台灣血脂衛教學會 學術研討會 高雄場
Holistic Care for the Patients with ASCVD

# Think Beyond Statin Monotherapy – Managing LDL-C with Ezetimibe Combination Treatment

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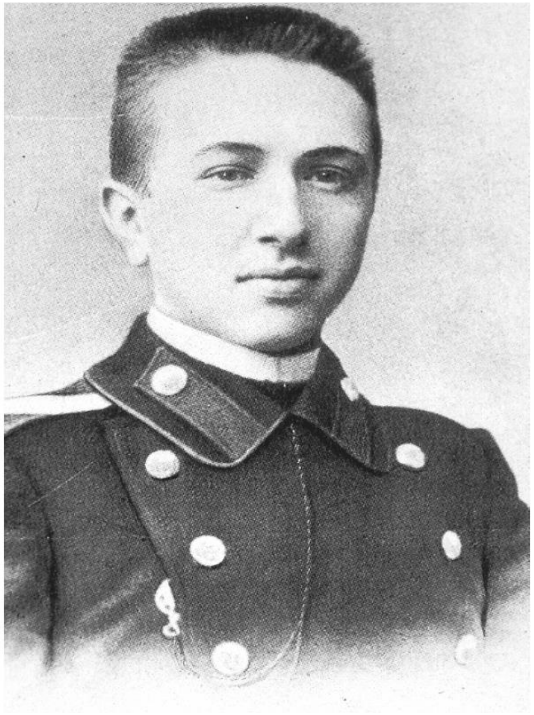
2019-09-01 (Sun)

# 沒有膽固醇就沒有粥狀動脈硬化



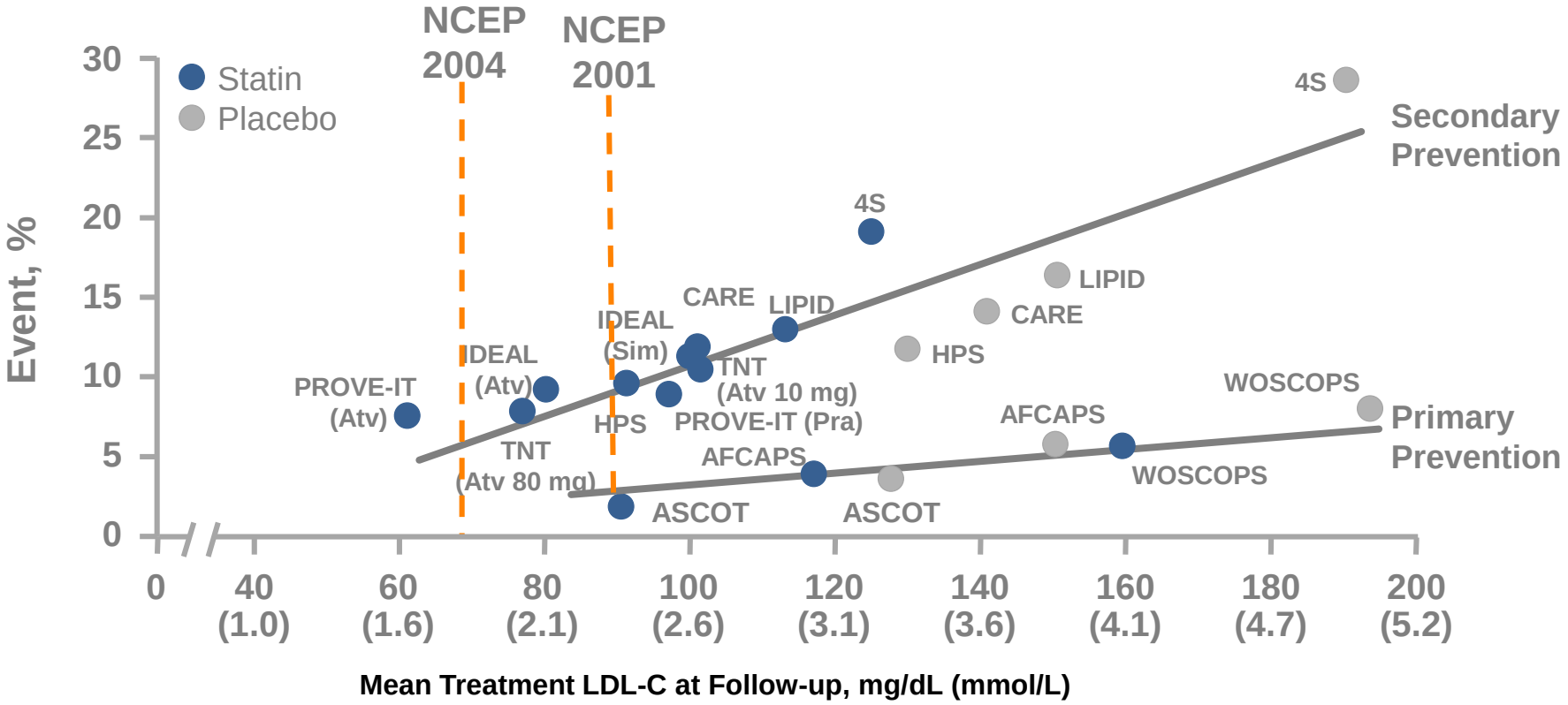
***Nikolay Nikolaevich Anichkov***
***1885~1964***

***"There is no atherosclerosis without cholesterol"***

1913


Tex Heart Inst J. 2006;33(4):417-23.

# Benefit of LDL Lowering




Atv=atorvastatin; Pra=pravastatin; Sim=simvastatin; PROVE-IT=Pravastatin or AtorVastatin Evaluation and Infection Therapy; IDEAL=Incremental Decrease in Endpoints through Aggressive Lipid Lowering; ASCOT=Anglo-Scandinavian Cardiac Outcomes Trial; AFCAPS=Air Force Coronary Atherosclerosis Prevention Study; WOSCOPS=West of Scotland Coronary Prevention Study.

Adapted from Rosenson RS. *Expert Opin Emerg Drugs*. 2004;9(2):269–279; LaRosa JC, et al. *N Engl J Med.* 2005;352(14):1425–1435;
Pedersen TR, et al. *JAMA*. 2005;294(19):2437–2445.


NEW
CHOLESTEROL
RECOMMENDATIONS
SOURCE:
AMERICAN HEART
ASSOCIATION
HEART DISEASE
DIABETES (TYPE 1 OR 2)
TAKE STATIN
10 YEAR RISK OVER 7.5%
BAD CHOLESTEROL OVER 190

**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**<br>**Rosuvastatin 20** *(40)* **mg**<br>  | **Atorvastatin 10** *(20)* **mg**<br>**Rosuvastatin** (*5*) **10 mg**<br>**Simvastatin 20–40 mg‡**<br>**Pravastatin 40** *(80)* **mg**<br>**Lovastatin 40 mg**<br>*Fluvastatin XL 80 mg*<br>**Fluvastatin 40 mg bid**<br>*Pitavastatin 2–4 mg* | *Simvastatin 10 mg*<br>**Pravastatin 10–20 mg**<br>**Lovastatin 20 mg**<br>*Fluvastatin 20–40 mg*<br>*Pitavastatin 1 mg* |

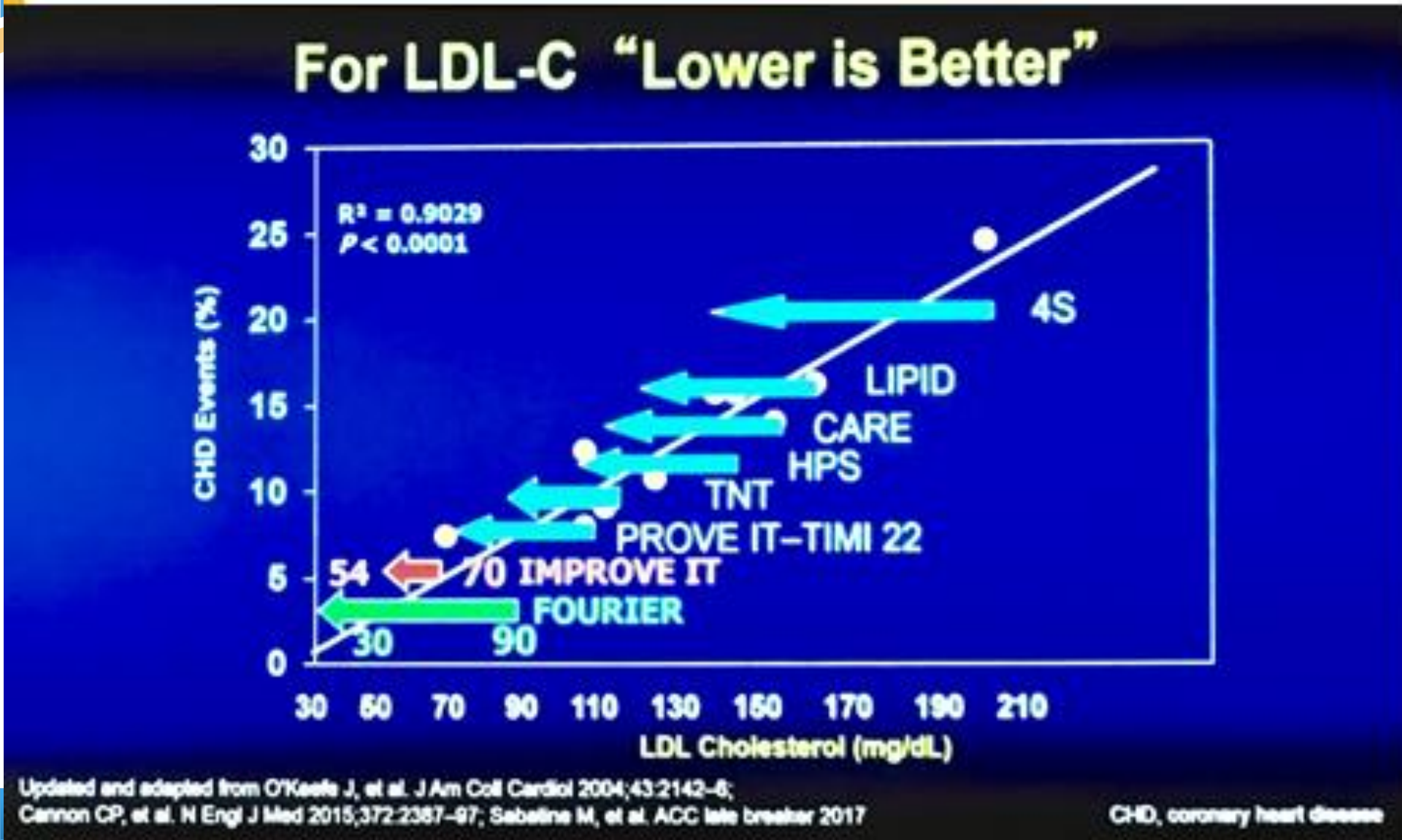
Specific statins and doses are noted in bold that were evaluated in RCTs (17,18,46-48,64-67,69-78) included in CQ1, CQ2 and the CTT 2010 meta-analysis included in CQ3 (20). All of these RCTs demonstrated a reduction in major cardiovascular events. Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in *italics*.

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.

†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (47).

‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

# PCSK9 inhibitor pushs the LDL-goal to 30 mg/dL

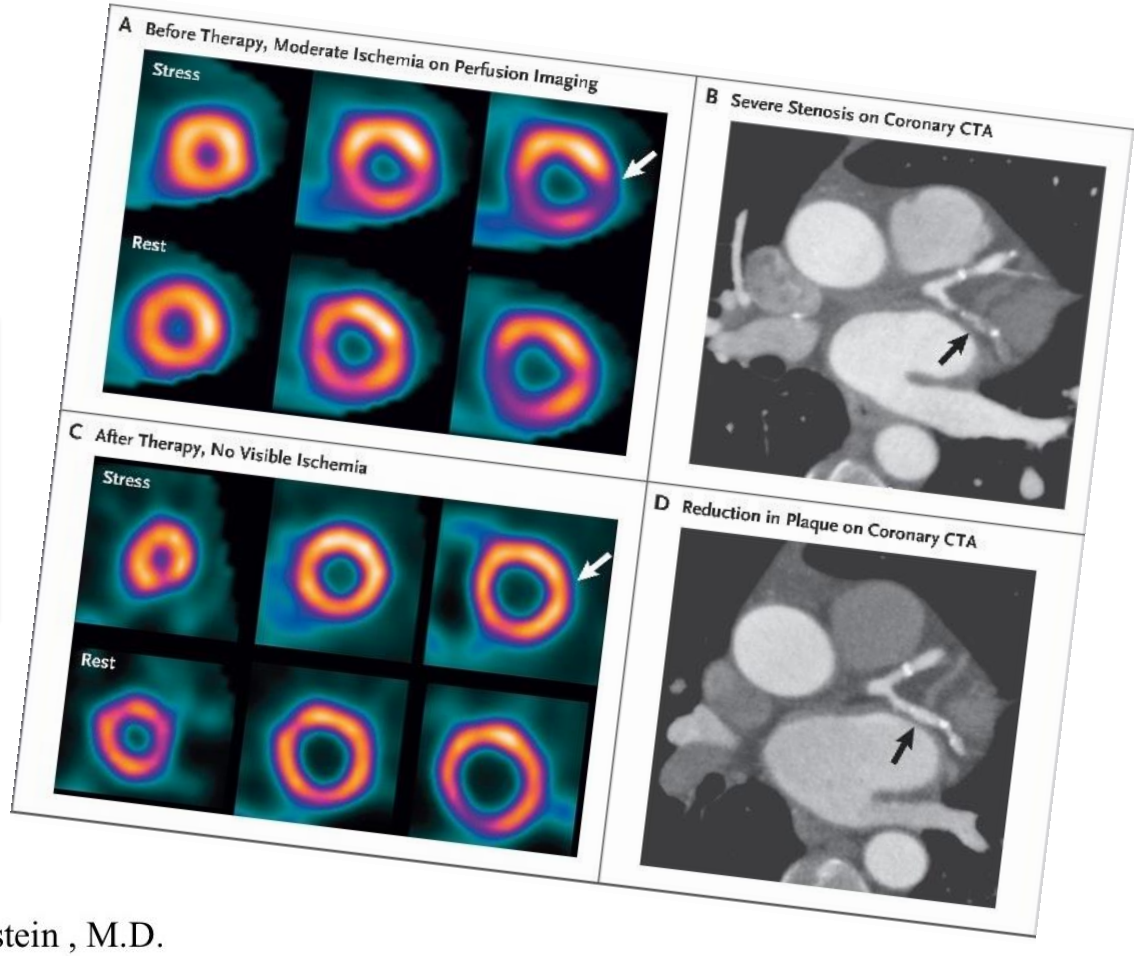



Updated and adapted from O'Keefe J, et al. J Am Coll Cardiol 2004;43:2142–6;
Cannon CP, et al. N Engl J Med 2015;372:2387–97; Sabatine M, et al. ACC late breaker 2017

CHD, coronary heart disease

# Why should we control lipid aggressively?

**Regression of Coronary Atherosclerosis with Medical Therapy**

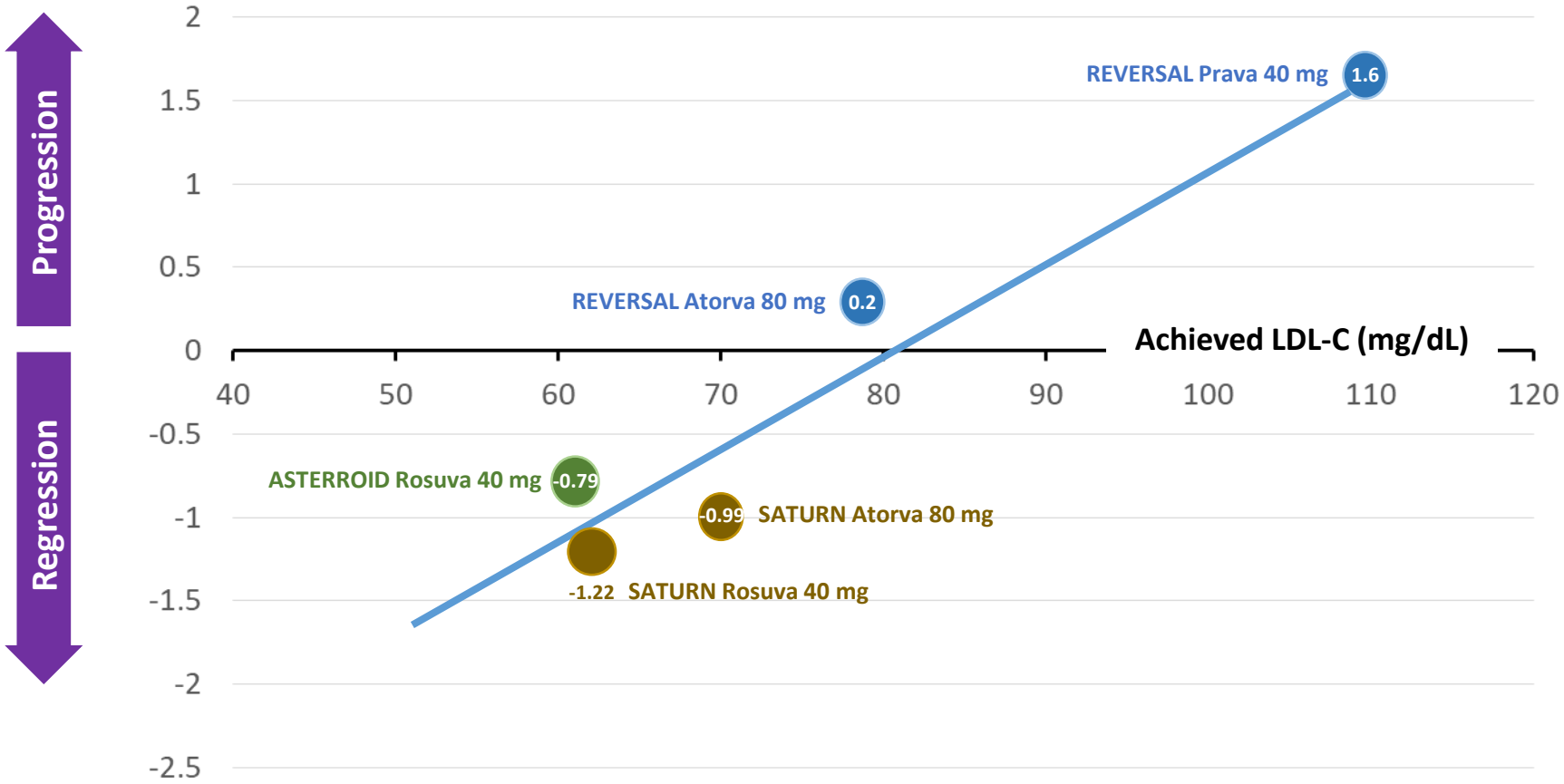



Abhishek Keraliya , M.D. , Ron Blankstein , M.D.

N Engl J Med 376:1370 - 1370 | April 6 , 2017

## Relationship Between LDL-C and PAV

# 多個臨床顯示 LDL-C 值與 PAV 的消長具有相關性




EZE=ezetimibe; PAV=percent atheroma volume.

# 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<br>小孩: < 135 mg/dL<br>有心血管疾病: < 70 mg/dL |

# 台灣血脂健保給付規範更新 (2019/02/01)

| | 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<br>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<br>LDL-C≧100mg/dL | TC＜160mg/dL或<br>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<br>LDL-C≧130mg/dL | TC＜200mg/dL或<br>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<br>LDL-C≧160mg/dL | TC＜240mg/dL或<br>LDL-C＜160mg/dL | |
| 個危險因子 | 給藥前應有3-6個月非藥物治療 | LDL-C≧190mg/dL | LDL-C＜190mg/dL | |

- 心血管疾病定義：

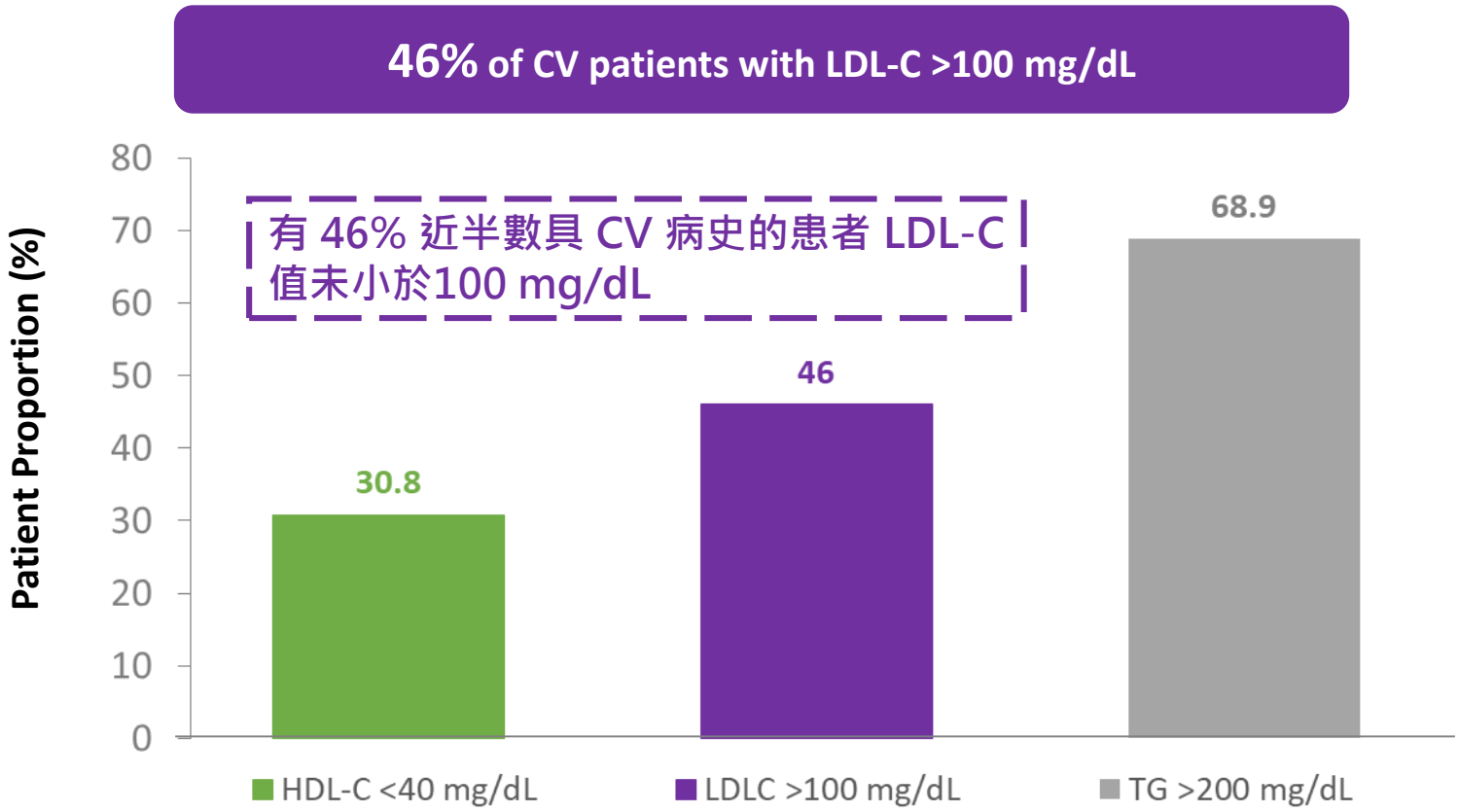
(一)冠狀動脈粥狀硬化患者包含：心絞痛病人，有心導管證實或缺氧性心電圖變化或負荷性試驗陽性反應者(附檢查報告)

(二)缺血型腦血管疾病患者包含：1.腦梗塞。2.暫時性腦缺血患者(TIA)。（診斷須由神經科醫師確立）3.有症狀之頸動脈狹窄。（診斷須由神經科醫師確立）

- 危險因子定義：1.高血壓2.男性≧45歲，女性≧55歲或停經者3.有早發性冠心病家族史(男性≦55歲，女性≦65歲)4.HDL-C<40mg/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)。

T-SPARCLE Study

# Suboptimal Control of LDL-C in Nearly Half of the CV Patients




HDL-C=high density lipoprotein cholesterol; LDL-C=low density lipoprotein cholesterol; TG, triglyceride.

