The LAPLACE-2 Trial: A Phase 3, Double-blind, Randomized, Placebo and Ezetimibe Controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of Evolocumab (AMG 145) in Combination With Statin Therapy in Subjects With Primary Hypercholesterolemia and Mixed Dyslipidemia

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Background

- Statins are the first-line therapy for reducing atherosclerotic cardiovascular disease (ASCVD).

- 2013 ACC/AHA Cholesterol Guidelines[1]
  - A high-intensity statin (≥ 50% LDL-C lowering) is recommended for high-risk patients.
    - Clinical ASCVD; aged ≤ 75 y
    - LDL-C ≥ 190 mg/dL (4.9 mmol/L)
    - Diabetes; aged 40-75 years with ≥ 7.5% 10-y ASCVD risk
  - A moderate-intensity statin (30-< 50% LDL-C lowering) is otherwise recommended.
  - Non-statin therapy is recommended for high-risk patients who cannot tolerate a high-intensity statin, have a less than anticipated therapeutic response, or have genetic hypercholesterolemia.

[1]*Circulation. Online ahead of print November 2013.*

Background

- Outside of the USA, guidelines recommend an LDL-C <100 mg/dL or <70 mg/dL, depending on the level of risk.[1-3]
- Many patients receiving moderate- or high-intensity statin therapy will require addition of another LDL-C lowering drug.[4-5]
- Evolocumab (AMG 145) is a human monoclonal antibody to PCSK9.
- Evolocumab was well tolerated and showed robust LDL-C lowering in phase 2 trials,[6-9] including a longer-term, 52-week study.[10]

1. *Can J Cardiol.* 2013;2:151-167.
2. *Atherosclerosis.* 2012;223:1-68.
3. *J Clin Lipidol* 2013;7:561-565.
4. *N Engl J Med.* 2005; 352:1425-1435.
5. *JAMA.* 2005;294:2437-2445.
6. *Lancet*. 2012;380:1995-2006.
7. *Lancet*. 2012;380:2007-2017.
8. *JAMA*. 2012;308:2497-2506.
9. *Circulation*. 2012;126:2408-2417.
10. *Circulation*. *Online ahead of print November 2013.*

