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VESALIUS-CV

The Effect of EVolocumab in PatiEntS at High CArdiovascuLar RIsk withoUt a Previous MI or Stroke

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The Effect of EVolocumab in PatiEntS at High CArdiovascuLar RIsk WithoUt Prior Myocardial Infarction or Stroke:

Primary Results of the VESALIUS-CV Study

Erin Bohula, MD DPhil

On behalf of the VESALIUS-CV Investigators

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ORIGINAL ARTICLE

Evolocumab in Patients without Previous Myocardial Infarction or Stroke

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Background

In the FOURIER trial in patients with established cardiovascular disease (previous myocardial infarction, stroke, symptomatic PAD), the addition of **evolocumab** to statin therapy

- **Lowered LDL-C**
- **Significantly reduced the risk of composite major adverse cardiovascular events**

Maximum LDL-C lowering occurred by 2 weeks after a single-dose of 140 mg of evolocumab

Evolocumab demonstrated a **long-term safety profile**, with a maximum exposure to evolocumab of 8.4 years

VESALIUS-CV was a randomized, double-blind, placebo-controlled, global phase 3 trial designed to evaluate the effects of evolocumab on major CV events in patients without a previous MI or stroke at high risk for a CV event

Sabatine MS, et al. *N Engl J Med*. 2017; Kasichayanula S, et al. *Clin Pharmacokinet.* 2018; O'Donoghue ML, et al. *Circulation*. 2022; Bohula EA, et al. *N Engl J Med*. 2025

VESALIUS-CV Eligibility

Disease (≥ 1 of the following)

Coronary artery disease	High-risk DM
Peripheral artery disease	Atherosclerotic cerebrovascular disease

Age

≥ 50 to < 80 years in men and ≥ 55 to < 80 years in women

Lipids

LDL-C ≥ 2.33 mmol/L, or non-HDL-C ≥ 3.10 mmol/L, or ApoB ≥ 1.56 µmol/L‡‡

High Risk Criteria (≥1 of the following)

- Age ≥ 65 years
- Current tobacco use
- LDL-C ≥ 3.36 mmol/L, or non-HDL-C ≥ 4.14 mmol/L, or ApoB ≥ 2.3 µmol/L (ApoB also represented as ≥ 2,300 nmol/L)
- DM or metabolic syndrome with CAD, CeVD, or PAD
- Family history of premature CAD
- High-risk DM with ≥ 1 arterial stenosis of ≥ 50%
- Polyvascular disease
- Familial hypercholesterolemia
- eGFR from 15 to < 45 mL/min/1.73 m^2
- Lp(a) > 125 nmol/L
- hsCRP ≥ 3.0 mg/L in the absence of acute illness
- Menopause before 40 years of age
- CAC ≥ 300 in a patient without coronary revascularization

Patients with a previous MI or stroke were excluded. Patients were eligible for inclusion if the four criteria were met.

Bohula EA, et al. *N Engl J Med*. 2025

VESALIUS-CV Endpoints

Two Primary Endpoints

- **3-point MACE:** Time to first occurrence of CHD death, MI, or ischemic stroke
- **4-point MACE:** Time to first occurrence of CHD death, MI, ischemic stroke, or any ischemia-driven arterial revascularization (IDR)

Secondary Endpoints

Time to first occurrence of:

- MI, ischemic stroke, or IDR
- CHD death, MI, or IDR
- CV death, MI, or ischemic stroke
- CHD death or MI
- Individual endpoints of MI, IDR, CHD death, CV death, all-cause death, and ischemic stroke

