JAMA Cardiology | **Brief Report**

# Clinical Efficacy and Safety of Evolocumab in High-Risk Patients Receiving a Statin
## Secondary Analysis of Patients With Low LDL Cholesterol Levels and in Those Already Receiving a Maximal-Potency Statin in a Randomized Clinical Trial

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**IMPORTANCE** Current guidelines for atherosclerotic cardiovascular disease focus on high-intensity statins and targeting or using a threshold low-density lipoprotein cholesterol (LDL-C) level of less than 70 mg/dL for the highest-risk patients. Whether further reduction of LDL-C beyond these boundaries would be beneficial is unknown.

**OBJECTIVE** To compare outcomes of evolocumab vs placebo in patients with stable atherosclerotic cardiovascular disease and a baseline LDL-C of less than 70 mg/dL and in those receiving background treatment with a maximal-potency statin.

**DESIGN, SETTING, AND PARTICIPANTS** This secondary ad hoc analysis of the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial compared randomized treatments in 2 subgroups of patients with stable atherosclerotic cardiovascular disease currently receiving statin. Patients were classified by a baseline LDL-C of less than 70 or at least 70 mg/dL and by statin intensity (maximal: atorvastatin calcium, 80 mg/d, or rosuvastatin, 40 mg/d; submaximal: all other dosages). Patients with baseline LDL of less than 70 mg/dL either had a final screening LDL-C of at least 70 mg/dL or a final screening non–high-density lipoprotein cholesterol level of at least 100 mg/dL. Data were retrieved from 2013 to 2016 and analyzed in 2017 based on intention to treat.

**MAIN OUTCOMES AND MEASURES** The primary efficacy endpoint was the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The secondary efficacy endpoint was the composite of cardiovascular death, myocardial infarction, or stroke. Safety outcomes included adverse events and events of interest identified in the FOURIER trial. Interaction testing was used to assess the consistency of results in patients who did vs did not satisfy the above criteria.

**RESULTS** A total of 27 564 patients (75.4% men and 24.6% women; mean [SD] age, 62.5 [9.0] years) were included in the analysis. Of 2034 patients (7.4%) who had a baseline LDL-C of less than 70 mg/dL, evolocumab reduced the risk for the primary endpoint (hazard ratio [HR], 0.80; 95% CI, 0.60-1.07) to a similar degree as in the 25 529 patients who had baseline LDL-C of at least 70 mg/dL (HR 0.86; 95% CI, 0.79-0.92; *P* = .65 for interaction; 1 patient was missing baseline LDL-C data). Of 7533 patients (27.3%) receiving maximal-potency statins, evolocumab significantly reduced the primary endpoint (HR, 0.86; 95% CI, 0.75-0.98) to a similar degree as in the 20 031 patients not receiving a maximal-potency statin (HR, 0.85; 95% CI, 0.78-0.93; *P* = .88 for interaction). The key secondary endpoint was reduced to a similar degree in both analyses. No major safety concerns were identified.

**CONCLUSIONS AND RELEVANCE** Evolocumab was equally effective in reducing cardiovascular events in patients with stable atherosclerotic cardiovascular disease regardless of whether the baseline LDL-C was less than 70 or at least 70 mg/dL and whether the background statin was of maximal or submaximal potency.

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Several guidelines endorse a target low-density lipoprotein cholesterol (LDL-C) level of less than 70 mg/dL (to convert to millimoles per liter, multiply by 0.0259) or a threshold for treatment of at least 70 mg/dL in the highest-risk patients for secondary prevention of cardiovascular events.[1-4] Likewise, high-intensity statin regimens (ie, atorvastatin calcium, ≥40 mg/d, or rosuvastatin, ≥20 mg/d) are recommended as foundational therapy. Whether more intensive lowering of LDL-C levels would benefit patients who already have an LDL-C level of less than 70 mg/dL or patients who are currently receiving maximal-potency statin therapy (highest doses possible) is, to our knowledge, unknown. We explored the efficacy and safety of evolocumab vs placebo in such patients in the Further Cardiovascular Outcomes Research With PCSK9 (proprotein convertase subtilisin/kexin type 9) Inhibition in Subjects With Elevated Risk (FOURIER) trial.[5,6]

