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

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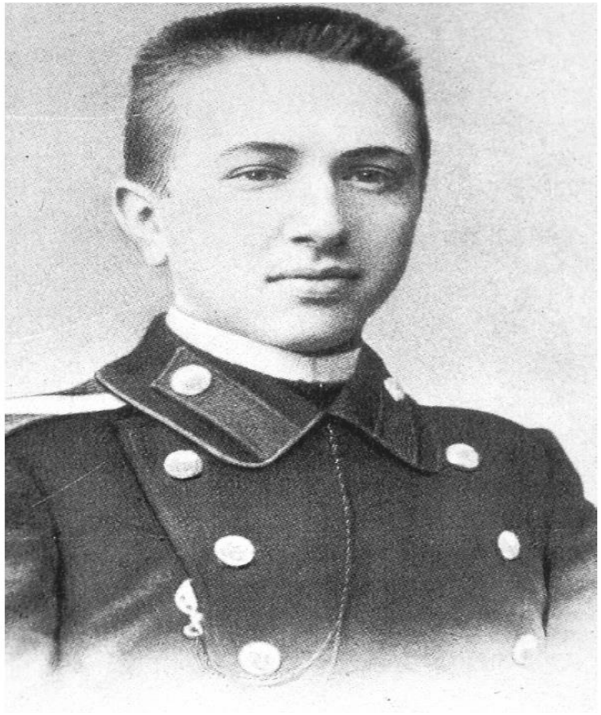


Nikolay Nikolaevich Anichkov
1885~1964

"There is no atherosclerosis without cholesterol"

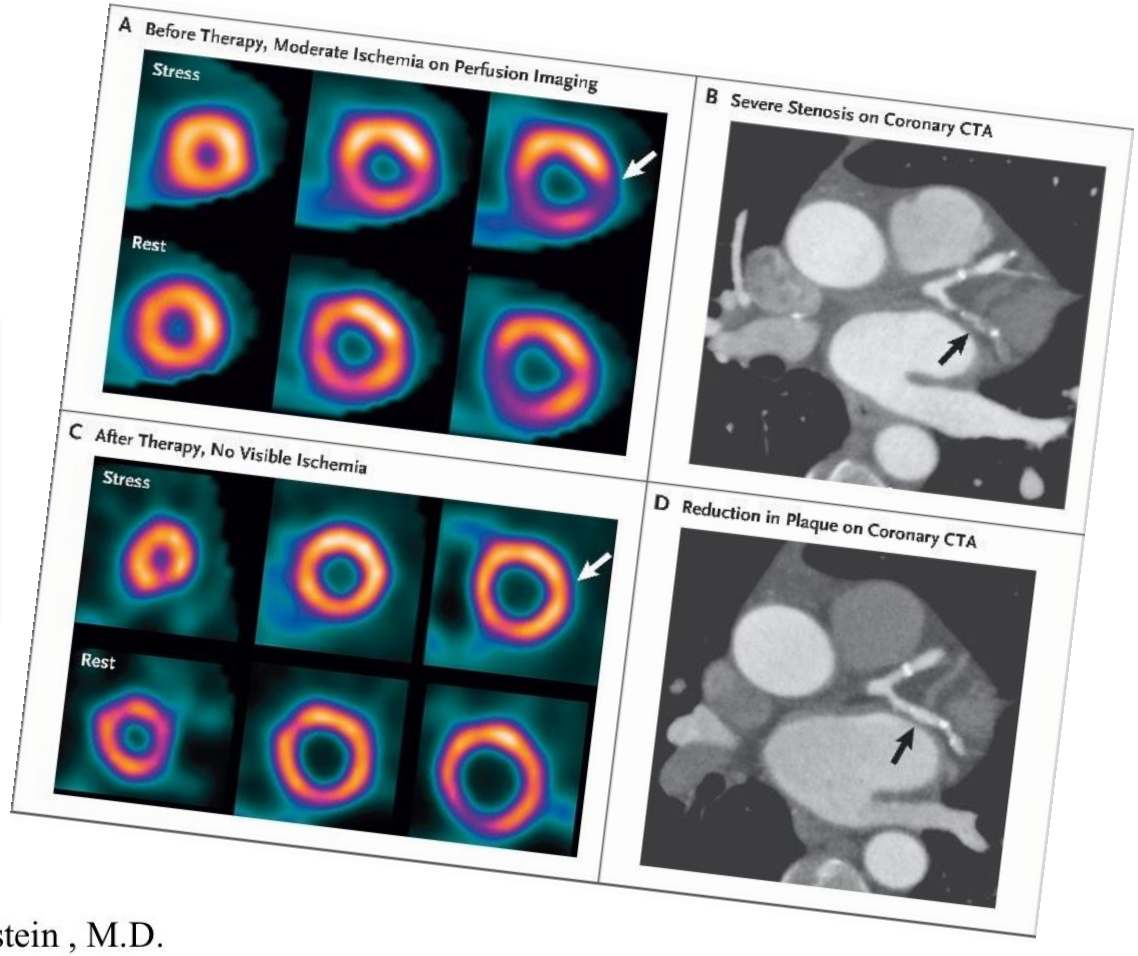
1913

沒有膽固醇就沒有粥狀動脈硬化

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

Why should we control lipid aggressively?

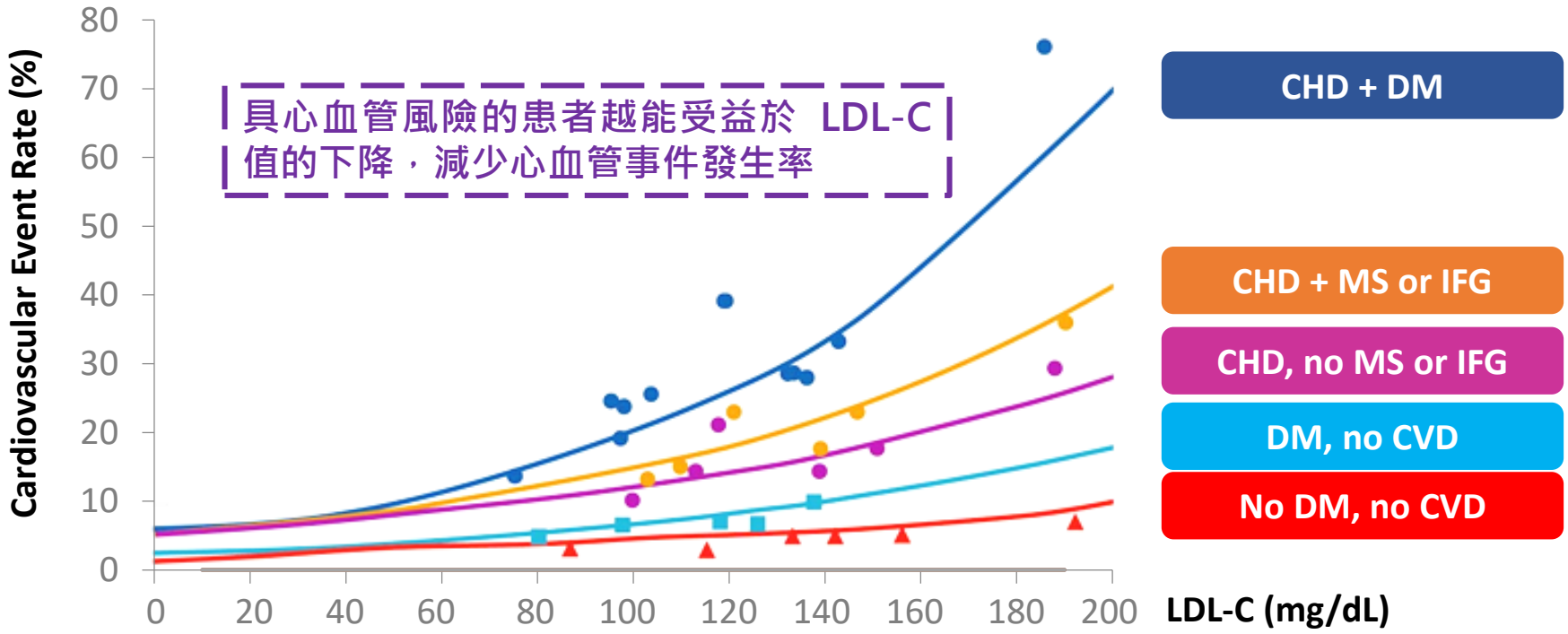
Regression of Coronary Atherosclerosis with Medical Therapy



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

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

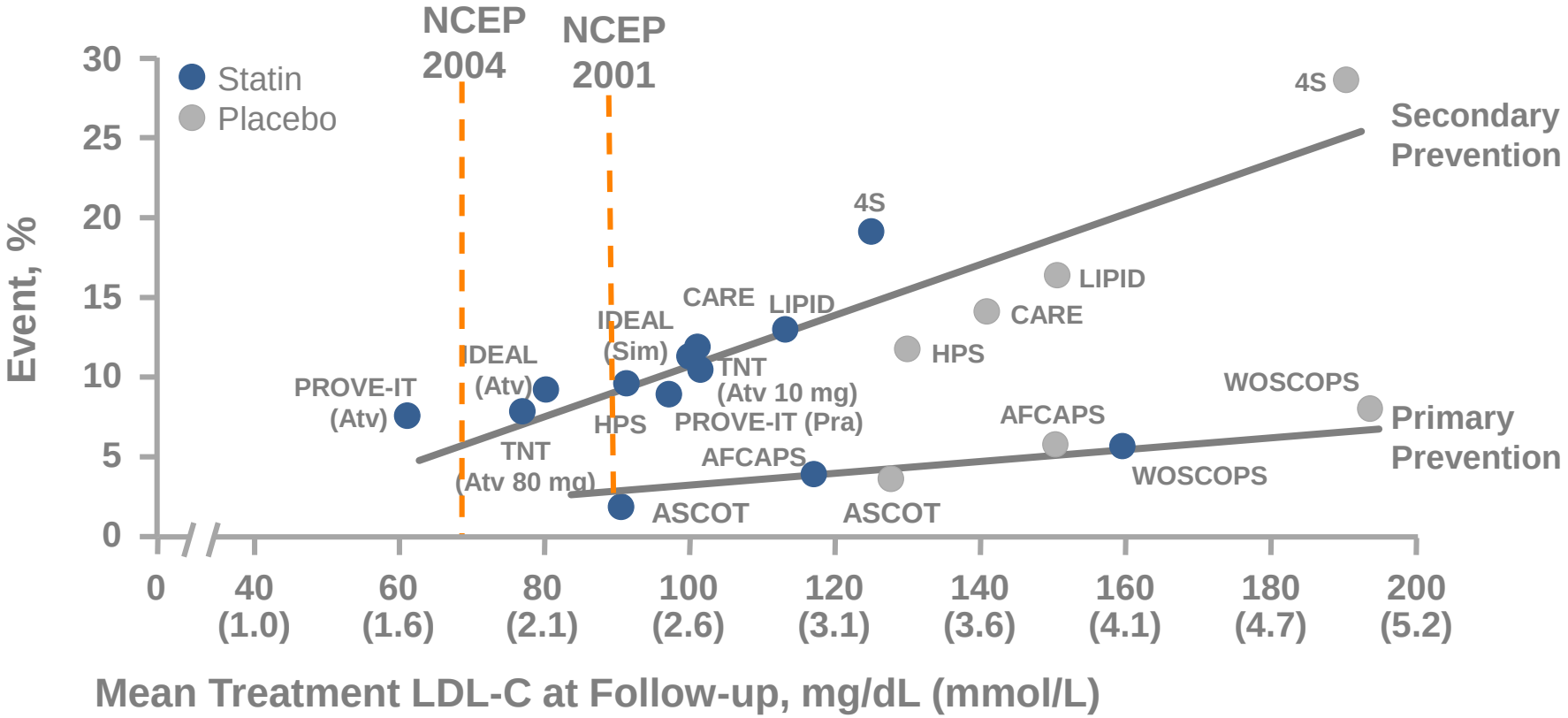
Intensive LDL-C Reduction May Be Beneficial to Patients with High CV Risk[1]



CV=cardiovascular; CHD=coronary heart disease; DM=diabetes mellitus; MS=metabolic syndrome; IFG=impaired fasting glucose; CVD=CV disease.

1. Robinson JG, et al. Am J Cardiol. 2006;98:1405-8.

Benefit of LDL Lowering

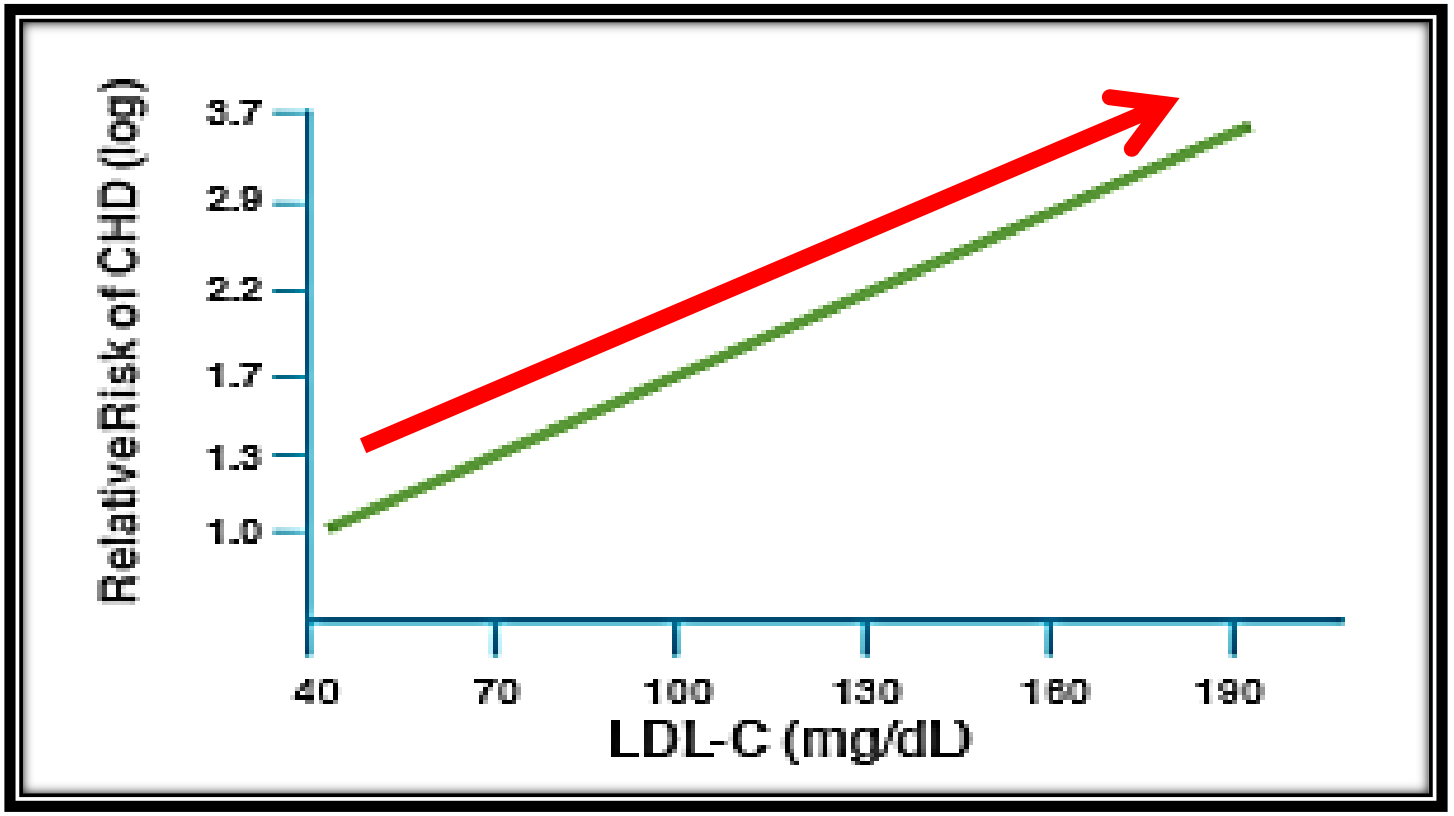


Atv=atorvastatin; Pra=pravastatin; Sim=simvastatin; PROVE-IT=Pravastatin or AtorVastatin Evaluation and Infection Therapy; IDEAL=Incremental Decrease in Endpoints through Aggressive Lipid Lowering; ASCOT=Anglo-Scandinavian Cardiac Outcomes Trial; AFCAPS=Air Force Coronary Atherosclerosis Prevention Study;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

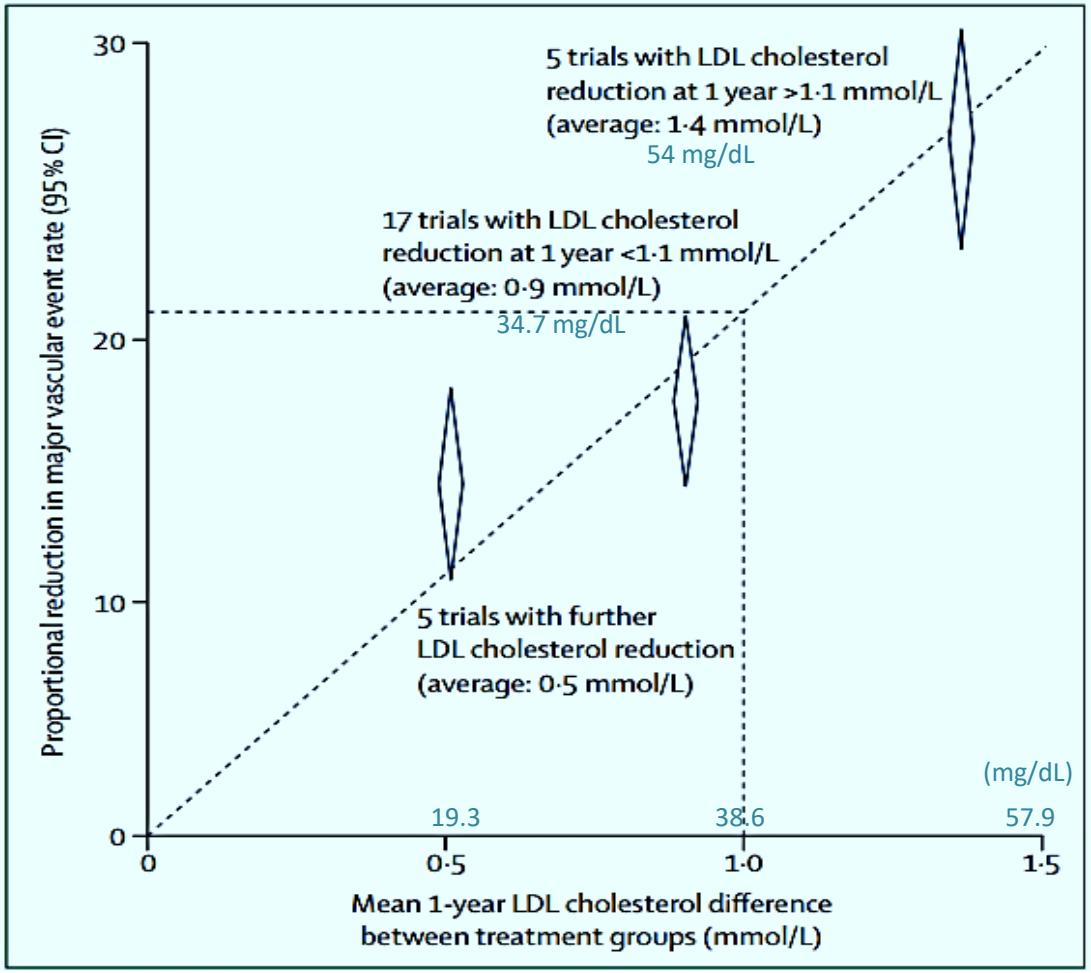
Relationship between LDL-C levels and relative risk for CHD

This relationship is consistent with a large body of epidemiological data and with data available from clinical trials of LDL-lowering therapy.



Adult Treatment Panel III, Scott M. Grundy et al. Circulation. 2004;110:227-239

Proportional Reduction in Major Vascular Events vs Absolute LDL-C Reduction



Correlation between LDL-C level and MACE reduction

CTT meta-analysis showed that LDL-C lowering with statins reduces major ASCVD events.

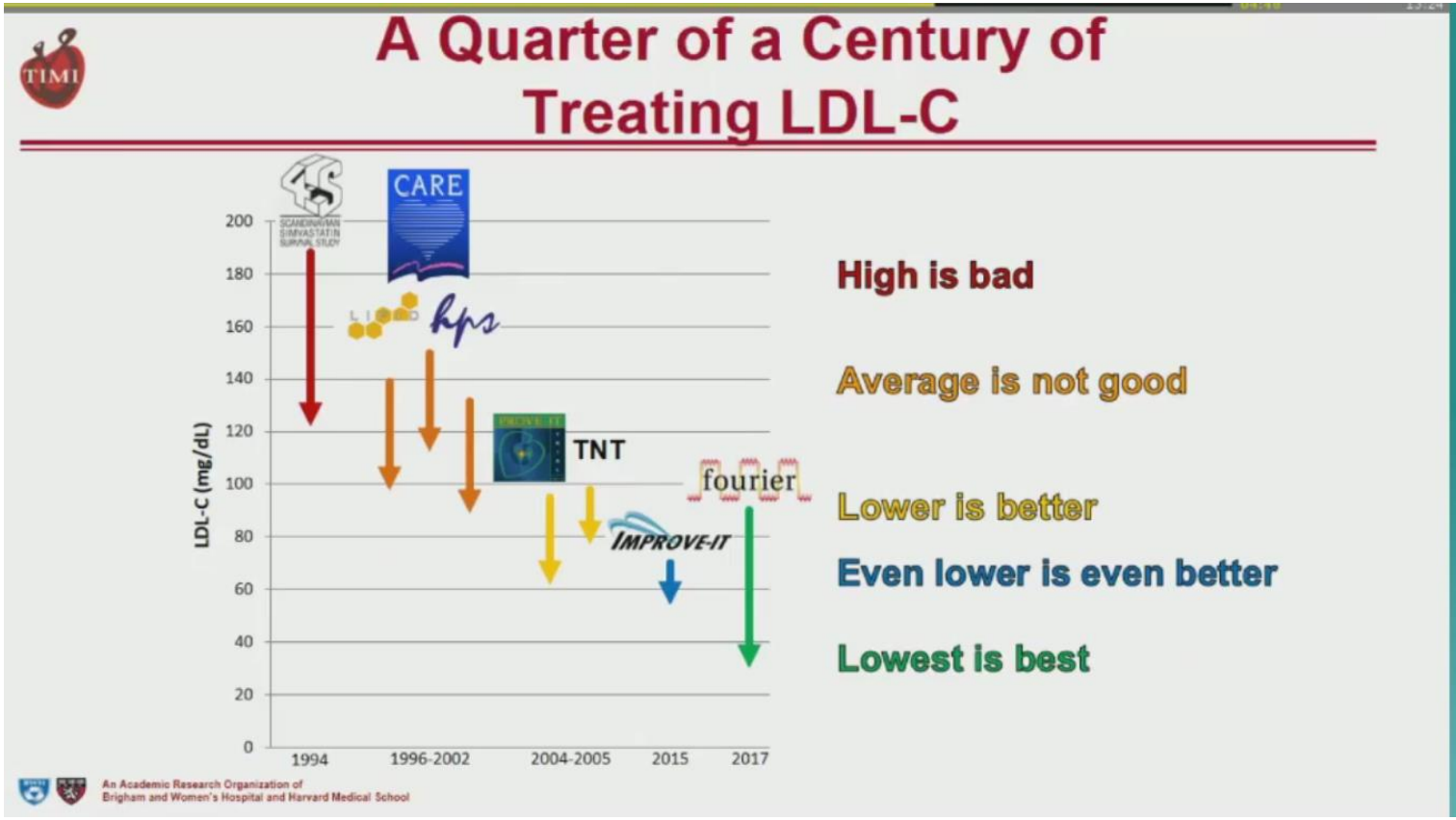
1 mmol/L LDL-C reduction

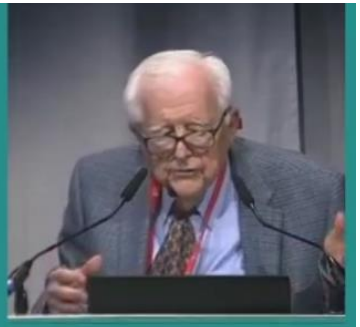
22% reduction in major vascular event rate

1 mmol/L = 38.6 mg/dL

Lancet 2016; 388: 2532–61

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

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 HYPERCHOLESTERO

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 ✓
ACEi or ARB + ß-blocker ✓
ACEi or ARB + 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

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)

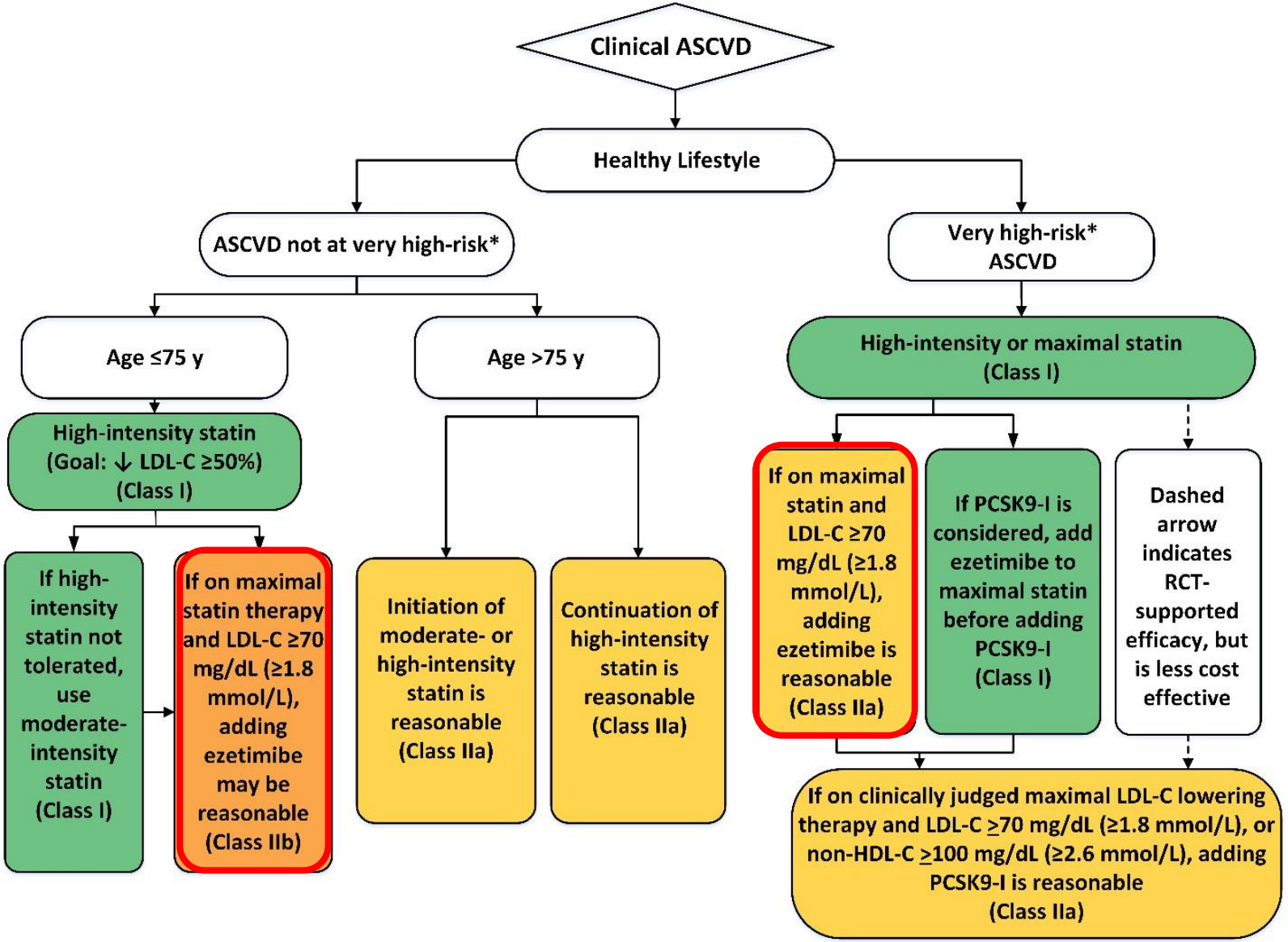
ACSVD risk factors: LDL-c≥100 mg/dL, high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD.

