Consistent LDL-C response with evolocumab among patient subgroups in PROFICIO: A pooled analysis of 3146 patients from phase 3 studies

Erik Stroes1 | Jennifer G. Robinson2 | Frederick J. Raal3 | Robert Dufour4 | David Sullivan5 | Helina Kassahun6 | Yuhui Ma6 | Scott M. Wasserman6 | Michael J. Koren7

1Department of Vascular Medicine, Academic Medical Center of Amsterdam, Amsterdam, Netherlands
2Departments of Epidemiology and Medicine, University of Iowa, Iowa City, Iowa
3Department of Medicine, University of the Witwatersrand, Faculty of Health Sciences, Johannesburg, South Africa
4Institut de recherches cliniques de Montréal, Université de Montréal, Montreal, Canada
5Department of Clinical Biochemistry, Prince Alfred Hospital, Camperdown, Australia
6Amgen Inc., Thousand Oaks, California
7Jacksonville Center for Clinical Research, Jacksonville, Florida

Correspondence
Erik Stroes, MD, PhD, F4.211, Academic Medical Center, Meibergdreef 9, 1105 AZ, Amsterdam, Netherlands
Email: e.s.stroes@amc.uva.nl

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Background: Evolocumab significantly lowers low-density lipoprotein cholesterol (LDL-C) when dosed 140 mg every 2 weeks (Q2W) or 420 mg monthly (QM) subcutaneously.

Hypothesis: LDL-C changes are comparable among different patient subgroups in a pooled analysis of data from phase 3 trials.

Methods: A total of 3146 patients received ≥1 dose of evolocumab or control in four 12-week phase 3 studies. Percent change from baseline in LDL-C for evolocumab 140 mg Q2W or 420 mg QM vs control was reported as the average of week 10 and 12 values. Quantitative and qualitative interactions between treatment group and subgroup by dose regimen were tested.

Results: In the pooled analysis, treatment differences vs placebo or ezetimibe were similar for both 140 mg Q2W and 420 mg QM doses across ages (<65 years, ≥65 years); gender; race (Asian, black, white, other); ethnicity (Hispanic, non-Hispanic); region (Europe, North America, Asia Pacific); glucose tolerance status (type 2 diabetes mellitus, metabolic syndrome, neither); National Cholesterol Education Program risk categories (high, moderately high, moderate, low); and European Society of Cardiology/European Atherosclerosis Society risk categories (very high, high, moderate, or low). Certain low-magnitude variations in LDL-C lowering among subgroups led to significant quantitative interaction P values that, when tested by qualitative interaction, were not significant. The incidences of adverse events were similar across groups treated with each evolocumab dosing regimen or control.

Conclusions: Consistent reductions in LDL-C were observed in the evolocumab group regardless of demographic and disease characteristics.

KEYWORDS
age, cardiovascular disease, diabetes, dose, gender, race

INTRODUCTION

The importance of reducing low-density lipoprotein cholesterol (LDL-C) to lower morbidity and mortality associated with cardiovascular disease is well established. Current guidelines recommend statins as first-line treatment for hypercholesterolemia in patients at high risk for cardiovascular mortality.1–5 Despite the cholesterol-lowering effect of statins, a subset of patients may require additional LDL-C-lowering to reach risk-stratified LDL-C levels or to further reduce cardiovascular risk.4,6–9 The development of monoclonal antibodies that bind proprotein convertase subtilisin/kexin type 9 (PCSK9) has allowed for additional highly effective treatment options for hypercholesterolemia.

Evolocumab is a human monoclonal antibody against PCSK9. The Program to Reduce LDL-C and Cardiovascular Outcomes Following Inhibition of PCSK9 (PROFICIO) is a comprehensive clinical trial program that established evolocumab efficacy and safety in diverse patient populations with hypercholesterolemia, including those with familial hypercholesterolemia or statin intolerance.10–19 Within each of these studies, approved evolocumab dosing regimens have substantially and consistently reduced LDL-C.
To further elucidate the LDL-C lowering associated with each evolocumab dosing regimen for patient subsets defined by demographic and disease characteristics, we performed a pooled analysis to assess evolocumab efficacy compared to placebo or control from patients enrolled in four randomized placebo- or ezetimibe-controlled phase 3 trials.

