ORIGINAL RESEARCH ARTICLE

Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease

Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk)

Editorial, see p 351

BACKGROUND: The PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor evolocumab reduced low-density lipoprotein cholesterol and cardiovascular events in the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). We investigated the efficacy and safety of evolocumab in patients with peripheral artery disease (PAD) as well as the effect on major adverse limb events.

METHODS: FOURIER was a randomized trial of evolocumab versus placebo in 27564 patients with atherosclerotic disease on statin therapy followed for a median of 2.2 years. Patients were identified as having PAD at baseline if they had intermittent claudication and an ankle brachial index of <0.85, or if they had a prior peripheral vascular procedure. The primary end point was a composite of cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina, or coronary revascularization. The key secondary end point was a composite of cardiovascular death, myocardial infarction, or stroke. An additional outcome of interest was major adverse limb events defined as acute limb ischemia, major amputation, or urgent peripheral revascularization for ischemia.

RESULTS: Three thousand six hundred forty-two patients (13.2%) had PAD (1505 with no prior myocardial infarction or stroke). Evolocumab significantly reduced the primary end point consistently in patients with PAD (hazard ratio [HR] 0.79; 95% confidence interval [CI], 0.66–0.94; $P=0.0098$) and without PAD (HR 0.86; 95% CI, 0.80–0.93; $P=0.0003$; $P_{interaction}=0.40$). For the key secondary end point, the HRs were 0.73 (0.59–0.91; $P=0.0040$) for those with PAD and 0.81 (0.73–0.90; $P<0.0001$) for those without PAD ($P_{interaction}=0.41$). Because of their higher risk, patients with PAD had larger absolute risk reductions for the primary end point (3.5% with PAD, 1.6% without PAD) and the key secondary end point (3.5% with PAD, 1.4% without PAD). Evolocumab reduced the risk of major adverse limb events in all patients (HR, 0.58; 95% CI, 0.38–0.88; $P=0.0093$) with consistent effects in those with and without known PAD. There was a consistent relationship between lower achieved low-density lipoprotein cholesterol and lower risk of limb events ($P=0.026$ for the beta coefficient) that extended down to <10 mg/dL.

CONCLUSIONS: Patients with PAD are at high risk of cardiovascular events, and PCSK9 inhibition with evolocumab significantly reduced that risk with large absolute risk reductions. Moreover, lowering of low-density lipoprotein cholesterol with evolocumab reduced the risk of major adverse limb events.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01764633.

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Clinical Perspective

What Is New?

- Lowering low-density lipoprotein cholesterol to very low levels (median, 31 mg/dL) with evolocumab in patients with symptomatic lower extremity peripheral artery disease significantly reduces major adverse cardiovascular events.
- Evolocumab significantly reduced major adverse limb events with consistent relative reductions in patients with and without peripheral artery disease.
- These benefits come with no offsetting side effects.
- When looking at the composite of major adverse cardiovascular events/major adverse limb events in patients with symptomatic lower extremity peripheral artery disease and no prior myocardial infarction or stroke, evolocumab resulted in an absolute risk reduction at 2.5 years of 6.3% yielding a number needed to treat of 16.

What Are the Clinical Implications?

- There are few therapies that have been proven to reduce major adverse cardiovascular events risk in patients with lower extremity peripheral artery disease, particularly those without concomitant myocardial infarction or stroke, and even fewer that reduce major adverse limb events.
- Lowering of low-density lipoprotein cholesterol to very low levels reduces major adverse cardiovascular events and major adverse limb events, with benefits of low low-density lipoprotein cholesterol extending to very low levels (<10 mg/dL) and with no offsetting safety concerns.
- These data support reducing low-density lipoprotein cholesterol levels to very low targets should be a core focus of preventive therapy in patients with symptomatic lower extremity peripheral artery disease, including those without concomitant coronary or cerebrovascular disease.

The presence of peripheral artery disease (PAD) is a marker of a malignant vascular phenotype with event rates exceeding those of other stable populations with atherosclerosis, particularly in the setting of polyvascular disease.[1–3] Thus, patients with symptomatic PAD are at heightened risk of major adverse cardiovascular events (MACE) including myocardial infarction, stroke, and cardiovascular death.[4,5] In addition, it is important to note that patients with PAD experience significant morbidity from major adverse limb events (MALE) including acute limb ischemia, urgent peripheral revascularization, and major amputation.[6–8]

Although lipid-lowering therapy has been shown to reduce MACE in stable patients with coronary heart disease or atherosclerosis risk factors, there have been few well-powered prospective randomized trials of low-density lipoprotein cholesterol (LDL-C) reduction specifically in patients with PAD.[9] Moreover, these trials have not specifically looked at the ability of LDL-C lowering to reduce the risk of MALE.[6,10–13] Last, because PAD has often been used simply as a risk enhancer, little is known about the effect of LDL-C lowering in patients who have PAD without prior myocardial infarction (MI) or stroke.[8,9,14,15]

The FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) was a very large cardiovascular outcomes trial of the PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor evolocumab that enrolled patients with atherosclerotic disease, in either the coronary, cerebrovascular, or peripheral arterial bed. FOURIER thus allowed us to test the following hypotheses: (1) patients with PAD would be at greater risk of MACE relative to patients with coronary or cerebrovascular disease without PAD; (2) consistent relative risk reductions in MACE with evolocumab would translate to larger absolute risk reductions in patients with PAD relative to those without; and (3) LDL-C reduction with evolocumab would significantly reduce MALE with benefits extending to very low levels of LDL-C.

METHODS

Study Population

The FOURIER trial design has been previously described.[16] The study was approved by an institutional review committee and all subjects gave informed consent. Patients with clinically evident atherosclerotic cardiovascular disease including prior MI, prior ischemic stroke, or symptomatic PAD were randomly assigned in a 1:1 ratio to evolocumab or placebo. Patients were eligible to qualify with symptomatic PAD if they had intermittent lower extremity claudication and an ankle brachial index <0.85, a history of a peripheral artery revascularization procedure, or a history of amputation attributable to atherosclerotic disease. In addition to the prespecified subgroup based on symptomatic lower extremity PAD, we also examined, as part of a post hoc exploratory analysis, a more restricted population defined as patients with symptomatic lower extremity PAD but with no history of MI or stroke.

