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Evolocumab in HIV-Infected Patients With Dyslipidemia

Primary Results of the Randomized, Double-Blind BEIJERINCK Study

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ABSTRACT

BACKGROUND People living with human immunodeficiency virus (PLHIV) are at increased risk of atherosclerotic cardiovascular disease (ASCVD) and are prone to statin-related adverse events from drug-drug interactions with certain antiretroviral regimens.

OBJECTIVES This study sought to evaluate the efficacy and safety of evolocumab in dyslipidemic PLHIV.

METHODS BEIJERINCK (EvolocumaB Effect on LDL-C Lowering in SubJEcts with Human Immunodeficiency VirRus and INcreased Cardiovascular RisK) is a randomized, double-blind, multinational trial comparing monthly subcutaneous evolocumab 420 mg with placebo in PLHIV with hypercholesterolemia/mixed dyslipidemia taking maximally-tolerated statin therapy. The primary endpoint was the percent change (baseline to week 24) in low-density lipoprotein cholesterol (LDL-C); secondary endpoints included achievement of LDL-C <70 mg/dl and percent change in other plasma lipid and lipoprotein levels. Treatment-emergent adverse events were also examined.

RESULTS A total of 464 patients were analyzed (mean age of 56.4 years, 82.5% male, mean duration with HIV of 17.4 years). ASCVD was documented in 35.6% of patients, and statin intolerance/contraindications to statin use were present in 20.7% of patients. Evolocumab reduced LDL-C by 56.9% (95% confidence interval: 61.6% to 52.3%) from baseline to week 24 versus placebo. An LDL-C level of <70 mg/dl was achieved in 73.3% of patients in the evolocumab group versus 7.9% in the placebo group. Evolocumab also significantly reduced other atherogenic lipid levels, including non-high-density lipoprotein cholesterol, apolipoprotein B, and lipoprotein(a) (all $p < 0.0001$). Evolocumab was well tolerated, and treatment-emergent adverse events patient incidence was similar among evolocumab and placebo groups.

CONCLUSIONS Evolocumab was safe and significantly reduced lipid levels in dyslipidemic PLHIV on maximally-tolerated statin therapy. Evolocumab is an effective therapy for lowering atherogenic lipoproteins in PLHIV with high cardiovascular risk. (Safety, Tolerability & Efficacy on LDL-C of Evolocumab in Subjects With HIV & Hyperlipidemia/Mixed Dyslipidemia; NCT02833844) (J Am Coll Cardiol 2020;75:2570–84) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Human immunodeficiency virus (HIV) infection has become a manageable chronic disease due to the success of highly effective antiretroviral therapy (ART). In the context of the aging population of HIV-infected individuals taking ART (1), people living with human immunodeficiency virus (PLHIV) are now facing the challenge of multiple comorbidities, including cardiovascular disease (CVD). Atherosclerotic cardiovascular disease (ASCVD) has particularly emerged as one of the most important comorbidities along with the risk of malignancies in PLHIV in countries with easy access to ART (2–4). Mechanisms associated with HIV-related ASCVD are complex, involving traditional CVD risk factors, such as tobacco, dyslipidemia, insulin resistance, and hypertension, but also factors related to HIV itself, such as immunodepression, immune activation, and chronic inflammation (4–6). Moreover, some ARTs have been associated with an increased risk of ASCVD, particularly first-generation protease inhibitors that directly or indirectly lead to endothelial dysfunction or metabolic disturbances (e.g., atherogenic dyslipidemia and insulin resistance) (3,4,6,7).

SEE PAGE 2585

Due to the link between HIV infection and ASCVD, HIV has been classified by the U.S. cholesterol and the European dyslipidemia guidelines as a risk-enhancing factor for ASCVD (8,9); therefore, PLHIV are considered as likely candidates for more intensive cholesterol-lowering medication. The treatment of both HIV-related dyslipidemia and the high CVD risk of PLHIV place statins as initial therapy (8,9). However, the prescription and tolerance of high-intensity statins are frequently limited by the risk of drug-drug interactions (DDIs) between some statins (simvastatin, lovastatin, atorvastatin, rosuvastatin) and some ARTs (protease inhibitors, cobicistat, efavirenz) (10). Additionally, statins increase the risk for statin-associated muscle symptoms (11).

Many studies have observed that treating dyslipidemia in PLHIV is challenging, with a lower rate of low-density lipoprotein cholesterol (LDL-C) goal achievement both in primary and secondary prevention and a lower rate of prescribed high-intensity statins (10,12–15). Thus, reducing CVD risk in this population with high CVD risk represents a significant unmet need.

Evolocumab, a fully human monoclonal antibody that binds proprotein convertase subtilisin/kexin type 9 (PCSK9) and diminishes LDL-receptor degradation, resulting in lower LDL-C levels among patients with primary hypercholesterolemia and mixed dyslipidemia (16). Anti-PCSK9 therapy has not been evaluated in PLHIV and could represent an opportunity to reduce LDL-C and the high CVD risk for this specific population.

BEIJERINCK (EvolocumaB Effect on LDL-C Lowering in SubJEcts with Human Immunodeficiency VirRus and INcreased Cardiovascular RisK; NCT02833844) is the first randomized, double-blind, placebo-controlled trial to examine the use of evolocumab, a PCSK9 inhibitor, in PLHIV who have elevated LDL-C or non-high-density lipoprotein cholesterol (non-HDL-C). The present study has evaluated the lipid-lowering efficacy and safety of 24 weeks of evolocumab compared with placebo in the double-blind period of the study in PLHIV with hypercholesterolemia or mixed dyslipidemia who received maximally tolerated statin therapy.

ABBREVIATIONS AND ACRONYMS

ART = antiretroviral therapy

ASCVD = atherosclerotic cardiovascular disease

DDI = drug-drug interaction

HIV = human immunodeficiency virus

LDL-C = low-density lipoprotein cholesterol

PCSK9 = proprotein convertase subtilisin/kexin type 9

PLHIV = people living with human immunodeficiency virus

TEAE = treatment-emergent adverse event

METHODS

PATIENT POPULATION. The multinational, randomized, double-blind BEIJERINCK trial was designed to assess the lipid-lowering efficacy and safety of evolocumab versus placebo in PLHIV and hypercholesterolemia/mixed dyslipidemia (2:1) on the background of maximally tolerated statin therapy. For some patients, "maximally tolerated statin" may indicate no statin at all due to statin intolerance or contraindication to statin therapy. Statin intolerance is defined as a trial of at least 2 statins with the failure of 1 of the statins (at an average daily dose at or below the following doses: atorvastatin 10 mg, simvastatin 10 mg, pravastatin 40 mg, rosuvastatin 5 mg, lovastatin 20 mg, fluvastatin 40 mg, or pitavastatin 2 mg) due to intolerable muscle symptoms (i.e., myalgia