2 | METHODS

Data were analyzed from patients enrolled in four randomized 12-week phase 3 evolocumab clinical trials (Table S1, Supporting information). Background lipid therapies included statin alone or with ezetimibe. The evolocumab dosing regimens were 140 mg subcutaneously every 2 weeks (Q2W) and 420 mg monthly (QM) (Table S1). An ezetimibe treatment arm was included in three trials. All patients provided written informed consent. The individual protocols were approved by each institutional review board and the investigations were in accordance with the Declaration of Helsinki. Additional methods for each trial have been reported elsewhere.

Patient subgroups for the current analysis were defined according to baseline demographic and disease characteristics (Table 1) and were prespecified in the statistical analysis plans.

2.1 | Efficacy and safety endpoints

For this analysis, the primary outcome was the difference in percent change from baseline in LDL-C between each evolocumab dosing regimen and control using the mean of week 10 and 12 LDL-C values. Key safety endpoints were treatment-emergent and serious adverse events (AEs), laboratory parameters, and anti-evolocumab antibodies.

2.2 | Statistical analysis

Data from 3146 patients who were randomized and received at least one dose of evolocumab or control were evaluated for efficacy and safety. Mean treatment effect differences and 95% confidence intervals (CIs) within each subgroup were estimated on the average of week 10 and 12 LDL-C values. Key safety endpoints were treatment-emergent and serious adverse events (AEs), laboratory parameters, and anti-evolocumab antibodies.

3 | RESULTS

3.1 | Baseline characteristics

The patient populations of the evolocumab trials included in this analysis are summarized in Table S1. Included in these trials were patients with primary hypercholesterolemia and cardiovascular risk of various levels, familial hypercholesterolemia, and prior intolerance to ≥2 statins. Baseline characteristics of the pooled population from the trials are summarized in Table S2. In the pooled population, the mean age of participants was 57.8 years, 49.4% of patients were women, 91.5% were white, and 54.1% were receiving statins. The mean (SD) baseline calculated LDL-C was 3.3 (1.3) mmol/L, and 33.8% of patients were at high risk according to National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) cardiovascular risk categories.

3.2 | LDL-C reduction in overall population

In the individual studies, the mean percent change from baseline in LDL-C ranged from −74.9% (95% CI: −84.5, −65.3) to −56.5% (95% CI: −59.9, −53.0) in patients receiving evolocumab 140 mg Q2W vs placebo; from −74.8% (95% CI: −83.0, −66.6) to −57.4% (95% CI: −60.7, −54.1) in patients receiving evolocumab 420 mg QM vs placebo; from −44.9% (95% CI: −54.3, −35.6) to −36.9% (95% CI: −42.3, −31.5) in patients receiving evolocumab 140 mg Q2W vs ezetimibe; and from −43.8% (95% CI: −52.1, −35.5) to −38.7% (95% CI: −43.1, −34.3) in patients receiving evolocumab 420 mg QM vs ezetimibe (Table S3).

Among all patients in this integrated population from all trials, mean percent changes from baseline in LDL-C were −65.7% (95% CI: −70.9, −60.6; evolocumab 140 mg Q2W) and −65.0% (95% CI: −69.5, −60.4; evolocumab 420 mg QM) vs placebo, and −38.9% (95% CI: −41.3, −36.4; evolocumab 140 mg Q2W) and −43.0% (95% CI: −42.6, −38.0; evolocumab 420 mg QM) vs ezetimibe (Table S4).

At the week 2, 8, 10, and 12 scheduled post-baseline assessments, mean percent change from baseline in LDL-C ranged from −53.7% to −60.5% and from −55.5% to −67.8% for the Q2W and QM regimens, respectively, and consistent reductions in LDL-C were observed in evolocumab-treated groups compared to placebo- or ezetimibe-treated groups (Figure 1). Waterfall plots demonstrate consistent patient-level LDL-C reductions with evolocumab plus statins compared to statin plus placebo (Figure 2A) or with evolocumab monotherapy compared to placebo alone (Figure 2B) among patients who were not statin intolerant. In the statin combination studies, the proportion of responders (LDL-C reduction of ≥15%) was 98.3% among evaluable patients receiving evolocumab 140 mg Q2W plus...
### Table 1: LDL-C reductions by evolocumab dosing regimen and patient subgroup

