Optimal Treatment for Patients with Dyslipidemia: A Must therapeutic strategy for high risk patients

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A Must therapeutic strategy for high risk patients with dyslipidemia---optimal treatment

- Why?
- How?

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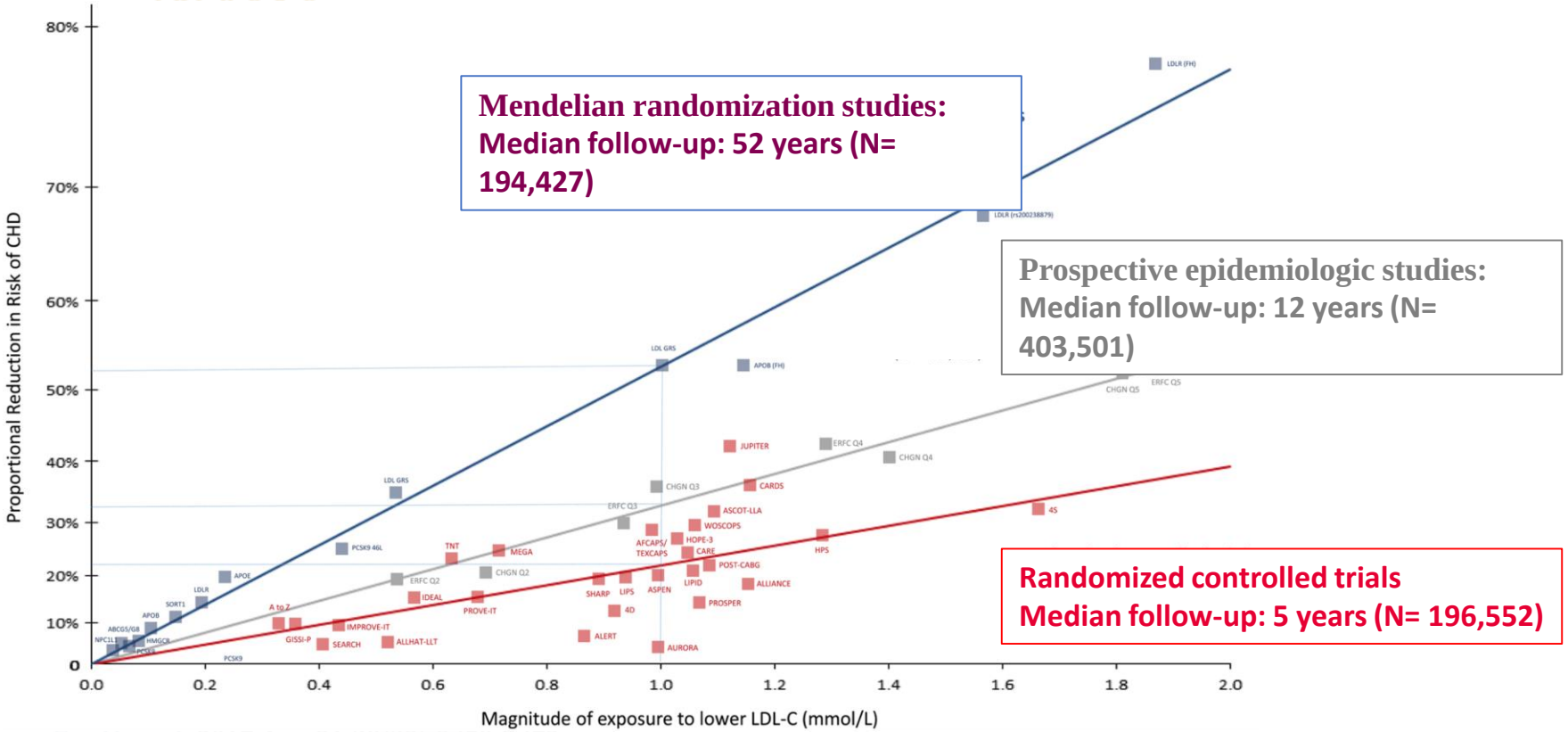
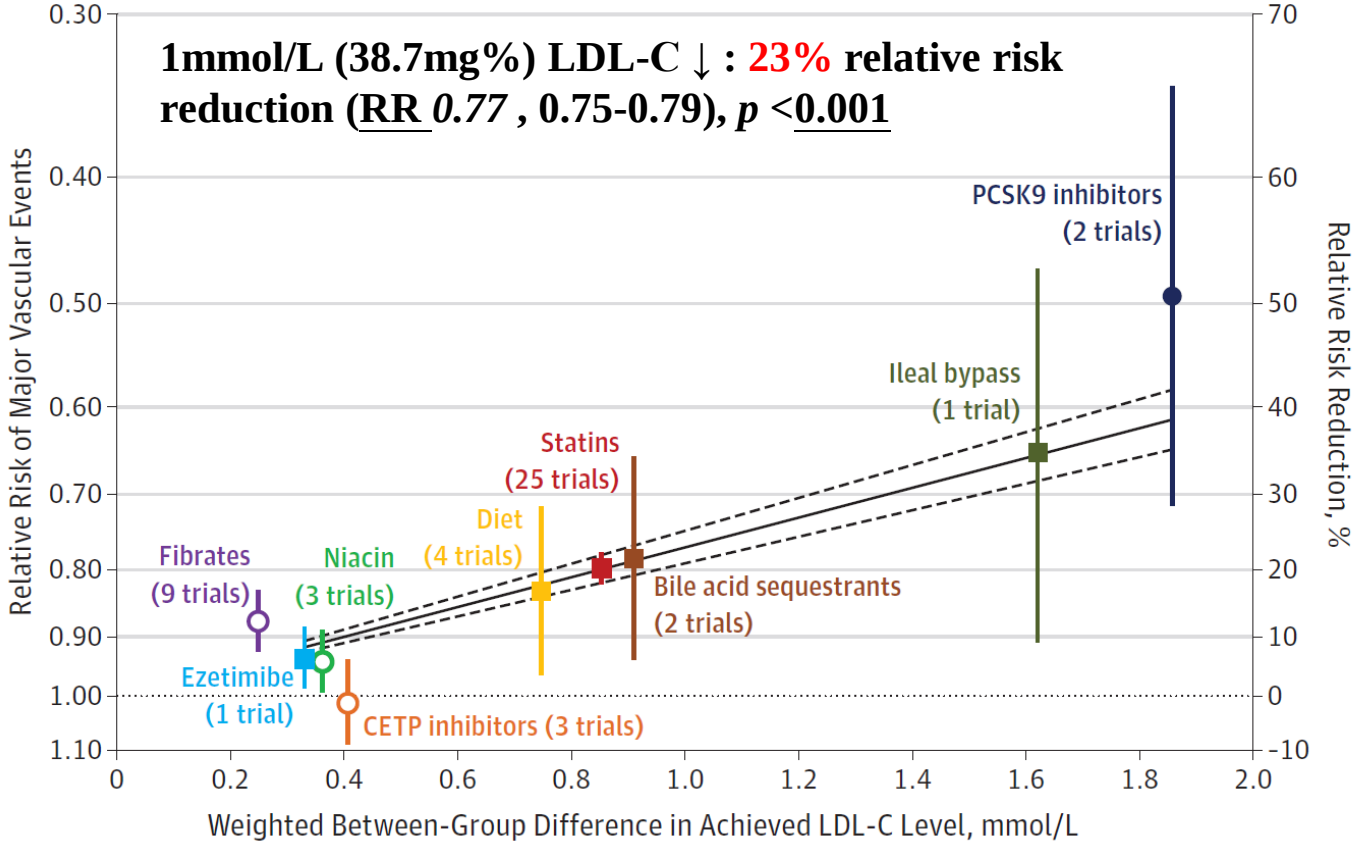
LDL cause atherosclerotic cardiovascular disease (ASCVD) : Evidence from genetic, epidemiologic, and clinical studies



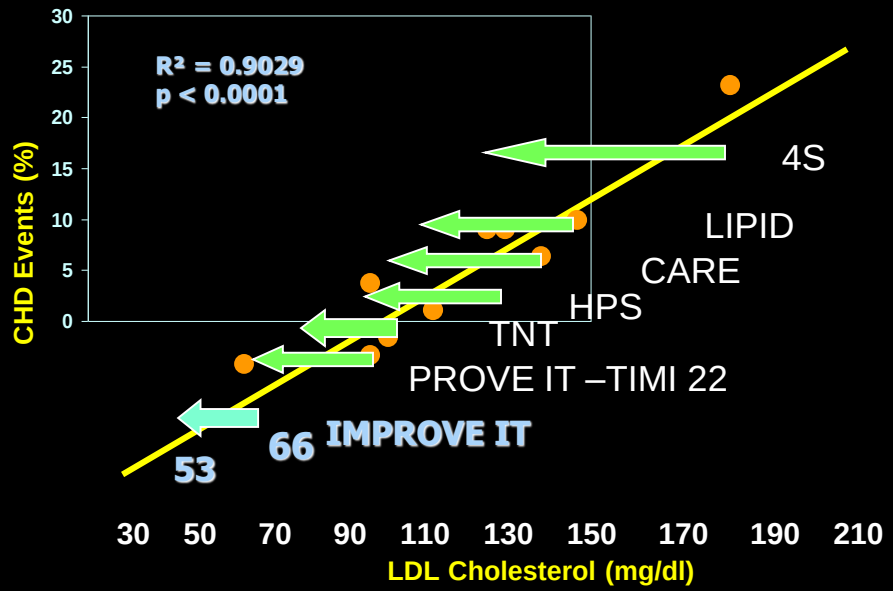
Eur Heart J. 2017 Aug 21;38(32):2459-2472.

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



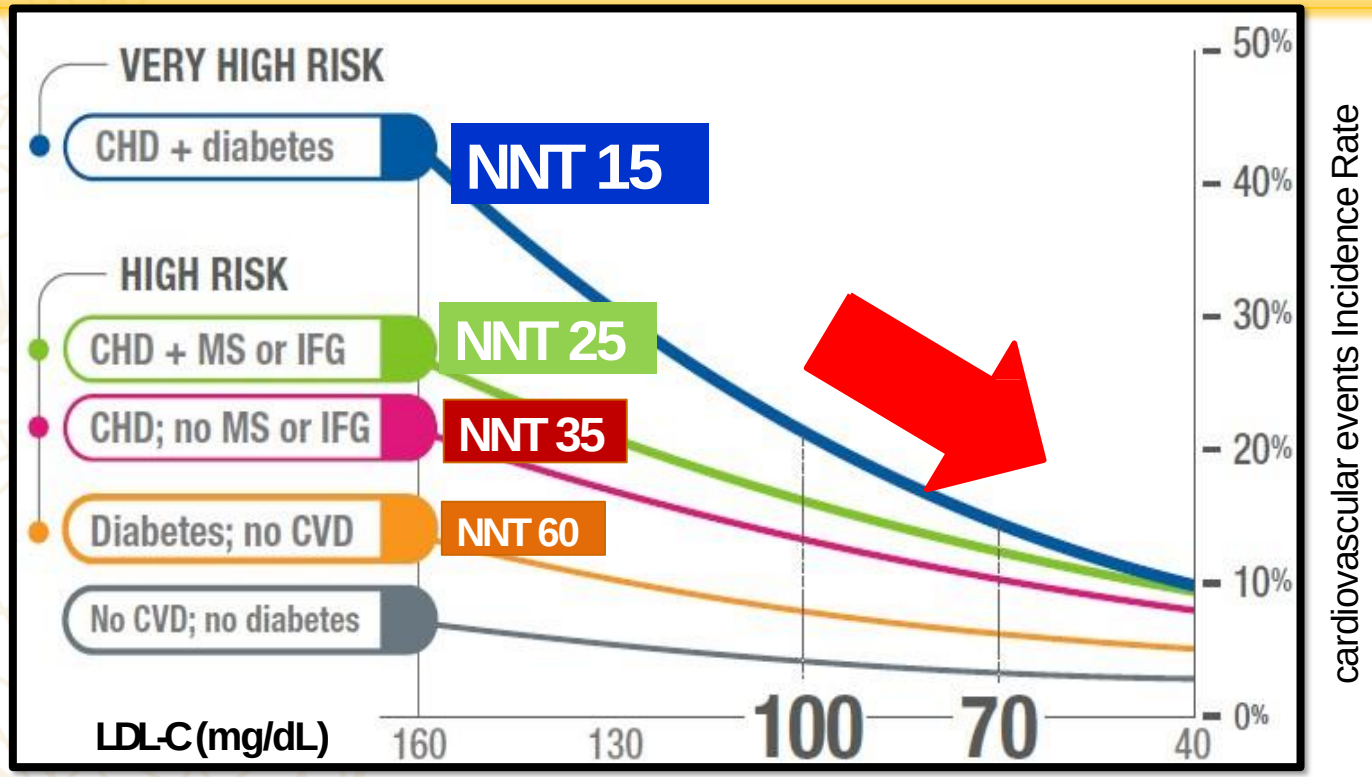
JAMA. 2016;316(12):1289-1297

The Statin Decade: For LDL: "Lower is Better"



Adapted and Updated from O'Keefe, J. et al., *J Am Coll Cardiol* 2004;43:2142-6.

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

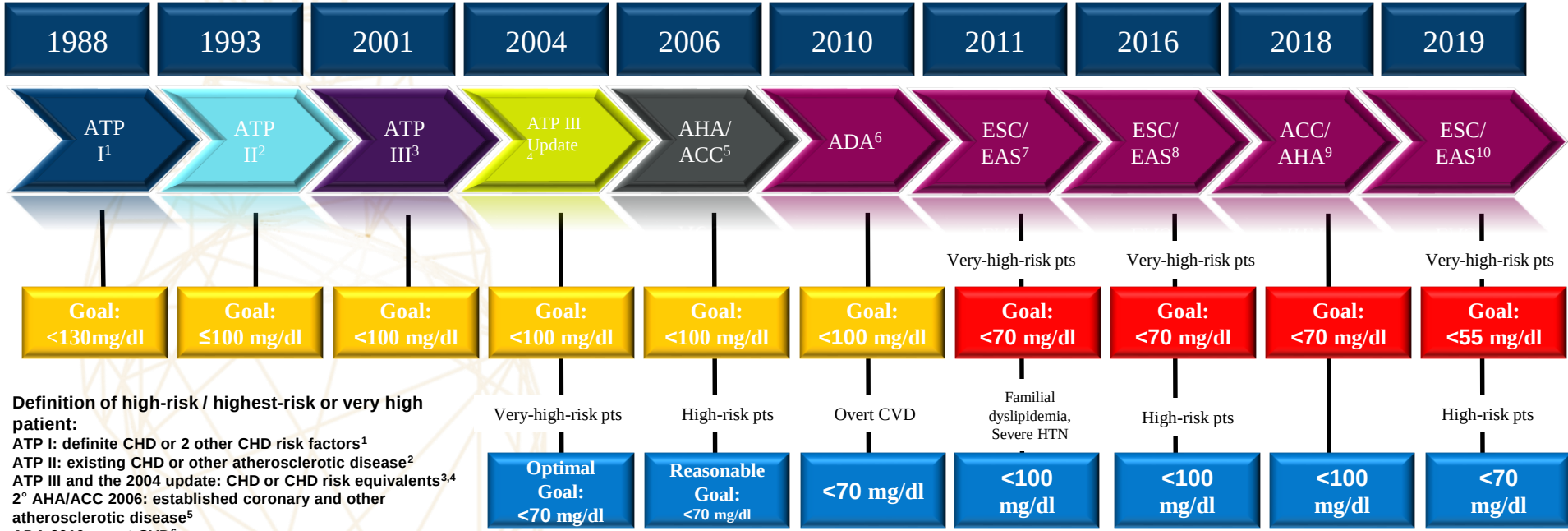


5-year NNT to prevent 1 ASCVD event; NNT: # of risk patients needed to be treated to prevent one event over 5 years

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.

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

2016 European Guidelines
Target levels for LDL-C and HDL-C

Patient group	LDL-C treatment goal
VERY-HIGH CV risk: -Documented CVD -DM or type-1 DM with target organ damage -Severe RD: GFR <30 ml/min/1.73 m^2 -10 year risk SCORE ≥10%	**LDL-c goal <70 mg/dl (1.8 mmol/L)** and/or **50% reduction** if baseline is 70-135 mg/dl (1.8-3.5 mmol/L)
HIGH CV risk: -Markedly elevated single risk factor -10 year risk SCORE ≥5% and <10% -Moderate RD: GFR 30-59 mg/ml/1.73 m^2	LDL-c goal <100 mg/l (2.6 mmol/L) or **50% reduction** if baseline is 100-200 mg/dl (2.6-5.1 mmol/L)
MODERATE CV risk: -10 year risk SCORE ≥1% and <5%	LDL-c goal <115 mg/dl (3.0 mmol/L)
HDL-C	No target but >1.0 mmol/L (>40 mg/dL) in men and >1.2 mmol/L (>45 mg/dL) in women indicate lower risk

SCORE = Systematic Coronary Risk Estimation

European Association for Cardiovascular Prevention & Rehabilitation. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)

European Heart Journal (2016) 37, 2999–3058

ASCVD Risk Categories and LDL-C Treatment Goals

Risk category	Risk factors/10-year risk	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	– Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very high risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% – DM or stage 3 or 4 CKD with 1 or more risk factor(s) – HeFH	<70	<100	<80
High risk	– ≥2 risk factors and 10-year risk 10%-20% – DM or stage 3 or 4 CKD with no other risk factors	<100	<130	<90
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

Recommendations for treatment goals for low-density lipoprotein cholesterol(1)

Recommendations	Class	Level
In secondary prevention for patients at very-high risk[c] ,an LDL-C reduction of at least 50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.	I	A
In primary prevention for individuals at very-high risk but without FH[c], an LDL-C reduction of at least 50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.	I	C
In primary prevention for individuals with FH at very-high risk, an LDL-C reduction of at least 50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.	IIa	C

[c]For definitions see Table 4.
[d]The term 'baseline' refers to the LDL-C level in a person not taking any LDL-C-lowering medication. In people who are taking LDL-C-lowering medication(s), the projected baseline (untreated) LDL-C levels should be estimated, based on the average LDL-C-lowering efficacy of the given medication or combination of medications.

