Arteriosclerosis, Thrombosis, and Vascular Biology

CLINICAL AND POPULATION STUDIES

Evolocumab Treatment in Pediatric Patients With Homozygous Familial Hypercholesterolemia: Pooled Data From Three Open-Label Studies

Frederick J. Raal, Robert A. Hegele, Andrea Ruzza, J. Antonio G. López, Ajay K. Bhatia, Johnny Wu, Huei Wang, Daniel Gaudet, Albert Wiegman, Jian Wang, Raul D. Santos

BACKGROUND: Pediatric patients with homozygous familial hypercholesterolemia (HoFH) have an increased risk of atherosclerotic cardiovascular disease and difficulty meeting low-density lipoprotein cholesterol (LDL-C) goals. In this post hoc analysis, we evaluated pooled safety and efficacy data from 3 studies in pediatric patients with HoFH treated with the PCSK9 (proprotein convertase subtilisin/kexin type 9) monoclonal antibody inhibitor evolocumab.

METHODS: Patients with HoFH aged 10 to 17 years received treatment with open-label evolocumab 420 mg subcutaneously monthly or biweekly in the TAUSSIG, RAMAN, or HAUSER-OLE clinical studies. All patients received background statins with or without ezetimibe. Study duration ranged from 12 to 260 weeks. The primary end point was treatment-emergent adverse events per 100 patient-years. Efficacy end points were changes from baseline to week 12 in lipids and PCSK9.

RESULTS: Of the 39 patients in the pooled analysis, 69.2% were males, median age was 13.0 years, and 79.5% (31/39) had genotyped HoFH with *LDLR* pathogenic variants. Overall, median exposure to evolocumab was 18.2 (Q1, Q3: 3.0, 18.5) months. Treatment-emergent adverse events with an exposure-adjusted patient incidence rate of ≥5% were upper respiratory tract infection (6.6%), influenza (5.2%), and acne (5.0%) per 100 patient-years. Exposure-adjusted patient incidence of serious treatment-emergent adverse events was 13.3% per 100 patient-years. Excluding 4 patients receiving lipoprotein apheresis, week 12 median percentage change from baseline in LDL-C was −2.9% (Q1, Q3: −21.7, 1.5); however, 42.9% (15/35) of patients achieved ≥15% reduction in LDL-C from baseline. Residual LDLR (LDL receptor) activity was not associated with a reduction in LDL-C.

CONCLUSIONS: In this pooled data analysis from 3 studies in pediatric patients with HoFH, evolocumab was well tolerated, with no new safety signals reported. These safety findings are consistent with findings from previous studies of evolocumab. Patients showed marked variability in LDL-C reduction. Results from this pooled analysis support guidelines suggesting a trial of PCSK9 inhibitor therapy regardless of estimated residual LDLR function.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01624142, NCT03403374, and NCT02624869.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: atherosclerosis ■ cardiovascular disease ■ hyperlipidemia ■ lipoproteins, LDL

Homozygous familial hypercholesterolemia (HoFH) is a serious, rare inherited disorder affecting ≈1 in 300 000 persons worldwide.[1] Most patients with HoFH have pathogenic variants in both alleles of the *LDLR* gene encoding the LDLR (LDL [low-density lipoprotein] receptor); however, the condition can also be caused by variants in the receptor-binding domain of the *APOB* gene encoding Apo (apolipoprotein) B, gain-of-function

Correspondence to: Frederick J. Raal, MD, PhD, Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Health Sciences, University of the Witwatersrand, Area 551, Department of Medicine, Johannesburg Hospital, 7 York Rd, Parktown, 2193, Johannesburg, South Africa. Email frederick.raal@wits.ac.za
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/ATVBAHA.123.320268.
For Sources of Funding and Disclosures, see page 1163.

Arterioscler Thromb Vasc Biol is available at www.ahajournals.org/journal/atvb

Nonstandard Abbreviations and Acronyms

HoFH	homozygous familial hypercholesterolemia
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
Lp(a)	lipoprotein(a)
PCSK9	proprotein convertase subtilisin/kexin type 9
TEAE	treatment-emergent adverse event

Highlights

- Safety and efficacy were determined from pooled data from 3 studies of pediatric patients with homozygous familial hypercholesterolemia treated with the PCSK9 (proprotein convertase subtilisin/kexin type 9) monoclonal antibody inhibitor evolocumab.
- Evolocumab was well tolerated, with no new safety signals reported, consistent with results from previous evolocumab clinical trials and real-world studies in adults.
- Pediatric patients with homozygous familial hypercholesterolemia treated with evolocumab showed marked variability in low-density lipoprotein cholesterol reduction.
- Results from the analysis of pooled data from the 3 evolocumab studies support guidelines suggesting a trial of PCSK9 inhibitor therapy in patients with homozygous familial hypercholesterolemia, regardless of estimated residual low-density lipoprotein receptor function.

variants in the *PCSK9* gene encoding PCSK9 (proprotein convertase subtilisin/kexin type 9), or rarely, the *LDLRAP1* gene encoding LDLR adaptor protein 1. As a result of markedly reduced hepatic clearance of LDL, plasma levels of LDL cholesterol (LDL-C) are markedly elevated, often 4-fold or greater, resulting in premature atherosclerotic cardiovascular disease and aortic/supra-aortic valve disease, often leading to disability or death at a very young age.[1] Lipid-lowering therapy should be initiated as early as possible to reduce the LDL-C burden. Unfortunately, high-intensity statins and ezetimibe, which act mainly by upregulating LDLR activity, are only partially effective in patients with HoFH, and additional lipid-lowering therapies are nearly always required.

