How to optimize statin therapy for very-high and high risk ASCVD patients in dyslipidemia?

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- Epidemiologic of ASCVD
- Mechanism of atherosclerosis
- Definition of high risk and very high risk ASCVD
- Jupiter Trial ⇒ Rationale, Results and Clinical impact
- High potency, efficacy and safe of Rosuvastatin
- Conclusions

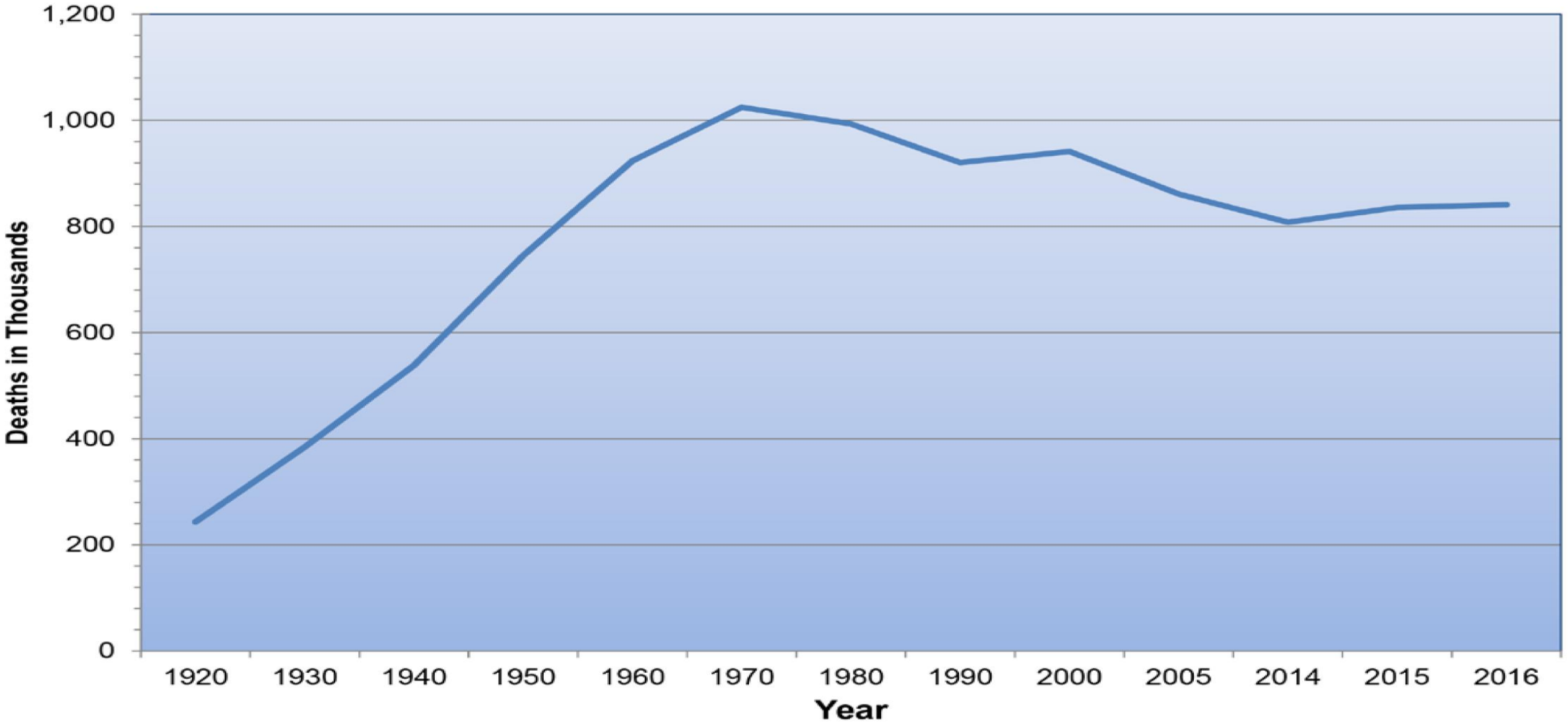
AHA STATISTICAL UPDATE

Heart Disease and Stroke Statistics—2019 Update

A Report From the American Heart Association

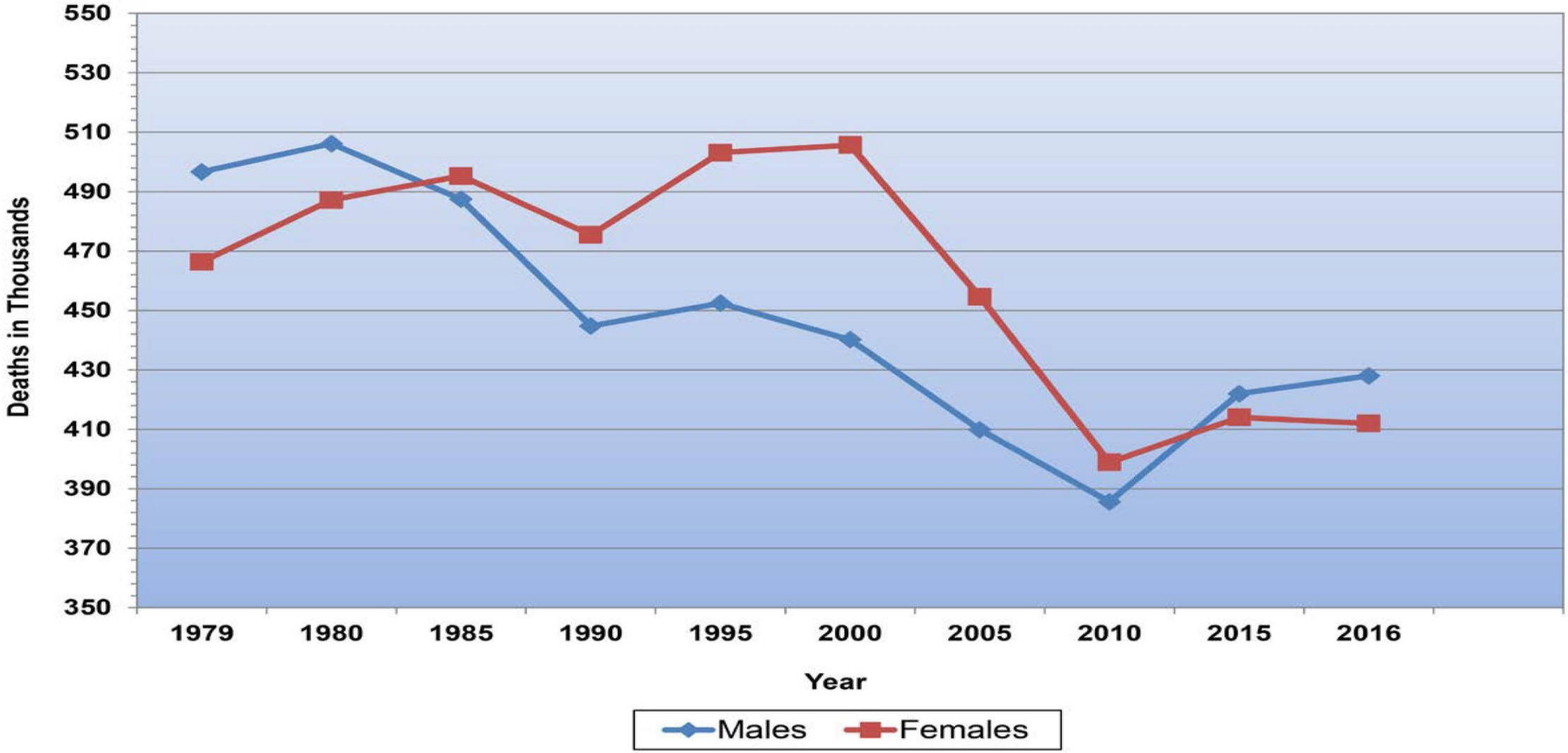
Circulation. 2019;139:e56–e528.

Cardiovascular Disease Death (US, 1910–2016)



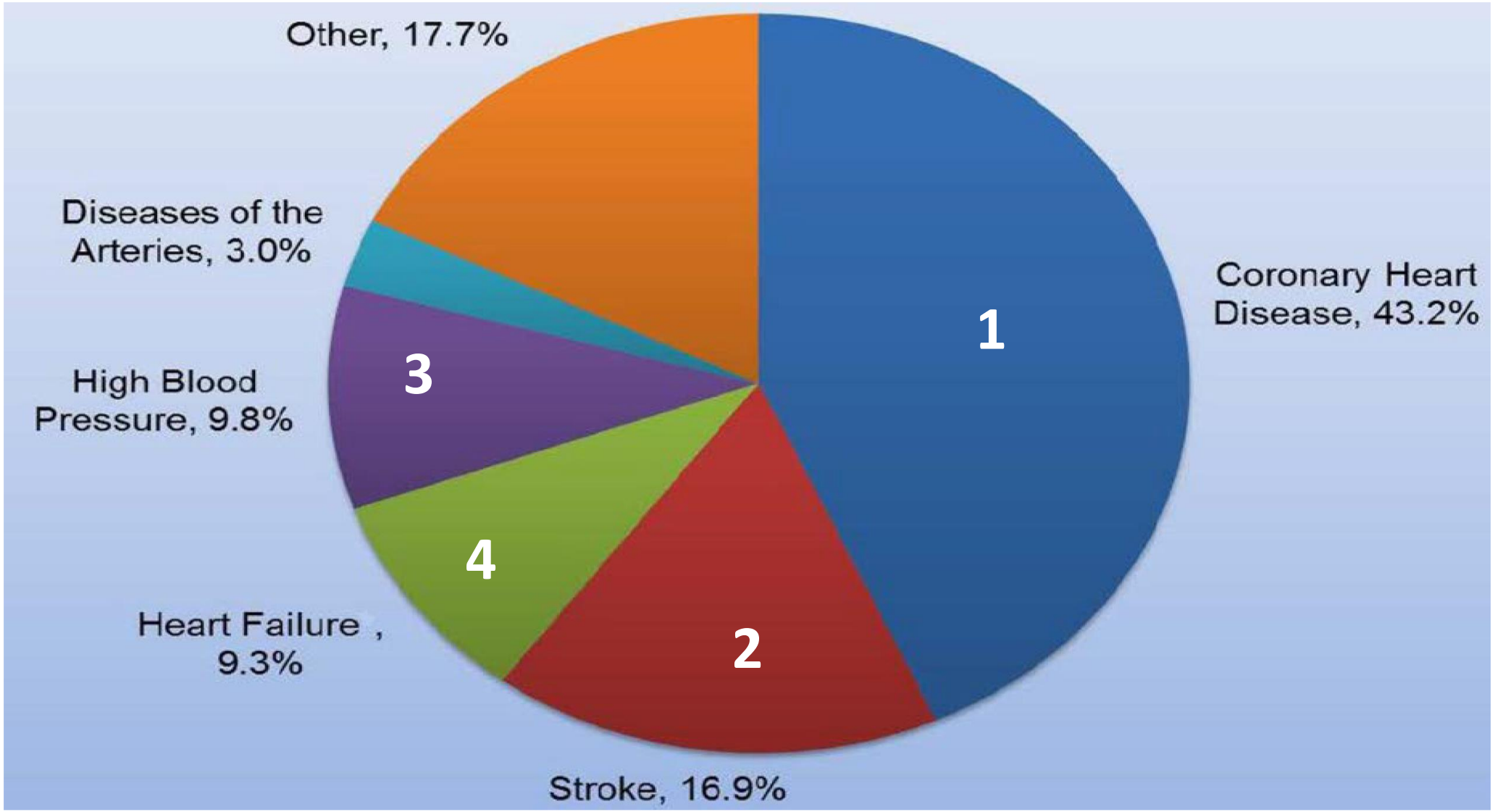
Circulation. 2019;139:e56–e528.

CVD Death, Male and Female (US, 1910–2016)

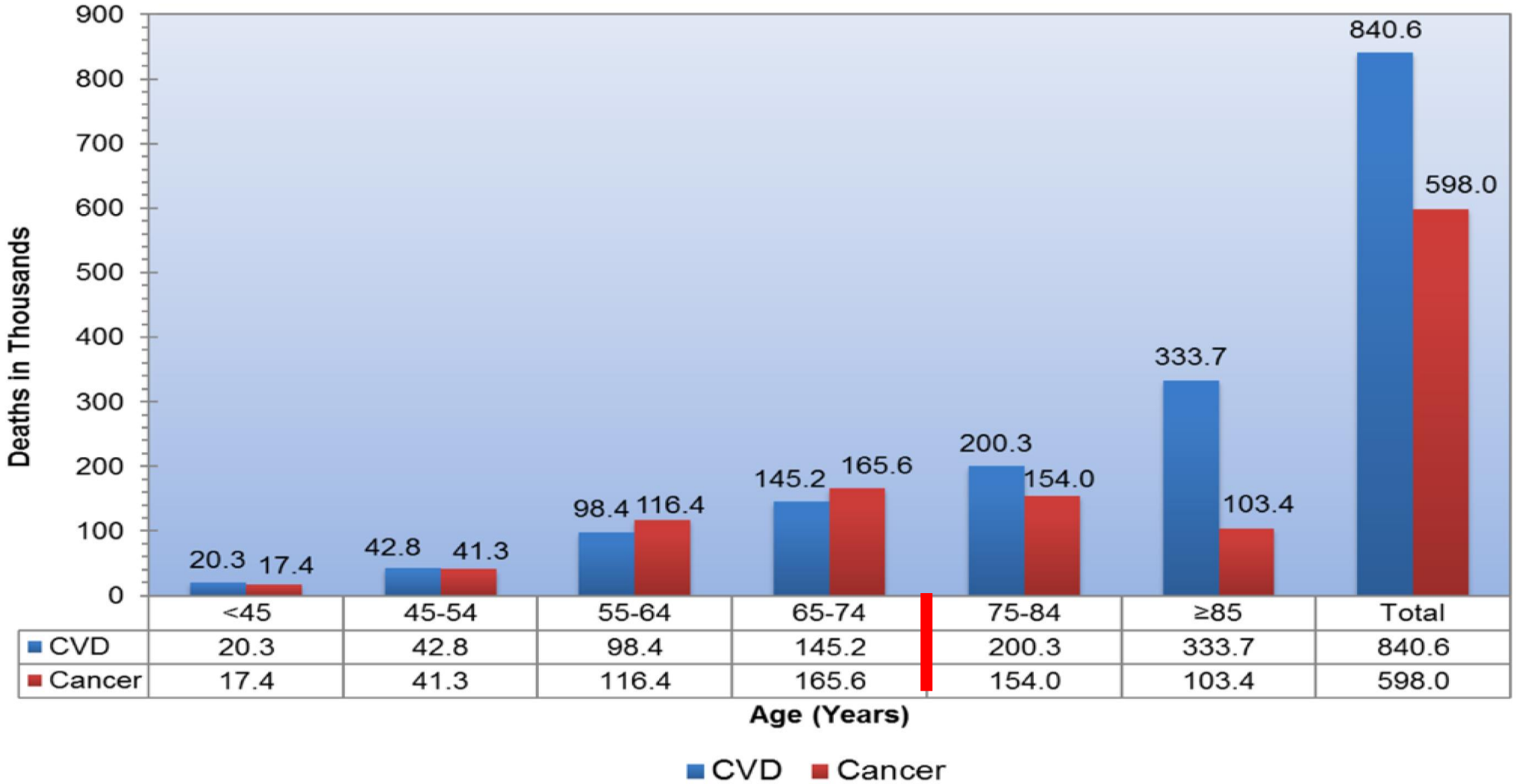


Circulation. 2019;139:e56–e528.

Deaths Attributable to Cardiovascular Disease



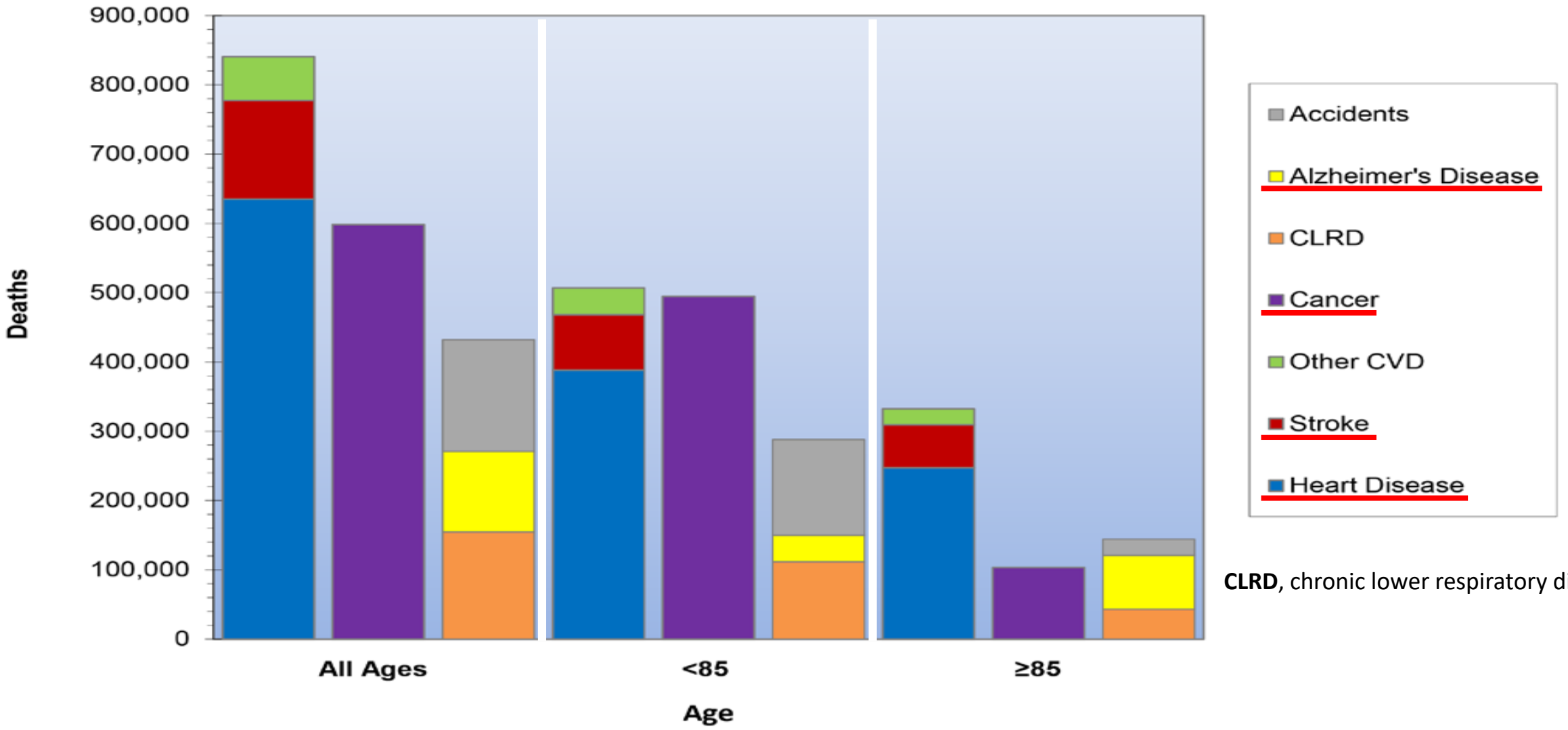
CVD Deaths vs Cancer Deaths (US, 2016)



