



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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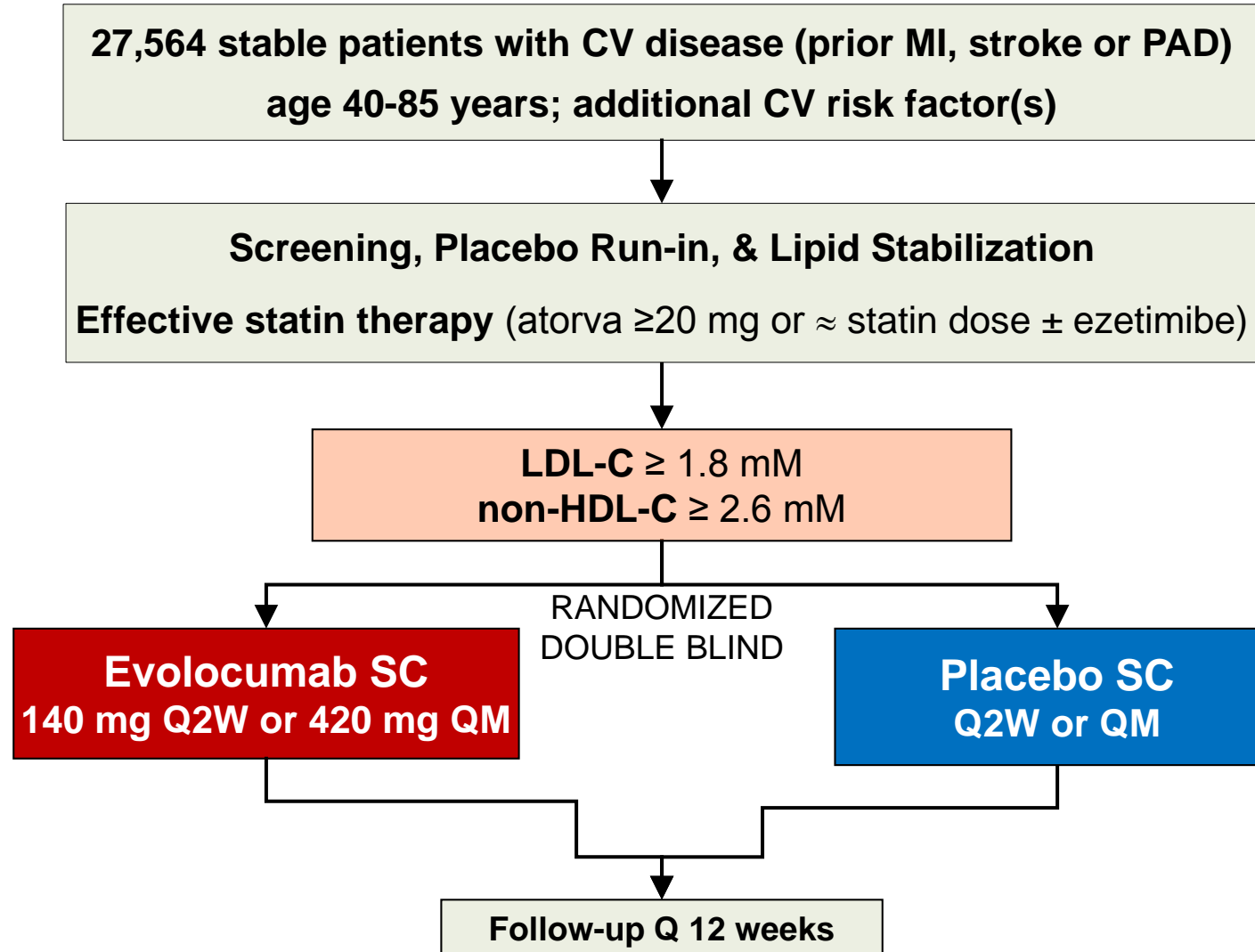
Declaration of interest

