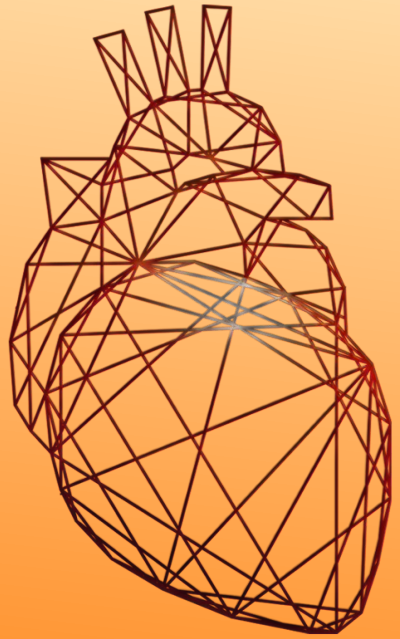


OPTIMAL TREATMENT FOR PATIENTS WITH DYSLIPIDEMIA：A MUST APPROACH FOR HIGH RISK PATIENTS

Speaker : 洪正中醫師

Date : 2019.09.01

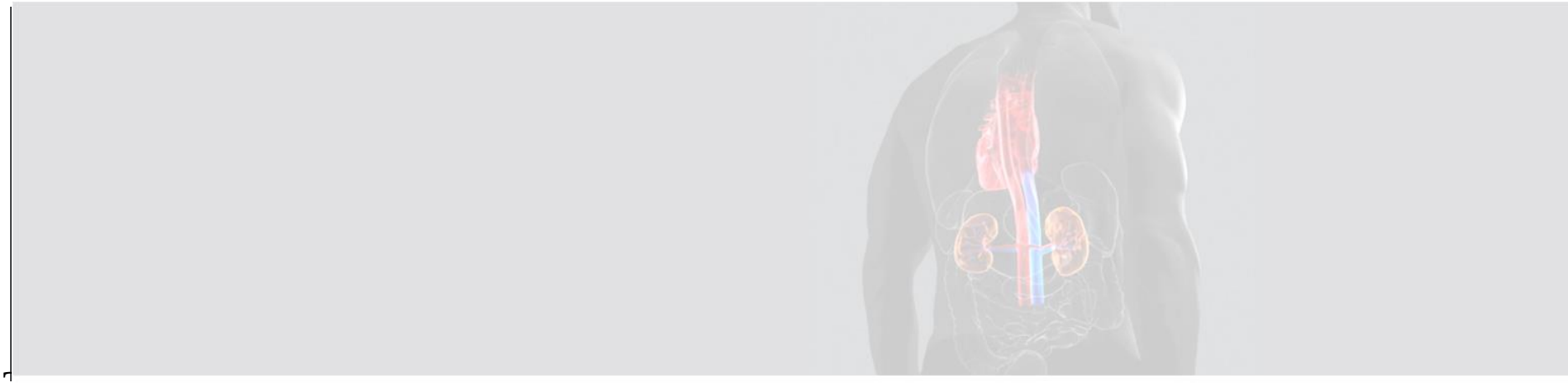
01 Implications of outcome study on guideline updates

02 Clinical data
between LDL-C 50% reduction and CV outcome

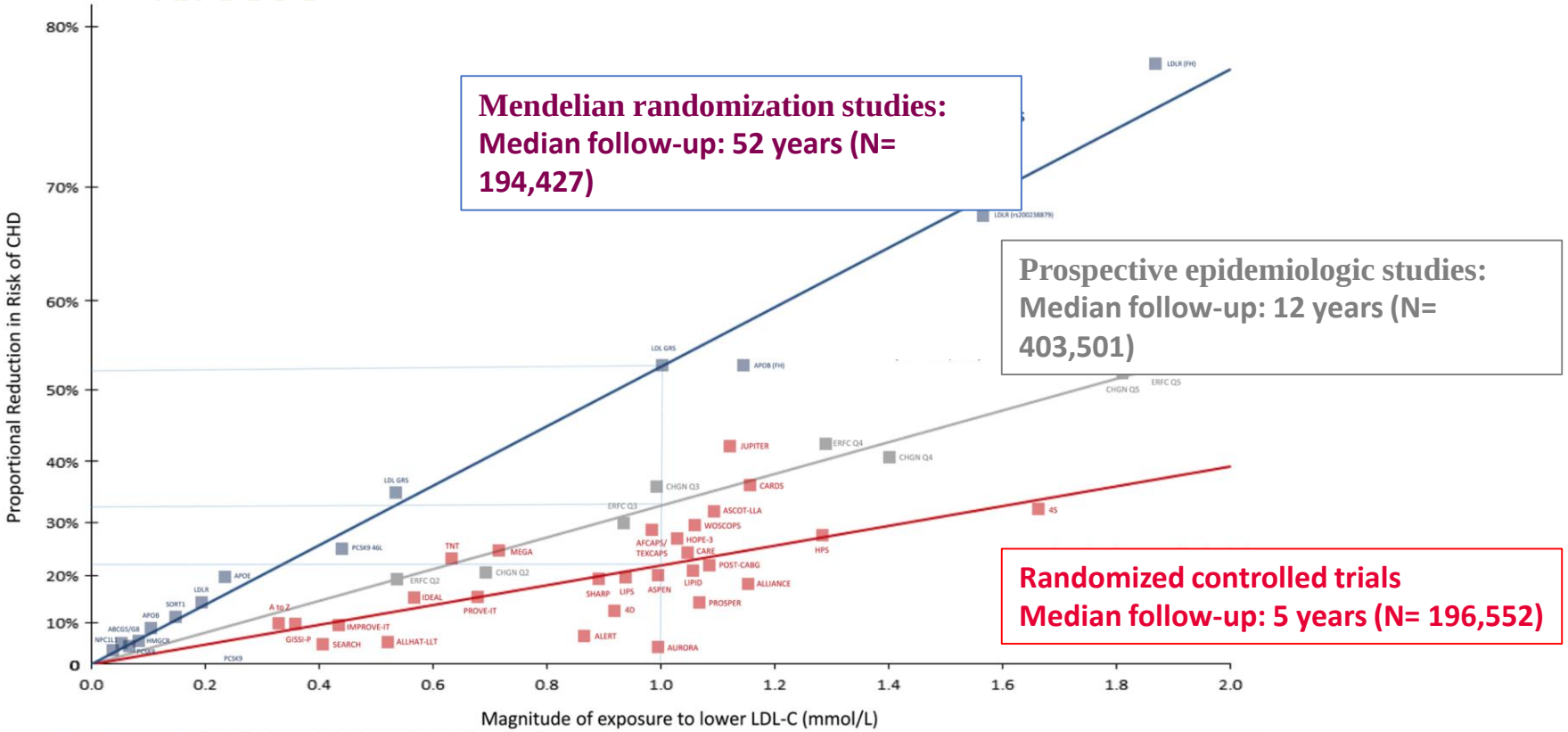
03 Remaining statin associated issues

Chapter 1

Implications of outcome study on guideline updates

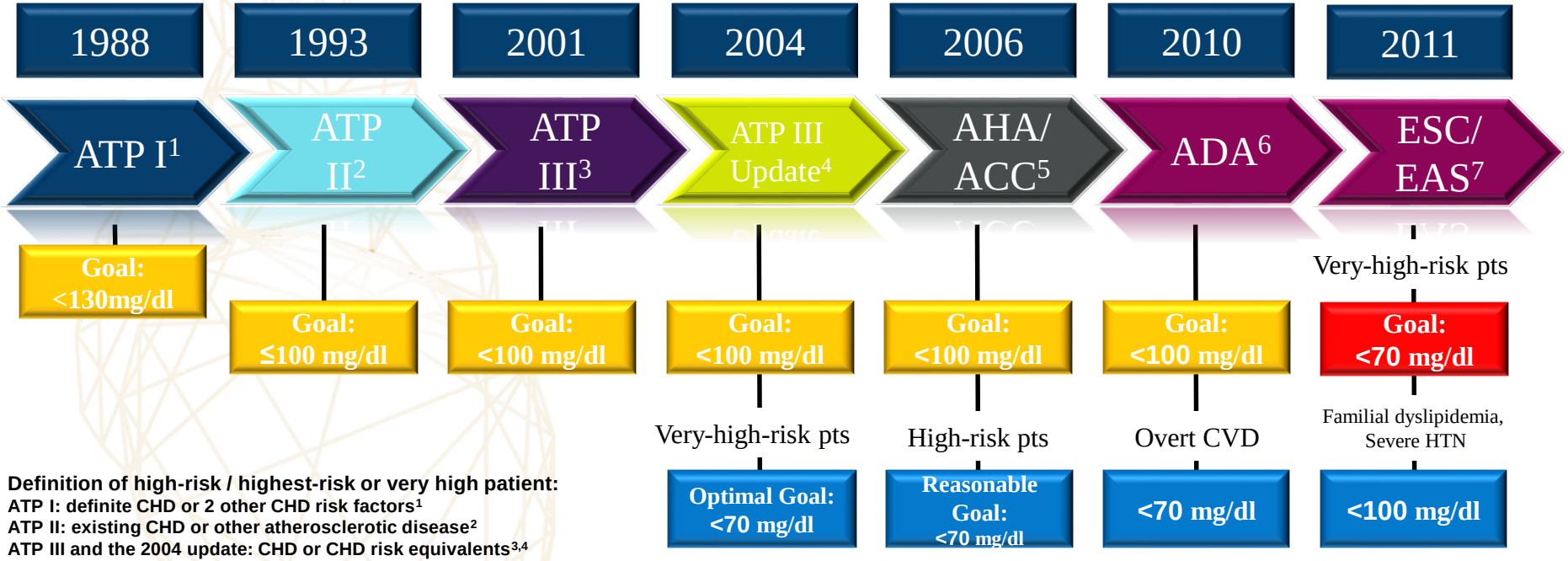


LDL cause atherosclerotic cardiovascular disease (ASCVD) : Evidence from genetic, epidemiologic, and clinical studies



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

Guideline continued to recommend lower LDL-C target

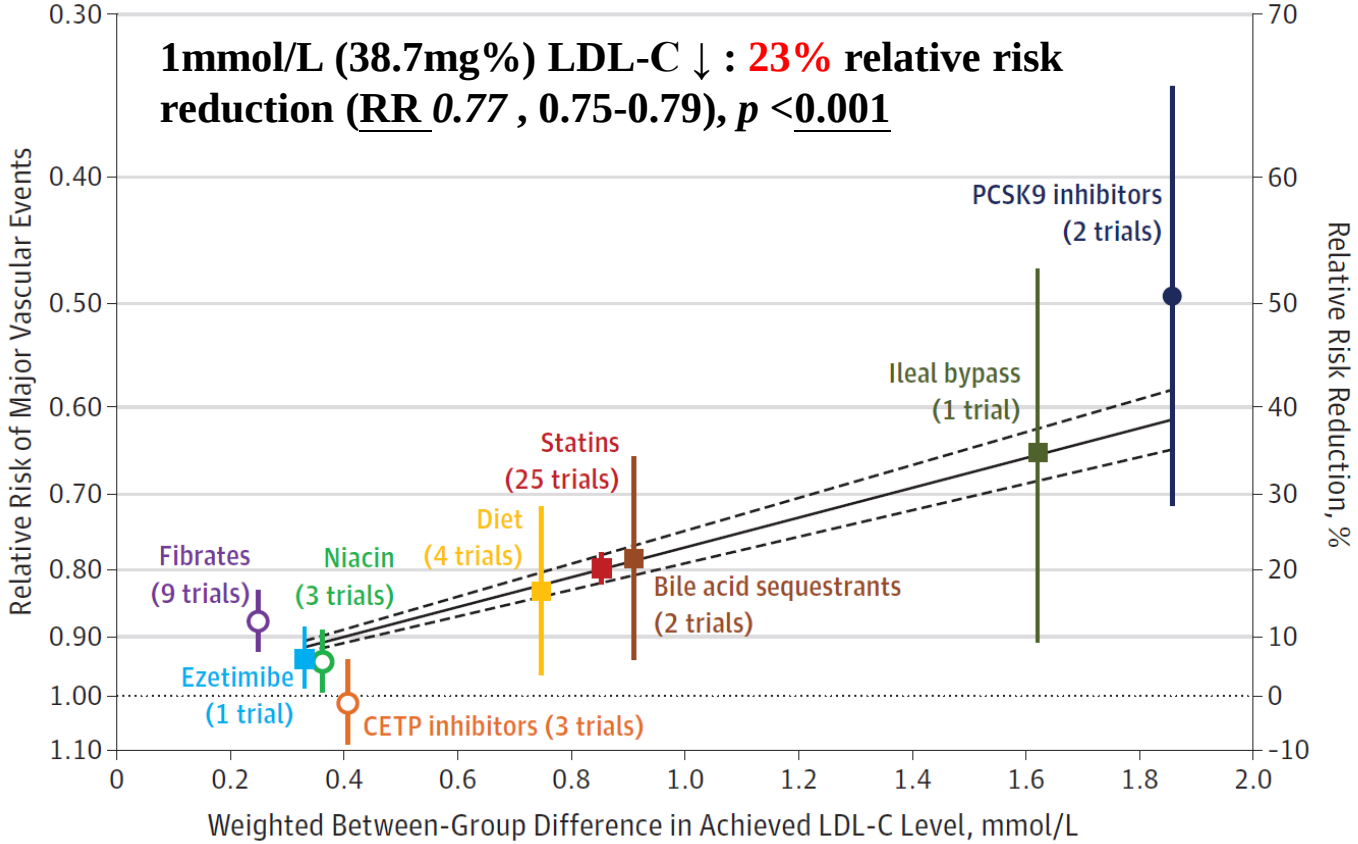


Definition of high-risk / highest-risk or very high patient:
ATP I: definite CHD or 2 other CHD risk factors[1]
ATP II: existing CHD or other atherosclerotic disease[2]
ATP III and the 2004 update: CHD or CHD risk equivalents[3,4]
2° AHA/ACC 2006: established coronary and other atherosclerotic disease[5]
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

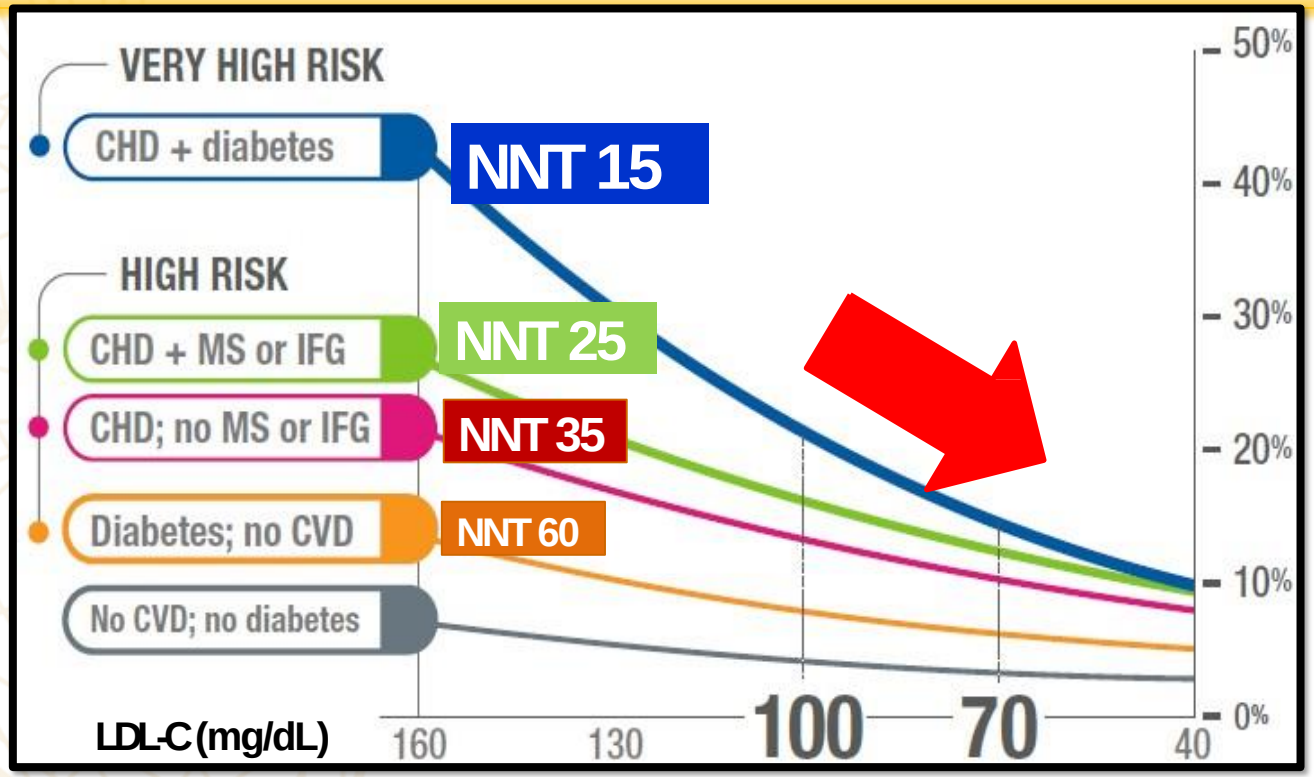
1. NCEP ATP I. Arch Intern Med. 1988;148:36–69; 2. NCEP ATP II. JAMA. 1993;269:3015–3023; 3. NCEP ATP III. JAMA. 2001;285:2486–2497; 4. Grundy SM et al. Circulation.2004;110:227–239; 5. Smith SC Jr et al. Circulation. 2006;113:2363–2372; 6. ADA. Diabetes Care. 2010;33(suppl 1):S11–S61. 7. Reiner Z. et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

Absolute reduction in LDL-C level :associated with the relative risk (RR) of major vascular coronary events



JAMA. 2016;316(12):1289-1297

Rate of CV Events are Related to Risk Level and LDL-C of CV Events are Related to Risk Level and LDL-C



5-year NNT to prevent 1 ASCVD event; NNT: # of risk patients needed to be treated to prevent one event over 5 years

Intent-to-treat LDL cholesterol level and risk for hard cardiovascular events (nonfatal MI, CHD death, and stroke) by the presence of CHD, metabolic syndrome (M impaired fasting glucose (IFG), or diabetes in placebo-controlled statin trials of approximately 5 years in duration

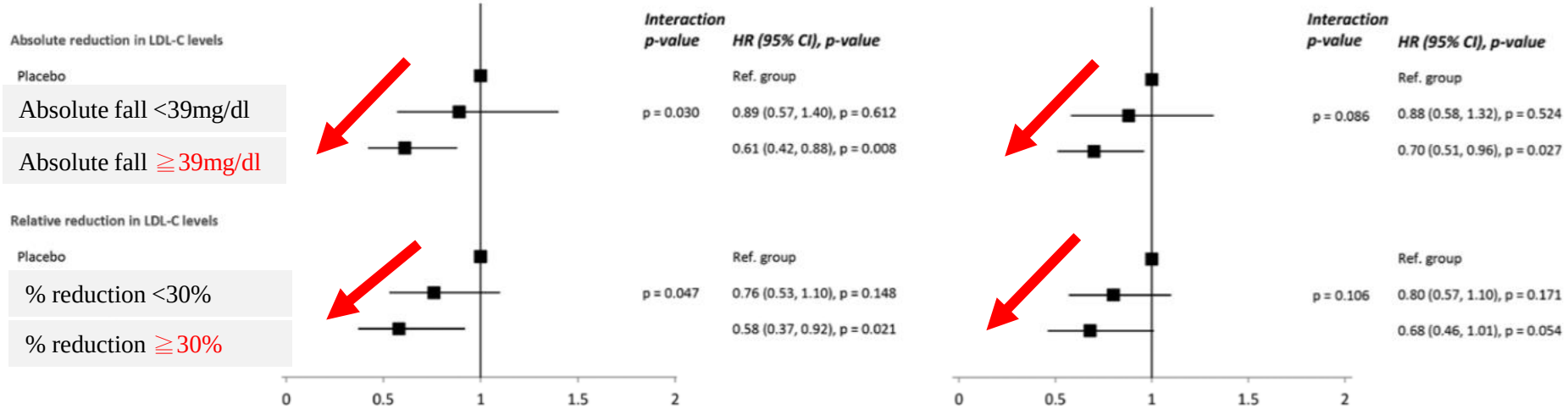
Robinson JG and Stone NJ. *Am J Cardiol.* 2006;98:1405–1408; Robinson JG. Curr Cardiol Rep. 2008;10:481–7.