| Subgroup | Evolocumab Q2W vs placebo | Evolocumab QM vs placebo | Evolocumab Q2W vs ezetimibe | Evolocumab QM vs ezetimibe |
|----------|----------------------------|--------------------------|-----------------------------|---------------------------|
| **Age, years** |                             |                           |                             |                           |
| <65      | −65.4 (−68.2, −62.6)        | −65.3 (−68.3, −62.3)      | −39.5 (−43.0, −35.9)        | −44.0 (−47.2, −40.8)      |
| ≥65      | −65.9 (−69.7, −62.0)        | −64.4 (−68.8, −60.1)      | −40.1 (−44.8, −35.4)        | −35.6 (−40.1, −31.0)      |
| Interaction P value (quantitative) | 0.86                      | 0.74                      | 0.83                        | 0.003                     |
| Interaction P value (qualitative) | NA                        | NA                        | NA                          | 0.5                       |
| **Gender** |                             |                           |                             |                           |
| Male     | −68.5 (−71.8, −65.2)        | −67.2 (−70.3, −64.1)      | −43.0 (−47.3, −38.7)        | −43.8 (−47.5, −40.1)      |
| Female   | −62.6 (−65.7, −59.4)        | −62.9 (−66.8, −59.0)      | −36.6 (−40.2, −33.0)        | −38.8 (−42.5, −35.1)      |
| Interaction P value (quantitative) | 0.01                      | 0.09                      | 0.025                       | 0.06                      |
| Interaction P value (qualitative) | NA                        | NA                        | NA                          | NA                       |
| **Race** |                             |                           |                             |                           |
| Asian    | −61.1 (−70.4, −51.8)        | −66.3 (−75.6, −56.9)      | −41.5 (−55.4, −27.7)        | −52.9 (−62.2, −43.7)      |
| Black    | −72.6 (−82.5, −62.6)        | −58.4 (−70.5, −46.3)      | −44.3 (−58.9, −29.8)        | −47.3 (−61.0, −33.6)      |
| White    | −65.7 (−68.1, −63.3)        | −65.2 (−67.8, −62.5)      | −39.2 (−42.2, −36.3)        | −40.6 (−43.4, −37.7)      |
| Other    | −70.5 (−89.1, −52.0)        | NA                        | NA                          | NA                       |
| Interaction P value (quantitative) | 0.37                      | 0.52                      | 0.75                        | 0.034                     |
| Interaction P value (qualitative) | NA                        | NA                        | NA                          | 0.875                     |
| **Ethnicity** |                             |                           |                             |                           |
| Hispanic | −77.4 (−92.6, −62.3)        | −63.5 (−79.0, −48.1)      | −36.6 (−46.8, −26.3)        | −38.1 (−52.1, −24.2)      |
| Non-Hispanic | −64.9 (−67.2, −62.7)    | −65.2 (−67.7, −62.7)      | −39.8 (−42.7, −36.9)        | −41.6 (−44.2, −38.9)      |
| Interaction P value (quantitative) | 0.11                      | 0.83                      | 0.54                        | 0.63                      |
| **Region** |                             |                           |                             |                           |
| Europe   | −66.7 (−69.9, −63.6)        | −63.2 (−66.8, −59.7)      | −38.5 (−43.2, −33.7)        | −40.6 (−44.7, −36.4)      |
| North America | −65.6 (−69.4, −61.9)    | −67.2 (−71.1, −63.2)      | −41.4 (−45.0, −37.9)        | −42.1 (−45.7, −38.5)      |
| Asia Pacific | −57.8 (−64.3, −51.3)    | −66.2 (−72.2, −60.2)      | −36.5 (−45.0, −28.1)        | −48.0 (−55.9, −40.0)      |
| Interaction P value (quantitative) | 0.051                     | 0.32                      | 0.43                        | 0.26                      |
| **Glucose tolerance** |                             |                           |                             |                           |
| Diabetic | −66.4 (−74.9, −57.9)        | −62.0 (−72.6, −51.3)      | −36.5 (−46.3, −26.6)        | −42.5 (−52.2, −32.9)      |
| Metabolic syndrome<sup>b</sup> | −70.0 (−74.1, −65.9)   | −63.8 (−67.7, −59.8)      | −40.9 (−44.8, −37.0)        | −44.8 (−49.2, −40.4)      |
| No diabetes or metabolic syndrome | −63.5 (−66.5, −60.5)    | −66.7 (−69.7, −63.6)      | −39.7 (−43.7, −35.6)        | −39.1 (−42.5, −35.7)      |
| Interaction P value (quantitative) | 0.04                      | 0.42                      | 0.70                        | 0.12                      |
| Interaction P value (qualitative) | 0.75                      | NA                        | NA                          | NA                       |
| **NCEP risk** |                             |                           |                             |                           |
| High     | −65.0 (−69.1, −61.0)        | −64.6 (−69.6, −59.6)      | −40.4 (−46.6, −34.2)        | −42.0 (−47.9, −36.1)      |
| Moderately high | −72.6 (−80.5, −64.6)   | −62.0 (−67.9, −56.1)      | −48.0 (−57.8, −38.3)        | −39.7 (−46.0, −33.4)      |
| Moderate | −67.9 (−72.5, −63.4)        | −64.9 (−69.5, −60.3)      | −39.4 (−43.9, −34.9)        | −42.1 (−47.0, −37.2)      |
| Low      | −61.8 (−65.7, −57.9)        | −65.6 (−69.7, −61.6)      | −36.7 (−40.9, −32.4)        | −41.0 (−44.8, −37.2)      |
| Interaction P value (quantitative) | 0.016                     | 0.47                      | 0.007                       | 0.89                      |
| Interaction P value (qualitative) | 0.875                     | NA                        | 0.875                       | NA                       |
| **ESC/EAS risk** |                             |                           |                             |                           |
| Very high | −66.5 (−70.4, −62.5)        | −62.7 (−67.2, −58.1)      | −41.1 (−46.8, −35.3)        | −40.4 (−45.7, −35.1)      |
| High     | −65.7 (−72.1, −59.3)        | −68.9 (−74.9, −62.9)      | −44.2 (−54.9, −33.4)        | −45.5 (−57.8, −33.2)      |
| Moderate | −66.0 (−69.7, −62.3)        | −65.0 (−68.9, −61.1)      | −37.9 (−41.8, −34.1)        | −38.8 (−42.4, −35.3)      |
| Low      | −60.5 (−67.3, −53.8)        | −67.8 (−73.7, −62.0)      | −41.5 (−47.4, −35.7)        | −48.5 (−54.1, −43.0)      |
| Interaction P value (quantitative) | 0.53                      | 0.19                      | 0.65                        | 0.009                     |
| Interaction P value (qualitative) | NA                        | NA                        | NA                          | 0.875                     |

