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Evolocumab in Patients without a Previous Myocardial Infarction or Stroke

Erin A. Bohula, M.D., D.Phil.,[1] Nicholas A. Marston, M.D., M.P.H.,[1] Ajay K. Bhatia, M.D., Ph.D.,[2] Gaetano M. De Ferrari, M.D.,[3] Lawrence A. Leiter, M.D.,[4] Jose C. Nicolau, M.D.,[5] Jeong-Gun Park, Ph.D.,[1] Julia F. Kuder, M.A.,[1] Sabina A. Murphy, M.P.H.,[1] Emileigh Walsh, Ph.D.,[2] Huei Wang, Ph.D.,[2] Vladimir Blaha, M.D., Ph.D.,[6] Andrzej Budaj, M.D., Ph.D.,[7] Jan H. Cornel, M.D., Ph.D.,[8] Assen Goudev, M.D.,[9] Robert Gabor Kiss, M.D.,[10] Alberto J. Lorenzatti, M.D.,[11] Alexander Parkhomenko, M.D.,[12] Marcoli Cyrille, M.D.,[2] Gabriel Paiva da Silva Lima, M.D.,[2] E. Magnus Ohman, M.D.,[2] Robert P. Giugliano, M.D.,[1] and Marc S. Sabatine, M.D., M.P.H.,[1] for the VESALIUS-CV Investigators*

ABSTRACT

BACKGROUND

The proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitor evolocumab reduces the risk of major adverse cardiovascular events (MACE) among patients with a previous myocardial infarction, stroke, or symptomatic peripheral artery disease. The effect of evolocumab on the risk of MACE among patients without a previous myocardial infarction or stroke is unknown.

METHODS

We conducted an international, double-blind, randomized, placebo-controlled trial of evolocumab in patients with atherosclerosis or diabetes and without a previous myocardial infarction or stroke who had a low-density lipoprotein cholesterol level of at least 90 mg per deciliter. Patients were randomly assigned in a 1:1 ratio to receive evolocumab at a dose of 140 mg every 2 weeks or placebo. The two primary end points were a composite of death from coronary heart disease, myocardial infarction, or ischemic stroke (3-point MACE) and a composite of 3-point MACE or ischemia-driven arterial revascularization (4-point MACE).

RESULTS

A total of 12,257 patients were randomly assigned to receive evolocumab (6129 patients) or placebo (6128) and were included in the efficacy analyses. The median age of the patients was 66 years, 43% were women, and 93% were White. The median follow-up was 4.6 years. A 3-point MACE event occurred in 336 patients (5-year Kaplan–Meier estimate, 6.2%) in the evolocumab group, as compared with 443 (8.0%) in the placebo group (hazard ratio, 0.75; 95% confidence interval [CI], 0.65 to 0.86; P<0.001). A 4-point MACE event occurred in 747 patients (5-year Kaplan–Meier estimate, 13.4%) in the evolocumab group, as compared with 907 (16.2%) in the placebo group (hazard ratio, 0.81; 95% CI, 0.73 to 0.89; P<0.001). No evidence of a between-group difference was seen in the incidence of safety events.

CONCLUSIONS

PCSK9 inhibition with evolocumab led to a lower risk of first cardiovascular events than placebo among patients with atherosclerosis or diabetes and without a previous myocardial infarction or stroke. (Funded by Amgen; VESALIUS-CV ClinicalTrials.gov number, NCT03872401.)

Author affiliations are listed at the end of the article. Erin A. Bohula can be contacted at ebohula@bwh.harvard.edu or at the TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, 60 Fenwood Rd., Suite 7022, Boston, MA 02115.

*Complete lists of the VESALIUS-CV investigators and steering committee members are provided in the Supplementary Appendix, available at NEJM.org.

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Low-density lipoprotein (LDL) cholesterol is a well-established modifiable cardiovascular risk factor.[1] Lowering LDL cholesterol levels with proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors reduces the risk of cardiovascular events, but this treatment has been studied primarily in patients at very high risk who had a previous major atherosclerotic cardiovascular disease event, such as myocardial infarction or stroke.[2,3] The effect of PCSK9 inhibition on cardiovascular events has not been well studied in populations without a previous major cardiovascular ischemic event.

The Effect of Evolocumab in Patients at High Cardiovascular Risk without Prior Myocardial Infarction or Stroke (VESALIUS-CV) trial was a dedicated cardiovascular-outcomes trial that tested whether evolocumab treatment would lead to a lower risk of a first major cardiovascular event than placebo among patients at high cardiovascular risk who had atherosclerosis or diabetes but had not had a myocardial infarction or stroke previously.[4] The trial was designed to have a median follow-up of at least 4.5 years in order to better characterize the long-term efficacy and safety of evolocumab therapy.