PCSK9 inhibitors have been shown to lower LDL-C levels by a further 21% to 30% in patients with HoFH who still exhibit some residual LDLR activity[2–5] but are poorly effective in those with minimal or complete absence of LDLR activity (eg, those with biallelic null variants). However, there is marked interindividual variability in response to PCSK9 inhibitor therapy, even in those with identical *LDLR* variants.[6]

Here, we report results from a post hoc analysis of pooled safety and efficacy data from patients who participated in one of the 3 clinical studies[4,7,8] that evaluated treatment with subcutaneous evolocumab 420 mg monthly or biweekly in pediatric patients with HoFH. We also report on the relationship between the reduction in LDL-C achieved and underlying genetic variants.

METHODS

All supporting data are available within the article and its Supplemental Material.

Data Sharing Statement

Qualified researchers may request data from Amgen clinical studies. Complete details are available at http://www.amgen.com/datasharing.

Study Design and Participants

In this post hoc analysis, data from pediatric patients aged 10 to 17 years with HoFH were pooled from 3 single-arm, open-label, multicenter studies of evolocumab treatment: TAUSSIG (ClinicalTrials.gov, NCT01624142), RAMAN (ClinicalTrials.gov, NCT03403374), and HAUSER-OLE (ClinicalTrials.gov, NCT02624869).

Detailed inclusion and exclusion criteria for the 3 studies that have been previously published,[4,7,8] and distinguishing details of the methods for each study are presented in Table S1. Data from patients with HoFH in the HAUSER-OLE study (n=13) have not previously been reported; therefore, treatment-emergent adverse events (TEAEs) and lipid results for this group of patients through the 80 weeks of the OLE were specifically analyzed and reported here. Patients included in the pooled post hoc analysis dataset were aged 10 to 17 years, received at least 1 dose of evolocumab, and had a diagnosis of HoFH either by genotype or clinical criteria (ie, history of untreated LDL-C>500 mg/dL [13 mmol/L] plus xanthomas before age 10 years or evidence of heterozygous familial hypercholesterolemia in both parents). All patients had plasma LDL-C≥3.4 mmol/L (130 mg/dL) and a triglyceride level ≤4.5 mmol/L (400 mg/dL) at screening. Patients were advised to follow a low-fat diet and received background-optimized lipid-lowering therapy per local guidelines.

Procedures

Methods and results from TAUSSIG[4] and RAMAN[7] have been previously published. Methods and results from HAUSER-OLE have been published only for patients with heterozygous familial hypercholesterolemia.[8] The 3 studies were similar in administering subcutaneous evolocumab 420 mg either monthly or biweekly, and all had a visit at week 12, which is the efficacy assessment point for this pooled analysis. The studies varied in length (12 weeks to 5 years), visit schedules, geographic location of patients, and time window of data collection (see Table S1). Adverse event data were collected at all visits.

All 3 studies were conducted in accordance with the principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference on Harmonisation,

and relevant regulatory requirements. The study protocols were approved by the local institutional review boards. Written informed consent was obtained from legal guardians, and patient assent was obtained per local guidelines.

Outcomes

The primary end point for this analysis was the occurrence of TEAEs during the entire treatment period of each study, which varied from 12 to 260 weeks. TEAEs were defined as adverse events that occurred between the first dose of the investigational product and up to 30 days after either the last dose of the investigational product or the end of the study, whichever occurred first. TEAEs and serious TEAEs could have been either observed by the investigator, based on a laboratory finding, or reported by the patient.

The following were also measured at baseline and week 12: LDL-C, non–high-density lipoprotein cholesterol, ApoB, high-density lipoprotein cholesterol, triglycerides, Lp(a) (lipoprotein[a]), and free PCSK9 concentrations. Absolute and percentage changes from baseline concentrations of lipids and free PCSK9 were also analyzed.

Sample Size

The sample size was determined by the number of patients available in each data set within the desired age range, and no power calculations were performed.

Statistical Analysis

Safety and efficacy analyses included all patients with HoFH in the 3 studies who met the baseline age criteria and received study medication (referred to as the pooled analysis set). No formal hypothesis testing or multiplicity adjustment for type I error were performed. All end points were analyzed descriptively with frequency and percentage for categorical variables and n, mean (and SD or SE), or median (and quartile [Q]1 and Q3) for continuous variables. Results are reported for the pooled analysis set overall and by lipoprotein apheresis status.

TEAE terms were coded using the Medical Dictionary for Regulatory Activities, version 24.0, and severity was graded using Common Terminology Criteria for Adverse Events, version 4.0. TEAEs were summarized by system organ class and preferred term. Because of the wide range of evolocumab exposure across the included studies, TEAEs are reported as exposure-adjusted patient incidence rate (ie, incidence per 100 patient-years).

For all patients with genetic information, *LDLR* genetic variants were identified and classified by residual LDLR activity per American College of Medical Genetics and Genomics/Association for Molecular Pathology criteria.[9] Although some of the genetic variants have been previously reported, *LDLR* variant classifications have been substantially updated since the publication of those results. Patients were categorized according to whether the LDLR activity in each allele was null or defective, with resulting categories of defective/defective, defective/null, and null/null. For summary analyses, patients with at least 1 defective allele were grouped together as non-null.

Observed data are reported, and missing values were not imputed. Descriptive analyses were performed with SAS version 9.4 (Cary, NC).

RESULTS

This pooled analysis set included 39 patients who received at least 1 dose of open-label evolocumab, of whom 4 received lipoprotein apheresis. Of the 35 patients who did not receive lipoprotein apheresis, 11/35 (31.4%) discontinued evolocumab during their study; 3/35 (8.6%) discontinued due to the patient's request, 7/35 (20.0%) discontinued due to the sponsor's decision to close the TAUSSIG study early for administrative reasons (ie, not due to efficacy or safety), and 1/35 (2.9%) discontinued due to the investigator's decision. Median (Q1, Q3) evolocumab exposure for the nonapheresis patients was 18.2 (2.9, 18.5) months. Of the patients receiving lipoprotein apheresis, 4/4 discontinued evolocumab during their study, 2/4 discontinued due to the sponsor's decision to close the TAUSSIG study for administrative reasons, and 2/4 discontinued due to the investigator's decision. Median (Q1, Q3) evolocumab exposure for the lipoprotein apheresis patients was 29.2 (6.4, 52.5) months. Across the 39 patients, median (Q1, Q3) exposure to evolocumab was 18.2 (3.0, 18.5) months. No patients discontinued because of adverse events, and all 39 patients had LDL-C data at week 12.

