



EAS 94th Congress

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Lipoprotein(a) Levels, Risk of Cardiovascular Events and Benefit of Evolocumab Findings From the VESALIUS-CV TIMI 66 Trial

Dr Victorien Monguillon, on behalf of VESALIUS-CV investigators

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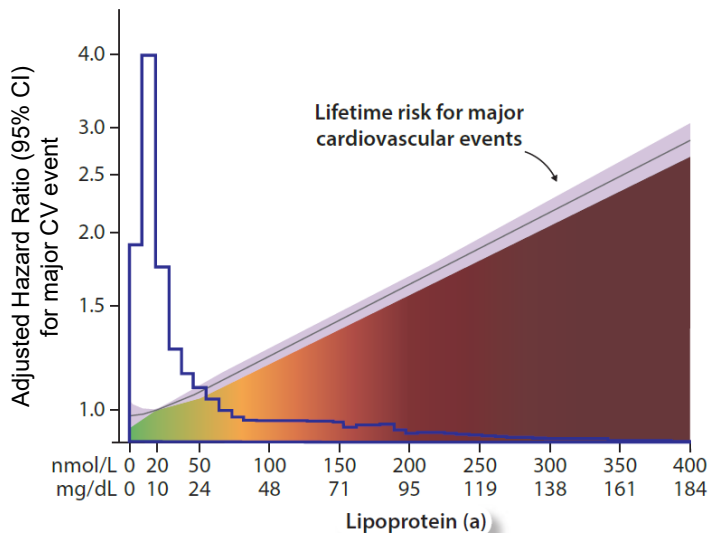


Disclosure

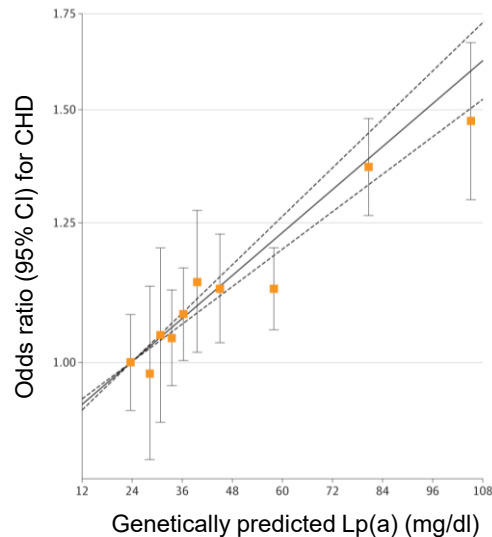
- Dr. Victorien Monguillon has received grant funding from Federation Francaise de Cardiologie and Action Study Group.
- The VESALIUS-CV trial was funded by Amgen Inc (NCT03872401)



Lp(a) is associated with increased CV risk



Genetic and Mendelian randomization studies support a causal role for Lp(a) in coronary heart disease



Recommendations for Lp(a) Testing

- European and US dyslipidemia guidelines now endorse measurement of Lp(a) at least once in all adults
- Questions remain about whether Lp(a) may help identify those who benefit from more intensive lipid-lowering therapy
- Statins do not lower Lp(a) levels, whereas PCSK9i reduce levels by ~25%

2025 ESC/EAS Dyslipidemia Guidelines

Recommendations	Class ^a	Level ^b
Lp(a) levels above 50 mg/dL (105 nmol/L) should be considered in all adults as a CV risk-enhancing factor, with higher Lp(a) levels associated with a greater increase in risk. ^{37,101}	IIa	B

2026 ACC/AHA Dyslipidemia Guidelines

1	B-NR
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1. In all individuals with elevated Lp(a) (≥ 125 nmol/L or ≥ 50 mg/dL), optimal early control of modifiable cardiovascular risk factors is recommended to reduce ASCVD risk.¹⁻⁴



VESALIUS-CV Trial Design

Median f/up
≥ 4.5yrs

Stable patients at high-risk for CV events
but no prior MI or stroke* (N = 12,257)

LDL-C ≥ 90 mg/dL (2.3 mmol/L or
non-HDL-C ≥ 120 mg/dL or
ApoB ≥ 80mg/dL

On optimized statin therapy (± ezetimibe)

- * ≥1 of the following
- CAD without MI
 - CVD without stroke
 - PAD
 - High-risk diabetes mellitus