Methods

Trial Design and Oversight

We conducted this international, double-blind, randomized, placebo-controlled clinical trial at 774 sites in 33 countries (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial was designed by the Thrombolysis in Myocardial Infarction (TIMI) Study Group in conjunction with the executive committee and the trial sponsor, Amgen. The trial protocol (available at NEJM.org) and amendments were approved by the relevant ethics committees for all the participating sites. The sponsor was responsible for data collection. The raw database was provided to the TIMI Study Group, which conducted all the analyses for this article. The first author wrote the initial draft of the manuscript, and all the authors participated in subsequent manuscript revisions. The authors vouch for the fidelity of the trial to the protocol. The authors from the TIMI Study Group assume responsibility for the accuracy and completeness of the data.

Trial Population

Eligible patients met criteria for age, qualifying lipid variables, disease category, and the presence of at least one high-risk criterion, as described previously.[4] Specifically, trial patients were required to be either 50 to 79 years of age (in men) or 55 to 79 years of age (in women) and to have an LDL cholesterol level of at least 90 mg per deciliter (2.3 mmol per liter), a non–high-density lipoprotein (non-HDL) cholesterol level of at least 120 mg per deciliter (3.1 mmol per liter), or an apolipoprotein B level of at least 80 mg per deciliter. Patients had to have been receiving stable, optimized lipid-lowering therapy for at least 2 weeks.

Eligible patients must have been without a history of myocardial infarction or stroke and had to meet trial criteria for at least one of the following four disease categories: coronary artery disease, atherosclerotic cerebrovascular disease, peripheral artery disease, or high-risk diabetes. The category of high-risk diabetes refers to patients with diabetes that is long-standing (≥10 years' duration), is treated with daily insulin, or is complicated by microvascular disease. Eligible patients were also required to have at least one additional criterion that placed them at higher risk for cardiovascular disease, such as an age of 65 years or older, active smoking, very elevated lipid levels, or concomitant atherosclerosis and diabetes. Full eligibility criteria are provided in the Supplementary Appendix. Written informed consent was obtained from all the patients.

Randomization

Eligible patients were randomly assigned in a 1:1 ratio to receive subcutaneous injections of evolocumab at a dose of 140 mg every 2 weeks or matching placebo. Evolocumab and placebo were supplied by the sponsor. Randomization was conducted with the use of stratification according to the LDL cholesterol level at screening (<160 mg per deciliter [4.14 mmol per liter] or ≥160 mg per deciliter) and geographic region (North America, Europe, or other). Randomization was performed in a double-blind fashion with the use of a central computerized, Web-based system.

End Points

The two primary efficacy end points of the trial were a composite of death from coronary heart

disease, myocardial infarction, or ischemic stroke (3-point major adverse cardiovascular event [MACE]) and a composite of death from coronary heart disease, myocardial infarction, ischemic stroke, or ischemia-driven arterial revascularization (4-point MACE). Ischemia-driven arterial revascularization was defined as arterial revascularization of any vascular bed, including the coronary, cerebrovascular, or peripheral arteries, performed in the presence of ischemia of the relevant end organ. Major, prespecified subgroups that were defined according to age, sex, geographic region, race, qualifying disease category, baseline LDL cholesterol level, statin intensity, and the use of ezetimibe were evaluated.

Secondary efficacy end points were tested in a prespecified hierarchical order. These end points were as follows, in order: a composite of myocardial infarction, ischemic stroke, or ischemia-driven arterial revascularization; a composite of death from coronary heart disease, myocardial infarction, or ischemia-driven arterial revascularization; a composite of death from cardiovascular causes, myocardial infarction, or ischemic stroke; a composite of death from coronary heart disease or myocardial infarction; and the individual end points of myocardial infarction, ischemia-driven arterial revascularization, death from coronary heart disease, death from cardiovascular causes, death from any cause, and ischemic stroke.

We also prespecified assessment of the Cholesterol Treatment Trialists' Collaboration end points of major coronary events (death due to acute myocardial infarction or nonfatal myocardial infarction) and major vascular events (defined as major coronary events, stroke, or coronary revascularization, which was limited to ischemia-driven in our dataset).[5] The change from baseline in the LDL cholesterol level with evolocumab as compared with placebo was a prespecified exploratory end point in a subgroup of randomly selected patients who underwent central lipid testing in the lipid substudy.[4] Analysis of safety was limited to the collection of adverse events that led to the discontinuation of evolocumab or placebo, as well as serious adverse events.

