Clinical Efficacy and Safety of Achieving Very Low LDL-C Levels With the PCSK9 Inhibitor Evolocumab in the FOURIER Outcomes Trial

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Clinical Trial Update I

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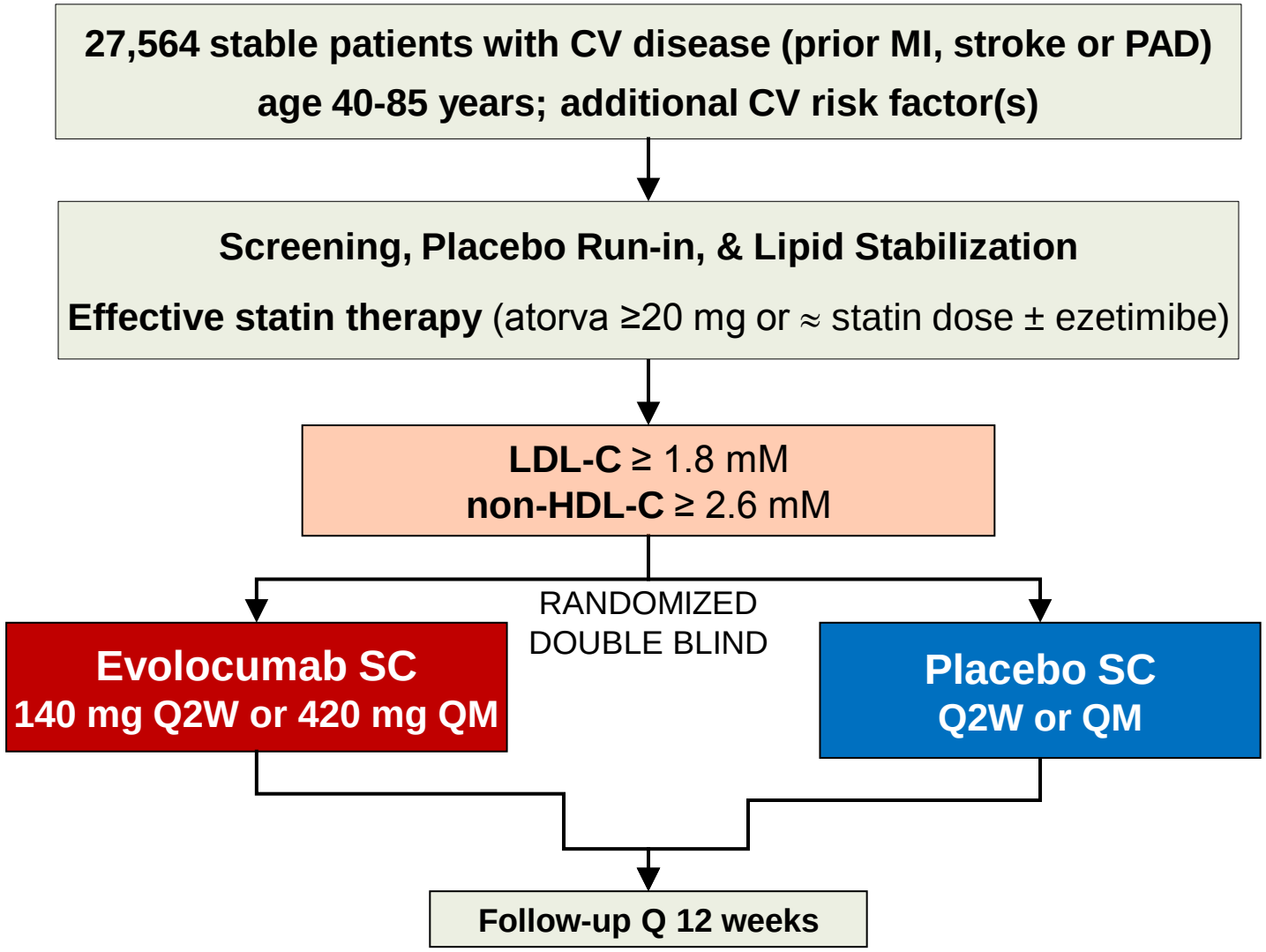
An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Declaration of interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Amgen, Bristol Myers Squibb, Merck, Pfizer, Daiichi Sankyo, GlaxoSmithKline)
- Research contracts (Amgen)

