Clinical Benefit of Evolocumab in Patients with a History of MI: An Analysis from FOURIER

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Peter S. Sever, and Terje R. Pedersen,
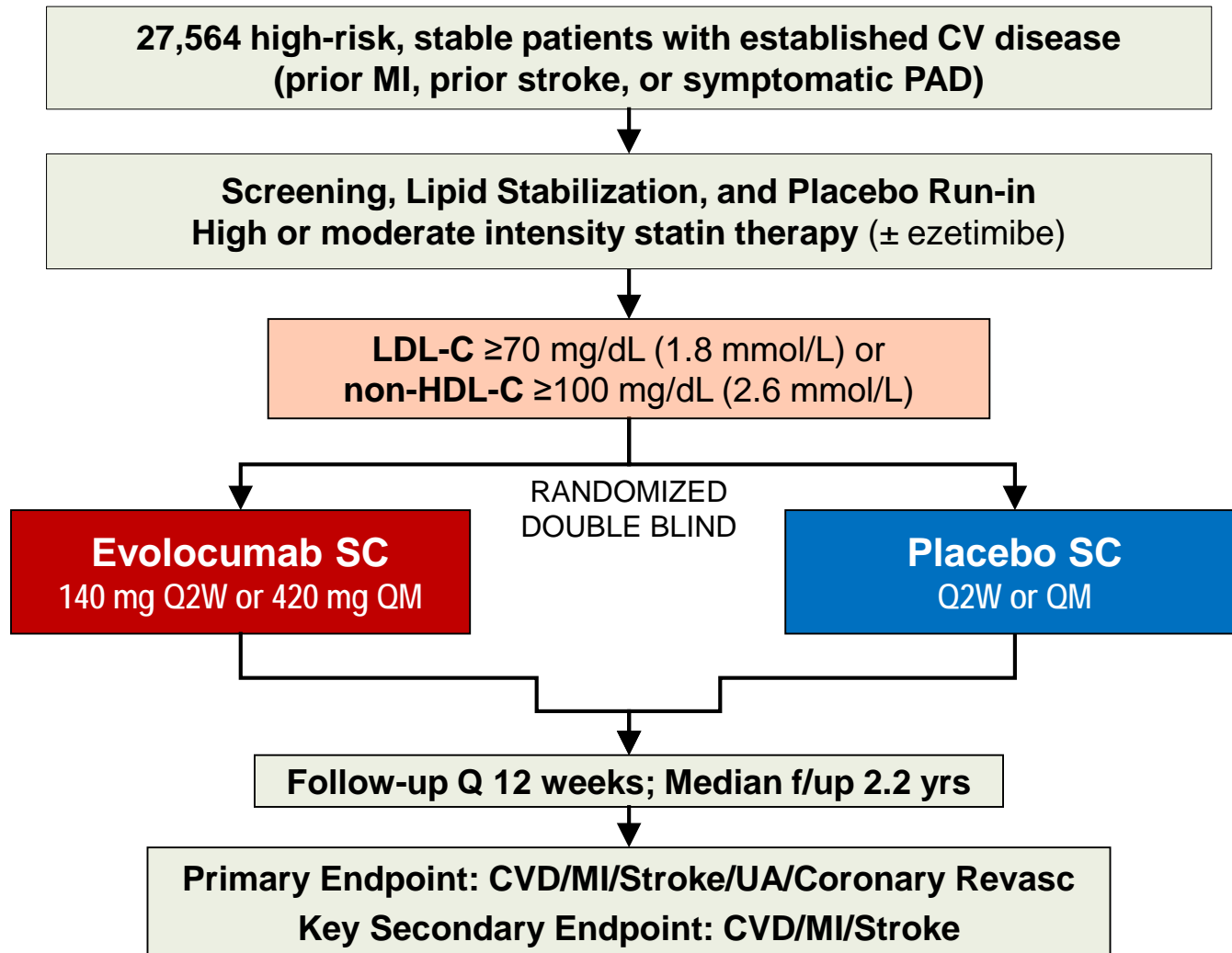for the FOURIER Steering Committee & Investigators

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Late-Breaking Science in Prevention

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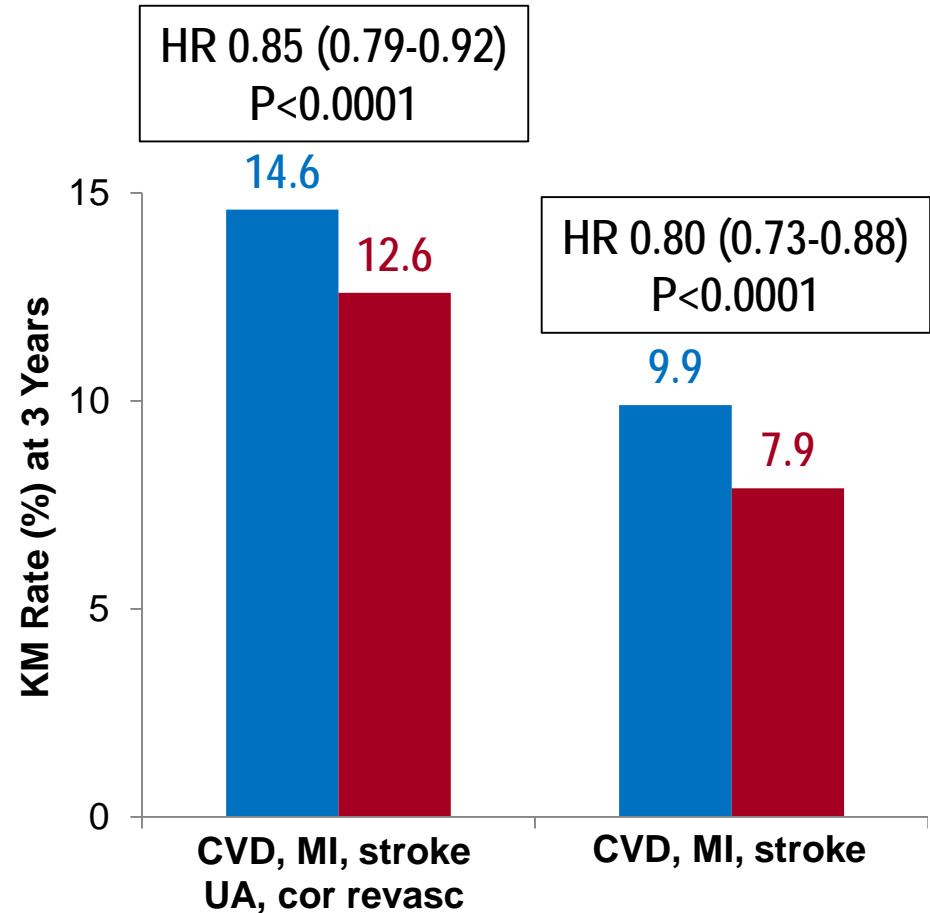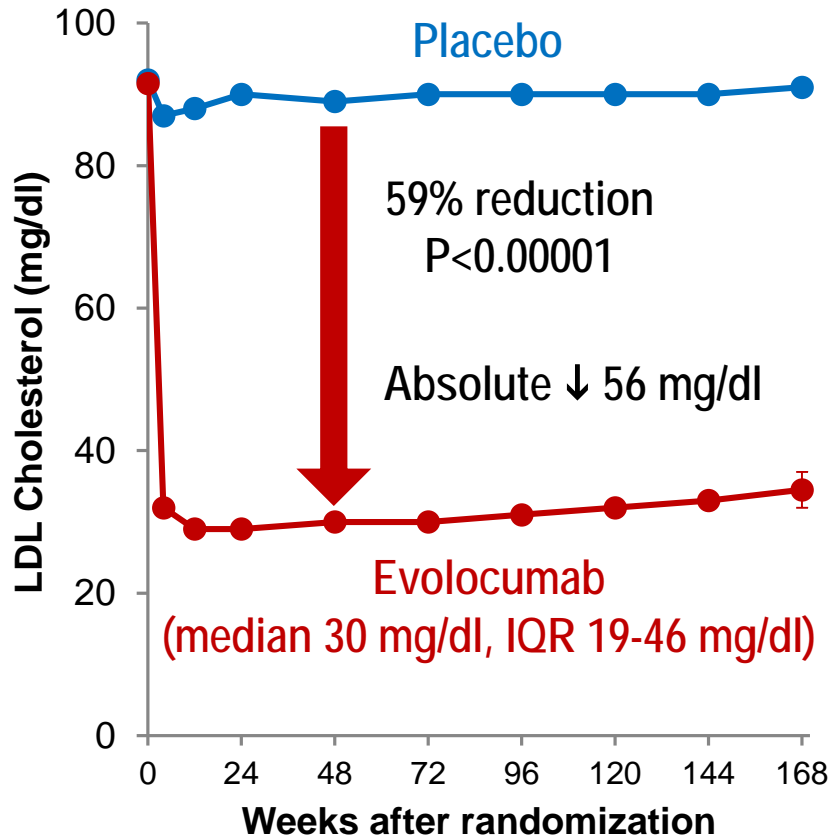Brigham and Women's Hospital and Harvard Medical School**

