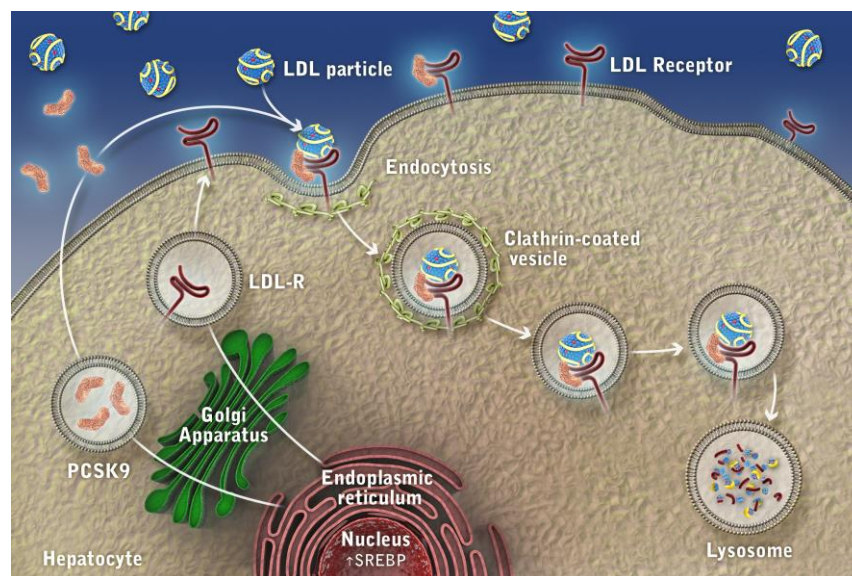


Lo mejor del año en 10 minutos:

Lípidos



Jacinto Fernández Pardo

Hospital General Universitario Reina Sofía de Murcia

XI Reunión de Riesgo Vascular

Madrid, 24 de abril de 2015

Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults

THE THIRD REPORT OF THE EXPERT PANEL ON DETECTION, EVALUATION, AND TREATMENT OF HIGH BLOOD CHOLESTEROL IN ADULTS (ADULT TREATMENT PANEL III, OR ATP III) constitutes the National Cholesterol Education Program's (NCEP's) updated clinical guidelines for cholesterol testing and management. The full ATP III document is an evidence-based and extensively referenced report that provides the scientific rationale for the recommendations contained in the executive summary. ATP III builds on previous reports and expands on intensive cholesterol management in clinical practice that these guidelines form, not replace, and judgment, to determine the appropriate management of each individual.

BACKGROUND
The third ATP III is a continuing management of the second. The NCEP updates ATP III clinical guidelines for cholesterol management.

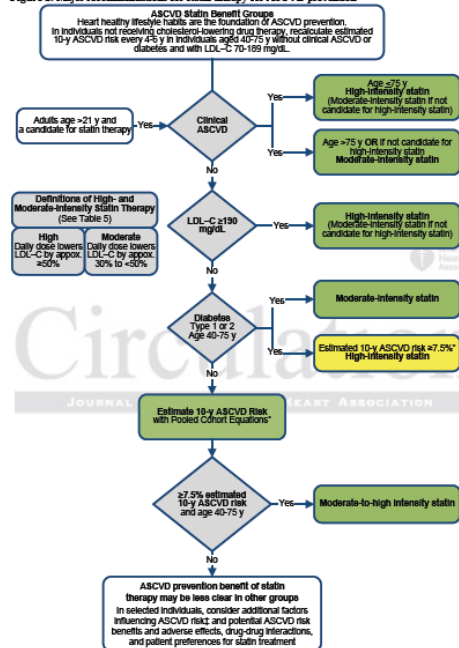
See also p 250

2486 JAMA, May 1

has a major thrust. ATP I outlined a strategy for primary prevention of coronary heart disease (CHD) in persons with high levels of low-density lipoprotein (LDL) cholesterol (≥ 160 mg/dL) or those with borderline high LDL cholesterol (130–159 mg/dL) and multiple (2+) risk factors. ATP II affirmed the importance of this approach and added a new feature: the intensive management of LDL cholesterol in persons with established CHD. For patients with CHD, ATP II set a lower LDL cholesterol goal of ≤ 100 mg/dL. ATP III adds a call for more intensive LDL-lowering therapy in certain groups of people, in certain clinical trial settings, and genetic forms of hypercholesterolemia indicate that elevated LDL cholesterol is a major cause of CHD. In addition, recent clinical trials robustly show that LDL-lowering therapy reduces risk for CHD for these reasons. ATP III also identifies newly elevated LDL cholesterol as a primary target for treatment.

Stone NJ, et al.
2013 ACC/AHA Blood Cholesterol Guideline

Figure 2. Major recommendations for statin therapy for ASCVD prevention



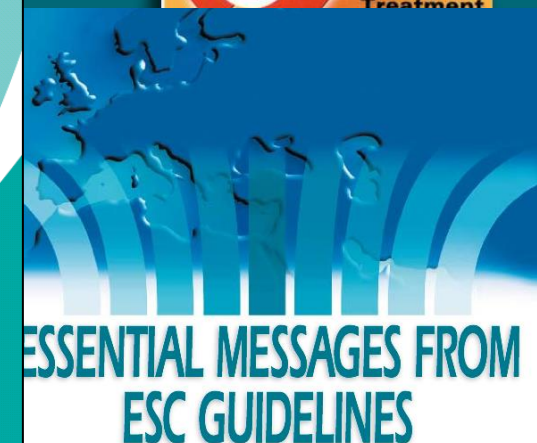
Quick reference guide

Issue date: May 2008 (reissued March 2010)

Lipid modification

Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease

NICE clinical guideline 67
Developed by the National Collaborating Centre for Primary Care



Committee for Practice Guidelines
To improve the quality of clinical practice and patient care in Europe



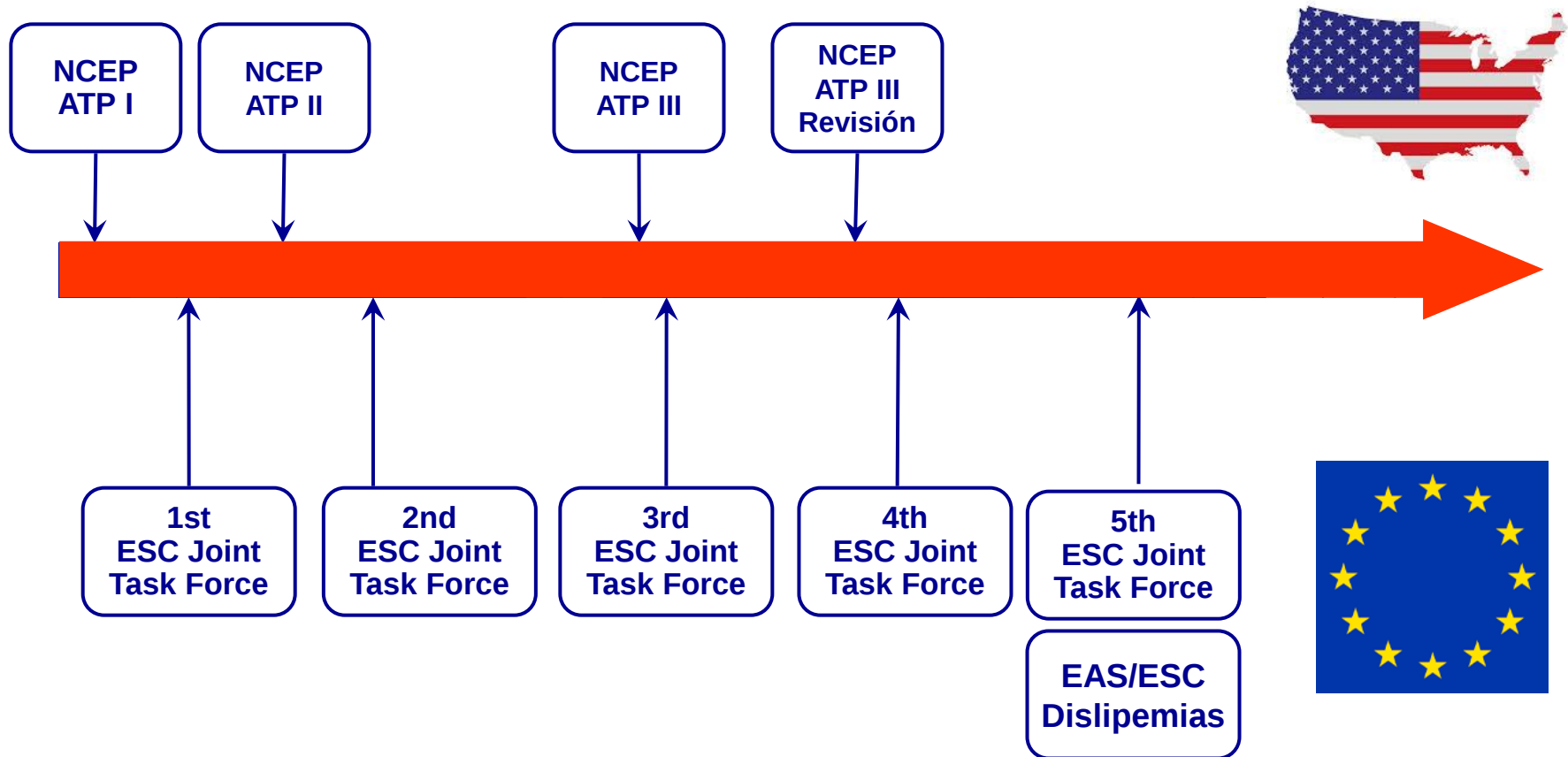
DYSLIPIDAEMIAS

ESC/EAS GUIDELINES
FOR THE MANAGEMENT OF DYSLIPIDAEMIAS

For more information
www.escardio.org/guidelines

- 10-year CHD Risk Calculator
- Other Cholesterol-Related Information

Evolución temporal de las guías





c-LDL

Objetivos terapéuticos c-LDL

Pacientes	Objetivo c-LDL	Clase	Nivel
Pacientes con riesgo “muy alto”	< 70 mg/dL (<1,8 mmol/l) y/o reducción del c-LDL > 50% cuando no pueda alcanzarse el objetivo	I	A^{1,2,3}
Pacientes con riesgo “alto”	< 100 mg/dL (<2,5 mmol/l)	Ila	A^{1,4,5}
Pacientes de riesgo “moderado”	< 115 mg/dL (< 3 mmol/l)	Ila	C

1. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA. 2005; 294:2437-45.
2. LaRosa JC, Grundy SM, Waters DD, et al; Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005; 352:1425-35.
3. Brugts JJ, Yetgin T, Hoeks SE, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. BMJ. 2009; 338:b2376.
4. Mills EJ, Rachlis B, Wu P, Devereaux PJ, Arora P, Perri D. Primary prevention of cardiovascular mortality and events with statin treatments. A network metaanalysis involving more than 65,000 patients. J Am Coll Cardiol. 2008; 52:1769-81. safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet. 2010; 376:1670-81.
5. Pedersen TR, Faergeman O, Kastelein JJ, et al; Incremental Decrease

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Neil J. Stone, Jennifer Robinson, Alice H. Lichtenstein, C. Noel Bairey Merz, Conrad B. Blum, Robert H. Eckel, Anne C. Goldberg, David Gordon, Daniel Levy, Donald M. Lloyd-Jones, Patrick McBride, J. Sanford Schwartz, Susan T. Shero, Sidney C. Smith, Jr, Karol Watson and Peter W.F. Wilson

Circulation. published online November 12, 2013;

