

# Ακάλυπτες Θεραπευτικές ανάγκες στη δυσλιπιδαιμία: Ο ρόλος των PCSK9 inhibitors



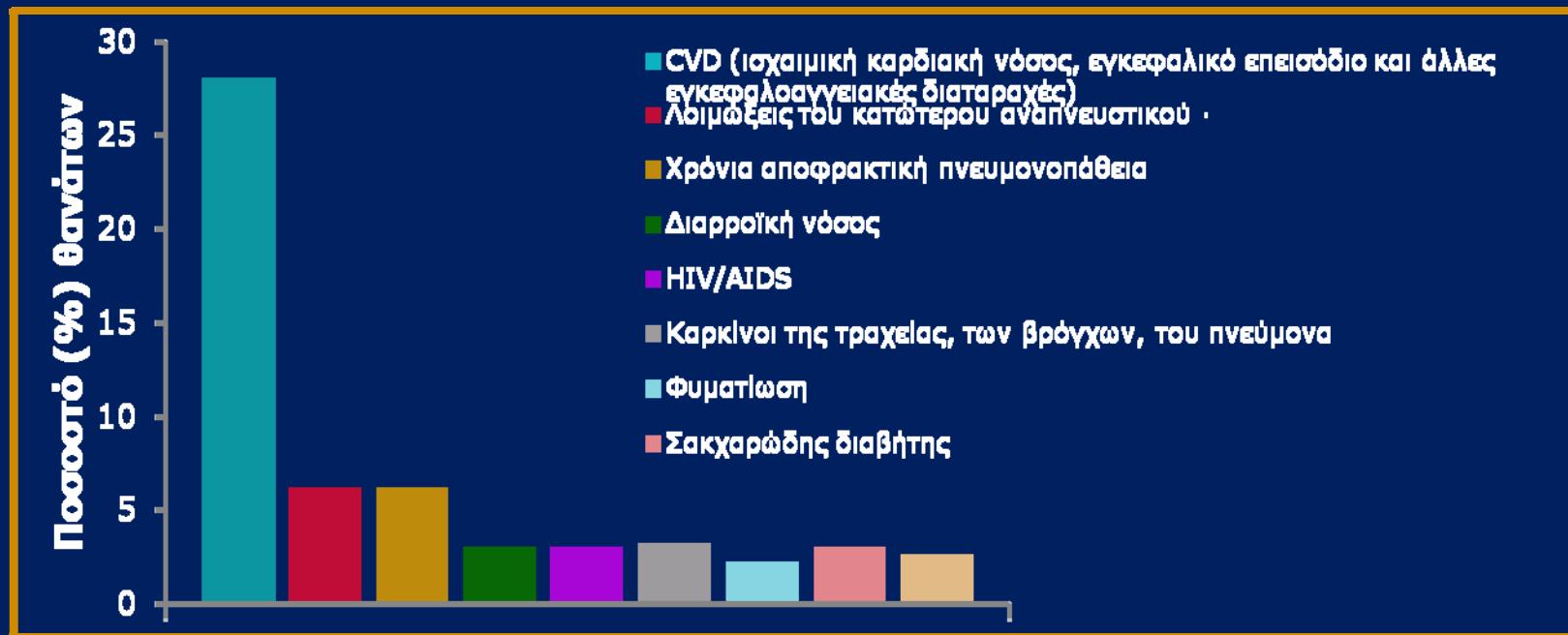
Β. Αθυρος, MD, FESC, FRSPH, FASA, FACS

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# Η Καρδιαγγειακή νόσος (CVD) είναι η νούμερο ένα αιτία θανάτων παγκοσμίως

- Σύνοψη των κύριων αιτιών θανάτου παγκοσμίως. **Μεταξύ των 10 κυριότερων αιτιών θανάτου παγκοσμίως το 2012, η Καρδιαγγειακή νόσος αντιπροσώπευε το 28% του συνόλου των θανάτων<sup>1</sup>**



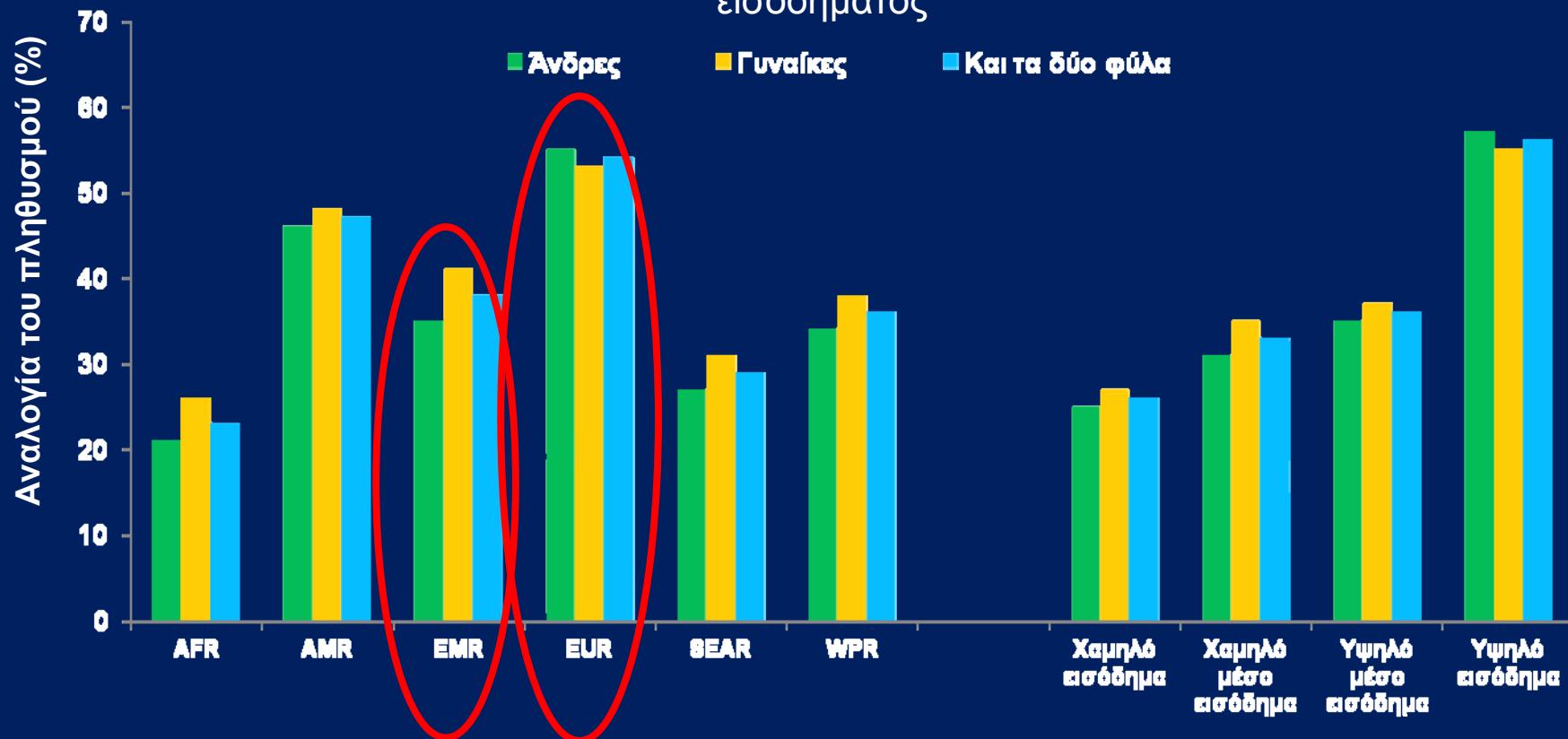
- Κατά μέσο όρο, 1 Αμερικανός πεθαίνει από CVD κάθε 40 δευτερόλεπτα, το οποίο αντιστοιχεί σε περίπου 2200 θανάτους ημερησίως<sup>2</sup>
- Κάθε χρόνο, η CVD προκαλεί πάνω από 4 εκατομμύρια θανάτους στην Ευρώπη και πάνω από 1,9 εκατομμύρια θανάτους στην Ευρωπαϊκή Ένωση<sup>3</sup>
- > 80% των θανάτων από καρδιαγγειακά νοσήματα συντελούνται σε χώρες χαμηλού και μεσαίου εισοδήματος και εμφανίζονται σε παρόμοια ποσοστά σε άνδρες και γυναίκες<sup>4</sup>
- Μέχρι το 2030, σχεδόν **23,3 εκατ.** άνθρωποι θα πεθάνουν από CVD παγκοσμίως σε ετήσια βάση, κυρίως από καρδιακή νόσο και εγκεφαλικό επεισόδιο<sup>5</sup>

1. Παγκόσμιος Οργανισμός Υγείας. The top 10 causes of death, factsheet No. 310. <http://who.int/mediacentre/factsheets/fs310/en/index.html>. Προστελάστηκε τον Ιούλιο του 2014.

2. Go AS et al. Σε κυκλοφορία. 2013; 127: E6-e245. 3. Nichols M et al. European Cardiovascular Disease Statistics. 4th ed. Brussels, Belgium: European Heart Network, 2012: 4. Παγκόσμιος Οργανισμός Υγείας. Cardiovascular Diseases (CVDs). <http://www.who.int/mediacentre/factsheets/fs317/en/index.html>. Προστελάστηκε στις 12 Φεβρουαρίου 2014. 5. Mathers CD, Loncar D. PLoS Med. 2006; 3(11):e442. doi:10.1371/journal.pmed.0030442.

## Επιπολασμός της δυσλιπιδαιμίας (ολική χοληστερόλη >200 mg/dL): παγκόσμια στοιχεία

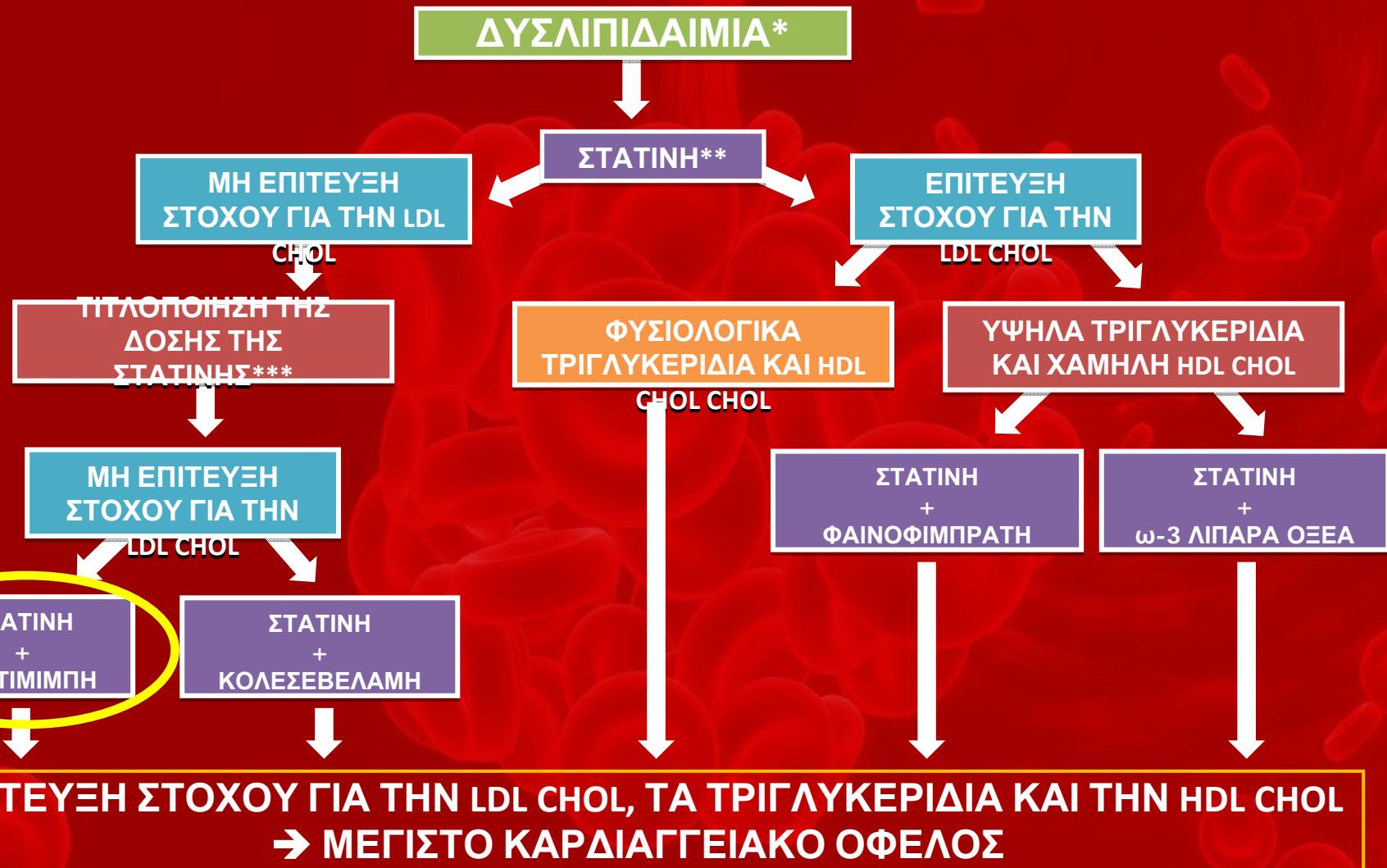
Η δυσλιπιδαιμία εξακολουθεί να είναι ένας από τους κυριότερους παράγοντες καρδιαγγειακού κινδύνου παγκοσμίως, ιδίως σε χώρες και πληθυσμούς υψηλού εισοδήματος



AFR, Αφρική, AMR, Αμερικανική Ήπειρος, EMR, Ανατολική Μεσόγειος, EUR, Ευρώπη, SEAR, Νοτιοανατολική Ασία, WPR, Δυτικός Ειρηνικός

WHO. Global Health Observatory: raised cholesterol – situation and trends. Διατίθεται στο δικτυακό τόπο:  
[http://www.who.int/gho/ncd/risk\\_factors/cholesterol\\_text/en/](http://www.who.int/gho/ncd/risk_factors/cholesterol_text/en/)

# Αλγόριθμος φαρμακευτικής θεραπευτικής προσέγγισης ασθενών με δυσλιπιδαιμία



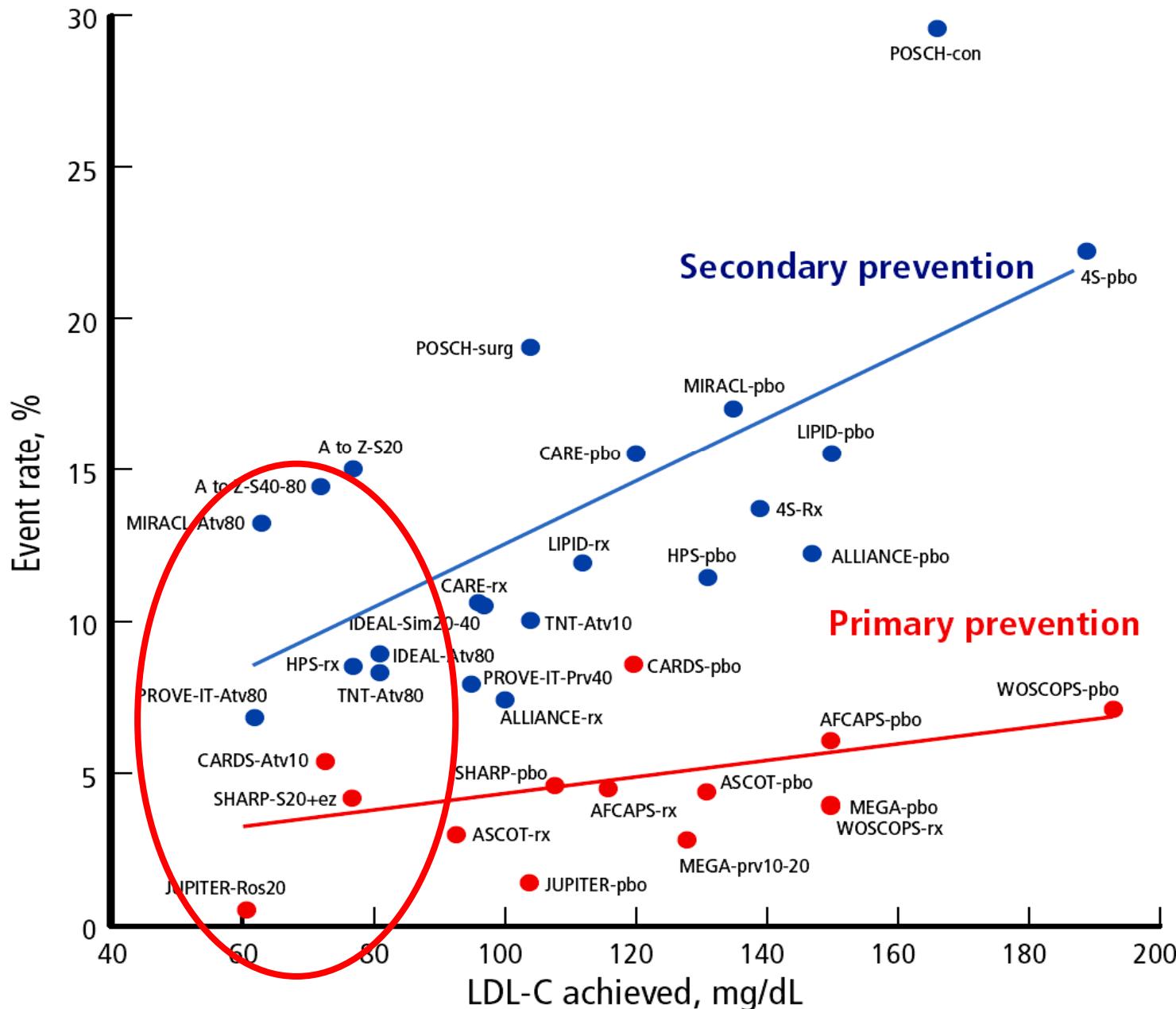
\*Αν τριγλυκερίδια νηστείας >500 mg/dL συνιστάται η άμεση χορήγηση μίας φιμπράτης ή/και ω-3 λιπαρών οξέων

\*\*Για την επίτευξη του στόχου της αυγής συνιστάται η χορήγηση μιας στατίνης σε δόση που αναμένεται να επιτύχει το στόχο της θεραπείας

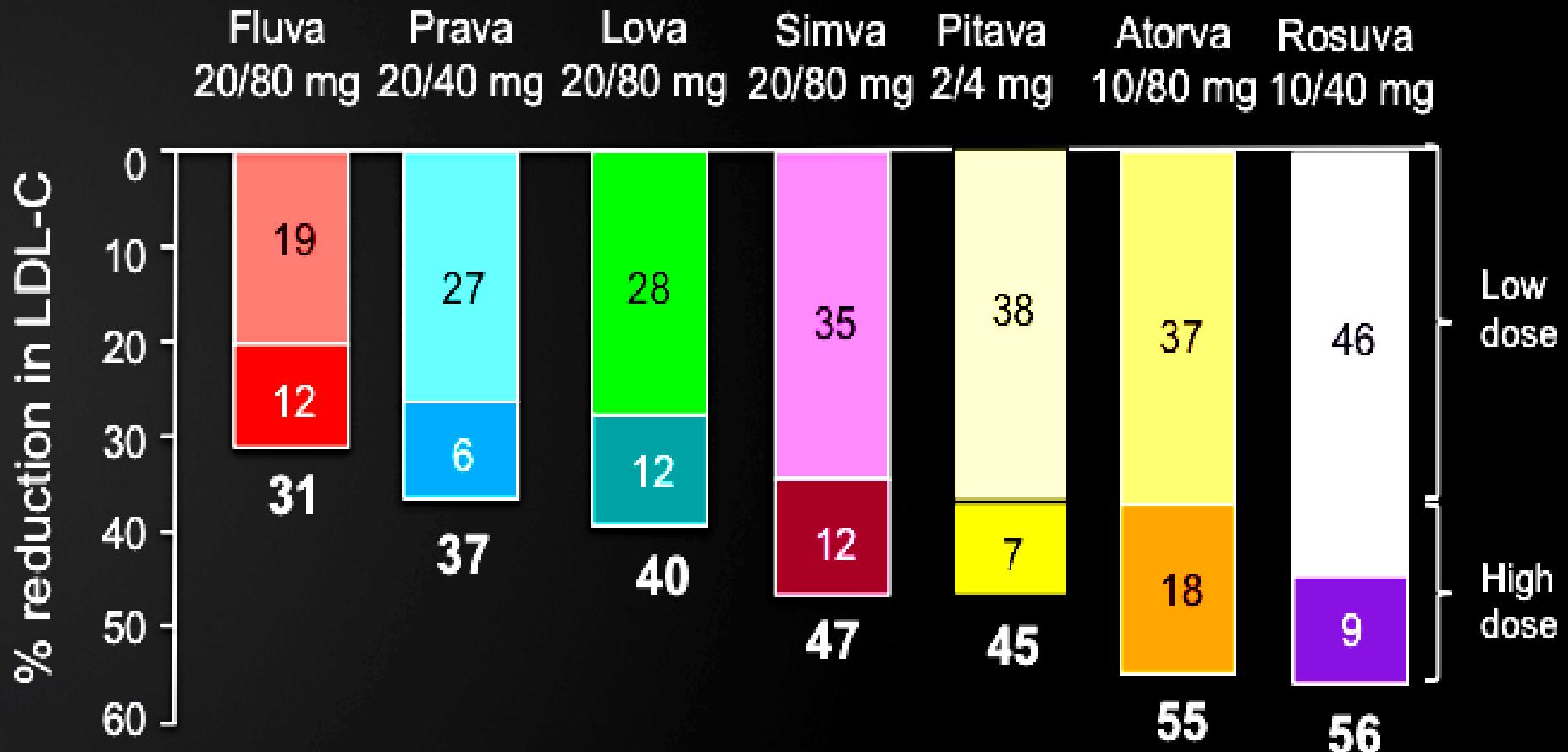
\*\*\*Κάθε διπλασιασμός της δόσης μίας στατίνης οδηγεί σε 6% περαιτέρω ελάττωση της LDL CHOL