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

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

WRITING COMMITTEE MEMBERS
Scott M. Grundy, MD, PhD, FAHA, *Chair**
Neil J. Stone, MD, FACC, FAHA, *Vice Chair**

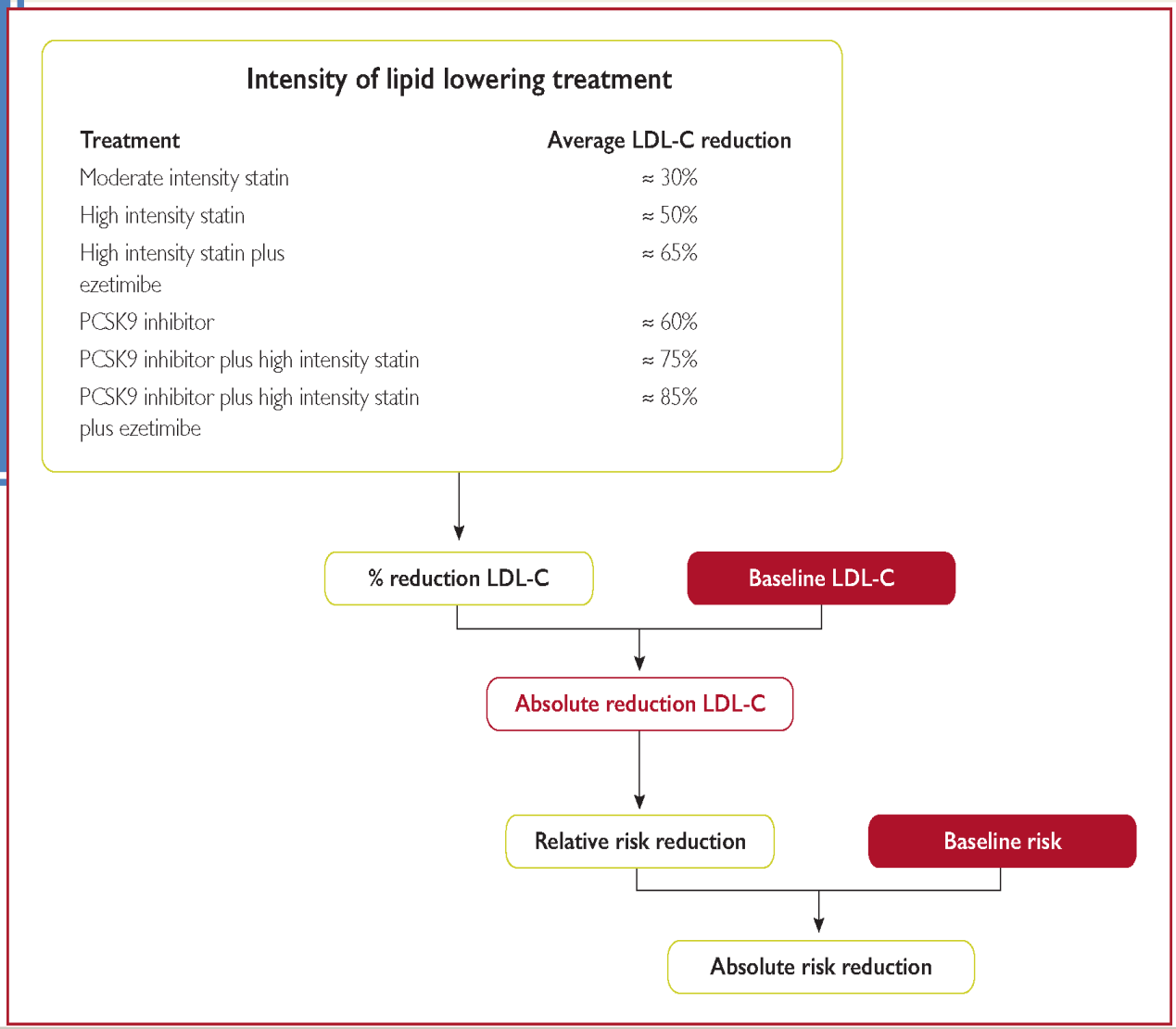
Secondary Prevention in Patients With Clinical ASCVD



2017台灣高風險病人血脂異常臨床治療指引

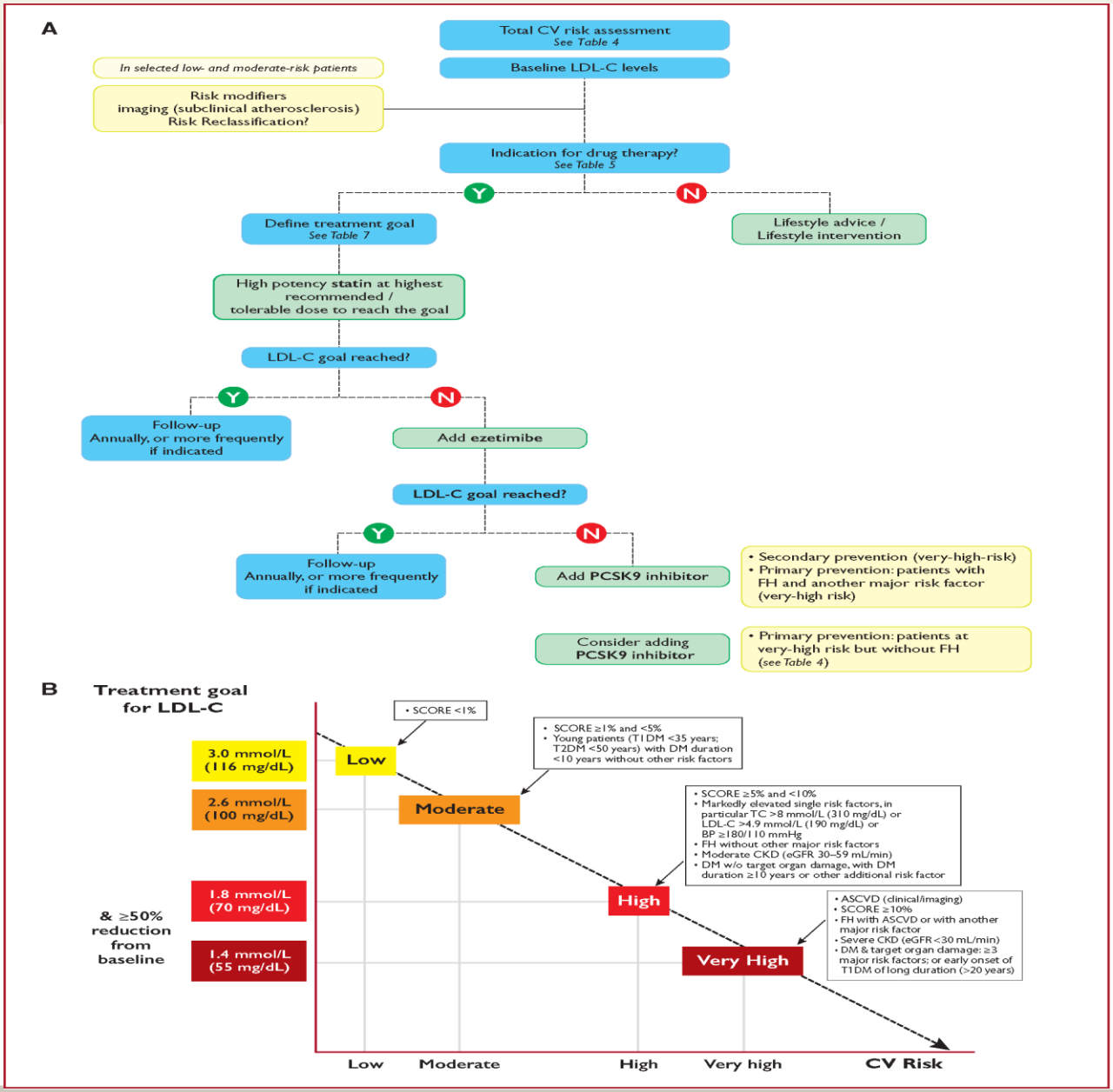
疾病 / 狀態	低密度膽固醇 (LDL-C) 之目標
急性冠心症候群	< 70 mg/dL
急性冠心症候群+ 糖尿病	< 55 mg/dL 可以考慮
穩定冠狀動脈疾病	< 70 mg/dL
缺血性腦中風或暫時性腦部缺氧	< 100 mg/dL
糖尿病	<100 mg/dL
糖尿病+心血管疾病	< 70 mg/dL
慢性腎臟病(階段 3a–5, eGFR < 60)	> 100 mg/dL 時開始治療
家族性高膽固醇血症	成人: < 100 mg/dL 小孩: < 135 mg/dL 有心血管疾病: < 70 mg/dL

Figure 3 Expected clinical benefits of low-density lipoprotein cholesterol-lowering therapies. The expected clinical ...



European Heart Journal, ehz455, https://doi.org/10.1093/eurheartj/ehz455

Figure 4 (A) Treatment algorithm for pharmacological low-density lipoprotein cholesterol lowering. (B) Treatment goals ...



European Heart Journal, ehz455, https://doi.org/10.1093/eurheartj/ehz455

Recommendations for pharmacological low-density lipoprotein cholesterol lowering

Recommendations	Class[a]	Level[b]
It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the goals set for the specific level of risk.[32,34,38]	I	A
If the goals[c] are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.[33]	I	B
For primary prevention patients at very-high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor may be considered.	IIb	C
For secondary prevention, patients at very-high risk not achieving their goal[c] on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.[119,120]	I	A
For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal[c] on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered.[197,265,353]	IIa	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor added to ezetimibe may also be considered.[197,265,353]	IIb	C
If the goal[c] is not achieved, statin combination with a bile acid sequestrant may be considered.	IIb	C

High Risk

- SCORE ≥5% and <10%
- Markedly elevated single risk factors, in particular TC >8 mmol/L (310 mg/dL) or LDL-C >4.9 mmol/L (190 mg/dL) or BP ≥180/110 mmHg
- FH without other major risk factors
- Moderate CKD (eGFR 30–59 mL/min)
- DM w/o target organ damage, with DM duration ≥10 years or other additional risk factor

Very High Risk

- ASCVD (clinical/imaging)
- SCORE ≥10%
- FH with ASCVD or with another major risk factor
- Severe CKD (eGFR <30 mL/min)
- DM & target organ damage: ≥3 major risk factors; or early onset of T1DM of long duration (>20 years)

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	
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: Determinants for achieving the LDL-C target of lipid control for secondary prevention of cardiovascular events in Taiwan
- Study Design

N=3,486
Prospective observation
Follow-up for 5 years

Patient Criteria:

Patients with Coronary artery disease (CAD) and cerebrovascular disease (CVD)

Data Collection:

- Vital signs
- Clinical endpoints
- Adverse events
- Concurrent medications
- Laboratory specimens

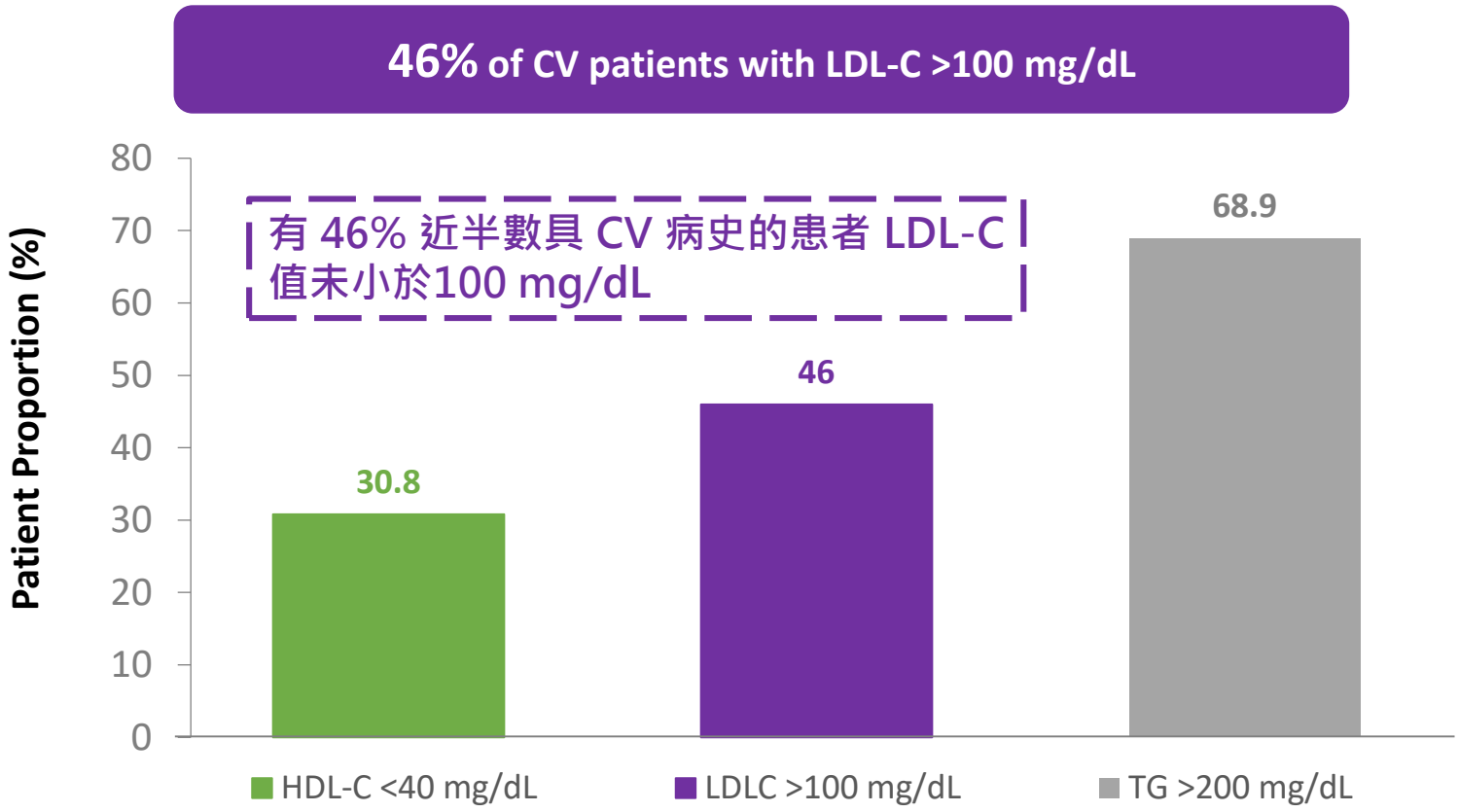
Items evaluated at baseline, and every year thereafter:

- The lipid profile (total cholesterol, high-density lipoprotein cholesterol, LDL-C, triglyceride)
- Liver enzymes
- Creatinine phosphokinase

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

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

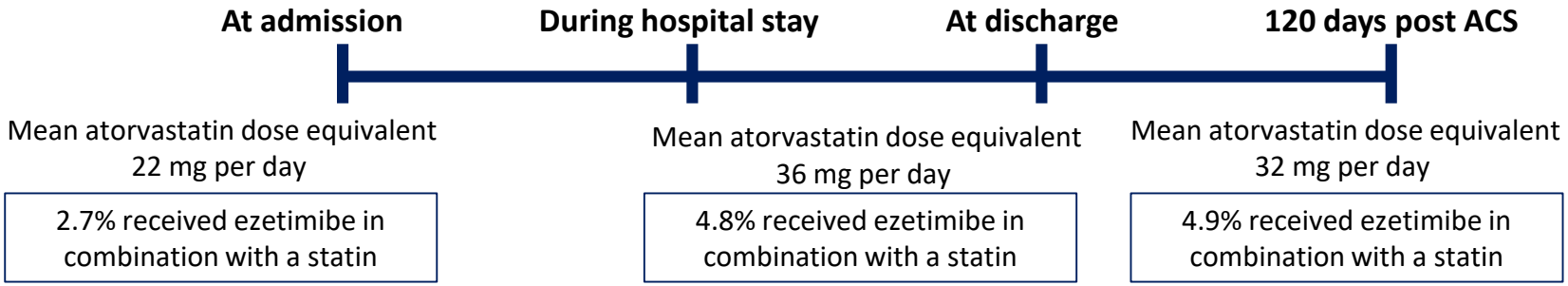
Contemporary data on treatment practices for low-density lipoprotein cholesterol in 3867 patients who had suffered an acute coronary syndrome across the world

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]

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

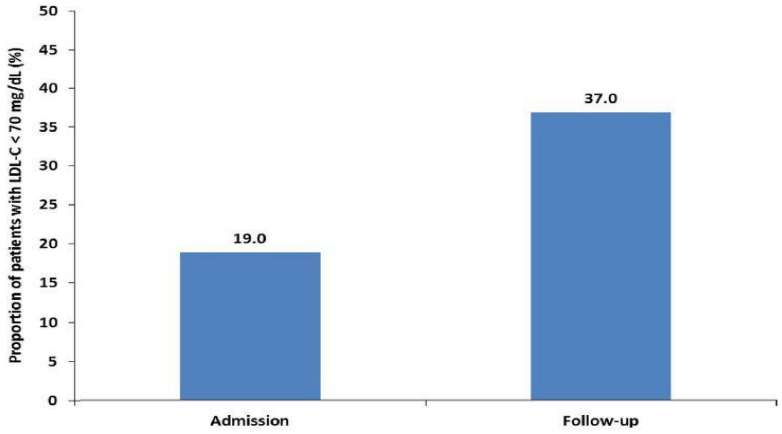
- ***Methods:*** a longitudinal, observational study in 3867 patients from 18 countries in Europe, the Middle East, South-, Southeast- and East-Asia. Patients were evaluated lipid profile *at the time of admission, during hospital stay, at discharge and follow-up for 120 days post-ACS*.

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).

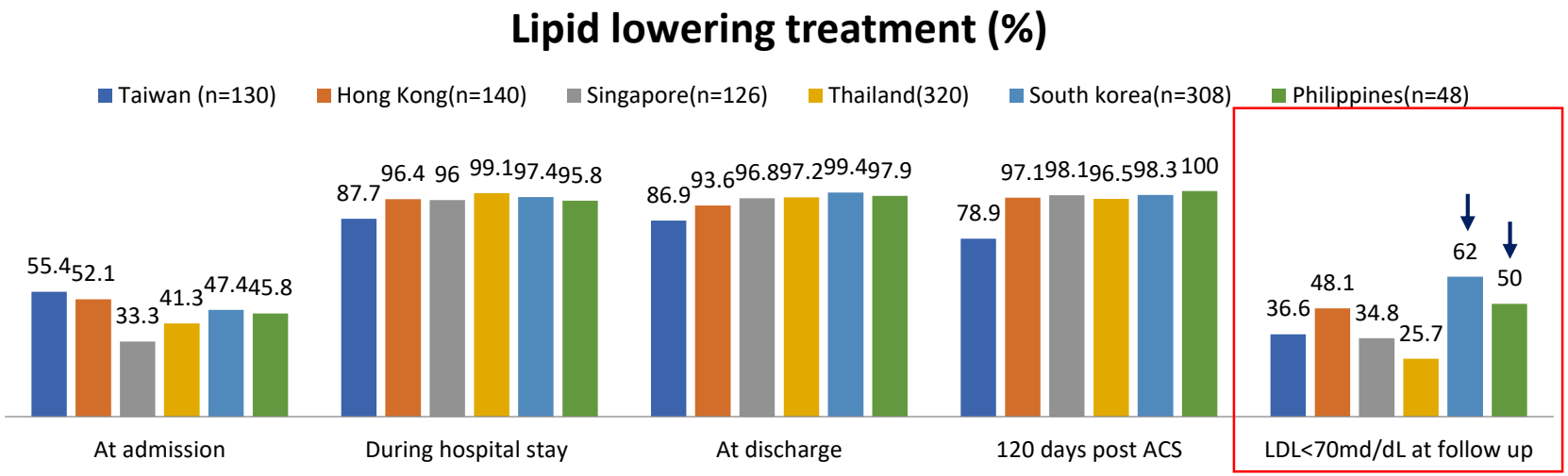
出院後四個月的LDL-C<70 mg/dL達標率，只有37%



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

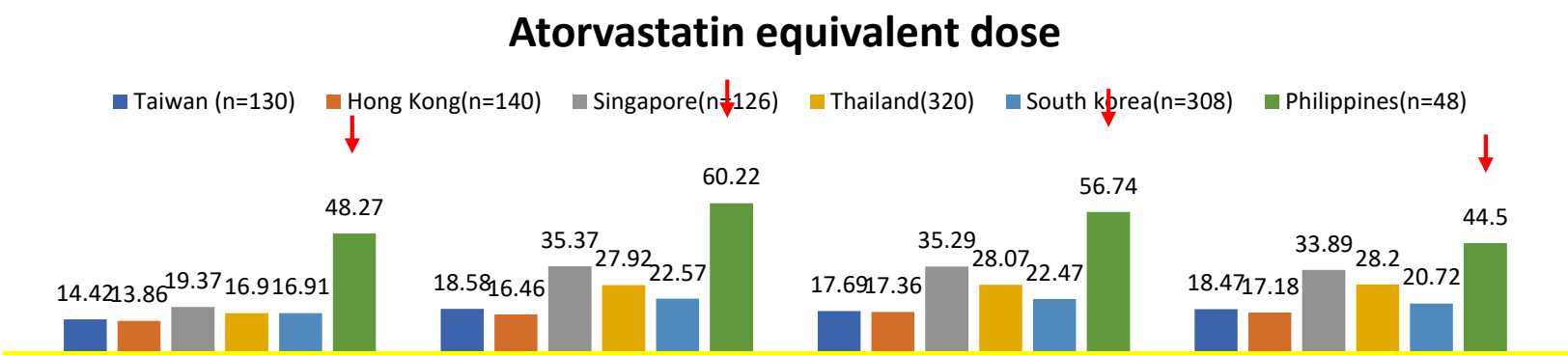
若只單看台灣鄰近國家，可以發現韓國和菲律賓在ACS出院後四個月的追蹤，其LDL<70mg/dL的達標率較台灣高

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.

