Think beyond statin monotherapy – Managing LDL Cholesterol with ezetimibe combination treatment

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- 研究領域 健保資料庫
- 藥物心血管病風險研究

演講內容聲明

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

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我們到底要LDL降到多低?

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 ✓ / β-blocker ✓ / Thiazide ✓

If not at goal (2–3 months)

Add calcium channel blocker, β-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

 DOI 10.4158/EP161682.CS

2017 Taiwan Lipid Guidelines

Treatment Target of LDL-C for High Risk Patients

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

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)。

把LDL降到70mg/dl是醫師的必要技能

LDL達標到底有多難?

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

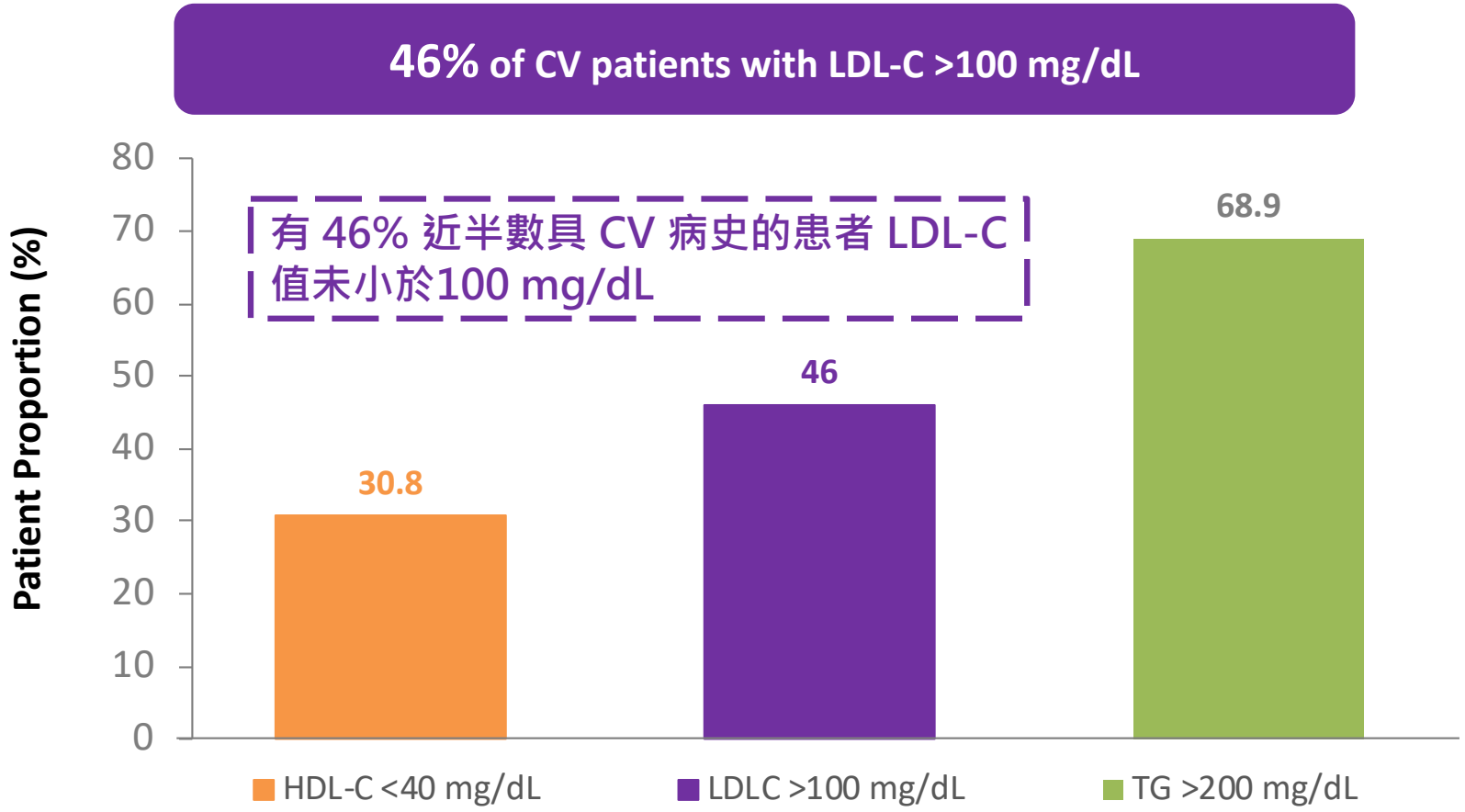
Items evaluated at baseline, and every year thereafter:

- 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.

DYSIS II ACS Study: Contemporary data on treatment practices for low-density lipoprotein cholesterol in 3,867 patients who had suffered an acute coronary syndrome across the world

Study Design

N=3,876
Longitudinal observation
Follow-up for 4 months

Patient Criteria:

Patients were hospitalized for an acute coronary syndrome (ACS)

Worldwide Survey
Real World Data

Objectives & Data Collection:

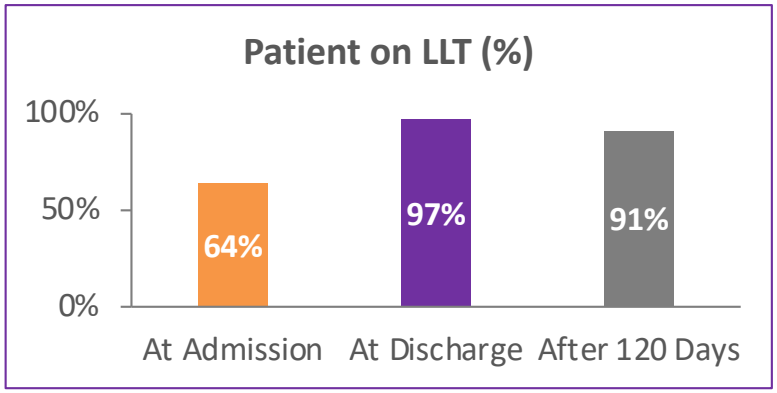
- Comparison of lipid lowering therapies administered in patients post acute coronary syndrome, as well as LDL-C target achievement
- Evaluations were performed at the time of admission and again 120 ±15 days following the date of admission (the follow-up time point)

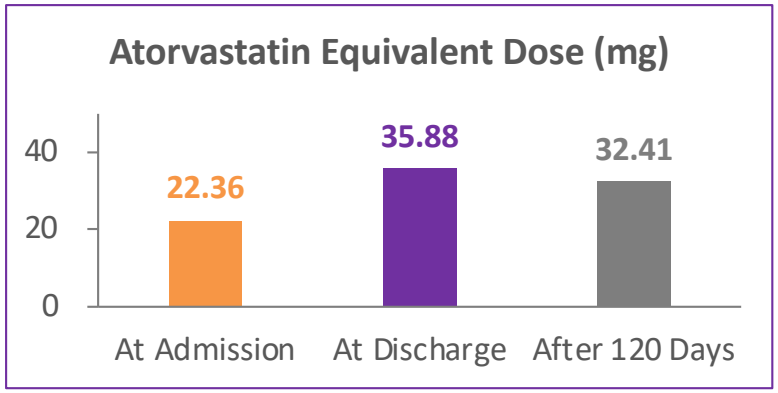
1. Gitt AK, et al. Data Brief. 2017 Nov 14;16:369-75.

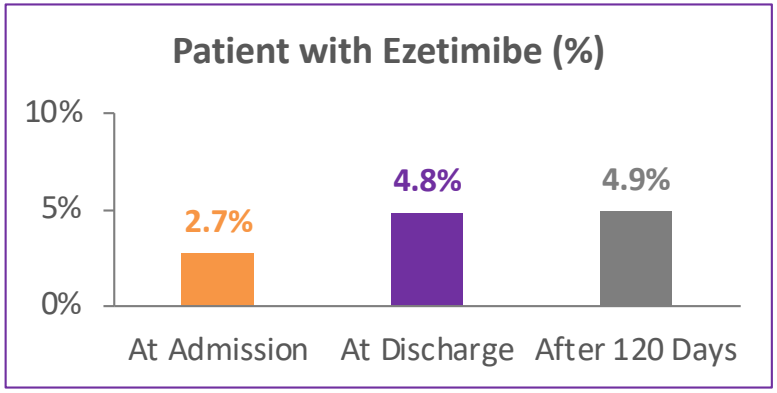
DYSIS II ACS Study

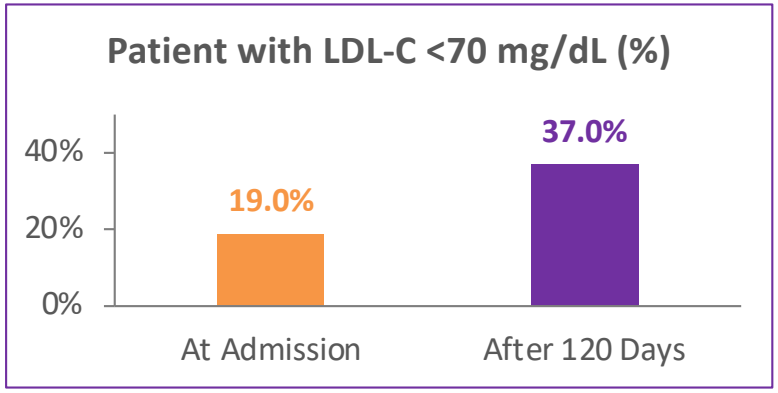
Only One-Third of Patients Achieved the LDL-C Target after An ACS Event

LOW in statin dose, ezetimibe combination, and achievement of LDL-C target









1. Gitt AK, et al. Data Brief. 2017 Nov 14;16:369-75.

LDL-C ATTAINMENT RATE AMONG TREATED PATIENTS WITH STABLE CHD: THE DYSLIPIDEMIA INTERNATIONAL STUDY

(DYSIS) II TAIWAN: identify unmet needs in lipid target achievements among stable CHD patients in Taiwan

在chronic heart disease的台灣病人中，
只有20.7%的病人達標LDL-C<70mg/dL

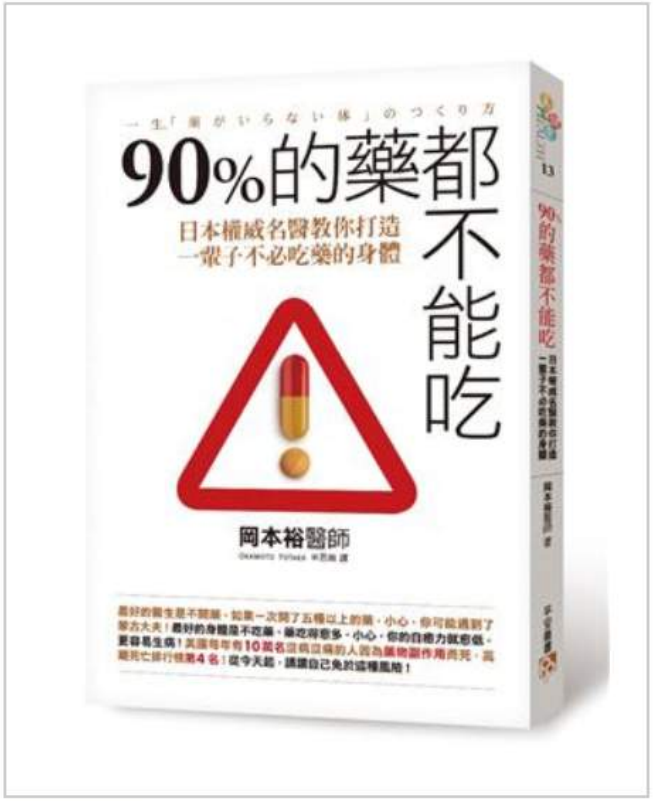
- *Population:* *800 stable* ***CHD patients*** with past acute coronary syndrome (ACS) events >3 months before enrollment), full lipid profile available 0-12 months prior to enrollment, on LLT ≥3 months or not treated at all were recruited (recruitment of patients in 2013-2014).
- *Methods:* DYSIS II is a multicenter, observational cross-sectional study conducted in 14 Taiwan hospitals.
- *Results:* 687 patients were on LLT, with ***only 20.7% achieving the <70 mg/dl LDL-C target***. ***84.7%*** of treated patients were on statin monotherapy and ***11.9%*** received ezetimibe plus statin.

DYSIS II

LDL能達到100mg/dl只有46%

LDL能夠降到70mg/dl只有20.7%

?



90%的藥都不能吃: 日本權威名醫教你打造一輩子不必吃藥的身體
一生、薬がいらない体のつくり方

作者 / 岡本裕

譯者 / 羊恩嫩

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內容簡介

最好的醫生是不開藥，如果一次開了五種以上的藥，小心，你可能遇到了蒙古大夫！
最好的身體是不吃藥，藥吃得愈多，小心，你的自癒力就愈低，更容易生病！

美國每年有10萬名沒病沒痛的人因為藥物副作用而死！高踞死亡排行榜第4名！從今天起，請讓自己免於這種風險。

現代人太依賴藥物，疼痛的時候馬上吃止痛藥，腸胃不舒服就吞腸胃藥，感冒的時候急著去看醫生拿藥，更別提有很多人是長期吃藥，例如高血壓、糖尿病患者，以及為失眠或憂鬱症所苦的人。

現在岡本裕醫師要大聲警告：90%的藥都不能吃，因為藥物就等於毒物！很多藥只是暫時緩解症狀，其實根本不能治病，長期吃下來只會讓你的身體愈來愈糟！

降血壓藥可以降低罹患心肌梗塞的機率，但整體來說卻反而提高了死亡的機率，因為血液循環變差，養分的吸收和廢物的排泄也會停滯。

長期吃安眠藥，負責免疫的淋巴球等於一直處在「爛醉如泥」的狀態，結果壽命就會減少。

但是明明身體就有病痛、不舒服呀！這時候該怎麼辦？岡本醫師在這本書中就要告訴大家：

不再需要藥物的運動法，譬如三十次深呼吸。
不再需要藥物的飲食法，譬如一週一次不吃午餐。
不再需要藥物的睡眠法，譬如小腿按摩。
不再需要藥物的壓力處理法，先檢查有沒有飲食過量。

針對長期吃藥者，岡本醫師更提出了「四個星期法則」終止你對藥物的依賴，以及指甲按摩法、熱冷水澡、易筋功等等，讓你在短短三個月內就能變健康。

打造不吃藥的身體，其實就是讓你的身體恢復原本的狀態。而身體原本具有的自癒能力，其實就是最好的醫生！

基長內科

87

上午 10:00

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是否真實?

上午 10:00

https://www.mohw.gov.tw/cp-17-45720-1.html

回應「一條領帶救心肌梗塞，國外盛行缺血...
點選此處以開啟此連結。

已讀 74
上午 10:13


高溫23至27度 各地早
台北
中天新聞
一條領帶救心肌梗塞!國外盛行"缺血適應法"
現在溫度 嘉義19.1℃

基長內科

87

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是否真實?

上午 10:00

https://www.mohw.gov.tw/cp-17-45720-1.html

回應「一條領帶救心肌梗塞，國外盛行缺血...
點選此處以開啟此連結。

已讀 74
上午 10:13

回應「一條領帶救心肌梗塞，國外盛行缺血適應法」報導：查非科學實證之急救方法

• 資料來源：醫事司 • 建檔日期：107-12-14 • 更新時間：107-12-14

有關中天新聞、中時電子報於107年11月27日報導「一條領帶救心肌梗塞」或「缺血適應法」等方法：

.....萬一遇到身邊的人有心肌梗塞的狀況，其實靠一條領帶、一隻襪子就可以搶救.....

經查，上述方法無嚴格的醫學佐證：

1. **本部已請該媒體將報導下架**：台灣急診醫學會、中華民國心臟學會、台灣急救加護醫學會已分別於12月4日、5日以正式新聞稿予以駁斥。為避免錯誤觀念資訊傳播渲染，延誤寶貴的急救黃金時間，本部已請該媒體將報導下架，並更正報導正確心肌梗塞急救訊息。

公關很重要

行政院衛生署國民健康局

2007 年台灣地區高血壓、高血糖、高血脂之追蹤調查研究

專　　輯

2007年台灣地區高膽固醇盛行率

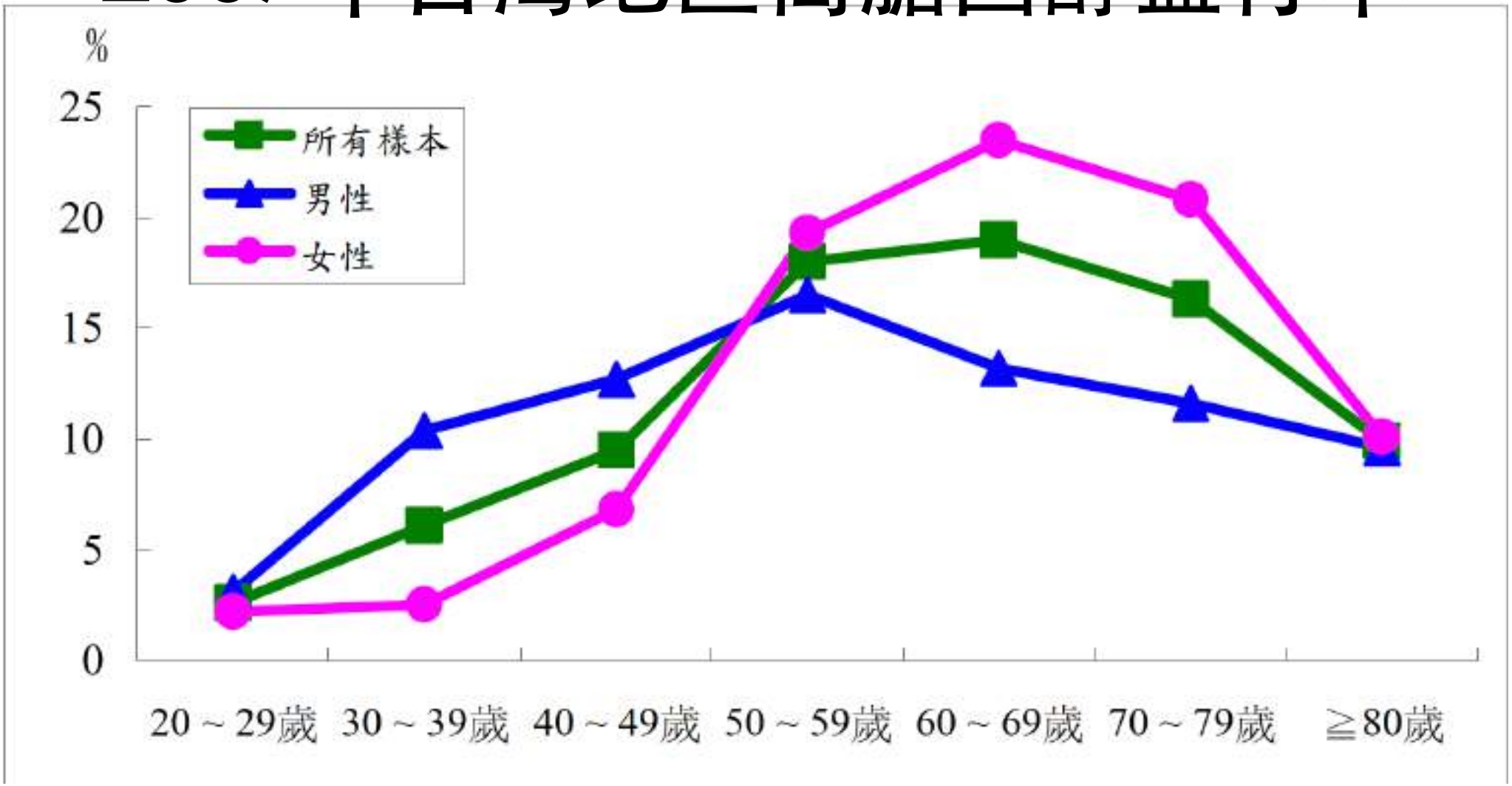


表 6-7-1 2007 年台灣地區高血脂盛行率，依性別、年齡、社經地位之分佈 (續)

變項	總人數	高血脂[1]		P 值[a]
		人數	(%)	
社經地位				
低社經地位	3,083	681	22.1	<0.001
中社經地位	888	138	15.5	
高社經地位	441	57	12.9	
男性				
低社經地位	1,349	324	24	0.155
中社經地位	426	98	23	
高社經地位	269	50	18.6	
女性				
低社經地位	1,734	357	20.6	<0.001
中社經地位	462	40	8.7	
高社經地位	172	7	4.1	

[1]: 高血脂之定義：膽固醇≧240mg/dL 或三酸甘油酯≧200mg/dL 或服用降血脂藥物。

[a]: Chi-square 檢定。

表 6-11 2007 年台灣地區高低密度膽固醇盛行率，依性別、年齡、社經地位之分佈 (續)

變項	總人數	高低密度膽固醇 [1]		P 值 [a]
		人數	(%)	
社經地位				
低社經地位	3,075	258	8.4	0.114
中社經地位	887	58	6.5	
高社經地位	441	29	6.6	
男性				
低社經地位	1,347	116	8.6	0.996
中社經地位	425	36	8.5	
高社經地位	269	23	8.6	
女性				
低社經地位	1,728	142	8.2	0.006
中社經地位	462	22	4.8	
高社經地位	172	6	3.5	

[1]: 高低密度膽固醇之定義：低密度膽固醇(LDL-C，low-density lipoprotein cholesterol)≧160 mg/dL。

[a]: Chi-square 檢定。

附錄 13 2007 年台灣地區 20 歲以上居民之血中膽固醇、三酸甘油酯、高密度及低密度膽固醇之平均值(±標準差)，依性別、年齡、社經地位、地區之分佈

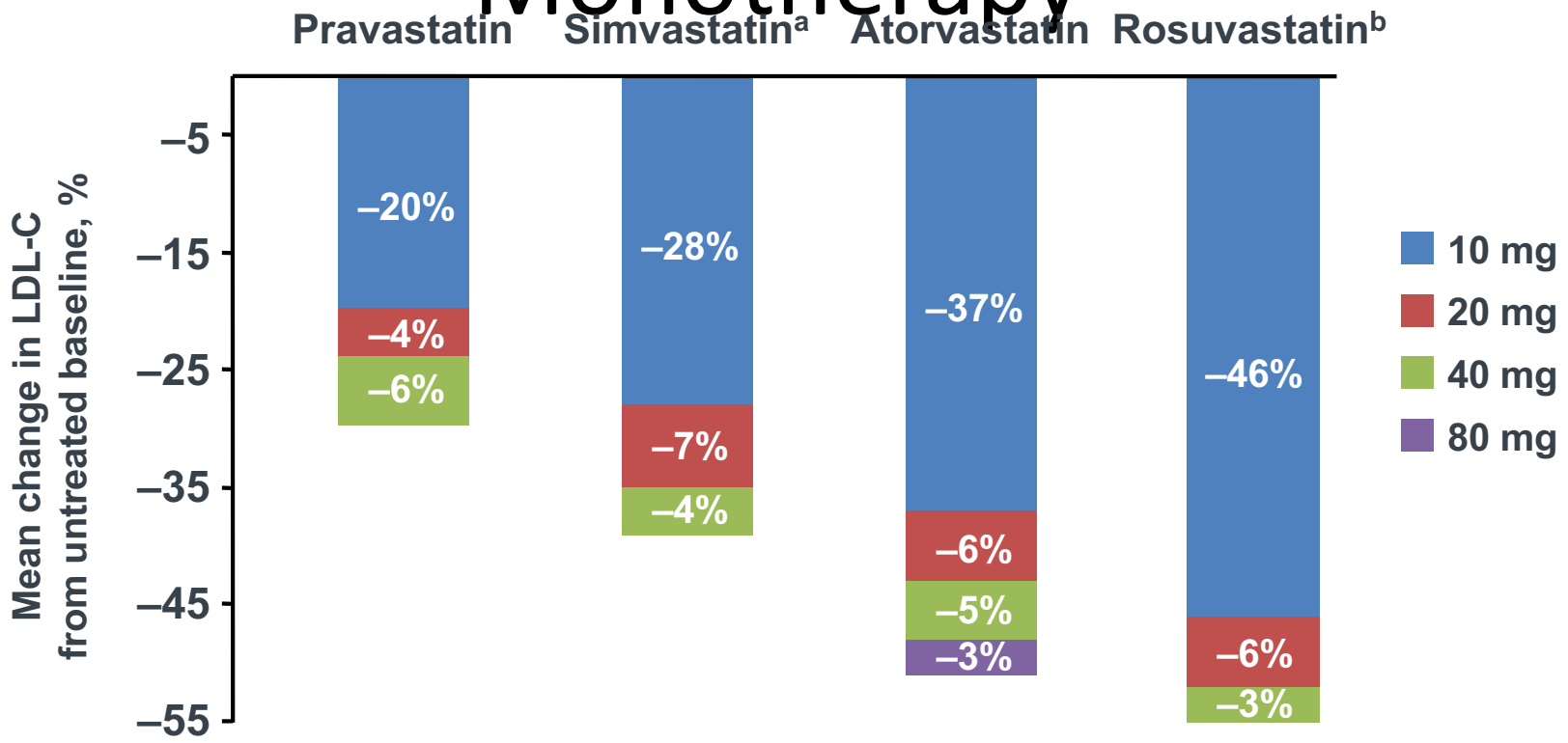
	膽固醇 [12] (mg/dL)		三酸甘油酯 [12] (mg/dL)		高密度膽固醇 [1] (mg/dL)		低密度膽固醇 [1] (mg/dL)	
	總人數	平均值±標準差	總人數	平均值±標準差	總人數	平均值±標準差	總人數	平均值±標準差
性別								
男性	1,937	177.75 ±37.22	1,937	139.62 ±107.00	2,041	48.66 ±9.59	2,041	112.81 ±33.27
女性	2,264	181.52 ±38.11	2,264	107.93 ±68.33	2,363	55.55 ±10.68	2,363	109.37 ±32.54
年齡								
20～24 歲	352	156.82 ±29.94	352	85.01 ±43.30	352	52.41 ±9.62	352	93.72 ±25.41
25～29 歲	367	163.59 ±35.71	367	95.36 ±53.09	367	52.59 ±10.46	367	99.19 ±31.72
30～34 歲	354	172.74 ±36.25	354	125.47 ±121.94	357	51.63 ±10.87	357	106.18 ±32.30
35～39 歲	391	174.65 ±35.37	391	123.62 ±96.55	397	52.61 ±11.87	397	105.96 ±31.21
40～44 歲	464	178.11 ±36.37	464	123.94 ±95.20	477	52.02 ±10.35	477	110.55 ±32.71
45～49 歲	529	186.63 ±37.36	529	132.47 ±104.67	546	53.12 ±10.87	546	115.32 ±32.05
50～54 歲	464	193.12 ±37.21	464	134.31 ±90.94	498	53.25 ±10.01	498	120.96 ±33.42
55～59 歲	382	191.19 ±36.27	382	139.94 ±91.83	420	52.48 ±10.63	420	117.40 ±34.59
60～64 歲	237	190.33 ±38.34	237	130.60 ±99.93	262	52.66 ±10.76	262	117.73 ±32.75
65～69 歲	207	193.10 ±35.40	207	123.45 ±67.33	231	53.50 ±11.60	231	121.26 ±31.85
70～74 歲	190	183.03 ±36.33	190	132.31 ±66.23	212	51.25 ±10.60	212	113.89 ±31.75
75～79 歲	130	178.92 ±38.40	130	124.72 ±67.36	143	49.45 ±11.67	143	110.02 ±32.51
≧80 歲	134	175.09 ±36.76	134	118.67 ±57.47	142	49.63 ±11.34	142	108.10 ±29.98

LDL降到70mg/dl需要多強的藥物?

112→70=38%

160→70=57%

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



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

[a]Mean change in LDL-C from untreated baseline after 6 weeks for simvastatin 80 mg was 46%.[1] The 80-mg dose of simvastatin is only recommended in patients at high CV risk who have not achieved treatment goals on lower doses and when the benefits are expected to outweigh the risks.[2]

[b]Across the dose range: $P<0.001$ for the difference between rosuvastatin vs pravastatin, simvastatin, and atorvastatin.[1]

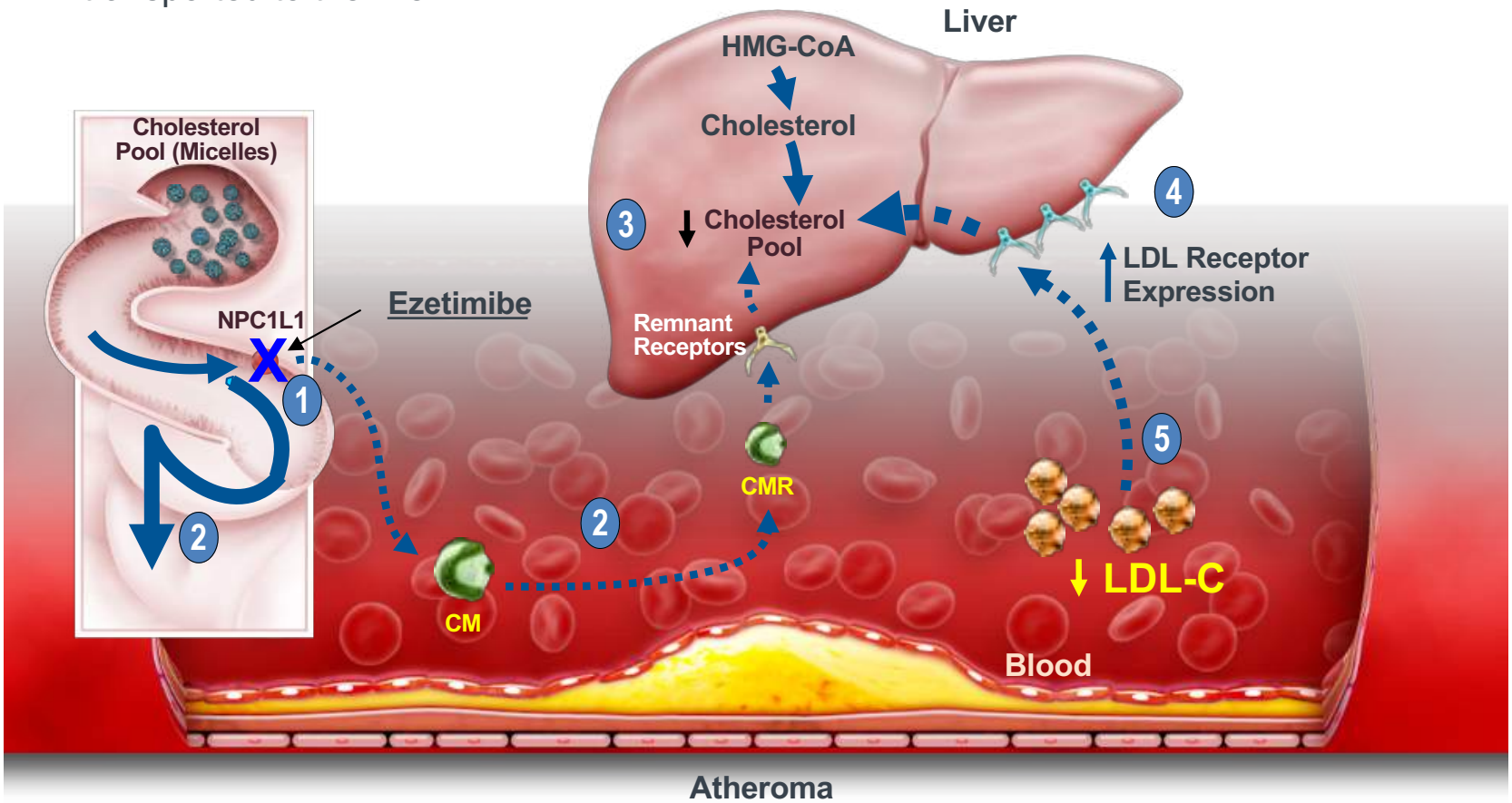
STELLAR = Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin.

1. Jones PH et al. Am J Cardiol. 2003;92:152–160. **2.** [Insert local label.]

Ezetimibe Inhibits Absorption of Cholesterol in the Small Intestine[1]

Ezetimibe: Mechanism of Action

1. Inhibition of NPC1L1 activity
2. Reduction of cholesterol transported to the liver
3. Reduction of hepatic cholesterol
4. Increased LDL receptor expression
5. Increased clearance of LDL-C



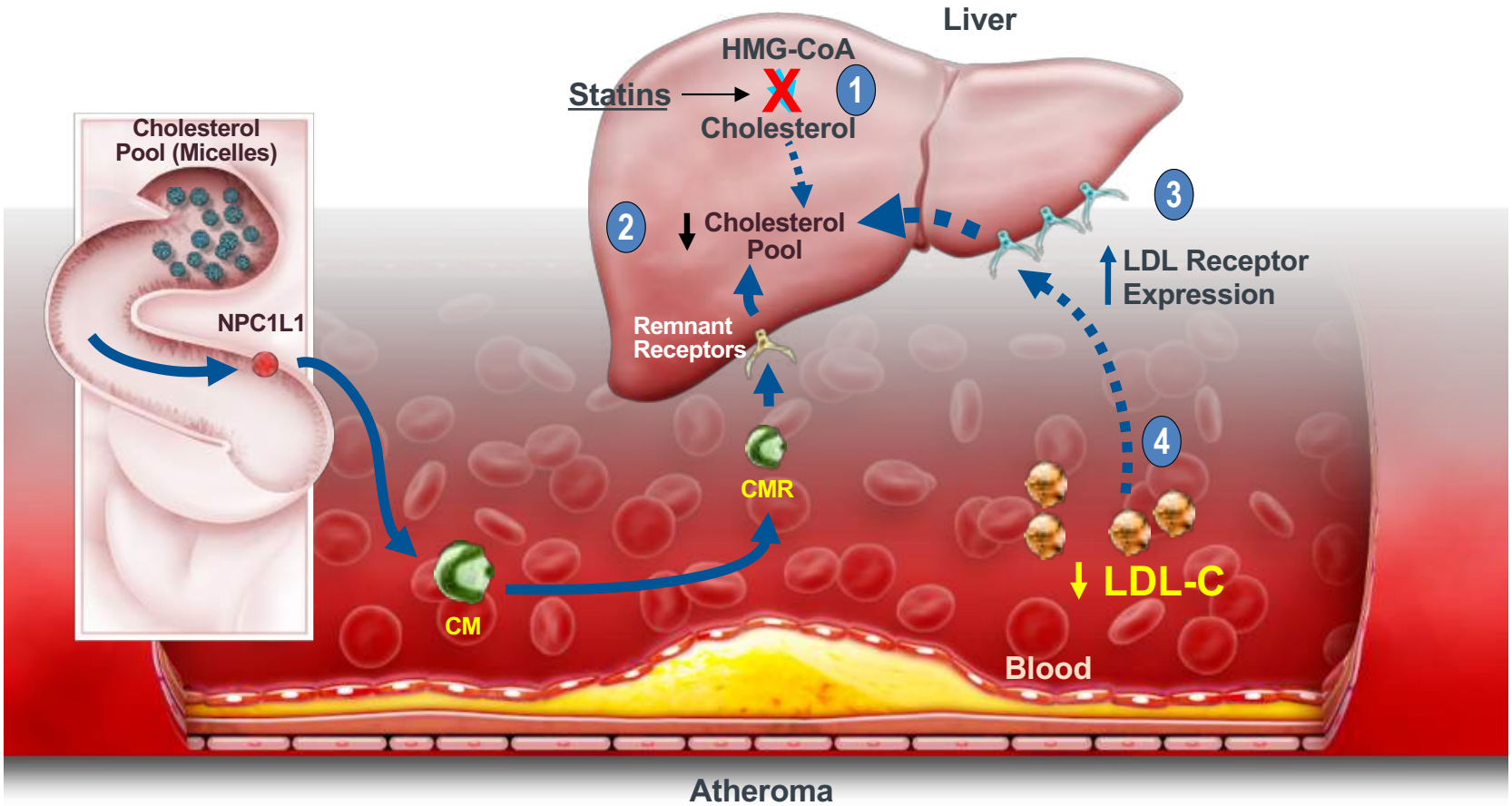
NPC1L1 = Niemann-Pick C1-like 1; HMG-CoA = 3-hydroxy-3-methylglutaryl acetyl coenzyme A; CMR = chylomicron remnant.

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

Statins Inhibit Synthesis of Cholesterol[1]

Statin: Mechanism of Action

1. Inhibition of HMG-CoA reductase activity
2. Reduction of hepatic cholesterol
3. Increased LDL receptor expression
4. Increased clearance of LDL-C



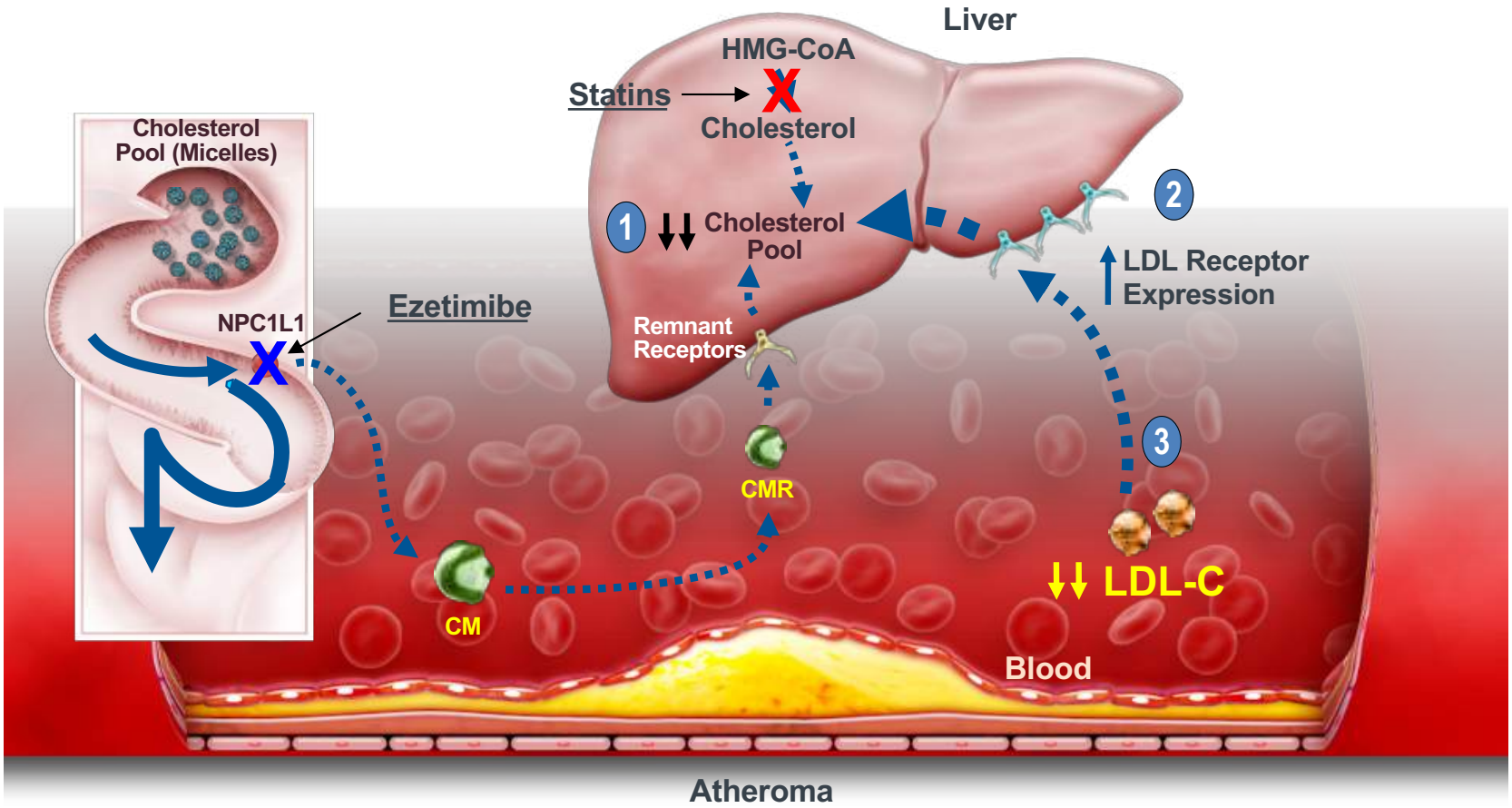
HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; NPC1L1 = Niemann-Pick C1-like 1; CMR = chylomicron remnant.

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

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.

Monotherapy is not enough

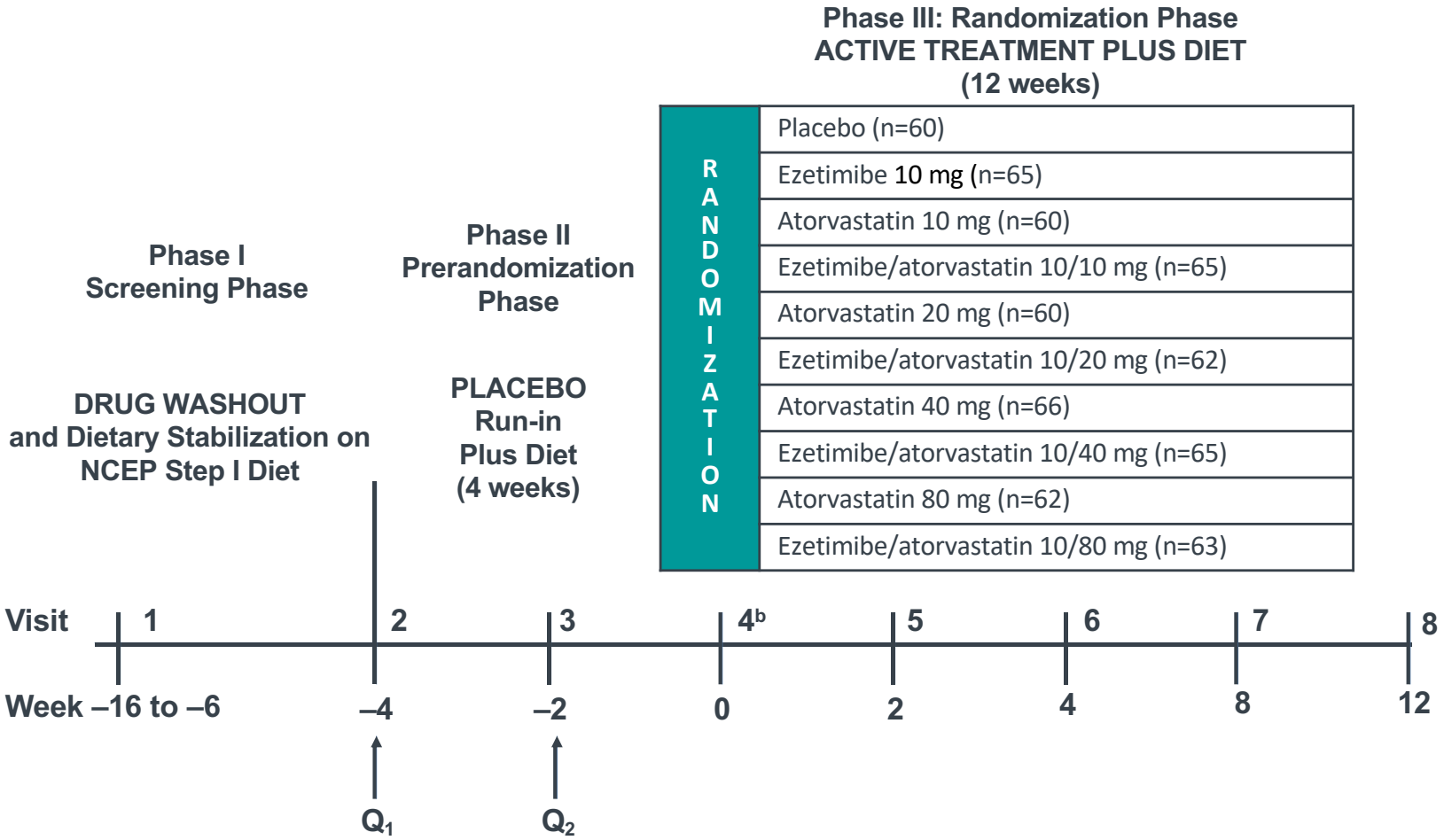
Enhance monotherapy ?
Combination therapy?

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]

Patients with hypercholesterolemia[a]



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

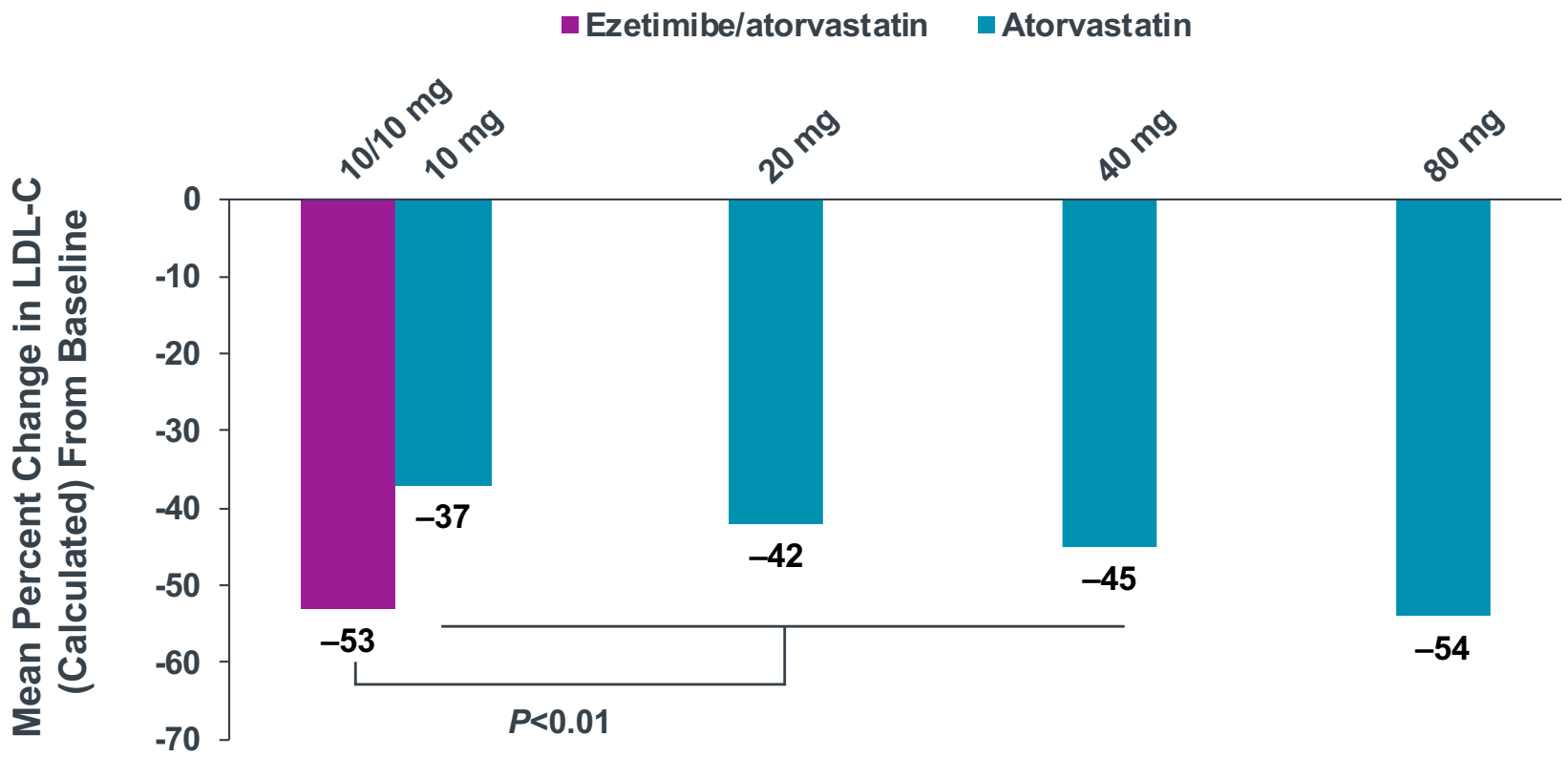
[a]Baseline LDL-C 145 to 250 mg/dL (~3.7 to 6.5 mmol/L) and triglycerides ≤350 mg/dL (~4.0 mmol/L).