	<45	45-54	55-64	65-74	75-84	≥85	Total
CVD	20.3	42.8	98.4	145.2	200.3	333.7	840.6
Cancer	17.4	41.3	116.4	165.6	154.0	103.4	598.0

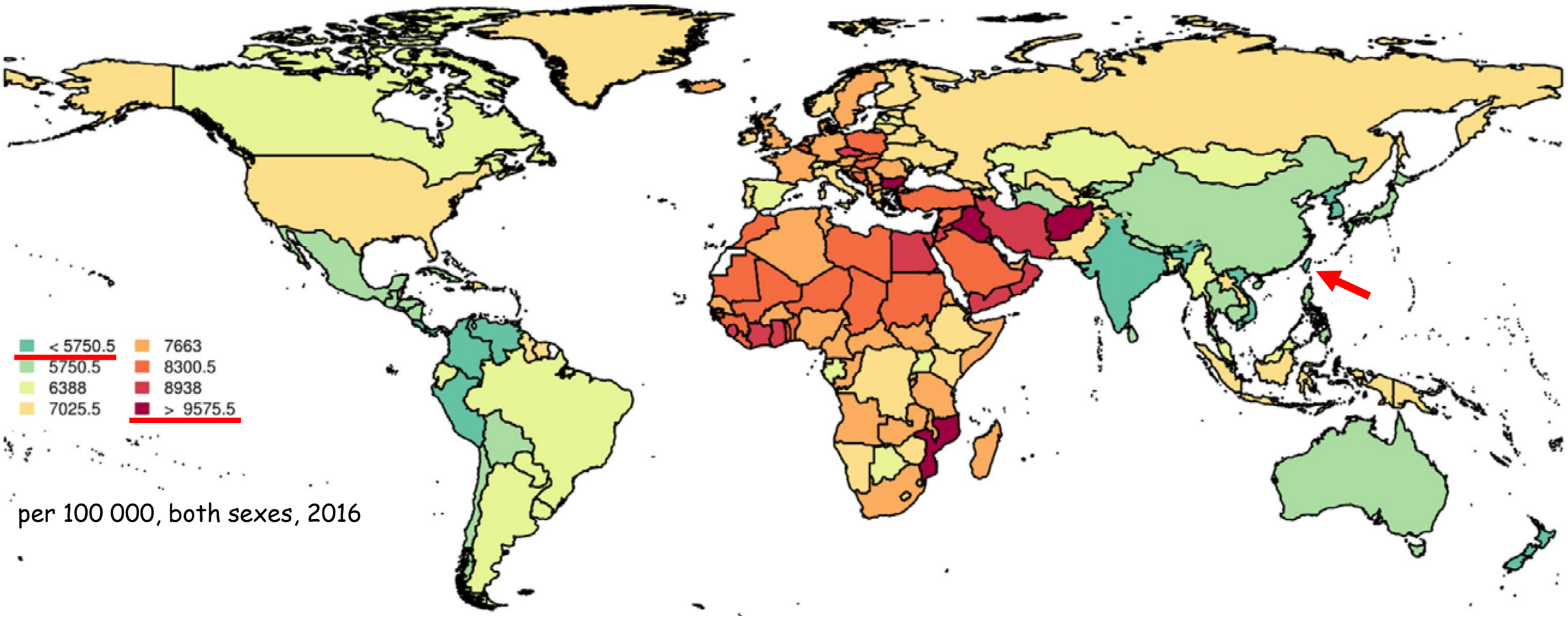
Circulation. 2019;139:e56–e528.

CVD and Other Major Causes of Death

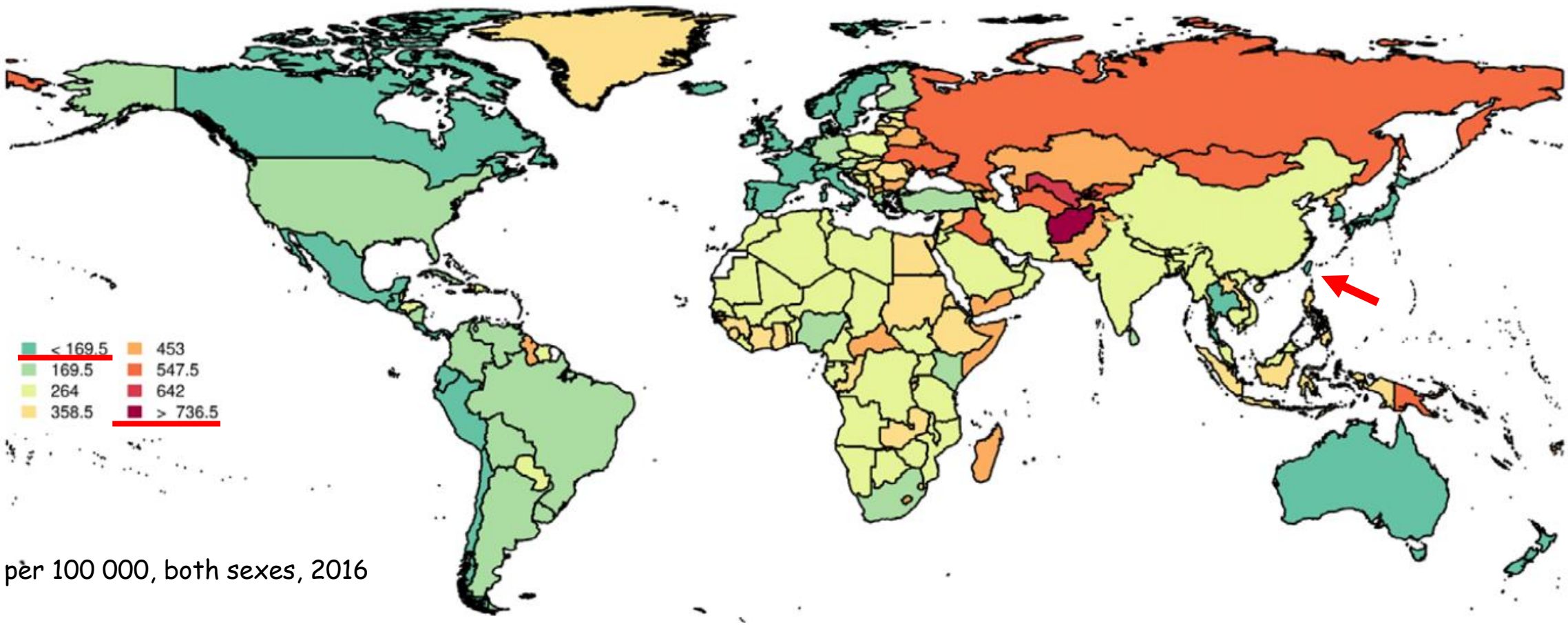


CLRD, chronic lower respiratory disease

Prevalence Rates of CV Diseases



Global Mortality Rates of CV Diseases



per 100 000, both sexes, 2016

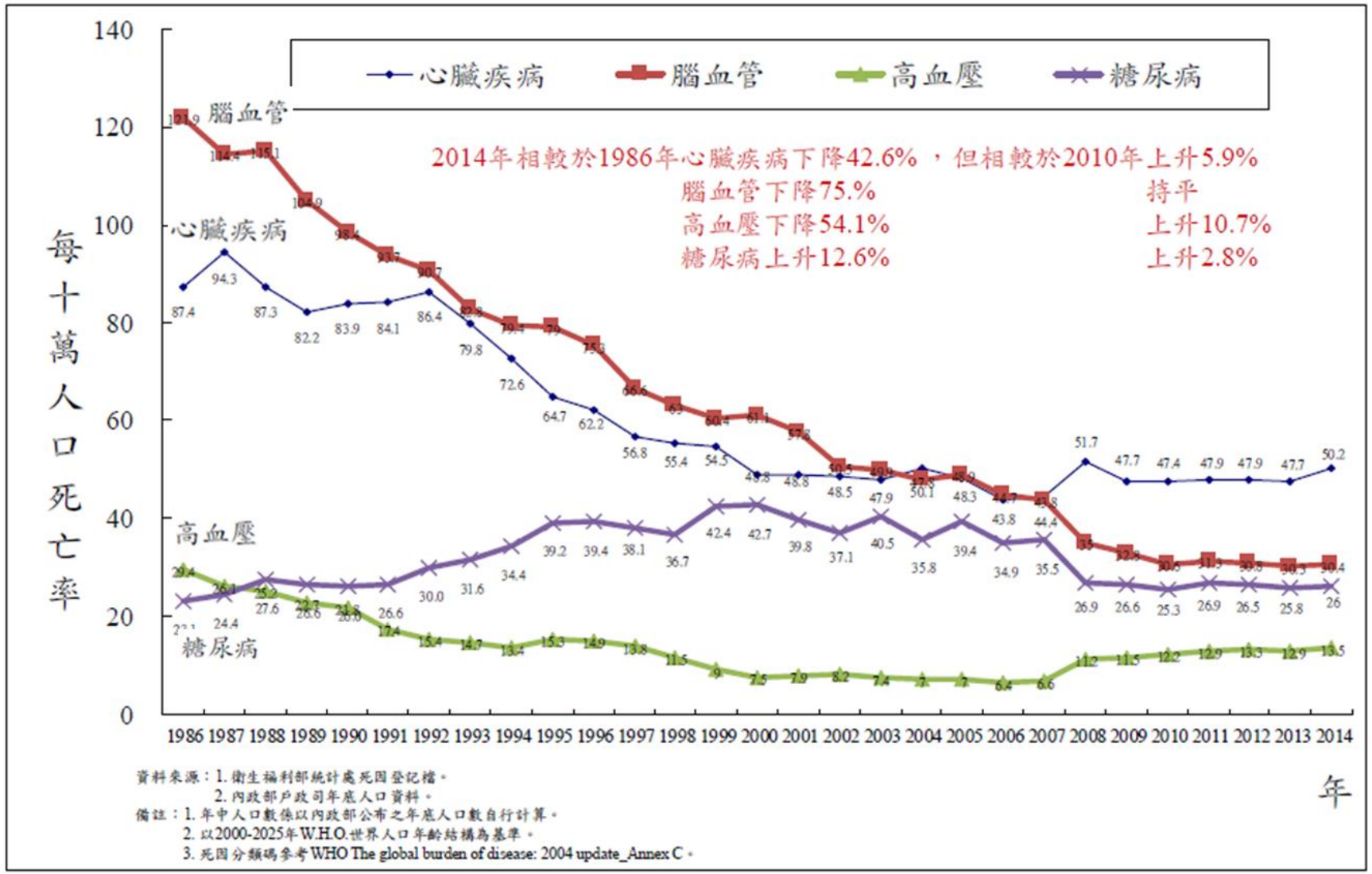
2018 台灣 十大死因死亡人數

順位	所有死亡原因	死亡人數(人) 107年	較上年增減%
		172,859	0.6
1	癌症	48,784	1.6
2	心臟疾病（高血壓性疾病除外）	21,569	4.5
3	肺炎	13,421	7.5
4	腦血管疾病	11,520	-2.0
5	糖尿病	9,374	-4.8
6	事故傷害	6,846	-1.7
7	慢性下呼吸道疾病	6,146	-1.8
8	高血壓性疾病	5,991	-1.3
9	腎炎、腎病症候群及腎病變	5,523	2.6
10	慢性肝病及肝硬化	4,315	-5.2

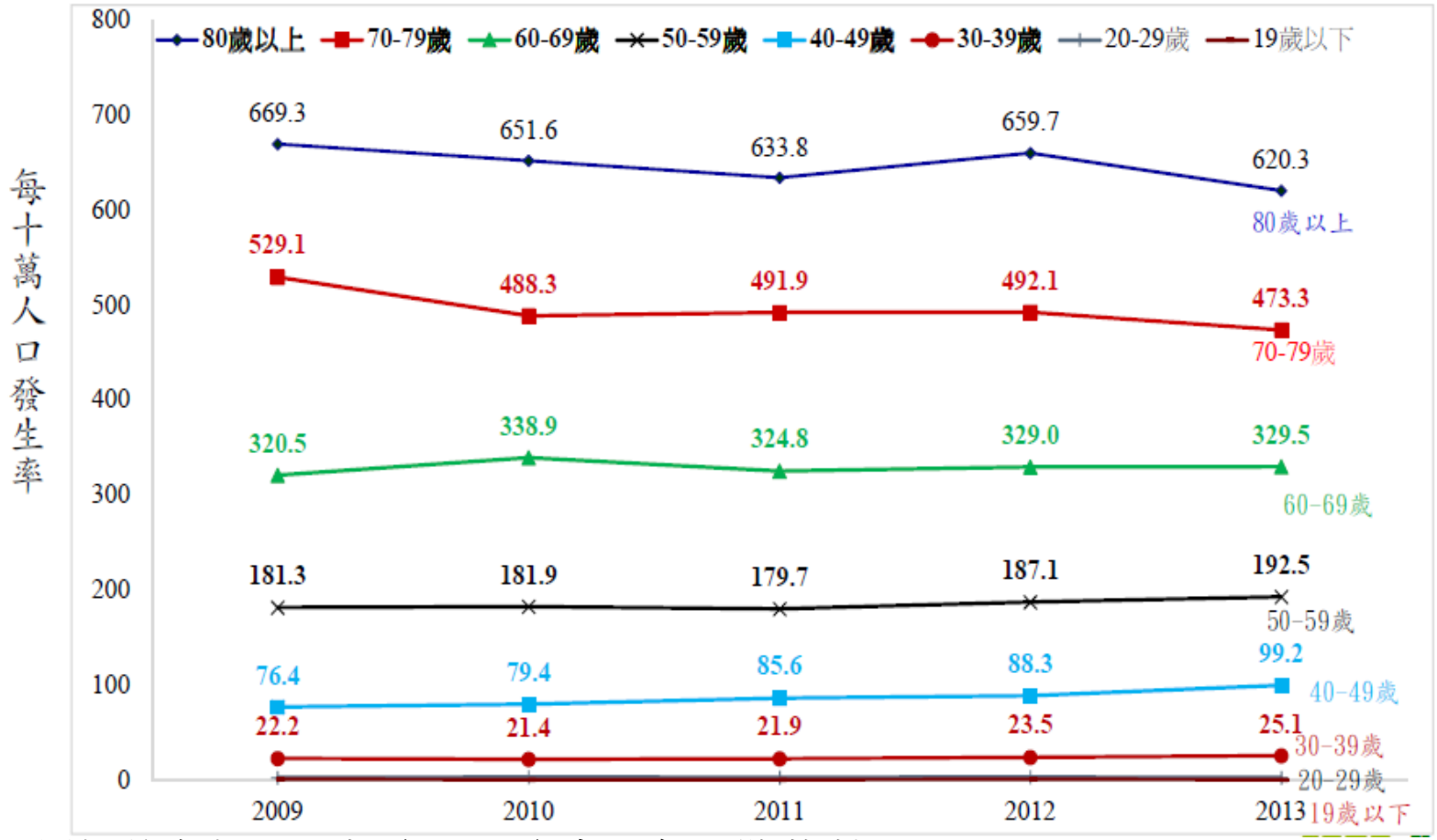
衛生福利部國民健康署

https://dep.mohw.gov.tw/DOS/lp-4472-113.html

國人心血管疾病及糖尿病標準化死亡率（1986-2014年）



2009-2013年男性各年齡層急性心肌梗塞發生率



30% ↑

1. 70歲以上男性的急性心肌梗塞發生率有逐年下降趨勢
2. 40～49歲民眾的發生率，卻從民國98年每十萬人76.4上升至102年的99.2，增加了30%

衛福部國民健康署 2015-9-22

Review

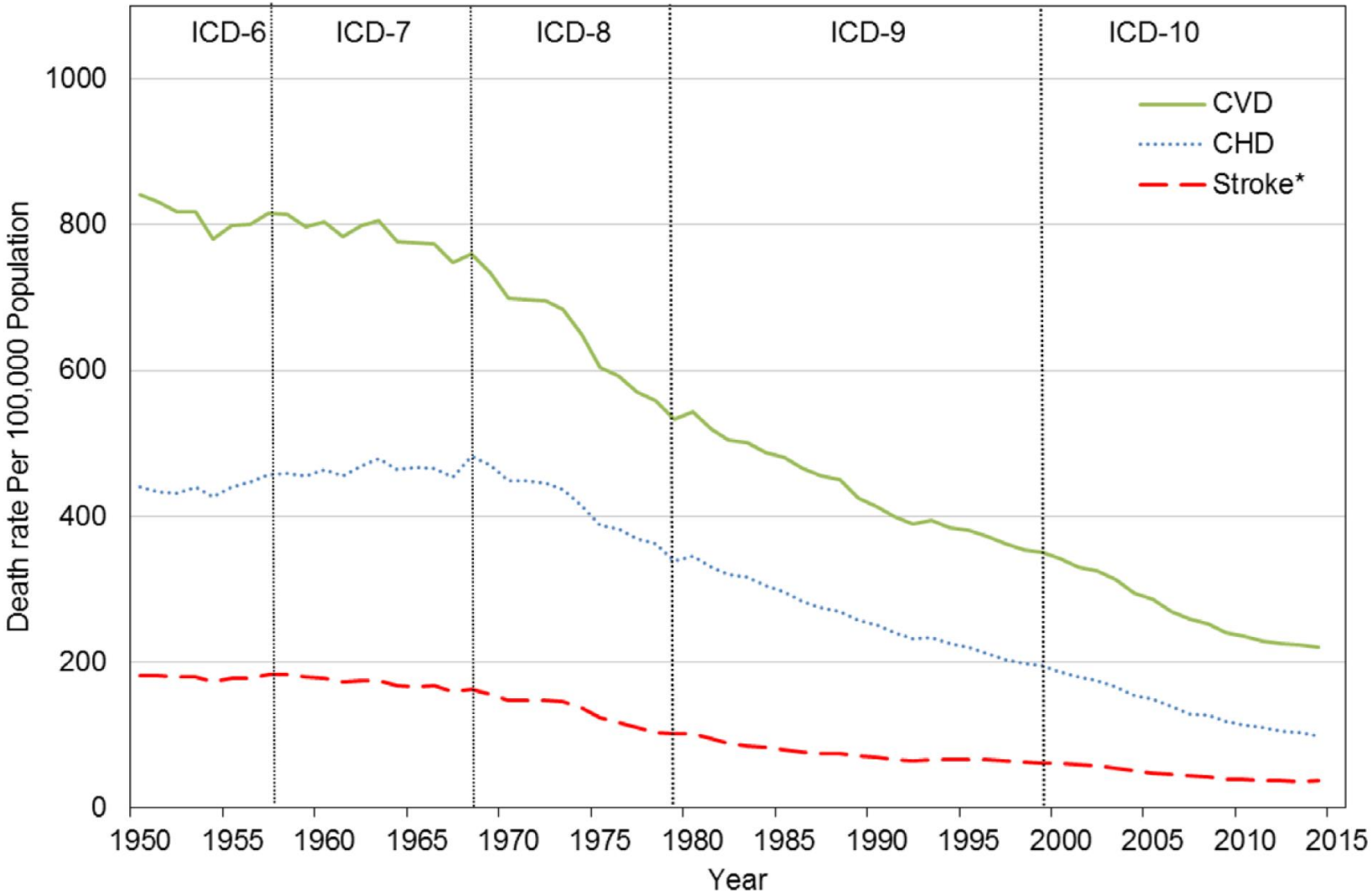
Decline in Cardiovascular Mortality

Possible Causes and Implications

George A. Mensah, Gina S. Wei, Paul D. Sorlie, Lawrence J. Fine, Yves Rosenberg, Peter G. Kaufmann, Michael E. Mussolino, Lucy L. Hsu, Ebyan Addou, Michael M. Engelgau, David Gordon