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a.citation>

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines



~~c-LDL~~

ESTATINAS

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

4 Grupos de tratamiento

Pacientes >21 a. con	Subgrupo	Trat. Estático
1. Enf. Cardiovascular	≤ 75 años > 75 años	Alta potencia Moderada potencia
2. cLDL ≥ 190 mg/dL		Alta potencia
3. 40-75 años DM 1 ó 2	RCV $\geq 7,5\%$ RCV $< 7,5\%$	Alta potencia Moderada potencia
4. 40-75 años RCV $\geq 7,5\%$		Moderada/alta potencia

10-Year ASCVD Risk

7.9%
calculated risk

6.3%
risk with optimal risk factors**

Lifetime ASCVD Risk



Lifetime Risk Calculator only provides lifetime risk estimates for individuals 20 to 59 years old

Recommendations

Gender

Male Female

Total Cholesterol (mg/dL)

160

Treatment for Hypertension

Yes **No**

Age

61



Note: Lifetime risk is only calculated for the 20 to 59 year range

HDL - Cholesterol (mg/dL)

50

Diabetes

Yes **No**

Race

☒ **White**
☐ **African American**
☐ **Other**

Systolic Blood Pressure

130

Smoker

Yes **No**

*Intended for use if there is not ASCVD and the LDL-cholesterol is <190 mg/dL

**Optimal risk factors include: Total cholesterol of 170 mg/dL, HDL-cholesterol of 50 mg/dL, Systolic BP of 110 mm Hg, Not taking medications for hypertension, Not a diabetic, Not a smoker

Colesterol LDL= 80 mg/dL; TG= 150 mg/dL



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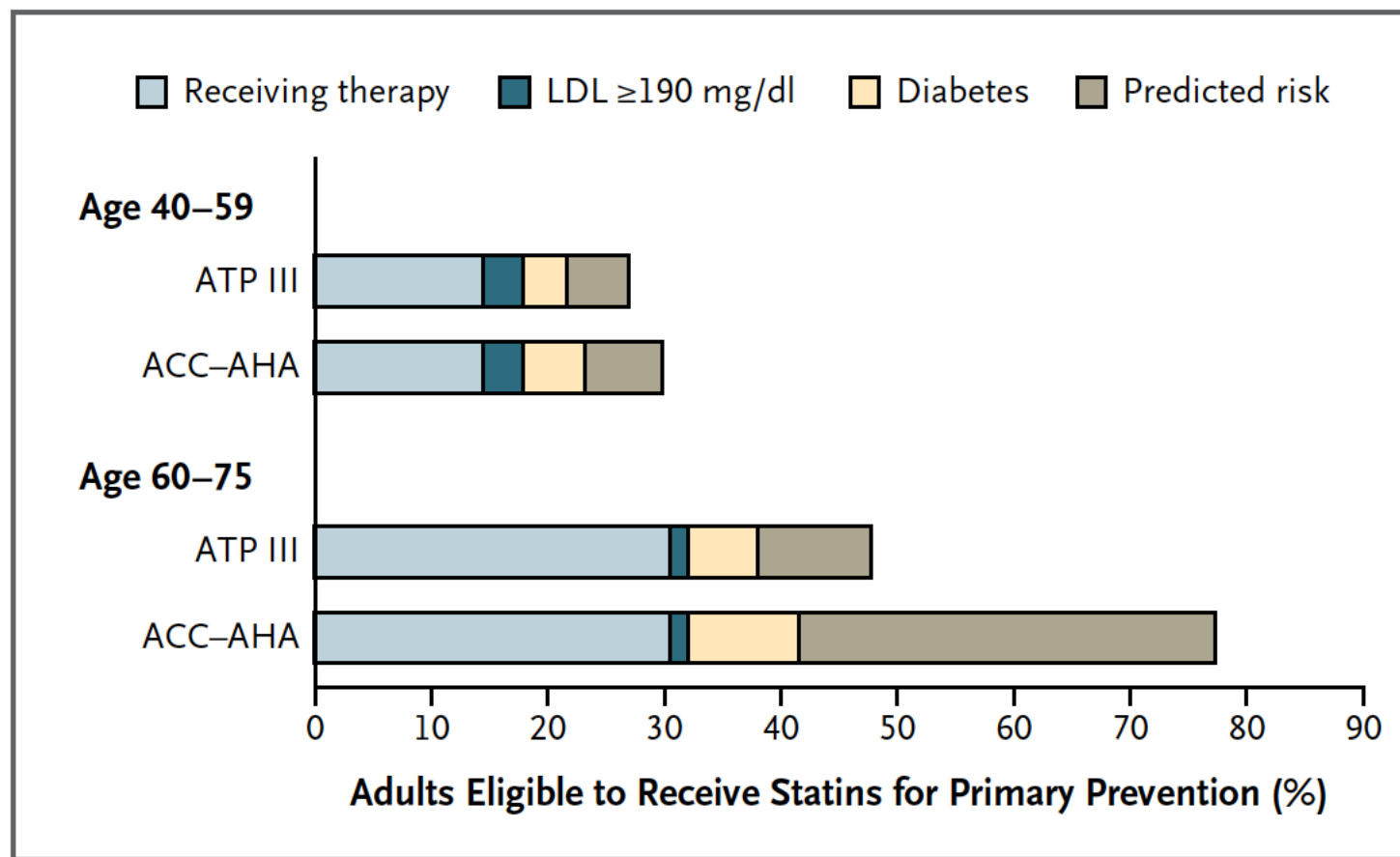


American
Heart
Association

Published jointly by ACC and AHA | © 2014

Percent of U.S. Adults Who Would Be Eligible for Statin Therapy for Primary Prevention

According to Set of Guidelines and Age Group



Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease

Issued: July 2014 last modified: September 2014

NICE clinical guideline 181

guidance.nice.org.uk/cg181

<http://www.nice.org.uk/guidance/cg181>

NICE guidelines [CG181]

Lipid modification

Prevención 1ª:

Ofrecer Atorvastatina 20mg/día a pacientes con RCV >10% a 10 años (QRISK2)

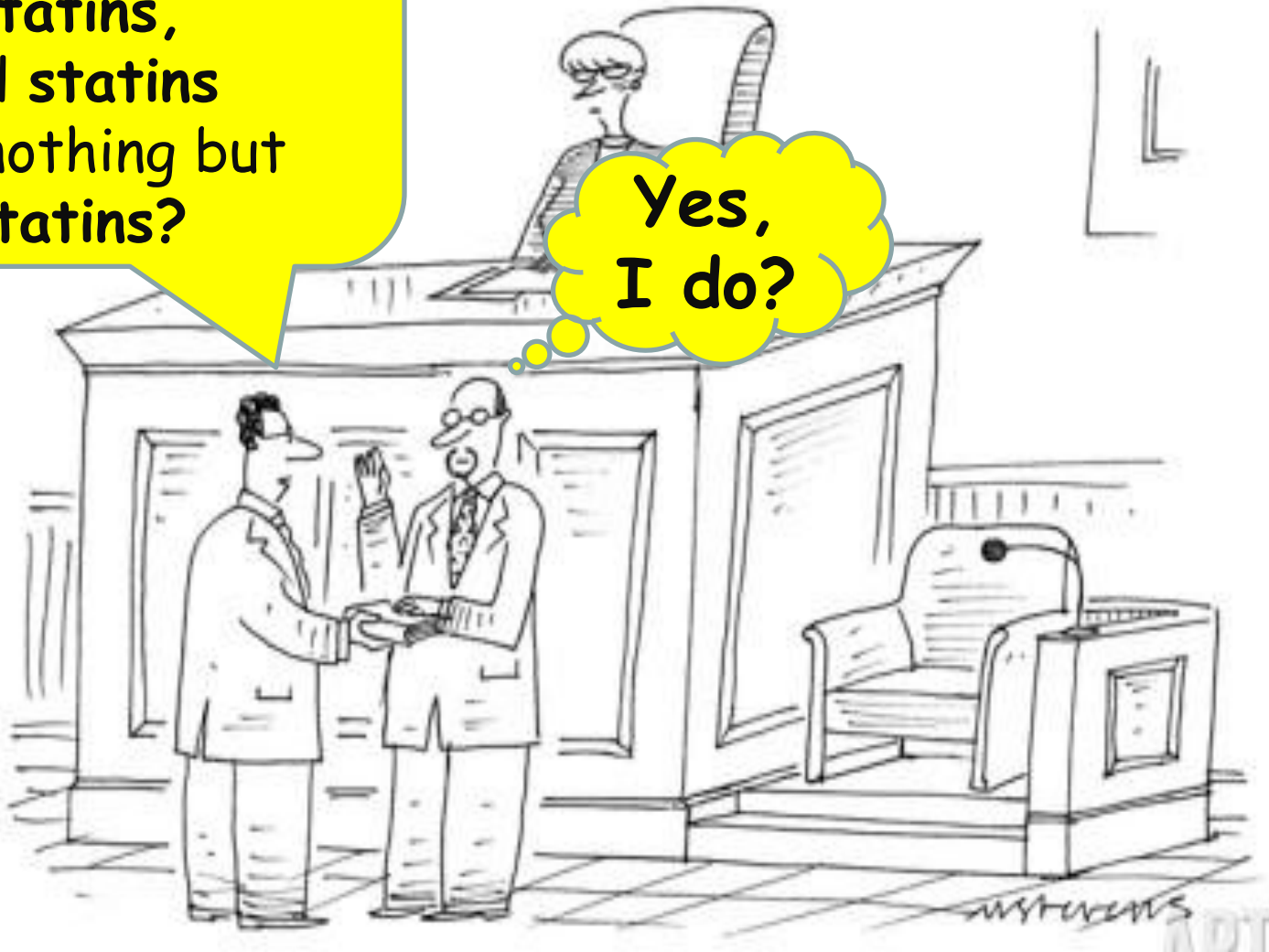
Prevención 2ª:

Iniciar Atorvastatina 80mg/día a pacientes con ECV, considerando una menor dosis en caso de interacciones, riesgo de efectos adversos muy alto y preferencia del paciente

Do you solemnly
swear to prescribe
statins,
all statins
and nothing but
statins?

New cholesterol
guidelines Court

Yes,
I do?