[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]

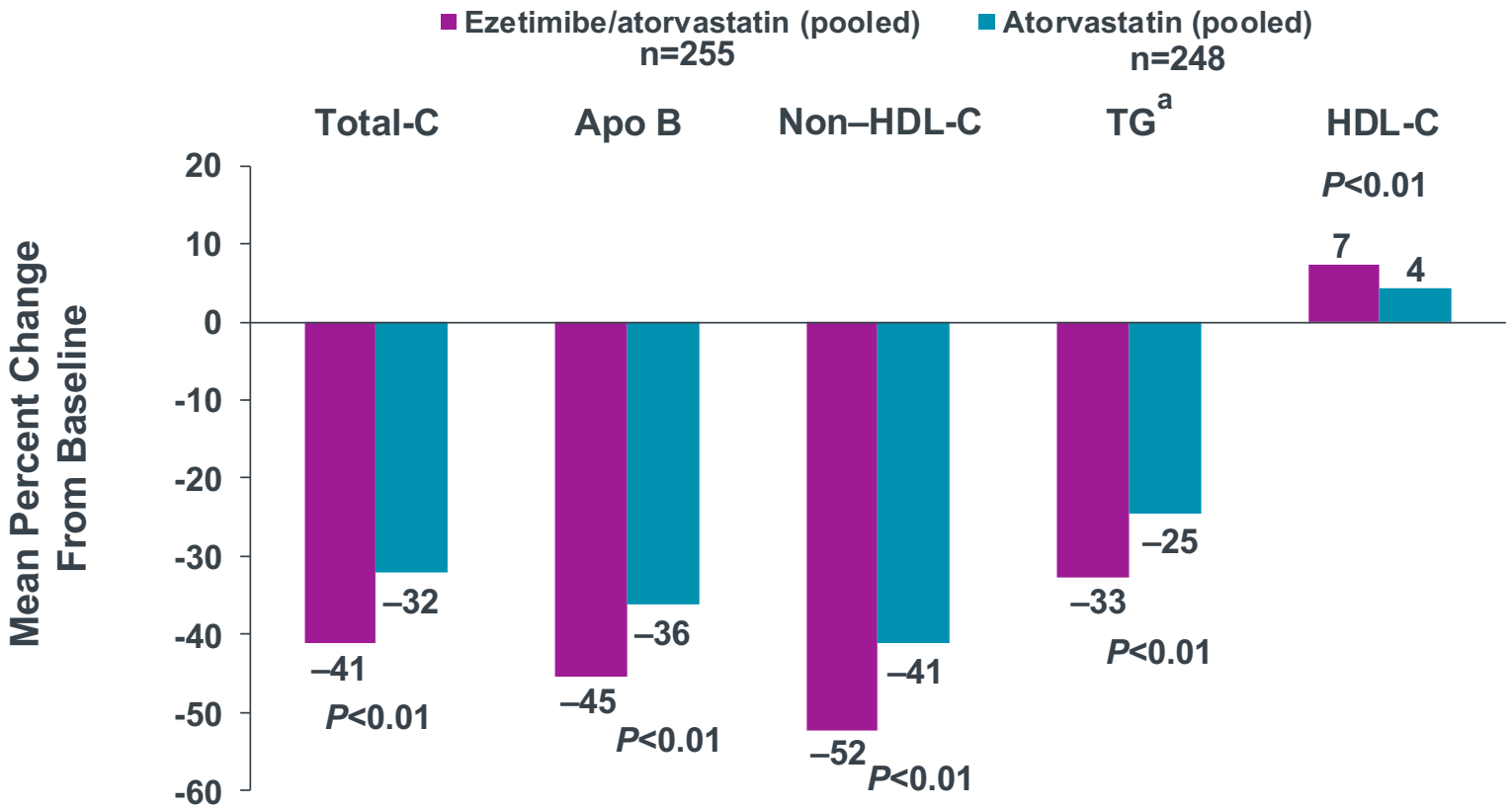


Mean baseline LDL-C was 182 mg/dL (~4.7 mmol/L) for ezetimibe/atorvastatin arms (n=255) and 181 mg/dL (~4.7 mmol/L) for atorvastatin arms (n=248).

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.

atorvastatin/eztimibe provide LDL 53% reduction

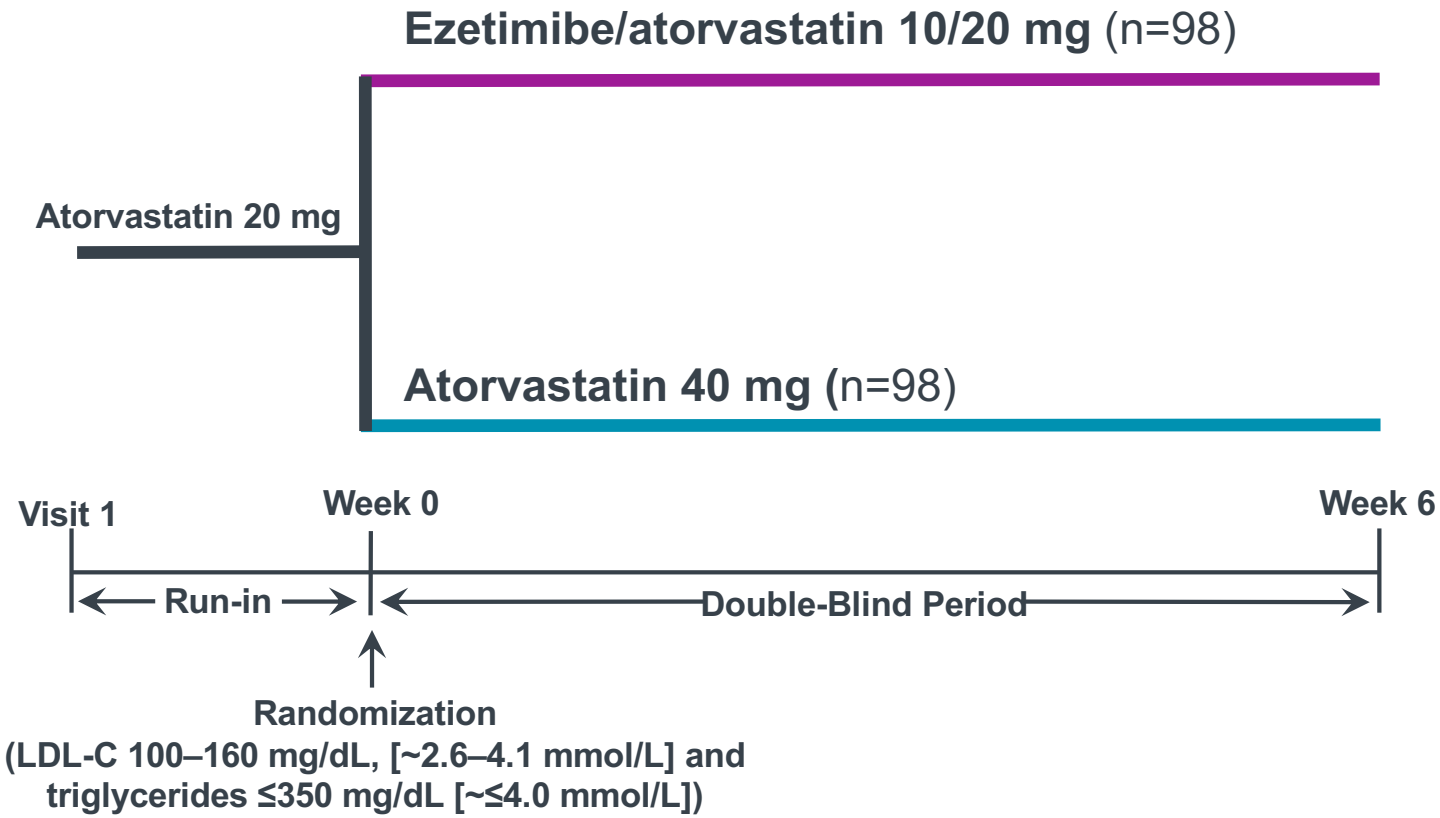
Switch of atorvastatin/eztimibe

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]

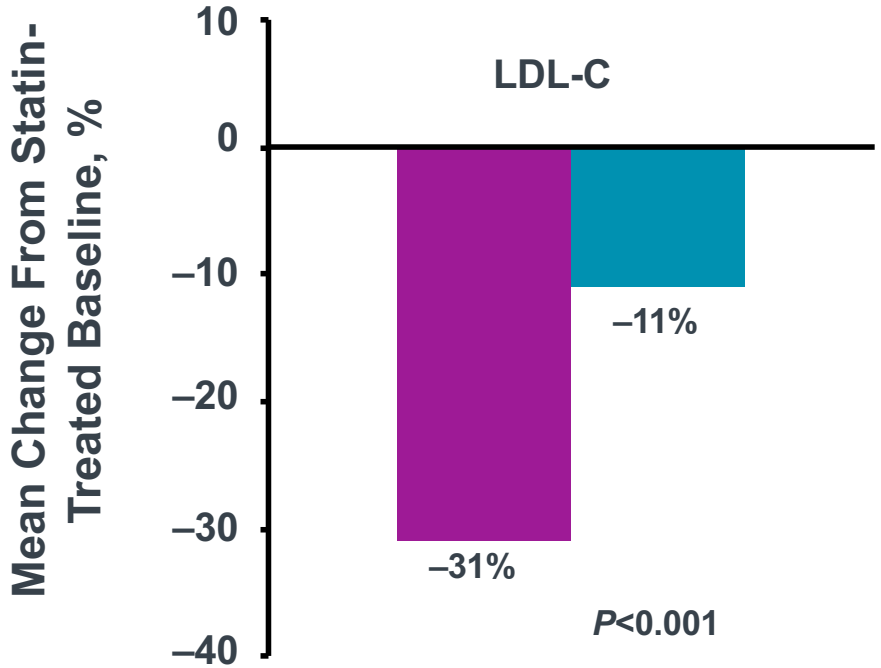
Patients with hypercholesterolemia at moderately high risk of CHD (based on NCEP ATP III criteria)



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)

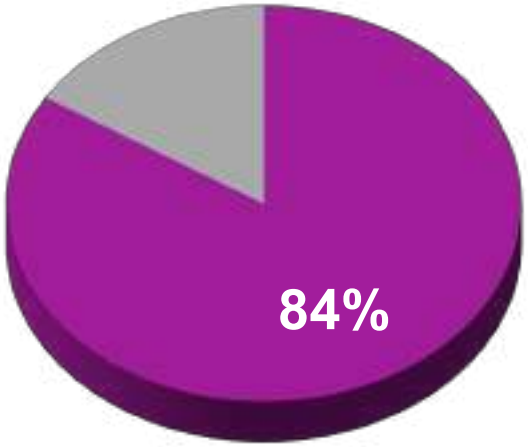
Atorvastatin 20 mg titrated to 40 mg (n=92) (mean on-statin baseline LDL-C = 118 mg/dL, ~3.1 mmol/L)

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

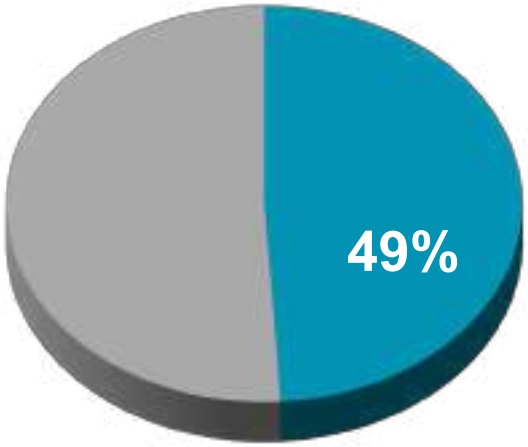
Ezetimibe/atorvastatin 10/20 mg
(n=92)



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

***P*<0.001**

Atorvastatin 40 mg
(n=92)

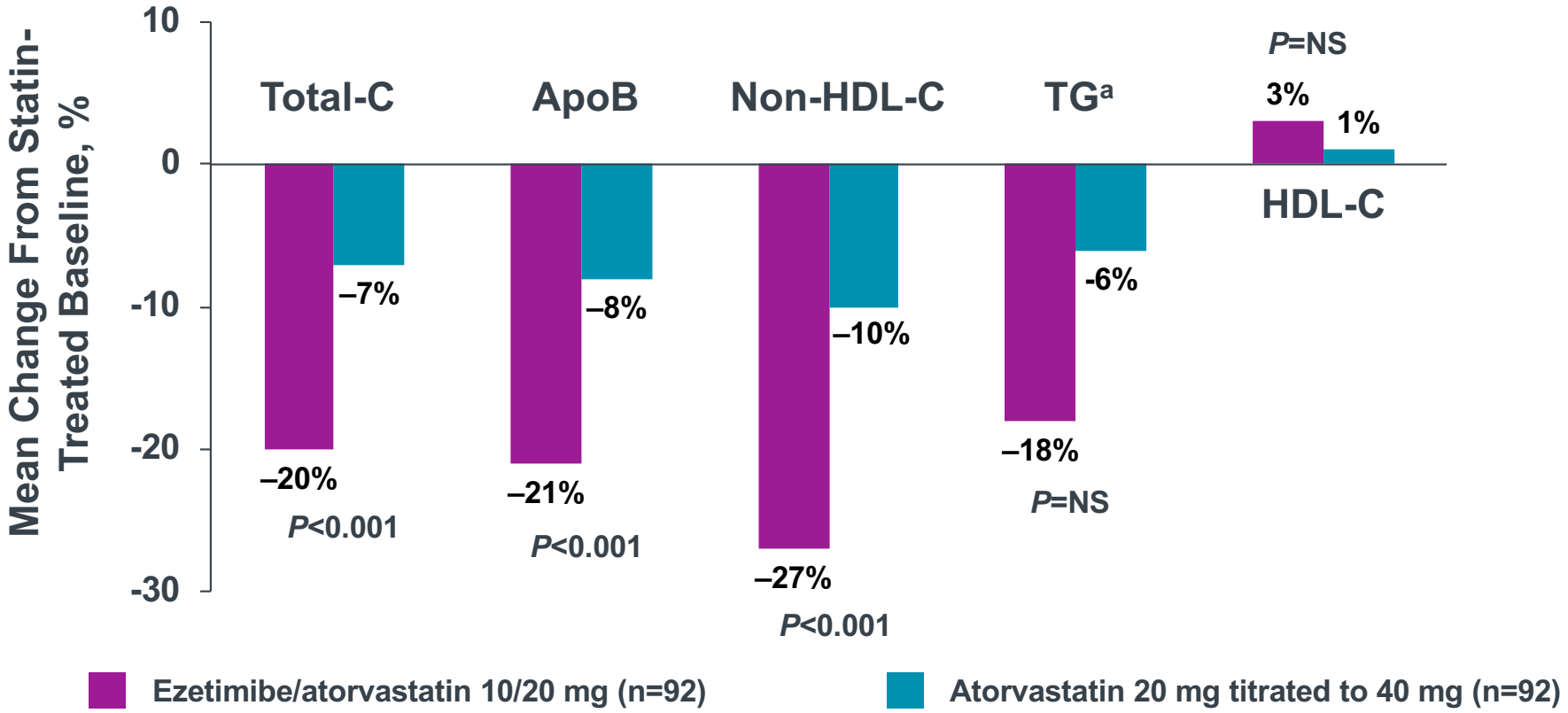


Mean Statin-Treated Baseline LDL-C: 118 mg/dL (~3.1 mmol/L)

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.

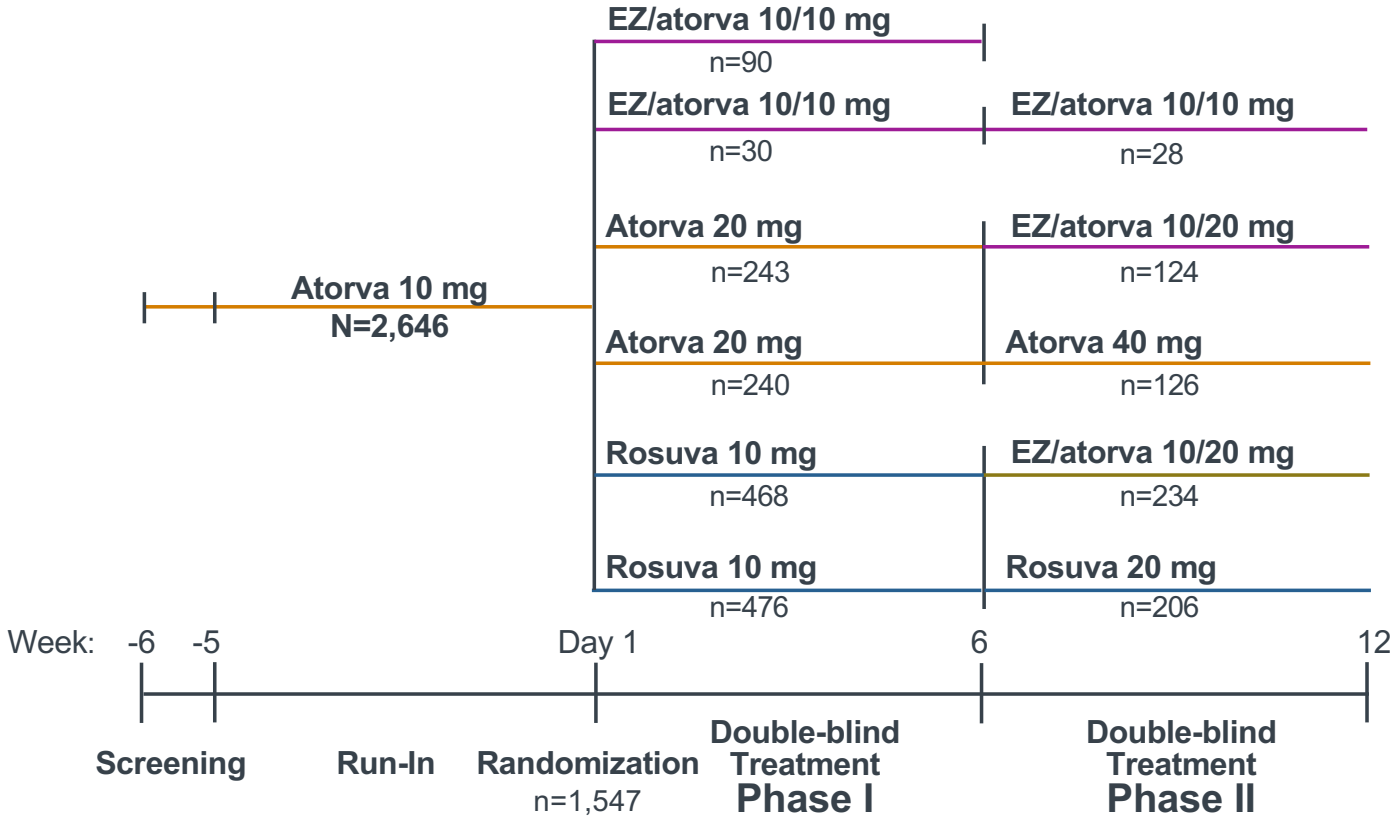
1. Conard SE et al. *Am J Cardiol*. 2008;102:1489–1494.

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



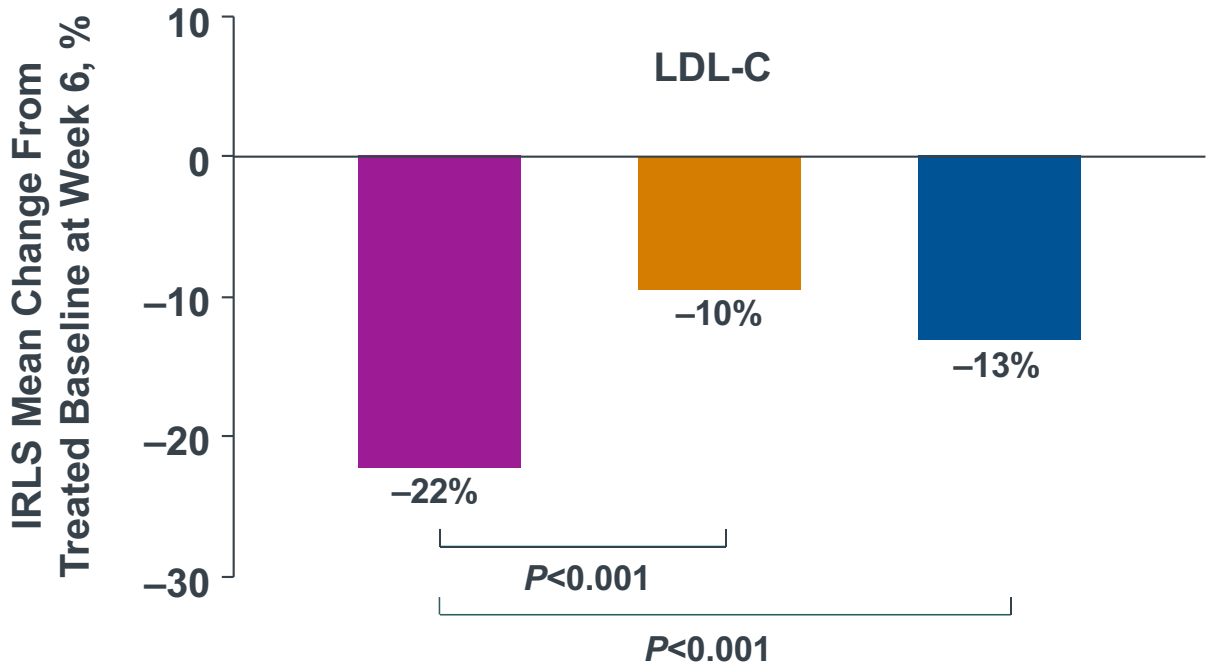
Adapted with permission from Bays HE et al.[1]

[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)

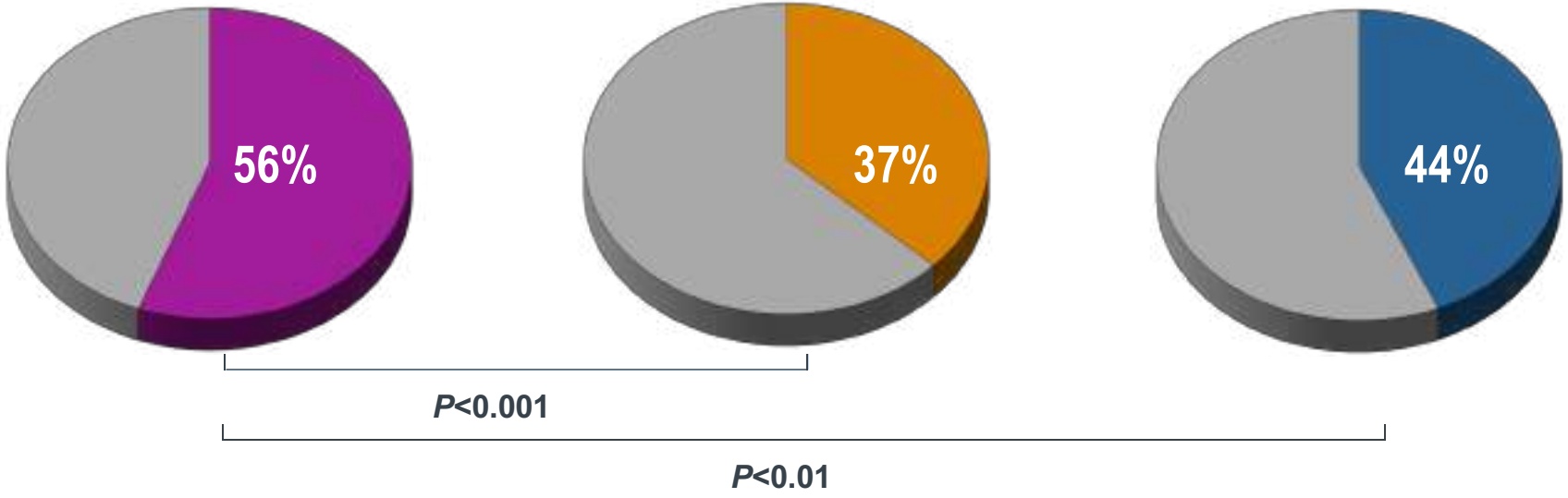
Mean treated baseline LDL-C:
121 mg/dL (~3.1 mmol/L)

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)



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.

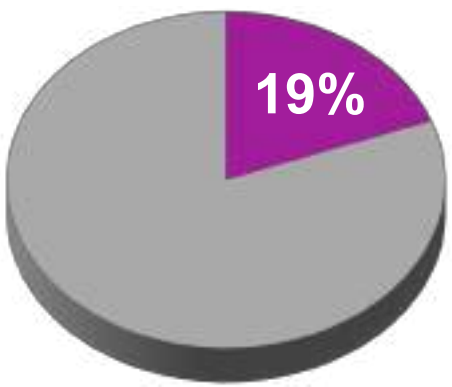
1. Bays HE et al. *Am J Cardiol*. 2013;112:1885–1895.

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

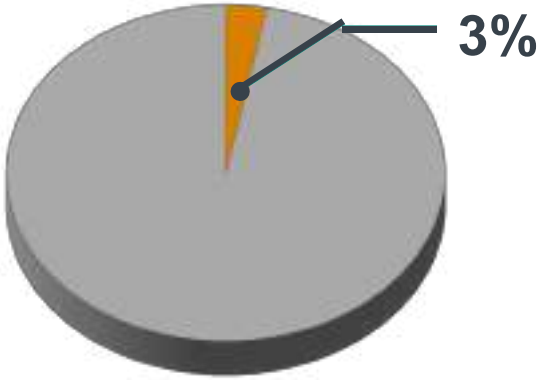
Ezetimibe/atorvastatin 10/10 mg
(n=119)

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



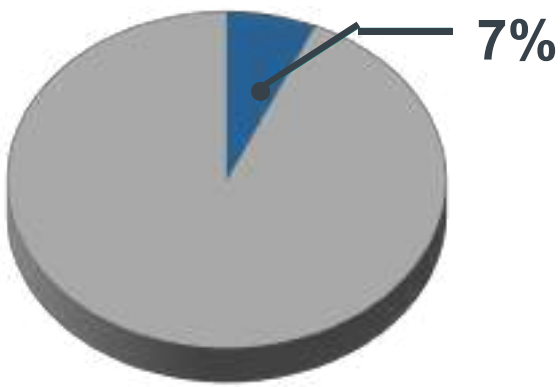
Atorvastatin 20 mg
(n=471)

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**

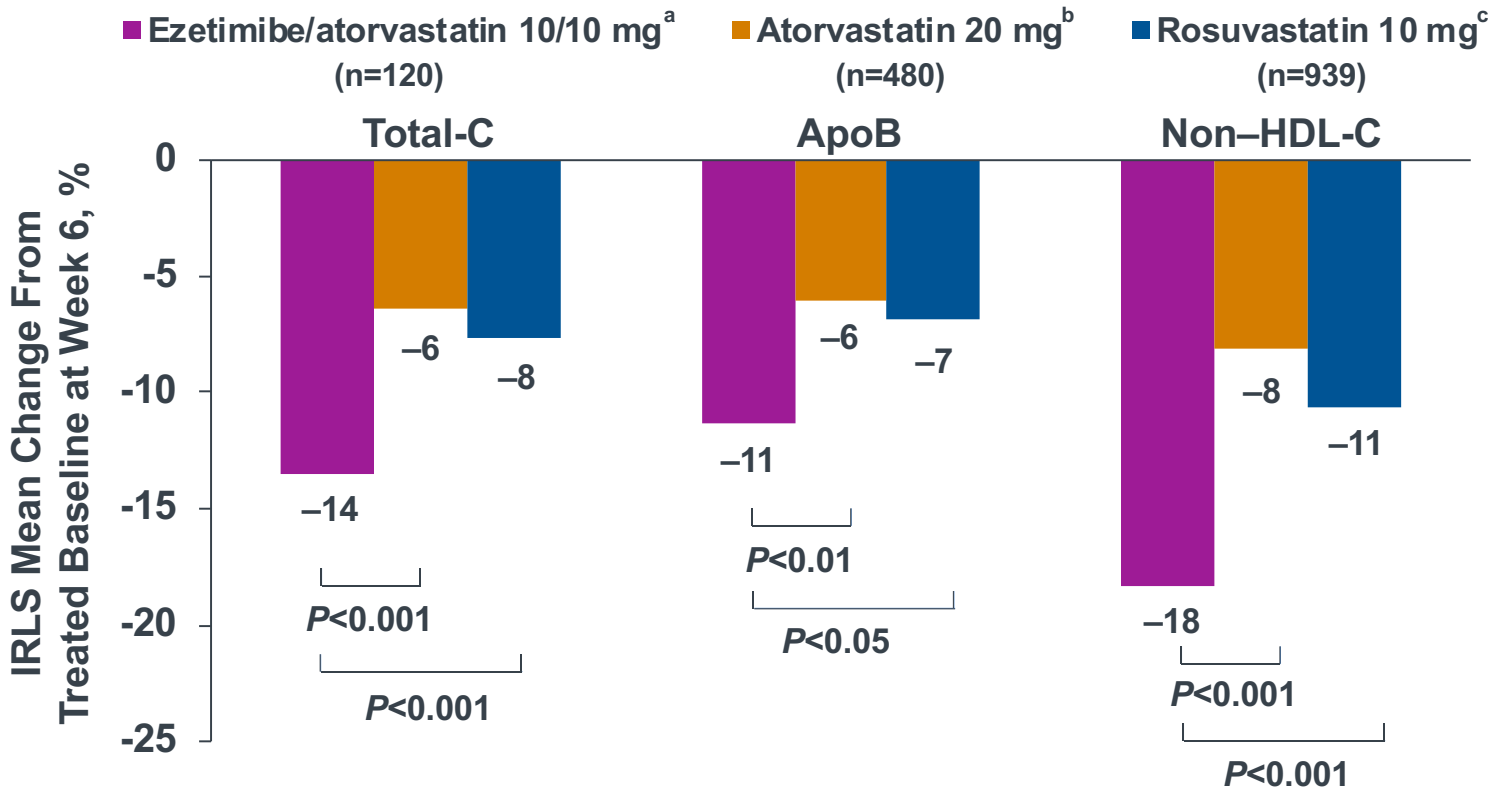
***P*<0.001**

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).

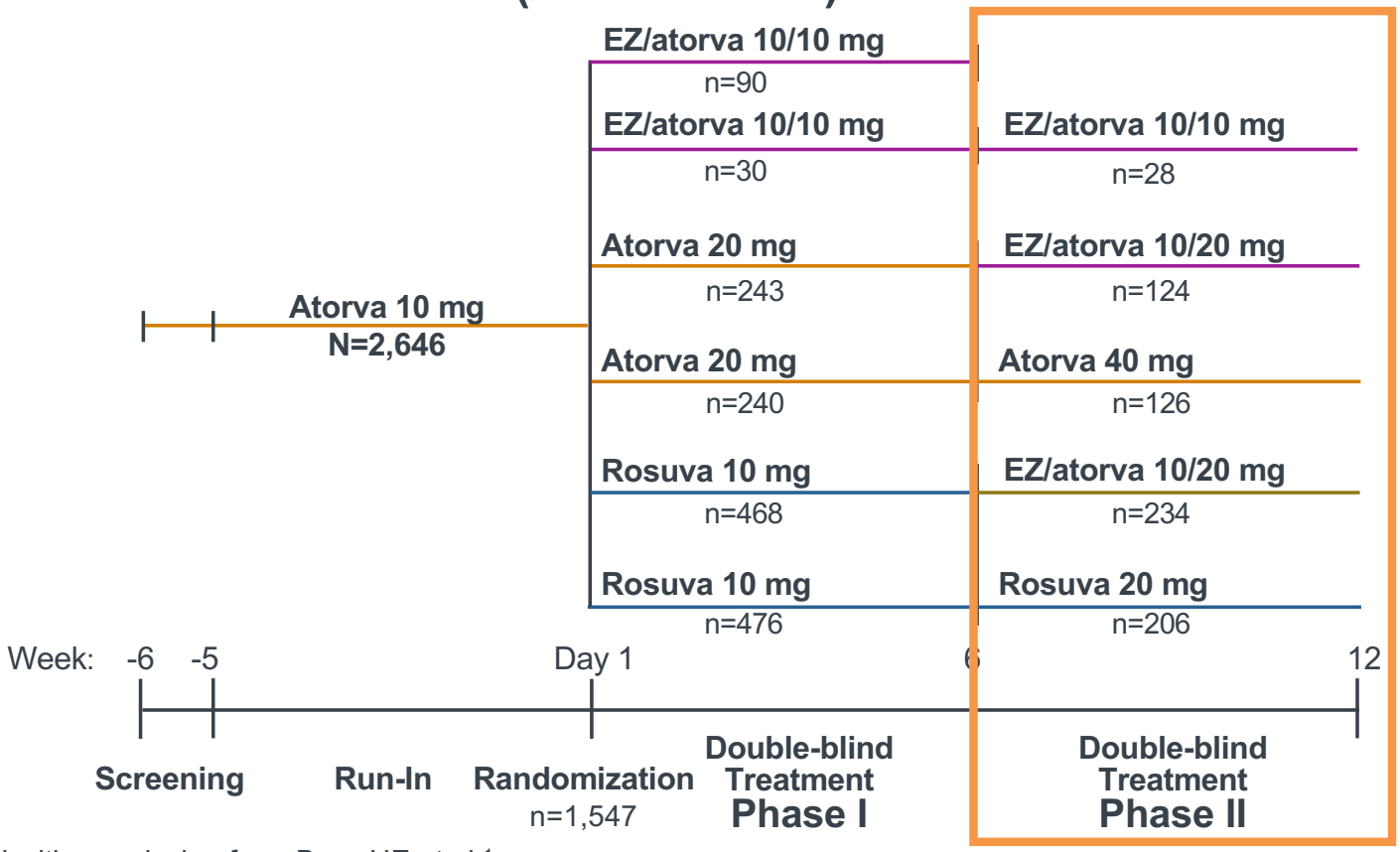
[c]Mean treated baselines for group switched to rosuvastatin 10 mg: Total-C 205 mg/dL (~5.3 mmol/L), apoB 104 mg/dL, and non–HDL-C 152 mg/dL (~3.9 mmol/L).

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



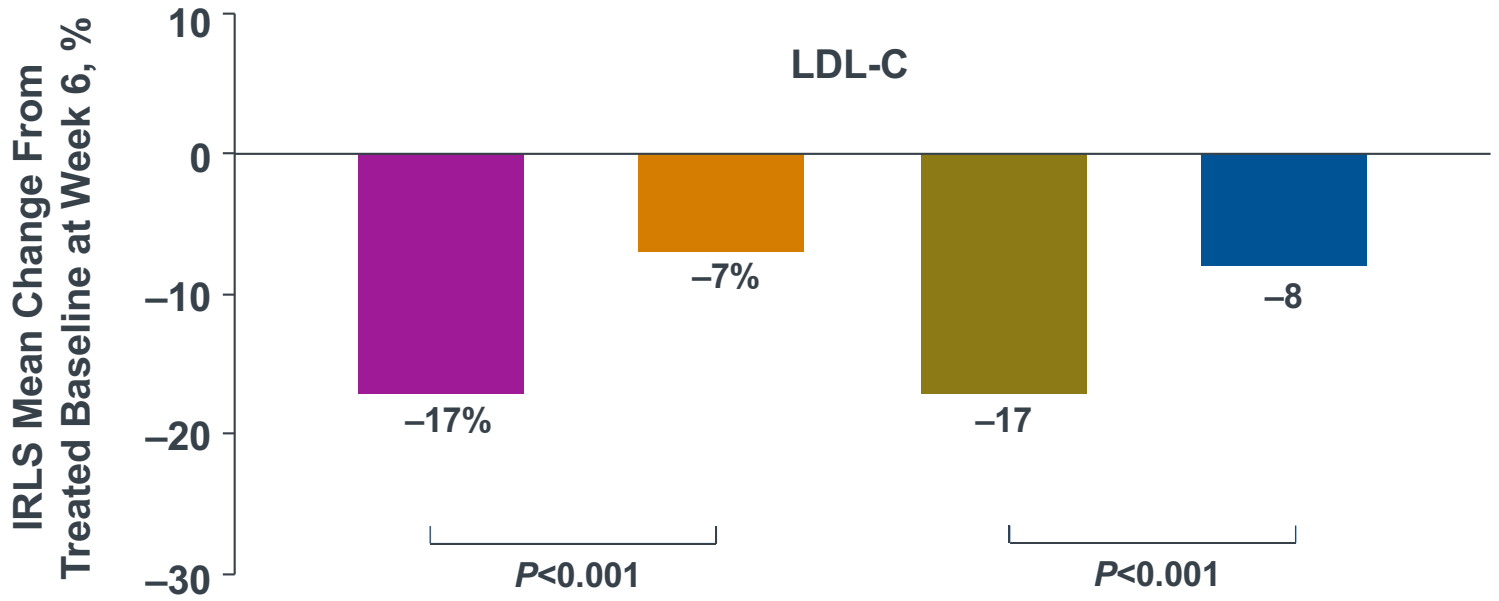
Adapted with permission from Bays HE et al.[1]

[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)

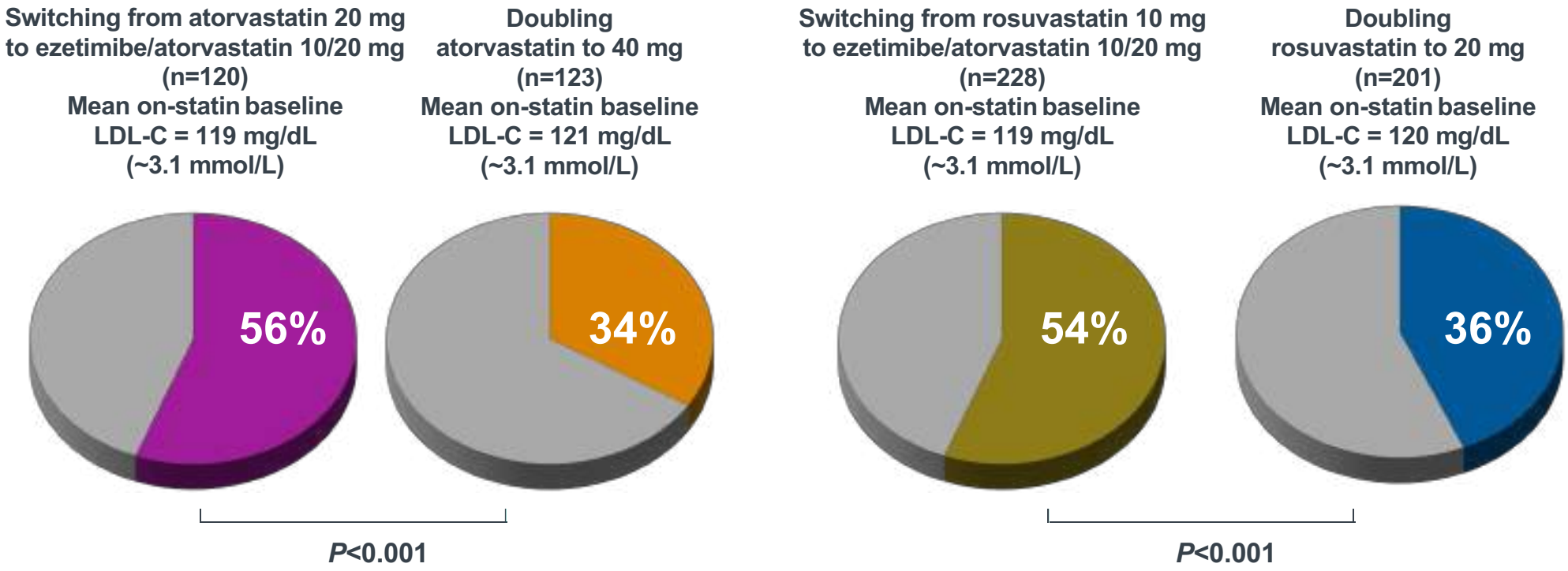
Doubling rosuvastatin to 20 mg (n=205) Mean on-statin baseline LDL-C = 120 mg/dL (~3.1 mmol/L)

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



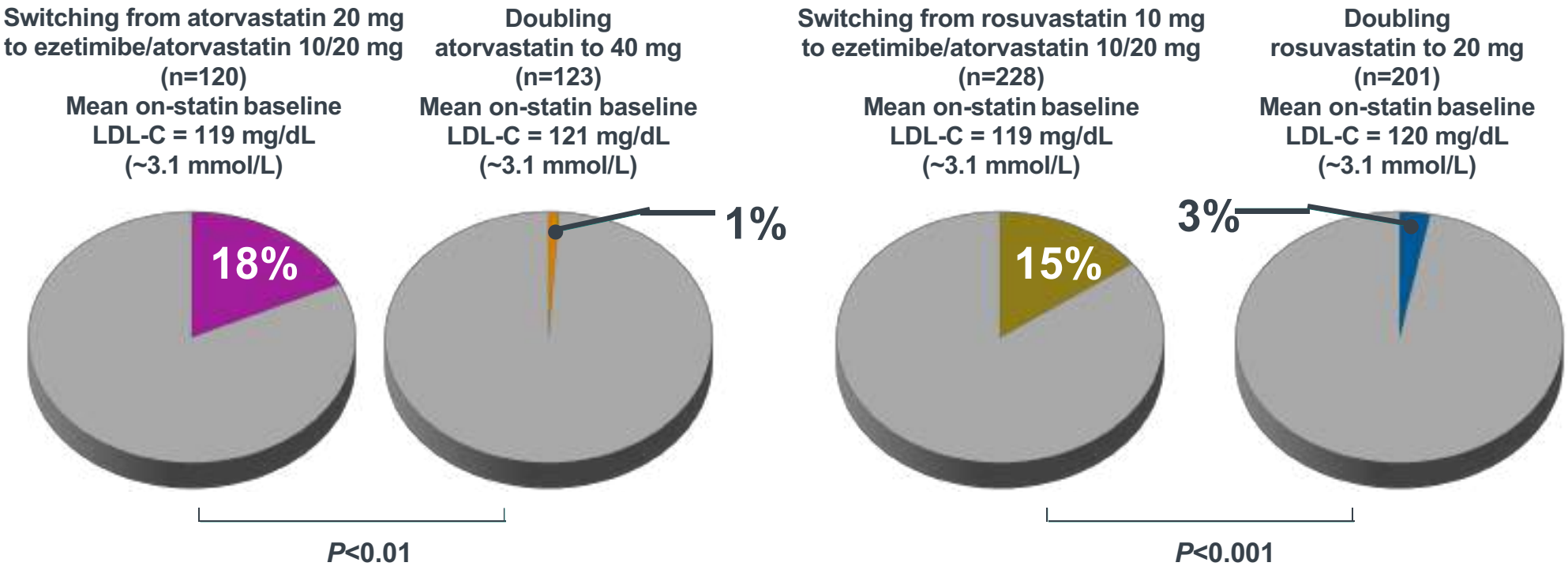
The IRLS mean decrease in LDL-C from statin-treated baseline was 17% with ezetimibe/atorvastatin 10/20 mg compared with 7% with doubling atorvastatin to 40 mg and 17% with ezetimibe/atorvastatin 10/20 mg compared with 8% with doubling rosuvastatin to 20 mg; *P*<0.001 for each comparison.

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

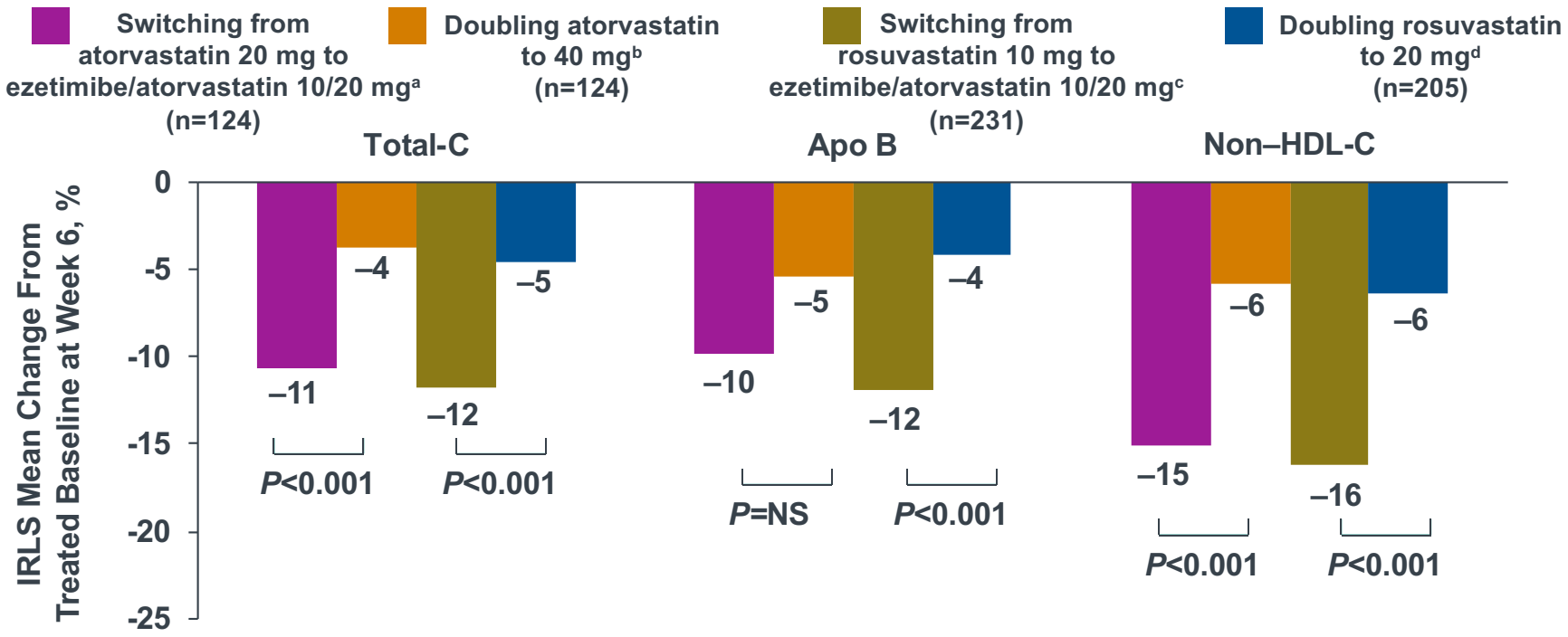


The IRLS mean decrease in LDL-C from statin-treated baseline was 17% with ezetimibe/atorvastatin 10/20 mg compared with 7% with doubling atorvastatin to 40 mg and 17% with ezetimibe/atorvastatin 10/20 mg compared with 8% with doubling rosuvastatin to 20 mg; *P*<0.001 for each comparison.

IRLS = iteratively reweighted least squares.

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.

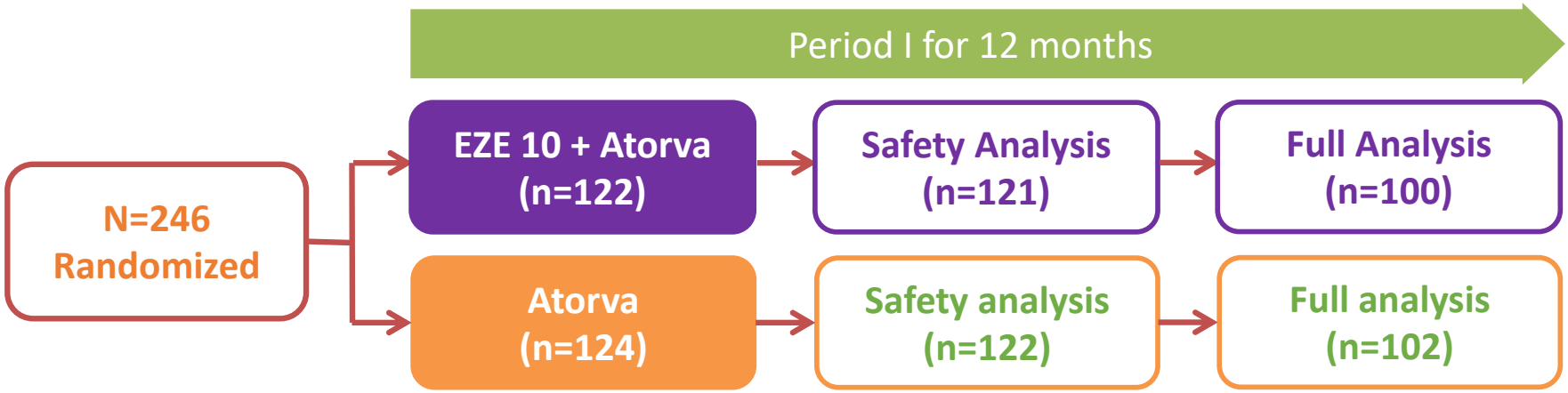
1. Bays HE et al. Am J Cardiol. 2013;112:1885–1895.

Eztimib/atorvastatin combination therapy provide more LDL reduction than statin monotherapy

Outcome?