2019 ESC/EAS Guidelines for the management of dyslipidemias: lipid modification to reduce cardiovascular risk

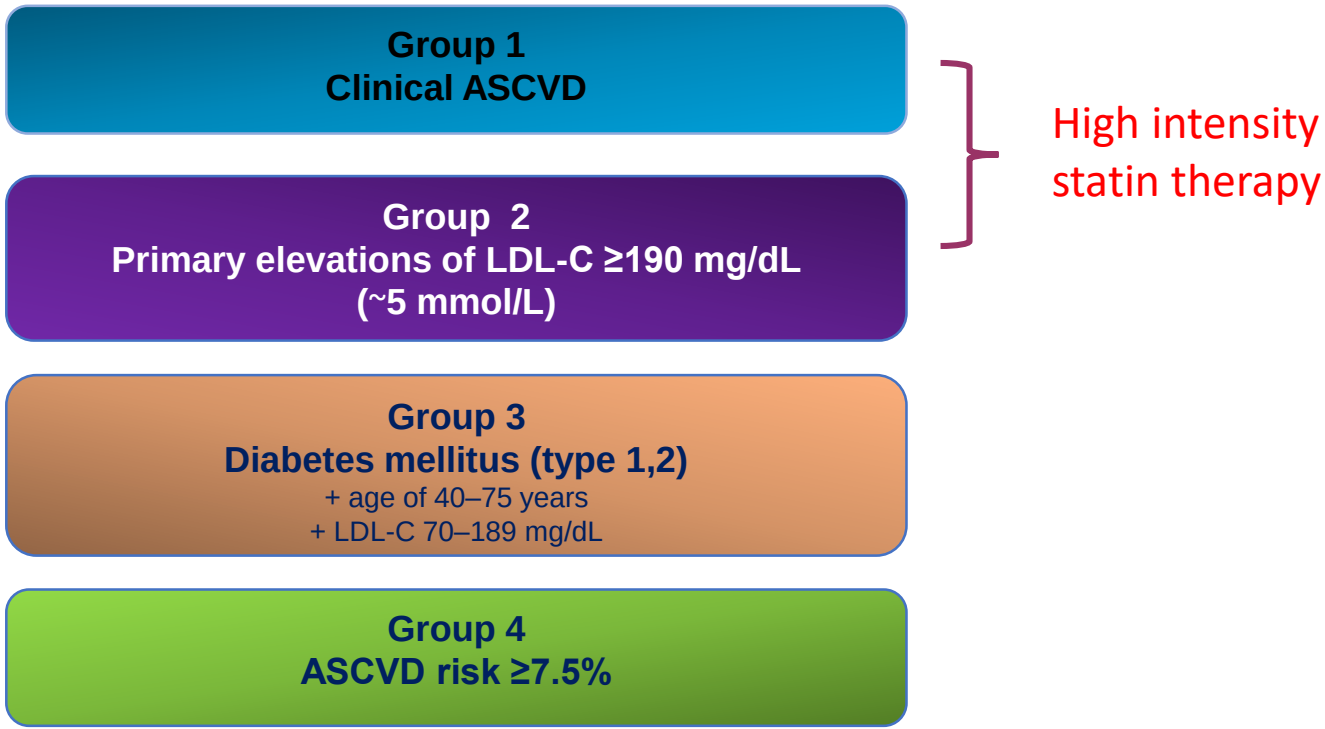
Recommendations for treatment goals for low-density lipoprotein cholesterol(2)

Recommendations	Class	Level
For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.	IIb	B
In patients at high risk[c], an LDL-C reduction of at least 50% from baseline[d] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.	I	A

[c]For definitions see Table 4.
[d]The term 'baseline' refers to the LDL-C level in a person not taking any LDL-C-lowering medication. In people who are taking LDL-C-lowering medication(s), the projected baseline (untreated) LDL-C levels should be estimated, based on the average LDL-C-lowering efficacy of the given medication or combination of medications.

2019 ESC/EAS Guidelines for the management of dyslipidemias: lipid modification to reduce cardiovascular risk

2013 AHA/ACC Guideline: Four statin benefit groups



ASCVD, atherosclerotic cardiovascular disease
CHD, coronary heart disease
LDL-C, low density lipoprotein-cholesterol

Stone NJ, et al.J Am Coll Cardiol 2013 Nov 7. Epub ahead of print

2013 ACC/AHA Statin分類準則:

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
LDL–C ↓ ≥50%	**LDL–C ↓ 30% to <50%**	**LDL–C ↓ <30%**
Atorvastatin (40†)–80 mg **Rosuvastatin 20 *(40)* mg**	Atorvastatin 10 *(20) mg* **Rosuvastatin *(5) 10 mg*** Simvastatin 20–40 mg‡ Pravastatin 40 *(80) mg* Lovastatin 40 mg *Fluvastatin XL 80 mg* Fluvastatin 40 mg bid *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* Pravastatin 10–20 mg Lovastatin 20 mg *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

Yellow= Not tested in RCT reviewed by Expert Panel

Rosuvastatin 40mg is not indicated in Taiwan.

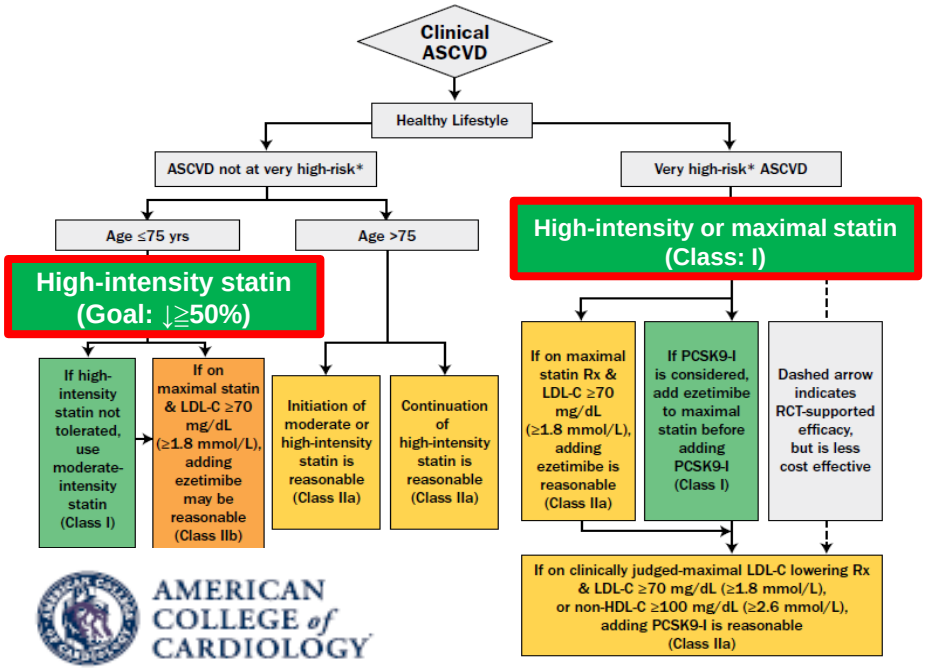
Stone NJ,et al. J AM Coll Cardiol. 2013:doi:10.1016/j.jacc.2013.11.002. Available at: http://content.onlinejacc.org/article.aspx?articleid=1770217. Accessed November 13, 2013

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

Secondary ASCVD Prevention

First Statin Benefit Group

Figure 1:
Secondary Prevention in Patients with Clinical ASCVD



AMERICAN COLLEGE of CARDIOLOGY

Very high-Risk for Future ASCVD Events*

Major ASCVD Events
Recent acute coronary syndrome (within the past 12 months)
History of myocardial infarction (other than recent acute coronary syndrome event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ankle brachial index <0.85, or previous revascularization or amputation)
High-Risk Conditions
Age ≥65 years
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or PCI outside of the major ASCVD event(s)
Diabetes Mellitus
Hypertension
Chronic kidney disease (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 heart failure

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

Circulation. 2018 Nov 10:CIR0000000000000625

Treatment Guideline in Taiwan (2017)

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

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

A Must therapeutic strategy for high risk patients with dyslipidemia---optimal treatment

- Why? ---Aggressive treatment
- How?

A Must therapeutic strategy for high risk patients with dyslipidemia---optimal treatment

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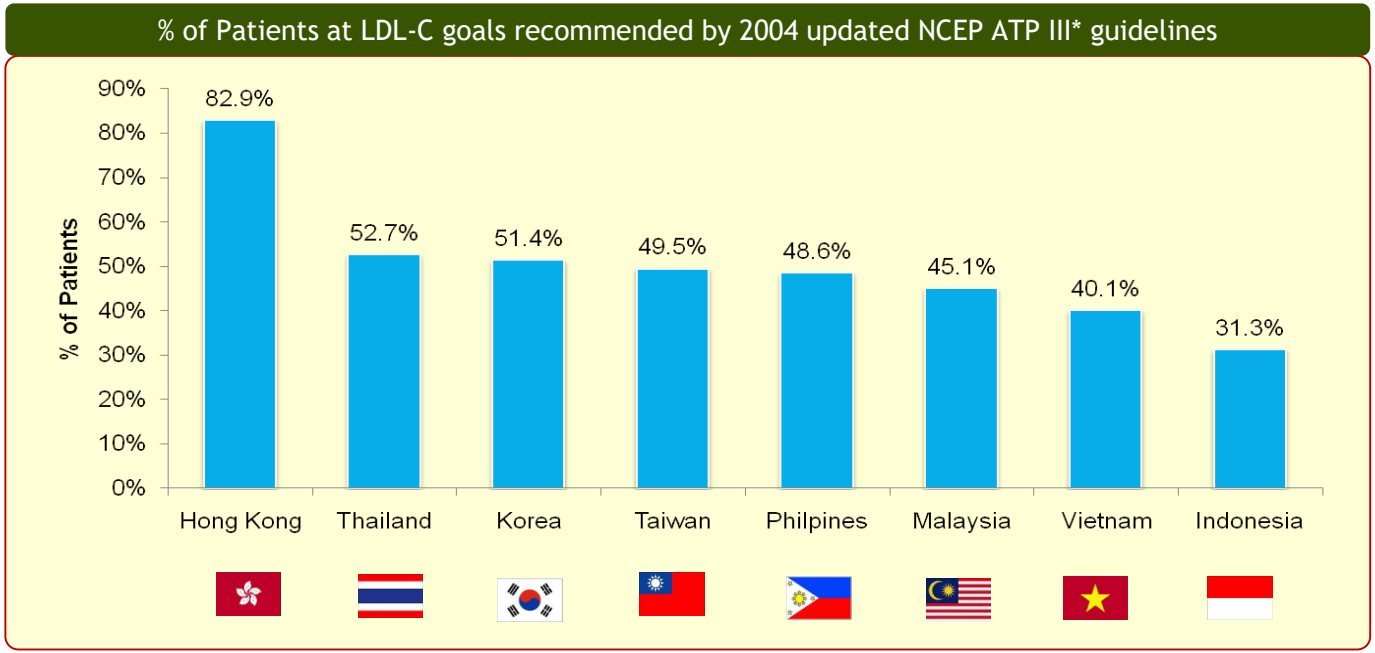
- Real world ?
- How?

Pan-Asian CEPHEUS (Pan Asian survey on undertreatment of hypercholesterolemia)

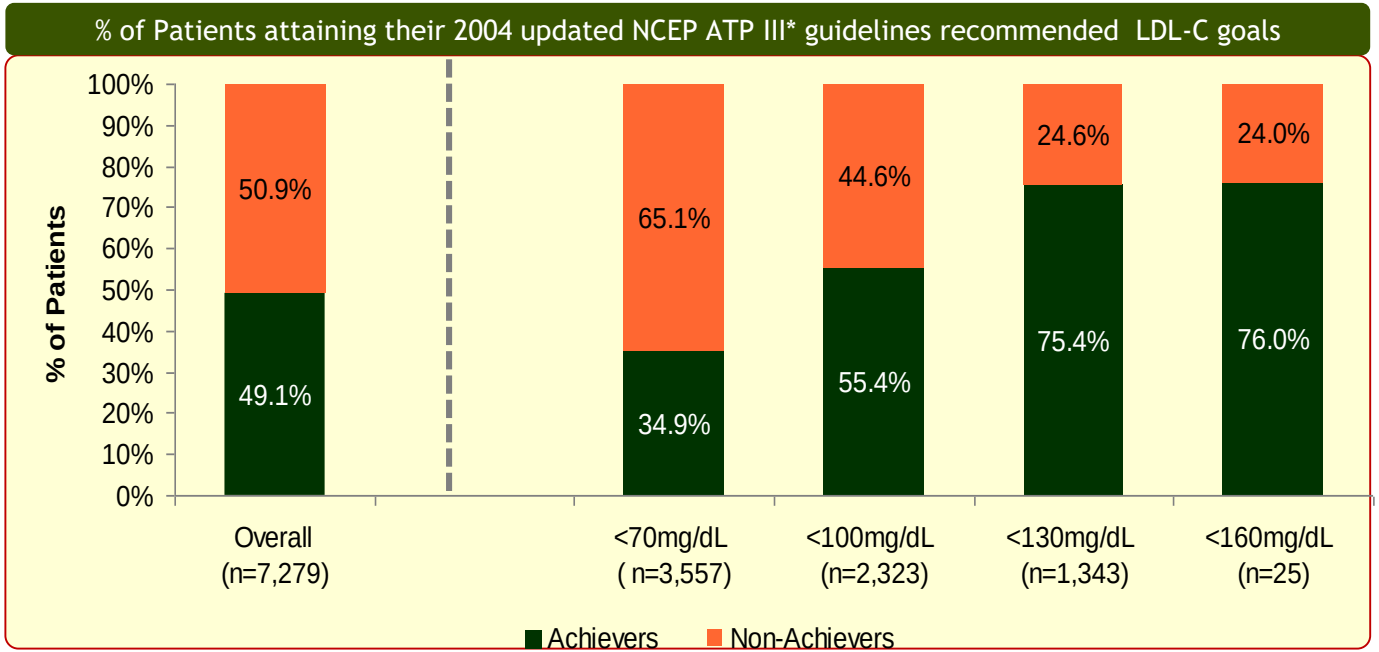
Eur J Cardiovasc Prev Rehabil. 2011

Percentage of Patients at LDL-C goals recommended by the 2004 updated NCEP ATP III* guidelines



- For patients in Hong Kong the treatment goal attainment rate was 82.9% while patients in other countries had very low LDL-C attainment rate (31.3 – 52.7%).

Proportion of patients attaining their 2004 updated NCEP ATP III-recommended LDL-C goals

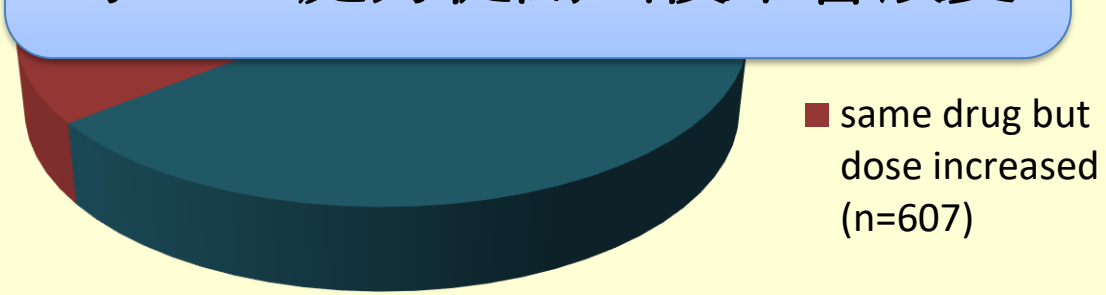


- Overall 49.1% LDL-C goal attainment rate among all patients surveyed across Asia.
- Proportion of patients attaining their respective LDL-C goal decreased with increasing cardiovascular risk.