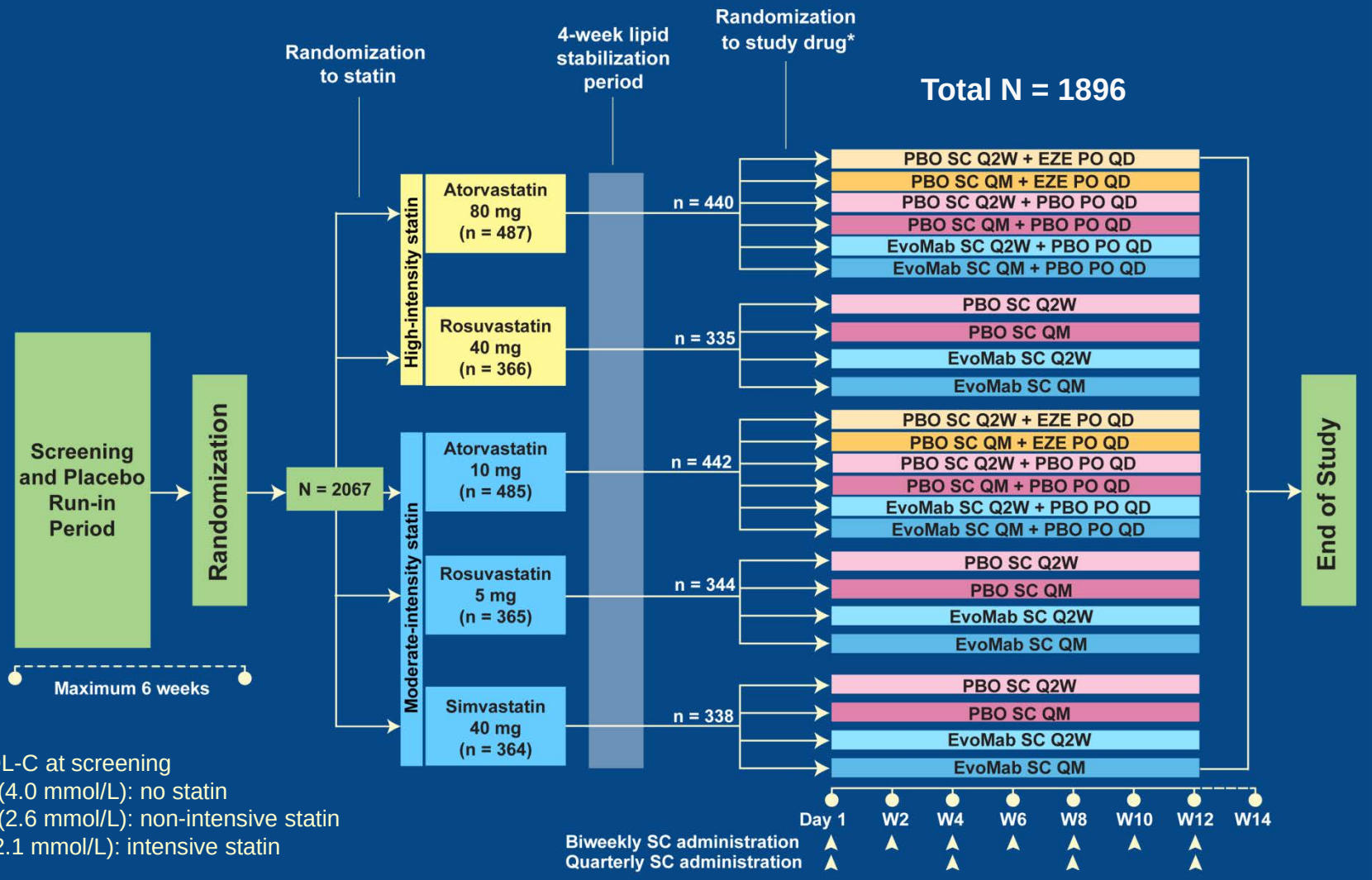
The LAPLACE-2 Study

LDL-C **A**ssessment with **P**CSK9 Monoclona**L** **A**ntibody Inhibition **C**ombined With Statin Th**E**rapy – 2 (NCT01763866)

Design:
A 12-week, randomized, double-blind, placebo- and ezetimibe-controlled, phase III study

Objective:
To evaluate the efficacy and safety of evolocumab administered biweekly (140 mg) or monthly (420 mg) in combination with a statin in hypercholesterolemic patients

LAPLACE-2: Study Design



Eligibility: LDL-C at screening
≥150 mg/dL (4.0 mmol/L): no statin
≥100 mg/dL (2.6 mmol/L): non-intensive statin
≥80 mg/dL (2.1 mmol/L): intensive statin

*1896 patients were randomized and received at least one dose of study drug. LDL-C, low-density lipoprotein cholesterol; PBO, placebo; EvoMab, evolocumab; EZE, ezetimibe; PO, oral; Q2W, biweekly; QM, monthly; QD, daily; SC, subcutaneous; W, week.

Clinical Cardiology. *Online ahead of print January 2014.*

LAPLACE-2: Baseline Characteristics

	Any Statin + Placebo (N = 558)	Atorvastatin + Ezetimibe (N = 221)	Any Statin + Evolocumab (N = 1117)
Age (years), mean (SD)	60 (10)	61 (9)	60 (10)
Female, %	48	49	44
Coronary artery disease, %	22	17	24
Peripheral arterial disease or cerebrovascular disease, %	10	9	11
Diabetes mellitus, Type 2, %	13	20	16