A central clinical-events committee, which was led by the TIMI Study Group and whose members were unaware of patients' lipid levels and trial-group assignments, adjudicated all the potential primary and secondary efficacy end-point events. Definitions of the end points are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The trial size was based on the 3-point MACE end point. We estimated that 751 patients would have to have a 3-point MACE event for the trial to have more than 90% power to detect a 23% lower risk with evolocumab than with placebo and that enrollment of 12,000 patients with a median follow-up of 4.5 years would provide the requisite number of patients with an event. The same sample size was estimated to yield at least 1254 patients with a 4-point MACE event, thus providing the trial with more than 95% power to detect a 20% lower risk with evolocumab than with placebo.[4]

The primary efficacy analyses were based on the time from randomization to the first occurrence of any element of the two primary efficacy end points being tested. To preserve the overall two-sided type I error rate at an alpha of 0.05 in the analysis of the two primary end points and the secondary efficacy end points, we applied a parallel gatekeeping strategy using a truncated Hochberg procedure (see the Supplementary Methods section in the Supplementary Appendix), which allowed unused alpha from the testing of the two primary end points to be passed to the secondary end-point testing if at least one of the two primary tests was successful. Each of the secondary end points were then tested with the unused alpha in a fixed sequential order, as described above.

The two primary efficacy analyses and the secondary efficacy analyses were performed in all the patients who underwent randomization (intention-to-treat method). Safety analyses included all the patients who underwent randomization and received at least one dose of evolocumab or placebo. Analyses in the lipid substudy were conducted in all the patients who had undergone randomization, were participating in the substudy, had received at least one dose of evolocumab or placebo, and had at least one post-baseline lipid measurement at the central laboratory. The primary analysis of time-to-event end points used the log-rank test with stratification according to the stratification factors at random-

ization. In addition, hazard ratios with 95% confidence intervals were estimated from a Cox model, with stratification according to the stratification factors at randomization. An independent data and safety monitoring committee reviewed available accumulating safety data approximately every 6 months and also conducted a single prespecified interim assessment of cardiovascular efficacy, as described previously.[4]

Given that ascertainment of the two primary end points was complete for 98.7% of the potential patient-years of follow-up, missing data were not imputed. Competing-risk sensitivity analyses for the two primary end points were conducted with the use of a stratified Fine–Gray subdistribution hazard model. All the presented rates are 5-year Kaplan–Meier estimates, unless otherwise specified. All the analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

TRIAL PATIENTS AND FOLLOW-UP

From June 2019 through November 2021, a total of 12,257 patients underwent randomization and were included in the efficacy analyses after the exclusion of 44 patients due to a sitewide serious breach and Good Clinical Practice violations. The characteristics of the patients at baseline appeared to be well balanced between the two trial groups (Table 1 and Table S1 in the Supplementary Appendix). The median age of the patients was 66 years (interquartile range, 60 to 71), and 43% were women. Approximately two thirds of the patients met criteria for qualifying atherosclerosis, including 45% with coronary artery disease, 10% with cerebrovascular disease, and 17% with peripheral artery disease; of those with qualifying atherosclerosis, 38% had diabetes and 24% had high-risk diabetes. Overall, close to 60% of the patients had diabetes, approximately half had high-risk diabetes, and one third had high-risk diabetes without qualifying atherosclerosis.

The median baseline LDL cholesterol level was 122 mg per deciliter (3.16 mmol per liter; interquartile range, 104 to 149 mg per deciliter [2.69 to 3.85 mmol per liter]) according to local laboratory testing. At baseline, 92% of the patients were taking lipid-lowering therapy, 72% were taking high-intensity lipid-lowering therapy, and 68% were taking high-intensity statin therapy; 13% of the patients were unable to take statins. A total of 20% of the patients were taking ezetimibe. During the trial, 0.8% of the patients in the evolocumab group and 3.9% of those in the placebo group began open-label treatment with a PCSK9 inhibitor (Table S2). By the end of the trial, 2.2% of the patients in the evolocumab group and 7.1% of those in the placebo group had increased the intensity of their lipid-lowering therapy.

A total of 12,247 patients (99.9%) received at least one dose of evolocumab or placebo. The rate of premature discontinuation of evolocumab or placebo was 4.5% per year (2530 total patients over a median of 4.6 years of follow-up), the rate of withdrawal of consent was 0.3% per year (197 total patients), and the rate of loss to follow-up was 0.1% per year (43 total patients) (Fig. S1). The median follow-up was 4.6 years (interquartile range, 4.0 to 5.2).