LDL reduction with CV benefit from primary prevention

- WOSCOPS study: 5-Year Randomized Trial and 20-Year Observational Follow-Up

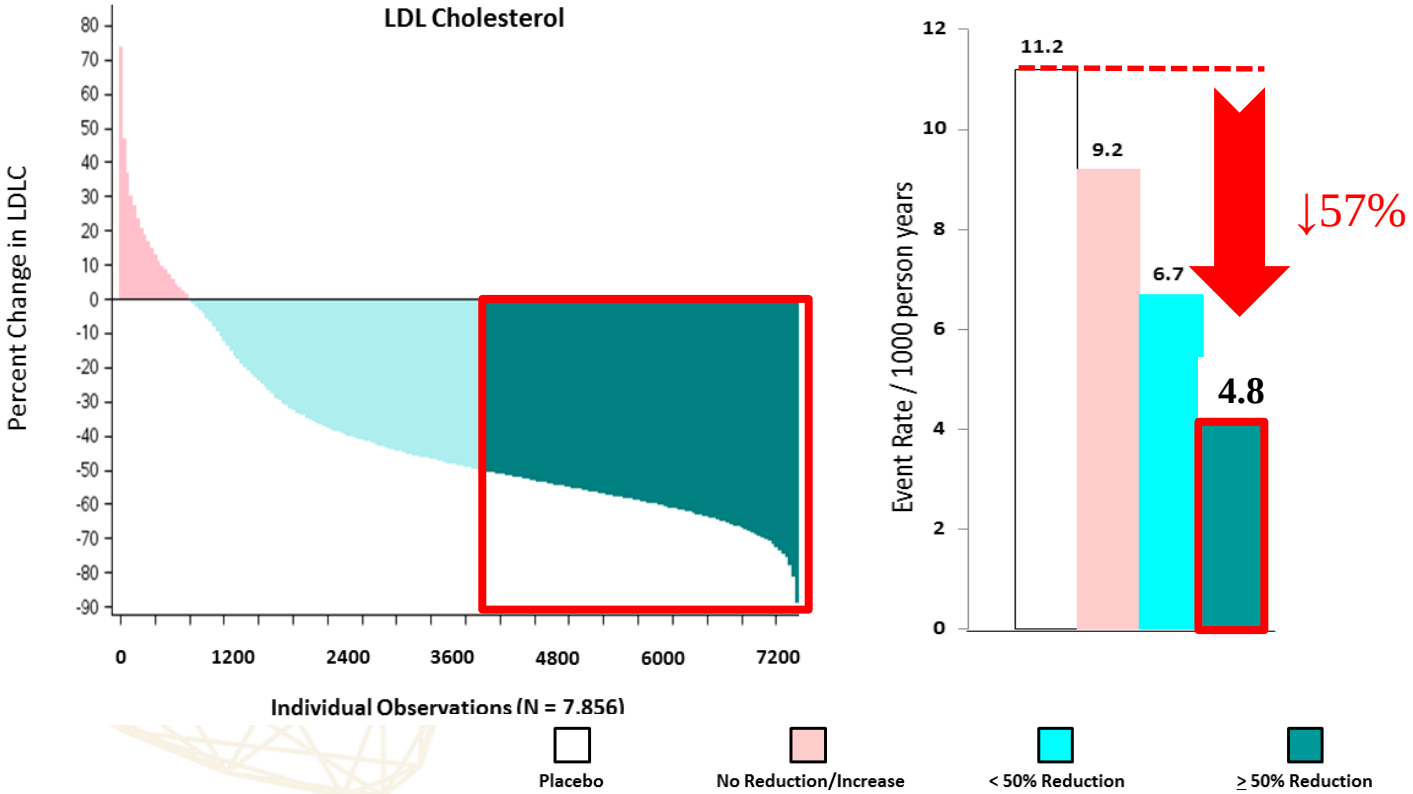
Coronary Heart Disease

MACE plus coronary revascularization



Circulation. 2017;136:1878–1891.

% LDL-C reduction : directly relates to efficacy of the Statin Rx.

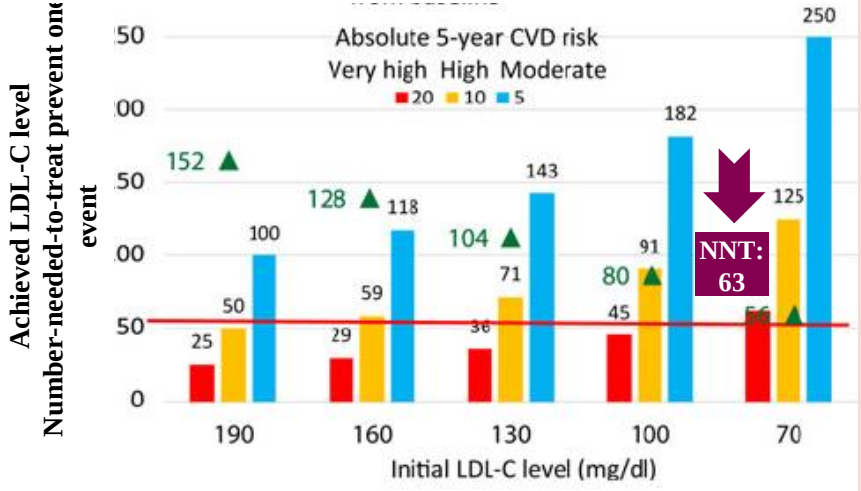


Eur Heart J 2016;350(May 1):2226

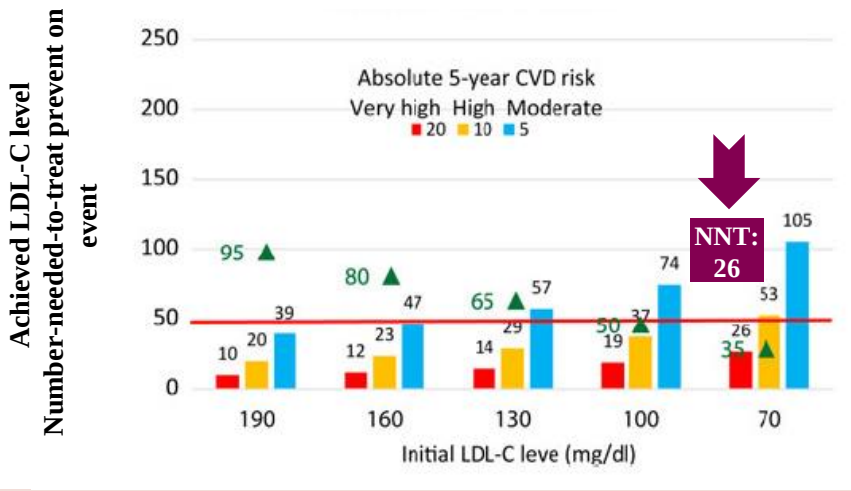
High intensity ≥50% reduction in LDL-C : Lower might be better

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.

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

LDL<70mg/dl

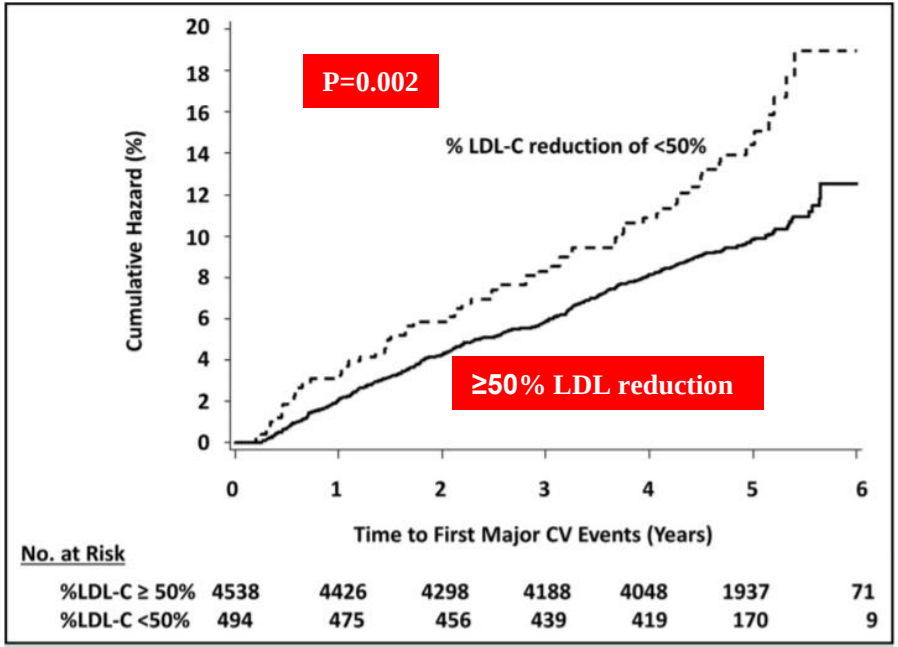


Figure 1 Major cardiovascular events in the cohort with attained LDL-C ≤70 mg/dL as a function of percent LDL-C reduction. LDL = low-density lipoprotein.

LDL>70mg/dl

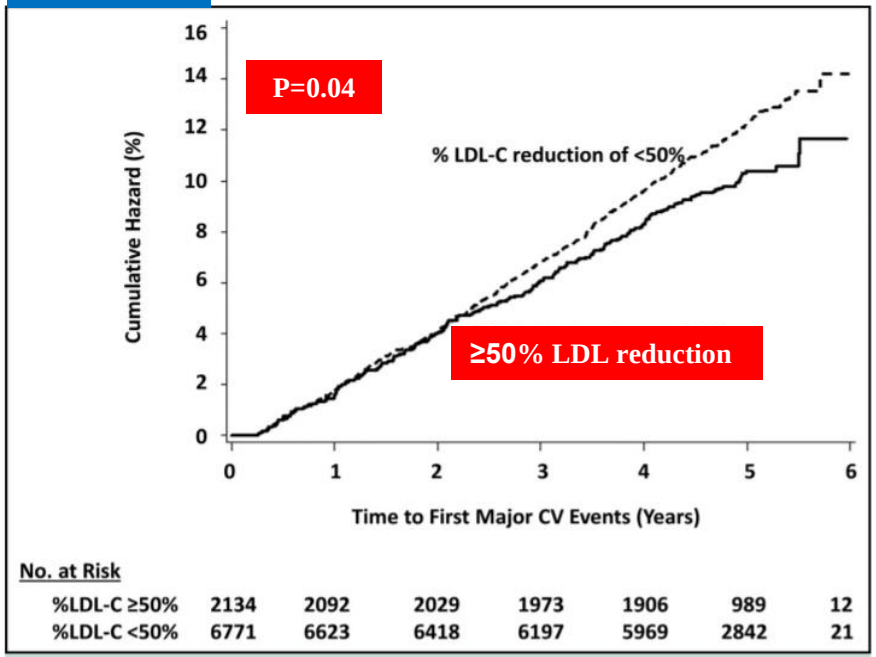
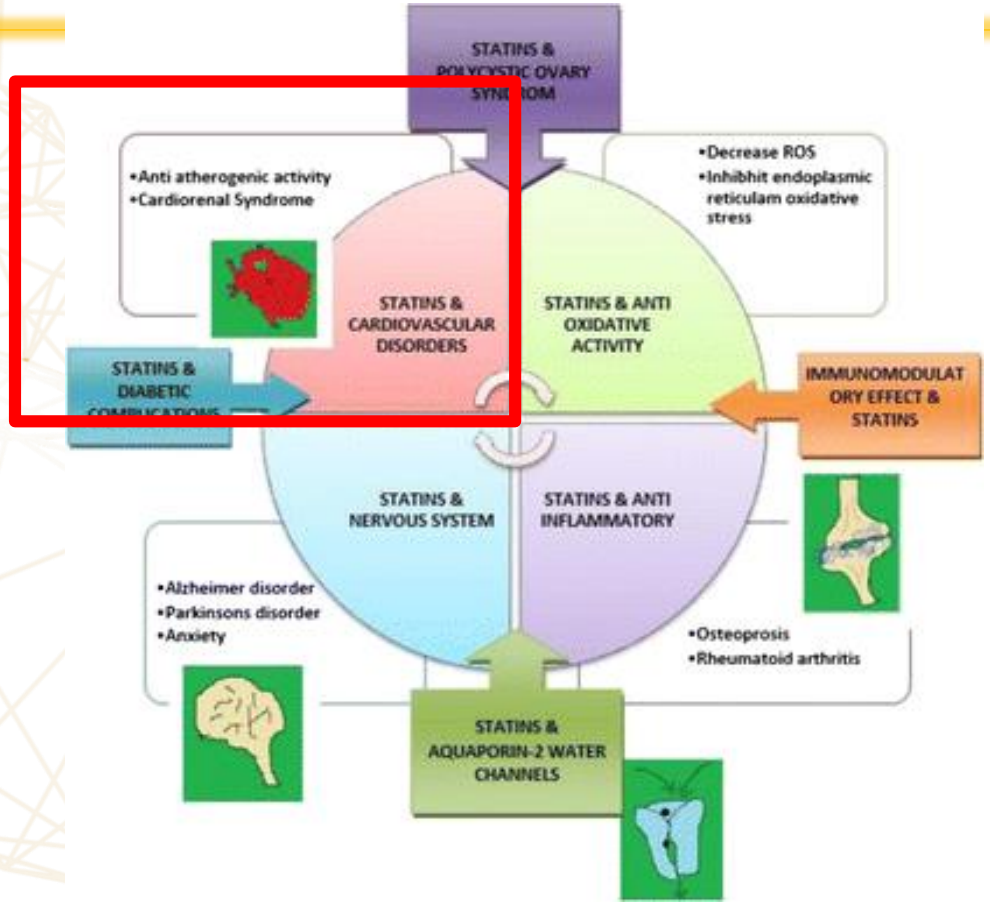


Figure 2 Major cardiovascular events in the cohort with attained LDL-C >70 mg/dL as a function of percent LDL-C reduction. LDL = low-density lipoprotein.

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

Pleiotropic effects of statin



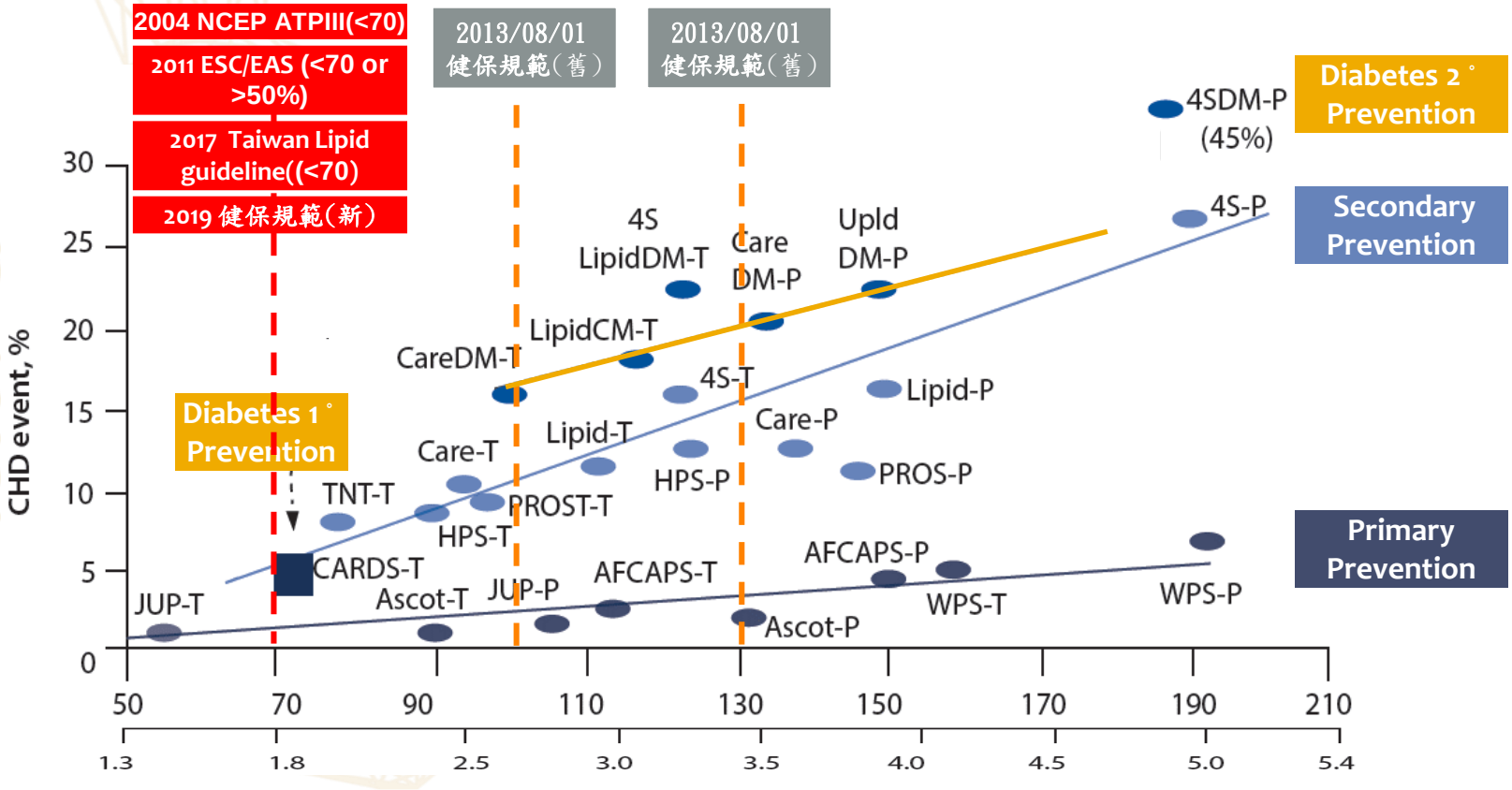
Naunyn Schmiedebergs Arch Pharmacol. 2016 Jul;389(7):695-712

More LDL-C reduction with LESS MACEs

	JUPITER	ASCOT-LLA	TNT	MEGA
	Rusuvastatin 20mg	Atorvastatin 10 mg	Atorvastatin 10 or 80 mg	Pravastatin 10 or 20mg
HR, *p*	-50%[1]	-30%[2]	-23.8%[3]	-18.0%[a]
Total CVEs	0.56 <0.00001	0.79 0.0005	0.78 <0.001	0·74 =0·01
Any MI (+fatal CHD)	0.46 0.0002	0.64 0.0005	0.80 0.002	0.67 0.01
Any Stroke	0.52 0.002	0.73 0.024	0.75 0.02	0.83 =0.33
Any Death	0.80 0.02	- *No Δ*	1.01 *0.92*	0.72 *=0.055*

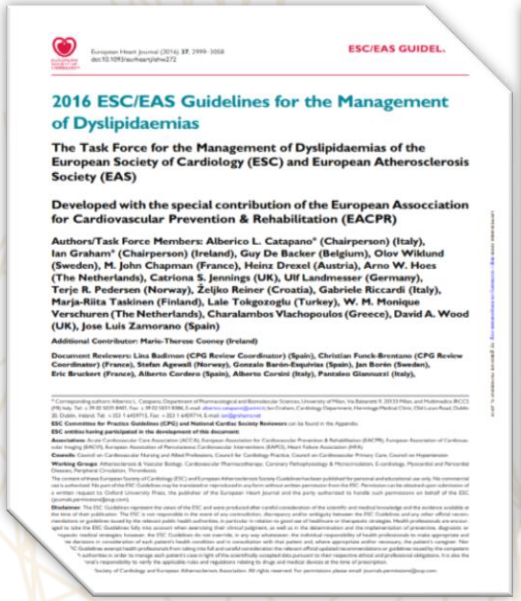
[1]JUPITER. NEJM 2008;359:2195
[2]ASCOT-LLA. Eur Heart J. 2006;27(24):2982-8.
[3]TNT. NEJM 2005;352:1425
[a] MEGA. Lancet 2006;368;1155

Established evidence of “Lower is Better”



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

Guidelines suggest : For high risk patients, the more LDL-C reduction, the more risk reduction with CVD risk

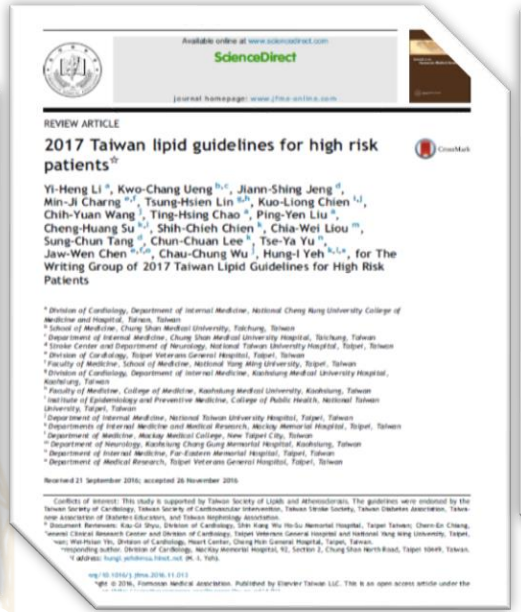


2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

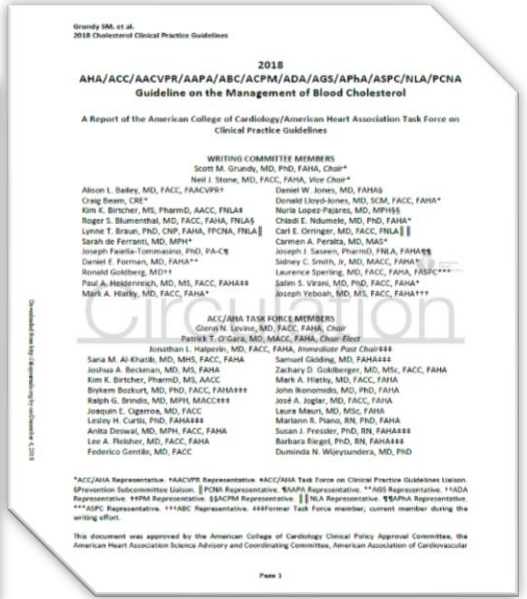
Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)

2016ESC/EAS Guidelines for the management of dyslipidemia



2017 Taiwan lipid guidelines for high risk patients☆

2017 Taiwan lipid guidelines for high risk patients



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

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

2018 Guideline on the Management of Blood Cholesterol

European Heart Journal (2016) 37, 2999–3058
Journal of the Formosan Medical Association (2017) 116, 217e248
Circulation. 2018 Nov 10:CIR0000000000000625

2016 ESC/EAS Guidelines : suggest LDL ≤70 mg/dL, or reduce >50% LDL when LDL-C level over 70–135 mg/dL

Table 4 Risk categories

Very high-risk	Subjects with any of the following:
CVD	• Documented cardiovascular disease (CVD), clinical or unequivocal on imaging. Documented CVD includes previous myocardial infarction (MI), acute coronary syndrome (ACS), coronary revascularisation (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)) and other arterial revascularization procedures, stroke and transient ischaemic attack (TIA), and peripheral arterial disease (PAD). Unequivocally documented CVD on imaging is what has been shown to be strongly predisposed to clinical events, such as significant plaque on coronary angiography or carotid ultrasound.
DM with target organ damage	• DM with target organ damage such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia.
Severe CKD	• Severe CKD (GFR <30 mL/min/1.73 m²).
	• A calculated SCORE ≥10% for 10-year risk of fatal CVD.
High-risk	Subjects with:
	• Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg.
	• Most other people with DM (some young people with type 1 diabetes may be at low or moderate risk).
	• Moderate CKD (GFR 30–59 mL/min/1.73 m²).
	• A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.