Trial Design

27,564 high-risk, stable patients with established CV disease
(prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in
High or moderate intensity statin therapy (± ezetimibe)

LDL-C ≥70 mg/dL (1.8 mmol/L) or
non-HDL-C ≥100 mg/dL (2.6 mmol/L)

RANDOMIZED
DOUBLE BLIND

Evolocumab SC
140 mg Q2W or 420 mg QM

Placebo SC
Q2W or QM

Follow-up Q 12 weeks; Median f/up 2.2 yrs

Primary Endpoint: CVD/MI/Stroke/UA/Coronary Revasc
Key Secondary Endpoint: CVD/MI/Stroke

Summary of Effects of PCSK9i Evolocumab

- **↓ LDL-C by 59% down to a median of 30 mg/dl**
- **↓ CV outcomes in patients on statin**
- **Safe and well-tolerated**

LDL Cholesterol plot:
- Placebo
- 59% reduction P<0.00001
- Absolute ↓ 56 mg/dl
- Evolocumab (median 30 mg/dl, IQR 19-46 mg/dl)
- X-axis: Weeks after randomization (0, 24, 48, 72, 96, 120, 144, 168)
- Y-axis: LDL Cholesterol (mg/dl)

Bar chart:
- HR 0.85 (0.79-0.92) P<0.0001
- HR 0.80 (0.73-0.88) P<0.0001
- CVD, MI, stroke UA, cor revasc: 14.6 / 12.6
- CVD, MI, stroke: 9.9 / 7.9
- Y-axis: KM Rate (%) at 3 Years

Background & Objective

Patients at higher CV risk may derive greater benefit from PCSK9 inhibition

Within the broad subgroup of patients w/ prior MI in FOURIER, we investigated if readily ascertainable clinical features of the CAD history identified patients:

1) At higher CV risk

2) Who derived greater benefit from PCSK9 inhibition

High-Risk Features in Patients with History of MI

21,162 patients with prior MI randomized to ticagrelor vs. placebo on a background of aspirin

	Subgroup	Placebo Arm 3-yr KM Rate of CVD/MI/Stroke	Relative Risk Reduction	Absolute Risk Reduction
	All patients	9.0%	16%	1.3%
Time from prior MI	<2 yrs	9.7%	23%	2.0%
	≥2 yrs	7.9%	4%	0.4%
# of prior MIs	≥2 MI's	15.2%	15%	1.6%
	1 MI	7.8%	17%	1.2%
Multivessel CAD	MVD	9.4%	19%	1.6%
	No MVD	8.6%	12%	0.9%

Bonaca MP et al. *NEJM* 2015;372:1791-1800
Dellborg M et al. *ESC* 2017
Bonaca MP et al. JACC 2017;70:1368-75
Bansilal S et al. *JACC* 2016;67(Suppl):2146

Methods

- **Analyses restricted to 22,351 Pts w/ prior MI**

- **Divided into subgroups on basis of 3 factors** (all of which were prespecified enrichment risk factors)**:**
  - Time from qualifying MI
  - # of prior MI's at baseline
  - Presence of residual multivessel disease at baseline