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





Trial Design

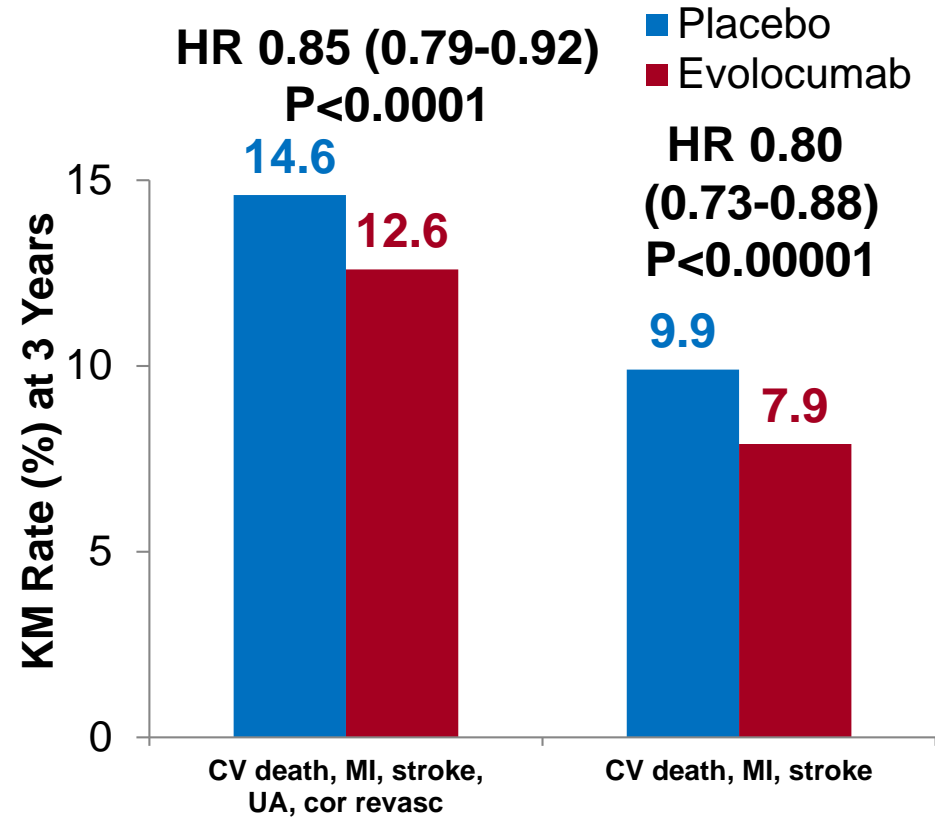
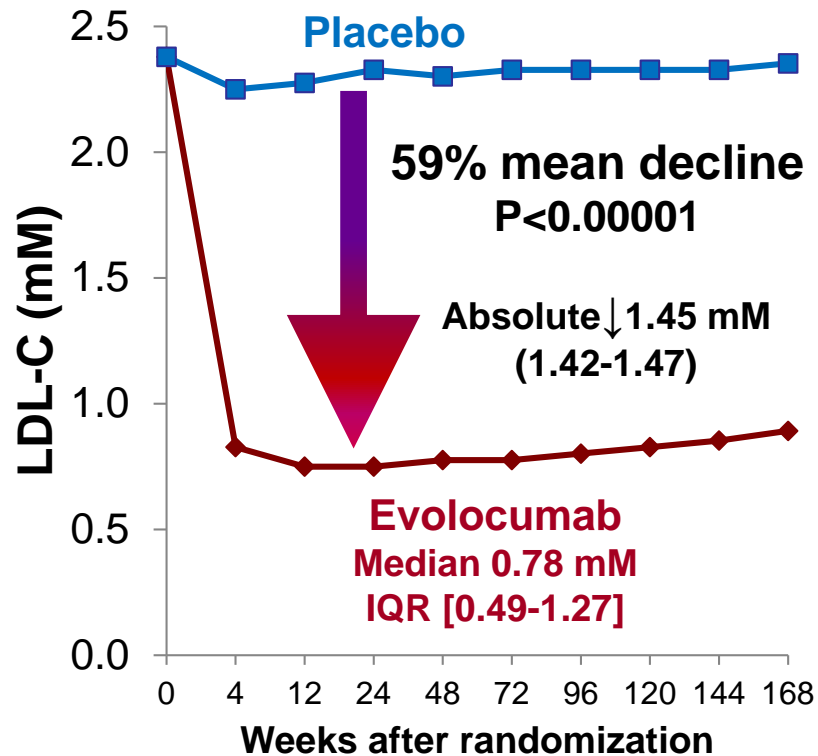




Summary of FOURIER



- ↓ 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





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) <0.5 mM (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

