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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Background

- **LDL-C is a well-established, modifiable CV risk factor**
- **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**
- **Clinical benefit of PCSK9 inhibition in patients *without a prior MI or stroke* is unknown**

Sabatine MS, et al. *NEJM.* 2017;376:1713-22.
Schwartz GG, et al. *NEJM.* 2018;379:2097-107.

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ASCVD Continuum

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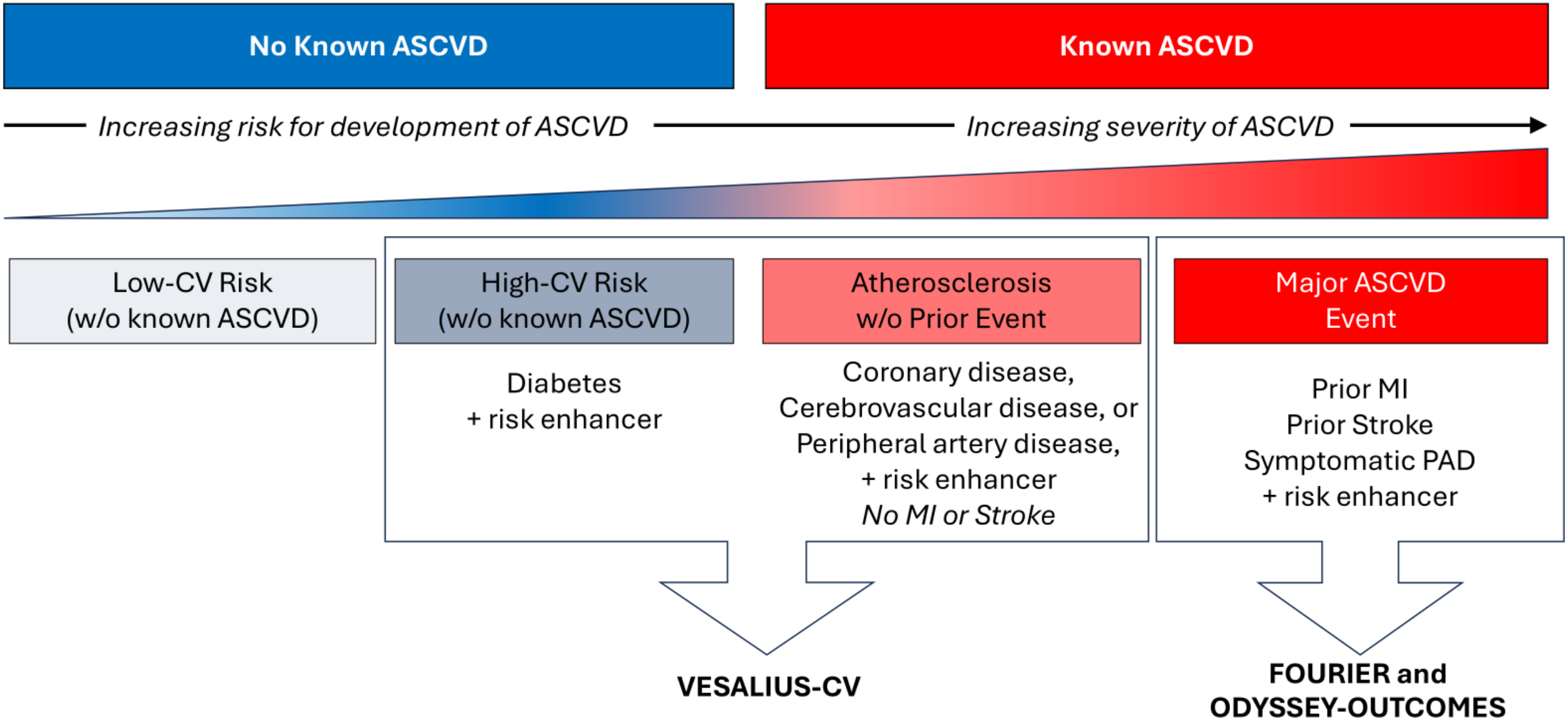

Trial Design

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N= 12,257

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

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

On optimized statin therapy (± ezetimibe)

