

REVIEW ARTICLE

Effects of Evolocumab on Cardiovascular Events

Nasser Mikhail*

OliveView-UCLA Medical Center, David-Geffen Medical School, Los Angeles, California, 14445 Olive View Dr, Sylmar, CA 91342, USA

Background: Evolocumab is a potent lipid-lowering drug that decreases plasma levels of low-density lipoprotein cholesterol (LDL-C) by 50-60%. FOURIER is a landmark randomized trial involving 27,564 patients with established cardiovascular disease already on statins and plasma LDL-C levels > 70 mg/dl.

Objective: The main objective of FOURIER was to examine the effects of evolocumab on cardiovascular events.

Results: After a mean follow-up of 2.2 years, evolocumab significantly decreased the primary endpoint (composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization) by 15% compared to placebo [hazard ratio 0.85 (95% CI, 0.79-0.92)], but no significant effect was found on mortality. The most common adverse effect of evolocumab was mild injection site reaction occurring in 2.1% of patients versus 1.6% of patients receiving placebo.

Conclusion: These results support the use of evolocumab as add-on therapy to statins for high cardiac-risk patients not achieving optimal goals of LDL-C. Longer-term studies are needed to further clarify the efficacy and safety of evolocumab.

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1. INTRODUCTION

LDL-C receptors located on the surface of hepatocytes are essential for clearance of LDL-C from the plasma. Pro-protein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease mainly produced by the liver, and to a lesser extent the intestines and kidneys [1]. This enzyme attaches to and internalizes LDL-C receptors into lysosomes, and therefore enhance their degradation. Evolocumab is a fully humanized monoclonal antibody that inhibits PCSK9 and therefore increases availability of LDL-C receptors leading to a decrease in circulating levels of LDL-C. In 2015, the Federal Drug Administration (FDA) approved evolocumab (Repatha) and another monoclonal antibody of PCSK9, alirocumab (Praluent) as adjunct to diet and maximally tolerated statin therapy for treatment of adults with clinical atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia who require additional lowering of LDL-C [2, 3]. In addition, evolocumab was approved by FDA for the treatment of subjects with homozygous hypercholesterolemia who require further LDL-C reduction despite taking multiple lipid-lowering drugs [2]. The European

Commission approved an additional indication for both drugs to be used in cases of intolerance or contraindication to statins. Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) is the first trial specifically designed to examine the effects of evolocumab on cardiovascular events and its safety in patients with established atherosclerotic cardiovascular disease already on statin therapy [4]. The main purpose of this review is to provide a critical appraisal on the FOURIER trial and discuss its clinical implications.

2. OVERVIEW OF FOURIER

FOURIER is a randomized, double-blind, placebo-controlled multinational trial. By including 27,564 patients, the FOURIER is the largest study of evolocumab or any other PCSK9 inhibitor published to date [4]. The main objective of the trial was to examine the effects of evolocumab added to statins on the incidence of cardiovascular effects in patients 40-85 years of age with clinically evident vascular disease [4]. Subjects had to have fasting LDL-C \geq 70 mg/dl or non-HDL-C \geq 100 mg/dl on optimized statin therapy with or without ezetimibe. Patients were randomized in a 1:1 ratio to receive evolocumab 140 mg sc q2 weeks or 240 mg sc every month according to patient's preference, or matching placebo. The primary end point of FOURIER was major cardiovascular events defined as composite of cardiovascular

*Address correspondence to this author at the OliveView-UCLA Medical Center, David-Geffen Medical School, Los Angeles, California, 14445 Olive View Dr, Sylmar, CA 91342, USA; Tel: 8183643205; Fax: 818-3644573; E-mail: nmikhail@dhs.lacounty.gov

death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary end point was the composite of cardiovascular death, myocardial infarction or stroke. The size of the trial population was based on the key secondary end point such that 1,630 secondary events were required to provide 90% statistical power for the detection of a 15% relative risk reduction with evolocumab compared with placebo [4]. After 1,829 such events had occurred (816 and 1,1013 events in the evolocumab and placebo respectively), the trial was terminated after a median duration of 26 months of follow-up (interquartile range, 22 to 30 [4]. The manufacturer of evolocumab, Amgen, was the sponsor that designed the study, collected and submitted the raw data to an independent academic organization: the Thrombolysis in Myocardial Infarction (TIMI) Study Group for data analysis [4]. Summary of design and main results of FOURIER are presented in Table 1.

