Effects of Evolocumab on Fatal Outcomes in Patients Without a Prior MI or Stroke:

Pre-specified Analysis of the VESALIUS-CV Trial

Vesalius, Andreas. *De humani corporis fabrica libri septem.* Basel: Johannes Oporinus, 1543, p. 164. Woodcut

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On behalf of the

VESALIUS-CV Investigators

ESC Congress 2026

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vesalius-cv

TIMI

Trial Design

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TIMI

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

***At least one of the following:**

- CAD *without MI*
- CVD *without stroke*
- PAD
- High-risk diabetes mellitus

Dual Primary Endpoints:

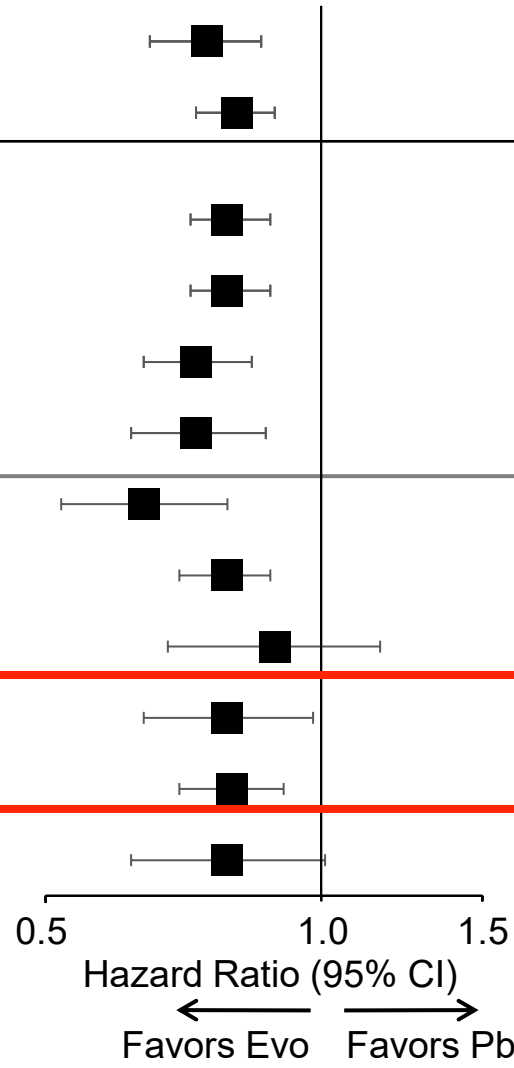
Time to coronary heart disease death, MI, or ischemic stroke (3-P MACE)

Time to 3-P MACE plus ischemia-driven arterial revascularization (4-P MACE)

Bohula EA, *Am Heart J.* 2024;269:179-90.