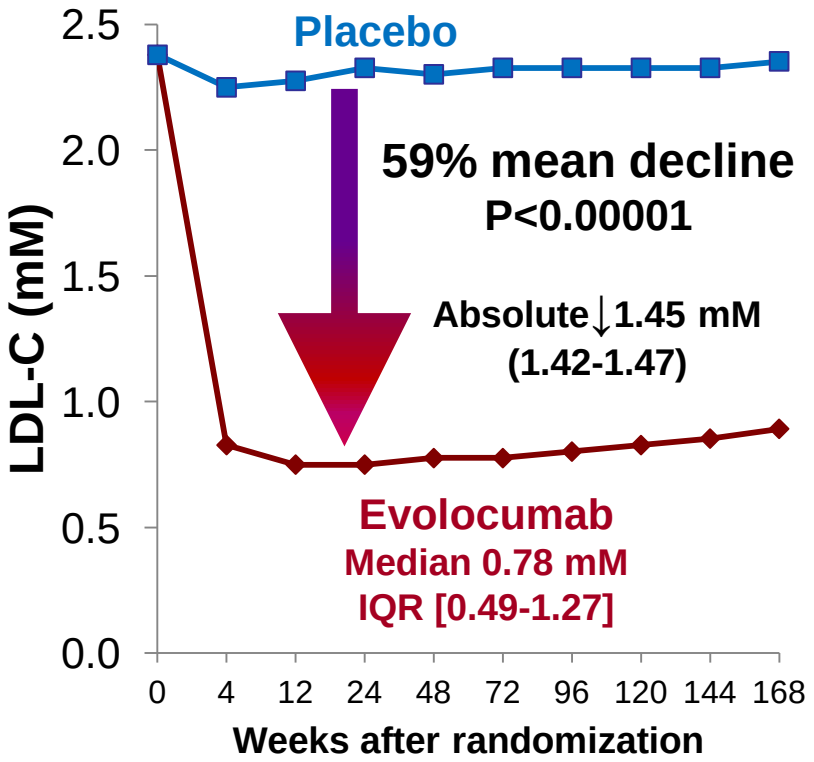
Trial Design

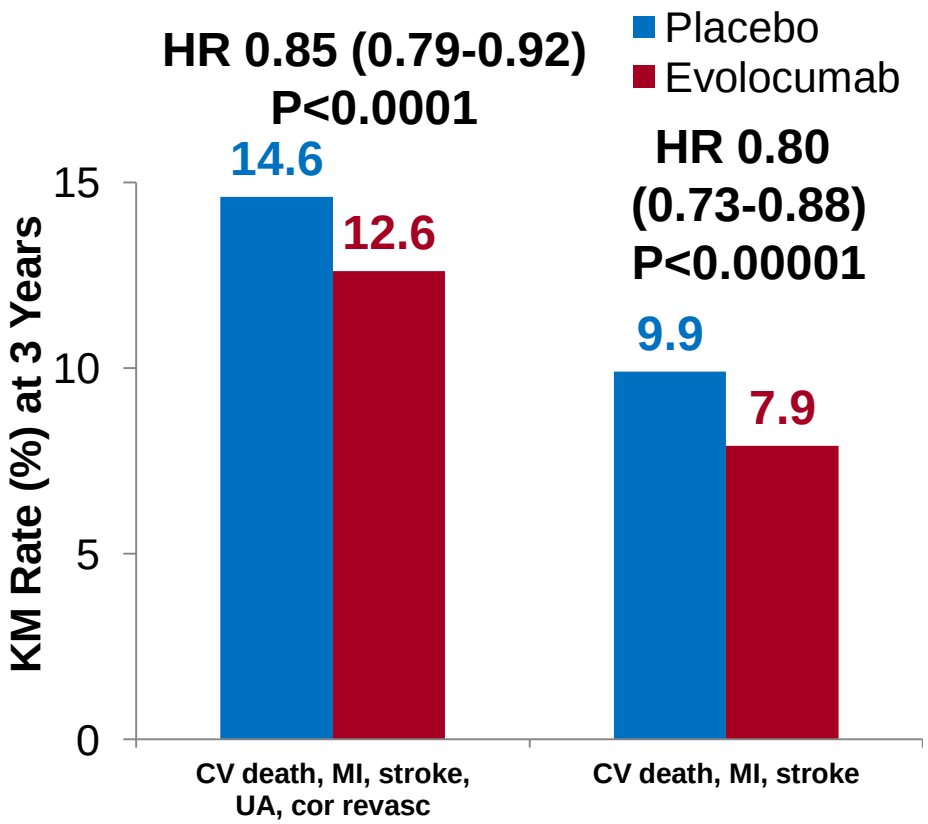


Sabatine MS et al. *Am Heart J* 2016;173:94-101

Summary of FOURIER

- ↓ LDL-C by 59% (from 2.4 -> 0.8 [0.5, 1.2] mM)
- ↓ CV outcomes in patients already on statin therapy
- Evolocumab was safe and well-tolerated





Sabatine MS et al. *New Engl J Med* 2017;376:1713-22

Aims

To explore the clinical efficacy and safety associated with progressively lower achieved LDL-C levels

Methods - 1

- LDL-C assessed at 4 wks (ultracentrifugation if <1 mM)
- Analyzed 5 groups by achieved LDL-C at 4 weeks
  1) <0.5mM (20 mg/dL)
  2) 0.5-1.3 mM (20- 49 mg/dL)
  3) 1.3-1.8 mM (50-69 mg/dL)
  4) 1.8-2.6mM (70-99 mg/dL)
  5) ≥2.6 mM (≥100 mg/dL) was the referent group
- Pooled results across 2 Rx groups (evo, placebo)

