Cardiovascular Efficacy of Evolocumab in Patients with Obesity:

Updates from The FOURIER Trial

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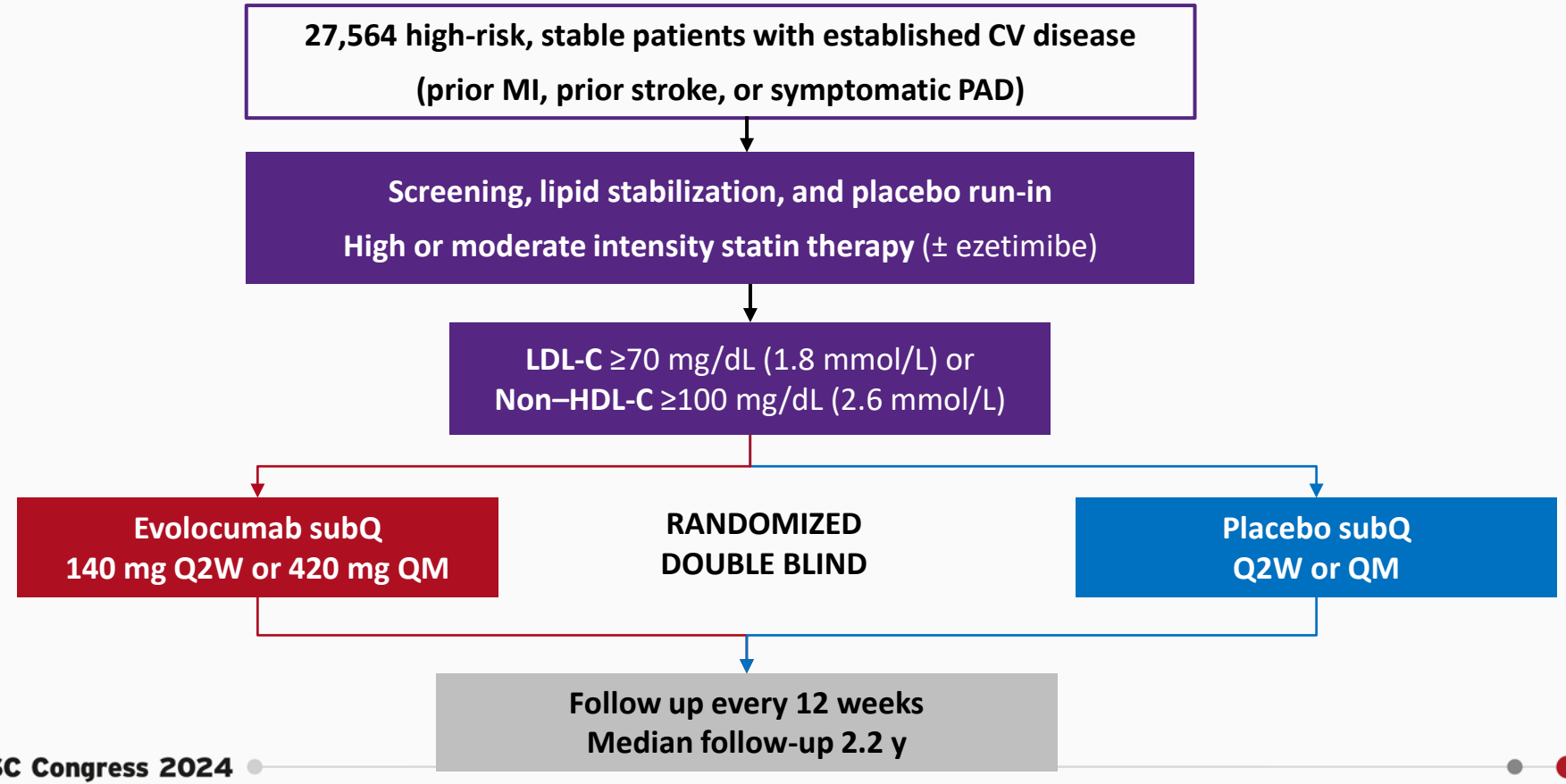
Background

- As of 2022, 1.9 billion adults are living with obesity globally.
- The PCSK9 inhibitor, evolocumab, markedly reduces LDL-C levels and lowers the risk of major adverse cardiovascular events (MACE).
- However, the efficacy of PCSK9 inhibitors in individuals across the range of baseline body mass index (BMI) remains understudied.