Evolocumab SC
140 mg Q2W

1:1
Randomization

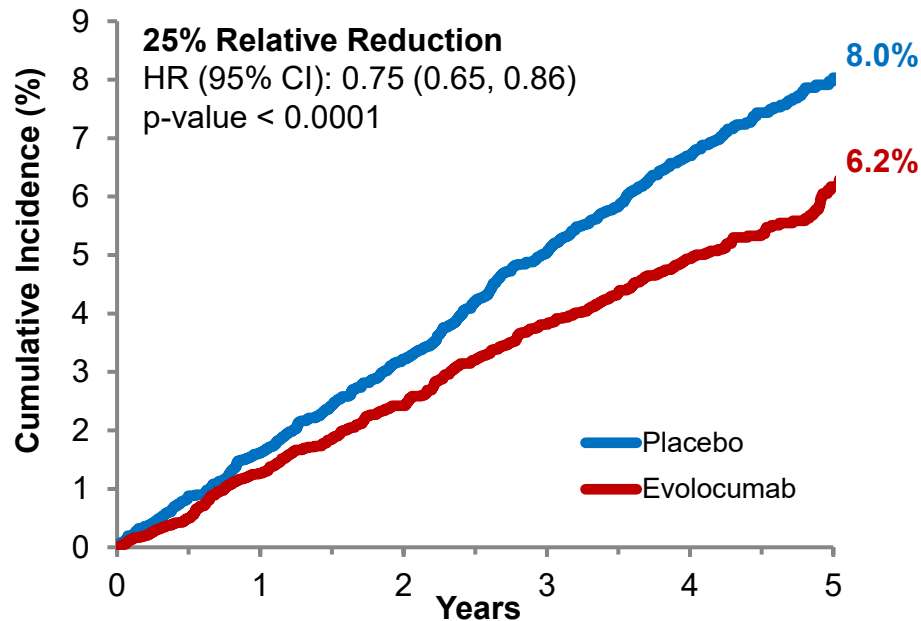
Placebo SC
Q2W

Dual primary Endpoint
3-P MACE and 4-P MACE

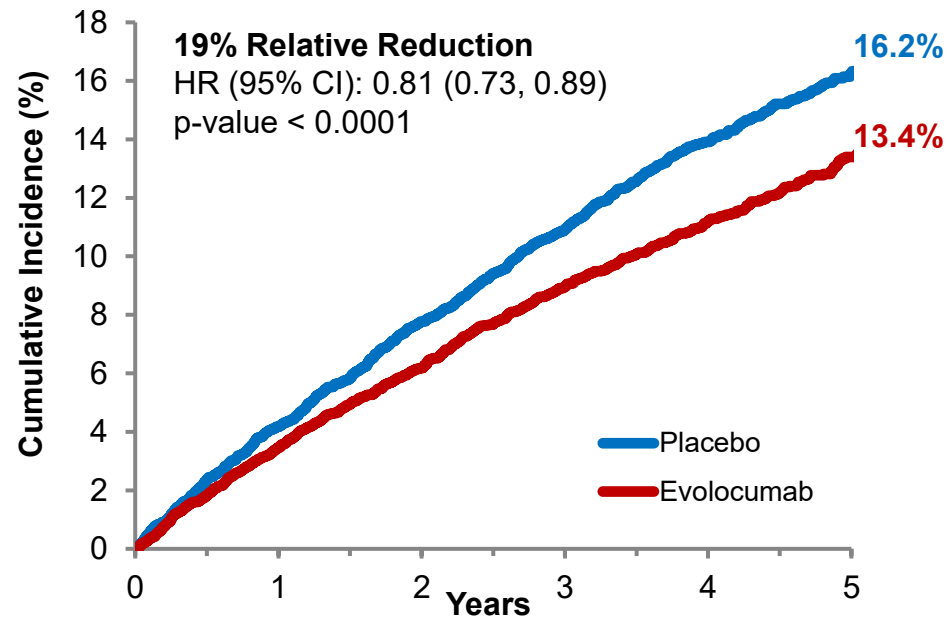


VESALIUS-CV Primary Results

3-P MACE (CHD death, MI, or ischemic stroke)



4-P MACE (CHD death, MI, ischemic stroke or IDR)



CHD: coronary heart disease, IDR: ischemia driven revascularization, MI: myocardial infarction

Objectives - Prespecified Lp(a) Substudy

1. Assess the **association between Lp(a)** and long-term risk of **cardiovascular events** in the placebo arm.
2. Evaluate the **effects of evolocumab on change in LDL-C and Lp(a)** from baseline to week 48.
3. Assess the **efficacy of evolocumab by baseline Lp(a) concentration**.



Methods - Prespecified Lp(a) Substudy

- Lp(a) was measured at baseline in 7,557 patients through central laboratories using an immunoturbidimetric assay (Roche Tina-quant Lipoprotein(a) Gen.2 and Randox)
- Lp(a) was modeled as a continuous covariate, and a dichotomous threshold of 105 nmol/L was applied consistent with ESC/EAS guidelines.