1:1 Randomization

Evolocumab SC 140 mg Q2W

Placebo SC Q2W

Event & f/up driven trial:
- 3-P MACE ≥ 751 events
- 4-P MACE ≥ 1,254 events
- Median f/up ≥ 4.5yrs

***At least one of the following:**
- CAD *without MI*
- CVD *without stroke*
- PAD
- High-risk diabetes mellitus

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)

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

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

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Baseline Characteristics

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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*

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LDL-C Over Time

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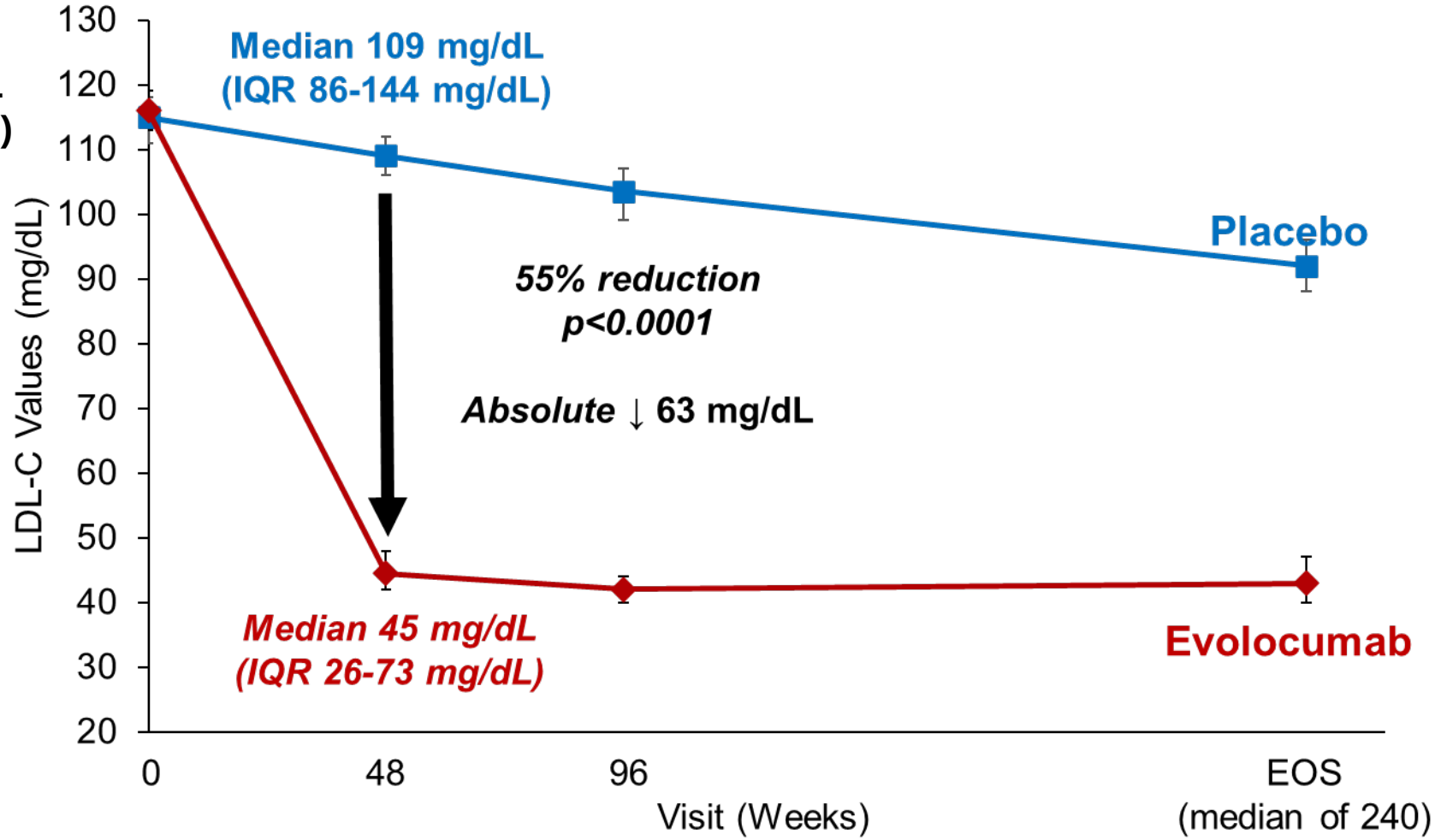
Baseline
Median 115 mg/dL
(IQR 94-143 mg/dL)