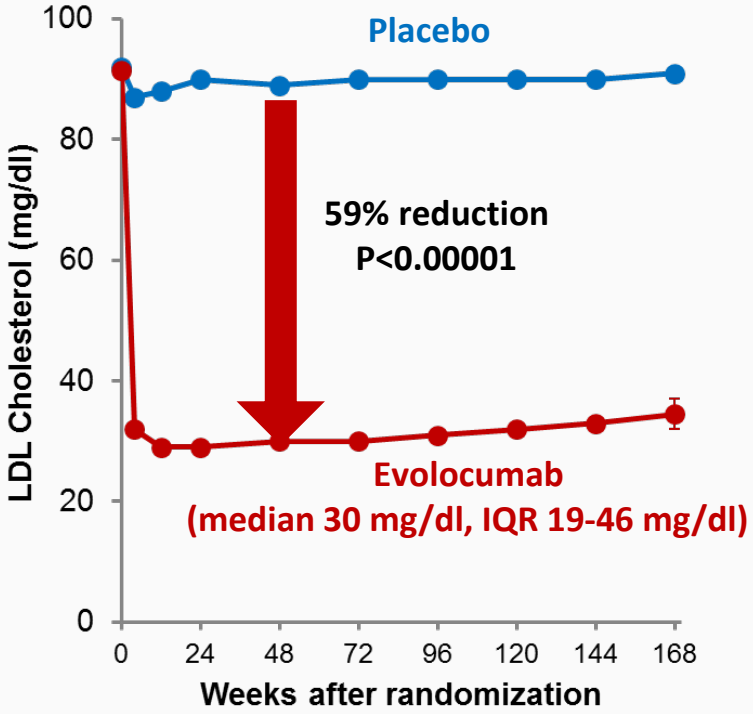
We aimed to investigate the efficacy of evolocumab by baseline BMI

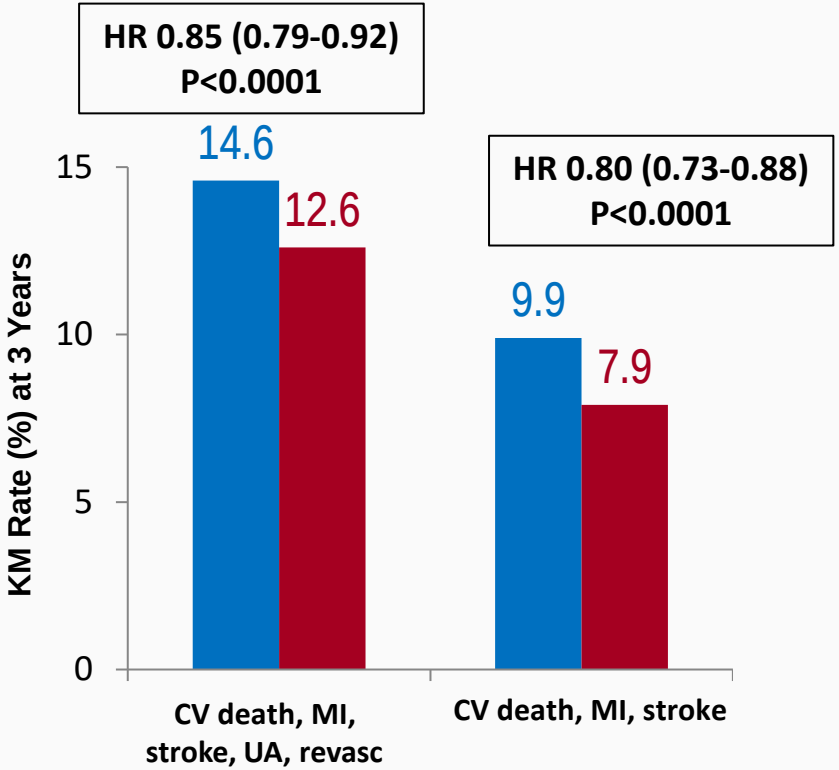
Trial Design



Efficacy of Evolocumab on MACE

27,564 Pts w/ prior MI, stroke or PAD on optimized statin therapy





Sabatine MS et al. *NEJM* 2017;376:1713-22

Methods

- The primary endpoint (PEP) was CV death, MI, stroke, hospitalization for UA, or coronary revascularization; the key secondary EP (SEP) was CV death, MI or stroke.
- The association between BMI and CV risk was examined in the placebo arm adjusting for clinical characteristics including baseline LDL cholesterol.
- The interaction between BMI and the effect of evolocumab on outcomes was assessed; Kaplan-Meier rates are reported at 3 years.
- BMI was modeled both as a continuous and as a categorical variable.