## Methods

### Study Design and Treatment

The design of the FOURIER trial has been reported elsewhere.[5,6] In brief, 27 564 patients with prior myocardial infarction, non-hemorrhagic stroke, or symptomatic peripheral artery disease and additional characteristics that placed them at higher cardiovascular risk (including 1 major and 2 minor criteria[5]) were randomized to receive the PCSK9 inhibitor evolocumab or placebo. Eligible patients had an LDL-C level of at least 70 mg/dL or a non-high-density lipoprotein cholesterol (non-HDL-C) level of at least 100 mg/dL at the end of screening while receiving moderate- or high-intensity statin therapy (defined as atorvastatin calcium, ≥20 mg/d, or the equivalent). In the FOURIER trial, LDL-C level was calculated on the basis of the Friedewald equation unless the calculated value was less than 40 mg/dL or the measured triglyceride level was greater than 400 mg/dL (to convert to millimoles per liter, multiply by 0.0113), in which case ultracentrifugation was performed. In the present ad hoc analysis, we compared outcomes of evolocumab treatment vs placebo in the following 2 subgroups: (1) patients with a baseline LDL-C level (the mean of the values obtained at the final screening visit and the day of randomization) of less than 70 (who either had a final screening LDL-C of at least 70 mg/dL or a final screening non-HDL-C of at least 100 mg/dL) vs at least 70 mg/dL and (2) patients receiving a maximal-potency background statin (ie, atorvastatin calcium, 80 mg/d, or rosuvastatin, 40 mg/d) vs submaximal statin at randomization. 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), and each patient provided written informed consent.

### Study Outcomes

Study data were retrieved from 2013 to 2016. The primary endpoint of the FOURIER trial was the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization; the key secondary endpoint was the composite of cardiovascular death, myocardial infarction, or stroke.[5,6] Safety endpoints included overall adverse events and adverse events of interest, including allergic and injection site reactions, and adverse events related to muscle symptoms, elevations in creatine kinase or transaminase levels, cataracts, new-onset diabetes, and neurocognitive events.

### Statistical Analysis

Data were analyzed in 2017. We compared baseline categorical variables using $\chi^2$ or Fisher exact tests and continuous variables using the Wilcoxon rank sum test. Efficacy analyses were performed in the intention-to-treat population, including all patients who underwent randomization and provided written informed consent. Hazard ratios (HRs) and 95% CIs of the time to the first efficacy event were generated using a Cox proportional hazards model, and $P$ values for time-to-event analyses were calculated using log-rank tests, with $P < .05$ indicating significance. Safety evaluations included all the patients who underwent randomization, who received at least 1 dose of a study agent, and for whom postdose data were available. Interaction testing was performed using Cox proportional hazards models for efficacy endpoints and logistic regression for safety endpoints.

## Results

### Patients With a Baseline LDL-C Level of Less Than 70 mg/dL

A total of 27 564 patients (75.4% men and 24.6% women; mean [SD] age, 62.5 [9.0] years) were included in the analysis. Baseline LDL-C level was unavailable for 1 patient. A total of 2034 patients (7.4%) had a baseline LDL-C level of less than 70 mg/dL. Compared with the 25 529 patients with LDL-C levels of at least 70 mg/dL at baseline, these patients tended to be younger (mean [SD] age, 62.1 [9.2] vs 62.5 [9.0] years) and have greater weight (mean [SD] weight, 88.2 [18.2] vs 85.0 [17.2] kg) and were more likely to be male (1632 [80.2%] vs 19 162 [75.1%]) and have had a prior stroke (430 [21.1%] vs 4907 [19.2%]), hypertension (1673 [82.3%] vs 20 410 [80.0%]), diabetes (987

Table 1. Patient Characteristics Stratified by Baseline LDL-C Level and Background Statin Intensity[a]