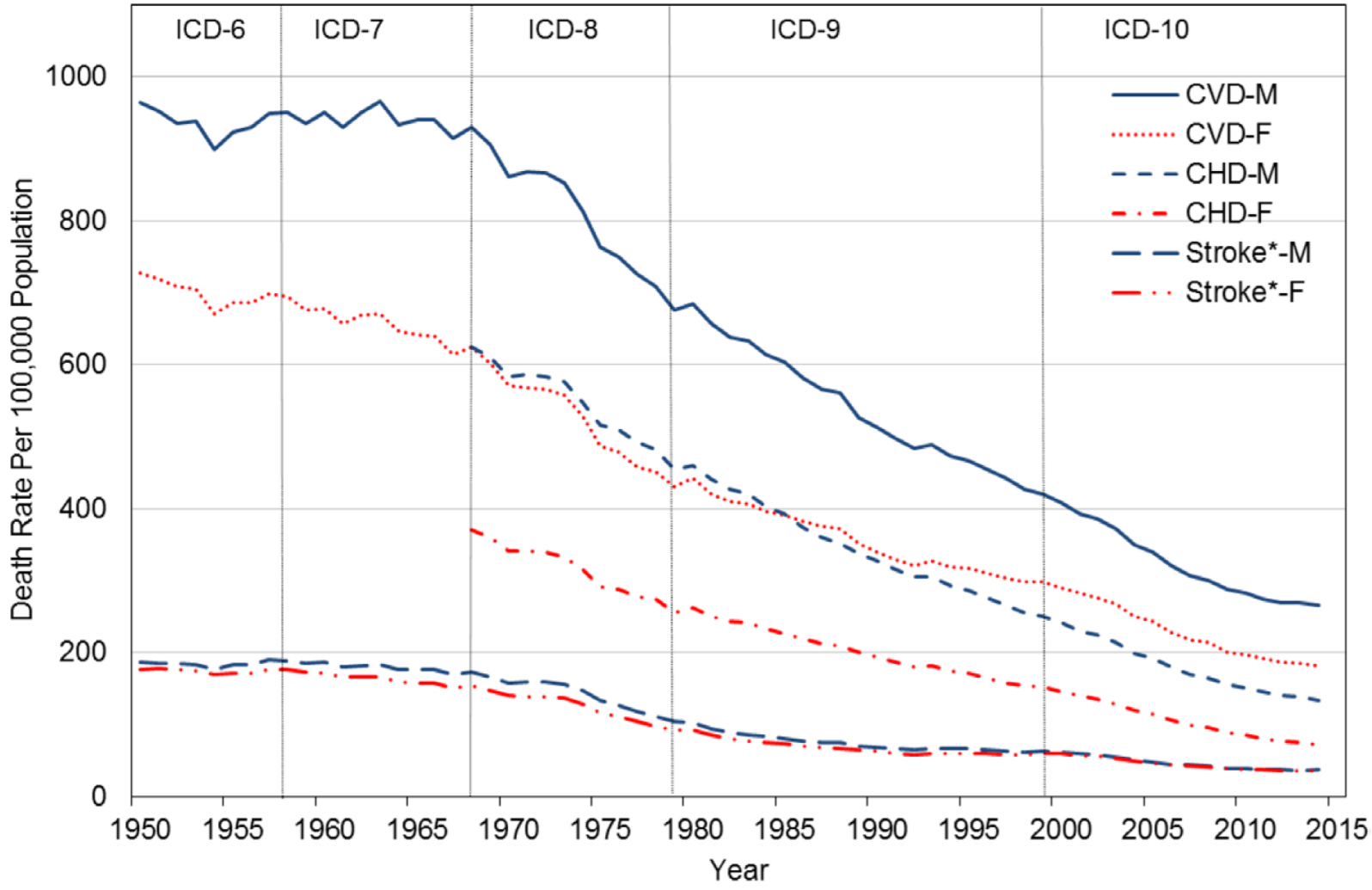
Circ Res. 2017;120:366-380

Sex-Adjusted CVD Mortality Rates, 1950 to 2014



Circ Res. 2017;120:366-380

Age-Adjusted CVD Mortality Rates by Sex, 1950 to 2014.



Circ Res. 2017;120:366-380

Abstract 1

- Control of infectious diseases ⇒ public health success story ⇒ the first half of the 20th century.
- Decline in mortality from CVD ⇒ success story of past 40 years
- Since 1970' ⇒ CVD and stroke ⇒ sharp decline in mortality rates
- This remarkable decline has been fueled by rapid progress in both **prevention** and **treatment**
- Including ⇒ declines in cigarette smoking, hypertension treatment, DM control, widespread use of statins, ACS treatment (stent, anti-platelet) and anti-coagulation.

Circ Res. 2017;120:366-380

Abstract 2

- There is evidence that the rate of decline may have abated and may even be showing early signs of reversal in some population groups.
- The National Heart, Lung, and Blood Institute ⇒ trends in CV mortality what has come before and what may lie ahead.

Circ Res. 2017;120:366-380

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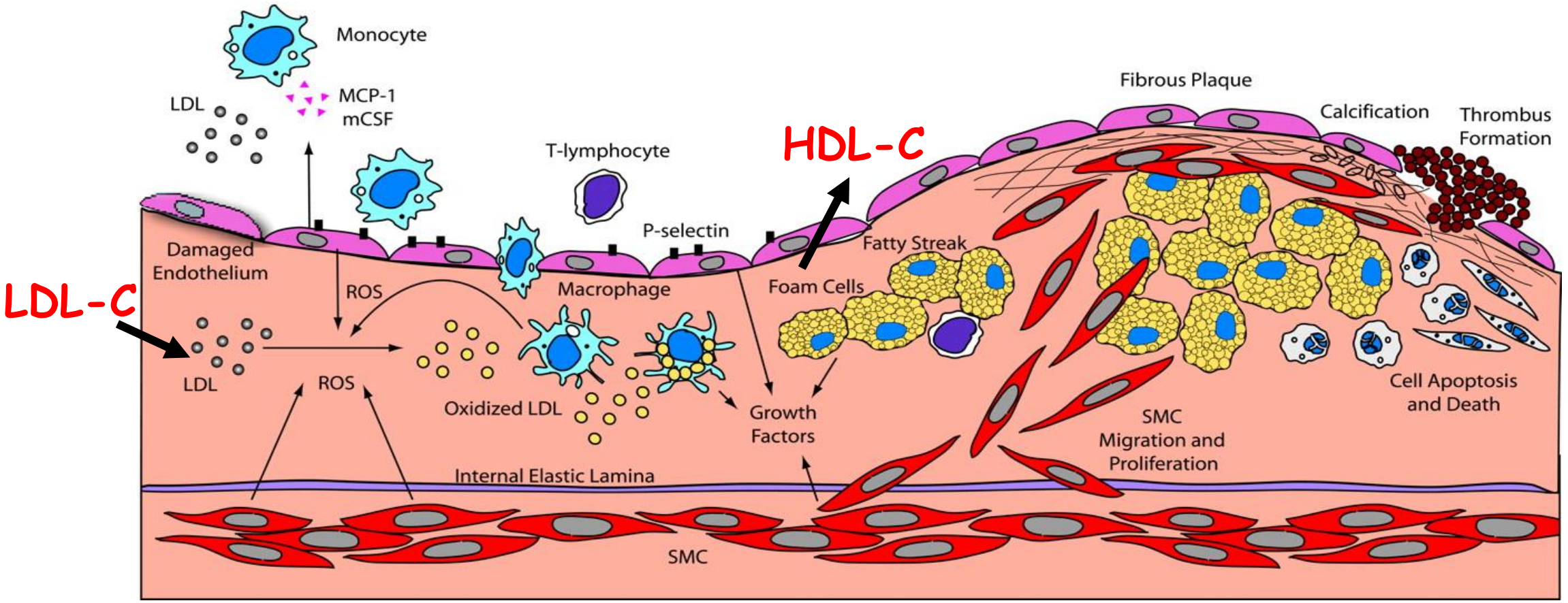
Atherosclerosis



Lipid hypothesis

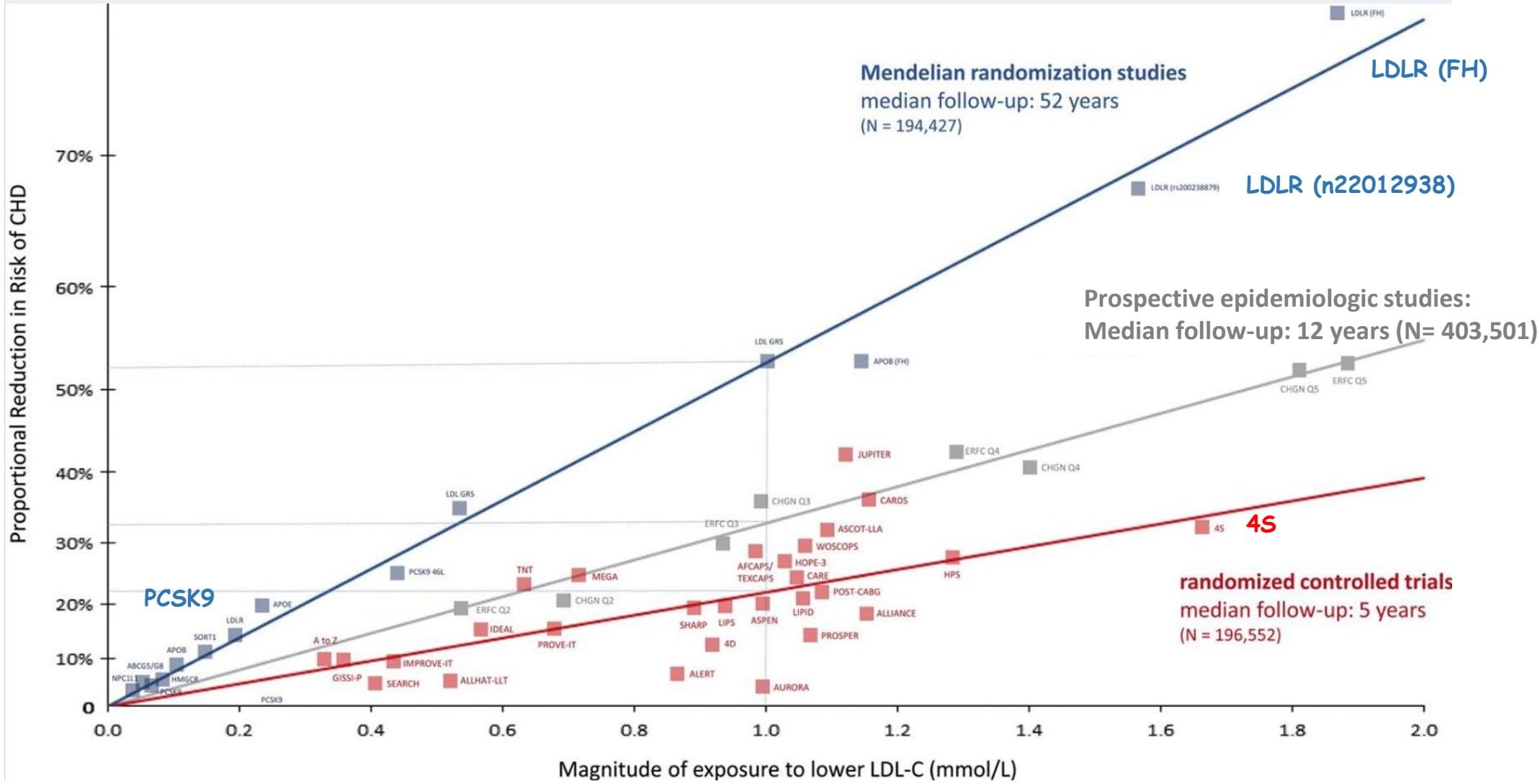
Atherosclerosis ⇒ inflammation process

LDL ↓, HDL↑ ⇒ atherosclerosis improved

Cell. 2001:104;503-16

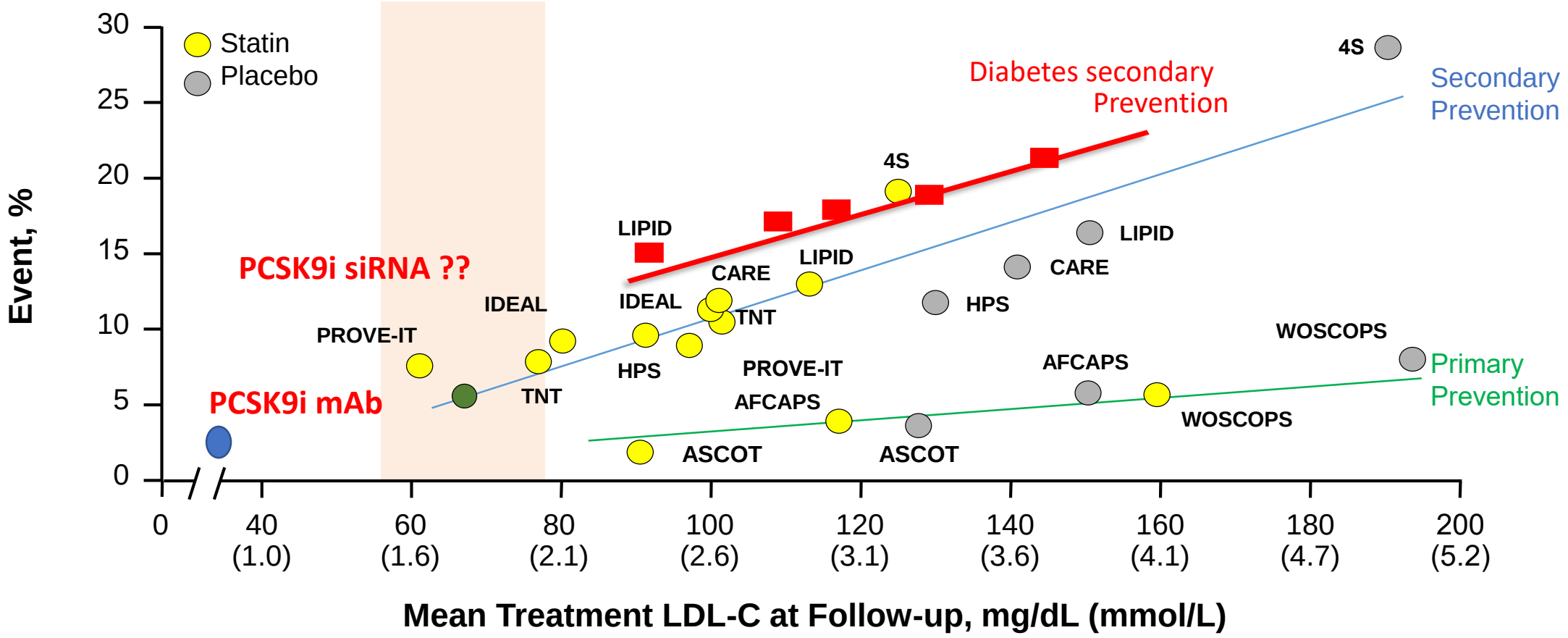
Nature 2002:420;868

LDL cause ASCVD
Evidence from Genetic, Epidemiologic, and Clinical Studies



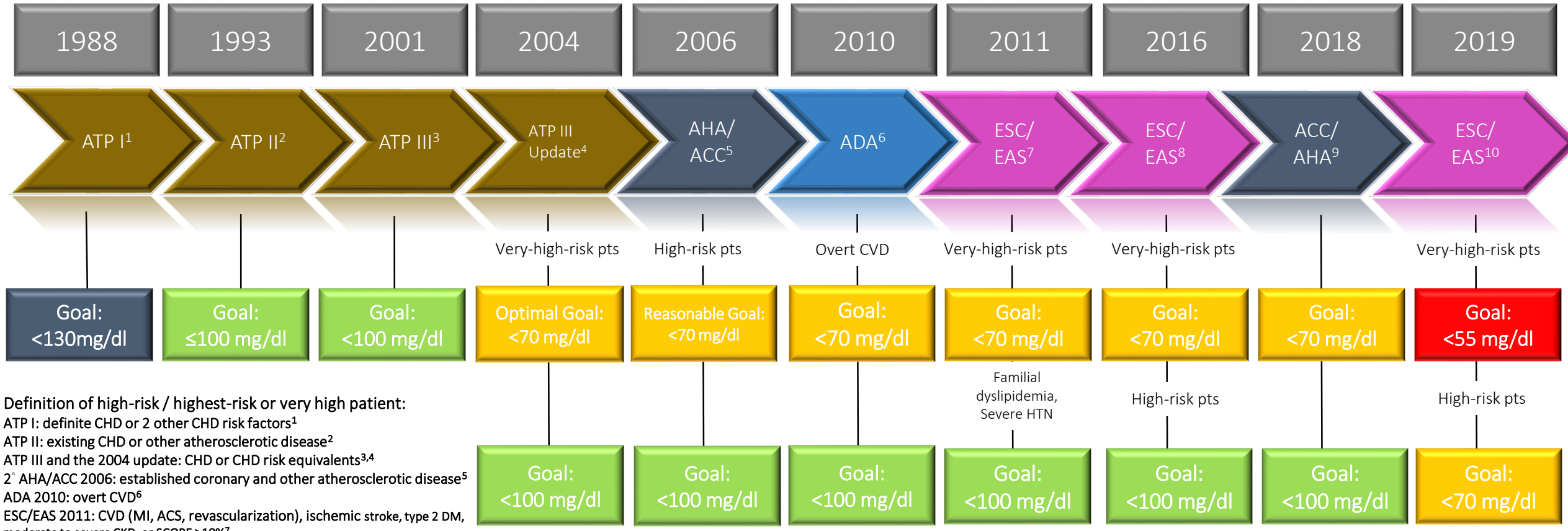
Eur Heart J. 2017 Aug 21;38(32):2459-2472.