Baseline demographic and disease characteristics of patients are shown in Table 1. The median (Q1, Q3) age of the 39 patients was 13.0 (12.0, 15.0) years; 69.2% (27/39) were male patients, and 30.8% (12/39) were female patients; 51.3% (20/39) were White patients and 38.5% (15/39) were Asian; and 20.5% (8/39) had a history of coronary artery disease. All patients had a diagnosis of HoFH at enrollment, with 79.5% (31/39) having genetic evidence for the HoFH diagnosis and 20.5% (8/39) having the HoFH diagnosis based on clinical criteria. Information on genetic variants for the 31 patients is shown in Table S2. All 31 patients had defects in the *LDLR* gene, with 45.2% (14/31) carrying at least 1 null variant. Defective/defective, defective/null, and null/null variant genotypes were encountered in 54.8% (17/31), 32.3% (10/31), and 12.9% (4/31) of patients, respectively.

One patient was not receiving statins at baseline (Table 1); the remaining patients were receiving high-intensity (87.2%, 34/39) or moderate-intensity (10.3%; 4/39) statin therapy, per the American College of Cardiology/American Heart Association/Multisociety Guideline on the Management of Blood Cholesterol definitions.[10] In addition, 87.2% (34/39) were receiving ezetimibe. One patient with background moderate-intensity statin therapy at baseline changed to high-intensity therapy after baseline. No other statin changes were recorded.

Safety

The overall exposure to evolocumab was 58.7 patient-years in the nonapheresis group, 10.0 patient-years in

Table 1. Baseline Characteristics

Characteristic	Patients with no lipoprotein apheresis (n=35)	Patients who received lipoprotein apheresis (n=4)	All patients (N=39)
Age, y			
Mean (SD)	13.4 (1.8)	14.3 (1.5)	13.5 (1.8)
Median (Q1, Q3)	13.0 (12.0, 14.0)	14.0 (13.0, 15.5)	13.0 (12.0, 15.0)
Sex, n (%)			
Males	24 (68.6)	3 (75.0)	27 (69.2)
Females	11 (31.4)	1 (25.0)	12 (30.8)
Ethnicity, n (%)			
Not Hispanic/Latino	35 (100.0)	2 (50.0)	37 (94.9)
Hispanic/Latino	0 (0)	2 (50.0)	2 (5.1)
Race,* n (%)			
White patients	18 (51.4)	2 (50.0)	20 (51.3)
Asian	15 (42.9)	0 (0)	15 (38.5)
Other	2 (5.7)	1 (25.0)	3 (7.7)
American Indian or Alaskan Native	0 (0)	1 (25.0)	1 (2.6)
Region, n (%)			
Asia Pacific	26 (74.3)	1 (25.0)	27 (69.2)
Europe	8 (22.9)	2 (50.0)	10 (25.6)
North America	1 (2.9)	1 (25.0)	2 (5.1)
Genetic evidence for diagnosis of HoFH, n (%)	27 (77.1)	4 (100.0)	31 (79.5)
LDLR mutation, n (%)	27 (77.1)	4 (100.0)	31 (79.5)
LDLR genotype, n (%)			
Homozygous (biallelic identical pathogenic variants)†	16 (45.7)	3 (75.0)	19 (48.7)
Compound heterozygous (biallelic different pathogenic variants)†	11 (31.4)	1 (25.0)	12 (30.8)
CHD characteristic, n (%)			
Low HDL-C‡	30 (85.7)	4 (100.0)	34 (87.2)
Family history of premature CHD	11 (31.4)	1 (25.0)	12 (30.8)
Coronary artery disease	6 (17.1)	2 (50.0)	8 (20.5)
Cerebrovascular or peripheral arterial disease	0 (0)	1 (25.0)	1 (2.6)
Hypertension	0 (0)	0 (0)	0 (0)
Type 2 diabetes	0 (0)	0 (0)	0 (0)
LLT at baseline, n (%)			
High-intensity statin§	32 (91.4)	2 (50.0)	34 (87.2)
Moderate-intensity statin§	2 (5.7)	2 (50.0)	4 (10.3)
No statin usage	1 (2.9)	0 (0)	1 (2.6)
Ezetimibe§	30 (85.7)	4 (100.0)	34 (87.2)
Lipids at baseline, median (Q1, Q3)			
LDL-C,‖ mmol/L	11.7 (8.9, 15.2)	8.7 (8.3, 9.1)	11.5 (8.7, 14.8)
Total cholesterol, mmol/L	13.1 (10.4, 16.3)	9.9 (9.4, 10.3)	12.5 (10.2, 15.8)
ApoB, g/L	2.5 (2.0, 3.3)	1.9 (1.8, 2.0)	2.5 (1.9, 3.2)
HDL-C, mmol/L	0.8 (0.6, 1.0)	0.8 (0.8, 0.9)	0.8 (0.6, 0.9)
Triglycerides, mmol/L	0.9 (0.8, 1.4)	0.7 (0.6, 0.9)	0.9 (0.7, 1.3)
Lp(a), nmol/L	110.0 (43.0, 187.0)	88.8 (25.3, 186.5)	110.0 (41.0, 187.0)
Free PCSK9,¶ nmol/L, median (Q1, Q3)	8.8 (6.3, 9.4)	6.1 (5.4, 7.7)	8.1 (6.1, 9.3)

CHD indicates coronary heart disease; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LDLR, LDL receptor; LLT, lipid-lowering therapy; Lp(a), lipoprotein(a); PCSK9, proprotein convertase subtilisin/kexin type 9; Q1, quartile 1; and Q3, quartile 3.

