



# **Evolocumab Reduces Cardiovascular Events in Patients with Baseline LDL-C <70 mg/dL and in Patients Already on Maximum Intensity Statin: *An Analysis from FOURIER***

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for the FOURIER Steering Committee & Investigators

*National Lipid Association Scientific Sessions  
Late-Breaking Clinical Trial  
May 20, 2017*



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



# Disclosures

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## **Research Grant Support through BWH:**

**Amgen; AstraZeneca; Daiichi-Sankyo; Eisai; GlaxoSmithKline; Intarcia; Janssen Research Development; MedImmune; Merck; Novartis; Pfizer; Poxel; Takeda**

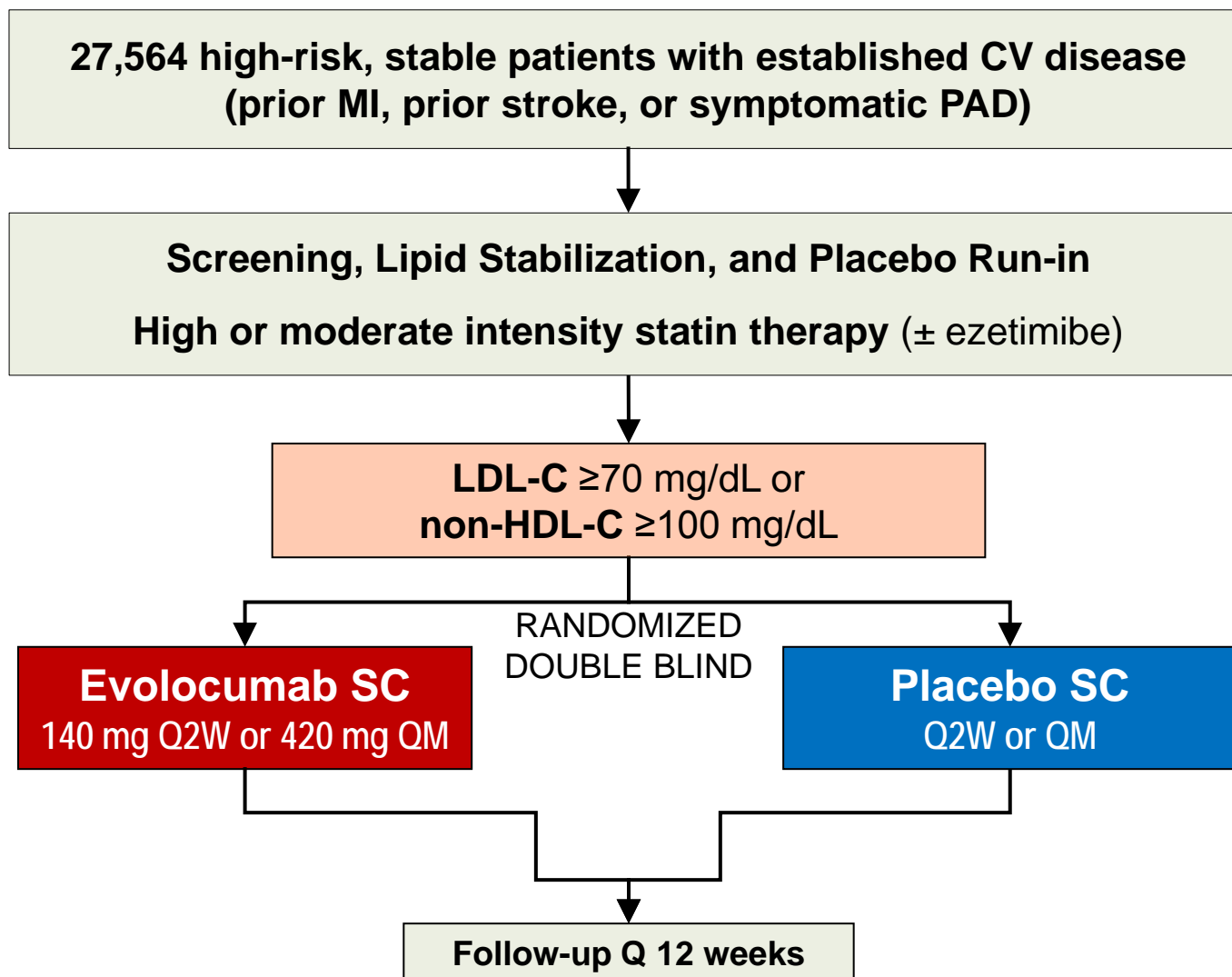
## **Scientific Advisory Boards & Consulting:**