1582 pts with events in first 4 wks or no LDL-C at week 4 were excluded

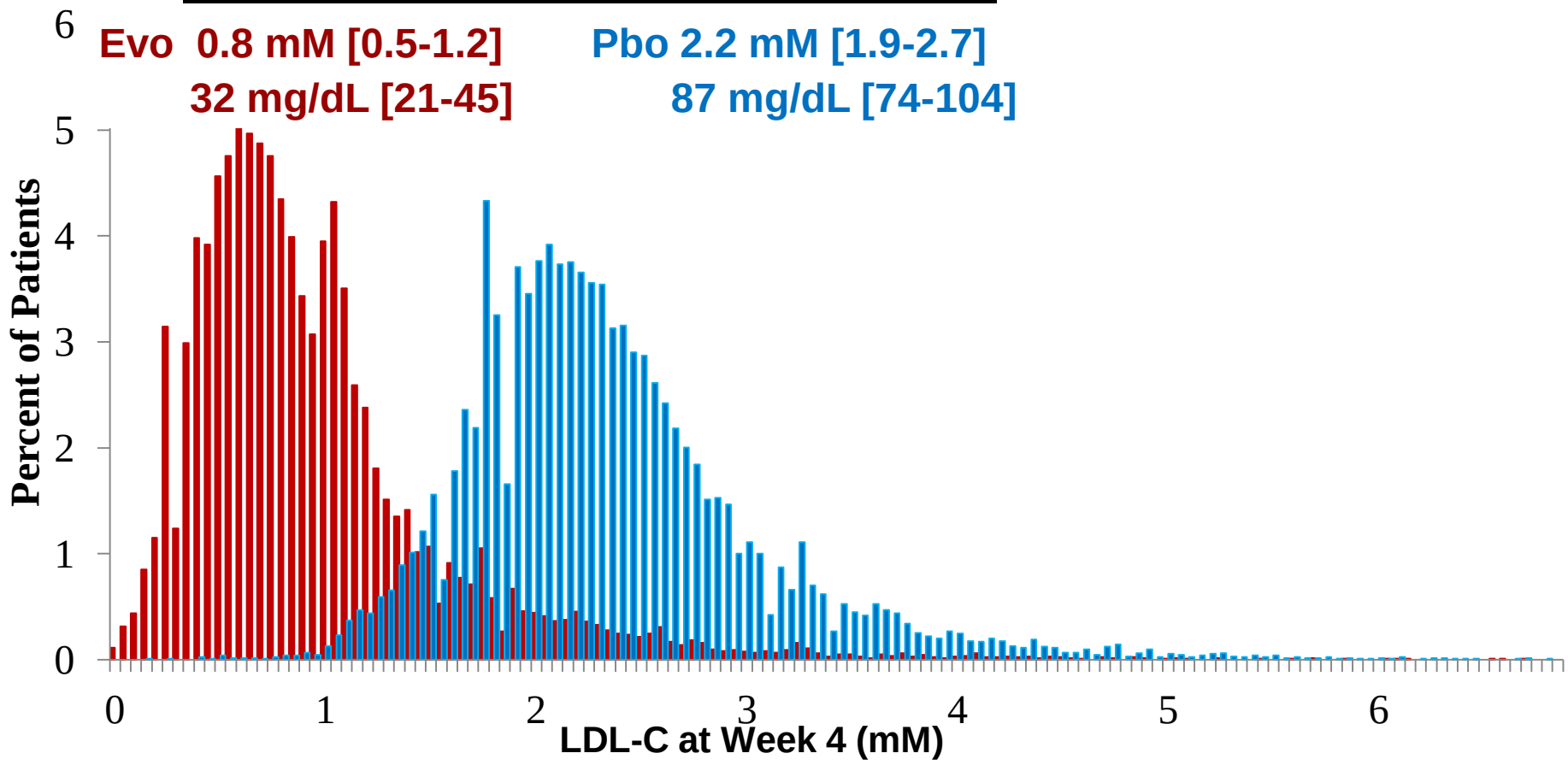
Methods - 2

- Prespecified 1° and 2° efficacy composite endpoints
- 10 safety adverse events evaluated:
  - Serious AE
  - Cancer
  - Hem stroke
  - New onset diabetes (adjudicated by CEC)
  - AE->drug discon
  - cataracts AEs
  - Neurocognitive
  - AST/ALT>3x
  - CK > 5x ULN
  - Non-CV death
- Cognition[1] assessed using CANTAB tool and pt survey of everyday cognition (ECog)

1. Giugliano RP et al. *N Engl J Med* 2017377:633-43

Achieved LDL-C at 4 Weeks

Median [IQR] LDL-C at 4 Weeks



LDL (mM)	<0.8	0.8-1.3	1.3-1.8	1.8-2.6	≥ 2.6
%Evo	99.6%	96.5%	41%	10%	9.6%
%Placebo	0.4%	3.5%	59%	90%	90.4%

Baseline Characteristics

	Achieved LDL-C in mM at 4 Weeks				
	<0.5 (N=2669)	0.5-1.3 (N=8003)	1.3-1.8 (N=3444)	1.8-2.6 (N=7471)	≥2.6 (N=4395)
Age (median), yrs*	64	63	62	63	61
Females*	16	23	27	24	28
Caucasian race*	80	86	84	85	88
Current smoker*	26	27	29	28	32
Prior MI	81	81	80	82	81
Prior stroke	20	19	19	19	20
Prior PAD	12	14	14	12	14
Hypertension	78	80	82	80	81
TIMI Risk Score 2° Prevention*	3.2	3.3	3.4	3.3	3.4