1. Ho LT, et al. PLoS One. 2015 Mar 10;10(3):e0116513.

Data Article

# Contemporary data on treatment practices for low-density lipoprotein cholesterol in 3867 patients who had suffered an acute coronary syndrome across the world

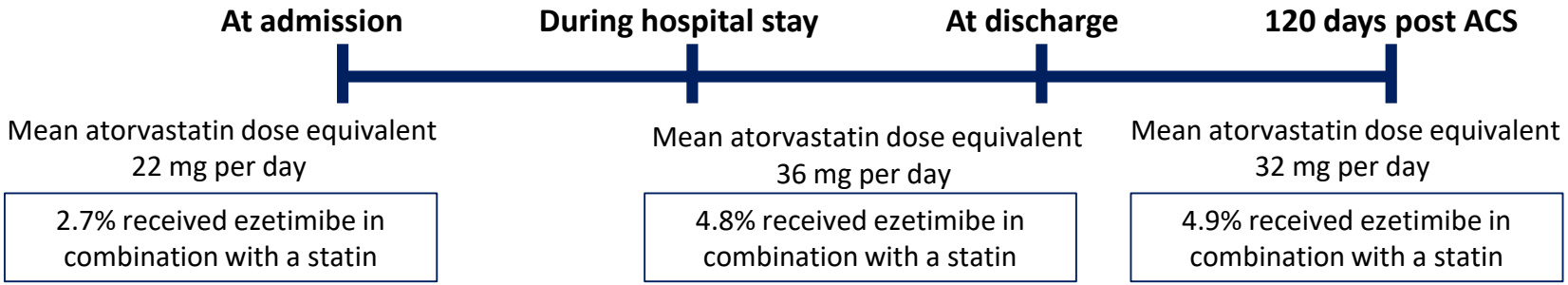
Anselm K. Gitt [a,b,*], Dominik Lautsch [c], Jean Ferrières [d], Gaetano M. De Ferrari [e], Ami Vyas [f], Carl A. Baxter [g], Lori D. Bash [c], Veronica Ashton [h], Martin Horack [b], Wael Almahmeed [i,j], Fu-Tien Chiang [k], Kian Keong Poh [l,m], Philippe Brudi [c], Baishali Ambegaonkar [c]

DYSIS II

- ***Population:*** 3867 *ACS patients* with full lipid profile available 0-120 days (recruitment of patients in 2013-2014

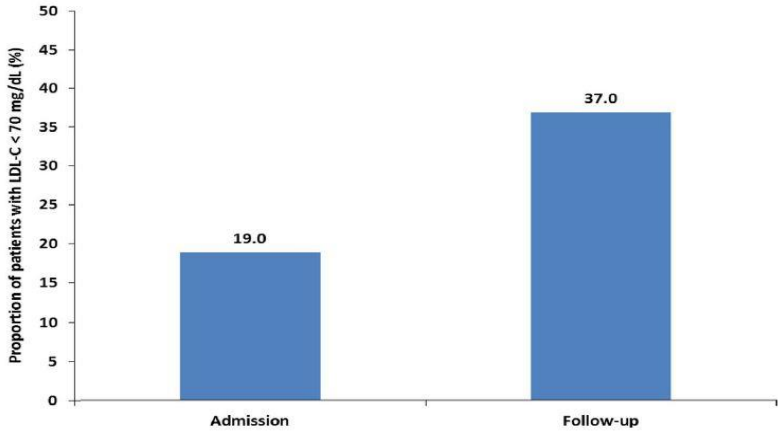
- ***Methods:*** a longitudinal, observational study in 3867 patients from 18 countries 18 countries in Europe, the Middle East, South-, Southeast- and East-Asia. Patients were evaluated lipid profile *at the time of admission, during hospital stay, at discharge and follow-up for 120 days post-ACS*.

**納入3867位ACS病人，橫跨歐洲, 中亞, 南亞和東南亞的研究發現，從住院到出院後四個月的ezetimibe in combination with statin的比例不到5%**




LDL-C target attainment for ACS cohort. Proportion of ACS patients with an LDL-C level of <70 mg/dL at hospital admission and at 120-day follow-up (for patients with values available at both time points, N=1071).

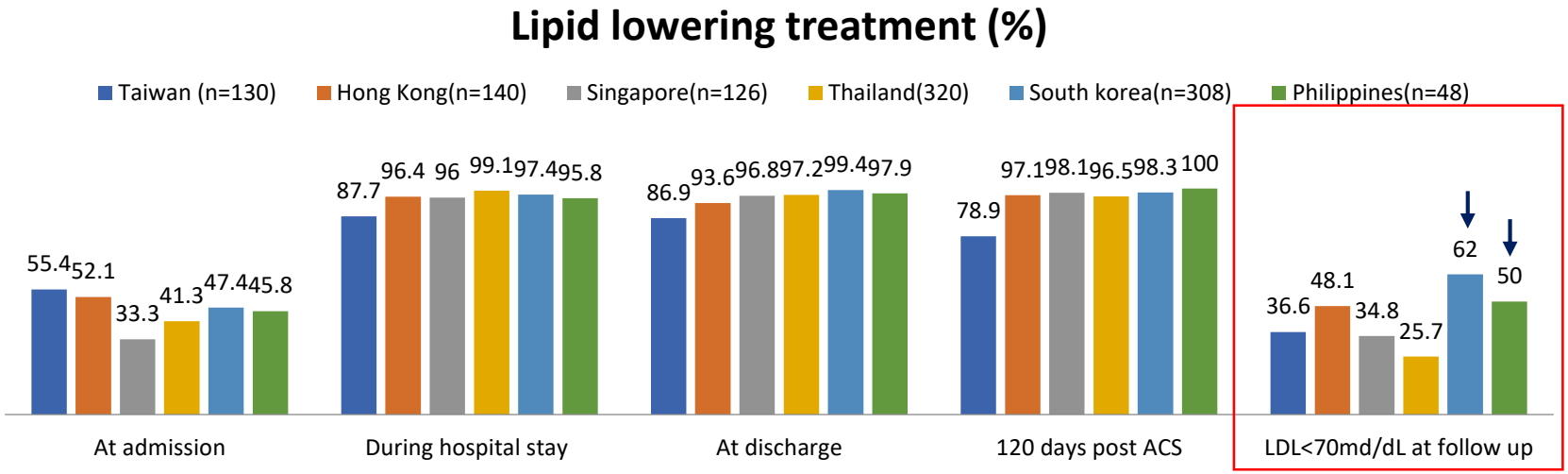
**出院後四個月的LDL-C<70 mg/dL達標率，只有37%**




A.K.Gittetal. Data in Brief 16(2018)369–375

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

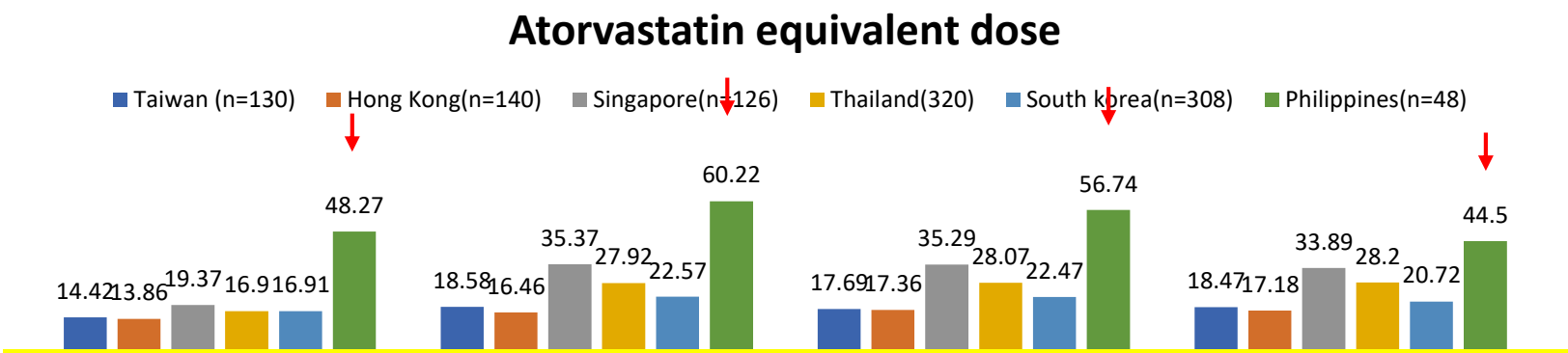
Indicates the change in lipid-lowering therapy at admission to a hospital for the treatment of an ACS, as well as the changes applied during hospital stay, at discharge and after a 120 day follow up period.



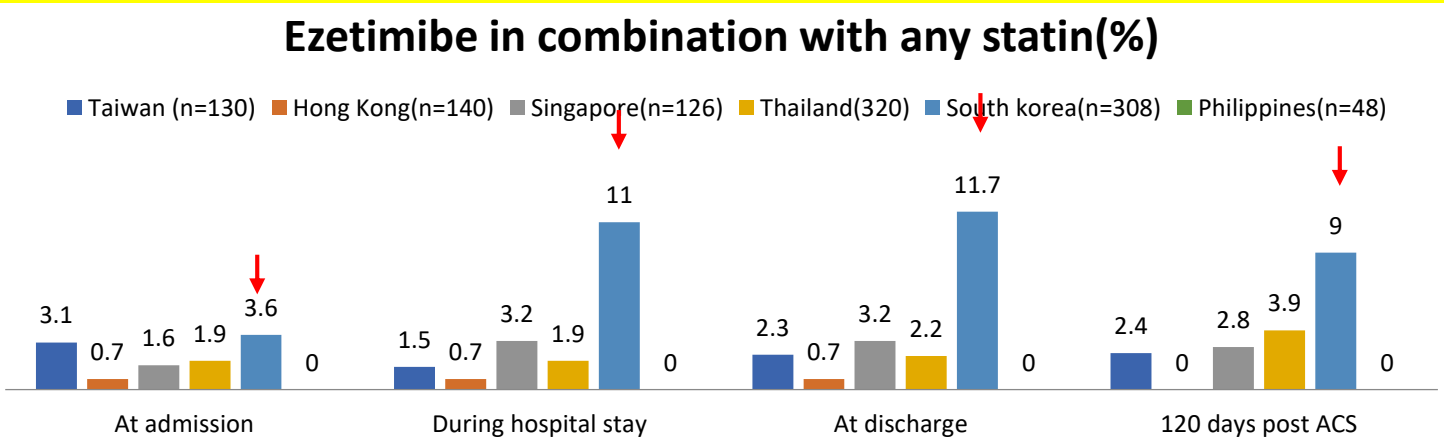

For internal use only; data was adapted

A.K.Gittetal. Data in Brief 16(2018)369–375

看atorvastatin的相對使用劑量，菲律賓使用明顯高於其他國家的statin劑量，可能為LDL-C goal attainment rate優於各國的原因 (但相對伴隨較多的副作用)




看add-on ezetimibe的比例，韓國明顯多於其他國家，可能為LDL-C goal attainment rate優於各國的原因 (我們還有繼續努力的空間)




A.K.Gittetal. Data in Brief 16(2018)369–375

# Treatment gaps persist in evidence-based use of statins in Taiwan…

Suboptimal Control of Lipid Levels: Results from 29 Countries Participating in the Centralized Pan-Regional Surveys on the Undertreatment of Hypercholesterolaemia (CEPHEUS)

**CEPHEUS (2016)**

CEPHEUS為亞太區的研究，針對35121位曾使用過降血脂藥物的病人，發現只有44.7%的病人LDL-C有達標(<100mg/dL)

DYSIS II

**Taiwan (2015)**

DYSIS II Taiwan為納入800 位post-ACS的病人的研究，發現只有20.7%的高風險病人LDL-C有達標 (<70mg/dL)

RESEARCH ARTICLE

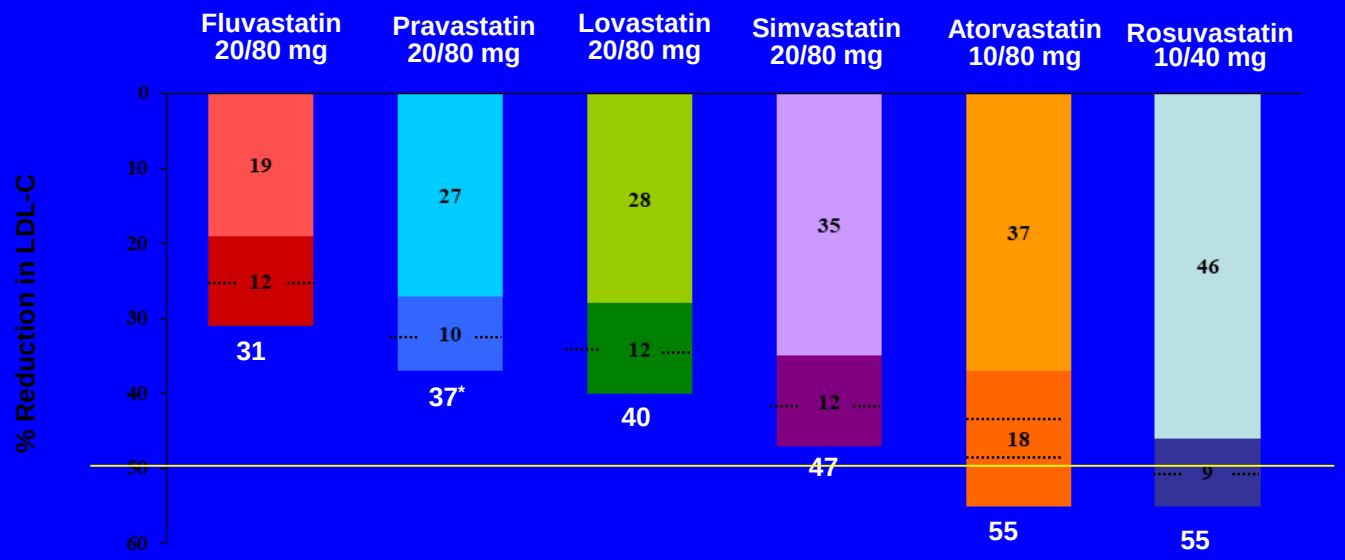
Determinants for Achieving the LDL-C Target of Lipid Control for Secondary Prevention of Cardiovascular Events in Taiwan

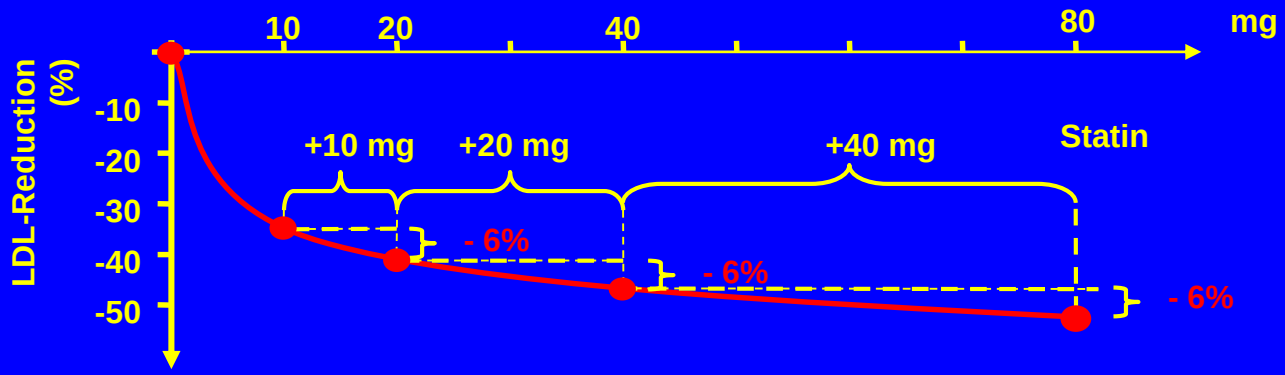
**T-SPARCLE (2015)**

T-SPARCLE 為台灣的研究，納入3486位有心臟疾病的病人，發現只有54%的病人LDL-C有達標 (<100mg/dL)

Atozet™
(ezetimibe and atorvastatin, MSD)

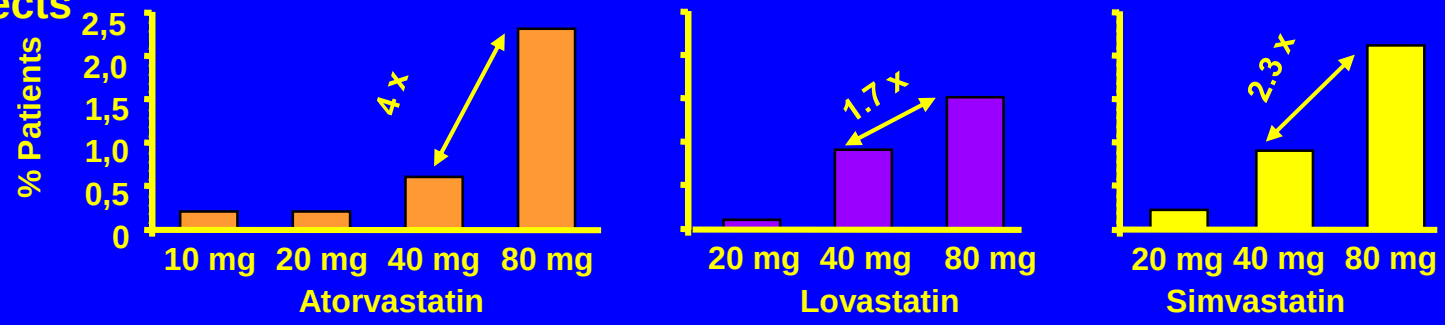
# 50% cut off - -對半切 - - by a simple click?




**“ Rule of 6 “**

## Adverse effects



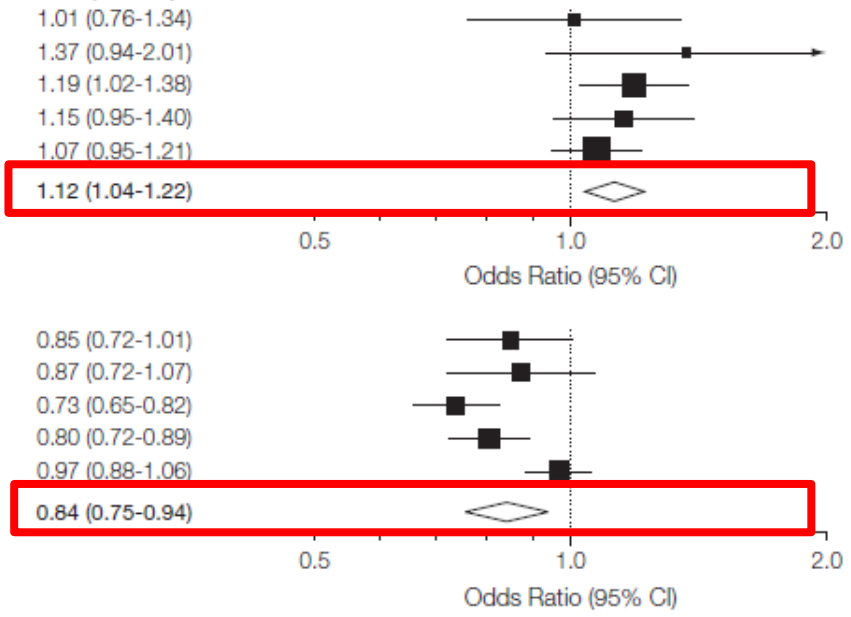

Med Clin North Am. 2000; 84:23

# 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

| | Cases/Total, No. (%) | | |
|---|---|---|---|
| | Intensive Dose | Moderate Dose | OR (95% CI) |
| **Incident Diabetes** | | | |
| PROVE IT–TIMI 22,[18] 2004 | 101/1707 (5.9) | 99/1688 (5.9) | 1.01 (0.76-1.34) |
| A to Z,[17] 2004 | 65/1768 (3.7) | 47/1736 (2.7) | 1.37 (0.94-2.01) |
| TNT,[15] 2005 | 418/3798 (11.0) | 358/3797 (9.4) | 1.19 (1.02-1.38) |
| IDEAL,[16] 2005 | 240/3737 (6.4) | 209/3724 (5.6) | 1.15 (0.95-1.40) |
| SEARCH,[5] 2010 | 625/5398 (11.6) | 587/5399 (10.9) | 1.07 (0.95-1.21) |
| **Pooled odds ratio** | **1449/16408 (8.8)** | **1300/16344 (8.0)** | **1.12 (1.04-1.22)** |
| Heterogeneity: $I^2=0\%$; $P=.60$ | | | |
| **Incident CVD** | | | |
| PROVE IT–TIMI 22,[18] 2004 | 315/1707 (18.4) | 355/1688 (21.0) | 0.85 (0.72-1.01) |
| A to Z,[17] 2004 | 212/1768 (12.0) | 234/1736 (13.5) | 0.87 (0.72-1.07) |
| TNT,[15] 2005 | 647/3798 (17.0) | 830/3797 (21.9) | 0.73 (0.65-0.82) |
| IDEAL,[16] 2005 | 776/3737 (20.8) | 917/3724 (24.6) | 0.80 (0.72-0.89) |
| SEARCH,[5] 2010 | 1184/5398 (21.9) | 1214/5399 (22.5) | 0.97 (0.88-1.06) |
| **Pooled odds ratio** | **3134/16408 (19.1)** | **3550/16344 (21.7)** | **0.84 (0.75-0.94)** |
| Heterogeneity: $I^2=74\%$; $P=.004$ | | | |




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

# Statin + Ezetamibe in combination exert Dual Inhibition: 18 ~25% LDL-C Reduction

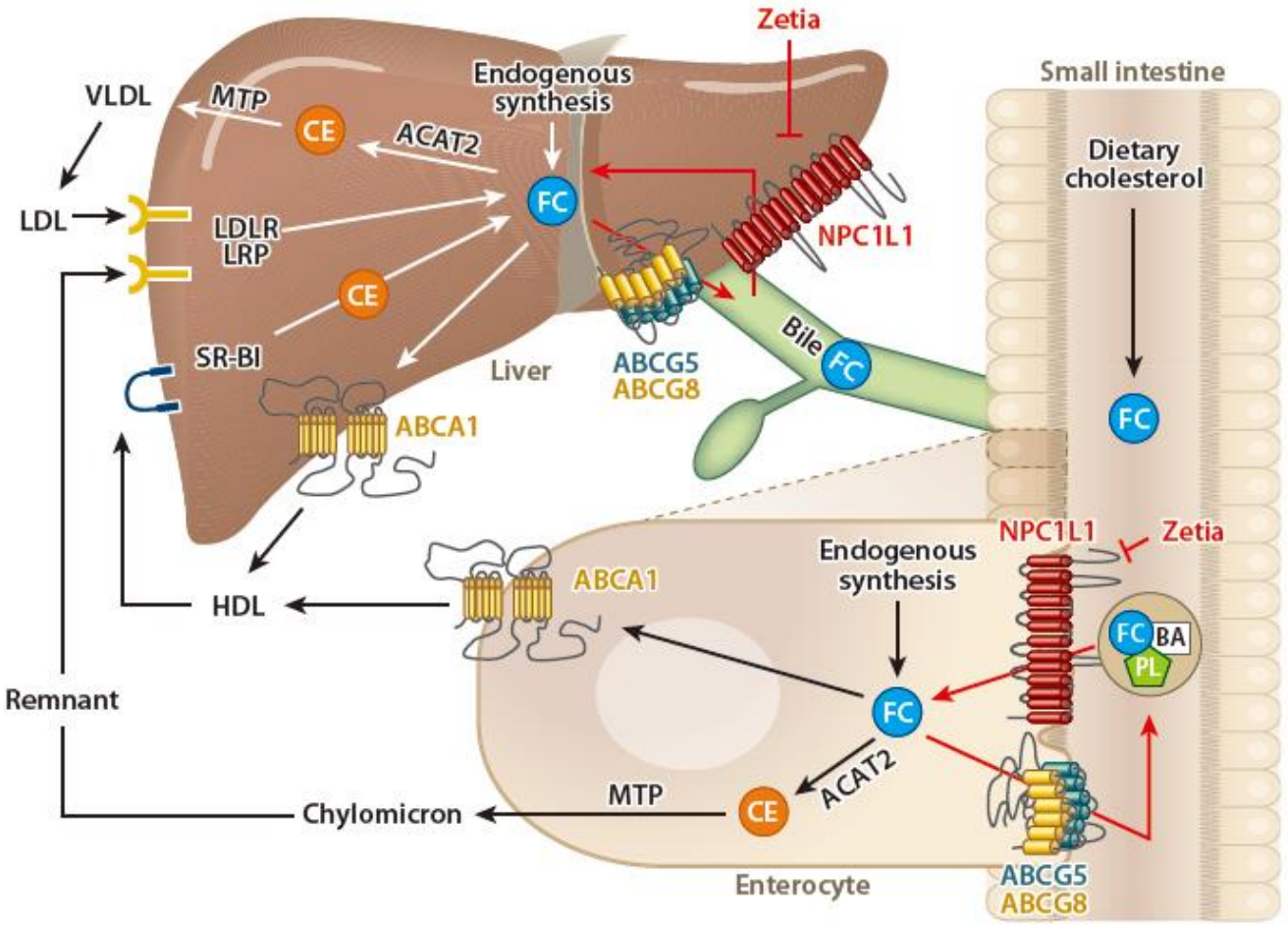
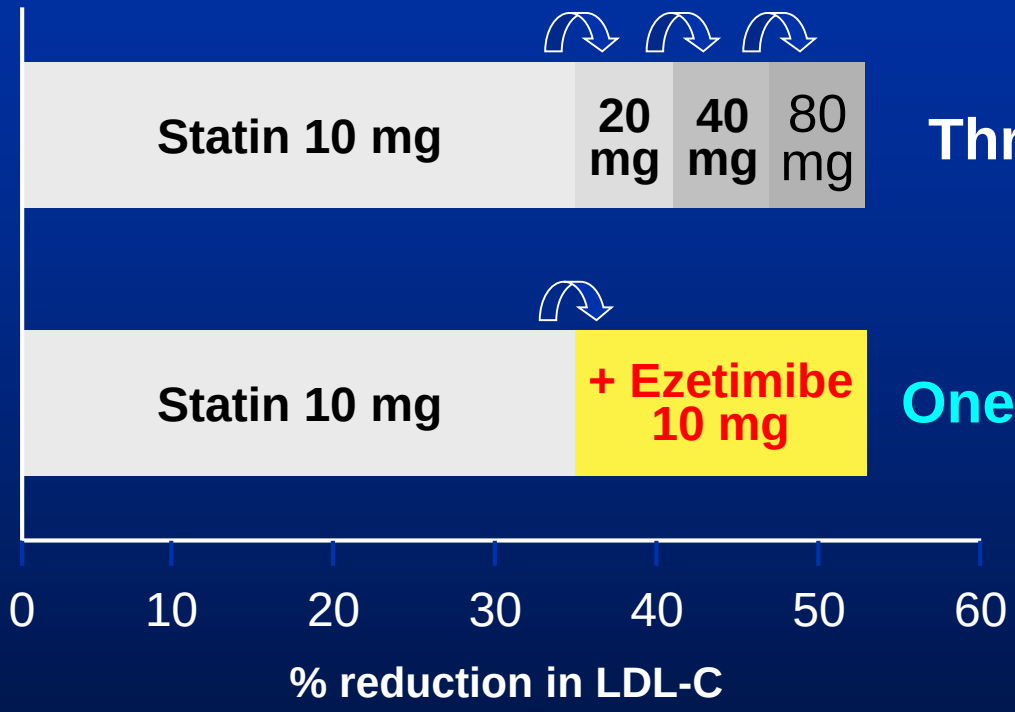



**Figure:** The role of Niemann-Pick C1-Like 1 (NPC1L1) in cholesterol transport in the small intestine and liver. In the lumen of the small intestine, unesterified free cholesterol (FC) from dietary intake and biliary secretion is solubilized in mixed micelles containing bile acids (BA) and phospholipids (PL). This solubilization is critical for the diffusion of FC across the unstirred water layer to reach intestinal brush border membranes, where FC is taken up into enterocytes by the apically localized NPC1L1 protein. Ezetimibe (Zetia) can inhibit this NPC1L1-dependent cholesterol uptake.