Total N = 1896*

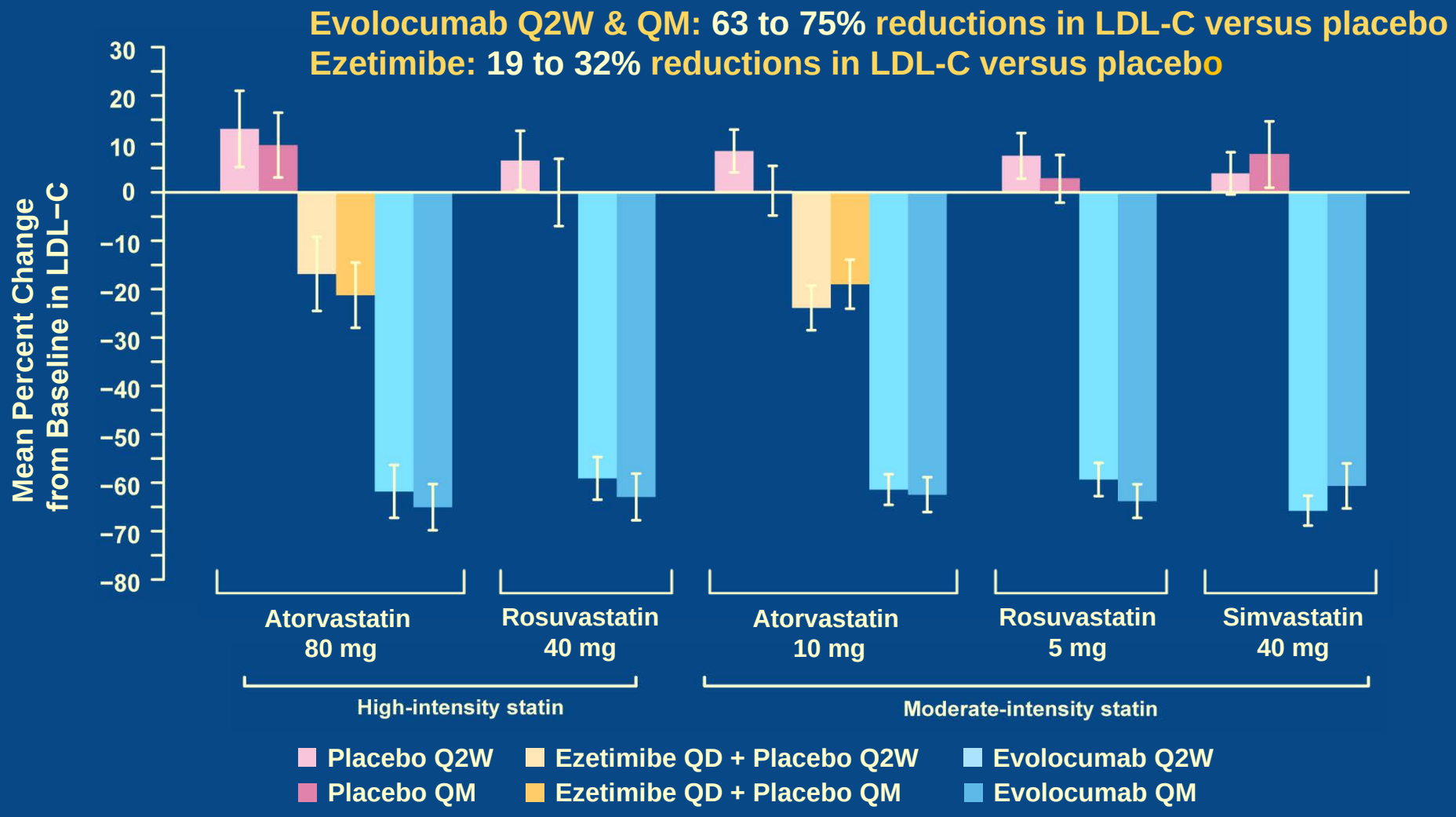
*__1896__ patients were randomized and received at least one dose of study drug. Baseline characteristics were collected at randomization to statin. SD, standard deviation.

LAPLACE-2: Baseline Lipids

	Any Statin + Placebo (N = 558)	Atorvastatin + Ezetimibe (N = 221)	Any Statin + Evolocumab (N = 1117)
LDL-C,[a] mg/dL, mean (SD)	108 (40)	109 (37)	110 (42)
ApoB, g/L, mean (SD)	88 (25)	90 (25)	90 (27)
TG, mg/dL, mean (SD)	129 (66)	136 (77)	137 (82)
HDL-C, mg/dL, mean (SD)	55 (17)	52 (15)	53 (16)
Lp(a), mg/dL, mean (SD)	86 (100)	92 (104)	91 (113)
PCSK9, ng/mL, mean (SD)	353 (114)	351 (112)	355 (111)

Baseline characteristics were collected at randomization to statin.
[a]Determined by the Friedewald formula with reflexive testing via preparative ultracentrifugation when calculated LDL-C was < 40 mg/dL or triglycerides were > 400 mg/dL.
LDL-C, low-density lipoprotein cholesterol; ApoB, apolipoprotein B; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; Lp(a), lipoprotein (a); PCSK9, proprotein convertase subtilisin/kexin type 9.