PRECISE-IVUS Study: Study Design

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



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

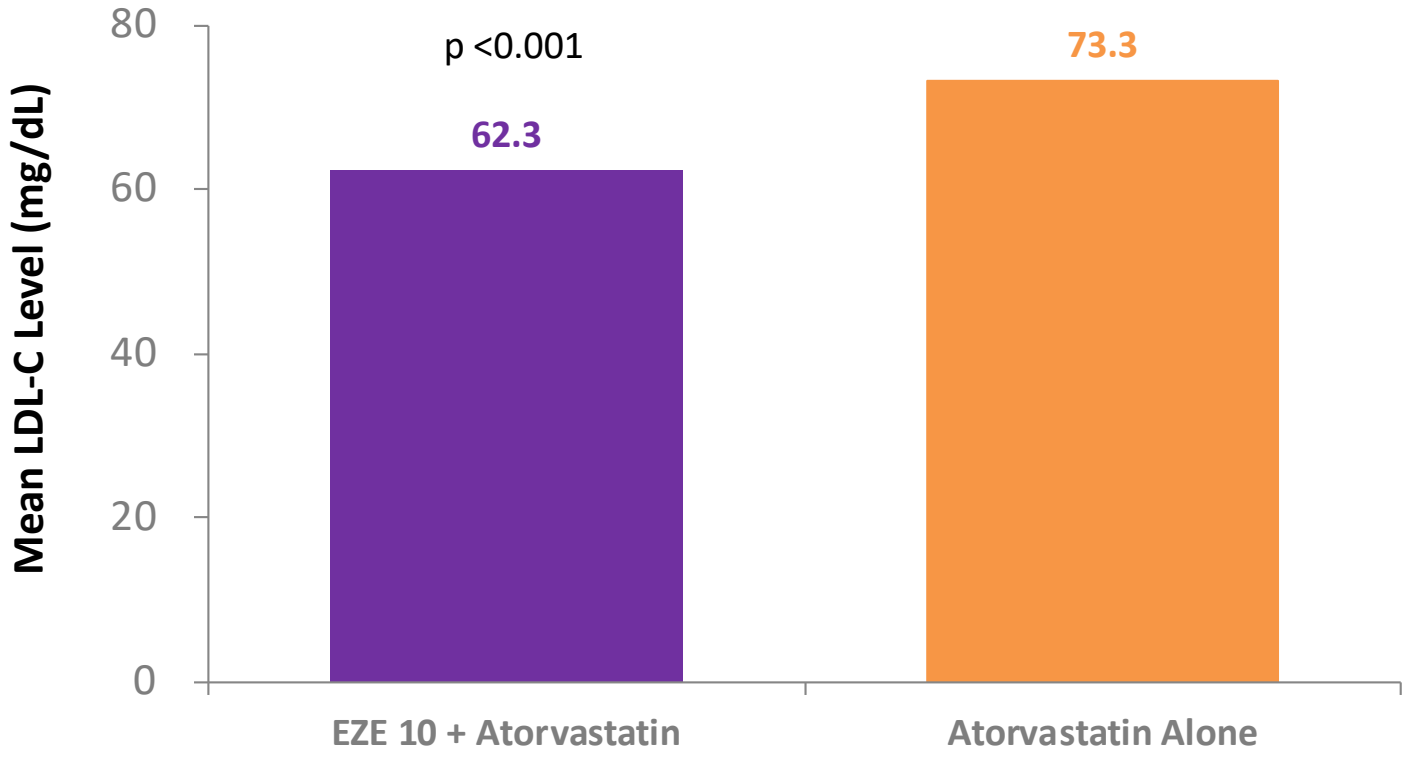
Atorva=atorvastatin; EZE=ezetimibe; CAD=coronary artery disease; PCI=percutaneous coronary intervention; ACS=acute coronary syndrome; SAP=stable angina pectoris;

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



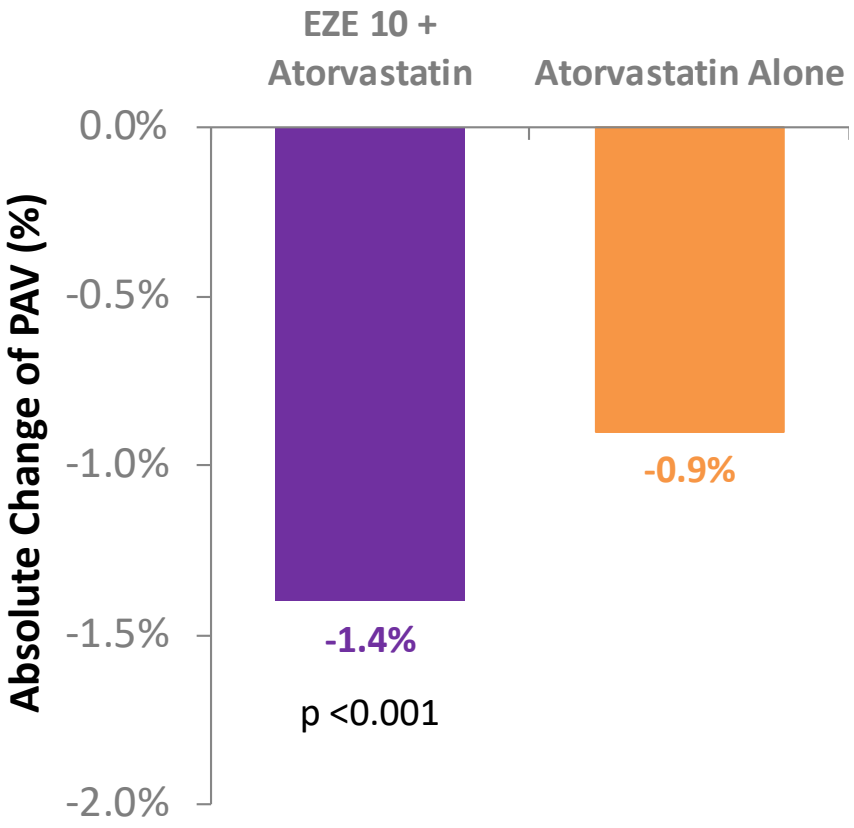
EZE=ezetimibe.

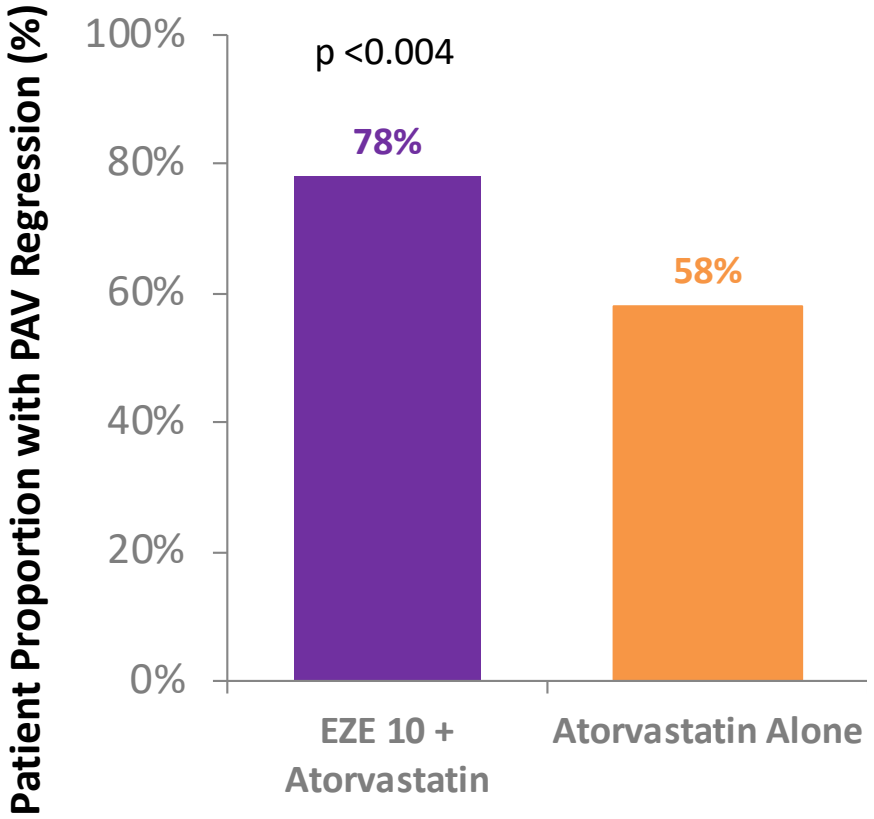
1. Tsujita K, et al. J Am Coll Cardiol. 2015;66(5):495-507.

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





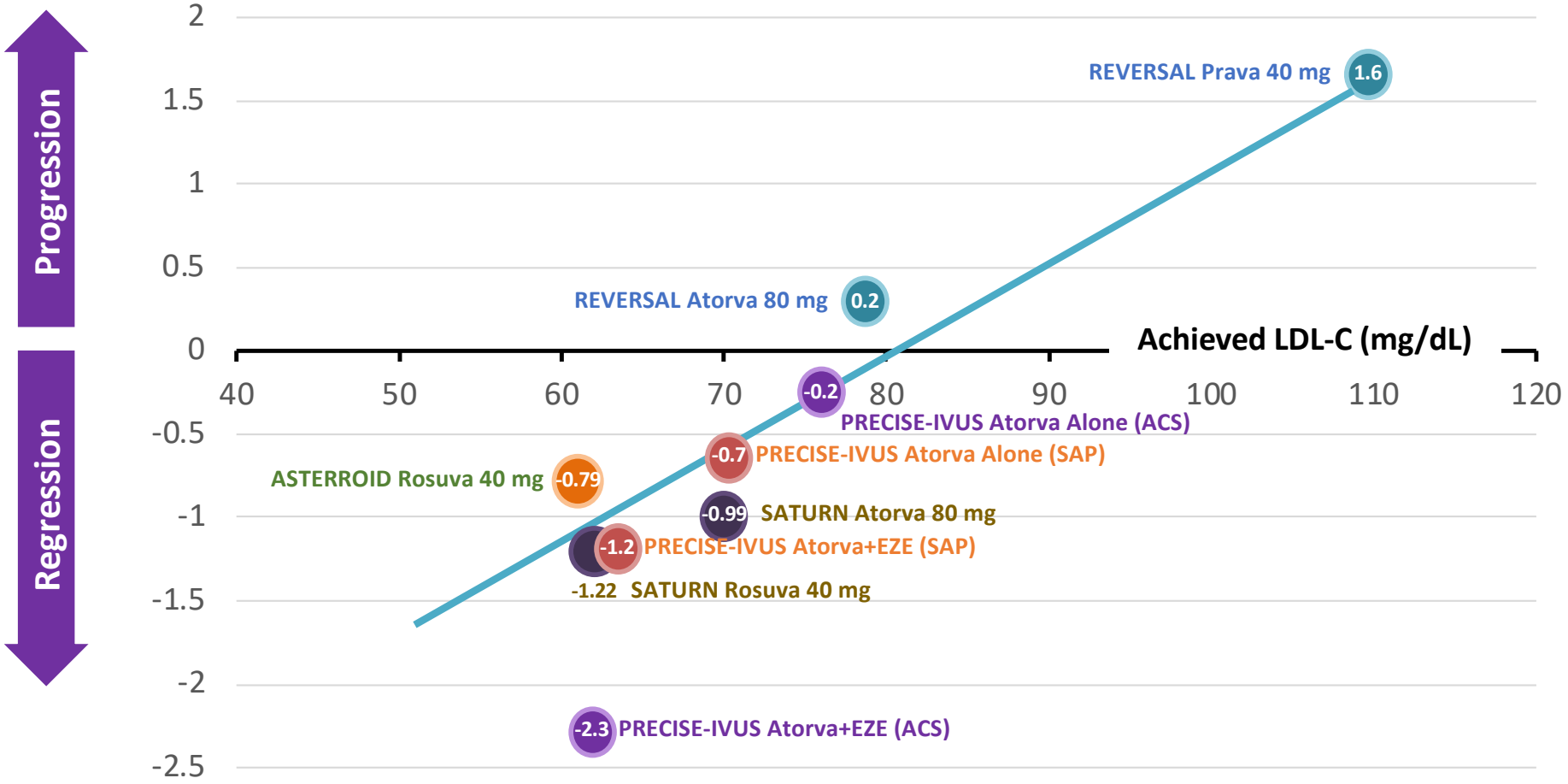
EZE=ezetimibe; PAV=percent atheroma volume.

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

PRECISE-IVUS Study

Relationship Between LDL-C and PAV

使用Atorva/Eze比起atorva alone，可使ACS病人其粥樣斑塊體積百分比(PAV%)額外下降2.1%; 穩定型心絞痛病人(SAP)其粥樣斑塊體積百分比(PAV%)額外下降0.5%

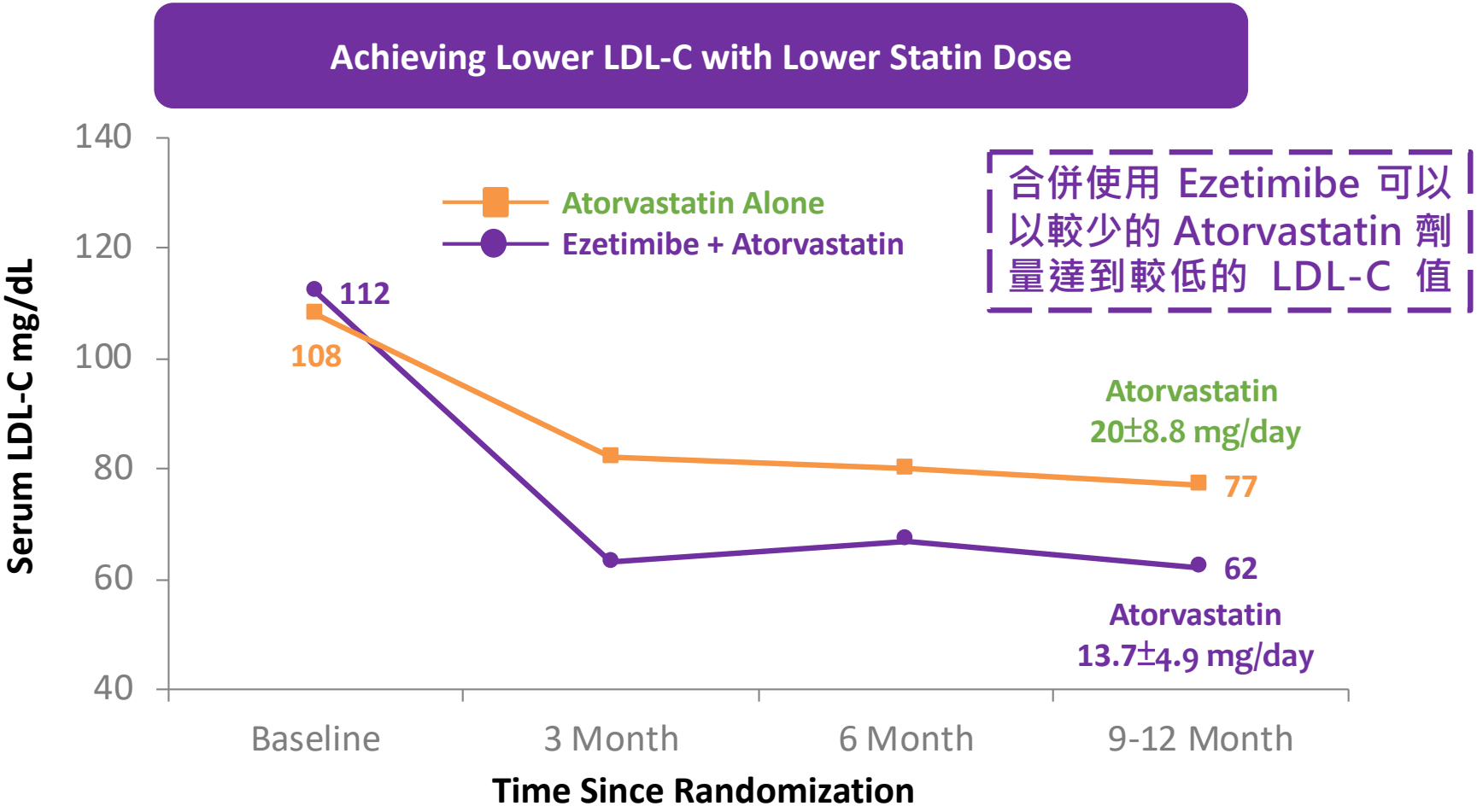


EZE=ezetimibe; PAV=percent atheroma volume.

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

PRECISE-IVUS Study: ACS Subgroup

Lower Statin Dose with Higher Potency While Combining with Ezetimibe



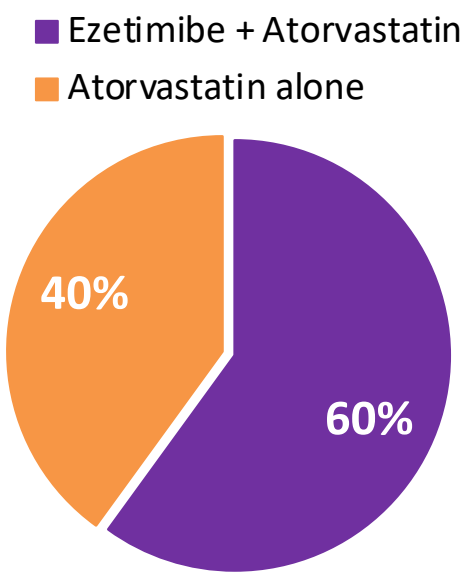
1. Tsujita K, et al. Atherosclerosis. 2016;251(5):367-72.

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

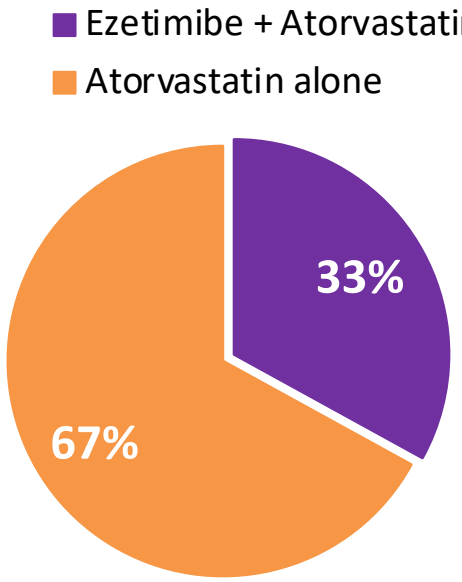
Regression in PAV (n=67)



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.

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

Combination therapy in CKD?

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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

Koichiro Fujisue [a], Suguru Nagamatsu [a], Hideki Shimomura [b], Takuro Yamashita [c], Koichi Nakao [d], Sunao Nakamura [e], Masaharu Ishihara [f], Kunihiko Matsui [g], Nobuyasu Yamamoto [h], Shunichi Koide [i], Toshiyuki Matsumura [j], Kazuteru Fujimoto [k], Ryusuke Tsunoda [l], Yasuhiro Morikami [m], Koshi Matsuyama [n], Shuichi Oshima [o], Kenji Sakamoto [a], Yasuhiro Izumiya [a], Koichi Kaikita [a], Seiji Hokimoto [a], Hisao Ogawa [p], Kenichi Tsujita [a,*]

[a] Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

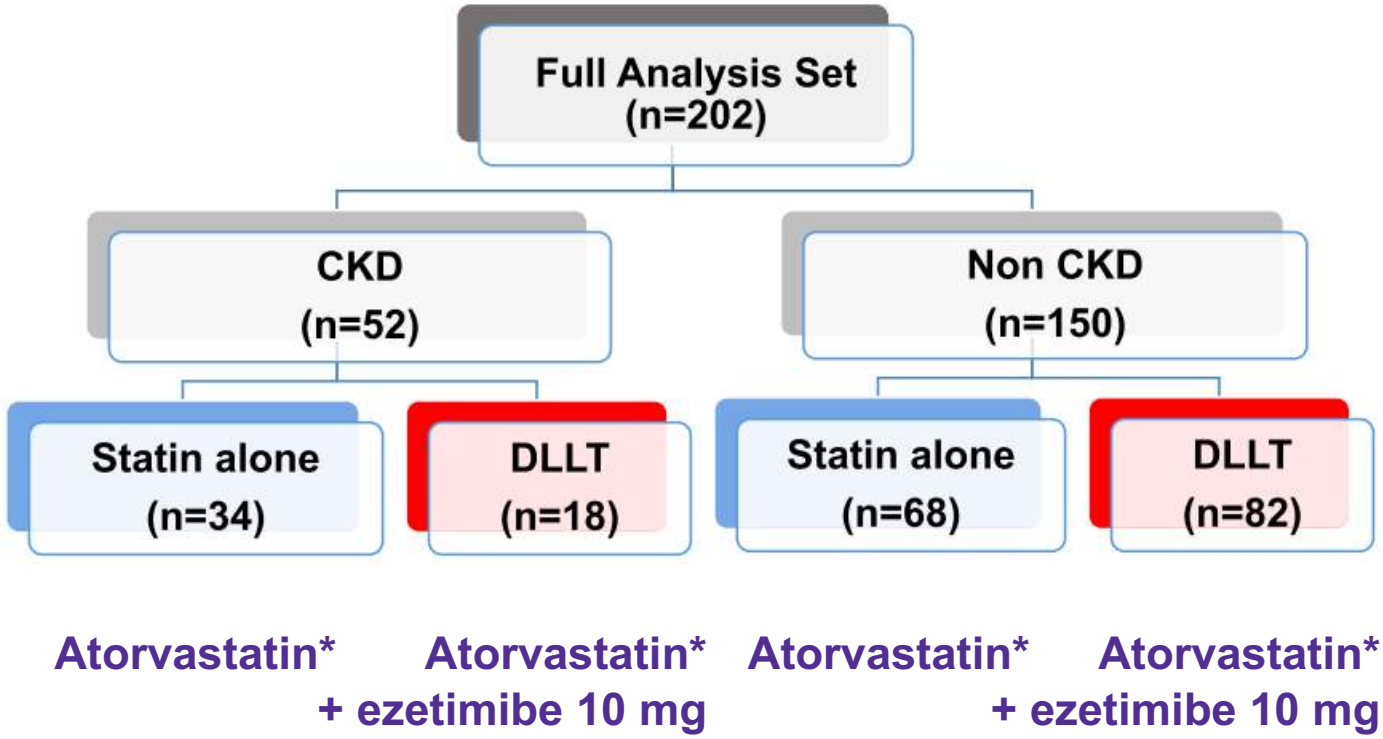
Objectives: hypothesized intensive lipid-lowering with statin/ezetimibe attenuated coronary atherosclerotic development even in patients with CKD.

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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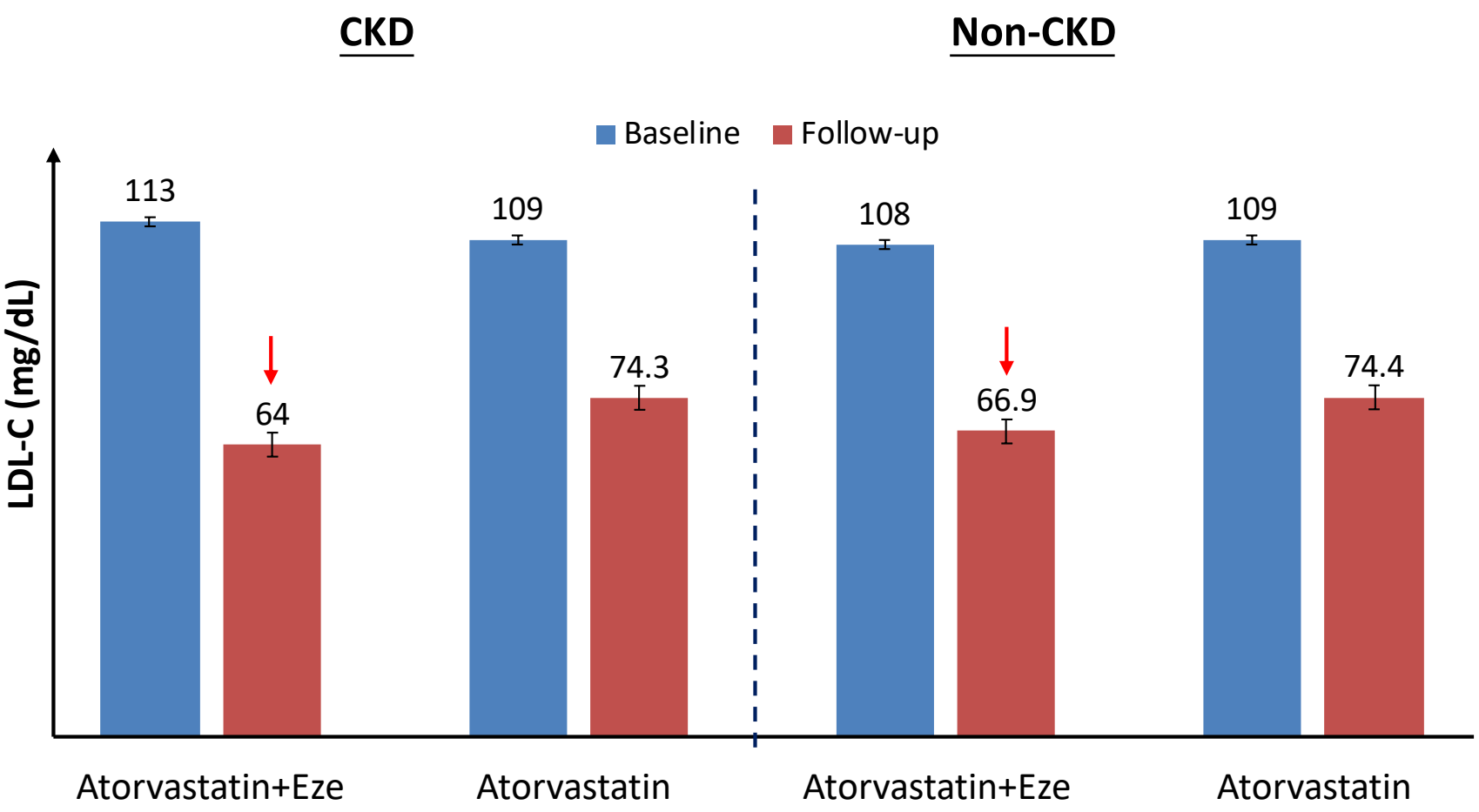

LDL-c reduction in **CKD pts**
Atorvastatin+Ezetimibe −49.0 (−56.2 to 38.9)%
Atorvastatin -34.7(−47.9 to −16.1)%

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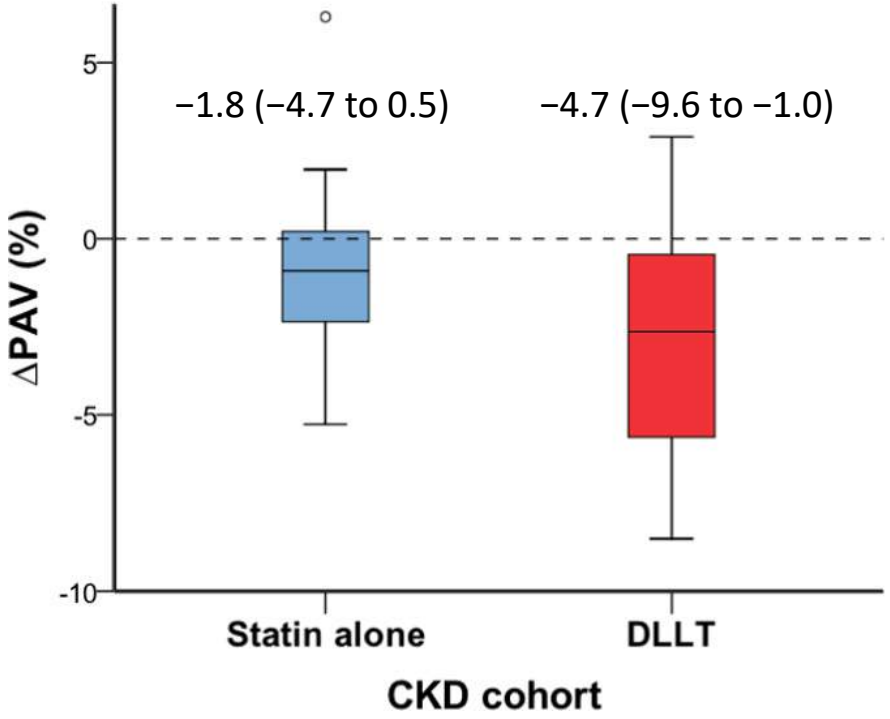
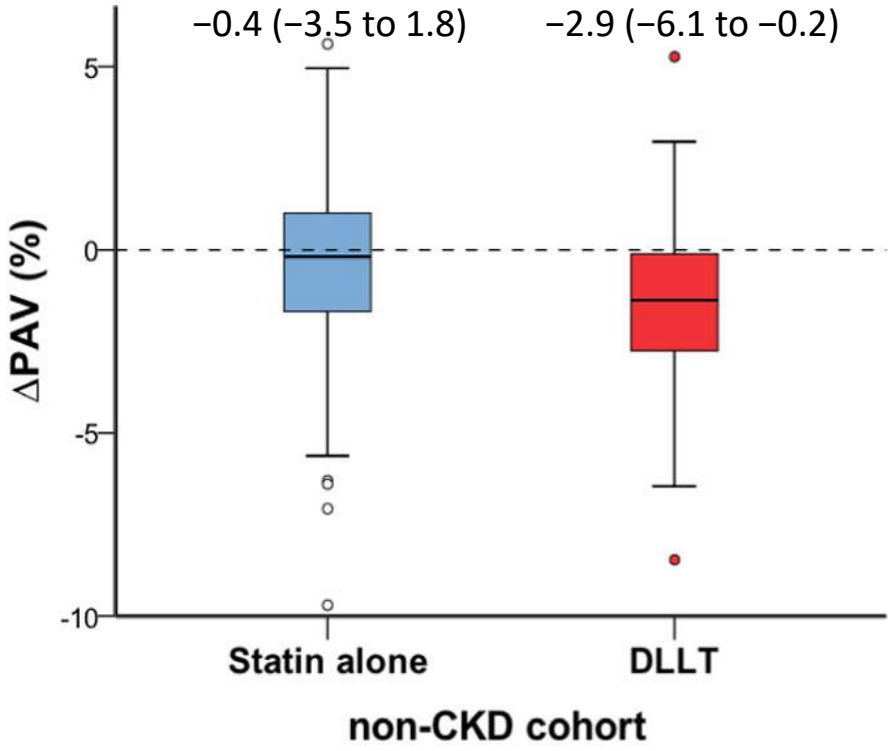
DLLT showed the significantly stronger regression in ΔPAV, compared with atorvastatin alone even in the CKD group.

ΔPAV −2.9 [−4.9 to −0.5]%



ΔPAV −2.5 [−2.6 to 1.2]%



International Journal of Cardiology 268 (2018) 23–26

Sub-Analysis of PRECISE-IVUS Trial: Study Design

- 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.

Outcome of eztimibe alone

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

Background

EWTOPIA75
ユートピア75

- An explosive increase in the population of older people aged ≥75 years has been documented in many countries including US, Europe, and Asian countries, especially Japan.

- Along with this population change, the number of patients aged ≥75 years with hypercholesterolemia has dramatically increased.

- However, prospective RCTs on the efficacy of LDL-cholesterol (C)-lowering therapy in patients aged ≥ 75 years of age with elevated LDL-C has not been conducted.

Aim of the EWTOPIA75 study

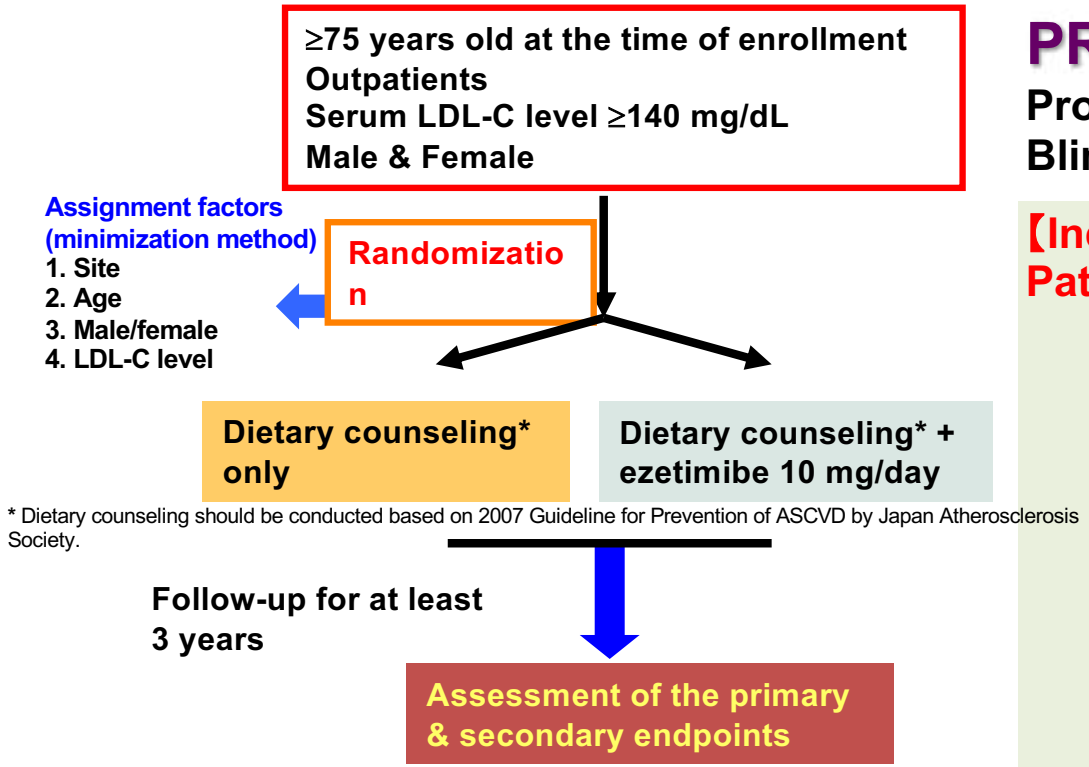
EWTOPIA75
ユートピア75

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
ユートピア75

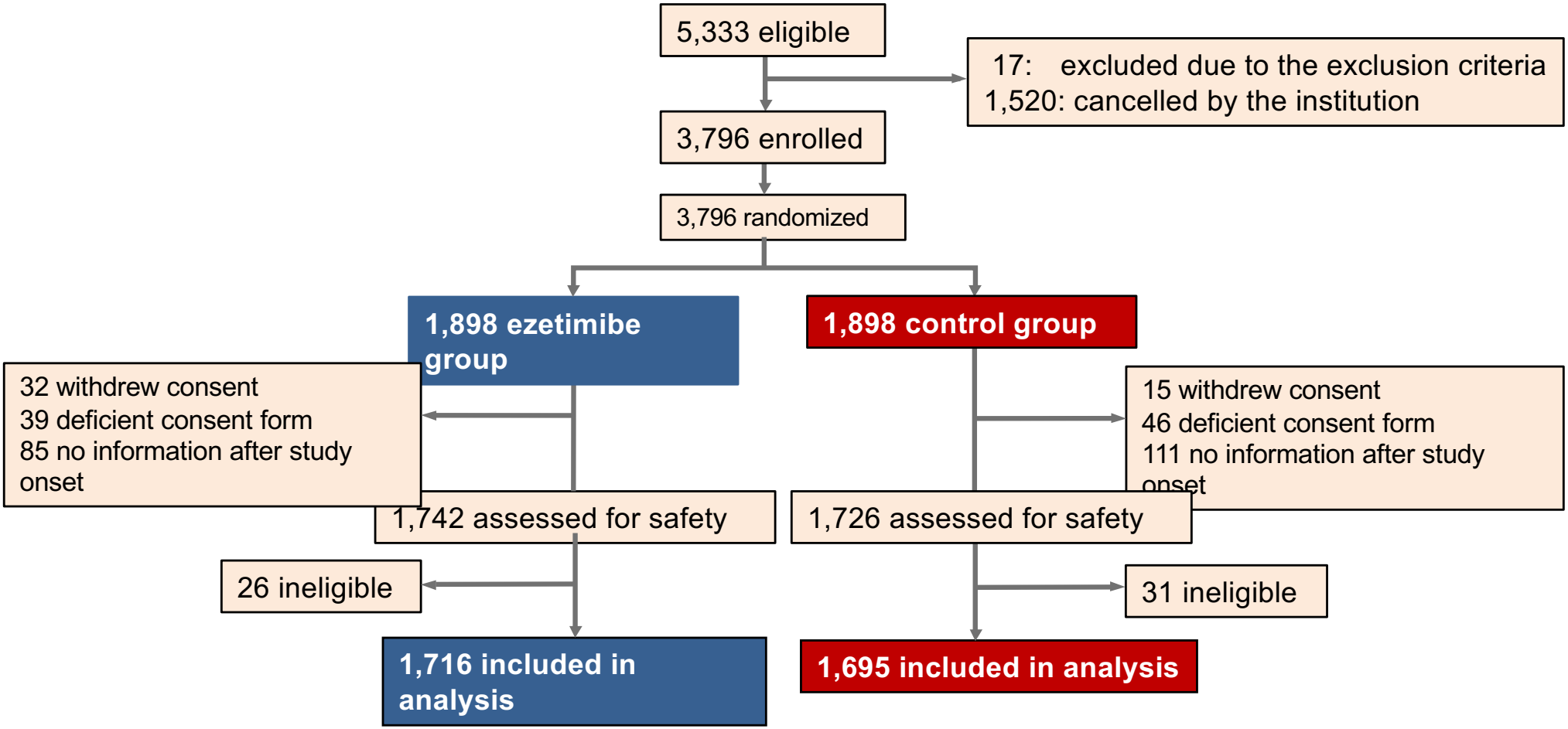
A composite of the following atherosclerotic cardiovascular events

- **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



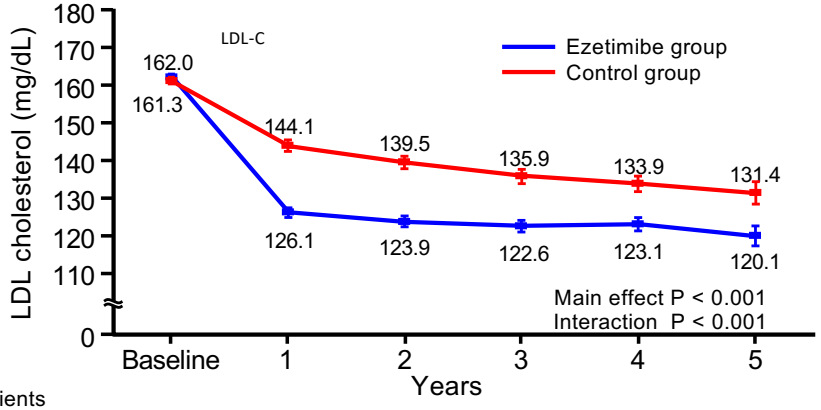
Baseline characteristics of patients

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

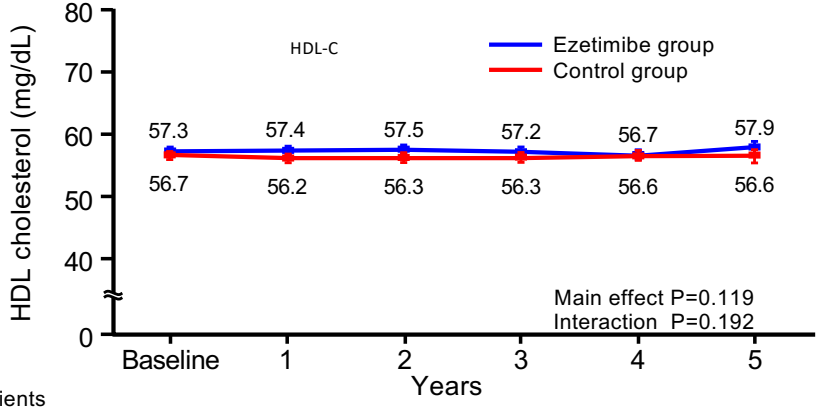
	Ezetimibe group (n=1,716)	Control group (n=1,695)
Age & Sex	80.6±4.7	80.6±4.7
Patients aged over 85 years	323 (18.8)	325 (19.2)
Male	440 (25.6)	432 (25.5)
Female	1276 (74.4)	1263 (74.5)
Body Constitution		
Height (cm)	150.7±8.7	150.6±8.6
Body weight (kg)	53.8±10.0	53.4±10.4
Body mass index (kg/m^2)	23.6±3.5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

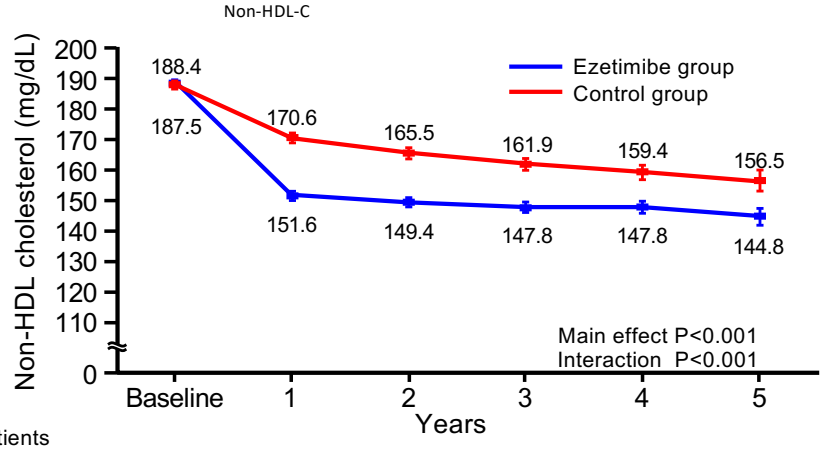
Lipid profile changes in Ezetimibe and Control groups



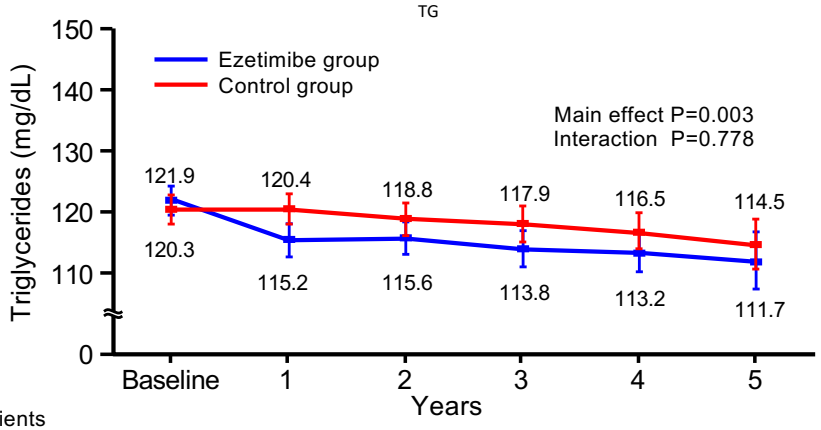
Number of Patients	Baseline	1	2	3	4	5
Treated by ezetimibe	1700	1489	1245	1009	685	311
Not treated by ezetimibe	1685	1464	1227	1023	706	314



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



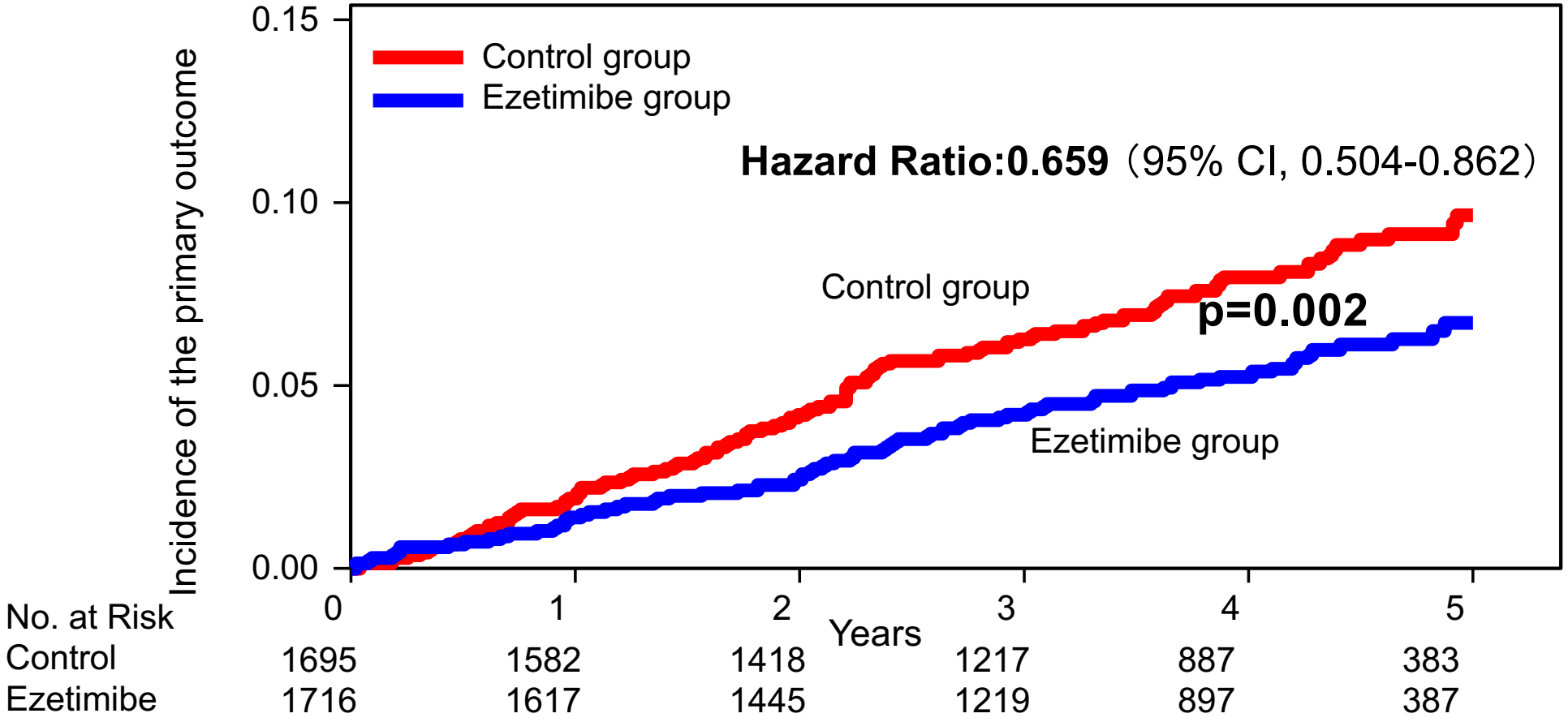
Number of Patients	Baseline	1	2	3	4	5
Treated by ezetimibe	1700	1490	1247	1009	687	311
Not treated by ezetimibe	1685	1466	1230	1024	707	314



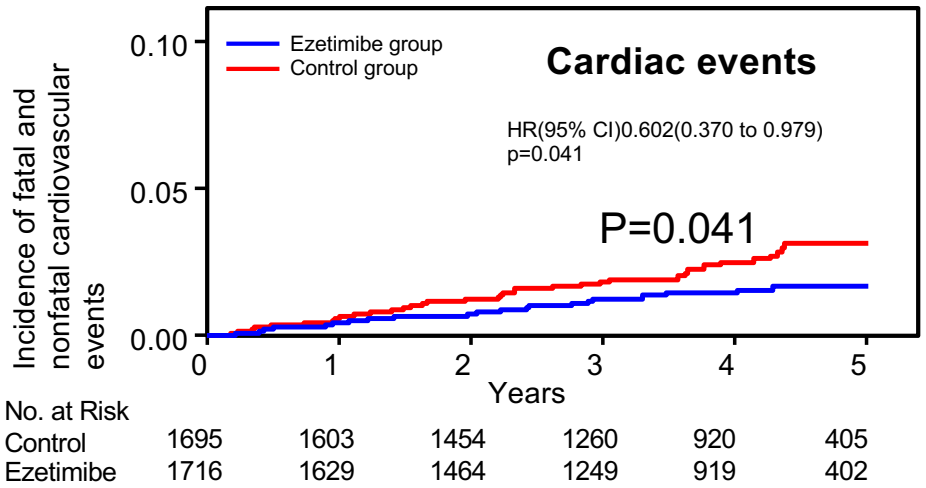
Number of Patients	Baseline	1	2	3	4	5
Treated by ezetimibe	1700	1507	1258	1019	699	317
Not treated by ezetimibe	1685	1484	1242	1029	717	321

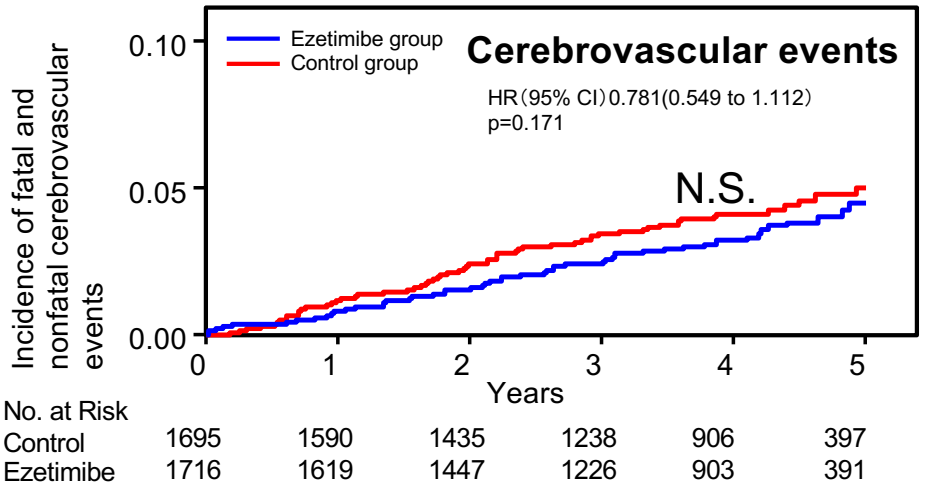
Effect of ezetimibe treatment on the primary end-point

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



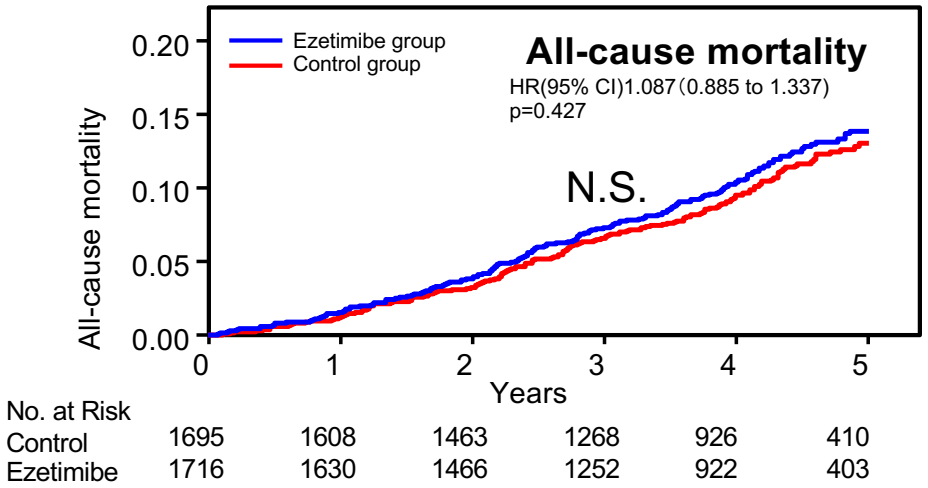
Effect of ezetimibe treatment on cardio-, cerebrovascular events, incidence of adverse events and all-cause mortality





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**



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.

