# ADVANCES IN CARDIAC ARRHYTMIAS AND GREAT INNOVATIONS IN CARDIOLOGY

Torino, October 13 – 15, 2016

## PCSK9 INHIBITORS: A HUGE LITERATURE, NOW WE ARE READY TO USE THEM

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# Patient Populations with an Unmet Need for Additional LDL-C Lowering

## FH Population in EU

- 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]

**79% with HeFH not at goal (<100 mg/dL [2.6 mmol/L]) [4]**

## High / Very High CV Risk Population

- Previous MI / stroke / CVD or multiple CV risk factors incl. T2DM
- Difficult to achieve LDL-C goals, despite current therapies [5]

**• 20% with CHD not at goal (<100 mg/dL [2.6 mol/L])**

**• 59% at very high CV risk not at goal (<70 mg/dL [1.8 mmol/L])**

## Statin-Intolerant Population

- 10-15% on high-intensity statins show intolerance [6]
- Many discontinue due to muscle pain and/or weakness

**Nearly all patients who need considerable LDL-C reductions will not reach goal**

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.

# PCSK9 mAbs developing programs

| Company | Drug (alternate name) | Phase |
|---|---|---|
| Sanofi/ Regeneron | Alirocumab (SAR236553/REGN72) | **Approved** |
| Amgen | Evolocumab (AMG-145) | **Approved** |
| Pfizer/ Rinat | Bococizumab (RN316/PF04950615) | **3** |
| Novartis | LGT-209 | Discontinued |
| Genentech | MPSK3169A-RG7652 | Discontinued |

# Overview of ODYSSEY Phase 3

**14 global phase 3 trials including >23,500 patients across >2,000 study centers**

## HeFH population

**Add-on to max-tolerated statin (± other LMT)**

**ODYSSEY FH I (NCT01623115; EFC12492)**
LDL-C ≥ 70 mg/dL OR LDL-C ≥100 mg/dL
N=486; 18 months

**ODYSSEY FH II (NCT01709500; CL1112)**
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=249; 18 months

**ODYSSEY HIGH FH (NCT01617655; EFC12732)**
LDL-C ≥160 mg/dL
N=107; 18 months

**ODYSSEY OLE (NCT01954394; LTS 13463)**
Open-label study for FH from EFC 12492, CL 1112, EFC 12732 or LTS 11717
N≥1000; 30 months

**ODYSSEY LONG TERM (NCT01507831; LTS11717)**
LDL-C ≥70 mg/dL
N=2,100; 18 months

## HC in high CV risk population

**Add-on to max-tolerated statin (± other LMT)**

**ODYSSEY COMBO I (NCT01644175; EFC11568)**
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=316; 12 months

***ODYSSEY COMBO II (NCT01644188; EFC11569)**
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=720; 24 months

**ODYSSEY CHOICE I (NCT01926782; CL1308)**
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=803; 12 months

**ODYSSEY OUTCOMES (NCT01663402; EFC11570)**
LDL-C ≥70 mg/dL
N=18,000; 64 months

## Additional populations

**ODYSSEY MONO (NCT01644474; EFC11716)**
Patients on no background LMTs
LDL-C ≥100 mg/dL
N=100; 6 months

**ODYSSEY ALTERNATIVE (NCT01709513; CL1119)**
Patients with defined statin intolerance
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=250; 6 months

**ODYSSEY CHOICE II (NCT02023879; EFC13786)**
Patients not treated with a statin
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=233; 6 months

**ODYSSEY OPTIONS I (NCT01730040; CL1110)**
Patients not at goal on moderate dose atorvastatin
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=355; 6 months

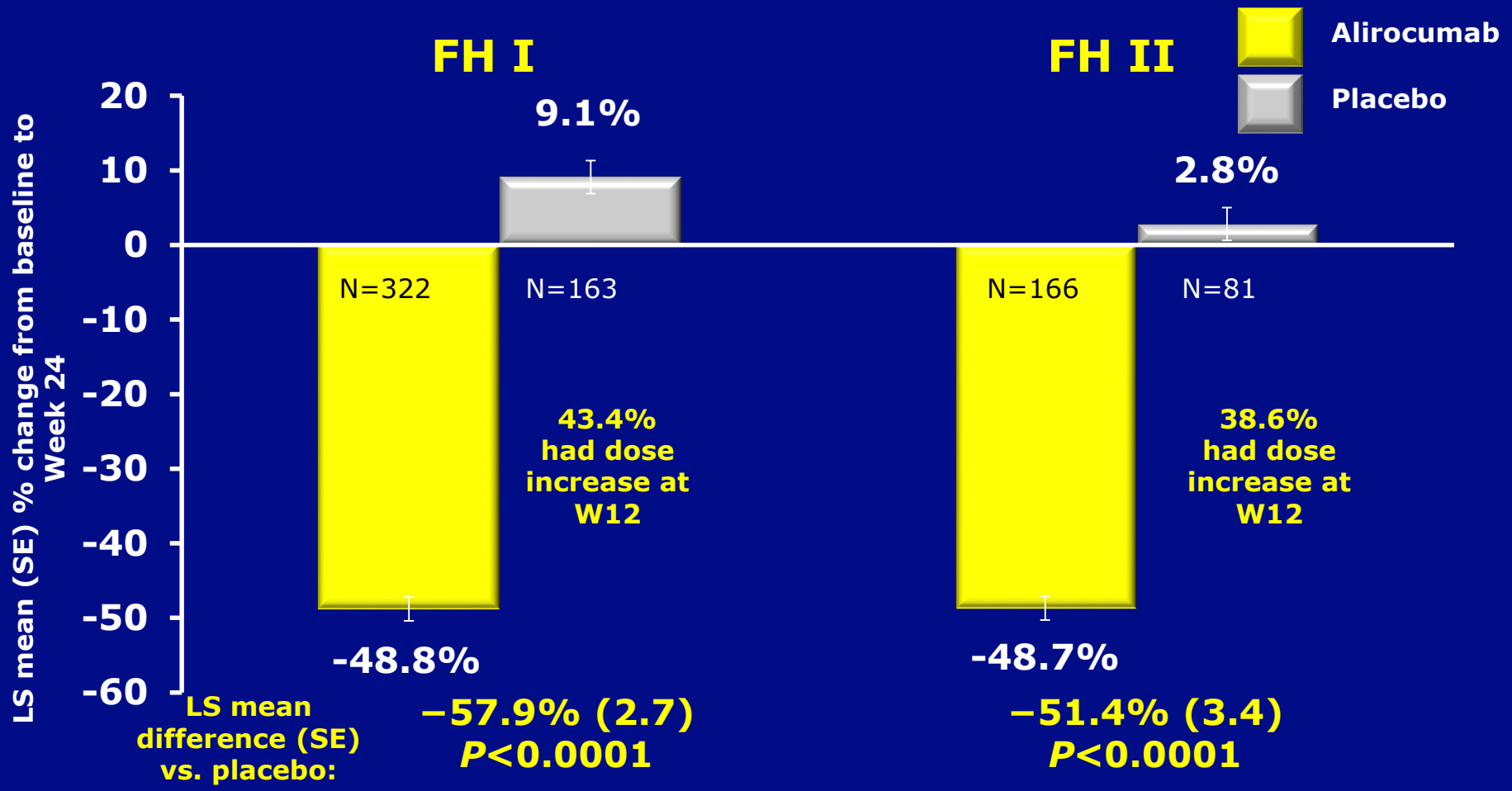
**ODYSSEY OPTIONS II (NCT01730053; CL1118)**
Patients not at goal on moderate dose rosuvastatin
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=305; 6 months

FH=familial hypercholesterolemia; HC=hypercholesterolemia; LMT=lipid-modifying therapy; OLE=open-label extension.
*For the ODYSSEY COMBO II other LMT not allowed at entry. ClinicalTrials.gov. ODYSSEY Phase 3 Trials. http://clinicaltrials.gov. Accessed February 12, 2014.

