Efficacy and Safety of PCSK9 Inhibition With Evolocumab in Reducing Cardiovascular Events in Patients With Metabolic Syndrome Receiving Statin Therapy
Secondary Analysis From the FOURIER Randomized Clinical Trial

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IMPORTANCE The PCSK9 inhibitor evolocumab reduced low-density lipoprotein cholesterol and cardiovascular events in the FOURIER randomized clinical trial. Patients with metabolic syndrome (MetS) are at increased cardiovascular risk.

OBJECTIVE To investigate outcomes with evolocumab in patients with and without MetS.

DESIGN, SETTING, AND PARTICIPANTS The FOURIER trial randomized patients worldwide with stable atherosclerotic cardiovascular disease receiving statin to evolocumab vs placebo with follow-up for a median of 2.2 years. Data were collected February 2013 to November 2016. For this prespecified analysis, patients with the requisite data were stratified based on the National Cholesterol Education Program Adult Treatment Panel III MetS criteria; in secondary analyses, patients were further substratified by diabetes at baseline. Analysis was intention to treat. Analysis began March 2018 and ended April 2020.

INTERVENTIONS Patients were randomized to evolocumab or placebo.

MAIN OUTCOMES AND MEASURES The primary end point was cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary end point was cardiovascular death, myocardial infarction, or stroke.

RESULTS Of 27,342 patients (mean [SD] age, 63 [9] years; 20,623 men [75.4%]) included in this analysis, 16,361 (59.8%) with baseline MetS were, when compared with patients without MetS, at higher risk of cardiovascular events (adjusted hazard ratio [95% CI], 1.31 [1.18-1.46]; \( P < .001 \) for the primary and 1.38 [1.20-1.57]; \( P < .001 \) for the key secondary end point).

Evolocumab reduced low-density lipoprotein cholesterol similarly in patients with MetS (median [interquartile range], 92 [79-109] mg/dL vs 30 [19-48] mg/dL; \( P < .001 \)) and without MetS (median [interquartile range], 92 [81-108] mg/dL vs 29 [18-44] mg/dL; \( P < .001 \)). For the primary end point, the hazard ratios (95% CI) with evolocumab vs placebo were 0.83 (0.76-0.91) and 0.89 (0.79-1.01) in patients with and without MetS \( (P \) for interaction = .39). For the key secondary end point, the corresponding hazard ratios (95% CIs) were 0.76 (0.68-0.86) and 0.86 (0.74-1.01) \( (P \) for interaction = .23), respectively. Evolocumab did not increase the risk of new-onset diabetes or other major safety outcomes including worsening glycemic control, compared with placebo in patients with MetS.

CONCLUSIONS AND RELEVANCE Patients with atherosclerotic cardiovascular disease and MetS have substantial residual risk of cardiovascular events despite statin therapy. Evolocumab significantly reduced low-density lipoprotein cholesterol and cardiovascular risk in patients with MetS without increasing new-onset diabetes, worsening glycemic control, or other major safety events. These data suggest the addition of evolocumab to statin therapy in patients with atherosclerotic cardiovascular disease and MetS is safe and efficacious to reduce residual cardiovascular risk.

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**Metabolic syndrome (MetS)** is a constellation of several metabolic and cardiovascular (CV) risk factors that include obesity and visceral adiposity, insulin resistance, glucose intolerance, hypertension, and atherogenic dyslipidemia. Because of the high incidence and increasing prevalence of overweight and obesity in the world, there are currently a large number of patients with MetS worldwide, and these numbers are increasing. It is known that patients with MetS are at an increased risk of developing diabetes and major adverse CV events (MACE). The 2018 US multisociety cholesterol guidelines have emphasized the importance of MetS by listing it as one of the risk-enhancing factors for MACE. Because of the associated atherogenic dyslipidemia and the increased risk of developing MACE, lipid-lowering therapy with statins is recommended for patients with MetS. Prior studies have shown that intensive lipid-lowering therapy with high-dose statins in patients with MetS and atherosclerotic CV disease (ASCVD) significantly reduced the risk of MACE. However, despite treatment with high-intensity statins, these patients continue to have a residual risk and are at high risk of developing MACE. Also, because these patients have or are at risk of developing diabetes, there is concern that treatment with statins further increases their risk of developing diabetes, either due to the drug itself or by affecting transmembrane cholesterol transport.

Recently, biologic agents targeting proprotein convertase subtilisin/kexin type 9 (PCSK9), when added to background statin therapy, have been shown to reduce low-density lipoprotein cholesterol (LDL-C) by 50% to 60% as well as reduce CV events. In the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial, treatment with evolocumab, a fully human monoclonal antibody targeting PCSK9, reduced the risk of MACE when added to moderate to high doses of statin therapy in patients with clinically evident ASCVD, including in patients with diabetes. However, the role of PCSK9 inhibition in reducing risk of MACE in patients with MetS has not been established. Consequently, we evaluated the efficacy and safety of treatment with evolocumab in patients with MetS in the FOURIER trial based on the definition established by the National Cholesterol Education Program Adult Treatment Panel III guidelines and endorsed by several other international scientific associations.