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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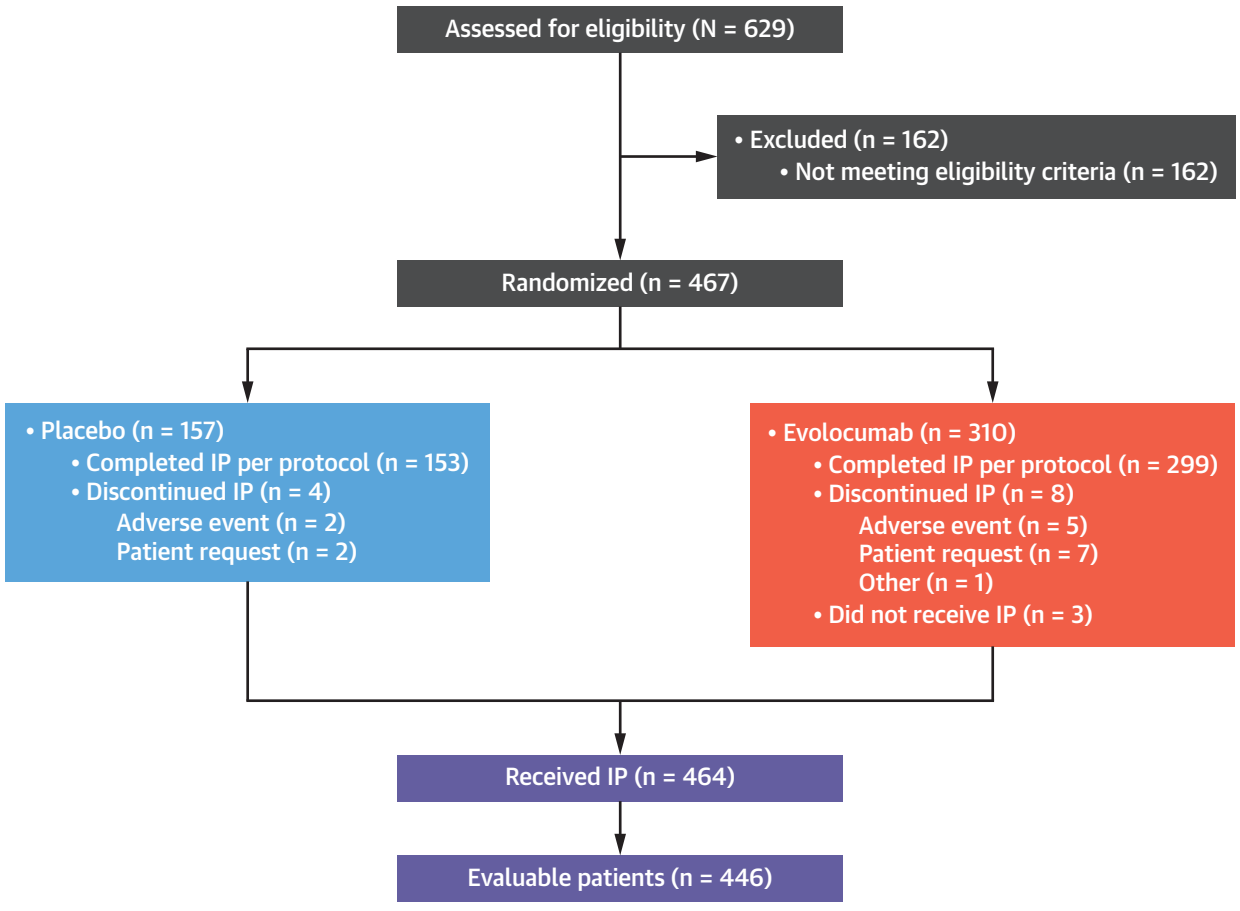
FIGURE 1 BEIJERINCK Study Profile



Consort flow chart of patient disposition in the BEIJERINCK study. Patients were screened for eligibility (n = 629) and randomized (n = 467) into the placebo (n = 157; **blue box**) or evolocumab (n = 310; **red box**) groups of the study. A total of 446 patients who received IP were evaluable for the primary endpoint. IP = investigational product.

[muscle pain, ache, or weakness without creatine kinase elevation], myositis [muscle symptoms with increased creatine kinase levels], or rhabdomyolysis [muscle symptoms with marked creatine elevation defined as creatine kinase >10× upper limit of normal (ULN)]), and symptoms resolved or improved when statin dose was decreased or discontinued. For rhabdomyolysis, failure of only 1 statin at any dose is acceptable (11). Patients were recruited from May 22, 2017, to January 23, 2019. Details of the BEIJERINCK study design and baseline characteristics of enrolled participants have previously been reported (17). Briefly, patients in the BEIJERINCK study were randomized to 24 weeks of double-blind monthly subcutaneous evolocumab 420 mg or placebo, after which all patients received 24 weeks of open-label evolocumab (17). Enrolled patients were on stable ART and lipid-lowering therapy and had fasting LDL-C ≥100 mg/dl or non-HDL-C ≥130 mg/dl, or fasting LDL-C ≥70 mg/dl or non-HDL-C ≥100 mg/dl with documented ASCVD. Patient eligibility criteria are as previously described (17). Randomization was stratified by entry statin treatment (yes/no) and by hepatitis C status (yes/no).

STUDY ENDPOINTS. The primary endpoint was the percent change in LDL-C from baseline to week 24 with evolocumab versus placebo. Secondary endpoints included the achievement of LDL-C <70 mg/dl, an LDL-C reduction ≥50%, and the percent change in other lipid and lipoprotein levels. Treatment-emergent adverse events (TEAEs) were also examined.

STATISTICAL ANALYSIS. With a planned sample size of 450 patients, randomized 2:1 to evolocumab and placebo, it was anticipated that 300 patients would be exposed to evolocumab 420 mg monthly, providing approximately 95% probability of detecting adverse events that occur at 1% and approximately 99% power

for the primary endpoint. This paper reports the primary analysis after all patients completed the double-blind treatment period. Repeated-measures linear mixed-effects models assessed continuous efficacy endpoints with terms for statin use, treatment group, scheduled visit, and the interaction of treatment with the scheduled visit. A Cochran-Mantel-Haenszel test adjusted by statin use was used to analyze LDL-C achievement and LDL-C response, with non-responses imputed for individuals with a missing value. Multiplicity adjustment for the primary and secondary efficacy endpoints was performed, as described previously (18), to preserve the family-wise error rate at 0.05 for the primary and secondary endpoints. Safety endpoints were summarized descriptively. For week 24, the following tier 1 secondary endpoints will be characterized: change from baseline in LDL-C, percent change from baseline in non-HDL-C, percent change from baseline in apolipoprotein B (apoB), percent change from baseline in TC, achievement of target LDL-C <70 mg/dl (1.8 mmol/l), and LDL-C response (50% reduction of LDL-C from baseline); and the following tier 2 secondary endpoints will be characterized: percent change from baseline in lipoprotein(a) [Lp(a)], percent change from baseline in triglycerides, percent change from baseline in HDL-C, and percent change from baseline in very low-density lipoprotein cholesterol (VLDL-C).

Evolocumab 420 mg or matching placebo was administered using an automated minidoser (also known as an "on-body infusor prefilled cartridge" in the United States) or as 3 consecutive injections using a pre-filled autoinjector/pen. An automated minidoser is a single-use, disposable, on-body electromechanical injection device, which is copackaged with a pre-filled Crystal Zenith cartridge containing 3.5 ml of deliverable volume of 120 mg/ml evolocumab or an identical volume of placebo. An autoinjector/pen is a single-use, disposable, handheld mechanical (spring-based) device for fixed-dose, subcutaneous injection of 140 mg evolocumab in 1.0 ml of the deliverable volume or an identical volume of placebo. Placebo was presented in identical containers and stored/packaged the same as evolocumab.

ETHICS COMMITTEE APPROVAL. All procedures in this study were conducted in accordance with the Declaration of Helsinki. The institutional review boards at each site reviewed and approved the final protocol. Informed consent forms were collected from all patients. Qualified researchers may request data from Amgen clinical studies (19).