**Amgen; CVS Caremark; Esperion; Intarcia; Ionis; MedImmune; Merck; Novartis**



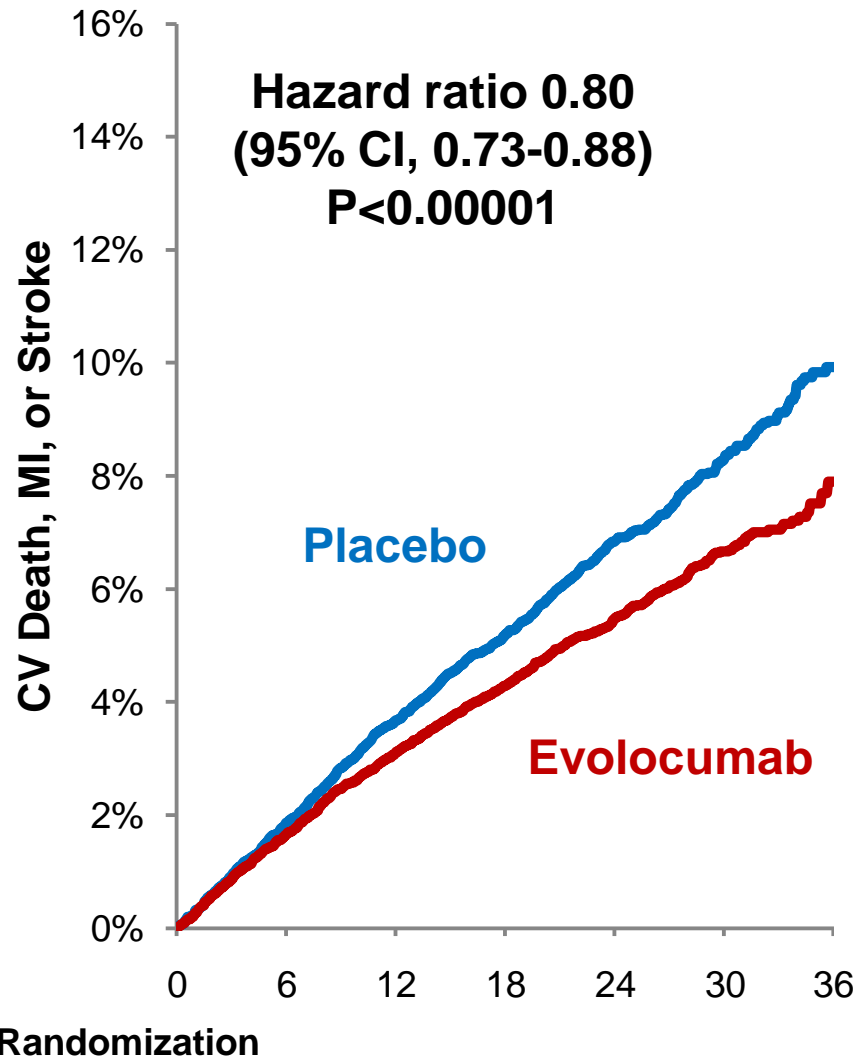
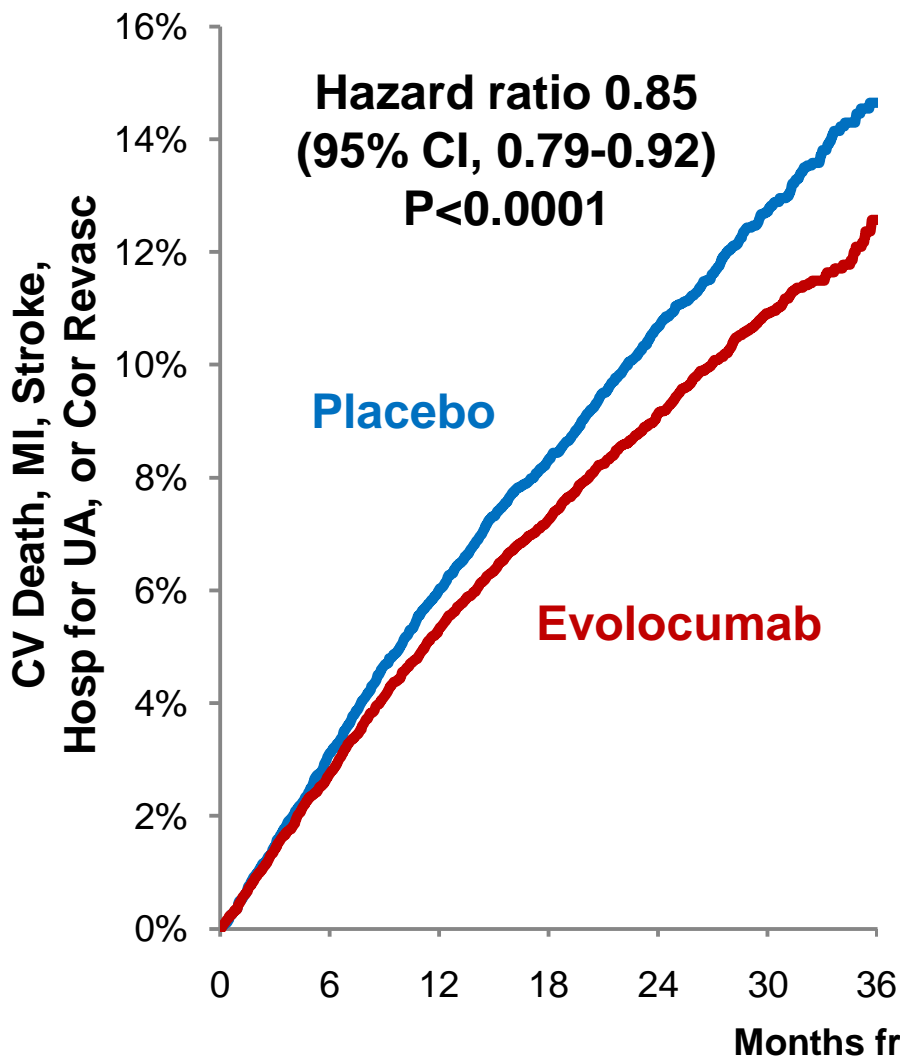