Vesalius-cv 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*



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

**Nominal p-value*

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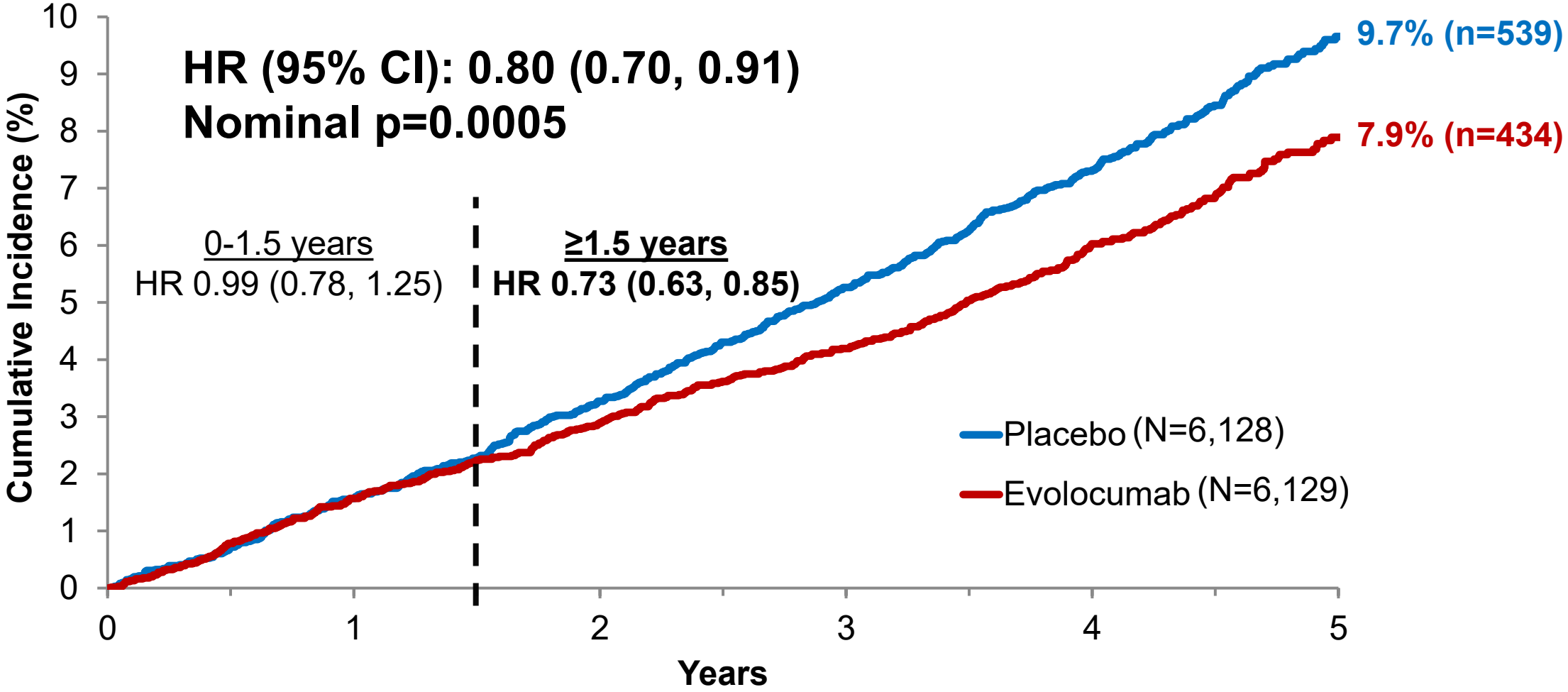
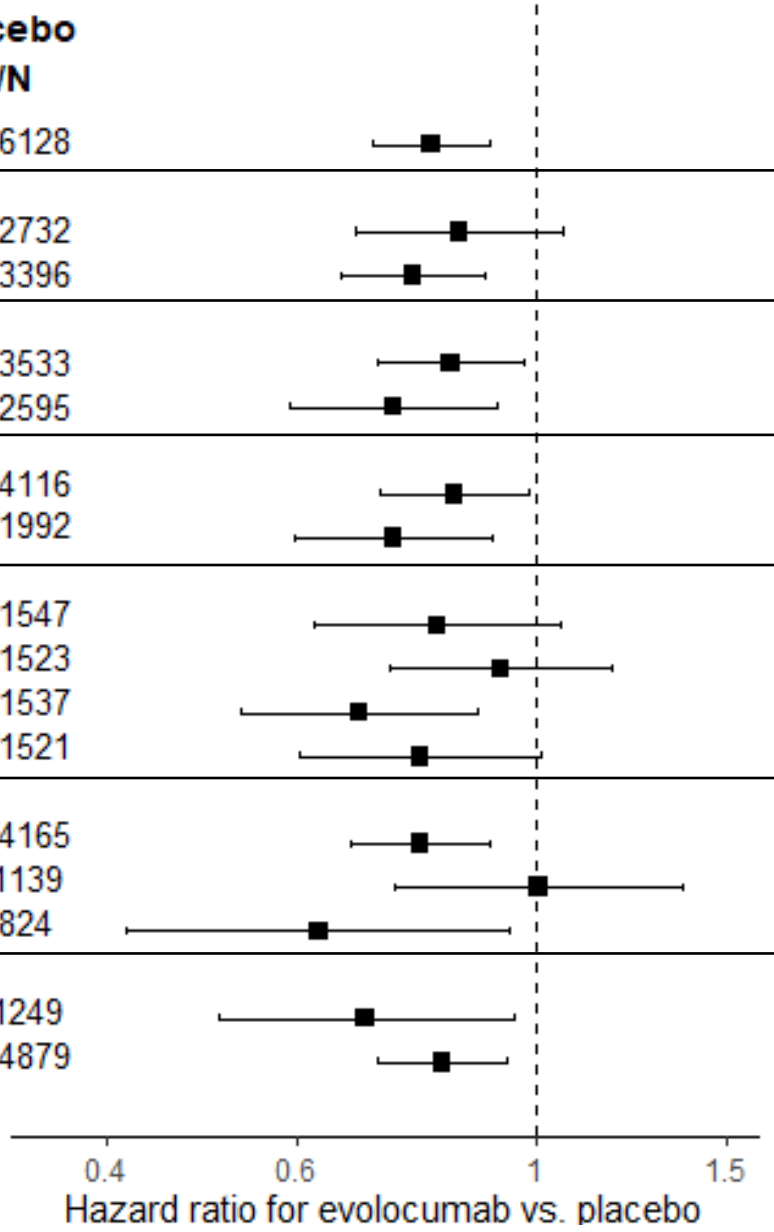
Bohula EA. *NEJM.* 2026;394:117-27