Table 11 Recommendations for treatment goals for low-density lipoprotein-cholesterol

Recommendations	Class [a]	Level [b]	Ref [c]
In patients at VERY HIGH CV risk[d], **LDL < 70mg/dl or reduction ≥50%** between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I	B	61, 62, 65, 68, 69, 128
In patients at HIGH CV risk[d], an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-C[e] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	I	B	65, 129
In subjects at LOW or MODERATE risk[d] an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C	-

European Heart Journal (2016) 37, 2999–3058

2016 ESC/EAS Guidelines for the management of Dyslipidemia

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Treatment goals for low-density lipoprotein-cholesterol

Recommendations	Class	Level
In patients at VERY HIGH CV risk an LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I	B
In patients at HIGH CV risk, an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-C is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	I	B
In subjects at LOW or MODERATE risk an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C

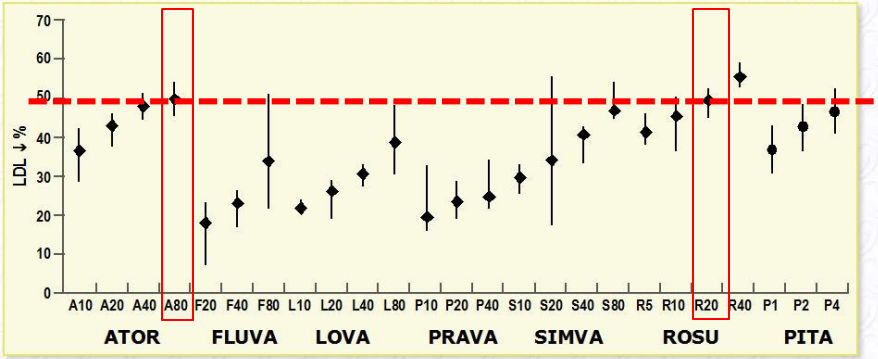
EAS www.escardio.org/guidelines

European Heart Journal 2016; 37:2999–3058 - doi:10.1093/eurheartj/ehv272
Atherosclerosis 253 (2016) 281-344-d oi:10.1016/j.atherosclerosis.2016.08.018

EUROPEAN SOCIETY OF CARDIOLOGY

48

A systematic review and meta-analysis of the therapeutic equivalence of statins



Weng TC, et al. *J Clin Pharm Ther.* 2010;35;139-151
Mukhtar RY, et al. *Int J Clin Pract.* 2005;59(2):239-252

EAS www.escardio.org/guidelines

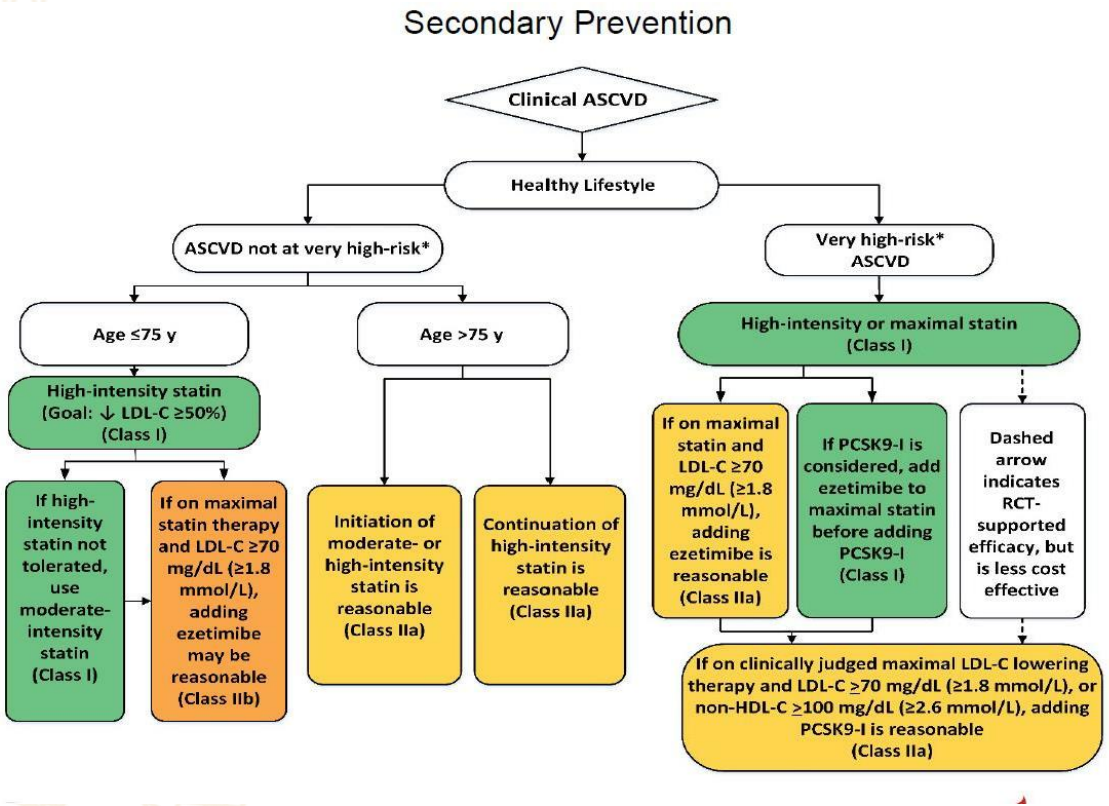
European Heart Journal 2016; 37:2999–3058 - doi:10.1093/eurheartj/ehv272
Atherosclerosis 253 (2016) 281-344-d oi:10.1016/j.atherosclerosis.2016.08.018

EUROPEAN SOCIETY OF CARDIOLOGY

Rosuvastatin 40mg is not indicated in Taiwan

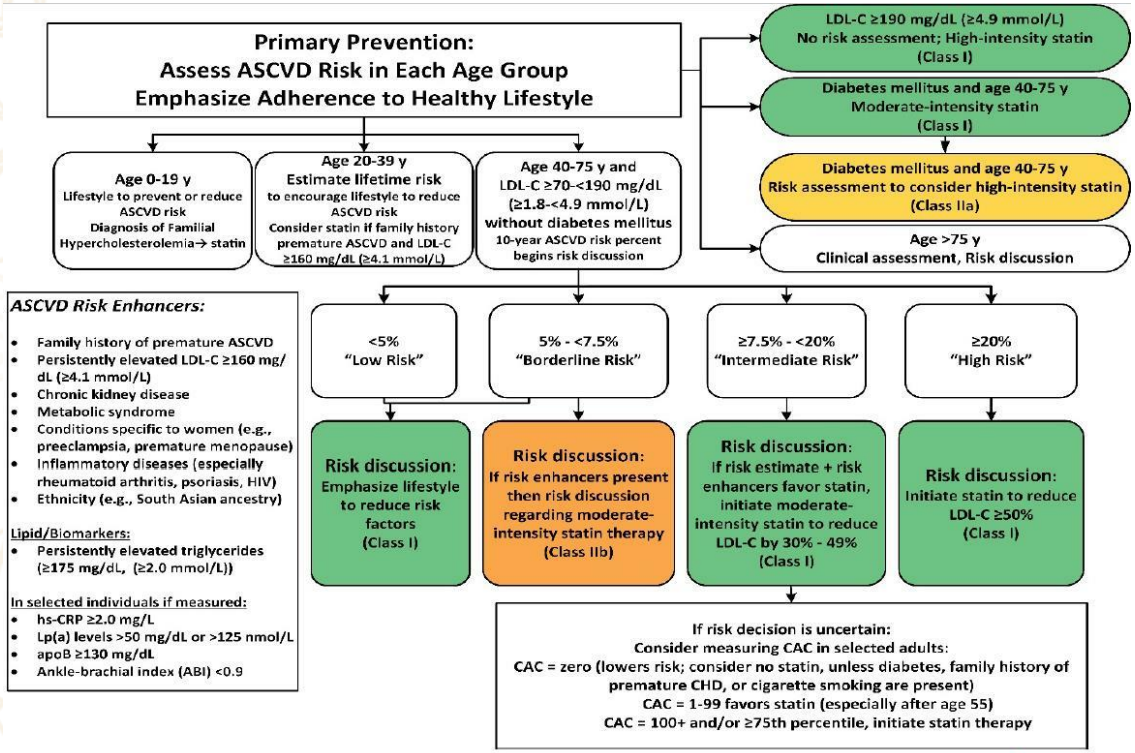
 European Heart Journal (2016) 37, 2999–3058

2018 AHA/ACC Guideline on the Management of Blood Cholesterol
- Secondary Prevention in Patients With Clinical ASCVD



Circulation. 2018 Nov 10:CIR0000000000000625

2018 AHA/ACC Guideline on the Management of Blood Cholesterol - Primary Prevention



Circulation. 2018 Nov 10:CIR0000000000000625

2017 Taiwan Lipid Guideline

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

* 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 update

	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)。**

Rosuvastatin的劑量範圍是5-20 mg每天一次

2018 ACC/AHA Guideline Recommendations for Statin Therapy

Statin Benefit Groups

Heart healthy lifestyle habits are the foundation of ASCVD prevention

1. *Secondary ASCVD Prevention*

- ≤ 75 yrs : High-intensity statin (Goal: ↓LDL-C ≧ 50 %) (Class I)
- >75yrs : Initiation of moderate or high-intensity statin is reasonable (Class IIa)

2. *Primary Prevention:* Severe Hypercholesterolemia *(LDL-C ≥190)*

- 20 to 75 years of age : High-intensity statin (Class I)
- 20 to 75 years of age : Reduce ≧ 50% reduction in LDL-C (Class Ila)

3. *Primary Prevention: Diabetes Mellitus with 40-75 Years*

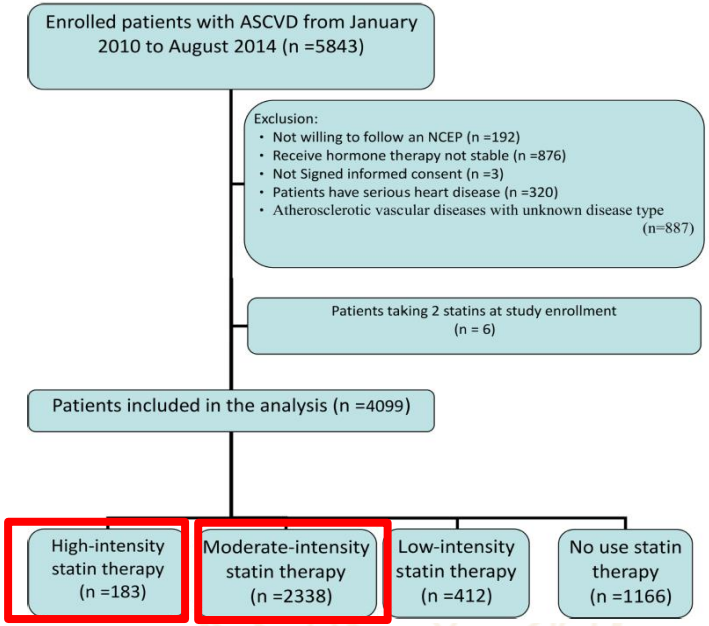
- Moderate-intensity statin (Class I)
- For those who achieve less than 50% reduction while receiving maximally tolerated statin, ezetimibe therapy is reasonable (Class IIb)

4. *Primary Prevention: assess ASCVD Risk in Each Age Group*

- High risk(≥20%): statin to reduce LDL-C ≧ 50% (Class I)
- Intermediate risk(7.5-20 %): moderate-intensity statin to reduce LDL-C by 30- 49% (Class I)
- Borderline risk (5-7.5%): moderate-intensity statin(Class IIb)
- Low risk (<5%): Healthy Lifestyle (Class I)

Circulation. 2018 Nov 10:CIR0000000000000625

Taiwan Secondary Prevention for patients with AtheRosCLErotic disease (T-SPARCLE) Study : only 44% 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

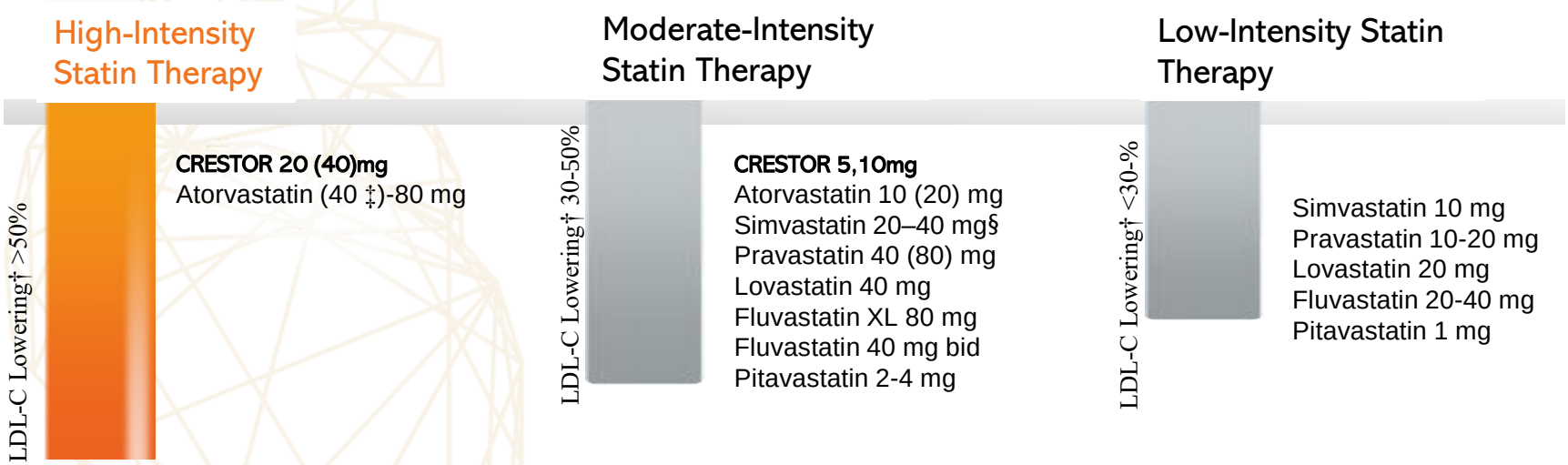
†Adjusted for age, gender, body mass index (BMI) level, cigarette smoking history, fibrate use, history of hypertension, heart failure, diabetes, myocardial infarction, ischemic stroke or transient ischemic attack, previous coronary or lower extremity arterial disease (LEAD) intervention and levels of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

Chapter 2

Clinical data between LDL-C 50% reduction and CV outcome

High-intensity statin therapy for ASCVD prevention & treatment



Percent LDL-C reductions with the primary statin medications used in clinical practice (atorvastatin, rosuvastatin, simvastatin) were estimated using the median reduction in LDL-C from the **VOYAGER** database
† 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
§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.

Rosuvastatin 40mg is not indicated in Taiwan”

Circulation. 2018 Nov 10:CIR0000000000000625

FDA: efficacy of CRESTOR 20mg is better than Atorvastatin 40mg

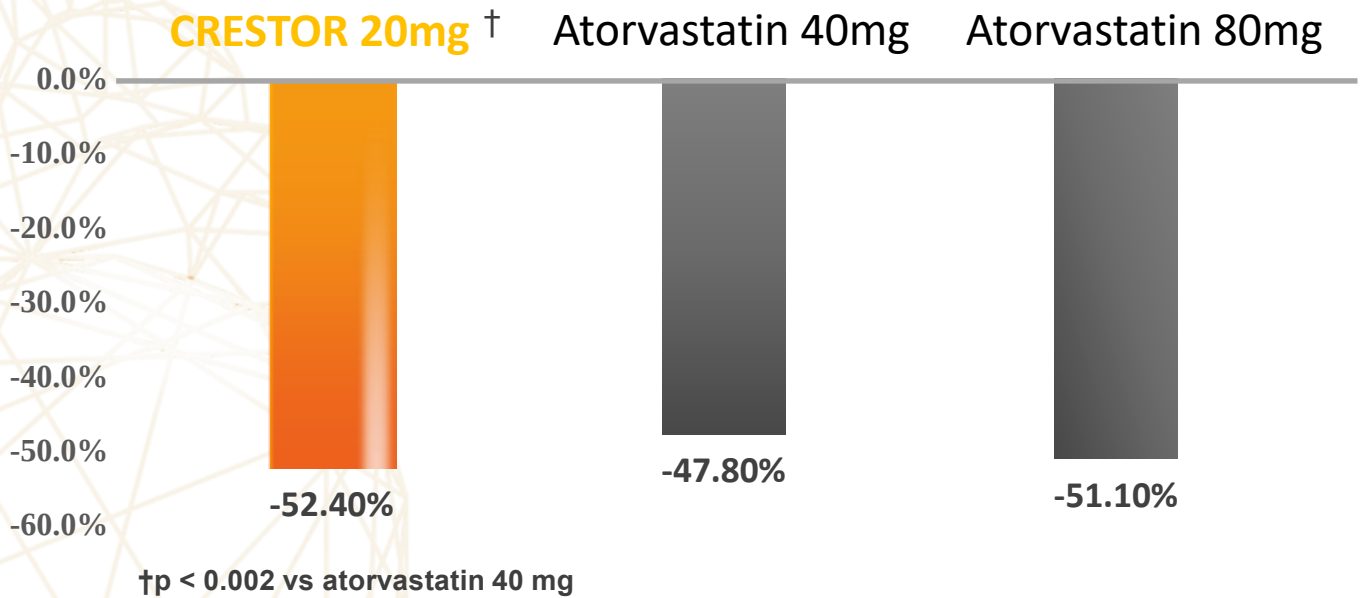
U.S Food and Drug Administration

Rosuvastatin	Atorva.	Fluva.	Pitava.	Lova.	Prava.	Ezitamibe /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; Rosuva=Rosuvastatin; 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

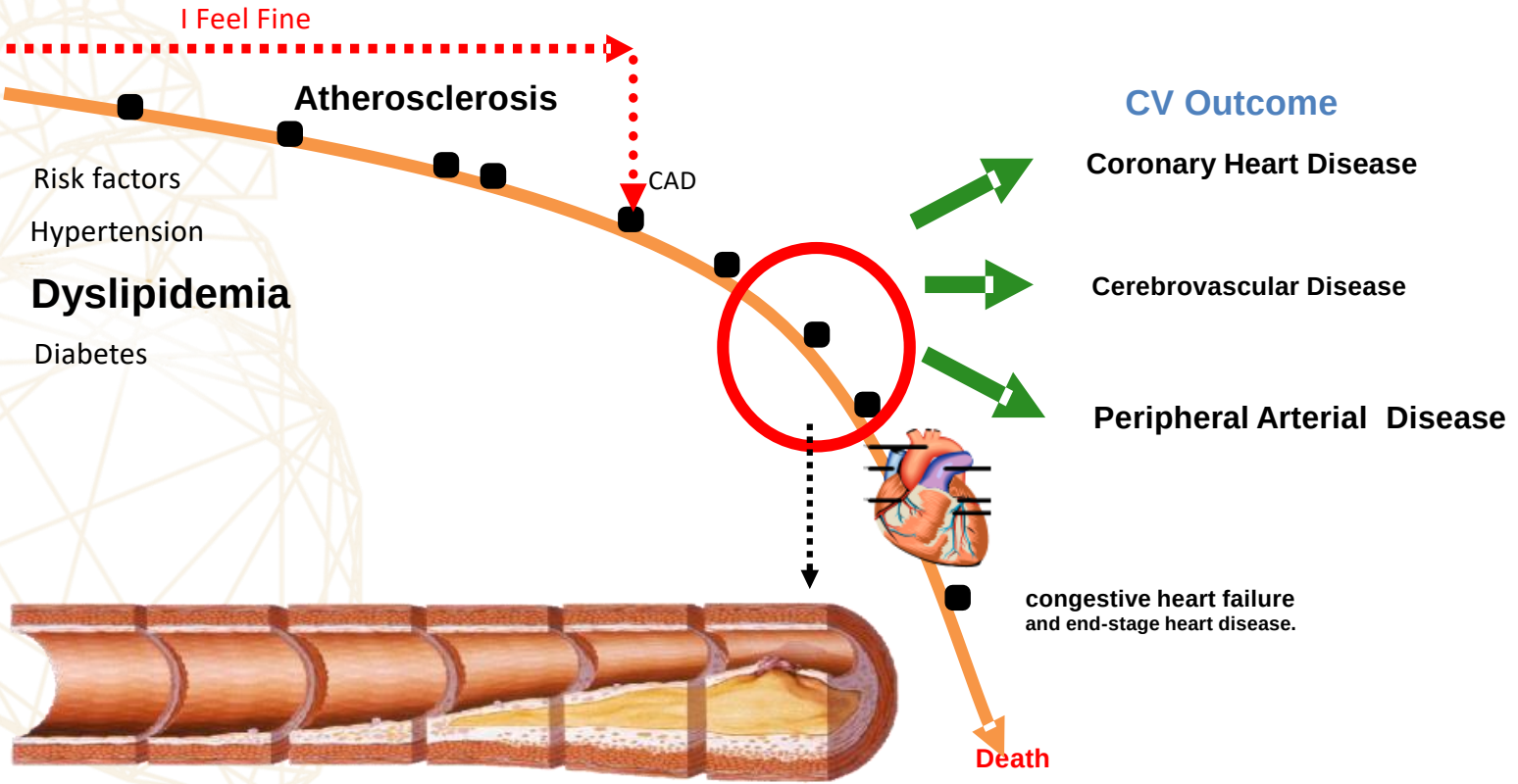
CRESTOR 20mg is better than Atorvastatin 40mg in LDL-C reduction



