FOURIER- ESTUDO DE INIBIÇÃO DA PCSK9 EM PACIENTES DE ALTO RISCO CARDIOVASCULAR

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CONFLITO DE INTERESSES

PROFIRO CONFERENCIAS REMUNERADAS PARA VARIAS INSTITUIÇÕES DA INDUSTRIA FARMACEUTICA O QUE NÃO COMPROMETE O MEU JUIZO CRITICO NEM ME PERMITE FUGIR DOS CONCEITOS E CONCLUSÕES DAS EVIDENCIAS CLINICAS DISPONIVEIS

fourier

Repatha Outcomes Trial: Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

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Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

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Background

- LDL-C is a well-established and modifiable risk factor for CVD.[1]
- Beginning with 4S in 1994 comparing simvastatin to placebo, and most recently with IMPROVE-IT in 2015 comparing ezetimibe/simvastatin to simvastatin, a consistent relationship between LDL-C reduction and CV event reduction has been observed.[2-5]
- Despite use of statins, many patients are unable to control their LDL-C and thus, their additional cardiovascular risk remains unaddressed.[6-8]

LDL-C = low-density lipoprotein cholesterol; CVD = cardiovascular

1. Kenan T. *Curr Cardiol Rep*. 2013;15(396):1-10 . 2. Pedersen TR, et al. *Lancet*. 1994;344:1383-1389. 3. Cannon CP, et al. *N Engl J Med*. 2015;372:2387-2397. 4. Cholesterol Treatment Trialists (CTT) Collaborators, et al. *Lancet*. 2005;366(9493):1267-1278. 5. Cholesterol Treatment Trialists Collaboration, et al Lancet 2010; 376: 1670–1681. 6. Cannon CP, et al. *N Engl J Med*. 2004;350:1495-1504. 7. Pederson TR, et al. *JAMA*. 2005;294: 2437-2445. 8. LaRosa JC, et al. *N Engl Med*. 2005;352:1425-1435.

Background

- Evolocumab, a fully human monoclonal antibody, is a PCSK9 inhibitor that reduces LDL-C by approximately 60% at the approved doses.[1-5]
- Longer-term studies of evolocumab, including GLAGOV (78 weeks), OSLER-1 (4 years), and pooled analyses of PROFICIO (~1 year) have demonstrated sustained LDL-C reduction, without evidence of new safety concerns, regardless of LDL-C level achieved.[6-8]

LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9

1. Blom DJ, et al. *N Engl J Med.* 2014;370:1809-19. 2. Robinson JG, et al. *JAMA.* 2014;311:1870-82. 3. Koren MJ, et al. *J Am Coll Cardiol.* 2014;63:2531-40. 4. Stroes E, et al. *J Am Coll Cardiol.* 2014;63:2541-8. 5. Raal FJ, et al. *Lancet* 2015;385:331–40. 6. Nicholls SJ, et al. *JAMA.* [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951. 7. Toth PP, et al. Circulation [published online ahead of print March 1, 2017]. doi.org/10.1161/CIRCULATIONAHA.116.025233. 8. Koren MJ, et al. *JAMA Cardiol.* [published online ahead of print March 14, 2017]. doi: 10.1001/jamacardio.2017.0747].

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Methods

Evolocumab Outcomes Trial: Study Population

FOURIER: **F**urther cardiovascular **OU**tcomes **R**esearch with PCSK9 **I**nhibition in subjects with **E**levated **R**isk

27,564 patients aged 40–85 years

Clinically evident CV disease
- History of myocardial infarction
- Nonhemorrhagic stroke
- Symptomatic peripheral artery disease

Plus additional risk factors

Fasting LDL-C ≥ 70 mg/dL or non–HDL-C ≥ 100 mg/dL after > 2 weeks of optimized stable lipid-lowering therapy*

*Ideally a high-intensity statin, but must be at least atorvastatin 20 mg daily or equivalent
CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.
Sabatine MS, et al. *Am Heart J*. 2016;173:94-101.
Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

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FOURIER: Key Inclusion Criteria

- Men or women aged 40–85 years
- History of clinically evident CVD (MI, nonhemorrhagic stroke, or symptomatic PAD*) plus additional risk factors (see table)
- Fasting LDL-C ≥ 70 mg/dL or non–HDL-C ≥ 100 mg/dL after ≥ 2 weeks of optimized stable lipid-lowering therapy**; fasting triglycerides ≤ 400 mg/dL

Major Risk Factors (One Required)	OR	Minor Risk Factors (Two Required)
Diabetes (type 1 or 2)		History of non-MI–related coronary revascularization
Age ≥ 65 years at randomization (≤85 years at time of informed consent)		Residual CAD with ≥ 40% stenosis in ≥ 2 large vessels
MI or non-hemorrhagic stroke at ≤ 6 months of screening		HDL-C < 40 mg/dL for men and < 50 mg/dL for women
Additional diagnosis of MI or non-hemorrhagic stroke excluding qualifying MI		LDL-C ≥ 130 mg/dL or non–HDL-C ≥ 160 mg/dL after ≥ 2 weeks of stable lipid-lowering therapy
Current daily smoking		hsCRP > 2.0 mg/L
History of symptomatic PAD* if eligible by MI or stroke history		Metabolic syndrome

*Symptomatic PAD, as evidenced by either intermittent claudication with ABI (ankle-branchial index) <0.85, or peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease. **Moderate to high intensity statin +/-ezetimibe
CAD, coronary artery disease; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral artery disease.

Sabatine MS, et al. *Am Heart J.* 2016;173:94-101.
Sabatine MS, et al . *NEJM.* [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

FOURIER: Key Exclusion Criteria

- Less than 4 weeks since most recent MI or stroke
- NYHA class III or IV or left ventricular fraction < 30%
- Known hemorrhagic stroke at any time
- Uncontrolled or recurrent ventricular tachycardia
- Planned cardiac surgery or revascularization ≤ 3 months after randomization
- Uncontrolled hypertension (SBP > 180 mmHg or diastolic BP > 110 mmHg)
- Prior use of PCSK9 inhibitor other than evolocumab or use of evolocumab < 12 weeks prior to screening
- Use of CETP inhibitors, mipomersen, or lomitapide ≤ 12 months prior to randomization; fenobrate therapy must be stable ≥ 6 weeks prior to screening
- LDL or plasma apheresis ≤ 12 months prior to randomization
- Laboratory values:
  - Thyroid stimulating hormone < lower limit of normal or > 1.5 x ULN
  - eGFR < 20 mL/min/1.73m^2
  - AST or ALT > 3 x ULN
  - CK > 5 x ULN

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CETP, cholesterol ester transfer protein; CK, creatine kinase; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; MI, myocardial infarction; NYHA, New York Heart Association; PCSK9, proprotein convertase subtilisin/kexin type 9; SBP, systolic BP; ULN, upper limit of normal.

Sabatine MS, et al. *Am Heart J*. 2016;173:94-101.
Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Evolocumab Outcomes Trial: Objective

FOURIER: **F**urther cardiovascular **OU**tcomes **R**esearch with PCSK9 **I**nhibition in subjects with **E**levated **R**isk

- Designed to test whether patients with established cardiovascular disease who are already on optimal cardiovascular therapy, including high to moderate intensity statins, benefit from maximal LDL-C reduction with evolocumab
- Additionally, will evaluate the clinical efficacy and safety of achieving unprecedented levels of low LDL-C with evolocumab
- Global randomized, placebo-controlled, double-blind trial (n = 27,564; 49 countries; 1,242 sites)

PCSK9, proprotein convertase subtilisin/kexin type 9.

Sabatine MS, et al. *Am Heart J.* 2016;173:94-101.
Sabatine MS, et al . *NEJM.* [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

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FOURIER: Study Drug

Evolocumab 140 mg Q2W or **Evolocumab 420 mg QM**

- One placebo run-in injection to assess tolerability of SC injections
- Patients may choose the dosing frequency of evolocumab and can elect to switch every 12 weeks
- Dose titrations are not permitted

Background lipid-lowering therapy

- Patients must be on an optimized lipid-lowering regimen (moderate to high intensity statin +/- ezetimibe)
- In general, patients are not to change open-label background lipid-lowering therapies after randomization

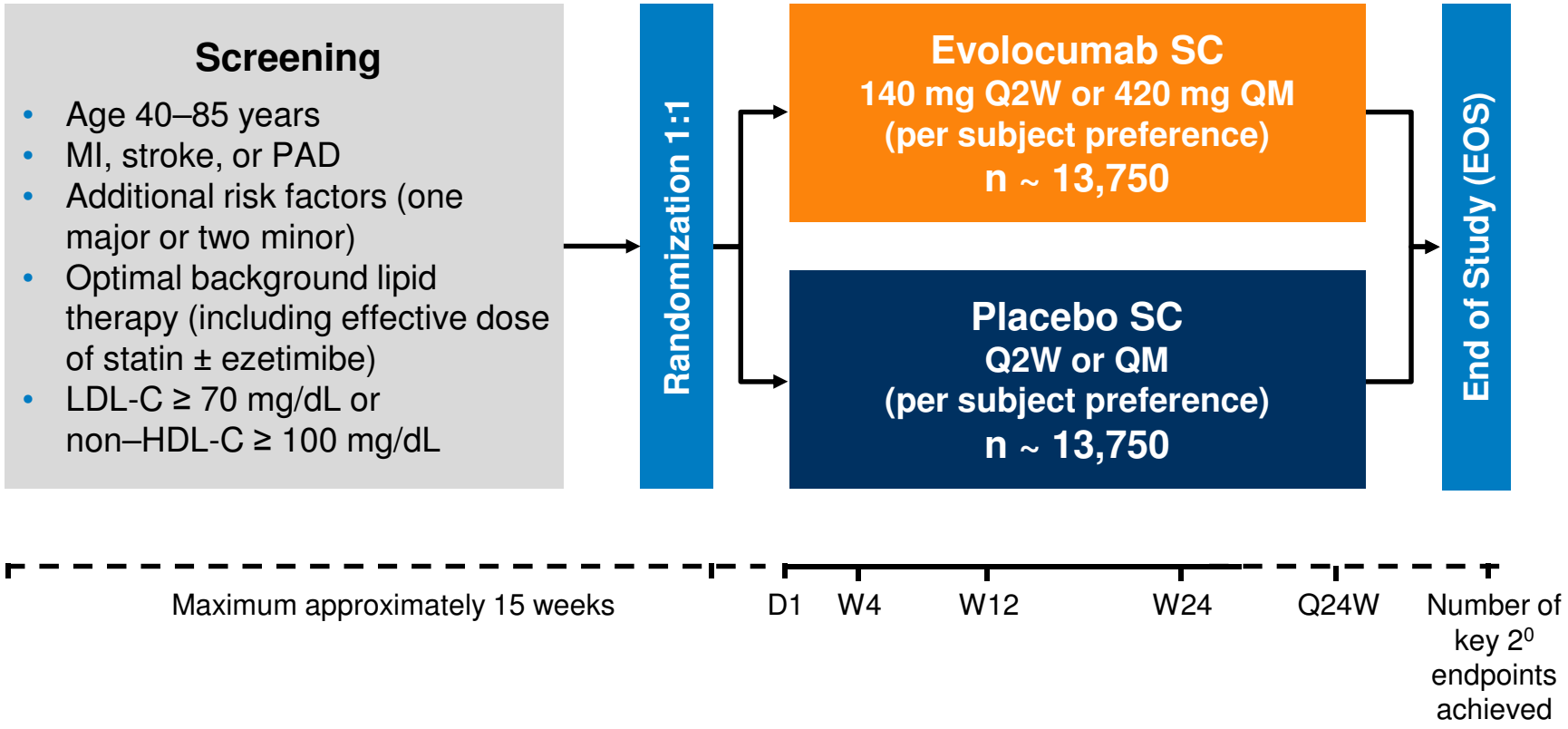
Q2W, every 2 weeks; QM, every month; SC, subcutaneous.
Sabatine MS, et al. *Am Heart J*. 2016;173:94-101.