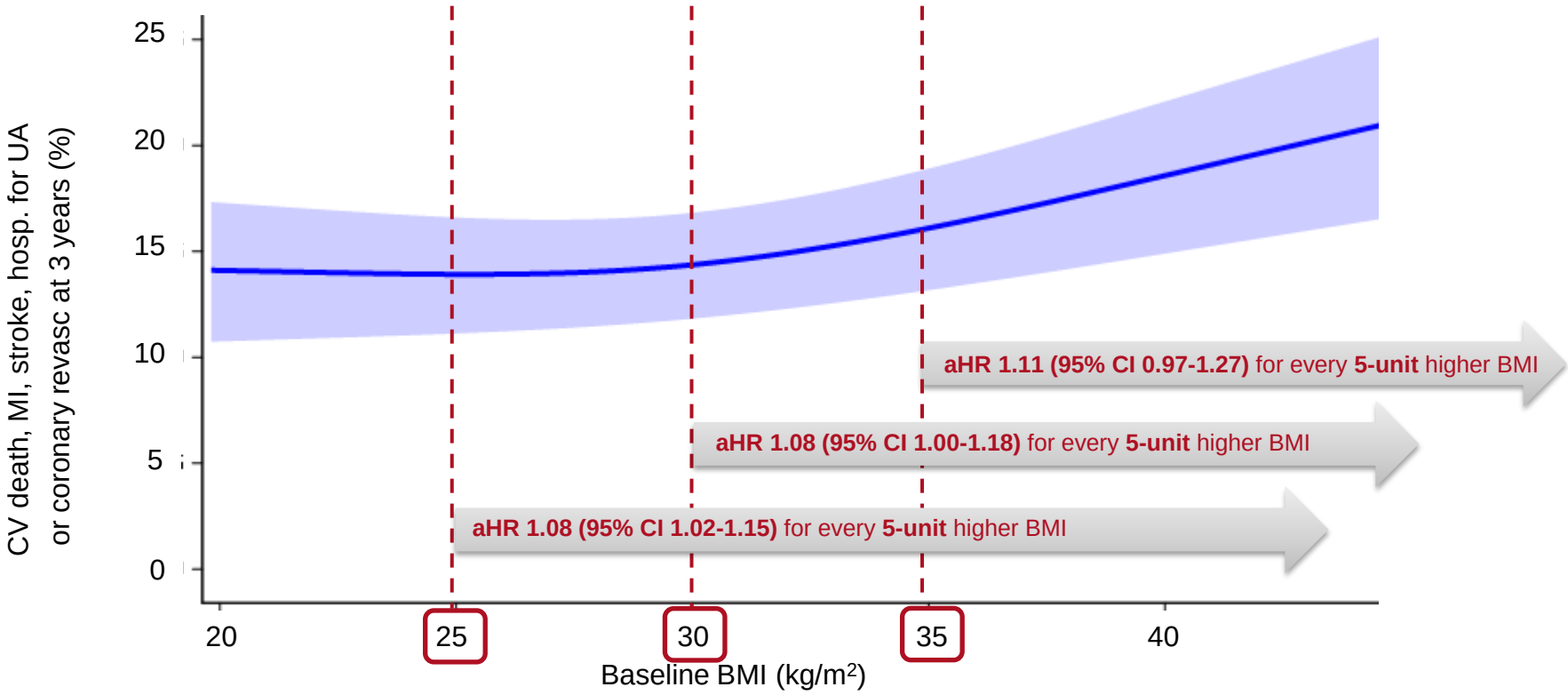
Baseline Characteristics

Characteristic	BMI Categories (kg/m²) BMI <25.0 N=5,012 (18%)	BMI 25.0-29.9 N=11,546 (42%)	BMI 30-34.9 N=7,496 (27%)	BMI ≥35 N=3,446 (13%)
Age (years)	64	64	62	60
Male	72%	80%	76%	65%
Region				
Asia Pacific	26%	14%	9%	7%
Europe	55%	66%	67%	57%
Latin America	7%	7%	6%	5%
North America	11%	14%	18%	31%
Prior coronary artery disease	83%	87%	87%	86%
Diabetes mellitus	25%	32%	43%	55%
