ACC Middle East Conference 2016

جمعية القلب السعودية
Saudi Heart Association

Dyslipidemia Treatment in 2016

Novel Agents

Combination Therapies

Statin Intolerance

BROWN
Alpert Medical School

Hani Sabbour MD FACC FHRS

Clinical Assistant Professor of Cardiology
Brown University Rhode Island USA
Consultant Cardiology
Cleveland Clinic Abu Dhabi UAE

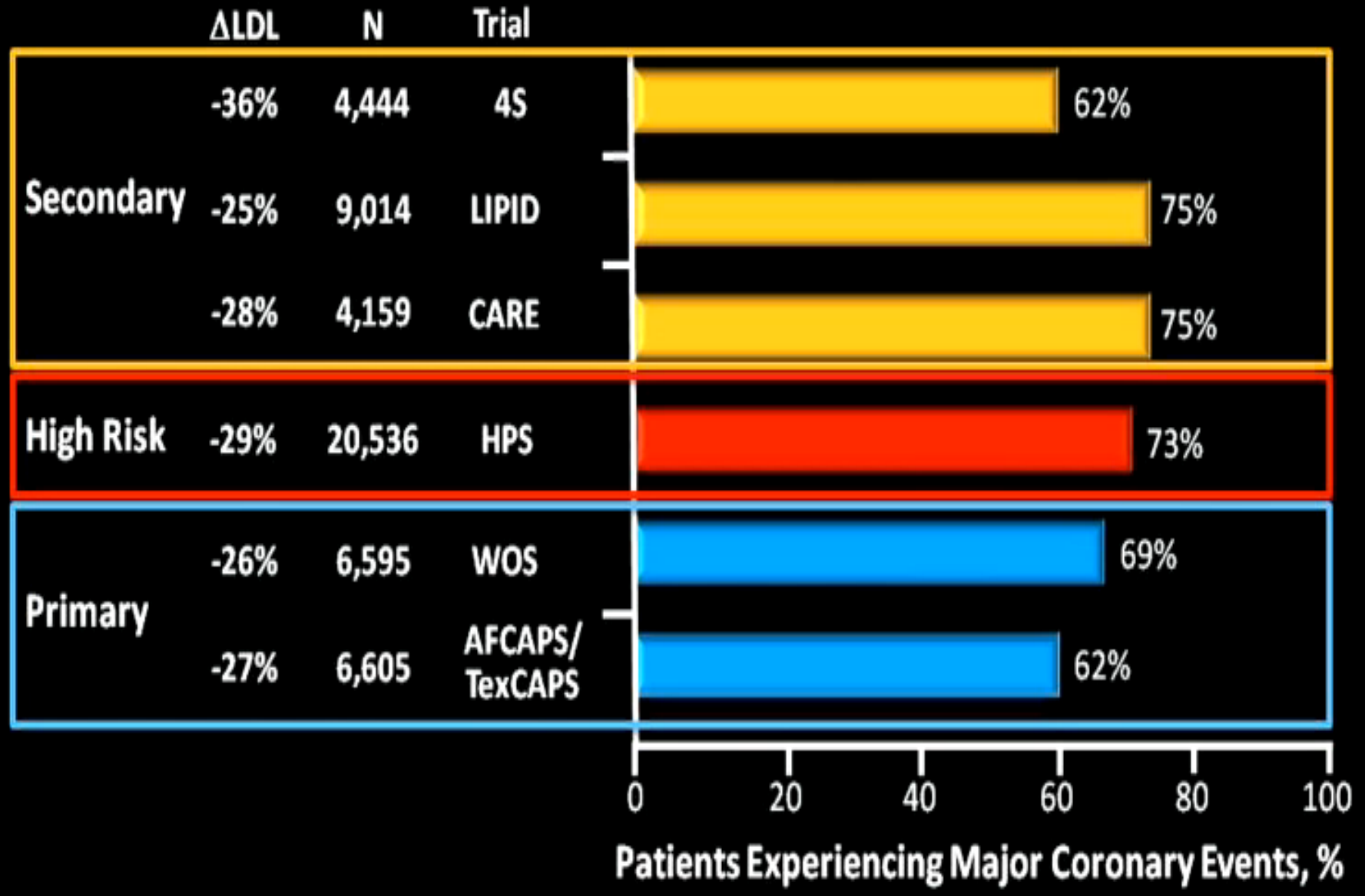
Update on Dyslipidemia Therapy in 2016

- High potency statins were the sole focus of the 2013 guidelines due to lack of RCT for other therapies
- HDL has lost ground as a therapeutic target but remains a critical marker of CVD risk
- CETP is almost out (waiting for anacetrapib REVEAL study) since ACCELERATE / evacetrapib was halted
- Residual risk is well defined
- Statin intolerance is now well defined (Gauss 2/3 studies)
- Combination therapy with niacin / fibrates is out
- Combination therapy with ezetimibe , BAS and PCSK9 is recommended

RESIDUAL RISK

- DESPITE MAXIMAL STATIN THERAPIES IN CLINICAL TRIALS
- Risk of CV mortality and MACE CV events are not eliminated (but certainly better than placebo or less potent therapy) estimated 60% residual risk
- Even after controlling for other risk factors – there is a need to further reduce dyslipidemia dependent risk of CV events
- Over the last decade research into add on therapies or alternative therapies has become the “HOLY GRAIL” of risk reduction in Dyslipidemia

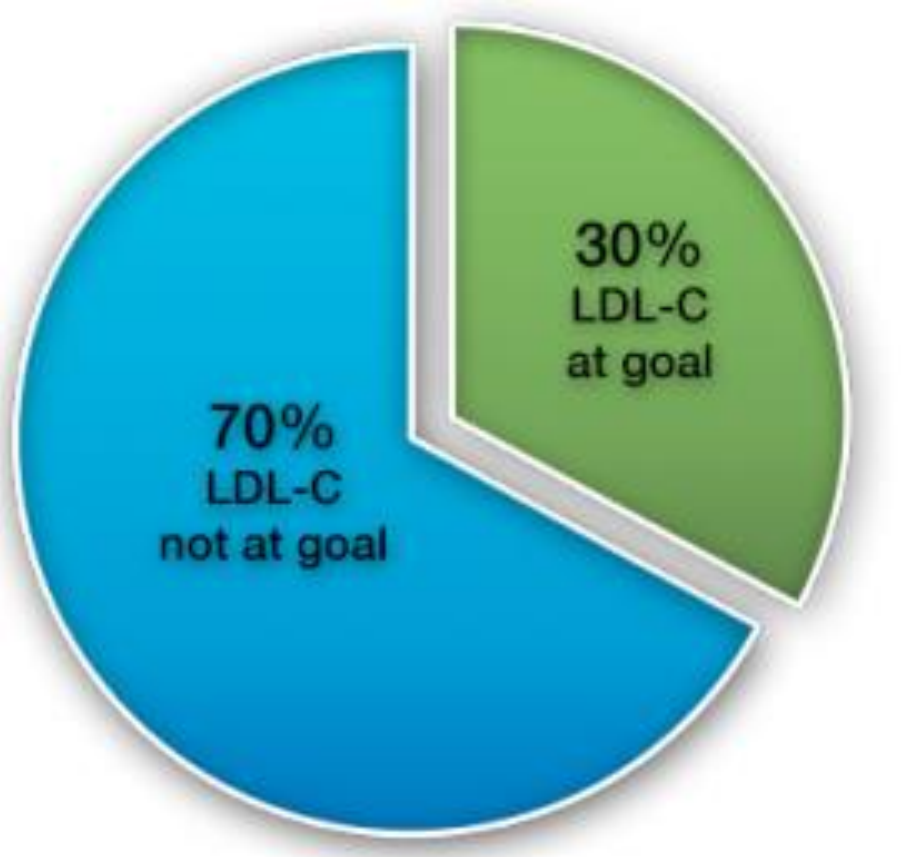
Residual Cardiovascular Risk in Major Statin Trials



Adapted from Libby PJ, et al. *J Am Coll Cardiol*. 2005.

Why targets matter

WHAT ABOUT THOSE PATIENTS WHO DON’T ACHIEVE THEIR TARGET?

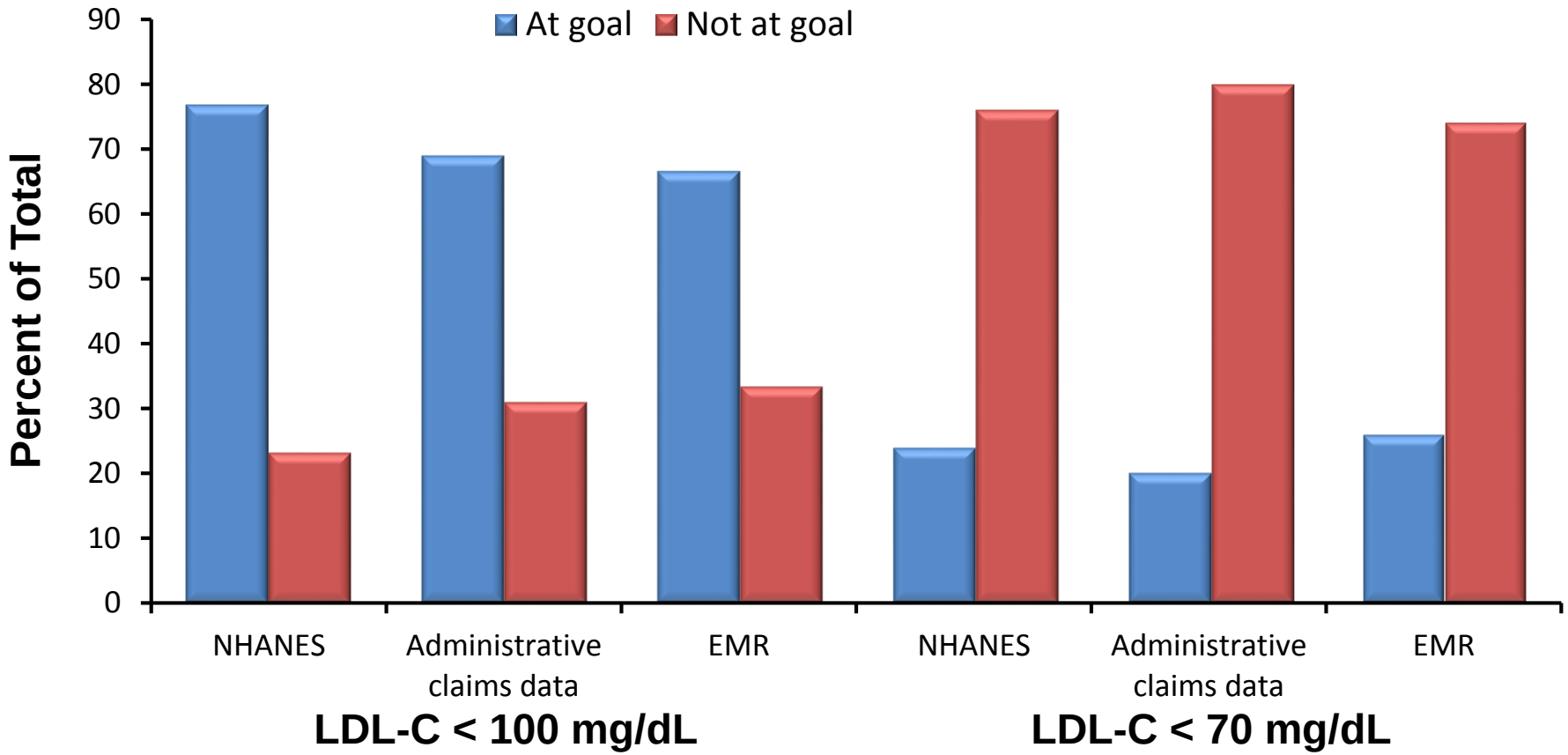


Approximately 70% of patients at the highest risk* are not at optional < 70 mg/dL (< 1.8 mmol/L)LDL-C goal†

* Very high risk defined as: CHD plus ≥ 2 major risk factors. Data shown are from a 2006-2007 multinational survey, of which 2,334 patients were considered very high risk. Countries in this analysis included the United States, Canada, Spain, the Netherlands, France, Taiwan, Korea, Brazil, and Mexico.

† National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) US optional goal < 70 mg/dL (1.8 mmol/L)

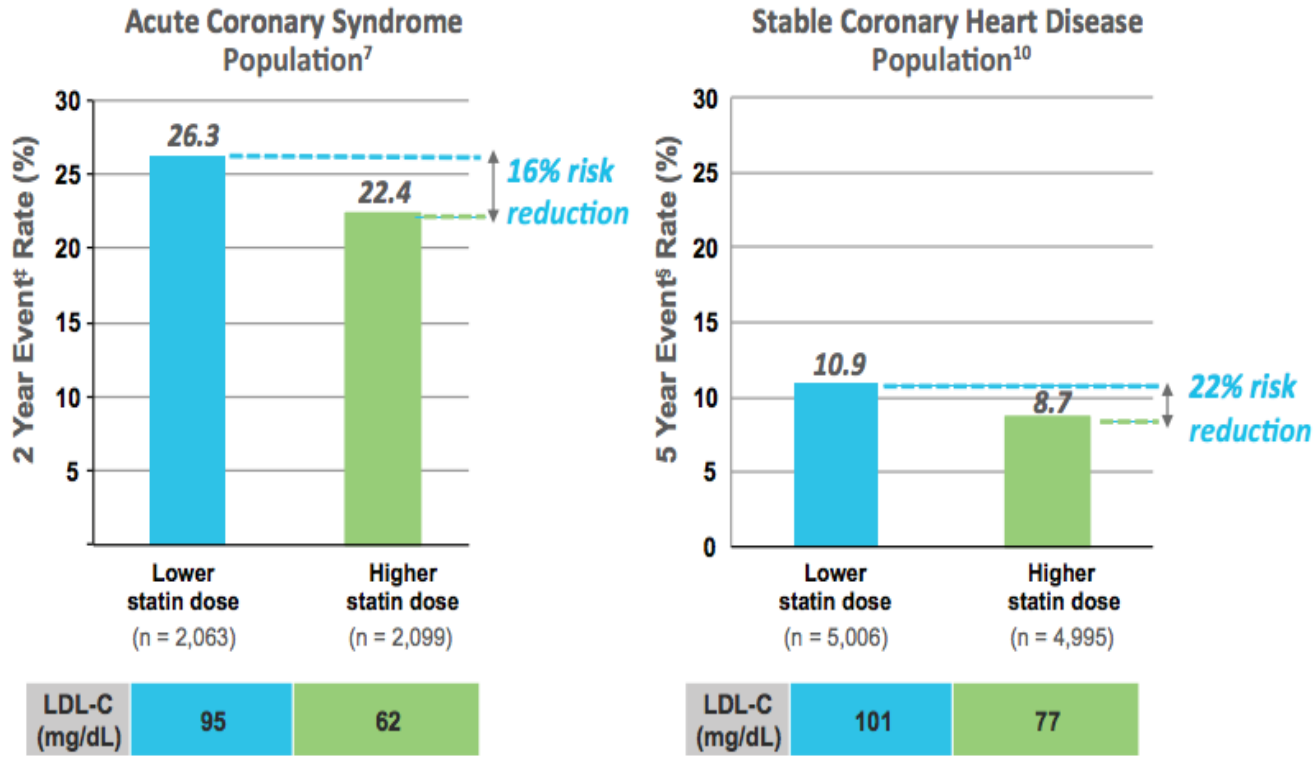
Number of High Risk US Adults Achieving LDL-C Levels of < 100 mg/dL or LDL-C Levels of < 70 mg/dL, AN EVEN BIGGER PROBLEM FOR HIGH RISK PATIENTS



High-risk patients were defined as patients older than 18 years with a history of CHD or CHD risk equivalent who had the latest complete lipid panel measurement and were treated with statin monotherapy for > 90 days.
EMR = electronic medical record database collected from 40,000 clinicians and 20,000 NP and PA (GE Centricity); Administrative Claims Database of the medical and pharmacy claims for 42MM patients enrolled in a large US managed care plan (Clinformatics DataMart, a product of Optuminsight Life Sciences); NHANES=National Health and Nutrition Examination Survey, a national public health survey conducted by the CDC of a nationally representative sample of 5000 individuals each year across a country.
As per NCEP ATP III, the LDL-C goal patients was <100 mg/dL. High-risk patients were also evaluated for the optional goal of LDL-C <70 mg/dL, as per the 2004 update to the NCEP ATP III Guidelines.

Jones, PH, et al. *J Am Heart Assoc*. 2012;1:e001800.

Residual CV risk remains even at lower LDL-C levels



‡ Death, MI, UA requiring hospitalization, revascularization (>30 days), stroke[7]
§ CHD death, non-procedure-related MI, resuscitation after cardiac arrest, stroke[10]

Despite lipid lowering therapy, patients still have residual CV risk. Therefore, these cardiovascular patients must be closely monitored.

HOW DOES THIS HAPPEN & DOES IT MATTER ?

- UNTREATED (Not following Guidelines ?)
- SUBOPTIMALLY TREATED
- UNABLE TO LOWER WITH STATIN(FAMILILAL HYPERLIPDEMIA)
- TREATMENT DISCONTINUED / STATIN INTOLERANCE
- **WHEN SUB OPTIMAL LDL IS PRESENT RISK CLEARLY INCREASES!!!**

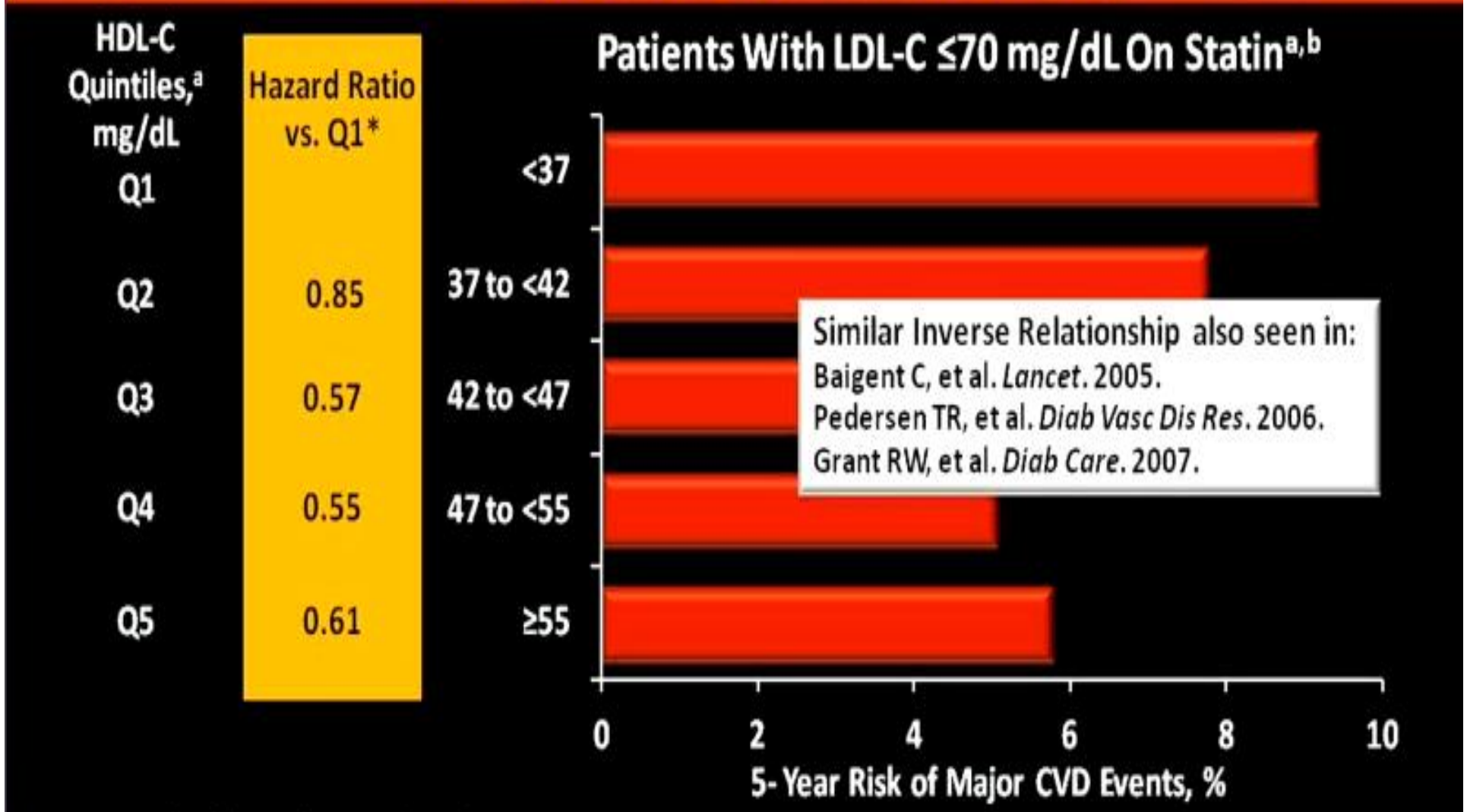
Residual Risk Should we use ALTERNATE non LDL Therapy ?