Changes in the lipid-lowering drug since first prescribed a drug

64%

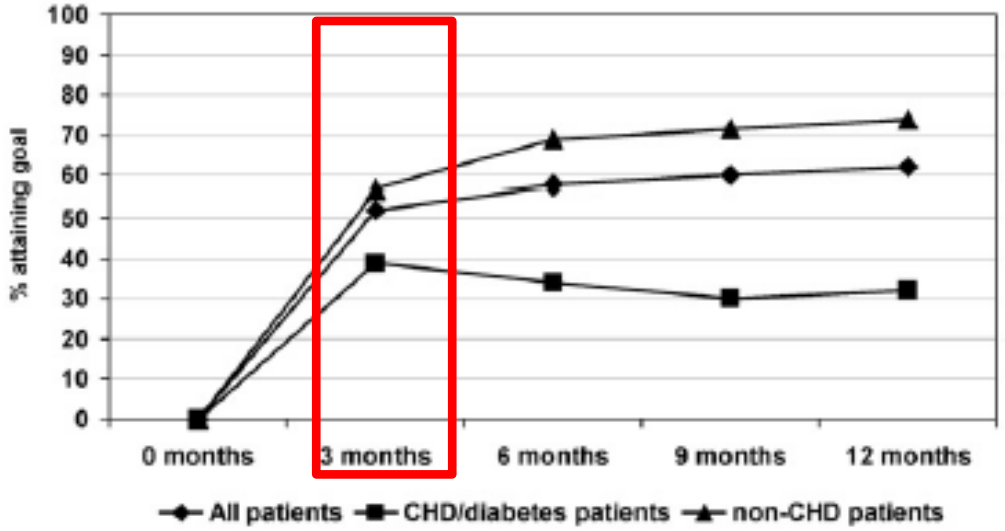
的statin處方從開出後不曾改變



- **For 64.1% of patients, initial treatment remained the same.**

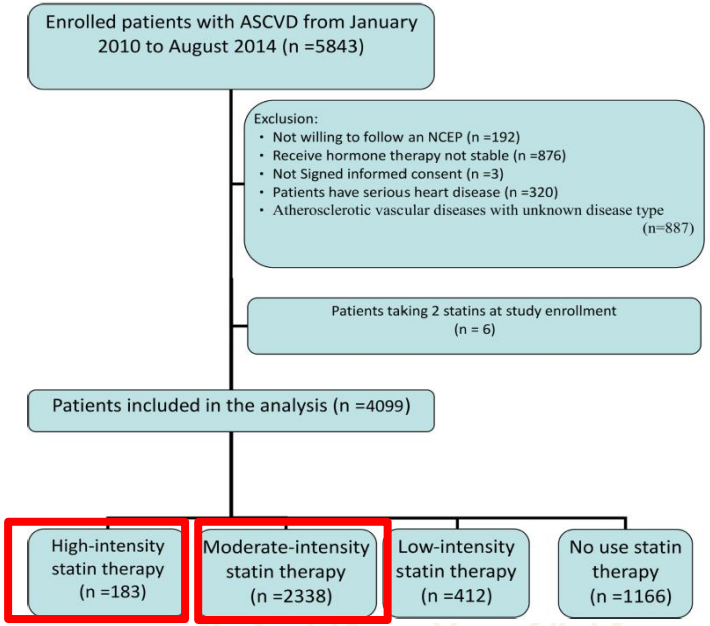
Park JE, Chiang CE, Munawar M, et al. Lipid-lowering treatment in hypercholesterolaemic patients: the CEPHEUS Pan-Asian survey. Eur J Prev Cardiol. 2012;19(4):781-794.

達標兩大關鍵：
- 把握前三個月黃金達標期，掌握先機
- 選擇高效能statin起始治療



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

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.

A Must therapeutic strategy for high risk patients with dyslipidemia---optimal treatment

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- Real world ? A gape between guideline and real world
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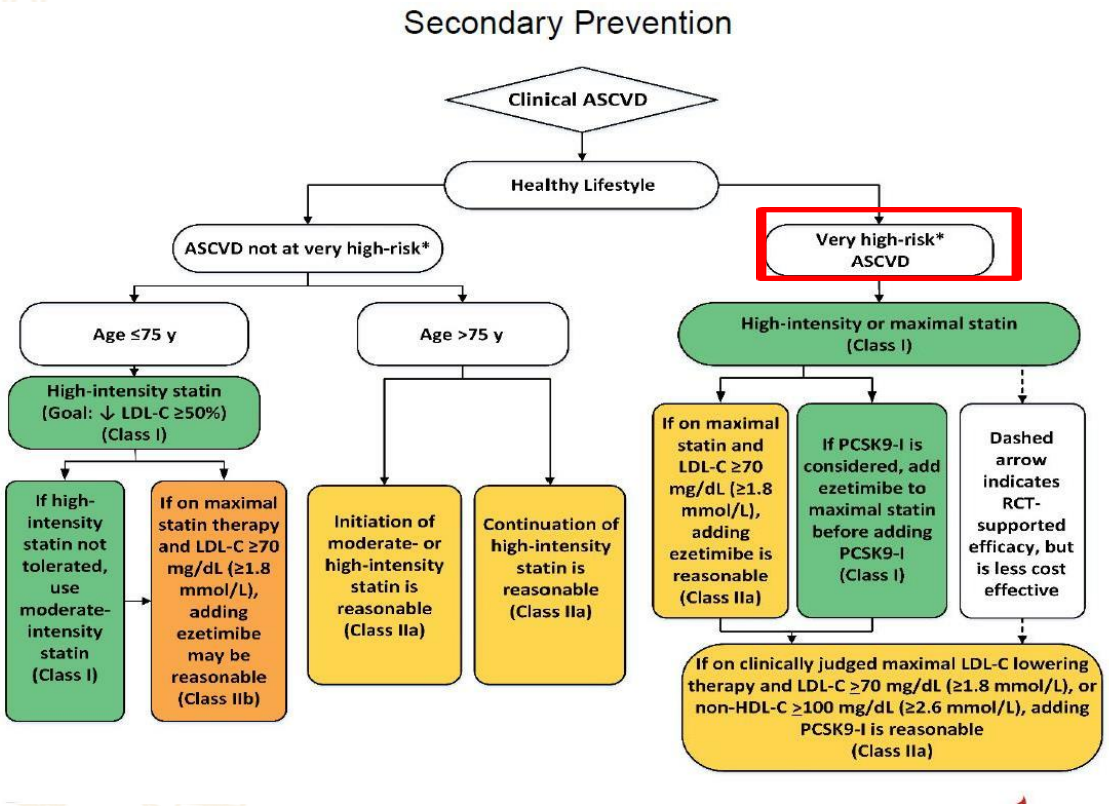
2018 AHA/ACC Guideline on the Management of Blood Cholesterol
- Secondary Prevention in Patients With Clinical ASCVD



Circulation. 2018 Nov 10:CIR0000000000000625

How ?

- Moderate- or high- intensity statin
- Combination therapy (statin +ezetimibe/bile acid sequestrant)
- Add on PCSK9-inhibitor

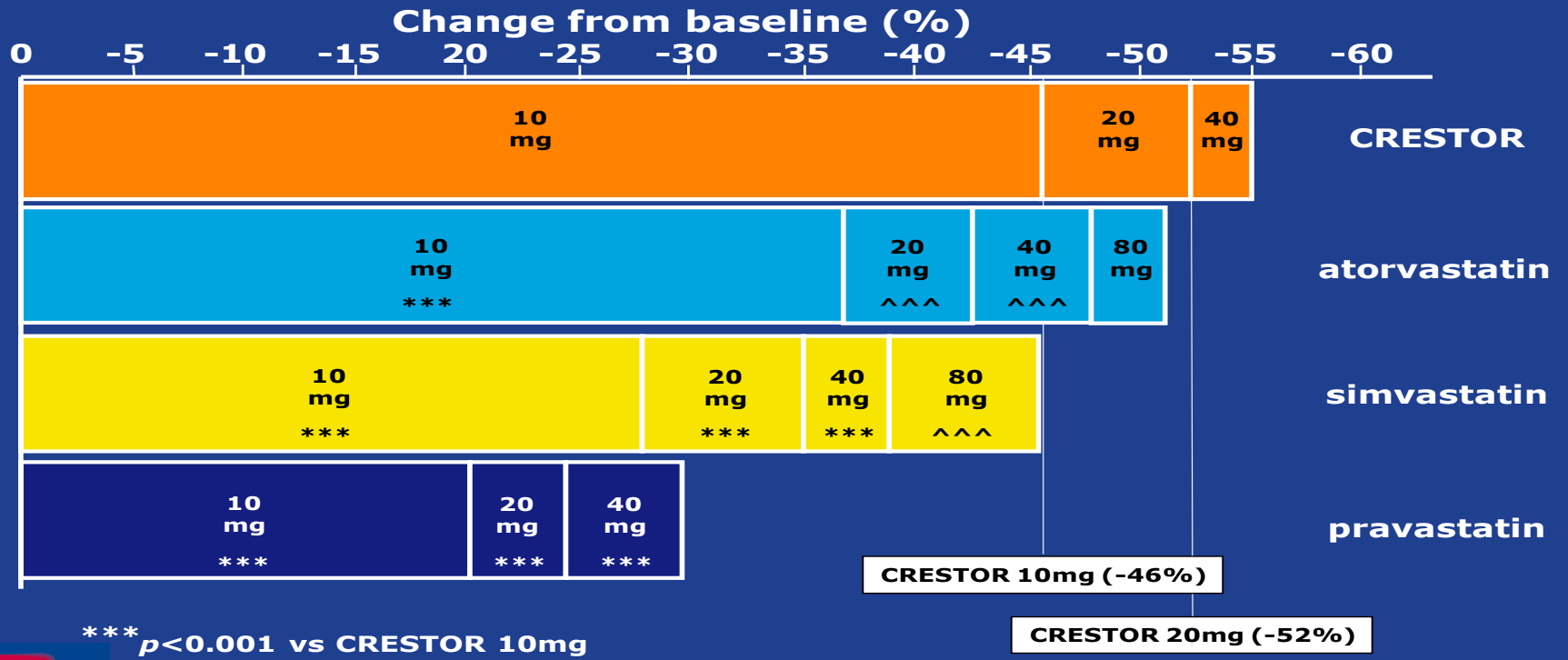
How ?

- Moderate- or high- intensity statin
- Combination therapy (statin +ezetimibe/bile acid sequestrant)
- Add on PCSK9-inhibitor

2016 ESC/EAS :Pharmacologic treatment of hypercholesterolemia

Recommendations	Class [a]	Level [b]
Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.	I	A
In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.	IIa	C
If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	IIa	B
If the goal is not reached, statin combination with a bile acid sequestrant may be considered.	IIb	C
In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	IIb	C

LDL-C: Percentage Change from Baseline at Week 6



*** $p<0.001$ vs CRESTOR 10mg

^^^ $p<0.002$ vs CRESTOR 20mg

STELLAR

FDA – Relative LDL –lowering efficacy

Relative LDL-lowering Efficacy of Statin and Statin-based Therapies*

Atorva	Fluva	Pitava	Lova	Prava	Rosuva	Vytorin†	Simva	% ↓ LDL-C
-	40 mg	1 mg	20 mg	20 mg	-	-	10 mg	30%
10 mg	80 mg	2 mg	40 or 80 mg	40mg	-	-	20 mg	38%
20 mg	-	4 mg	80 mg	80 mg	1 mg	10/10 mg	40 mg	41%
40 mg	-		-	-	10 mg	10/20 mg	80 mg	47%
80 mg	-		-	-	20 mg	10/40 mg	-	55%
	-		-	-	40 mg	10/80 mg	-	63%

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

2013 ACC/AHA Statin分類準則:

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
LDL–C ↓ ≥50%	**LDL–C ↓ 30% to <50%**	**LDL–C ↓ <30%**
Atorvastatin (40†)–80 mg **Rosuvastatin 20 *(40)* mg**	Atorvastatin 10 *(20) mg* **Rosuvastatin *(5) 10 mg*** Simvastatin 20–40 mg‡ Pravastatin 40 *(80) mg* Lovastatin 40 mg *Fluvastatin XL 80 mg* Fluvastatin 40 mg bid *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* Pravastatin 10–20 mg Lovastatin 20 mg *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

Yellow= Not tested in RCT reviewed by Expert Panel

Rosuvastatin 40mg is not indicated in Taiwan.

Stone NJ,et al. J AM Coll Cardiol. 2013:doi:10.1016/j.jacc.2013.11.002. Available at: http://content.onlinejacc.org/article.aspx?articleid=1770217. Accessed November 13, 2013

- Atorvastatin

Atorvastatin

1. Primary prevention

(1) ASCOT-LLA (10mg)……Hypertension

(2) CARDS (10mg)……Diabetes

2. Secondary prevention:

(1) TNT (10 vs. 80mg)

(2) IDEAL (80mg)

} stable CAD

(3) MIRACL (80mg)

(4) PROVE IT-TIMI 22 (80mg)

(5) REVERSAL (80mg)

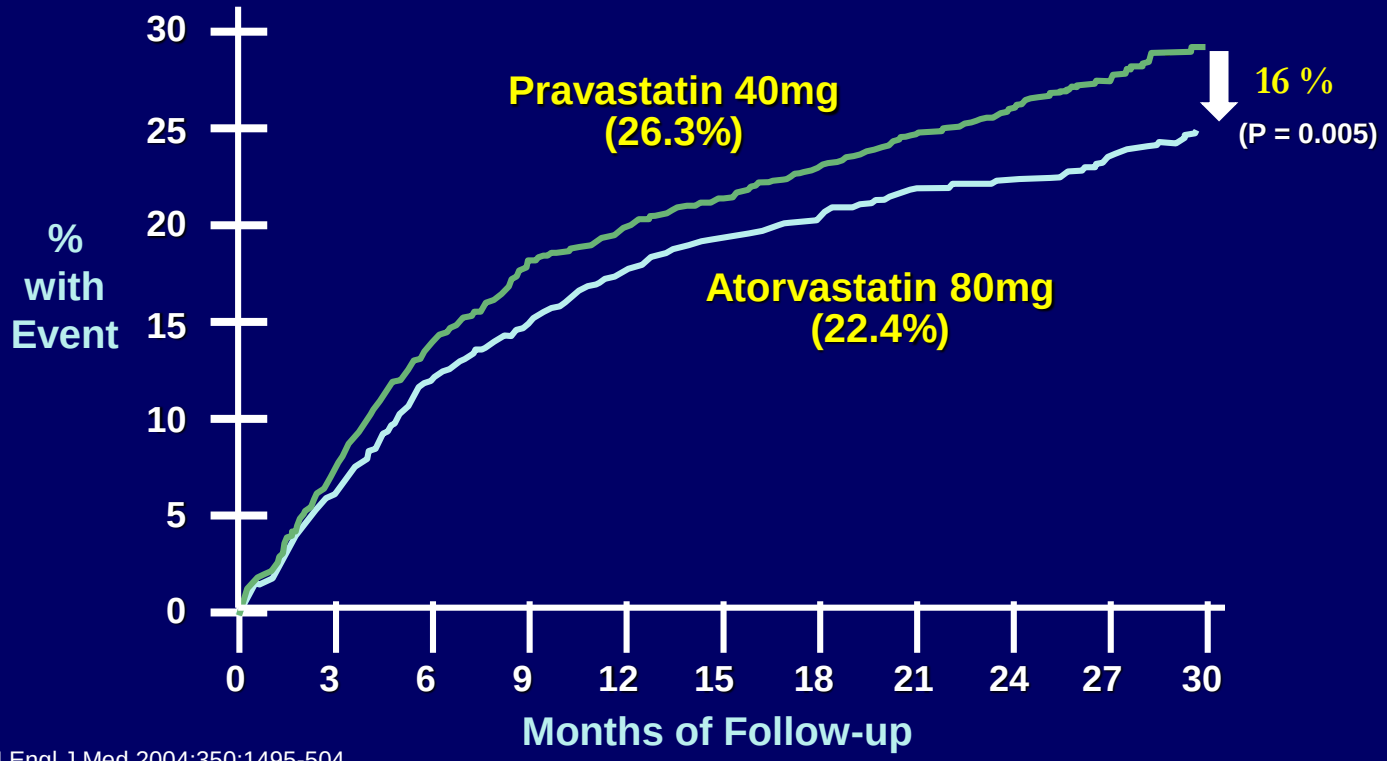
} ACS

Prove-It: Aggressive Lowering LDL and CRP by Atorvastatin

	atorvastatin 80mg	pravastatin 40mg	*P* value
Base-line LDL-C (mg/dL)	106	106	
Final mean LDL-C (mg/dL)	62 (-42%)	95 (-10%)	P<0.001
Base-line CRP (mg/L)	12.3	12.3	
Final mean CRP (mg/L)	1.3 (-89%)	2.1 (-83%)	P<0.001

N Engl J Med 2004;350.