## Major lipid trials: LDL-C levels vs rates of coronary events



## Statins can lower LDL-C by up to 55%



Adapted from Illingworth DR. *Med Clin North Am.* 2000;84:23-42

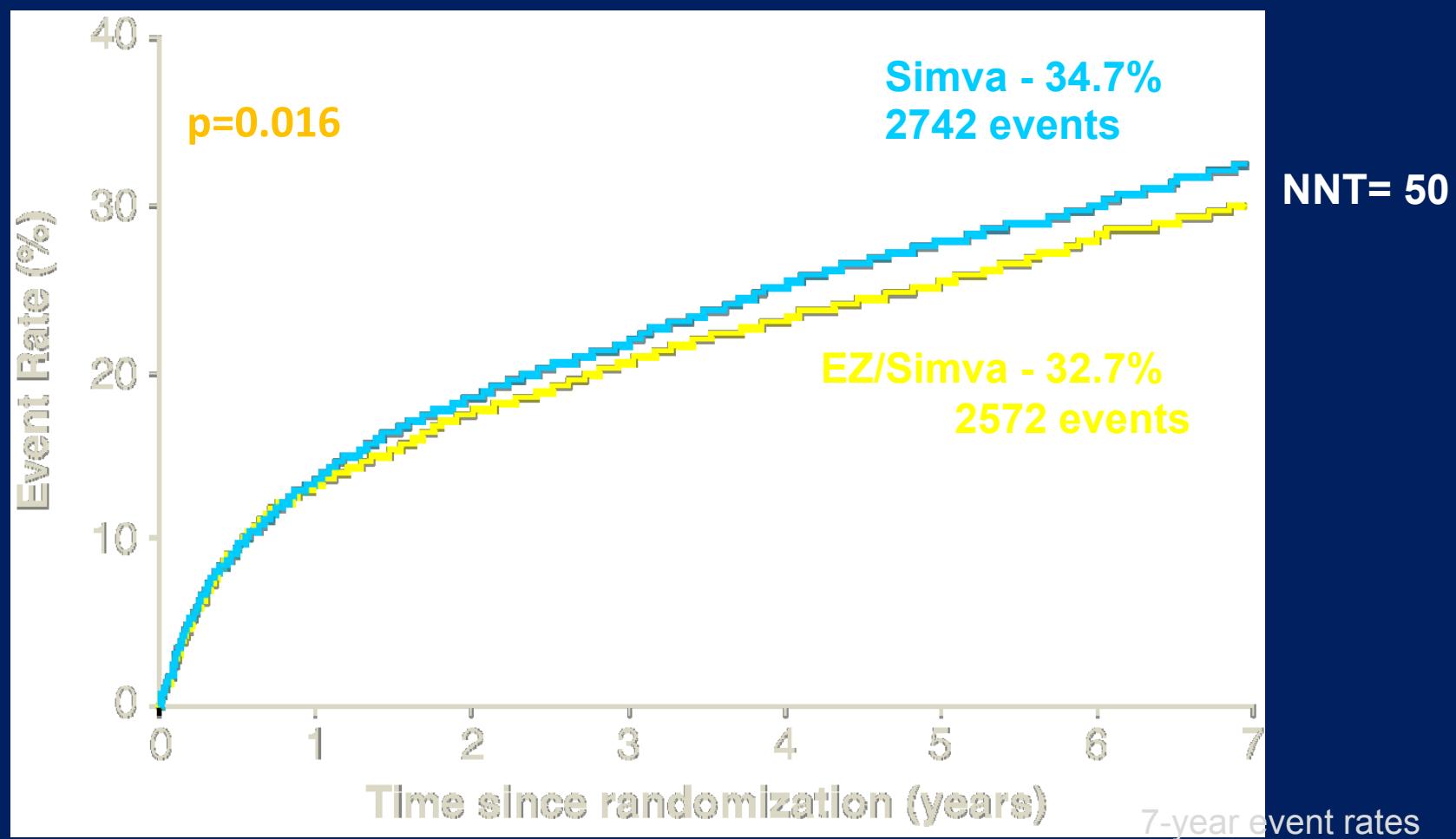
Budinski D, et al. *Clin Lipidol.* 2009;4: 291-302

Jones PH, et al. *Am J Cardiol* 2003;93:152–60

## Primary Endpoint – ITT



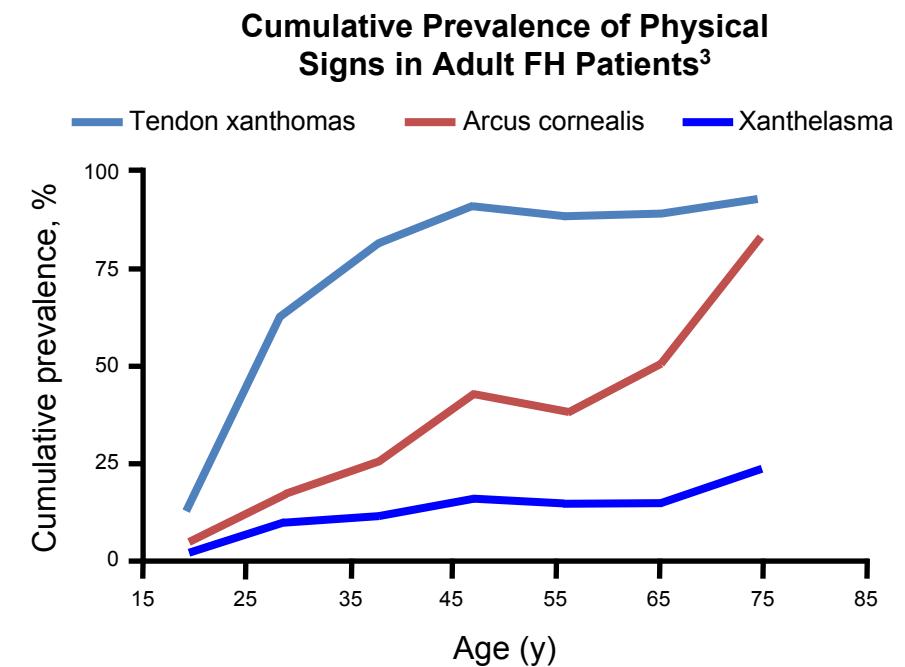
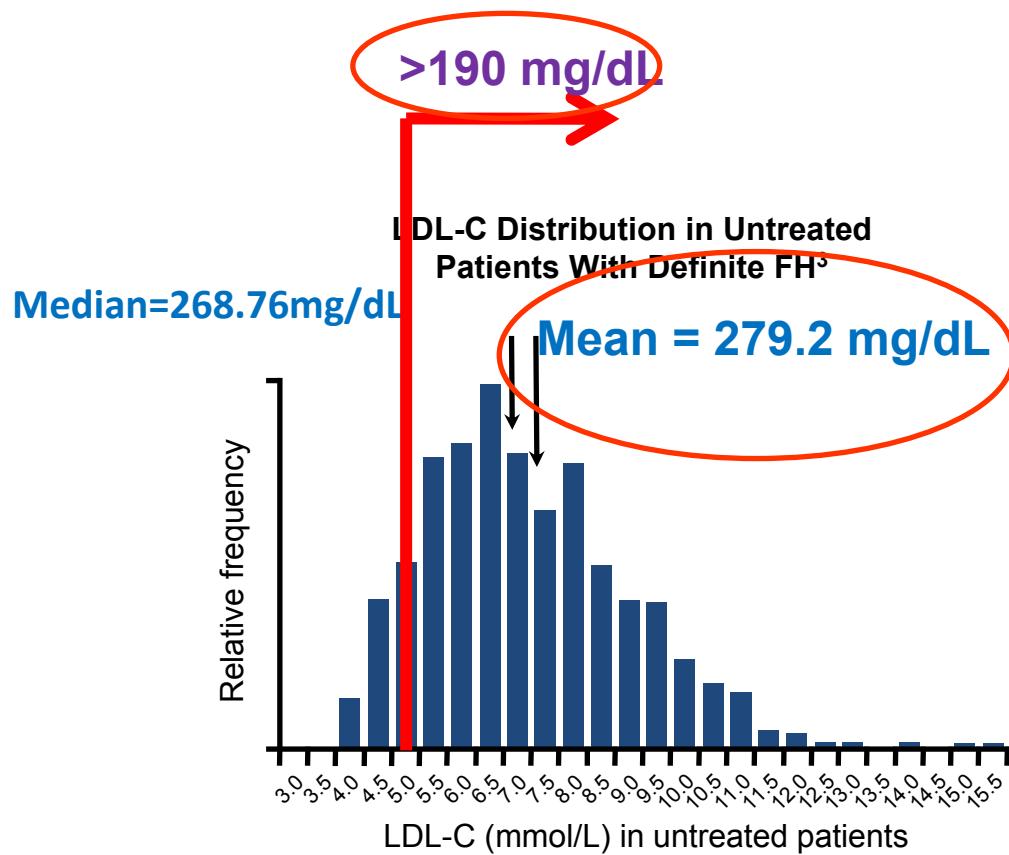
*Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization ( $\geq 30$  days), or stroke*



## **Ακάλυπτες θεραπευτικές ανάγκες στη δυσλιπιδαιμία:**

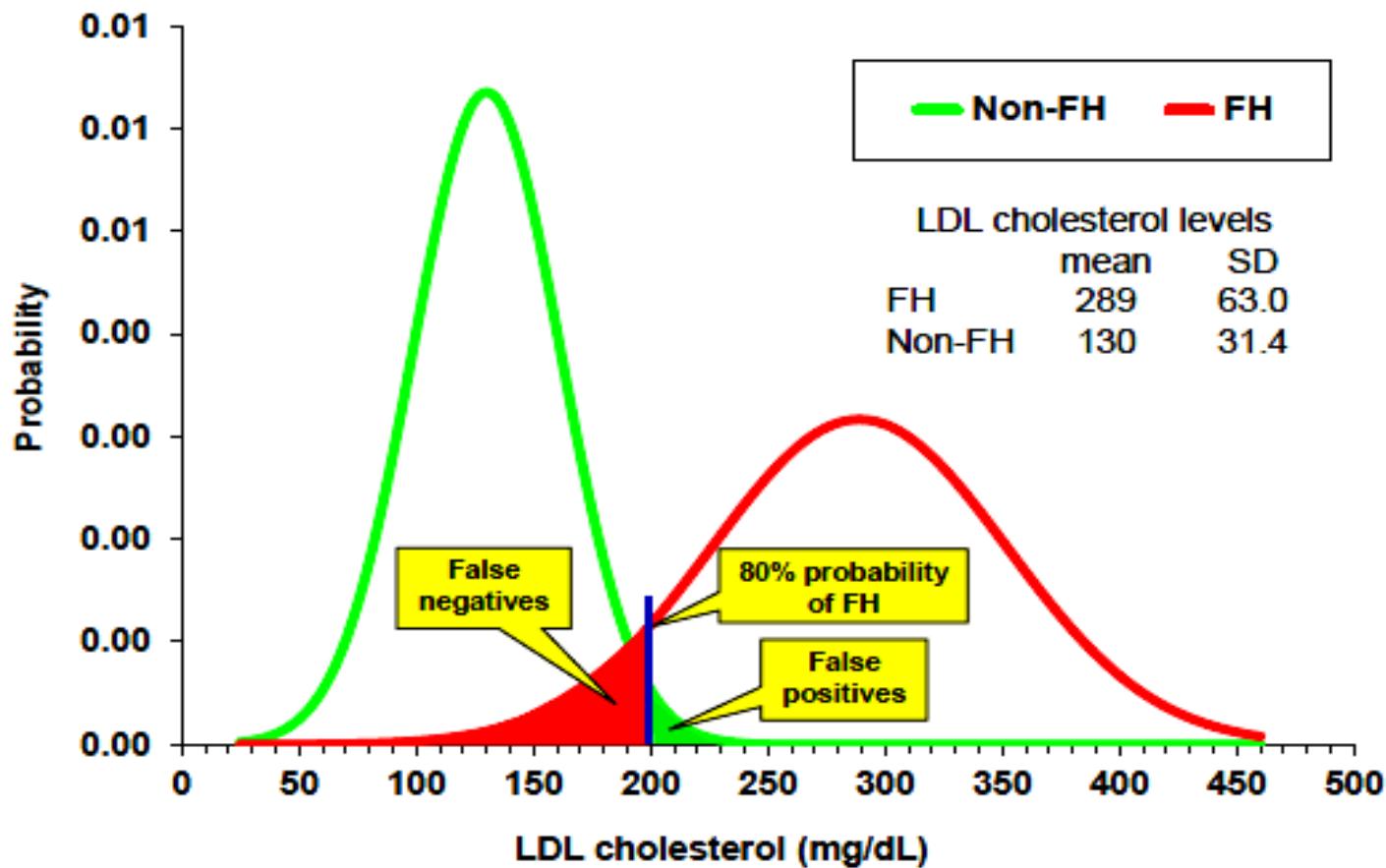
1. Ασθενείς με **οικογενή υπερχοληστερολαιμία** (υπολογίζονται σε **40.000 άτομα στην Ελλάδα**). Πρόκειται για μια κληρονομική νόσο που χαρακτηρίζεται από πολύ υψηλά επίπεδα LDL-X τα οποία δεν μπορούν να ελαττώσουν σε ικανοποιητικό επίπεδο (θεραπευτικό στόχο) ακόμη και οι συνδυασμοί των ισχυρότερων υπολιπιδαιμικών.
2. **Ασθενείς που δεν μπορούν να ανεχθούν τις στατίνες λόγω ανεπιθύμητων ενεργειών από τους μυς ή το ήπαρ (υπολογίζοντα σε **60.000-100.000 άτομα** με πραγματική δυσανεξία στις στατίνες).**
3. **Ασθενείς υψηλού κυρίως κινδύνου που λόγω αρχικά υψηλών LDL χοληστερόλης ή μη ικανοποιητικής απάντησης στη θεραπεία δεν επιτυγχάνουν τους θεραπευτικούς στόχους (άγνωστος αριθμός ασθενών).**

# LDL-C concentrations and physical signs in untreated FH patients

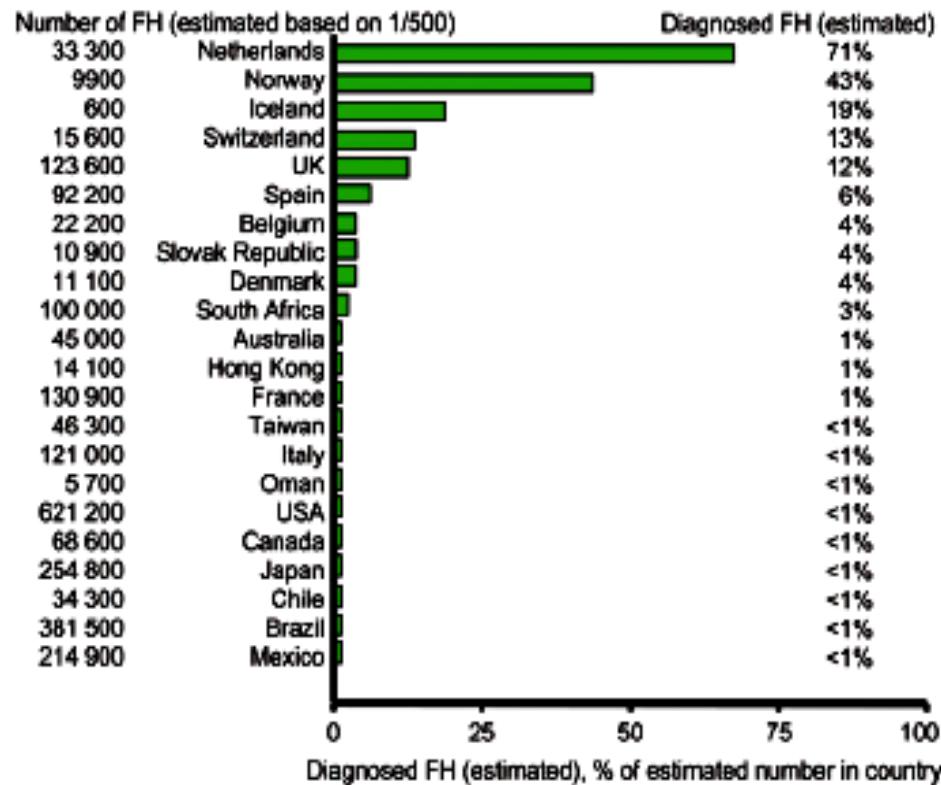


1. Marais AD. *Clin Biochem Rev.* 2004;25(1):49-68.
2. Raal FJ, et al. *Atherosclerosis.* 2000;150(2):421-428.
3. Blom DJ, et al. *S Afr Fam Pract.* 2011;53(1):11-18.

# Κατανομή LDL-X στην FH



# FH: Underdiagnosed?



**Figure 1** Estimated per cent of individuals diagnosed with familial hypercholesterolaemia in different countries/territories, as a fraction of those theoretically predicted based on a frequency of 1/500 in the general population. As most countries do not have valid nationwide registries for familial hypercholesterolaemia, several values in this figure represent informed estimates from clinicians/scientists with recognized expertise in and knowledge of familial hypercholesterolaemia in their respective countries. Numbers were provided by Michael Livingston, Steve E. Humphries (UK), Olivier S. Descamps (Belgium).

# The Netherland experience

- Prevalence of HoFH higher than theoretical  
( $\approx 1:400.000$ )
- 25-35 ασθενείς στην Ελλάδα
- Large variability in the phenotypes found
- Phenotypic criteria of HoFH underestimate the actual number of HoADH patients
- Actual number of HeFH,  $\approx 1:250$
- $\approx 40.000$  ασθενείς στην Ελλάδα

# Ακάλυπτες θεραπευτικές ανάγκες στη δυσλιπιδαιμία:

Ασθενείς που δεν μπορούν να ανεχθούν τις στατίνες λόγω ανεπιθύμητων ενεργειών από τους μυς ή το ήπαρ (υπολογίζονται σε **60.000-100.000 άτομα** με πραγματική δυσανεξία στις στατίνες).

1. Αύξηση τρανσαμινασών
2. Μυοσύτιδα με αύξηση CPK
3. Μυαλγίες

Σε δύο τουλάχιστον στατίνες σε μικρές δόσεις.

Μπορεί εναλλακτικά να χορηγηθεί ατορβαστατίνη 10 mg ή ροσουβαστατίνη 5 mg 2 ή 3 φορές την εβδομάδα και εζετιμίμπη κάθε μέρα.

