Indispensable Role of Ezetimibe/Atorvastatin Combination therapy in ACS/CHD Patients

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AGENDA

- Implications of outcome study on guideline updates
- Unmet needs of current lipid management
- The role of Ezetimibe in lipid management

Evolution of lipid management guidelines

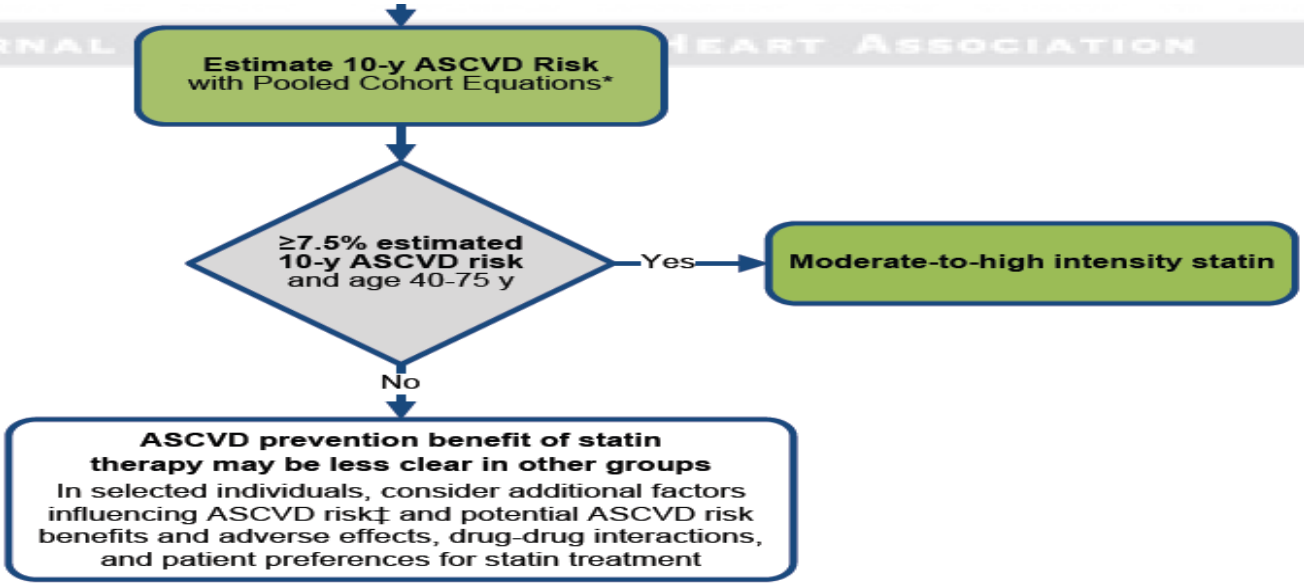
ATP I 1988	ATP II 1993	ATP III 2001	ATP III Update 2004
Exclusive focus on LDL-C	Risk assessment guides therapy	Lower LDL-C threshold for therapy initiation in high-risk patients	Lower LDL-C threshold for therapy initiation in very-high-risk patients
Strong support for resins, niacin	LDL-C goal reduced for CHD (≤100mg/dL)	LDL-C goal <100 mg/dL for CHD equivalent	Optional LDL-C goal <70 mg/dL for CVD+multiple/severe risk or ACS
Statins, fibrates not first line	Statins included in "major drugs," fibrates for mixed HPL	Non-HDL-C and metabolic syndrome as secondary targets	Optional LDL-C goal<100 mg/dL for moderately high-risk primary prevention

Low-to moderate-dose monotherapy

Moderate-to high-dose statin

High-dose statin, increased combination therapy

ACC/AHA 2013 Guidelines:
More aggressive target for very high-risk patients



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

- Even though statin therapy was considered as a "first line treatment," recommendations for **non-statin therapy** were constructed to allow for consideration of individual patient's circumstance.

BUT, no supporting trials were available.

Study Design

IMPROVE-IT

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

*3.2mM
**2.6mM

N=18,144

Standard Medical & Interventional Therapy

Simvastatin 40 mg

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

Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

90% power to detect ~9% difference

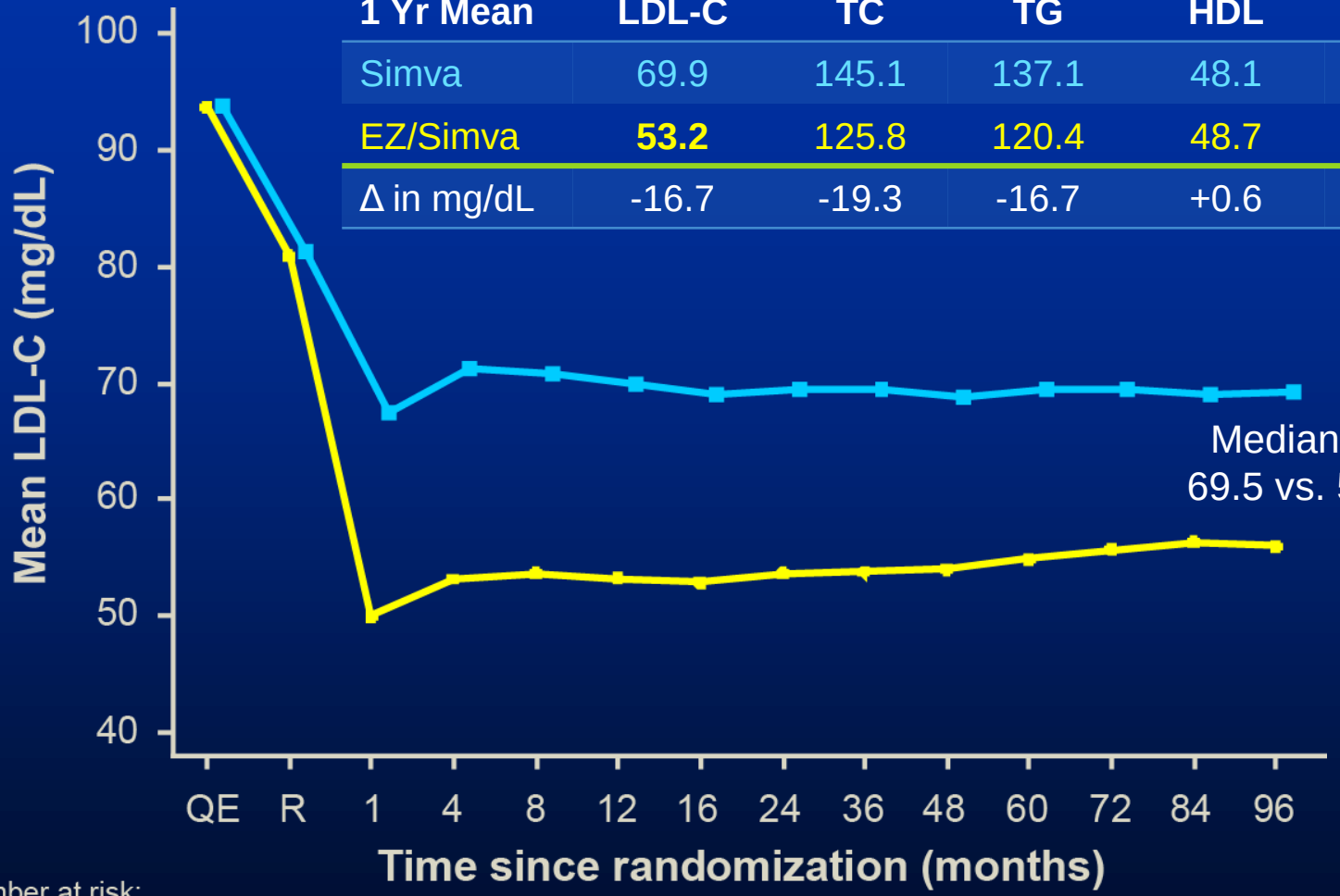
Duration: Minimum 2 ½-year follow-up **(at least 5250 events)**

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

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

LDL-C and Lipid Changes

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



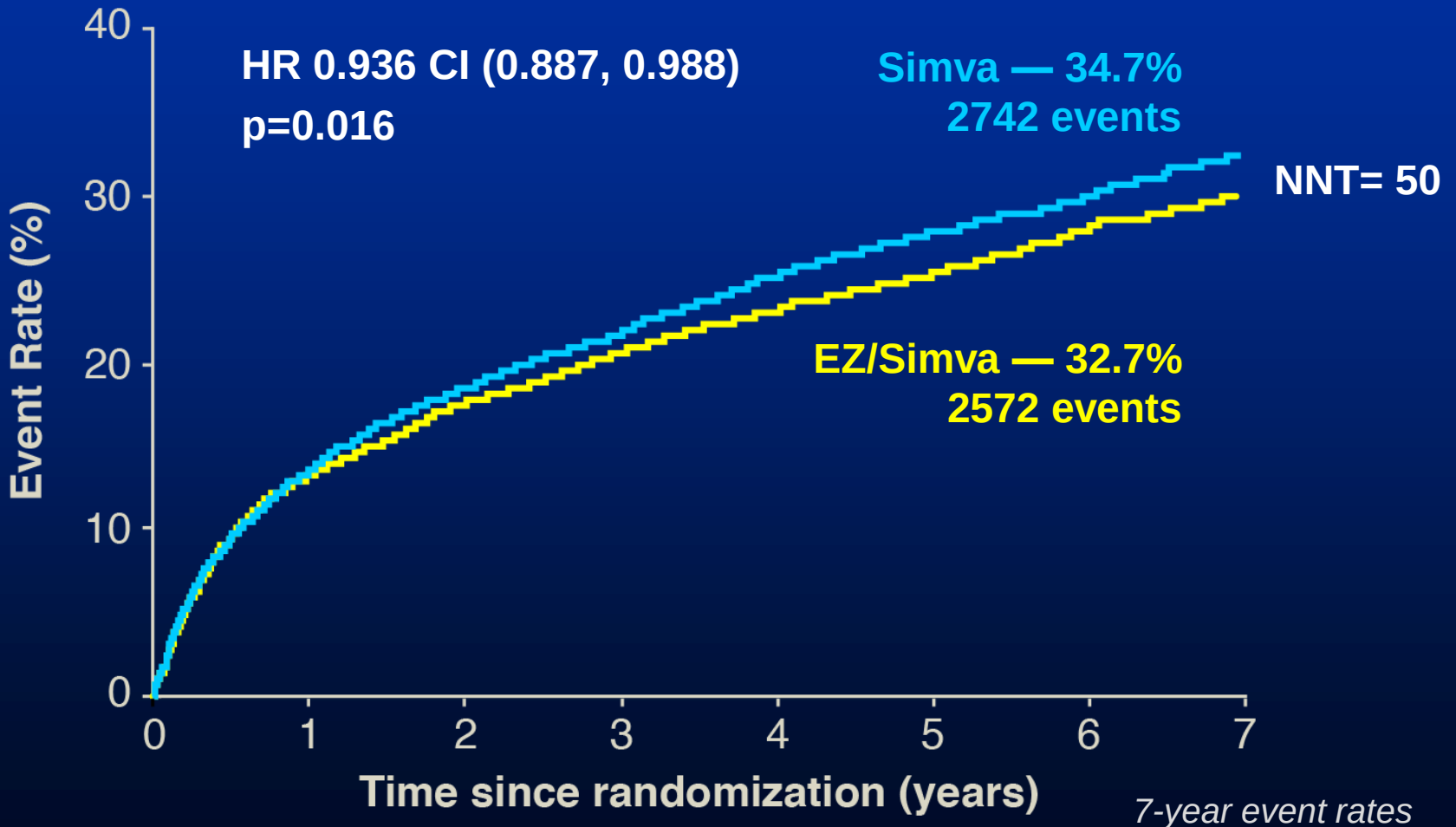
Median Time avg
69.5 vs. 53.7 mg/dL

Number at risk:

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

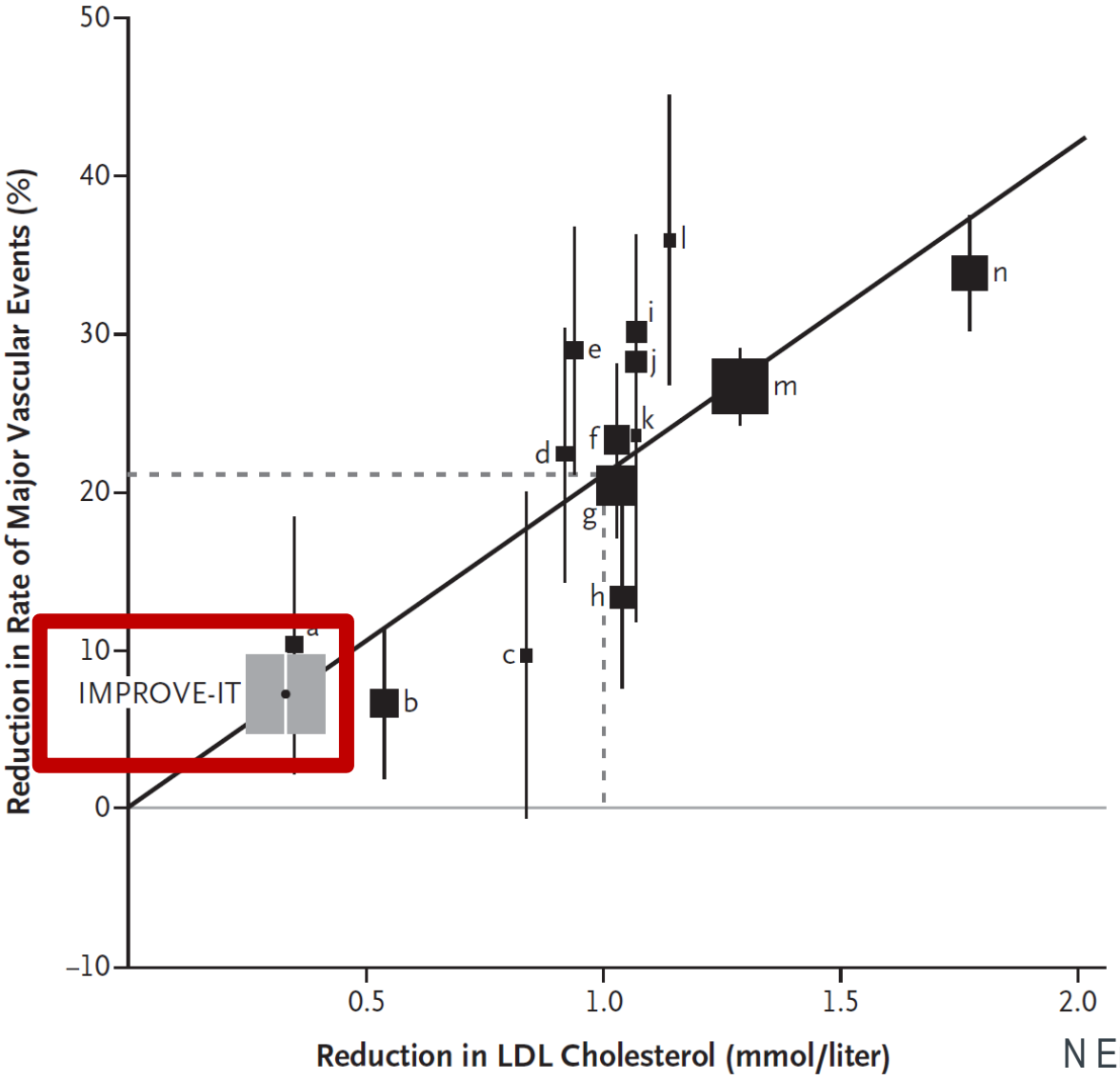
Primary Endpoint — ITT

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



7-year event rates

Low-Density Lipoprotein (LDL) Cholesterol versus Clinical Benefit



a: Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI Prevenzione)27; b: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid Lowering Trial (ALLHAT-LLT)28; c: Assessment of Lescol in Renal Transplantation (ALERT)29; d: Lescol Intervention Prevention Study (LIPS)30; e: Air Force/Texas Coronary Atherosclerosis Prevention Study AFCAPS/TexCAPS)31; f: Cholesterol and Recurrent Events (CARE)32; g: Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID)33; h: Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)34; i: Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA)35; j: West of Scotland Coronary Prevention Study (WOSCOPS)36; k: Post–Coronary Artery Bypass Graft (Post CABG)37; l:Collaborative Atorvastatin Diabetes Study (CARDS)38; m: Heart Protection Study (HPS)2; and n: Scandinavian Simvastatin Survival Study (4S)1.

N Engl J Med. 2015 Jun 18;372(25):2387-97

Changing the "concept" of lipid management

high-intensity statin

High-intensity
" cholesterol-lowering therapy "

Even with the highest doses of the most efficient statins, it is difficult to reduce LDL cholesterol beyond 50%.

