Effect of evolocumab in patients at high cardiovascular risk without prior myocardial infarction or stroke: primary results of the VESALIUS-CV trial

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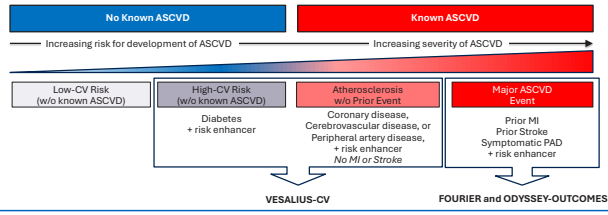
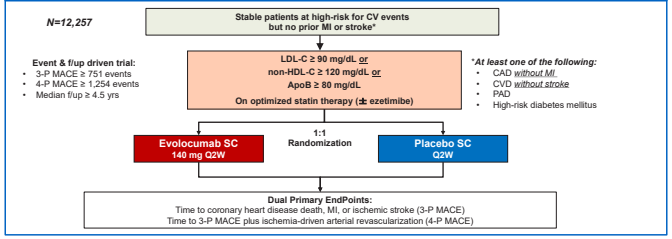
Background

- LDL-C is a well-established, modifiable CV risk factor[1]
- Lowering LDL-C with PCSK9 inhibitors, including evolocumab, ↓ the risk of CV events in patients with a prior, major ASCVD event, such as MI or stroke[2]
- Clinical benefit of PCSK9 inhibition in patients *without a prior MI or stroke* is unknown

ASCVD Continuum



Trial Design[3]



Trial Organization

TIMI Study Group
Marc Sabatine (Study Chair), Robert Giugliano (Co-Principal Investigator), Erin Bohula (Co-Principal Investigator), Nicholas Marston (Investigator), P. Fish, A. Pricken, R. Striar, S. Ewing (Ops) S. Murphy, J. Kuder, JG. Park (Stats), Christian Ruff (CEC)

Amgen (Sponsor)
Narimon Honarpour, E. Magnus Ohman, Gabriel Paiva da Silva Lima, Ajay Bhatia, Marcoli Cyrille, Vineet Shastri, J. Bayley, G. Harding, Y. Potapova (Ops) H. Wang, L. Liu, E. Walsh (Stats)

Executive Committee
Marc Sabatine (Chair), Robert Giugliano, Jose Nicolau, Lawrence Leiter, Gaetano De Ferrari

Independent Data Monitoring Committee
Charles Hennekens (Chair), Felicita Andreotti, W. Virgil Brown, Barry Davis

Enrollment and Retention

774 enrolling sites from 33 countries

- 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

†Excludes 44 from site with serious breach and GCP violations

Baseline Characteristics

Demographics	N=12,257
Age (years)	66 [60, 71]
Female	43%
White	93%
Hispanic	17%
Diabetes	58%

Qualifying Disease Categories*	
Any qualifying atherosclerosis	67%
CAD w/o MI	45%
CVD w/o stroke	10%
PAD	17%
High-risk diabetes	49%
With no qualifying atherosclerosis	33%

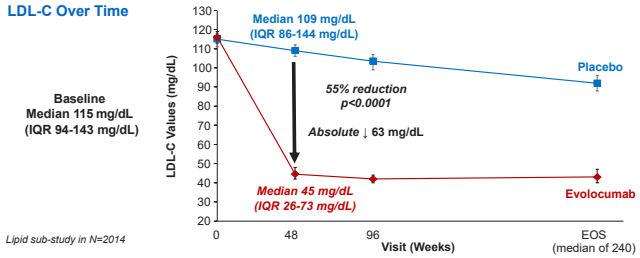
Lipid-lowering therapy (LLT)	
Any LLT	92%
High-intensity LLT regimen	72%
Any statin	87%
High-intensity statin	68%
Ezetimibe	20%

Lipid Values (mg/dL)	
LDL-C	122 [104, 149]
Non-HDL-C	153 [130, 182]
Apolipoprotein-B	100 [89, 121]

% or median and interquartile range.
Pooled data; no difference between treatment arms.
**Qualifying disease categories of CAD, CVD, PAD and high-risk diabetes are not mutually exclusive*