Data shown are % patients unless otherwise specified

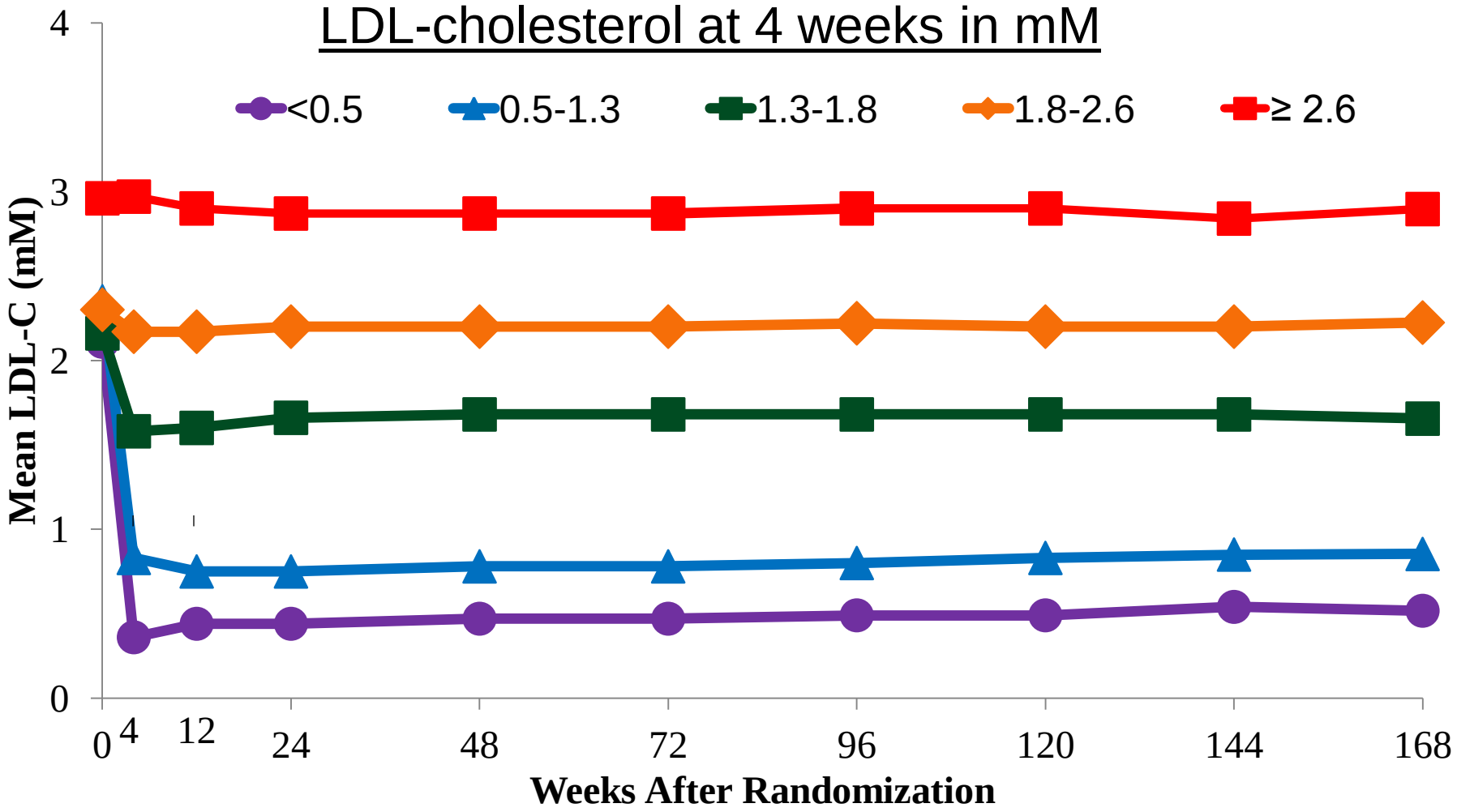
***$P_{trend} \leq 0.0001$**

Lipids and Lipid Rx at Randomization

At Randomization	Achieved LDL-C in mM at 4 Weeks				
	<0.5 (N=2669)	0.5-1.3 (N=8003)	1.3-1.8 (N=3444)	1.8-2.6 (N=7471)	≥2.6 (N=4395)
Median Lipid values					
LDL-C, mM	2.1	2.4	2.2	2.3	3.0
Total cholesterol, mM	4.0	4.3	4.2	4.2	5.0
Triglycerides, mM	1.5	1.5	1.6	1.4	1.6
HDL-C, mM	1.1	1.1	1.1	1.1	1.2
Lipoprotein (a), nM	22	43	32	37	48
High potency statin, % (≥ Atorvastatin 40 mg/d)	63	69	70	70	72
Ezetimibe, %	4.1	5.0	5.4	4.6	7.4