TABLE 1 Baseline Demographics and Clinical Characteristics

	Placebo QM (n = 157)	Evolocumab QM (n = 307)	Overall (n = 464)
Demographics			
Age, yrs	56.2 ± 8.0	56.4 ± 9.1	56.4 ± 8.7
Male	120 (76.4)	263 (85.7)	383 (82.5)
Race			
White	125 (79.6)	245 (79.8)	370 (79.7)
Black or African American	25 (15.9)	52 (16.9)	77 (16.6)
Clinical characteristics			
Years since HIV diagnosis at randomization	18.1 ± 8.9	17.0 ± 8.9	17.4 ± 8.9
CD4 count, cells/mm^3	638 (478, 857)	670 (511, 852)	656 (506, 853)
HIV viral load <50 copies/ml	154 (98.1)	298 (97.1)	452 (97.4)
ASCVD	53 (33.8)	112 (36.5)	165 (35.6)
Cardiovascular risk factors			
Hypertension	68 (43.3)	154 (50.2)	222 (47.8)
Current cigarette smoking	46 (29.3)	82 (26.7)	128 (27.6)
Type 2 diabetes mellitus	24 (15.3)	51 (16.6)	75 (16.2)
Medication use			
Lipid-lowering therapy			
No statin use	35 (22.3)	61 (19.9)	96 (20.7)
Statin use	122 (77.7)	246 (80.1)	368 (79.3)
Moderate-intensity	62 (39.5)	137 (44.6)	199 (42.9)
High-intensity	52 (33.1)	95 (30.9)	147 (31.9)
Ezetimibe	37 (23.6)	53 (17.3)	90 (19.4)
Fibrates	17 (10.8)	29 (9.4)	46 (9.9)
Fenofibrate	16 (10.2)	20 (6.5)	36 (7.8)
Gemfibrozil	0 (0.0)	3 (1.0)	3 (0.6)
Other	1 (0.6)	6 (2.0)	7 (1.5)
Antiretroviral therapy	157 (100)	307 (100)	464 (100)
NRTI	129 (82.2)	248 (80.8)	377 (81.3)
Integrase inhibitor	89 (56.7)	155 (50.5)	244 (52.4)
Elvitegravir boosted with cobicistat	29 (18.5)	37 (12.1)	66 (14.2)
Boosted protease inhibitor	57 (36.3)	125 (40.7)	182 (39.2)
NNRTI	57 (36.3)	126 (41.0)	183 (39.4)
Lipid levels at baseline			
LDL-C, mg/dl*	133.3 ± 40.0	133.3 ± 40.3	133.3 ± 40.1
Total cholesterol, mg/dl	219.5 ± 46.8	220.1 ± 45.5	219.9 ± 45.9
ApoB, mg/dl	112.2 ± 26.7	113.7 ± 26.3	113.2 ± 26.4
Non-HDL-C, mg/dl	169.1 ± 46.4	172.8 ± 45.8	171.6 ± 46.0
HDL-C, mg/dl	50.4 ± 15.0	47.3 ± 13.2	48.3 ± 13.9
VLDL-C, mg/dl	36.2 ± 21.3	41.0 ± 24.9	39.4 ± 23.9
Triglycerides, mg/dl	177.2 ± 91.4	202.0 ± 115.4	193.5 ± 108.4
Lp(a), nmol/l	54.5 (20.0, 181.5)	54.5 (15.5, 186.5)	54.5 (18.0, 186.0)
PCSK9, ng/ml	558.4 ± 201.8	534.6 ± 180.4	542.6 ± 188.1
hsCRP, mg/l	1.7 (0.9, 3.6)	2.1 (1.1, 4.4)	1.9 (1.1, 4.1)

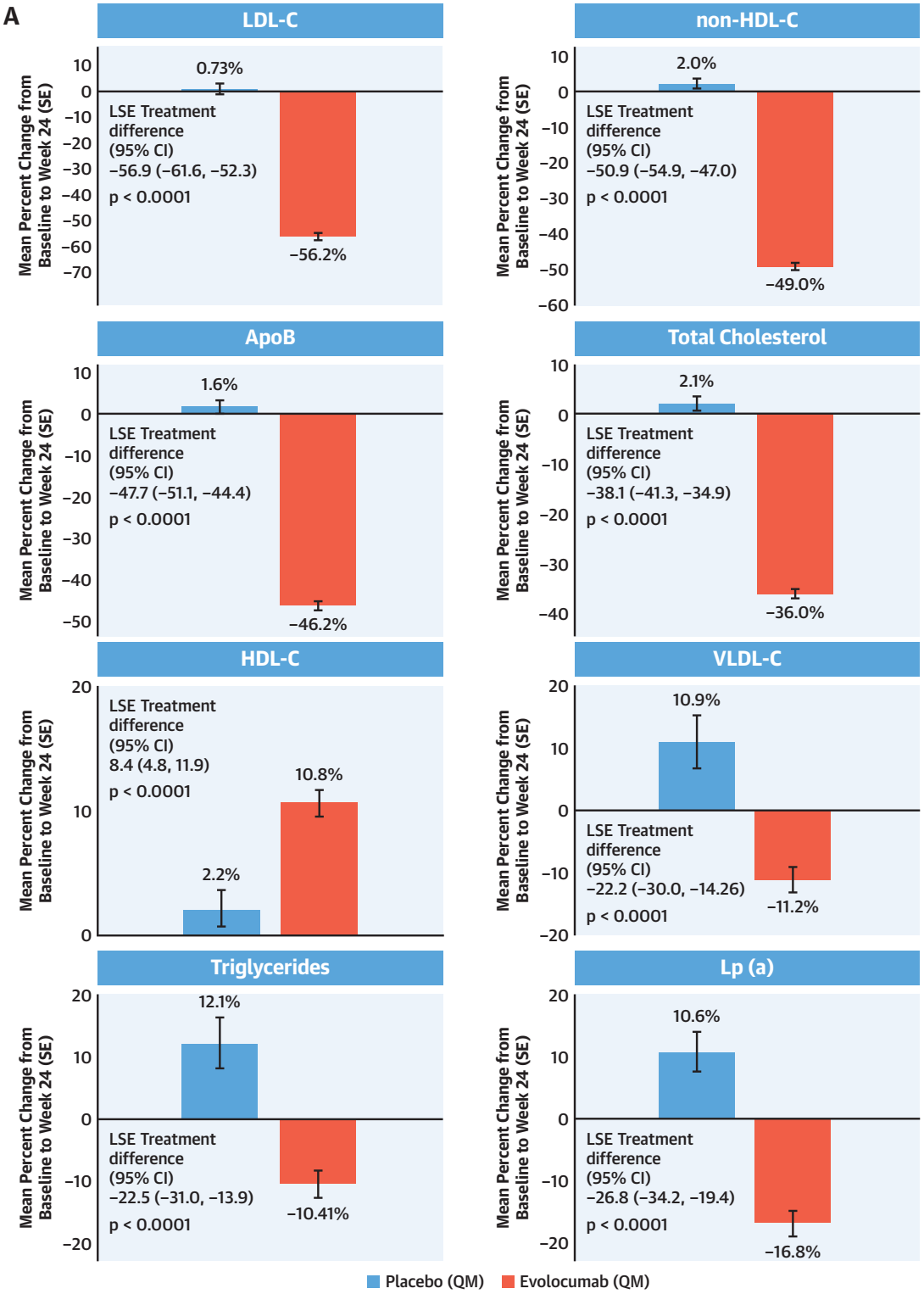
Values are mean ± SD, n (%), or median (Q1, Q3). *Ultracentrifugation LDL-C was used when calculated LDL-C was <40 mg/dl or triglycerides were >400 mg/dl.

ApoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; CD4 = cluster of differentiation 4; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PCSK9 = proprotein convertase subtilisin/kexin type 9; Q = quartile; QM = monthly; VLDL-C = very low-density lipoprotein cholesterol.

RESULTS

STUDY POPULATION. In total, 629 patients were screened for eligibility in the BEIJERINCK study, of

FIGURE 2 Primary and Secondary Efficacy Endpoints of BEIJERINCK Study



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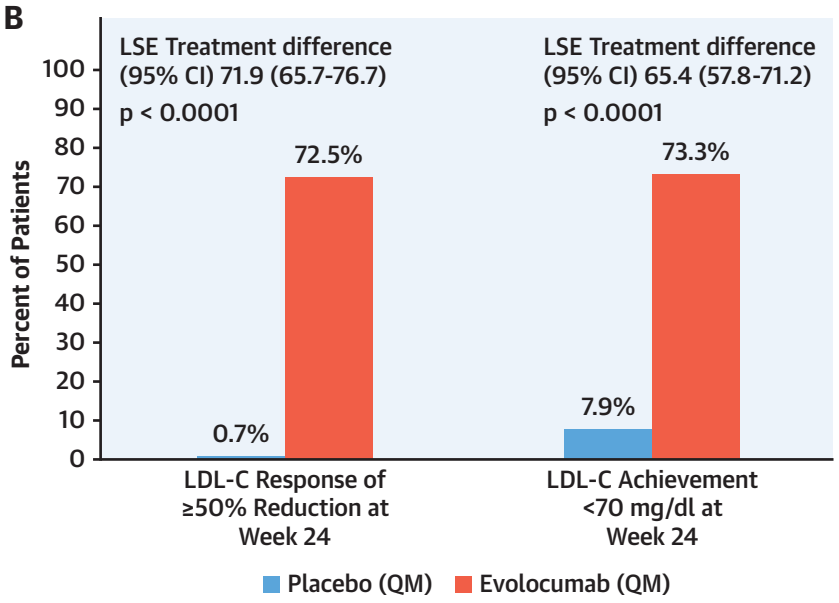

The effect of evolocumab, compared with placebo, on LDL-C, triglycerides, and atherogenic lipoproteins was tested. **(A)** Evolocumab significantly reduced LDL-C, non-HDL-C, ApoB, total cholesterol, VLDL-C, triglycerides, and Lp(a), and increased HDL-C. **(B)** Evolocumab treatment resulted in significantly more patients achieving the secondary efficacy endpoints of LDL-C reduction of ≥50% and LDL-C <70 mg/dl compared with placebo. apoB = apolipoprotein B; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); LSE = least squares estimate; QM = monthly; VLDL-C = very low-density lipoprotein cholesterol.

which 467 patients were randomized (162 patients failed screening because of not meet eligibility criteria) into the evolocumab or placebo groups of the study. Of the 467 patients randomized, 464 received at least 1 dose of evolocumab (n = 307) or placebo (n = 157), 12 patients prematurely discontinued double-blind IP, and 446 patients were evaluable for the primary analysis (Figure 1) (17). Mean study duration of the double-blind period was 24.4 ± 0.5 weeks. Patients had an extensive mean duration of HIV infection (17.4 years) and a viral load at screening of ≤50 copies/ml. Clinical ASCVD was present in 35.6% of patients, and cardiovascular risk factors were common (hypertension [47.8%], cigarette use [27.6%]). Statin use at baseline was limited by the presence of complete statin intolerance (i.e., intolerance to any statin dose) or contraindications to statin use, with 79.3% of patients receiving statins; of these, 39.9% received high-intensity statins. Mean LDL-C at baseline was 133.3 ± 40.1 mg/dl (Table 1). Of note, 7 (1.5%) patients had a definite diagnosis of heterozygous familial hypercholesterolemia (5 evolocumab and 2 placebo), and 15 (3.2%) patients had a probable diagnosis (10 [3.2%] evolocumab and 5 [3.2%] placebo) according to Simon Broome register group diagnostic criteria (20).

PRIMARY AND SECONDARY ENDPOINTS. The placebo-corrected mean percent change in LDL-C with evolocumab was −56.9% (95% CI: −61.6% to −52.3%) at 24 weeks (Figure 2A); absolute change in LDL-C from baseline to week 24 was −74.6 and 0.7 mg/dl for evolocumab and placebo groups, respectively (Figure 3A). An LDL-C level <70 mg/dl was achieved in 73.3% of patients in the evolocumab group versus 7.9% in the placebo group (Figure 2B). Similarly, an LDL-C response of ≥50% reduction in LDL-C was reached by 72.5% versus 0.7% of patients in the evolocumab versus the placebo group, respectively (Figure 2B). Evolocumab also significantly reduced other atherogenic lipid levels, including non-HDL-C, ApoB, VLDL-C, and Lp(a), and triglyceride levels (Figures 2A and 3A). Evolocumab significantly improved the primary and all secondary endpoints compared with placebo, with multiplicity adjusted p values <0.0001. Results of sensitivity