Outcome of ez/simva vs atovastatin

Ezetimibe-Simvastatin Therapy Reduce Recurrent Ischemic Stroke Risks in Type 2 Diabetic Patients

Chi-Hung Liu,* Tien-Hsing Chen,* Ming-Shyan Lin, Ming-Jui Hung, Chang-Ming Chung, Wen-Jin Cherng, Tsong-Hai Lee, and Yu-Sheng Lin

Stroke Center and Department of Neurology (C.-H.L., T.-H.L.), Chang Gung Memorial Hospital, Linkou Medical Center, Chang Gung University College of Medicine, Taoyuan, Taiwan 61363; Division of Cardiology (T.-H.C., M.-J.H., W.-J.C.), Department of Internal Medicine, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Keelung, Taiwan 61363; Division of Cardiology (M.-S.L.), Department of Internal Medicine, Chang Gung Memorial Hospital, Yunlin, Taiwan 61363; and Department of Medicine (C.-M.C., Y.-S.L.), College of Medicine, Chang Gung University, Taoyuan, and Division of Cardiology, Department of Internal Medicine, Chang Gung Memorial Hospital, Chiayi, Taiwan 61363

Context: Statin is the main lipid-lowering therapy for type 2 diabetes mellitus patients. Recent evidence suggested the cardiovascular protective effects of ezetimibe-simvastatin in acute coronary syndrome patients.

Objective: To investigate the effect of ezetimibe-simvastatin combination therapy on stroke prevention among diabetic stroke patients.

Design, Setting, Participants, and Outcome Measures: This is a retrospective cohort study. Between March 1, 2009 and December 31, 2011, all patients with type 2 diabetes mellitus in Taiwan's National Health Insurance Research Database were screened. Those admitted for ischemic stroke (IS) were recruited and divided into 10-mg ezetimibe-20-mg simvastatin (EZ-SIM), 40-mg atorvastatin (ATOR), and 20-mg simvastatin (SIM) groups for further analyses. The primary outcomes were IS, myocardial infarction, and death from any cause. Patients were followed from index hospitalization to the date of death, loss of follow-up, or study termination.

Results: During the 34-month follow-up period, the risk of recurrent IS in the SIM group was higher than that of the ATOR (hazard ratio [HR], 2.03; 95% confidence interval [CI], 1.46–2.82) and EZ-SIM (HR, 1.69; 95% CI, 1.14–2.50) groups. The risk of recurrent IS was not significantly lower in the EZ-SIM compared with the ATOR group (HR, 1.20; 95% CI, 0.85–1.69). The incidence of composite endpoint was highest in the SIM group (28.2%), followed by the ATOR (16.1%) and EZ-SIM (15.4%) groups. The multivariate adjusted survival curve showed lower trends of recurrent IS in the EZ-SIM and ATOR groups compared with the SIM group.

Conclusions: High-potency lipid-lowering therapy effectively reduces the risk of recurrent IS in diabetic patients regardless of ATOR or EZ-SIM combination therapy. (*J Clin Endocrinol Metab* **101: 2994–3001, 2016**)

Stroke is a major cause of death and disability worldwide. Secondary prevention of ischemic stroke (IS) is important and risk factor modifications are crucial for reducing recurrence (1). Treatment strategies of cholesterol control may be updated as clinical evidence increases (2, 3). The strategy of "treat-to-target" has changed to

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* C.-H.L. and T.-H.C. contributed equally to this work.

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; ATOR, 40-mg atorvastatin; CAD, coronary artery disease; CI, confidence interval; CVA, cerebrovascular accident; DM, diabetes mellitus; DPP-4, dipeptidyl peptidase-4; EZ-SIM, 10-mg ezetimibe-20-mg simvastatin; HR, hazard ratio; HS, hemorrhagic stroke; IMPROVE-IT, IMProved Reduction of Outcomes: VYTORIN Efficacy International Trial; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; MI, myocardial infarction; NHI, National Health Insurance; NHIRD, NHI Research Database; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial.

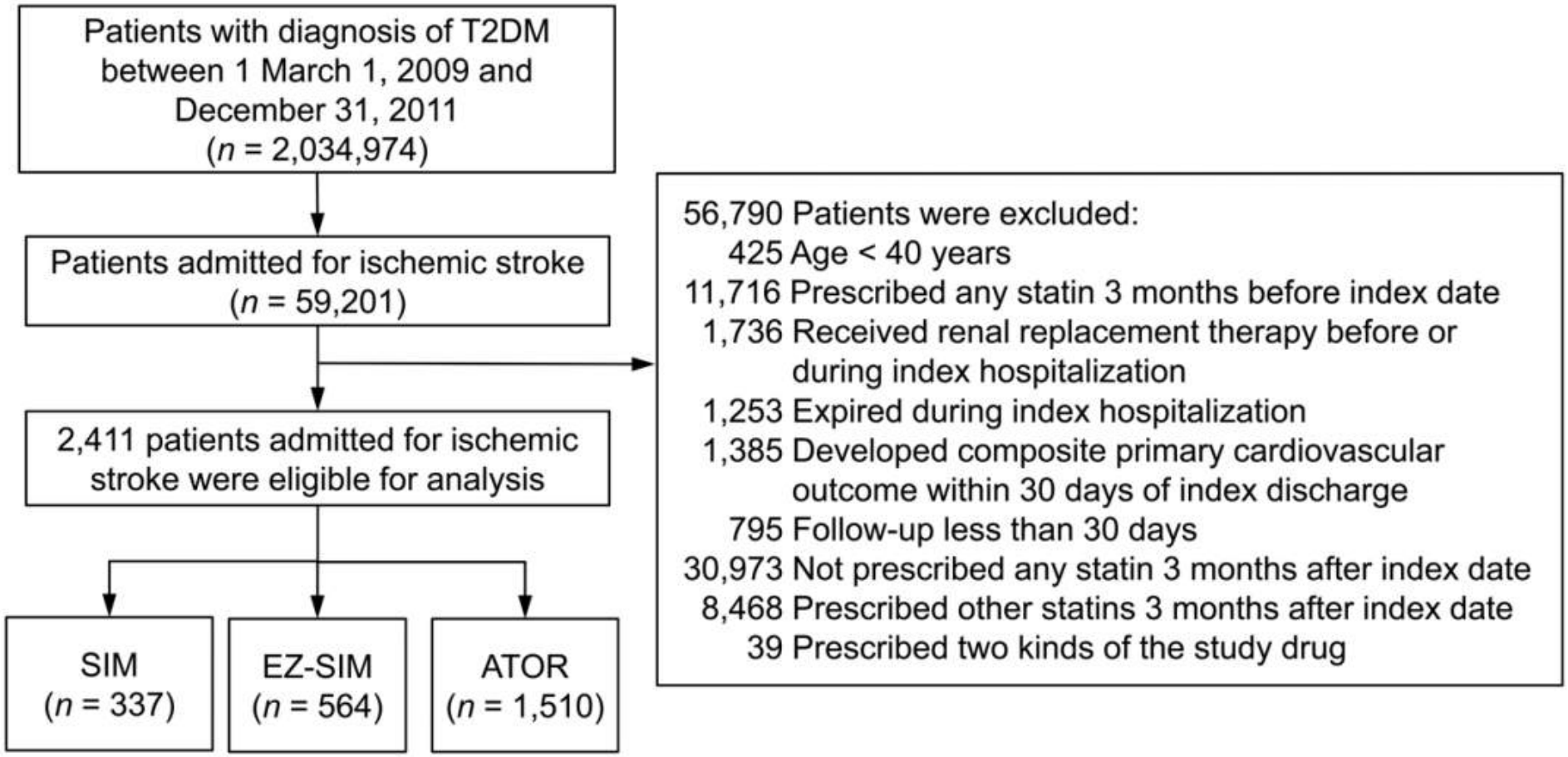
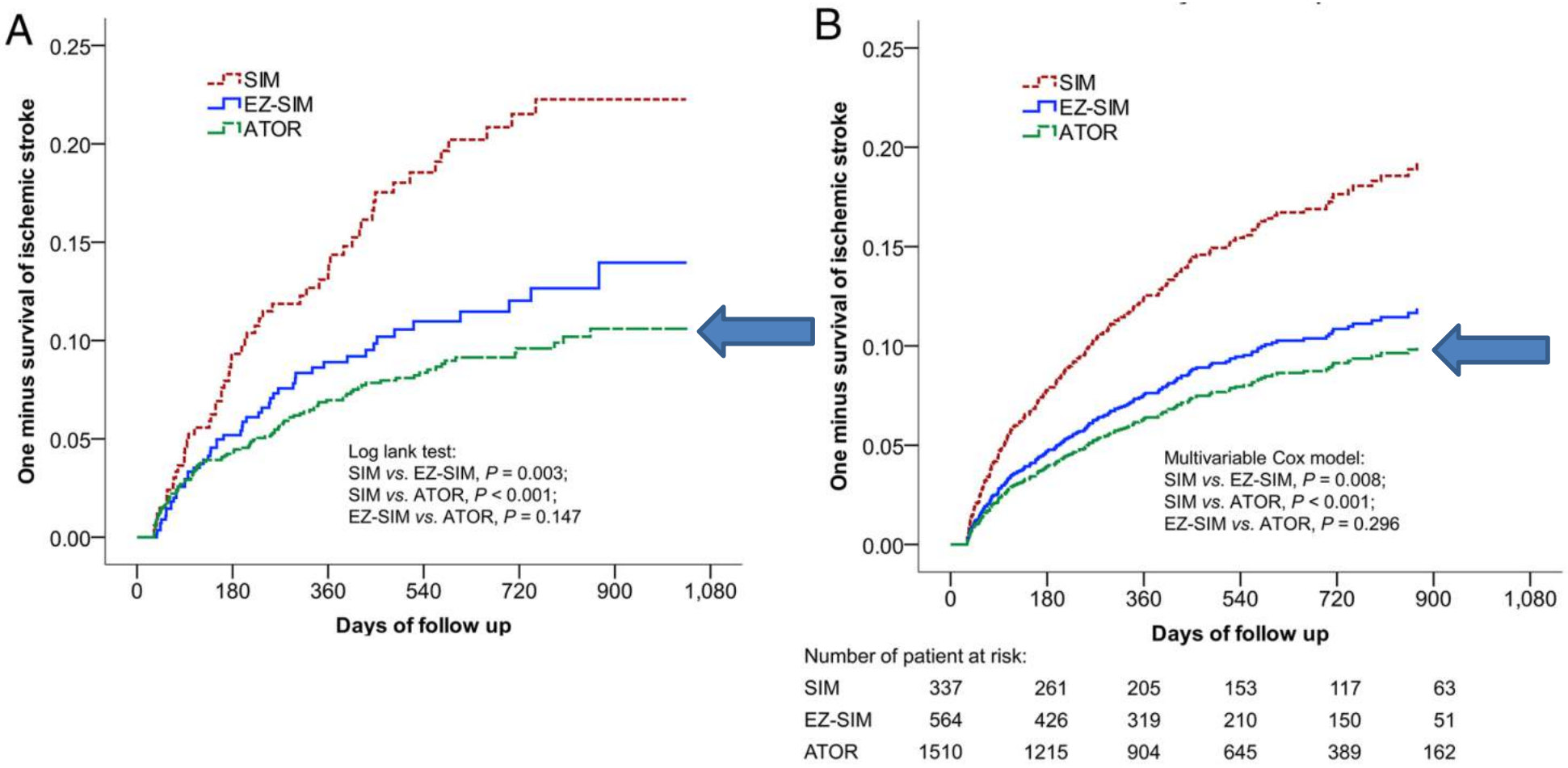


Figure 1. Flow chart of the study patient selection. Patients with T2DM admitted for IS were included after relevant exclusions and were further divided into 3 groups according to the prescribed LLT. T2DM, type 2 DM.



Number of patient at risk:

SIM	337	261	205	153	117	63
EZ-SIM	564	426	319	210	150	51
ATOR	1510	1215	904	645	389	162

Combination therapy is better than monotherapy because of more LDL reduction

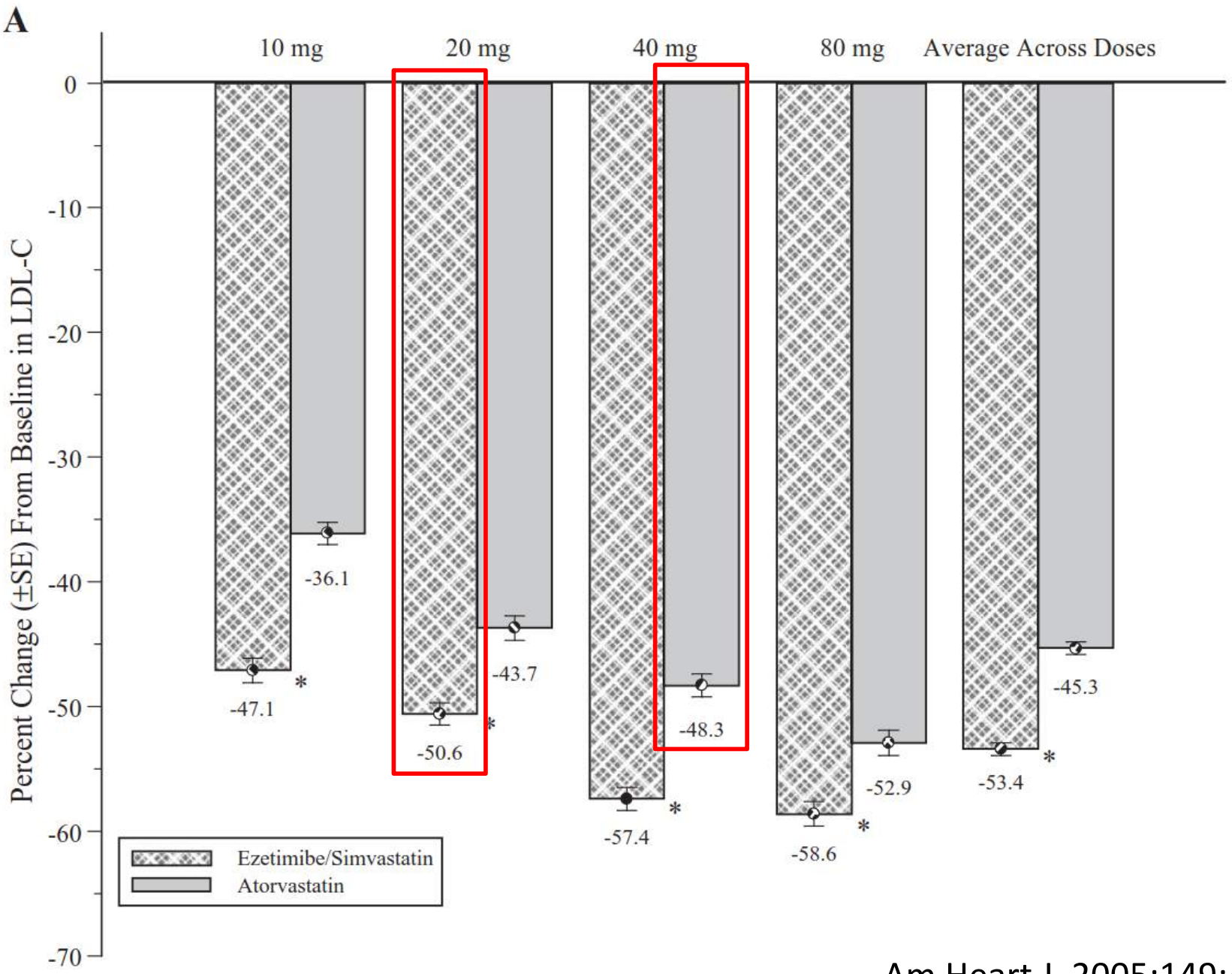
If same LDL reduction in ACS?

Exposure of study statin

In study period, participants received statin based on the NHI program lipid-lowering guidelines. Patients with elevated cholesterol levels (low-density lipoprotein cholesterol [LDL-C] level >130 mg/dL) received NHI-paid LLT in either study cohorts and they would keep their LLT when their LDL-C levels reached the therapeutic goal. The treatment goal was less than 100 mg/dL. Crossover use of LLT and dosage adjustments were controlled. Therefore, patients who had any statin prescription 3 months before index hospitalization, nonstudy statin after index hospitalization, and either other study cohort statin or nonstudy cohort statin were not enrolled.

Eligible patients were further divided into 3 groups according to the prescribed LLT including, 1) EZ-SIM, 2) ATOR, and 3) SIM. The ATOR and SIM groups were categorized as high-intensity and moderate-intensity statin therapy respectively. The LDL-C lowering effects of EZ-SIM are theoretically similar to ATOR (4, 24), and could also be categorized as high-potency LLT (25). The first hospitalization for IS throughout the study period was considered the index hospitalization. The follow-up period was based on the index hospitalization to date of death, loss to follow-up, or December 31, 2011.

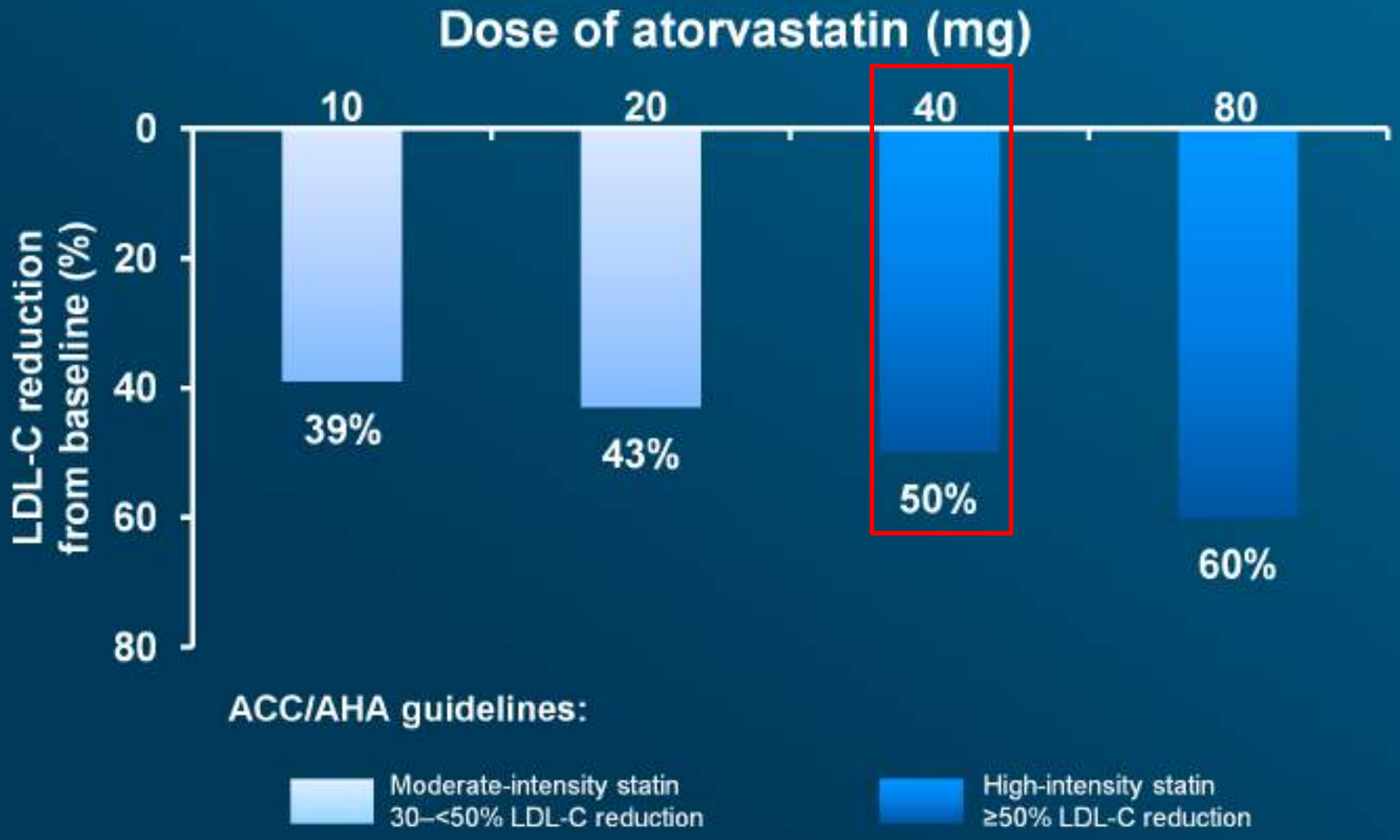
atorvastatin (10, 20, 40, or 80 mg) or to ezetimibe/simvastatin (10/10, 10/20, 10/40, or 10/80 mg)



Am Heart J. 2005;149:464 – 473.

Increasing doses of atorvastatin produce increasing LDL-C reductions by 39% to 60%

Pooled results from two studies

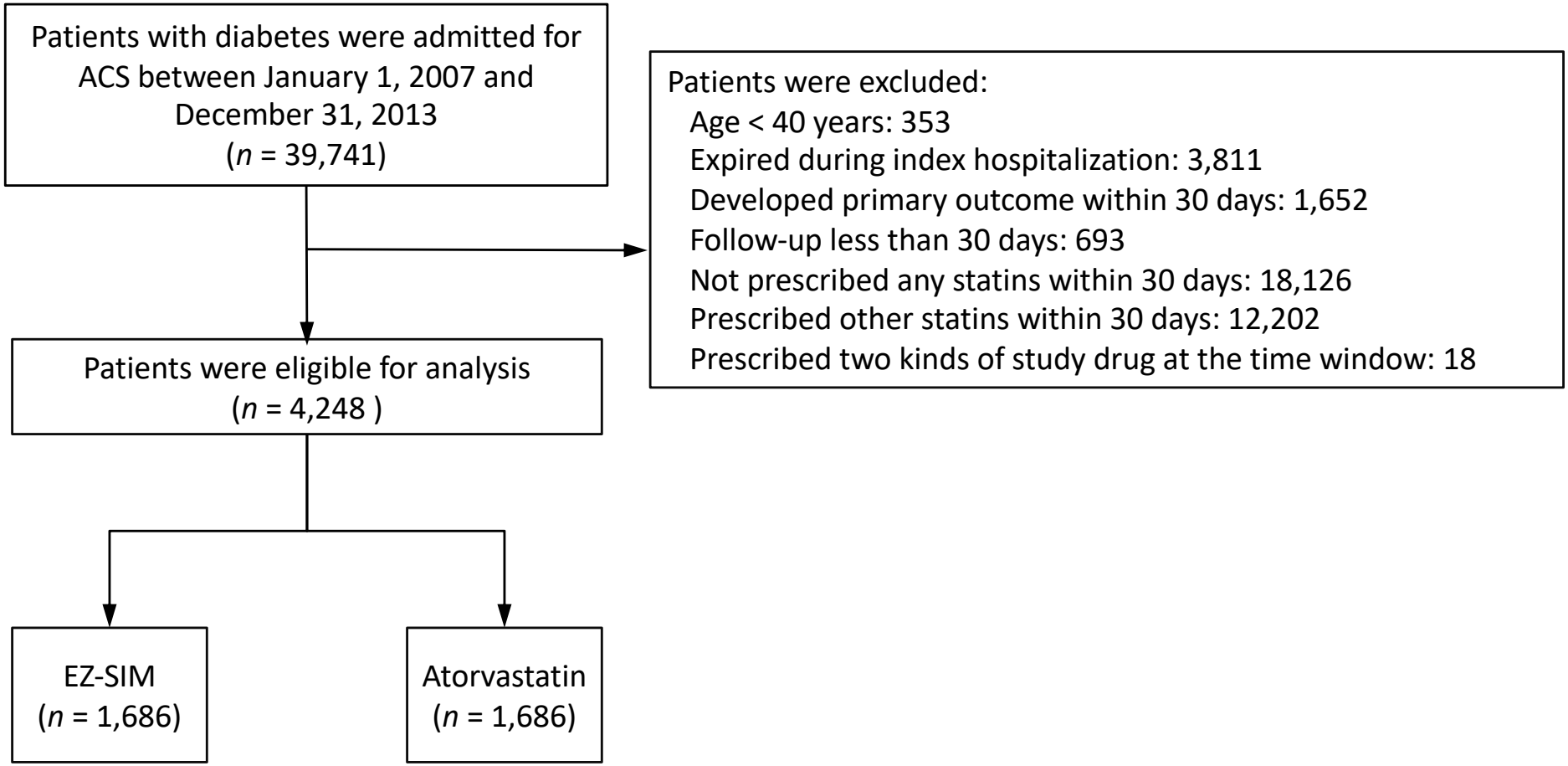


Lipitor Highlights of US Prescribing Information, 2013

Same LDL reduction in ACS: Simvastatin 20mg/eztimibe 10mg V.S atovastation 40mg

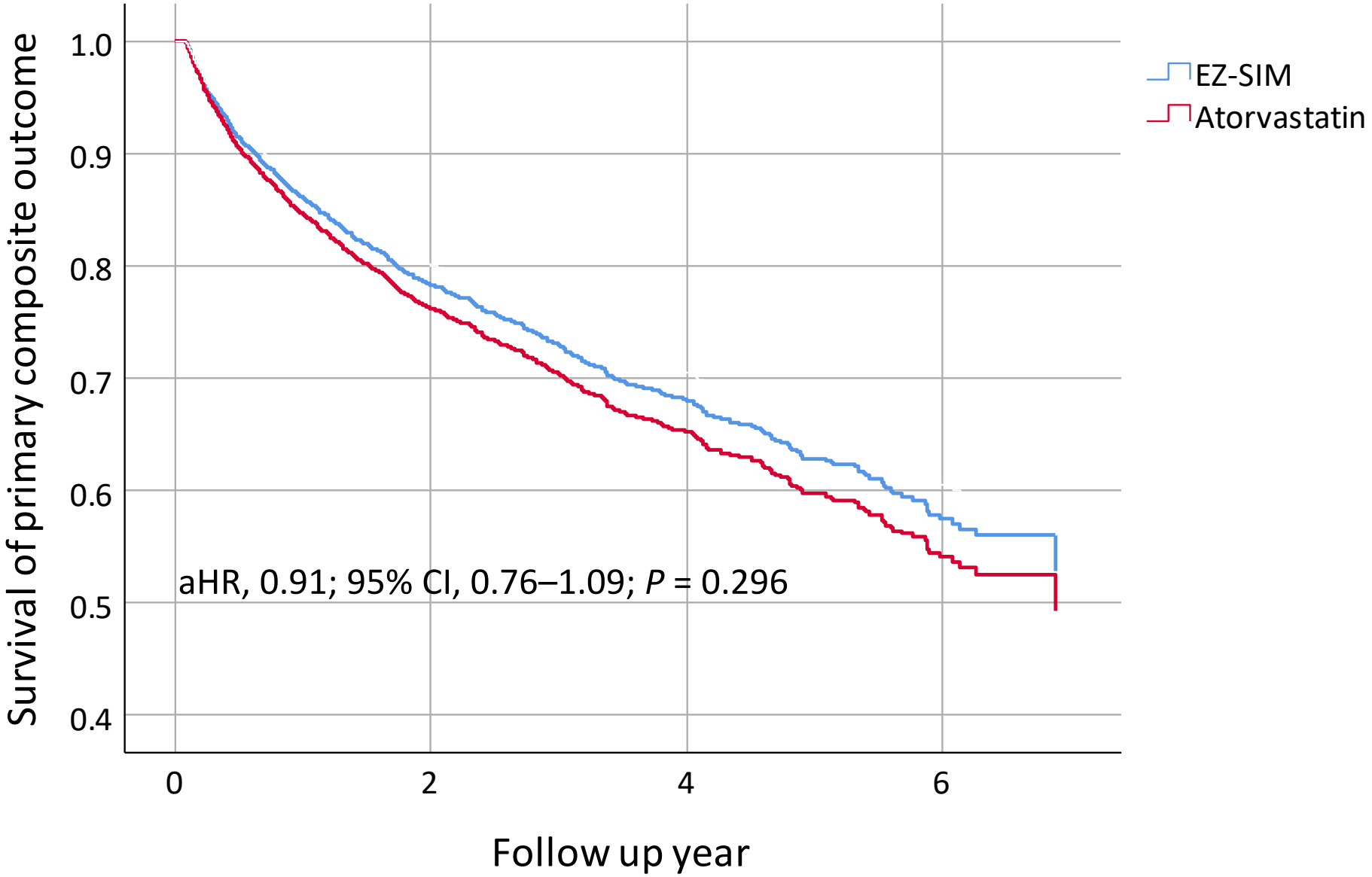
Hypothesis

- Atovastatin 40mg and simvastatin 20mg/eztimibe 10mg have similar LDL reduction ◦
- Inclusion: All ACS patient with T2DM in Taiwan
- Outcome: non-fatal MI, stroke, CV death.

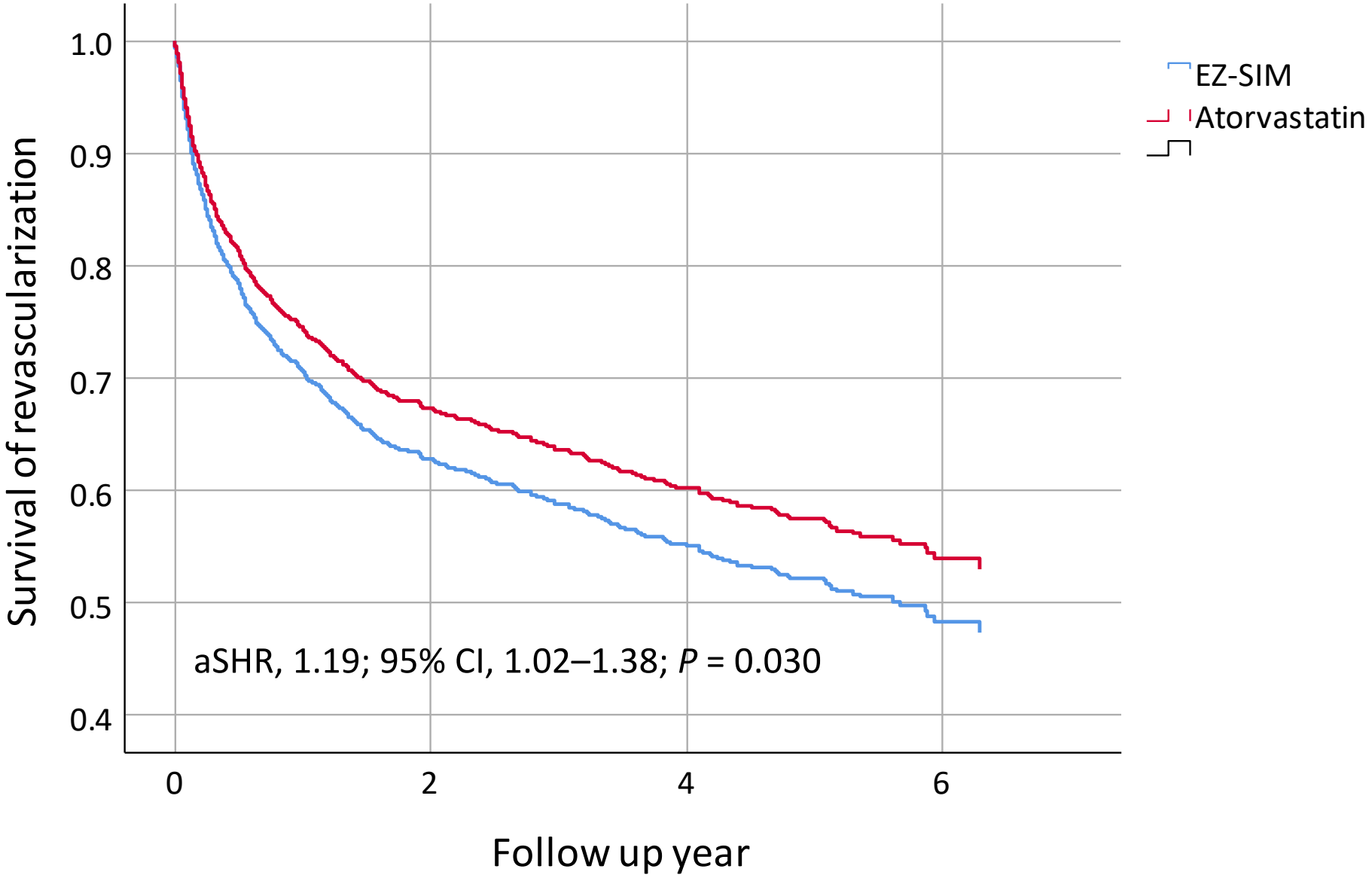

Patients with diabetes were admitted for ACS between January 1, 2007 and December 31, 2013 (n = 39,741)
Patients were excluded:
Age < 40 years: 353
Expired during index hospitalization: 3,811
Developed primary outcome within 30 days: 1,652
Follow-up less than 30 days: 693
Not prescribed any statins within 30 days: 18,126
Prescribed other statins within 30 days: 12,202
Prescribed two kinds of study drug at the time window: 18
Patients were eligible for analysis (n = 4,248)
EZ-SIM (n = 1,686)
Atorvastatin (n = 1,686)

Variable	Atorvastatin (*n* = 1,686)	EZ-SIM (*n* = 1,686)	HR or SHR (95% CI)	*P* value
Primary composite outcomes†	422 (25.0)	398 (23.6)	1.09 (0.95–1.25)	0.207
Components of primary outcome				
Non-fatal myocardial infarction	97 (5.8)	100 (5.9)	0.98 (0.74–1.29)	0.861
Non-fatal stroke	225 (13.3)	200 (11.9)	1.15 (0.96–1.38)	0.134
CV death	160 (9.5)	152 (9.0)	1.06 (0.85–1.32)	0.596
Other CV outcomes				
Myocardial infarction	109 (6.5)	110 (6.5)	1.00 (0.77–1.30)	0.991
Stroke	235 (13.9)	209 (12.4)	1.15 (0.96–1.38)	0.122
Ischemic stroke	224 (13.3)	194 (11.5)	1.18 (0.98–1.42)	0.076
Hemorrhagic stroke	15 (0.9)	21 (1.2)	0.72 (0.38–1.38)	0.323
All-cause mortality	292 (17.3)	273 (16.2)	1.09 (0.92–1.28)	0.324
Hospitalization for heart failure	145 (8.6)	138 (8.2)	1.05 (0.84–1.32)	0.676
Coronary intervention	239 (14.2)	292 (17.3)	0.81 (0.69–0.95)	0.010
PCI	215 (12.8)	261 (15.5)	0.82 (0.69–0.97)	0.020
CABG	28 (1.7)	45 (2.7)	0.62 (0.40–0.97)	0.038
Safety outcomes				
New diagnosed dementia	85 (5.0)	87 (5.2)	0.98 (0.73–1.33)	0.910
Rhabdomyolysis	5 (0.3)	8 (0.5)	0.63 (0.21–1.91)	0.411
Acute hepatitis	10 (0.6)	4 (0.2)	2.52 (0.79–8.02)	0.118
New diagnosed malignancy	73 (4.3)	65 (3.9)	1.14 (0.82–1.57)	0.437

Non-fatal MI, Stroke, CV death



ACS+PCI+CABG


Survival of revascularization
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0
2
4
6
Follow up year
EZ-SIM
Atorvastatin
aSHR, 1.19; 95% CI, 1.02–1.38; P = 0.030

Even in same LDL reduction, high intensity statin alone had modest CV benefit than ezt/simva

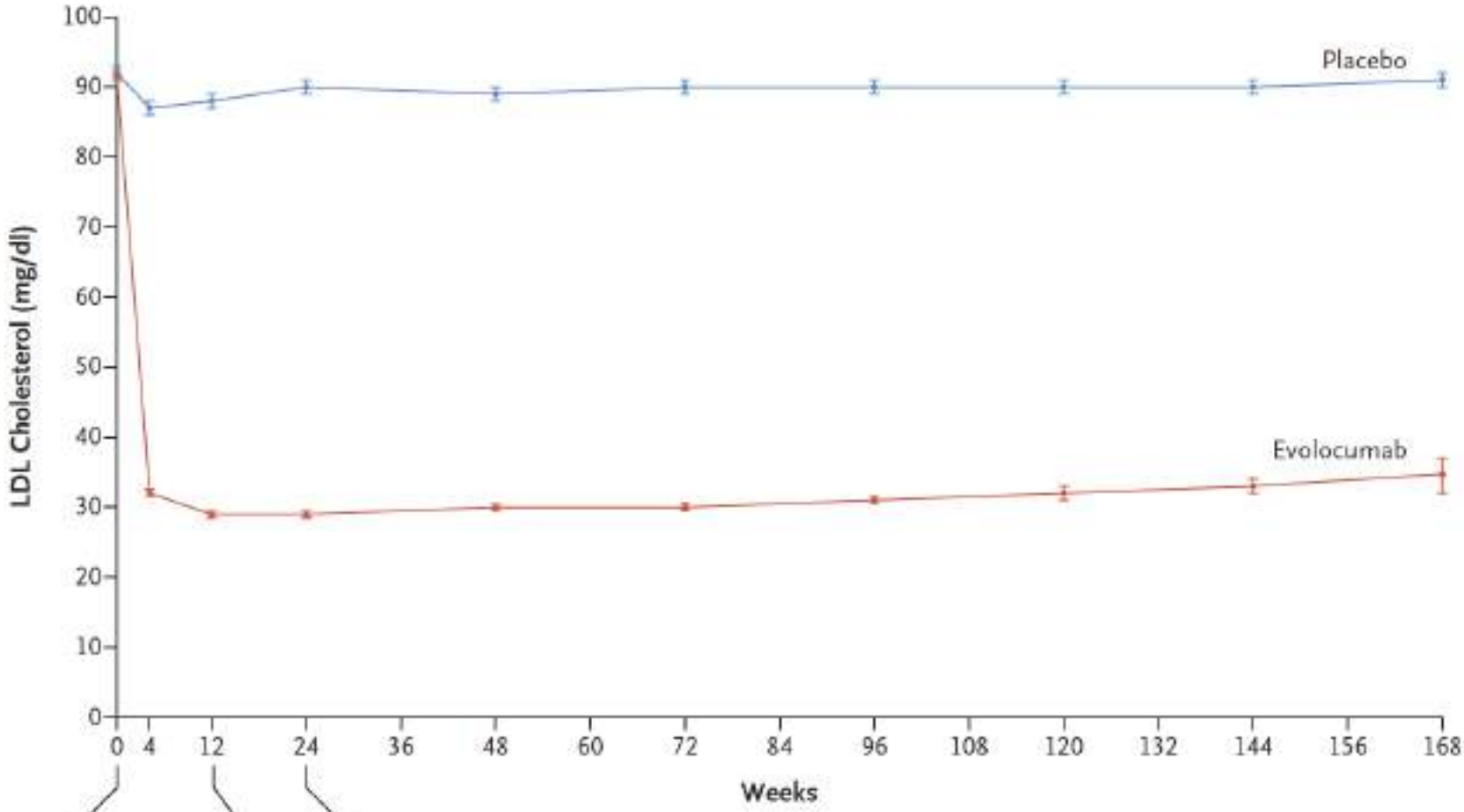
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 4, 2017 VOL. 376 NO. 18

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

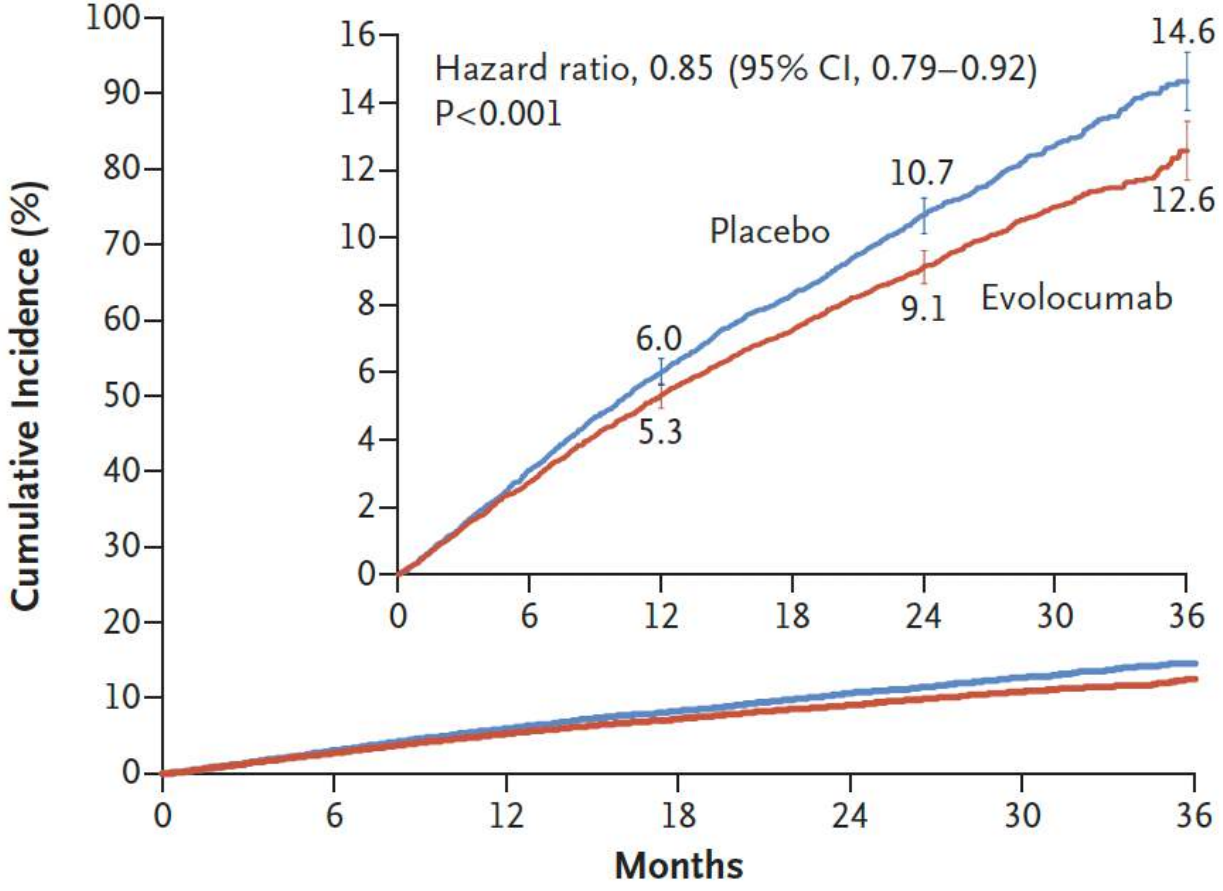
Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

Characteristics	Evolocumab (N=13,784)	Placebo (N=13,780)
Age — yr	62.5±9.1	62.5±8.9
Male sex — no. (%)	10,397 (75.4)	10,398 (75.5)
White race — no. (%)†	11,748 (85.2)	11,710 (85.0)
Weight — kg	85.0±17.3	85.5±17.4
Region		
North America	2,287 (16.6)	2,284 (16.6)
Europe	8,666 (62.9)	8,669 (62.9)
Latin America	913 (6.6)	910 (6.6)
Asia Pacific and South Africa	1,918 (13.9)	1,917 (13.9)
Type of atherosclerosis‡		
Myocardial infarction — no. (%)	11,145 (80.9)	11,206 (81.3)
Median time from most recent previous myocardial infarction (IQR) — yr	3.4 (1.0–7.4)	3.3 (0.9–7.7)
Nonhemorrhagic stroke	2686 (19.5)	2651 (19.2)
Median time from most recent previous stroke (IQR) — yr	3.2 (1.1–7.1)	3.3 (1.1–7.3)
Peripheral artery disease — no. (%)	1,858 (13.5)	1,784 (12.9)
Cardiovascular risk factors		
Hypertension — no./total no. (%)	11,045/13,784 (80.1)	11,039/13,779 (80.1)
Diabetes mellitus — no. (%)	5,054 (36.7)	5,027 (36.5)
Current cigarette use — no./total no. (%)	3854/13,783 (28.0)	3923/13,779 (28.5)
Statin use — no. (%)§		
High intensity	9,585 (69.5)	9,518 (69.1)
Moderate intensity	4,161 (30.2)	4,231 (30.7)
Low intensity, unknown intensity, or no data	38 (0.3)	31 (0.2)
Ezetimibe — no. (%)	726 (5.3)	714 (5.2)



No. at Risk										
Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6926	3352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6958	3323	768
Absolute difference (mg/dl)		54	58	57	56	55	54	52	53	50
Percentage difference		57	61	61	59	58	57	55	56	54
P value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

A Primary Efficacy End Point



No. at Risk

Placebo	13,780	13,278	12,825	11,871	7610	3690	686
Evolocumab	13,784	13,351	12,939	12,070	7771	3746	689

CONCLUSIONS

In our trial, inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 30 mg per deciliter (0.78 mmol per liter) and reduced the risk of cardiovascular events. These findings show that patients with atherosclerotic cardiovascular disease benefit from lowering of LDL cholesterol levels below current targets. (Funded by Amgen; FOURIER ClinicalTrials.gov number, NCT01764633.)

Conclusion

- Statin monotherapy is not enough for most patient with high CV risks
- Combination therapy(Atovastatin/eztimibe) proved 53% LDL reduction at least.
- Combination therapy(Atovastatin/eztimibe) did reduce atheroma burden in high CV risk patient

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**

2018/11/28 New Cholesterol Guidelines Make Room for Non-Statin Therapy and CAC Screening | tctmd.com

tctMD/the heart beat

NEWS | AHA 2018

New Cholesterol Guidelines Make Room for Non-Statin Therapy and CAC Screening

While the guidelines don't recommend a specific target for treatment, they do suggest additional therapy in high-risk patients with LDL-C 70 mg/dL or higher.

By Michael O'Riordan November 10, 2018

2018 AHA Cholesterol Guideline

- LOWER IS BETTER
- RISK ASSESSMENT – Smoking, high blood pressure, cholesterol, diabetes…
- (static.heart.org/riskcalc/app/index.html#!/baseline-risk)
- Coronary Artery Calcium test (CAC test) – for patients ages 40 - 75

Top 10 Take-Home Messages

2018 Cholesterol Guidelines

AMERICAN COLLEGE of CARDIOLOGY

American Heart Association.

Top 10 Take Home Messages

1. In all individuals, emphasize a heart-healthy lifestyle across the life course.

2. In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.

3. In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L)to consider addition of nonstatins to statin therapy.

4. In patients with severe primary hypercholesterolemia (LDL-C level ≥ 190 mg/dL[≥4.9 mmol/L])without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk.

5. In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk.

Top 10 Take Home Messages

6. In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.

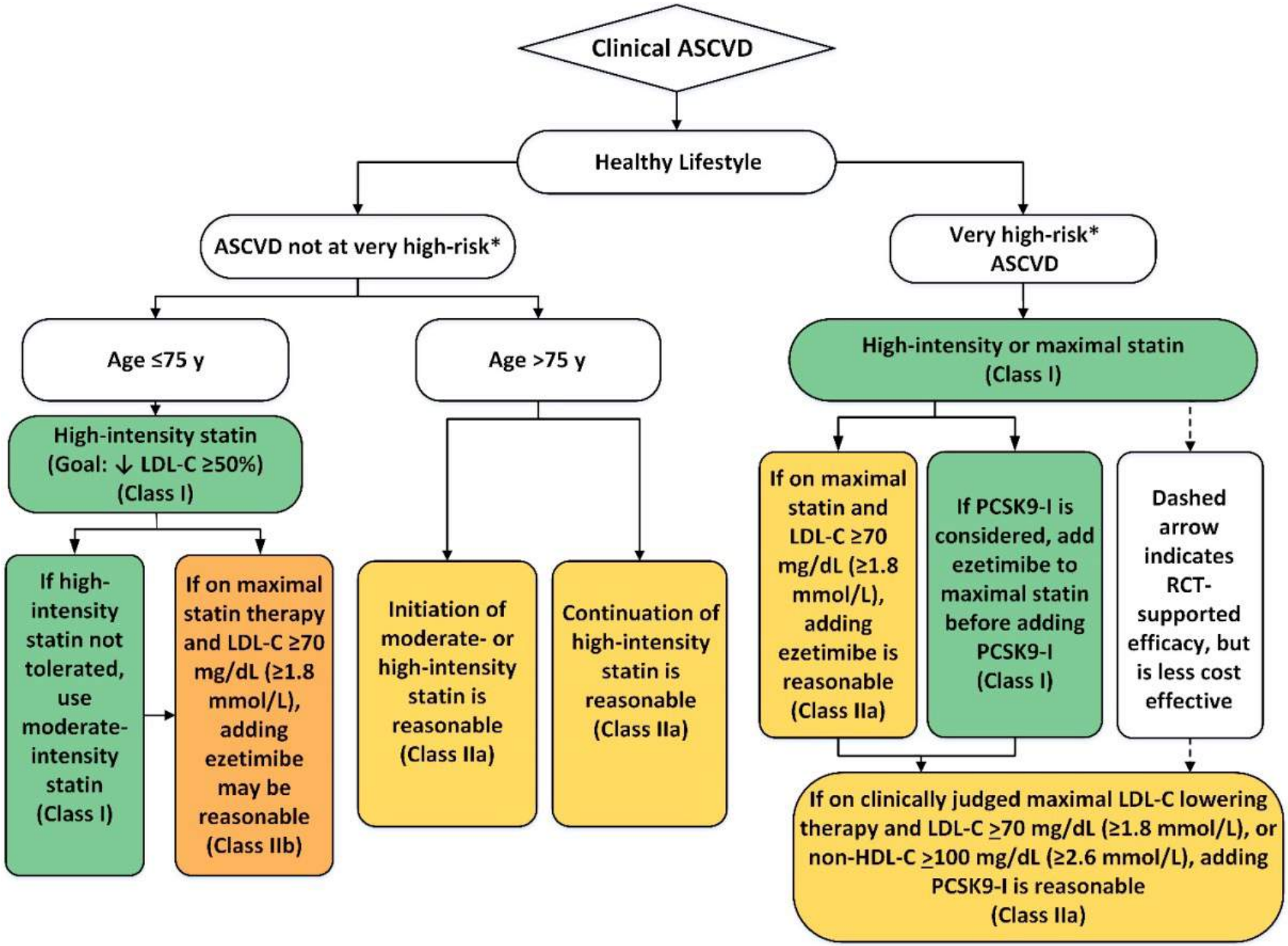
7. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.