| Characteristic | Baseline LDL-C Level, mg/dL (N = 27 563)[b] | | | Baseline Statin Potency (N = 27 564) | | |
| | <70 (n = 2034)[c] | ≥70 (n = 25 529) | P Value | Maximal[d] (n = 7533) | Submaximal (n = 20 031) | P Value |
| --- | --- | --- | --- | --- | --- | --- |
| Age, mean (SD), y | 62.1 (9.2) | 62.5 (9.0) | .051 | 61.1 (8.9) | 63.0 (9.0) | <.001 |
| Weight, mean (SD), kg | 88.2 (18.2) | 85.0 (17.2) | <.001 | 88.2 (17.6) | 84.2 (17.2) | <.001 |
| Male | 1632 (80.2) | 19 162 (75.1) | <.001 | 5722 (76.0) | 15 073 (75.2) | .22 |
| White race[e] | 1708 (84.0) | 21 749 (85.2) | .14 | 7027 (93.3) | 16 431 (82.0) | <.001 |
| Region | | | | | | |
| North America | 348 (17.1) | 4223 (16.5) | | 1877 (24.9) | 2694 (13.4) | |
| Europe | 1226 (60.3) | 16 108 (63.1) | <.001 | 4862 (64.5) | 12 473 (62.3) | <.001 |
| Latin America | 178 (8.8) | 1645 (6.4) | | 180 (2.4) | 1643 (8.2) | |
| Asia, Pacific, South Africa | 282 (13.9) | 3553 (13.9) | | 614 (8.2) | 3221 (16.1) | |
| Type of atherosclerosis[f] | | | | | | |
| Myocardial infarction | 1591 (78.2) | 20 759 (81.3) | <.001 | 6499 (86.3) | 15 852 (79.1) | <.001 |
| Nonhemorrhagic stroke | 430 (21.1) | 4907 (19.2) | .04 | 1182 (15.7) | 4155 (20.7) | <.001 |
| Peripheral artery disease | 276 (13.6) | 3366 (13.2) | .62 | 1012 (13.4) | 2630 (13.1) | .51 |
| Cardiovascular risk factors | | | | | | |
| Hypertension | 1673 (82.3) | 20 410 (80.0) | .01 | 6019 (79.9) | 16 065 (80.2) | .57 |
| Diabetes | 987 (48.5) | 9093 (35.6) | <.001 | 2536 (33.7) | 7545 (37.7) | <.001 |
| Metabolic syndrome | 1481 (72.8) | 14 869 (58.2) | <.001 | 4501 (59.8) | 11 850 (59.2) | .38 |
| Current cigarette use | 544 (26.7) | 7232 (28.3) | .13 | 2067 (27.4) | 5710 (28.5) | .08 |
| TIMI Risk Score for secondary prevention, mean (SD)[g] | 3.4 (1.2) | 3.3 (1.2) | <.001 | 3.3 (1.3) | 3.3 (1.2) | .002 |
| Statin intensity at baseline[h] | | | .02 | | | |
| High | 1365 (67.1) | 17 737 (69.5) | NA | 7533 (100) | 11 570 (57.8) | NA |
| Atorvastatin calcium, 80 mg/d, or rosuvastatin, 40 mg/d | 524 (25.8) | 7008 (27.5) | .10 | 7533 (100) | 0 | NA |
| Moderate | 667 (32.8) | 7725 (30.3) | NA | 0 | 8392 (41.9) | NA |
| Low, unknown, or no data | 2 (0.1) | 67 (0.3) | NA | 0 | 69 (0.3) | NA |
| Ezetimibe treatment | 83 (4.1) | 1357 (5.3) | .02 | 672 (8.9) | 768 (3.8) | <.001 |
| Other cardiovascular medications[i] | | | | | | |
| Aspirin and/or P2Y$_{12}$ inhibitor | 1875 (92.2) | 23 556 (92.4) | .77 | 7122 (94.6) | 18 310 (91.5) | <.001 |
| β-Blocker | 1582 (77.8) | 19 232 (75.4) | .02 | 6056 (80.4) | 14 759 (73.8) | <.001 |
| Renin-angiotensin-aldosterone inhibitor | 1626 (79.9) | 19 906 (78.1) | .047 | 6016 (79.9) | 15 517 (77.5) | <.001 |
| Lipid levels, median (IQR), mg/dL | | | | | | |
| LDL-C | 65.5 (61.0-68.0) | 93.5 (82.0.110.5) | NA | 93.0 (80.0-111.5) | 91.0 (79.5-107.5) | <.001 |
| Total cholesterol | 141.0 (132.0-152.0) | 170.0 (153.5-190.5) | NA | 168.0 (150.5-190.5) | 167.0 (151.0-187.5) | .004 |
| HDL-C | 38.5 (32.5.47.0) | 44.0 (37.5-52.5) | NA | 43.0 (36.5-51.5) | 44.0 (37.0-53.0) | <.001 |
| Triglycerides | 181.0 (115.0-252.0) | 131.0 (99.5-177.0) | NA | 133.0 (98.5-181.0) | 133.0 (100.0-182.0) | .19 |
| LDL-C level <70 mg/dL at baseline | 2034 (100) | 0 | NA | 524 (7.0) | 1510 (7.5) | .10 |