Achieve European goal of 116 mg/dl (3.0 mmol/L) at the end of treatment:
92% of CRESTOR 20mg
80% of Atorvastatin 40mg (P=0.007 vs CRESTOR 20mg)
81% of Atorvastatin 40mg (P=0.02 vs CRESTOR 20mg)

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

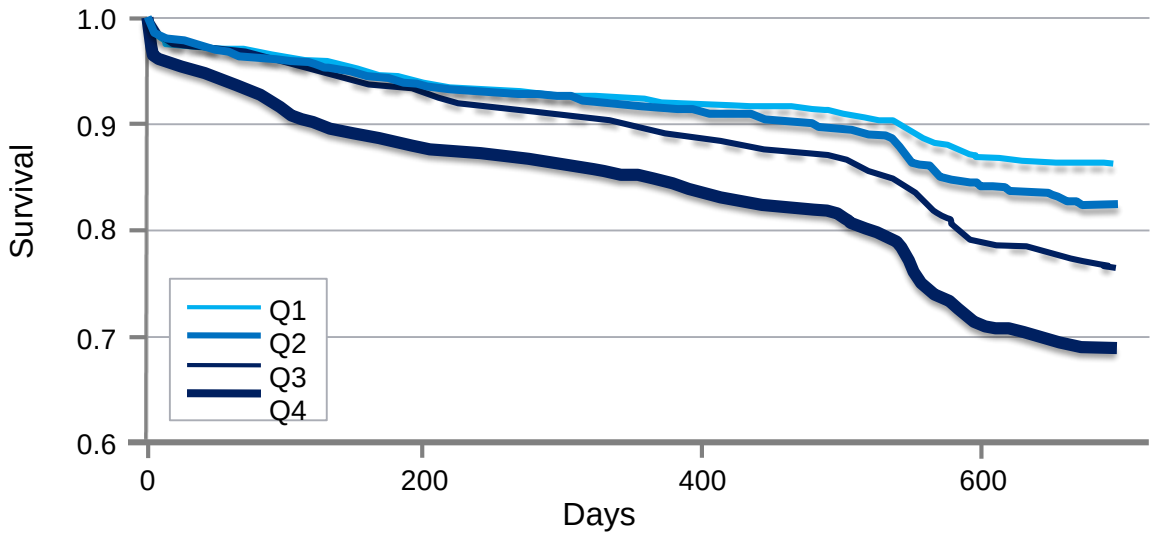
Patients in atherosclerosis are subject to CHD, Stroke, and PAD



Adapted from: Dzau V, et al. Am Heart J 1991;121:1244–1263

Relationship Between Coronary Atheroma Burden and Cardiovascular Events

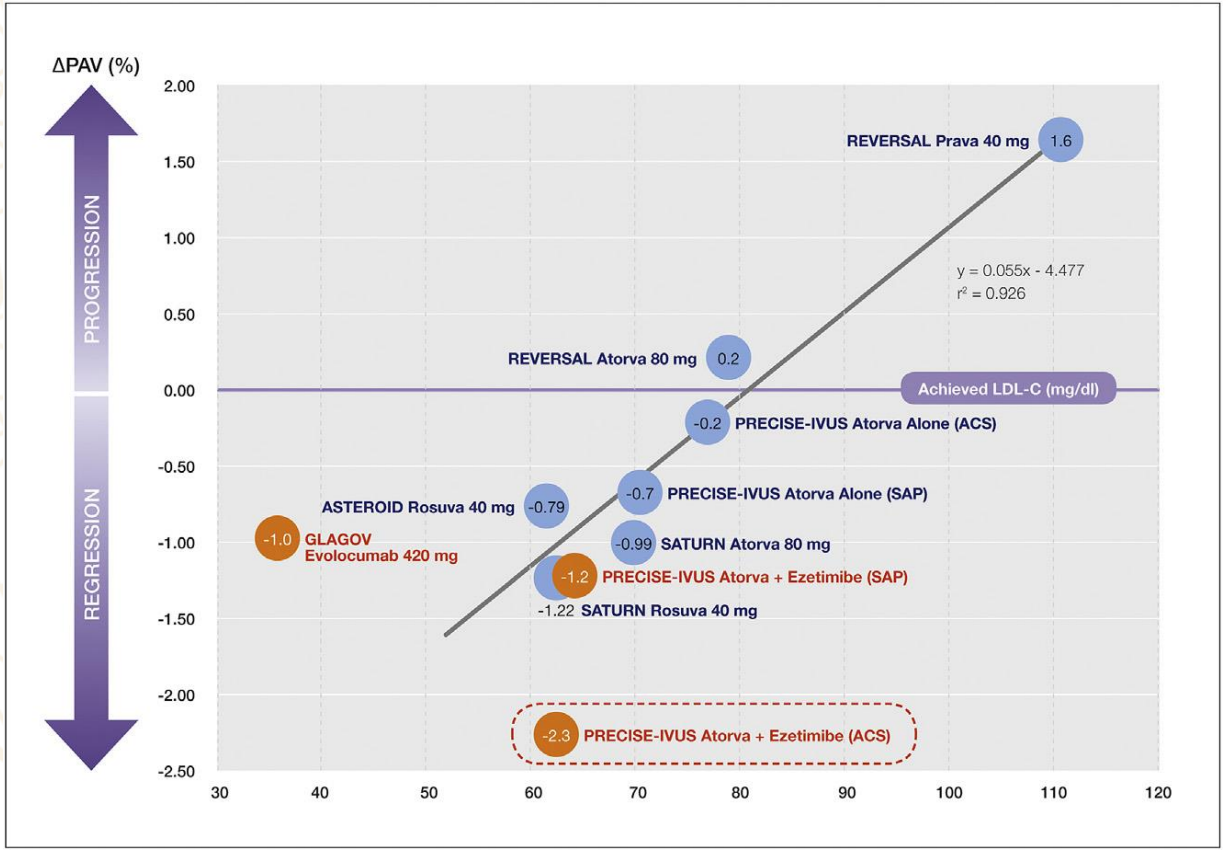
Survival from cardiovascular events (death, myocardial infarction, and coronary revascularization) in patients stratified according to quartiles (Q) of percent atheroma volume at baseline.



- CV=cardiovascular; MI=myocardial infarction
- Coronary plaque progression was evaluated in 4,137 patients in 6 clinical trials that used serial IVUS.

Nicholls SJ et al. J Am Coll Cardiol 2010;55:2399–2407

Progression of atherosclerosis plaque volume when achieving LDL-C of 70mg/dl



[33] Atherosclerosis. 2018 Feb;269:219-228.

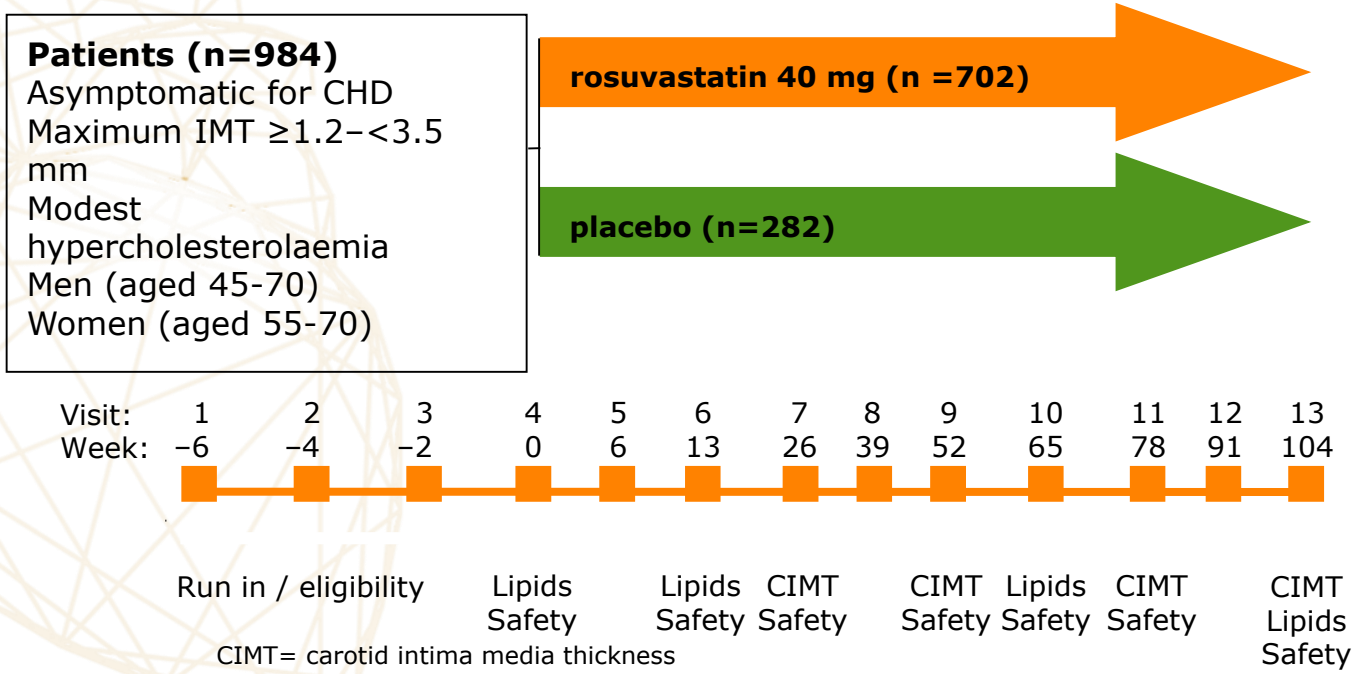
Changes in atheroma burden according to MACEs

Clinical Event	Percent Atheroma Volume (%)		
	No	Yes	p Value
Entire cohort			
Death, myocardial infarction, coronary revascularization	0.46 ± 0.16	0.95 ± 0.19	<0.001
Death	0.56 ± 0.17	−0.60 ± 1.55	0.45
Myocardial infarction	0.56 ± 0.17	0.61 ± 0.44	0.90
Coronary revascularization	0.46 ± 0.16	0.96 ± 0.19	<0.001
Excluding experimental therapies			
Death, myocardial infarction, coronary revascularization	0.44 ± 0.16	1.06 ± 0.20	<0.001
Death	0.56 ± 0.16	−1.89 ± 2.14	0.25
Myocardial infarction	0.56 ± 0.16	0.76 ± 0.59	0.73
Coronary revascularization	0.44 ± 0.16	1.08 ± 0.20	<0.001

Nicholls SJ et al. J Am Coll Cardiol 2010;55:2399–2407

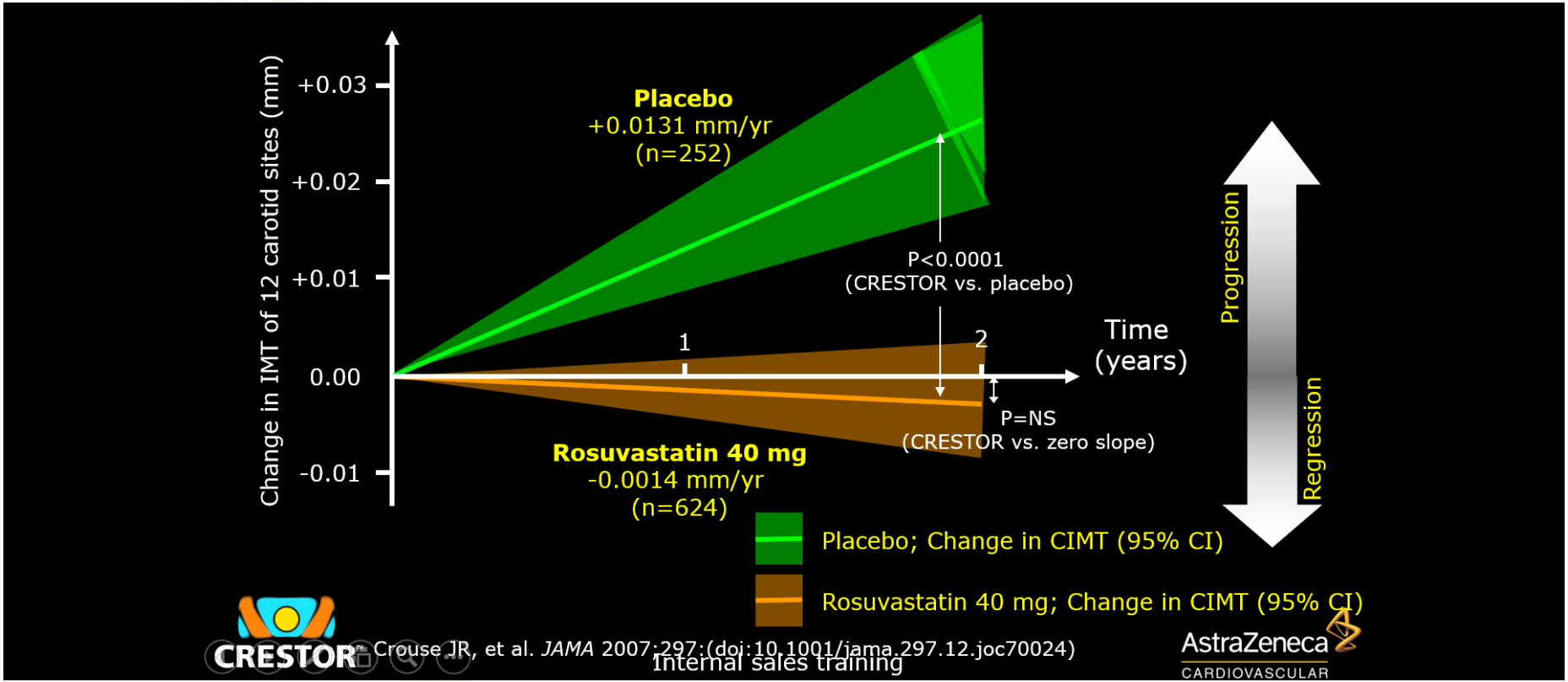
METEOR study-
Coronary plaque regression with high-intensity statin

- **Measuring Effects on intima media Thickness: an Evaluation Of Rosuvastatin**



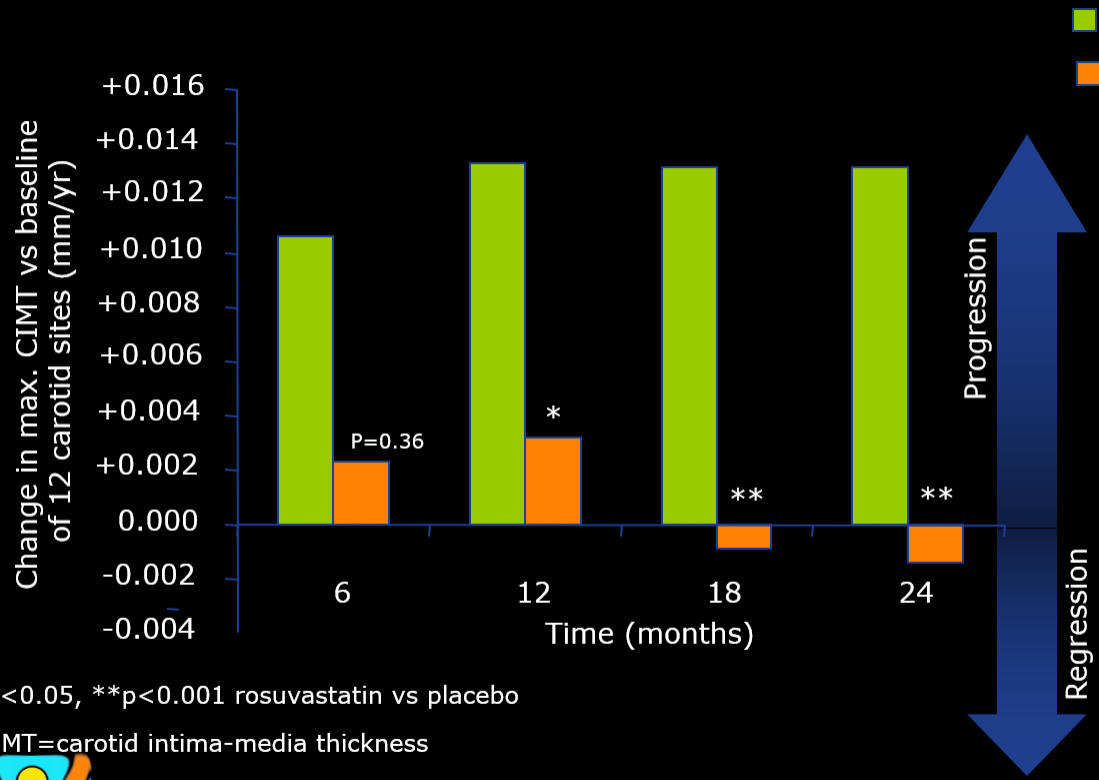
Adapted from Crouse JR et al. *Cardiovasc Drugs Ther* 2004; 18: 231–238

METEOR primary endpoint:
Rate of change of maximum IMT at 12 carotid sites Rosuvastatin vs placebo



Bots ML, *et al. Circulation 2007*;**116** (Suppl II): 17 (Abstract 194)

METEOR additional analysis:
Rate of change of maximum CIMT at 12 carotid sites Rosuvastatin vs placebo



*p<0.05, **p<0.001 rosuvastatin vs placebo

CIMT=carotid intima-media thickness

CRESTOR™

Bots ML, *et al*. *Circulation 2007*;**116** (Suppl II): 17 (Abstract 194)

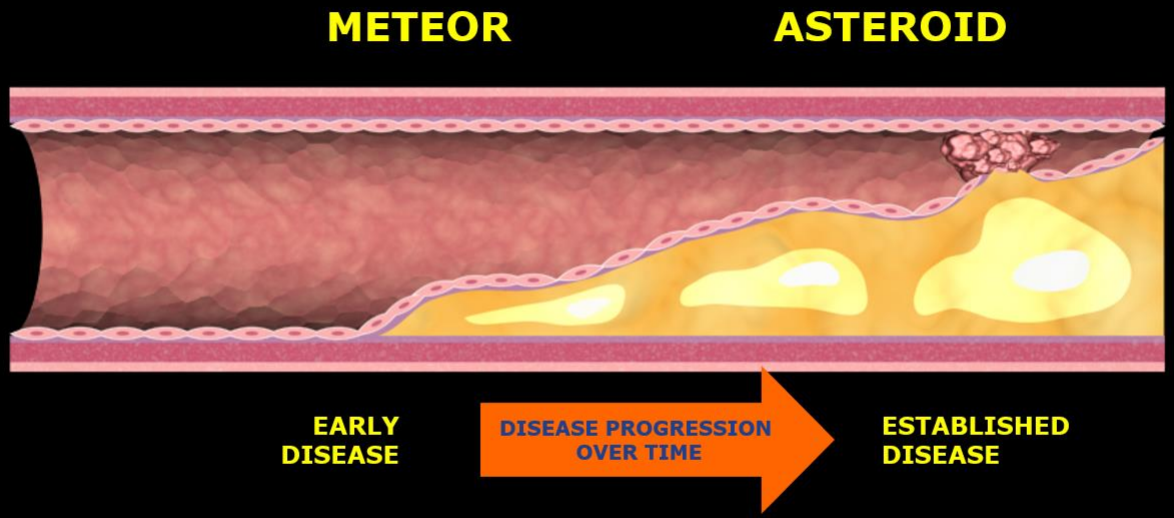
Internal sales training

AstraZeneca CARDIOVASCULAR

Bots ML, *et al*. *Circulation 2007*;**116** (Suppl II): 17 (Abstract 194)

Clinical perspective II

METEOR, supported by ASTEROID, demonstrates that rosuvastatin has a significant impact on atherosclerosis across the spectrum of the disease (in both early and more established disease)[1,2]



In addition, the experimental study ORION has shown the potential for rosuvastatin to shrink the lipid rich necrotic core and so improve plaque stability

Artists impression; NOTE – METEOR studies the progression of atherosclerosis in the carotid artery and ASTEROID in the coronary artery. Each used different measurement techniques