Correlation Between LDL-C and CHD Risk



- LDL-C 1% ↓ ⇒ CV event 1% ↓
- LDLC 1 mmole/L (38.7mg/dL) ↓ ⇒ CV event 21% ↓

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

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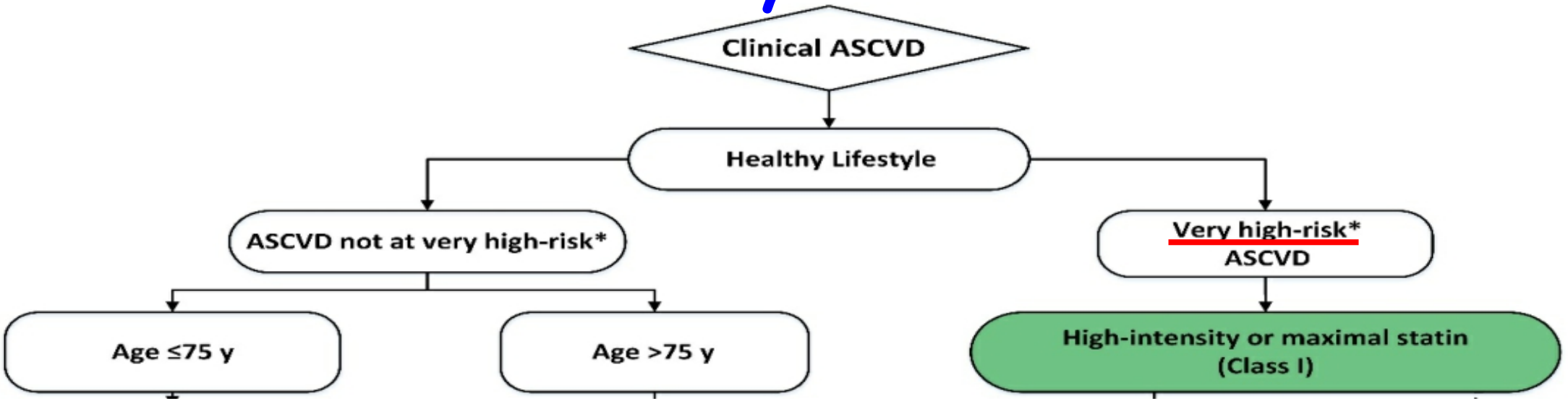
Secondary Prevention



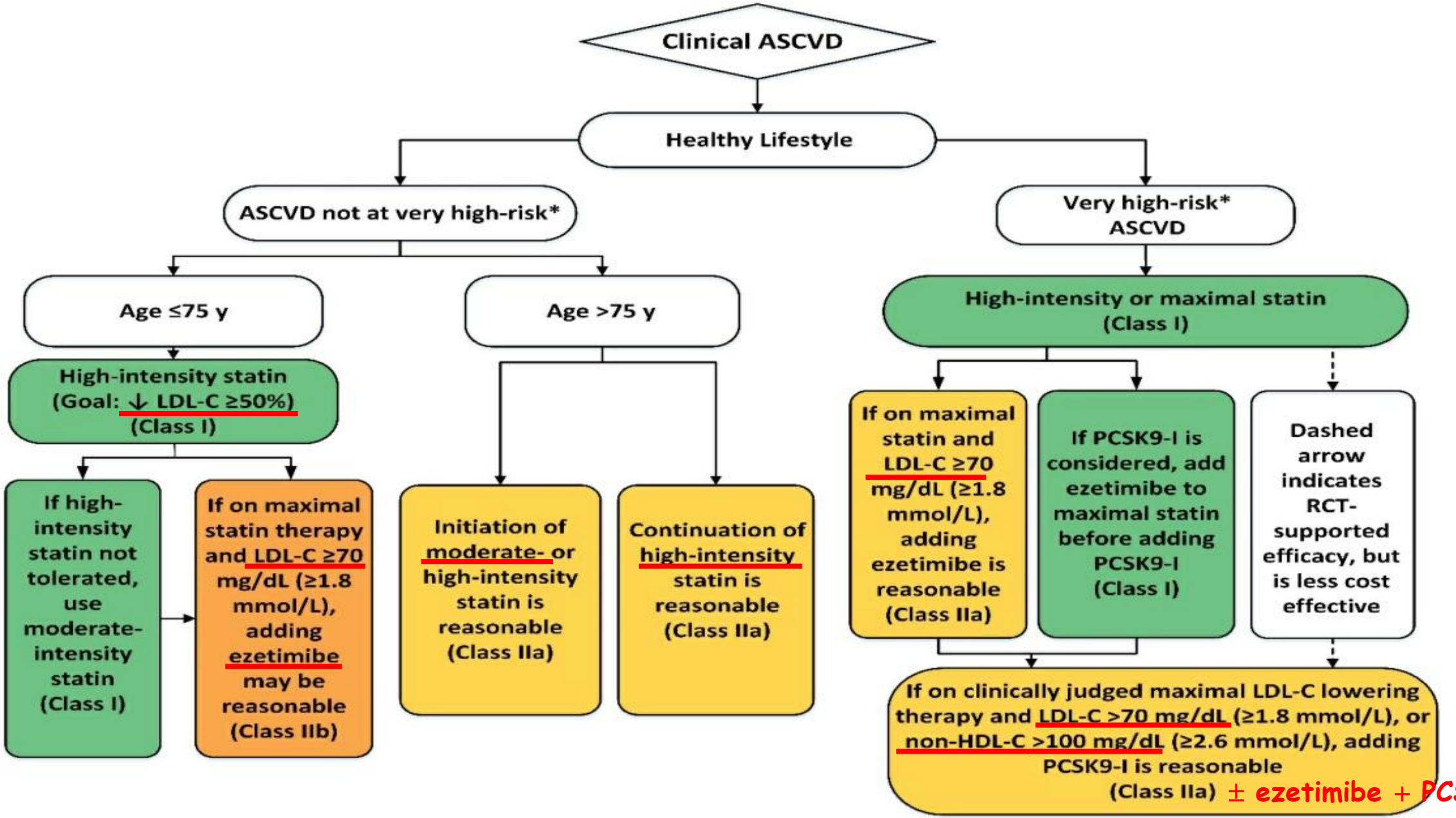
Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation)

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)
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

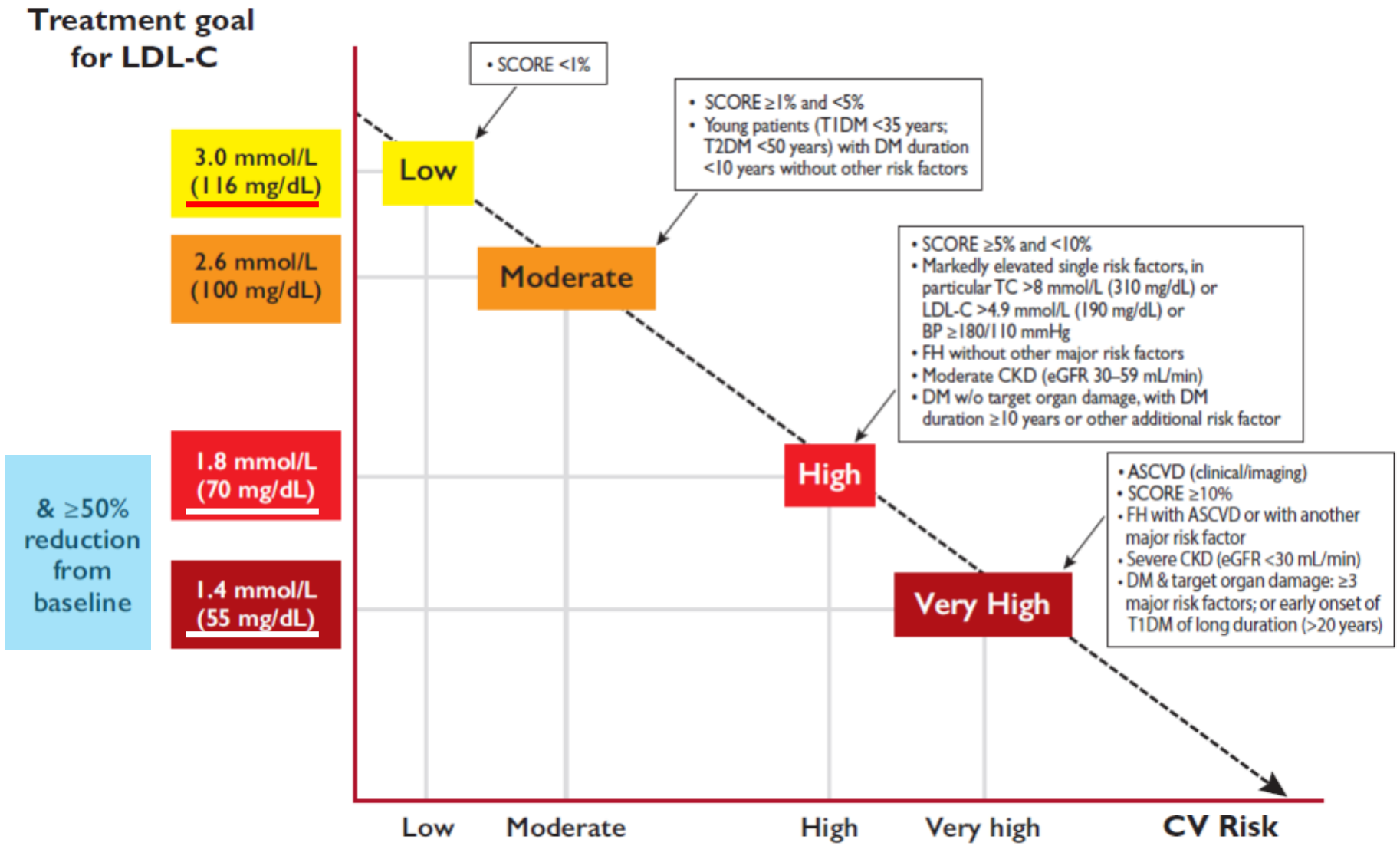
ASCVD ⇒ high risk ⇒ ACS, old MI, stable or unstable angina or post PCI, stroke, TIA, or PAD, aortic aneurysm
Very high-risk ⇒ multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions

Circulation. 2019;139:e1082–e1143

Secondary Prevention



2019 ESC/EAS guideline LDL treatment goal



European Heart Journal (2019) 00, 1-78

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.

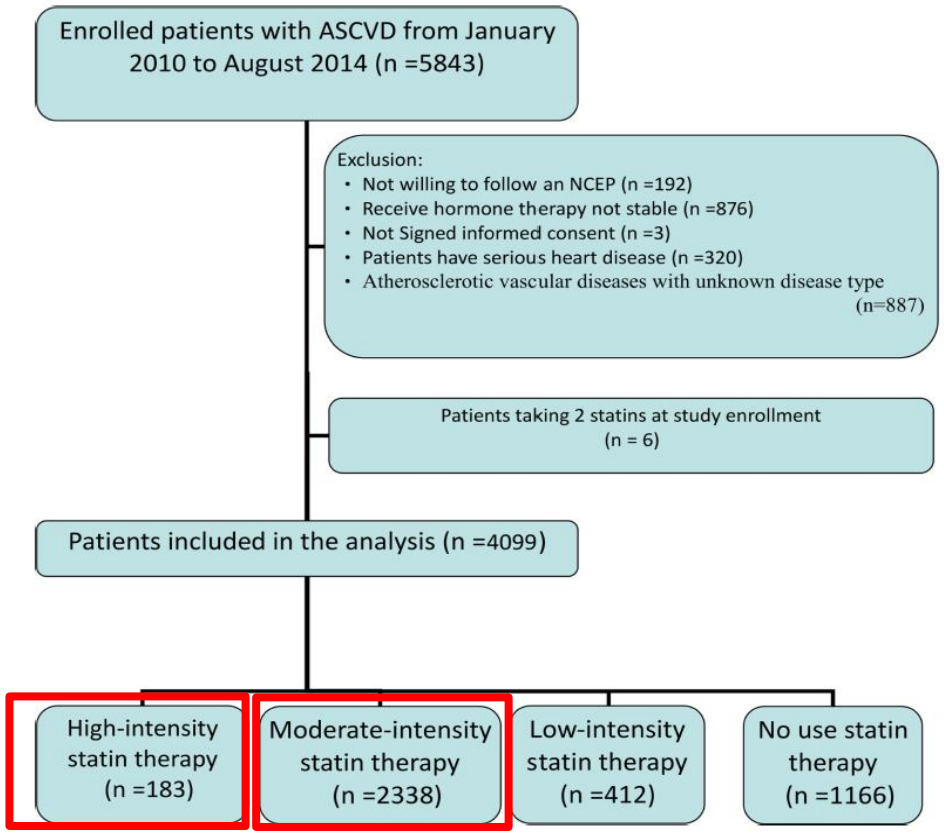
2019 健保給付更新: ACS, PCI & CABG病人血脂目標值LDL-C< 70 mg/dL

	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)。

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 **44%**
- 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

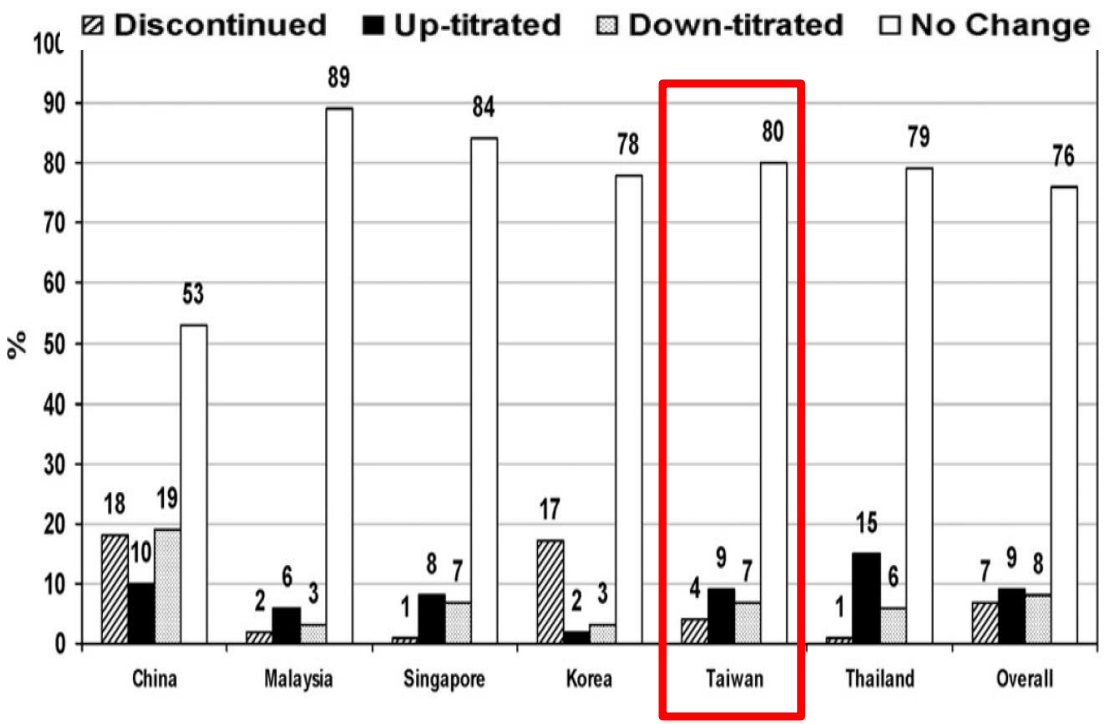
†Adjusted for age, gender, body mass index (BMI) level, cigarette smoking history, fibrate use, history of hypertension, heart failure, diabetes, myocardial infarction, ischemic stroke or transient ischemic attack, previous coronary or lower extremity arterial disease (LEAD) intervention and levels of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

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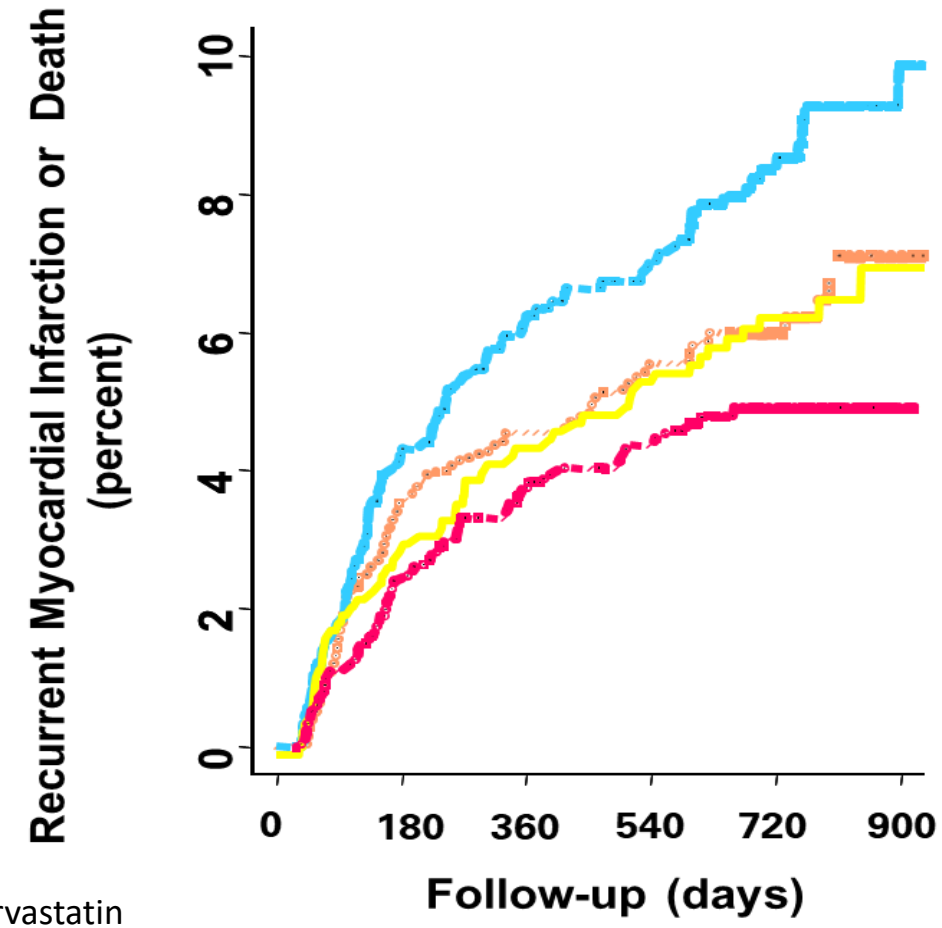
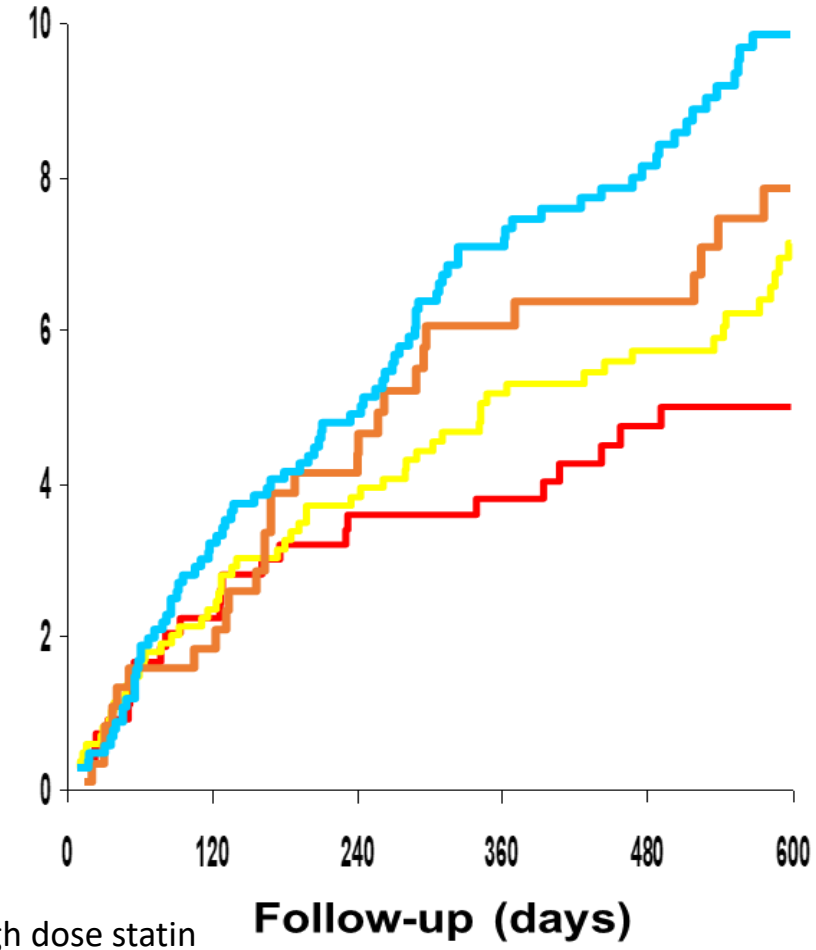
LDL-C and hsCRP Level of Statin Tx in ACS

LDL>70, hsCRP>2 LDL>70, hsCRP<2 LDL<70, hsCRP>2 LDL<70, hsCRP<2



High dose atorvastatin vs mod dose pravastatin in ACS p't

PROVE IT – TIMI 22
NEJM 2005;352:20-28.