Multivessel disease	21%	22%	22%	23%
High-intensity statin use	62%	69%	72%	74%
Baseline LDL-C (mg/dL)	92	92	92	91
Baseline lipoprotein(a) (nmol/L)	42	37	34	35
Baseline hsCRP (mg/L)	1.3	1.5	2.0	2.9

Continuous variables are presented as the median, and categorical variables are expressed as proportions (%).

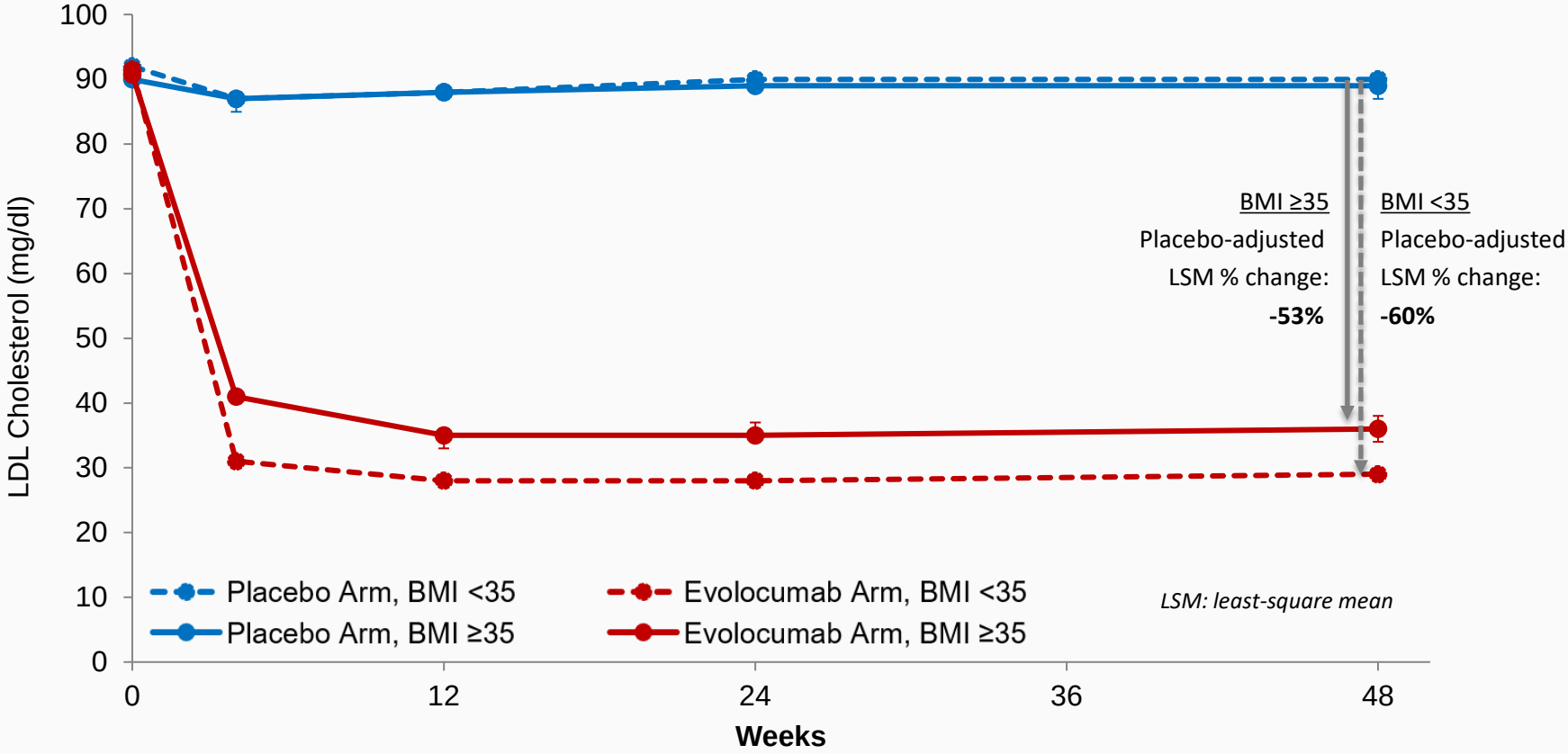
P-Trend < 0.01 for all characteristics displayed except multivessel disease.