End Points

The primary efficacy end point in FOURIER was major cardiovascular events, defined as the composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary end point was the composite of cardiovascular (CV) death, MI, or stroke. Other secondary end points included the components of the primary end point. Cardiovascular events were adjudicated by a blinded clinical event committee. Limb outcomes were prospectively ascertained through investigator reporting on dedicated electronic case report form pages and through adverse event forms. Limb outcomes were adjudicated by 2 blinded vascular medicine specialists (Cohen κ for adjudicator agreement, 0.903). Similar to other recent trials evaluating

medical therapies in patients with PAD, MALE was defined as the composite of acute limb ischemia (ALI), major amputation (above the knee or below the knee, excluding forefoot or toe), or urgent revascularization (thrombolysis or urgent vascular intervention for ischemia).[3,8,14,15,17] ALI required both a clinical presentation consistent with acute ischemia (symptoms consistent with a rapid or sudden decrease in limb perfusion lasting <2 weeks) including findings on physical examination or imaging.[17] In addition, all peripheral artery revascularization and amputation procedures were recorded by the site in the electronic case report form. Analogous to other trials, a combined end point of MACE and MALE was examined.[14,18] Prespecified safety end points as defined in the primary analysis were included for the PAD subgroup.[19]

Statistical Considerations

As part of a prespecified analysis, patients were stratified into those with or without symptomatic lower extremity PAD at baseline. Baseline characteristics of the subgroups were compared by using Wilcoxon rank sum tests for continuous data and χ^2 tests for categorical data. All efficacy analyses of evolocumab versus placebo were done on an intention-to-treat basis (ie, all patients who were randomly assigned were analyzed, irrespective of study drug compliance). Safety analyses included all randomly assigned patients who received at least 1 dose of study treatment and for whom postdose data were available. P values for time-to-event analyses are from log-rank tests; Kaplan-Meier event rates were calculated up to 2.5 years. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the effect of evolocumab versus placebo were generated by use of a Cox proportional hazards model, without adjustment (because of the randomized design) but stratifying by region and screening LDL-C values. We tested effect modification by PAD on the efficacy of evolocumab by incorporating interaction terms into Cox models. For the analysis of risk of cardiovascular outcomes comparing patients with and without PAD in the placebo group, a multivariable-adjusted HR was obtained from a Cox model that included the following baseline covariates: age, sex, race, body mass index, hypertension, diabetes mellitus, smoking status, renal dysfunction, congestive heart failure, prior MI, coronary artery bypass grafting surgery or percutaneous coronary intervention, and prior stroke or transient ischemic attack. Proportional hazards assumptions were not violated. A repeated-measures linear mixed-effects model was used to obtain the least-squares means percentage and absolute reduction in LDL-C between the 2 treatment groups. For analyses evaluating the relationship of achieved LDL-C at 1 month and outcomes, we plotted the relationship between end points and achieved LDL cholesterol using a smoothing function applied to the averages of the estimated event rates at each LDL level based on the adjusted Cox models. Analyses were adjusted for significant predictors of LDL-C cholesterol at 1 month after randomization including age, BMI, LDL-C at baseline, sex, race randomized in North America, current smoker, and high intensity statin.[20] P values <0.05 were regarded as significant. We used SAS (version 9.4) for the statistical analyses. The data and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure at this time; however, the entire FOURIER clinical database has been made available to the US Food and Drug Administration for review and validation.

RESULTS

Populations

Of the 27 564 patients randomized, 3642 (13.2%) had a history of symptomatic lower extremity PAD at baseline (Figure 1). A total of 2067 patients (56.8%) had a history of prior peripheral revascularization, 126 (3.5%) had a history of amputation for vascular cause, and 2518 (69.3%) had an ankle brachial index <0.85 and symptoms of claudication (with some patients having >1 of these factors). Patients with PAD were older, were more frequently female, and had a greater prevalence of risk factors including hypertension, current smoking, renal insufficiency, and diabetes mellitus (Table 1). At baseline, 89% of patients were taking antiplatelet therapy, 69% were taking high-intensity statin therapy, 30% were taking moderate-intensity statin therapy, and 6.6% were taking ezetimibe. Of the PAD subgroup, 1812 patients (49.8%) had a history of MI and 545 (15.0%) had a history of stroke; there were 1505 (41% of those with PAD and 5% of the total population) who had PAD and no prior MI or stroke.

Risk of Vascular Events in Patients With and Without PAD

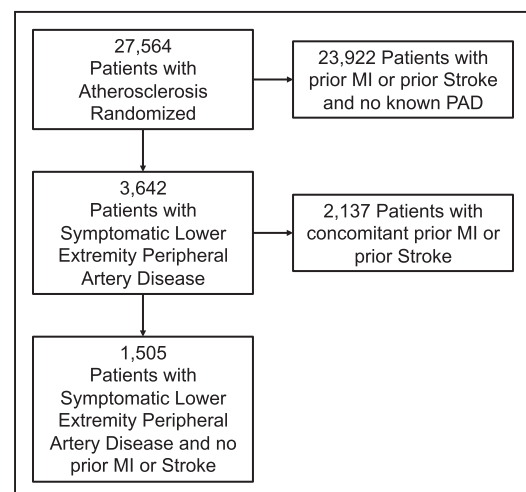Among patients in the placebo arm, patients with PAD in comparison with patients without PAD had higher

Figure 1. Patients with peripheral artery disease in the FOURIER trial.
Consort diagram describing the subgroup of patients with symptomatic lower extremity peripheral artery disease including those without prior myocardial infarction or stroke. MI indicates myocardial infarction; and PAD, peripheral artery disease. FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk.

Table 1. Baseline Characteristics by Presence of Prior PAD

	No PAD N=23 922	PAD N=3642
Age, median (IQR)	63 (56–69)	64 (58–69)
Female sex, n (%)	5743 (24.0)	1026 (28.2)
Body mass index, median (IQR)	29 (26–32)	29 (26–32)
White, n (%)	20 156 (84.3)	3302 (90.7)
History of hypertension, n (%)	18 993 (79.4)	3091 (84.9)
Current smoker, n (%)	6451 (27.0)	1326 (36.4)
Renal insufficiency, n (%)	1323 (5.5)	340 (9.3)
History of atrial fibrillation, n (%)	2022 (8.5)	320 (8.8)
History of diabetes mellitus, n (%)	8501 (35.5)	1580 (43.4)
History of stroke/TIA, n (%)	5101 (21.3)	685 (18.8)
History of myocardial infarction, n (%)	20 539 (85.9)	1812 (49.8)
History of CHF, n (%)	5625 (23.5)	769 (21.1)
Prior CABG, n (%)	4387 (18.4)	839 (23.0)
History of PCI, n (%)	14 029 (58.7)	1444 (39.7)
Peripheral artery disease history		
Symptomatic peripheral artery disease and no prior MI or stroke	0	1505 (41.3)
Current intermittent claudication and ABI <0.85, n (%)	0	2518 (69.3)
Prior peripheral revascularization, n (%)	0	2067 (56.8)
Time from peripheral revascularization, y, median (IQR)	0	3.7 (1.3–7.8)
Limb amputation for vascular cause, n (%)	0	126 (3.5)
Medications at baseline		
High-intensity statin use at baseline, n (%)	16 579 (69.3)	2524 (69.3)
Moderate-intensity statin use at baseline, n (%)	7282 (30.4)	1110 (30.5)
Low-intensity statin use at baseline, n (%)	51 (0.2)	5 (0.1)
Ezetimibe use at baseline, n (%)	1200 (5.0)	240 (6.6)
Antiplatelet therapy, n (%)	22 216 (92.9)	3246 (89.3)
Anticoagulant therapy, n (%)	1805 (7.6)	391 (10.8)
ACE-I or ARB use at baseline, n (%)	18 526 (77.5)	2747 (75.6)