Exploratory Endpoint

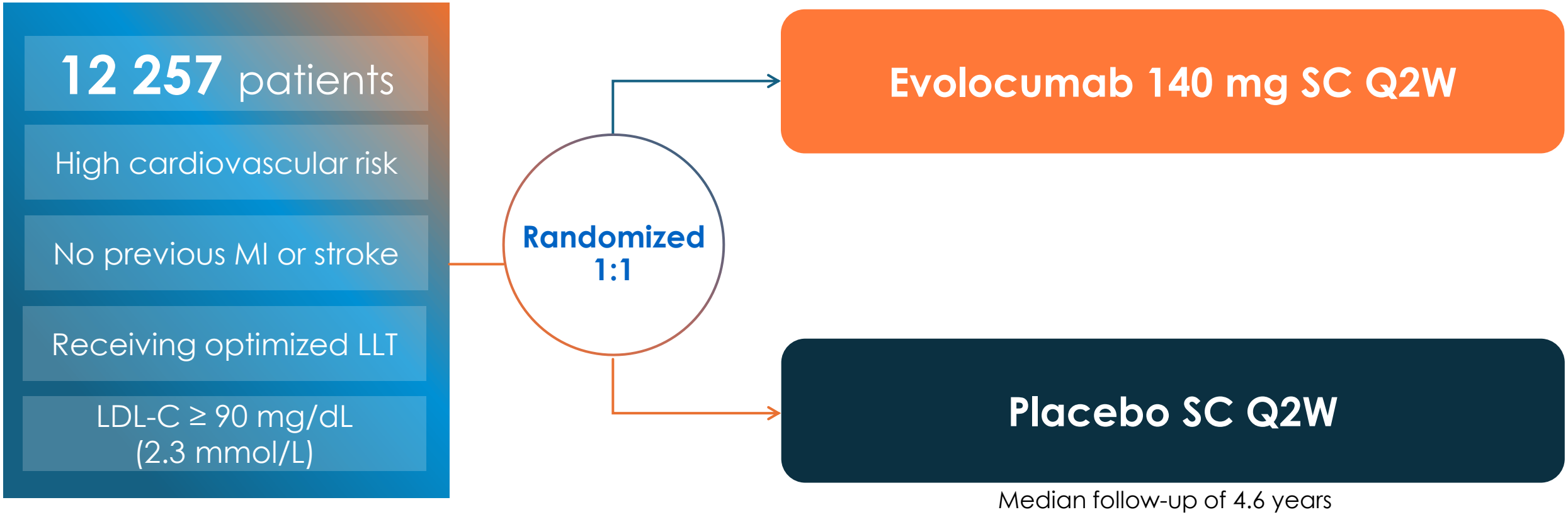
- Change in LDL-C from baseline

Safety Endpoints

- Treatment-emergent serious AEs and those that led to treatment discontinuation

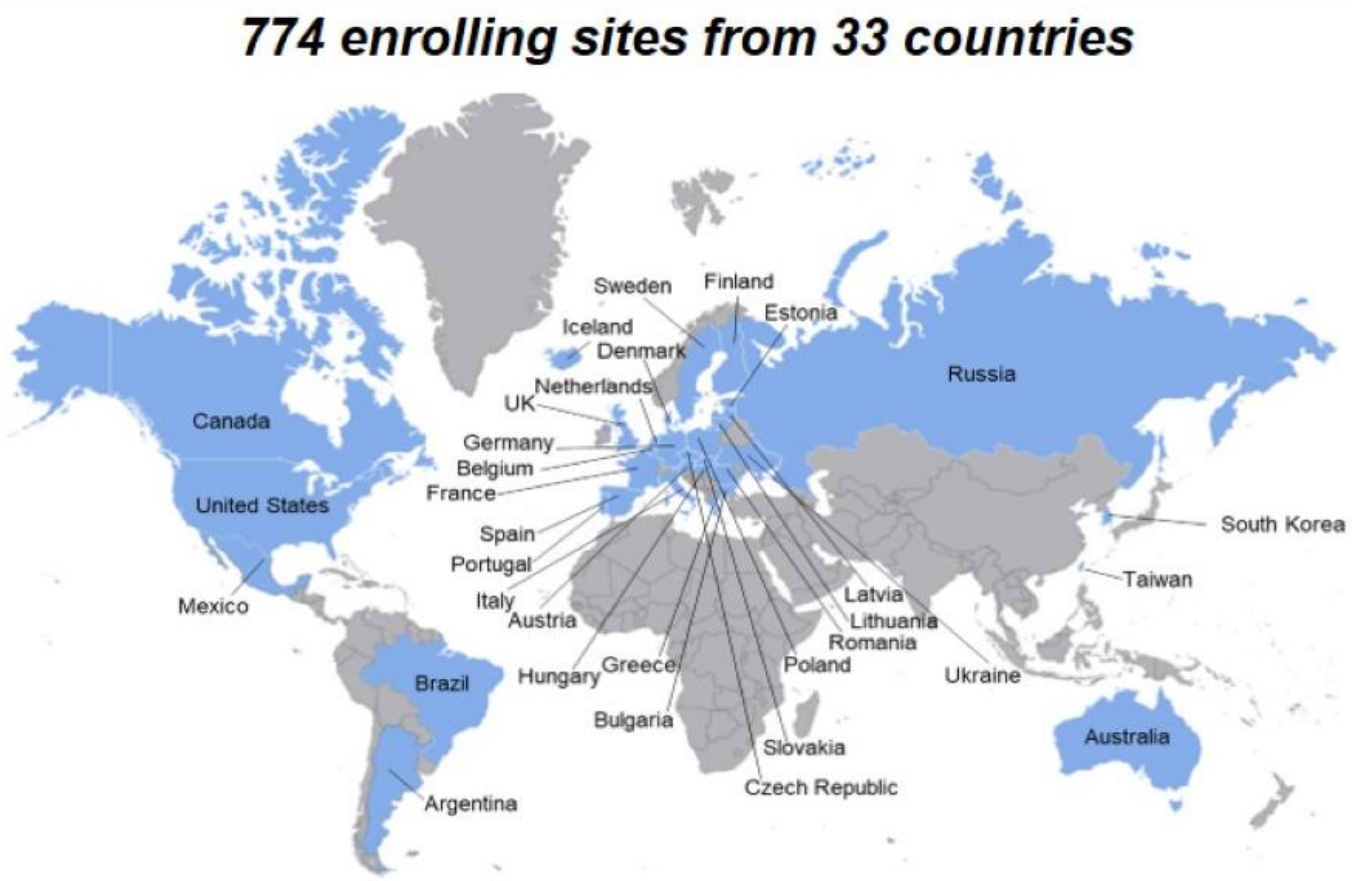
VESALIUS-CV Phase 3 Trial Schema

Randomized, double-blind, placebo-controlled, global trial evaluating the effect of evolocumab on major cardiovascular events in patients at high cardiovascular risk without a previous myocardial infarction (MI) or stroke



Bohula EA, et al. *N Engl J Med*. 2025; Bohula E, et al. *Am Heart J. 2024*

Enrollment and Retention



- 12,257† in analytic population
- Over a median follow up of 4.6 years, annualized rates of:
  - Premature drug d/c: 4.5%
  - Withdrawal of consent: 0.3%
  - Lost to follow-up: 0.08%
- Follow up for primary end points for 98.7% of total potential patient-years

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

†*Excludes 44 from site with serious breach and GCP violations*

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VESALIUS-CV Baseline Characteristics

