Establish the Standard of Care for Dyslipidemia Treatment on High Risk Patient

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2020/7/12

演講內容聲明

本次研討會由美商默沙東藥廠股份有限公司台灣分公司贊助。研討會之演講者與贊助公司間無任何聘用、受雇關係。各演講者均本其專業學識經歷發表相關演說，不代表贊助單位立場。贊助單位就演講者之論述無任何不當干預，僅依法述明。

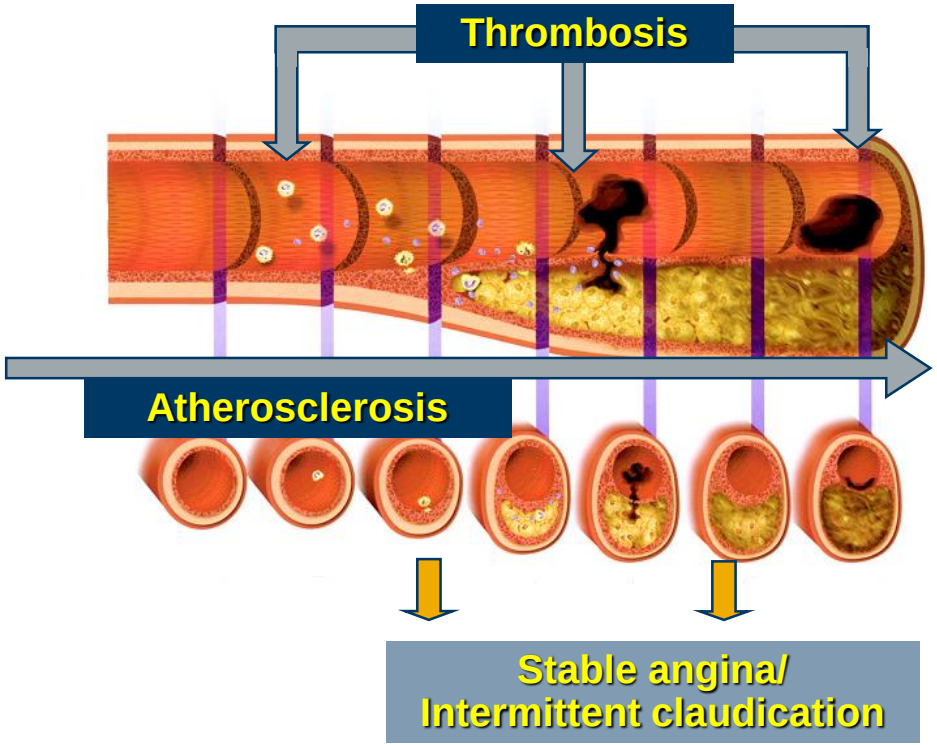
由於各個國家的法規要求，藥品所核准的適應症及用法可能因而不同，處方前請詳閱各製造廠之全文藥品仿單說明書，本公司不建議以任何方式將我們的產品使用在非仿單核准的範圍。

Outline

- Current status of dyslipidemia treatment
- Clinical considerations of different statin use
  - Benefit & Risk
- Treatment gap of lipid lowering treatment in Asia
- Think beyond of statin monotherapy
  - powerful LDL-c reduction of ATOZET
- The evidences of ezetimibe in CVD risk reduction in ACS and high risk patient
- Change of dyslipidemia guideline
  - From past to now
- Take Home Message

Current status of dyslipidemia treatment

Atherothrombosis:
A Generalized and Progressive Process



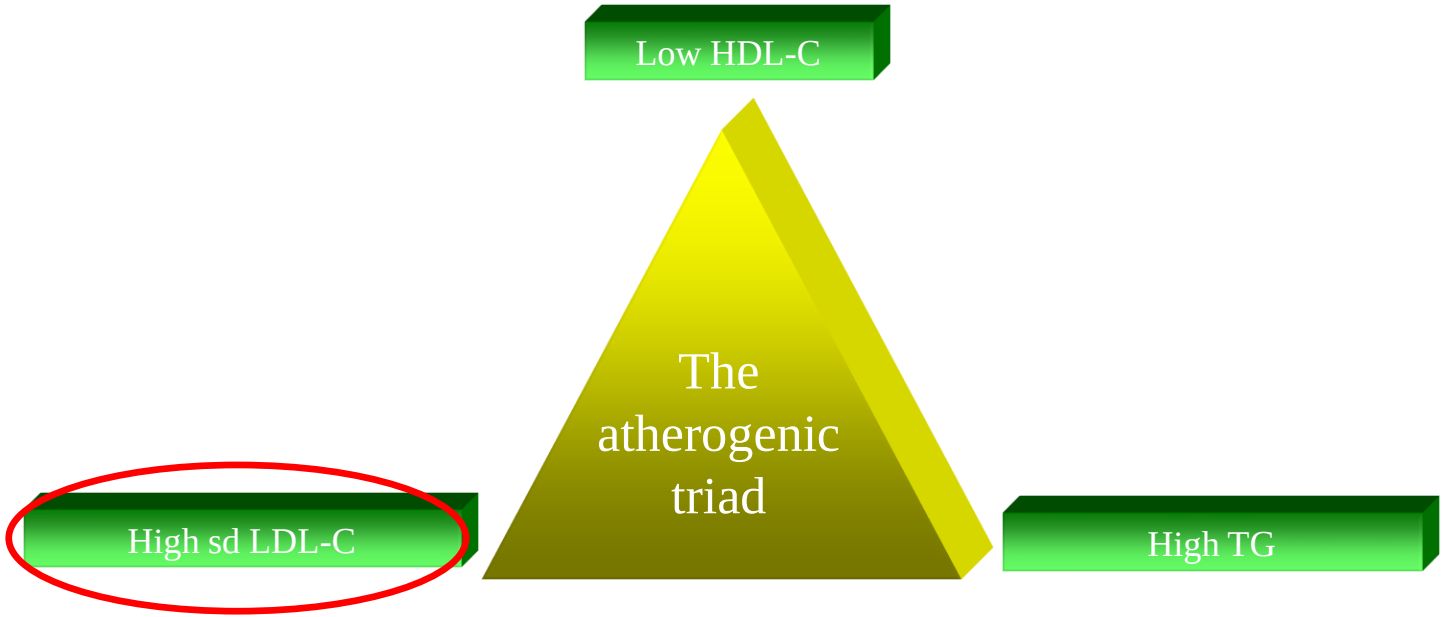
- Unstable angina
- MI

ACS

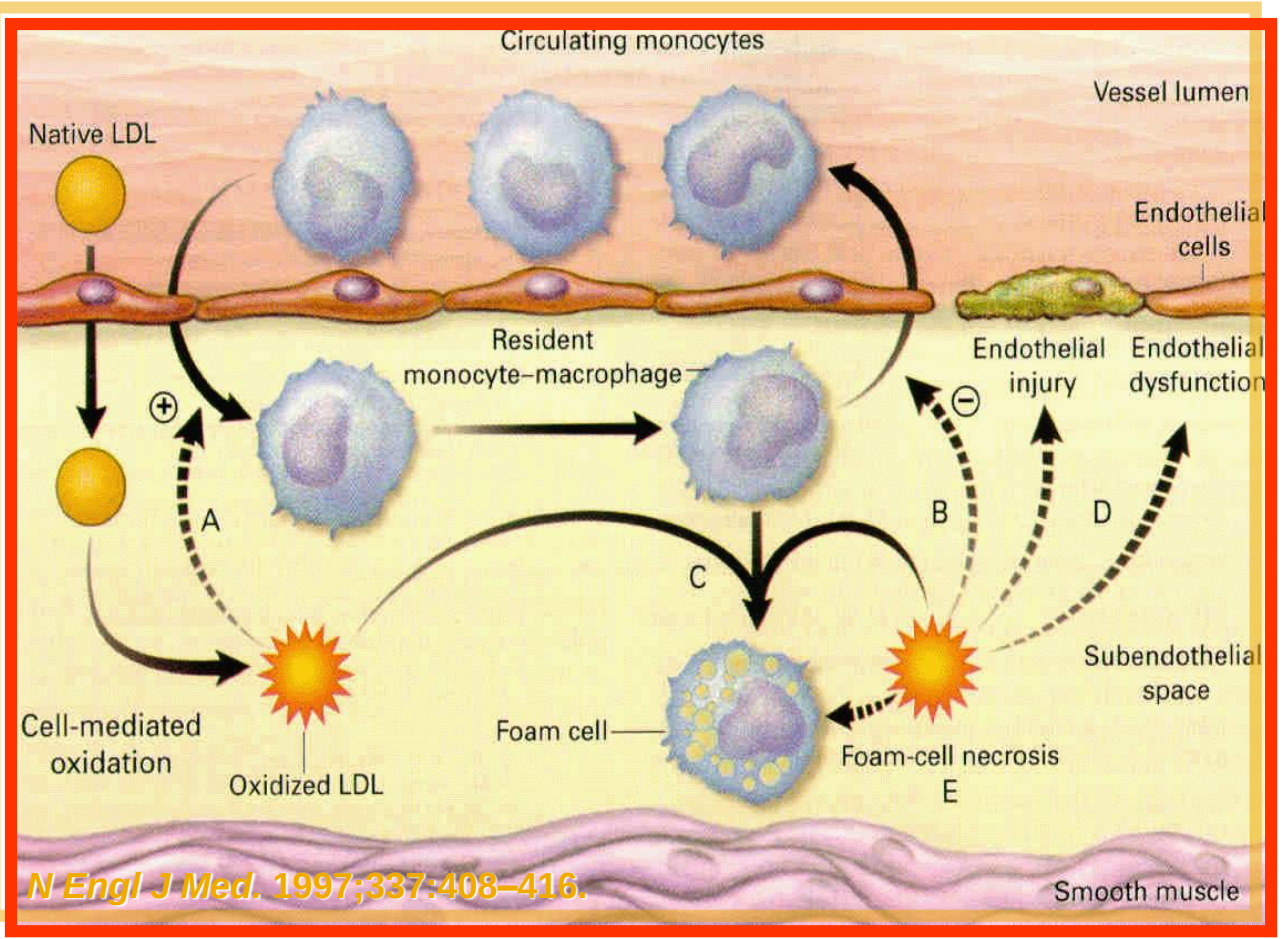
- Ischemic stroke/TIA
- Critical leg ischemia
- Intermitent claudication
- CV death

Circulation. 2001;104:365-72

Atherogenic dyslipidemia之特徵
- The atherogenic triad -

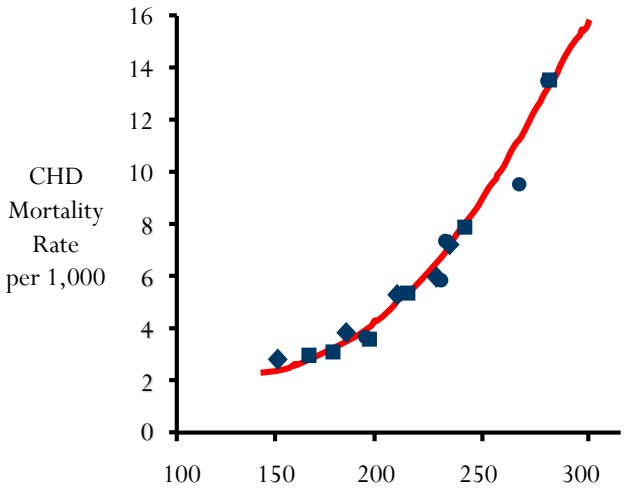


Importance of Cholesterol in Atherosclerosis

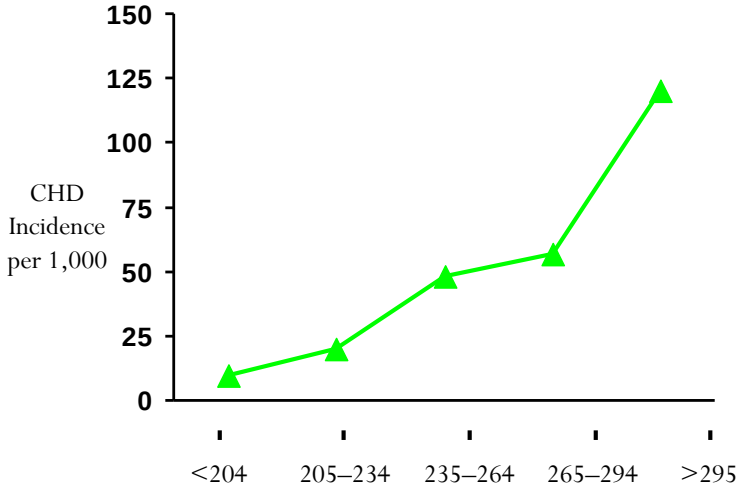


CHD Risk Increases as Plasma Cholesterol Increases

MRFIT (n=356,222)[1]



Framingham Study (n=5,209)[2]

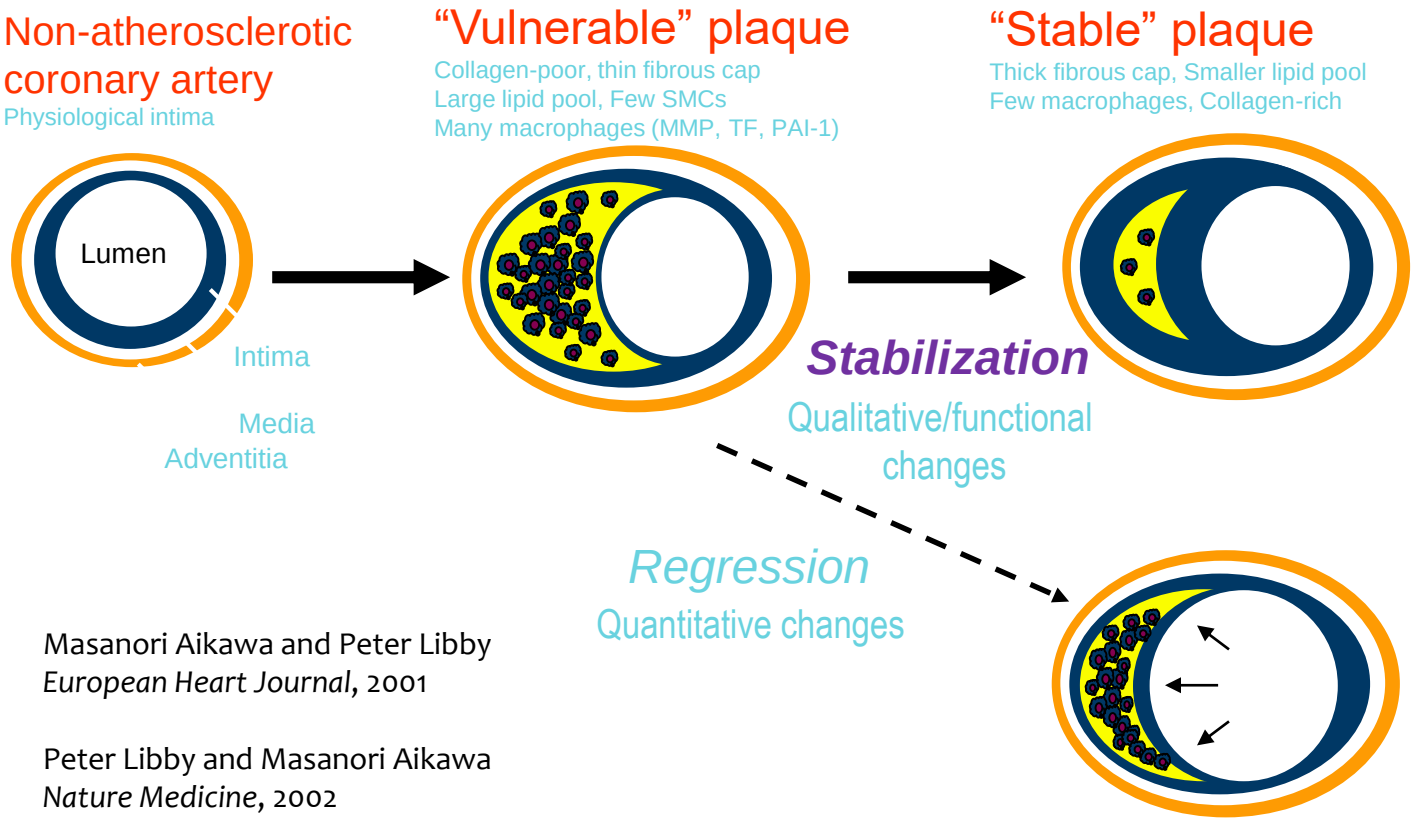


CHD = coronary heart disease; MRFIT = Multiple Risk Factor Intervention Trial.

1. Stamler J et al. *JAMA*. 1986;256:2823–2828.

2. Reprinted from *Am J Med,* Vol 76, WP Castelli, Epidemiology of coronary heart disease: the Framingham Study, pp. 4–12, Copyright 1984, with permission from Excerpta Medica Inc.

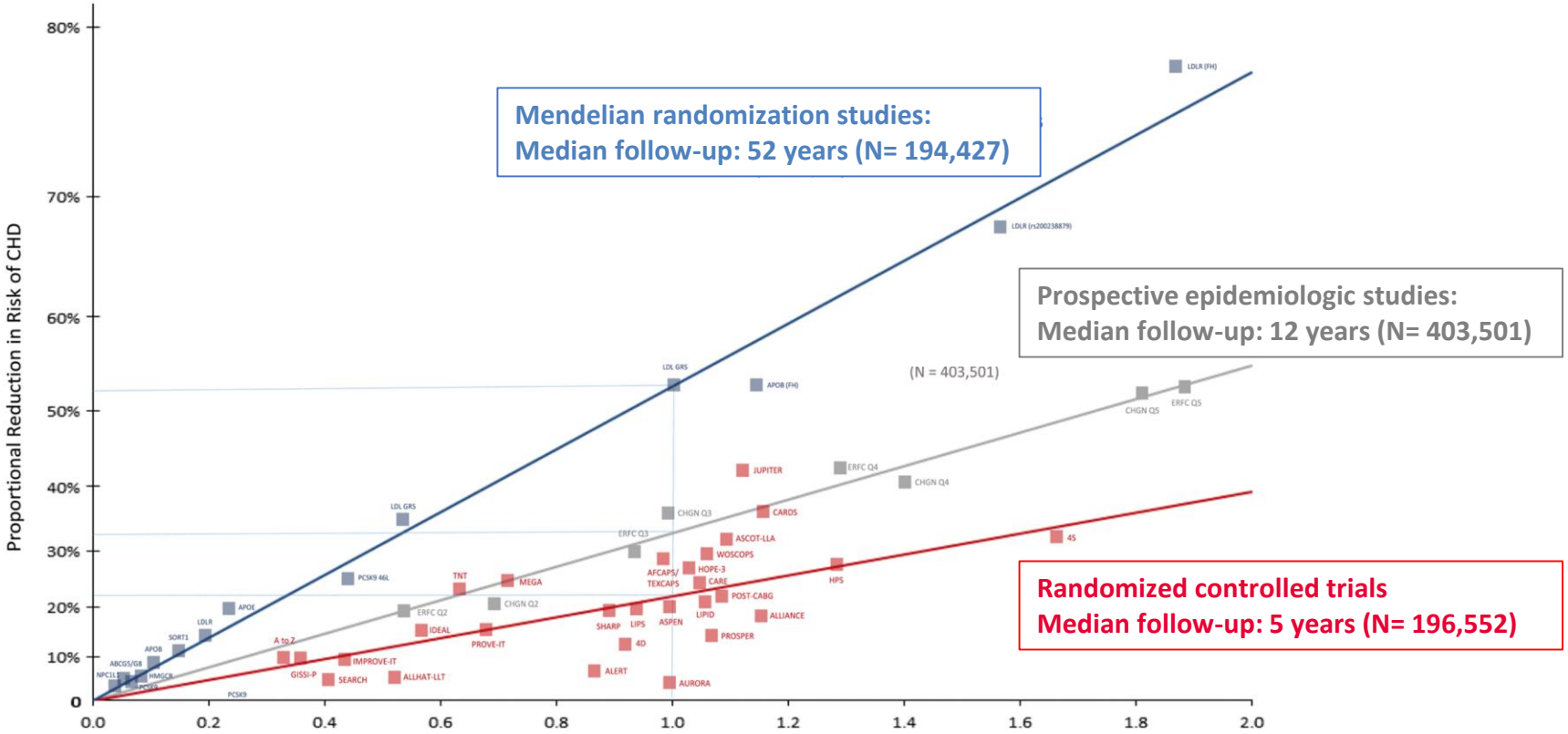
Stabilization of 'vulnerable' plaques by lipid lowering



Masanori Aikawa and Peter Libby
European Heart Journal, 2001

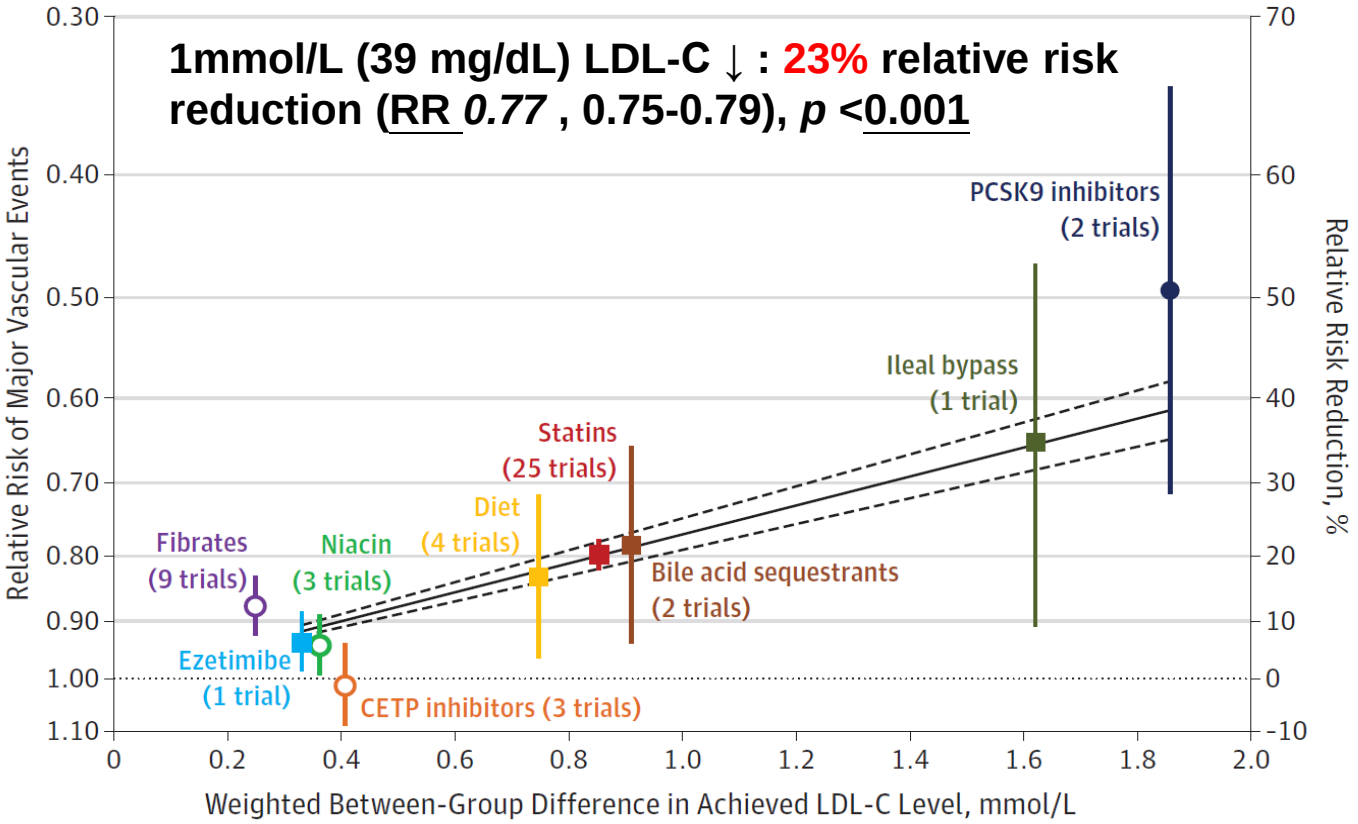
Peter Libby and Masanori Aikawa
Nature Medicine, 2002

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



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

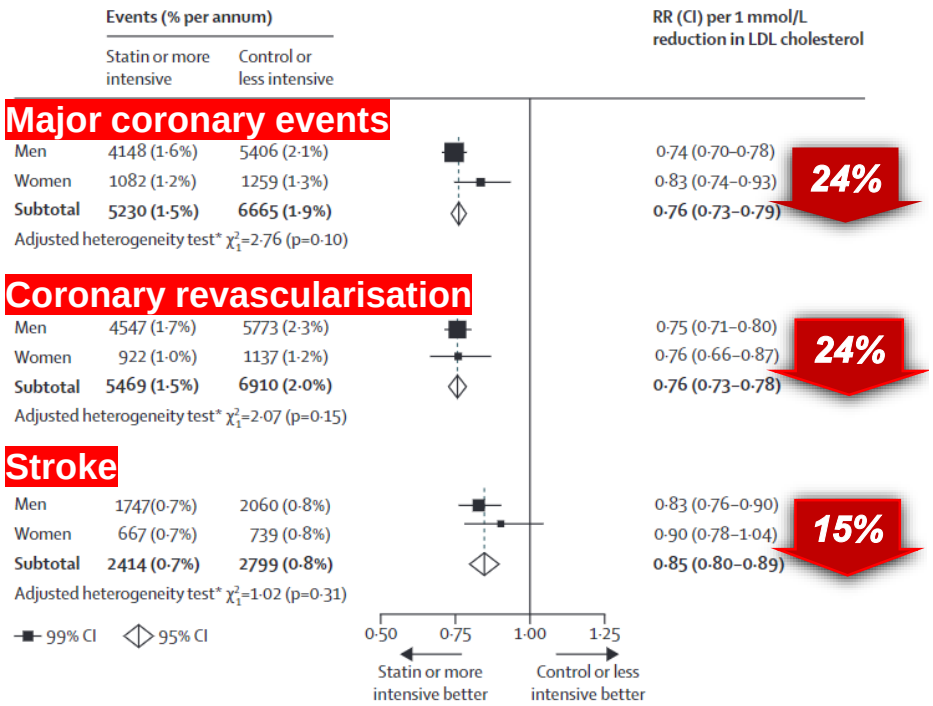
Absolute reduction in LDL-C level is associated with lower relative risk of major vascular coronary events

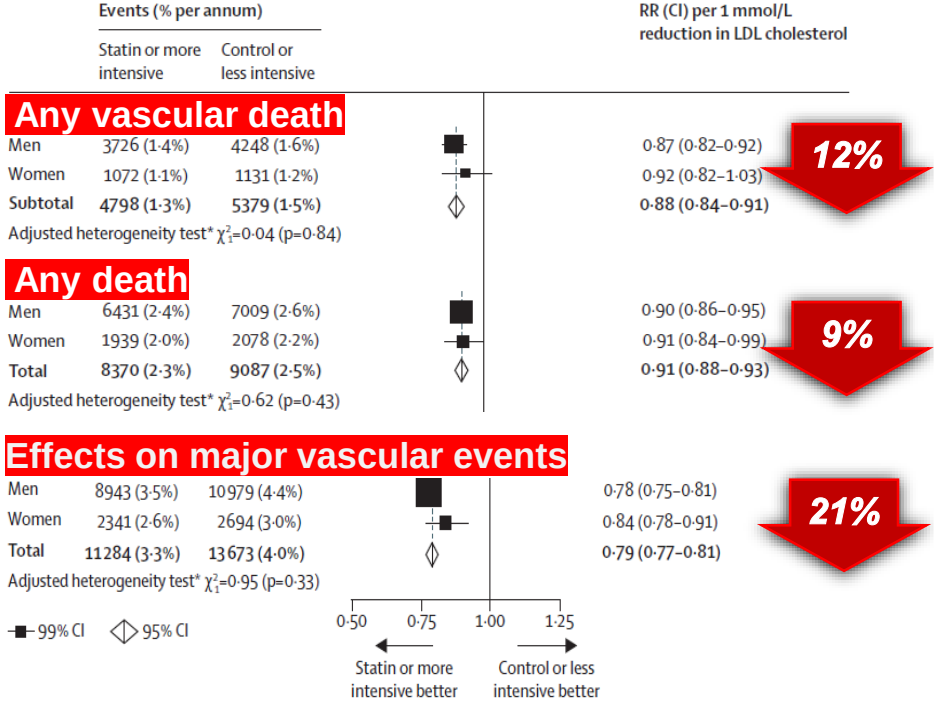


JAMA. 2016;316(12):1289-1297

Reduce 39mg/dL (1 mmol/L) LDL-C by statin: reduce 24% risk of major coronary events

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

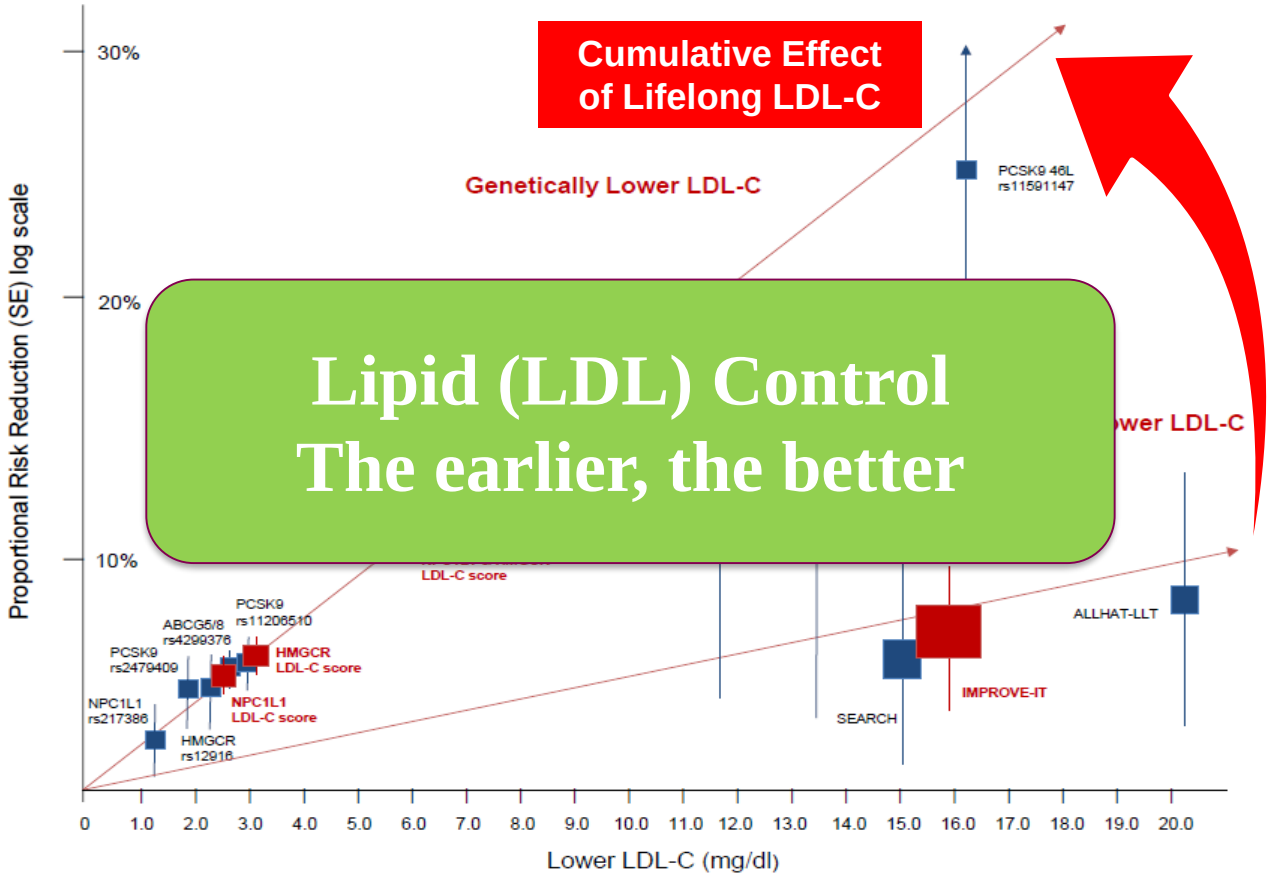




* LDL 1.0 mmol/L =39 mg/dL

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

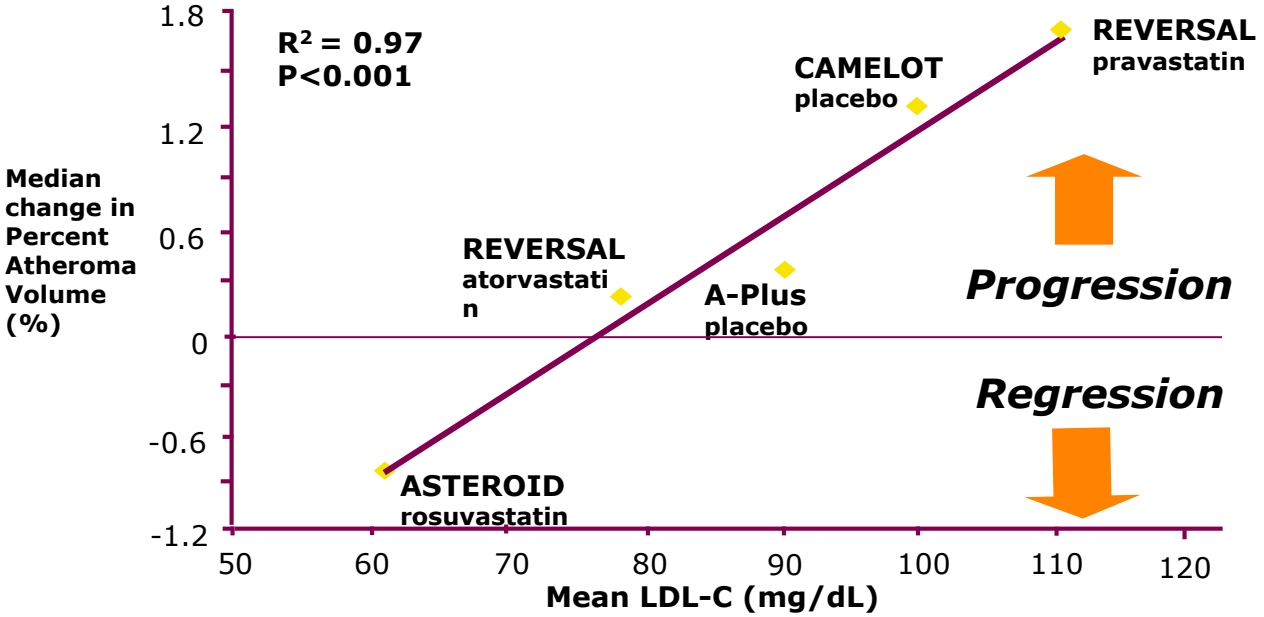
Log-Linear Effect of Lower LDL-C on CHD



Ference, BA et al. J Am Coll Cardiol 2015;doi:10.1016/j.jacc.2015.02.020).

