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# Effect of the PCSK9 Inhibitor Evolocumab on Total Cardiovascular Events in Patients With Cardiovascular Disease
## A Prespecified Analysis From the FOURIER Trial

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**IMPORTANCE** The PCSK9 inhibitor evolocumab reduced low-density lipoprotein cholesterol and first cardiovascular events in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial, but patients remain at high risk of recurrent cardiovascular events.

**OBJECTIVE** To evaluate the effect of evolocumab on total cardiovascular events, given the importance of total number of cardiovascular events to patients, clinicians, and health economists.

**DESIGN, SETTING, AND PARTICIPANTS** Secondary analysis of a randomized, double-blind clinical trial. The FOURIER trial compared evolocumab or matching placebo and followed up patients for a median of 2.2 years. The study included 27 564 patients with stable atherosclerotic disease receiving statin therapy. Data were analyzed between May 2017 and February 2019.

**MAIN OUTCOMES AND MEASURES** The primary end point (PEP) was time to first cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization; the key secondary end point was time to first cardiovascular death, myocardial infarction, or stroke. In a prespecified analysis, total cardiovascular events were evaluated between treatment arms.

**RESULTS** The mean age of patients was 63 years, 69% of patients were taking high-intensity statin therapy, and the median LDL-C at baseline was 92 mg/dL (to convert to millimoles per liter, multiply by 0.0259). There were 2907 first PEP events and 4906 total PEP events during the trial. Evolocumab reduced total PEP events by 18% (incidence rate ratio [RR], 0.82; 95% CI, 0.75-0.90; $P < .001$) including both first events (hazard ratio, 0.85; 95% CI, 0.79-0.92; $P < .001$) and subsequent events (RR, 0.74; 95% CI, 0.65-0.85). There were 2192 total primary events in the evolocumab group and 2714 total events in the placebo group. For every 1000 patients treated for 3 years, evolocumab prevented 22 first PEP events and 52 total PEP events. Reductions in total events were driven by fewer total myocardial infarctions (RR, 0.74; 95% CI, 0.65-0.84; $P < .001$), strokes (RR, 0.77; 95% CI, 0.64-0.93; $P = .007$), and coronary revascularizations (RR, 0.78; 95% CI, 0.71-0.87; $P < .001$).

**CONCLUSIONS AND RELEVANCE** The addition of the PCSK9 inhibitor evolocumab to statin therapy improved clinical outcomes, with significant reductions in total PEP events, driven by decreases in myocardial infarction, stroke, and coronary revascularization. More than double the number of events were prevented with evolocumab vs placebo as compared with the analysis of only first events. These data provide further support for the benefit of continuing aggressive lipid-lowering therapy to prevent recurrent cardiovascular events.

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Supplemental content

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When assessing efficacy, many long-term cardiovascular trials use survival analysis methods that consider only the first event that a patient experiences during the study. Such designs do not capture the entirety of the clinical effect of the therapy on patients, particularly if the primary event is a composite of many different component events. Indeed, a first-event analysis is a somewhat limited evaluation of efficacy because patients with a nonfatal event continue to be followed up during the trial and can experience additional events during the follow-up period.

Low-density lipoprotein cholesterol (LDL-C)-lowering trials have examined total events for comparing high-intensity vs moderate-intensity statins. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) and the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trials, analyses demonstrated that lower LDL-C achieved with high-intensity statins reduced both the first cardiovascular event as well as the total number of cardiovascular events compared with moderate-intensity statins.[1,2] Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) showed that further reductions in LDL-C with a nonstatin lipid-lowering agent, ezetimibe, in addition to statin therapy, reduced both the first and subsequent cardiovascular events compared with treatment with simvastatin alone.[3]

Despite ongoing treatment with statin therapy, patients with stable cardiovascular disease remain at high risk of recurrent cardiovascular events. The PCSK9 inhibitor evolocumab was shown to significantly reduce the risk of a first cardiovascular event in patients with atherosclerotic cardiovascular disease receiving statin therapy.[4] We now report the efficacy of evolocumab on total cardiovascular events in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial among patients with stable vascular disease, concomitantly treated with statin therapy.

