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FASTTRACK CLINICAL RESEARCH
Dyslipidaemias

Effect of evolocumab on acute arterial events across all vascular territories : results from the FOURIER trial

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Aims We assessed the impact of the proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitor evolocumab on acute arterial events across all vascular territories, including coronary, cerebrovascular, and peripheral vascular beds, in patients with established atherosclerotic cardiovascular disease (ASCVD).

Methods and results In the FOURIER trial, 27 564 patients with stable ASCVD on statin therapy were randomly assigned to evolocumab or placebo. Acute arterial events were a composite of acute coronary (coronary heart disease death, myocardial infarction, or urgent coronary revascularization), cerebrovascular (ischaemic stroke, transient ischaemic attack, or urgent cerebral revascularization), or peripheral vascular (acute limb ischaemia, major amputation, or urgent peripheral revascularization) events. Of the 2210 first acute arterial events, 74% were coronary, 22% were cerebrovascular, and 4% were peripheral vascular. Evolocumab reduced first acute arterial events by 19% (hazard ratio [HR] 0.81 [95% confidence interval 0.74–0.88]; $P < 0.001$), with significant individual reductions in acute coronary (HR 0.83 [0.75–0.91]), cerebrovascular (HR 0.77 [0.65–0.92]), and peripheral vascular (HR 0.58 [0.38–0.88]) events. There were 3437 total events (first plus recurrent), with evolocumab reducing total events by 24% (incidence rate ratio 0.76 [0.69–0.85]). The magnitude of reduction in acute arterial events with evolocumab numerically increased over time, with a 16% reduction (HR 0.84 [0.75–0.95]) in the first year followed by a 24% reduction (HR 0.76 [0.67–0.85]) thereafter.

Conclusion The addition of the PCSK9 inhibitor evolocumab to statin therapy reduced acute arterial events across all vascular territories with a robust effect over time, indicating a pan-vascular impact of aggressive lipid-lowering therapy on these acute and clinically meaningful events.

Clinical Trial Registration URL: https://www.clinicaltrials.gov. Unique identifier: NCT01764633.

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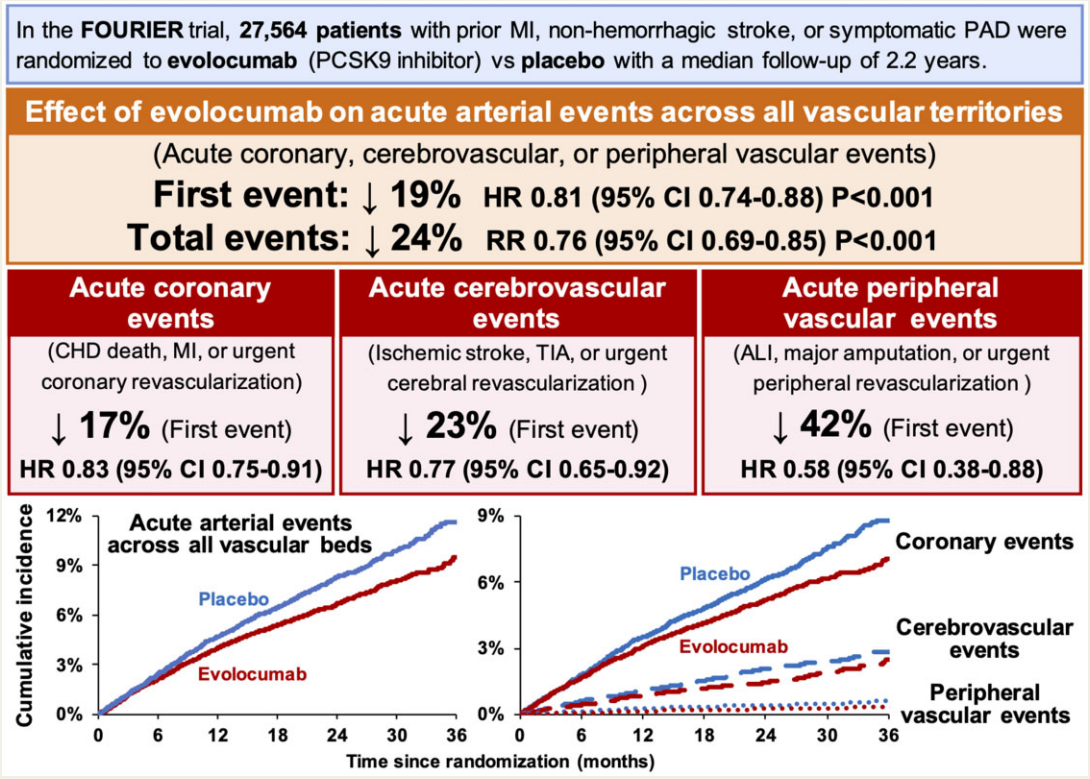
Graphical Abstract



Effect of evolocumab on acute arterial events across all vascular territories. ALI, acute limb ischaemia; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; PAD, peripheral artery disease; PCSK9, proprotein convertase subtilisin-kexin type 9; RR, incidence rate ratio; TIA, transient ischaemic attack.