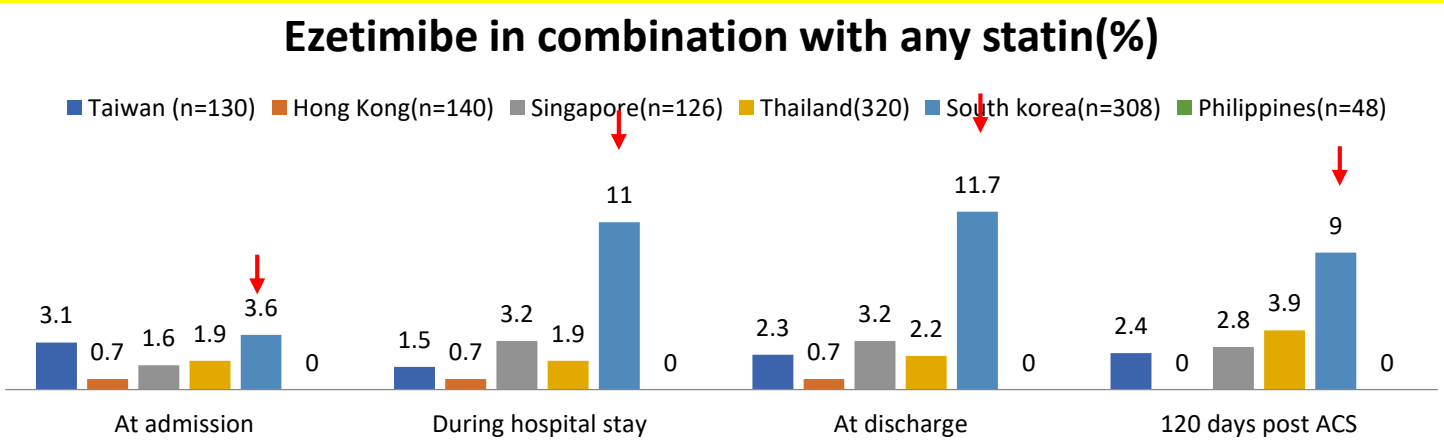


A.K.Gittetal. Data in Brief 16(2018)369–375

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

在曾經處方過lipid-lowering drugs的亞洲區高膽固醇血症病人中，只有44.7%的病人達標LDL-C<100mg/dL

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

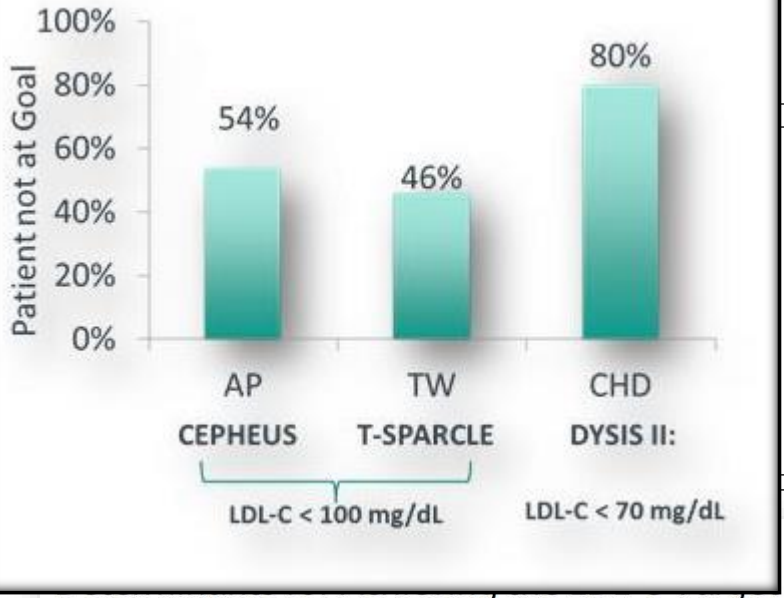
Chern-En Chiang[1], Jean Ferrières[2], Nina N Gotcheva[3], Frederick J Raal[4], Abdulla Shehab[5], Jidong Sung[6], Karin M Henriksson[7,8] and Michel P Hermans[9]

- *Population:* 35,121 patients aged ≥18 and who had been prescribed lipid-lowering drugs for at least 3 months without dose changes for at least 6 weeks (2006-2010).
- *Results: only **44.7%** of patients reached their recommended LDL-C level(<100mg/dL).*
- *Methods:* a multicenter, prospective, cross-sectional study conducted ***in 29 countries across Asia*** *(Hong Kong, Indonesia, malaysia, Philippines, South Korea, Taiwan, Thailand, and Vietnam)*

Chiang CE et al., J Atheroscler Thromb. 2016 May 2;23(5):567-87. doi: 10.5551/jat.31179.

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)



of Lipid Control for Secondary Prevention of Cardiovascular Events in Taiwan

T-SPARCLE (2015)

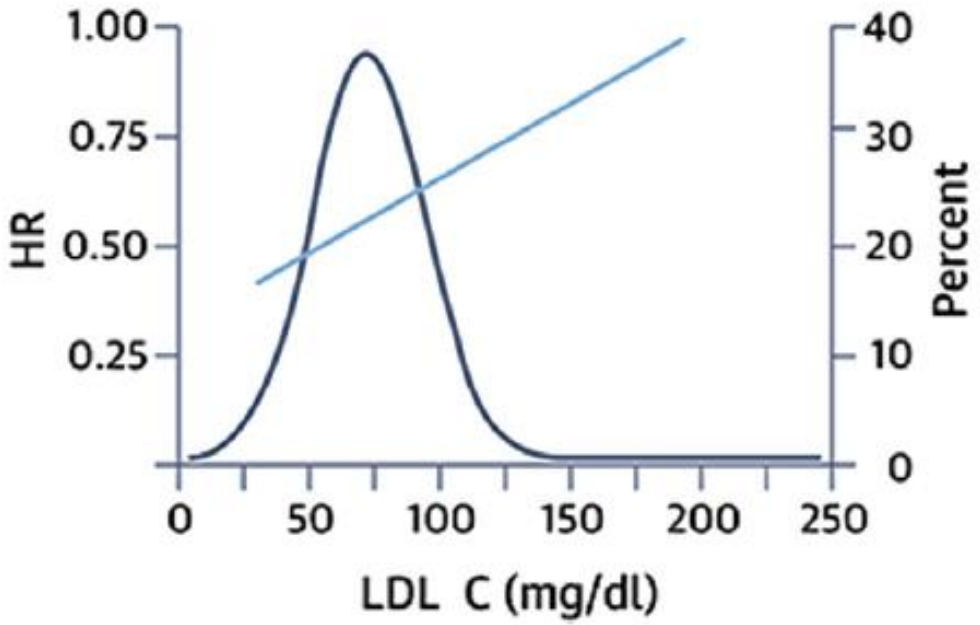
CEPHEUS為亞太區的研究，針對35121位曾使用過降血脂藥物的病人，發現只有44.7%的病人LDL-C有達標(<100mg/dL)

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)

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)

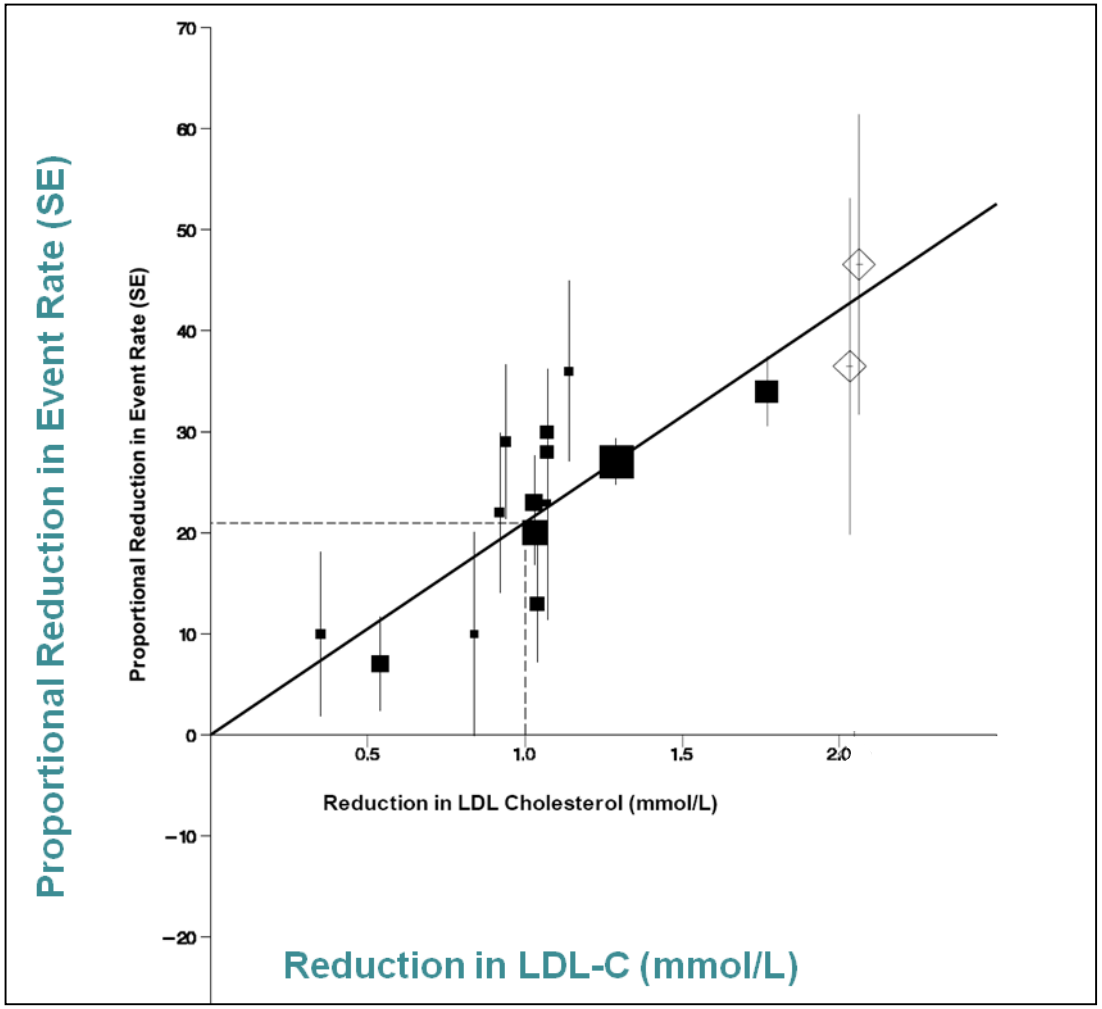
When LDLc is reduced to 50mg/dL or lower, the risk for CV events is reduced by more than half

CONCLUSIONS The reductions of LDL-C, non-HDL-C, and apoB levels achieved with statin therapy displayed large interindividual variation. Among trial participants treated with high-dose statin therapy, >40% did not reach an LDL-C target <70 mg/dl. Patients who achieve very low LDL-C levels have a lower risk for major cardiovascular events than do those achieving moderately low levels. (J Am Coll Cardiol 2014;64:485-94) © 2014 by the American College of Cardiology Foundation.



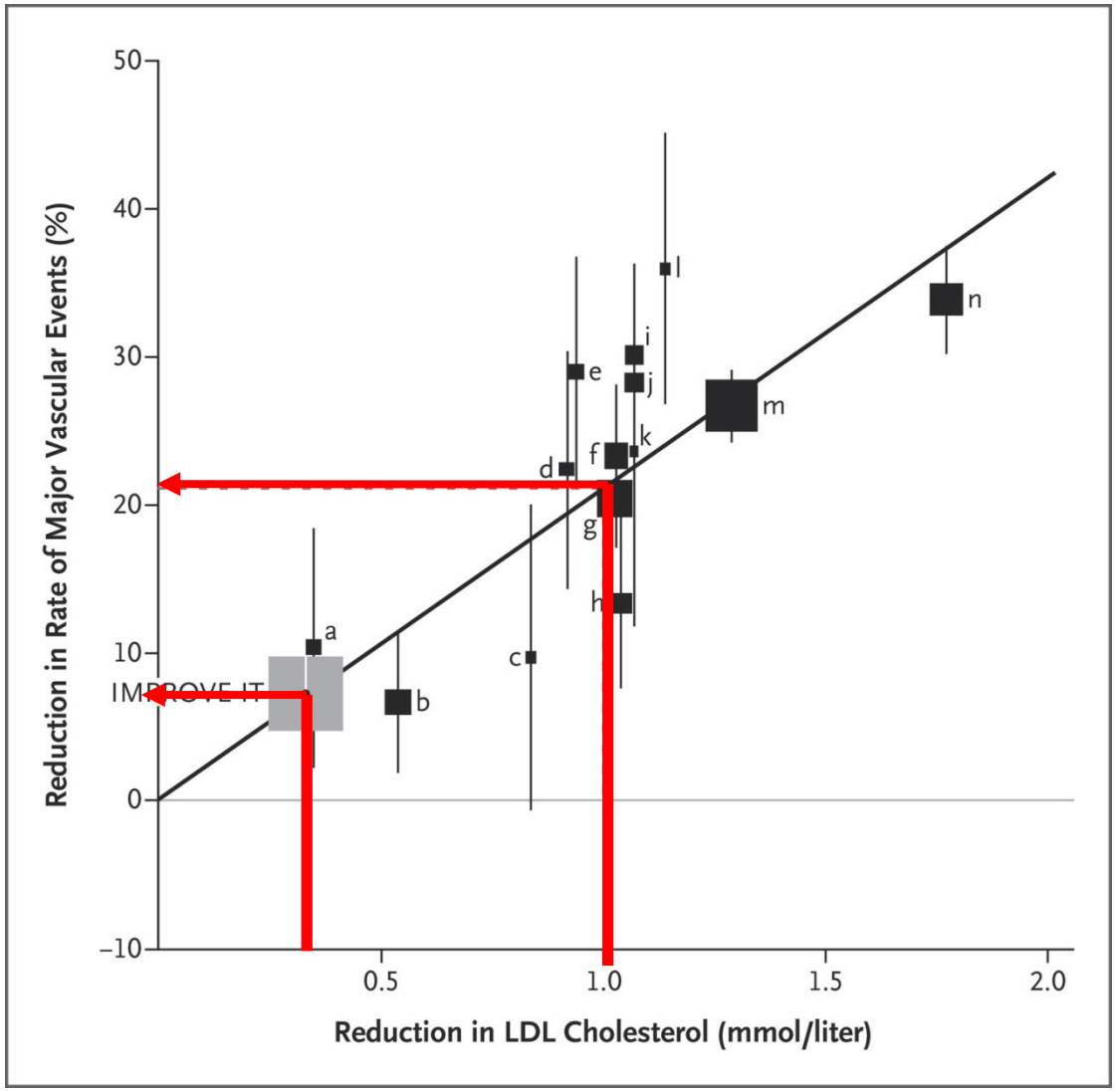
J Am Coll Cardiol. 2014 Aug 5;64(5):485-94

LDL-cholesterol and reduction in cardio-vascular events – only statin??



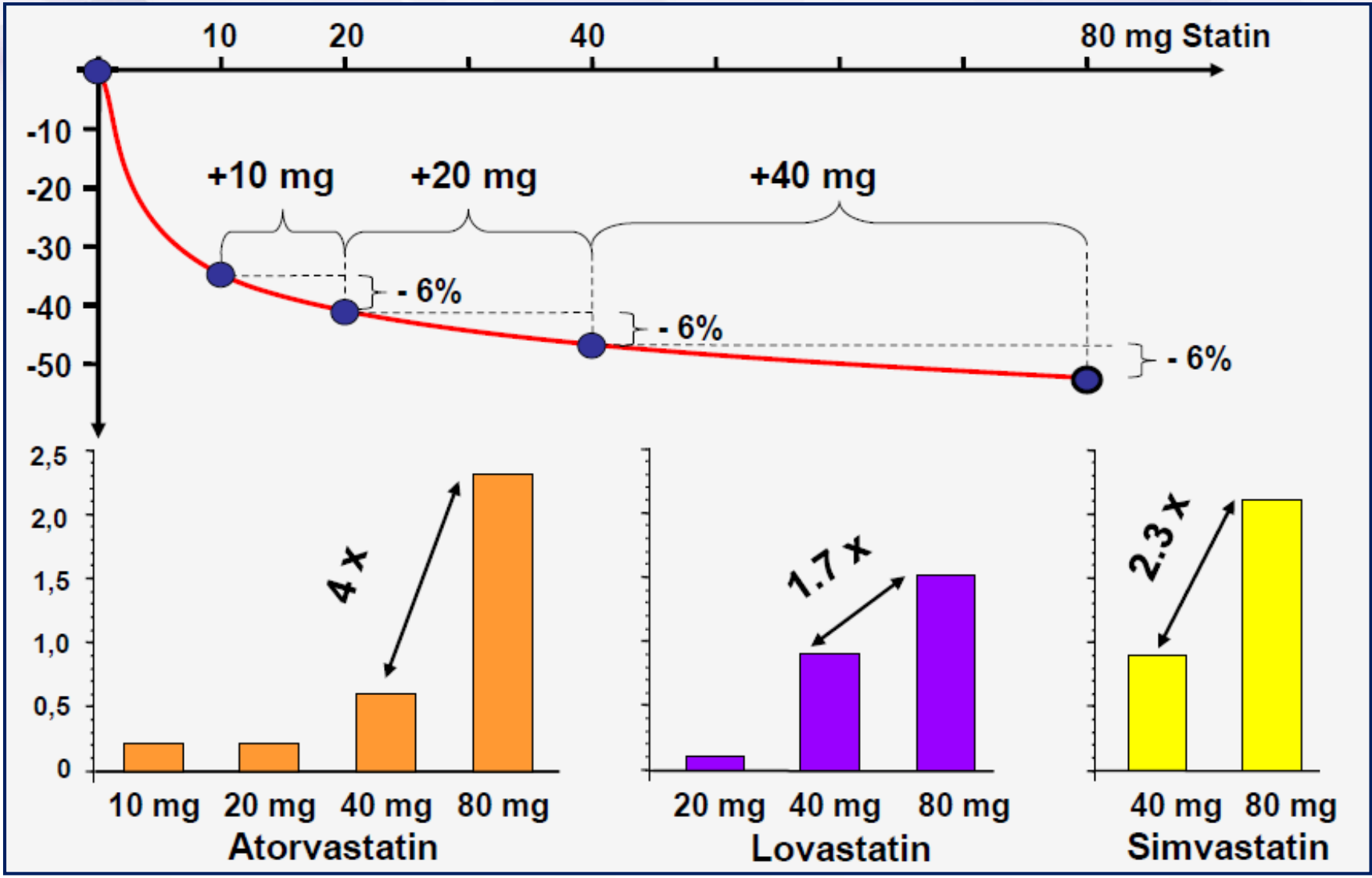
Holme I et al. Am J Cardiol 2010;105:1802–1808

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



Cannon CP et al. N Engl J Med 2015;372:2387-2397.

LDL-reduction and side effects with increasing doses of statins

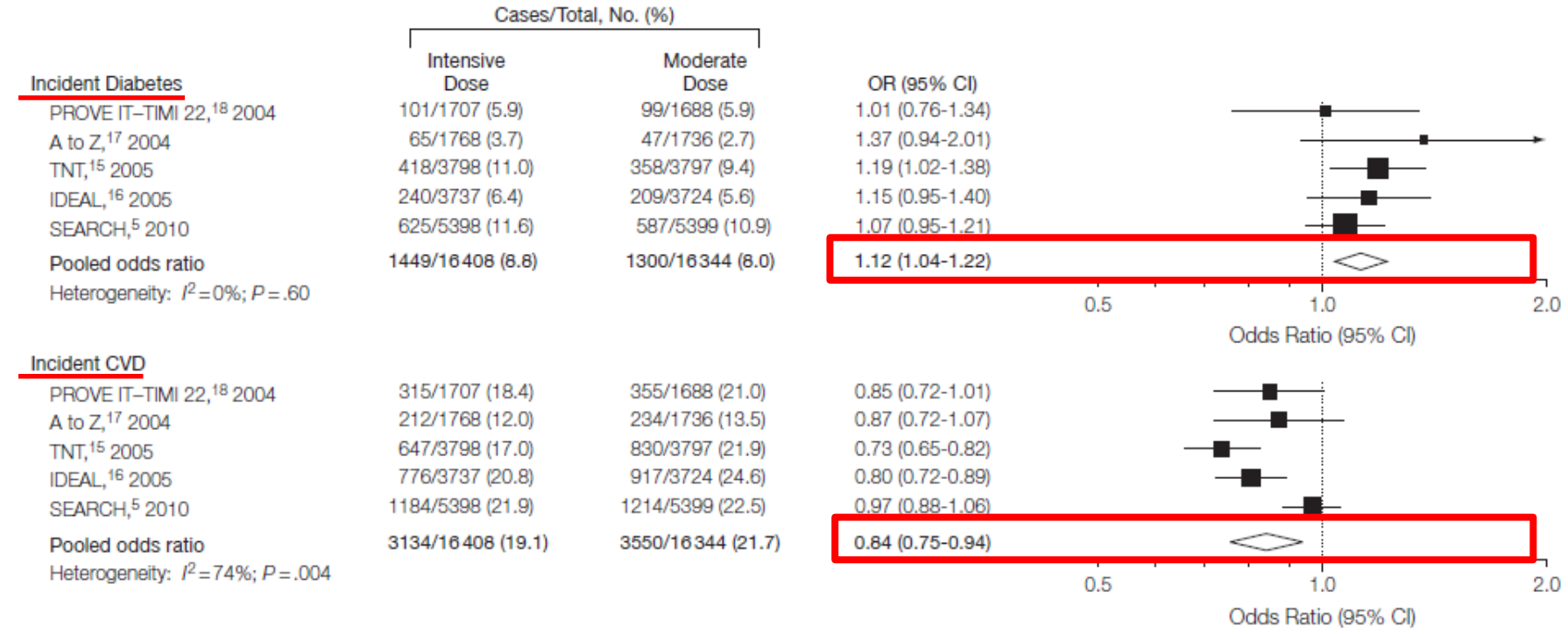


Leitersdorff et al. Europ. Heart J. 2001

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

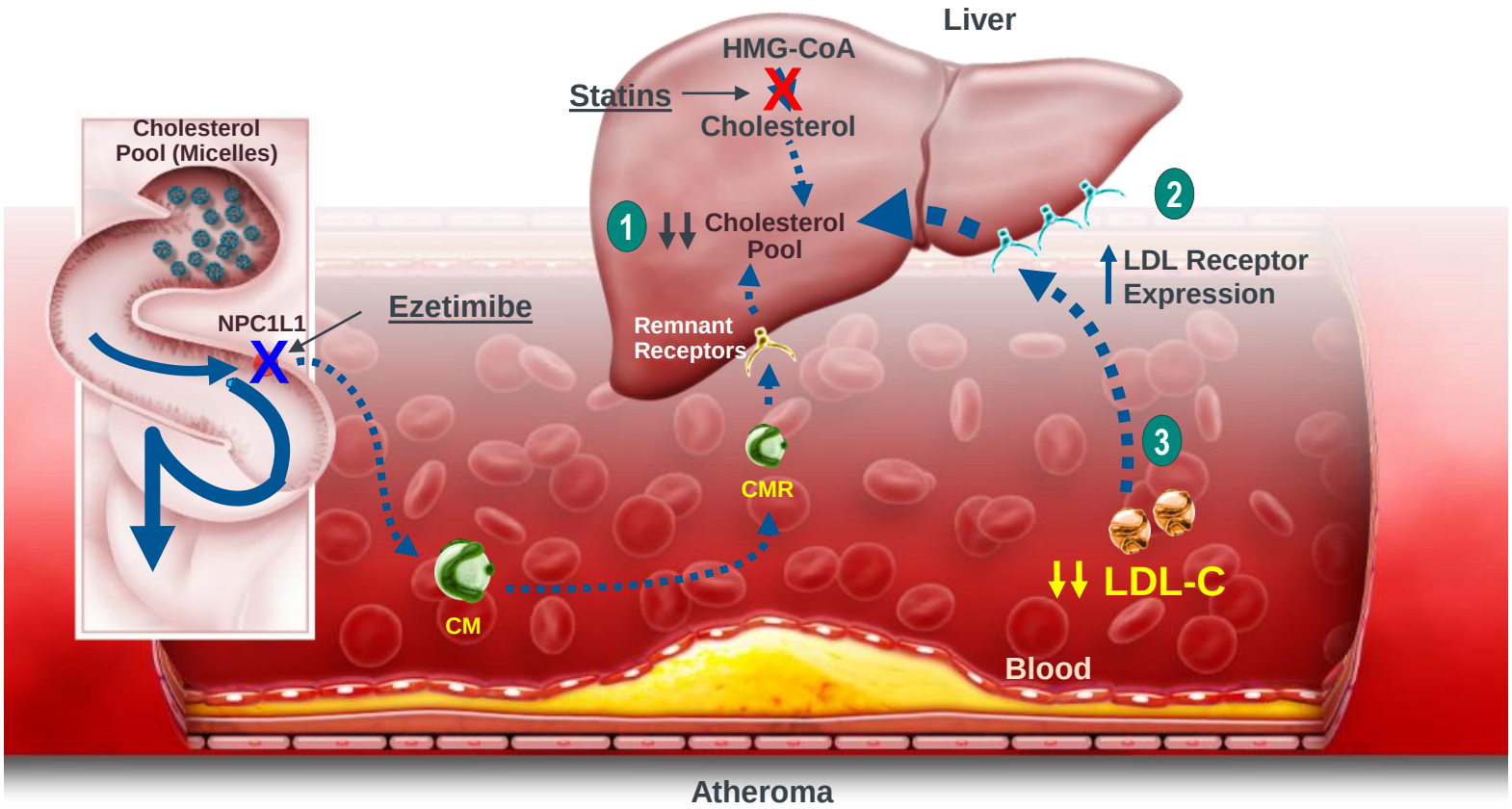


Combination Therapy: An Approach To Help Treat Hypercholesterolemia

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.

Multiple Clinical Trials Demonstrated the Benefits of Atorvastatin for Reduction of Cardiovascular Events[1–4]

Study	Patient Population	Intervention	Outcomes Benefit
ASCOT[1]	Hypertension; aged 40–79 years; TOTAL-C ≤6.5 mmol/L (~251 mg/dL); and at least 3 other CV risk factors; N=10,305	Atorva 10 mg vs placebo; median 3.3 years	**36% reduction in nonfatal MI and fatal CHD**; *P*=0.0005
CARDS[2]	Type 2 diabetes; aged 40–75 years; LDL-C ≤4.14 mmol/L (~160 mg/dL); TG ≤6.8 mmol/L (~602 mg/dL); at least 1 additional risk factor; N=2,838	Atorva 10 mg vs placebo; median 3.9 years	**37% reduction in major CV events** (MI, acute CHD death, UA, resuscitated cardiac arrest, coronary revascularization, or stroke); *P*=0.001
TNT[3]	Clinically evident, stable CHD; aged 35-75 years; LDL-C <130 mg/dL (~3.4 mmol/L); N=10,001	Atorva 10 mg vs atorva 80 mg; median 4.9 years	**22% reduction in major CV events** (death from CHD, nonfatal MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke); in the 80-mg vs 10-mg group; *P*<0.001
MIRACL[4]	Acute coronary syndrome (non–Q-wave MI or unstable angina); aged ≥18 years; N=3,086	Atorva 80 mg vs placebo; 16 weeks	**16% reduction in ischemic events** (death, nonfatal MI, cardiac arrest with resuscitation or angina pectoris with evidence of myocardial ischemia requiring hospitalization); *P*=0.048
PROVEIT	ACS patients ; aged ≥18 years; N=4,162	Atorva 80mg vs pravastatin 40mg; median 24 months	**16% reduction in major CV events** (death from any cause, MI, documented unstable angina requiring re-hospitalization, revascularization, and stroke); p=0.005

The incremental benefit of ezetimibe/atorvastatin on cardiovascular morbidity and mortality over and above that demonstrated for atorvastatin has not been established.

ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; TOTAL-C = total cholesterol; CV = cardiovascular; Atorva = atorvastatin; MI = myocardial infarction; CHD = coronary heart disease; CARDS = Collaborative Atorvastatin Diabetes Study;
TG = triglycerides; UA = unstable angina; TNT = Treating to New Targets; MIRACL = Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering.

1. Sever PS et al. *Lancet.* 2003;361:1149–1158. **2**. Colhoun HM et al. *Lancet*. 2004;364:685–696. **3.** LaRosa JC et al. *N Engl J Med* 2005;352:1425–1435.
4. Schwartz GG et al. *JAMA.* 2001;285:1711–1718.

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

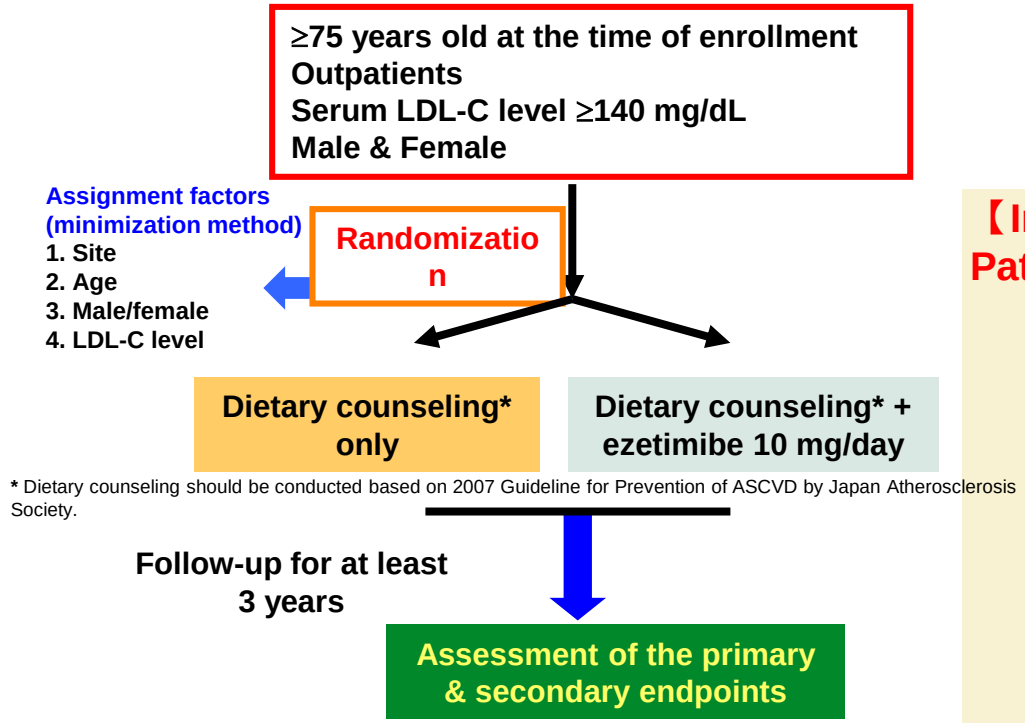
Aim of the EWTOPIA75 study

To test the hypothesis that ….

LDL-cholesterol-lowering therapy for patients ≥75 years with elevated LDL-C level who have no history of coronary artery disease can significantly prevent the occurrence of cerebro- and cardio-vascular events.

As LDL-cholesterol-lowering therapy, ezetimibe, an inhibitor of cholesterol absorption in the intestine, was used.

Study Design of EWTOPIA 75



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

Primary Endpoint

EWTOPIA75
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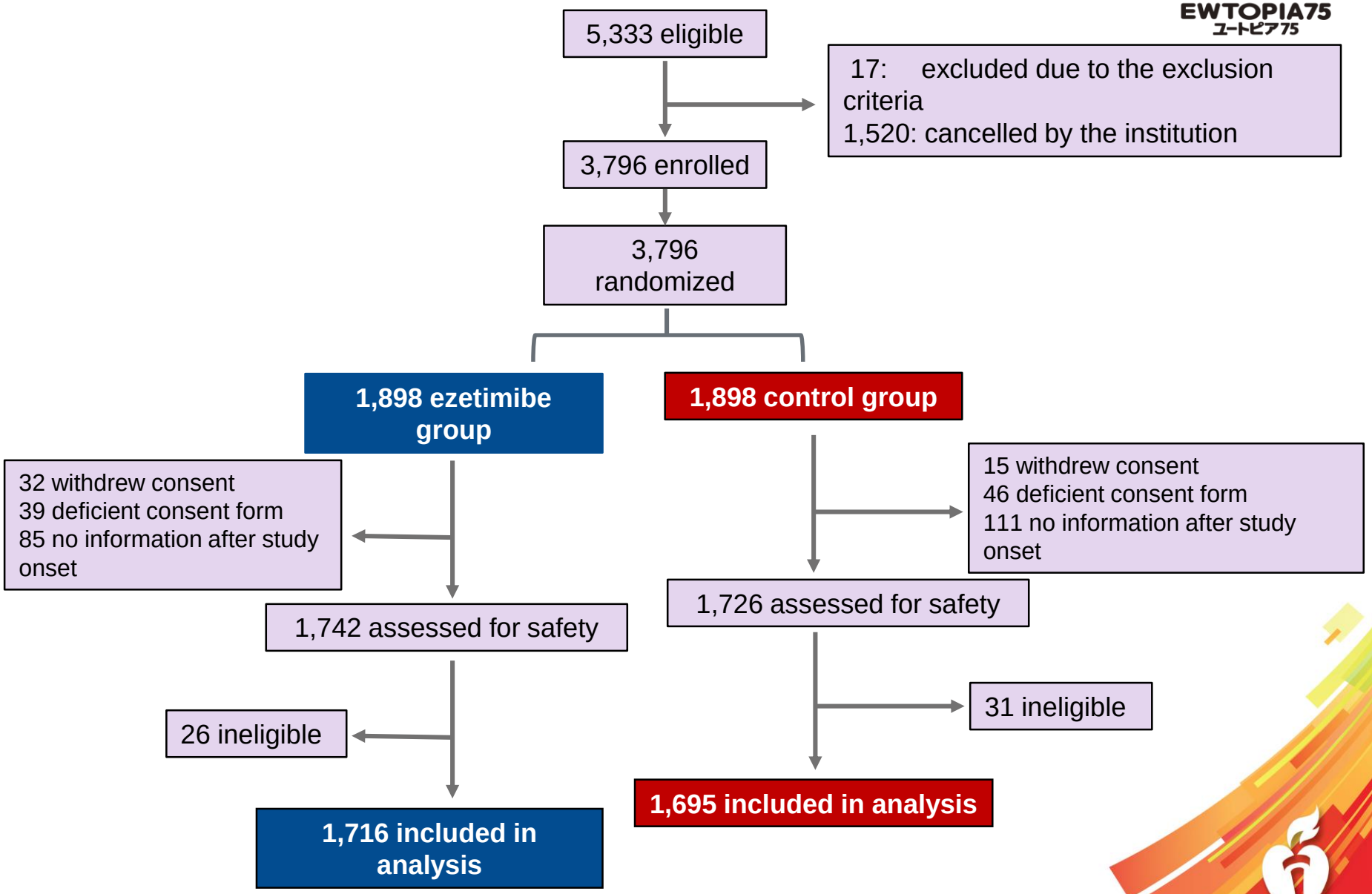
A composite of the following atherosclerotic cardiovascular events

- **Sudden cardiac death**
- **Fatal & nonfatal myocardial infarction**
- **Coronary revascularization (PCI or CABG)**
- **Fatal & nonfatal stroke**

Major secondary endpoints

- **All types of cardiac events** including sudden cardiac death, fatal & nonfatal myocardial infarction, and coronary revascularization (PCI or CABG)
- **All types of stroke** including fatal & nonfatal cerebral infarction, and cerebral hemorrhage, Fatal & nonfatal cerebral infarction, TIA, Fatal & nonfatal cerebral hemorrhage
- **Revascularization** of carotid artery (CAS or CEA) or peripheral arteries (PPI or bypass surgery)
- **Aortic diseases** including Aortic dissection, Rupture of aortic aneurysm, Surgical intervention of aortic aneurysm
- **All-cause mortality**
- **New onset of malignant tumors etc**

EWTOPIA75 Diagram



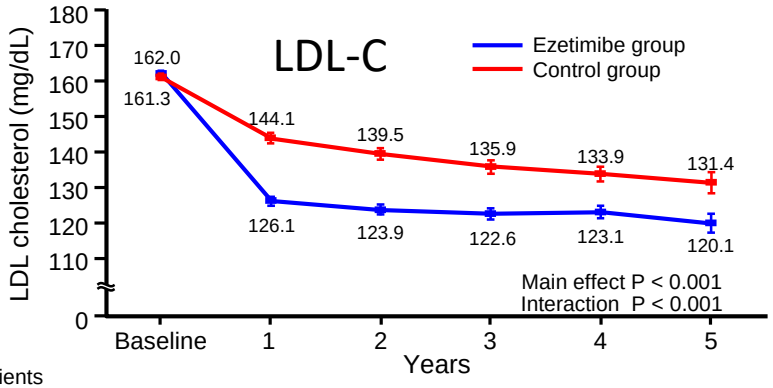
Baseline characteristics of patients

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

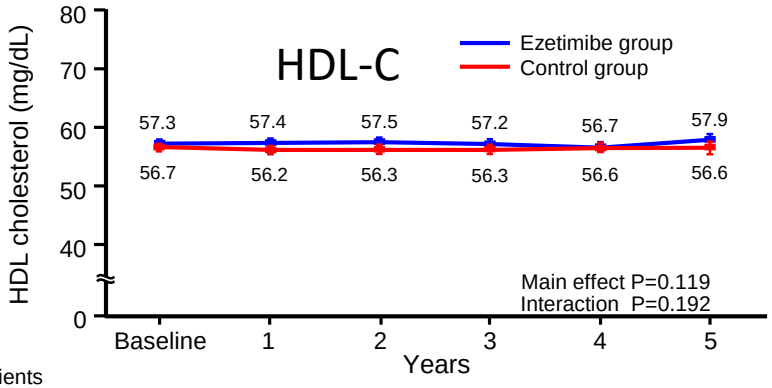
	Ezetimibe group (n=1,716)	Control group (n=1,695)
Age & Sex	80.6±4.7	80.6±4.7
Patients aged over 85 years	323 (18.8)	325 (19.2)
Male	440 (25.6)	432 (25.5)
Female	1276 (74.4)	1263 (74.5)
Body Constitution		
Height (cm)	150.7±8.7	150.6±8.6
Body weight (kg)	53.8±10.0	53.4±10.4
Body mass index (kg/m^2)	23.6±3.5	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

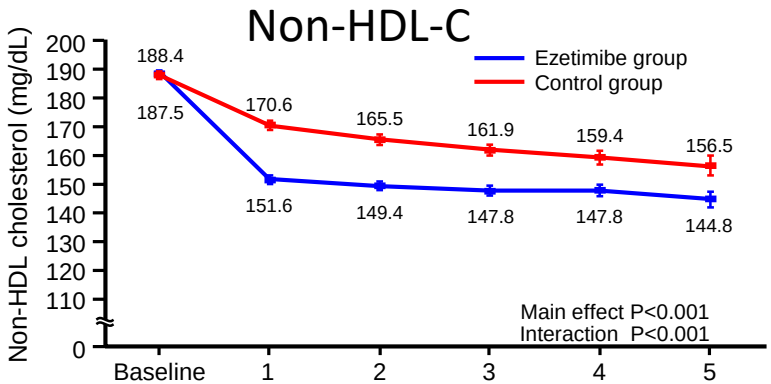
Lipid profile changes in Ezetimibe and Control groups



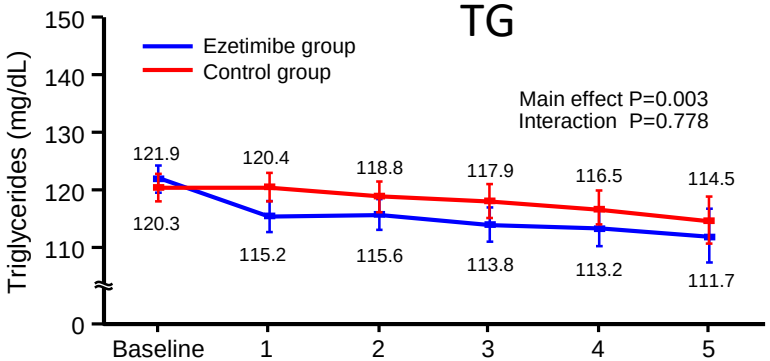
Number of Patients	Baseline	1	2	3	4	5
Treated by ezetimibe	1700	1489	1245	1009	685	311
Not treated by ezetimibe	1685	1464	1227	1023	706	314



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



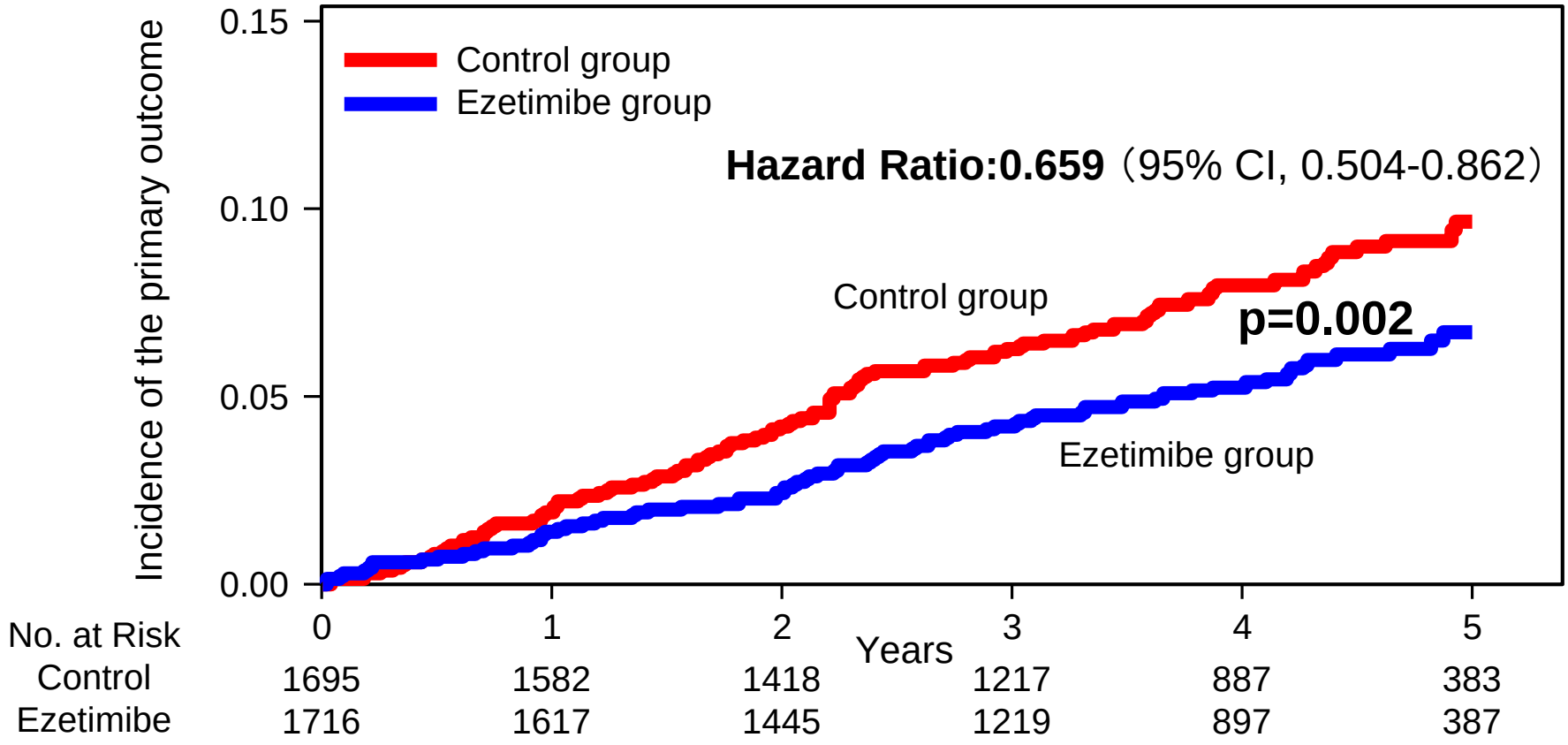
Number of Patients	Baseline	1	2	3	4	5
Treated by ezetimibe	1700	1490	1247	1009	687	311
Not treated by ezetimibe	1685	1466	1230	1024	707	314



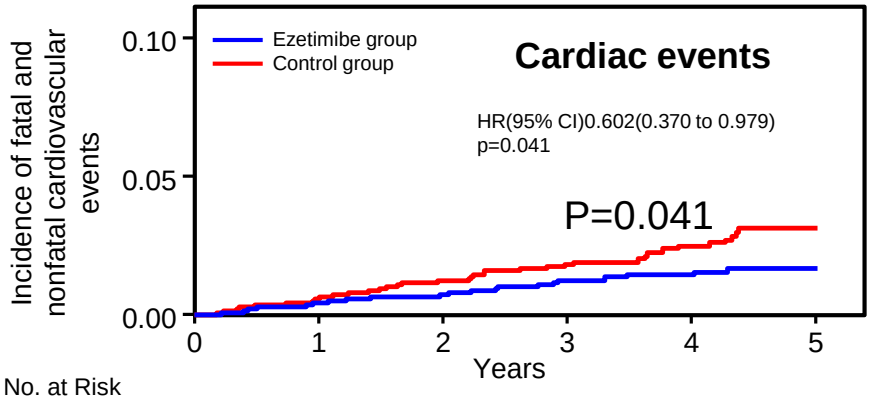
Number of Patients	Baseline	1	2	3	4	5
Treated by ezetimibe	1700	1507	1258	1019	699	317
Not treated by ezetimibe	1685	1484	1242	1029	717	321

Effect of ezetimibe treatment on the primary end-point

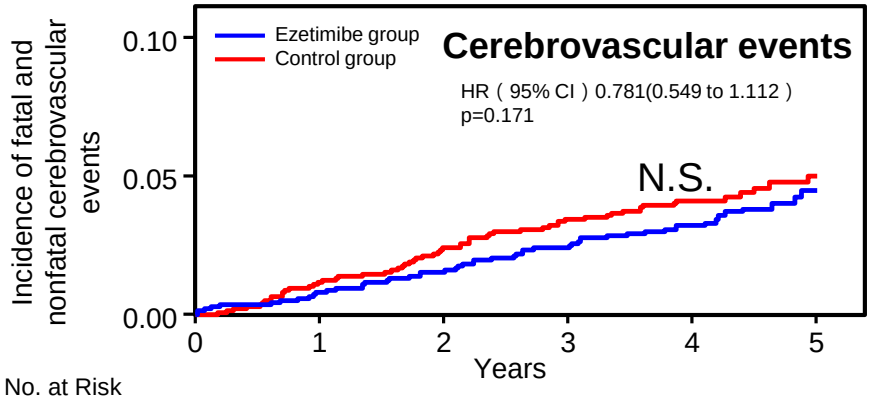
A composite of the atherosclerotic cardiovascular events
(Sudden cardiac death, myocardial infarction, PCI or CABG, and/or stroke)



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



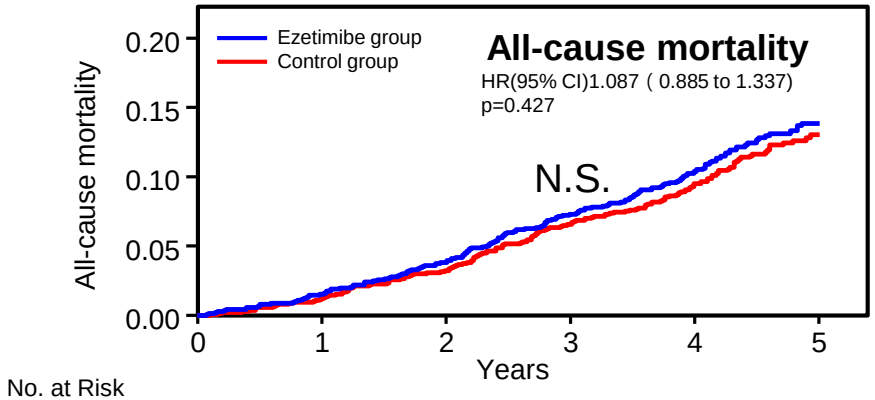
No. at Risk						
Control	1695	1603	1454	1260	920	405
Ezetimibe	1716	1629	1464	1249	919	402



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

EWTOPIA75
ユートピア75

- 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.

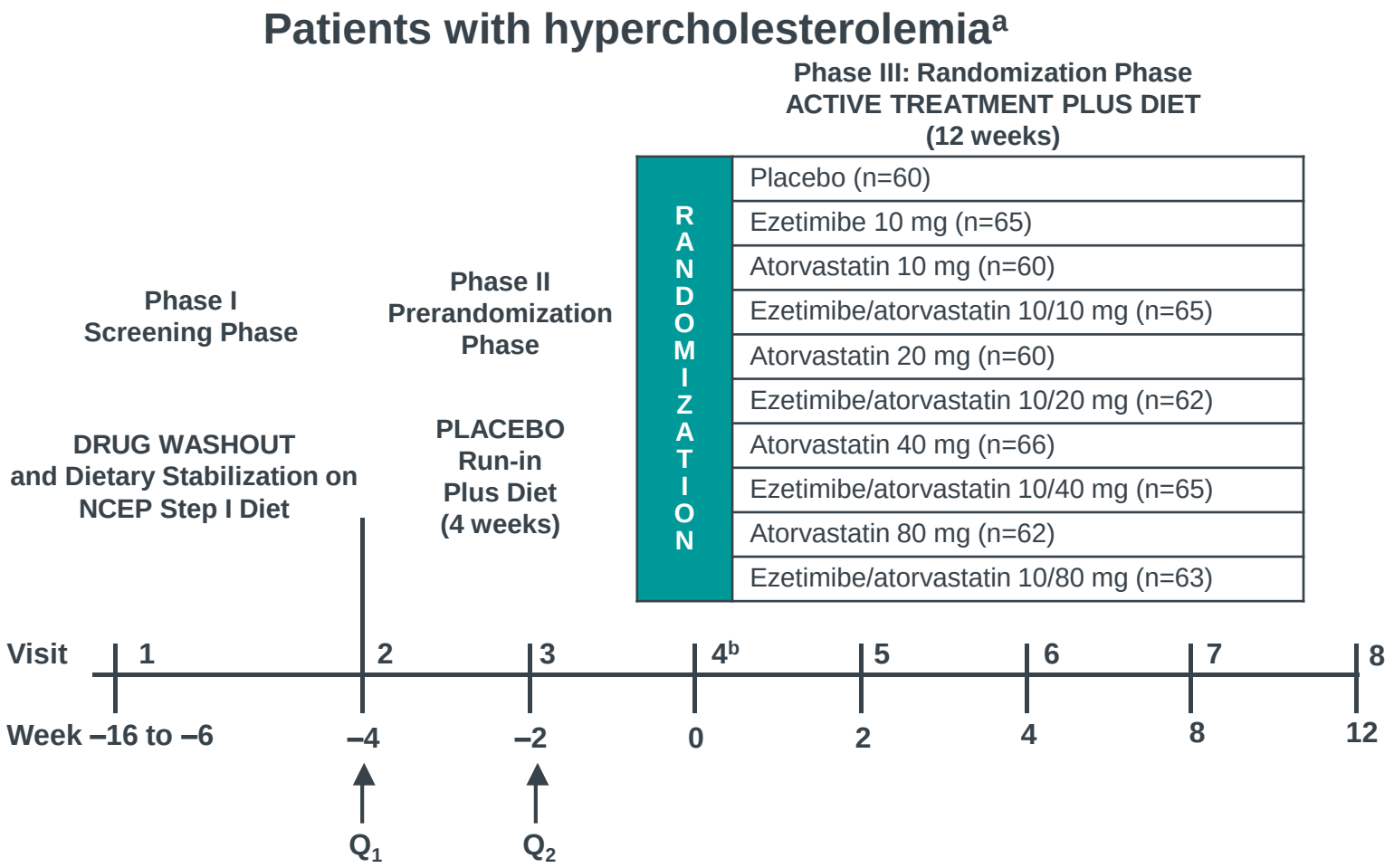
- This was true for cardiac events by secondary end-point analysis.