Abbreviations: CI, confidence interval; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; NCEP, National Cholesterol Education Program; Q2W, every 2 weeks; QM, monthly.

*All treatment differences between evolocumab and control were statistically significant with a P value < 0.001.

*Defined as no type 2 diabetes mellitus and three or more of the following conditions: fasting glucose ≥100 mg/dL, triglycerides ≥150 mg/dL, high blood pressure based on systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or answer of "Yes" to the hypertension question on case report form (CRF), elevated waist circumference, or answer of "Yes" to the question "Low HDL" on CRF."
statins, 96.9% among patients receiving evolocumab 420 mg QM plus statins, and 12.5% among patients receiving placebo plus statins. In the monotherapy study, the proportion of responders was 100% among evaluable patients receiving evolocumab 140 mg Q2W, 100% among patients receiving evolocumab 420 mg QM, and 8.8% among patients receiving placebo.

3.3 | LDL-C reduction by subgroup

Treatment differences in mean percent change from baseline in LDL-C between evolocumab and placebo and between evolocumab and ezetimibe were similar for both 140 mg Q2W and 420 mg QM doses across studies and subgroups (Table 1 and Figure 3). Within each subgroup, evolocumab 140 mg Q2W and 420 QM demonstrated statistically significant mean reductions in LDL-C from baseline as compared to placebo or ezetimibe (P < 0.001).

Due to the large sample size from the four integrated studies, a small magnitude of variation in LDL-C reduction among subgroups led to quantitative interaction P values of <0.05 for certain subgroups. In patients treated with evolocumab Q2W vs ezetimibe, greater LDL-C reductions were observed in men (interaction P = 0.025) and patients with NCEP risk category of moderately high vs other risk categories (interaction P = 0.007). In patients treated with evolocumab Q2W vs placebo, greater LDL-C reductions were observed in men vs women (interaction P = 0.01), in patients with metabolic syndrome vs those with diabetes or without diabetes/metabolic syndrome (interaction P = 0.04), and in patients with NCEP risk category of moderately high vs other risk categories (interaction P = 0.016). In patients treated with evolocumab QM vs ezetimibe, greater LDL-C reductions were observed in patients younger than 65 years old (interaction P = 0.003), Asian patients (interaction P = 0.034), and patients with ESC/EAS risk category of low (interaction P = 0.009). For these subgroups, qualitative interaction testing demonstrated common directionality of LDL-C lowering effect among subgroups and non-significant P values. No significant quantitative interactions were observed in the evolocumab QM vs placebo group.