Keywords PCSK9 inhibitor • LDL-C • Cerebrovascular events • Coronary events • Peripheral vascular events

Introduction

Cardiovascular disease remains the leading cause of death worldwide, with the greatest burden attributable to arterial atherosclerosis.[1] Acute arterial vascular events in the coronary, cerebrovascular, and peripheral beds are oftentimes critical or disabling and represent the most feared manifestations of atherosclerosis.[2–5] While these acute events across vascular territories share related underlying pathobiologies, the total burden of acute arterial events has rarely been described in an at-risk cohort.[6] Nor has the aggregate impact of lipid-lowering therapy on pan-vascular acute events been well-described.[7,8]

The FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial compared the proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitor evolocumab vs. placebo in patients with stable atherosclerotic cardiovascular disease (ASCVD) on optimized statin therapy.[9,10] Evolocumab reduced major adverse cardiovascular events in these patients, with favourable effects on coronary, cerebrovascular, and peripheral vascular events when examined separately.[10–12] However, the effect of evolocumab on the aggregate of acute events across vascular territories has not been explored. The objectives of this analysis were to describe the relative burden of acute arterial events across vascular territories and to investigate the comprehensive effect of aggressive lipid lowering with evolocumab on these events and in subgroups.

Methods

Study design and population

This is a *post hoc* analysis from the FOURIER trial undertaken after secondary analyses of events in individual vascular beds had been completed. FOURIER was a randomized, double-blind, placebo-controlled trial performed at 1242 sites in 49 countries.[9,10] The trial included 27 564 patients aged 40–85 years with prior myocardial infarction (MI), non-haemorrhagic stroke, or symptomatic peripheral artery disease (PAD), placing

them at increased cardiovascular risk. Patients were required to have a low-density lipoprotein cholesterol (LDL-C) level ≥70 mg/dL or non-high-density lipoprotein cholesterol (non-HDL-C) level ≥100 mg/dL while on a high- or moderate-intensity statin (defined as equivalent to a dose of atorvastatin ≥20 mg daily) with or without ezetimibe. Key exclusion criteria were recent MI or stroke within 4 weeks, planned or expected cardiac surgery or revascularization within 3 months after randomization, previous haemorrhagic stroke, estimated glomerular filtration rate (eGFR) <20 mL/min/1.73 m^2, New York Heart Association class III or IV heart failure, or left ventricular ejection fraction <30%. Patients were randomly assigned to receive either subcutaneous evolocumab (either 140 mg every 2 weeks or 420 mg once per month, per patient preference) or matching placebo and were followed for a median of 2.2 years (interquartile range 1.8–2.5 years).[10] All patients provided written informed consent, and the study protocol was approved by relevant ethics committees.

Outcomes

Acute arterial events were defined as a composite of coronary [coronary heart disease (CHD) death, MI, or urgent coronary revascularization], cerebrovascular [ischaemic stroke, transient ischaemic attack (TIA), or urgent cerebral revascularization], or peripheral vascular [acute limb ischaemia (ALI), major amputation, or urgent peripheral revascularization] events. Cardiovascular events were adjudicated by a central Clinical Events Committee. Acute cerebrovascular revascularization procedures were defined as those occurring within 30 days of a stroke or TIA. Limb outcomes were prospectively ascertained through investigator reporting on dedicated electronic case report form pages and through adverse event forms as previously described.[11] ALI required both a clinical presentation consistent with acute ischaemia (symptoms consistent with a rapid or sudden decrease in limb perfusion lasting <2 weeks) including findings on physical examination or imaging.

Statistical analysis

Baseline data were reported as *n* (%), mean ± standard deviation, or medians and interquartile range according to the distribution. In the analyses of acute arterial event rates by the type of vascular disease at baseline in the placebo arm, patients were categorized based on their prior MI, prior stroke, symptomatic PAD, or arterial disease in more than one vascular territory at baseline. Kaplan–Meier event rates were calculated through 3 years and compared with log-rank tests. Associations of types of ASCVD at baseline with event rates were analysed using univariate Cox proportional hazards models. All efficacy analyses of evolocumab vs. placebo were conducted on an intention-to-treat basis. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the effect of evolocumab vs. placebo were generated using a Cox proportional hazards model which included the randomization stratification variables (LDL-C level and region).[13,14] The first acute arterial event in any vascular territory was analysed in the time-to-first event analysis. For territory-specific analyses (e.g. acute coronary events), the first event in that particular vascular territory was included in the time-to-first event analyses. The effect of evolocumab across subgroups was tested by incorporating interaction terms into the Cox models. Schoenfeld residuals were assessed in the Cox models and the proportional hazards assumptions were not violated.