- Not taking a statin or unable to take a statin (non adherence / intolerance) therefore becomes a major cause of residual risk as the patient is unable to take the most effective therapy in CV risk prevention
- Can we lower risk by non LDL targeted therapy in combination or alone ?
- Raising HDL – niacin , fibrates , CETP
- Lowering TG- fibrates
- Inflammation – methotrexate
- PCSk9 inhibition

Residual Risk & LDL Targets

- Combination therapy implies need for ADDITIONAL effectiveness
- Or should we just lower LDL even more :-
- Statin Combination with Ezetemibe
- Profound LDL lowering with PCSk9
- **WHAT IS THE EVIDENCE BASE ?**

Low HDL-C Increases CVD Risk Even if LDL-C Levels Are *Very Well* Controlled



[a]On-treatment level (3 months statin therapy); N=2,661

[b]Mean LDL-C, 58 mg/dL; mean TG, 126 mg/dL; **P*=.03 for differences among quartiles of HDL-C

Barter P, et al. *N Engl J Med*. 2007.

Lipid Effects of CETP-Inhibitors

Agent	Change from Baseline					
	HDL-C	Apo A-I	LDL-C	Lp(a)	TG	CETP Inhibition
Dalcetrapib[1] 600 mg/day	↑31%	↑14%	↑11%	ND	↑5%	Partial (~↓50%)
Anacetrapib[2] 100 mg/day	↑138%	↑45%	↓40%	↓36%	↓7%	Very high
Evacetrapib[3] 100 mg/day	↑79%[3]	(↑36%[4])	↓14%[3]	ND	↓6%[3]	High

- Changes added to background statin therapy
- (Anacetrapib partitions to adipocytes and has est. $T_{½}$ >1y[5])

[1]Stein EA. *Am J Cardiol.* 2009 (12 Weeks);
[2]Cannon CP. *N Engl J Med.* 2010 (24 Weeks);
[3]Nicholls S. *JAMA.* 2011 (12 weeks; changes with atorva 20 mg/day);
[4]Suico JG, et al. *J Pharm Pharmacol.* 2014 (2 weeks, *no statin*);
[5] Small DS, et al. *J Clin Pharmacol.* 2015.

ND=no data

ACCELERATE TRIAL

(Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition With Evacetrapib in Patients at a High-Risk for Vascular Outcomes)

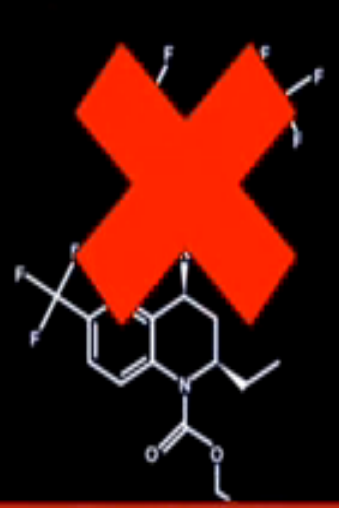
- N=12,000 with:
  - ACS (30-365 days earlier), or
  - CVA, or PAD, or
  - T2DM with CAD
- Background LDL-C lowering with statin
- Randomized to evacetrapib 130 mg/day (new formulation) vs. placebo
- Scheduled follow-up: 4 years (started October 2012, estimated completion July 2016)
- Primary outcome: composite endpoint of CV death, nonfatal MI, CVA, hospitalization for unstable angina, or coronary revascularization

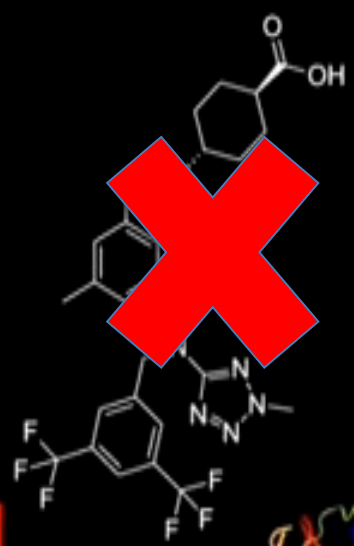
Nicholls SJ. Presented at ESC 2012; https://clinicaltrials.gov/ct2/show/NCT01687998.

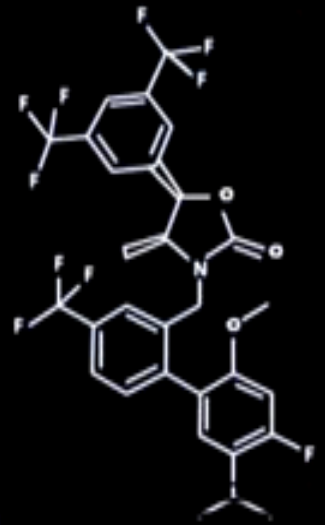
CETP Inhibitor Development

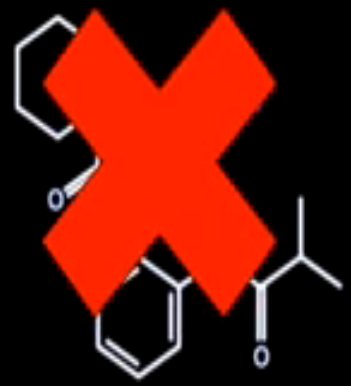
↑HDL-C

~80%	~80%	~140%	~30%
Torcetrapib	Evacetrapib	Anacetrapib	Dalcetrapib









↑CVD (25%)
but OK HDL function
(off-target eff.?)

CETP

*No ↓CVD,
but OK HDL function
+/- anti athero?

*Dalcetrapib development stopped May 7, 2012 due to lack of efficacy in the Dal-Outcomes CVD endpoint trial.

Barter et al. *N Engl J Med.* 2007; Qiu X, et al. *Nat Struct Mol Biol.* 2007;
http://www.ama-http assn.org/ama1/pub/upload/mm/365/dalcetrapib.doc; http://www.amaassn.org/ama1/pub/upload/mm/365/torcetrapib.doc;
http://www.ama-assn.org/ama1/pub/upload/mm/365/anacetrapib.pdf; http://www.roche.com/media/media_releases/med-cor-2012-05-07.htm.

HPS-3/TIMI-55/REVEAL: CVD Endpoint Trial of Anacetrapib

(Randomized EValuation of the Effects of Anacetrapib through Lipid-modification)

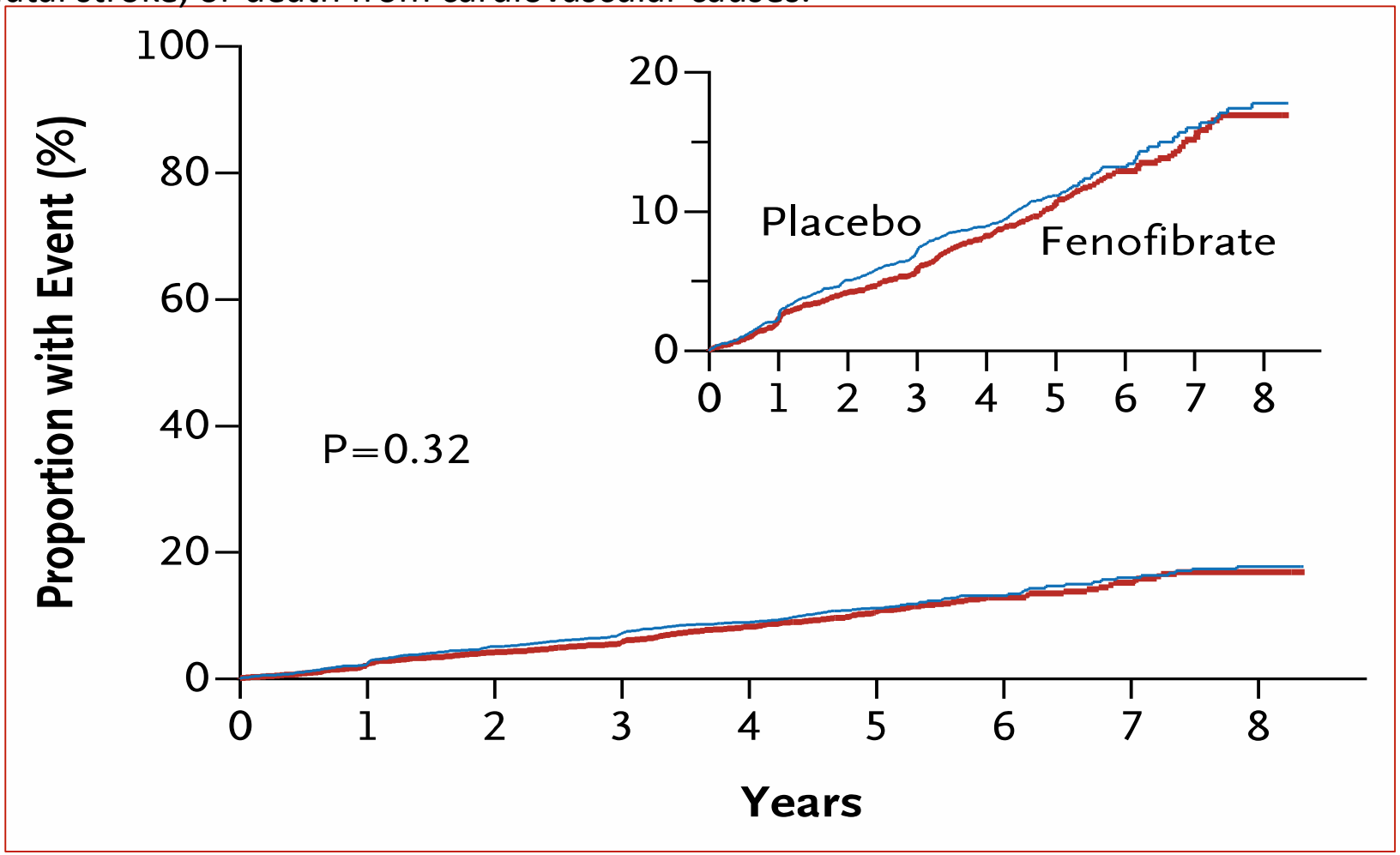
- N=30,624, prior CVD; recruiting in North America, Europe, and Asia
- Background LDL-C lowering with atorvastatin
- Randomized to anacetrapib 100 mg/day vs. placebo
- Scheduled follow-up: 4 years (started 6/2011, estimated completion 1/2017)
- Primary outcome: major coronary event defined as CV death, MI, or coronary revascularization procedure

http://www.revealtrial.org;
http://clinicaltrials.gov/ct2/show/NCT01252953?term=anacetrapib&rank=4.

WHAT ABOUT COMBINATION WITH FIBRATES AND NIACIN ?

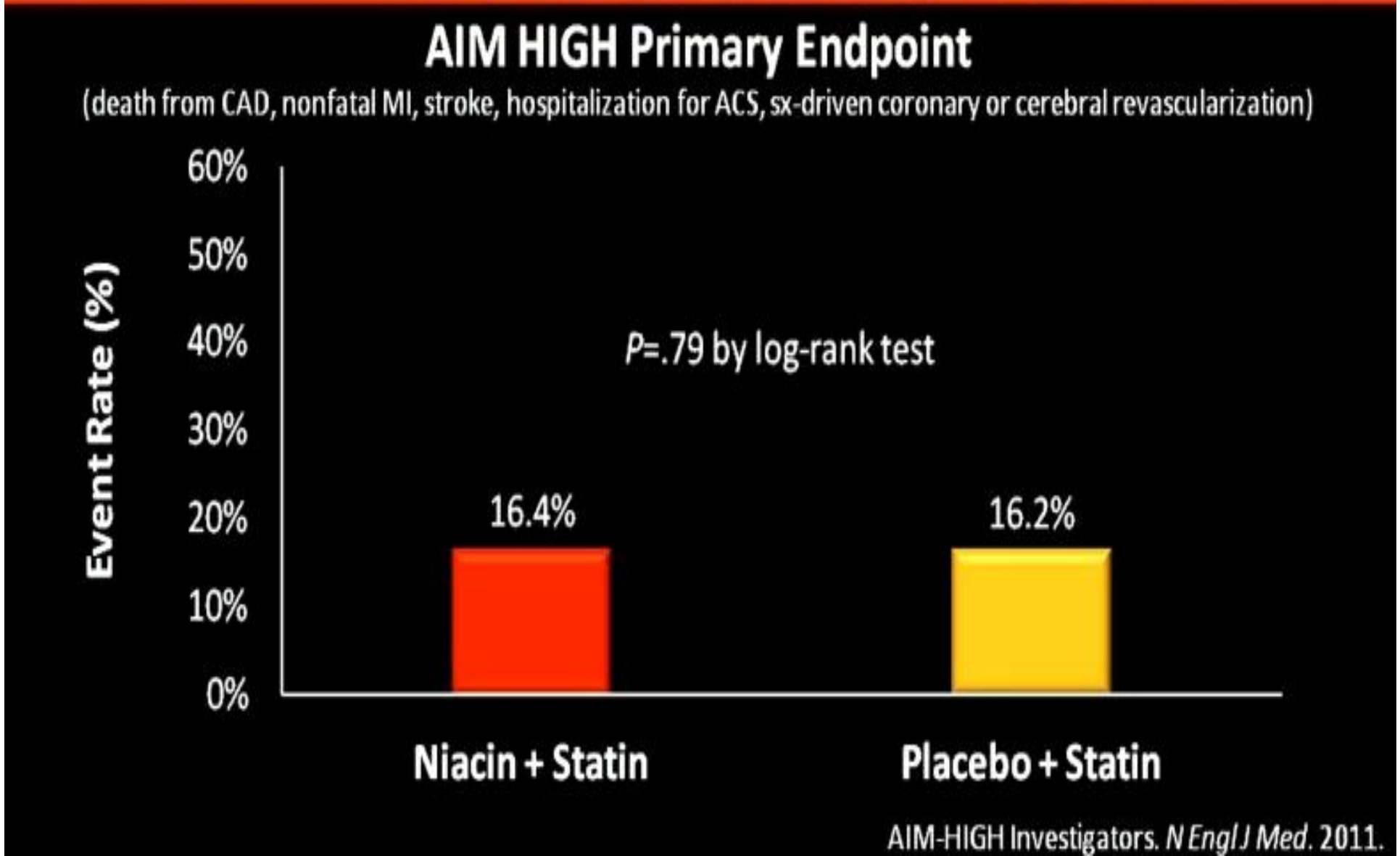
ACCORD Lipid

- Primary Outcome: First occurrence of nonfatal MI, nonfatal stroke, or CV death
- 5518 pts T2DM treated with simvastatin randomized to fenofibrate or placebo
- The primary outcome was the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.



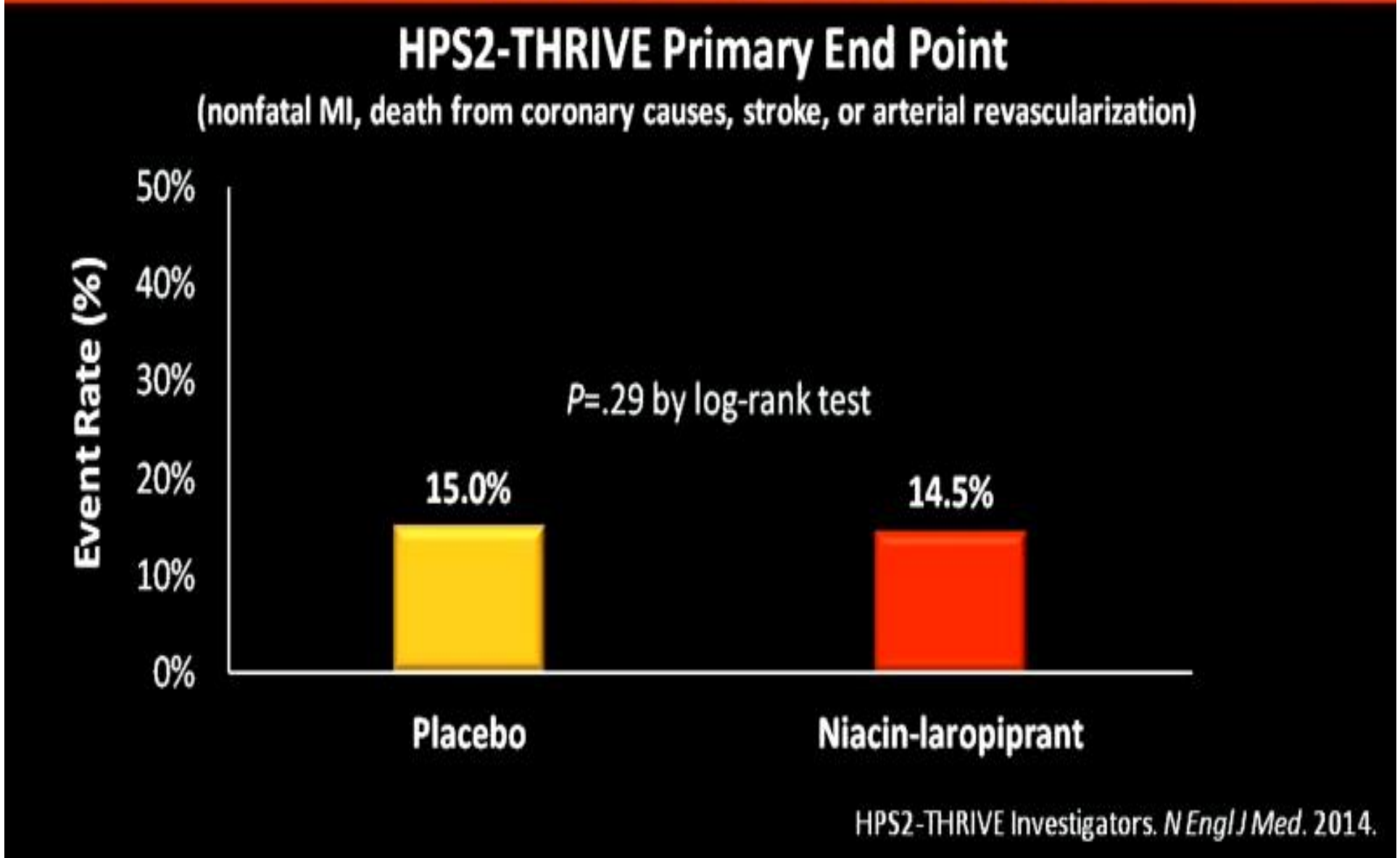
ACCORD Study Group. NEJM 2010; 362:1563-74.

Combination Therapy – Statins and Niacin



AIM-HIGH Investigators. *N Engl J Med*. 2011.