# Alirocumab Significantly Reduced LDL-C from Baseline to Week 24 versus Placebo in EFH

**Primary Endpoint: Percent Change from Baseline to Week 24 in LDL-C**

All patients on background max-tolerated statin ±other lipid-lowering therapy



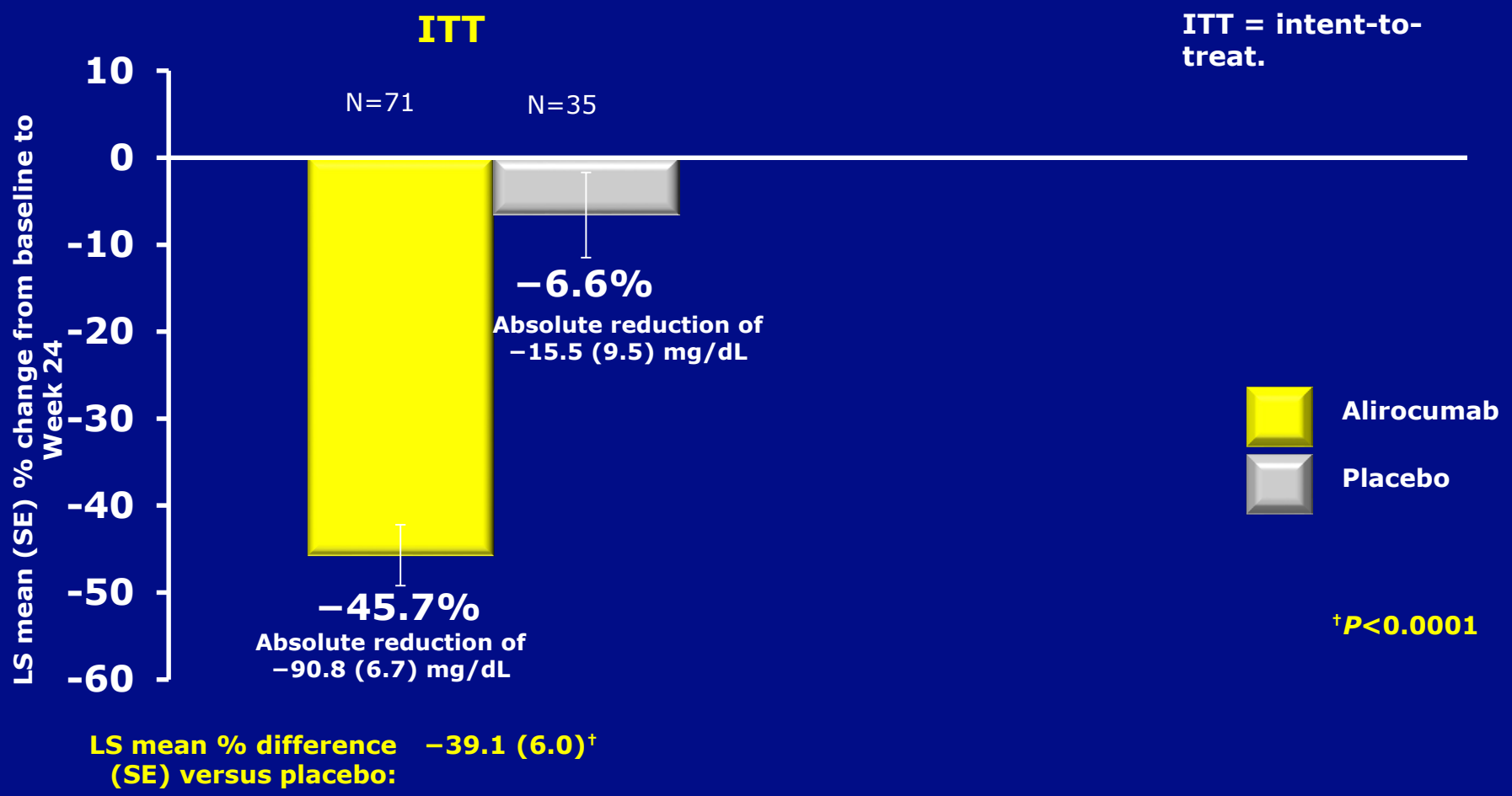

Intent-to-treat (ITT) Analysis

doi: 10.1093/eurheartj/ehv370

# Alirocumab Significantly Reduced LDL-C at Week 24 in EFH with LDL>160mg/dl

**Primary endpoint: % change from baseline to Week 24 in calculated LDL-C**

All patients on background max-tolerated statin ±other LLT

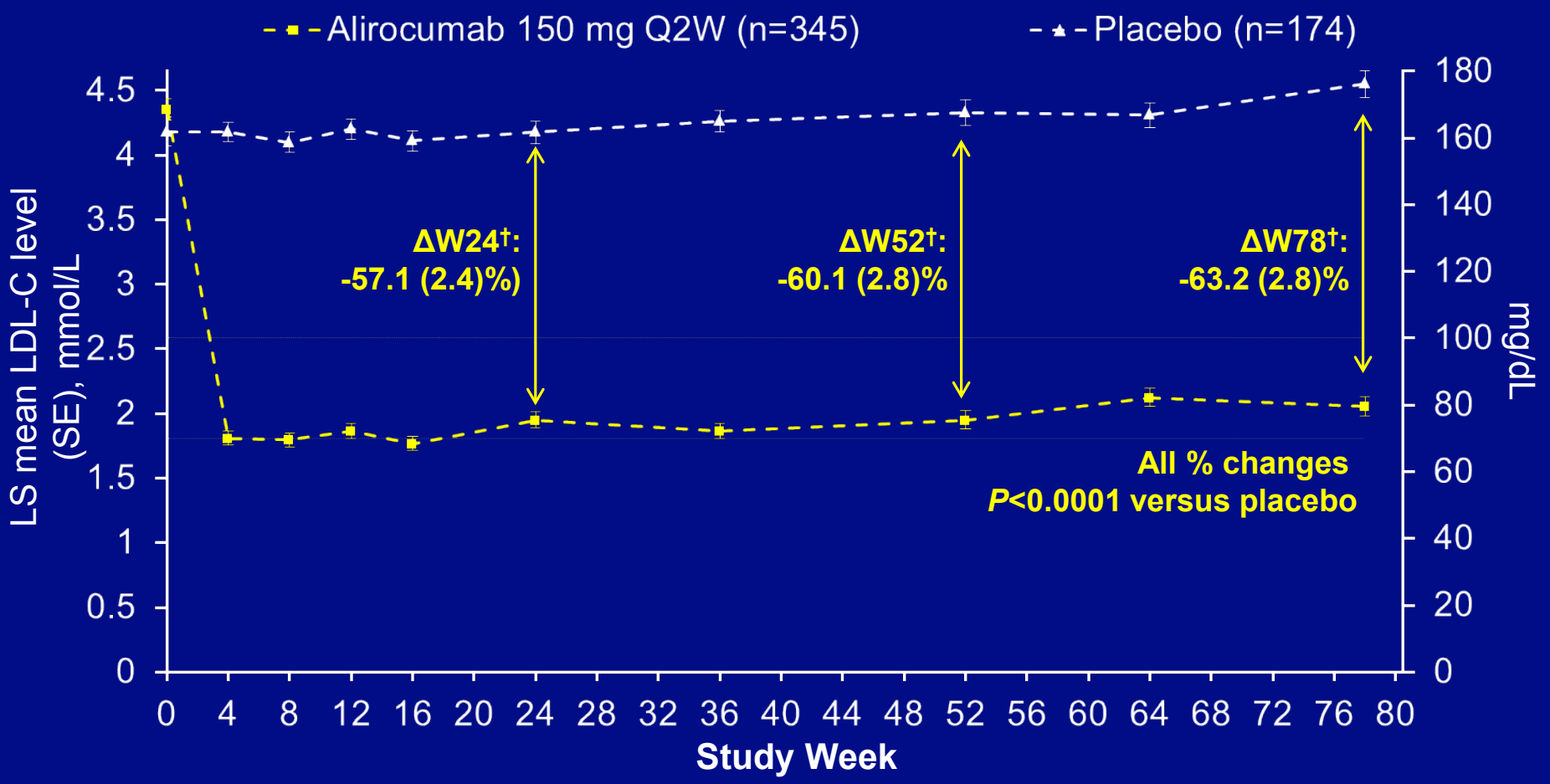



*Ginsberg HN, Oral Presentation at AHA 2014*

ODYSSEY

# Mean Calculated LDL-C Levels (mITT)

## Pool of LONG TERM (HeFH Patients only) and HIGH FH (Alirocumab 150 mg Q2W)



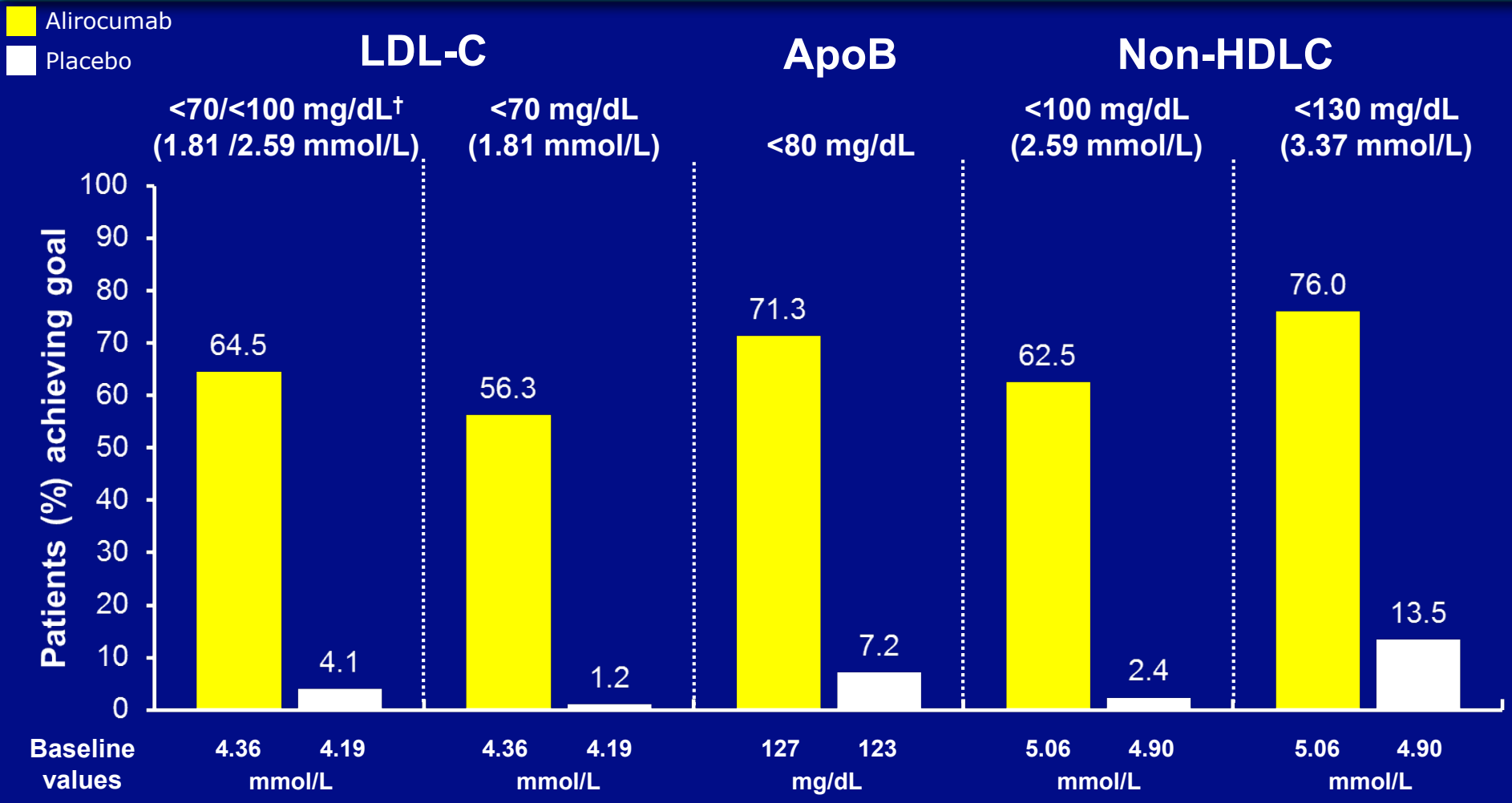

†ΔW24/52/78 defined as LS mean (SE) % difference versus placebo in calculated LDL-C from baseline to Week 24/52/78. Figure shows on-treatment analysis on modified ITT population, including all lipid data throughout the duration of study collected while the patients were still receiving study treatment.

*Kastelein JJP, Oral Presentation at ESC 2015*