Landmark analyses were performed for the evolocumab vs placebo comparison at 0–12 and >12 months. Negative binomial regression models were performed to compare the total number of events between patients in the evolocumab and placebo groups as previously described.[15] In sensitivity analyses for total acute arterial events, urgent coronary revascularizations within 3 days of MI, urgent cerebral revascularizations within 3 days of stroke or TIA, and urgent peripheral revascularizations or major amputations within 3 days of ALI were excluded. All analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC, USA). *P*-values <0.05 were considered statistically significant with no adjustment for multiple comparisons.

Results

Analysis population

Of 27 564 patients in the FOURIER trial, 2210 experienced an acute arterial event during a median follow-up of 2.2 years: 1596 experienced acute coronary events only, 451 experienced acute cerebrovascular events only, 79 experienced acute peripheral vascular events only, and 84 experienced acute arterial events in two or more vascular territories. Baseline characteristics of subjects experiencing acute arterial events during the trial are shown by arterial bed in *Table 1*. Patients with acute arterial events during the trial tended to have higher rates of cardiovascular risk factors such as diabetes, hypertension, and chronic kidney disease than did patients experiencing no acute arterial events.

Arterial event rates by the type of vascular disease at baseline in the placebo arm

Patients with polyvascular disease ($n = 1766$) had the highest rate of acute arterial events during follow-up (18.7%), followed by patients with symptomatic PAD ($n = 748$; 13.2%), prior stroke (n=1671; 10.6%), and prior MI (n=9588; 10.3%) (*Figure 1* and Supplementary material online, *Table S1*). The rates of acute arterial events in a specific bed were highest in those enrolled with a known history of disease in that bed (*Figure 1* and Supplementary material online, *Table S1*).

Effect of evolocumab on first acute arterial events across all vascular territories

Evolocumab reduced the risk of a first acute arterial event by 19% (HR 0.81; 95% CI 0.74–0.88; $P < 0.001$), with significant individual reductions in acute coronary (HR 0.83; 95% CI 0.75–0.91; $P < 0.001$), acute cerebrovascular (HR 0.77; 95% CI 0.65–0.92; $P = 0.004$), and acute peripheral vascular (HR 0.58; 0.38–0.88; $P = 0.01$) events (*Figure 2* and *Graphical abstract*). The effect of evolocumab on each component of these composite endpoints is shown inSupplementary material online, *Table S2*.

The benefits of evolocumab were consistent across major subgroups, including those based on age, sex, type of baseline atherosclerotic vascular disease, baseline LDL-C value of ≥70 or <70 mg/dL, and high-intensity statin use at baseline (*Figure 3*). The magnitude of the risk reduction in first acute arterial events with evolocumab numerically increased over time, with a 16% reduction (HR 0.84; 95% CI 0.75–0.95; $P = 0.004$) in the first year followed by a 24% reduction (HR 0.76; 95% CI 0.67–0.85; $P < 0.001$) thereafter (*Figure 4*). The landmark analyses for individual arterial beds are shown in Supplementary material online, *Figure S1*.

Table 1 **Baseline characteristics of patients with vs without acute arterial events during follow-up**