1. Luis Masana, *et al*. IMPROVE-IT clinical implications. Should the "high-intensity cholesterol-lowering therapy" strategy replace the "high-intensity statin therapy?". *Atherosclerosis*. 2015;240:161-162

Updates of Various Guidelines After IMPROVE-IT Study

Key Changes after IMPROVE-IT Study

- **More aggressive lipid-lowering therapy** is warranted for both **high and very-high risk patients.**
- **Ezetimibe add-on therapy** is in the spotlight with an evidence from IMPROVE-IT study.
- Patients may be eligible for the 2nd-line lipid lowering therapy with **ezetimibe being the first-line of choice if,**
  1. patient's therapeutic **goal is not achieved at the maximal tolerated statin dose***
  2. patients are **intolerant to statins**
  3. patients who have **contraindications to statins**

*not a firm trigger for adding medication, but a factor that may be considered within the broader context of an individual patient's clinical situation

American Diabetes Association
Standards of Medical Care in Diabetes 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

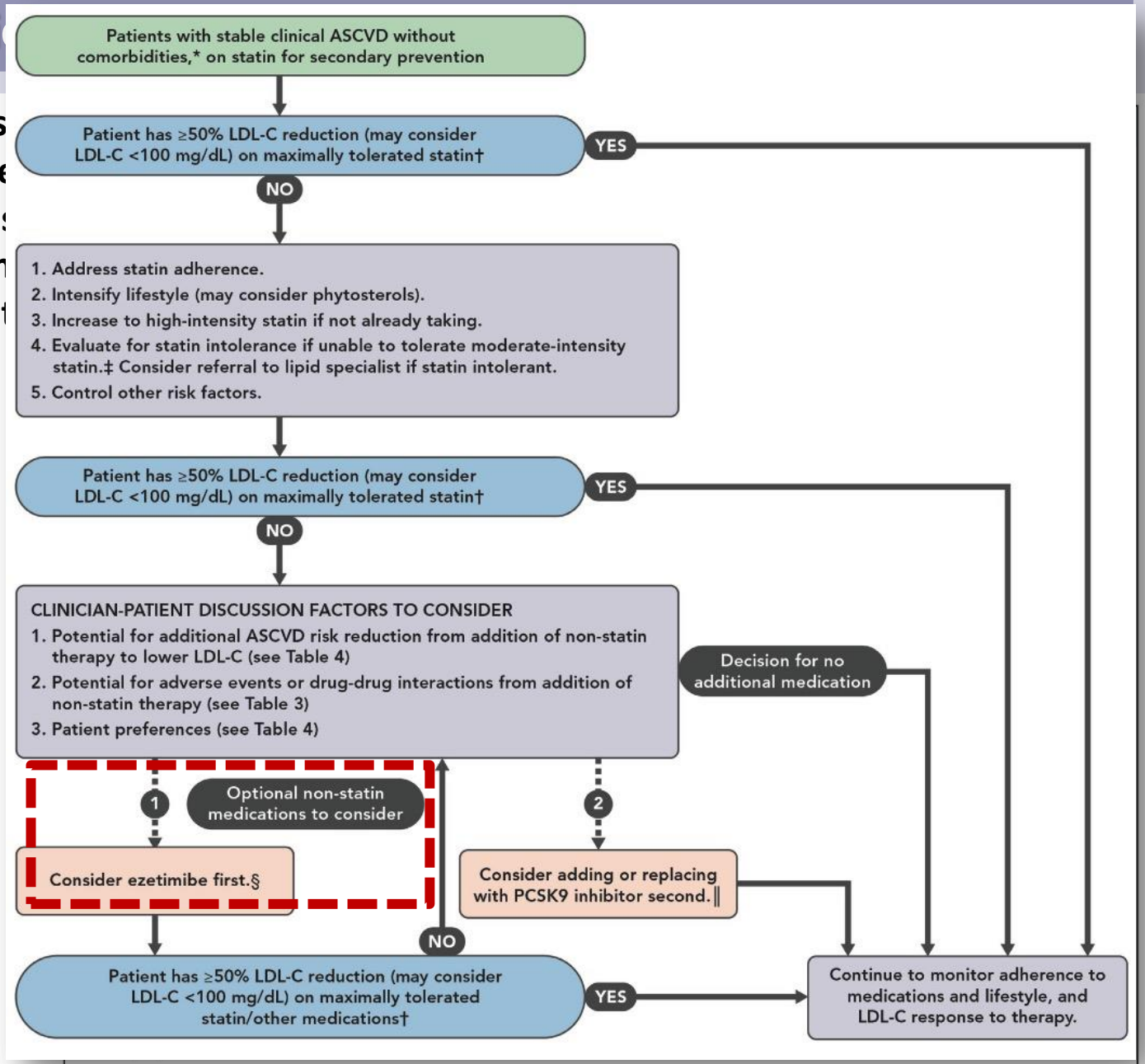
*In addition to lifestyle therapy.
**ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, overweight and obesity, and family history of premature ASCVD.

Cefalu et al. Diabetes Care 2016; 39 (Suppl. 1): S60-S71.

ASCVD (Atherosclerotic Cardiovascular Disease)

Highlights from the recently published 2016 ACC Expert Consensus Decisi

- **Threshold LDL-C levels can be considered whe deciding whether to us non-statin therapies in select high-risk patient**



J Am Coll Cardiol. 2016;68:92-125

2016 ESC/EAS Guidelines for the Management of Dyslipidemias

	LDL-C	Non–HDL-C	Apo B
	Primary Target	**Secondary Targets**	
Very high risk **Documented CVD, previous AMI, ACS, coronary or other arterial revascularization, stroke, TIA, aortic aneurysm, PAD, DM with target organ damage (such as proteinuria or with a major RF such as smoking or marked hypercholesterolemia or marked hypertension), severe CKD (GFR <30mL/min/1.73m^2), or a calculated 10 year risk SCORE ≥ 10%**	**<70mg/dL** or **≥50%** reduction from baseline between 70-135 mg/dL	<100mg/dL	<80mg/dL
High risk **Markedly elevated single risk factors such as familial dyslipidemia and severe hypertension, most other people with DM, moderate CKD (GFR 30-59mL/min/1.73^2) or a calculated SCORE ≥5% and <10% for 10 year risk of fatal CVD**	**<100mg/dL** or **≥50%** reduction from baseline between 100-200 mg/dL	<130mg/dL	<100mg/dL
Moderate risk **SCORE is ≥1% and <5% at 10 years, many middle-aged subjects**	<115mg/dL	<145mg/dL	Not defined

Catapano AL, et al. Eur Heart J . 2016 Aug;23(11):NP1-NP96.

ESC/EAS Recommendations for the pharmacological treatment of hypercholesterolaemia : 2011 vs. 2016

2011

Table 14 Recommendations for the pharmacological treatment of hypercholesterolaemia

sequestrants or nicotinic acid should be considered.	IIa	B	108, 120
A cholesterol absorption inhibitor, alone or in combination with bile acid sequestrants or nicotinic acid, may also be considered in the case of statin intolerance.	IIb	C	-
If target level is not reached, statin combination with a cholesterol absorption inhibitor or bile acid sequestrant or nicotinic acid may be considered.	IIb	C	-

[a]Class of recommendation.
[b]Level of evidence.
[c]References.

- **May be -> Should be !**
- **Class of recommendation and level of evidence has been ascended from IIb,C to IIa, B.**

2016

Table 16 Recommendations for the pharmacological treatment of hypercholesterolaemia

Recommendations	Class [a]	Level [b]	Ref [c]
escribe statin up to the highest commended dose or highest erable dose to reach the goal.	I	A	62, 64, 68
the case of statin intolerance, etimibe or bile acid sequestrants, these combined, should be considered.	IIa	C	239, 256, 257
If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	IIa	B	63
If the goal is not reached, statin combination with a bile acid sequestrant may be considered.	IIb	C	
In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	IIb	C	115, 116

LDL-C = low-density lipoprotein-cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Further Application of IMPROVE-IT Trial

AACE/ACE Consensus Statement

CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM – *2017 EXECUTIVE SUMMARY*

AACE/ACE recommends adding Ezetimibe to Statin to high-risk patients with diabetes !

ASCVD RISK FACTOR MODIFICATIONS ALGORITHM

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

- **LDL-C**를 낮추기 위해 스타틴 강화, **에제티미브**, PCSK9i, 콜레세브이람 또는 니아신 추가

* Even more intensive therapy might be warranted

AACE : American Association of Clinical Endocrinologists, ACE : American college of endocrinology, DM : Diabetes mellitus, ASCVD : Atherosclerotic cardiovascular disease, HTN : Hypertension, Fam Hx : Familial history, HDL-C : High-density lipoprotein cholesterol, CKD : Chronic kidney disease, CVD : Cardiovascular disease, LDL-C : Low density liproprotein cholesteol, Non-HDL-C : Non-high-density liproprotein cholesterol, TG : Triglyceride, Apo B : Apolipoprotein B

1. Garber AJ, *et al*. Consensus statement by the american association of clinical endocrinologists and american college of endocrinology on the comprehensive type 2 diabetes management algorithm – 2017 executive summary. *Endocrine prictice*. 2017;23(2):207-238.

European Heart Journal Acute Cardiovascular Care
EUROPEAN SOCIETY OF CARDIOLOGY®

Clinical Practice/Education

European Heart Journal: Acute Cardiovascular Care
1–12

DOI: 10.1177/2048872616679791
acc.sagepub.com
SAGE

A consensus statement on lipid management after acute coronary syndrome

François Schiele[1], Michel Farnier[2], Michel Krempf[3], Eric Bruckert[4] and Jean Ferrières[5] on behalf of the French Group[a]

More Aggressive Treatment Goal for Very-High Risk Patients !

- For **ACS patients, LDL-C target of < 55mg/dL** has been proposed by French Consensus Statement based on the IMPROVE-IT study that patients with an LDL-C of 55 mg/dL had a more favourable clinical outcome than those with an LDL-C of 70 mg/dL

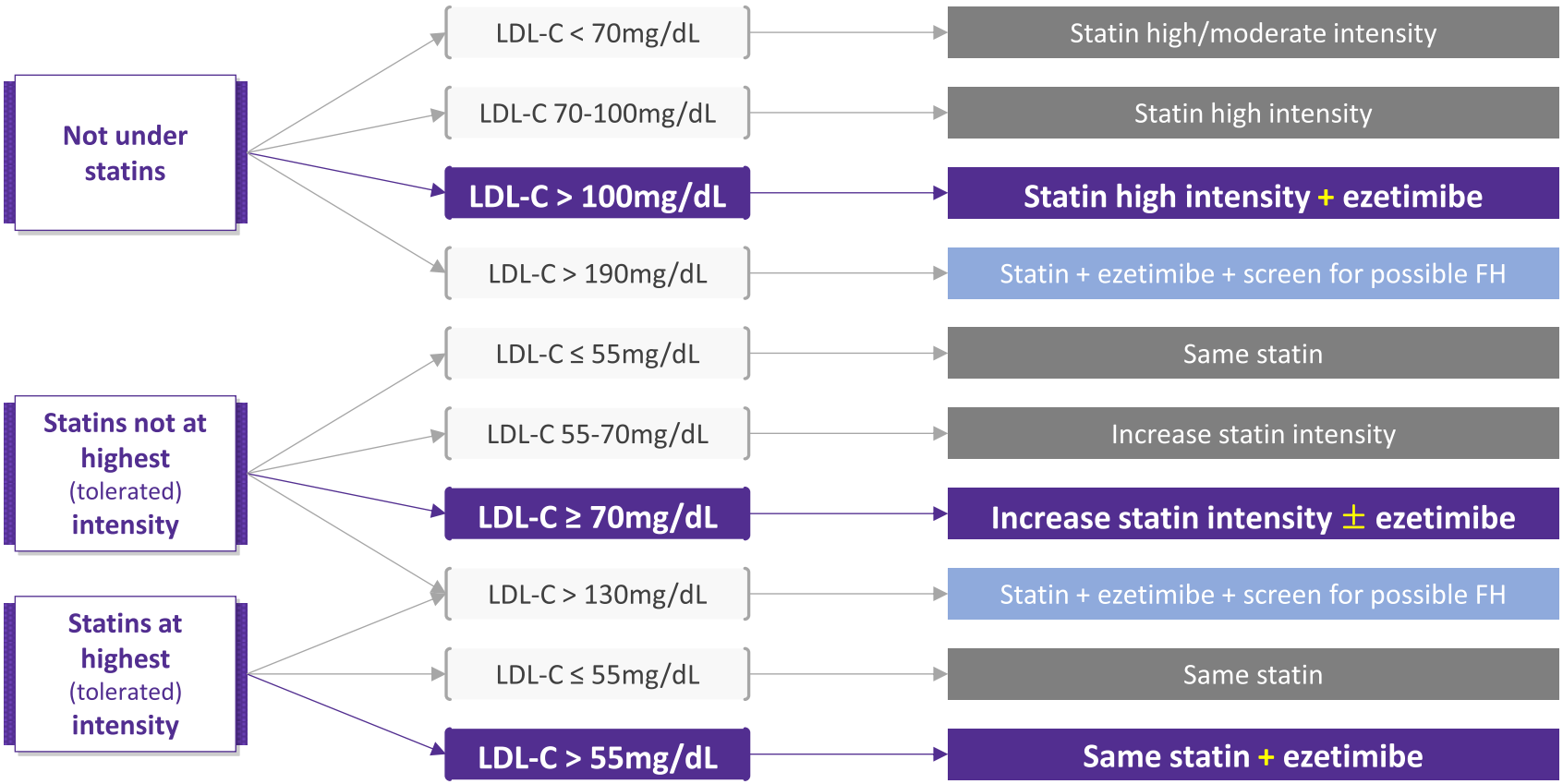
ACS Patients

Lower	Even Lower
< 70mg/dL	< 55mg/dL

Schiele F, et al. Eur Heart J Acute Cardiovasc Care. 2016 Nov 17. pii: 2048872616679791. [Epub ahead of print]

2016 A Consensus Statement on Lipid Management after Acute Coronary Syndrome

Decision Algorithm for ACS at Admission.



Improve-it : Improved rediction of outcomes, Vytorin Efficacy international trial, FH : Familial hypercholesterolaemia, , LDL-C : Low density lipoprotein-cholesterol, ACS : Acute coronary syndrome

1. Schiele F, *et al*. *Eur Heart J Acute Cardiovasc Care*. 2016 Nov 17. pii: 2048872616679791. [Epub ahead of print]

2016 A Consensus Statement on Lipid Management after Acute Coronary Syndrome

Decision Algorithm at Follow-up (4-8 weeks)

- **Statin discontinued**
  - Compliance → Explain benefit/risk of statins, check tolerance
  - Tolerance → Ensure intolerance : Decrease/stop for 2 weeks. Re-introduce statins at lower dose ± change drug. Check tolerance/compliance after decreased statin intensity. Consider ezetimibe.
- **Statin low/ moderate intensity**
- **Statin high intensity**
- **Statin highest tolerated intensity + ezetimibe**

Improve-it : Improved rediction of outcomes, V

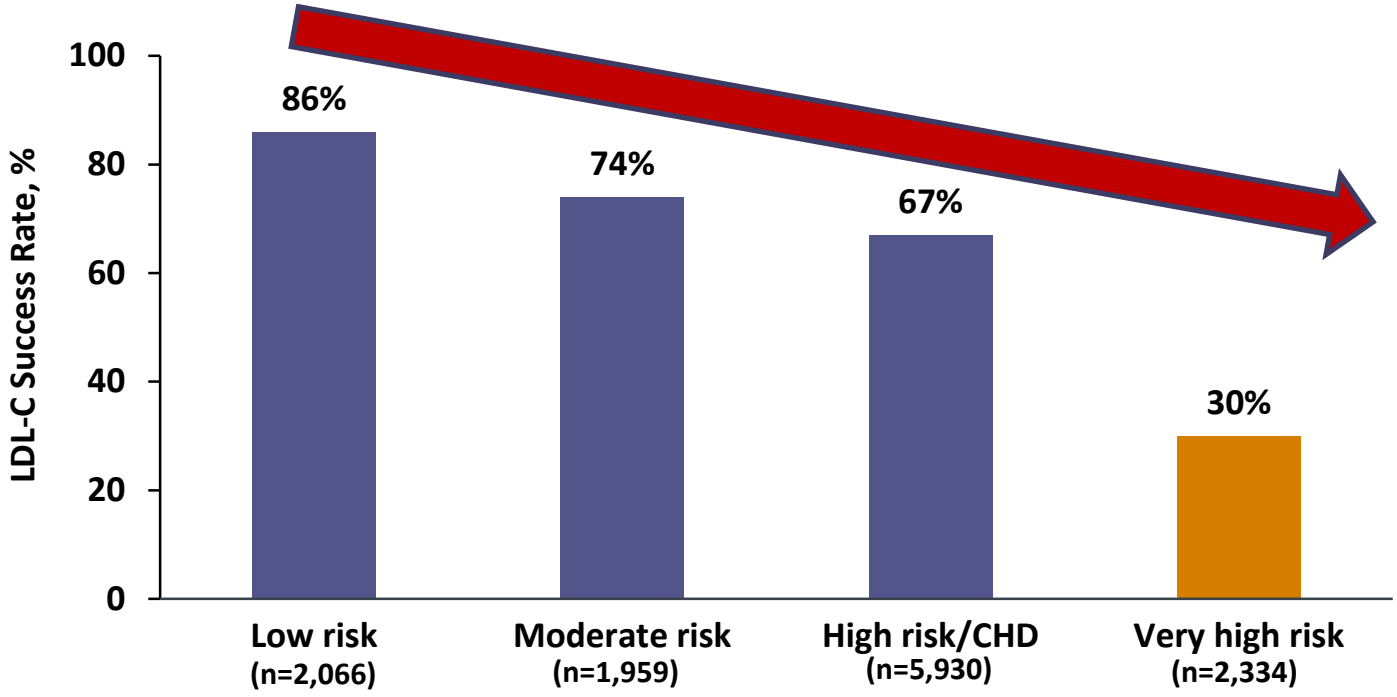
1. Schiele F, *et al. Eur Heart J Acute Cardiovasc*

Figure 2. The *Mona Lisa* by Leonardo da Vinci (left panel) and an *Elderly Lady* by Frans Hals (right panel). Cutaneous markers of familial hypercholesterolaemia, such as possible xanthoma and xanthelasma, are easily recognizable, even by non-physicians.