Cannon CP, et al. AHA, November, 17 2014

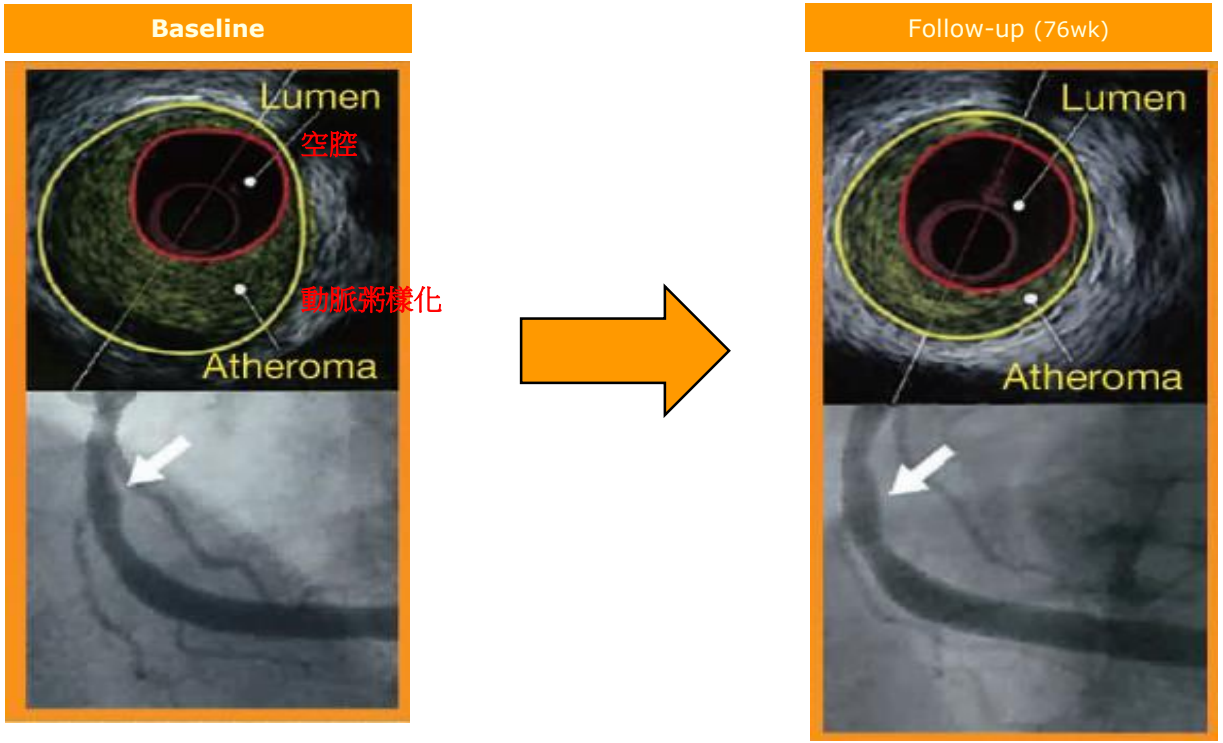
Relationship between LDL-C levels and change in percent atheroma volume for several IVUS trials



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

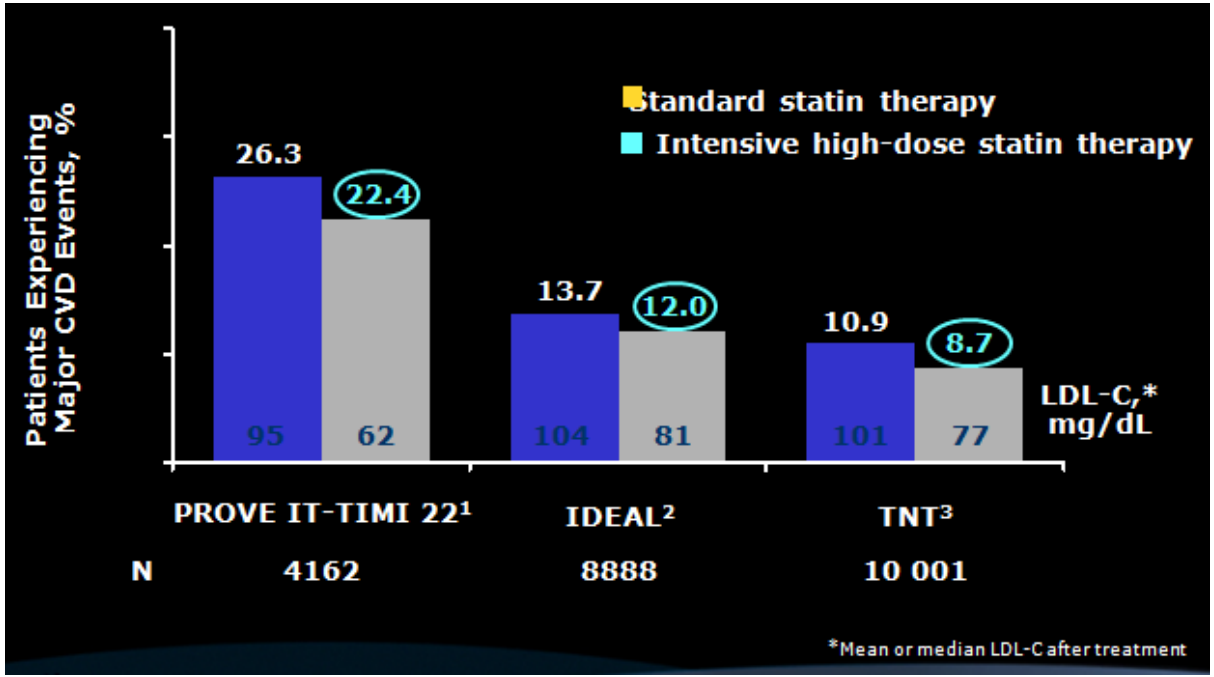
Statin exerted significant regression of coronary plaque volume in Japanese patients with stable CAD

The COSMOS study



Takayama T et al. *Circ J* 2009; 73: 2110–2117

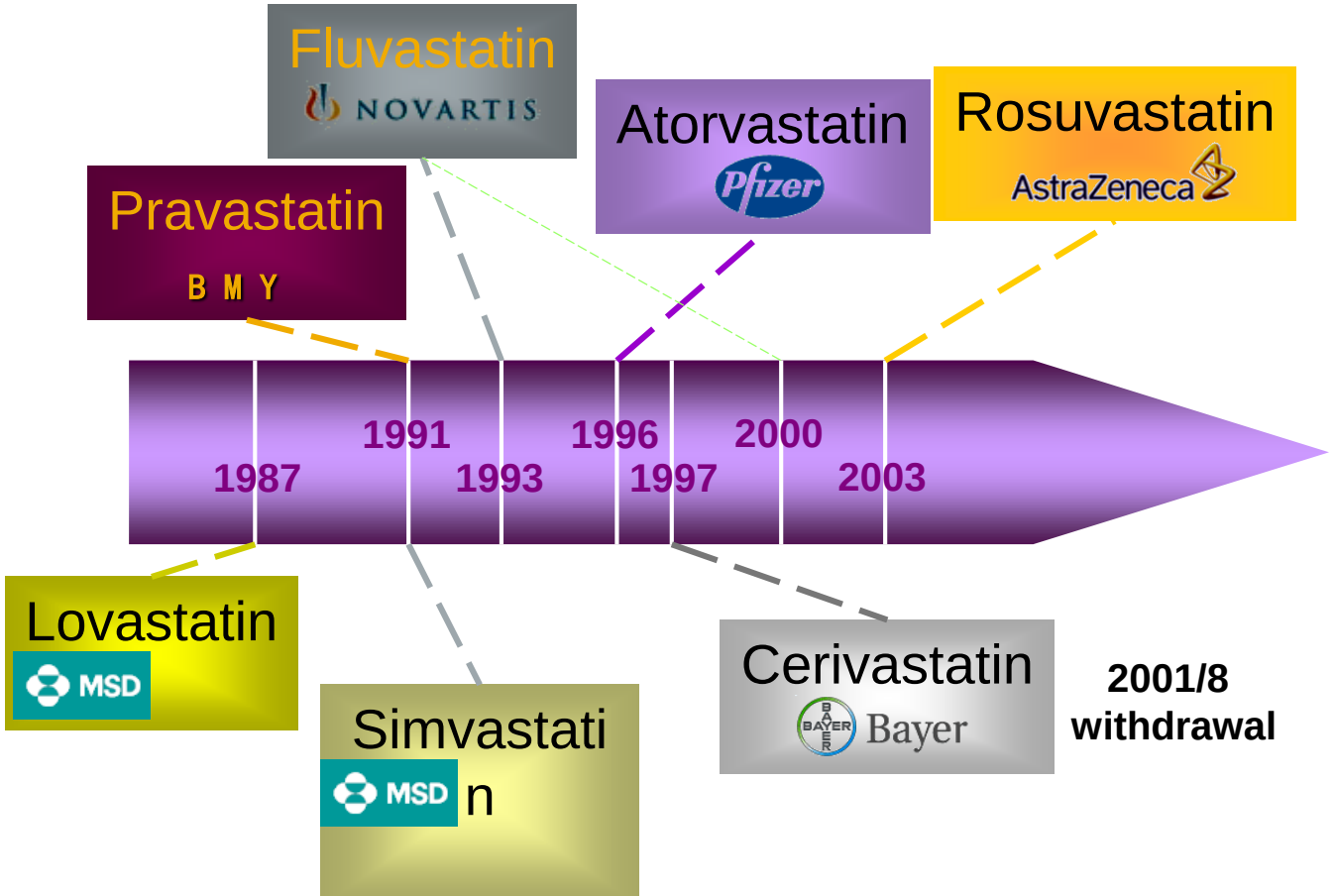
Residual CVD Risk in Patients Treated With Intensive Statin Therapy



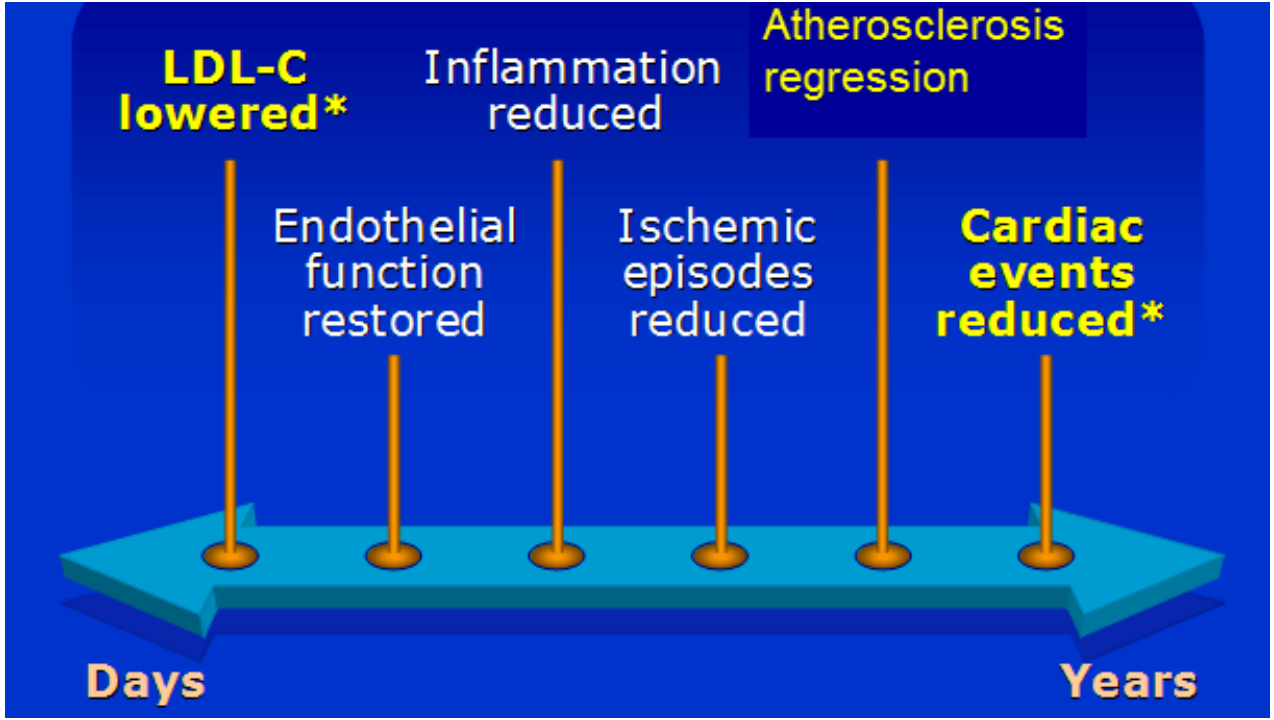
Cannon CP, et al. *N Engl J Med.* 2004;350:1495-1504.
[2] Pedersen TR, et al. *JAMA.* 2005;294:2437-2445.
[3] LaRosa JC, et al. *N Engl J Med.* 2005;352:1425-1435.

Clinical considerations of different statin use - Benefit & Risk

History of Statins



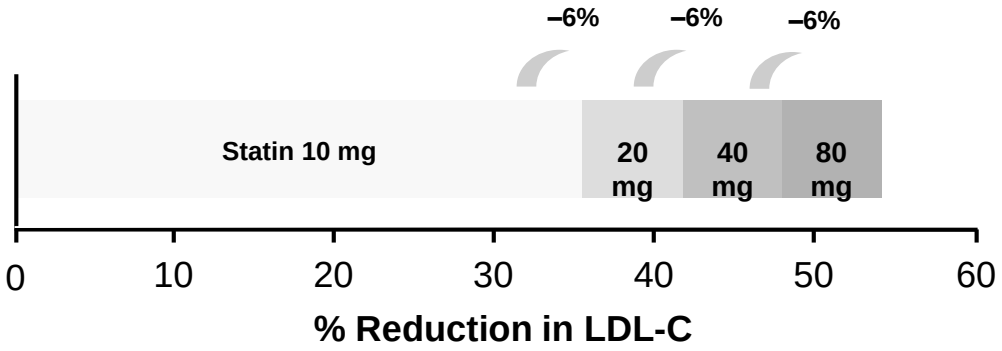
Potential time course of statin effect



www.lipidsonline.org

Statin Dose Titration

- Monotherapy is the traditional approach
- Current practice based on up-titration of statin dose
- “Rule of 6”
- For every doubling of the statin dose, LDL-C is lowered only by another 6%



Adapted from Grundy SM et al *J Am Coll Cardiol* 2004;43:2142–2146; Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults *Circulation* 2002;106:3143–3421; Knopp RH *N Engl J Med* 1999;341:498–509; Stein E *Eur Heart J Suppl* 2001;3(Suppl E):E11–E16.

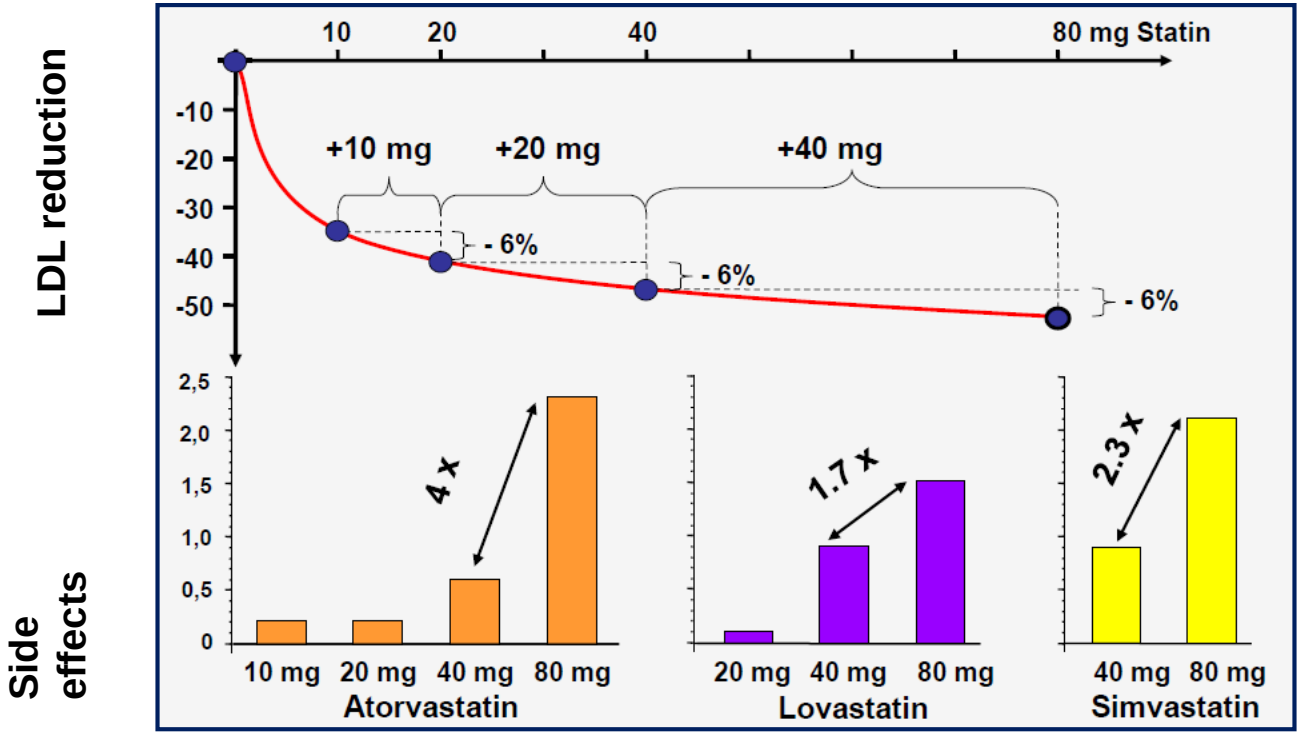
Lipid Management Pharmacotherapy

Therapy	TC	LDL	HDL	TG	Patient tolerability
Statins*	↓ 19-37%	↓ 25-50%	4-12%	↓ 14-29%	Good
Ezetimibe	↓ 13%	↓ 18%	1%	↓ 9%	Good
Bile acid sequestrants	↓ 7-10%	↓ 10-18%	3%	Neutral or	Poor
Nicotinic acid	↓ 10-20%	↓ 10-20%	14-35%	↓ 30-70%	Reasonable to Poor
Fibrates	↓ 19%	↓ 4-21%	11-13%	↓ 30%	Good

HDL-C=High-density lipoprotein cholesterol, LDL-C=Low-density lipoprotein cholesterol, TC=Total cholesterol, TG=Triglycerides

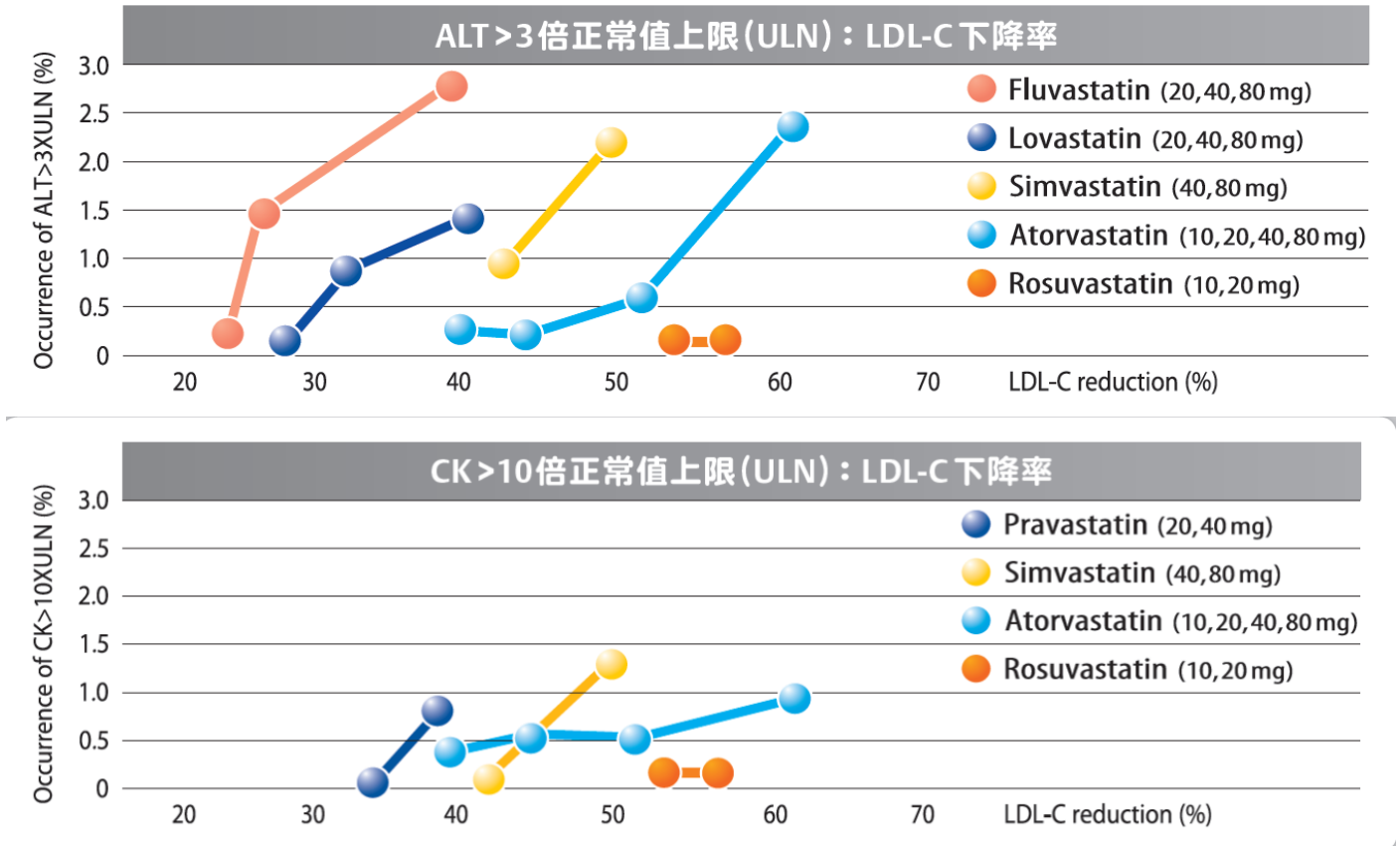
*Daily dose of 40mg of each drug, excluding rosuvastatin.

LDL-reduction and side effects with increasing doses of statins



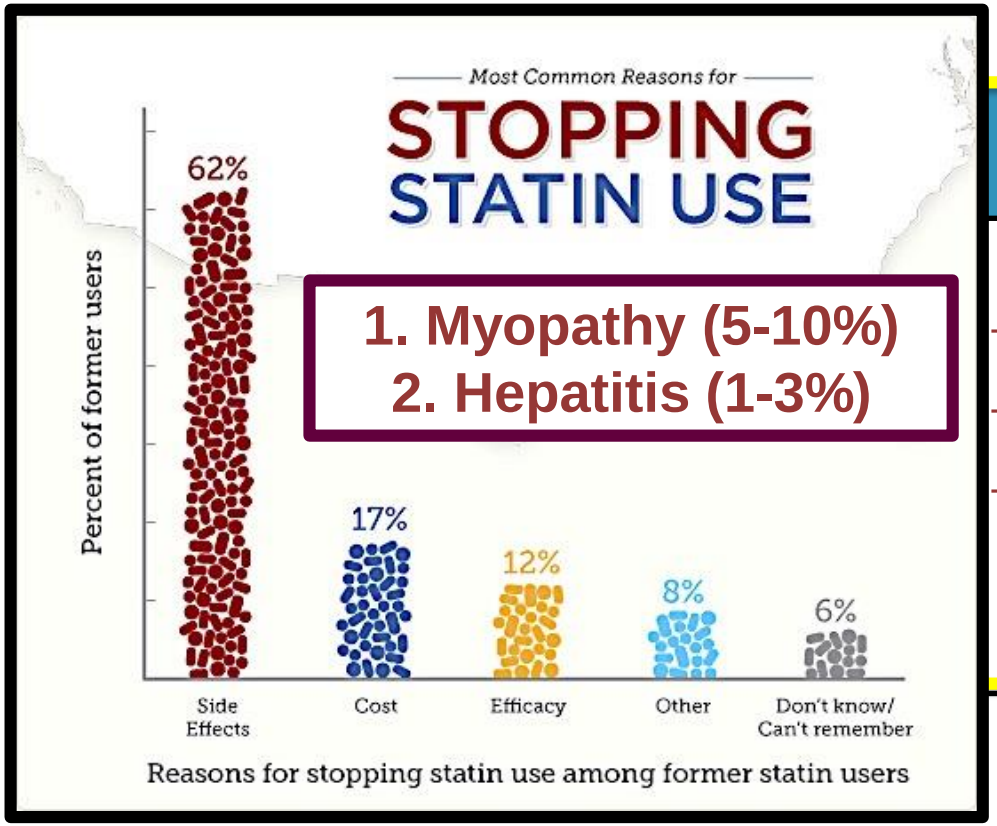
Leitersdorff et al. Europ. Heart J. 2001

Higher statin dose, higher side effect



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

Adverse Effect of Statin



1. Myopathy (5-10%)
2. Hepatitis (1-3%)

Other considerations

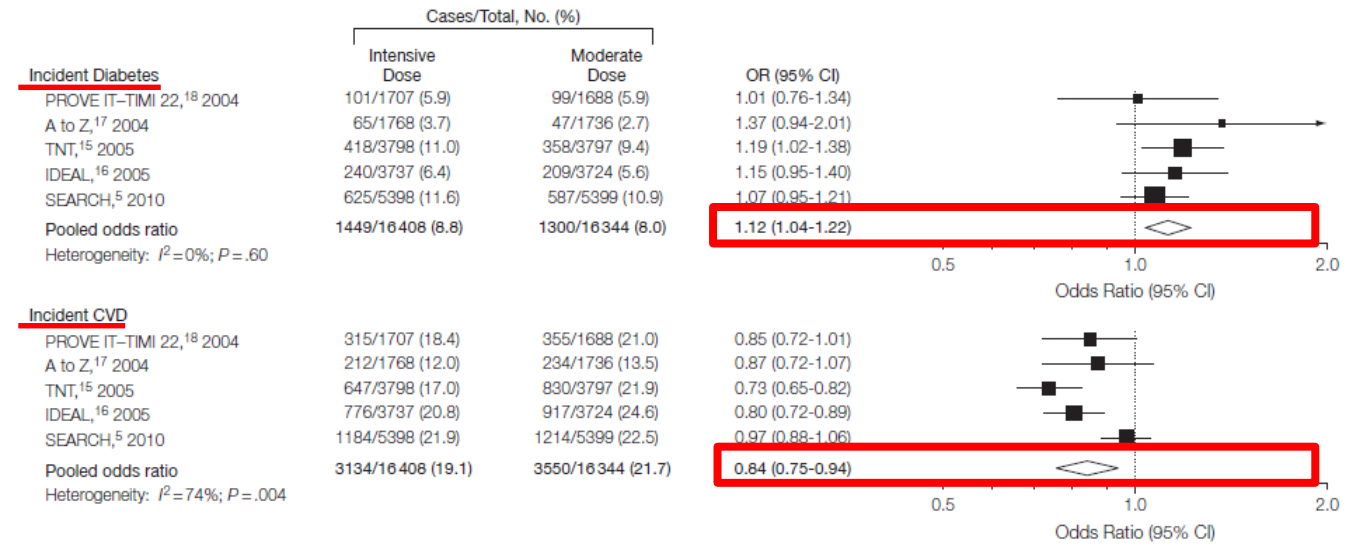
- Rhabdomyolysis
- Cognitive decline
- New-onset diabetes

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

Risk of Incident Diabetes With Intensive-Dose Compared With Moderate-Dose Statin Therapy - A Meta-analysis

Odds ratios were **1.12** for **new-onset diabetes** and **0.84** for **cardiovascular events** for participants receiving intensive therapy compared with moderate-dose therapy.

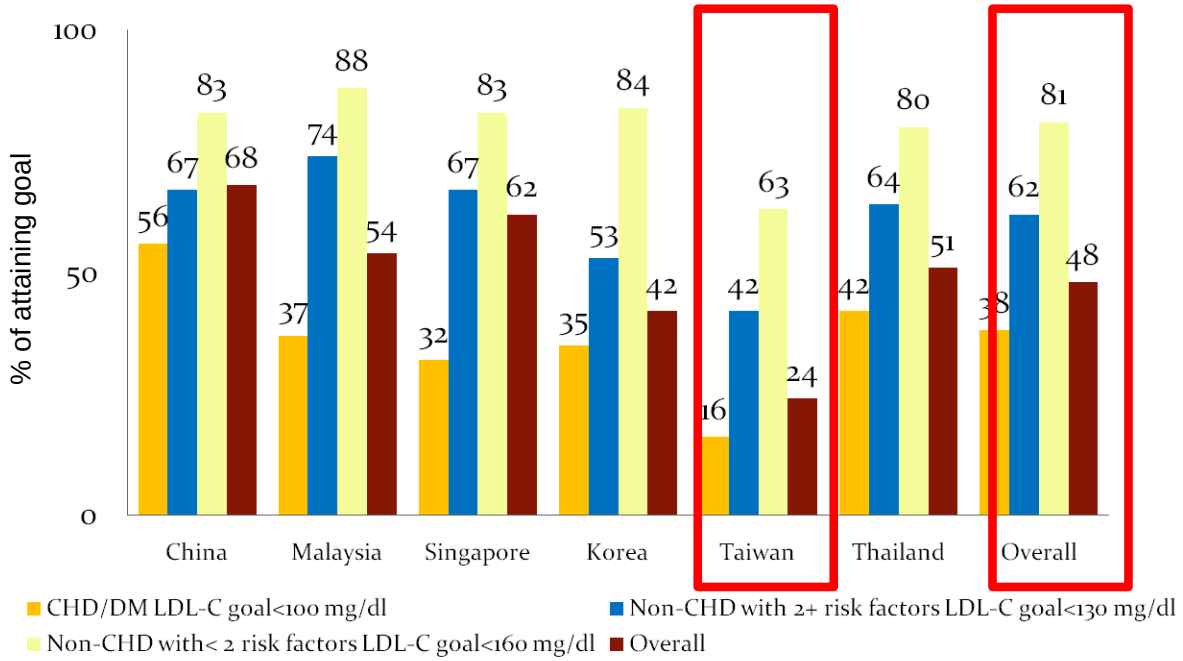
Figure 2. Meta-analysis of New-Onset Diabetes and First Major Cardiovascular Events in 5 Large Trials Comparing Intensive-Dose to Moderate-Dose Statin Therapy



JAMA. 2011;305(24):2556-2564

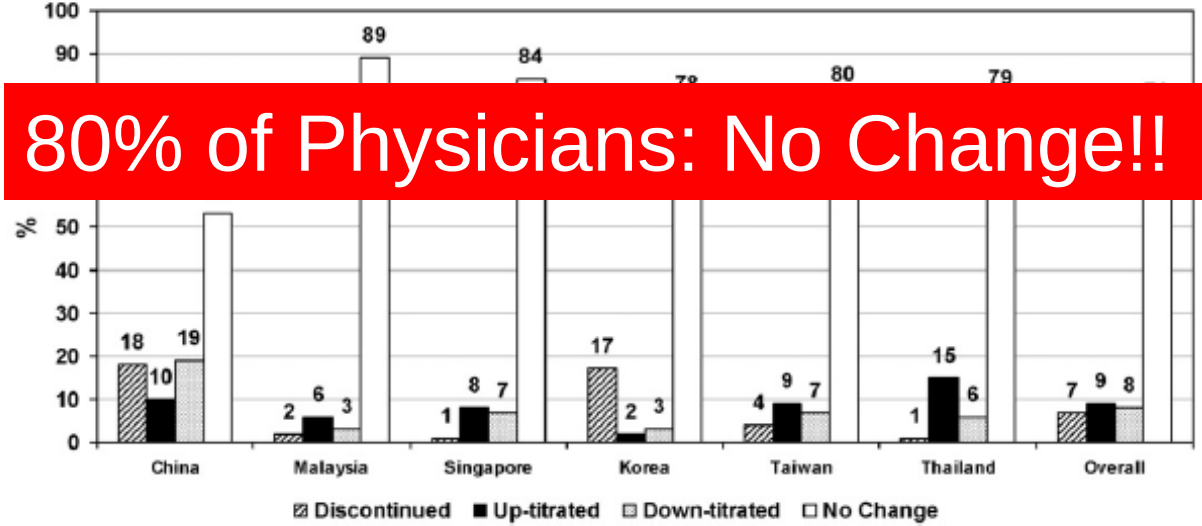
Treatment gap of lipid lowering treatment in Asia

***Reality-Asia:** to evaluate cholesterol goal attainment in the 'real world'*



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

Physician inertia in in REALITY-Asia

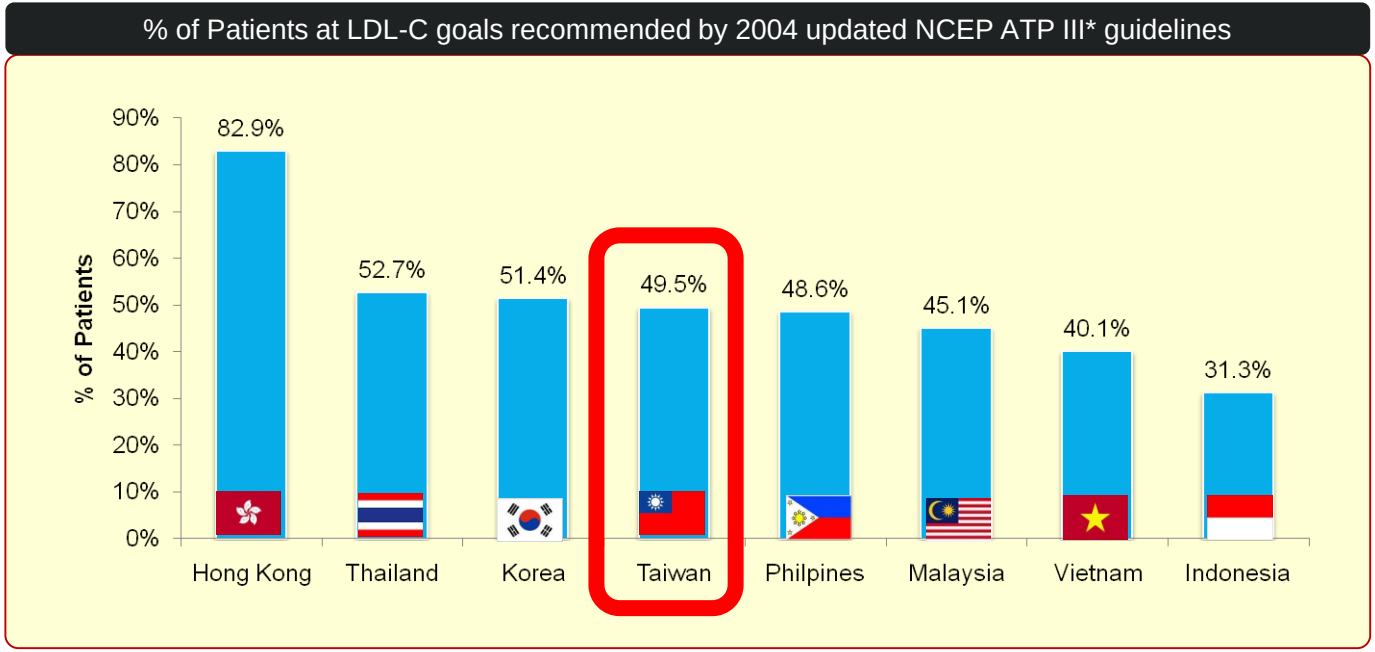


Curr Med Res Opin. 2008 Jul; 24(7): 1951-63

A large-scale, multinational study evaluating the current treatment status of hypercholesterolemia in Asia and investigating possible association of patient and physician characteristics, as well as their attitude towards the management of hypercholesterolemia

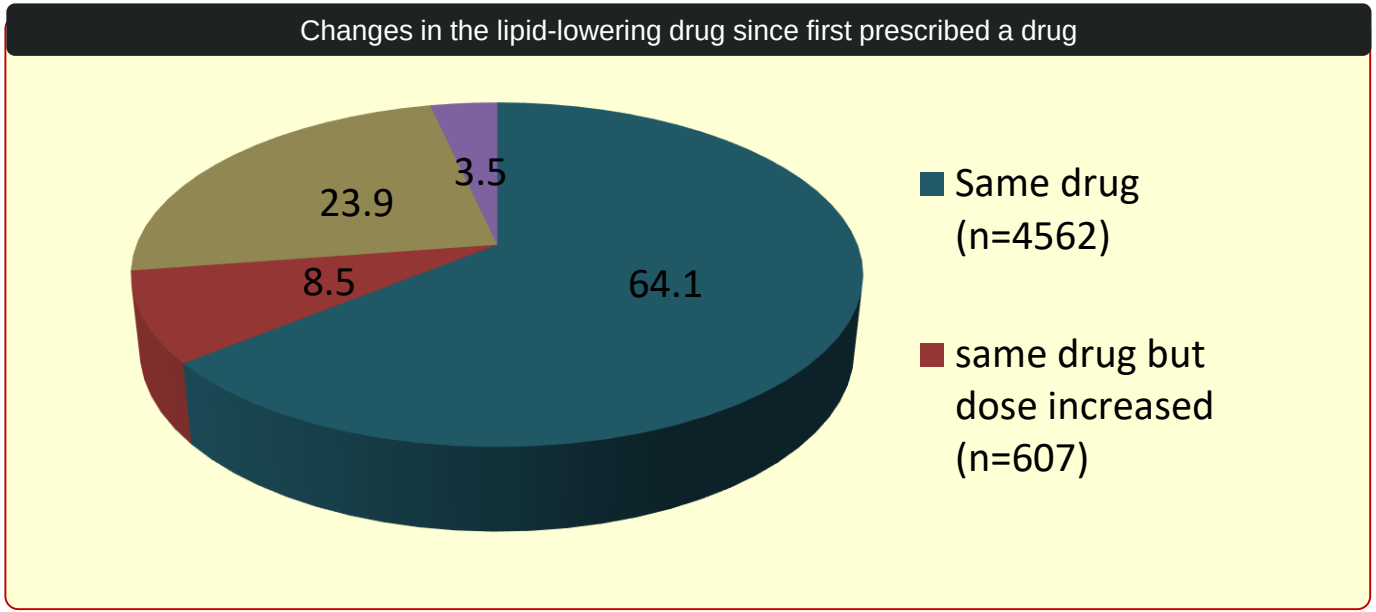
European Journal of Cardiovascular Prevention & Rehabilitation **March 7, 2011**
1741826710397100

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



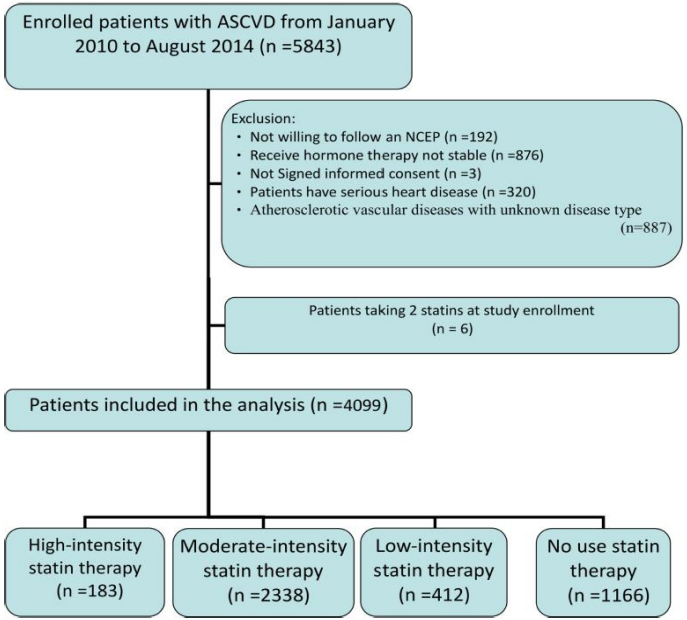
- For patients in Hong Kong the treatment goal attainment rate was 82.9% while patients in other countries had very low LDL-C attainment rate (31.3 – 52.7%).

