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STUDY REVIEW

Long-Term Evolocumab in Patients with Established Atherosclerotic Cardiovascular Disease: FOURIER OLE

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Independent commentary by Associate Professor John Amerena

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Publication overview

Monoclonal antibodies inhibiting proprotein convertase subtilisin/kexin type 9 (PCSK9) have emerged as a treatment option to robustly lower low-density lipoprotein cholesterol (LDL-C) and reduce the risk of major adverse cardiovascular events (MACE).[1, 2]

However, large-scale, very long-term follow-up data have been limited for PCSK9 inhibitors – studies of evolocumab and alirocumab have reported positive effects on MACE with median follow-ups of 2.2 and 2.8 years, respectively.[3]

The Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk (FOURIER) trial investigated the efficacy and safety of evolocumab added to moderate- or high-intensity statin therapy in patients with clinically evident atherosclerotic cardiovascular disease (ASCVD).[4, 5] Significant reductions in LDL-C and the risk of MACE were demonstrated in FOURIER with a median follow-up of 2.2 years.[4]

However, there are limited very long-term follow-up data for PCSK9 inhibitors, including evolocumab.[6] Therefore, an open-label extension programme to FOURIER (FOURIER-OLE) was designed to capture long-term safety tolerability, efficacy and outcomes data in patients receiving continued evolocumab therapy.[3]

FOURIER was an international, randomized, placebo-controlled clinical trial.[4] At the conclusion of the study, patients in the US and Eastern Europe were considered for participation in the open-label long-term extension (FOURIER-OLE); enrolment was subsequently expanded to include eligible patients in Western Europe.[3]

This publication presents results from FOURIER-OLE with a median duration of follow-up of 5.0 years and a maximum follow-up time of 5.5 years. For patients randomized to receive evolocumab during the parent FOURIER trial *and* the OLE, the combined median follow-up is 7.1 years, with a maximum of 8.4 years.[3] This represents the longest follow-up of exposure to a PCSK9 inhibitor to date.[6]

Introduction

Cardiovascular disease (CVD) is a major global burden, with around 18.6 million people worldwide estimated to have died from CVD in 2019.[7] More than 4.3 million deaths each year, including from ischaemic heart disease and stroke, can be linked to elevated levels of LDL-C.[8, 9]

LDL-C is a well-established and modifiable risk factor for CVD, and most patients with elevated serum cholesterol will generally receive first-line treatment with an HMG-CoA reductase inhibitor (statin).[1, 2] Lipid management is risk-based, and patients who are at high or very-high risk CV have relatively aggressive LDL-C goals which may not be achieved with statin treatment alone – this often requires an add-on therapy.[1, 2]

Monoclonal antibodies that inhibit PCSK9 have emerged as highly effective lipid lowering therapies.[1, 2] Clinical trials of PCSK9 inhibitors, either alone or in combination with statins and/or other lipid-lowering therapies, have demonstrated significant reductions in LDL-C by an average of around 60%, depending on the dose.[2]

Genetic studies have also shown that people who carry *PCSK9* loss-of-function alleles have lower LDL-C levels and a reduced risk of coronary heart disease and myocardial infarction.[10, 11]

Compared with studies of statins and other non-statin lipid lowering therapies, the duration of follow-up for PCSK9 inhibitor studies is shorter.[3] As such, there is a need for data to characterise the longer-term effects of therapy, including safety, efficacy and outcomes such as MACE.[6]

Evolocumab (REPATHA®, Product Information) is a fully human immunoglobulin G subclass (IgG2) monoclonal antibody that binds selectively and with high affinity to PCSK9.[12] Evolocumab inhibits circulating PCSK9 from binding to the low-density lipoprotein receptor (LDLR) on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation.[12]

Elevated levels of total cholesterol (TC), non-high-density lipoprotein cholesterol (non-HDL-C), LDL-C and apolipoprotein B (ApoB, the major protein constituent of LDL) promote atherosclerosis in humans.[12] In clinical trials of patients with primary hypercholesterolaemia, evolocumab reduced LDL-C, TC, AboB, non-HDL-C, the ratios of TC/HDL-C and ApoB/apolipoprotein A1 (ApoA1), very-low-density lipoprotein cholesterol, triglycerides and lipoprotein(a); it also increased HDL-C and ApoA1.[12]