All P values <0.05 except history of atrial fibrillation (P=0.50) and statin use/intensity (P=0.57). Statin dose at baseline missing in 10 (<0.1%) without PAD and 3 (0.1%) with PAD. ABI indicates ankle brachial index; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting surgery; CHF, congestive heart failure; IQR, interquartile range; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; and TIA, transient ischemic attack.

rates of both the primary end point (Kaplan-Meier rate at 2.5 years: 16.8% versus 12.1%, P<0.001) and the key secondary end point (13.0% versus 7.6%, P<0.001) (Table I and Figure I in the online-only Data

Supplement). After adjusting for baseline differences, patients with PAD remained at significantly higher risk of the primary end point (adjusted HR, 1.57; 95% CI, 1.36–1.80; P<0.001) and the key secondary end point (adjusted HR, 1.81; 95% CI, 1.53–2.14; P<0.001; Table I and Figure I in the online-only Data Supplement).

When stratifying the population with PAD by history of concomitant prior MI or stroke (polyvascular disease), those with polyvascular disease had higher rates of CV death, MI, or stroke than those without (14.9% versus 10.3%, P=0.0028; Figure II in the online-only Data Supplement). Patients with PAD and no prior MI or stroke, however, still had higher rates of CV death, MI, or stroke than patients with prior MI or stroke and no symptomatic PAD (10.3% versus 7.6%; adjusted HR, 2.07; 95% CI, 1.42–3.01; P=0.0001; Figure II in the online-only Data Supplement). When evaluating the individual components, CV death appeared especially higher (4.4% versus 1.7%, P=0.0029) in those with PAD and no prior MI or stroke versus patients with no PAD, although rates of MI and stroke were numerically higher as well (Figure IIIA in the online-only Data Supplement).

As expected, patients with symptomatic PAD had higher rates of limb outcomes relative to those without PAD including MALE (2.4% versus 0.2%; adjusted HR, 11.67; 95% CI, 6.25–21.79; P<0.001) and the composite of ALI and major amputation (1.5% versus 0.1%; adjusted HR, 7.88; 95% CI, 3.67–16.92; P<0.001; Table I in the online-only Data Supplement). Findings were consistent in the subgroup with PAD and no MI or stroke versus patients with no PAD (Figure IIIB in the online-only Data Supplement).

LDL-C Lowering With Evolocumab

The median LDL-C level at baseline among the symptomatic PAD group was 94 mg/dL (interquartile range, 81–112). At 48 weeks, the percentage reduction in LDL-C with evolocumab, relative to placebo, was 59% (least-squares mean percentage, 95% CI, 57–61; P<0.001) or a mean absolute reduction of 57 mg/dL (95% CI, 55–60), resulting in a median LDL-C of 31 mg/dL (interquartile range, 19–49; Figure IV in the online-only Data Supplement). The reduction in LDL-C levels was maintained over time (Figure IV in the online-only Data Supplement).

Cardiovascular Efficacy With Evolocumab

In patients with PAD, evolocumab significantly reduced the primary end point by 21% (2.5-year Kaplan-Meier rate, 13.3% versus 16.8%; HR, 0.79; 95% CI, 0.66–0.94; P=0.0098; Table 2, Figure 2A) and the composite of CV death, MI, or stroke by 27% (9.5% versus 13.0%; HR, 0.73; 95% CI, 0.59–0.91; P=0.0040; Table 2, Figure 2B). The relative risk reductions for both end points

Table 2. Efficacy of Evolocumab in Patients with Peripheral Artery Disease

Outcome	Efficacy Outcomes							
	Symptomatic PAD				Symptomatic PAD Without Prior MI or Stroke			
	Placebo n=1784	Evolocumab n=1858	Hazard Ratio (95% CI)	P Value	Placebo n=748	Evolocumab n=757	Hazard Ratio (95% CI)	P Value
Primary end point	16.8	13.3	0.79 (0.66–0.94)	0.0098	12.6	7.7	0.67 (0.47–0.96)	0.0283
CV death, MI, stroke (MACE)	13.0	9.5	0.73 (0.59–0.91)	0.0040	10.3	5.5	0.57 (0.38–0.88)	0.0095
CVD	3.8	4.0	1.02 (0.71–1.48)		4.4	2.9	0.78 (0.39–1.57)	
MI	7.9	5.2	0.69 (0.52–0.91)		5.7	2.9	0.66 (0.38–1.14)	
Stroke	3.1	1.8	0.59 (0.38–0.92)		2.5	0.7	0.30 (0.11–0.82)	
Ischemic stroke	2.9	1.7	0.57 (0.35–0.90)		2.4	0.5	0.25 (0.08–0.77)	
Coronary revascularization	9.6	7.0	0.79 (0.62–1.01)		6.9	4.0	0.70 (0.44–1.13)	
All death	6.7	6.2	0.92 (0.69–1.23)		6.4	4.9	0.86 (0.51–1.45)	

Outcomes are shown by 2.5-y KM rate (%). CI indicates confidence interval; CV, cardiovascular; CVD, cardiovascular disease; KM, Kaplan-Meier; MACE, major adverse cardiovascular events; MI, myocardial infarction; and PAD, peripheral artery disease.

were consistent in patients with and without PAD ($P_{interaction}$=0.40 and 0.41, respectively). However, because of the higher absolute risk in patients with PAD, the absolute risk reductions [ARRs] for both end points were greater in those with PAD versus those without (ARR for the primary end point, 3.5% [95% CI, 0.8%–6.2%] in PAD; 1.6% [95% CI, 0.7%–2.5%] without PAD; ARR for CV death, MI, or stroke 3.5% [95% CI, 1.0%–6.0%] in PAD; 1.4% [95% CI, 0.7%–2.1%] without PAD). Relative and ARRs were consistent in the population of patients with PAD and no prior MI or stroke including a 4.9% ARR (95% CI, 1.0%–8.8%) in the primary end point and a 4.8% ARR (95% CI, 1.2%–8.4%) in the composite of CV death, MI, or stroke translating in a number needed to treat (NNT)$_{2.5y}$ of 21 for each (Table 2, Figure VA and VB in the online-only Data Supplement).