LIPID DATA

A total of 2014 patients participated in the lipid substudy and underwent testing at the central laboratory. The median baseline LDL cholesterol level in this substudy was 115 mg per deciliter (2.98 mmol per liter; interquartile range, 94 to 143 mg per deciliter [2.43 to 3.70 mmol per liter]). The change in the LDL cholesterol level over the course of the trial is shown in Figure S2. At 48 weeks, the least-squares mean percentage change in the LDL cholesterol level with evolocumab as compared with placebo in the lipid substudy was −55% (95% confidence interval [CI], −59 to −52), for a least-squares mean absolute difference of −63 mg per deciliter (−1.63 mmol per liter; 95% CI, −67 to −59 mg per deciliter [−1.73 to −1.52 mmol per liter]). The median LDL cholesterol level at 48 weeks was 45 mg per deciliter (1.16 mmol per liter; interquartile range, 26 to 73 mg per deciliter [0.67 to 1.89 mmol per liter]) in the evolocumab group and 109 mg per deciliter (2.82 mmol per liter; interquartile range, 86 to 144 mg per deciliter [2.23 to 3.73 mmol per liter]) in the placebo group. Evolocumab therapy also led to greater reductions than placebo in other atherogenic lipids at 48 weeks, for a least-squares mean percentage change of −47% in the non-HDL cholesterol level and of −44% in the apolipoprotein B level. Details of the lipid data are provided in Table S3.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Evolocumab (N=6129)	Placebo (N=6128)
Median age (IQR) — yr	66 (60–71)	66 (60–71)
Female sex — no. (%)	2619 (43)	2595 (42)
White race — no./total no. (%)†	5708/6128 (93)	5693/6122 (93)
Hispanic ethnic group — no./total no. (%)†	1017/6127 (17)	1016/6126 (17)
Median weight (IQR) — kg	85 (74–97)	85 (74–96)
Median body-mass index (IQR)‡	30 (27–34)	30 (27–33)
Geographic region — no. (%)		
North America	678 (11)	679 (11)
Europe	4238 (69)	4234 (69)
Asia–Pacific	320 (5)	307 (5)
Central or South America	893 (15)	908 (15)
Coexisting conditions — no. (%)		
Hypertension	5351 (87)	5319 (87)
Diabetes	3598 (59)	3524 (58)
Current smoking	1681 (27)	1715 (28)
Qualifying disease categories for inclusion — no. (%)§		
Any qualifying atherosclerosis	4092 (67)	4116 (67)
Coronary artery disease without previous myocardial infarction	2755 (45)	2771 (45)
Cerebrovascular disease without previous stroke	607 (10)	606 (10)
Peripheral artery disease	1050 (17)	1086 (18)
High-risk diabetes	3052 (50)	2950 (48)
High-risk diabetes without qualifying atherosclerosis	2009 (33)	1992 (33)
Lipid-lowering therapy — no. (%)		
Any lipid-lowering therapy	5641 (92)	5609 (92)
High-intensity lipid-lowering therapy¶	4407 (72)	4447 (73)
Any statin	5339 (87)	5304 (87)
High-intensity statin‖	4160 (68)	4165 (68)
Moderate- or low-intensity statin	1179 (19)	1139 (19)
Ezetimibe	1188 (19)	1249 (20)
Lipid values (IQR) — mg/dl**		
Low-density lipoprotein cholesterol	122 (104–149)	122 (104–149)
Non–high-density lipoprotein cholesterol	152 (130–182)	153 (130–182)
High-density lipoprotein cholesterol	47 (40–57)	47 (40–57)
Total cholesterol	201 (178–233)	202 (178–233)
Triglycerides	153 (111–216)	152 (111–220)
Apolipoprotein B	102 (89–123)	100 (88–119)
Median estimated GFR (IQR) — ml/min/1.73 m^2	79 (66–93)	78 (65–93)

* GFR denotes glomerular filtration rate, and IQR interquartile range.
† Race and ethnic group were reported by the patient.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The individual qualifying disease categories for inclusion are not mutually exclusive.
¶ High-intensity lipid-lowering therapy was defined as either a high-intensity statin (e.g., atorvastatin at a dose of ≥40 mg daily or rosuvastatin at a dose of ≥20 mg daily) or a combination of a statin and ezetimibe.
‖ High-intensity statins were defined in accordance with the American College of Cardiology and American Heart Association joint guidelines.[6]
** Lipid values were based on local testing. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.

Table 2. Primary and Secondary End Points.*

End Point	Evolocumab (N=6129)	Placebo (N=6128)	Hazard Ratio (95% CI)	P Value
	no. (5-yr Kaplan–Meier estimate, %)			
Primary end points†				
3-Point MACE	336 (6.2)	443 (8.0)	0.75 (0.65–0.86)	<0.001
4-Point MACE	747 (13.4)	907 (16.2)	0.81 (0.73–0.89)	<0.001
Secondary end points‡				
Myocardial infarction, ischemic stroke, or ischemia-driven arterial revascularization	674 (12.2)	834 (15.0)	0.79 (0.72–0.88)	<0.001
Death from coronary heart disease, myocardial infarction, or ischemia-driven arterial revascularization	664 (11.9)	819 (14.6)	0.79 (0.72–0.88)	<0.001
Death from cardiovascular causes, myocardial infarction, or ischemic stroke	374 (6.8)	503 (9.1)	0.73 (0.64–0.84)	<0.001
Death from coronary heart disease or myocardial infarction	232 (4.2)	313 (5.6)	0.73 (0.62–0.87)	<0.001
Myocardial infarction	149 (2.7)	229 (4.1)	0.64 (0.52–0.79)	<0.001
Ischemia-driven arterial revascularization	561 (10.1)	699 (12.5)	0.79 (0.70–0.88)	<0.001
Death from coronary heart disease	105 (1.9)	117 (2.1)	0.89 (0.68–1.16)	0.39
Death from cardiovascular causes	156 (2.8)	195 (3.6)	0.79 (0.64–0.98)	NA
Death from any cause	434 (7.9)	539 (9.7)	0.80 (0.70–0.91)	NA
Ischemic stroke	115 (2.3)	144 (2.7)	0.79 (0.62–1.01)	NA

* Shown are the numbers of patients with a first event and the Kaplan–Meier estimate at 5 years in the intention-to-treat population, which included all the patients who had undergone randomization. NA denotes not applicable.