Abbreviations: HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; NA not applicable; TIMI, Thrombolysis in Myocardial Infarction.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millomoles per liter, multiply by 0.0113.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and may not total 100. We found no nominally significant differences between the randomized treatments in either group stratified by baseline LDL-C level or stratified by baseline maximal statin potency except for baseline triglyceride in the submaximal statin intensity subgroup (P = .05).

[b] Baseline LDL-C data were not available for 1 patient.

[c] These patients either had a final screening LDL-C of at least 70 mg/dL or a final screening non–HDL-C level of at least 100 mg/dL.

[d] Maximal statin potency indicates atorvastatin calcium, 80 mg/d, or rosuvastatin, 40 mg/d. All other statin regimens were considered to be submaximal.

[e] Reported by the patients.

[f] Patients could have more than 1 type of atherosclerosis.

[g] As described by Bohula et al,[7] scores range from 0 to 9, with higher scores indicating higher risk.

[h] Categorized in accordance with the guidelines of the American College of Cardiology and American Heart Association.[4]

[i] Owing to missing patient data, denominators may be less than column headings.

Figure 1. Efficacy Outcomes Stratified by Baseline Low-Density Lipoprotein Cholesterol (LDL-C) Levels and Intensity of Background Statin Treatment
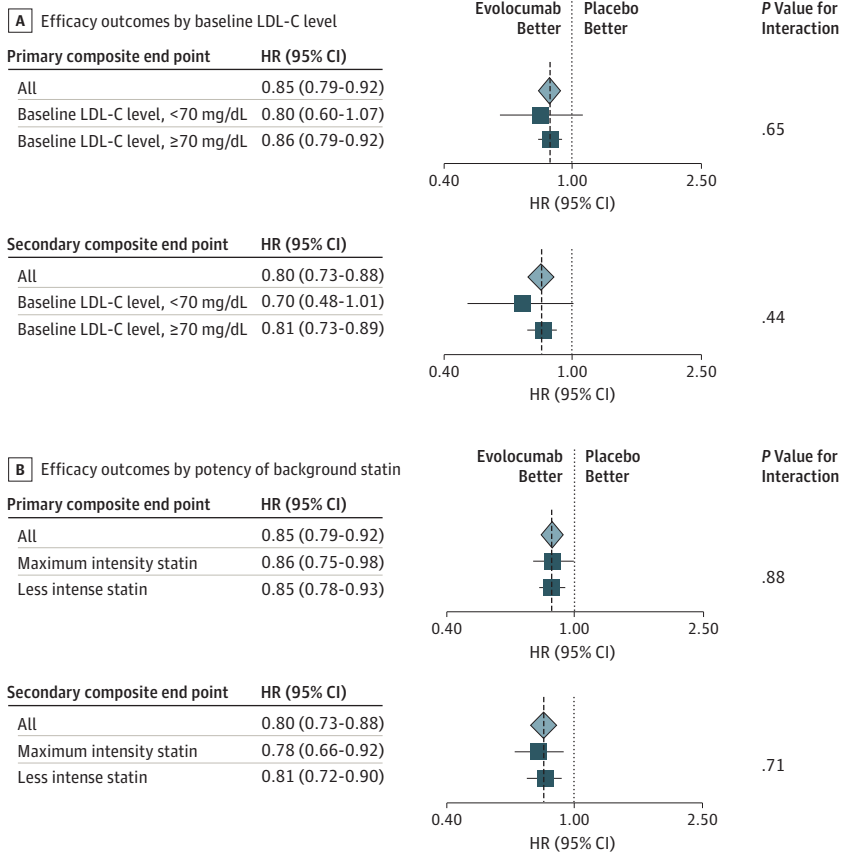


Hazard ratios (HRs) and 95% CIs are shown for the primary (composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, and coronary revascularization) and the key secondary (composite of cardiovascular death, myocardial infarction, and stroke) efficacy composite endpoints in the total population and (A) in patients with baseline LDL-C levels of less than 70 mg/dL vs those with LDL-C levels of at least 70 mg/dL and (B) in patients treated with maximal (atorvastatin calcium, 80 mg/d, or rosuvastatin, 40 mg/d) and submaximal background statin therapy.