- **Outcome of interest: CV death, MI, or stroke**

- **Analyses**
  - Risk of CV events in placebo arm in patients w/ or w/o a specific high-risk feature
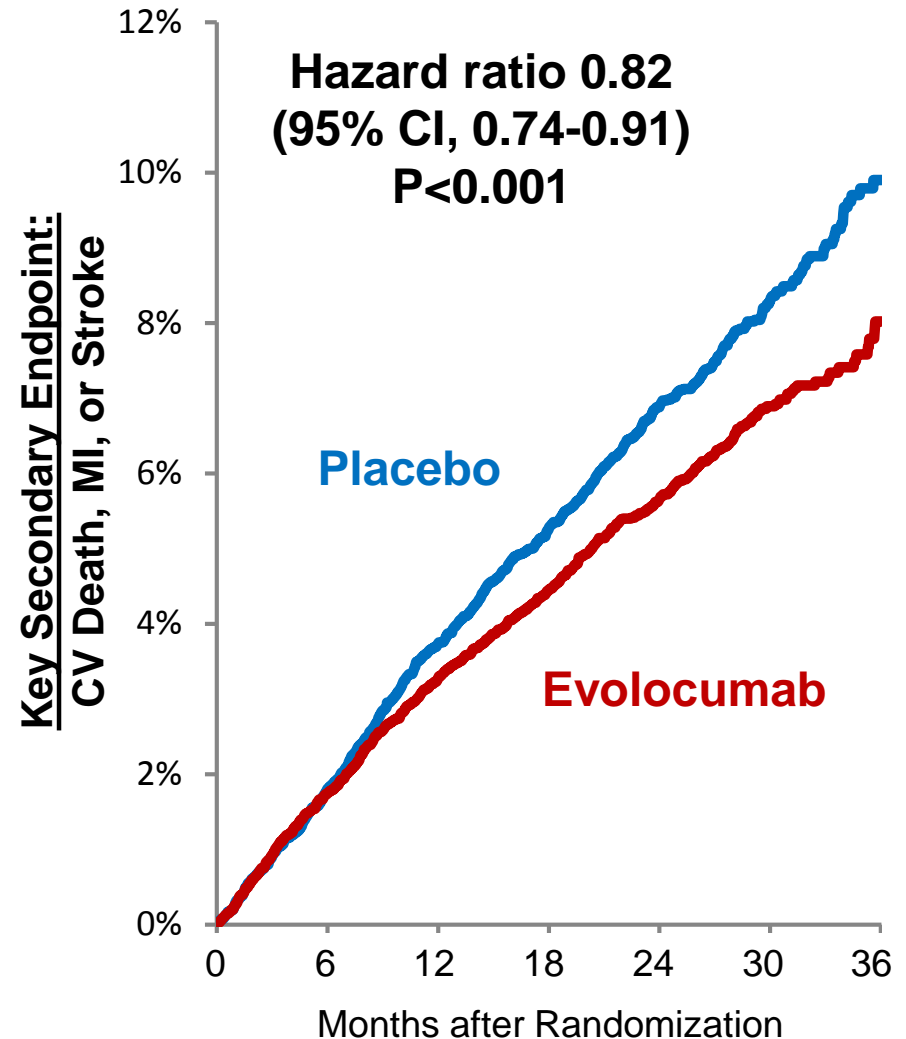 - Efficacy of evolocumab vs. placebo within each subgroup

Prior MI Overall

22,351 patients (81% of overall trial)

Characteristic	Value
Age, mean (SD)	62 (9)
Male sex (%)	78
Hypertension (%)	79
Diabetes mellitus (%)	35
Current smoker (%)	28
High-intensity statin (%)	71
LDL-C, mg/dL (IQR)	92 (80-109)
LDL-C w/ EvoMab at 48 wk, mg/dL (IQR)	30 (19-46)

**Hazard ratio 0.82
(95% CI, 0.74-0.91)
P<0.001**

Key Secondary Endpoint:
CV Death, MI, or Stroke

Placebo

Evolocumab

Months after Randomization

High-Risk Features and Other Baseline Characteristics

Characteristic	Time from Qualifying MI		# Prior MIs		Residual Multivessel CAD	
	<2 y ago N=8402 (38%)	≥2 y ago N=13,918 (62%)	≥2 N=5285 (24%)	1 N=17,047 (76%)	MVD N=5618 (25%)	No MVD N=16,715 (75%)
Age, mean (SD)	60 (9)	63 (9)	62 (9)	62 (9)	62 (9)	62 (9)
Male sex (%)	77	79	82	77	81	78
Hypertension (%)	75	81	81	78	82	78
Diabetes mellitus (%)	31	38	36	35	35	35
Current smoker (%)	28	28	26	28	26	28
High-intensity statin (%)	76	69	75	70	74	70
LDL-C, mg/dL (IQR)	90 (79-106)	93 (80-110)	92 (81-105)	92 (80-108)	93 (81-110)	92 (80-108)
LDL-C w/ EvoMab at 48 wk, mg/dL (IQR)	29 (19-45)	30 (18-46)	30 (19-46)	29 (19-46)	30 (19-46)	29 (18-46)

Risk of CV Death, MI or Stroke with Each Risk Factor

HR 1.19 (1.04-1.37) P=0.01

HR 2.04 (1.78-2.35) P<0.001

HR 1.47 (1.27-1.70) P<0.001

CVD, MI or Stroke (3-yr KM) in Pbo

Years from Qualifying MI
- <2 yrs: 10.8%
- ≥2 yrs: 9.3%

# of Prior MIs
- ≥2: 15.0%
- 1: 8.2%

Multivessel Disease
- Yes: 12.6%
- No: 8.9%

Analyses in placebo arm
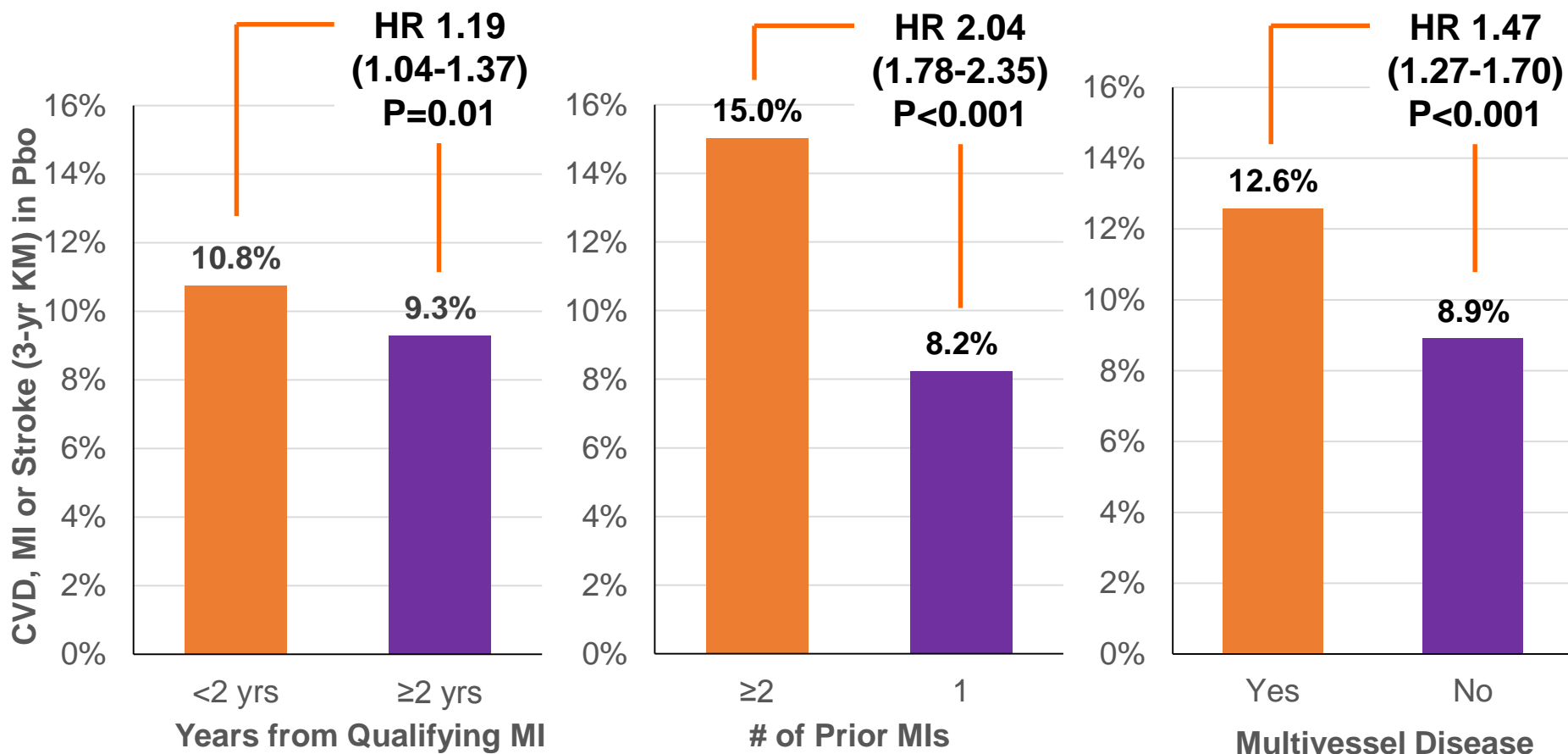
Multivariable Adjusted Analyses of All 3 Factors

