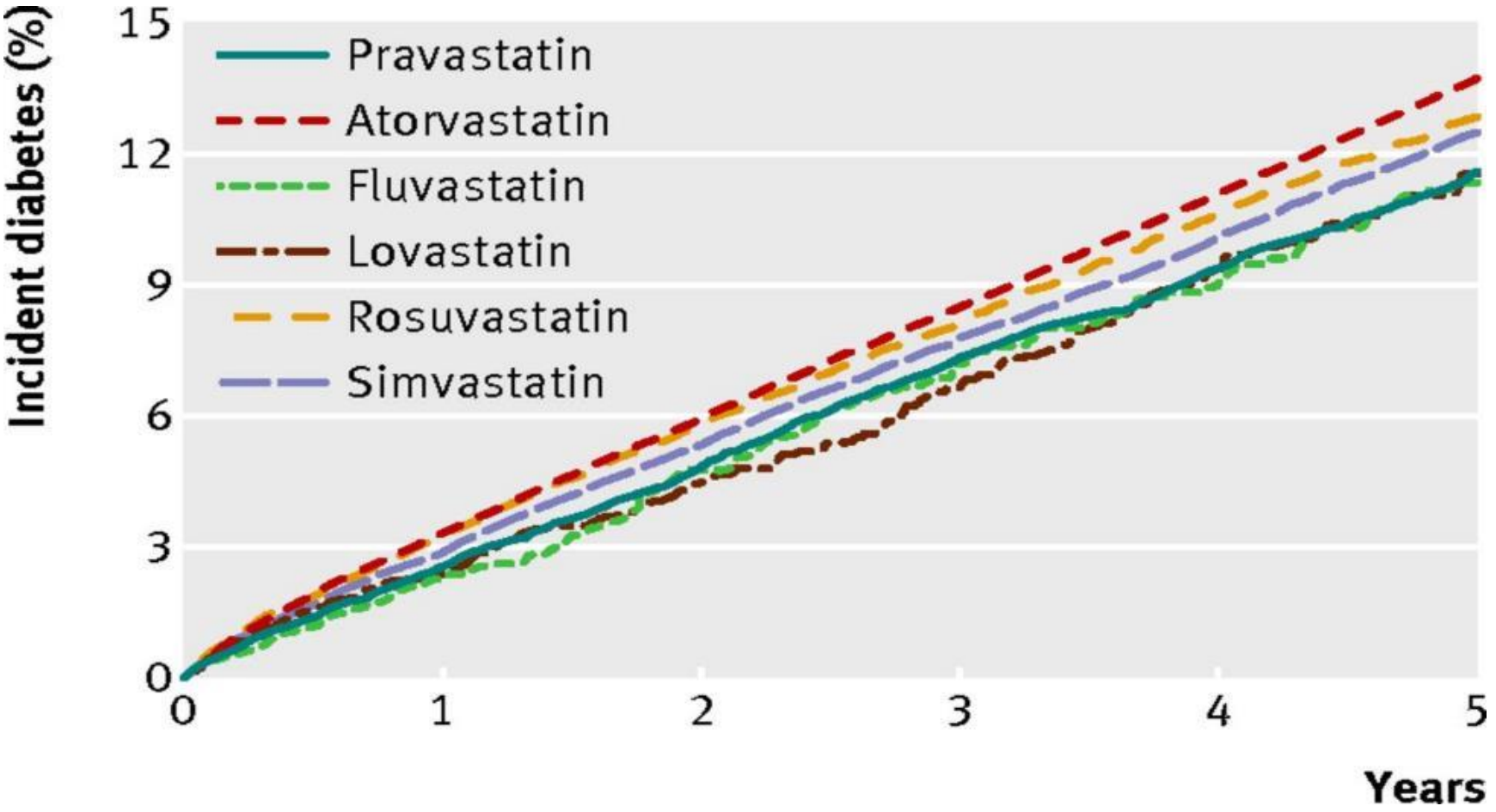
Methods We searched Medline, Embase, and the Cochrane Central Register of Controlled Trials from 1994 to 2009, for randomised controlled endpoint trials of statins. We included only trials with more than 1000 patients, with identical follow-up in both groups and duration of more than 1 year. We excluded trials of patients with organ transplants or who needed haemodialysis. We used the I^2 statistic to measure heterogeneity between trials and calculated risk estimates for incident diabetes with random-effect meta-analysis.

Findings We identified 13 statin trials with 91140 participants, of whom 4278 (2226 assigned statins and 2052 assigned control treatment) developed diabetes during a mean of 4 years. 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 (I^2=11%) between trials. Meta-regression showed that risk of development of diabetes with statins was highest in trials with older participants, but neither baseline body-mass index nor change in LDL-cholesterol concentrations accounted for residual variation in risk. Treatment of 255 (95% CI 150–852) patients with statins for 4 years resulted in one extra case of diabetes.

Interpretation Statin therapy is associated with a slightly increased risk of development of diabetes, but the risk is low both in absolute terms and when compared with the reduction in coronary events. Clinical practice in patients with moderate or high cardiovascular risk or existing cardiovascular disease should not change.

