JAMA Cardiology | Brief Report

Interindividual Variation in Low-Density Lipoprotein Cholesterol Level Reduction With Evolocumab
An Analysis of FOURIER Trial Data

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IMPORTANCE Little is known about the heterogeneity in low-density lipoprotein cholesterol levels (LDL-C) lowering with proprotein convertase subtilisin kexin 9 (PCSK9) inhibitor medications.

OBJECTIVE To evaluate the interindividual variability in LDL-C reduction with the PCSK9 inhibitor drug evolocumab.

DESIGN, SETTING, AND PARTICIPANTS We examined the percentage change in LDL-C levels from baseline in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial, a placebo-controlled randomized clinical trial of the PCSK9 inhibitor evolocumab in patients with stable atherosclerotic cardiovascular disease who were taking statin medications. Patients in either treatment arm who had high baseline LDL-C variability during screening and either did not receive the study drug, altered their background lipid-lowering therapy regimen, or had no LDL-C level sample in week 4 were excluded from the primary analysis. Analyses in the patients were stratified by treatment arm. Data was collected from 2013 to 2016, and data were analyzed from January 2018 to November 2018.

MAIN OUTCOMES AND MEASURES Interindividual variation in percent reduction in LDL-C with evolocumab.

RESULTS There were 27 564 individuals in the cohort; after exclusions for baseline variability (n = 3524) or alterations in background lipid therapy and other causes (n = 2272), 21 768 patients remained. At week 4, the median percent reduction in LDL-C levels from baseline was 66% (interquartile range, 54%-76%; median [interquartile range] baseline value, 90 [79-105] mg/dL; postchange value, 31 [21-44] mg/dL) with evolocumab. During the first year, a total of 10 325 of 10902 patients in the evolocumab group (94.7%) had a reduction 50% or greater in LDL-C levels, 10 669 of 10 902 (97.9%) had a reduction 30% or more, and 10 849 of 10 902 (99.5%) had any reduction in LDL-C levels. Fifty-three patients (0.5%) had no apparent reduction in LDL-C levels. In the placebo arm, the median LDL-C reduction was 4% (interquartile range, 6% increase to 13% reduction; baseline median [IQR] value, 90 [79-106] mg/dL; postchange value, 87 [74-103] mg/dL) at 4 weeks. Waterfall plots showed notable variability in the top and bottom 5% of patients for both evolocumab and placebo groups, with large changes in LDL-C levels in the placebo group (increases of ≥25%, 531 patients [4.9%]; decreases of ≥25%, 985 patients [9.1%]). At 4 weeks, the placebo-adjusted reductions in LDL-C levels with evolocumab were 50% or greater in 9839 of 10 866 patients (90.5%) and 30% or greater in 10 846 of 10 866 patients (99.8%). Results were consistent across clinically relevant subgroups.

CONCLUSIONS AND RELEVANCE There appears to be a highly consistent robust reduction in LDL-C levels with evolocumab use.

TRIAL REGISTRATION ClinicalTrials.gov identifier: NCT01764633

JAMA Cardiol. 2019;4(1):59-63. doi:10.1001/jamacardio.2018.4178
Published online December 12, 2018.

Supplemental content

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Concerns have been raised for interindividual variation in the magnitude of low-density lipoprotein cholesterol (LDL-C) level reduction with statin medications and ezetimibe.[1-3] Inhibition of proprotein convertase subtilisin-kexin type 9 (PCSK9) with monoclonal antibodies is an additional approach to lowering LDL-C levels in patients receiving maximally tolerated statin therapy. In the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial (NCT01764633), inhibition of PCSK9 with evolocumab, a fully human monoclonal antibody active against PCSK9, taken with a background of statin therapy reduced LDL-C levels and the risk of cardiovascular events in patients with stable atherosclerotic cardiovascular disease.[4]

As with statin medications and ezetimibe, questions about interindividual variability in LDL-C level reduction in response to PCSK9 inhibitors have been raised. Furthermore, many payors require subsequent laboratory testing to demonstrate an optimal LDL-C reduction with PCSK9 inhibitors. The magnitude of individual-level heterogeneity in LDL-C level reduction with evolocumab has not been defined in a large-scale trial. Therefore, we examined the interindividual variability in LDL-C level reduction in response to PCSK9 inhibition with evolocumab in the FOURIER trial.