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

Clinical Data for Ezetimibe/Atorvastatin: Effect of Ezetimibe Coadministered With Atorvastatin in 628 Patients With Primary Hypercholesterolemia

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

Ballantyne 2003: Ezetimibe/Atorvastatin in Patients With Primary Hypercholesterolemia (Study Design)[1]



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

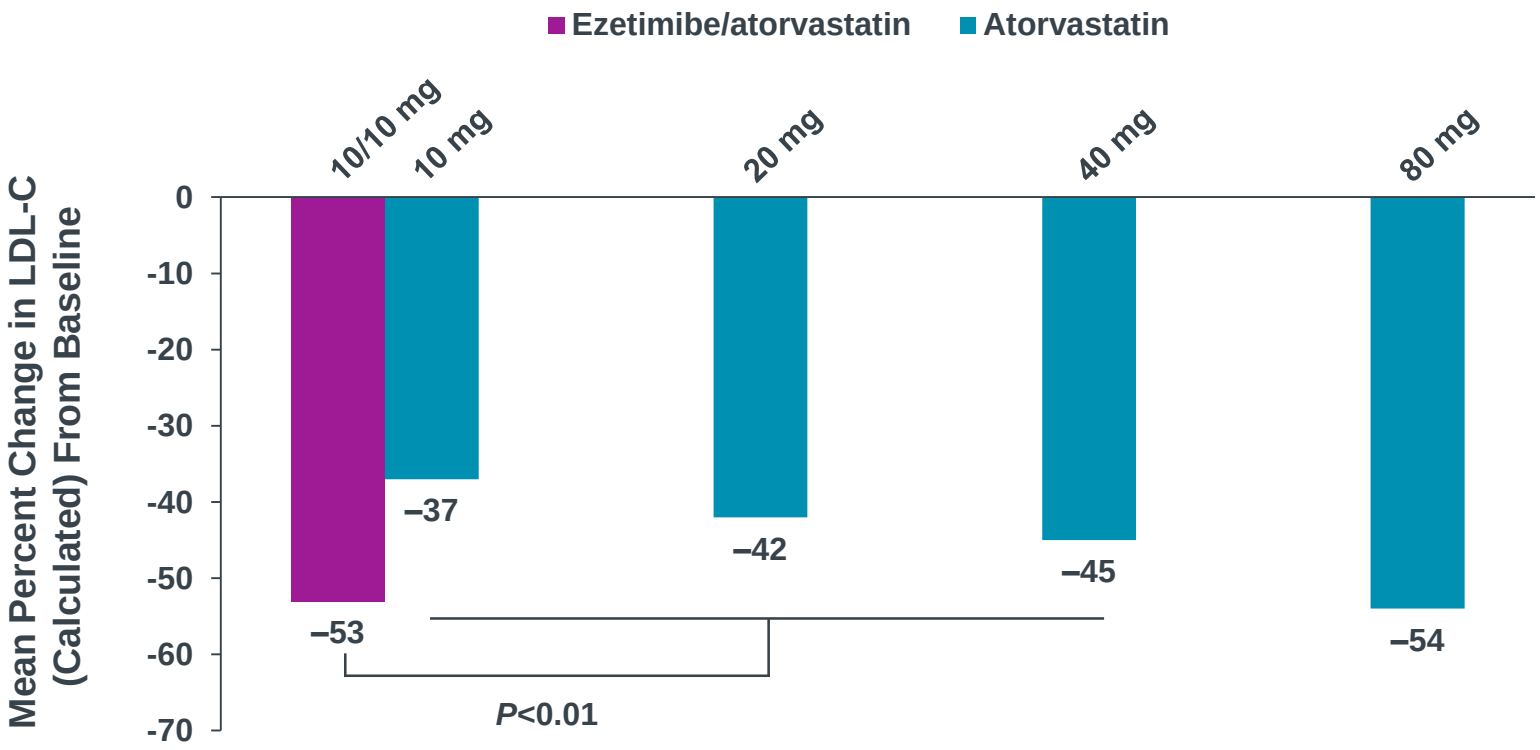
[a]Baseline LDL-C 145 to 250 mg/dL (~3.7 to 6.5 mmol/L) and triglycerides ≤350 mg/dL (~4.0 mmol/L).

[b]Random assignment to double-blind treatment occurred at visit 4.

NCEP = National Cholesterol Education Program; Q_1 = first qualifying calculated LDL-C value; Q_2 = second qualifying calculated LDL-C value; blood samples for Q_1 and Q_2 were collected at least 1 week apart.

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

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

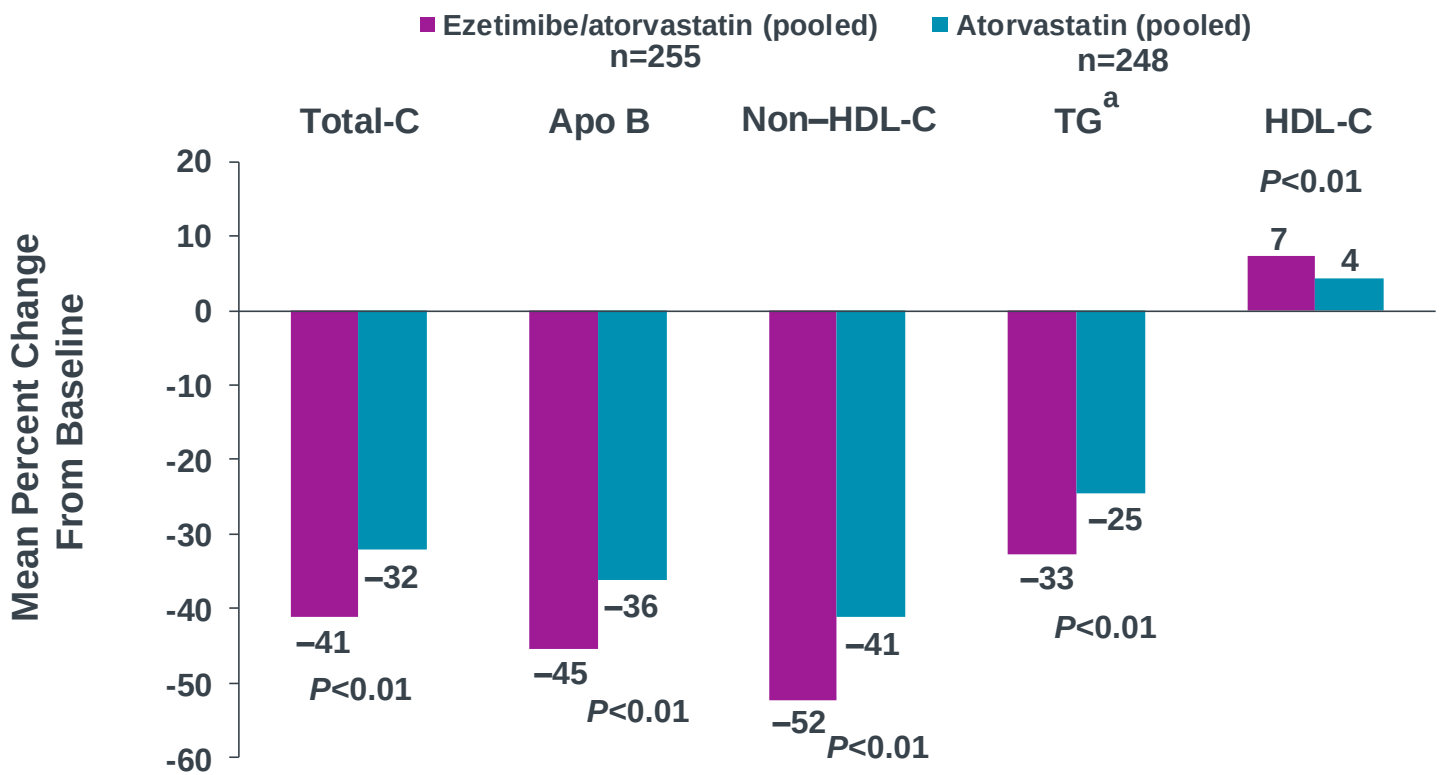


Mean baseline LDL-C was 182 mg/dL (~4.7 mmol/L) for ezetimibe/atorvastatin arms (n=255) and 181 mg/dL (~4.7 mmol/L) for atorvastatin arms (n=248).

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

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

Ballantyne 2003: Ezetimibe/Atorvastatin Provided Significantly Greater Reduction in Total-C, Apo B, Non–HDL-C, and TG and Increase in HDL-C Compared with Atorvastatin Monotherapy[1]



[a]Median percent change from baseline.

Total-C = total cholesterol; ApoB = apolipoprotein B; TG = triglycerides.

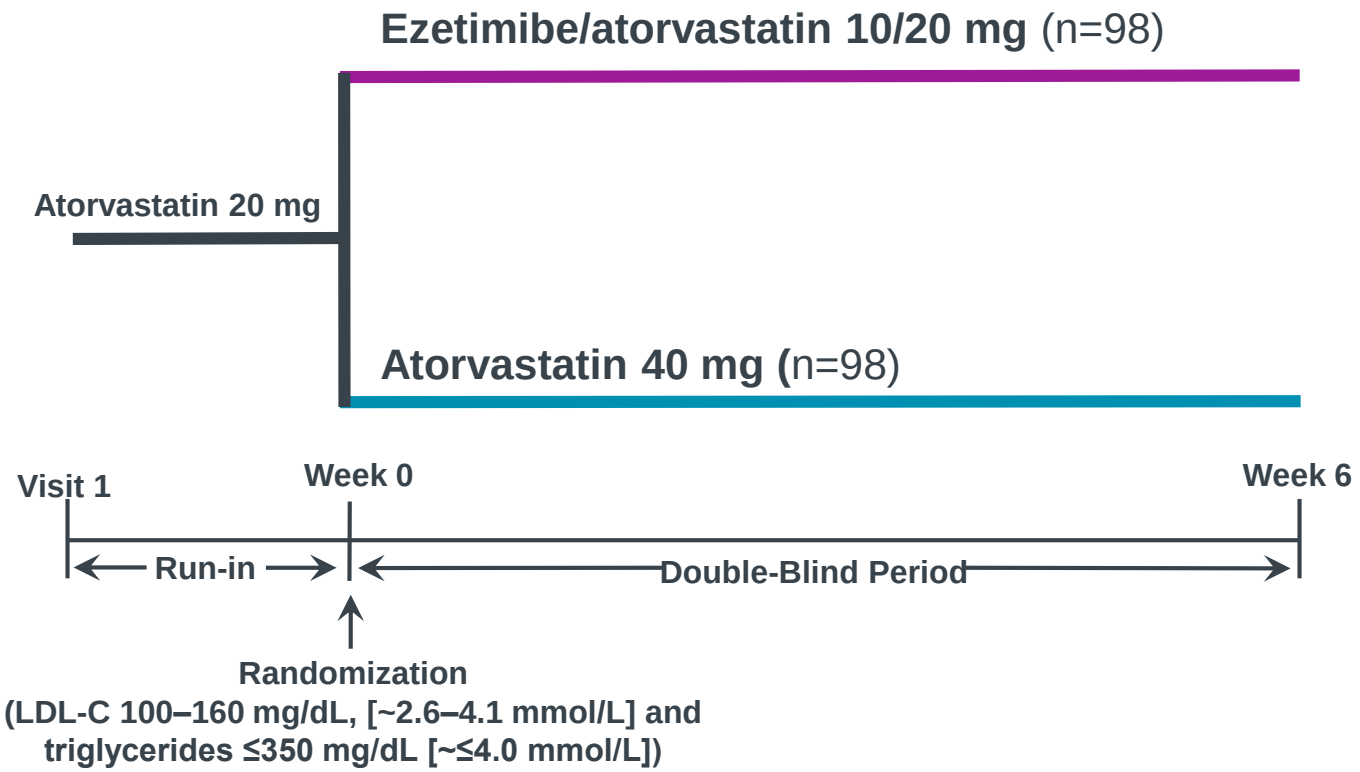
1. Ballantyne CM et al. *Circulation*. 2003;107:2409–2415.

Clinical Data for Ezetimibe/Atorvastatin: Efficacy and Safety of Ezetimibe Added on to Atorvastatin (20 mg) Versus Uptitration of Atorvastatin (to 40 mg) in Hypercholesterolemic Patients at Moderately High Risk for Coronary Heart Disease (TEMPO Study)

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

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

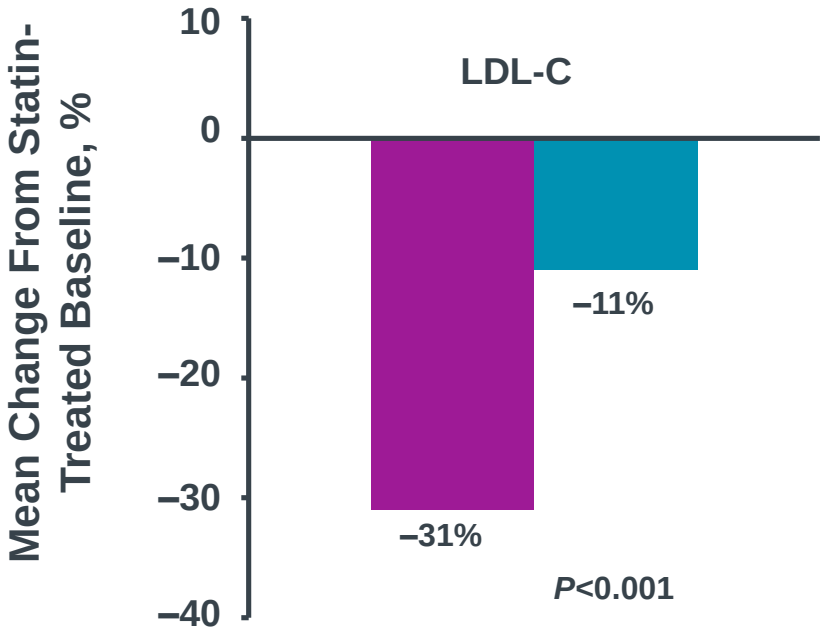
Patients with hypercholesterolemia at moderately high risk of CHD (based on NCEP ATP III criteria)



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)

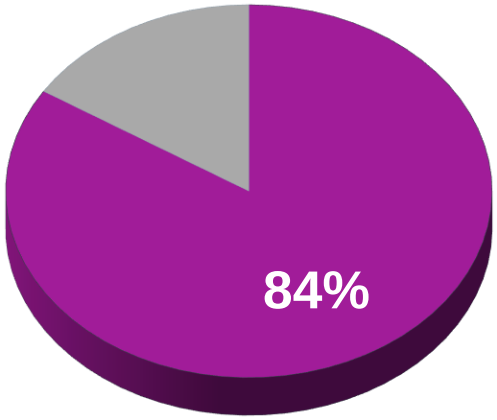
Atorvastatin 20 mg titrated to 40 mg (n=92) (mean on-statin baseline LDL-C = 118 mg/dL, ~3.1 mmol/L)

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

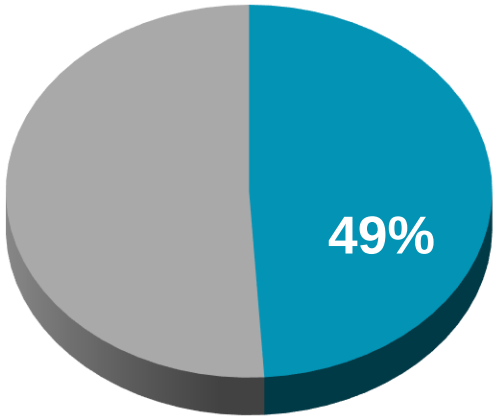
Ezetimibe/atorvastatin 10/20 mg
(n=92)



Mean Statin-Treated Baseline LDL-C: 120 mg/dL (~3.1 mmol/L)

***P*<0.001**

Atorvastatin 40 mg
(n=92)

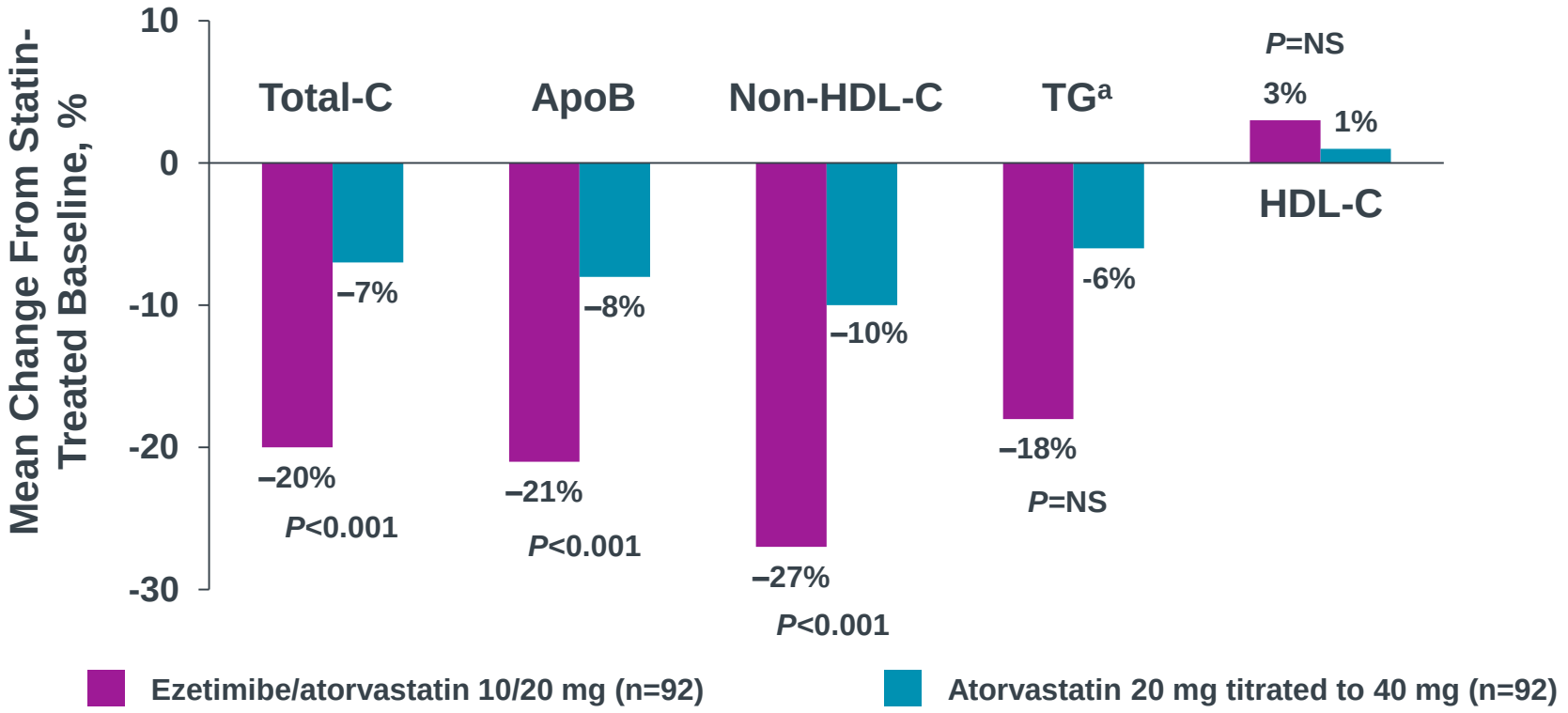


Mean Statin-Treated Baseline LDL-C: 118 mg/dL (~3.1 mmol/L)

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.

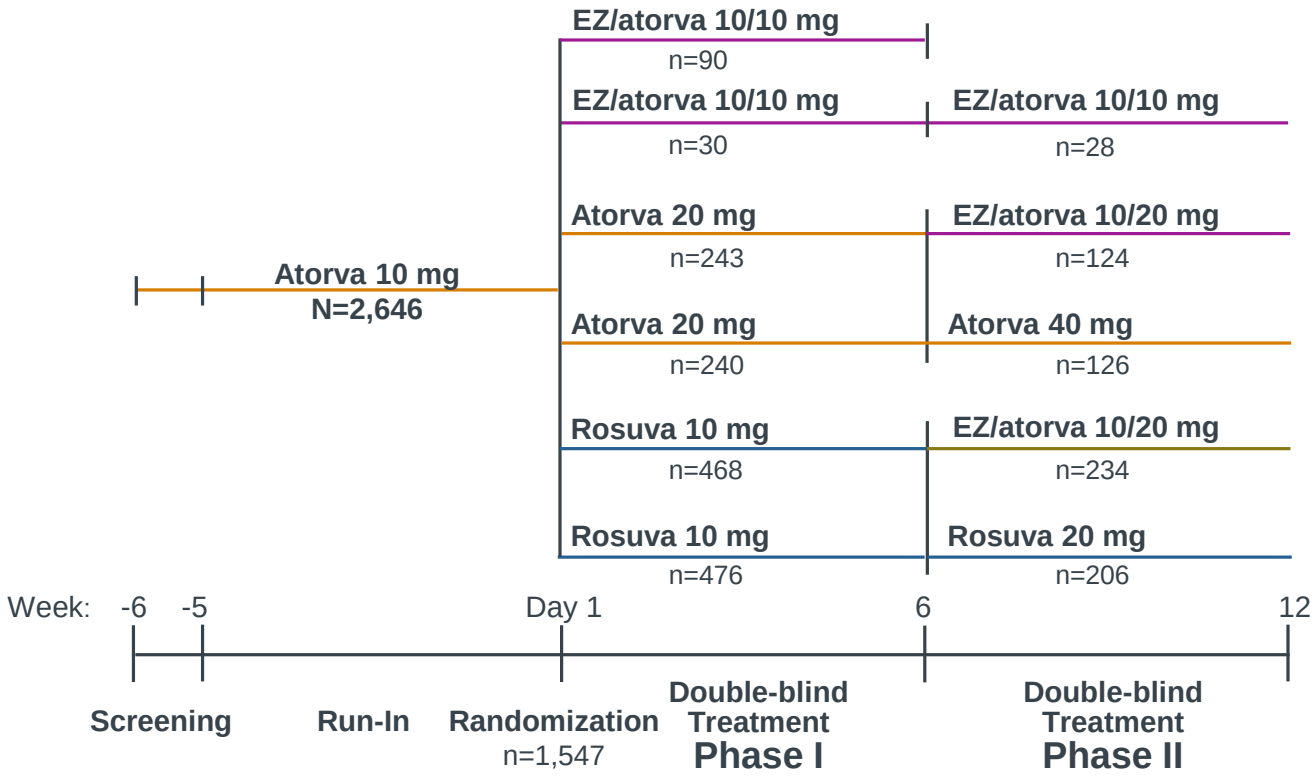
1. Conard SE et al. *Am J Cardiol*. 2008;102:1489–1494.

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]

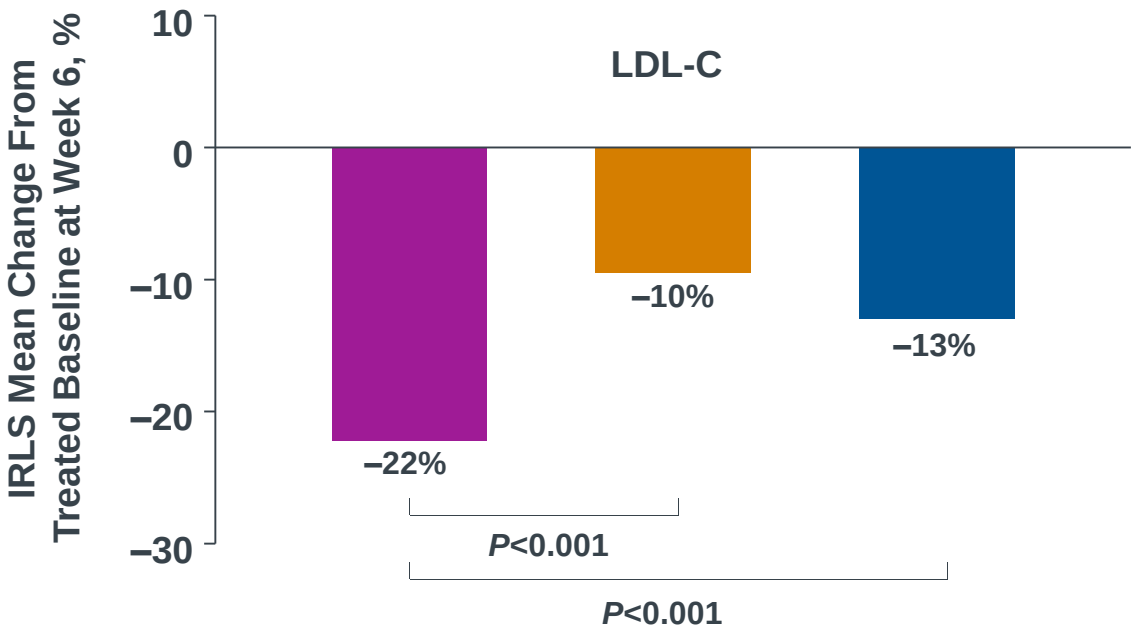
[a]High risk of CHD was defined as: 1) subjects without CVD who had type 2 diabetes, or ≥2 risk factors and a 10-year risk for CHD >20% as determined by the Framingham calculation, or 2) subjects with CVD, including established coronary or other atherosclerotic vascular disease.

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.

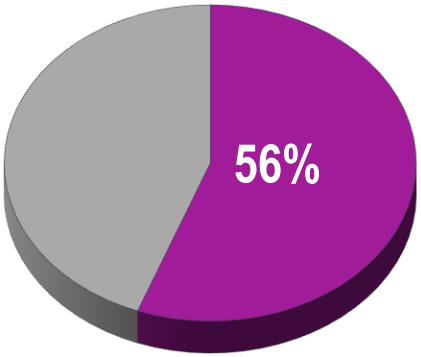
1. Bays HE et al. *Am J Cardiol*. 2013;112:1885–1895.

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

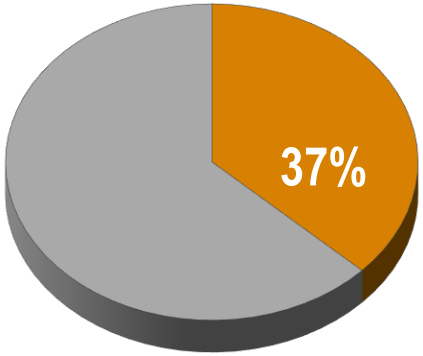
Ezetimibe/atorvastatin 10/10 mg
(n=119)

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



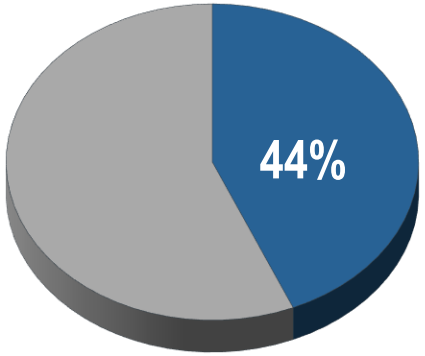
Atorvastatin 20 mg
(n=471)

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.