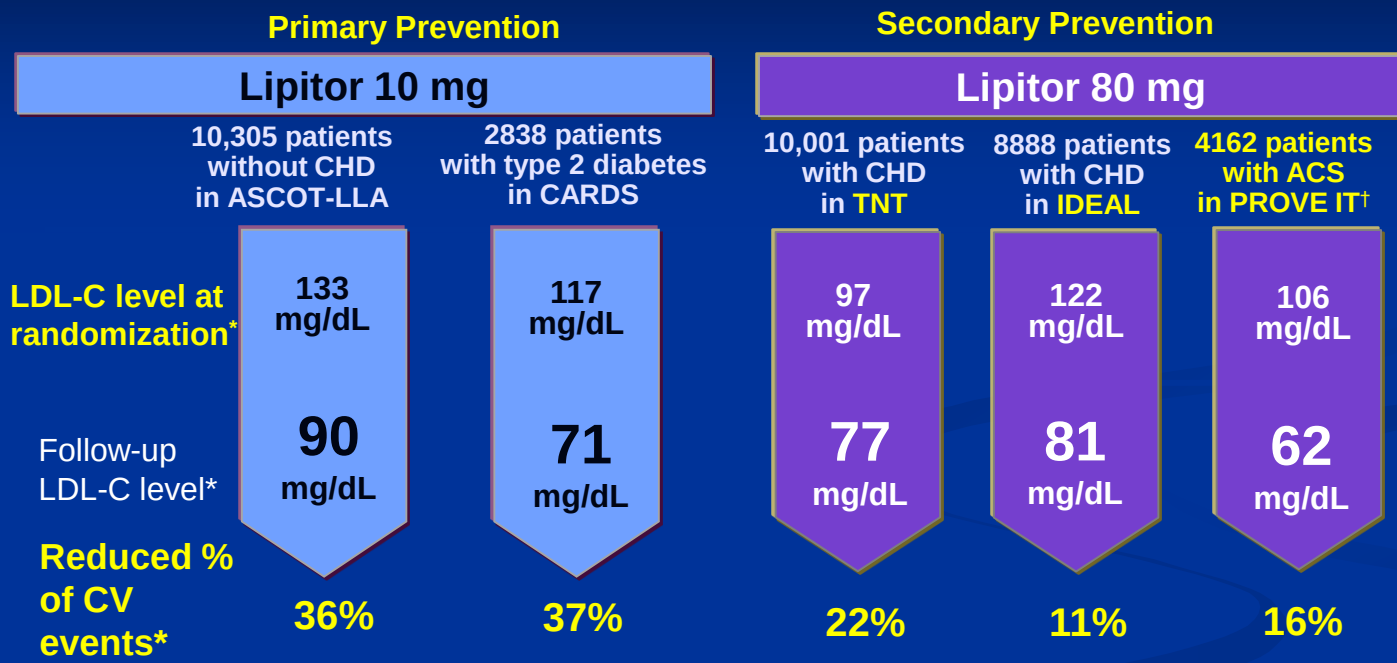
All-Cause Death or Major CV Events in All Randomized Subjects



N Engl J Med 2004;350:1495-504.

LIP-EM-06005

Lipitor Provides Significant LDL Reductions Across a Broad Spectrum of CV Risk



*Data from ASCOT-LLA, TNT, and IDEAL represent mean levels; CARDS and PROVE IT are median levels
†Study sponsored by Bristol-Myers Squibb Company and Sankyo

To convert from mmol/L to mg/dL for cholesterol multiply by 38·7

1. ASCOT study. *Lancet* 2003;361:1149-58; 2. CARD. *Lancet* 2004;364:685-96; 3. TNT. *N Engl J Med* 2005;352:1425-35; 4. IDEAL. *JAMA* 2005;294:2437-45; 5. PROVE-IT. *N Engl J Med* 2004;350:1495-504.

- Rosuvastatin

Efficacy and Safety of Rosuvastatin 20 and 40 mg versus Atorvastatin 80 mg in ACS

LUNAR Study Design

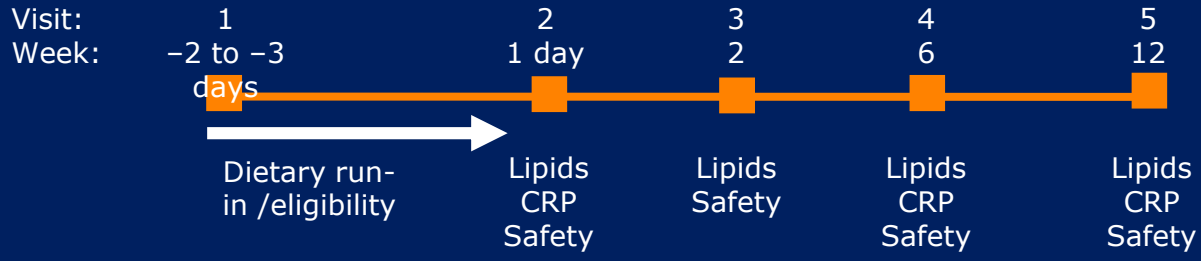
Patients (n=825), 18–75 years with:

Non-ST or ST segment elevation ACS receiving optimal reperfusion therapy

Evidence of CAD

LDL-C >70mg/dL (~1.8 mmol/L) and fasting triglycerides <500 mg/dL (~5.6 mmol/L)

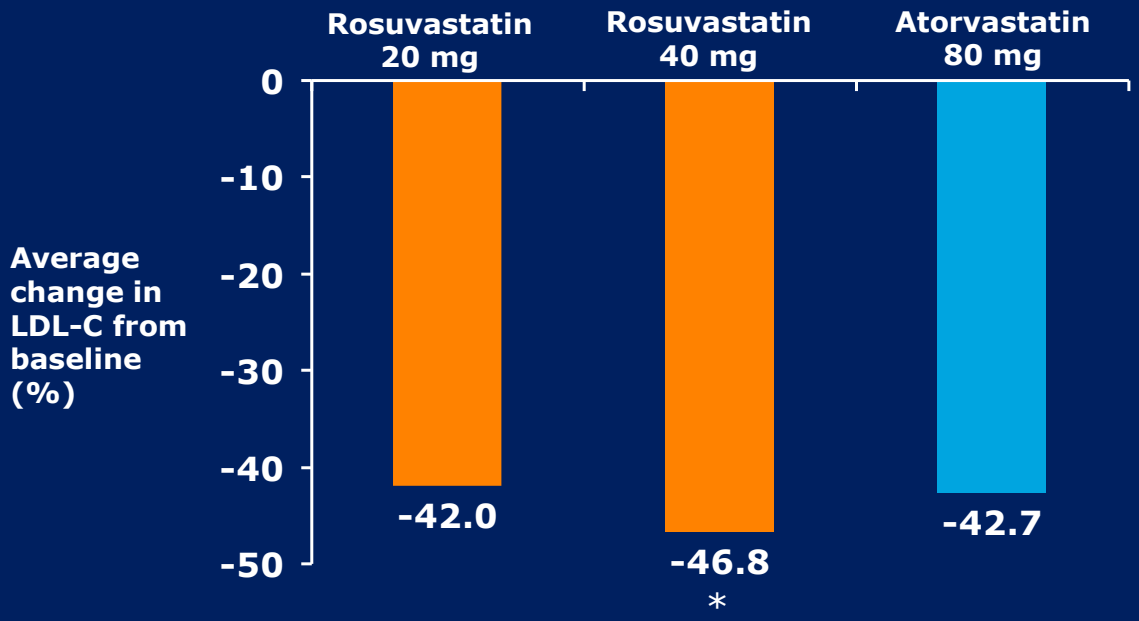
- **Rosuvastatin 20 mg (n=277)**
- **Rosuvastatin 40 mg (n=270)**
- **Atorvastatin 80 mg (n=278)**



Pitt B et al. *Am J Cardiol* 2012; in press

Rosuvastatin 40 mg Reduces LDL-C more than Atorvastatin 80 mg in ACS

Results from LUNAR

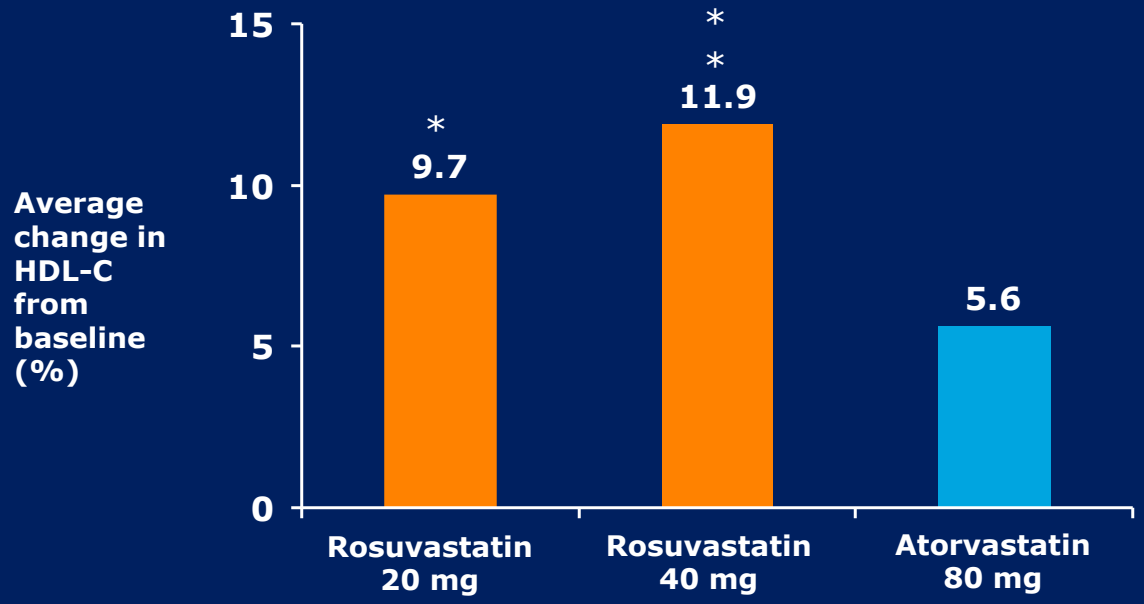


*p=0.0219 vs atorvastatin 80 mg

Pitt B et al. *Am J Cardiol* 2012; in press

Rosuvastatin 20 mg and 40 mg Increases HDL-C more than Atorvastatin 80 mg in ACS

Results from LUNAR



*p<0.01 vs atorvastatin 80 mg; **p<0.001 vs atorvastatin 80 mg

Pitt B et al. *Am J Cardiol* 2012; in press

ASTEROID – study design

Patients

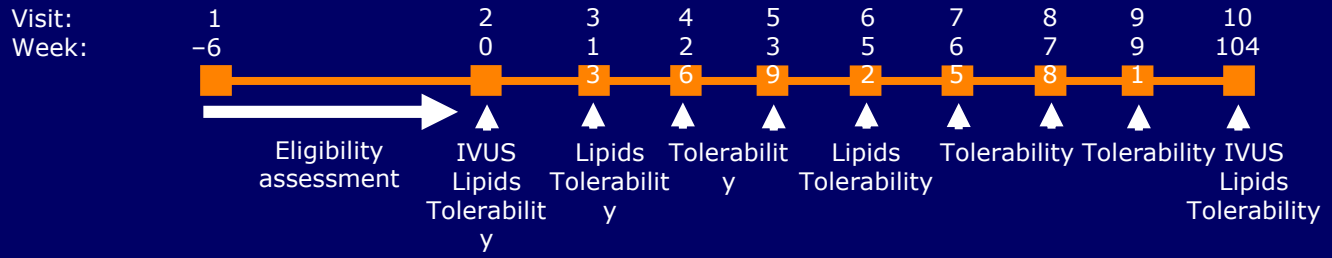
CAD, undergoing coronary angiography

Target coronary artery: ≤50% reduction in lumen diameter of ≥40 mm segment

No cholesterol entry criteria

≥18 years

Rosuvastatin 40 mg
(n=349 evaluated serial IVUS examinations)

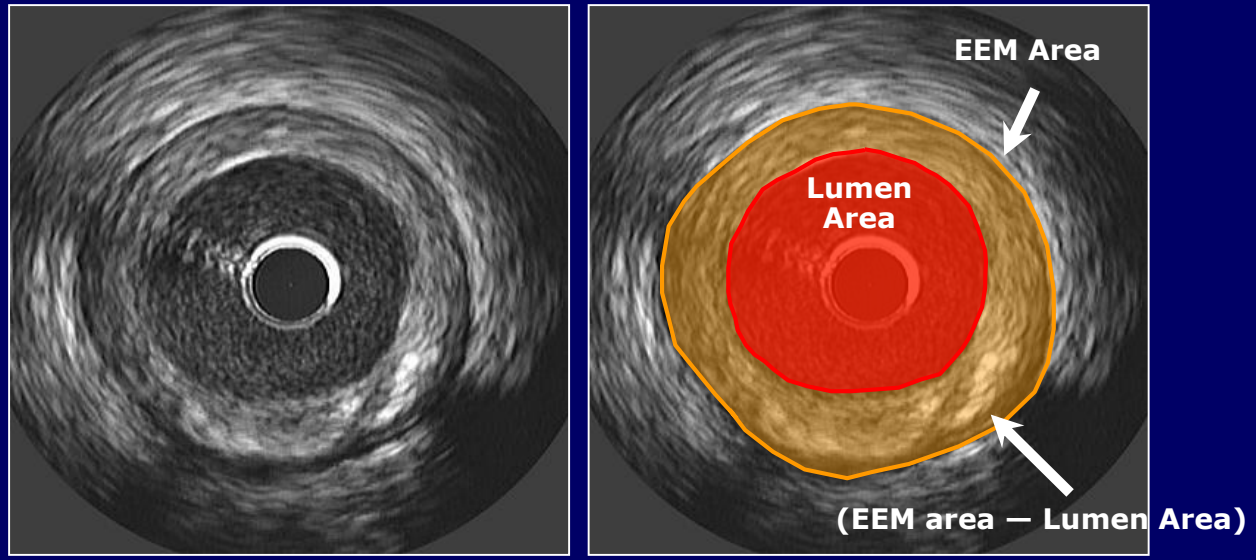


CAD=coronary artery disease; PCI=percutaneous coronary intervention; IVUS=intravascular ultrasound

ASTEROID

IVUS Determination of Atheroma Area

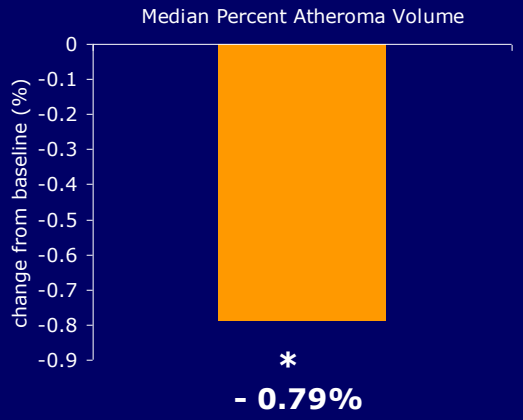
Precise Planimetry of EEM and Lumen Borders
allows calculation of Atheroma Cross-sectional Area



Images courtesy of Cleveland Clinic Intravascular Ultrasound Core Laboratory

EEM = External Elastic Membrane

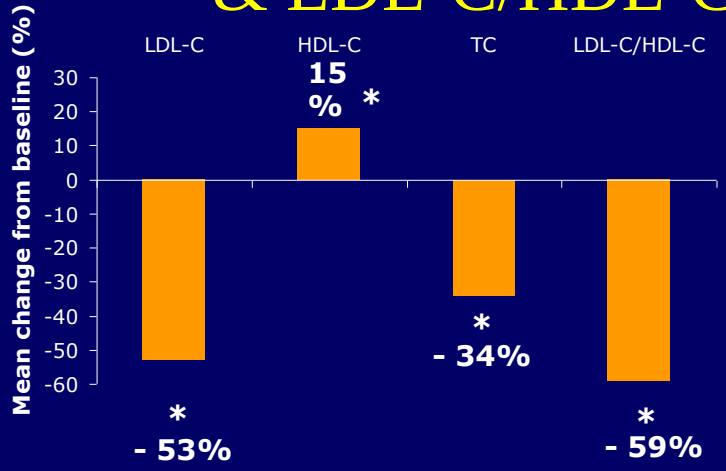
Endpoint analysis: Change in median percentage atheroma volume



* p<0.001 for difference from baseline values. Wilcoxon signed rank test

Ref: Nissen S *et al.* JAMA 2006; **295**: e-publication ahead of print

Percentage change[#] in LDL-C, HDL-C, TC & LDL-C/HDL-C Ratio



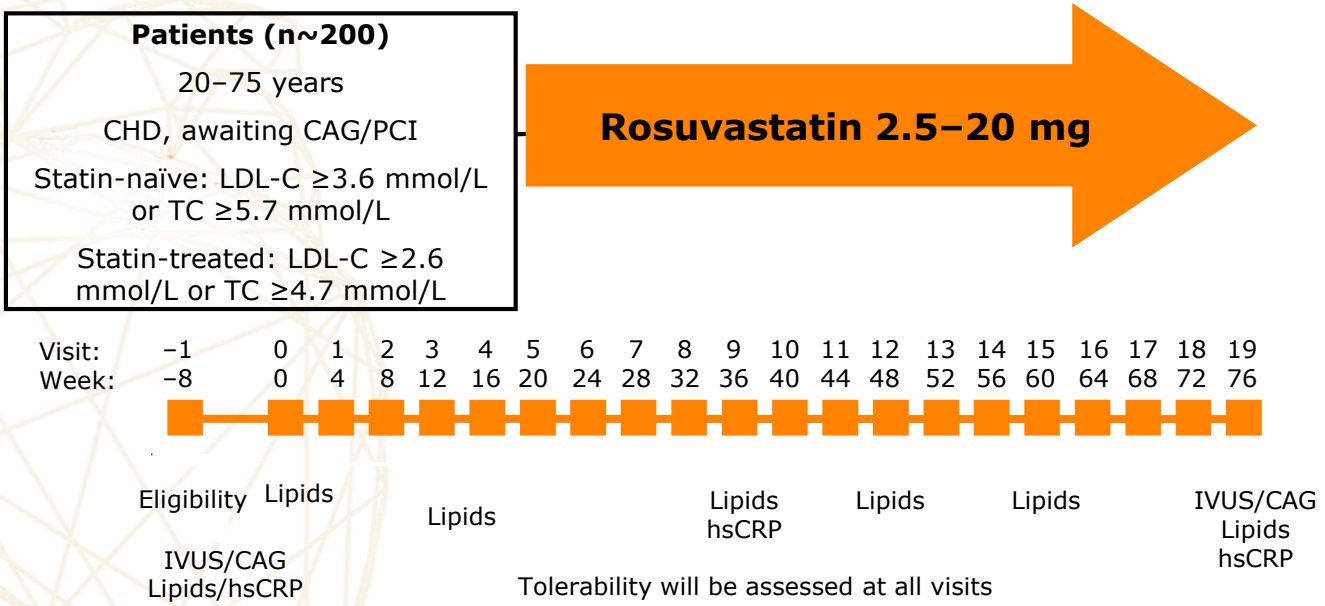
LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; TC=total cholesterol