All-Cause Death



All-Cause Mortality in Key Subgroups

	Evolocumab n/N	Placebo n/N	Hazard ratio (95% CI)
Overall	434/6129	539/6128	0.80 (0.70–0.91)
Age			
<65 yr	141/2657	169/2732	0.85 (0.68–1.06)
≥65 yr	293/3472	370/3396	0.77 (0.66–0.90)
Sex			
Male	294/3510	354/3533	0.83 (0.71–0.97)
Female	140/2619	185/2595	0.74 (0.59–0.92)
Qualifying disease category			
Any qualifying atherosclerosis	282/4092	337/4116	0.84 (0.72–0.98)
High-risk DM w/o qual athero	151/2009	200/1992	0.74 (0.60–0.91)
LDL cholesterol at baseline			
≤104 mg/dl	100/1546	124/1547	0.81 (0.62–1.05)
>104–122 mg/dl	131/1550	138/1523	0.93 (0.73–1.18)
>122–149 mg/dl	101/1512	147/1537	0.69 (0.53–0.88)
>149 mg/dl	102/1520	130/1521	0.78 (0.60–1.01)
Statin intensity			
High	312/4160	398/4165	0.78 (0.67–0.91)
Moderate or low	85/1179	80/1139	1.00 (0.74–1.36)
None	37/790	61/824	0.63 (0.42–0.94)
Ezetimibe			
Yes	65/1188	95/1249	0.69 (0.51–0.95)
No	369/4941	444/4879	0.82 (0.71–0.94)