MALE Reduction With Evolocumab

Overall, evolocumab reduced the risk of MALE by 42% (0.27% versus 0.45%; HR, 0.58; 95% CI, 0.38–0.88; P=0.0093; ARR, 0.18%; Table 3, Figure 3A) and the pattern of efficacy was consistent across all components of MALE (Table 3). The reduction in MALE with evolocumab was consistent regardless of background statin intensity ($P_{interaction}$=0.81) and remained significant even when restricted to the 19 103 patients on high-intensity statin therapy at baseline (HR, 0.56; 95% CI, 0.33–0.93; P=0.022).

The relative risk reduction in MALE with evolocumab was also consistent in those with PAD (HR, 0.63; 95% CI, 0.39–1.03) and those without PAD (HR, 0.37; 95% CI, 0.16–0.88; $P_{interaction}$=0.29; Figure 3B and 3C). Naturally, given the higher event rates in patients with known PAD, the ARRs were greater in those with PAD (1.5% versus 2.4%; ARR, 0.9%) than in those without (0.076% versus 0.16%; ARR, 0.08%). In the 1505 patients with PAD and no prior MI or stroke, reductions in

MALE were consistent (1.3% versus 2.6%; HR, 0.43; 95% CI, 0.19–0.99; ARR, 1.3%; Table 3, Figure VC in the online-only Data Supplement).

Composite Outcome of MACE and MALE in Patients With PAD

Overall, evolocumab reduced the composite of MACE (CV death, MI, or stroke) or MALE (ALI, major amputation, or urgent revascularization) by 21% (HR, 0.79; 95% CI, 0.72–0.87; P<0.001; 6.9% versus 8.7%; ARR, 1.8%; NNT, 56; Table 3). The relative risk reduction in MACE or MALE with evolocumab was consistent in those with PAD (HR, 0.73; 95% CI, 0.60–0.88; 10.9% versus 15.0%; ARR, 4.1%; NNT, 25) and those without PAD (HR, 0.80; 95% CI, 0.72–0.89; 6.3% versus 7.8%; ARR, 1.5%; NNT, 67; $P_{interaction}$=0.39, Figure 4). In the 1505 patients with PAD and no prior MI or stroke, reductions in the composite of MACE or MALE were consistent (HR, 0.52; 95% CI, 0.35–0.76; 6.5% versus 12.8%; ARR, 6.3%; NNT, 16 (Table 3, Figure VI in the online-only Data Supplement).

Safety of Evolocumab in Patients With PAD

There were no differences in the incidence of adverse or serious adverse events with evolocumab relative to placebo in patients with PAD (Table II in the online-only Data Supplement). There was no excess of adverse events leading to treatment discontinuation (1.3% evolocumab versus 1.5% placebo, P=0.57).

Association of Achieved LDL-C and Risk of MALE and MACE

Overall, lower achieved LDL-C was associated with a significantly lower risk of MALE with a roughly linear
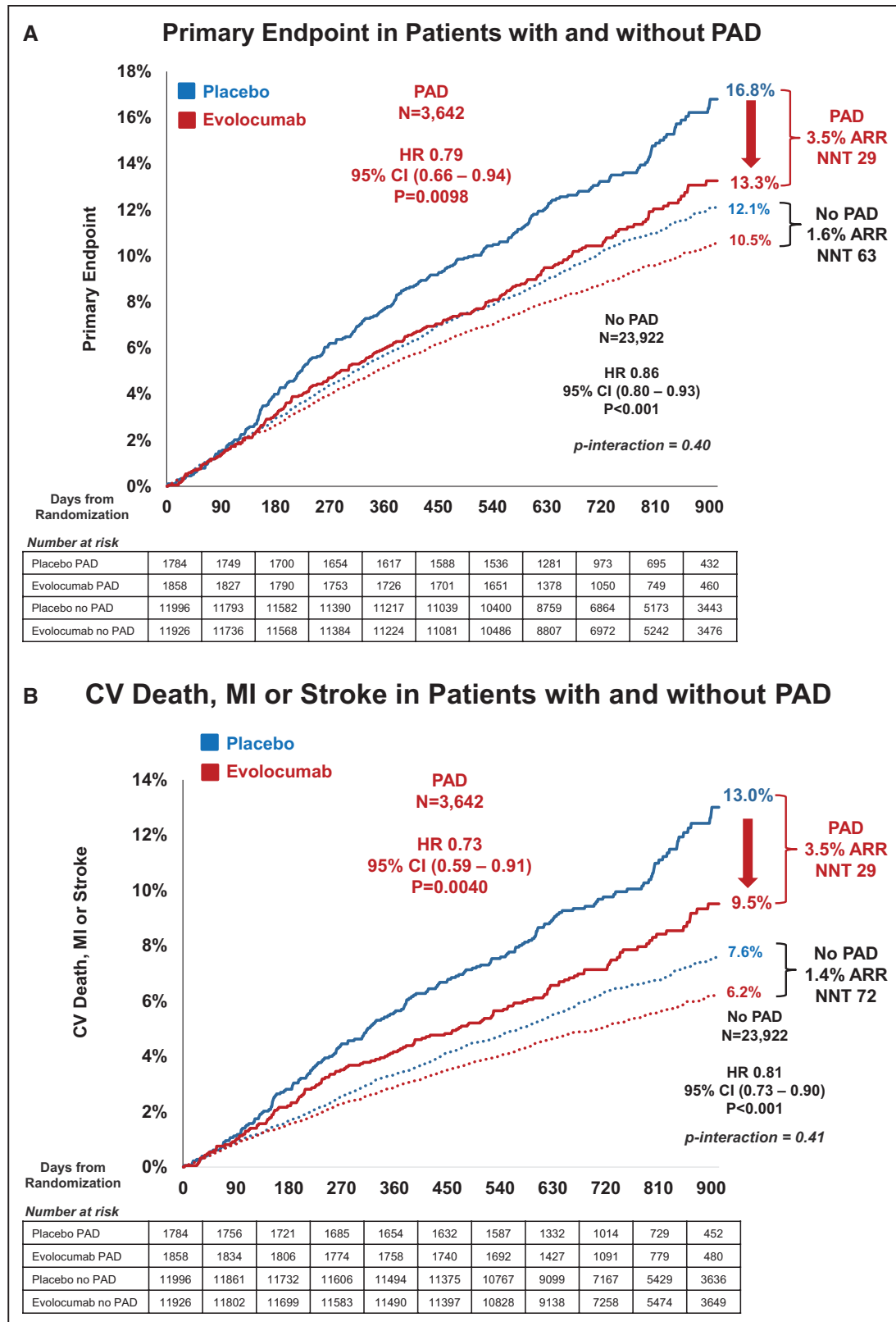
Figure 2. Primary and key secondary end points in patients with and without peripheral artery disease.
A, The primary composite end point (cardiovascular death, myocardial infarction, stroke, unstable angina, coronary revascularization) by treatment (evolocumab in red, placebo in blue) in patients with (solid lines) and without (dashed lines) symptomatic PAD. **B,** The key secondary composite end point (cardiovascular death, myocardial infarction, stroke) by treatment (evolocumab in red, placebo in blue) in patients with (solid lines) and without (dashed lines) symptomatic PAD. ARR indicates absolute risk reduction; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; NNT, number needed to treat; and PAD, peripheral artery disease.