Results

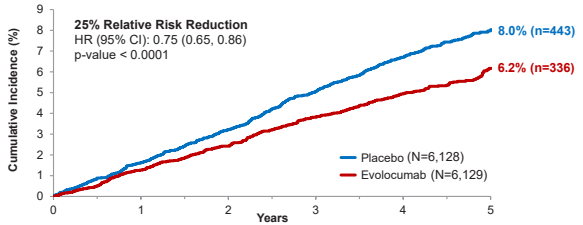
LDL-C Over Time



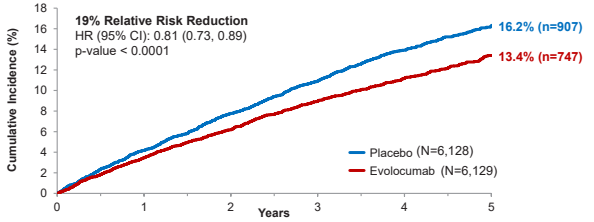
Lipid sub-study in N=2014

Dual Primary Endpoint

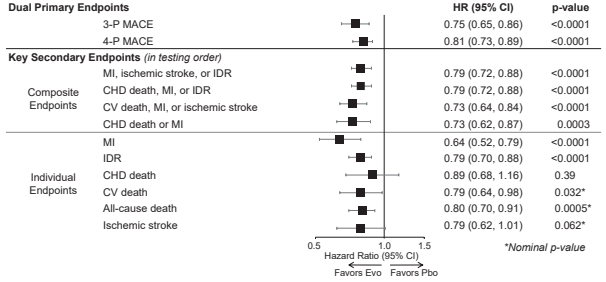
3-P MACE (CHD death, MI, or ischemic stroke)



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



Primary & Key Secondary EPs

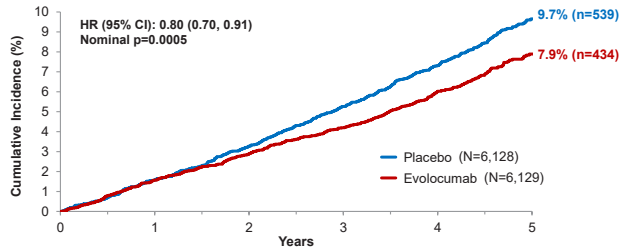


Conclusions

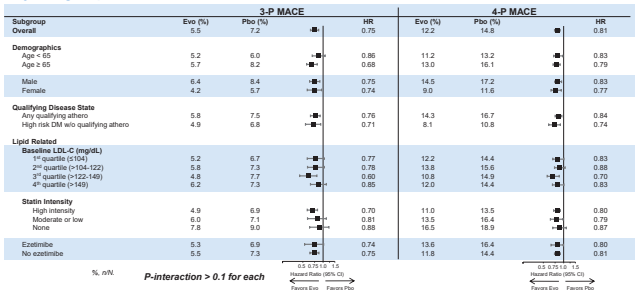
- **Guidelines have progressively recommended lower LDL-C goals of < 70 or < 55 mg/dL in very high-risk patients, and most recently < 40 mg/dL in extreme-risk patients.[6]**
- **The reduction in MACE seen in VESALIUS-CV, with an achieved LDL-C of ~40 mg/dL in the evolocumab arm, supports intensive LDL-C lowering to this level, even in patients without a prior major ASCVD event.[7,8]**

Results

All-Cause Death



Key Subgroups

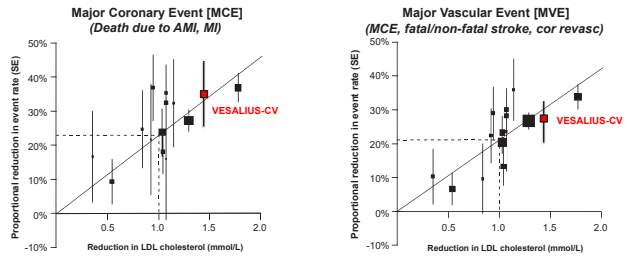


Subgroup	3-P MACE Evo (%)	3-P MACE Pbo (%)	3-P MACE HR	4-P MACE Evo (%)	4-P MACE Pbo (%)	4-P MACE HR
Overall	5.5	7.2	0.75	12.2	14.8	0.81
Demographics						
Age < 65	5.2	6.0	0.86	11.2	13.2	0.83
Age ≥ 65	5.7	8.2	0.68	13.0	16.1	0.79
Male	6.4	8.4	0.75	14.5	17.2	0.83
Female	4.2	5.7	0.74	9.0	11.6	0.77
Qualifying Disease State						
Any qualifying athero	5.8	7.5	0.76	14.3	16.7	0.84
High risk DM w/o qualifying athero	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

