



# Cardiovascular Benefit of Lowering LDL-C Below $\sim 1$ mmol/L (40 mg/dl)

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# ESC Dyslipidemia Guidelines



ESC

European Society  
of Cardiology

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ESC/EAS GUIDELINES



## 2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

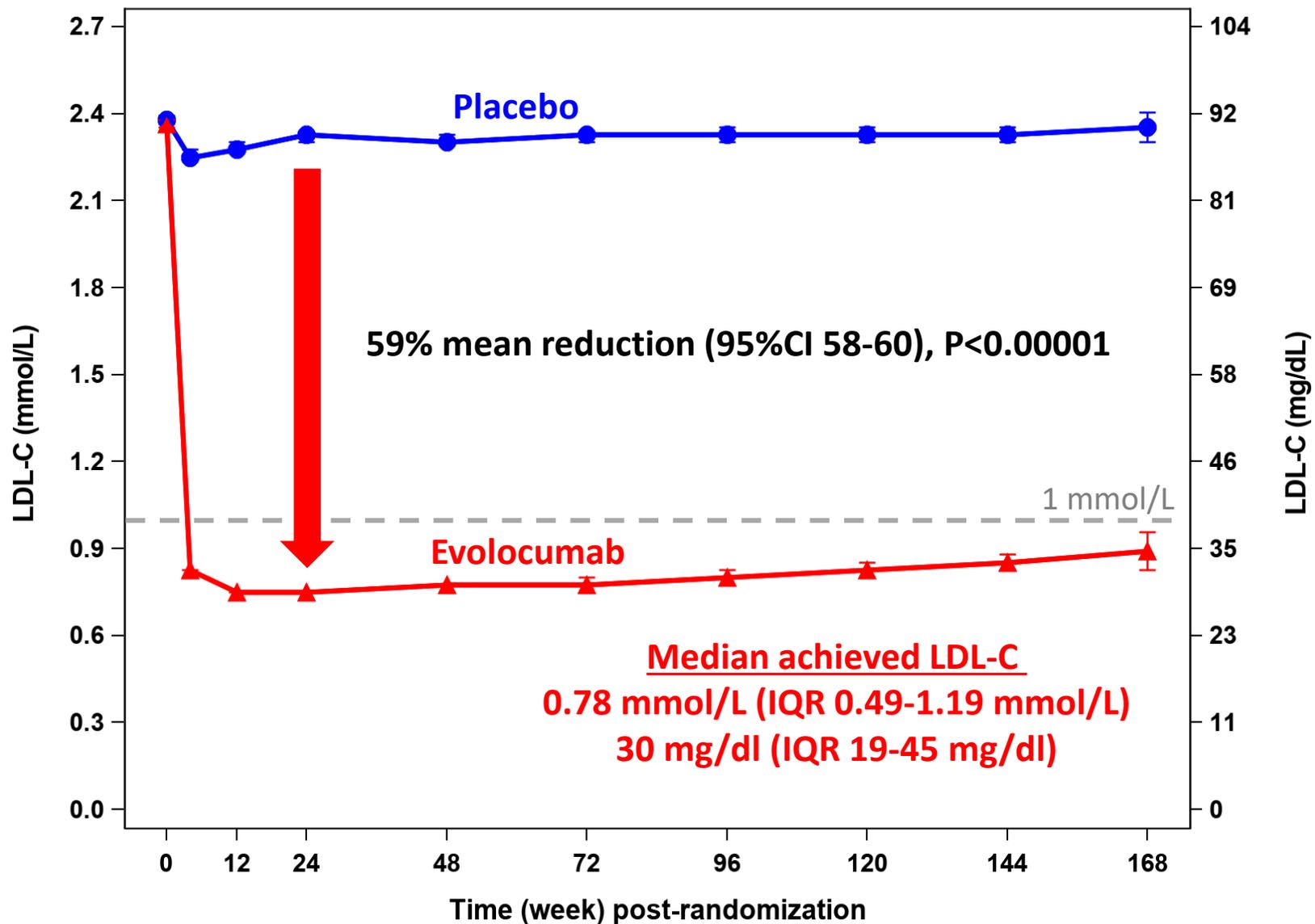
Risk Category	LDL-C Goal
<b>High-Risk ASCVD</b>	<b>&lt;1.4 mmol/L (55 mg/dl)</b> is recommended
<b>ASCVD with 2 CV events in 2 years (despite taking optimal statin therapy)</b>	<b>&lt;1 mmol/L (40 mg/dl)</b> may be considered