**Annu. Rev. Physiol. 2011. 73:3.1–3.21**

# Ezetimibe Co-administered with Statins: Easier Control of LDL-C

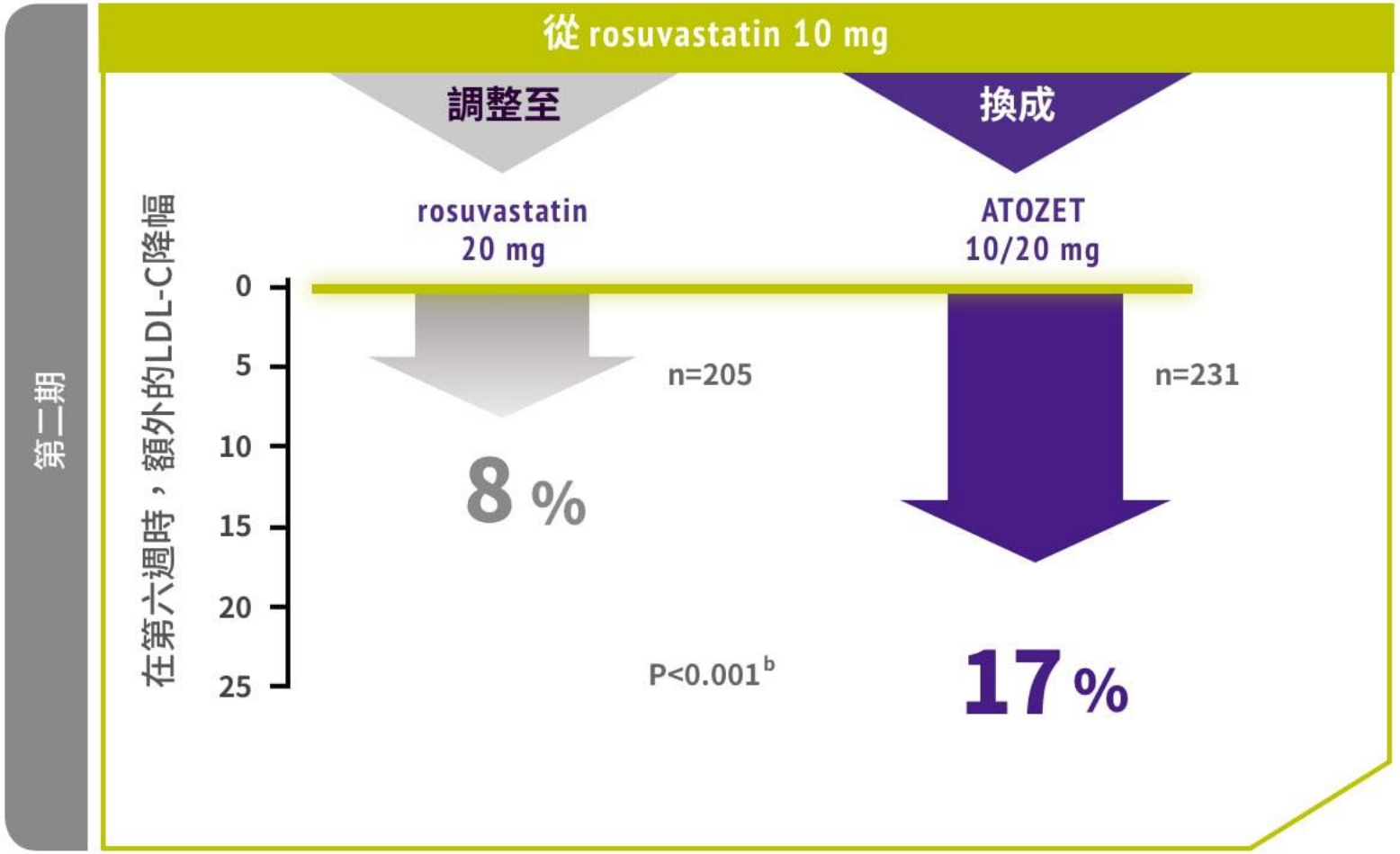



** One-step co-administration of ezetimibe equivalent to three-step statin titration

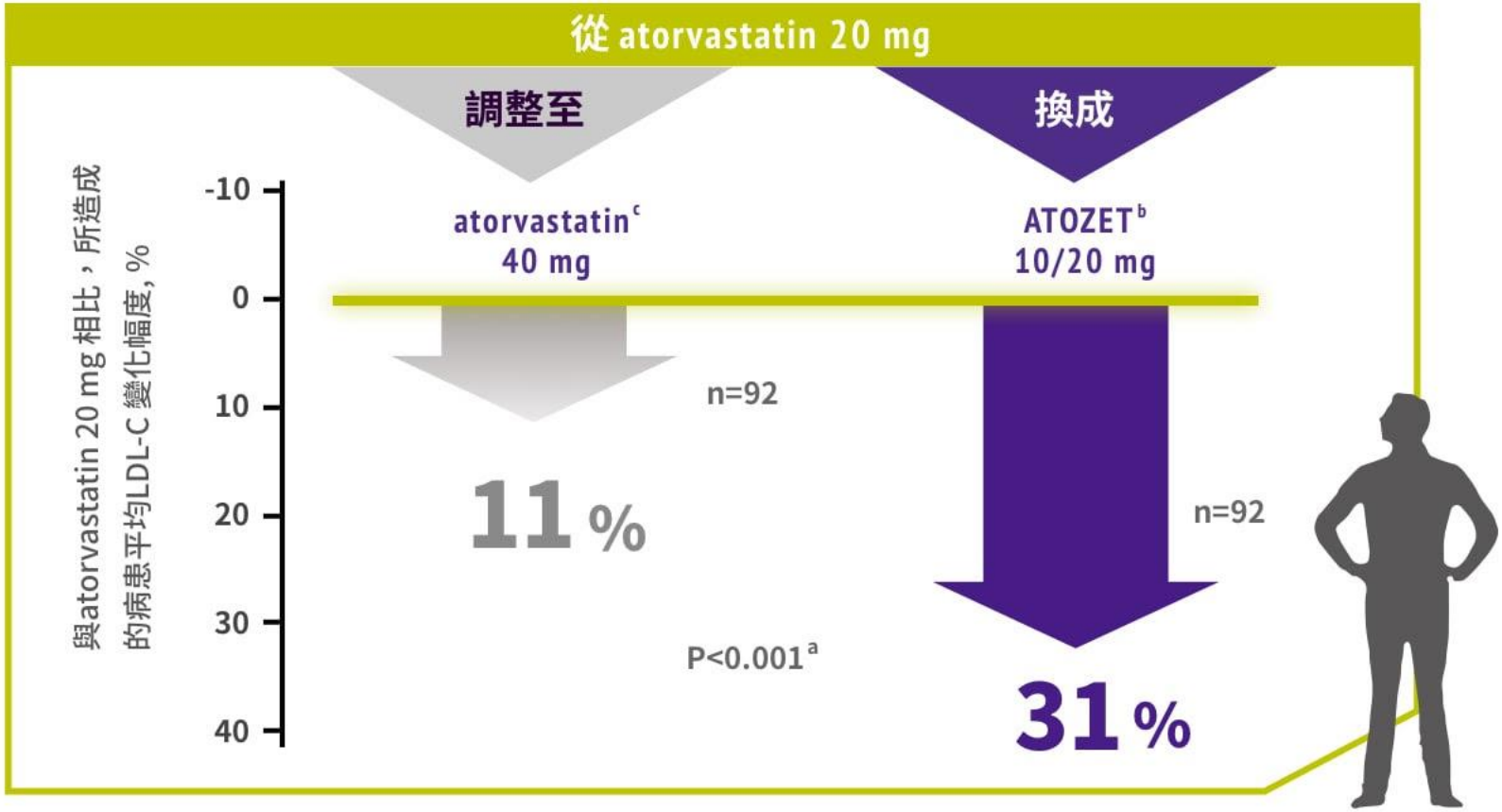
Adapted from Stein E *Eur Heart J Suppl* 2001;3(suppl E):E11-E16.

# “Strategy Challenge - -”

在一項針對第一期結束時使用 rosuvastatin 10 mg 治療 6 週後仍未達 LDL-C <100 mg/dL的高風險高膽固醇血症患者[a]進行的試驗中[1,2]



**在一項針對使用atorvastatin 20 mg 時 ，**
**LDL-C並未 < 100 mg/dL 的中等高風險高膽固醇血症患者* 進行的試驗中**




摘錄自Conard et al, 2008[1]

[a] ATOZET 10/20 mg vs atrovastatin 40 mg.

[b] mean on-statin baseline LDL-C = 120 mg/dL,

[c] mean on-statin baseline LDL-C = 118 mg/dL,

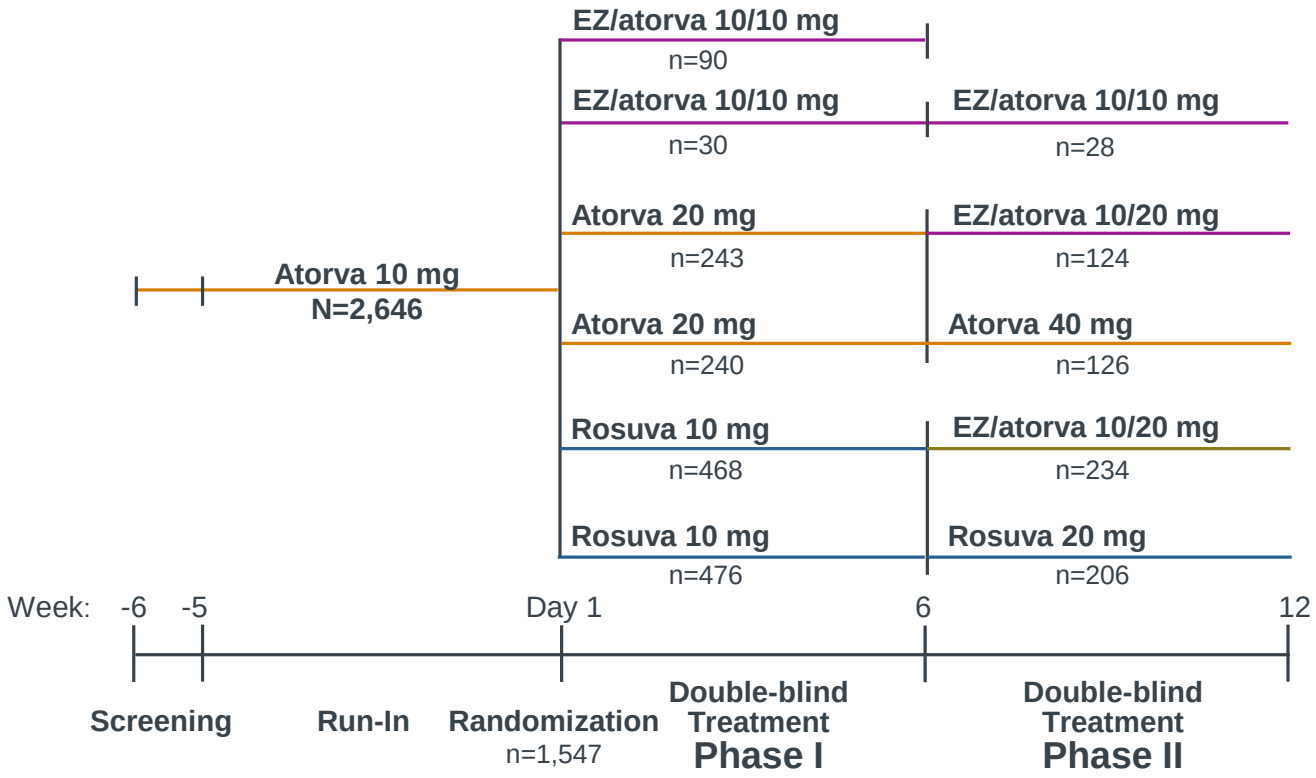
* Based on National Cholesterol Education Program Adult Treatment Panel III guidelines.[2]

# Clinical Data for Ezetimibe/Atorvastatin: Efficacy and Safety of Ezetimibe Added to Atorvastatin Versus Atorvastatin Uptitration or Switching to Rosuvastatin in Patients With Primary Hypercholesterolemia (PACE Study)

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

# 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) on atorvastatin 10 mg**



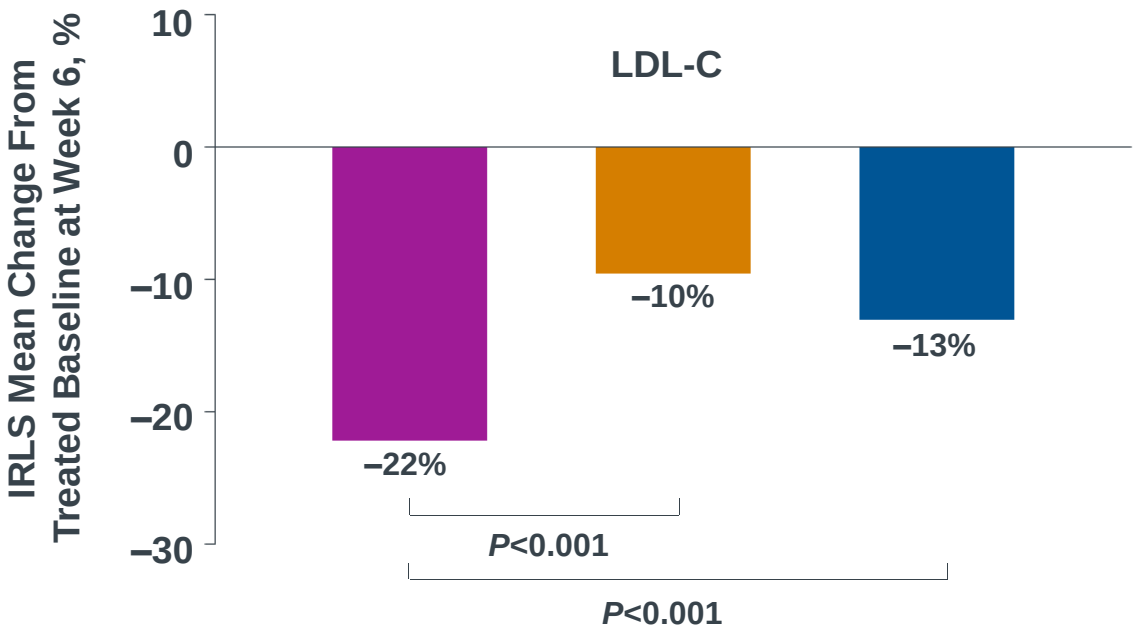

Adapted with permission from Bays HE et al.[1]

[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 I: Ezetimibe/Atorvastatin 10/10 mg Provided Greater Additional LDL-C Reduction vs Doubling Atorvastatin to 20 mg or Switching to Rosuvastatin 10 mg[1]




**Switching to ezetimibe/atorvastatin 10/10 mg**
**(n=120)**
**Mean on-statin baseline LDL-C = 121 mg/dL (~3.1 mmol/L)**

**Doubling atorvastatin to 20 mg**
**(n=480)**
**Mean on-statin baseline LDL-C = 120 mg/dL (~3.1 mmol/L)**

**Switching to rosuvastatin 10 mg**
**(n=939)**
**Mean on-statin baseline LDL-C = 121 mg/dL (~3.1 mmol/L)**

IRLS = iteratively reweighted least squares.

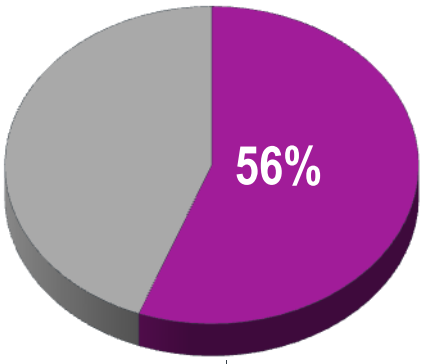
**1.** Bays HE et al. *Am J Cardiol*. 2013;112:1885–1895.

# PACE Phase I: Ezetimibe/Atorvastatin 10/10 mg Resulted in Greater Attainment of LDL-C <100 mg/dL (~2.6 mmol/L) vs Doubling Atorvastatin to 20 mg or Switching to Rosuvastatin 10 mg[1]

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

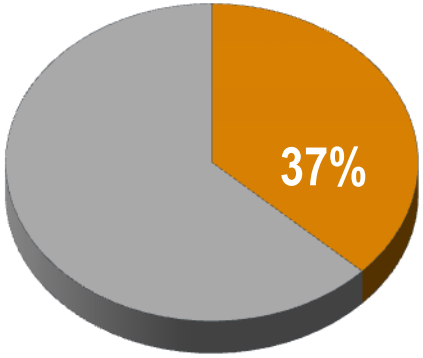
**Ezetimibe/atorvastatin 10/10 mg**
(n=119)

Mean treated baseline LDL-C:
121 mg/dL (~3.1 mmol/L)



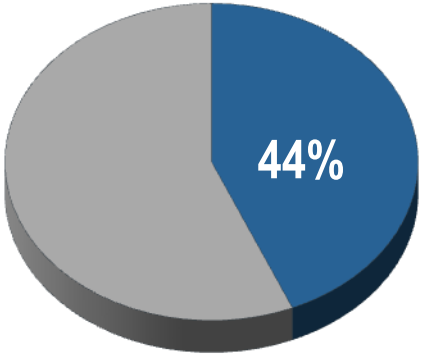

**Atorvastatin 20 mg**
(n=471)

Mean treated baseline LDL-C:
120 mg/dL (~3.1 mmol/L)




**Rosuvastatin 10 mg**
(n=915)

Mean treated baseline LDL-C:
121 mg/dL (~3.1 mmol/L)




***P*<0.001**

***P*<0.01**

**The IRLS mean decrease in LDL-C from statin-treated baseline was 22% with ezetimibe + atorvastatin 10 mg compared with 10% with atorvastatin 20 mg and 13% with rosuvastatin 10 mg; *P*<0.001 for each comparison vs ezetimibe + atorvastatin 10 mg.**

IRLS = iteratively reweighted least squares.

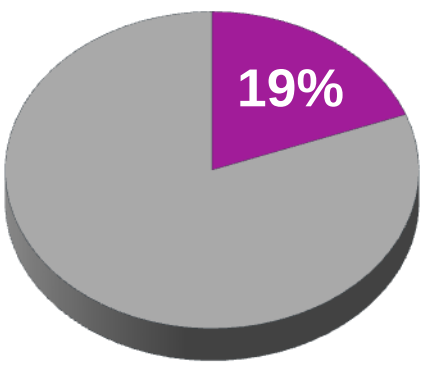
**1.** Bays HE et al. *Am J Cardiol*. 2013;112:1885–1895.

# PACE Phase I: Ezetimibe/Atorvastatin 10/10 mg Resulted in Greater Attainment of LDL-C <70 mg/dL (~1.8 mmol/L) vs Doubling Atorvastatin to 20 mg or Switching to Rosuvastatin 10 mg[1]

## High-risk Patients Reaching LDL-C <70 mg/dL (~1.8 mmol/L) at 6 weeks, as a Result of Greater LDL-C Reduction

**Ezetimibe/atorvastatin 10/10 mg**
(n=119)

Mean treated baseline LDL-C:
121 mg/dL (~3.1 mmol/L)

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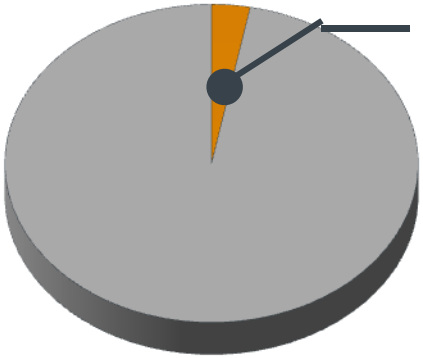
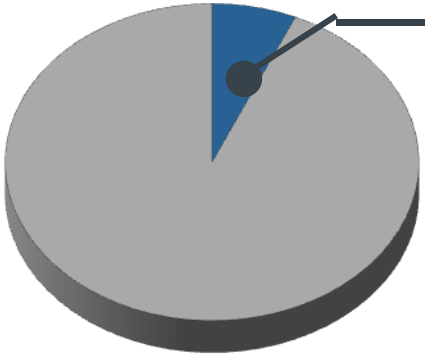
Mean treated baseline LDL-C:
120 mg/dL (~3.1 mmol/L)




**Rosuvastatin 10 mg**
(n=915)

Mean treated baseline LDL-C:
121 mg/dL (~3.1 mmol/L)

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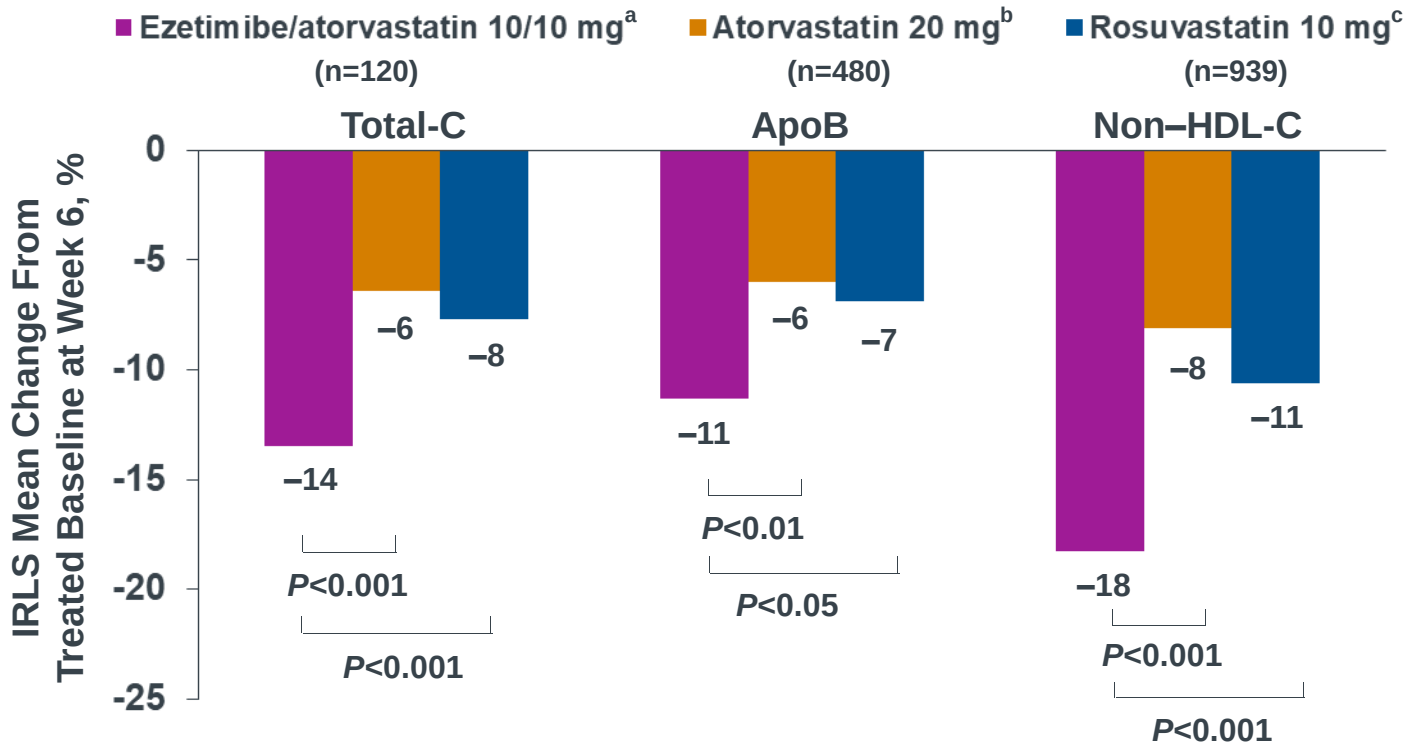
# PACE Phase I: Effect on Multiple Lipid Parameters[1]




[a]Mean treated baselines for group receiving ezetimibe/atorvastatin 10/10 mg: Total-C 203 mg/dL (~5.2 mmol/L), apoB 102 mg/dL, and non–HDL-C 150 mg/dL (~3.9 mmol/L).