Combination Therapy – Statins and Niacin



HPS2-THRIVE Investigators. *N Engl J Med*. 2014.

Statins for
Secondary Prevention

Statins for
Primary Prevention

Fenofibrates

Niacin
(HDL Hypothesis

Patient Populations with HIGH Unmet Need for Additional LDL-C Lowering

FH Population in EU	High / Very High CV Risk Population	Statin-Intolerant Population
• Genetic disorder • High risk of early CHD • HeFH prevalence 1:200 to 1:250[1,2] • Untreated LDL-C of 200-400 mg/dL[3]	• Previous MI/stroke / CVD or multiple CV risk factors incl. T2DM • Difficult to achieve LDL-C goals, despite current therapies[5]	• 10-15% on high-intensity statins show intolerance[6] • Many discontinue due to muscle pain and/or weakness
79% with HeFH not at goal (<100 mg/dL [2.6 mmol/L])[4]	**• 20% with CHD not at goal (<100 mg/dL [2.6 mmol/L])** **• 59% at very high CV risk not at goal (<70 mg/dL [1.8 mmol/L])**	**Nearly all patients who need considerable LDL-C reductions will not reach goal**

[1]Nordestgaard et al. *Eur Heart J* 2013;34:3478-90. [2]Sjouke et al. *Eur Heart J.* 2015 Mar 1;36(9):560-5.
[3] 2011 ESC/EAS Guidelines for the management of dyslipidaemias Eur Heart J. 2011;32(14):1769-818.
[4] Pijlman et al. *Atherosclerosis* 2010;209:189-94. [5] Virani et al. *Am Heart J* 2011;161:1140-6.
[6] Arca et al. *Diabetes Metab Syndr Obes* 2011;4:155-66.

Dyslipidemia in Familial Hypercholesterolemia

PATIENTS WITH VERY HIGH BASELINE AND HYPORESPONDERS TO STATINS

= UNABLE TO ACHIEVE TARGET WITH STATIN THERAPY

Familial Hypercholesterolemia Phenotypes

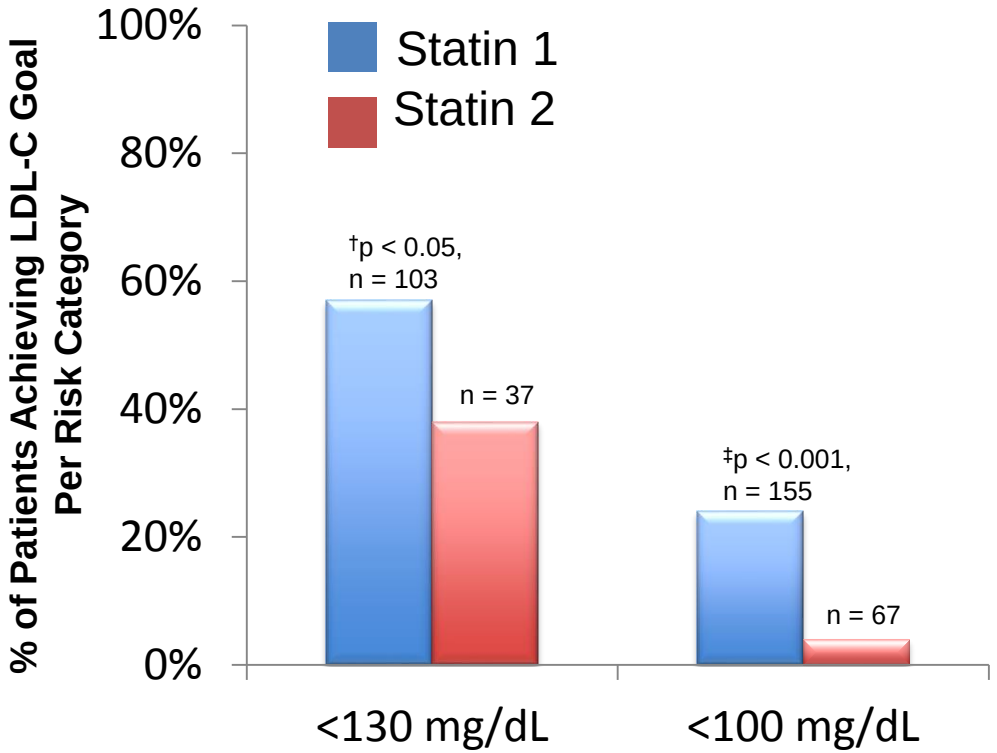
FH Heterozygotes	FH Homozygotes
~ 1 in 200 to 1:500 persons worldwide[1,4]	~ 1 in 1,000,000 persons worldwide[1]
1 mutated allele[1]	2 mutated alleles[1]
TC: 350 to 500 mg/dL[3]	TC: > 500 to > 1,000 mg/dL[1]
LDL-C: 200–400 mg/dL[1,2]	**LDL-C: > 600 mg/dL[2]**
Half the number of LDLR expressed[3]	LDLR activity absent or dysfunctional[3]

TC = total cholesterol

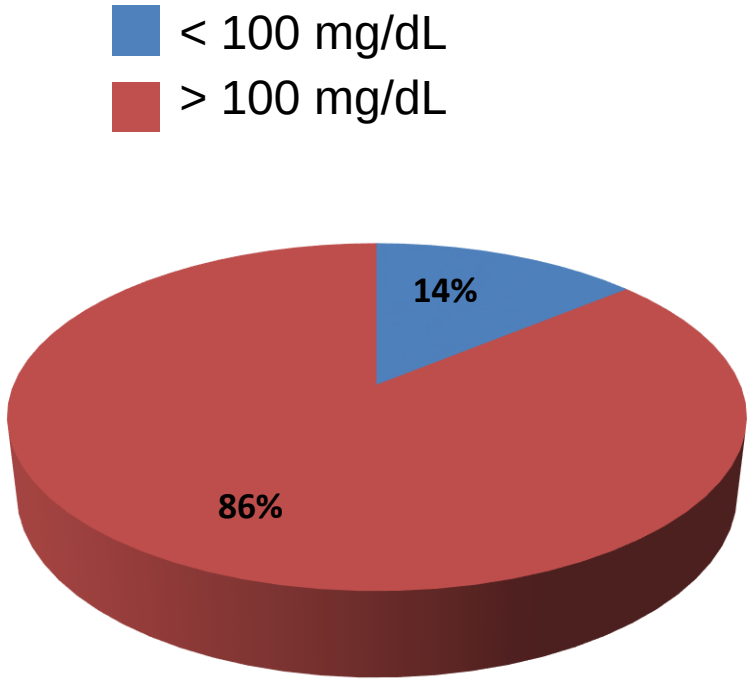
1. Rader DJ, et al. In: Longo DL, et al, eds. *Harrison's Principles of Internal Medicine*. Vol II.18th ed. New York, NY: McGraw Hill Medical. 2012:3145-3161. **2.** Robinson JG. *J Manag Care Pharm.* 2013;19:139-149. **3**. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Circulation*. 2002;106:3143-3421. **4**. Nordestgaard BG, et al. *European Heart Journal*. 2013;34:3478–3490.

Despite Maximal Treatment, A Low Percentage of Patients with HeFH Achieve LDL-C < 100 mg/dL

In a Randomized Global Clinical Trial of HeFH Patients, A Low Percentage Achieved LDL-C Levels of < 100 mg/dL on Maximal Treatment*



In Netherlands Estimates of HeFH Patients On Maximal Lipid Lowering Therapy Achieving LDL-C < 100 mg/dL**



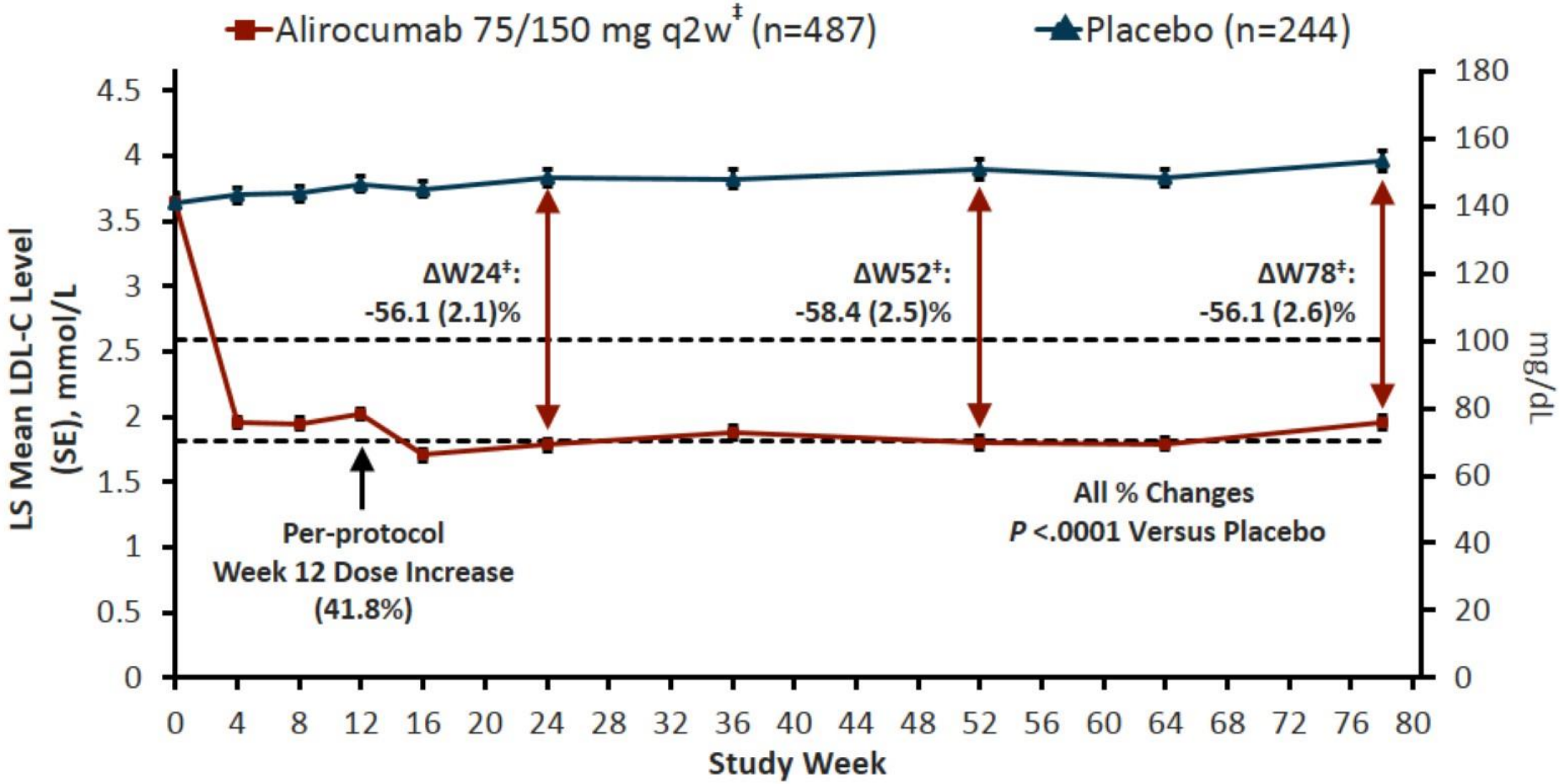
*NCEP Adult Treatment Panel III Risk Category: Medium Risk: <130 mg/dL (3.4 mmol/L); ≥ 2 risk factors,10-year risk of coronary artery disease ≤ 20%; High Risk: <100 mg/dL (2.6 mmol/L); coronary artery disease or its risk equivalents (atherosclerosis, diabetes, or 10-year risk > 20%).18 week RCT, double-blind parallel group where heterozygous (He) FH patients initiated statin treatment at 20 mg with forced titration to 40 and 80 mg in 1999-2000. N = 623 randomized; p Values were obtained from a logistic regression model . Global population consisted of 31% US patients.

**Adults with HeFH were part of a cross-sectional study. 96% were on statin treatment where 34% were on maximum dose. N = 1249 met inclusion criteria. n = 304 patients on maximal therapy; Maximum lipid-lowering therapy was defined as maximum statin doses in combination with ezetimibe. Using outpatient visits to Lipid Clinics after February 2006.

1. Stein EA, et al. *Am J Cardiol.* 2003; 92:1287-1293. **2.** Pijlman AH, et al. *Atherosclerosis.* 2010; 209:189-194.

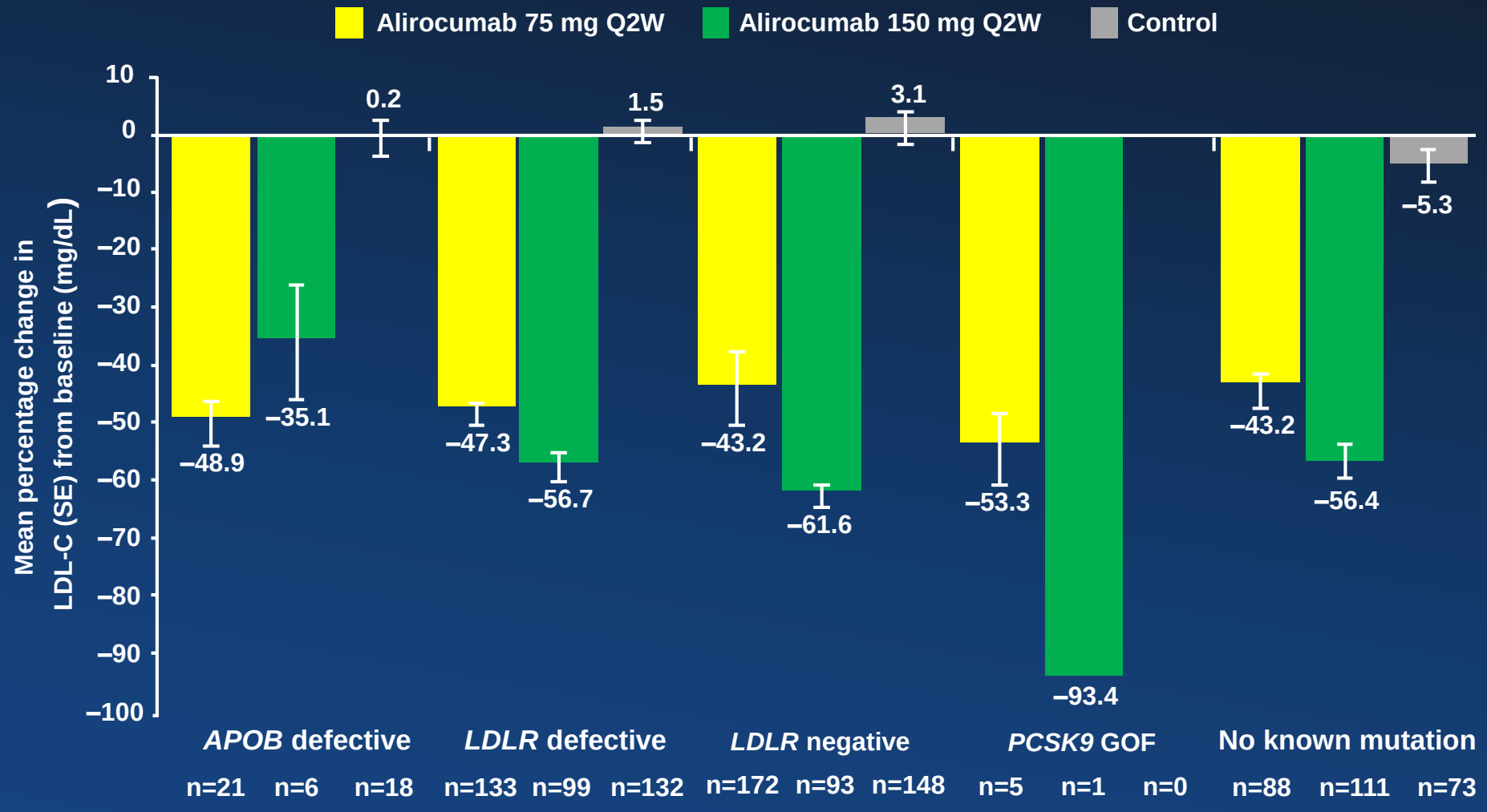
Mean Calculated LDL-C Levels

Pool of FH I and II Studies (Alirocumab 75/150 mg q2w)



Kastelein JJ, et al. ESC 2015. Abstract 5772.

Reduction in LDL-C Level from Baseline at Week 12 According to Mutation Status for Heterozygous FH Patients



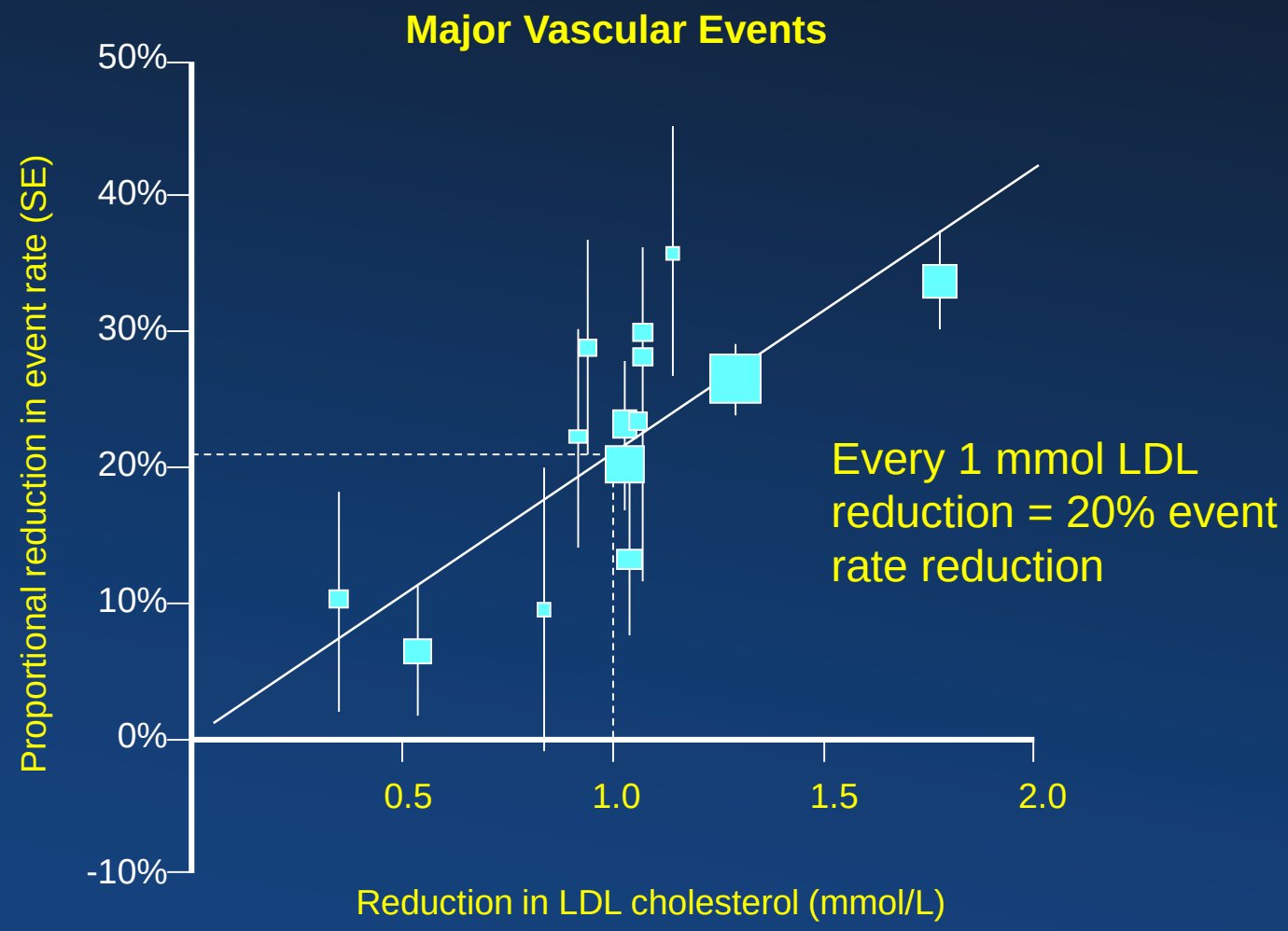
SE, standard error

Kastelein et al. Presented at ACC 2016.
Poster number 1293M-05

THE PROMISE OF COMBINATION PCSK9 IN ATHEROSCLEROSIS

FOR THE HIGH RISK PATIENT SHOULD WE NOW GO EVEN LOWER WITH LDL ? AND HOW COULD WE ACHIEVE THIS GOAL ?