# PCSK9 Inhibition in *fourier*

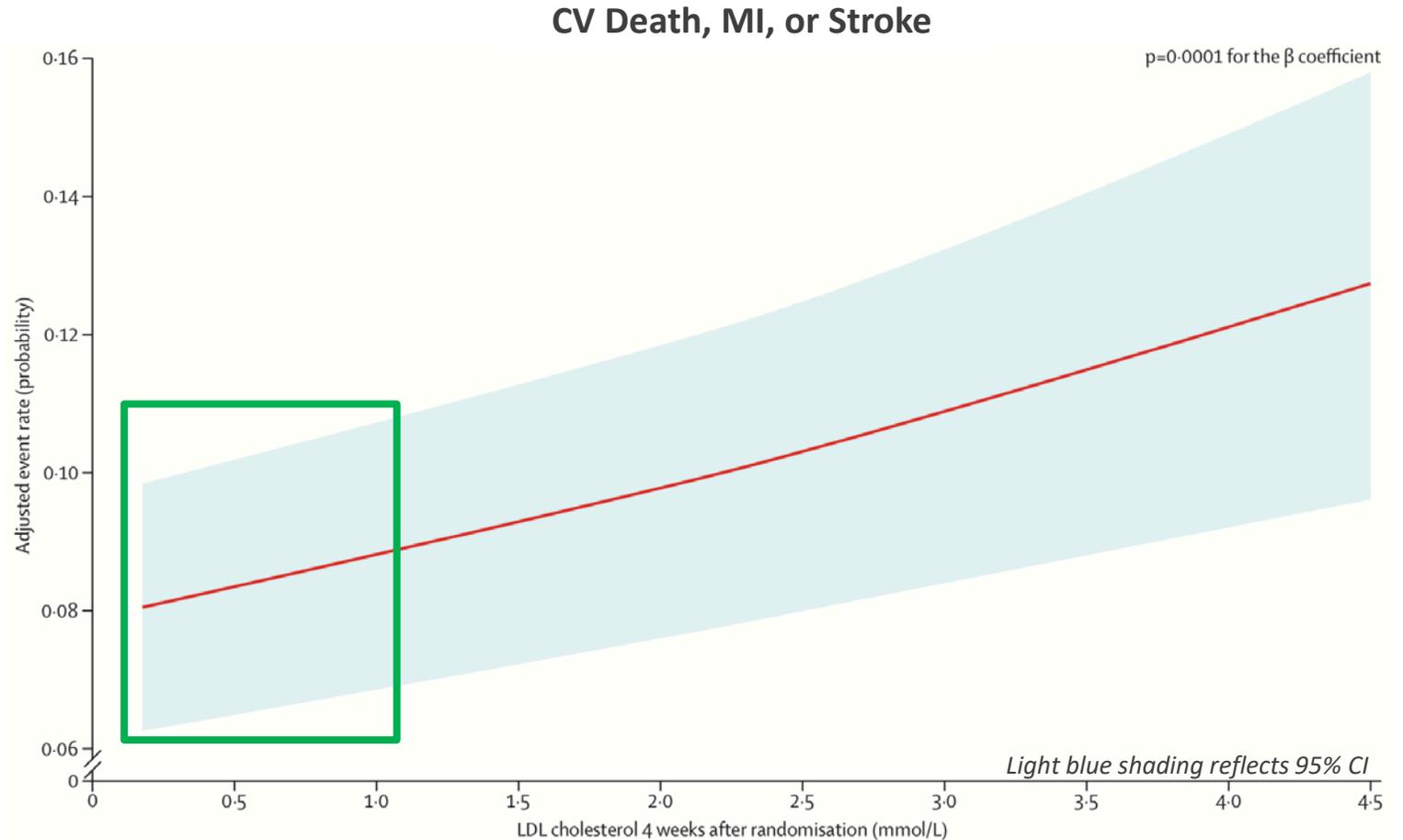


- The addition of PCSK9 inhibitors to statin therapy allows us to achieve LDL-C levels well below 1 mmol/L in many patients
- However, the clinical benefit of LDL-C lowering beyond this level has recently been debated