Early high dose statin in ACS

A to Z
Circulation 2006;114:281-8

Ridker et al,

Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

Paul M Ridker, M.D., Eleanor Danielson, M.I.A., Francisco A.H. Fonseca, M.D., Jacques Genest, M.D., Antonio M. Gotto, Jr., M.D., John J.P. Kastelein, M.D., Wolfgang Koenig, M.D., Peter Libby, M.D., Alberto J. Lorenzatti, M.D., Jean G. MacFadyen, B.A., Børge G. Nordestgaard, M.D., James Shepherd, M.D., James T. Willerson, M.D., and Robert J. Glynn, Sc.D., for the JUPITER Study Group*

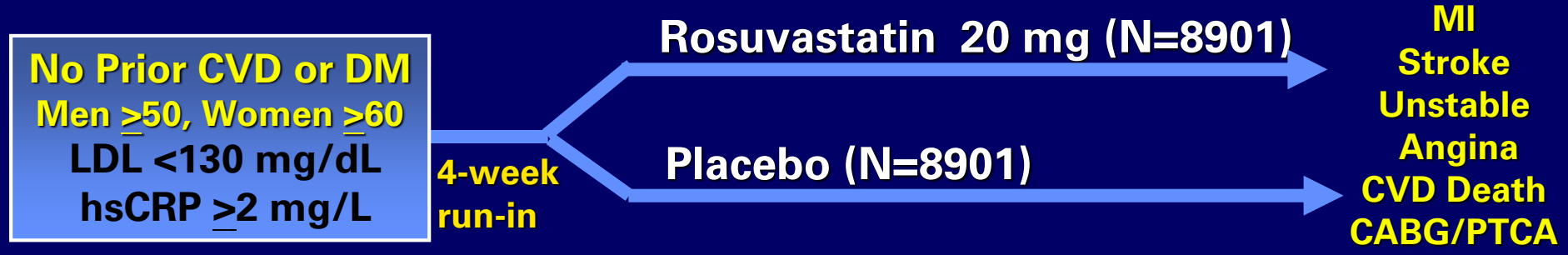
N Engl J Med 2008;359:2195-207

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais, D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, Z. Kobalava, L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi, R.P.T. Troquay, P. Libby, and R.J. Glynn, for the CANTOS Trial Group*

N Engl J Med 2017;377:1119-31

JUPITER

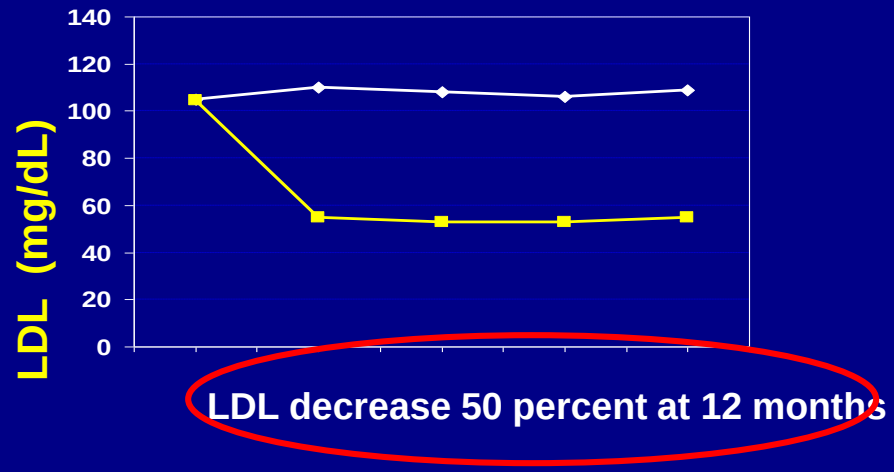


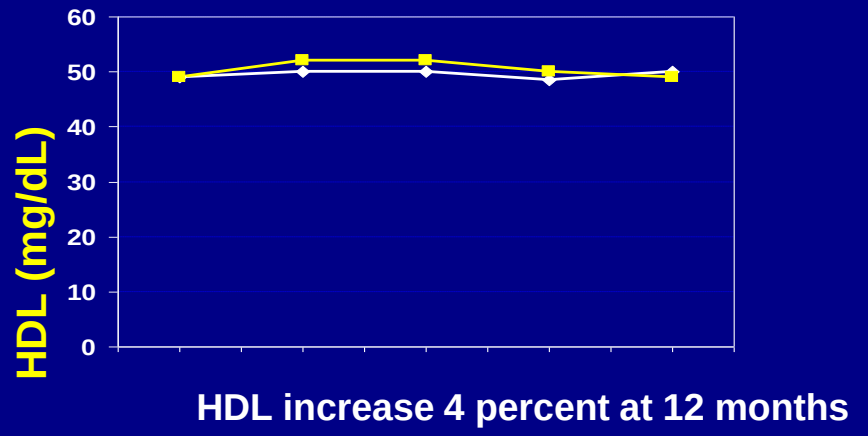
N Engl J Med 2008; 359:2195-2207

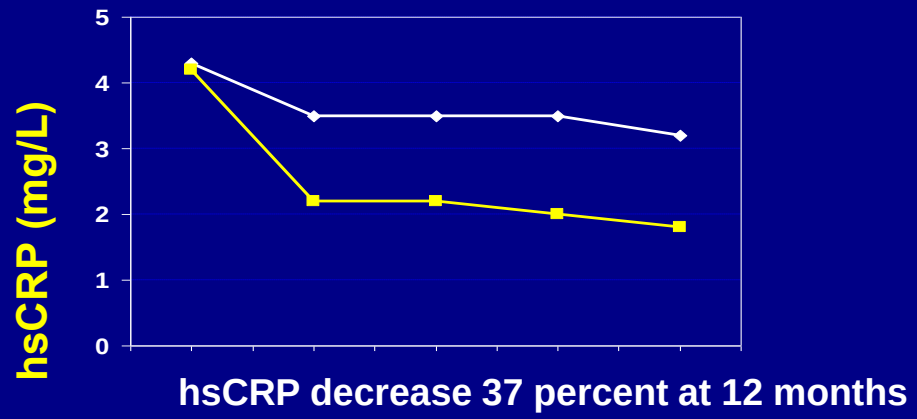
JUPITER

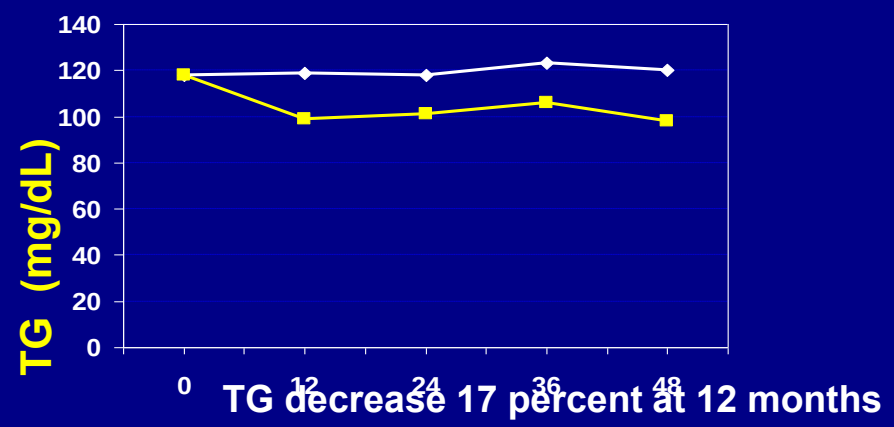
Ridker et al NEJM 2008

Effects of rosuvastatin 20 mg on LDL, HDL, TG, and hsCRP







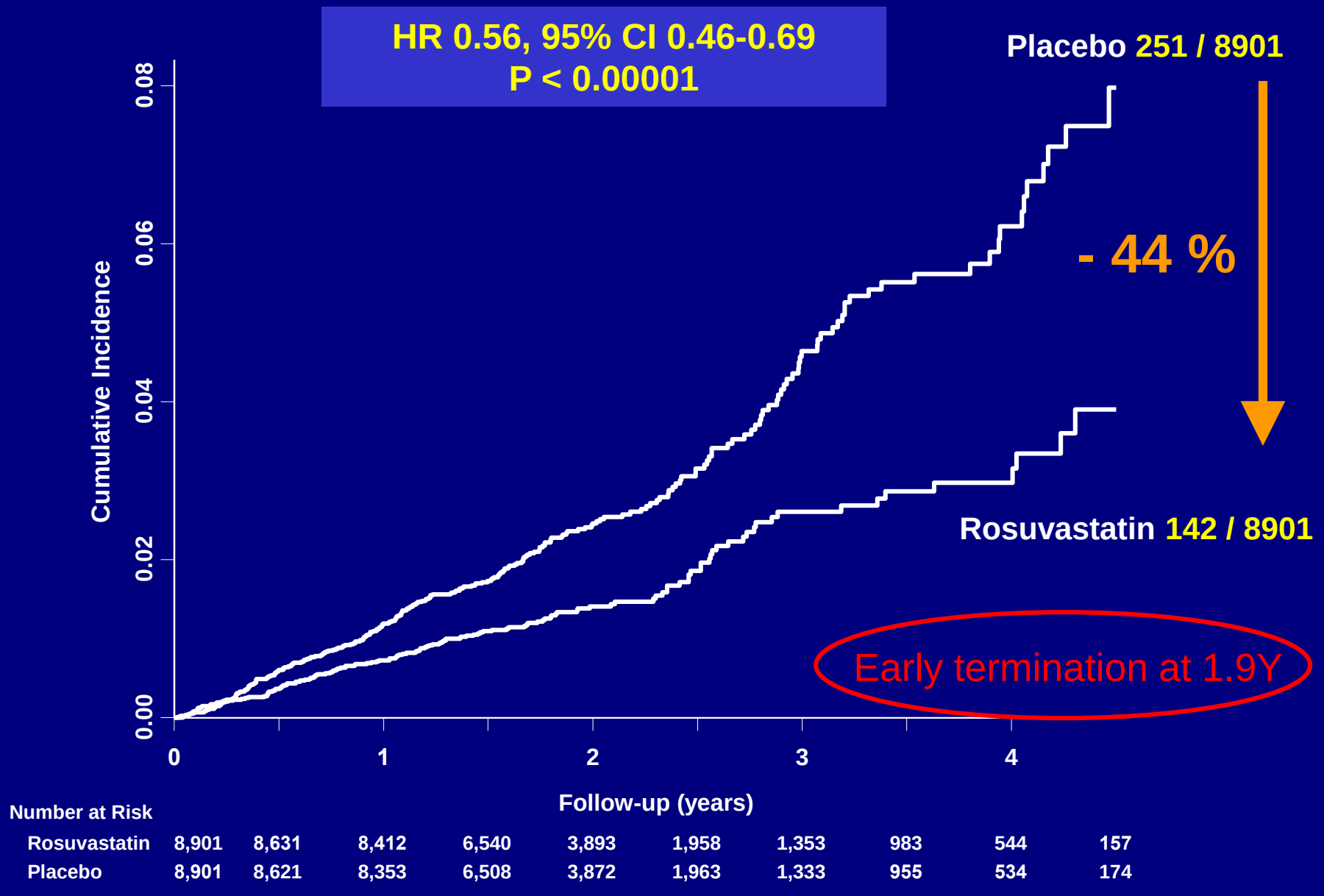


N Engl J Med 2008; 359:2195-2207

JUPITER

Ridker et al NEJM 2008

Primary Trial Endpoint：MI, Stroke, UA/Revascularization, CV Death

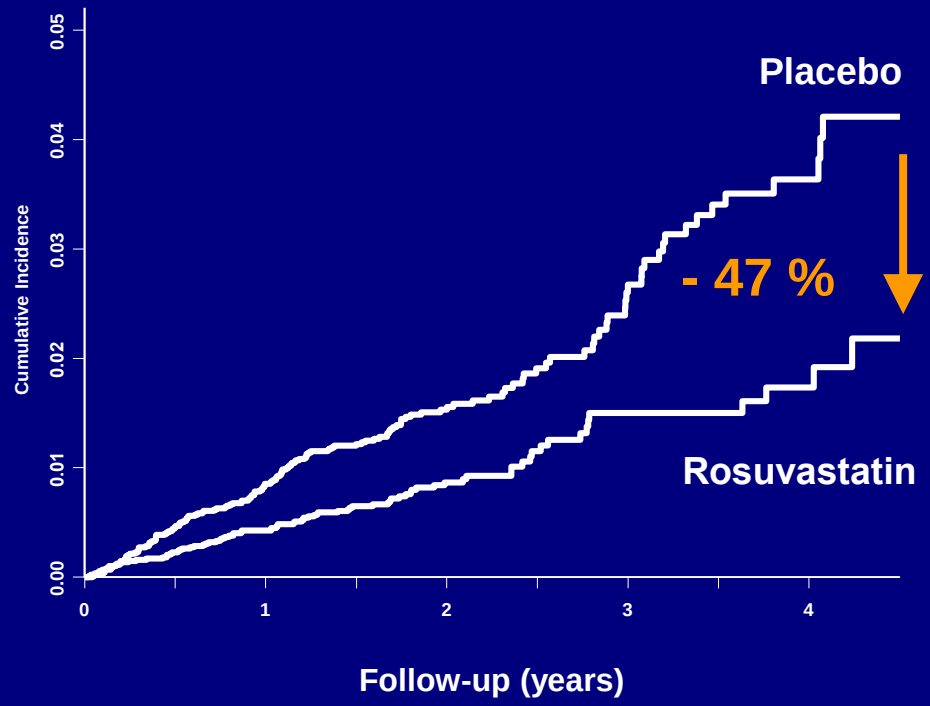


JUPITER
Grouped Components of the Primary Endpoint

Ridker et al NEJM 2008

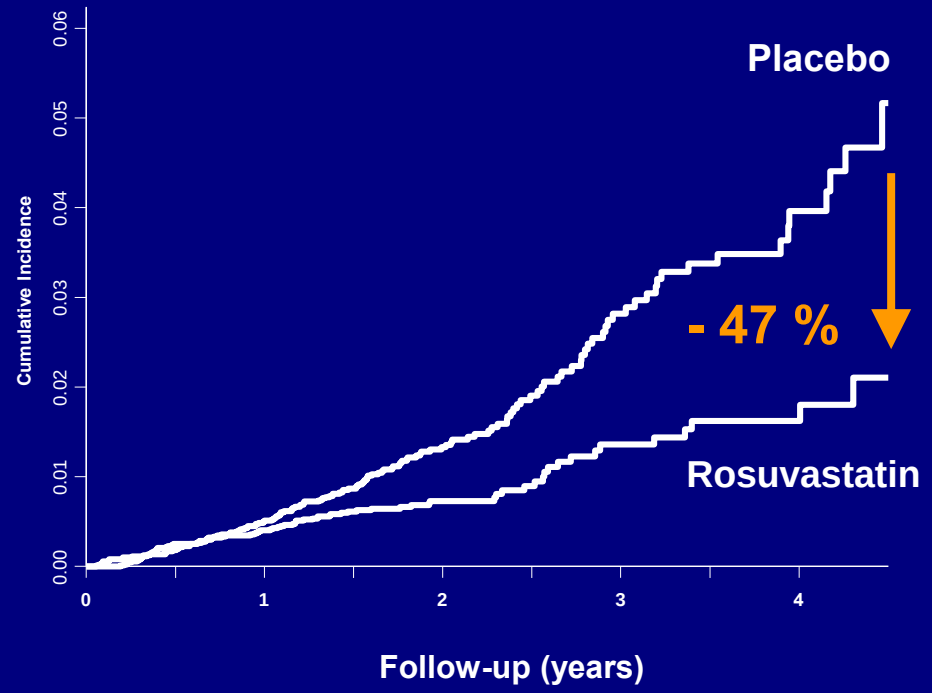
Myocardial Infarction, Stroke, or Cardiovascular Death