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SCIENCE FROM NEWS
SS14
SCIENTIFIC SESSIONS



IMPROVE-IT Trial: A Comparison of Ezetimibe/Simvastatin versus Simvastatin Monotherapy on Cardiovascular Outcomes After Acute Coronary Syndromes

Christopher P Cannon | Brigham and Women's Hospital Boston, MA

[Presentation Slides \(PDF\)](#) | [Summary Slide \(PDF\)](#) | [Abstract \(PDF\)](#) | [Discussant Slides \(PDF\)](#) | [News Release](#) | [Video Interview \(opens in a new window\)](#) | [Video Round-Table \(opens in a new window\)](#)

http://my.americanheart.org/professional/Sessions/ScientificSessions/ScienceNews/SS14-Late-Breaking-Clinical-Trials_UCM_468855_Article.jsp

Study Design



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*

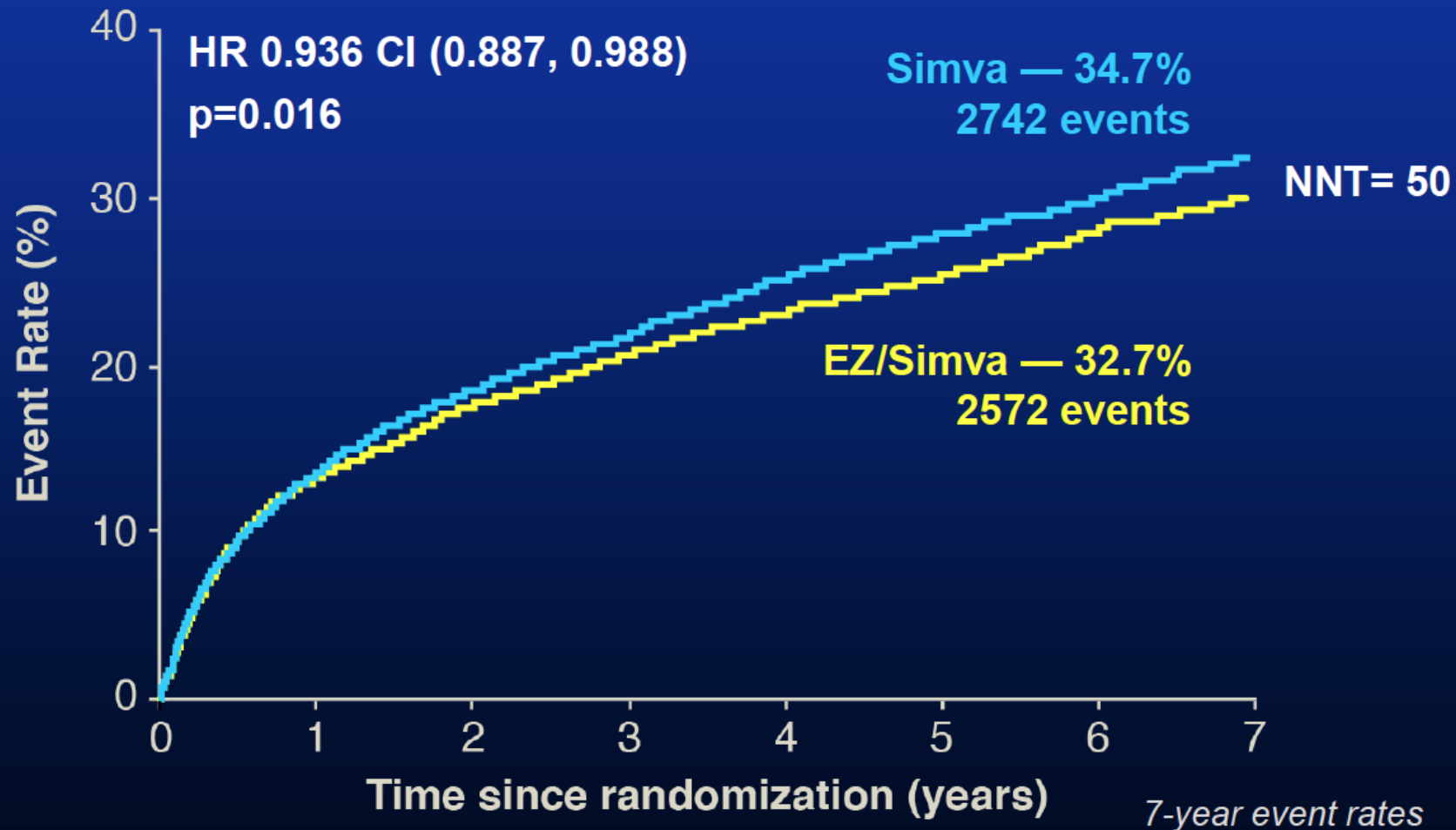
Duration: Minimum 2 ½-year follow-up (at least 5250 events)

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

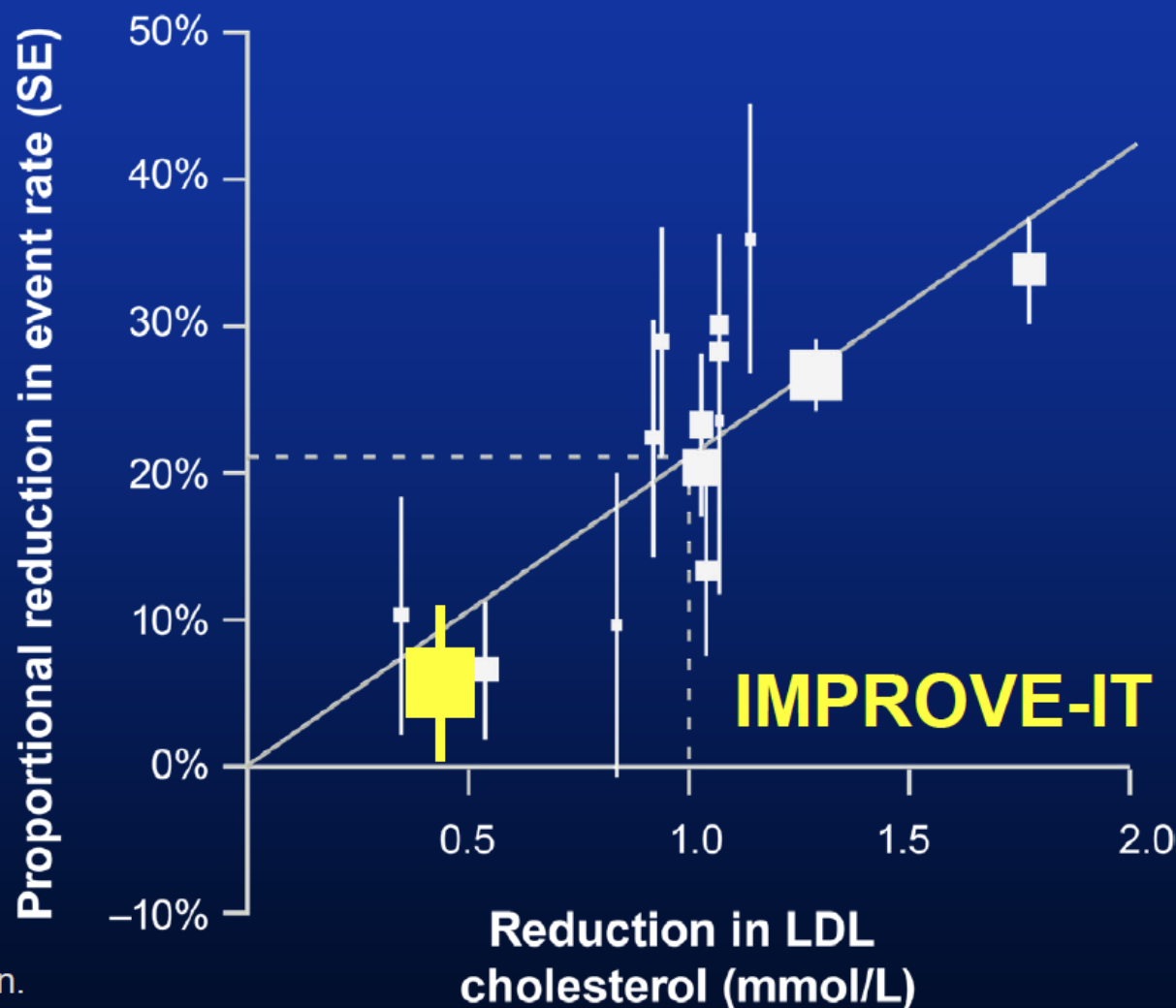
Primary Endpoint — ITT



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



IMPROVE-IT vs. CTT: Ezetimibe vs. Statin Benefit



CTT Collaboration.
Lancet 2005; 366:1267-78;
Lancet 2010;376:1670-81.

http://my.americanheart.org/professional/Sessions/ScientificSessions/ScienceNews/SS14-Late-Breaking-Clinical-Trials_UCM_468855_Article.jsp



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64th Annual Scientific Session & Expo

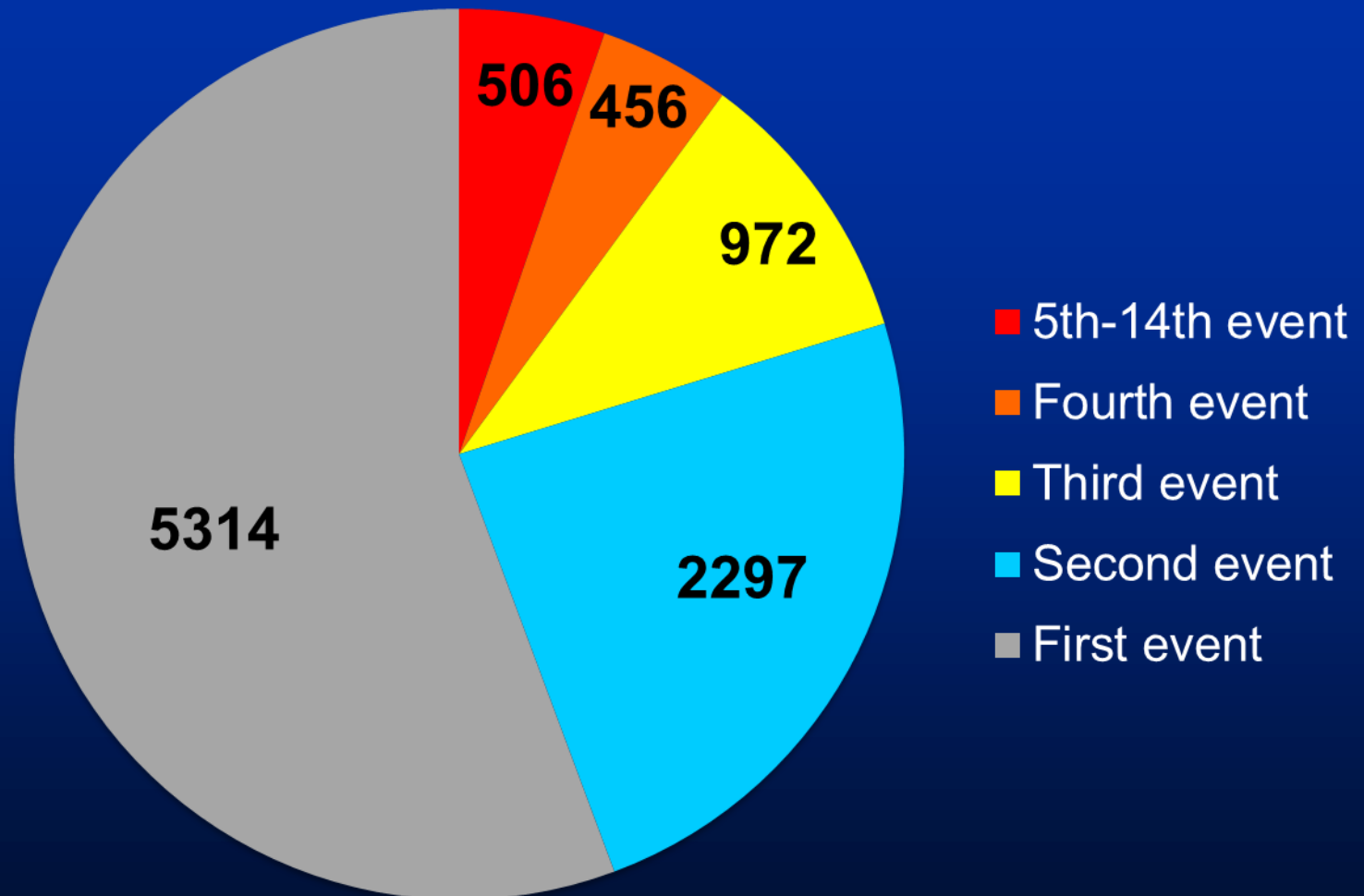


Reduction in Total (First and Recurrent) Cardiovascular Events with Ezetimibe/Simvastatin compared with Simvastatin Alone post ACS in the IMPROVE-IT Trial