8. In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy.

9. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL-189 mg/dL (≥1.8-4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.

10. Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.

Secondary Prevention in Patients With Clinical ASCVD



Very High-Risk* of Future ASCVD Events

Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation (S4.1-39))

High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2) (S4.1-15, S4.1-17)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

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 ✓ / β-blocker ✓ / Thiazide ✓

If not at goal (2–3 months)

Add calcium channel blocker, β-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

 DOI 10.4158/EP161682.CS

2018 ADA guideline on lipid management in patients with diabetes

2015

Table 8.1—Recommendations for statin treatment in people with diabetes

Age	Risk factors	Recommended statin dose*	Monitoring with lipid panel
<40 years	None	None	Annually or as needed to monitor for adherence
	CVD risk factor(s)**	Moderate or high	
	Overt CVD***	High	
40–75 years	None	Moderate	As needed to monitor adherence
	CVD risk factors	High	
	Overt CVD	High	
>75 years	None	Moderate	As needed to monitor adherence
	CVD risk factors	Moderate or high	
	Overt CVD	High	

*In addition to lifestyle therapy.
**CVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, and overweight and obesity.
***Overt CVD includes those with previous cardiovascular events or acute coronary syndromes.

2016

Table 8.1—Recommendations for statin and combination treatment in people with diabetes

Age	Risk factors	Recommended statin intensity*
<40 years	None	None
	ASCVD risk factor(s)**	Moderate or high
	ASCVD	High
40–75 years	None	Moderate
	ASCVD risk factors	High
	ASCVD	High
	ACS and LDL cholesterol >50 mg/dL (1.3 mmol/L) in patients who cannot tolerate high-dose statins	Moderate plus ezetimibe
>75 years	None	Moderate
	ASCVD risk factors	Moderate or high
	ASCVD	High
	ACS and LDL cholesterol >50 mg/dL (1.3 mmol/L) in patients who cannot tolerate high-dose statins	Moderate plus ezetimibe

*In addition to lifestyle therapy.
**ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, overweight and obesity, and family history of premature ASCVD.

2018

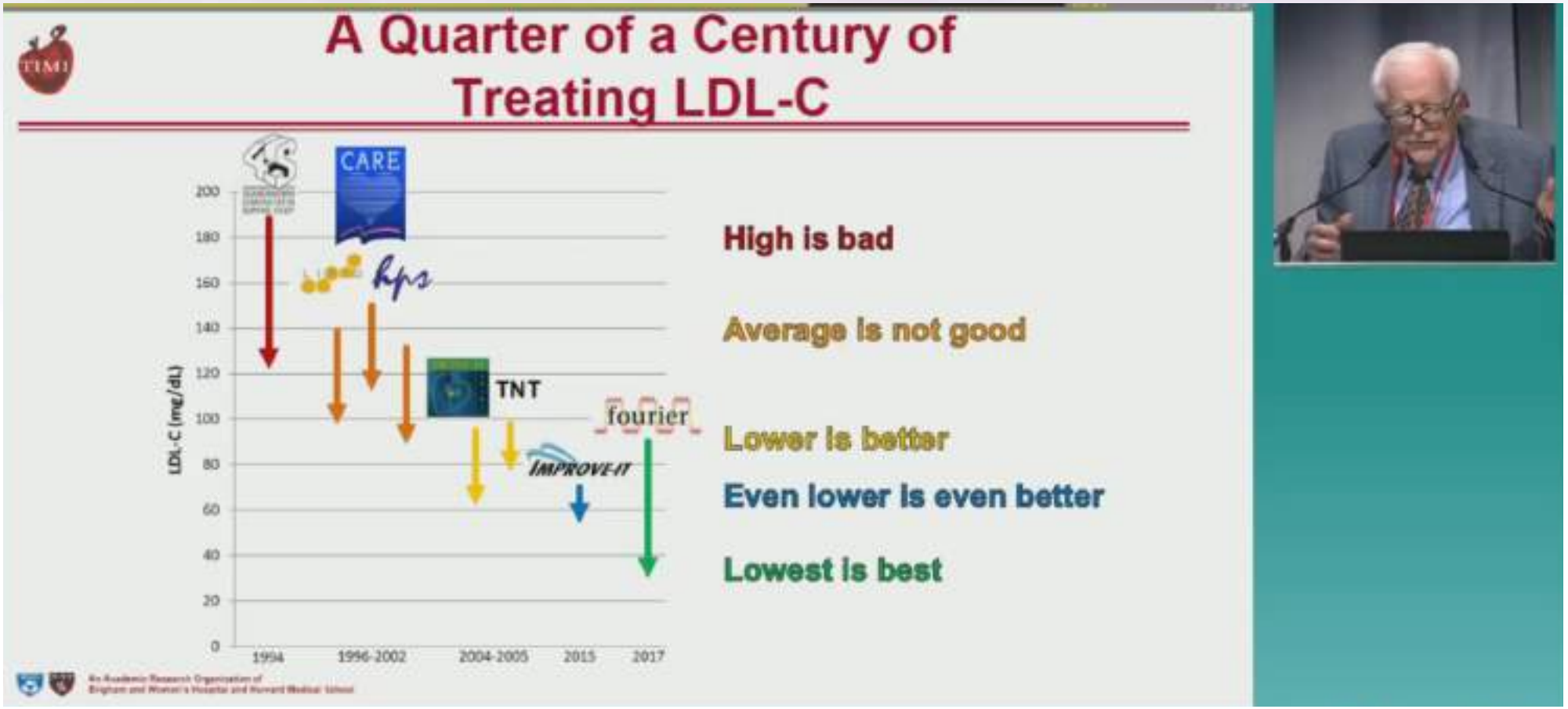
Table 9.2—Recommendations for statin and combination treatment in adults with diabetes

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)

1. Ho LT, et al. PLoS C

Prof Eugene Braunwald from Havard Medical School:

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



ESC
European Society of Cardiology

2017 Taiwan Lipid Guidelines

Treatment Target of LDL-C for High Risk Patients

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

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

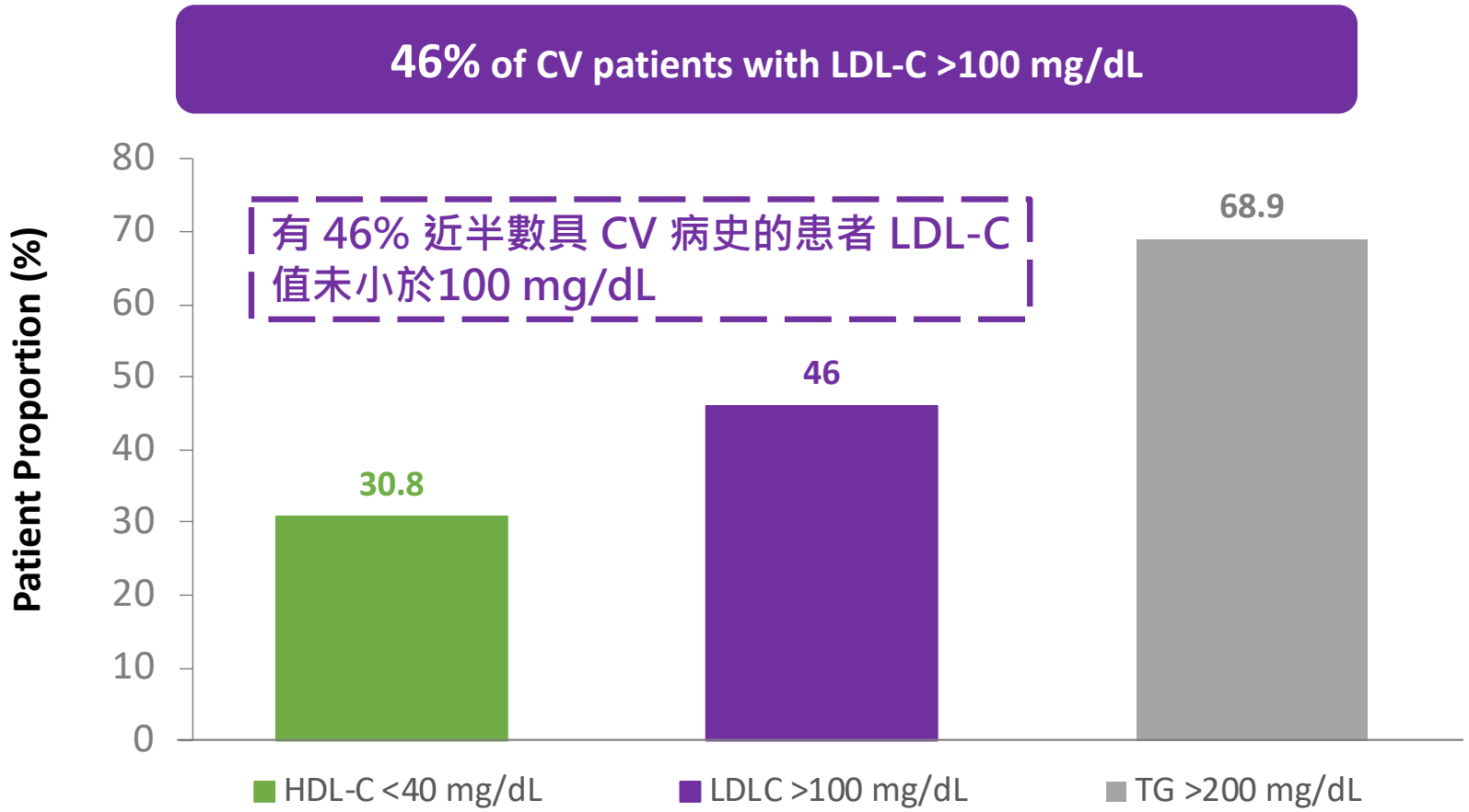
Items evaluated at baseline, and every year thereafter:

- 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.

DYSIS II ACS Study: Contemporary data on treatment practices for low-density lipoprotein cholesterol in 3,867 patients who had suffered an acute coronary syndrome across the world

Study Design

N=3,876
Longitudinal observation
Follow-up for 4 months

Patient Criteria:

Patients were hospitalized for an acute coronary syndrome (ACS)

Worldwide Survey
Real World Data

Objectives & Data Collection:

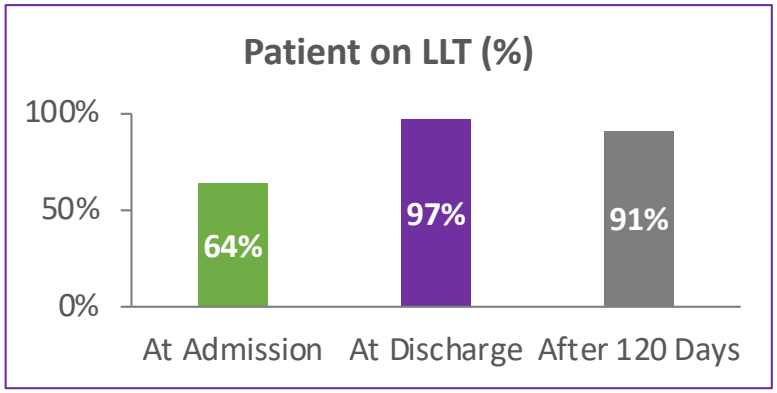
- Comparison of lipid lowering therapies administered in patients post acute coronary syndrome, as well as LDL-C target achievement
- Evaluations were performed at the time of admission and again 120 ±15 days following the date of admission (the follow-up time point)

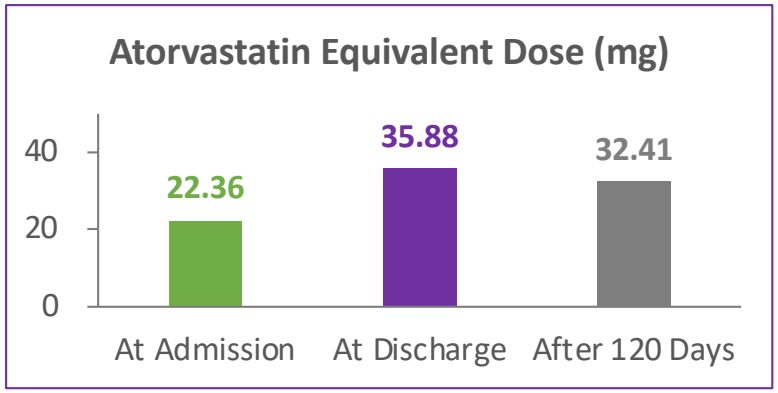
1. Gitt AK, et al. Data Brief. 2017 Nov 14;16:369-75.

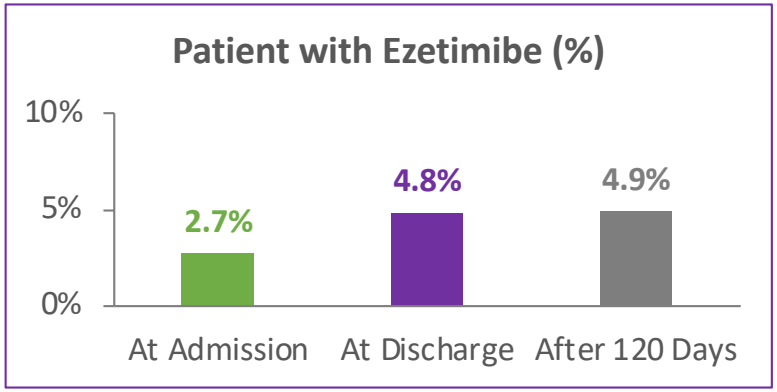
DYSIS II ACS Study

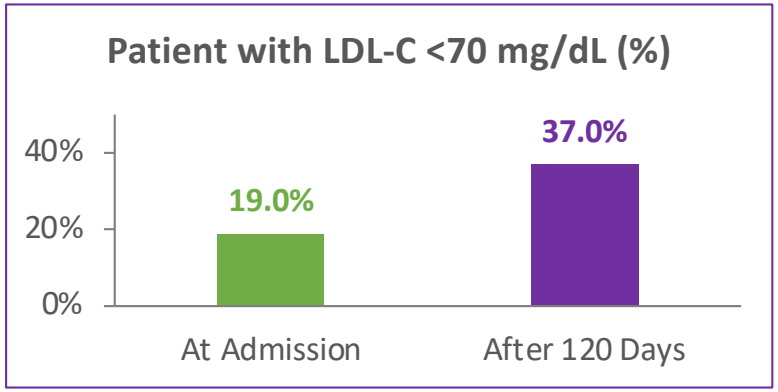
Only One-Third of Patients Achieved the LDL-C Target after An ACS Event

LOW in statin dose, ezetimibe combination, and achievement of LDL-C target









1. Gitt AK, et al. Data Brief. 2017 Nov 14;16:369-75.

LDL-C ATTAINMENT RATE AMONG TREATED PATIENTS WITH STABLE CHD: THE DYSLIPIDEMIA INTERNATIONAL STUDY

(DYSIS) II TAIWAN: identify unmet needs in lipid target achievements among stable CHD patients in Taiwan

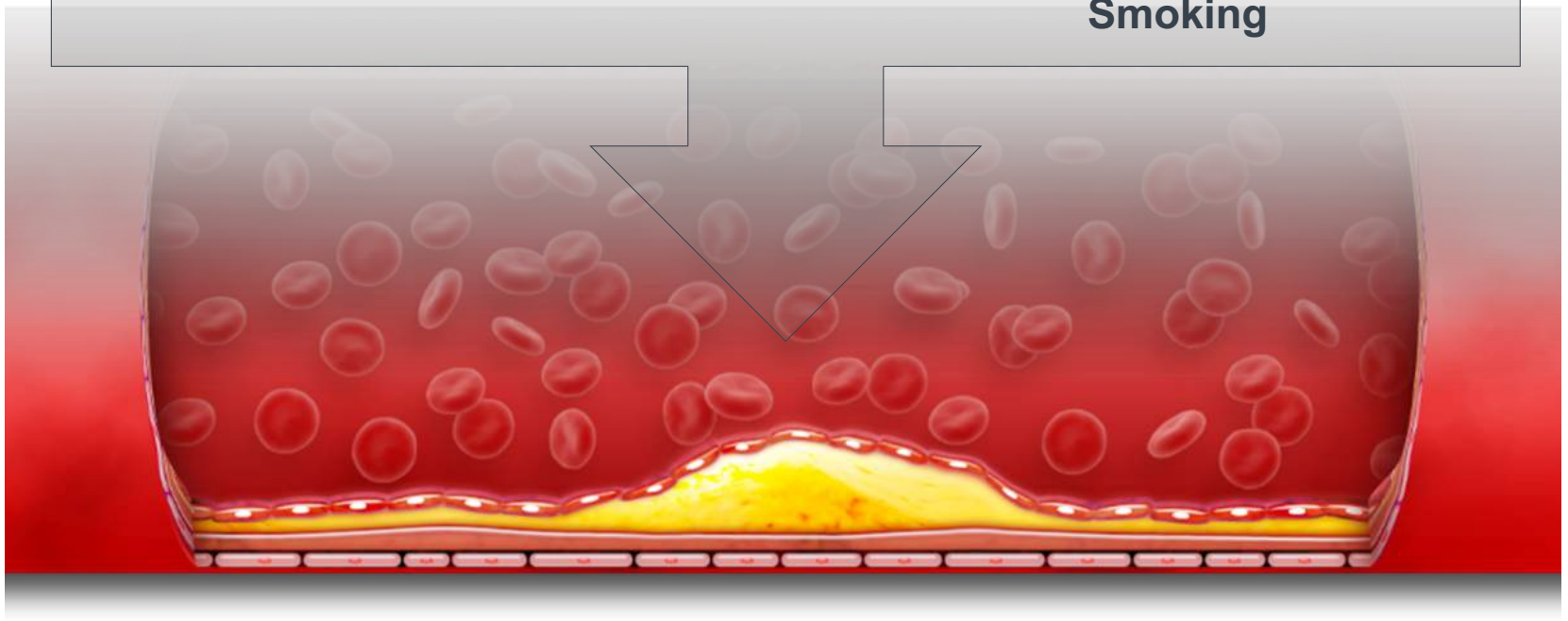
在chronic heart disease的台灣病人中，
只有20.7%的病人達標LDL-C<70mg/dL

- *Population:* *800 stable* ***CHD patients*** with past acute coronary syndrome (ACS) events >3 months before enrollment), full lipid profile available 0-12 months prior to enrollment, on LLT ≥3 months or not treated at all were recruited (recruitment of patients in 2013-2014).
- *Methods:* DYSIS II is a multicenter, observational cross-sectional study conducted in 14 Taiwan hospitals.
- *Results:* 687 patients were on LLT, with ***only 20.7% achieving the <70 mg/dl LDL-C target***. ***84.7%*** of treated patients were on statin monotherapy and ***11.9%*** received ezetimibe plus statin.

DYSIS II

Multiple Factors May Contribute to Coronary Heart Disease Risk[1]

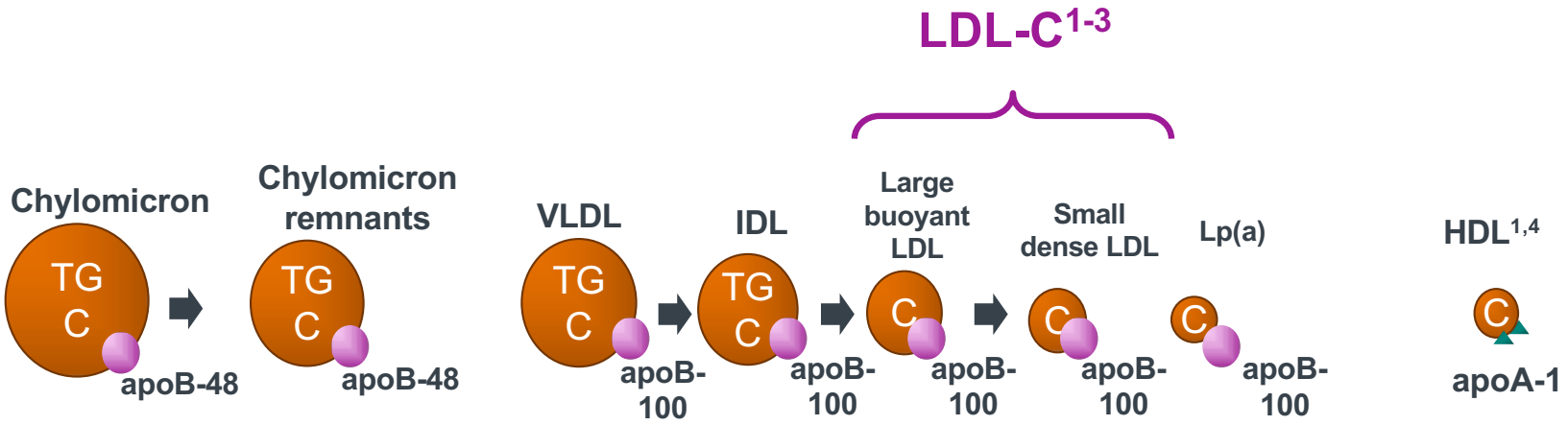
NONMODIFIABLE	MODIFIABLE
Aging	Atherogenic Diet
Gender	Elevated Blood Pressure
Family History	Diabetes
	Hyperlipidemia
	Obesity
	Physical Inactivity
	Smoking



1. NCEP ATP III Expert Panel. *Circulation*. 2002;106:3143–3421.

LDL-C Is a Risk Factor for CHD

- Multiple lines of evidence (animal studies, laboratory investigations, epidemiology, genetic forms of hypercholesterolemia, and controlled trials) indicate a strong causal association between elevated LDL-C and CHD[1]

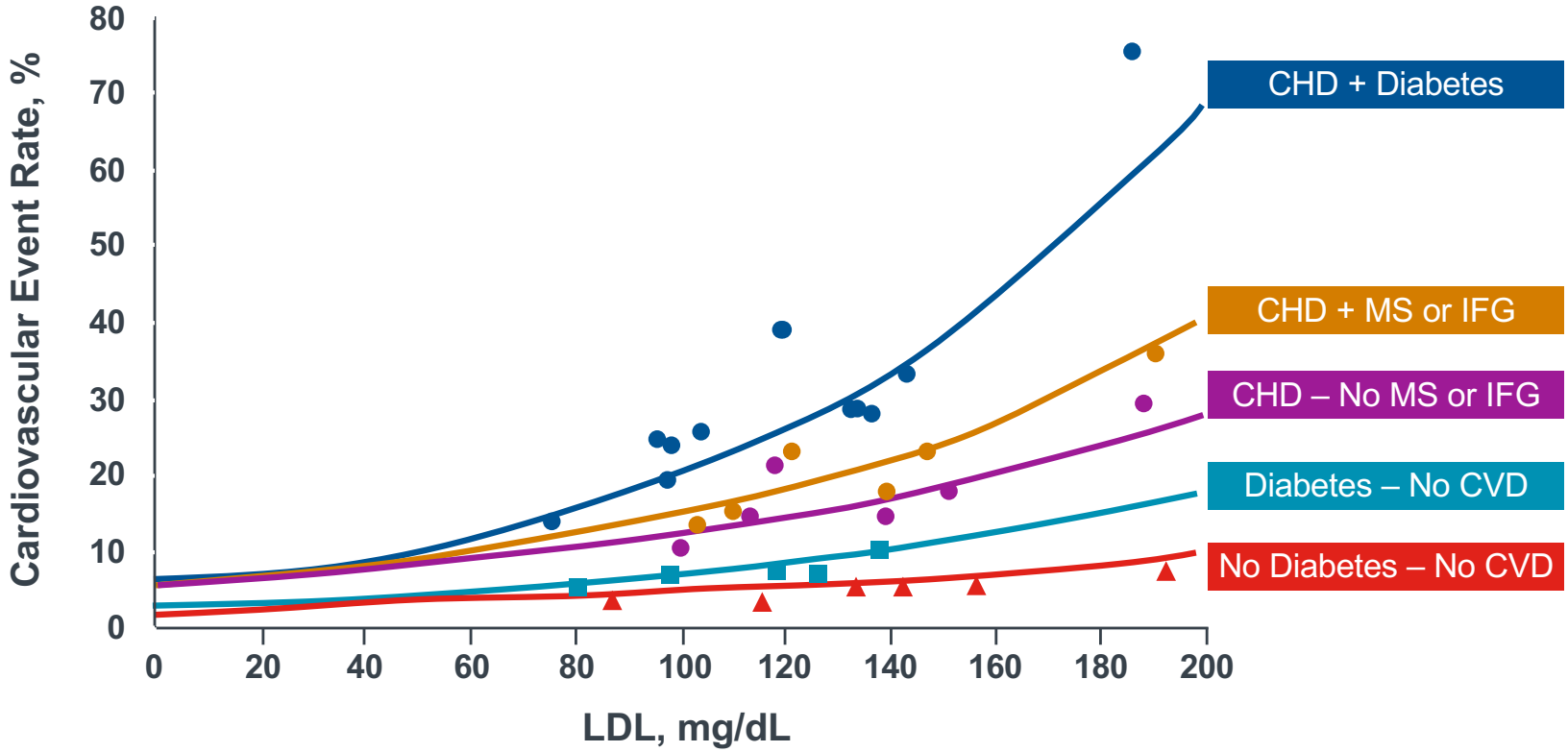


Adapted with permission from Walldius G et al.[5]

CHD = coronary heart disease; TG = triglyceride; Apo = apolipoprotein; VLDL = very low-density lipoprotein; IDL = intermediate-density lipoprotein; Lp(a) = lipoprotein (a); C = cholesterol.

1. NCEP ATP III Expert Panel. *Circulation*. 2002;106:3143–3421. **2.** Rana JS et al. *Curr Opin Cardiol*. 2010;25:622–626. **3**. Chapman MJ et al. *Eur Heart J Suppl*. 2004;6(suppl A):A43–A48. **4.** Barter P. In: Ballantyne CM. *Clinical Lipidology: A Companion to Braunwald's Heart Disease*. Saunders, an imprint of Elsevier Inc; 2009:387–395. **5**. Walldius G et al. *J Intern Med*. 2004;255:188–205.

Robinson 2006: Intensive LDL-C Reduction May Be Appropriate for Patients at High CV Risk[1]



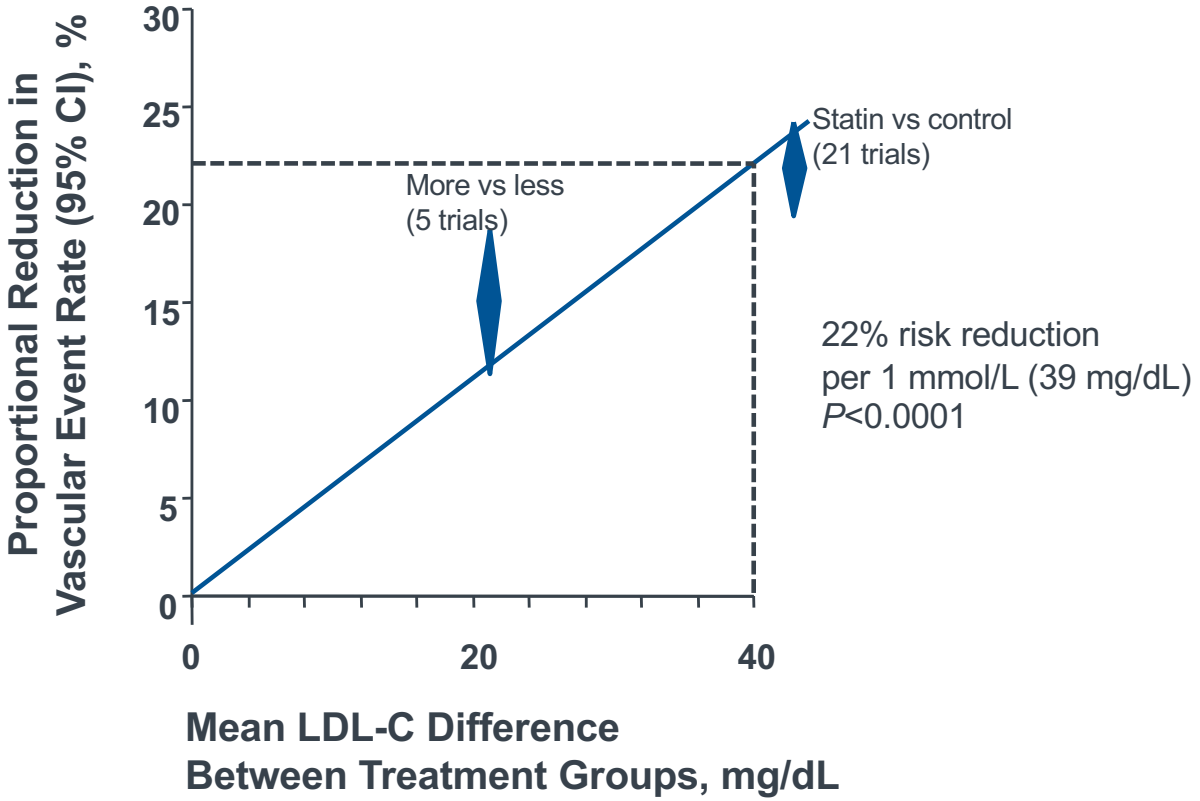
The incremental benefit of ezetimibe/atorvastatin on cardiovascular morbidity and mortality over and above that demonstrated for atorvastatin has not been established.

Adapted with permission from Robinson JG et al.[1]

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

1. Robinson JG et al. *Am J Cardiol.* 2006;98:1405–1408.

CTT Meta-Analysis: The Relationship Between Absolute Reduction in LDL-C and Proportional Reduction in Vascular Events Is Linear[1]



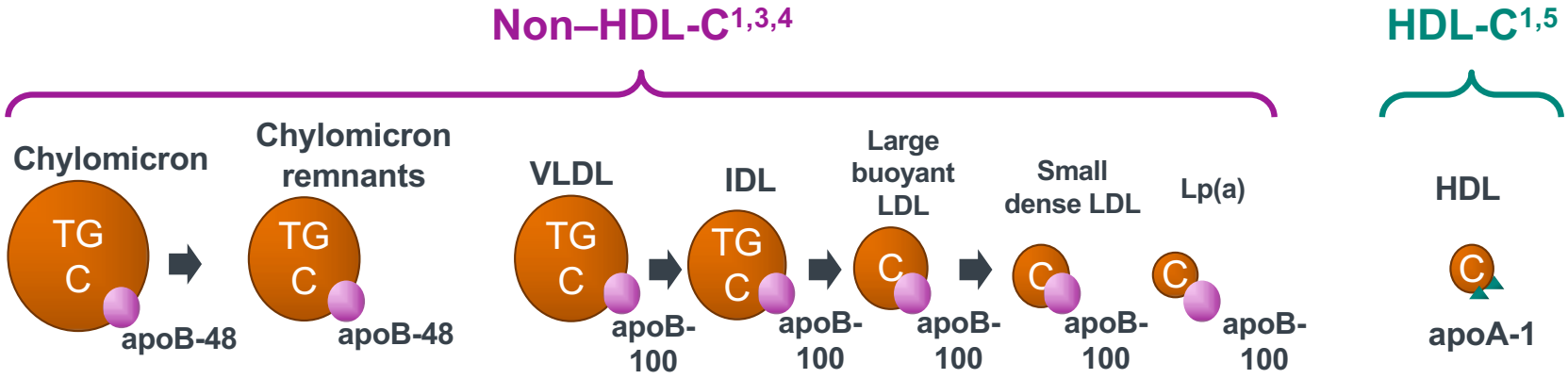
The incremental benefit of ezetimibe/atorvastatin on cardiovascular morbidity and mortality over and above that demonstrated for atorvastatin has not been established.

CTT = Cholesterol Treatment Trialists; CI = confidence interval.

1. Cholesterol Treatment Trialists' (CTT) Collaboration. *Lancet.* 2010;376:1670–1681.

Non–HDL-C Is a Risk Factor for CHD

- Non–HDL-C represents the cholesterol content of all apoB-containing lipoproteins, including VLDL, IDL, LDL, Lp(a), and chylomicrons and chylomicron remnants[1,2]
  - Non–HDL-C = total cholesterol – HDL-C[1]
- When TG levels are ≥200 mg/dL (~2.3 mmol/L), non–HDL-C may better represent the concentration of all atherogenic lipoproteins than does LDL-C alone[1]
- Multiple prospective cohort studies have shown that non–HDL-C may be superior to LDL-C for CV risk assessment[3]



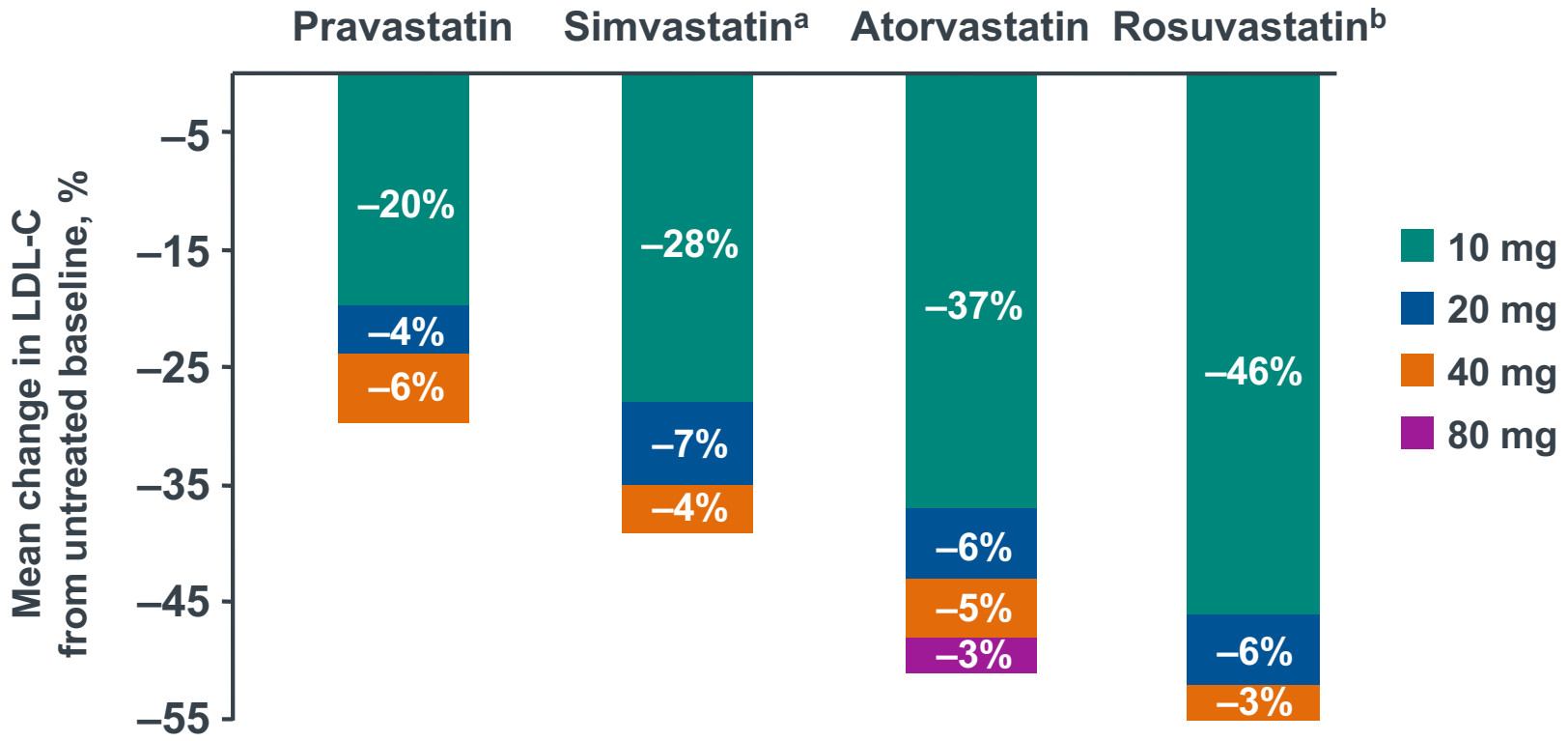
Adapted with permission from Walldius G et al.[6]

Other major risk factors (beyond dyslipoproteinemia) include smoking, hypertension, and family history of premature CAD.

CHD = coronary heart disease; ApoB = apolipoprotein B; VLDL = very low-density lipoprotein; IDL = intermediate-density lipoprotein; Lp(a) = lipoprotein (a); CV = cardiovascular; C = cholesterol; CAD = coronary artery disease.

1. NCEP ATP III Expert Panel. *Circulation*. 2002;106:3143–3421. **2**. Rana JS et al. *Curr Opin Cardiol*. 2010;25:622–626. **3.** Hoenig MR. *Vasc Health Risk Manag*. 2008;4:143–156. **4**. Chapman M et al. *Eur Heart J Suppl*. 2004;6(suppl A):A43–A48. **5.** Barter P. In: Ballantyne CM. *Clinical Lipidology: A Companion to Braunwald's Heart Disease*. Saunders, an imprint of Elsevier Inc; 2009:387–395 **6.** Walldius G et al. *J Intern Med*. 2004;255:188–205.

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



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

[a]Mean change in LDL-C from untreated baseline after 6 weeks for simvastatin 80 mg was 46%.[1] The 80-mg dose of simvastatin is only recommended in patients at high CV risk who have not achieved treatment goals on lower doses and when the benefits are expected to outweigh the risks.[2]

[b]Across the dose range: $P<0.001$ for the difference between rosuvastatin vs pravastatin, simvastatin, and atorvastatin.[1]

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

1. Jones PH et al. Am J Cardiol. 2003;92:152–160. **2.** [Insert local label.]

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

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

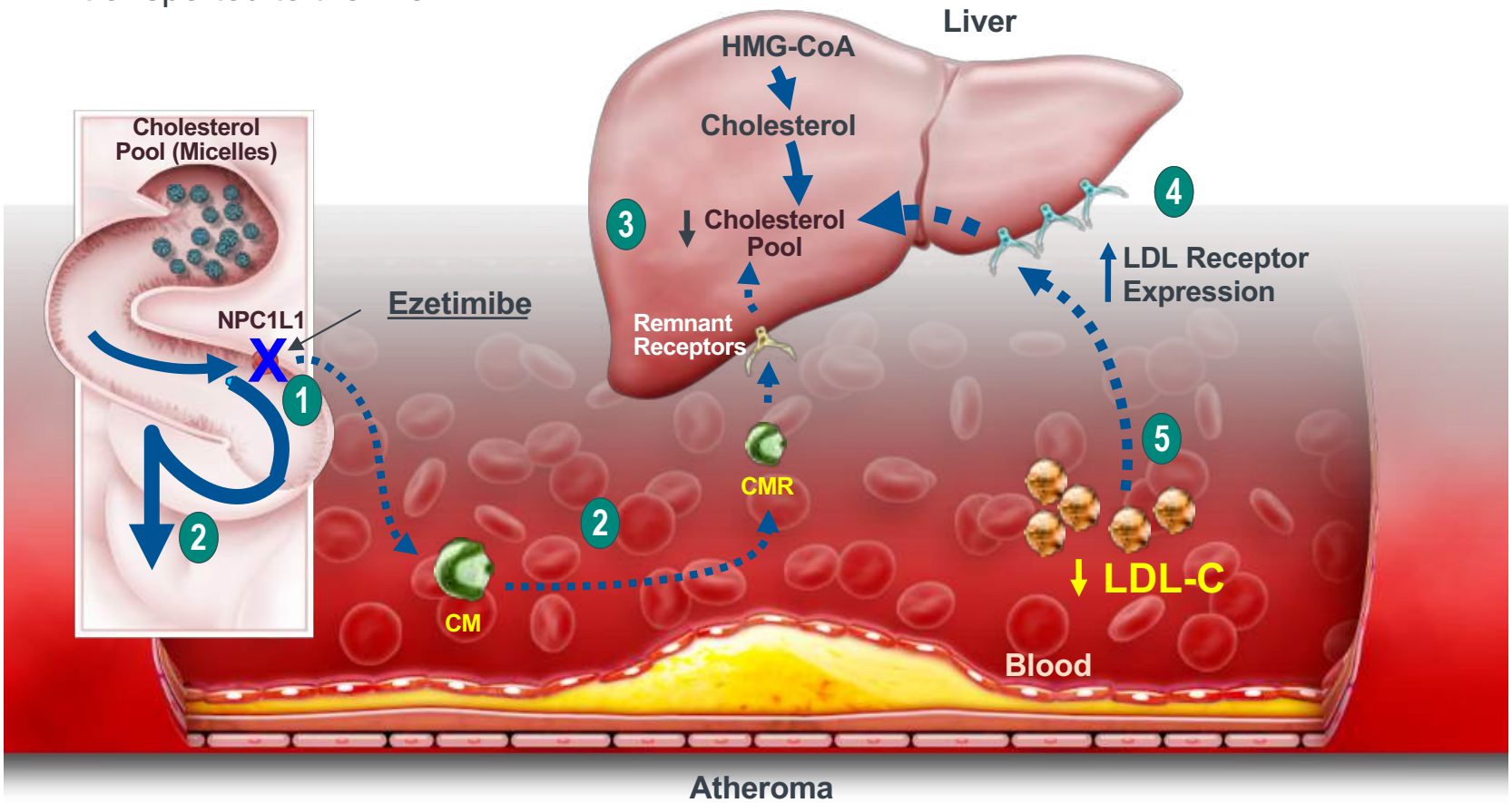
ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; TOTAL-C = total cholesterol; CV = cardiovascular; Atorva = atorvastatin; MI = myocardial infarction; CHD = coronary heart disease; CARDS = Collaborative Atorvastatin Diabetes Study; TG = triglycerides; UA = unstable angina; TNT = Treating to New Targets; 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 Inhibits Absorption of Cholesterol in the Small Intestine[1]

Ezetimibe: Mechanism of Action

1. Inhibition of NPC1L1 activity
2. Reduction of cholesterol transported to the liver
3. Reduction of hepatic cholesterol
4. Increased LDL receptor expression
5. Increased clearance of LDL-C



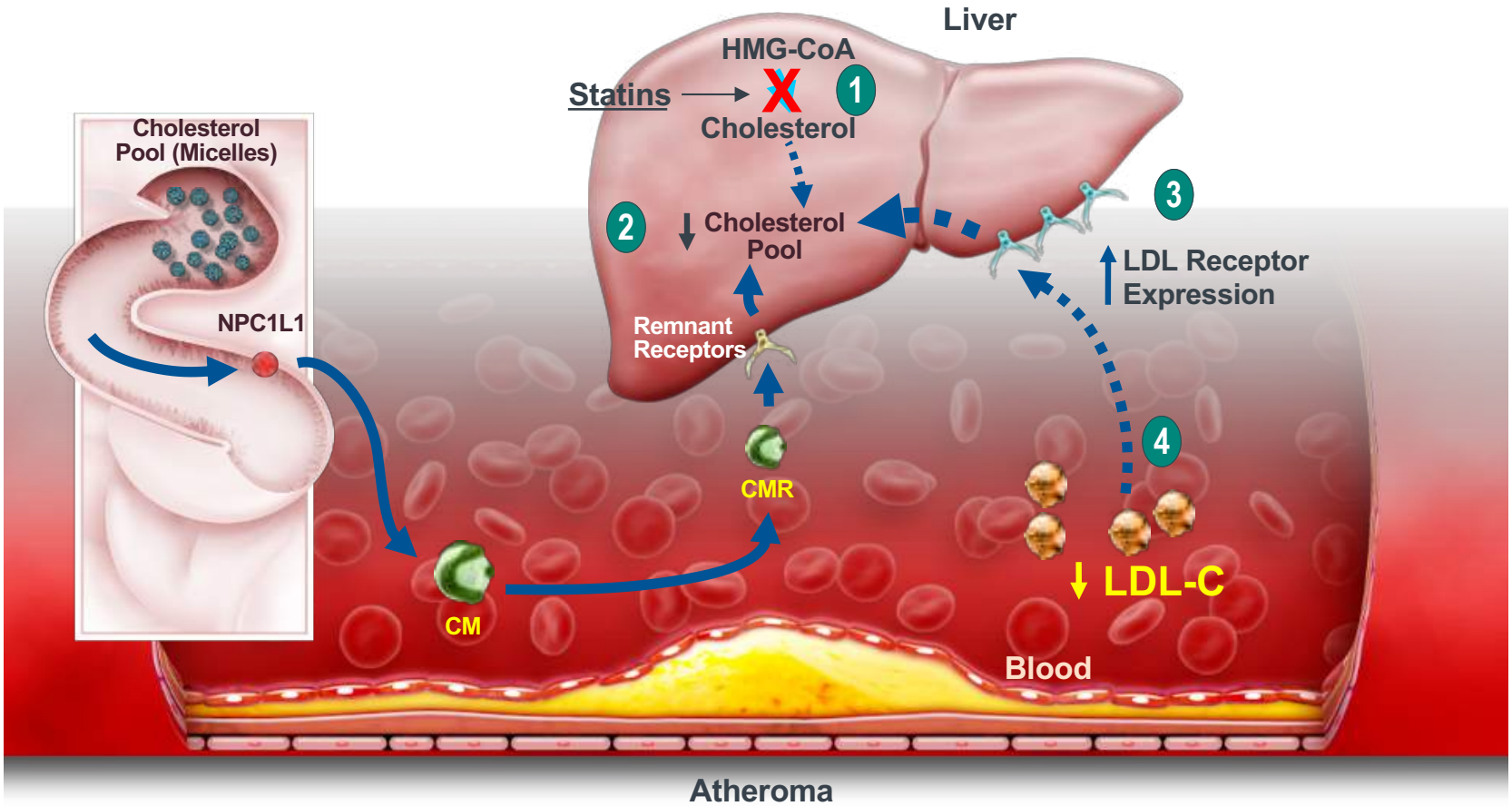
NPC1L1 = Niemann-Pick C1-like 1; HMG-CoA = 3-hydroxy-3-methylglutaryl acetyl coenzyme A; CMR = chylomicron remnant.

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

Statins Inhibit Synthesis of Cholesterol[1]

Statin: Mechanism of Action

1. Inhibition of HMG-CoA reductase activity
2. Reduction of hepatic cholesterol
3. Increased LDL receptor expression
4. Increased clearance of LDL-C



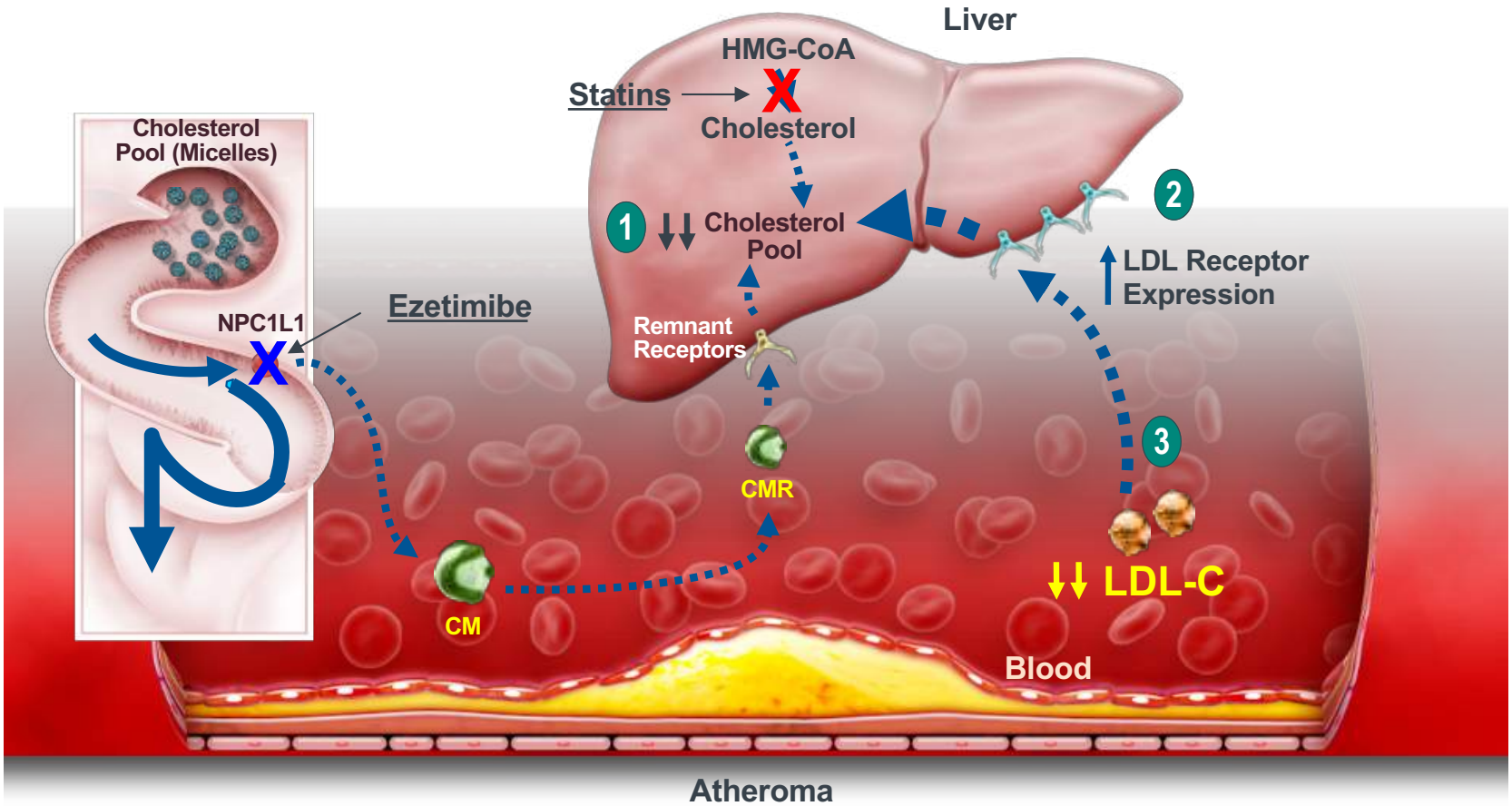
HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; NPC1L1 = Niemann-Pick C1-like 1; CMR = chylomicron remnant.