HR 0.53, CI 0.40-0.69
P < 0.00001



Arterial Revascularization or Hospitalization for Unstable Angina

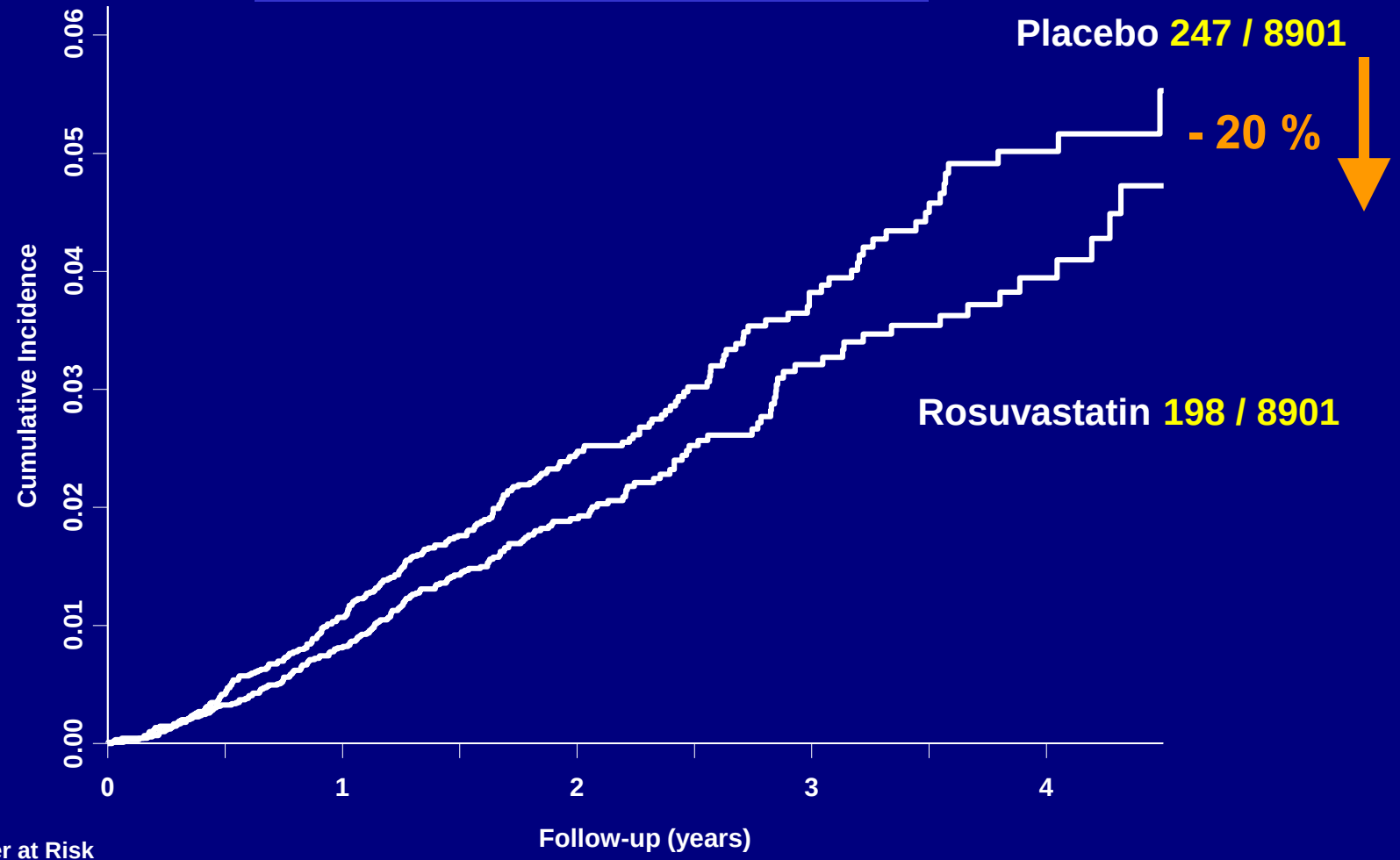
HR 0.53, CI 0.40-0.70
P < 0.00001



JUPITER
Secondary Endpoint – All Cause Mortality

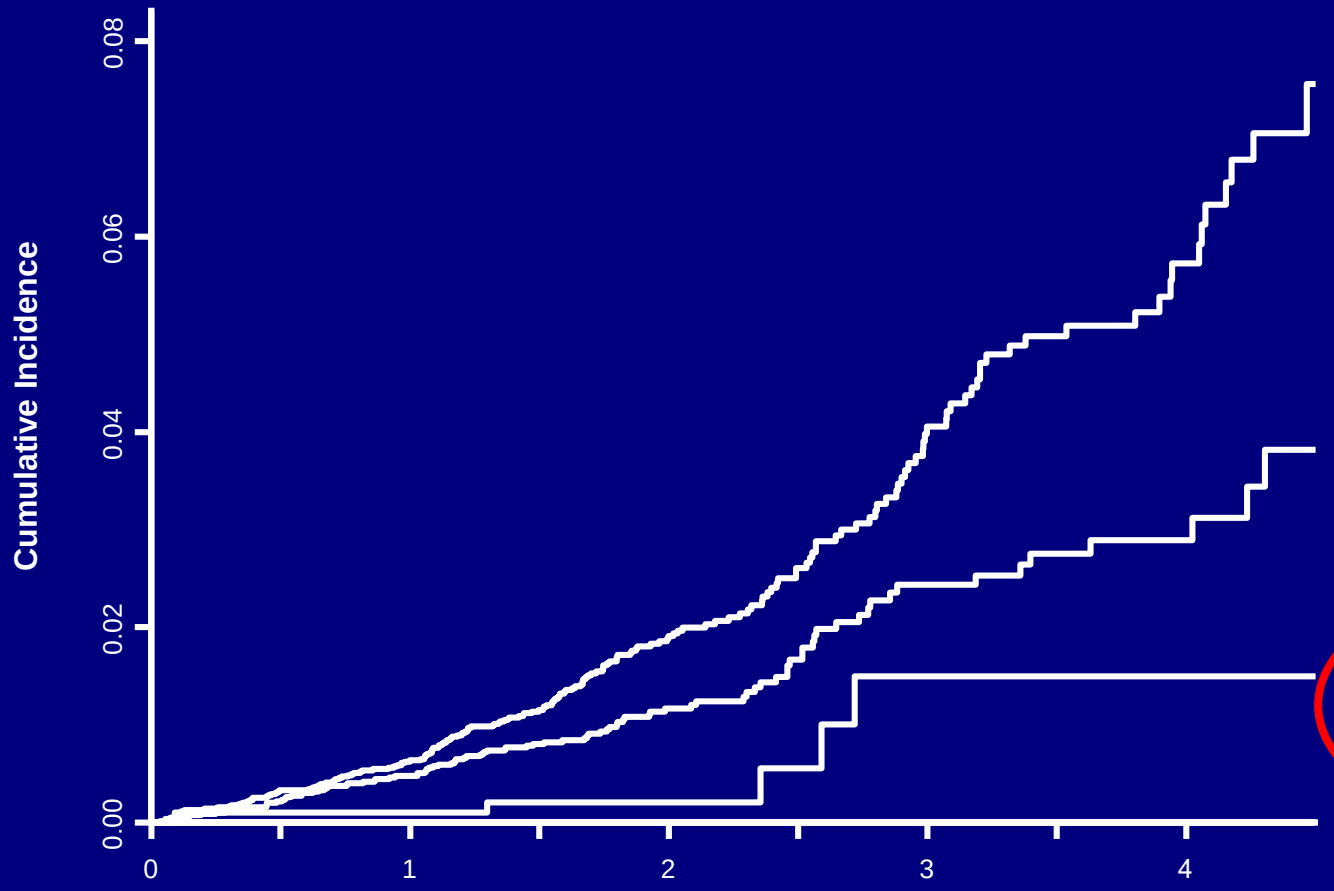
Ridker et al NEJM 2008

HR 0.80, 95%CI 0.67-0.97
P= 0.02



Number at Risk										
Rosuvastatin	8,901	8,847	8,787	6,999	4,312	2,268	1,602	1,192	683	227
Placebo	8,901	8,852	8,775	6,987	4,319	2,295	1,614	1,196	684	246

JUPITER
Dual Target Analysis: LDLC<70 mg/dL, hsCRP<1 mg/L



Placebo
HR 1.0 (referent)

LDL > 70 mg/dL
and / or
hsCRP > 1 mg/L
HR 0.59 (0.46-0.75)

LDL < 70 mg/dL
and
hsCRP < 1 mg/L
HR 0.21 (0.09-0.51)

P < 0.0001

Number at Risk										
Rosuvastatin	7,716	7,699	7,678	6,040	3,608	1,812	1,254	913	508	145
Placebo	7,832	7,806	7,777	6,114	3,656	1,863	1,263	905	507	168

N Engl J Med 2008; 359:2195-2207

JUPITER
Adverse Events and Measured Safety Parameters

Ridker et al NEJM 2008

Event	Rosuvastatin	Placebo	P
Any SAE	1,352 (15.2)	1,337 (15.5)	0.60
Muscle weakness	1,421 (16.0)	1,375 (15.4)	0.34
Myopathy	10 (0.1)	9 (0.1)	0.82
Rhabdomyolysis	1 (0.01)*	0 (0.0)	--
Incident Cancer	298 (3.4)	314 (3.5)	0.51
Cancer Deaths	35 (0.4)	58 (0.7)	0.02
Hemorrhagic stroke	6 (0.1)	9 (0.1)	0.44
GFR (ml/min/1.73m^2 at 12 mth)	66.8 (59.1-76.5)	66.6 (58.8-76.2)	0.02
ALT > 3xULN	23 (0.3)	17 (0.2)	0.34
Fasting glucose (24 mth)	98 (91-107)	98 (90-106)	0.12
HbA1c (% at 24 mth)	5.9 (5.7-6.1)	5.8 (5.6-6.1)	0.01
Glucosuria (12 mth)	36 (0.5)	32 (0.4)	0.64
Incident Diabetes**	270 (3.0)	216 (2.4)	0.01

*Occurred after trial completion, trauma induced.

**Physician reported

All values are median (interquartile range) or N (%)

JUPITER and It's Satellites Studies

- In healthy men and women, hsCRP ↑ ⇒ rosuvastatin therapy ⇒ both LDLC *and* hsCRP ↓ ⇒ event-free survival ↑ **(N Engl J Med. 2008;359(21):2195-207)**

- Rosuvastatin therapy ⇒ Venous Thromboembolism ↓ **(Glynn et al NEJM 2009)**

- Rosuvastatin therapy ⇒ Ischemia stroke↓ **(Circulation. 2010;121:143-150)**

- Rosuvastatin therapy ⇒ CKD p't 1st CV event and all cause mortality↓
(J Am Coll Cardiol 2010;55:1266–73 5:1266–73)

- Rosuvastatin therapy ⇒ Osteoporosis, bone fracture ⇒ no effects **(JAMA Intern Med. 2015;175(2):171-7)**

FDA did not approve its indication (anti-inflammation) !!

- Epidemiologic of ASCVD
- Definition of high risk and very high risk ASCVD
- Jupiter Trial ⇒ Rationale, Results and Clinical impact
- **High potency, efficacy and safe of Rosuvastatin**
- Conclusions

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.

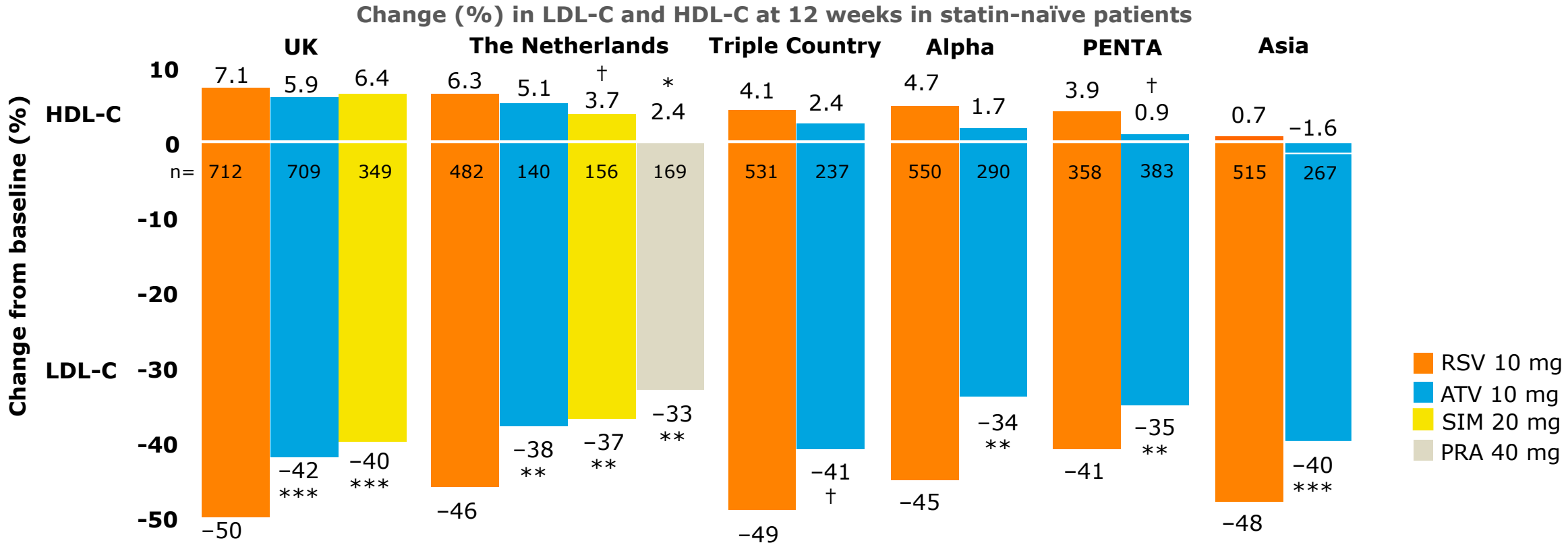
1. Adapted from FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. U.S. Food and Drug Administration. Updated 2016. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm Last accessed: 19.12.2016.

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

* Rosuvastatin 40mg is not indicated in Taiwan

CRESTOR® rosuvastatin calcium

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



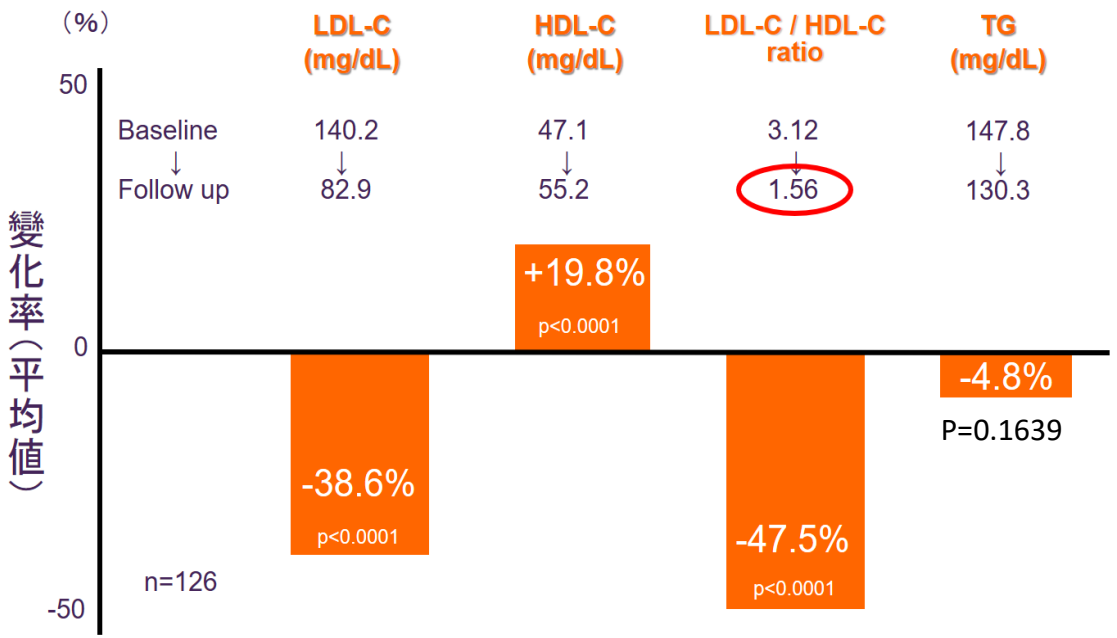
Curr Ther Res 2006; 67: 21–43.
Int J Clin Pract 2005; 59: 1387–1394.
Curr Med Res Opin 2005; 21: 1307–1315
Br J Cardiol 2006; 13: 72–76.
Clin Ther 2004; 26: 1821–1833.
Curr Med Res Opin 2007; 23: 3055–3068

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

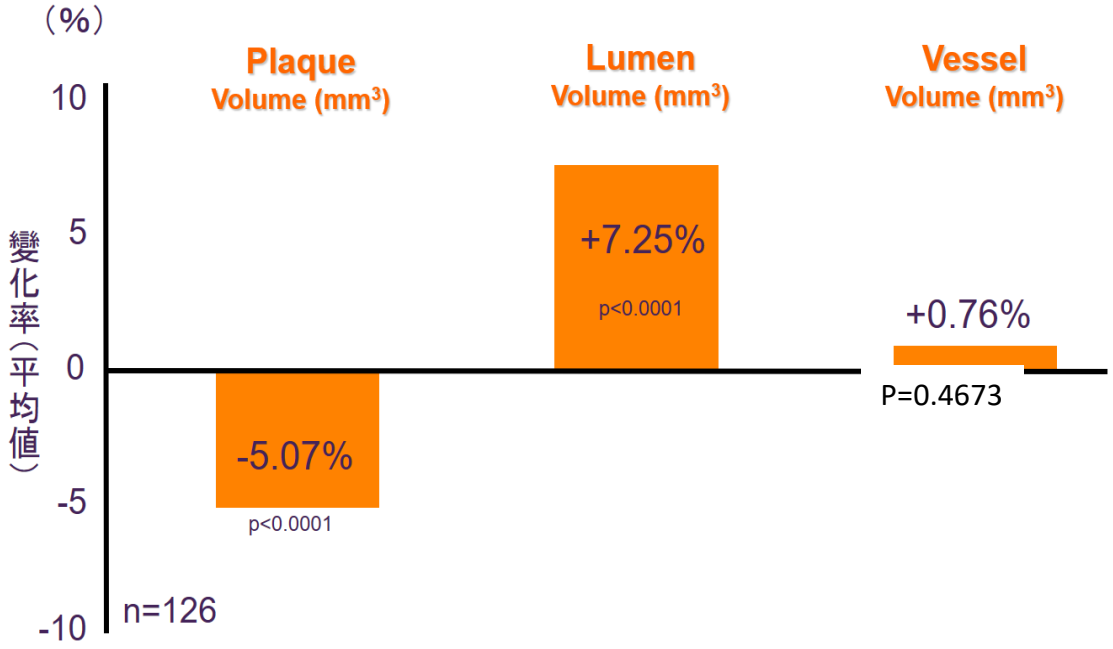
Based on individual statin efficacy data, not head-to-head comparisons between statins.

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

COSMOS Lipid Profiles



Reduction of Plaque Volume

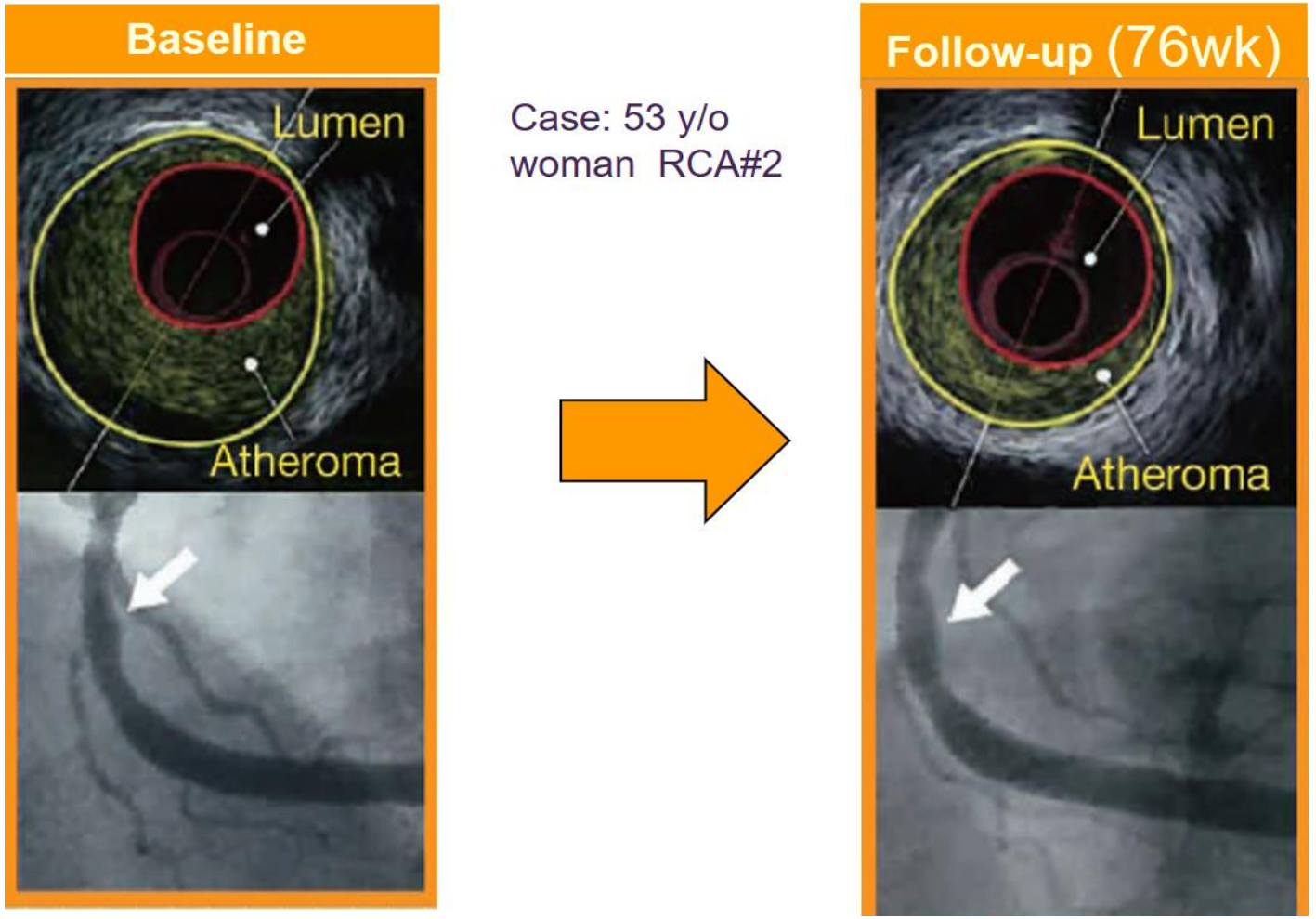


- Study design: A 18 month, open-label, multicentre, single-arm study using intravascular ultrasound (IVUS) to evaluate the effect of CRESTOR 2.5mg-20mg on the progression of plaque volume in Japanese subjects with hypercholesterolaemia and coronary heart disease

*CRESTOR的劑量範圍是5-20mg每天一次, 並應根據治療目標及患者的反應個別調整劑量;
AstraZeneca does not recommend the use of rosuvastatin for indication other than hyperlipidemia and mixed dyslipidemia.