# Trial Design



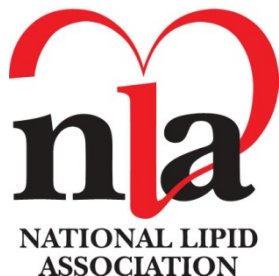


# Primary & Key Secondary Endpoints





# Current Guidelines: LDL-C Targets

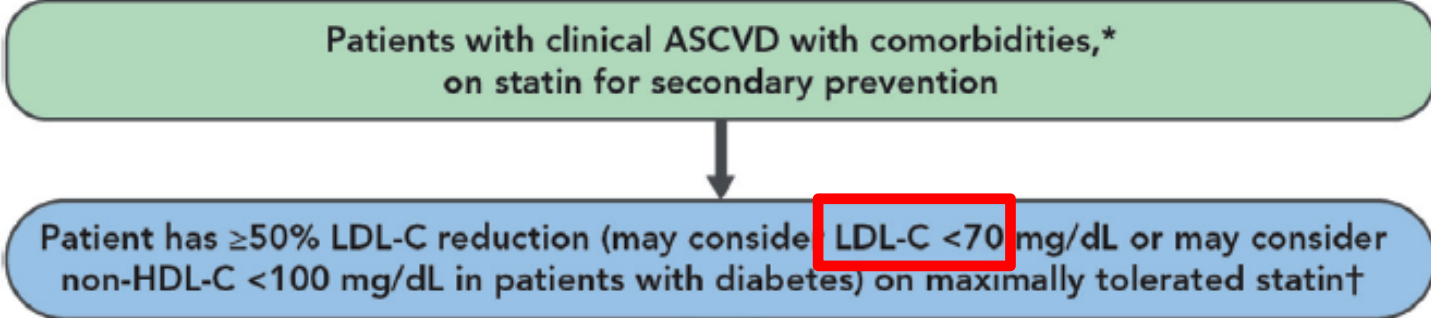


**Table 2** Treatment goals for non-HDL-C, LDL-C, and Apo B in mg/dL

Risk category	Treatment goal		
	Non-HDL-C	LDL-C	Apo B*
Very high	<100	<b>&lt;70</b>	<80

**Lipids**  
LDL-C is the primary target

**Very high-risk: LDL-C <1.8 mmol/L (70 mg/dL)** or a reduction of at least 50% if the baseline<sup>b</sup> is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).





# Current Guidelines: Statin Intensity



Table 12 Intensity of statin

High-intensity daily dosage ↓ LDL-C ≥50%

Atorvastatin, 40–80 mg  
Rosuvastatin, 20–40 mg

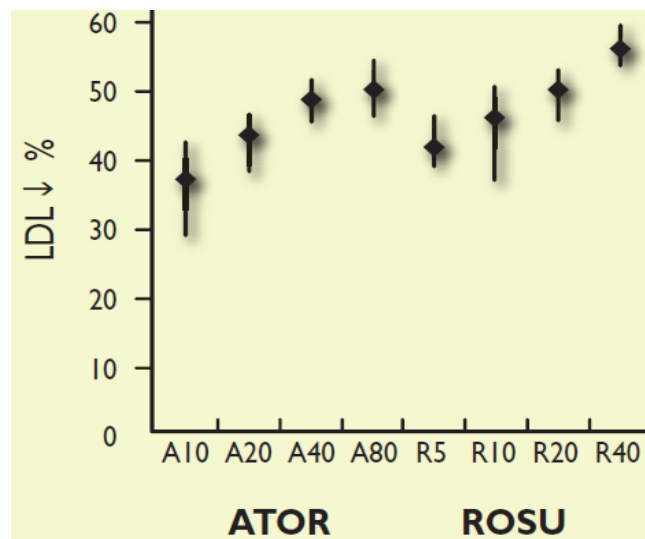
### Recommendations

Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.

### High-Intensity Statin Therapy

Daily dose lowers LDL-C, on average, by approximately ≥50%

Atorvastatin (40†)–80 mg  
Rosuvastatin 20 (40) mg





# Hypothesis



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**Even patients starting with an LDL-C below current targets or already on maximum intensity statin therapy will derive additional cardiovascular risk reduction from further lipid lowering with evolocumab.**





# Objectives



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**To evaluate efficacy and safety of evolocumab in two key subgroups:**

- **Patients with baseline LDL-C <70 mg/dL\***
- **Patients on maximum intensity statin therapy, defined as atorvastatin 80 mg/d or rosuvastatin 40 mg/d**

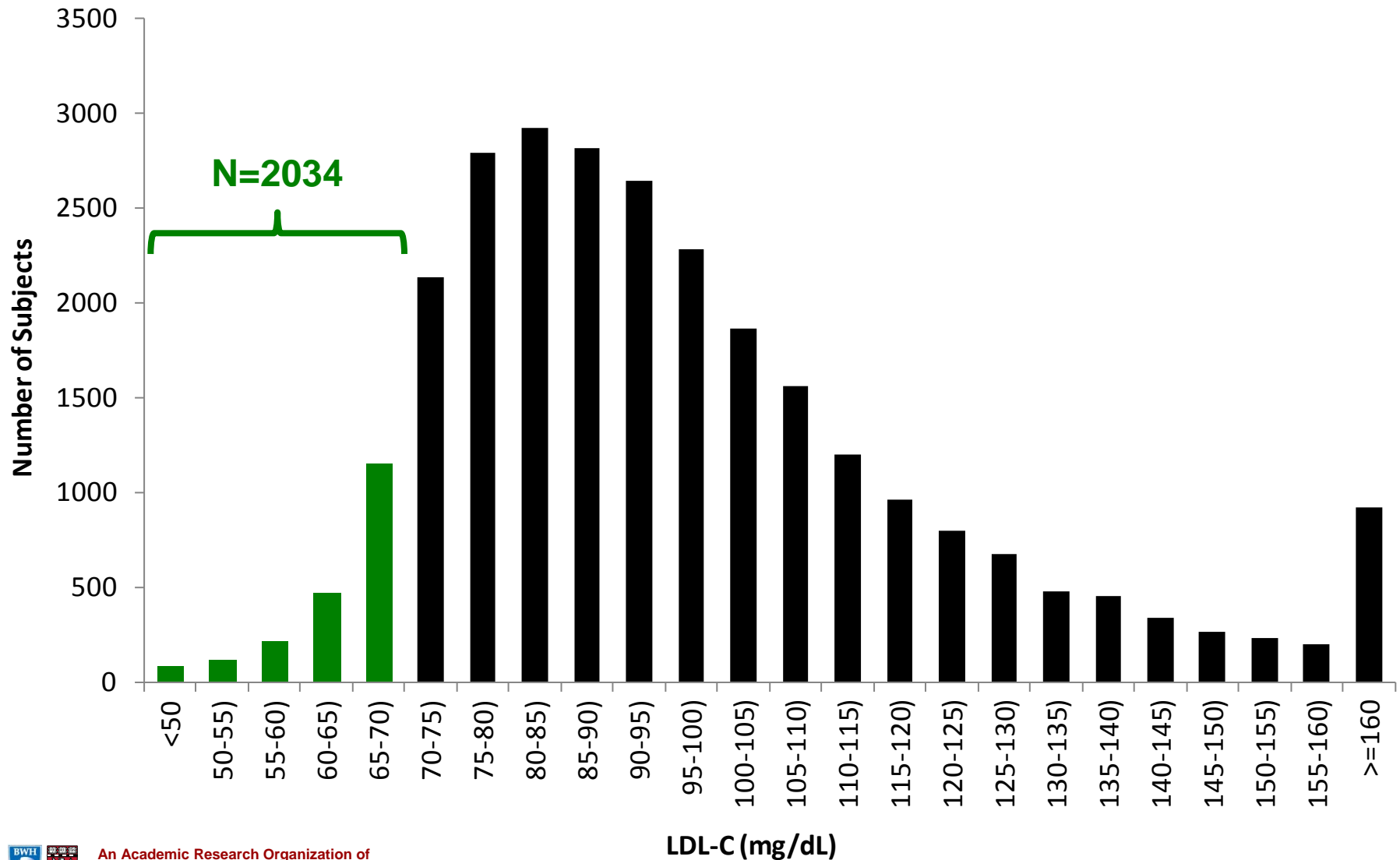
\*Could have had final screening lipids prior to day of randomization that demonstrated either non-HDL-C  $\geq 100$  mg/dL or LDL-C  $\geq 70$  mg/dL. LDL-C was calculated using Friedewald equation, except if  $< 40$  mg/dL or if TG  $> 400$  mg/dL, in which case LDL-C was measured by preparative ultracentrifugation.







