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Clinical Benefit of Evolocumab by Severity and Extent of Coronary Artery Disease: An Analysis from FOURIER

Short Title: Benefit of Evolocumab in Patients with Coronary Disease

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Background: The FOURIER trial recently showed that the PCSK9 inhibitor evolocumab significantly reduced major vascular events in patients with stable atherosclerotic cardiovascular disease, including patients with prior MI. Within the broad group of patients with prior MI, we hypothesized that readily ascertainable features would identify subsets that derive greater clinical risk reduction with evolocumab.

Methods: The 22,351 patients with a prior MI were characterized based on time from most recent MI, number of prior MIs, and presence of residual multivessel coronary artery disease ($\geq 40\%$ stenosis in ≥ 2 large vessels). The relative and absolute risk reductions in major vascular events including the primary endpoint (CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) and the key secondary endpoint (CV death, MI or stroke) with evolocumab in these subgroups were compared.

Results: A total of 8402 patients (38%) were within 2 years of their most recent MI, 5285 patients (24%) had ≥ 2 prior MIs, and 5618 patients (25%) had residual multivessel CAD. In a multivariable adjusted model that simultaneously included all three high-risk features as well as other baseline covariates, more recent MI, multiple prior MIs, and residual multivessel coronary disease remained independent predictors of cardiovascular outcomes, with adjusted HRs for the primary endpoint of 1.37 (1.22-1.53), 1.78 (1.59-1.99) and 1.39 (1.24-1.56), all $P < 0.001$. The relative risk reductions with evolocumab for the primary endpoint tended to be greater in the high-risk subgroups and were 20% (HR 0.80, 0.71-0.91), 18% (HR 0.82, 0.72-0.93), and 21% (HR 0.79, 0.69-0.91) for those with more recent MI, multiple prior MIs, and residual multivessel CAD, whereas they were 5% (HR 0.95, 0.85-1.05), 8% (HR 0.92, 0.84-1.02), and 7% (HR 0.93, 0.85-1.02) in those without, respectively. Given the higher baseline risk, the respective absolute risk reductions at 3 years exceeded 3% in the high-risk groups (3.4%, 3.7%, and 3.6%) vs. approximately 1% in the low-risk groups (0.8%, 1.3%, and 1.2%).

Conclusion: Patients closer to their most recent MI, with multiple prior MIs or with residual multivessel CAD are at high risk for major vascular events and experience substantial risk reductions with LDL-C lowering with evolocumab.

Clinical trial registration: NCT01764633

Clinical Perspective

What Is New?

- We tested whether readily ascertainable features would identify subsets of patients that derive greater clinical risk reduction with the PCSK9 inhibitor evolocumab.
- Patients with a more recent MI (within the past 2 years), multiple prior MIs, and residual multivessel coronary disease were at significantly higher risk of cardiovascular outcomes.
- The relative and absolute risk reductions in cardiovascular outcomes with evolocumab tended to be greater in these high-risk subgroups, with correspondingly lower numbers needed to treat.

What Are the Clinical Implications?

- Patients with a history of MI who are closer to their most recent event, have had multiple prior MIs or have residual multivessel CAD are at high risk for major vascular events and experienced substantial relative and absolute risk reductions with LDL-C lowering with evolocumab.
- Among patients with a history of MI it would be reasonable to preferentially target PCSK9 inhibition to these high-risk patients.

Introduction

Lowering low-density lipoprotein cholesterol (LDL-C) has been an integral part of the treatment of patients with myocardial infarction (MI), with statins being the mainstay of therapy.¹ Recently the Further cardiovascular Outcomes Research with PCSK9 Inhibition in patients with Elevated Risk (FOURIER) trial showed that the proprotein convertase subtilisin-kexin type 9 (PCSK9) monoclonal antibody evolocumab, when added to statin therapy, lowered LDL-C by 59% and significantly reduced the risk of cardiovascular events in patients with stable atherosclerotic cardiovascular disease, the majority of whom had a history of MI.² These data led the FDA to issue a new indication in December 2017 for evolocumab to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease and incorporation of evolocumab into guideline recommendations for patients with atherosclerotic cardiovascular disease, including prior MI.^{3,4}

In accord with a growing desire for personalized and cost-efficient medicine,⁵ it is reasonable to seek to identify subgroups of patients who benefit the most from potential therapies. To that end, we have previously shown that within the broad group of patients with a history of MI, several readily ascertainable features of the coronary artery disease history identified patients at high risk who derived greater relative and/or absolute risk reduction from therapies. In those other studies, those features were: the timing from the most recent myocardial infarction, the number of prior myocardial infarctions, and the presence of residual multivessel coronary artery disease.⁶⁻⁹ We tested the efficacy of evolocumab in these three subgroups in the FOURIER trial.

Methods

Study Population

FOURIER was a randomized, double-blind, placebo-controlled trial that enrolled 27,564 patients age 40-85 years with clinically evident atherosclerotic cardiovascular disease (prior MI, prior non-hemorrhagic stroke, or symptomatic peripheral arterial disease) and additional risk factors placing them at increased cardiovascular risk as previously described.^{2,10} Patients were required to have an LDL-C \geq 70 mg/dL or non-HDL-C \geq 100 mg/dL during screening while taking an optimized lipid-lowering regimen (at least atorvastatin 20mg daily or its equivalent, with or without ezetimibe). Relevant exclusions were recent MI or stroke within 4 weeks, planned or expected cardiac surgery or revascularization within 3 months after randomization, New York Heart Association class III or IV heart failure, or left ventricular ejection fraction $<$ 0.30. Full inclusion and exclusion criteria have been published previously.¹⁰ The number of prior MIs and date of a patient's most recent MI were recorded as was the presence of residual multivessel coronary artery disease defined as \geq 40% stenosis in \geq 2 large vessels. The protocol was approved by ethics committees at each center and all patients provided written informed consent. Patients were randomized 1:1 to receive subcutaneous evolocumab (either 140 mg every 2 weeks or 420 mg monthly, per patient preference) or matching placebo injection and were followed for a median of 2.2 years [interquartile range 1.8-2.5 years]. We encourage parties interested in collaboration and data sharing to contact the corresponding author directly for further discussions.

Outcomes

The primary endpoint of FOURIER was the composite of cardiovascular death, MI, stroke, coronary revascularization, or hospitalization for unstable angina; the key secondary endpoint was the composite of cardiovascular death, MI, or stroke. A central clinical events committee led by the TIMI Study Group, whose members were unaware of treatment assignment and lipid levels, adjudicated all efficacy end points. Definitions of the end points have been published previously.¹⁰

Statistical Analyses

As part of a prespecified analysis, patients were stratified based on the number of prior MIs, the timing of prior MIs, and the extent of coronary disease. Baseline characteristics of the subgroups were compared using Kruskal-Wallis tests and Chi-squared tests for continuous and categorical data, respectively. All efficacy analyses of evolocumab vs. placebo were conducted on an intention-to-treat basis. Kaplan-Meier event rates were calculated through 3 years and P values for time-to-event analyses are from log-rank tests. For the analysis of risk of cardiovascular outcomes in patients with and without a high-risk feature in the placebo arm, a multivariable-adjusted hazard ratio was obtained from a Cox model that included covariates that were imbalanced between patients with and without a high-risk feature including: age, sex, self-reported race, weight, region, history of stroke, peripheral artery disease, hypertension, diabetes, current smoking, estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m², high-intensity statin use, and LDL-C at baseline. Hazard ratios and 95% confidence intervals for the effect of evolocumab vs. placebo were generated using a Cox proportional hazards model without adjustment given the randomized comparison. Effect modification by subgroup on the efficacy

of evolocumab was tested by incorporating interaction terms into Cox models. Schoenfeld residuals were assessed in the Cox models and the proportional hazards assumptions were not violated. Negative binomial regression analysis was performed to compare the total number of primary and key secondary endpoints between patients in the evolocumab and placebo groups. This model included an exposure variable for duration of follow-up as this could vary by subject. Incidence rate ratio and corresponding 95% confidence intervals are reported from the negative binomial regression model. All analyses were conducted using Stata/IC, version 14.2 (StataCorp LP, College Station, TX, USA) or SAS, version 9.4 (SAS Institute, Cary, NC, USA). P values <0.05 were considered significant.

Results

Study Population

A total of 22,351 patients (81% of overall trial) had a history of prior myocardial infarction and constituted the study population for these analyses. The baseline characteristics of these patients and those of the overall trial are shown in Supplemental Table 1. A total of 2506 patients experienced the primary endpoint and 1518 the key secondary endpoint. Evolocumab significantly reduced the risk of both the primary endpoint [3-year Kaplan-Meier rate 13.3% vs. 15.1%, HR 0.89 (95% CI 0.82-0.96), P=0.002] and the key secondary endpoint [8.0% vs. 9.9%, HR 0.82 (0.74-0.91), P<0.001].