Cholesterol Trialist Collaboration
Meta-Analysis of Dyslipidemia Trials



CTT Collaborators. *Lancet.* 2005; 366:1267-78

Percent Reduction vs. Treat-to-Target

ACC/AHA (2013) Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults	
Clinical risk categories	**Treatment**
Those with clinical ASCVD	High-intensity *statin therapy*. If 50% reduction is not reached drug combination may be considered
Diabetes mellitus (Type I or Type II) without ASCVD but with LDL-C between 1.8 and 4.9 mmol/L	Diabetes with high risk:High-intensity *statin therapy*. Diabetes with low risk:Moderate-intensity statin therapy
Those with primary elevation of LDL-cholesterol (LDL-C) >4.9 mmol/L	High-intensity *statin therapy*, aimed at achieving at least 50% reduction of LDL-C
If none of the above but with estimated 10-year ASCVD risk of 7.5% or more using a pooled populations risk calculator If risk-based assessment treatment decision uncertain assessment of 1 or more of family history, hs-C-reactive protein, CAC Score or ABPI may be considered (Class IIb, Level E), contribution of ApoB, CKD, microalbuminuria or cardio-respiratory fitness is uncertain (Level N) and CIMT is not recommended for routine assessment of individual patients (Level N)	Moderate-to-high-intensity *statin therapy* if ASCVD risk >7.5%. If risk 5–7.5% risk of CVD event: Reasonable to consider moderate-intensity statin therapy

NO TARGET

ESC/EAS (2011) Guidelines for the management of dyslipidaemias	
Clinical risk categories	**Treatment**
Those with CVD	LDL-C <1.8 mmol/L or 50% reduction in LDL-C
Diabetes mellitus (Type II) or Type I with target organ damage	LDL-C <1.8 mmol/L or 50% reduction in LDL-C
Familial dyslipidaemia (FH or FCH or chylomicronaemia)	LDL-C <2.5 mmol/L or maximal reduction in LDL-C with any possible drug combination plus LDL apheresis
If none of the above estimate 10 year risk of a first fatal atherosclerotic CV event (SCORE), with a SCORE >10% considered, very high risk, SCORE 5–10% considered high risk and SCORE 1–5% moderate risk Above risk can be modified if additional information is available on: ↑ TGs, social deprivation, central obesity, ↑ Lipoprotein(a), familial hypercholesterolaemia, subclinical atherosclerosis, CKD, family history of pre-mature CVD (× 1.7 – women, × 2 – men), very high HDL-C, family history of longevity	Very high risk LDL-C <1.8 mmol/L or 50% reduction in LDL-C, high-risk LDL-C <2.5 mmol/L, moderate risk LDL-C <3.0 mmol/L

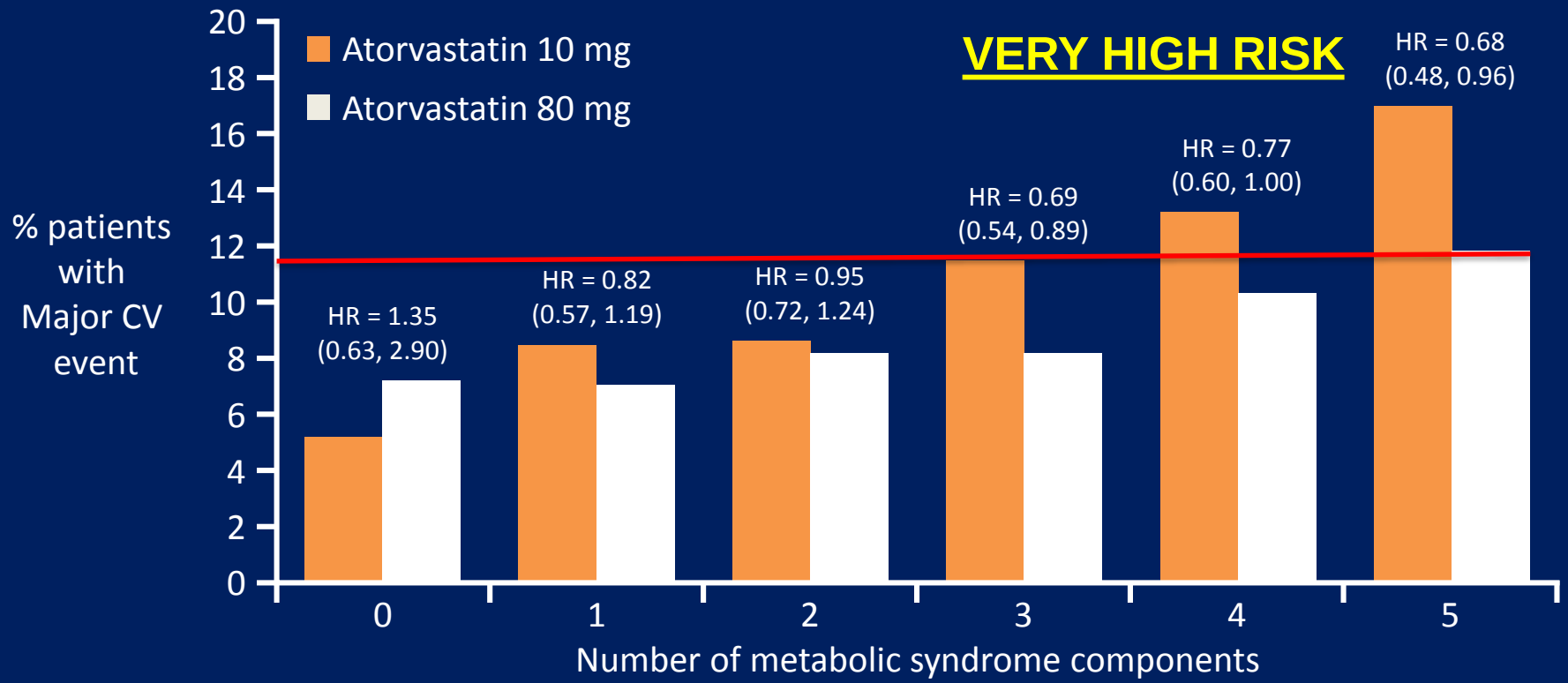
TARGET CLEARLY DEFINED BY RISK GROUP

European Heart Journal doi:10.1093/eurheartj/ehu107

Ray KK et al. Eur Heart J. 2014;35(15):960-8

Residual Risk Despite Statin Therapy in TNT effect of additional Risk Factors

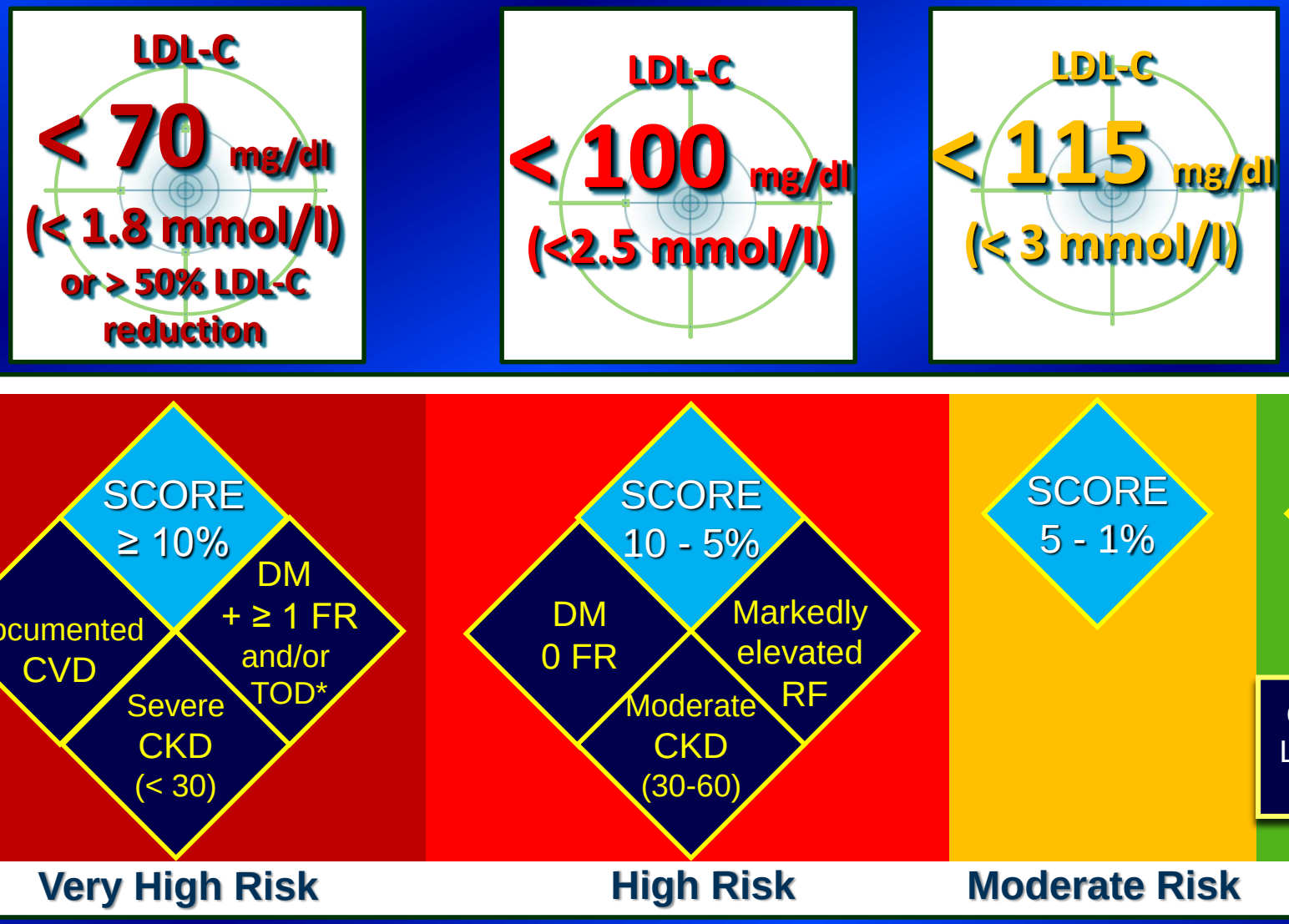
The TNT study was a prospective, double blind, parallel-group trial done at 256 sites in 14 countries between April, 1998, and August, 2004, with a median follow-up of 4.9 years. 10,001 patients were enrolled aged 35-75 years with clinically evident coronary heart disease. Our analysis includes 5584 patients with metabolic syndrome based on the 2005 NCEP ATP III criteria. Patients were randomly assigned to receive either atorvastatin 10 mg per day (n=2820) or 80 mg per day (n=2764). The primary outcome measure was time to first major cardiovascular event, defined as death from coronary heart disease, non-fatal non-procedure-related myocardial infarction, resuscitated cardiac arrest, or fatal or non-fatal stroke.



Atorvastatin 10 mg:	11/209	65/761	105/1216	147/1282	141/1073	79/465
Atorvastatin 80 mg:	16/223	52/739	104/1269	109/1342	99/965	54/457

Deedwania P et al. Lancet 2006;368:919–28

ESC / EAS Guidelines Risk Based Targets



* TOD= target organ damage (such as microalbuminuria 30-300 mg/24h)

Joint ESC Guidelines. Eur J Prev Cardiol 2012; 19: 585-667

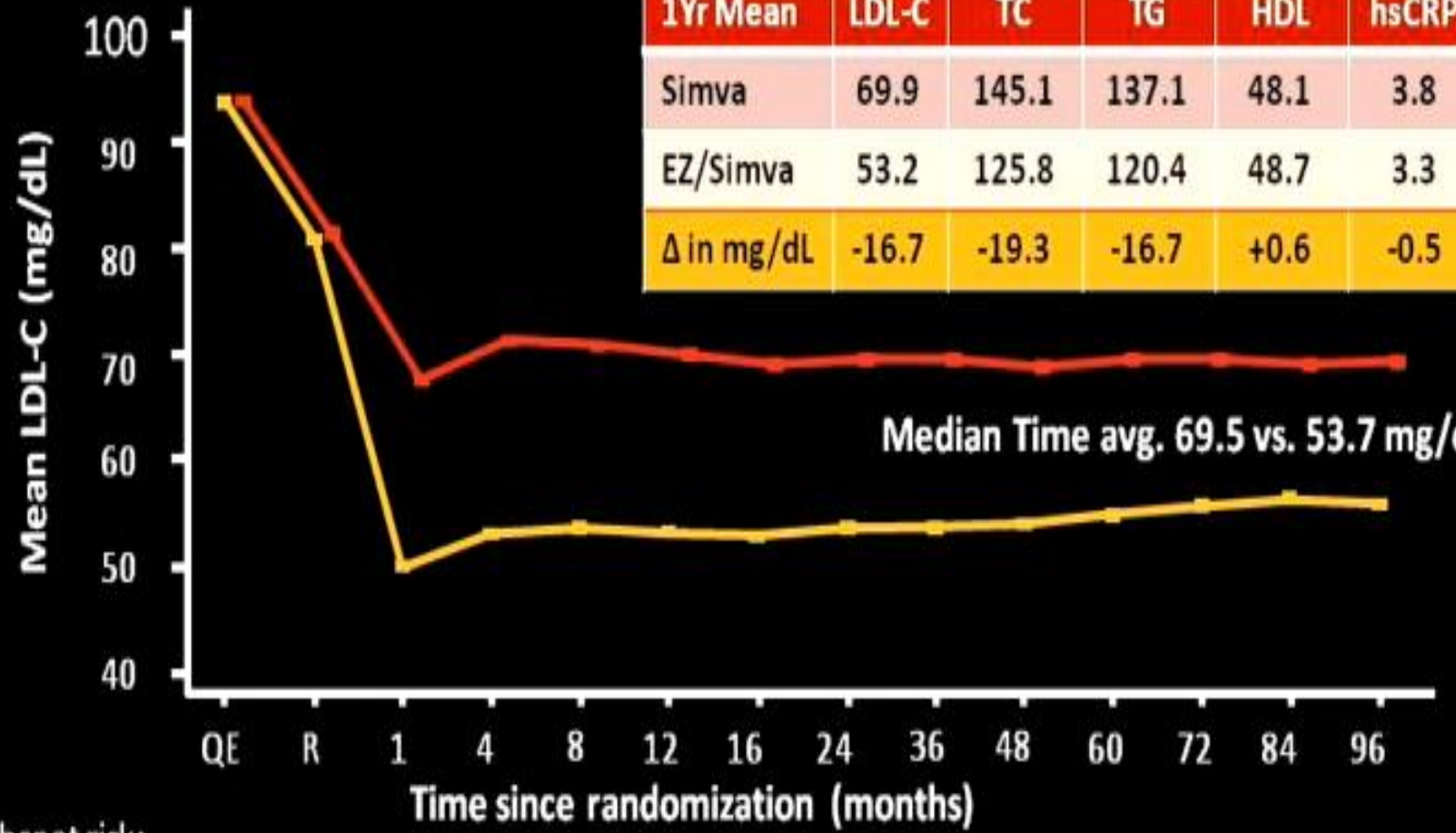
ESC/EAS Guidelines. Eur Heart J 2011; 32: 1769-1818

IMPROVE IT - LOWER IS BETTER REAFFIRMED

- Combination STATIN (simvastatin 40 mg with Ezetimibe 10 mg)
- REVISITED AGAIN IN IMPROVE IT **IN HIGH and VERY HIGH RISK ASCVD AND ACS** PATIENTS
- ACHIEVED LOWER LDL 53 MG/DL THAN THE HIGH INTENSITY STATIN 69 MG/DL
- SIGNIFICANT REDUCTION IN 7 POINT MACCE CV OUTCOME OVER 6 YEARS OF STUDY

IMPROVE-IT: LDL-C and Lipid Changes

1Yr 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



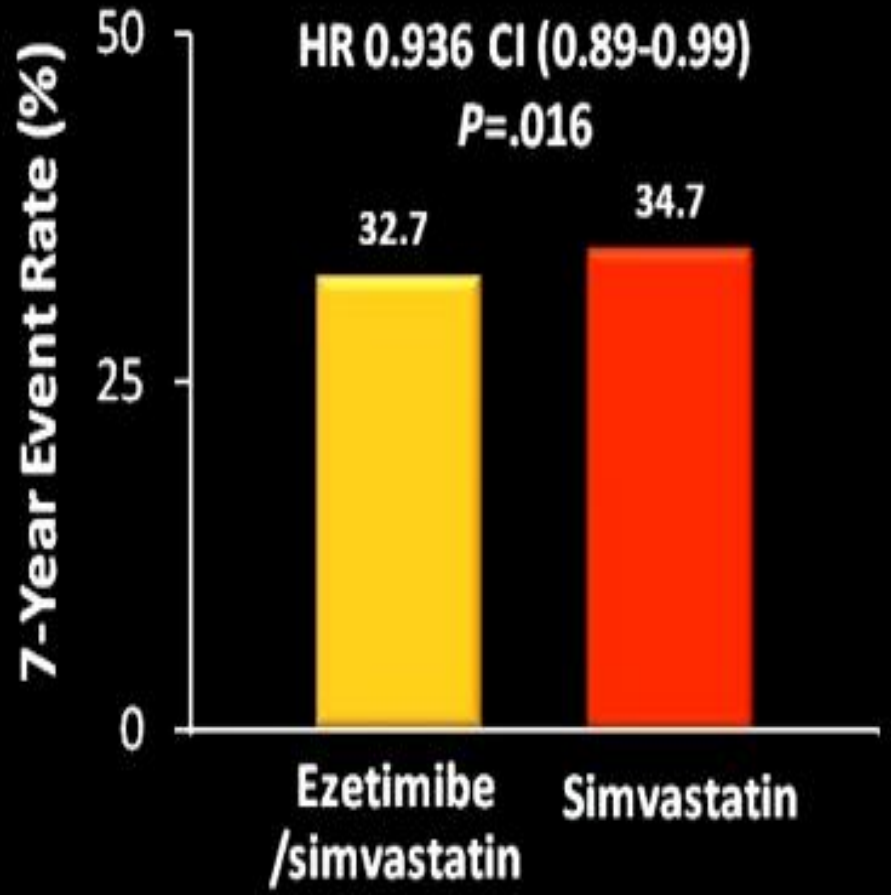
Number at risk:

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

Cannon CP, et al. Presented at AHA 2014.