Risk Factor	Adjusted HR (95% CI) for CV death, MI or stroke	P value
Qualifying MI <2 y ago	1.36 (1.18-1.57)	<0.001
≥2 Prior MIs	1.90 (1.65-2.19)	<0.001
Residual multivessel CAD	1.34 (1.16-1.55)	<0.001

Model in placebo arm of trial includes all 3 risk factors plus the following covariates: age, sex, weight, race, region, h/o stroke, h/o PAD, HTN, DM, current smoking, eGFR ≥60, high-intensity statin use, and LDL-C at baseline.
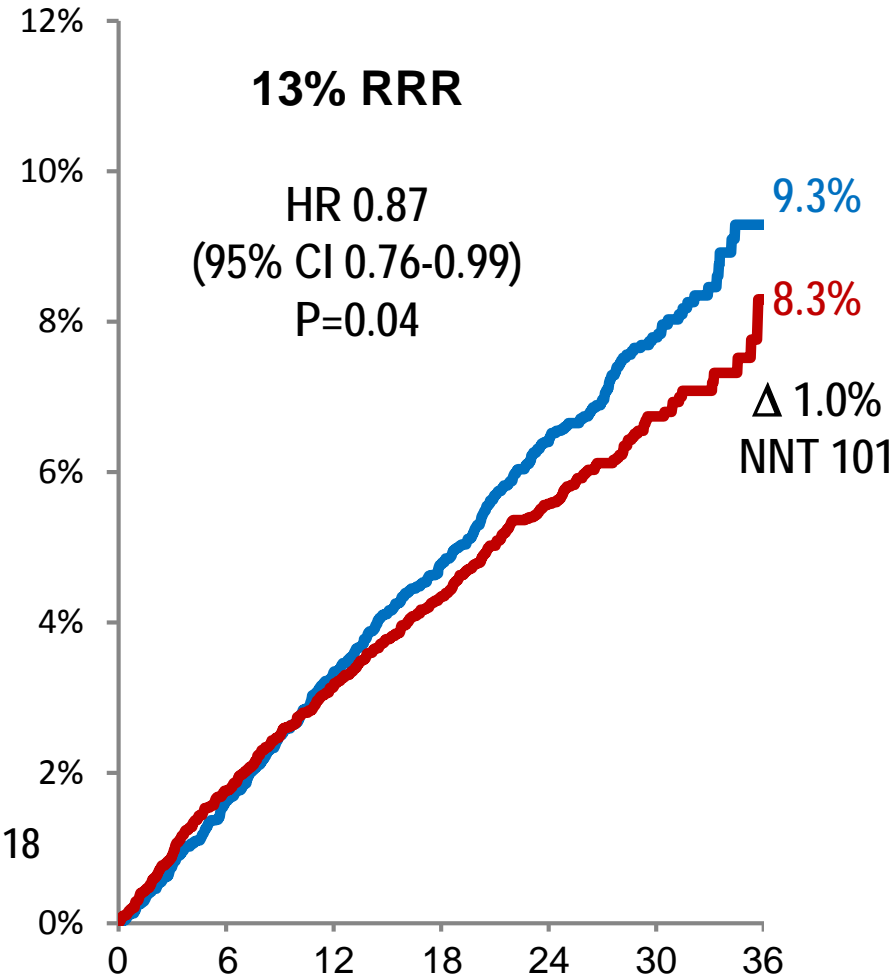
Benefit of EvoMab Based on Time from Qualifying MI