[b]Mean treated baselines for group doubled to atorvastatin 20 mg: Total-C 203 mg/dL (~5.2 mmol/L), apoB 103 mg/dL, and non–HDL-C 150 mg/dL (~3.9 mmol/L).

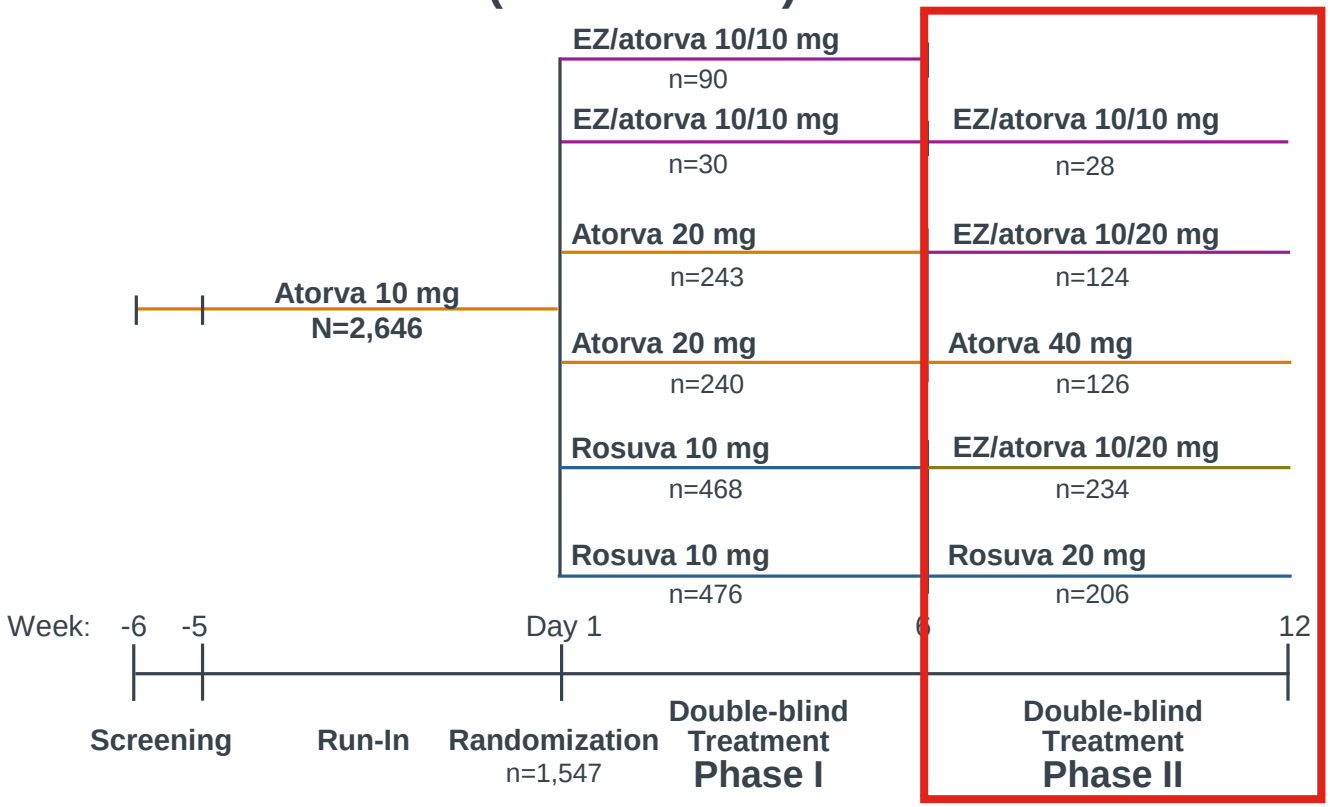
[c]Mean treated baselines for group switched to rosuvastatin 10 mg: Total-C 205 mg/dL (~5.3 mmol/L), apoB 104 mg/dL, and non–HDL-C 152 mg/dL (~3.9 mmol/L).

IRLS = iteratively reweighted least squares; Total-C = total cholesterol; ApoB = apolipoprotein B.

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

# 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**

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EZ = ezetimibe; Atorva = atorvastatin; Rosuva = rosuvastatin; CHD = coronary heart disease; CVD = cardiovascular disease.

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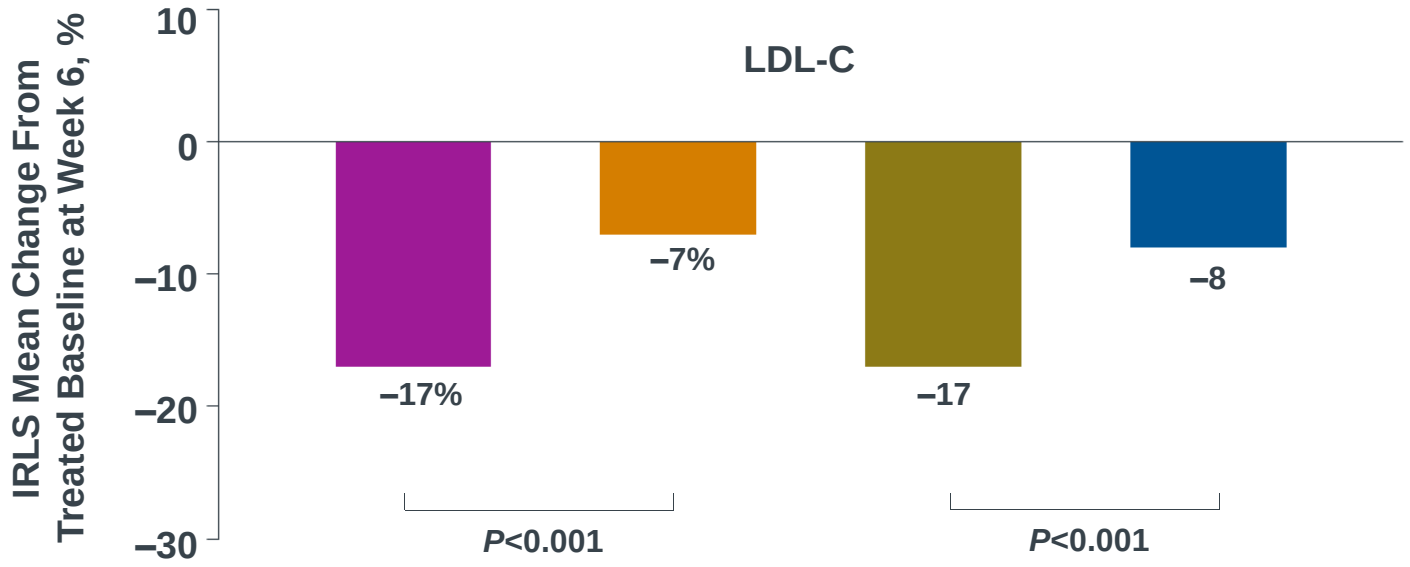
# PACE Phase II: Greater Additional LDL-C Reduction With Ezetimibe/Atorvastatin 10/20 mg[1]




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.

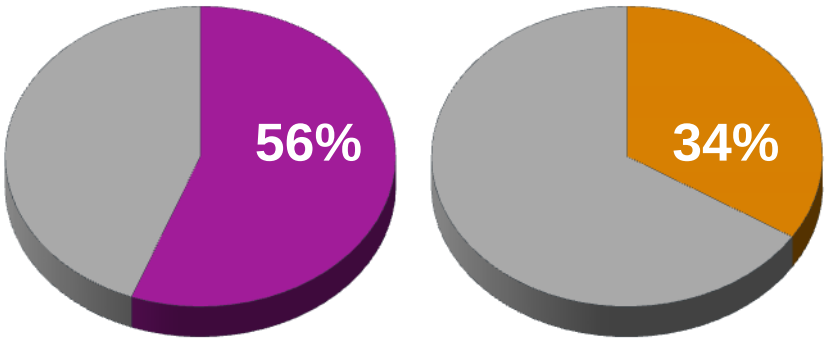
**1.** Bays HE et al. *Am J Cardiol*. 2013;112:1885–1895.

# 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

**Switching from atorvastatin 20 mg to ezetimibe/atorvastatin 10/20 mg (n=120) Mean on-statin baseline LDL-C = 119 mg/dL (~3.1 mmol/L)**

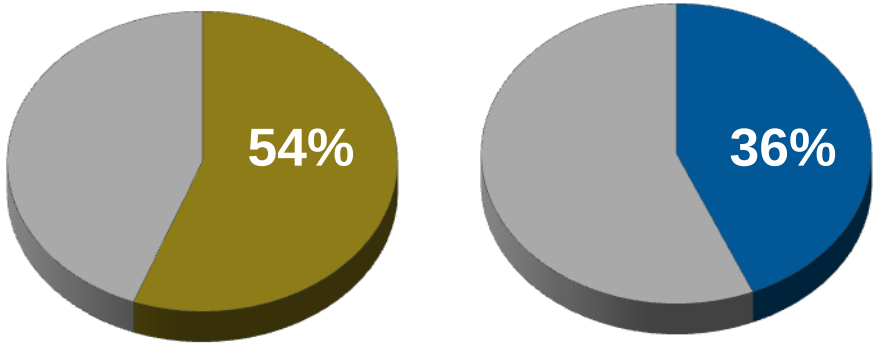
**Doubling atorvastatin to 40 mg (n=123) Mean on-statin baseline LDL-C = 121 mg/dL (~3.1 mmol/L)**




***P*<0.001**

**Switching from rosuvastatin 10 mg to ezetimibe/atorvastatin 10/20 mg (n=228) Mean on-statin baseline LDL-C = 119 mg/dL (~3.1 mmol/L)**

**Doubling rosuvastatin to 20 mg (n=201) Mean on-statin baseline LDL-C = 120 mg/dL (~3.1 mmol/L)**




***P*<0.001**

**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.

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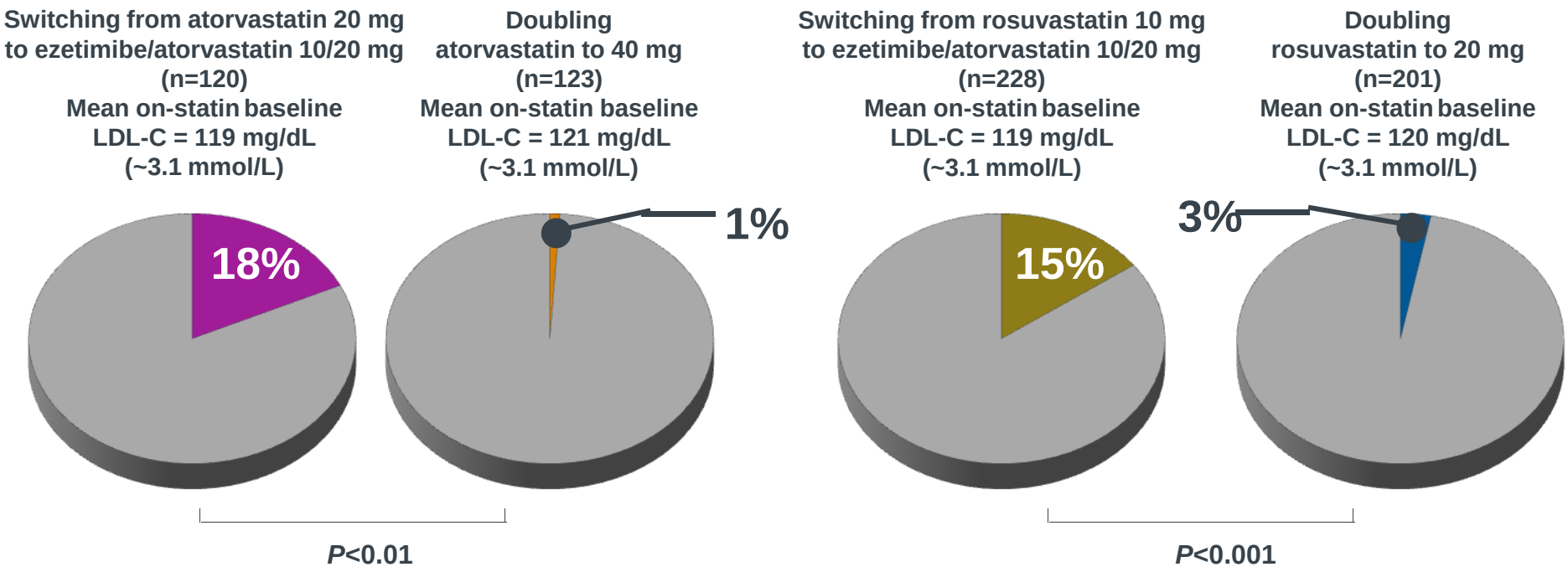
# PACE Phase II: Greater Attainment of LDL-C <70 mg/dL With Ezetimibe/Atorvastatin 10/20 mg[1]

## 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.**

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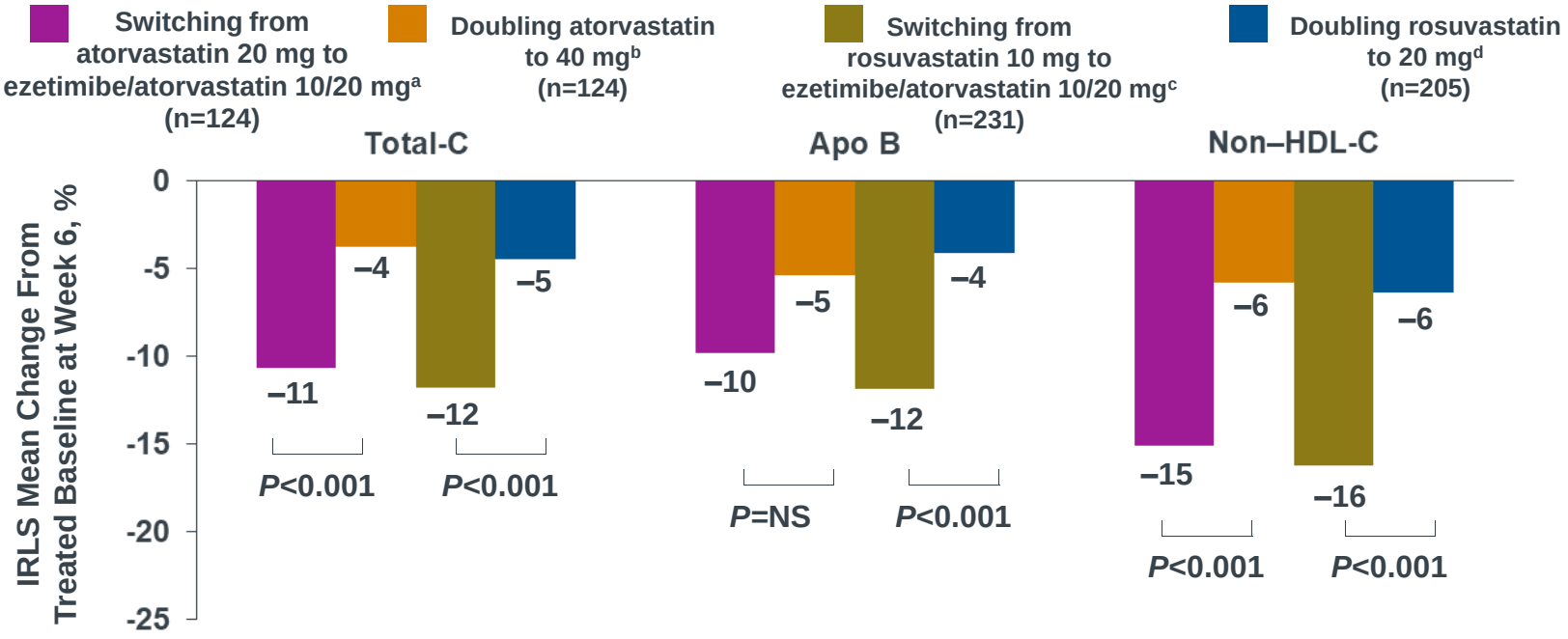



[a]Mean treated baseline for group switched from atorvastatin 20 mg to ezetimibe/atorvastatin 10/20 mg: Total-C 202 mg/dL (~5.2 mmol/L), apoB 102 mg/dL, non–HDL-C 151 mg/dL (~3.9 mmol/L)

[b]Mean treated baseline for group doubled to atorvastatin 40 mg: Total-C 203 mg/dL (~5.2 mmol/L), apoB 103 mg/dL, non–HDL-C 151 mg/dL (~3.9 mmol/L).

[c]Mean treated baseline for group switched from rosuvastatin 10 mg to ezetimibe/atorvastatin 10/20 mg: Total-C 204 mg/dL (~5.3 mmol/L), apoB 102 mg/dL, non–HDL-C 151 mg/dL (~3.9 mmol/L).

[d]Mean treated baseline for group doubled to rosuvastatin 20 mg: Total-C 203 mg/dL (~5.2 mmol/L), apoB 103 mg/dL, non–HDL-C 150 mg/dL (~3.9 mmol/L).

IRLS = iteratively reweighted least squares; Total-C = total cholesterol.

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

# Study Design

IMPROVE-IT

**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*

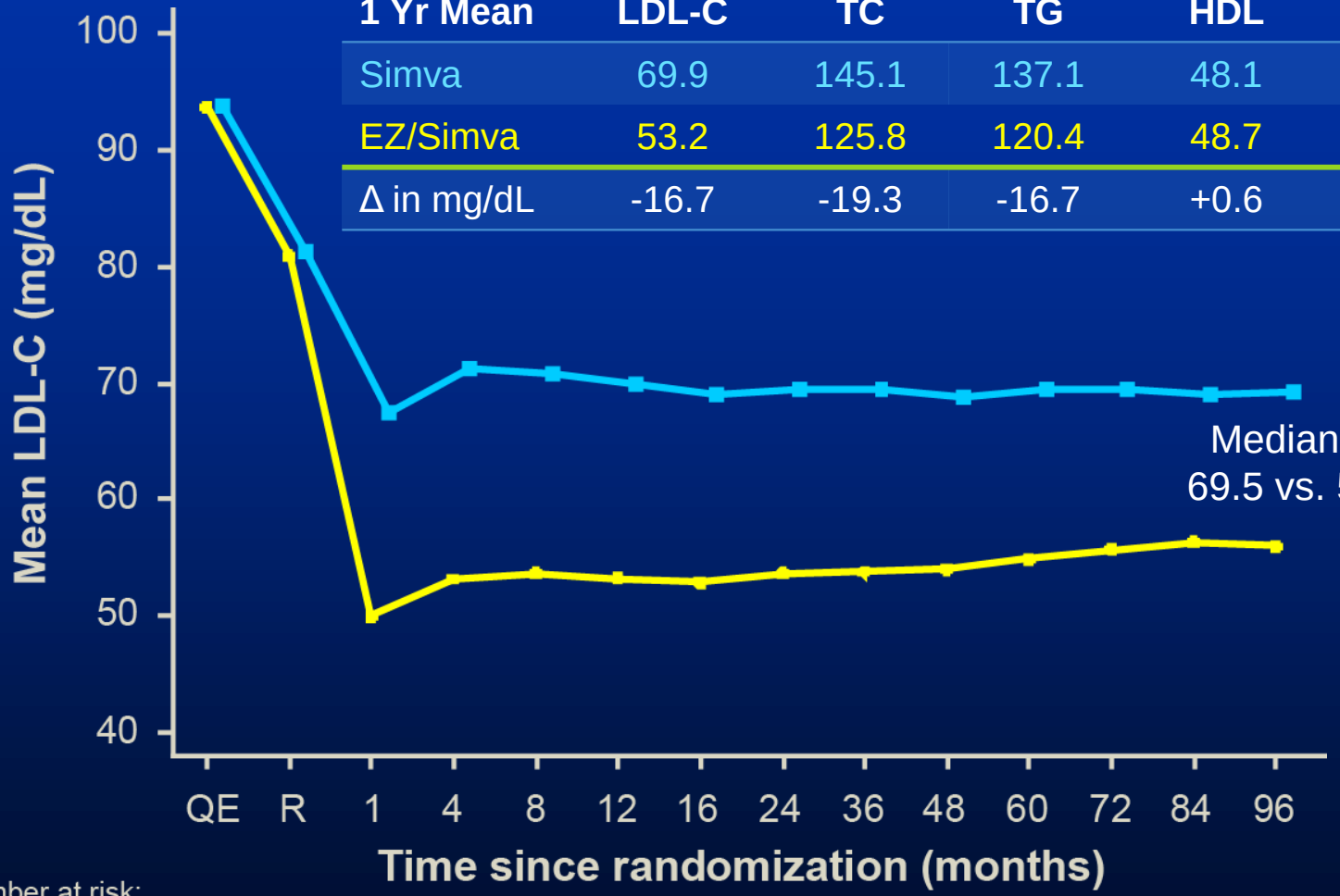
**Duration:** Minimum 2 ½-year follow-up **(at least 5250 events)**