IMPROVE-IT: Primary Endpoint (ITT)

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



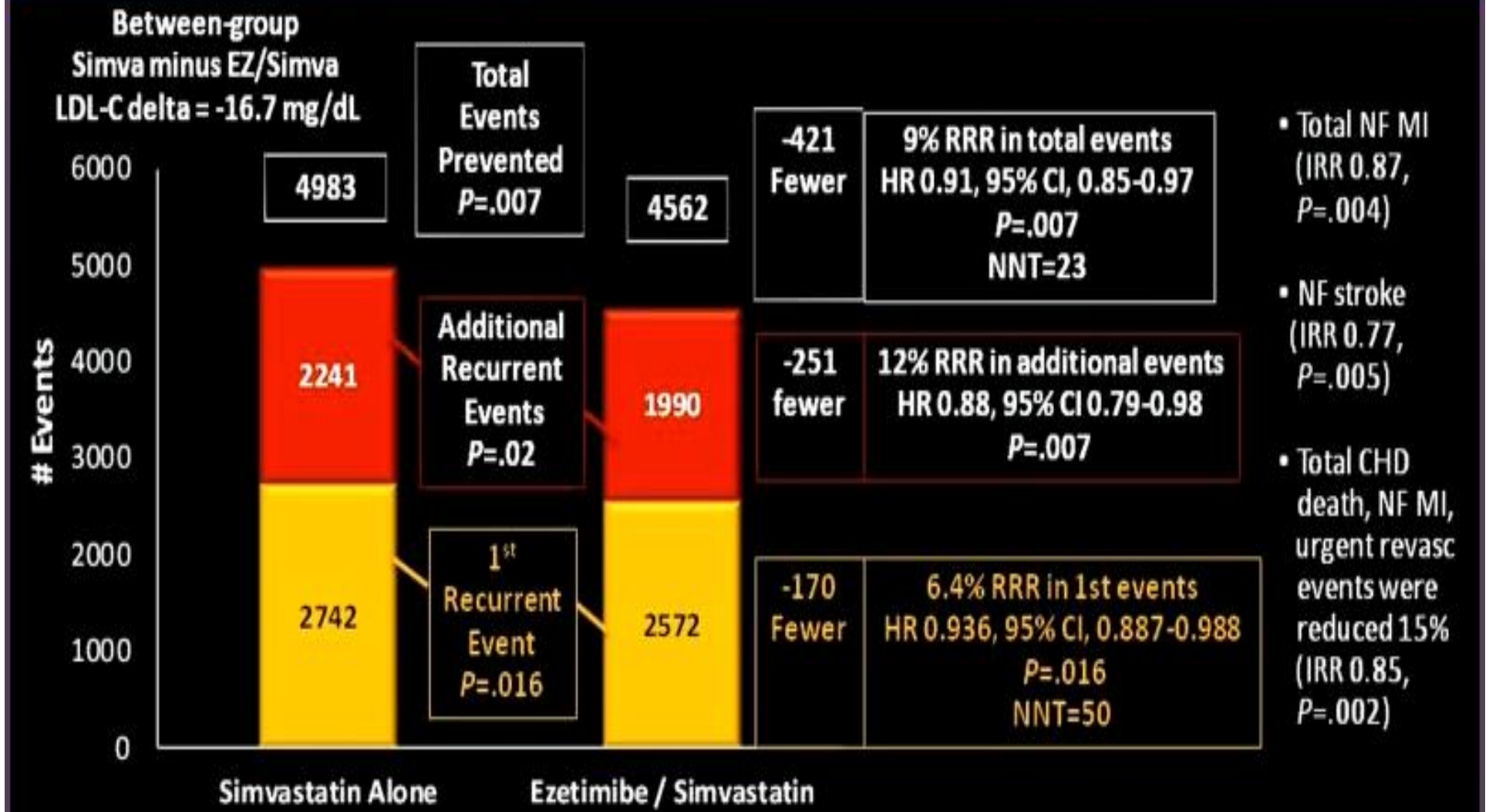
Simvastatin
2,742 events

Ezetimibe/Simvastatin
2,572 events

NTT=50

Cannon CP, et al. *N Engl J Med*. 2015.

Reduction in Total (First and Additional Recurrent) Cardiovascular Events with Ezetimibe/Simvastatin Compared with Simvastatin Alone Post Acute Coronary Syndromes in the IMPROVE-IT Trial



Murphy SA, et al. Presented at ACC 2015.

THE TREATMENT GAP

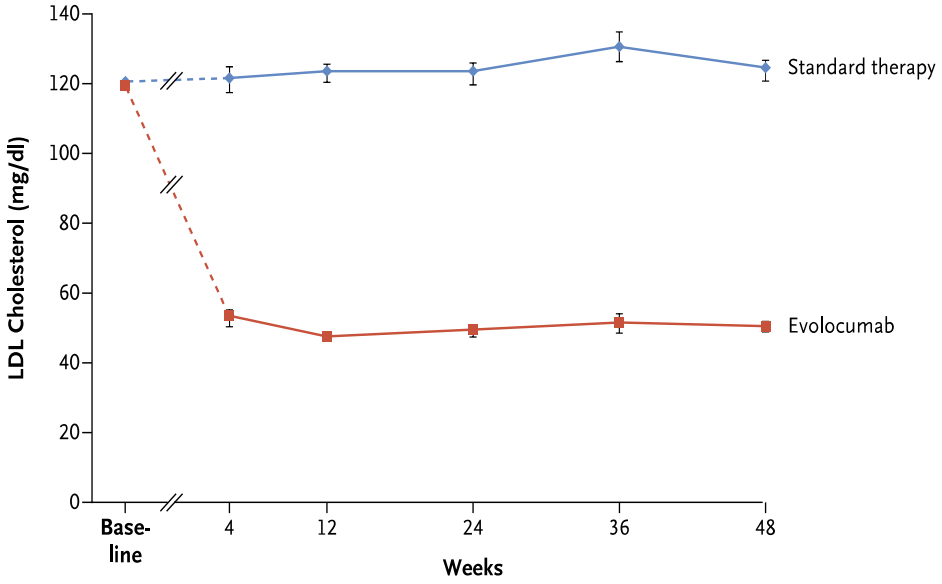
- IT IS INSUFFIENT TO BE COMPLACENT ABOUT JUST BEING ON A STATIN
- THE GOALS FOR TRETAMENT HAVE BEEN REEMPHASIZED
- REACHING A GOAL OF LDL LESS THAN 70 HAS AN IMPACT ON ASCVD
- NEED TO RE FOCUS ON ACHIEVING THESE GOALS
- 1IN 3 DEATHS ARE DUE TO CVD AND 17 MILLION WORLDWIDE – STATINS HAVE IMPACTED THIS SIGNIFICANTLY BUT INCOMPLTELY

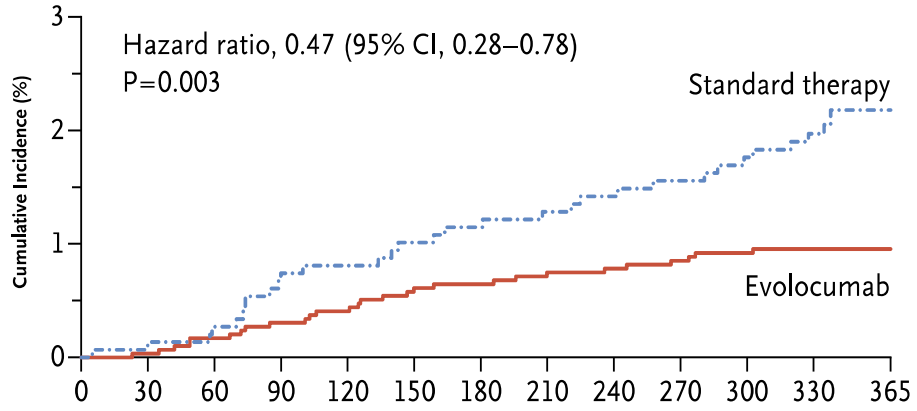
Incremental Reduction of LDL New therapeutic strategies

- **DOUBLING STATIN DOSE ONLY REDUCES LDL BY ADDITIONAL 6-7% (CEILING EFFECT)**
- It was not until 2015 that the ability to improve clinical CV outcomes by adding a non-statin lipid-lowering agent to a statin was confirmed in the IMPROVE IT STUDY
- This finding is particularly important in light of the conservative approach to adding non-statins in 2013 clinical guidelines.
- Moreover, the ability to improve clinical outcomes by incrementally reducing LDL-C levels has raised the expectations for other new classes of drugs, such as PCSK9 inhibitors.

OSLER

- OSLER-1 and -2 4,465 patients randomized open-label treatment with **evolocumab** (140 mg sq every 2 weeks or 420 mg monthly) vs standard therapy
- CV events nearly reduced by 50%

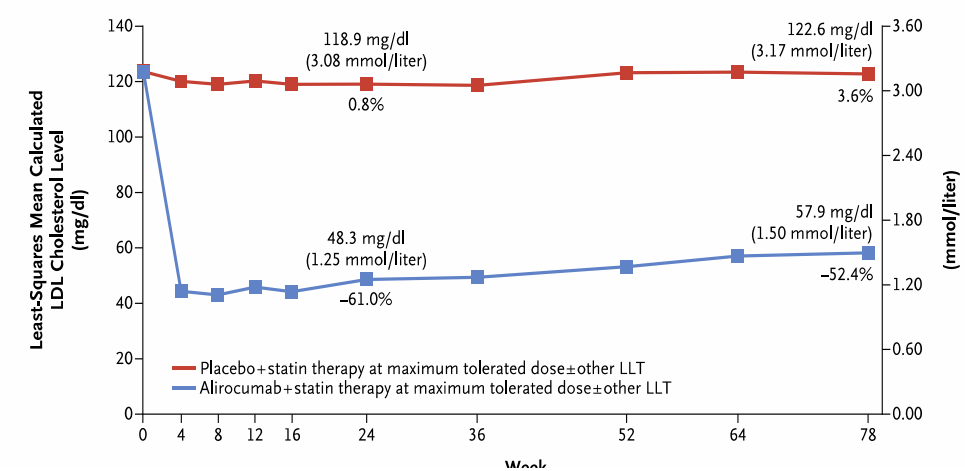


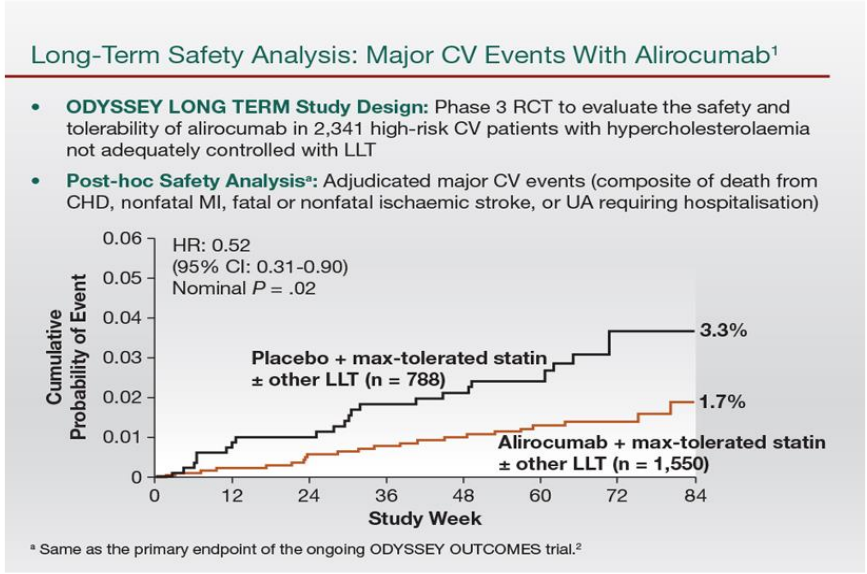


Sabatine MS, et al. NEJM 2015

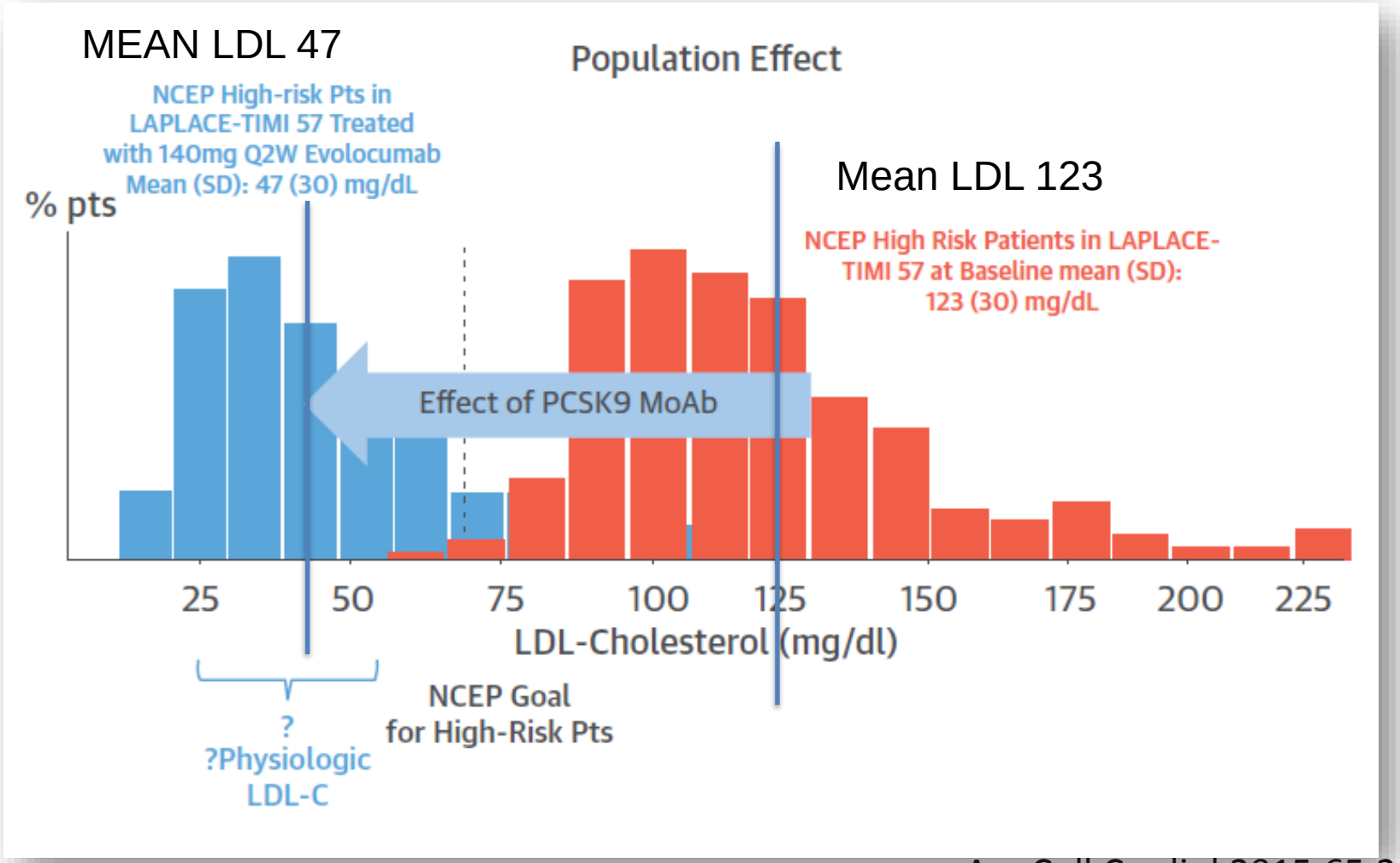
ODYSSEY Long-Term

- 2,300 patients randomized to 150 mg of alirocumab or placebo as a 1-mL subcutaneous injection every 2 weeks for 78 weeks.
- MACE reduced to 1.7% in the alirocumab group vs 3.3% in the placebo group (p=0.02)





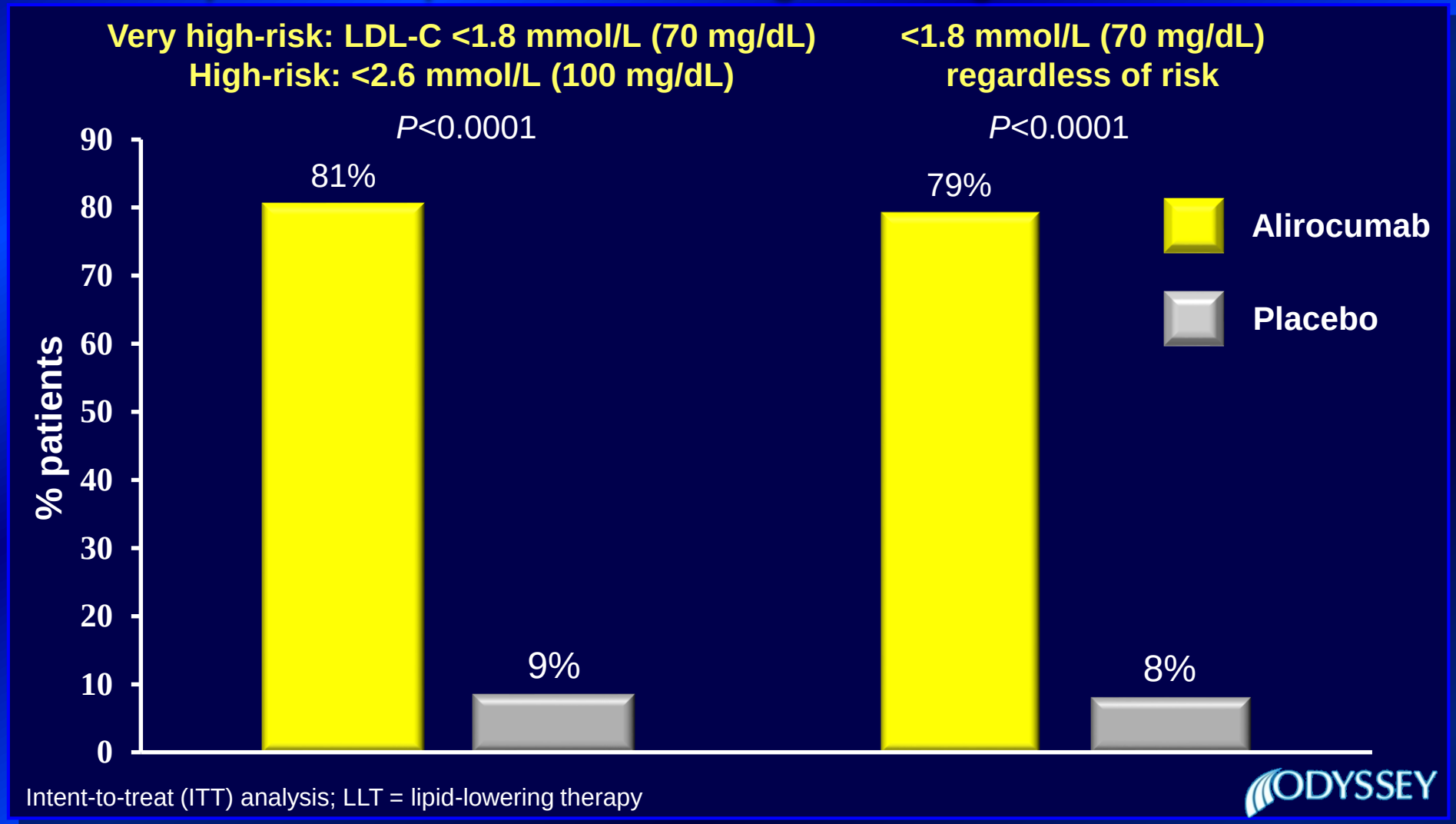
Shift in Distribution of LDL-C in a Population of High-Risk Individuals With Use of PCSK9 Inhibitor



Am Coll Cardiol 2015;65:2638–51

LONG TERM : Most Patients Receiving Alirocumab on Background Statin ± Other LLT Achieved LDL-C Goals