# Baseline LDL-C





# Baseline Characteristics



Characteristic	LDL-C <70 mg/dl	LDL-C ≥70 mg/dl
Number	2034	25,529
Age, years, mean (SD)	62 (9)	63 (9)
Male sex (%)	80	75
Type of cardiovascular disease (%)		
Myocardial infarction	78	81
Stroke (non-hemorrhagic)	21	19
Symptomatic PAD	14	12
Diabetes (%)	49	36





# Baseline Characteristics



Characteristic	LDL-C <70 mg/dl	LDL-C ≥70 mg/dl
Maximum intensity statin (%)	26	27
High but not max intensity statin (%)	41	42
Ezetimibe (%)	4	5
LDL-C, mg/dL, median (IQR)	65.5 (61-68)	93.5 (82-110.5)
Non-HDL-C, mg/dL, median (IQR)	100 (89-111)	123 (108-143)

Maximum intensity statin: atorvastatin ≥80 mg/d or rosuvastatin ≥40 mg/d

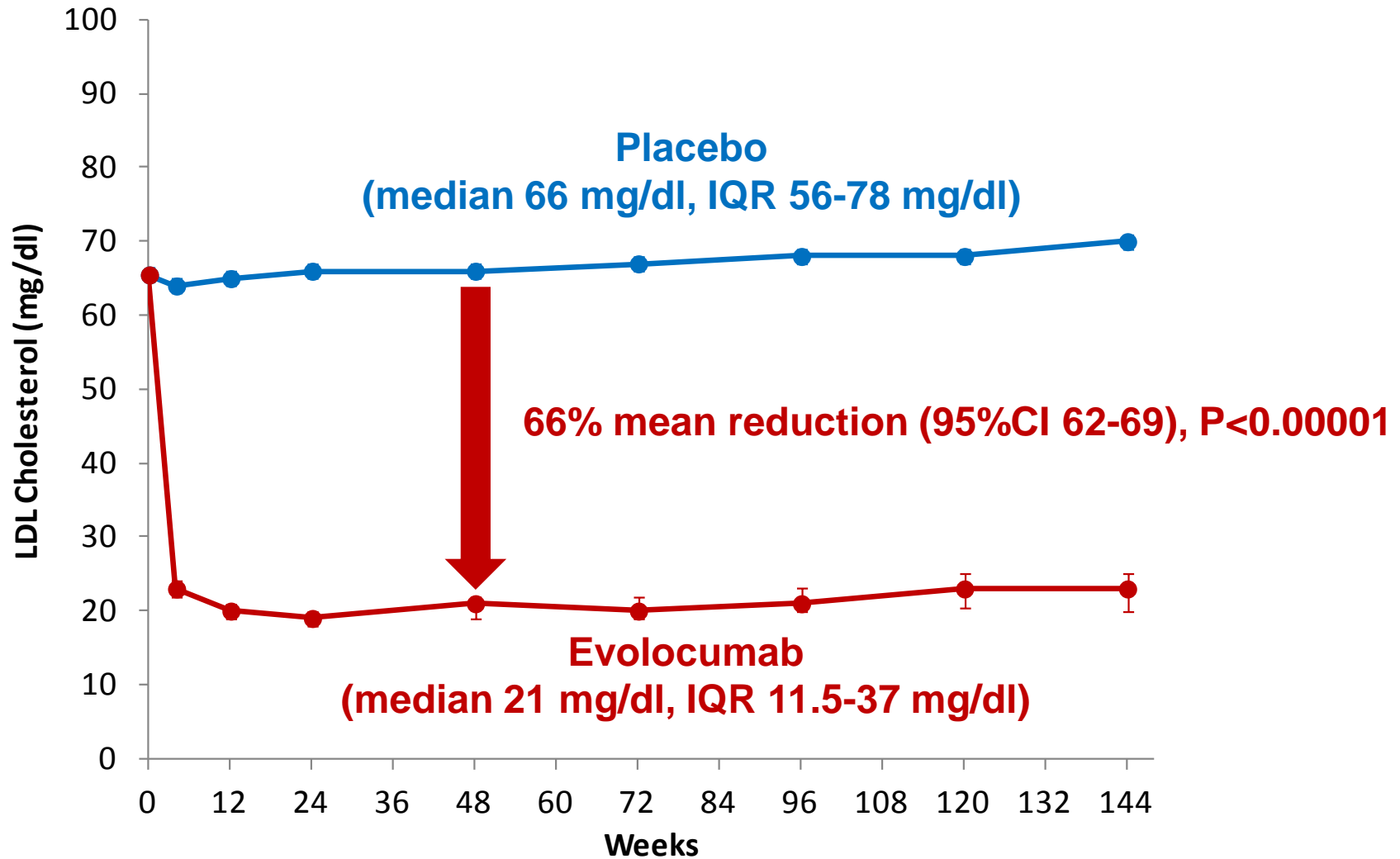
High but not max intensity statin: atorvastatin 40 to <80 mg/d, rosuvastatin 20 to <40 mg/d, or simvastatin 80 mg/d