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Dual Primary Endpoint

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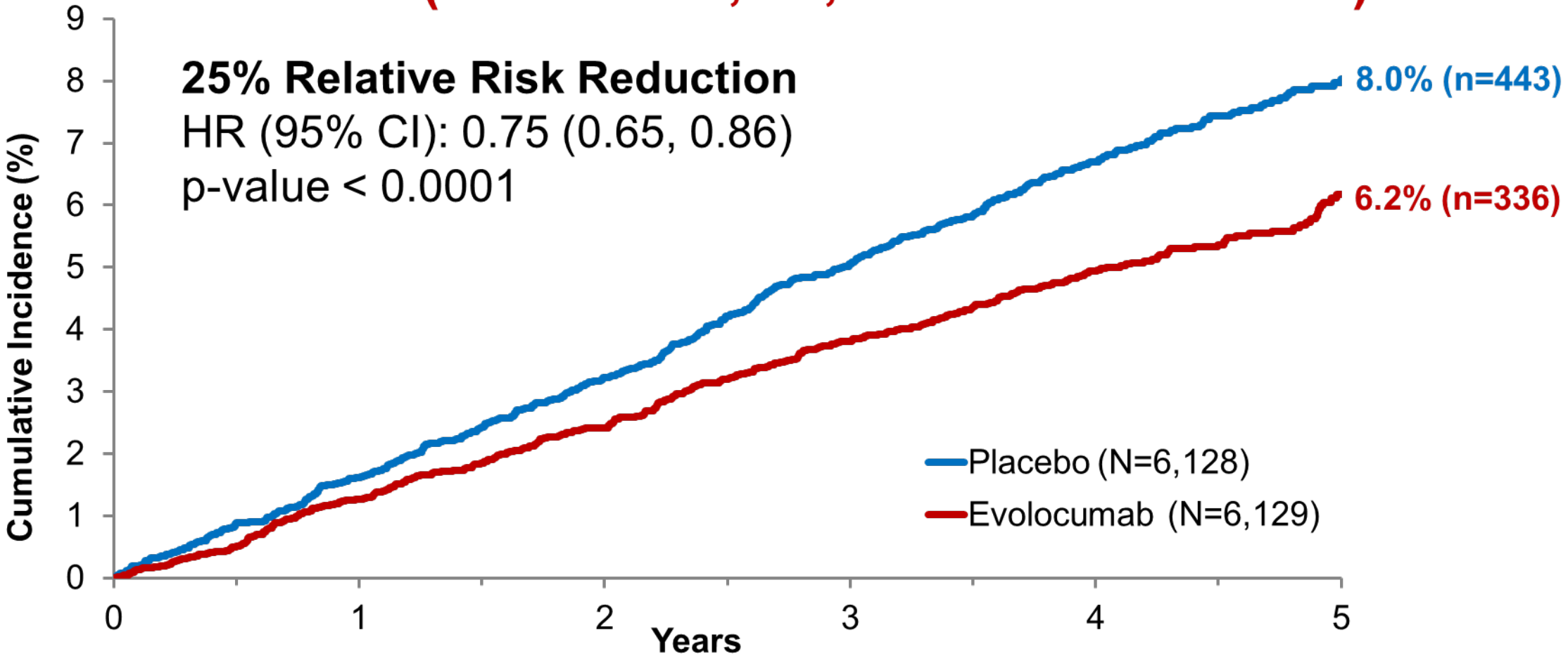
3-P MACE (CHD death, MI, or ischemic stroke)