Proportion of patients reaching LDL-C goal at Week 24

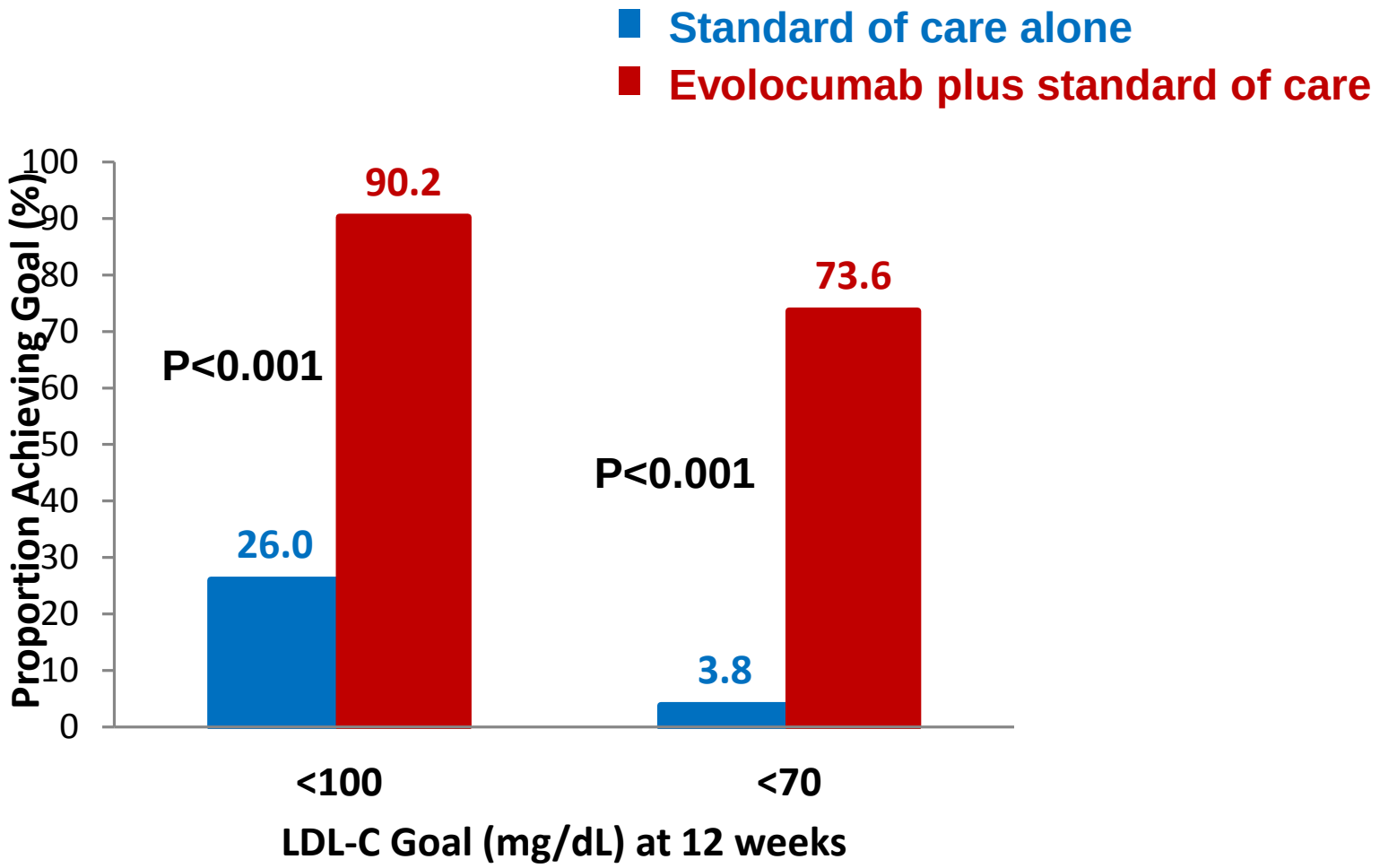


Intent-to-treat (ITT) analysis; LLT = lipid-lowering therapy

ODYSSEY

Robinson et al. N Enl J Med 2015;372(16):1489-99

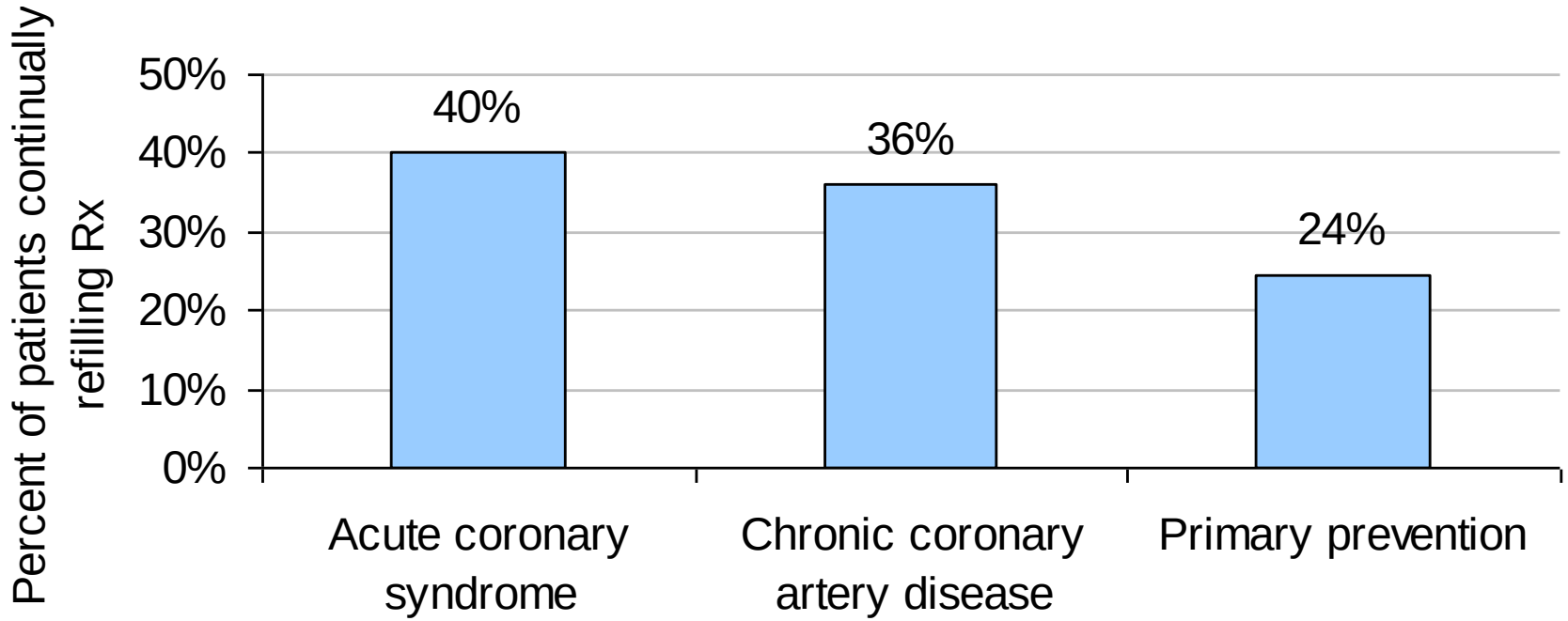
LDL Cholesterol Goals
73 % ACHIEVED <70 LDL



Use of COMBINATION OR ALTERNATE THEARPY to address statin intolerance and statin non adherence

CAN STATIN NON ADHERANCE AND INTOLERANCE AND ITS RESULTANT INCREASED CV RISK BE CHANGED ?

Adherence to statins after two years, by condition EVEN IN HIGH RISK



Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. JAMA 2002;288:462-467

Why don't patients adhere to their medication therapy?

- Complex therapies
- **Side Effects (WELL PUBLICIZED IN MEDIA)**
- Failure to understand the need for the medication
- High out-of-pocket costs

Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. JAMA 2002;288:455-461

Non-adherence—Mortality, Hospitalizations, ED Visits

- **Non-adherence causes ~30% to 50% of treatment failures and 125,000 deaths annually**
- ***Non-adherence to STATINS increased relative risk for mortality (~12% to 25%)***
- ***Non-adherence to cardioprotective medications increased risk of cardiovascular hospitalizations (10% to 40%) and mortality (50% to 80%)***
- **Poor adherence to heart failure medications increased the number of cardiovascular-related emergency department (ED) visits**

Sources: Ho 2009, Circulation; Edmondson 2013, Br J of Health Psychology; George & Shalansky 2006, Br J Clin Phar

Note the percentage in the placebo arm

Prevalance of SMS in JUPITER Study

Adverse Events and Measured Safety Parameters

Event	Rosuvastatin	Placebo	P
Any SAE	1352 (15.2)	1337 (15.5)	0.60
Muscle weakness	1421 (16.0)	1375 (15.4)	0.34
Myopathy	10 (0.1)	9 (0.1)	0.82
Rhabdomyolysis	1 (0.01)*	0 (0)	-
Incident cancer	298 (3.4)	314 (3.5)	0.51
Cancer deaths	35 (0.4)	58 (0.7)	0.02
Haemorrhagic stroke	6 (0.1)	9 (0.1)	0.44
GFR (mL/min/1.73m^2 at 12 months)	66.8 (59.1–76.5)	66.6 (58.8–76.2)	0.0
ALT > 3x ULN	23 (0.3)	17 (0.2)	0.34
Fasting glucose (24 months)	98 (91–107)	98 (90–106)	0.12
HbA1c (% at 24 months)	5.9 (5.7–6.1)	5.8 (5.6–6.1)	0.01
Glucosuria (12 months)	36 (0.5)	32 (0.4)	0.64
Incident diabetes**	270 (3.0)	216 (2.4)	0.01

*Occurred after trial completion, trauma induced. All values are median (interquartile range) or N (%); **Physician reported.
JUPITER, Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin.
Ridker PM, et al. N Engl J Med 2008;359:2195–207.

Insurance criteria Statin Intolerance

4. Is the patient intolerant (defined as the inability to tolerate any dose or increase the dose above the smallest tablet strength) to at least 2 different statins? ☐ Yes ☐ No
   If yes, please provide the statins tried and a description of the intolerance: _____

5. For **Initial Requests**, has the patient achieved less than 50% reduction in LDL-C while on a maximally tolerated lipid lowering regimen? ☐ Yes ☐ No

6. Is the requested medication being prescribed by a specialist in the area of practice related to the patient's diagnosis (e.g., cardiologist, lipidologist, or endocrinologist) or in consultation with a specialist? ☐ Yes ☐ No

7. Has the patient experienced any of the following cardiovascular events? (check all that apply)
   ☐ Acute coronary syndrome ☐ History of myocardial infarction ☐ Stable or unstable angina ☐ Transient ischemic attack
   ☐ Coronary or other arterial revascularization ☐ Stroke ☐ Peripheral arterial disease presumed to be of atherosclerotic origin

8. Please list all reasons for selecting the requested **medication, dosing schedule and quantity** over alternatives (e.g. contraindications, allergies or history of adverse drug reactions to alternatives, lower dose tried.) _____

9. Please list all medications the patient will use **in combination with the requested medication** for treatment of this diagnosis. _____

10. Please list all medications the patient has **previously tried and failed for treatment of this diagnosis.** _____

Please fax or mail this form to:
Prime Therapeutics LLC
Clinical Review Department
1305 Corporate Center Drive
Eagan, Minnesota 55121
TOLL FREE

Summary

- SMS is a real phenomenon
  - Major reason for statin non-adherence/discontinuation
  - Contributes to decreased CVD benefit by statins
- Current incidence is ‘too’ high, emphasising the need for ‘elaborate’ selection of SMS patients
  - Characteristic clinical presentation (location/time course)
  - Apply repetitive de/rechallenges with alternative statins
- The unmet need in these SMS patients can be met using non-statin strategies
  - PCSK9-ab offers 50–60% LDL-C reduction with minimal side effects in SMS patients

The GAUSS-3 Trial

Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects-3

Steven E. Nissen MD MACC*
Erik Stroes MD PhD

***Disclosure**

Study Sponsor: Amgen
Consulting: Many pharmaceutical companies
Clinical Trials: Amgen**,** AstraZeneca, Cerenis, Eli Lilly, Novartis, Novo Nordisk, The Medicines Company, Orexigen, Takeda, and Pfizer.
Companies are directed to pay any honoraria, speaking or consulting fees directly to charity so that neither income nor tax deduction is received.

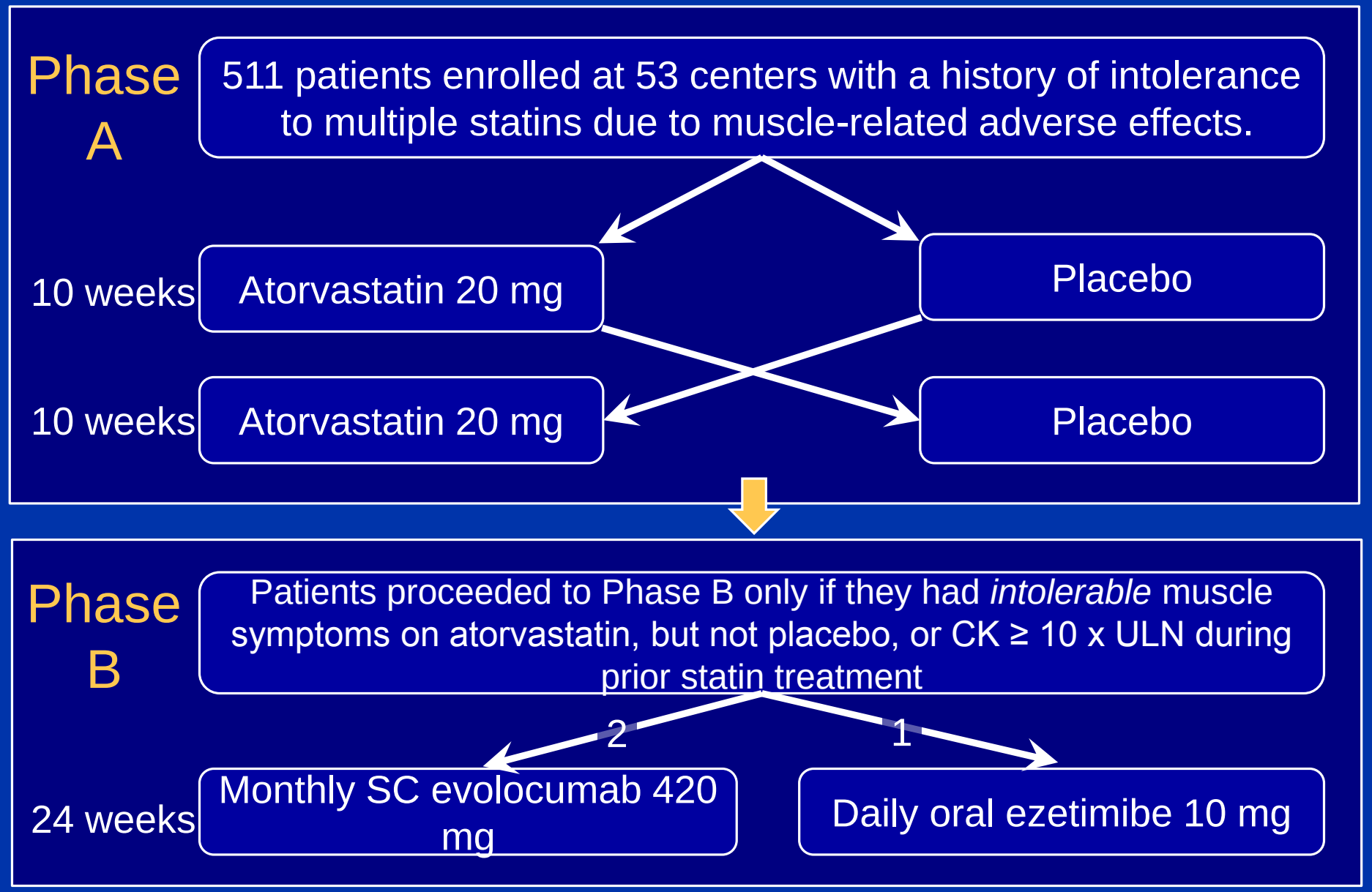
SMS

Controversy has surrounded the issue of statin- associated muscle symptoms because of large differences in the incidence of this disorder in randomized trials and observational studies.

The GAUSS-3 trial demonstrates that muscle-related **intolerance is reproducible during blinded statin rechallenge in a substantial fraction (about 40%)** of patients with a history of symptoms.

Accordingly, development of alternative approaches to LDL-C reduction for these patients represents an important medical priority.

Study Design: Two Double-Blind Phases



Selected Baseline Characteristics

Characteristic	Phase A (n=491)	Phase B (n=218)	
		Ezetimibe (n=73)	Evolocumab (n=145)
Age (years)	61	59	59
Male Gender	50%	47%	54%
Coronary Heart Disease	35%	29%	33%
NCEP-ATP III High Risk	63%	52%	58%
Intolerance to ≥ 3 statins	**82%**	82%	82%
Total Cholesterol (mg/dL)	301	308	307
LDL-C (mg/dL)	**212**	222	219
HDL-C (mg/dL)	51	50	50

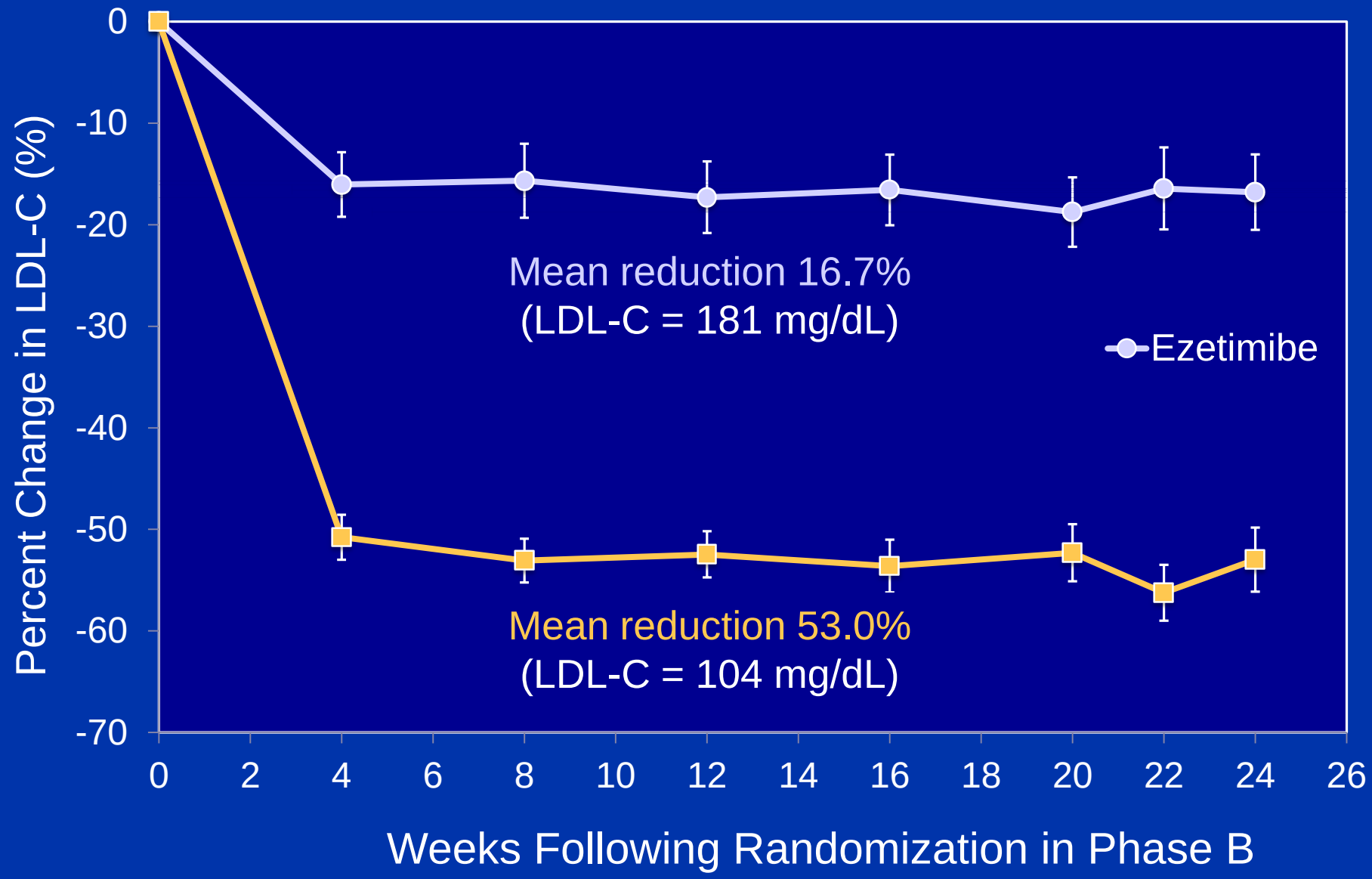
Phase A: Study Drug Discontinuation Events