**Methods**

**Study Protocol**

The details of the FOURIER trial have been described previously, and the study protocol is available in Supplement 1. In brief, patients aged 40 to 85 years with ASCVD and additional CV risk factors (including diabetes, MetS, and others) were enrolled from February 2013 to June 2015. Clinically evident ASCVD was defined as prior myocardial infarction (MI), prior nonhemorrhagic stroke, or symptomatic peripheral arterial disease. A fasting LDL-C level of 70 mg/dL (to convert to millimoles per liter, multiply by 0.0259) or higher or non–high-density lipoprotein cholesterol (HDL-C) of 100

**Key Points**

**Question** Can further reduction of low-density lipoprotein cholesterol with evolocumab safely and effectively reduce the residual risk in patients with metabolic syndrome and stable atherosclerotic cardiovascular disease?

**Findings** In this prespecified analysis of the FOURIER randomized clinical trial of patients with atherosclerotic cardiovascular disease receiving statin, 16,361 individuals with metabolic syndrome were at higher risk for cardiovascular events than 10,981 patients without metabolic syndrome. In these high-risk patients, compared with placebo, evolocumab significantly reduced low-density lipoprotein cholesterol and the risk of cardiovascular events without increasing the risk of safety events, new-onset diabetes, or worsening glycemic control.

**Meaning** The PCSK9 inhibitor evolocumab significantly reduced cardiovascular events in patients with atherosclerotic cardiovascular disease and metabolic syndrome without an increase in serious safety events, including new-onset diabetes.

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Efficacy and Safety of PCSK9 Inhibition With Evolocumab in Reducing Cardiovascular Events

Original Investigation Research

End Points and Outcomes
The primary end point of the FOURIER trial was the composite of CV death, MI, stroke, coronary revascularization, or hospitalization for unstable angina; the key secondary end point was the composite of CV death, MI, or stroke. Safety was assessed through collection of adverse events and central laboratory testing. An independent clinical events committee, whose members were unaware of treatment assignment and lipid levels, adjudicated all efficacy end points and new-onset diabetes. Measures of worsening glycemic control included adjudicated new-onset diabetes, glycated hemoglobin A1c level 7.0% or higher at 48 weeks, and new use of insulin therapy after randomization. Definitions of the end points have been published previously. Diabetes was defined according to the American Diabetes Association and National Diabetes Information Clearinghouse definitions.

Statistical Analyses
For this analysis, patients were stratified into those with MetS or not (based on the Adult Treatment Panel III MetS criteria described earlier) and secondarily further stratified based on the presence or absence of diabetes. Baseline characteristics were compared using Kruskal-Wallis tests and χ2 tests for continuous and categorical data, respectively. All efficacy analyses of evolocumab vs placebo were conducted on an intention-to-treat basis (ie, all patients who were randomized were analyzed, regardless of study drug compliance). Safety evaluations included all randomized patients who received at least 1 dose of study treatment and for whom postdose data were available. Kaplan-Meier event rates were calculated through 3 years, and P values for time-to-event analyses were from log-rank tests. Hazard ratios (HRs) and 95% CIs for the effect of evolocumab vs placebo were generated using a Cox proportional hazards model. Effect modification by MetS subgroup on the efficacy of evolocumab was tested by incorporating interaction terms into Cox models. For the analysis of risk of CV outcomes in patients with vs without MetS in the placebo arm, a multivariable-adjusted HR was obtained from a Cox model that included the following covariates: age, sex, white race, history of MI, current smoking, history of heart failure, estimated eGFR less than 60 mL/min/1.73 m², baseline LDL-C, and high-intensity statin use. Schoenfeld residuals were assessed in the Cox models and the proportional hazards assumptions were not violated. SAS version 9.4 (SAS Institute) and Stata version 16.1 (StataCorp) were used. Two-sided P values less than .05 were considered significant. Analysis began March 2018 and ended April 2020.