Subgroups and risk of cardiovascular outcomes

A total of 8402 patients (38%) had their qualifying MI within 2 years of randomization. Their median time from that MI was 0.6 years (IQR 0.3-1.2), in contrast to patients with an MI >2 years prior to randomization, in whom the median time was 6 years (3.7-11.0). The baseline

characteristics of patients whose MI was recent vs. remote are shown in Table 1. In the placebo arm, compared with patients with a remote MI, those with a recent MI were at significantly higher risk of the primary endpoint [3-year Kaplan-Meier rate 16.9% vs. 14.0%; HR 1.25 (95% CI 1.13-1.40), $P<0.001$] and of the key secondary endpoint [10.8% vs. 9.3%; HR 1.19 (1.04-1.37), $P=0.011$] (Table 2, Supplemental Table 2).

A total of 5285 patients (24%) had 2 or more prior MIs (with 1123 having 3 or more prior MIs) and the baseline characteristics of patients with and without multiple prior MIs are shown in Table 1. In the placebo arm, compared with patients without multiple MIs, those with them were at significantly higher risk of the primary endpoint [22.4% vs. 12.8%; HR 1.91 (95% CI 1.71-2.14), $P<0.001$] and of the key secondary endpoint [15.0% vs. 8.2%; HR 2.04 (1.78-2.35), $P<0.001$] (Table 2, Supplemental Table 2).

Lastly, 5618 patients (25%) had residual multivessel coronary artery disease and the baseline characteristics of patients with and without multivessel disease are shown in Table 1. In the placebo arm, compared with patients without multivessel disease, those with it were at significantly higher risk of the primary endpoint [19.4% vs. 13.6%; HR 1.52 (95% CI 1.35-1.70), $P<0.001$] and of the key secondary endpoint [12.6% vs. 8.9%; HR 1.47 (1.27-1.70), $P<0.001$] (Table 2, Supplemental Table 2).

After adjusting for baseline characteristics that were imbalanced between those with and without a high-risk feature, the high-risk features were still independent predictors of cardiovascular outcomes (Table 2). Furthermore, in a multivariable adjusted model that simultaneously included all three high-risk features as well as the other baseline covariates, more recent MI, multiple prior MIs, and residual multivessel coronary disease remained independent

predictors of the cardiovascular outcomes, with adjusted HRs for the primary endpoint of 1.37 (1.22-1.53), 1.78 (1.59-1.99) and 1.39 (1.24-1.56), and for the key secondary endpoint of 1.36 (1.18-1.57), 1.90 (1.65-2.19) and 1.34 (1.16-1.55), respectively, all $P < 0.001$ (see Supplemental Table 3 for details of the full model).

Subgroups and benefit of LDL-C lowering with evolocumab

Evolocumab consistently lowered LDL-C by 59-61% regardless of time from most recent MI, number of prior MIs or presence of residual multivessel CAD, with median achieved LDL-C in the evolocumab arm of 29-30 mg/dL (Supplemental Table 4). With regard to timing of prior MI, evolocumab reduced the primary endpoint by 20% (HR 0.80, 0.71-0.91) in those with a more recent MI vs. 5% (HR 0.95, 0.85-1.05) in those without; likewise, evolocumab reduced the key secondary endpoint by 24% (HR 0.76, 0.64-0.89) vs. 13% (HR 0.87, 0.76-0.99) (Figure 1, 2a, 3a). With regard to number of prior MIs, evolocumab reduced the primary endpoint by 18% (HR 0.82, 0.72-0.93) in those with multiple prior MIs vs. 8% (HR 0.92, 0.84-1.02) in those with only 1 MI; likewise, evolocumab reduced the key secondary endpoint by 21% (HR 0.79, 0.67-0.94) vs. 16% (HR 0.84, 0.74-0.96) (Figure 1, 2b, 3b). Lastly, in terms of residual multivessel coronary artery disease, evolocumab reduced the primary endpoint by 21% (HR 0.79, 0.69-0.91) in those with multivessel disease vs. 7% (HR 0.93, 0.85-1.02) in those without; likewise, evolocumab reduced the key secondary endpoint by 30% (HR 0.70, 0.58-0.84) vs. 11% (HR 0.89, 0.79-1.00) (Figure 1, 2c, 3c).

Given both the higher baseline risk and the tendency towards greater relative risk reductions in patients with high-risk features, the absolute risk reductions tended to be greater in those with high-risk features. For the primary and key secondary endpoints, they were: 3.4% vs.

0.8% and 2.9% vs. 1.0%, respectively for those within 2 years vs. 2 years or more from their qualifying MI; 3.7% vs. 1.3% and 2.6% vs. 1.7%, respectively for those with multiple prior MIs vs. only 1 prior MI; and 3.6% vs. 1.2% and 3.4% vs. 1.3%, respectively for those with residual multivessel coronary artery disease vs. those without (Figures 1-3). The absolute risk reductions of the primary endpoint in the high-risk subgroups translated into a number needed to treat over 3 years of 27-30, as compared with 54 in the entire subgroup of patients with MI. Furthermore, the cumulative incidence curves appeared to diverge after only approximately 6 months in the higher risk subgroups vs. after at least 12 months in the lower risk subgroups (Figures 2-3).

Combining subgroups

A total of 13,973 patients (63% of the MI subpopulation) had at least 1 of the high-risk features. Baseline characteristics comparing patients with any high-risk feature vs. no high-risk features are shown in Supplemental Table 5. Evolocumab reduced the risk of the primary endpoint by 17% from 17.3% to 14.4%, HR 0.83 (0.76-0.91) and the key secondary endpoint by 22% from 11.0% to 8.6%, HR 0.78 (0.69-0.88). In contrast, among the 8343 patients with none of the high-risk features, the rates of the primary and key secondary endpoints with placebo and evolocumab were 11.1%, vs. 11.7%, HR 1.03 (0.89-1.19) and 7.8% vs. 7.3%, HR 0.94 (0.78-1.13) (Figure 4).

The absolute risk reductions with evolocumab for the primary and key secondary endpoints in patients with any high-risk feature were 3.0% (1.3, 4.6%) and 2.5% (1.1, 3.9%), respectively. In contrast, the corresponding values were -0.6% (-3.0, 1.8%) and 0.5% (-1.7, 2.7%) in patients with no high-risk features. Whereas the cumulative incidence curves appeared

to diverge after only approximately 6 months in the high-risk subgroup, the event curves only started to appear to diverge after 2 years in the low-risk group.

In a landmark analysis of patients with at least 1 high-risk feature, the reduction CV death, MI or stroke was 19% in the first year (HR 0.81, 0.68-0.95) and 27% beyond the first year (HR 0.73, 0.62-0.86) (Supplemental Figure 1). In terms of total events (first and recurrent), there were 1371 total primary endpoint events in the evolocumab arm and 1776 in the placebo arm, giving an incidence rate ratio of 0.80 (95% CI 0.71-0.89, $P < 0.001$). Likewise, there were 583 total key secondary endpoint events in the evolocumab arm and 779 in the placebo arm, giving an incidence rate ratio of 0.77 (95% CI 0.67-0.88, $P < 0.001$). Correspondingly, whereas the number of first primary endpoint events prevented for every 1000 patients treated for 3 years was 29, the number of total events prevented was 75.

Discussion

We found that among patients with prior MI, those with a more recent MI, multiple prior MIs, or residual multivessel coronary artery disease were at higher risk of cardiovascular events and tended to experience greater and earlier cardiovascular risk reduction LDL-C lowering with evolocumab. Conversely, patients who had had only one prior MI in the more distant past and no residual multivessel coronary artery disease were at lower risk, with no significant benefit from LDL-C lowering with evolocumab, at least over the timeframe studied, with divergence of the event curves only starting to appear after 2 years.

The three high-risk features are based on their predictive ability in prior studies of patients with MI.^{6-9,11,12} Our findings in FOURIER validate the ability of these 3 readily ascertainable factors to predict risk. The greater absolute risk reductions observed with LDL-C

lowering with evolocumab in these subgroups are thus, in part, a consequence of the higher baseline risk these patients. Greater absolute risk reductions translate into lower numbers needed to treat. In this case, to prevent 1 primary endpoint over 3 years, the number needed to treat was 27-30 in each of the high-risk groups versus 54 in the overall group of patients with prior MI, and 79-130 in the low-risk subgroups. Such findings have implications for helping define the patient populations that could benefit most from treatment and could be used to inform cost-effectiveness analyses.¹³⁻¹⁵

There also tended to be greater *relative* risk reductions in cardiovascular outcomes with evolocumab in these high-risk subgroups. Such an observation suggests these factors are identifying patients whose pathobiology is more quickly and significantly modifiable in response to LDL-C lowering. Indeed, we know from intracoronary vascular ultrasound studies that LDL-C lowering with evolocumab causes coronary plaque regression.¹⁶ Furthermore, it has been shown with both statins and evolocumab that coronary plaque regression is greater in patients with greater baseline atheroma burden.^{16,17} It thus stands to reason that patients with the greatest burden of coronary atherosclerosis have the greatest potential for clinical benefit from aggressive LDL-C lowering. Complementing the findings using clinical variables, we and others have also demonstrated a similar pattern using genetic variants associated with coronary disease.^{18,19} Patients with minimal coronary atherosclerosis should still benefit from LDL-C lowering in terms of preventing plaque development, as has been shown in statin primary prevention trials.¹ However, such benefits would likely take more years to clearly manifest clinically than patients were followed in FOURIER.

