LDL Management

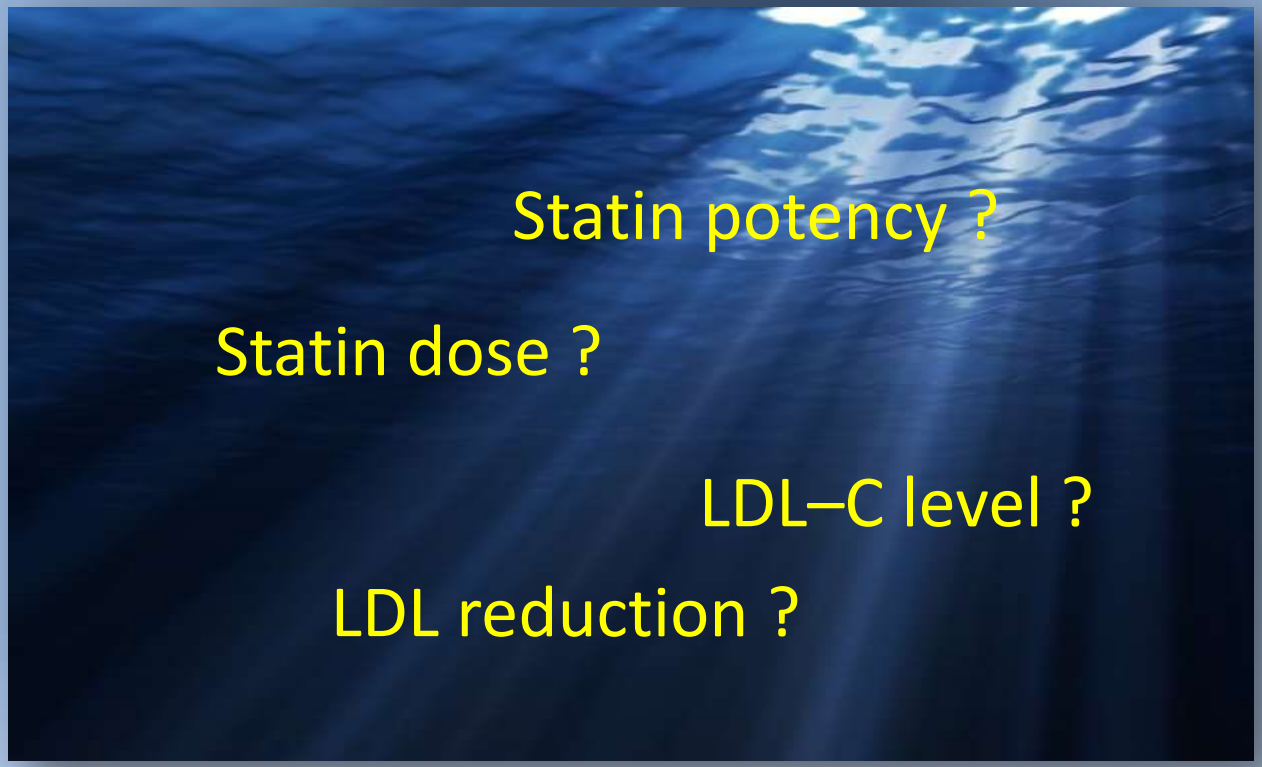
Beyond Statin Monotherapy

HOW deep should we go ?
HOW can we reach ?

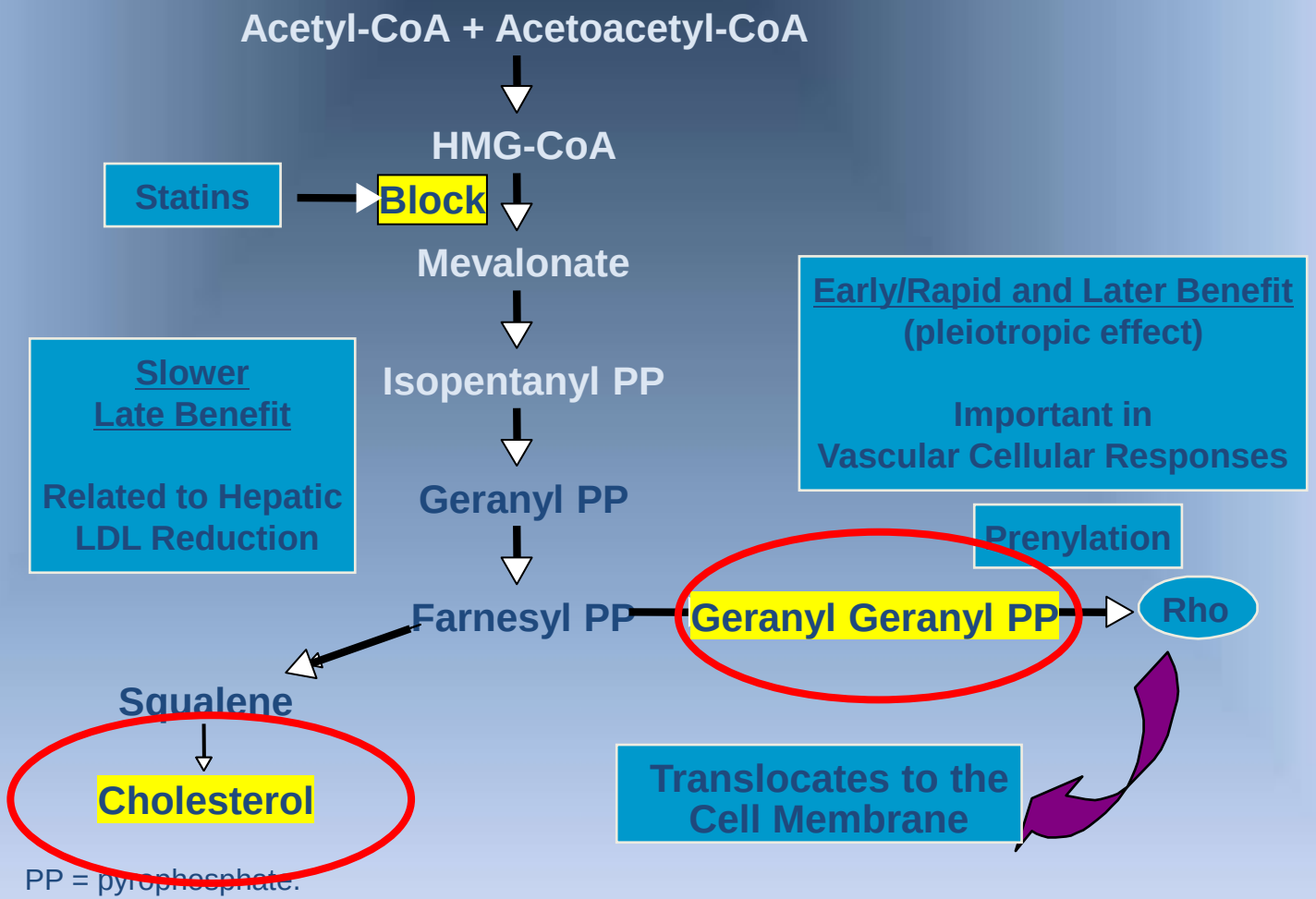
AMC
Han, Ki Hoon

Statin or LDL ?

Unsolved Problems



Metabolic Pathways Blocked By Statins

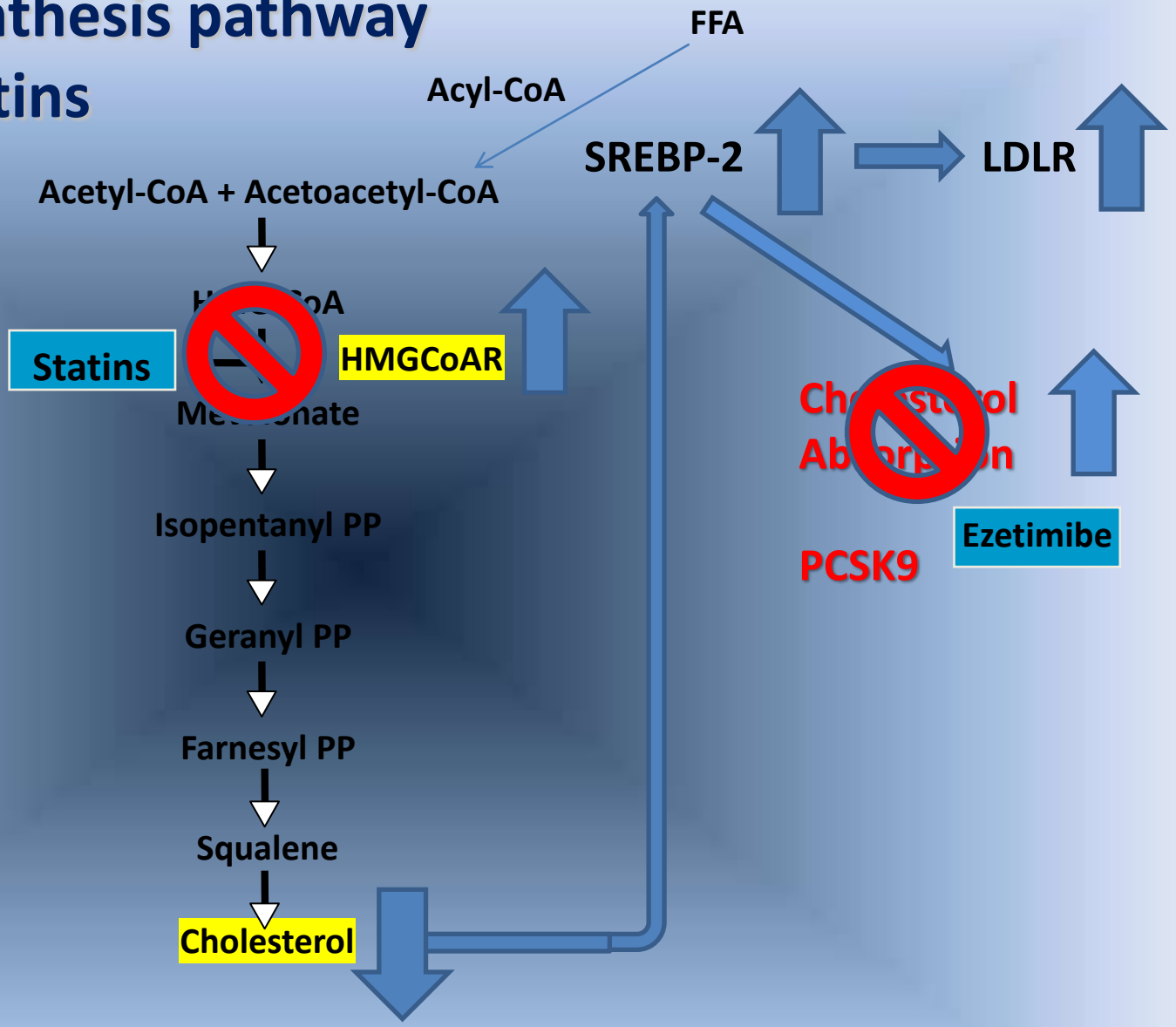


PP = pyrophosphate.

Reproduced from Ray and Cannon. *Curr Opin Lipidol*. 2004;15:637, with permission.

Ray and Cannon. *Am J Cardiol*. 2005;96(suppl):54F.

Cholesterol synthesis pathway Blocked By Statins

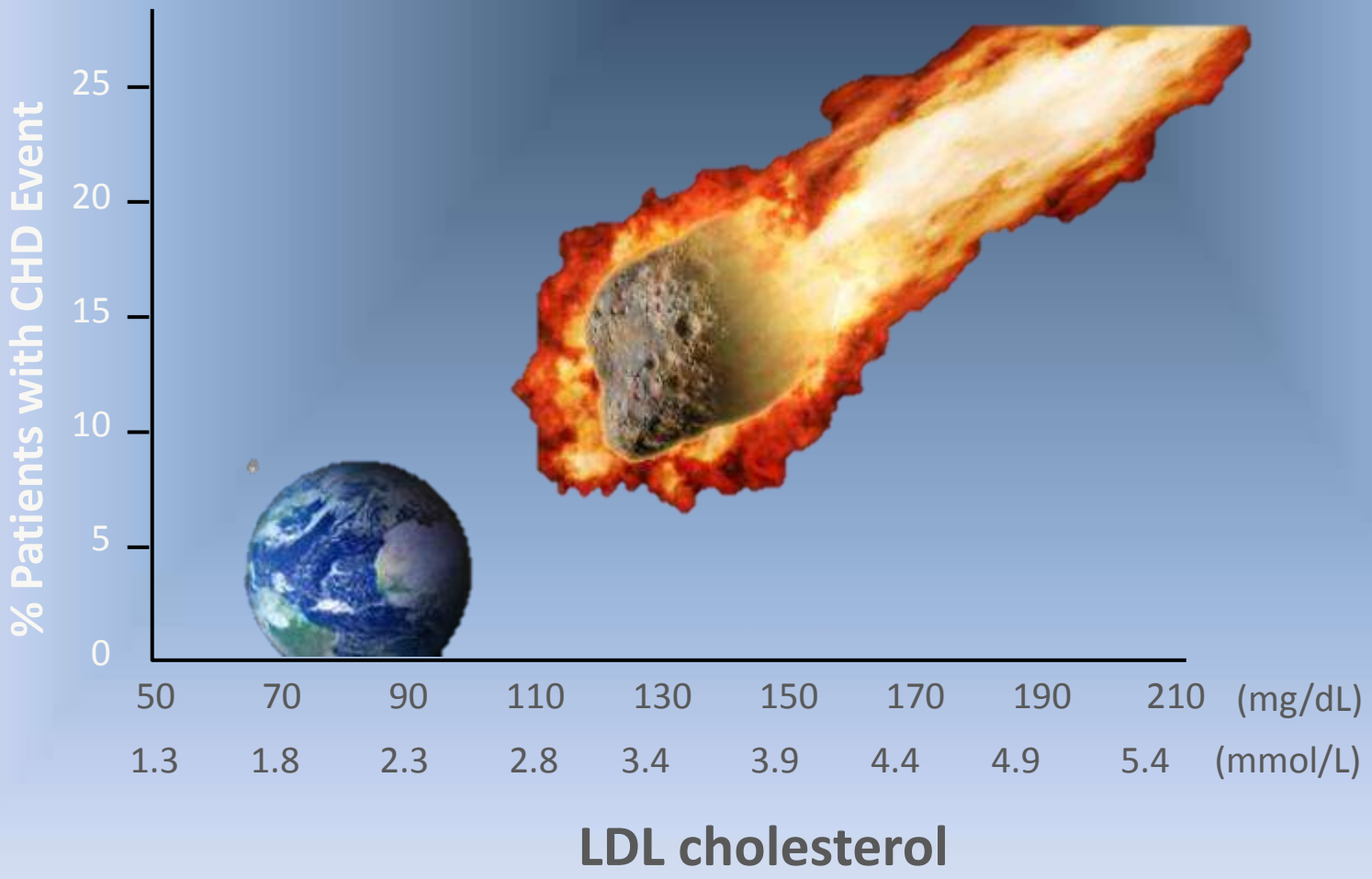


PP = pyrophosphate.