Circ J 2009; **73:** 2110 – 2117

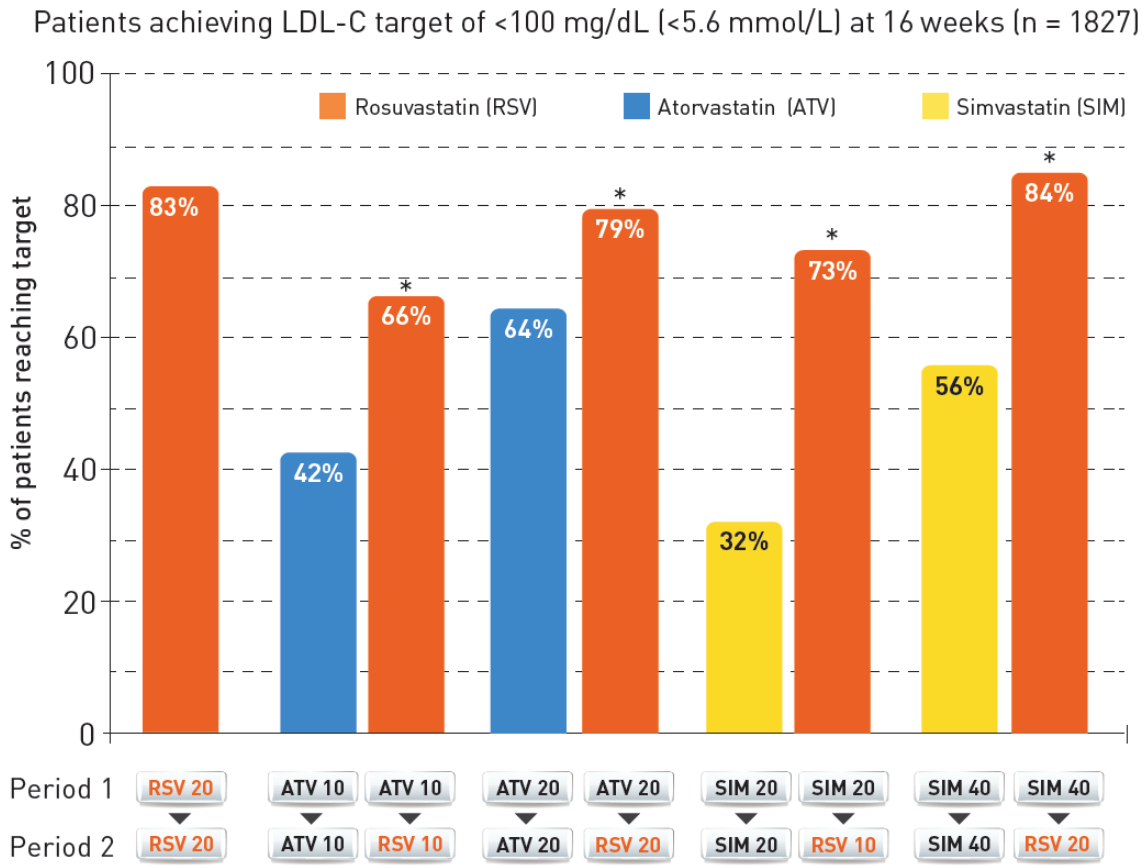
CRESTOR shows significant regression of coronary plaque volume in Japanese hyperlipidemia patients with stable CAD

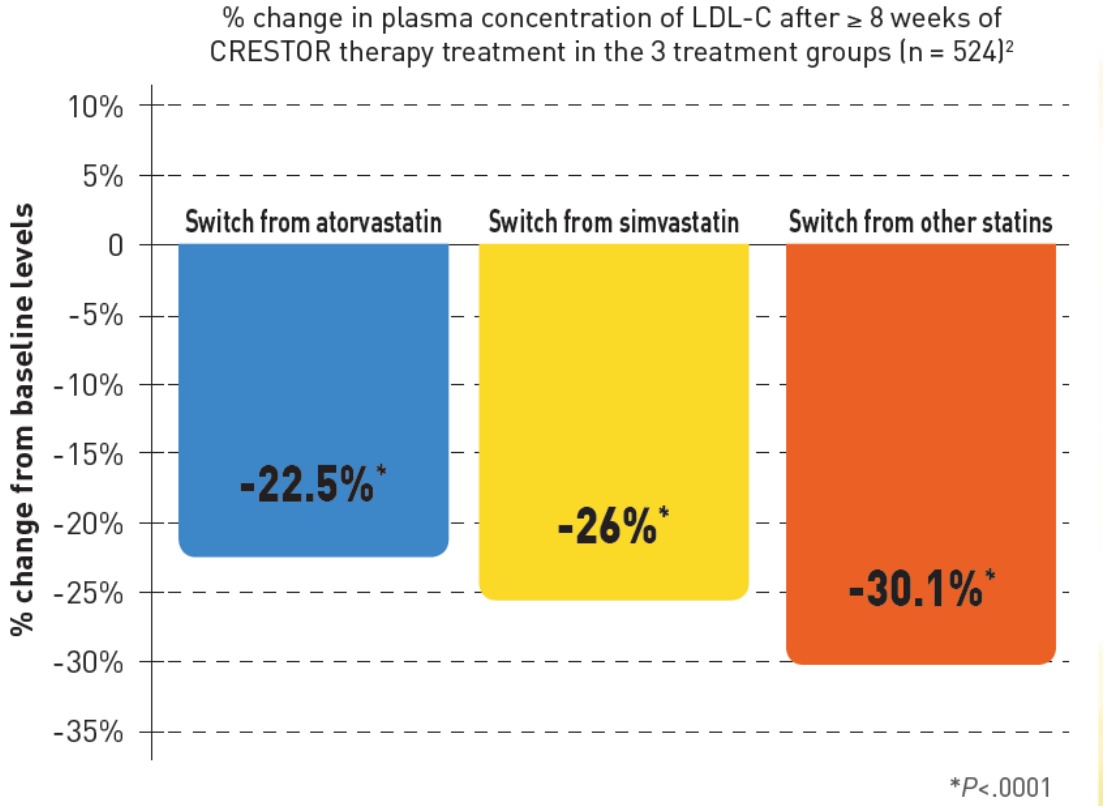


*CRESTOR的劑量範圍是5-20mg每天一次, 並應根據治療目標及患者的反應個別調整劑量;
AstraZeneca does not recommend the use of rosuvastatin for indication other than hyperlipidemia and mixed dyslipidemia.

Circ J 2009; **73:** 2110 – 2117

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



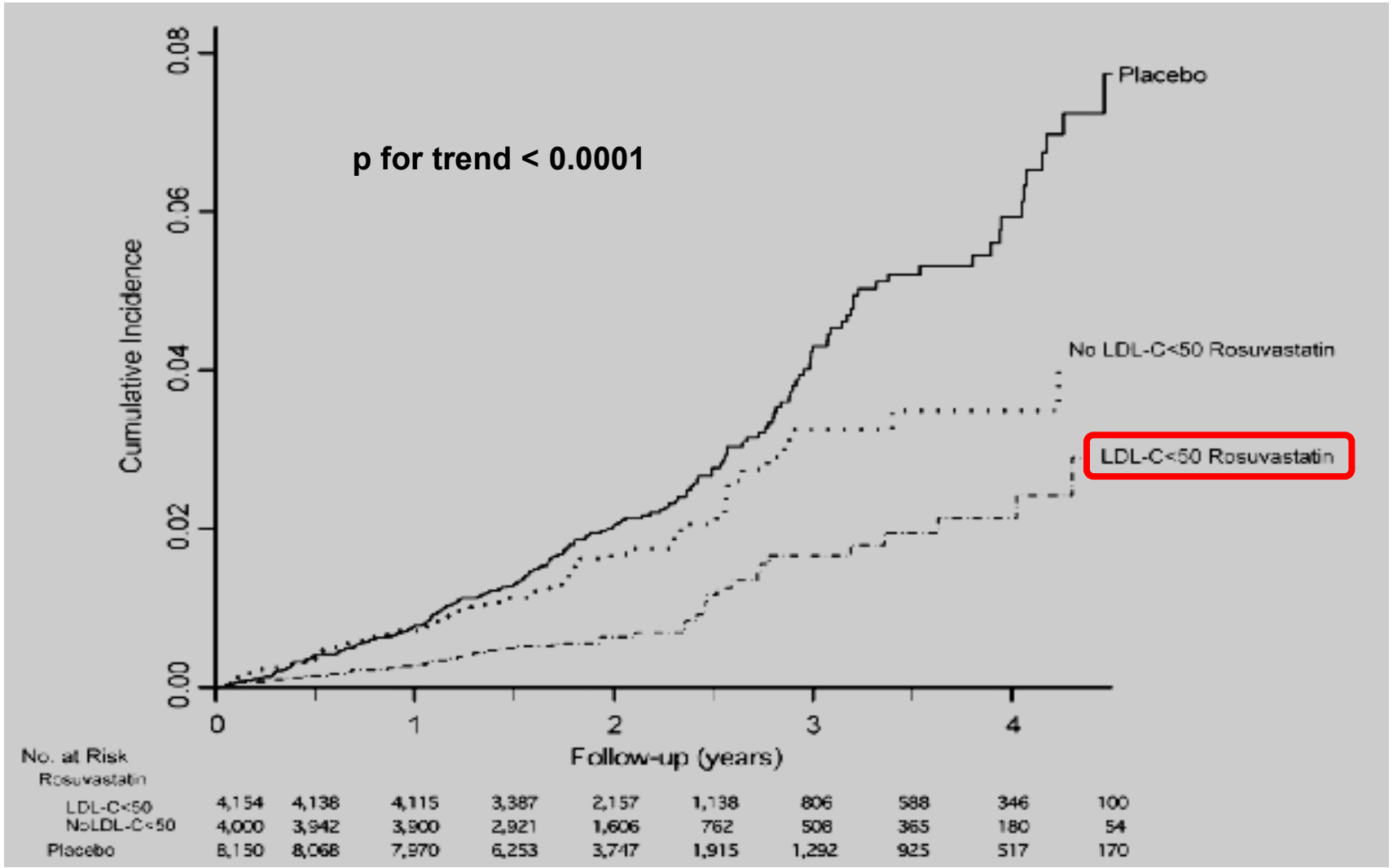


LDL-C goals were achieved in a greater proportion of high-risk patients (n = 1011) after switching to rosuvastatin compared to those remaining on atorvastatin or simvastatin[1]

- 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

- Epidemiologic of ASCVD
- Definition of high risk and very high risk ASCVD
- Jupiter Trial ⇒ Rationale, Results and Clinical impact
- High potency, efficacy and **safe of Rosuvastatin**
- Conclusions

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

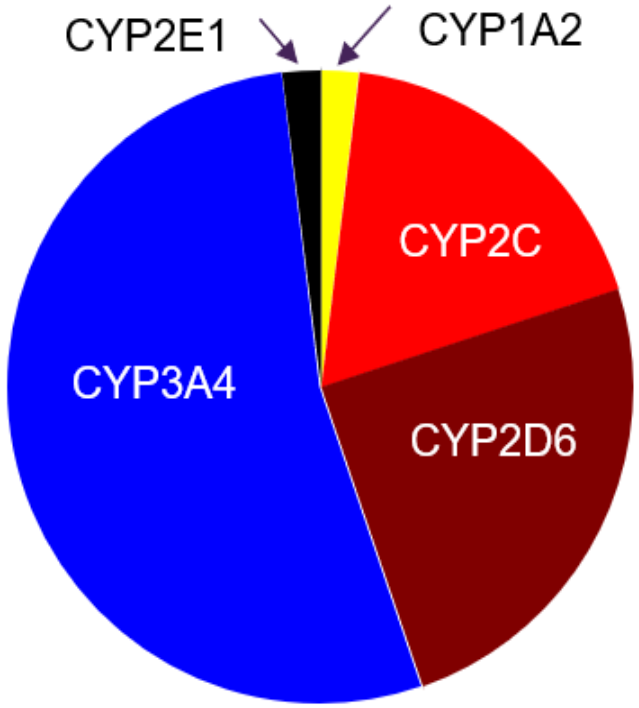
CRESTOR® rosuvastatin calcium

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



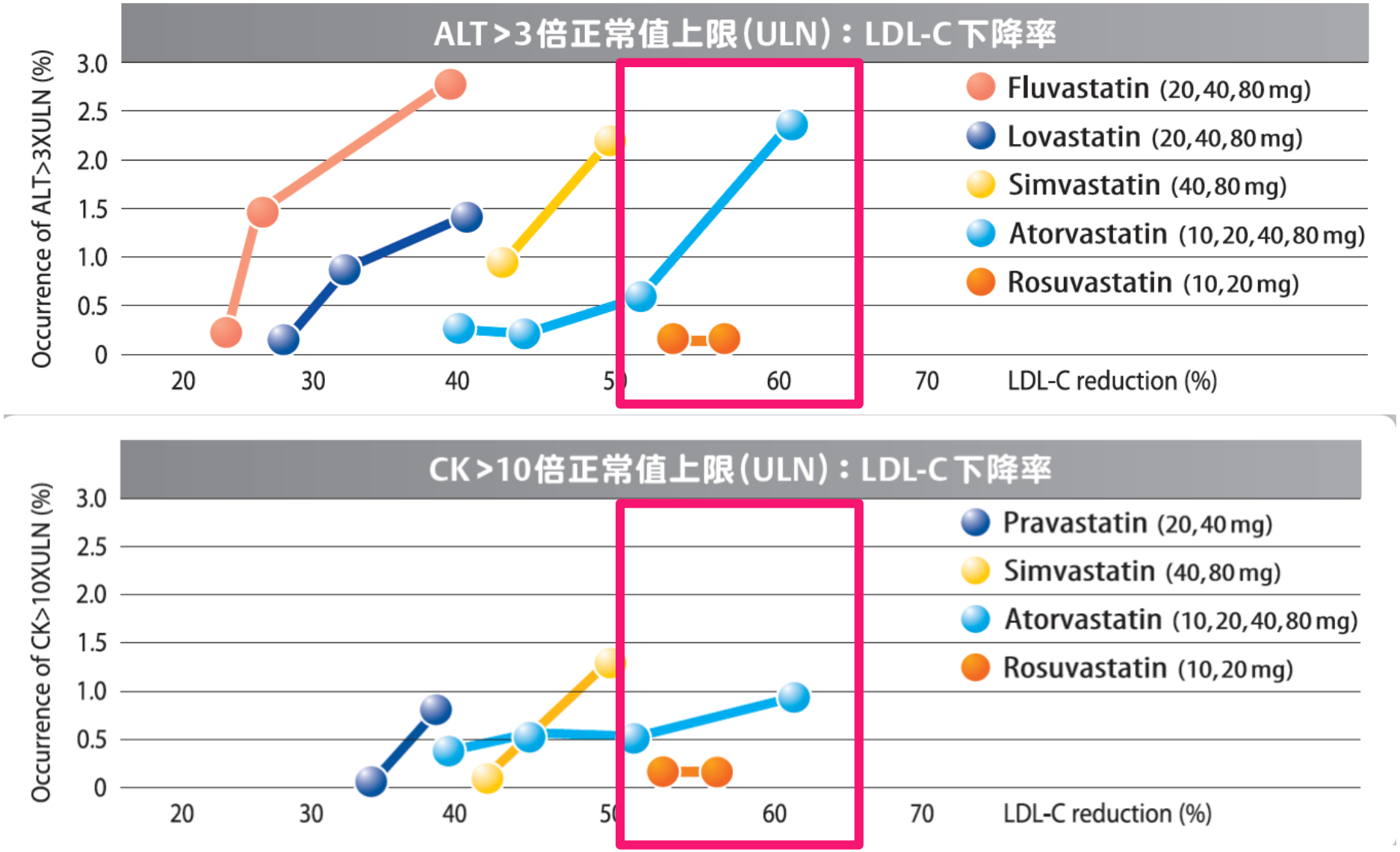
CYP 2C9

- 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

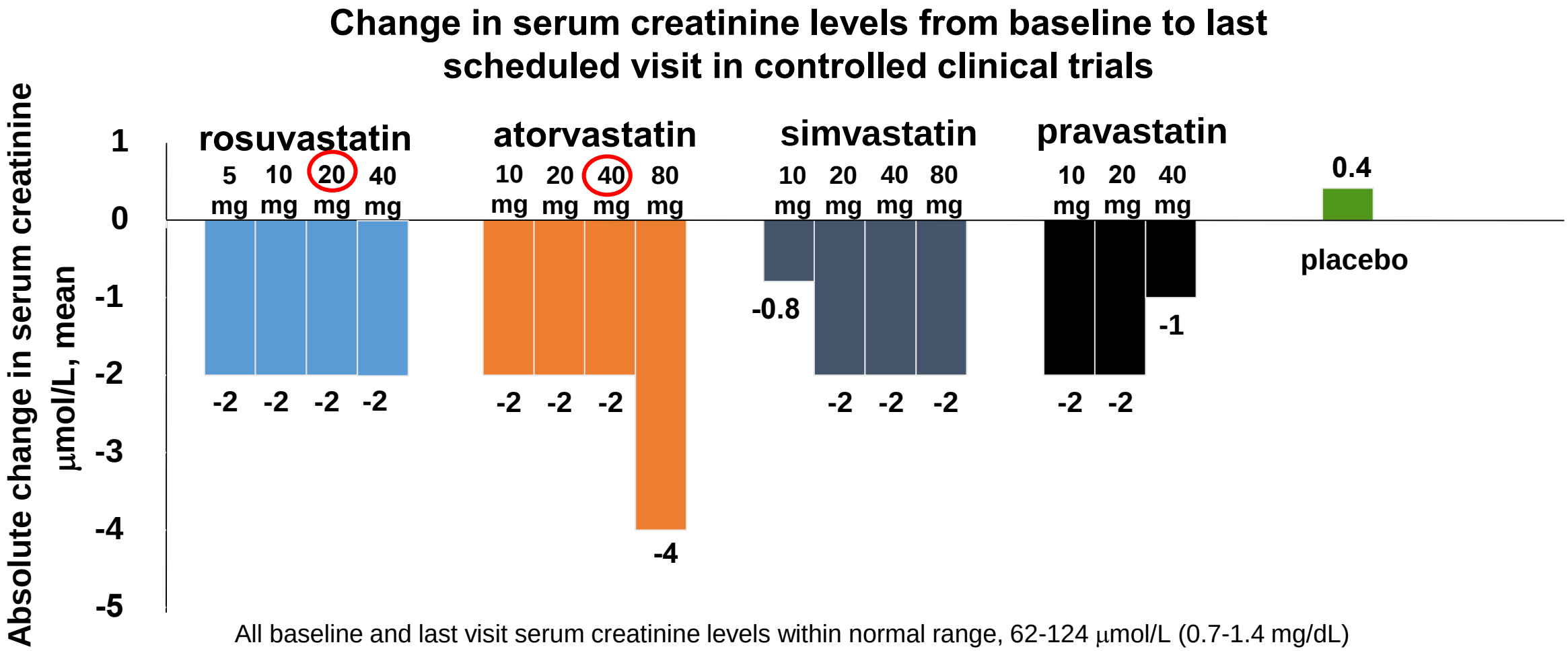
CRESTOR® rosuvastatin calcium

CRESTOR : 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

CRESTOR : 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)