† The two primary end points were the composites of death from coronary heart disease, myocardial infarction, or ischemic stroke (3-point major adverse cardiac events [MACE]) and of 3-point MACE or ischemia-driven arterial revascularization (4-point MACE).

‡ Secondary end points are listed in the order of hierarchical testing (see the Supplementary Appendix). The widths of the confidence intervals for secondary end points that were not tested statistically were not adjusted for multiplicity and thus should not be used to infer treatment effect.

CARDIOVASCULAR EFFICACY END POINTS

Evolocumab therapy led to significantly lower risks of the two primary efficacy end points than placebo. A 3-point MACE event (death from coronary heart disease, myocardial infarction, or ischemic stroke) occurred in 336 patients (5-year Kaplan–Meier estimate, 6.2%) in the evolocumab group, as compared with 443 patients (8.0%) in the placebo group (hazard ratio, 0.75; 95% CI, 0.65 to 0.86; P<0.001), which corresponded to a 25% lower risk (Table 2, Fig. 1A, and Fig. S3). A 4-point MACE event (3-point MACE event or ischemia-driven arterial revascularization) occurred in 747 patients (5-year Kaplan–Meier estimate, 13.4%) in the evolocumab group, as compared with 907 patients (16.2%) in the placebo group (hazard ratio, 0.81; 95% CI, 0.73 to 0.89; P<0.001), which corresponded to a 19% lower risk (Table 2 and Fig. 1B).

Evolocumab therapy also led to significantly lower risks than placebo of the majority of the secondary end points in the testing hierarchy: a 21% (95% CI, 12 to 28) lower risk of the composite of myocardial infarction, ischemic stroke, or ischemia-driven arterial revascularization; a 21% (95% CI, 12 to 28) lower risk of the composite of death from coronary heart disease, myocardial infarction, or ischemia-driven arterial revascularization; a 27% (95% CI, 16 to 36) lower risk of the composite of death from cardiovascular causes, myocardial infarction, or ischemic stroke; a 27% (95% CI, 13 to 38) lower risk of death from coronary heart disease or myocardial infarction; a 36% (95% CI, 21 to 48) lower risk of myocardial infarction; and a 21% (95% CI, 12 to 30) lower risk of ischemia-driven arterial revascularization (Table 2). Death from coronary heart disease occurred in 105 patients (5-year Kaplan–Meier

estimate, 1.9%) in the evolocumab group and in 117 patients (2.1%) in the placebo group (hazard ratio, 0.89; 95% CI, 0.68 to 1.16; P=0.39).

Given that evolocumab therapy had no significant effect on death from coronary heart disease, results for the remaining secondary end points in the testing hierarchy should be considered exploratory (Table 2). Death from cardiovascular causes occurred in 156 patients (5-year Kaplan–Meier estimate, 2.8%) in the evolocumab group and in 195 patients (3.6%) in the placebo group (hazard ratio, 0.79; 95% CI, 0.64 to 0.98) (Table 2 and Fig. S4). Death from any cause occurred in 434 patients (5-year Kaplan–Meier estimate, 7.9%) in the evolocumab group and in 539 patients (9.7%) in the placebo group (hazard ratio, 0.80; 95% CI, 0.70 to 0.91) (Table 2). The results for the Cholesterol Treatment Trialists' Collaboration (CTTC)–defined end points of major coronary and major vascular events are shown in Table S4 and Figure S5. In that analysis, we observed an apparent 35% lower risk of major coronary events and an apparent 27% lower risk of major vascular events with evolocumab than with placebo. On the basis of the between-group difference in the LDL cholesterol level (calculated with the use of the CTTC approach with imputation for missing values), the CTTC meta-regression analysis would predict risk reductions of 31% and 29%, respectively.

The clinical benefits of evolocumab therapy appeared to be generally consistent for the two primary end points across key subgroups (Fig. 2). Competing-risk sensitivity analyses for the two primary end points yielded findings similar to those of the primary analysis.

SAFETY

No evidence of a between-group difference was seen in the incidence of adverse events leading to the discontinuation of evolocumab or placebo or in the incidence of serious adverse events. Details are provided in Table S5.