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

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



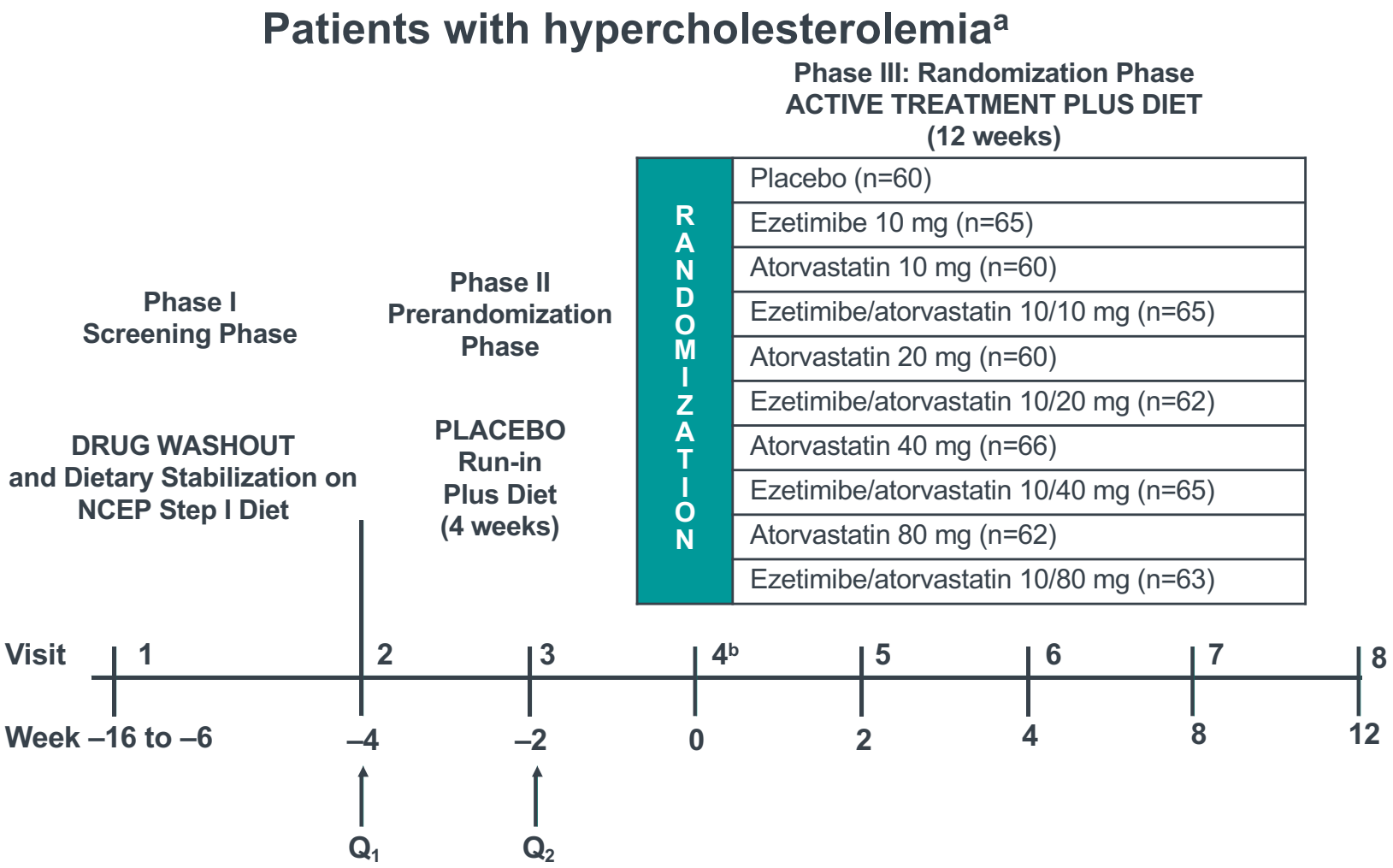
NPC1L1 = Niemann-Pick C1-like 1; HMG-CoA = 3-hydroxy-3-methylglutaryl acetyl coenzyme A; CMR = chylomicron remnant.

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

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]

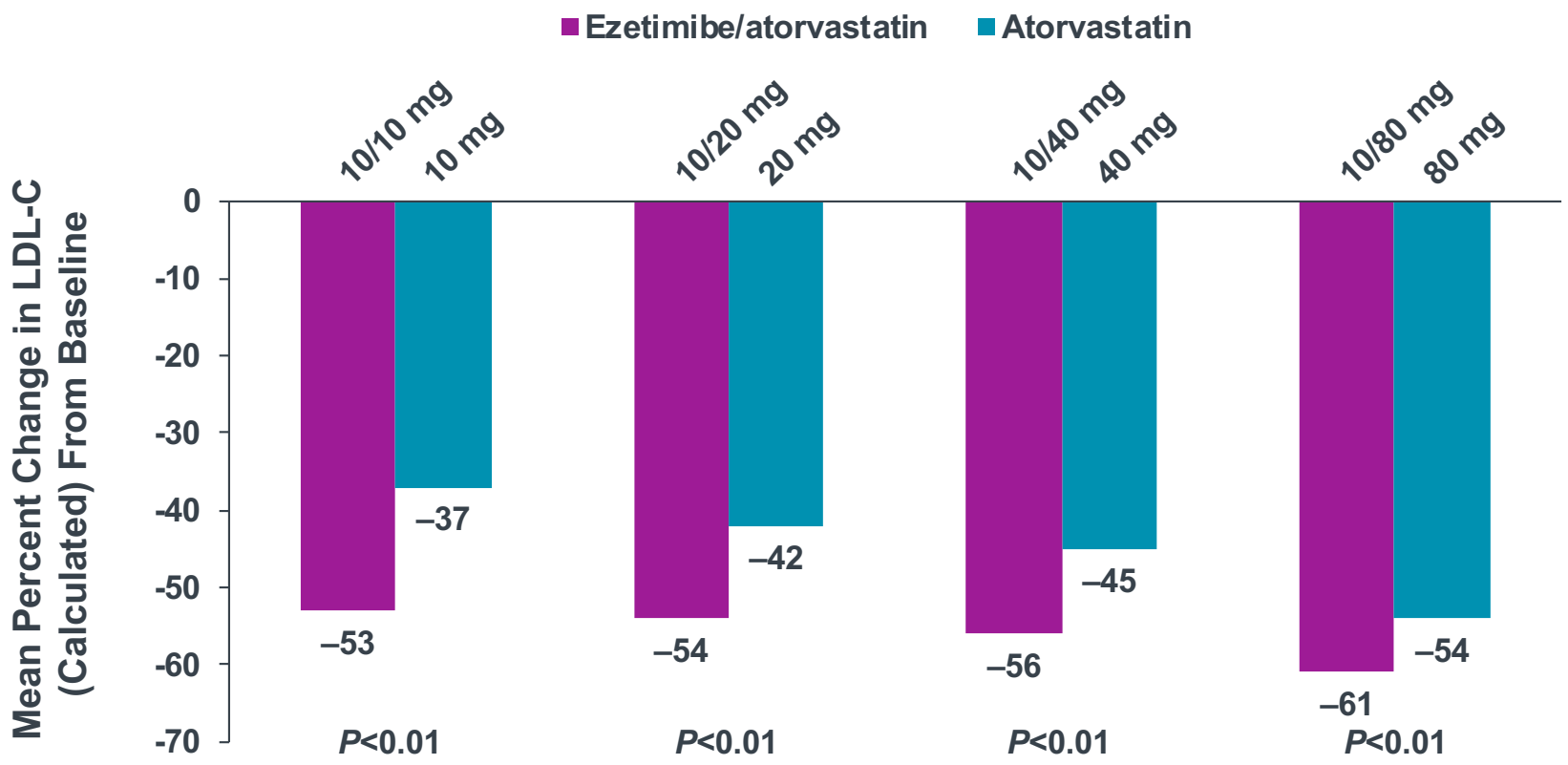
[a]Baseline LDL-C 145 to 250 mg/dL (~3.7 to 6.5 mmol/L) and triglycerides ≤350 mg/dL (~4.0 mmol/L).

[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 Provided Significantly Greater LDL-C Reduction Compared With Corresponding Atorvastatin Doses[1]

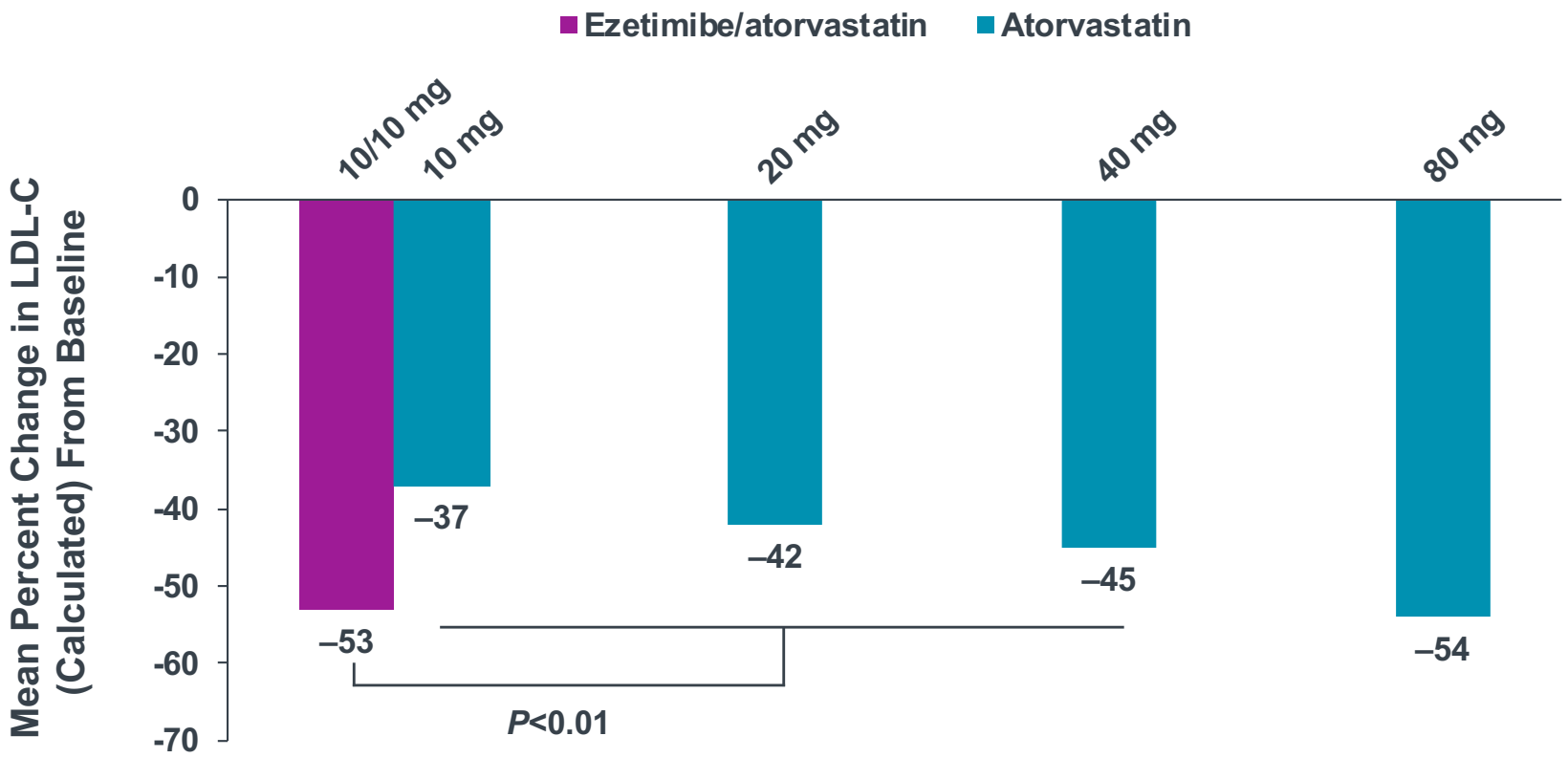


Mean baseline LDL-C was 182 mg/dL (~4.7 mmol/L) for ezetimibe/atorvastatin arms (n=255) and 181 mg/dL (~4.7 mmol/L) for atorvastatin arms (n=248).

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

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

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



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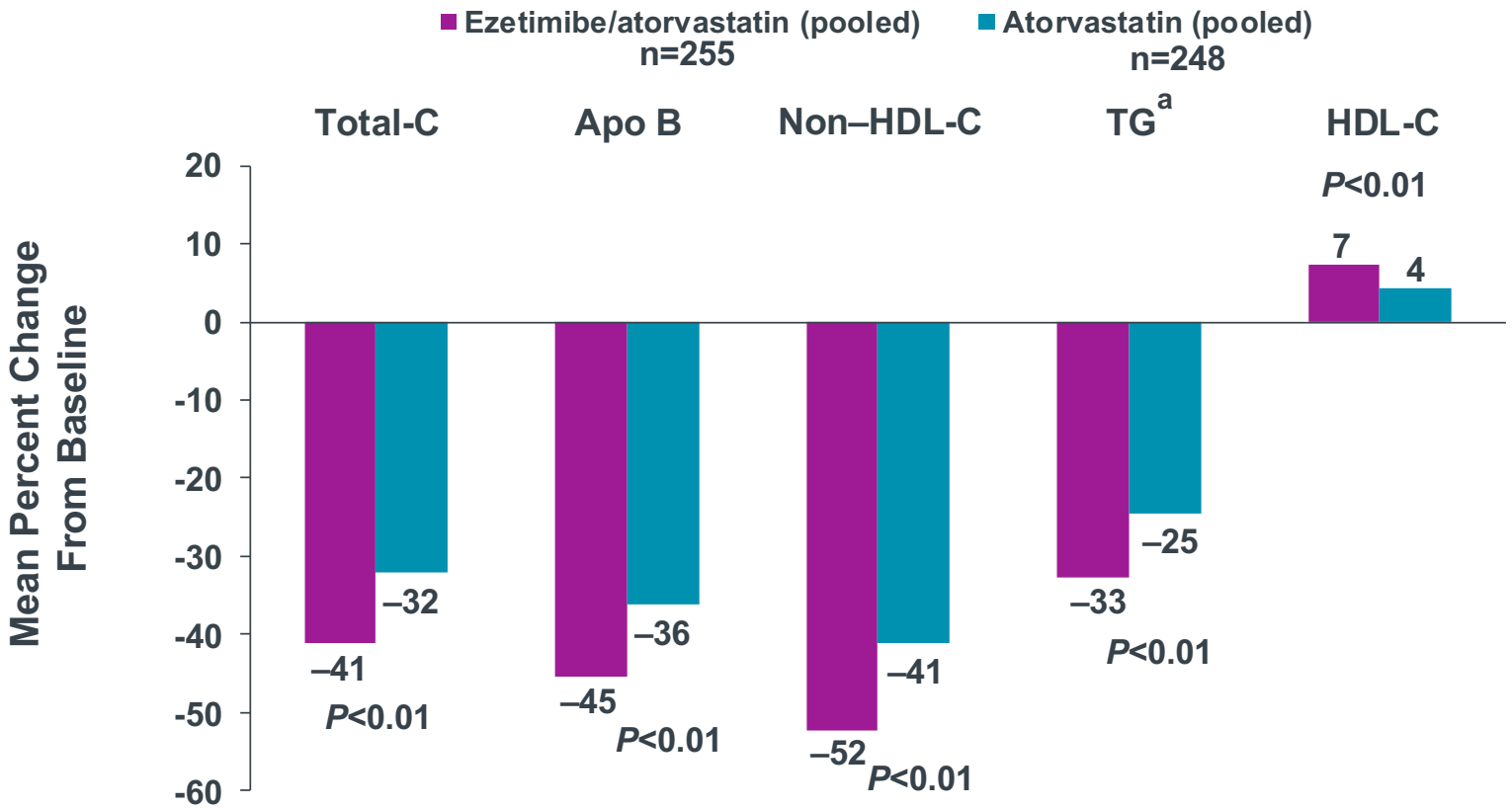
1. Ballantyne CM et al. *Circulation*. 2003;107:2409–2415.

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.

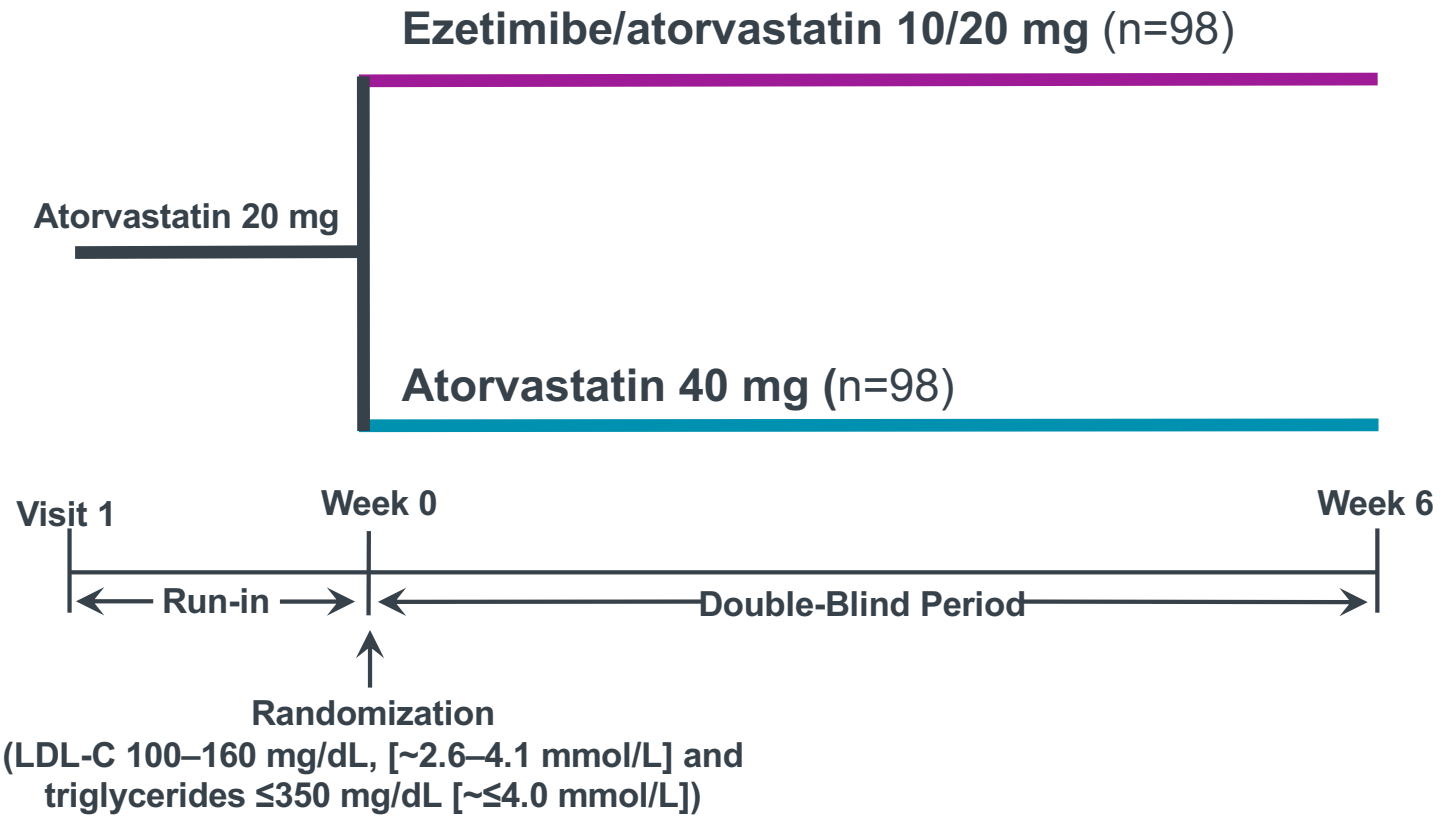
1. Ballantyne CM et al. *Circulation*. 2003;107:2409–2415.

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]

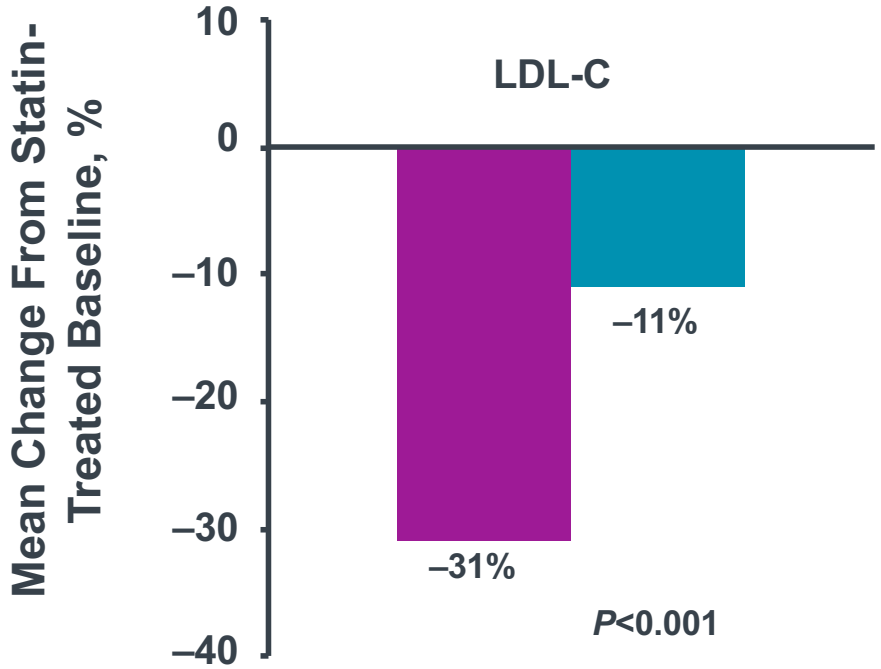
Patients with hypercholesterolemia at moderately high risk of CHD (based on NCEP ATP III criteria)



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)

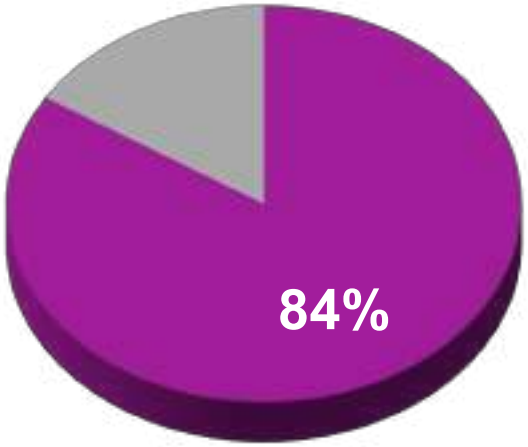
Atorvastatin 20 mg titrated to 40 mg (n=92) (mean on-statin baseline LDL-C = 118 mg/dL, ~3.1 mmol/L)

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

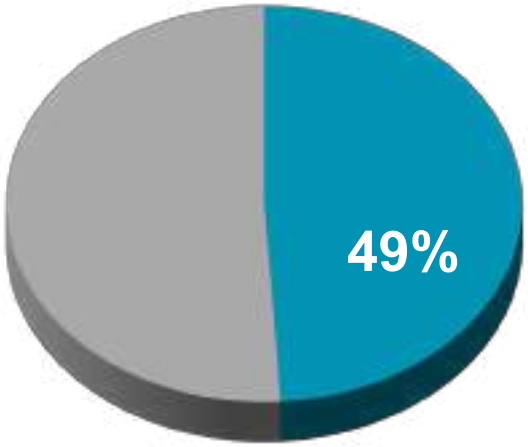
Ezetimibe/atorvastatin 10/20 mg
(n=92)



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

***P*<0.001**

Atorvastatin 40 mg
(n=92)

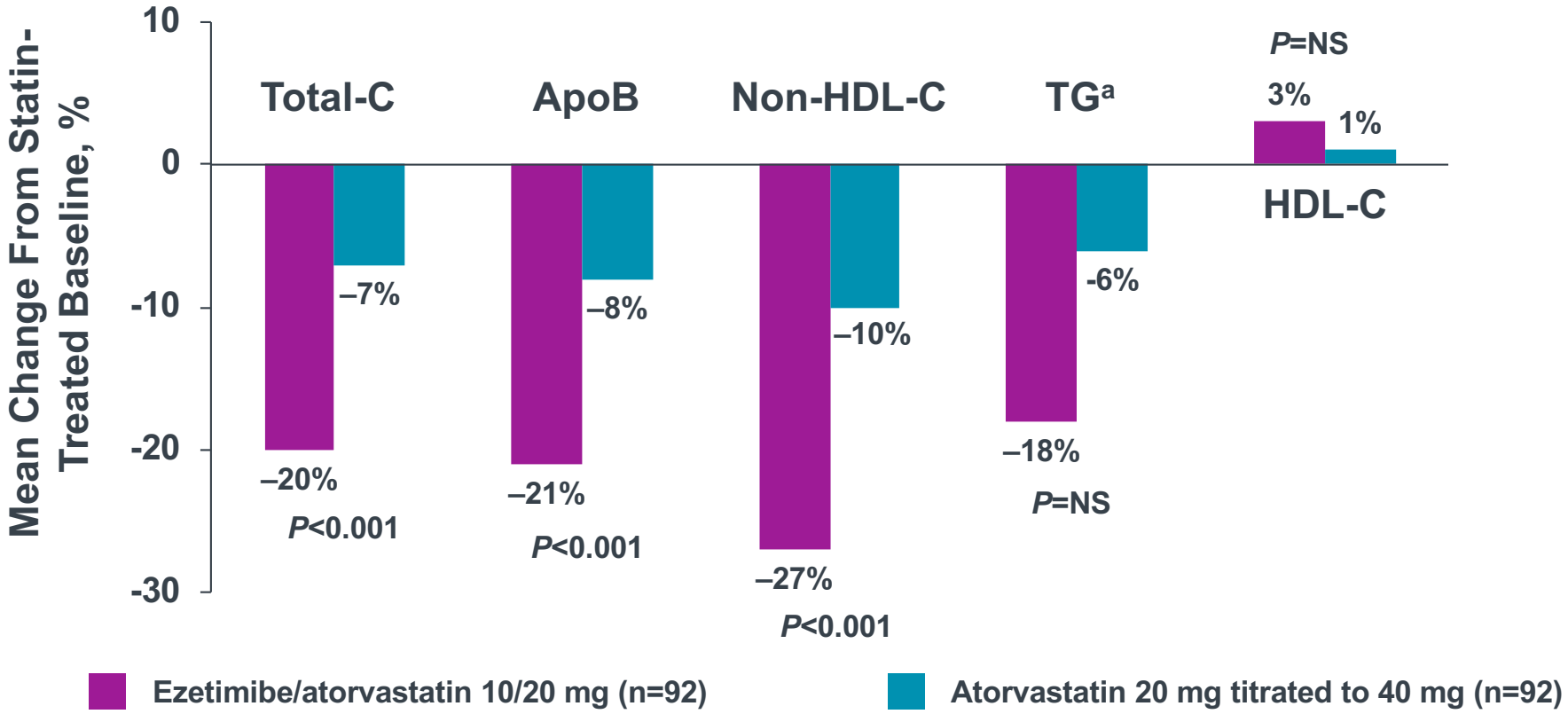


Mean Statin-Treated Baseline LDL-C: 118 mg/dL (~3.1 mmol/L)

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.

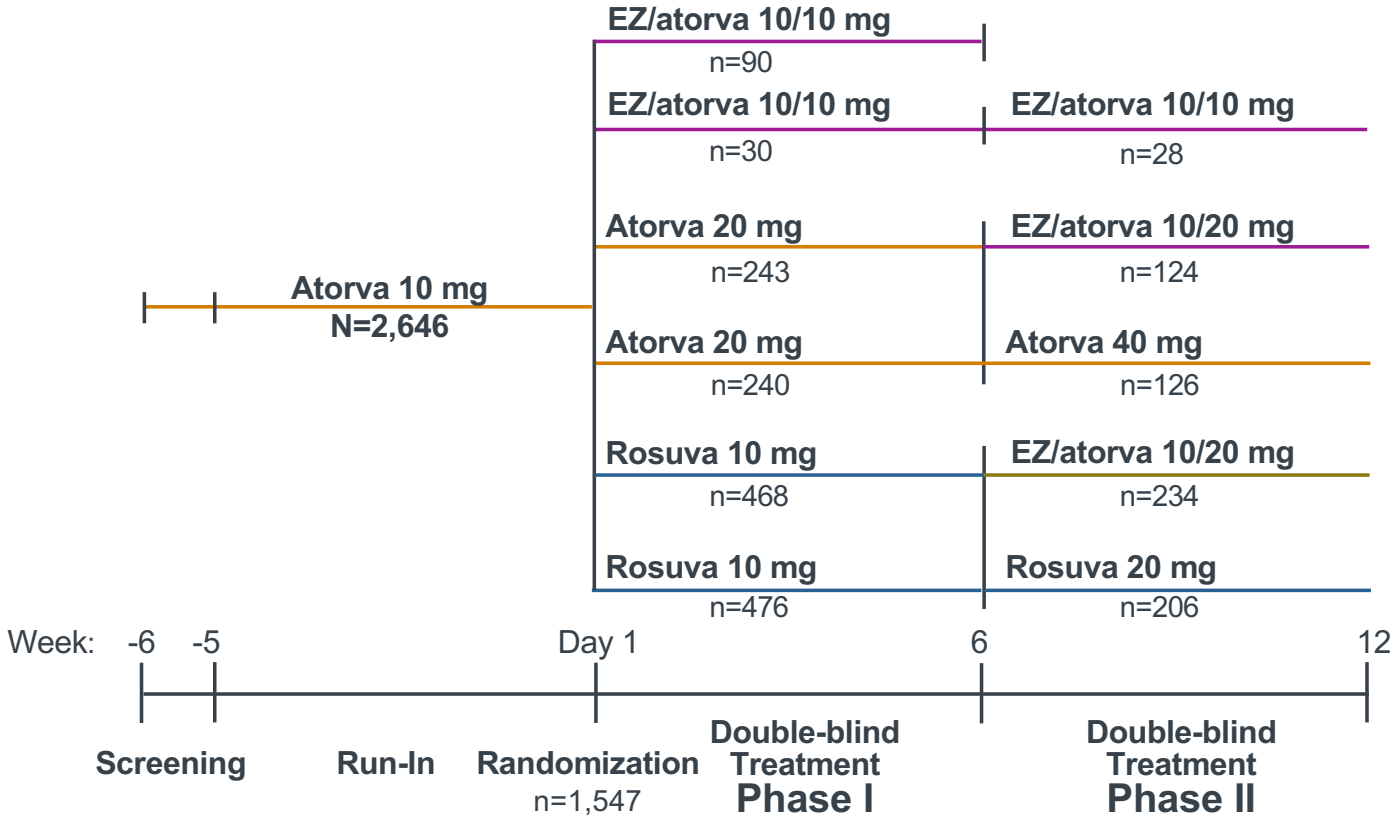
1. Conard SE et al. *Am J Cardiol*. 2008;102:1489–1494.

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



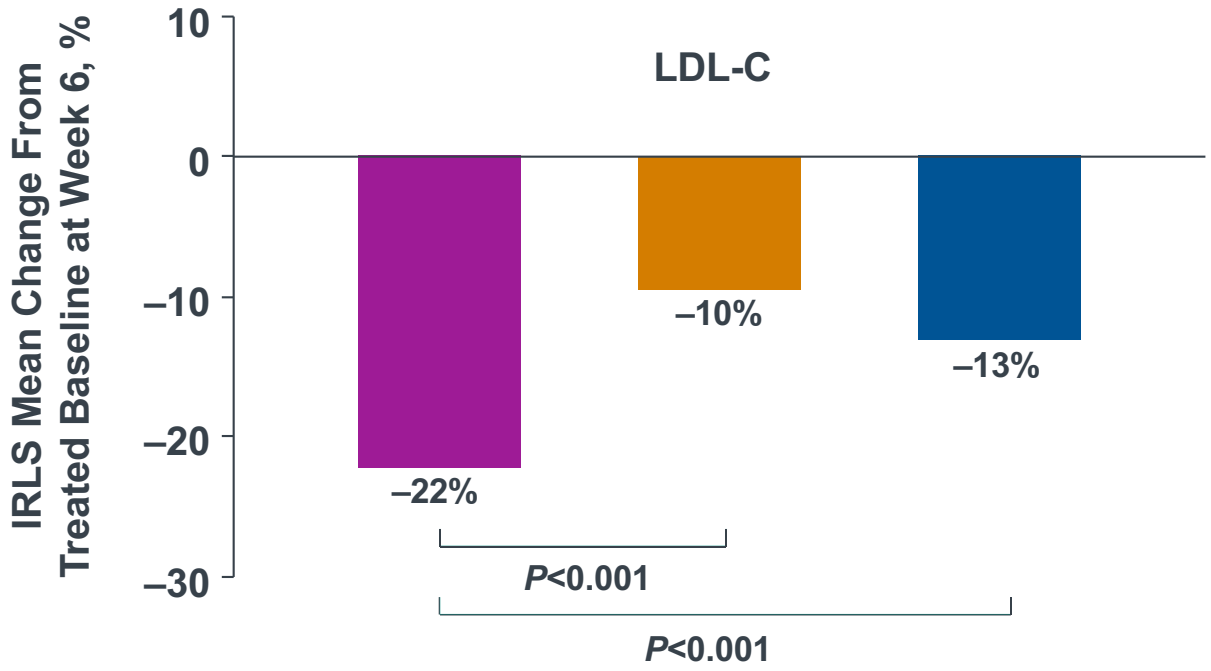
Adapted with permission from Bays HE et al.[1]

[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)

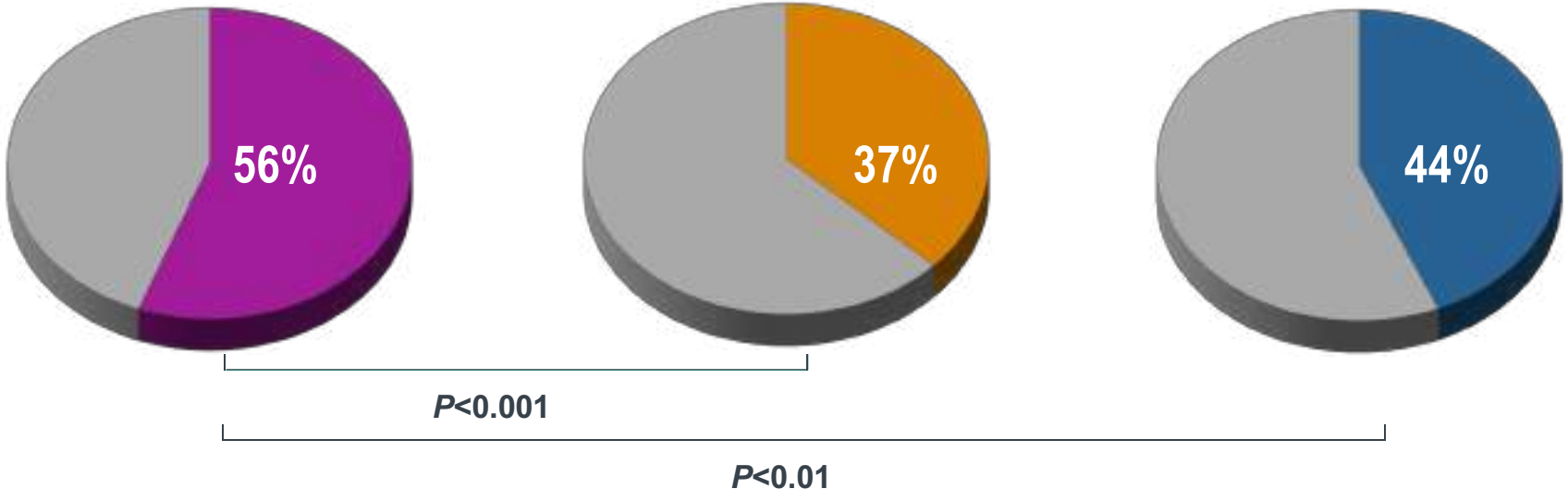
Mean treated baseline LDL-C:
121 mg/dL (~3.1 mmol/L)

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)



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.

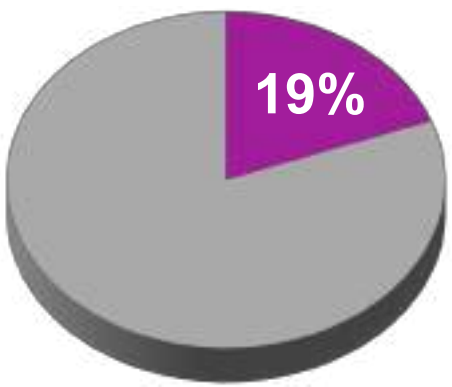
1. Bays HE et al. *Am J Cardiol*. 2013;112:1885–1895.

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

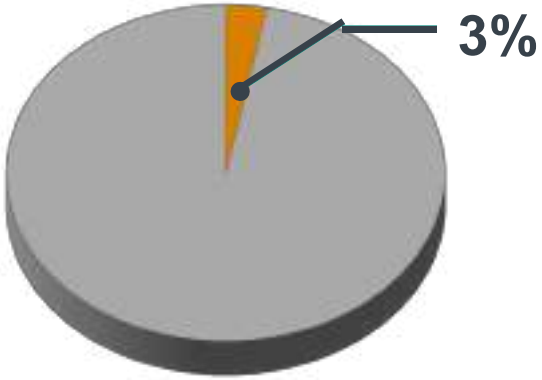
Ezetimibe/atorvastatin 10/10 mg
(n=119)

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



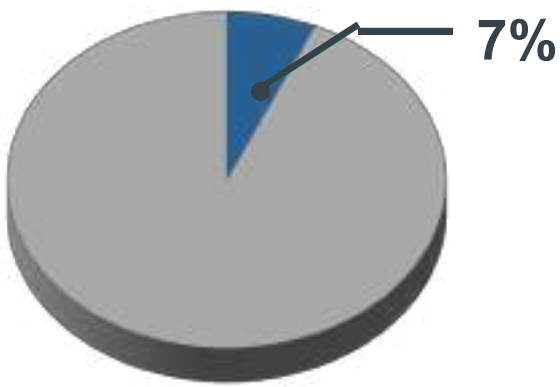
Atorvastatin 20 mg
(n=471)

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**

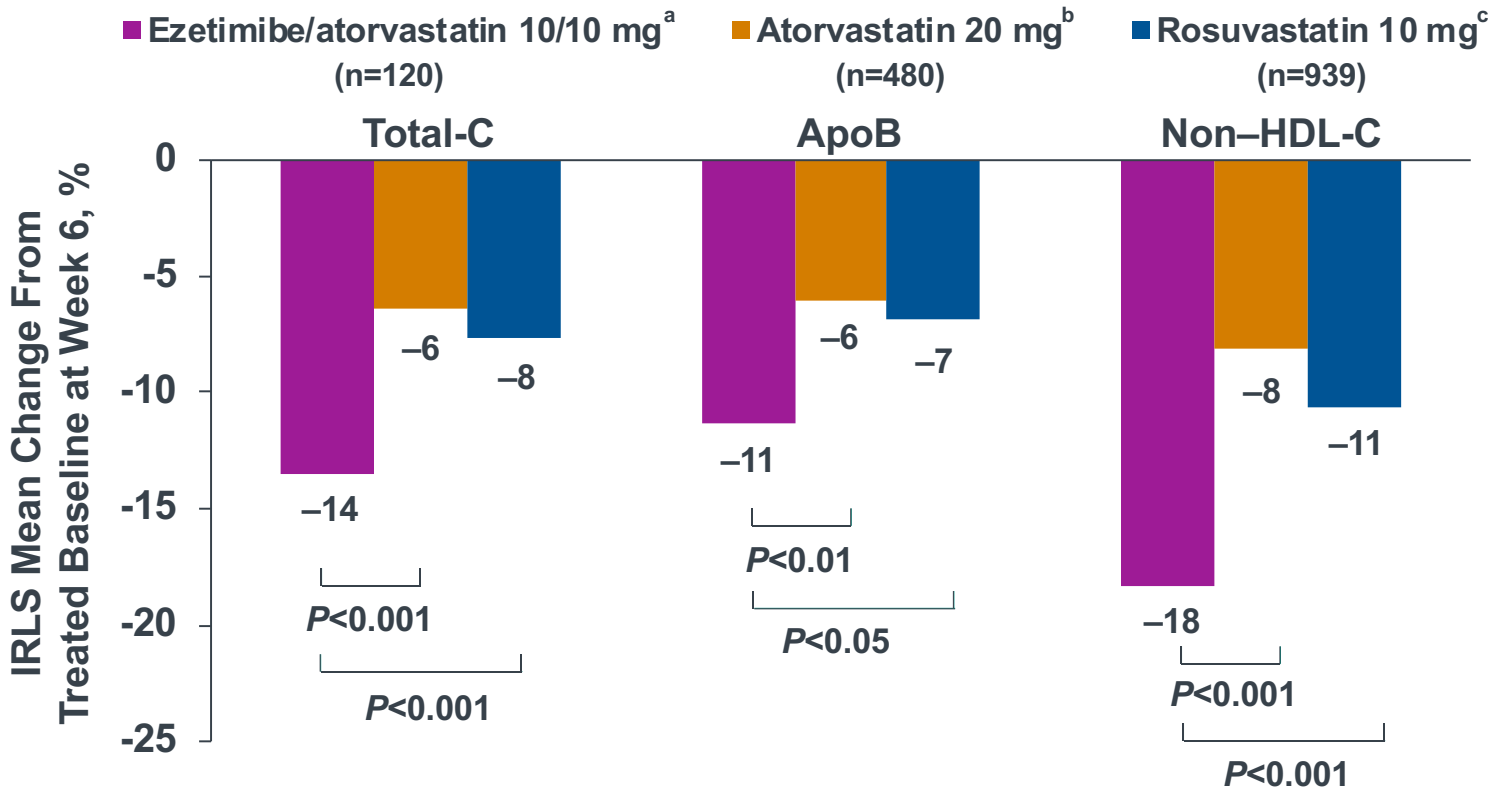
***P*<0.001**

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).

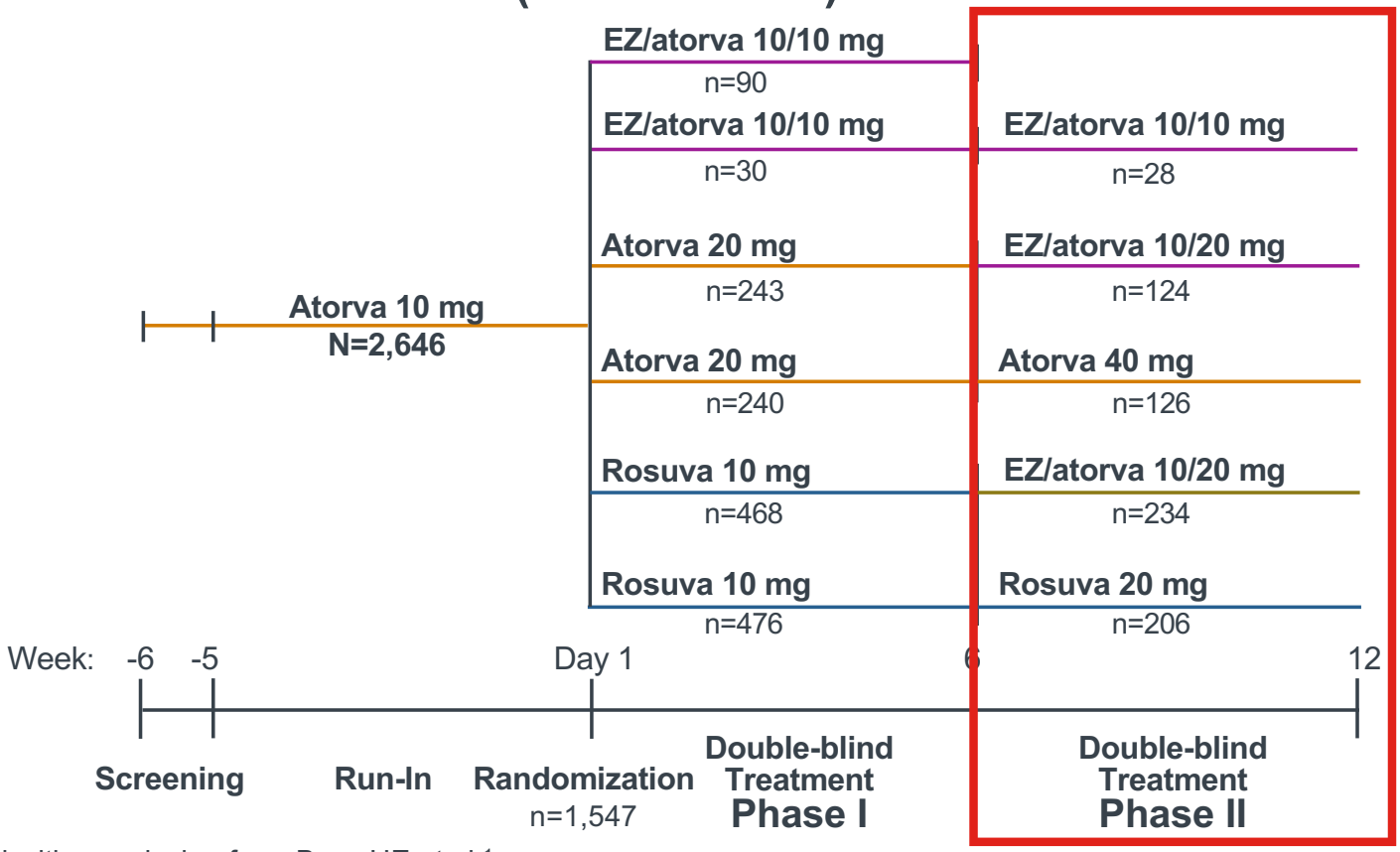
[c]Mean treated baselines for group switched to rosuvastatin 10 mg: Total-C 205 mg/dL (~5.3 mmol/L), apoB 104 mg/dL, and non–HDL-C 152 mg/dL (~3.9 mmol/L).