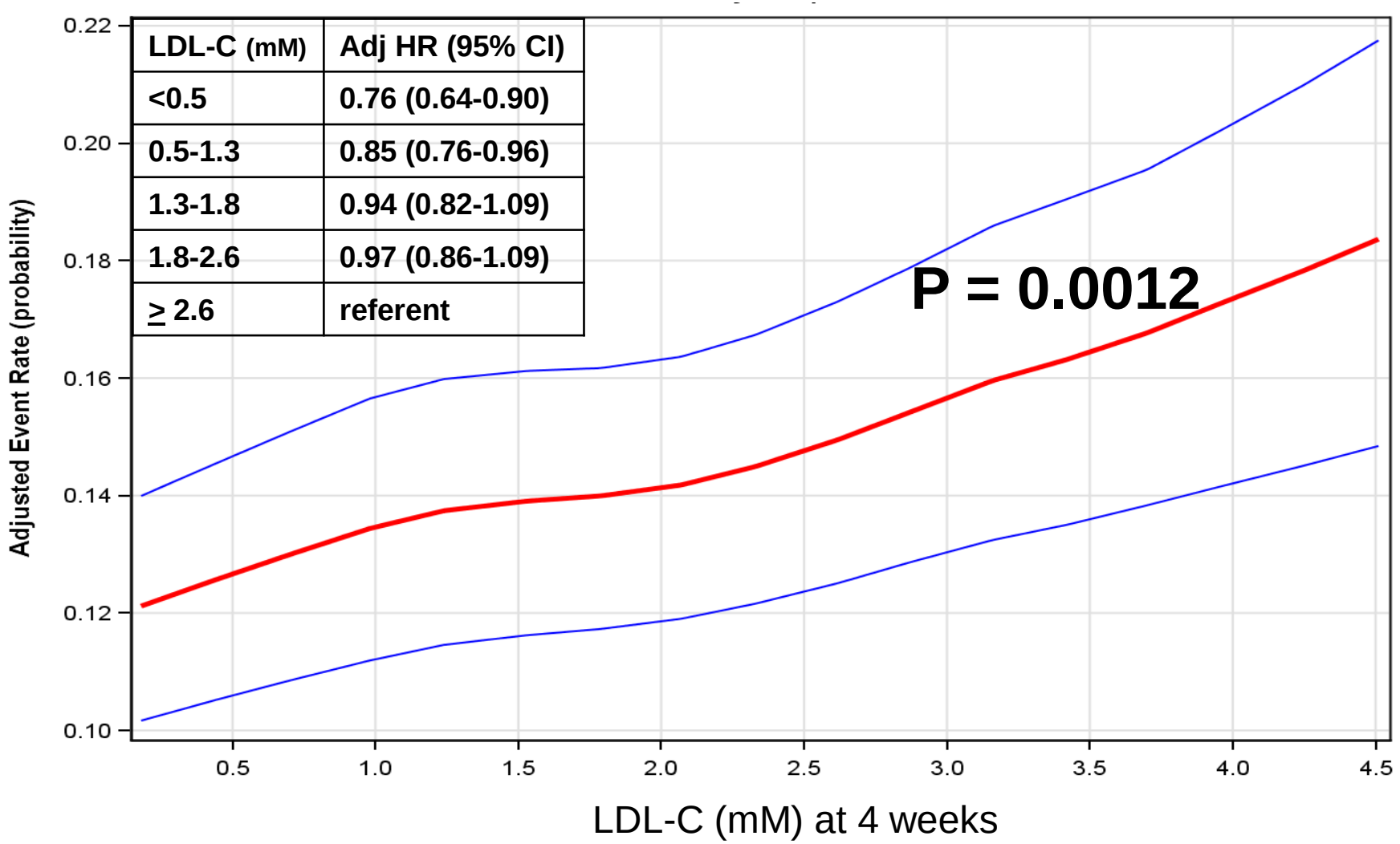
$P_{trend} \leq 0.0001$ for each

LDL-C Over Time



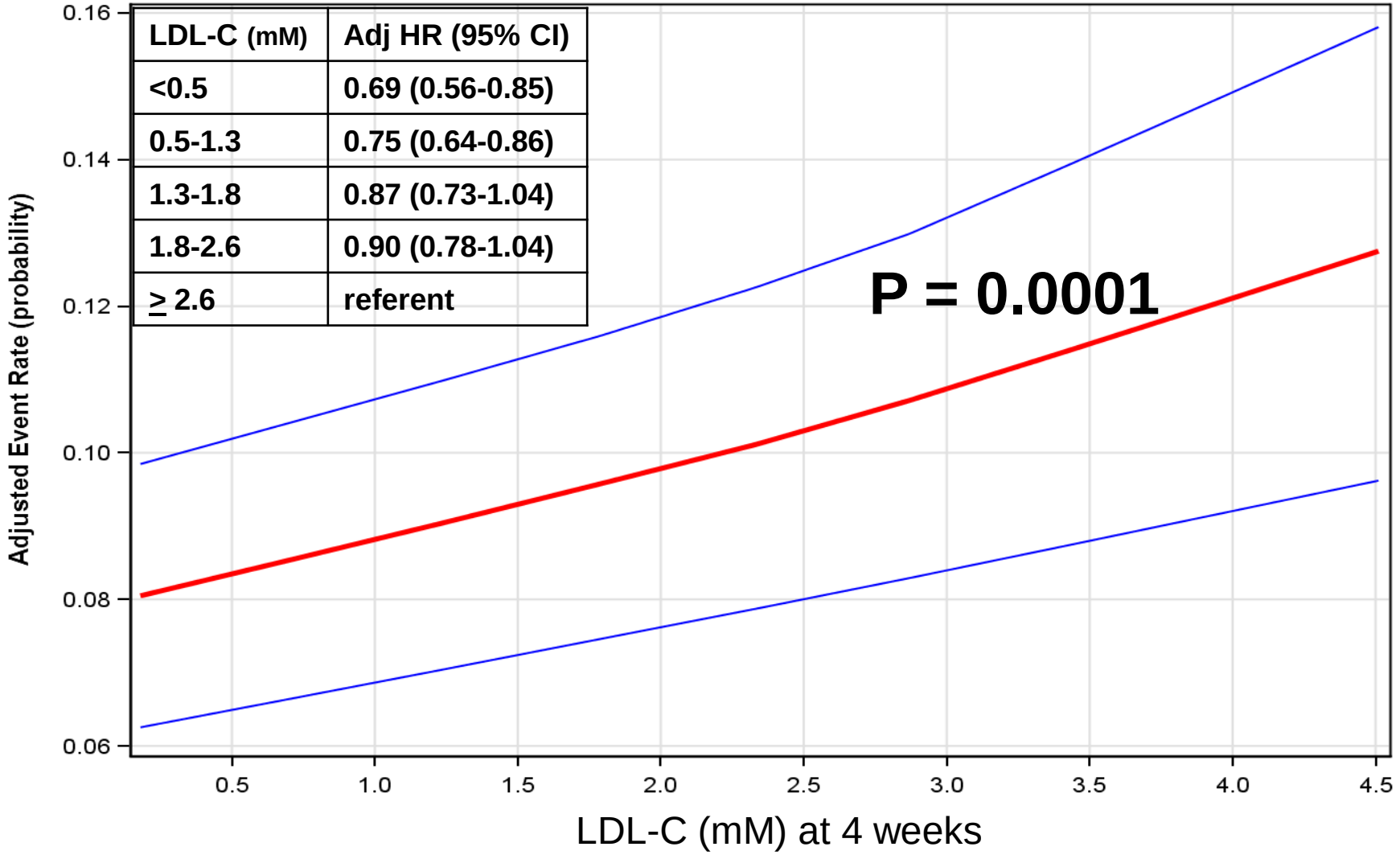
CV Death, MI, Stroke, UA, or Coronary Revasc