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



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

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



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

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

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

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

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

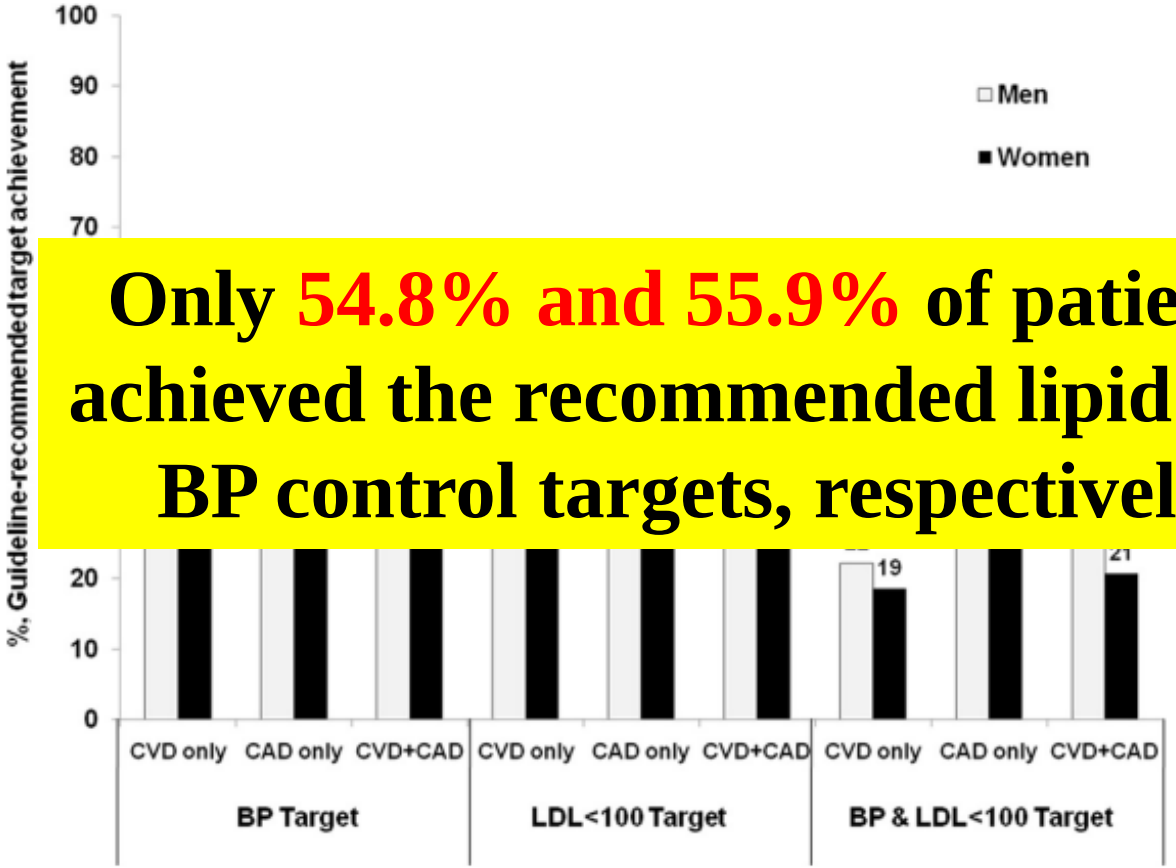
PLoS One. 2017 Oct 26;12(10):e0186861.

ORIGINAL ARTICLE

Guideline-adherent therapy in patients with cardiovascular diseases in Taiwan

Jiann-Shing Jeng [a], Wei-Hsian Yin [b,c], Chin-Chou Huang [d,e], Shao-Yuan Chuang [f], Hung-I Yeh [g], Ching-Chang Fang [h], Tsung-Hsien Lin [i], Kuo-Yang Wang [j,k], Wei-Kung Tseng [l,m], Lien-Chi Huang [n], Kwo-Chang Ueng [o,p], I-Chang Hsieh [q], Yi-Heng Li [r], Wen-Harn Pan [f], Chau-Chung Wu [s,t,*], Jaw-Wen Chen [d,e] on behalf of the Taiwanese Secondary Prevention for Patients with AtheRosCLErotic Disease (T-SPARCLE) Registry Investigators

Journal of the Formosan Medical Association (2015)114, 1000e1007



Only 54.8% and 55.9% of patients achieved the recommended lipid and BP control targets, respectively.

Journal of the Formosan Medical Association (2015)114, 1000e1007

Received: 14 February 2019 | Revised: 10 August 2019 | Accepted: 19 August 2019
DOI: 10.1111/jep.13286

ORIGINAL PAPER

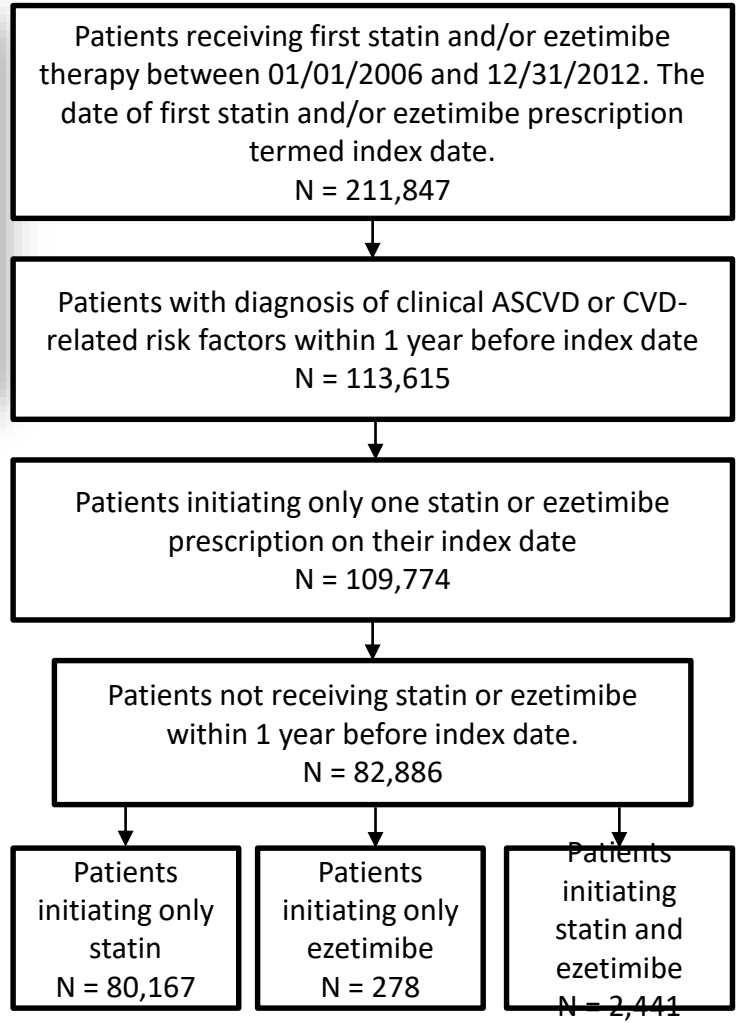
WILEY Journal of Evaluation in Clinical Practice
International Journal of Public Health Policy and Health Services Research

Treatment patterns of lipid-lowering therapies and possible statin intolerance among statin users with clinical atherosclerotic cardiovascular disease (ASCVD) or diabetes mellitus (DM) in Taiwan

評估台灣ASCVD或DM患者使用「statin類藥物」或「statin合併ezetimibe」的治療模式以及「statin類藥物」可能引起的不耐受性

- A retrospective cohort study using Taiwan's 2005 to 2013 NHIRD.
- Patients with history of clinical ASCVD or DM (without previous clinical ASCVD) and initiating statin or statin plus ezetimibe therapy during 2006 to 2012
- 分析藥物的治療方式（包括停藥、重新使用、減藥、加藥、換藥）、藥物順從性（藥品持有率medication possession ratio, MPR)、用藥持續性（間隔小於60天），以及statin類藥物可能引起的不耐受性（從藥物使用開始追蹤12個月）

J Eval Clin Pract. 2019 Oct 23



19.9%的ASCVD患者和21.4%的DM患者，可能對於statin類藥物產生不耐受性（可能產生不耐受性的定義為劑量的改變、停藥、或是改用其他非statin類藥物）

TABLE 4 Statin intolerance

	Overall		By Index Lipid-lowering Agents				By History of Clinical ASCVD or CVD-related Risk Factors			
			Statin Only		Statin + Ezetimibe		Clinical ASCVD		Diabetes Mellitus but without Clinical ASCVD	
All patients (n, row %)	82 608	100.00%	80 167	97.05%	2441	2.95%	11 092	13.43%	31 100	37.65%
Patients with more than one treatment modification (n, row %)	67 253	100.00%	65 304	97.10%	1949	2.90%	8579	12.76%	24 897	37.02%
Possible statin intolerance	18 260	22.10%	17 718	22.10%	542	22.20%	2207	19.90%	6640	21.35%
Possible statin ineffectiveness	4045	4.90%	3902	4.87%	143	5.86%	507	4.57%	1560	5.02%
Possible statin intolerance and/or ineffectiveness	4565	5.53%	4417	5.51%	148	6.06%	587	5.29%	1809	5.82%
Possible nonstatin intolerance and/or ineffectiveness	719	0.87%	140	0.17%	579	23.72%	98	0.88%	287	0.92%

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease.

	全部 **(n=82608)**	次分析	
		ASCVD患者 (n=11092)	DM患者 (n=31100)
患者停止降血脂治療	59.64%	54.0%	57.5%
平均藥物順從性(MPR)	0.59	0.62	0.60
用藥持續性	40.43%	46.1%	42.6%
Statin類藥物可能的不耐受性	22.10%	19.9%	21.4%

J Eval Clin Pract. 2019 Oct 23

高血脂症治療需要找出更有效率的方式

	Overall		By Index Lipid-lowering Agents				By History of Clinical ASCVD or CVD-related Risk Factors			
			Statin Only		Statin + Ezetimibe		Clinical ASCVD		Diabetes Mellitus but Without Clinical ASCVD	
Discontinuation										
Patients who discontinued treatment	49 265	59.64%	48 014	59.89%	1251	51.25%	5990	54.00%	17 869	57.46%
Patients with statin discontinuation only (n, column %[a])	48 017	97.47%	48 014	100.00%	3	0.24%	5806	96.93%	17 420	97.49%
Patients with statin and ezetimibe discontinuation (n, column %[a])	1234	2.50%	0	0.0%	1234	98.64%	181	3.02%	442	2.47%
Patients with ezetimibe discontinuation only (n, column %[a])	14	0.03%	0	0.0%	14	1.12%	3	0.05%	7	0.04%

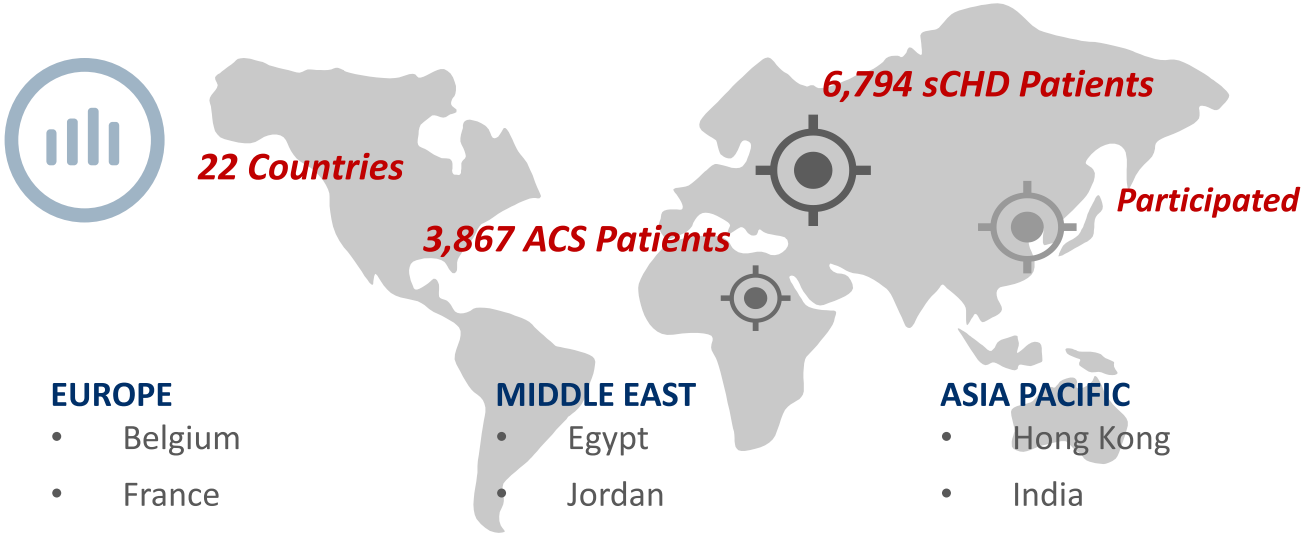
台灣的族群中有過半數(59.64%)的患者停止了降血脂治療

進一步分析可以發現，分別有54.0%的ASCVD患者(n=5990)和57.5%的DM患者(n=17869)停止了藥物治療。

患者使用statin類藥物之平均藥物順從性(MPR)的整體表現也不佳(ASCVD患者 =0.62、DM患者＝0.60)，其中藥物順從性佳(MPR>0.8)的比例僅約三分之一(ASCVD患者=38.7% 、 DM 患者＝33.4%）。用藥持續性也都未達半數，總體約為40%，其中ASCVD患者為 46.1% 、 DM患者為42.6%。

J Eval Clin Pract. 2019 Oct 23

Investigator & Sites - Global



EUROPE

- Belgium
- France
- Greece
- Germany
- Ireland
- Italy
- Russia

MIDDLE EAST

- Egypt
- Jordan
- Kuwait
- Lebanon
- Saudi Arabia
- UAE

ASIA PACIFIC

- Hong Kong
- India
- Indonesia
- Philippines
- South Korea
- Singapore
- Taiwan
- Thailand
- Vietnam

Data on File CSR #MK-0653A-427

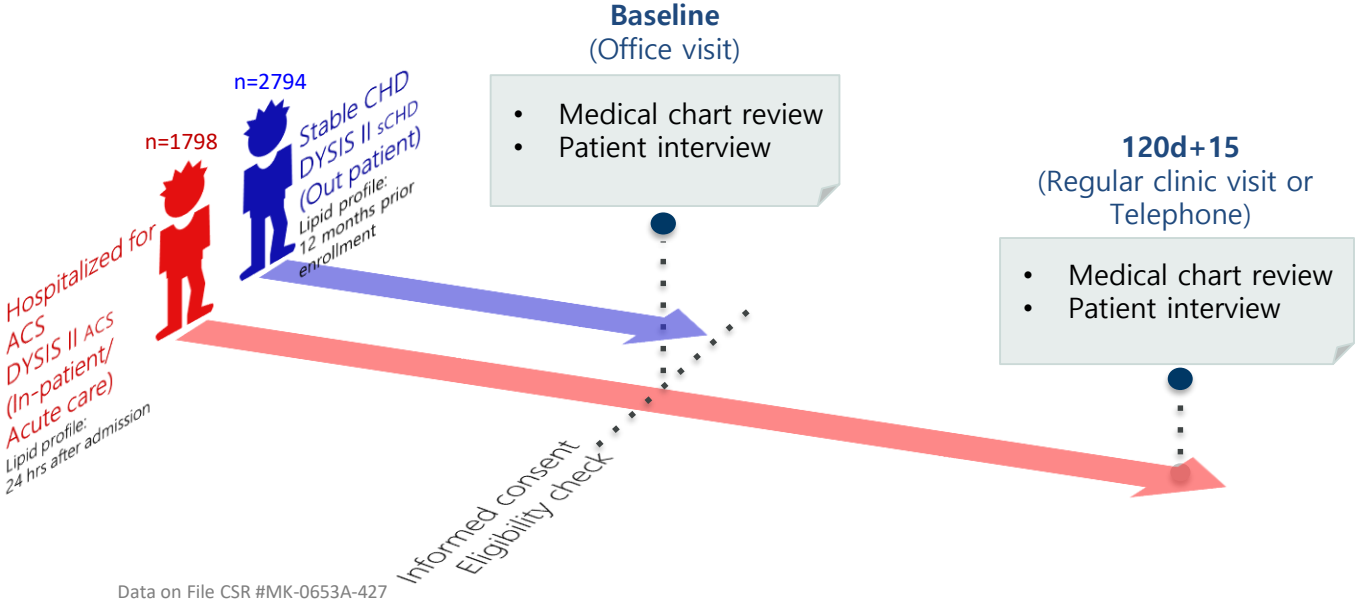
DYSIS II AP - Study Design

Multi-national, Multi-site, Prospective, Observational Study

- Patients are treated per standard of care
- No additional tests or procedures performed as part of this study
- Consecutive enrollment to avoid selection bias

Primary Objective

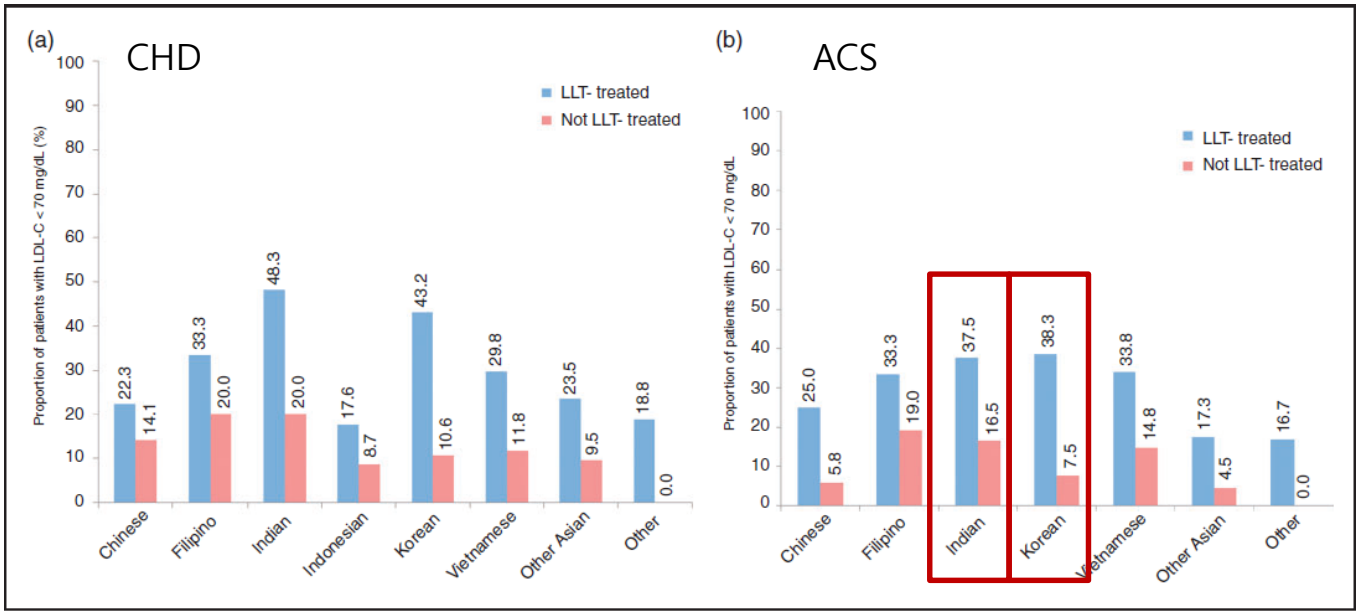
- To globally document real-life lipid levels relative to the new "ESC/EAS Guidelines for the management of Dyslipidemias" in patients with CHD (stable CHD or ACS)



Data on File CSR #MK-0653A-427

DYSIS II AP: Attainment of LDL-C levels less than 70 mg/dL at baseline

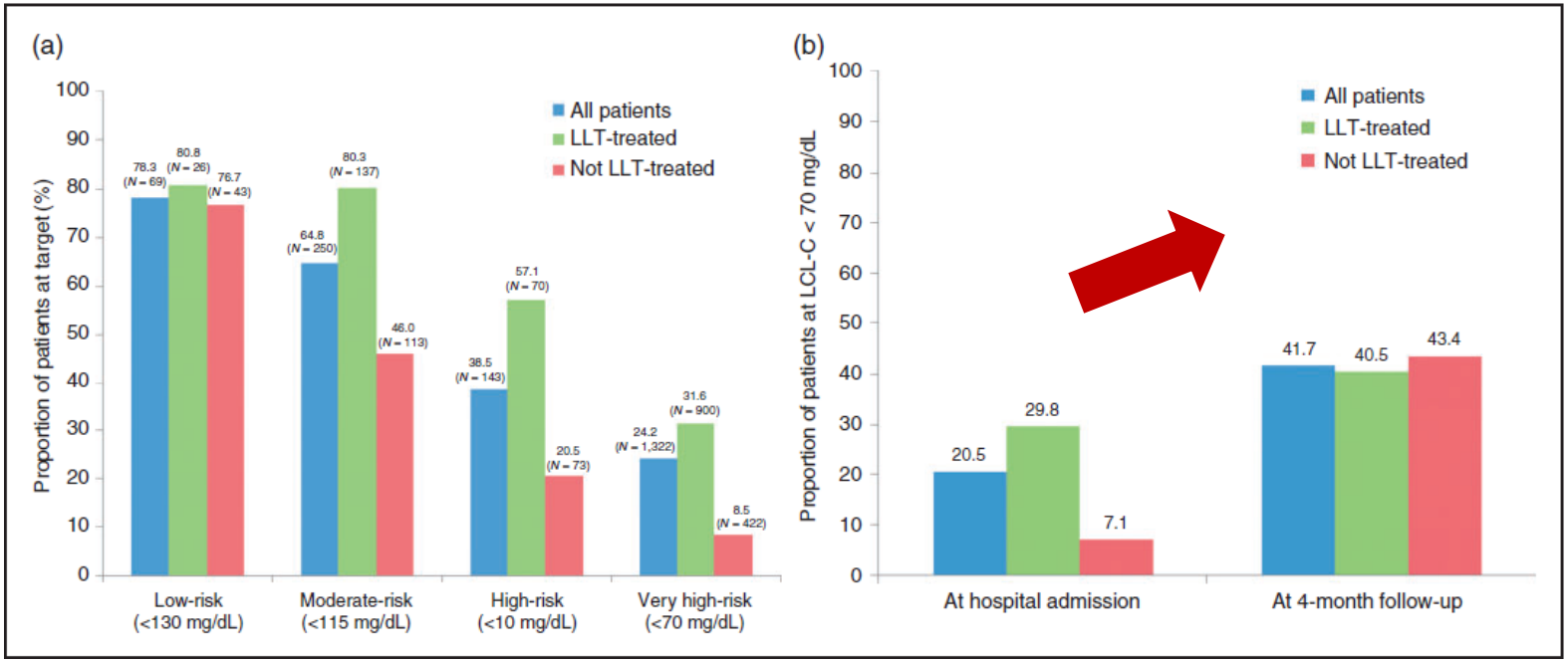
Korean and Indian LLT-treated ACS patients displayed the highest LDL cholesterol target attainment



*The 'other' category includes black, Caucasian, Hispanic and other ethnicities.

(Poh et. al. Eur J Prev Cardiol. 2018 Dec;25(18):1950-1963.)

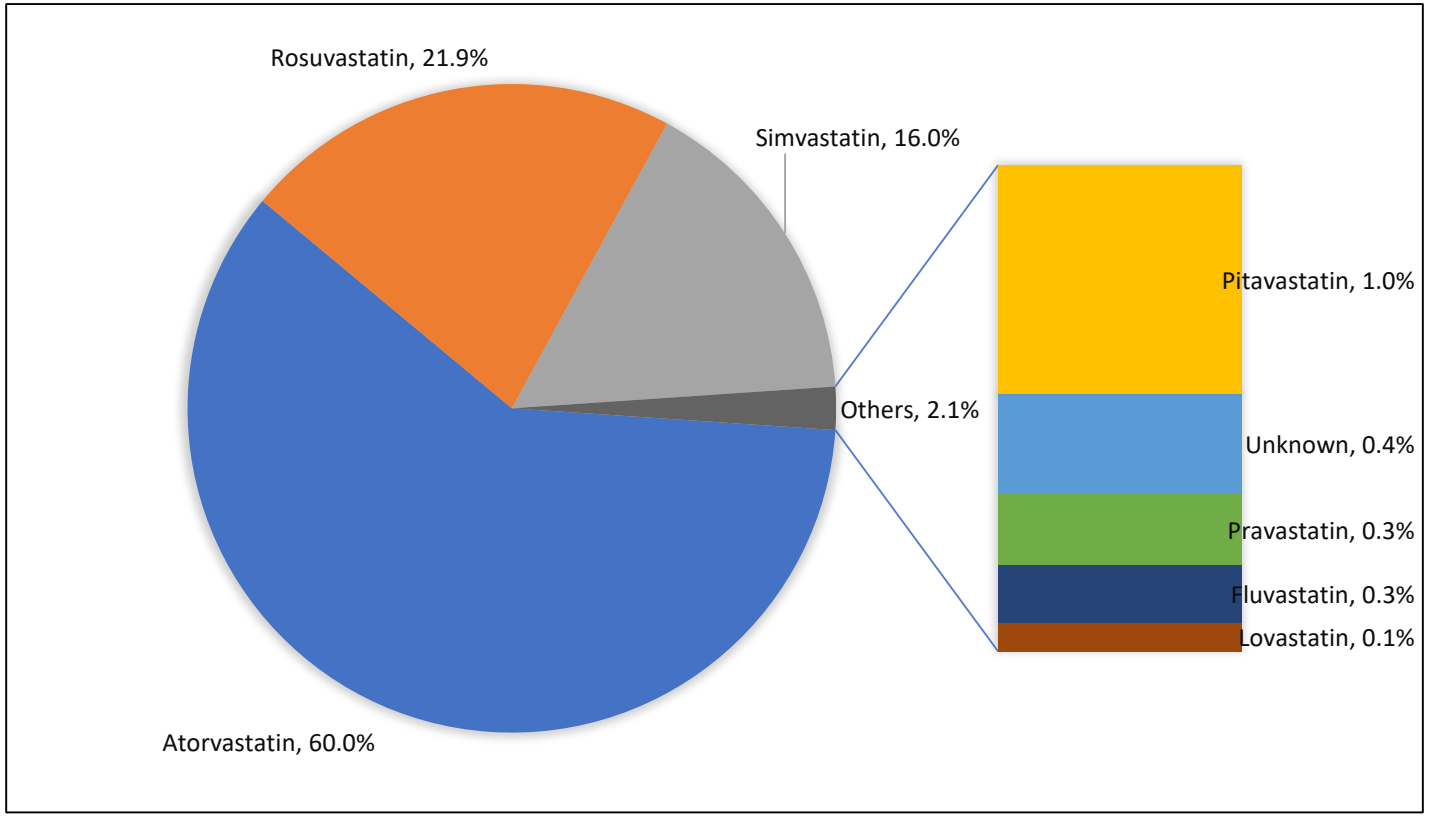
DYSIS II AP: Target LDL-C level attainment in ACS patients



*risk categories and LDL cholesterol targets defined as per European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) 2011 guidelines

(Poh et. al. Eur J Prev Cardiol. 2018 Dec;25(18):1950-1963.)

DYSIS II AP: Use of lipid-lowering therapy in ACS – 4-Month Follow-up



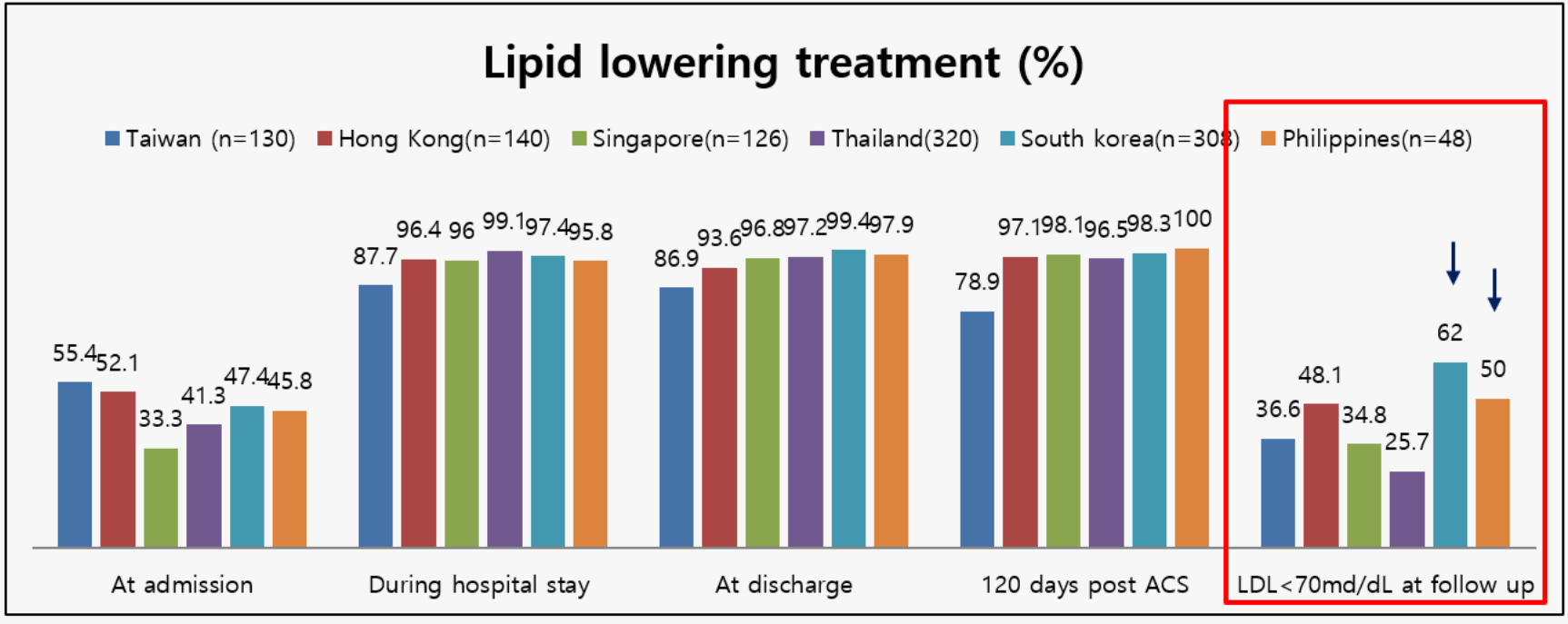
Mean atorvastatin-equivalent statin dosage : 27+-18 mg/day.