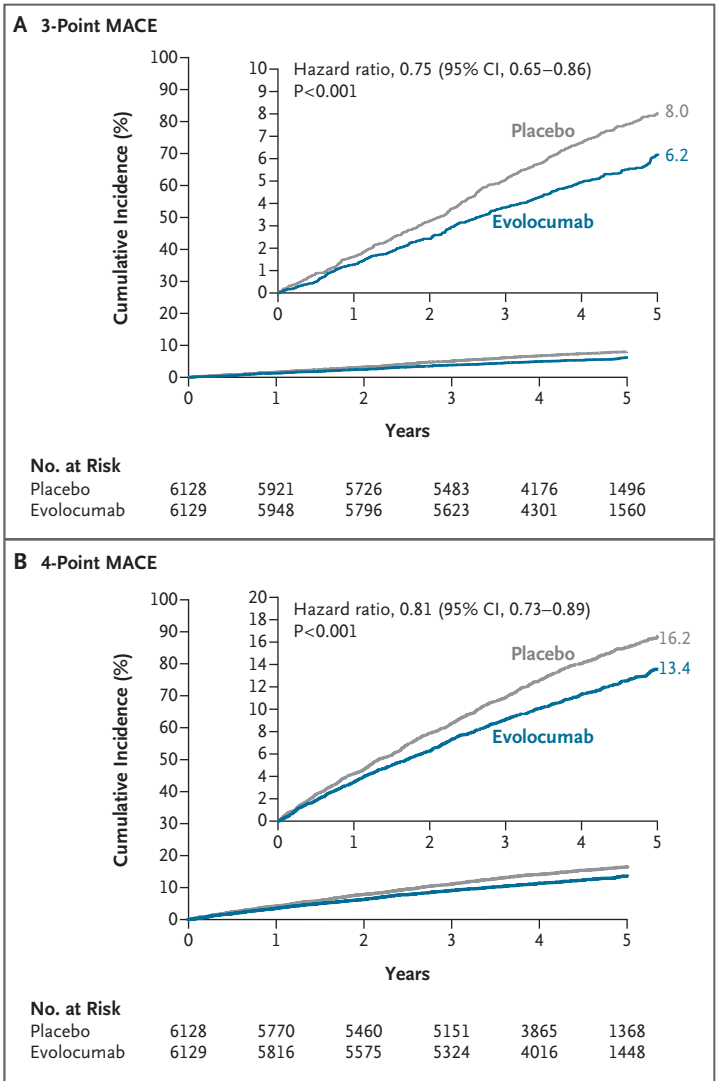


Figure 1. Primary Efficacy End Points over Time.

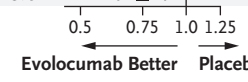
Shown is the cumulative incidence of the two primary end points: the composites of death from coronary heart disease, myocardial infarction, or ischemic stroke (3-point major adverse cardiac events [MACE]) (Panel A) and of 3-point MACE or ischemia-driven arterial revascularization (4-point MACE) (Panel B). Five-year Kaplan–Meier estimates and hazard ratios with 95% confidence intervals are shown with P values for superiority. In both panels, the inset shows the same data on an expanded y axis.

DISCUSSION

In this cardiovascular-outcomes trial, the addition of the PCSK9 inhibitor evolocumab to baseline lipid-lowering therapy led to significantly lower rates of major adverse cardiovascular events among patients at high risk for a first major cardiovascular event, with a 25% lower risk of the primary composite of death from coronary heart disease, myocardial infarction, or ischemic stroke and a 19% lower risk of the expanded primary composite end point, 4-point MACE, which included ischemia-driven revascularization. In addition, in this placebo-controlled trial, evolocumab therapy led to a 27% lower risk of the composite of death from cardiovascular causes, myocardial infarction, or ischemic stroke, as well as to a 27% lower risk

A 3-Point MACE

Subgroup	Evolocumab	Placebo	Hazard Ratio (95% CI)
	no. of events/no. of patients		
Overall	336/6129	443/6128	0.75 (0.65–0.86)
Age			
<65 yr	139/2657	165/2732	0.86 (0.69–1.08)
≥65 yr	197/3472	278/3396	0.68 (0.57–0.82)
Sex			
Male	226/3510	296/3533	0.75 (0.63–0.90)
Female	110/2619	147/2595	0.74 (0.58–0.95)
Geographic region			
North America	49/678	81/679	0.60 (0.42–0.85)
Europe	221/4238	282/4234	0.77 (0.65–0.92)
Other	66/1213	80/1215	0.80 (0.58–1.11)
Race			
White	306/5708	407/5693	0.74 (0.64–0.85)
Non-White	30/420	36/429	0.87 (0.53–1.41)
Qualifying disease category			
Any qualifying atherosclerosis	237/4092	307/4116	0.76 (0.65–0.91)
High-risk diabetes without qualifying atherosclerosis	99/2009	136/1992	0.71 (0.55–0.92)
LDL cholesterol at baseline			
≤104 mg/dl	80/1546	103/1547	0.77 (0.58–1.03)
>104–122 mg/dl	90/1550	111/1523	0.78 (0.59–1.04)
>122–149 mg/dl	72/1512	118/1537	0.60 (0.45–0.81)
>149 mg/dl	94/1520	111/1521	0.85 (0.65–1.12)
Statin intensity			
High	203/4160	288/4165	0.70 (0.58–0.83)
Moderate or low	71/1179	81/1139	0.81 (0.59–1.12)
None	62/790	74/824	0.88 (0.63–1.23)
Ezetimibe			
Yes	63/1188	86/1249	0.74 (0.53–1.02)
No	273/4941	357/4879	0.75 (0.64–0.87)