P-int >0.16 for each subgroup

Favors evolocumab

Favors placebo

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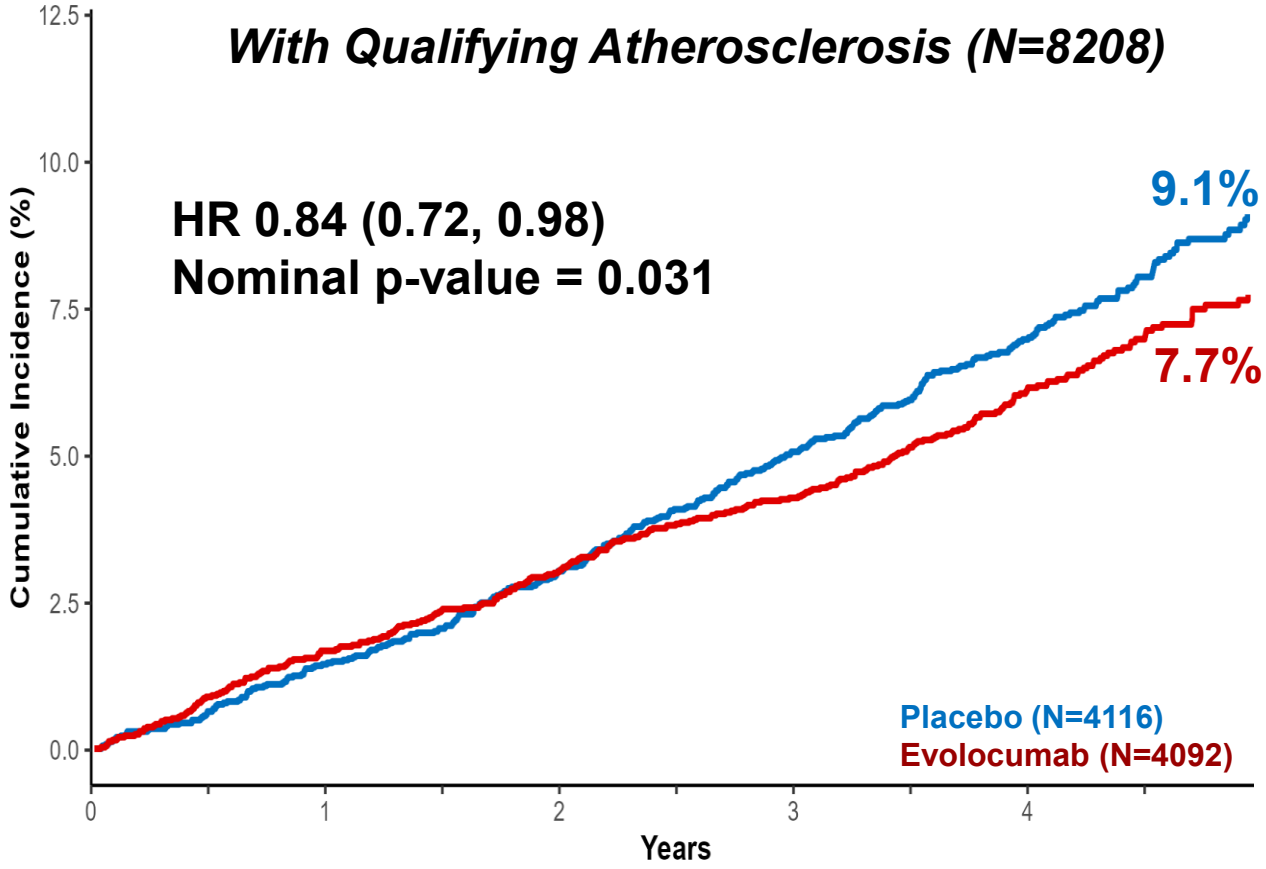
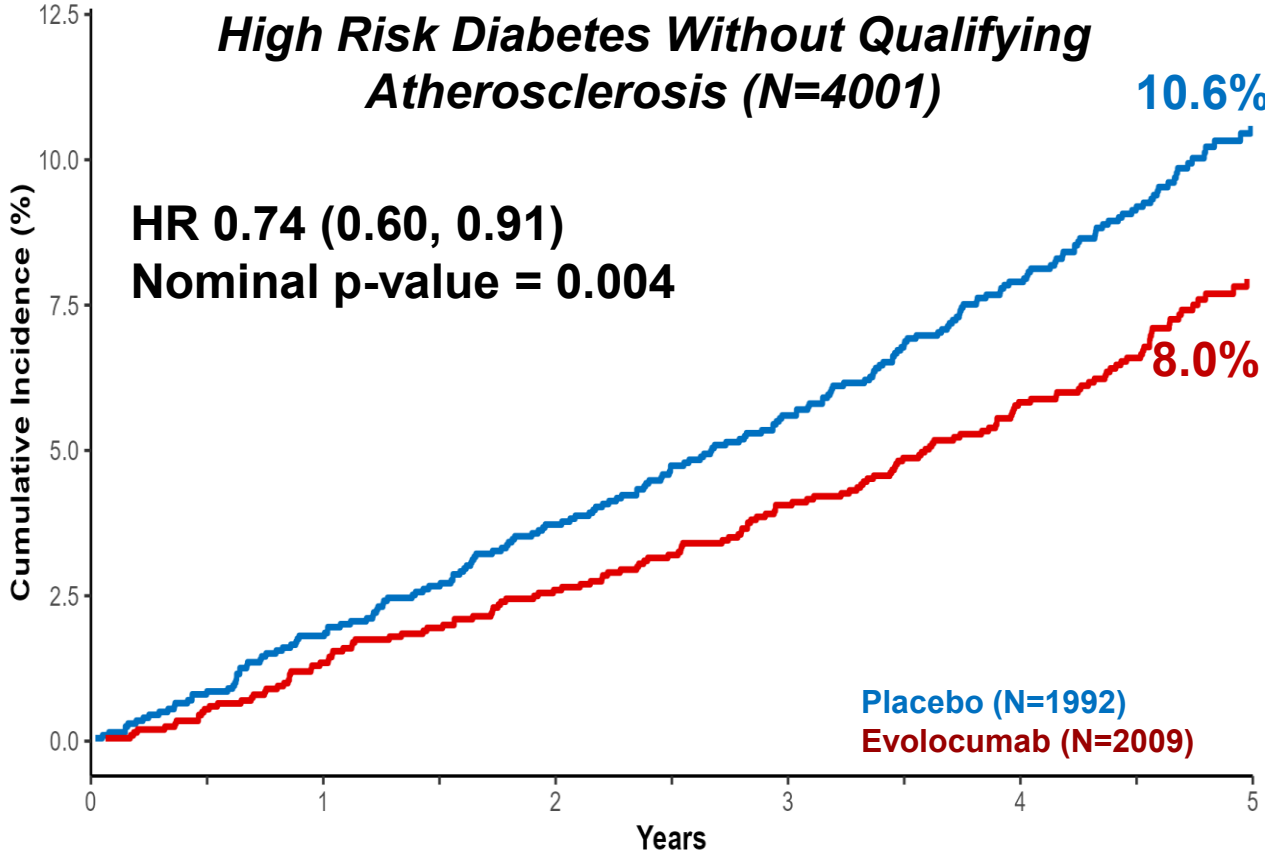
All-Cause Mortality By Qualifying Disease State