AGENDA

- Implications of outcome study on guideline updates
- **Unmet needs of current lipid management**
- The role of Ezetimibe in lipid management

LTAP 2 (2006–2007): Many patients receiving lipid-lowering therapy did not achieve their LDL-C goals[1,a]



75% of patients were on statin therapy

Low-risk patients = 0 or 1 risk factor.
Moderate-risk patients = 2 or more risk factors.
High-risk/CHD patients = coronary or other atherosclerotic vascular disease, or diabetes.
Very high–risk patients = CHD with 2 or more risk factors (LDL-C goal <70 mg/dL [1.8 mmol/L]).

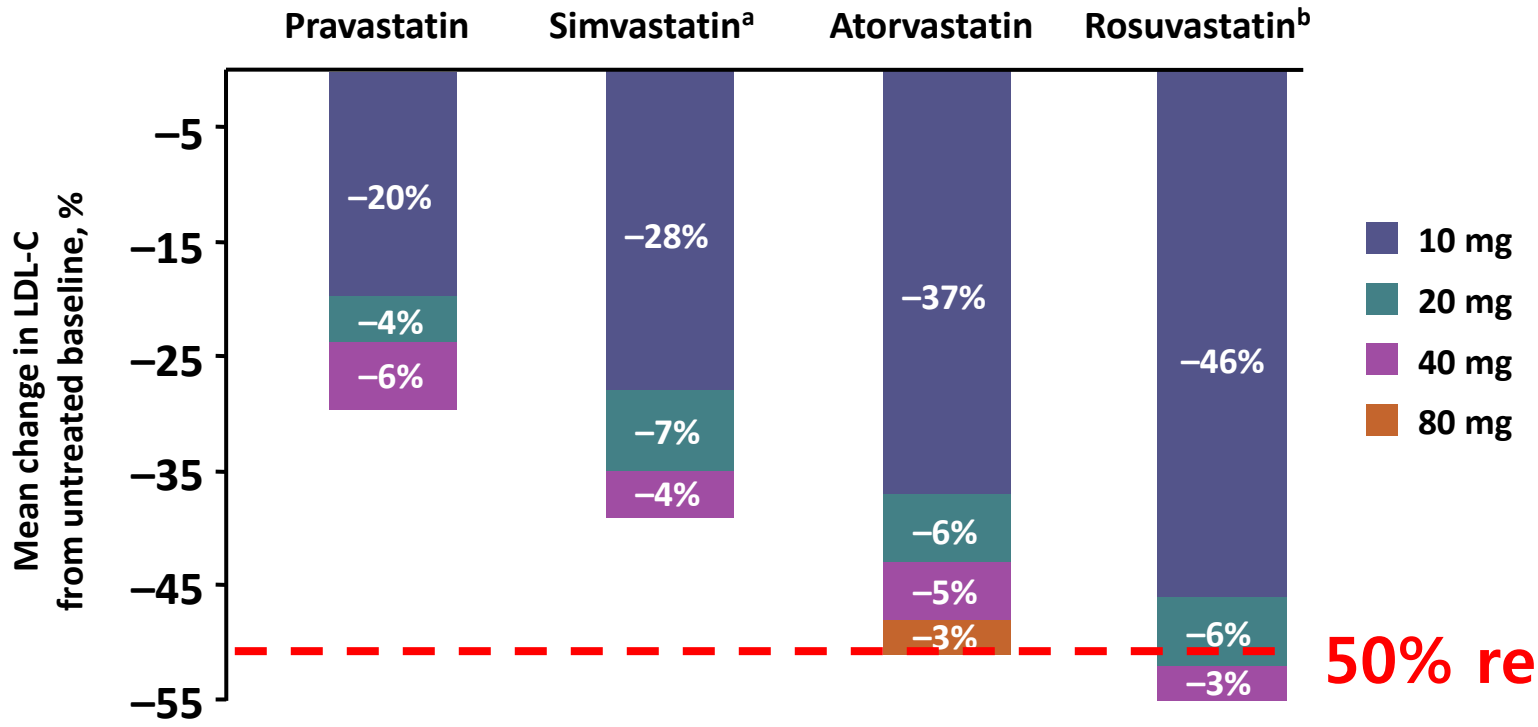
[a]Study population: >10,000 patients in 9 countries (United States, Canada, Mexico, Brazil, Spain, the Netherlands, France, Taiwan, and Korea) between Sept 2006 & April 2007; the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III guidelines, the 2003 Joint European Societies guidelines, and the 2003 Canadian Working Group guidelines were used for each corresponding geographic area.

LTAP = Lipid Treatment Assessment Project; CHD = coronary heart disease.

1. Adapted from Waters DD et al. *Circulation*. 2009;120:28–34.

LDL-reduction by statin-doubling; definitely high-dose statin needed

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]

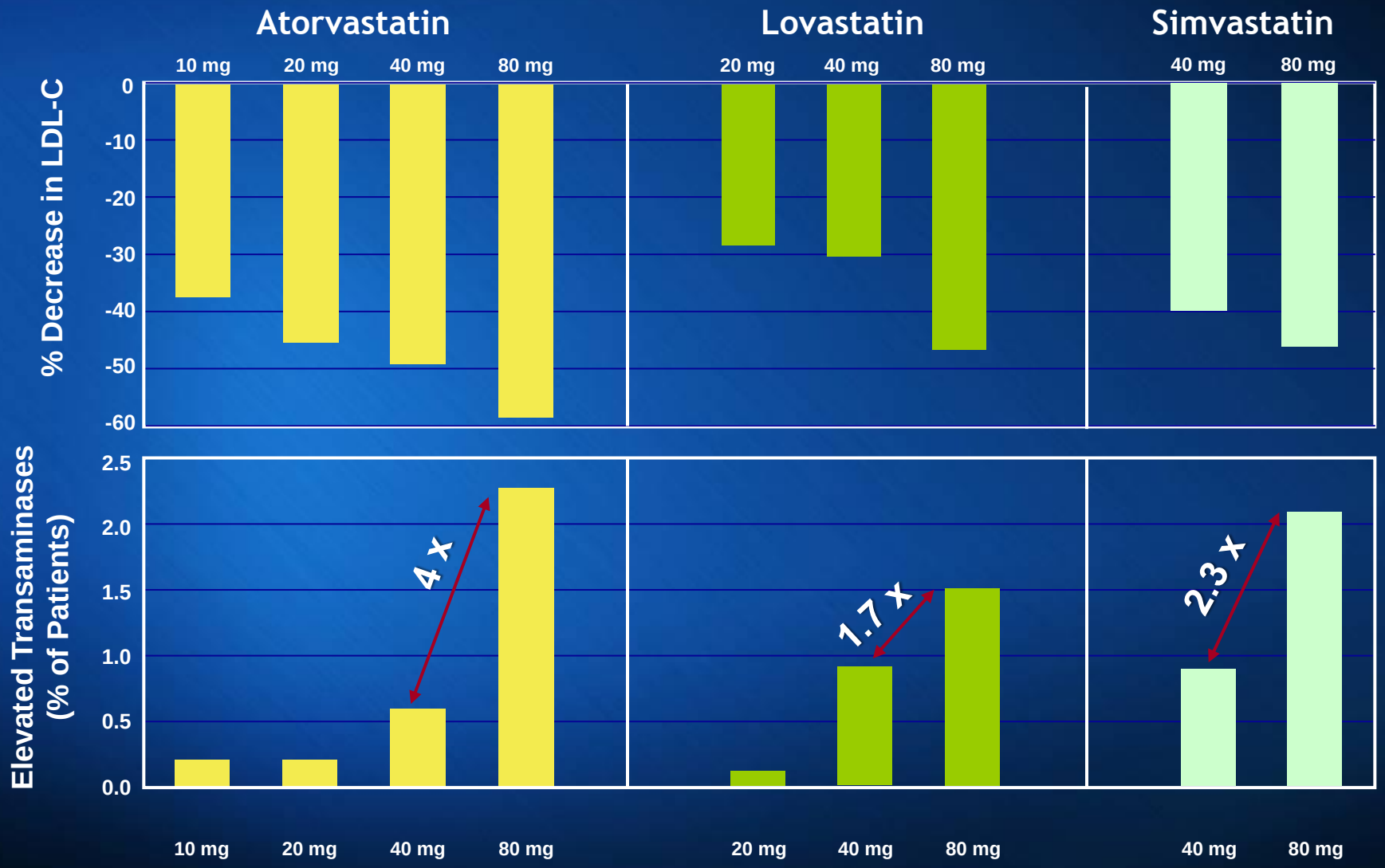
[b]Across the dose range: $P<0.001$ for the difference between rosuvastatin vs pravastatin, simvastatin, and atorvastatin.[1]

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

1. Jones PH et al. Am J Cardiol. 2003;92:152–160.

What about the long-term safety of the high-dose statin therapy?

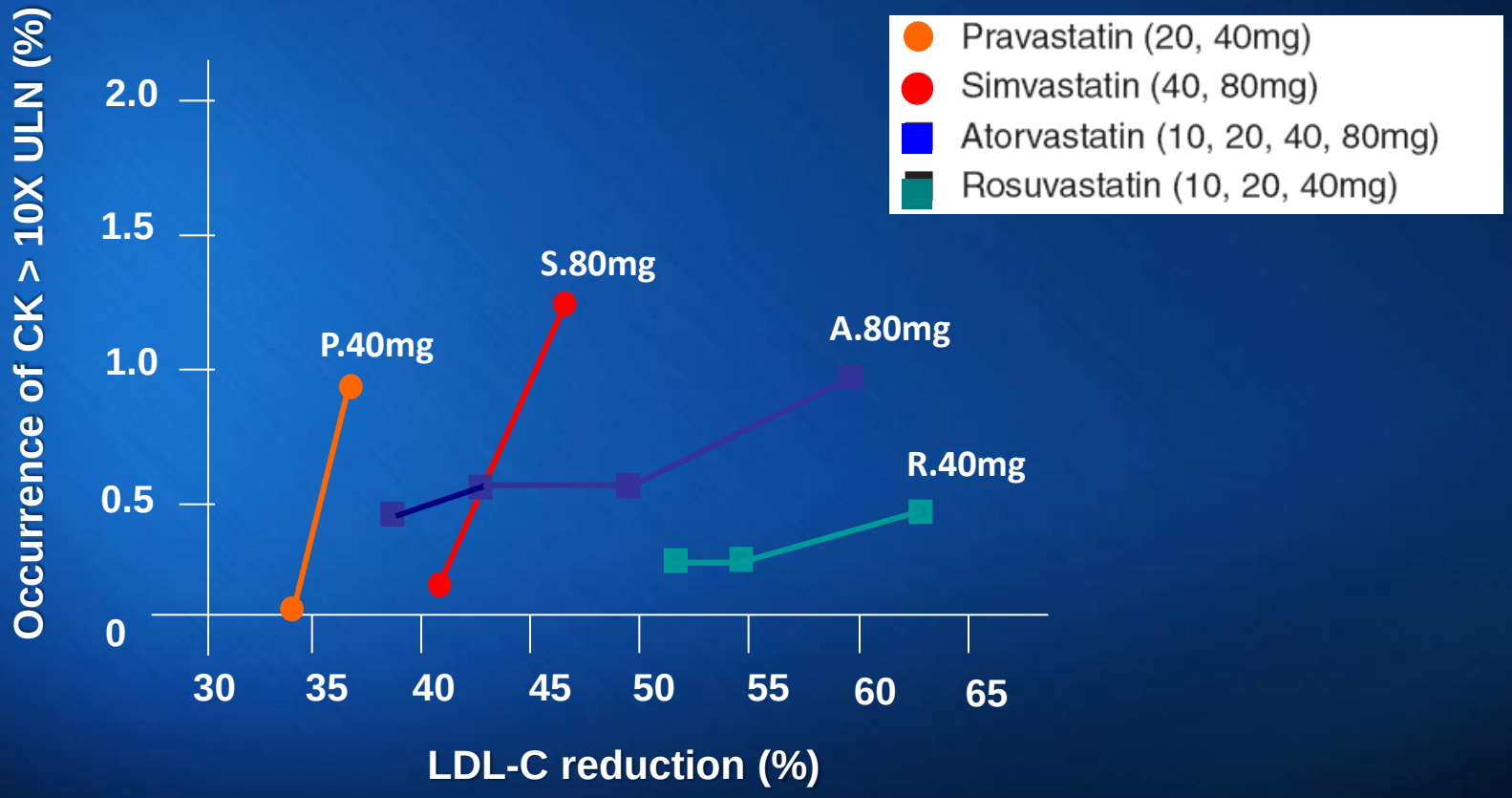
Highest doses associated with increased hepatic toxicity



Data from prescribing information for atorvastatin, lovastatin, simvastatin. This does not represent data from a comparative study.

Drug safety 2006;29(5):421-448

Highest doses associated with increased muscle injury(> 10X CK)



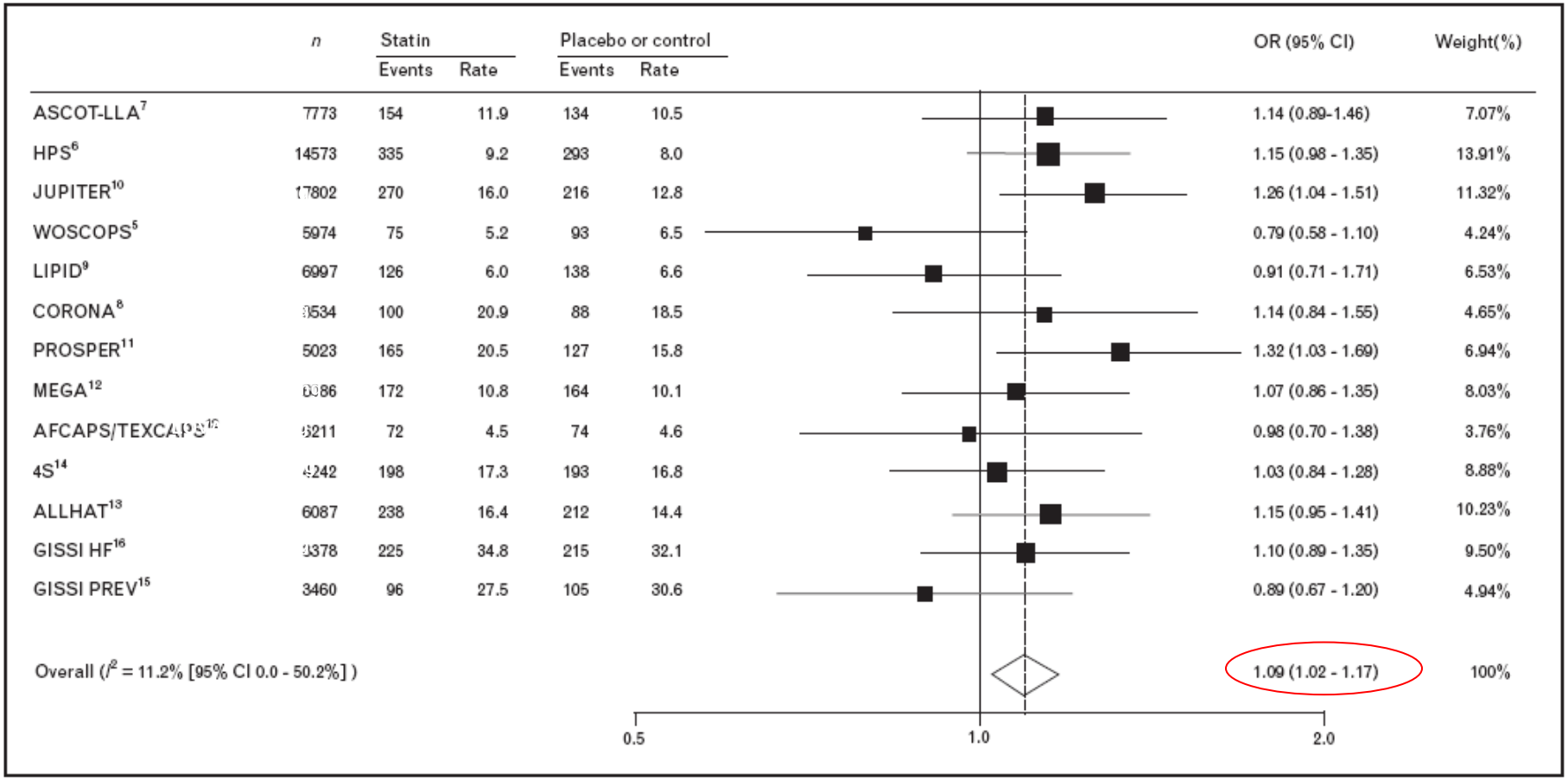
Drug safety 2006;29(5):421-448

Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials

Sattar N, et al. *Lancet* 2010; 375:735-742

In meta-analysis of 13 major trials with 91,140 participants

Statin therapy was associated with a 9% increased risk for incident diabetes

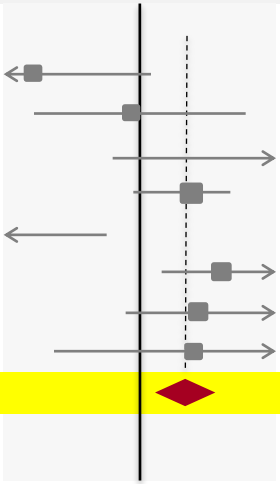


The risk of new onset diabetes of with high dose statin therapy

- **Higher potency statin therapy was associated with a 26% increased risk for new-onset diabetes compared with lower potency agents diabetes within 120 days.[1]**

Rate ratios for new onset diabetes within 120 days of starting higher potency or lower potency statins after a major CV event or procedure (as-treated analysis).

Subgroup	Low dose statins Cases	Low dose statins Controls	High dose statins Cases	High dose statins Controls	Rate ratio (95% CI)	Weight (%)	Rate ratio (95% CI)
≤120 days of current therapy							
Alberta	26	159	31	306		6.3	0.57 (0.30 to 1.07)
CPRD	30	282	50	495		7.9	0.96 (0.55 to 1.69)
Manitoba	9	113	52	425		3.9	1.89 (0.85 to 4.20)
Marketscan	86	773	195	1,452		33.0	1.29 (0.98 to 1.70)
Nova Scotia	9	46		56		1.1	0.20 (0.04 to 0.91)
Ontario	62	758	197	1,696		23.8	1.52 (1.10 to 2.11)
Quebec	57	550	123	959		18.7	1.40 (0.97 to 2.02)
Saskatchewan	17	137	69	442		5.3	1.31 (0.66 to 2.60)
Total	296	2,818	720	5,831		**100.0**	**1.26 (1.07 to 1.47)**



Test for heterogeneity: x^2=15.22, df=7, *P*=0.03, I^2=54%

Test for overall effect: Z=2.84, *P*=0.04

Study design; 8 population based cohort studies and a meta-analysis was conducted in 136,966 patients aged ≥40 years newly treated with statins . Within each cohort of patients newly prescribed a statin after hospitalisation for a major CV event or procedure, This was performed as-treated, nested case-control analyses to compare diabetes incidence in users of higher potency statins with incidence in users of lower potency statins. This was to evaluate the incremental increase in new onset diabetes from higher potency statins compared with lower potency statins when used for secondary prevention.

CV, cardiovascular; CI, confidence interval. 1. Dormuth CR, et al. BMJ. 2014;348:g3244.

Dyslipidemia International Study II

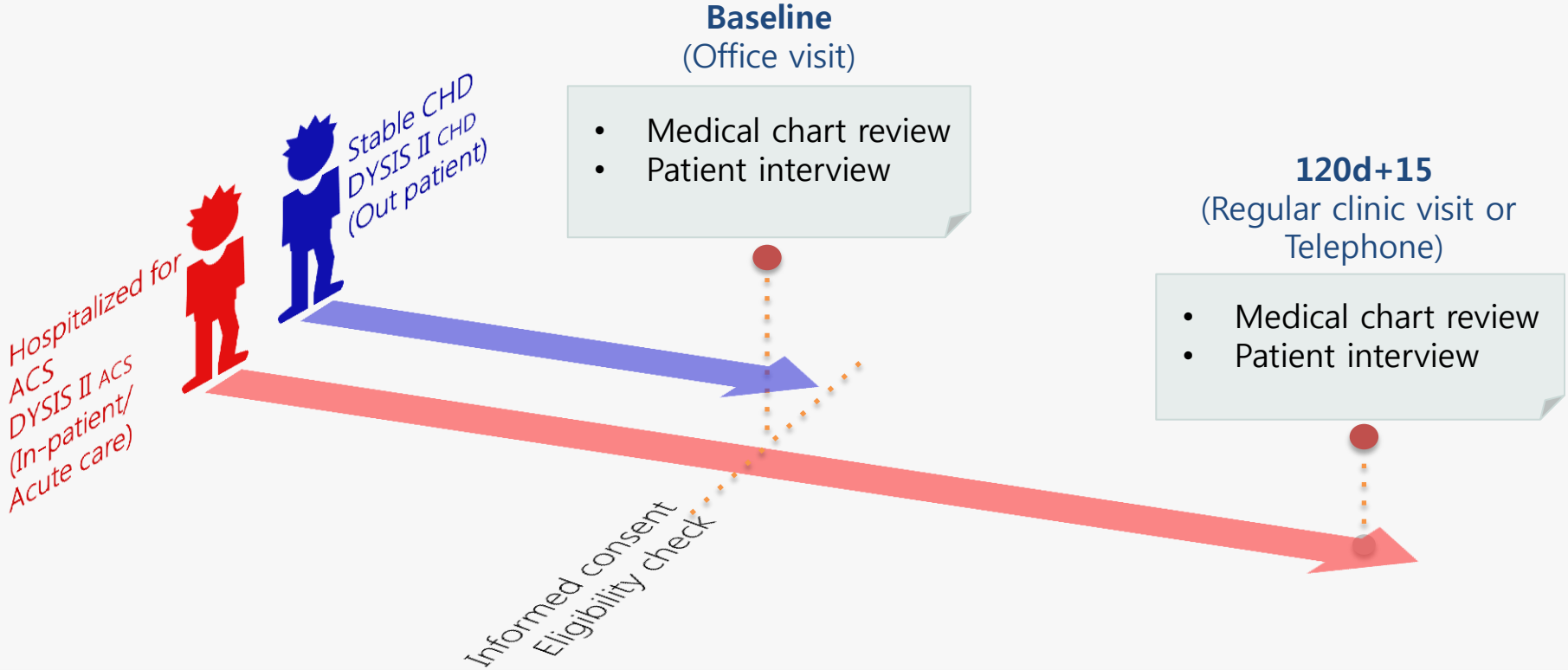
Study Design

Primary Objective

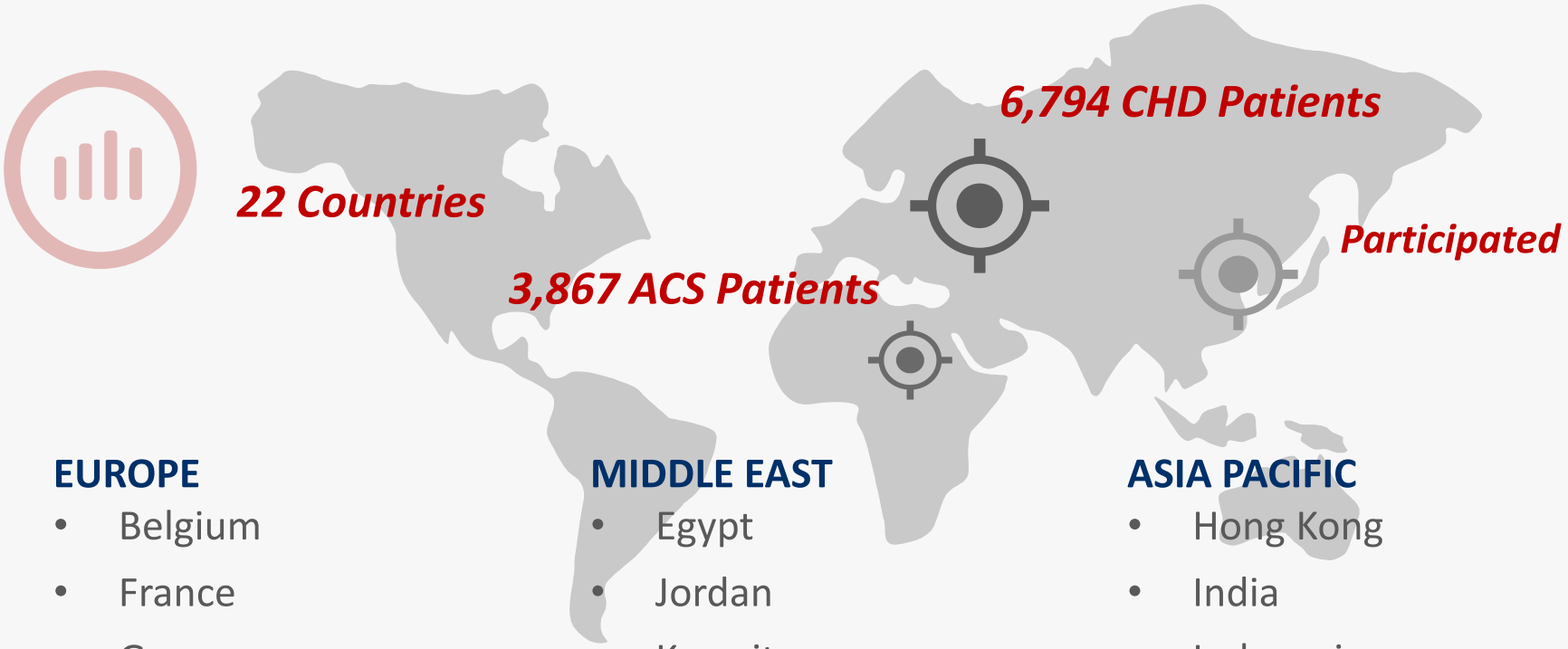
- To globally document real-life lipid levels relative to the new "ESC/EAS Guidelines for the management of Dyslipidemias" in patients with CHD (stable CHD or ACS)

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

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



Investigator & Sites - Global



EUROPE

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

MIDDLE EAST

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

ASIA PACIFIC

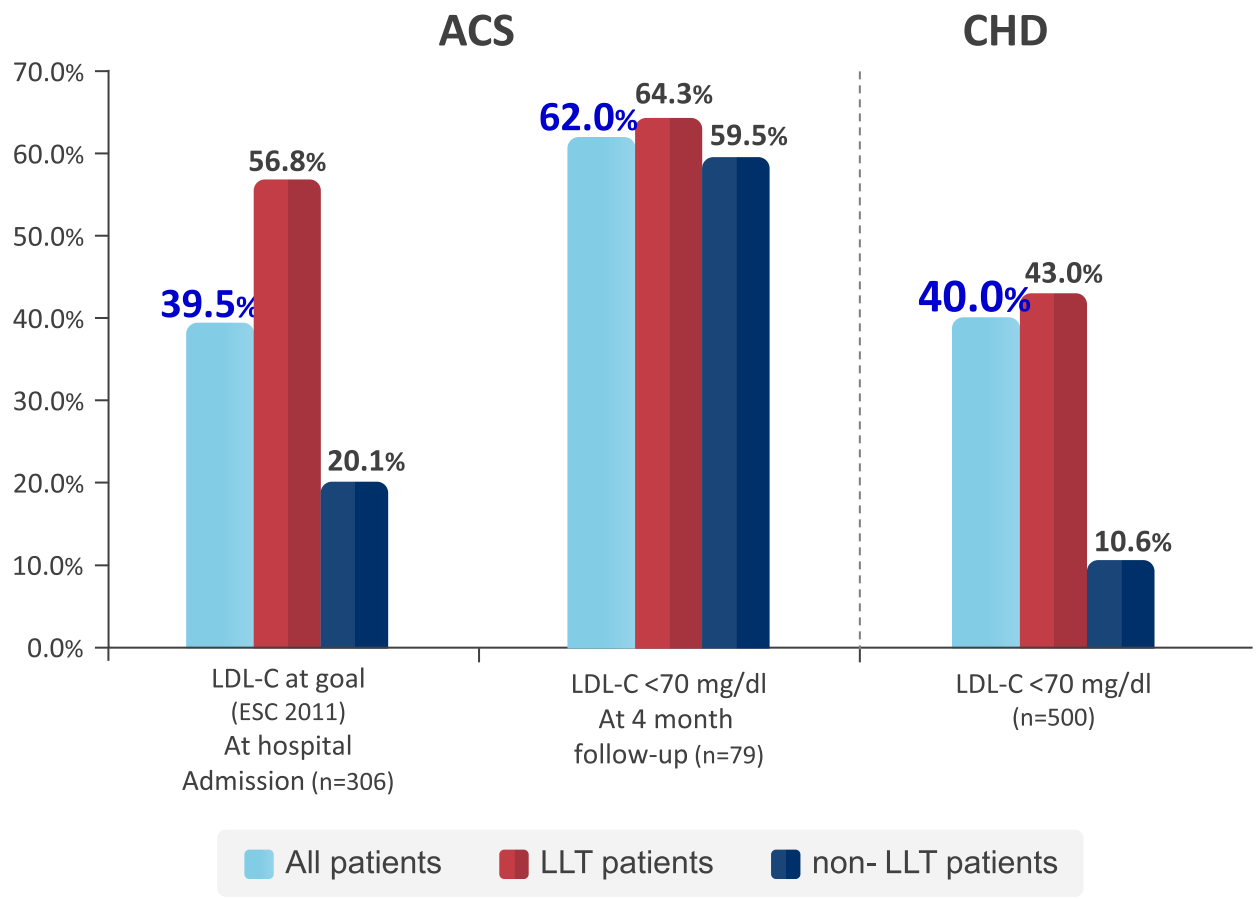
- Hong Kong
- India
- Indonesia
- Philippines
- South Korea
- Singapore
- Taiwan
- Thailand
- Vietnam

DYSIS II Country Report for South Korea

Lipid Target Achievement

ACS | CHD

Lipid Target Achievement

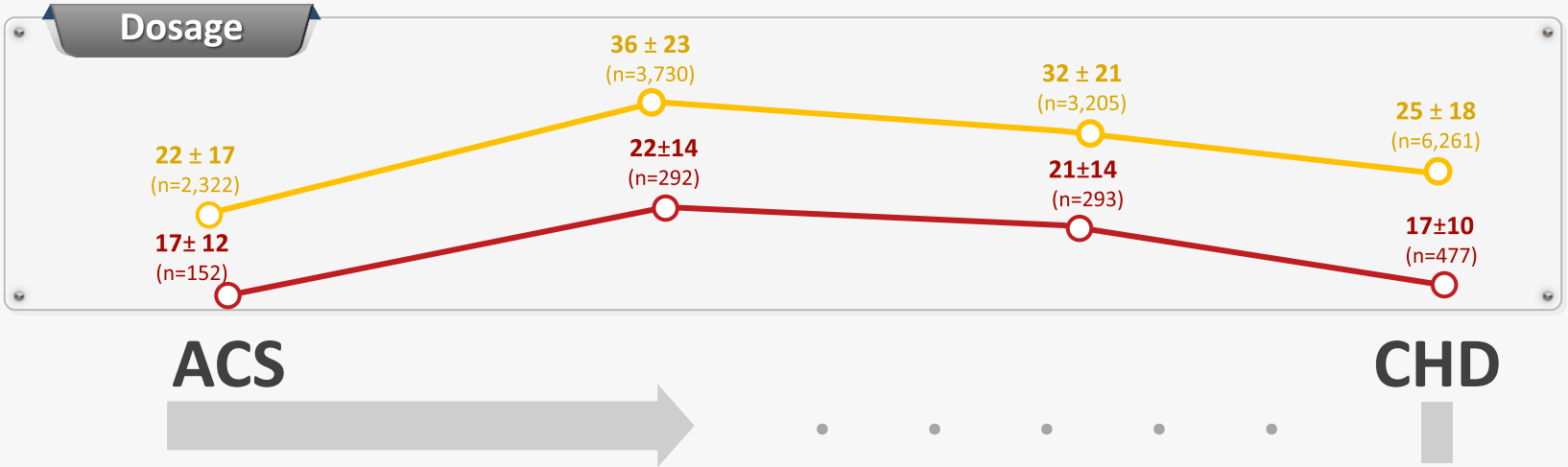


- Among 308 ACS patients, 162 patients were treated with LLTs while 146 were not.
- Among 500 CHD patients, 10% were still not treated with LLTs.

DYSIS II

DYSIS II for Global vs South Korea

ACS | CHD



	Goal Attainment			
	Admission		4-Month F/U	> 4-Month
	Pre ACS (LDL-C<70or100 mg/dL)	Post ACS (LDL-C<70 mg/dL)		
Global	30% (n=3,866)	19%	37% (n=1,071)	30% (n=6,792)
South KOREA	40% (n=308)	24%	62% (n=79)	40% (n=500)

What Accounts for the Low LDL-C Goal Attainment Rate in the Real World?

ACS | CHD

- Are we **strictly following the Guidelines?**
- Are ACS and CHD patients **regularly followed-up with lipid profile?**
- Are we **reluctant to use the high-intensity statin** due to adverse reactions?
- Is **statin alone adequate enough to achieve the LDL-C goal?**

No Definite Answers!!!