*No patients of race Black, Native Hawaiian/Other Pacific Islander, Multiple, or Unknown were enrolled.

†Nomenclature per Cuchel et al.[1]

‡Defined as baseline HDL-C<40 mg/dL for males and females who were aged 10 to <16 years. For patients with age ≥16 years, low LDL-C was defined as <40 mg/dL in males and <50 mg/dL in females.

§Per definition of the 2018 American Heart Association/American College of Cardiology/Multisociety Guideline on the Management of Blood Cholesterol.

‖When calculated LDL-C (by Friedewald equation) was <40 mg/dL or triglycerides were >400 mg/dL, calculated LDL-C was replaced with ultracentrifugation LDL-C from the same blood sample, if available.

¶PCSK9 data were not collected in the RAMAN study.

the lipoprotein apheresis group, and 68.7 patient-years for the total 39 patients.

In the nonapheresis group, at least 1 TEAE occurred in 21/35 (60.0%) patients (exposure-adjusted patient incidence rate of 114.8 per 100 patient-years; Table 2). The most frequent TEAEs were upper respiratory tract infection (7.9 per 100 patient-years), influenza (6.3 per 100 patient-years), and acne (3.8 per 100 patient-years). At least 1 serious TEAE occurred in 7/35 (20.0%) patients (16.4 per 100 patient-years). Serious TEAEs were appendicitis (in 2 patients), coronary artery occlusion, noncardiac chest pain, pleuritic pain, aortic stenosis, nephrolithiasis, ovarian germ cell teratoma, arteriovenous fistula aneurysm, and syncope (each occurring in 1 patient). One patient had a nonserious event of rash that led to discontinuation of evolocumab. Nonserious injection-site events (pain, swelling, and hemorrhage) occurred in 3 patients. No deaths occurred.

In the lipoprotein apheresis group, at least 1 TEAE occurred in 2/4 patients (118.6 per 100 patient-years). No TEAEs occurred in >1 person. No serious TEAEs, TEAEs leading to discontinuation, or injection-site reactions occurred in this group. No deaths occurred.

Across the 39 patients, TEAEs with an exposure-adjusted patient incidence rate of ≥5% were upper respiratory tract infection (6.6%), influenza (5.2%), and acne (5.0%). Exposure-adjusted patient incidence of serious TEAEs was 13.3%.

Changes in Lipids and Free PCSK9 Concentrations

Lipid-lowering response to evolocumab treatment varied across patients (Figure 1A; Table 3). Patients who were not receiving lipoprotein apheresis had a median (Q1, Q3) change in LDL-C of −2.9% (−21.7, 1.5; mean [SD], −10.0 [21.2]) at week 12, but with 42.9% (15/35) of patients achieving at least 15% reduction in LDL-C. The 4 patients receiving lipoprotein apheresis had a median (Q1, Q3) increase in LDL-C of 10.7% (−3.8, 29.6; mean [SD], 12.9 [20.8]) at week 12.

Of the 27 nonapheresis patients who had available genetic information and could be categorized according to LDLR residual activity, most patients (24/27; 88.9%) were categorized as defective/defective or defective/null. The patients had a range of responses to evolocumab at week 12 (Figure 2A), from 24.1% to −54.6% change in LDL-C, with a median (Q1, Q3) change of −3.0% (−29.9, 0.9). The 3/27 (11.1%) patients with null/null status had a median (Q1, Q3) change in LDL of −0.7% (−16.6, −0.2). Of the 4 apheresis patients, 3 were categorized as defective/defective or defective/null and had LDL-C changes of 38.1%, 0.3%, and −8.0% (Figure 2B). The 1 patient categorized as null/null had a 21.1% increase in LDL-C. Responses to evolocumab at week 12 for all 39 patients in the study, including those with and without genetic variant information, are shown in Figure S1.

Other atherogenic lipid measures (ApoB, Lp[a], non–high-density lipoprotein cholesterol, and triglycerides) showed overall patterns of minimal percentage improvements in the nonapheresis group and worsening in the lipoprotein apheresis group, with substantial variability across patients (Figure 1B and 1C; Table 3).

Free PCSK9 levels (Figure 1D; Table 3) had a median change of −54.7% (−69.0, −15.4) in the patients who were not receiving lipoprotein apheresis and −95.0% (−95.2, −94.6) in the 4 patients receiving lipoprotein apheresis.

Table 2. Exposure-Adjusted TEAEs

TEAE type	No lipoprotein apheresis (n=35)		Received lipoprotein apheresis (n=4)		Total (N=39)	
	No. of patients with events; time to first event in patient-years*	Exposure-adjusted patient rate per 100 patient-years	No. of patients with events; time to first event in patient-years*	Exposure-adjusted patient rate per 100 patient-years	No. of patients with events; time to first event in patient-years*	Exposure-adjusted patient rate per 100 patient-years
Any TEAE	21; 18.3	114.8	2; 1.7	118.6	23; 20.0	115.1
Serious TEAE	7; 42.7	16.4†	0; 10.0	0	7; 52.7	13.3
TEAE leading to discontinuation of evolocumab	1; 55.8	1.8‡	0; 10.0	0	1; 65.8	1.5
TEAEs with exposure-adjusted patient incidence rate of ≥5 per 100 patient-years across all patients						
Upper respiratory tract infection	4; 50.8	7.9	0; 10.0	0	4; 60.8	6.6
Influenza	3; 47.8	6.3	0; 10.0	0	3; 57.8	5.2
Acne	2; 53.0	3.8	1; 6.9	14.5	3; 60.0	5.0

MedDRA indicates Medical Dictionary for Regulatory Activities; and TEAE, treatment-emergent adverse event.

*Sum of the time to first event or the total exposure if no events occurred.