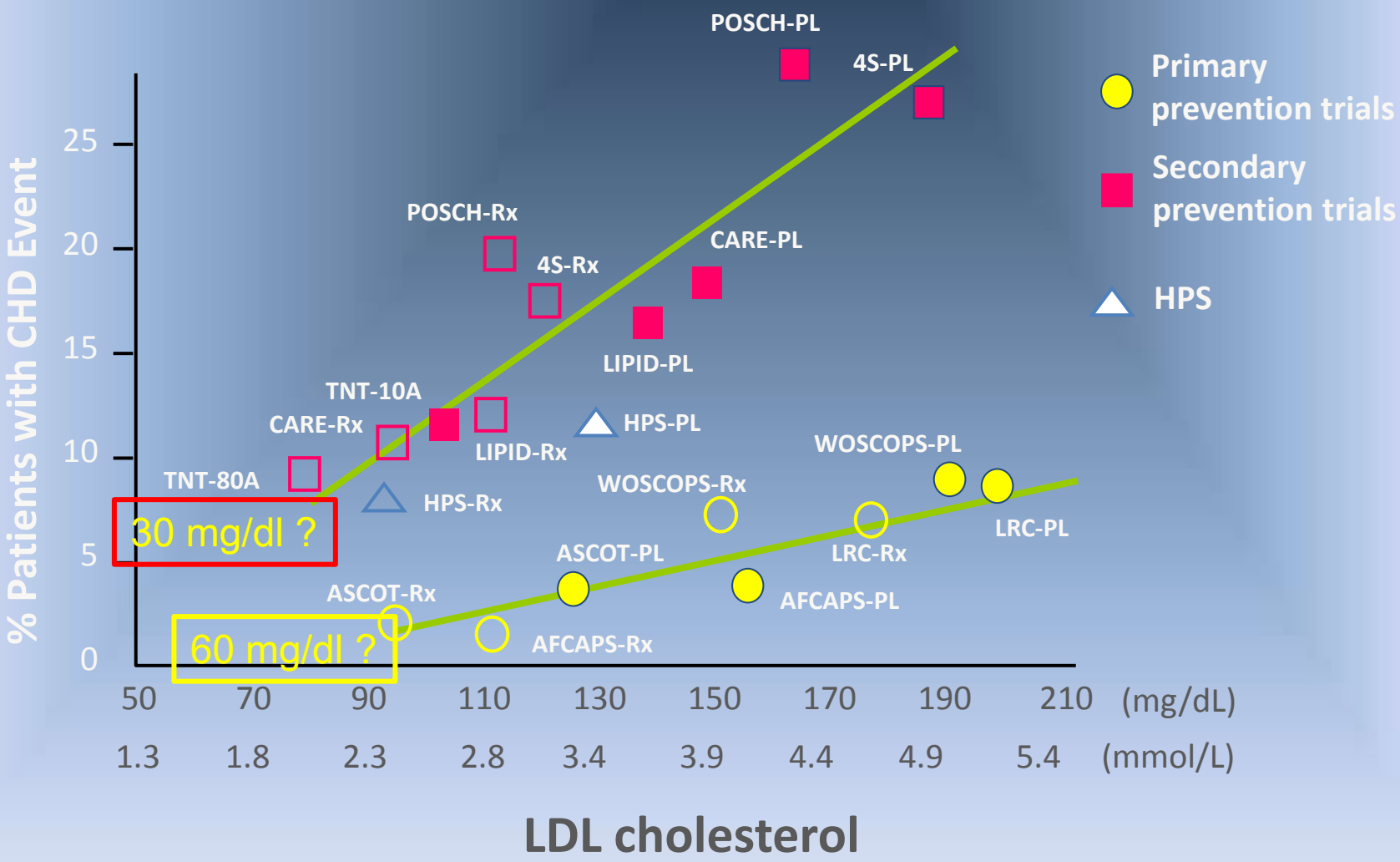
Reproduced from Ray and Cannon. *Curr Opin Lipidol*. 2004;15:637, with permission.

Ray and Cannon. *Am J Cardiol*. 2005;96(suppl):54F.

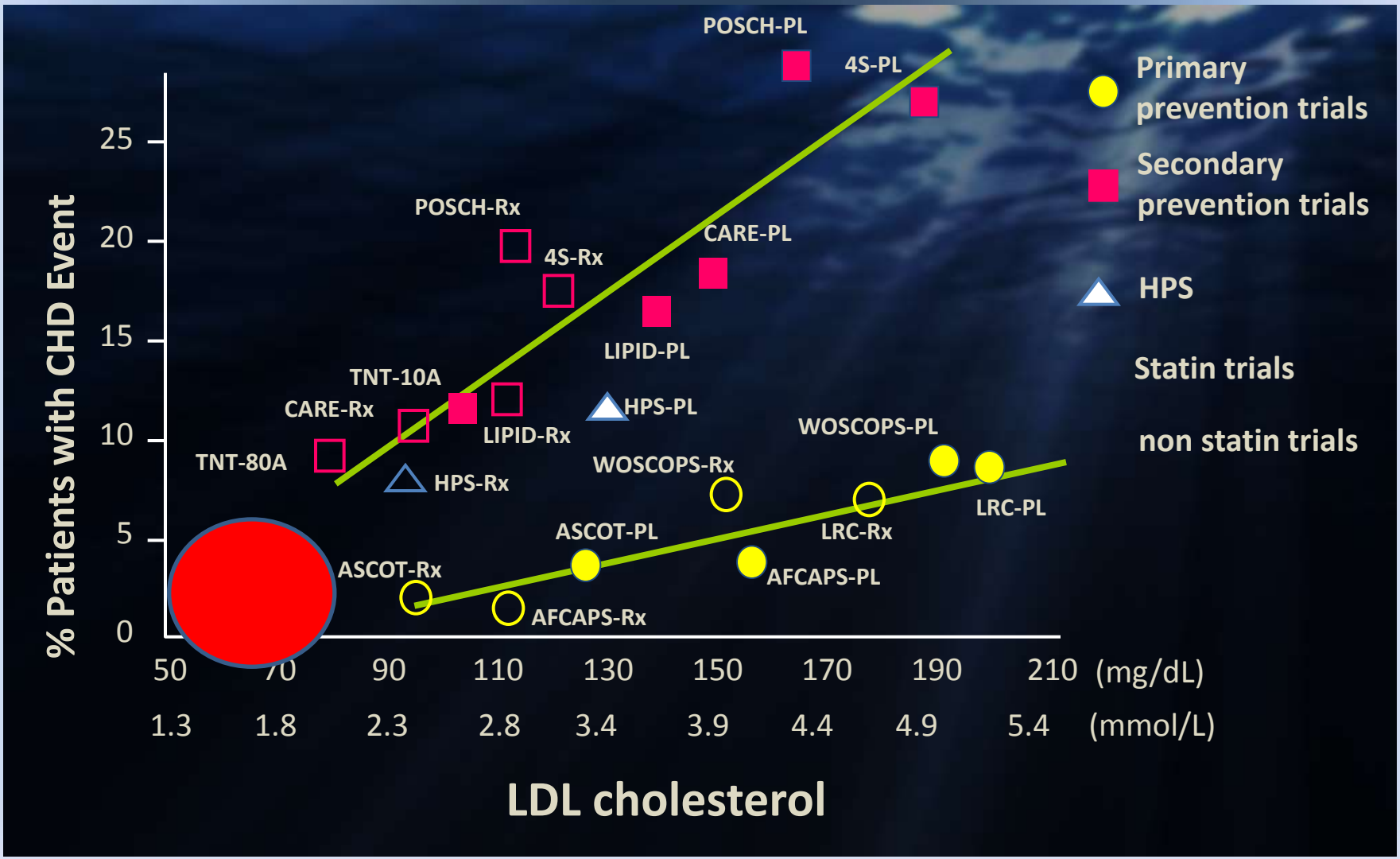
Anyway, LDL-C; Lower, the better



LDL-C ; Lower, the better



Positioning of IMPROVE-IT



“IM-PROVED” # 1. LDL

- **LDL(-C) is mediator as well as marker**
- **Lowering LDL-C is still a best strategy for CVD risk reduction**
- **Pleiotropic effect of statin may work, but still unclear (dose and duration)**

Patient Population

IMPROVE-IT

Inclusion Criteria:

- Hospitalization for STEMI, NSTEMI/UA < 10 days
- Age ≥ 50 years, and ≥ 1 high-risk feature:
  - New ST chg, + troponin, DM, prior MI, PAD, cerebrovasc, prior CABG > 3 years, multivessel CAD
- LDL-C 50-125 mg/dL (50–100 mg/dL if prior lipid-lowering Rx)

Major Exclusion Criteria:

- CABG for treatment of qualifying ACS
- Current statin Rx more potent than simva 40mg
- Creat Cl < 30mL/min, active liver disease

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 first events)

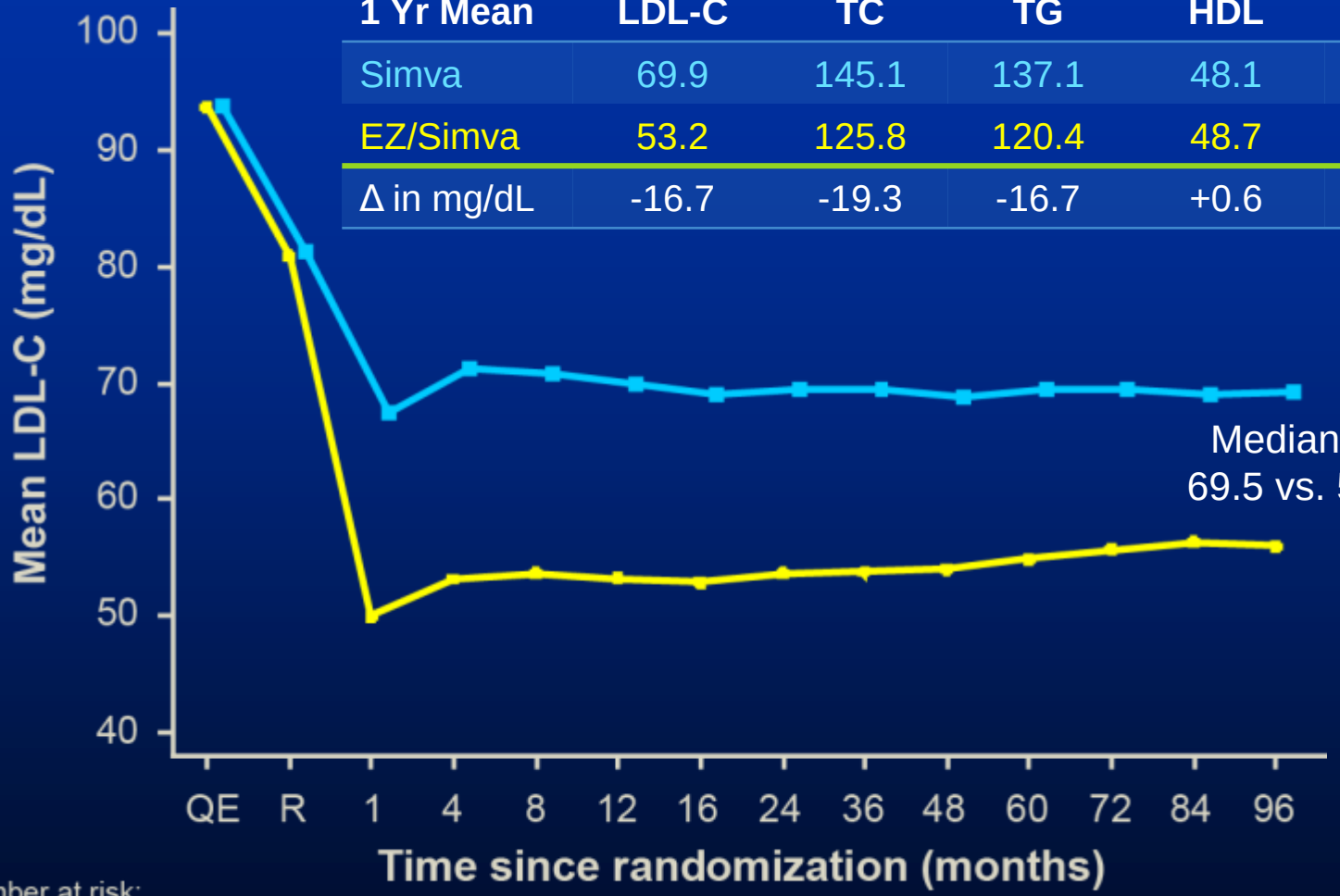
Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

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

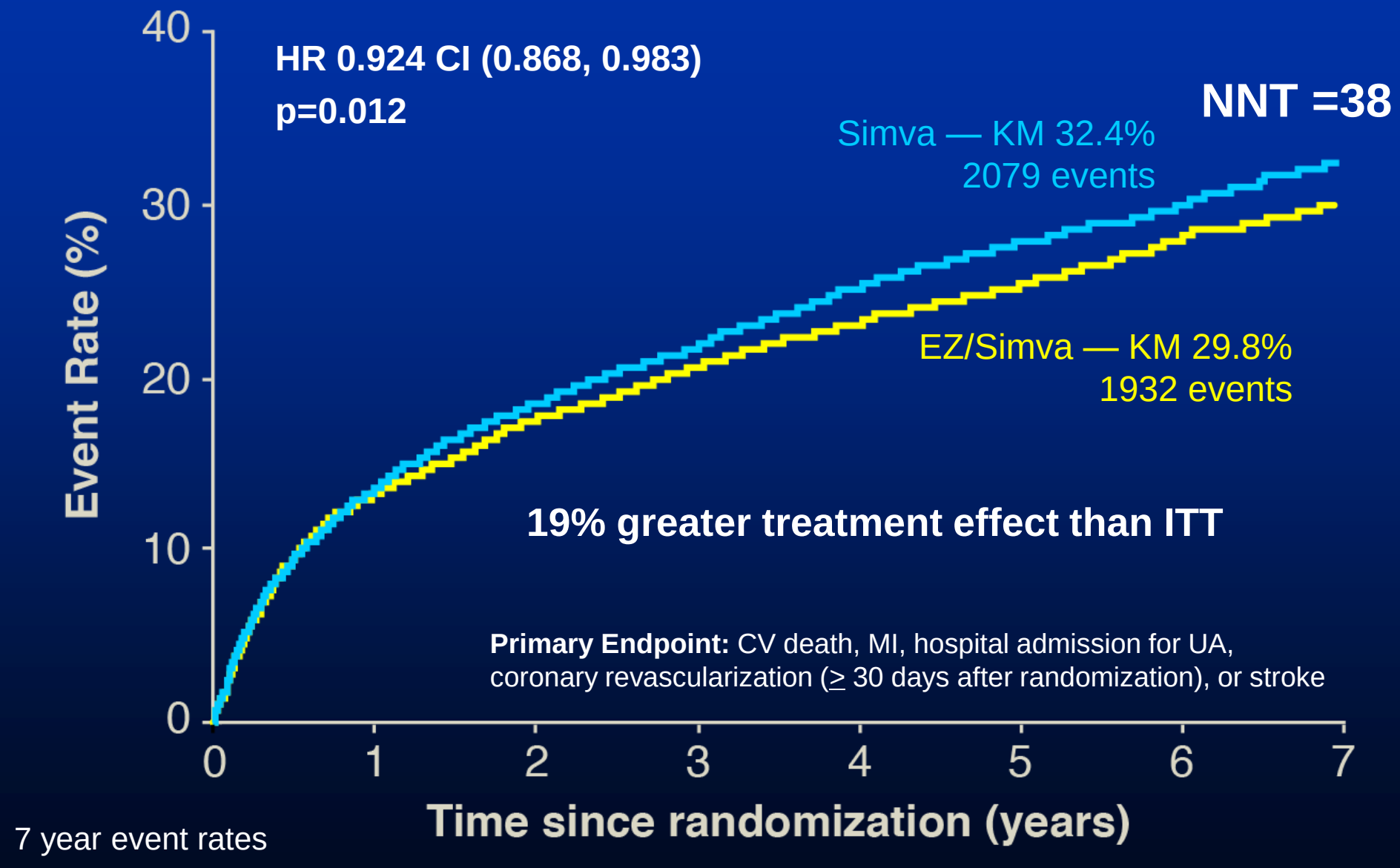
IMPROVE-IT

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

Primary Endpoint On Treatment



7 year event rates

Trend of statin trials (2ndary prevention)

Study	4S (n=4444)	CARE (n=4159)	LIPID (n=9014)	HPS (n=20,536)	TNT (n=10,001)
% Men	81	86	83	75	81
Age range (years)	35-69	21-75	31-75	40-80	29-76
% >65 years	22	–	39	52	37
Years since qualifying event	3.35 ± 3.46	10 months	1.0 (0.5, 1.9)	–	1.73 ± 2.61
% Smokers	26	21	10	14	13
% Hypertension	26	43	41	41	54
% Diabetes	4.5	14	9	29	15
Concomitant medications					
Aspirin	37	83	82	63	88
β-blocker	57	40	47	26	55
Calcium antagonist	31	39	35	–	26
LDL-C, mg/dL	188	139	150	131	98
(mmol/L)	(4.9)	(3.6)	(3.9)	(3.4)	(2.5)

Modified from Waters DD, et al. *Am J Cardiol.* 2004;93:15

175/151/47/98

IMPROVE-IT & TNT ; similar reduction of absolute risk ?