Risk of MACE by Baseline BMI in Placebo Arm



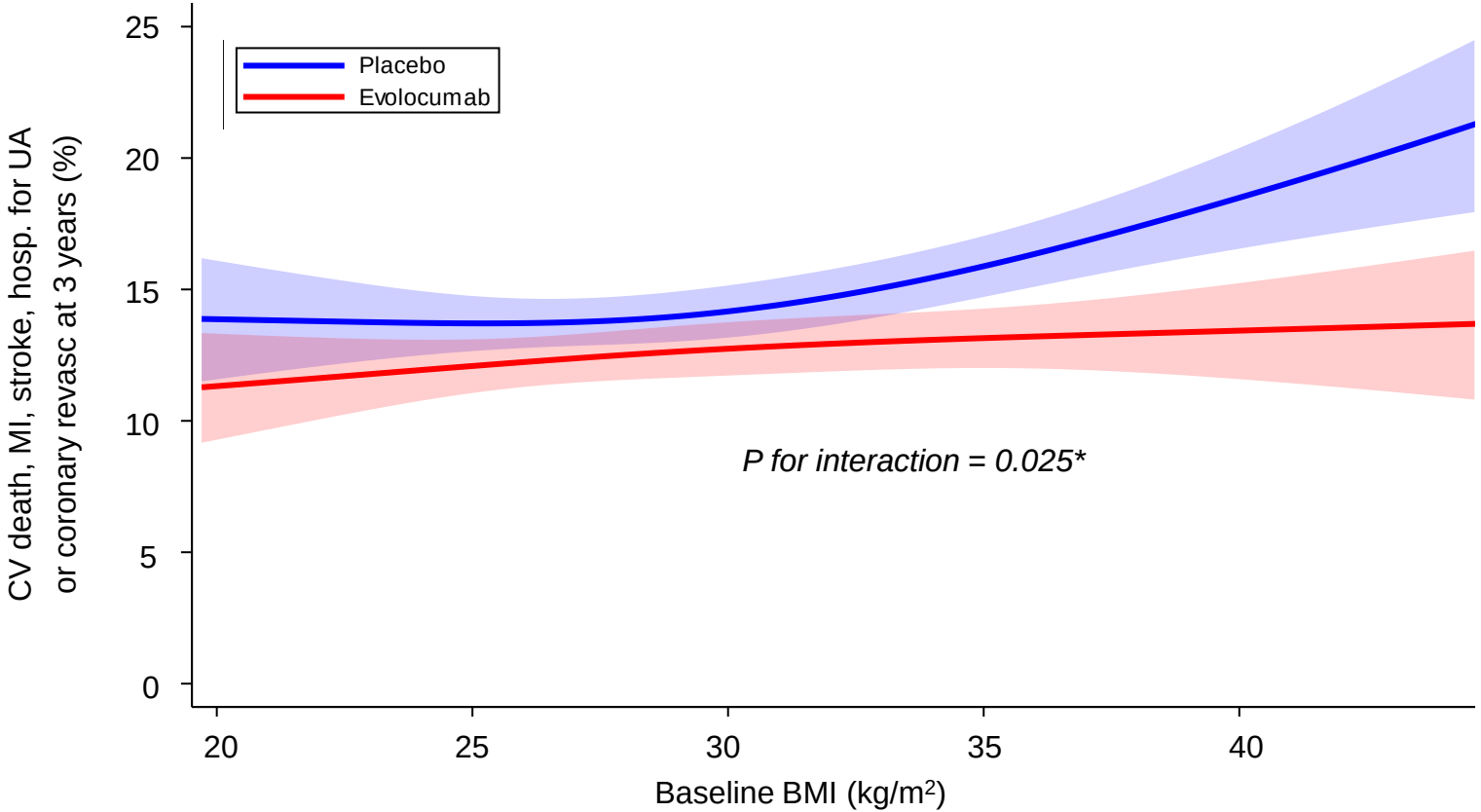
**Adjusted for age, sex, smoking status, diabetes mellitus, hypertension, high-intensity statin use, baseline LDL-C, eGFR and geographic region*