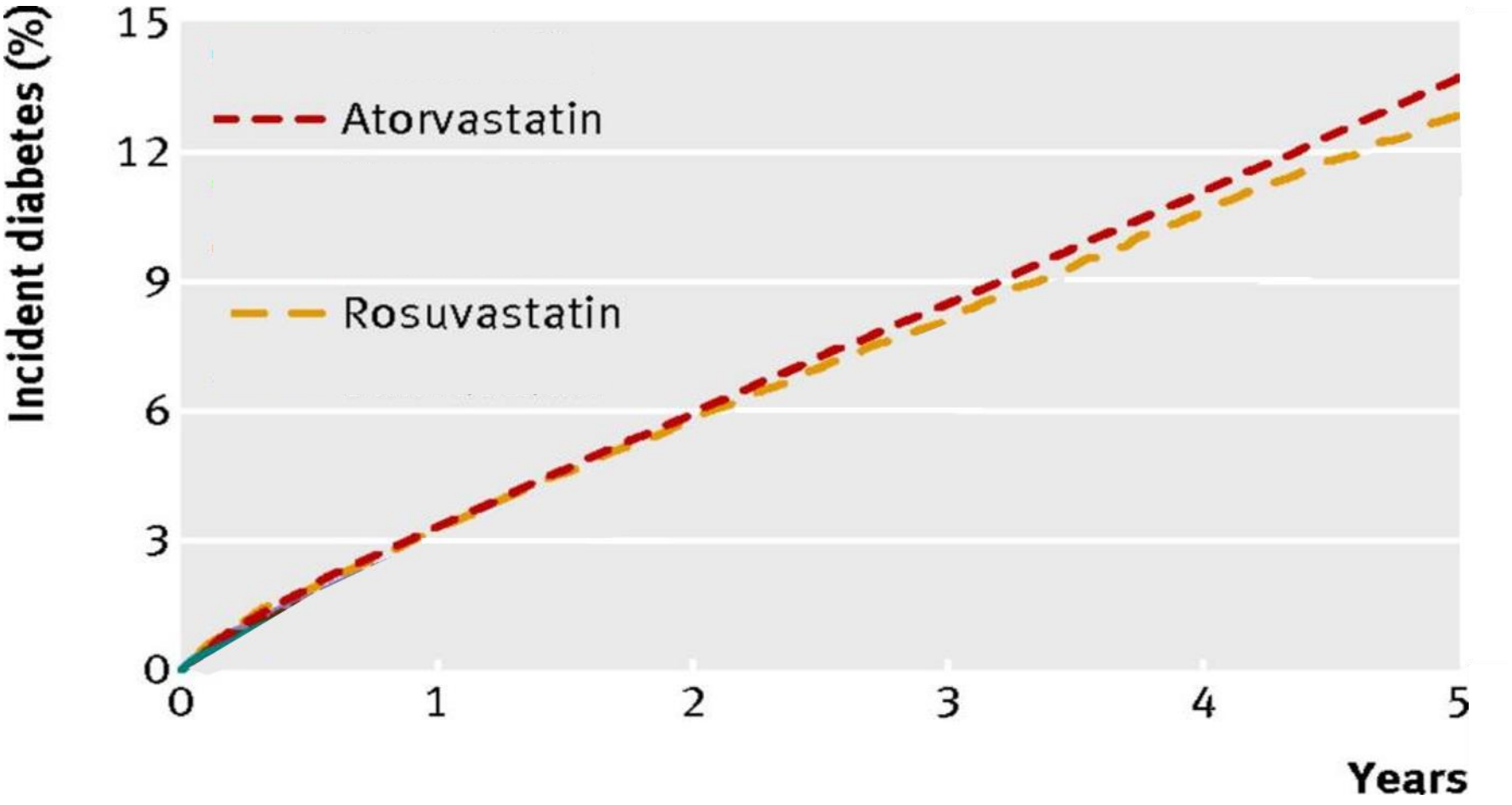
Lancet 2010; 375: 735–42

Adjusted survival curves for incident diabetes among new users of statins



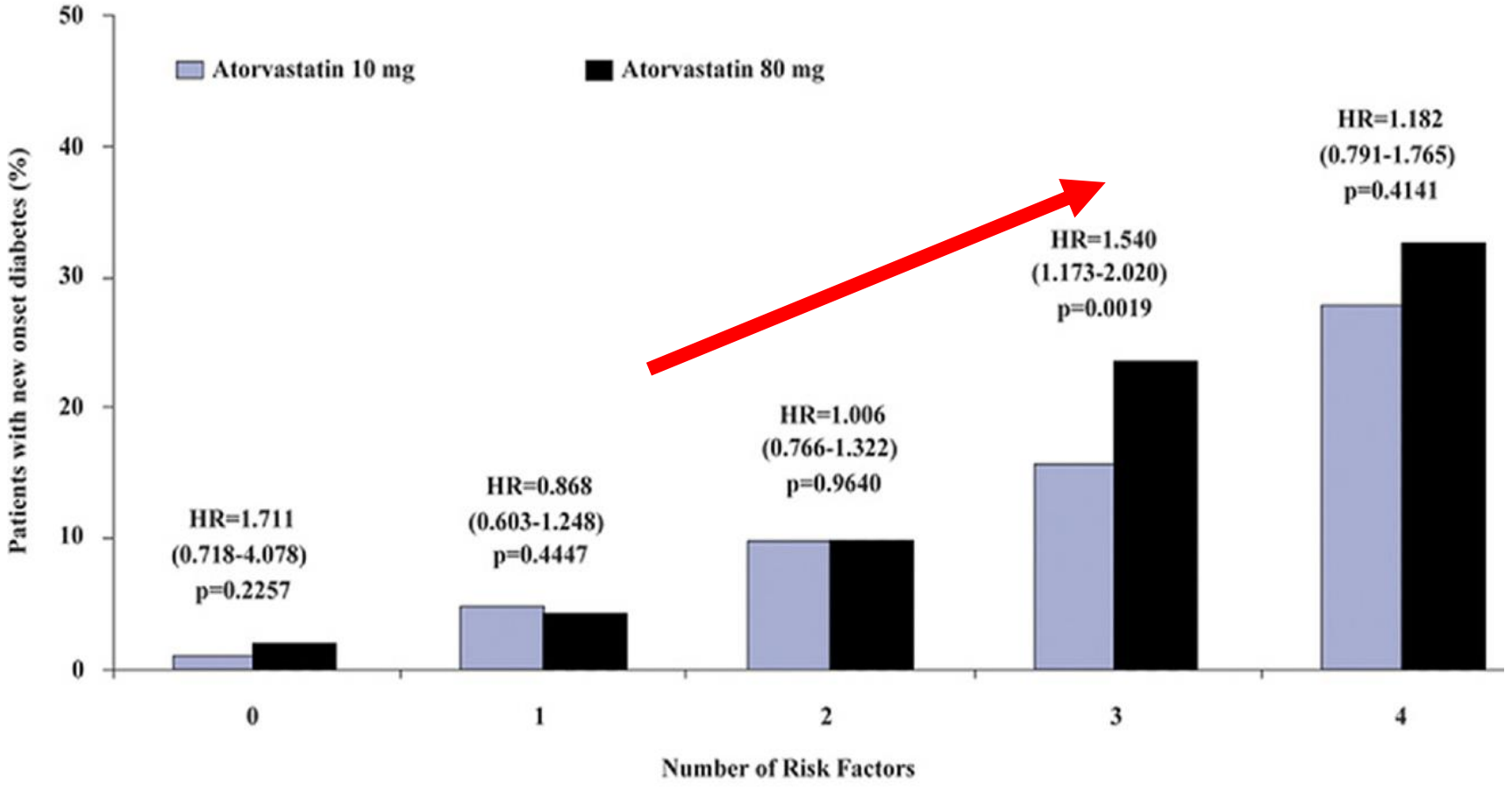
Carter A A et al. BMJ 2013;346:bmj.f2610