### Key Points

**Question** Does the PCSK9 inhibitor evolocumab affect the total number of cardiovascular events among patients with stable atherosclerotic disease receiving statin therapy?

**Findings** In a prespecified secondary analysis of the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial, evolocumab improved clinical outcomes with significant reductions in total primary end point events, driven by decreases in myocardial infarction, stroke, and coronary revascularization, which revealed more than double the number of events prevented compared with an analysis of only first events.

**Meaning** The addition of evolocumab to statin therapy provides further support for the benefit of continuing aggressive lipid-lowering therapy to prevent recurrent cardiovascular events.

## Methods

### Study Population

The study design and primary results of the FOURIER trial have been published previously.[4,5] The FOURIER trial was a randomized, double-blind, placebo-controlled clinical trial that enrolled 27 564 patients aged 40 to 85 years with clinically evident atherosclerotic cardiovascular disease (prior myocardial infarction, prior nonhemorrhagic stroke, or symptomatic peripheral arterial disease) and additional risk factors placing them at increased cardiovascular risk.[5] Patients were required to have an LDL-C level of at least 70 mg/dL or non-high-density lipoprotein cholesterol levels of 100 mg/dL while taking an optimized lipid-lowering regimen including a high-intensity or moderate-intensity statin (to convert cholesterol levels to millimoles per liter, multiply by 0.0259). Patients were randomized 1 to 1 to receive subcutaneous evolocumab (either 140 mg every 2 weeks or 420 mg monthly, per patient preference) or matching placebo injection. Patients were followed up for a median of 2.2 years (interquartile range [IQR], 1.8-2.5 years; maximum, 3.6 years). Ethics committee approvals for the FOURIER trial were obtained from all relevant organizations locally or through a central institutional review board within the country. Each patient provided written informed consent. The formal trial protocols can be found in Supplement 1.

### Outcomes

The primary end point was time to first occurrence of the composite of cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina; the key secondary end point was time to first occurrence of the composite of cardiovascular death, myocardial infarction, or stroke. A central clinical events committee led by the TIMI Study Group, whose members were unaware of treatment assignment and lipid levels, adjudicated all efficacy end points. Definitions of the end points have been published previously.[5]

### Statistical Analyses

As part of a prespecified analysis, negative binomial regression models were performed to compare the total number of primary end points and other end points between patients in the evolocumab and placebo groups. The models included an exposure variable for duration of follow-up because this could vary by patient. Incidence rate ratio [RR] and corresponding 95% confidence intervals are reported from the negative binomial regression model. In addition, we performed a prespecified analysis using the Wei et al method,[6] which is a marginal model and an extension of survival models based on the Cox proportional hazard. The first 4 events that could have occurred in a patient were evaluated in the model. With the Wei et al method, each patient is simultaneously at risk from randomization through follow-up for up to 4 events; this preserves the randomization and allows for treatment effect estimation for events beyond the first event. We used only the first 4 events because the number of patients with more than 4 events was relatively infrequent and would not provide for a stable effect estimate. An Andersen Gill model was also performed as a sensitivity analysis. Sensitivity analyses were performed (1) excluding revascularizations within 3 days of an

Table. Baseline Characteristics in Patients With No Events, Single Event, or Multiple Events in Pooled Randomization Groups