2013 ACC/AHA Blood Cholesterol Guidelines

Statin	Statin Intensity		
	High	Moderate	Low
Atorvastatin	≥40 mg	10 to <40 mg	<10 mg
Rosuvastatin	≥20 mg	5 to <20 mg	<5 mg
Simvastatin	80 mg	20 to <80 mg	<20 mg
Pravastatin		≥40 mg	<40 mg
Lovastatin		≥40 mg	<40 mg
Fluvastatin		80 mg	<80 mg
Pitavastatin		≥2 mg	<2 mg

Stone NJ, et al. 2013 ACC/AHA Blood Cholesterol Guideline. DOI: 10.1161/01.cir.0000437738.63853.7a.
Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664
(Supplemental Methods – Appendix B)

Evolocumab Outcomes Trial: Study Design Overview



D = day; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PAD = peripheral artery disease; Q2W = every 2 weeks; Q24W = every 24 weeks; QM = every month; SC = subcutaneous; W = week.

Sabatine MS, et al. *Am Heart J*. 2016;173:94-101.

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Evolocumab Outcomes Trial: Study Endpoints

Endpoint	Description
Primary*	• Composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization
Key secondary†	• Composite of CV death, MI, or stroke
Other Secondary	• All-cause death; CV death; MI; stroke; coronary revascularization; CV death or hospitalization for heart failure; ischemic stroke or transient ischemic attack

- Sample size based on key secondary endpoint and powered to detect a 15% risk reduction at 90% power
  - Assuming 2% per year event rate in placebo arm, 27,500 patients followed up for a median of ~43 months should have provided 1,630 key secondary endpoints
- Efficacy analysis was hierarchical:
  - If primary endpoint was significantly reduced, then key secondary endpoint was to be tested, followed in order by CV death, all-cause mortality, then additional secondary endpoints

*Time to CV death, MI, stroke, hospitalization for UA, or coronary revascularization, whichever occurs first
†Time to CV death, MI, or stroke, whichever occurs first
CV = cardiovascular; MI = myocardial infarction
Sabatine MS, et al. *Am Heart J*. 2016;173:94-101.
Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

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Evolocumab Outcomes Trial: Other Assessments

Analysis Type	Description
Exploratory	• Absolute and percentage changes in LDL-C and other lipid parameters
Safety	• Collection of AEs • Laboratory testing (liver function tests, creatine kinase, fasting glucose, glycated hemoglobin) • Anti-evolocumab antibodies • Adjudication of new-onset diabetes mellitus • Formal neurocognitive testing in a subset of patients (EBBINGHAUS study)

AE = adverse event; LDL-C, low-density lipoprotein cholesterol

Sabatine MS, et al. *Am Heart J*. 2016;173:94-101.

Evolocumab Outcomes Trial: Landmark Analysis

Analysis Type	Description
Landmark	• Goal of a landmark analysis is to estimate the time to event probabilities for a specific timeframe • In this study, landmark analyses for CV events performed for 2 timeframes: year 0 to 1, and year 1 and beyond • Patients alive at the start of each timeframe were included • Landmark analysis was based on the first event after the start of each timeframe

Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664 (Supplement)
Dafni U. *Circ Cardiovasc Qual Outcomes*. 2011;4:363-371.

Evolocumab Outcomes Trial: CTTC Analysis

Analysis Type	Description

CTTC (Cholesterol Treatment Trialists Collaboration)	• Meta-analysis evaluated the safety and efficacy of more intensive LDL-C lowering using patient level data from 26 randomized trials with a median duration of 4.9 years
	• Composite endpoint of CTTC is major vascular events:
	  • Coronary heart death or nonfatal myocardial infarction, stroke, or coronary revascularization
	• Demonstrated a linear relationship between LDL-C reduction and reduction in CV events[1]
	  • 1 mmol/L (38.6 mg/dL) LDL-C reduction = 22% relative risk reduction in major vascular events
	• For comparison to CTTC data, the between group difference in LDL-C at 48 weeks was applied to this study, per the CTTC approach
	• The CV risk reduction per 1 mmol/L (38.6 mg/dL) reduction in LDL-C was calculated for year 0 to 1, and year 1 and beyond.

CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol

1. Cholesterol Treatment Trialists Collaboration, et al. *Lancet.* 2010; 376: 1670–81.
2. Sabatine MS, et al . *NEJM.* [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664 (Supplement)

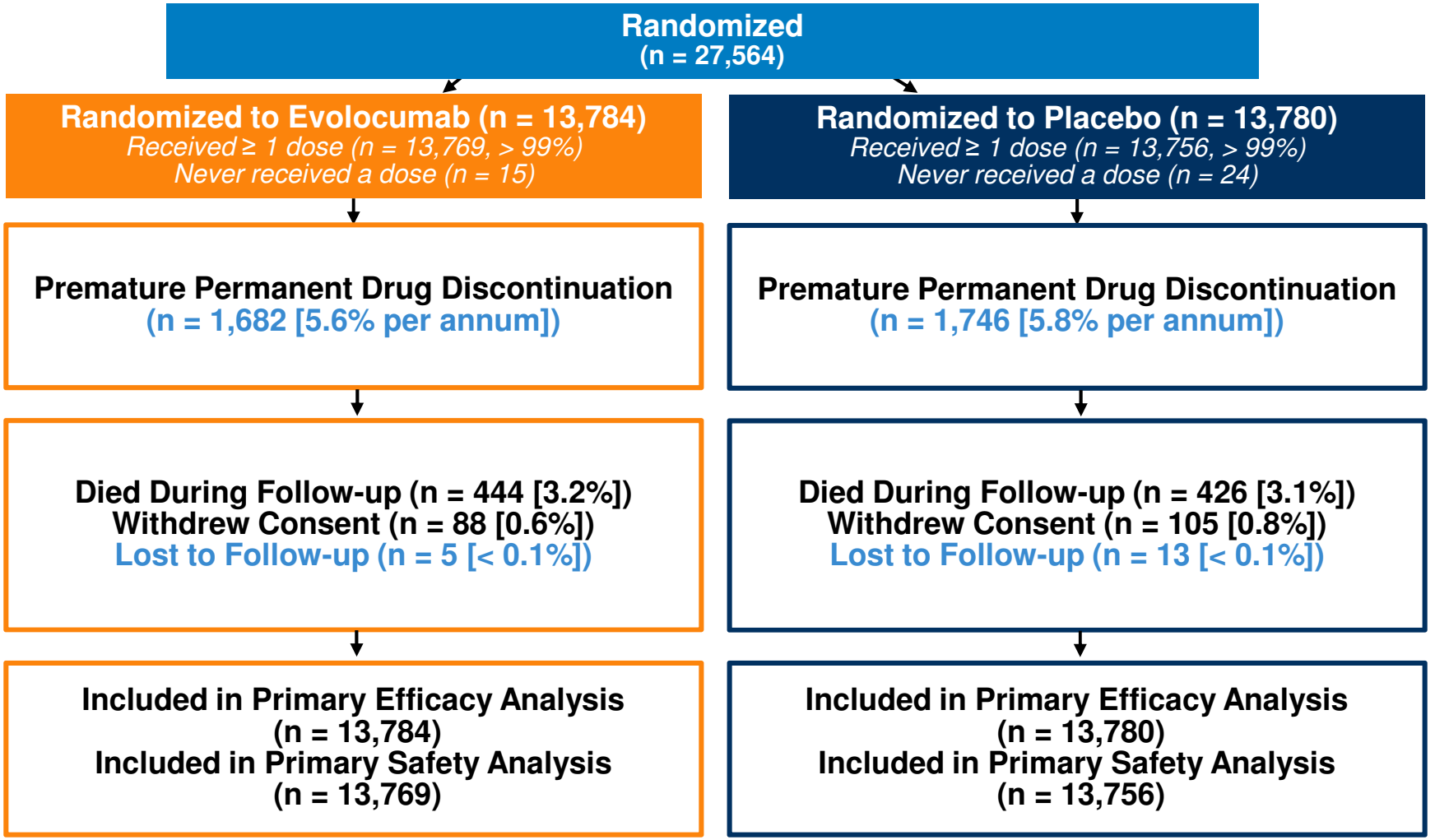
Evolocumab Outcomes Trial: Key Eligibility Criteria

- Men or women aged 40–85 years
- Clinically evident CVD (prior MI, prior non-hemorrhagic stroke, or symptomatic PAD)
- At least 1 major additional risk factor (e.g., diabetes, current smoker, MI or non-hemorrhagic stroke at ≤ 6 months of screening) or 2 minor additional risk factors (e.g., history of non-MI–related coronary revascularization, metabolic syndrome, LDL-C ≥ 130 mg/dL or non–HDL-C ≥ 160 mg/dL)
- Fasting LDL-C ≥ 70 mg/dL or non–HDL-C ≥ 100 mg/dL on an optimized stable lipid-lowering therapy
  - At least atorvastatin 20 mg daily or equivalent +/- ezetimibe

CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral artery disease.

Sabatine MS, et al. *Am Heart J*. 2016;173:94-101.
Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664 (Supplementary Appendix C)

Disposition of Patients During the Study



Sabatine MS, et al. *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664 (Supplemental Figure S1 – Trial Consort Diagram). Sabatine MS, et al. *American College of Cardiology – 66th Annual Scientific Session Late-Breaking Clinical Trial*. Washington, D.C. March 17, 2017.