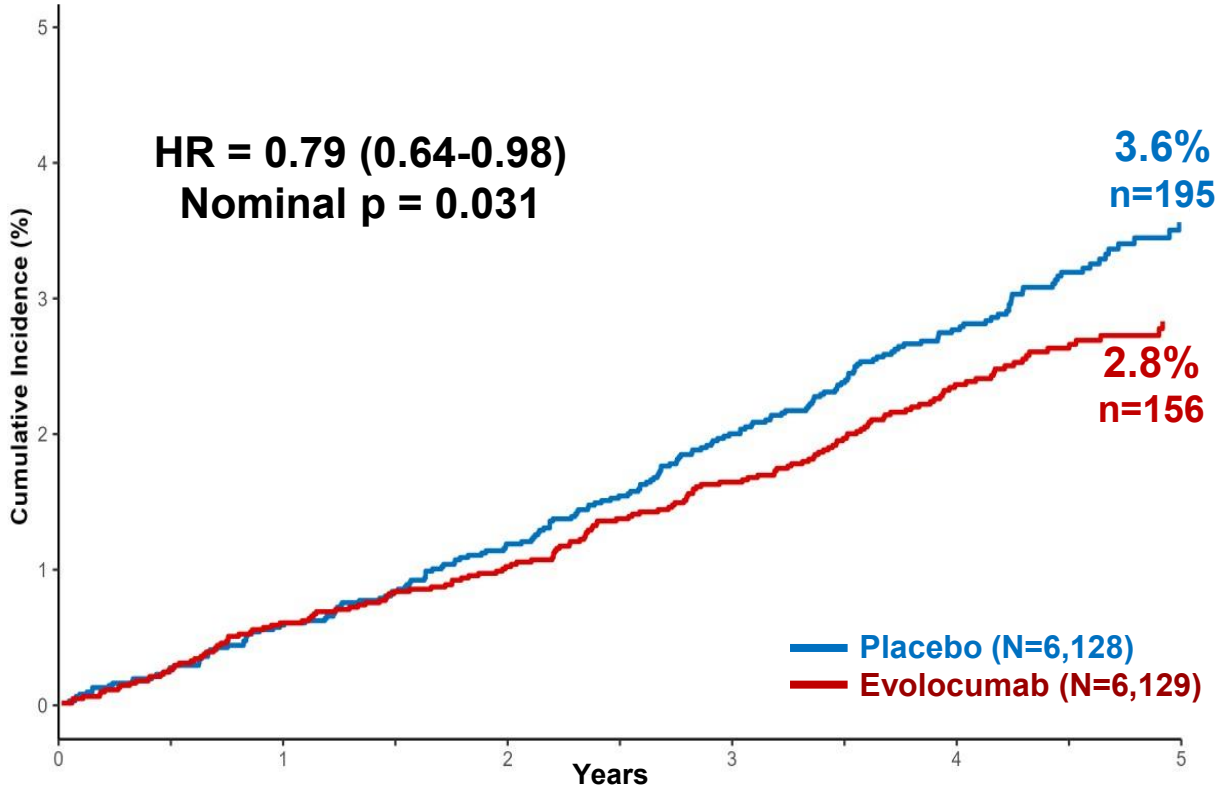




P-interaction = 0.34

CV and Non-CV Death

Cardiovascular Death



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Causes of Death

TIMI

	No. events (5-yr KM rate, %)		HR (95% CI)	P Value
	Evolocumab	Placebo		
All-cause mortality	434 (7.9)	539 (9.7)	0.80 (0.70–0.91)	0.0005*
Cardiovascular (CV)	156 (2.8)	195 (3.6)	0.79 (0.64–0.98)	0.031*
Non-Cardiovascular	229 (4.2)	268 (5.0)	0.85 (0.71–1.01)	0.065**
Undetermined	49 (1.1)	76 (1.4)	0.64 (0.45–0.92)	0.014**

*P-values are nominal because coronary heart disease death, which was higher on the prespecified hierarchy, was not statistically significant
**These endpoints were not prespecified in the hierarchical testing

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Types of CV Death

TIMI

	No. events (5-yr KM rate, %)		HR (95% CI)
	Evolocumab	Placebo	
Cardiovascular Death	156 (2.8)	195 (3.6)	0.79 (0.64–0.98)
Sudden Cardiac Death*	87 (1.6)	87 (1.5)	0.99 (0.74–1.34)
Heart Failure	25 (0.4)	33 (0.6)	0.75 (0.45–1.26)
Acute myocardial infarction	19 (0.4)	25 (0.5)	0.76 (0.42–1.37)
Stroke	15 (0.3)	24 (0.4)	0.62 (0.33–1.18)
Cardiovascular Procedure	3 (0.1)	10 (0.2)	0.29 (0.08–1.07)
Cardiovascular Hemorrhage	3 (0.1)	5 (0.1)	0.59 (0.14–2.48)
Other Cardiovascular Causes	4 (0.1)	11 (0.2)	0.36 (0.11–1.13)