The details regarding prior MIs were based on medical history rather than review of laboratory data and ECG tracings, as is typical for large, global cardiovascular outcomes trials.

Furthermore, the protocol did not mandate dedicated imaging of the extent of residual coronary artery disease in all patients, but again relied on medical history. We do not think the specific degree of stenosis is important, as the issue is a not a hemodynamic one. Rather, we think the key point is the presence of appreciable coronary artery disease in more than one vessel. These data suggest that going forward, for both clinical trials and clinical practice, assessment of the burden of coronary artery disease either clinically or through imaging may be useful for identifying high-risk patients whose risk is most immediately modifiable. Although there was significant heterogeneity for the relative risk reduction in patients with any vs. no high-risk features ($P=0.015$), the tests for heterogeneity with individual high-risk subgroups were borderline (P values ranging from 0.04 to 0.15 for the primary endpoint). Another limitation is the relatively short duration of the trial may have precluded seeing a clear benefit emerge in lower risk patients with a history of MI. Longer duration trials of PCSK9 inhibition would be needed to explore this issue.

In conclusion, patients with a history of MI who are closer to their most recent event, have had multiple prior MIs or have residual multivessel CAD are at high risk for major vascular events and experienced substantial relative and absolute risk reductions with LDL-C lowering with evolocumab. With a goal of personalized medicine, among patients with a history of MI it would be reasonable to preferentially target therapy to these high-risk patients.

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Figure Legends

Figure 1: Forest plot of the effect of evolocumab on the primary endpoint (top) and key secondary endpoint (bottom), overall (diamonds) and stratified by subgroups (squares depicting the point estimate and horizontal lines depicting 95% confidence intervals). Kaplan-Meier event rate estimates, hazard ratios and absolute risk reductions with 95% confidence intervals are shown, as are the P values for interactions testing for the hazard ratios.

Figure 2: Cumulative incidence curves for the primary endpoint by treatment arm in patients stratified by time from qualifying MI (panel a), number of prior MIs (panel b), and presence of residual multivessel coronary artery disease (panel c).

Figure 3: Cumulative incidence curves for the key secondary endpoint by treatment arm in patients stratified by time from qualifying MI (panel a), number of prior MIs (panel b), and presence of residual multivessel coronary artery disease (panel c).

Figure 4: Cumulative incidence curves for the primary (panel a) and key secondary endpoint (panel b) by treatment arm in patients stratified into those with at least one high-risk feature (solid lines) or no high-risk features (dashed lines). P value for interaction between treatment and subgroup were 0.015 for the primary endpoint and 0.11 for the key secondary endpoint. RRR, relative risk reduction, ARR, absolute risk reduction.

Table 1: Risk of Cardiovascular Outcomes by Risk Group

Characteristics	Timing of Qualifying Prior MI			# of Prior MIs			Residual Multivessel Coronary Artery Disease		
	<2 years (N = 8402)	≥2 years (N = 13,918)	P value	≥2 (N = 5285)	1 (N = 17,047)	P value	Present (N = 5618)	Absent (N = 16,715)	P value
Demographics									
Age – y, mean (SD)	60.1 (9.3)	63.4 (8.6)	<0.001	62.2 (8.9)	62.2 (9.1)	<0.67	61.7 (8.8)	62.3 (9.1)	<0.001
Male sex	77.3	79.2	0.001	82.4	77.3	<0.001	81.2	77.6	<0.001
White race	84.1	87.1	<0.001	88.7	85.1	<0.001	85.2	86.2	0.057
Mean weight – kg, mean (SD)	84.2 (16.9)	86.7 (17.2)	<0.001	87.1 (17.1)	85.3 (17.1)	<0.001	86.0 (17.2)	85.7 (17.1)	0.29
Region			<0.001			<0.001			0.015
North America	12.6	18.6		18.8	15.7		17.2	16.1	
Europe	65.2	62.0		63.5	63.1		62.9	63.3	
Latin America	7.7	6.6		6.6	7.1		6.2	7.2	
Asia Pacific and South Africa	14.5	12.8		11.1	14.2		13.8	13.4	
Other types of atherosclerosis									
Non-hemorrhagic stroke	5.3	8.6	<0.001	7.7)	7.3)	0.34	7.6	7.3	0.50
Peripheral artery disease	5.4	9.7	<0.001	9.0)	7.8)	0.008	9.6	7.6	<0.001
Cardiovascular risk factors									
Hypertension	74.7	81.3	<0.001	81.0	78.2	<0.001	82.2	77.7	<0.001
Diabetes mellitus	31.3	37.6	<0.001	36.1	35.0	0.12	35.3	35.2	0.97
Current cigarette use	27.8	27.5	0.66	25.9	28.2	0.001	25.6	28.3	<0.001
Statin use*			<0.001			<0.001			<0.001
High intensity	75.5	68.8		75.3	70.1		74.2	70.3	
Moderate intensity	24.2	31.0		24.5	29.7		25.5	29.5	
Ezetimibe	3.5	6.8	<0.001	7.0	5.1	<0.001	6.2	5.3	0.017
LDL cholesterol – mg/dL, median (IQR)	90 (79, 106)	93 (80, 110)	<0.001	92 (81, 109)	92 (80, 108)	0.015	93 (81, 110)	92 (80, 108)	<0.001
eGFR <60 ml/min/1.73 m ²	15.7	19.3	<0.001	19.8	17.3	<0.001	17.5	18.1	0.35

Data are % unless otherwise noted. *<0.3% of patients were on low-intensity, no statin, or had missing data.

Table 2: Risk of Cardiovascular Outcomes by Risk Group

	Prior MI <2 years (n=4293)		Prior MI ≥2 years (n=6898)		HR (95% CI)	P value	HR_{adj} (95% CI)	P value
CV death, MI, stroke, hospitalization for unstable angina, coronary revascularization	589	16.9%	740	14.0%	1.25 (1.13-1.40)	<0.001	1.44 (1.29-1.61)	<0.001
CV death, MI, stroke	362	10.8%	470	9.3%	1.19 (1.04-1.37)	0.011	1.44 (1.25-1.66)	<0.001
	≥2 prior MIs (n=2628)		Only 1 prior MI (n=8570)		HR (95% CI)	P value		
CV death, MI, stroke, hospitalization for unstable angina, coronary revascularization	485	22.4%	844	12.8%	1.91 (1.71-2.14)	<0.001	1.85 (1.66-2.08)	<0.001
CV death, MI, stroke	320	15.0%	512	8.2%	2.04 (1.78-2.35)	<0.001	1.97 (1.71-2.27)	<0.001
	Multivessel CAD (n=2806)		No multivessel CAD (n=8390)		HR (95% CI)	P value		
CV death, MI, stroke, hospitalization for unstable angina, coronary revascularization	441	19.4%	884	13.6%	1.52 (1.35-1.70)	<0.001	1.45 (1.29-1.63)	<0.001
CV death, MI, stroke	272	12.6%	556	8.9%	1.47 (1.27-1.70)	<0.001	1.40 (1.21-1.62)	<0.001

Analyses in placebo arm only. Covariates in model include: age, sex, self-reported race, weight, region, history of stroke, peripheral artery disease, hypertension, diabetes, current smoking, estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m², high-intensity statin use, and LDL-C at baseline.