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Baseline Characteristics

Baseline Demographics

Characteristics	Evolocumab (N = 13,784)	Placebo (N = 13,780)
Demographics		
Age – y (SD)	62.5 (9.1)	62.5 (8.9)
Male sex – n (%)	10,397 (75.4)	10,398 (75.5)
White race* – n (%)	11,748 (85.2)	11,710 (85.0)
Weight – kg (SD)	85.0 (17.3)	85.5 (17.4)
Region		
North America	2,287 (16.6)	2,284 (16.6)
Europe	8,666 (62.9)	8,669 (62.9)
Latin America	913 (6.6)	910 (6.6)
Asia Pacific and South Africa	1,918 (13.9)	1,917 (13.9)

*Race was self-reported. There were no nominally statistically significant differences in baseline characteristics between the two arms except for weight (P=0.014).

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Baseline CV Risk Factors

Characteristics	Evolocumab (N = 13,784)	Placebo (N = 13,780)
Type of atherosclerosis* – n (%)		
Myocardial infarction	11,145 (80.9)	11,206 (81.3)
Time from most recent prior MI – yr (IQR)	3.4 (1.0-7.4)	3.3 (0.9-7.7)
Non-hemorrhagic stroke	2,686 (19.5)	2,651 (19.2)
Time from most recent prior stroke – yr (IQR)	3.2 (1.1-7.1)	3.3 (1.1-7.3)
Peripheral artery disease – n (%)	1,858 (13.5)	1,784 (12.9)
Cardiovascular risk factors		
Hypertension – n/total n (%)	11,045/13,784 (80.1)	11,039/13,779 (80.1)
Diabetes mellitus – n (%)	5,054 (36.7)	5,027 (36.5)
Current cigarette use – n/total n (%)	3,854/13,783 (28.0)	3,923/13,779 (28.5)

*Patients could have more than one type of atherosclerosis.
CV = cardiovascular; MI = myocardial infarction.
Sabatine MS, et al . *NEJM.* [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Baseline Lipid-Lowering Therapies and Lipid Parameters

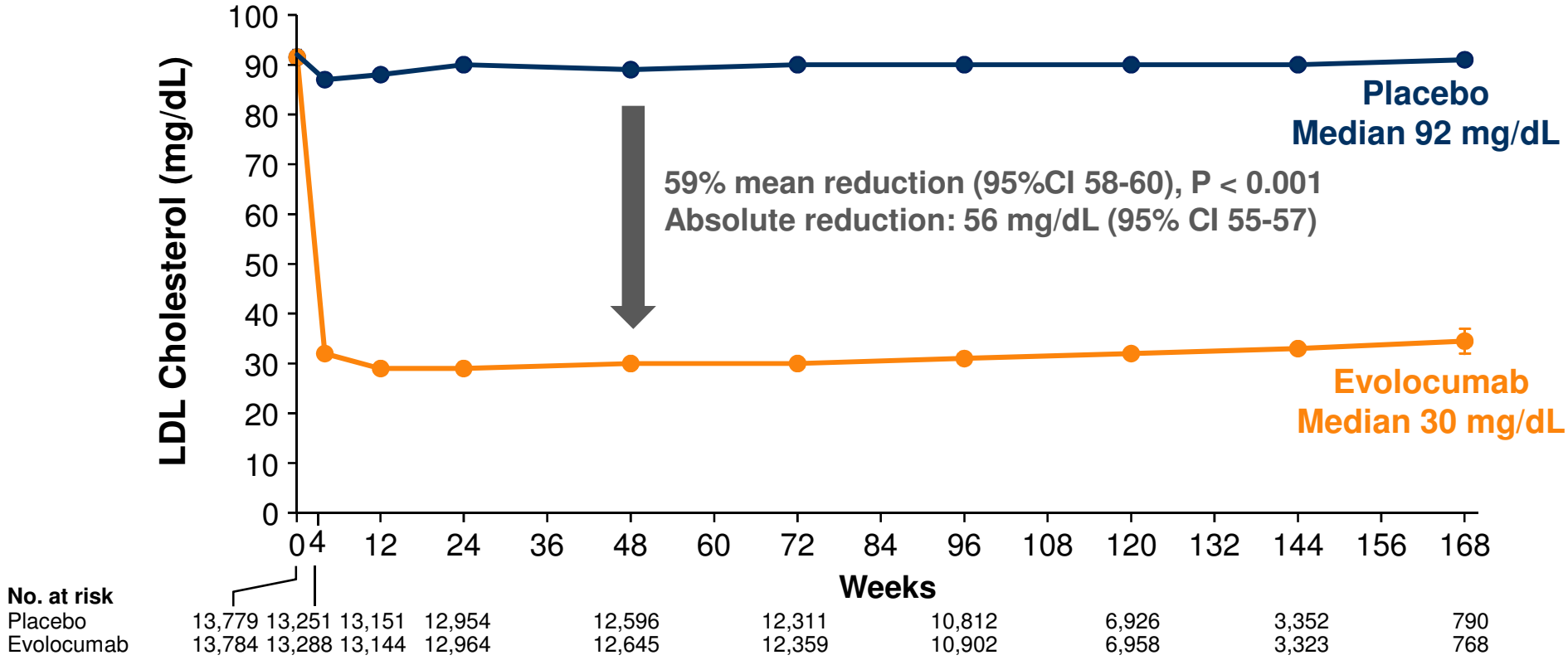
Characteristics	Evolocumab (N = 13,784)	Placebo (N = 13,780)
Statin use* – n (%)		
High intensity	9,585 (69.5)	9,518 (69.1)
Moderate intensity	4,161 (30.2)	4,231 (30.7)
Low intensity, unknown intensity, or no data	38 (0.3)	31 (0.2)
Ezetimibe – n (%)	726 (5.3)	714 (5.2)
Other cardiovascular medications – n/total n (%)		
Aspirin and/or $P2Y_{12}$ inhibitor	12,766/13,772 (92.7)	12,666/13,767 (92.0)
Beta-blocker	10,441/13,772 (75.8)	10,374/13,767 (75.4)
ACE inhibitor or ARB and/or aldosterone antagonist	10,803/13,772 (78.4)	10,730/13,767 (77.9)
Lipid measures - Median (IQR) – mg/dL		
LDL cholesterol – mg/dL	92 (80, 109)	92 (80, 109)
Total cholesterol – mg/dL	168 (151, 188)	168 (151, 189)
HDL cholesterol – mg/dL	44 (37, 53)	44 (37, 53)
Triglycerides – mg/dL	134 (101, 183)	133 (99, 181)
Lp(a) - nmol/L	37 (13, 166)	37 (13, 164)

*Statin intensity was categorized per the ACC/AHA Guidelines. Note, that in some countries where FOURIER was conducted, higher statin doses are not approved. HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a) = Lipoprotein(a); IQR = Inter-quartile range

Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664
Malinowski HJ, et all. *J Clin Pharmacol*. 2008;48:900-908

Results

Median LDL-C Levels Over Time: All Patients



LDL-C was significantly reduced in the evolocumab group (median: 30 mg/dL) including 42% who achieved levels ≤ 25 mg/dL vs < 0.1% in the placebo group

Data shown are median values with 95% confidence intervals in the two arms; ITT.

Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

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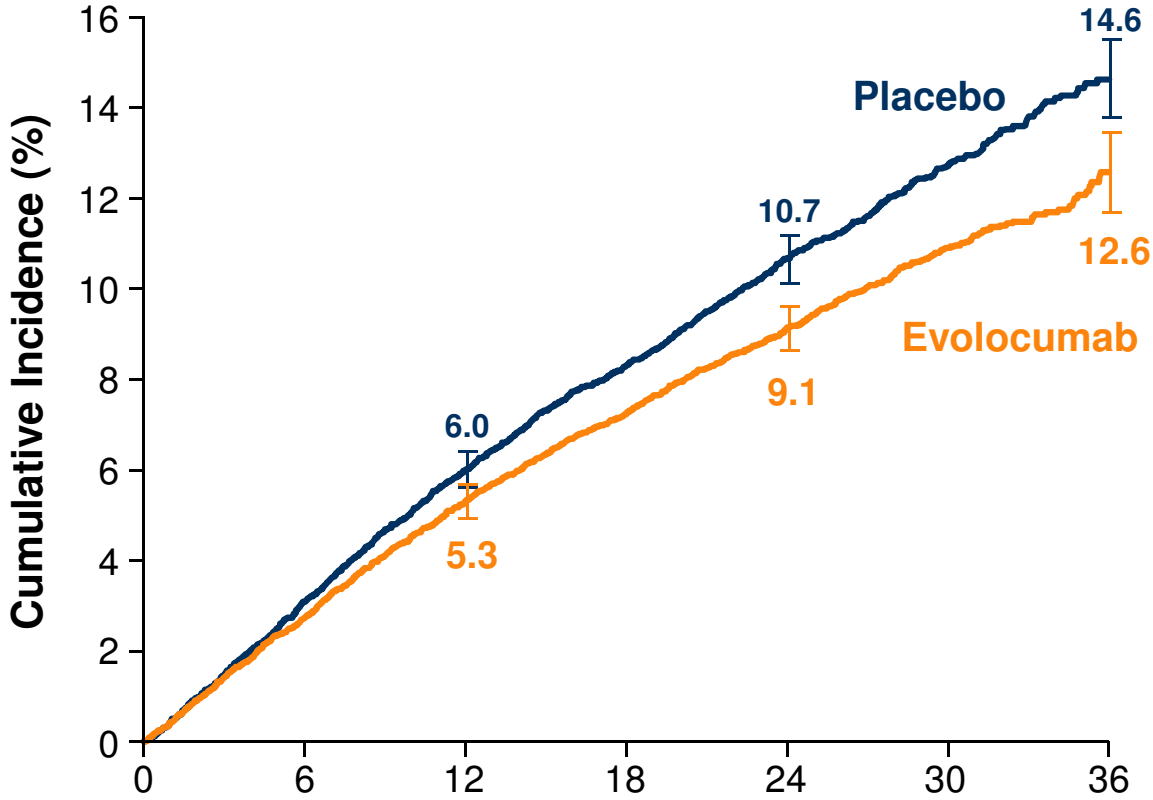
Primary Endpoint: Composite of CV Death, MI, Stroke, Hospitalization for UA, or Coronary Revascularization



No. at Risk							
Placebo	13,780	13,278	12,825	11,871	7,610	3,690	686
Evolocumab	13,784	13,351	12,939	12,070	7,771	3,746	689

HR 0.85 (95% CI 0.79 to 0.92); *P* < 0.001

CV = Cardiovascular; MI = Myocardial infarction; UA = Unstable angina; HR = Hazard ratio

Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

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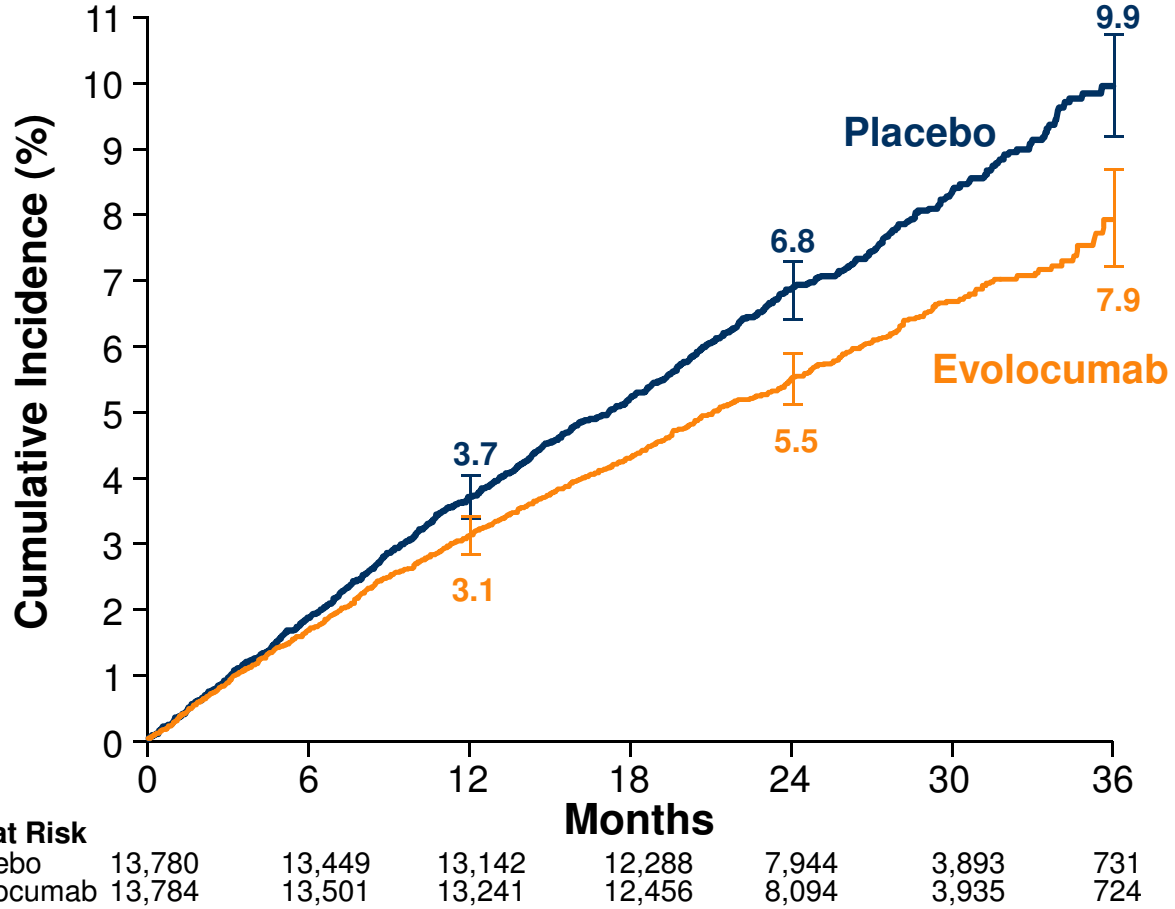
Key Secondary Endpoint:
Composite of CV Death, MI, or Stroke



No. at Risk							
Placebo	13,780	13,449	13,142	12,288	7,944	3,893	731
Evolocumab	13,784	13,501	13,241	12,456	8,094	3,935	724

HR 0.80 (95% CI 0.73 to 0.88); *P* < 0.001

CV = Cardiovascular; MI = Myocardial infarction; HR = Hazard ratio

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Primary, Key Secondary, and Other Endpoints

Outcome	Evolocumab (n = 13,784) n (%)	Placebo (n = 13,780) n (%)	HR (95% CI)	P-value‡
Primary endpoint*	1,344 (9.8)	1,563 (11.3)	0.85 (0.79-0.92)	<0.001
Key secondary endpoint†	816 (5.9)	1,013 (7.4)	0.80 (0.73-0.88)	<0.001
Other endpoints				
CV death	251 (1.8)	240 (1.7)	1.05 (0.88-1.25)	0.62
Death from any cause	444 (3.2)	426 (3.1)	1.04 (0.91-1.19)	0.54
MI	468 (3.4)	639 (4.6)	0.73 (0.65-0.82)	<0.001
Hospitalization for UA	236 (1.7)	239 (1.7)	0.99 (0.82-1.18)	0.89
Stroke	207 (1.5)	262 (1.9)	0.79 (0.66-0.95)	0.01
Coronary revascularization	759 (5.5)	965 (7.0)	0.78 (0.71-0.86)	<0.001
CV Death or Hospitalization for Worsening Heart Failure	402 (2.9)	408 (3.0)	0.98 (0.86-1.13)	0.82
Ischemic stroke or TIA	229 (1.7)	295 (2.1)	0.77 (0.65-0.92)	0.003
CTTC composite endpoint**	1,271 (9.2)	1,512 (11.0)	0.83 (0.77-0.90)	<0.001

The primary endpoint was driven by reductions in MI, stroke, and coronary revascularization

*Time to CV death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization, whichever occurs first †CV death, myocardial infarction, or stroke, whichever occurs first ‡Given the hierarchical nature of the statistical testing, the P values for the primary and key secondary endpoint should be considered statistically significant, whereas all other P values should be considered nominal.
**CTTC stands for Cholesterol Treatment Trialists Collaboration and the composite endpoint consists of coronary heart death, nonfatal MI, stroke, or coronary revascularization
MI = Myocardial infarction; UA = Unstable angina; TIA = Transient ischemic attack
Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Primary, Key Secondary, and Other Endpoints (2/2)

Outcome	Evolocumab (n = 13,784) n (%)	Placebo (n = 13,780) n (%)	HR (95% CI)	P-value*
Other endpoints				
Coronary revascularization	759 (5.5)	965 (7.0)	0.78 (0.71-0.86)	<0.001
Urgent	403 (2.9)	547 (4.0)	0.73 (0.64-0.83)	
Elective	420 (3.0)	504 (3.7)	0.83 (0.73-0.95)	
CV Death or Hospitalization for Worsening Heart Failure	402 (2.9)	408 (3.0)	0.98 (0.86-1.13)	0.82
Ischemic stroke or TIA	229 (1.7)	295 (2.1)	0.77 (0.65-0.92)	0.003
CTTC composite endpoint†	1271 (9.2)	1512 (11.0)	0.83 (0.77-0.90)	<0.001

*Given the hierarchical nature of the statistical testing, the P values for the primary and key secondary endpoint should be considered statistically significant whereas all other P values should be considered nominal. † CTTC stands for Cholesterol Treatment Trialists Collaboration and the composite endpoint consists of coronary heart death, nonfatal MI, stroke, or coronary revascularization
MI = Myocardial infarction; TIA = Transient ischemic attack
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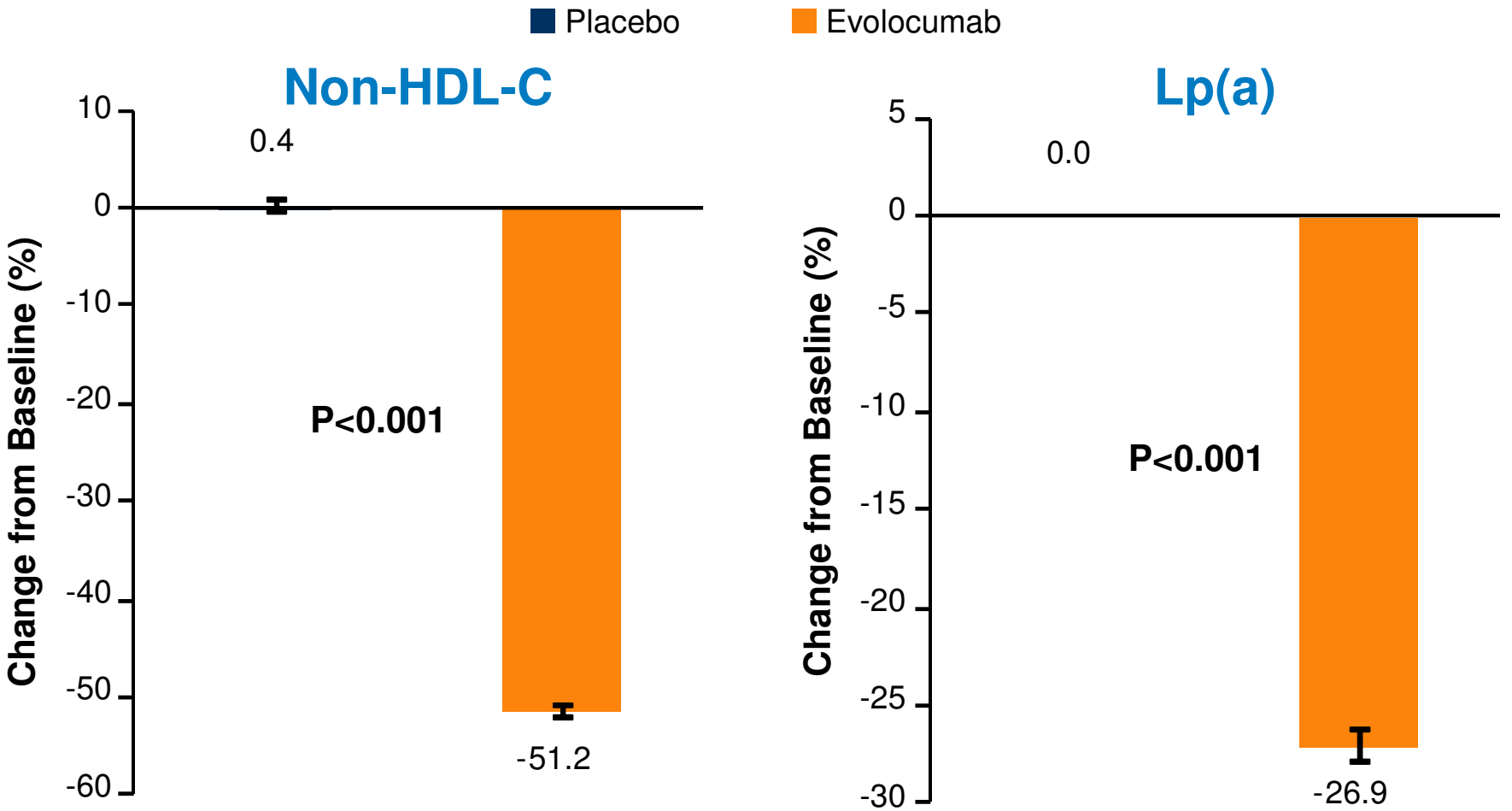
Other Lipid Measures



Displayed are mean changes at 48 weeks except Lp(a), which is median change. Errors bars denote 95% CI.