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

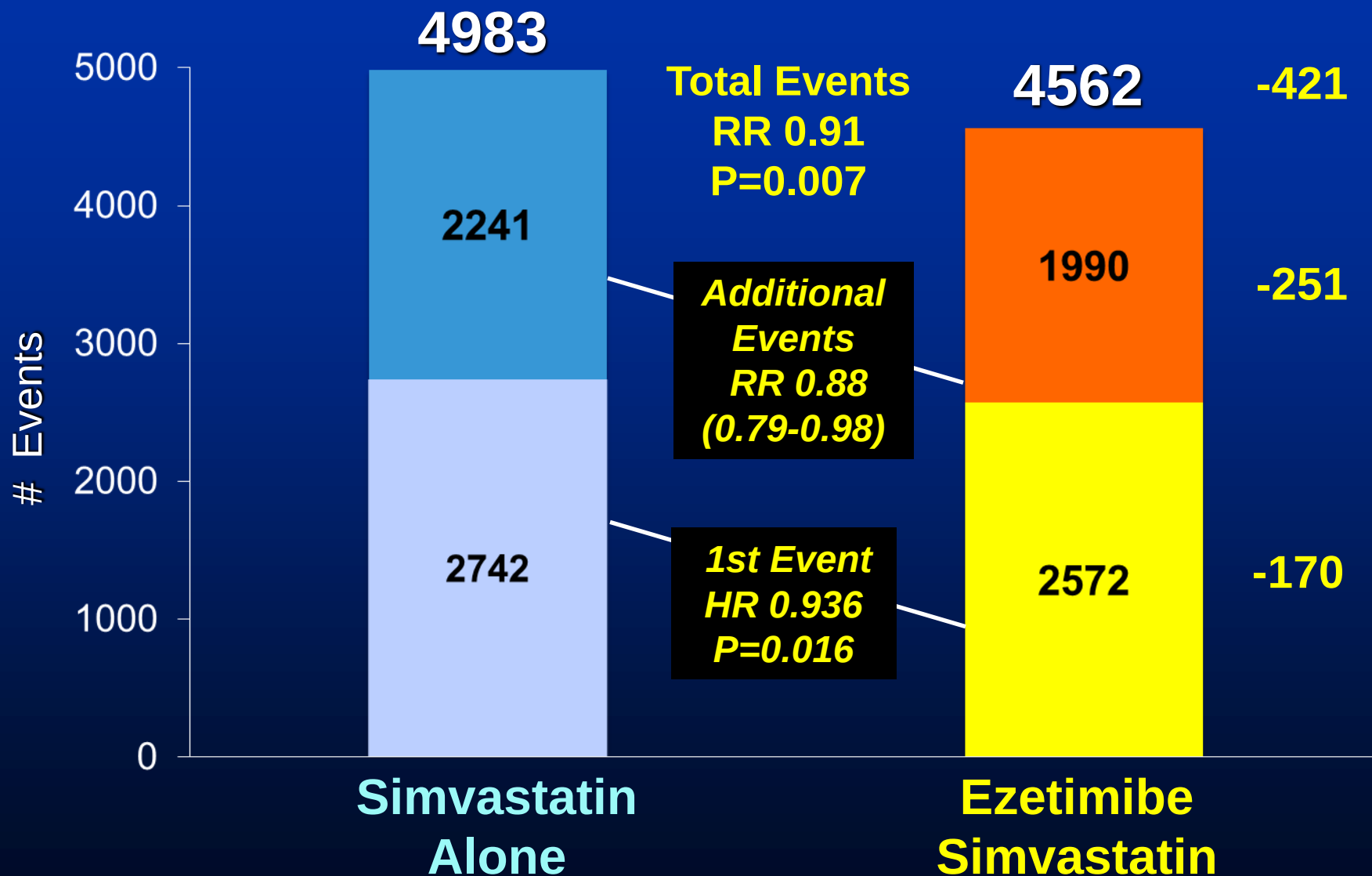
On behalf of the IMPROVE IT Investigators

Total Primary Endpoint Events



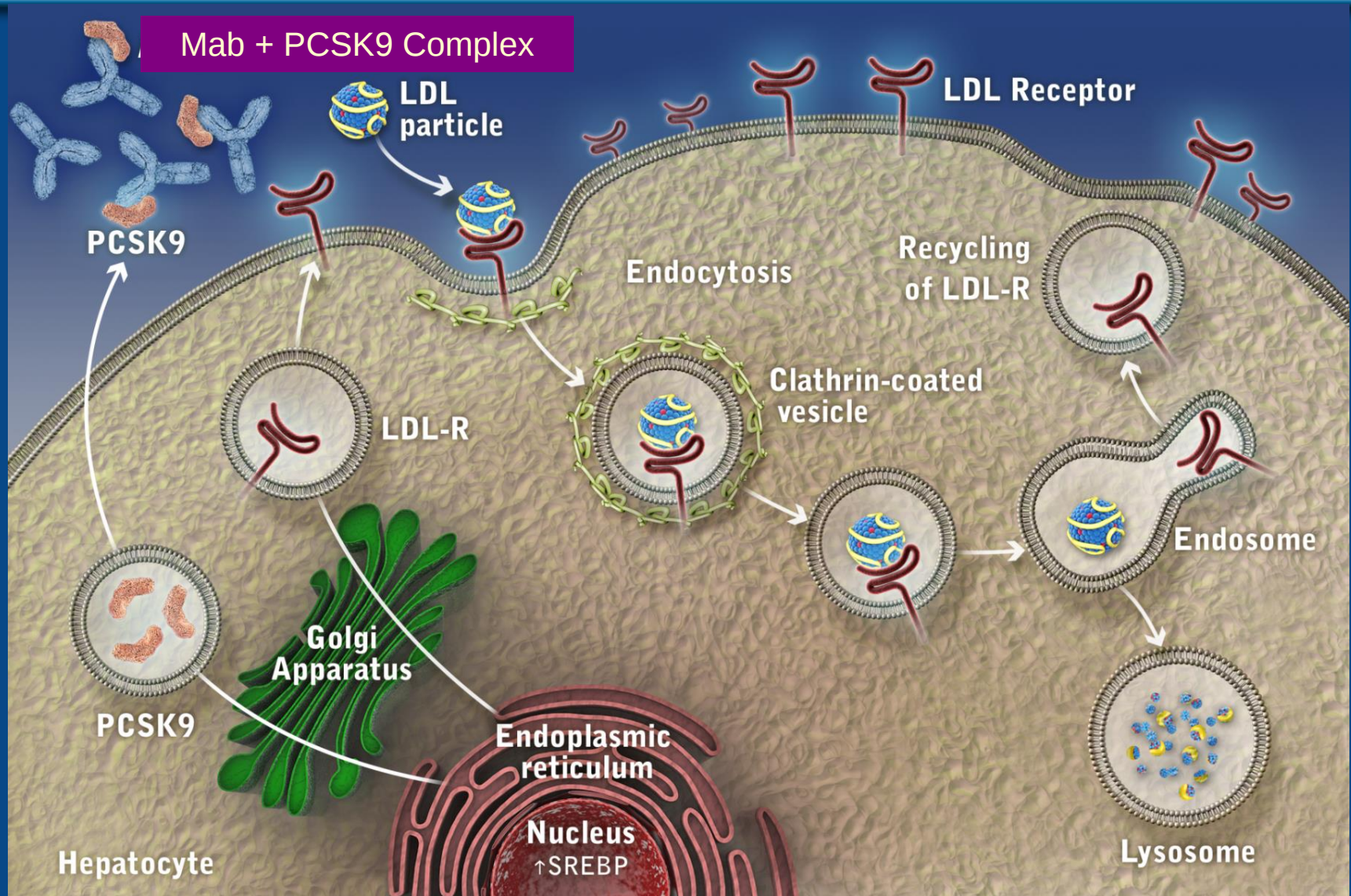
Total
N=9545

Total Primary Endpoint Events





Impact of Monoclonal Antibodies on LDL Receptor Expression



PCSK9 Inhibitors in Development

Investigational Product	Company	Stage of Development
Monoclonal antibodies		
Alirocumab (SAR236553, REGN727)	Sanofi (Regeneron)	Phase III
Evolocumab (AMG 145)	Amgen	Phase III
Bococizumab (PF-0490615, RN316)	Pfizer (Rinat)	Phase III
LY3015014	Lilly	Phase II
Other PCSK9 biologics		
ALN-PCS (siRNA)	Alnylam, The Medicines Comp	Phase I



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SCIENTIFIC SESSIONS 2014



Efficacy and Safety of Combining Alirocumab With Atorvastatin or Rosuvastatin versus Statin Intensification or Adding Ezetimibe in High Cardiovascular Risk Patients: ODYSSEY OPTIONS I and II

Harold Bays | Louisville Metabolic and Atherosclerosis Research Center, Louisville, KY

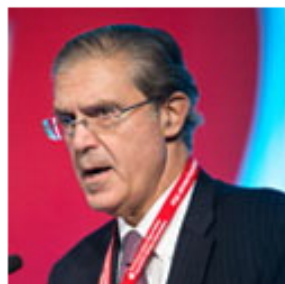
[Presentation Slides \(PDF\)](#) | [Abstract \(PDF\)](#)



ODYSSEY HIGH FH: Efficacy and Safety of Alirocumab in Patients With Severe Heterozygous Familial Hypercholesterolemia

Henry N Ginsberg | Columbia University College of Physicians and Surgeons, New York, NY

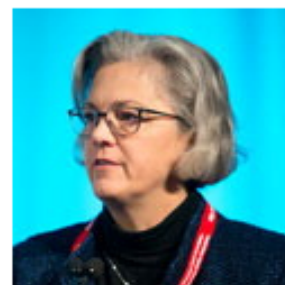
[Presentation Slides \(PDF\)](#) | [Abstract \(PDF\)](#)



Efficacy and Safety of Alirocumab in High Cardiovascular Risk Patients With Suboptimally Controlled Hypercholesterolemia on Maximally Tolerated Doses of Statins: The ODYSSEY COMBO I Study

Dean J Kereiakes | The Christ Hospital Heart and Vascular Center/The Lindner Research Center, Cincinnati, OH

[Presentation Slides \(PDF\)](#) | [Abstract \(PDF\)](#)



Long-term Safety, Tolerability and Efficacy of Alirocumab versus Placebo in 2,341 High Cardiovascular Risk Patients: ODYSSEY LONG TERM

Jennifer G Robinson | University of Iowa, Iowa City, IA

[Presentation Slides \(PDF\)](#) | [Abstract \(PDF\)](#)

http://my.americanheart.org/professional/Sessions/ScientificSessions/ScienceNews/SS14-Clinical-Science-Special-Reports_UCM_468860_Article.jsp