Adjusted survival curves for incident diabetes among new users of statins



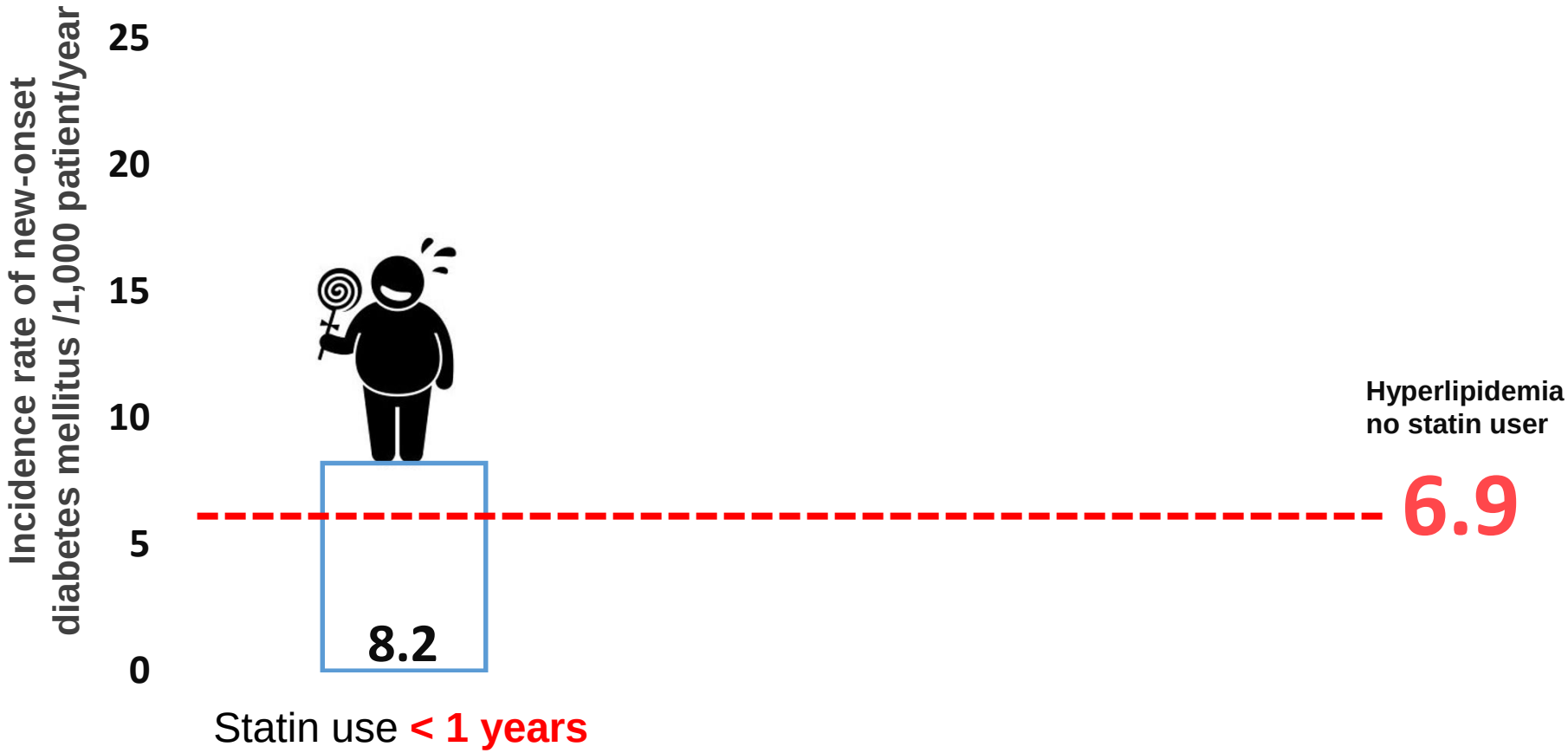
Carter A A et al. BMJ 2013;346:bmj.f2610

Statin induced-NODM is Dose dependent



Diabetes Care 2006; 29:1220-1226

Statin induced-NODM is Time dependent



J Am Heart Assoc 2019 Apr 16;8(8):e011320

Clock is ticking….

Effect of pitavastatin on new onset DM

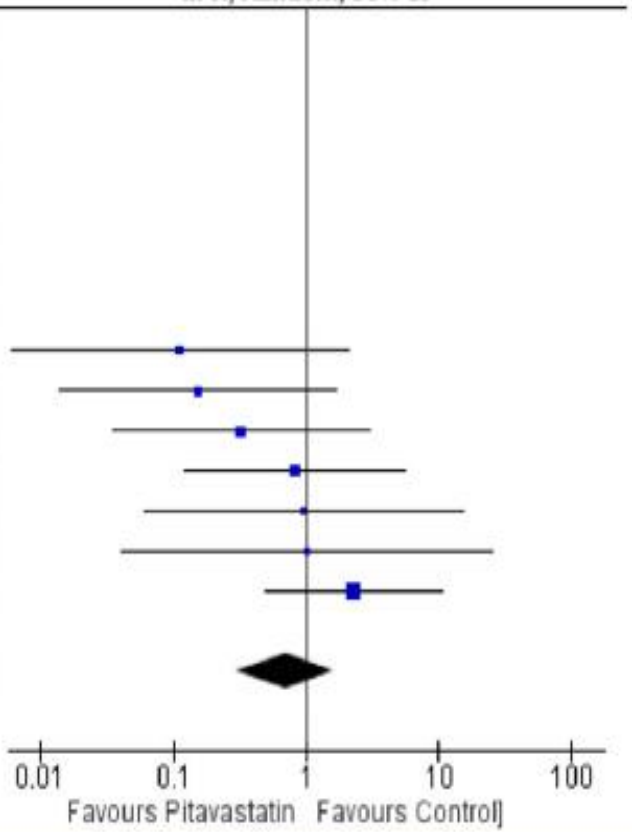
C. New onset diabetes – Risk Ratio

Study or Subgroup	Pitavastatin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Eriksson M et al, 2011	0	218	0	111		Not estimable
NK-104-203	0	202	0	49		Not estimable
PREVAIL-US	0	143	0	131		Not estimable
NK-104-202	0	206	0	54		Not estimable
PAPAGO-T	0	50	0	50		Not estimable
PEACE	0	70	0	81		Not estimable
VISION	0	21	0	21		Not estimable
Stender S et al, 2013	0	597	0	288		Not estimable
INTREPID	0	123	4	124	8.2%	0.11 [0.01, 2.06]
Budinski D et al, 2009	1	576	2	179	12.1%	0.16 [0.01, 1.70]
COMPACT-CAD	1	36	3	35	14.2%	0.32 [0.04, 2.97]
TRUTH	2	38	2	31	19.3%	0.82 [0.12, 5.46]
Saito Y et al, 2002	1	84	1	81	9.2%	0.96 [0.06, 15.16]
Ose L et al, 2009	1	592	0	202	6.8%	1.03 [0.04, 25.11]
NK-104-4.01CH	9	280	2	142	30.2%	2.28 [0.50, 10.42]
Total (95% CI)		**3236**		**1579**	**100.0%**	**0.70 [0.30, 1.61]**
Total events	15		14			

Pr
At
At
Pr
Pr
Si
At

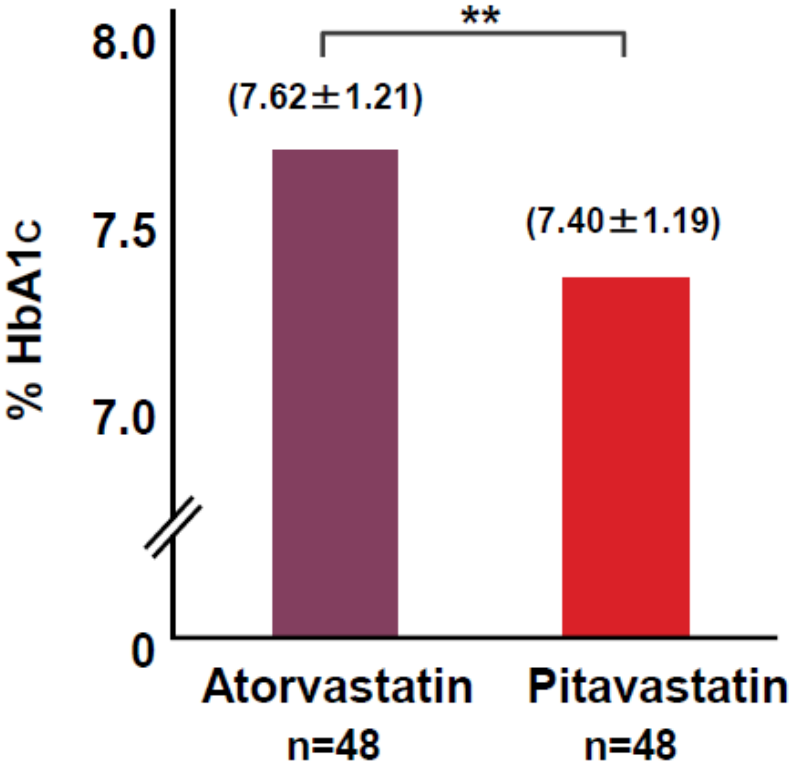
Heterogeneity: Tau² = 0.00; Chi² = 5.97, df = 6 (P = 0.43); I² = 0%