(Poh et. al. Eur J Prev Cardiol. 2018 Dec;25(18):1950-1963.)

DYSIS II ACS: Use of lipid-lowering therapy in ACS – 4-Month Follow-up

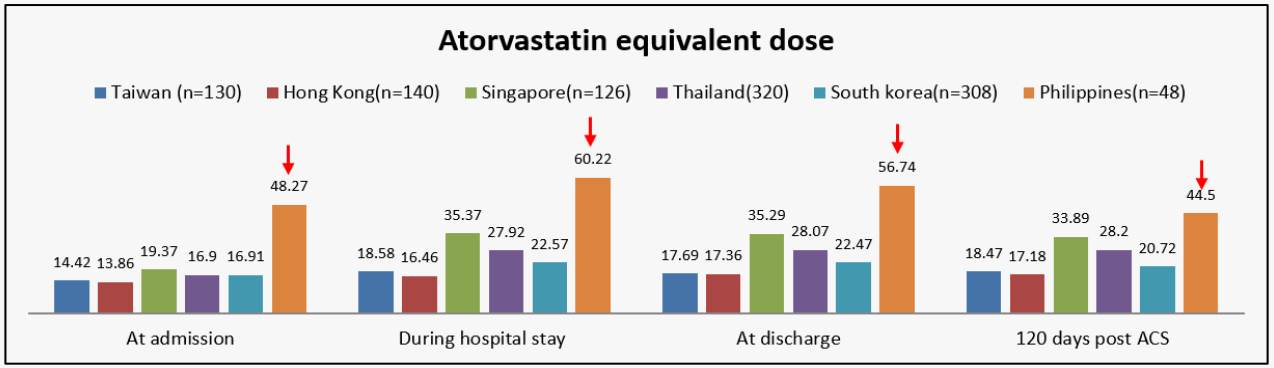
若只單看台灣鄰近國家，可以發現韓國和菲律賓在ACS出院後四個月的追蹤，其LDL<70mg/dL的達標率較台灣高

Indicates the change in lipid-lowering therapy at admission to a hospital for the treatment of an ACS, as well as the changes applied during hospital stay, at discharge and after a 120 day follow up period.

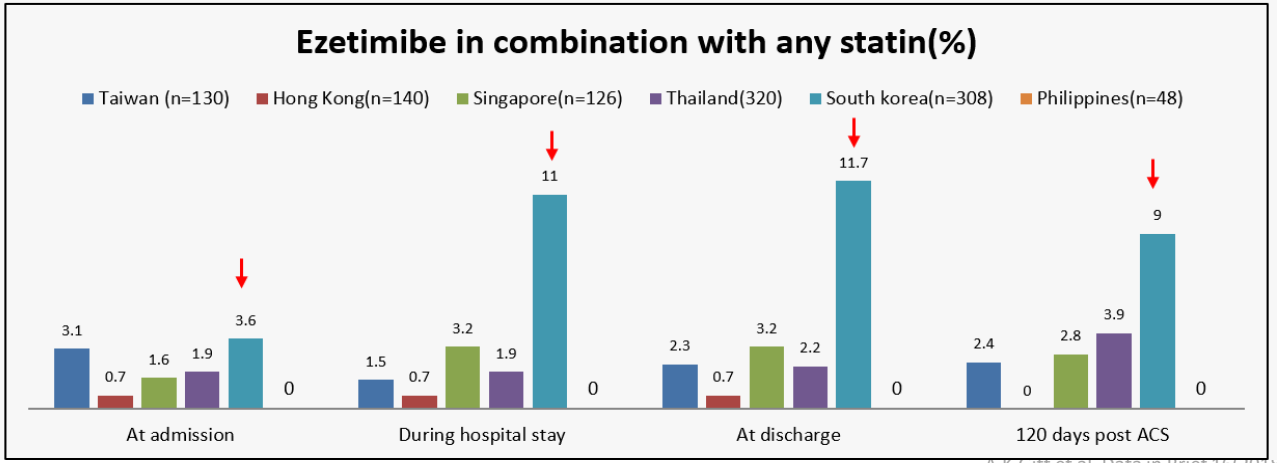


DYSIS II ACS: Use of lipid-lowering therapy in ACS – 4-Month Follow-up

- Filipinos receiving higher doses of atorvastatin / day



- Koreans receiving higher proportion of ezetimibe in combination with statin

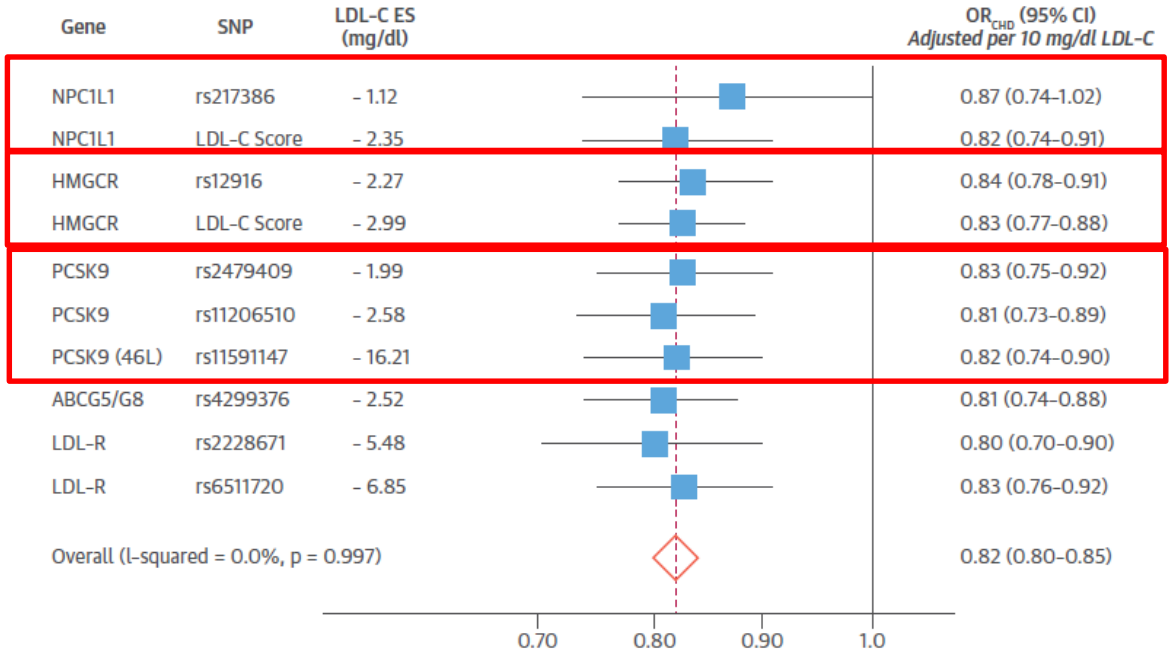


A.K.Gitt et al. Data in Brief 16(2018)369–375

Think beyond of statin monotherapy – powerful LDL-c reduction of ATOZET

Consistent Effect Per Unit Lower LDL-C on Risk of CHD

- Comparison of polymorphisms in genes that lower LDL-C through common final pathway of LDL receptor (*including PCSK9*) adjusted per unit lower LDL-C
- Up to 63,746 cases of CHD and 130,681 control subjects



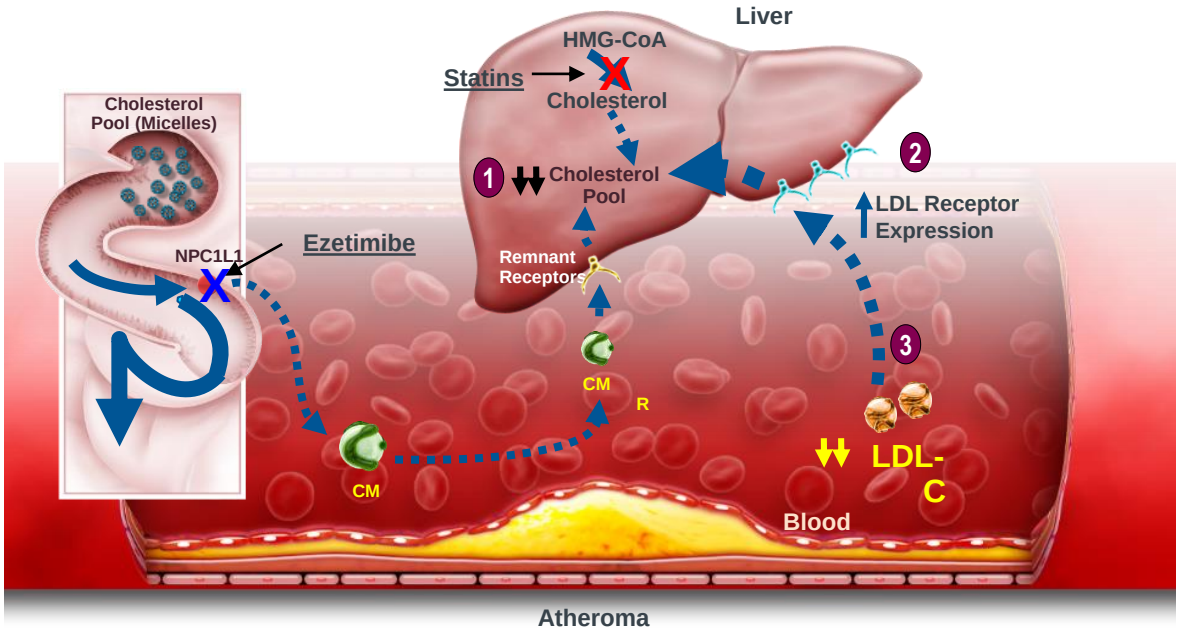
Ference, BA et al. J Am Coll Cardiol 2015;doi:10.1016/j.jacc.2015.02.020).

http://www.CARDIOGRAMPLUSC4D.org

Ezetimibe and Statins Have Complementary Mechanisms of Action[1]

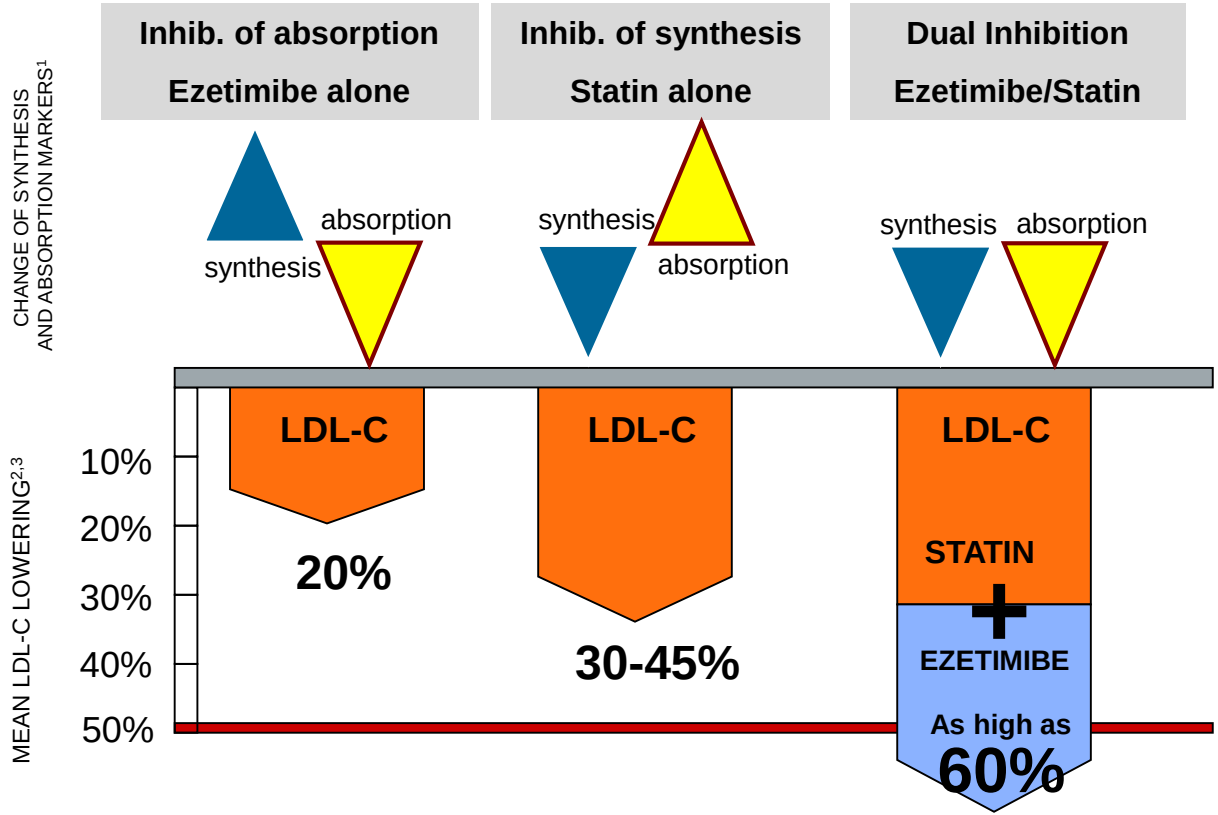
Together, ezetimibe in combination with a statin provides:

1. Reduction of hepatic cholesterol
2. Increased LDL receptor expression
3. Increased clearance of plasma LDL-C

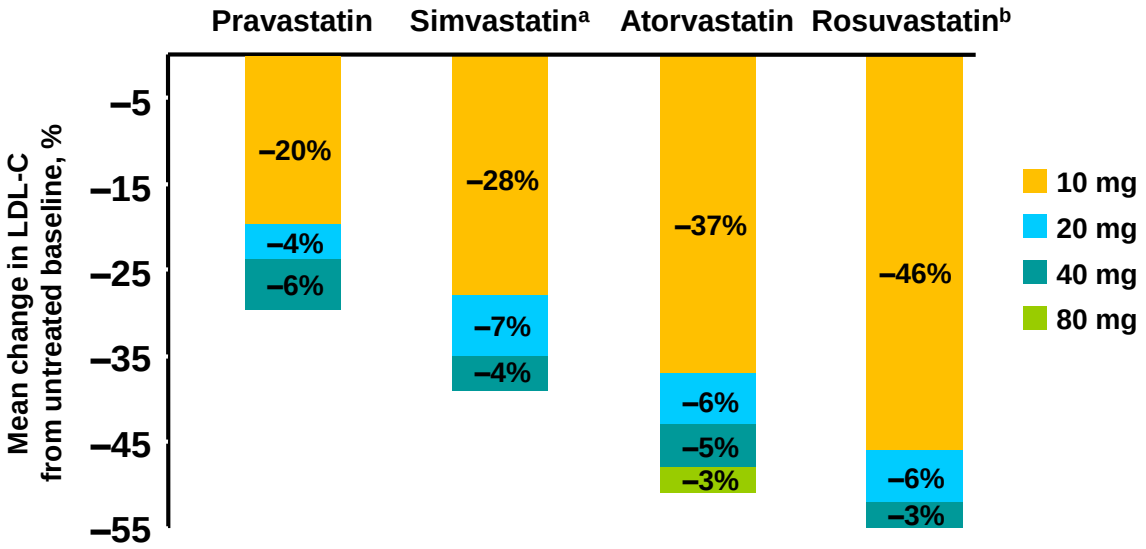


NPC1L1 = Niemann-Pick C1-like 1; HMG-CoA = 3-hydroxy-3-methylglutaryl acetyl coenzyme A; CMR = chylomicron remnant.

1. Grigore L et al. *Vas Health Risk Manag*. 2008;4:267–278.


Inhib. of absorption
Ezetimibe alone
Inhib. of synthesis
Statin alone
Dual Inhibition
Ezetimibe/Statin
CHANGE OF SYNTHESIS AND ABSORPTION MARKERS[1]
absorption
synthesis
synthesis
absorption
synthesis
absorption
MEAN LDL-C LOWERING[2,3]
10%
20%
30%
40%
50%
LDL-C
LDL-C
LDL-C
20%
30-45%
STATIN
+
EZETIMIBE
As high as
60%

STELLAR: LDL-C Reductions With Statin Monotherapy[1]



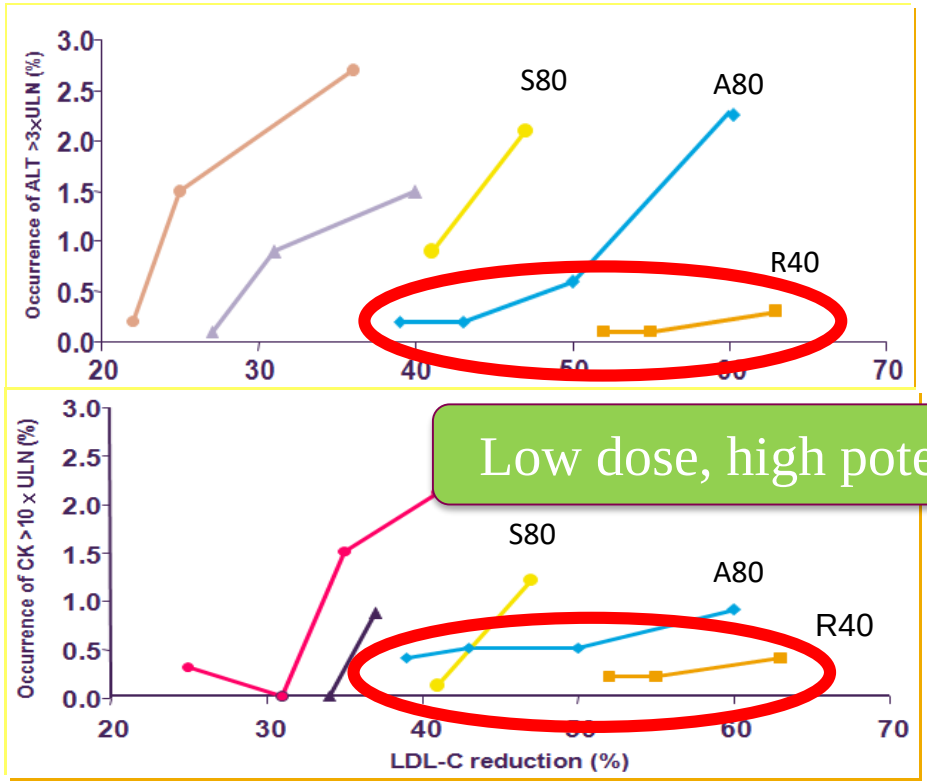
A 6-week, parallel group, open-label, randomized, multicenter study comparing LDL-reducing efficacy of rosuvastatin vs atorvastatin, simvastatin, and pravastatin across the dose ranges in adults with hypercholesterolemia (n=2,431; per dose group, n=156–167), after dietary lead-in.

STELLAR = Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin.

1. Jones PH et al. Am J Cardiol. 2003;92:152–160. **2.** MSD. Worldwide product circular. IPC–MK0733-T-102012.

Safety of Intensive-Dose Statin

Percentage changes in liver and muscle enzymes by percent LDL-C reduction[1]



Statin藥物不良反應發生率取決於藥物劑量，而非LDL-C efficacy

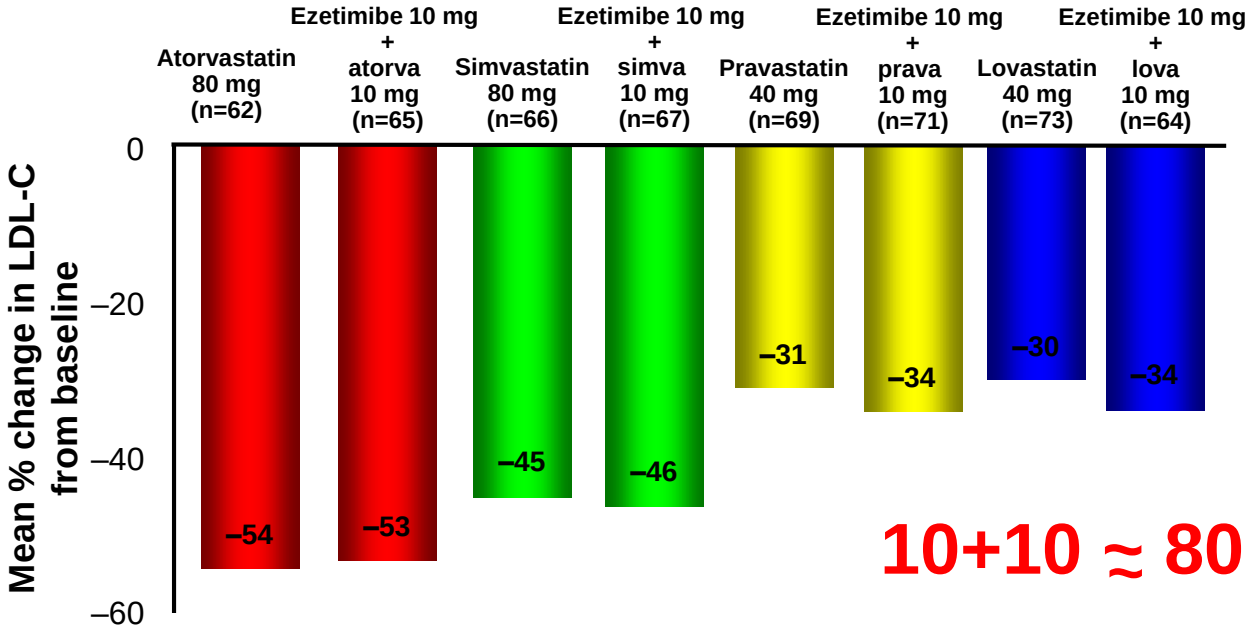
- Rosuvastatin (10, 20, 40 mg)
- Atorvastatin (10, 20, 40, 80 mg)
- Simvastatin (40, 80 mg)
- Lovastatin (20, 40, 80 mg)
- Fluvastatin (20, 40, 80 mg)

Low dose, high potency will be better

Reference:
1. Davidson MH, Expert Opin Drug Saf 2004; 3(6): 547-557.
2. Jones P et al. Am J Cardiol 2003; 92: 152-160.

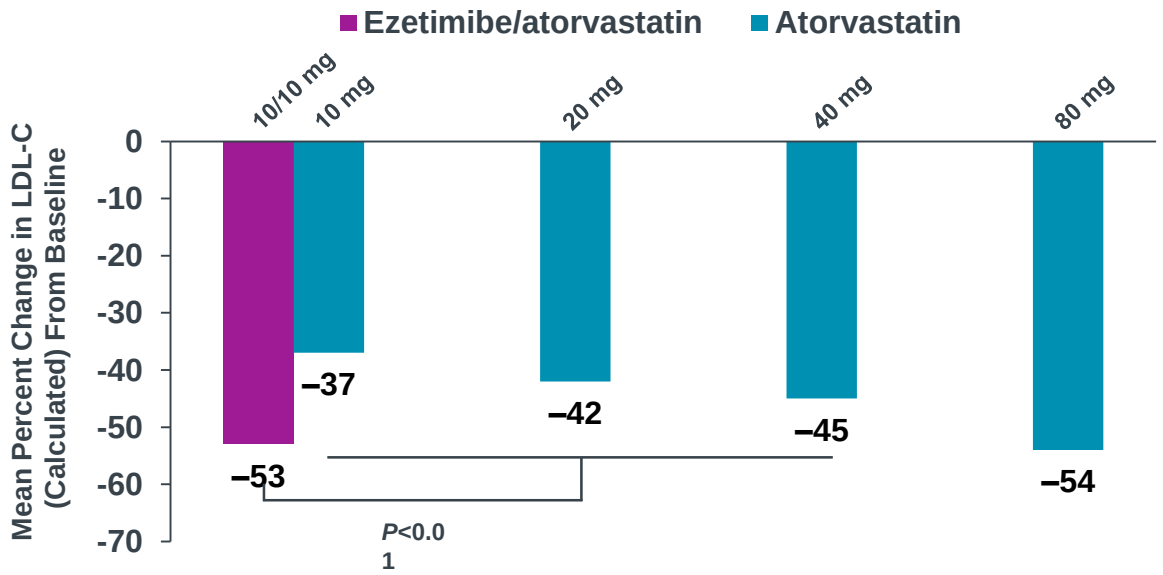
Rosuvastatin 40mg is not indicated in Taiwan.

Ezetimibe Co-administered with Statins versus High-Dose Statins



Ezetimibe 10 mg once daily together with the lowest statin dose reduced plasma LDL-C as much as or more than the highest dose tested of statin alone.

Ballantyne 2003: Ezetimibe/Atorvastatin 10/10 mg Provided Significantly Greater LDL-C Reduction Compared With Atorvastatin 10, 20, and 40 mg[1,2]



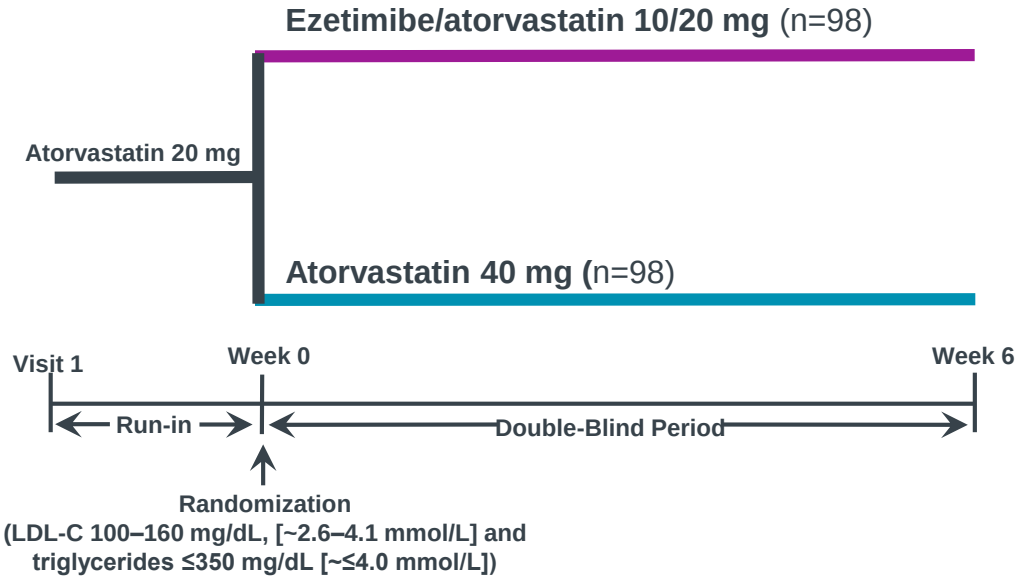
Mean baseline LDL-C was 182 mg/dL (~4.7 mmol/L) for ezetimibe/atorvastatin arms (n=255) and 181 mg/dL (~4.7 mmol/L) for atorvastatin arms (n=248).

Adapted with permission from Ballantyne CM et al.[1]

1. Ballantyne CM et al. *Circulation*. 2003;107:2409–2415.

TEMPO: Ezetimibe/Atorvastatin 10/20 mg vs Doubling Atorvastatin Dose to 40 mg (Study Design)[1]

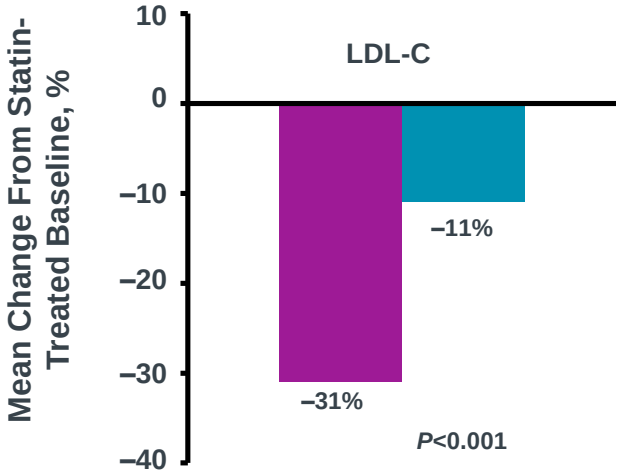
Patients with hypercholesterolemia at moderately high risk of CHD (based on NCEP ATP III criteria)



CHD = coronary heart disease; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III.

1. Conard SE et al. *Am J Cardiol*. 2008;102:1489–1494.

TEMPO: Ezetimibe/Atorvastatin 10/20 mg Provided Greater Additional LDL-C Reduction vs Doubling Atorvastatin Dose to 40 mg[1]



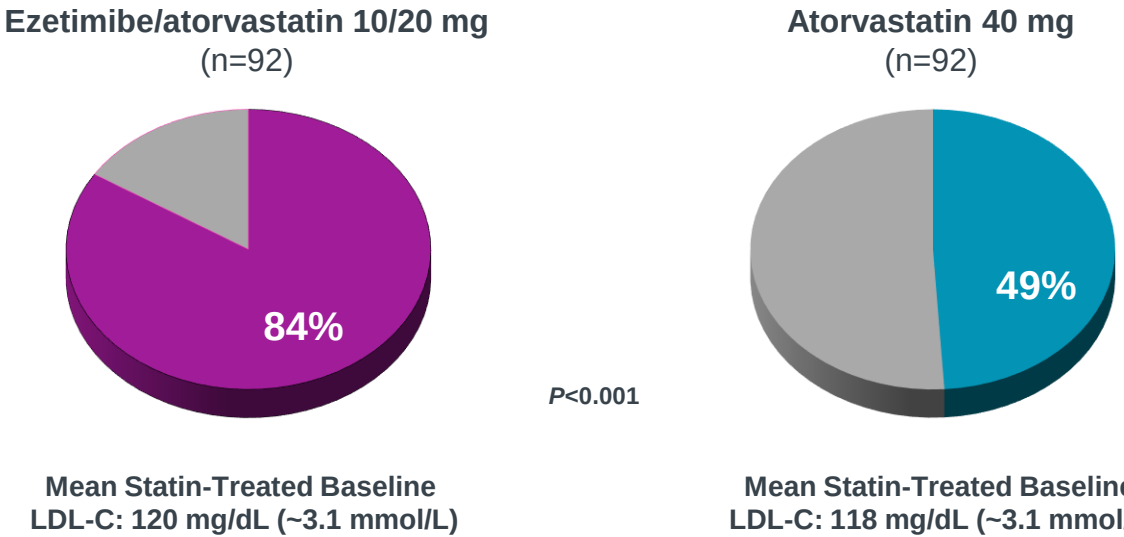
Ezetimibe/atorvastatin 10/20 mg (n=92)
(mean on-statin baseline LDL-C = 120 mg/dL, ~3.1 mmol/L)

Atorvastatin 20 mg titrated to 40 mg (n=92)
(mean on-statin baseline LDL-C = 118 mg/dL, ~3.1 mmol/L)

1. Conard SE et al. *Am J Cardiol*. 2008;102:1489–1494.

TEMPO: Greater Percentage of Patients Reached LDL-C <100 mg/dL With Ezetimibe/Atorvastatin 10/20 mg vs Doubling Atorvastatin Dose to 40 mg[1]

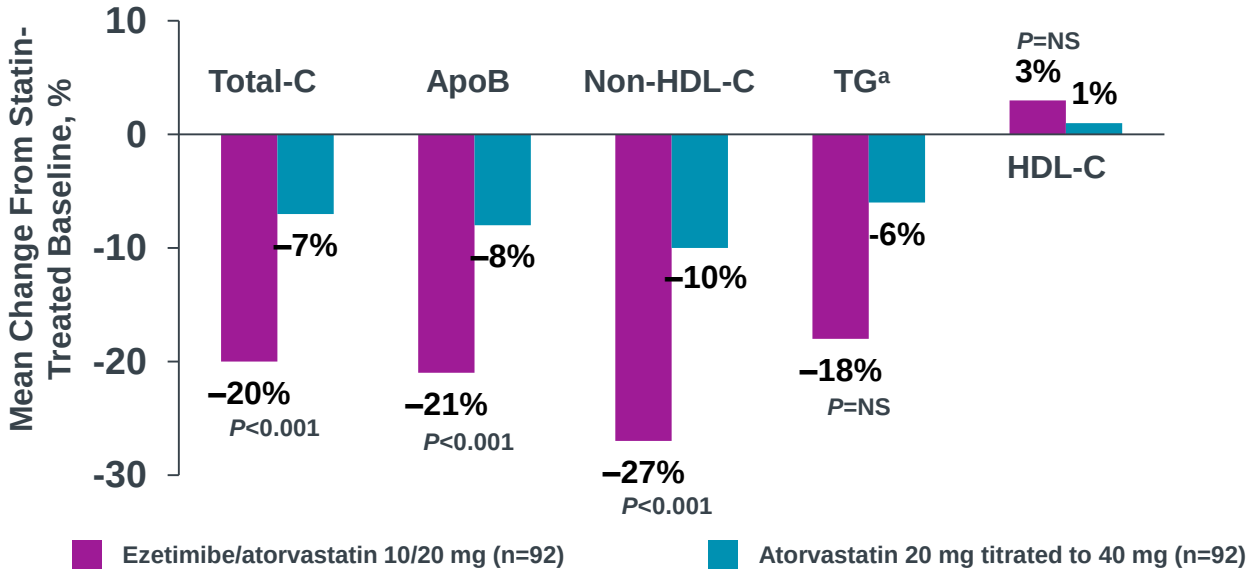
Patients Reaching LDL-C <100 mg/dL (~2.6 mmol/L), at 6 weeks, as a Result of Greater LDL-C Reduction



The mean decrease in LDL-C from statin-treated baseline was 31% with ezetimibe/atorvastatin 10/20 mg compared with 11% with atorvastatin 40 mg; *P*<0.001.

1. Conard SE et al. *Am J Cardiol*. 2008;102:1489–1494.

TEMPO: Effect on Multiple Lipid Parameters[1]

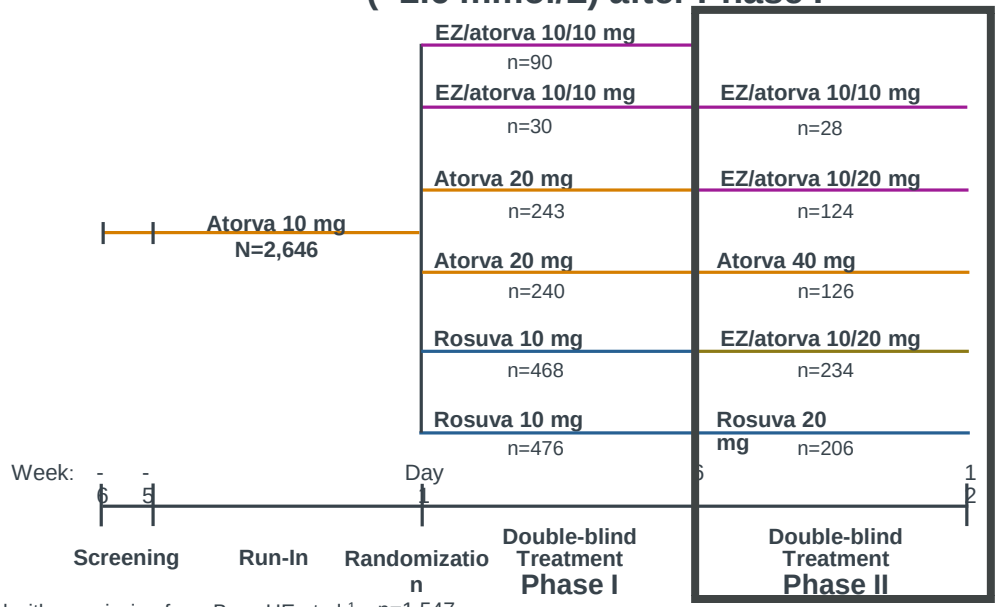


[a]Median change from statin-treated baseline.
NS = not significant.