[48.5%] vs 9093 [35.6%]), and metabolic syndrome (1481 [72.8%] vs 14 869 [58.2%]) (Table 1).[7] The median baseline LDL-C level was 65.5 mg/dL (interquartile range [IQR], 61.0-68.0 mg/dL). In this subgroup, 1030 patients (51%) had a baseline non-HDL-C level of at least 100 mg/dL and 1004 patients (49%) had a non-HDL-C level less than 100 mg/dL.

At 48 weeks, the least-squares mean percentage reduction in LDL-C level with evolocumab treatment, compared with placebo, was 66%, for a mean absolute reduction of 42 mg/dL and a median achieved concentration at 48 weeks of 21.0 mg/dL (IQR, 11.5-37.0 mg/dL). Evolocumab reduced the risk for the primary composite endpoint by 20% (HR, 0.80; 95% CI, 0.60-1.07) in patients with a baseline LDL-C level of less than 70 mg/dL and by 14% (HR, 0.86; 95% CI, 0.79-0.92) in patients with an LDL-C level of at least 70 mg/dL, with no evidence of treatment effect modification by baseline LDL-C (*P* = .65 for interaction) (**Figure 1**A). Likewise, evolocumab reduced the risk for the key secondary endpoint by 30% (HR, 0.70; 95% CI, 0.48-1.01) in patients with a baseline LDL-C level of less than 70 mg/dL (**Figure 2**A) and by 19% (HR, 0.81; 95% CI, 0.73-0.89) in patients with an LDL-C level of at least 70 mg/dL, with no evidence of treatment effect modification owing to baseline LDL-C level (*P* = .44 for interaction) (Figure 1A). We found no heterogeneity for any of the individual outcomes (eTable 1 in the Supplement).

Likewise, we found no heterogeneity in the safety profile of evolocumab as a function of baseline LDL-C level (**Table 2**).

## Patients Receiving a Maximal-Potency Statin

A total of 7533 patients (27.3%) were receiving a maximal-intensity statin (baseline characteristics are shown in Table 1). The median baseline LDL-C level was 93.0 mg/dL (IQR, 80.0-111.5 mg/dL). At 48 weeks, the least-squares mean percentage reduction in LDL-C levels with evolocumab, compared with placebo, was 58%, for a mean absolute reduction of 57 mg/dL; the median achieved LDL-C concentration at 48 weeks was 32.0 mg/dL (IQR, 20.0-49.0 mg/dL). Evolocumab reduced the risk for the primary composite endpoint by 14% (HR, 0.86; 95% CI, 0.75-0.98) in patients receiving maximal-potency statin therapy and by 15% (HR, 0.85; 95% CI, 0.78-0.93) in patients treated with a submaximal statin, with no evidence of treatment effect modification owing to background statin intensity (*P* = .88 for interaction) (Figure 1B). Likewise, evolocumab reduced the risk for the key secondary endpoint by 22% (HR, 0.78; 95% CI, 0.66-0.92) in patients receiving maximal-potency statin therapy (Figure 2B) and by 19% (HR, 0.81; 95% CI, 0.72-0.90) in patients receiving less potent statin regimens, with no evidence of treatment effect modification owing to intensity of background statin therapy (*P* = .71 for interaction) (Figure 1B). We

**Figure 2. Cumulative Event Rate of the Key Secondary Endpoint With Evolocumab vs Placebo**

A  Cardiovascular death, myocardial infarction, or stroke in patients with baseline LDL-C level <70 mg/dL

HR, 0.70; 95% CI, 0.48-1.01

B  Cardiovascular death, myocardial infarction, or stroke in patients receiving maximal potency background statin

HR, 0.78; 95% CI, 0.66-0.92

No. at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| Placebo group | 1004 | 985 | 963 | 901 | 608 | 293 |
| Evolocumab group | 1030 | 1014 | 989 | 939 | 616 | 270 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Placebo group | 3775 | 3684 | 3596 | 3501 | 2590 | 1581 |
| Evolocumab group | 3758 | 3684 | 3614 | 3517 | 2616 | 1582 |

Cumulative event rate of the key secondary endpoint with evolocumab compared with placebo in (A) patients with a baseline LDL-C level of less than 70 mg/dL (evolocumab vs placebo, 5.2% vs 7.7%) and (B) in patients treated with a maximal-potency statin (evolocumab vs placebo, 6.8% vs 8.9%). To convert cholesterol levels to to millimoles per liter, multiply by 0.0259.