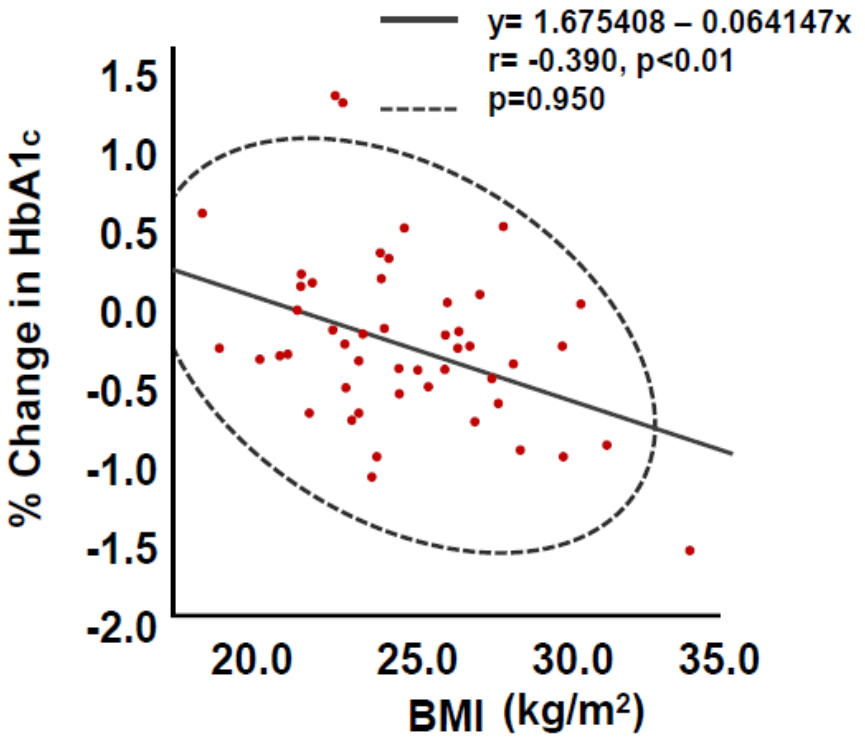
Test for overall effect: Z = 0.84 (P = 0.40)



Atherosclerosis 2015 Volume 241, Issue 2, Pages 409–418

Pitavasatin have better outcome in HbA1c compared to atorvastatin





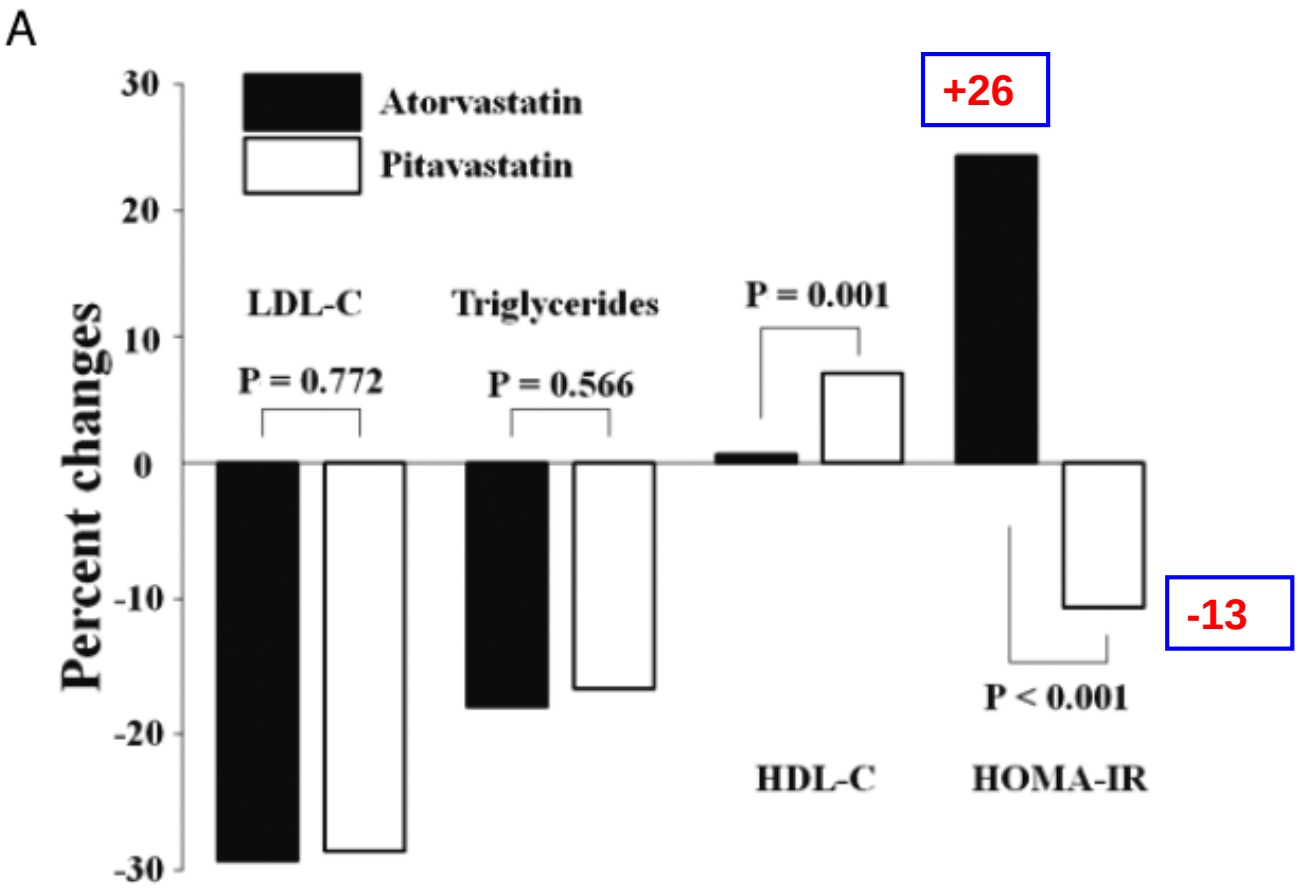
Patients: Hypercholesterolemia with type 2 Diabetes (n=48)

Method : Patients receiving atorvastatin 10mg/day for 6 months switched to pitavastatin mg/day for at least another 6 months

Yasumoto S, er al. Pharma medica 2007 25(5) 155-160

Pitavastatin may have greater benefits for improving insulin resistance

(A) Changes in the lipid profiles and HOMA-IR



J Atheroscler Thromb, 2015; 22: 1158-1171.