# Achieved LDL-C and Outcomes

- A post-hoc analysis from FOURIER showed a strong relationship between achieved LDL-C at 1 month & adjusted CV events, seen down to 0.2 mmol/L of LDL-C
- However, this was a post-randomization association





# Aim



To determine whether there is continued cardiovascular benefit from lowering LDL-C below  $\sim 1$  mmol/L (40 mg/dl) while maintaining randomization

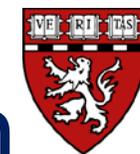


# Methods

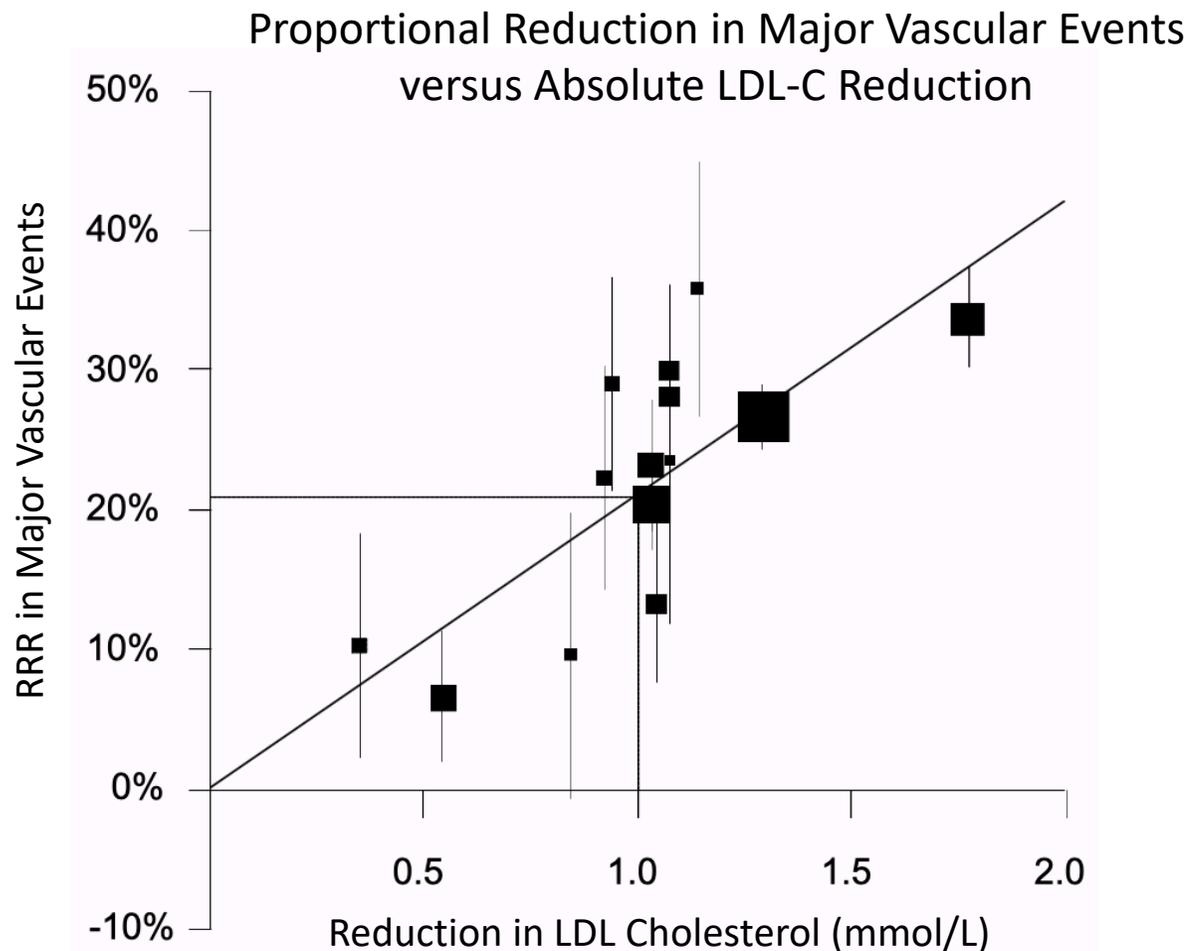
- We performed an exploratory analysis in the FOURIER trial
- FOURIER was a cardiovascular outcomes trial comparing evolocumab vs. placebo in patients with stable ASCVD on optimized statin therapy
- All 27,564 patients from FOURIER were included in this analysis
- The endpoint of major adverse cardiovascular event (MACE) was defined as CV death, MI, or stroke
- The median follow-up was 2.2 years