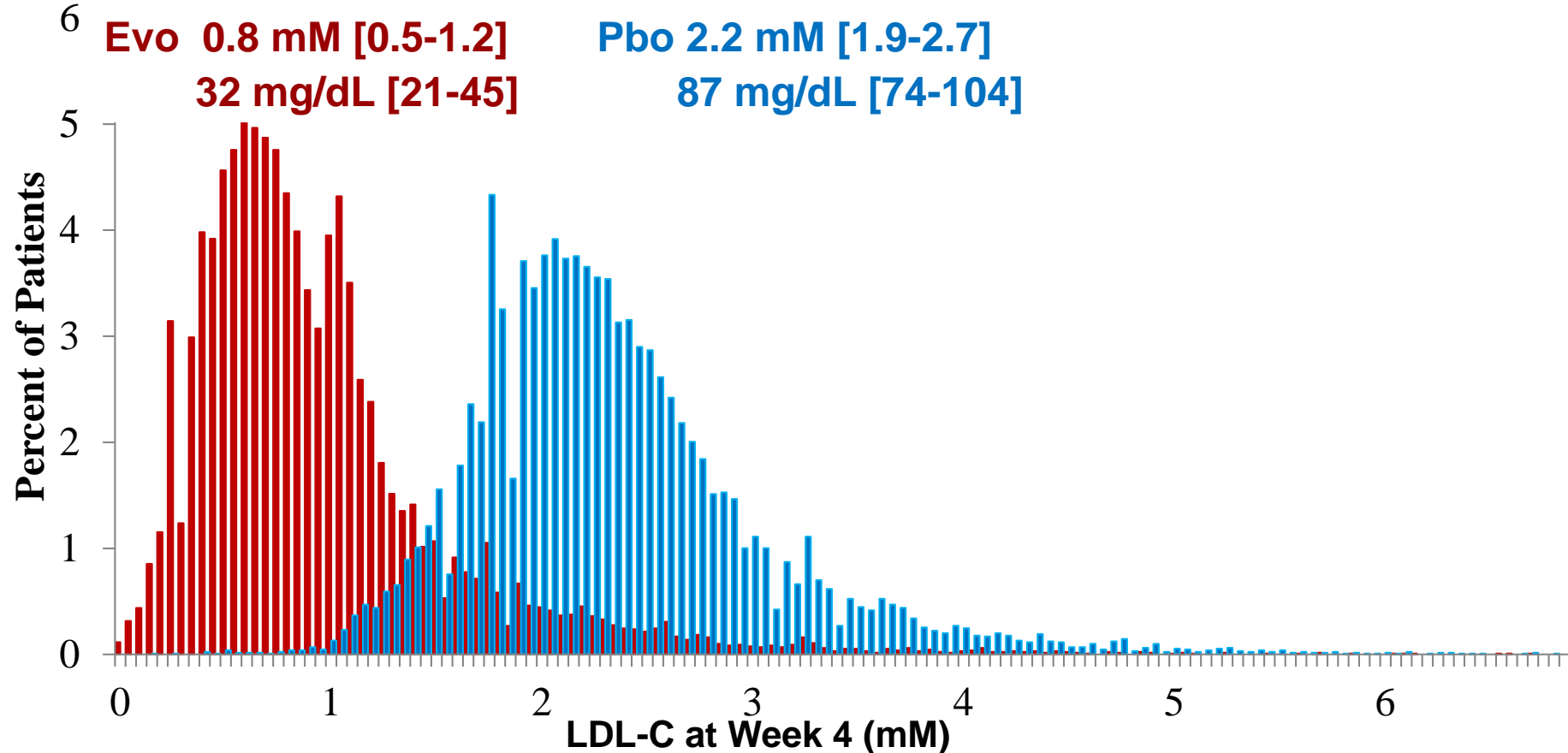
- Prespecified 1° and 2° efficacy composite endpoints
- 10 safety adverse events evaluated:
 - Serious AE
 - Cancer
 - Hem stroke
 - New onset diabetes (adjudicated by CEC)
 - AE->drug discon
 - cataracts AEs
 - Neurocognitive
 - AST/ALT>3x
 - CK > 5x ULN
 - Non-CV death
- Cognition¹ assessed using CANTAB tool and pt survey of everyday cognition (ECog)