**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

| 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 |



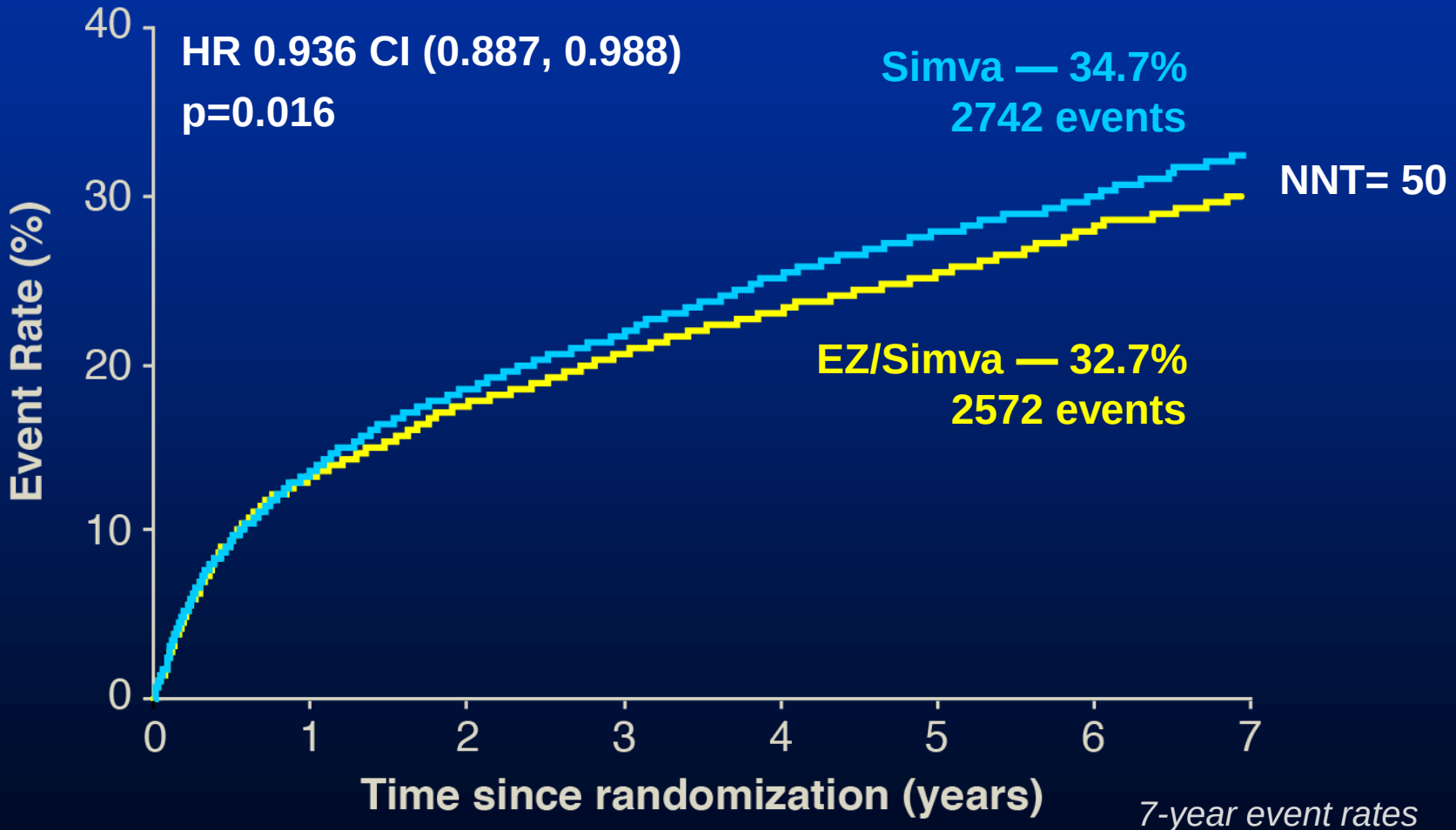

Median Time avg
69.5 vs. 53.7 mg/dL

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 |

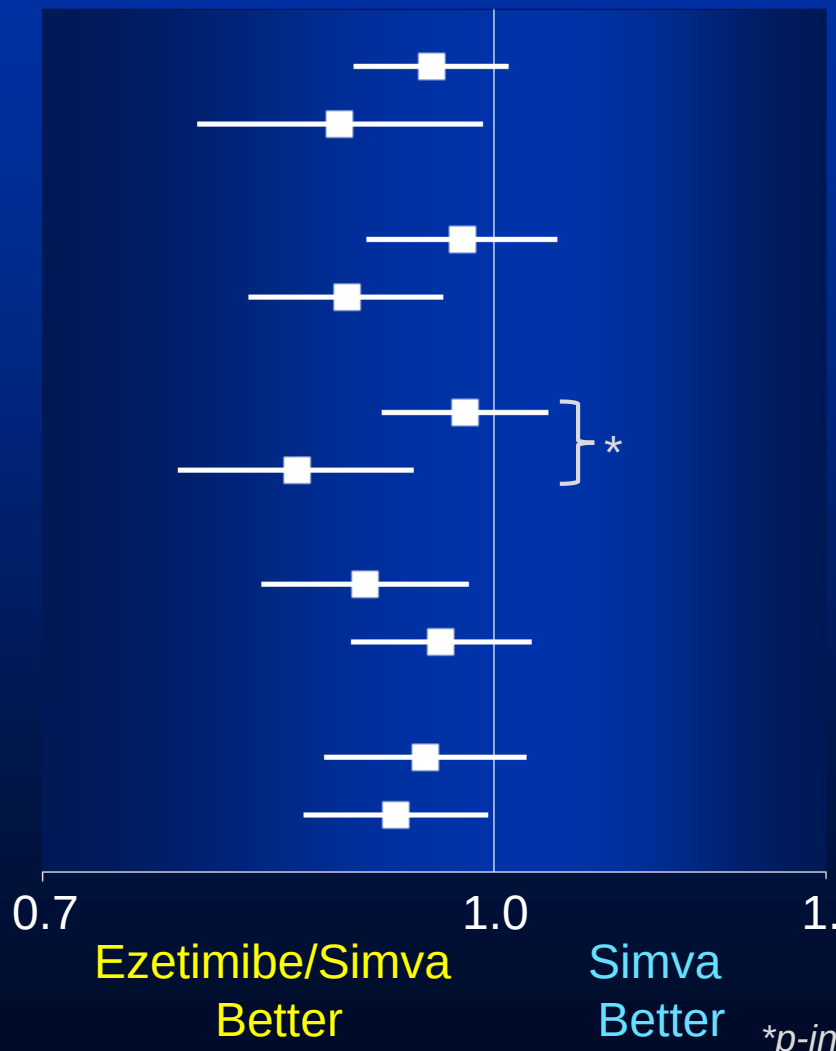
# Primary Endpoint — ITT

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




*7-year event rates*

# Major Pre-specified Subgroups

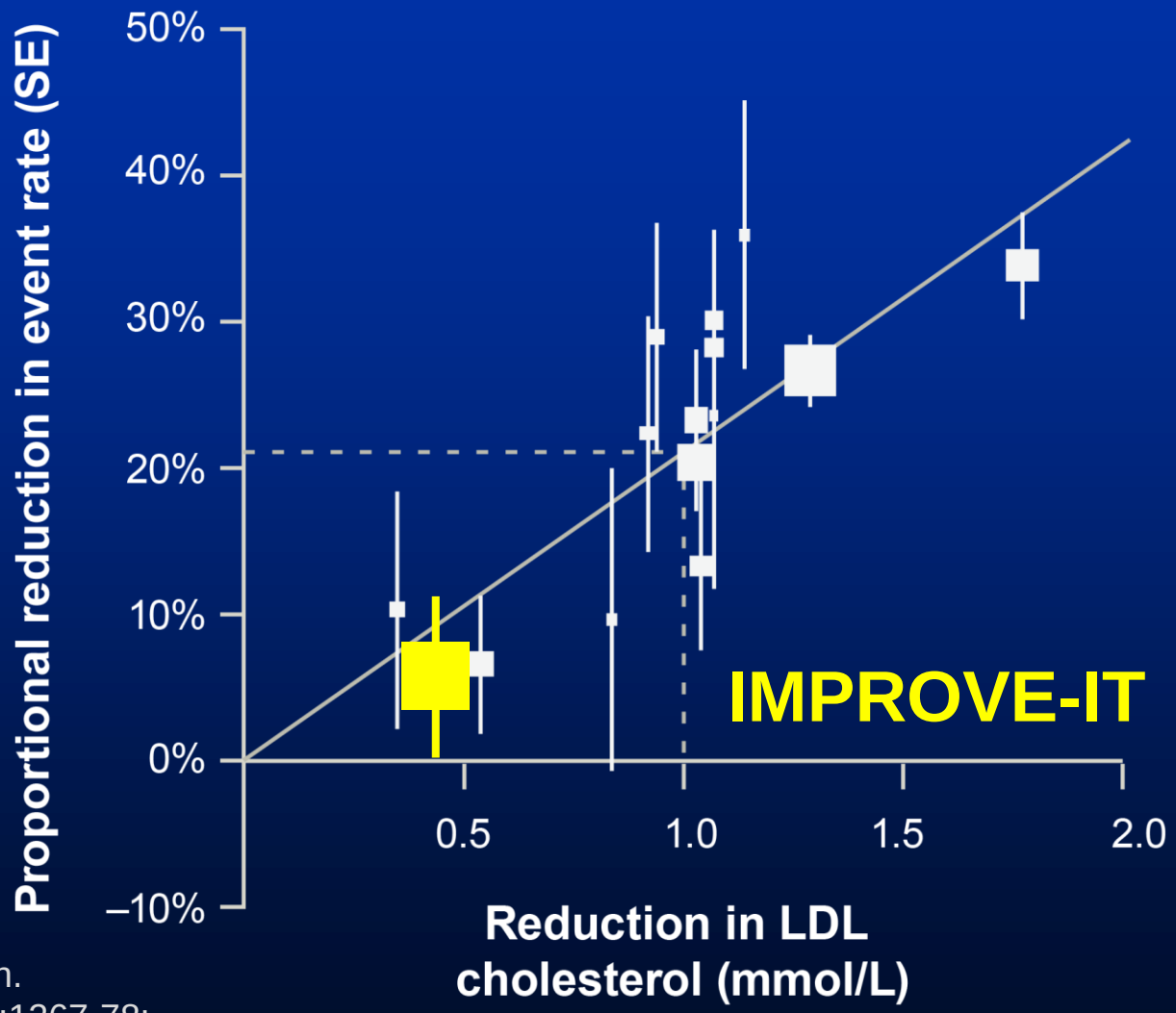



| | Simva† | EZ/Simva† |
|---|---|---|
| Male | 34.9 | 33.3 |
| Female | 34.0 | 31.0 |
| Age < 65 years | 30.8 | 29.9 |
| Age ≥ 65 years | 39.9 | 36.4 |
| No diabetes | 30.8 | 30.2 |
| Diabetes | 45.5 | 40.0 |
| Prior LLT | 43.4 | 40.7 |
| No prior LLT | 30.0 | 28.6 |
| LDL-C > 95 mg/dl | 31.2 | 29.6 |
| LDL-C ≤ 95 mg/dl | 38.4 | 36.0 |

†*7-year event rates*

**p-interaction = 0.023, otherwise > 0.05*

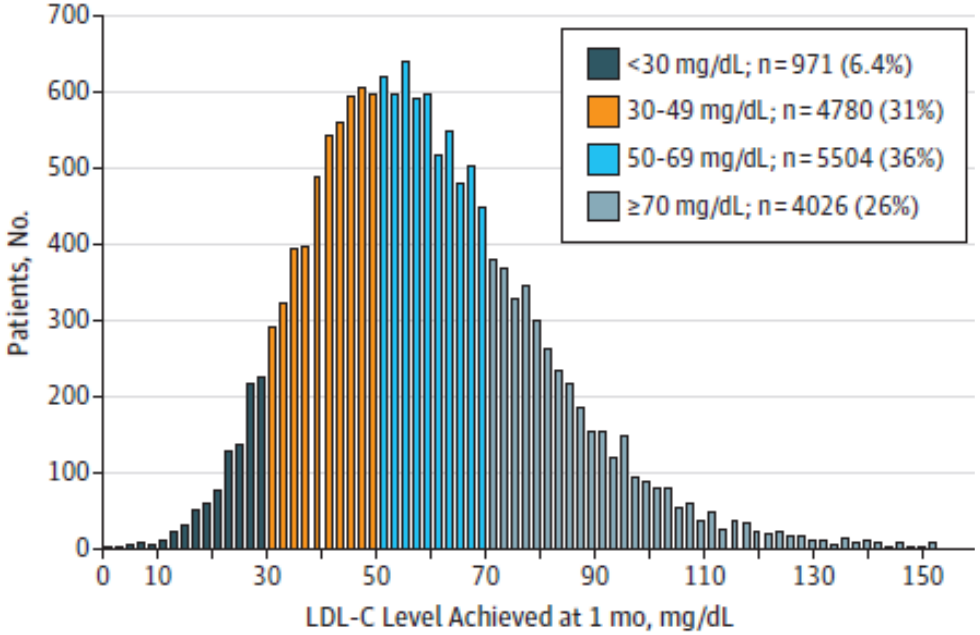
# IMPROVE-IT vs. CTT: Ezetimibe vs. Statin Benefit

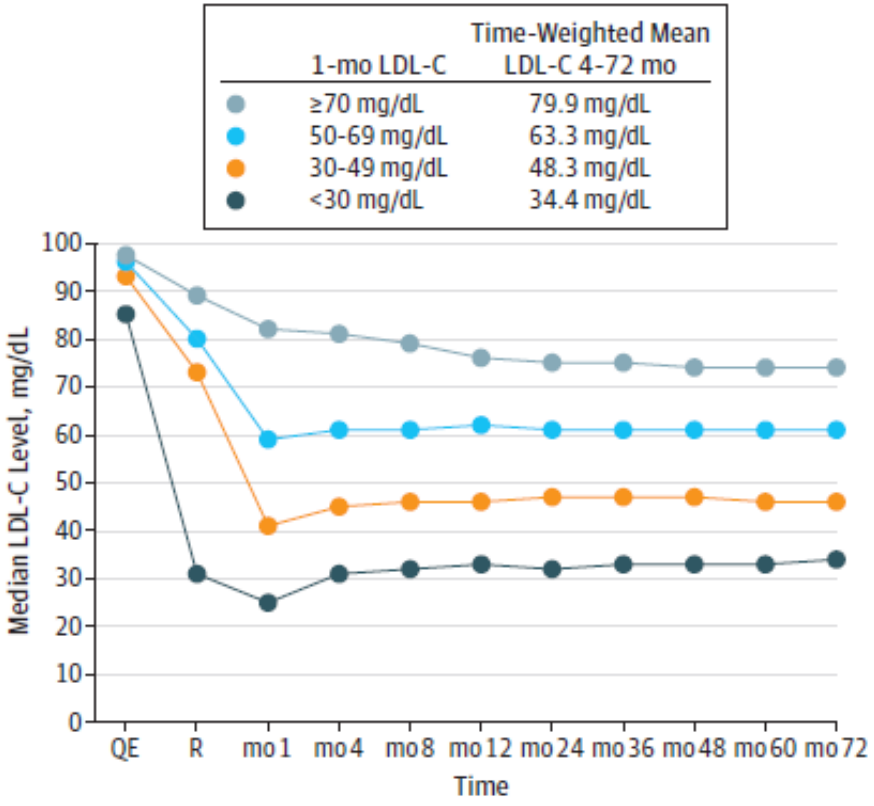



CTT Collaboration.
Lancet 2005; 366:1267-78;
Lancet 2010;376:1670-81.

# 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.

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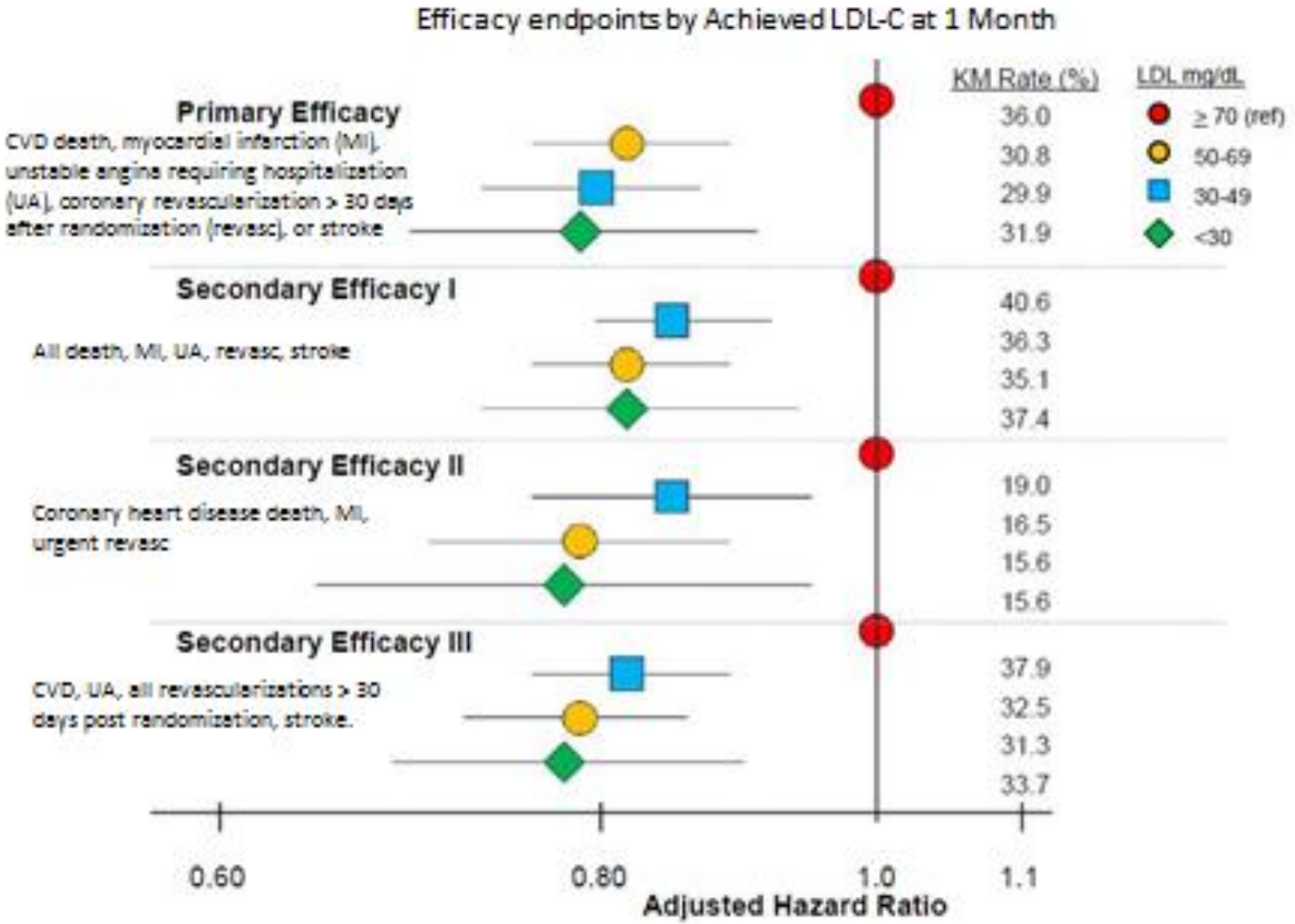
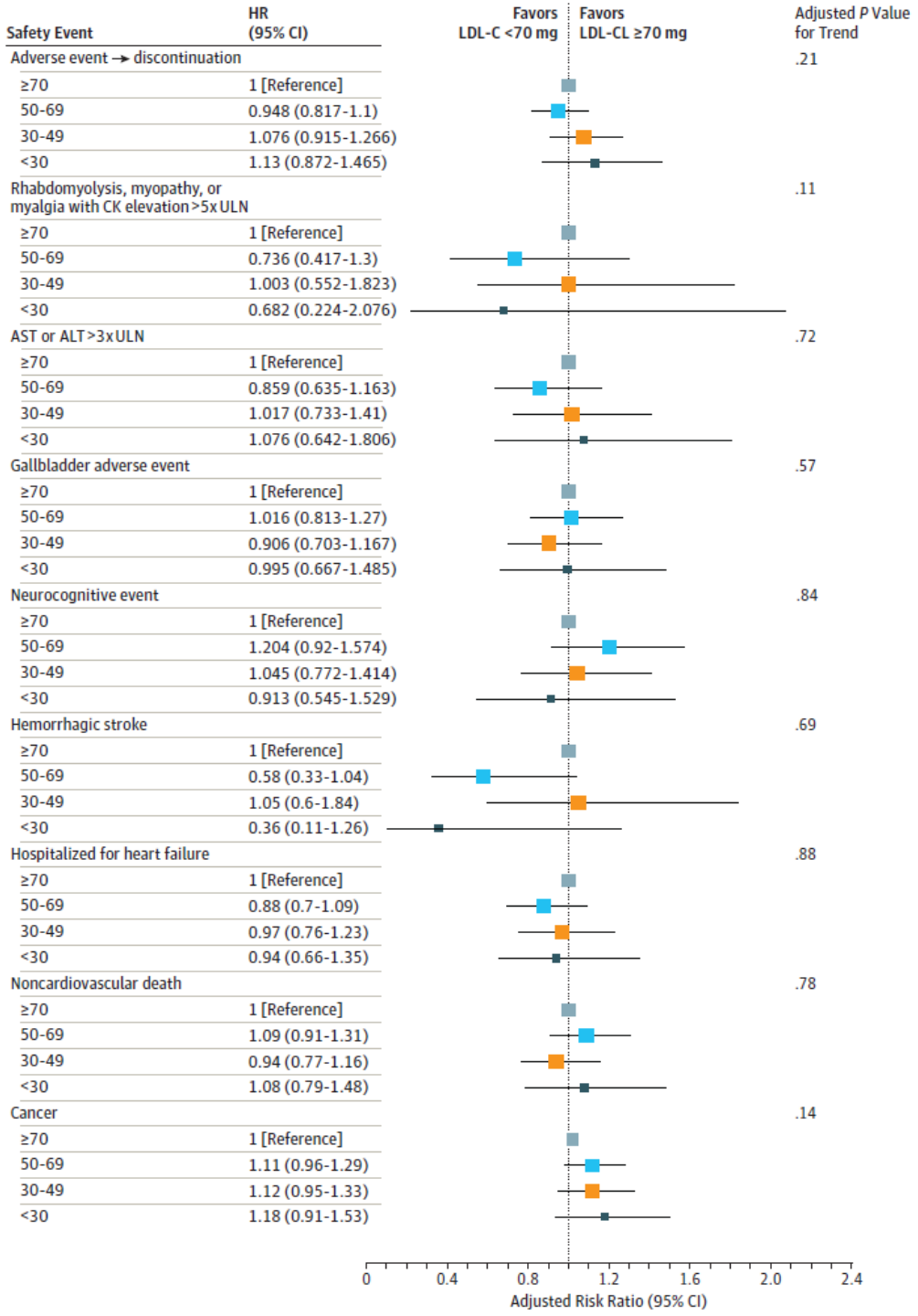



**JAMA Cardiol. 2017;2(5):547-555.**

Safety Events by Achieved LDL-C at 1 Month In IMPROVE-IT

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# IMPROVE-IT clinical implications. Should the "high-intensity cholesterol-lowering therapy" strategy replace the "high-intensity statin therapy"?

Atherosclerosis 240 (2015) 161–162

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Invited commentary

## IMPROVE-IT clinical implications. Should the "high-intensity cholesterol-lowering therapy" strategy replace the "high-intensity statin therapy"?

Luis Masana [a], Juan Pedro-Botet [b], Fernando Civeira [c, *]

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[b] Lipid and Vascular Risk Unit, Hospital del Mar, Universitat Autònoma de Barcelona, Barcelona, Spain
[c] Head Lipid Unit, Hospital Universitario Miguel Servet, IIS Aragon, Red Cardiovascular Research Network (RIC), Zaragoza, Spain

Classification of cholesterol-lowering therapy according to LDL cholesterol reduction intensity.

| Low-intensity cholesterol-lowering therapy (LICLT) ↓ LDLc < 30% | Mild-intensity cholesterol-lowering therapy (MICLT) ↓ LDLc 30–49% | High-intensity cholesterol-lowering therapy (HICLT) ↓ LDLc 50–60% | Very-high-intensity cholesterol-lowering therapy (VHICLT) ↓ LDLc > 60% |
|---|---|---|---|
| Simvastatin 10 mg | Atorvastatin 10–20 mg | Atorvastatin 40–80 mg | Atorvastatin 40–80 mg + Ezetimibe 10 mg |
| Pravastatin 10–20 mg | Rosuvastatin 5–10 mg | Rosuvastatin 20–40 mg | R –40 mg + Ezetimibe 10 mg |
| Lovastatin 10–20 mg | Simvastatin 20–40 mg | Simvastatin 20–40 mg + Ezetimibe 10 mg | |
| Fluvastatin 40 mg | Pravastatin 40 mg | Pravastatin 40 mg + Ezetimibe 10 mg | |
| Pitavastatin 1 mg | Lovastatin 40 mg | Lovastatin 40 mg + Ezetimibe 10 mg | |
| Ezetimibe 10 mg | Fluvastatin XL 80 mg | Fluvastatin 80 mg + Ezetimibe 10 mg | |
| | Pitavastatin 2–4 mg | Pitavastatin 2–4 mg + Ezetimibe 10 mg | |
| | Simvastatin 10 mg + Ezetimibe 10 mg | Atorvastatin 10–20 mg + Ezetimibe 10 mg | |
| | Pravastatin 20 mg + Ezetimibe 10 mg | | |
| | Lovastatin 20 mg + Ezetimibe 10 mg | Rosuvastatin 5–10 mg + Ezetimibe 10 mg | |
| | Fluvastatin 40 mg + Ezetimibe 10 mg | | |
| | Pitavastatin 1 mg + Ezetimibe 10 mg | | |

LDLc, low-density lipoprotein cholesterol.