	No acute arterial events (*n* = 25 354)	Acute arterial events (*n* = 2210)	Coronary events alone (*n* = 1596)	Cerebrovascular events alone (*n* = 451)	Peripheral vascular events alone (*n* = 79)	Polyvascular events (*n* = 84)
Age, years, mean ± SD	62.5 ± 9.0	63.0 ± 9.3	62.5 ± 9.3	64.6 ± 9.1	63.4 ± 9.3	64.4 ± 9.2
Female sex, *n* (%)	6257 (25)	512 (23)	349 (22)	121 (27)	23 (29)	19 (23)
White race, *n* (%)	21 549 (85)	1909 (86)	1389 (87)	376 (83)	71 (90)	73 (87)
BMI, kg/m^2, mean ± SD	29.4 ± 5.1	29.8 ± 5.6	29.9 ± 5.7	29.5 ± 5.4	28.7 ± 5.1	29.6 ± 5.6
Hypertension, *n* (%)	20 228 (80)	1856 (84)	1333 (84)	382 (85)	67 (85)	74 (88)
Diabetes mellitus, *n* (%)	9098 (36)	983 (45)	693 (43)	212 (47)	29 (37)	49 (58)
Current cigarette use, *n* (%)	7171 (28)	606 (27)	431 (27)	124 (28)	32 (41)	19 (23)
Type of vascular disease, *n* (%)						
Prior MI alone	17 728 (70)	1385 (63)	1132 (71)	192 (43)	20 (25)	41 (49)
Prior ischaemic stroke alone	3159 (12)	207 (9.4)	74 (4.6)	122 (27)	2 (2.5)	9 (11)
Symptomatic PAD alone	1385 (5.5)	120 (5.4)	66 (4.1)	23 (5.1)	24 (30)	7 (8.3)
Polyvascular disease	3066 (12)	497 (23)	324 (20)	113 (25)	33 (42)	27 (32)
History of coronary revascularization, *n* (%)	16 602 (65)	1591 (72)	1229 (77)	249 (55)	52 (66)	61 (73)
Heart failure, *n* (%)	5783 (23)	611 (28)	454 (28)	121 (27)	13 (17)	23 (27)
eGFR, mL/min/1.73 m^2, median (IQR)	76 (64–88)	72 (60–86)	73 (61–86)	72 (60–84)	70 (58–82)	65 (55–79)
Lipids, mg/dL, median (IQR)						
LDL-C	92 (80–108)	94 (82–112)	95 (82–112)	93 (79–110)	94 (83–115)	94 (85–108)
Total cholesterol	167 (151–188)	169 (152–192)	169 (152–191)	169 (151–194)	174 (161–201)	172 (155–191)
HDL-C	44 (37–53)	43 (36–51)	43 (36–51)	44 (37–53)	49 (40–55)	43 (37–51)
Non-HDL-C	121 (106–141)	124 (108–146)	125 (109–145)	123 (106–146)	121 (108–151)	124 (113–147)
Triglycerides	133 (100–182)	136 (102–184)	136 (103–183)	135 (98–189)	134 (97–200)	140 (113–172)
High-intensity statin use, *n* (%)	17 520 (69)	1583 (72)	1172 (73)	301 (67)	54 (68)	56 (67)

BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral artery disease; SD, standard deviation.