Table 3.   Major Adverse Limb Outcomes With Evolocumab Versus Placebo

	Efficacy Outcomes								
	Overall Population			Patients With PAD			Patients With PAD and No MI or Stroke		
Outcome	Placebo n=13 780	Evolocumab n=13 784	Hazard Ratio (95% CI)	Placebo n=1784	Evolocumab n=1858	Hazard Ratio (95% CI)	Placebo n=748	Evolocumab n=757	Hazard Ratio (95% CI)
MALE*	0.45	0.27	0.58 (0.38–0.88) P=0.0093	2.4	1.5	0.63 (0.39–1.03) P=0.063	2.6	1.3	0.43 (0.19–0.99) P=0.042
ALI or major amputation	0.29	0.17	0.52 (0.31–0.89)	1.5	0.9	0.60 (0.32–1.13)	1.8	0.6	0.33 (0.10–1.01)
ALI	0.24	0.15	0.55 (0.31–0.97)	1.1	0.8	0.73 (0.37–1.48)	1.2	0.6	0.48 (0.15–1.61)
Major amputation	0.05	0.03	0.57 (0.17–1.95)	0.4	0.2	0.41 (0.11–1.57)	0.6	0.1	0.26 (0.03–2.32)
Urgent revascularization	0.21	0.13	0.69 (0.38–1.26)	1.2	0.9	0.75 (0.39–1.45)	1.2	0.9	0.72 (0.25–2.08)
Any peripheral revascularization	2.38	2.59	1.08 (0.92–1.27) P=0.33	12.4	13.3	1.02 (0.84–1.23) P=0.88	12.3	15.1	1.17 (0.87–1.57) P=0.30
CV death, MI, stroke, MALE	8.70	6.91	0.79 (0.72–0.87) P<0.001	15.0	10.9	0.73 (0.60–0.88) P=0.0014	12.8	6.5	0.52 (0.35–0.76) P=0.0006

Outcomes are shown by n and the 2.5-y KM rate (%). AKA indicates above knee amputation; ALI, acute limb ischemia; BKA, below knee amputation; CI, confidence interval; CV, cardiovascular; KM, Kaplan-Meier; MALE, major adverse limb events; MI, myocardial infarction; and PAD, peripheral artery disease.

*MALE is the composite of ALI, major amputation (AKA or BKA), or urgent peripheral revascularization for ischemia.

relationship down to LDL-C of 10 mg/dL (P=0.026 for the beta coefficient) with consistent patterns in patients with PAD and those with PAD and no prior MI or stroke (Figure 5, Figure VII in the online-only Data Supplement). There was no apparent inflection or plateau in the relationship between LDL-C and outcome. This pattern was consistent for the broader composite outcome of MACE or MALE overall and for patients with PAD (Figure VIII in the online-only Data Supplement) and patients with PAD and no prior MI or stroke (Figure IX in the online-only Data Supplement).

DISCUSSION

This study confirms that patients with symptomatic lower extremity PAD are at higher risk of both MACE and MALE relative to patients with prior MI or stroke and no PAD. Evolocumab significantly reduced the risk of MACE in patients with symptomatic PAD, including those without prior MI or stroke, and the higher risk in patients with PAD translated into greater ARRs. Furthermore, LDL-C lowering with evolocumab reduced the risk of MALE including ALI and major amputation. Thus, when considering both MACE and MALE, the ARR with LDL-C lowering in patients with PAD was quite robust, with an NNT for 2.5 years of only 25. Last, akin to what has been observed for MACE, there was a consistent lower risk of MALE with lower levels of achieved LDL-C, down to 10 mg/dL.

The higher ischemic risk in patients with symptomatic PAD in comparison with those without has been recognized.[21,22] This observation, however, is complex because there is heterogeneity in risk within the broad population of patients with PAD. Those patients with multiple symptomatic territories (eg, PAD and prior MI or prior stroke), called polyvascular disease, are at clearly heightened risk and appear to derive robust reductions in MACE risk from more intensive antithrombotic therapy.[3,23,24] For patients with symptomatic PAD and no prior MI or stroke, there were fewer proven medical therapies.[4,5,15,25] The current study builds on observations from the Heart Protection Study and observational analyses to demonstrate that intensive lipid lowering is beneficial in this population and has no offsetting side effects such as bleeding with antithrombotic therapy.[3,8,14,25]

In the current study, we have examined 2 symptomatic PAD populations: a broad population including those with polyvascular disease, and a restricted population with symptomatic lower extremity PAD who have never experienced an acute atherothrombotic event (MI or stroke). The benefits of intensive lipid lowering with evolocumab were consistent in both populations. These findings therefore highlight that patients with symptomatic PAD as the primary manifestation of atherosclerotic vascular disease enjoy robust benefits from lipid lowering and supports the hypothesis that the biology of MACE risk in this population is modifiable with LDL-C lowering.

There are limited prior randomized, controlled data on the effect of LDL-C lowering on clinical outcomes in PAD. The Heart Protection Study randomly assigned 20 536 patients with vascular disease with a total cholesterol of at least 3.5 mmol/L (135 mg/dL) to simvastatin 40 mg daily or placebo and included 6748 patients with PAD.[26] Over 5 years of follow-up, simvastatin reduced major vascular events relative to pla-

