Reduction in Total Cardiovascular Events with Evolocumab in Patients with no Prior MI or Stroke:

A Pre-specified Analysis of VESALIUS-CV

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On behalf of the VESALIUS-CV Investigators

European Society of Cardiology

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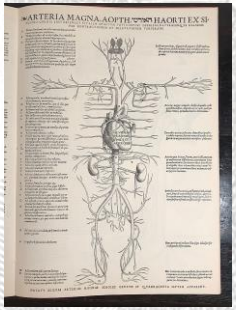

Arteria magna, a thoracis
Tabulae Anatomicae Sex
A. Vesalius. 1538

vesalius-cv

TIMI

Background

- In VESALIUS-CV, intensive LDL-C lowering with evolocumab reduced risk of 1st CV events in patients w/o prior MI or stroke and w/ qualifying atherosclerosis and/or high-risk diabetes[1]
- Subsequent CV events are common and important to patients, clinicians, and healthcare systems
- In this prespecified analysis of VESALIUS-CV, we evaluated the effect of evolocumab on total events, including both first and subsequent CV events

[1]Bohula EA, et al. *NEJM.* 2026;394:117-127.

Trial Design & Methods

N= 12,257

Stable patients at high-risk for CV events but no prior MI or stroke*

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

LDL-C ≥ 90 mg/dL or
non-HDL-C ≥ 120 mg/dL or
ApoB ≥ 80mg/dL

On optimized statin therapy (± ezetimibe)

Median f/u of 4.6 yrs

Evolocumab SC 140 mg Q2W

1:1 Randomization

Placebo SC Q2W

Dual Primary Endpoints:
Time to coronary heart disease death, MI, or ischemic stroke (3-P MACE)
Time to 3-P MACE plus ischemia-driven arterial revascularization (4-P MACE)

Total Events Analytic Approach:

- Primary:
  - Negative binomial regression models (count-based)
  - Compares the total number of events (first and all subsequent)
- Sensitivity:
  - Wei, Lin, & Weissfeld (WLW) method (extension of survival analysis)
  - Compares time from randomization to specified event number (e.g. 2nd event)

Bohula EA, et al. *Am Heart J.* 2024;269:179-190.

Vesalius-cv
Total Events

First and Subsequent Events

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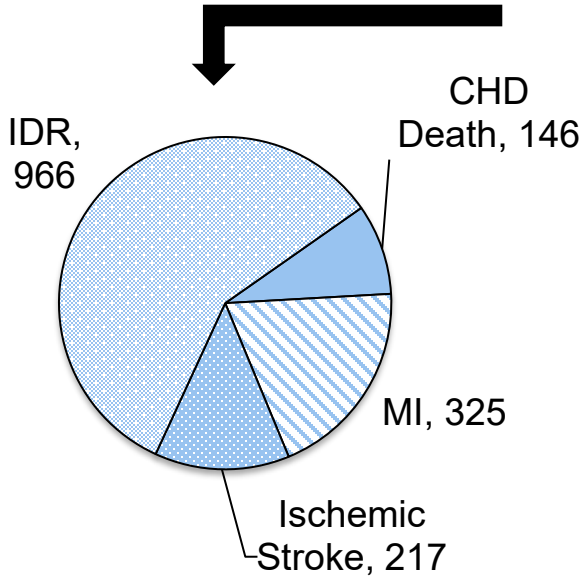
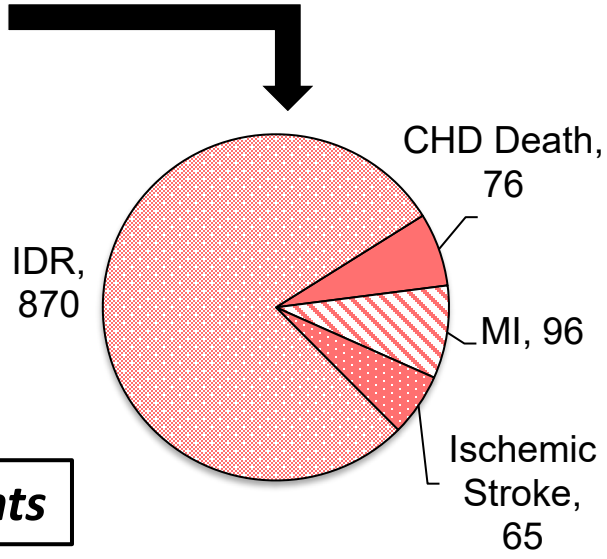
Total 4-P MACE = 2761