But Certainly, Many Factors that Were **Neglected** to be

CONSIDERED

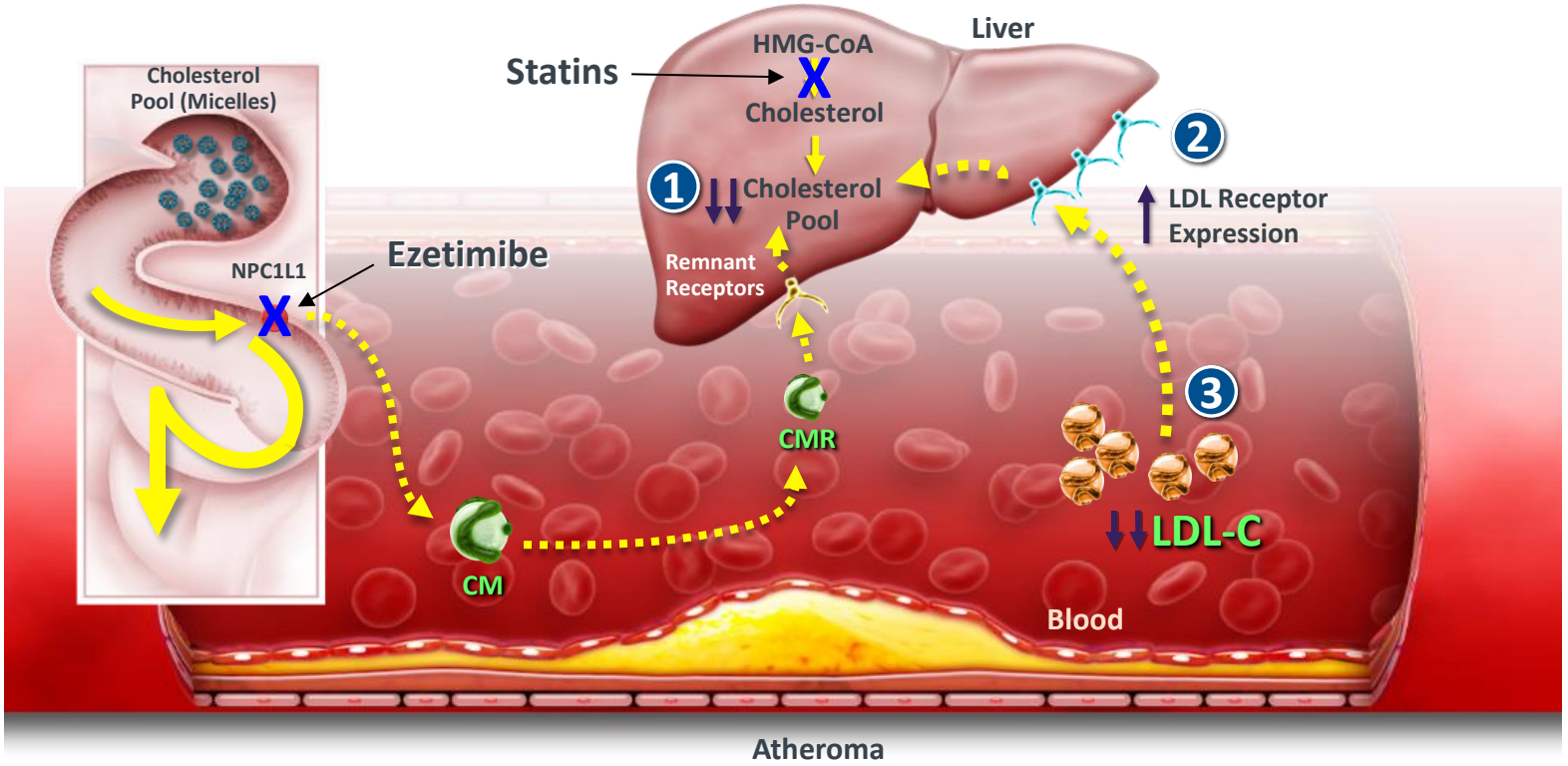
DYSIS II

AGENDA

- Implications of outcome study on guideline updates
- Unmet needs of current lipid management
- **The role of Ezetimibe in lipid management**

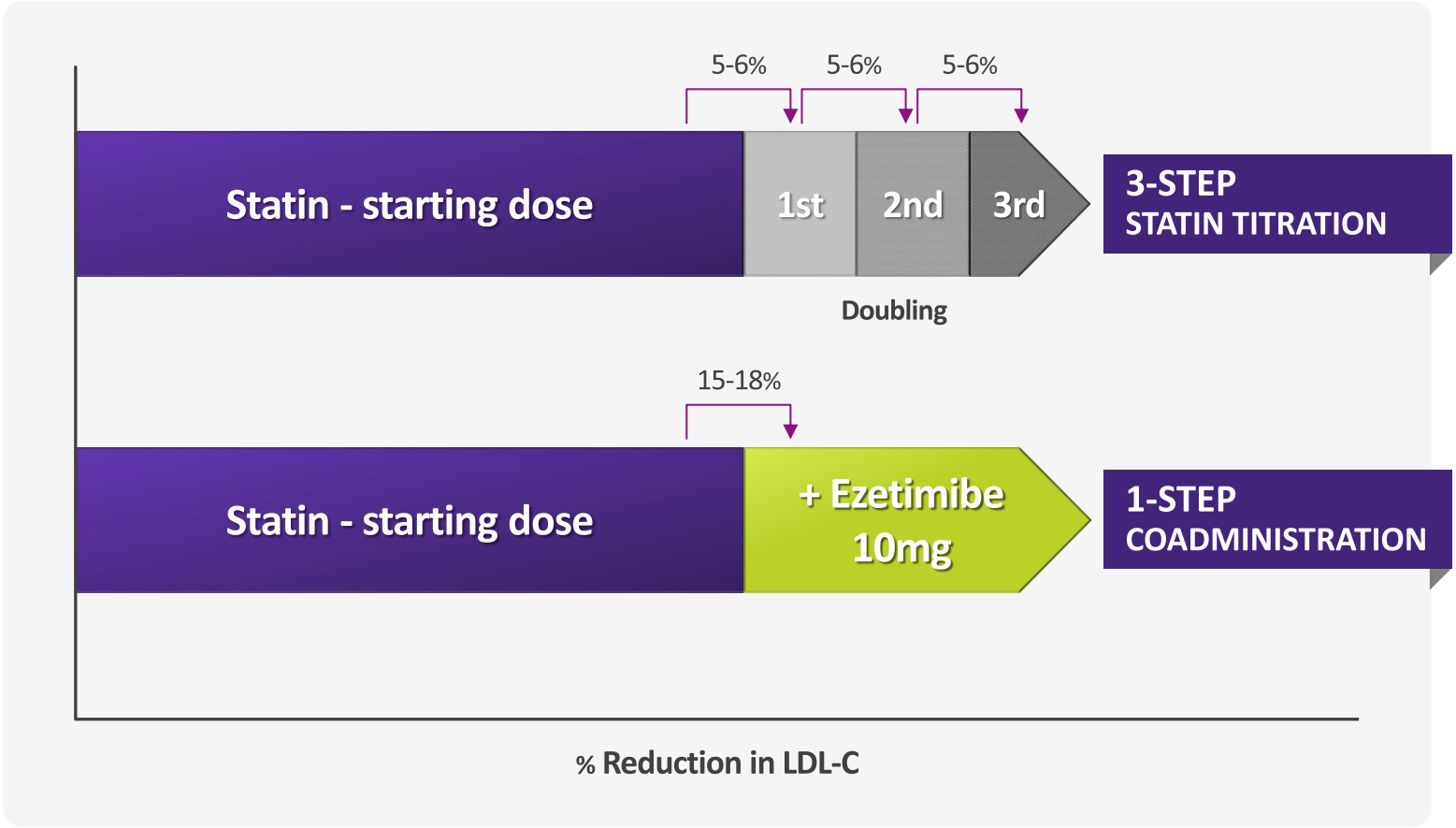
Ezetimibe and Statins Have Complementary Mechanisms of Action[1]

- 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; LDL-C, low-density lipoprotein cholesterol; HMG-CoA, 3-hydroxy-3-methylglutaryl acetyl coenzyme A; CMR, chylomicron remnant.. Grigore L, et al. *Vas Health Risk Manag.* 2008;4:267-278.

Ezetimibe add-on therapy was comparable to 3-step statin up-titration in % LDL-C reduction

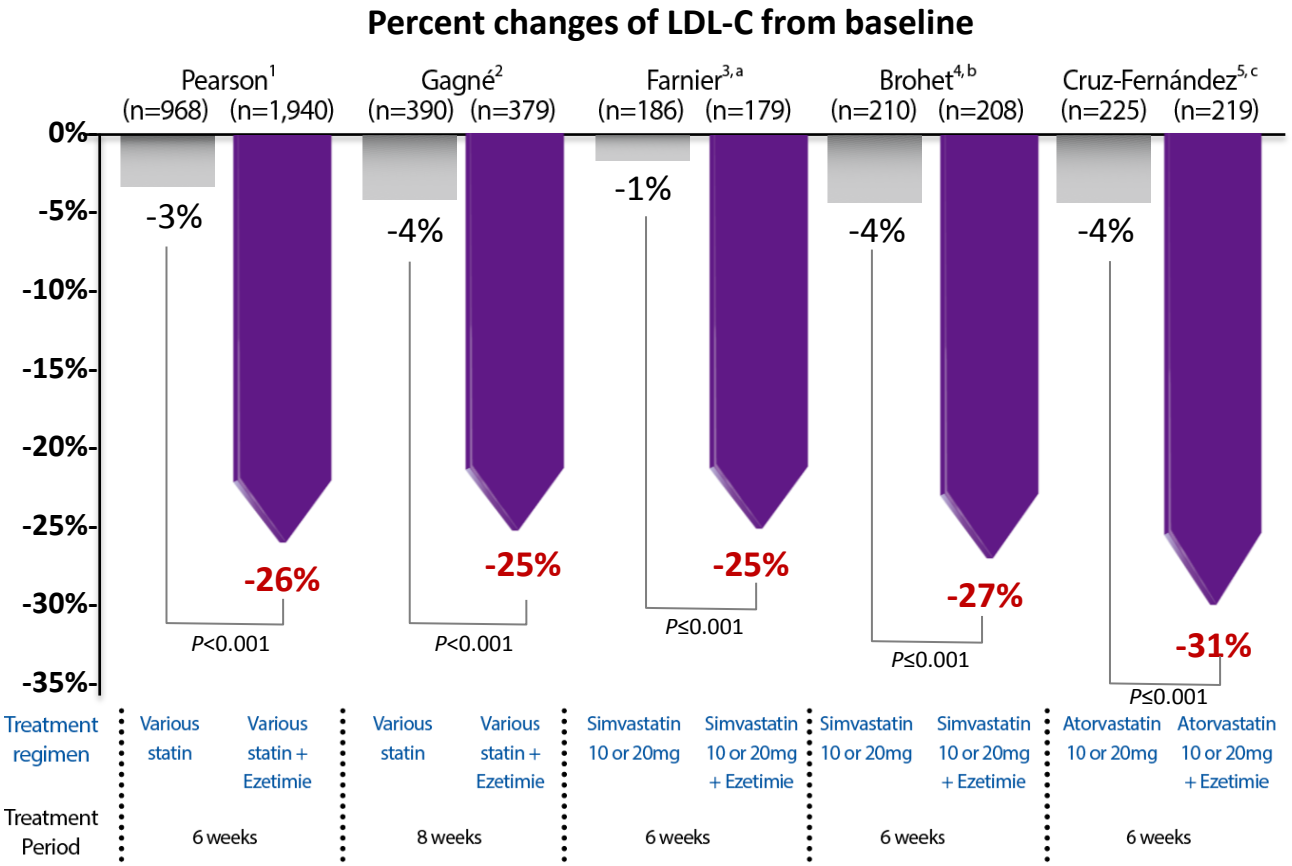


LDL-C : Low-density liopoprotein cholesterol

1. Harold E, *et al*. A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Factorial Design Study to Evaluate the Lipid-Altering Efficacy and Safety Profile of the Ezetimibe/Simvastatin Tablet Compared with Ezetimibe and Simvastatin Monotherapy in Patients with Primary Hypercholesterolemia. *Clin Ther*. 2004;26:1758-1773

Additional reduction of LDL-C by ezetimibe add-on

✓ Ezetimibe add-on to any statin provided **additional 25-31% reduction of LDL-C** in 5 separate clinical trials[1-5]



[a] In hypercholesterolemia patients with CHD. The primary endpoint was the percentage of patients reaching an LDL-C target of ≤2.6 mmol/l at study endpoint. [Result : Ezetimibe group vs Placebo group, 74.3% vs 16.7%, $p \leq 0001$)[3]

[b] In CHD patients with hypercholesterolemia. The primary endpoint was the percentage of patients reaching an LDL-C target of ≤2.6 mmol/l at study endpoint. [Result : Ezetimibe group vs Placebo group, 80.4% vs 17.4%, $p \leq 0001$)[4]

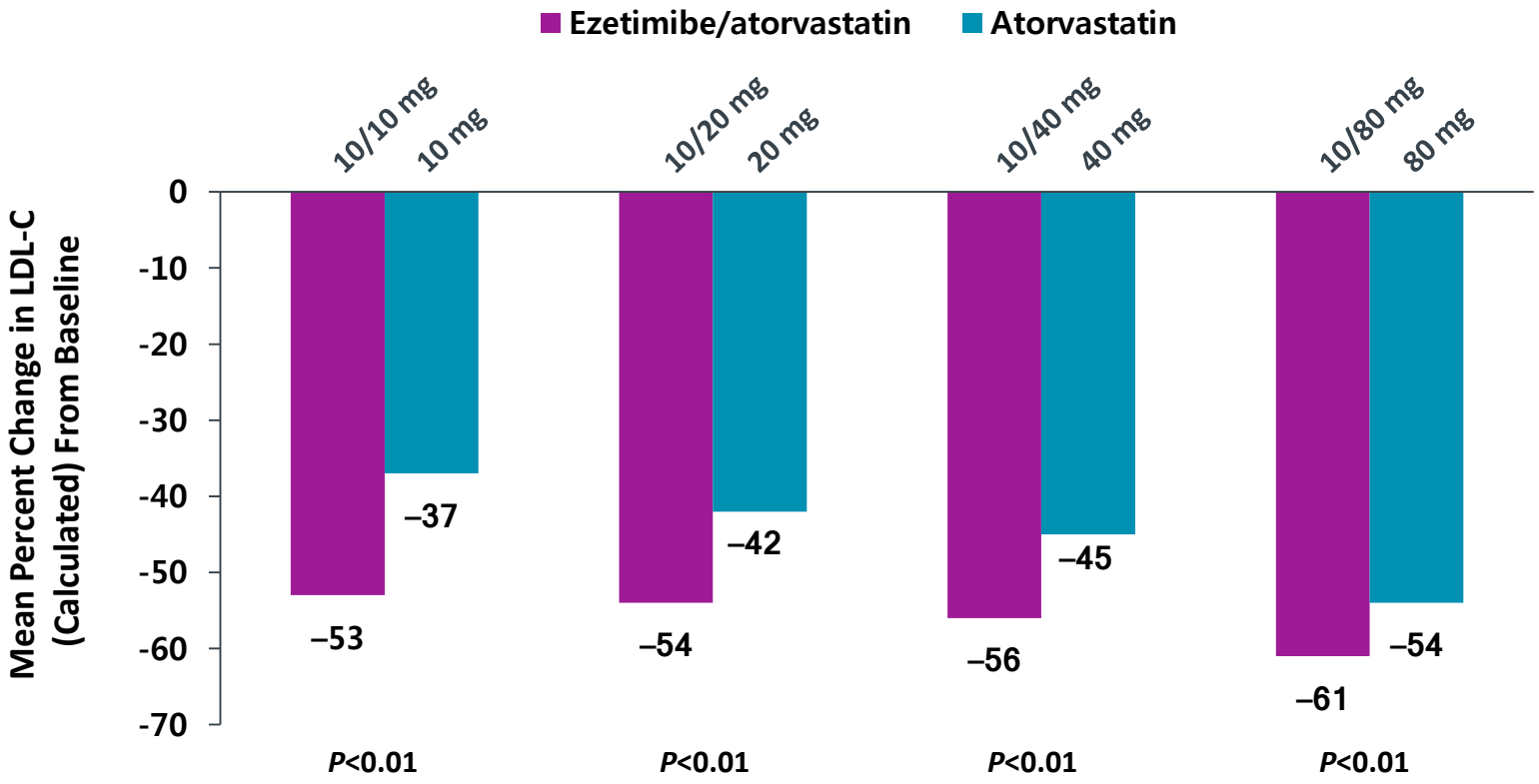
[c] In hypercholesterolemia patients with CHD. The primary endpoint was the percentage of patients achieving LDL-C ≤2.6 mmol/l at study endpoint. [Result : Ezetimibe group vs Placebo group, 81.3% vs 21.8%, $p \leq 0001$)[5]

Study design; In 5 separate randomized, double-blind, placebo-controlled trials of patients with hypercholesterolemia (2 of them examined the percent change in LDL-C as a primary endpoint, 3 of them evaluated it as a secondary endpoint),

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

1. Pearson TA et al. Mayo Clin Proc 2005;80:587-595; 2. Gagné C et al. Am J Cardiol 2002;90:1084-1091; 3. Farnier M et al. Int J Cardiol 2005;102:327-332; 4. Brohet C et al. Curr Med Res Opin 2005;21:571-578; 5. Cruz-Fernández JM et al. Int J Clin Pract 2005;59:619-627

Ezetimibe/Atorvastatin provided significantly greater LDL-C reduction compared with corresponding Atorvastatin dose