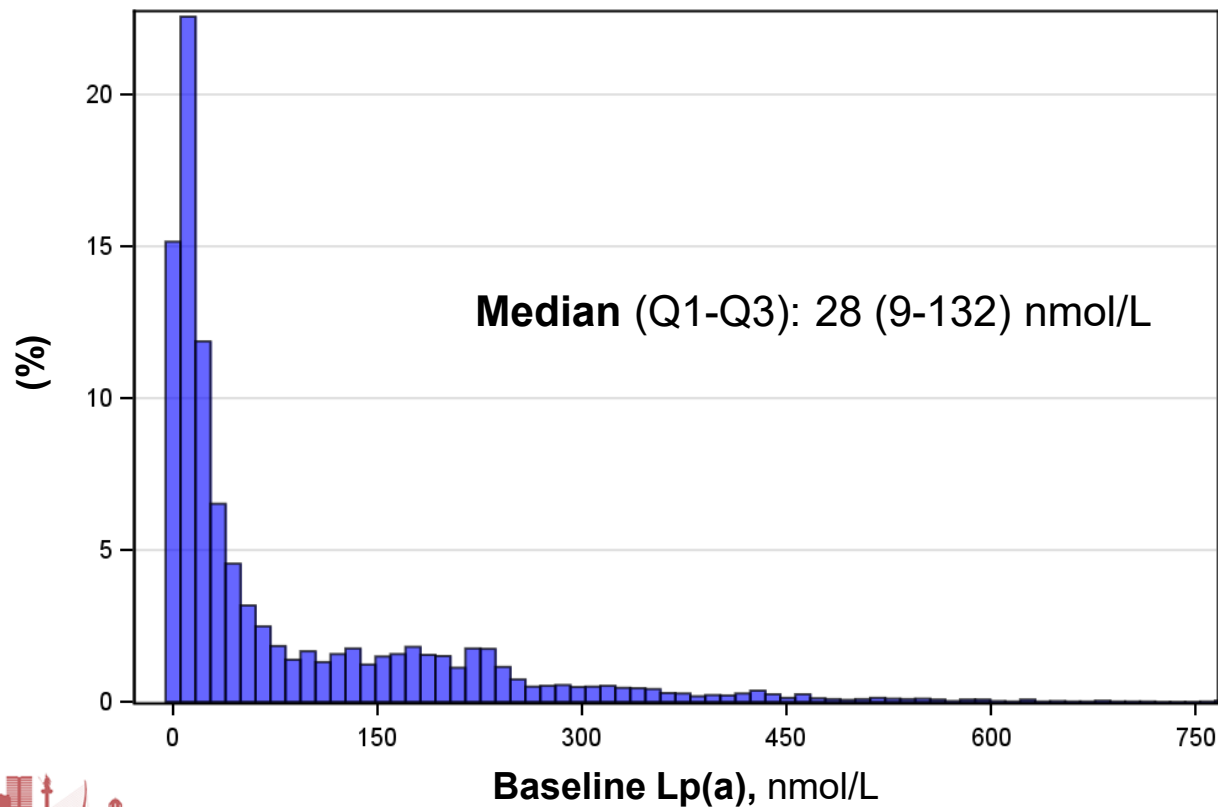


Baseline Lp(a) Distribution



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Baseline Characteristics



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	Lp(a) ≤ 105 nmol/L	Lp(a) > 105 nmol/L	p-value
	N=5391 (71%)	N=2166 (29%)	
Age, years, median	66	65	0.69
Women, %	41	47	<0.001
Race, %			
White	96	94	<0.001
Black or African American	1.1	3.6	
Asian	1.3	1.6	
Other	1.2	1.2	
BMI, kg/m², median	30.1	29.5	<0.001
Hypertension, %	87	85	0.009
Diabetes mellitus, %	62	53	<0.001
Current smoking, %	29	25	<0.001
Significant CAD, %	40	49	<0.001

BMI: body mass index; CAD: coronary artery disease



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Baseline Characteristics

	Lp(a) ≤ 105 nmol/L	Lp(a) > 105 nmol/L	
	N=5391	N=2166	p-value
<i>Lipid lowering therapies</i>			
High intensity Statin, %	66	67	0.47
Ezetimibe, %	18	22	<0.001
<i>Baseline lipids (median values)</i>			
Total cholesterol, mg/dL	203	201	0.17
LDL-C, mg/dL	122	120	0.13
Non-HDL-C, mg/dL	154	150	0.001
HDL-C, mg/dL	47	49	<0.001

LLT: lipid lowering therapies

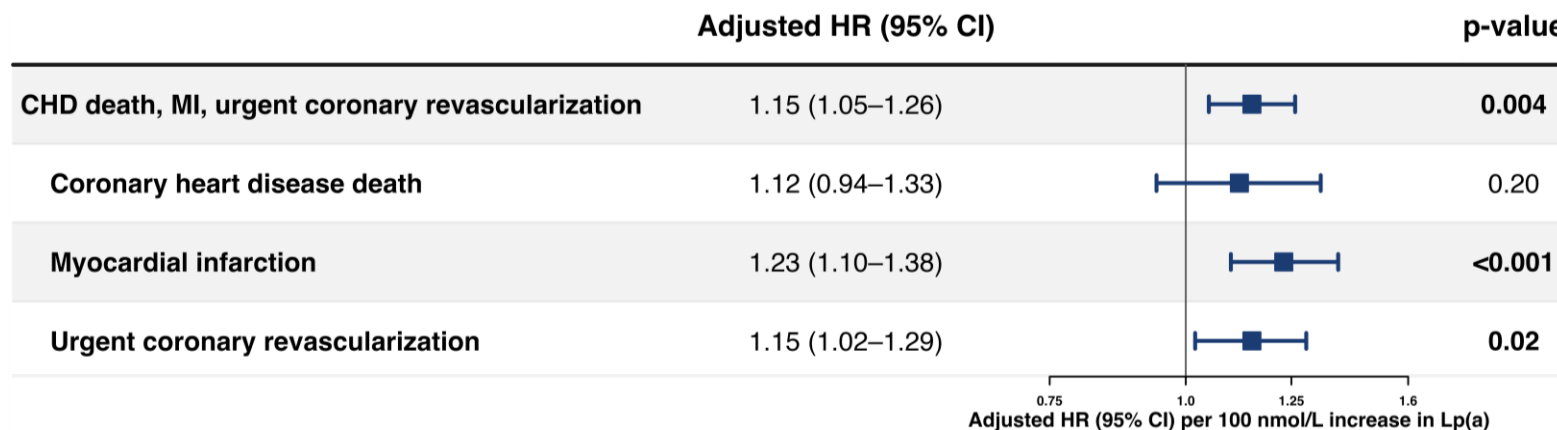


Baseline Lp(a) and Adjusted Risk of Major Adverse Cardiovascular Events (Placebo Arm)



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Adjusted for age, sex, BMI, race, hypertension, diabetes mellitus, active smoking, baseline LDL-C, and baseline eGFR < 60 mL/min/1.73m²



Baseline Lp(a) and Adjusted Risk of Major Adverse Cardiovascular Events (Placebo Arm)



