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)

Bonaca, M.P.; Nault, P.; Giugliano, R.P.; Keech, A.C.; Pineda, A.L.; Kanevsky, E.; ... ; Sabatine, M.S.

LDL Cholesterol Lowering with Evolocumab and Outcomes in Patients with Peripheral Artery Disease: Insights from the FOURIER Trial

Short Title: LDL Lowering in Patients with PAD

Marc P. Bonaca, M.D., M.P.H.[1], Patrice Nault, M.D.[2], Robert P. Giugliano, M.D.[1], Anthony C. Keech, M.D.[3], Armando Lira Pineda, M.D.[4], Estella Kanevsky, B.S.[1], Julia Kuder, M.A.[1], Sabina A. Murphy, M.P.H.[1], J. Wouter Jukema, M.D., Ph.D.[5], Basil S. Lewis, M.D.[6], Lale Tokgozoglu, M.D.[7], Ransi Somaratne, M.D.[8], Peter S. Sever, Ph.D.[9], Terje R. Pedersen, M.D.[10], Marc S. Sabatine, M.D., M.P.H.[1]

[1]TIMI Study Group, Brigham and Women's Hospital Heart & Vascular Center, Boston, MA USA
[2]McGill University, Montreal, Quebec, Canada, Division of Vascular and Endovascular Surgery, CISSSO, Gatineau, Quebec, Canada
[3]Sydney Medical School, NHMRC Clinical Trials Centre, University of Sydney, Sydney, NSW, Australia
[4]Amgen, Thousand Oaks, CA, USA
[5]Dept of Cardiology, Leiden University Medical Center, Leiden, the Netherlands.
[6]Lady Davis Carmel Medical Center and the Ruth and Bruce Rappaport School of Medicine, Technion-IIT, Haifa, Israel
[7]Professor of Cardiology, Hacettepe University,Ankara Turkey
[8]International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, [9]London, UK
[10]Oslo University Hospital, Ullevål and Medical Faculty, University of Oslo, Oslo, Norway

Corresponding author:
Marc P. Bonaca, MD
TIMI Study Group, Cardiovascular Division
Brigham and Women's Hospital
75 Francis Street
Boston, MA 02115
Phone: 617-278-0071; Fax: 617-734-7329
Email: mbonaca@partners.org

ABSTRACT

Background: The PCSK9 inhibitor evolocumab reduced LDL cholesterol and cardiovascular events in the FOURIER trial. 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 endpoint was a composite of cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina, or coronary revascularization. The key secondary endpoint was a composite of cardiovascular death, myocardial infarction, or stroke. An additional outcome of interest was major adverse limb events (MALE) defined as acute limb ischemia (ALI), major amputation or urgent peripheral revascularization for ischemia.

Results: 3,642 patients (13.2%) had PAD (1505 with no prior MI or stroke). Evolocumab significantly reduced the primary endpoint consistently in patients with and without PAD PAD HR 0.79, 95%CI 0·66–0·94; p=0·0098; no PAD HR 0·86, 95% CI0·80–0·93; p=0·0003, $p_{\text{-interaction}}$=0·40). For the key secondary endpoint, 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 ($p_{\text{interaction}}$=0·41). Due to their higher risk, patients with PAD had larger absolute risk reductions for the primary endpoint (3.5% PAD, 1.6% no PAD) and the key secondary endpoint (3.5% PAD, 1.4% no PAD). Evolocumab reduced the risk of MALE 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 LDL-C and lower risk of limb events (P=0.0049) 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 LDL-C with evolocumab reduced the risk of major adverse limb events.

Clinical Trial Registration: http://www.clinicaltrials.gov NCT01764633

Key Words: Peripheral artery disease, PAD, atherosclerosis, LDL-C, MALE, major adverse limb events, amputation, acute limb ischemia, evolocumab, PCSK9 inhibition

Clinical Perspective

What is new?