B 4-Point MACE

Subgroup	Evolocumab	Placebo	Hazard Ratio (95% CI)
	no. of events/no. of patients		
Overall	747/6129	907/6128	0.81 (0.73–0.89)
Age			
<65 yr	297 2657	361/2732	0.83 (0.71–0.97)
≥65 yr	450/3472	546/3396	0.79 (0.70–0.89)
Sex			
Male	510/3510	606/3533	0.83 (0.73–0.93)
Female	237/2619	301/2595	0.77 (0.65–0.92)
Geographic region			
North America	104/678	154/679	0.66 (0.52–0.85)
Europe	513/4238	603/4234	0.84 (0.74–0.94)
Other	130/1213	150/1215	0.84 (0.66–1.06)
Race			
White	684/5708	832/5693	0.80 (0.72–0.89)
Non-White	63/420	74/429	0.87 (0.62–1.22)
Qualifying disease category			
Any qualifying atherosclerosis	584/4092	687/4116	0.84 (0.75–0.94)
High-risk diabetes without qualifying atherosclerosis	163/2009	216/1992	0.74 (0.60–0.90)
LDL cholesterol at baseline			
≤104 mg/dl	188/1546	222/1547	0.83 (0.69–1.01)
>104–122 mg/dl	214/1550	237/1523	0.88 (0.73–1.05)
>122–149 mg/dl	163/1512	229/1537	0.70 (0.57–0.86)
>149 mg/dl	182/1520	219/1521	0.83 (0.68–1.01)
Statin intensity			
High	458/4160	564/4165	0.80 (0.71–0.90)
Moderate or low	159/1179	187/1139	0.79 (0.64–0.98)
None	130/790	156/824	0.87 (0.69–1.10)
Ezetimibe			
Yes	162/1188	205/1249	0.80 (0.65–0.99)
No	585/4941	702/4879	0.81 (0.73–0.90)

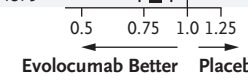


Figure 2 (facing page). Key Subgroup Analyses for the Primary Efficacy End Points.

Shown are the numbers of end-point events, the numbers of patients included in the analyses, and the hazard ratios with 95% confidence intervals for the primary composite end points of 3-point MACE (death from coronary heart disease, myocardial infarction, or ischemic stroke) and 4-point MACE (3-point MACE or ischemia-driven arterial revascularization). The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer treatment effect. Race was reported by the patient. Baseline levels of low-density lipoprotein (LDL) cholesterol were divided into quartiles. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. The arrow indicates that the 95% confidence interval extends outside the graphed area.

of death from coronary heart disease or myocardial infarction and a 36% lower risk of myocardial infarction. Although the prespecified hierarchical testing plan precluded formal hypothesis testing and conclusions may not be drawn, the observed rates of death from cardiovascular causes and of death from any cause appeared to be lower in the evolocumab group than in the placebo group.

Atherosclerotic cardiovascular disease can be conceptualized as a continuum of risk. Patients at highest risk have had one or more major atherosclerotic cardiovascular disease events, such as a myocardial infarction or stroke. Patients at intermediate risk are those with evidence of atherosclerotic disease but without a major atherosclerotic cardiovascular disease event; within the population, risk estimates may be further modified when the extent of atherosclerosis on imaging is considered. Finally, some patients do not have known atherosclerosis but are deemed to be at high risk for the development and manifestations of atherosclerotic cardiovascular disease by virtue of high-risk conditions such as diabetes and dyslipidemia. Lowering of the LDL cholesterol level with statins has been proven to be effective at preventing major cardiovascular events across this continuum.[5,7,8]

To date, PCSK9 inhibitors have been studied in the highest-risk populations — patients with a major, previous atherosclerotic cardiovascular disease event — in whom they prevented recurrent major adverse cardiovascular events.[2,3] The findings presented here support the use of the PCSK9 inhibition to prevent a first major cardiovascular event in a population along the atherosclerotic cardiovascular disease continuum that is at lower risk than populations previously studied, with benefit in patients with atherosclerosis without a previous myocardial infarction or stroke, as well as in patients with diabetes without qualifying atherosclerosis, who totaled one third of the trial population. Ongoing trials of PCSK9 inhibitors that include populations that overlap with the VESALIUS-CV trial population, including the VICTORION-1 PREVENT trial (ClinicalTrials.gov number, NCT05739383) and the CORALreef Outcomes–TIMI 77 trial (NCT06008756), may provide further insights.