1. Crouse JR et al. *JAMA* 2007 **297**:1344-1353
2. Nissen S *et al. JAMA* 2006 **295**:1556-1565

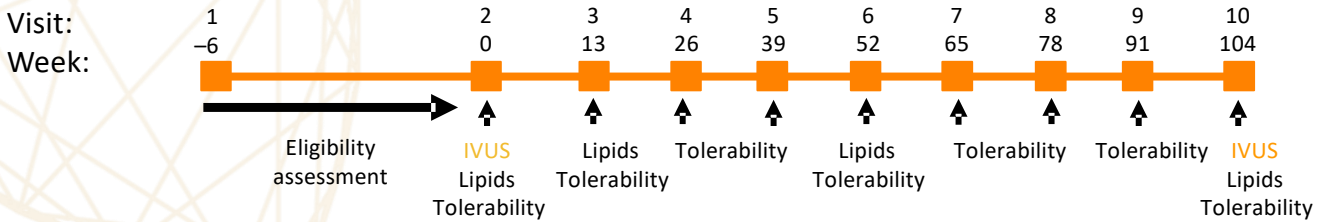
ASTEROID study :
Coronary plaque regression with high-intensity statin

To evaluate whether long-term treatment with rosuvastatin 40 mg in CAD pts resulted in coronary plaque regression

Patients : **CAD**,
undergoing coronary angiography
Target coronary artery:
≤50% reduction in lumen diameter
of ≥40 mm segment
No cholesterol entry criteria
≥18 years

- Design: Prospective, open-label blinded end-points trial
- Primary endpoint: The change in Percent Atheroma Volume and the change in nominal atheroma volume in the 10-mm subsegment with the greatest disease severity at baseline

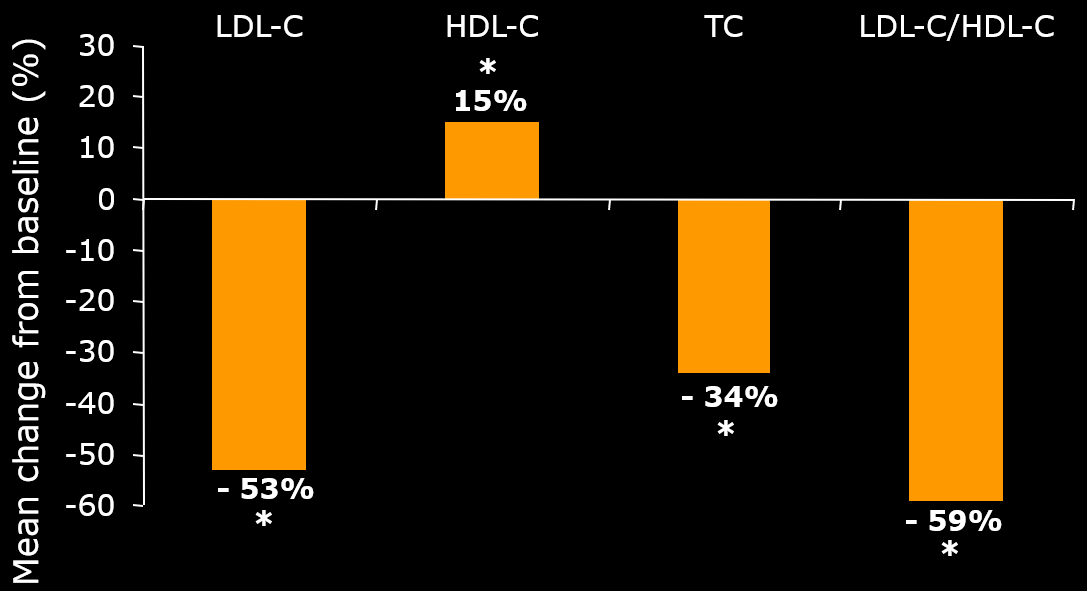
(n=349 evaluated serial IVUS examinations)



IVUS=intravascular ultrasound

Nissen et al; JAMA 2006; 296:1556

LDL-C >50% reduction may result in coronary plaque regression

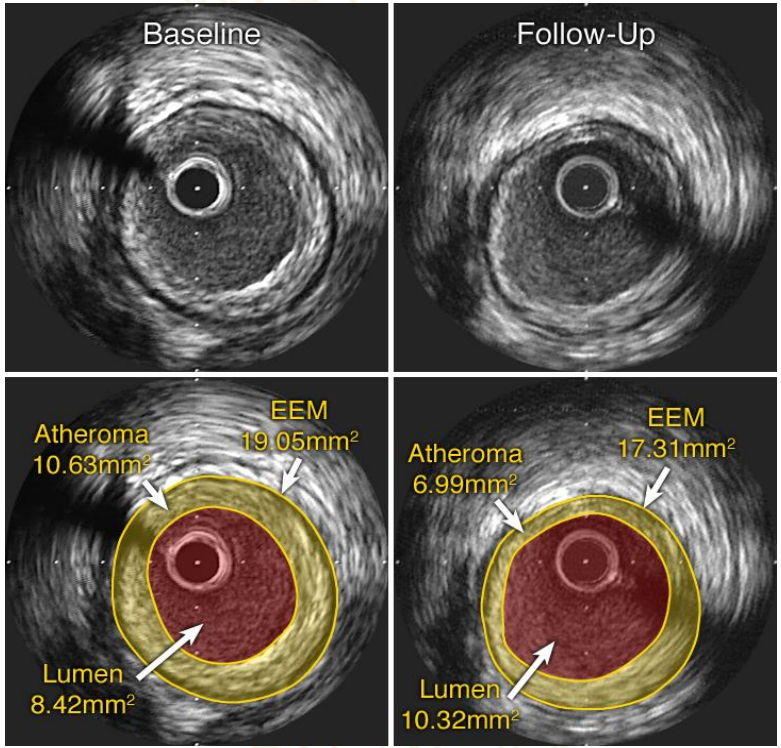


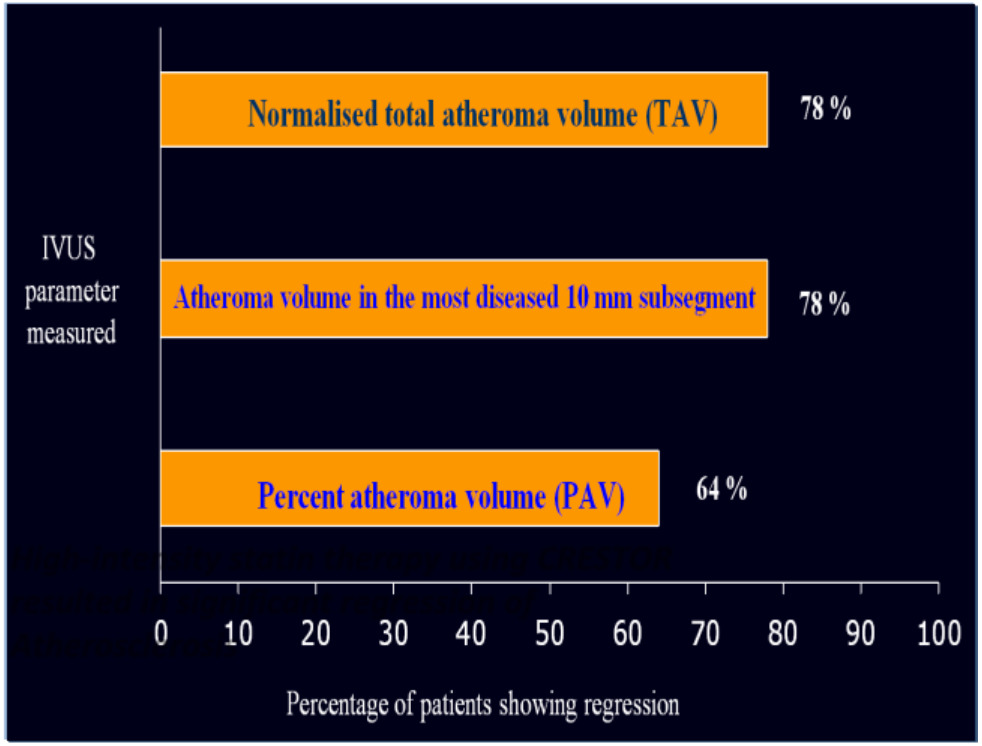
LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; TC=total cholesterol

from time weighted average throughout the duration of therapy; * p<0.001

Nissen S *et al.* JAMA 2006;295 (13):1556-1565.

High-intensity statin therapy using CRESTOR resulted in significant regression of atherosclerosis



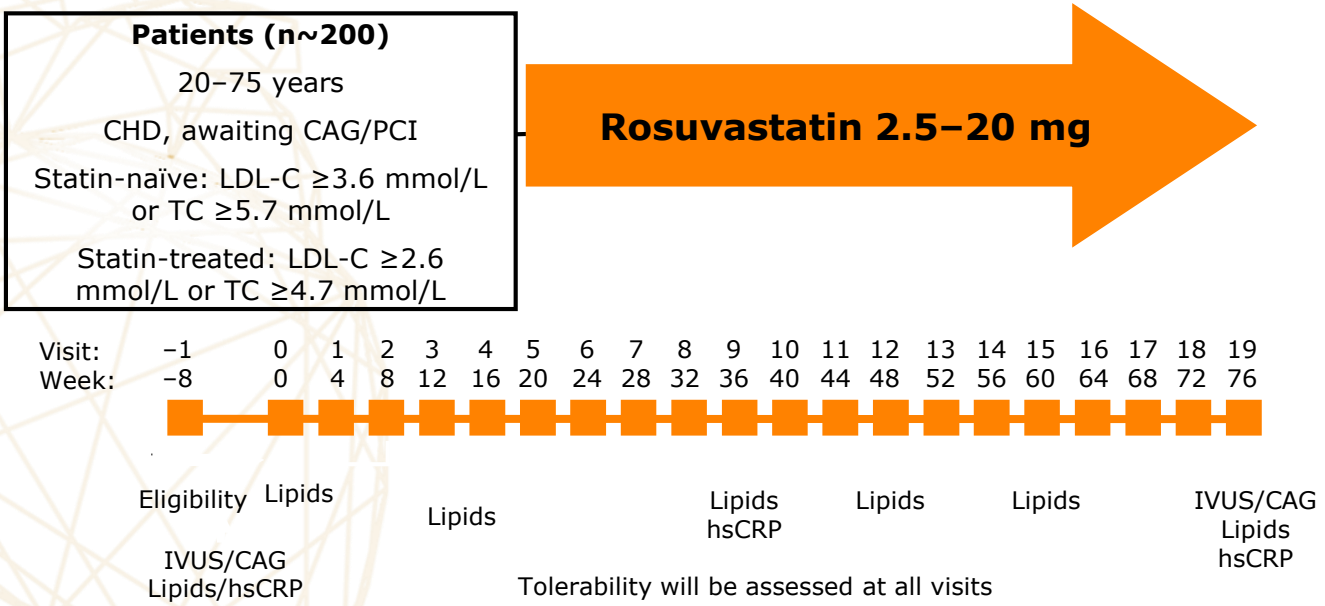


Number(%) of patients showing regression measured by each IVUS parameter

Nissen et al; JAMA 2006; 296:1556, Pic.) Cleve Clin J Med, 2006; 73:937-944.

COSMOS study:
Coronary plaque regression with high-intensity statin in Asia group

- Evaluate the effect of CRESTOR on the progression of plaque volume in Japanese subjects with hypercholesterolaemia and coronary heart disease

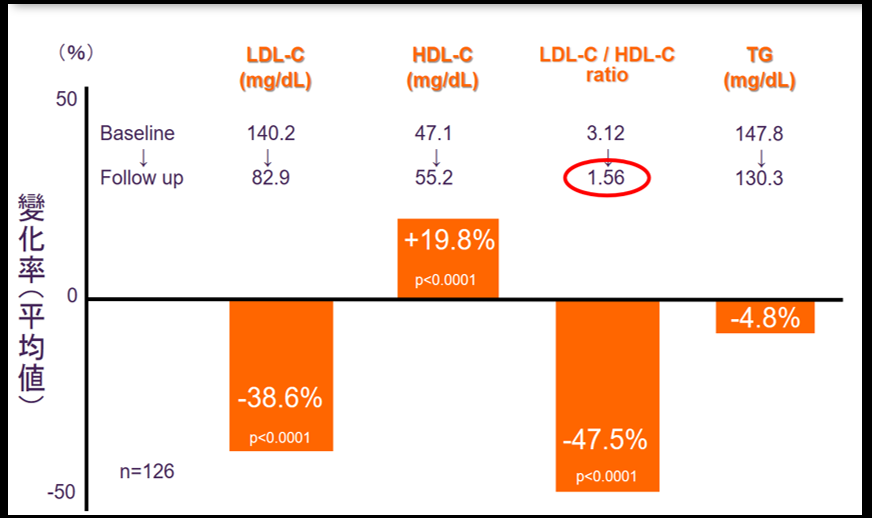


CHD=coronary heart disease; CAG=coronary angiography; PCI=percutaneous coronary intervention; LDL-C=low-density lipoprotein cholesterol; TC=total cholesterol; IVUS=intravascular ultrasound; hsCRP=high-sensitivity C-reactive protein

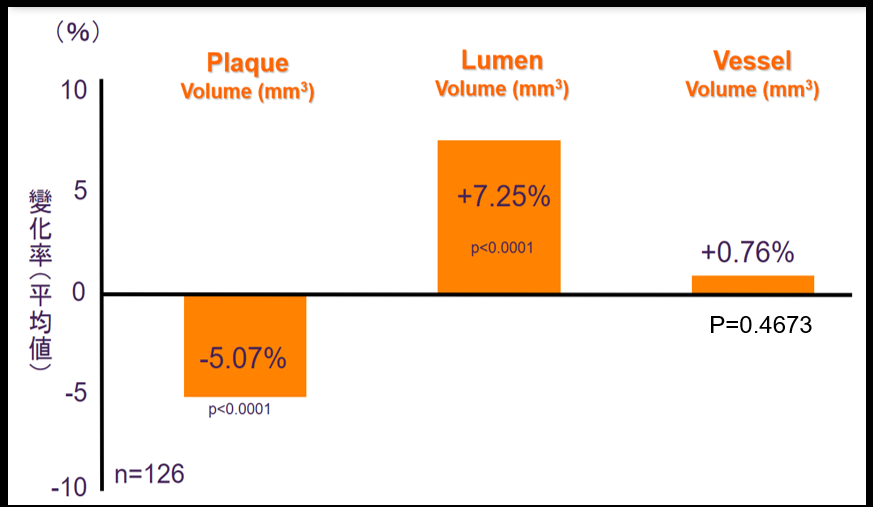
Circ J 2009; **73:** 2110 – 2117

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

COSMOS Lipid Profiles



Reduction of Plaque Volume

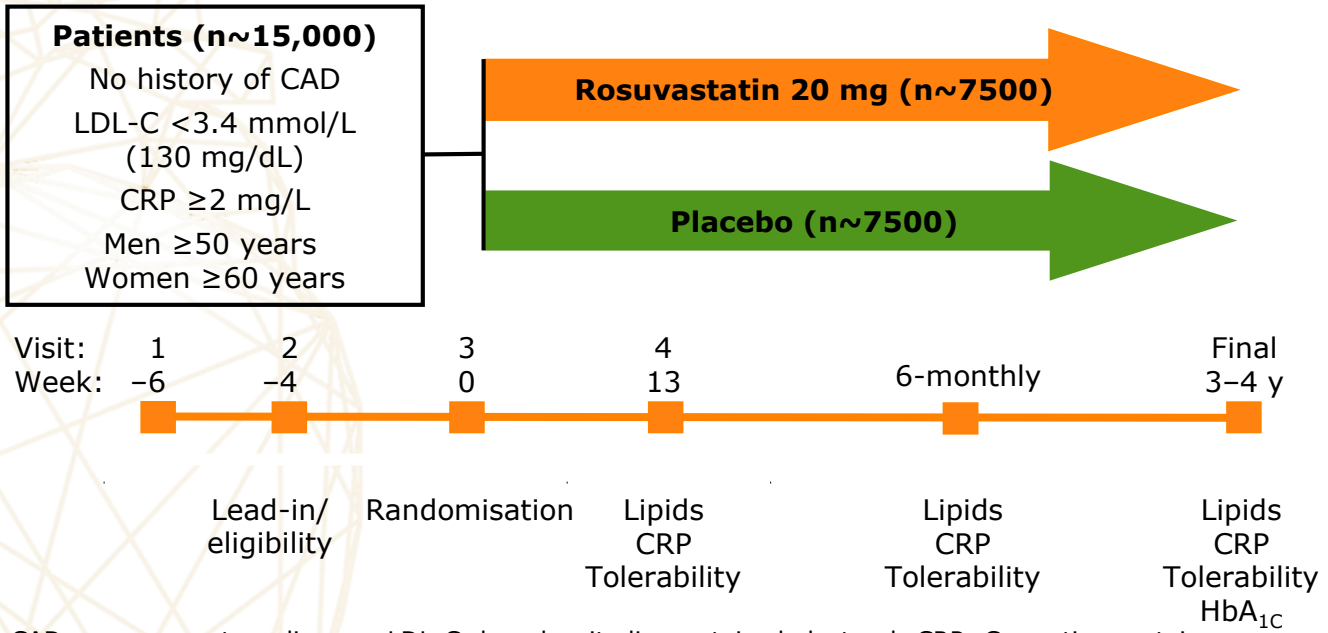


Crestor的劑量範圍是5-20mg每天一次，並應根據治療目標及患者的反應個別調整劑量"

Circ J 2009; **73:** 2110 – 2117

JUPITER study–
Justification for time to the first occurrence of a major cardiovascular event

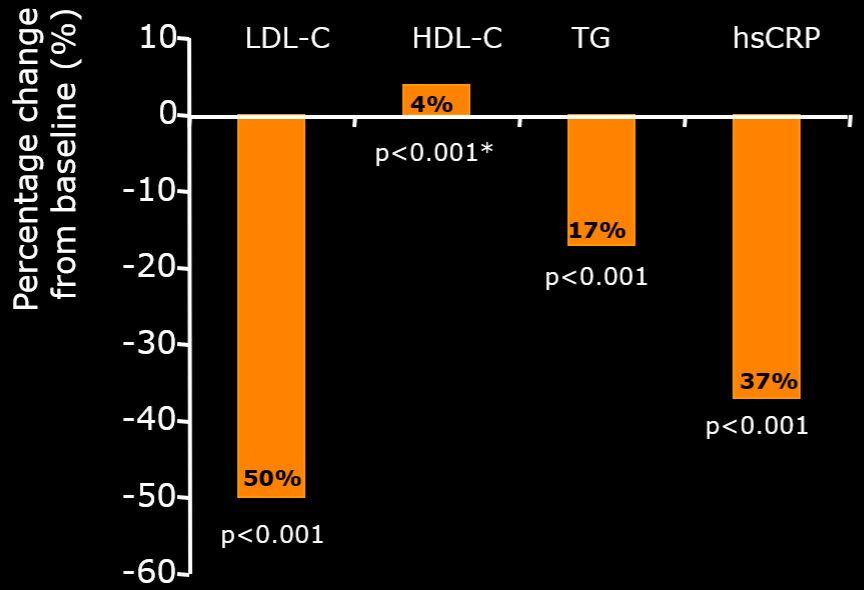
To assess CRESTOR 20mg in the primary prevention of cardiovascular events in 15000 subjects with low LDL-C levels and elevated levels of C-reactive protein (CRP)



CAD=coronary artery disease; LDL-C=low-density lipoprotein cholesterol; CRP=C-reactive protein; HbA_{1c}=glycated haemoglobin
Ridker PM. *Circulation* 2003; 108: 2292–2297

Ridker P *et al*. *N Eng J Med* 2008;359: 2195-2207

CRESTOR 20mg : Effects on LDL-C, HDL-C, TG and hsCRP at 12 months



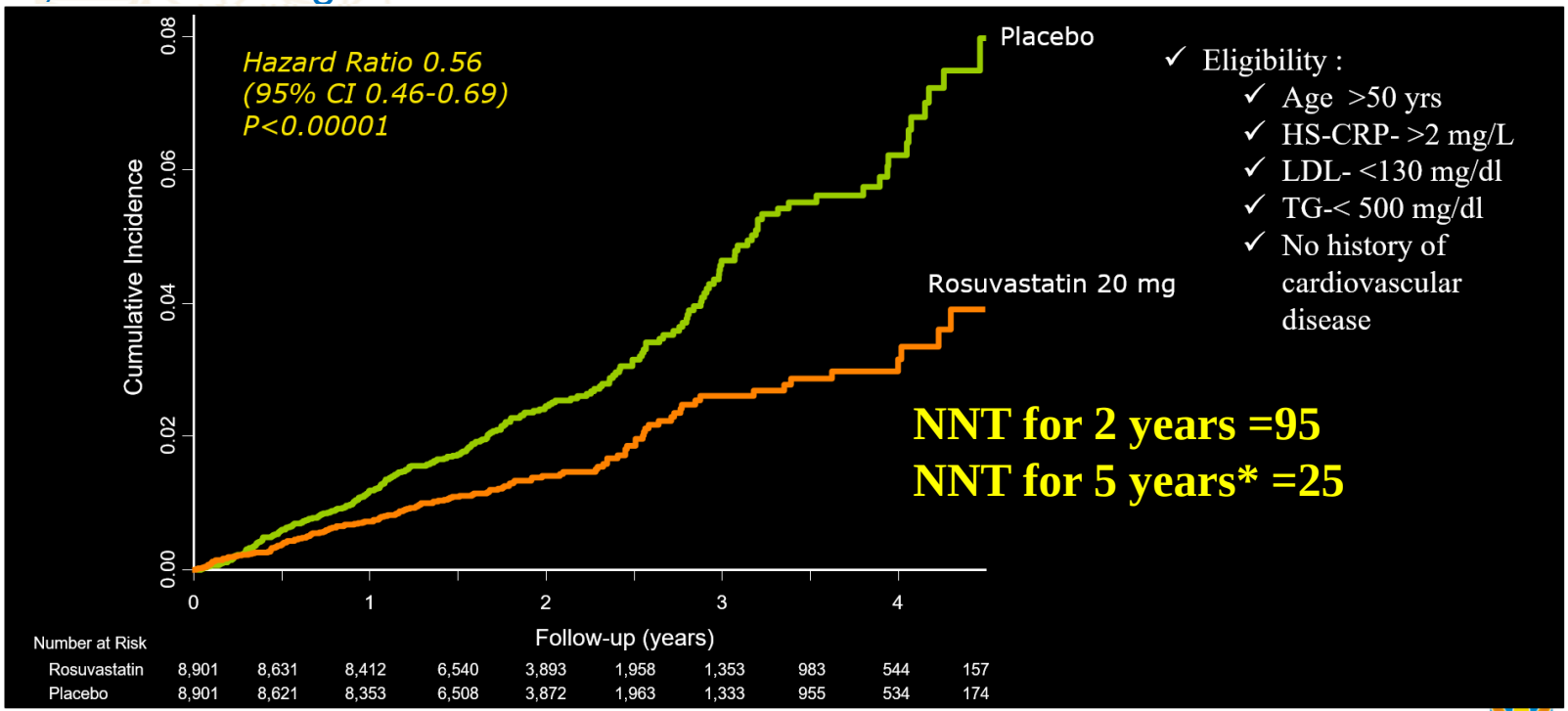
Rosuvastatin 20mg reduced LDL-C, TG and hsCRP; and increased HDL-C levels