Qualifying MI <2 yrs ago

24% RRR

HR 0.76
(95% CI 0.64-0.89)
P<0.001

Δ 2.9%
NNT 35

10.8%

7.9%

Placebo

Evolocumab

CV Death, MI, or Stroke

Qualifying MI ≥2 yrs ago

13% RRR

HR 0.87
(95% CI 0.76-0.99)
P=0.04

9.3%

8.3%

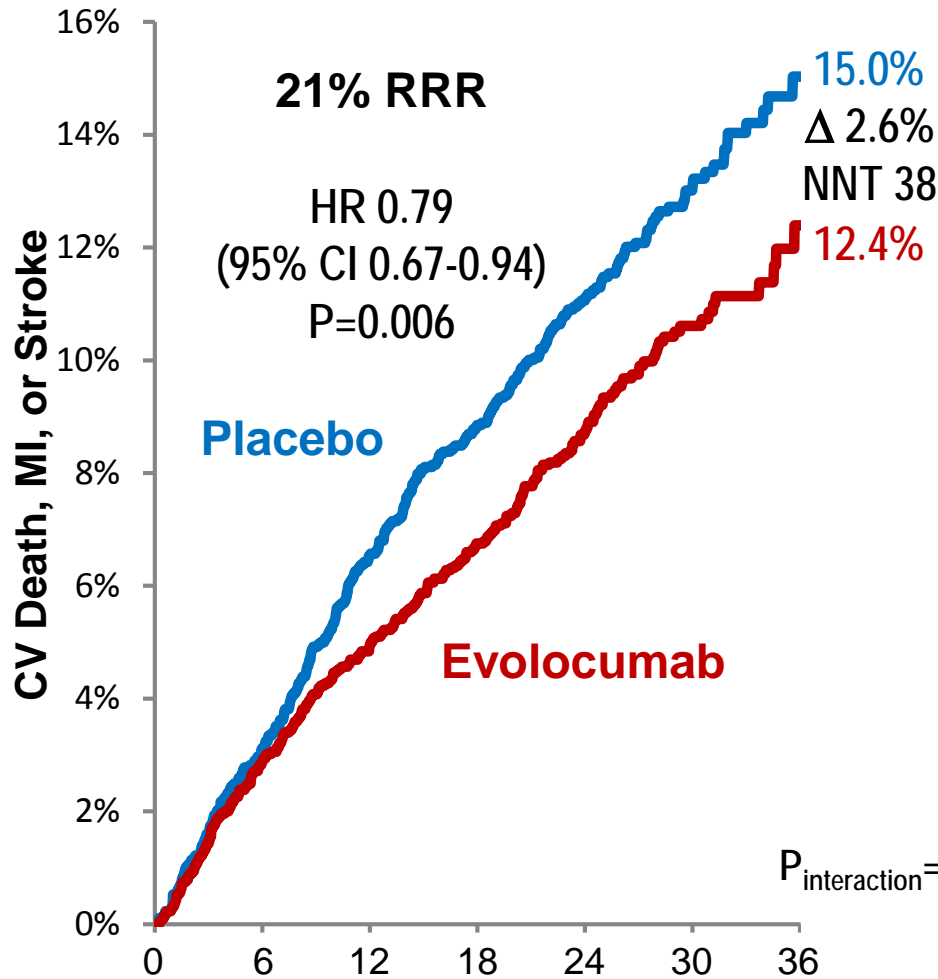Δ 1.0%
NNT 101

$P_{interaction}=0.18$

Months after Randomization
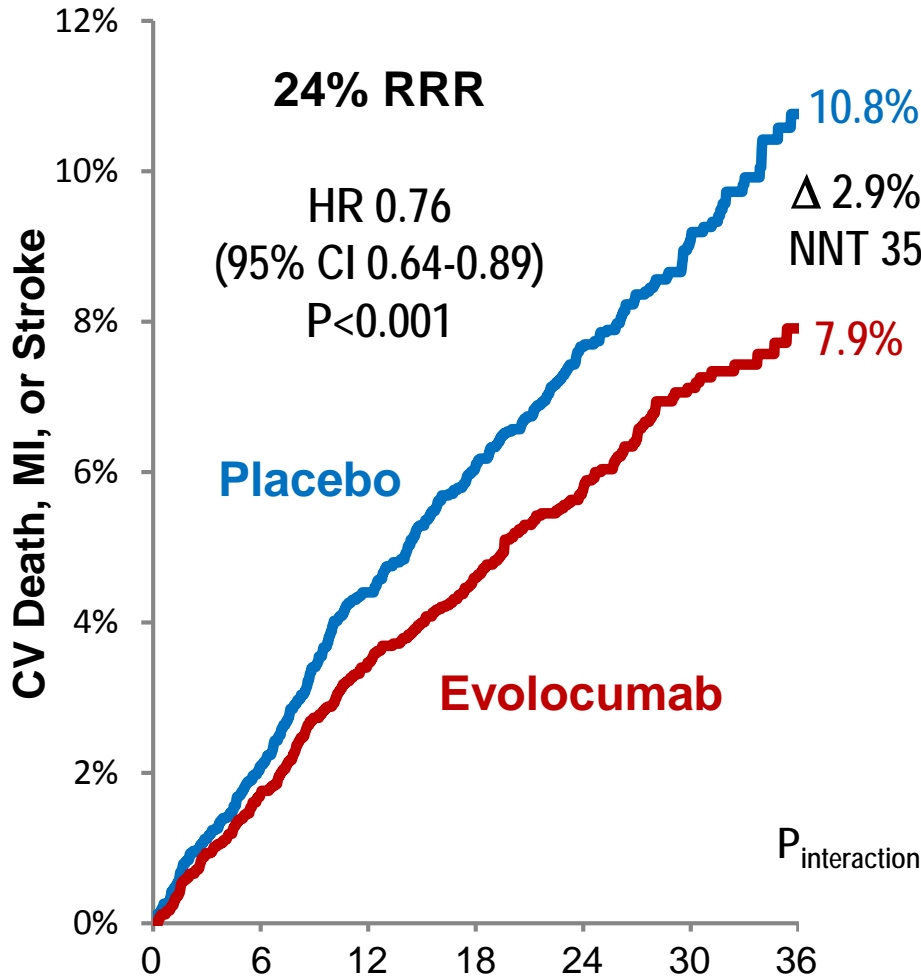
Benefit of EvoMab Based on # of Prior MIs

≥2 Prior MIs

21% RRR

HR 0.79
(95% CI 0.67-0.94)
P=0.006

Δ 2.6%
NNT 38

15.0%

12.4%

Placebo

Evolocumab

$P_{interaction}$=0.57

1 Prior MI

16% RRR

HR 0.84
(95% CI 0.74-0.96)
P=0.008

8.2%

6.6%

Δ 1.7%
NNT 60

CV Death, MI, or Stroke

Months after Randomization
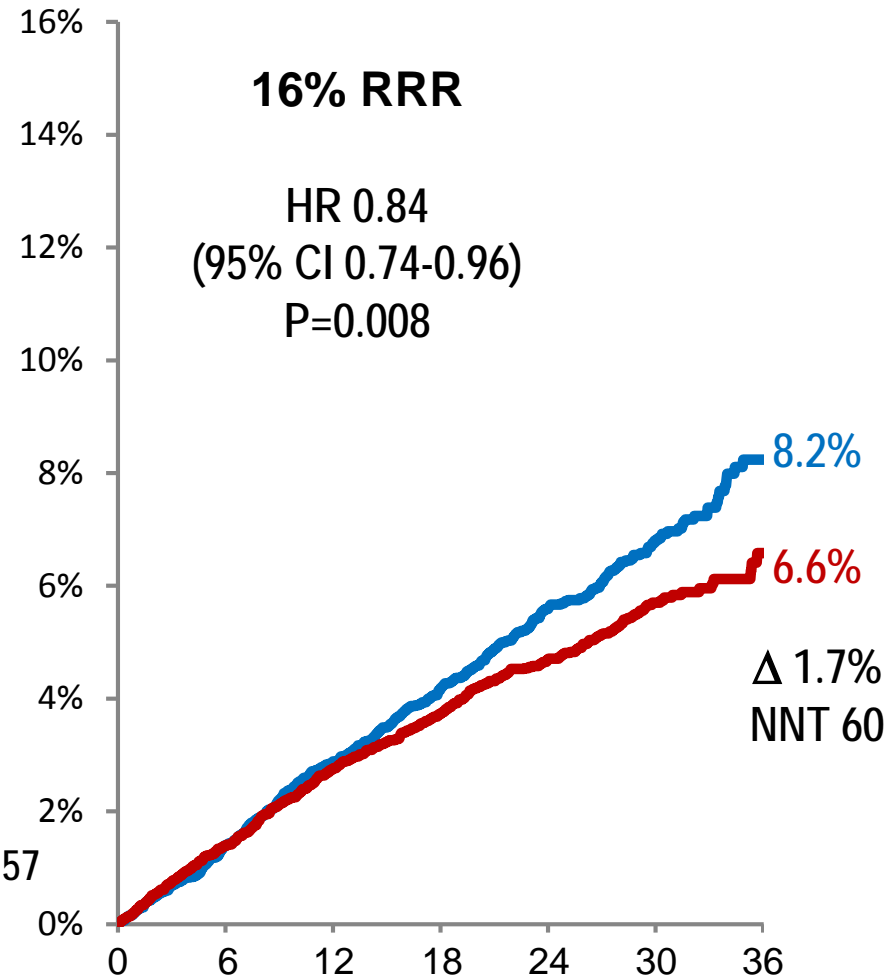
Benefit of EvoMab Based on Multivessel Disease