1. Conard SE et al. *Am J Cardiol*. 2008;102:1489–1494.

PACE: Efficacy of Ezetimibe/Atorvastatin vs Atorvastatin Uptitration or Switching to Rosuvastatin (Study Design)[1]

High-risk patients[a] with hypercholesterolemia not at LDL-C <100 mg/dL (~2.6 mmol/L) after Phase I



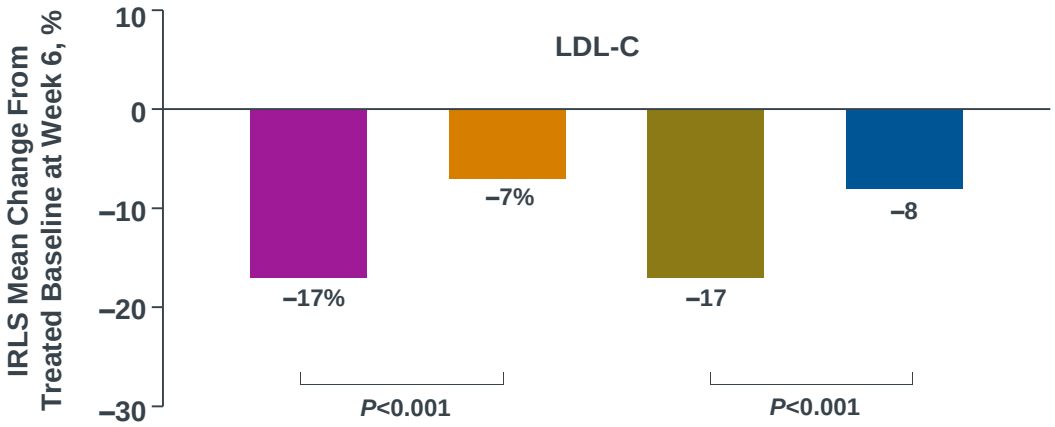
Adapted with permission from Bays HE et al.[1]

[a]High risk of CHD was defined as: 1) subjects without CVD who had type 2 diabetes, or ≥2 risk factors and a 10-year risk for CHD >20% as determined by the Framingham calculation, or 2) subjects with CVD, including established coronary or other atherosclerotic vascular disease.

PACE = a randomized, double-blind, active-controlled, multicenter study of patients with **P**rimary hypercholesterolemia and high cardiovascular risk who are not adequately controlled with **A**torvastatin 10 mg: a **C**omparison of the efficacy and safety of switching to coadministration **E**zetimibe and atorvastatin versus doubling the dose of atorvastatin or switching to rosuvastatin;
EZ = ezetimibe; Atorva = atorvastatin; Rosuva = rosuvastatin; CHD = coronary heart disease; CVD = cardiovascular disease.

1. Bays HE et al. *Am J Cardiol*. 2013;112:1885–1895.

PACE Phase II: Greater Additional LDL-C Reduction With Ezetimibe/Atorvastatin 10/20 mg[1]



Switching from atorvastatin 20 mg to ezetimibe/atorvastatin 10/20 mg (n=124) Mean on-statin baseline LDL-C = 119 mg/dL (~3.1 mmol/L)

Doubling atorvastatin to 40 mg (n=124) Mean on-statin baseline LDL-C = 121 mg/dL (~3.1 mmol/L)

Switching from rosuvastatin 10 mg to ezetimibe/atorvastatin 10/20 mg (n=231) Mean on-statin baseline LDL-C = 119 mg/dL (~3.1 mmol/L)

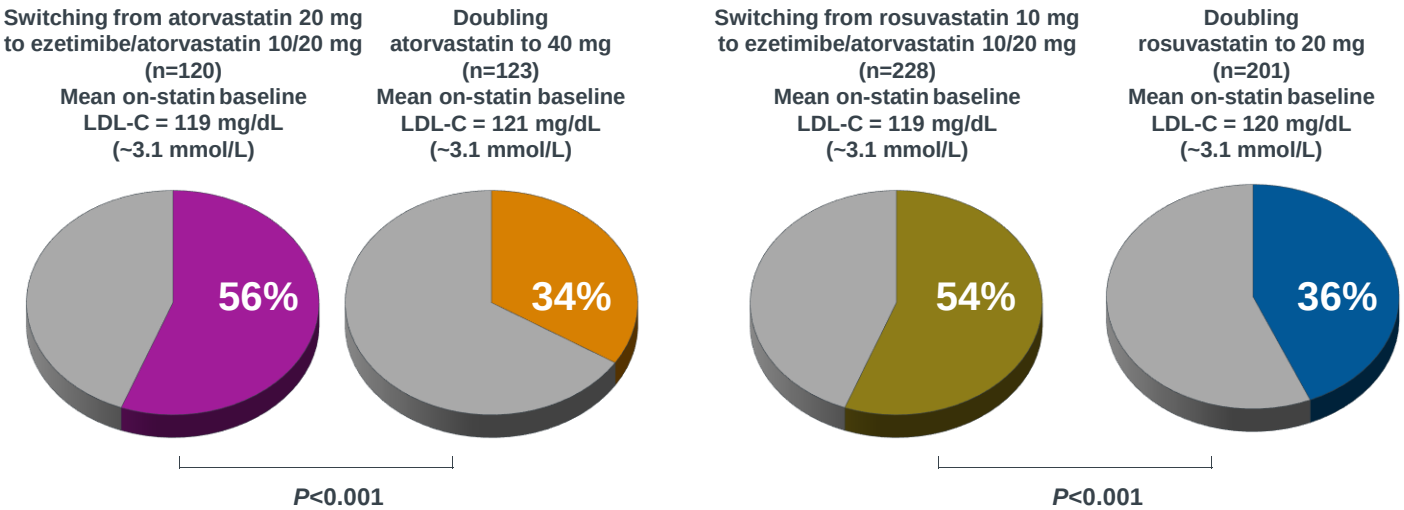
Doubling rosuvastatin to 20 mg (n=205) Mean on-statin baseline LDL-C = 120 mg/dL (~3.1 mmol/L)

IRLS = iteratively reweighted least squares.

1. Bays HE et al. *Am J Cardiol*. 2013;112:1885–1895.

PACE Phase II: Greater Attainment of LDL-C <100 mg/dL With Ezetimibe/Atorvastatin 10/20 mg[1]

High-risk Patients Reaching LDL-C <100 mg/dL (~2.6 mmol/L) as a Result of Greater LDL-C Reduction



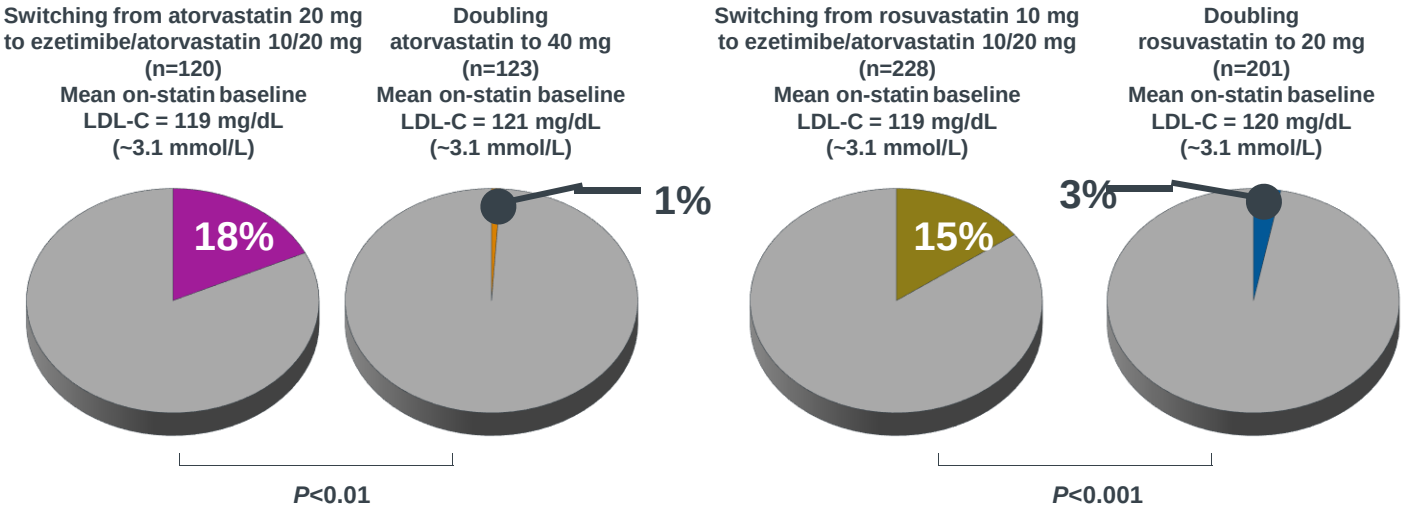
The IRLS mean decrease in LDL-C from statin-treated baseline was 17% with ezetimibe/atorvastatin 10/20 mg compared with 7% with doubling atorvastatin to 40 mg and 17% with ezetimibe/atorvastatin 10/20 mg compared with 8% with doubling rosuvastatin to 20 mg; *P*<0.001 for each comparison.

IRLS = iteratively reweighted least squares.

1. Bays HE et al. *Am J Cardiol*. 2013;112:1885–1895.

PACE Phase II: Greater Attainment of LDL-C <70 mg/dL With Ezetimibe/Atorvastatin 10/20 mg[1]

High-risk Patients Reaching LDL-C <70 mg/dL (~1.8 mmol/L) as a Result of Greater LDL-C Reduction



The IRLS mean decrease in LDL-C from statin-treated baseline was 17% with ezetimibe/atorvastatin 10/20 mg compared with 7% with doubling atorvastatin to 40 mg and 17% with ezetimibe/atorvastatin 10/20 mg compared with 8% with doubling rosuvastatin to 20 mg; *P*<0.001 for each comparison.

IRLS = iteratively reweighted least squares.

1. Bays HE et al. *Am J Cardiol*. 2013;112:1885–1895.

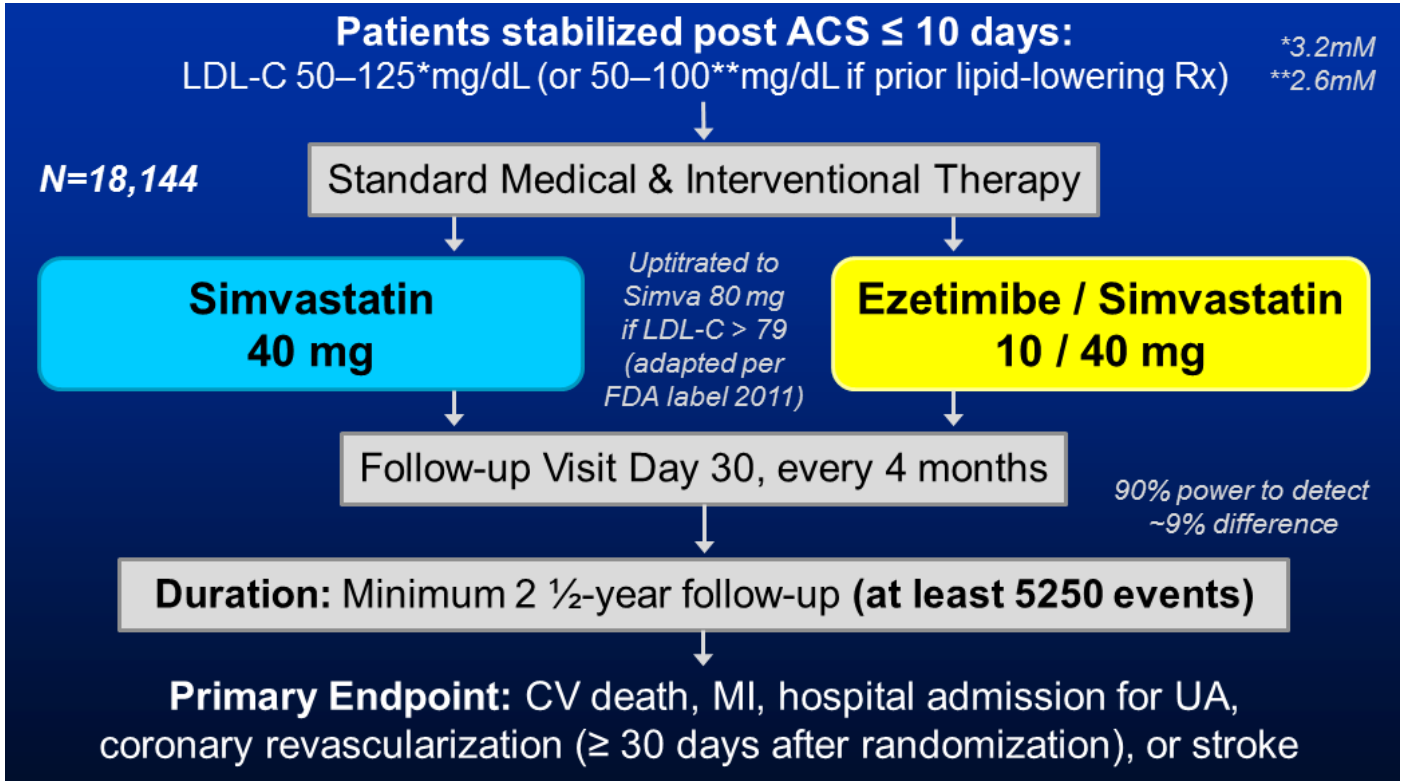
The evidences of ezetimibe in CVD risk reduction in ACS and high risk patients

IMPROVE-IT

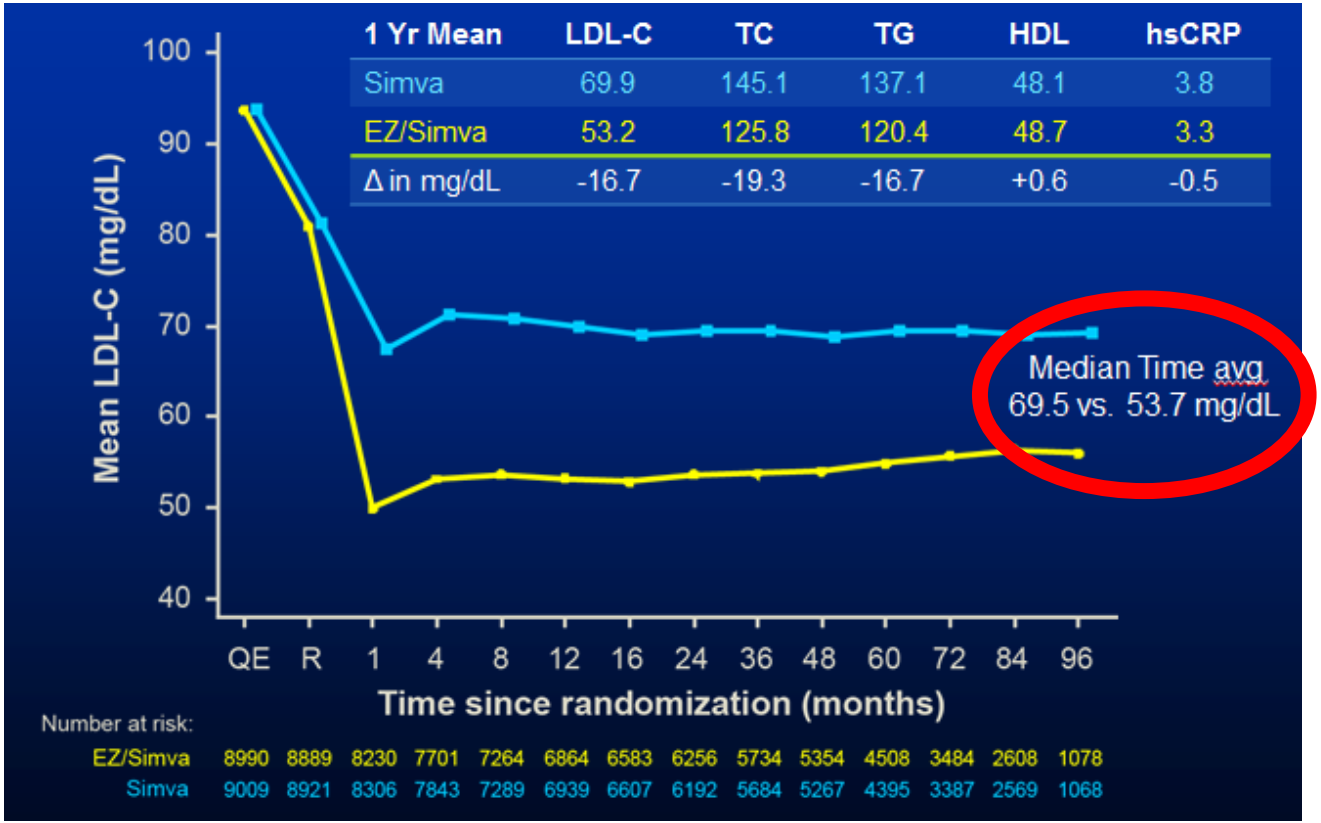
IMProved Reduction of Outcomes: Vytorin Efficacy International Trial

A Multicenter, Double-Blind, Randomized Study to Establish the Clinical Benefit and Safety of Vytorin (Ezetimibe/Simvastatin Tablet) vs Simvastatin Monotherapy in High-Risk Subjects Presenting With Acute Coronary Syndrome

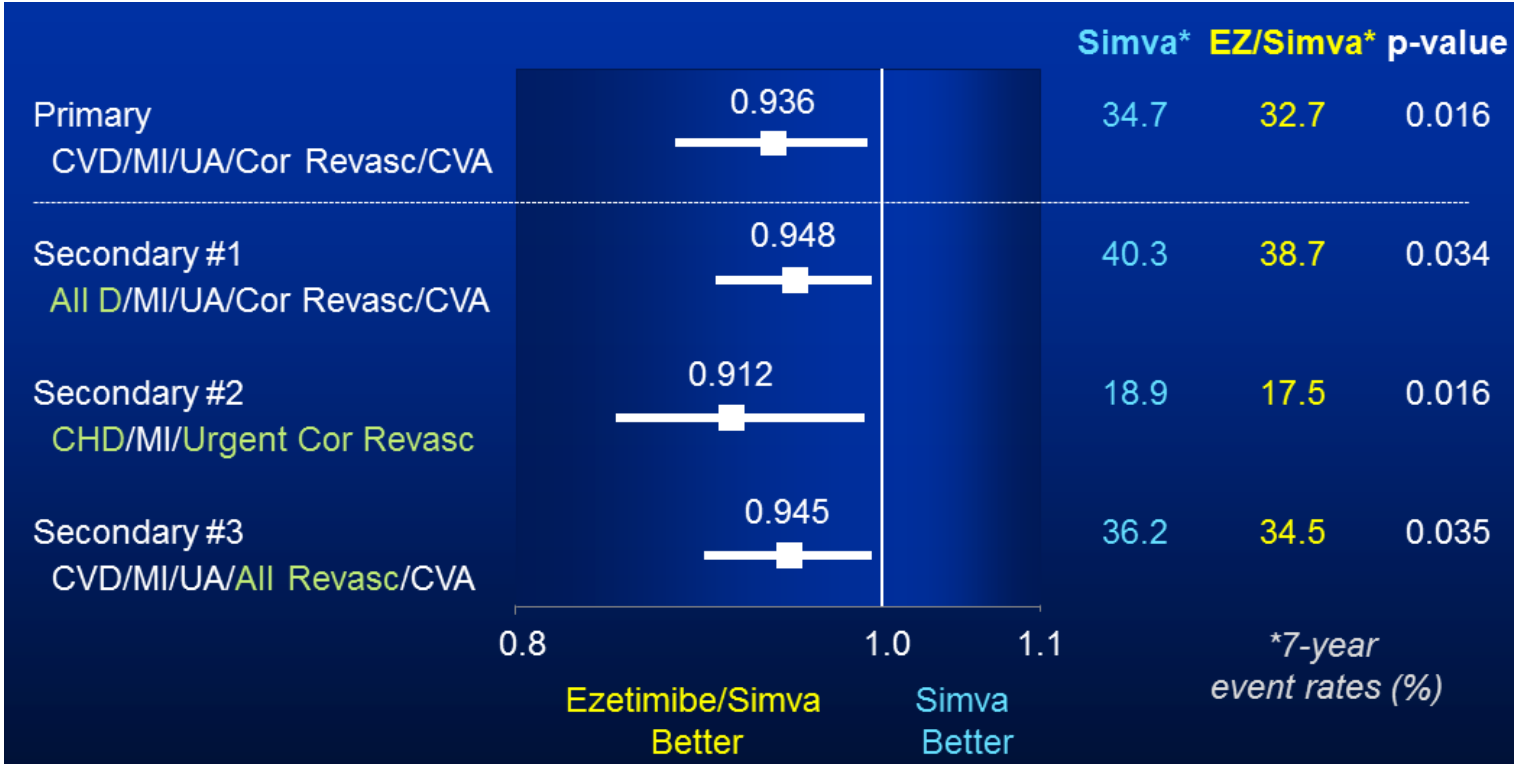
Study design



LDL-C & lipid changes

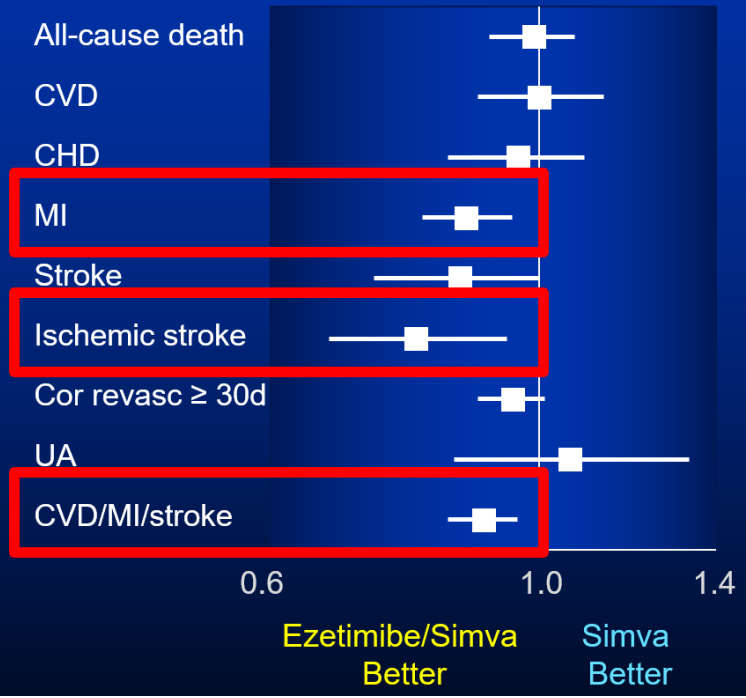


Primary and 3 Prespecified Secondary Endpoints — ITT



Individual Cardiovascular Endpoints and CVD/MI/Stroke

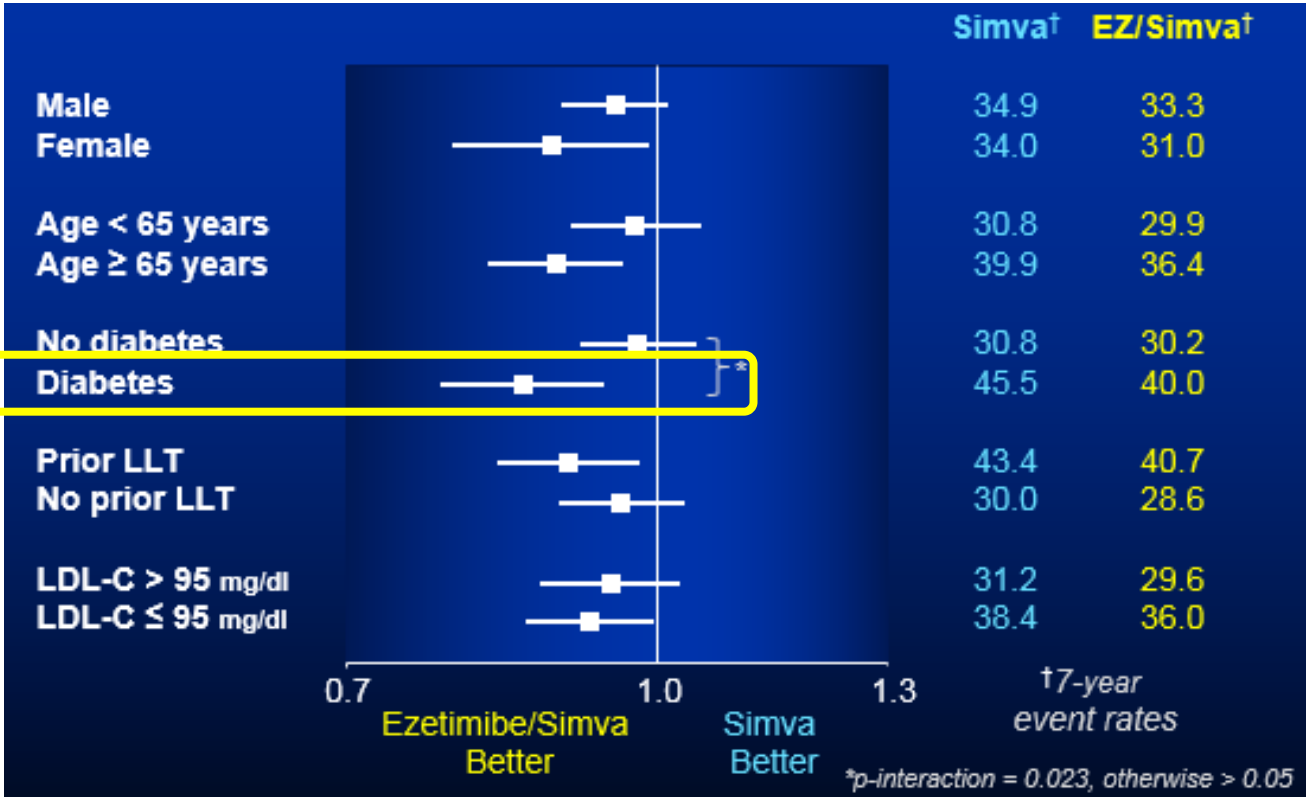
IMPROVE-IT



	HR	Simva*	EZ/Simva*	p-value
All-cause death	0.99	15.3	15.4	0.782
CVD	1.00	6.8	6.9	0.997
CHD	0.96	5.8	5.7	0.499
MI	0.87	14.8	13.1	0.002
Stroke	0.86	4.8	4.2	0.052
Ischemic stroke	0.79	4.1	3.4	0.008
Cor revasc ≥ 30d	0.95	23.4	21.8	0.107
UA	1.06	1.9	2.1	0.618
CVD/MI/stroke	0.90	22.2	20.4	0.003

7-year event rates (%)

Major Pre-specified Subgroups



Safety — ITT

IMPROVE-IT

No statistically significant differences in cancer or muscle- or gallbladder-related events

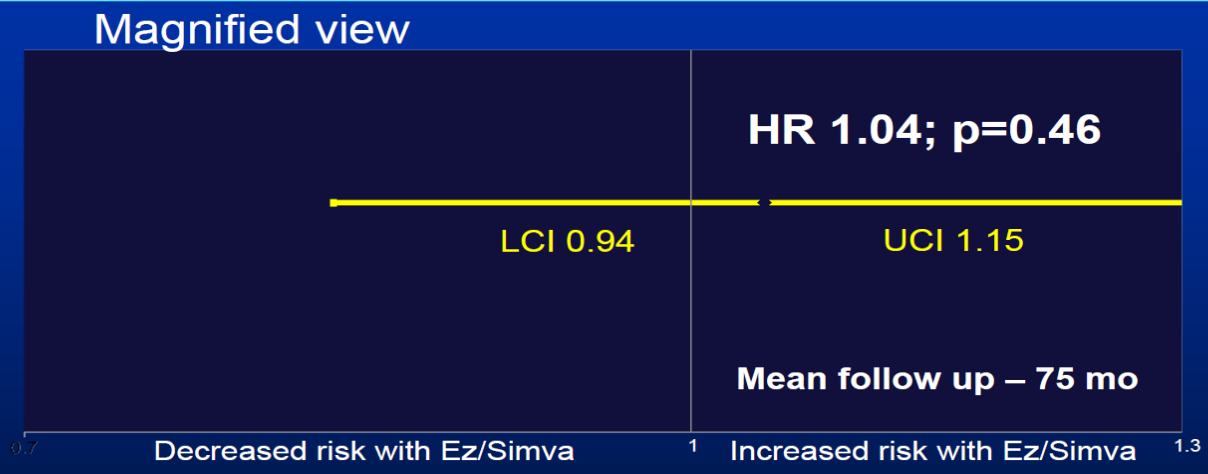
	Simva n=9077 %	EZ/Simva n=9067 %	p
ALT and/or AST≥3x ULN	2.3	2.5	0.43
Cholecystectomy	1.5	1.5	0.96
Gallbladder-related AEs	3.5	3.1	0.10
Rhabdomyolysis*	0.2	0.1	0.37
Myopathy*	0.1	0.2	0.32
Rhabdo, myopathy, myalgia with CK elevation*	0.6	0.6	0.64
Cancer* (7-yr KM %)	10.2	10.2	0.57

** Adjudicated by Clinical Events Committee*

% = n/N for the trial duration

Primary outcome - NODM

IMPROVE-IT



1,414 (13.3%) patients with NODM

EZ/S = 720 **S = 694**

NODM = antihyperglycemic med and/or 2 fasting glucoses ≥ 7 mmol/L

Treatment Differences in Lipids and hs-CRP During the Trial

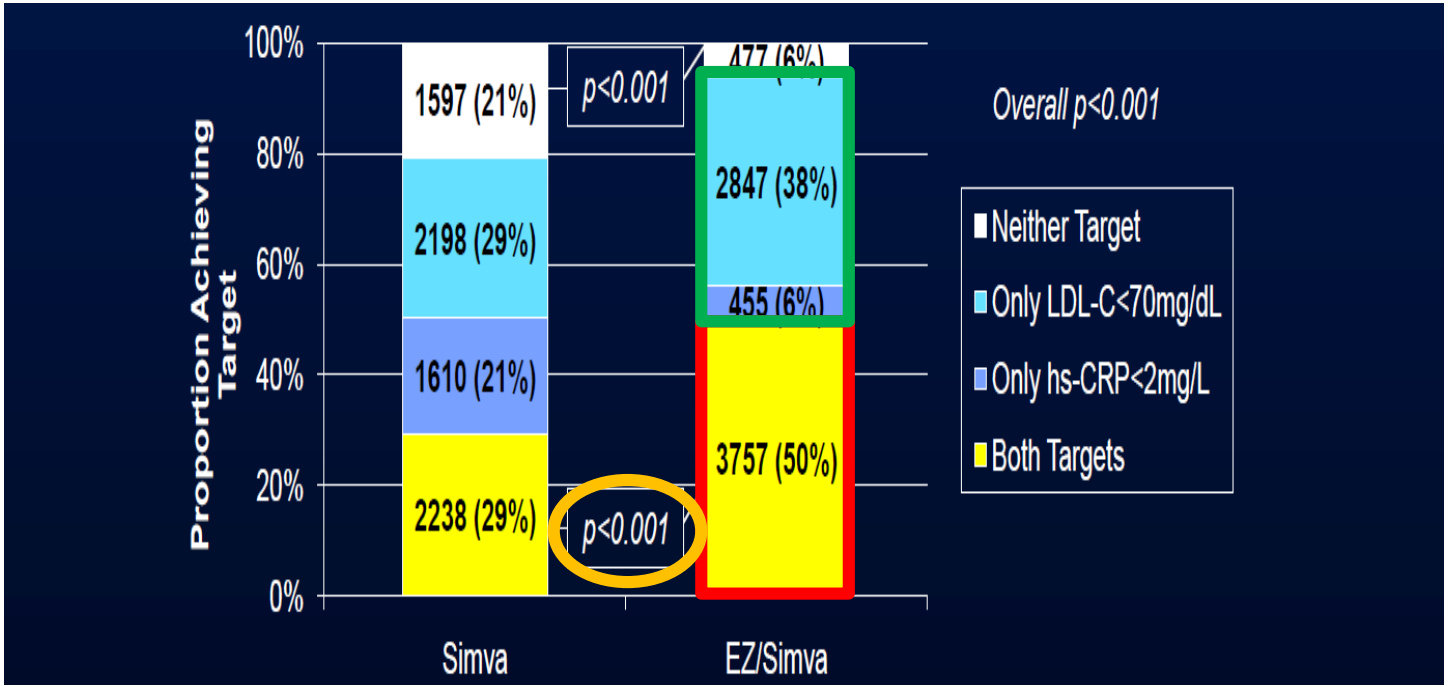
IMPROVE-IT

Placebo-adjusted differences between treatments in the changes from baseline* to the time-weighted average during the trial†

Parameter	No Diabetes (ΔE/S – ΔP/S)	DM Present (ΔE/S – ΔP/S)	P_{int}
LDL-C	**-0.37 mM/L**	**-0.43 mM/L**	**0.03**
Triglycerides	-0.09 mM/L	-0.13 mM/L	0.59
HDL-C	+0.013 mM/L	+0.008 mM/L	0.30
hs-CRP*	**-0.05 mg/L**	**-1.09 mg/L**	**0.03**

* baseline hs-CRP at randomization; baseline lipids obtained at admission
† from month 1 to end of trial

Pre-specified LDL-C and hs-CRP target achievement at 1 month by randomized treatment



IMPROVE-IT study (LDL 70 vs 54)

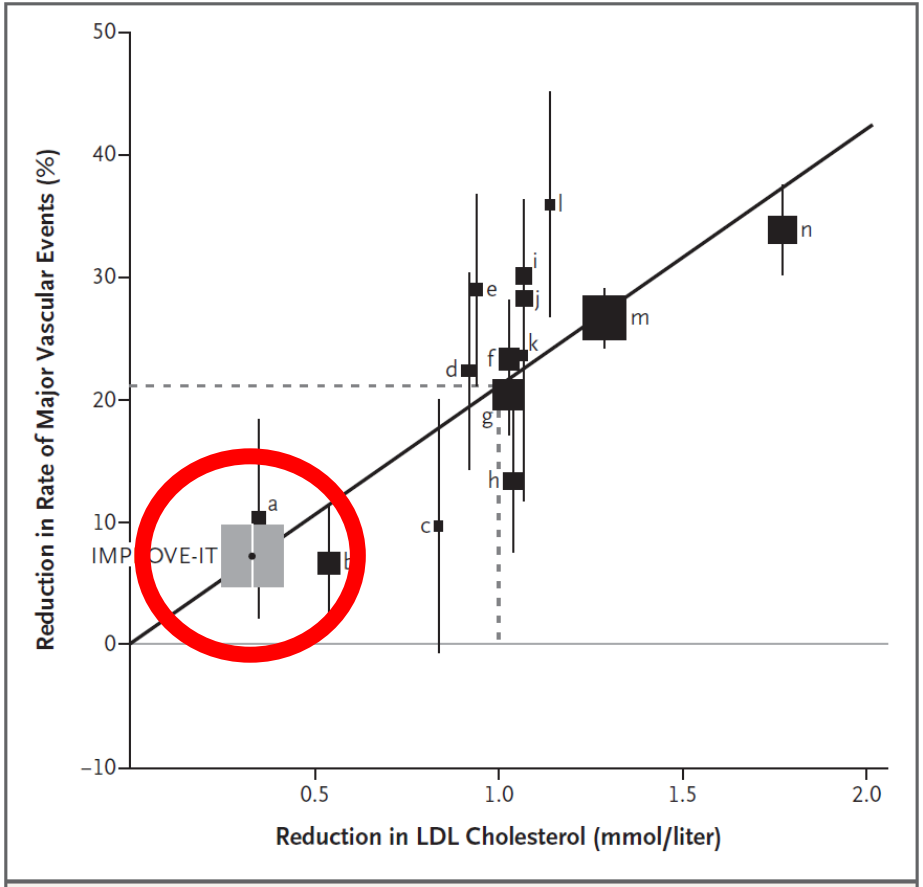


Figure 2. Plot of the IMPROVE-IT Trial Data and Statin Trials for Change in Low-Density Lipoprotein (LDL) Cholesterol versus Clinical Benefit.