Atherosclerosis. 2015 May;240(1):161-2

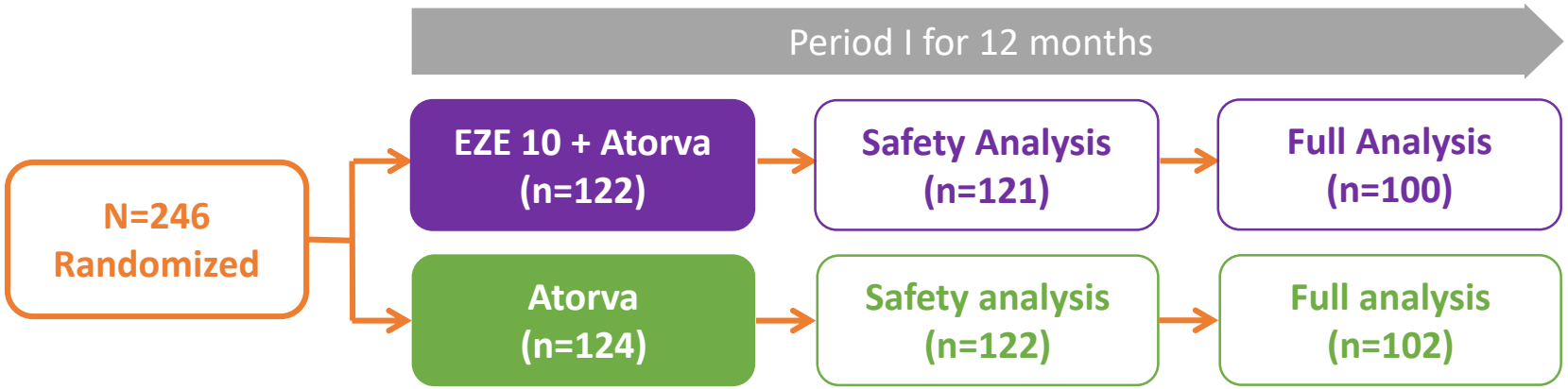
# PRECISE-IVUS Study

## Impact of Dual Lipid-Lowering Strategy with Ezetimibe and Atorvastatin on Coronary Plaque Regression in Patients with Percutaneous Coronary Intervention

Atozet™
(ezetimibe and atorvastatin, MSD)

# PRECISE-IVUS Study: Study Design

隨機、雙盲、為期 1 年的對照研究，比較 Ezetimibe + Atorvastatin 與 Atorvastatin 單獨治療的效益及安全性




**Patient Criteria:**

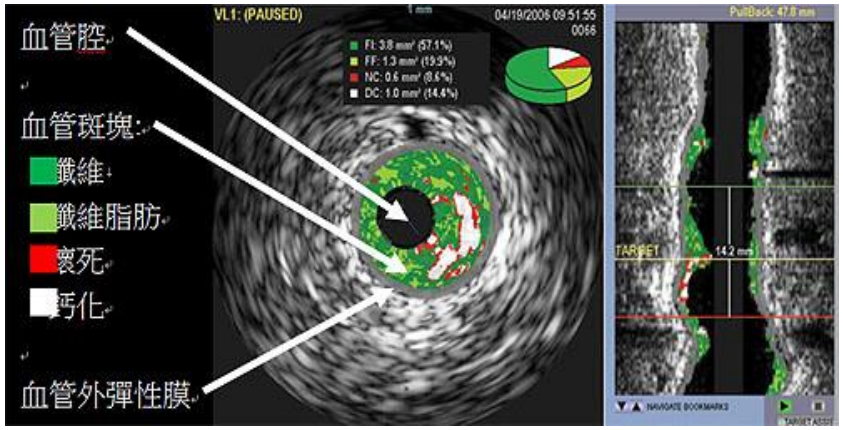
- Patients aged 30 to 85 with CAD underwent successful coronary angiography or PCI under IVUS guidance to treat ACS or SAP
- With an LDL-C level >100 mg/dl at entry
- Lipid profiles and other biomarker levels were measured at baseline and follow-up at 9 to 12 months

**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

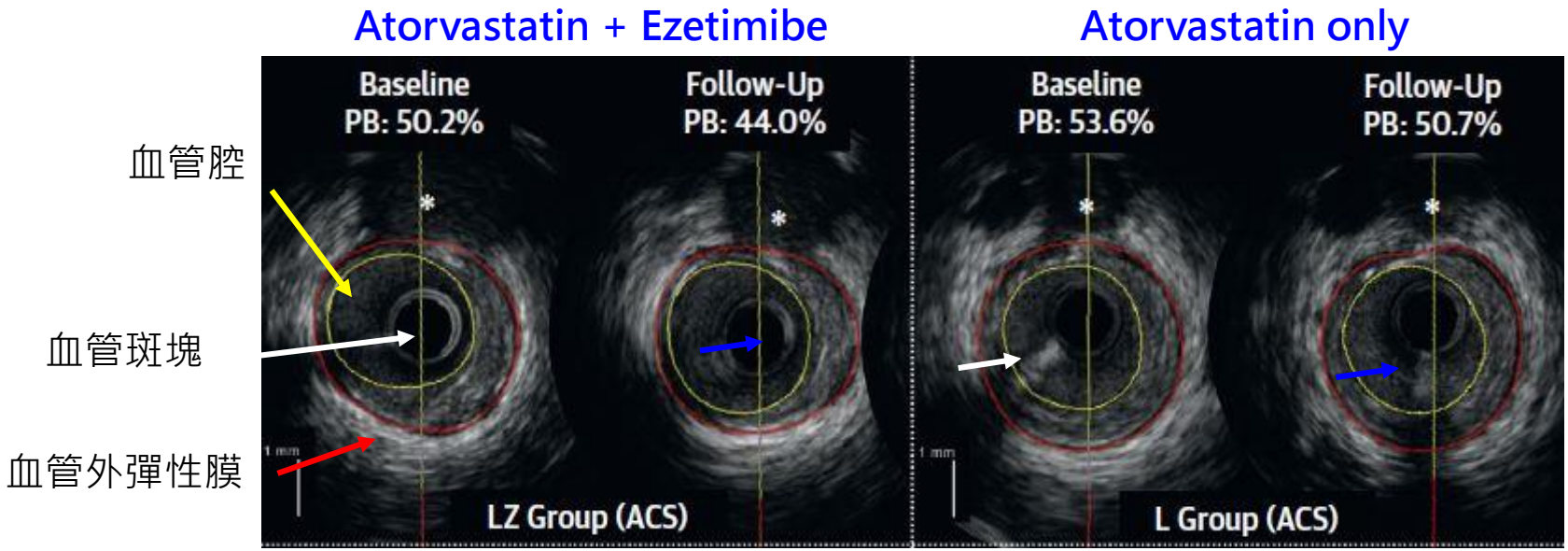
Atorva=atorvastatin; EZE=ezetimibe; CAD=coronary artery disease; PCI=percutaneous coronary intervention; ACS=acute coronary syndrome; SAP=stable angina pectoris;

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




For PAV, a significantly greater percentage of patients who received atorvastatin/ezetimibe showed coronary plaque regression .

**在病人使用Atorvastatin+Eze治療時，其粥樣斑塊體積百分比(PAV%)下降最為顯著**




IVUS images of the same cross sections at baseline and follow-up show outlined leading edges of lumen (yellow line) and external elastic membrane(red line)

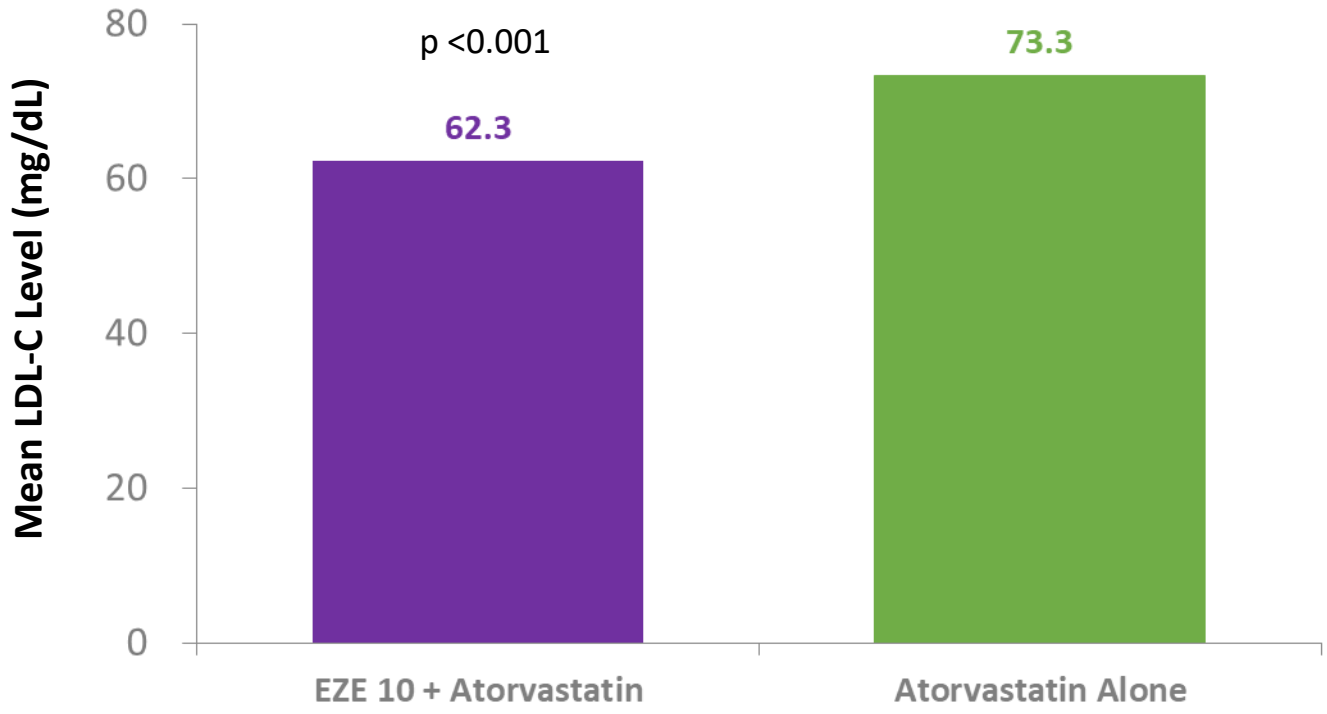
PB : plaque burden(粥狀硬化斑塊乘載量)

Tsujita K, et al J Am Coll Cardiol. 2015 Aug 4;66(5):495-507.

## PRECISE-IVUS Study

# Lower LDL-C with Ezetimibe + Atorvastatin

Ezetimibe + Atorvastatin 可達到顯著較低的 LDL-C 值

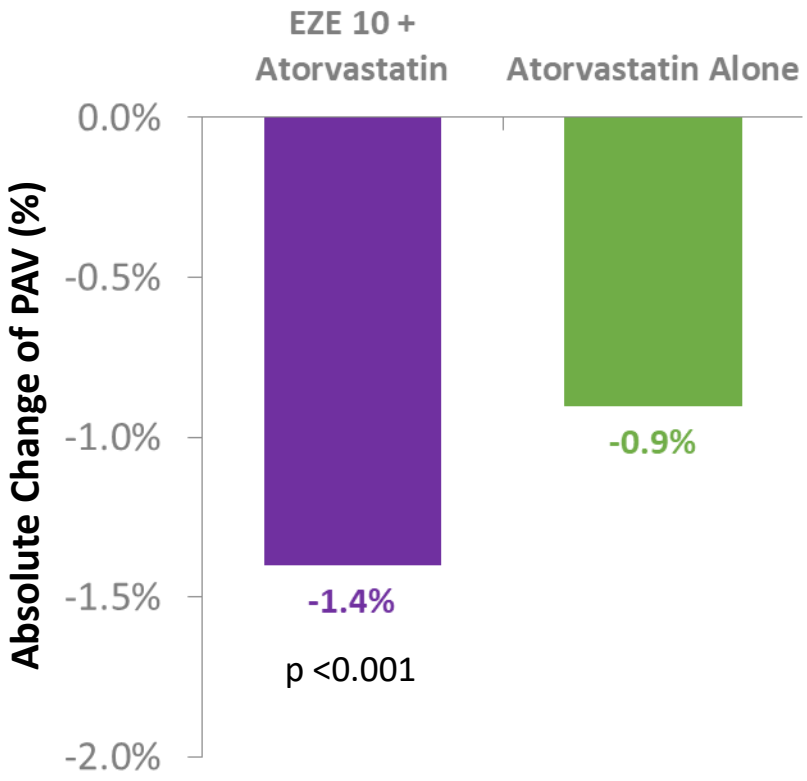


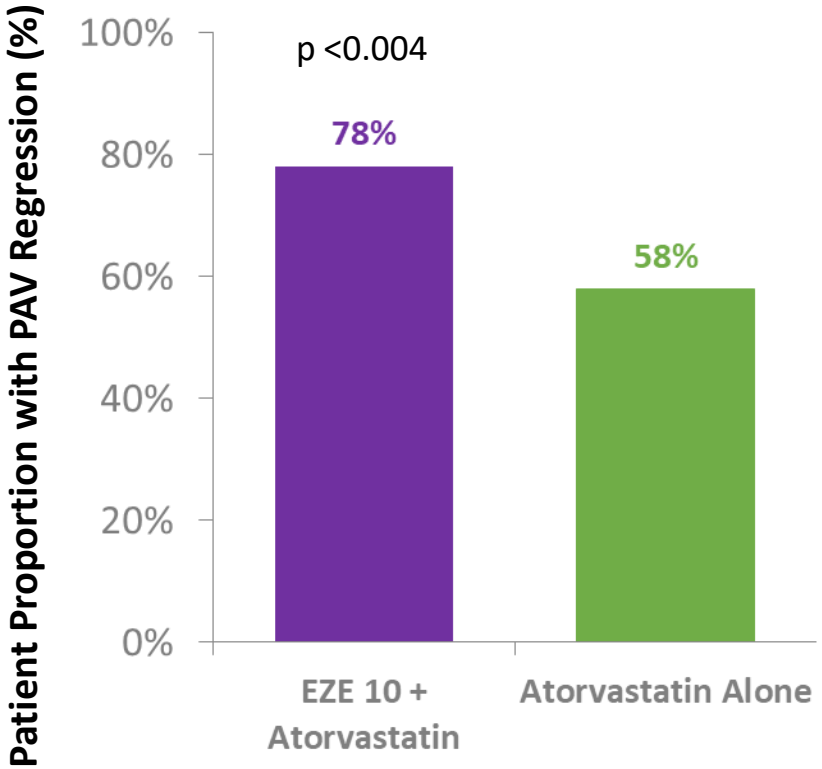

EZE=ezetimibe.

## PRECISE-IVUS Study

# Significantly Better Improvement in PAV

接受 Ezetimibe + Atorvastatin 的患者 PAV 消退的比例較高、且 PAV 消退的患者比例較多

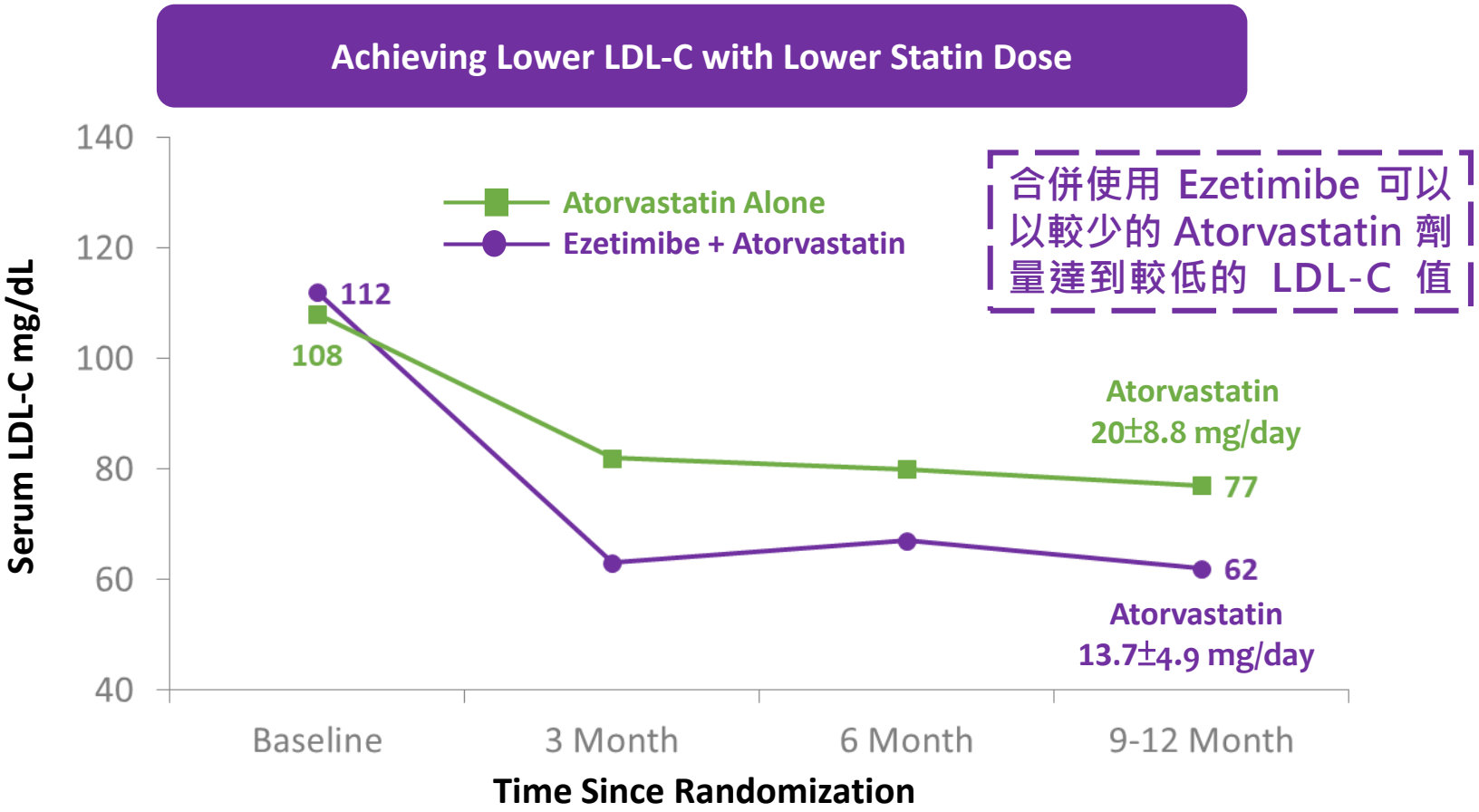



EZE=ezetimibe; PAV=percent atheroma volume.

PRECISE-IVUS Study: ACS Subgroup

# Lower Statin Dose with Higher Potency While Combining with Ezetimibe



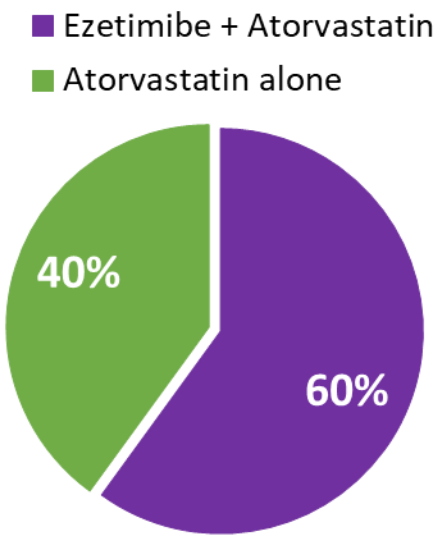

1. Tsujita K, et al. Atherosclerosis. 2016;251(5):367-72.

PRECISE-IVUS Study: ACS Subgroup

# Achieving LDL-C Target Is the Predictor of Coronary Plaque Regression

PAV 消退的患者有 60% 接受 Ezetimibe 合併治療，且平均 LDL-C 值顯著較低為 62±14 mg/dL

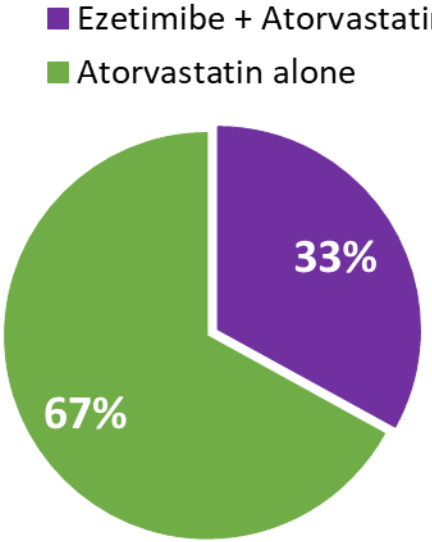
**Regression in PAV (n=67)**




**60%** patients
on ezetimibe+atorvastatin

**62±14 mg/dL**
LDL-C at follow-up, p=0.004

**Progression in PAV (n=33)**



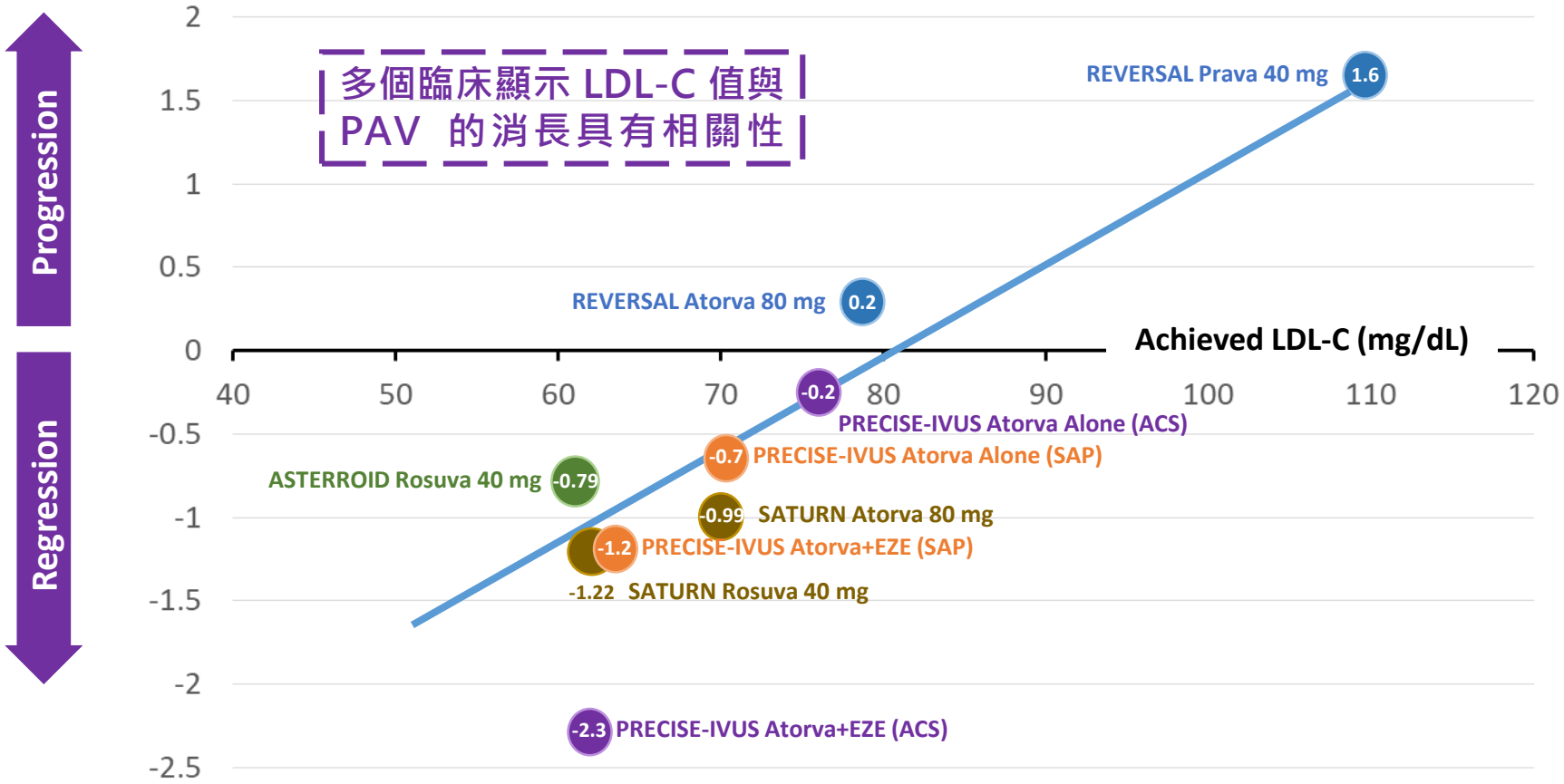

**67%** patients
on atorvastatin alone

**81±22 mg/dL**
LDL-C at follow-up

Atorva=atorvastatin; EZE=ezetimibe; PAV=percent atheroma volume.