3. EFFECTS OF EVOLOCUMAB ON PLASMA LIPIDS

At 48 weeks, as compared to placebo, the least-squares mean reduction in LDL-C concentrations with evolocumab was 59% (95% CI 58-60, $P < 0.001$) [4]. This difference corresponded to a mean absolute reduction in LDL-C levels of 56 mg/dl (95% CI, 55-57 mg/dl). In fact, from a median baseline LDL-C of 92 mg/dl, evolocumab lowered LDL-C to a median of 30 mg/dl at end of follow-up [4]. In terms of time course, maximum reduction in LDL-C levels occurred after 4 weeks, and was generally sustained to the end of trial [4]. The durability of lipid-lowering effect of evolocumab may be attributed to its low immunogenicity effect. Thus,

in the FOURIER trial, new binding antibodies developed in 43 evolocumab-treated patients (0.3%), with no patients developing neutralizing antibodies [4]. In contrast, another PCSK9 monoclonal antibody, bococizumab, was discontinued by the manufacturer after the observation that its efficacy waned with time as result of development of neutralizing antibodies in 29% of patients [5, 6]. In addition, for unclear reasons, there was wide variability in response to its LDL-C-lowering effects even in antibody-negative subjects [5, 6]. There were also beneficial changes with evolocumab in other lipid parameters as summarized in Table 2 [4].

4. EFFECT ON C-REACTIVE PROTEIN

There were no significant changes in C-reactive protein, mean levels being 1.7 mg/L at baseline and 1.4 mg/L in both evolocumab and placebo groups at 48 weeks. This finding suggests that evolocumab lacks an anti-inflammatory action as opposed to statins that consistently decrease C-reactive levels reflecting their anti-inflammatory effect [7]. The lack of effect of evolocumab on C-reactive protein appears to be a class effect because a meta-analysis of 16 trials of various PCSK9 monoclonal antibodies, including evolocumab, also showed no effect on C-reactive protein [8].

5. EFFECT OF EVOLOCUMAB ON CLINICAL END POINTS

Due to the high cardiovascular risk of patients at baseline, the number of cardiovascular events was elevated despite the short duration of follow-up [4]. Thus, the primary end point occurred in 1344 patients (9.8%) in the evolocumab group and in 1563 patients (11.3%) in the placebo group [4]. The decrease in events in the evolocumab group

Table 1. Main findings of FOURIER trial.

Design	Randomized, Double-blind, Placebo-controlled. Multinational, 2 Groups
Patients	N= 27,525 with established atherosclerotic cardiovascular disease
Mean age	63 years
Women/Men	24.6%/75.4%
Ethnicity	Whites 75%
Baseline median LDL-C	92 mg/dl in both groups
Intervention	Evolocumab (n=13,784) either 140 mg sc q2 weeks or 420 mg sc qmonth versus matching placebo (n=13,780)
Concomitant therapy	Statins: 69.3% (high-intensity), 30.4% (moderate-intensity), 5.2% ezetimibe
Type of vascular disease at entry	Myocardial infarction (81%), non-hemorrhagic stroke (19%), symptomatic peripheral vascular disease (17%)
Follow-up	Median 2.2 years, interquartile range 22-30 months
Primary outcome	Composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization
Secondary outcome	Composite of cardiovascular death, myocardial infarction or stroke
Premature discontinuation rate	Evolocumab 12%, placebo 13%
Effects on primary end point	Evolocumab 9.8% (n=1344 patients) versus placebo 11.3% (1563 patients). HR 0.85 (95% CI 0.79-0.92, $P < 0.001$)
Effects on secondary endpoints	Evolocumab 5.9% (n=816 patients) versus placebo 7.4% (n=1013 patients). HR 0.80, 95% CI 0.73-0.88, $P < 0.001$.

Table 2. Effects of evolocumab on plasma lipid parameters at 48 weeks*.