Evolocumab is administered as a subcutaneous injection, and is available as either a pre-filled syringe or pre-filled pen injector containing 140 mg/mL, or as pre-filled cartridge with an automated mini-doser (AMD) containing 420 mg/3.5 mL solution.[12] The recommended dosage for primary hypercholesterolaemia and prevention of cardiovascular events is 140 mg every 2 weeks (one single-use pre-filled pen) or 420 mg once monthly (one single-use AMD with 3.5 mL pre-filled cartridge OR three single-use pre-filled pens administered consecutively within 30 minutes); both doses are clinically equivalent.[12]

Study background

The parent study, FOURIER, was a randomised, double-blind, placebo-controlled trial including 1,242 patients across 49 countries.[4] At the completion of the study, patients at sites in the US and Europe were considered for participation in the long-term extension programme, FOURIER-OLE.[3]

FOURIER-OLE was initially started at 197 sites in the US and Eastern Europe, and enrolment was subsequently expanded (via a separate protocol) to include 86 sites in Western Europe.[3] Both protocols had similar entry criteria and assessments, and data were pooled for analysis.[3]

During the extension period, patients were treated with open-label subcutaneous injections of evolocumab, either 140 mg every 2 weeks or 420 mg every month – according to patient preference.[3] All patients received evolocumab, regardless of whether they were originally randomised to receive evolocumab or placebo in the original FOURIER study.[3] Any patients who discontinued treatment during the extension period were asked to remain part of the follow-up for the duration of the study.[3]

Expert comment

The seminal trials that demonstrated beneficial effects of statin therapy in patients with established ASCVD have all been of relatively short duration. The benefits were substantial in terms of a reduction in MACE and CV mortality as a combined endpoint, but none were able to show a reduction in CV or all-cause mortality, as the studies were event driven and were stopped when the primary endpoint became statistically significant. Patients are on lipid lowering therapy for many years so it is important to have long term follow up, such as in this extension study, to ensure the benefits seen in the original trial are maintained, and to ensure no safety signals develop with long term exposure to lipid lowering therapy, in this case evolocumab. In this open label extension, patients on placebo in the parent trial were supplied with evolocumab, whereas the patients on it during the trial continued. This design enables to see if there is a legacy effect in patients with longer exposure to the therapy, and whether patients who were on placebo catch up.

Study design and methods

Patients and treatment

Patients included in the FOURIER trial were those with a history of established ASCVD, and a fasting LDL-C level of ≥70 mg/dL (≥1.8 mmol/L) or non-HDL-C level of 100 mg/dL (3 mmol/L) while on a statin.[4, 5] Patients were eligible for FOURIER-OLE if they completed either arm of the FOURIER study (evolocumab or placebo) at a site that was participating in the OLE programme.[4]

Exclusion criteria included patients who discontinued treatment during the FOURIER study for any reason, including an adverse event (AE) or serious AE (SAE).[3] Patients who were participating in another study with an investigational drug or device or who would not be expected to complete follow-up for the duration of the OLE programme were also excluded.[3]

Endpoints and analyses

The primary endpoint was the subject incidence of treatment-emergent adverse events (TEAEs).[3]

The secondary endpoints were the percentage change in LDL-C from initial (FOURIER) baseline, and achievement of an LDL-C ≤40 mg/dL (≤1 mmol/L) at each scheduled visit.[3]

An analysis of the proportion of patients who achieved LDL-C below other relevant thresholds was prespecified, including <70, <55 and <20 mg/dL (<1.8, <1.4 and <0.5 mmol/L).[3]

MACE were prespecified exploratory endpoints, and included:

- The primary CV composite outcome of CV death, myocardial infarction, stroke, or hospitalisation for unstable angina or coronary revascularisation
- The key secondary CV composite outcome of CV death, myocardial infarction, or stroke.[3]

Safety evaluations for TEAEs included all enrolled patients who received at least one dose of study drug and for whom post-dose data were available.[3] Any patients who permanently discontinued study drug were censored for safety analysis 30 days post-discontinuation.[3] Annualised subject incidence rates for AEs of interest were calculated by randomised treatment arm during the FOURIER parent study, and combined for patients treated with evolocumab during the parent and OLE studies, yielding the longest duration of evolocumab exposure.[3]

Lipids were reported as summary statistics, and the percentage change in least-squares mean (LSM) for repeated measures.[3] The distribution for TG and lipoprotein(a) were skewed, and so descriptive changes were reported as median percentage change, without the use of a mixed repeated measures model.[3]

Analyses for MACE were conducted on an intention-to-treat basis.[3] For analyses of events occurring only during the OLE follow-up period, patients were considered to have a first event even if they had experienced a non-fatal event during the original FOURIER study.[3] Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated based on stratified Cox models, with the prespecified stratification factors as covariates.[3] Yearly landmark analyses were performed for the primary and secondary CV composite endpoints.[3]