Key Points

Question What is the magnitude of interindividual variation in low-density lipoprotein cholesterol level reduction with the proprotein convertase subtilisin kexin 9 inhibitor evolocumab?

Findings In an analysis of the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial data, placebo-adjusted analyses show that evolocumab reduced low-density lipoprotein cholesterol levels by 50% or more in 90.5% of patients and by 30% or more in 99.8% of patients.

Meaning The addition of evolocumab to statin therapy provides a consistent and reliable low-density lipoprotein cholesterol level reduction in most patients.

Methods

Study Design and Treatment

The design of the FOURIER trial has been published previously.[4,5] In brief, FOURIER randomly assigned 27 564 patients with prior myocardial infarction, nonhemorrhagic stroke, or symptomatic peripheral artery disease to receive either evolocumab or placebo. To be eligible, patients were required at the end of the screening period to have an LDL-C level of 70 mg/dL or greater or a non-high-density lipoprotein (HDL) cholesterol of 100 mg/dL or more while taking background lipid-lowering therapies (to convert cholesterol values to millimoles per liter, multiply by 0.0259).

Ethics committee approvals for the FOURIER trial were obtained from all relevant organizations locally or through a central institutional review board within the country (including 1242 centers from 49 countries). Each patient provided written informed consent.

At the first 2 or 3 study drug administrations, patients were supervised in the administration of the study drug. After the week 4 visit, patients administered the study drug on their own. Levels of LDL-C were measured on the day of first administration of the study drug and at week 4, week 12, week 24, and every 6 months thereafter.

In the present analysis, we examined the interindividual variation in percentage reduction in LDL-C from baseline with evolocumab and with placebo at 4 weeks and over the course of the first year. Patients with high baseline LDL-C level variability prior to randomization (defined as a >90th percentile [32 mg/dL] difference between final screening phase and randomization LDL-C values) were excluded from the primary analysis (1763 patients in the evolocumab arm and 1761 patients in the placebo arm). Furthermore, patients in the evolocumab and placebo groups who did not receive the study drug, acknowledged an alteration in background lipid-lowering therapy, or had missing LDL-C levels at week 4 were excluded (1119 patients in the evolocumab arm and 1153 patients in the placebo arm).

Statistical Analysis

Waterfall plots were used to display the interindividual variation in percent change in LDL-C levels at week 4 in participants using evolocumab and placebo. To generate the placebo-adjusted difference, the percentage of LDL-C reduction was rank ordered among patients in each treatment arm, and the value in the placebo arm was subtracted from the corresponding value in the evolocumab arm. Based on the noted criteria, there were 10 902 patients eligible for the analysis in the evolocumab arm and 10 866 in the placebo arm (79% of the number of participants randomized in each arm). To generate exactly equal numbers to permit placebo-adjusted analysis of the rank-ordered results, 36 patients in the evolocumab arm whose values were closest to the median percentage of LDL-C reduction were excluded from the placebo-adjusted analysis. Analyses were done in Stata, version 14.2 (StataCorp). Study data were collected from 2013 to 2016, and data were analyzed in 2018.

Results

A total of 21 768 patients were included in this analysis. The baseline characteristics of the patients in the 2 treatment groups were comparable and are shown in the **Table**.