CHD, coronary heart disease

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Dual Primary Endpoint

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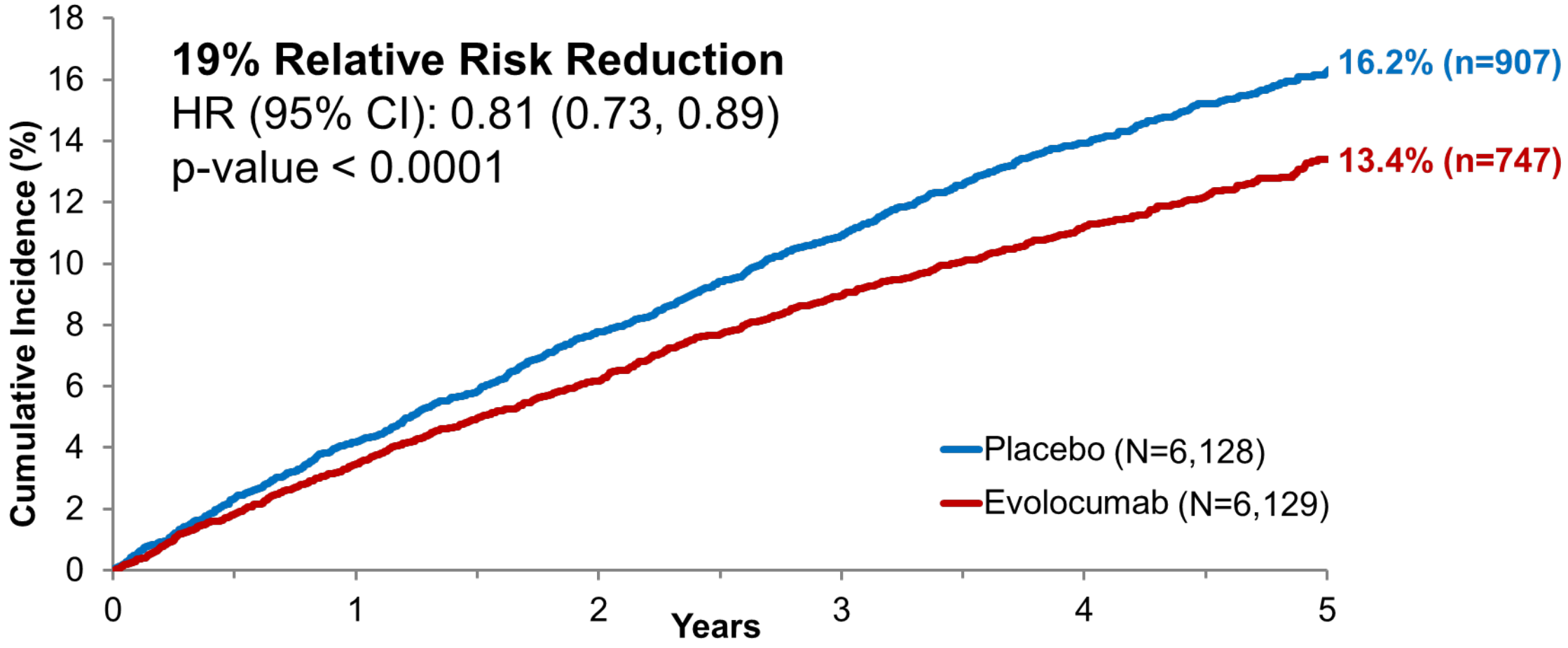
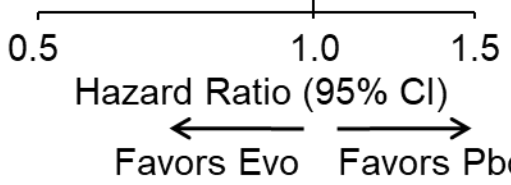
4-P MACE (CHD death, MI, ischemic stroke, or IDR)