Study results

Patient characteristics

FOURIER-OLE enrolled 6,635 patients, including 2,201 (33.2%) from the US and 4,434 (66.8%) from Europe.[3] The proportion of patients who entered FOURIER-OLE after receiving evolocumab or placebo during the parent study was similar (3,355 patients (50.6%) and 3,280 patients (49.4%), respectively).[3]

The mean (±SD) age of patients participating in FOURIER-OLE was 62.4 (±8.6) years at randomisation; 5,086 patients were men (76.7%) and 1,549 were women (23.3%).[3] The baseline characteristics of patients in FOURIER-OLE were well balanced across groups by the original treatment randomisation during FOURIER. The population was similar to the complete FOURIER population, except for including more White patients (95.4% vs 85.1%) and patients from the US (33.2% vs 16.6%).[3]

5,559 patients (83.3%) had a history of myocardial infarction, 1,064 (16%) had a history of non-haemorrhagic stroke, and 948 (14.3%) had symptomatic peripheral artery disease.[3]

The median duration of follow-up in the overall OLE population was 5.0 years (IQR 4.6–5.1), and in patients who received evolocumab during the FOURIER study and the OLE (evolocumab-evolocumab), the median follow-up was 7.1 years. The maximum duration of follow-up was 5.5 in the overall OLE population, and 8.4 years in evolocumab-evolocumab patients.[3]

Safety

Primary endpoint – TEAEs

The annualised incidence of all AEs of interest were similar by randomised treatment arm in the original FOURIER study, except for a slightly higher rate of injection-site reactions in patients receiving evolocumab (**Table 1**). Importantly, in FOURIER-OLE, there was no observed trend towards an increase in the incidence of any of the AEs of interest studied over time, including SAEs, injection-site reactions, potential drug-related allergic reactions, muscle-related and rhabdomyolysis/myopathy events, new-onset diabetes mellitus, cataract formation or haemorrhagic stroke (**Table 1**).

Of interest, the annualised incidence rates for AEs of interest in evolocumab-evolocumab patients (those with the longest evolocumab exposure) did not exceed those of placebo-evolocumab patients (**Table 1**).

Table 1. Annualised incidence of AEs of interest in FOURIER and FOURIER-OLE[3]

Event type	FOURIER placebo arm (n=3,277)*	FOURIER evolocumab arm (n=3,353)*	FOURIER-OLE (evolocumab-evolucumab patients; n=3,353)	Year of evolocumab exposure (evolocumab-evolucumab patients; n=3,353)							
				1st (n=3,353)	2nd (n=3,353)	3rd (n=3,346)	4th (n=3,261)	5th (n=3,139)	6th (n=3,018)	7th (n=2,863)	8th (n=1,768)
SAE	813 (12.5)	845 (12,8)	**1,618 (10.2)**	454 (14.6)	428 (13.7)	413 (13.4)	395 (13.1)	374 (12.9)	340 (12.2)	260 (11.1)	87 (9.9)
Injection-site reactions	49 (0.65)	62 (0.81)	**92 (0.42)**	47 (1.4)	15 (0.45)	13 (0.39)	11 (0.34)	3 (0.10)	5 (0.17)	3 (0.12)	2 (0.22)
Potential drug-related allergic reactions	83 (1.1)	83 (1.1)	**128 (0.58)**	48 (1.4)	32 (0.96)	16 (0.49)	12 (0.37)	10 (0.33)	13 (0.44)	6 (0.24)	2 (0.22)
Muscle-related events	140 (1.9)	157 (2.1)	**247 (1.2)**	117 (3.6)	50 (1.5)	43 (1.3)	24 (0.75)	24 (0.78)	17 (0.58)	10 (0.41)	1 (0.11)
Rhabdomyolysis/myopathy events	4 (0.05)	3 (0.04)	**8 (0.04)**	1 (0.03)	2 (0.06)	2 (0.06)	0	1 (0.03)	2 (0.07)	1 (0.04)	0
New-onset diabetes mellitus†	107/2,033 (2.32)	90/2,155 (1.84)	**166/2,155 (1.21)**	32/2155 (1.49)	40/2123 (1.90)	27/2068 (1.34)	22/1963 (1.15)	12/1871 (0.66)	15/1796 (0.86)	14/1707 (0.96)	4/1023 (0.78)
Cataract formation	64 (0.85)	55 (0.72)	**163 (0.74)**	25 (0.75)	26 (0.78)	26 (0.79)	26 (0.81)	27 (0.88)	26 (0.89)	14 (0.57)	5 (0.55)
Haemorrhagic stroke	4 (0.05)	0	**10 (0.04)**	0	0	2 (0.06)	2 (0.06)	1 (0.03)	3 (0.10)	3 (0.12)	0

* Only includes data for patients who entered FOURIER-OLE (not the entire FOURIER population)
† Does not include patients with diabetes mellitus at baseline
SAE = serious adverse event.