A Major Adverse Limb Events – All Patients

HR 0.58
95% CI (0.38 – 0.88)
P=0.0093

B Major Adverse Limb Events – Patients with PAD

HR 0.63
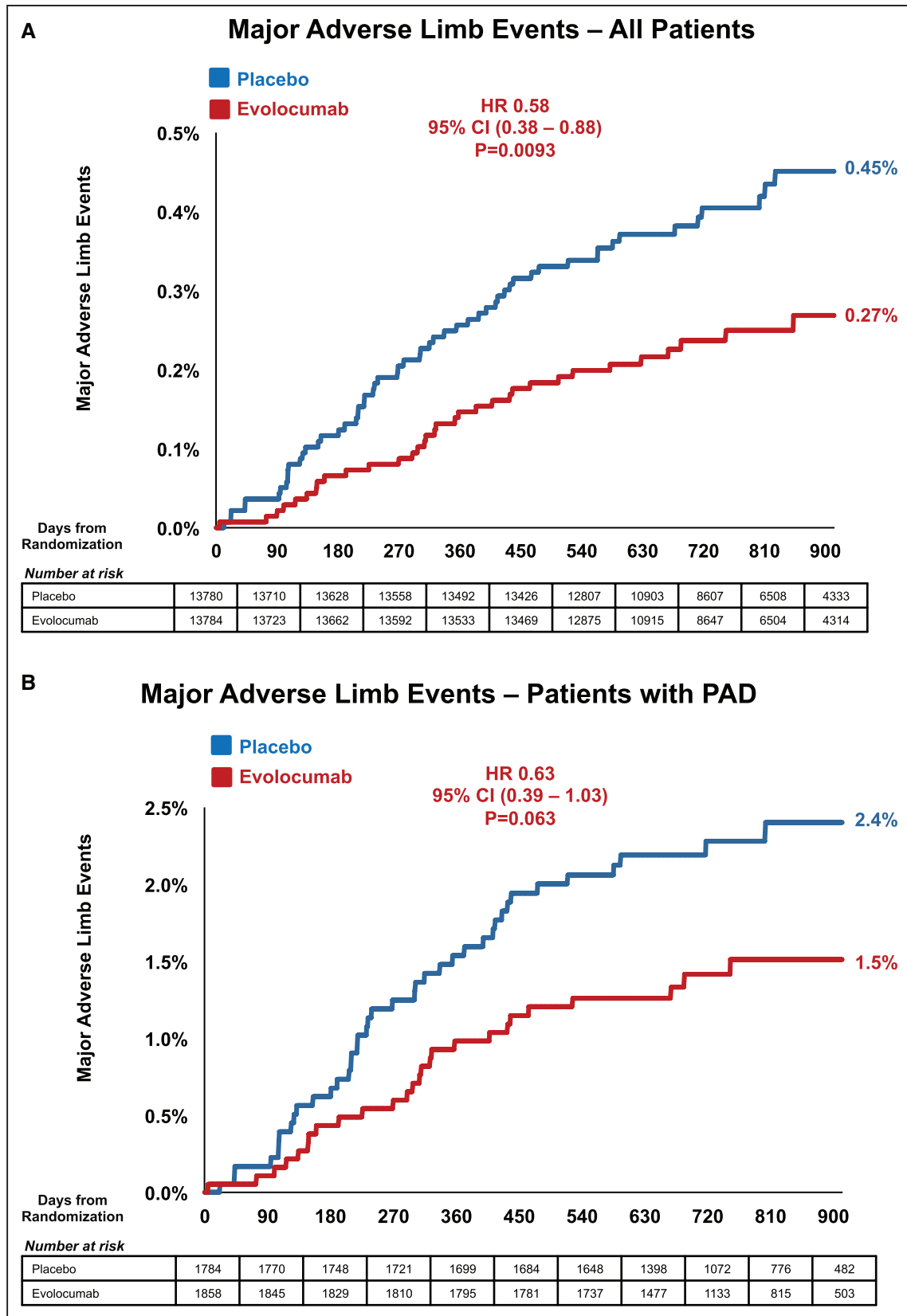95% CI (0.39 – 1.03)
P=0.063

Figure 3. Major adverse limb events.
Major adverse limb events (composite of acute limb ischemia, major amputation, or urgent revascularization) by treatment (evolocumab in red, placebo in blue) in all randomly assigned patients (**A**), in patients with symptomatic PAD (**B**), and in patients with no known PAD (**C**). CI indicates confidence interval; HR, hazard ratio; and PAD, peripheral artery disease. (*continued*)
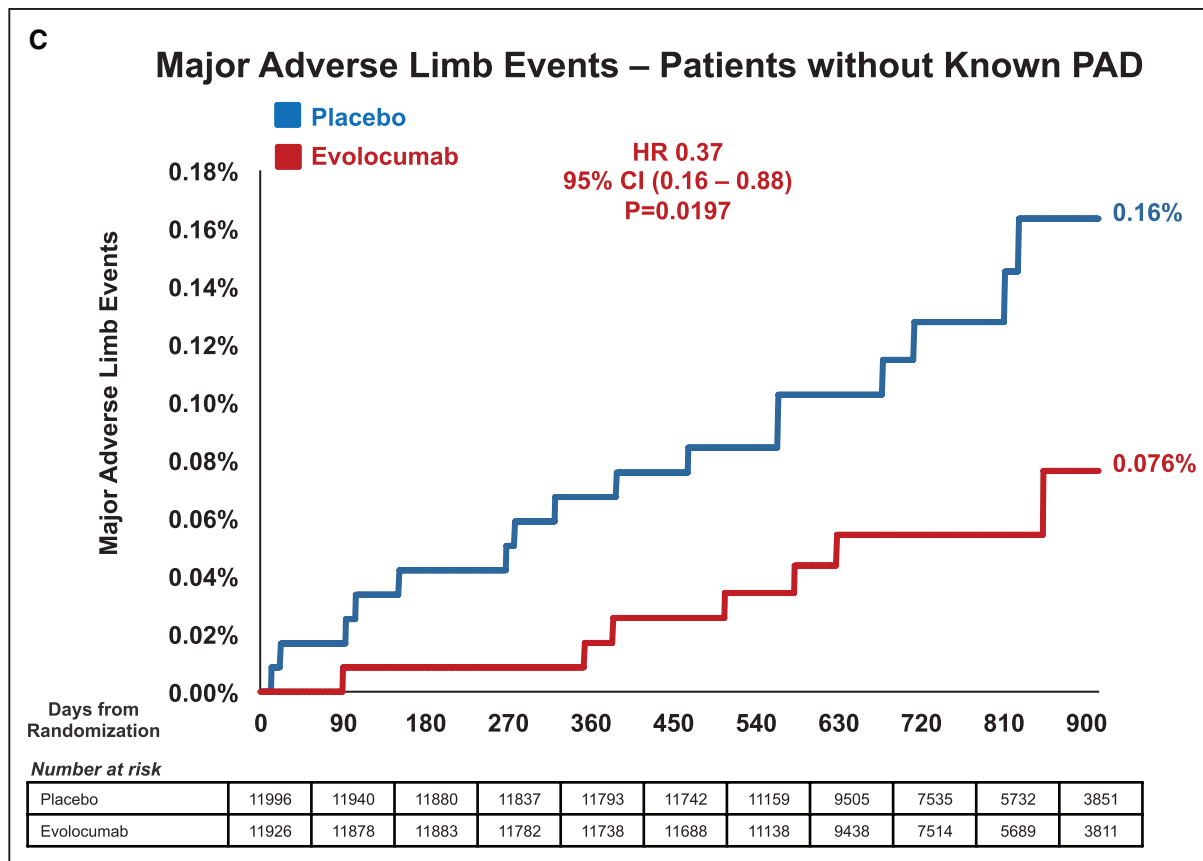
Figure 3 Continued.