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



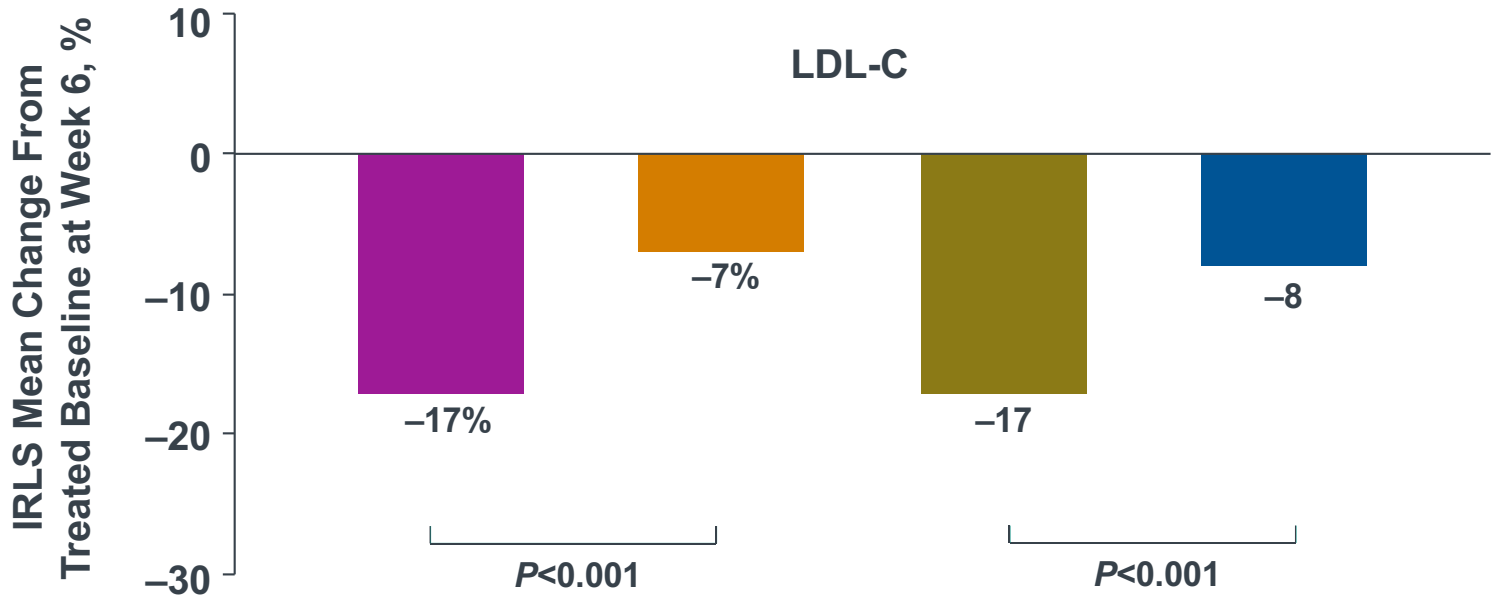
Adapted with permission from Bays HE et al.[1]

[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)

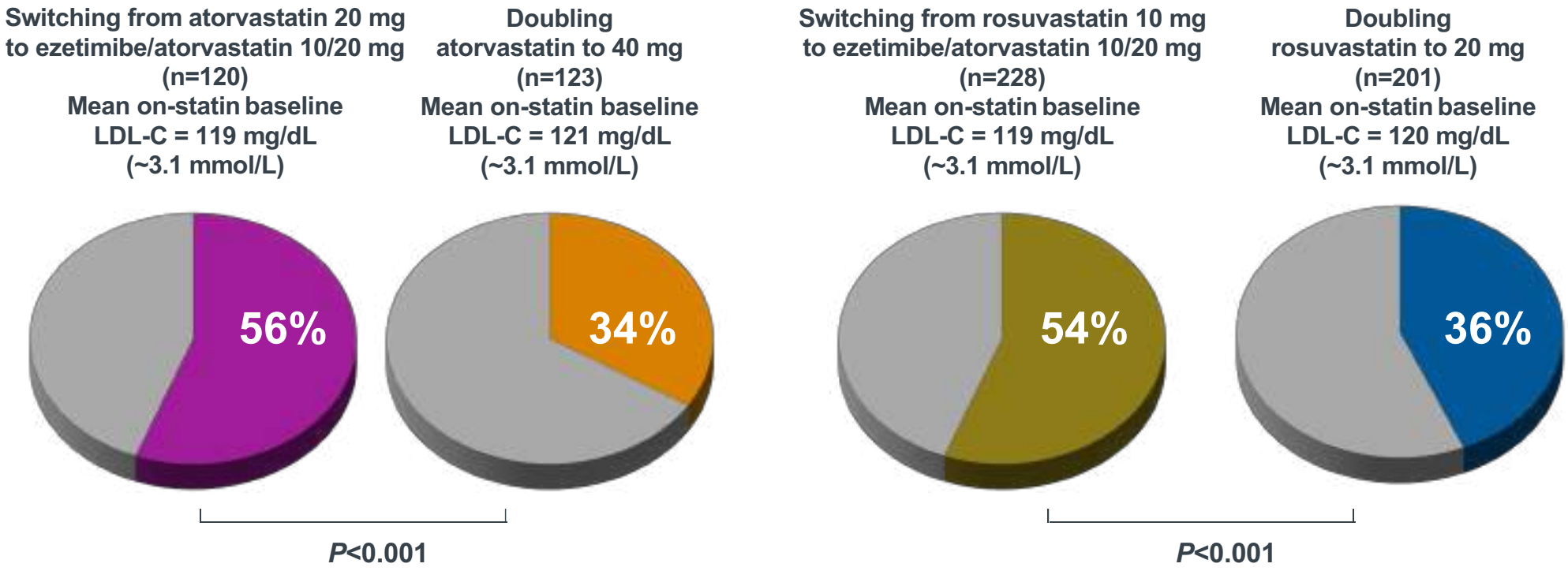
Doubling rosuvastatin to 20 mg (n=205) Mean on-statin baseline LDL-C = 120 mg/dL (~3.1 mmol/L)

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



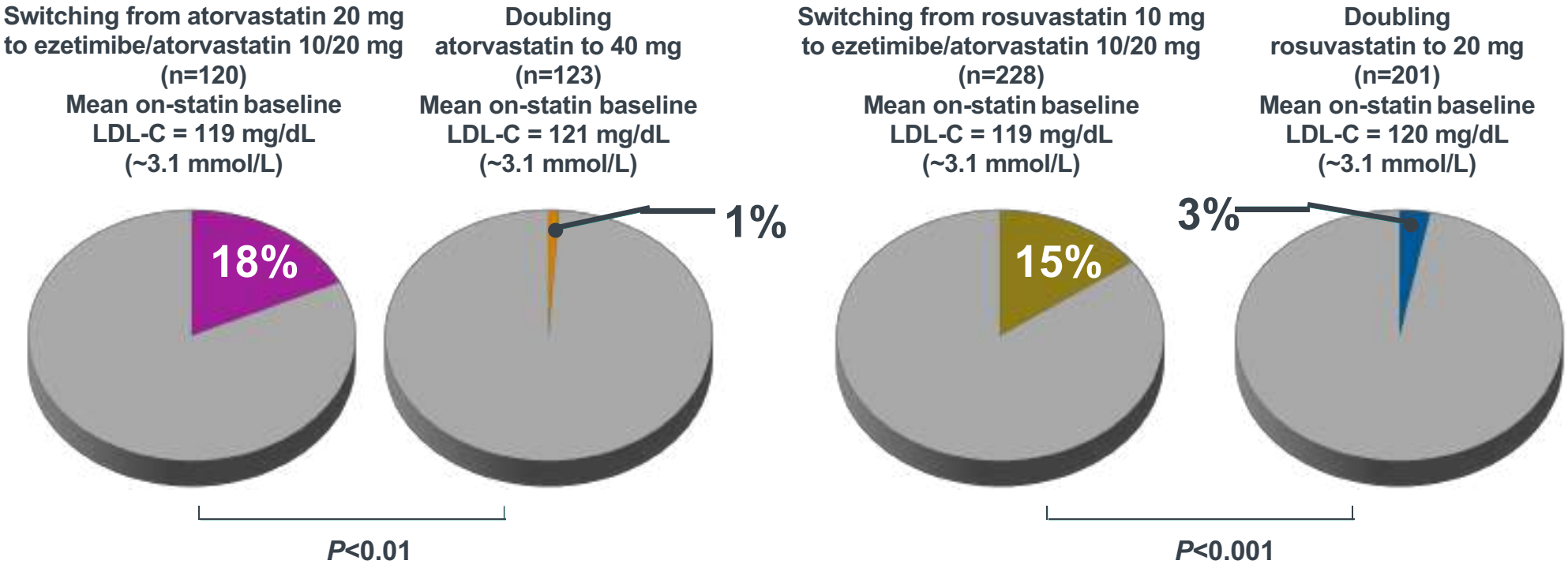
The IRLS mean decrease in LDL-C from statin-treated baseline was 17% with ezetimibe/atorvastatin 10/20 mg compared with 7% with doubling atorvastatin to 40 mg and 17% with ezetimibe/atorvastatin 10/20 mg compared with 8% with doubling rosuvastatin to 20 mg; *P*<0.001 for each comparison.

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

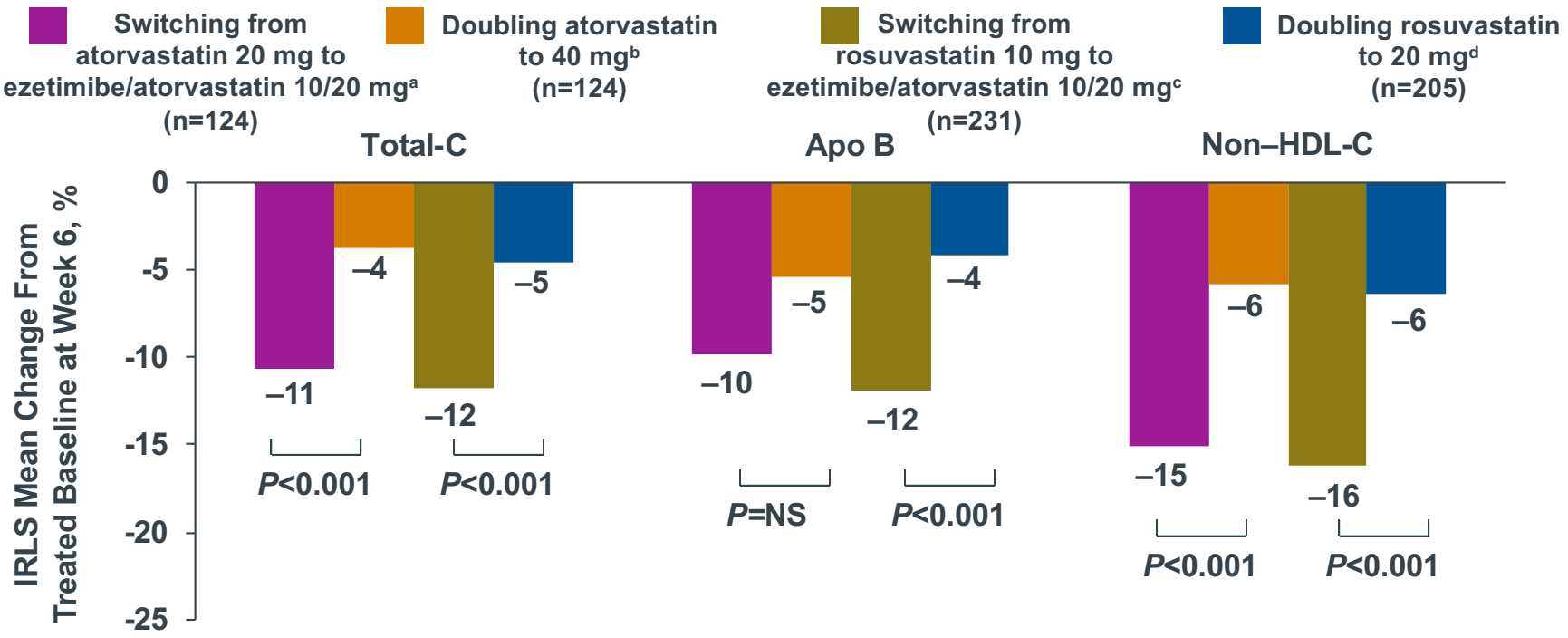


The IRLS mean decrease in LDL-C from statin-treated baseline was 17% with ezetimibe/atorvastatin 10/20 mg compared with 7% with doubling atorvastatin to 40 mg and 17% with ezetimibe/atorvastatin 10/20 mg compared with 8% with doubling rosuvastatin to 20 mg; *P*<0.001 for each comparison.

IRLS = iteratively reweighted least squares.

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.

Additional Clinical Trials Have Demonstrated Greater LDL-C Reduction With Ezetimibe/Atorvastatin Compared With Atorvastatin Monotherapy[1,2]

Study	Patient Population	Intervention	LDL-C-Lowering Efficacy
Gagné 2002[1] **(atorva sub-group analysis)**	Hypercholesterolemia; stable atorva therapy for ≥6 weeks; LDL-C levels exceeding NCEP ATP II guidelines; N=308	Eze/atorva vs placebo/atorva; 8-week study	**25% reduction with eze/atorva vs 4% reduction with placebo/atorva**
Stein 2004[2]	Hypercholesterolemia and documented CHD, ≥2 CV risk factors or HeFH; LDL-C ≥130 mg/dL (~3.4 mmol/L) and TG ≤350 mg/dL (~4.0 mmol/L) while on atorva 10 mg and dietary modifications; N=621	Eze/atorva 10/10 mg vs atorva 20 mg; Atorva dose doubled at weeks 5 and 10 if LDL-C >100 mg/dL (~2.6 mmol/L); 14-week study	**24% reduction (calculated LDL-C) with eze/atorva 10/10 mg vs 9% with atorva 20 mg** at 4 weeks; *P*<0.01

Atorva = atorvastatin; NCEP ATP II = National Cholesterol Education Program Adult Treatment Panel II; Eze = ezetimibe; CHD = coronary heart disease; CV= cardiovascular; HeFH = heterozygous familial hypercholesterolemia; TG = triglycerides.

1. Gagné C et al. *Am J Cardiol.* 2002;90:1084–1091. **2**. Stein E et al. *Am Heart J*. 2004;148:447–455.

A systematic review and meta analysis of combination therapy and monotherapy were conducted

Ai *et al. Lipids in Health and Disease* (2018) 17:239
https://doi.org/10.1186/s12944-018-0880-8

Lipids in Health and Disease

REVIEW Open Access

Comparing the combination therapy of ezetimibe and atorvastatin with atorvastatin monotherapy for regulating blood lipids: a systematic review and meta-analyse

Cong Ai[1], Shanshan Zhang[2], Qiao He[1] and Jingpu Shi[1*]

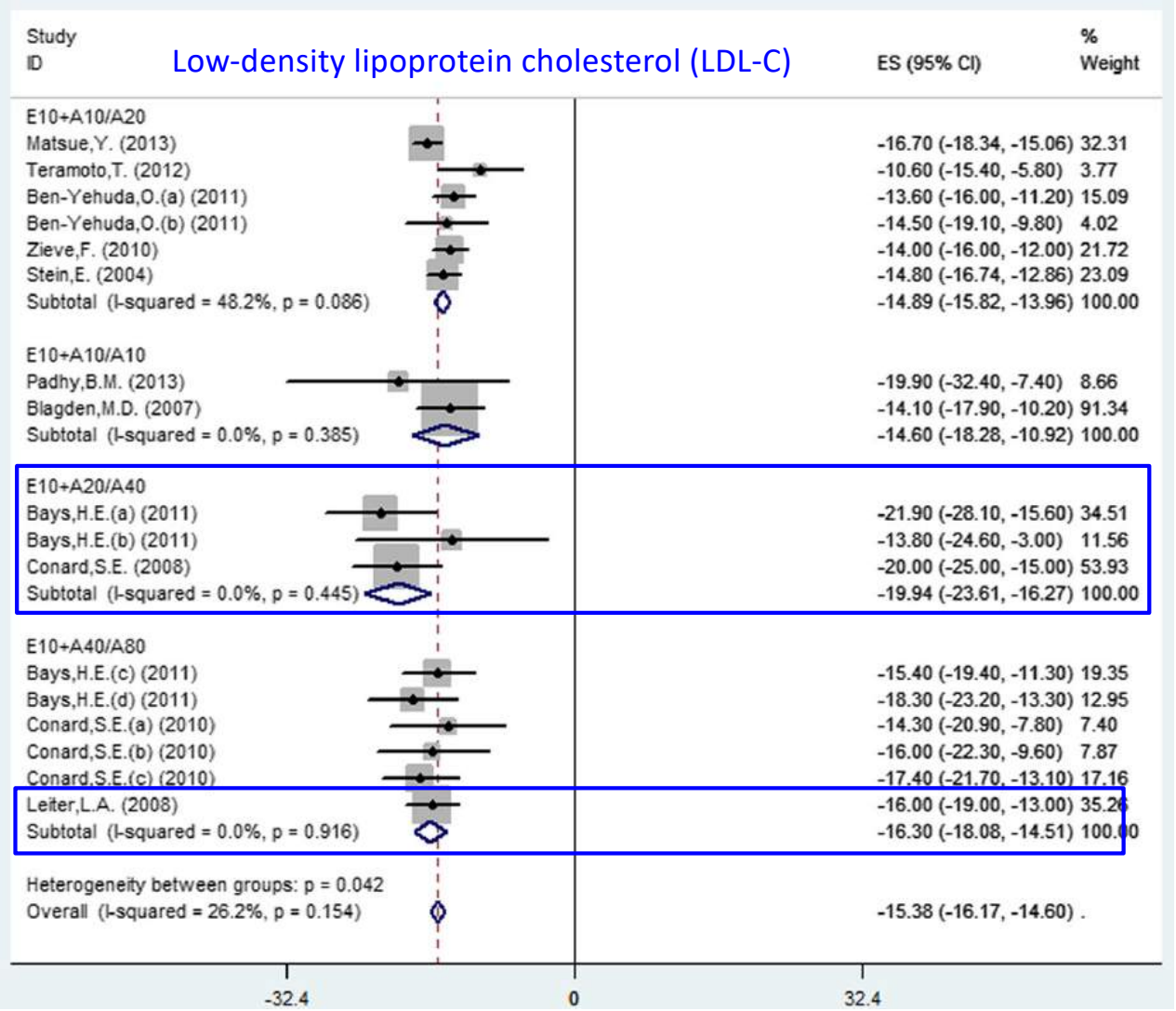
A systematic review and meta analysis of combination therapy and monotherapy were conducted

- 11 publications were included in the meta analysis.
- Three studies were from Asia, four from US, and four from Europe.
- All randomized controlled trials (RCTs) were carried out for more than 4 weeks.

Author, year, country, Reference	Study design	Dose (mg)	Included number		LDL-C		HDL-C		TC		TG	
			E + A	A	Mean	Treatment difference (95% CI)	Mean	Treatment difference (95% CI)	Mean	Treatment difference (95% CI)	Mean	Treatment difference (95% CI)
Matsue,Y., 2013,Japan,19	randomized, open-labeled, parallel-group	E10 + A10/A20	115	128	−16.7	(−18.34,-15.06)	0.47	(−2.05,2.99)	−9.6	(−11.07,-8.13)	−5.3	(− 9.59,-1.01)
Teramoto,T., 2012,Japan,20	multicenter, randomized, open-label, parallel-group	E10 + A10/A20	47	46	−10.6	(−15.4,-5.8)	4	(−0.3,8.3)	− 7.6	(− 11.4,− 3.8)	-3	(−18.8,12.7)
Ben-Yehuda,O., 2011,USA,21	multicenter, randomized, double-blind, parallel-arm	(a)E10 + A10/A20 (b)E10 + A10/A20	404 111	408 107	−13.6 − 14.5	(− 16,-11.2) (− 19.1,-9.8)	1.3 4.2	(− 0.5,3.1) (0.7,7.6)	−7.8 − 8.4	(−9.4,-6.2) (− 11.5,-5.3)	− 5.7 − 7.6	(− 8.9,-2.4) (− 13.3,-2)
Zieve,F., 2010,Russia,22	multicenter, randomized, doubleblind, parallel-arm	E10 + A10/A20	515	515	− 14	(− 16,-12)	2	(0.3,4)	−8	(− 9,-7)	−6	(− 9,-3)
Stein,E., 2004,Spain,23	multicenter, randomized, double-blind, active-controlled	E10 + A10/A20	293	303	−14.8	(− 16.74,-12.86)	0.8	(− 0.86,2.46)	− 11.2	(− 12.86,-9.54)	−5.4	(− 10.11,-0.69)
Padhy,B.M., 2013,India,24	randomised, double-blind, parallel-group, comparator-controlled	E10 + A10/A10	15	15	−19.9	(−32.4,-7.4)	6.3	(−7.2,19.8)	−14.4	(−27.7,-1)	−33	(−54.1,-11.9)
Blagden,M.D., 2007,UK,25	randomised, double-blind, parallel-group, placebocontrolled	E10 + A10/A10	72	76	−14.1	(− 17.9,-10.2)	−0.3	(−4.3,3.6)	−9.2	(− 12.4,-6)	−8.3	NR
Bays,H.E., 2011,USA,26	multicenter, randomized, double-blind, parallel-group	(a)E10 + A20/A40 (b)E10 + A20/A40 (c)E10 + A40/A80 (d)E10 + A40/A80	73 19 176 101	64 28 159 120	−21.9 −13.8 − 15.4 − 18.3	(− 28.1,-15.6) (− 24.6,-3) (− 19.4,-11.3) (− 23.2,-13.3)	3 − 0.1 − 0.2 1.5	(−1.9,7.9) (− 8.7,8.5) (− 2.3,1.9) (−1.1,4.1)	− 13.2 − 9.4 − 9.6 − 10.7	(− 17.5,-9) (− 16.7,-2.1) (− 12.3,-7) (− 13.9,-7.4)	−7.6 − 11.8 − 6.7 − 7.9	(−19,3) (− 25.4,1.3) (− 12.5,-1.2) (− 14.5,-1.7)
Conard,S.E., 2008,USA,27	multicenter, randomized, double-blind, parallel-group	E10 + A20/A40	92	92	−20	(−25,-15)	2	(−2,7)	−12	(− 16,− 9)	-9	(− 18,0)
Conard,S.E., 2010,USA,28	multicentre, randomized, double-blind, parallel-group	(a)E10 + A40/A80 (b)E10 + A40/A80 (c)E10 + A40/A80	61 67 149	66 68 145	−14.3 − 16 − 17.4	(− 20.9,-7.8) (− 22.3,-9.6) (− 21.7,-13.1)	2 1.9 − 0.8	(−1.4,5.4) (−1.4,5.2) (− 3,1.4	−8.9 − 10.1 − 10.4	(−13.2,-4.6) (− 14.2,-5.9) (− 13.2,-7.6)	−6.4 − 7.2 − 7.7	(− 15.1,2.3) (− 15.9,1.6) (− 13.6,-1.8)
Leiter,L.A., 2008,Canada,29	multicenter, randomized, double-blind, parallel-group	E10 + A40/A80	277	279	−16	(−19,-13)	0	(−1,2)	−10	(− 12,-8)	− 7	(− 11,-3)

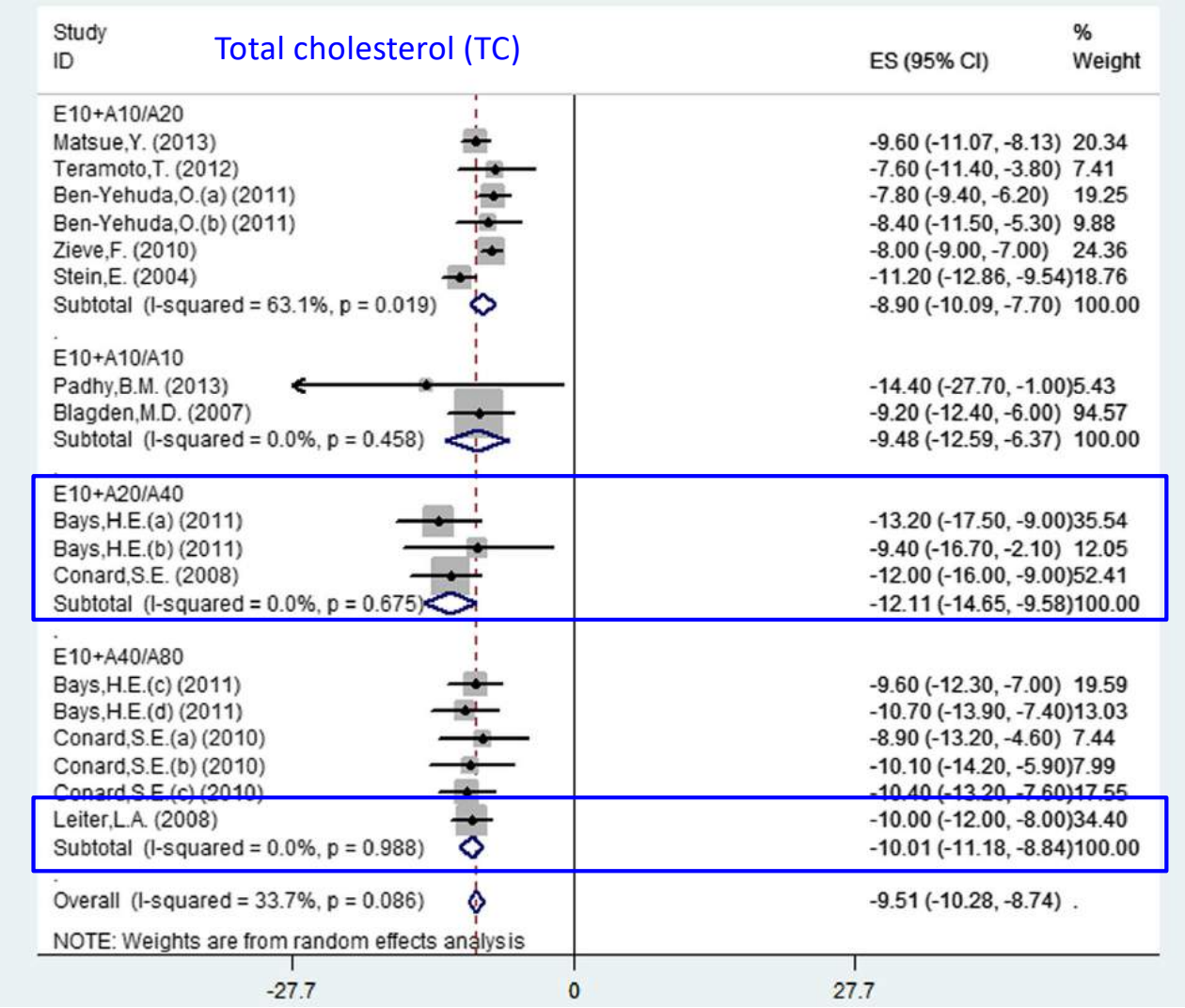
Combination therapy led to a significant reduction in LDL-c

- Pooled data using a fixed-effects model displayed that combination therapy led to a significant reduction in LDL-C (MD = − 15.38, 95% CI: -16.17 to − 14.60, P < 0.0001) with moderate heterogeneity (P = 0.12, I2 = 26.2%) among studies
- **E10 + A20 vs. A40 group was the most obvious (MD = − 19.94, 95% CI: -23.61 to − 16.27, P < 0.0001), by subgroup.**



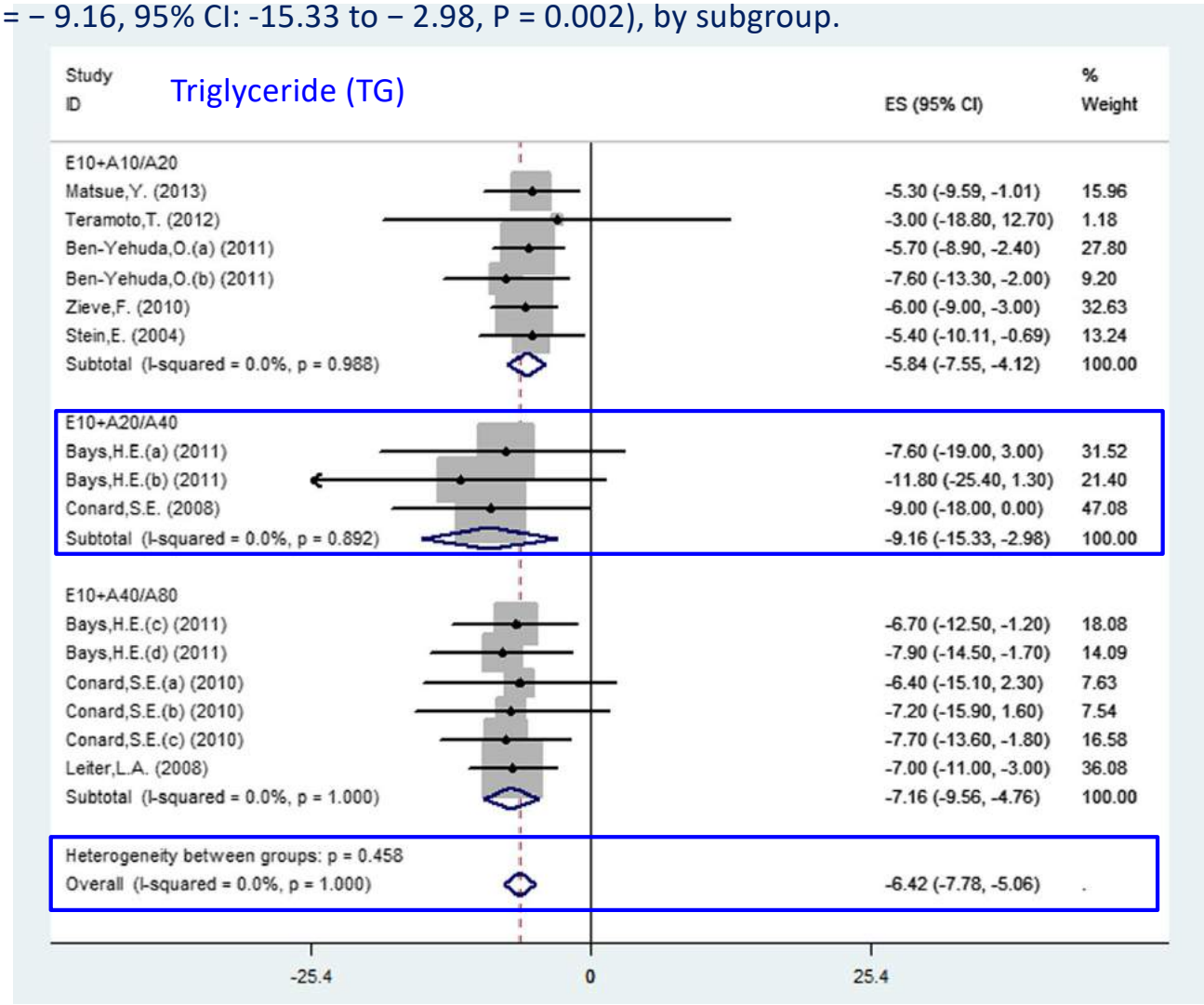
Combination therapy led to a significant reduction in total cholesterol

- There was significant difference between combination and monotherapy (MD = − 9.51, 95% CI: -10.28 to − 8.74, P < 0.0001).
- **E10 + A20 vs. A40 group was the most obvious (MD= − 12.11, 95% CI: -14.65 to − 9.58, P < 0.0001), by subgroup.**



Combination therapy led to a significant reduction in TG

- Combination therapy led to a significant reduction in TG (MD = − 6.42, 95% CI: -7.78 to − 5.06, P < 0.0001) with no heterogeneity (P = 1.00, I2 = 0%) among studies
- The results showed that there **was significant difference in the three doses and the E10 + A20 vs. A40 group was the most obvious** (MD = − 9.16, 95% CI: -15.33 to − 2.98, P = 0.002), by subgroup.



A systematic review and meta analysis of combination therapy and monotherapy were conducted

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Lipids in Health and Disease

REVIEW Open Access

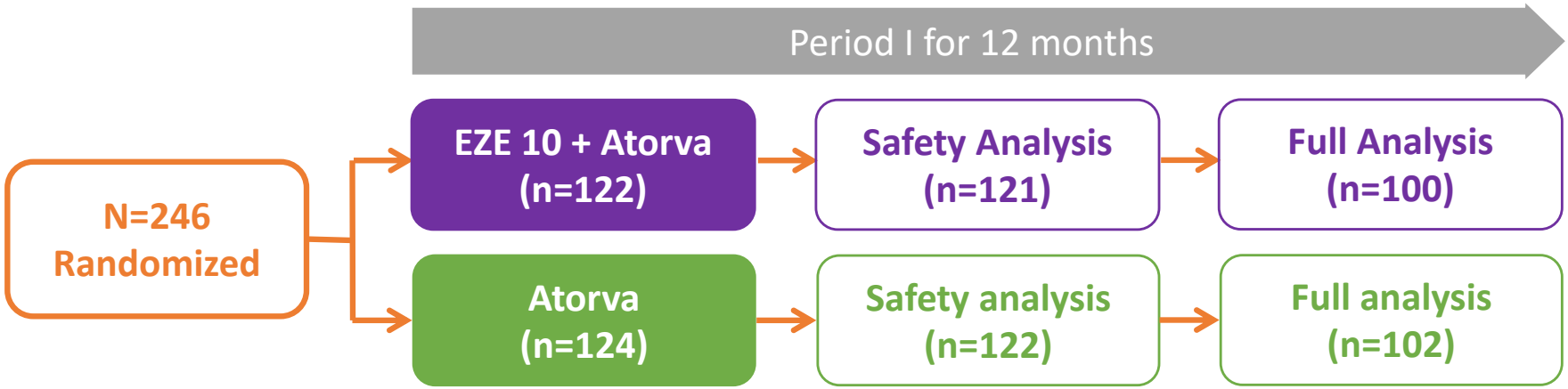
Comparing the combination therapy of ezetimibe and atorvastatin with atorvastatin monotherapy for regulating blood lipids: a systematic review and meta-analyse

Cong Ai[1], Shanshan Zhang[2], Qiao He[1] and Jingpu Shi[1*]

The results of this meta-analysis showed that the overall effectiveness of combination therapy of Ezetimibe and Atorvastatin was significantly better than Atorvastatin monotherapy on lowering LDL-C, TC and TG among all the four doses comparison (E10 + A10/A20; E10 +A10/A10; E10 + A20/A40; E10 + A40/A80)

PRECISE-IVUS Study: Study Design

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



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

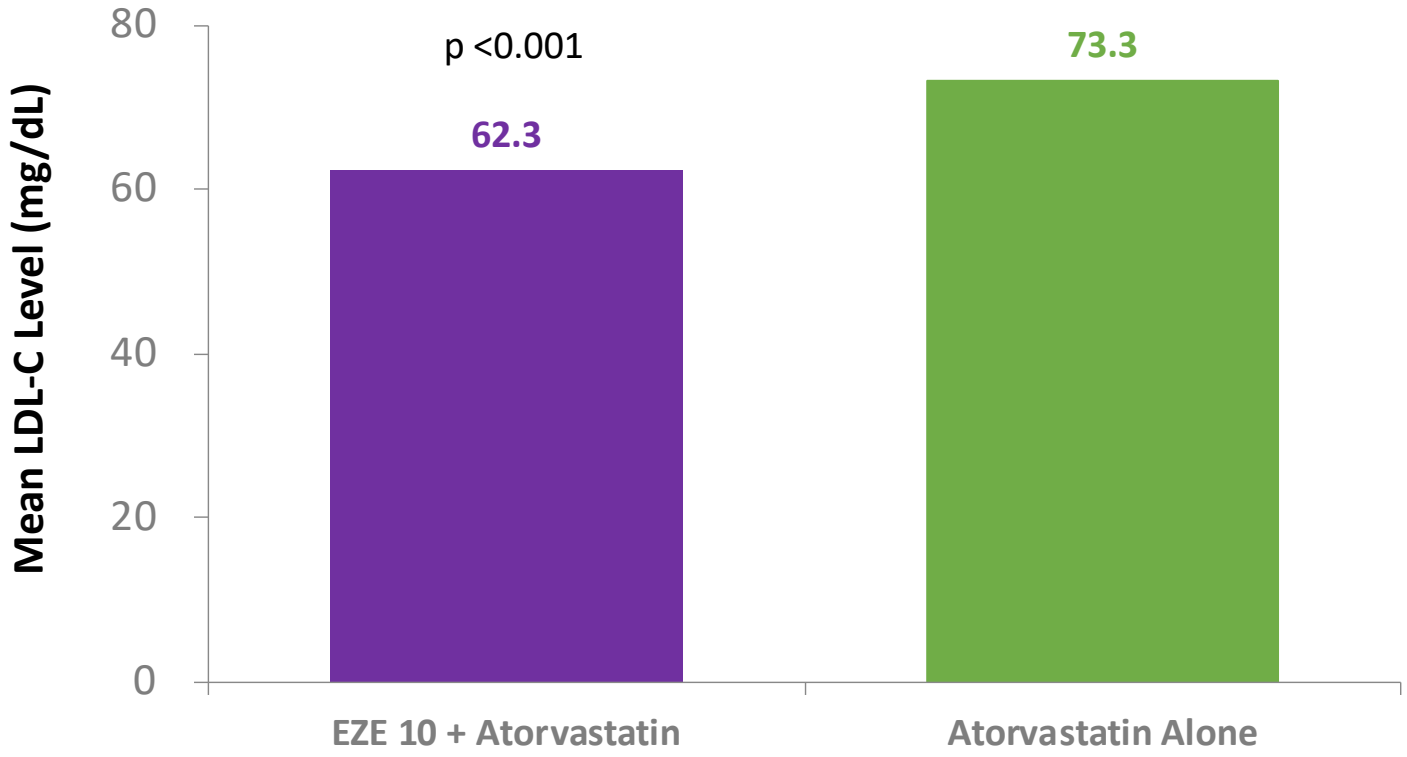
Atorva=atorvastatin; EZE=ezetimibe; CAD=coronary artery disease; PCI=percutaneous coronary intervention; ACS=acute coronary syndrome; SAP=stable angina pectoris;

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

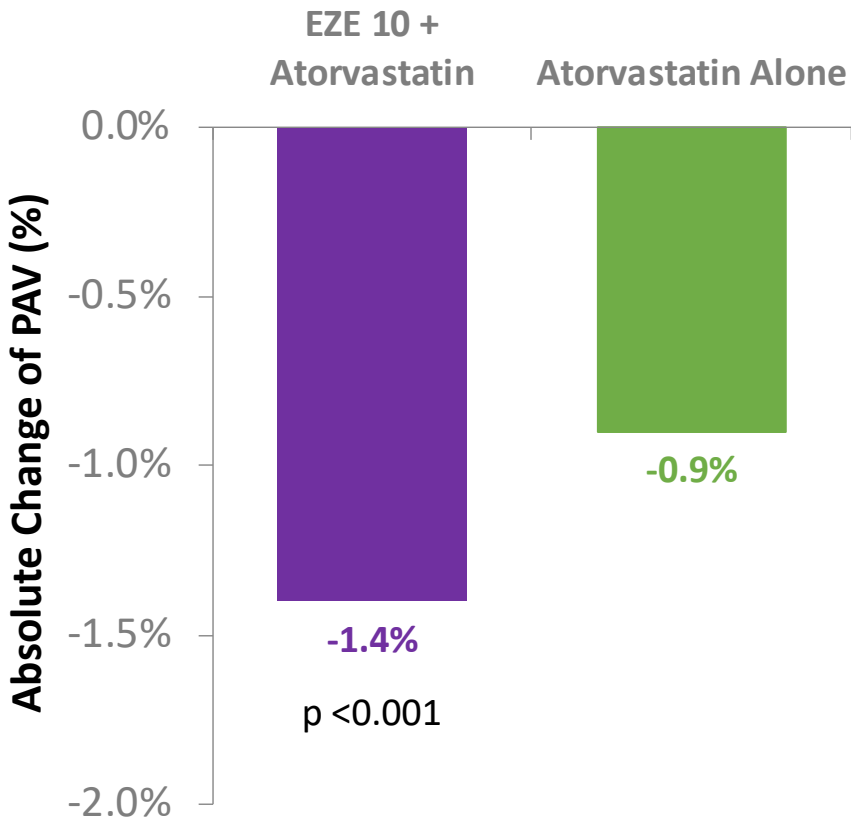


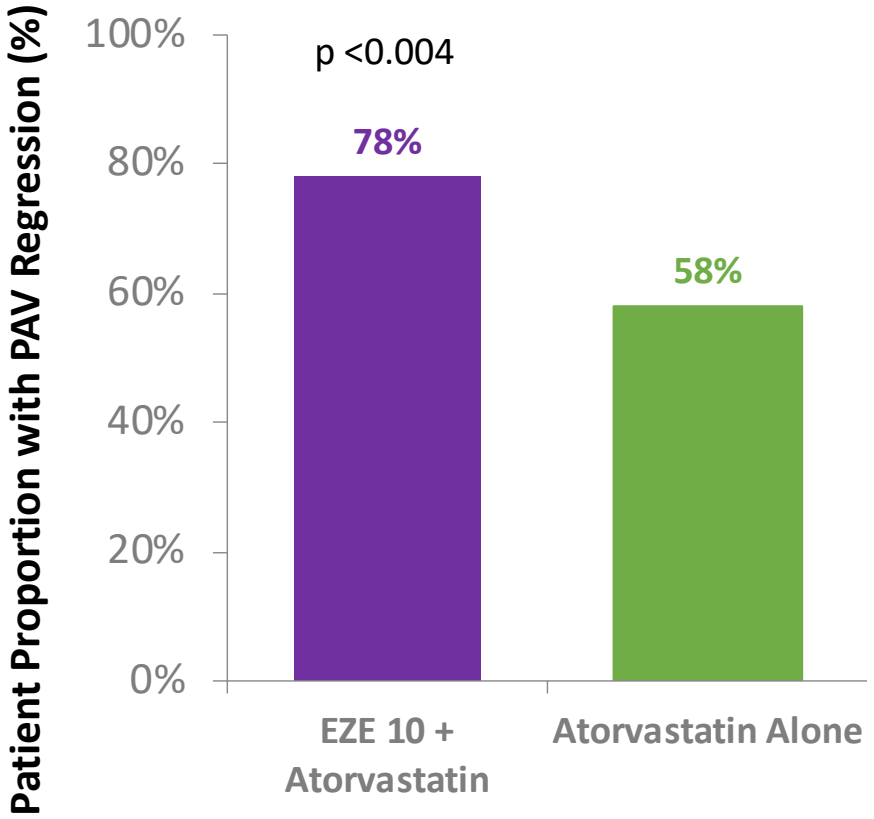
EZE=ezetimibe.

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



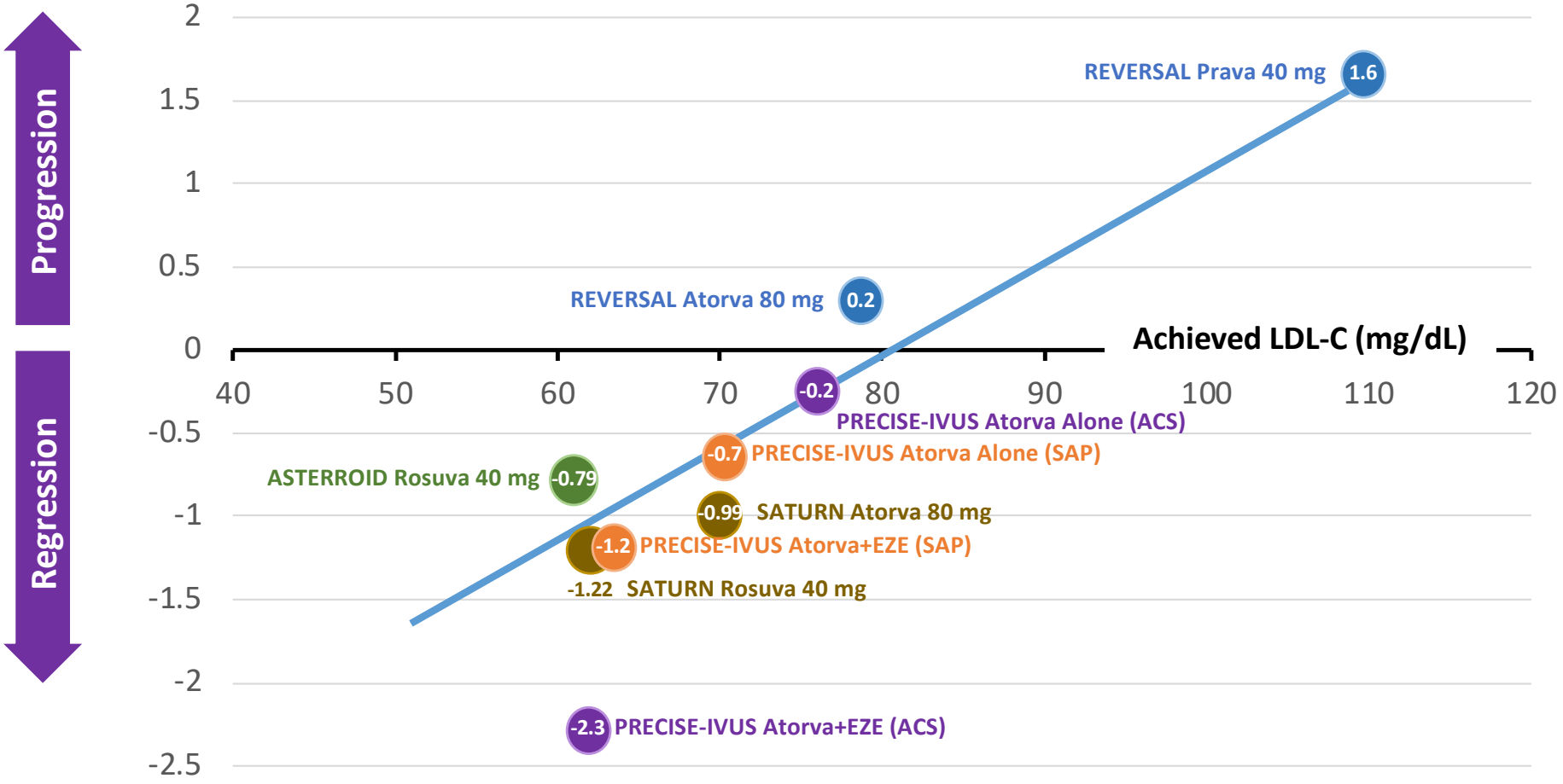


EZE=ezetimibe; PAV=percent atheroma volume.

PRECISE-IVUS Study

Relationship Between LDL-C and PAV

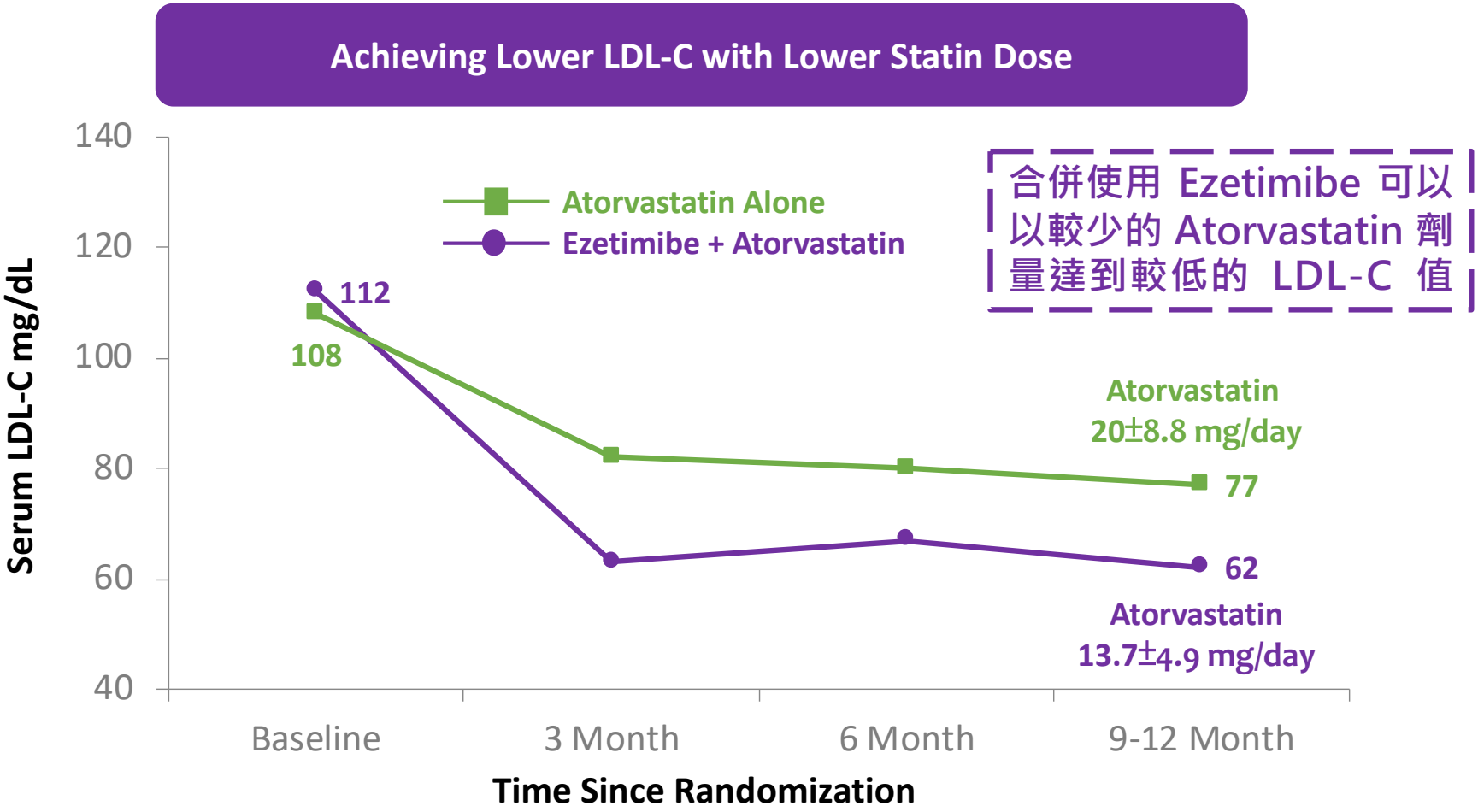
使用Atorva/Eze比起atorva alone，可使ACS病人其粥樣斑塊體積百分比(PAV%)額外下降2.1%;
穩定型心絞痛病人(SAP)其粥樣斑塊體積百分比(PAV%)額外下降0.5%



EZE=ezetimibe; PAV=percent atheroma volume.

PRECISE-IVUS Study: ACS Subgroup

Lower Statin Dose with Higher Potency While Combining with Ezetimibe



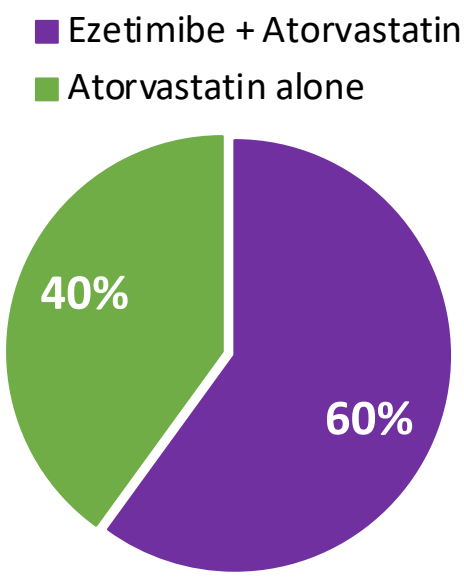
1. Tsujita K, et al. Atherosclerosis. 2016;251(5):367-72.

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

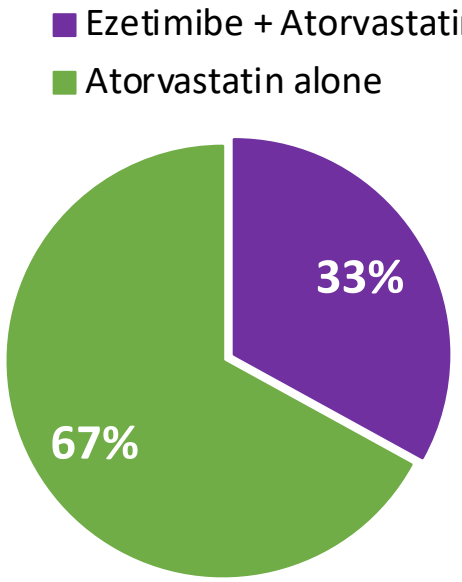
Regression in PAV (n=67)



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.