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doi: 10.1056/NEJMoa1615664 (Supplementary Figure S3)

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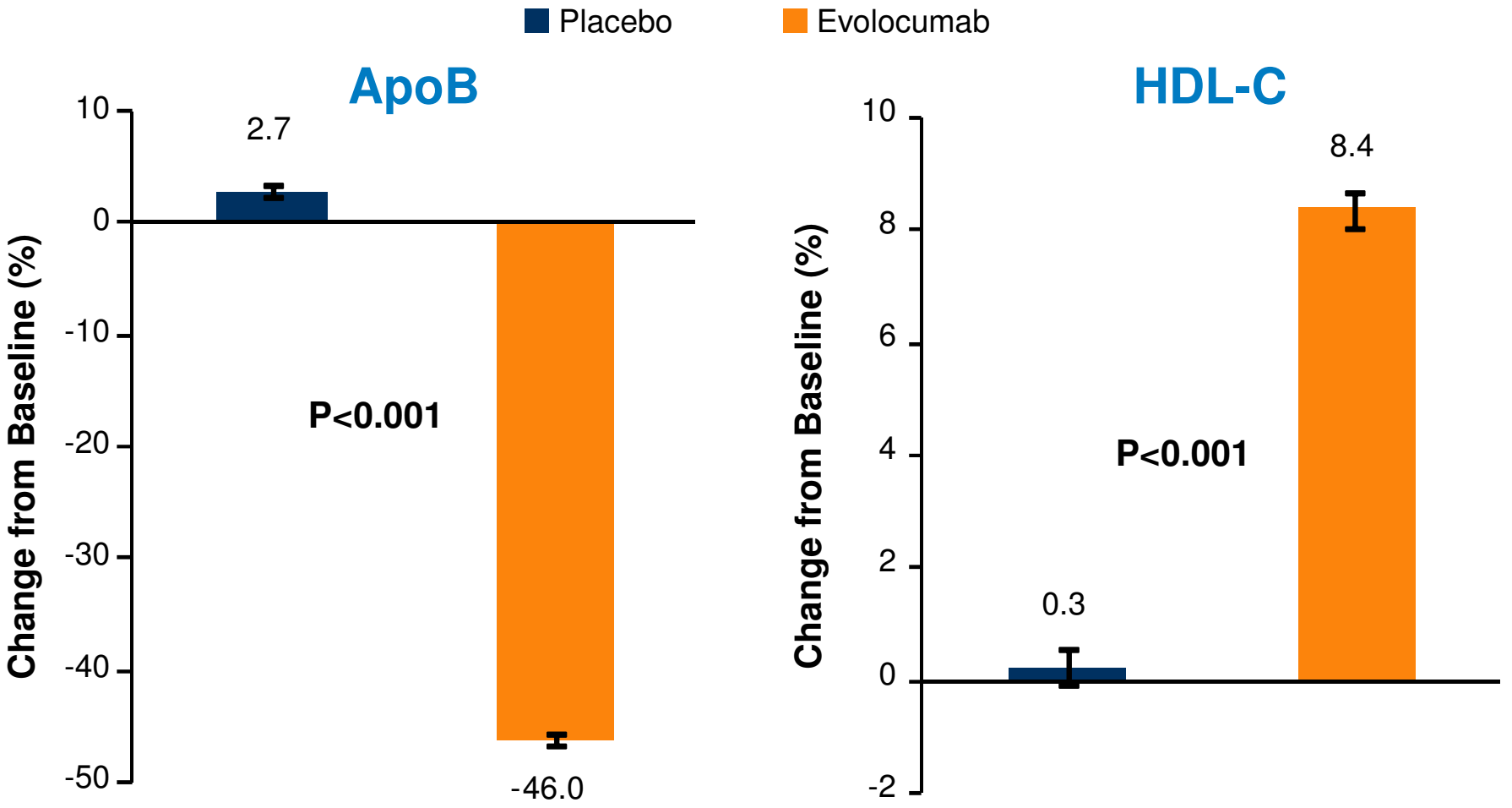
Other Lipid Measures



Displayed are mean changes at 48 weeks. Errors bars denote 95% CI.

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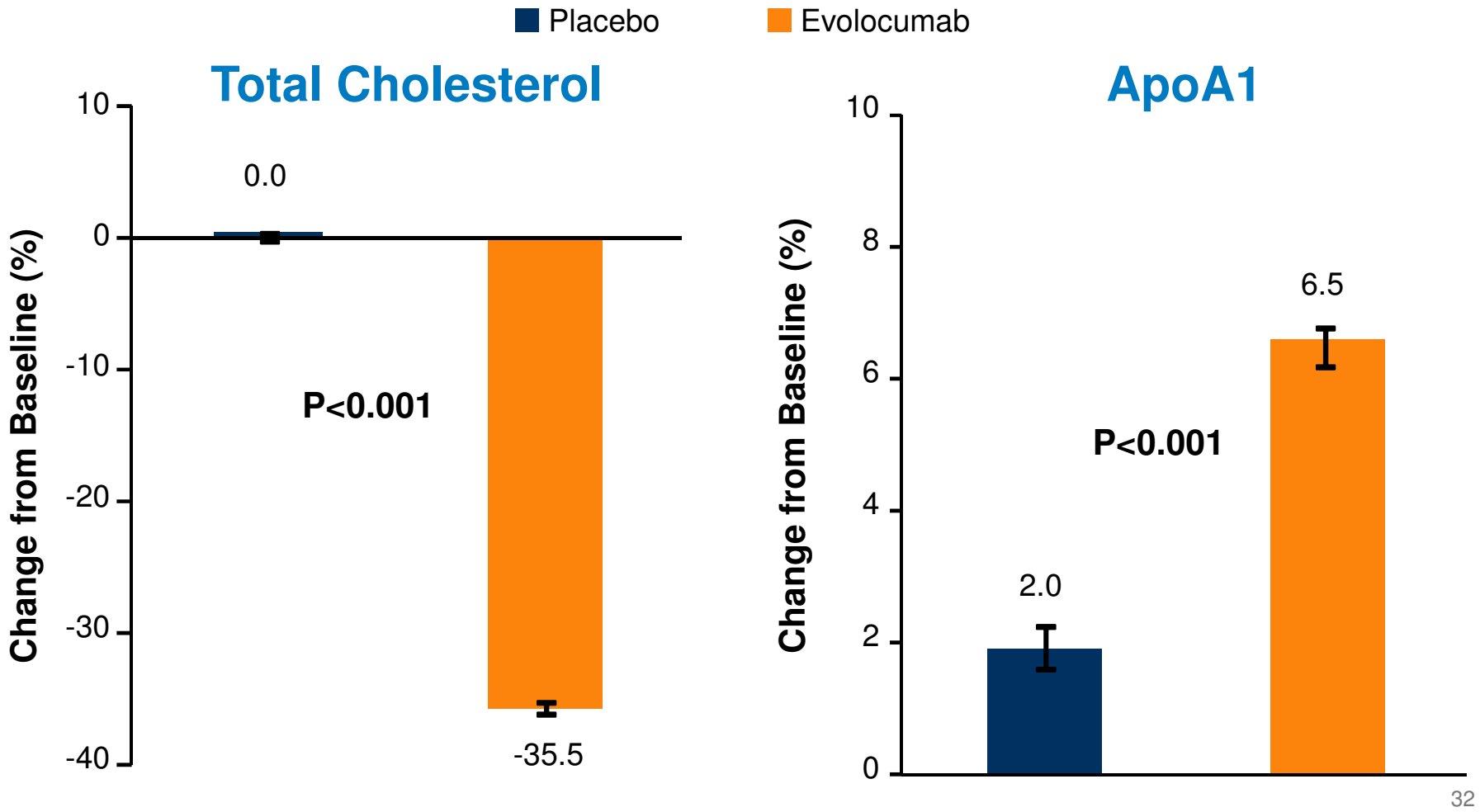
Other Lipid Measures



Displayed are mean changes at 48 weeks. Errors bars denote 95% CI.

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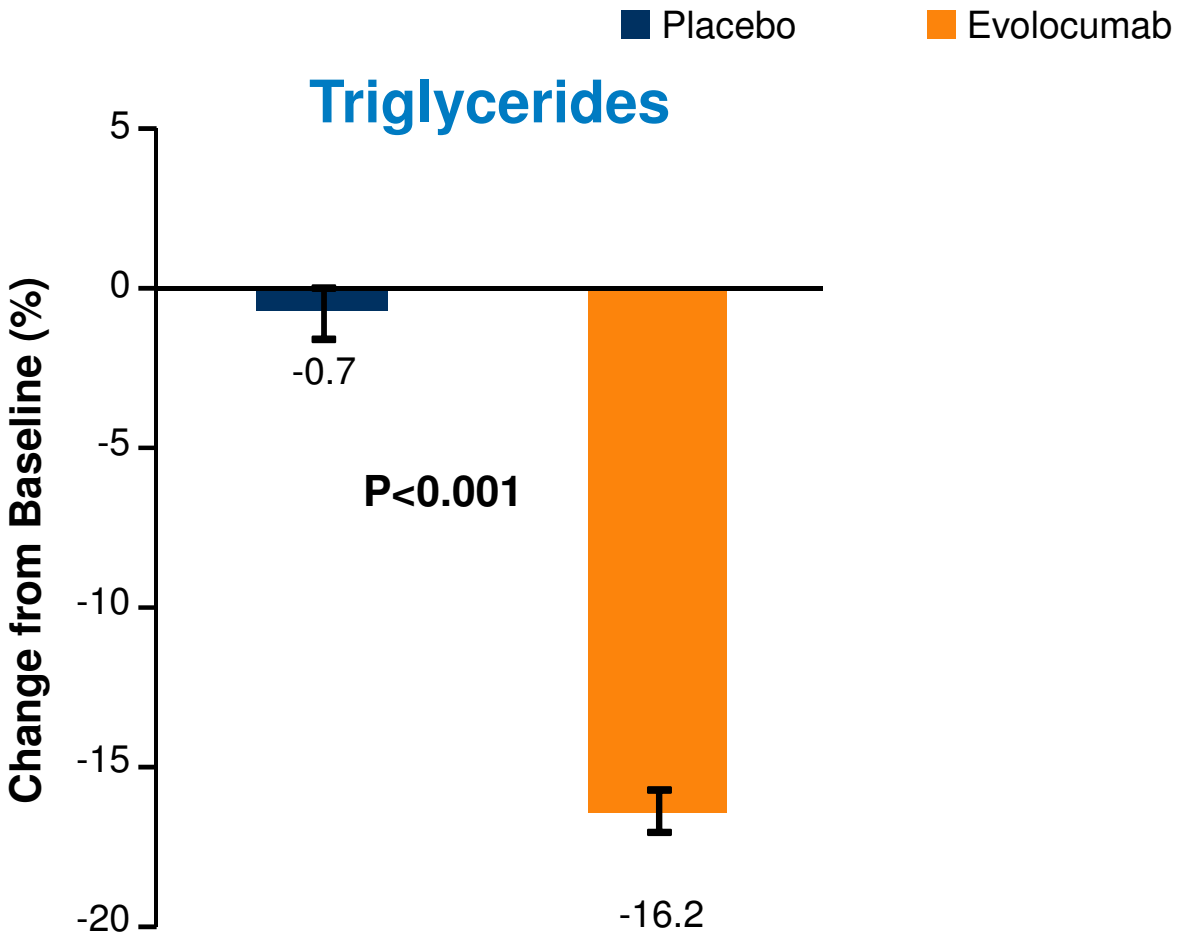
Other Lipid Measures



Displayed are median changes at 48 weeks. Errors bars denote 95% CI.