*88 (51%) of the 174 SCDs were unwitnessed

Sudden Cardiac Death

Subcategories of Sudden Cardiac Death*	Total (%)	Evo	Pbo
Witnessed and new or worsening symptoms	32 (18.4%)	15	17
Unsuccessful resuscitation from cardiac arrest	25 (14.4%)	11	14
Witnessed ≤ 60 min onset of new or worsening cardiac symptoms	21 (12.1%)	10	11
Witnessed and due to arrhythmia	8 (4.6%)	3	5

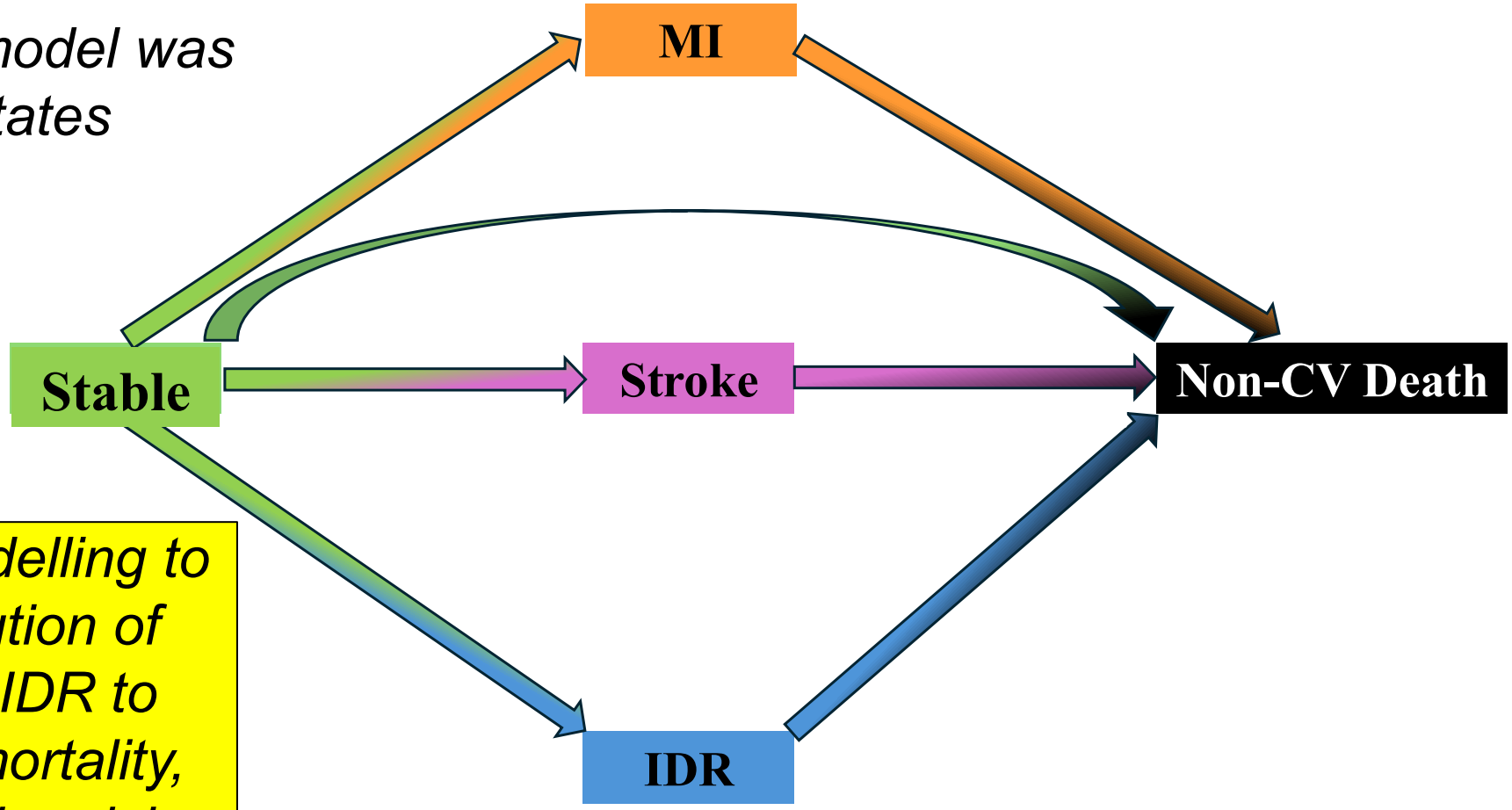
If only including witnessed events or deaths due to cardiac arrest, then 39 (evolocumab) vs 47 (placebo) events, HR 0.82 (0.54-1.26)

Evo, evolocumab; Pbo, placebo

*From the 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. Hicks KA. *Circulation.* 2018;137:961–972.