Study	Statin		Placebo/Comparator*	
	Achieved LDL-C, mg/dL (mmol/L)	CHD event rate (% patients)	Achieved LDL-C, mg/dL (mmol/L)	CHD event rate (% patients)
4S[1]	122 (3.2)	19.4	190 (4.9)	28.0
LIPID[2]	112 (2.9)	12.3	150 (3.9)	15.9
CARE[3]	98 (2.5)	10.2	135 (3.5)	13.2
HPS[4]	89 (2.3)	8.7	128 (3.3)	11.8
TNT*[5]	**77 (2.0)**	**6.7**	**101 (2.6)**	**8.3**

*Comparator in TNT was atorvastatin 10 mg

1. 4S Group. *Lancet*. 1994;344:1383-9
2. The LIPID Study Group. *N Engl J Med*. 1998;339:1349-57
3. Sacks FM, et al. *N Engl J Med*. 1996;335:1001-9
4. HPS Collaborative Group. *Lancet*. 2002;360:7-22
5. LaRosa JC, et al. *N Engl J Med*. 2005;352

IMPROVE-IT ; inspired by A to Z ?

4497 ACS Within 10 days

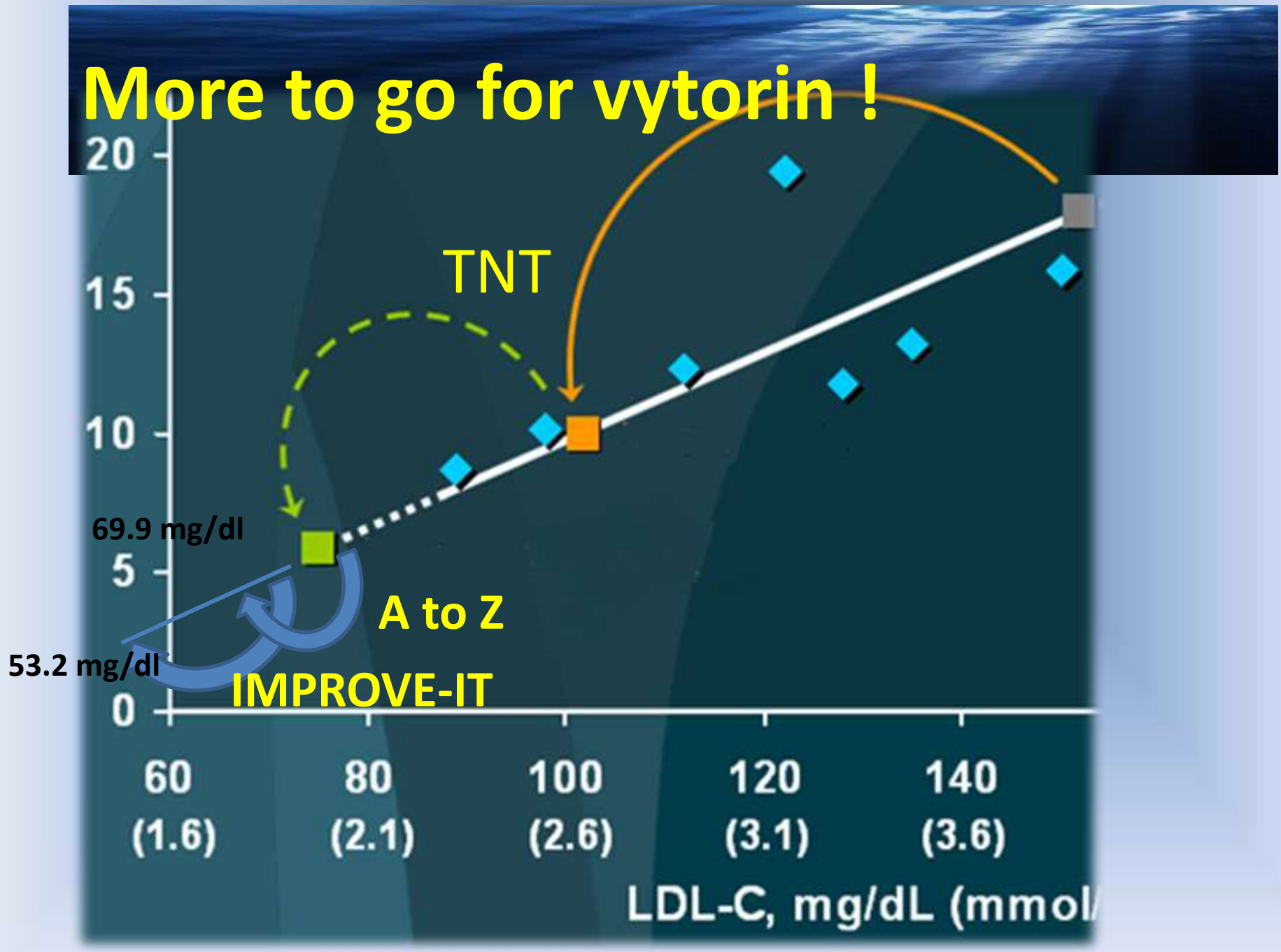
Placebo for 4 months and 20 mg/d

40 mg for 1 month and 80 mg/d

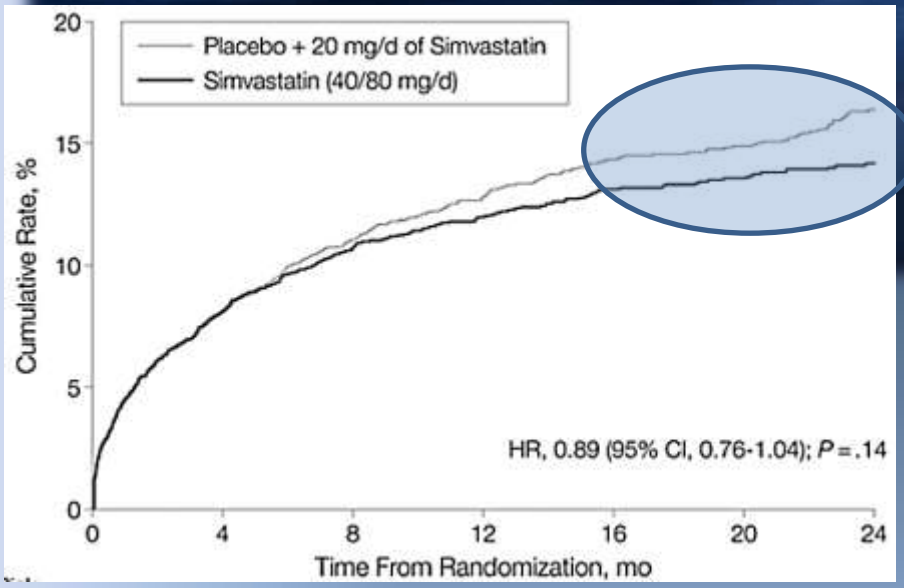
		Time From Randomization, mo			
	Baseline	1	4	8	24
Total cholesterol, mg/dL					
Placebo + 20 mg/d of simvastatin	184 (165-206)	198 (176-223)	202 (180-227)	152 (134-172)	157 (138-176)
Simvastatin (40/80 mg/d)	185 (163-205)	138 (119-157)	132 (116-153)	135 (118-155)	138 (122-158)
P value		<.001	<.001	<.001	<.001
LDL cholesterol, mg/dL					
Placebo + 20 mg/d of simvastatin	111 (95-131)	122 (104-143)	124 (106-147)	77 (64-95)	81 (66-96)
Simvastatin (40/80 mg/d)	112 (94-130)	68 (54-84)	62 (48-77)	63 (50-79)	66 (54-82)
P value		<.001	<.001	<.001	<.001
HDL cholesterol, mg/dL					
Placebo + 20 mg/d of simvastatin	39 (33-46)	39 (33-46)	41 (35-48)	43 (37-51)	44 (38-53)
Simvastatin (40/80 mg/d)	39 (33-45)	40 (34-48)	43 (36-50)	43 (37-51)	44 (38-52)
P value		<.001	<.001	.87	.31
Triglycerides, mg/dL					
Placebo + 20 mg/d of simvastatin	149 (116-199)	156 (114-219)	154 (110-215)	125 (90-183)	128 (93-178)
Simvastatin (40/80 mg/d)	149 (115-199)	123 (94-172)	118 (88-162)	118 (87-165)	116 (88-157)
P value		<.001	<.001	<.001	<.001
C-reactive protein, mg/L					
Placebo + 20 mg/d of simvastatin	20.4 (8.2-47.0)	2.5 (1.3-5.6)	2.3 (1.1-4.5)	1.8 (0.9-3.9)	NA
Simvastatin (40/80 mg/d)	20.1 (7.7-43.4)	2.4 (1.1-5.4)	1.7 (0.9-3.7)	1.5 (0.8-3.2)	NA
P value		.70	<.001	<.001	NA

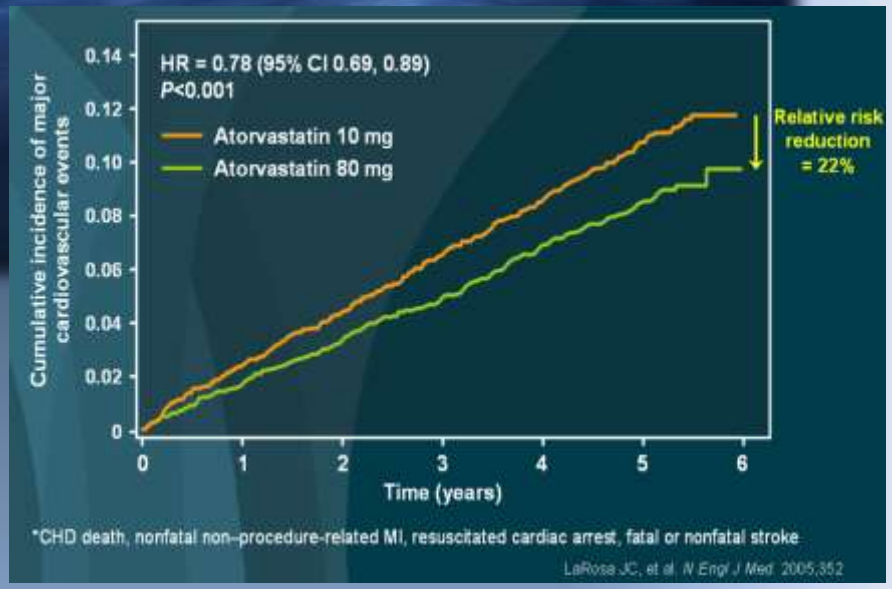
Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not measured.
SI conversion factors: To convert HDL, LDL, and total cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113.
*Values are expressed as median (25th-75th percentiles) unless otherwise indicated.

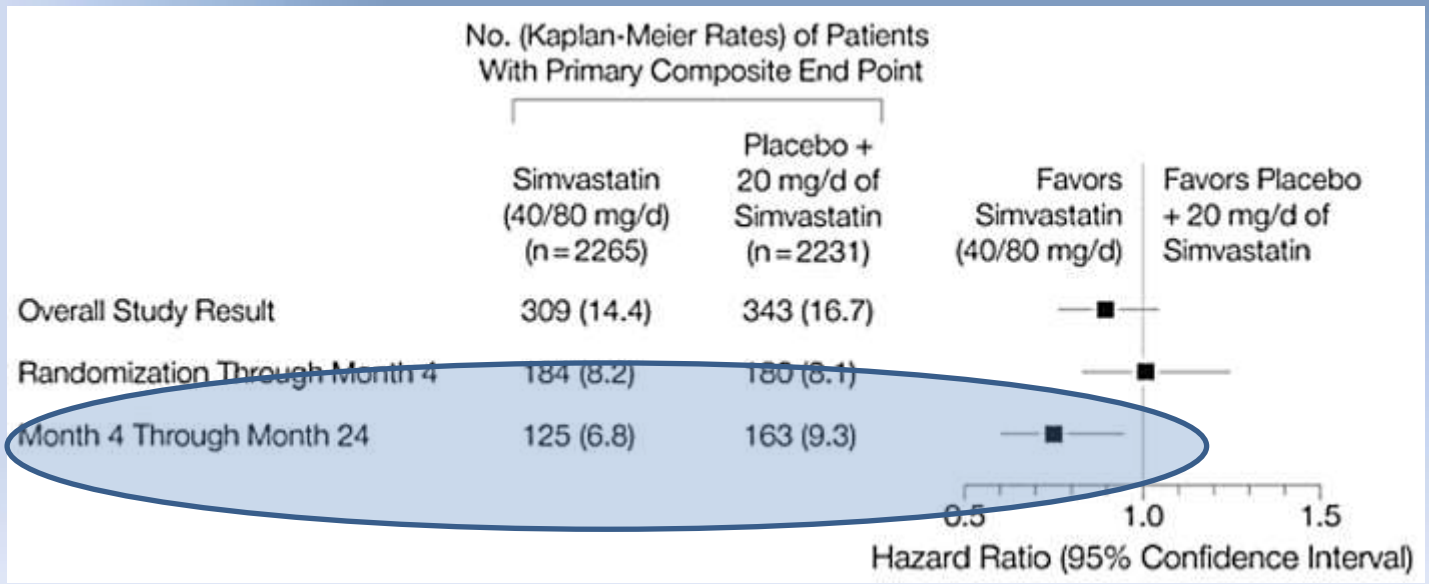
More to go for vytorin !