In the evolocumab group, the median percentage of reduction in LDL-C levels from baseline to week 4 was 66% (interquartile range [IQR], 54%-76%; median [interquartile range] baseline value, 90 [79-105] mg/dL; postchange value, 31 [21-44] mg/dL) at 4 weeks (**Figure 1**A). Of the 10 902 patients in the evolocumab group, 10 700 (98.1%) demonstrated at least some reduction in LDL-C levels, 10 124 (92.9%) had a reduction of 30% or greater, and 8744 (80.2%) had a reduction of 50% or greater. Among the 2158 patients (19.8%) who did not have at least a 50% reduction in LDL-C level at 4 weeks, 2125 (98.5%) had LDL-C levels measured within the first

year, and of those, 1581 (74.4%) had a reduction of 50% or greater. Thus, during the first year in the evolocumab group, 10 325 of 10 902 participants (94.7%) had a reduction of 50% or greater in LDL-C level, 10 669 (97.9%) had a reduction of 30% or greater, and 10 849 patients (99.5%) had at least some reduction in LDL-C levels. Fifty-three patients (0.5%) had no apparent reduction in LDL-C level within the first year.

In the placebo group, the median percentage of reduction in LDL-C level from baseline was 4% (IQR, 13% reduction to 6% increase; baseline median [IQR] value, 90 [79-106] mg/dL; postchange value, 87 [74-103] mg/dL) at 4 weeks (Figure 1B). Despite the exclusion of patients who acknowledged altering their background lipid-lowering therapy use, 531 of 10 866 patients (4.9%) showed an increase of 25% or more in LDL-C levels and 985 of 10 866 patients (9.1%) showed a decrease of 25% or more in LDL-C levels.

In the placebo-adjusted analysis, the median percentage of reduction in LDL-C levels with evolocumab was 61% (IQR, 58%-63%) at 4 weeks (**Figure 2**). Evolocumab reduced the level of LDL-C by 50% or greater in 9839 of 10 866 patients (90.5%) and by 30% or more in 10 846 of 10 866 patients (99.8%), adjusted for changes in the placebo group. This pattern of LDL-C level reduction was consistent across all major subgroups (eTable in the Supplement). A sensitivity analysis that included the 3524 additional patients with high baseline variability in LDL-C levels also showed consistent results with a median percentage of reduction in LDL-C levels of 60% (IQR, 57%-62%) with evolocumab, with 30% or more reduction in 12 601 of 12 627 patients (99.8%).

Table. Characteristics of Patients at Baseline[a]

Characteristic	No. (%)	
	Evolocumab (n = 10 902)	Placebo (n = 10 866)
Age, mean (SD), y	62.7 (9.0)	62.6 (8.9)
Male	8237 (75.6)	8241 (75.8)
Weight, mean (SD), kg	85.2 (17.3)	85.6 (17.5)
White[b]	9306 (85.4)	9239 (85.0)
Region		
North America	1854 (17.0)	1869 (17.2)
Europe	6898 (63.3)	6844 (63.0)
Latin America	696 (6.4)	682 (6.3)
Asia Pacific and South Africa	1454 (13.3)	1471 (13.5)
Type of atherosclerosis		
Myocardial infarction	8844 (81.1)	8855 (81.5)
Nonhemorrhagic stroke	2071 (19.0)	2094 (19.3)
Peripheral artery disease	1457 (13.4)	1364 (12.6)
Cardiovascular risk factors		
Hypertension	8767 (80.4)	8744 (80.5)
Diabetes mellitus	3962 (36.3)	3915 (36.0)
Current cigarette use	2992 (27.4)	3066 (28.2)
Statin use intensity[c]		
High	7529 (69.1)	7456 (68.6)
Moderate	3350 (30.7)	3392 (31.2)
Low, unknown, or no data	23 (0.2)	18 (0.2)
Ezetimibe use at baseline	545 (5.0)	519 (4.8)
Baseline lipid measures, median (IQR), mg/dL		
Low-density lipoprotein cholesterol	90 (79-105)	90 (79-106)
Total cholesterol	165 (150-184)	165 (150-185)
High-density lipoprotein cholesterol	44 (37-53)	44 (37-53)
Triglycerides	132 (100-179)	131 (98-179)
Estimated glomerular filtration rate at baseline, mean (SD), mL/min/1.73m^2	75.4 (18.8)	75.8 (18.6)

Abbreviation: IQR, interquartile range.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; to convert estimated glomerular filtration rate to milliliters per second, multiply by 0.0167.