Figure 1

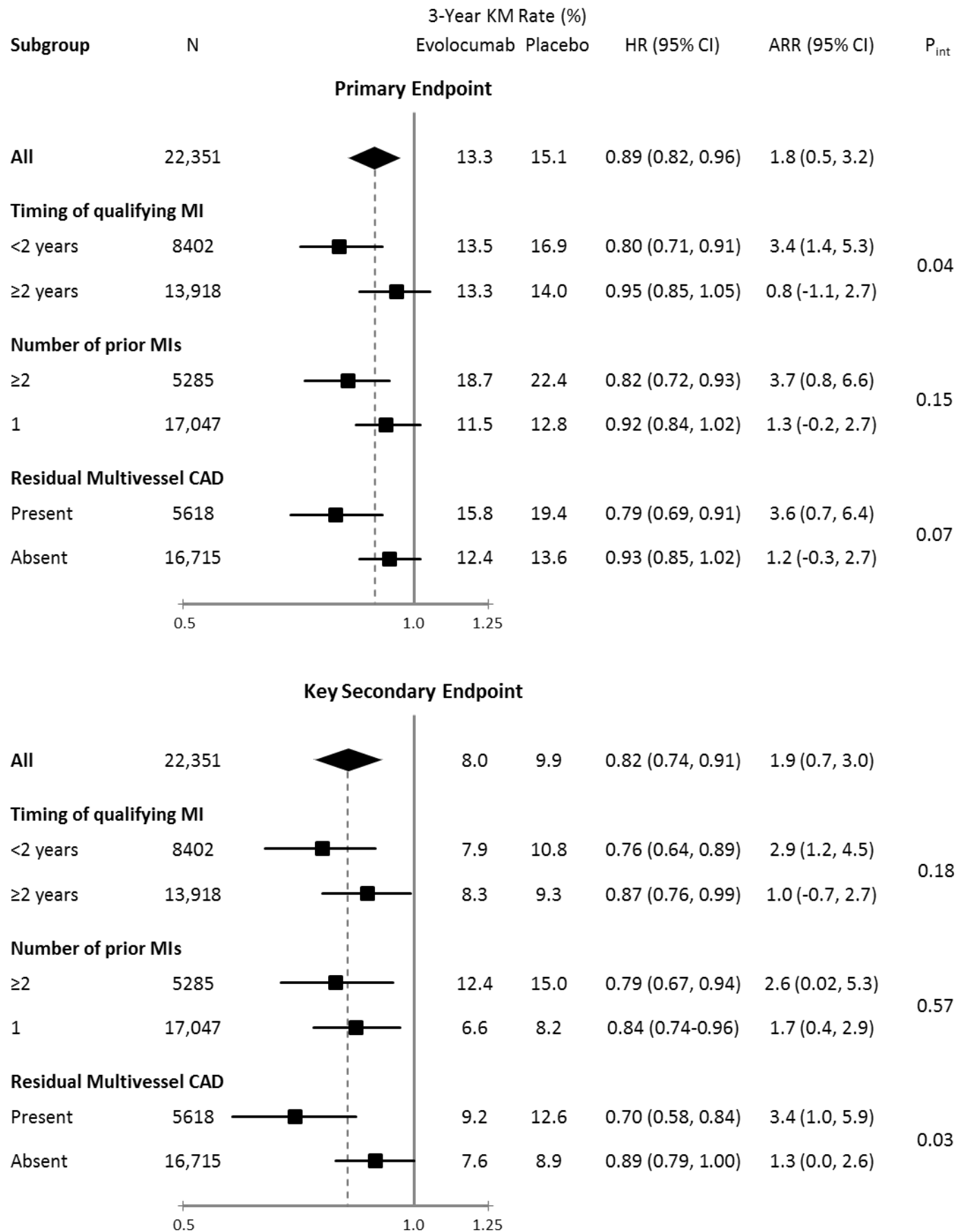


Figure 2a

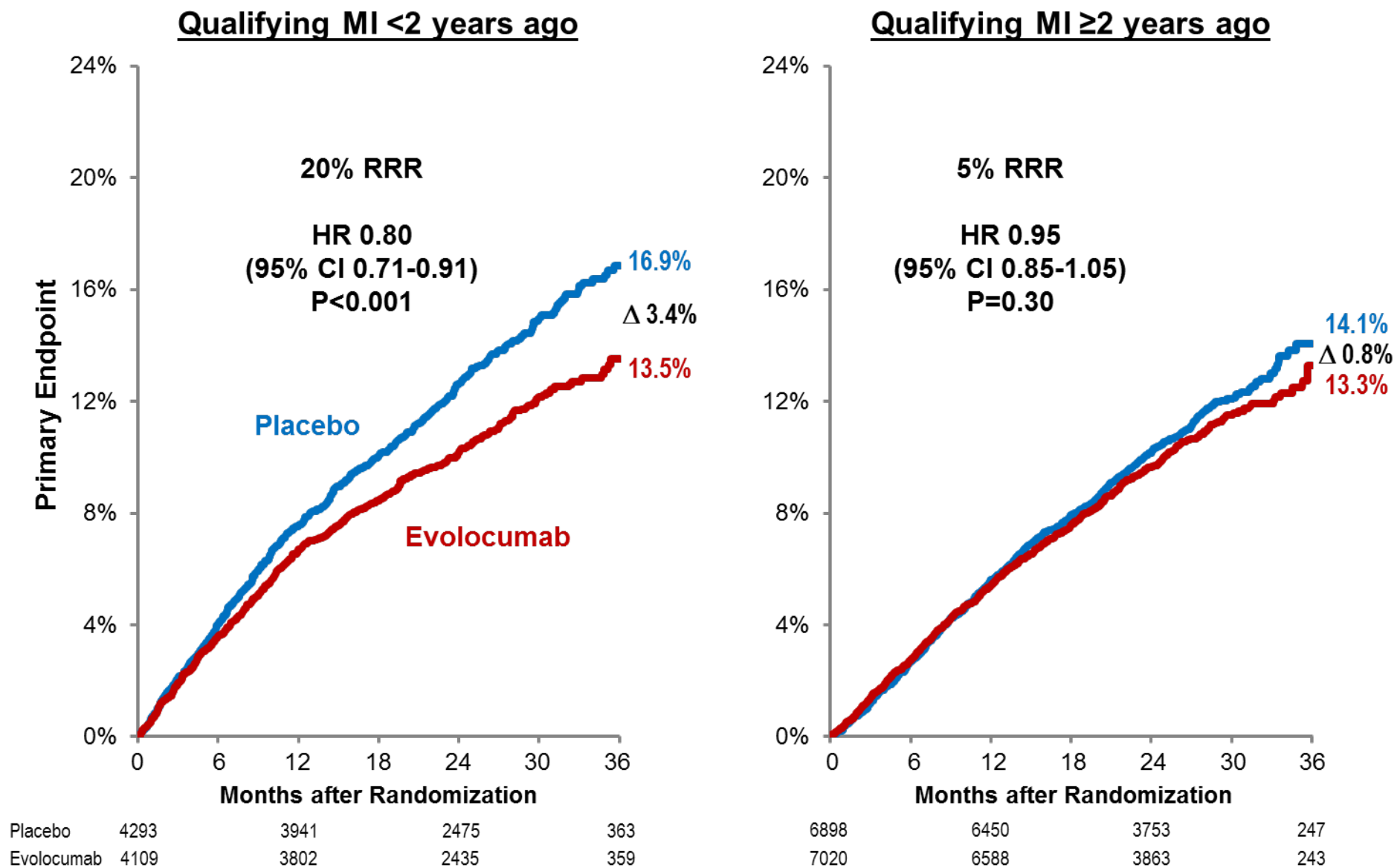


Figure 2b

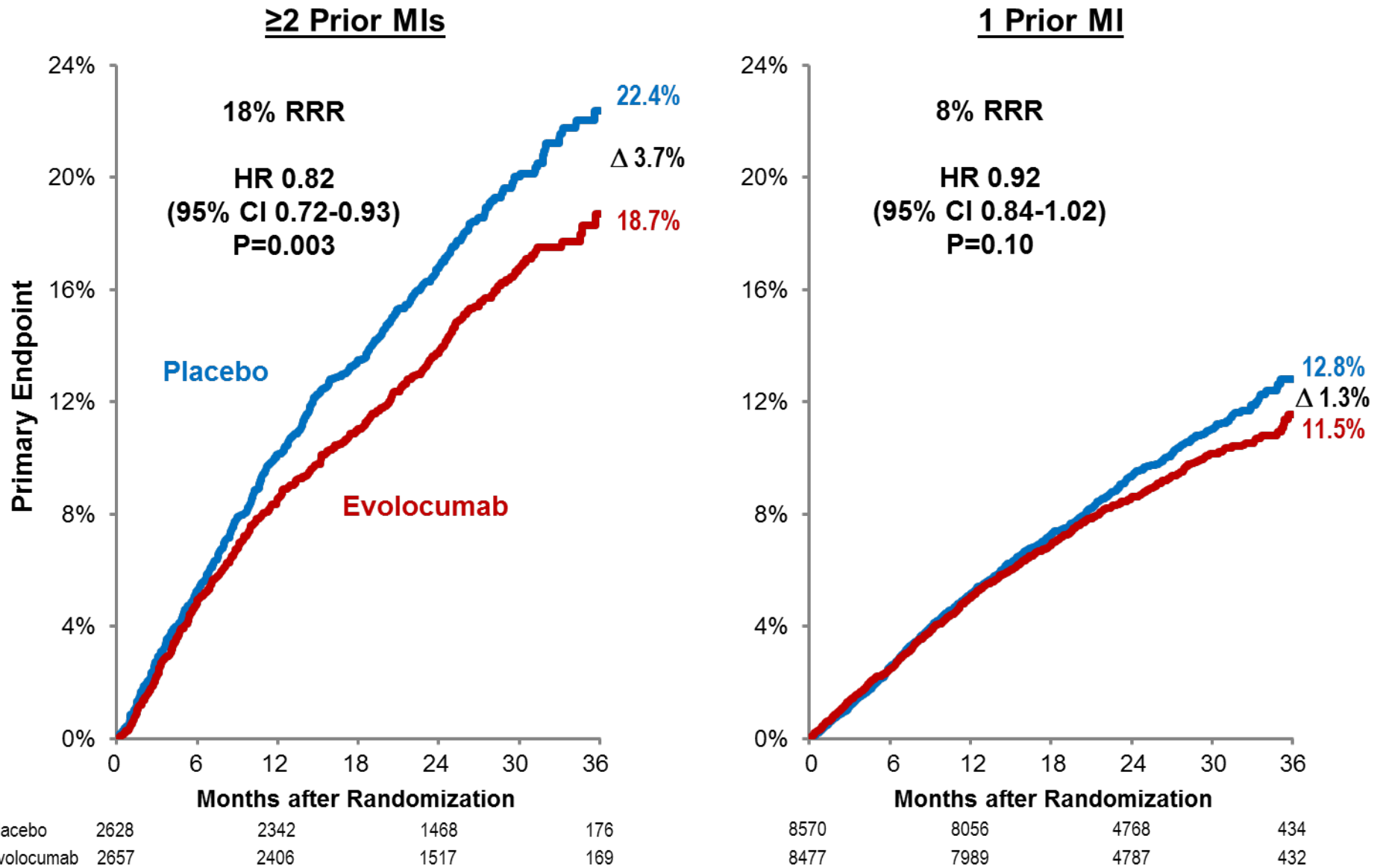


Figure 2c

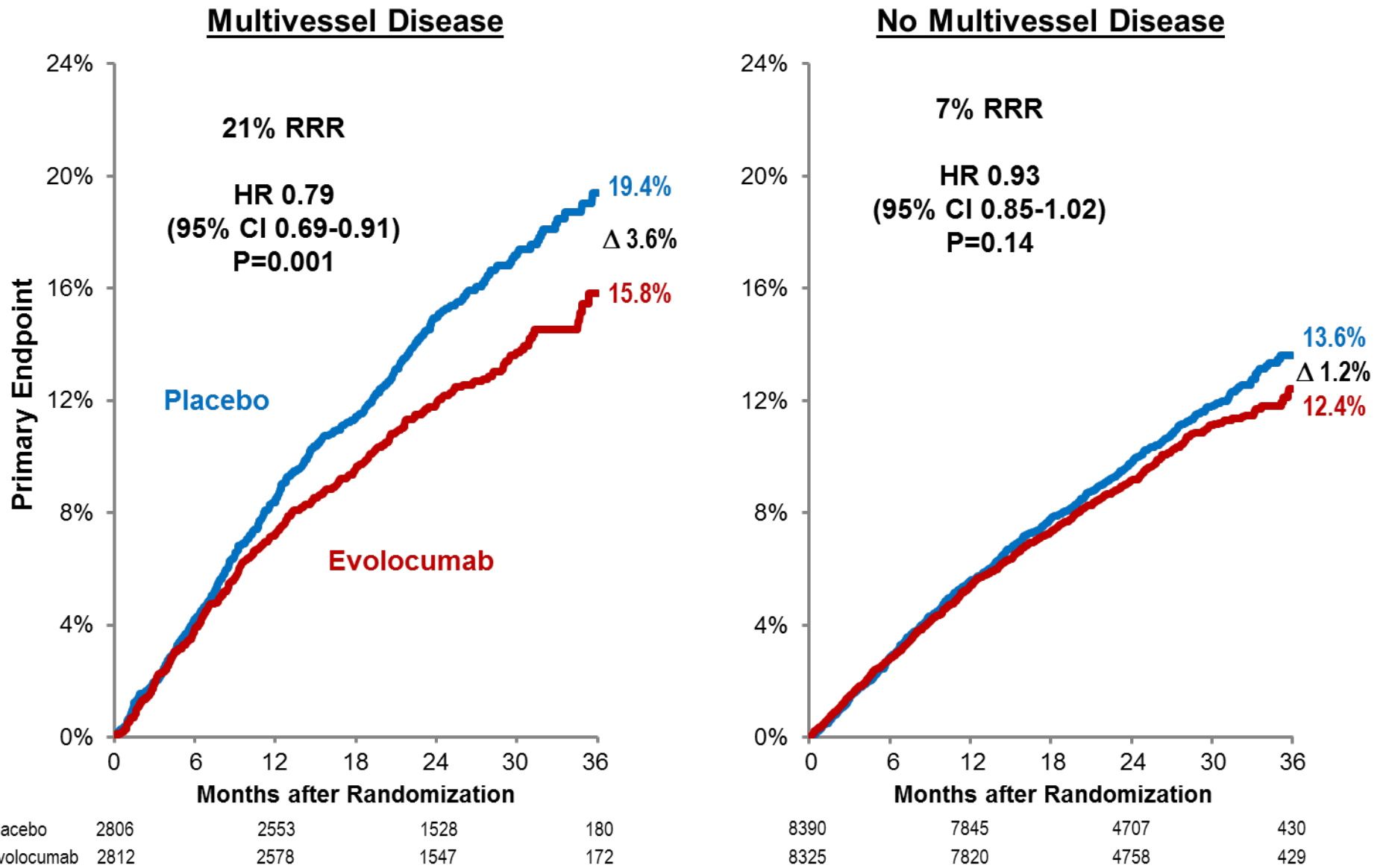


Figure 3a

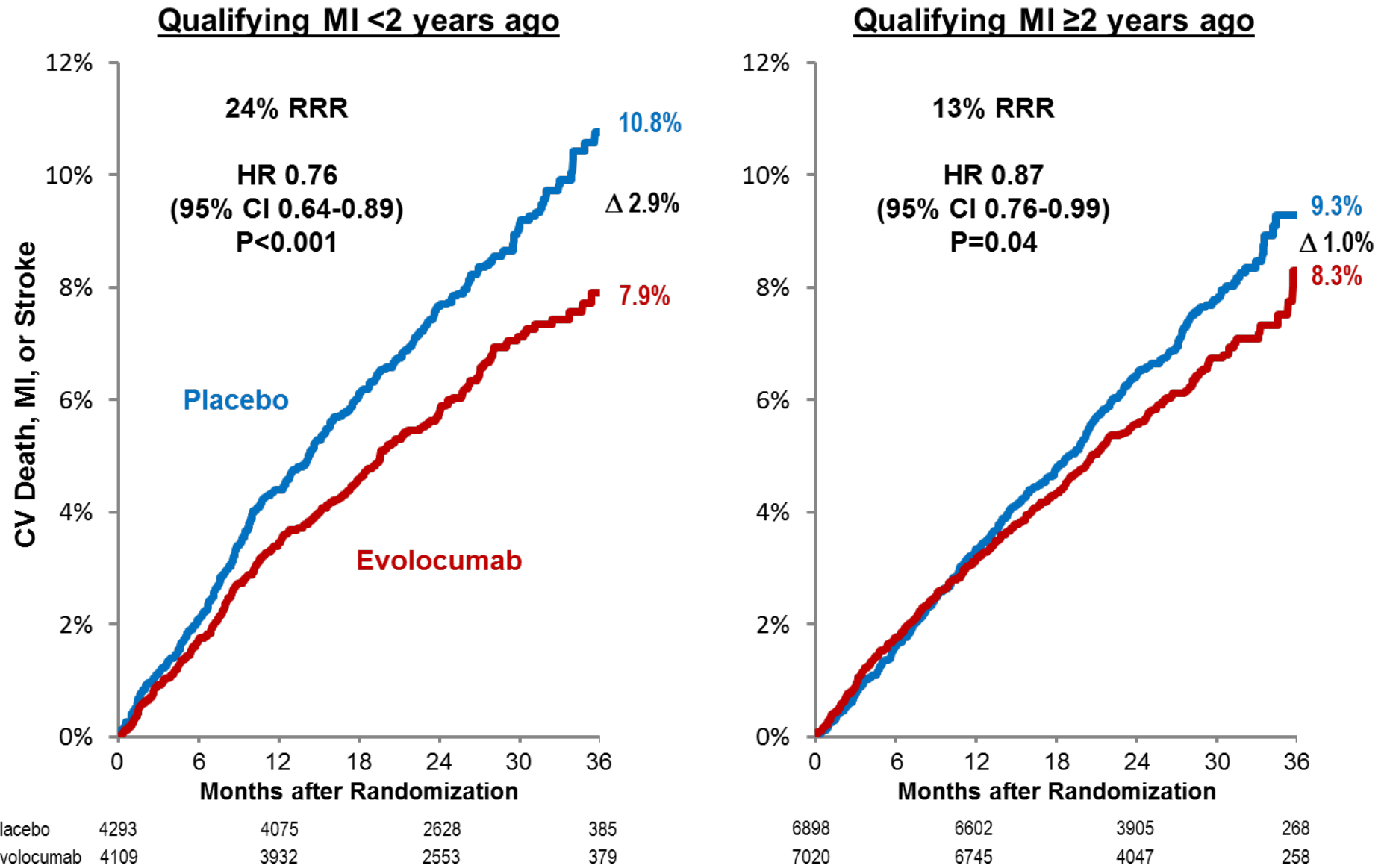


Figure 3b

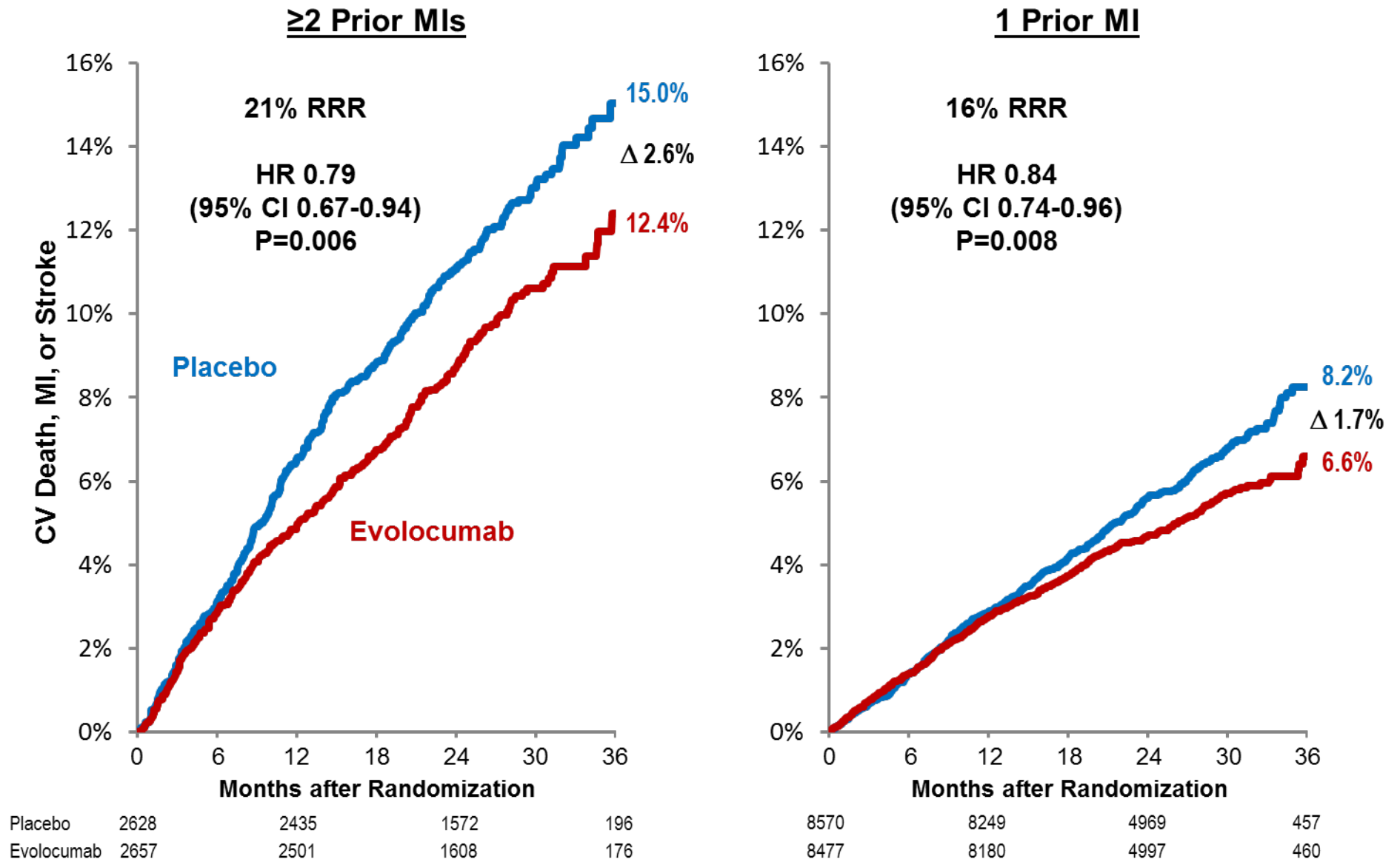


Figure 3c

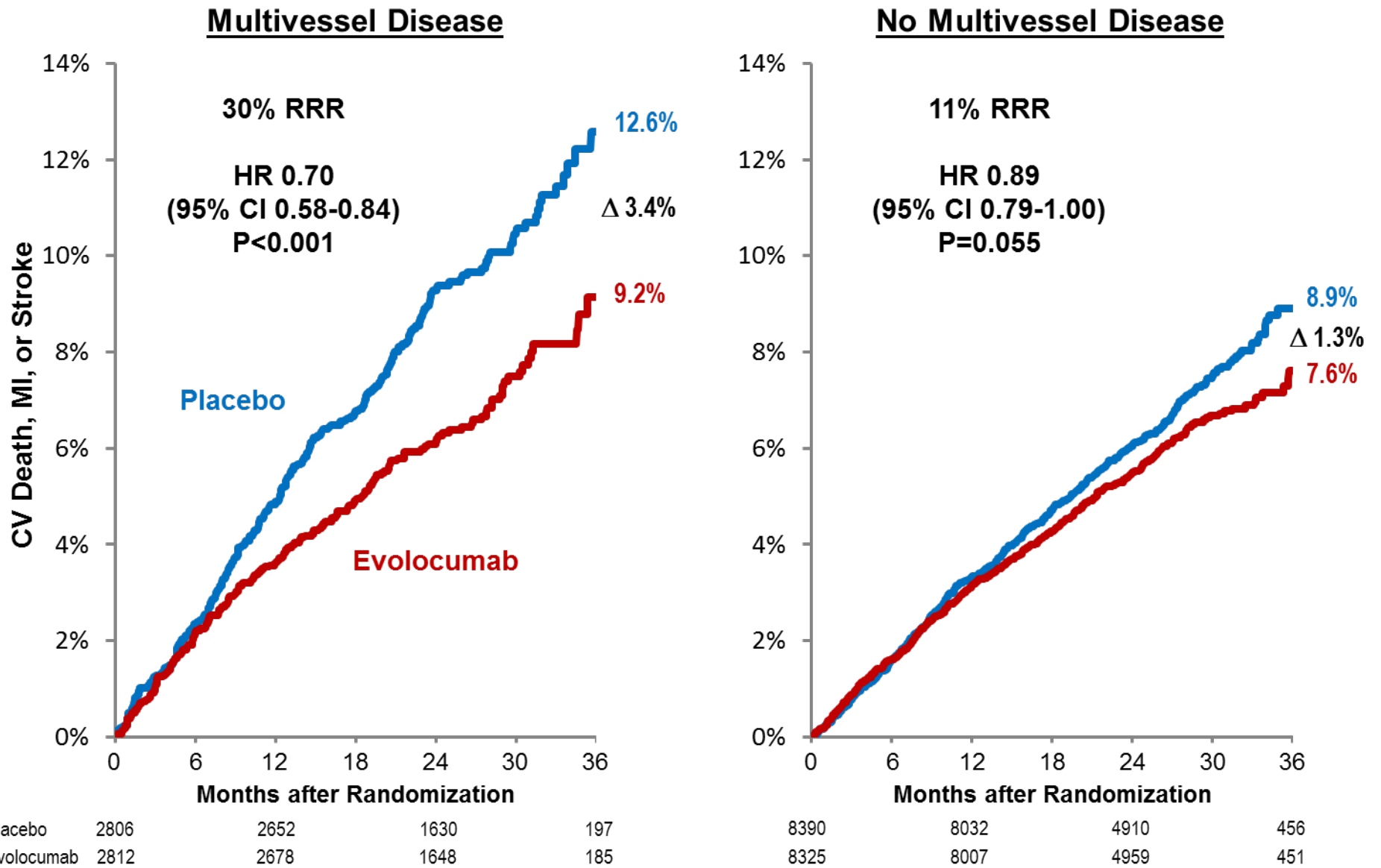
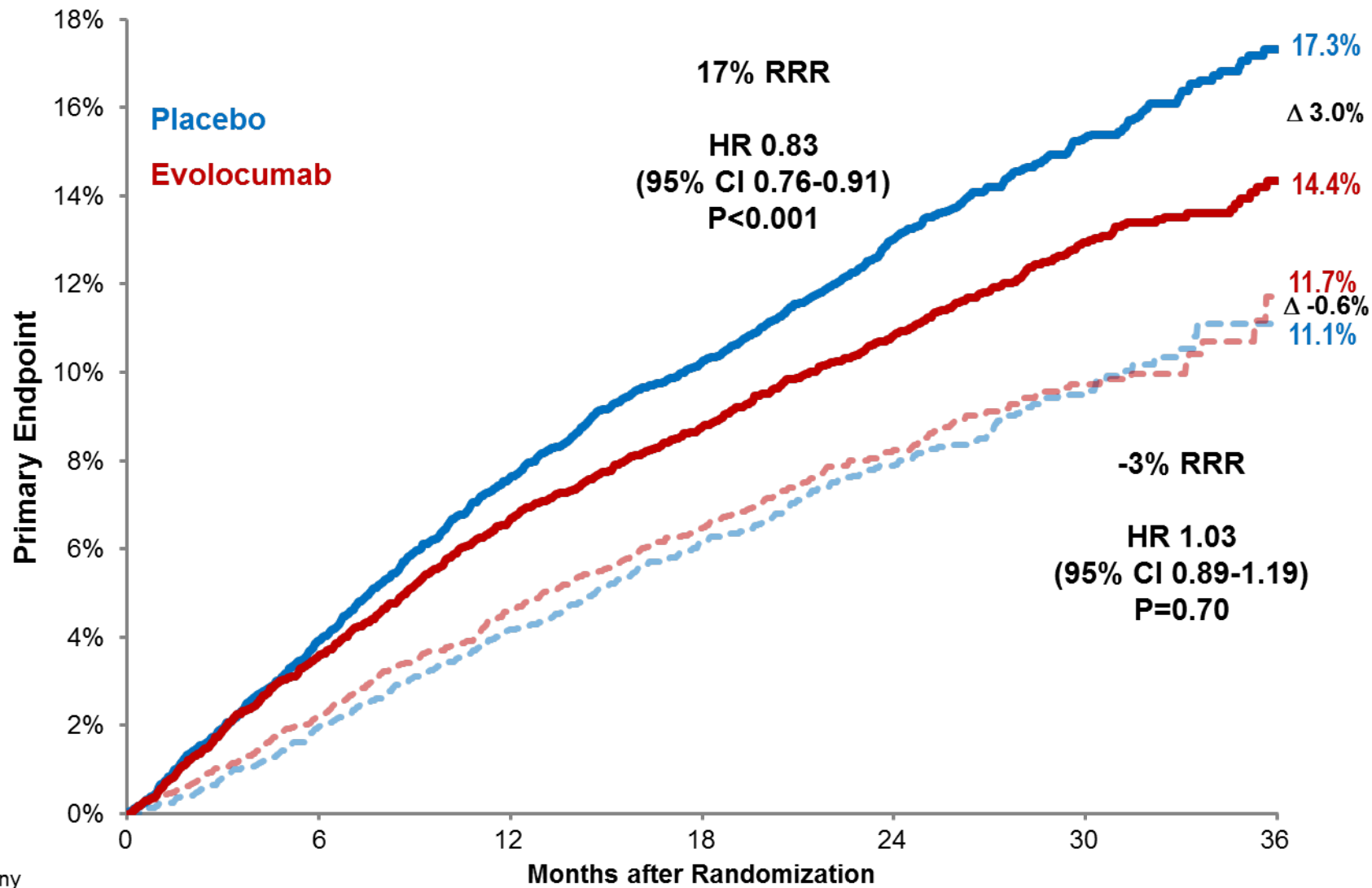
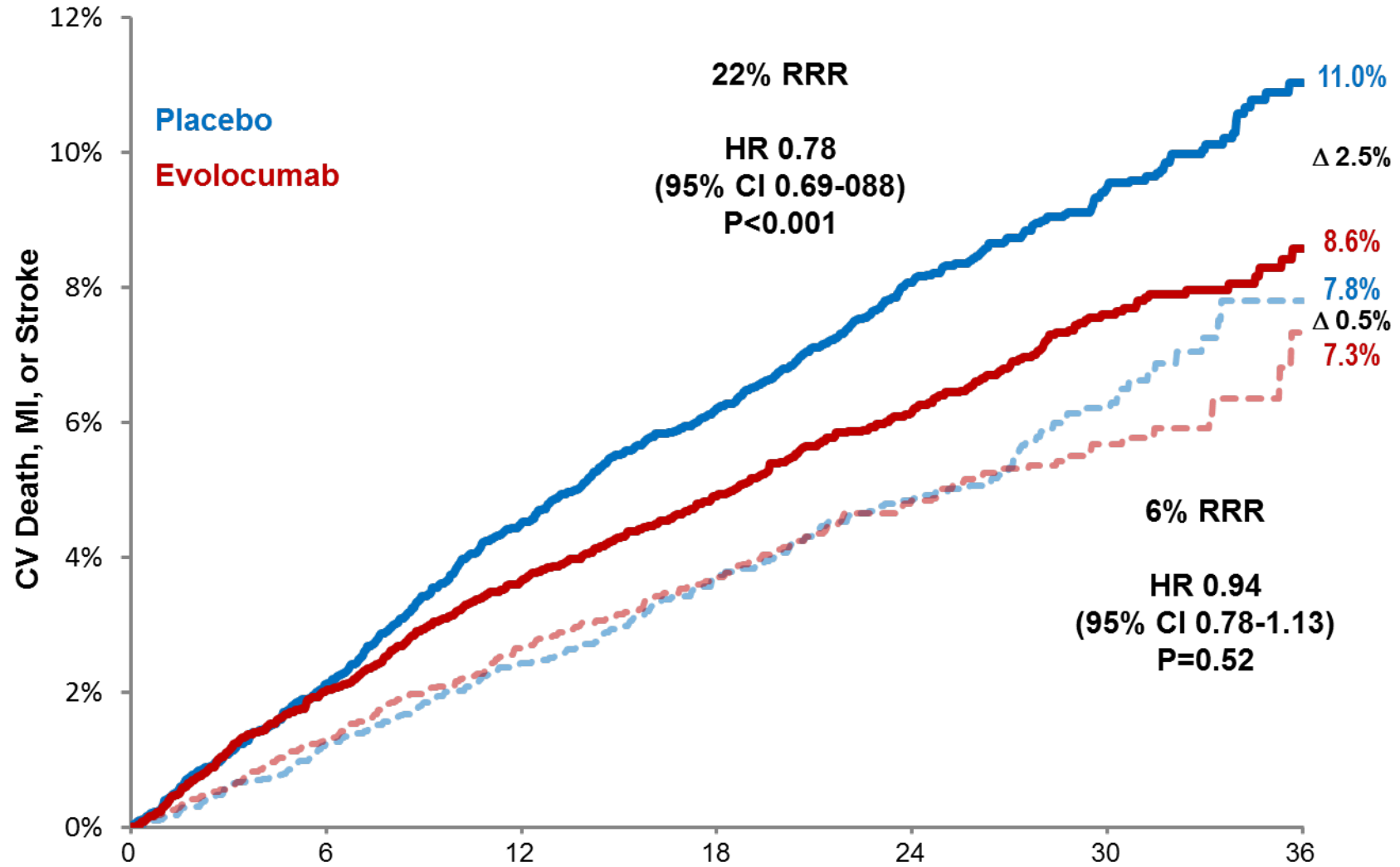


Figure 4a



		Months after Randomization			
		0	12	24	36
<u>Any</u>					
Placebo	7012	6432	3942	476	
Evolocumab	6961	6440	3985	481	
<u>None</u>					
Placebo	4176	3957	2285	134	
Evolocumab	4167	3948	2312	120	

Figure 4b



		Months after Randomization			
<u>Any</u>					
Placebo	7012	6647		4175	515
Evolocumab	6961	6647		4197	507