*P-value at study completion (48 months) = 0.34

Ridker P *et al*. *N Eng J Med* 2008;359: 2195-2207

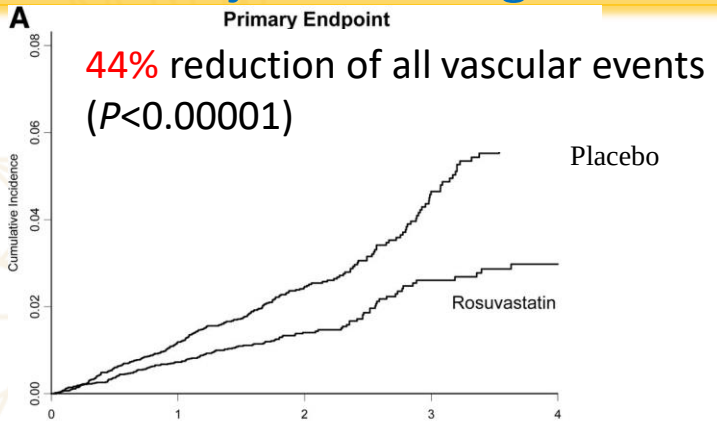
JUPITER - Primary Endpoint

- Time to first occurrence of a CV death, non-fatal stroke, non-fatal MI, unstable angina or arterial revascularization

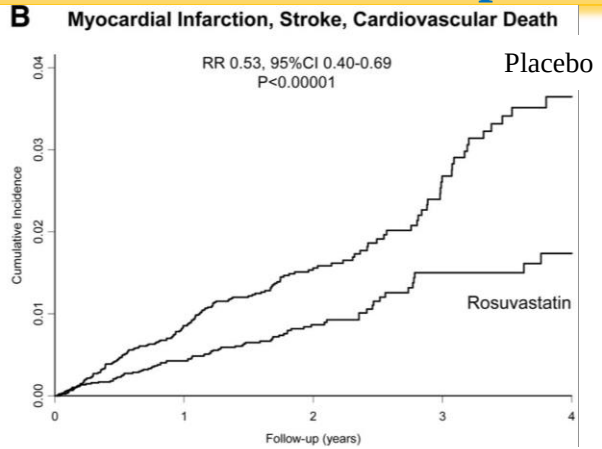


Ridker P *et al*. *N Eng J Med* 2008;359: 2195-2207

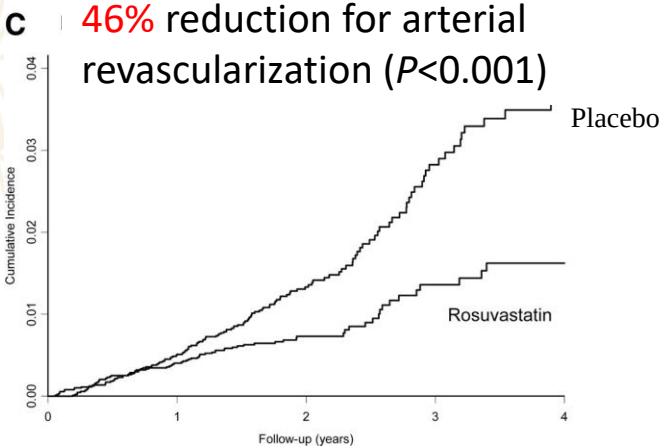
CRESTOR 20mg : stopped early at the recommendation of its Independent Data and Safety Monitoring Board after a median follow-up of 1.9 years



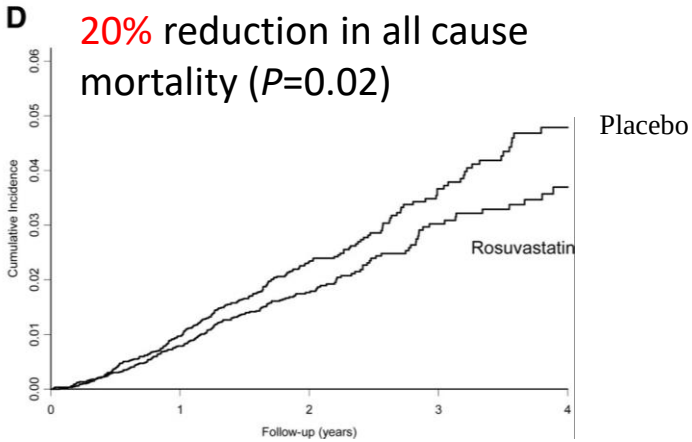
44% reduction of all vascular events (*P*<0.00001)



- 54% reduction in myocardial infarction (*P*=0.0002)
- 48% reduction in stroke (*P*=0.002)



46% reduction for arterial revascularization (*P*<0.001)

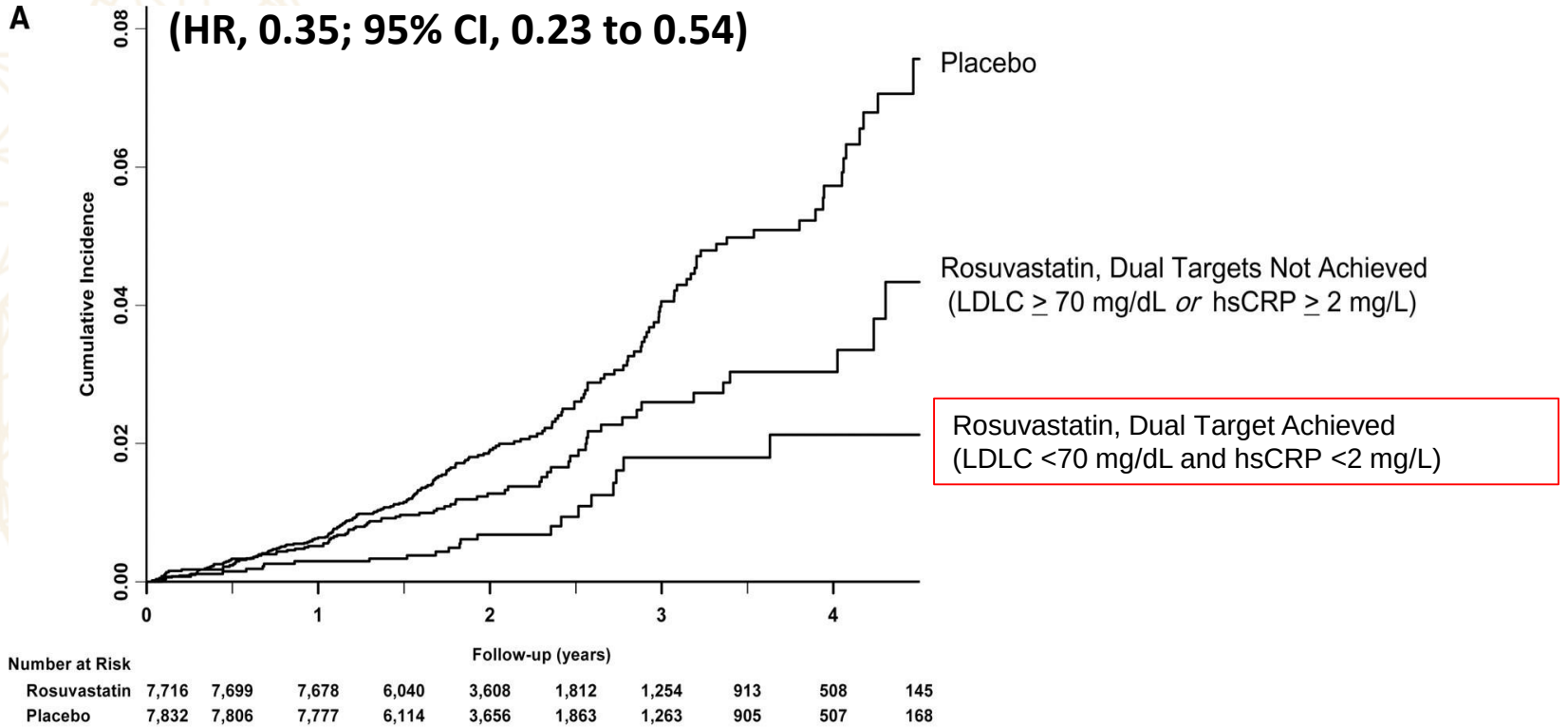


20% reduction in all cause mortality (*P*=0.02)

Circ Cardiovasc Qual Outcomes. 2009 May;2(3):279-85.

CRESTOR 20mg : achieved the even more aggressive targets of LDLC <70 mg/dL and hsCRP <2 mg/L

65% reduction in the hazard of vascular events
(HR, 0.35; 95% CI, 0.23 to 0.54)



Circ Cardiovasc Qual Outcomes. 2009 May;2(3):279-85.

Time to Benefit for Low-Density Lipoprotein-Cholesterol–Lowering Strategies

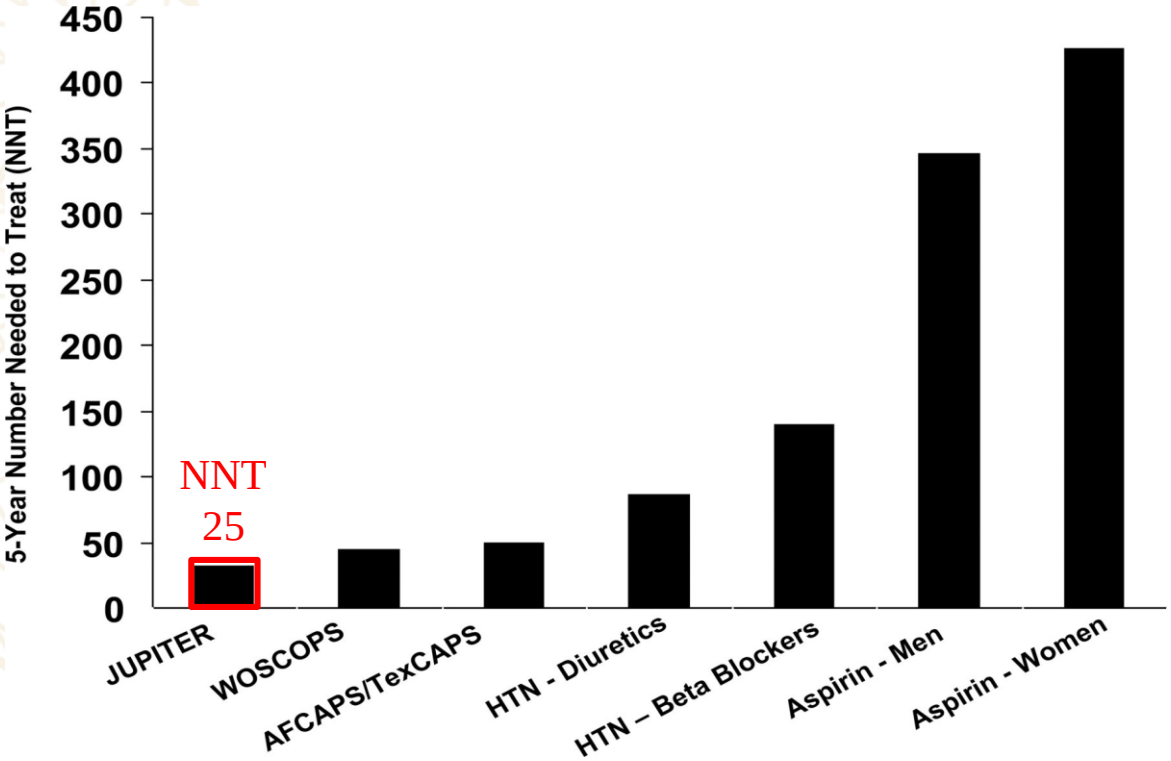
Nonstatins	Control	Trial	Time to Benefit, y
Cholestyramine	Placebo	LRC-CPPT[57]	7.4
Partial ileal bypass surgery	No surgery	POSCH[58]	9.7
Ezetimibe with simvastatin 40 mg	Placebo with simvastatin 40 mg	IMPROVE-IT[56]	7.0
Statins			
Rosuvastatin	Placebo	JUPITER[12]	1.9
Pravastatin	Placebo	WOSCOPS[8]	5.0
	Placebo	CARE[6]	5.0
	Placebo	LIPID[17]	6.1
Atorvastatin	Placebo	SPARCL[184]	4.9
	Placebo	ASCOT-LLA[11]	3.3
Lovastatin	Placebo	AFCAPS/Tex-CAPS[9]	5.2
Simvastatin	Placebo	HPS[10]	2.0
	Placebo	4S[5]	5.4
Fluvastatin	Placebo	LIPS[16]	3.9

4S indicates Scandinavian Simvastatin Survival Study; AFCAPS/Tex-CAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ASCOT-LLA, Prevention of Coronary and Stroke Events With Atorvastatin in Hypertensive Patients who Have Average or Lower-Than-Average Cholesterol Concentrations, in the AngloScandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; CARE, the Effect of Pravastatin on Coronary Events After Myocardial Infarction in Patients With Average Cholesterol Levels; HPS, Heart Protection Study; IMPROVEIT, Ezetimibe Added to Statin Therapy After Acute Coronary Syndromes; JUPITER, Rosuvastatin to Prevent Vascular Events in Men and Women With Elevated C-Reactive Protein; LIPID, the Long-Term Intervention With Pravastatin in Ischaemic Disease; LIPS, the Lescol Intervention Prevention Study; LRC-CPPT, Lipid Research Clinic-Coronary Primary Prevention Trial; POSCH, Effect of Partial Ileal Bypass Surgery on Mortality and Morbidity From Coronary Heart Disease in Patients With Hypercholesterolemia. Report of the Program on the Surgical Control of the Hyperlipidemias; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels; and WOSCOPS, Prevention of Coronary Heart Disease With Pravastatin in Men With Hypercholesterolemia.

Circ Res. 2018 Sep 28;123(8):e20.

CRESTOR 20mg: effective in the primary prevention of cardiovascular disease comparing to HTN medication and Aspirin

- 5-year NNT values in primary prevention

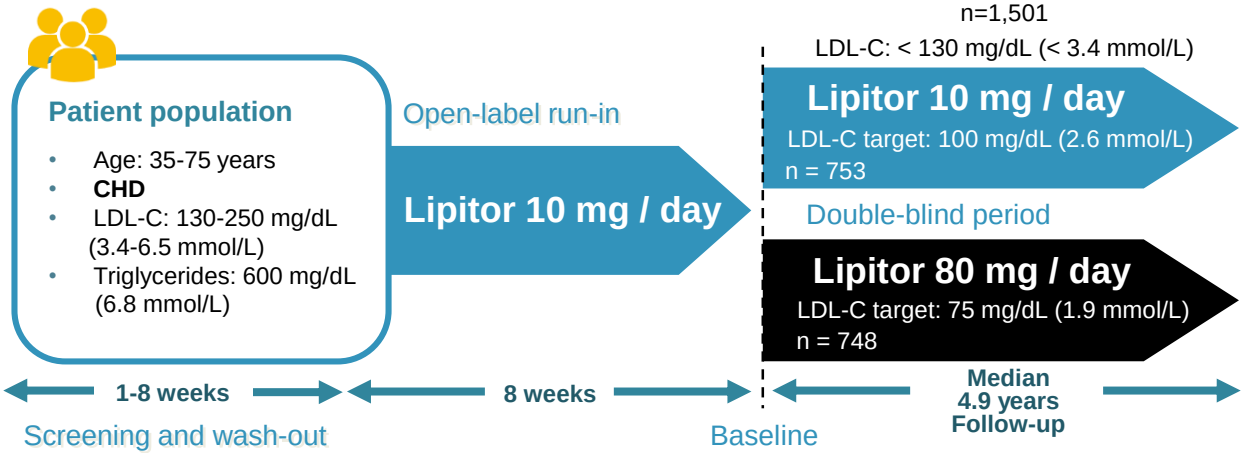


Circ Cardiovasc Qual Outcomes. 2009 May;2(3):279-85.

DM + CVD

Lipitor Study

TNT (DM subgroup)



Primary End Point

Time to occurrence of a major CV event:

- CHD death
- Nonfatal, non–procedure-related MI
- Resuscitated cardiac arrest
- Fatal or nonfatal stroke

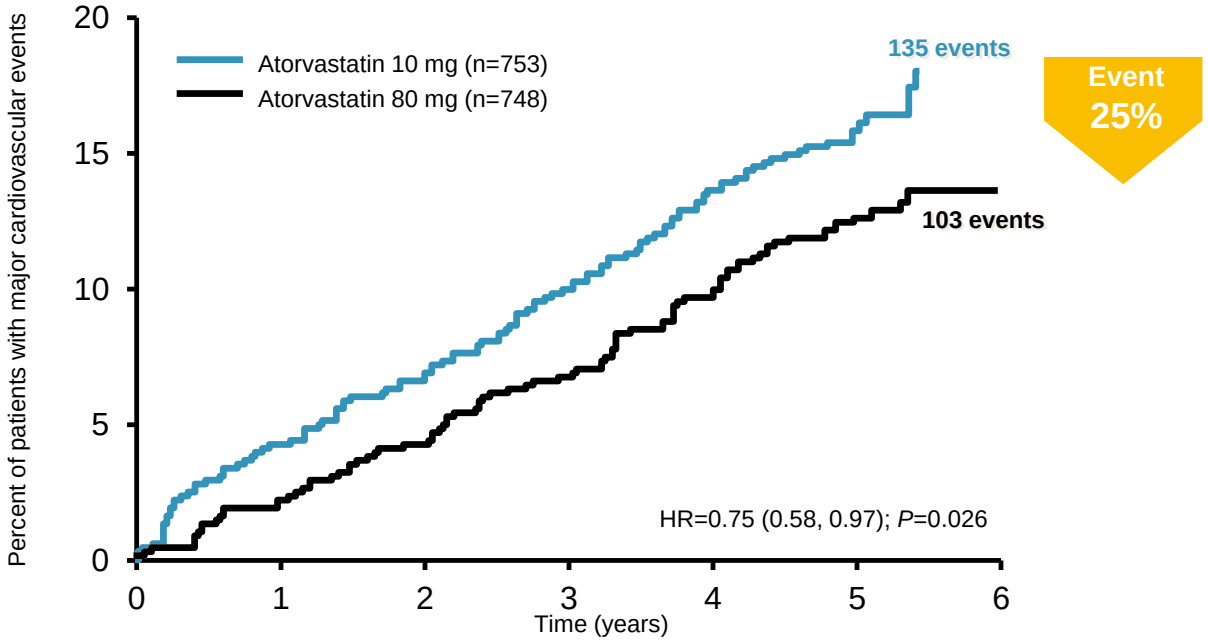
Diabetes Care. 2006;29:1220-1226.

DM + CVD

Lipitor Study

TNT (DM subgroup)

Time to first major cardiovascular event* in patients with diabetes



*CHD death, nonfatal non–procedure-related MI, resuscitated cardiac arrest, fatal or nonfatal stroke.

Diabetes Care. 2006;29:1220-1226.