Multivessel Disease
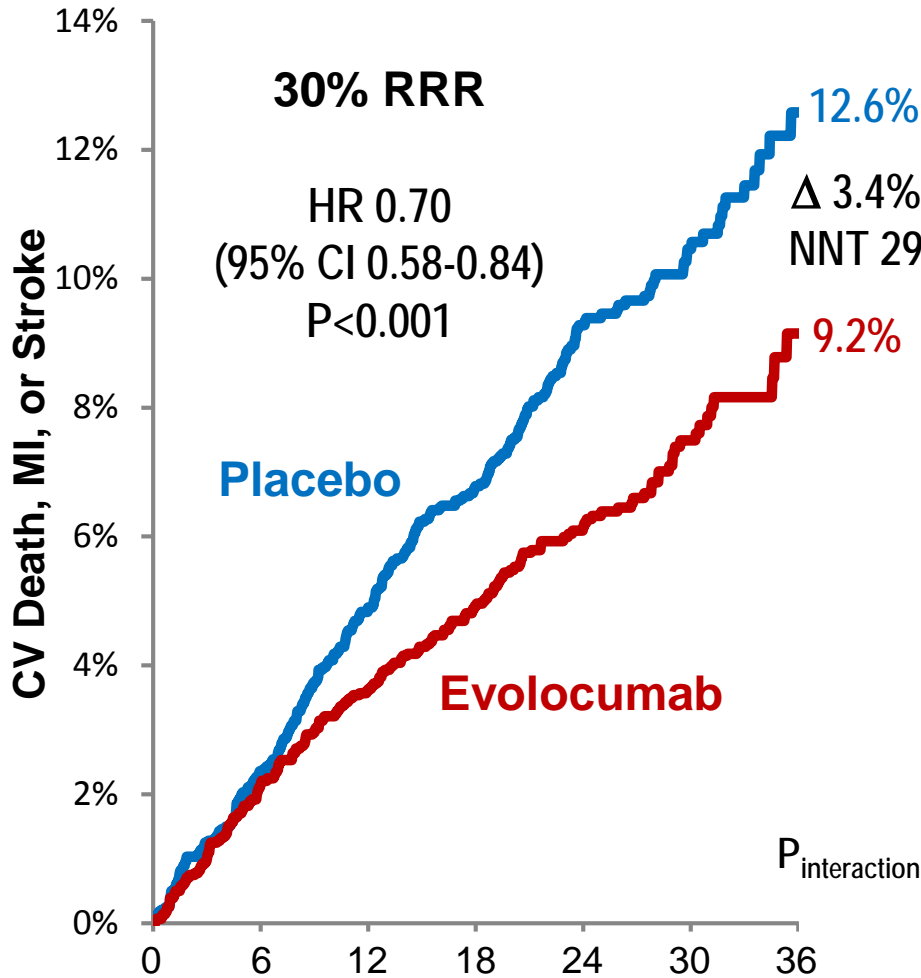
No Multivessel Disease