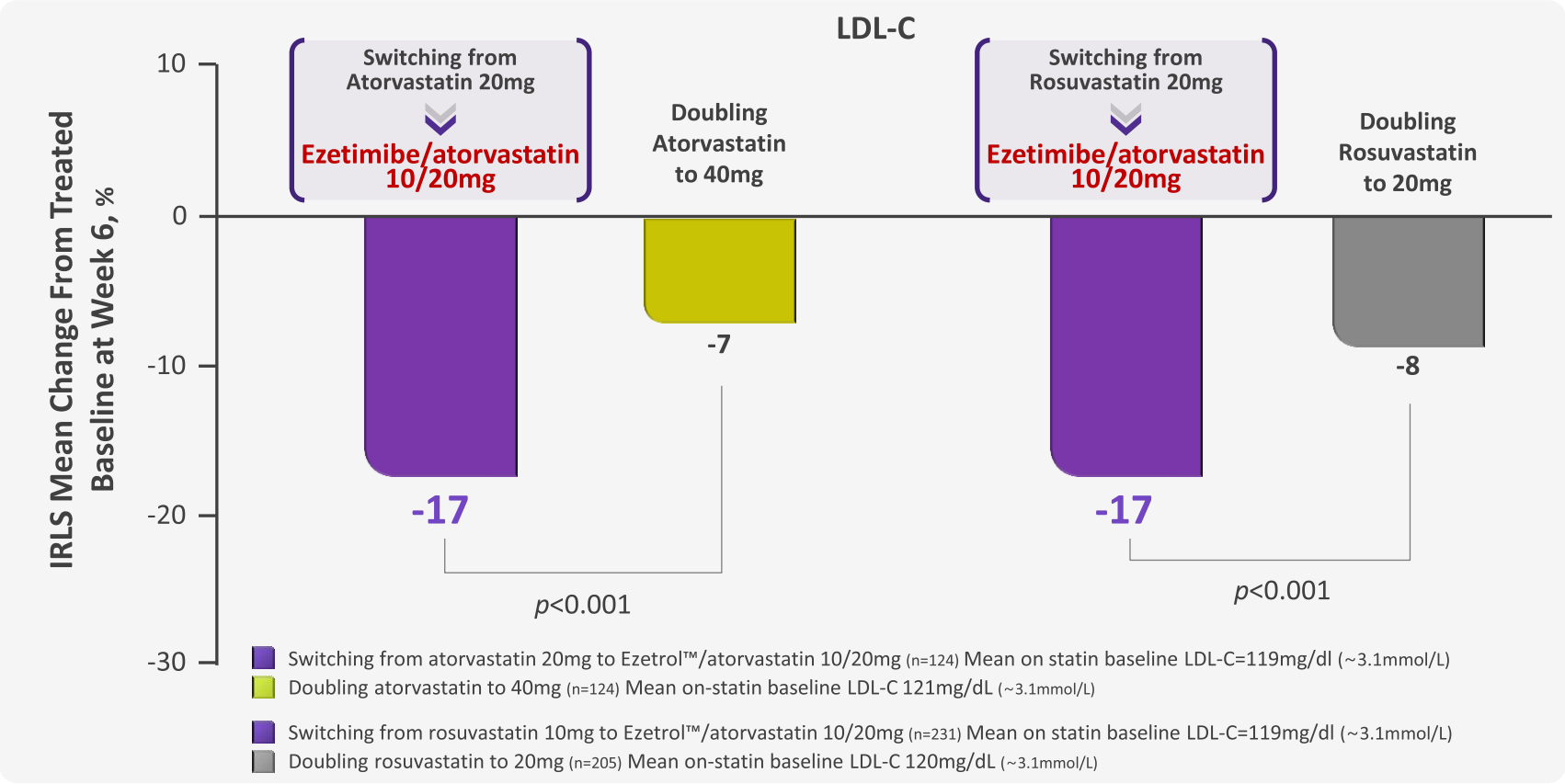
Mean baseline LDL-C was 182 mg/dL (~4.7 mmol/L) for ezetimibe/atorvastatin arms (n=255) and 181 mg/dL (~4.7 mmol/L) for atorvastatin arms (n=248).

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

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

Switching to Ezetimibe/Atorvastatin for patients not at goal provided significantly greater LDL-C reduction vs. statin doubling

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



LDL-C : Low-density lipoprotein cholesterol, IRLS : Iteratively reweighted least squares.

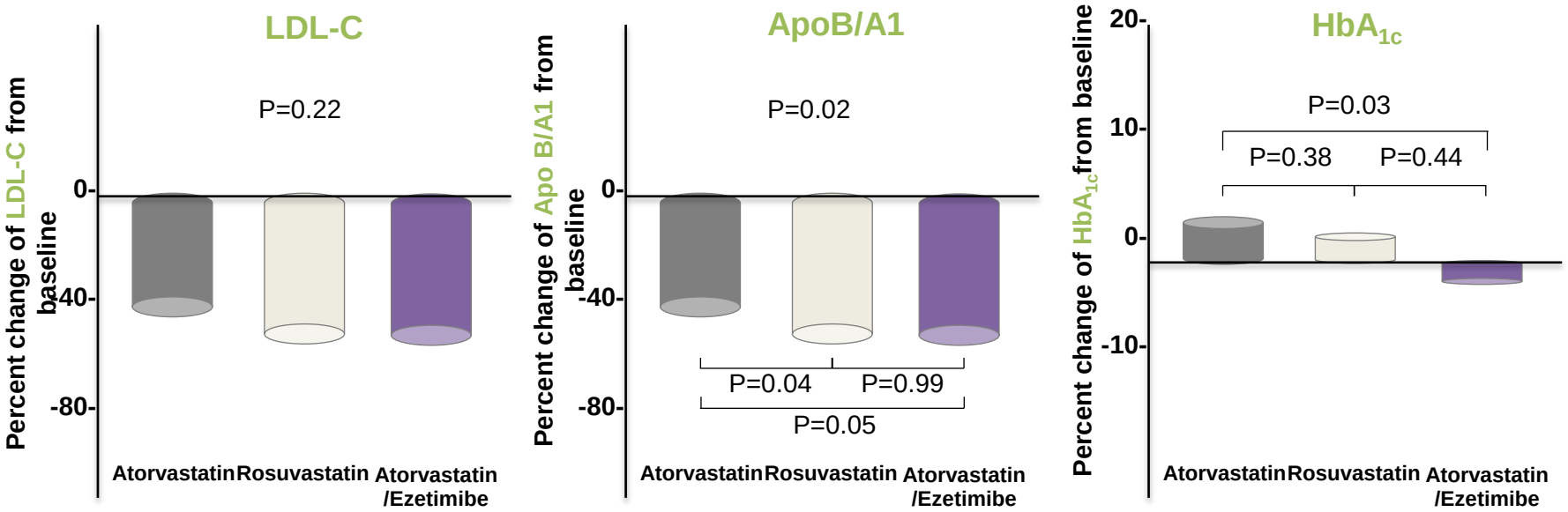
study design A randomized, double-blind, active-controlled, multicenter study in subjects aged 18 to 79 years with primary hypercholesterolemia at high cardiovascular risk according to the National Cholesterol Education Program Adult Treatment Panel III and 2011 European Society of Cardiology/European Atherosclerosis Society recommendations who were not adequately controlled with atorvastatin 10 mg.

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

Effects of ezetimibe/atorvastatin on lipoproteins and glucose metabolism

Ezetimibe/atorvastatin 5 mg/5 mg was more efficacious in improving Apo B/A1 ratio than atorvastatin 20 mg after comparable LDL-C reduction. On the other hand, atorvastatin 20 mg showed greater increase in HbA_{1c} than ezetimibe/atorvastatin 5 mg/5 mg.[1]

Change of LDL-C and the glucose metabolism-related parameters (n=76) at week 8



Atorvastatin 20 mg (n=25**), Rosuvastatin 10 mg** (n=25), **Atorvastatin/Ezetimibe 5 mg/5 mg** (n=26)

This clinical result is based on sources including off-label indications

Study design; This 12-week (4-week dietary lead-in period followed by 8 weeks of drug treatment), randomized, open-label, single center study was conducted in 90 hypercholeserolemic patients to 1 of 3 treatment groups : atorvastatin 20 mg, rosuvastatin 10 mg, or atorvastatin/ezetimibe 5 mg/5 mg. The primary end point was the percentage changes in the apolipoprotein B/A1 ratio and hemoglobin A1c from baseline to week 8 of drug treatment.

HbA_{1c}=glycosylated hemoglobin, LDL-C=low-density lipoprotein cholesterol, Apo=apolipoprotein

1.Her AY et al. J Cardiovascular Pharm and Therapeutics 2010;15 167–174

Ezetimibe/Statin vs. Statin doubling

Table 3. Percent changes in serum lipids and apolipoproteins and glucose metabolism parameters after 12-week treatment

Variable	Pravastatin + ezetimibe			Double-dose pravastatin			p value †
	n	Means (SD)	p value*	n	Means (SD)	p value*	
Body weight	96	−0.3 (1.6)	0.02	95	−0.4 (2.1)	0.02	0.72
Waist circumference	96	−1.1 (2.3)	<0.0001	95	−0.4 (2.3)	0.10	0.02
Total cholesterol	96	−11.1 (11.7)	<0.0001	95	−3.6 (13.9)	0.0004	<0.0001
Non-HDL-C	96	−16.1 (14.1)	<0.0001	95	−5.0 (17.7)	0.0002	<0.0001
LDL-C	96	−15.6 (15.4)	<0.0001	95	−5.9 (18.3)	0.0004	<0.0001
HDL-C	96	4.4 (12.7)	0.002	95	1.4 (14.1)	0.53	0.08
TG	84	−4.8 (29.3)	0.06	87	17.4 (47.3)	0.01	0.002
Apo A	96	4.1 (10.8)	0.0005	95	4.3 (13.0)	0.002	0.71
Apo B	96	−13.9 (13.2)	<0.0001	95	−4.4 (14.9)	0.0007	<0.0001
Apo E	96	−5.9 (12.4)	<0.0001	95	1.9 (14.8)	0.88	0.0002
Fasting glucose	84	0.5 (7.5)	0.82	87	1.7 (9.3)	0.10	0.32
Fasting insulin	84	17.8 (66.4)	0.10	87	33.8 (70.3)	<0.0001	0.03
HOMA-IR	84	20.0 (71.7)	0.09	87	38.9 (82.7)	<0.0001	0.04
HbA1c	96	0.3 (3.5)	0.26	95	−0.5 (4.1)	0.28	0.13
hs-CRP	94	28.3 (134)	0.82	90	25.1 (133)	0.83	0.996
Adiponectin ‡	94	3.4 (27.1)	0.88	95	7.0 (44.1)	0.30	0.58

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Apo = apolipoprotein; HOMA-IR = homeostasis model assessment of insulin resistance index; hs-CRP = high-sensitivity C-reactive protein.
* Within-group comparison for difference from the baseline.
† Between-group comparison.
‡ High-molecular weight adiponectin

Sasaki et al. J Atheroscler Thromb, 2011

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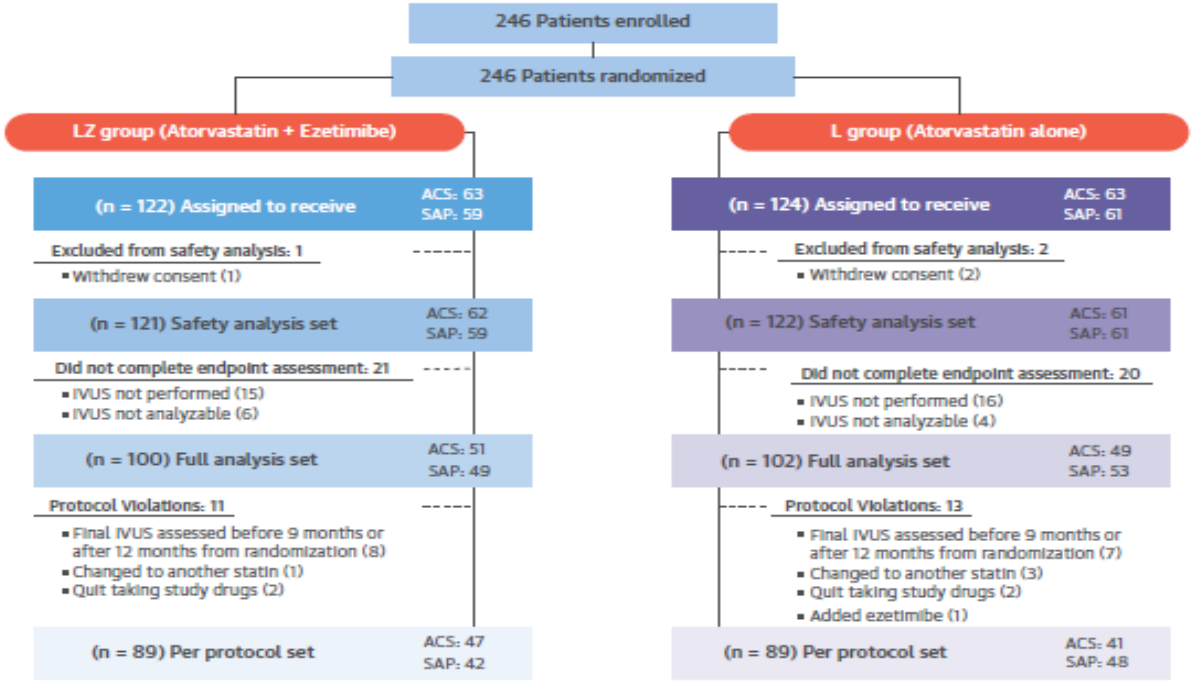
ORIGINAL INVESTIGATIONS

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

The Multicenter Randomized Controlled PRECISE-IVUS Trial

OBJECTIVES.
To evaluate the **effects of ezetimibe plus atorvastatin** vs. atorvastatin monotherapy on the lipid profile and coronary atherosclerosis in Japanese patients who underwent PCI.

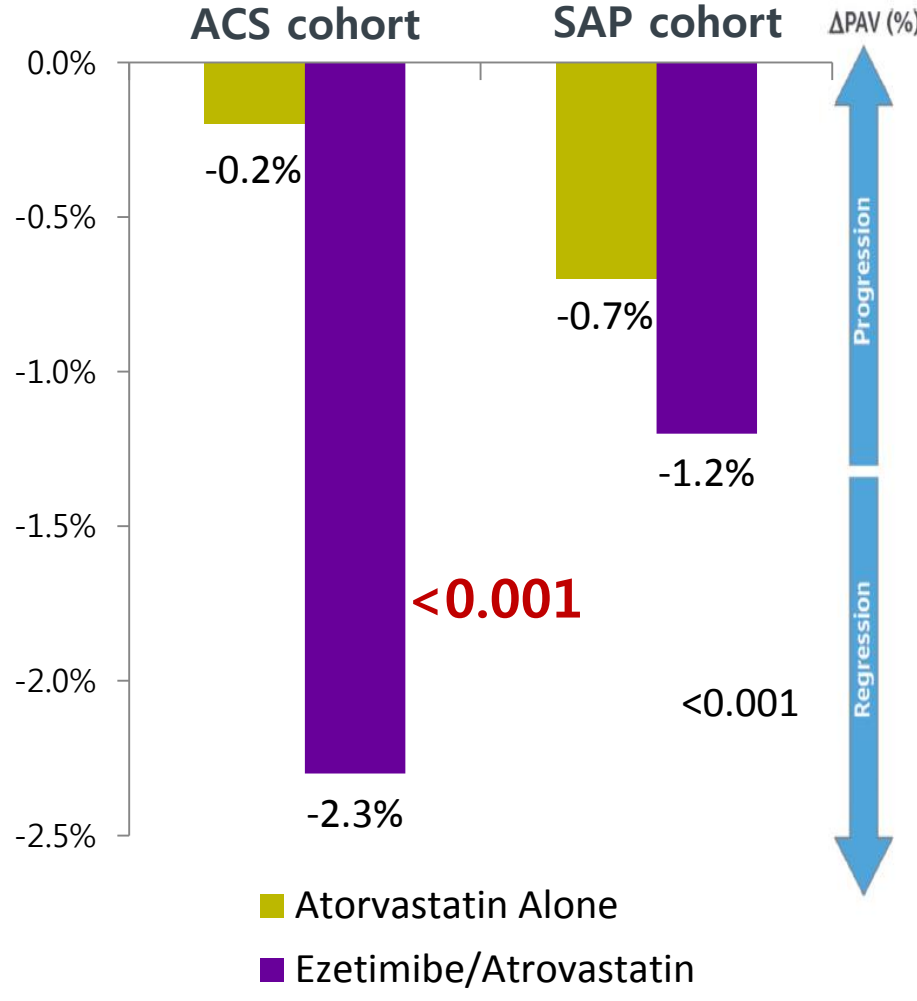


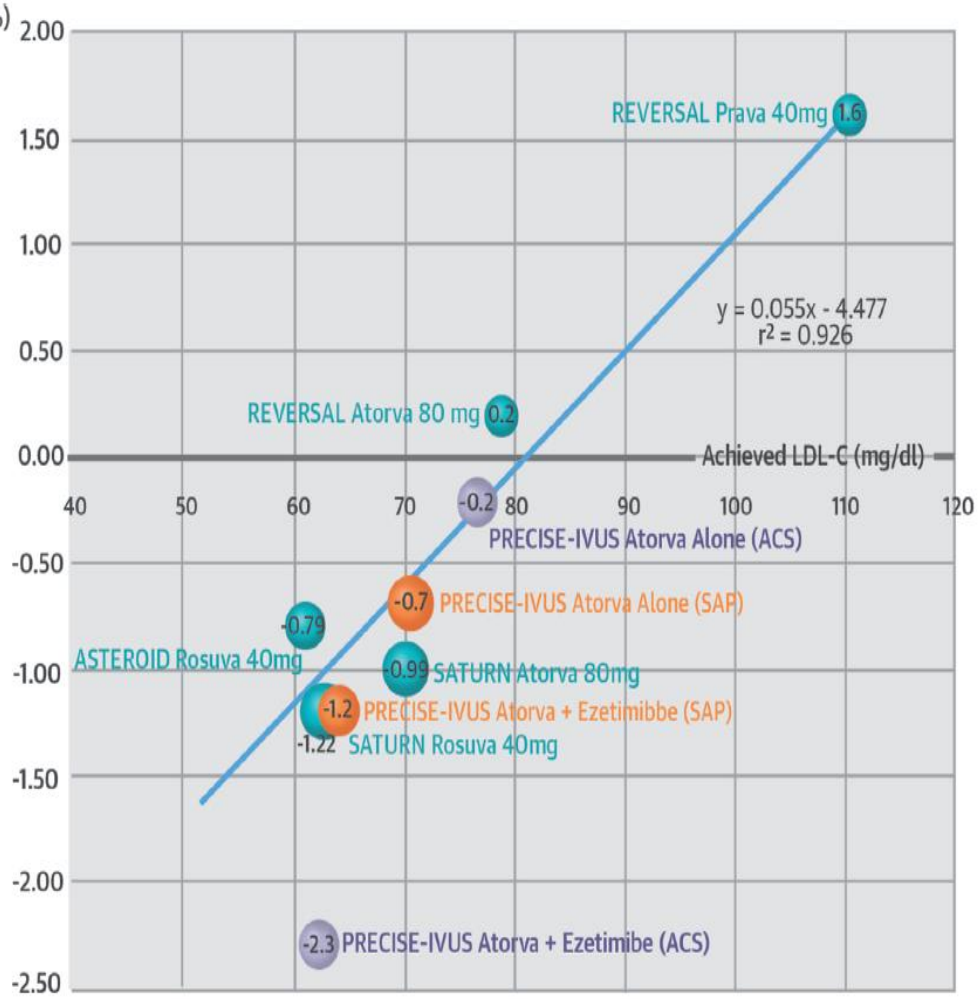
Tsujita K, et al. JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY. 2015

Ezetimibe and Atorvastatin on Coronary Plaque Regression in Patients With PCI

✓ Follow-up LDL-C :atorvastatin/ezetimibe (**63.2** ± 16.3 mg/dl) vs. atorvastatin monotherapy **73.3** ± 20.3 mg/dl; p < 0.001).