†Serious TEAEs were MedDRA (version 21.0) preferred terms of appendicitis (in 2 patients), coronary artery occlusion, noncardiac chest pain, pleuritic pain, aortic stenosis, nephrolithiasis, ovarian germ cell teratoma, arteriovenous fistula aneurysm, and syncope (in 1 patient each).

‡The TEAE was a nonserious event of rash.

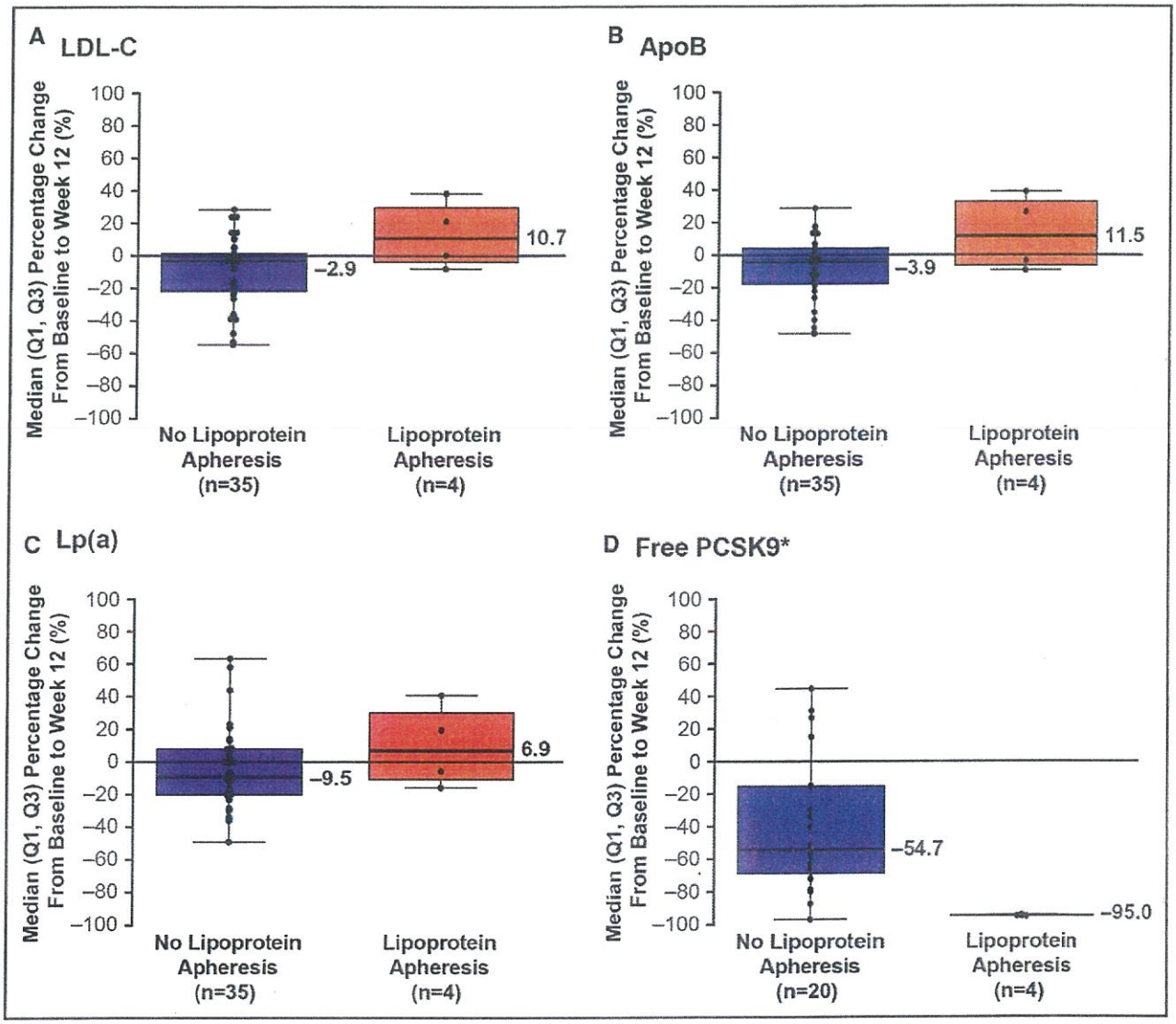

Figure 1. Median percentage change from baseline to week 12.
A, LDL-C; **B**, ApoB; **C**, Lp(a); and **D**, free PCSK9. Box represents quartile 1 (Q1), quartile 3 (Q3); middle line represents median, whiskers represent minimum and maximum. *PCSK9 data were not collected in the RAMAN study. LDL-C indicates low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); and PCSK9, proprotein convertase subtilisin/kexin type 9.

Data From Patients With HoFH in HAUSER-OLE

A summary of the safety and efficacy data to week 80 for the 12 patients with HoFH from the HAUSER-OLE study who received evolocumab is provided in Supplemental Material and shown in Tables S3 through S5.

DISCUSSION

This pooled analysis of pediatric patients with HoFH showed that evolocumab was well tolerated with no new safety signals. These safety findings are consistent with findings from a range of clinical trials and real-world studies of evolocumab treatment in adults and children with heterozygous familial hypercholesterolemia.[4,8] The safety and lipid-lowering findings in our pooled study are also consistent with results from studies of PCSK9 inhibitor evolocumab in both adults and pediatric patients with HoFH.[2–4] Although the overall reduction in LDL-C was less than expected compared with results observed in other studies of HoFH populations,[2–4] 42.9% of patients not receiving lipoprotein apheresis had a 15% or greater reduction in LDL-C. The mean LDL-C level at baseline in the nonapheresis cohort was very high (mean [SD], 457.8 [163.5] mg/dL), with a 15% reduction translating into an absolute reduction of > 60 mg/dL, which is likely clinically meaningful.[11]

The analysis also demonstrates that LDL-C reduction with PCSK9 inhibitor therapy in pediatric patients with HoFH is highly variable and difficult to predict. Some