# LDL Cholesterol

In patients with baseline LDL-C < 70 mg/dL





# Clinical Outcomes by Baseline LDL-C



## CVD, MI, stroke, UA, or cor revasc

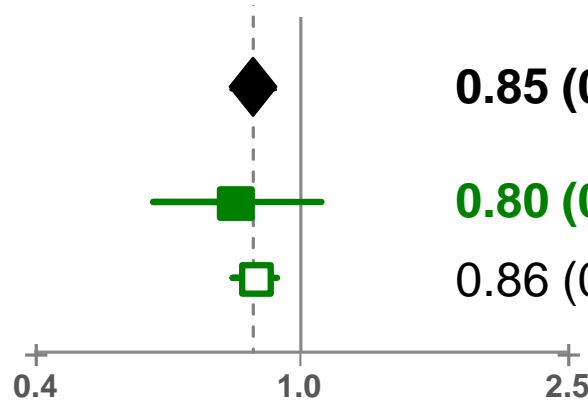
HR (95% CI)

$P_{\text{interaction}}$

*All Patients*

Baseline LDL-C <70 mg/dL

Baseline LDL-C ≥70 mg/dL



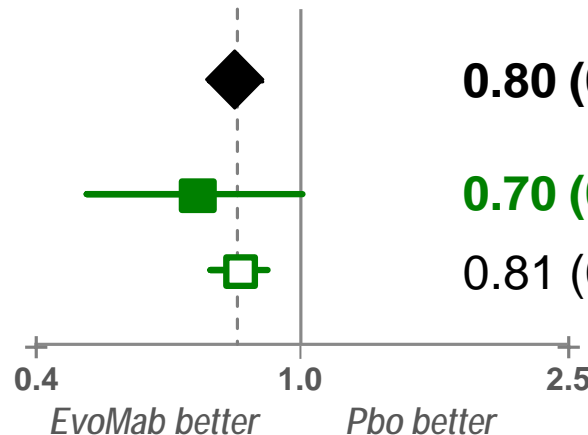
0.65

## CVD, MI, or stroke

*All Patients*

Baseline LDL-C <70 mg/dL

Baseline LDL-C ≥70 mg/dL

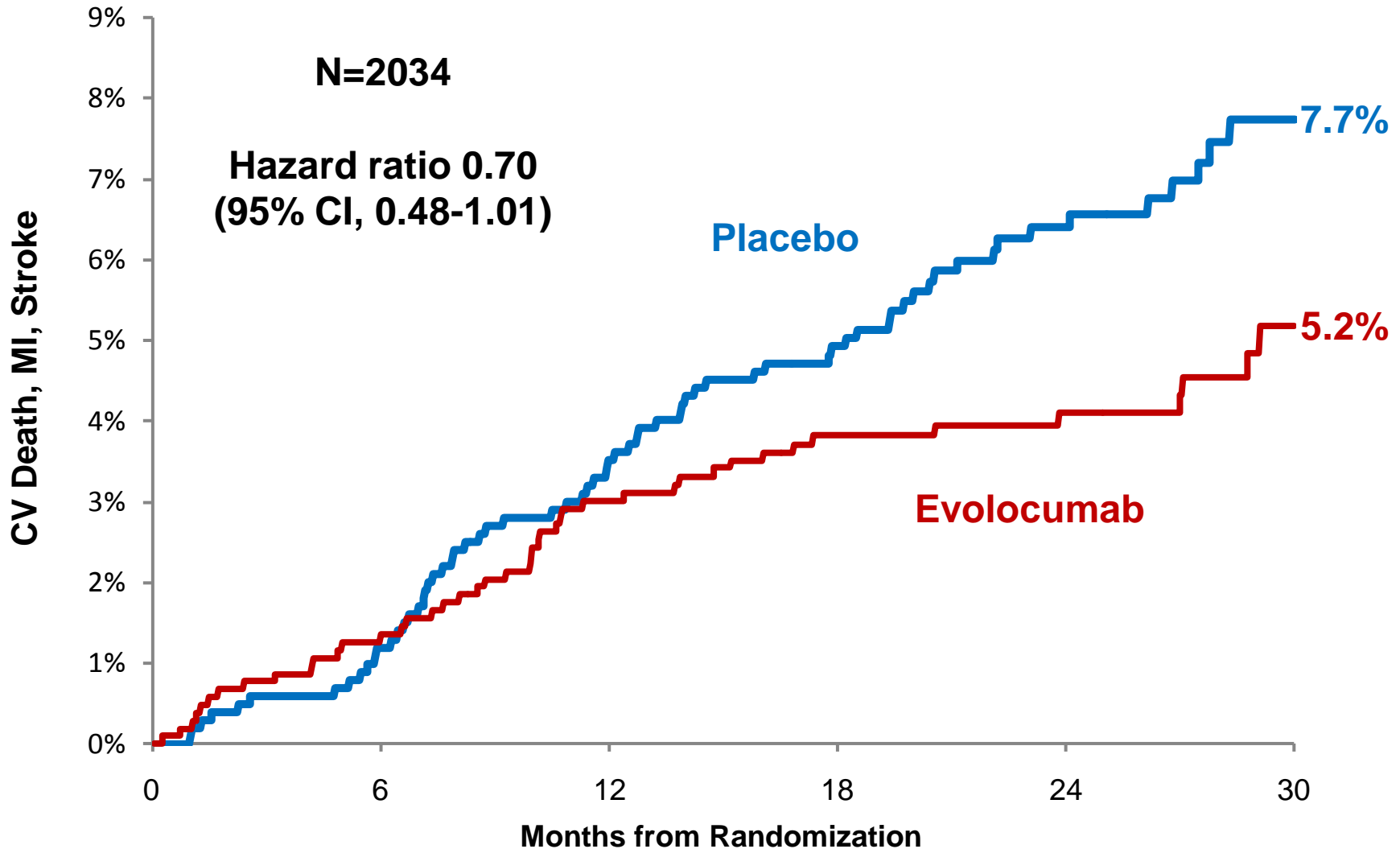


0.44





# Patients with Baseline LDL-C <70 mg/dL





# Safety



*In patients with baseline LDL-C < 70 mg/dL*

	<b>Evolocumab (N=1030)</b>	<b>Placebo (N=1003)</b>
<b>Adverse events (%)</b>		
Any	<b>79.7</b>	<b>77.9</b>
Serious	<b>26.0</b>	<b>27.3</b>
Allergic reaction	<b>3.8</b>	<b>3.3</b>
Injection-site reaction	<b>2.9</b>	<b>1.6</b>
Treatment-related and led to d/c of study drug	<b>1.8</b>	<b>1.9</b>
Muscle-related	<b>4.8</b>	<b>6.0</b>
Cataract	<b>1.8</b>	<b>1.6</b>
Diabetes (new-onset)	<b>8.8</b>	<b>11.2</b>
Neurocognitive	<b>1.7</b>	<b>1.2</b>