The relationship between gender and LDL-C reduction with evolocumab Q2W vs placebo or ezetimibe was further evaluated. Results from the individual phase 3 studies did not show a consistent pattern. Exploratory analyses adjusting for the covariates of age, body mass index, baseline LDL-C, baseline PCSK9, and baseline statin in both univariate and multivariate settings did not result in notable changes in treatment effect and interaction P value of treatment by gender, indicating no evidence of confounding factors.

3.4 | Safety

In the integrated population, the incidences of AEs and laboratory parameter elevations were similar across groups treated with each evolocumab dosing regimen or control. The rates of overall AEs were 43.8% (evolocumab 140 mg Q2W), 43.4% (evolocumab 420 mg QM), 48.8% (ezetimibe), and 41.8% (placebo) (Table 2). Serious AEs occurred in 2.6%, 1.7%, 1.5%, and 2.3% of patients across the same groups, respectively. Muscle-related AEs were highest in the ezetimibe-treated group (7.8%) as compared to evolocumab 140 mg Q2W (3.5%), evolocumab 420 mg QM (3.8%), or placebo (2.9%). A creatine kinase elevation of >5 times the upper limit of normal (xULN) occurred in <1% of patients in any arm. Injection site reactions occurred with similar incidence between the evolocumab-treated arms (2.5%, 140 mg Q2W; 3.0%, 420 mg QM) and the control-treated arms (2.9%, ezetimibe; 2.4%, placebo). Neurocognitive events were infrequent, occurring in 0.1% of evolocumab-treated patients, 0.6% of ezetimibe-treated patients, and in no patients receiving placebo. Liver enzyme elevations of >3 xULN occurred in 0.5% (evolocumab 140 mg Q2W), 0.2% (evolocumab 420 mg QM), 0.8% (ezetimibe), and 1.3% (placebo) of patients. One of the four studies evaluated evolocumab in patients not receiving statins. Among this cohort, new-onset diabetes was observed in 1 (0.6%) evolocumab-treated patient. Binding anti-evolocumab antibodies were observed in three patients after evolocumab dosing; of these patients, one had binding antibodies at baseline. No neutralizing anti-evolocumab antibodies were detected. The low numbers of individual AEs precluded analysis of safety by subgroup.

FIGURE 1 Percent change from baseline in LDL-C by scheduled visit and treatment group. Abbreviations: LDL-C, low-density lipoprotein cholesterol; PO, orally; QD, daily; QM, monthly; Q2W, every 2 weeks; SC, subcutaneously; SE, standard error.
This pooled analysis demonstrated substantial reductions in LDL-C across various patient subgroups treated with evolocumab. A very low nonresponder rate was seen compared to placebo or placebo plus statins with or without other lipid-lowering therapy (such as ezetimibe), as illustrated in the waterfall plots. These plots indicate patient-level data for all patients enrolled with the exception of statin-intolerant patients (those enrolled in GAUSS-2), who were not eligible for efficacy analysis according to statin use. No substantial differences in responsiveness across dosing regimens and subgroups defined by demographic and disease characteristics were observed. Certain quantitative interactions between subgroup and LDL-C reduction by evolocumab reached statistical significance despite their small magnitude.

FIGURE 2 Waterfall plots showing percent change from baseline in LDL-C at the mean of weeks 10 and 12 in patients who did (A) and did not (B) receive combination statin therapy. Plot is based on observed data; no imputation is used for missing values. *patients with early termination. Abbreviations: LDL-C, low-density lipoprotein cholesterol; n, number of patients randomized, dosed and who were evaluable for LDL-C at the timepoint; QM, monthly; Q2W, every 2 weeks

4 | DISCUSSION

This pooled analysis demonstrated substantial reductions in LDL-C across various patient subgroups treated with evolocumab. A very low nonresponder rate was seen compared to placebo or placebo plus statins with or without other lipid-lowering therapy (such as ezetimibe), as illustrated in the waterfall plots. These plots indicate patient-level data for all patients enrolled with the exception of statin-intolerant patients (those enrolled in GAUSS-2), who were not eligible for efficacy analysis according to statin use. No substantial differences in responsiveness across dosing regimens and subgroups defined by demographic and disease characteristics were observed. Certain quantitative interactions between subgroup and LDL-C reduction by evolocumab reached statistical significance despite their small magnitude.
For example, in patients treated with evolocumab Q2W vs placebo or vs ezetimibe, greater LDL-C reductions were observed in men vs women, and in patients with NCEP risk category of moderately high vs other risk categories. These observations are not surprising, given that the sample size for each subgroup was large and evolocumab has a substantial treatment effect. The quantitative interaction test detected small differences in the magnitude of the treatment effect across the subgroups that are not clinically meaningful. Furthermore, qualitative interaction analysis demonstrated consistent directionality of effect and no statistically significant differences.