[a] There were no statistically significant differences ($P < .05$) between the 2 groups for the baseline characteristics described above.

[b] Race was reported by the patients.

[c] Statin intensity was categorized in accordance with the guidelines of the American College of Cardiology and American Heart Association.

Discussion

In this secondary analysis of a large randomized clinical trial, the addition of evolocumab to statin therapy lowered LDL-C levels by 50% or greater in more than 90% of patients and by 30% or greater in more than 99% of patients. These findings support the consistency of robust LDL-C level reduction with evolocumab.

The concerns for large interindividual variability in LDL-C level reduction response with PCSK9 inhibitors were first raised in clinical trials with bococizumab, a humanized but not fully human monoclonal antibody targeting PCSK9.[6] In a pooled analysis of the SPIRE trials (the Evaluation of Bococizumab [PF-04950615; RN316] in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects [SPIRE-1] and the Evaluation of Bococizumab [PF-04950615; RN316] in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects [SPIRE-2]), waterfall plots showed a large interindividual variation in the LDL-C level reduction with bococizumab, even among patients in whom antidrug antibodies were not detected.[6] In addition, although rare, neutralizing antidrug antibodies have also been noted for alirocumab.[7] Neutralizing antidrug antibodies have not been seen with evolocumab,[4] to our knowledge.

Interindividual variation in LDL-C level reduction with statin use has been observed.[1,2] These variations have been attributed to demographic, phenotypic, and genetic factors.[8,9] We[10] and others[2] have shown that in patients receiving a high-intensity statin only approximately 45% of patients achieve an LDL-C reduction of 50% or greater. In comparison, almost all patients receiving evolocumab achieved a 50% or greater LDL-C level reduction. Because many payors require subsequent laboratory testing to demonstrate an optimal reduction in LDL-C with PCSK9 inhibitors, our findings should reassure clinicians and payors that nearly all patients have a robust LDL-C level reduction and such testing is largely unnecessary.

In general practice, nonadherence is likely the most common cause of considerable variation in LDL-C level lowering with a drug.[11,12] In this study, we excluded patients who

Figure 1. Waterfall Plot Showing Distribution of Percentage Change in Low-Density Lipoprotein Cholesterol (LDL-C) Levels at 4 Weeks

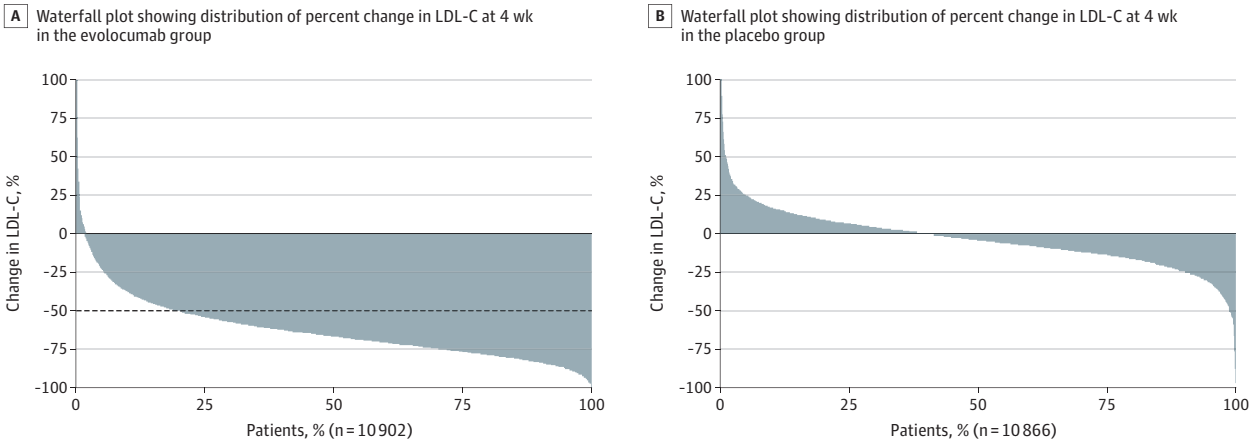
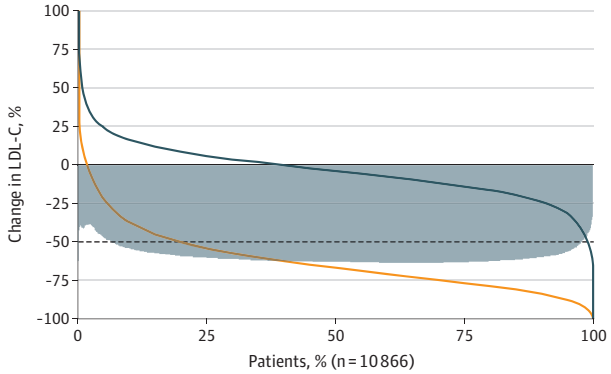