CV Death, MI, or Stroke

30% RRR

HR 0.70
(95% CI 0.58-0.84)
P<0.001

Placebo

12.6%

Δ 3.4%
NNT 29

9.2%

Evolocumab

$P_{interaction}$=0.03

11% RRR

HR 0.89
(95% CI 0.79-1.00)
P=0.055

8.9%

7.6%

Δ 1.3%
NNT 78

Months after Randomization

Overlap Between Factors

22,351 patients w/ prior MI

8402 Pts <2 y from MI

5285 Pts ≥2 MIs

5618 Pts w/ MVD

Overlap Between Factors

37% of the population

63% of the population
w/ at least 1 risk factor
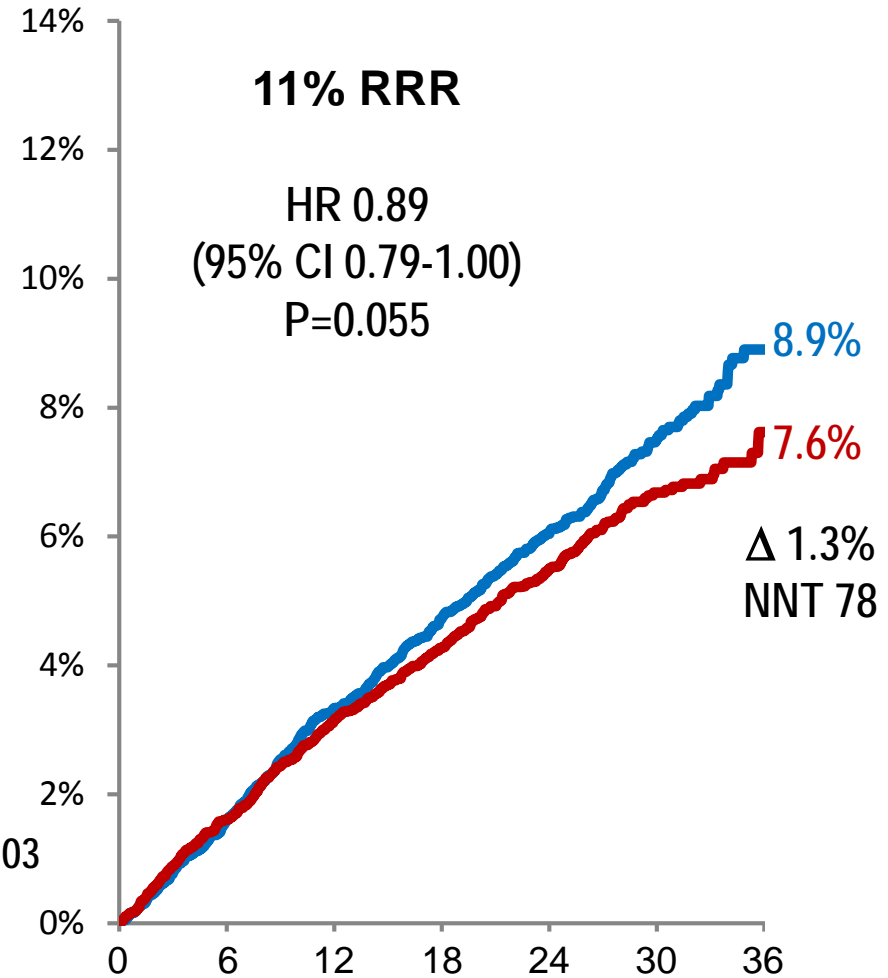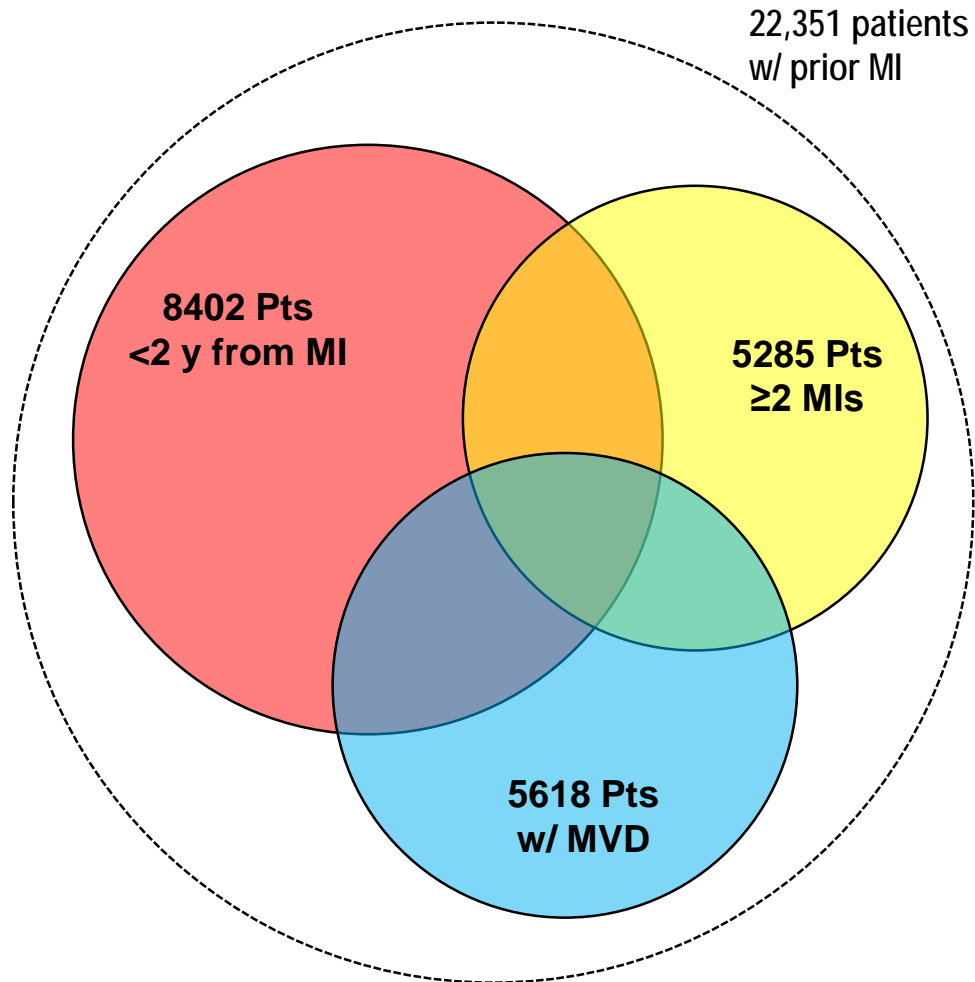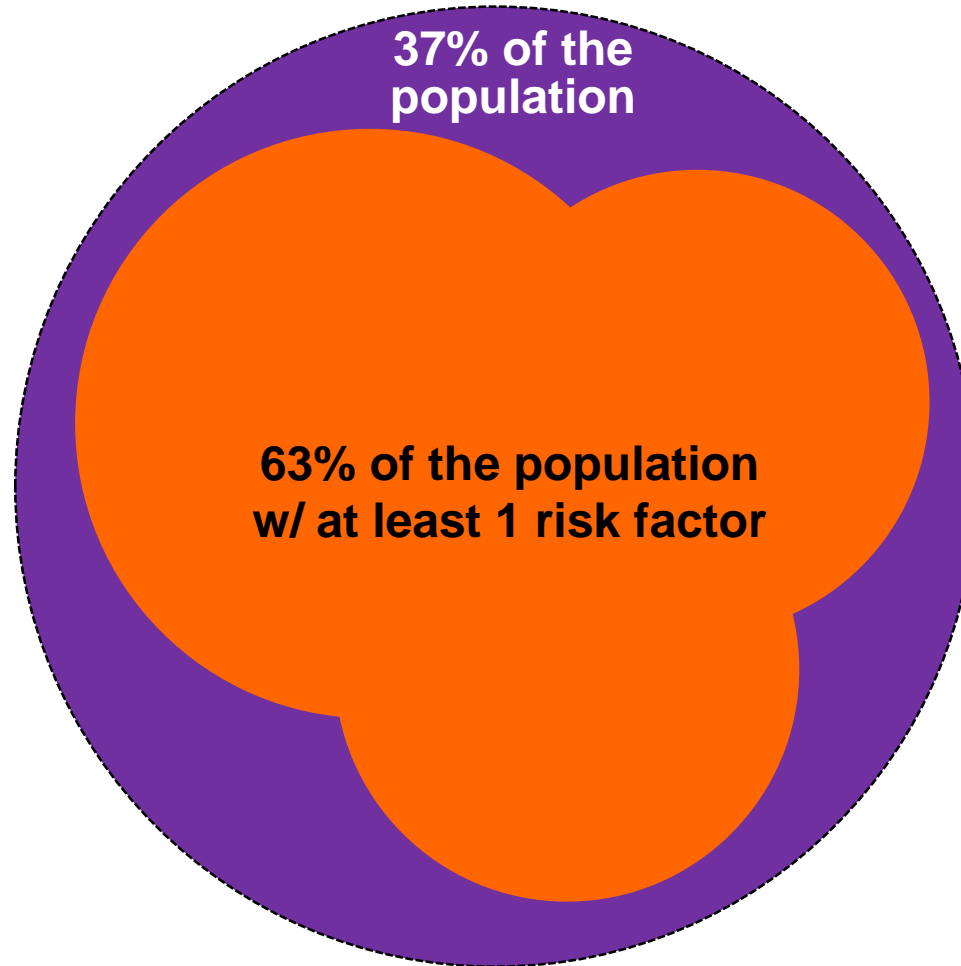
Benefit of EvoMab Based on # of High-Risk MI Features

High-risk feature: <2 yrs from qualifying MI, ≥2 prior MIs, or residual multivessel disease

Placebo
Evolocumab

≥1 Feature
22% RRR
2.5% ARR

P_interaction=0.11

N=13,973 (63% of prior MI trial population)