**Table 2. Safety Outcomes of Evolocumab Treatment vs Placebo Stratified by Baseline LDL-C Levels[a]**

| Outcome | Baseline LDL-C Level | | | |
|---|---|---|---|---|
| | <70 mg/dL (n = 2033)[b] | | ≥70 mg/dL (n = 25 491) | |
| | Evolocumab (n = 1030) | Placebo (n = 1003) | Evolocumab (n = 12 739) | Placebo (n = 12 752) |
| Serious adverse event | 268 (26.0) | 274 (27.3) | 3142 (24.7) | 3130 (24.5) |
| Adverse event related to study drug and leading to therapy discontinuation | 19 (1.8) | 19 (1.9) | 207 (1.6) | 182 (1.4) |
| Injection site reaction | 30 (2.9)[c] | 16 (1.6) | 266 (2.1)[c] | 203 (1.6) |
| Muscle-related event | 49 (4.8) | 60 (6.0) | 633 (5.0) | 596 (4.7) |
| Cataract | 19 (1.8) | 16 (1.6) | 209 (1.6) | 226 (1.8) |
| New-onset diabetes (CEC adjudicated)[d] | 45/509 (8.8) | 53/475 (11.2) | 632/7828 (8.1) | 591/7864 (7.5) |
| Neurocognitive event | 17 (1.7) | 12 (1.2) | 200 (1.6) | 190 (1.5) |
| AST or ALT level >3 times normal[e] | 27 (2.7) | 23 (2.3) | 213 (1.7) | 219 (1.7) |
| Creatine kinase level >5 times normal | 9 (0.9) | 9 (0.9) | 86 (0.7) | 90 (0.7) |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CEC, Clinical End Point Committee; LDL-C, low-density lipoprotein cholesterol.

SI conversion factor: To convert LDL-C to millimoles per liter, multiply by 0.0259.

[a] Baseline LDL-C level was not available for 1 patient, and 39 patients who did not receive the study drug were excluded. Unless otherwise indicated, data are expressed as number (percentage) of patients. No significant treatment × subgroup interaction was found.

[b] These patients either had a final screening LDL-C of at least 70 mg/dL or a final screening non–high-density lipoprotein cholesterol level of at least 100 mg/dL.

[c] Nominal P < .05 vs placebo.

[d] Patients with prevalent diabetes were excluded.

[e] Owing to missing patient data, denominators may be less than column headings.

found no heterogeneity for any of the individual outcomes (eTable 2 in the Supplement). In addition, we found no heterogeneity in the safety profile of evolocumab as a function of intensity of background statin therapy (**Table 3**).

## Discussion

The principal findings of this analysis were that high-risk patients with stable atherosclerotic cardiovascular disease who were treated with statins derived similar clinical ben-

efit with the addition of evolocumab during a median follow-up of 2.2 years regardless of whether the baseline LDL-C level was below 70 or at least 70 mg/dL and regardless of the intensity of background statin therapy (maximal vs submaximal). Patients enrolled with LDL-C levels of less than 70 mg/dL represented patients who either had a final screening LDL-C of at least 70 mg/dL or a final screening non–HDL-C level of at least 100 mg/dL; thus, these patients were more likely to have diabetes or metabolic syndrome and on average were younger and had more cardiovascular risk factors.