<u>None</u>					
Placebo	4176	4028		2357	138
Evolocumab	4167	4028		2402	129

SUPPLEMENT

Supplemental Table 1. Baseline Characteristics

Characteristics	Prior MI (N = 22,351)	Entire Trial (N = 27,564)
Demographics		
Age – y, mean (SD)	62.2 (9.0)	62.5 (9.0)
Male sex - n (%)	17544 (78.5)	20795 (75.4)
White race - n (%)	19216 (86.0)	23458 (85.1)
Mean weight – kg, mean (SD)	85.7 (17.1)	85.3 (17.4)
Region		
North America	3663 (16.4)	4571 (16.6)
Europe	14125 (63.2)	17335 (62.9)
Latin America	1556 (7.0)	1823 (6.6)
Asia Pacific and South Africa	3007 (13.5)	3835 (13.9)
Other types of atherosclerosis - n (%)		
Non-hemorrhagic stroke	1646 (7.4)	5337 (19.4)
Peripheral artery disease	1812 (8.1)	3642 (13.2)
Cardiovascular risk factors		
Hypertension – n/total n (%)	17624 (78.9)	22084 (80.1)
Diabetes mellitus - n (%)	7876 (35.2)	10081 (36.6)
Current cigarette use – n/total n (%)	6167 (27.6)	7777 (28.2)
Statin use - n (%)		
High intensity	15939 (71.3)	19013 (69.3)
Moderate intensity	6362 (28.5)	8392 (30.4)
Low intensity, unknown intensity, or no data	50 (0.2)	69 (0.3)
Ezetimibe - n (%)	1239 (5.5)	1440 (5.2)
LDL cholesterol – mg/dL, median (IQR)	91.5 (79.5, 108.5)	91.5 (79.5, 108.5)
eGFR <60 ml/min/1.73 m ² – n/total n (%)	4007 (17.9)	5202 (18.9)

Supplemental Table 2: Risk of Individual Outcomes by Risk Group

	Prior MI <2 years (n=4293)		Prior MI ≥2 years (n=6898)		HR (95% CI)
CV death	75	2.4%	113	2.2%	1.01 (0.75-1.35)
MI	273	7.8%	297	6.2%	1.43 (1.21-1.68)
Stroke	64	2.1%	111	2.0%	0.88 (0.65-1.20)