Potentially explanatory investigations into the cause of the observed numerical treatment effect in gender did not reveal alternative factors that could explain the results. In addition, P values were not adjusted for multiplicity; therefore, it is reasonable to suggest that the observed difference of treatment effect in gender was obtained by chance.

Results of the current study are consistent with those of a pooled analysis of phase 2 evolocumab studies. That pooled analysis, which included 1359 patients from 4 studies, demonstrated similar reductions in LDL-C with evolocumab dosed at 140 mg Q2W or 420 mg Q2W, every 2 weeks.
QM among subgroups defined by age, gender, statin use, baseline LDL-C level, and baseline triglyceride level. In this analysis, the interaction between evolocumab Q2W dosing and gender was also statistically significant (interaction $P = 0.03$), with women showing less LDL-C response than men. In the literature, various impacts of gender or gender-specific conditions on cholesterol and PCSK9 have been identified, including hormone therapy and menopause.22–29 However, data regarding hormone therapy or menopause were not collected in PROFICIO, and the potential role of any of the identified factors on the results of our current dataset is unknown. While this study was not designed to explore the biological and physiological pathways that underlie the gender differences in LDL-C reduction, it is hypothesis-generating for additional mechanistic studies.

The safety profile revealed no new concerns. Together with efficacy data, these results support a favorable benefit–risk profile for evolocumab across diverse patient populations.

A strength of this analysis is that it includes a very diverse population with patients who had participated in monotherapy, statin combination therapy, statin intolerance, and heterozygous familial hypercholesterolemia evolocumab trials. The analysis also includes data from two dosing options, Q2W and QM, and from both placebo- and ezetimibe-controlled trials. A limitation of our analysis is that this analysis was post hoc, with pooled data from four randomized studies.

5 | CONCLUSIONS

In this pooled analysis of data from patients enrolled in four phase 3 trials, evolocumab 140 mg Q2W and 420 mg QM demonstrated significantly greater reductions in LDL-C vs placebo or ezetimibe for all demographic and disease status subgroups. Substantial reductions in LDL-C were observed in the evolocumab group, regardless of age, race, background statin dose, or cardiovascular risk. Although several subgroup quantitative interaction comparisons were significant at the $P < 0.05$ level, the differences were of small magnitude. Very few non-responders were observed in comparison to patients on statins and other commonly employed compounds, including ezetimibe. Adverse events for the evolocumab 140 mg Q2W and 420 mg QM dosing regimens were overall similar to those observed with control.

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Conflict of interest

Dr. Stroes reports that his institution has received lecturing fees/grants from Amgen Inc., Merck, Novartis, Regeneron Pharmaceuticals, and Sanofi.

Dr. Robinson reports consulting fees from Amgen Inc., Eli Lilly, Merck, Pfizer, Regeneron Pharmaceuticals, and Sanofi, and reports that her institution has received grants from Acasci Pharma, Amarin Corporation, Amgen Inc., AstraZeneca, Eisai, Esperion, Merck, Pfizer, Regeneron Pharmaceuticals, Sanofi, and Takeda Pharmaceutical Company Ltd.

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Dr. Sullivan reports advisory committee/lecture fees from Abbott, Amgen Inc., AstraZeneca, Mylan, and Pfizer; and that he has received grants from Abbott, Amgen Inc., Mylan, Sanofi, and Novartis.

Drs. Kassahun and Wasserman are employees of and stockholders in Amgen Inc. Dr. Wasserman appears on a number of pending patents owned by Amgen Inc. relating to evolocumab and PCSK9 inhibition. Dr. Ma is employed on behalf of Amgen Inc.

Dr. Koren is employed by a company that has received research grants and consulting fees from Amgen Inc. and other companies developing therapies for hyperlipidemia.

ORCID

Erik Stroes https://orcid.org/0000-0001-9555-6260

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Sup- porting Information section at the end of the article.

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