[#] from time weighted average throughout the duration of therapy; * $p<0.001$

Ref: Nissen S *et al.* JAMA 2006; **295**: e-publication ahead of print

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

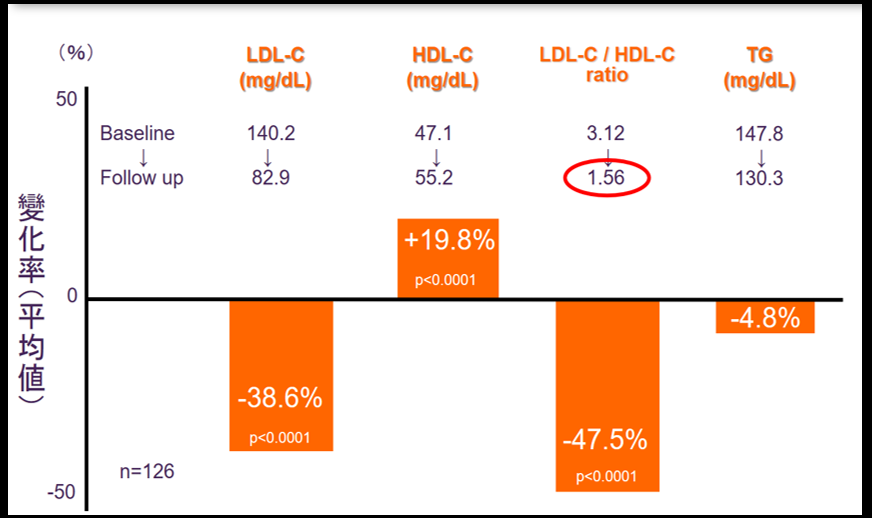


CHD=coronary heart disease; CAG=coronary angiography; PCI=percutaneous coronary intervention; LDL-C=low-density lipoprotein cholesterol; TC=total cholesterol; IVUS=intravascular ultrasound; hsCRP=high-sensitivity C-reactive protein

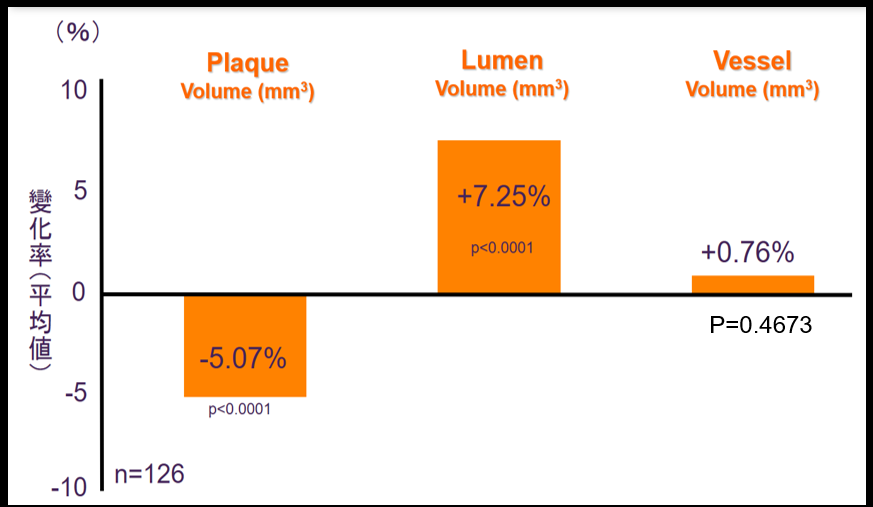
Circ J 2009; **73:** 2110 – 2117

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

COSMOS Lipid Profiles



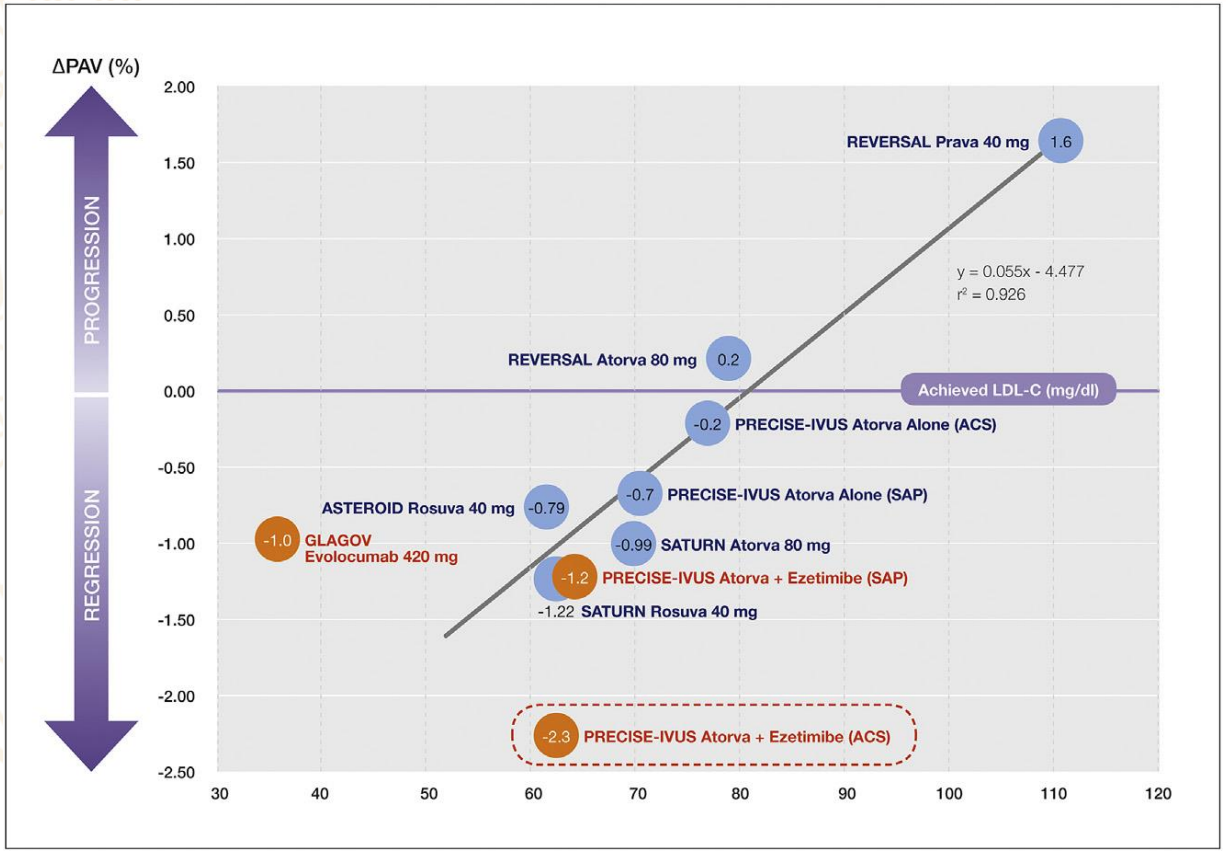
Reduction of Plaque Volume



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

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

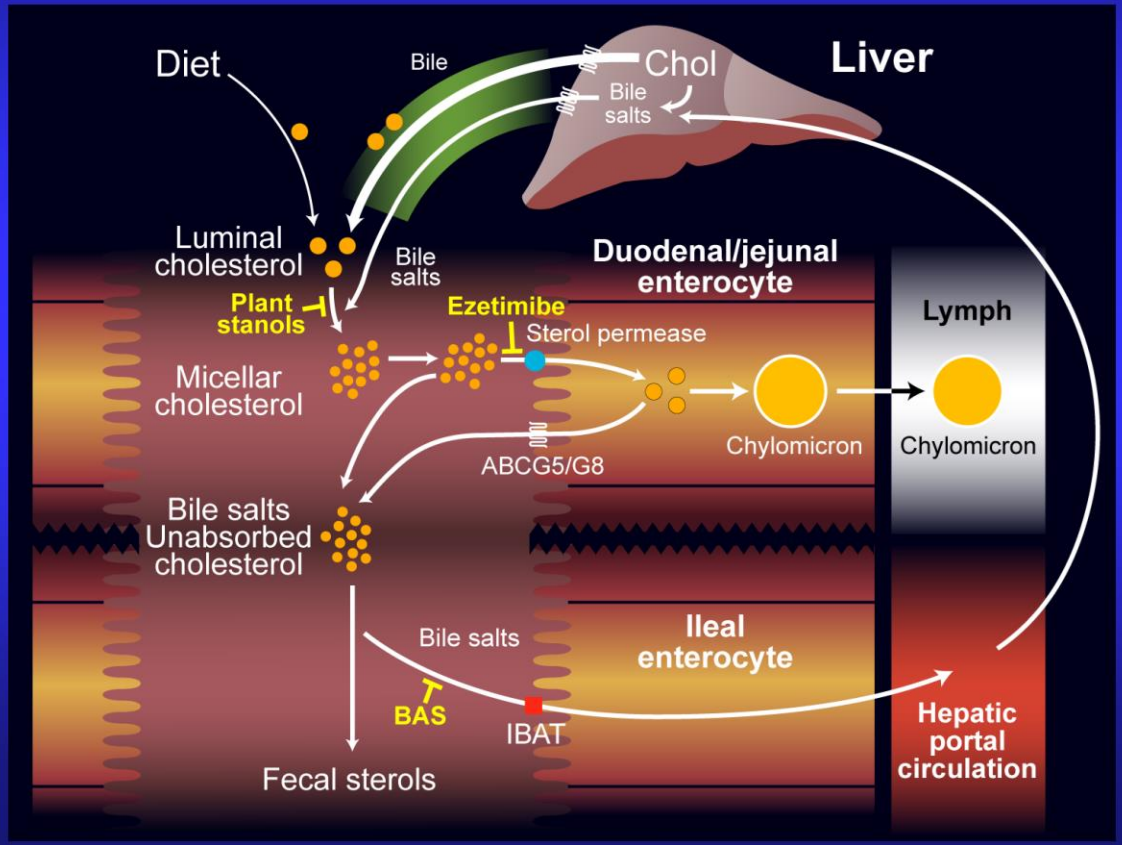


[50] Atherosclerosis. 2018 Feb;269:219-228.

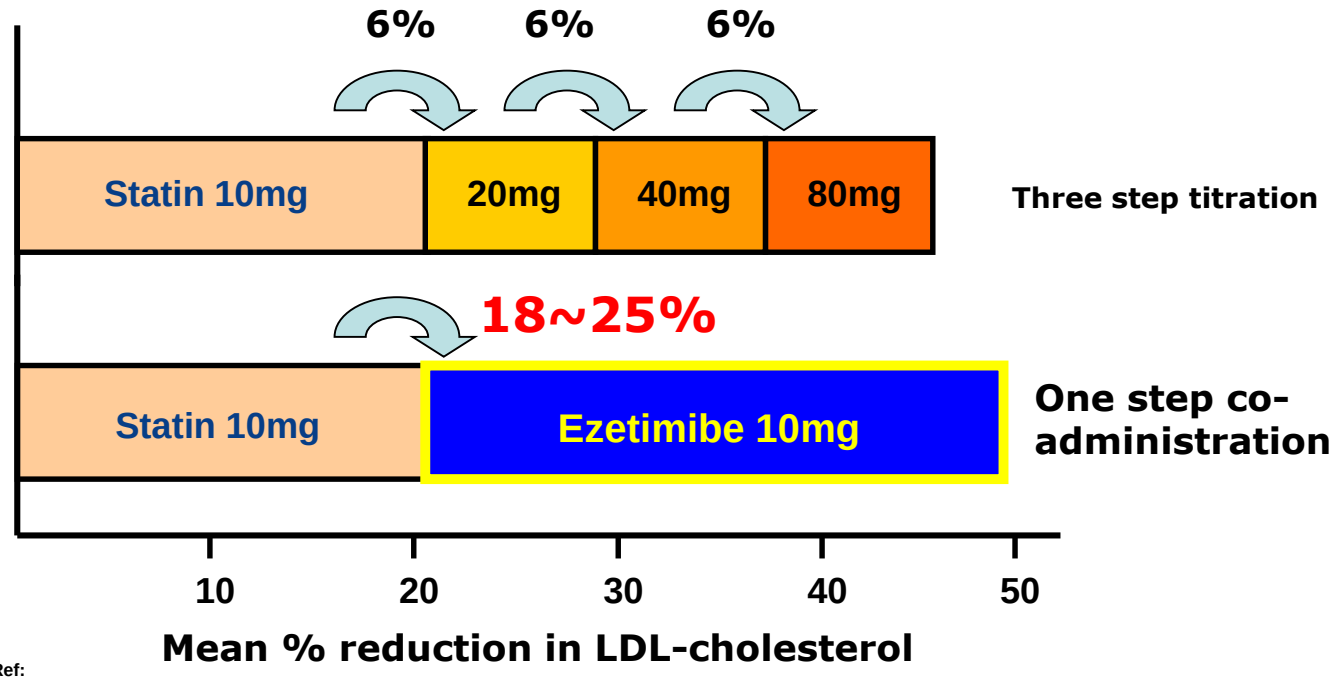
How ?

- Moderate- or high- intensity statin
- Combination therapy (statin +ezetimibe/bile acid sequestrant)
- Add on PCSK9-inhibitor

Mechanism of Intestinal-Acting Agents



Low-dose Combination vs. Statin Up-titration



Ref:

1. Stein E. Results of phase I/II clinical trials with ezetimibe, a novel selective cholesterol absorption inhibitor. *Eur Heart J 2001;3(suppl E):E11-E16.*
2. Grigore L. Combination therapy in cholesterol reduction: focus on ezetimibe and statins. *Vasc Health Risk Manag 2008:4(1) 1-12*

Study Design

Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

*3.2mM

**2.6mM

N=18,144

Standard Medical & Interventional Therapy

Simvastatin 40 mg

Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)

Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

90% power to detect ~9% difference

Duration: Minimum 2 ½-year follow-up **(at least 5250 events)**

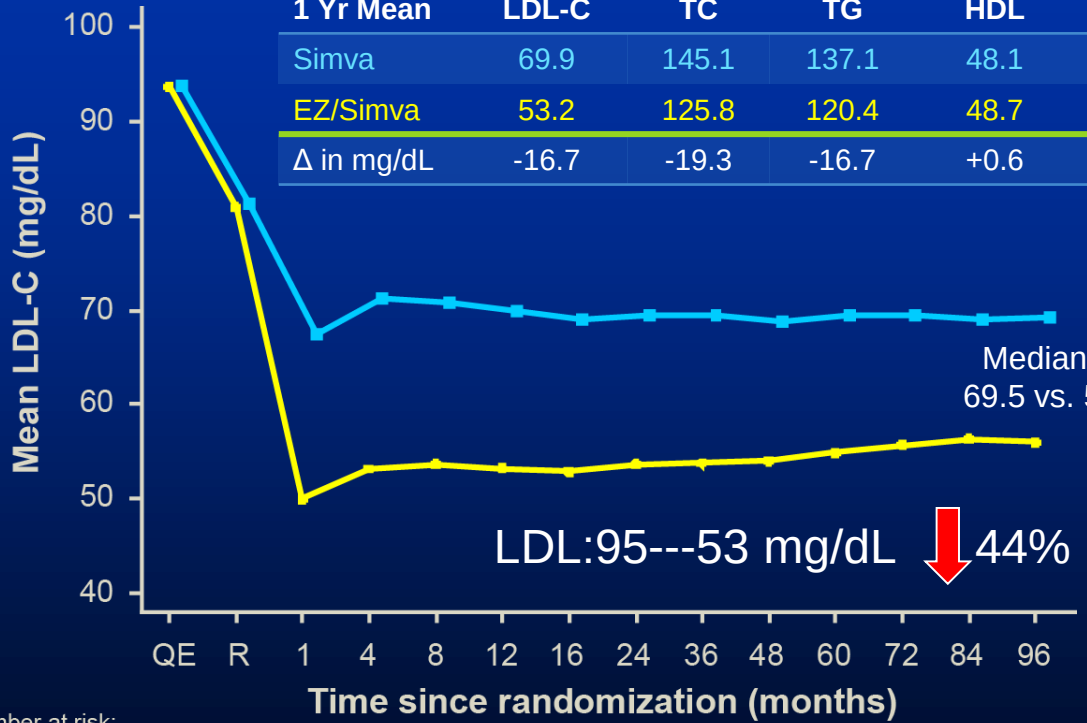
Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