FIGURE 3 Effect of Evolocumab on Absolute Changes in Lipid Levels and hsCRP

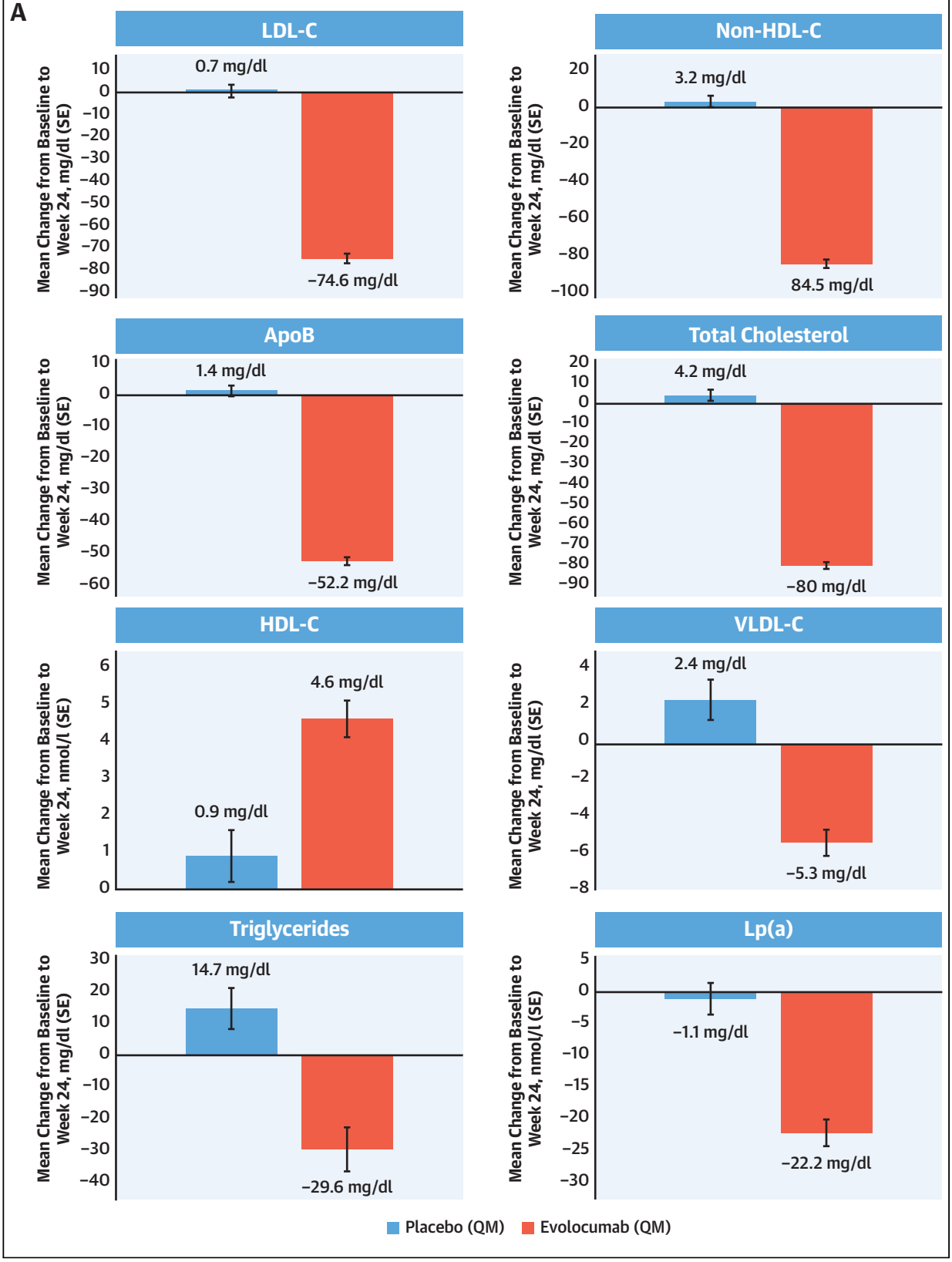

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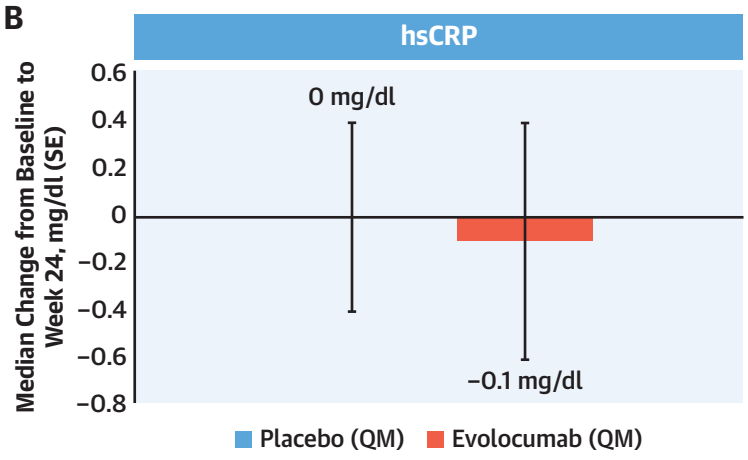
FIGURE 3 Continued



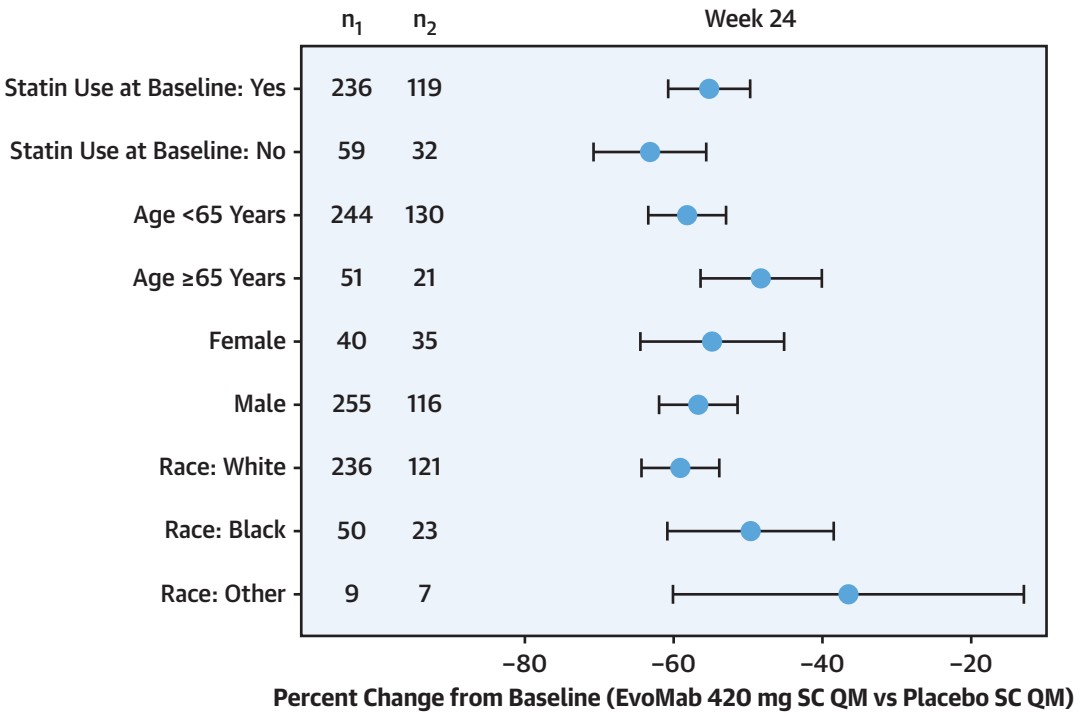
(A) Evolocumab, compared with placebo, significantly reduces the absolute levels of LDL-C (mg/dl), non–HDL-C (mg/dl), apoB (mg/dl), total cholesterol (mg/dl), VLDL-C (mg/dl), triglycerides (mg/dl), and Lp(a) (nmol/l), and increases HDL-C (mg/dl). **(B)** Evolocumab, compared with placebo, significantly reduces the absolute levels of hsCRP (mg/l). hsCRP = high-sensitivity C-reactive protein; other abbreviations as in Figure 2.

analyses of the primary endpoint of percent change from baseline in LDL-C, including the completer analysis, nonparametric analysis, and multiple imputation analysis, were consistent and similar in magnitude to the primary efficacy analysis. Evolocumab was effective in all 18 subgroups relative to placebo, with no notable differences between subgroups (Figure 4). Analyses that adjusted for each of the covariates in the primary analysis showed results that were consistent with the primary analysis, with treatment differences ranging from 55.2% to 57.2%; $p < 0.0001$ for all. Median ± SE change from baseline at week 24 in high-sensitivity C-reactive protein (the exploratory endpoint) was 0.0 ± 0.4 mg/l and −0.1 ± 0.5 mg/l for the placebo and evolocumab groups, respectively (Figure 3B).

SAFETY ENDPOINTS. The patient incidence of TEAEs and serious adverse events in patients was similar between evolocumab and placebo groups (67.5% vs. 61.9% and 5.1% vs. 3.3%, respectively) (Table 2). Treatment-emergent cardiovascular events did occur in both the placebo (n = 3 [1.9%]: 1 with coronary artery disease with myocardial ischemia, 1 with atrial fibrillation, and 1 with vascular hypertensive disease with a hypertensive emergency) and evolocumab (n = 4 [1.3%]: 1 with coronary artery disease, 1 with angina pectoris, 1 with ventricular tachycardia, and 1 with heart failure) groups. There were no episodes of myocardial infarction, coronary revascularization, or ischemic stroke. Administration injection site reactions were 8 (5.1%) for placebo and 7 (2.3%) for evolocumab, similar to the PROFICIO program (21). Adverse events leading to study drug discontinuation were infrequent (3 [1.9%] and 7 [2.3%] patients in the placebo and evolocumab groups). The most common TEAEs (>2%) in the evolocumab group were back pain, influenza, diarrhea, nasopharyngitis, arthralgia, upper respiratory tract infection, pain in extremity, and paresthesia. No notable differences were observed in the overall incidence of TEAEs in patients in the evolocumab group who were on a statin at baseline (n = 153 of 253; 60.5%) versus those who were not on a statin at baseline (n = 37 of 54; 68.5%).