# Cholesterol Treatment Trialists Collaboration

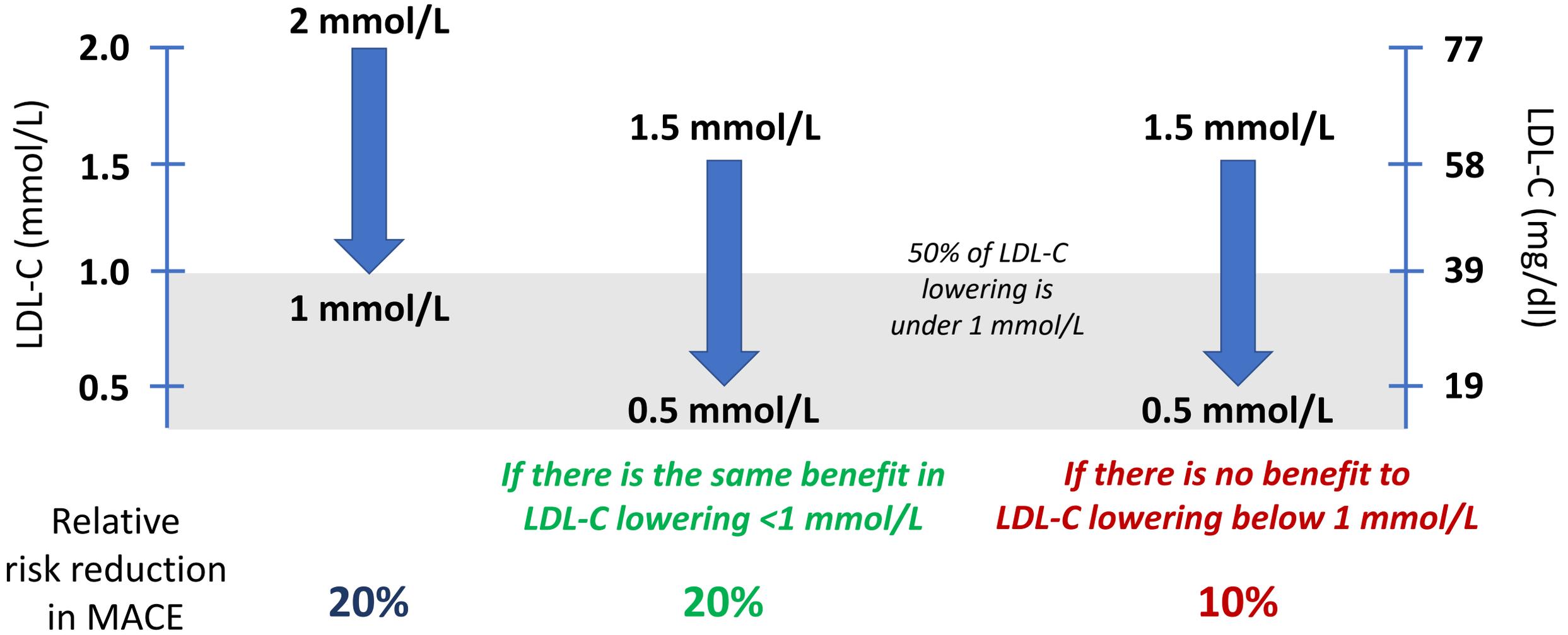


- Treatment benefit is directly proportional to the absolute amount of LDL-C reduction
- However, these data did not include many patients with achieved levels of LDL-C <1 mmol/L