LDL-C and Lipid Changes

IMPROVE-IT

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5

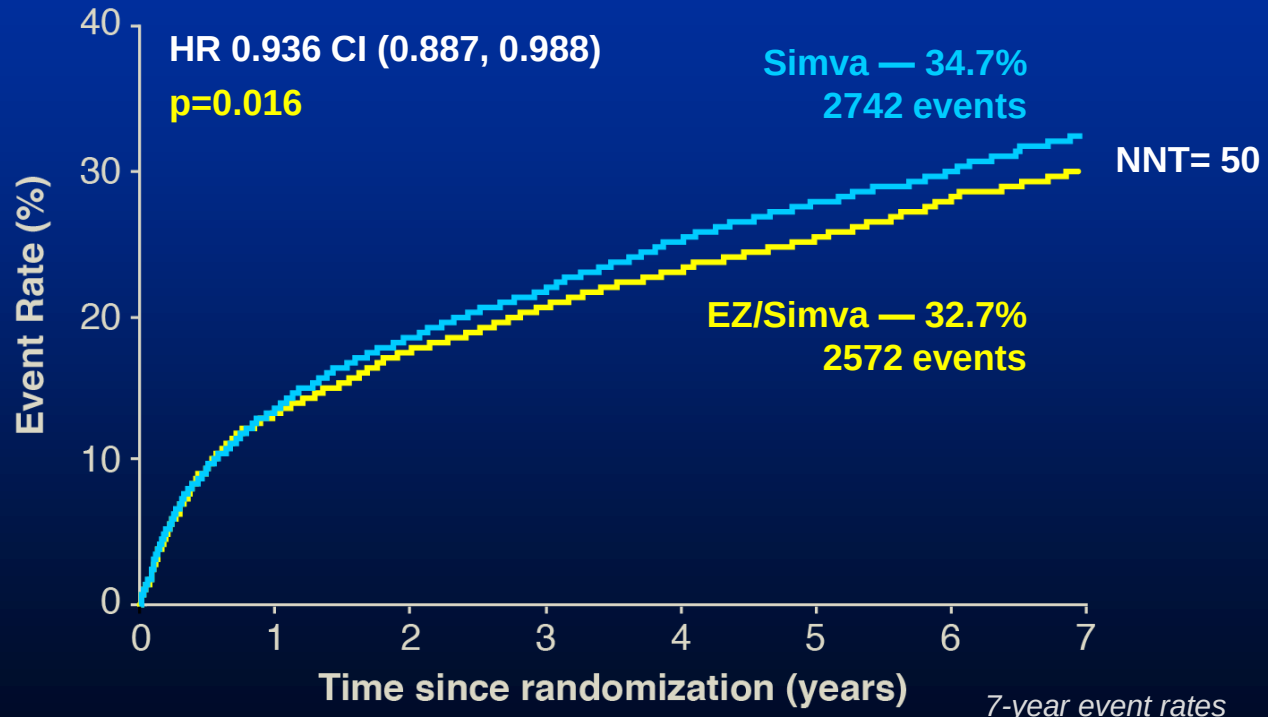


Number at risk:

EZ/Simva	8990	8889	8230	7701	7264	6864	6583	6256	5734	5354	4508	3484	2608	1078
Simva	9009	8921	8306	7843	7289	6939	6607	6192	5684	5267	4395	3387	2569	1068

Primary Endpoint — ITT

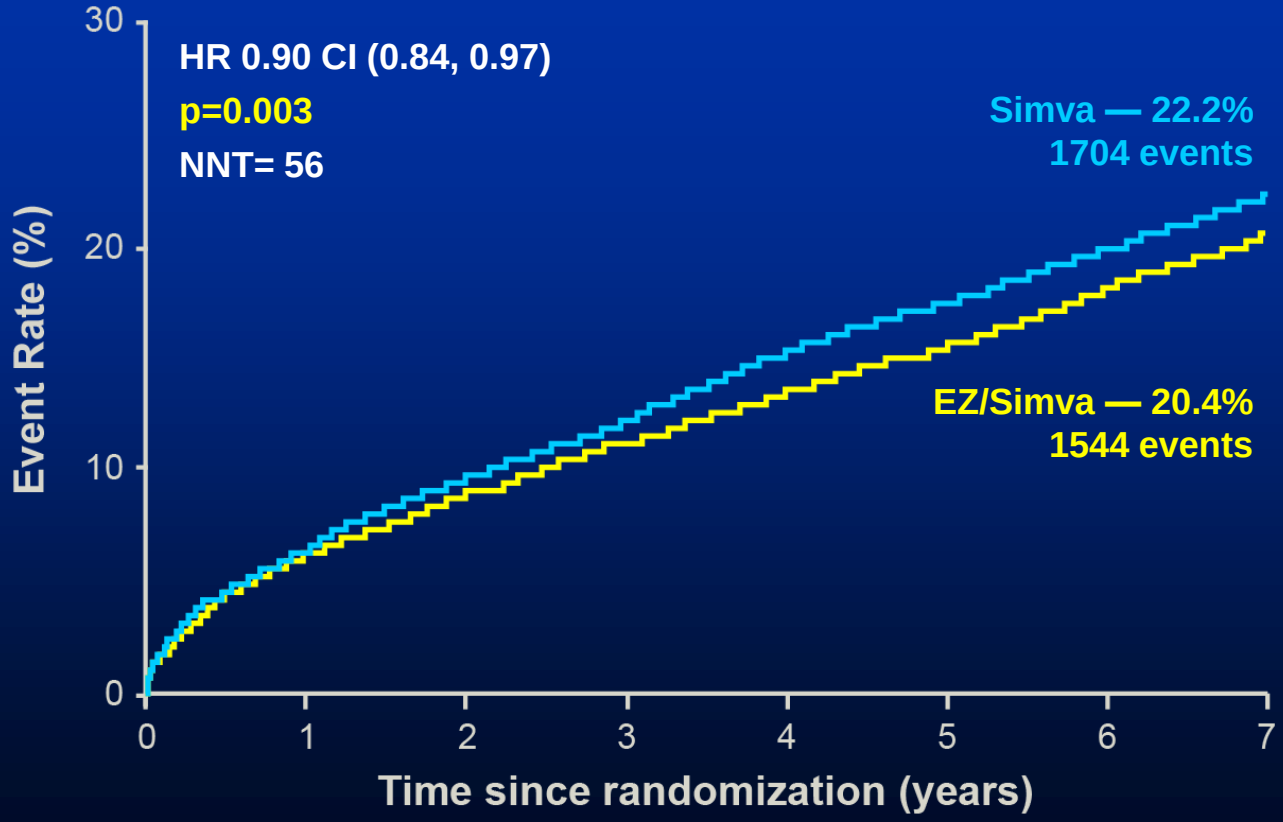
Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke



7-year event rates

CV Death, Non-fatal MI, or Non-fatal Stroke

IMPROVE-IT

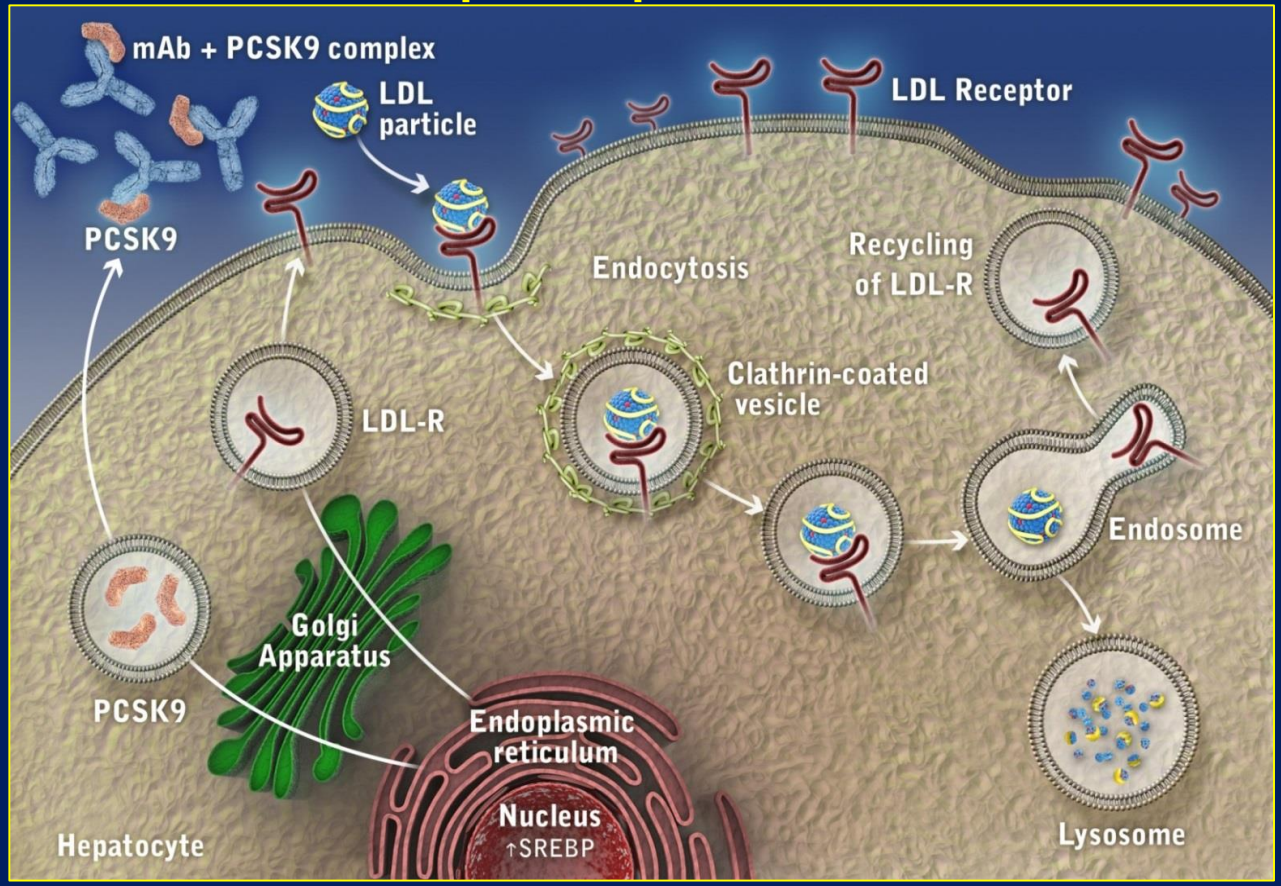


7-year event rates

How ?

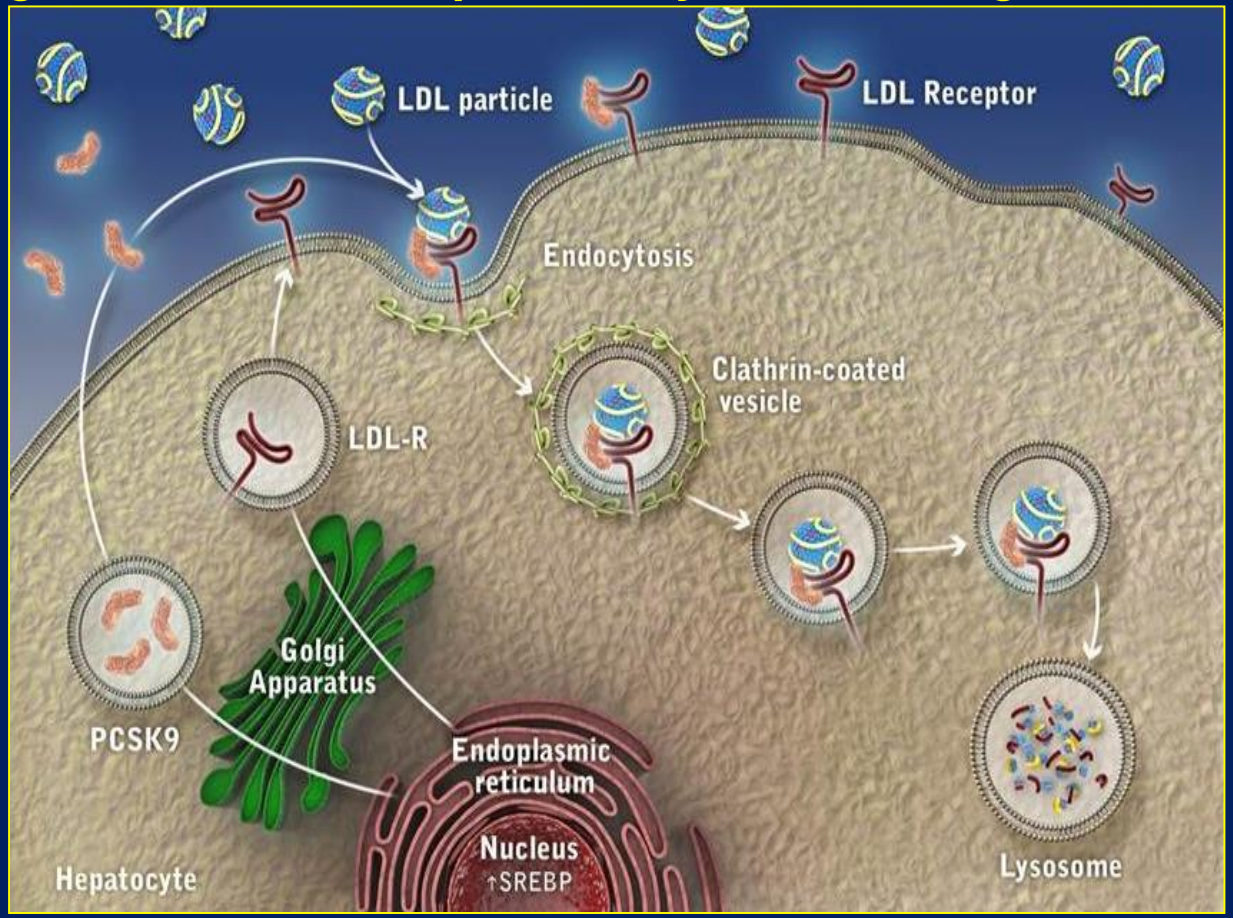
- Moderate- or high- intensity statin
- Combination therapy (statin +ezetimibe/bile acid sequestrant)
- Add on PCSK9-inhibitor

PCSK9 Monoclonal Antibodies Inactivate PCSK9 → Increase LDL-Receptor Expression → ↓ LDL-C levels



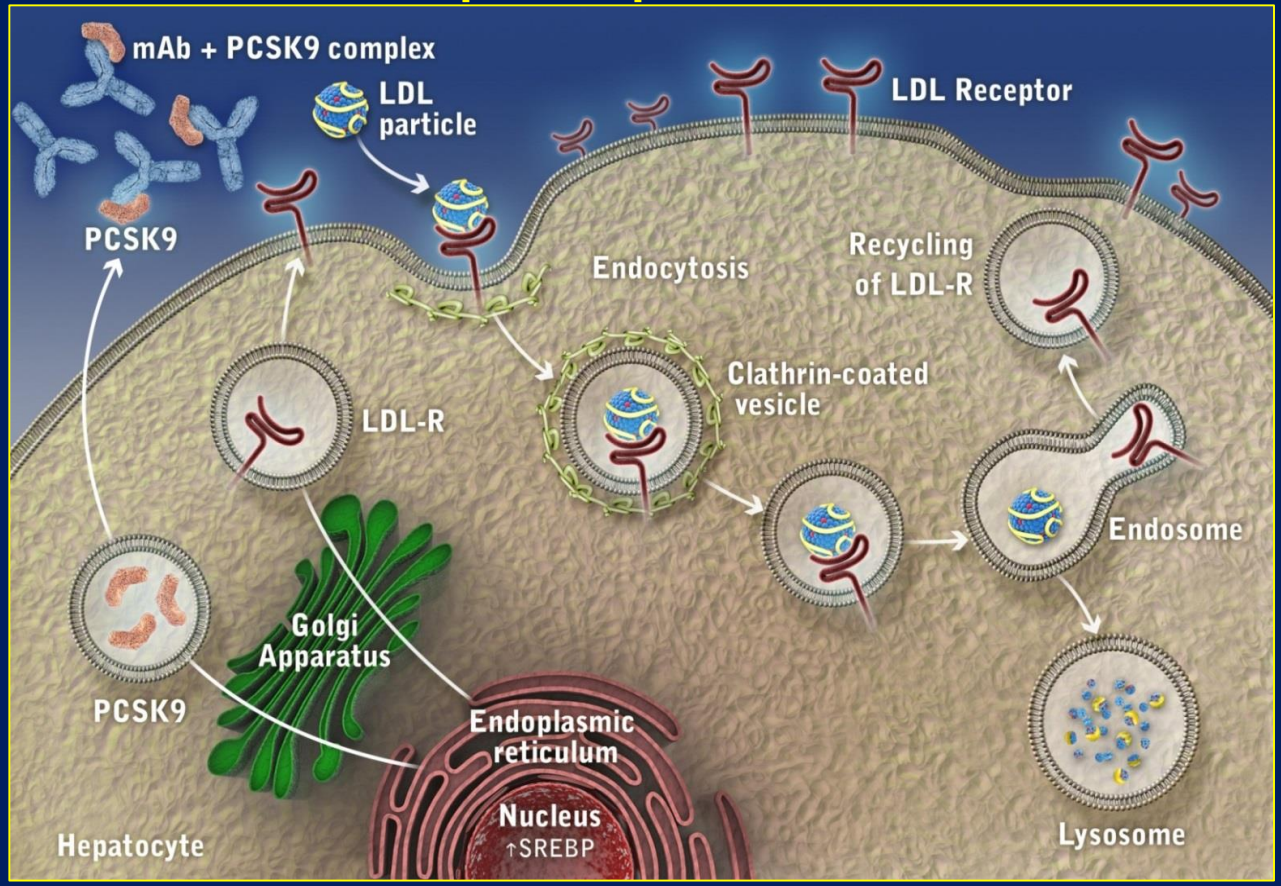
LDL=low-density lipoprotein; LDL-R=LDL receptor; mAb=monoclonal antibody; PCSK9=proprotein convertase subtilisin/kinexin type 9; SREBP-2=sterol regulatory element-binding protein-2.; Adapted from: Catapano AL, Papadopoulos N. *Atherosclerosis* 2013;228:18–28.