No trends indicative of clinically important treatment-related laboratory abnormalities were observed in this study. Liver enzymes and creatine kinase (CK) levels were balanced in the evolocumab and placebo groups. Among patients with normal CK values at baseline, post-baseline elevations of CK >5× ULN occurred in 4 (1.3%) patients in the evolocumab group and 2 (1.3%) patients in the placebo group; CK elevations >10× ULN in patients with normal baseline values were observed in 2 (0.8%) patients in the evolocumab group and no patients in the placebo group. Two patients (1 in the placebo and 1 in the evolocumab group) at baseline had detectable hepatitis C virus viral load: one had no recorded adverse events (placebo group), and the other had 2 adverse events during the double-blind period

FIGURE 4 Subgroup Analysis of Primary Efficacy Endpoint



Forest plot of placebo-corrected (evolocumab [420 mg SC QM] vs. placebo [QM]) percent change in LDL-C from baseline to week 24. Evolocumab treatment resulted in a significant reduction of LDL-C from baseline to week 24 in all 18 subgroups. n_1/n_2 = number of patients in the subgroup of interest included in the repeated-measures model receiving evolocumab/placebo. When the calculated LDL-C is <40 mg/dl or triglycerides are >400 mg/dl, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available. Least squares mean differences and 95% CIs are from the repeated-measures model. No imputation is used for missing values. BMI = body mass index; CHD = coronary heart disease; CI = confidence interval; EvoMab = evolocumab; LDL-C = low-density lipoprotein cholesterol; NCEP = national cholesterol education program; PCSK9 = proprotein convertase subtilisin/kexin type 9; QM = monthly; SC = subcutaneous.

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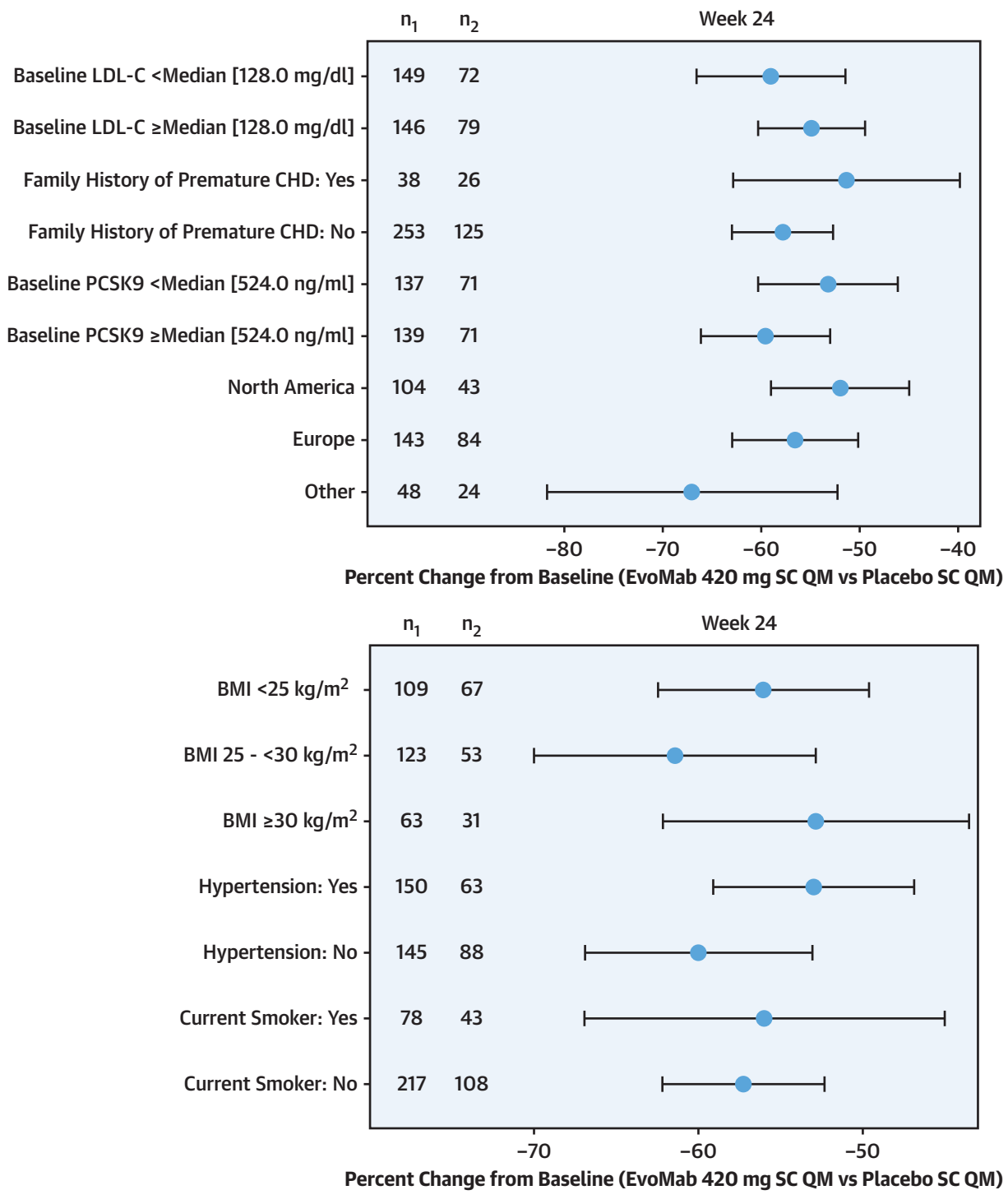
(evolocumab group; viral infection and upper abdominal pain). Nine patients (4 in the placebo and 5 in the evolocumab group) started a new ART during the double-blind period of the study, of which 1 reported an adverse event as the cause. Mean (min, max) percent change in body mass index (BMI) after 24 weeks was 0.5 ± 3.9% (−12.4%, 15.9%) for evolocumab and 0.03 ± 4.1% (−11.4%, 13.7%) for placebo; 56 patients changed BMI category during the study (21 in the placebo and 35 in the evolocumab group). Mean (min, max) percent change from baseline to week 24 in waist circumference was 0.07 ± 8.3% (-26.4%, 113.2%) in the evolocumab group and 0.1 ± 14.7% (−34.1%, 163.9%) in the placebo group. The HIV viral load remained <50 copies/ml in >93% of patients across time points for placebo (147 of 157 patients) and >95% of patients for evolocumab (294 of 307 patients). CD4 counts ranged from 653 cells/μl (placebo; n = 140) to 750 cells/μl (evolocumab; n = 286) across treatment groups and time points.

CONCOMITANT MEDICATIONS. Statins were used in 368 of 464 patients (79.3%) at baseline. Most of these patients (98% in the evolocumab group and 95% in the placebo group) had no change in their statin use during the double-blind period of the study. Of the patients without baseline statin use, 99% had no change during the double-blind period.