CHD, coronary heart disease; IDR, ischemia-driven arterial revasc

Primary & Key Secondary EPs

		HR (95% CI)	p-value
Dual Primary Endpoints			
	3-P MACE	0.75 (0.65, 0.86)	<0.0001
	4-P MACE	0.81 (0.73, 0.89)	<0.0001
Key Secondary Endpoints *(in testing order)*			
Composite Endpoints	MI, ischemic stroke, or IDR	0.79 (0.72, 0.88)	<0.0001
	CHD death, MI, or IDR	0.79 (0.72, 0.88)	<0.0001
	CV death, MI, or ischemic stroke	0.73 (0.64, 0.84)	<0.0001
	CHD death or MI	0.73 (0.62, 0.87)	0.0003
Individual Endpoints	MI	0.64 (0.52, 0.79)	<0.0001
	IDR	0.79 (0.70, 0.88)	<0.0001
	CHD death	0.89 (0.68, 1.16)	0.39
	CV death	0.79 (0.64, 0.98)	0.032*
	All-cause death	0.80 (0.70, 0.91)	0.0005*
	Ischemic stroke	0.79 (0.62, 1.01)	0.062*



**Nominal p-value*

CHD, coronary heart disease
IDR, ischemia-driven arterial revasc

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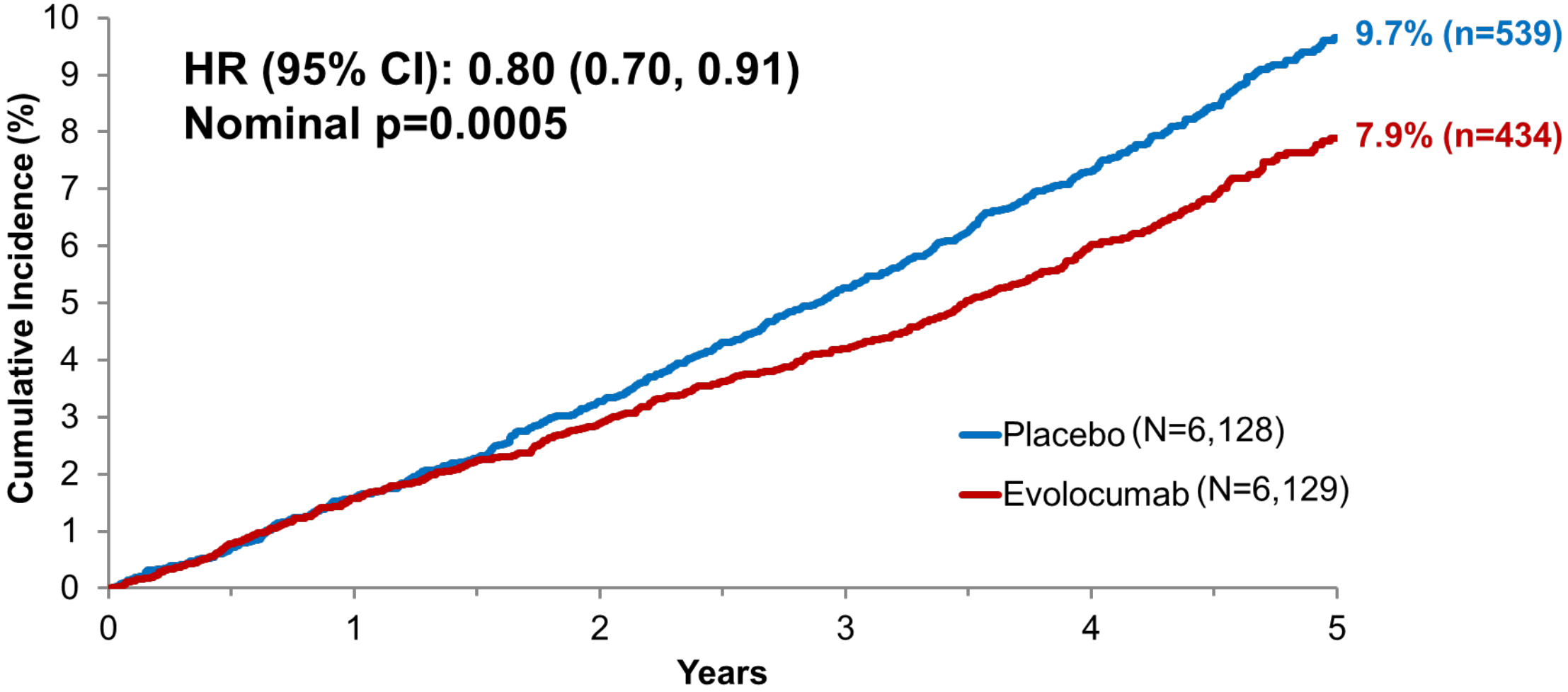
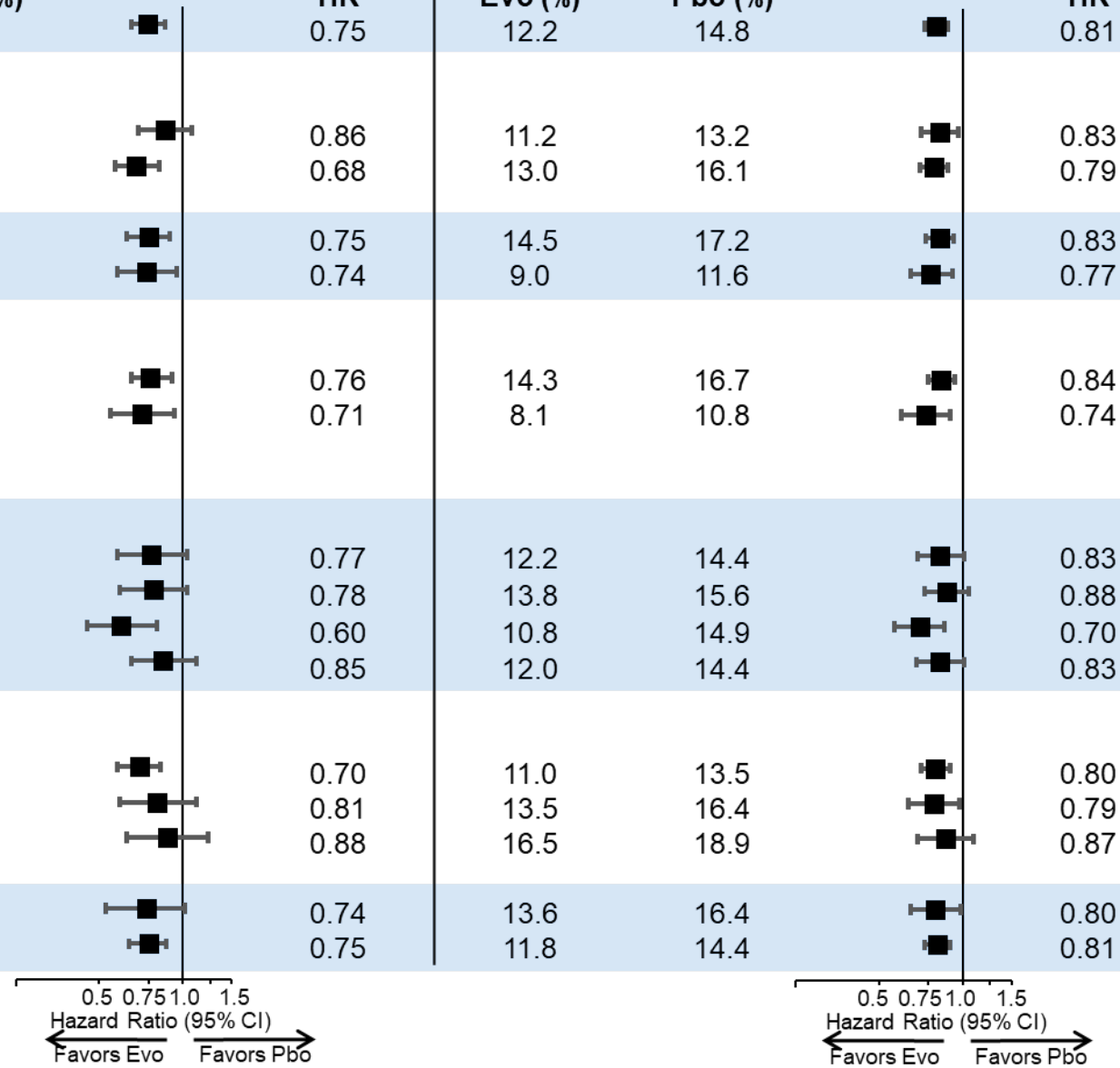
All-Cause Death