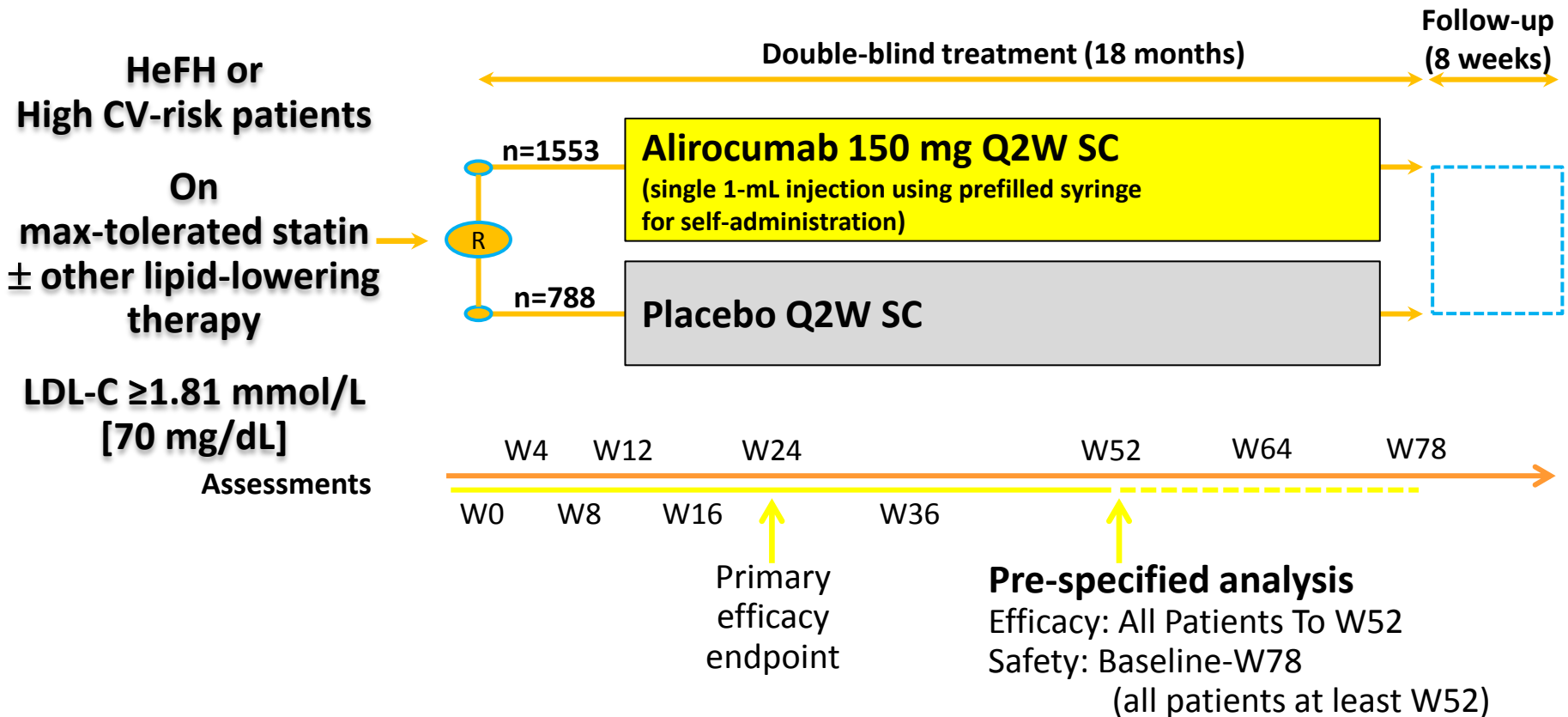
ORIGINAL ARTICLE

Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

Jennifer G. Robinson, M.D., M.P.H., Michel Farnier, M.D., Ph.D.,
Michel Krempf, M.D., Jean Bergeron, M.D., Gérald Luc, M.D.,
Maurizio Averna, M.D., Erik S. Stroes, M.D., Ph.D., Gisle Langslet, M.D.,
Frederick J. Raal, M.D., Ph.D., Mahfouz El Shahawy, M.D., Michael J. Koren, M.D.,
Norman E. Lepor, M.D., Christelle Lorenzato, M.Sc., Robert Pordy, M.D.,
Umesh Chaudhari, M.D., and John J.P. Kastelein, M.D., Ph.D.,
for the ODYSSEY LONG TERM Investigators*

ODYSSEY LONG TERM

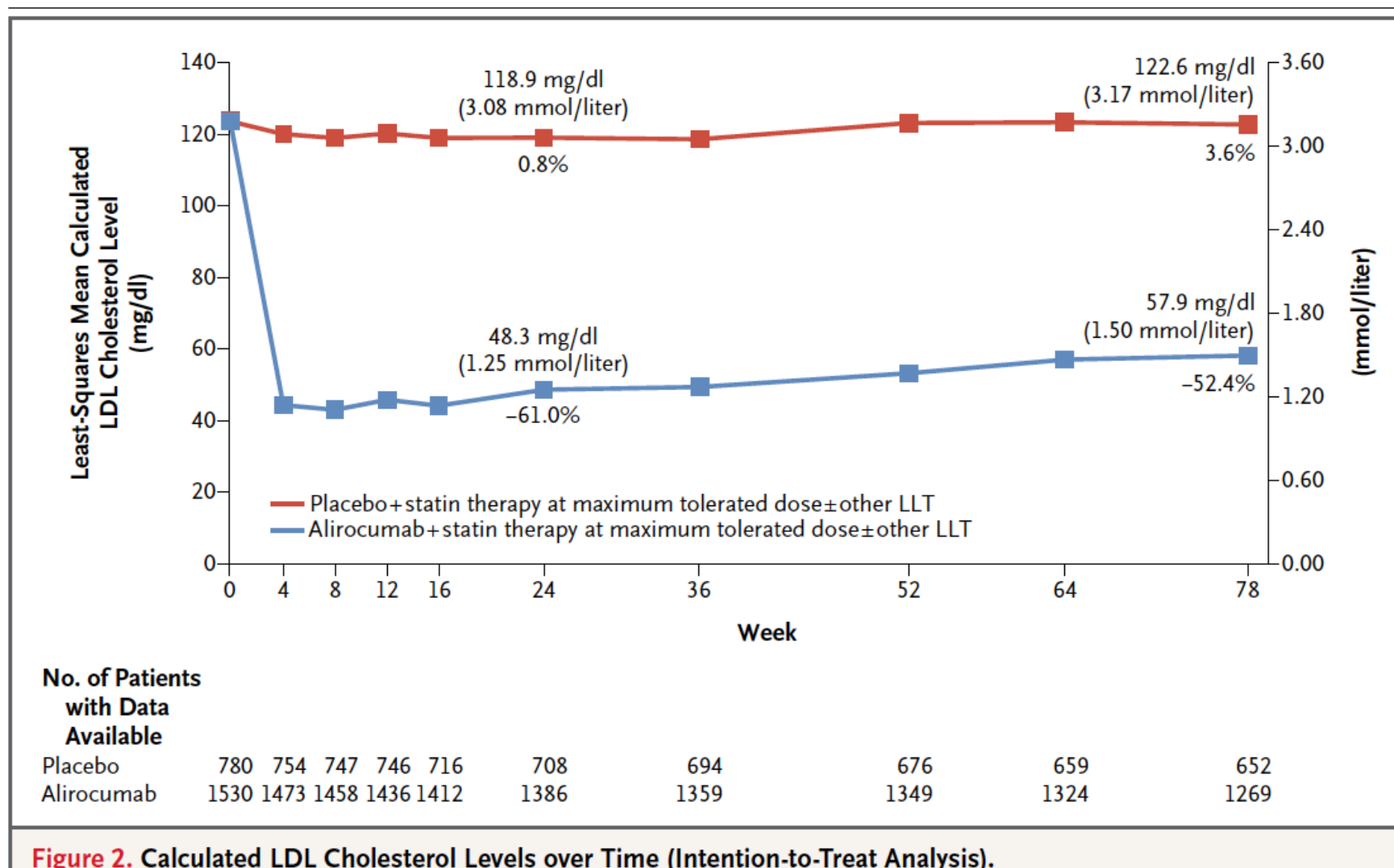
Study Design



86% (2011/2341) completed 52 weeks (both treatment arms)

26.1% (405/1553 alirocumab) and 25.6% (202/788 placebo) had completed 78 weeks by time of this analysis

Mean treatment duration: 65 weeks (both treatment arms)



TEAEs Comparable in Patients With 2 Consecutive LDL-C < 0.65 mmol/L (25 mg/dL)

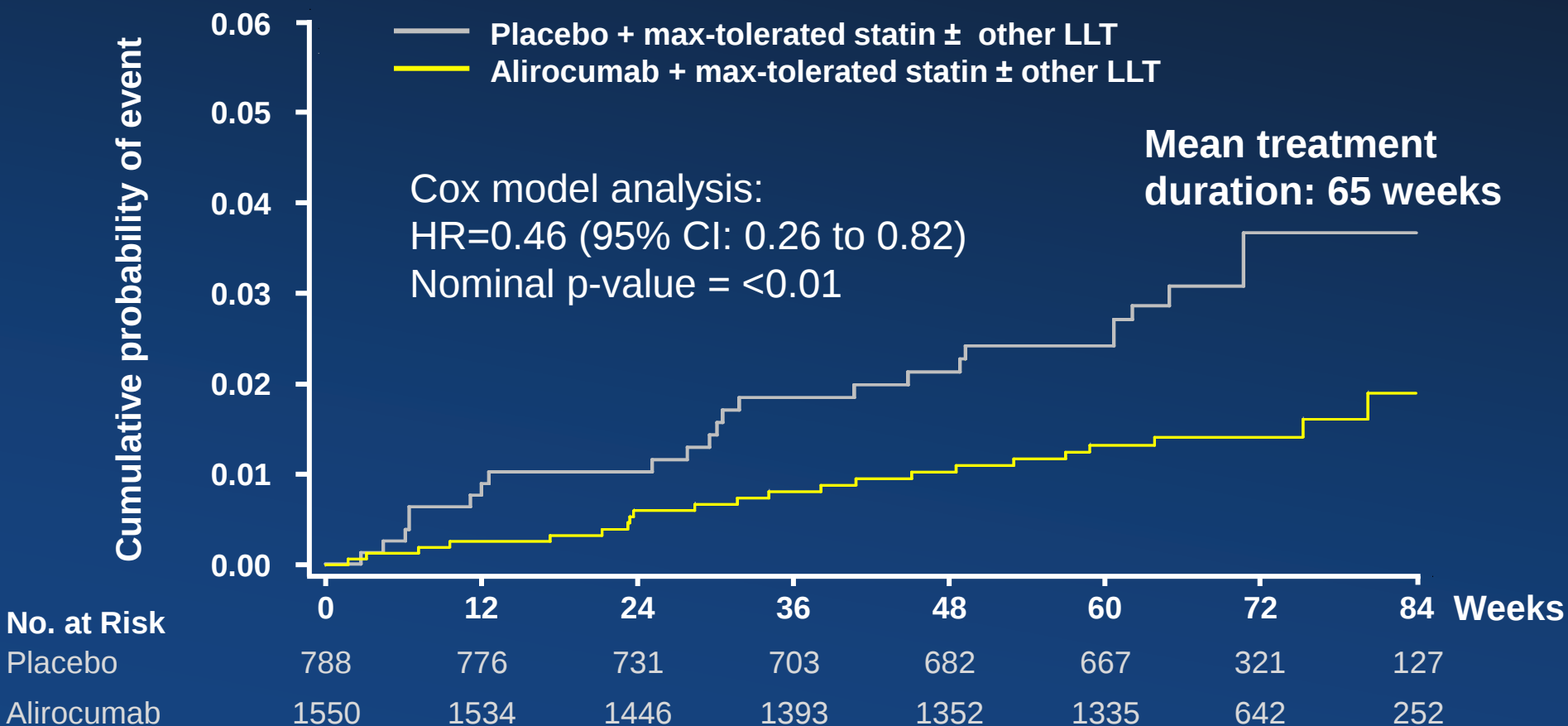
% (n) of patients All pts on background of maximal statin therapy ± other lipid-lowering therapy	Alirocumab (n=1550)	Alirocumab with 2 consecutive LDL-C <25 mg/dL (n=562, 37%)	Placebo (n=788)
Infections + infestations	48.3% (748)	42.3% (243)	48.6% (383)
Musculoskeletal + connective tissue disorders	30.1% (467)	26.1% (150)	30.7% (242)
Gastrointestinal disorders	20.5% (318)	16.7% (96)	20.6% (162)
Nervous system disorders	18.6% (289)	12.9% (74)	19.7% (155)
General disorders + administration site conditions	16.1% (250)	11.3% (65)	17.0% (140)
Injury, poisoning, + procedural complications	15.5% (241)	13.2% (76)	15.7% (124)
Respiratory, thoracic, + mediastinal disorders	11.7% (182)	8.9% (51)	12.6% (99)
Cardiac disorders	11.0% (171)	10.6% (61)	12.9% (102)
Skin + subcutaneous tissue disorders	10.1% (156)	8.3% (48)	9.4% (74)
Metabolism + nutrition disorders	10.2% (158)	9.6% (55)	9.3% (73)
Vascular disorders	8.6% (133)	5.4% (31)	10.0% (79)
Eye disorders	7.0% (108)	7.0% (40)	6.2% (49)
Laboratory investigations	6.4% (99)	4.3% (25)	5.5% (43)
Psychiatric disorders	6.5% (101)	5.2% (30)	8.5% (67)
Renal + urinary disorders	5.5% (85)	4.7% (27)	6.6% (52)
Neoplasms, benign, malignant (incl cysts/polyps)	3.0% (47)	3.8% (22)	4.3% (34)
Reproductive system + breast disorders	3.2% (50)	2.8% (16)	3.4% (27)
Blood + lymphatic system disorders	3.0% (46)	2.4% (14)	3.7% (29)
Ear + labyrinth disorders	2.4% (37)	1.7% (10)	3.9% (31)