LDL-C (mM)	Adj HR (95% CI)
<0.5	0.76 (0.64-0.90)
0.5-1.3	0.85 (0.76-0.96)
1.3-1.8	0.94 (0.82-1.09)
1.8-2.6	0.97 (0.86-1.09)
≥ 2.6	referent

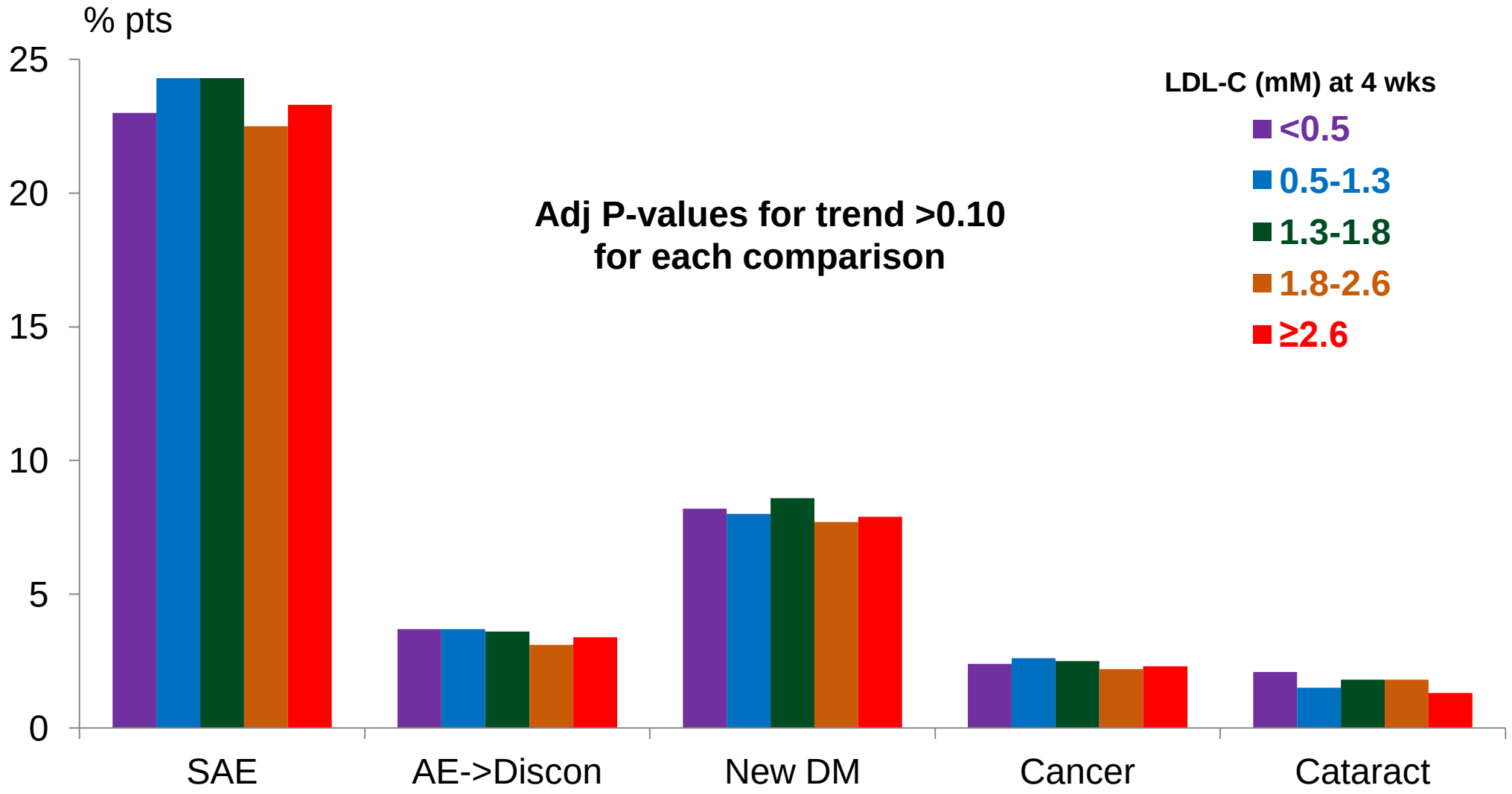


CV Death, MI, or Stroke

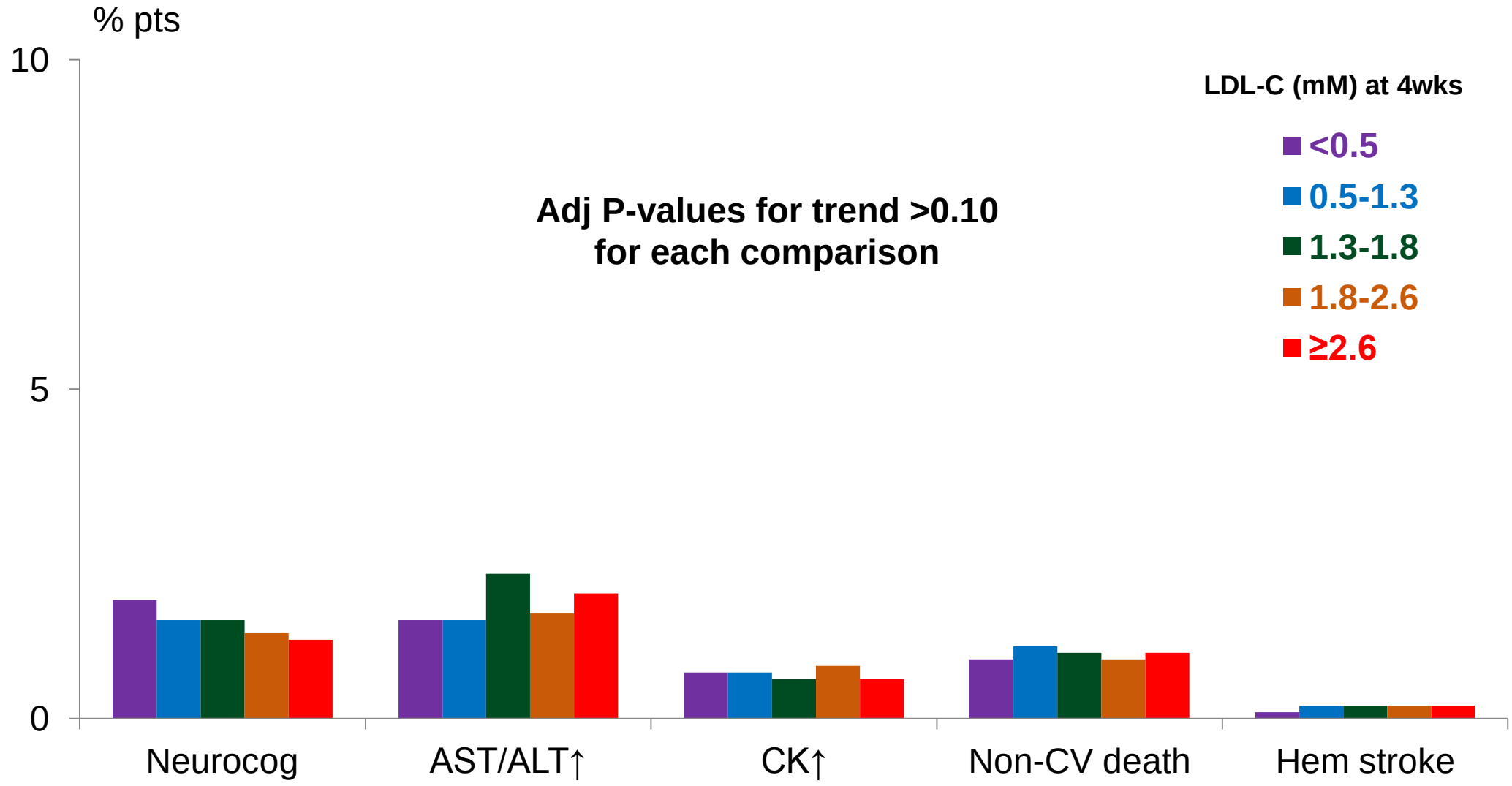
LDL-C (mM)	Adj HR (95% CI)
<0.5	0.69 (0.56-0.85)
0.5-1.3	0.75 (0.64-0.86)
1.3-1.8	0.87 (0.73-1.04)
1.8-2.6	0.90 (0.78-1.04)
≥ 2.6	referent