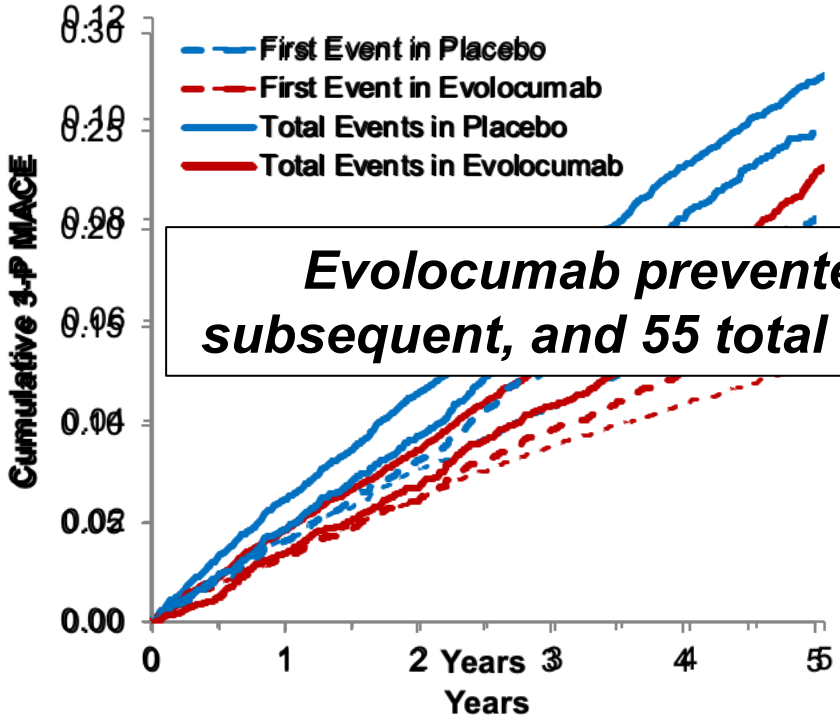


67% more subsequent events

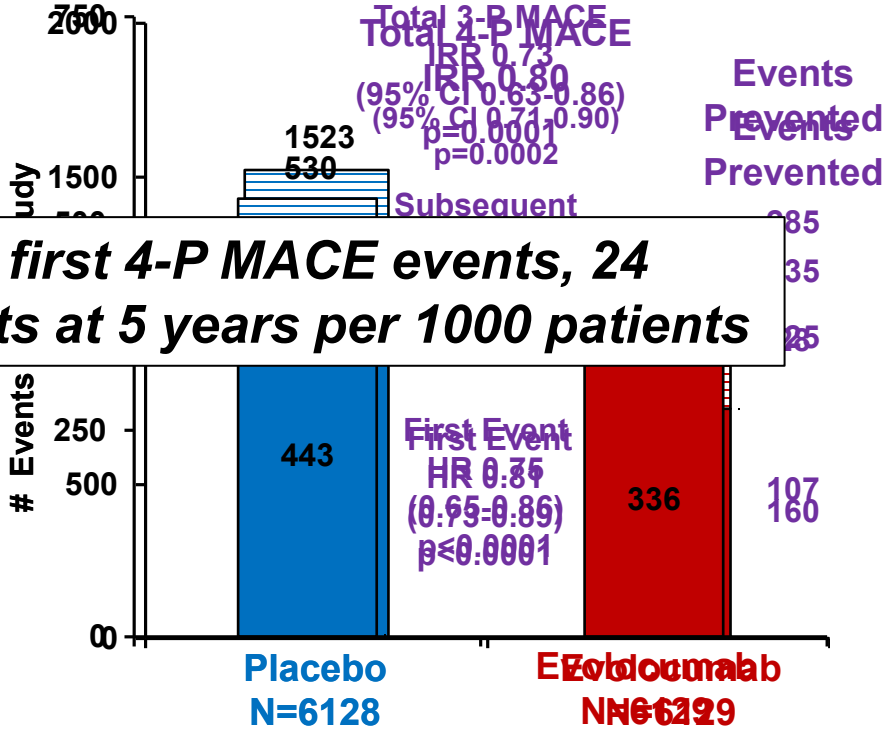
Vesalius-cv
Total Events

First and Total 3-P MACE

First & Total Event Accrual Over Time



First & Total Events At End of Study



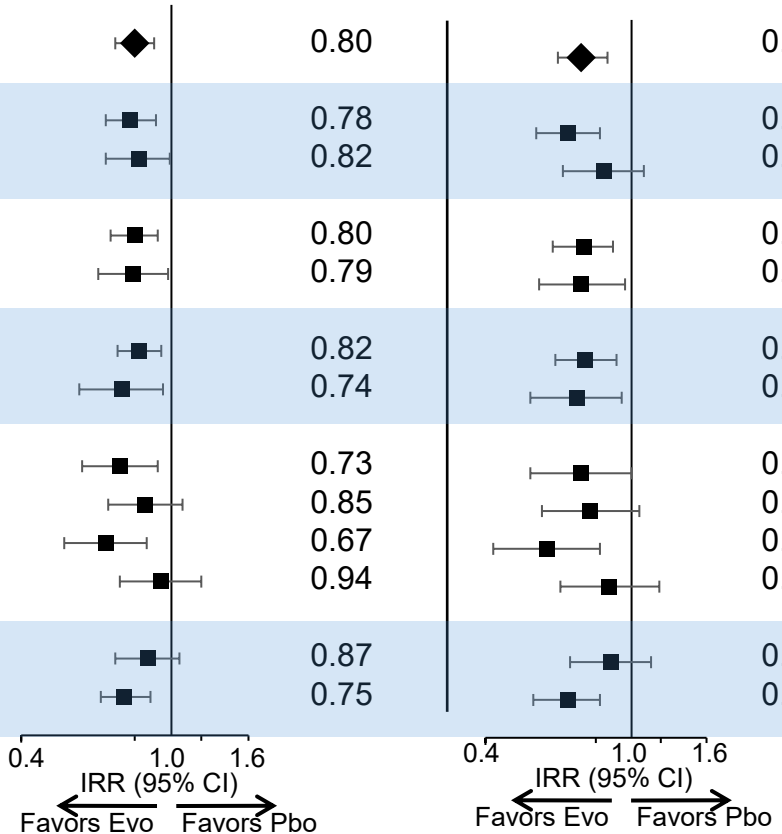
Evolocumab prevented 31 first 4-P MACE events, 24 subsequent, and 55 total events at 5 years per 1000 patients

4-P MACE: CHD death, MI, ischemic stroke, or IDR
3-P MACE: CHD death, MI, or ischemic stroke
IRR, incidence rate ratio.

Vesalius-cv
Total Events

Key Subgroups

Subgroup	N	4-MACE IRR	3-MACE IRR
Overall	12257	0.80	0.73
Age ≥ 65	6868	0.78	0.67
Age < 65	5389	0.82	0.84
Male	7043	0.80	0.74
Female	5214	0.79	0.73
Any qualifying athero	8208	0.82	0.75
High-risk DM w/o qual athero	4001	0.74	0.71
LDL-C Q1 (≤104)	3093	0.73	0.73
LDL-C Q2 (>104-122)	3073	0.85	0.77
LDL-C Q3 (>122-149)	3049	0.67	0.59
LDL-C Q4 (>149)	3041	0.94	0.87
No/Low/Mod intensity statin	3932	0.87	0.88
High intensity statin	8325	0.75	0.67



p-interaction > 0.05 for each

An Academic Research Organization of
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4-P MACE: CHD death, MI, ischemic stroke, or IDR; 3-P MACE: 4-P MACE w/o IDR; IRR, incidence rate ratio