CV Death, MI, or Stroke

Months after Randomization
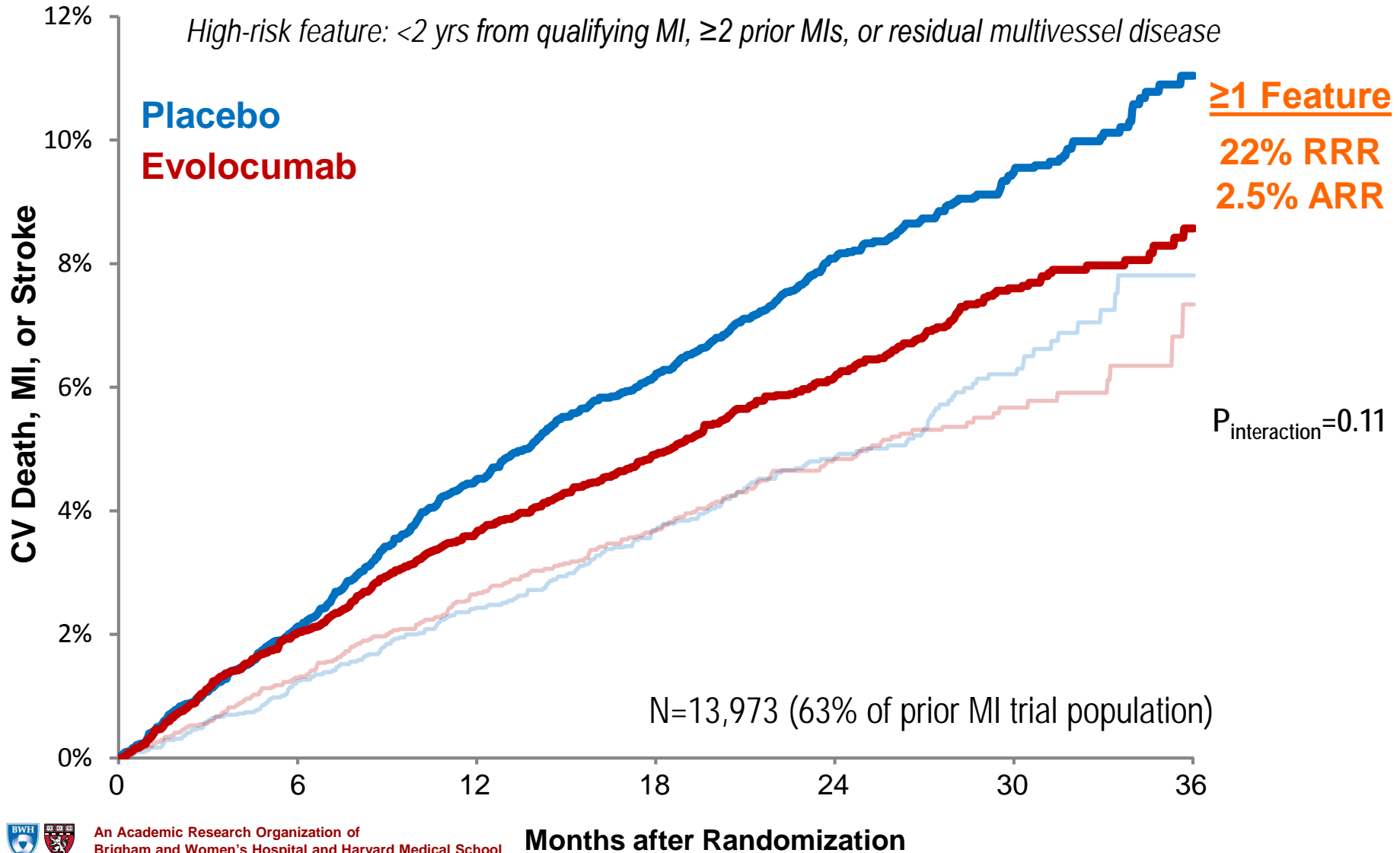
Landmark Analyses in Pts w/ a High-Risk MI Feature
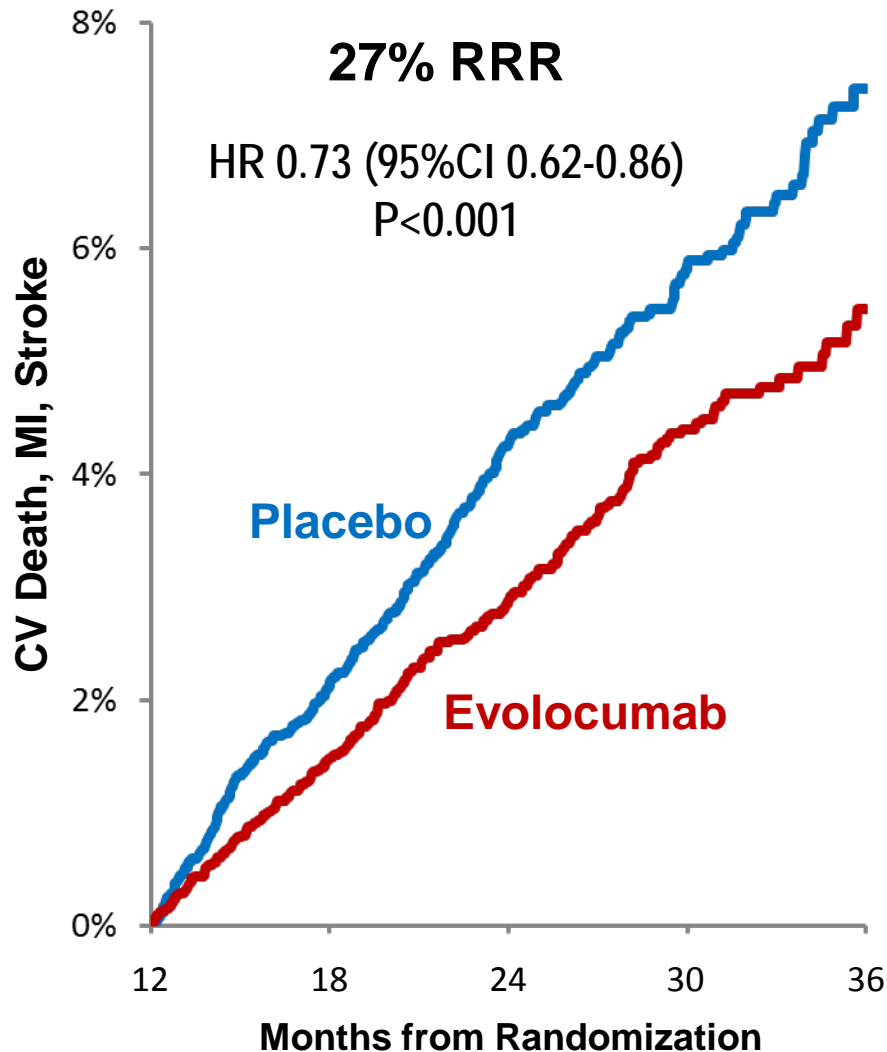
19% RRR

HR 0.81 (95%CI 0.68-0.95)
P=0.01

27% RRR

HR 0.73 (95%CI 0.62-0.86)
P<0.001

CV Death, MI, Stroke

Placebo

Evolocumab

Months from Randomization

High-risk feature: <2 yrs from qualifying MI, ≥2 prior MIs, or multivessel disease

Summary

- **Patients** (1) closer to their most recent MI,
  (2) with multiple prior MIs, or
  (3) with multivessel disease
  are at 34-90% ↑ risk for major vascular events

- **These patients experience substantial:**
  - relative risk reductions (21-30%) and
  - absolute risk reductions (2.6-3.4% over 3 yrs)
  with intensive LDL-C lowering w/ the PCSK9i evolocumab

  These readily ascertainable clinical features offer one approach to tailoring therapy