ODYSSEY

# Goal Attainment (ITT)

## Pool of LONG TERM (HeFH Patients only) and HIGH FH (Alirocumab 150 mg Q2W)




**All *P*<0.0001 versus placebo**

†Depending on CV risk; goals analysed using multiple imputation followed by logistic regression.
Figure shows ITT analysis performed on ITT population.

*Kastelein JJP, Oral Presentation at ESC 2015*

ODYSSEY

# Efficacy and Safety of Combining Alirocumab With Atorvastatin or Rosuvastatin Versus Adding Ezetimibe, Doubling Statin Dose or Switching Statin Therapy in High Cardiovascular Risk Patients: ODYSSEY OPTIONS I and II

Harold Bays,[1] Michel Farnier,[2] Daniel Gaudet,[3] Robert Weiss,[4] Juan Lima Ruiz,[5] Gerald F. Watts,[6] Ioanna Gouni-Berthold,[7] Jennifer G. Robinson,[8] Peter Jones,[9] Randall Severance,[10] Maurizio Averna,[11] Elisabeth Steinhagen-Thiessen,[12] Helen M. Colhoun,[13] Jian Zhao,[14] Yunling Du,[14] Corinne Hanotin,[15] Stephen Donahue[14]

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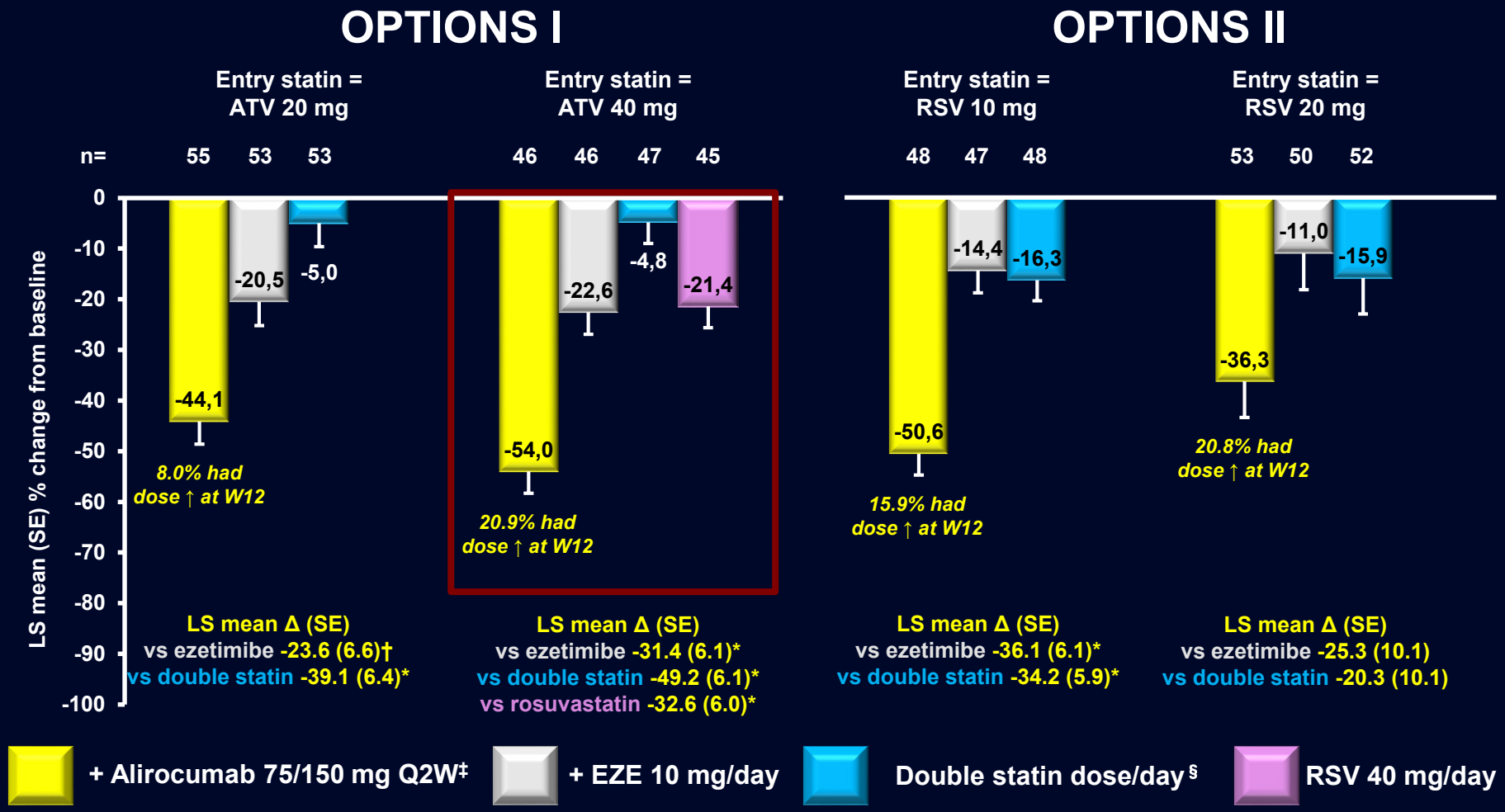
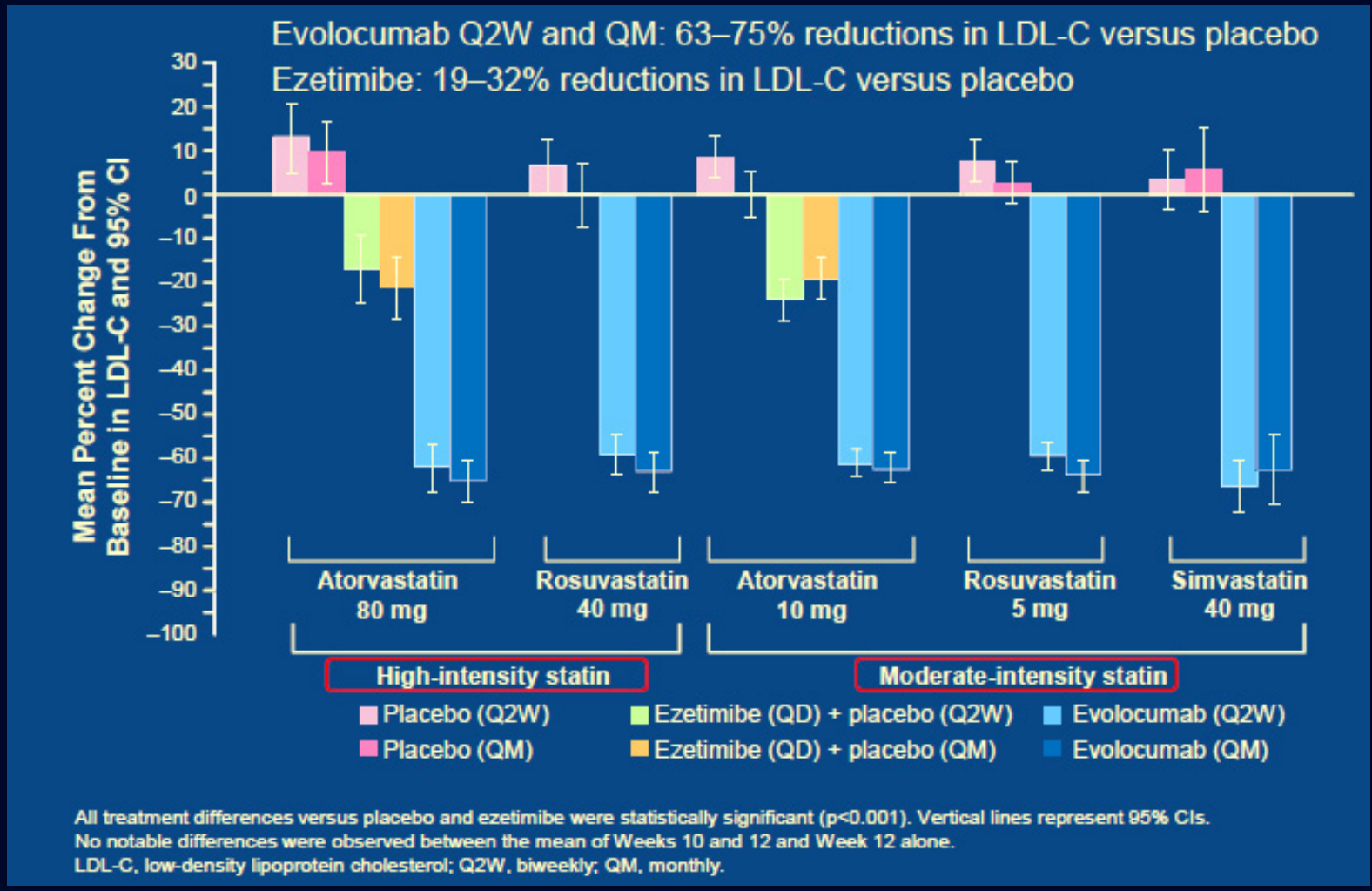
**This study was funded by Sanofi and Regeneron Pharmaceuticals, Inc.**