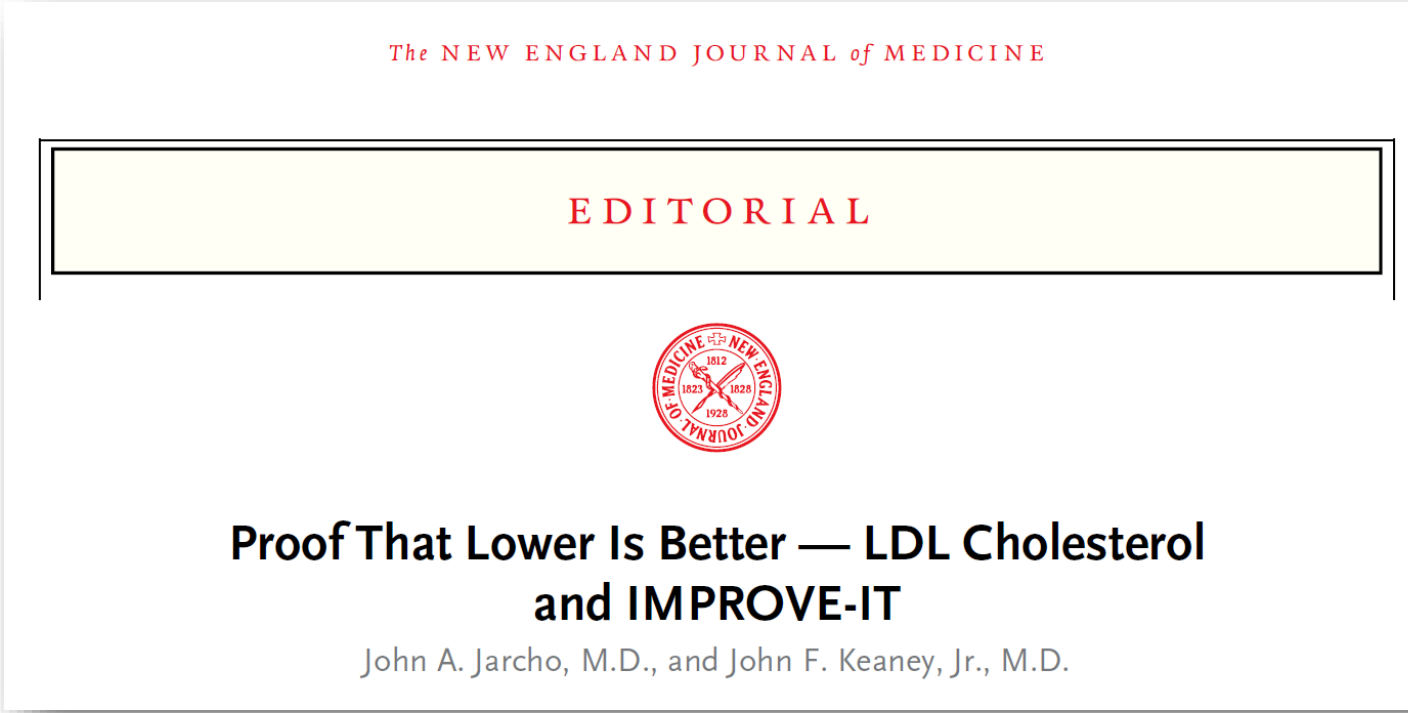
N Engl J Med. 2015 Jun 3. [Epub ahead of print]

IMPROVE-IT study Conclusions

- **IMPROVE-IT:** First trial demonstrating incremental clinical benefit when adding a non-statin agent (ezetimibe) to statin therapy:
  - **YES:** *Non-statin* lowering LDL-C with ezetimibe reduces cardiovascular events
  - **YES:** Even Lower is Even Better (achieved mean LDL-C 54 vs. 70 mg/dL at 1 year)
  - **YES:** Confirms ezetimibe safety profile

- **Reaffirms the LDL hypothesis,** that reducing LDL-C prevents cardiovascular events

- Results could be considered for future guidelines



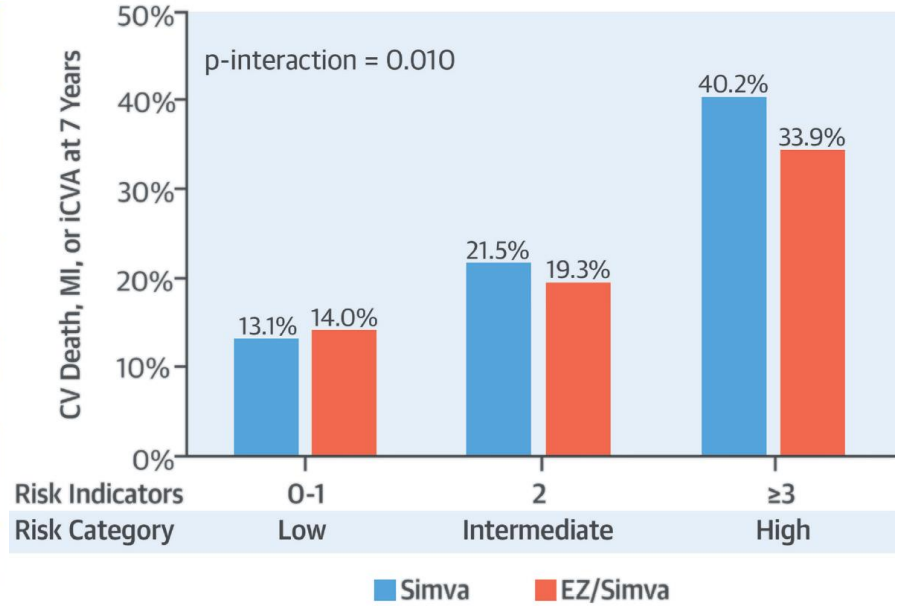
- Perhaps the **LDL hypothesis** should now be considered the **"LDL principle"**.

N Engl J Med. 2015 Jun 3. [Epub ahead of print]

Atherothrombotic Risk Stratification and Ezetimibe for Secondary Prevention

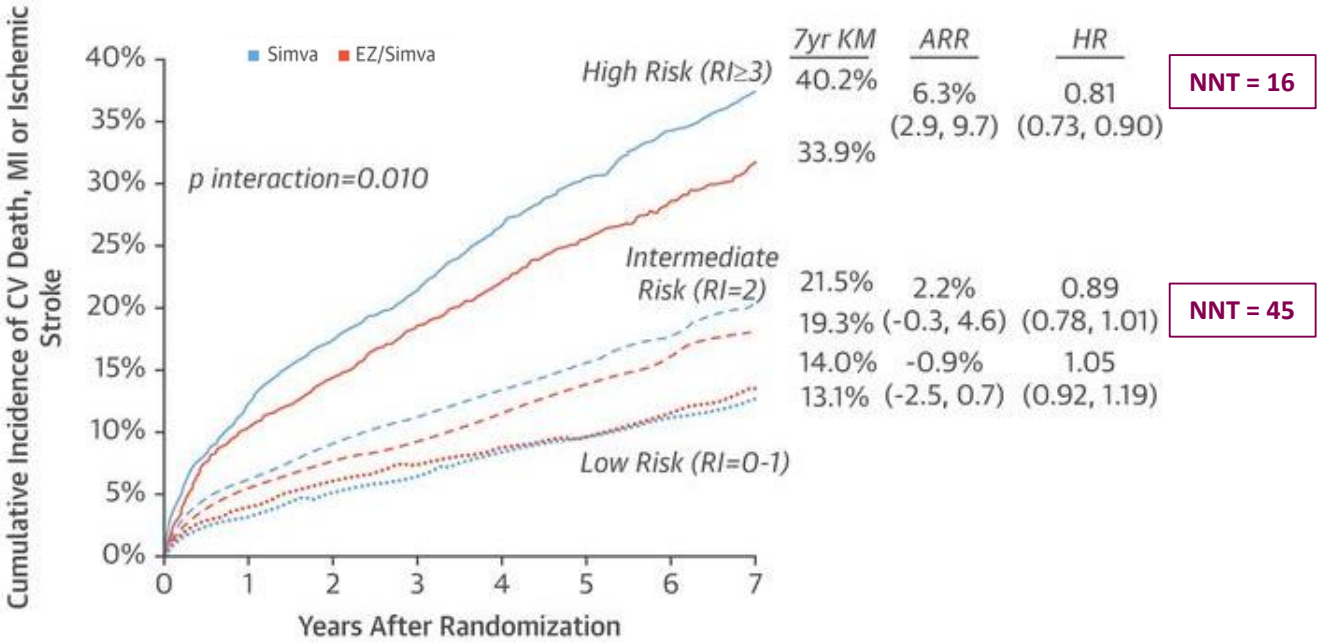
Ezetimibe add-on showed more benefit on patients with higher risk

TRS 2°P Risk Indicators	Points
CHF	1
HTN	1
Age ≥75	1
DM	1
Prior Stroke	1
Prior CABG	1
PAD	1
eGFR <60	1
Smoking	1
Maximum Possible	9



J Am Coll Cardiol 2017;69:911–21

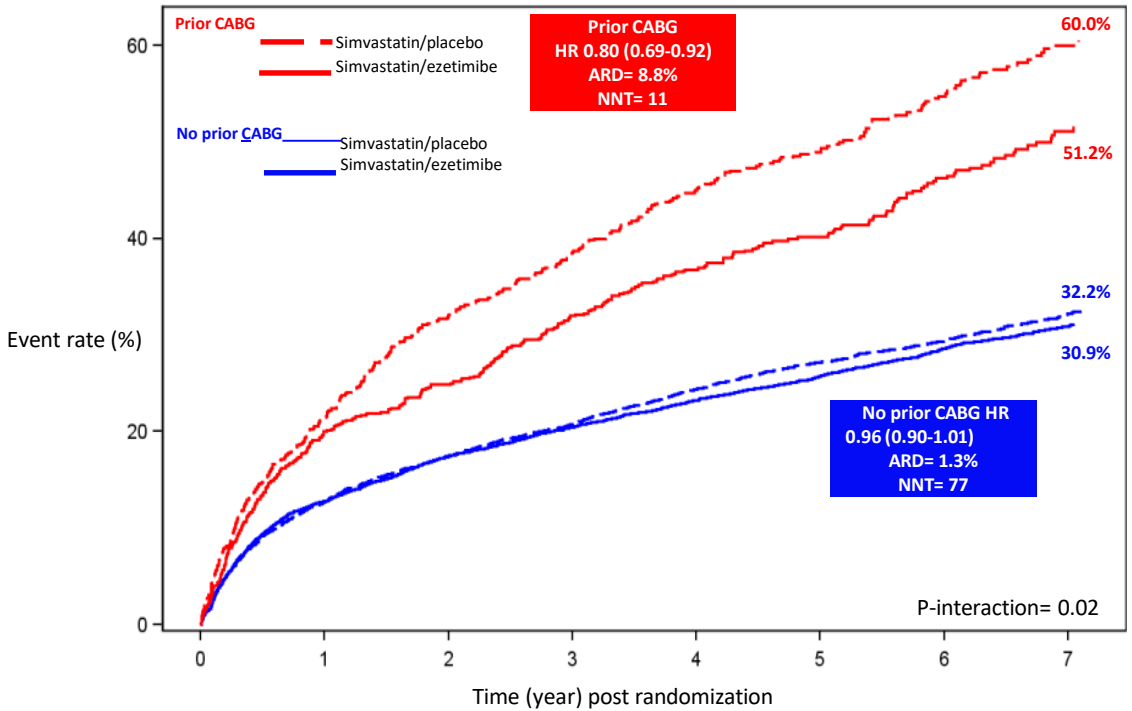
The use of more intensive lipid lowering therapy with ezetimibe add on to statin in higher risk patients showed more CV risk reduction



*Nine independent risk indicators (1 point per indicator): age≥75 yrs, diabetes, hypertension, current smoking, peripheral artery disease, prior stroke, prior coronary artery bypass grafting, history of heart failure, and renal dysfunction (eGFR<60 ml/min/1.73m²).

J Am Coll Cardiol 2017;69:911–21

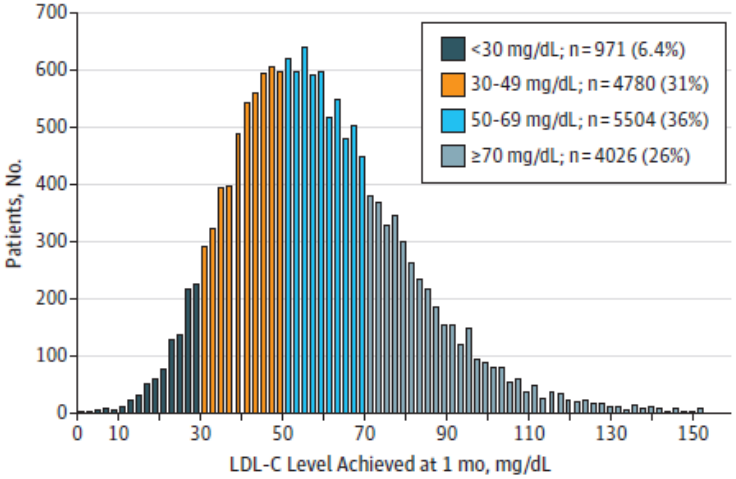
Primary endpoint: Prior CABG or not

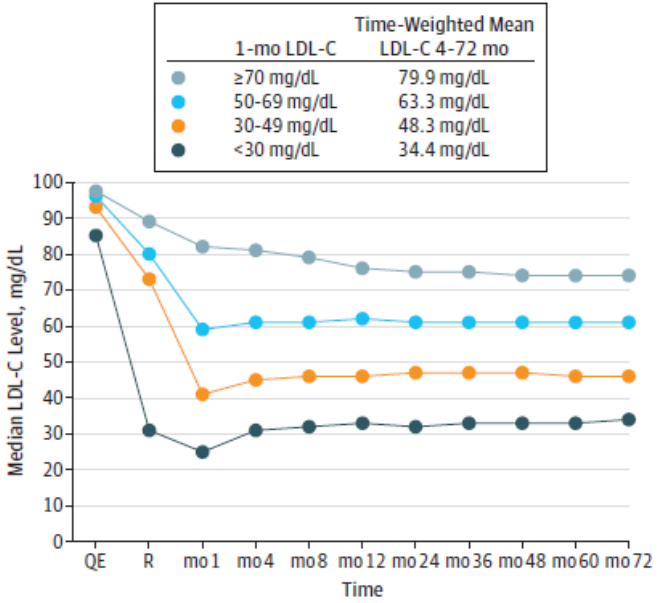


Eur Heart J 2016 - Early Online - Aug 28, 2016

Long-term Safety and Efficacy of Achieving Very Low Levels of Low-Density Lipoprotein Cholesterol

A Prespecified Analysis of the IMPROVE-IT Trial

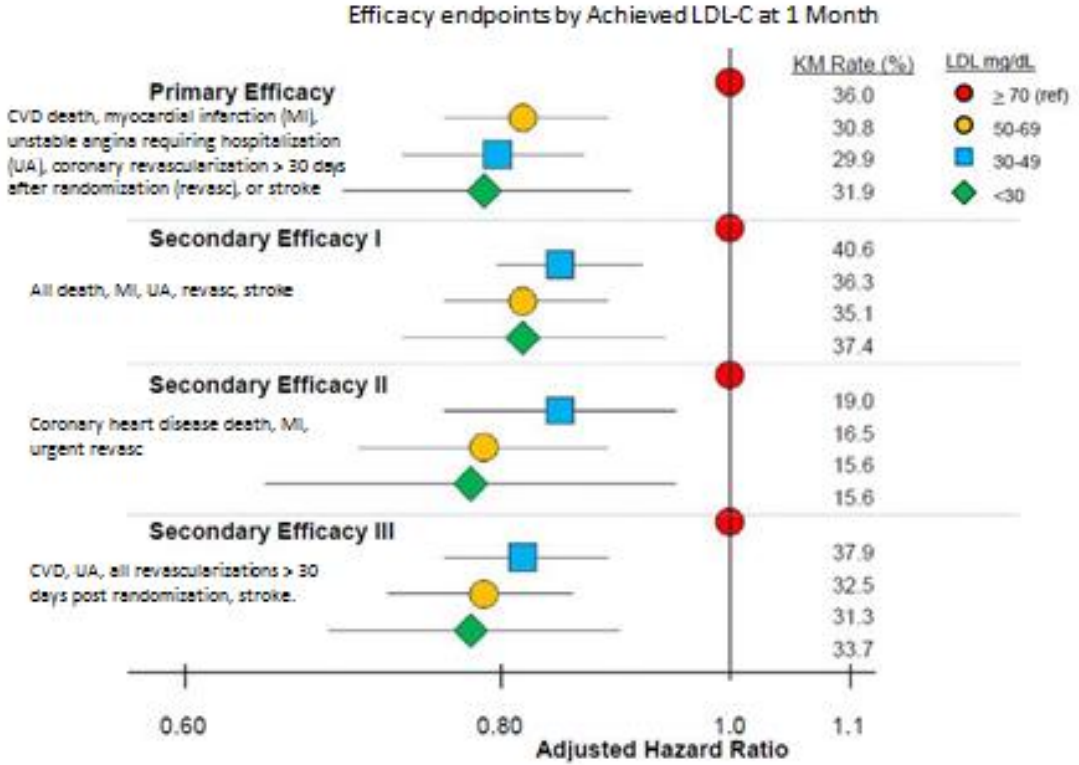




JAMA Cardiol. 2017;2(5):547-555.

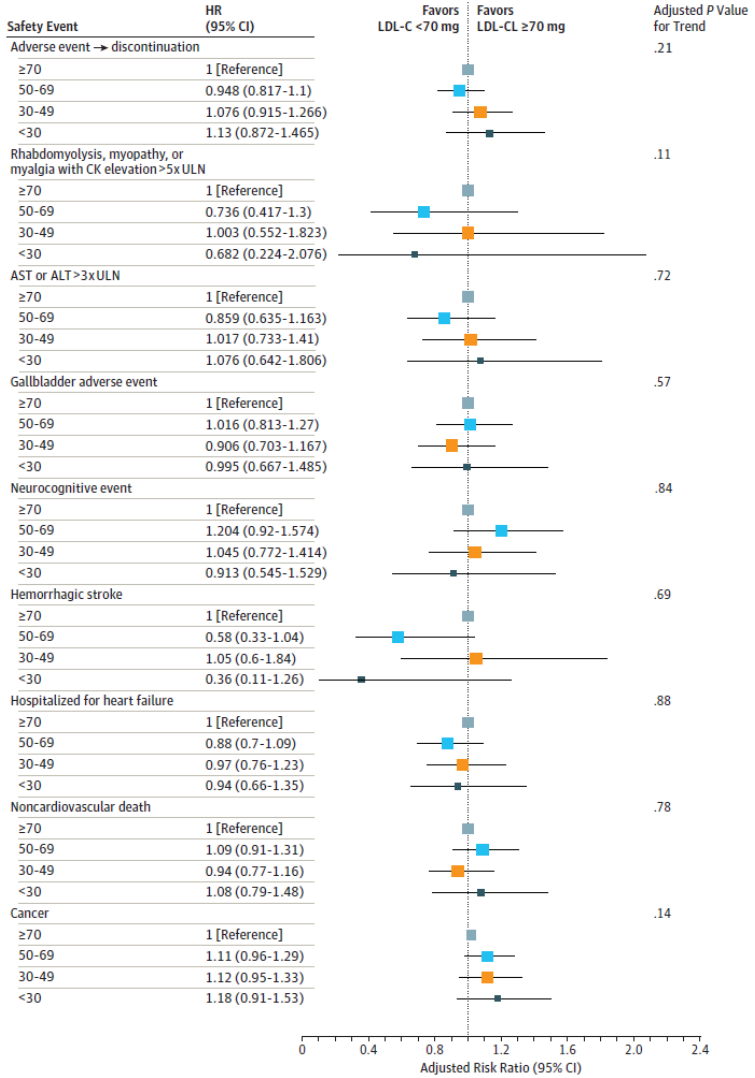
Long-term Safety and Efficacy of Achieving Very Low Levels of Low-Density Lipoprotein Cholesterol

A Prespecified Analysis of the IMPROVE-IT Trial



JAMA Cardiol. 2017;2(5):547-555.

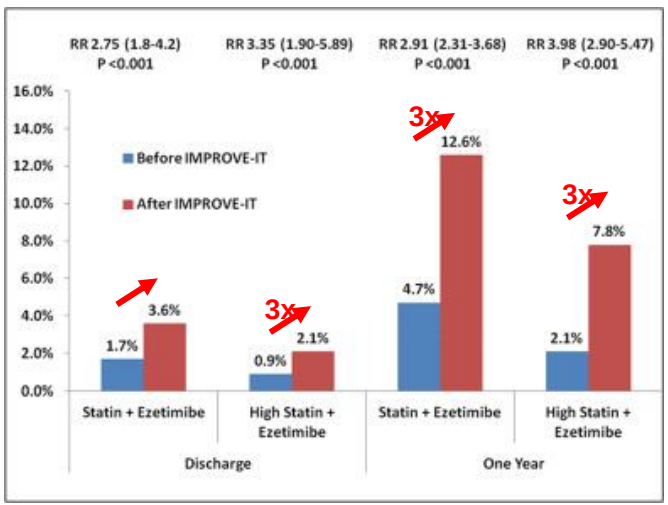
Safety Events by Achieved Low-Density Lipoprotein Cholesterol (LDL-C) Level at 1 Month In MPROVE-IT

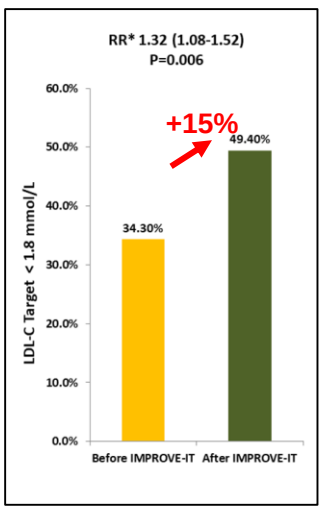


JAMA Cardiol. 2017;2(5):547-555.

After the publication of the IMPROVE-IT trial, the use of ezetimibe was increased by three-fold in a large contemporary cohort of ACS patients, concomitant with an improved LDL-C target achievement

- A prospective Swiss cohort of 6266 patients hospitalized for ACS between 2009 and 2017 with a one year follow-up.
- The primary endpoints were the ezetimibe use overall or in combination with high-intensity statin at discharge and at one year after ACS.
- Secondary endpoint was LDL-C target achievement at one year in a subsample of 2984 patients.



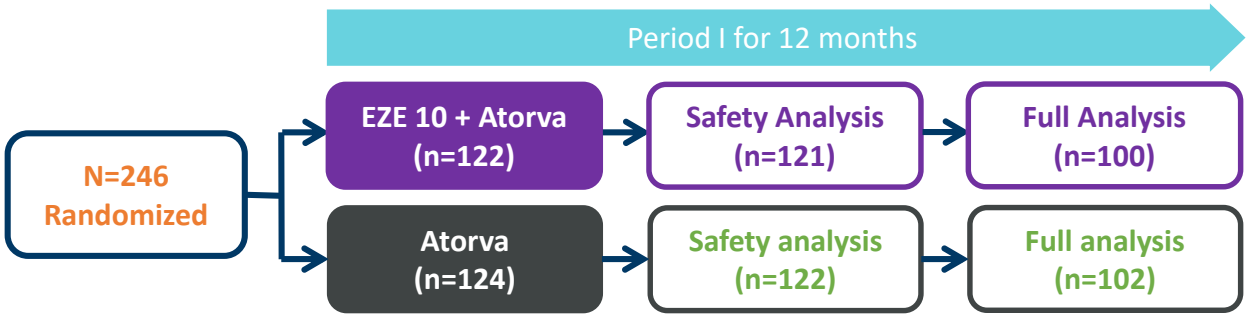


Process outcomes	Before IMPROVE-IT	After IMPROVE-IT	Adjusted relative ratio[a] (95% CI)	P-value
At discharge n (%)	N = 5389	N = 803		
Ezetimibe, n (%)	100 (1.8)	31 (3.8)	2.85 (1.90–4.25)	<0.001
Statin, n (%)	5344 (99.2)	795 (99.0)	Not assessed	0.644
At one year n (%)	N = 5038	N = 718		
Ezetimibe, n (%)	254 (5.0)	99 (13.8)	3.00 (2.40–3.75)	<0.001
Statin, n (%)	4676 (93.2)	650 (90.8)	Not assessed	0.023

Post-IMPROVE-IT, a significant increase in use of ezetimibe was observed at hospital discharge and at one year. The use of statin was similar across both periods.

Int J Cardiol. 2019 Dec 10.

PRECISE-IVUS Study: Study Design



Patient Criteria:

- Patients aged 30 to 85 with CAD underwent successful coronary angiography or PCI under IVUS guidance to treat ACS or SAP
- With an LDL-C level >100 mg/dl at entry
- Lipid profiles and other biomarker levels were measured at baseline and follow-up at 9 to 12 months

Data Collection:

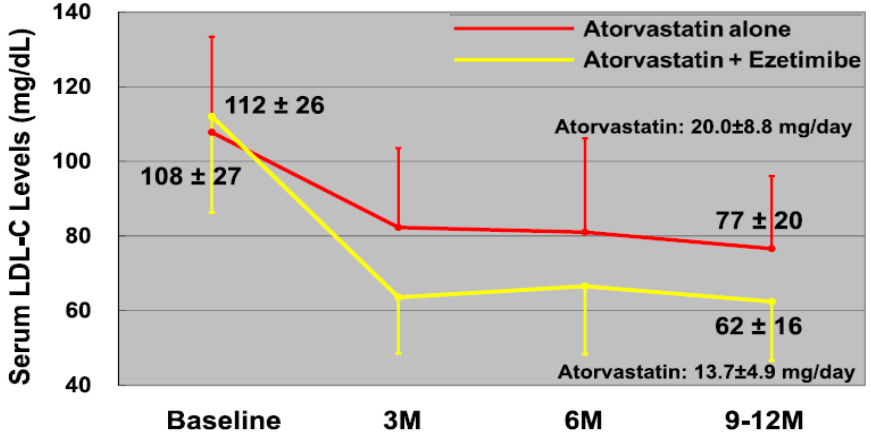
- Lipid profiles and other biomarker levels were measured at baseline and 9 to 12 months
- Serial volumetric intravascular ultrasound was performed at baseline and 9 to 12 months

Atorva=atorvastatin; EZE=ezetimibe; CAD=coronary artery disease; PCI=percutaneous coronary intervention; ACS=acute coronary syndrome; SAP=stable angina pectoris;

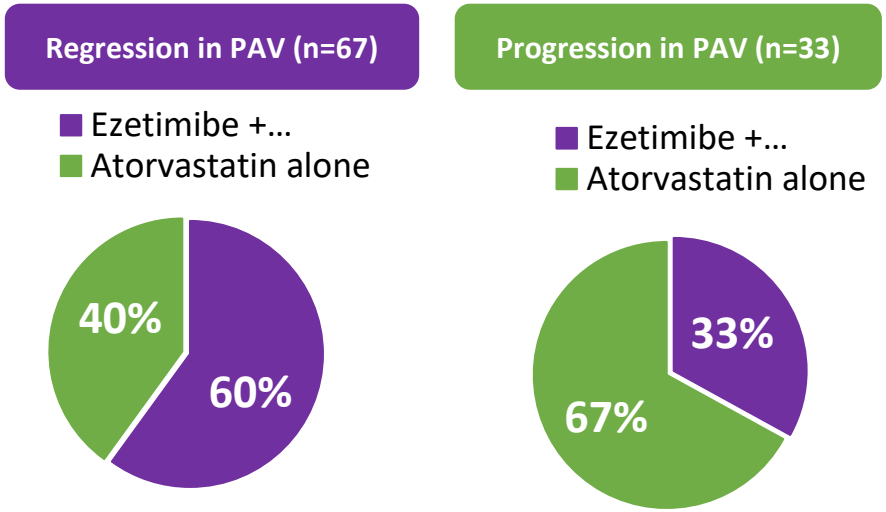
PRECISE-IVUS study

Incremental LDL-C lowering by dual lipid lowering therapy was associated with stronger coronary plaque regression:

Serial change in serum low-density lipoprotein cholesterol



Comparison between the patients with regression vs. progression.



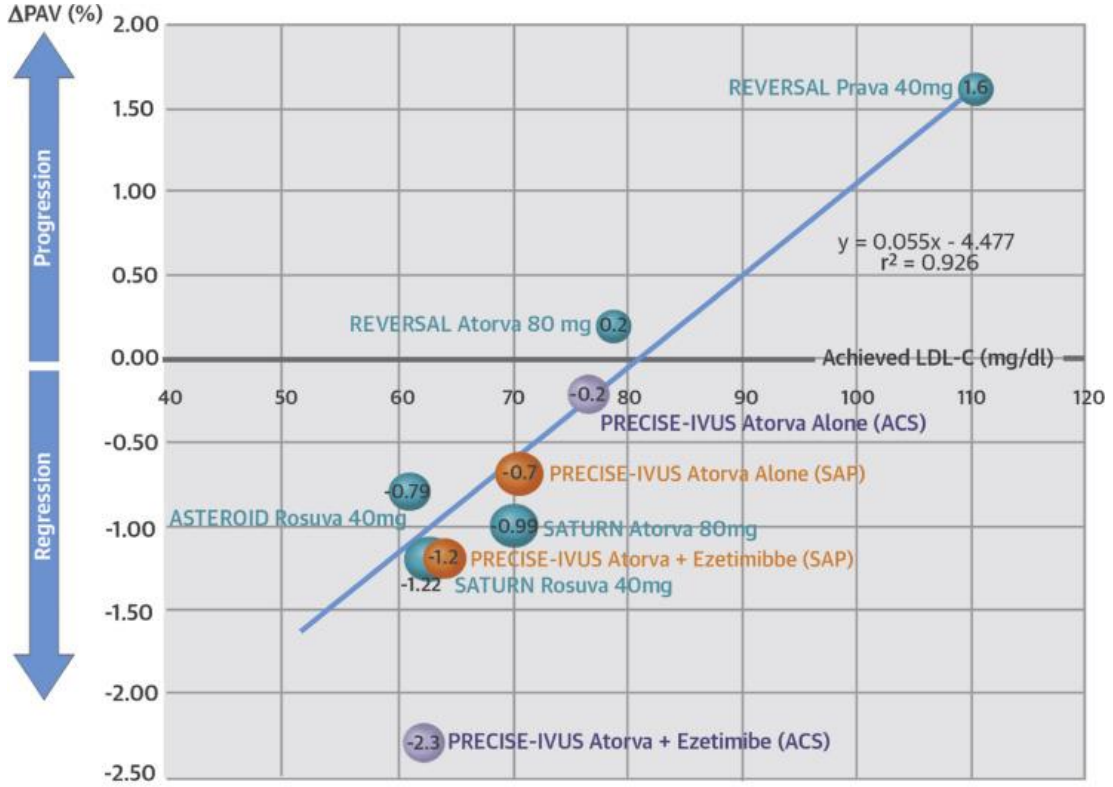
Tsujita K, et al Atherosclerosis 2016;251:367-72..

60% patients on ezetimibe+atorvastatin
62±14 mg/dL LDL-C at follow-up, p=0.004

67% patients on atorvastatin alone
81±22 mg/dL LDL-C at follow-up

PRECISE-IVUS Study

Relationship Between LDL-C and PAV



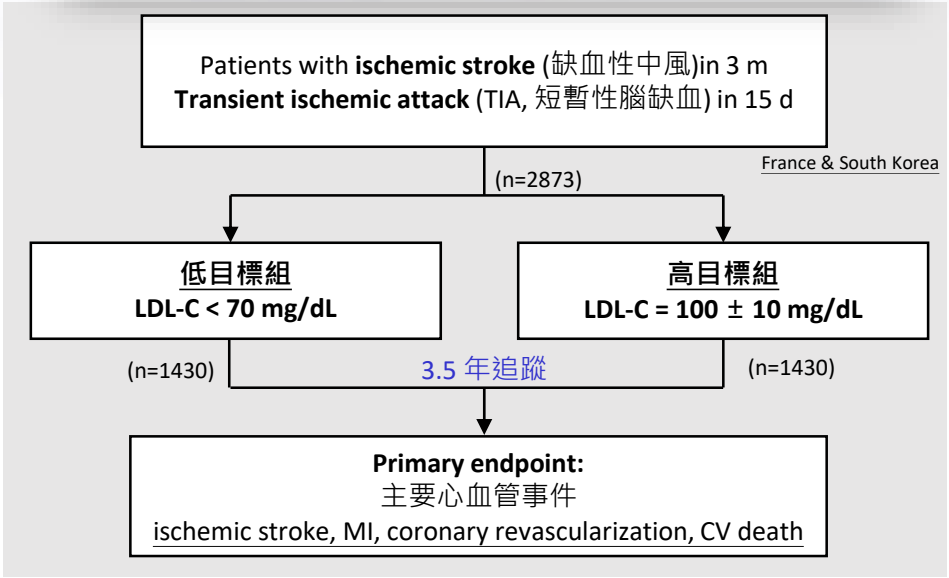
Tsujita, K. et al. J Am Coll Cardiol. 2015; 66(5):495-507.