***Intolerable* Muscle Symptoms**	**N = 491**
On atorvastatin, but not placebo	209 (42.6%)*
On placebo, but not atorvastatin	130 (26.5%)
On both placebo and atorvastatin	48 (9.8%)
No symptoms on either treatment	85 (17.3%)
Did not complete Phase A	*20/511*

Bypassed Phase A due to CK elevation ≥ 10 x ULN	19 (3.9%)*

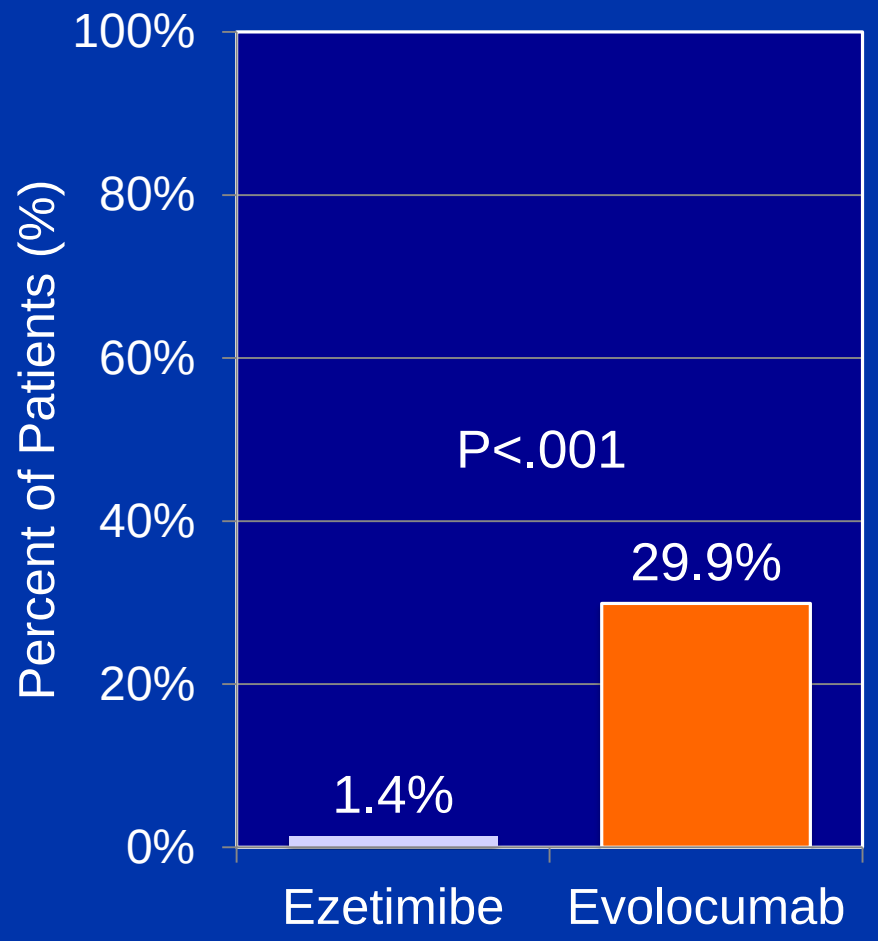
**218 of these 228 eligible patients proceeded to Phase B*

LDL-C Values Over Time During Phase B

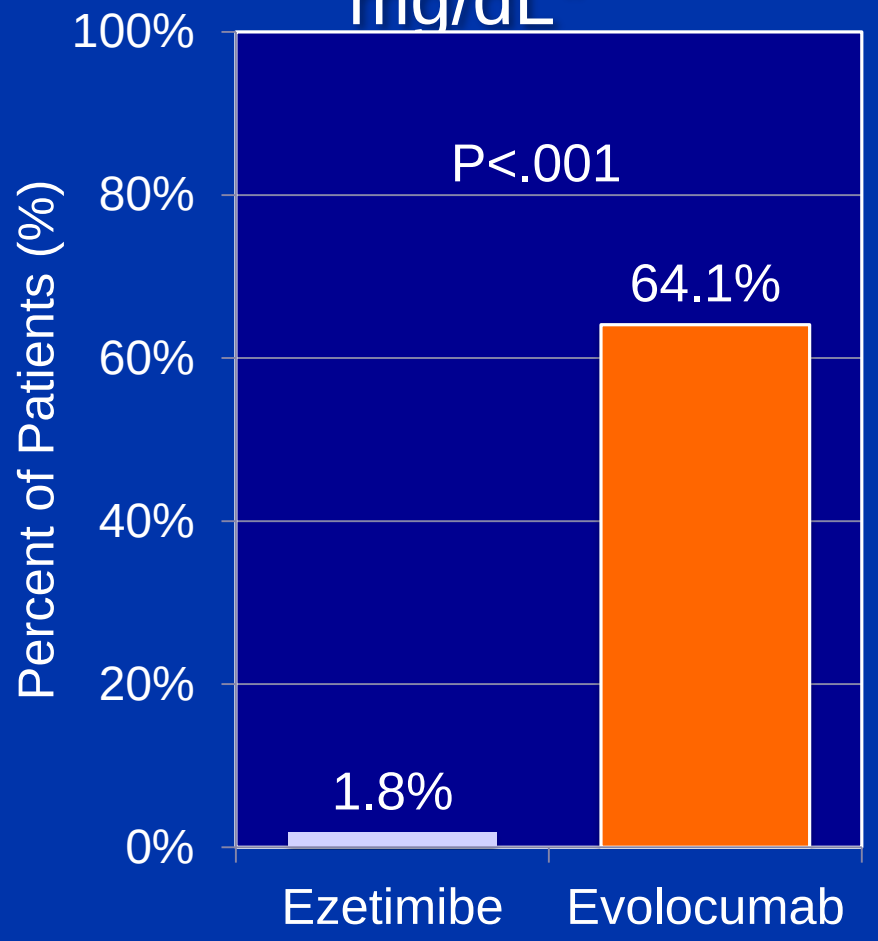


Achievement of Common LDL-C Target Levels
65% OF TRUE SMS PTS DID ACHIEVE A TARGET

LDL-C < 70 mg/dL

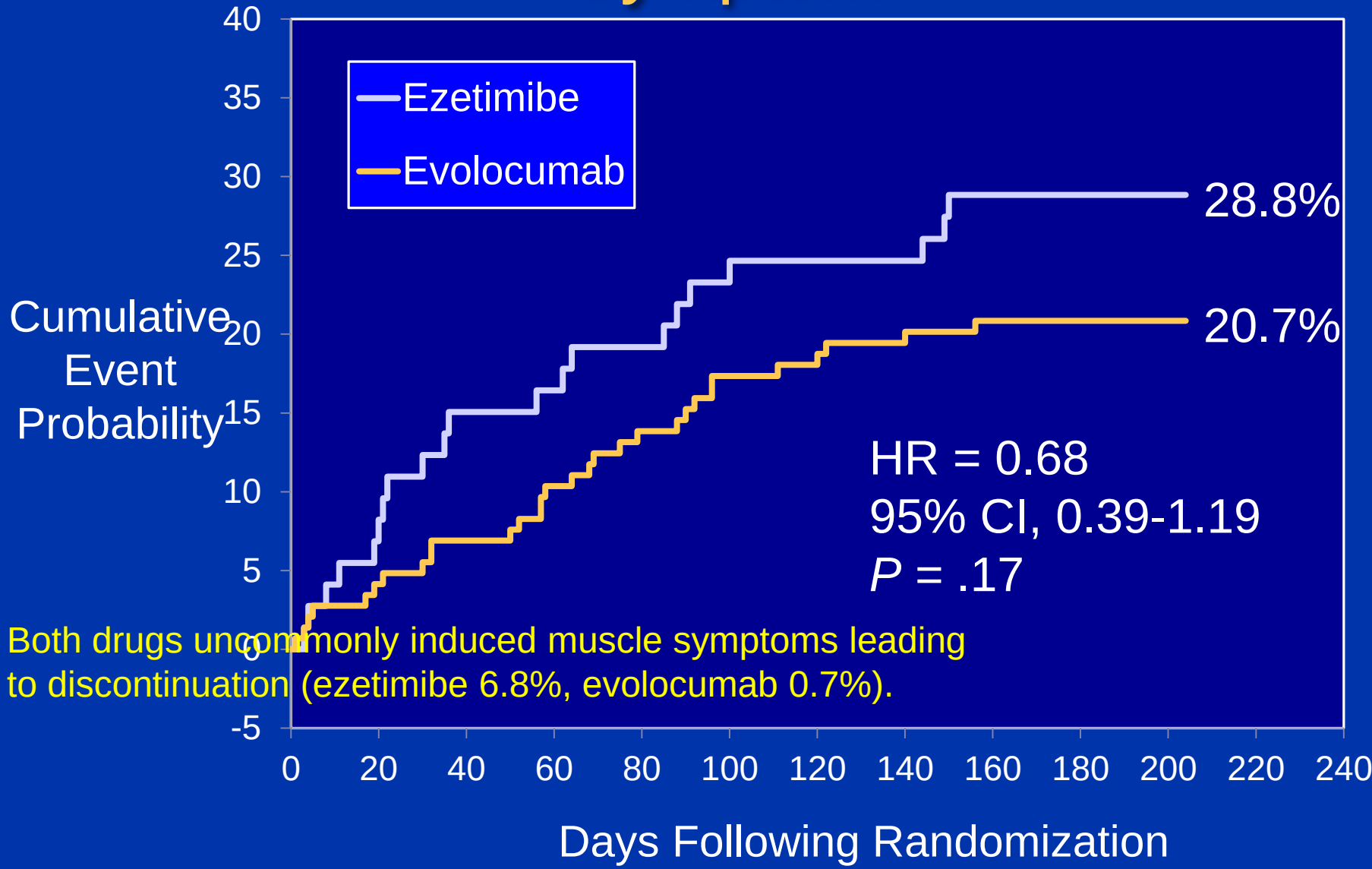


LDL-C < 100 mg/dL*



*not a protocol prespecified analysis

Phase B: Time to Any Muscle-Related Symptom



Both drugs uncommonly induced muscle symptoms leading to discontinuation (ezetimibe 6.8%, evolocumab 0.7%).

Conclusions

- A substantial proportion (42.6%) of patients with a history of muscle-related statin intolerance have symptoms when re-challenged with atorvastatin 20 mg, but not placebo.
- A smaller fraction of patients (26.5%) report muscle-related symptoms when administered placebo, but not atorvastatin.
- In patients with statin-associated muscle symptoms, evolocumab, compared with ezetimibe, produced significantly larger reductions in LDL-C and other atherogenic lipoproteins.
- Both drugs uncommonly induced muscle symptoms leading to discontinuation (ezetimibe 6.8%, evolocumab 0.7%).

Patient Populations with HIGH Unmet Need for Additional LDL-C Lowering

FH Population in EU	High / Very High CV Risk Population	Statin-Intolerant Population
• Genetic disorder • High risk of early CHD • HeFH prevalence 1:200 to 1:250[1,2] • Untreated LDL-C of 200-400 mg/dL[3]	• Previous MI/stroke / CVD or multiple CV risk factors incl. T2DM • Difficult to achieve LDL-C goals, despite current therapies[5]	• 10-15% on high-intensity statins show intolerance[6] • Many discontinue due to muscle pain and/or weakness
79% with HeFH not at goal (<100 mg/dL [2.6 mmol/L])[4]	**• 20% with CHD not at goal (<100 mg/dL [2.6 mmol/L])** **• 59% at very high CV risk not at goal (<70 mg/dL [1.8 mmol/L])**	**Nearly all patients who need considerable LDL-C reductions will not reach goal**

[1]Nordestgaard et al. *Eur Heart J* 2013;34:3478-90. [2]Sjouke et al. *Eur Heart J.* 2015 Mar 1;36(9):560-5.
[3] 2011 ESC/EAS Guidelines for the management of dyslipidaemias Eur Heart J. 2011;32(14):1769-818.
[4] Pijlman et al. *Atherosclerosis* 2010;209:189-94. [5] Virani et al. *Am Heart J* 2011;161:1140-6.
[6] Arca et al. *Diabetes Metab Syndr Obes* 2011;4:155-66.

JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents

Endorsed by the National Lipid Association

WRITING COMMITTEE

Donald M. Lloyd-Jones, MD, FACC, Chair
Pamela B. Morris, MD, FACC, Vice Chair
Christie M. Ballantyne, MD, FACC
Kim K. Birtcher, PharmD, AACC
David D. Daly, Jr, MD
Sondra M. DePalma, MHS, PA-C, CLS AACC
Margo B. Minissian, PhDc, ACNP, AACC
Carl E. Orringer, MD, FACC, FNLA*
Sidney C. Smith, Jr, MD, FACC

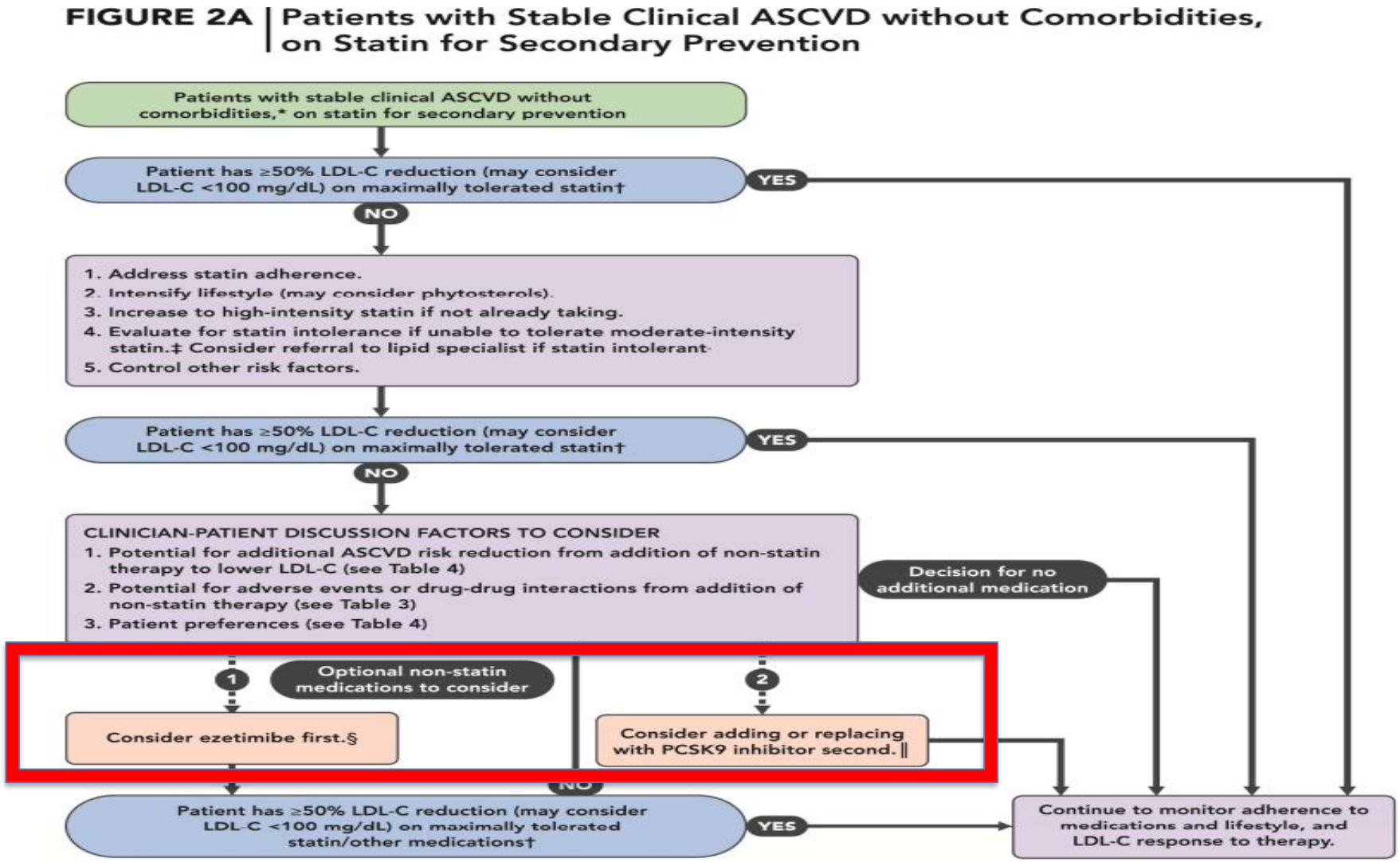
Guideline Update 2016
COMBINATION THERAPY

- Incorporates RCT data since 2013 as well as expert consensus
- Clearly addresses benefit in RCT from non statin therapies
- Re assesses the high risk groups that residual risk and further management of dyslipidemia that benefit from PCSK9 and Ezitimibe with no evidence of harm
- Niacin and fibrates as add on therapy remain out - lack of benefit and possible harm

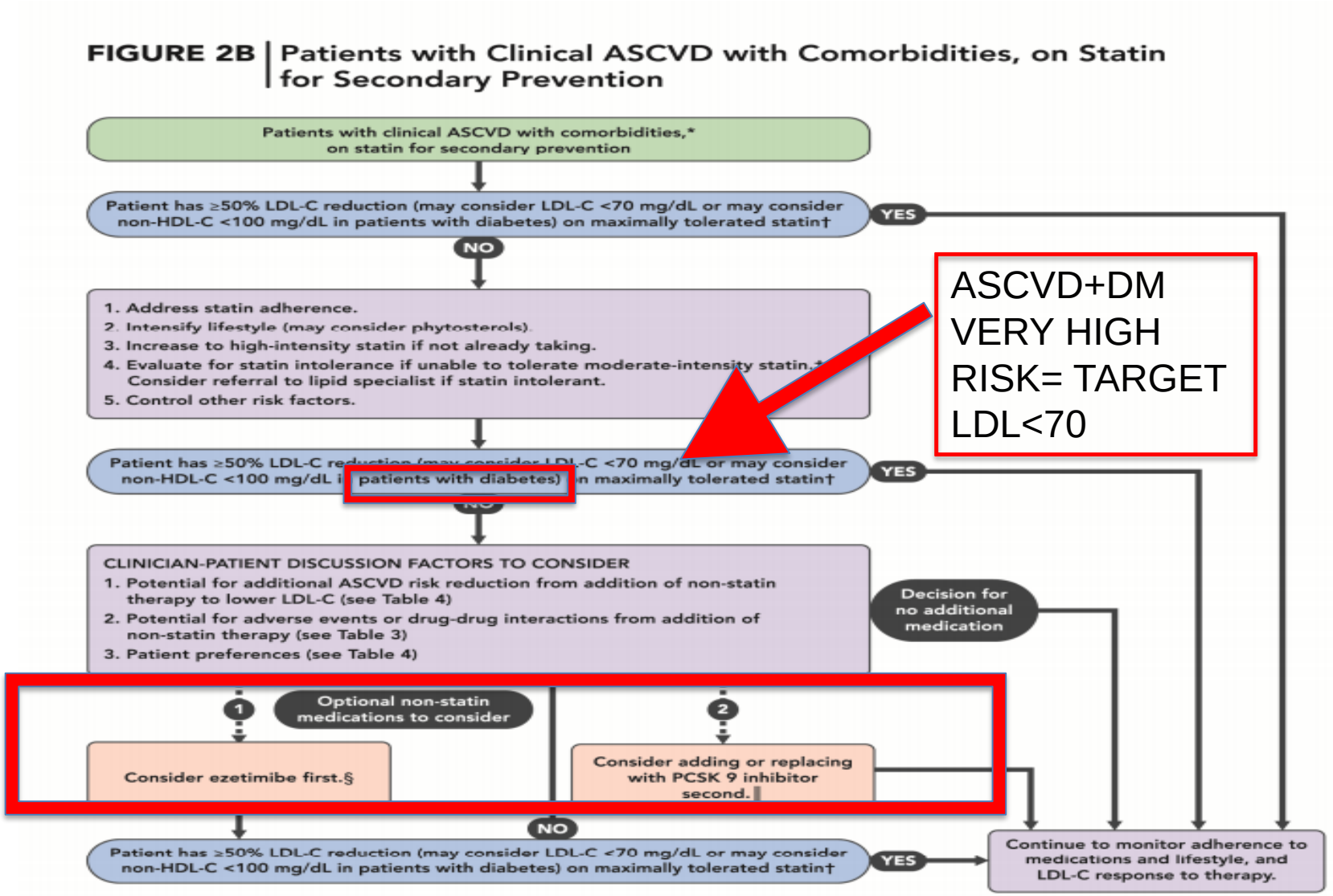
HIGH RISK MARKERS

- The Committee identified several high-risk markers that may be informative, including:
- 10-year ASCVD risk ≥20%;
- Primary LDL-C ≥160 mg /dL at baseline;
- Other major ASCVD risk factor(s) that are poorly controlled
- Family history of premature ASCVD with or without elevated lipoprotein(a)
- Evidence of accelerated subclinical atherosclerosis (e.g., coronary artery calcification)
- Elevated hs-CRP; and other risk-modifying conditions, such as CKD, HIV, and chronic inflammatory disorders.