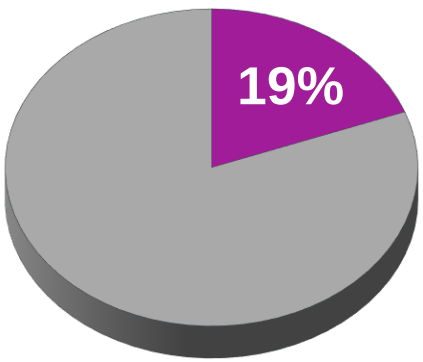
1. Bays HE et al. *Am J Cardiol*. 2013;112:1885–1895.

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

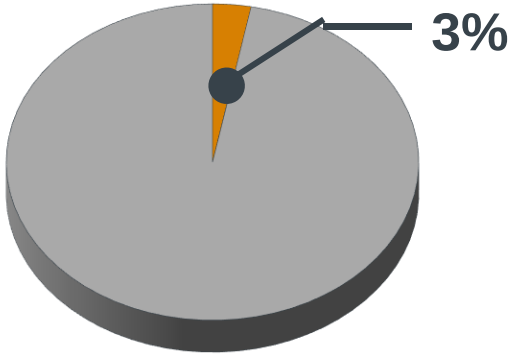
Ezetimibe/atorvastatin 10/10 mg
(n=119)

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



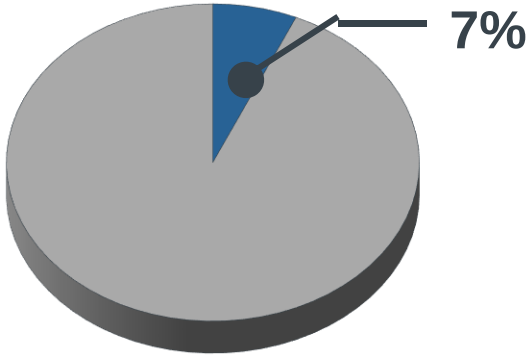
Atorvastatin 20 mg
(n=471)

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**

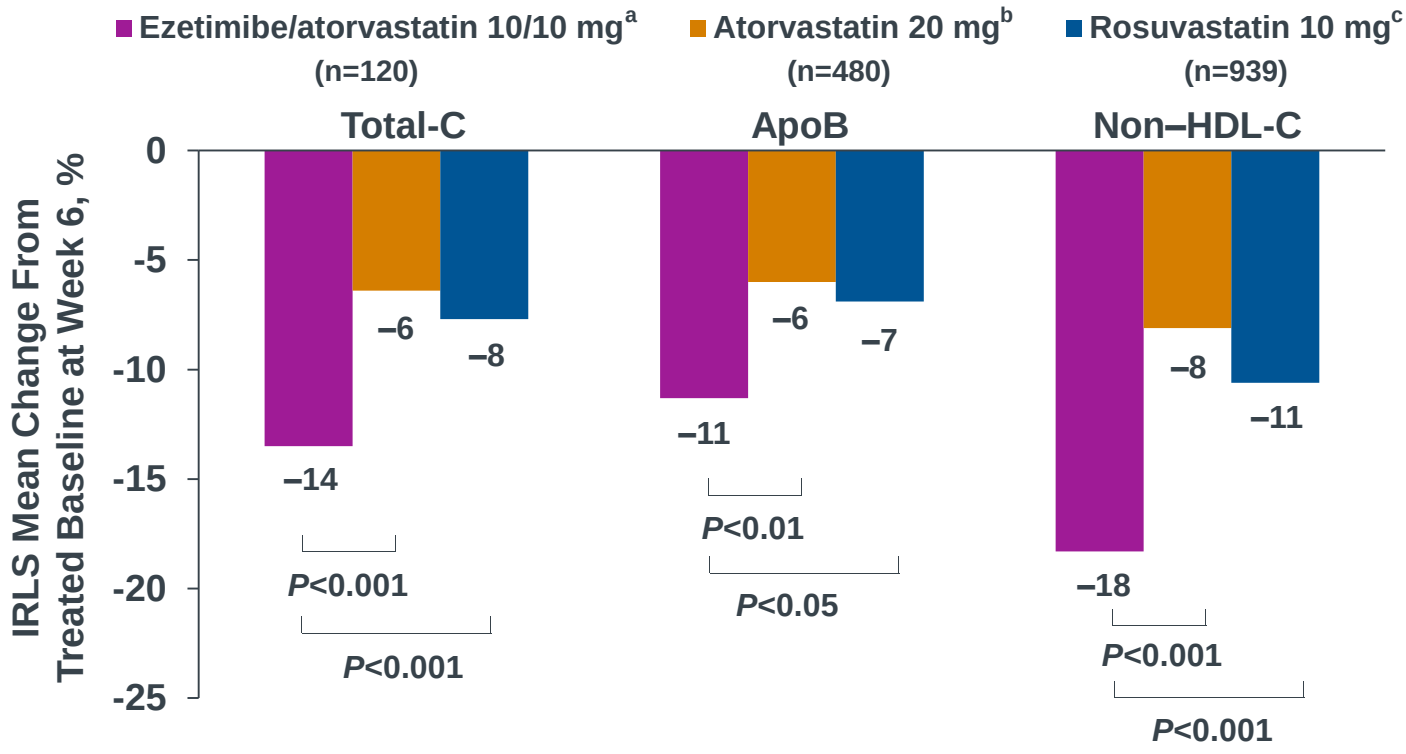
***P*<0.001**

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: 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).

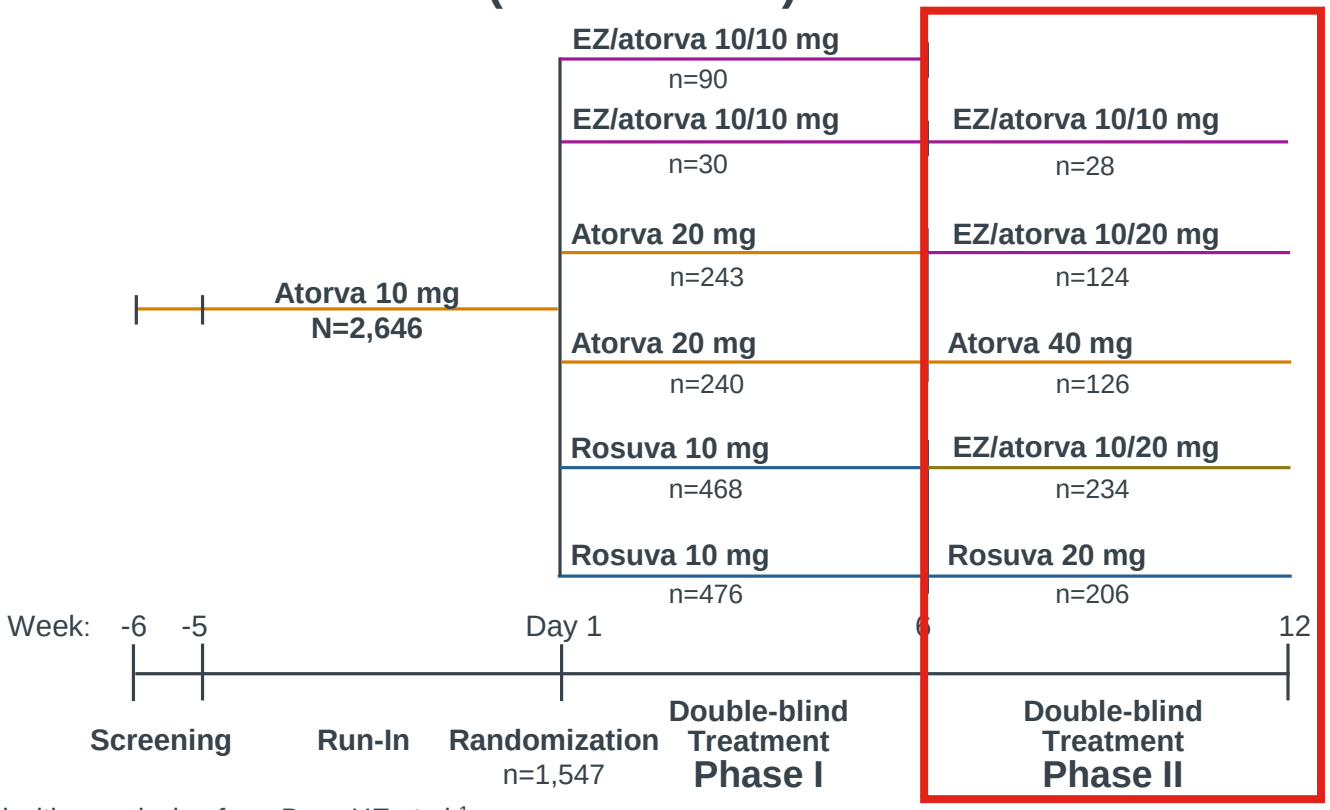
[c]Mean treated baselines for group switched to rosuvastatin 10 mg: Total-C 205 mg/dL (~5.3 mmol/L), apoB 104 mg/dL, and non–HDL-C 152 mg/dL (~3.9 mmol/L).

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



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

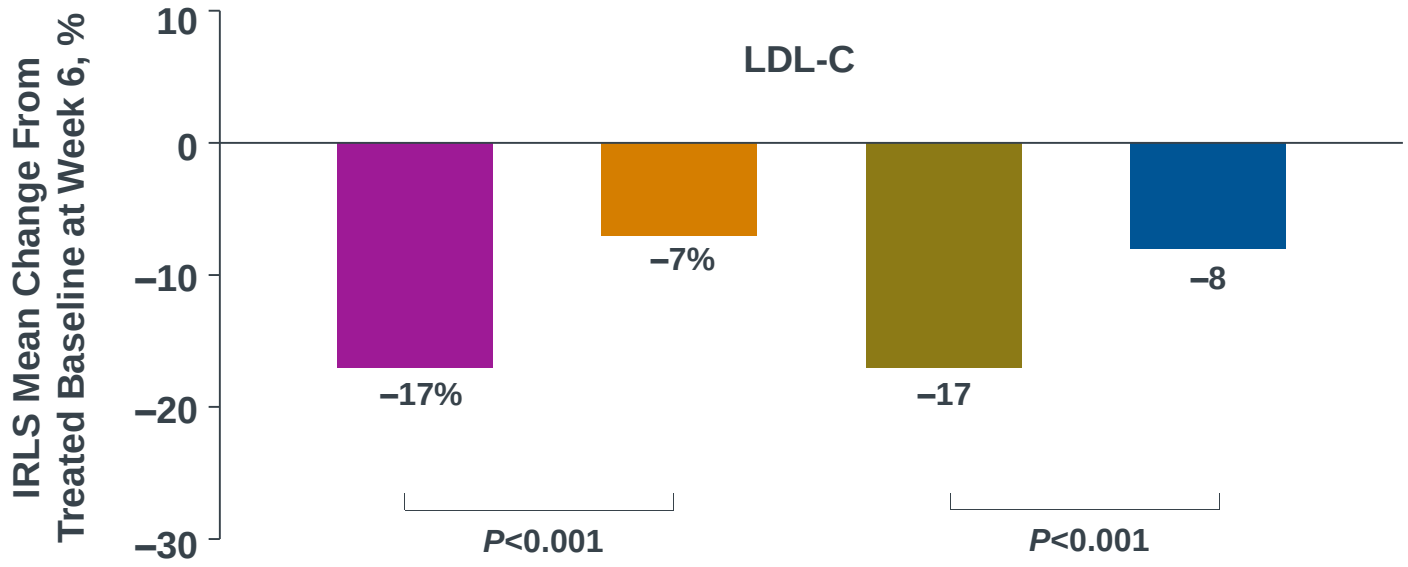
[a]High risk of CHD was defined as: 1) subjects without CVD who had type 2 diabetes, or ≥2 risk factors and a 10-year risk for CHD >20% as determined by the Framingham calculation, or 2) subjects with CVD, including established coronary or other atherosclerotic vascular disease.

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)

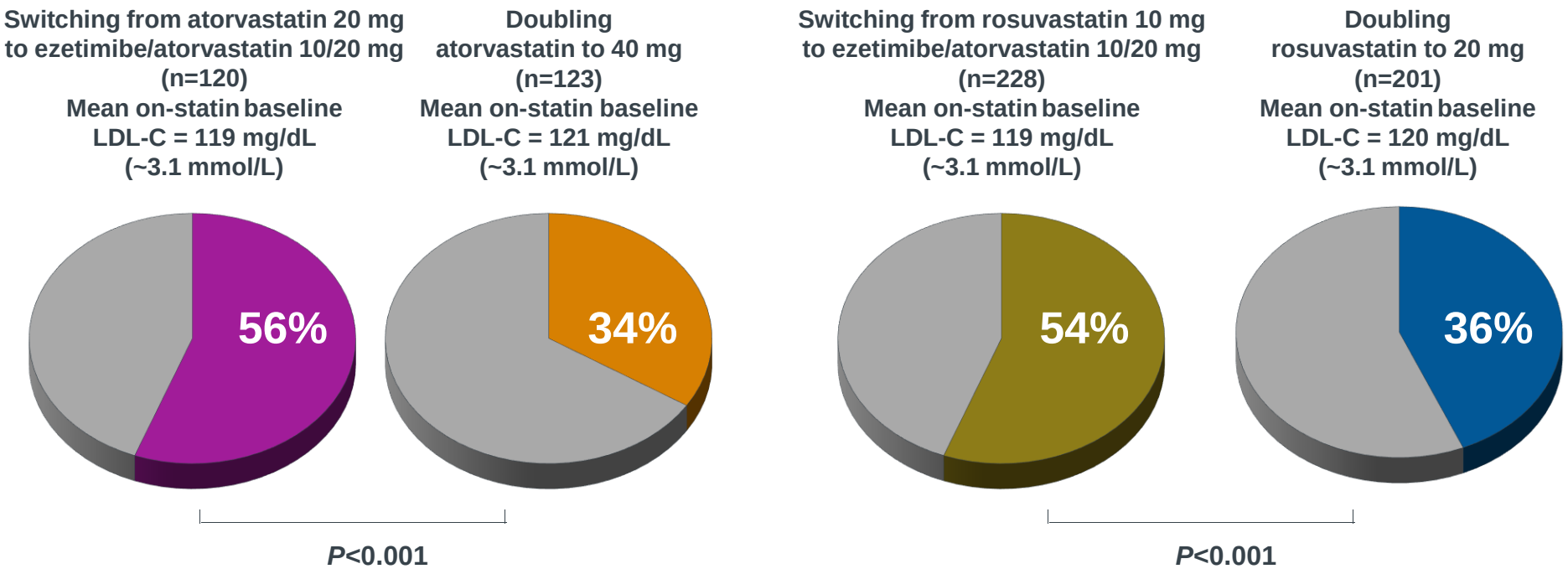
Doubling rosuvastatin to 20 mg (n=205) Mean on-statin baseline LDL-C = 120 mg/dL (~3.1 mmol/L)

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



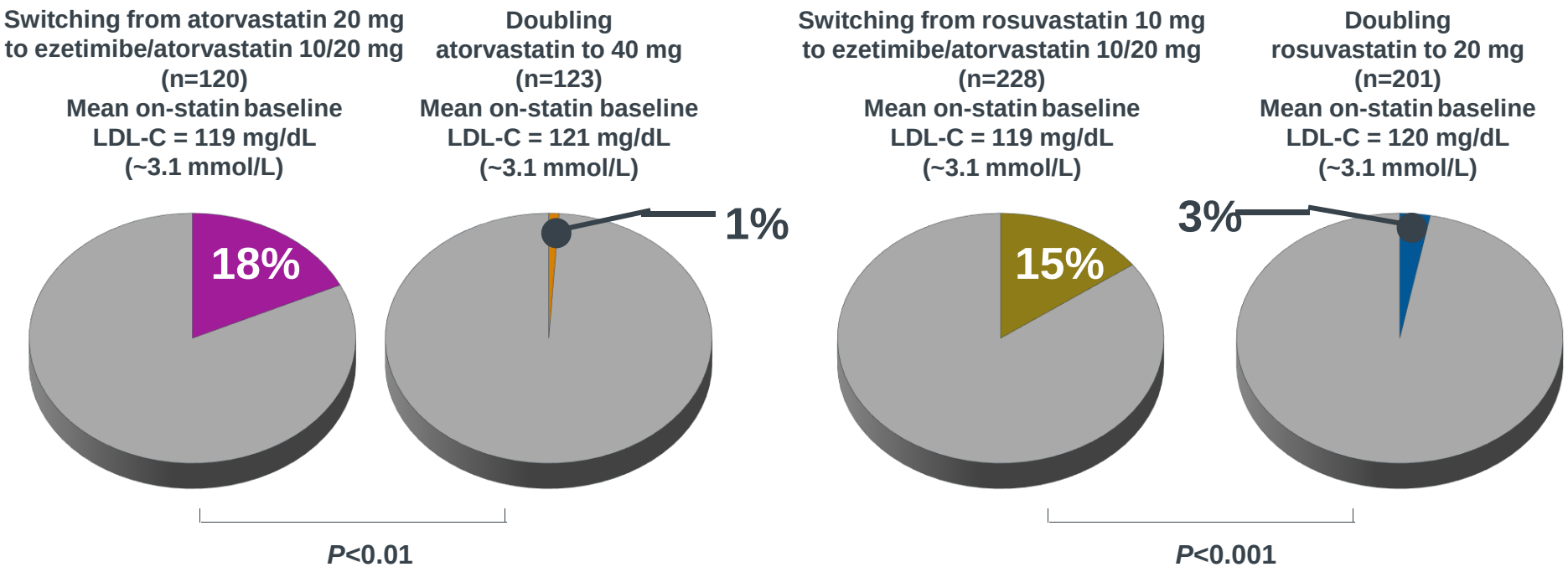
The IRLS mean decrease in LDL-C from statin-treated baseline was 17% with ezetimibe/atorvastatin 10/20 mg compared with 7% with doubling atorvastatin to 40 mg and 17% with ezetimibe/atorvastatin 10/20 mg compared with 8% with doubling rosuvastatin to 20 mg; *P*<0.001 for each comparison.

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.

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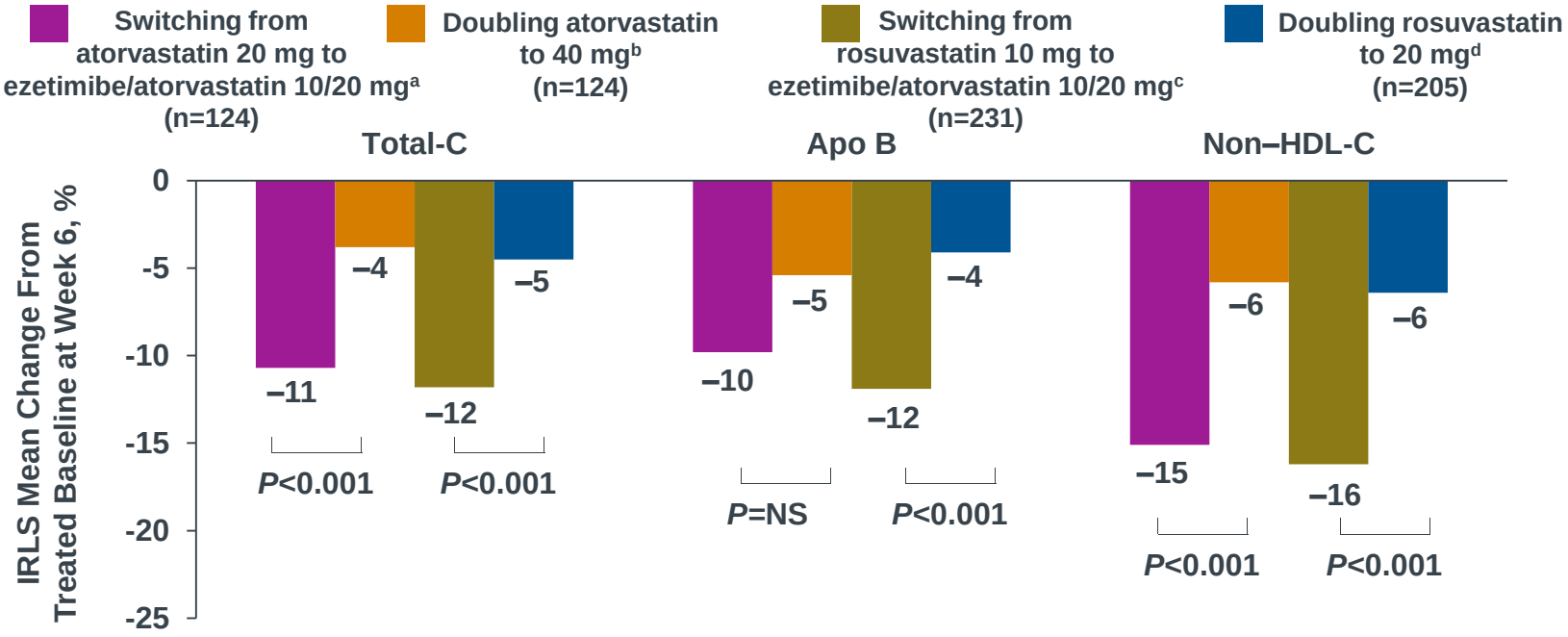
1. Bays HE et al. *Am J Cardiol*. 2013;112:1885–1895.

PACE Phase II: Effect on Multiple Lipid Parameters[1]



[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

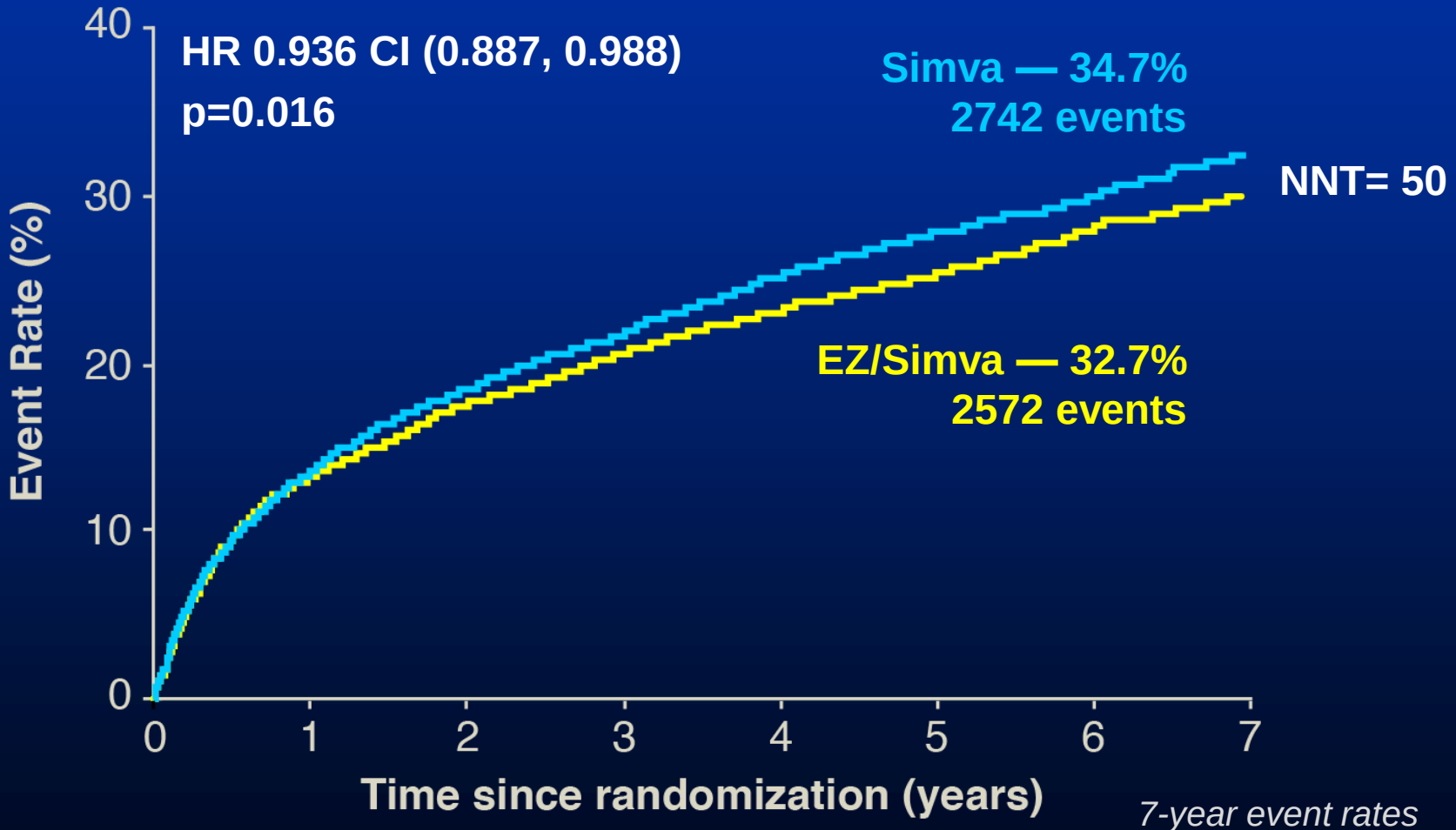
Duration: Minimum 2 ½-year follow-up **(at least 5250 events)**