<b>Laboratory results (%)</b>		
ALT or AST >3× ULN	<b>2.7</b>	<b>2.3</b>
CK >5× ULN	<b>0.9</b>	<b>0.9</b>

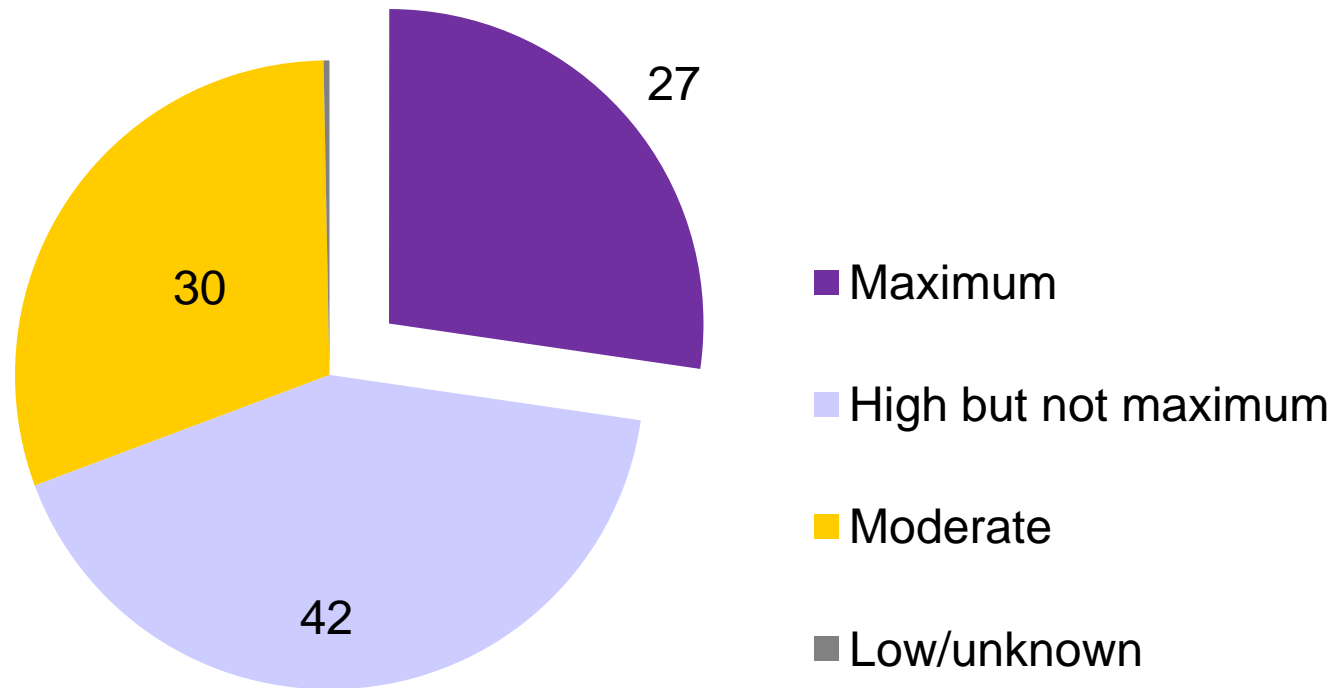
New-onset diabetes assessed in patients without diabetes at baseline; adjudicated by CEC.

No significant interactions between baseline LDL-C, evolocumab, and the rates of adverse events.





# Baseline Statin Intensity



Maximum intensity statin: atorvastatin  $\geq 80$  mg/d or rosuvastatin  $\geq 40$  mg/d

High but not max intensity statin: atorvastatin 40 to  $< 80$  mg/d, rosuvastatin 20 to  $< 40$  mg/d, or simvastatin 80 mg/d







# Baseline Characteristics



Characteristic	Maximum Intensity Statin	Non-Maximum Intensity Statin
<b>Number</b>	<b>7533</b>	<b>20,031</b>
<b>Age, years, mean (SD)</b>	<b>61 (9)</b>	<b>63 (9)</b>
<b>Male sex (%)</b>	<b>76</b>	<b>75</b>
<b>Type of cardiovascular disease (%)</b>		
Myocardial infarction	<b>86</b>	<b>79</b>
Stroke (non-hemorrhagic)	<b>16</b>	<b>21</b>
Symptomatic PAD	<b>13</b>	<b>13</b>
<b>Diabetes (%)</b>	<b>34</b>	<b>38</b>