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

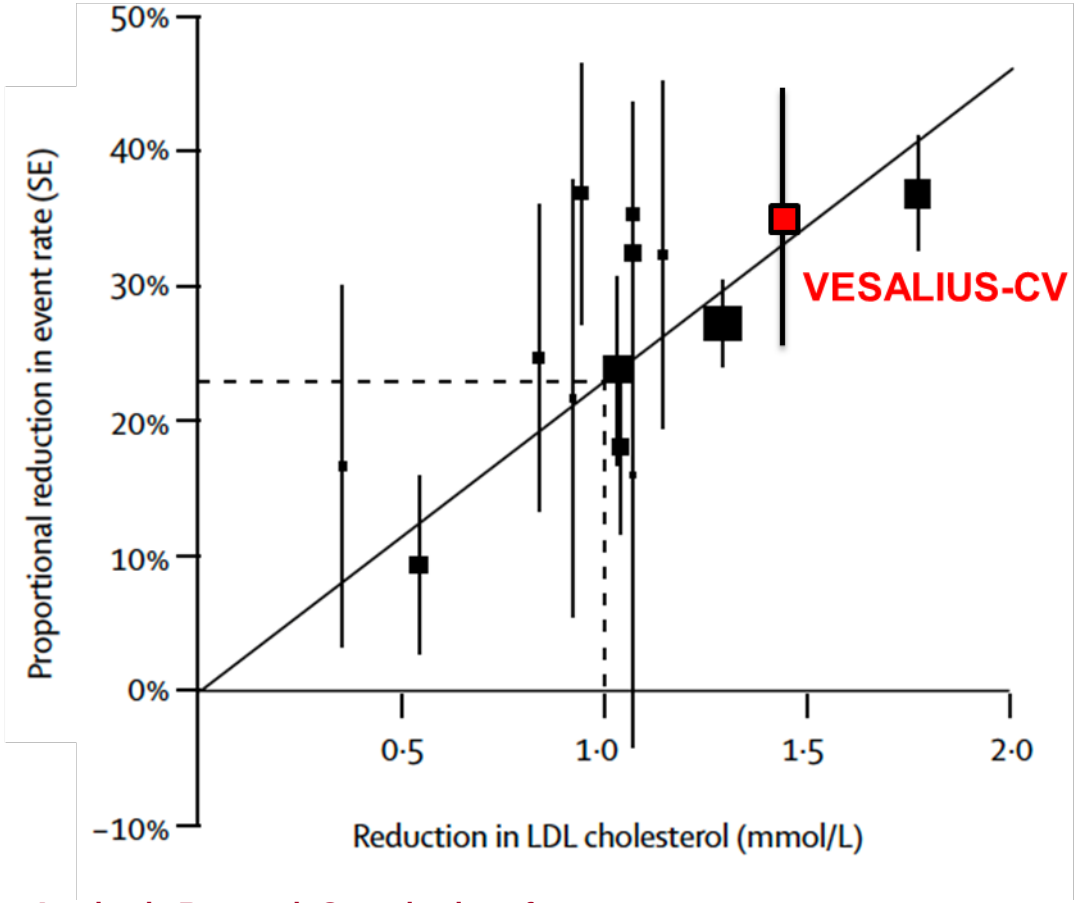


%, n/N.