PRECISE-IVUS Study

# Relationship Between LDL-C and PAV




EZE=ezetimibe; PAV=percent atheroma volume.

# Ezetimibe in Prevention of Cerebro- and Cardiovascular Events in Middle- to High-Risk, Elderly (75 Years Old or Over) Patients With Elevated LDL-Cholesterol: A Multicenter, Randomized, Controlled, Open-Label Trial

## EWTOPIA 75

*The present study is registered, number UMIN000001988.

Hidenori Arai, Jun Sasaki, Koutaro Yokote, Masanari Kuwabara, Kazumasa Harada, Takumi Imai, Shiro Tanaka, Yasuo Ohashi, Hideki Ito, Yasuyoshi Ouchi, on behalf of the EWTOPIA investigators

P.I.: **Yasuyoshi Ouchi**, M.D., Ph.D.
Federation of National Public Service Personnel
Mutual Aid Associations Toranomon Hospital, Tokyo, Japan
Professor Emeritus, University of Tokyo

SCIENTIFIC 2018 SESSIONS

**Late-breaking clinical trials session**
**November 10, 2018 Chicago, IL, USA**

# Study Design of EWTOPIA 75

EWTOPIA75
ユートピア75

≥75 years old at the time of enrollment
Outpatients
Serum LDL-C level ≥140 mg/dL
Male & Female

Assignment factors
(minimization method)
1. Site
2. Age
3. Male/female
4. LDL-C level

Randomization

Dietary counseling* only

Dietary counseling* + ezetimibe 10 mg/day

* Dietary counseling should be conducted based on 2007 Guideline for Prevention of ASCVD by Japan Atherosclerosis Society.

Follow-up for at least 3 years

Assessment of the primary & secondary endpoints

## PROBE design

**Prospective Randomized Open-label Blinded- Endpoint**

【Inclusion criteria】
Patients with at least 1 of 7 conditions

1. Diabetes mellitus
2. Hypertension
3. Low HDL-cholesterolemia
4. Hypertriglyceridemia
5. Smoking
6. Previous history of cerebral infarction documented by apparent clinical symptoms and CT/MRI scanning
7. Peripheral artery disease

◉ Enrollment period: February 2009 to December 2014 (363 institutions participated.)
◉ Follow-up period: February 2009 to March 2016

A composite of the following atherosclerotic cardiovascular events
◉ Sudden cardiac death ◉ Fatal & nonfatal myocardial infarction
◉ Coronary revascularization (PCI or CABG) ◉ Fatal & nonfatal stroke

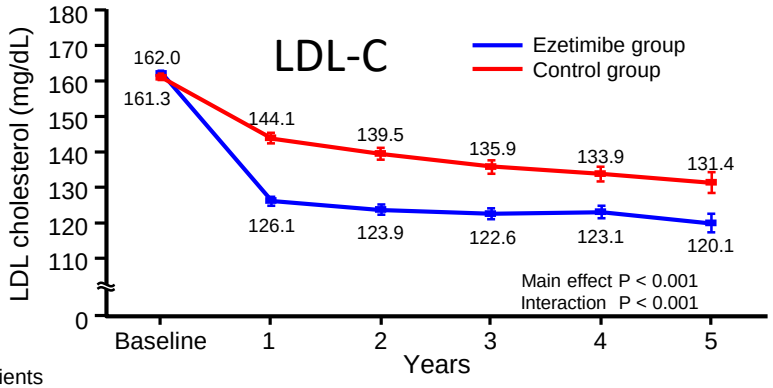
# *Baseline characteristics of patients*

Data are expressed as mean±SD or number (%)

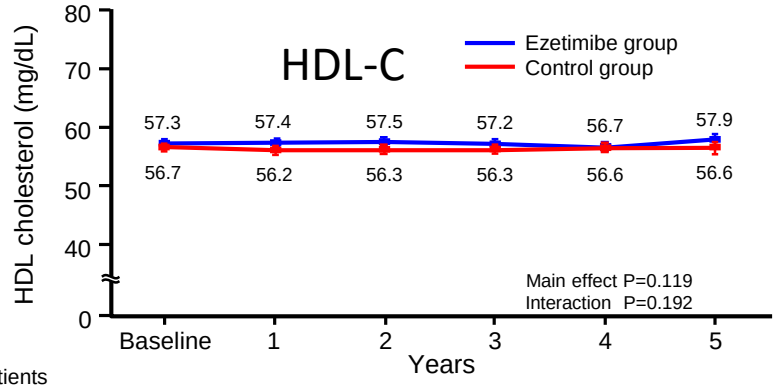
| | Ezetimibe group (n=1,716) | Control group (n=1,695) |
|---|---|---|
| **Age & Sex** | 80.6±4.7 | 80.6±4.7 |
| Patients aged over 85 years | 323 (18.8) | 325 (19.2) |
| Male | 440 (25.6) | 432 (25.5) |
| Female | 1276 (74.4) | 1263 (74.5) |
| **Body Constitution** | | |
| Height (cm) | 150.7±8.7 | 150.6±8.6 |
| Body weight (kg) | 53.8±10.0 | 53.4±10.4 |
| Body mass index (kg/m$^2$) | 23.6±3.5 | 23.5±3.7 |
| **Lipid Profile** | | |
| Total cholesterol (mg/dL) | 245.6±25.5 | 244.1±24.4 |
| HDL-cholesterol (mg/dL) | 57.3±14.2 | 56.6±13.9 |
| Triglyceride (mg/dL) | 132.1±54.5 | 131.1±55.9 |
| LDL-cholesterol (mg/dL) | **161.9±20.1** | **161.3±19.4** |
| non-HDL-cholesterol (mg/dL) | 188.4±23.8 | 187.5±23.3 |
| **Blood Pressure** (mmHg) | | |
| SBP | 137.0±15.8 | 135.8±15.9 |
| DBP | 74.4±10.4 | 74.0±10.4 |
| **Smoking status** | | |
| Never smoked | 1466 (85.4) | 1456 (85.9) |
| Former smoker | 161 (9.4) | 157 (9.3) |
| Current smoker | 89 (5.2) | 82 (4.8) |
| **Comorbidities** | | |
| Hypertension | 1520 (88.6) | 1509 (89.0) |
| Diabetes mellitus | 433 (25.2) | 434 (25.6) |
| Metabolic syndrome | 290 (16.9) | 276 (16.3) |

EWTOPIA75
ユートピア75

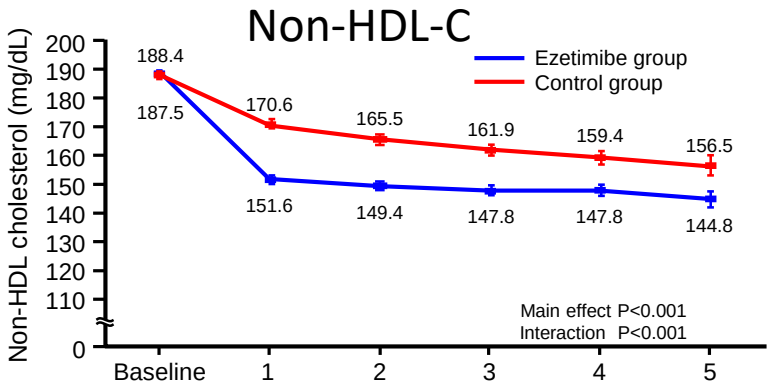
# *Lipid profile changes in Ezetimibe and Control groups*



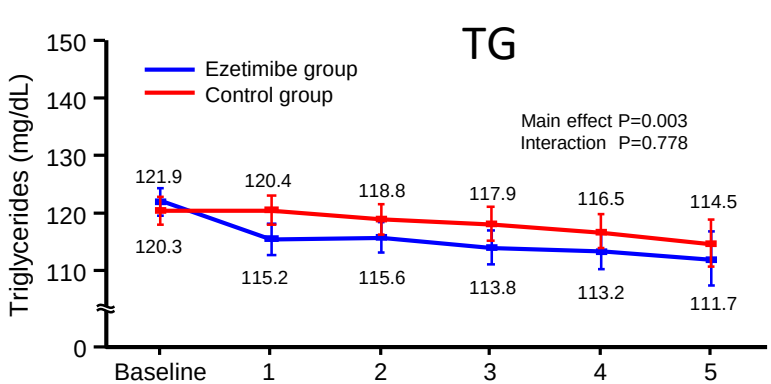

| Number of Patients | Baseline | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| Treated by ezetimibe | 1700 | 1489 | 1245 | 1009 | 685 | 311 |
| Not treated by ezetimibe | 1685 | 1464 | 1227 | 1023 | 706 | 314 |




| Number of Patients | Baseline | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| Treated by ezetimibe | 1700 | 1508 | 1259 | 1018 | 701 | 318 |
| Not treated by ezetimibe | 1685 | 1484 | 1244 | 1028 | 718 | 319 |




| Number of Patients | Baseline | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| Treated by ezetimibe | 1700 | 1490 | 1247 | 1009 | 687 | 311 |
| Not treated by ezetimibe | 1685 | 1466 | 1230 | 1024 | 707 | 314 |

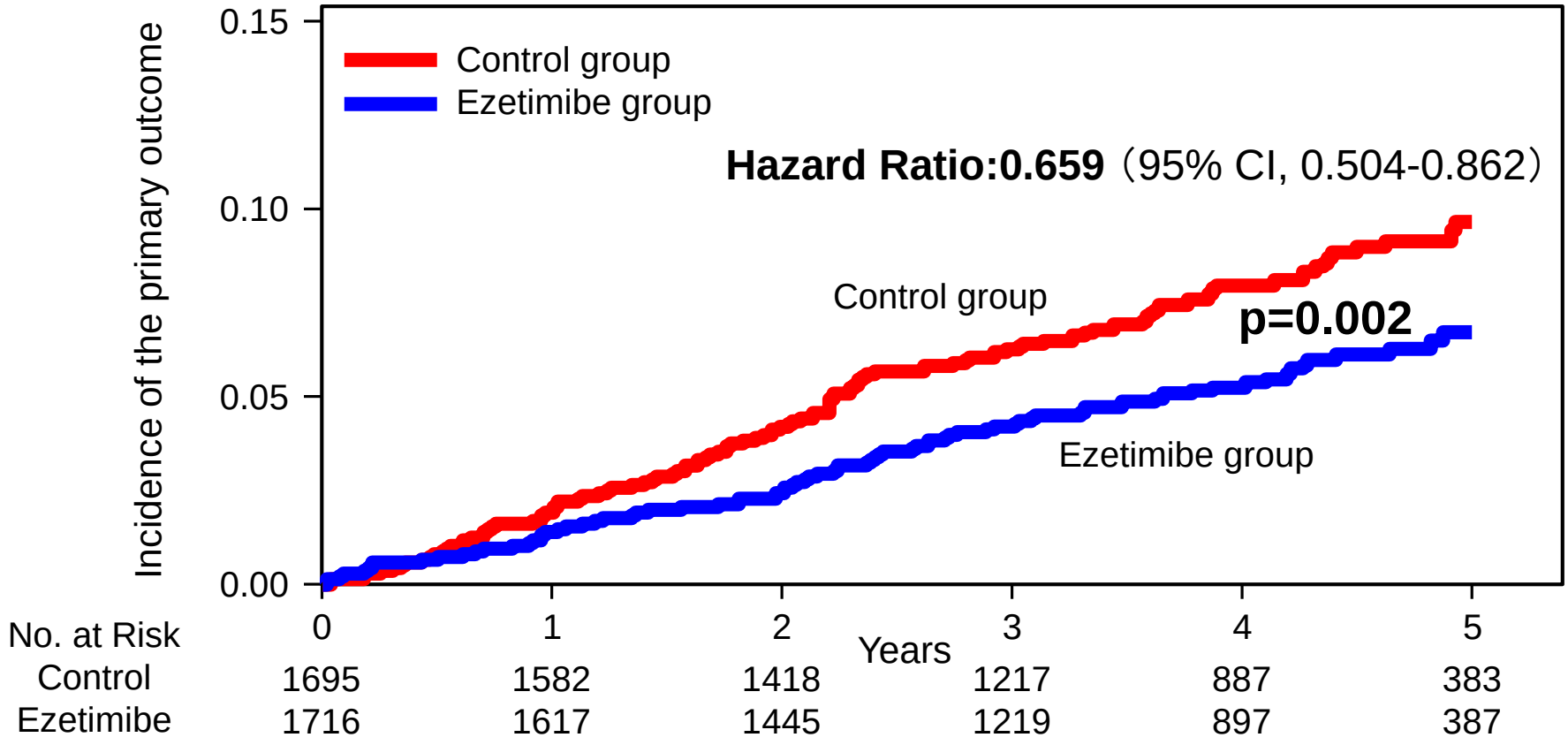



| Number of Patients | Baseline | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| Treated by ezetimibe | 1700 | 1507 | 1258 | 1019 | 699 | 317 |
| Not treated by ezetimibe | 1685 | 1484 | 1242 | 1029 | 717 | 321 |

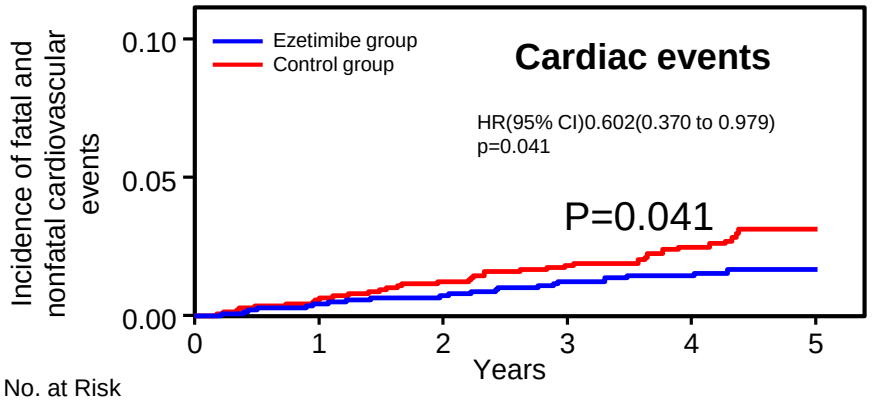
# *Effect of ezetimibe treatment on the primary end-point*

EWTOPIA75
ユートピア75

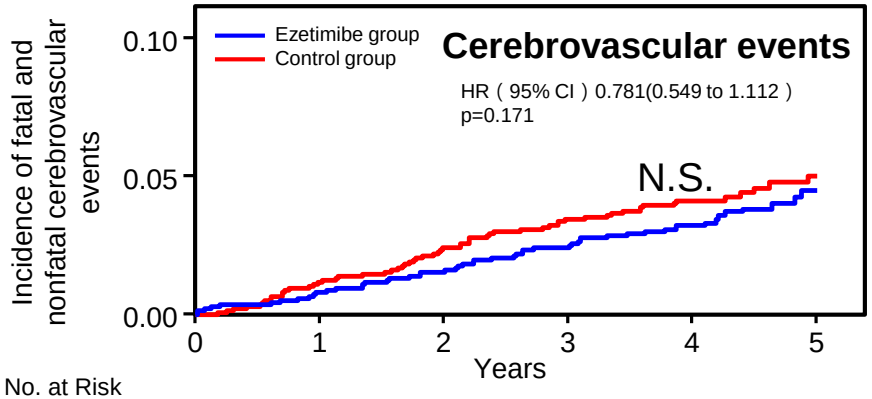
**A composite of the atherosclerotic cardiovascular events**
**(Sudden cardiac death, myocardial infarction, PCI or CABG, and/or stroke)**



# Effect of ezetimibe treatment on cardio-, cerebrovascular events, incidence of adverse events and all-cause mortality



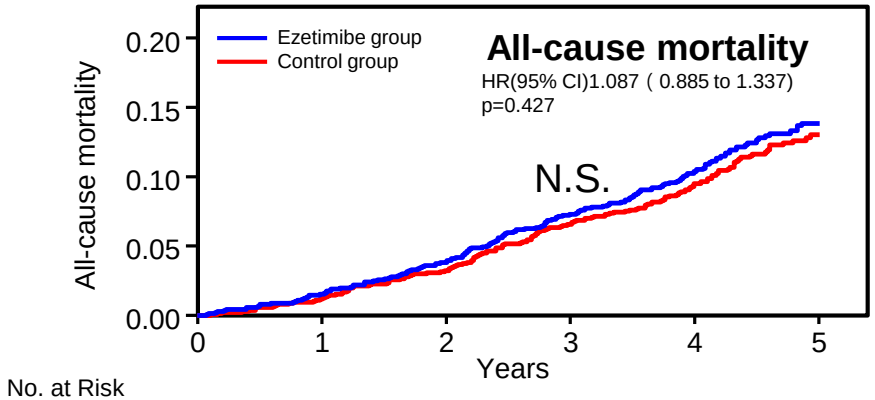

| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Control | 1695 | 1603 | 1454 | 1260 | 920 | 405 |
| Ezetimibe | 1716 | 1629 | 1464 | 1249 | 919 | 402 |




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Control | 1695 | 1590 | 1435 | 1238 | 906 | 397 |
| Ezetimibe | 1716 | 1619 | 1447 | 1226 | 903 | 391 |

## Adverse events

| | Ezetimibe group (n=1,742) | Control group (n=1,726) |
|---|---|---|
| Respiratory | 22 | 23 |
| GI & Hepatobiliary | 24 | 21 |
| Neurologic symptoms | 13 | 6 |
| Cardiovascular | 14 | 23 |
| Renal | 8 | 5 |
| Endocrine | 7 | 5 |
| Muscle & Bone | 40 | 41 |
| ENT | 12 | 16 |
| Urologic | 4 | 4 |
| Eye | 3 | 1 |
| Skin | 14 | 5 |
| Oral & Dental | 0 | 1 |
| Infection | 4 | 3 |
| Abnormal Lab exam | 7 | 3 |
| Others | 13 | 9 |
| **Total** | **185** | **166** |




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Control | 1695 | 1608 | 1463 | 1268 | 926 | 410 |
| Ezetimibe | 1716 | 1630 | 1466 | 1252 | 922 | 403 |

# *Major findings & Implications*

- Lipid-lowering monotherapy with ***ezetimibe*** prevented the occurrence of a composite of atherosclerotic cardiovascular events in patients aged > 75 years with elevated LDL-C level who had no history of coronary artery disease.

- This was also true for cardiac events by 2$^{nd}$ end-point analysis.

- The result obtained in this study is the first evidence suggesting that the primary prevention of atherosclerotic cardiovascular events is possible by non-statin lipid-lowering therapy for eligible older patients aged > 75 years or older.

# ADA guideline on lipid management in patients with **T2DM**

**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<br>• 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<br>• If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor) |

78

**2019**

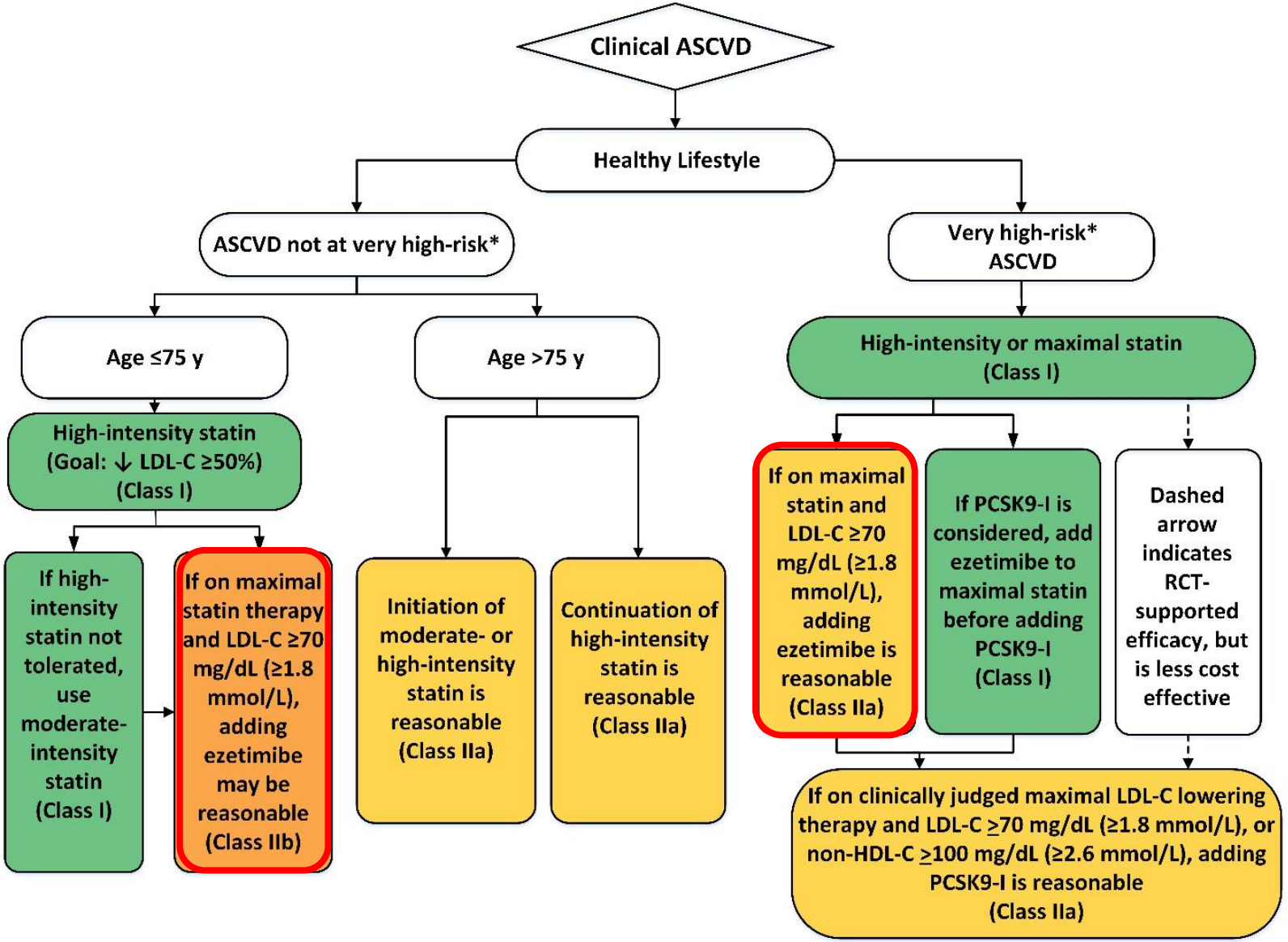
**Table 10.2—Recommendations for statin and combination treatment in adults with diabetes**

| Age | ASCVD or 10-year ASCVD risk >20% | Recommended statin intensity^ and combination treatment* |
|---|---|---|
| <40 years | No | None† |
| | Yes | High<br>• 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<br>• 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.