## **Ακάλυπτες θεραπευτικές ανάγκες στη δυσλιπιδαιμία:**

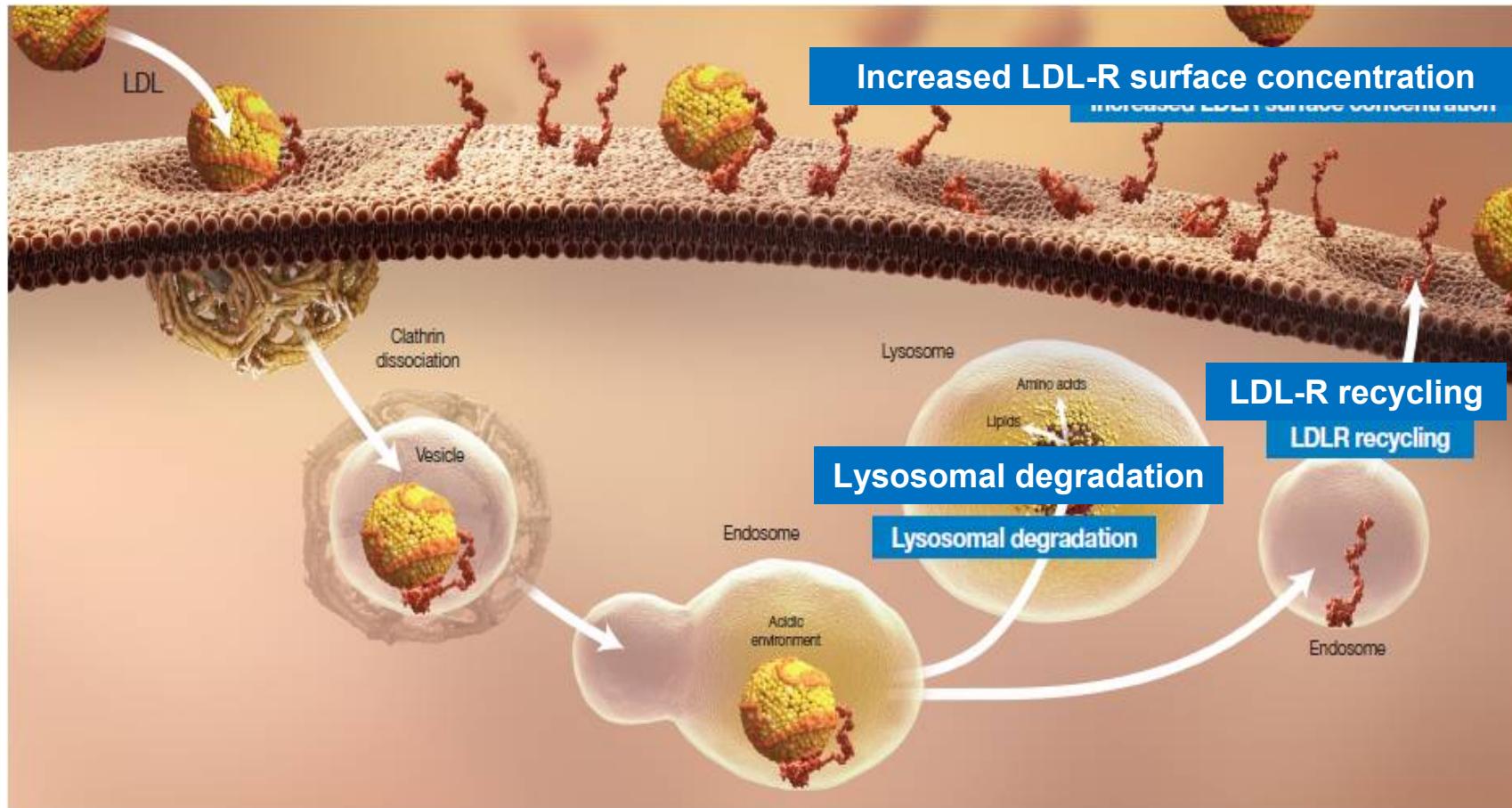
**Ασθενείς υψηλού κυρίως κινδύνου που λόγω αρχικά υψηλών τιμών LDL χοληστερόλης ή μη ικανοποιητικής απάντησης στη θεραπεία δεν επιτυγχάνουν τους θεραπευτικούς στόχους (άγνωστος αριθμός ασθενών).**

## Ανάγκη θεραπείας της δυσλιπιδαιμίας πέρα από στατίνες



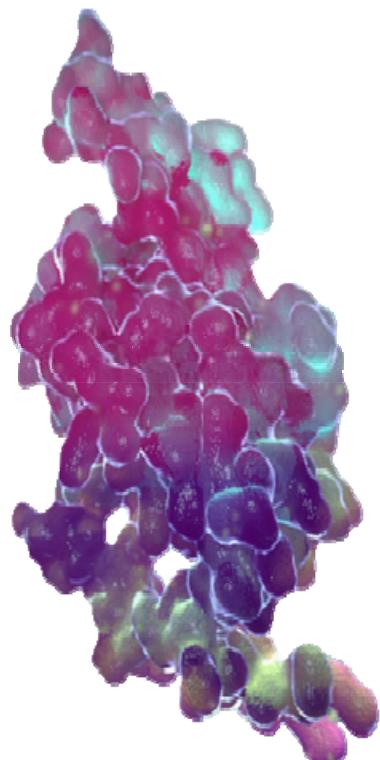
Οι παραπάνω κατηγορίες έχουν ανάγκη θεραπείας με αντισώματα έναντι της PCSK9

# Recycling of LDLR Enables Efficient Clearance of LDL Particles



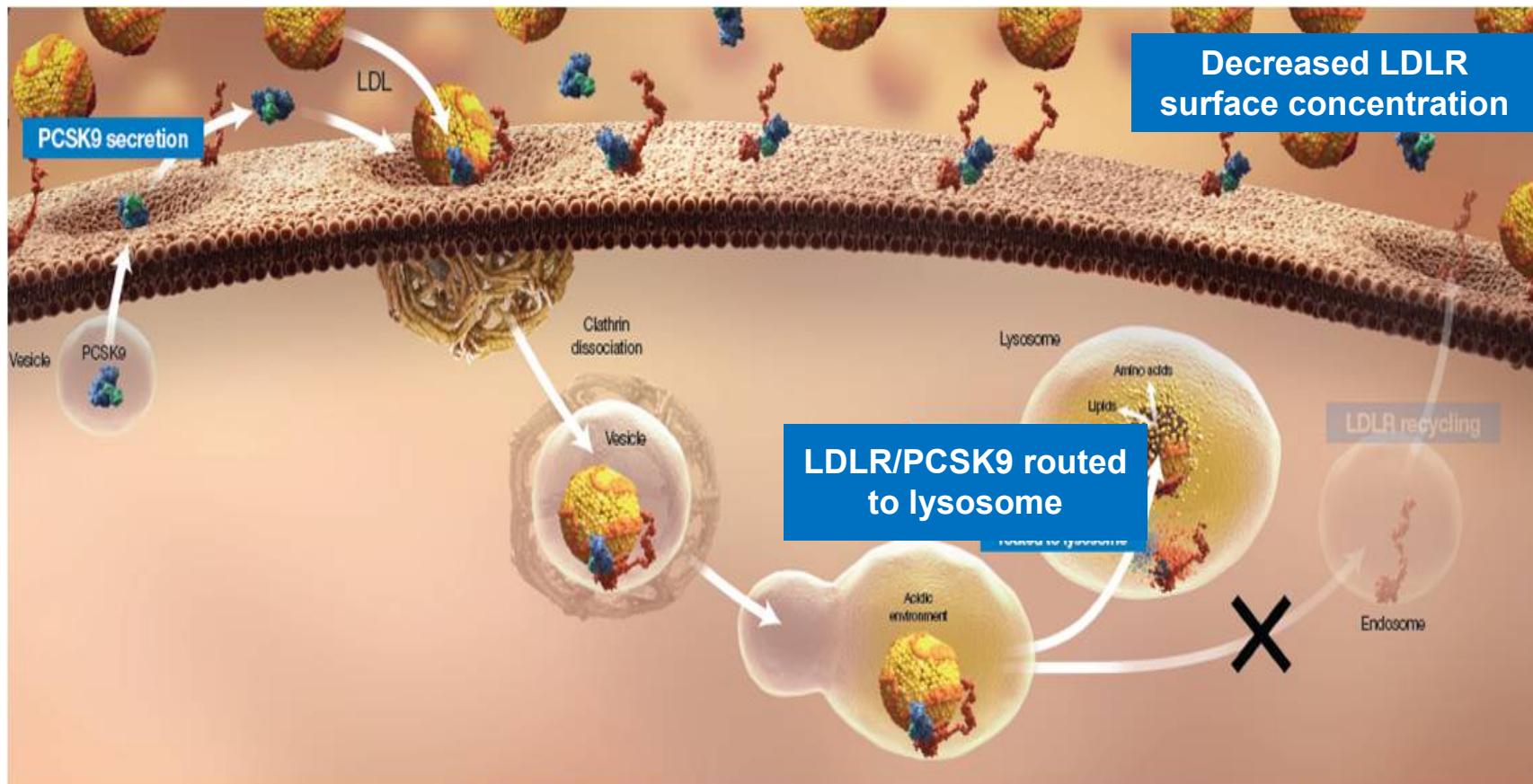
1. Brown MS, Goldstein JL. Proc Natl Acad Sci U S A. 1979;76:3330-3337.
2. Steinberg D, Witztum JL. Proc Natl Acad Sci U S A. 2009;106:9546-9547.
3. Goldstein JL, Brown MS. Arterioscler Thromb Vasc Biol. 2009;29:431-438.

# Τι είναι η PCSK9 ?



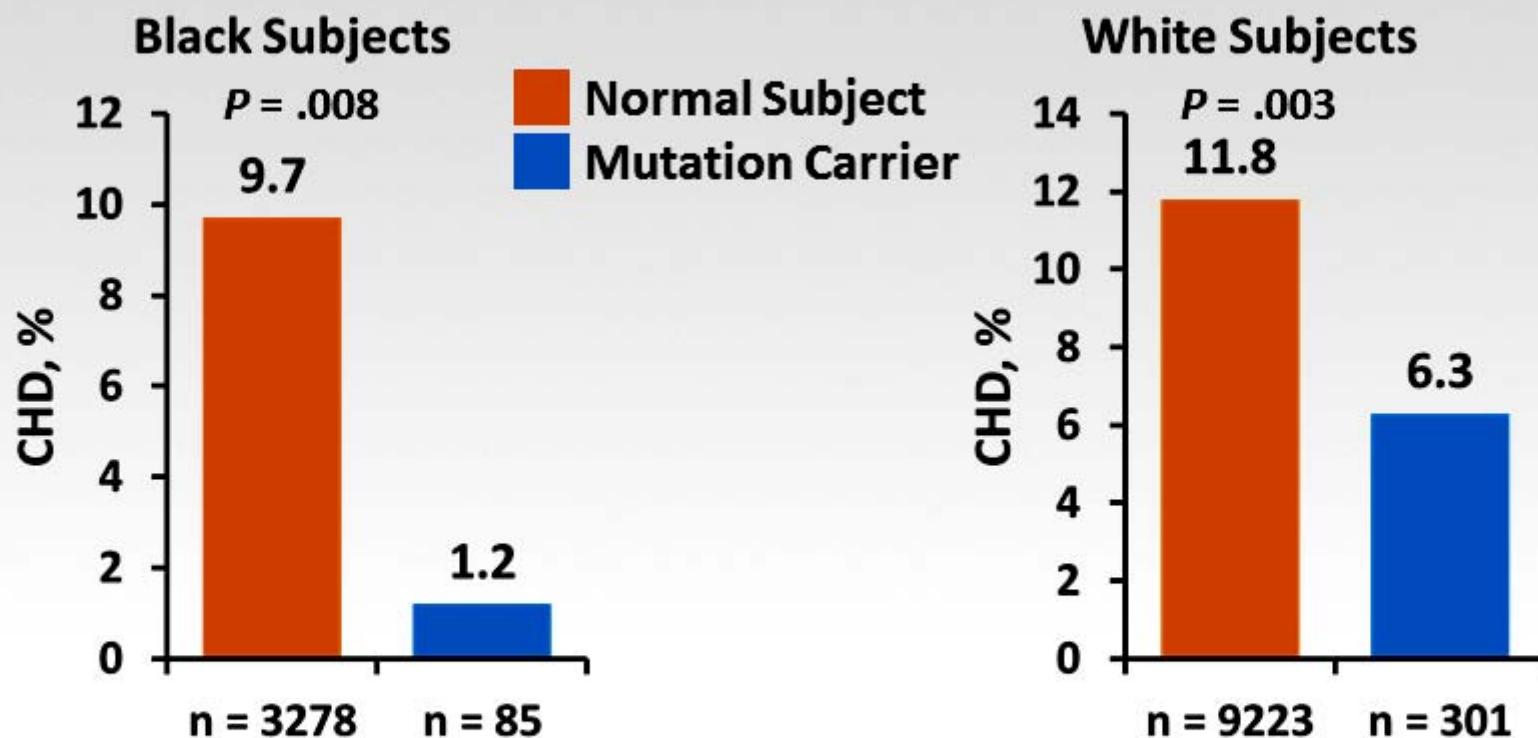
- Η Proprotein convertase subtilisin/kexin type 9 ή PCSK9 είναι μία φυσικά παραγόμενη πρωτεΐνη που συντίθεται στο ηπατοκύτταρο<sup>1,2</sup>
- Η PCSK9 έχει ρόλο κλειδί στη ρύθμιση των υποδοχέων της LDL-C στην επιφάνεια του ηπατοκυττάρου και στον καθορισμό των επίπεδων της LDL χοληστερόλης που κυκλοφορεί στο πλάσμα
- Επίσης βρίσκεται και σε άλλα όργανα όπως στο έντερο και στο νεφρό<sup>1,2</sup>
- Σύντομη παραμονή στο πλάσμα(<10 min); Αφαίρεση από το πλάσμα βασικά μέσω του LDLR<sup>1,2</sup>

# PCSK9 Regulates the Recycling of LDLR by Targeting the LDLR for Degradation



1. Qian YW, Schmidt RJ, Zhang Y, et al. *J Lipid Res.* 2007;48:1488-1498.
2. Horton JD, Cohen JC, Hobbs HH. *J Lipid Res.* 2009;50(suppl):S172-S177
3. Rashid S et al. *PNAS* 2005;102:5374-5379

# **PCSK9 Loss-of-Function Mutations Resulted in Low LDL-C Levels and Reduced CHD Rates<sup>a</sup>**



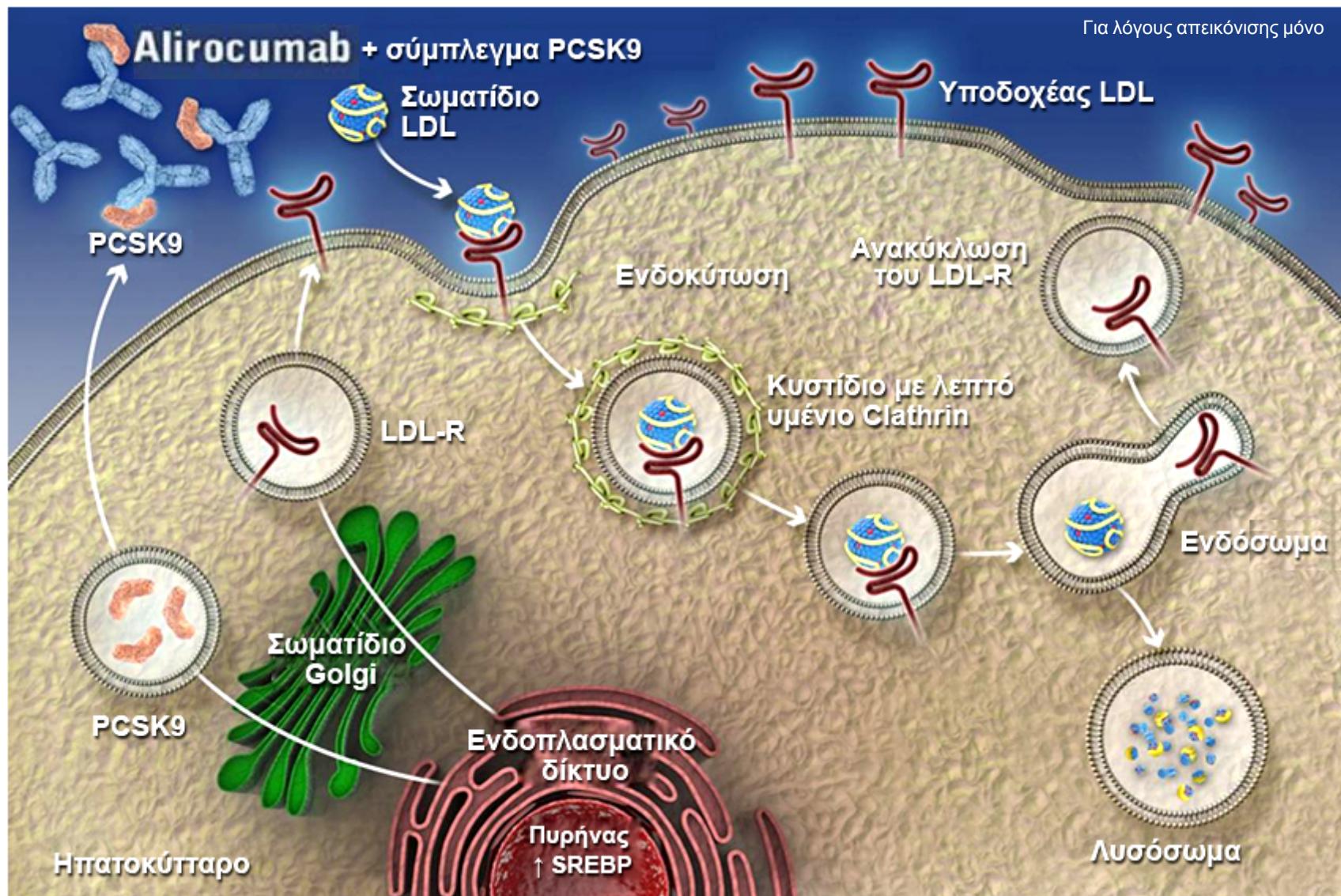
- Wild-type PCSK9 degrades LDL receptors<sup>b-c</sup>
- Loss-of-function mutations increase hepatic *LDLR* expression, reducing LDL-C levels by 15%-40%<sup>a,c</sup>
- CHD was reduced 47%-88% in PCSK9 loss-of-function mutation carriers compared with normal individuals<sup>a</sup>

a. Cohen JC, et al. *N Engl J Med*. 2006;354:1264-1272.

b. Peterson AS, et al. *J Lipid Res*. 2008;49:1595-1599.

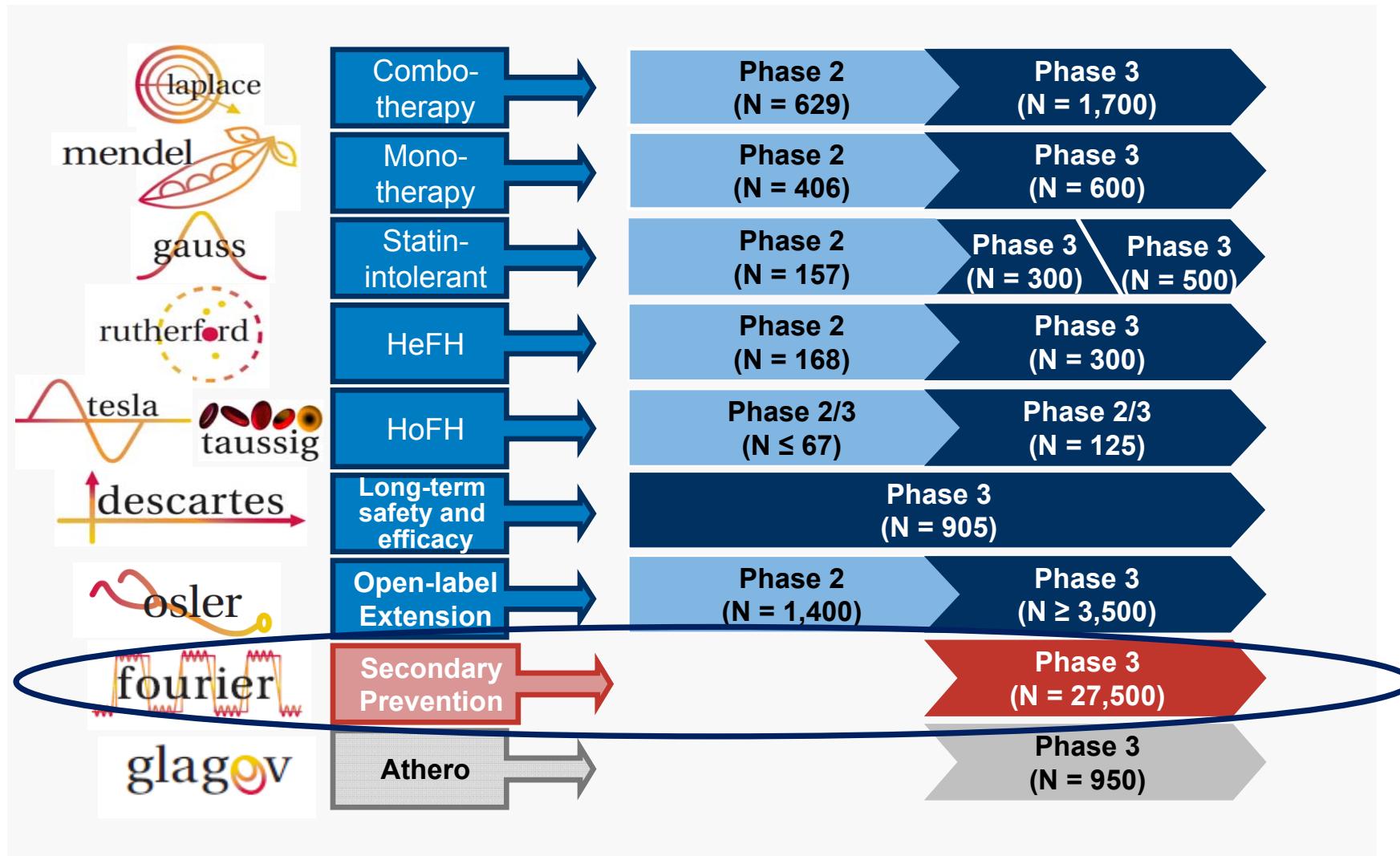
c. Cohen J, et al. *Nat Genet*. 2005;37:161-165.