LAPLACE-2: LDL-C Response at Mean of Weeks 10 and 12

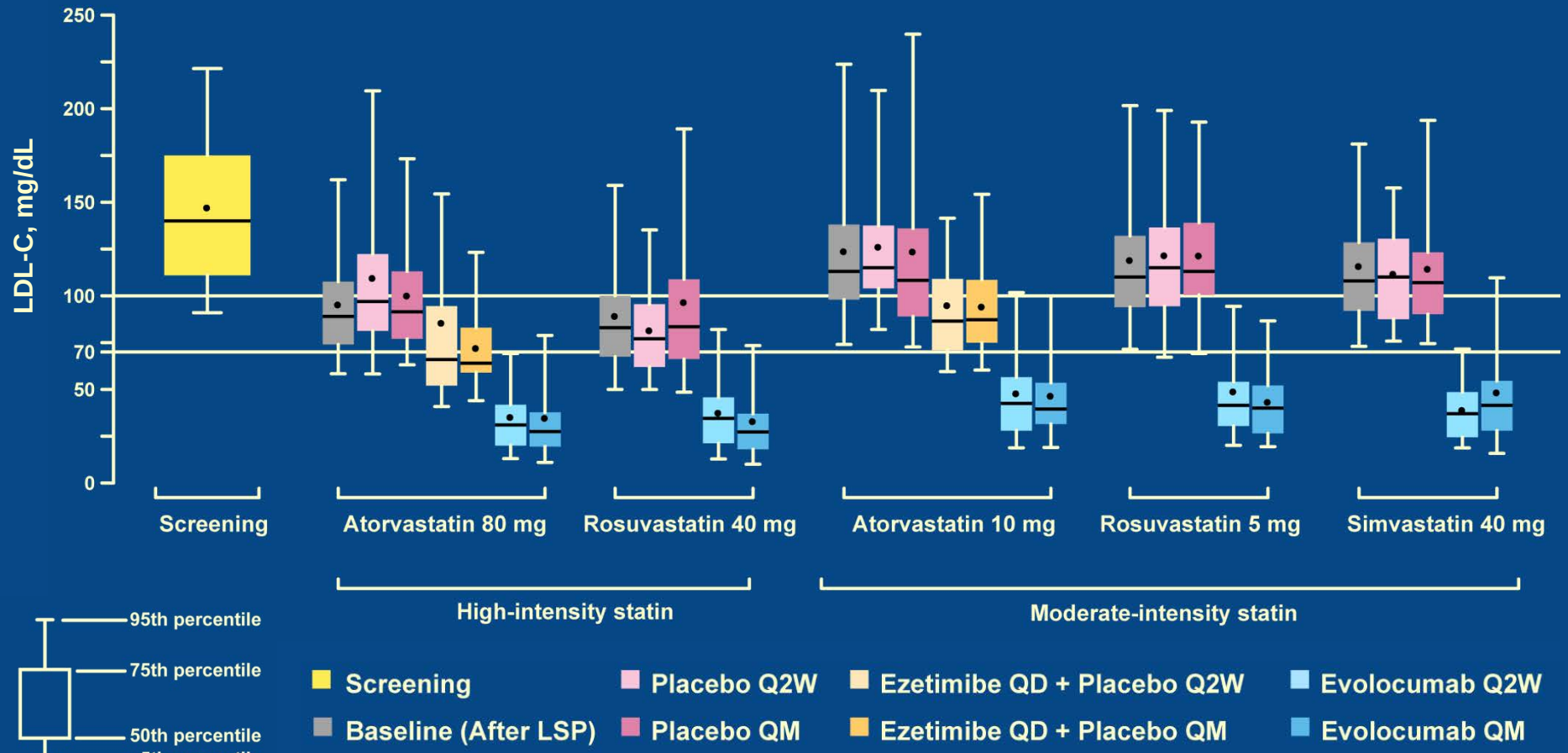


All treatment differences versus placebo and ezetimibe were statistically significant (P<0.001).
No notable differences were observed between the mean of weeks 10 and 12 and week 12 alone.
LDL-C, low-density lipoprotein cholesterol; Q2W, biweekly; QM, monthly. Vertical lines represent 95% CIs.