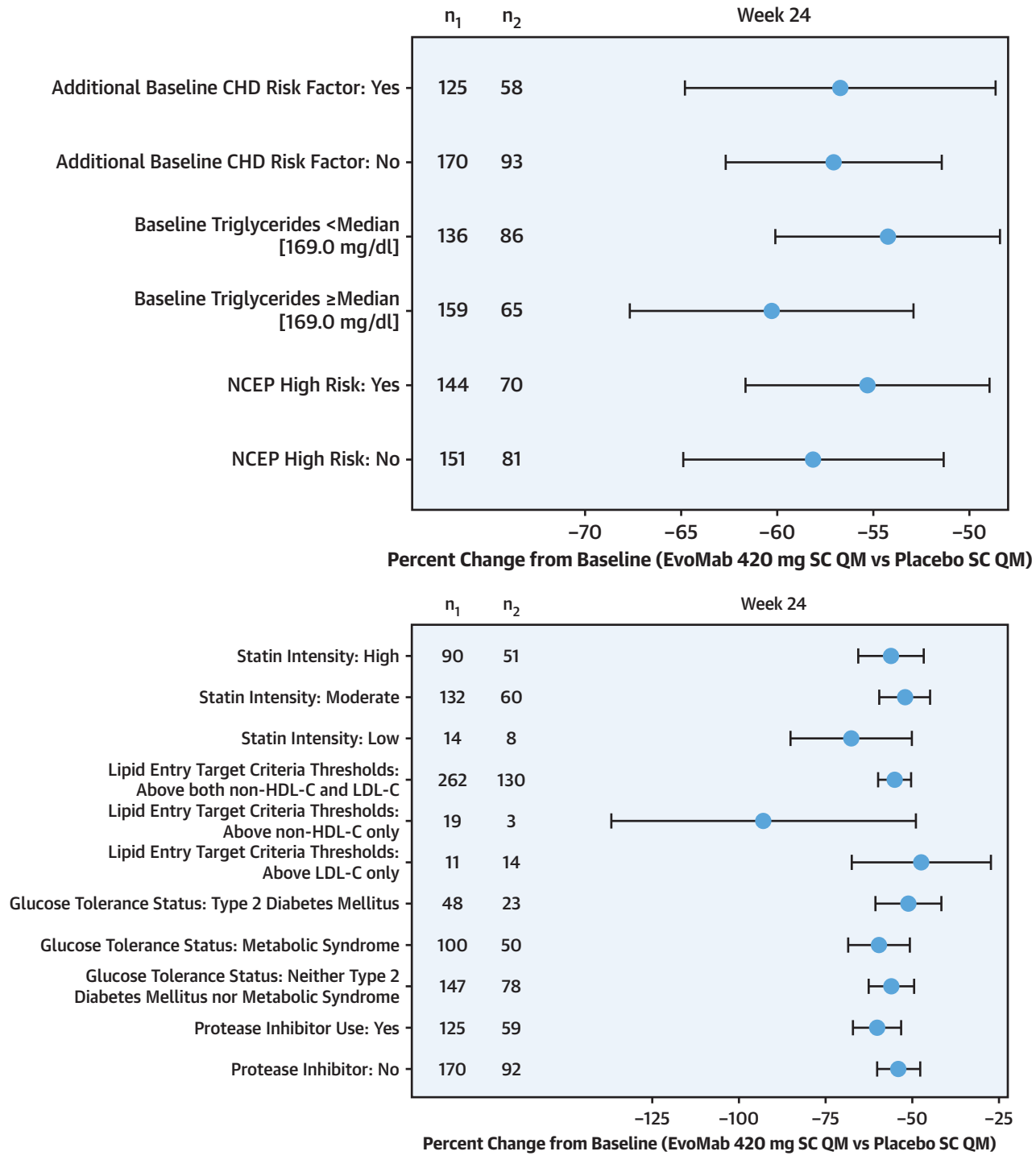
All patients were receiving ART at baseline. A total of 98.1% had no change in ART during double-blind treatment, 9 (1.9%) patients started an alternative or additional ART after the first dose of evolocumab, and no patient ended ART before the end of the double-blind period.

FIGURE 4 Continued



ANTIEVOLOCUMAB ANTIBODY. A total of 307 patients in the evolocumab group had available samples for antibody analysis. No patient had antievolocumab-binding antibodies at baseline, and 1 (0.3%) patient in the evolocumab group transiently developed antievolocumab-binding antibodies post-baseline. No patient tested positive for antievolocumab-neutralizing antibodies.

FIGURE 4 Continued



DISCUSSION

In the BEIJERINCK study, evolocumab administered monthly yielded a significant reduction in LDL-C in hypercholesterolemic PLHIV on maximally tolerated statin therapy. Evolocumab treatment resulted in a 56.9% reduction in LDL-C at week 24 compared with placebo, which was consistent with previous studies using evolocumab (22,23) (**Central Illustration**).

TABLE 2 Safety Data

	Placebo QM (n = 157)	Evolocumab QM (n = 307)
TEAEs	106 (67.5)	190 (61.9)
SAEs	8 (5.1)	10 (3.3)
Leading to study drug discontinuation	3 (1.9)	7 (2.3)
Most common TEAEs (>2% in the evolocumab group)		
Back pain	4 (2.5)	12 (3.9)
Influenza	4 (2.5)	12 (3.9)
Diarrhea	7 (4.5)	11 (3.6)
Nasopharyngitis	2 (1.3)	10 (3.3)
Arthralgia	3 (1.9)	9 (2.9)
Upper respiratory tract infection	4 (2.5)	7 (2.3)
Pain in extremity	3 (1.9)	7 (2.3)
Paresthesia	0 (0.0)	7 (2.3)
Any post-baseline visit		
ALT or AST >3 × ULN	0 (0.0)	1 (0.4)
CK >5 × ULN	2 (1.3)	4 (1.3)
Binding antibodies	0 (0.0)	1 (0.3)
Neutralizing antibodies	0 (0.0)	0 (0.0)
Injection-site reactions	8 (5.1)	7 (2.3)

Values are n (%).

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; SAE = serious adverse event; QM = monthly; TEAE = treatment-emergent adverse event; ULN = upper limit of normal.

SECONDARY ENDPOINTS AND SUBGROUP ANALYSIS BY ASCVD. A total of 73.3% and 72.5% of patients in the evolocumab group achieved an LDL-C <70 mg/dl and ≥50% reduction in LDL-C compared with 7.9% and 0.7% in the placebo group, respectively. For patients treated in the context of primary prevention (no ASCVD), 88.3% of patients in the evolocumab group achieved an LDL-C <100 mg/dl compared with 12.0% in the placebo group; for secondary prevention (ASCVD), 87.0% of patients in the evolocumab group achieved an LDL-C <70 mg/dl compared with 17.6% in the placebo group.

CLINICAL IMPLICATIONS. Both American Heart Association/American College of Cardiology 2018 Multisociety Cholesterol (8) and the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) 2019 (9) dyslipidemia guidelines classify HIV as a risk-enhancing factor among the chronic inflammatory conditions. The American Heart Association/American College of Cardiology 2018 guidelines recommend that a 40- to 75-year-old PLHIV at intermediate ASCVD risk (≥7.5%) should be prescribed moderate- to high-intensity statin therapy (Class II recommendation; Level of Evidence: B-NR). Meanwhile, ESC/EAS 2019 dyslipidemia guidelines recommend dyslipidemic PLHIV to be on lipid-lowering therapy (mostly statins) to achieve the LDL-C goal defined for high-risk patients (<70 mg/dl) with a Class IIa of recommendation, Level of Evidence: C. No data exist on the effects of lipid-lowering therapy on cardiovascular events in PLHIV. Moreover, the ESC/EAS 2019 guidelines underline the lack of evidence for the use of PCSK9 inhibitors in some specific populations such as PLHIV.