# Επίδραση του Evolocumab στην έκφραση του υποδοχέα της LDL

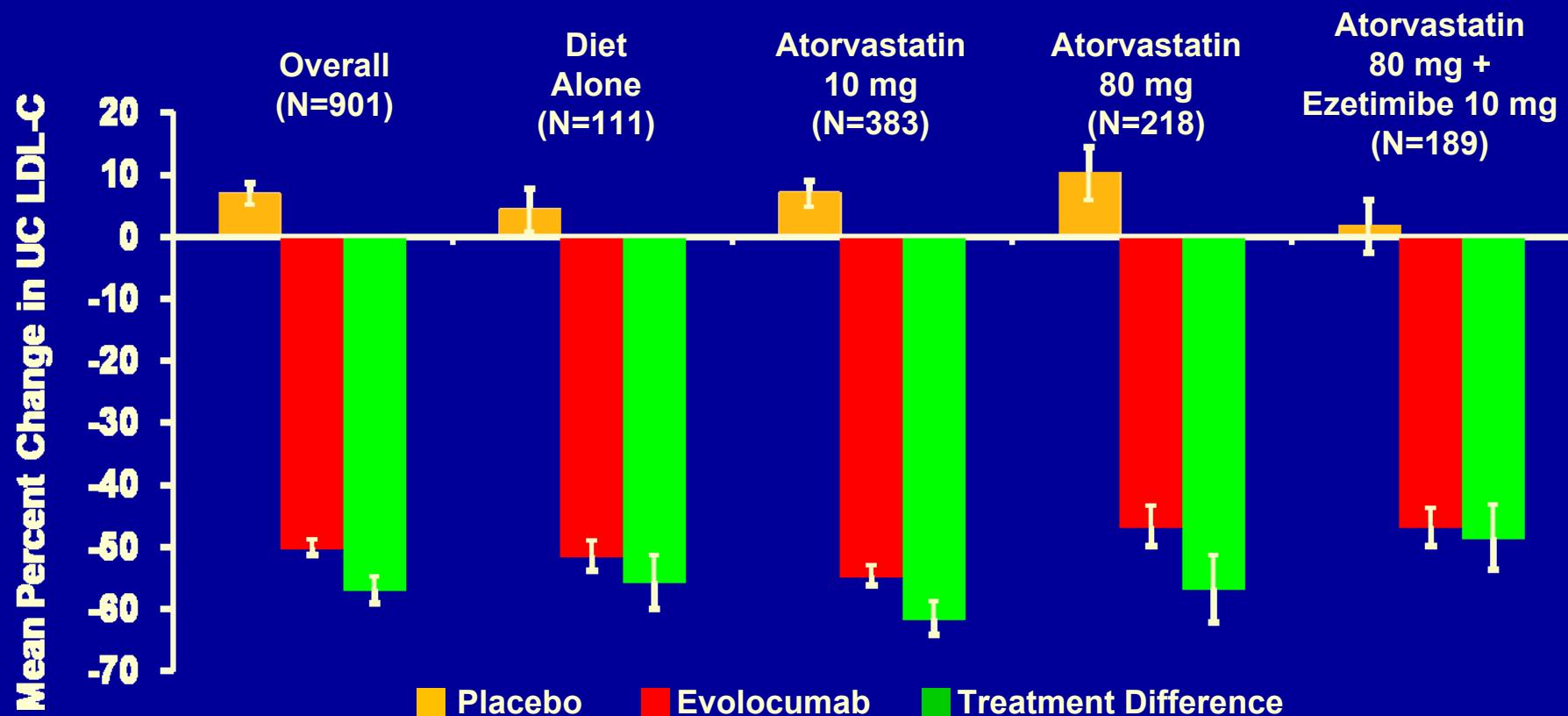


# PROFICIO

Program to Reduce LDL-C and Cardiovascular Outcomes Following Inhibition of PCSK9 In Different Populations



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

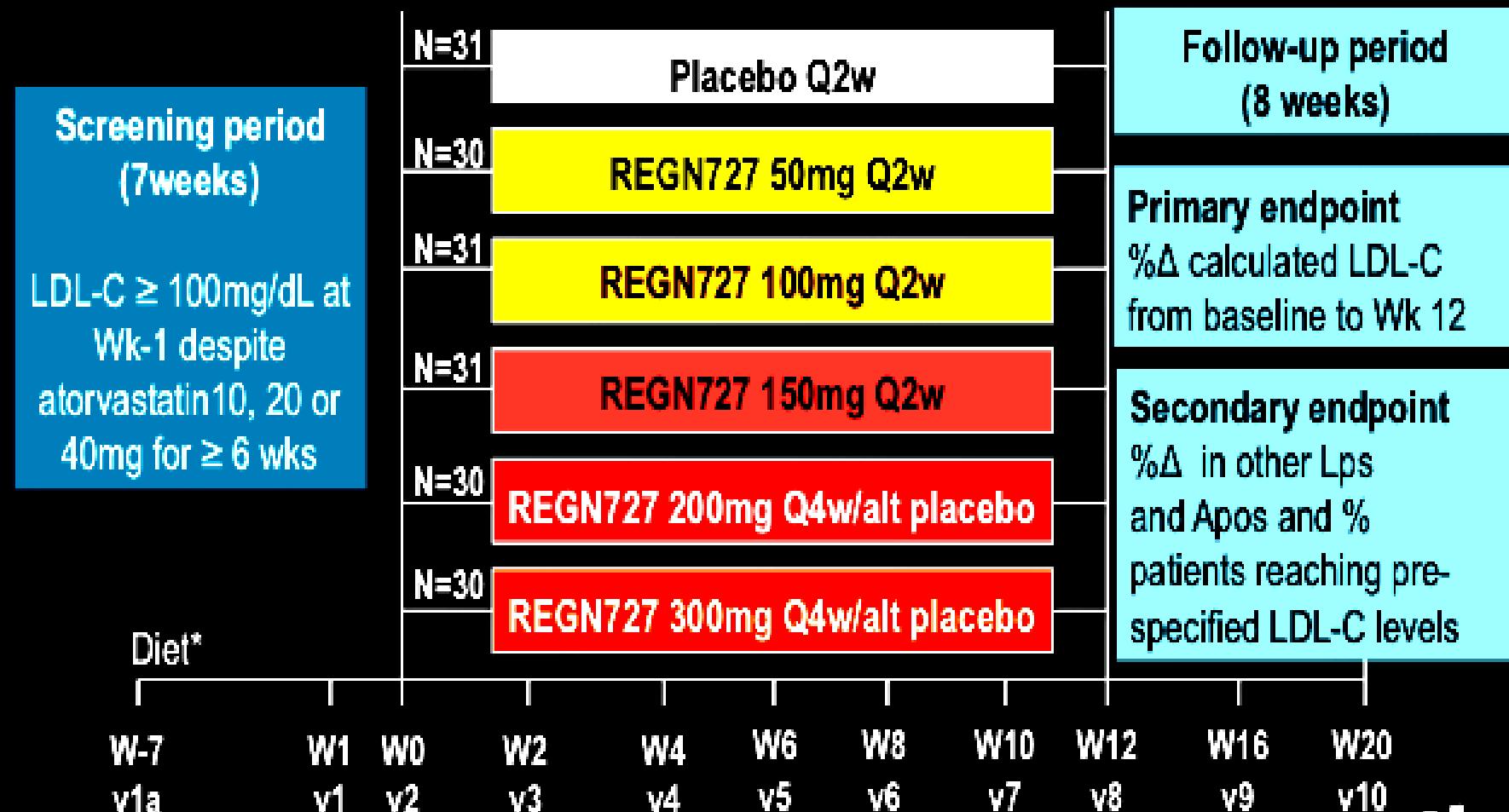


Blom DJ et. al N Engl J Med 2014;370:1809–19

- 6.8% increase from baseline in LDL-C observed in placebo group (n=302)
- 50.1% decrease from baseline in LDL-C observed in evolocumab group (n=599)\*
- 57% treatment difference

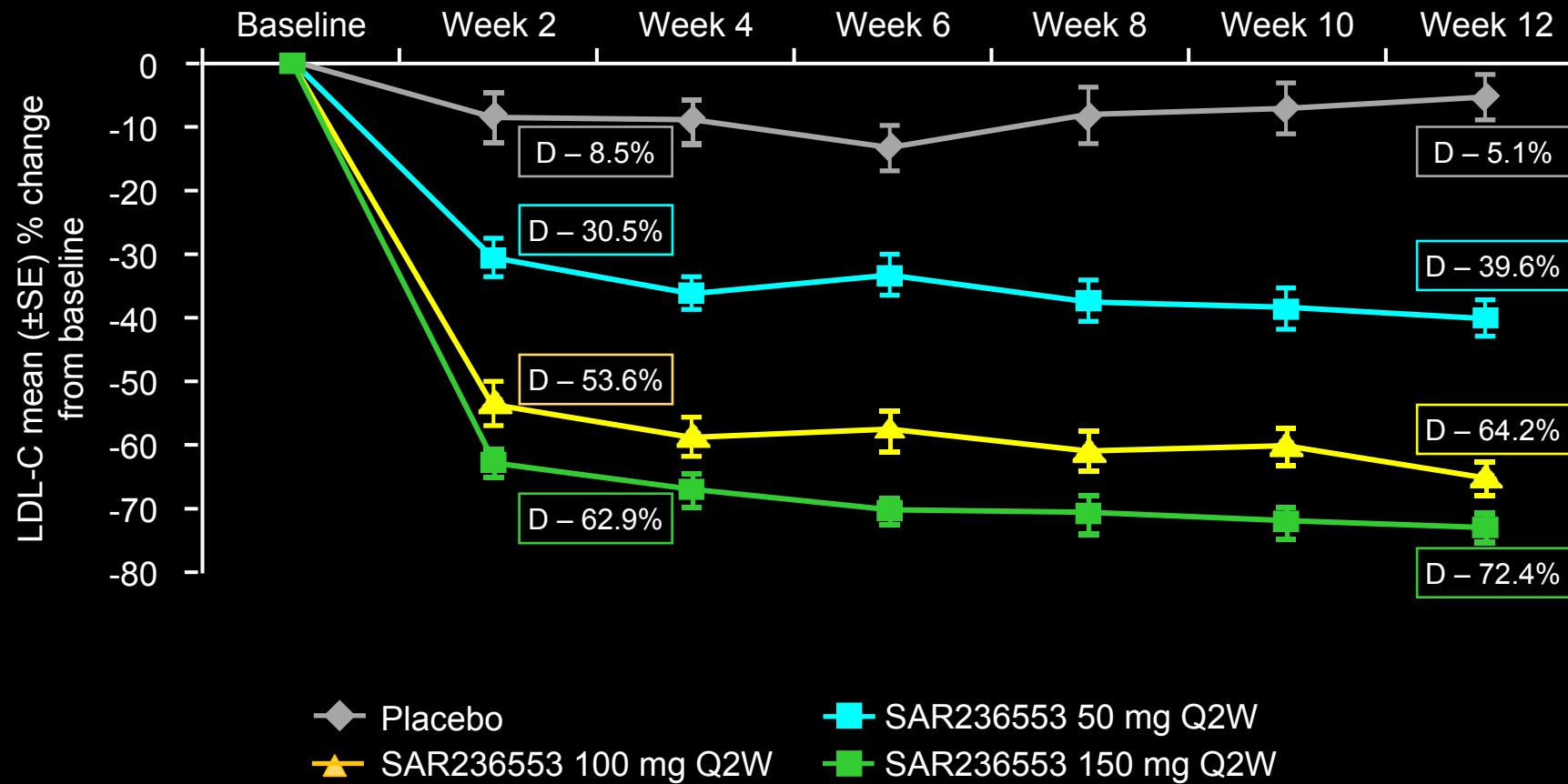
Error bars represent standard error for treatment difference. Treatment difference are least squares mean derived from a repeated measures model. \*Average of all evolocumab patients. UC, ultracentrifugation

## Phase 2 trial of the anti-PCSK9 mAb, REGN727: Study 3 design



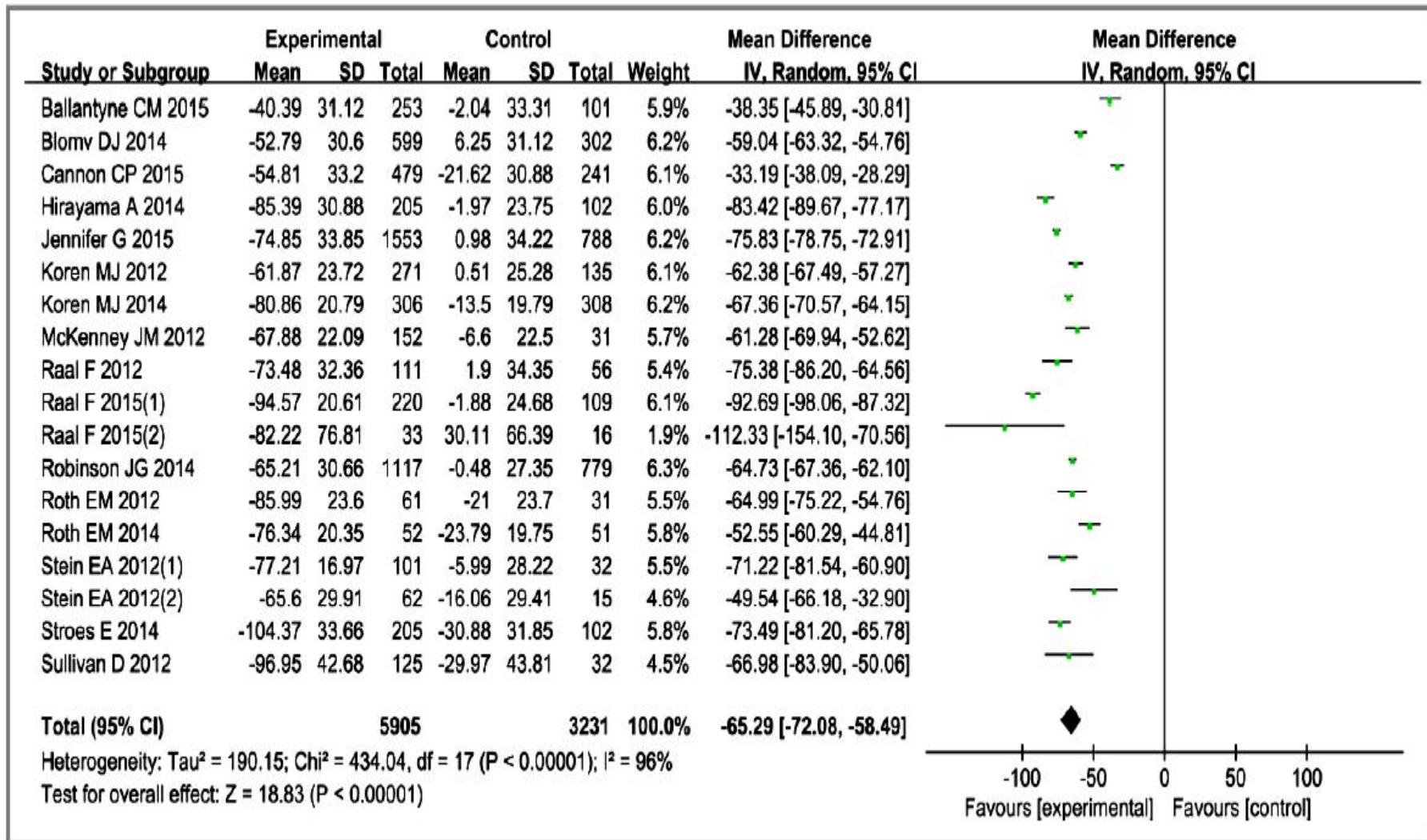
McKenney, et al. J Am Coll Cardiol. 2012;59:2344-53

## Effects on LDL-C of adding alirocumab every 2 weeks to atorvastatin



Mean percentage change in calculated LDL-C from baseline to weeks 2, 4, 6, 7, 10 and 12 in the modified intent-to-treat (mITT) population, by treatment group. Week 12 estimation using LOCF method

## Meta-Analysis of 20 trials on PCSK9 Monoclonal Antibodies



**Figure 3.** Forest plots depicting the effect of PCSK9 monoclonal antibodies on LDL-C. LDL-C indicates low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin9.

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

### ABSTRACT

#### BACKGROUND

Evolocumab, a monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9), significantly reduced low-density lipoprotein (LDL) cholesterol levels in short-term studies. We conducted two extension studies to obtain longer-term data.

#### METHODS

In two open-label, randomized trials, we enrolled 4465 patients who had completed 1 of 12 phase 2 or 3 studies ("parent trials") of evolocumab. Regardless of study-group assignments in the parent trials, eligible patients were randomly assigned in

From the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, and the Department of Medicine, Harvard Medical School, Boston (M.S.S., R.P.G., S.D.W.); the Carbohydrate and Lipid Metabolism Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg (F.J.R.), and the Division of Lipidology, Department of Medicine, University of Cape Town, Cape Town (D.I.B.).



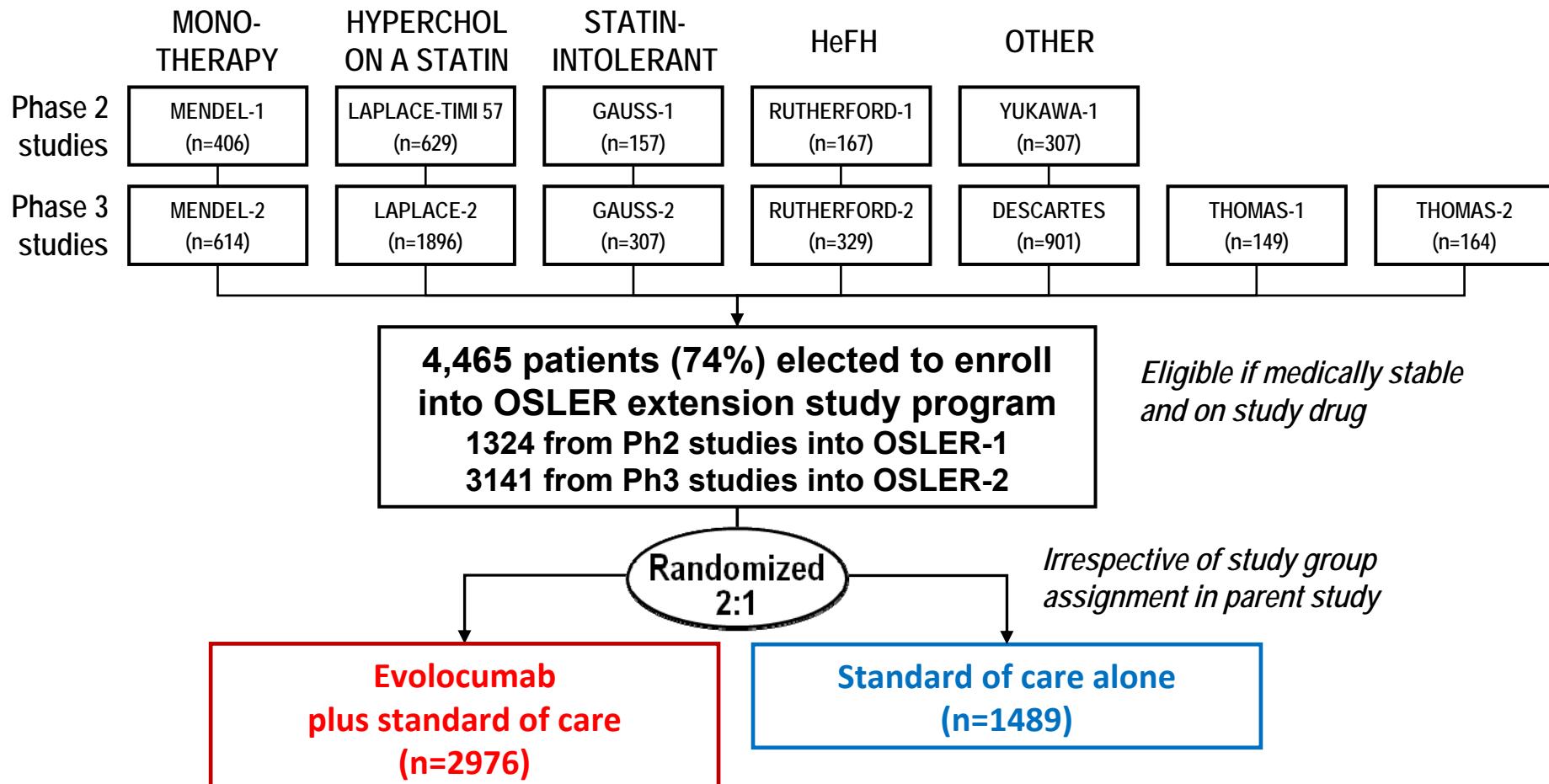
# OSLER

## Efficacy And Safety Of Evolocumab in Reducing Lipids And Cardiovascular Events

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<sup>1</sup>From the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, and the Department of Medicine, Harvard Medical School, Boston (M.S.S., R.P.G., S.D.W.); the Carbohydrate and Lipid Metabolism Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg (F.J.R.), and the Division of Lipidology, Department of Medicine, University of Cape Town, Cape Town (D.J.B.) - both in South Africa; the Departments of Epidemiology and Medicine, College of Public Health, University of Iowa, Iowa City (J.R.); the Sections of Cardiovascular Research and Cardiology, Department of Medicine, Baylor College of Medicine, and the Center for Cardiovascular Disease Prevention, Houston Methodist DeBakey Heart and Vascular Center, Houston (C.M.B.); Amgen, Thousand Oaks, CA (R. Somaratne, J.L., S.M.W., R. Scott); Jacksonville Center for Clinical Research, Jacksonville, FL (M.J.K.); and the Metabolic and Atherosclerosis Research Center, Cincinnati (E.A.S.).