# Secondary Prevention in Patients With Clinical ASCVD

American Heart Association. 2018



# ASCVD Risk Factor Modifications Algorithm

## DYSLIPIDEMIA

**LIFESTYLE THERAPY** (Including Medically Assisted Weight Loss)

**LIPID PANEL: Assess ASCVD Risk**

**STATIN THERAPY**
If TG > 500 mg/dL, fibrates, Rx-grade omega-3 fatty acids, niacin

If statin-intolerant

Try alternate statin, lower statin dose or frequency, or add nonstatin LDL-C- lowering therapies

Repeat lipid panel; assess adequacy, tolerance of therapy

Intensify therapies to attain goals according to risk levels

| RISK LEVELS | HIGH | VERY HIGH | EXTREME |
|---|---|---|---|
| | DESIRABLE LEVELS | DESIRABLE LEVELS | DESIRABLE LEVELS |
| LDL-C (mg/dL) | <100 | <70 | <55 |
| Non-HDL-C (mg/dL) | <130 | <100 | <80 |
| TG (mg/dL) | <150 | <150 | <150 |
| Apo B (mg/dL) | <90 | <80 | <70 |

**RISK LEVELS:**
- **HIGH:** DM but no other major risk and/or age <40
- **VERY HIGH:** DM + major ASCVD risk(s) (HTN, Fam Hx, low HDL-C, smoking, CKD3,4)*
- **EXTREME:** DM plus established clinical CVD

| | |
|---|---|
| **If not at desirable levels:** | Intensify lifestyle therapy (weight loss, physical activity, dietary changes) and glycemic control; consider additional therapy |
| **To lower LDL-C:** | Intensify statin, add ezetimibe, PCSK9i, colesevelam, or niacin |
| **To lower Non-HDL-C, TG:** | Intensify statin and/or add Rx-grade OM3 fatty acid, fibrate, and/or niacin |
| **To lower Apo B, LDL-P:** | Intensify statin and/or add ezetimibe, PCSK9i, colesevelam, and/or niacin |
| **To lower LDL-C in FH:**** | Statin + PCSK9i |

Assess adequacy & tolerance of therapy with focused laboratory evaluations and patient follow-up

* EVEN MORE INTENSIVE THERAPY MIGHT BE WARRANTED ** FAMILIAL HYPERCHOLESTEROLEMIA



## HYPERTENSION

**GOAL: SYSTOLIC <130, DIASTOLIC <80 mm Hg**

**ACEi or ARB**

For initial blood pressure >150/100 mm Hg:
**DUAL THERAPY**

**ACEi or ARB** + Calcium Channel Blocker ✓ / ß-blocker ✓ / Thiazide ✓

If not at goal (2–3 months)

**Add calcium channel blocker, ß-blocker or thiazide diuretic**

If not at goal (2–3 months)

**Add next agent from the above group, repeat**

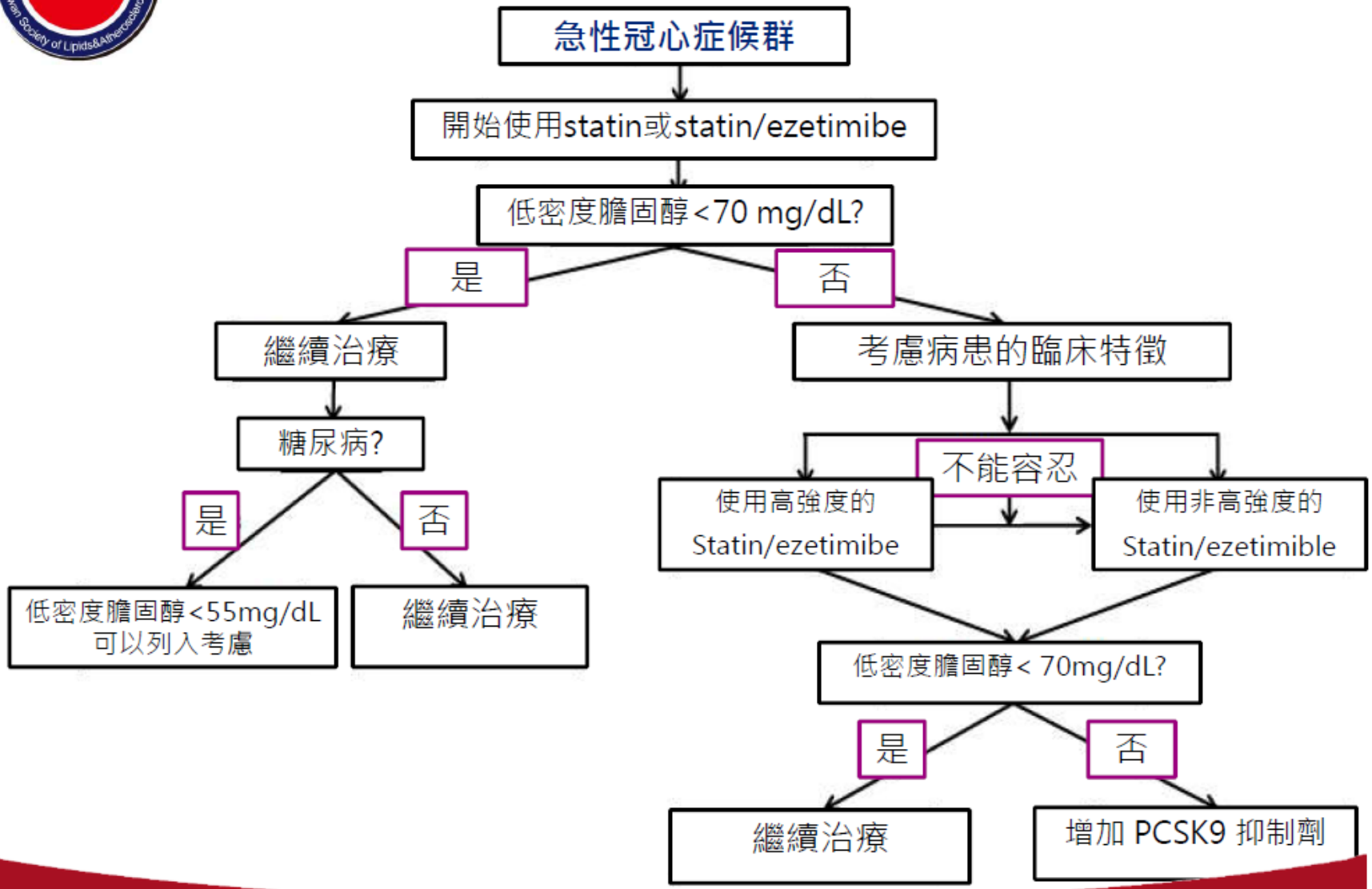
If not at goal (2–3 months)

**Additional choices (α-blockers, central agents, vasodilators, aldosterone antagonist)**

**Achievement of target blood pressure is critical**

2019 AACE Guideline

# 台灣高風險病人之血脂指引



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]

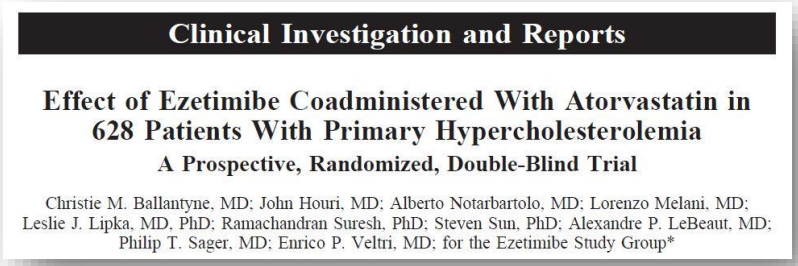
**1.** Ballantyne CM et al. Circulation. 2003 May 20;107(19):2409-15. Epub 2003 Apr 28.

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 |
| 胃腸道疾患 | **常見：** 腹瀉<br>**不常見：** 腹部不適；腹脹；腹痛；下腹痛；上腹痛；便秘；消化不良；脹氣；排便頻繁；胃炎；噁心；胃部不適 |
| 皮膚與皮下組織疾患 | **不常見：** 痤瘡；蕁麻疹 |
| 肌肉骨骼與結締組織疾患 | **常見：**肌肉痛<br>**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。 |

**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。**

# **Atozet** key scientific messages



Clinical Investigation and Reports

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

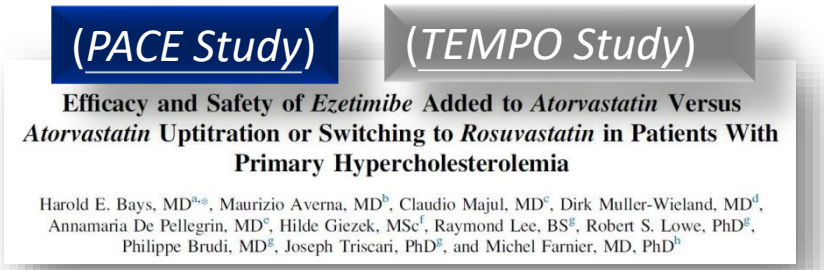
**A Prospective, Randomized, Double-Blind Trial**

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*

Pts with hypercholesterolemic

使用atorva 10mg+eze 10mg降LDL-C的幅度與atorva 80mg alone的效果一樣好

(*PACE Study*) (*TEMPO Study*)

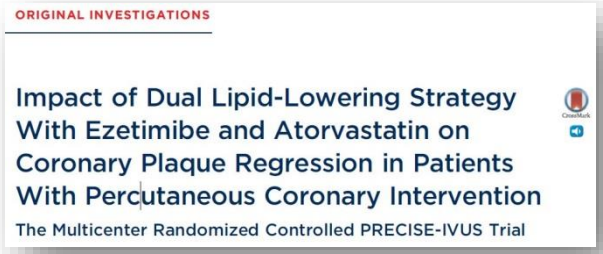


**Efficacy and Safety of *Ezetimibe* Added to *Atorvastatin* Versus *Atorvastatin* Uptitration or Switching to *Rosuvastatin* in Patients With Primary Hypercholesterolemia**

Harold E. Bays, MD[a,*], Maurizio Averna, MD[b], Claudio Majul, MD[c], Dirk Muller-Wieland, MD[d], Annamaria De Pellegrin, MD[e], Hilde Giezek, MSc[f], Raymond Lee, BS[g], Robert S. Lowe, PhD[g], Philippe Brudi, MD[g], Joseph Triscari, PhD[g], and Michel Farnier, MD, PhD[h]

Pts with hypercholesterolemic

- ✓ Atorva/eze (10/10)比起atorva 20mg，可以額外降12%的LDL-c (22% vs 10%)
- ✓ Atorva/eze (10/20)比起rosuva 20mg，可以額外降9%的LDL-c (17% vs 8%)
- ✓ Atorva/eze (10/20)比起atorva 40mg，可以額外降20%的LDL-c (31% vs 11% )



ORIGINAL INVESTIGATIONS

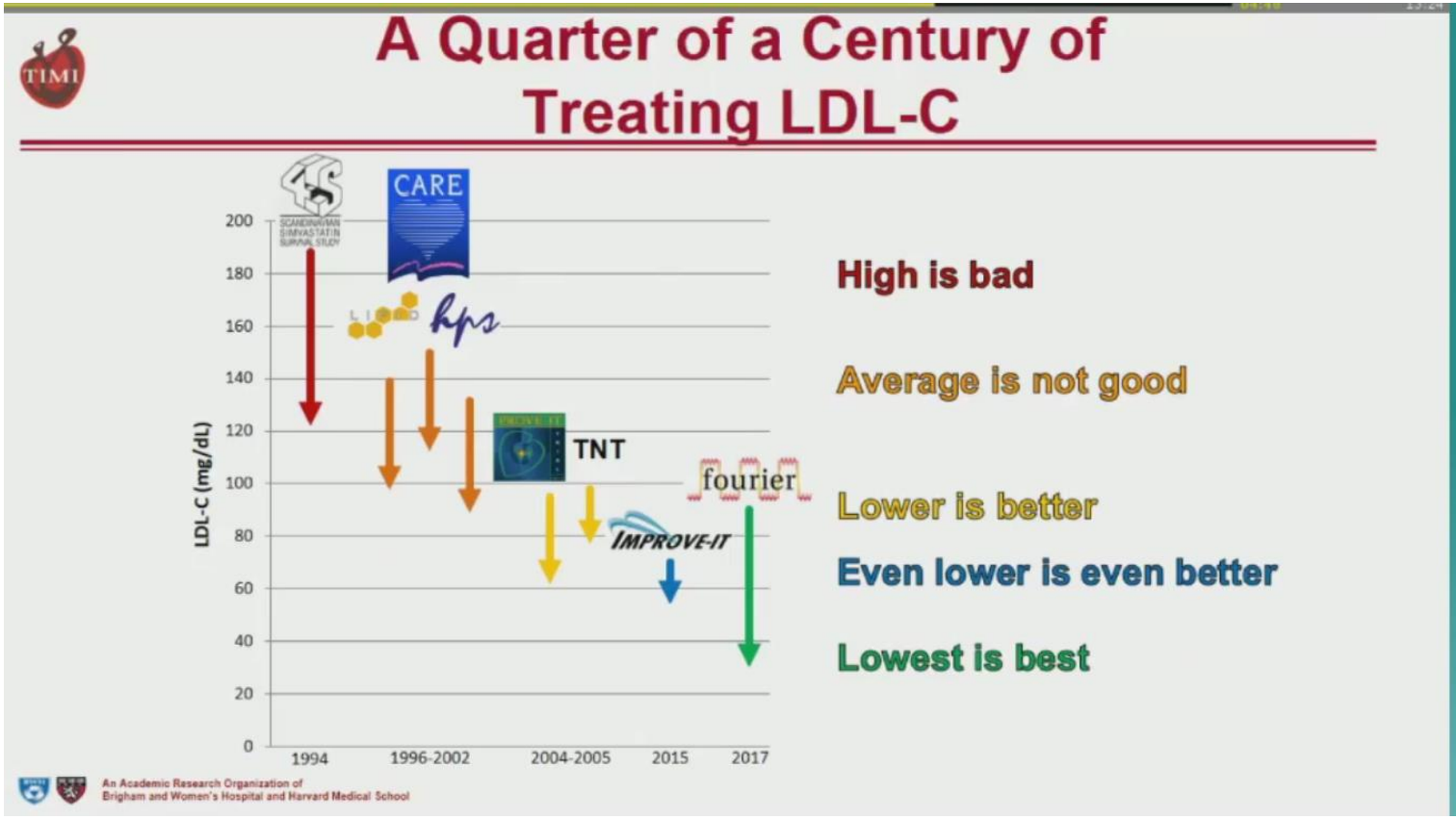
**Impact of Dual Lipid-Lowering Strategy With Ezetimibe and Atorvastatin on Coronary Plaque Regression in Patients With Percutaneous Coronary Intervention**

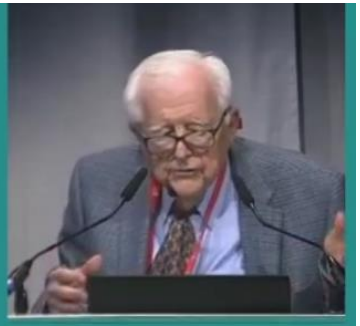
The Multicenter Randomized Controlled PRECISE-IVUS Trial

Pts who underwent percutaneous coronary intervention (PCI) due to ACS or stable angina

- ✓ 使用Atorva/Eze可以顯著降低LDL-C 達40%
- ✓ 越低的LDL-C和越好的冠狀動脈粥狀斑塊消退(regression)有相關性。

# Prof. Eugene Braunwald from Harvard Medical School: *we should strive achieve very low levels of LDL-C early in individuals to maximize cardiovascular benefit*



ESC
European Society of Cardiology

# 當LDL達標後，該持續降低LDL還是處理殘餘風險？？？

**Adding to statins? Notable outcome studies**

| Study | Drug/combination | Population | % reduction in risk of MACE | Trial ID |
|---|---|---|---|---|
| Reduce-IT | Vascepa (EPA plus statin) | High-risk patients with mixed dyslipidemia | 25% | NCT01492361 |
| Fourier | Repatha (PCSK9 plus statin) | High-risk patients with CV disease | 15% | NCT01764633 |
| Odyssey Outcomes | Praluent (PCSK9 plus statin) | High-risk ACS patients | 15% | NCT01663402 |
| Improve-IT | Vytorin (simvastatin plus ezetimibe) | High-risk ACS patients | 6.4% | NCT00202878 |

*Notes: CAD=coronary arterial disease. Source: company press releases, JAMA Cardiology.*


Omega-3
PCSK9i
Niacin
Statin
Ezetrol
Fenofibrate

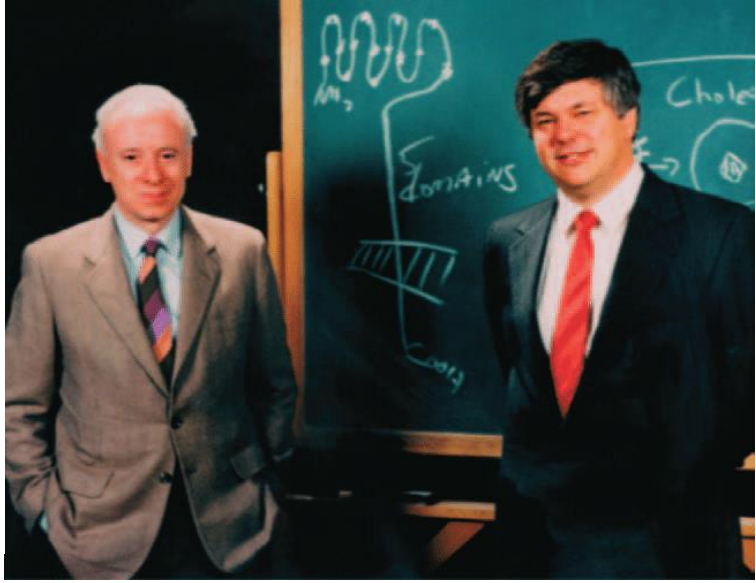
# A RECEPTOR-MEDIATED PATHWAY FOR CHOLESTEROL HOMEOSTASIS

Nobel lecture, 9 December, 1985

by

MICHAEL S. BROWN AND JOSEPH L. GOLDSTEIN

Department of Molecular Genetics, University of Texas Health Science Center, Southwestern Medical School, 5323 Harry Hines Blvd. Dallas, Texas, U.S.A.



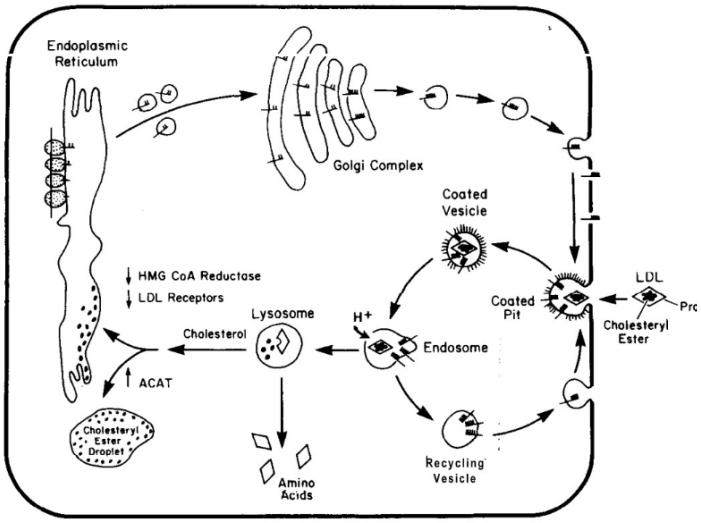



*Fig. 6.* Itinerary of the LDL receptor in mammalian cells. The receptor begins life in the endopl mic reticulum from which it travels to the Golgi complex, cell surface, coated pit, endosome, a back to the surface. HMG CoA reductase denotes 3-hydroxy-3-methylglutary1 CoA reducta ACAT denotes acyl-CoA: cholesterol acyltransferase. Vertical arrows indicate the direction regulatory effects. (Reprinted from ref. 131 with permission.)

The LDL receptor studies lend experimental support to the epidemiologists' suggestion that the levels of plasma cholesterol usually seen' in Western industrialized societies are inappropriately high (9). This support derives from knowledge of the affinity of the LDL receptor for LDL. The receptor binds LDL optimally when the lipoprotein is present at a cholesterol concentration of 2.5 mg/dl (28). In view of the 10 to 1 gradient between concentrations of LDL in plasma and interstitial fluid, a level of LDL-cholesterol in plasma of 25 mg/dl would be sufficient to nourish body cells with cholesterol (118). This is roughly one-fifth of the level usually seen in Western societies (Fig. 16 and ref. 119). Several lines of evidence suggest that plasma levels of LDL-cholesterol in the range of 25-60 mg/dl (total plasma cholesterol of 110 to 150 mg/dl) might indeed be physiologic for human beings. First, in other mammalian species that do not develop atherosclerosis, the plasma LDL-cholesterol level is generally less than 80 mg/dl (Fig. 16 and ref. 120). In these animals the affinity of the

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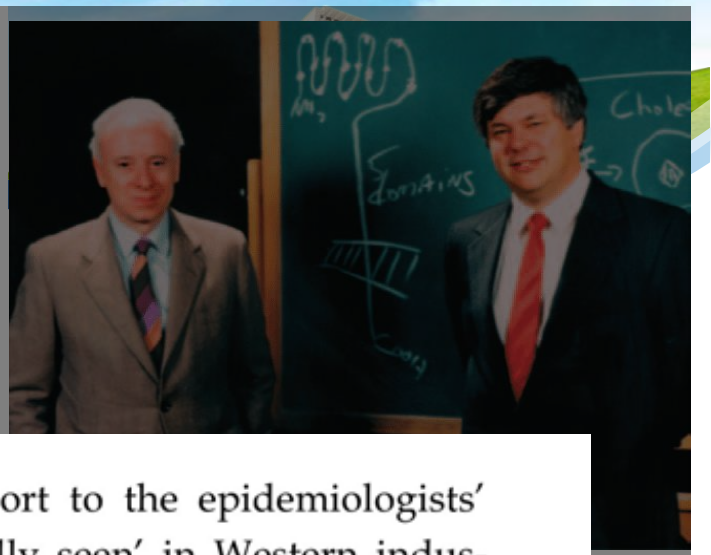

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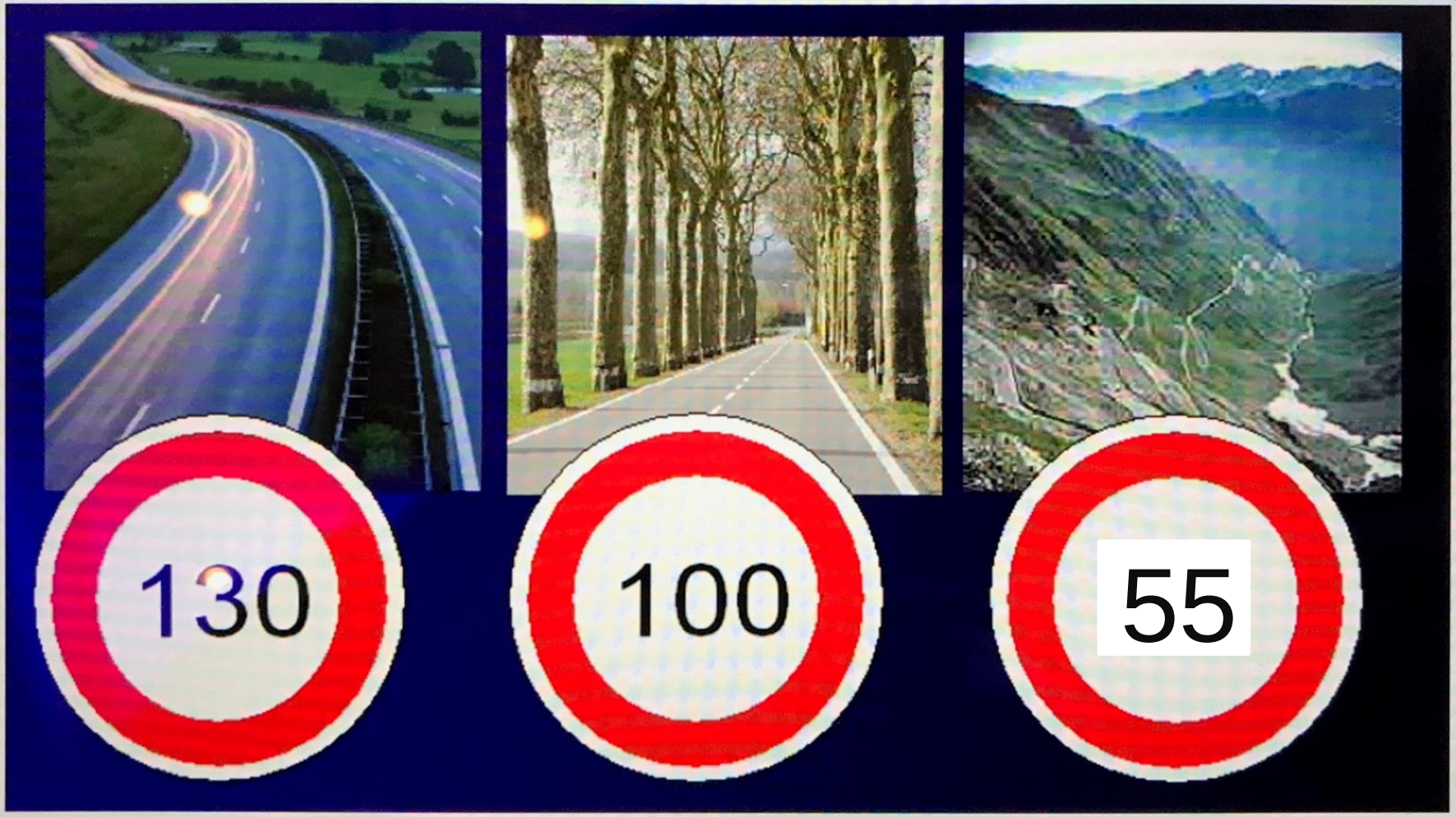
# ACS / PCI / CABG in T2DM

## Cholesterol-lowering treatment made easy

### LDL-cholesterol targets




Thank You