Potent statins台灣仿單

Livalo

病患接受HMG-CoA 還原酶抑制劑治療後，曾有醣化血色素/或空腹血漿血糖上升情況，但依上市後安全監測或預測性研究，pitavastatin 並未有明確造成糖尿病徵兆

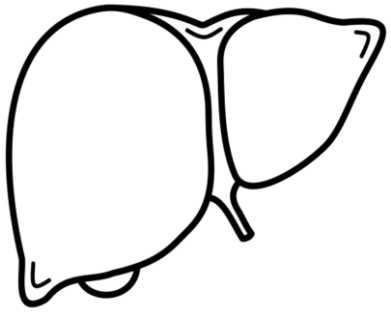
Lipitor

醣化血色素上升，病患接受HMG-CoA 還原酶抑制劑治療後，曾有醣化血色素/或空腹血漿血糖上升情況

Crestor

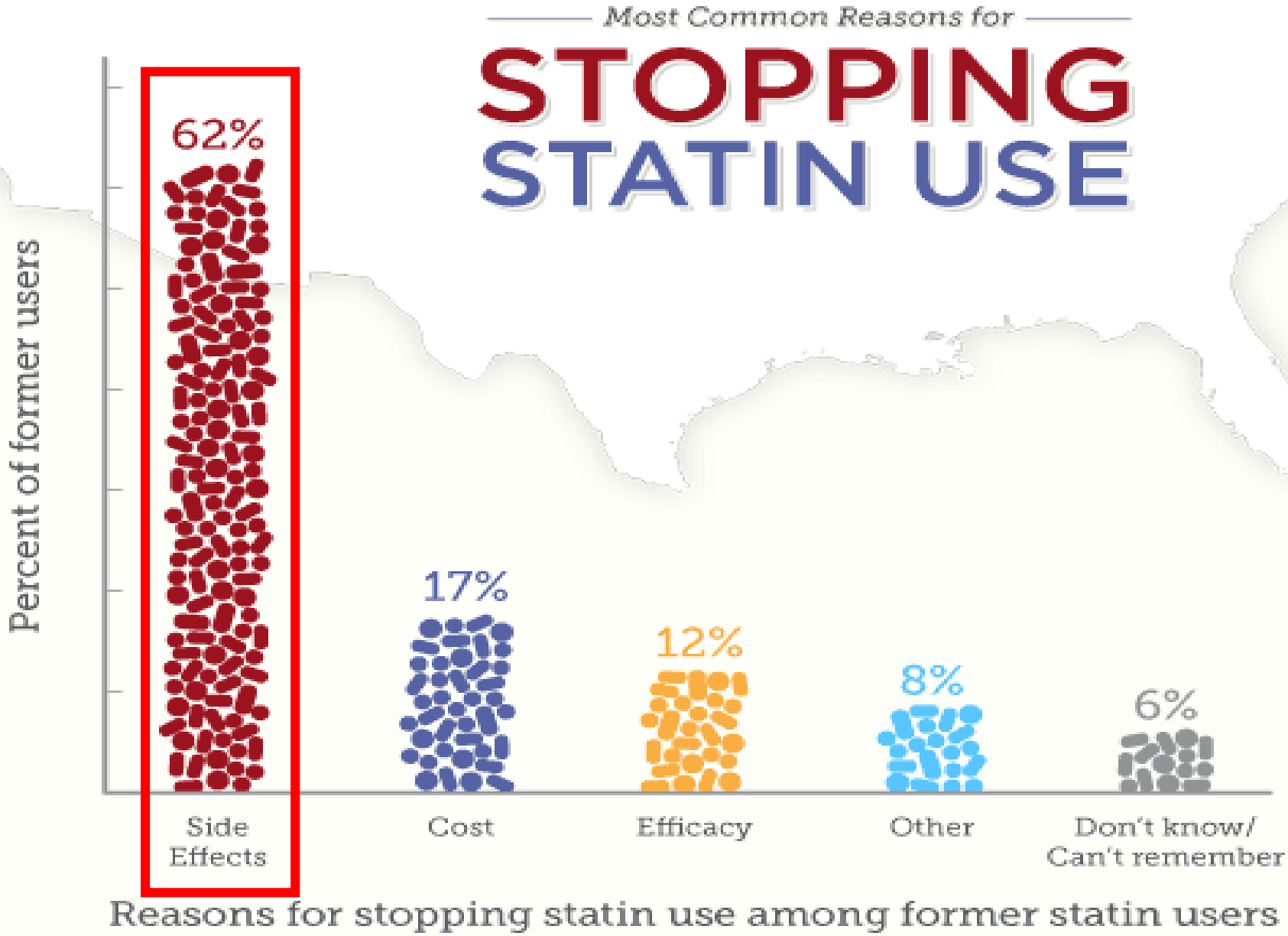
醣化血色素上升，病患接受HMG-CoA 還原酶抑制劑治療後，曾有醣化血色素/或空腹血漿血糖上升情況。使用 HMG-CoA 還原酶抑制劑(包括Crestor)曾有HbA_{1c}和空腹血糖值增加的報告