# OSLER Program



IQR = Interquartile range;

HeFH = Heterozygous familial hypercholesterolemia;

Hyperchol = Hypercholesterolemia

**Median follow-up of 11.1 months (IQR 11.0-12.8)**

**7% discontinued evolocumab early**

**96% completed follow-up**

# Methods

- Evolocumab
  - Open-label randomized, controlled study; subcutaneous injections
  - Dosed 420 mg QM (OSLER-1); either 140 mg Q2W or 420 mg QM on the basis of patient choice (OSLER-2)
- Primary Endpoints:
  - **Incidence of adverse events (AE) & tolerability**
- Secondary Endpoints:
  - **Percent change in LDL-C level & other lipid parameters**
- **CV clinical events (pre-specified, exploratory):** adjudicated by TIMI Study Group CEC\*, blinded to treatment
  - Death
  - Coronary: myocardial infarction (MI), unstable angina (UA) requiring hospitalization, revascularization
  - Cerebrovascular: stroke or transient ischemic attack (TIA)
  - Heart failure (HF) requiring hospitalization

*Patients had in-person clinic visits on day 1 and then quarterly at weeks 12, 24, 36 and 48.*

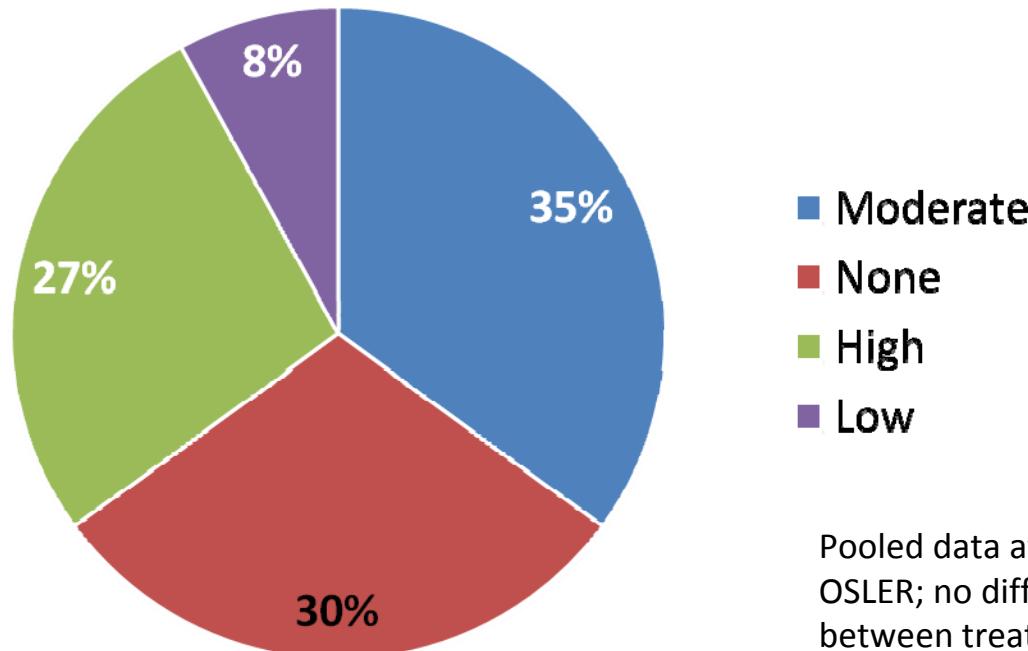
\*Thrombolysis in Myocardial Infarction (TIMI) Study Group Clinical Events Committee (CEC)

# Baseline Characteristics

Characteristic	Value
Age, years, mean (SD)	58 (11)
Male sex (%)	51
Cardiovascular risk factor (%)	80
Hypertension	52
Diabetes mellitus (DM)	13
Metabolic syndrome	34
Current cigarette use	15
Family history of premature CAD	24
Known FH	10
Known vascular disease (%)	29
Coronary	20
Cerebrovascular or Peripheral	9

Pooled data; no differences between treatment arms; FH=familial hypercholesterolemia

# Statin Use and Intensity at Baseline<sup>1</sup>



Pooled data at the start of  
OSLER; no differences  
between treatment arms

High<sup>2,\*</sup>: ↓ LDL-C by ~≥50% (e.g., atorvastatin 40-80 mg; rosuvastatin 20-40 mg or equivalent)

Moderate<sup>2,\*</sup>: ↓ LDL-C by ~30-≤50% (e.g., atorvastatin 10-20 mg; rosuvastatin 5-10 mg; simvastatin 20-40 mg; pravastatin 40-80 mg or equivalent)

Low<sup>2,\*</sup>: ↓ LDL-C by ~<30% (e.g., simvastatin 10 mg; pravastatin 10-20 mg or equivalent)

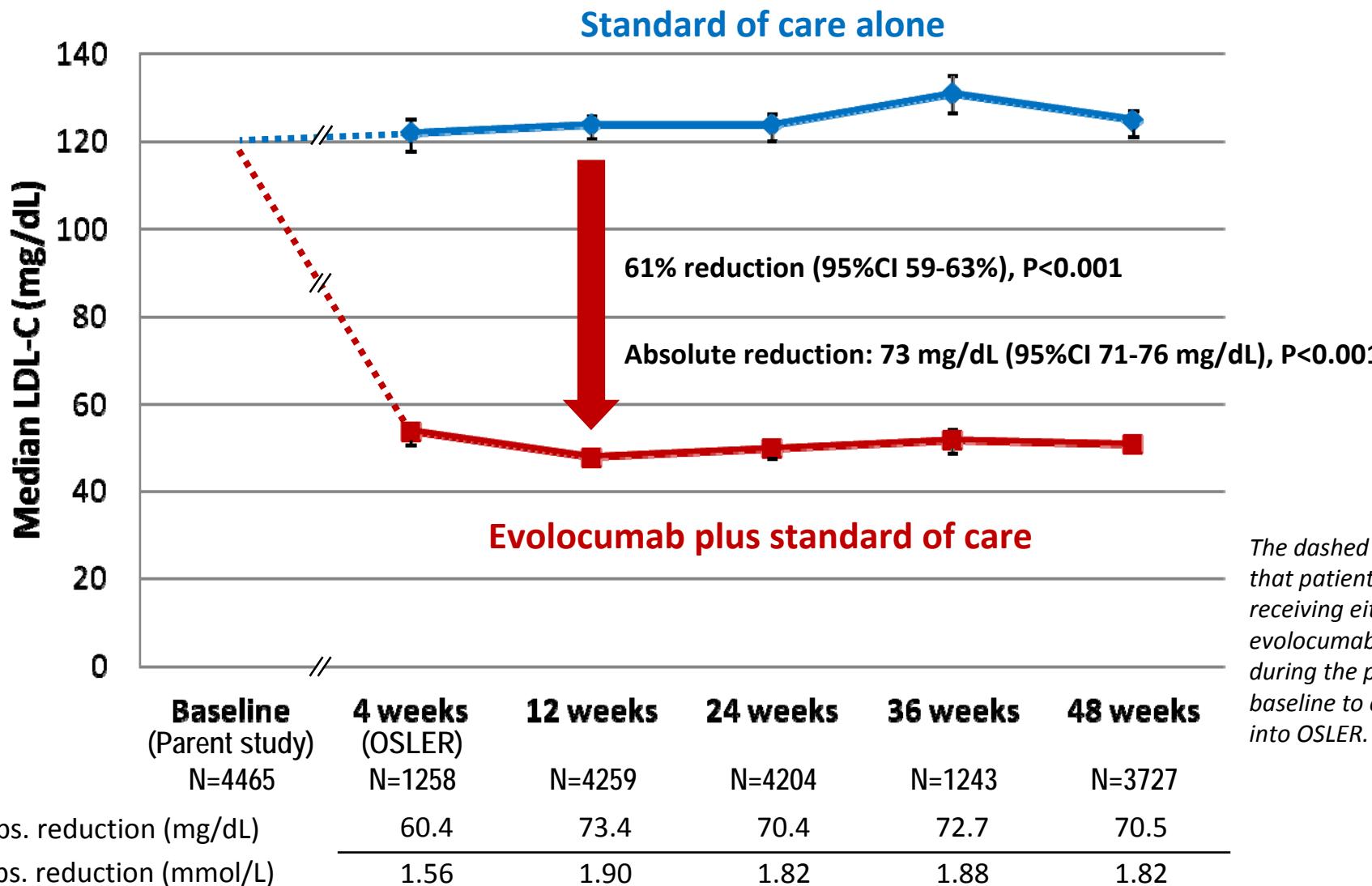
\*Statin intensity classifications defined according to ACC/AHA guidelines based on review of randomized control trials (RCTs). Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice.

1. Sabatine et al. N Engl J Med. 2015 Apr 16;372(16):1500-9. 2. Stone et al. J Am Coll Cardiol. 2014 Jul 1;63(25 Pt B):2889-934



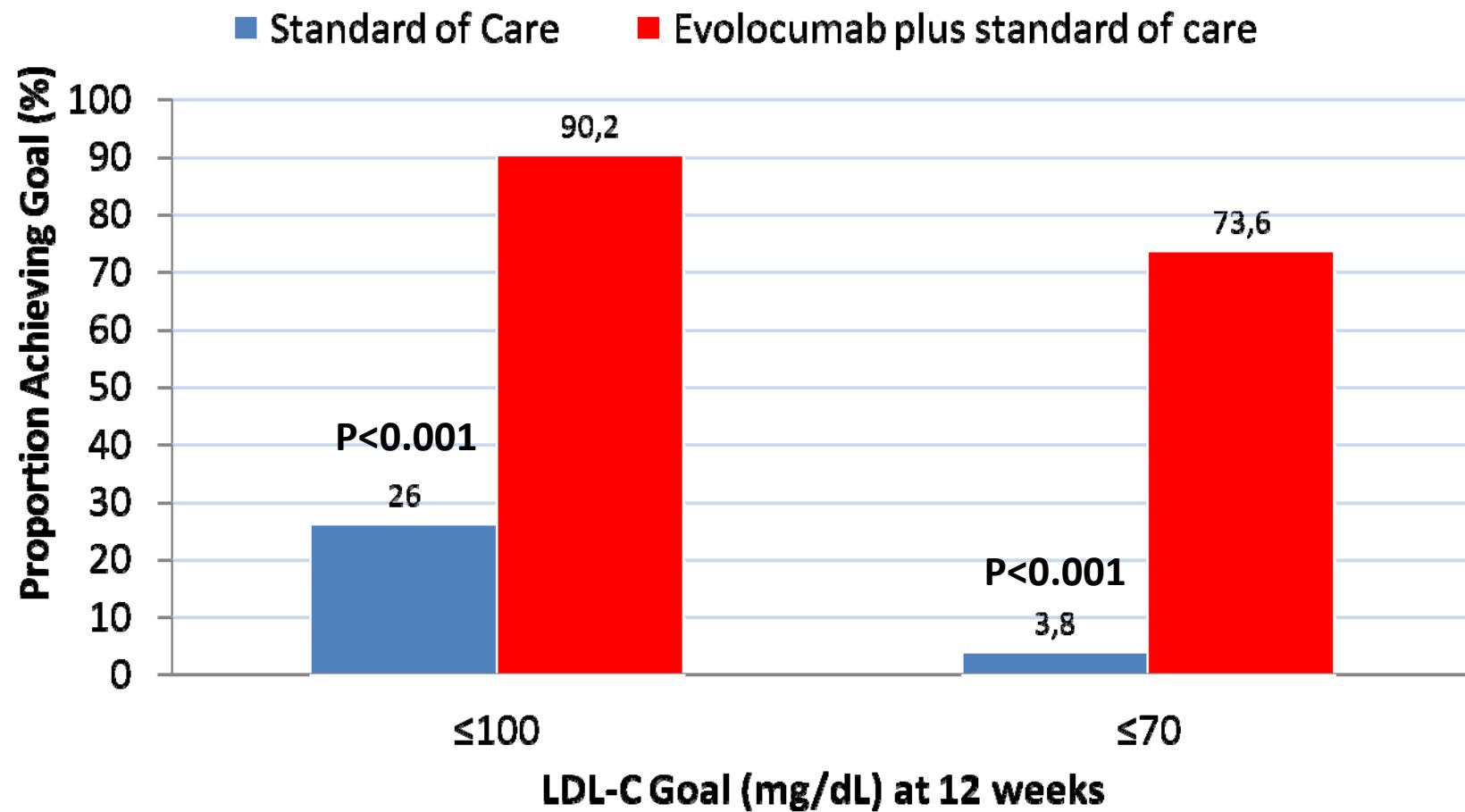
# Results

# LDL Cholesterol



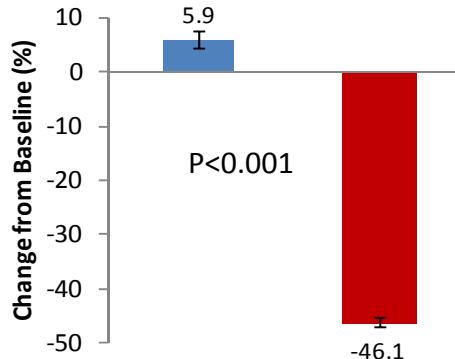
*The dashed line indicate that patients were receiving either evolocumab or placebo during the period from baseline to enrollment into OSLER.*

# LDL Cholesterol Goals

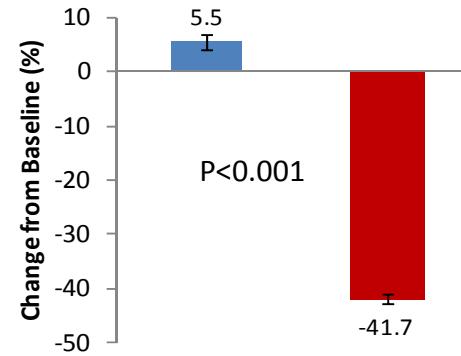


# Other Lipid Parameters

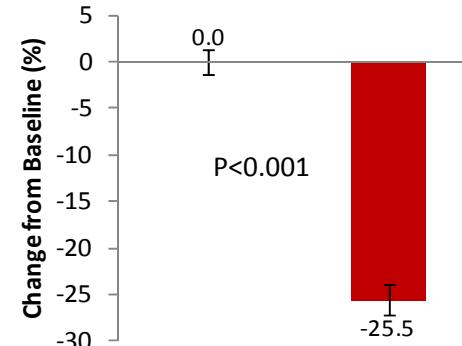
**52% ↓ in Non-HDL-C**



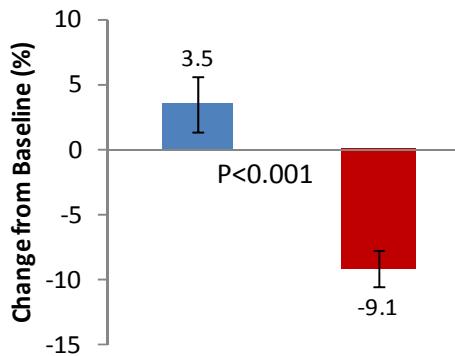
**47% ↓ in ApoB**



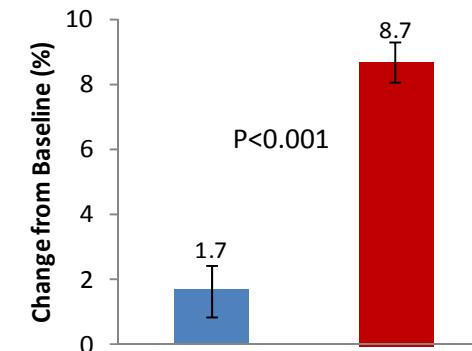
**26% ↓ in Lp(a)**



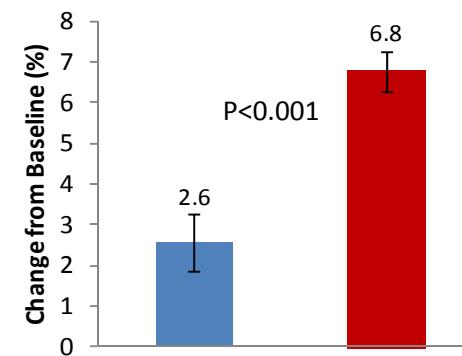
**13% ↓ in Triglycerides**



**7% ↑ in HDL-C**



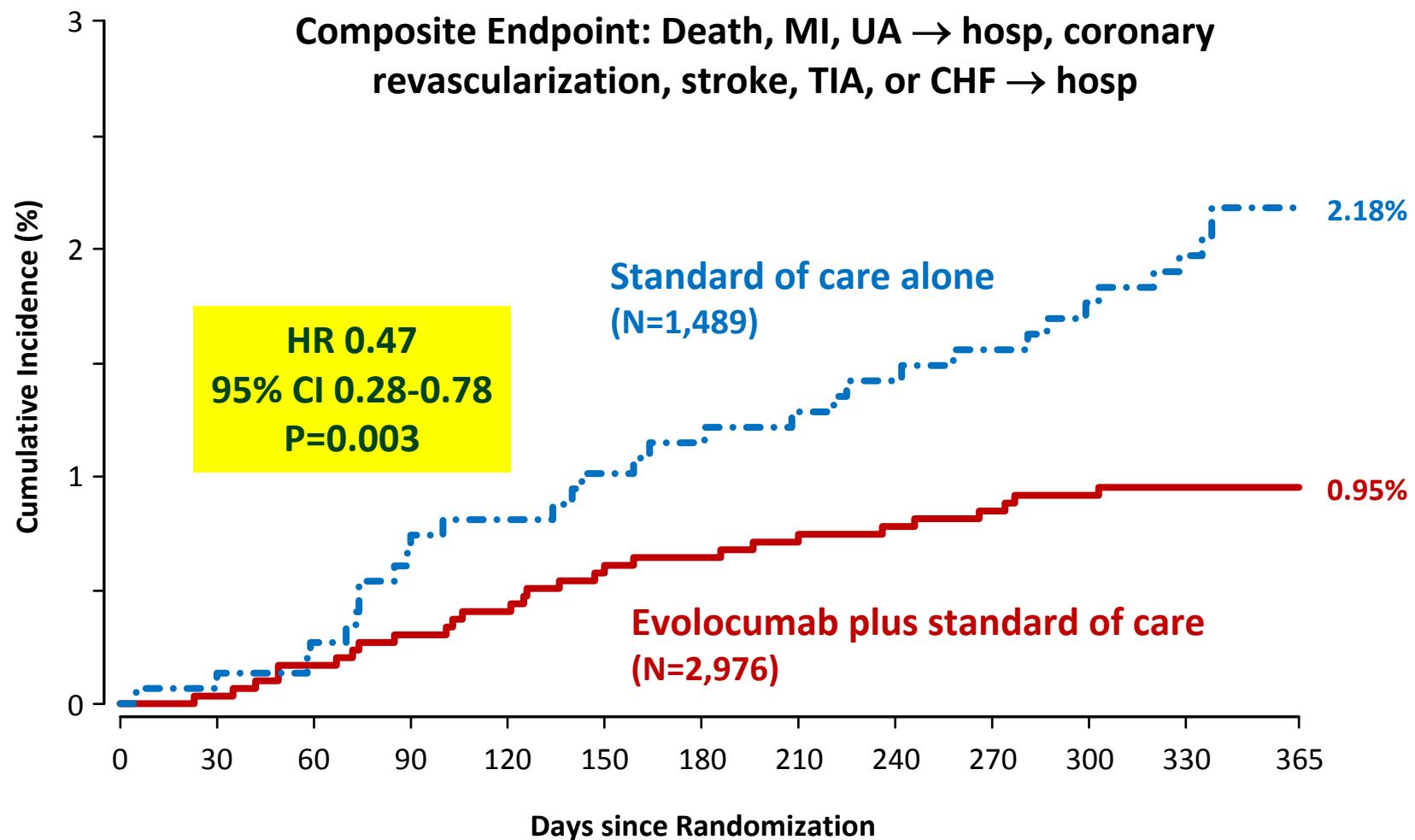
**4% ↑ in ApoA1**



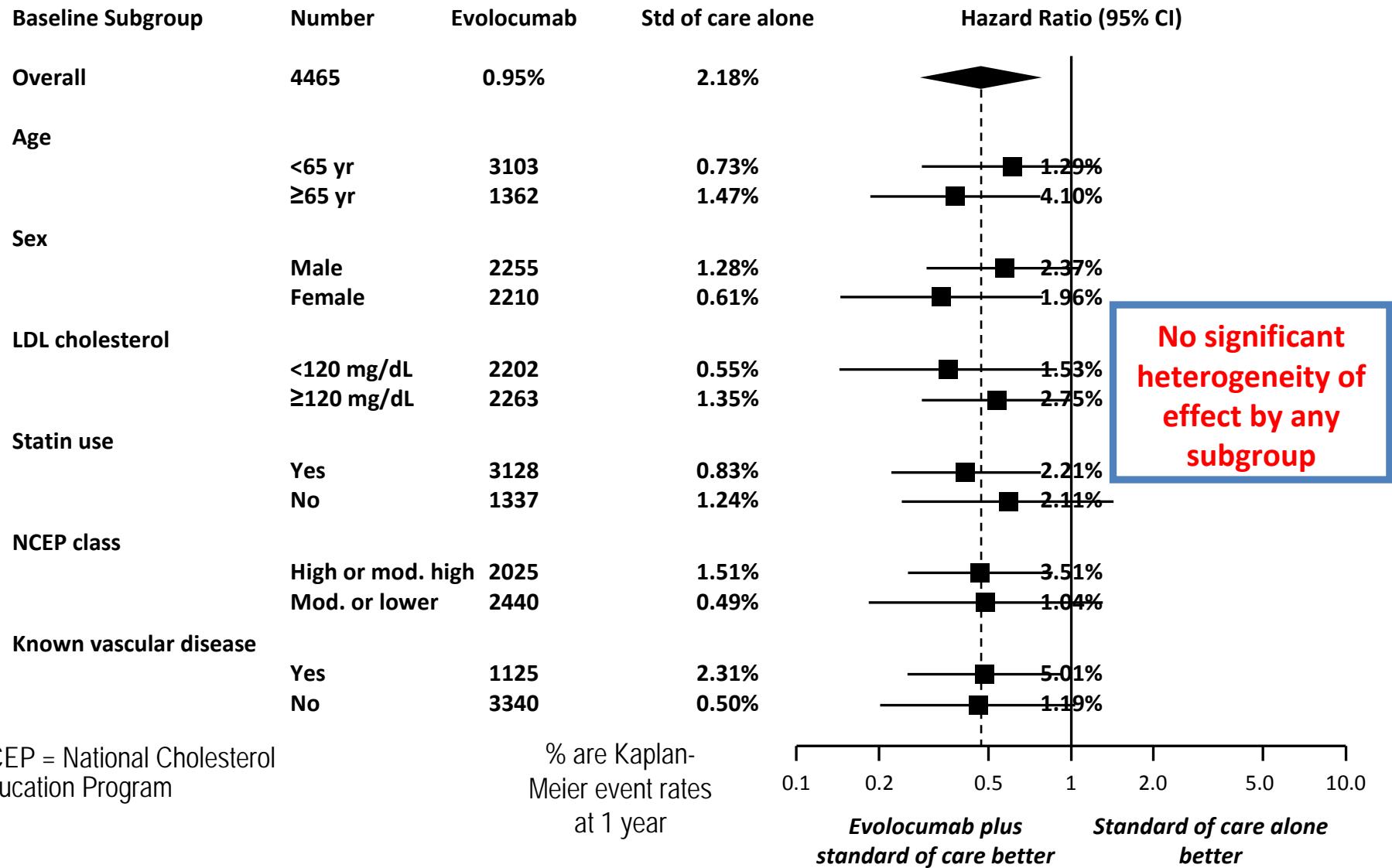
■ Standard of care alone  
■ Evolocumab plus standard of care

**Week 12 data; values are means  
except for TG and Lp(a) which are medians.  
Error bars are 95% CI**

# Cardiovascular Outcomes



# Cardiovascular Events in Subgroups



# Η μελέτη ODYSSEY LONG TERM

- ◆ Αυτή η μεγάλη διπλά τυφλή μελέτη 2341 ασθενών υψηλού κινδύνου παρέχει δεδομένα της μακροχρόνιας αποτελεσματικότητας και ασφάλειας του alirocumab σε μία θεραπευτική περίοδο 78 εβδομάδων όταν προστέθηκε στη μέγιστη ανεκτή δόση στατίνης με ή χωρίς άλλη LLT
- ◆ Συνολικά, το alirocumab μείωσε τα επίπεδα της LDL-C κατά 62% έναντι του placebo στις 24 εβδομάδες
  - Η μείωση της LDL-C στην ομάδα του alirocumab ήταν συνεπής στη διάρκεια της θεραπευτικής περιόδου των 78 εβδομάδων
- ◆ Με βάση τα αποτελέσματα μίας post-hoc analysis, υπήρξαν ενδείξεις χαμηλότερου ποσοστού καρδιαγγειακών συμβαμάτων στην ομάδα του alirocumab

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

The NEW ENGLAND JOURNAL of MEDICINE

## 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 Langset, 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\*

## ABSTRACT

### BACKGROUND

Alirocumab, a monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9), has been shown to reduce low-density lipoprotein (LDL) cholesterol levels in patients who are receiving statin therapy. Larger and longer-term studies are needed to establish safety and efficacy.