- Lowering LDL-C 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 (MACE).
- Evolocumab significantly reduced major adverse limb (MALE) with consistent relative reductions in patients with and without PAD.
- These benefits come with no offsetting side effects.
- When looking at the composite of MACE/MALE in patients with symptomatic lower extremity PAD and no prior MI or stroke, evolocumab resulted in an absolute risk reduction at 2.5 years of 6.3% and an NNT of 16.

What are the clinical implications?

- There are few therapies that have been proven to reduce MACE risk in patients with lower extremity peripheral artery disease, particularly those without concomitant MI or stroke, and even fewer that reduce MALE.
- Lowering of LDL-C to very low levels reduces MACE and MALE, with benefits of low LDL-C extending to very low levels (< 10 mg/dL) and with no offsetting safety concerns.
- These data support that LDL-C lowering to very low targets should be a core focus of preventive therapy in patients with symptomatic lower extremity PAD including those without concomitant coronary or cerebrovascular disease.

Abbreviations

ABI – ankle brachial index
AKA – above the knee amputation
ALI – acute limb ischemia
ARR – absolute risk reduction
BKA – below the knee amputation
BMI – body mass index
CABG – coronary artery bypass grafting surgery
HR – hazard ratio
IQR – intraquartile range
KM – Kaplan Meier
LDL-C – low-density lipoprotein cholesterol
MACE – major adverse cardiovascular events
MALE – major adverse limb events
MI – myocardial infarction
NNT – number needed to treat
PAD – peripheral artery disease
PCSK9 – proprotein convertase subtilisin/kexin type 9
PCI – percutaneous coronary intervention
TIA – transient ischemic attack

Introduction

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 and importantly, patients with PAD suffer 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 LDL 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] Lastly, as PAD has often been used simply as a risk enhancer, little is known about the effect of LDL-C lowering in PAD patients without prior MI or stroke. [8,9,14,15]

FOURIER was a very large cardiovascular outcomes trial of the PCSK9 inhibitor evolocumab and 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 myocardial infarction, prior ischemic stroke, or symptomatic peripheral artery disease were randomized in a 1:1 ratio to evolocumab or placebo. Patients were eligible to qualify with symptomatic peripheral artery disease if they had either: intermittent claudication and an ankle brachial index (ABI) < 0.85, a history of a peripheral artery revascularization procedure, or a history of amputation due 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.

Endpoints

The primary efficacy endpoint 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 endpoint was the composite of CV death, MI or stroke. Other secondary endpoints included the components of the primary

endpoint. Cardiovascular events were adjudicated by a blinded clinical event committee (CEC). 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 two blinded vascular medicine specialists (Cohen's Kappa 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, AKA or below the knee BKA, excluding forefoot or toe), or urgent revascularization (thrombolysis or urgent vascular intervention for ischemia). [3,8,14,15,17] Acute limb ischemia (ALI) required both a clinical presentation consistent with acute ischemia (symptoms consistent with a rapid or sudden decrease in limb perfusion lasting less than 2 weeks) including findings on physical examination and/or imaging." [17] Acute limb ischemia and urgent revascularization for ischemia were identified by trained vascular medicine specialists blinded to treatment assignment. [3]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 endpoint of MACE and MALE was examined. [14,18] Prespecified safety endpoints 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 as described above. Baseline characteristics of the subgroups were compared using Wilcoxon rank sum tests for continuous data and $\chi 2$ 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 one dose of study treatment and for whom post-dose 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% 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, BMI, hypertension, diabetes, smoking status, renal dysfunction, CHF, prior MI, CABG or PCI and prior stroke or TIA. Proportional hazards assumptions were not violated. A repeated measures linear mixed effects model was used to obtain the least square means percentage and absolute reduction in LDL-C between the two treatment groups. For analyses evaluating the relationship of achieved LDL-C at one month and outcomes, we plotted the relationship between composite efficacy endpoints and achieved LDL cholesterol using a smoothing function applied to the averages of estimated event rates at each LDL level based on the unadjusted Cox models, as has been done previously applying the same exclusion criteria.[20] P values below 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 FDA for review and validation

RESULTS

Populations

Of the 27,564 patients randomized, 3,642 (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 ABI <0.85 and symptoms of claudication (with some patients having more than one of these factors). Patients with PAD were older, more frequently female, and had a greater prevalence of risk factors including hypertension, current smoking, renal insufficiency and diabetes (Table 1). At baseline 89% of patients were taking antiplatelet therapy, 69% high-intensity statin therapy, 30% moderate-intensity statin therapy, and 6.6% were taking ezetimibe. Of the PAD subgroup, 1,812 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.