Table 3. Absolute and Percentage Changes From Baseline to Week 12 in Lipids and Free PCSK9

Variable	No lipoprotein apheresis (n=35)	Received lipoprotein apheresis (n=4)
LDL-C, change from baseline to week 12		
Absolute change, mmol/L		
Median (Q1, Q3)	−0.4 (−2.3, 0.2)	1.0 (−0.3, 2.7)
Mean (SD)	−1.1 (2.2)	1.2 (1.8)
Percentage change		
Median (Q1, Q3)	−2.9 (−21.7, 1.5)	10.7 (−3.8, 29.6)
Mean (SD)	−10.0 (21.2)	12.9 (20.8)
Patients with ≥25% decrease in LDL-C, n (%)	7 (20.0)	0
Patients with ≥15% decrease in LDL-C, n (%)	15 (42.9)	0
Non-HDL-C, change from baseline to week 12		
Absolute change, mmol/L		
Median (Q1, Q3)	−0.5 (−2.4, 0.2)	1.2 (−0.3, 2.8)
Mean (SD)	−1.1 (2.3)	1.3 (2.0)
Percentage change		
Median (Q1, Q3)	−3.3 (−21.5, 2.1)	12.0 (−3.6, 30.3)
Mean (SD)	−9.9 (20.6)	13.4 (21.5)
HDL-C, change from baseline to week 12		
Absolute change, mmol/L		
Median (Q1, Q3)	0.03 (0.0, 0.1)	0.01 (−0.1, 0.1)
Mean (SD)	0.1 (0.2)	0.0 (0.1)
Percentage change		
Median (Q1, Q3)	3.4 (−3.5, 19.5)	1.4 (−8.5, 10.8)
Mean (SD)	8.1 (22.6)	1.1 (14.6)
Lp(a), change from baseline to week 12		
Absolute change, nmol/L		
Median (Q1, Q3)	−3.0 (−20.0, 7.0)	3.3 (−7.5, 31.8)
Mean (SD)	−9.0 (67.8)	12.1 (30.2)
Percentage change		
Median (Q1, Q3)	−9.5 (−20.2, 7.9)	6.9 (−10.7, 30.1)
Mean (SD)	−4.2 (25.2)	9.7 (25.4)
Triglycerides, change from baseline to week 12		
Absolute change, mmol/L		
Median (Q1, Q3)	−0.03 (−0.4, 0.2)	0.3 (−0.1, 0.5)
Mean (SD)	−0.03 (0.4)	0.2 (0.4)
Percentage change		
Median (Q1, Q3)	−5.4 (−24.8, 16.7)	48.8 (−9.3, 70.3)
Mean (SD)	1.0 (41.6)	30.5 (56.5)
ApoB, change from baseline to week 12		
Absolute change, g/L		
Median (Q1, Q3)	−0.1 (−0.5, 0.1)	0.2 (−0.1, 0.7)
Mean (SD)	−0.2 (0.5)	0.3 (0.5)
Percentage change		
Median (Q1, Q3)	−3.9 (−17.8, 4.3)	11.5 (−6.4, 32.7)
Mean (SD)	−8.2 (18.8)	13.1 (23.3)
Free PCSK9,* change from baseline to week 12	n=20	n=4
Absolute change, nmol/L		
Median (Q1, Q3)	−3.9 (−5.4, −1.1)	−5.8 (−7.3, −5.2)
Mean (SD)	−3.5 (3.4)	−6.2 (1.8)
Percentage change		
Median (Q1, Q3)	−54.7 (−69.0, −15.4)	−95.0 (−95.2, −94.6)
Mean (SD)	−39.3 (41.6)	−94.9 (0.5)

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PCSK9, proprotein convertase subtilisin/kexin type 9; Q1, quartile 1; and Q3, quartile 3.

*PCSK9 data were not collected in the RAMAN study.

patients with the null/null *LDLR* variant may respond. On the other hand, in those with non-null *LDLR* variants and, therefore, with residual LDLR function, the response varied from minimal to >50% reduction in LDL-C despite robust reductions in PCSK9 blood concentrations. Clinicians should, therefore, consider PCSK9 inhibitor therapy in pediatric patients with HoFH who have not responded adequately to high-intensity statin plus ezetimibe therapy as recommended in the latest HoFH consensus statement.[1] If LDL-C is reduced by an additional 15% or more, PCSK9 inhibitor therapy should be continued.[1] If not, additional therapies that act independently of LDLR function, such as lomitapide or evinacumab, may be introduced with or without lipoprotein apheresis.

This pooled analysis included 12 patients with HoFH from the HAUSER-OLE study for whom data had not been previously published. These patients were followed for up to 80 weeks, and the results showed that evolocumab treatment was safe and well tolerated. Overall, modest lipid lowering was observed in these patients, with substantial variability across patients, similar to the pattern shown in the full pooled data set.

A limitation of this study is the relatively small number of patients (n=39), but, as far as we are aware, this analysis is the largest report on the use of PCSK9 inhibitor therapy in pediatric patients with HoFH. Another limitation is that only 31 of the 39 patients had confirmed genetic molecular diagnosis of HoFH, with the remaining 8 patients having an HoFH diagnosis based on clinical criteria alone. Of note, the median (Q1, Q3) change in LDL-C at week 12 was similar for patients whether they had genetic evidence or clinical diagnosis of HoFH (−2.8% [−21.7, 1.5] versus −5.2% [−16.4, 14.2], respectively).