Simvastatin in ACS ? ; A to Z and TNT





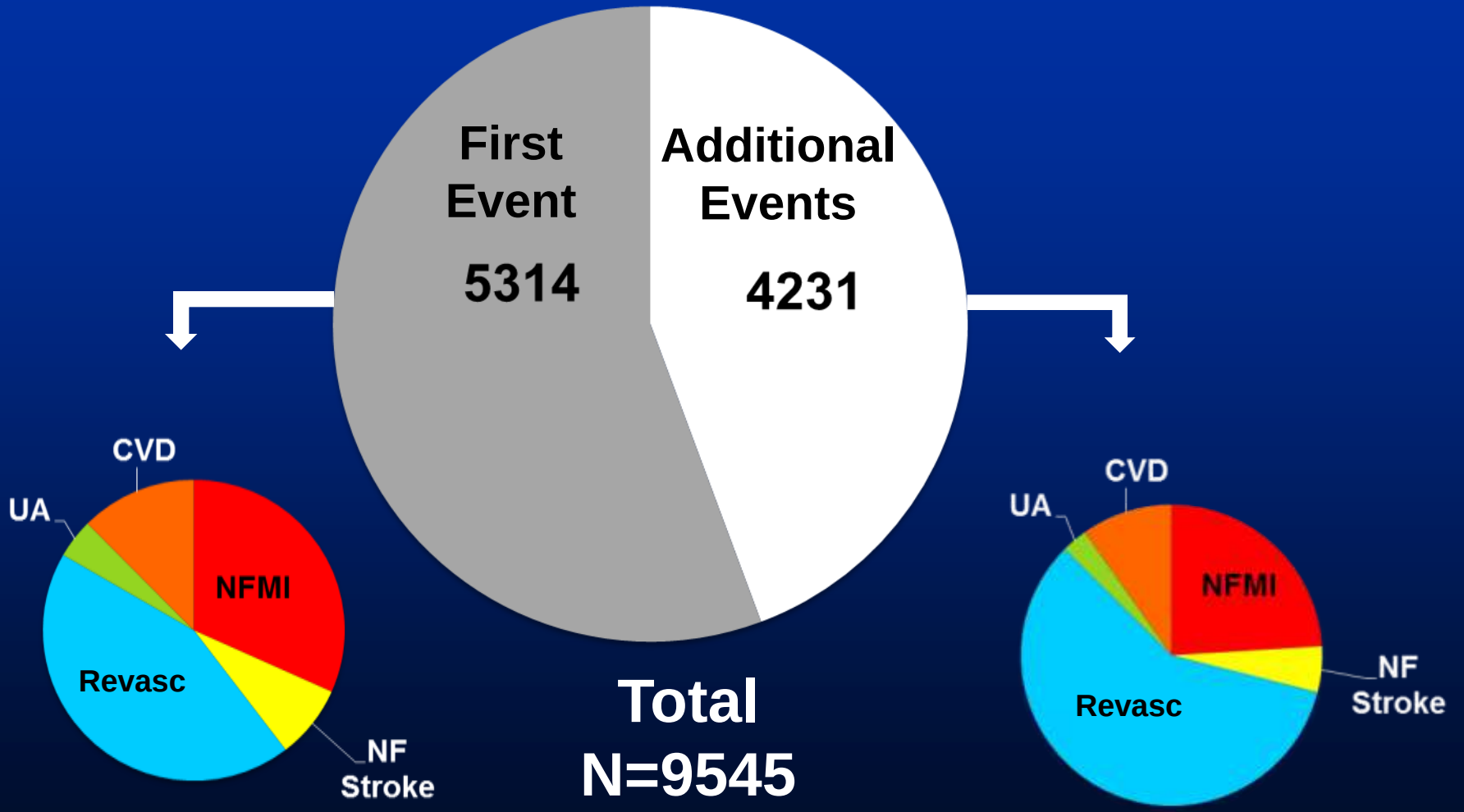


Reduction in Total (First and Recurrent) Cardiovascular Events with Ezetimibe/Simvastatin compared with Simvastatin Alone post ACS in the IMPROVE-IT Trial

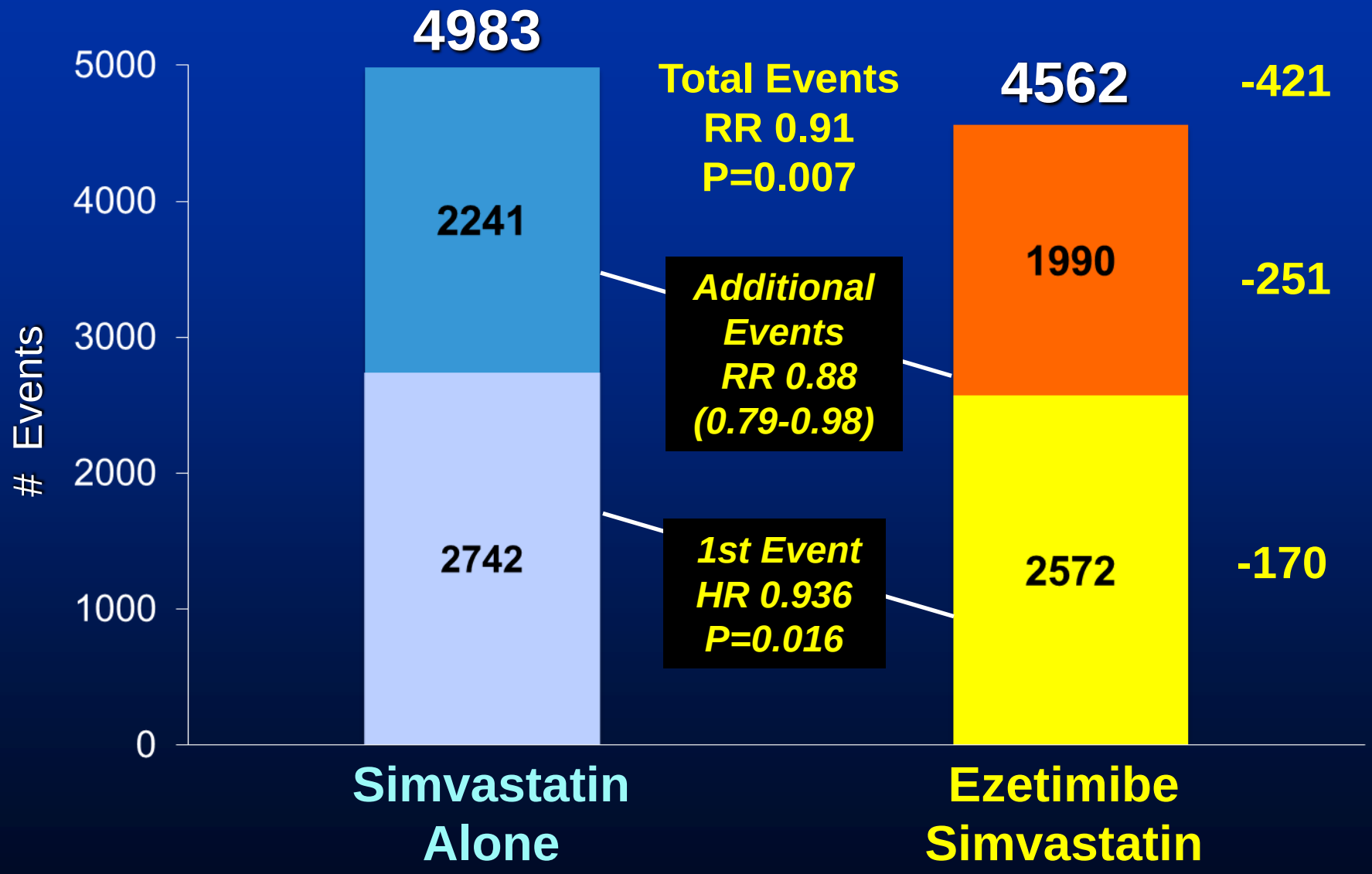
Sabina A. Murphy, Christopher Cannon, Robert Giugliano, Michael Blazing, Thomas Musliner, Andrew Tershakovec, Jennifer White, Kelly Im, Naveen Deenadayalu, Haral Darius, Witold Ruzyllo, Andrew Tonkin, Uma Kher, Robert Califf, Eugene Braunwald