Post-hoc Adjudicated Cardiovascular TEAEs[†]

Safety Analysis (at least 52 weeks for all patients in ongoing study)

Kaplan-Meier Estimates for Time to First Adjudicated Major CV Event

Safety Analysis (at least 52 weeks for all patients continuing treatment, including 607 patients who completed W78 visit)



[†]Primary endpoint for the ODYSSEY OUTCOMES trial: CHD death, Non-fatal MI, Fatal and non-fatal ischemic stroke, Unstable angina requiring hospitalisation. LLT, lipid-lowering therapy

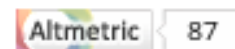
Articles

Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial

Prof [Frederick J Raal](#), PhD, [Narimon Honarpour](#), MD, [Dirk J Blom](#), MD, [G Kees Hovingh](#), MD, [Feng Xu](#), MS, [Rob Scott](#), MD, [Scott M Wasserman](#), MD, Prof [Evan A Stein](#), PhD  , for the TESLA Investigators

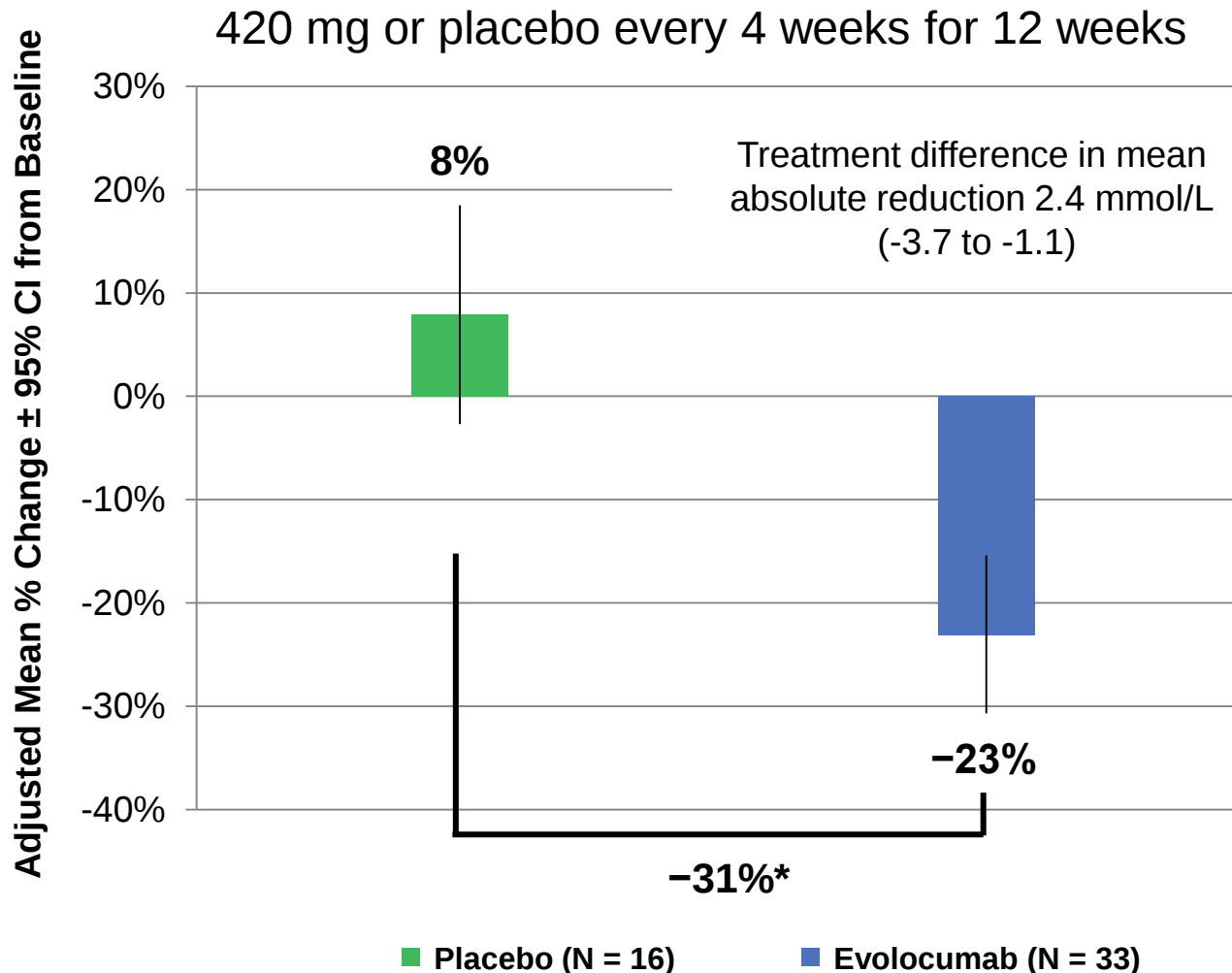
[†] The TESLA study investigators are listed in the appendix

Published Online: 01 October 2014



TESLA Part B:

Week 12 mean % Change in UC LDL-C from Baseline

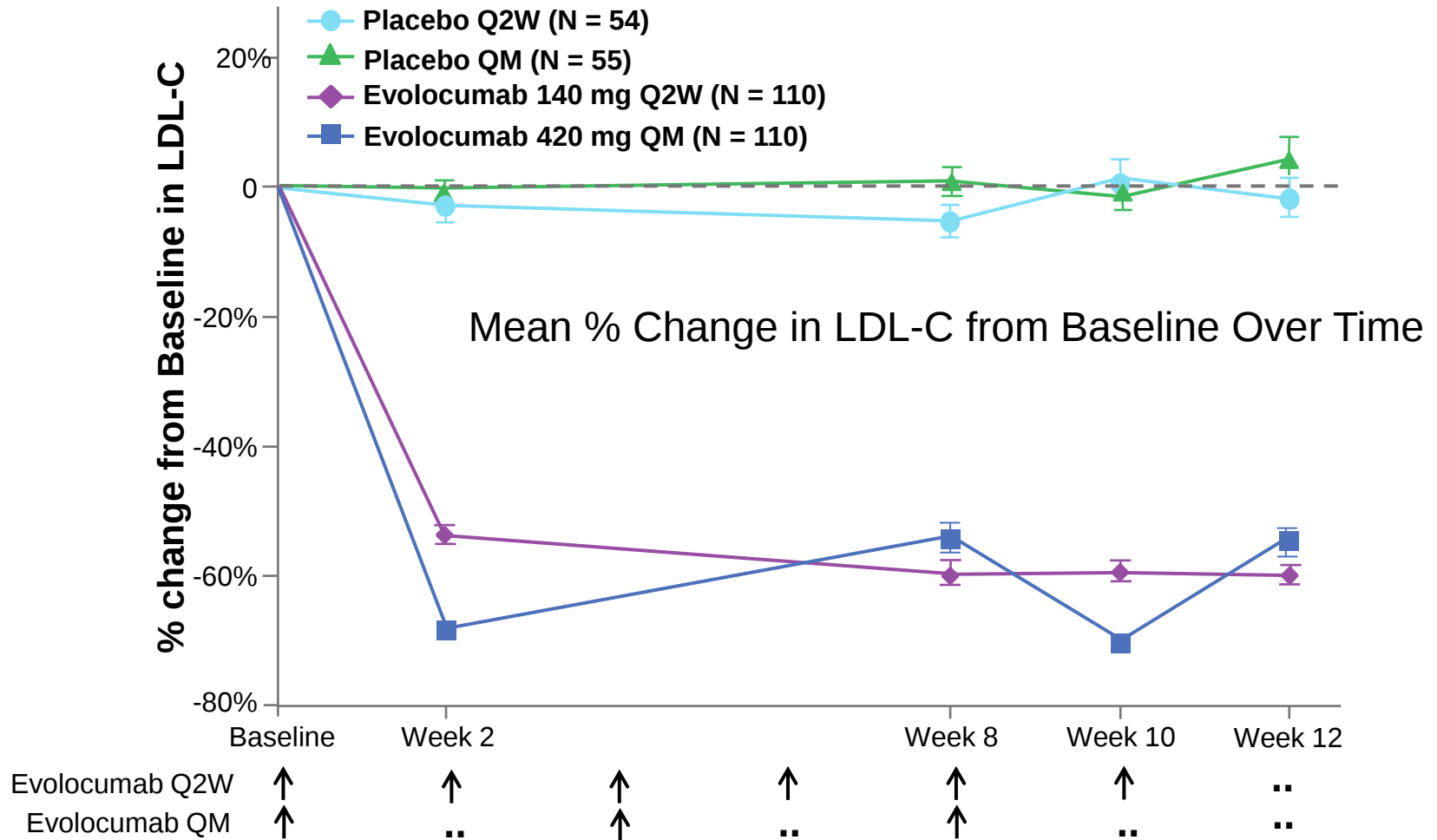


*P<0.0001 evolocumab treatment difference vs placebo.

UC LDL-C, uncentrifugated LDL-cholesterol.