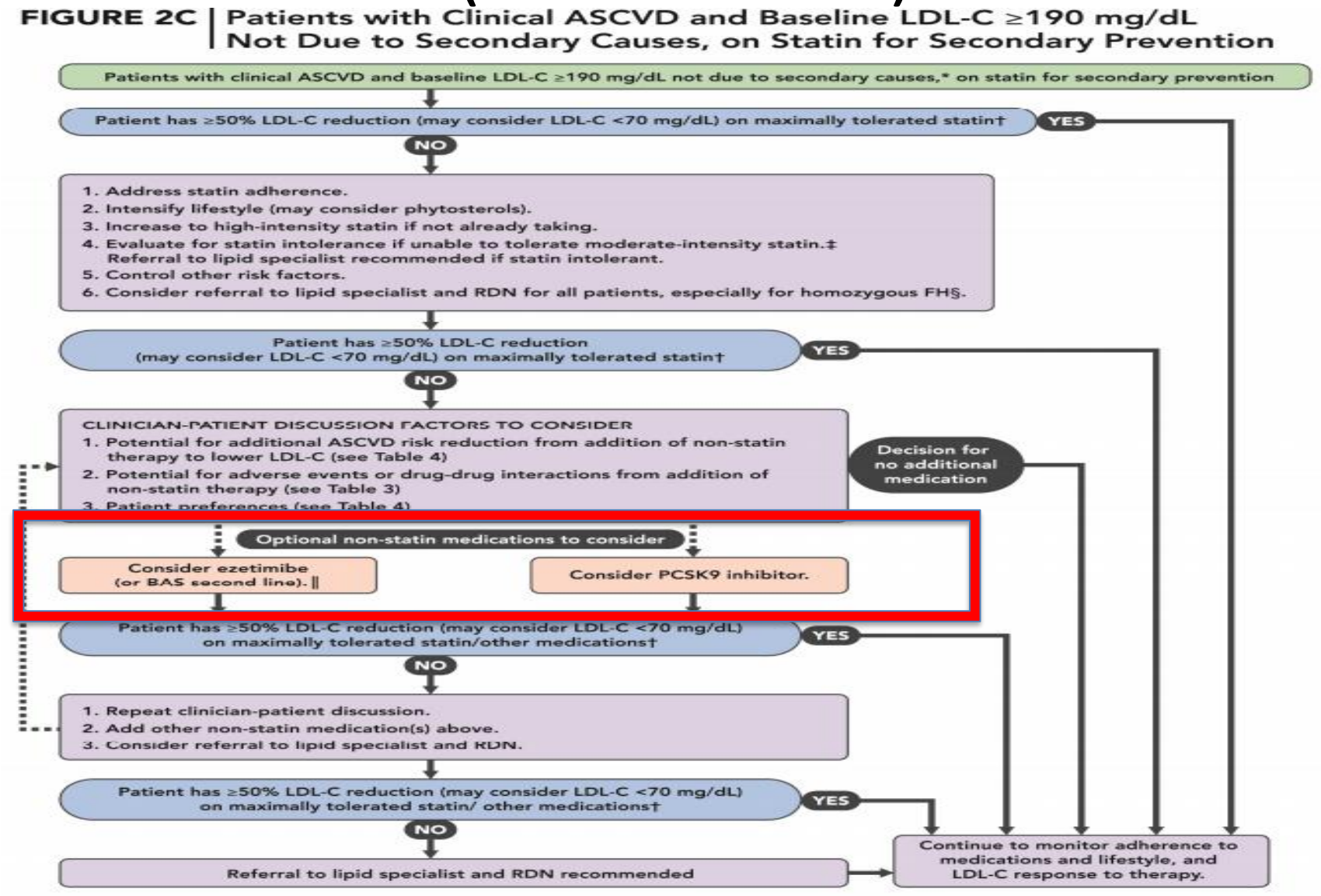
1-SECONDARY PREVENTION CVD ALREADY ON STATIN



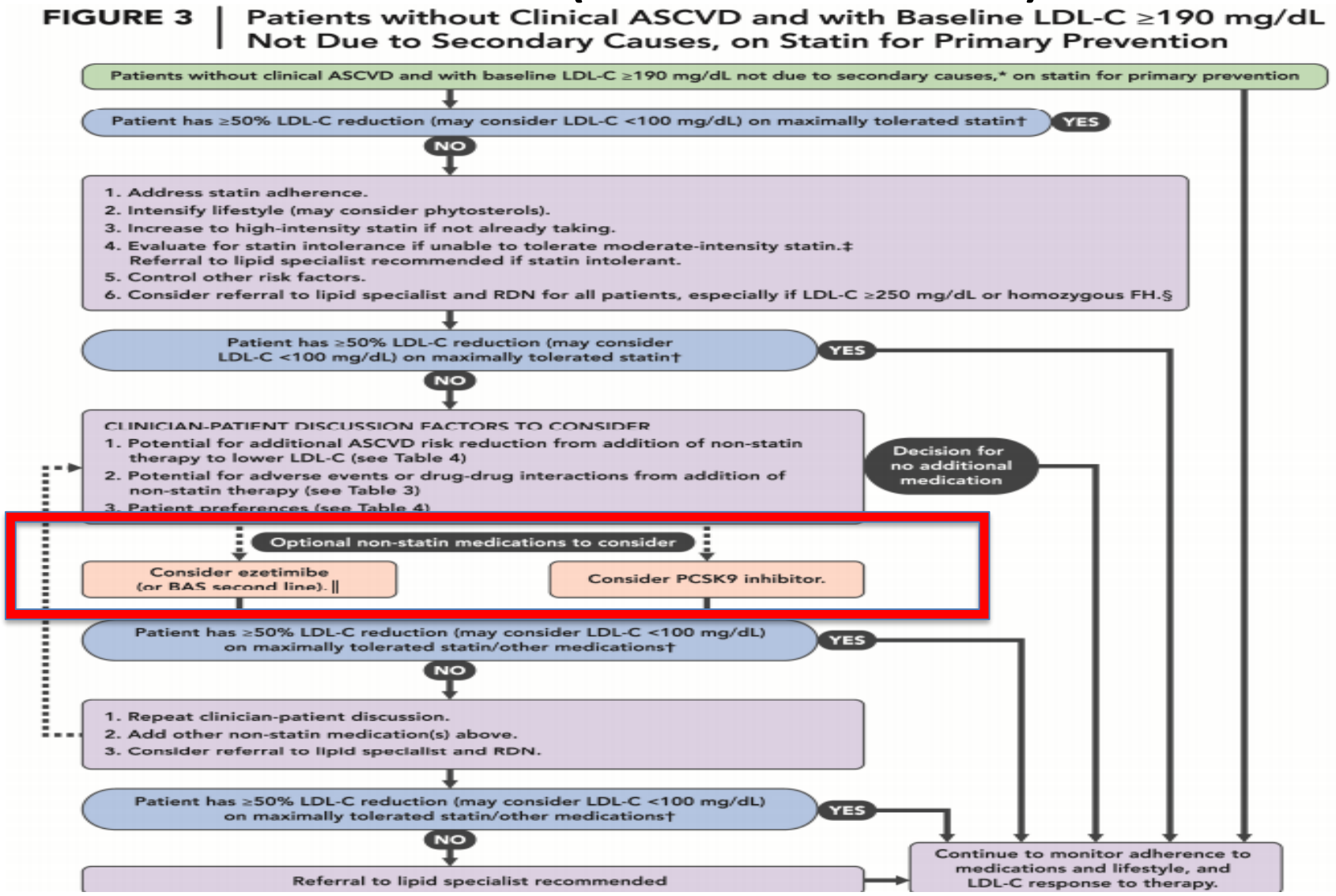
2-Patient with established ASCVD and Comorbiditites SECONDARY PREVENTION OF CVD ON STATIN



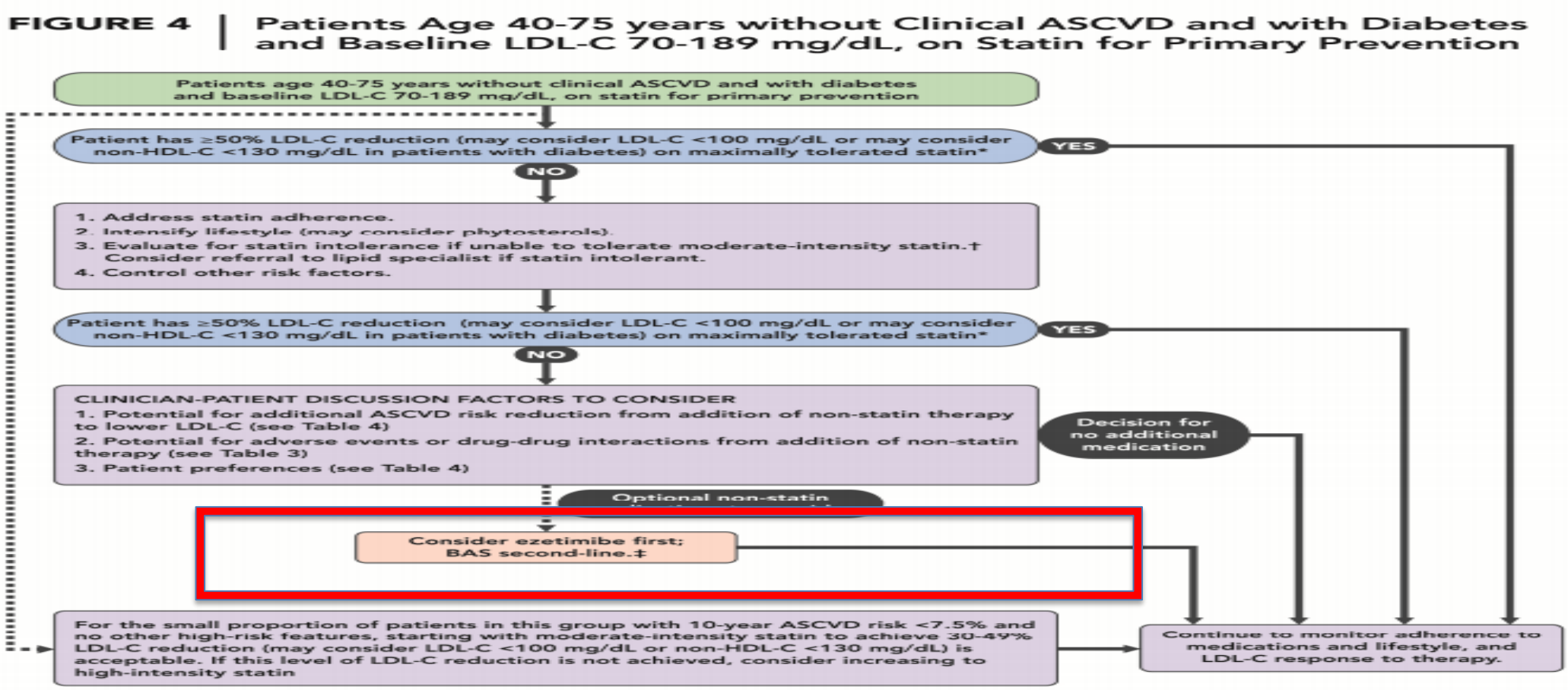
3-SECONDARY PREVENTION , LDL>190 ON STATIN (LIKELY HEFH)



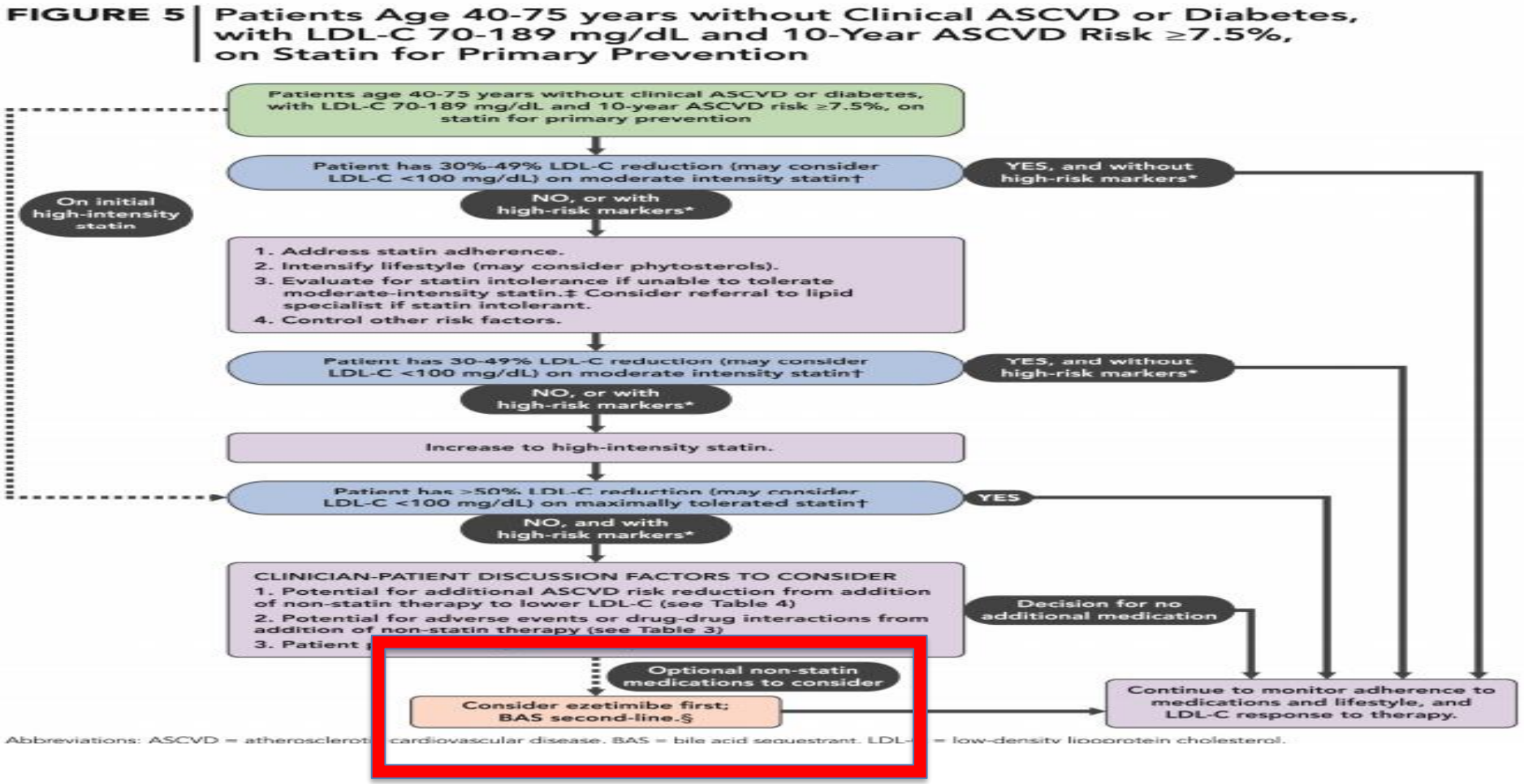
4-PRIMARY PREVENTION & PRIMARY LDL >190 , ON STATIN(LIKELY HEFH)



5-DIABETICS 40-75 , LDL 70-190 , ON STATIN FOR PRIMARY PREVENTION



6-PRIMARY PREVENTION , 40-75 YEARS , LDL 70-190 & CVD RISK >7.5%



- Diagnose & manage secondary causes of dyslipidemia
- Optimally manage other ASCVD risk factors
- Implement appropriate nutrition and physical activity

Administer maximally tolerated statin

Lipid blood testing to assess if LDL-C level exceeds "threshold" LDL OF 70 (or 100) treatment level. If so . . .

Add non-statin therapy

Reassess &Treat to lipid "goals"

2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

"If, after these interventions, the patient still has <50% reduction in LDL-C (and may consider LDL-C ≥70 mg/dL), the patient and clinician should enter into a discussion focused on shared decision making regarding the addition of a non-statin medication to the current regimen.

2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

”In the opinion of the Expert Consensus Writing Committee, in a patient with ASCVD and baseline LDL-C ≥190 mg/dL* with <50% reduction in LDL-C (and may consider LDL-C ≥70 mg/dL) it is reasonable to consider a PCSK9 inhibitor as a first step rather than ezetimibe or BAS given PCSK9 inhibitors’ greater LDL-C lowering efficacy.”

*THESE ARE PROBABLE HEFH PTS

European Heart Journal Advance Access published May 23, 2016

Combination Therapy Updates:

- Data indicate that combination therapy with ezetimibe also brings a benefit that is in line with the Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis supporting the notion that LDL-C reduction is key to the achieved benefit independent of the approach used.

- **They are recommended as combination therapy with statins in selected patients when a specific goal is not reached with the maximal tolerated dose of a statin.**

- **Patients with dyslipidaemia, particularly those with established CVD, DM or asymptomatic high-risk individuals, may not always reach treatment goals, even with the highest tolerated statin dose.**

- Therefore, combination treatment may be needed. **It must be stressed, however, that the only combination that has evidence of clinical benefit (one large RCT) is that of a statin combined with ezetimibe**

European Heart Journal Advance Access published May 23, 2016

PCSK9 Inhibitors

- Regarding new therapies, recent data from phase I–III trials show that PCSK9 inhibitors sharply decrease LDL-C by up to 60%, either as monotherapy or in addition to the maximal statin dose.
- Whether this approach results in the predicted reduction in CV events is being addressed in large outcome trials; preliminary evidence suggests that this is the case.

When to consider PCSK9 Inhibitors

1. FH-Het.
2. High risk patients with ASCVD (recurrent ASCVD events).
3. Patients with ASCVD not attaining the goal on maximally tolerated Statin and Ezetimibe.
4. Statin Intolerance.

Thank You