On behalf of the IMPROVE IT Investigators

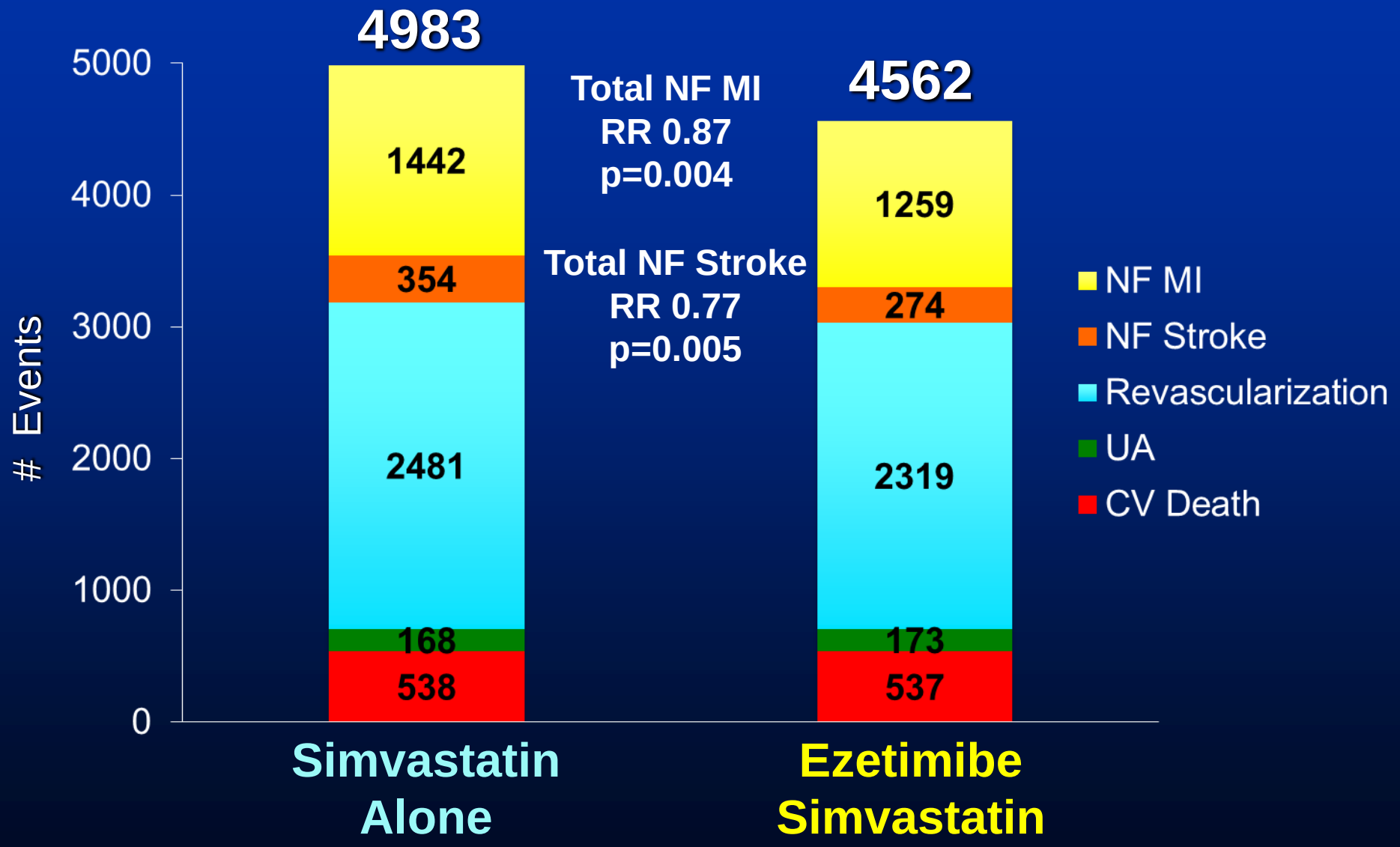
Number of Primary Endpoint Events



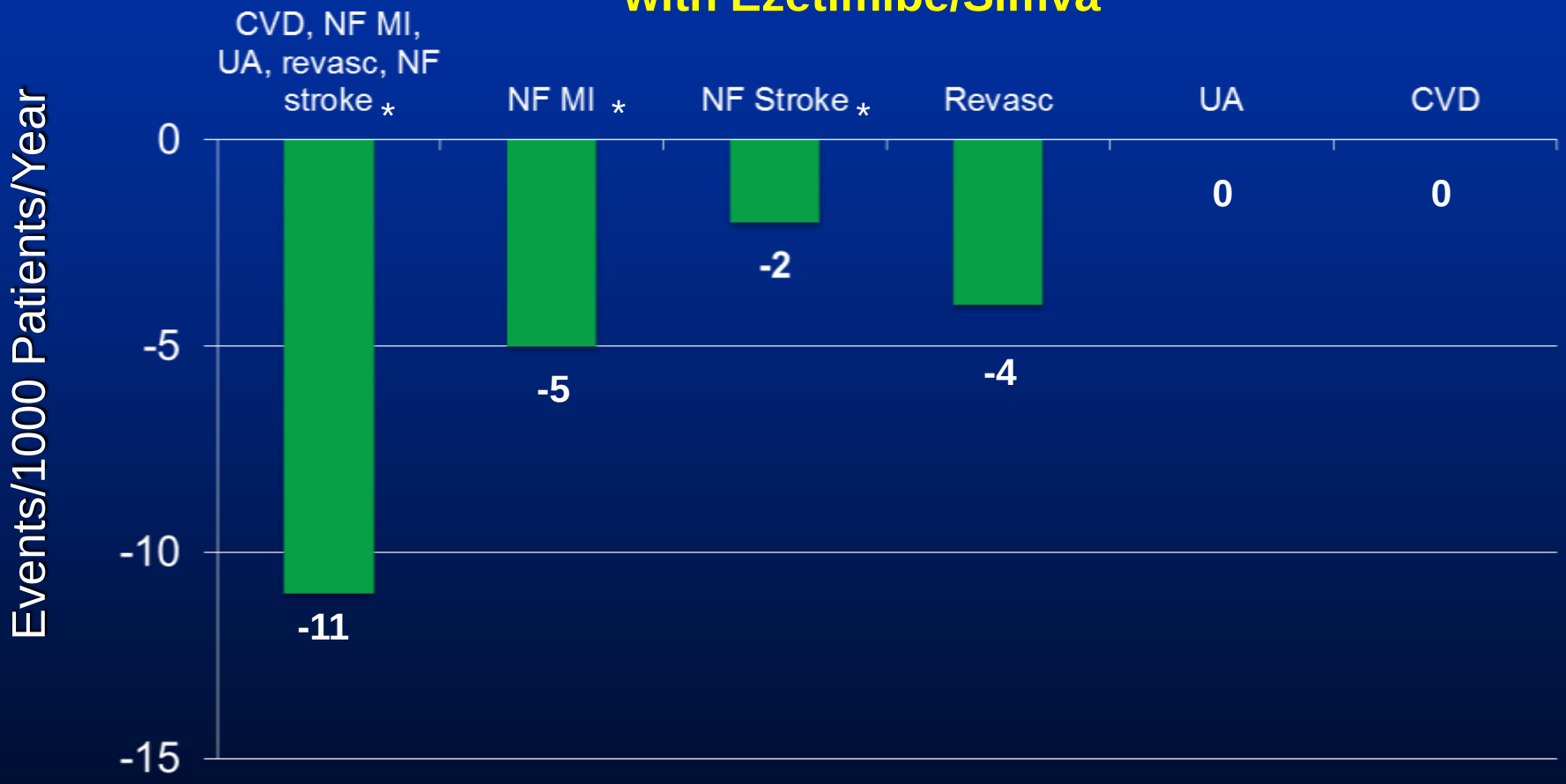
Total Primary Endpoint Events



Total PEP Events by Type of Event

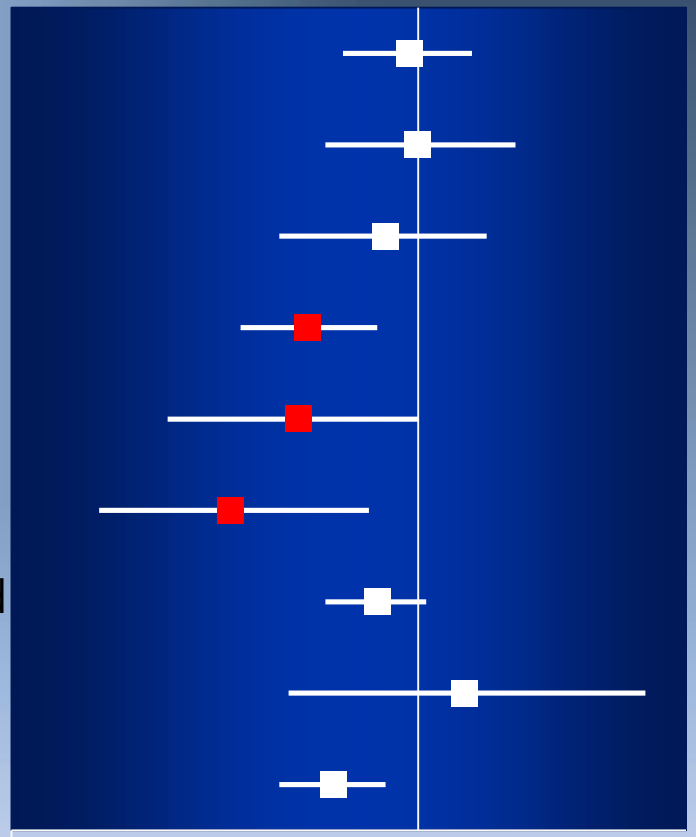


Total Primary Endpoint Events



* p<0.05; others NS

"IM-PROVED" # 2. STROKE



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

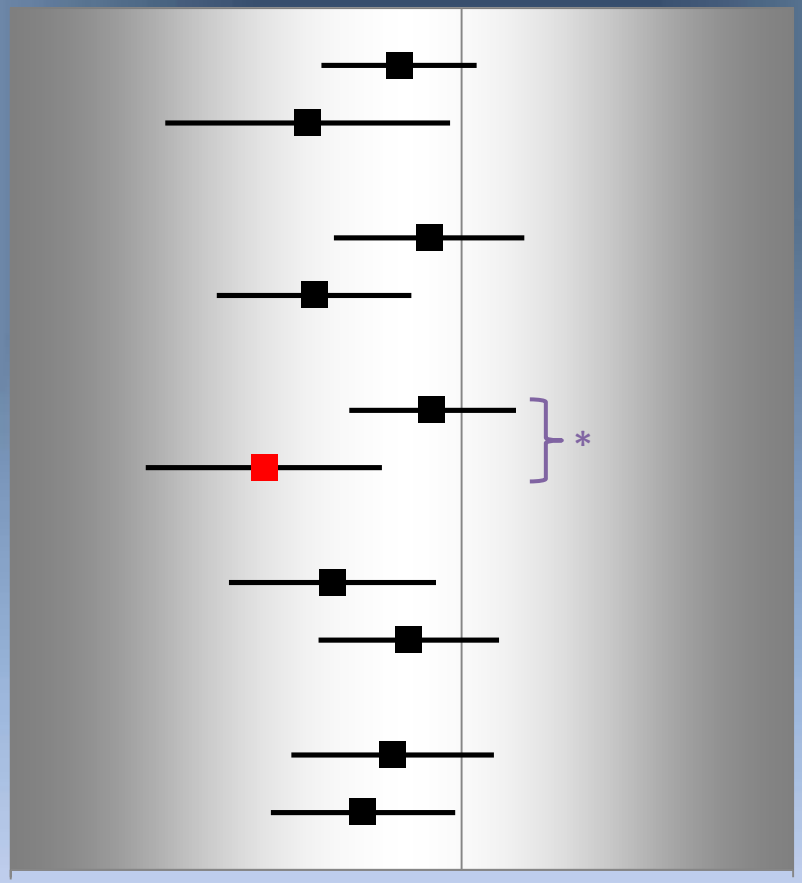
*7-year event rates (%)

Prevention of Stroke in Patients With Documented Cardiovascular Disease

Atorvastatin is not indicated for secondary prevention of CVD.

Adapted from LaRosa JC et al. N Engl J Med. 2005;352:1425-1435; Scandinavian Simvastatin Survival Study Group. Lancet. 1994;344:1383-1389; Sacks FM et al. N Engl J Med. 1996;336:1001-1009; LIPID Study Group. N Engl J Med. 1998;339:1349-1357; HPS Collaborative Group. Lancet. 2002;360:7-22; Shepherd J et al. Lancet. 2002;360:1623-1630; KLIS Study Group. J Atheroscler Thromb. 2000;7:110-121; Athyros VG et al. Curr Med Res Opin. 2002;18:220-228; Koren MJ et al. J Am Coll Cardiol. 2004;44:1772-1779.

"IM-PROVED" # 3. DIABETES



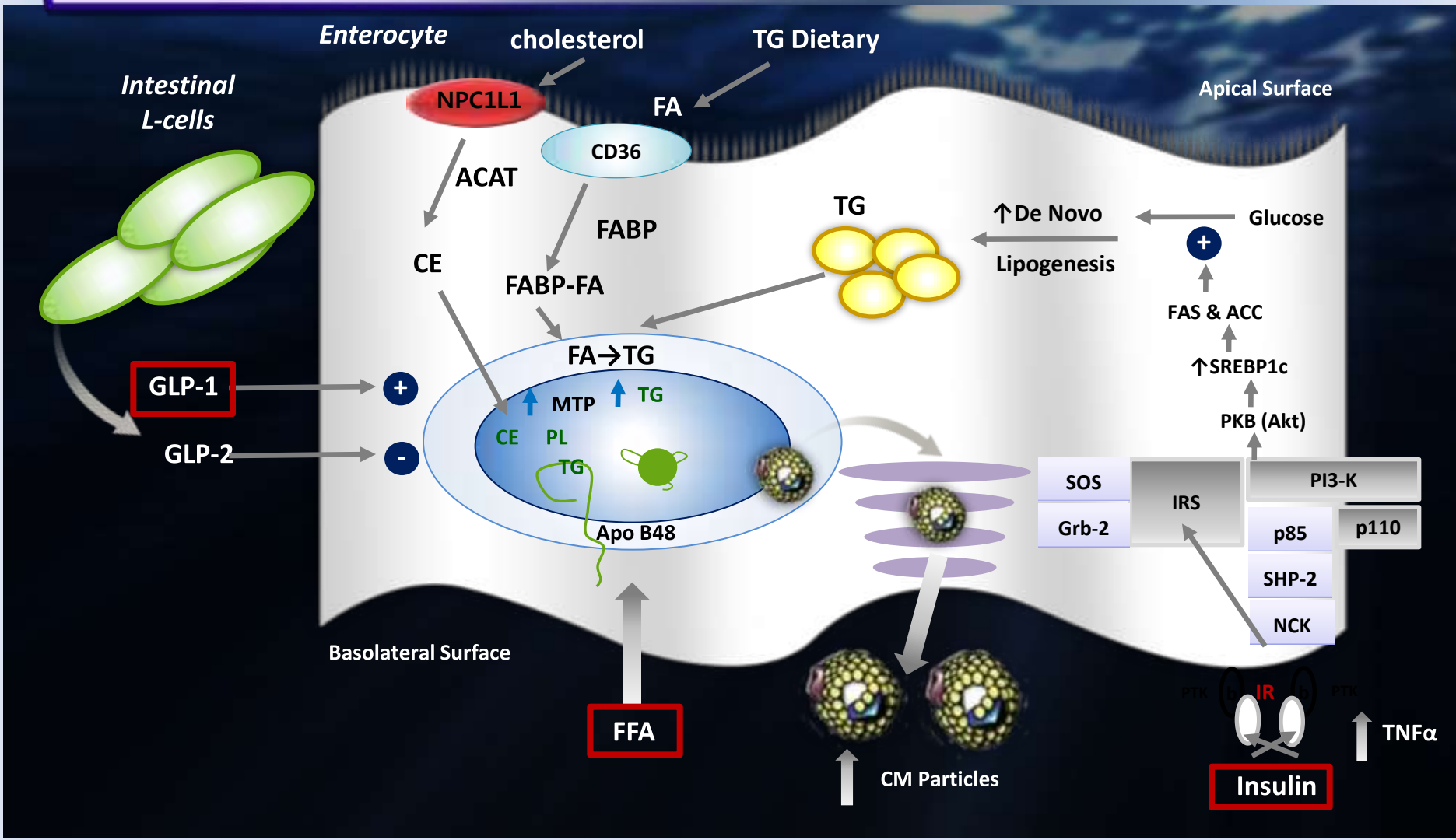
	Simva†	EZ/Simva†
Male	34.9	33.3
Female	34.0	31.0
Age < 65 years	30.8	29.9
Age ≥ 65 years	39.9	36.4
No diabetes	30.8	30.2
Diabetes	45.5	40.0
Prior LLT	43.4	40.7
No prior LLT	30.0	28.6
LDL-C > 95 mg/dl	31.2	29.6
LDL-C ≤ 95 mg/dl	38.4	36.0

†*7-year event rates*

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

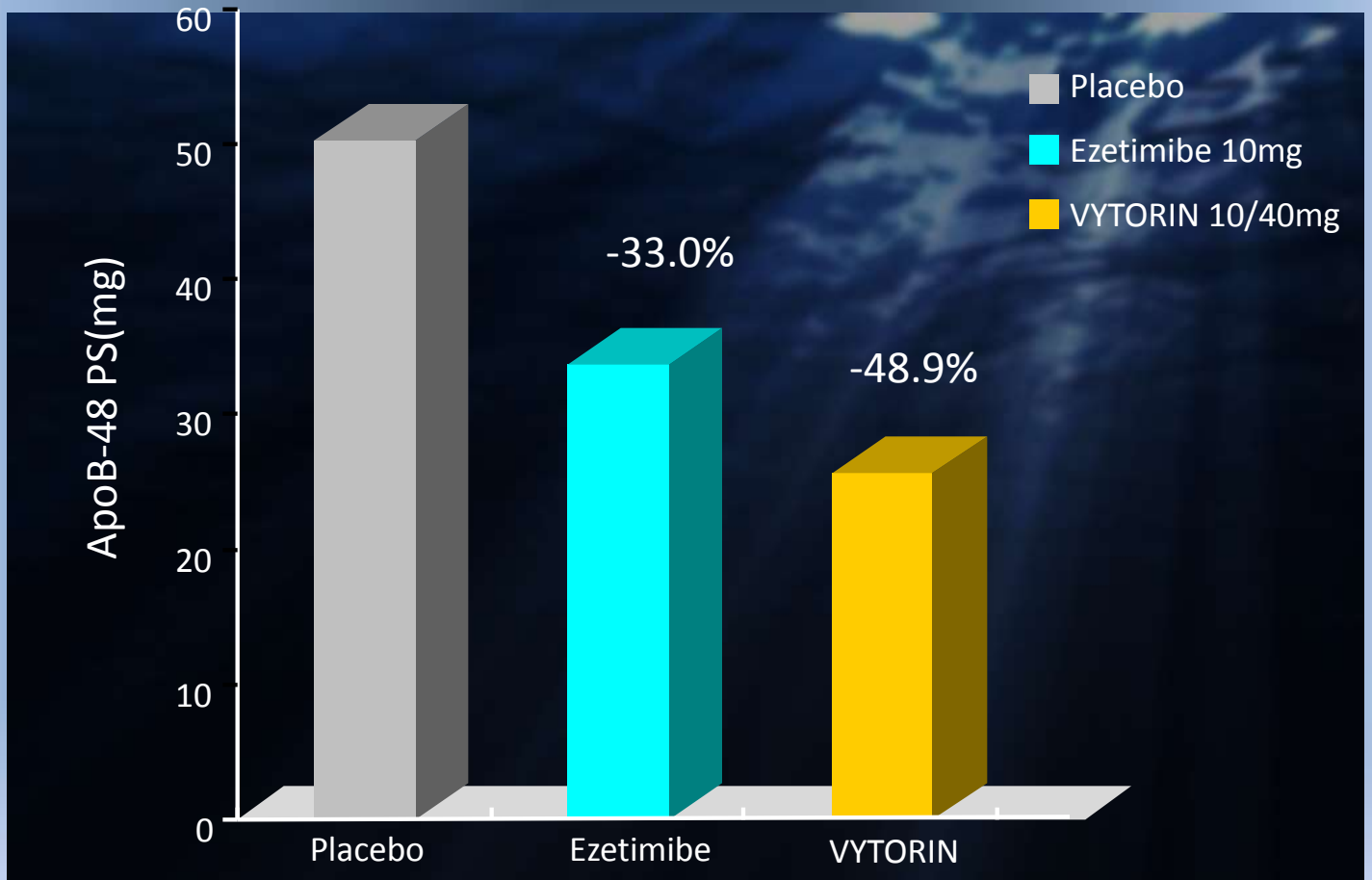
Ezetimbe inhibits CM formation esp. under diabetic condition

CM formation and secretion



Adeli K. *Curr Opin Lipidol* 2008;19:221–28.