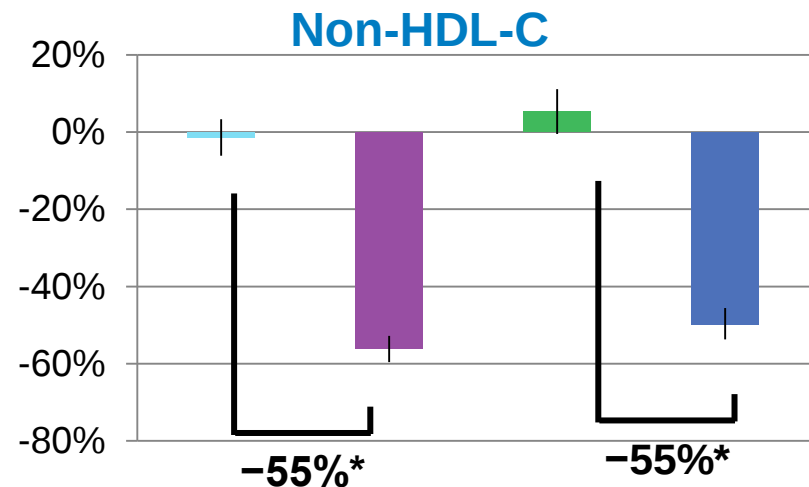
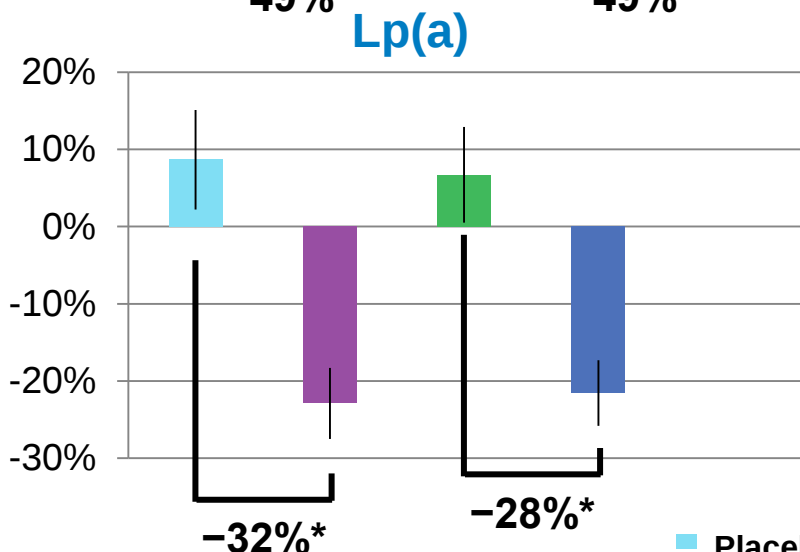
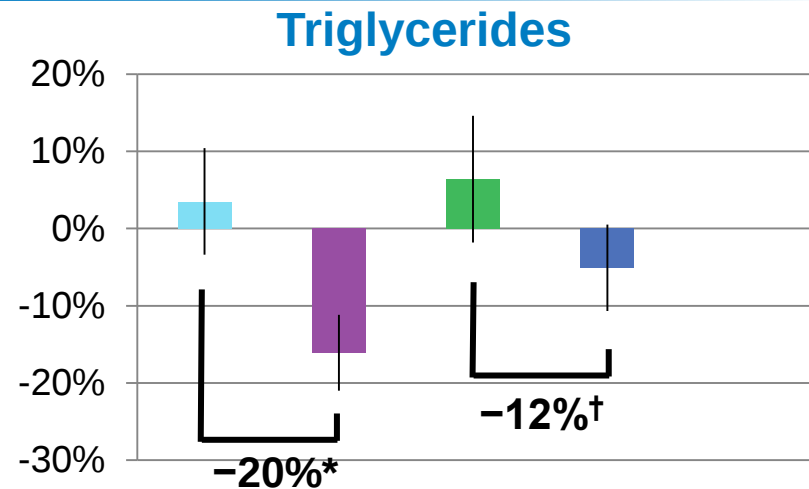
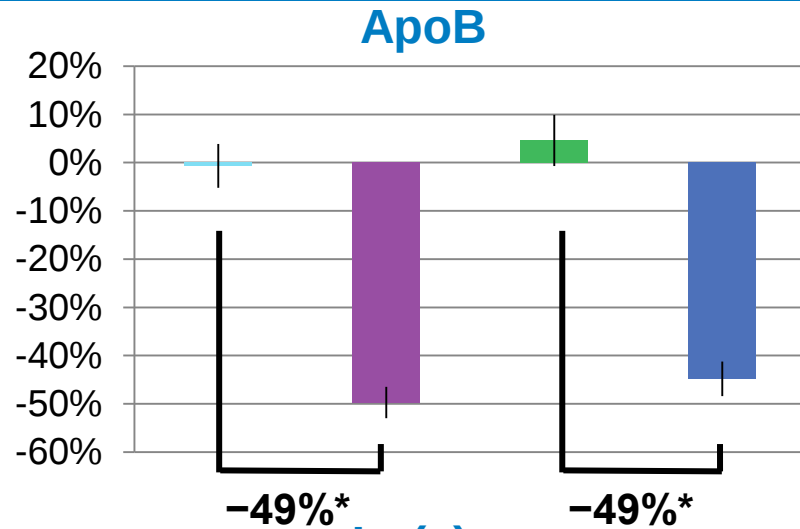
Raal FJ, et al. Lancet 2014; doi.org/10.1016/S0140-6736(14)61374-X.

PCSK9 inhibition with evolocumab* (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial



RUTHERFORD-2:

% Changes in Other Atherogenic Lipids (Week 12)



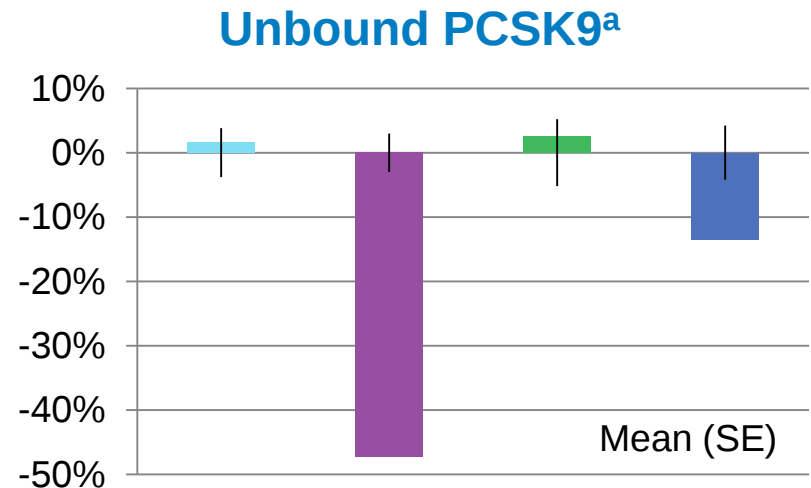
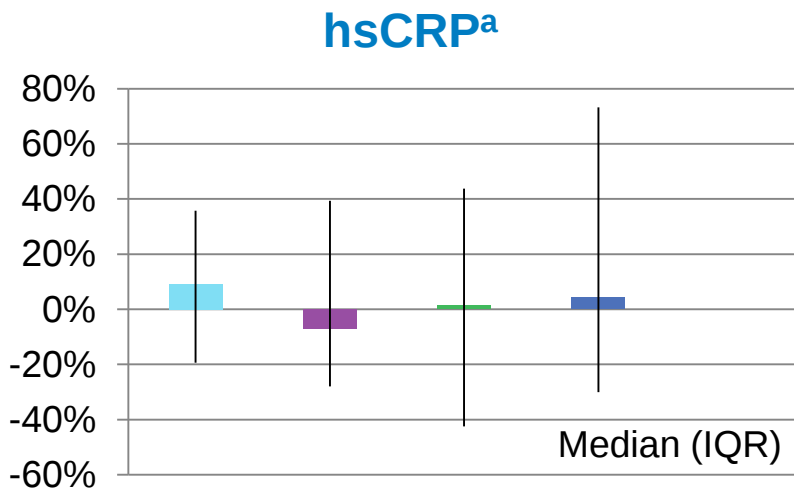
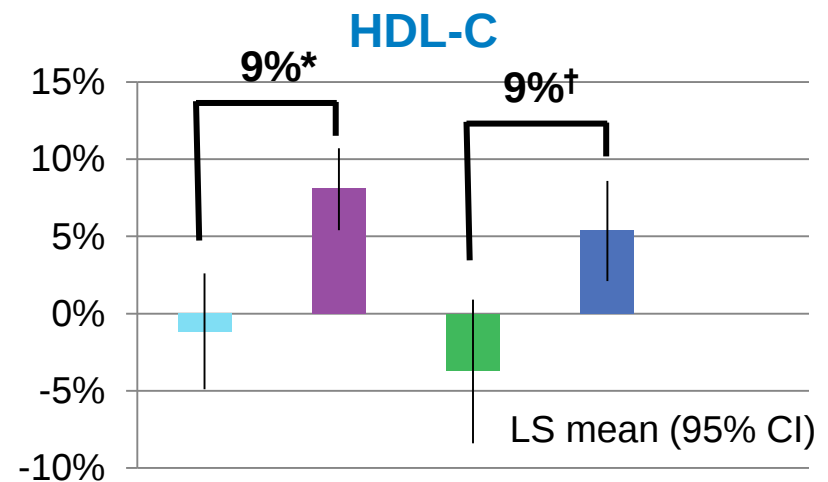
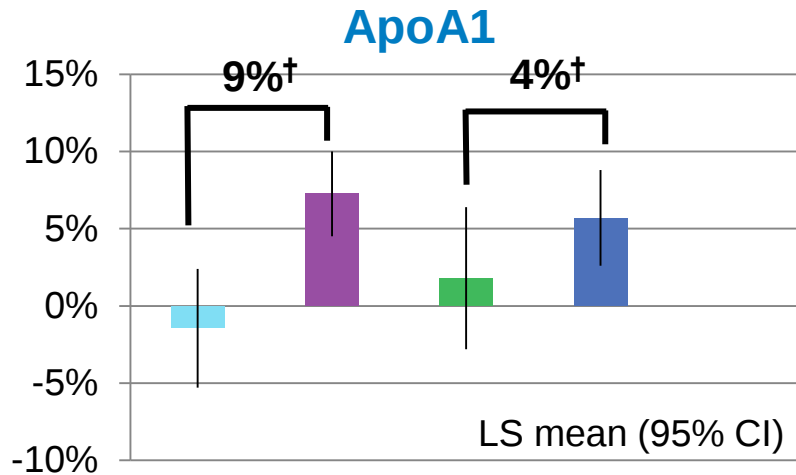
*P<0.0001 ; †P<0.05

Raal FJ, et al. Lancet 2014;

doi.org/10.1016/S0140-6736(14)61399-4.

■ Placebo Q2W (N = 54)
■ Placebo QM (N = 55)
■ Evolocumab 140 mg Q2W (N = 110)
■ Evolocumab 420 mg QM (N = 110)

RUTHERFORD-2: % Changes in ApoA1, HDL-C and hsCRP (Week 12)



*P<0.0001 ; †P<0.05

Raal FJ, et al. Lancet 2014;
doi.org/10.1016/S0140-6736(14)61399-4.

■ Placebo Q2W (N = 54)
■ Placebo QM (N = 55)
■ Evolocumab 140 mg Q2W (N = 110)
■ Evolocumab 420 mg QM (N = 110)