A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke

The NEW ENGLAND JOURNAL of MEDICINE

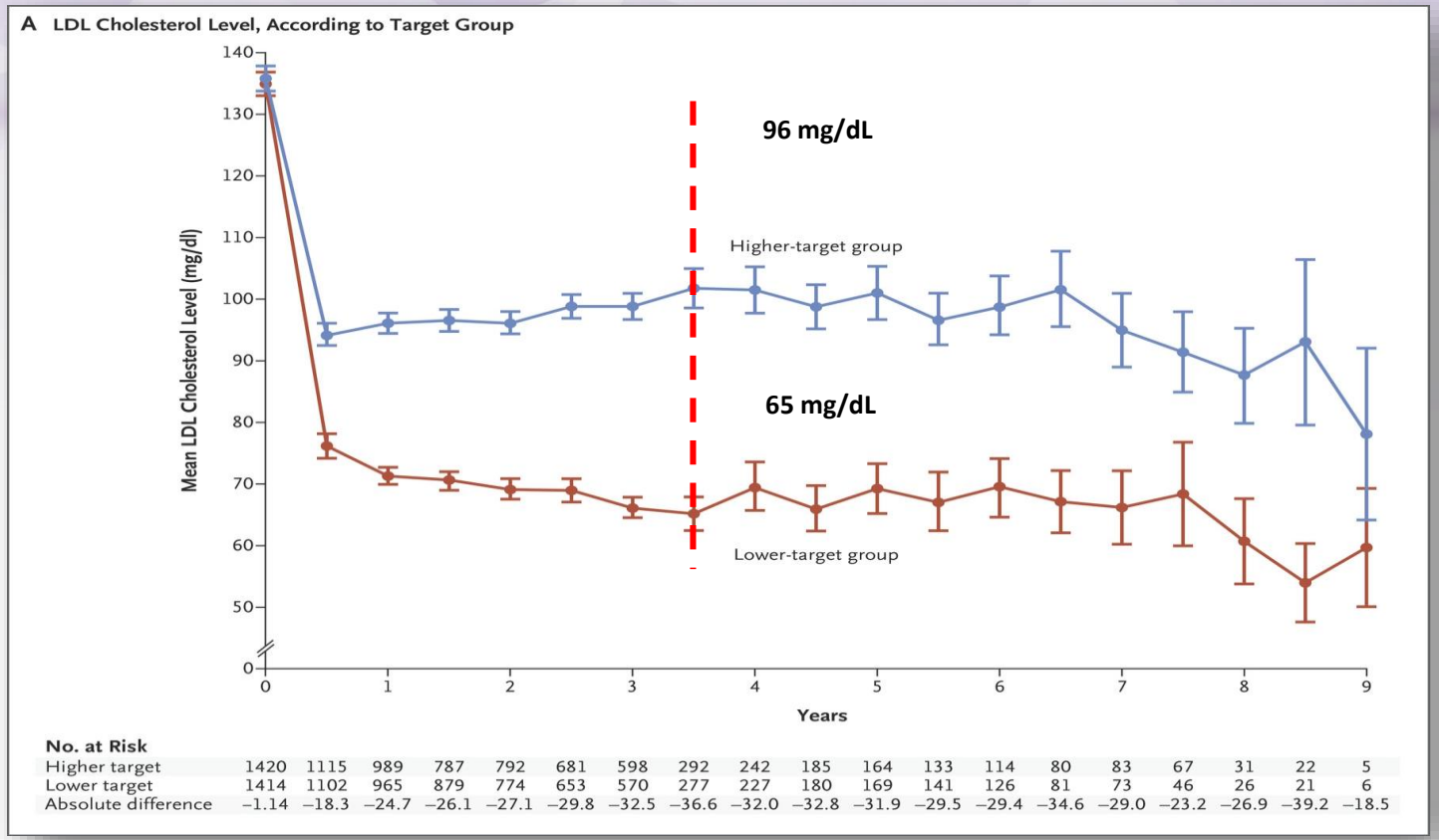
ORIGINAL ARTICLE

A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke



N Engl J Med. 2020 Jan 2;382(1):9.

LDL Cholesterol Levels according to target group

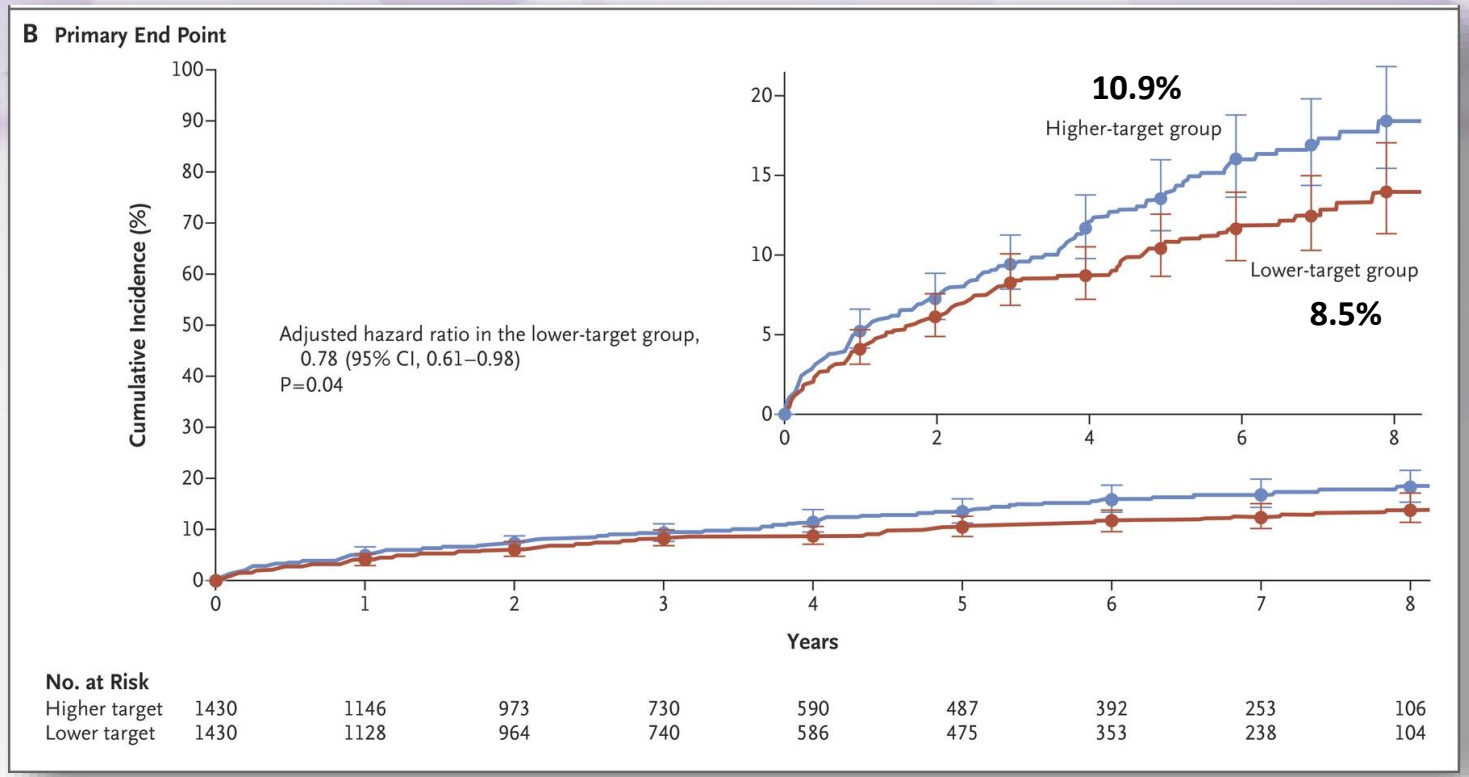


No. at Risk

Higher target	1420	1115	989	787	792	681	598	292	242	185	164	133	114	80	83	67	31	22	5
Lower target	1414	1102	965	879	774	653	570	277	227	180	169	141	126	81	73	46	26	21	6
Absolute difference	−1.14	−18.3	−24.7	−26.1	−27.1	−29.8	−32.5	−36.6	−32.0	−32.8	−31.9	−29.5	−29.4	−34.6	−29.0	−23.2	−26.9	−39.2	−18.5

Atozet™
(ezetimibe and atorvastatin, MSD)

Patients who had a target LDL-C level of < 70 mg/dL had a lower risk of subsequent cardiovascular events than those who had a higher target range



具有缺血性中風或是短暫性腦缺血TIA的病人，LDL-c < 70 mg/dL的病人相較於LDL-C 介於90-110 mg/dL的病人，後續發生心血管事件的比例更低。

Atozet™ (ezetimibe and atorvastatin, MSD)

Hazard Ratios for Adjudicated Clinical End Points.

Table 2. Hazard Ratios for Adjudicated Clinical End Points.

End Points	Lower-Target Group (N = 1430)	Higher-Target Group (N = 1430)	Hazard Ratio (95% CI)	P Value
Primary end point				
Major cardiovascular event — no. (%)	121 (8.5)	156 (10.9)	0.78 (0.61–0.98)*	0.04
Death from cardiovascular causes	17 (1.2)	24 (1.7)	—	
Fatal cerebral infarction or stroke of undetermined origin	3 (0.2)	6 (0.4)	—	
Fatal myocardial infarction	1 (0.1)	1 (0.1)	—	
Other cardiovascular death	7 (0.5)	6 (0.4)	—	
Sudden death of undetermined origin	6 (0.4)	11 (0.8)	—	
Nonfatal cerebral infarction or stroke of undetermined origin	81 (5.7)	100 (7.0)	—	
Nonfatal acute coronary syndrome	15 (1.0)	23 (1.6)	—	
Urgent coronary revascularization	5 (0.3)	6 (0.4)	—	
Urgent carotid revascularization	3 (0.2)	3 (0.2)	—	

Medication Use and Adjudicated Clinical End Points

Table S2. Persistence: medication use

Medications	At 6 months		At 1 year		At 2 years		At 3 years	
	<70 mg/dL (N=1181)	100±10 mg/dL (N=1181)	<70 mg/dL (N=1024)	100±10 mg/dL (N=1037)	<70 mg/dL (N=924)	100±10 mg/dL (N=926)	<70 mg/dL (N=623)	100±10 mg/dL (N=649)
Statin + Ezetimibe	292/1167 (25.0)	57/1174 (4.9)	329/996 (33.0)	56/1036 (5.4)	330/898 (36.8)	51/911 (5.6)	231/570 (40.5)	41/579 (7.1)
Ezetimibe only	4/1167 (0.4)	4/1174 (0.3)	3/994 (0.3)	3/1036 (0.3)	2/898 (0.2)	3/911 (0.3)	1/570 (0.2)	2/579 (0.3)

低目標組(LDLC <70)的病人有較低的主要心血管事件風險發生率，
且有更高的比例使用 statin + Ezetimibe

Table 2. Hazard Ratios for Adjudicated Clinical End Points.

End Points		Lower-Target Group (N=1430)	Higher-Target Group (N=1430)	Hazard Ratio (95% CI)	P Value
Intracranial hemorrhage — no. (%)	顱內出血	18 (1.3)	13 (0.9)	1.38 (0.68–2.82)	
Newly diagnosed diabetes — no. (%)§	新生糖尿病	103 (7.2)	82 (5.7)	1.27 (0.95–1.70)	

低目標組的病人其顱內出血及新生糖尿病(HbA1c>6.5)的比例無顯著性的差異。

*且此研究中的NOD發生比例，小於SPARCLE研究中的NOD 發生比例30% (atorva 80 mg vs. placebo)

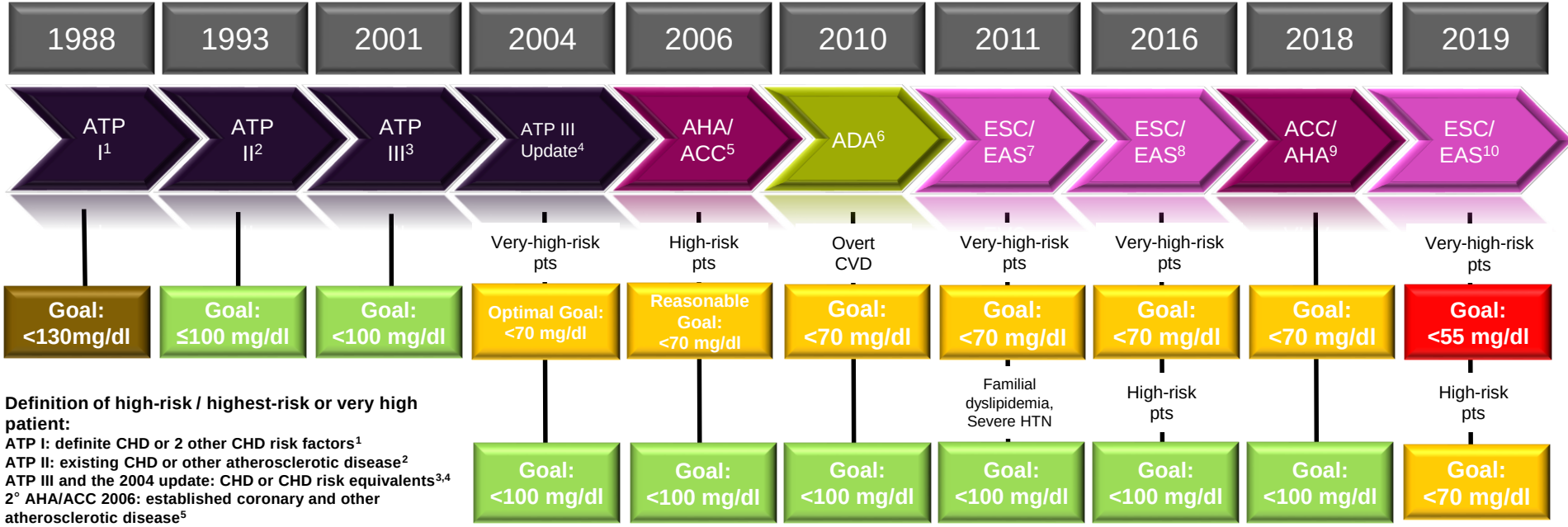
*P values for additional secondary end points were not calculated after there was no significant between-group difference for the first end point on hierarchical testing.

N Engl J Med. 2020 Jan 2;382(1):9.

Atozet™ (ezetimibe and atorvastatin, MSD)

Change of dyslipidemia guideline
From past to now

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]

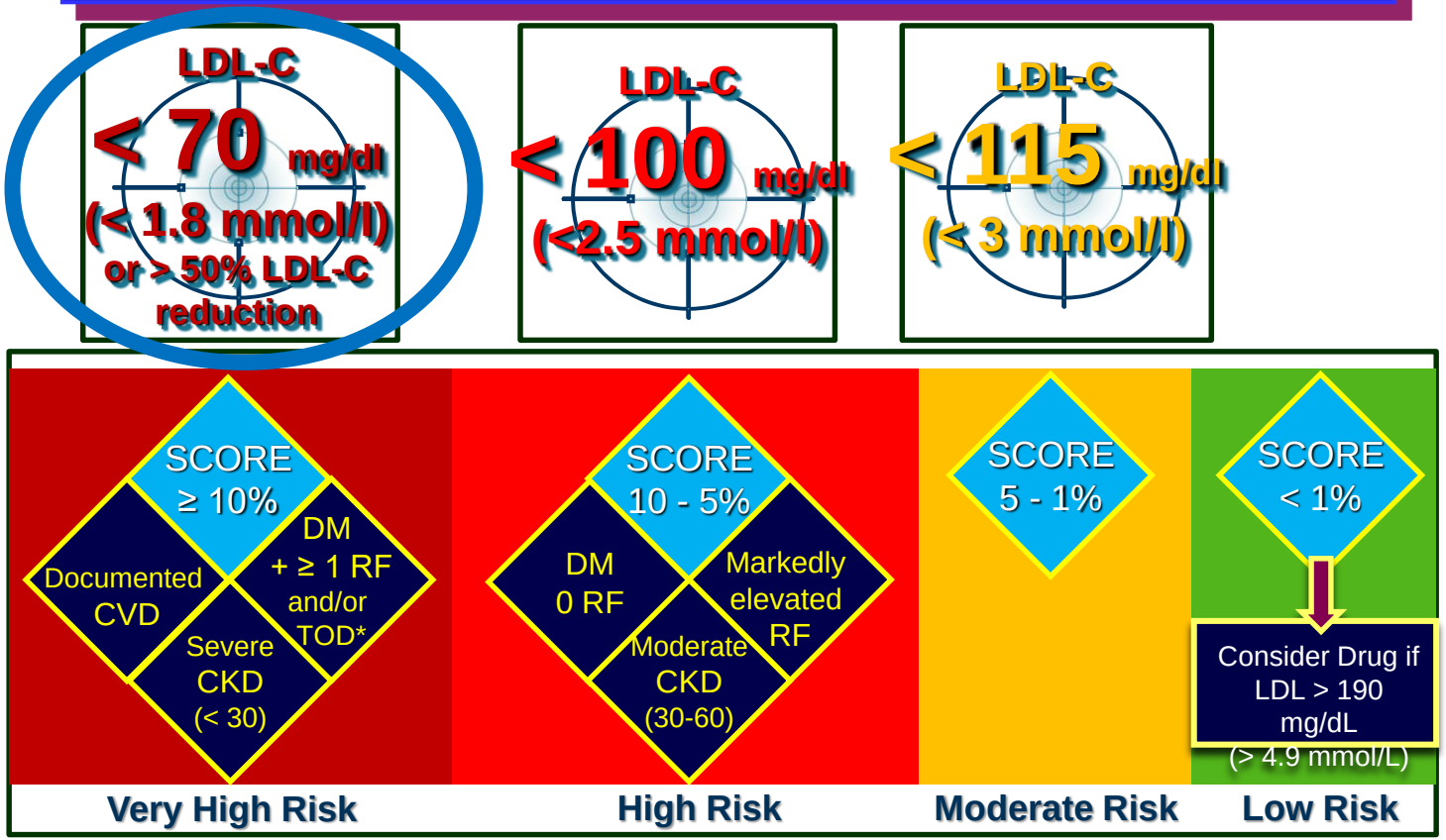
ADA 2010: overt CVD[6]

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

ESC / EAS Guidelines



* TOD= target organ damage (such as microalbuminuria 30-300 mg/24h)

Joint ESC Guidelines. Eur J Prev Cardiol 2012; 19: 585-667

ESC/EAS Guidelines. Eur Heart J 2011; 32: 1769-1818

2013 ACC / AHA Guidelines

4 Major Statin Benefit Groups

1. Clinical ASCVD (ACS or history of MI, stable or unstable angina, revascularisation, stroke, TIA, or PAD presumed to be of atherosclerotic origin)

2. LDL-C ≥ 190 mg/dL

3. Diabetes aged 40-75 y with LDL-C 70-189 mg/dL

4. Estimated 10-year ASCVD risk ≥ 7.5 % with LDL-C 70-189 mg/dL (and age 40-75 y)

2013 ACC/AHA Guideline: High-Moderate statin

Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <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*

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.

2013 ACC/AHA Guideline: Summary

- 此guideline的更新主要的根據是以RCT試驗的結果
- 藉由RCT試驗結果，找出了四個最能得到statin好處的群組
- 可藉由新的ASCVD風險預測的程式來計算出十年或終生風險
- 生活型態的調整在ASCVD的風險降低上仍是非常的重要
- **沒有證據支持使用LDL或是non-HDL goal來作為血脂治療標準**
- Non-statin的藥物治療不管是單獨或是附加到statin使用，都無法獲得顯著ASCVD風險降低的好處
- 高強度statin治療是指可降低LDL≥ 50%, 中強度statin治療則是指降低LDL 30-50%
- Treat to target以及lower is best不再是治療的策略，應該是以treat to ASCVD risk為現今治療的策略

2016 ESC/EAS guidelines for dyslipidemia

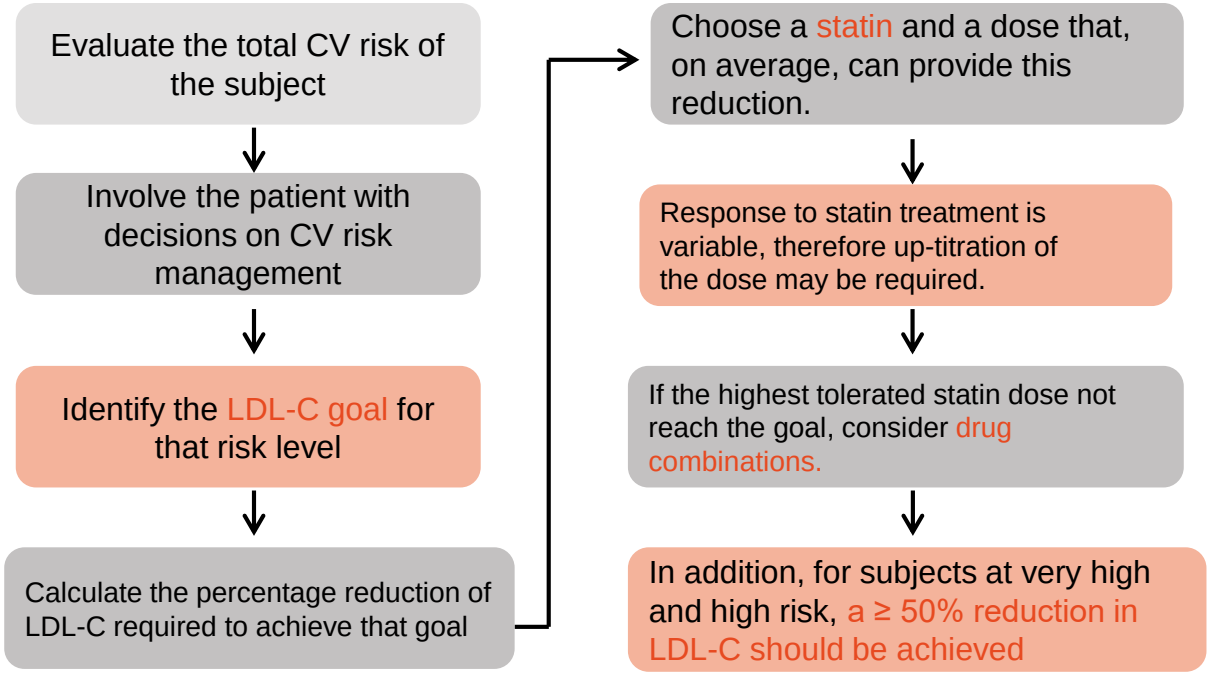
Lipids LDL-C the primary target	**Very high-risk: LDL-C <1.8 mmol/L (70 mg/dL)** or a reduction of at least 50% if the baseline[b] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).
	High-risk: LDL-C <2.6 mmol/L (100 mg/dL) or a reduction of at least 50% if the baseline[b] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL).
	Low to moderate risk: LDL-C <3.0 mmol/L (115 mg/dL).
	Non-HDL-C secondary targets are <2.6, 3.4 and 3.8 mmol/L (100, 130 and 145 mg/dL) for very high-, high- and moderate-risk subjects, respectively.
	HDL-C: no target, but >1.0 mmol/L (40 mg/dL) in men and >1.2 mmol/L (48 mg/dL) in women indicates lower risk.
	TG: no target but <1.7 mmol/L (150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.

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], an LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C[e] is 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	-

ESC guideline:
Statin 若無法達到治療目標，應考慮合併治療

- ESC suggest the following scheme may be proposed:



Authors/Task Force Members, et al. Atherosclerosis 2016;253:281-344.

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http://dx.doi.org/10.1016/j.jacc.2016.03.519

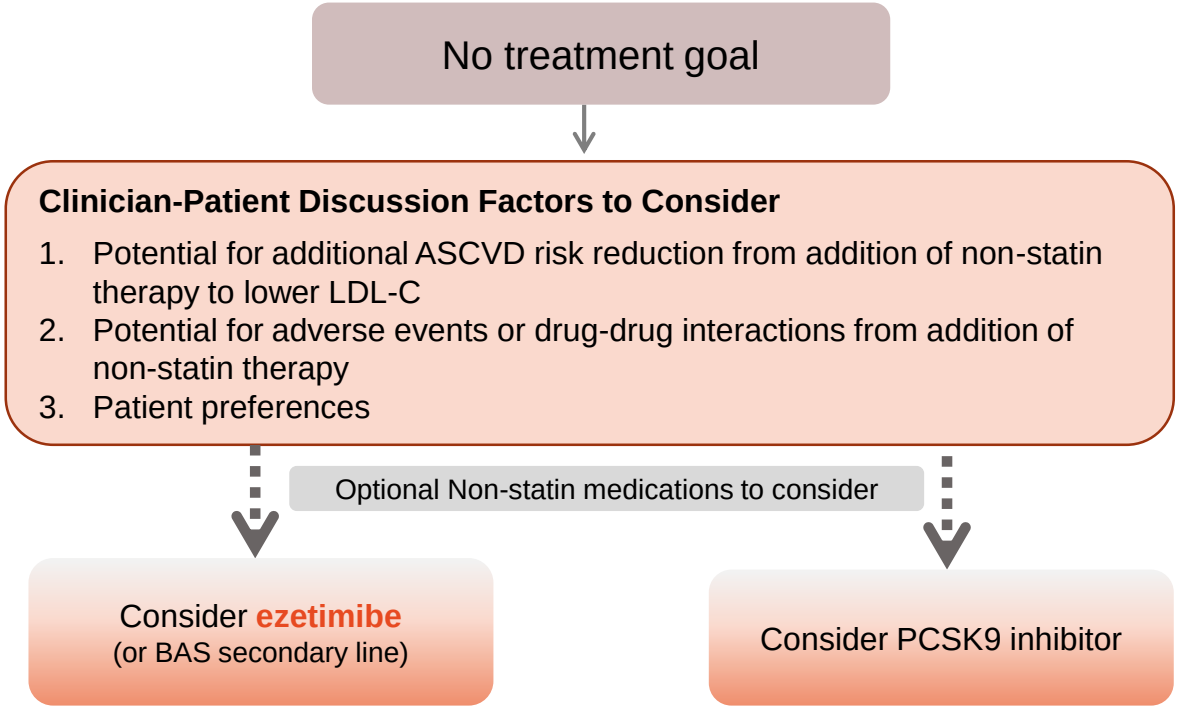
EXPERT CONSENSUS DECISION PATHWAY

2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents

Endorsed by the National Lipid Association

ACC expert consensus:
未能達到血脂目標患者，可考慮合併 Non-statin治療



ASCVD, atherosclerotic cardiovascular disease; BAS, bile acid sequestrant.

Writing Committee, et al. J Am Coll Cardiol 2016;68:92-125.

2017 Taiwan lipid guideline

REVIEW ARTICLE

2017 Taiwan lipid guidelines for high risk patients☆

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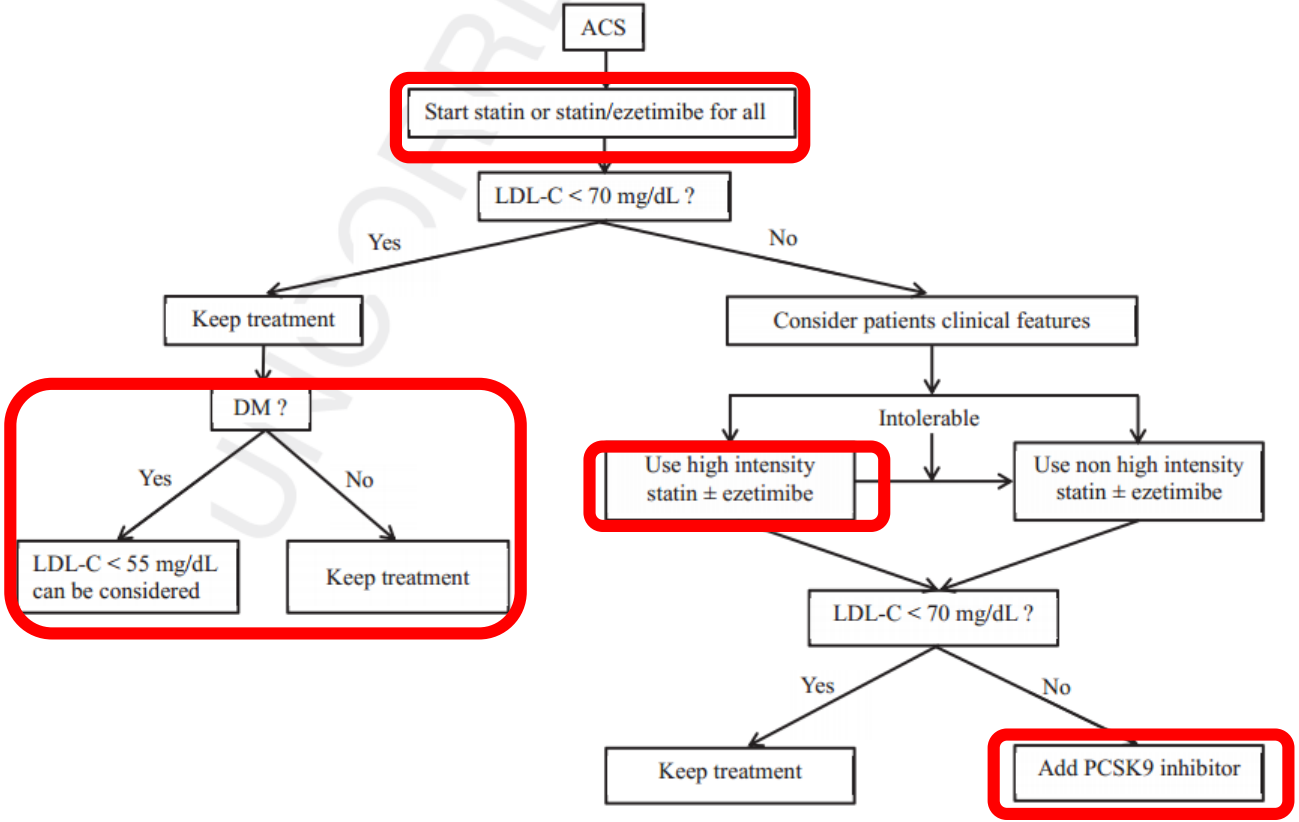
Journal of the Formosan Medical Association (2017) 116, 217e248

2017 Taiwan lipid guideline



2017 Taiwan lipid guideline

Table 7 LDL-C targets in ACS, CAD, and PAD.

Disease category	LDL-C target
Primary target	
ACS	LDL-C < 70 mg/dL
ACS + DM	LDL-C < 55 mg/dL can be considered
Stable CAD	LDL < 70 mg/dL
PAD	LDL < 100 mg/dL
PAD + CAD	LDL < 70 mg/dL
Secondary target	
ACS, stable CAD, PAD with TG >200 mg/dL	Non-HDL-C < 100 mg/dL

ACS = acute coronary syndrome; CAD = coronary artery disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PAD = peripheral arterial disease; TG = triglyceride.

Table 9 Lipid recommendations for diabetic patients.