| Characteristic | Event, No. (%) | | | *P* Value (1 vs ≥2 Events)[a] |
|---|---|---|---|---|
| | None (n = 24 657) | 1 (n = 1574) | Multiple (n = 1333) | |
| Male | 18 498 (75.0) | 1261 (80.1) | 1036 (77.7) | .11 |
| White | 20 944 (84.9) | 1354 (86.0) | 1160 (87.0) | .43 |
| Age, mean (SD), y | 62.5 (9.0) | 63.0 (9.1) | 62.1 (9.2) | .01 |
| Region | | | | |
| North America | 3900 (15.8) | 322 (20.5) | 349 (26.2) | <.001 |
| Europe | 15 591 (63.2) | 945 (60.0) | 799 (59.9) | |
| Latin America | 1651 (6.7) | 112 (7.1) | 60 (4.5) | |
| Asia | 3515 (14.3) | 195 (12.4) | 125 (9.4) | |
| Type of atherosclerosis | | | | |
| Myocardial infarction | 19 845 (80.5) | 1326 (84.2) | 1180 (88.5) | <.001 |
| Nonhemorrhagic stroke | 4778 (19.4) | 341 (21.7) | 218 (16.4) | <.001 |
| Peripheral artery disease | 3168 (12.8) | 256 (16.3) | 218 (16.4) | .95 |
| Time from MI to randomization, No./total No. (%), y | | | | |
| <1 | 4980/19 817 (25.1) | 355/1324 (26.8) | 376/1179 (31.9) | .02 |
| 1 to <2 | 2374/19 817 (12.0) | 169/1324 (12.8) | 148/1179 (12.6) | |
| ≥2 | 12 463/19 817 (62.9) | 800/1324 (60.4) | 655/1179 (55.6) | |
| History, No./total No. (%) | | | | |
| Hypertension | 19 649/24 656 (79.7) | 1322 (84.0) | 1113 (83.5) | .72 |
| Diabetes | 8826 (35.8) | 670 (42.6) | 585 (43.9) | .47 |
| Current smoker | 7025/24 655 (28.5) | 385 (24.5) | 367 (27.5) | .06 |
| History CHF | 5594 (22.7) | 442 (28.1) | 358 (26.9) | .46 |
| eGFR, mean (SD), mL/min/1.73m$^2$ | 76.0 (18.7) | 73.8 (20.2) | 73.8 (19.8) | .87 |
| Statin intensity at baseline | | | | |
| None/low/unknown | 60 (0.2) | 8 (0.5) | 1 (0.1) | .11 |
| Moderate | 7578 (30.7) | 437 (27.8) | 377 (28.3) | |
| High | 17 019 (69.0) | 1129 (71.7) | 955 (71.6) | |
| Ezetimibe use at baseline | 1246 (5.1) | 105 (6.7) | 89 (6.7) | >.99 |
| Lipid measures, median (IQR), mg/dL | | | | |
| LDL cholesterol | 92 (80-108) | 92 (81-110) | 95 (82-113) | .007 |
| Total cholesterol | 168 (151-188) | 167 (150-188) | 170 (153-192) | .006 |
| HDL cholesterol | 44 (37-53) | 43 (36-51) | 43 (36-51) | .98 |
| Triglycerides | 133 (100-182) | 138 (102-182) | 136 (103-186) | .60 |

Abbreviations: HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein.

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

[a] For 3-way comparison, all *P* < .005 except age (*P* = .04), white race (*P* = .07), and triglycerides (*P* = .03).

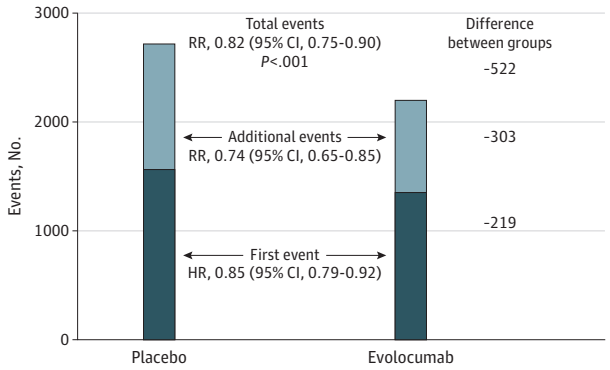
acute coronary syndrome and (2) including only events that occurred during the on-treatment period (treatment end date plus 30 days). All tests were 2-sided, with a *P* value of less than .05 considered to be significant.

Baseline clinical characteristics are presented as frequencies for categorical variables and medians and interquartile ranges for continuous variables. Comparisons between baseline characteristics for patients with no events, a single event, or multiple events, as well as for the comparison of evolocumab with placebo in the cohort of patients with at least 1 event (eTable 1 in Supplement 2), were made using $\chi^2$ test for categorical variables and Wilcoxon rank for continuous variables. Analyses were conducted with Stata/IC, version 14.2 (StataCorp LP) or SAS, version 9.4 (SAS Institute Inc).