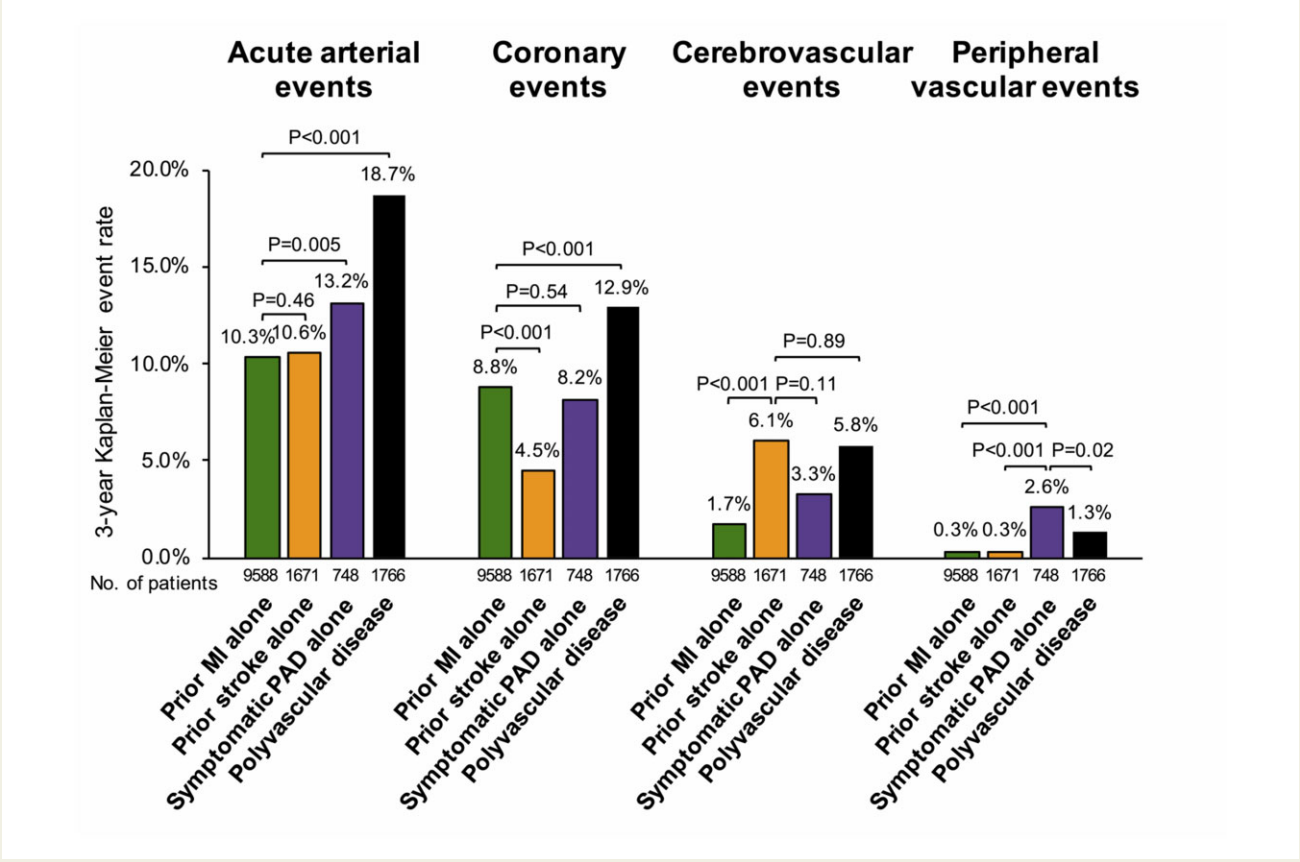


Figure 1 Risk of first acute arterial events in the placebo arm by type of arterial disease at baseline. Patients in the placebo arm were categorized by the type of pre-existing arterial disease at baseline. Rates of incident acute coronary, cerebrovascular, and peripheral arterial events are shown. *P*-values for all comparisons are provided in Supplementary material online, *Table S1*. MI, myocardial infarction; PAD, peripheral artery disease.

Effect of evolocumab on total acute arterial events

There were 2210 first and 3437 total acute arterial events during the trial. Evolocumab reduced total acute arterial events by 24% [incidence rate ratio (RR) 0.76; 95% CI 0.69–0.85; $P < 0.001$] including first events by 19% (HR 0.81; 95% CI 0.74–0.88; $P < 0.001$) and subsequent events by 35% (RR 0.65; 95% CI 0.58–0.73; $P < 0.001$; *Figure 5*). In sensitivity analyses, 534 urgent revascularizations within 3 days of major ischaemic events were excluded; the effect of evolocumab on total acute arterial events remained similar (RR 0.80; 95% CI 0.72–0.88; $P < 0.001$). The effects of evolocumab on first, recurrent, and total arterial events in each vascular territory are shown in Supplementary material online, *Table S3*.

Discussion

In this analysis from the FOURIER trial, we found that evolocumab reduced the risk of acute arterial events across all vascular territories with consistent benefits in key subgroups. Acute coronary events, including CHD death, MI, and urgent revascularization, were the most common event type in these high-risk patients with established ASCVD, followed by acute cerebrovascular and peripheral vascular events. There was a robust effect of evolocumab on total acute arterial events, with a 19% reduction in first events and a 35% reduction in subsequent events.

Despite a shared pathobiology of atherosclerotic vascular disease across arterial beds, aggregate acute arterial events are rarely described in at-risk cohorts.[6] Given the clinical importance of these oftentimes life-threatening and costly events and the established benefits in individual vascular territories of aggressive lipid-lowering therapy with PCSK9 inhibition,[10–12] we showed here a pan-vascular effect of evolocumab across multiple vascular territories.

The paucity of comparative prospective data on the incidence of acute arterial events across vascular territories in the general population inspired the Oxford Vascular Study, which reported rates of incident acute coronary, cerebrovascular, and peripheral vascular events in a large population of adults in the UK ($n = 91\,106$).[6] In this cohort, there were 2024 acute vascular events over 3 years, of which 45% were cerebrovascular, 42% were coronary, 9% were peripheral vascular, and 4% were unclassifiable. There was a strong relationship between subject age and event rates across vascular territories.