In pediatric patients with HoFH pooled from 3 clinical trials who were treated with evolocumab, safety findings were consistent with data from previous studies of evolocumab. LDL-C reduction was variable and not

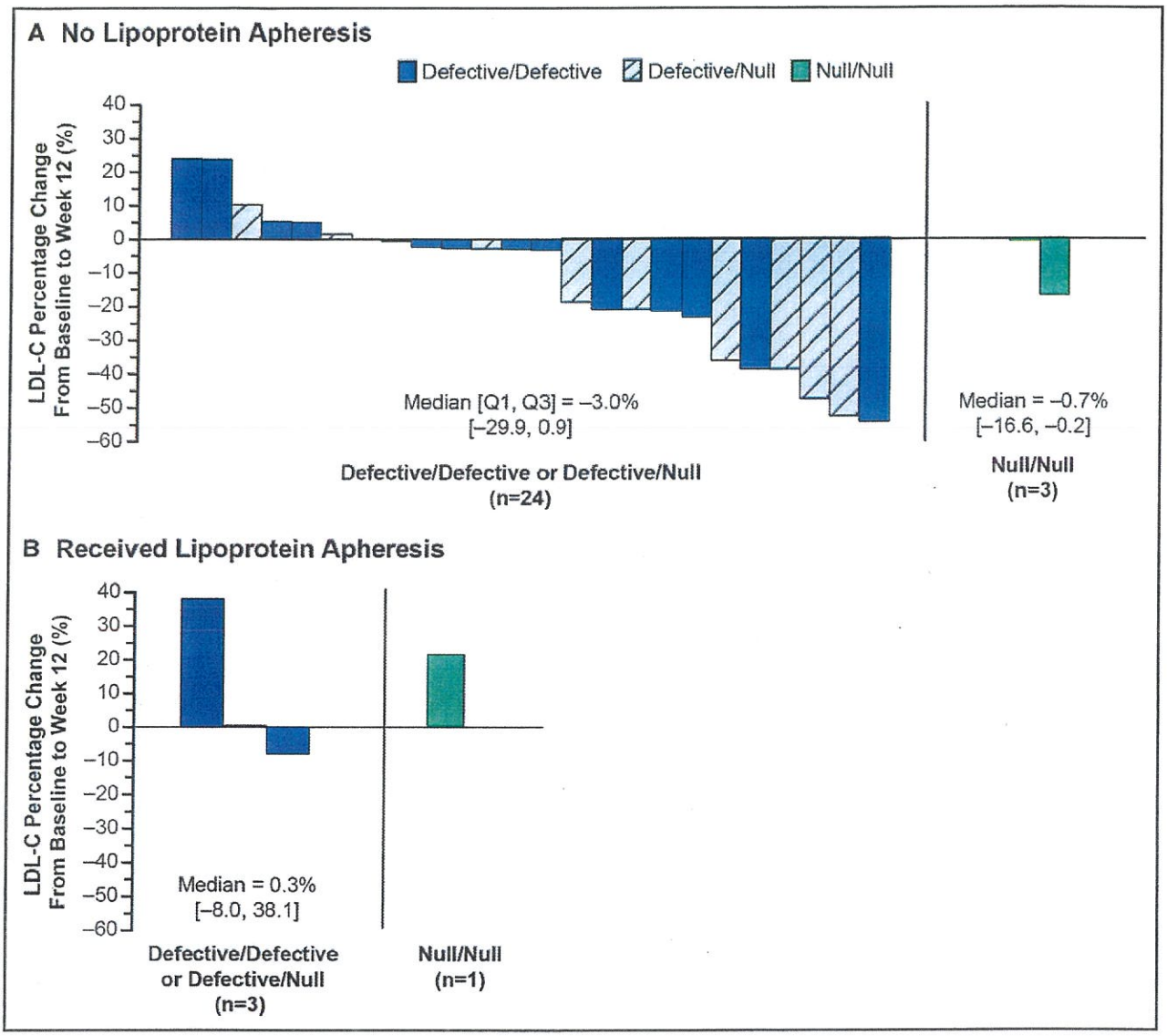

Figure 2. Percentage change from baseline to week 12 in LDL-C for individual patients by LDLR functional genotype.
This figure includes only patients who had available genetic information. *LDLR* genetic variants were identified and classified by residual LDLR activity per American College of Medical Genetics and Genomics criteria. Patients were categorized according to the LDLR activity in both alleles. **A**, No lipoprotein apheresis. **B**, Received lipoprotein apheresis. LDL-C indicates low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; Q1, quartile 1; and Q3, quartile 3.

related to estimated LDLR residual activity. For pediatric patients with HoFH who cannot meet LDL-C goals with other treatments, a trial of PCSK9 inhibitor therapy may be appropriate.

ARTICLE INFORMATION

Received October 31, 2023; accepted March 6, 2024.

Congress presentation: Portions of the data in this manuscript were presented at the 91st European Atherosclerosis Society Congress in Mannheim, Germany, May 2023.

Affiliations

Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa (F.J.R.). Department of Medicine and Biochemistry, Robarts Research Institute, University of Western Ontario, London, Canada (R.A.H., J.W.). Global Development (A.R., J.A.G.L., A.K.B.) and Global Biostatistics (J.W., H.W.), Amgen Inc., Thousand Oaks, CA. Clinical Lipidology and Rare Lipid Disorders Unit, Community Genomic Medicine Centre and ECOGENE-21, Department of Medicine, Université de Montreal, Chicoutimi, Quebec, Canada (D.G.). Department of Paediatrics, Amsterdam UMC, Location AMC, the Netherlands (A.W.). Lipid Clinic Heart Institute (InCor), University of Sao Paulo Medical School Hospital and Hospital Israelita Albert Einstein, Sao Paulo, Brazil (R.D.S.).

Acknowledgments

Ellen Stoltzfus, PhD, of Amgen and Martha Mutomba, PhD, on behalf of Amgen Inc, provided medical writing assistance.

Sources of Funding

This research was funded by Amgen Inc. (Thousand Oaks, CA).