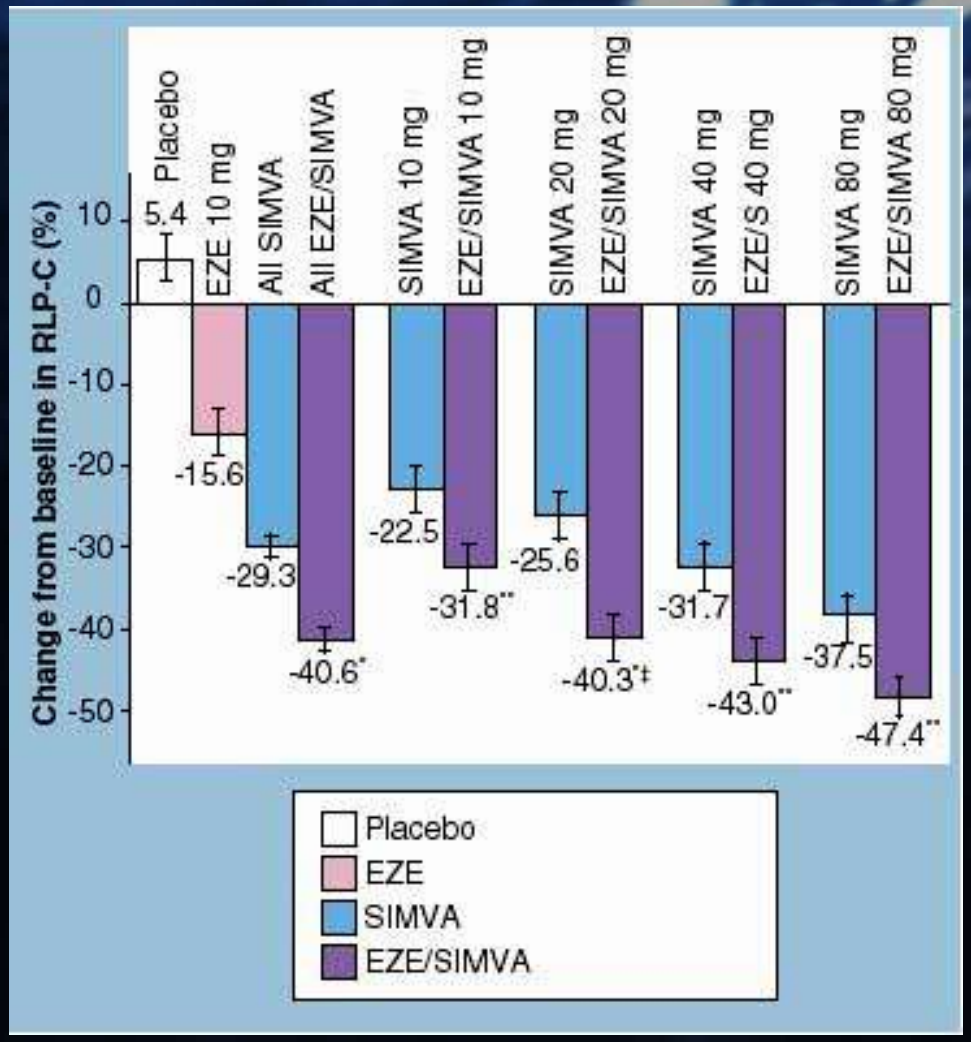
Ezetimibe reduces ApoB48



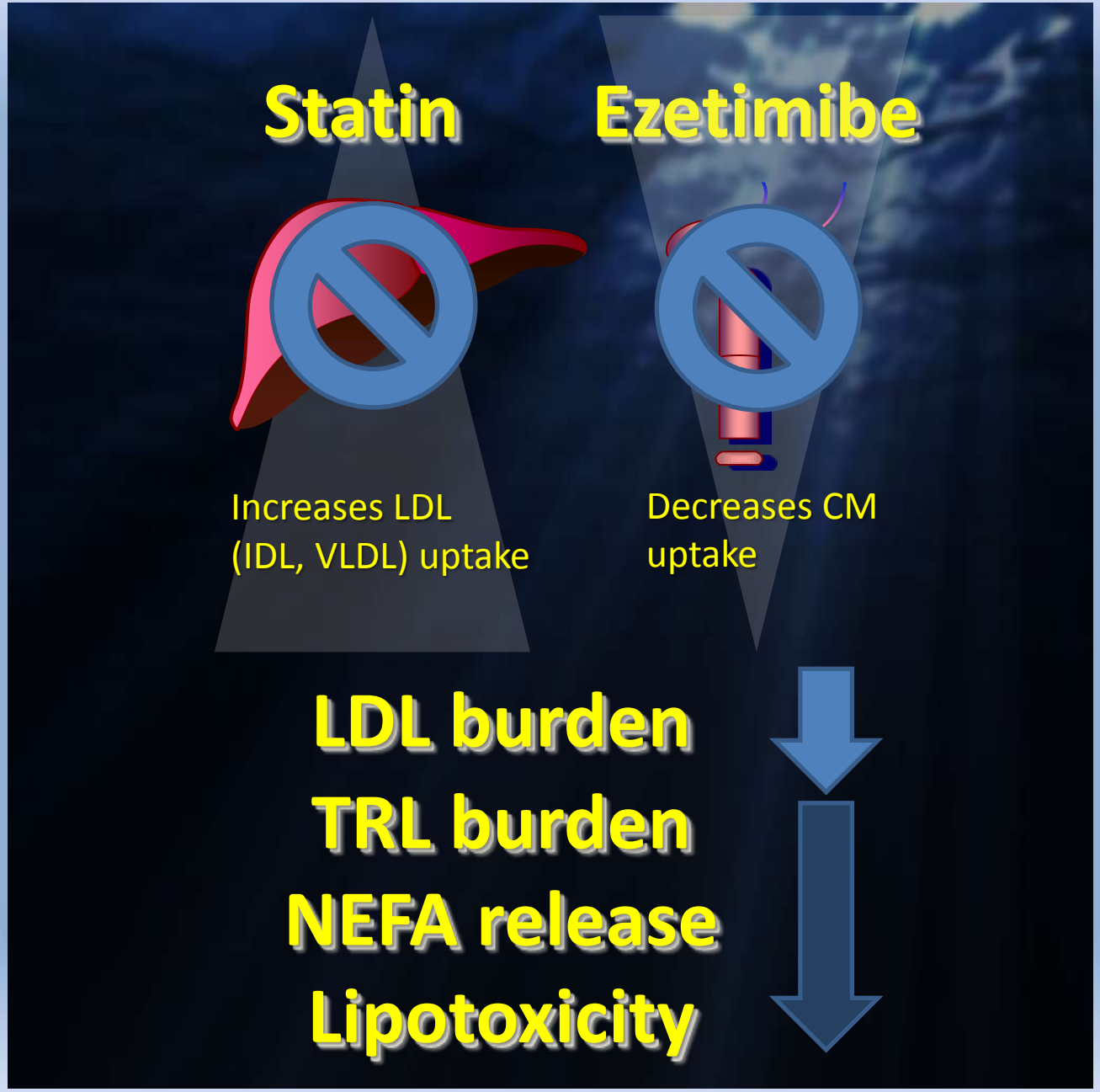
P < 0.05 for both ezetimibe and simvastatin vs. placebo

J Lipid Res. 2009 Jul;50(7):1463-71.

Ezetimibe reduces RLP-C



*; p<0.001, **; p<0.05 vs. same dose of SIMVA, ++; p<0.05 vs. next higher dose of SIMVA (Expert Review Cardiovasc Ther 2008;6(4);447-470)


Statin
Ezetimibe
Increases LDL (IDL, VLDL) uptake
Decreases CM uptake
LDL burden
TRL burden
NEFA release
Lipotoxicity

Expanding Horizon

- Can lowering LDL with the non-statin ezetimibe lower cardiac events?
- Is it worthwhile to take an already low LDL cholesterol (65 mg/dL) even lower (50 mg/dL)?
- Is ezetimibe safe?

ALL YES

Statin in 2ndary prevention

Variable	Pravastatin or Atorvastatin Evaluation and Infection Therapy [13]		A to Z Trial [14]		ALLIANCE Study [16]		Treating to New Targets[a] [17]	
Number of patients	4,162		4,497		2,442		10,001	
Duration follow-up (years)	2		2		4.5		4.9	
Statin used	Ator, 80 mg	Pravachol, 40 mg	Early intensive treatment	Delayed, low-dose treatment	Ator, 80 mg	Usual care	Ator, 80 mg	Ator, 10 mg
Reduction from baseline, total cholesterol			25%	15%	24%	16%	Not available	Not available
Reduction from baseline, LDL-C	51% (32%)[b]	22% (0%)	41%	27%	34%	23%	21%[c]	−3%
Primary end point	Cardiovascular event		Cardiovascular event		Cardiovascular event		Cardiovascular event	
Relative risk with high dose treatment (95% CI)	0.84 (0.74–0.95)		0.89 (0.76–1.04)		0.83 (0.71–0.97)		0.78 (0.69–0.89)	
Significance (*p* value)	$p = 0.005$		$p = 0.14$		$p = 0.02$		$p < 0.001$	
NNT	26		43		25		45	

[a]All patients on atorvastatin 10 mg daily at baseline.
[b]Patients not on prior statin saw LDL-C reduction of 51% and 22% while on atorvastatin 80 mg and pravastatin 40 mg, respectively. Patients previously on a statin saw further LDL-C reduction of 32% and 0% while on atorvastatin 80 mg and pravastatin 40 mg, respectively.
[c]During the trial mean reduction in LDL-C of 21% was noted with 80 mg atorvastatin and an increase in LDL-C of 3% was noted on continued 10 mg atorvastatin.
Ator, atorvastatin.
DOI: 10.1371/journal.pmed.0030050.t003

A80

PLoS Med 3(3): e50.

Statin in 2ndary prevention (II)

Variable	Scandinavian Simvastatin Survival Study Group [1]	Cholesterol and Recurrent Events Trial [3]	Long-Term Intervention with Pravastatin in Ischemic Disease Study [4]	Heart Protection Study Collaborative Group [6]	Lescol Intervention Prevention Study [8]
Number of patients	4,444	4,159	9,014	20,536	1,677
Duration follow-up (years)	5.4	5	6.1	5	3.9
Statin used	Simvastatin, 5 to 40 mg	Pra, 40 mg	Pra, 40 mg	Simvastatin, 40 mg	Fluvastatin, 80 mg
Reduction from baseline, total cholesterol	25%	20%	18%	20%	
Reduction from baseline, LDL-C	35%	28%	25%	29%	22%
Primary end point	Total mortality	Coronary mortality, nonfatal MI	Coronary mortality	Total mortality	Major adverse cardiac events
Relative risk with statin treatment (95% confidence interval)	0.7 (0.58–0.85)	0.76 (0.64–0.91)	0.76 (0.65–0.88)	0.87 (0.81–0.94)	0.78 (0.69–0.95)
Significance (*p* value)	$p = 0.0003$	$p = 0.003$	$p = 0.0001$	$p = 0.0003$	$p = 0.01$
NNT	25	33	53	56	19

MI, myocardial infarction; pra, pravastatin.
DOI: 10.1371/journal.pmed.0030050.t001

S P P S F

PLoS Med 3(3): e50.

Statin in primary prevention

Variable	West of Scotland Coronary Prevention Study [2]	AFCAPS/TexCAPS [5]	Pravastatin in Elderly Individuals at Risk of Vascular Disease [9]	Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial [10]	Anglo-Scandinavian Cardiac Outcomes Trial [11]	Collaborative Atorvastatin Diabetes Study [12]
Number of patients	6,595	6,605	5,804	10,355	10,305	2,838
Duration follow-up (years)	4.9	5.2	3.2	4.8	3.3	3.9
Statin used	Pra, 40 mg	Lovastatin, 20 to 40 mg	Pra, 40 mg	Pra, 40 mg	Ator, 10 mg	Ator, 10 mg
Reduction from baseline, total cholesterol	20%	18%		10%*	24%	26%
Reduction from baseline, LDL-C	26%	25%	34%	17%*	35%	40%
Primary end point	Nonfatal MI, coronary mortality	MI, unstable angina, sudden cardiac death	Coronary mortality, nonfatal MI, stroke	Total mortality	Fatal coronary heart disease, nonfatal MI	Acute coronary event, Revascularisation, stroke
Relative risk with statin treatment (95% confidence interval)	0.69 (0.57–0.83)	0.63 (0.50–0.79)	0.85 (0.74–0.97)	0.99 (0.89–1.11)	0.64	0.63
Significance (p value)	$p < 0.001$	$p < 0.001$	$p = 0.014$	$p = 0.88$	$p = 0.0005$	$p = 0.001$
NNT	42	49	48	250	91	31

*Patients not on prior statin saw an LDL reduction of 51% and 22% while on atorvastatin and pravastatin 40 mg, respectively. Patients previously on a statin saw further LDL-C reduction of 32% and 0% while on atorvastatin 80 mg and pravastatin 40 mg, respectively.

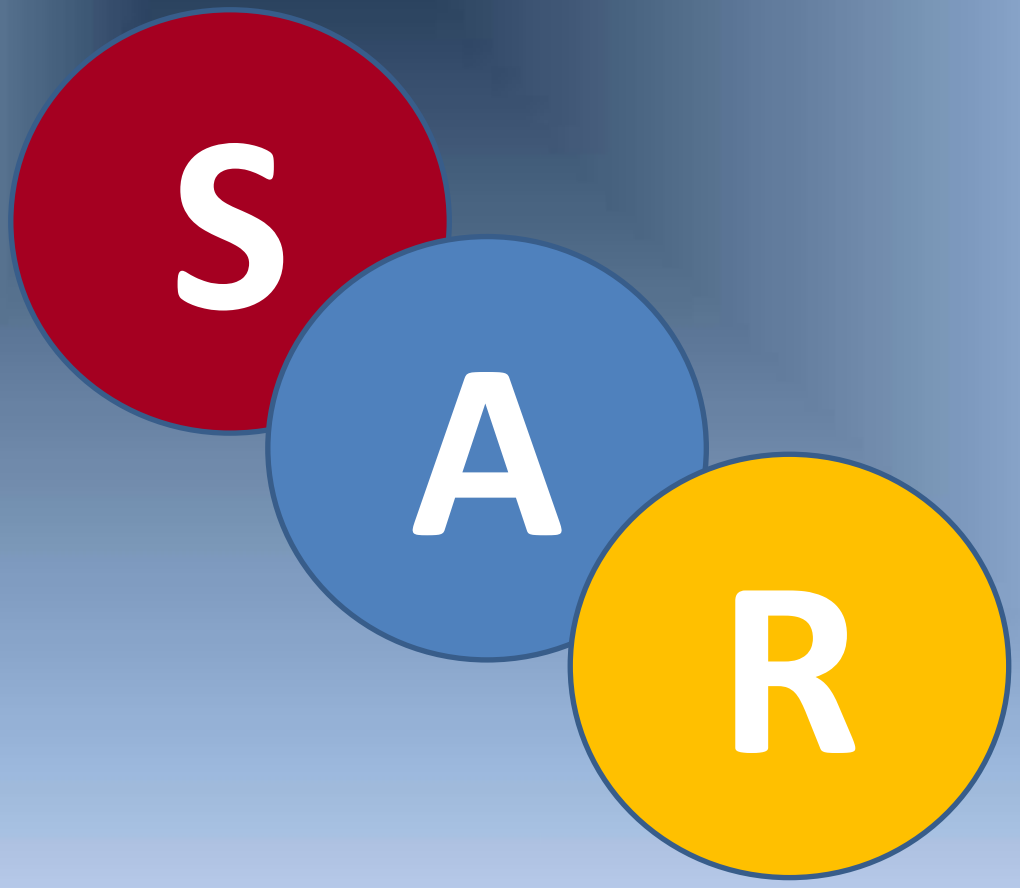
MI, myocardial infarction; pra, pravastatin; ator, atorvastatin.

DOI: 10.1371/journal.pmed.0030050

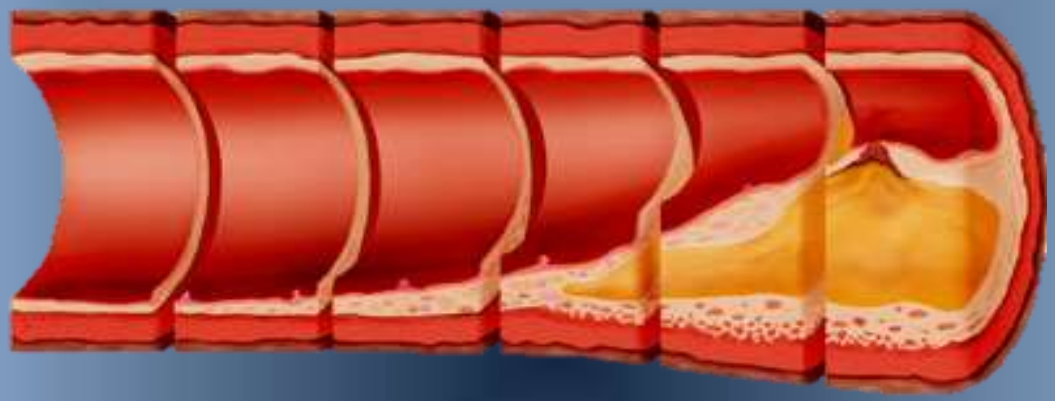
P L P A A

PLoS Med 3(3): e50.