Figure 2. Waterfall Plot Showing Distribution of Placebo-Adjusted Percentage Change in Low-Density Lipoprotein Cholesterol (LDL-C) Levels at 4 Weeks



To generate placebo-controlled difference (gray) in the percentage of change in LDL-C, the percentage of change in LDL-C was rank ordered among patients in each treatment group and the value in the placebo group (dark blue) was subtracted from the corresponding value in the evolocumab group (orange).

acknowledged alteration in background lipid-lowering therapy and those who did not receive or missed the study drug. However, inclusion of patients who did alter background lipid-lowering therapy but did not acknowledge it may explain the suboptimal response in LDL-C level reduction observed in a small subset of patients allocated to receive evolocumab. Other potential contributors might include changes in dietary intake, lifestyle modifications, concomitant use of medications that influence lipid metabolism, unappreciated errors in study drug assignment (eg, a wrong kit provided) or administration (eg, improper injection technique), mistakes in laboratory sample labeling or handling, or problems with assays. These factors may also explain the significant changes in LDL-C level (increases or decreases of at least 25%) that were noted in 14% of patients in the placebo arm.

In contrast with what was observed for bococizumab, development of neutralizing antidrug antibodies were not seen in any patient in the FOURIER trial or in follow-up through 5 years in the Open Label Study of Long Term Evaluation Against LDL-C Trial (OSLER) and Open Label Study of Long Term Evaluation Against LDL-C Trial-2 (OSLER-2).[13] However, other theoretical possibilities exist, such as more rapid clearance of evolocumab or diminished efficacy owing to drug target alterations (eg, rare mutations in the LDL receptor). In the present study, only 53 patients (0.5%) in the evolocumab group had no reduction in LDL-C level at any time within the first year. The biological basis of suboptimal response to PCSK9 inhibition in these patients warrants further investigation.

Limitations

Potential limitations should be acknowledged. First, we calculated the placebo-adjusted difference by subtracting the rank-ordered percentage of LDL-C change within the placebo arm from the corresponding value within the evolocumab arm. Although the baseline characteristics of the 2 groups were comparable, the potential for unmeasured imbalances remains. Second, this analysis was limited to selected population enrolled in a clinical trial; thus, our findings may not be generalizable to the population taking evolocumab. Third, we excluded patients with admitted noncompliance with the study drug but could not exclude patients with unacknowledged noncompliance or unappreciated technical issues in study drug administration. These issues would have no influence on the placebo arm data but potentially a large influence on the evolocumab arm data. The exclusion of patients with noncompliance with the study drug was necessary but does represent a postrandomization variable; however, the baseline characteristics of the patients in the 2 treatment arms used in this analysis remained very similar.

Conclusions

Evolocumab reduced LDL-C levels by 50% or greater in more than 90% of patients and by 30% or greater in more than 99% of patients. These findings provide reassurance that LDL-C level can be robustly reduced with evolocumab without concern for considerable individual-level variability in response.