Peripheral Artery Disease and Risk in Patients Randomized to Placebo

Among patients in the placebo arm, patients with PAD as compared with patients without PAD had higher rates of both the primary endpoint (Kaplan-Meier rate at 2.5 years: 16.8% vs 12.1%, P<0.001) and the key secondary endpoint (13.0% vs 7.6%, P<0.001) (Supplemental Table 1, Supplemental Figure 1). After adjusting for baseline differences,

patients with PAD remained at significantly higher risk of the primary endpoint (Adj. HR 1.57, 95% CI 1.36 – 1.80, p<0.001) and the key secondary endpoint (Adj. HR 1.81, 95% CI 1.53 – 2.14, p<0.001, Supplemental Table 1, Supplemental Figure 1).

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 compared to those without (14.9% vs. 10.3%, p=0.0028, Supplemental Figure 2). Patient 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% vs 7.6%, Adjusted HR 2.07, 95% CI 1.42 – 3.01, p=0.0001, Supplemental Figure 2). When evaluating the individual components, CV death appeared especially higher (4.4% vs. 1.9%, p<0.001) 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 (Supplemental Figure 3a).

As expected, patients with symptomatic PAD had higher rates of limb outcomes relative to those without PAD including MALE (2.4% vs 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% vs. 0.1%, adjusted HR 7.88, 95% CI 3.67 – 16.92, p<0.001, Supplemental Table 1). Findings were consistent in the subgroup with PAD and no MI or stroke vs patients with no PAD (Supplemental Figure 3b).

LDL-Cholesterol Lowering with Evolocumab

The median LDL-C level at baseline among the symptomatic PAD group was 94 mg/dL (IQR 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 to 61, p<0.001) or a mean absolute reduction of 57 mg/dL (95% CI 55 to 60), resulting in a median LDL-C of 31.0 mg/dL (IQR 19.0 – 49.0, Supplemental Figure 4). The reduction in LDL cholesterol levels was maintained over time (Supplemental Figure 4).

Cardiovascular Efficacy with Evolocumab

In patients with PAD, evolocumab significantly reduced the primary endpoint by 21% (2.5-year KM rate 13.3% vs. 16.8%, HR 0.79, 95% CI 0.66 – 0.94, p=0.0089, Table 2, Figure 2a) and the composite of CV death, MI or stroke by 27% (9.5% vs. 13.0%, HR 0.73, 95% CI 0.59 – 0.91, p=0.0040, Table 2, Figure 2b). The relative risk reductions for both endpoints were consistent in patients with and without PAD (p-interaction 0.40 and 0.41 respectively). However, due to higher absolute risk in patients with PAD, the absolute risk reductions for both endpoints were greater in those with PAD vs. those without [absolute risk reduction (ARR) for primary endpoint 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 absolute risk reductions 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 endpoint and a 4.8% ARR (95% CI 1.2% - 8.4%) in the composite of CV death, MI or stroke translating in $NNT_{2.5y}$ of 21 for each (Table 2, Supplemental Figures 5a and 5b).

Major Adverse Limb Event Reduction with Evolocumab

Overall evolocumab reduced the risk of MALE by 42% (0.26% vs. 0.45%, HR 0.58, 95% CI 0.38 – 0.88, p=0.0093, ARR 0.19%, 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 restricting 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 absolute risk reductions were greater in those with PAD (1.5% vs. 2.4%, ARR 0.9%) than in those without (0.076% vs. 0.16%, ARR 0.08%). In the 1,505 patients with PAD and no prior MI or Stroke, reductions in MALE were consistent (1.3% vs. 2.6%, HR 0.43, 95% CI 0.19 – 0.99, ARR 1.3%, Table 3, Supplemental Figure 5c).