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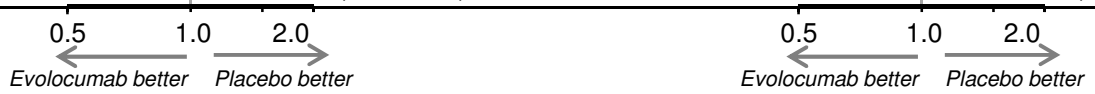
Efficacy in Key Subgroups: Primary and Key Secondary Endpoints

		PRIMARY ENDPOINT: 3-yr KM rate (%)					KEY SECONDARY ENDPOINT: 3-yr KM rate (%)				
	Patients	Evo	Pbo	HR (95% CI)	HR (95% CI)	$P_{interaction}$	Evo	Pbo	HR (95% CI)	HR (95% CI)	$P_{interaction}$
OVERALL	27564	12.6	14.6		0.85 (0.79-0.92)		7.9	9.9		0.80 (0.73-0.88)	
Age						0.9					0.79
<65	15310	12.6	14.6		0.86 (0.78-0.94)		7.3	9.1		0.79 (0.69 -0.90)	
≥65	12254	12.6	14.6		0.85 (0.76-0.95)		8.7	10.9		0.81 (0.71 -0.92)	
Sex						0.48					0.44
Female	6769	9.9	12.5		0.81 (0.69-0.95)		6.5	9.2		0.74 (0.61 -0.90)	
Male	20795	13.5	15.3		0.86 (0.80-0.94)		8.4	10.2		0.81 (0.73 -0.90)	
Race						0.036					0.048
Caucasian	23458	12.7	14.4		0.88 (0.81-0.95)		7.8	9.6		0.83 (0.75-0.92)	
Non-Caucasian	4106	12.5	16.2		0.70 (0.57-0.86)		9.0	12.4		0.64 (0.50-0.81)	
Region						0.15					0.012
North America	4571	15.7	20.8		0.77 (0.66 -0.90)		8.6	13.5		0.62 (0.51-0.76)	
Europe	17335	11.9	13.1		0.91 (0.83 -1.00)		7.6	8.9		0.90 (0.80-1.01)	
Latin America	1823	14.9	14.3		0.85 (0.63-1.15)		11.3	10.8		0.85 (0.58-1.24)	
Asia/Pacific	3835	14.1	13.5		0.73 (0.58-0.91)		9.2	10.1		0.67 (0.51-0.88)	



Primary and secondary composite endpoint results were consistent across all key subgroups

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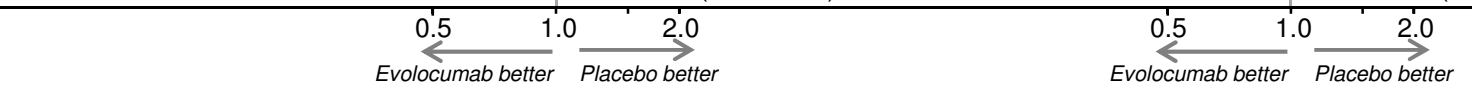
Efficacy in Key Subgroups: Primary and Key Secondary Endpoints *continued*

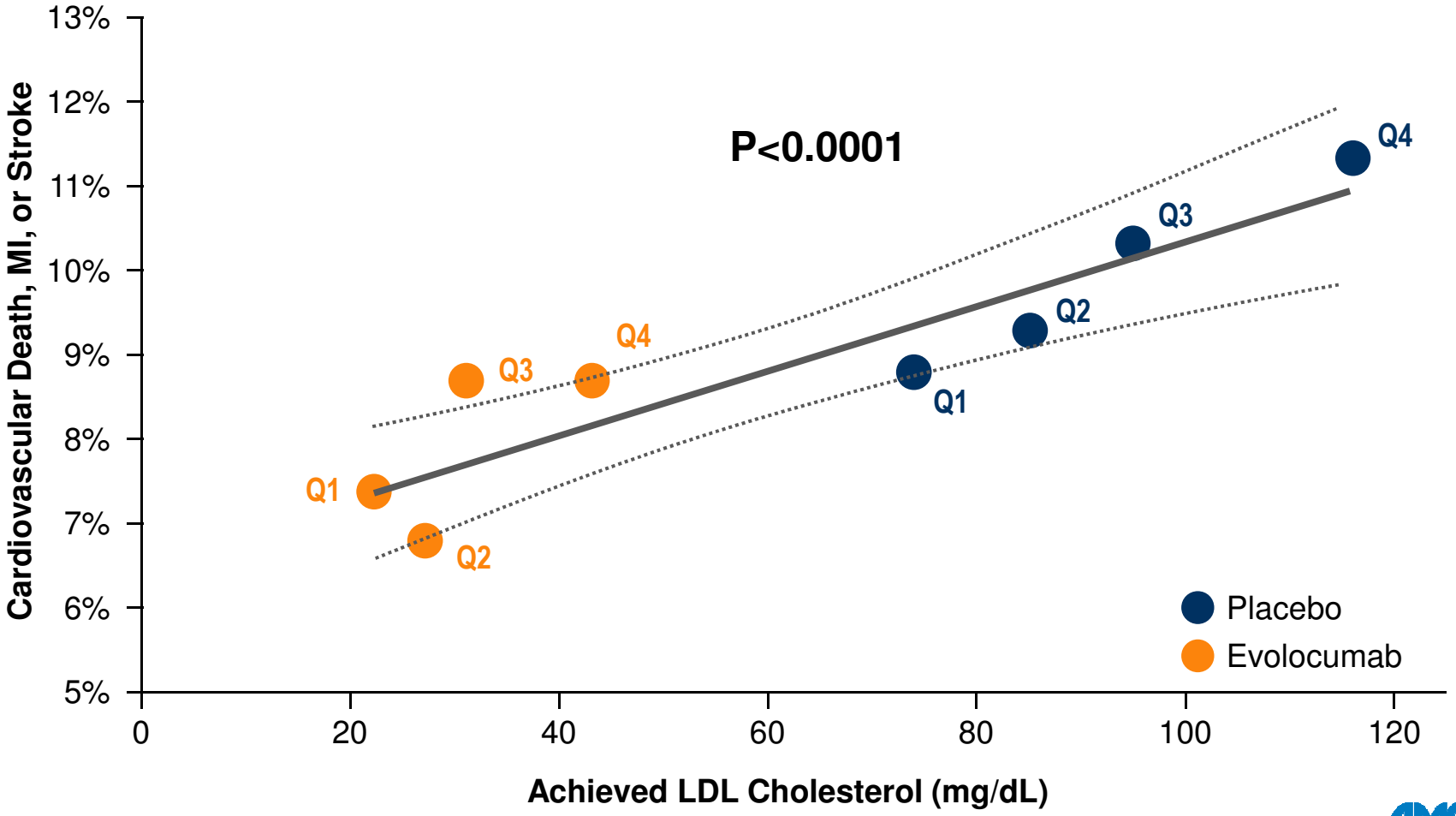
		PRIMARY ENDPOINT: 3-yr KM rate (%)					KEY SECONDARY ENDPOINT: 3-yr KM rate (%)				
	Patients	Evo	Pbo	HR (95% CI)	HR (95% CI)	$P_{interaction}$	Evo	Pbo	HR (95% CI)	HR (95% CI)	$P_{interaction}$
OVERALL	27564	12.6	14.6		0.85 (0.79-0.92)		7.9	9.9		0.80 (0.73-0.88)	
Type of disease						0.19					0.38
MI alone	19113	11.7	13.9		0.88 (0.80-0.96)		6.5	8.7		0.80 (0.71 -0.90)	
Stroke alone	3366	9.1	11.7		0.70 (0.54-0.90)		8.0	9.6		0.77 (0.58 -1.02)	
PAD alone	1505	9.4	12.6		0.67 (0.47-0.96)		5.5	10.3		0.57 (0.38-0.88)	
Polyvasculardisease	3563	21.5	21.5		0.88 (0.75-1.03)		16.0	16.7		0.86 (0.71-1.04)	
Baseline LDL-C						0.69					0.96
Q1 (<80 mg/dL)	6961	11.0	13.6		0.80 (0.69 -0.93)		7.4	8.8		0.78 (0.64-0.95)	
Q2 (80 -<92 mg/dL)	6886	11.4	14.4		0.82 (0.71 -0.96)		6.8	9.3		0.79 (0.65-0.96)	
Q3 (92 -109 mg/dL)	6887	13.6	14.3		0.89 (0.77 -1.03)		8.7	10.3		0.79 (0.66-0.94)	
Q4 (>109 mg/dL)	6829	14.2	16.2		0.89 (0.77-1.02)		8.7	11.3		0.83 (0.70-0.99)	
Baseline statin intensity						0.37					0.33
High	19103	12.7	14.7		0.87 (0.80-0.95)		8.0	9.8		0.82 (0.74 -0.92)	
Not High	8461	12.9	14.8		0.80 (0.70-0.92)		8.0	10.6		0.74 (0.63 -0.88)	
Ezetimibe						0.26					0.76
Yes	1440	16.1	17.0		0.98 (0.74-1.31)		9.4	13.0		0.74 (0.52-1.06)	
No	26124	12.4	14.5		0.84 (0.78-0.91)		7.8	9.7		0.80 (0.73-0.88)	
Initial Dosing Regimen						0.83					0.89
Every 2 weeks	24774	12.7	14.6		0.85 (0.79 -0.92)		8.0	10.0		0.80 (0.72-0.88)	
Monthly	2790	10.3	15.6		0.82 (0.64 -1.04)		5.8	10.9		0.80 (0.59-1.09)	