## Results

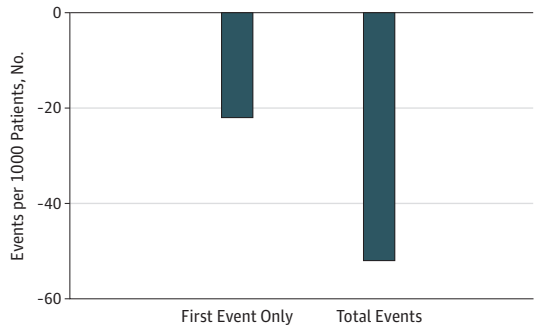
The median length of follow-up was 2.2 years (IQR, 1.8-2.5 years). Baseline characteristics among patients experiencing at least 1 event comparing those randomized to evolocumab and placebo were similar (eTable 1 in Supplement 2). The **Table** shows the baseline and clinical characteristics for those with none, 1, or more than 1 event. Compared with

Figure 1. First, Additional, and Total Primary End Point Events During Follow-up by Randomization Group




The first occurrence of the primary end point was significantly reduced in the evolocumab group compared with the placebo group (hazard ratio [HR], 0.85; 95% CI, 0.79-0.92; $P < .001$), as were additional events (incidence rate ratio [RR], 0.74; 95% CI, 0.65-0.85) and total events (RR, 0.82; 95% CI, 0.75-0.90; $P < .001$).

Figure 2. Risk Differences for 1000 Patients Treated for 3 Years With Evolocumab for the First and Total Number of the Primary End Point




For every 1000 patients treated for 3 years, 22 first primary end point events and 52 total primary end point events were prevented with evolocumab.

those with only 1 event, patients with multiple events were more likely to have a prior myocardial infarction (88.5% [n = 1180 of 1333] vs 84.2% [n = 1326 of 1574]; $P < .001$) and to have had the myocardial infarction in the year prior to study entry (31.9% [n = 376 of 1179] vs 26.8% [n = 355 of 1324]; $P = .02$). Patients with multiple events also had slightly higher median baseline LDL-C levels compared with patients with only 1 event (95 mg/dL vs 92 mg/dL; $P = .007$). There was a stepwise association between 1-month LDL-C levels and number of primary events, with lowest levels in those without a subsequent primary end point event and highest in those with more than 1 primary end point event (median, 64 mg/dL; IQR, 31-80 mg/dL if no event; median, 66 mg/dL; IQR, 34-91 mg/dL if 1 event; and median, 72 mg/dL; IQR, 38-96 mg/dL if more than 1 event; $P < .001$ for trend).

## Events

During the trial, a total of 4906 primary end point events occurred. Of these, 2907 were first events, which were included in the primary FOURIER trial analysis for time to first events[4]; there were an additional 1999 events that occurred after the first primary end point event during the trial that were not included in the time to first event analysis. Likewise, a total of 2282 key secondary end point events occurred. Of these, 1829 were first events and 453 were additional events. Overall, there were somewhat fewer myocardial infarctions and more coronary revascularizations among the additional events (eTable 2 in Supplement 2).

When considering the total number of events, of the 27 564 patients, 89.5% (n = 24 657) had no events, 5.7% (n = 1574) had a single event, and 3.5% (n = 960) had 2 primary end point events, while 1.4% (n = 373) had 3 or more such events (eTable 3 in Supplement 2). The maximum number of events experienced was 11 events each in 2 patients, during their 1.8 years and 3.1 years of follow-up, respectively.