# Alirocumab Significantly Reduced LDL-C in Patients on an Entry Statin of ATV 20 Or 40 mg, Or RSV 10 mg




Intent-to-treat (ITT) analysis. LS mean difference *$P$<0.0001; †$P$=0.0004; ns = not significant alirocumab versus comparator.
Level of statistical significance: 0.01 (OPTIONS I) and 0.0125 (OPTIONS II) following Bonferroni adjustment for multiplicity.
‡ Dose ↑ at W12 if W8 LDL-C ≥70 or ≥100 mg/dL (depending on CV risk) among patients with at least one injection after Week 12.
§ Statin dose ↑ at randomization from 20 to 40, or 40 to 80 mg/day in OPTIONS I, and from 10 to 20, or 20 to 40 mg/day in OPTIONS II.

# LAPLACE-2: EFFICACY OF EVOLOCUMAB IN HIGH RISK PATIENTS IN RELATION TO BACKGROUND THERAPY




Adapted from Robinson JG et al. JAMA 2014; 311: 1870-82

The NEW ENGLAND JOURNAL of MEDICINE

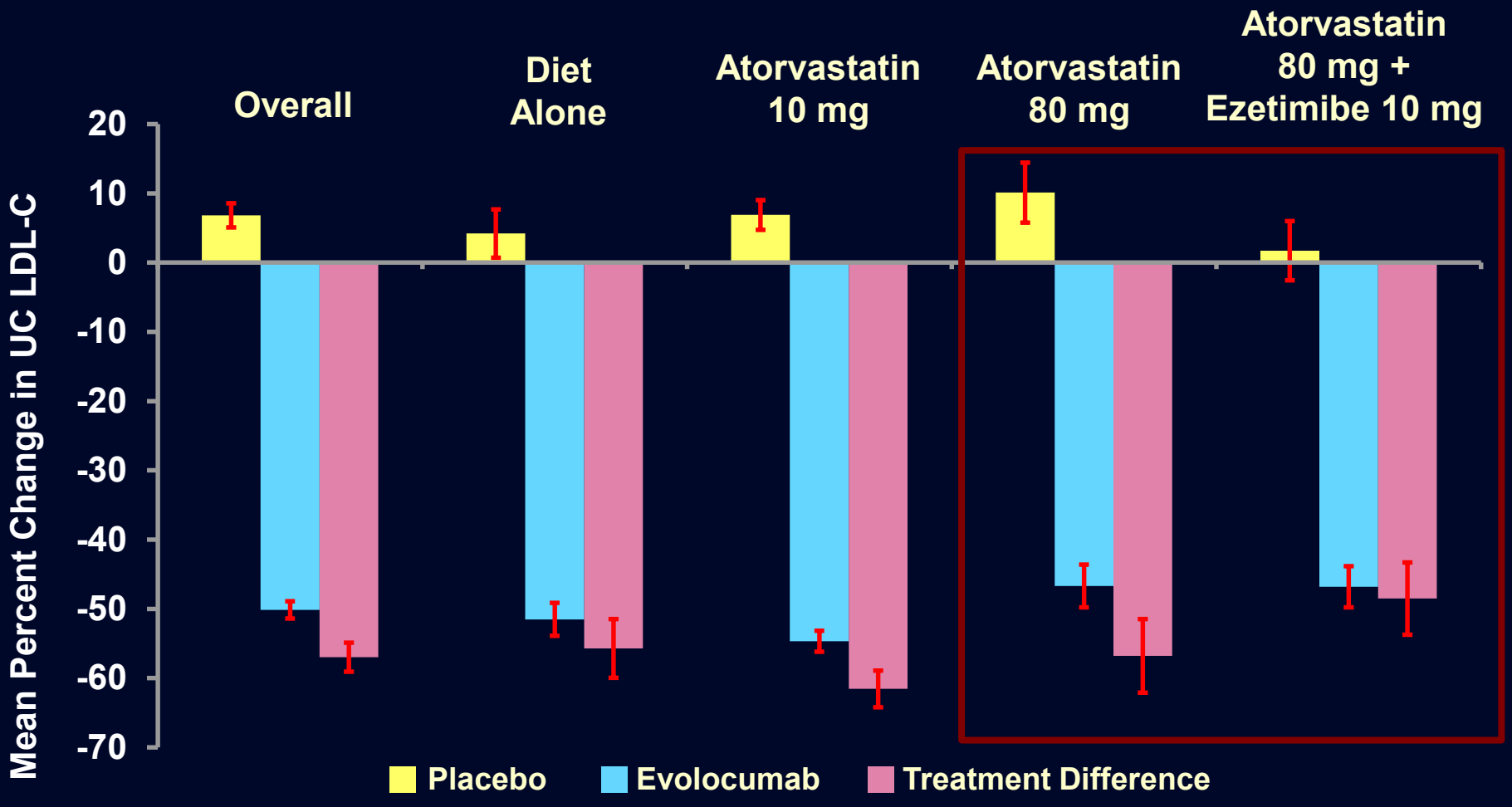
ORIGINAL ARTICLE

# A 52-Week Placebo-Controlled Trial of Evolocumab in Hyperlipidemia

Dirk J. Blom, M.D., Ph.D., Tomas Hala, M.D., Michael Bolognese, M.D., Michael J. Lillestol, M.D., Phillip D. Toth, M.D., Lesley Burgess, M.B., B.Ch., M.Med., Ph.D., Richard Ceska, M.D., Ph.D., Eli Roth, M.D., Michael J. Koren, M.D., Christie M. Ballantyne, M.D., Maria Laura Monsalvo, M.D., Kate Tsirtsonis, M.Sc., Jae B. Kim, M.D., Rob Scott, M.D., Scott M. Wasserman, M.D., and Evan A. Stein, M.D., Ph.D., for the DESCARTES Investigators*