Achieved LDL-C at 4 Weeks

Median [IQR] LDL-C at 4 Weeks



LDL (mM)	<0.5	0.5-1.3	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

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





Lipids and Lipid Rx at Randomization

Achieved LDL-C in mM at 4 Weeks

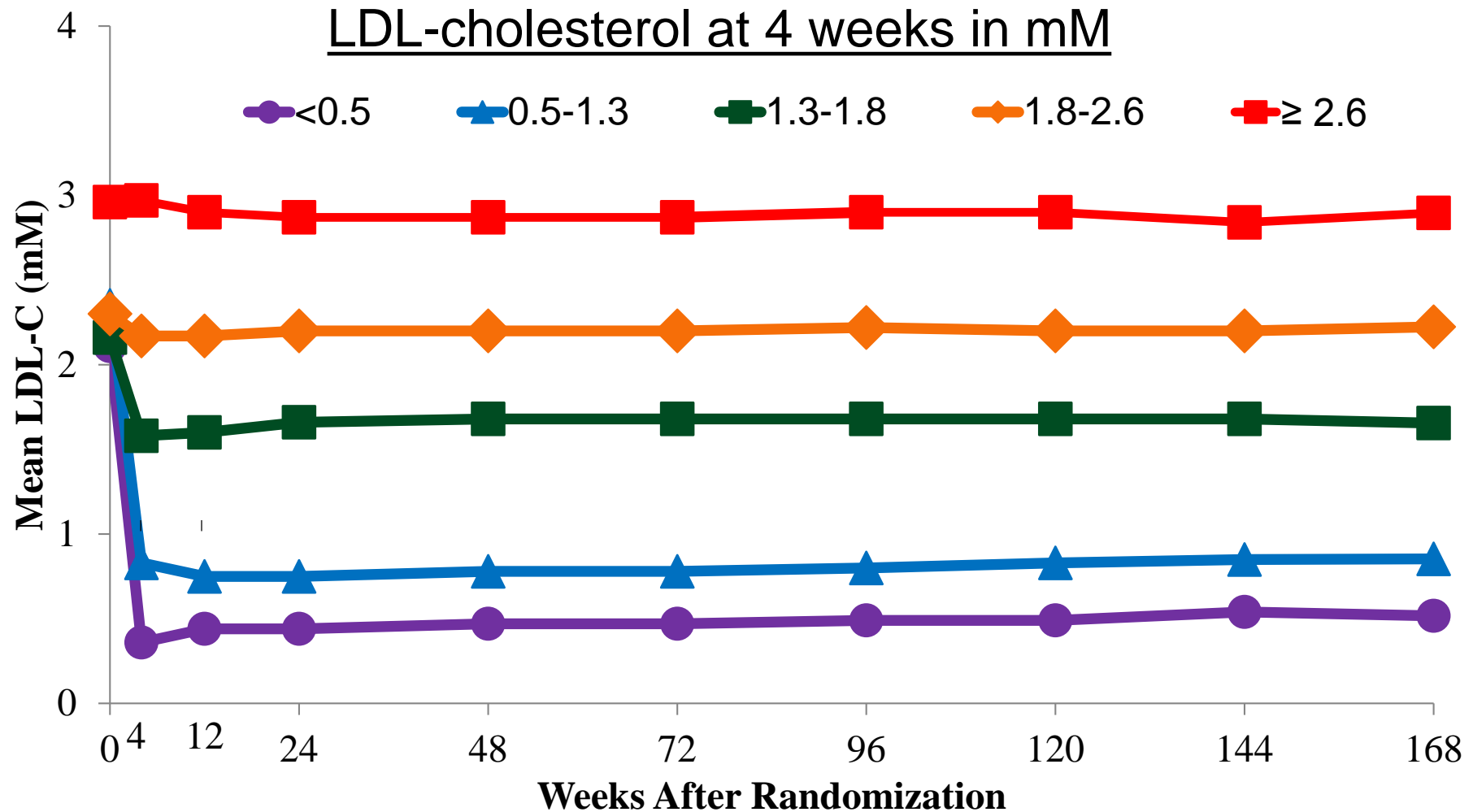
At Randomization	<0.5 (N=2669)	0.5-1.3 (N=8003)	1.3-1.8 (N=3444)	1.8-2.6 (N=7471)	≥2.6 (N=4395)
Median Lipid values					
LDL-C, mM	2.1	2.4	2.2	2.3	3.0
Total cholesterol, mM	4.0	4.3	4.2	4.2	5.0
Triglycerides, mM	1.5	1.5	1.6	1.4	1.6
HDL-C, mM	1.1	1.1	1.1	1.1	1.2
Lipoprotein (a), nM	22	43	32	37	48
High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