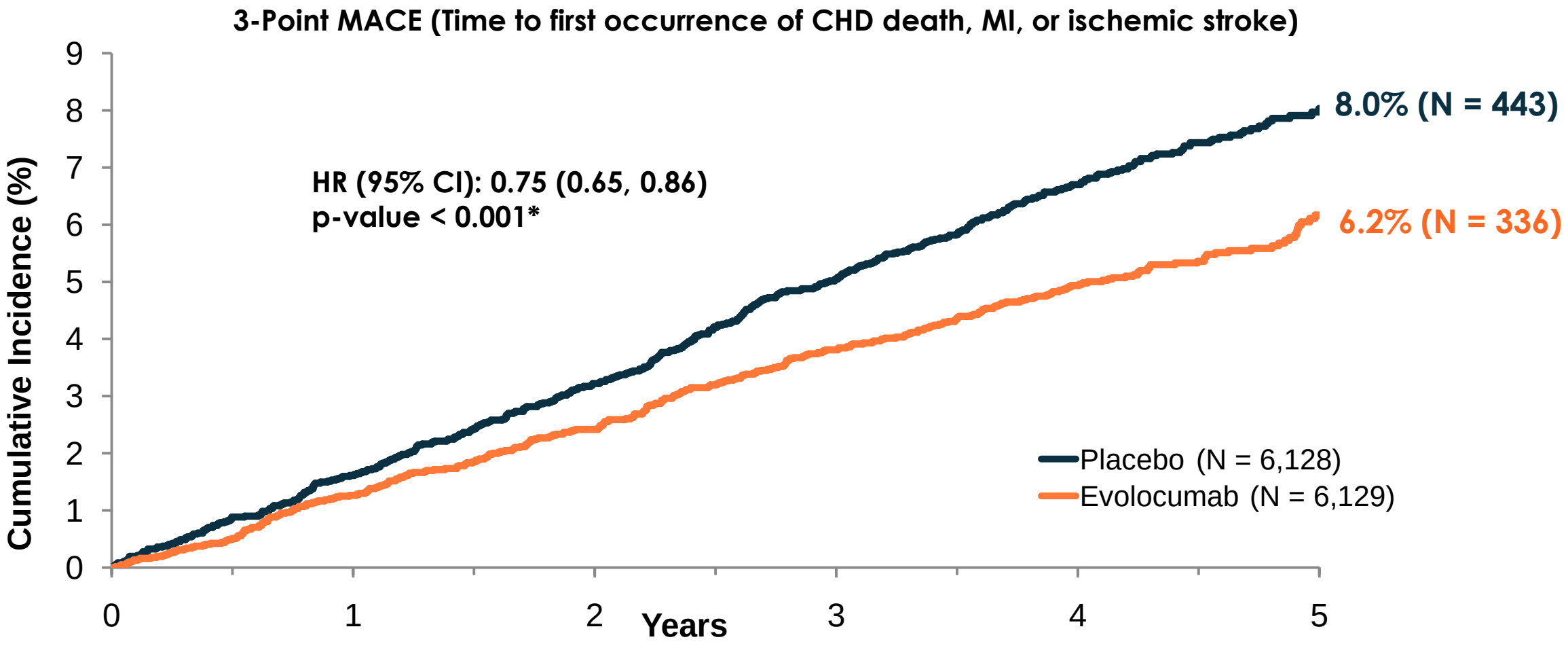
Characteristic	Evolocumab (N = 6129)	Placebo (N = 6128)
Median Age (IQR)	66 years (60, 71)	66 years (60, 71)
Female	43%	42%
White	93%	93%
Europe/North America/Asia-Pacific	69% / 11% / 5%	69% / 11% / 5%
Comorbidities		
Hypertension	87%	87%
Diabetes mellitus	59%	58%
Disease category		
Any atherosclerosis	67%	67%
Coronary artery disease without previous MI	45%	45%
Cerebrovascular disease without previous stroke	10%	10%
Peripheral artery disease	17%	18%
High-risk diabetes mellitus	50%	48%
High-risk diabetes without qualifying atherosclerosis	33%	33%

VESALIUS-CV Baseline Characteristics

Characteristic	Evolocumab (N = 6129)	Placebo (N = 6128)
Most common high-risk criteria		
Age ≥ 65 years	57%	55%
LDL-C ≥ 3.36 mmol/L , non-HDL-C ≥ 4.14 mmol/L, or ApoB ≥ 2.3 µmol/L	51%	51%
DM or metabolic syndrome with CAD, CeVD, or PAD	31%	30%
Current tobacco use	28%	28%
Family history of premature CAD	22%	22%
Background lipid-lowering therapy		
High-intensity lipid-lowering regimen	72%	73%
Any statin	87%	87%
High-intensity statin	68%	68%
Moderate- or low-intensity statin	19%	19%
Ezetimibe	19%	20%
Median baseline LDL-C level, mmol/L (IQR)	3.15 (2.69, 3.85)	3.15 (2.69, 3.85)