Recommended Target	Individuals who should be targeted for lipid modification
LDL-C: - Without CVD: < 100 mg/dL - With CVD: < 70 mg/dL or 30–40% reduction	1. All diabetic patients aged ≥40 y 2. Diabetic patients aged <40 y who have overt ASCVD or ASCVD risk factors

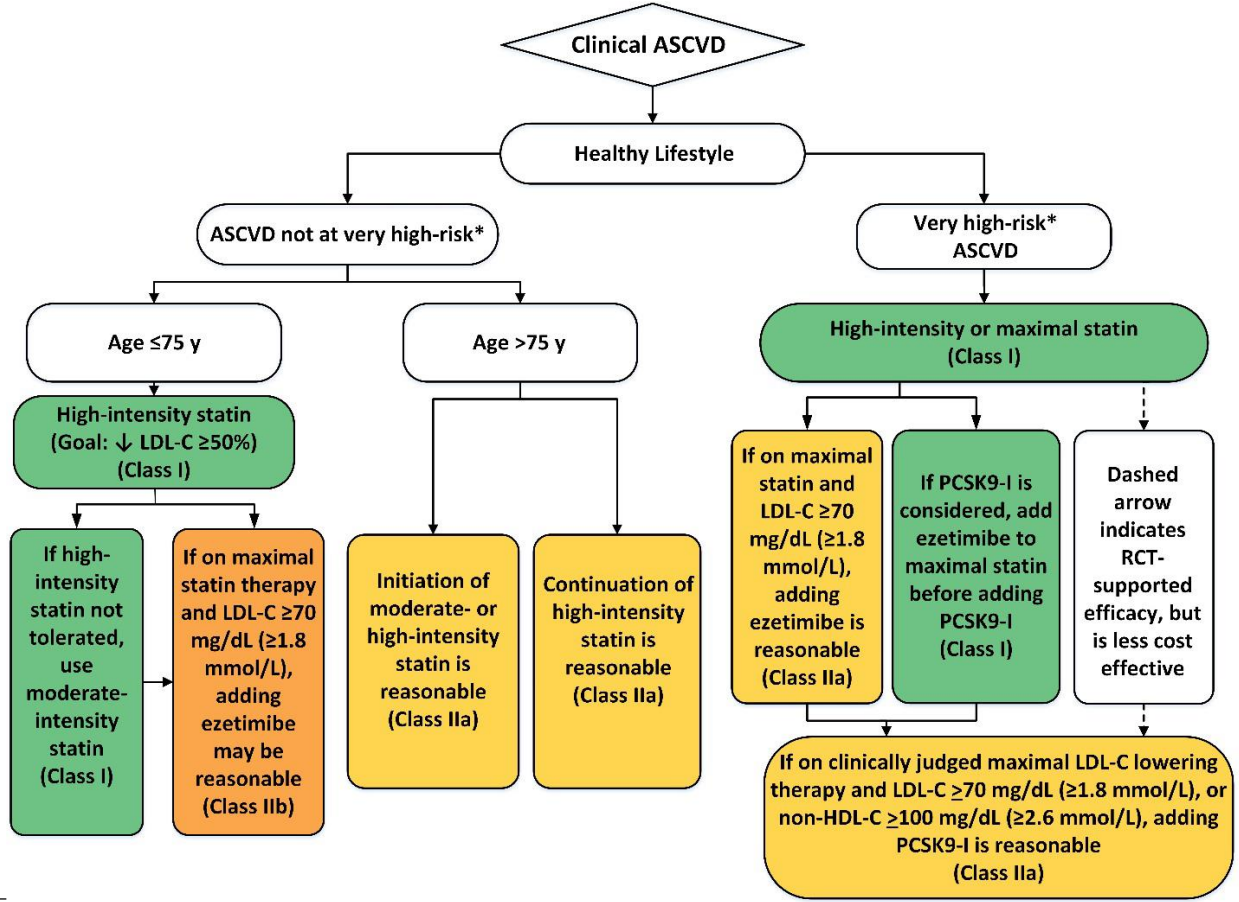
2017 AACE lipidemia guideline

Table 6
Atherosclerotic Cardiovascular Disease Risk Categories and LDL-C Treatment Goals

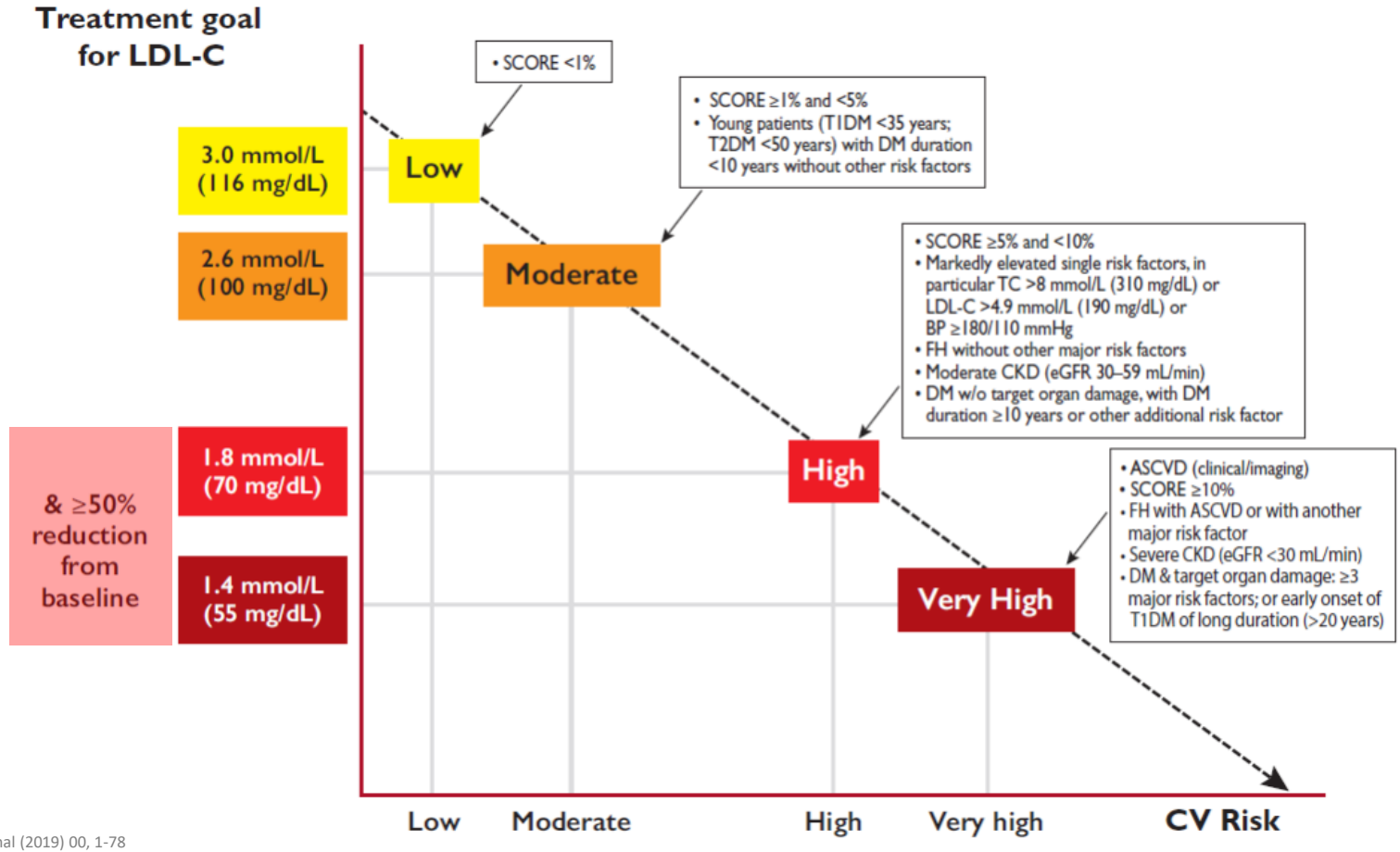
Risk category	Risk factors[a]/10-year risk[b]	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	– Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH – 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% – Diabetes or CKD 3/4 with 1 or more risk factor(s) – HeFH	<70	<100	<80
High risk	– ≥2 risk factors and 10-year risk 10-20% – Diabetes or CKD 3/4 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

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

Circulation. 2018 Nov 10



2019 ESC/EAS guideline LDL treatment goal



European Heart Journal (2019) 00, 1-78

- **New/revised concepts**

More intensive reduction of LDL-C across CV risk categories

- For secondary prevention in very-high-risk patients, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.
  - 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 therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.
- In primary prevention, for individuals at very-high risk but without FH, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended. For individuals at very-high risk (that is, with another risk factor but without ASCVD), in primary prevention the same goals for LDL-C lowering should be considered.
- For patients at high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.
- For individuals at moderate risk, an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered.
- For individuals at low risk, an LDL-C goal of <3.0 mmol/L (<116 mg/dL) may be considered.

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 therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered

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

2019 ESC/EAS Recommendations	Class	Level	2016 ESC/EAS Recommendations	Class	Level
In secondary prevention for patients at **very-high risk:** an **LDL-C reduction of ≥50%** from baselined **AND** an **LDL-C goal of <55 mg/dL** are recommended.	I	A	In patients at **very-high CV risk:** an **LDL-C goal of <70 mg/dL** **OR** a **reduction of at least 50%** if the baseline LDL-C is between 70 and 135 mg/dL is recommended.	I	B

2019 Very-high risk definition

People with any of the following:

- **Documented ASCVD**, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and PAD. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound.
- **DM with target organ damage***, or at least three major risk factors, or early onset of T1DM of long duration (>20 years).
- **Severe CKD** (eGFR <30 mL/min/1.73 m^2).
- A calculated SCORE ≥10% for 10-year risk of fatal CVD.
- FH with ASCVD or with another major risk factor.

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

2016 Very-high risk definition

Subjects with any of the following:

- **Documented CVD**, clinical or unequivocal on imaging. Documented CVD includes previous MI, ACS, coronary revascularisation (PCI, CABG) and other arterial revascularization procedures, stroke and TIA, and 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** such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia.
- **Severe CKD** (GFR <30 mL/min/1.73 m2).
- A calculated SCORE ≥10% for 10-year risk of fatal CVD.

European Heart Journal (2019) 00, 1-78; European Heart Journal (2016) 37, 2999–3058

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

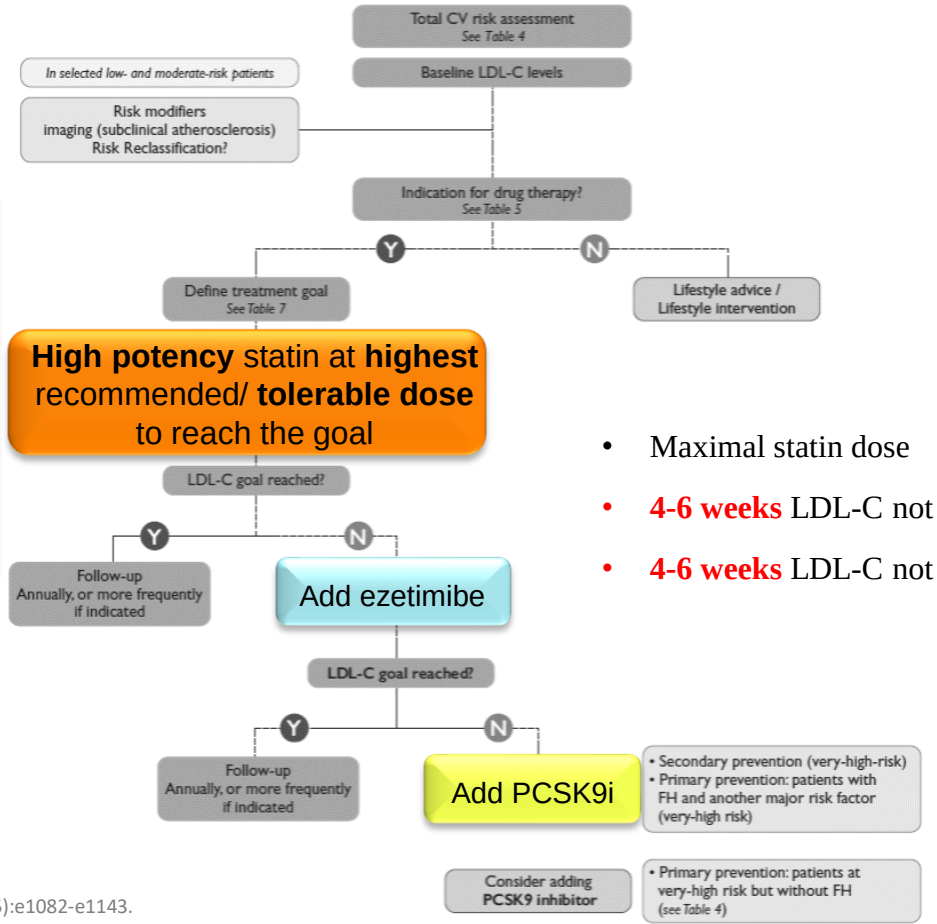
Management of patients with ACS	Class	Level
In **all ACS patients** without any contraindication or definite history of intolerance, it is recommended that **high-dose statin therapy** is initiated or continued as early as possible, **regardless of initial LDL-C values**.	I	A
If the LDL-C goal is not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

European Heart Journal (2019) 00, 1-78

2019 ESC/EAS guideline treatment algorithm:

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

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

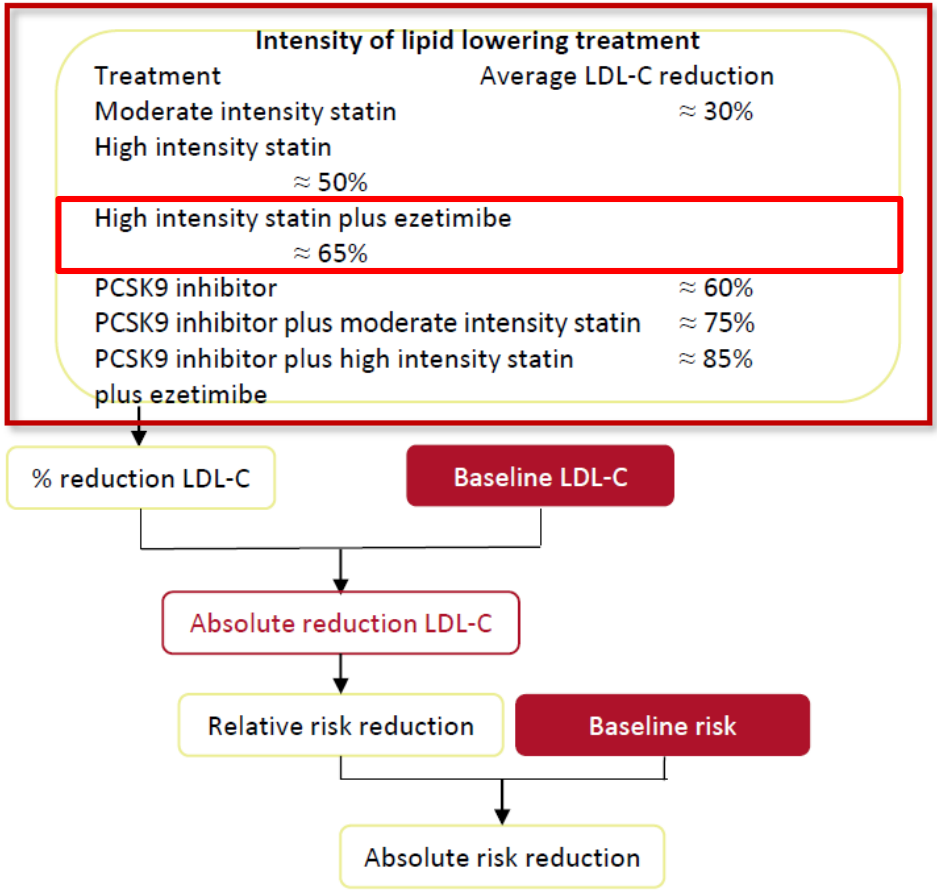


- Maximal statin dose
- **4-6 weeks** LDL-C not at goal + ezetimibe
- **4-6 weeks** LDL-C not at goal + PCSK9i

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

EAS ESC European Society of Cardiology

Using baseline LDL-C and risk of ASCVD to estimate expected clinical benefit of low-density lipoprotein lowering therapies



LDL-C = low-density lipoprotein cholesterol;
PCSK9 = proprotein convertase subtilisin/kexin type 9.

ADA guideline on lipid management in patients with diabetes

2018

Table 9.2—Recommendations for statin and combination treatment in adults with diabetes

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

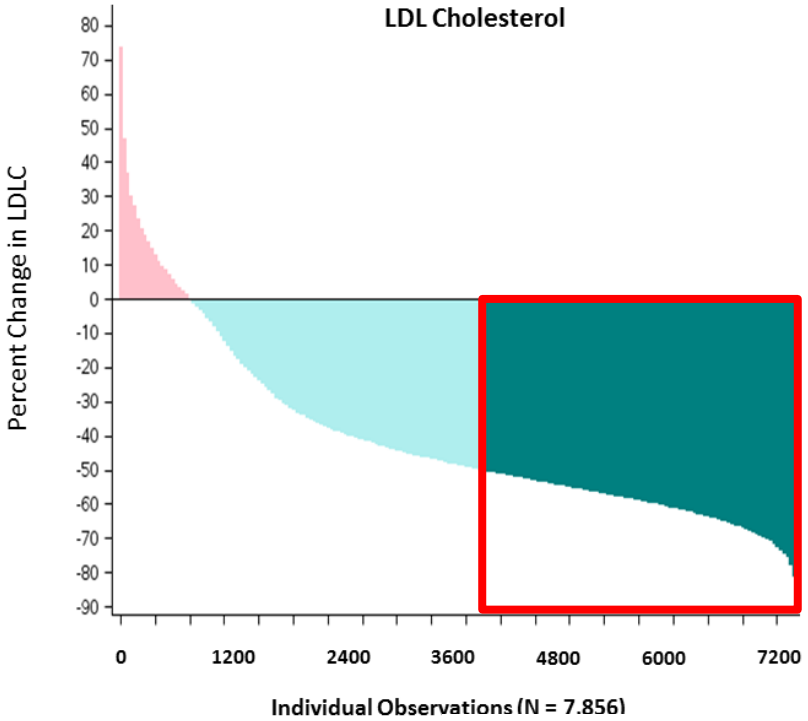
2019

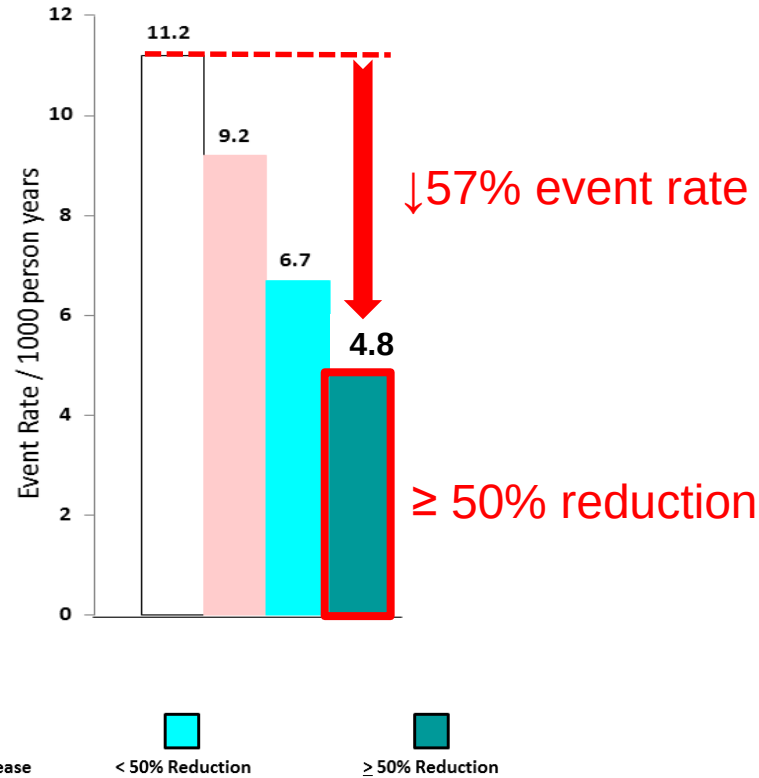
Table 10.2—Recommendations for statin and combination treatment in adults with diabetes

Age	ASCVD or 10-year ASCVD risk >20%	Recommended statin intensity^ and combination treatment*
<40 years	No	None†
	Yes	High • In patients with ASCVD, if LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)#
≥40 years	No	Moderate‡
	Yes	High • In patients with ASCVD, if LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

ACSVD risk factors: LDL-c≥100 mg/dL, high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD.

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





European Heart Journal (2016) 37, 1373–1379

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

Attained LDL≤70mg/dl

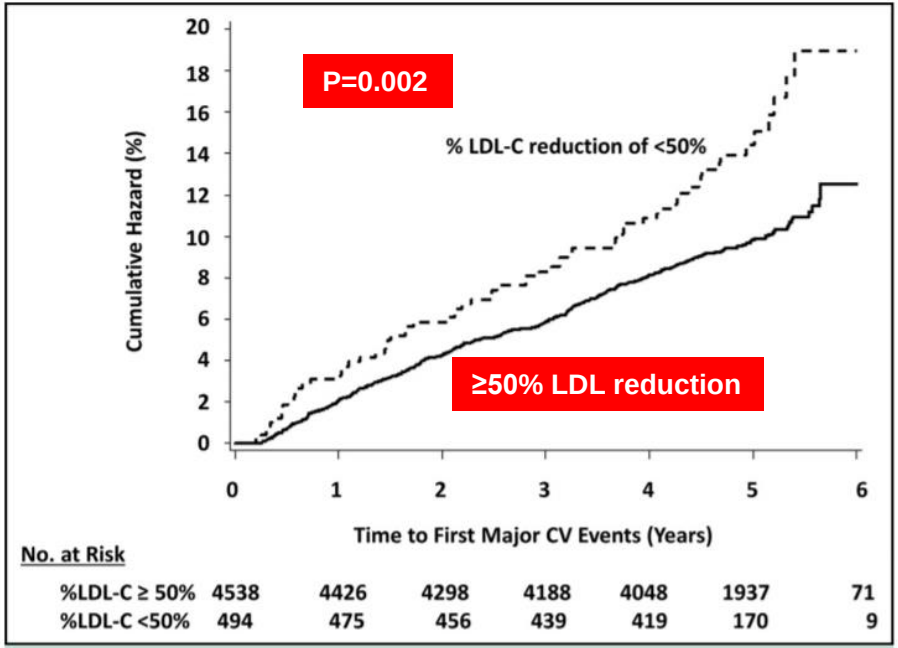


Figure 1 Major cardiovascular events in the cohort with attained LDL-C ≤70 mg/dL as a function of percent LDL-C reduction. LDL = low-density lipoprotein.

Attained LDL>70mg/dl

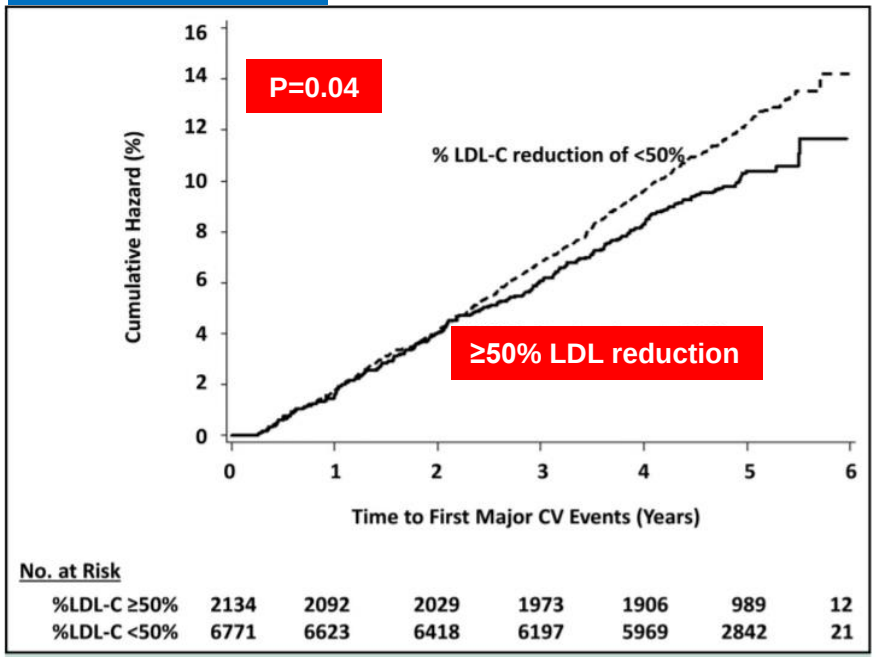


Figure 2 Major cardiovascular events in the cohort with attained LDL-C >70 mg/dL as a function of percent LDL-C reduction. LDL = low-density lipoprotein.

台灣血脂健保給付規範更新(108/02/01)

	起始藥物治療血脂值	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(108/2/1)	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	

- 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/dL5.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)。

Ezetimibe NHI reimbursement -2017/8/1更新

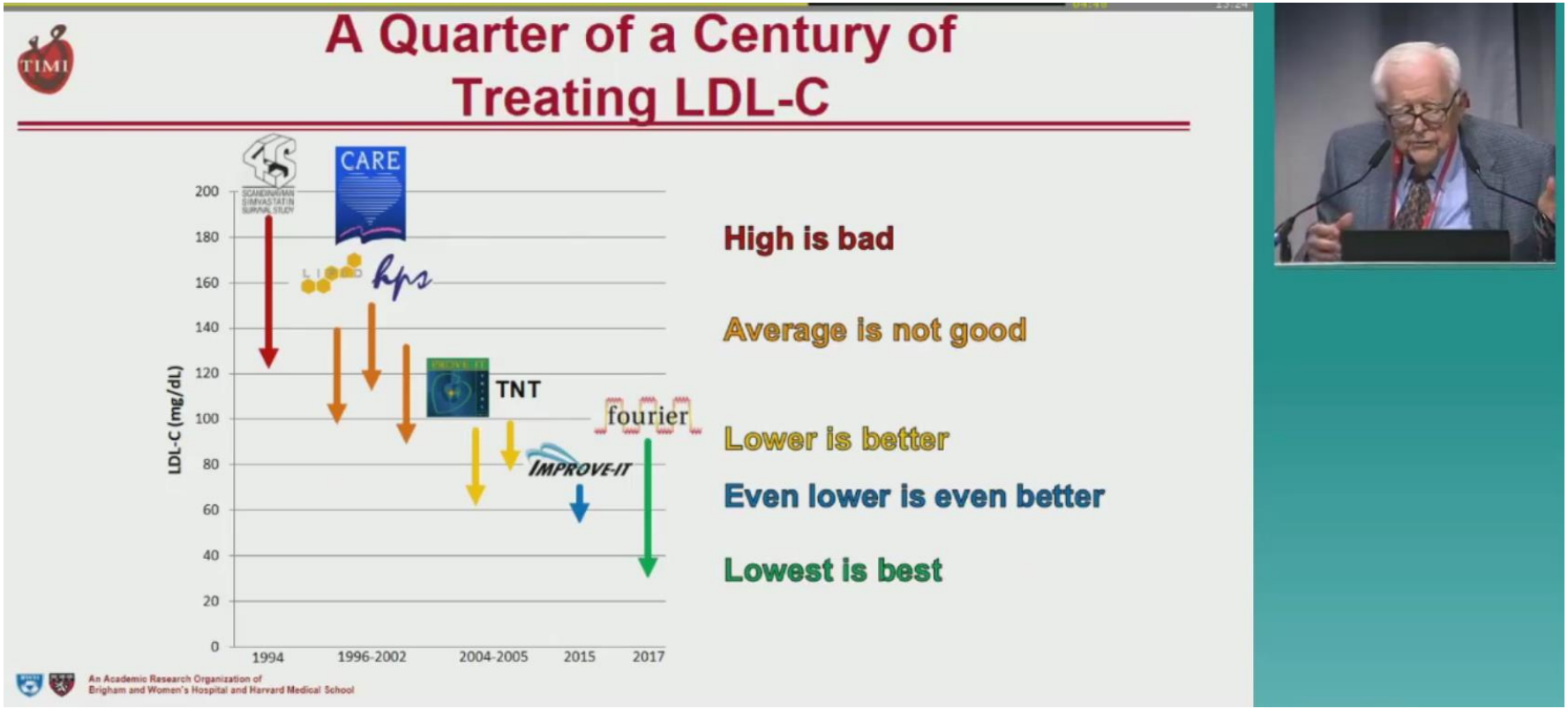
- Ezetimibe 相關藥品健保給付規範被規定為第二線治療
- Vytorin/ Atozet只能使用statin類治療3個月未達治療目標者

Ezetimibe 健保規範	Vytorin/ Atozet 更新健保規範
原發性高膽固醇血症、同型接合子家族性高膽固醇血症、同型接合子性麥脂醇血症(植物脂醇血症)患者並符合下列條件之一者： 1.符合全民健康保險降血脂藥物給付規定表經使用Statins類藥品單一治療3個月未達治療目標者。 2.符合全民健康保險降血脂藥物給付規定表且對Statins類藥品發生無法耐受藥物不良反應（如Severe myalgia、Myositis）者。	1. 限用於原發性高膽固醇血症、同型接合子家族性高膽固醇血症(HOFH)病患並符合全民健康保險降血脂藥物給付規定表，經使用statin類藥品單一治療3個月未達治療目標者 (106/8/1)。 2.本品不得與gemfibrozil併用。 (106/8/1)

2.6.3. Ezetimibe + simvastatin（如 Vytorin 10/20mg、Vytorin 10/10mg）：(95/12/1)：限用於原發性高膽固醇血症、同型接合子家族性高膽固醇血症(HOFH) 病患並符合全民健康保險降血脂藥物給付規定表者。

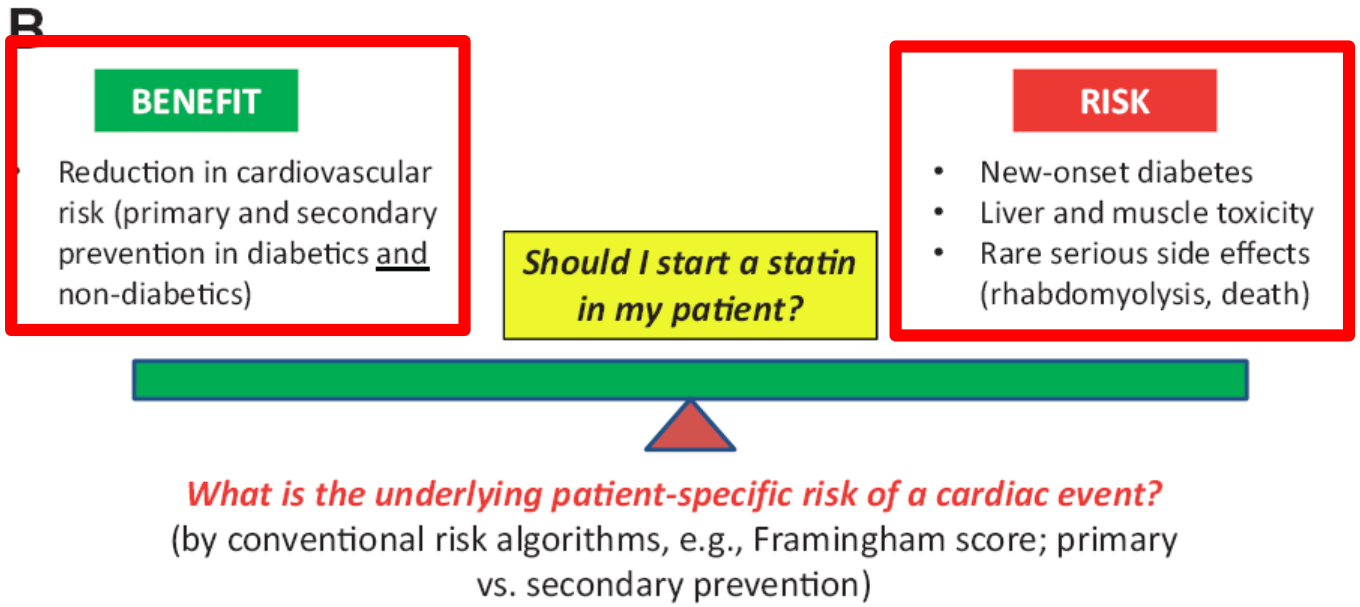
Prof Eugene Braunwald from Harvard Medical School:

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



Statin side effect

Maximizing Benefit, Minimizing Risk



Circulation. 2012;126:e282-e284

European Heart Journal
doi:10.1093/eurheartj/ehv043

與statin相關的肌肉副作用主要來自於高劑量的statin therapy

Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management

Factors that influence the pharmacokinetics of statins and risk for statin-associated muscle symptoms (SAMS)

- Pre-existing risk factors and co-morbidities: see Box 1
- High-dose statin therapy
- Polypharmacy
- Drug–drug interactions: concomitant use of certain drugs including gemfibrozil, macrolides, azole antifungal agents, protease inhibitors, and immunosuppressive drugs such as cyclosporine, and inhibitors of CYP450 isoenzymes, OATP 1B1, or P-gp, can affect the metabolism of statins, increase their circulating levels and, consequently, the risk for SAMS.
- Pharmacogenetic considerations may be relevant (see Overview of the pathophysiology of statin-induced myopathy)

CYP450, cytochrome P450; OATP 1B1, organic anion-transporting polypeptide 1B1; P-gp, P-glycoprotein 1.

Management of statin-associated muscle symptoms

- Ensure that there is an indication for statin use and that the patient is fully aware of the expected benefit in cardiovascular disease risk reduction that can be achieved with this treatment
- Ensure that there are no contraindications to statin use
- Counsel patients regarding the risk of 'side effects' and the high probability that these can be dealt with successfully
- Emphasize dietary and other lifestyle measures
- Use statin-based strategies preferentially notwithstanding the presence of statin-attributed muscle-related symptoms
- If re-challenge does not work; use a low or intermittent dosing preferably of a different (potent or efficacious) statin
- Use non-statin therapies as adjuncts as needed to achieve low-density lipoprotein cholesterol goal
- Do not recommend supplements to alleviate muscle symptoms as there is no good evidence to support their use

Reproduced with permission from Mancini *et al.*[9]

Effect of Ezetimibe Coadministered With Atorvastatin in 628 Patients With Primary Hypercholesterolemia

A Prospective, Randomized, Double-Blind Trial

Christie M. Ballantyne, MD; John Houri, MD; Alberto Notarbartolo, MD; Lorenzo Melani, MD; Leslie J. Lipka, MD, PhD; Ramachandran Suresh, PhD; Steven Sun, PhD; Alexandre P. LeBeaut, MD; Philip T. Sager, MD; Enrico P. Veltri, MD; for the Ezetimibe Study Group*

Other measurements of safety **did not suggest any clinically meaningful differences between the safety profiles of combination therapy and atorvastatin monotherapy** in the study overall or in subgroups defined by sex, age, or race. There was no evidence that ezetimibe worsened statin intolerance or statin-related toxicity.

	Placebo (n=60)	Ezetimibe (10 mg) (n=65)	All Atorvastatin (n=248)	All Ezetimibe + Atorvastatin (n=255)
All adverse events	34 (57)	41 (63)	146 (59)	148 (58)
Treatment-related adverse events	12 (20)	12 (18)	42 (17)	58 (23)
Gastrointestinal adverse events 腸胃道不良反應	6 (10)	4 (6)	13 (5)	20 (8)
Musculoskeletal disorders 肌肉骨骼不適	3 (5)	3 (5)	14 (6)	20 (8)
Discontinuations due to adverse events	3 (5)	3 (5)	13 (5)	15 (6)
Liver function tests ≥3×ULN, 2 consecutive times				
Alanine aminotransferase ALT	0	0	1 (<1)	4 (2)
Aspartate aminotransferase AST	0	0	1 (<1)	2 (<1)
Creatine phosphokinase ≥10×ULN 肌酸磷酸酵素	0	0	0	1 (<1)

Adapted with permission from Ballantyne CM et al.[1]

1. Ballantyne CM et al. Circulation. 2003 May 20;107(19):2409-15. Epub 2003 Apr 28.

在使用 ATOZET 的患者中，曾通報下列常見（≥1/100 且 <1/10）或不常見（≥1/1,000 且 <1/100）的藥物相關不良經驗：

身體系統器官類別	不良反應和頻率
感染與寄生蟲侵染	不常見：流行性感冒
精神疾患	不常見：憂鬱、失眠、睡眠疾患
神經系統疾患	不常見：頭暈；味覺障礙；頭痛；感覺異常
心臟疾患	不常見：竇性心搏過緩
血管疾患	不常見：熱潮紅
呼吸道、胸腔與縱膈疾患	不常見：呼吸困難
皮膚與皮下組織疾患	不常見：搔癢，蕁麻疹
肌肉骨骼與結締組織疾患	常見：肌肉痛 不常見：關節痛；背痛；肌肉疲累；肌肉痙攣；肌肉無力；肢體疼痛
全身性疾患與投藥部位症狀	不常見：無力；疲累；全身不適；水腫
檢查發現	不常見：ALT 和／或 AST 上升；鹼性磷酸酶上升；血中肌酸激酶(CK)上升；γ-麩胺醯轉移酶上升；肝臟酵素上升；肝功能檢測異常；體重上升。 在對照性臨床研究中，使用ATOZET治療之患者出現血清轉胺酶連續升高現象(≥3倍ULN)的發生率為0.6%。這些轉胺酶升高的現象通常都沒有症狀，也未伴隨發生膽汁鬱滯，並且在停止治療之後或繼續治療期間都會回復到基礎值。 在接受 ATOZET 治療的患者中，沒有人的CK 濃度≥10 x ULN。

ATOZET已在 7 項臨床試驗內，
共超過 2,400 名患者，顯示良好的安全性。

Take Home Message (1)

- **LDL is still the primary goal** of dyslipidemia therapy
- **2019 ESC lipid guidelines** suggest
  - **LDL < 70 mg/dl for high risk**
  - **LDL <55 mg/dl for very high risk**
  - **LDL < 40mg/dl for ASCVD with second vascular events within 2 years**
- However, **LDL goal was difficult to achieved** according to the literatures
- Physicians seldomly adjust statin dose after drug prescription

  → **physician Inertia or afraid of side effect**
- **High dose statin** may increase **side effects of treatment**

  Ex: Liver function impairment, muscle pain, new-onset DM

Take Home Message (2)

- **Using Atozet or high potency low dose statin combined with ezetimibe** is a good choice for LDL control & may decrease statin-related side effects **if not using high dose statin**
- If LDL goal can not be reached by statin or patient can not tolerate high dose statin, further **add on ezetimibe** is the best policy for **LDL goal achievement** **and** **avoiding side effect of statin**
- **PCSK9i is not frequently needed** under the usage of stain +/- ezetimibe
- **Current national health insurance in Taiwan** already changed

  → which may benefit more people in Taiwan and help them get healthier life

Thanks for your attention

謝謝聆聽