LAPLACE-2: Screening, Baseline, and On-treatment LDL-C[a]

LDL-C < 70 mg/dL: High-intensity statin Q2W 94%; QM 93 to 95%

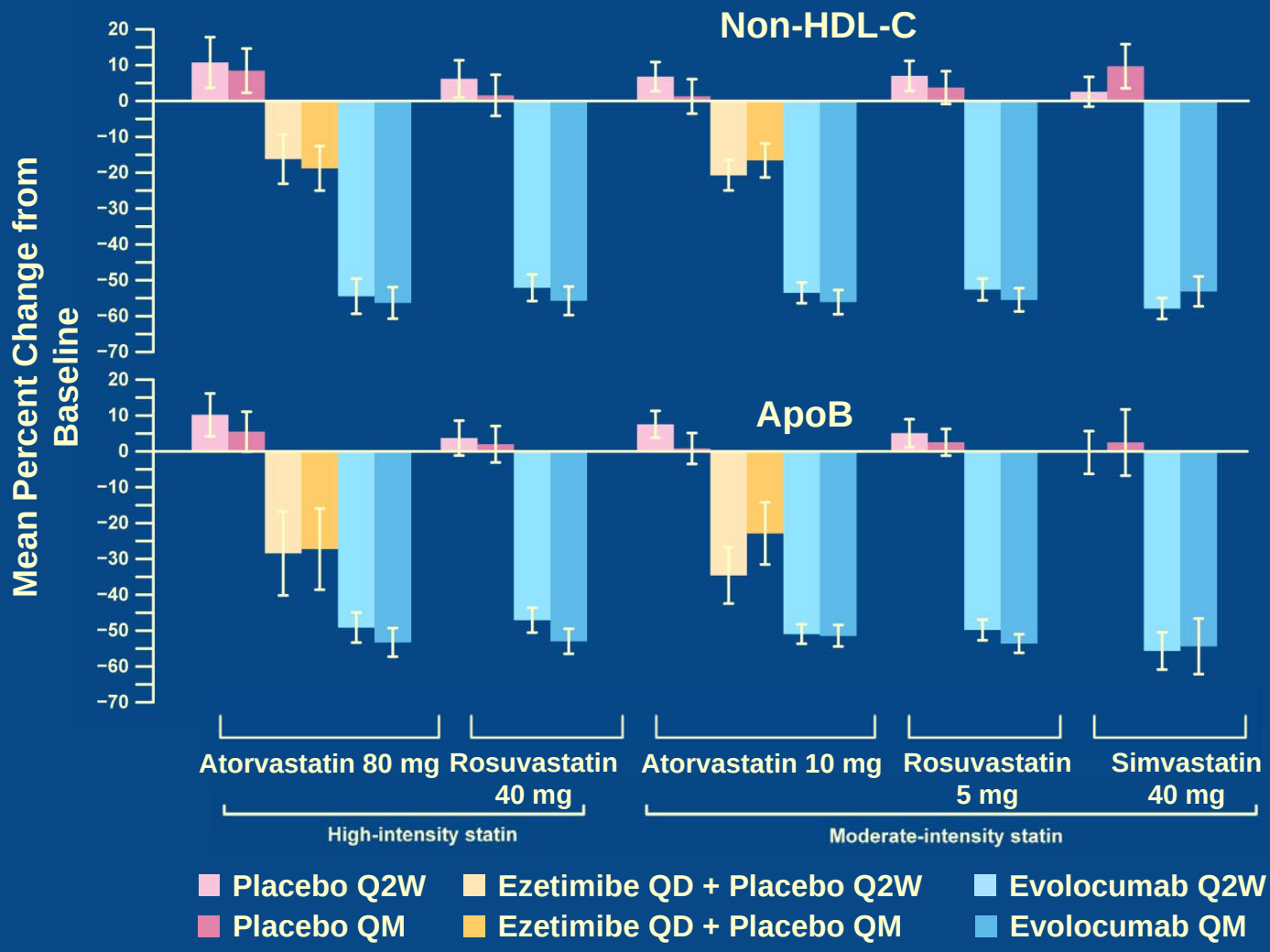
LDL-C < 70 mg/dL: Moderate-intensity statin Q2W 88 to 94%; QM 86 to 90%



[a]Mean of weeks 10 and 12. No notable differences were observed between the mean of weeks 10 and 12 and week 12 alone.