% Change in Atheroma Volume



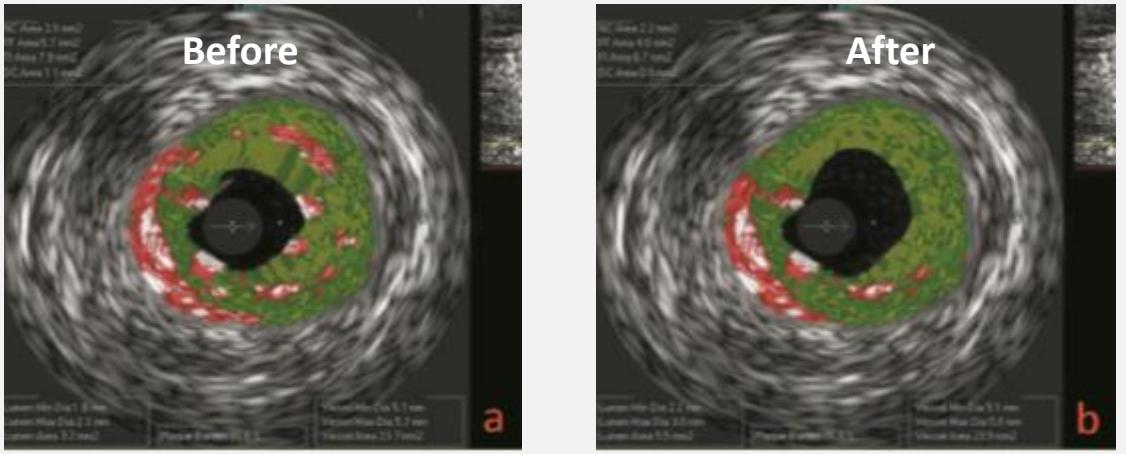


Tsujita, K. et al. *J Am Coll Cardiol. 2015; 66(5):495–507.*

Effect of combination of ezetimibe and rosuvastatin on coronary artery plaque in patients with coronary heart disease

(1) Ezetimibe (10 mg) plus rosuvastatin (10 mg) (n = 55) or
(2) Rosuvastatin alone (10 mg) (n = 51)

Image combined treatment with Rosuvastatin+Ezetimibe



Analysis of gray scale and virtual histology–IVUS images in the two groups of patients (X±S).

	n	EEM (mm^2)	MLA (mm^2)	Plaque burden (%)	Plaque cross-sectional area (mm^2)	The percentage of necrotic plaque composition(%)
Ezetimibe + rosuvastatin group						
Pre-treatment	50	12.3±3.2	3.1±1.2	73.4±19.8	9.6±3.7	48±10
Post-treatment	50	11.9±3.5	4.0±0.7*#	62.1±7.2*#	5.2±1.4*#	26±5*#
Rosuvastatin group						
Pre-treatment	48	12.2±2.5	3.2±1.3	73.1±19.1	9.8±3.8	46±8
Post-treatment	48	11.3±3.3	3.6±0.6	68.2±8.3*	7.3±1.6*	31±7*

*P < 0.05, vs pre-treatment in the same group;
#P < 0.05, vs rosuvastatin group.
IVUS: intravascular ultrasonography; EEM:extravascular elastic membrane area; MLA: minimal lumen area.

Ref) Wang X et al. *Heart, lung and circulation* 2015; pii: S1443-9506(15)01463-8

The earlier The better, The lower The better!
: Strategies to further lower LDL-cholesterol

High- and Very-high-intensity statin therapy

High-intensity cholesterol-lowering therapy (HILCLT) ↓ LDLc 50-60%	Very-high-intensity cholesterol-lowering therapy (VHILCLT) ↓ LDLc 60%
• **Atorvastatin 40-80 mg**	• **Atorvastatin 40-80 mg + Ezetrol™ 10 mg**
• **Rosuvastatin 20-40 mg**	• Rosuvastatin 20-40 mg + Ezetrol™ 10 mg
• Simvastatin 20 -40 mg + Ezetrol™ 10 mg	
• Pravastatin 40 mg + Ezetrol™ 10 mg	
• Lovastatin 40 mg + Ezetrol™ 10 mg	
• Fluvastatin 80 mg + Ezetrol™ 10 mg	
• Pitavastatin 2-4 mg + Ezetrol™ 10 mg	
• **Atorvastatin 10-20 mg + Ezetrol™ 10 mg**	
• Rosuvastatin 5-10 mg + Ezetrol™ 10 mg	

Adapted from Masana L, *et al.*

1. Masana L, Pedro-Botet J, and Civeira F. IMPROVE-IT clinical implications. Should the "high-intensity cholesterol-lowering therapy" strategy replace the "high-intensity statin therapy?" *Atherosclerosis*. 2015;240(1):161-2.

Take-home message

What are the arguments to use a "Combination with ezetimibe" ?

- **Re-affirms the LDL hypothesis, that reducing LDL-C prevents cardiovascular events.**

- **Combination therapy with ezetimibe has a greater efficacy in lower doses of statin.**

Ezetimibe combination could be an answer with **superior efficacy and less side effects** for high risk patients secondary prevention including the **reduction of the concerns regarding new DM** associated with high-dose statin.

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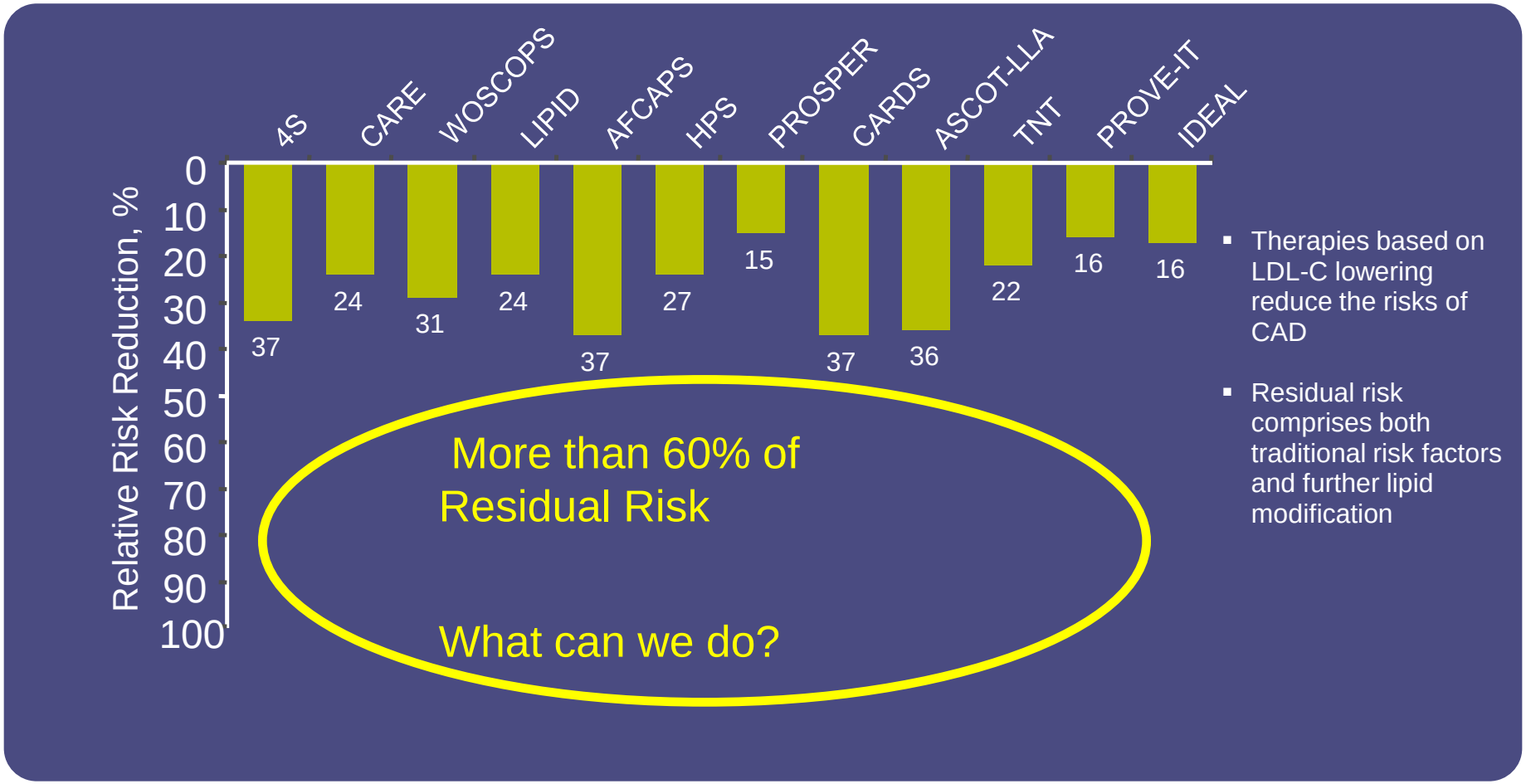
BACK-UP

Even after intensive LDL-C reduction, still more than 60% residual risk exits

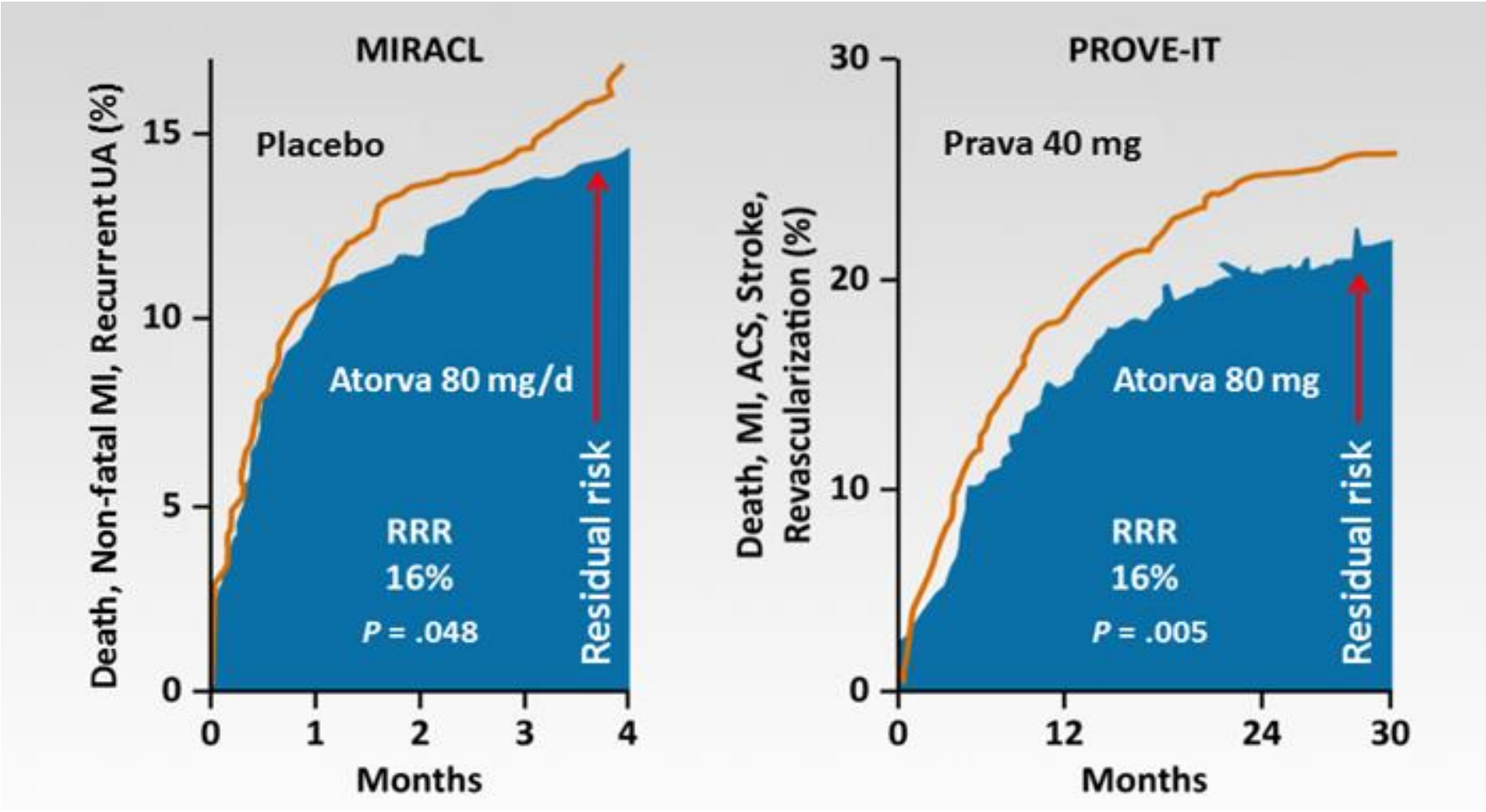


- Therapies based on LDL-C lowering reduce the risks of CAD
- Residual risk comprises both traditional risk factors and further lipid modification

PROVE-IT = PRavastatin Or atorVastatin Evaluation and Infection Therapy; IDEAL = Incremental Decrease in End points through Aggressive Lipid lowering; CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; CAD = coronary artery disease.

Adapted from Chapman J. *Eur Heart J*. 2005;7(suppl F):F56–F62.
[4S Study Group]. *Lancet.* 1994;344:1383–1389; Sacks FM et al. *N Engl J Med.* 1996;335:1001–1009; Shepherd J et al. *N Engl J Med.* 1995;333:1301–1307; The Long-Term Intervention With Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med.* 1998;339:1349–1357; Downs JR et al. *JAMA.* 1998;279:1615–1622; Heart Protection Study Collaborative Group. *Lancet.* 2002;36:7–22; Shepherd J et al. *Lancet.* 2002;360:1623–1630; Colhoun HM et al. *Lancet.* 2004;364:685–696; Sever PS et al. *Lancet.* 2003;361:1149–1158; LaRosa JC et al. *N Engl J Med.* 2005;352:1425–1435; Cannon CP et al. *N Engl J Med.* 2004;350:1495–1505; Pedersen TR et al. *JAMA*. 2005;294:2437–3092.

Substantial Residual Cardiovascular Risk After Intensive Statin Therapy Post-ACS



schwarts GG, et,al. JAMA. 2001;285;1711-1718
Cannon CP, et al. N Engl J Med. 2004;350;1495-1504.