Safety Events - 1



Safety Events - 2



Evaluation of Cognition

CANTAB Tests	Adj P_{trend}
Executive function	0.11
Working memory	0.61
Episodic memory	0.61
Reaction Time	0.47
Global Score	**0.30**

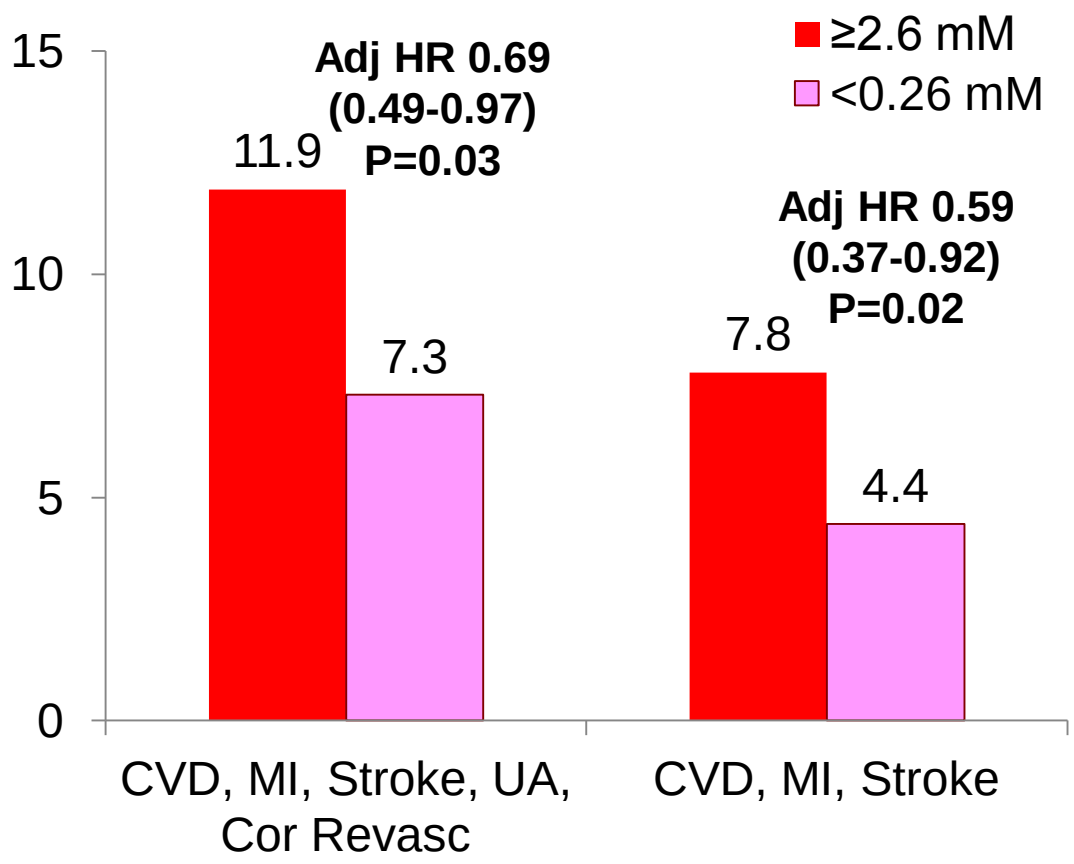
Everyday Cognition Self Survey	Adj P_{trend}
Memory	0.11
Executive function	0.12
Planning	0.27
Organization	0.98
Divided attention	0.038
Total Score	**0.017**