# Baseline Characteristics



Characteristic	Maximum Intensity Statin	Non-Maximum Intensity Statin
Maximum intensity statin (%)	100	0
High but not max intensity statin (%)	0	58
Ezetimibe (%)	9	4
LDL-C, mg/dL, median (IQR)	93 (80-112)	91 (80-108)
Non-HDL-C, mg/dL, median (IQR)	122 (107-145)	121 (106-140)

Maximum intensity statin: atorvastatin  $\geq 80$  mg/d or rosuvastatin  $\geq 40$  mg/d

High but not max intensity statin: atorvastatin 40 to  $< 80$  mg/d, rosuvastatin 20 to  $< 40$  mg/d, or simvastatin 80 mg/d

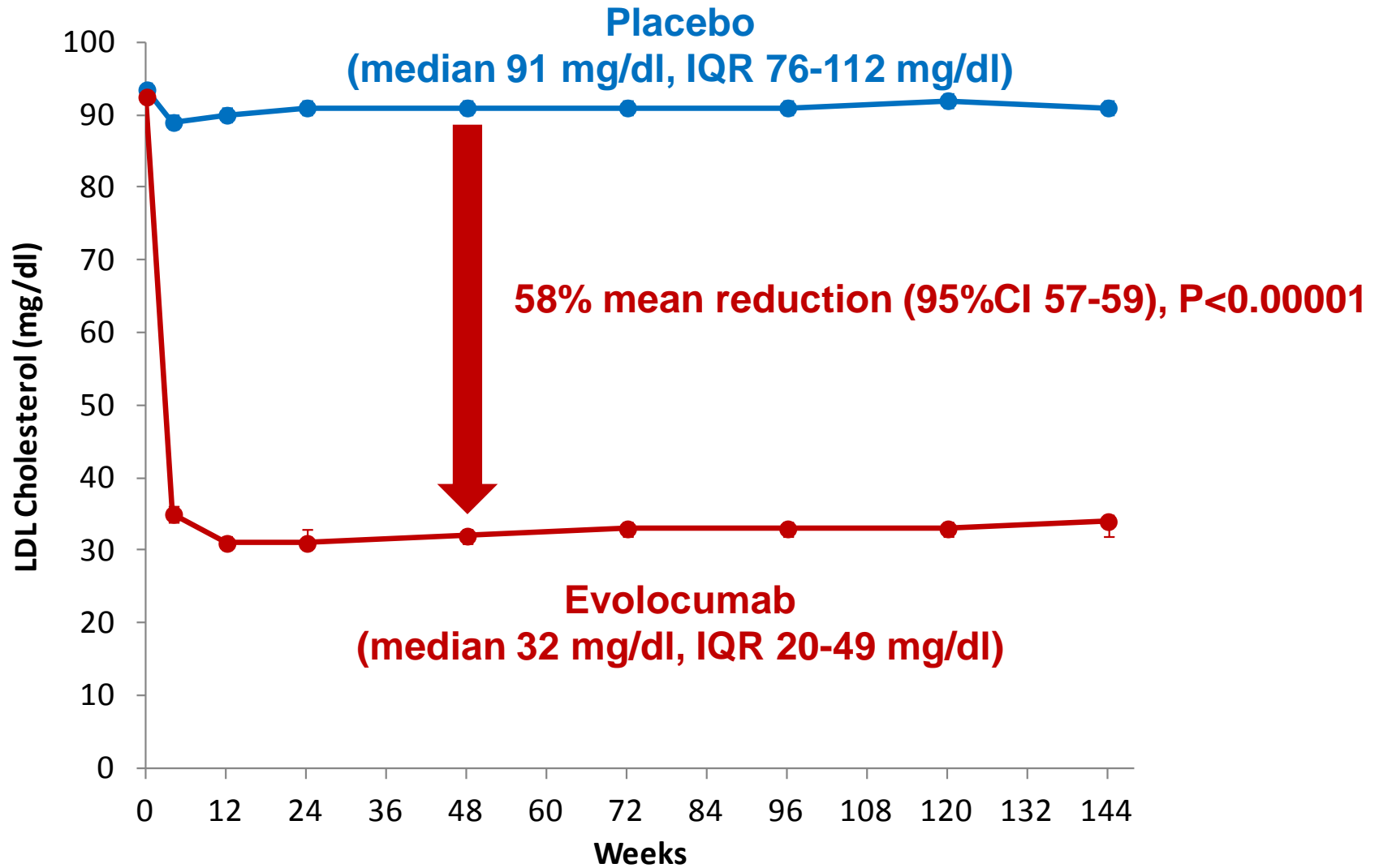




# LDL Cholesterol



*In patients on maximum intensity statin*





# Clinical Outcomes by Statin Intensity



## CVD, MI, stroke, UA, or cor revasc

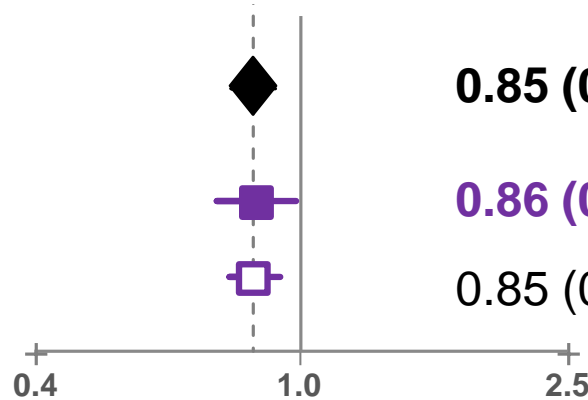
HR (95% CI)