P_{trend} ≤0.0001 for each



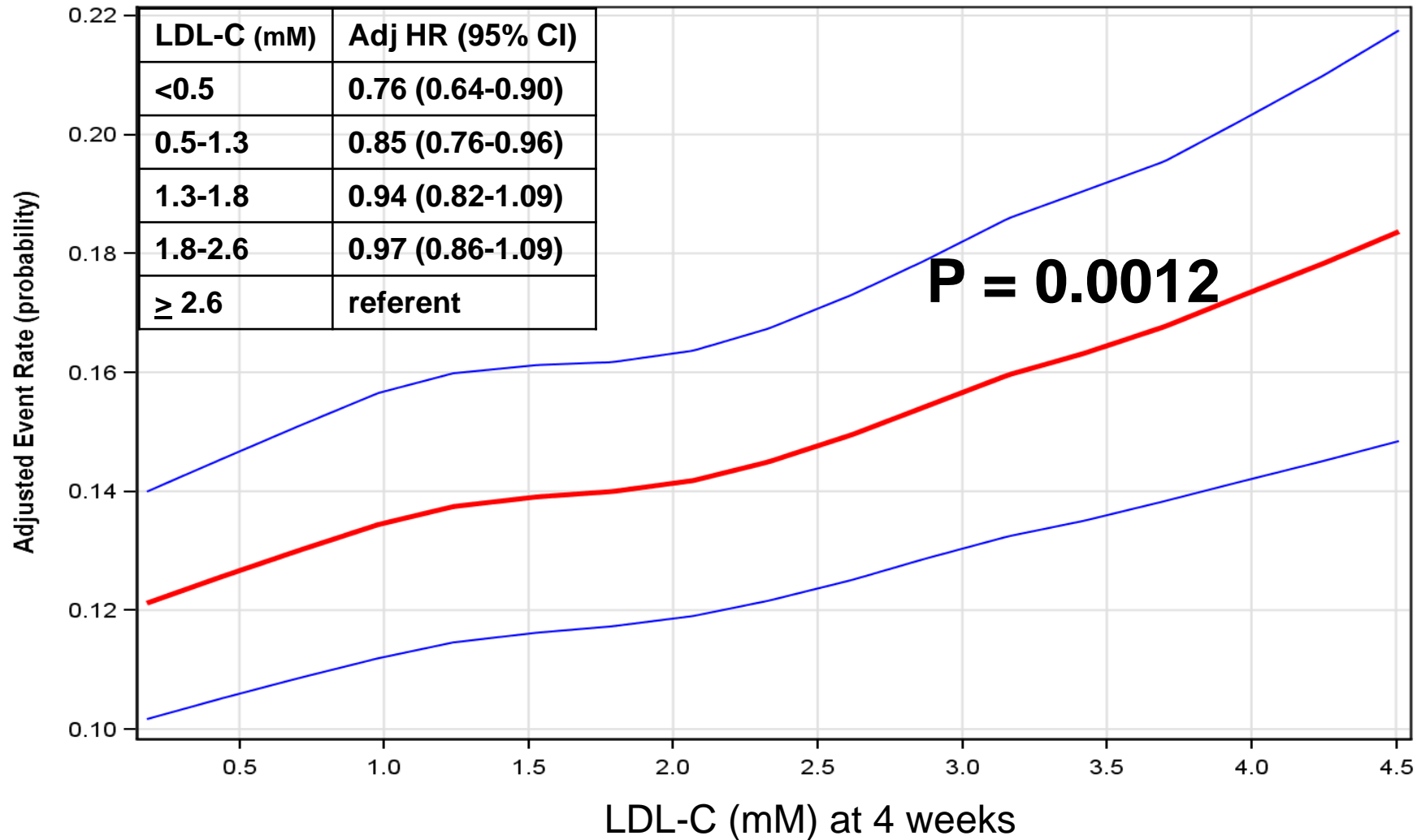


LDL-C Over Time



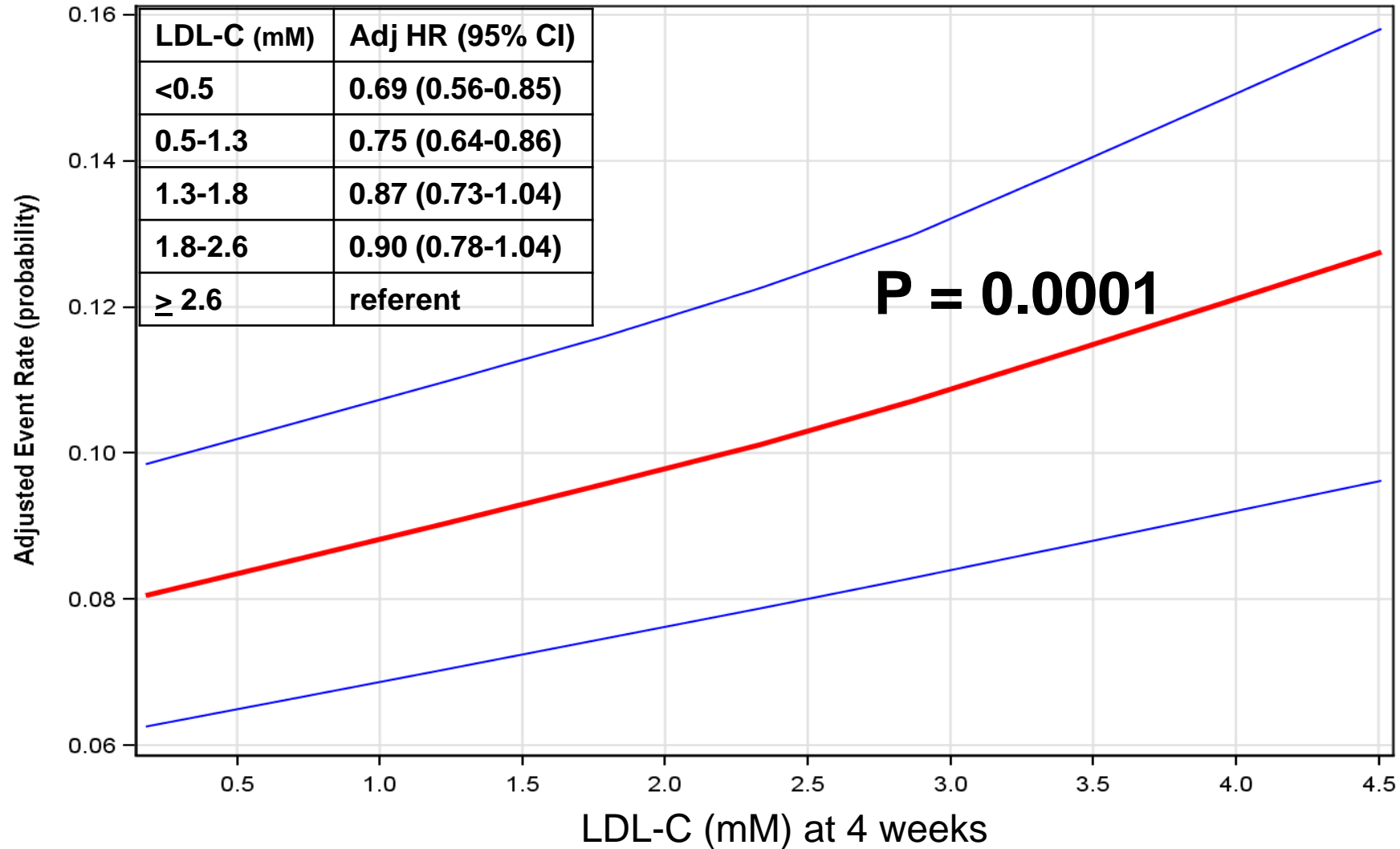


CV Death, MI, Stroke, UA, or Coronary Revasc