Table 3. Safety Outcomes of Evolocumab Treatment vs Placebo Stratified by Potency of a Background Statin[a]

| Outcome | Maximal Potency Background Statin (n = 7524) | | Submaximal Potency Background Statin (n = 20 001) | |
|---|---|---|---|---|
| | Evolocumab (n = 3754) | Placebo (n = 3770) | Evolocumab (n = 10 015) | Placebo (n = 9986) |
| Serious adverse event | 979 (26.1) | 1010 (26.8) | 2431 (24.3) | 2394 (24.0) |
| Adverse event related to study drug and leading to drug discontinuation | 53 (1.4) | 53 (1.4) | 173 (1.7) | 148 (1.5) |
| Injection site reaction | 84 (2.2) | 68 (1.8) | 212 (2.1)[b] | 151 (1.5) |
| Muscle-related event | 207 (5.5) | 194 (5.1) | 475 (4.7) | 462 (4.6) |
| Cataract | 53 (1.4) | 64 (1.7) | 175 (1.7) | 178 (1.8) |
| New-onset diabetes (CEC adjudicated)[c] | 214/2385 (9.0)[b] | 176/2383 (7.4) | 463/5952 (7.8) | 468/5956 (7.9) |
| Neurocognitive event | 64 (1.7) | 63 (1.7) | 153 (1.5) | 139 (1.4) |
| AST or ALT level >3 times normal[d] | 84 (2.3) | 81 (2.2) | 156 (1.6) | 161 (1.6) |
| Creatine kinase level >5 times normal[d] | 28 (0.8) | 33 (0.9) | 67 (0.7) | 66 (0.7) |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CEC, Clinical End Point Committee; LDL-C, low-density lipoprotein cholesterol.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients in the safety cohort. No significant treatment × subgroup interaction was found.

[b] Nominal $P < .05$ vs placebo.

[c] Patients with prevalent diabetes were excluded.

[d] Owing to missing patient data, denominators may be less than column headings.

These findings extend prior observations reported with other therapies to lower lipid levels. For statins, the meta-analysis by the Cholesterol Treatment Trialists Collaboration[8] oted consistent benefit in patients starting with an LDL-C level of less than 77 mg/dL, but because of the range of baseline LDL-C levels in these trials, few patients would have had an LDL-C level of less than 70 mg/dL. The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)[9] reported a consistent benefit of statin therapy in patients starting with an LDL-C level of no more than 60 mg/dL, but only 511 individuals were in that subgroup and the comparator was placebo. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)[10] recently showed that the addition of ezetimibe to a background moderate-intensity statin (simvastatin, 40 mg/d) reduced cardiovascular events by 6.4% during a median of 6 years after acute coronary syndrome, with consistent benefit even among patients in the lowest quartile of baseline LDL-C level (<64 mg/dL); however, the achieved LDL-C level in that subgroup with the combination of ezetimibe and simvastatin was 45 mg/dL.[11] More recently, the Heart Protection Study 3/Thrombolysis in Myocardial Infarction 55-Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification (HPS3/TIMI55-REVEAL) Collaborative Group[12] reported that patients with stable atherosclerotic disease and a baseline mean LDL-C level of 61 mg/dL who were randomized to the cholesterol ester transfer protein inhibitor anacetrapib had reduced mean LDL-C levels to 53 mg/dL and experienced an 9% reduction in major coronary events compared with those randomized to placebo. In the present analysis, we showed consistent benefit when starting with an LDL-C level of less than 70 mg/dL; the LDL-C levels were lowered by 66% to a median of 21.0 mg/dL, with 25% of patients having an LDL-C level of less than 11.5 mg/dL.

## Strengths and Limitations

The consistent clinical benefit seen with randomized allocation to therapy that reduced LDL-C to a median concentration of 21 mg/dL supports and extends observational analyses that have shown that achievment of progressively lower LDL-C levels was associated with further reductions of major cardiovascular events.[13-15] Before the FOURIER trial, no nonstatin therapy had shown clinical benefit when added to a background of maximal statin therapy. Last, the safety profile of evolocumab was consistent regardless of baseline LDL-C level or intensity of statin therapy. All patients in the FOURIER trial were at high risk, and a minority received ezetimibe; whether patients at lower risk or receiving ezetimibe and maximal statin would have similar benefit requires additional studies.

## Conclusions

Evolocumab safely reduced cardiovascular events in patients with stable atherosclerotic cardiovascular disease to a similar degree whether the baseline LDL-C level was less than or at least 70 mg/dL and regardless of whether the background statin dosage was maximal or submaximal intensity. These findings support using evolocumab beyond what is recommended in current guidelines and, more broadly, the value of lowering LDL-C levels to approximately 20 mg/dL,[16] even in high-risk patients starting at levels below current guideline targets or thresholds for treatment.

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