^aTreatment difference not available

OSLER study

ORIGINAL ARTICLE

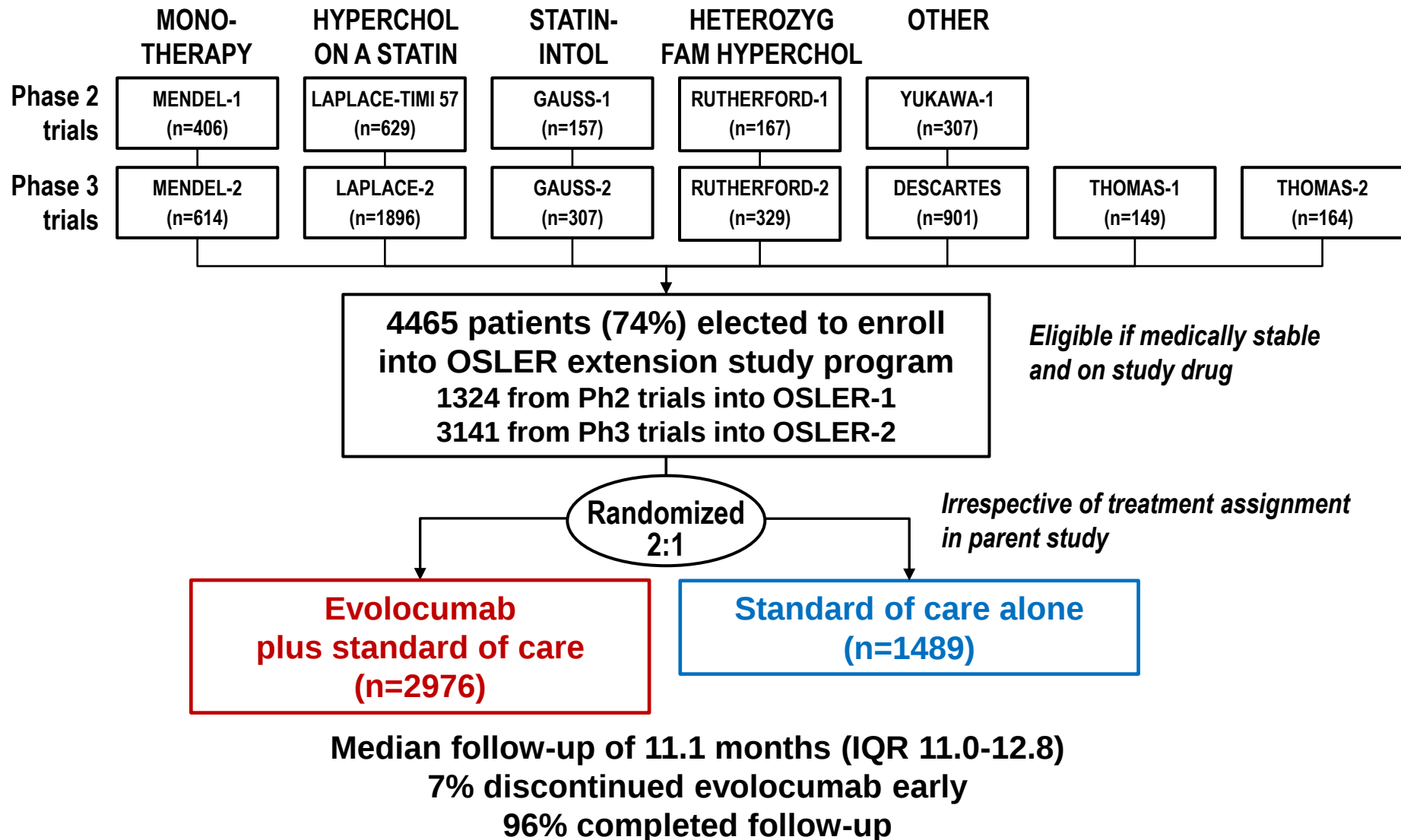
Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Stephen D. Wiviott, M.D., Frederick J. Raal, M.B., B.Ch., M.Med., Ph.D., Dirk J. Blom, M.B., Ch.B., M.Med., Ph.D., Jennifer Robinson, M.D., M.P.H., Christie M. Ballantyne, M.D., Ransi Somaratne, M.D., Jason Legg, Ph.D., Scott M. Wasserman, M.D., Robert Scott, M.D., Michael J. Koren, M.D., and Evan A. Stein, M.D., Ph.D. for the Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators

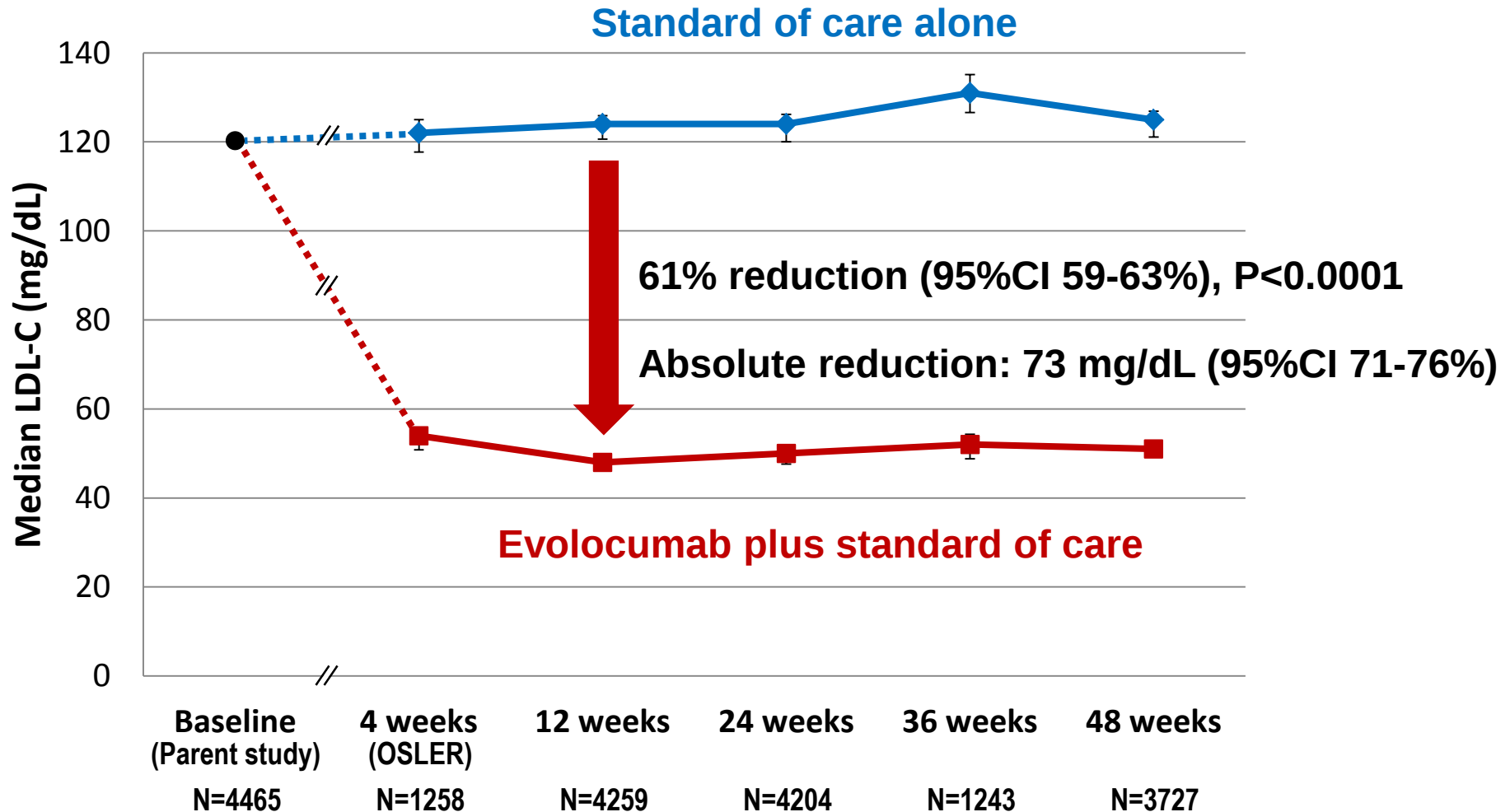
Conclusions

During approximately 1 year of therapy, the use of evolocumab plus standard therapy, as compared with standard therapy alone, significantly reduced LDL cholesterol levels and reduced the incidence of cardiovascular events in a prespecified but exploratory analysis.

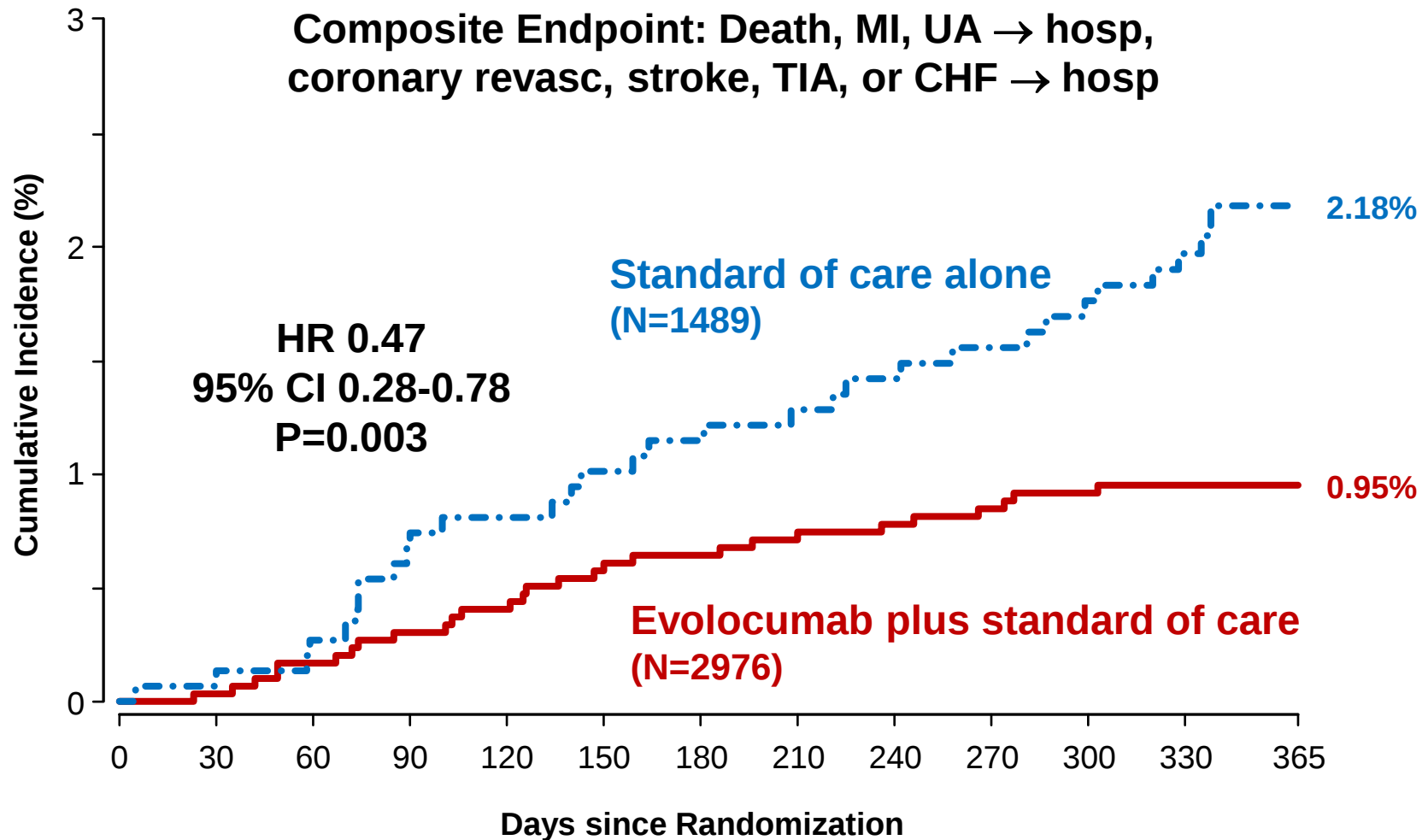
OSLER Program



LDL Cholesterol



Cardiovascular Outcomes



Adverse Events by Achieved LDL-C



	Evolocumab subjects stratified by minimum achieved LDL-C				All EvoMab (n=2976)	Std of Care Alone (n=1489)
	<25 mg/dL (n=773)	25 to <40 mg/dL (n=759)	<40 mg/dL (n=1532)	≥40 mg/dL (n=1426)		
Adverse Events (%)						
Any	70.0	68.1	69.1	70.1	69.2	64.8
Serious	7.6	6.9	7.2	7.8	7.5	7.5
Muscle-related	4.9	7.1	6.0	6.9	6.4	6.0
Neurocognitive	0.5	1.2	0.8	1.0	0.9	0.3
Lab results (%)						
ALT/AST >3×ULN	0.9	0.8	0.8	1.3	1.0	1.2
CK >5×ULN	0.4	0.9	0.7	0.5	0.6	1.2



ACC.15

TCT@ACC-12 | innovation in intervention

Program

Updated: 1-21

Prevention - Scientific Session

Session #607

Lipid Guidelines: Evolution, Revolution or Devolution

Saturday, March 14, 2015, 8 a.m. - 9:30 a.m.

Room 6B

CME Hours: 1.5 / CNE Hours: 1.5

Co-Chair: John J.P. Kastelein

Co-Chair: Vijay Nambi

8:00 a.m.

Lipid Guidelines: Let's Find Some Common Ground