Which Statin ?



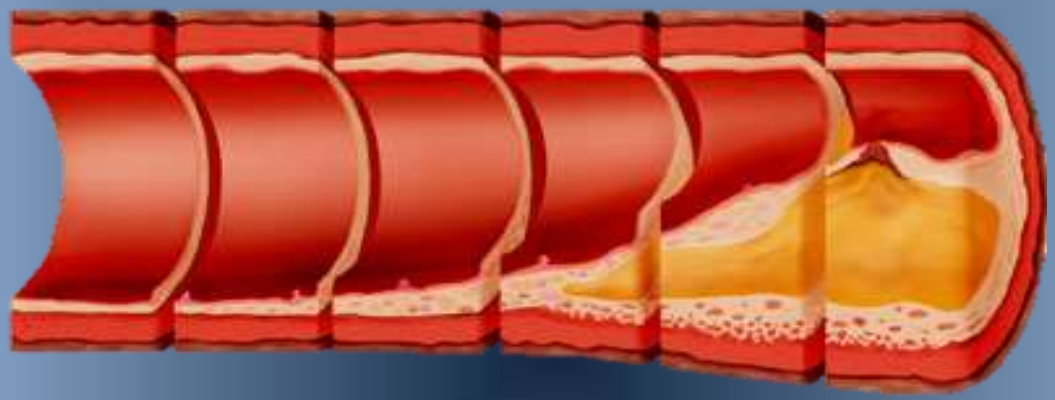
Simvastatin



HPS

SSSS

Atorvastatin



ASCOT

REVERSAL

MIRACL

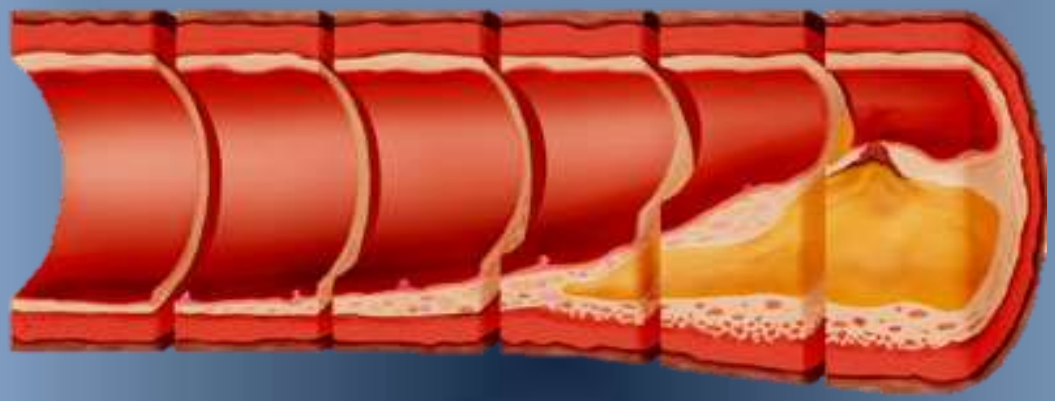
CARDS

PROVE-IT

IDEAL

TNT

Rosuvastatin

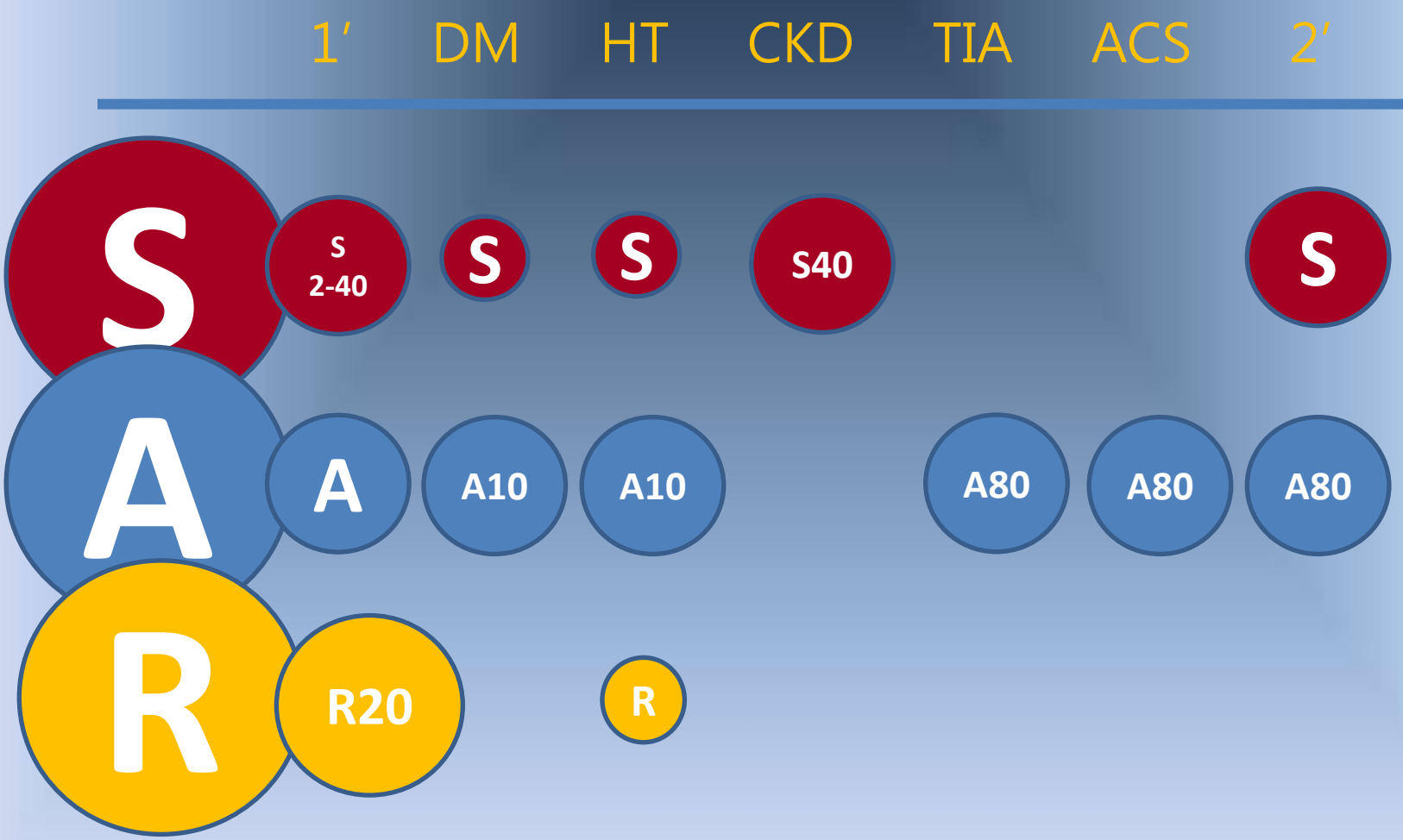


JUPITER

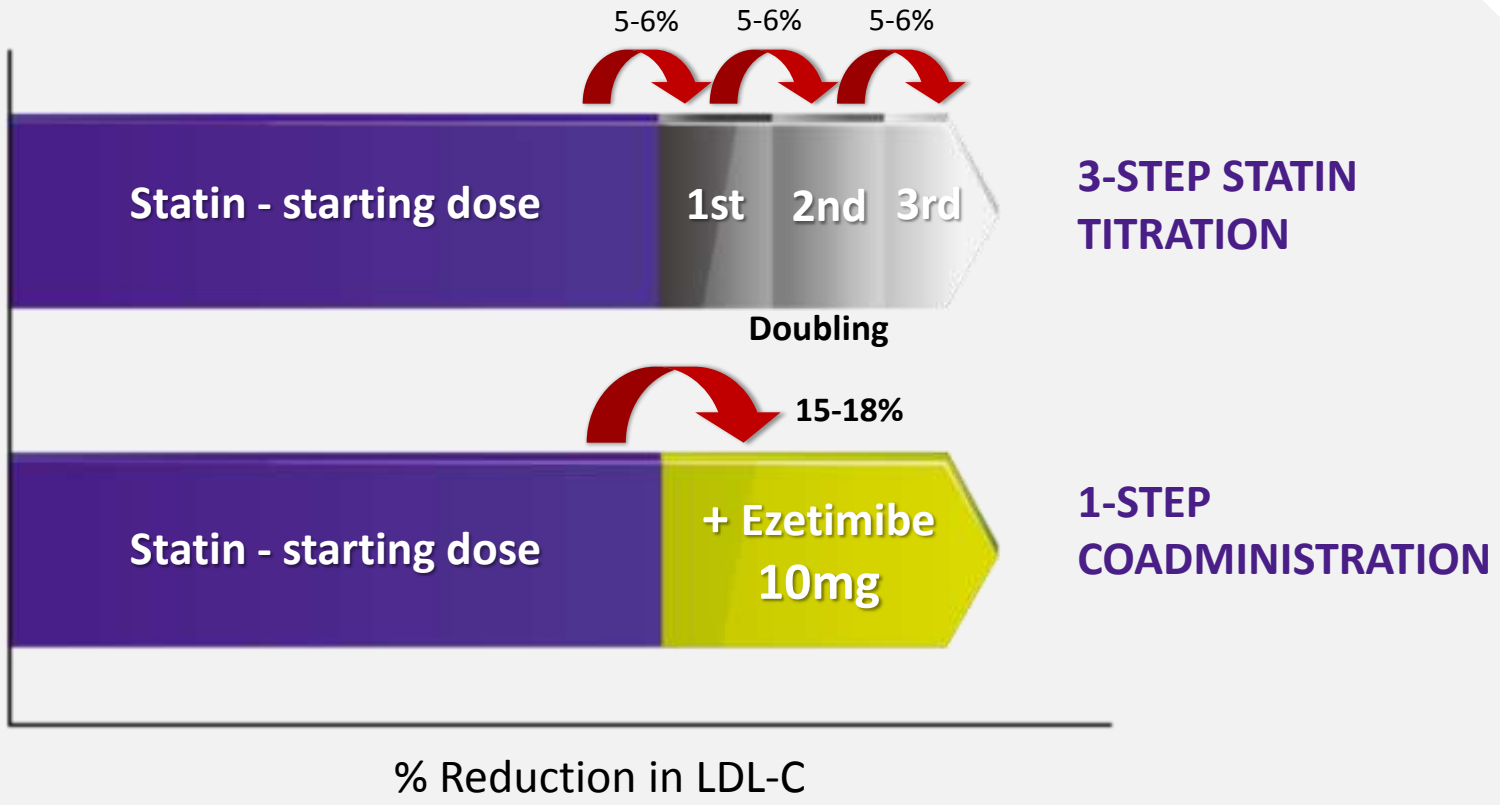
ASTEROID

Statin and Ezetimibe

Which Statin ?