# Conceptual Approach

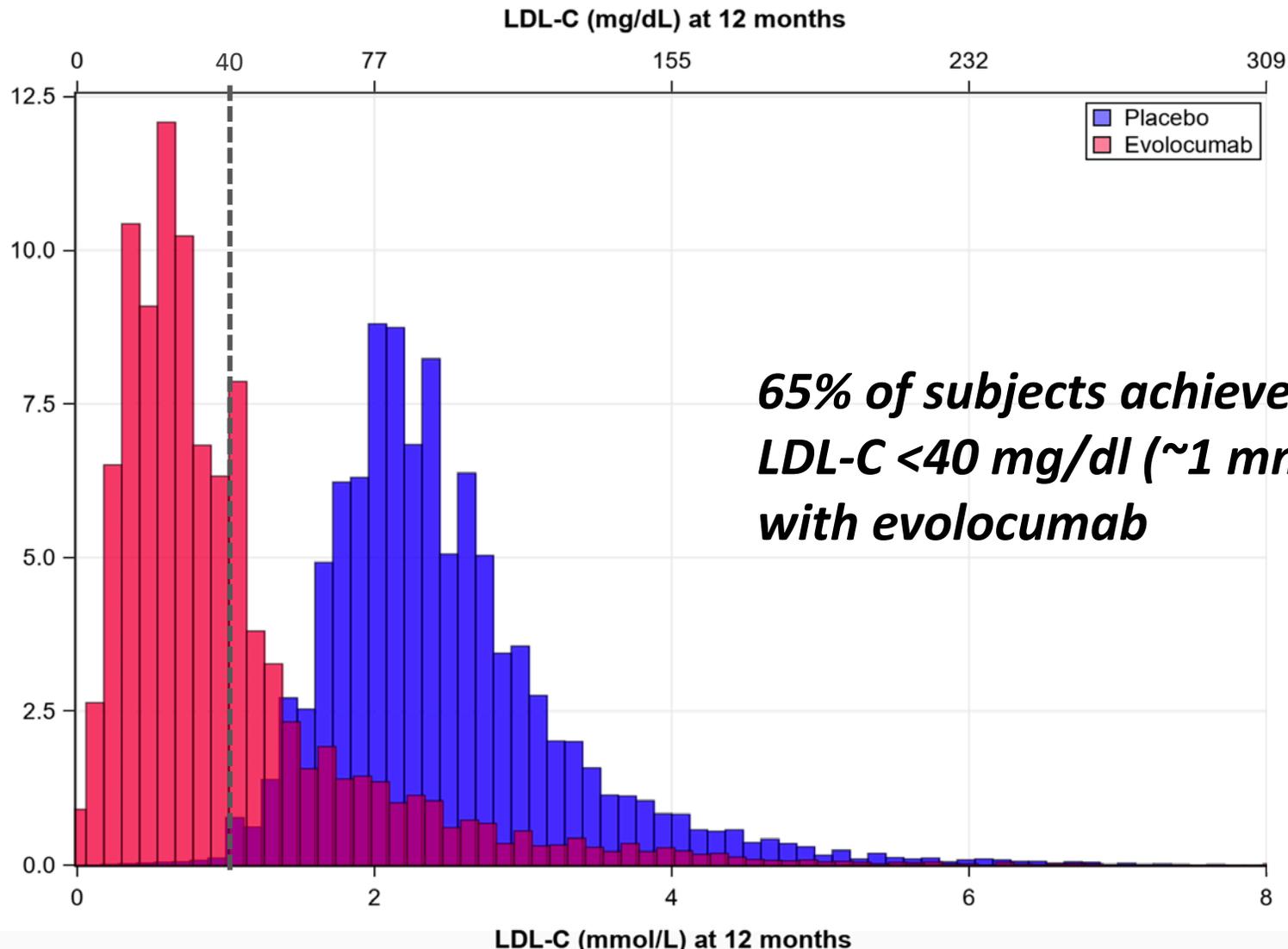




# Pooled Baseline Characteristics

Characteristic	Value
<b>Age, years, mean (SD)</b>	<b>63 (9)</b>
<b>Male sex (%)</b>	<b>75</b>
<b>Type of cardiovascular disease (%)</b>	
Myocardial infarction	<b>81</b>
Stroke (non-hemorrhagic)	<b>19</b>
Symptomatic PAD	<b>13</b>
<b>Cardiovascular risk factor</b>	
Hypertension (%)	<b>80</b>
Diabetes mellitus (%)	<b>37</b>
Current cigarette use (%)	<b>28</b>
LDL-C, mmol/L, median (IQR)	<b>2.4 (2.1-2.8)</b>
LDL-C, mg/dl, median (IQR)	<b>92 (80-109)</b>
<b>Moderate or High Intensity Statin Use (%)</b>	<b>99</b>