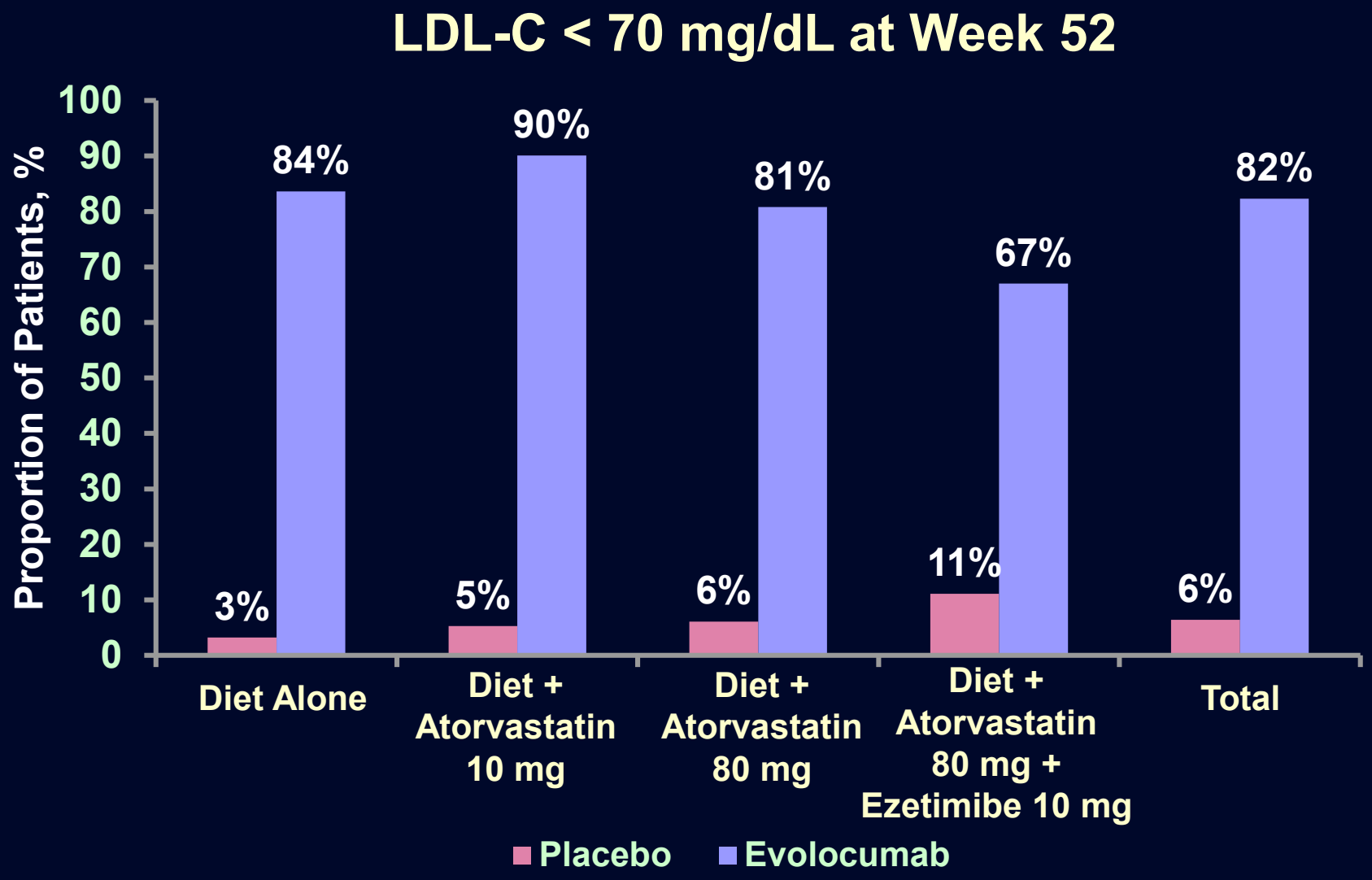
DOI: 10.1056/NEJMoa1316222

# DESCARTES: % Change in UC LDL-C from Baseline at Week 52




Error bars represent standard error for treatment difference
Treatment difference are least squares mean derived from a repeated measures model

# DESCARTES: UC LDL-C Goal Achievement



# Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

Jennifer G. Robinson,[1] Michel Farnier,[2] Michel Krempf,[3] Jean Bergeron,[4] Gérald Luc,[5] Maurizio Averna,[6] Erik S. Stroes,[7] Gisle Langslet,[8] Frederick J. Raal,[9] Mahfouz El Shahawy,[10] Michael J. Koren,[11] Norman E. Lepor,[12] Christelle Lorenzato,[13] Robert Pordy,[14] Umesh Chaudhari,[15] John J.P. Kastelein[7]
for the ODYSSEY LONG TERM investigators

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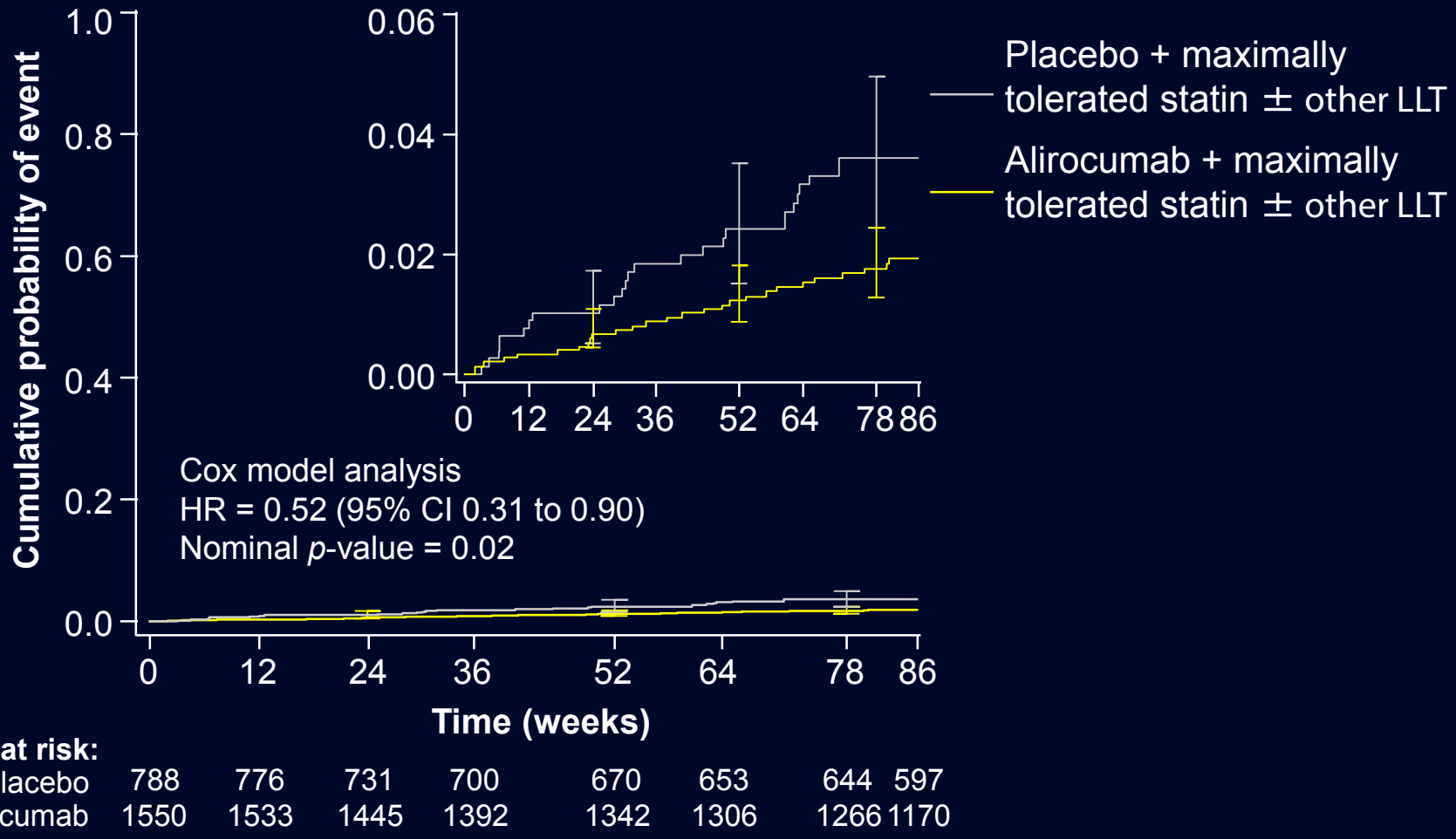
**This study was funded by Sanofi and Regeneron Pharmaceuticals**

Robinson JG et al. *NEJM* 2015; 372:1489-99.