Bohula EA, et al. *N Engl J Med*. 2025

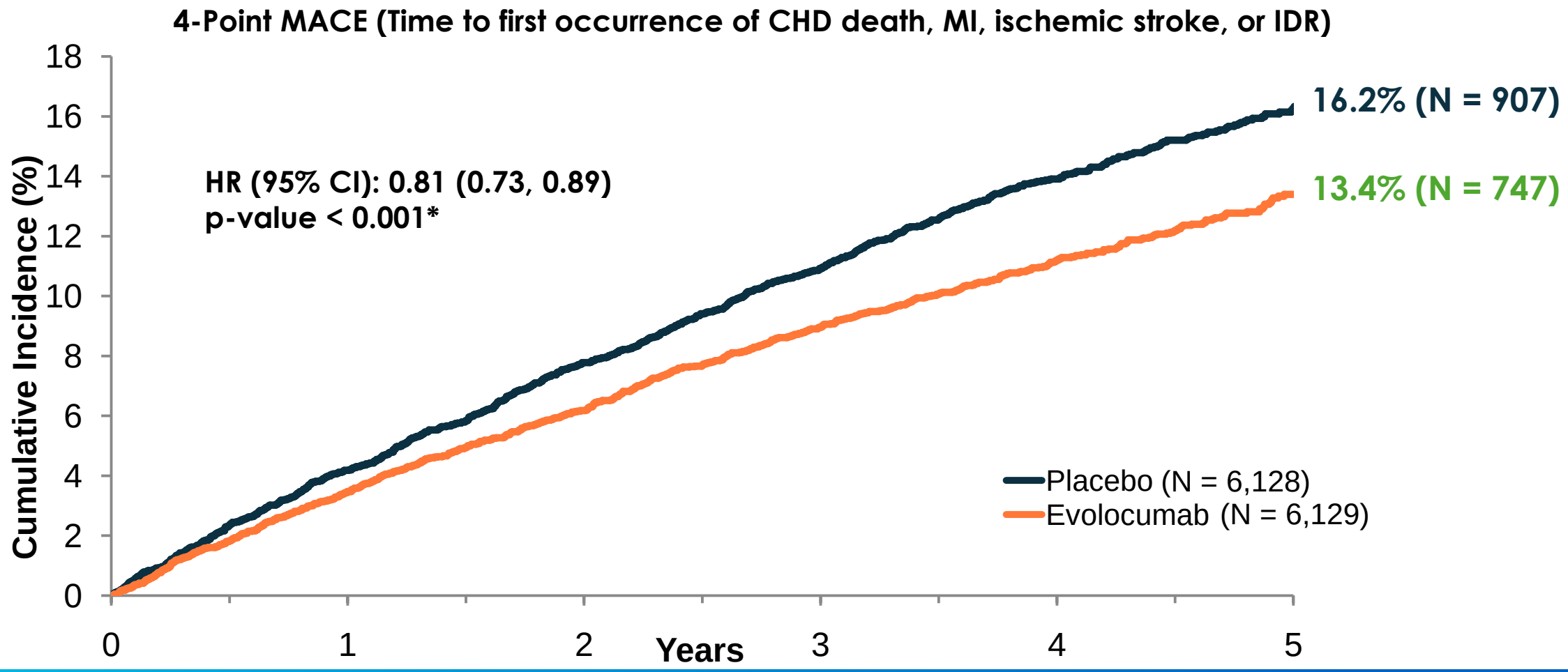
VESALIUS-CV Met Its Two Primary Endpoints



Evolocumab reduced the relative risk of composite 3-point MACE by 25%

Bohula EA, et al. *N Engl J Med*. 2025

VESALIUS-CV Met Its Two Primary Endpoints



Evolocumab reduced the relative risk of composite 4-point MACE by 19%

Bohula EA, et al. *N Engl J Med*. 2025

VESALIUS-CV Secondary Endpoints

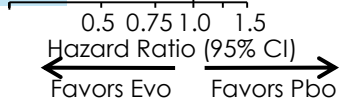
Secondary Endpoints	Hazard Ratio (95% CI) Evolocumab vs Placebo	*p*-value
MI, ischemic stroke, or IDR	0.79 (0.72, 0.88)	<0.001
CHD death, MI, or IDR	0.79 (0.72, 0.88)	<0.001
CV death, MI, or ischemic stroke	0.73 (0.64, 0.84)	<0.001
CHD death or MI	0.73 (0.62, 0.87)	<0.001
MI	0.64 (0.52, 0.79)	<0.001
IDR	0.79 (0.70, 0.88)	<0.001
CHD death	0.89 (0.68, 1.16)	0.39
CV death	0.79 (0.64, 0.98)	NA
All-cause death	0.80 (0.70, 0.91)	NA
Ischemic stroke	0.79 (0.62, 1.01)	NA