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

Primary Endpoint — ITT

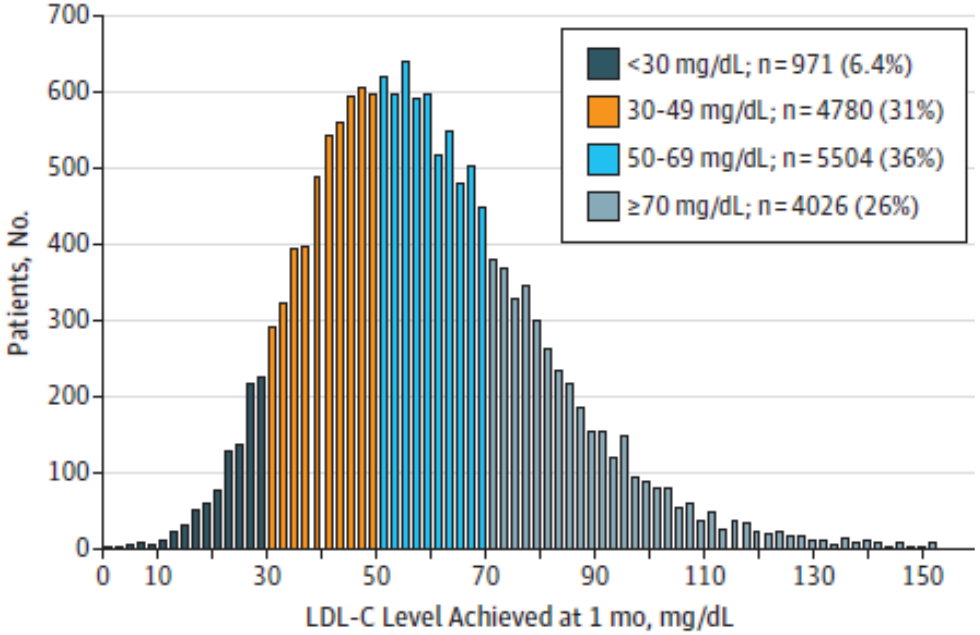
Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

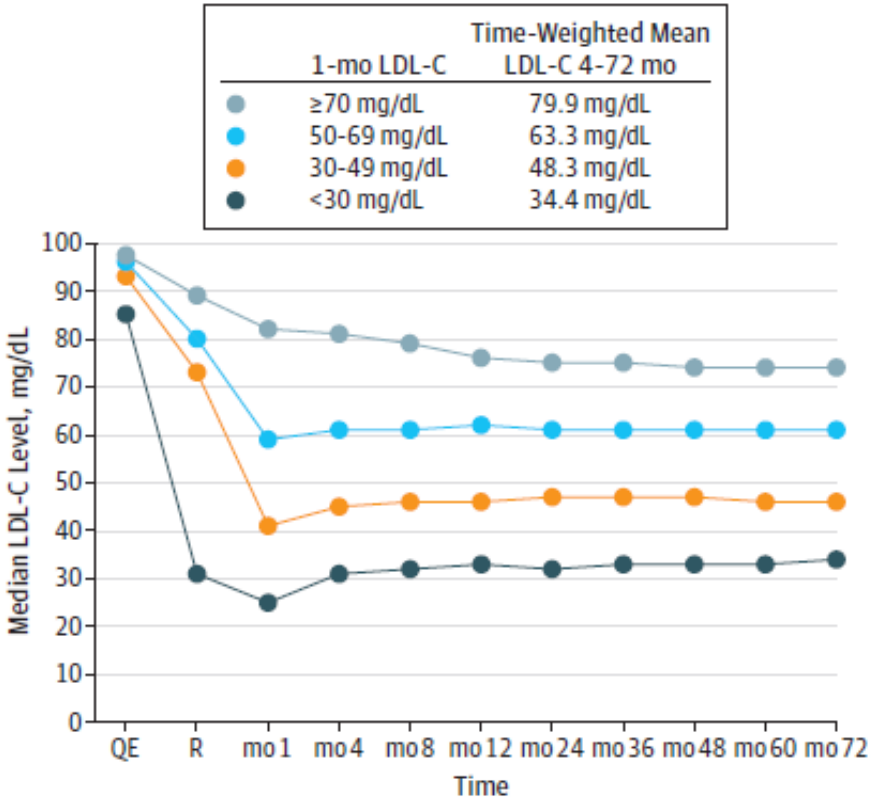


7-year event rates

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

A Prespecified Analysis of the IMPROVE-IT Trial

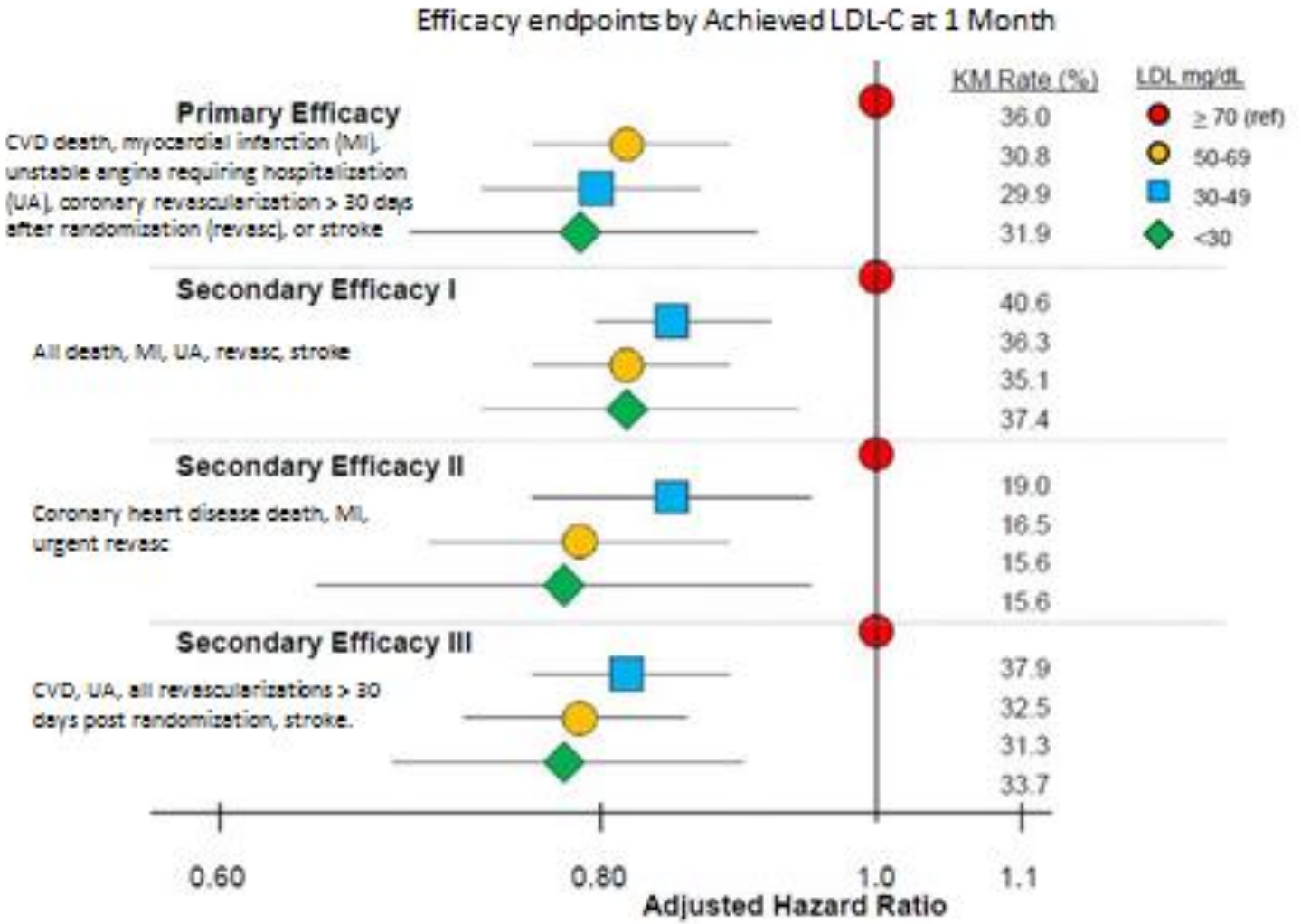




JAMA Cardiol. 2017;2(5):547-555.

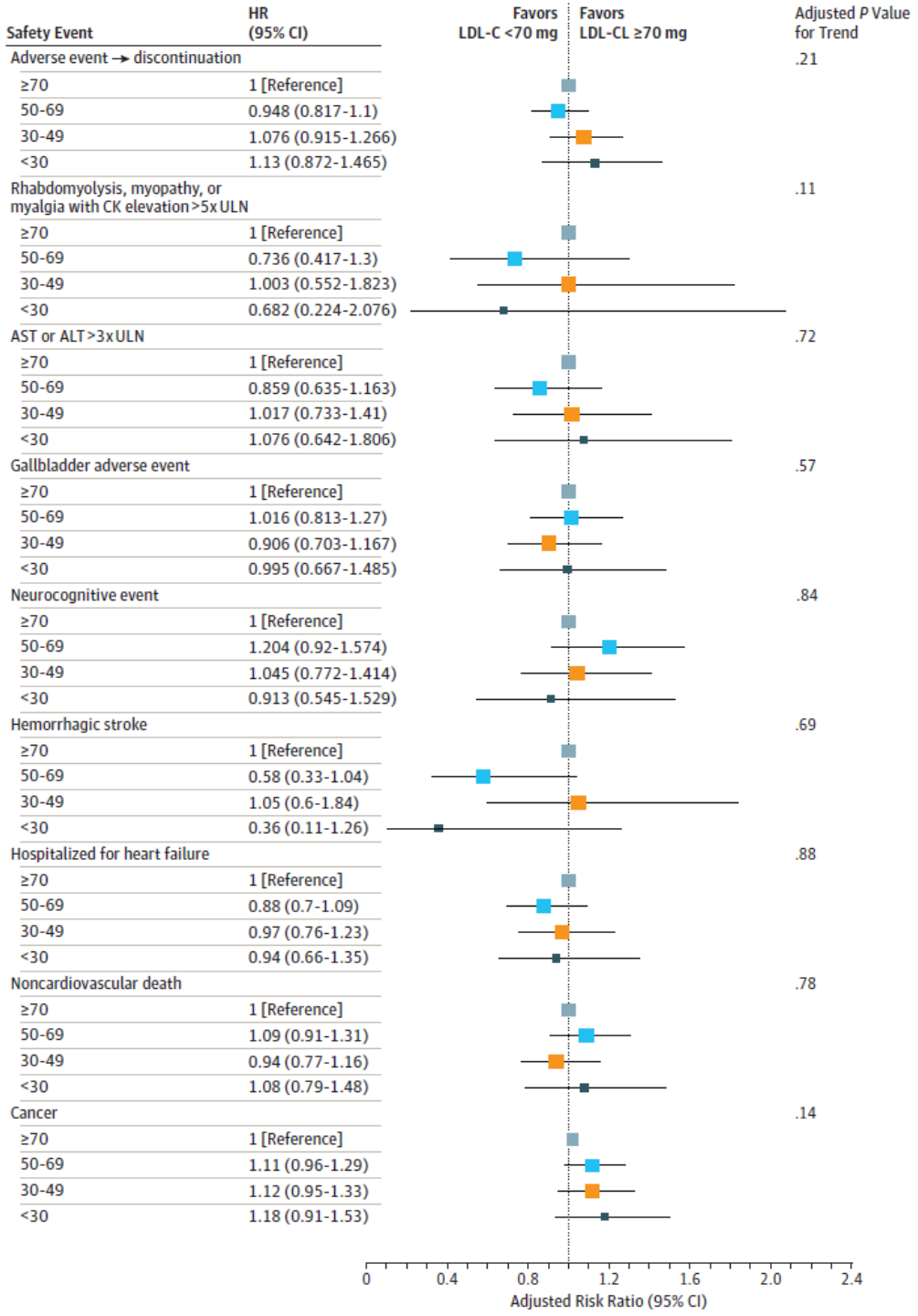
Long-term Safety and Efficacy of Achieving Very Low Levels of Low-Density Lipoprotein Cholesterol

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



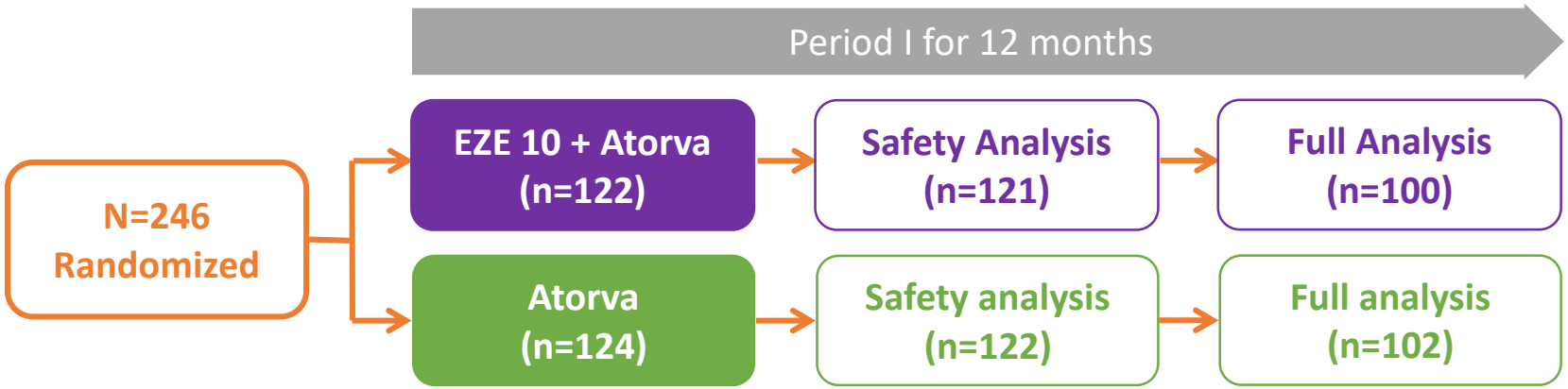
JAMA Cardiol. 2017;2(5):547-555.

PRECISE-IVUS Study

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

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

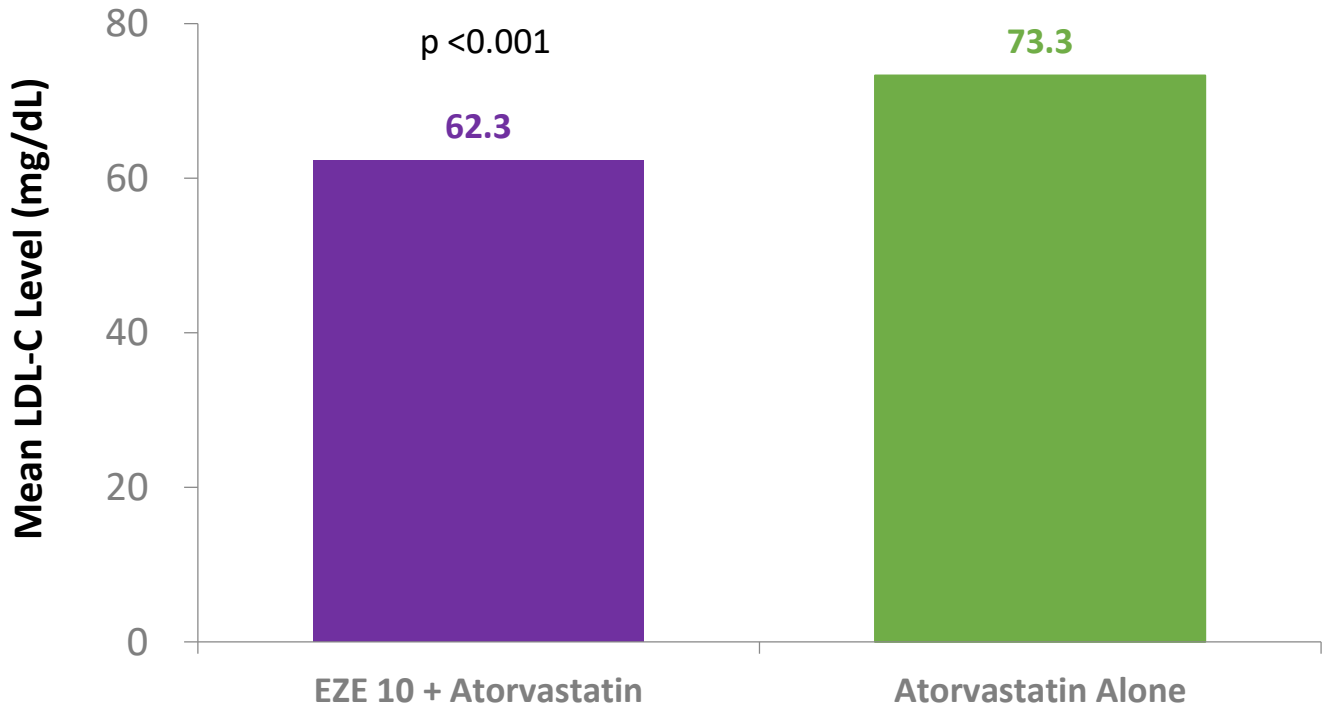
Atorva=atorvastatin; EZE=ezetimibe; CAD=coronary artery disease; PCI=percutaneous coronary intervention; ACS=acute coronary syndrome; SAP=stable angina pectoris;

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

PRECISE-IVUS Study

Lower LDL-C with Ezetimibe + Atorvastatin

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

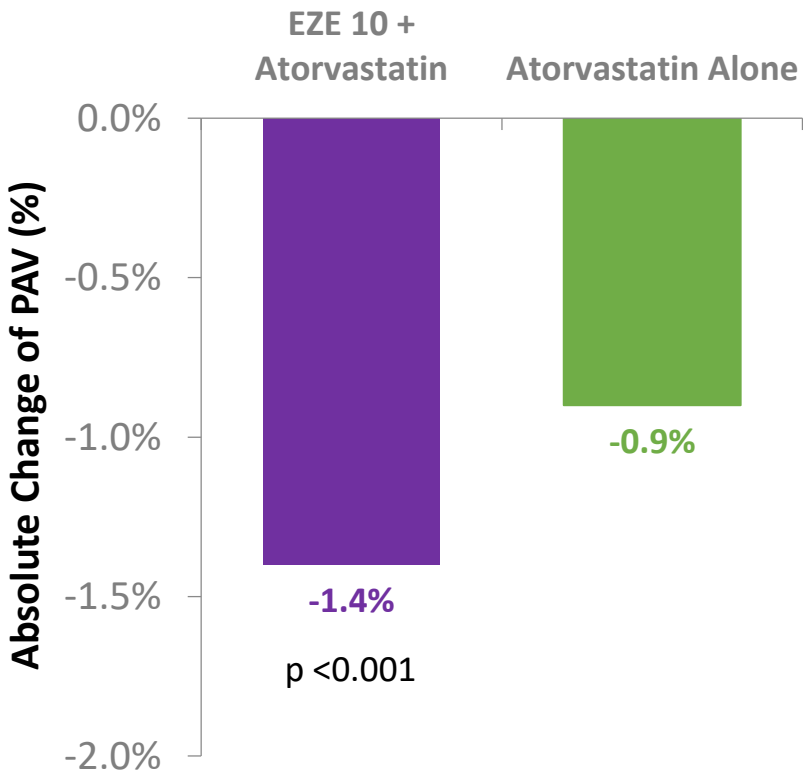


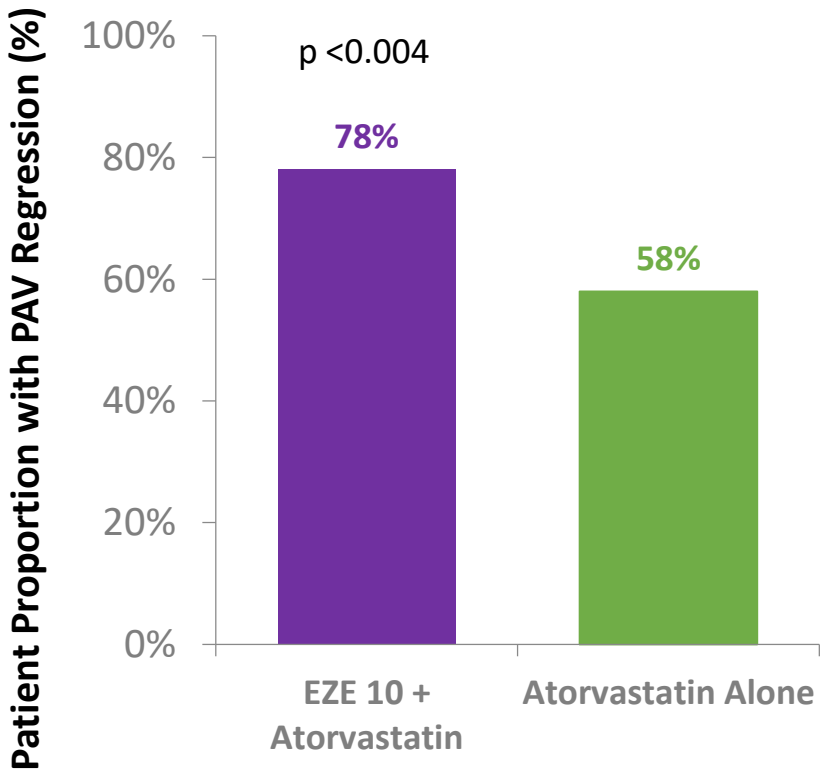
EZE=ezetimibe.

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

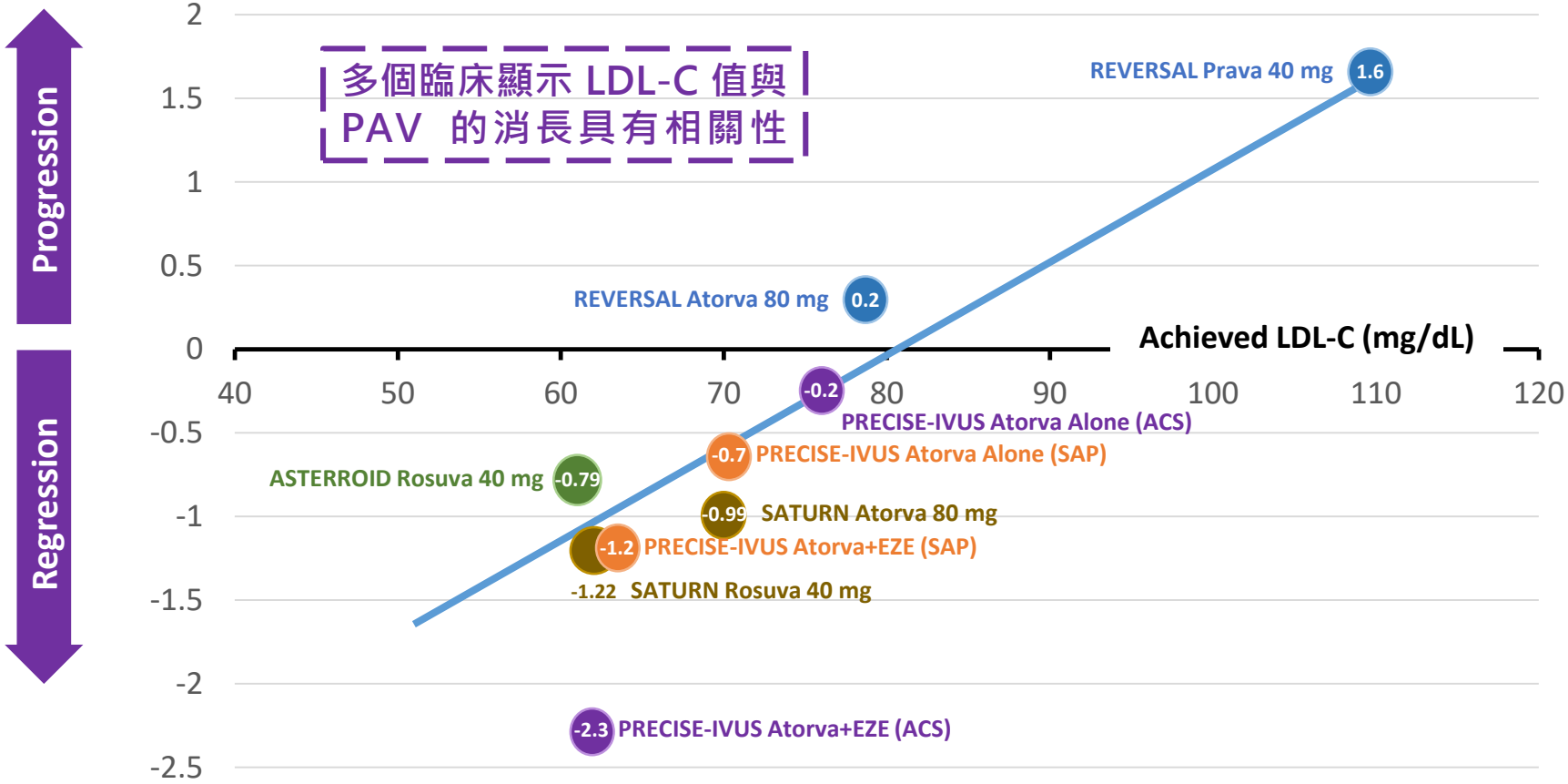




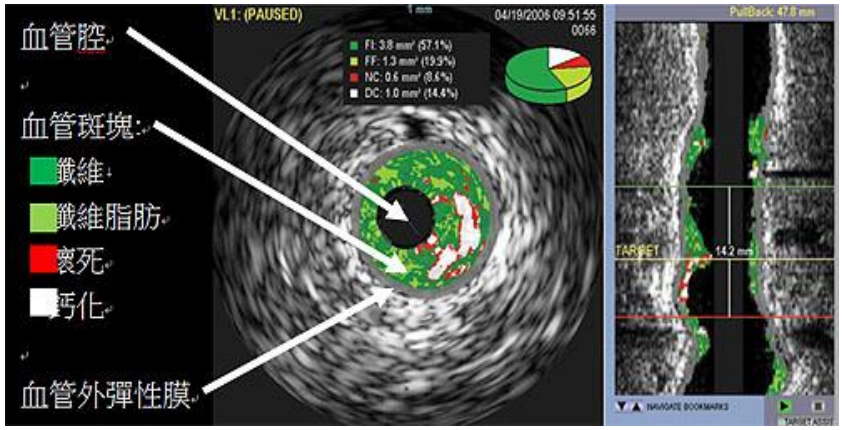
EZE=ezetimibe; PAV=percent atheroma volume.