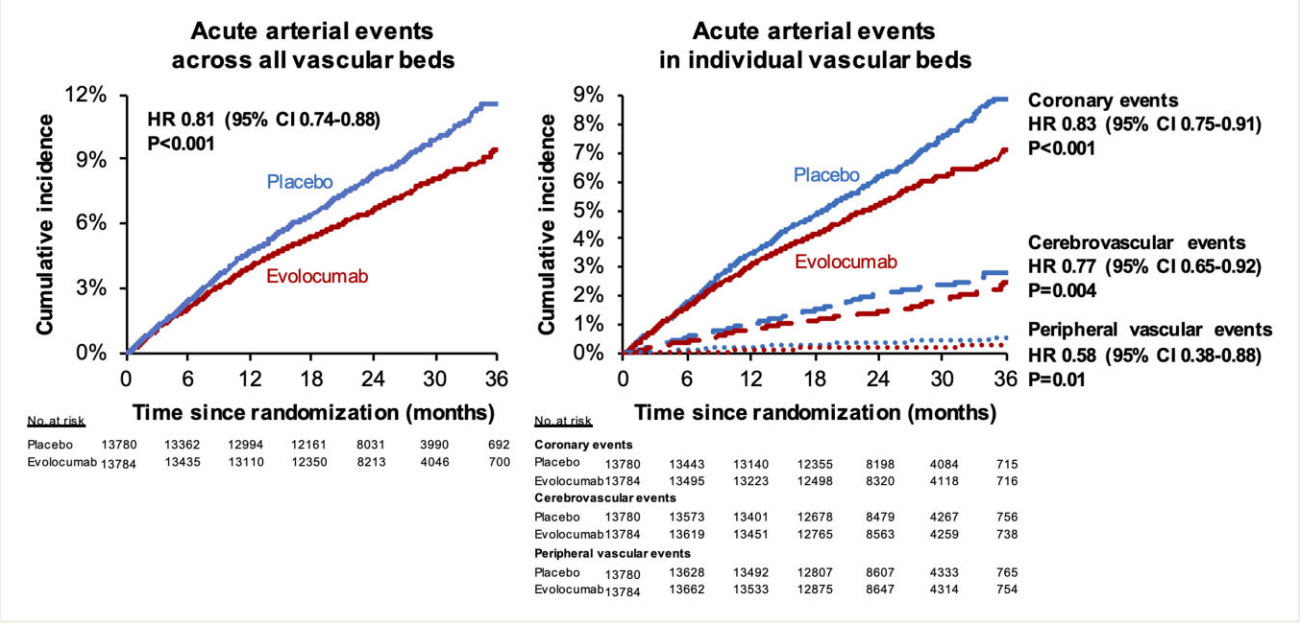


Figure 2 Effect of evolocumab on first acute arterial events. HR, hazard ratio; CI, confidence interval.

Whereas the Oxford Vascular Study enrolled a general population largely comprising primary prevention, the population studied here is exclusively a secondary prevention cohort with a large proportion having a history of MI. The comparison of event rates based on pre-existing vascular disease in this FOURIER population emphasizes the high pan-vascular risk of subjects with symptomatic PAD, as these patients had higher rates of any acute arterial event than those with prior MI or prior stroke. Further, patients with symptomatic PAD had similar rates of acute coronary events to those with prior MI as well as similar rates of acute cerebrovascular events to those with prior stroke.

Limited data examine the effect of lipid-lowering therapies on acute arterial events across territories. Prior reports from the trials with PCSK9 inhibitors, for example, generally focused on events in individual arterial beds. The FOURIER trial primarily investigated the effect of evolocumab on the composite outcome of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization in patients with stable ASCVD, and we have separately examined the effects of evolocumab on individual coronary, cerebrovascular, and major adverse limb events.[10–12,16] Similarly, effects of alirocumab have been reported separately for coronary, cerebrovascular, and peripheral vascular territories in secondary analyses from the ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial.[17–19]

By contrast, our current research indicates the comprehensive impact of evolocumab on acute arterial events across all territories. The totality of benefit of evolocumab both in terms of vascular bed and time course offers an important perspective on treatment strategies in high-risk patients, as prevention of acute arterial events has important ramifications for patients and health care systems. These events are oftentimes critical, impair quality of life and are costly to society.[20–22] Of particular note is the magnitude of evolocumab effect on total events across vascular territories, with a 35% reduction in recurrent events as compared to a 19% reduction in first events. This finding likely reflects the emergence over time of the full clinical benefit of aggressive lipid-lowering therapy, a phenomenon also observed with statins and ezetimibe.[23,24]

The clinical benefit of evolocumab in reducing acute peripheral vascular and cerebrovascular events appeared to manifest particularly early. This finding may be due to chance given the smaller number of events in these territories, though it is also possible that the early, robust treatment effect observed in these territories may in part reflect differences in clinical practice in patients at risk for peripheral vascular or cerebrovascular events compared to coronary events. Indeed, the rate of high-intensity statin use at baseline was lower in patients who experienced acute peripheral vascular or cerebrovascular events than in those who experienced acute coronary events.