### METHODS

We conducted a randomized trial involving 2341 patients at high risk for cardiovascular events who had LDL cholesterol levels of 70 mg per deciliter (1.8 mmol per liter) or more and were receiving treatment with statins at the maximum tolerated dose (the highest dose associated with an acceptable side-effect profile), with or without other lipid-lowering therapy. Patients were randomly assigned in a 2:1 ratio to receive alirocumab (150 mg) or placebo as a 1-mL subcutaneous injection every 2 weeks for 78 weeks. The primary efficacy end point was the percentage change in calculated LDL cholesterol level from baseline to week 24.

### RESULTS

At week 24, the difference between the alirocumab and placebo groups in the mean percentage change from baseline in calculated LDL cholesterol level was –62 percentage points ( $P<0.001$ ); the treatment effect remained consistent over a period of 78 weeks. The alirocumab group, as compared with the placebo group, had higher rates of injection-site reactions (5.9% vs. 4.2%), myalgia (5.4% vs. 2.9%), neurocognitive events (1.2% vs. 0.5%), and ophthalmologic events (2.9% vs. 1.9%). In a post hoc analysis, the rate of major adverse cardiovascular events (death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) was lower with alirocumab than with placebo (1.7% vs. 3.3%; hazard ratio, 0.52; 95% confidence interval, 0.31 to 0.90; nominal  $P=0.02$ ).

### CONCLUSIONS

Over a period of 78 weeks, alirocumab, when added to statin therapy at the maximum tolerated dose, significantly reduced LDL cholesterol levels. In a post hoc analysis, there was evidence of a reduction in the rate of cardiovascular events with alirocumab. (Funded by Sanofi and Regeneron Pharmaceuticals; ODYSSEY LONG TERM ClinicalTrials.gov number, NCT01507831.)

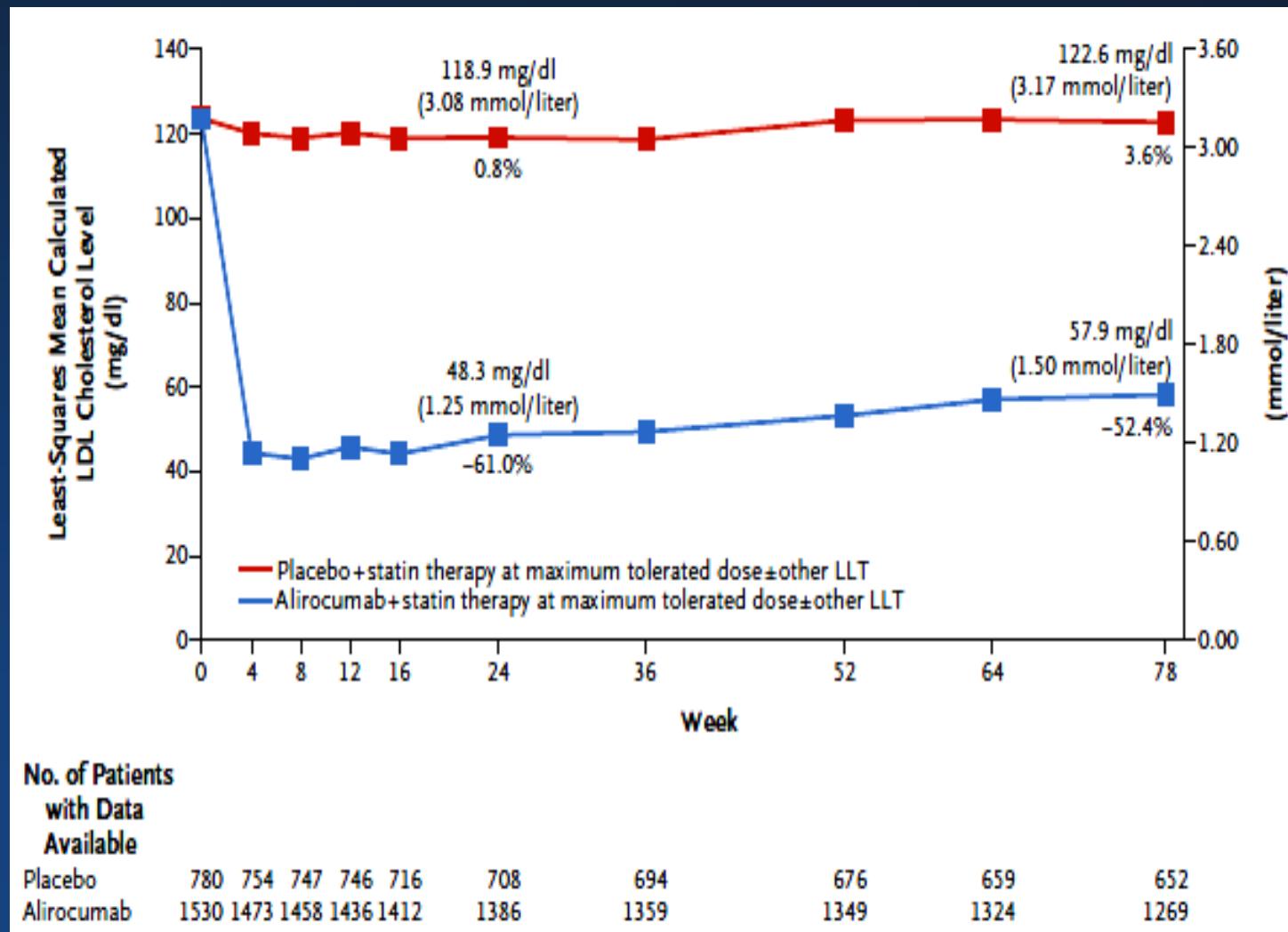
From the University of Iowa, Iowa City (J.G.R.); Point Médical, Dijon (M.F.), Centre Hospitalier Universitaire de Nantes-Hôpital Nord Laennec, Saint-Herblain (M.K.), University Hospital of Lille, Lille (G.Luc), and Sanofi, Chilly-Mazarin (C.L.) — all in France; Clinique des Maladies Lipidiques de Québec, Québec, QC, Canada (J.B.); Università di Palermo—Polyclinico P. Giaccone, Palermo, Italy (M.A.); the Department of Vascular Medicine, Academic Medical Center, Amsterdam (E.S., J.J.P.K.); Lipid Clinic, Oslo University Hospital, Oslo (G. Langset); University of the Witwatersrand, Johannesburg (F.J.R.); Cardiovascular Center of Sarasota, Sarasota (M.E.S.), and Jacksonville Center for Clinical Research, Jacksonville (M.J.K.) — both in Florida; Westside Medical Associates of Los Angeles, Beverly Hills, CA (N.E.L.); Regeneron Pharmaceuticals, Tarrytown, NY (R.P.); and Sanofi, Bridgewater, NJ (U.C.). Address reprint requests to Dr. Robinson at the Departments of Epidemiology and Medicine, Prevention Intervention Center, College of Public Health, University of Iowa, 145 N. Riverside Dr., S455 CPBH, Iowa City, IA 52242, or at jennifer.g-robinson@uiowa.edu.

\*A list of principal investigators in the Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM) study is provided in the Supplementary Appendix, available at NEJM.org.

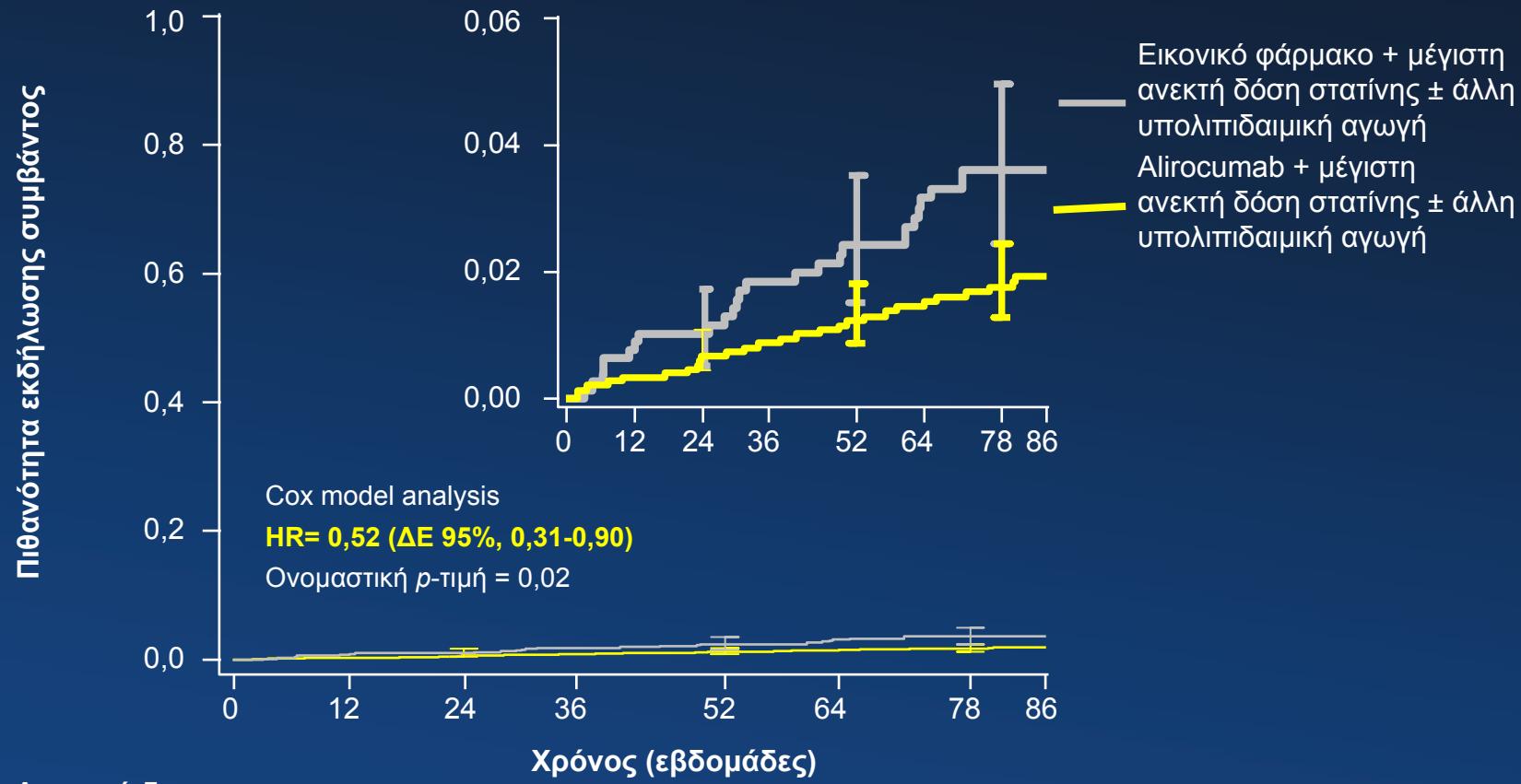
This article was published on March 13, 2015, at NEJM.org.

DOI: 10.1056/NEJMoa1501031  
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# Η μελέτη ODYSSEY LONG TERM



# *Post hoc* ανάλυση τεκμηριωμένων μειζόνων καρδιαγγειακών συμβαμάτων\*



## Αρ. σε κίνδυνο

Εικονικό φάρμακο	788	776	731	700	670	653	644	597
Alirocumab	1550	1533	1445	1392	1342	1306	1266	1170

\*Σύμφωνα με το πρωτεύον καταληκτικό σημείο της μελέτης ODYSSEY OUTCOMES, περιλαμβανομένων θανάτου από καρδιαγγειακά αίτια, μη θανατηφόρο EM, θανατηφόρο και μη θανατηφόρο ισχαιμικό εγκεφαλικό επεισόδιο, και, ασταθή στηθάγχη που απαιτεί νοσηλεία. Η ασταθής στηθάγχη που απαιτεί νοσηλεία τεκμηριώθηκε βάσει αυστηρών κριτηρίων/σαφούς εξέλιξης ισχαιμίας.

# Safety

	Evolocumab + Standard of Care (N=2976)	Standard of Care alone (N=1489)
Adverse events	no. (%)	
Any	2060 (69.2)	965 (64.8)
Serious	222 (7.5)	111 (7.5)
Leading to discontinuation of evolocumab	71 (2.4)	n/a
Injection-site reactions	129 (4.3)	n/a
Muscle-related	190 (6.4)	90 (6.0)
Neurocognitive*	27 (0.9)	4 (0.3)
Other		
Arthralgia	137 (4.6)	48 (3.2)
Headache	106 (3.6)	32 (2.1)
Limb pain	99 (3.3)	32 (2.1)
Fatigue	83 (2.8)	15 (1.0)
Laboratory results	no. (%)	
ALT or AST >3×ULN	31 (1.0)	18 (1.2)
Creatine kinase >5×ULN	17 (0.6)	17 (1.1)

\*Neurocognitive events were delirium (including confusion), cognitive and attention disorders and disturbances, dementia and amnestic conditions, disturbances in thinking and perception, and mental impairment disorders.

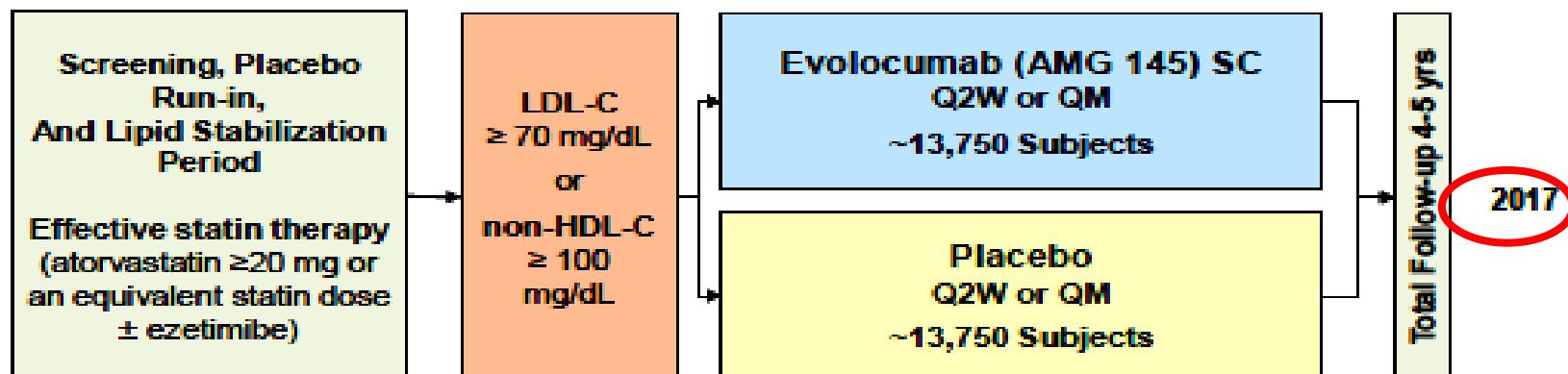
# Adverse Events by Achieved LDL-C

	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	1.1

# FOURIER

27,500 patients with cardiovascular disease (prior MI, stroke or PAD)

Age 40 to 85 years  
≥1 other high-risk feature



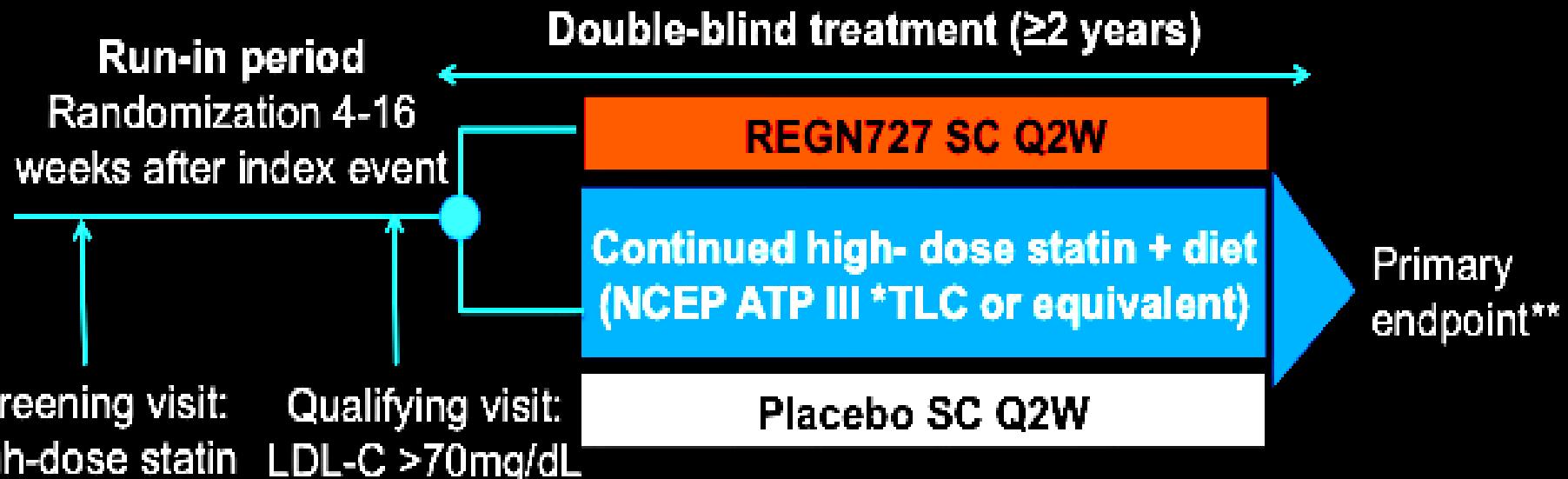
Primary Endpoint: CV death, MI, hosp for UA, stroke, coronary revasc



An Academic Research Organization of  
Brigham and Women's Hospital and Harvard Medical School

NCT01764633

## ODYSSEY OUTCOMES: Phase 3 REGN727 study



\*\*TLC = therapeutic lifestyle change; \*\*Composite endpoint of CHD death, non-fatal MI, fatal and non-fatal ischemic stroke and unstable angina requiring hospitalization

2012: Enrollment in all Phase 3 trials

2015: First launch expected; 2016: Global launch

2018: Outcomes trial expected to conclude

# Περίληψη PCSK9



ODYSSEY LONG TERM

- ↓ LDL-C by 61% at 12 weeks
  - Absolute decrease of 70 mg/dL
  - Median achieved LDL-C of 45 mg/dL
- ↓ CV outcomes by 50% over 12-18 months
  - Safety trial with pre-specified, exploratory outcome with relatively few events
  - Event curves diverged early and continued to separate over time
  - Consistent effect on death, coronary, and cerebrovascular. events
  - Consistent effect in major subgroups
- Appeared to be safe and well-tolerated
  - AEs largely balanced, good tolerability in this extension study
  - No gradient in incidence of any AE by achieved LDL-C, including in those with LDL-C <25 mg/dL (0.65 mmol/L)



# OSLER Study Limitations

- **Open-label design of the studies could influence the reporting of events**, both cardiovascular and safety
  - This would be a **particular concern for coronary revascularization**, the single most frequently reported cardiovascular event, since the decision to perform this procedure could have been influenced by knowledge of treatment assignment
- The **numbers of cardiovascular and select adverse events were relatively small**
- Although rates of adverse events and study-drug discontinuation were low in the parent studies, **patients were eligible to transition to the OSLER study if they had not had an adverse event that led to discontinuation of the drug.**
  - Thus, **data on safety** and side-effect profiles in our study come from a **cohort of patients who had all successfully received injections** and many of whom had received evolocumab for at least 12 weeks.
- The OSLER program included a **mix of patients with varying degrees of cardiovascular risk and use and intensity of statin therapy.**
  - Thus, **not all the study patients** would necessarily have been the **optimal target population** for this novel treatment.