Vesalius-cv
Total Events

Benefit for Subsequent Events

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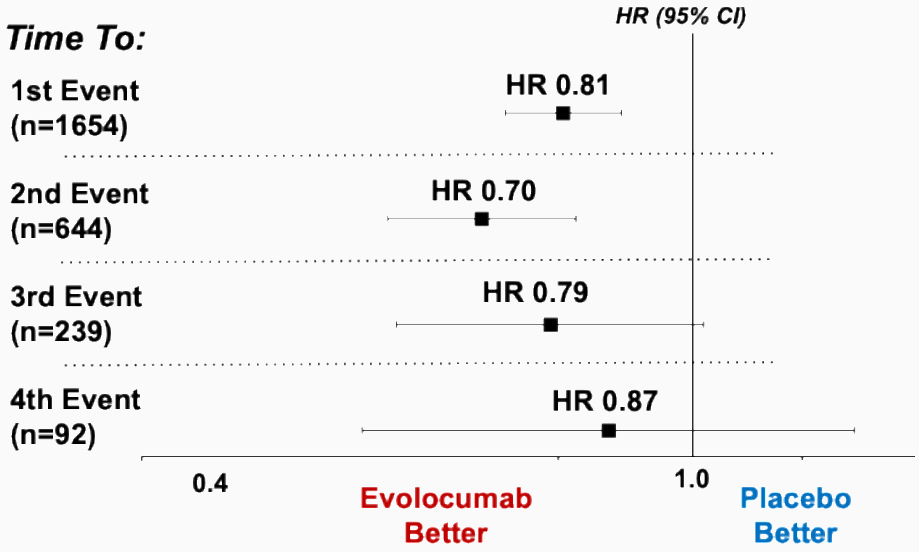
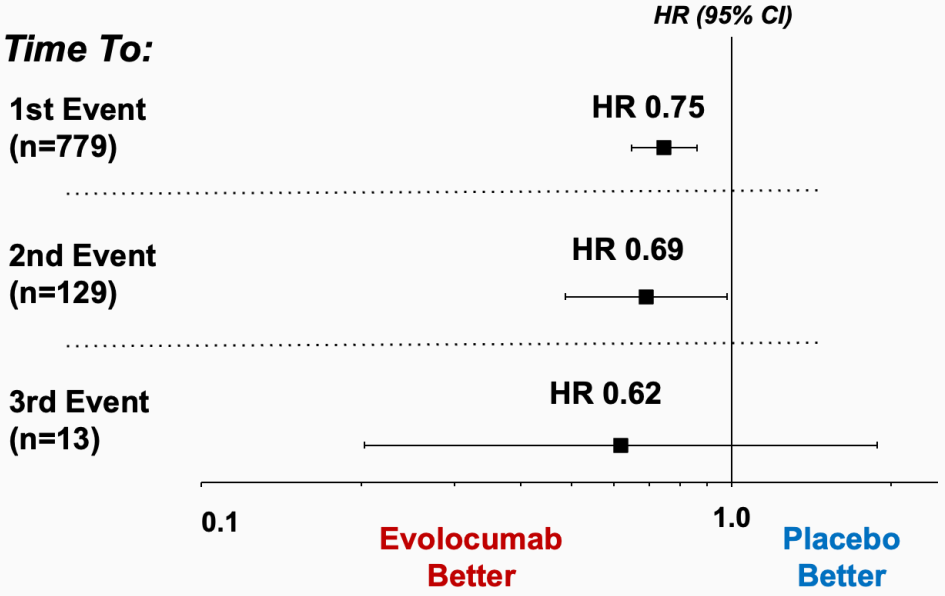
Wei, Lin, and Weissfeld (WLW) Method