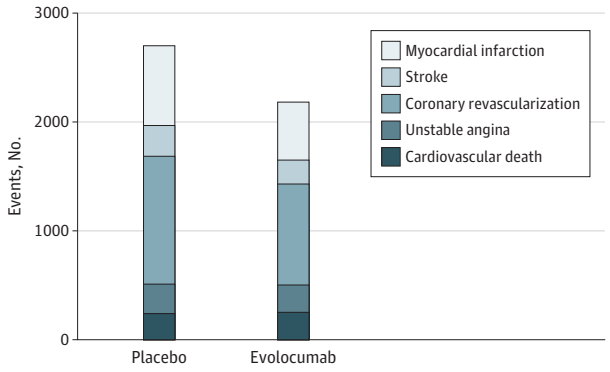
## Efficacy

As previously reported,[4] the primary end point of first occurrence of cardiovascular death, myocardial infarction, stroke, unstable angina, or coronary revascularization was significantly reduced by 219 events in the evolocumab group compared with the placebo group (3-year Kaplan-Meier rate, 12.6% [n = 1344] vs 14.6% [n = 1563]; hazard ratio, 0.85; 95% CI, 0.79-0.92; $P < .001$). In addition to this reduction in first primary events, there were 303 fewer subsequent events in the evolocumab group (n = 848 in the evolocumab group vs n = 1151 in the placebo group, **Figure 1**; eTable 2 in Supplement 2), resulting in 522 fewer total primary events during follow-up (total events, n = 2192 vs n = 2714; RR, 0.82; 95% CI, 0.75-0.90; $P < .001$). For every 1000 patients treated for 3 years, evolocumab prevented 22 first primary end point events and 52 total primary end point events (**Figure 2**). When comparing evolocumab vs placebo, there was a 26% reduction in the total number of myocardial infarctions (RR, 0.74; 95% CI, 0.65-0.84; $P < .001$), a 23% reduction in the total number of strokes (RR, 0.77; 95% CI, 0.64-0.93; $P = .007$), and a 22% reduction in coronary revascularizations (RR, 0.78; 95% CI, 0.71-0.87; $P < .001$) (**Figure 3**). The number of total hospitalizations for unstable angina was similar between treatment groups, as was the number of cardiovascular deaths. In a sensitivity analyses, revascularizations within 3 days of an acute coronary syndrome (n = 784) were excluded; the results were similar (RR, 0.84; 95% CI, 0.77-0.91; $P < .001$).

Total events were also reduced in the evolocumab group for the key secondary end point of cardiovascular death, myocardial infarction, or stroke (RR, 0.81; 95% CI, 0.73-0.90; $P < .001$; **Figure 4**), with 254 fewer events overall when considering both first and additional events. For every 1000 patients treated for 3 years, evolocumab prevented 20 first key secondary end point events and 26 total secondary end point events.

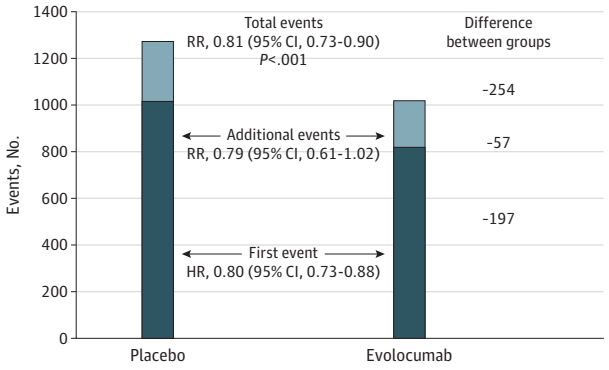
In a sensitivity analysis using the Wei et al Cox model, evolocumab significantly reduced occurrence of additional primary end point events, ranging from 24% for second events through 40% for 4 or more events (eFigure in Supplement 2).

Figure 3. Total Events During Follow-up by Randomization Group for Components of the Primary End Point




Total events were significantly reduced with evolocumab vs placebo for the component of myocardial infarction (incidence rate ratio [RR], 0.74; 95% CI, 0.65-0.84; *P* < .001) and stroke (RR, 0.77; 95% CI, 0.64-0.93; *P* = .007) and coronary revascularizations (RR, 0.78; 95% CI, 0.71-0.87; *P* < .001). There was no difference between treatment groups in total hospitalization for unstable angina events or in cardiovascular deaths.

Figure 4. Total Events During Follow-up by Randomization Group for Key Secondary End Point of Cardiovascular Death, Myocardial Infarction, or Stroke




Total events were reduced with evolocumab (incidence rate ratio [RR], 0.81; 95% CI, 0.73-0.90; *P* < .001). HR indicates hazard ratio.

Likewise, when evaluated using an Andersen-Gill model, the overall primary end point findings were consistent for a reduction in total events with evolocumab (hazard ratio, 0.81; 95% CI, 0.75-0.88; *P* < .001).