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

Frederick J. Raal,<sup>1</sup> Narimon Honarpour,<sup>2</sup> Dirk J. Blom,<sup>3</sup> G. Kees Hovingh,<sup>4</sup> Feng Xu,<sup>2</sup> Rob Scott,<sup>2</sup> Scott M. Wasserman,<sup>2</sup> Evan A. Stein,<sup>5</sup> for the TESLA Investigators

<sup>1</sup>Carbohydrate and Lipid Metabolism Research Unit, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa;

<sup>2</sup>Amgen Inc, One Amgen Center Drive, Thousand Oaks, CA, USA; <sup>3</sup>Division of Lipidology, Department of Medicine, University of Cape Town, UCT Faculty Health Sciences, Cape Town, South Africa; <sup>4</sup>Vascular Medicine, Academic Medical Centre, Amsterdam, Netherlands; <sup>5</sup>Metabolic and Atherosclerosis Research Center, Cincinnati, OH, USA

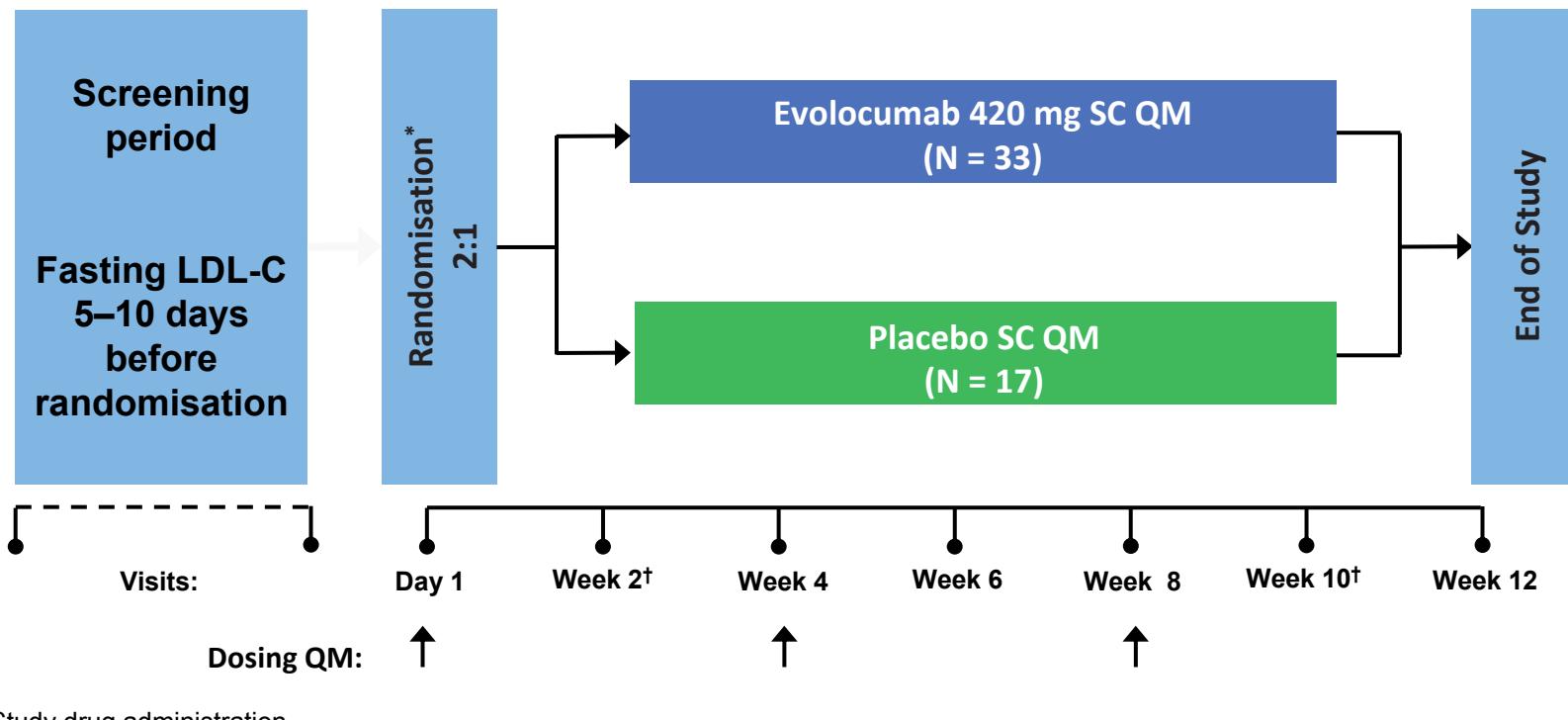
## The TESLA Study Part B

- Trial Evaluating PCSK9 Antibody in Subjects with LDL Receptor Abnormalities Part B
- Design  
A 12-week, randomised, double-blind, placebo-controlled, multicentre Phase 3 study
- Objective  
To evaluate the efficacy and safety of evolocumab in patients with HoFH

PCSK9, proprotein convertase subtilisin/kexin type 9

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

## TESLA Part B: Study Design



\*Randomisation stratified by screening LDL-C (< 11 mmol/L or ≥ 11 mmol/L).

<sup>†</sup>Week 2 and week 10 study visits were optional.

SC, subcutaneous; QM, every 4 weeks

Primary endpoint: % change from baseline in ultracentrifugation (UC) LDL-C at week 12

## TESLA Part B: Baseline Characteristics

	Placebo QM (N = 16*)	Evolocumab 420 mg QM (N = 33)	Total (N = 49)
Age (years), mean (SD) [range]	32 (14) [14–57]	30 (12) [13–51]	31 (13) [13–57]
Female, % (n)	50% (8)	48% (16)	49% (24)
Ethnicity (white), % (n)	94% (15)	88% (29)	90% (44)
Coronary artery disease, <sup>†</sup> % (n)	38% (6)	46% (15)	43% (21)
Prior coronary artery bypass surgery	25% (4)	24% (8)	25% (12)
Aortic valve replacement	19% (3)	12% (4)	14% (7)
Lipid-lowering therapy, % (n)			
Statin	100% (16)	100% (33)	100% (49)
Atorvastatin	63% (10)	67% (22)	65% (32)
Rosuvastatin	38% (6)	33% (11)	35% (17)
Ezetimibe	94% (15)	91% (30)	92% (45)

\*1 patient randomised to placebo did not receive study drug and was excluded from the analysis

<sup>†</sup>Clinically evident

## TESLA Part B: Baseline Lipids

<b>Mean (SD)</b>	<b>Placebo QM (N = 16)</b>	<b>Evolocumab 420 mg QM (N = 33)</b>	<b>Total (N = 49)</b>
LDL-C, UC (mmol/L), mean (SD)	8.7 (3.8)	9.2 (3.5)	9.0 (3.5)
LDL-C, calculated (mmol/L), mean (SD)	8.7 (3.7)	9.2 (3.5)	9.0 (3.6)
ApoB (g/L), mean (SD)	2.1 (0.8)	2.1 (0.7)	2.1 (0.7)
Lp(a) (nmol/L), median (IQR)	128 (80–201)	76 (26–145)	101 (31–146)
ApoA1 (g/L), mean (SD)	1.1 (0.4)	1.1 (0.2)	1.1 (0.3)
HDL-C (mmol/L), mean (SD)	1.0 (0.4)	1.0 (0.3)	1.0 (0.3)
Triglycerides (mmol/L), mean (SD)	1.3 (0.7)	1.2 (0.6)	1.2 (0.6)
Free PCSK9 (nmol/L), mean (SD)	9.4 (2.5)	8.9 (2.9)	9.0 (2.7)

Lp(a), lipoprotein(a); IQR, interquartile range; ApoA1, apolipoprotein A1;  
HDL-C, high-density lipoprotein cholesterol; UC, ultracentrifugation.

## TESLA Part B: Genotype

Genotype, n (%)	Placebo QM (N = 16)	Evolocumab 420 mg QM (N = 33)	Total (N = 49)
LDL receptor mutations	14 (88)	31 (94)	45 (92)
True homozygous	7 (44)	15 (45)	22 (45)
Compound heterozygous	7 (44)	16 (48)	23 (47)
Heterozygous*	0	1 (3)	1 (2)
ApoB mutation	2 (13)	0	2 (4)
Autosomal recessive hypercholesterolemia	0	1 (3)	1 (2)

\*Patient met clinical diagnostic criteria for HoFH based on history of untreated LDL-C concentration > 13 mmol/L plus either xanthoma before 10 years old or evidence of HeFH in both parents.

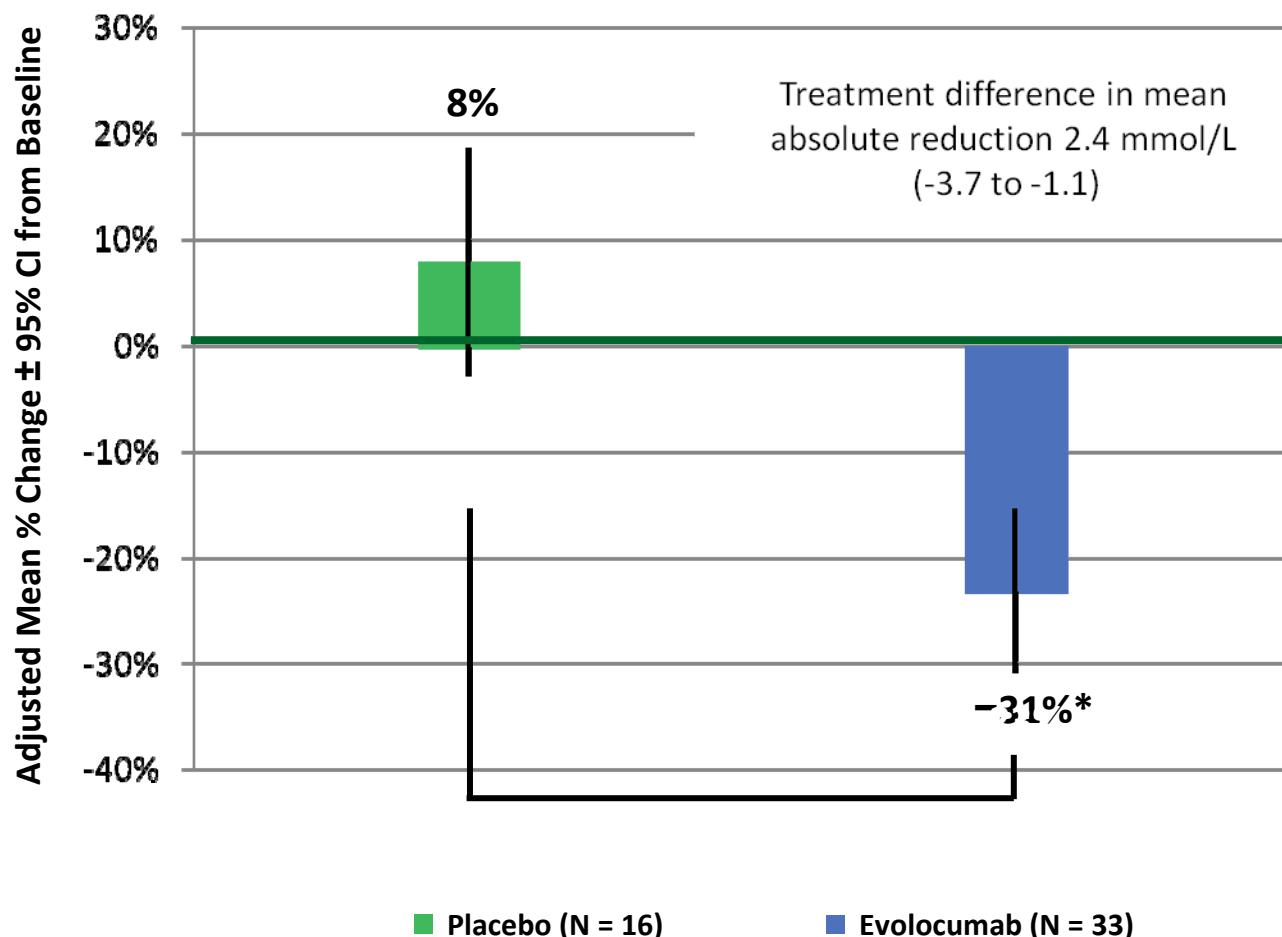
ApoB, apolipoprotein B.

## TESLA Part B: LDL Receptor Function

LDLR function, n*	Placebo QM (N = 16)	Evolocumab 420 mg QM (N = 33)	Total (N = 49)
Defective in ≥ 1 allele	8	20	28
Defective/defective	5	8	13
Defective/negative	3	6	9
Negative/negative	0	1	1
Unclassified	6	16	22

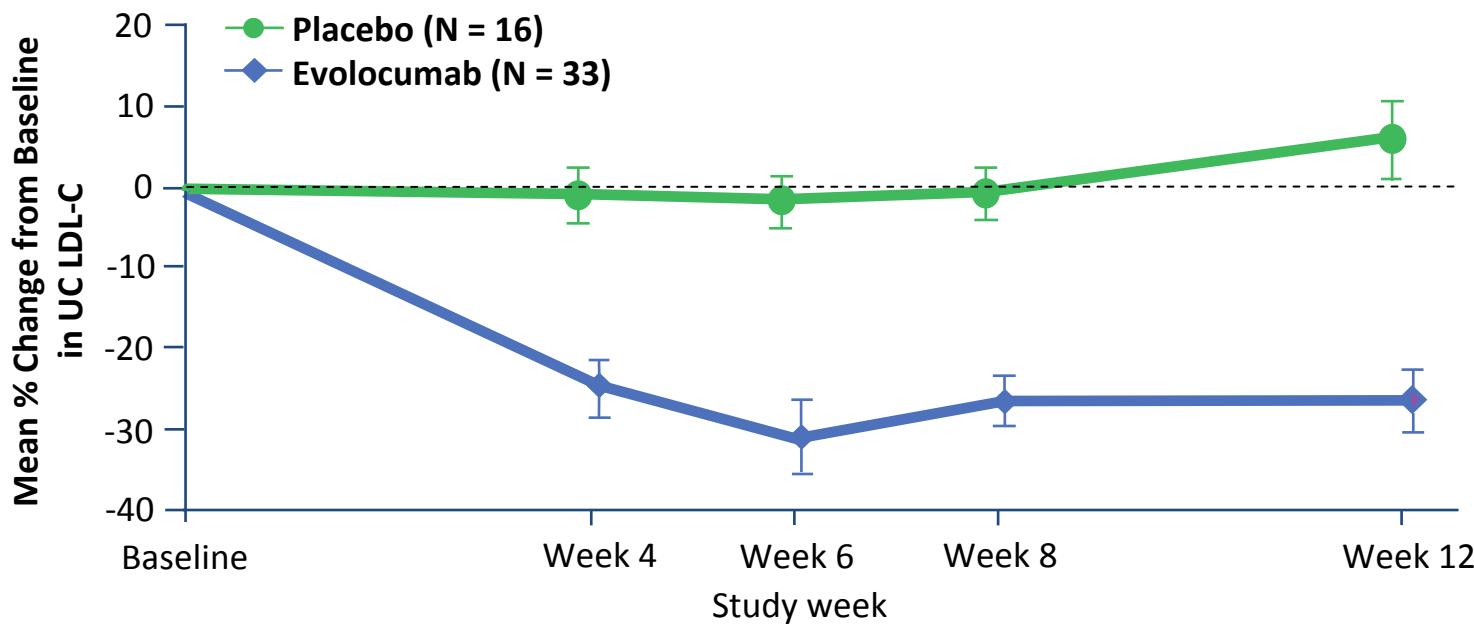
\*Total n does not sum to N as the categories are not mutually exclusive  
 Raal FJ, et al. Lancet 2014; doi.org/10.1016/S0140-6736(14)61374-X and supplementary material

## 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.

## TESLA Part B: Mean % Change in UC LDL-C from Baseline over Time

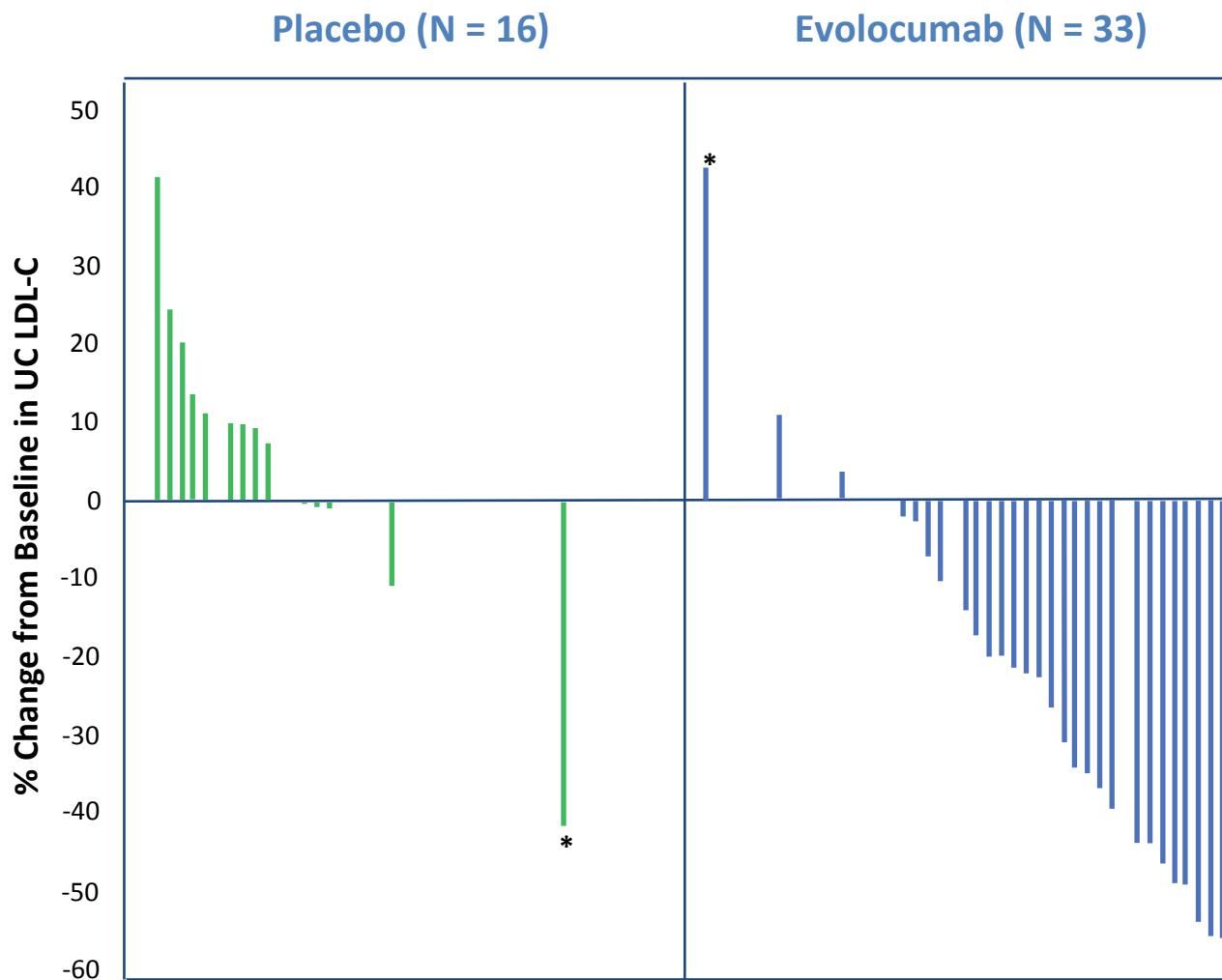


**Number of patients  
analysed at each visit**

Placebo	16	16	15	16	15
Evolocumab	33	32	28	32	29

## TESLA Part B:

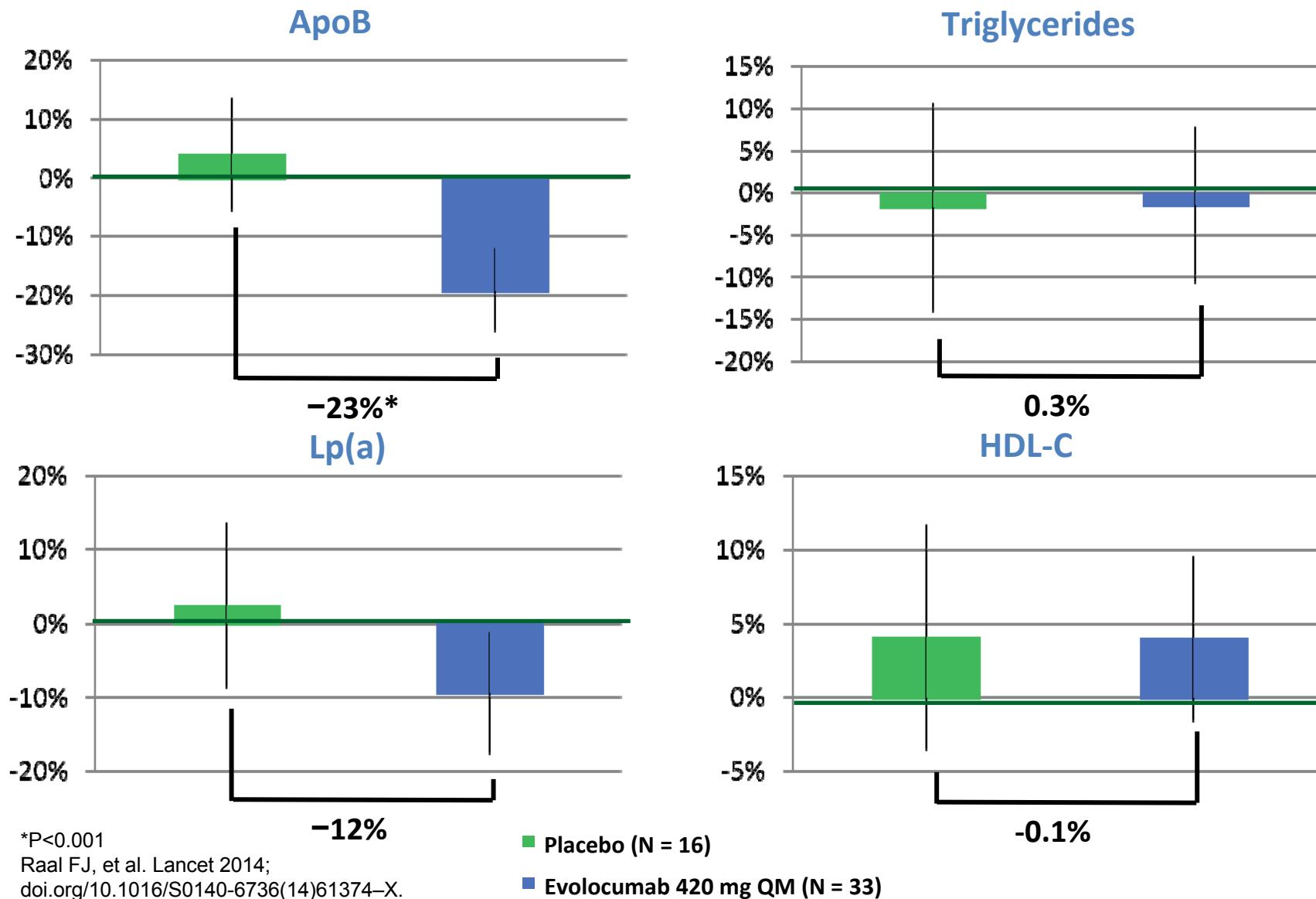
### Week 12 % Change in UC LDL-C in Individual Patients from Baseline