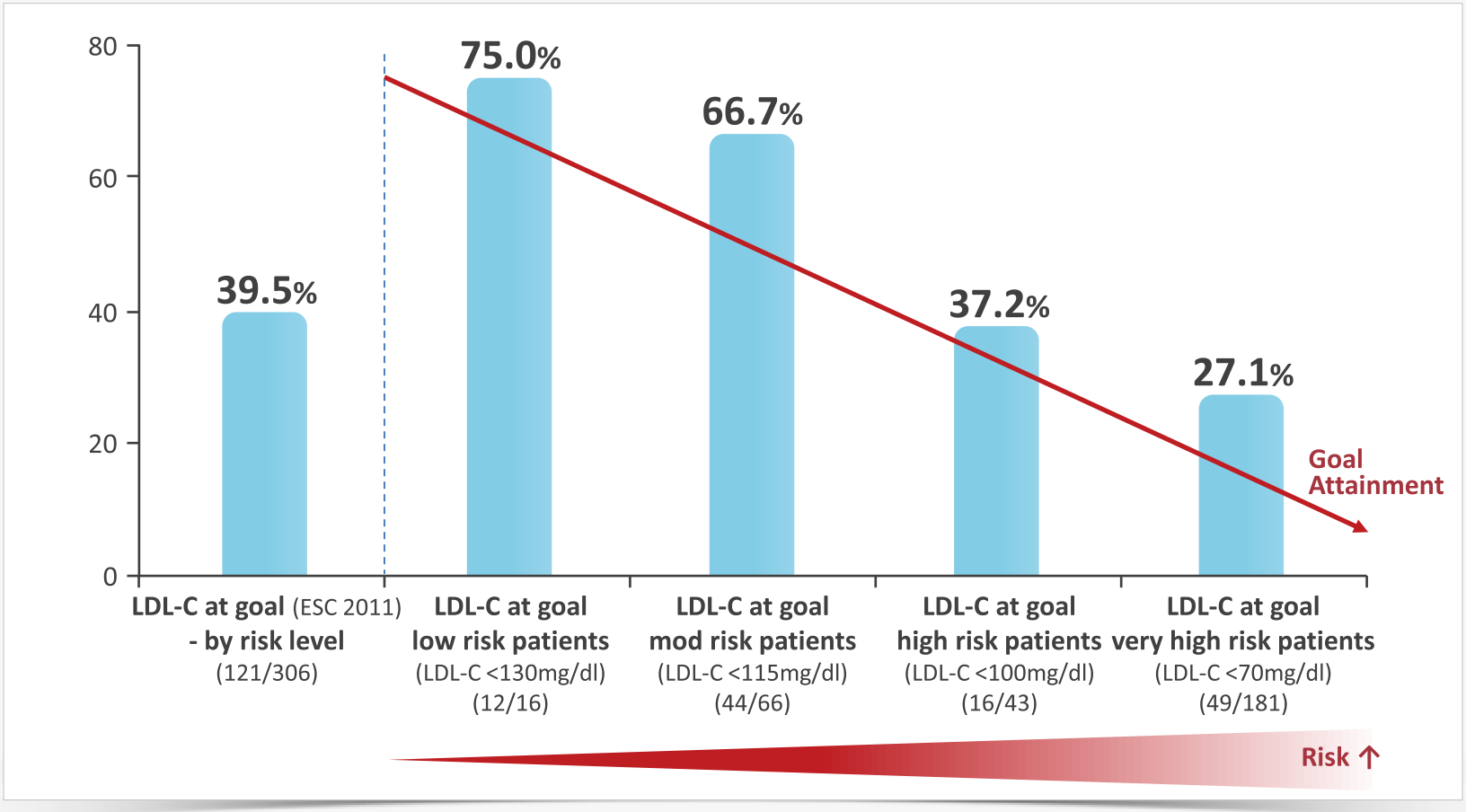
Back up slides
Dyslipidemia International Study II

LDL-C Goal Attainment Rate by Risk Level

ACS CHD

- **The LDL-C goal attainment rate decreased as pre-admission CVD risk status as defined in 2011 ESC Guideline increased.**

Target Attainment by ESC 2011 Risk Level



DYSIS II Dyslipidemia International Study II

Predictors for LDL-C at Goal

ACS CHD

- **Statin dose was found to be associated with higher odds of attaining the LDL-C target** (OR 1.049 [p-value 0.0095]).

Predictors for LDL-C at Goal for Patients Treated with LLT

Predictor	Odds Ratio	Lower 95% Confidence Limit for Odds Ratio	Upper 95% Confidence Limit for Odds Ratio	*P*-value
Age >= 70	1.466	0.667	3.221	0.3409
Females	0.581	0.246	1.374	0.2164
BMI > 30kg/m^2 (obesity)	1.110	0.207	5.960	0.9033
Current smoking	2.018	0.718	5.678	0.1832
Sedentary lifestyle	0.359	0.161	0.804	0.0128
Stable angina	0.639	0.214	1.906	0.4223
CKD	2.285	0.173	30.232	0.5304
T2DM	1.159	0.548	2.452	0.7003
Hypertension	1.338	0.573	3.120	0.5009
Statin dose (calculated in Atorvastatin, mg/day)	1.049	1.012	1.087	0.0095

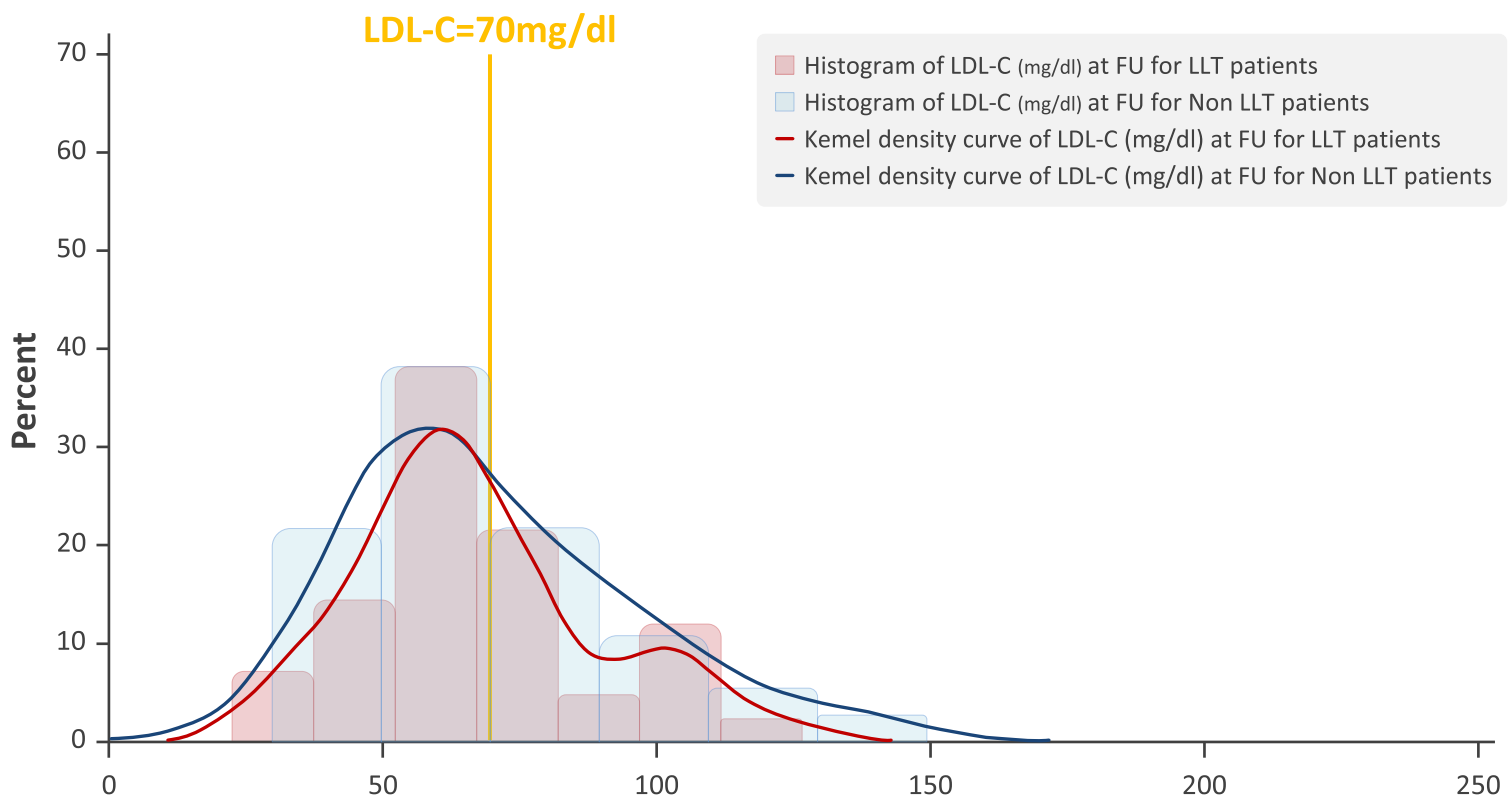
ACS, Acute coronary syndrome; BMI, Body mass index; CKD, Chronic kidney disease; LDL-C, Low-density lipoprotein; LLT, lipid-lowering therapy; T2DM, Type 2 diabetes mellitus

DYSIS II Dyslipidemia International Study II

Distribution of LDL-C for LLT vs. Non-LLT

ACS CHD

DYSIS II Kernel Density Curves of LDL-C Cholesterol (mg/dl) at Follow-Up: LLT versus Non LLT at Time of Latest Lipid Test

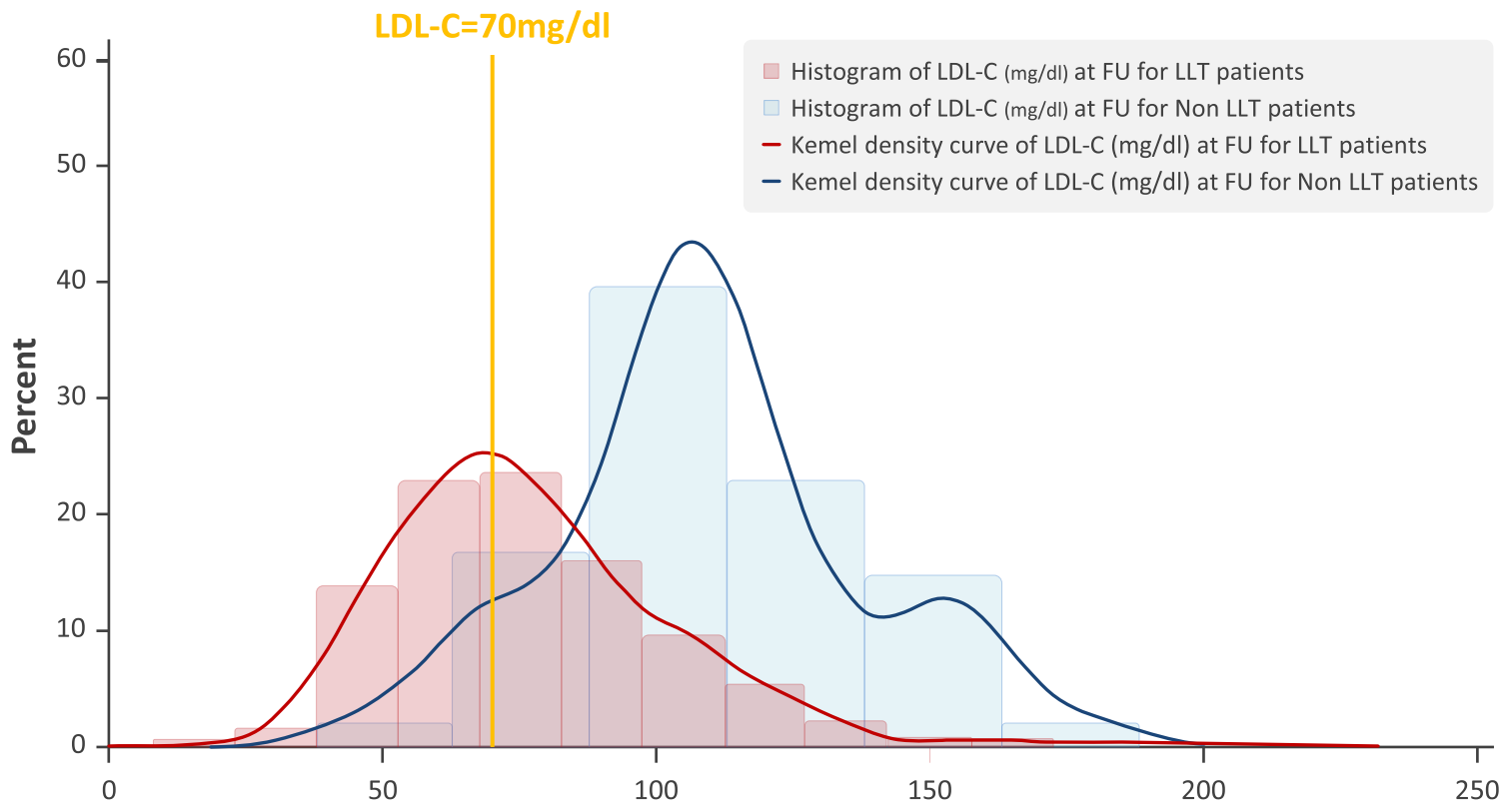


DYSIS II Dyslipidemia International Study II

Distribution of LDL-C for LLT vs. Non-LLT

ACS CHD

DYSIS II Kernel Density Curves of LDL-C Cholesterol
LLT ver. Non LLT at Time of Latest Lipid Test



Subgroup Analysis for ACS Patients with Type II DM

Lipid Profile at Baseline for Type II DM

ACS | CHD

- 94 out of 308 ACS patients had T2DM concomitantly.
- Mean (±SD) total cholesterol and LDL-C levels for ACS patients with T2DM were lower than total ACS patients at baseline.
- Rate of LLT for ACS patients with T2DM was higher than total ACS patients at baseline(70% vs. 53%).

Lipid Profile & Lipid Parameters within 24 Hours of Admission

	T2DM patients	LLT	Non LLT	*P*-value
T2DM	100.0% (94/94)	100.0% (66/66)	100.0% (28/28)	
Total cholesterol (mg/dl)	157.7 ± 41.8, n=94	147.7 ± 40.0, n=66	181.4 ± 36.3, n=28	< 0.0001
LDL-C (mg/dl)	91.3 ± 36.0, n=94	78.9 ± 25.6, n=66	120.5 ± 40.2, n=28	< 0.0001
HDL –C mg/dl)	38.6 ± 9.6, n=94	38.9 ± 9.5, n=66	38.0 ± 10.0, n=28	0.87
TG (mg/dl)	167.4 ± 171.8, n=94	186.8 ± 195.1, n=66	121.8 ± 83.1, n=28	< 0.01
Non-HDL-C (mg/dl)	119.1 ± 42.0, n=94	108.8 ± 40.6, n=66	143.4 ± 35.2, n=28	<0.0001

DYSIS II
Dyslipidemia International Study II

LDL-C Goal Attainment Rate at Baseline for Type II DM

- **LDL-C goal attainment rate of patients with T2DM was lower than total ACS population.**

LDL-C Goal [ESC 2011, <70mg/dl] **Attainment Rate at Baseline**
Total vs. T2DM

Total Population (N=306)

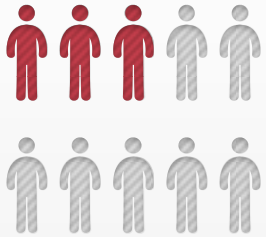
LDL-C at goal

39.5%
(n=121)

T2DM (N=94)

LDL-C at goal

29.8%
(n=28)



DYSIS II
Dyslipidemia International Study II

LDL-C Goal Attainment Rate at 4-month Follow-up

ACS | CHD

- Only 30 out of 94 ACS patient with T2DM had both Lipid profile at 4-month follow-up.
- LDL-C goal attainment rate of patients with T2DM was higher than total ACS population at 4-month follow-up

LDL-C Goal [ESC 2011, <70mg/dl] **Attainment Rate at 4-month Follow-up**
Total vs. T2DM

Total Population (N=79)

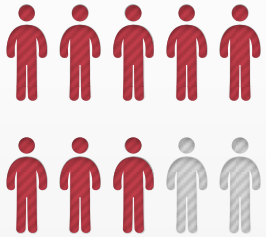
LDL-C at goal

62.0%
(N=49)

T2DM (N=30)

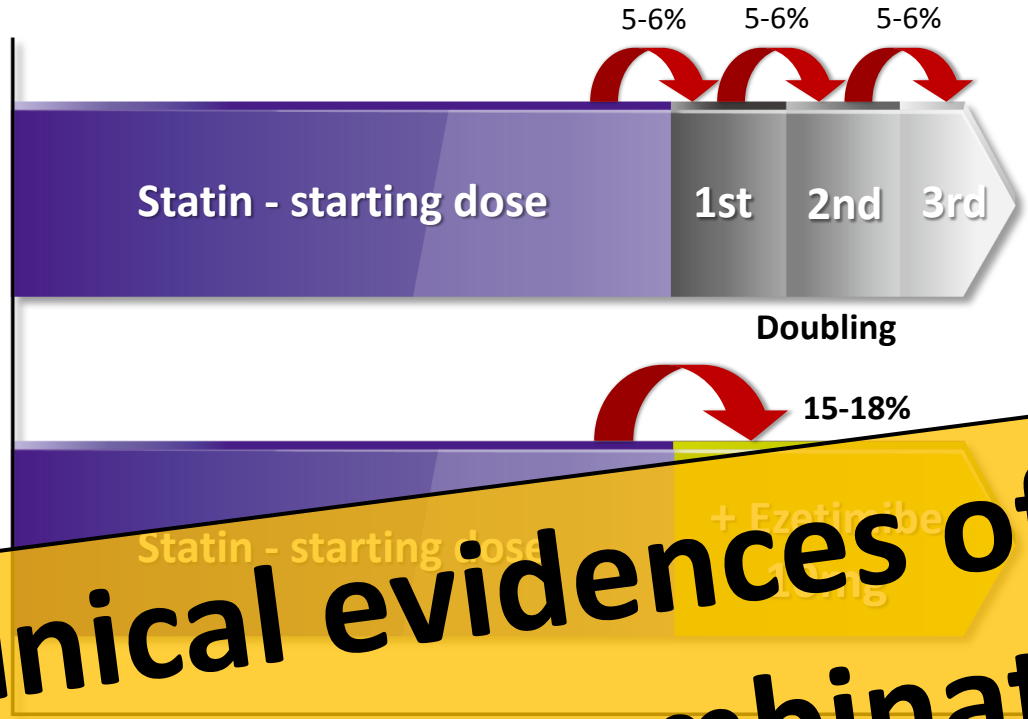
LDL-C at goal

80.0%
(N=24)



DYSIS II
Dyslipidemia International Study II

Ezetimibe + Statin vs. Statin titration



Clinical evidences of ezetimibe combination?

LDL-C, low-density liopoprotein cholesterol

1. Harold E. Bays, MD, et al. Clin ther. 2004;26:1758-1773