Hospitalization for unstable angina	104	2.9%	119	2.6%	1.35 (1.04-1.76)
Coronary revascularization	405	11.8%	455	8.7%	1.39 (1.22-1.59)
	≥2 prior MIs (n=2628)		Only 1 prior MI (n=8570)		HR (95% CI)
CV death	71	3.9%	117	1.8%	1.91 (1.42-2.57)
MI	233	10.8%	337	5.5%	2.25 (1.91-2.66)
Stroke	64	3.0%	111	1.8%	1.83 (1.35-2.50)
Hospitalization for unstable angina	91	4.4%	132	2.1%	2.21 (1.69-2.89)
Coronary revascularization	310	14.6%	550	8.5%	1.85 (1.61-2.12)
	Multivessel CAD (n=2806)		No multivessel CAD (n=8390)		HR (95% CI)
CV death	64	2.9%	122	2.1%	1.55 (1.14-2.09)
MI	199	9.1%	369	6.0%	1.61 (1.36-1.92)
Stroke	53	2.7%	122	1.9%	1.29 (0.93-1.78)
Hospitalization for unstable angina	74	3.2%	149	2.5%	1.47 (1.11-1.95)
Coronary revascularization	299	13.2%	559	8.9%	1.61 (1.40-1.86)

Analyses in placebo arm only.