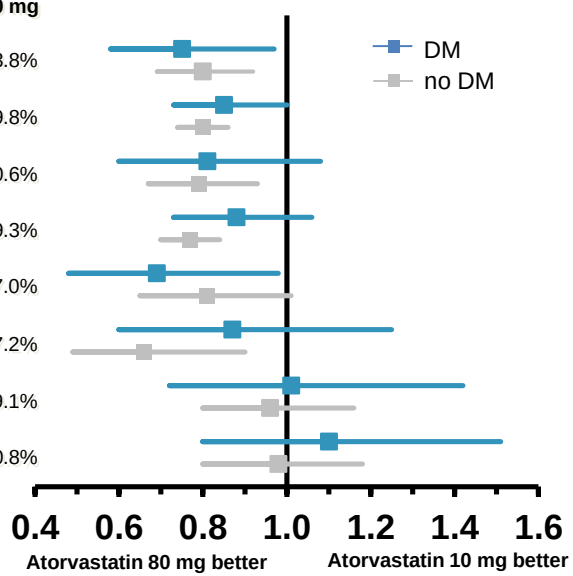
DM + CVD

Lipitor Study

TNT (DM subgroup)

Time to first major cardiovascular event in patients with diabetes

diabetes)	Event rate (diabetes) 10 mg	80 mg	Event rate (no 10 mg	80 mg
Major CV event	17.9%	13.8%	9.7%	7.8%
Any CV event	44.1%	39.8%	31.6%	26.1%
Major coronary	12.9%	10.6%	7.5%	6.0%
Any coronary	32.0%	29.3%	25.5%	20.2%
Cerebrovascular	10.0%	7.0%	4.2%	3.4%
CHF with hospitalization	8.2%	7.2%	2.4%	1.6%
PAD	8.9%	9.1%	5.1%	4.9%
All-cause mortality	9.8%	10.8%	4.9%	4.8%



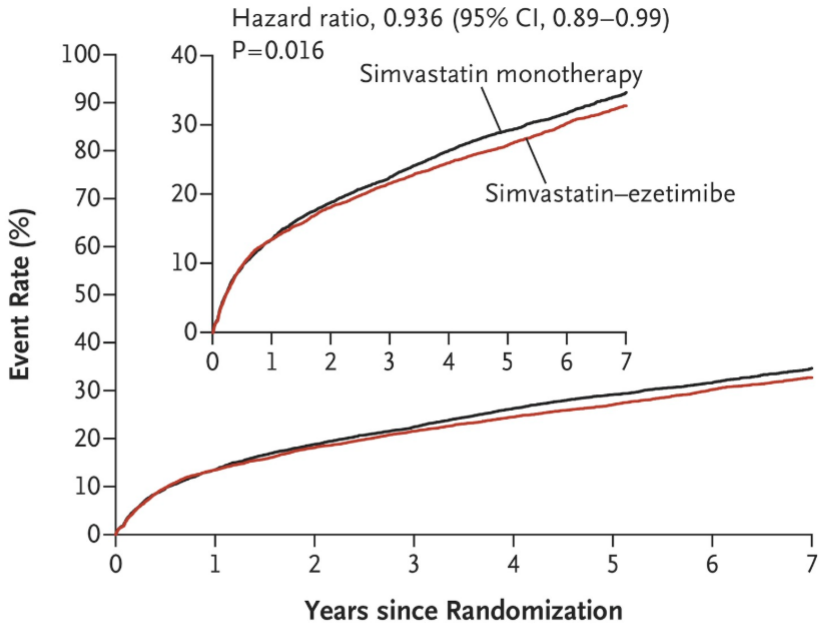
Diabetes Care. 2006;29:1220-1226.

ORIGINAL ARTICLE

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D., Amy McCagg, B.S., Jennifer A. White, M.S., Pierre Theroux, M.D., Harald Darius, M.D., Basil S. Lewis, M.D., Ton Oude Ophuis, M.D., Ph.D., J. Wouter Jukema, M.D., Ph.D., Gaetano M. De Ferrari, M.D., Witold Ruzyllo, M.D., et al., for the IMPROVE-IT Investigators*

June 18, 2015
N Engl J Med 2015; 372:2387-2397
DOI: 10.1056/NEJMoa1410489
Chinese Translation 中文翻译



No. at Risk

Simvastatin–ezetimibe	9067	7371	6801	6375	5839	4284	3301	1906
Simvastatin	9077	7455	6799	6327	5729	4206	3284	1857

Figure 1. Kaplan–Meier Curves for the Primary Efficacy End Point.

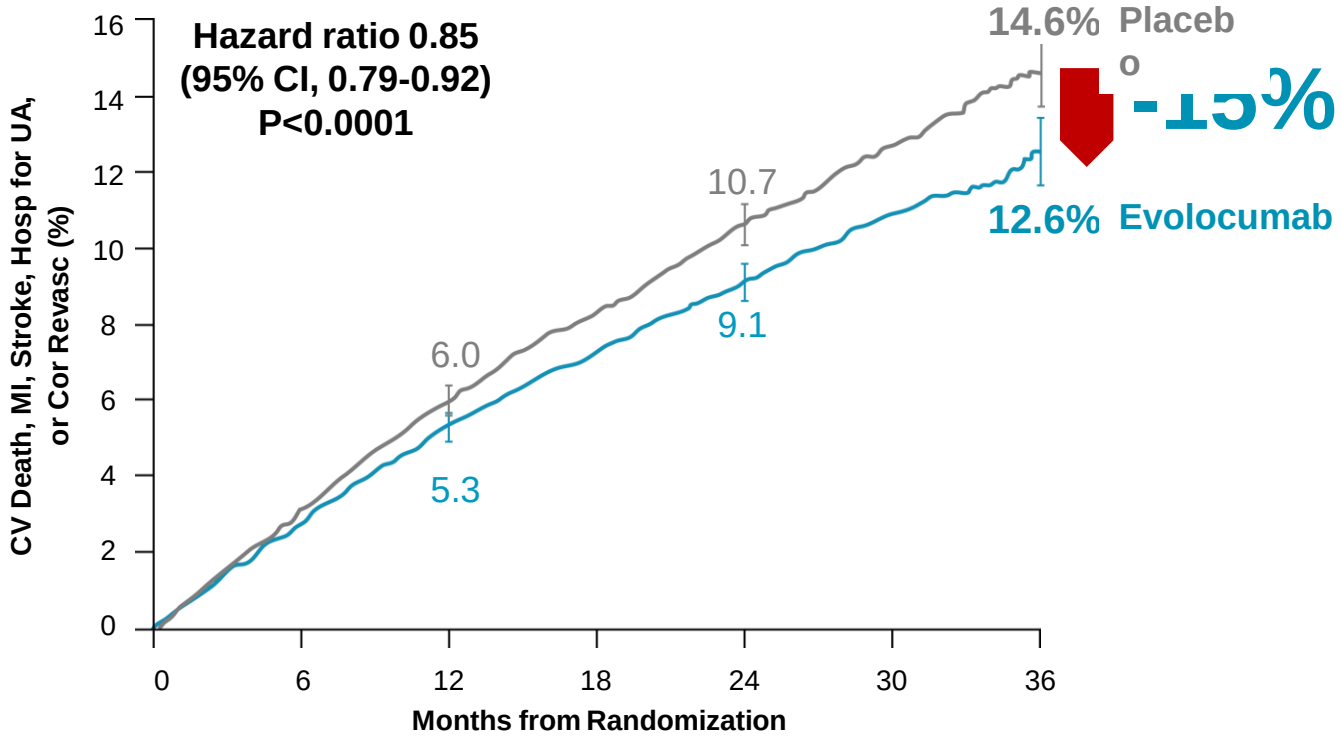
Shown are the cumulative event rates for the primary composite end point of death from cardiovascular disease, a major coronary event (nonfatal myocardial infarction, documented unstable angina requiring hospital admission, or coronary revascularization occurring at least 30 days after randomization), or nonfatal stroke in the intention-to-treat population during the overall study period (i.e., beginning from the time of randomization to the day of the first occurrence of a primary end-point event, the day of the last office or phone visit, or the day of death during follow-up). The inset shows the same data on an enlarged y axis.

PCSK9 Inhibitor CV Outcomes Trials

	Evolocumab (AMG 145)	Alirocumab (SAR236553/REGN727)
Sponsor	Amgen	Sanofi/ Regeron
Trial	FOURIER[1]	ODYSSEY Outcomes[2]
Sample size	22,500	18.000
Patients	MI, Stroke, or PAD	4-52 wk post ACS
Statin	Atorva> 20 mg or equivalent	Evidence-based management
LDL-C, mg/dL (mmol/L)	≥70 (≥1.8)	≥70 (≥1.8)
PCSK9 Inhibitor dosing	Q2W or Q4W	Q2W
Endpoint	Primary: CV death, MI, stroke, revascularization, or hospitalization for UA Key secondary: CV death, MI, or stroke	CHD death, MI, ischemic stroke, or hospitalization for UA
Completion	November 2016	December 2017

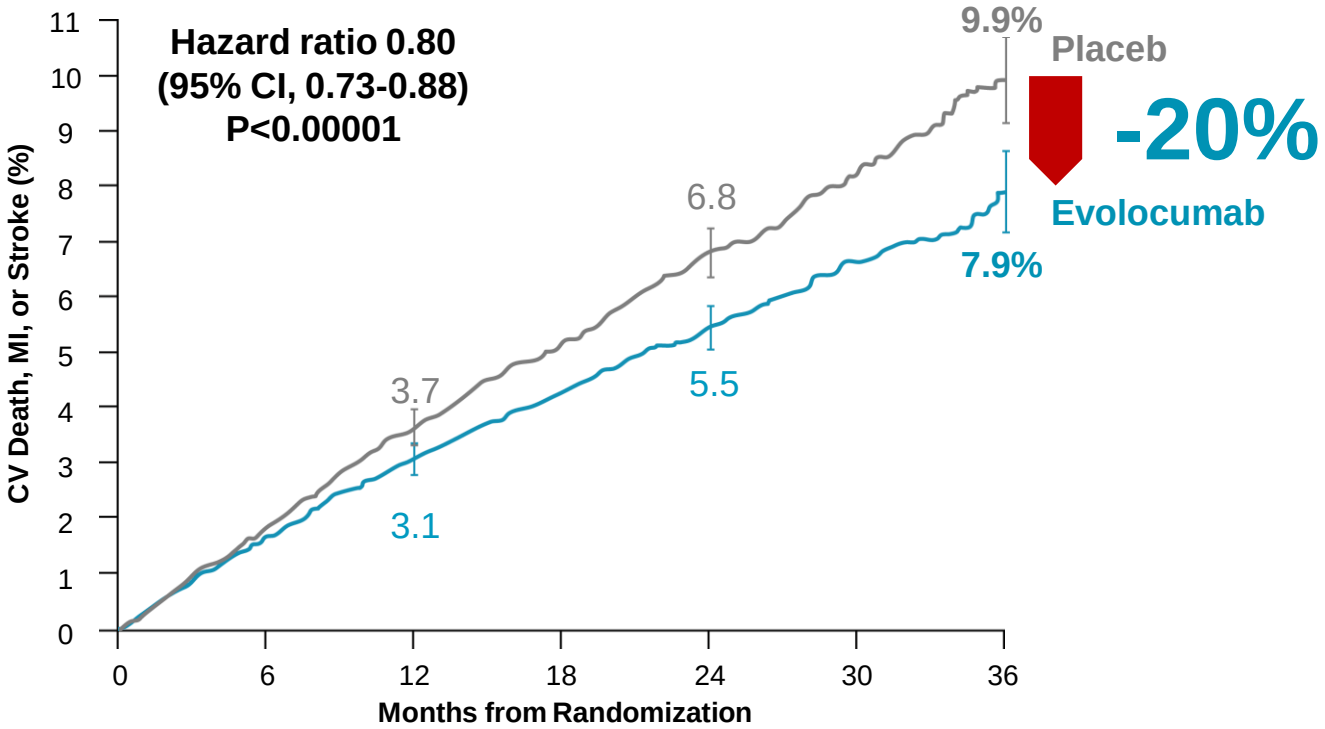
1. ClinicalTrials.gov.NCT01764633, https://clinicaltrials.gov/ct2/show/NCT01764633. **2.** ClinicalTrials.gov. NCT01663402, https://clinicaltrials.gov/ct2/show/NCT01663402

FOURIER Study : Primary Endpoint Results



FOURIER Trial Follow-up: Sabatine MS et al. *N Engl J Med*, *2017*(376), 1713-1722.

FOURIER Study : Key Secondary Endpoint



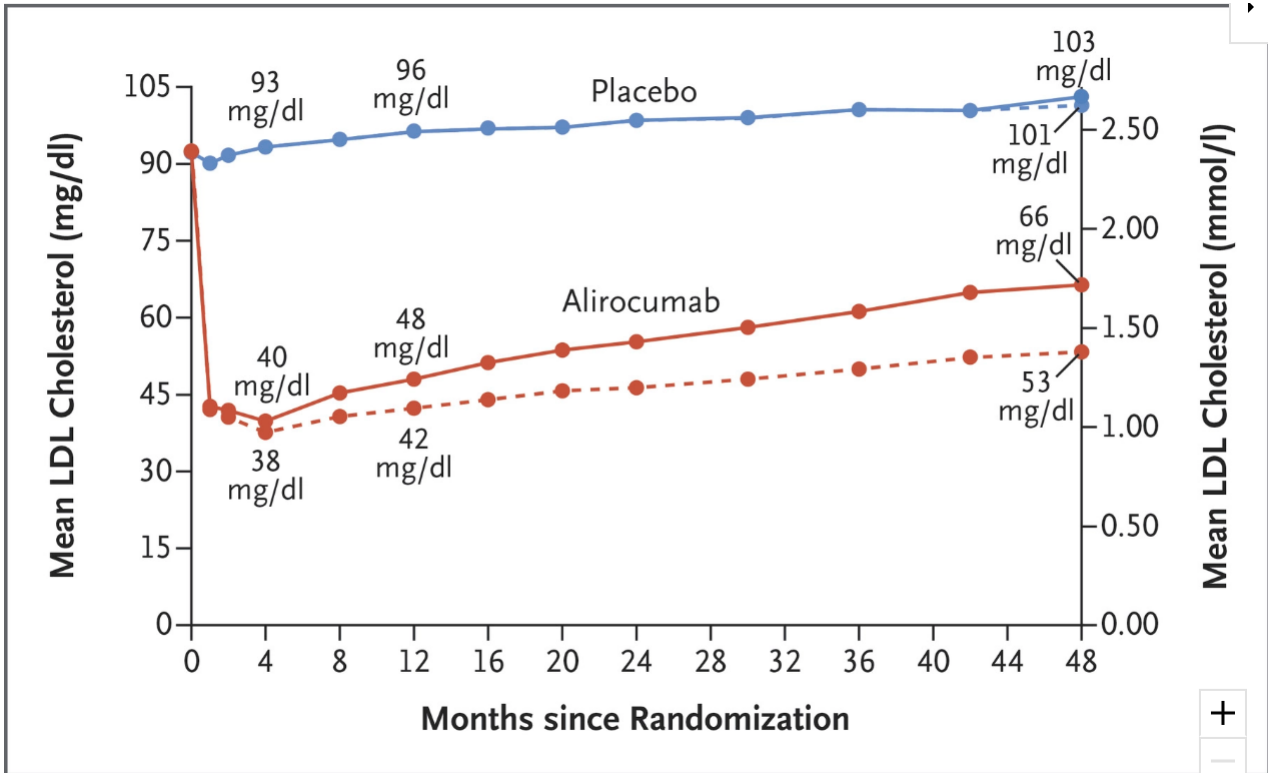
FOURIER Trial Follow-up: Sabatine MS et al. *N Engl J Med*, *2017*(376), 1713-1722.

ORIGINAL ARTICLE

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

Gregory G. Schwartz, M.D., Ph.D., P. Gabriel Steg, M.D., Michael Szarek, Ph.D., Deepak L. Bhatt, M.D., M.P.H., Vera A. Bittner, M.D., M.S.P.H., Rafael Diaz, M.D., Jay M. Edelberg, M.D., Ph.D., Shaun G. Goodman, M.D., Corinne Hanotin, M.D., Robert A. Harrington, M.D., J. Wouter Jukema, M.D., Ph.D., Guillaume Lecorps, M.Sc., et al., for the ODYSSEY OUTCOMES Committees and Investigators*

November 29, 2018
N Engl J Med 2018; 379:2097-2107
DOI: 10.1056/NEJMoa1801174
Chinese Translation 中文翻译


Mean LDL Cholesterol (mg/dl)
105
90
75
60
45
30
15
0
93 mg/dl
96 mg/dl
Placebo
103 mg/dl
101 mg/dl
66 mg/dl
Alirocumab
48 mg/dl
40 mg/dl
53 mg/dl
38 mg/dl
42 mg/dl
0
4
8
12
16
20
24
28
32
36
40
44
48
Months since Randomization
Mean LDL Cholesterol (mmol/l)
2.50
2.00
1.50
1.00
0.50
0.00

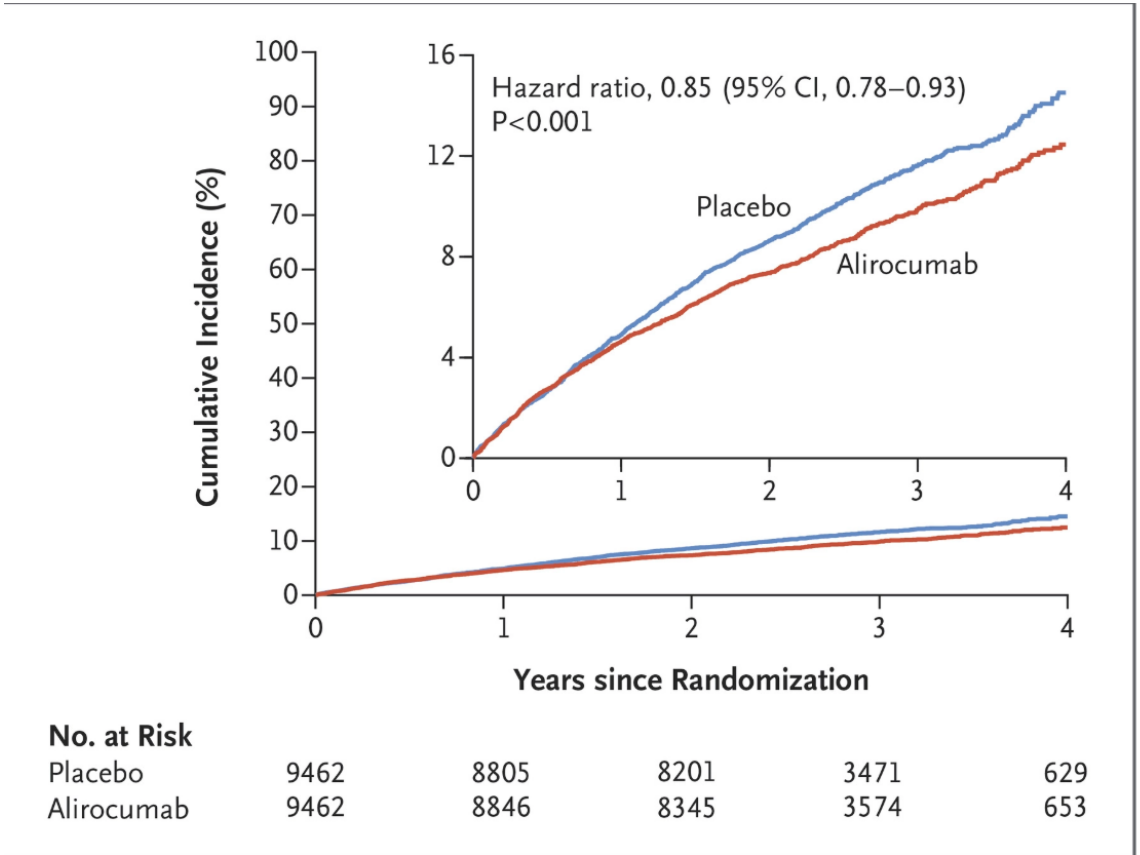


Figure 2. Cumulative Incidence of the Composite Primary End Point.

Shown is the cumulative incidence of the primary efficacy end point (a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization). The Kaplan–Meier rates for the primary end point at 4 years were 12.5% (95% CI, 11.5 to 13.5) in the alirocumab group and 14.5% (95% CI, 13.5 to 15.6) in the placebo group. The inset shows the same data on an enlarged y axis. The P value was calculated with the use of log-rank tests, stratified according to geographic region.

Chapter 3

Remaining statin associated issues

CRESTOR : hydrophilic statin with less adverse side effect

Table 1. Pharmacologic Characteristics of Statins

Drug	Dose (mg)	CYP450 Pathway	Bioavailability (%)	Absorption (%)	Lipophilicity	Half-life (h)
Atorvastatin	10-80	CYP2C9 (<10%)	12	30	Yes	15-30
Fluvastatin	20-80	CYP2C9, CYP3A4 (minor)	19-29	98	Yes	0.5-2.3
Lovastatin	10-80	CYP3A4	<5	30	Yes	2.9
Pitavastatin	1-4	Glucuronidation, CYP2C9 (minor), CYP3A4 (minor)	51	50	Yes	8-12
Pravastatin	40-80	None	18	24	No	1.3-2.8
Rosuvastatin	5-40	CYP2C (<10%), CYP2C19 (minor)	20	Rapid	No	15-30
Simvastatin	5-80	CYP3A4, CYP3A5	<5	60-80	Yes	2-3

Source: References 6, 9, 20-26.

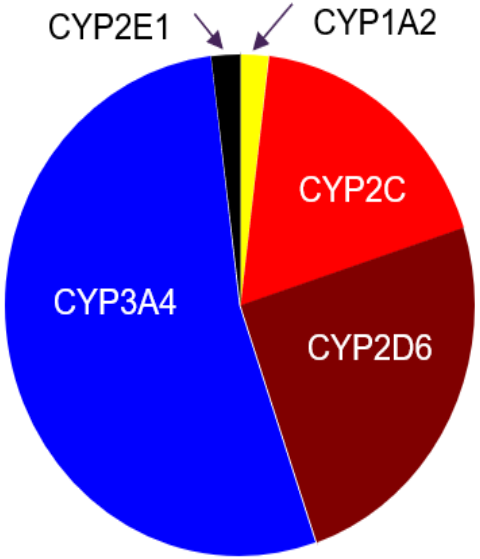
US Pharm. 2012;37(2):55-59.