Glucose fluctuation & NODM



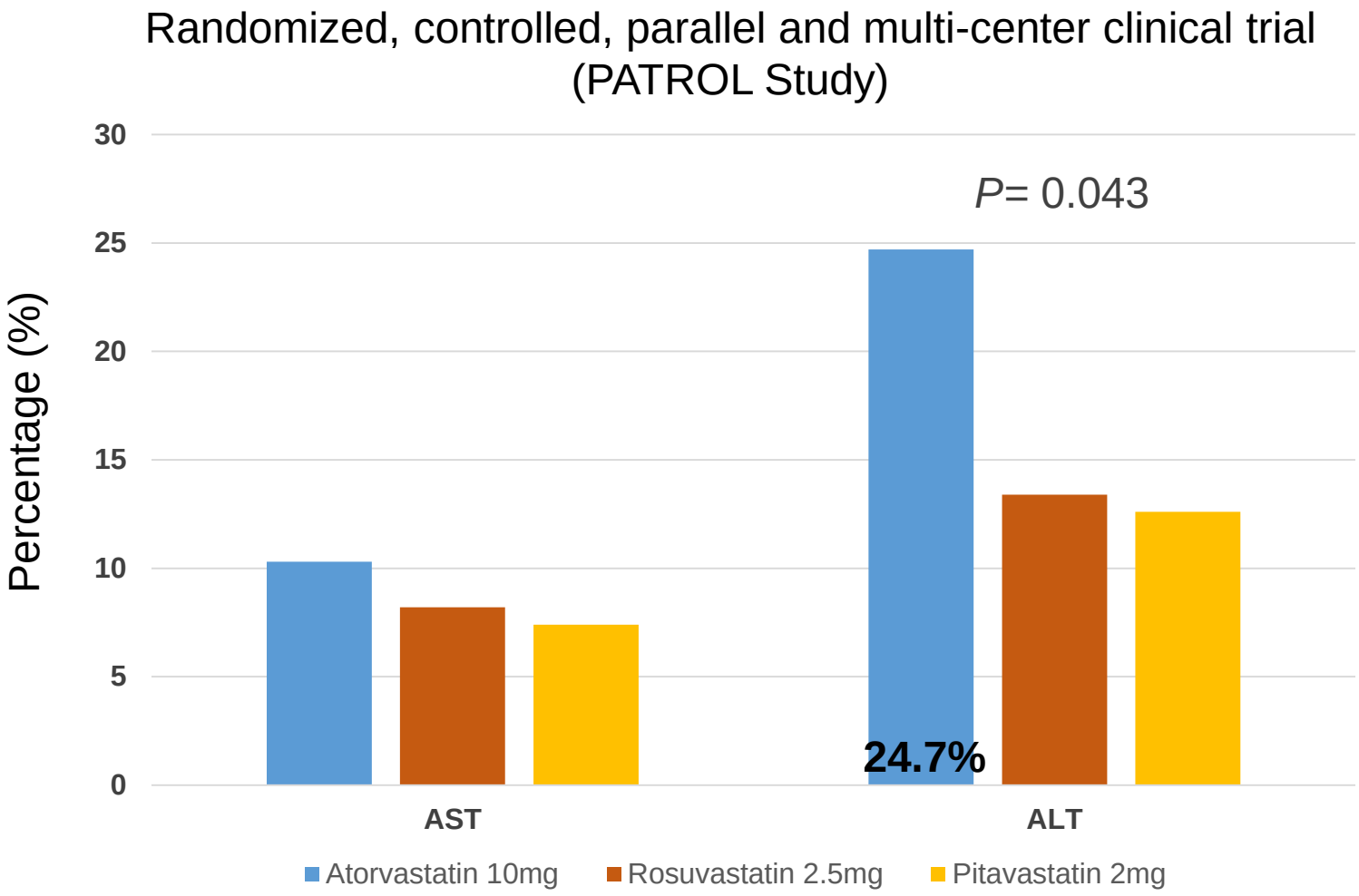
AST/ALT elevation

Drug-Drug interaction



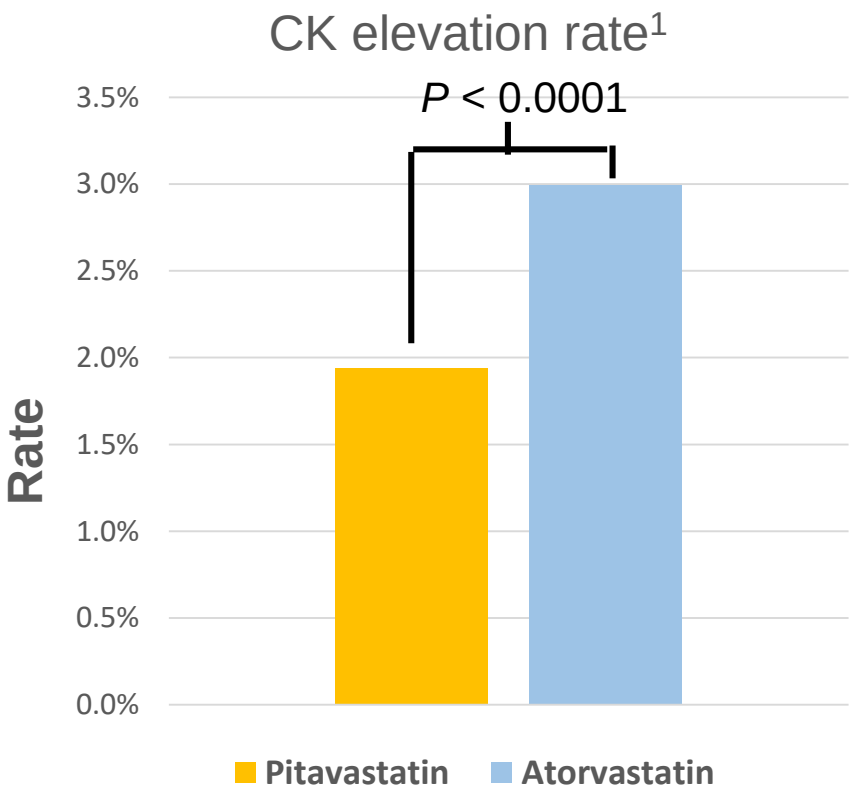
The USAGE survey is supported by Kowa Pharmaceuticals America, Inc. and the National Lipid Association.
GEN-1014

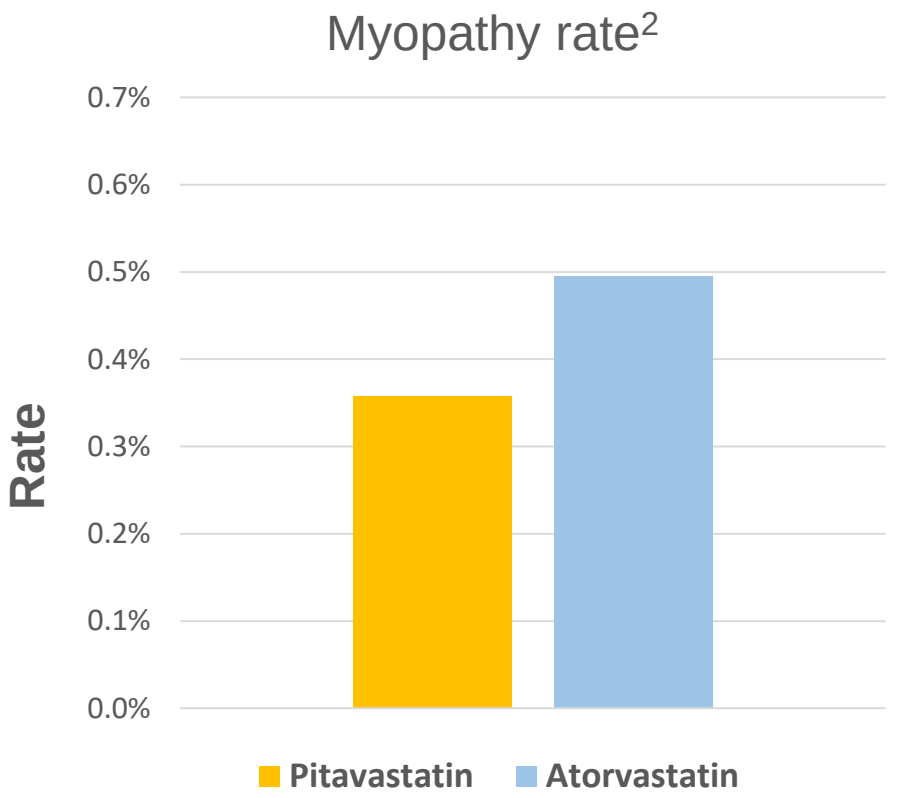
Atorvastatin group: more patients experienced in ALT abnormality