cebo with consistent relative risk reductions in those with and without PAD.[27] An exploratory outcome of noncoronary vascular intervention (including carotid intervention) was also lower with simvastatin.[27] There was no difference in the risk of amputation with simvastatin versus placebo. Observational analyses have reported associations between statin intensity and reductions in MACE in patients with stable PAD or those presenting with critical limb ischemia.[28–30] Beyond these observations, there are no well-powered randomized studies showing that achieving lower LDL-C or that adding a nonstatin lipid-lowering agent to a statin is beneficial in PAD.[9] The current study now adds additional data from a well-powered randomized trial that achieving lower LDL-C with a nonstatin agent added to high- or moderate-intensity statin therapy is beneficial in patients with symptomatic lower extremity PAD, including those without prior MI or stroke.[9]

In addition to robust benefits for MACE, the current study is the first randomized trial to demonstrate a benefit for intensive LDL-C lowering for MALE risk. As noted above, the Heart Protection Study noted a reduction in the outcome of noncoronary revascularization procedures; however, this was not specific to etiology and included procedures beyond the lower extremities such as carotid revascularization.[27] MALE was not specifically

reported and there was no difference in amputations.[27]. Prior small studies have described potential symptomatic benefits with statin therapy but have not been powered for MALE.[10,11,31] A single study has reported a significant 36% reduction in amputations with 5 years of treatment with fenofibrate versus placebo in people with type 2 diabetes mellitus, mostly among individuals with PAD, prior amputation, or neuropathy, and likely via non–LDL-C–mediated mechanisms.[32] Analyses from large registries have observed an association between lower amputation rates and statin therapy; however, the potential for residual confounding has remained and the intensity of statin therapy or achieved LDL-C was not reported.[6,33,34] Smaller observational studies in patients with critical limb ischemia have shown mixed results for the association between statins in limb events with some showing no significant reduction in amputation and others showing improved limb salvage in patients presenting for endovascular therapy for critical limb ischemia.[29,30,35]

The current study demonstrates that nonstatin LDL-C lowering added to statins reduces MALE in patients with symptomatic atherosclerosis and that the benefits extend to very low achieved LDL-C. This benefit was statistically significant in the overall population with consistent effects in those with and without recognized lower extremity PAD. The benefit in those without known PAD reflects both the
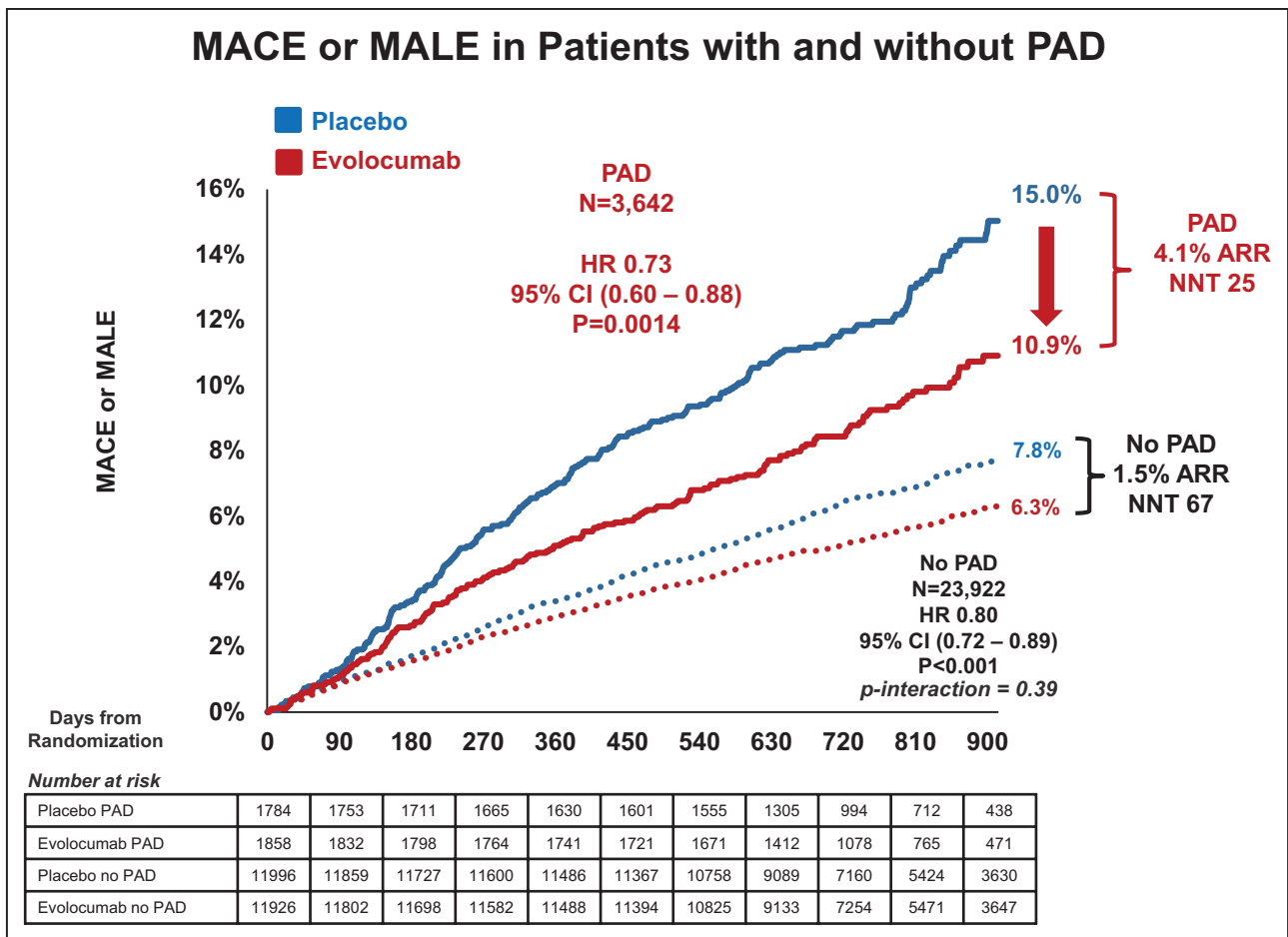
Figure 4. Major adverse cardiovascular and limb events in patients with and without peripheral artery disease.
The composite of major adverse cardiovascular events (MACE; cardiovascular death, myocardial infarction, or stroke) and major adverse limb events (MALE; acute limb ischemia, major amputation, or urgent revascularization) by treatment (evolocumab in red, placebo in blue) in patients with (solid lines) and without (dashed lines) symptomatic PAD. ARR indicates absolute risk reduction; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; MALE, major adverse limb event; NNT, number needed to treat; and PAD, peripheral artery disease.

heightened risk of PAD in patients with coronary or cerebrovascular disease, as well as the underdiagnosis in populations where systematic screening is not conducted. These observations support ascertainment of MALE outcomes in trials of preventive therapies in broader populations with atherosclerosis and not only those with recognized PAD.