Lipid parameter	Evolocumab	Placebo
LDL-C**	59 % reduction compared with placebo	
Non-HDL-C	-51.2%	0.4%
Lipoprotein a	-26.9%	0.0%
Apoprotein B	-46.0%	2.7%
Triglycerides	-16.2%	-0.7%
Total Cholesterol	-35.5%	0.0%

*Expressed as mean percentage changes except for triglycerides and lipoprotein a, which are median changes.

** Changes in LDL-C values compared with baseline in the evolocumab and placebo group were not reported.

was statistically significant with a hazard ratio of 0.85 (95% CI 0.79-0.92), *i.e.* 15% relative risk reduction compared with placebo. Similarly, there was a significant relative risk reduction of 20% in key secondary end points; the proportions of patients having a secondary event being 5.9% and 7.4%, in the evolocumab and placebo group; hazard ratio 0.80, 95% CI 0.73-0.88 [4]. The difference in primary and key secondary end points started to emerge at 12 months of intervention and becomes wider with longer duration of intervention. For instance, risk reduction in primary outcome with evolocumab increases from 12% (95% CI 3-20) at year 1 to 19% (95% CI 11-27) beyond first year [4]. Regarding individual outcomes, risk reduction in primary and secondary end points was mainly driven by significant reduction in myocardial infarction (3.4% evolocumab versus 4.6% placebo), coronary revascularization (5.5% evolocumab versus 7.0% placebo) and stroke (1.5% evolocumab versus 1.9% placebo) [4]. Meanwhile, there was no significant difference between the 2 groups of patients in death from any cause (3.2% evolocumab versus 3.1% placebo), and cardiovascular death (evolocumab 1.8% versus 1.7% placebo), possibly due to short duration of follow-up [4]. The study was not sufficiently powered to detect differences in mortality between the 2 groups. The decrease in myocardial infarction and coronary revascularization events in evolocumab-treated subjects are in keeping with results of the recent trial conducted by Nicholis *et al.* showing that addition of evolocumab to statins in patients with coronary disease was associated with greater decrease in coronary atheroma volume after 76 weeks of treatment as compared with placebo [9]. In addition, greater percentage of patients randomized to evolocumab demonstrated plaque regression 64.3%, versus 47.3% in the placebo group [9].

6. SUBGROUP ANALYSIS OF FOURIER TRIAL

The effects of evolocumab on various outcomes was consistent across patient subgroups classified based on age (above versus below 65 years), gender, types of vascular disease at study entry, quartiles of baseline LDL-C levels, dosing regimen (140 mg every 2 weeks vs. 420 mg monthly) [4]. However, a significant interaction was found in terms of race, with non-Caucasians showing greater reduction in events compared with Caucasians (HR 0.70 and 0.88, respectively; P value for interaction = 0.036). Unfortunately,

cardiovascular effects of evolocumab were not reported in the subgroup of patients with diabetes that represented 36% of study population [4]. Whereas available data suggest that lipid-lowering efficacy of evolocumab was similar in patients with and without diabetes, effects of the drug on cardiovascular events may not be necessarily the same [10, 11]. Interestingly, in the study of Nicholis *et al.*, the decrease in atheroma volume associated with evolocumab was similar in the subgroup of patients with diabetes (21% of study population) compared with subjects without diabetes [9].

7. SAFETY OF EVOLOCUMAB

7.1. Short-term Safety

In the FOURIER trial, evolocumab was well tolerated. There were no differences between evolocumab and placebo in overall rates of adverse effects, serious adverse effects, and adverse effects leading to drug discontinuation [4]. Injection site reactions were significantly more common in evolocumab group compared with the placebo group, 2.1% and 1.6%, respectively [4]. Approximately 90% of these reactions were described as mild. Only 0.1% of patients in each treatment group stopped the medication due to skin reaction [4]. These low rates of mild skin reactions are consistent with the low immunogenicity potential of evolocumab. In contrast, injection skin reactions developed in 10.4% of bococizumab-treated subjects compared with 1.3% with placebo, most likely due to the high rate of development of neutralizing antibodies as mentioned earlier [5, 6].

7.2. Adverse Effects of Particular Interest

In the FOURIER trial, as discussed below, there was a marginal trend of some adverse effects of particular interest to occur more frequently in the evolocumab group than placebo including muscle-related events, incidence of diabetes, and neurocognitive events as discussed below [4].