Changes in LDL-C with Evolocumab by Baseline BMI



Efficacy of Evolocumab by Baseline BMI

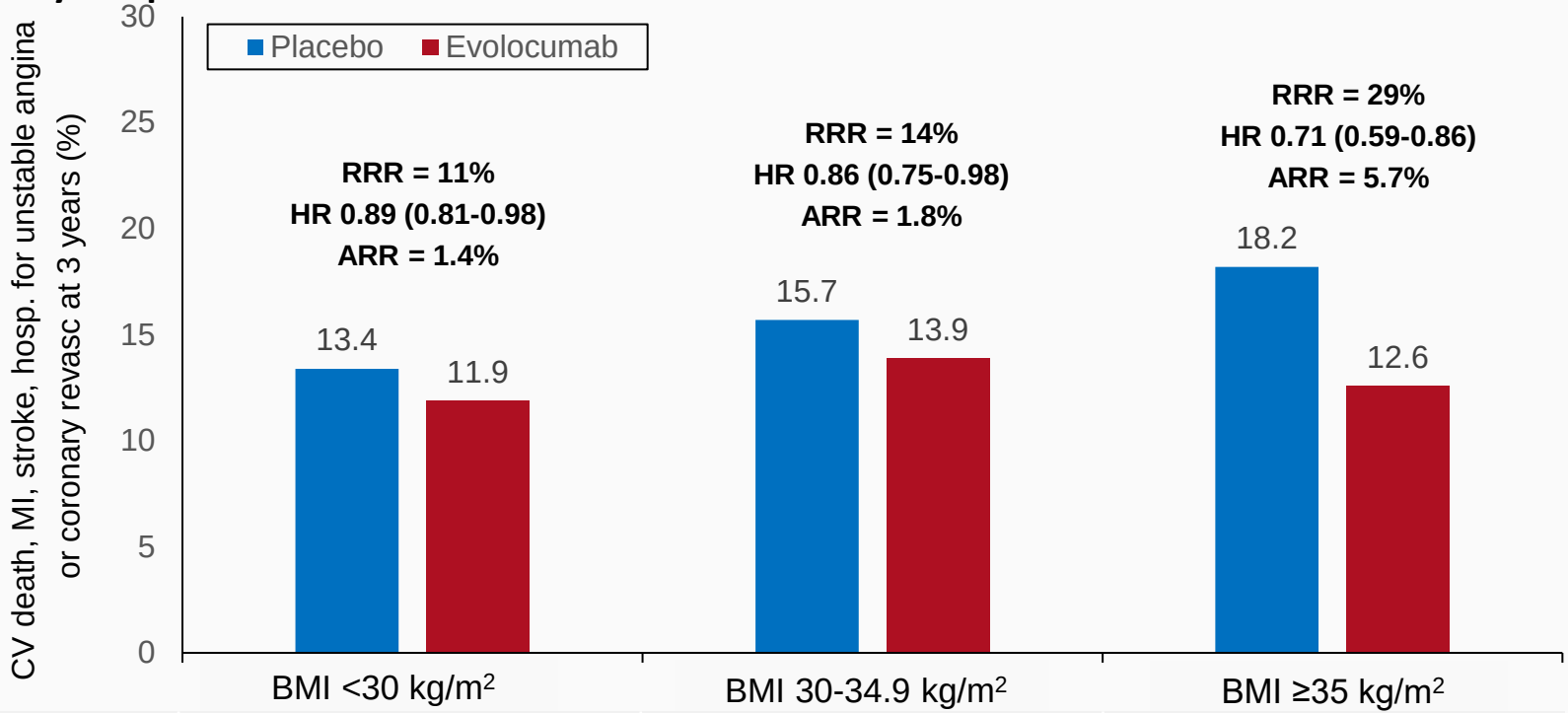
Primary endpoint



*Interaction per 5 unit increase in BMI above 30 kg/m²

Efficacy of Evolocumab by Baseline BMI

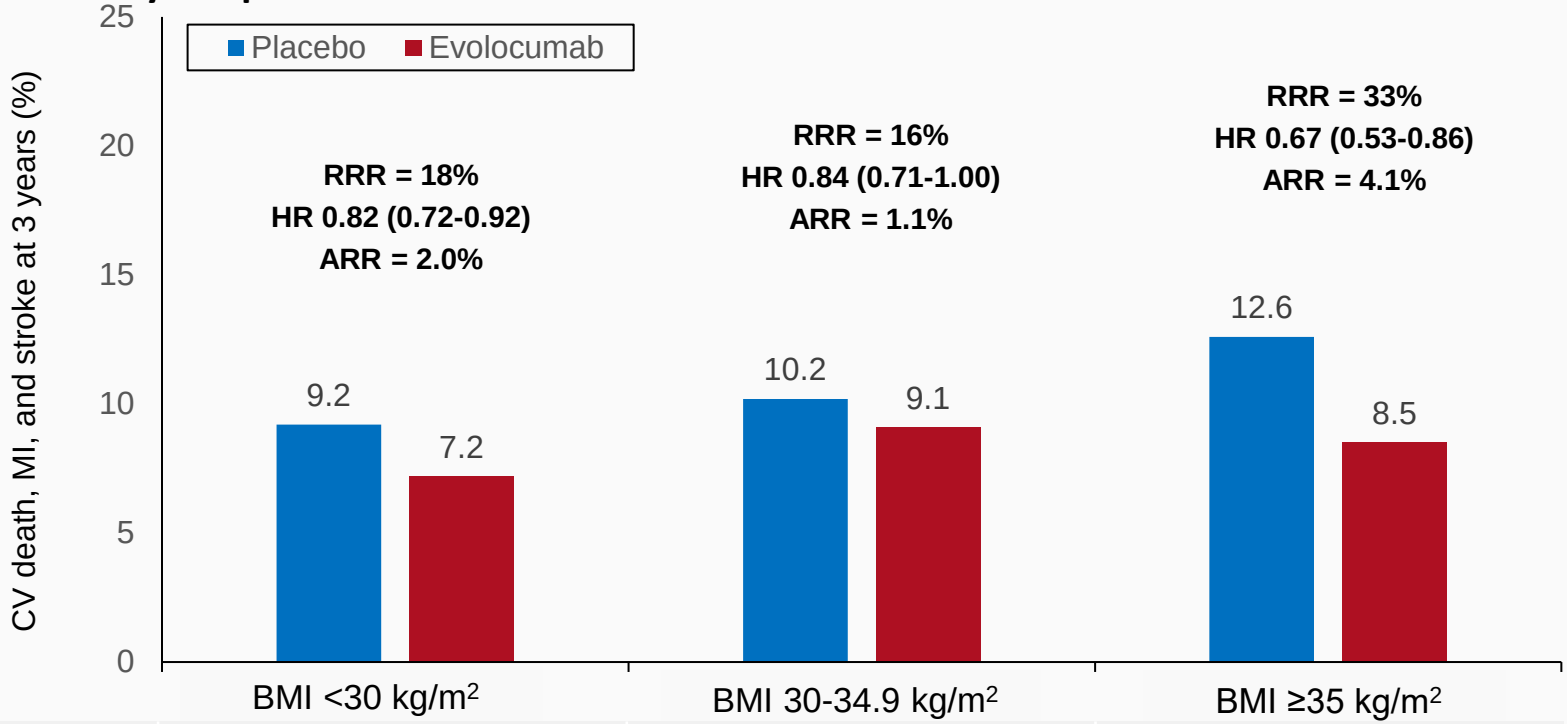
Primary endpoint



N (%) at risk	16558 (60%)	7496 (27%)	3446 (13%)

Efficacy of Evolocumab by Baseline BMI

Key secondary endpoint



N (%) at risk	16558 (60%)	7496 (27%)	3446 (13%)

Limitations

- As with all subgroup analyses, the possibility of type 1 error cannot be completely excluded
- Visceral or ectopic adiposity were not assessed

Conclusions

- Individuals with obesity and ASCVD are at increased risk of MACE.
- The clinical efficacy of evolocumab appears to be more pronounced in patients with obesity (particularly class 2 or 3 obesity).
- Therefore, intensive LDL-C control should be strongly considered in individuals with obesity to help mitigate their high CV risk.
- Further investigation is needed to understand the mechanisms by which those with obesity may derive enhanced benefit from PCSK9 inhibition with evolocumab.