ARTICLE INFORMATION

Accepted for Publication: October 23, 2018.

Published Online: December 12, 2018. doi:10.1001/jamacardio.2018.4178

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Author Contributions: Drs Qamar and Sabatine had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition, analysis, or interpretation of data: Qamar, Giugliano, Kuder, Murphy, Kurtz, Wasserman, Pedersen, Sabatine.
Drafting of the manuscript: Qamar, Kuder.
Critical revision of the manuscript for important intellectual content: Qamar, Giugliano, Murphy, Kurtz, Wasserman, Sever, Pedersen, Sabatine.
Statistical analysis: Qamar, Kuder, Murphy, Sever.
Obtained funding: Wasserman.
Administrative, technical, or material support: Wasserman.
Supervision: Giugliano, Wasserman, Pedersen.

Conflict of Interest Disclosures: Dr Qamar reports receiving support from the National Heart, Lung, and Blood Institute T32 postdoctoral training grant (grant T32HL007604) and the American Heart Association Strategically Focused Research Network in Vascular Disease grant (grants 18SFRN33900085 and 18SFRN33960262). Dr Giugliano reports receiving grants from Amgen during the conduct of the study, grants and personal fees from Merck, and personal fees from Akcea, American College of Cardiology, BristolMyers Squibb, CVS Caremark, Daiichi Sankyo, GlaxoSmithKline, Janssen, Pfizer, and Sanofi. Dr Keech reports receiving grants and personal fees from Abbott and Mylan and personal fees from Amgen Inc, AstraZeneca, and Pfizer. Ms Kuder reports grants from Abbott Laboratories, grants from Amgen, AstraZeneca, Critical Diagnostics, Daiichi Sankyo, Eisai, GlaxoSmithKline, Intarcia, Merck, Roche Diagnostics, Takeda, Gilead, Poxel, Novartis, MedImmune, Janssen Research Development, Genzyme, and Pfizer. Ms Murphy reports receiving grants from Abbott Laboratories, Amarin, Amgen, AstraZeneca, Critical Diagnostics, Daiichi Sankyo, Eisai, GlaxoSmithKline, Intarcia Therapeutics, Merck and Co, Roche Diagnostics, Takeda, Gilead, Poxel, Novartis, MedImmune, Janssen Research Development, and Genzyme and personal fees from Amgen. Dr Kurtz is an employee of Amgen and reports support from Amgen Inc during the conduct of the study. Dr Wasserman is an employee of Amgen and reports support from Amgen Inc during the conduct of the study. Dr Sever reports receiving grants and personal fees from Amgen and Pfizer. Dr Pedersen reports receiving grants and personal fees from Amgen during the conduct of the study and personal fees from Amgen, Sanofi, Boehringer Ingelheim, the Medicines Company, and Merck and Co. Dr Sabatine reports research grant support through Brigham and Women's Hospital from Abbott Laboratories, Amgen, AstraZeneca, Critical Diagnostics, Daiichi Sankyo, Eisai, Genzyme, Gilead, GlaxoSmithKline, Intarcia, Janssen Research and Development, Medicines Company, MedImmune, Merck, Novartis, Poxel, Pfizer, Roche Diagnostics, and Takeda and personal fees from Alnylam, BristolMyers Squibb, CVS Caremark, Dyrnamix, Esperion, Ionis, and MyoKardia. No other disclosures are reported.

Funding/Support: The FOURIER trial was supported by a research grant from Amgen.

Role of the Funder/Sponsor: The FOURIER trial was designed, conducted, and managed in a collaborative effort between the FOURIER Executive and Steering Committees, the FOURIER Investigators, and the sponsor, Amgen Inc. The sponsor also collected the data. However, Amgen Inc played no role in the analysis and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: Dr Sabatine is Deputy Editor of *JAMA Cardiology*, but he was not involved in any of the decisions regarding review of the manuscript or its acceptance.

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