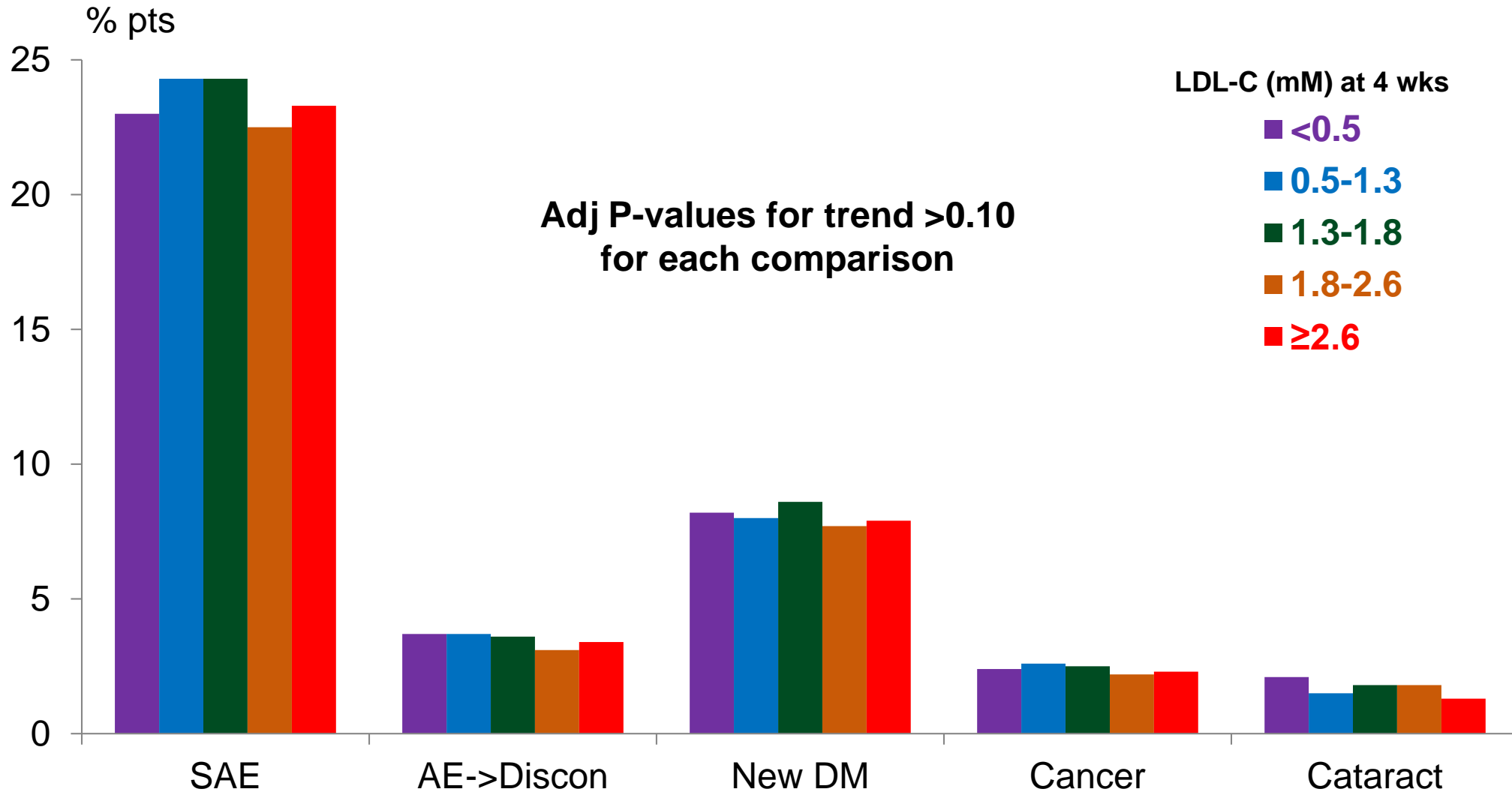


CV Death, MI, or Stroke



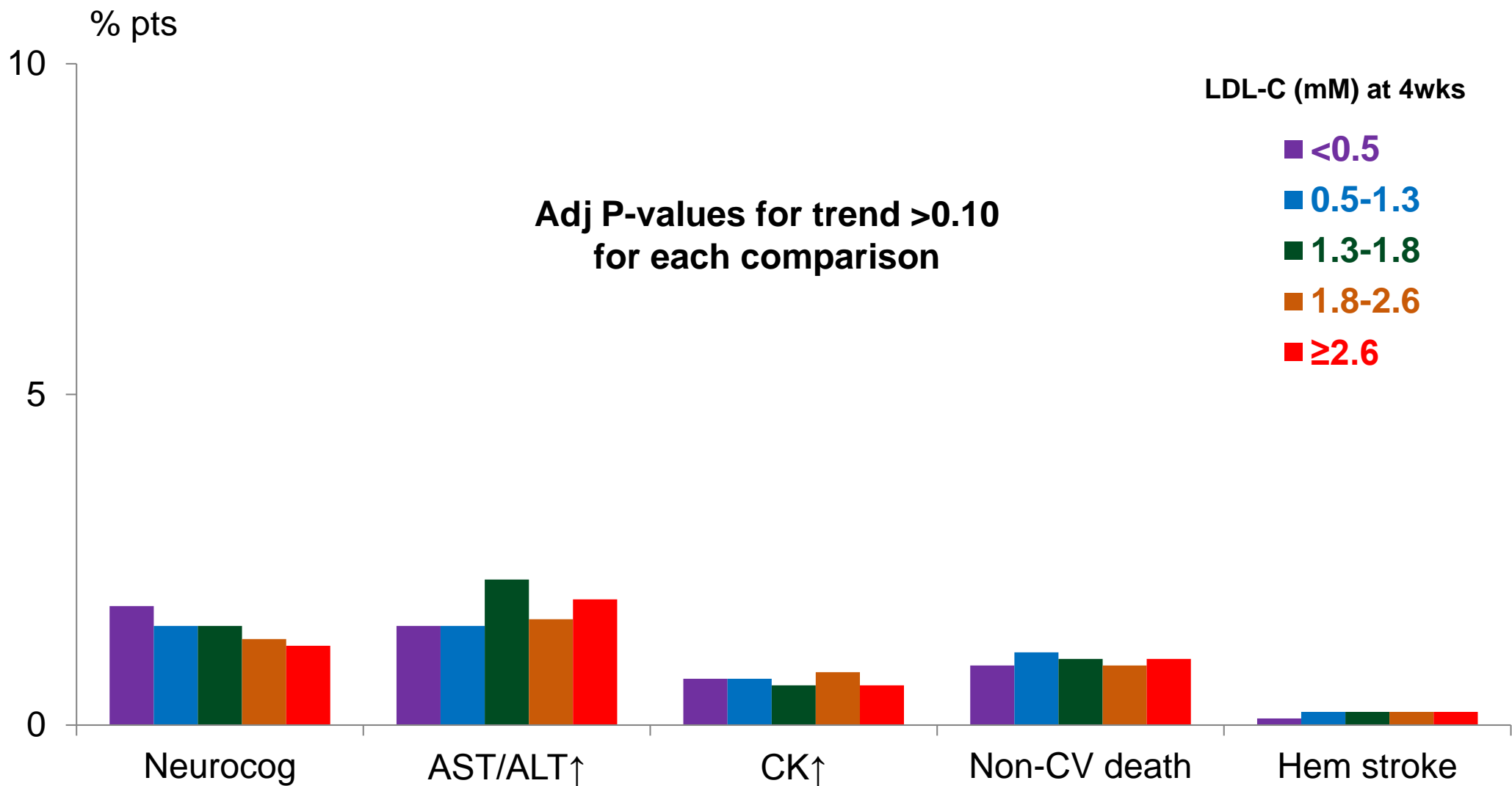


Safety Events - 1





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