Among the 4906 primary end point events, 649 events (13.2%) occurred outside of the on-treatment window; these were balanced by treatment arm (13.2% [n = 289 of 2192] in the evolocumab arm and 13.3% [n = 360 of 2714] in the placebo arm). The treatment effect for the overall analysis was therefore similar when excluding off-treatment events in a sensitivity analysis (RR, 0.82; 95% CI, 0.75-0.91; *P* < .001). Likewise, for the key secondary end point of cardiovascular death, myocardial infarction, or stroke, a similar proportion of events occurred outside of the on-treatment window (20.1% [n = 204 of 1014] and 18.3% [n = 232 of 1268], respectively), resulting in a similar treatment effect as the overall analysis (RR, 0.79; 95% CI, 0.71-0.89; *P* < .001) when examining only events during the on-treatment period.

## Discussion

The FOURIER trial previously established that, relative to placebo, evolocumab significantly reduced the first occurrence of the primary end point by 15% and the key secondary end point by 20%, but whether the benefit would be extended beyond the first event was unknown. This study extends the main findings of the FOURIER study, demonstrating a reduction in not only first events but in total events during long-term follow-up with the addition of evolocumab to statin therapy.

Despite a relatively short period of 2.2 years median follow-up in the FOURIER trial, there was substantial risk of multiple vascular events in this stable atherosclerotic disease cohort. This resulted in 1333 of the 27 564 patients having more than 1 occurrence of the primary composite end point. The first event contributed 59% of all events (n = 2907); thus, 1999 events (41%) were not analyzed in the initial primary analysis of the trial[4] when performing traditional Cox survival analysis of time to first event. Accounting for total events more than doubled the number of events prevented with evolocumab vs placebo compared with first events alone. In terms of the narrower key secondary end point of cardiovascular death, myocardial infarction, or stroke, first events accounted for 80% of all events; thus, 20% of key secondary end points were not analyzed in the time to first analysis of the trial. By further clarifying the magnitude of benefit, these observations have implications not only for clinical decision making but also for quality-of-life and cost-effectiveness analyses; important considerations for patients, health care clinicians, and payors. The reduction in additional events with evolocumab included clinically important events of myocardial infarction and stroke, as well as coronary revascularization.

Our findings are supported by prior work we and others have done with other lipid-lowering therapy studies. Specifically, there is a reduction in first and total cardiovascular events associated with more aggressive statin regimens.[7-14] Likewise, the nonstatin lipid-lowering agent, ezetimibe, added to simvastatin was shown in IMPROVE-IT to reduce total events following acute coronary syndrome.

In terms of practical implications, the 2017 European Society of Cardiology/European Atherosclerosis Society task force consensus statement focused on absolute risk reduction in determining which patients should be treated with a PCSK9 inhibitor[15]; these data suggest that not only the absolute risk reduction in first events should be considered but also the total number of events prevented may also be warranted because total events more fully reflect the disease burden of the patient over time.

### Limitations

Several limitations of total events analyses should be addressed. Recurrent events within patients are often correlated and thus may violate the assumption of independence

of events. Additionally, after a nonfatal event, many patients discontinue blinded study drug, which can result in a higher proportion of subsequent events occurring off study drug as compared with the first event. To address this limitation, an on-treatment analysis was performed, which showed findings consistent with the intent-to-treat analysis. Although nonfatal components of the primary end point can occur multiple times, the component of cardiovascular death precludes the occurrence of subsequent events. This becomes particularly important when there is an imbalance between treatment arms in the number of cardiovascular deaths. However, in this study, the number of cardiovascular deaths was nearly identical between randomization groups (n = 251 for evolocumab and n = 240 for placebo). A final limitation of the study was the relatively short duration of follow-up of a median of 2.2 years as compared with other lipid-lowering trials.

## Conclusions

In conclusion, lipid-lowering therapy with the PCSK9 inhibitor evolocumab improved clinical efficacy, with reductions in total primary end point events in patients with stable cardiovascular disease receiving statin therapy. These reductions were observed for the clinically important end points of both myocardial infarction and stroke, providing further support for the benefit of continuing aggressive lipid-lowering therapy to prevent recurrent cardiovascular events.


### ARTICLE INFORMATION

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**Author Contributions:** Ms Murphy and Dr Im 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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