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

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

Koichiro Fujisue [a], Suguru Nagamatsu [a], Hideki Shimomura [b], Takuro Yamashita [c], Koichi Nakao [d], Sunao Nakamura [e], Masaharu Ishihara [f], Kunihiko Matsui [g], Nobuyasu Yamamoto [h], Shunichi Koide [i], Toshiyuki Matsumura [j], Kazuteru Fujimoto [k], Ryusuke Tsunoda [l], Yasuhiro Morikami [m], Koshi Matsuyama [n], Shuichi Oshima [o], Kenji Sakamoto [a], Yasuhiro Izumiya [a], Koichi Kaikita [a], Seiji Hokimoto [a], Hisao Ogawa [p], Kenichi Tsujita [a,*]

[a] Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

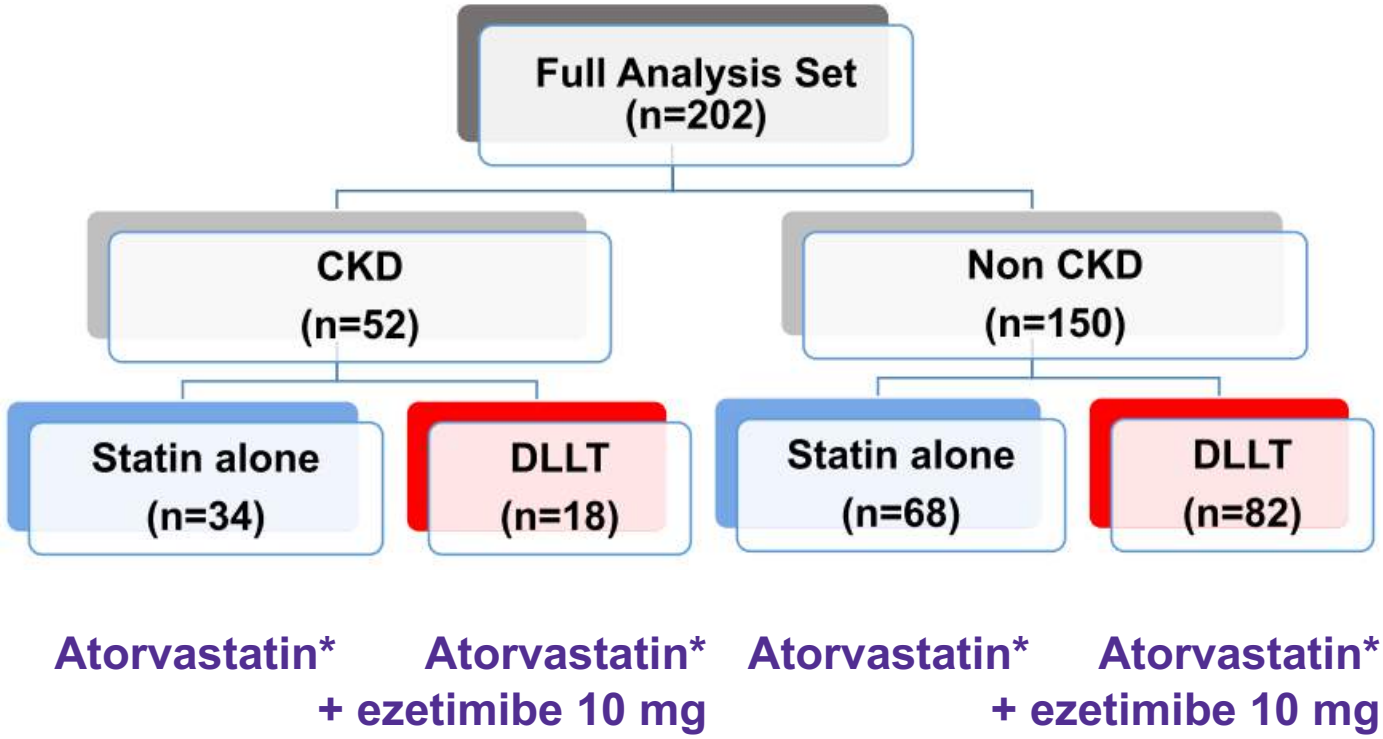
Objectives: hypothesized intensive lipid-lowering with statin/ezetimibe attenuated coronary atherosclerotic development even in patients with CKD.

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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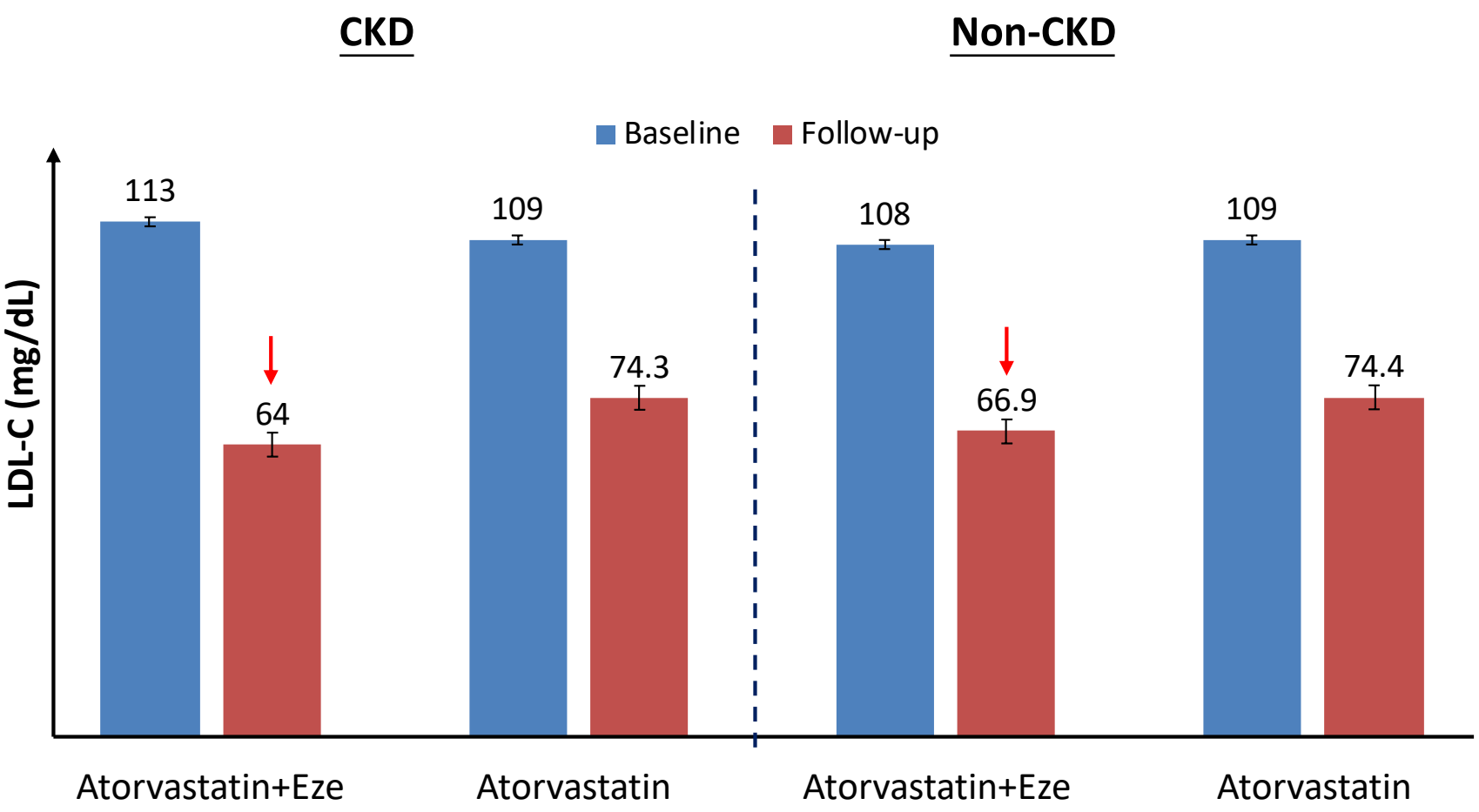

LDL-c reduction in **CKD pts**
Atorvastatin+Ezetimibe −49.0 (−56.2 to 38.9)%
Atorvastatin -34.7(−47.9 to −16.1)%

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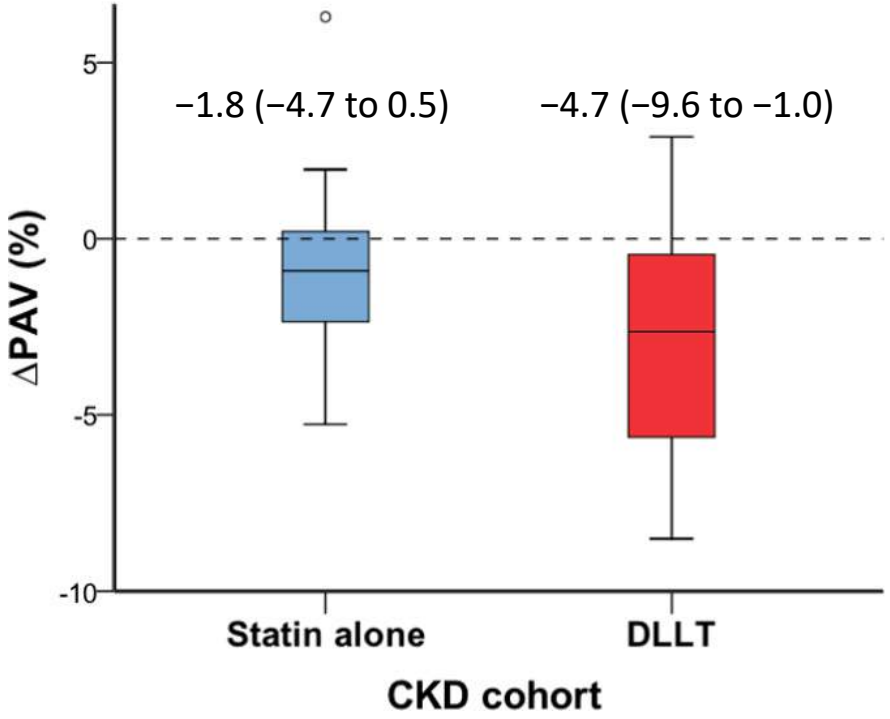
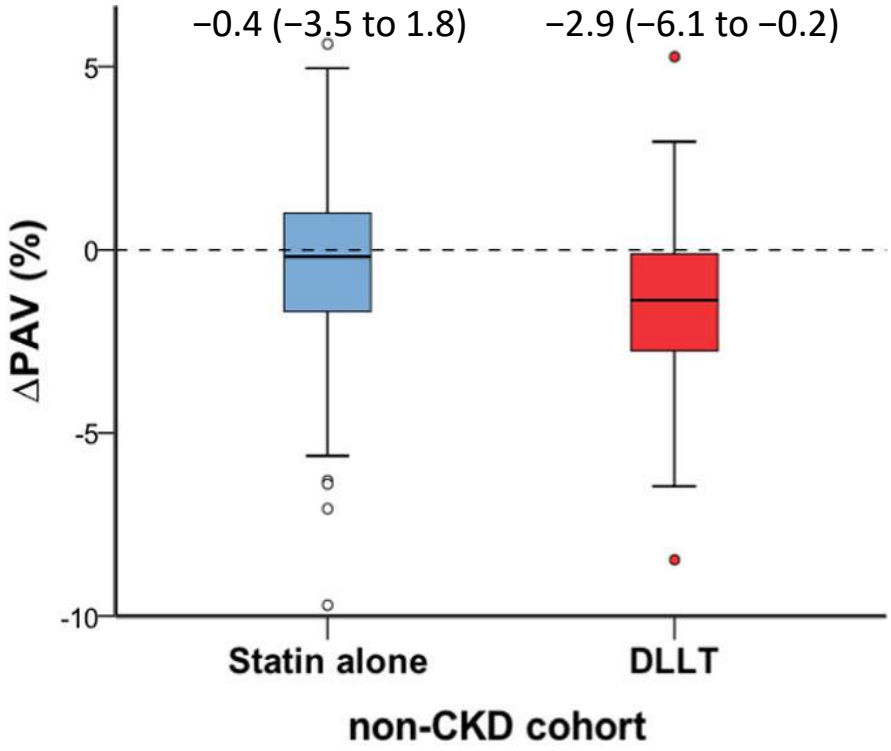
DLLT showed the significantly stronger regression in ΔPAV, compared with atorvastatin alone even in the CKD group.

ΔPAV −2.9 [−4.9 to −0.5]%



ΔPAV −2.5 [−2.6 to 1.2]%



International Journal of Cardiology 268 (2018) 23–26

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

- 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.

European Heart Journal
doi:10.1093/eurheartj/ehv043

REVIEW

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]

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*

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。

EZETROL, VYTORIN, ATOZET健保給付規範

Ezetimibe (如Ezetrol Tablets)：(94/6/1)
原發性高膽固醇血症、同型接合子家族性高膽固醇血症、同型接合子性麥脂醇血症(植物脂醇血症)患者並符合下列條件之一者：
1.符合全民健康保險降血脂藥物給付規定表且對Statins類藥品發生無法耐受藥物不良反應（如Severe myalgia、Myositis）者。
2.符合全民健康保險降血脂藥物給付規定表經使用Statins類藥品單一治療3個月未達治療目標者，得合併使用本案藥品與Statins類藥品。

含ezetimibe及statin類之複方製劑（如Vytorin、Atozet）：
(95/12/1、106/8/1)：
1.限用於原發性高膽固醇血症、同型接合子家族性高膽固醇血症(HOFH)病患並符合全民健康保險降血脂藥物給付規定表，經使用statin類藥品單一治療3個月未達治療目標者(106/8/1)。

Reference:台灣健保署官方網站 https://www.nhi.gov.tw/BBS_Detail.aspx?n=73CEDFC921268679&sms=D6D5367550F18590&s=36B4E98DB1F70A23. Accessed on Jan. 16. 2019.

10/10毫克　衛部藥輸字第 026643 號
10/20毫克　衛部藥輸字第 027283 號

優泰脂膜衣錠 10/10 毫克 , 10/20毫克
ATOZET (Ezetimibe/Atorvastatin) F.C. Tablets 10/10 mg, 10/20 mg

1 適應症與用途

對因高膽固醇血症而使發生動脈粥樣硬化性血管疾病之風險明顯升高的患者，使用血脂改變藥物治療應只是多重危險因子介入治療的一部份。應於僅採取限制飽和脂肪與膽固醇的飲食控制法及其他非藥物方法不足以達到效果時，再以藥物治療輔助飲食控制。

1.1 高膽固醇血症

對於患有原發性 (異型接合子家族性及非家族性) 高膽固醇血症或混合型高血脂症的患者，ATOZET® 可作為飲食之外的輔助治療，以降低升高的總膽固醇 (total-C)、低密度脂蛋白膽固醇 (LDL-C)、載脂蛋白 B (Apo B)、三酸甘油脂 (TG) 及非高密度脂蛋白膽固醇 (non-HDL-C)，並增加高密度脂蛋白膽固醇 (HDL-C)。

1.2 使用限制

在心血管罹病率及死亡率方面，除了 atorvastatin 已證實的效益之外，ATOZET 尚未確定可提供更多的效益。目前尚未針對 Fredrickson 第 I、III、IV 及第 V 型血脂異常進行過 ATOZET 的研究。

2 劑量與用法

2.1 建議劑量

ATOZET 的劑量範圍為 10/10 mg-ezetimibe/atorvastatin 10/80 mg，每日一次。ATOZET 的起始建議劑量為 10/10 mg 或 ezetimibe/atorvastatin 10/20 mg，每日一次。ATOZET 可於一天當中的任何時間隨食物或不隨食物投予單一劑量。對需要較大幅度之 LDL-C 降低效果 (大於 55%) 的患者，建議的起始劑量為 ezetimibe/atorvastatin 10/40 毫克/日。在開始使用 ATOZET 之後及/或調整劑量時，應於 2 週 (含) 以上的時間內進行血脂檢測，並據以調整劑量。患者應將 ATOZET 錠劑整粒吞服。不可將錠劑研碎、溶解或咀嚼使用。

2.3 與其他藥品併用

ATOZET 的給藥時間應在膽酸螯合劑服藥前 ≥2 小時或服藥後 ≥4 小時。若患者正接受 cyclosporine 或人類免疫缺乏病毒 (HIV) 蛋白酶抑制劑-tipranavir 併用 ritonavir 或 C 型肝炎病毒蛋白酶抑制劑-telaprevir 治療，應避免給予 ATOZET。若患者正接受人類免疫缺乏病毒 (HIV) 蛋白酶抑制劑-lopinavir 併用 ritonavir 治療，則使用 ATOZET 時應小心並應給予最低劑量。若患者正接受 clarithromycin、itraconazole，或 C 型肝炎抗病毒藥物-elbasvir、grazoprevir 等，或患者正接受人類免疫缺乏病毒 (HIV) 蛋白酶抑制劑-saquinavir 併用 ritonavir、darunavir 併用 ritonavir、fosamprenavir，或 fosamprenavir 併用 ritonavir 治療，則 ezetimibe/atorvastatin 的劑量不得超過 10/20 mg，同時應進行適當的臨床評估以確保所給予的 ezetimibe/atorvastatin 劑量為最低必要劑量。若患者正接受人類免疫缺乏病毒 (HIV) 蛋白酶抑制劑-nelfinavir，或 C 型肝炎病毒蛋白酶抑制劑-boceprevir 治療，則 ezetimibe/atorvastatin 的劑量不得超過 10/40 mg，同時應進行適當的臨床評估以確保所給予的 ezetimibe/atorvastatin 劑量為最低必要劑量 。ATOZET 不建議與 gemfibrozil 併用。

3 劑型與劑量規格

ATOZET 10 mg/10 mg (ezetimibe 10 mg/atorvastatin 10 mg) 錠劑為白色至乳白色膠囊形狀、雙面突起的膜衣錠，一面有 ”257” 的字樣。

ATOZET 10 mg/20 mg (ezetimibe 10 mg/atorvastatin 20 mg) 錠劑為白色至乳白色膠囊形狀、雙面突起的膜衣錠，一面有 “333”的字樣。

本藥須由醫師處方使用

Selected Safety Information

適應症與用途
對因高膽固醇血症而使發生動脈粥樣硬化性血管疾病之風險明顯升高的患者，使用血脂改變藥物治療應只是多重危險因子介入治療的一部份。應於僅採取限制飽和脂肪與膽固醇的飲食控制法及其他非藥物方法不足以達到效果時，再以藥物治療輔助飲食控制。

安全性資訊摘要

禁忌
活動性肝病或不明原因的肝臟轉胺酶持續升高。

對ATOZET的任何成分過敏。

已經懷孕或可能已經懷孕的婦女。對孕婦投予ATOZET可能會導致胎兒損害。在正常懷孕期間，血中膽固醇與三酸甘油脂都會升高，且膽固醇或膽固醇衍生物乃是胎兒發育的必需物質。動脈粥樣硬化是一個長期發展的過程，因此，在懷孕期間停用降血脂藥物對原發性高膽固醇血症之長期治療結果的影響應該極小。目前並無適當且控制良好的在懷孕期間使用ATOZET的研究；不過，有極少數的報告指出，在出生前暴露於statin類藥物之後，曾觀察到發生先天性異常的現象。

授乳母親。目前並不確知atorvastatin是否會分泌進入人類的乳汁；不過，同類別的另一種藥物則有少量會移行進入乳汁。由於statin類藥物可能會使餵哺母乳的嬰兒發生嚴重的不良反應，因此，須使用ATOZET治療的婦女不可為她們的嬰兒餵哺母乳。

警告及注意事項
肌病變/橫紋肌溶解症
Atorvastatin
使用atorvastatin及其他這類藥物曾發生過橫紋肌溶解症伴隨肌球蛋白尿(myoglobinuria)，繼之發生急性腎衰竭之罕見個案。腎功能不全病史可能為引發橫紋肌溶解症的危險因子。這些患者使用本藥時，應嚴密監測其對骨骼肌的影響。
Ezetimibe
在ezetimibe的上市後使用經驗中，曾有發生肌病及橫紋肌溶解的病例報告。發生橫紋肌溶解的患者大部份在開始使用ezetimibe前都正在使用statin類藥物。不過，在單獨使用ezetimibe治療時，以及將ezetimibe與已知會升高發生橫紋肌溶解之風險的藥物(如fibric acid衍生物)併用時，也曾有發生橫紋肌溶解的報告。將ATOZET與fenofibrate併用時，如果確診或疑似發生肌病，應立即停用這兩種藥物。如果出現肌肉症狀且CPK檢測值>10倍正常值之上限 (ULN)，即表示發生肌病。

肝臟酵素
肝臟酵素檢測建議在ATOZET 開始治療前先進行，並視臨床需要重覆檢測。患者接受statins(包括atorvastatin)治療曾發生過致死性及非致死性肝衰竭的罕見上市後報告。ATOZET治療期間如出現具臨床症狀的嚴重肝臟受損及/或高膽紅素血症或黃疸，應立刻中斷治療。若無法找出其他的可能病因，則ATOZET不可重新給藥。
若患者飲酒過度及/或有肝病病史，則使用ATOZET時應小心。有活動性肝病或不明原因的轉氨酶濃度持續升高者，禁止使用ATOZET 。

內分泌功能
有報告指出，使用HMG-CoA還原酶抑制劑(包括atorvastatin)治療會使糖化血色素及空腹血糖值上升。

不良反應
橫紋肌溶解與肌病
肝臟酵素異常

上市後的使用經驗
血液與淋巴系統疾患：血小板減少症
神經系統疾患：頭痛；感覺遲鈍；感覺異常；周邊神經病變
眼部疾患：視力模糊；視覺障礙
耳朵和內耳方面疾患：耳鳴；聽力喪失
血管疾患：高血壓
呼吸道、胸部和縱膈方面疾患：咳嗽；咽喉痛；鼻出血
胃腸道疾患：胰臟炎；胃食道逆流；打嗝；嘔吐
皮膚與皮下組織疾患：禿頭症；搔癢症；皮疹；多型性紅斑；血管神經性水腫；水泡性皮膚病(包括多型性紅斑、Stevens-Johnson症侯群以及毒性上皮壞死溶解症)
肌肉骨骼與結締組織疾患：肌病/橫紋肌溶解；頸部疼痛；關節腫脹；肌炎；肌腱炎，嚴重時導致肌腱斷裂
曾有極少數在使用statin類藥物期間伴隨發生免疫媒介性壞死性肌病(IMNM；一種自體免疫性肌肉病變)的報告
生殖系統與乳房方面疾患：男性乳房發育症

其他仿單內容，處方前請詳閱藥品仿單說明書。

Combination Therapy: An Approach To Help Treat Hypercholesterolemia

Before initiating therapy, please consult the manufacturer's Prescribing Information.

MSD does not recommend the use of any product in any different manner than as described in the Prescribing Information, which is available at this presentation.

TW-ATO-00001 05/12/2020 (CARD-1114533-0000 10/14)

BACK UP SLIDE

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

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

	健保價
EZETROL	21.6
VYTORIN	22.4
ATOZET 10/20	26.2

Atorvastatin	健保價
10mg	13.3
20mg	22.2
40mg	26.4
80mg	52.8 (40mg*2)

Rosuvastatin	健保價
5mg	12.2 - 15
10mg	15.2 - 18.5
20mg	26.4 - 31.7

*Rosuvastatin最低價格為generic價格，最高價格為Crestor價格

*超過50% LDL-c降幅的lipid lowering therapy中，Atozet 10/20健保價最低，療效較強

Atozet
(ezetimibe and atorvastatin, MSD)

European Heart Journal (2016) 0, 1–9
doi:10.1093/eurheartj/ehw377

Acute coronary syndromes

The benefit of adding ezetimibe to statin therapy in patients with prior coronary artery bypass graft surgery and acute coronary syndrome in the IMPROVE-IT trial

- **Objective: To examine the efficacy and safety of ezetimibe added to statin in patients with prior coronary artery bypass graft surgery (CABG) following hospitalization for an acute coronary syndrome (ACS).**

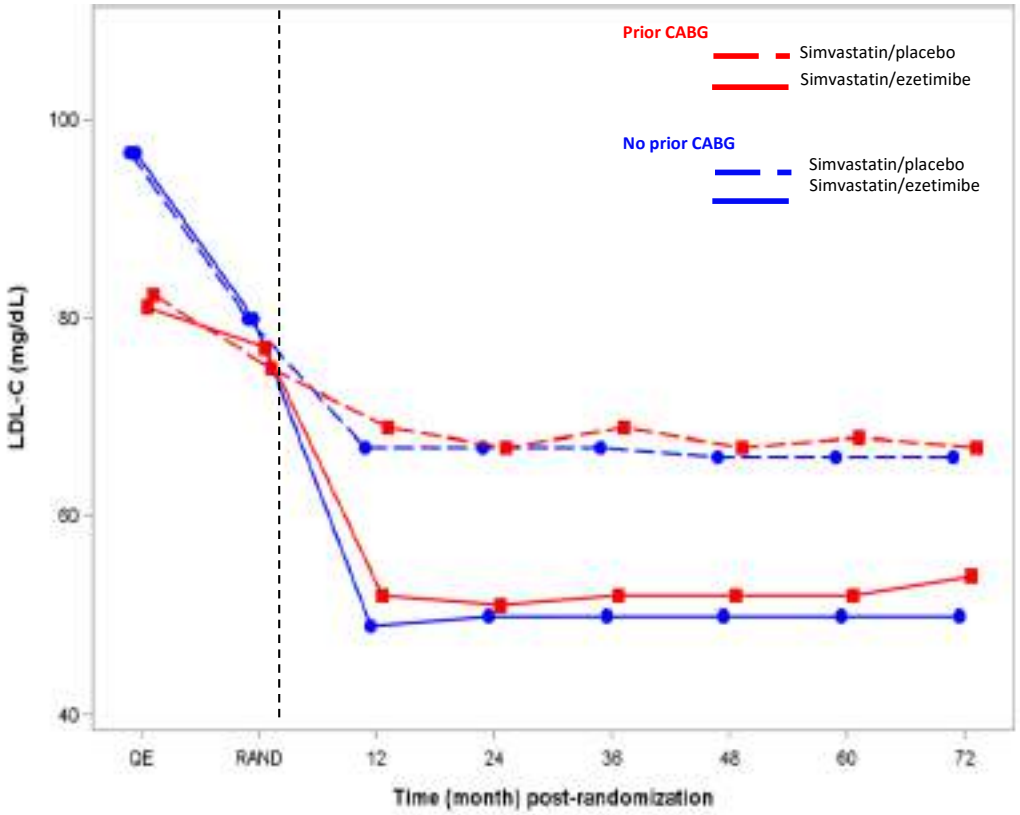
- **Conclusion: The clinical benefit of adding ezetimibe to statin appears to be enhanced in patients with prior CABG, supporting the use of intensive lipid lowering therapy in these high-risk patients following ACS.**

Characteristics—n (%)	Total (n = 18 134)	Prior CABG (n = 1684)	No prior CABG (n = 16 450)	P-value
Age, median (IQR), years	63.2 (56.8, 71.1)	68.9 (61.9, 75.2)	62.7 (56.4, 70.5)	<0.001
Age ≥ 75 years	2796 (15.4)	432 (25.7)	2364 (14.4)	<0.001
Male	13 723 (75.7)	1385 (82.2)	12 338 (75.0)	<0.001
White Race	15 195 (83.8)	1443 (85.7)	13 752 (83.6)	0.03
BMI, median (IQR), kg/m^2	27.5 (24.9, 30.9)	27.7 (25.1, 30.9)	27.5 (24.8, 30.9)	0.05
Region				<0.001
North America	6970 (38.4)	661 (39.3)	6309 (38.4)	
Western Europe	7267 (40.1)	695 (41.3)	6572 (40.0)	
Eastern Europe	1416 (7.8)	113 (6.7)	1303 (7.9)	
Asia Pacific	896 (4.9)	46 (2.7)	850 (5.2)	
South America	1585 (8.7)	169 (10.0)	1416 (8.6)	
Diabetes mellitus	4933 (27.2)	686 (40.7)	4247 (25.8)	<0.001
Hypertension	11 136 (61.4)	1327 (78.8)	9809 (59.6)	<0.001
Hypercholesterolemia	13 151 (72.5)	1521 (90.3)	11 630 (70.7)	<0.001
Congestive heart failure	790 (4.4)	252 (15.0)	538 (3.3)	<0.001
Peripheral artery disease	1005 (5.5)	245 (14.5)	760 (4.6)	<0.001
Current smoker	5978 (33.0)	280 (16.6)	5698 (34.6)	<0.001
Previous MI	3806 (21.0)	999 (59.4)	2807 (17.1)	<0.001
Previous PCI	3562 (19.6)	756 (45.0)	2806 (17.1)	<0.001
Previous stroke/TIA	1071 (5.9)	167 (9.9)	904 (5.5)	<0.001
Medications before index ACS				
Statin	6246 (34.5)	1317 (78.3)	4929 (30.0)	<0.001
Aspirin	7654 (42.2)	1408 (83.7)	6246 (38.0)	<0.001
At index ACS event				
Type of event				
STEMI	5189 (28.6)	96 (5.7)	5093 (31.0)	<0.001
NSTEMI	8555 (47.2)	832 (49.4)	7723 (47.0)	0.06
Unstable angina	4386 (24.2)	756 (44.9)	3630 (22.1)	<0.001
Diagnostic catheterization	15 923 (87.8)	1328 (78.9)	14 595 (88.8)	<0.001
Pre-randomization PCI	12 705 (70.1)	832 (49.4)	11 873 (72.2)	<0.001
Lipid profile				
LDL-C, median (IQR), mg/dL	95.0 (79.0, 110.0)	81.2 (69.6, 94.0)	96.7 (81.0, 111.4)	<0.001
HDL-C, median (IQR), mg/dL	40.0 (33.0, 49.0)	38.3 (31.3, 46.0)	40.0 (33.0, 49.1)	<0.001
Total cholesterol, median (IQR), mg/dL	162.4 (144.0, 181.0)	146.9 (131.5, 164.0)	165.0 (146.1, 181.7)	<0.001
Triglycerides, median (IQR), mg/dL	120.0 (88.0, 172.0)	121.0 (88.0, 174.0)	120.0 (85.0, 171.8)	0.19
Creatinine clearance, median (IQR), mL/min	84.6 (65.8, 107.0)	74.6 (57.1, 94.4)	85.6 (66.8, 108.0)	<0.001
Medications at time of randomization				
Aspirin	17 591 (97.0)	1596 (94.8)	15 995 (97.3)	<0.001
Thienopyridine	15 601 (86.5)	1331 (79.0)	14 350 (87.2)	<0.001
Beta blocker	15 791 (87.1)	1484 (88.1)	14 307 (87.0)	0.19
ACE-I or ARB	13 699 (75.6)	1322 (78.5)	12 377 (75.3)	0.003

Eisen A et al., European Heart Journal (2016) 0, 1–9. doi:10.1093/eurheartj/ehw377

LDL-C levels by prior CABG and treatment arm

The median time-weighted LDL-C level during the trial was 55.0mg/dL with simvastatin/ ezetimibe and 69.9mg/dL with simvastatin/ placebo in patients with prior CABG (P<0.001), and these values were 53.6 and 69.5mg/dL, respectively, in patients without prior CABG (P<0.001).



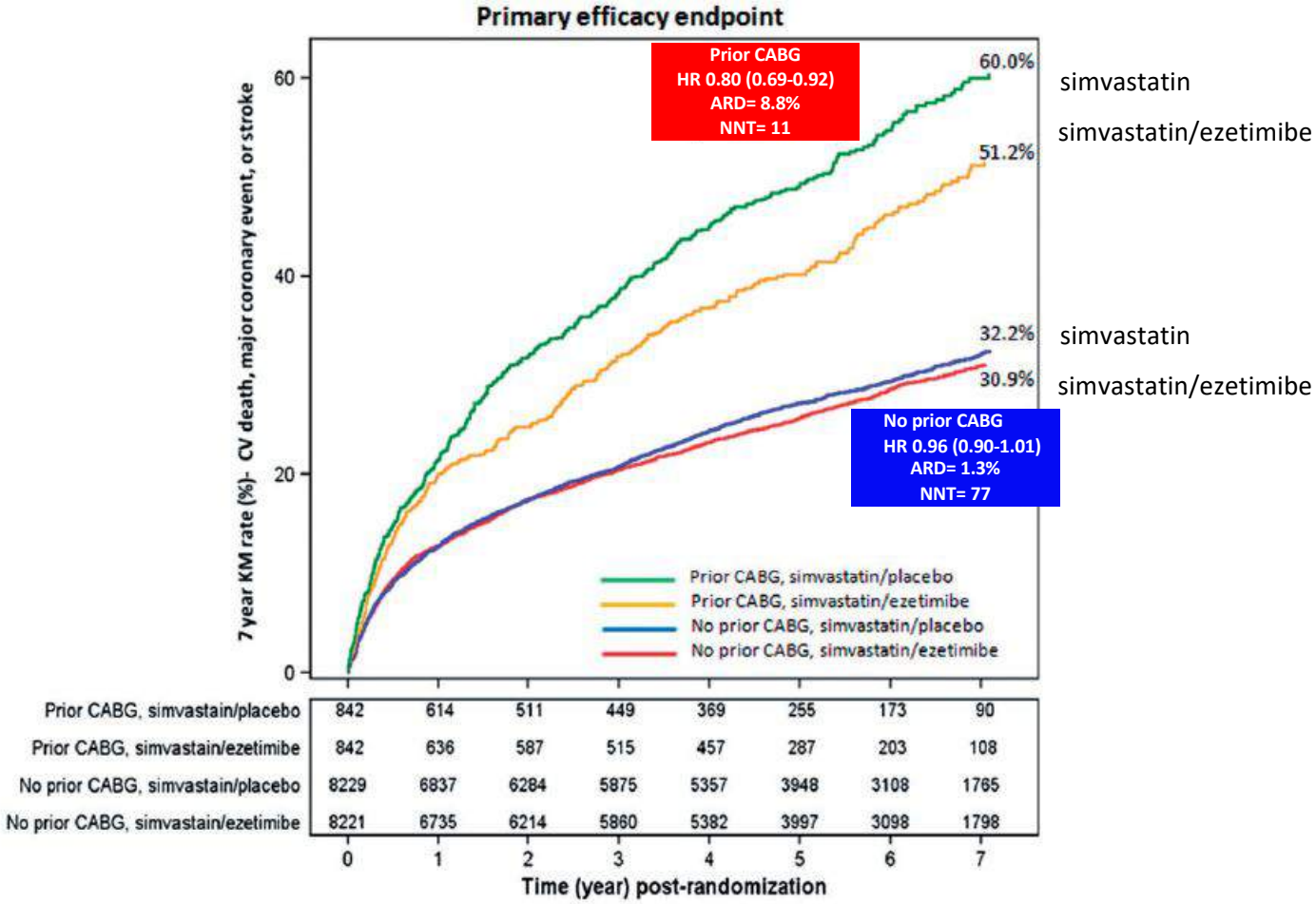
Median time-weighted LDL-C (mg/dL)

69.9
69.5
P<0.001
55.0
53.6
P<0.001

For both pts with prior CABG or not, Eze add-on benefits equally

Eisen A et al., European Heart Journal (2016) 0, 1–9. doi:10.1093/eurheartj/ehw377

Primary endpoint



Kaplan-Meier curves for the primary efficacy endpoint by prior CABG status and treatment arm.

Eisen A et al., European Heart Journal (2016) 0, 1–9. doi:10.1093/eurheartj/ehw377

‘Hard’ endpoints

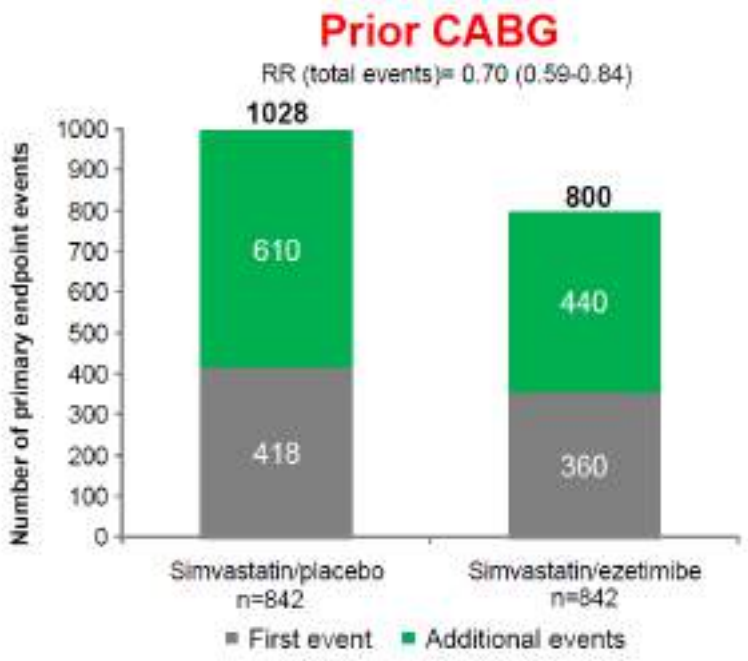
Endpoint- % *	Prior CABG			No prior CABG			P-interaction
	Simvastatin/ placebo (n=842)	Simvastatin/ ezetimibe (n=842)	HR (95% CI)	Simvastatin/ placebo (n=8229)	Simvastatin/ ezetimibe (n=8221)	HR (95% CI)	
CV death, MI, stroke	**47.8**	**39.0**	**0.77 (0.66-0.91)**	**19.8**	**18.6**	**0.93 (0.86-1.00)**	0.05

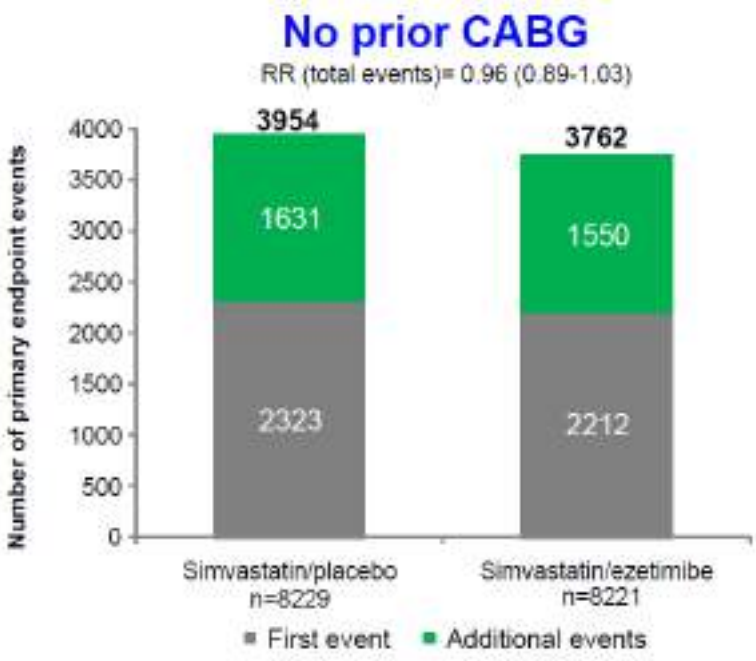
* % denotes 7-Y KM Rate

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

Fewer total primary events during follow-up in the prior CABG group with simvastatin/ezetimibe (n=800) vs. simvastatin/placebo (n=1028, RR 0.70 [0.59–0.84]), and in patients without prior CABG (n=3762 vs. n=3954, RR 0.96[0.89–1.03]

First, additional, and total primary endpoint events





* Note different scales of Y axis

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There was no significant interaction by prior CABG status and treatment arm for any of the safety endpoints

Safety endpoints

IMPROVE-IT

Safety endpoint- %	Prior CABG		No prior CABG	
	Simvastatin/ placebo (n=842)	Simvastatin/ ezetimibe (n=842)	Simvastatin/ placebo (n=8229)	Simvastatin/ ezetimibe (n=8221)
Elevated liver enzymes*	2.6	2.7	2.3	2.4
Gallbladder-related adverse events	5.0	4.4	3.4	3.0
Rhabdomyolysis, myopathy, myalgia with CK elevation≥ 5X ULN	0.5	0.8	0.7	0.6
Cancer ‡	13.4	12.2	9.9	10.0

P values for each endpoint within each group and p-interaction by prior CABG status are non-significant.

* Elevated liver enzymes were defined as ALT and/or AST≥ 3x ULN.
‡ Percentages for cancer are 7-year Kaplan-Meier estimates. Cancer includes any new, relapsing, or progressing cancer, excluding non-melanoma skin cancer.

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Conclusions:

In this **very high-risk group, the addition of ezetimibe to simvastatin reduced the risk of the primary endpoint by 20%.** In addition, the simvastatin/ezetimibe group exhibited a more robust reduction of additional (non-first) events in the prior CABG group.

(ezetimibe added to statin reduces CV events in patients after ACS, it appears to have a particularly enhanced benefit in high-risk individuals.)

Limitations:

- Patients with prior CABG represent only 9% of the IMPROVE-IT population, thus limiting the power to detect differences in the composite and individual endpoints.
- It should not be concluded, based on these findings, that patients without prior CABG do not deserve intensive lipid-lowering therapy post-ACS, since other high risk features (e.g. advanced age, diabetes, prior stroke) may be present that warrant aggressive treatment to reduce the future risk of a CV event.

Eisen A et al., European Heart Journal (2016) 0, 1–9. doi:10.1093/eurheartj/ehw377

Top 10 Take Home Messages from 2018 AHA Guideline

1. In all individuals, emphasize a heart-healthy lifestyle across the life course.
   強調有助於心臟健康的生活方式

2. In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.
   針對具有ASCVD的病人，可使用高強度的Statin或是使用到最高容忍劑量Statin以降低LDL-c

3. In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L)to consider addition of nonstatins to statin therapy.
   針對非常高風險ASCVD的病人，為了達到降低LDL-c小於70 mg/dL的標準，可以考慮使用non-statin therapy

4. In patients with severe primary hypercholesterolemia (LDL-C level ≥ 190 mg/dL[≥4.9 mmol/L])without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk.
   針對具有嚴重原發性高膽固醇血症 (LDL-c ≥ 190 mg/dL)、而未計算十年ASCVD風險的病人，建議以高強度Statin進行起始治療。

5. In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk.
   針對年紀介於40-75歲之間、且LDL-c ≥70 mg/dL 、而未計算十年ASCVD風險的糖尿病病人，建議以高強度Statin進行起始治療。

Top 10 Take Home Messages from 2018 AHA Guideline

6. In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.
針對年紀介於40-75歲之間、考量Primary ASCVD Prevention的病人，在使用Statin therapy之前，醫師與病人間可針對風險因子進行討論

7. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.
針對年紀介於40-75歲之間、沒有糖尿病病史、LDL-c ≥70 mg/dL、且十年風險ASCVD因子≥7.5%的病人，若討論結果偏向Statin療法，建議以中強度的statin做起使治療

8. In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy.
針對年紀介於40-75歲之間、沒有糖尿病病史、十年風險估算值介於7.5% - 19.9% (中等風險)，建議使用Statin療法做起始治療

9. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL-189 mg/dL (≥1.8-4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.
針對年紀介於40-75歲之間、沒有糖尿病病史、LDL-c ≥70 mg/dL、十年風險估算值介於7.5% - 19.9% ，可考慮衡量Coronary Artery Calcium test (CAC test) 冠狀動脈電腦斷層造影以決定是否使用Statin治療

10. Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.
在使用statin起始治療、或有劑量調整4-12周後，每3-12個月可評估病患服藥順從度、LDL-c降幅、生活習慣以調整治療。

Top 10 Take Home Messages from 2018 AHA Guideline

1. In all individuals, emphasize a heart-healthy lifestyle across the life course.
   強調有助於心臟健康的生活方式
2. In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.
   針對具有ASCVD的病人，可使用高強度的Statin或是使用到最高容忍劑量Statin以降低LDL-c
3. In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L)to consider addition of nonstatins to statin therapy.
   針對非常高風險ASCVD的病人，為了達到降低LDL-c小於70 mg/dL的標準，可以考慮使用non-statin therapy
4. In patients with severe primary hypercholesterolemia (LDL-C level ≥ 190 mg/dL[≥4.9 mmol/L])without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk.
   針對具有嚴重原發性高膽固醇血症 (LDL-c ≥ 190 mg/dL)、而未計算十年ASCVD風險的病人，建議以高強度Statin進行起始治療。
5. In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk.
   針對年紀介於40-75歲之間、且LDL-c ≥70 mg/dL 、而未計算十年ASCVD風險的糖尿病病人，建議以高強度Statin進行起始治療。

Top 10 Take Home Messages from 2018 AHA Guideline

6. In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.

   針對年紀介於40-75歲之間、考量Primary ASCVD Prevention的病人，在使用Statin therapy之前，醫師與病人間可針對風險因子進行討論

7. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.

   針對年紀介於40-75歲之間、沒有糖尿病病史、LDL-c ≥70 mg/dL、且十年風險ASCVD因子≥7.5%的病人，若討論結果偏向Statin療法，建議以中強度的statin做起使治療

8. In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy.

   針對年紀介於40-75歲之間、沒有糖尿病病史、十年風險估算值介於7.5% - 19.9% (中等風險)，建議使用Statin療法做起始治療

9. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL-189 mg/dL (≥1.8-4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.

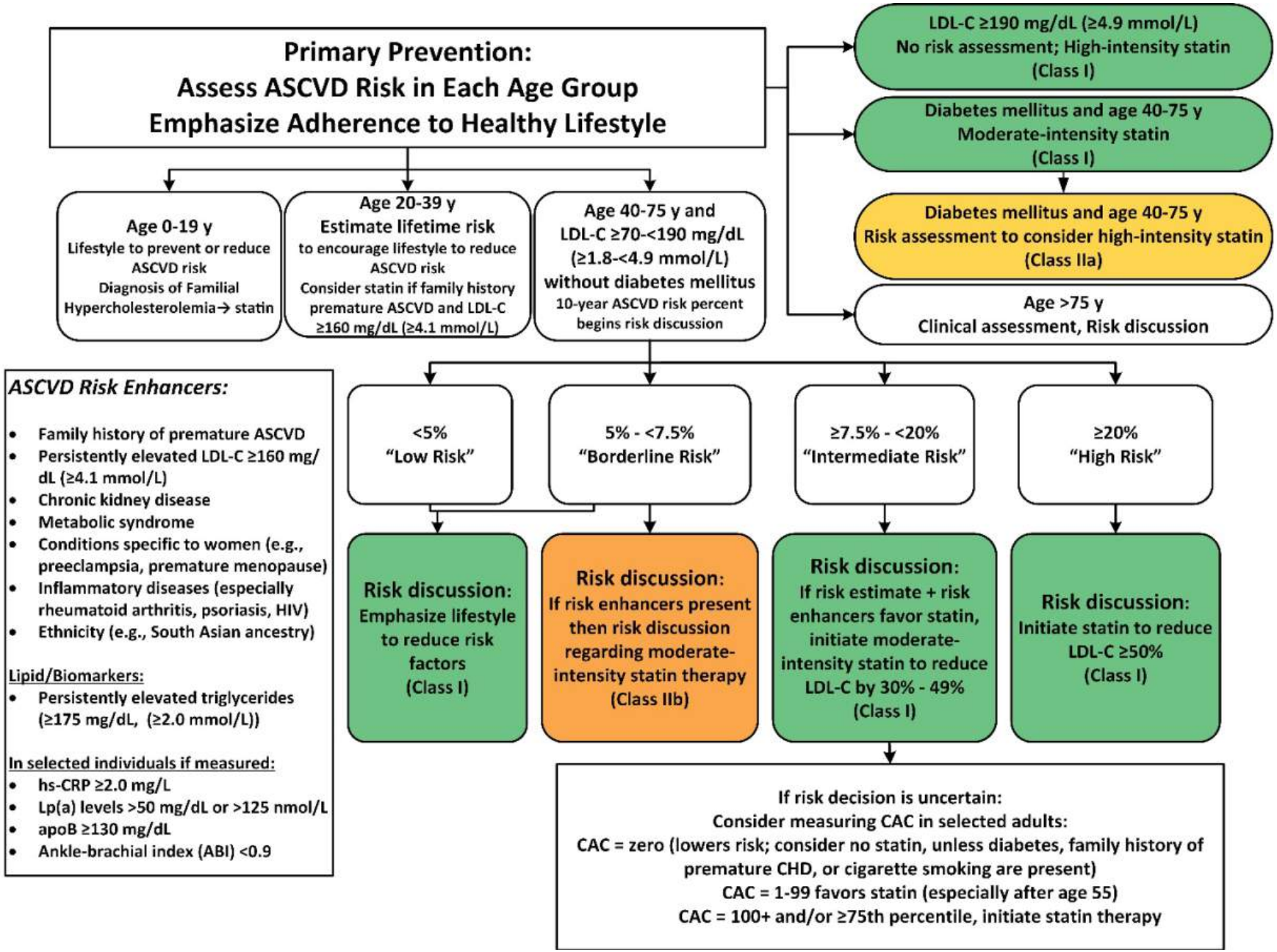
   針對年紀介於40-75歲之間、沒有糖尿病病史、LDL-c ≥70 mg/dL、十年風險估算值介於7.5% - 19.9% ，可考慮衡量Coronary Artery Calcium test (CAC test) 冠狀動脈電腦斷層造影以決定是否使用Statin治療

10. Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.

    在使用statin起始治療、或有劑量調整4-12周後，每3-12個月可評估病患服藥順從度、LDL-c降幅、生活習慣以調整治療。

Atozet
(ezetimibe and atorvastatin, MSD)

Primary Prevention



Risk-Enhancing Factors for Clinician–Patient Risk Discussion

Risk-Enhancing Factors

• **Family history of premature ASCVD** (males, age <55 y; females, age <65 y)
• **Primary hypercholesterolemia** (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L); non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])*
• **Metabolic syndrome** (increased waist circumference, elevated triglycerides [>175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL] are factors; tally of 3 makes the diagnosis)
• **Chronic kidney disease** (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)
• **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS
• **History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia**
• **High-risk race/ethnicities** (e.g., South Asian ancestry)
• **Lipid/biomarkers**: Associated with increased ASCVD risk
  ○ Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dL);
  ○ If measured:
  ▪ **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L)
  ▪ **Elevated Lp(a)**: A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor especially at higher levels of Lp(a).

▪ **Elevated apoB** ≥130 mg/dL: A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor ▪ **ABI** <0.9