Vesalius-cv Multistate Modelling of Non-CV Death

Post randomization, model was comprised of 5 states



Can use multistate modelling to calculate the contribution of non-fatal MI, IS, and IDR to subsequent non-CV mortality, accounting for competing risks

Risk of Non-CV Death After a Non-Fatal CV Event*

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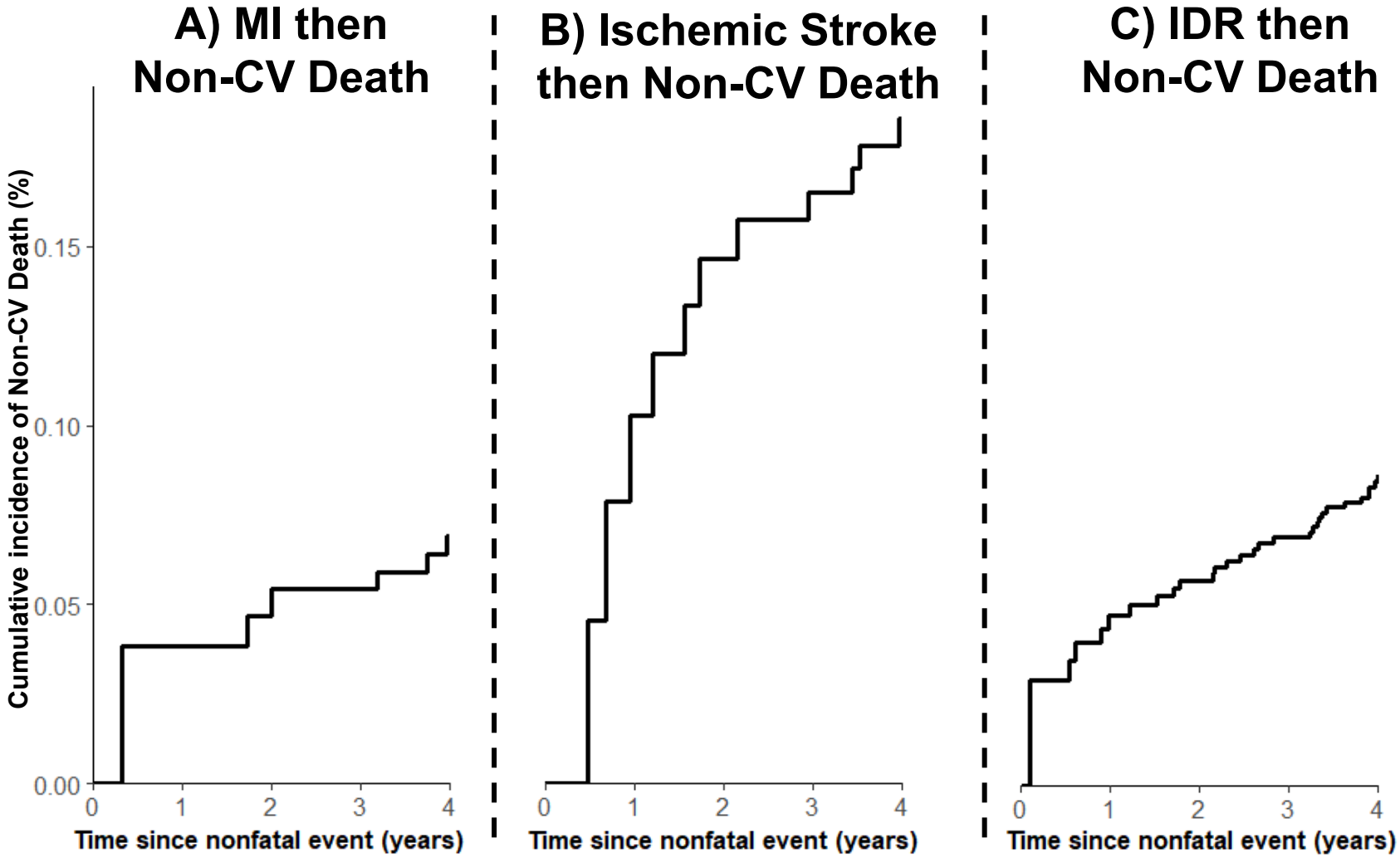
TIMI

Cumulative hazard of a non-CV death after:
A) Myocardial infarction
B) Ischemic stroke
C) Ischemia-driven revasc

Independent of Rx group, non-fatal CV events were assoc. with a high risk of subsequent non-CV mortality, especially early after an event