# *Post hoc* Analysis of Adjudicated Major Adverse Cardiovascular Events*




**No. at risk:**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo | 788 | 776 | 731 | 700 | 670 | 653 | 644 | 597 |
| Alirocumab | 1550 | 1533 | 1445 | 1392 | 1342 | 1306 | 1266 | 1170 |

*Based on primary endpoint for the ODYSSEY OUTCOMES trial, including CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, and unstable angina requiring hospitalization.Unstable angina requiring hospitalization was considered based on strict criteria / clear progression of ischemia.

Robinson JG et al. *NEJM* 2015; 372:1489-99.

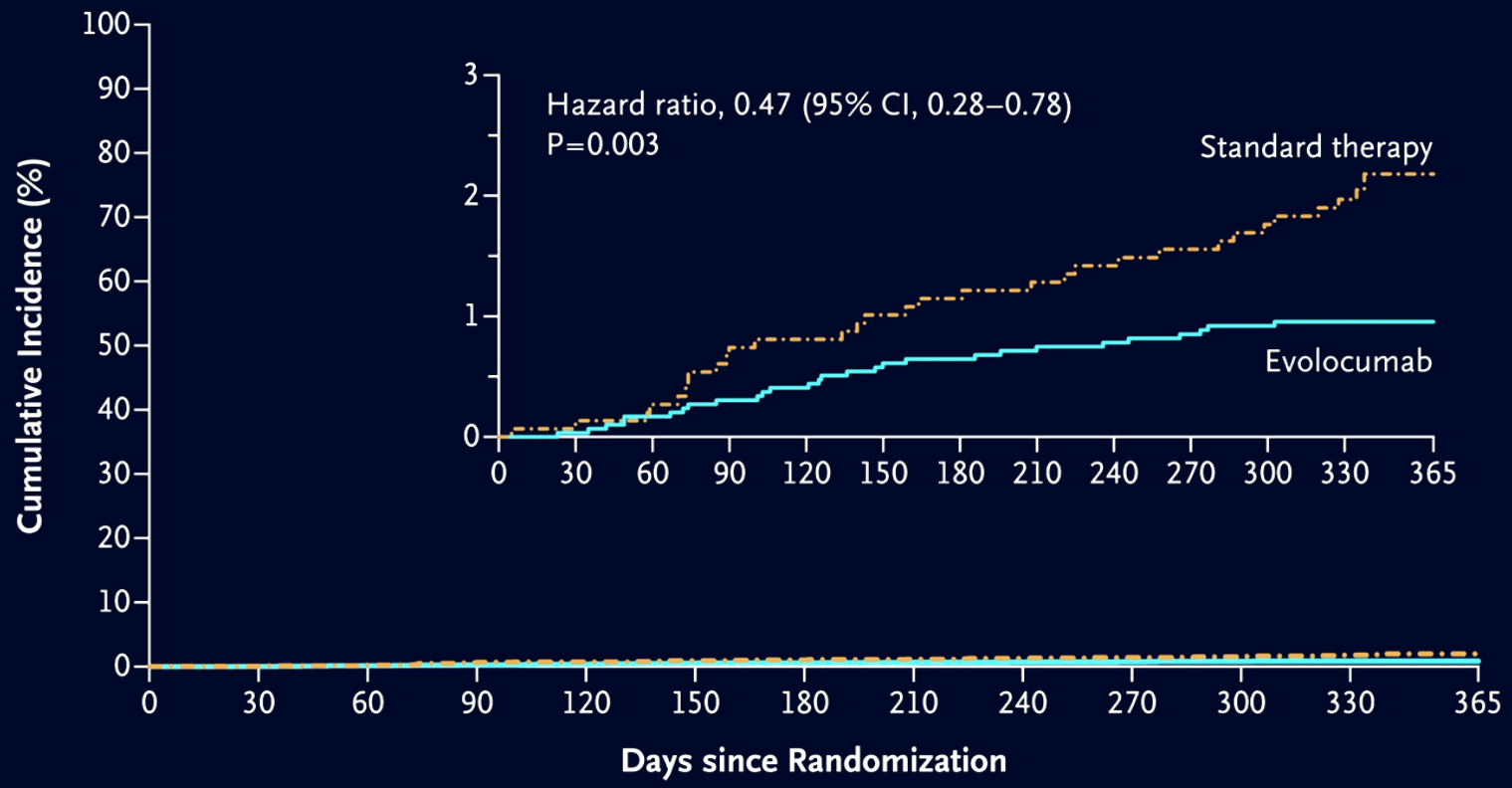
ORIGINAL ARTICLE

# 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

# Cumulative Incidence of Cardiovascular Events

**Included among the cardiovascular events were death, myocardial infarction, unstable angina requiring hospitalization, coronary revascularization, stroke, transient ischemic attack, and hospitalization for heart failure. Cardiovascular events were reported in 29 of 2976 patients in the evolocumab group (Kaplan–Meier 1-year event rate, 0.95%) and in 31 of 1489 patients in the standard-therapy group (Kaplan–Meier 1-year event rate, 2.18%). The inset shows the same data on an expanded y axis. The P value was calculated with the use of a log-rank test**




**No. at Risk**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Standard therapy | 1489 | 1486 | 1481 | 1473 | 1467 | 1463 | 1458 | 1454 | 1447 | 1438 | 1428 | 1361 | 407 |
| Evolocumab | 2976 | 2970 | 2962 | 2949 | 2938 | 2930 | 2920 | 2910 | 2901 | 2885 | 2871 | 2778 | 843 |

*N Engl J Med. 2015 Apr 16;372(16):1500-9*

REVIEW

Annals of Internal Medicine

# Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia

## A Systematic Review and Meta-analysis

**Eliano Pio Navarese, MD, PhD*; Michalina Kołodziejczak, MD*; Volker Schulze, MD; Paul A. Gurbel, MD; Udaya Tantry, PhD; Yingfeng Lin, MD; Maximilian Brockmeyer, MD; David E. Kandzari, MD; Julia M. Kubica, MD; Ralph B. D'Agostino Sr., PhD; Jacek Kubica, MD, PhD; Massimo Volpe, MD; Stefan Agewall, MD; Dean J. Kereiakes, MD; and Malte Kelm, MD**

**Background:** Guidelines recommend statins as first-line therapy for dyslipidemia. Monoclonal antibodies targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) is a new lipid-lowering approach.

**Purpose:** To assess the efficacy and safety of PCSK9 antibodies in adults with hypercholesterolemia.

**Data Sources:** MEDLINE, PubMed Central, and Google Scholar; conference proceedings; and the ClinicalTrials.gov registry through 4 April 2015.

**Study Selection:** Phase 2 or 3 randomized, controlled trials (RCTs) comparing treatment using PCSK9 antibodies with no anti-PCSK9 therapy in adults with hypercholesterolemia.

**Data Extraction:** Two investigators independently extracted data on study characteristics and lipid and clinical outcomes, and rated risk of bias of trials. Prespecified primary end points were all-cause and cardiovascular mortality.

**Data Synthesis:** Twenty-four RCTs comprising 10 159 patients were included. Compared with no antibody, treatment with PCSK9 antibodies led to marked reductions in low-density lipoprotein cholesterol levels (mean difference, −47.49% [95% CI, −69.64% to −25.35%]; $P < 0.001$] and other atherogenic lipid fractions, and it reduced all-cause mortality (odds ratio [OR], 0.45 [CI, 0.23 to 0.86]; $P = 0.015$; heterogeneity $P = 0.63$; $I^2 = 0\%$) and cardiovascular mortality (OR, 0.50 [CI, 0.23 to 1.10]; $P = 0.084$; heterogeneity $P = 0.78$; $I^2 = 0\%$). The rate of myocardial infarction was significantly reduced with use of PCSK9 antibodies (OR, 0.49 [CI, 0.26 to 0.93]; $P = 0.030$; heterogeneity $P = 0.45$; $I^2 = 0\%$), and increases in the serum creatine kinase level were reduced (OR, 0.72 [CI, 0.54 to 0.96]; $P = 0.026$; heterogeneity $P = 0.65$; $I^2 = 0\%$). Serious adverse events did not increase with administration of PCSK9 antibodies.

**Limitation:** Results were derived from study-level data rather than patient-level data, and clinical outcome data are rare.

**Conclusion:** PCSK9 antibodies seem to be safe and effective for adults with dyslipidemia.

**Primary Funding Source:** CRC 1116 Masterswitches in Myocardial Ischemia, German Research Council DFG.

*Ann Intern Med.* 2015;163:40-51. doi:10.7326/M14-2957 **www.annals.org**

For author affiliations, see end of text.

This article was published online first at www.annals.org on 28 April 2015.

* Drs. Navarese and Kołodziejczak contributed equally to this work.