$P_{\text{interaction}}$

*All Patients*

Maximum intensity statin

Lesser intensity statin



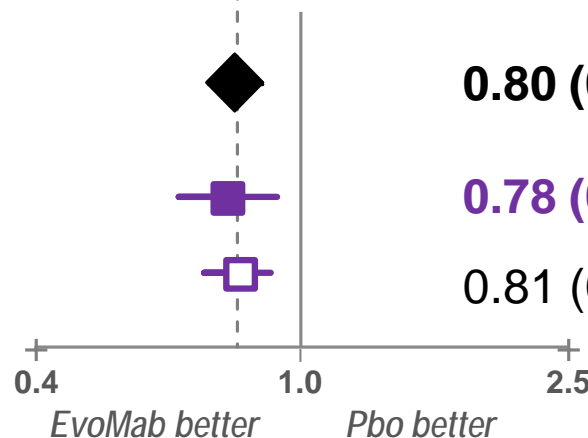
0.88

## CVD, MI, or stroke

*All Patients*

Maximum intensity statin

Lesser intensity statin

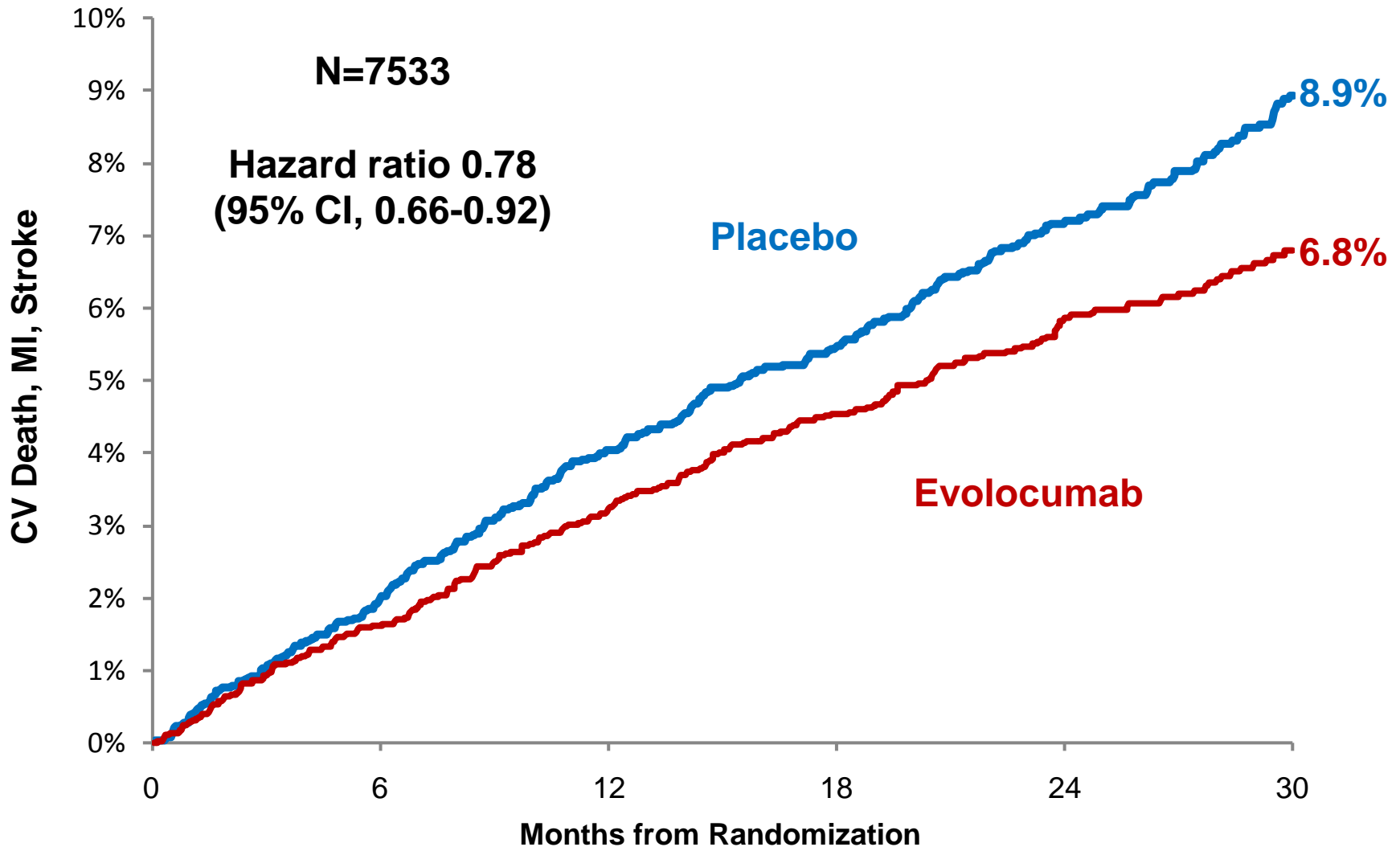


0.71





# Patients on Maximum Intensity Statin





# Safety



*In patients on maximum intensity statin*

	<b>Evolocumab (N=3754)</b>	<b>Placebo (N=3770)</b>
<b>Adverse events (%)</b>		
Any	<b>78.4</b>	<b>79.7</b>
Serious	<b>26.1</b>	<b>26.8</b>
Allergic reaction	<b>3.8</b>	<b>3.3</b>
Injection-site reaction	<b>2.2</b>	<b>1.8</b>
Treatment-related and led to d/c of study drug	<b>1.4</b>	<b>1.4</b>
Muscle-related	<b>5.5</b>	<b>5.1</b>
Cataract	<b>1.4</b>	<b>1.7</b>
Diabetes (new-onset)	<b>9.0</b>	<b>7.4</b>
Neurocognitive	<b>1.7</b>	<b>1.7</b>
<b>Laboratory results (%)</b>		
ALT or AST >3× ULN	<b>2.3</b>	<b>2.2</b>
CK >5× ULN	<b>0.8</b>	<b>0.9</b>

New-onset diabetes assessed in patients without diabetes at baseline; adjudicated by CEC.

No significant interactions between statin intensity, evolocumab, and the rates of adverse events.





# Conclusions



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**Evolocumab safely ↓ CV events in patients w/ stable ASCVD to a similar degree whether the baseline LDL-C was  $<70$  or  $\geq 70$  mg/dL, and regardless of whether the background statin was maximal intensity or not.**

**These findings support using evolocumab to go beyond what is recommended in current guidelines to lower CV risk in well-treated patients.**