LDL-C, low-density lipoprotein cholesterol; ISP, lipid-stabilization period; Q2W, biweekly; QM, monthly.

LAPLACE-2: Other Lipids at Mean Weeks 10/12



Q2W **–58 to –65%** vs placebo

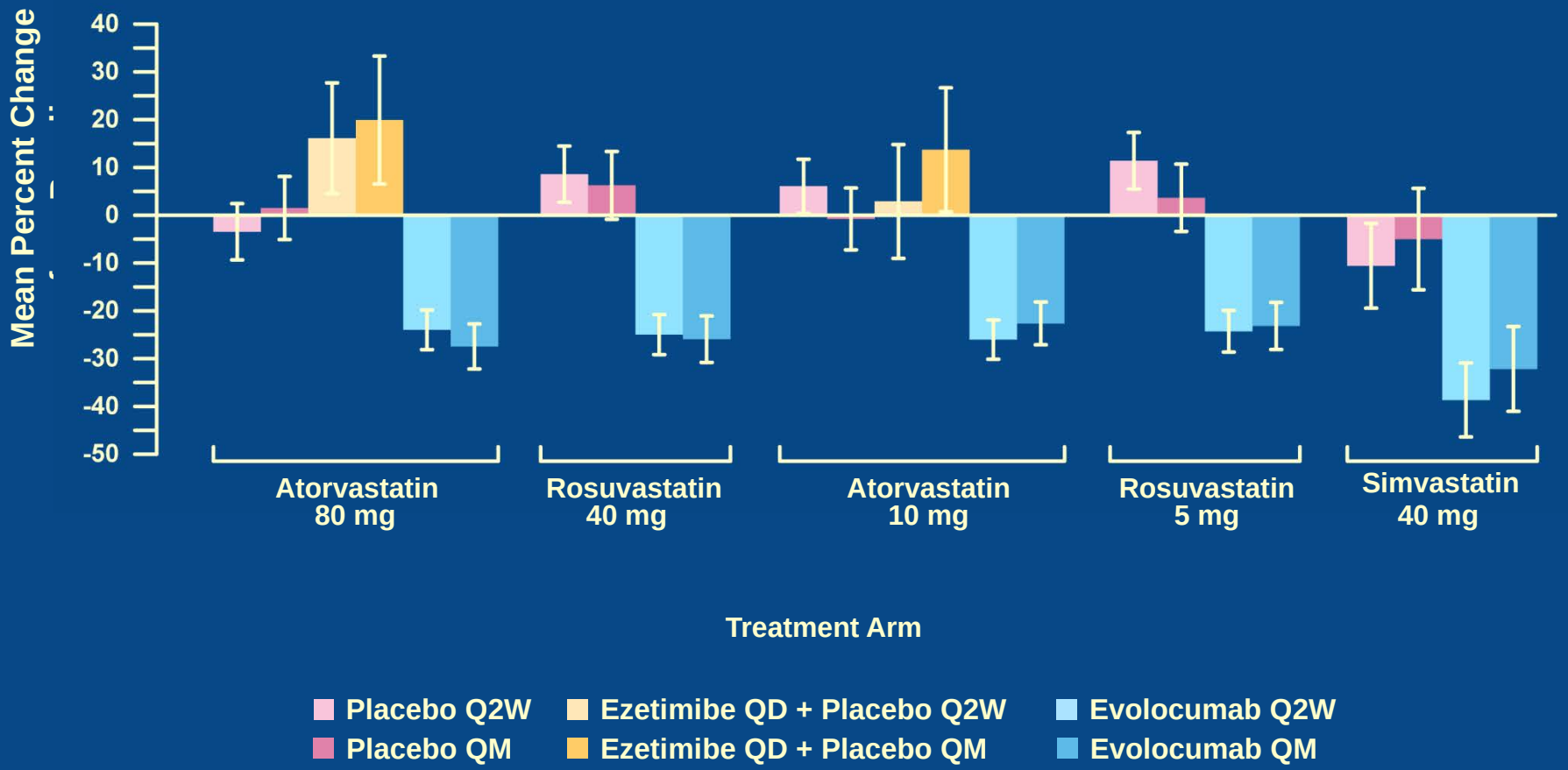
Q2W **–51 to –59%** vs placebo

All treatment differences vs placebo and ezetimibe were statistically significant (P<0.05). Vertical lines represent 95% CIs.
No notable differences were observed between the mean of weeks 10 and 12 and week 12 alone. Non-HDL-C, non high-density lipoprotein cholesterol; ApoB, apolipoprotein B; Q2W, biweekly; QM, monthly.

LAPLACE-2: Other Lipids at Mean Weeks 10/12

Lipoprotein (a)

Q2W **–21 to –36%** vs placebo



All treatment differences vs placebo and ezetimibe were statistically significant (P<0.05).
No notable differences were observed between the mean of weeks 10 and 12 and week 12 alone.
Vertical lines represent 95% CIs. Q2W, biweekly; QM, monthly.

LAPLACE-2: Safety and Tolerability

n (%)	Any Statin + Placebo (N = 558)	Atorvastatin + Ezetimibe (N = 221)	Any Statin + Evolocumab (N = 1117)
Treatment-emergent AEs	219 (39)	89 (40)	406 (36)
Most common AEs[a]			
Back pain	14 (3)	7 (3)	20 (2)
Arthralgia	9 (2)	4 (2)	19 (2)
Headache	15 (3)	5 (2)	19 (2)
Muscle spasms	6 (1)	6 (3)	17 (2)
Pain in extremity	7 (1)	3 (1)	17 (2)
Serious AEs	13 (2)	2 (1)	23 (2)
AEs leading to study drug discontinuation	12 (2)	4 (2)	21 (2)
Deaths	1 (0.2)	0 (0)[b]	0 (0)
CK > 5 x ULN	2 (0.4)	0 (0)	1 (0.1)
ALT or AST > 3 x ULN	6 (1)	3 (1)	4 (0.4)
Potential injection site reactions[c]	8 (1)	2 (1)	15 (1)
Neurocognitive AEs			
Cognitive deterioration	0 (0)	1 (0.5)	0 (0)
Disorientation	0 (0)	1 (0.5)	0 (0)
Post-baseline binding antibodies	NA	NA	1 (0.1)[d]