PRECISE-IVUS Study

Relationship Between LDL-C and PAV

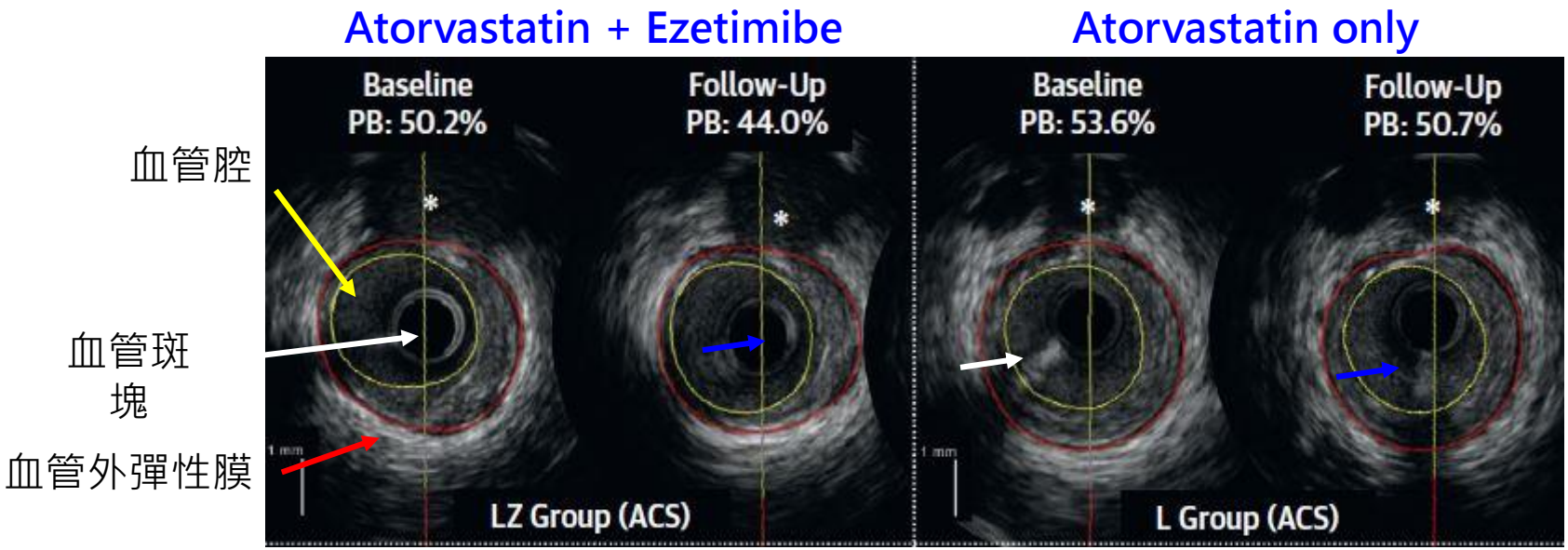


EZE=ezetimibe; PAV=percent atheroma volume.



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



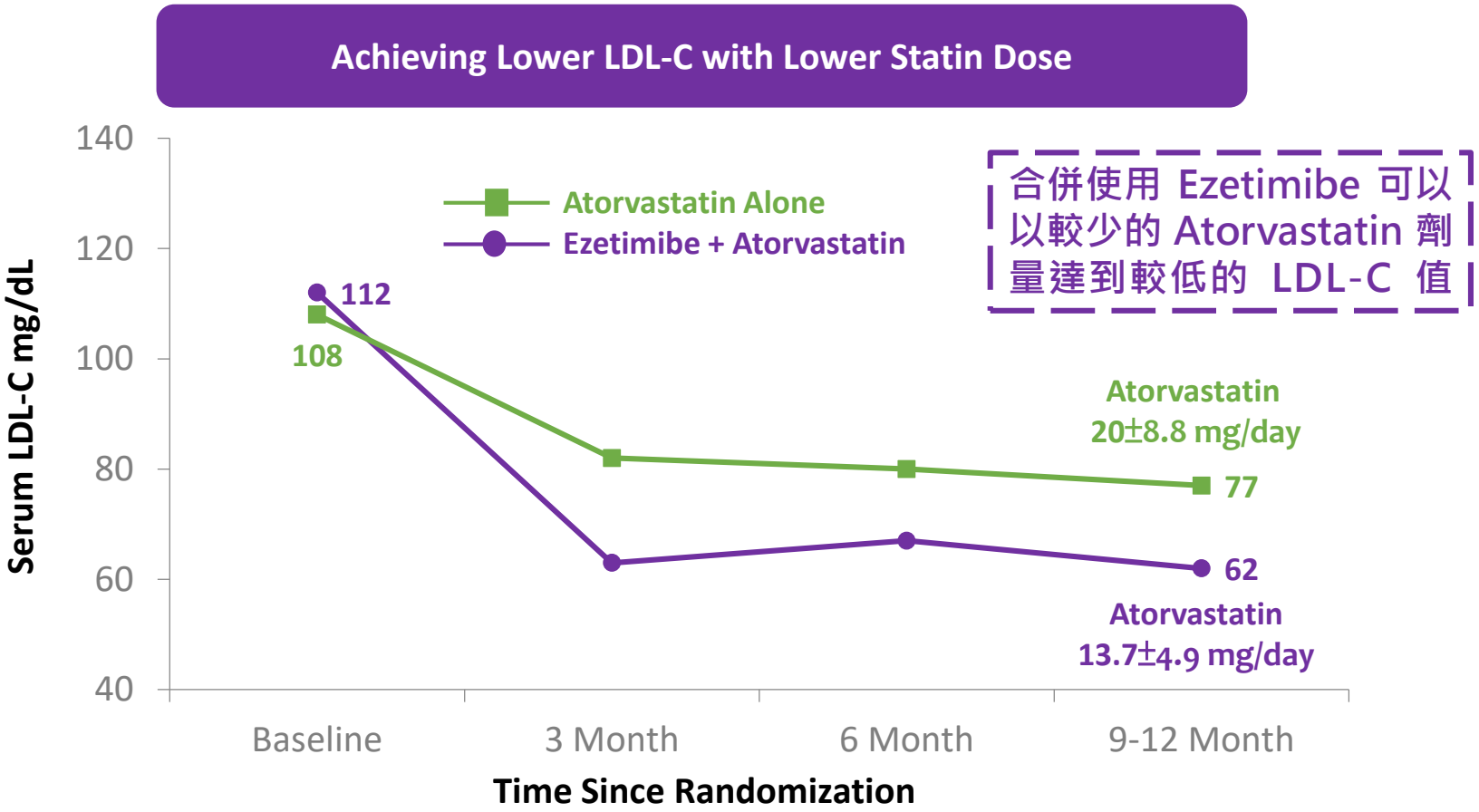
IVUS images of the same cross sections at baseline and follow-up show outlined leading edges of lumen (yellow line) and external elastic membrane(red line)

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: ACS Subgroup

Lower Statin Dose with Higher Potency While Combining with Ezetimibe



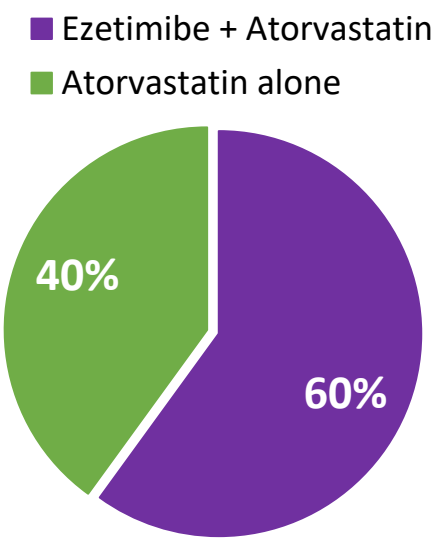
1. Tsujita K, et al. Atherosclerosis. 2016;251(5):367-72.

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

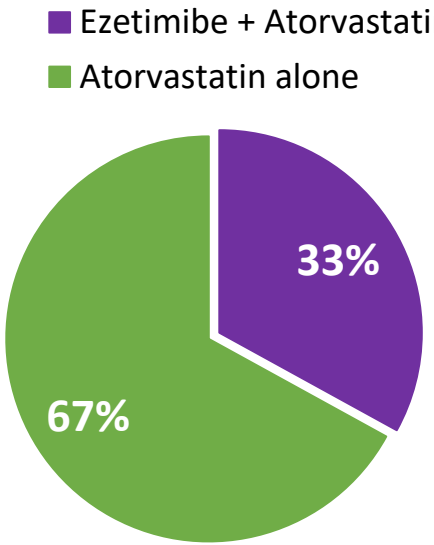
Regression in PAV (n=67)



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.

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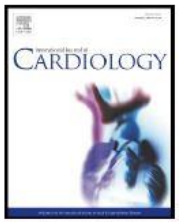

Short communication

Impact of statin-ezetimibe combination on coronary atheroma plaque in patients with and without chronic kidney disease — Sub-analysis of PRECISE-IVUS trial

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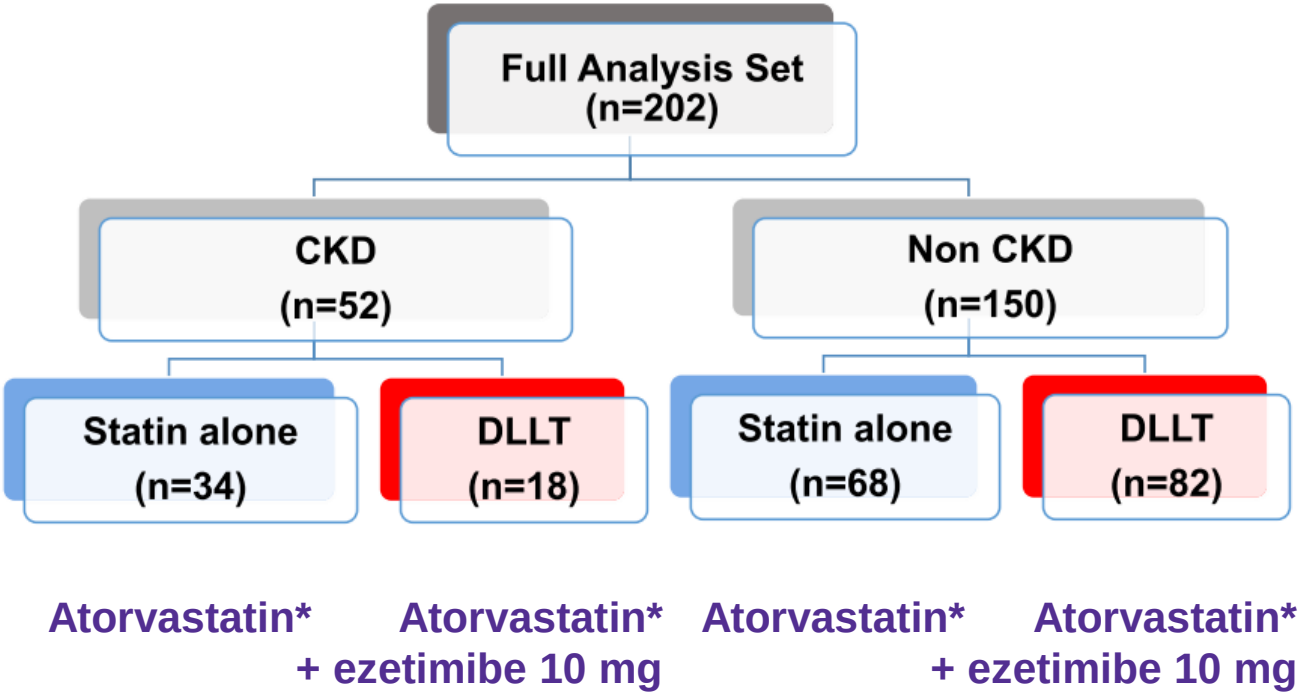
Objectives: hypothesized intensive lipid-lowering with statin/ezetimibe attenuated coronary atherosclerotic development even in patients with CKD.

Methods and population: prospective, randomized, controlled, multicenter PRECISE-IVUS trial. 202 patients undergoing intravascular ultrasound (IVUS)-guided PCI were randomly assigned to receive atorvastatin/ezetimibe combination or atorvastatin alone (the dosage of atorvastatin was up-titrated to achieve the level of LDL-C<70 mg/dL. Median follow-up time was 9-12 months.

Baseline characteristics: 26% of patients were CKD stage 3-4 ($15<eGFR<60mL/min/1.73m^2$), CKD group was significantly older (71.5 ±8.6 years vs. 64.4±9.6 years, P<0.001) and had higher ratio of using insulin (12% vs. 1%, P = 0.001); LDL-C baseline were comparable in CKD group (111(85-126)mg/dL) and non-CKD group (109(94-125)mg/dL) and similar prevalence of comorbid coronary risk factors.

Conclusions: Atorvastatin plus Ezetimibe significantly reduced ΔPAV both in the non-CKD group and in the CKD group

Sub-Analysis of **PRECISE-IVUS** Trial: Study Design



Patients 30 to 85 years of age with CAD who satisfied all criteria for inclusion were enrolled after having undergone successful coronary angiography or percutaneous coronary intervention (PCI) under IVUS guidance to treat ACS or stable angina pectoris (SAP). Participants were required to have an LDL-C level at entry of >100 mg/dl.

*The dosage of atorvastatin was up-titrated to achieve the level of LDL-C <70 mg/dL
CKD=chronic kidney disease, DLLT=dual lipid-lowering therapy.
Int J Cardiol. 2018 Oct 1;268:23-26.
J Am Coll Cardiol. 2015 Aug 4;66(5):495-507.

Baseline characteristics

	CKD		Non-CKD	
	Atorvastain	Atorvastatin+Eze	Atorvastain	Atorvastatin+Eze
Age (yrs)	70.9 ± 7.8	72.6 ± 10.0	64.3 ± 9.9	64.4 ± 9.4
Male, n(%)	26 (76)	13 (72)	54 (79)	65 (79)
BMI	24.9 ± 3.6	23.3 ± 3.4	24.9 ± 2.9	25.1 ± 3.3
History of PCI, n(%)	6 (18)	2 (11)	9 (13)	17 (21)
History of PAD, n(%)	2 (6)	1 (6)	2 (3)	2 (2)
History of MI, n(%)	6 (18)	3 (17)	7 (10)	12 (15)
Hypertension, n(%)	25 (74)	11 (61)	42 (62)	65 (79)*
Dyslipidemia, n(%)	22 (65)	9 (50)	48 (71)	63 (77)
Diabetes, n(%)	14 (41)	6 (33)	17 (25)	23 (28)
Insulin, n(%)	4 (12)	2 (11)	0 (0)	2 (2)
Presentation of ACS, n(%)	15 (44)	8 (44)	32 (47)	39 (48)
LDL-C, mg/dL	109 (77 to 125)	113 (95 to 126)	109 (94 to 123)	108 (95 to 127)
TC, mg/dl	169 (137 to 194)	178 (165 to 189)	176 (156 to 191)	173 (156 to 195)
HDL-C, mg/dl	38 (31 to 44)	38 (32 to 52)	40 (33 to 46)	39 (35 to 46)
Plaque volume, mm^3	94 (64 to 132)	83 (43 to 112)	68 (44 to 115)	70 (36 to 118)
Vessel volume, mm^3	176 (128 to 257)	139 (86 to 245)	142 (88 to 242)	150 (75 to 217)
PAV, %	53.5 ± 11.1	53.0 ± 8.1	49.5 ± 11.4	50.9 ± 11.3

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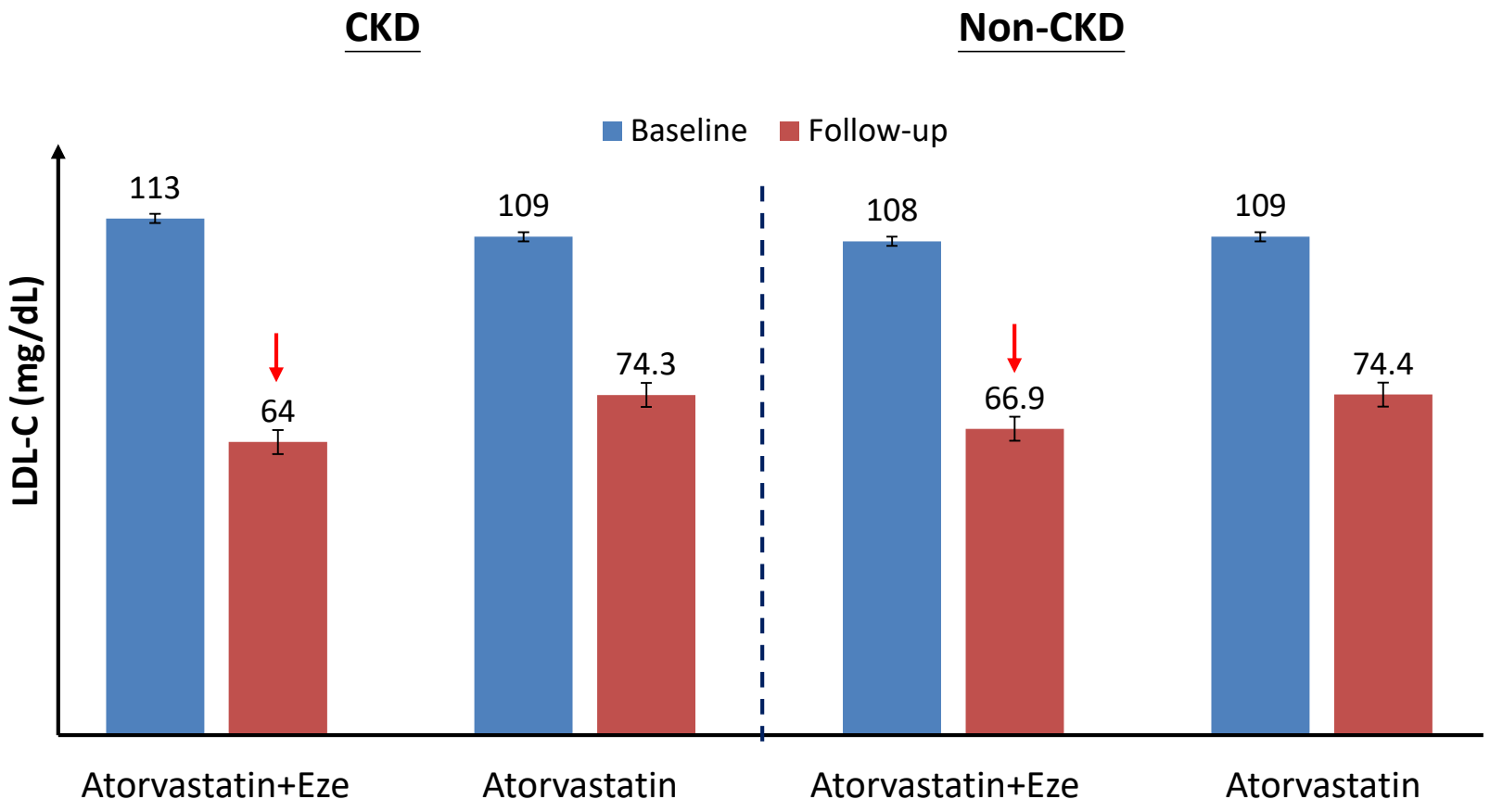

LDL-c reduction in **CKD pts**
Atorvastatin+Ezetimibe −49.0 (−56.2 to 38.9)%
Atorvastatin -34.7(−47.9 to −16.1)%

LDL-c reduction in **non-CKD pts**
Atorvastatin+Ezetimibe −41.1 (−52.9 to −29.1)
Atorvastatin −34.6 (−50.0 to −12.1)%

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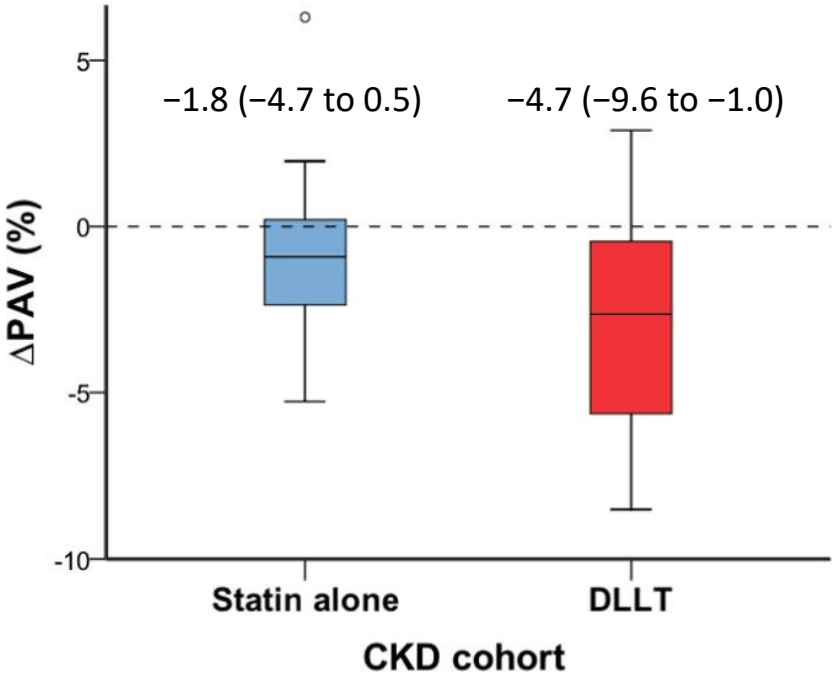
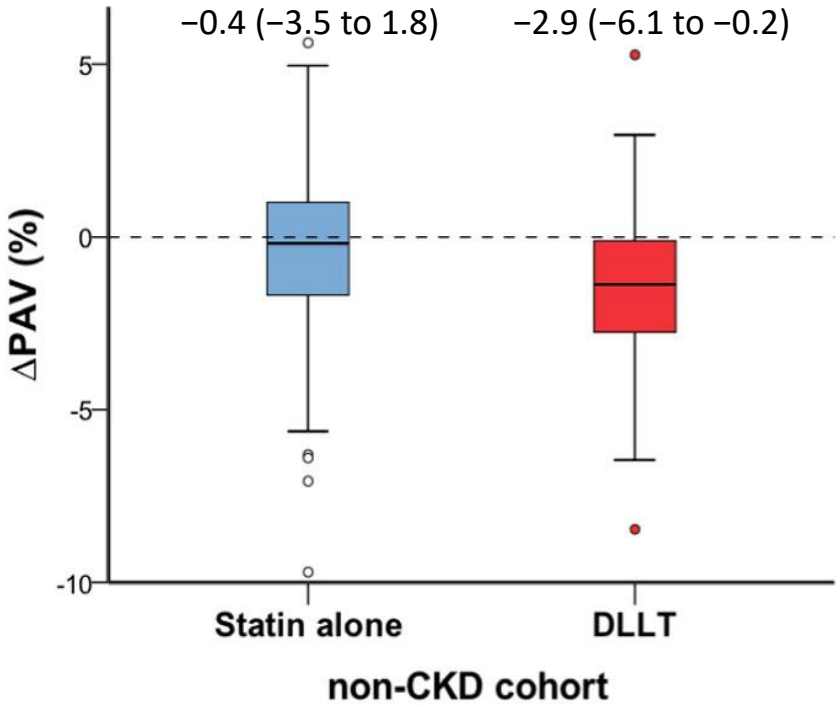
DLLT showed the significantly stronger regression in ΔPAV, compared with atorvastatin alone even in the CKD group.

ΔPAV −2.9 [−4.9 to −0.5]%



ΔPAV −2.5 [−2.6 to 1.2]%



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Sub-Analysis of **PRECISE-IVUS** Trial: Conclusion

- As with non-CKD, intensive lipid-lowering therapy with atorvastatin/ezetimibe demonstrated stronger coronary plaque regression effect even in patients with CKD compared with atorvastatin monotherapy.

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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

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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]

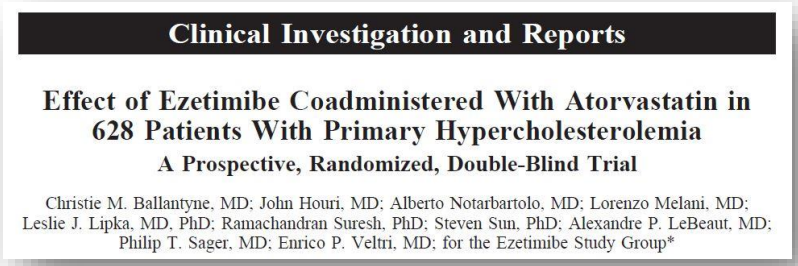
1. Ballantyne CM et al. Circulation. 2003 May 20;107(19):2409-15. Epub 2003 Apr 28.

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 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 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

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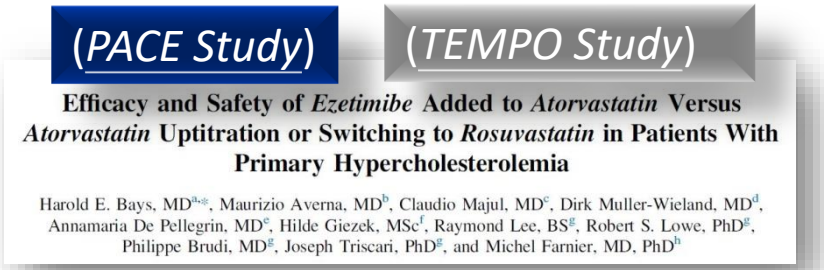
Pts with hypercholesterolemic

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*)

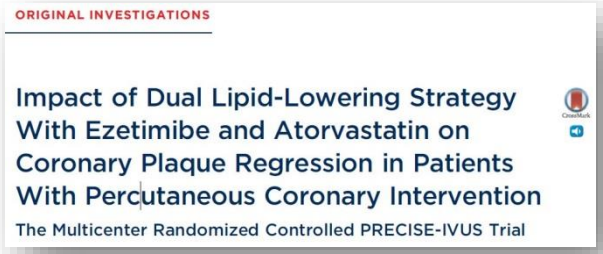


Efficacy and Safety of *Ezetimibe* Added to *Atorvastatin* Versus *Atorvastatin* Uptitration or Switching to *Rosuvastatin* in Patients With Primary Hypercholesterolemia

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有相關性。


Thanks for Your Attention
黑白分明的沉思者