Better scores at lower achieved LDL-C

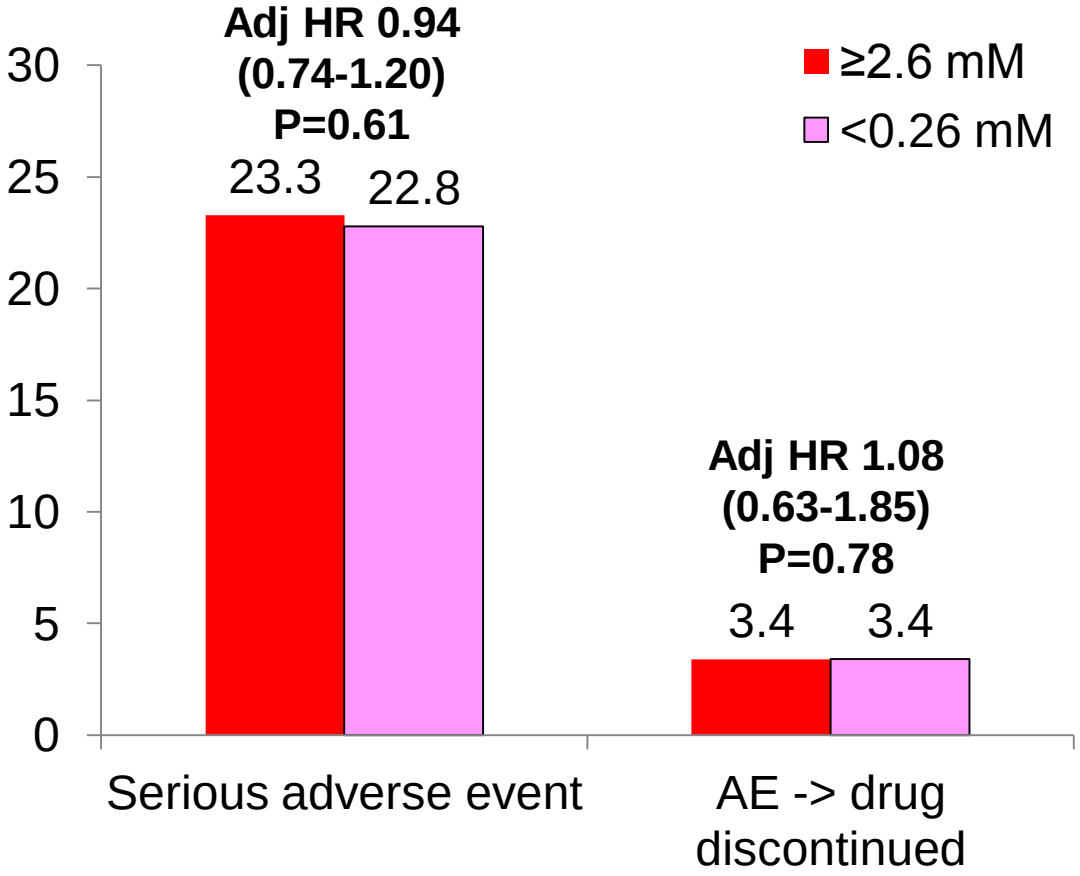
Exploratory Analysis Pts with LDL-C <0.26 mM (<10 mg/dL) at 4 wks

N=504: Median [IQR] LDL-C 0.18 [0.13-0.23] mM = 7 [5-9] mg/dL

Cardiovascular Efficacy



Safety



Conclusions

- LDL-C can now be reduced to unprecedented low levels with statin + PCSK9i (<< 1 mM)
- A strong progressive relationship of achieved LDL-C and CV events seen, down to LDL <0.26 mM (<10 mg/dL)
- No excess in safety events with very low achieved LDL-C <0.5 mM (<20 mg/dL) at 2.2 years

These data suggest that we should target considerably lower LDL-C than is currently recommended for our patients with atherosclerotic CV disease

Further Details

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Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial

Robert P Giugliano, Terje R Pedersen, Jeong-Gun Park, Gaetano M De Ferrari, Zbigniew A Gaciong, Richard Ceska, Kalman Toth, Ioanna Gouni-Berthold, Jose Lopez-Miranda, François Schiele, François Mach, Brian R Ott, Estella Kanevsky, Armando Lira Pineda, Ransi Somaratne, Scott M Wasserman, Anthony C Keech, Peter S Sever, Marc S Sabatine, on behalf of the FOURIER Investigators

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