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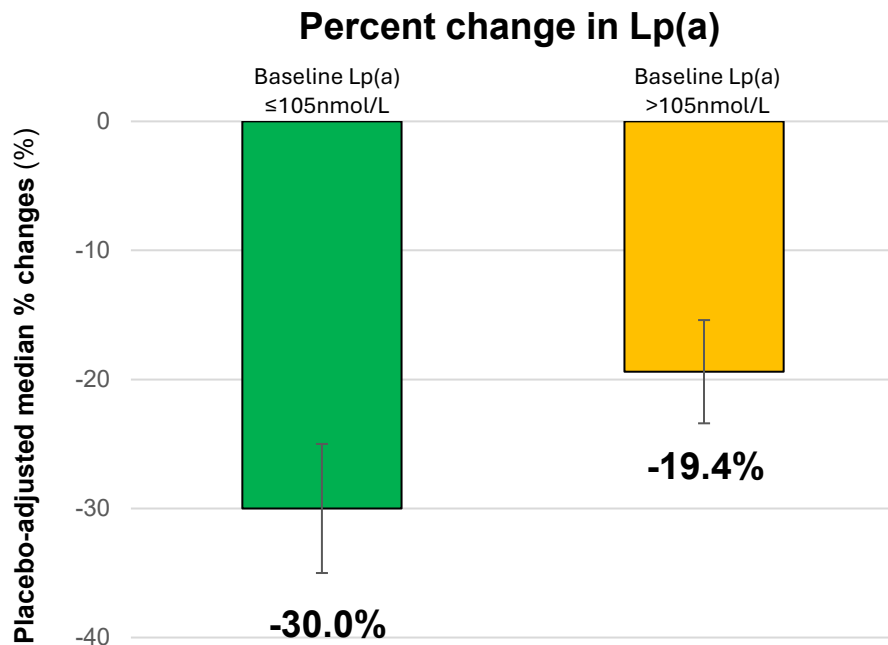
Adjusted for age, sex, BMI, race, hypertension, diabetes mellitus, active smoking, baseline LDL-C, and baseline eGFR < 60 mL/min/1.73m²



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Change in Lp(a) to Week 48 by Baseline Lp(a)



Lipid substudy (n=2014)

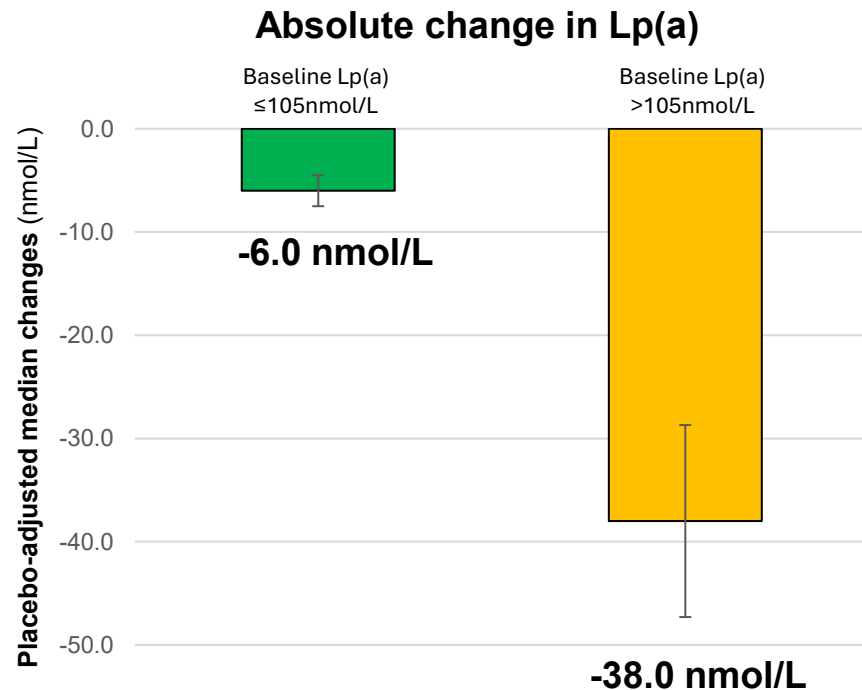
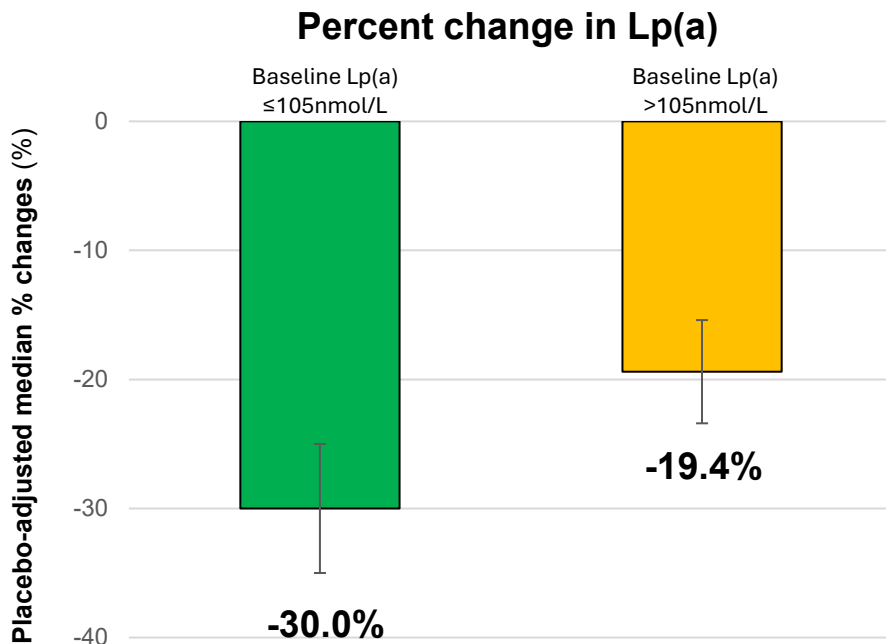