Results
MetS was present in 16 361 of 27 342 patients (59.8%) enrolled in the FOURIER trial with available data on the criteria
for MetS. Among those with MetS, 7434 (45.4%) fulfilled 3 criteria, 5743 (35.1%) had 4, and 3184 (19.5%) had all 5 of the Adult Treatment Panel III MetS criteria. Patients with vs without MetS had numerous significant differences in baseline characteristics. In addition to expected differences in diabetes, body mass index, hypertension, HDL-C, and triglyceride levels, there also were significant differences in that patients with MetS were more likely to be women, were younger, had peripheral artery disease, and had lower eGFR (Table 1). A similar pattern of a greater prevalence of CV risk factors was evident in patients with metabolic syndrome (MetS) and those without MetS. Analyses

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Risk of MACE Related to Metabolic Syndrome
After adjusting for baseline parameters that included age, sex, white race, smoking, history of MI, history of heart failure, eGFR less than 60 mL/min/1.73 m², baseline LDL-C level, and high-intensity statin use, patients with MetS were found to be at significantly greater risk for the primary and key secondary end points (adjusted HR, 1.31; 95% CI, 1.18-1.46; P < .001 and adjusted HR, 1.38; 95% CI, 1.20-1.57; P < .001, respectively) (Figure 1).

Clinical Efficacy of Evolocumab
Evolocumab reduced the primary end point compared with placebo in patients with MetS (Kaplan-Meier rates at 3 years: 13.5% with evolocumab vs 15.8% with placebo; HR, 0.83; 95% CI, 0.76-0.91) and in patients without MetS (11.2% vs 12.9%; HR, 0.76; 95% CI, 0.68-0.86) to a similar degree (P for interaction = .39). Similarly, the key secondary end point was reduced by evolocumab in both patients with MetS (8.6% vs 10.9%; HR, 0.76; 95% CI, 0.68-0.86) and without MetS (6.8% vs 8.5%; HR, 0.86; 95% CI, 0.74-1.01, P for interaction = .23). Because clinicians often consider patients with diabetes and MetS to represent distinct subgroups and many patients with diabetes also have MetS, we analyzed the efficacy of evolocumab in 4 groups based on the presence or absence of diabetes and/or MetS. For the primary end point, the HRs (95% CIs) were diabetes and MetS, 0.85 (0.76-0.96); diabetes without MetS, 0.78 (0.60-1.01); MetS without diabetes, 0.80 (0.70-0.92); and neither diabetes nor MetS, 0.91 (0.76-1.09) (P for interaction = .47) (Figure 2). The absolute risk reduction (ARR) in the primary end point over 3 years with evolocumab in patients with diabetes and MetS was 2.1%; in patients with diabetes without MetS, 4.9%; in patients with MetS without diabetes, 2.5%; and in patients with neither, 0.9%. The number needed to treat was 47 in patients with diabetes and MetS, 20 in patients with diabetes without MetS, 41 in patients with MetS...
without diabetes, and 114 in those with neither. The HRs (95% CIs) for the secondary end point in these same 4 groups were diabetes and MetS, 0.84 (0.73-0.97); diabetes without MetS, 0.74 (0.54-1.01); MetS without diabetes, 0.65 (0.54-0.79); and neither MetS nor diabetes, 0.91 (0.76-1.09) (P for interaction = .07) (Figure 3).

Although the relative risk reductions with evolocumab did not statistically significantly differ between the 4 groups, they tended to be larger in patients with MetS, diabetes, or both compared with patients with neither. Given the higher baseline risk in these patients, the ARR with evolocumab also were numerically greater.

**Safety of Evolocumab**

The overall rates of adverse events and serious adverse events were similar in patients with vs without MetS (Table 2), with 1 exception. As expected, the incidence of new-onset diabetes was more common in patients with MetS than in patients without MetS (909 of 7746 [11.7%; 95% CI, 11.0%-12.5%] vs 404 of 8791 [4.6%; 95% CI, 4.2%-5.1%]; P < .001). However, there was no increase in new-onset diabetes or other measures of worsening glycemic control with evolocumab vs placebo in patients with or without MetS. The rates of other specific adverse events of interest were similar between treatment arms when stratified by MetS; the only exception was injection site reactions, which occurred more frequently (absolute increase in rates of 5-6 per 1000) in patients treated with evolocumab regardless of the presence or absence of MetS. No patients developed neutralizing antibodies.

**Discussion**

Our analyses yielded several important findings. First, among patients with ASCVD, the presence of MetS was common (60% of patients) and independently associated with a substantially increased residual risk of CV morbidity and mortality despite receiving statin therapy. Second, evolocumab lowered LDL-C and other atherogenic lipoproteins and significantly reduced the relative risk of CV events in patients with and with-
out MetS. Owing to their heightened baseline risk of CV events, patients with diabetes (without or without MetS) and those with MetS without diabetes had a numerically greater ARR with evolocumab therapy. Third, evolocumab did not increase the risk of serious adverse events in patients with MetS, including new-onset diabetes or worsening glycemia, over a median follow-up of 2.2 years.