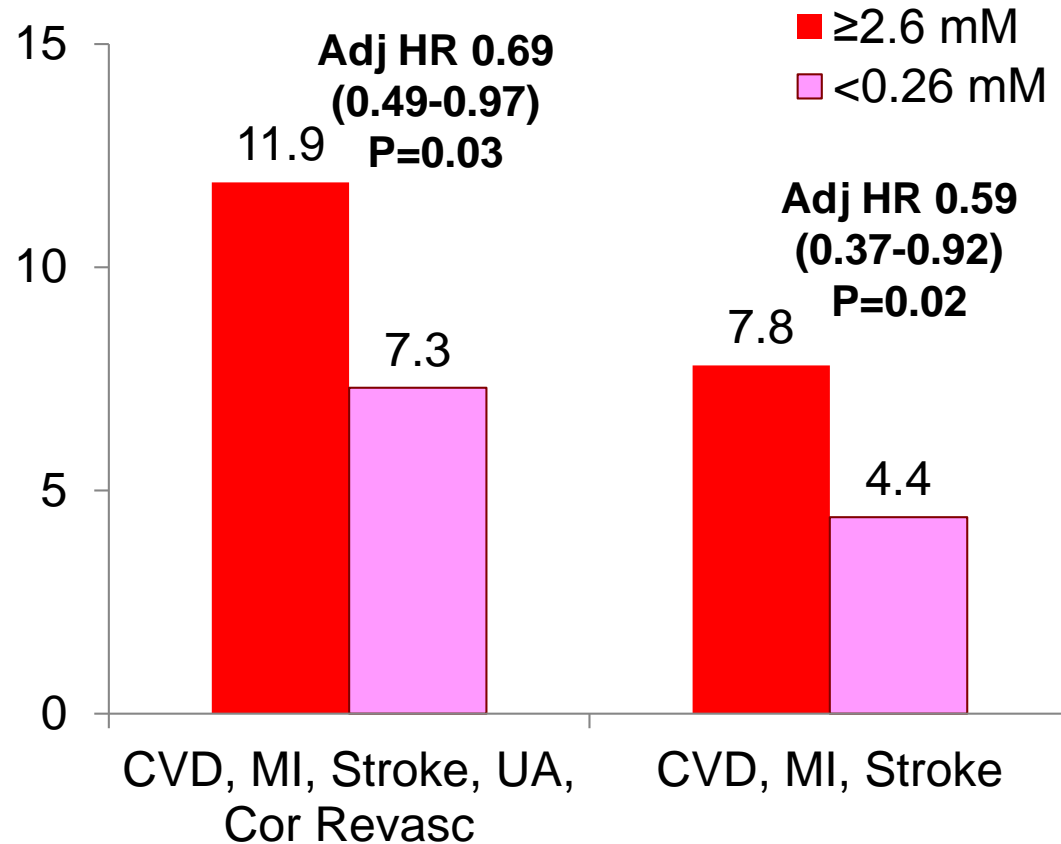




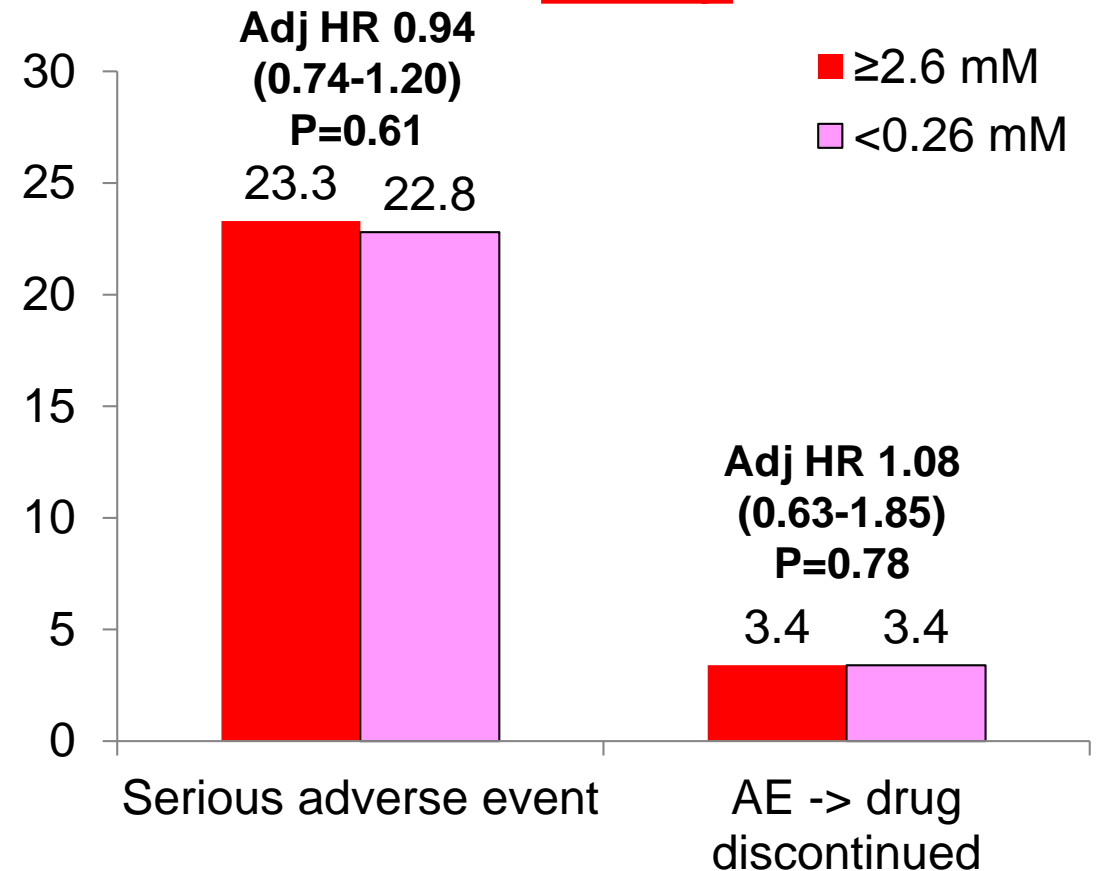
Exploratory Analysis Pts with LDL-C <math><0.26\text{ mM}</math> (<math><10\text{ mg/dL}</math>) at 4 wks

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 ($\ll 1$ 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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