These considerations aside, there was overall a consistent benefit of evolocumab across clinical subgroups, including baseline LDL-C level and statin intensity. Whereas the 2018 US society guidelines on the management of blood cholesterol recommend an LDL-C level threshold of ≥70 mg/dL for addition of further agents beyond maximally tolerated statin therapy in high-risk secondary prevention patients,[8] there was no heterogeneity observed here between baseline LDL-C concentration and the reduction in acute arterial events across all vascular territories, thereby illustrating that further LDL-C reduction could potentially be beneficial even in patients starting with LDL-C < 70 mg/dL. Furthermore, taken together with the total events analyses, our observations indicate that long-term and aggressive lipid lowering may have a robust pan-vascular impact on these events.

Study limitations

While this study benefits from a large, randomized sample with prospective event capture and central adjudication, there are important

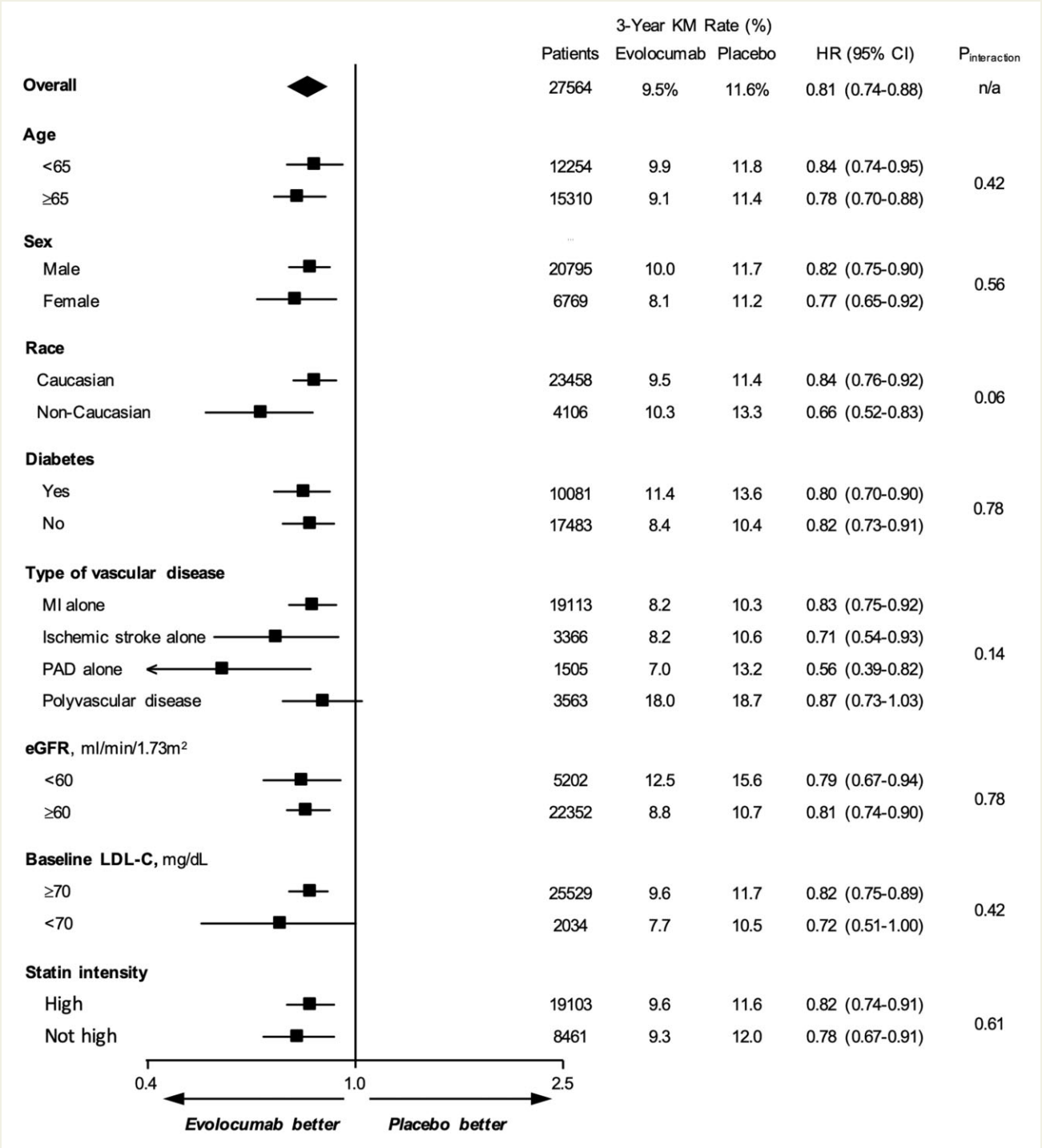


Figure 3 Effect of evolocumab on first acute arterial events in key subgroups. CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; KM, Kaplan–Meier; LDL-C, low-density lipoprotein cholesterol.

limitations. First, the FOURIER trial was powered based on all eligible patients for the primary composite endpoint rather than for the individual endpoints explored in this *post hoc* analysis. Second, urgent cerebral and peripheral revascularization and amputation procedures were reported by the investigator and not adjudicated. This may have resulted in underascertainment of these outcomes but would not be expected to bias the assessment of randomized treatment effects. Finally, the relatively short duration of follow-up (2.2 years) limited the ability to detect potential long-term effects of PCSK9 inhibition, including on mortality. However, according to the present findings, we may be able to expect the magnitude of the risk reduction in acute arterial events to increase over time.