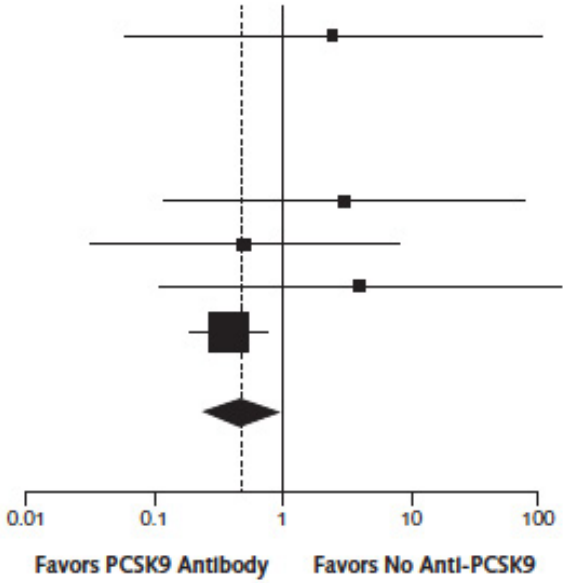
*Figure 3.* Myocardial infarction (*top*) and unstable angina (*bottom*).

**MI**

| Study | Events/Total, *n/N* | | Odds Ratio (95% CI) | Weight, % |
|---|---|---|---|---|
| | PCSK9 Antibody | No Anti-PCSK9 | | |
| DESCARTES | 1/599 | 0/302 | 2.51 (0.06–102.80) | 3.0 |
| LAPLACE-TIMI 57 | 0/158 | 0/157 | – | 0.0 |
| McKenney et al | 0/31 | 0/31 | – | 0.0 |
| MENDEL | 0/90 | 0/135 | – | 0.0 |
| ODYSSEY ALTERNATIVE | 1/126 | 0/125 | 3.02 (0.12–75.06) | 4.0 |
| ODYSSEY COMBO I | 1/209 | 1/107 | 0.51 (0.03–8.23) | 5.4 |
| ODYSSEY FH I and FH II | 2/490 | 0/245 | 4.02 (0.11–147.57) | 3.2 |
| ODYSSEY LONG TERM | 14/1553 | 18/788 | 0.39 (0.19–0.79) | 84.3 |
| TESLA Part B | 0/33 | 0/16 | – | 0.0 |
| Fixed-effect model | 19/3289 | 19/1906 | 0.49 (0.26–0.93) | 100 |

Heterogeneity: $I^2 = 0\%$; $\tau^2 = 0$; $P = 0.4492$

Test for overall effect: $Z = -2.17$ ($P = 0.030$)

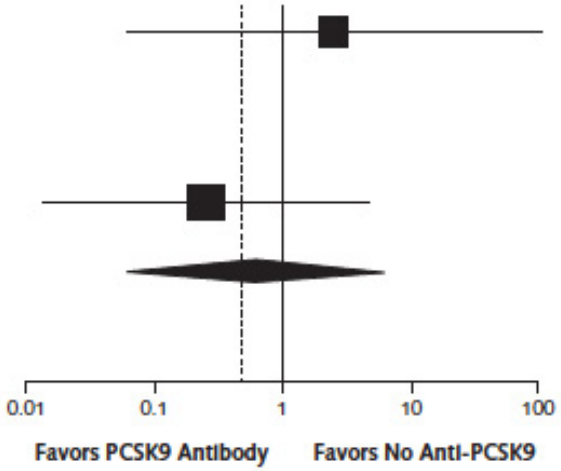



**UA**

| Study | Events/Total, *n/N* | | Odds Ratio (95% CI) | Weight, % |
|---|---|---|---|---|
| | PCSK9 Antibody | No Anti-PCSK9 | | |
| DESCARTES | 1/599 | 0/302 | 2.51 (0.06–102.80) | 38.6 |
| McKenney et al | 0/31 | 0/31 | – | 0.0 |
| MENDEL | 0/90 | 0/135 | – | 0.0 |
| ODYSSEY COMBO I | 0/209 | 0/107 | – | 0.0 |
| ODYSSEY LONG TERM | 0/1553 | 1/788 | 0.25 (0.01–4.78) | 61.4 |
| TESLA Part B | 0/33 | 0/16 | – | 0.0 |
| Fixed-effect model | 1/2515 | 1/1379 | 0.61 (0.06–6.14) | 100 |

Heterogeneity: $I^2 = 0\%$; $\tau^2 = 0$; $P = 0.3415$

Test for overall effect: $Z = -0.42$ ($P = 0.676$)




See the legend for **Figure 1** for abbreviation expansions.

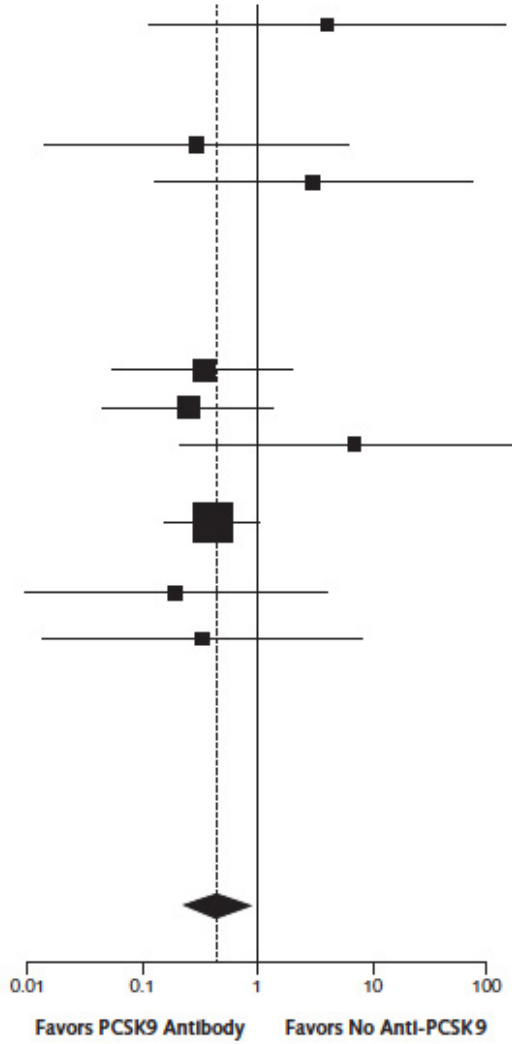
*Figure 1.* All-cause mortality.

**MORTALITY**

| Study | Events/Total, *n/N* | | Odds Ratio (95% CI) | Weight, % |
|---|---|---|---|---|
| | PCSK9 Antibody | No Anti-PCSK9 | | |
| DESCARTES | 2/599 | 0/302 | 4.02 (0.11–146.40) | 3.3 |
| GAUSS | 0/32 | 0/33 | – | 0.0 |
| GAUSS-2 | 0/205 | 0/102 | – | 0.0 |
| LAPLACE-2 | 0/1117 | 1/779 | 0.29 (0.01–6.09) | 4.6 |
| LAPLACE-TIMI 57 | 1/158 | 0/157 | 3.01 (0.12–74.77) | 4.1 |
| McKenney et al | 0/31 | 0/31 | – | 0.0 |
| MENDEL | 0/90 | 0/135 | – | 0.0 |
| MENDEL-2 | 0/306 | 0/308 | – | 0.0 |
| ODYSSEY ALTERNATIVE | 0/126 | 0/125 | – | 0.0 |
| ODYSSEY COMBO I | 2/209 | 3/107 | 0.33 (0.06–2.04) | 13.0 |
| ODYSSEY COMBO II | 2/479 | 4/241 | 0.25 (0.05–1.37) | 14.5 |
| ODYSSEY FH I and FH II | 4/490 | 0/245 | 7.06 (0.21–237.78) | 3.4 |
| ODYSSEY HIGH FH | 0/72 | 0/35 | – | 0.0 |
| ODYSSEY LONG TERM | 8/1553 | 10/788 | 0.40 (0.16–1.02) | 48.5 |
| ODYSSEY MONO | 0/52 | 0/51 | – | 0.0 |
| ODYSSEY OPTIONS I | 0/104 | 2/102 | 0.19 (0.01–4.06) | 4.6 |
| ODYSSEY OPTIONS II | 0/103 | 1/101 | 0.33 (0.01–8.06) | 4.1 |
| Roth et al (2012) | 0/30 | 0/31 | – | 0.0 |
| RUTHERFORD | 0/56 | 0/56 | – | 0.0 |
| RUTHERFORD-2 | 0/221 | 0/110 | – | 0.0 |
| Stein et al | 0/16 | 0/15 | – | 0.0 |
| TESLA Part B | 0/33 | 0/16 | – | 0.0 |
| YUKAWA | 0/105 | 0/102 | – | 0.0 |
| Fixed-effect model | 19/6187 | 21/3972 | 0.45 (0.23–0.86) | 100 |