[a] Top 5 in evolocumab treatment group. [b] One subject died after the end of study. [c] Reported using high-level term groupings which included injection site (IS) rash, IS inflammation, IS pruritus, IS reaction, and IS urticaria.
[d] Binding antibody was present at baseline and at the end of study. No neutralizing antibodies were detected.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

LAPLACE-2: Conclusions

- Evolocumab significantly lowered LDL-C at the mean of weeks 10/12 in patients with hypercholesterolemia on background statin therapy.
  - There were no notable differences in percent reductions for moderate and high-intensity background statin therapies.
- Evolocumab 140 mg biweekly and 420 mg monthly dosing regimens are clinically equivalent.
- When combined with atorvastatin, LDL-C lowering was significantly greater in patients receiving evolocumab (63-75%) versus those receiving ezetimibe (19-32%).
- LDL-C < 70 mg/dL was achieved in most patients on evolocumab.
  - 86-94% (moderate-intensity statin)
  - 93-95% (high-intensity statin)
- There were no notable differences in safety & tolerability in evolocumab-, placebo-, and ezetimibe-treated patients.

FOURIER

- An ASCVD outcomes trial is underway
  - Evolocumab Q2W or QM added to moderate or high intensity statin therapy
  - Patients are those with clinical ASCVD (N = 22,500)
  - The trial is evaluating atherosclerotic cardiovascular disease (ASCVD) event reduction and safety

Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER). Available at: http://clinicaltrials.gov/ct2/show/NCT01764633.

Disclosures

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