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% vs. 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% vs. 15.0%, ARR 4.1%, NNT 25,) and those without PAD (HR 0.80, 95% CI 0.72 – 0.89, 6.3% vs. 7.8%, ARR 1.5%, NNT 67) (p-interaction 0.39, Figure 4). In the 1,505 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% vs. 12.8%, ARR 6.3%, NNT 16, Table 3, Supplemental Figure 6).

Safety of Evolocumab in Patients with PAD

There were no differences in incidence adverse or serious adverse events with evolocumab relative to placebo in patients with PAD (Supplemental Table 2). There was no excess of adverse events leading to treatment discontinuation (1.3% evolocumab vs 1.5% placebo, p=0.57).

Association of achieved LDL-Cholesterol and risk of MALE and MACE

Overall lower achieved LDL-C was associated with a significantly lower risk of MALE with a roughly linear relationship down to LDL-C of 10 mg/dL (p=0.0049 for slope) with consistent patterns in patients with PAD and those with PAD and no prior MI or stroke (Figure 5, Supplemental Figure 7). 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 (Supplemental Figure 8) and patients with PAD and no prior MI or stroke (Supplemental Figure 9).

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 PAD patients translated into greater absolute risk reductions. Furthermore, LDL-C lowering with evolocumab reduced the risk of MALE including ALI and major amputation. Thus when considering both MACE and MALE, the absolute risk reduction with LDL-C lowering in patients with PAD was quite robust, with an NNT over 2.5 years of only 25. Lastly, 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 as compared to those without has been recognized.[21,22] This observation, however, is complex as there is heterogeneity in risk within the broad population of patients with PAD. Those patients with multiple symptomatic territories (e.g. 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 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 with no offsetting side effects such as bleeding with anti-thrombotic therapy.[3,8,14,25]

In the current study, we have shown two symptomatic PAD populations, a broad population including those with polyvascular disease as well as a restricted population with symptomatic lower extremity PAD that has never experienced an acute atherothrombotic event (MI or stroke). In the current study the benefits of intensive lipid lowering with evolocumab were consistent in both populations. These findings therefore highlight a distinct population characterized by symptomatic PAD only where lipid lowering provides robust benefits 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 randomized 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 6,748 patients with PAD. [26] Over 5 years of follow up, simvastatin reduced major vascular events relative to placebo with consistent relative risk reductions in those with and without PAD. [27] An exploratory outcome of non-coronary vascular intervention (including carotid intervention) was also lower with simvastatin. [27] There was no difference in the risk of amputation with simvastatin vs. placebo. Observational analyses have reported associations between statin intensity and reductions in MACE in patients with stable PAD or those presenting with CLI. [28-30] Beyond these observations, there are no well-powered randomized studies showing that achieving lower LDL-C or that the use of a non-statin 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 non-statin 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 non-coronary revascularization procedures; however, this was not specific to etiology and included procedures beyond the lower extremities such as carotid revascularization. [27] Major adverse limb events were not 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 treatment with fenofibrate versus placebo in people with type 2 diabetes in, 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, potential for residual confounding has remained and intensity of statin therapy or achieved LDL-C was not reported. [6,33,34] Smaller observational studies in patients with CLI 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 CLI. [29,35,36]

The current study demonstrates that non-statin 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 heightened risk of PAD in patients with coronary or cerebrovascular disease as well as under-diagnosis 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 endpoints in three randomized trials of more intensive antithrombotic therapy and endpoints that have been adopted as elements of primary or key secondary endpoints 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 other such as vorapaxar. [8] Possible explanations for the lack of benefit for this broad endpoint include that lipid lowering does not improve symptoms or alternatively, 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 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 NCT02504216) have utilized a composite endpoint including both cardiovascular and limb outcomes. [14] This composite provides a global picture of benefit against which harms 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 absolute risk reduction at 2.5 years of 4.1% and an NNT of 25. Extending this observation to 5 years, as is typically done for lipid lowering therapy, translates to a NNT approximately 13. Findings were consistent in patients with PAD and no prior MI or stroke where an absolute risk reduction of 6.3% translated to an NNT of 16 at 2.5 years or 8 at 5 years. In contrast to anti-thrombotic therapies, this benefit comes with no safety tradeoff 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 utilized 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 endpoint 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. [26,37-39] 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 eCRF pages for peripheral outcomes and not focused specifically on ALI. This may have resulted in under ascertainment of ALI outcomes but would not bias treatment effects. Finally, relationships between achieved LDL-C and outcome were not randomized and while 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 risks. 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 major adverse limb events, 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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Figure Legends