Circ J 2011; 75: 1493–1505

Livalo had lower CK elevation & myopathy rate





1. Ther Res. 2007; 28:733-9
. 2.J Jpn Soc Hosp Pharm. 2010;46(8):993–997. Japanese

Glucose fluctuation & NODM

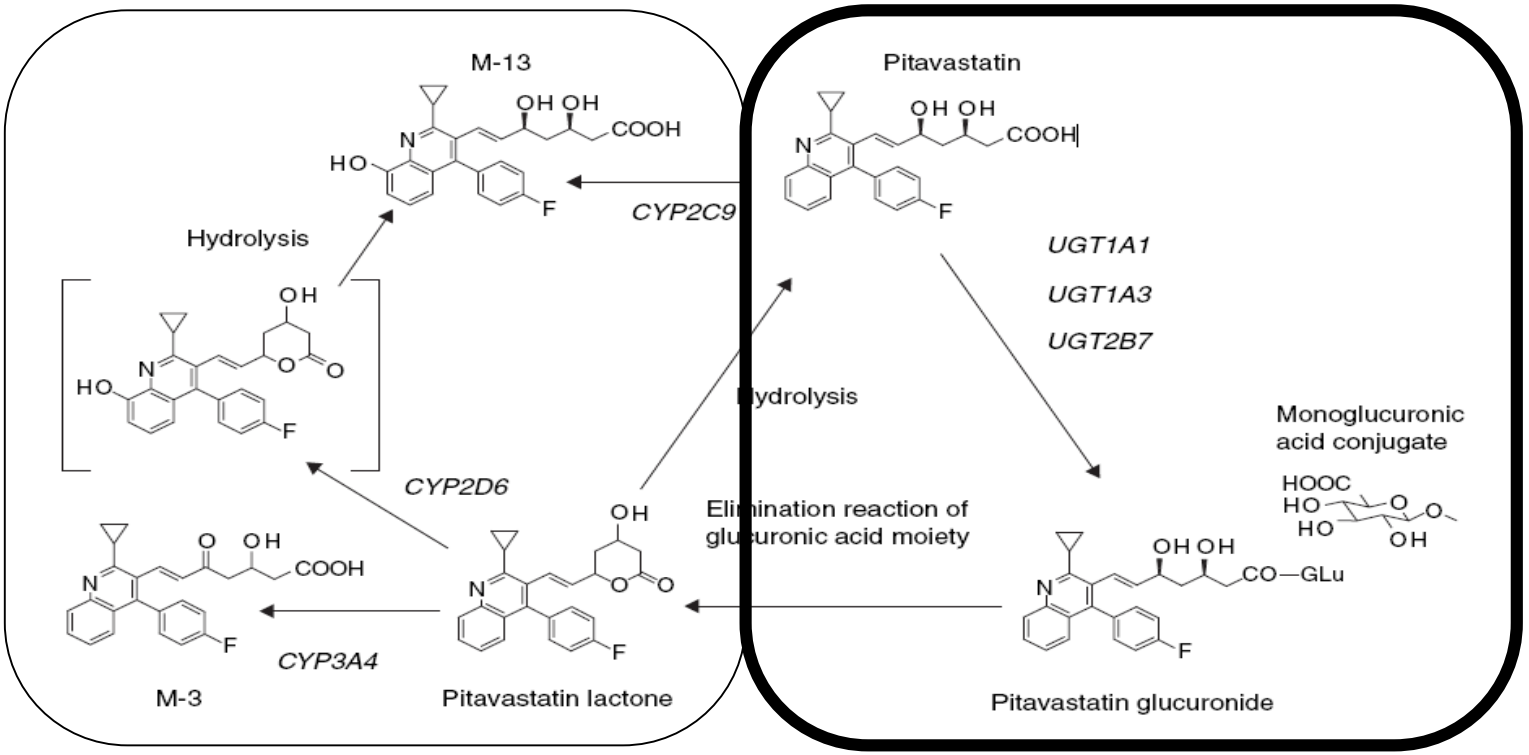
AST/ALT elevation

Drug-Drug interaction

Livalo rarely metabolism by CYP3A4 & CYP2C9

CYP (Minor)

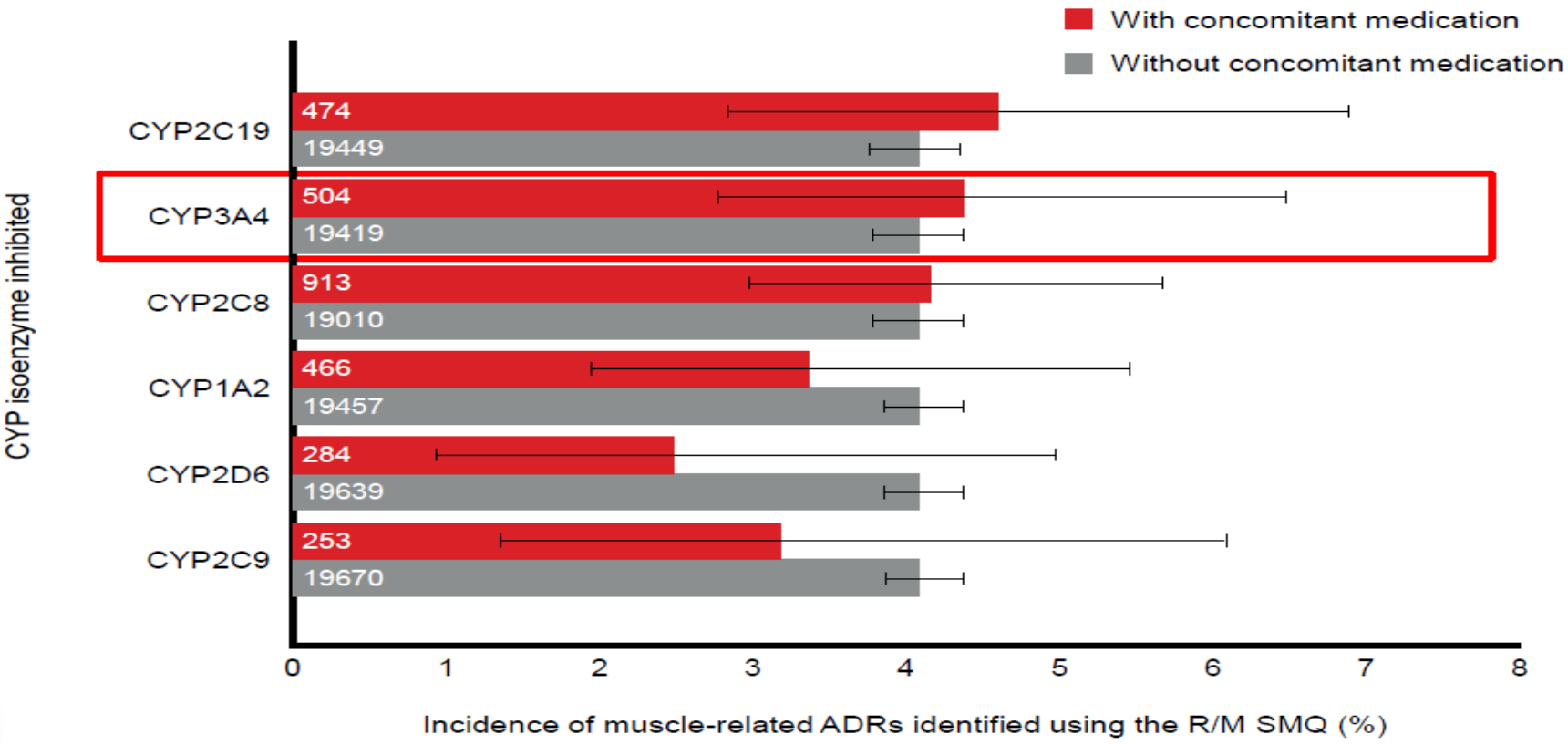
Glucuronidation (Major)