%, n/N. ***P-interaction > 0.1 for each***

Favors Evo / Favors Pbo

CTTC Meta-Regression[4,5]



Summary

- **In pts at high CV risk w/o prior MI or stroke, addition of the PCSK9 inhibitor, evolocumab, to baseline LLRx resulted in:**
  - Median achieved LDL-C of 45 mg/dL (1.16 mmol/L)
  - 25% ↓ in 3-P MACE and 19% ↓ in 4-P MACE
  - Consistency across subgroups, including in those with diabetes and no qualifying atherosclerosis
  - 27% ↓ in CV death, MI or ischemic stroke and 36% ↓ in MI
  - Nominally lower rates of CV and all-cause death

ABBREVIATIONS: **3-P**, three-point; **4-P**, four-point; **ASCVD**, atherosclerotic cardiovascular disease; **AMI**, acute myocardial infarction; **apoB**, apolipoprotein B; **ARR**, absolute risk reduction; **athero**, atherosclerosis; **BMI**, body mass index; **CAC**, coronary artery calcium; **CAD**, Coronary artery disease; **CHD**, coronary heart disease; **CI**, confidence interval; **cor revasc**, coronary revascularization; **CTTC**, Cholesterol Treatment Trialists' Collaboration; **CV**, cardiovascular; **CVD**, cerebrovascular disease; **d/c**, discontinuation; **DM**, diabetes mellitus; **EP**, endpoint; **EOS**, end of study; **Evo**, evolocumab; **FOURIER**, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; **f/up**, follow-up; **GCP**, good clinical practice; **HDL-C**, high-density lipoprotein cholesterol; **HR**, hazard ratio; **IDR**, ischemia-driven revascularization; **IQR**, Interquartile range; **KM**, Kaplan-Meier; **LDL-C**, low-density lipoprotein cholesterol; **LLT**, lipid-lowering therapy; **LLRx**, lipid-lowering therapy; **mAb**, monoclonal antibody; **MACE**, major adverse cardiovascular event; **MCE**, major coronary event; **MI**, myocardial infarction; **MVE**, major vascular event; **non-HDL-C**, non-high-density lipoprotein cholesterol; **ODYSSEY**, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; **PAD**, peripheral artery disease; **Pbo**, placebo; **PCSK9**, proprotein convertase subtilisin/kexin type 9; **pts**, patients; **Q2W**, every 2 weeks; **RRR**, relative risk reduction; **SC**, subcutaneous; **SE**, standard error; **VESALIUS-CV**, Effect of EVolocumab in PatiEntS at High CArdiovascuLar RIsk WithoUt Prior Myocardial Infarction or Stroke; **w/o**, without; **yrs**, years.

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REFERENCES: **1**. Sabatine MS, et al. *N Engl J Med*. 2017;376:1713-1722. **2**. Schwartz GG, et al. *N Engl J Med*. 2018;379:2097-2107. **3**. Bohula EA, et al. *Am Heart J*. 2024;269:179-190. **4**. Baigent C, et al. *Lancet*. 2005;366:1267-1278. **5**. Cholesterol Treatment Trialists' Collaboration. *Lancet*. 2010;376:1670-1681. **6**. Grundy SM, et al. *Circulation*. 2019;139:e1046-e1081. **7**. Mach F, et al. *Eur Heart J*. 2020;41:111-188. **8**. Mach F, et al. *Atherosclerosis*. 2025;409:120479.

DISCLAIMER: This study was previously presented at the American Heart Association (AHA) Scientific Sessions 2025, New Orleans, Louisiana, USA, 7-10 November 2025. These results were subsequently published in the New England Journal of Medicine (Bohula EA, et al. *N Engl J Med*. 2026;394:117-127).

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