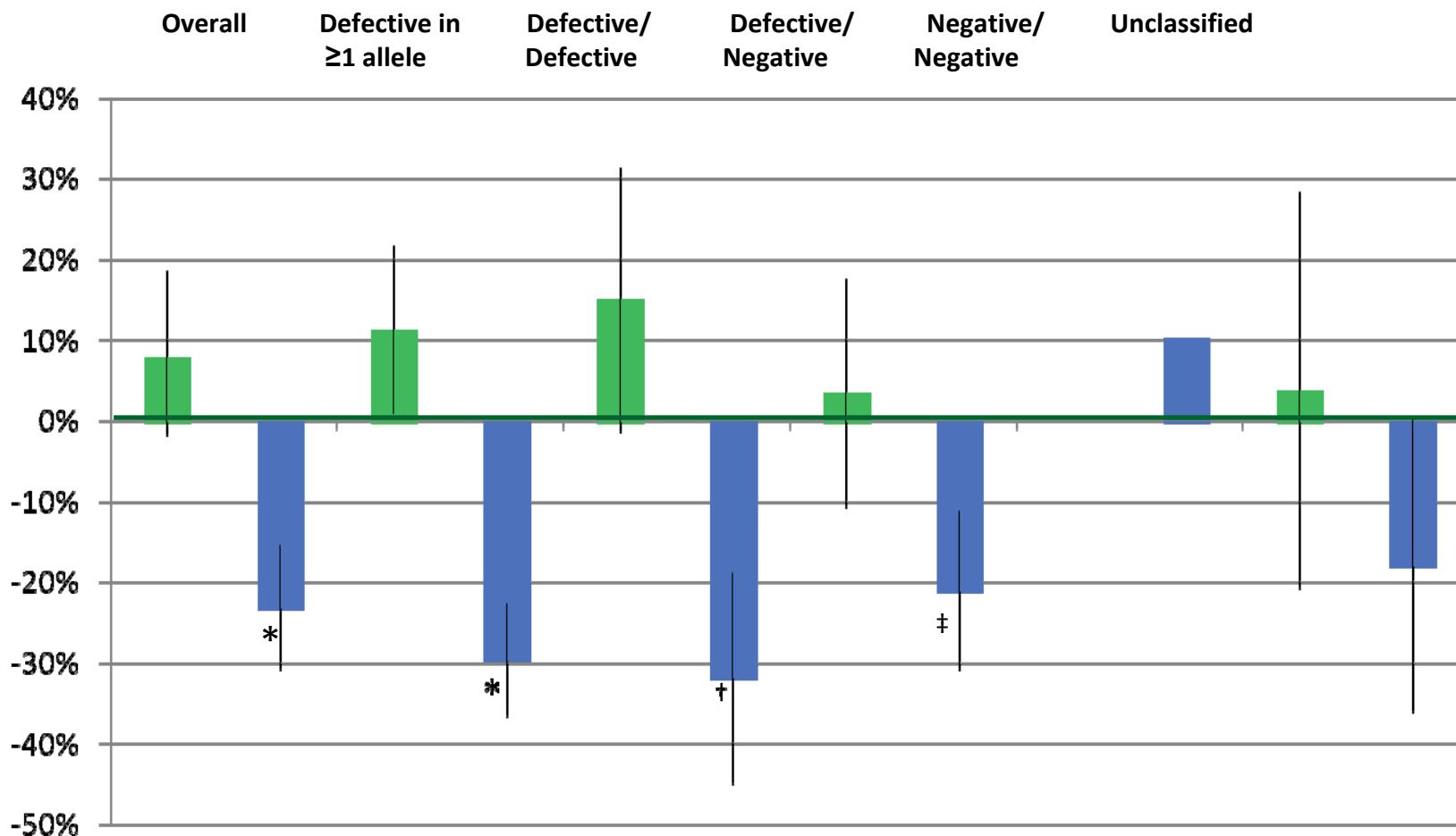
\*Patient indicated via case report form that background lipid-lowering therapy remained unchanged over the study duration.

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

## TESLA Part B: Week 12 % Changes in Other Lipids from Baseline



## TESLA Part B: Week 12 % Change in UC LDL-C from Baseline by Receptor Mutation Status



Data are least squares (LS) mean (95% CI) for groups with sufficient data; otherwise data are actual value at Week 12. LS mean is from the repeated measures model, which includes treatment group, screening LDL, scheduled visit and the interaction of treatment with scheduled visit as covariates. \*Adjusted P<0.0001; †P<0.001; ‡P<0.05.

# TESLA Part B: Safety and Tolerability

Adverse Events (AEs), % (n)	Placebo (N = 16)	Evolocumab (N = 33)
Treatment-emergent AEs	63% (10)	36% (12)
Serious AEs	0	0
AEs leading to treatment discontinuation	0	0
Deaths	0	0
Frequent AEs*		
URTI	6% (1)	9% (3)
Influenza	0	9% (3)
Gastroenteritis	0	6% (2)
Nasopharyngitis	0	6% (2)
Nausea	13% (2)	0
Musculoskeletal pain	0	3% (1)

\*Reported in ≥ 1 patient in either or both treatment arms.

URTI, upper respiratory tract infection.

## TESLA Part B: Safety and Tolerability: Events of Interest

Adverse Events (AEs), % (n)	Placebo (N = 16)	Evolocumab (N = 33)
Potential injection-site reactions*	6% (1)	0
Neurocognitive AEs <sup>†</sup>	0	0
Abnormal laboratory tests		
ALT or AST > 3x ULN	6% (1)	6% (2)
Creatine kinase > 5x ULN	6% (1)	3% (1)
Creatine kinase > 10x ULN	0	3% (1)
Anti-evolocumab antibodies, %		
Binding antibodies	0	0 <sup>‡</sup>
Neutralising antibodies	0	0

\*Reported using high-level term grouping, which includes injection site (IS) rash, IS inflammation, IS pruritus, IS reaction, and IS urticaria; †Searched with use of high-level grouping, which includes deliria (including confusion), cognitive and attention disorders and disturbances, dementia and amnestic disorders; excludes 1 patient who had a positive binding antibody test at baseline and negative antibody testing at all other study assessments. <sup>‡</sup>Excludes 1 patient with positive binding antibody test at baseline.

## Conclusions TESLA Part B:

- In HoFH patients not receiving apheresis, evolocumab 420 mg QM on top of stable background therapy resulted in:
  - **Significant LDL-C reductions of 31% vs placebo**
    - Substantial reduction on top of current best available treatment
  - **Significant ApoB reductions of 23% vs placebo**
  - **LDL-C reductions of 41% vs placebo in patients with ≥1 mutation associated with defective LDLR activity**
    - LDL-C reduction via antibody-mediated PCSK9 inhibition requires remainder LDLR function – LDLR null variants do not respond
- **Evolocumab was well tolerated and may offer an effective additional option to reduce LDL-C as part of the clinical management of HoFH**

# **Trial Assessing Long-Term Use of PCSK9 Inhibition in Patients with Genetic LDL Disorders (**TAUSSIG**): Efficacy and Safety in Patients with Familial Hypercholesterolemia Receiving Lipid Apheresis**

Eric Bruckert<sup>1</sup>, Vladimir Blaha<sup>2</sup>, Evan A. Stein<sup>3</sup>, Frederick J. Raal<sup>4</sup>, Christopher Kurtz<sup>5</sup>, Narimon Honarpour<sup>5</sup>, Feng Xu<sup>6</sup>, John Gibbs<sup>5</sup>, Scott M. Wasserman<sup>5</sup>, Rob Scott<sup>5</sup>, Patrick Couture<sup>7</sup>

<sup>1</sup>Hôpital Pitié Salpêtrière, Assistance-Publique Hôpitaux de Paris, Paris, France; <sup>2</sup>Charles University, Hradec Kralove, Czech Republic; <sup>3</sup>Metabolic and Atherosclerosis Research Center, Cincinnati, OH, USA;

<sup>4</sup>Carbohydrate & Lipid Metabolism Research Unit, University of Witwatersrand, Johannesburg, South Africa; <sup>5</sup>Amgen Inc., Thousand Oaks, CA, USA; <sup>6</sup>Formerly of Amgen; <sup>7</sup>Centre Hospitalier Universitaire de Québec, Quebec City, Canada

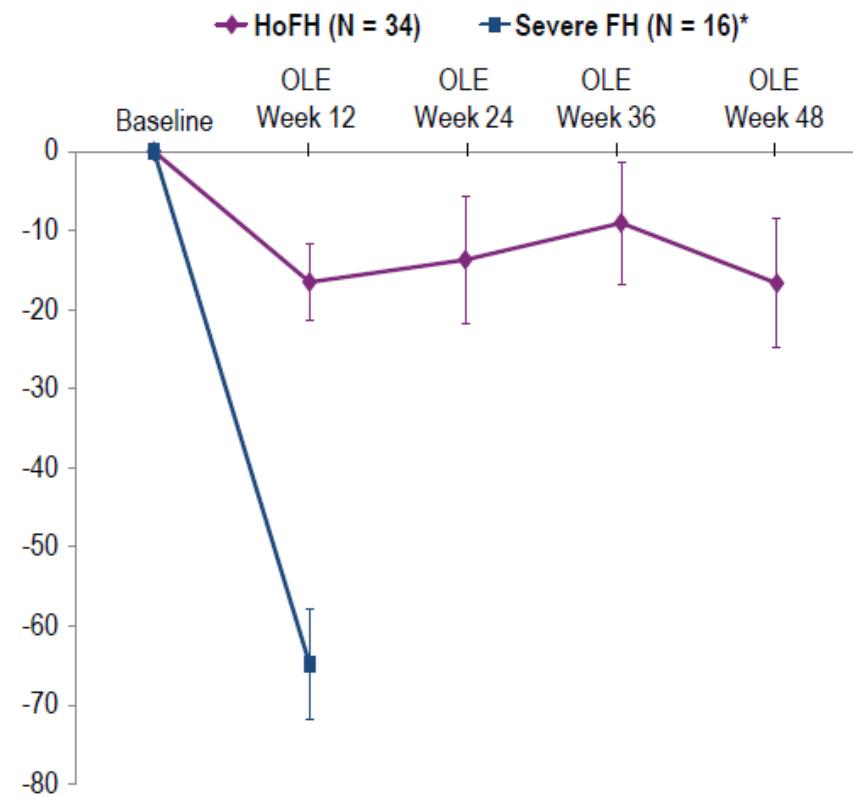
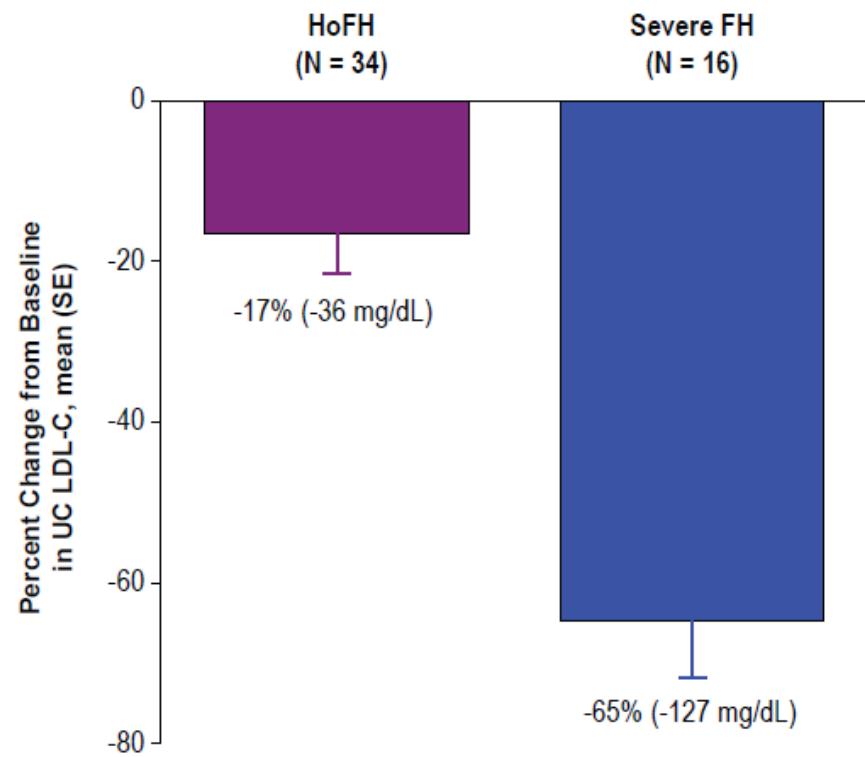
# Objective

- To evaluate the efficacy and safety of evolocumab in patients with HoFH or severe FH receiving apheresis

# Methods

- **Design:**
  - Multicenter, single-arm, open-label, active treatment-only
  - Up to 5 years
- Key study inclusion criteria for apheresis patients:
  - HoFH or an objectively supported diagnosis of FH
  - 48 of 50 patients had genotyping confirming an FH-causing mutation
  - Age  $\geq$  12 to  $\leq$  80 years
  - Stable low-fat diet and lipid-lowering therapy for  $\geq$  4 weeks
  - Biweekly apheresis schedule
- All apheresis patients received evolocumab 420 mg Q2W, given post-apheresis
- Lipids were assessed pre-apheresis

## Percent Change from Baseline in UC LDL-C in Patients with HoFH and Severe FH on Apheresis



\* Week 12 is the most recent data available for patients with severe FH

# Percent Change from Baseline at OLE Week 12 in UC LDL-C in Patients with HoFH on Apheresis by Genotype

	n	Change in UC LDL-C, mean (SE), %
<b>LDL receptor mutation status</b>		
All patients	34	-17 (5)
One or both alleles defective	12	-26 (6)
Unclassified	18	-18 (6)
Negative/negative	4	10 (13)
<b>Other gene mutations</b>		
ApoB	1	-48
Double heterozygous (PCSK9 GoF and LDL receptor negative mutation)	2	-80 (10)
Autosomal recessive hypercholesterolemia	2	-10 (8)

# Reduction of Apheresis

- In the HoFH group, 5 of 34 patients (15%) stopped or reduced the frequency of apheresis:
  - 2 patients (6%) were able to stop apheresis
  - 3 patients (9%) were able to decrease apheresis frequency from biweekly to monthly
- In the severe FH group, 5 of 16 patients (31%) stopped or reduced the frequency of apheresis:
  - 4 patients (25%) were able to stop apheresis
  - 1 patient (6%) was able to decrease apheresis frequency from biweekly to monthly
  - At Week 12, 10 patients (63%) had stopped apheresis or achieved pre-apheresis LDL-C of < 70 mg/dL

# Reduction of Apheresis

## LDL-C Levels at the Time of Change in Apheresis

	n	Baseline LDL-C, mean (range), mg/dL	UC LDL-C at time of change,* mean (range), mg/dL	Change in UC LDL-C, mean (range), %
<b>HoFH</b>				
Patients stopping apheresis	2	155 (181 – 129)	30 (16 – 43)	-82 (-88 – -76)
Patients changing frequency to monthly	3	174 (136 – 250)	90 (46 – 115)	-39 (-82 – -15)
<b>Severe FH</b>				
Patients stopping apheresis	4	179 (146 – 212)	36 (21 – 47)	-79 (-90 – -70)
Patients changing frequency to monthly	1	214	62	-71

\* Change or cessation; pre-apheresis UC LDL-C on the day of the last scheduled apheresis session (if apheresis was stopped) or on the day of the last apheresis session at the frequency of every two weeks.

# Safety and Tolerability

n (%)	HoFH (N = 34)	Severe FH (N = 16)
<b>Adverse events</b>		
Any	26 (77)	8 (50)
Serious*	4 (12)	1 (6)
Deaths	0	0
Leading to discontinuation	0	0
Positively adjudicated cardiovascular events**	1 (3)	1 (6)
Muscle-related adverse events	0	0
<b>Laboratory results</b>		
ALT or AST > 3X ULN (any post-baseline value)†	1 (3)	0
CK > 5X ULN (any post-baseline value)	0	0
Anti-evolocumab antibodies	0	0

\*Included myocardial ischemia, AV fistula thrombosis, hematuria occurring after apheresis, and carotid artery stenosis in a patient with known cerebrovascular disease in HoFH; angina pectoris in severe FH

\*\* Both events were coronary revascularization

† Peak ALT elevation 3.1X ULN, resolved without discontinuing evolocumab

# Conclusions -TAUSSIG

- In patients with HoFH and severe FH receiving apheresis, evolocumab decreased LDL-C:
  - 17% (36 mg/dL) decrease in patients with HoFH at open-label extension Week 12
  - 65% (127 mg/dL) decrease in patients with severe FH at open-label extension Week 12
- Patients were able to stop or reduce frequency of apheresis:
  - 15% of patients with HoFH
  - 31% of patients with severe FH
- Efficacy corresponded to the genetic cause of FH, supporting and extending the results of TESLA part B.<sup>1</sup>
- Evolocumab may offer a new and less-invasive treatment option to additionally reduce LDL-C in patients with FH receiving apheresis.

# Highlights on Evolocumab

## Υπερχοληστερολαιμία και μικτή δυσλιπιδαιμία

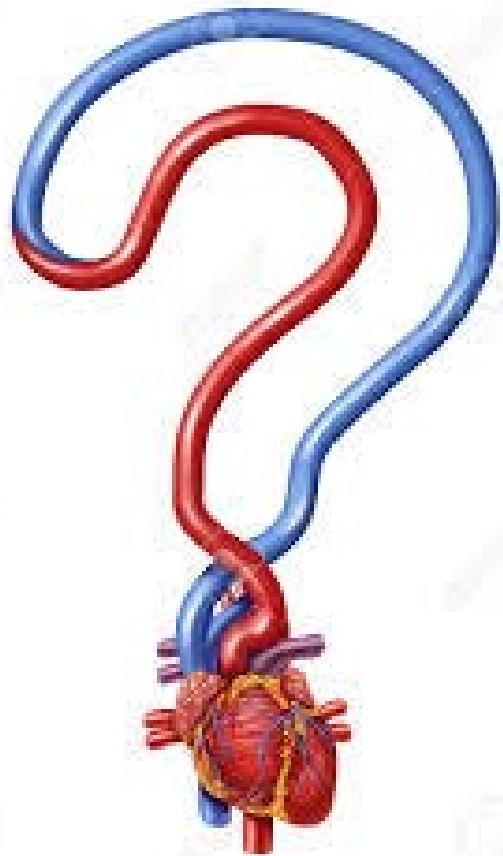
**Το Repatha ενδείκνυται σε ενήλικες με πρωτοπαθή υπερχοληστερολαιμία (ετερόζυγο οικογενή και μη οικογενή) ή μικτή δυσλιπιδαιμία, ως συμπλήρωμα της δίαιτας:**

- **σε συνδυασμό με μία στατίνη ή συνδυασμό με στατίνη και άλλες υπολιπιδαιμικές θεραπείες σε ασθενείς στους οποίους δεν μπορούν να επιτευχθούν οι στόχοι της LDL-C με τη μέγιστη ανεκτή δόση μιας στατίνης, ή**
- **μόνο ή σε συνδυασμό με άλλες υπολιπιδαιμικές θεραπείες σε ασθενείς με δυσανεξία στις στατίνες ή στους οποίους αντενδείκνυνται οι στατίνες.**

## Ομόζυγος οικογενής υπερχοληστερολαιμία

**Το Repatha ενδείκνυται σε ενήλικες και εφήβους ηλικίας 12 ετών και άνω με ομόζυγο οικογενή υπερχοληστερολαιμία σε συνδυασμό με άλλες υπολιπιδαιμικές θεραπείες.**

Η επίδραση του Repatha στην καρδιαγγειακή νοσηρότητα και θνησιμότητα δεν έχει ακόμα προσδιοριστεί.



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Συμπληρώνοντας την “ΚΙΤΡΙΝΗ ΚΑΡΤΑ”**

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