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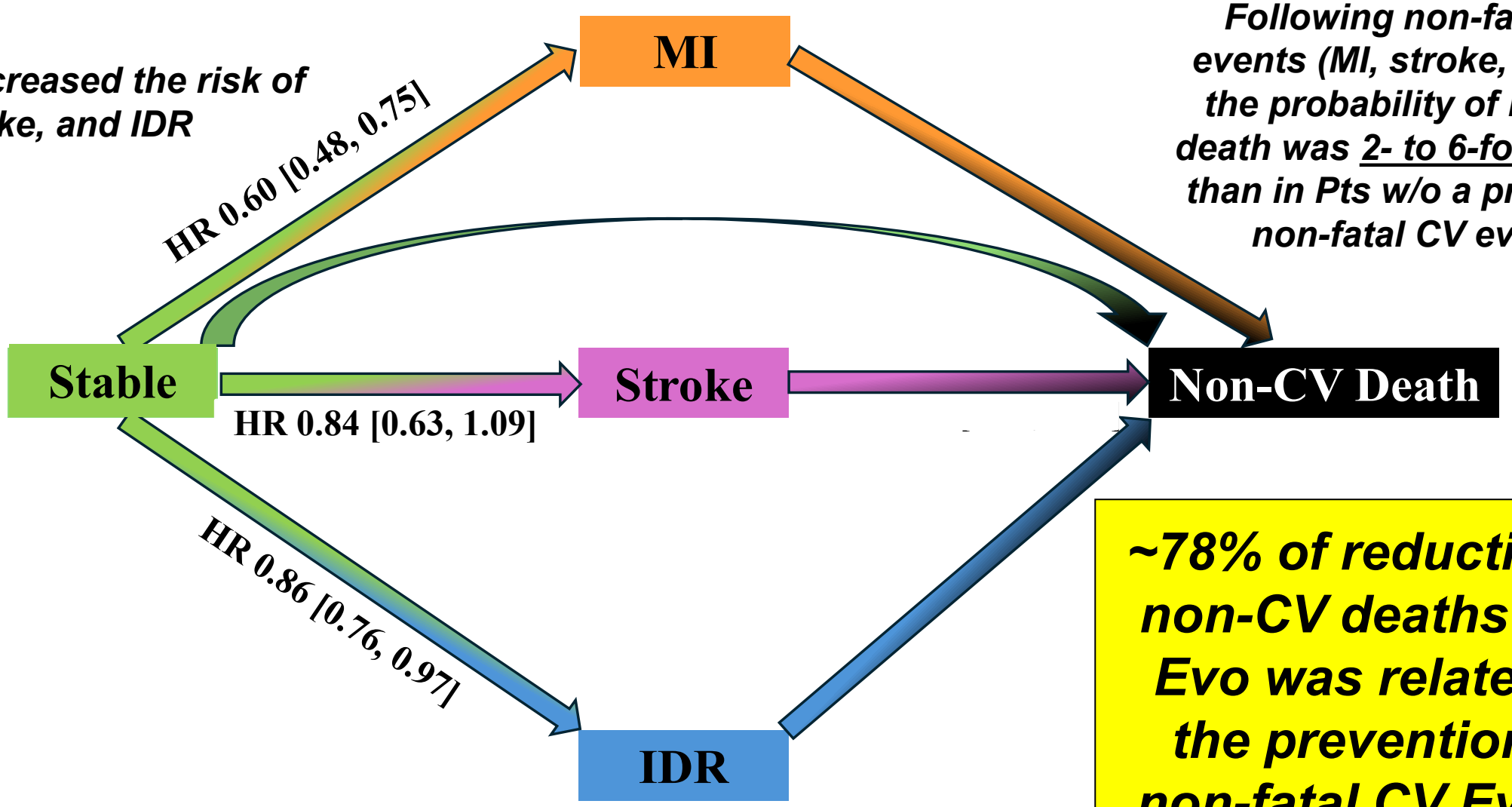
CV, cardiovascular; MI, myocardial infarction; IDR, ischemia-driven arterial revascularization

*independent of randomized treatment

Multistate Modelling



Evo decreased the risk of MI, stroke, and IDR

Following non-fatal CV events (MI, stroke, or IDR), the probability of non-CV death was 2- to 6-fold higher than in Pts w/o a preceding non-fatal CV event

~78% of reduction in non-CV deaths with Evo was related to the prevention of non-fatal CV Events

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Summary

TIMI

1. Evolocumab was associated with lower rates of:
   - ➢ All-cause mortality (20%↓)
   - ➢ CV death (21%↓), non-CV death (15%↓)
2. Findings consistently favored evolocumab in subgroups and for specific causes of CV death (except for unwitnessed sudden deaths)
3. Reduction in non-CV deaths appeared to be largely explained by lower rates of non-fatal MI, stroke and IDR with evolocumab

Circulation

Effects of Evolocumab on Mortality Outcomes in Patients Without Prior Myocardial Infarction or Stroke: A Prespecified Analysis of the VESALIUS-CV Randomized Clinical Trial

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