CRESTOR : lower potential of drug-drug interaction by 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**



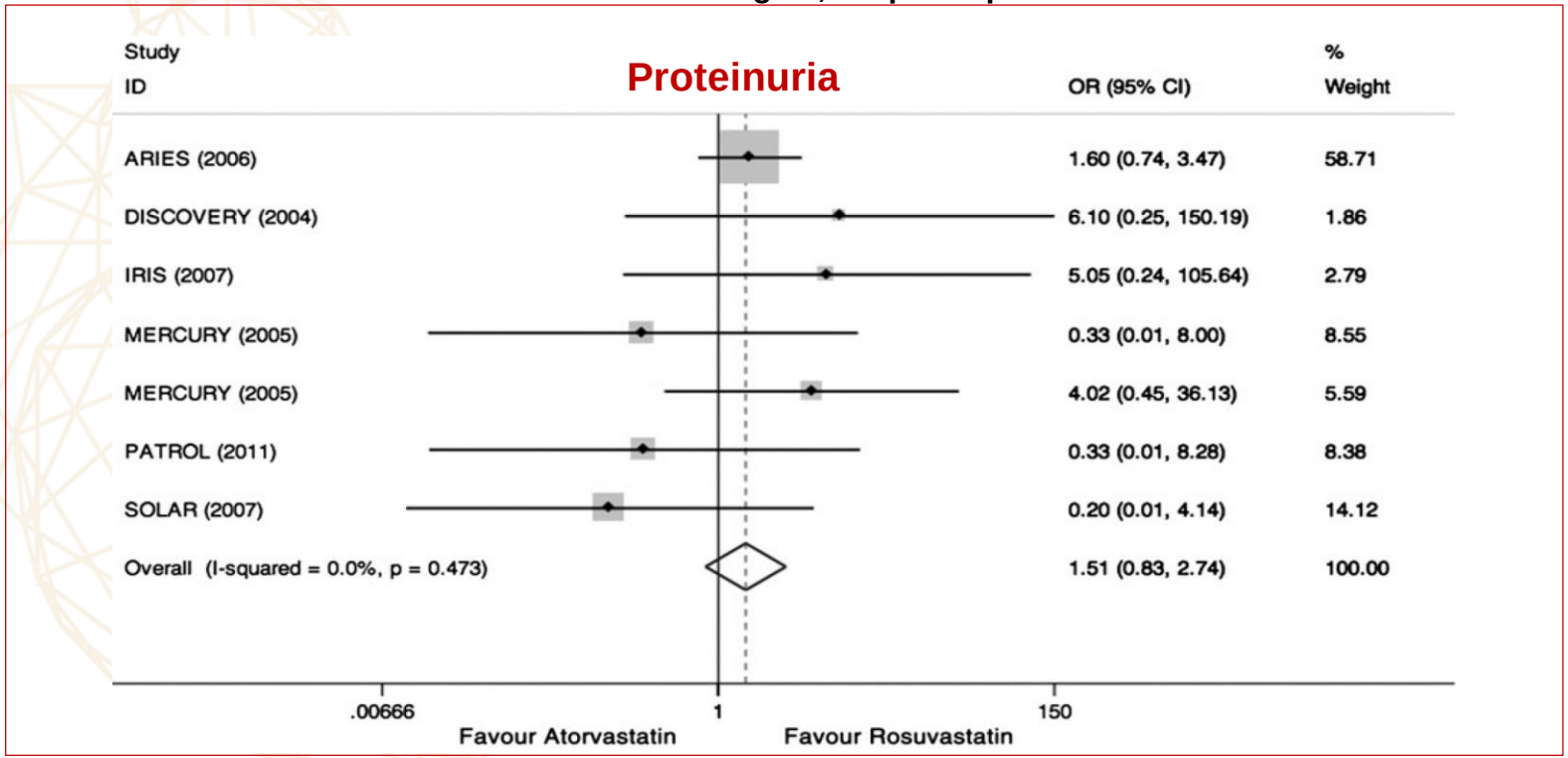
CYP 2C9

- Rosuvastatin
- **Fluvastatin**
- **Phynytoin**
- **Fluconazole**
- **Warfarin**

Shimada T et al. J Pharmacol Exp Ther 1994;270(1):414.

Effect of Atorvastatin and Rosuvastatin on Renal function (Meta-analysis 23 trials)

23 trials enrolling 29,147 participants



Savarese G et al. Int J Cardiol 2013;167:2482-2489

Effect of Atorvastatin and Rosuvastatin on Renal function (Meta-analysis 23 trials)

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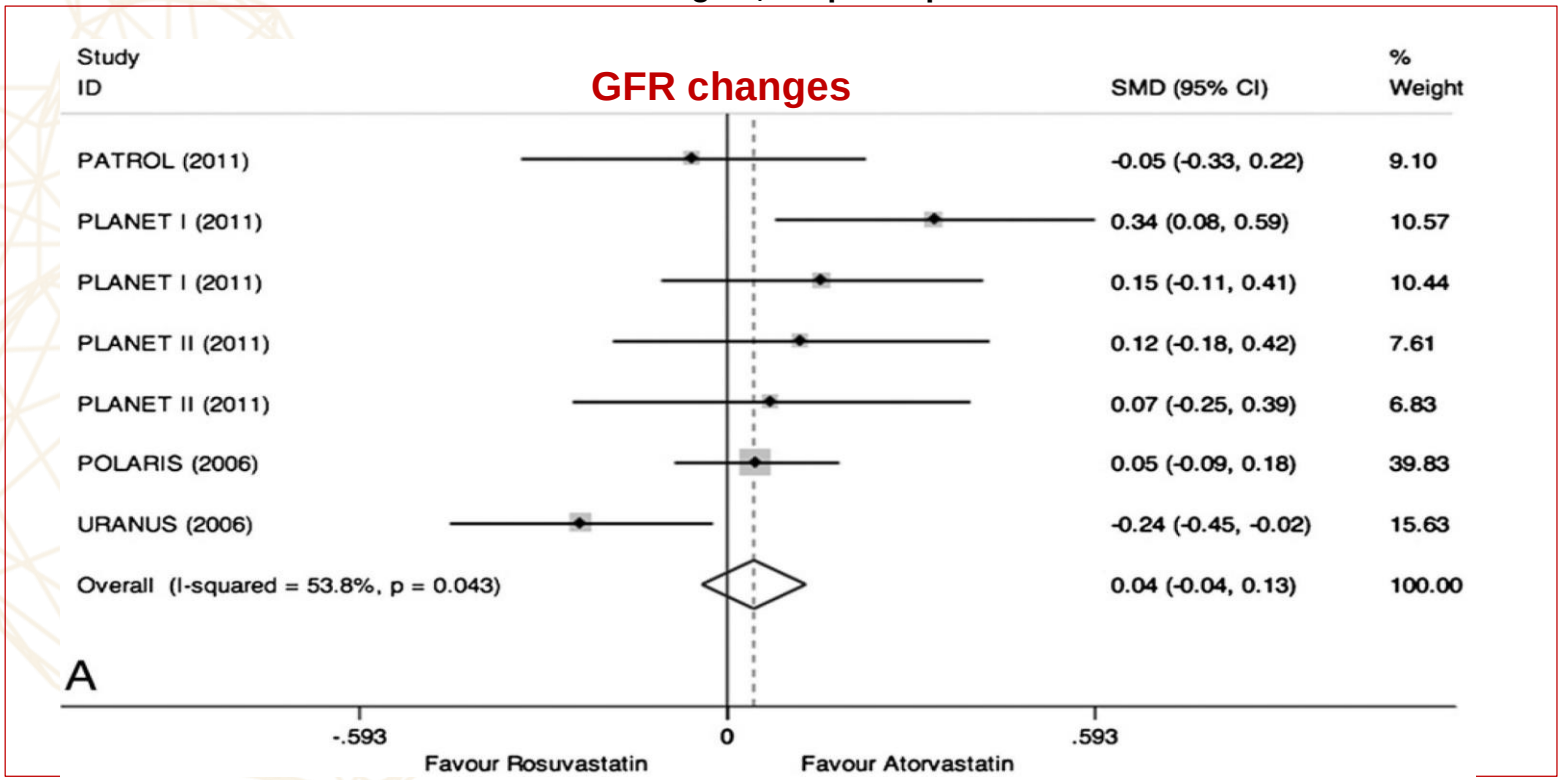
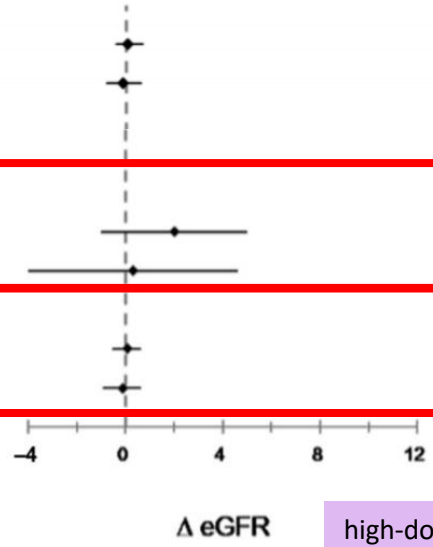


Savarese G et al. Int J Cardiol 2013;167:2482-2489

Both rosuvastatin and atorvastatin showed a similar phenomenon in eGFR

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				0.54
Atorvastatin	3431	0.1 ,	−0.5 to 0.6	
Rosuvastatin	1903	−0.1 ,	−0.9 to 0.6	



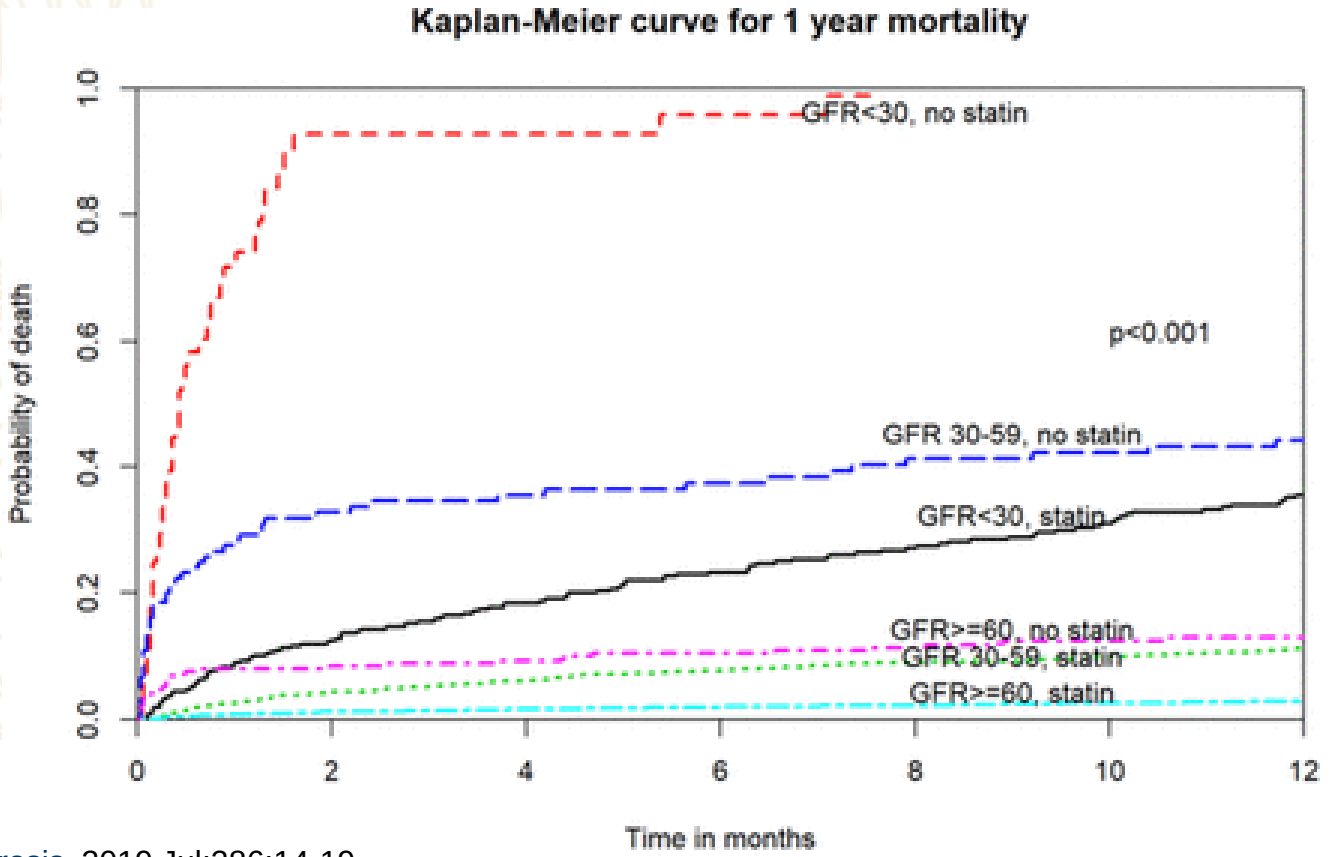
依仿單, Crestor的劑量範圍是5-20mg每天一次

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.

Statins beneficial effect : maintained among chronic kidney disease regardless of their eGFR



Atherosclerosis. 2019 Jul;286:14-19.

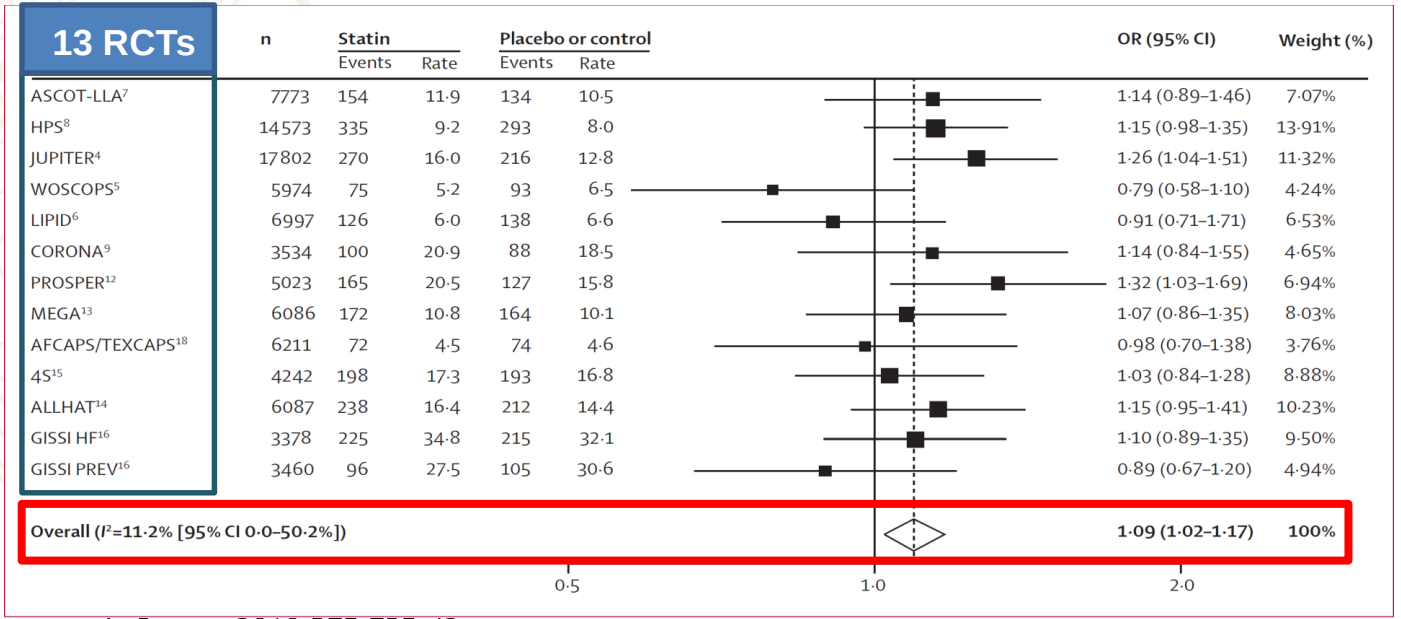
What about New Onset DM in Statin treatment?

All statins could induce New Onset DM

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

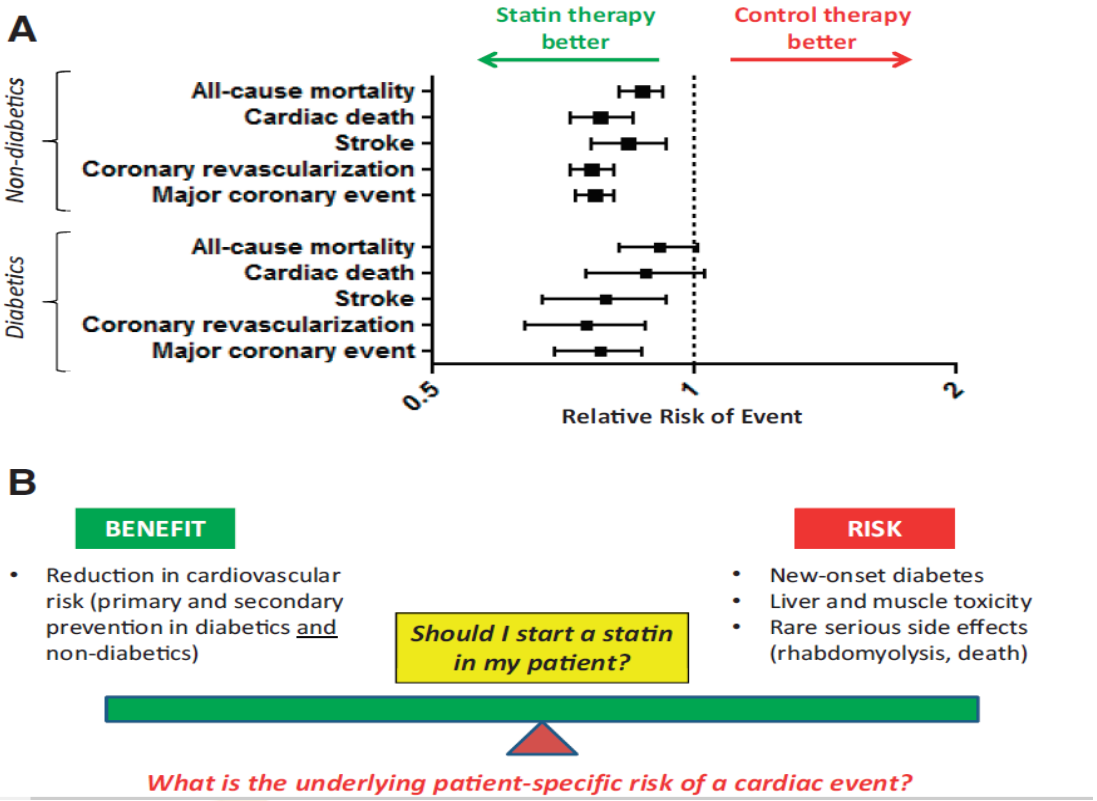
13 RCTs



	n	Statin Events	Statin Rate	Placebo or control Events	Placebo or control Rate	OR (95% CI)	Weight (%)
ASCOT-LLA[7]	7773	154	11·9	134	10·5	1·14 (0·89–1·46)	7·07%
HPS[8]	14573	335	9·2	293	8·0	1·15 (0·98–1·35)	13·91%
JUPITER[4]	17802	270	16·0	216	12·8	1·26 (1·04–1·51)	11·32%
WOSCOPS[5]	5974	75	5·2	93	6·5	0·79 (0·58–1·10)	4·24%
LIPID[6]	6997	126	6·0	138	6·6	0·91 (0·71–1·71)	6·53%
CORONA[9]	3534	100	20·9	88	18·5	1·14 (0·84–1·55)	4·65%
PROSPER[12]	5023	165	20·5	127	15·8	1·32 (1·03–1·69)	6·94%
MEGA[13]	6086	172	10·8	164	10·1	1·07 (0·86–1·35)	8·03%
AFCAPS/TEXCAPS[18]	6211	72	4·5	74	4·6	0·98 (0·70–1·38)	3·76%
4S[15]	4242	198	17·3	193	16·8	1·03 (0·84–1·28)	8·88%
ALLHAT[14]	6087	238	16·4	212	14·4	1·15 (0·95–1·41)	10·23%
GISSI HF[16]	3378	225	34·8	215	32·1	1·10 (0·89–1·35)	9·50%
GISSI PREV[16]	3460	96	27·5	105	30·6	0·89 (0·67–1·20)	4·94%
Overall (I^2=11·2% [95% CI 0·0–50·2%])						**1·09 (1·02–1·17)**	**100%**

Naveed Sattar et al., Lancet 2010;375:735-42

Reduce 40 mg/dl LDL-C with statin: reduce ASCVD risk by 20%



Circulation. 2012;126:e282-e284.

Conclusion

- “Lower is Better” : LDL–C 50% reduction strategy should be considered to treat and prevent ASCVD with high-intensity statin including Lipitor/CRESTOR
- CRESTOR/lipitor is the meaningful treatment option to target atherosclerosis which has consistently shown the benefits in atherosclerosis in patients with CAD, ACS, and subclinical atherosclerosis through 50% LDL–C reduction and beyond LDL-C effect
- CRESTOR/lipitor has similar safety profiles (NODM and renal function) compared with other statins