Proprotein Convertase Subtilisin-like/kexin type 9 (PCSK9) Targets the LDL-Receptor for Lysosomal Degradation



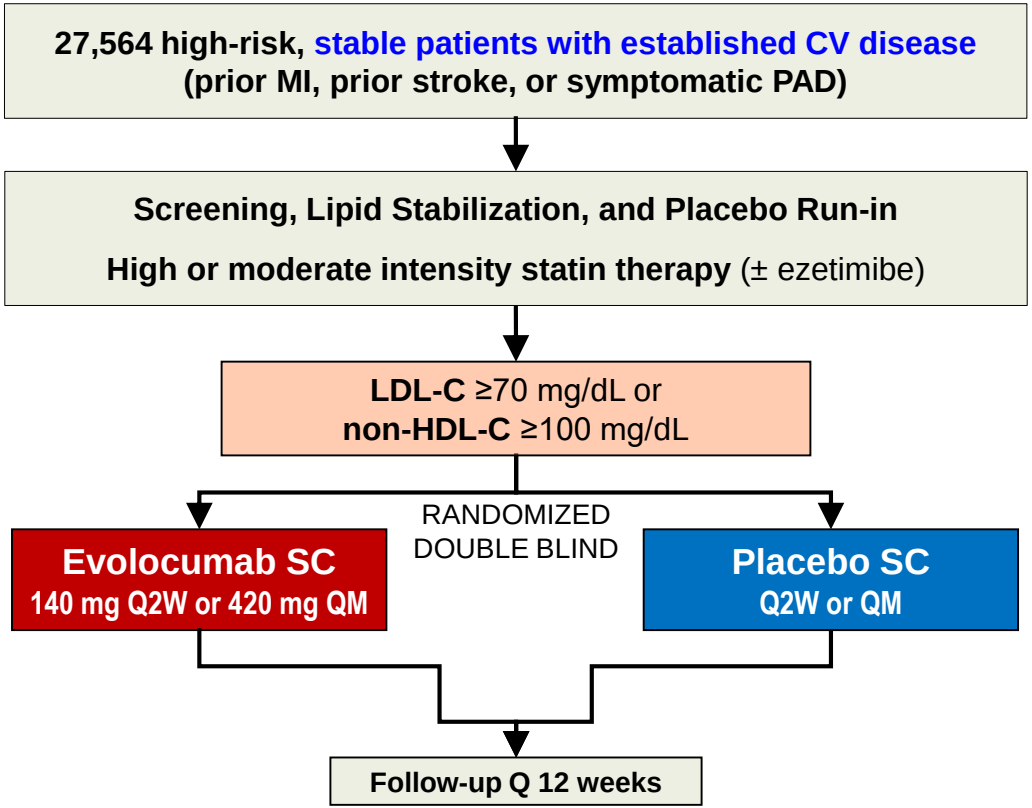
Adapted from: Catapano AL, Papadopoulos N. *Atherosclerosis* 2013;228:18–28.

PCSK9 Monoclonal Antibodies Inactivate PCSK9 → Increase LDL-Receptor Expression → ↓ LDL-C levels



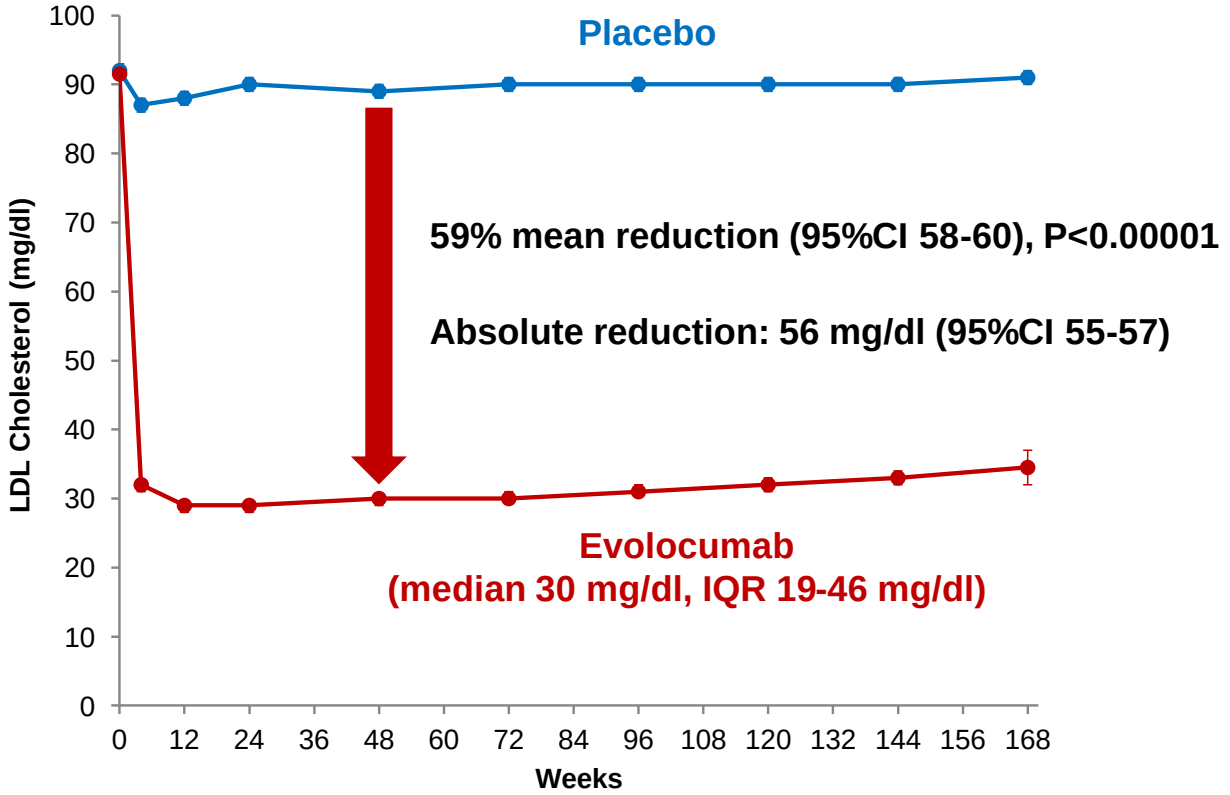
LDL=low-density lipoprotein; LDL-R=LDL receptor; mAb=monoclonal antibody; PCSK9=proprotein convertase subtilisin/kinexin type 9; SREBP-2=sterol regulatory element-binding protein-2.; Adapted from: Catapano AL, Papadopoulos N. *Atherosclerosis* 2013;228:18–28.

Trial Design

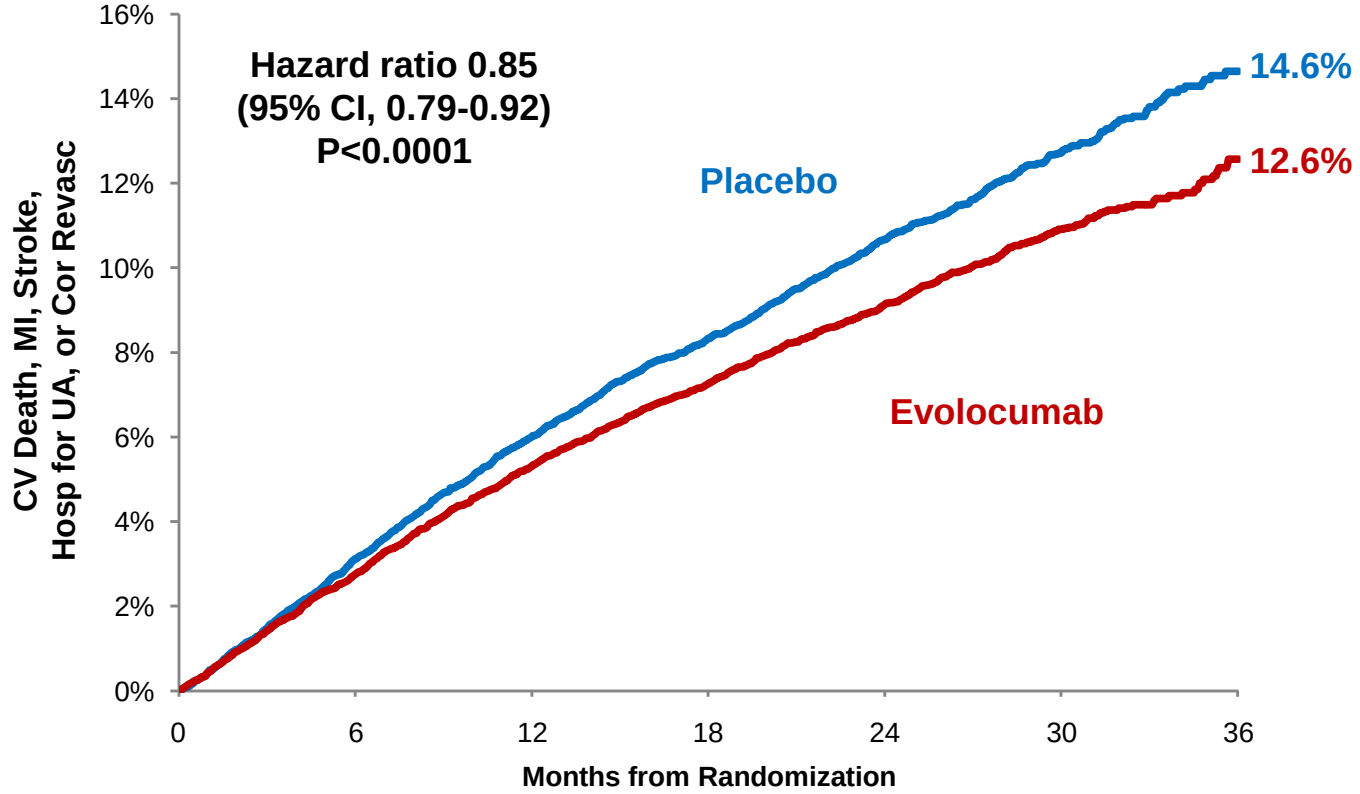


Sabatine MS et al. *Am Heart J* 2016;173:94-101

LDL Cholesterol



Primary Endpoint

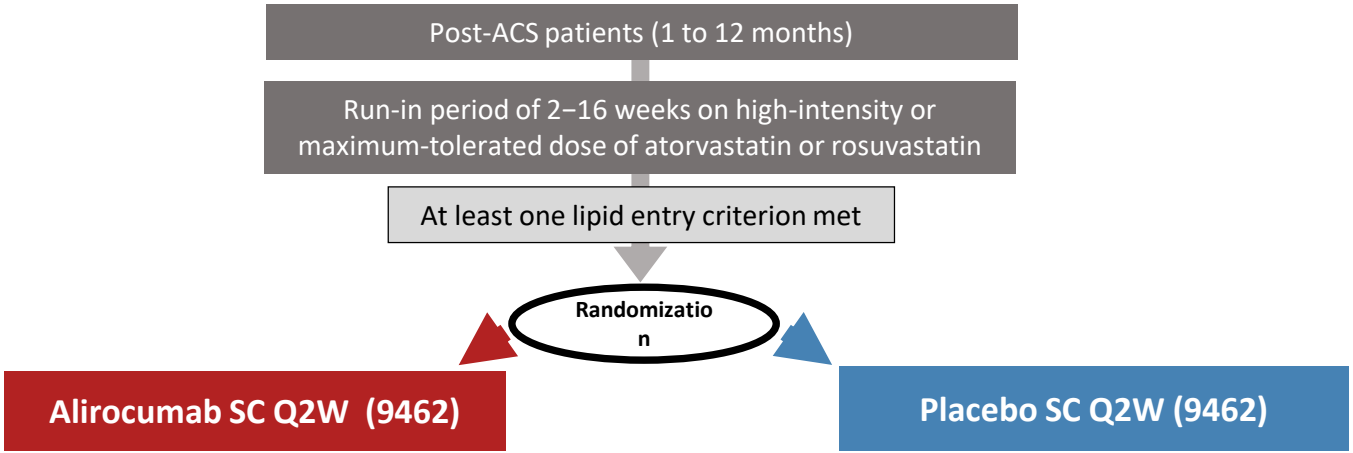


Types of CV Outcomes

Endpoint	Evolocumab (N=13,784)	Placebo (N=13,780)	HR (95% CI)
CVD, MI, stroke, UA, or revasc	12.6	14.6	0.85 (0.79-0.92)
CV death, MI, or stroke	7.9	9.9	0.80 (0.73-0.88)
Cardiovascular death	2.5	2.4	1.05 (0.88-1.25)
MI	4.4	6.3	0.73 (0.65-0.82)
Stroke	2.2	2.6	0.79 (0.66-0.95)
Hosp for unstable angina	2.2	2.3	0.99 (0.82-1.18)
Coronary revasc	7.0	9.2	0.78 (0.71-0.86)
Urgent	3.7	5.4	0.73 (0.64-0.83)
Elective	3.9	4.6	0.83 (0.73-0.95)
Death from any cause	4.8	4.3	1.04 (0.91-1.19)

No Benefit in CV and All Cause Survival Rate

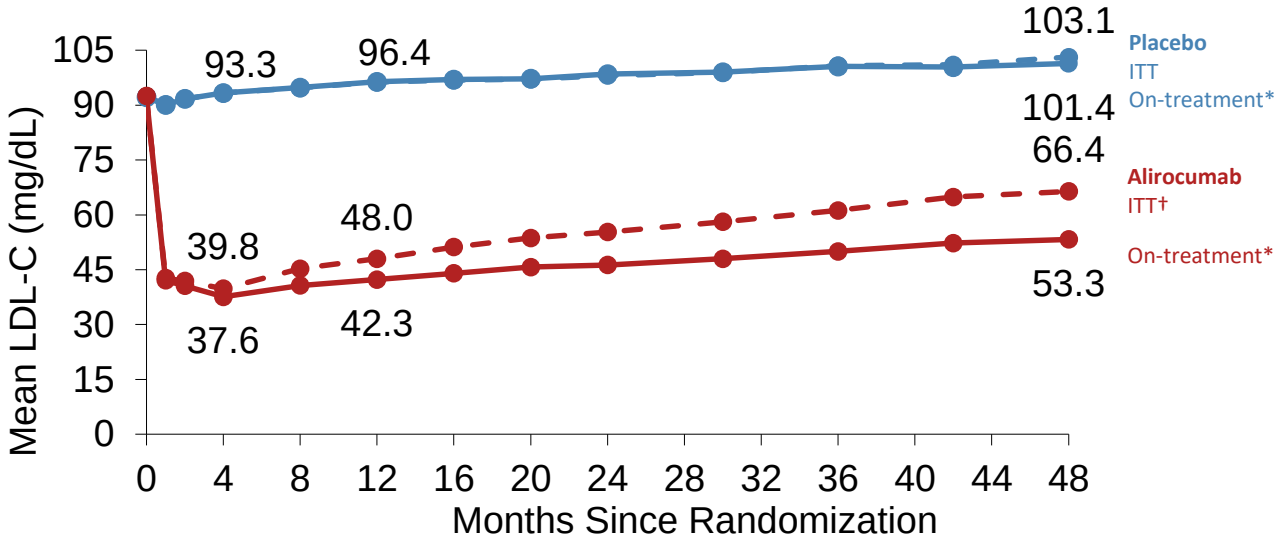
ODYSSEY CVOT:Treatment Assignment



Patient and investigators remained blinded to treatment and lipid levels for the entire duration of the study

Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

LDL-C: ITT and On-Treatment Analyses

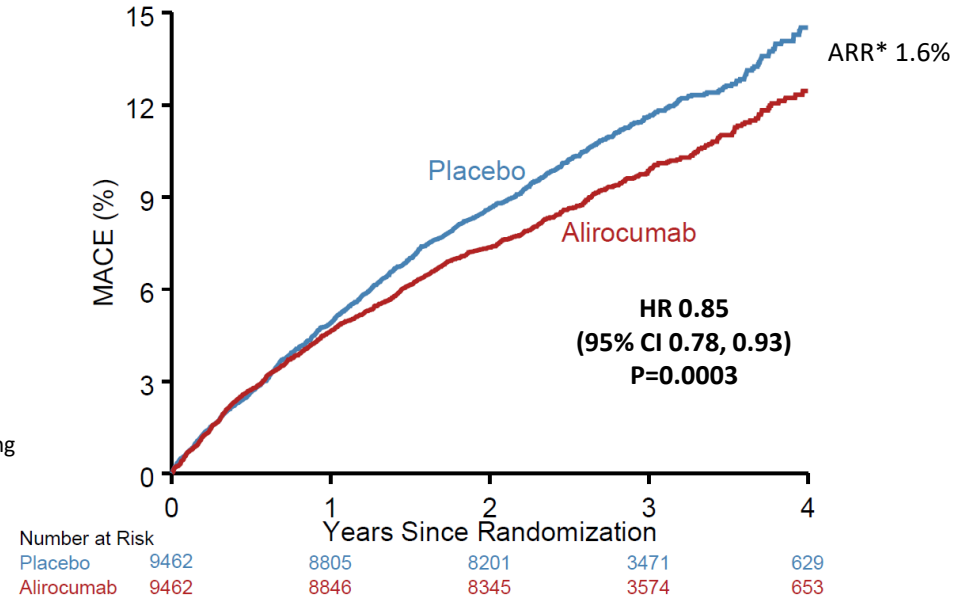


*Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
†All LDL-C values, including those after premature treatment discontinuation, blinded down titration, or blinded switch to placebo