Change in Lp(a) to Week 48 by Baseline Lp(a)



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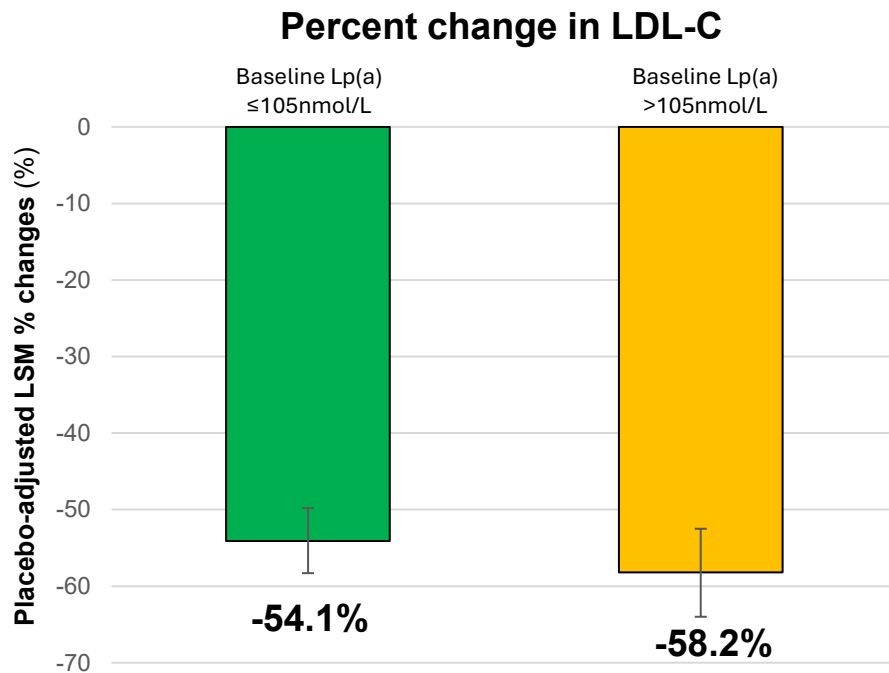
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Lipid substudy (n=2014)



Change in LDL-C to Week 48 by Baseline Lp(a)

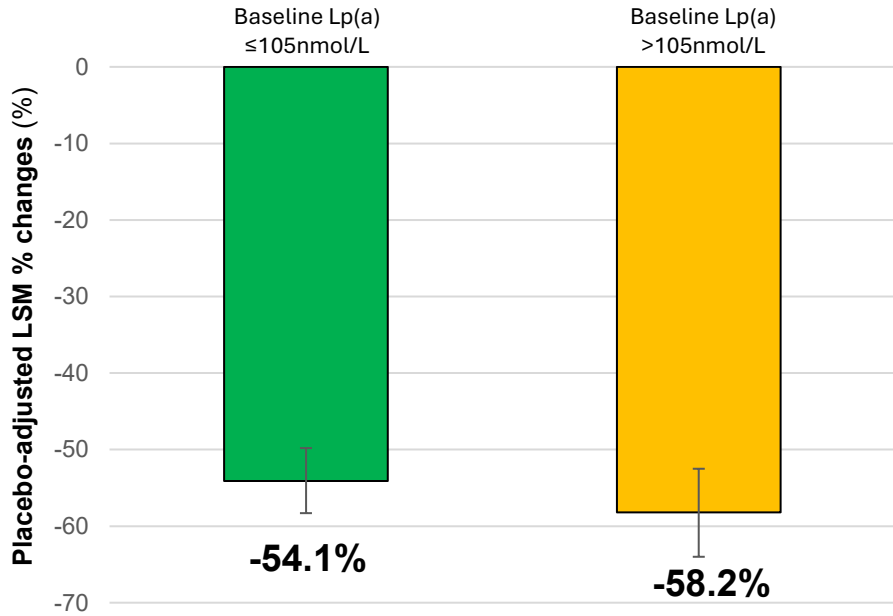


Lipid substudy (n=2014)

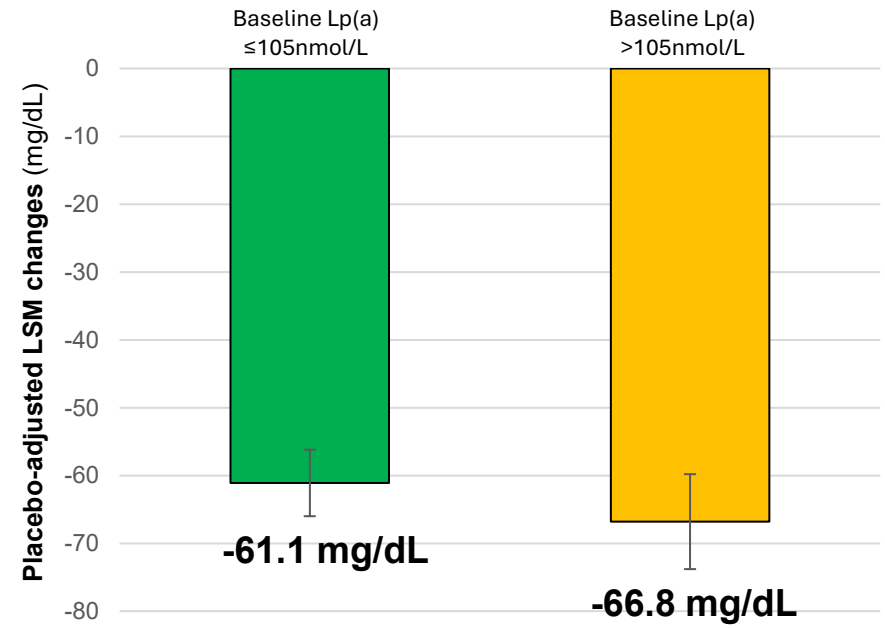


Change in LDL-C to Week 48 by Baseline Lp(a)