Expert Opin. Pharmacother. (2007) 8(14):2315-2327

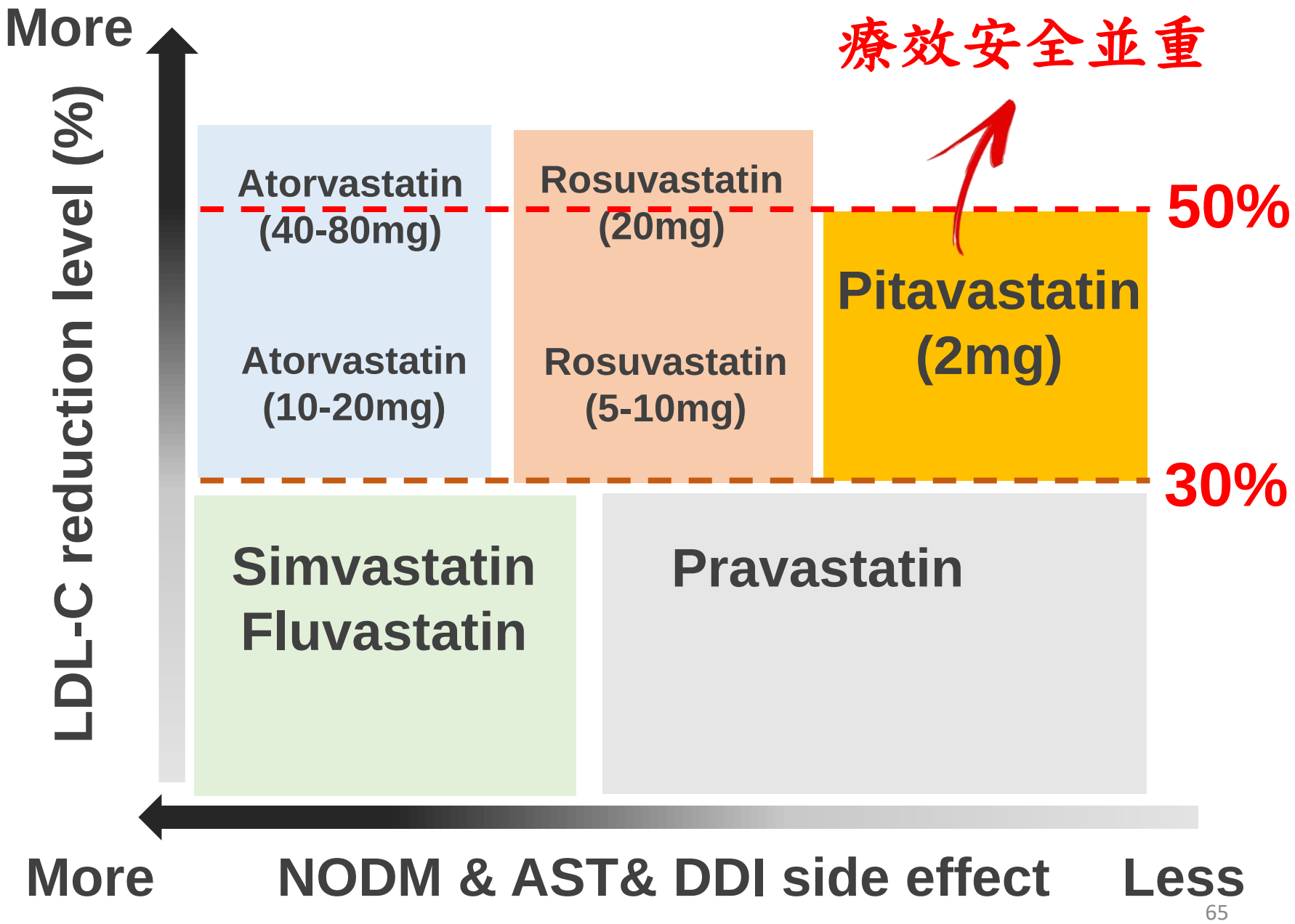
Livalo is rarely drug-drug interaction

Pitavastatin + CYP-inhibiting medication do not increase muscle related ADR(LIVES Study)



CYP isoenzyme	Inhibitors
CYP2C19	Omeprazole, fluvoxamine maleate, fluconazole
CYP3A4	Itraconazole, erythromycin, cimetidine, cyclosporine, clarithromycin, ketoconazole, atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, telithromycin, amiodarone, fluvoxamine
CYP2C8	Thiazolidinediones, trimethoprim
CYP1A2	Quinolone antibiotics, fluvoxamine maleate, cimetidine, amiodarone
CYP2D6	Quinidine, cimetidine, paroxetine, amiodarone, ritonavir
CYP2C9	Trimethoprim-sulphamethoxazole, fluconazole, amiodarone, cimetidine, ketoconazole, fluvoxamine maleate

Int. J of Clin. Pharmacol. and Thera. 2015, June 24th


More
LDL-C reduction level (%)
療效安全並重
Atorvastatin
(40-80mg)
Rosuvastatin
(20mg)
Pitavastatin
(2mg)
50%
Atorvastatin
(10-20mg)
Rosuvastatin
(5-10mg)
30%
Simvastatin
Fluvastatin
Pravastatin
More
NODM & AST& DDI side effect
Less

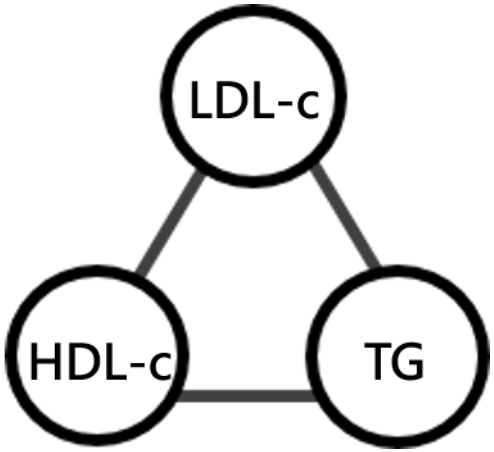
2016 ESC/EAS guideline for the management of dyslipidemias - Summary

	Pitava	Atorva	Rosuva	Prava	Fluva	Simva
TG lowering	V	V	V	-	-	-
Lower risk of Myopathy	V	-	V	V	-	-
Non-CYP via	V	-	V	V	-	-
CKD preferred	V	V	-	-	V	-
Combine with tacrolimus	V	-	V	V	V	-
HIV	V	V	V	V	V	

Modified from European Heart Journal 2011, 32, 1769- 1818

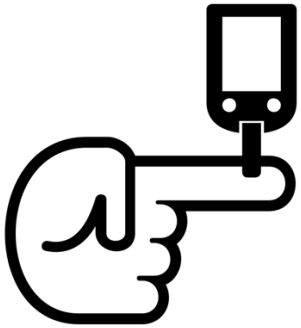
Summary:
Maximizing statin benefits for primary prevention

Get to the target !

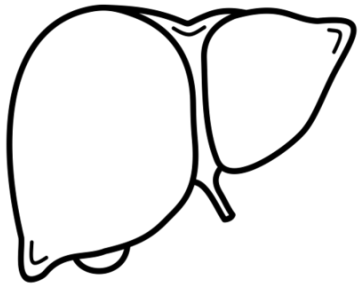


Minimize the side effects !

Lipid Triad



Minor
Glucose fluctuation
&
NODM



Minor
AST/ALT elevation

Minor
Drug-Drug interaction
No CYP3A4

Minor
Myopathy

Thank you for your attention!!