Here, we report the results of a placebo-controlled cardiovascular-outcomes trial of a PCSK9 inhibitor with a median follow-up of 4.6 years, which provided longer-term follow-up than other PCSK9 inhibitor cardiovascular-outcomes trials and is on par with the average follow-up in the seminal statin trials.[5] The lag in the onset of cardiovascular benefit with lowering of the LDL cholesterol level has been well described, with the magnitude of clinical benefit increasing over time.[5,9] Thus, the previous, shorter trials of PCSK9 inhibitors are likely to have underestimated the long-term clinical benefit.[2,3] With the longer follow-up in the VESALIUS-CV trial, the magnitude of cardiovascular benefit, normalized to the amount of lowering of the LDL cholesterol level, appeared to be consistent with the previous meta-regression analyses for statin therapy.[5,9]

Moreover, the duration of follow-up is particularly relevant for detecting a benefit for fatal outcomes, as seen in statin trials in which the effect only became apparent after several years of follow-up.[10,11] Although the observed lower rates of death from cardiovascular causes and death from any cause in the evolocumab group than in the placebo group in the VESALIUS-CV trial are exploratory on the basis of the testing hierarchy, these observations, coupled with the data from mendelian randomization studies showing that *PCSK9* variants were associated with a lower risk of death from coronary heart disease, and the observed effects on death from cardiovascular causes in the FOURIER-OLE (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk–Open Label Extension) trial and on death from any

cause in the ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes after an Acute Coronary Syndrome during Treatment with Alirocumab) trial, support the notion that long-term lowering of LDL cholesterol levels with PCSK9 inhibitors, as with statins, can help prevent fatal events.[3,12,13]

In the cohort of patients included in the lipid substudy, the median LDL cholesterol level at 48 weeks was 45 mg per deciliter in the evolocumab group. Guidelines have recommended progressively lower goals for LDL cholesterol of less than 70 mg per deciliter (1.80 mmol per liter) and, more recently, less than 55 mg per deciliter (1.40 mmol per liter) in patients at very high risk; in fact, the most recent European guideline endorsed consideration of a goal below 40 mg per deciliter (1.05 mmol per liter) in patients at extreme risk.[6,14-16] The current trial, in which patients in the evolocumab group in the lipid substudy had a median LDL cholesterol level of 45 mg per deciliter at 48 weeks, provides evidence in support of a target in this range for patients without a previous major atherosclerotic cardiovascular disease event.

This trial has some limitations. Although the majority of patients were taking a high-intensity statin or high-intensity lipid-lowering therapy, the trial included a subset of patients with less-intensive or no background lipid-lowering therapy. However, the benefit of evolocumab therapy appeared to be consistent regardless of the intensity of statin therapy or ezetimibe use, and the percentages of patients taking high-intensity lipid-lowering therapy in this trial were greater than those observed in multiple registries around the world.[17-19] The vast majority of the patients were White, which reflects the demographic characteristics of the countries that contributed most to enrollment, so our findings may not be generalizable to other populations. The representativeness of the trial population is discussed in Table S6.

In this trial, we found that treatment with the PCSK9 inhibitor evolocumab led to a lower risk of first major adverse cardiovascular events than placebo among patients with atherosclerosis or diabetes and without a previous myocardial infarction or stroke.

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AUTHOR INFORMATION

[1] Thrombolysis in Myocardial Infarction (TIMI) Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston; [2] Amgen, Thousand Oaks, CA; [3] Cardiology Division, Department of Medical Sciences, University of Turin and Azienda Ospedaliero–Universitaria Città della Salute e della Scienza, Turin, Italy; [4] Division of Endocrinology and Metabolism, St. Michael's Hospital, University of Toronto, Toronto; [5] Instituto do Coracao, Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo, Universidade de São Paulo, São Paulo; [6] Third Department of Internal Medicine–Metabolism and Gerontology, Faculty of Medicine in Hradec Králové, University Hospital Hradec Králové and Charles University, Hradec Králové, Czech Republic; [7] Department of Cardiology, Center of Postgraduate Medical Education, Grochowski Hospital, Warsaw, Poland; [8] Department of Cardiology, Noordwest Ziekenhuisgroep, Alkmaar and Radboudumc, Nijmegen, the Netherlands; [9] Clinic of Cardiology, Tsaritsa Yoanna Hospital, Medical University–Sofia, Sofia, Bulgaria; [10] Cardiovascular Center, Semmelweis University, Budapest, Hungary; [11] DAMIC (Docencia Asistencia Médica e Investigación Clínica) Medical Institute and Rusculleda Foundation for Research, Cordoba, Argentina; [12] National Scientific Center "M.D. Strazhesko Institute of Cardiology," Kyiv, Ukraine.

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