Supplemental Table 3. Full multivariable model for primary endpoint

Characteristics	HR	95% CI	P value
MI within 2 years	1.37	1.22-1.53	<0.001
≥2 prior MIs	1.78	1.59-1.99	<0.001
Multivessel coronary disease	1.39	1.24-1.56	<0.001
Age (per year)	1.003	0.996-1.010	0.46
Male sex	1.22	1.06-1.42	0.007
White race	0.86	0.70-1.07	0.17
Weight (per kg)	1.004	1.001-1.008	0.02
Region (vs. North America)			
Europe	0.68	0.60-0.79	<0.001
Latin America	0.71	0.55-0.91	0.008
Asia Pacific and South Africa	0.63	0.50-0.80	<0.001
Non-hemorrhagic stroke	1.42	1.19-1.70	<0.001
Peripheral artery disease	1.62	1.38-1.92	<0.001
Hypertension	1.20	1.03-1.40	0.02
Diabetes mellitus	1.28	1.14-1.43	<0.001
Current cigarette use	0.98	0.86-1.12	0.79
High-intensity statin use	0.95	0.84-1.08	0.42
LDL cholesterol (per mg/dL)	1.003	1.001-1.005	0.001
eGFR <60 ml/min/1.73 m ²	1.10	0.95-1.27	0.19

Supplemental Table 4. LDL-C Lowering by Subgroup

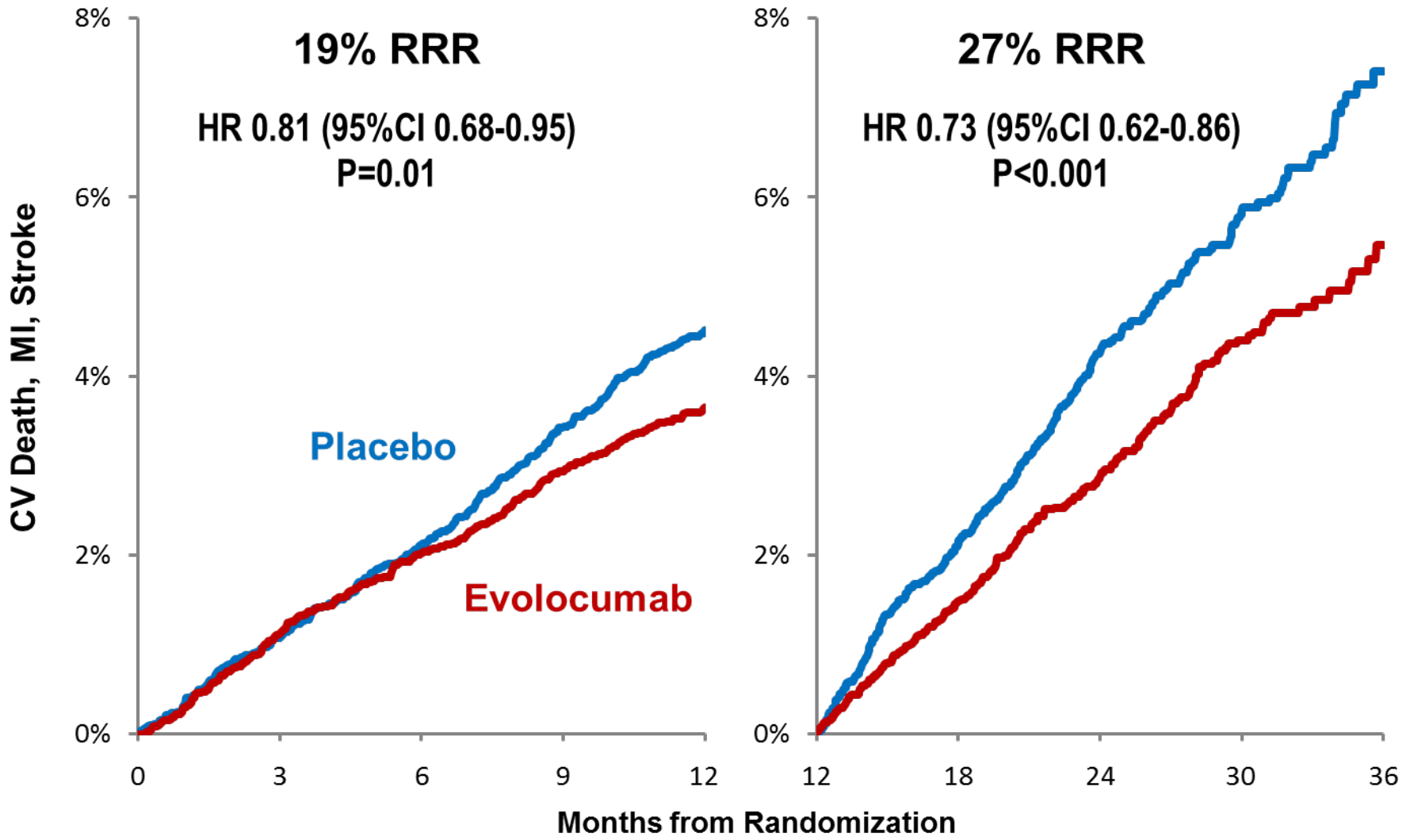
Parameter at 48 weeks	Qualifying MI		# of Prior MIs		Multivessel Disease	
	<2 years	≥2 years	≥2	1	Present	Absent
Percent LDL-C reduction	60 (59-62)	59 (58-60)	61 (59-62)	59 (58-60)	60 (58-61)	60 (59-60)
Absolute LDL-C reduction, mg/dL	56 (55-58)	57 (56-58)	58 (56-60)	56 (55-57)	58 (56-59)	56 (55-57)
Achieved LDL-C in evolocumab arm, mg/dL	29 (19-45)	30 (18-46)	30 (19-46)	29 (19-46)	30 (19-46)	29 (18-46)

Reductions are placebo-controlled and presented as mean (95% CI) and achieved LDL-C is presented as median (IQR).

Supplemental Table 5. Baseline Characteristics of Patients by Presence of Any High-Risk Feature

Characteristics	Any High-Risk Feature (N = 13,973)	No High-Risk Features (N = 8,343)	P value
Demographics			
Age – y, mean (SD)	61.2 (9.1)	63.8 (8.7)	<0.001
Male sex - n (%)	11073 (79.2)	6442 (77.2)	<0.001
White race - n (%)	11923 (85.3)	7263 (87.1)	<0.001
Mean weight – kg, mean (SD)	85.3 (17.2)	86.4 (17.0)	<0.001
Region			<0.001
North America	2181 (15.6)	1470 (17.6)	
Europe	8879 (63.5)	5230 (62.7)	
Latin America	997 (7.1)	559 (6.7)	
Asia Pacific and South Africa	1916 (13.7)	1084 (13.0)	
Other types of atherosclerosis - n (%)			
Non-hemorrhagic stroke	933 (6.7)	708 (8.5)	<0.001
Peripheral artery disease	1075 (7.7)	733 (8.8)	0.004
Cardiovascular risk factors			
Hypertension – n/total n (%)	10875/13972 (77.8)	6716 (80.5)	<0.001
Diabetes mellitus - n (%)	4692 (33.6)	3172 (38.0)	<0.001
Current cigarette use – n/total n (%)	3733/13972 (26.7)	2430 (29.1)	<0.001
Statin use - n (%)			<0.001
High intensity	10377 (74.3)	5540 (66.4)	
Moderate intensity	3567 (25.5)	2782 (33.3)	
Low intensity, unknown intensity, or no data	29 (0.2)	21 (0.3)	
Ezetimibe - n (%)	723 (5.2)	514 (6.2)	0.002
LDL cholesterol – mg/dL, median (IQR)	91.5 (79.5, 108)	92 (80, 109)	0.062
eGFR <60 ml/min/1.73 m ² – n/total n (%)	2411/13969 (17.3)	1592/8339 (19.1)	<0.001

Supplemental Figure 1



Cumulative incidence curves over the first year (left panel) and beyond the first year (right panel) in patients with at least one high-risk feature.