Percent change in LDL-C



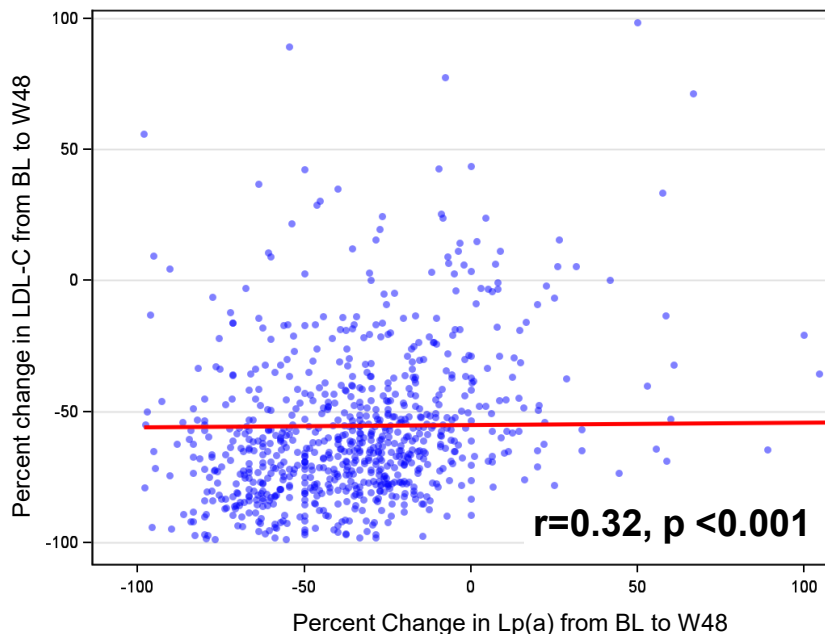
Absolute change in LDL-C



Lipid substudy (n=2014)



Modest Correlation Between % Change in Lp(a) & LDL-C with Evolocumab



Restricted to participants randomized to evolocumab



Efficacy of Evolocumab by Baseline Lp(a)

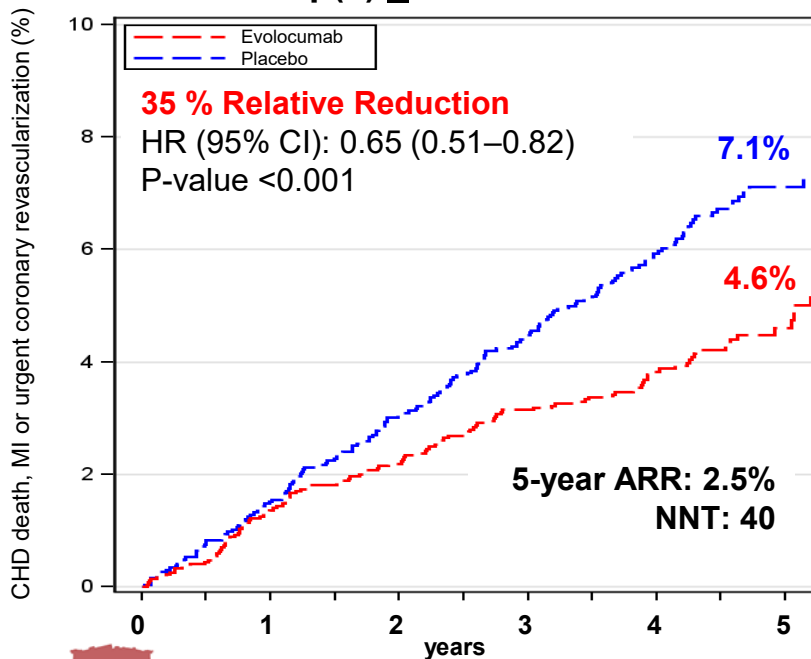


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CHD death, MI or Urgent Coronary Revascularization

Lp(a) \leq 105nmol/L



ARR: absolute risk reduction, CHD: coronary heart disease, HR: hazard ratio, MI: myocardial infarction, NNT: number needed to treat.