Disclosures

F.J. Raal has received research grants, honoraria, or consulting fees for professional input and lectures from Sanofi, Regeneron, Amgen, and Novartis; and

travel support to attend the 2023 European Atherosclerosis Society (EAS) Congress from EAS. R.A. Hegele reports receiving consulting fees from Acasti, Aegerion, Akcea/Ionis, Amgen, Boston Heart, HLS Therapeutics, Novartis, Pfizer, Regeneron, Sanofi, and Ultragenyx; and lecture fees from Amgen, HLS Therapeutics, and Novartis. A. Ruzza is a former employee and a stockholder of Amgen. He is a current employee and a stockholder of GlaxoSmithKline. He holds a pending patent application PCT/US2021/034489 on PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors and methods of use thereof to treat cholesterol-related disorders. J.A.G. López, A.K. Bhatia, H. Wang, and J. Wu are employees and stockholders of Amgen. D. Gaudet reports receiving research grants, honoraria, or consulting fees for professional input and lectures from Alnylam, Amgen, Applied Therapeutics, Arrowhead, Boehringer Ingelhein, Chiesi (Amryt), CRISPR Therapeutics, Eli Lilly, Esperion, Ionis, Kowa, New Amsterdam Pharma, Novartis, Novo Nordisk, Pfizer, Regeneron, Sanofi, Ultragenyx, Uniqure, and Verve Therapeutics. A. Wiegman reports research support for pharmaceutical trials of lipid-lowering agents from Amgen, Sanofi-Regeneron Pharmaceuticals, Novartis, Silence Therapeutics, Esperion, and Ultragenyx; and is member of a safety board for Amryt. R.D. Santos reports receiving consulting fees and lecture fees from Abbott, Amgen, Amryt, AstraZeneca, Aché, Biolab, Getz Pharma, Eli Lilly, Libbs, Merck, PTC Therapeutics, Novo Nordisk, Novartis, and Sanofi-Regeneron Pharmaceuticals; and grant support from Amgen, Kowa, Esperion, Novartis, and Sanofi-Regeneron Pharmaceuticals. The other author reports no conflicts.

Supplemental Material

Tables S1–S5
Figure S1
Supplemental Text

REFERENCES

1. Cuchel M, Raal FJ, Hegele RA, Al-Rasadi K, Arca M, Averna M, Bruckert E, Freiberger T, Gaudet D, Harada-Shiba M, et al. 2023 Update on European Atherosclerosis Society consensus statement on homozygous familial hypercholesterolaemia: new treatments and clinical guidance. *Eur Heart J*. 2023;44:2277–2291. doi: 10.1093/eurheartj/ehad197
2. Raal FJ, Honarpour N, Blom DJ, Hovingh GK, Xu F, Scott R, Wasserman SM, Stein EA; TESLA Investigators. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2015;385:341–350. doi: 10.1016/S0140-6736(14)61374-X
3. Raal FJ, Hovingh GK, Blom D, Santos RD, Harada-Shiba M, Bruckert E, Couture P, Soran H, Watts GF, Kurtz C, et al. Long-term treatment with evolocumab added to conventional drug therapy, with or without apheresis, in patients with homozygous familial hypercholesterolaemia: an interim subset analysis of the open-label TAUSSIG study. *Lancet Diabetes Endocrinol*. 2017;5:280–290. doi: 10.1016/S2213-8587(17)30044-X
4. Santos RD, Stein EA, Hovingh GK, Blom DJ, Soran H, Watts GF, López JAG, Bray S, Kurtz CE, Hamer AW, et al. Long-term evolocumab in patients with familial hypercholesterolemia. *J Am Coll Cardiol*. 2020;75:565–574. doi: 10.1016/j.jacc.2019.12.020
5. Blom DJ, Harada-Shiba M, Rubba P, Gaudet D, Kastelein JJP, Charng M-J, Pordy R, Donahue S, Ali S, Dong Y, et al. Efficacy and safety of alirocumab in adults with homozygous familial hypercholesterolemia: the ODYSSEY HoFH trial. *J Am Coll Cardiol*. 2020;76:131–142. doi: 10.1016/j.jacc.2020.05.027
6. Thedrez A, Blom DJ, Ramin-Mangata S, Blanchard V, Croyal M, Chemello K, Nativel B, Pichelin M, Cariou B, Bourane S, et al. Homozygous familial hypercholesterolemia patients with identical mutations variably express the LDLR (low-density lipoprotein receptor): implications for the efficacy of evolocumab. *Arterioscler Thromb Vasc Biol*. 2018;38:592–598. doi: 10.1161/ATVBAHA.117.310217
7. Bansal S, Ruzza A, Sawhney JPS, Kulkarni G, Iyengar S, Mehta V, Hamer A, Wu Y, Raal FJ. Evolocumab in patients with homozygous familial hypercholesterolemia in India. *J Clin Lipidol*. 2021;15:814–821. doi: 10.1016/j.jacl.2021.10.003
8. Santos RD, Ruzza A, Hovingh GK, Stefanutti C, Mach F, Descamps OS, Bergeron J, Wang B, Bartuli A, Buonuomo PS, et al. Paediatric patients with heterozygous familial hypercholesterolaemia treated with evolocumab for 80 weeks (HAUSER-OLE): a single-arm, multicentre, open-label extension of HAUSER-RCT. *Lancet Diabetes Endocrinol*. 2022;10:732–740. doi: 10.1016/S2213-8587(22)00221-2
9. Chora JR, Iacocca MA, Tichý L, Wand H, Kurtz CL, Zimmermann H, Leon A, Williams M, Humphries SE, Hooper AJ, et al; ClinGen Familial Hypercholesterolemia Expert Panel. The Clinical Genome Resource (ClinGen) Familial Hypercholesterolemia Variant Curation Expert Panel consensus guidelines for LDLR variant classification. *Genet Med*. 2022;24:293–306. doi: 10.1016/j.gim.2021.09.012
10. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73:3168–3209. doi: 10.1016/j.jacc.2018.11.002
11. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, et al; Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–1681. doi: 10.1016/S0140-6736(10)61350-5