Primary and secondary composite endpoint results were consistent across all key subgroups

Association of LDL-C Levels and CV Events

Patients divided by quartile of baseline LDL-C and by treatment arm



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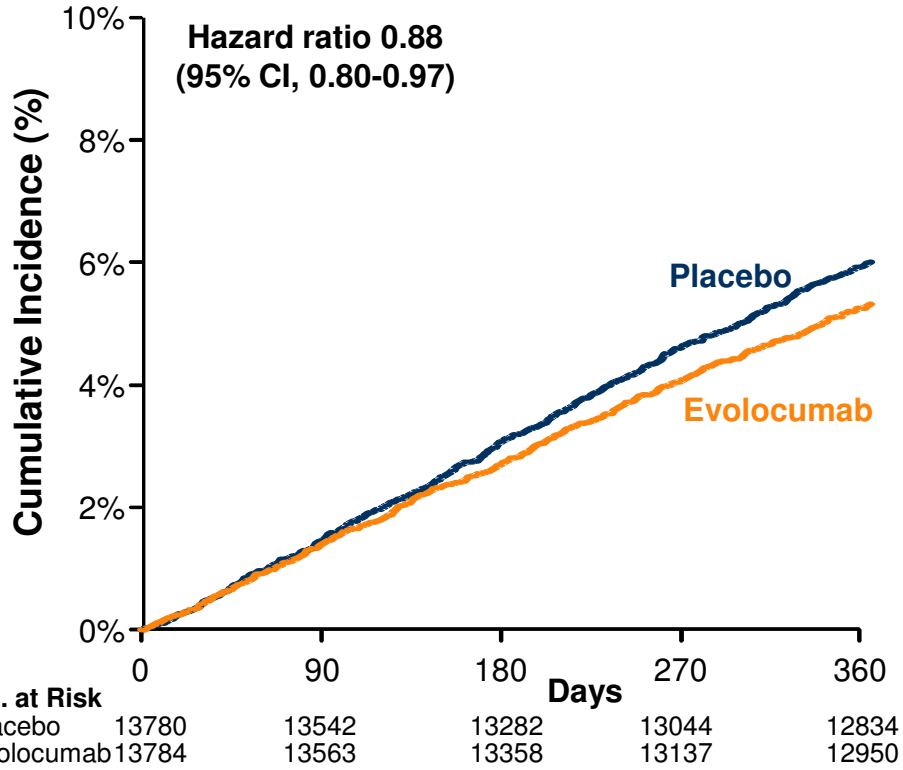
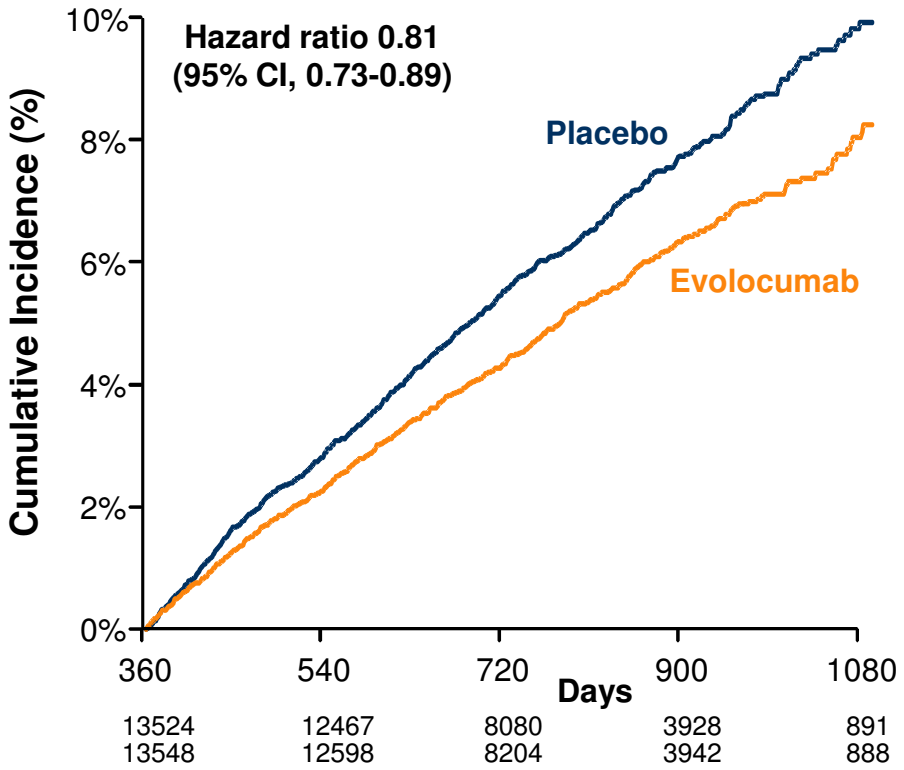
Landmark Analysis of Primary Endpoint

Year 1: RRR 12%



No. at Risk					
Placebo	13780	13542	13282	13044	12834
Evolocumab	13784	13563	13358	13137	12950

> Year 1: RRR 19%



Placebo	13524	12467	8080	3928	891
Evolocumab	13548	12598	8204	3942	888

Longer duration of treatment and follow up suggests larger risk reduction

Landmark analyses were performed in which patients who were alive and in follow-up at the start of the period of interest formed the group at risk.

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doi: 10.1056/NEJMoa1615664 (Supplementary Figure S4)

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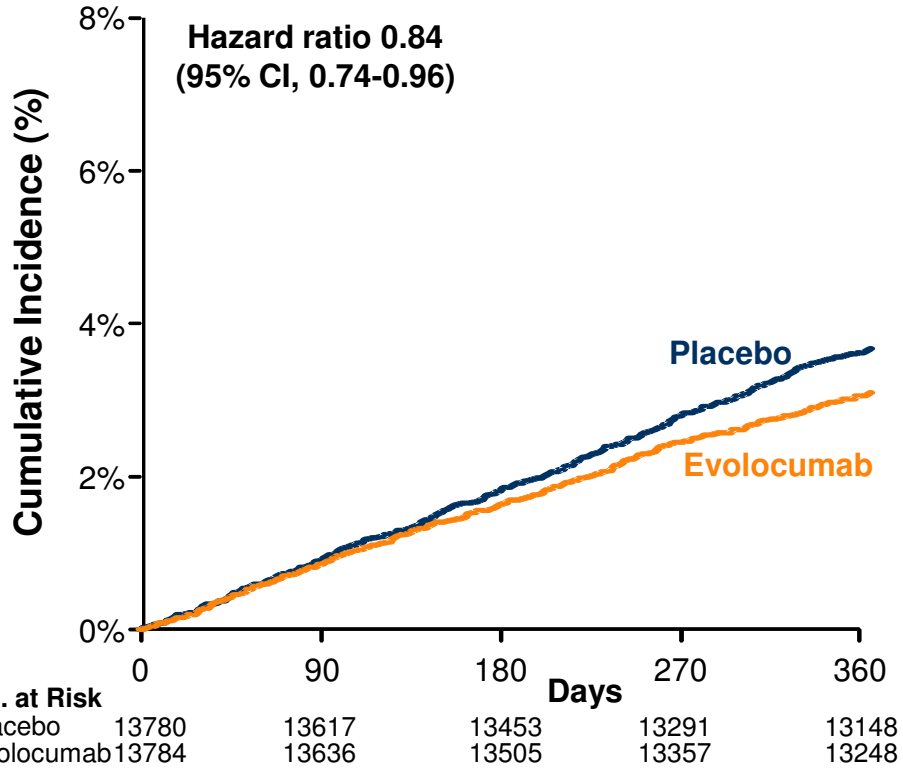
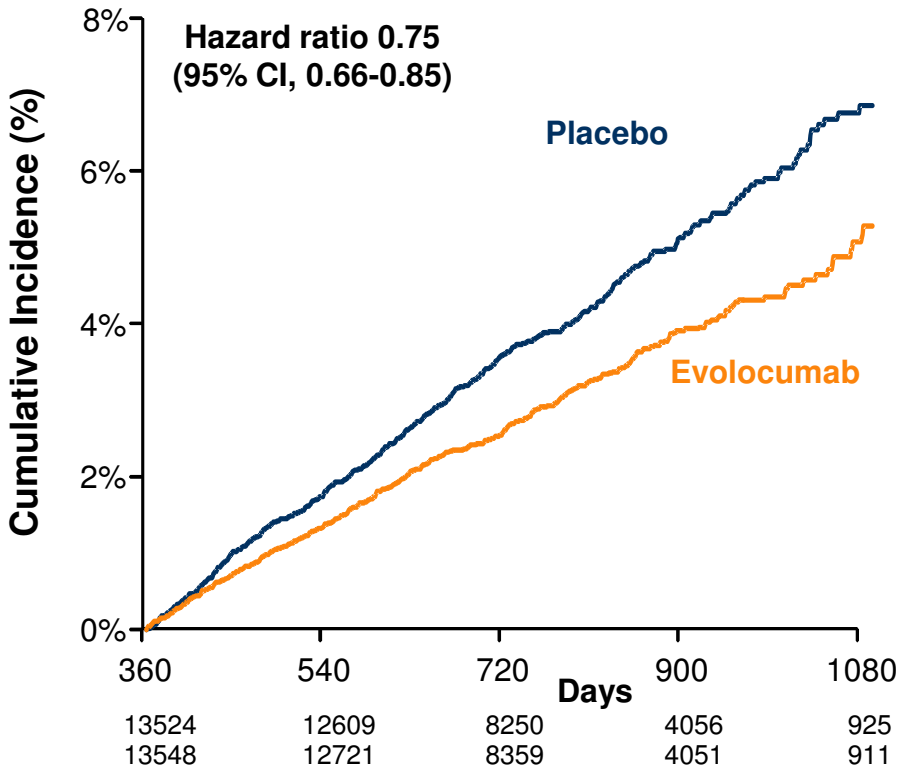
Landmark Analysis of Key Secondary Endpoint

Year 1: RRR 16%



No. at Risk					
Placebo	13780	13617	13453	13291	13148
Evolocumab	13784	13636	13505	13357	13248

> Year 1: RRR 25%



Placebo	13524	12609	8250	4056	925
Evolocumab	13548	12721	8359	4051	911

Longer duration of treatment and follow up suggests larger risk reduction

Landmark analyses were performed in which patients who were alive and in follow-up at the start of the period of interest formed the group at risk.