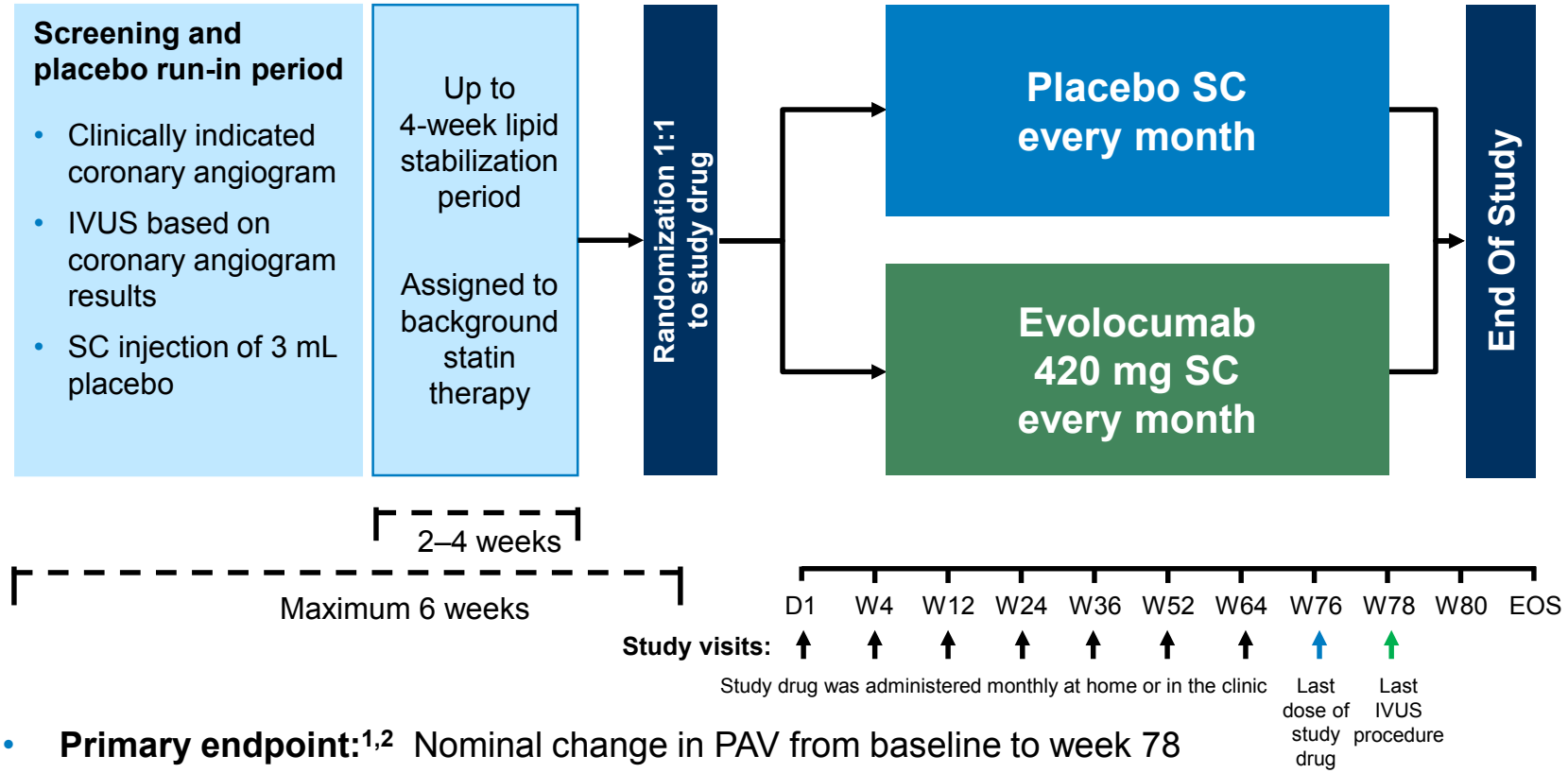
Heterogeneity: $I^2 = 0\%$; $\tau^2 = 0$; $P = 0.6296$

Test for overall effect: $Z = -2.43$ ($P = 0.015$)




Expanded study abbreviations are as follows: DESCARTES = Durable Effect of PCSK9 Antibody Compared with Placebo Study; GAUSS = Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects; LAPLACE-2 = LDL-C Assessment with PCKS9 Monoclonal Antibody Inhibition Combined With Statin Therapy-2; LAPLACE-TIMI 57 = LDL-C Assessment with PCKS9 Monoclonal Antibody Inhibition Combined With Statin Therapy = Thrombosis in Myocardial Infarction 57; MENDEL = Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Patients Currently Not Receiving Drug Therapy For Easing Lipid Levels; RUTHERFORD = The Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familiar Hypercholesterolemia Disorder; PCSK9 = proprotein convertase subtilisin/kexin type 9; TESLA = Trial Evaluating PCSK9 Antibody in Subjects with LDL Receptor Abnormalities; YUKAWA = Study of LDL-Cholesterol Reduction Using a Monoclonal PCSK9 Antibody in Japanese Patients With Advanced Cardiovascular Risk.

# GLAGOV: Study Design




- **Primary endpoint:**[1,2] Nominal change in PAV from baseline to week 78
- **Key secondary endpoints:**[1,2]
  - Nominal change in TAV from baseline to week 78
  - Percentage of patients demonstrating regression (any reduction from baseline) in either PAV or TAV from baseline to week 78

**1.** Puri R, et al. *Am Heart J*. doi: 10.1016/j.ahj.2016.01.019. **2.** ClinicalTrials.gov. NCT01813422. https://clinicaltrials.gov/ct2/show/NCT01813422. Accessed March 15,2016.

# Adverse events in Patients with LDL-C < 25 or 15 mg/dL in 14 trials of Alirocumab

## *Selected TEAEs (%)*

| | Pooled control (n=1894) | Pooled Alirocumab (n=3340) | Pooled Alirocumab LDL-C < 25 mg/dL (n=796) | Pooled Alirocumab LDL-C < 15 mg/dL (n=288) |
|---|---|---|---|---|
| Infections and Infestations | 36.3 | 38.5 | 34.0 | 35.4 |
| Musculoskeletal disorders | 25.2 | 24.2 | 21.1 | 20.1 |
| Injection-site reaction | 3.9 | 5.7 | 3.0 | 3.5 |
| Nervous system disorders | 14.9 | 14.9 | 10.3 | 9.0 |
| Diabetes mellitus | 1.3 | 1.2 | 1.5 | 2.4 |
| Neoplasms | 2.5 | 2.5 | 2.8 | 2.4 |

TEAE : Treatment Emergent Adverse Event

*Robinson et al. ACC 2015*

# PCSK9 inhibitor upcoming CVOTs

| Mnf/ Molecule | Main trial | Patients & Inclusion criteria | Comparator | Primary CV Outcome | Expected Lipid Reduction† |
|---|---|---|---|---|---|
| Amgen<br><br>**Evolocumab AMG 145** | FOURIER<br>Phase III<br>Recruiting<br><br>Trial results Q1 2017 | 28 000<br>• History of a prior CV event or PAD and at high risk for a recurrent event<br>• *Fasting LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL on a background of atorvastatin*<br>• *Fasting triglycerides ≤ 400 mg/dL* | Statin + AMG 145<br><br>vs.<br><br>Statin + placebo | Time to first of:<br>- cardiovascular death<br>- myocardial infarction<br>- hospitalization for unstable angina, stroke, or coronary revascularzation | ~65% LDL-C reduction |
| Sanofi/Regeneron<br><br>**Alirocumab (REGN 727**) | ODYSSEY<br>Phase III<br>Recruiting<br><br>Trial results Q1 2018 | 18 000<br>• Recently hospitalized for ACS<br>• *>40 yrs recently hospitalized for ACS event (4-52 wks post ACS event)*<br>• *>70mg/dL on background of atorvastatin, rosuvastatin, or with demonstrated statin intolerance* | Statin + REGN 727<br><br>vs.<br><br>Statin + placebo | Occurrence of CV events -composite endpoint consisting of:<br>- coronary heart disease death<br>- non-fatal myocardial infarction<br>- fatal/non-fatal ischemic stroke<br>- unstable angina requiring hospitalization | ~50% LDL-C reduction |

Sources: clinicaltrials.gov - NCT01764633 and NCT01663402, Internal IMS Research

# WHAT PCSK9 CLINICAL TRIALS TOLD US (SO FAR)

- >50% EFFICACY FOR LDL REDUCTION IN ALL POPULATIONS STUDIED
- SUSTAINED EFFICACY IN LONG TERM (UP TO 78 WEEKS) STUDIES
- EFFICACY INDEPENDENT ON BACKGROUND THERAPY OR AS MONOTHERAPY
- REASSURING SAFETY PROFILE UP TO 78 WEEKS
- VERY FAVOURABLE PRELIMINARY DATA ON CLINICAL OUTCOMES