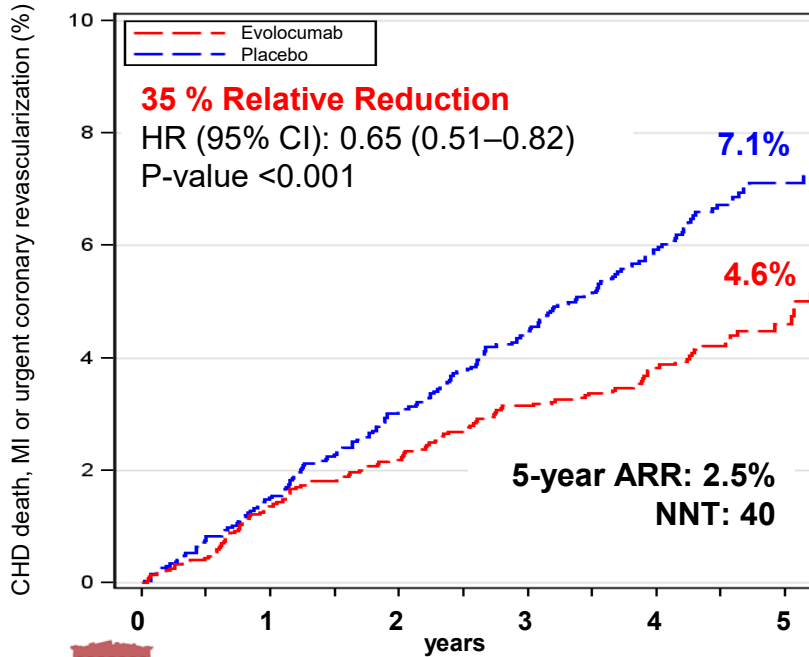
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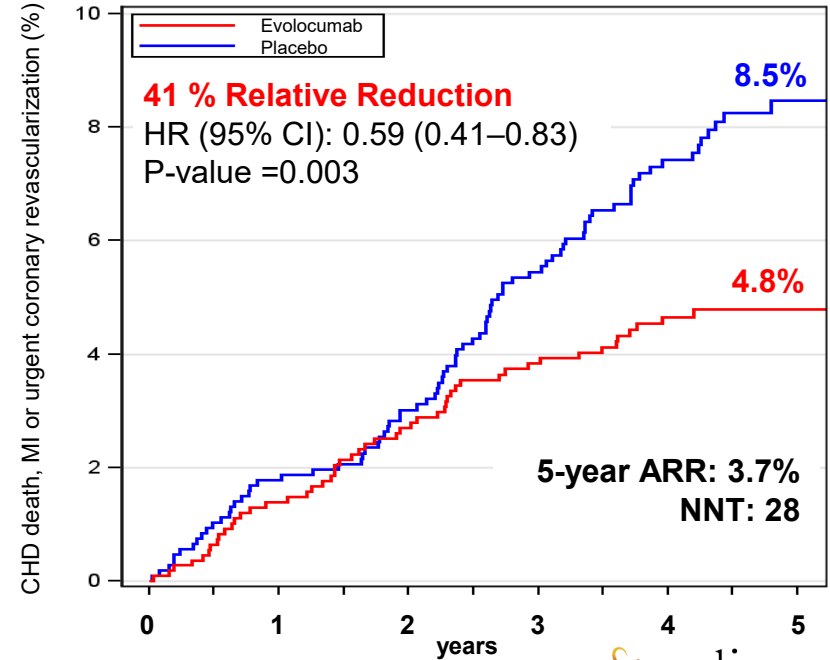
Efficacy of Evolocumab by Baseline Lp(a)

CHD death, MI or Urgent Coronary Revascularization

Lp(a) \leq 105nmol/L



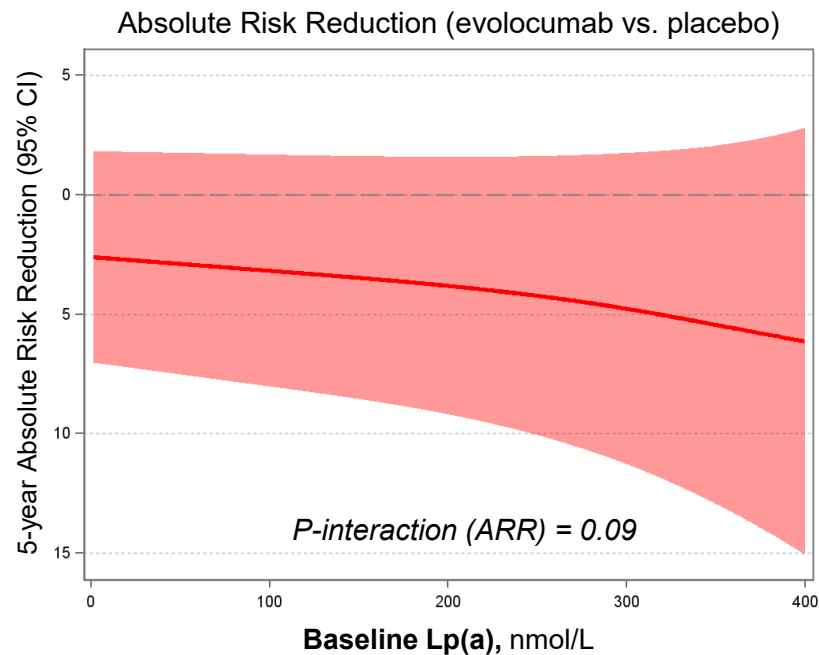
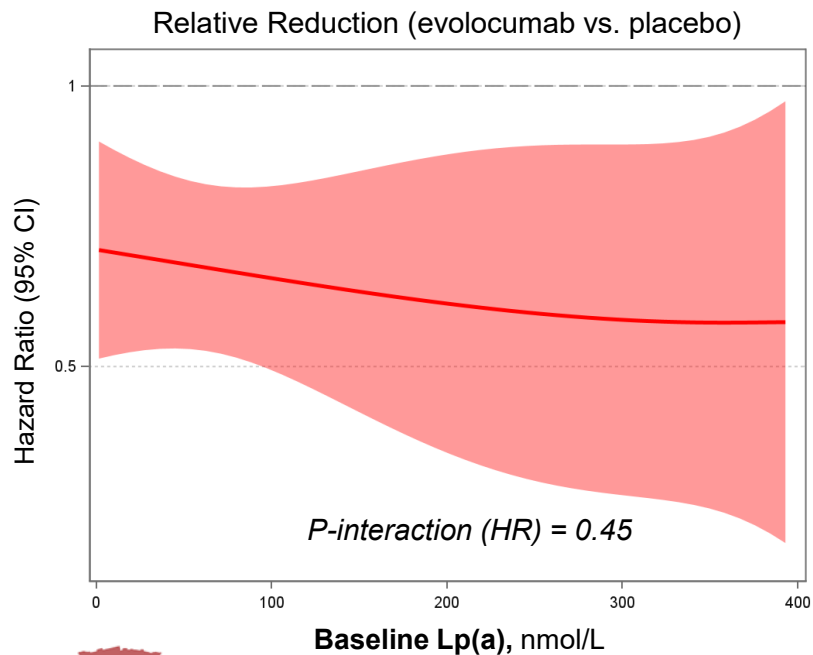
Lp(a) > 105nmol/L