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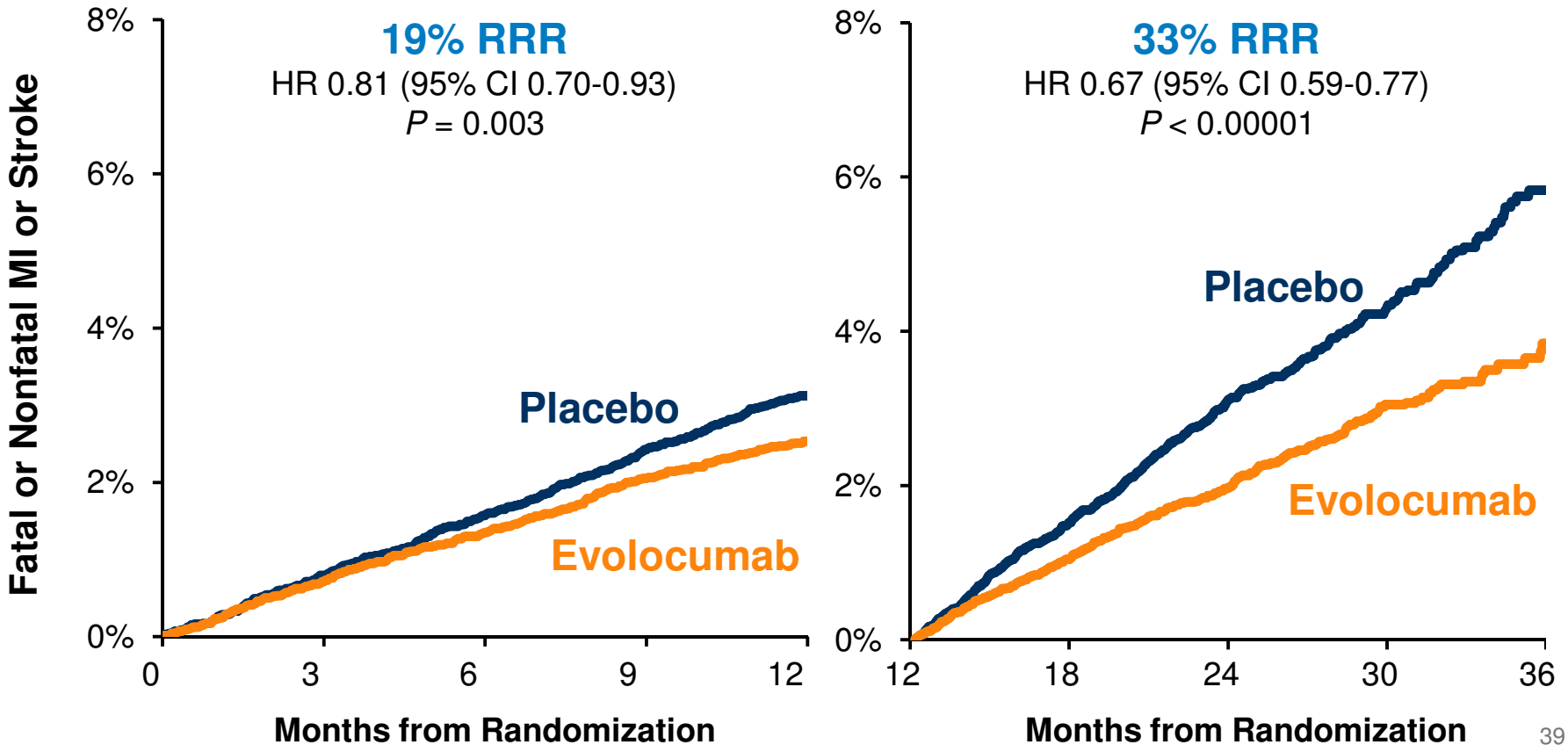
Fatal or Nonfatal MI or Stroke



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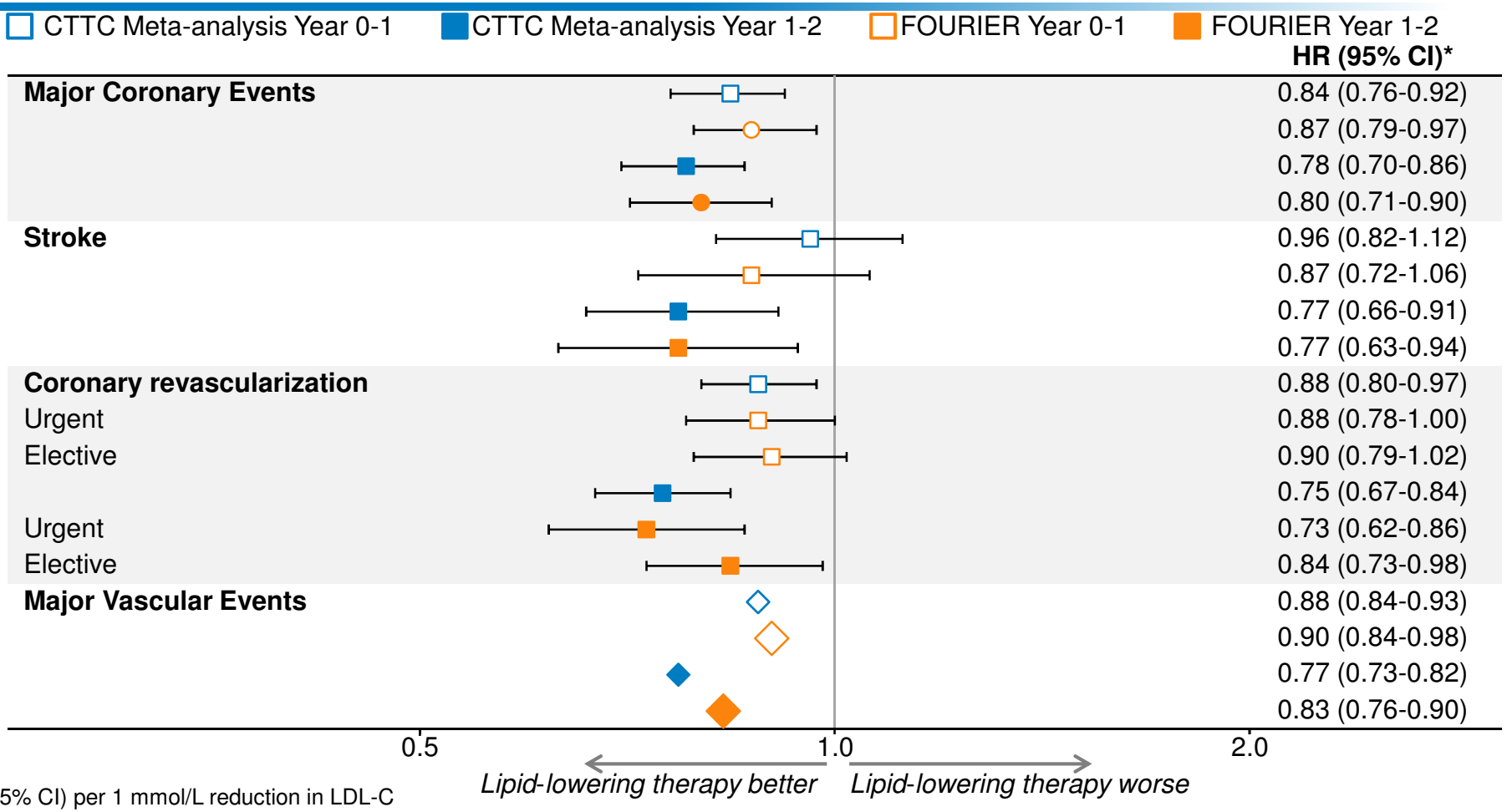
Evolocumab Outcomes Trial Analysis in CTTC Meta-Analysis



*HR (95% CI) per 1 mmol/L reduction in LDL-C

The results of the evolocumab outcomes trial was in line with what was seen with statins in the CTTC meta-analysis, based on the study duration

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Safety

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Adverse Events in the Safety Population*

Adverse Events, n (%)	Evolocumab (N = 13,769)	Placebo (N = 13,756)
Any	10,664 (77.4)	10,644 (77.4)
Serious	3,410 (24.8)	3,404 (24.7)
Thought to be related to the study agent and leading to discontinuation of study regimen	226 (1.6)	201 (1.5)

No notable differences in the rate of AEs, SAEs, or AEs leading to discontinuation

*Safety evaluations included all randomized patients who received at least one dose of study treatment and for whom post-dose data are available.

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Adverse Events of Interest and Laboratory Measures in the Safety Population*

Adverse Events, n (%)	Evolocumab (N = 13,769)	Placebo (N = 13,756)
Injection-site reaction**	296 (2.1)	219 (1.6)
Allergic reactions	420 (3.1)	393 (2.9)
Muscle-related event	682 (5.0)	656 (4.8)
Rhabdomyolysis	8 (0.1)	11 (0.1)
Cataract	228 (1.7)	242 (1.8)
Adjudicated case of new-onset diabetes†	677 (8.1)	644 (7.7)
Neurocognitive event	217 (1.6)	202 (1.5)
Laboratory results - n/total n (%)		
Aminotransferase >3x ULN	240/13,543 (1.8)	242/13,523 (1.8)
Creatinine kinase >5x ULN	95/13,543 (0.7)	99/13,523 (0.7)

*Safety evaluations included all randomized patients who received at least one dose of study treatment and for whom post-dose data are available. **The between-group difference was nominally significant (P<0.001). †HR 1.05 (95% CI 0.94-1.17); denominators of 8337 (evolocumab) and 8339 (placebo) because patients with prevalent diabetes at the start of the trial were excluded.

- **Incidence of neurocognitive events, cataracts, and new-onset diabetes were similar between the two arms**
- **Post-baseline anti-evolocumab antibodies were detected in 0.3%, with no neutralizing antibodies detected**

ULN = Upper Limit of Normal

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Summary

Summary *continued*

- The number needed to treat to prevent a cardiovascular death, myocardial infarction, or stroke was 50 over 3 years and 74 over 2 years.
- The standard of care through use of evidence based therapies was high in the evolocumab outcomes study population, with large majority of patients on high to moderate intensity statins, as well as other CV therapies such as beta blockers, ACE inhibitors, and ARBs.
- With the achievement of very low LDL-C during the study, no new safety concerns were identified, and there was no difference in the incidence of AEs, SAEs, or AEs leading to study discontinuation between the treatment arms. The incidence of NODM, cataracts, and neurocognitive AEs were similar between the 2 treatment arms as well.
- The magnitude of benefit with evolocumab is in line with the CTTC, and these findings demonstrate that patients with ASCVD benefit from LDL cholesterol lowering below current targets.

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