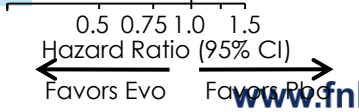
Evolocumab reduced the risk of a first MI by 36%

Bohula EA, et al. *N Engl J Med*. 2025

VESALIUS-CV Subgroup Analyses

Subgroup	3-Point MACE Evo (%)*	3-Point MACE Pbo (%)*	3-Point MACE HR	4-Point MACE Evo (%)*	4-Point MACE Pbo (%)*	4-Point MACE HR
Overall	5.5	7.2	0.75	12.2	14.8	0.81
Demographics						
Age < 65	5.2	6.0	0.86	11.2	13.2	0.83
Age ≥ 65	5.7	8.2	0.68	13.0	16.1	0.79
Male	6.4	8.4	0.75	14.5	17.2	0.83
Female	4.2	5.7	0.74	9.0	11.6	0.77
Qualifying Disease State						
Any qualifying atherosclerosis	5.8	7.5	0.76	14.3	16.7	0.84
High risk DM w/o qualifying atherosclerosis	4.9	6.8	0.71	8.1	10.8	0.74
Lipid Related						
Baseline LDL-C (mg/dL)						
1st quartile (≤104)	5.2	6.7	0.77	12.2	14.4	0.83
2nd quartile (>104-122)	5.8	7.3	0.78	13.8	15.6	0.88
3rd quartile (>122-149)	4.8	7.7	0.60	10.8	14.9	0.70
4th quartile (>149)	6.2	7.3	0.85	12.0	14.4	0.83
Statin Intensity						
High intensity	4.9	6.9	0.70	11.0	13.5	0.80
Moderate or low	6.0	7.1	0.81	13.5	16.4	0.79
None	7.8	9.0	0.88	16.5	18.9	0.87
Ezetimibe	5.3	6.9	0.74	13.6	16.4	0.80
No ezetimibe	5.5	7.3	0.75	11.8	14.4	0.81

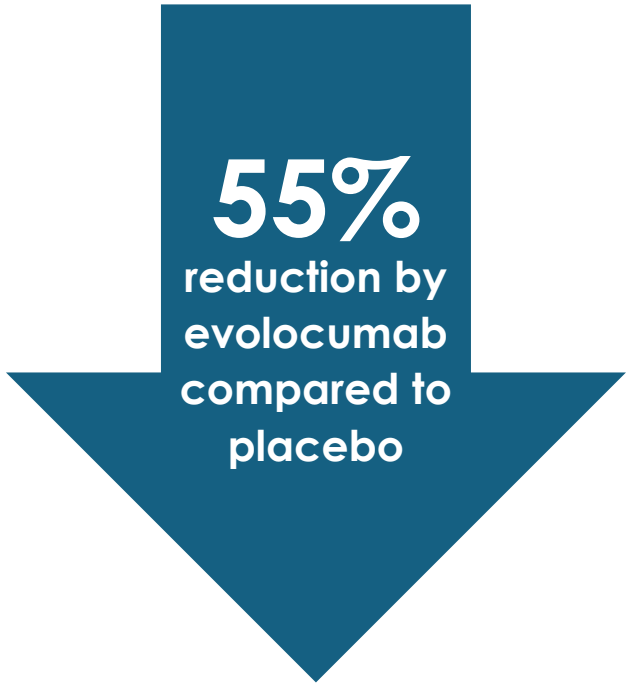




VESALIUS-CV LDL-C Levels

Lipid sub-study included 2,014 patients with central lab testing

Mean % LDL-C Change from Baseline at Week 48



LDL-C Levels on Treatment (48 weeks)