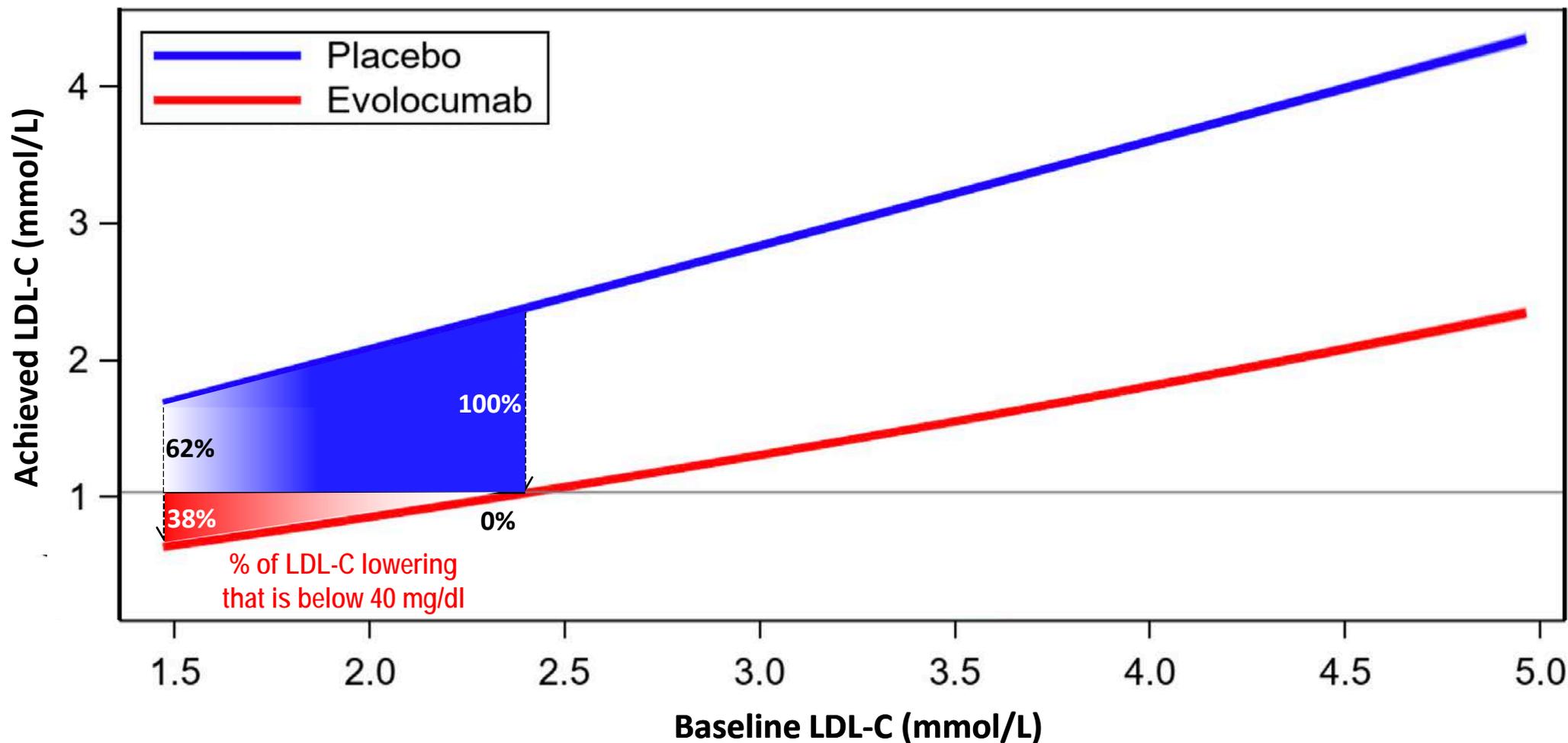
# Achieved LDL-C Levels in FOURIER



*65% of subjects achieved LDL-C < 40 mg/dl (~1 mmol/L) with evolocumab*

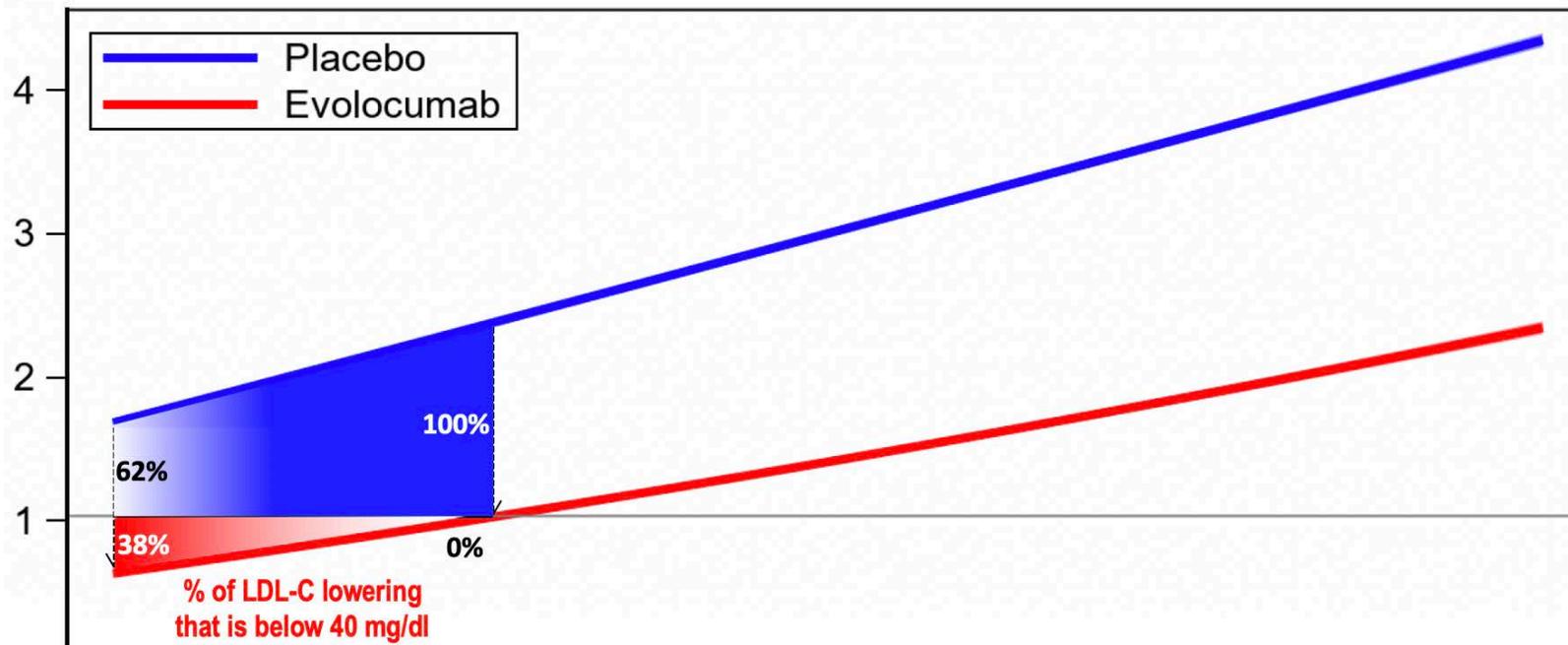


# Achieved LDL-C at 48 weeks and the percentage of LDL-C difference between treatment arms due to lowering LDL-C below ~1 mmol/L (<40 mg/dl) as a function of baseline LDL-C