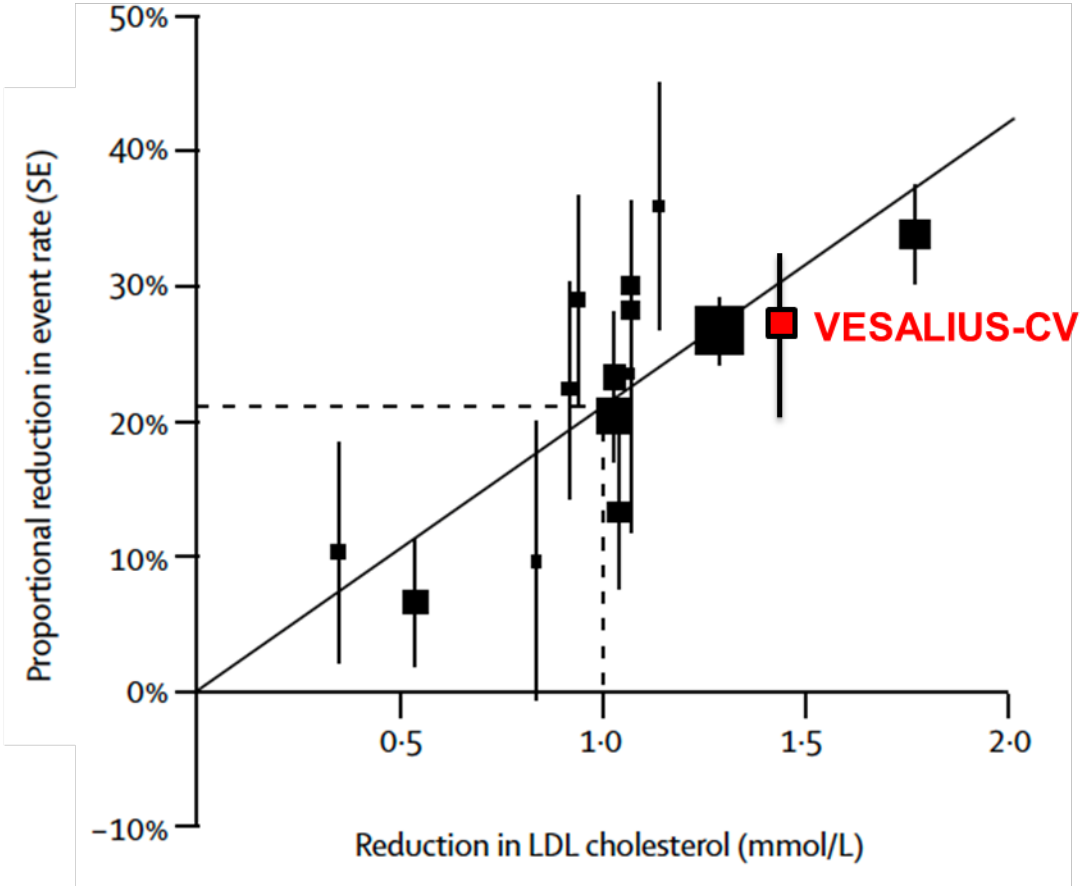
P-interaction > 0.1 for each

CTTC Meta-Regression

Major Coronary Event [MCE]
(Death due to AMI, MI)



Major Vascular Event [MVE]
(MCE, fatal/non-fatal stroke, cor revasc)



Lancet. 2005;366:1267-78.
Lancet. 2010;376:1670-81.

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Summary

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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

Conclusion

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.

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.

Grundy SM et al. *Circulation.* 2019;139:e1046-e81.
Mach F et al. *Eur Heart J.* 2020;41:111-88.
Mach F et al. *Atheroclerosis.* 2025:120479.

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ORIGINAL ARTICLE

Evolocumab in Patients without Previous Myocardial Infarction or Stroke

Erin A. Bohula, M.D., D.Phil.,[1] Nicholas A. Marston, M.D., M.P.H.,[1] Ajay K. Bhatia, M.D., Ph.D.,[2] Gaetano M. De Ferrari, M.D.,[3] Lawrence A. Leiter, M.D.,[4] Jose C. Nicolau, M.D.,[5] Jeong-Gun Park, Ph.D.,[1] Julia F. Kuder, M.A.,[1] Sabina A. Murphy, M.P.H.,[1] Emileigh Walsh, Ph.D.,[2] Huei Wang, Ph.D.,[2] Vladimir Blaha, M.D., Ph.D.,[6] Andrzej Budaj, M.D., Ph.D.,[7] Jan H. Cornel, M.D., Ph.D.,[8] Assen Goudev, M.D.,[9] Robert Gabor Kiss, M.D.,[10] Alberto J. Lorenzatti, M.D.,[11] Alexander Parkhomenko, M.D.,[12] Marcoli Cyrille, M.D.,[2] Gabriel Paiva da Silva Lima, M.D.,[2] E. Magnus Ohman, M.D.,[2] Robert P. Giugliano, M.D.,[1] and Marc S. Sabatine, M.D., M.P.H.,[1] for the VESALIUS-CV Investigators*

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