The reduction in MALE with evolocumab was consistent for all the components, which have now been established as modifiable limb end points in 3 randomized trials of more intensive antithrombotic therapy and end points that have been adopted as elements of primary or key secondary end points in trials including patients with PAD.[3,8,14,15] There was no apparent benefit for reducing peripheral revascularizations including elective procedures for claudication as has been described for others such as vorapaxar.[8] Possible explanations for the lack of benefit for this broad end point include that lipid lowering does not improve symptoms or, alternatively, that it does but over a longer period of exposure and therefore was not seen in the relatively short duration of follow-up (median, 2.2 years) in the

current study. Supporting the latter explanation is the observation that benefits for peripheral revascularization and symptoms with vorapaxar were not apparent until almost 2 years of exposure and were not significant until 3 years. Additional longer-term studies are necessary to determine whether long-term reduction in LDL-C will modify disease progression and ameliorate symptoms.

In evaluating the overall benefits of preventive therapies in patients with PAD, recent and ongoing trials (VOYAGER PAD [Efficacy and Safety of Rivaroxaban in Reducing the Risk of Major Thrombotic Vascular Events in Subjects With Symptomatic Peripheral Artery Disease Undergoing Peripheral Revascularization Procedures of the Lower Extremities], ClinicalTrials.org; NCT02504216) have used a composite end point including both cardiovascular and limb outcomes.[14] This composite provides a global picture of benefit against which harm and cost can be weighed. In the current study, in the broader population of patients with PAD, robust reductions in the composite of MACE or MALE resulted in an ARR at 2.5 years of 4.1% and
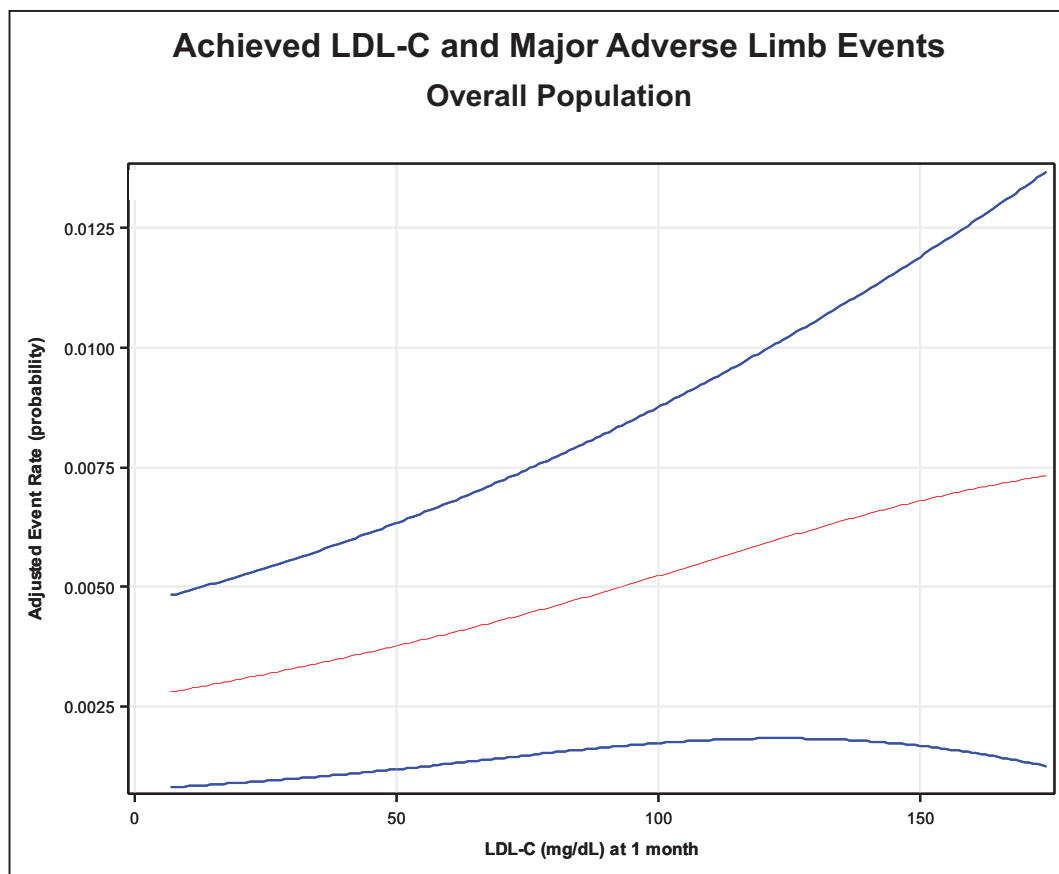
Figure 5. The relationship of achieved LDL-C and major adverse limb events.
Adjusted relationship between achieved LDL-C at 1 month and major adverse limb events (acute limb ischemia, major amputation, or urgent revascularization) in the overall population. *P*=0.026 for the beta coefficient. LDL-C indicates low-density lipoprotein cholesterol.

an NNT of 25. Extending this observation to 5 years, as is typically done for lipid-lowering therapy, translates to a NNT of ≈13. Findings were consistent in patients with PAD and no prior MI or stroke where an ARR of 6.3% translated to a NNT of 16 at 2.5 years or 8 at 5 years. In contrast to antithrombotic therapies, this benefit comes with no safety trade-off in terms of bleeding or other adverse events. These considerations may be important to clinicians in personalizing intensive therapies to their patients.

Limitations

There are several limitations to the current analysis. First, subgroup analyses are generally used to evaluate for consistency of findings with the overall trial and therefore may be underpowered for efficacy and safety outcomes. In the current analysis, the PAD subgroup was adequately powered to demonstrate statistically significant benefits for the primary end point and key secondary. Consistent with the overall trial, there was no significant reduction in CV death with evolocumab at 2.5 years, a benefit that generally has emerged only with longer follow-up in lipid-lowering trials.[26,36–38] The power to detect differences in rare safety events may have been limited by the size of the

PAD subgroup; however, the pattern of safety was consistent with the overall trial. Limb outcomes were collected on broad electronic case report form pages for peripheral outcomes and not focused specifically on ALI. This may have resulted in underascertainment of ALI outcomes but would not bias treatment effects. Finally, relationships between achieved LDL-C and outcome were not randomized and, although adjusted for confounders, the potential for residual confounding remains and should be recognized.

Conclusions

Patients with symptomatic lower extremity PAD are at heightened risk of major adverse cardiovascular and limb events. Evolocumab added to statin therapy significantly and robustly reduces the risk of MACE, even in patients with PAD and no prior MI or stroke. Likewise, the addition of evolocumab to a statin reduced the risk of MALE, and the relationship between achieved LDL-C and lower risk of limb events extended down to very low achieved levels of LDL. These benefits come with no offsetting safety concerns. Thus, LDL-C reduction to very low levels should be considered in patients with PAD, regardless of a history of MI or stroke, to reduce the risk of MACE and MALE.

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FOOTNOTES

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