A. Muscle-associated Events

Muscle-related events, occurred in 5% and 4.8% with evolocumab and placebo, respectively [4]. It should be emphasized that although the incidence of muscle-associated symptoms are low and close to placebo in statin randomized trials, these symptoms are reported by much higher proportions of patients in observational studies and clinical practice reaching 7-29% of patients using statins [12]. In patients

intolerant to statins, short-term data suggest that evolocumab may be used as an alternative. In a well-designed study conducted by Nissen and co-workers, patients with documented statin muscle-intolerance were randomized in a double-blind fashion to receive evolocumab 420 mg/month or ezetimibe 10 mg/d for 24 weeks [13]. Muscle symptoms were reported by 28.8% and 20.7% in the ezetimibe and evolocumab group, respectively ($P=0.17$) [13]. Only 1 of 145 (0.7%) the evolocumab-treated patients stopped the drug due to muscle symptoms compared with 5 of 73 (6.8%) ezetimibe-treated patients [13]. In terms of efficacy, evolocumab was clearly superior to ezetimibe with mean reduction in LDL-C levels of 54.5% and 16.7%, respectively [13]. The results of this short-term trial suggest that evolocumab can be virtually an effective and safe alternative to statins in subjects intolerant to statins due to muscle symptoms. However, as we learned from the lesson of statins, it is essential to closely monitor the incidence of muscle symptoms associated with evolocumab use outside the setting of clinical trials and in post-marketing studies for long duration of time.

B. New-onset Diabetes

Newly diagnosed diabetes, another complication of statin therapy, occurred in 8.1% and 7.7% of evolocumab and placebo group, respectively, hazard ratio 1.05; 95% CI 0.94-1.17 [4]. A post-hoc analysis of a smaller study ($n=905$), showed that evolocumab did not have significant effects on plasma levels of fasting glucose and insulin, insulin resistance (assessed by homeostatic model), body weight, and new onset diabetes after 52 weeks of therapy compared with placebo [11]. While absence of statistically significant association between diabetes incidence and short-term exposure to evolocumab is somewhat reassuring, it may be simply due to the relatively small number of events of type 2 diabetes and short duration of follow-up. Indeed, the link between statins and new onset diabetes was only discovered after more than 4,000 diabetes events were reported during a mean duration of 4 years [14]. Using the Mendelian randomization approach, several studies showed that genetic PCSK9 variants that mimic the effect of PCSK9 inhibitors were associated with increased risk of diabetes [15, 16]. Interestingly, the increased risk of diabetes associated with the PCSK9 variants was similar in magnitude, and additive to, the increased risk associated with genetic variant of HMGCR, the target of statins [16]. Thus, definitive conclusion regarding any possible association between PCSK9 inhibitors and incidence of diabetes should await more studies and longer follow-up.

C. Cognitive Function

In the FOURIER trial, neurocognitive events were reported by 1.6% and 1.5% of patients randomized to evolocumab and placebo, respectively [4]. Deterioration of neurocognition is a particular concern of extreme LDL-C lowering because cholesterol plays important role in brain synapse and function [17]. In a post-hoc analysis from JUPITER, a randomized double-blind trial of rosuvastatin, the subgroup of patients who achieved LDL-C <30 mg/dl ($n=767$) had more type 2 DM (hazard ratio 1.56, 95% CI, 1.09-2.23), hematuria (hazard ratio 2.1, 95% CI, 1.39-3.19), hepatobiliary disorders (hazard ratio 1.77, 95% CI, 1.15-2.73), and insomnia (hazard ratio 1.59, 95% CI 1.03-2.48) compared with the larger sub-

group of rosuvastatin-treated patients ($n=7,387$) who achieved LDL-C >30 mg/dl [18]. However, no increase in memory impairment was reported by the subgroup of patients who achieved LDL-C levels <30 mg/dl [18]. While data derived from trials of statins are generally reassuring [19], it is not excluded that further lowering of plasma cholesterol by PCSK9 inhibitors could affect cognition. In fact, in previous trials of PCSK9 monoclonal antibodies, there were some signals suggesting worsening cognitive function [20]. EBBINGHAUS is a nested study within FOURIER designed to evaluate the effect of evolocumab on cognitive function among a subgroup of 1974 patients [17]. Preliminary results of EBBINGHAUS were recently released in The American College of Cardiology Meeting, and showed overall no significant effect of evolocumab on various measures of cognitive function for up to 20 months of follow-up [21].