Efficacy

Effect on lipids

The median baseline LDL-C in patients entering the FOURIER study was 2.3 mmol/L, and at the end of that study, median LDL-C levels were significantly lower in patients randomised to evolocumab, compared with placebo (0.7 mmol/l vs 2.3 mmol/L; **Figure 1**).[3] Evolocumab-evolocumab patients in FOURIER-OLE experienced consistent LDL-C levels over the median 7.1 years of follow-up (**Figure 1**).[3] Unsurprisingly, placebo-evolocumab patients experienced substantial reductions in LDL-C when switched to evolocumab (**Figure 1**), dropping to a similar level as the overall study population at 12 weeks after initiation of FOURIER-OLE.[3]

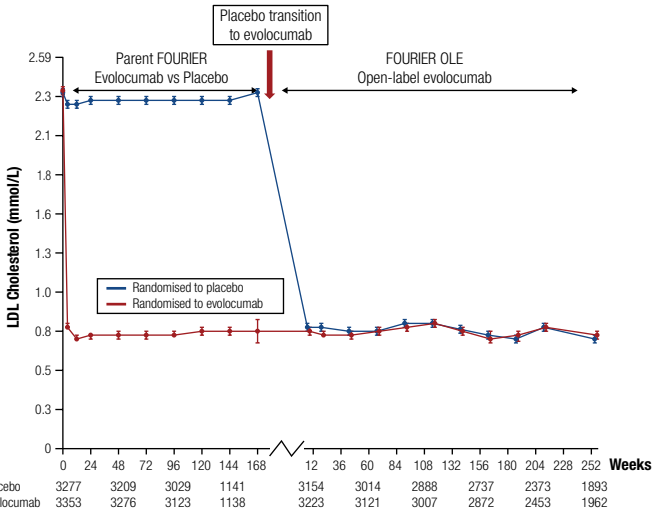

Figure 1. LDL-C by randomised treatment are in FOURIER and FOURIER-OLE[3]
Values are median (95% CI)

In the overall population of FOURIER-OLE, at 12 weeks:

- The LSM percentage reduction in LDL-C from baseline was 58.4%
- LDL-C was:
  - <1.8 mmol/l in 87.3%
  - <1.4 mmol/l in 80.3%
  - <1.0 mmol/L in 63.2%
  - <0.5 mmol/l in 26.6%
- Non-HDL-C was reduced by 50.2% (95% CI 49.4–50.9; p<0.001)
- ApoB was reduced by 44.4% (95% CI 43.7–45.2; p<0.001).[3]

MACE outcomes

In FOURIER-OLE, evolocumab-evolocumab patients had a lower incidence of the primary MACE composite outcome (CV death, myocardial infarction, stroke, or hospitalisation for unstable angina or coronary revascularisation), compared with placebo-evolocumab patients (HR 0.85; 95% CI 0.75–0.96; p=0.008).[3]

Evolocumab-evolocumab patients also had a significantly lower incidence of the key secondary MACE composite outcome (CV death, myocardial infarction, or stroke), compared with placebo-evolocumab patients (HR 0.77; 95% CI 0.60–0.99; p=0.04).[3] In addition, evolocumab-evolocumab patients had a 23% lower risk of CV death, compared with placebo-evolocumab patients (HR 0.77; 95% CI 0.60–0.99; p=0.04).

The yearly landmark analyses showed that the clinical benefits of evolocumab in terms of MACE outcomes were more apparent in the first 3 years of FOURIER-OLE (**Figure 2**).