Evolocumab Group
Median LDL-C = 1.16 mmol/L (IQR 0.67, 1.89)
(Median LDL-C at baseline = 3.0 mmol/L)

Placebo Group
Median LDL-C = 2.82 mmol/L (IQR 2.22, 3.72)
(Median baseline LDL-C = 2.97 mmol/L)

Bohula EA, et al. *N Engl J Med*. 2025

VESALIUS-CV Safety

Characteristic	Evolocumab (N = 6125)	Placebo (N = 6122)
Serious adverse events	28.2%	28.9%
Adverse events leading to study drug discontinuation	3.3%	3.7%

Bohula EA, et al. *N Engl J Med*. 2025

Závěr

- **Evolokumab** po přidání ke standardní hypolipidemické léčbě významně snížil riziko kombinovaných kardiovaskulárních příhod u pacientů s vysokým rizikem bez předchozího infarktu myokardu nebo cévní mozkové příhody.
- Snížil relativní riziko 3bodového MACE o **25 %** a 4bodového MACE o **19 %** (dva primární cílové ukazatele)
- Snížil riziko prvního infarktu myokardu o **36 %**
- **Konzistentní přínos napříč podskupinami**, včetně pacientů s diabetem a bez prokázané aterosklerózy

V podstudii studie VESALIUS-CV evolokumab významně snížil hladinu LDL-C v průměru o **55 %** ve srovnání s placebem, medián dosažené hodnoty LDL-C po 48 týdnech činil **1,16** mmol/l.

Výskyt závažných nežádoucích účinků (AE) činil 28,2 % u evolokumabu a 28,9 % u placeba.

ACC.26

Evolocumab in Patients without Known Atherosclerosis and with Diabetes:

Secondary Analysis from VESALIUS-CV

Nicholas Marston, MD, MPH

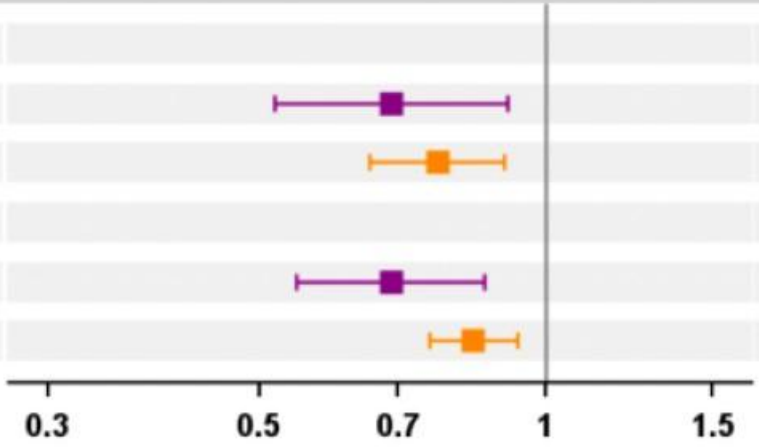
Investigator, TIMI Study Group

Cardiologist, Brigham and Women's Hospital

Harvard Medical School

Without vs With Known Significant Athero

Dual Primary Endpoints	n (%) Evolocumab	Placebo	HR (95% CI)	Interaction p-value
3-P MACE				
W/O significant Athero	83 (4.5)	117 (6.5)	0.69 (0.52, 0.91)	0.507
W/ significant Athero	253 (5.9)	326 (7.5)	0.77 (0.65, 0.91)	
4-P MACE				
W/O significant Athero	127 (6.9)	178 (9.9)	0.69 (0.55, 0.86)	0.122
W/ significant Athero	620 (14.5)	729 (16.9)	0.84 (0.76, 0.94)	



Conclusions

- The benefits seen in this subgroup support intensification of lipid-lowering therapy beyond statins earlier in the atherosclerotic cardiovascular disease process
- The consistency of the magnitude of clinical benefit with that expected from CTTC underscores the value of lowering LDL-C down to ~40 mg/dL in these patients
- ***Thus, these data strongly support that in these lower-risk patients we should be targeting LDL-C goals typically reserved for very high-risk secondary prevention patients***

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