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 (MI) or stroke.

Figure 2 – Primary and Key Secondary Endpoints in Patients with and without Peripheral Artery Disease
Figure left (panel 2a), the primary composite endpoint 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**.** Figure right (panel 2b), the key secondary composite endpoint (cardiovascular death, myocardial infarction, stroke) by treatment (evolocumab in red, placebo in blue) in patients with (solid lines) and without (dashed lines) symptomatic PAD

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 randomized patients (panel 3a), in patients with symptomatic PAD (panel 3b) and in patients with no known PAD (panel 3c).

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

Figure 5 – The Relationship of Achieved LDL Cholesterol and Major Adverse Limb Events

Relationship between achieved LDL-C and major adverse limb events (MALE; acute limb ischemia, major amputation or urgent revascularization) in the overall population.

Table 1 Baseline Characteristics by presence of prior PAD

	No PAD N=23,922	PAD N=3,642
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)
Caucasian, n (%)	20156 (84.3)	3302 (90.7)
History Hypertension, n (%)	18993 (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, n (%)	8501 (35.5)	1580 (43.4)
History of Stroke/TIA, n (%)	5101 (21.3)	685 (18.8)
History of Myocardial Infarction, n (%)	20539 (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 (%)	14029 (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 & ABI < 0.85, n (%)	0	2518 (69.3)
Prior Peripheral Revascularization, n (%)	0	2067 (56.8)
Time from Peripheral Revascularization, years, 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 (%)	16579 (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 (%)	22216 (92.9)	3246 (89.3)
Anticoagulant therapy, n (%)	1805 (7.6)	391 (10.8)
ACE-I or ARB use at baseline, n (%)	18526 (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 (0.0%) without PAD and 3 (0.1%) with PAD

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

Efficacy Outcomes	**Symptomatic PAD**				**Symptomatic PAD without prior MI or Stroke**			
Outcome,	**Placebo N=1,784 2.5 yr KM rate (%)**	**Evolocumab N=1,858 2.5 yr KM rate (%)**	**Hazard Ratio (95% CI)**	**p-value**	**Placebo N=748 2.5 yr KM rate (%)**	**Evolocumab N=757 2.5 yr KM rate (%)**	**Hazard Ratio (95% CI)**	**p-value**
Primary Endpoint	**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)	

Table 3. Major Adverse Limb Outcomes with Evolocumab vs Placebo in the Overall Population

Efficacy Outcomes	**Overall Population**			**Patients with PAD**			**Patients with PAD and no MI or Stroke**		
Outcome **n, 2.5yr KM rate (%)**	**Placebo N=13,780**	**Evolocumab N=13,784**	**Hazard Ratio (95% CI)**	**Placebo N=1,784**	**Evolocumab N=1,858**	**Hazard Ratio (95% CI)**	**Placebo N=748**	**Evolocumab N=757**	**Hazard Ratio (95% CI)**
Limb Outcomes									
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)	0.58%	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	2.37%	2.59%	1.08 (0.92 – 1.27) P=0.33	12.4%	13.2%	1.01 (0.84 – 1.23) P=0.88	12.1%	14.9%	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**

MALE – composite of acute limb ischemia (ALI), major amputation (AKA or BKA), or urgent peripheral revascularization for ischemia

MI=myocardial infarction, AKA=above knee amputation, BKA=below knee amputation, ALI=acute limb ischemia