4-P MACE



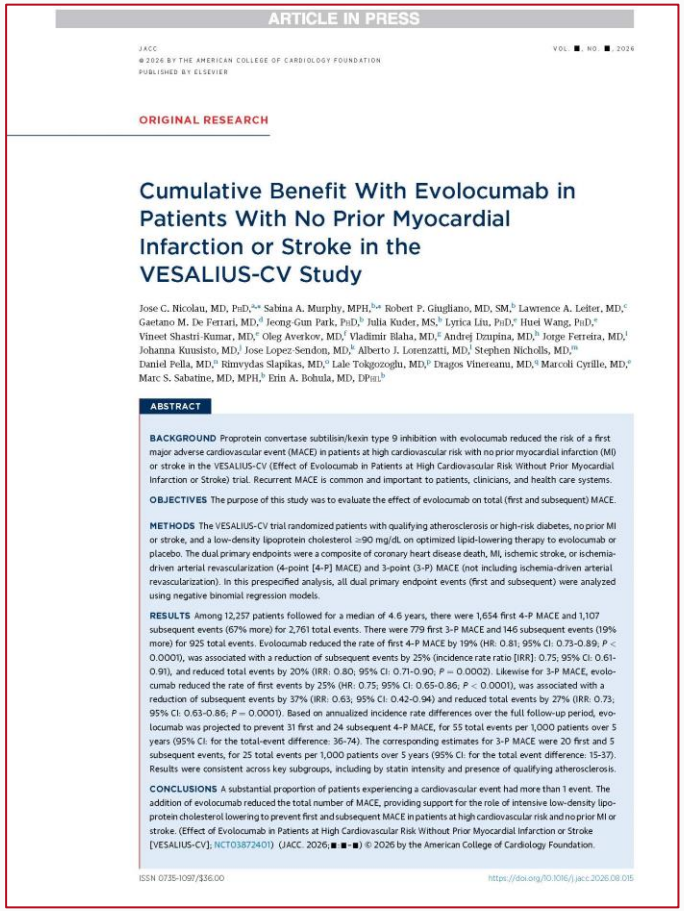
3-P MACE



4-P MACE: CHD death, MI, ischemic stroke, or IDR; 3-P MACE: 4-P MACE w/o IDR

Summary & Conclusions

- Evolocumab significantly reduced the rate of **total** MACE, where evolocumab prevented 31 first 4-P MACE events, 24 subsequent, and 55 total events at 5 years per 1000 patients
- Results support intensive LDL-C lowering in patients without a prior MI or stroke to prevent first and subsequent MACE
- Considering the full burden of CV events has important implications for patients, providers, and healthcare systems



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ORIGINAL RESEARCH

Cumulative Benefit With Evolocumab in Patients With No Prior Myocardial Infarction or Stroke in the VESALIUS-CV Study

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ABSTRACT

BACKGROUND Proprotein convertase subtilisin/kexin type 9 inhibition with evolocumab reduced the risk of a first major adverse cardiovascular event (MACE) in patients at high cardiovascular risk with no prior myocardial infarction (MI) or stroke in the VESALIUS-CV (Effect of Evolocumab in Patients at High Cardiovascular Risk Without Prior Myocardial Infarction or Stroke) trial. Recurrent MACE is common and important to patients, clinicians, and health care systems.

OBJECTIVES The purpose of this study was to evaluate the effect of evolocumab on total (first and subsequent) MACE.

METHODS The VESALIUS-CV trial randomized patients with qualifying atherosclerosis or high-risk diabetes, no prior MI or stroke, and a low-density lipoprotein cholesterol ≥90 mg/dL on optimized lipid-lowering therapy to evolocumab or placebo. The dual primary endpoints were a composite of coronary heart disease death, MI, ischemic stroke, or ischemia-driven arterial revascularization (4-point [4-P] MACE) and 3-point (3-P) MACE (not including ischemia-driven arterial revascularization). In this prespecified analysis, all dual primary endpoint events (first and subsequent) were analyzed using negative binomial regression models.

RESULTS Among 12,257 patients followed for a median of 4.6 years, there were 1,654 first 4-P MACE and 1,107 subsequent events (67% more) for 2,761 total events. There were 779 first 3-P MACE and 146 subsequent events (19% more) for 925 total events. Evolocumab reduced the rate of first 4-P MACE by 19% (HR: 0.81; 95% CI: 0.73-0.89; $P < 0.0001$), was associated with a reduction of subsequent events by 25% (incidence rate ratio [IRR]: 0.75; 95% CI: 0.61-0.91), and reduced total events by 20% (IRR: 0.80; 95% CI: 0.71-0.90; $P = 0.0002$). Likewise for 3-P MACE, evolocumab reduced the rate of first events by 25% (HR: 0.75; 95% CI: 0.65-0.86; $P < 0.0001$), was associated with a reduction of subsequent events by 37% (IRR: 0.63; 95% CI: 0.42-0.94) and reduced total events by 27% (IRR: 0.73; 95% CI: 0.63-0.86; $P = 0.0001$). Based on annualized incidence rate differences over the full follow-up period, evolocumab was projected to prevent 31 first and 24 subsequent 4-P MACE, for 55 total events per 1,000 patients over 5 years (95% CI: for the total-event difference: 36-74). The corresponding estimates for 3-P MACE were 20 first and 5 subsequent events, for 25 total events per 1,000 patients over 5 years (95% CI: for the total event difference: 15-37). Results were consistent across key subgroups, including by statin intensity and presence of qualifying atherosclerosis.

CONCLUSIONS A substantial proportion of patients experiencing a cardiovascular event had more than 1 event. The addition of evolocumab reduced the total number of MACE, providing support for the role of intensive low-density lipoprotein cholesterol lowering to prevent first and subsequent MACE in patients at high cardiovascular risk and no prior MI or stroke. (Effect of Evolocumab in Patients at High Cardiovascular Risk Without Prior Myocardial Infarction or Stroke [VESALIUS-CV]; NCT03872401) (JACC. 2026;■:■-■:■) © 2026 by the American College of Cardiology Foundation.

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