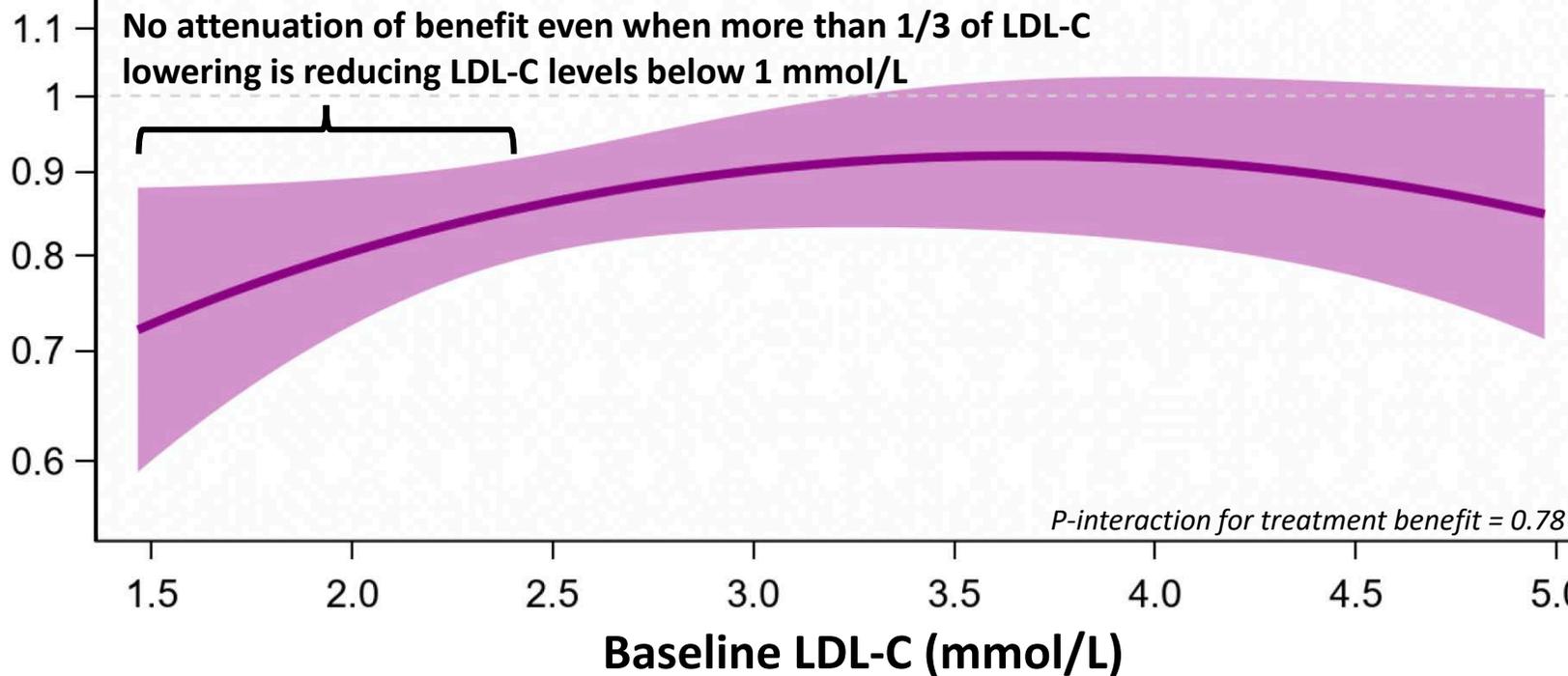


Achieved LDL-C (mmol/L)



**Upper Panel:** Achieved LDL-C at 48 weeks and the percentage of LDL-C difference between treatment arms due to lowering LDL-C below 1 mmol/L (<40 mg/dl) as a function of baseline LDL-C.

HR with Evolocumab vs. Placebo for CV Death, MI, Stroke (per mmol/L Reduction in LDL-C)



**Lower Panel:** Hazard ratio for evolocumab vs. placebo for CV Death, MI, or Stroke per 1 mmol/L reduction in LDL-C as a function of baseline LDL-C.



# Conclusions

- There is no evidence for attenuation of the clinical benefit of lowering LDL-C below 1 mmol/L (40 mg/dl)
- These data support the ESC/EAS Dyslipidemia Guideline recommendations and suggest lowering LDL-C below 1 mmol/L in a wider range of patients with ASCVD would further lower CV risk