8. STRENGTHS AND LIMITATIONS OF FOURIER

Major strengths of the FOURIER trial include the large number, adequate statistical power, the double-blind design, and independent adjudication of clinical outcomes by members of central committee unaware of study group assignment. Meanwhile, the FOURIER study suffers from several limitations. First, the trial duration is insufficiently long to assess long-term efficacy and safety of evolocumab. In this regard, the longest-term available data of evolocumab were derived from selected patients ($n=812$) previously involved in double-blind trials and chose to participate in open-label extension up to 4 years [22]. These data are overall reassuring and showed durable efficacy of evolocumab, with no evidence of increase in incidence of adverse effects over time [22]. Second, many diseases were excluded from the FOURIER trial such as patients with severe renal dysfunction defined as estimated glomerular filtration rate <20 ml/min/1.73 m², uncontrolled hypertension defined as systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg, heart failure NYHA class III or IV, or left ventricular ejection fraction $<30\%$ [23]. Thus, efficacy and safety of evolocumab are unknown these patients. One exclusion of particular importance was patients with liver dysfunction having transaminases >3 times upper normal limits because such patients are also not candidates to take statins. A small study of patients with mild and moderate hepatic impairment (Child-Pugh Class A and B) showed a single 140 mg-dose of evolocumab did not have clinically significant effects on the drug pharmacokinetics and dynamics, a finding that supports its use without dose adjustment in patients with mild to moderate hepatic impairment [24]. Clearly, more studies are needed to clarify safety of evolocumab in patients with various degrees of hepatic dysfunction.

In the FOURIER, subjects cannot be randomized within 4 weeks of their most recent myocardial infarction or stroke [23]. Intensive LDL-C lowering by atorvastatin (80 mg/d) given within 10 days after hospitalization for an acute coronary syndrome decreased mortality or cardiovascular events by 16% compared with standard regimen formed of pravastatin 40 mg/d [7]. It remains to be seen whether evolocumab administration in the near post-infarction period would decrease cardiovascular events. Finally, it should be emphasized that the patients included in FOURIER were very high-cardiac risk at baseline. Thus, these results should not be

extrapolated to patients with milder degree of cardiac risk or in the setting of primary prevention.

9. COST-EFFECTIVENESS OF EVOLOCUMAB

The main problem that prevents widespread use of evolocumab is its high cost. With a list annual price of \$ 14,523, evolocumab is a very expensive drug [25]. Recently, Fonarow *et al.* [25] evaluated the cost-effectiveness of evolocumab based on results of FOURIER. The authors concluded that in order to be cost-effective, the annual net price would need to be substantially lower, \$ 9,669 for US patients with atherosclerotic cardiovascular disease already on statin therapy [25].

CONCLUSION AND CURRENT NEEDS

No doubt, the introduction of fully humanized PCSK9 monoclonal antibodies, such as evolocumab, represents an excellent addition to lipid-lowering therapy. The FOURIER trial confirmed the efficacy and safety of evolocumab over approximately 2 years. This landmark study showed that reduction of LDL-C plasma concentrations to historically low values conferred further cardiovascular benefit and was safe at short-term. Indeed, at 48 weeks, 42% of patients in the evolocumab group had LDL-C concentrations 25 mg/dl or lower, and 67% of patients had 40 mg/dl or lower. The results of FOURIER therefore may lead to change current guidelines toward more aggressive lower LDL-C targets. The high cost of evolocumab represents an important obstacle for its widespread use [25]. At present, this agent may be considered in individuals with very high cardiovascular risk as add-on therapy to high-intensity statin and ezetimibe, and patients with familial hypercholesterolemia. Another indication may be an alternative to statins in patients with documented statin intolerance. Long-term data are urgently needed to prove its durability in terms of efficacy and to establish its safety. New or unexpected adverse effects might emerge with longer duration of use. Both ongoing trials and post-marketing studies should carefully monitor the incidence of diabetes, muscle-associated and neurocognitive events and cancer. Finally, the impact of evolocumab on cardiovascular and overall mortality has yet to be demonstrated.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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