ARR: absolute risk reduction, CHD: coronary heart disease, HR: hazard ratio, MI: myocardial infarction, NNT: number needed to treat.

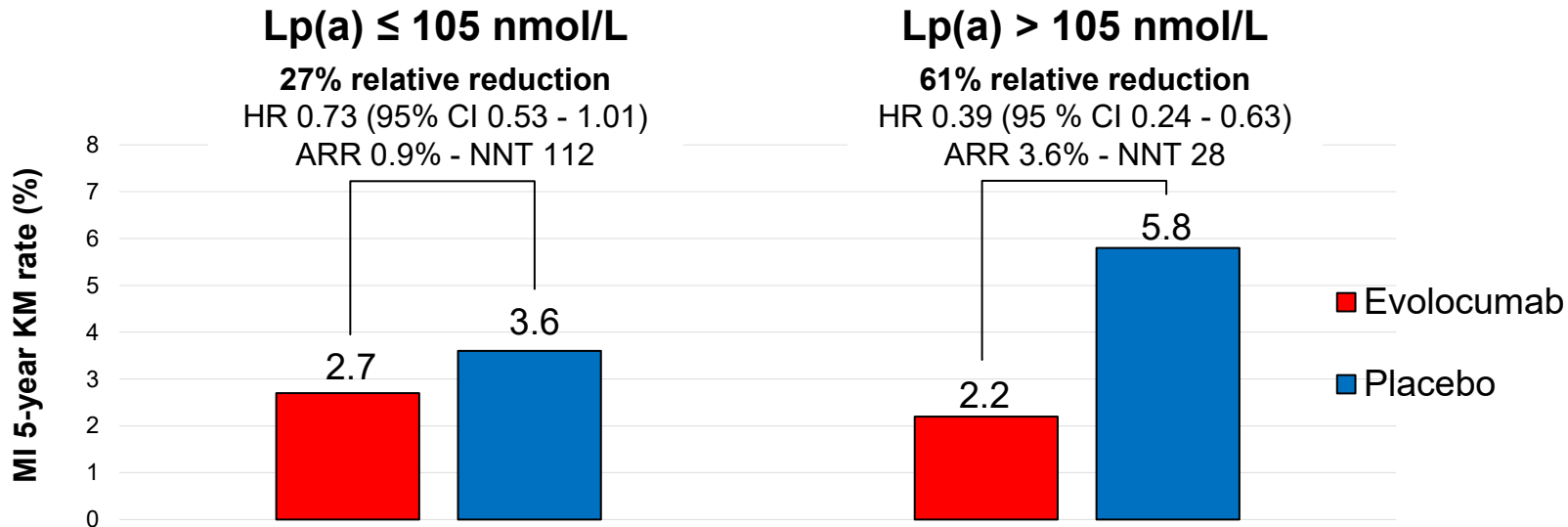
Efficacy of Evolocumab by Baseline Lp(a) Modeled on a Continuous Basis

CHD death, MI or Urgent Coronary Revascularization



ARR: absolute risk reduction, CHD: coronary heart disease, HR: hazard ratio, MI: myocardial infarction

Efficacy of Evolocumab for Risk of First Myocardial Infarction by Baseline Lp(a)



P-interaction (HR) = 0.03 [Lp(a) dichotomous]; 0.17 [Lp(a) continuous]

ARR: absolute risk reduction, HR: hazard ratio, KM: Kaplan Meier, NNT: number needed to treat.



Limitations

- This prespecified secondary analysis was not adjusted for multiplicity and should be interpreted as exploratory.
- Baseline Lp(a) was measured in a subset of the VESALIUS-CV population (60%) with limited racial and ethnic diversity.
- Participants were required to have an LDL-C ≥ 90 mg/dl at screening, therefore potential interactions between Lp(a) and lower levels of LDL-C could not be explored.



KEY SUMMARY

- In patients with atherosclerosis or high-risk diabetes, but without prior MI or stroke, Lp(a) was independently associated with an increased risk of **major coronary events**, but not ischemic stroke.
- Evolocumab reduced the relative rate of major coronary events to a similar degree irrespective of baseline Lp(a), with a numerically **greater absolute risk reduction** in patients with elevated Lp(a) (NNT 28 vs 40).
- Ongoing trials of potent Lp(a)-lowering therapies will be important to better understand if lowering Lp(a) translates into improved outcomes.





Circulation



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Lipoprotein(a) Levels, Risk of Cardiovascular Events and Benefit of Evolocumab: Findings From the VESALIUS-CV Trial

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