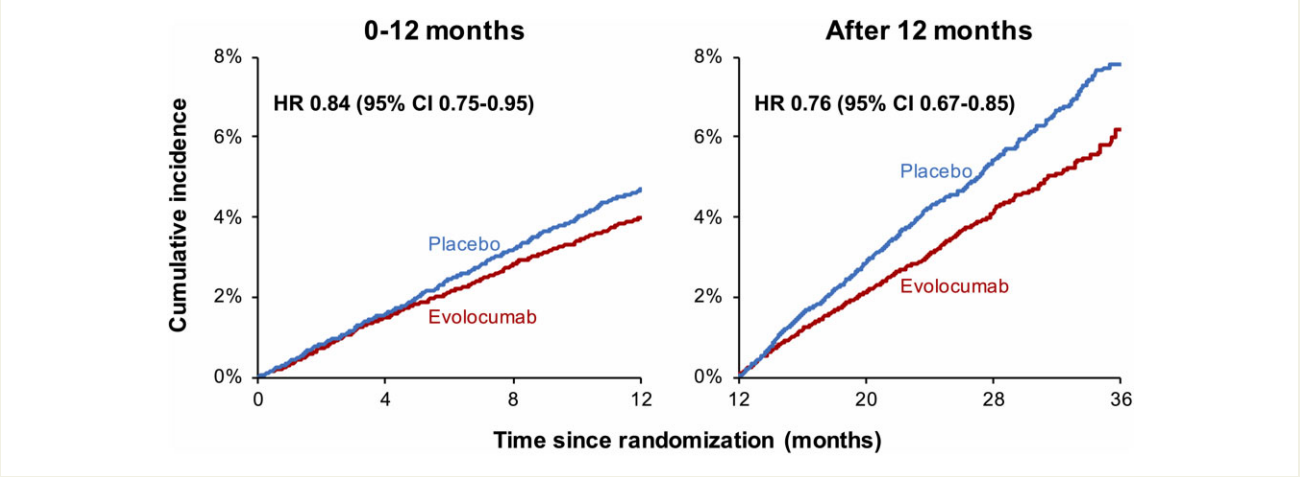


Figure 4 Landmark analyses for the effect of evolocumab on first acute arterial events. CI, confidence interval; HR, hazard ratio.

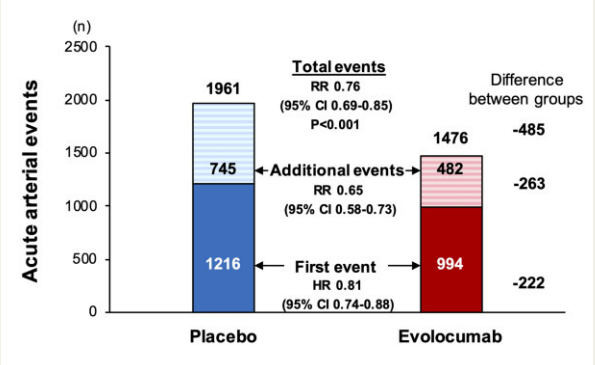


Figure 5 Effect of evolocumab on first, recurrent, and total acute arterial events. CI, confidence interval; HR, hazard ratio; RR, incidence rate ratio.

Conclusions

Adding the PCSK9 inhibitor evolocumab to statin therapy reduced the risk of acute arterial events across all vascular territories with a robust effect over time on both first and recurrent events and with consistent benefits in key subgroups. These findings indicate a pan-vascular impact of aggressive lipid-lowering therapy on these acute events, which are oftentimes critical, impair quality of life, and are costly to society.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc., Daiichi-Sankyo, Eisai, GlaxoSmithKline, Intarcia, Janssen, MedImmune, Merck, Novartis, Pfizer, Poxel, Quark Pharmaceuticals, Roche, Takeda, The Medicines Company, and Zora Biosciences.

Data availability

We encourage parties interested in collaboration and data sharing to contact the corresponding author directly for further discussions.

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