ODYSSEY OUTCOMES

Primary Efficacy Endpoint: MACE

MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization



*Based on cumulative incidence

Primary Efficacy and Components

Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
MACE	**903 (9.5)**	**1052 (11.1)**	**0.85 (0.78, 0.93)**	**0.0003**
CHD death	**205 (2.2)**	**222 (2.3)**	0.92 (0.76, 1.11)	0.38
Non-fatal MI	**626 (6.6)**	**722 (7.6)**	0.86 (0.77, 0.96)	0.006
Ischemic stroke	**111 (1.2)**	**152 (1.6)**	0.73 (0.57, 0.93)	0.01

ODYSSEY OUTCOMES

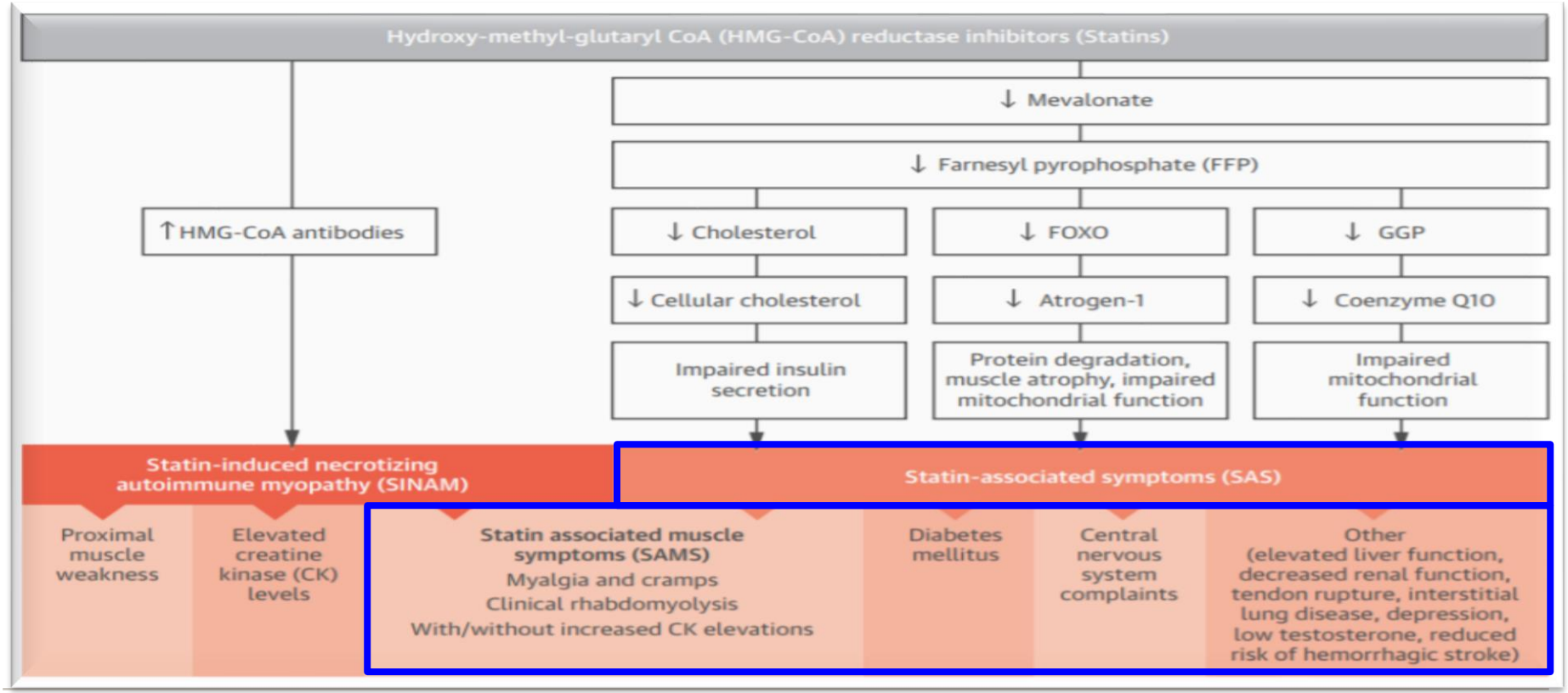
ODYSSEY OUTCOMES & FOURIER Study Populations

	ODYSSEY OUTCOMES	FOURIER
Patient population	Recent ACS (4-52 weeks)	MI, stroke, symptomatic PAD, plus risk factors
Duration	Median 33 months 2-to-5 years follow-up	Median 26 months 1-to-3.5 years follow-up
% High-intensity statins	89.5%	69.2%

Schwartz GG. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of ODYSSEY outcomes trial. Am Heart J. 2014 Nov.

- Do not fear to treat dyslipidemic patients aggressively for the sake of side effects

Statin-Associated Side Effects



J Am Coll Cardiol. 2016; 67(20): 2395–410.

Incidence of Myopathy with Rosuvastatin

Pooled Analysis of All Controlled Studies

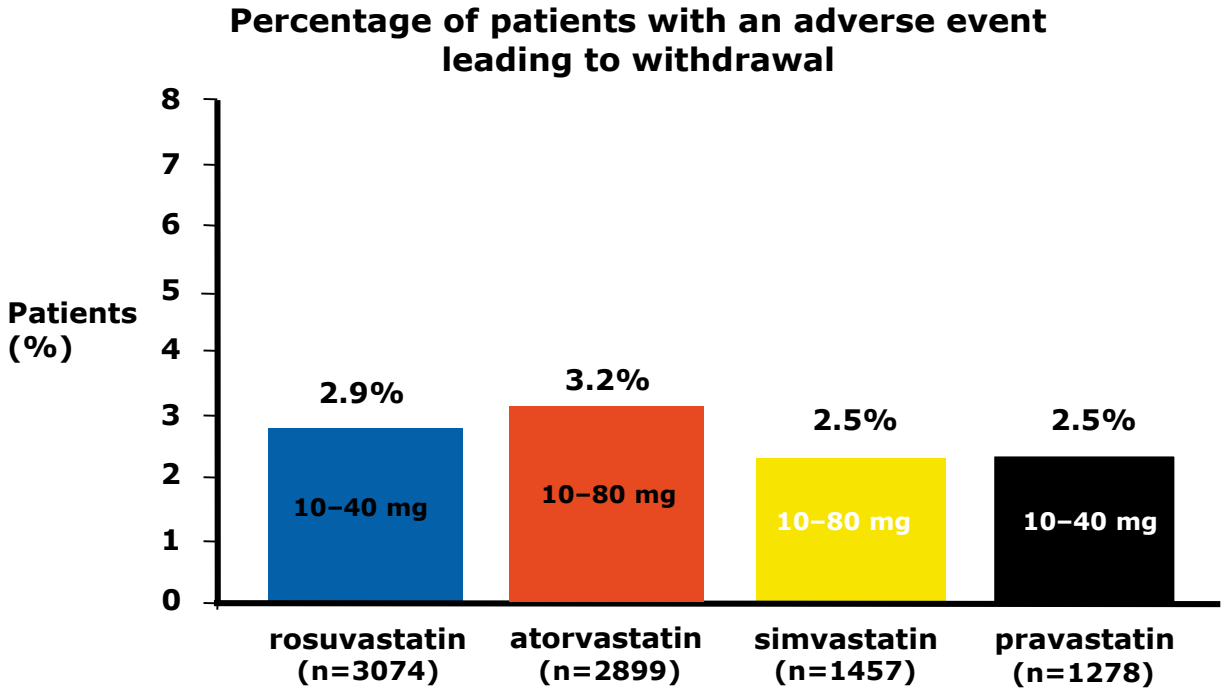
Rosuvastain, dose	N	Percent of patients reported with CK≥ 10x ULN and muscle pain
5 mg	833	0.4%
10 mg	3193	0.1%
20 mg	2113	0.1%
40 mg	2804	0.4%
80 mg	988	0.9%

Persistent ALT Elevations by Dose

Combined All Controlled/Uncontrolled and RTLD Pool

Rosuvastatin, dose	N	> 3 × ULN on 2 occasions, %
5 mg	1317	0.5
10 mg	7726	0.1
20 mg	3882	0.1
40 mg	3700	0.2
80 mg	1574	1.4
Total	**12,458**	**0.4**

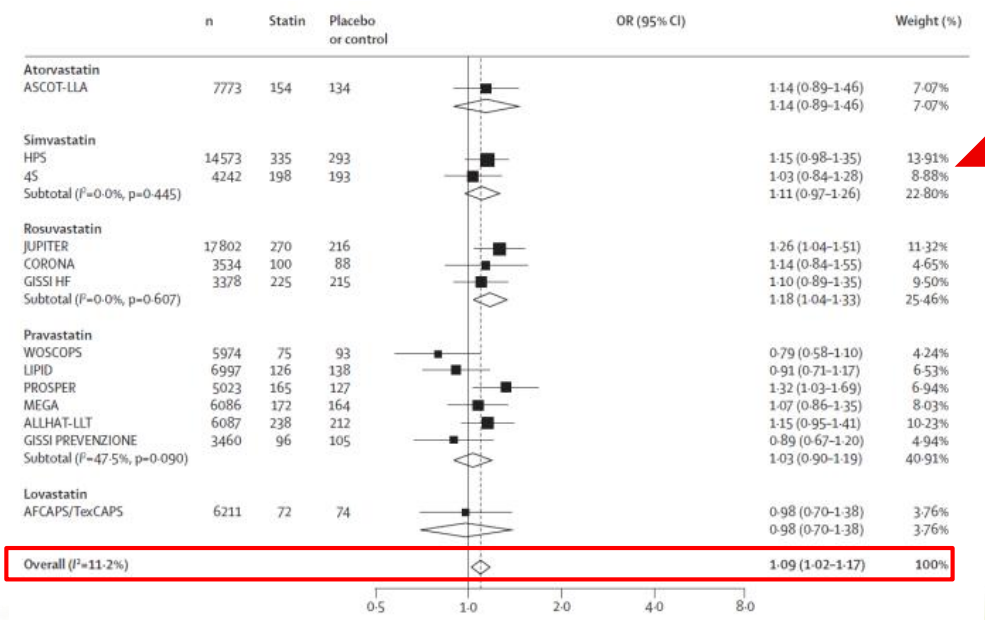
Rosuvastatin Tolerability and Safety - Withdrawals due to Adverse Events



Brewer HB. *Am J Cardiol* 2003;92(Suppl):23K–29K

Statins vs. risk of new-onset DM
Meta-analysis of randomized statin trials

Statin therapy was associated with a 9% increased risk for DM development.



	n	Statin	Placebo or control	OR (95% CI)	Weight (%)
Atorvastatin					
ASCOT-LLA	7773	154	134	1·14 (0·89–1·46)	7·07%
				1·14 (0·89–1·46)	7·07%
Simvastatin					
HPS	14573	335	293	1·15 (0·98–1·35)	13·91%
4S	4242	198	193	1·03 (0·84–1·28)	8·88%
Subtotal (I^2=0·0%, p=0·445)				1·11 (0·97–1·26)	22·80%
Rosuvastatin					
JUPITER	17802	270	216	1·26 (1·04–1·51)	11·32%
CORONA	3534	100	88	1·14 (0·84–1·55)	4·65%
GISSI HF	3378	225	215	1·10 (0·89–1·35)	9·50%
Subtotal (I^2=0·0%, p=0·607)				1·18 (1·04–1·33)	25·46%
Pravastatin					
WOSCOPS	5974	75	93	0·79 (0·58–1·10)	4·24%
LIPID	6997	126	138	0·91 (0·71–1·17)	6·53%
PROSPER	5023	165	127	1·32 (1·03–1·69)	6·94%
MEGA	6086	172	164	1·07 (0·86–1·35)	8·03%
ALLHAT-LLT	6087	238	212	1·15 (0·95–1·41)	10·23%
GISSI PREVENZIONE	3460	96	105	0·89 (0·67–1·20)	4·94%
Subtotal (I^2=47·5%, p=0·090)				1·03 (0·90–1·19)	40·91%
Lovastatin					
AFCAPS/TexCAPS	6211	72	74	0·98 (0·70–1·38)	3·76%
				0·98 (0·70–1·38)	3·76%
Overall (I^2=11·2%)				**1·09 (1·02–1·17)**	**100%**

0·5 1·0 2·0 4·0 8·0

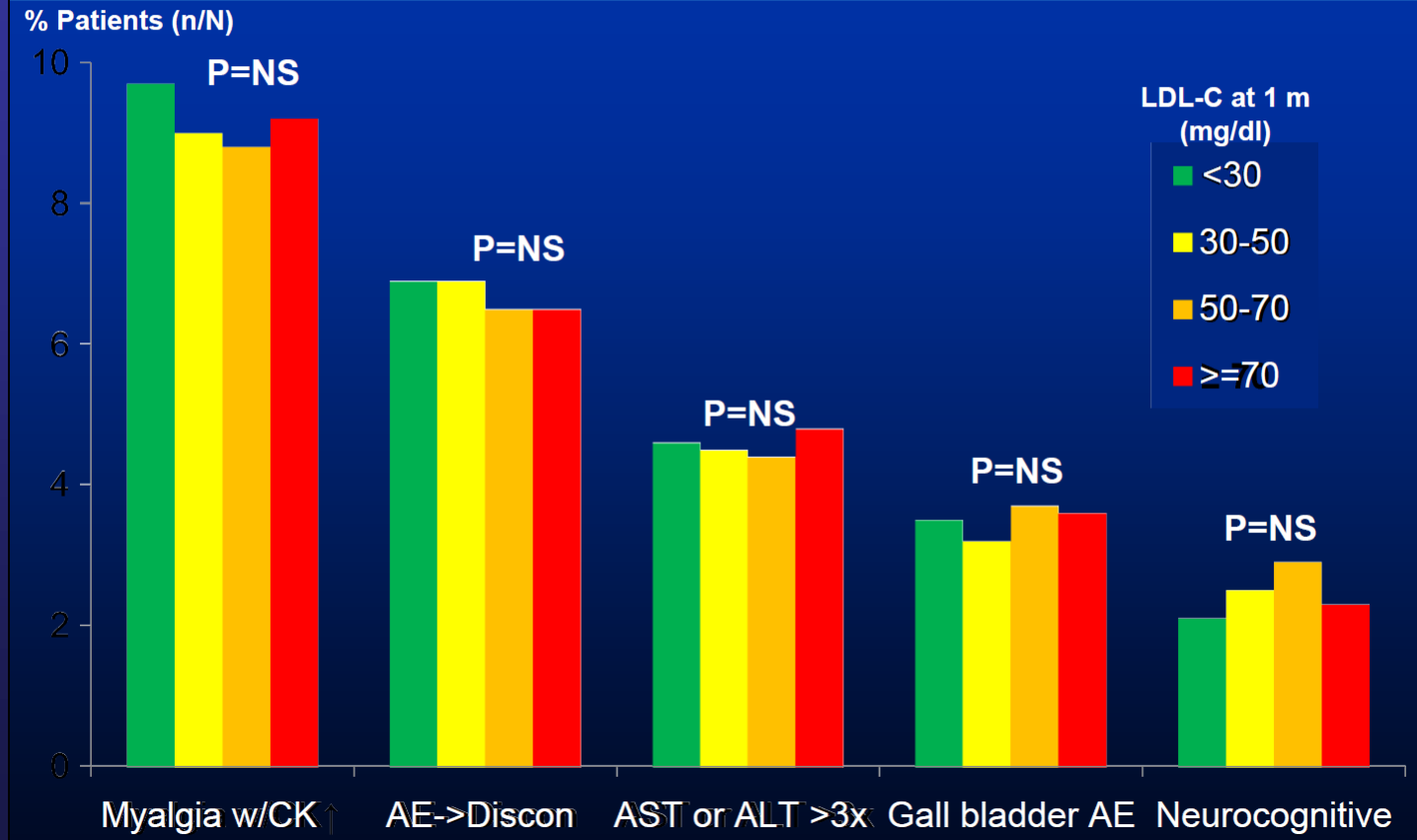
+9%
(OR=1.09)
risk of new-onset DM

Statin therapy

CI=confidence interval; DM=diabetes mellitus; OR=odds ratio

Sattar N, et al. Lancet. 2010;375(9716):735-42.

Safety Events



Safety

	Evolocumab (N=13,769)	Placebo (N=13,756)
Adverse events (%)		
Any	77.4	77.4
Serious	24.8	24.7
Allergic reaction	3.1	2.9
Injection-site reaction	2.1	1.6
Treatment-related and led to d/c of study drug	1.6	1.5
Muscle-related	5.0	4.8
Cataract	1.7	1.8
Diabetes (new-onset)	8.1	7.7
Neurocognitive	1.6	1.5
Laboratory results (%)		
Binding Ab	0.3	n/a
Neutralizing Ab	*none*	n/a

New-onset diabetes assessed in patients without diabetes at baseline; adjudicated by CEC

Take home message:

A Must therapeutic strategy for high risk patients with dyslipidemia – optimal treatment

- Why: Only 50% achieved target level of LDL, less up-titrate of statin dose, lower target was recommended by guidelines
- How: high-intensity statin (rosuvastatin is the most powerful)----combined with ezetimibe------add on PCSK9-inhibitor


Thank you for your attention!!