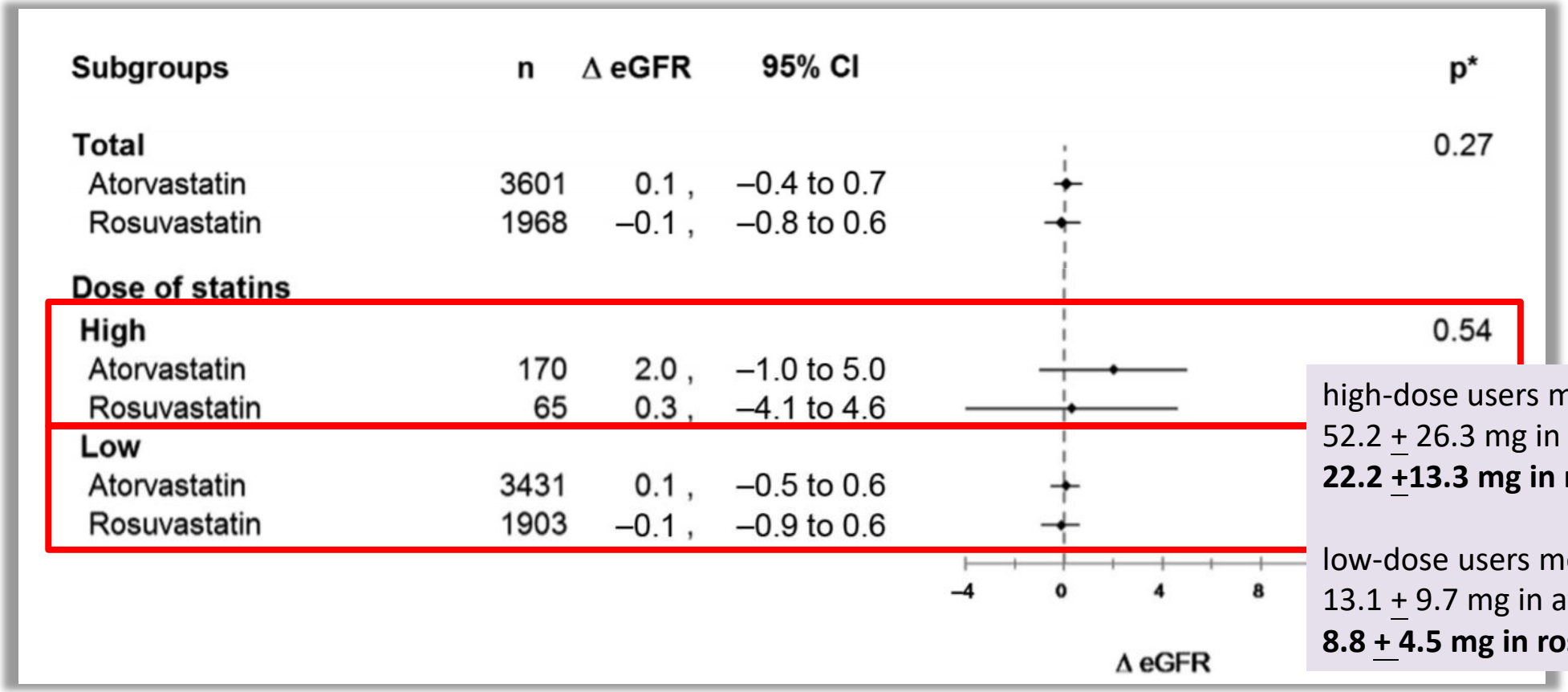
*Rosuvastatin 40mg is not indicated in Taiwan

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

Taiwan RWE: CRESTOR 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,*]



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	

N= 5556

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.

*依照仿單, CRESTOR的劑量範圍是5-20mg每天一次

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.

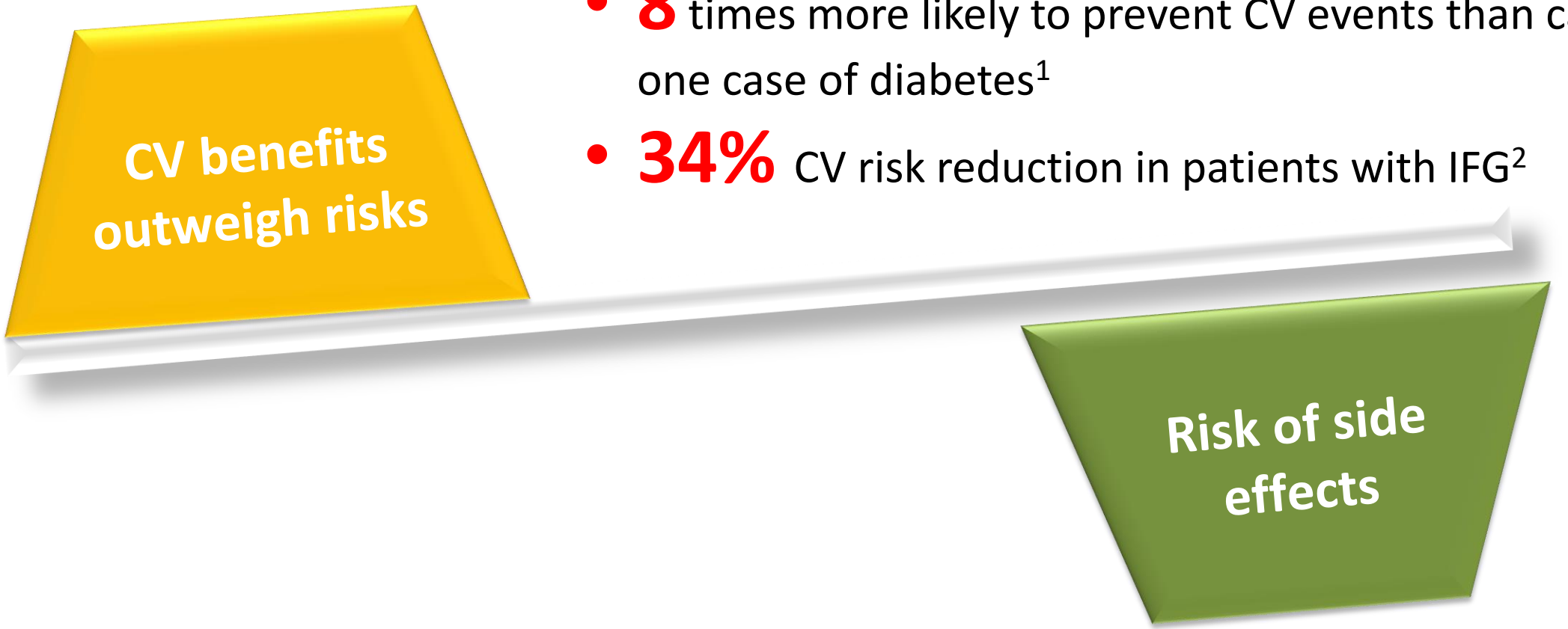
Cox univariate analysis of incidence of hazard ratios (HRs) with 95% CIs for patients with new-onset diabetes (NOD) according to prescriptions for statins compared with non-NOD subjects.

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.

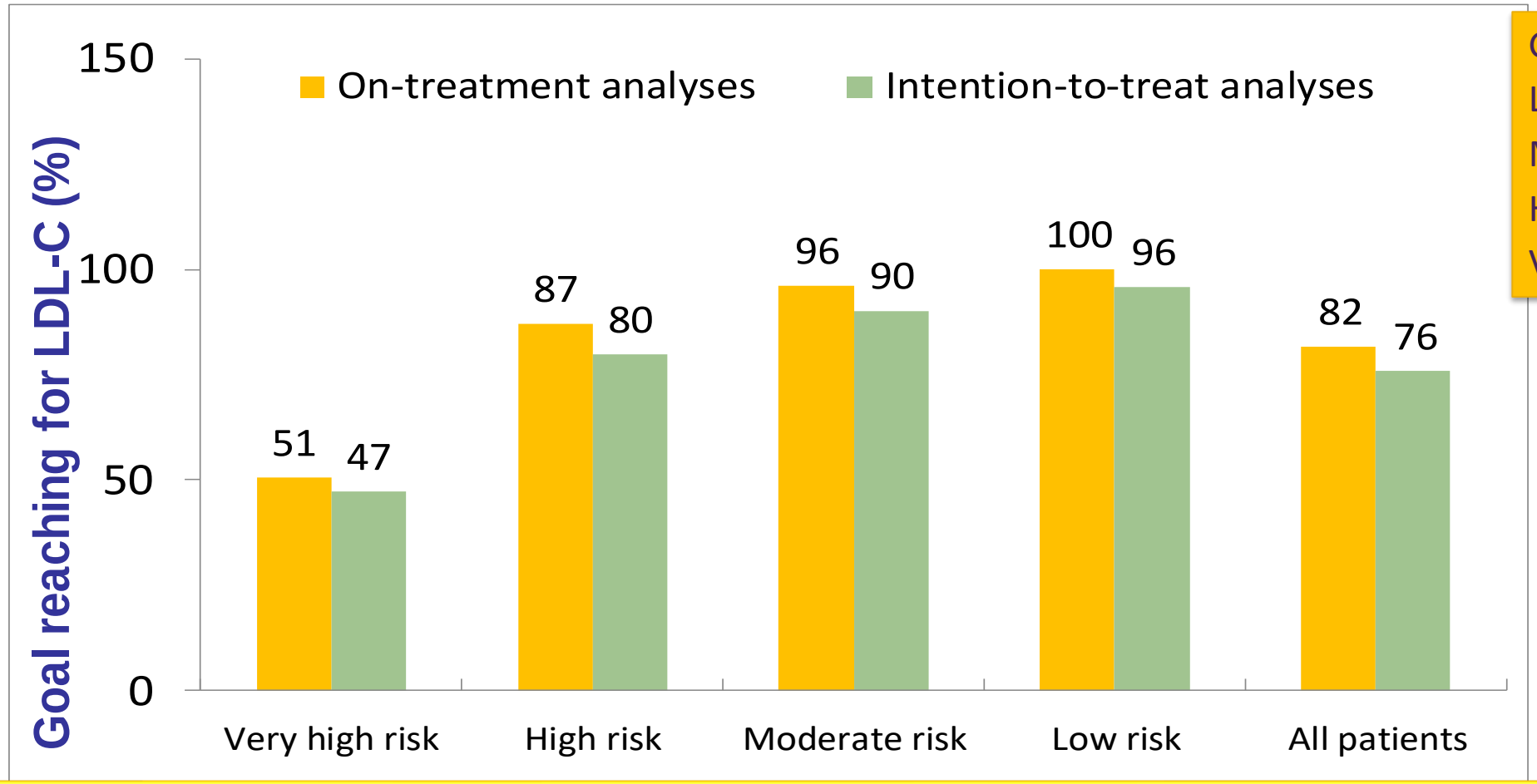
Statin risk summary: CV benefits outweigh risks



- **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.

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



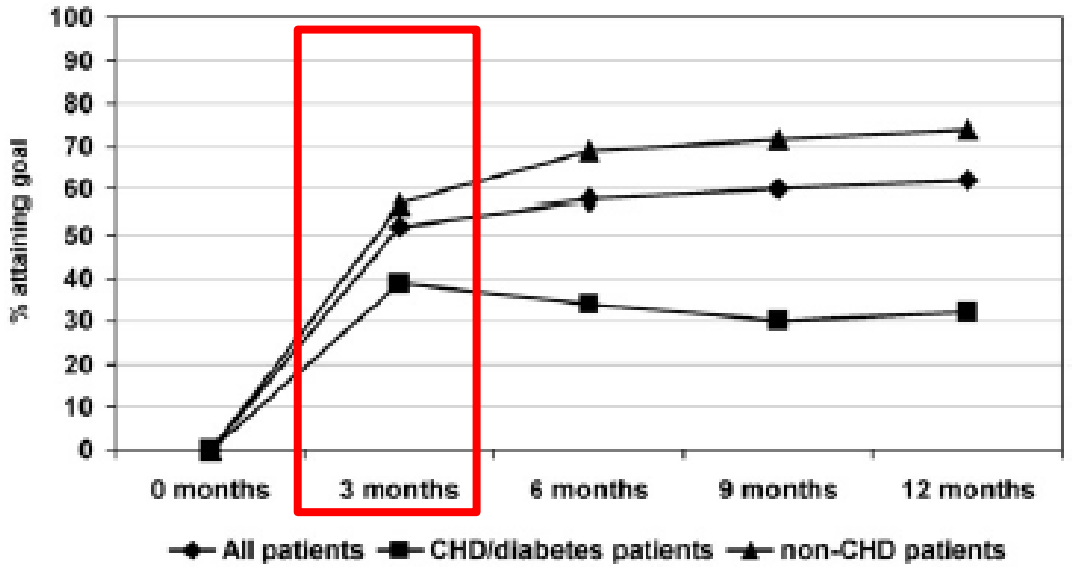
Goal (mg/dL)
Low risk < 160
Moderate risk < 130
High risk <100
Very high risk <70

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

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

Associated with goal attainment icluding two factors:
(a) Initial statin potency (b) Early Treatment to Target in 3 months

Statin equidose potency (referent = 1)		
Potency = 2	1.473 (0.962–2.255)	0.0744
Potency = 3	1.796 (1.187–2.719)	0.0056
Potency ≥ 4	2.253 (1.364–3.722)	0.0015
Discontinued therapy	1.353 (0.913–2.004)	0.1315
Switched from initial statin (vs remained on initial statin)	0.859 (0.597–1.235)	0.4117
Up-titrated initial statin dose	1.015 (0.694–1.484)	0.9380
Down-titrated initial statin dose	1.254 (0.852–1.846)	0.2517



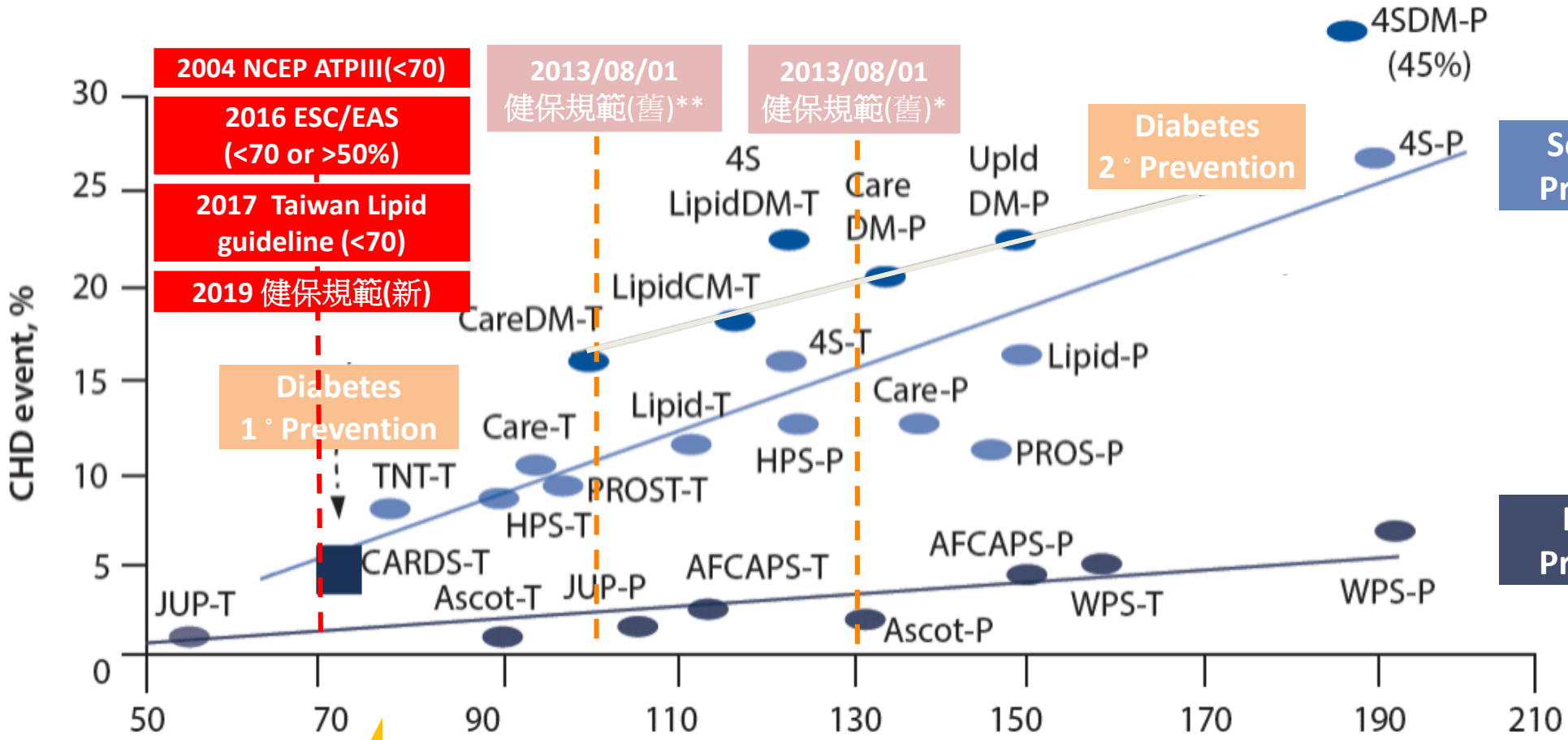
Curr Med Res Opin. 2008 Jul; 24(7): 1951-63

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

CRESTOR® rosuvastatin calcium

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

Conclusions

- ASCVD showing early signs of reversal in some population groups.
- Atherosclerosis ⇒ inflammation disease
- LDL-C ⇒ the lower , the better
- Low risk ⇒ LDL-C 116mg/dL, High risk ⇒ LDL-C 70mg/dL,
- Very high risk ⇒ LDL-C 55mg/dL (and 50% ↓ from baseline)
- Rosuvastatin ⇒ 10mg: LDL-C 47%↓, 20mg: LDL-C 55%↓
- Rosuvastatin ⇒ Low dose, high potency, safe.

Cardiovascular Center, TCVGH

Take Home Messages

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

CRESTOR®
rosuvastatin

提供血脂患者的治療首選

CRESTOR 10mg
有效降脂 47% 輕鬆達標

CRESTOR 20mg
優越降脂 55% 積極達標

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