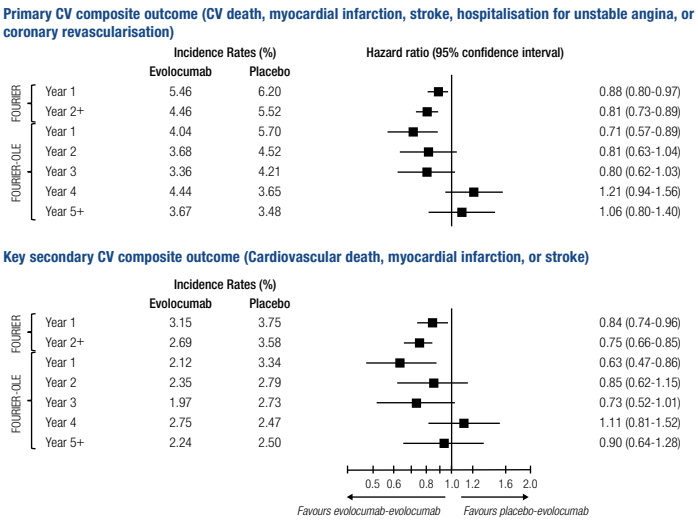

Figure 2. Forest plots of yearly landmark analyses of primary and key secondary CV composite outcomes[3]

Expert comment

This data shows the safety and efficacy of evolocumab seen in the FOURIER trial continued with long-term aggressive lipid lowering in patients with ASCVD. It is of particular interest that CV mortality was reduced in the patients who received evolocumab for an average of 7.1 years, and that there was a catch up in patients who originally received placebo after 3 years of receiving open label evolocumab, implying it is never too late to initiate this therapy in patients with ASCVD, although there will be lag before the benefits become evident.

Study interpretation

FOURIER-OLE represents the longest follow-up available to date with a PCSK9 inhibitor.[3, 6] This long-term extension study of the original FOURIER trial demonstrates that continued treatment with evolocumab effectively maintains reduced LDL-C levels, and was not associated with any apparent increase in AEs of interest.[3]

Moreover, there appears to be a legacy effect from increased evolocumab exposure: patients who received evolocumab in FOURIER had significantly lower incidences of CV composite outcomes in FOURIER-OLE, compared with those originally receiving placebo.[3] This is consistent with clinical trials of statins, where a legacy effect of intensively lowering LDL-C has previously been reported.[3] The observed lag between the start of therapy and full clinical benefit (e.g., prevention of MACE) observed with evolocumab (**Figure 2**) likely reflects that the underlying disease modification does not result in immediate effects, but with adequate follow-up (e.g., ≥5 years) become apparent.[3]

International guidelines recommend aggressive LDL-C goals in patients who are at high- (<1.8 mmol/L) or very high-risk (<1.4 mmol/L).[1, 2] In FOURIER-OLE, the proportion of patients achieving relevant LDL-C thresholds (including these) was examined as a prespecified secondary endpoint; overall, 87.3% of patients achieved an LDL-C level <1.8 mmol/L, and 63.2% achieved a level of <1.4 mmol/L.[3]

A substantial proportion of patients achieved very low LDL-C levels on evolocumab treatment, with 63% of patients achieving a level of <1.0 mmol/L at Week 12 of FOURIER-OLE.[3] Early epidemiologic studies suggested that very low LDL-C levels may be associated with increased risks for haemorrhagic stroke or neurocognitive effects. FOURIER-OLE demonstrated that the frequency of AEs of interest (which included haemorrhagic stroke) did not increase with continued exposure to evolocumab, and did not exceed the incidences of those in the placebo arm of the FOURIER study;[3] this is consistent with safety observations with long-term low LDL-C in patients treated with statins and ezetimibe.[13, 14]

There are limitations of the current study: there was no placebo arm during the OLE; although patients in FOURIER-OLE were generally similar to those participating in FOURIER, there were some differences in race and region; only patients who were alive at the end of FOURIER were able to participate in FOURIER-OLE, which may reflect patients entering the OLE being at an inherently lower risk of mortality; not all patients were on a high-intensity statin or ezetimibe; and MACE outcomes were prespecified, but exploratory.[3]

Take-home messages

- FOURIER-OLE assessed the long-term safety and efficacy of evolocumab in patients with clinically evident ASCVD
- It reports the longest follow-up available to date with a PCSK9 inhibitor, with some patients receiving evolocumab for 8.4 years over FOURIER and FOURIER-OLE
- There is no apparent increase over time in the incidence of AEs of interest, which are broadly similar to those in patients randomised to placebo in FOURIER, suggesting no negative effects of continued LDL-C lowering
- In prespecified, exploratory analyses, continued treatment with evolocumab was associated with significant reductions in MACE composite outcomes and CV mortality, compared with patients initially receiving placebo.[3]

Expert's concluding comments

This open-label extension study is very reassuring that long term aggressive lipid lowering with evolocumab is beneficial and safe in our patients with established ASCVD. The PBS has recently liberalised the criteria for reimbursement for PCSK9 inhibitors,[15] so we should be considering using these agents in these high risk patients, to improve their outcomes.

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