The greater relative risk reductions in CV outcomes seen with LDL-C lowering with evolocumab in patients with MetS is supported by analogous observations for LDL-C lowering with statin therapy, as demonstrated in the Treating to New Target study.5 In the Treating to New Target study,5 the higher intensity statin therapy (atorvastatin, 80 mg) was associated with significantly greater reductions in CV events compared with lower-dose statin (atorvastatin, 10 mg), presumably owing to greater reduction in LDL-C.5 These findings, along with our results showing that patients with ASCVD and MetS continue to have significant residual risk for developing CV events while receiving statin therapy, have important therapeutic implications. The 2018 US multisociety cholesterol guidelines have emphasized MetS as a risk-enhancing factor.3 Our findings are in line with those recommendations and emphasize the need for aggressive LDL-C-reducing therapy in patients with MetS and ASCVD.18

Furthermore, our findings have implications from a health economics perspective, as our data provide additional guidance to clinicians in identifying high-risk patients who are likely to experience particularly large ARRs with the addition of PCSK9 inhibition. Specifically, patients with ASCVD and diabetes and those without diabetes but with MetS had the greatest absolute benefit. These observations are in line with the recommendations of professional societies that have focused on the ARR as a means by which to determine which patients should be treated with a PCSK9 inhibitor.19 The number needed to treat over 3 years to prevent 1 primary end point was 48 in patients with diabetes and MetS and 42 in patients with MetS without diabetes, suggesting that evolocumab use in patients with ASCVD with diabetes and MetS or MetS without diabetes might be especially attractive from a cost-effectiveness consideration.

The cumulative event rates for the key secondary efficacy end point (the composite of cardiovascular death, myocardial infarction, stroke) in the evolocumab and placebo treatment arms, in patients with diabetes and metabolic syndrome (A), diabetes without metabolic syndrome (B), metabolic syndrome without diabetes (C), neither diabetes nor metabolic syndrome (D) are displayed. P values were calculated using log-rank tests. Hazard ratios (HRs) and 95% CI are from a Cox model. The 4-way interaction P value was .07. ARR indicates absolute risk reduction; NNT, number needed to treat.

### Table

<table>
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<th>Group</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>ARR (%)</th>
<th>NNT</th>
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<td></td>
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<td><strong>B: Diabetes and no metabolic syndrome</strong></td>
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<tr>
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<td>.06</td>
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<td>Evolocumab</td>
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<td><strong>C: Metabolic syndrome and no diabetes</strong></td>
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Treatment with evolocumab was also safe in patients with MetS. In addition to providing reassurance that the overall safety profile was similar in patients with and without MetS, the risk of new-onset diabetes (as adjudicated using a centralized clinical events committee) and worsening glycemic control were similar in all treatment arms. Our findings are supported by similar observations from smaller data sets with the PCSK9 inhibitors alirocumab and bococizumab, neither of which was associated with an increased risk of new-onset diabetes.20,21 These data also complement a recent analysis in which there was no association between low levels of achieved LDL-C and the risk of developing diabetes.22 These findings are important, as it is well known that patients with MetS are at relatively higher risk of developing new-onset diabetes during treatment with statins.6,7

Limitations

This was a prespecified subgroup analysis from a randomized clinical trial that applied strict entry criteria; therefore, results may not apply to all patients in clinical practice. The trial was not powered for subgroup analyses, and results should be considered exploratory. Investigators identified the characteristics of MetS at randomization based on available clinical data and without independent review; thus, some degree of inconsistency and/or misclassification may have occurred.

Conclusions

Our results show that patients with ASCVD and MetS remain at high risk of future CV events despite receiving statin therapy. Treatment with evolocumab is associated with significant reductions in MACE in patients with ASCVD and MetS, regardless of the presence or absence of diabetes. Owing to their heightened baseline risk of CV events, patients with diabetes and/or MetS had greater numerical ARRs with evolocumab therapy than those with neither diabetes nor MetS. Evolocumab did not increase the risk of new-onset diabetes or worsen glycemic control. These data suggest that treatment with evolocumab in patients with ASCVD and diabetes or MetS is efficacious and safe. These results can be helpful in guiding the selection of patients who are most likely to benefit from treatment with PCSK9 inhibitor therapy.

ARTICLE INFORMATION

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Acquisition, analysis, or interpretation of data: Deedwania, Murphy, Scheen, Badariene, Lira Pineda, Honarpour, Pedersen, Sabatine, Giugliano.

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Administrative, technical, or material support: Deedwania, Lira Pineda, Giugliano.

Supervision: Deedwania, Badariene, Pedersen, Sabatine, Giugliano.

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Role of the Funding/Sponsor: FOURIER was designed in collaboration between the executive committee and Amgen, the trial sponsor. The protocol and amendments were approved by the relevant ethics committees at all participating sites. The sponsor was responsible for data collection. The raw database was provided to the TIMI Study Group, which conducted data analyses independently of the sponsor. The first draft of the manuscript was written by the first author. All coauthors participated in subsequent revisions of the manuscript. The executive committee assumes responsibility for the accuracy and completeness of the data and analyses.

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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