Ezetimibe + Statin vs. Statin Titration

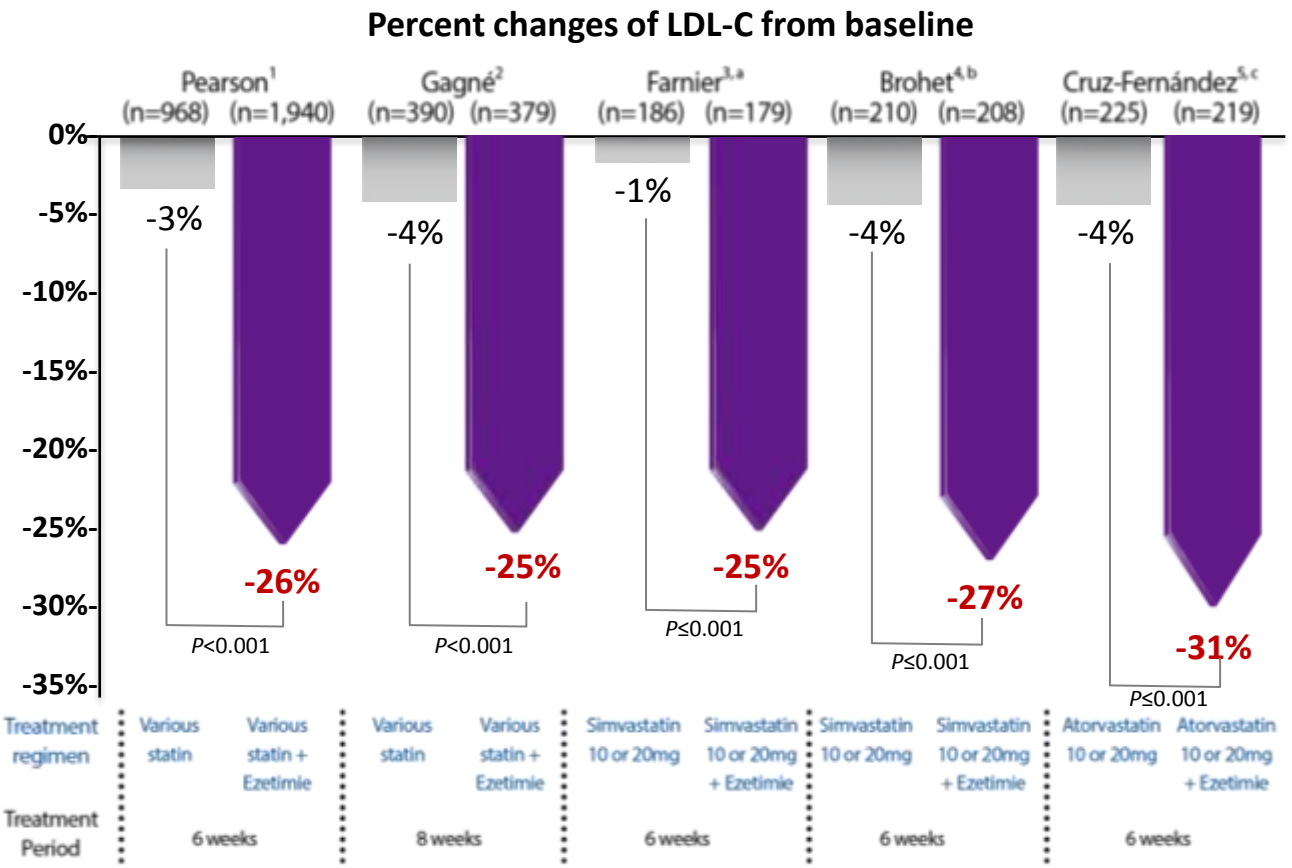


LDL-C, low-density liopoprotein cholesterol

1. Harold E. Bays, MD, et al. 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]

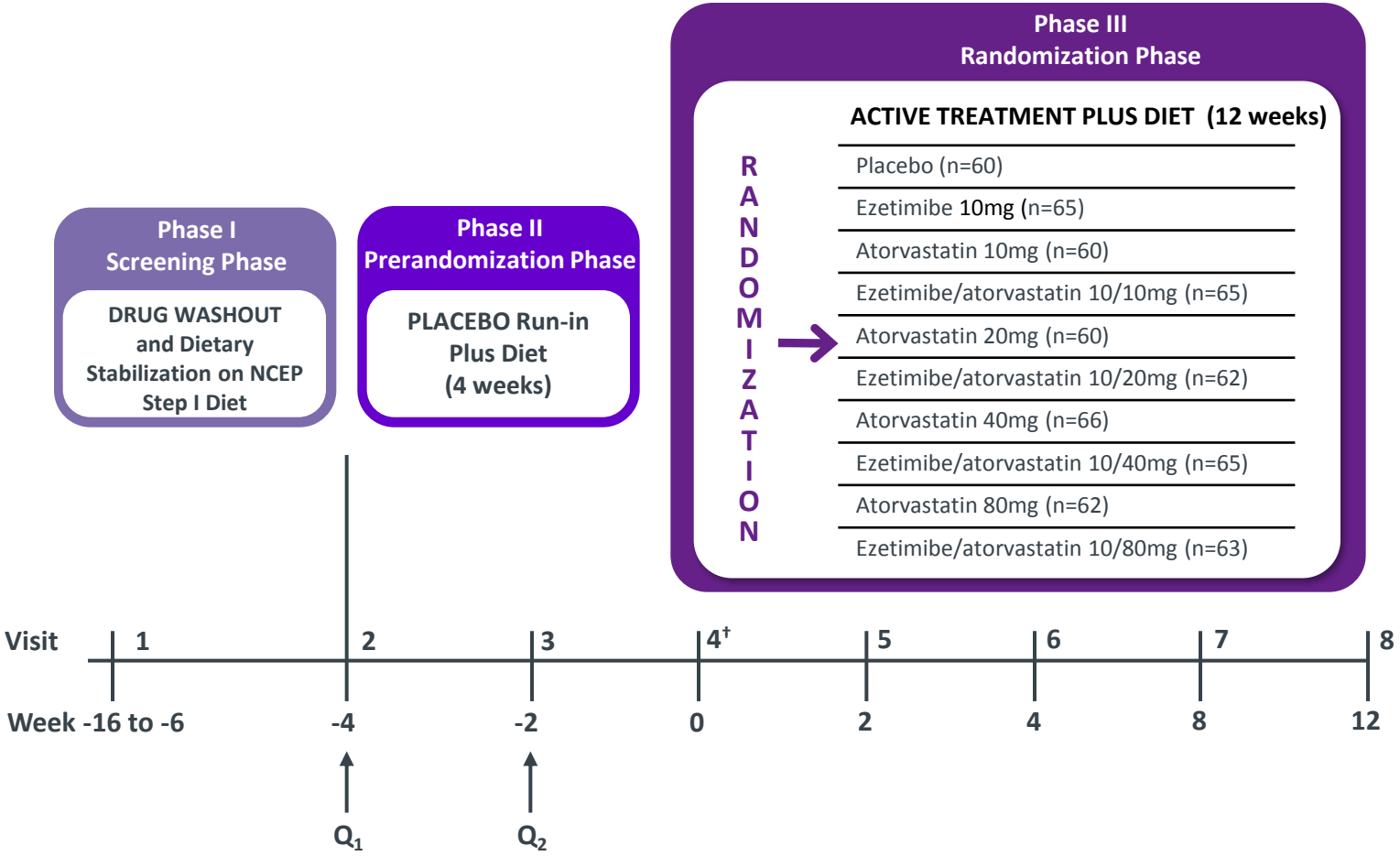
Study design; In 5 separate randomized, double-blind, placebo-controlled trials of patients with hypercholesterolemia (2 of them examined the percent change in LDL-C as a primary endpoint, 3 of them evaluated it as a secondary endpoint),

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

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

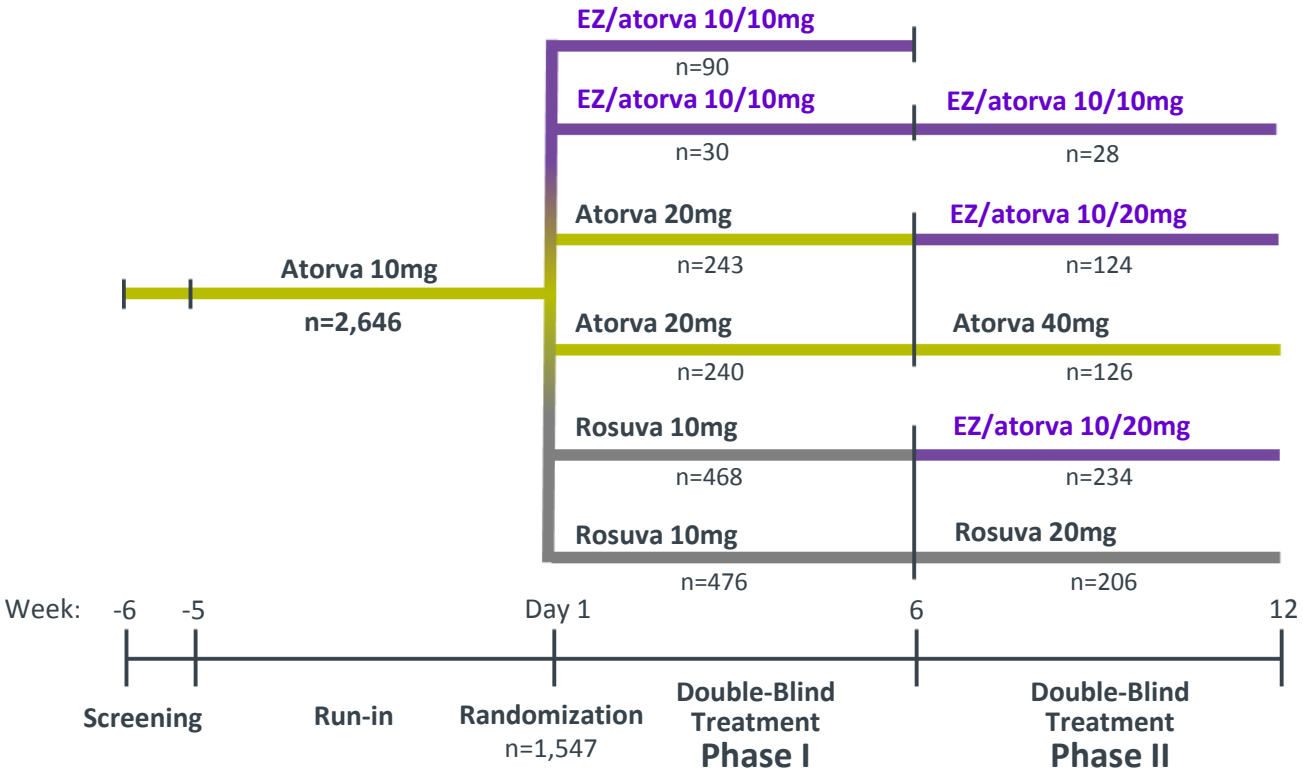
- Patients with hypercholesterolemia*



Adapted with permission from Ballantyne CM, et al.[1]
*Baseline LDL-C 145 to 250mg/dL (~3.7 to 6.5mmol/L) and triglycerides ≤350mg/dL (~4.0mmol/L).
‡Random assignment to double-blind treatment occurred at visit 4.
NCEP, National Cholesterol Education Program; Q1, first qualifying calculated LDL-C value; Q2, second qualifying calculated LDL-C value; blood samples for Q1 and Q2 were collected at least 1 week apart; LDL-C, low-density lipoprotein cholesterol.
1. Ballantyne CM, et al. *Circulation.* 2003;107:2409-2415.

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

- High-risk patients* with hypercholesterolemia not at LDL-C <100mg/dL (~2.6mmol/L) on atorvastatin 10mg.



Adapted with permission from Bays HE, et al.1

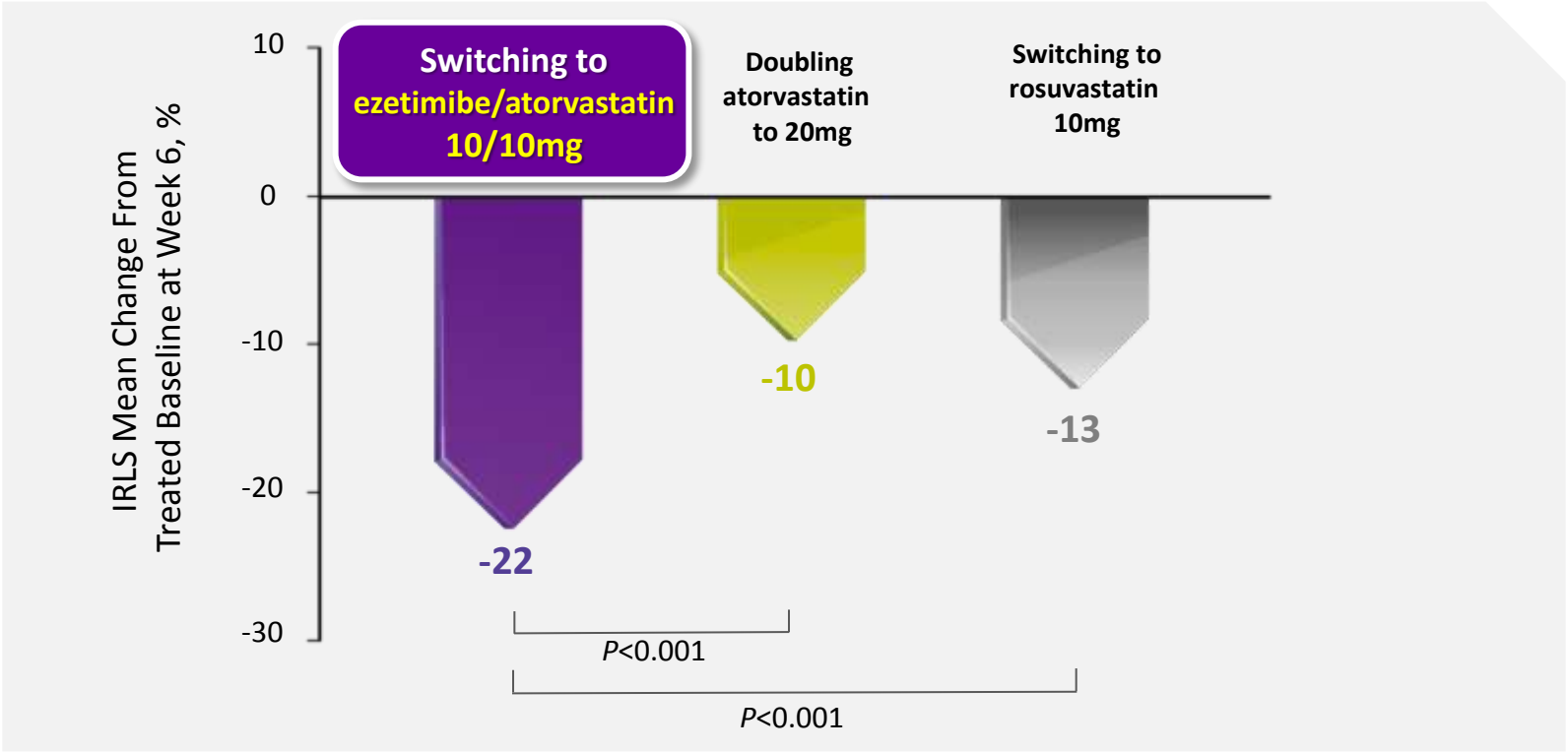
*High risk of CHD was defined as: 1) subjects without CVD who had type 2 diabetes, or ≥2 risk factors and a 10-year risk for CHD >20% as determined by the Framingham calculation, or 2) subjects with CVD, including established coronary or other atherosclerotic vascular disease.

PACE, a randomized, double-blind, active-controlled, multicenter study of patients with Primary hypercholesterolemia and high cardiovascular risk who are not adequately controlled with Atorvastatin 10 mg: a Comparison of the efficacy and safety of switching to coadministration Ezetimibe 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 10/10mg Provided Greater Additional LDL-C Reduction vs. Doubling Atorvastatin to 20mg or Switching to Rosuvastatin 10mg[1]

LDL-C



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

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

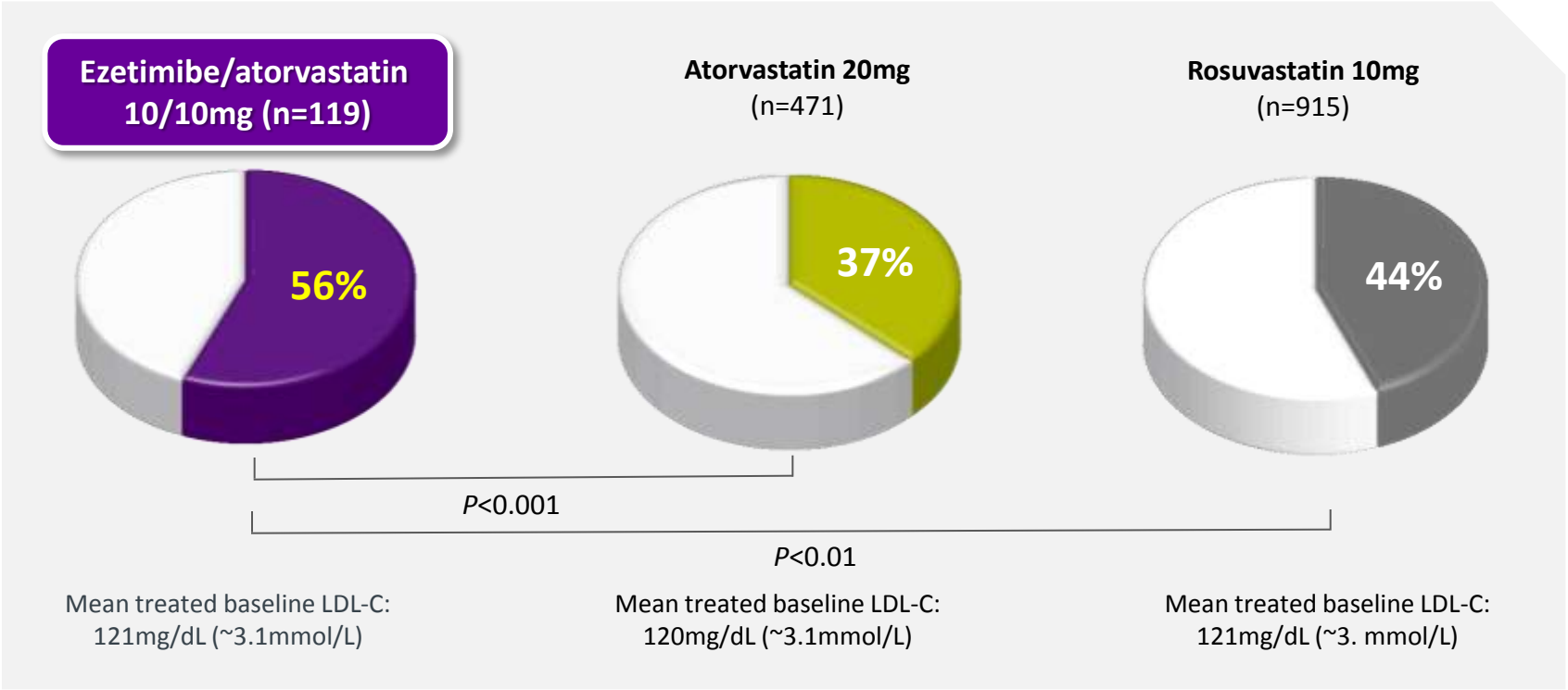
Switching to rosuvastatin 10mg
(n=939)
Mean on-statin baseline LDL-C=121mg/dL (~3.1mmol/L)

LDL-C, low-density lipoprotein cholesterol; IRLS, iteratively reweighted least squares.

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

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

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



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

IRLS, iteratively reweighted least squares.

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

HAPPY 2015 APsummit