BEIJERINCK is the first study to evaluate the efficacy and safety of a PCSK9 inhibitor in PLHIV. PLHIV are at increased risk of ASCVD; reduction of both the risk for ASCVD and lipid levels is challenging in this high-risk population. First of all, the risk for ASCVD is difficult to measure due to many factors not accounted for in traditional risk score assessments, such as long-term use of some ARTs (particularly first-generation protease inhibitors), chronic immune activation, and inflammation, which could all together underestimate the risk for ASCVD (24,25). Additionally, the use of high-intensity statin therapy is often limited by the risk for DDIs; hence, underutilization of moderate- to high-intensity statin therapy has been broadly observed (10,13,26). The population included in the BEIJERINCK study is representative of the HIV population in Western countries requiring lipid-lowering drug therapy, with around 53% to 87% of the population in the study at intermediate to high CVD risk, depending on the risk score used. Furthermore, at least 40% of the PLHIV included in the BEIJERINCK study had potential DDIs between a high-intensity statin and ART (protease inhibitors, cobicistat, and non-nucleoside reverse transcriptase therapy prescribed); notably, 20.7% of PLHIV included in the BEIJERINCK study had total intolerance or absolute contraindication to statin therapy. These observations support the need for an alternative lipid-lowering therapy in high-risk PLHIV.

The effects of evolocumab on all other lipid parameters in PLHIV were concordant with those in uninfected patients in other evolocumab studies (20,27); the placebo-corrected mean percent changes in non-HDL-C, triglycerides and VLDL-C, Lp(a), and HDL-C from baseline to week 24 were -51%, -22%, -27%, and 8%, respectively.

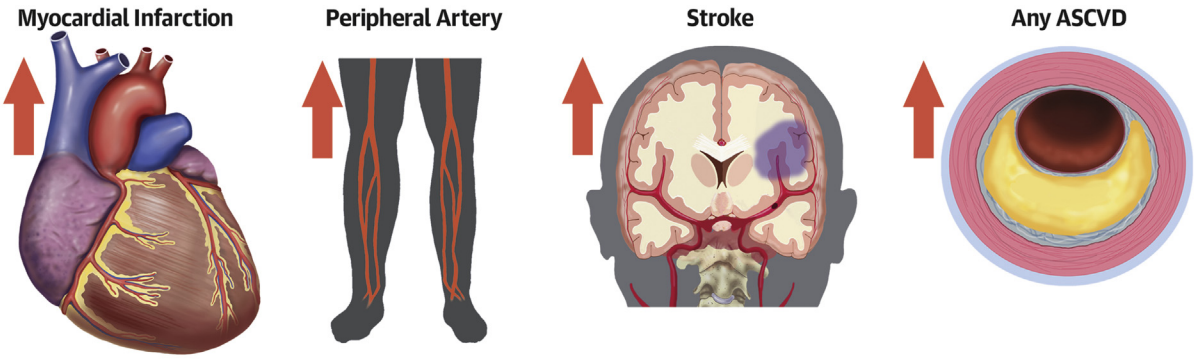
In agreement with other trials involving evolocumab, we did not find an effect on high-sensitivity C-reactive protein. However, the effects of PCSK9 inhibition on inflammatory cells requires further investigation (28). Recently, Hoogeveen et al. (29) showed that 14 weeks of alirocumab could decrease arterial wall inflammation at the carotid level using 18F-fluorodeoxyglucose positron emission tomography/computed tomography imaging, reinforcing the hypothesis that PCSK9 inhibitors may have local anti-inflammatory but not systemic effects. Two studies

CENTRAL ILLUSTRATION **Effect of Evolocumab on Lipid Parameters**

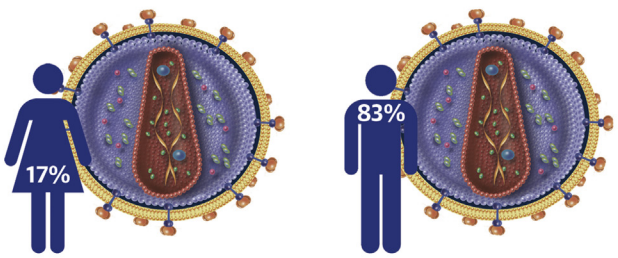
38 Million Individuals Live With HIV Worldwide with 1.1 Million in the United States

ASCVD → Leading cause of morbidity and mortality worldwide

Relative Risks of ASCVD Manifestations Globally Are 1.5 to 2-Fold Greater for PLHIV

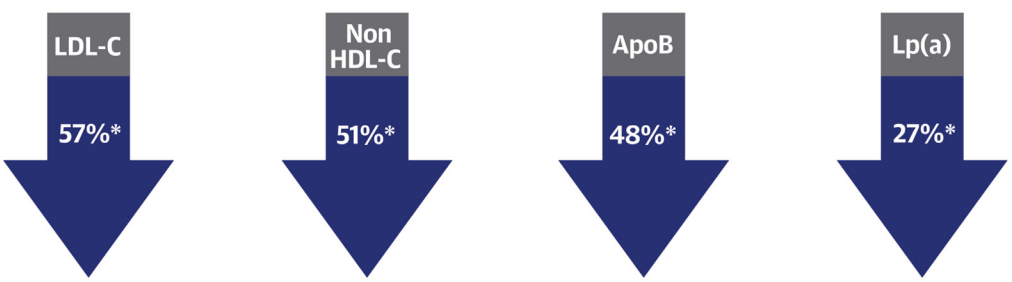


BEIJERINCK Study: People Living With HIV (PLHIV)



- Statin use → 79%
- Ezetimibe use → 19%
- Statin intolerance/ contraindications → 21%

Evolocumab Significantly Reduced Lipid Level Compared to Placebo (Baseline to Week 24)



* Mean % change after correcting for placebo (LSE treatment difference)

Boccara, F. et al. J Am Coll Cardiol. 2020;75(20):2570–84.

In the BEIJERINCK study, people living with HIV included were representative of the high CV-risk HIV population in western countries with a low rate of high-intensity statin use and a high rate of statin intolerance. Evolocumab was associated with a reduction in all atherogenic lipoproteins. ASCVD = atherosclerotic cardiovascular disease; BEIJERINCK = EvolocumaB Effect on LDL-C Lowering in SubJEcts with Human Immunodeficiency VirRus and INcreased Cardiovascular RisK; HIV = human immunodeficiency virus; LSE = least squares estimate; PLHIV = people living with human immunodeficiency virus.

evaluating the effects of PCSK9 inhibitors at the vessel level are underway in PLHIV. The first study is assessing the effect of evolocumab on coronary endothelial function (30,31), and the other one is assessing the effect of alirocumab on vascular wall inflammation (32). In fact, in PLHIV, PCSK9 levels were found to be higher than those in uninfected patients and were associated with HIV infection severity (33), cannabis use (34), monocyte activation (35), and lipid parameters as in the general population (33). Notably, coinfected HIV/hepatitis C virus patients have a higher level of PCSK9 compared with HIV-infected patients alone and uninfected patients despite a lower level of LDL-C (36). Moreover, a higher level of PCSK9 has been associated with endothelial dysfunction in PLHIV (30), reinforcing the need to evaluate the effects of PCSK9 inhibitors in PLHIV at the vessel level.

The BEIJERINCK study is the first randomized trial evaluating the safety of evolocumab in PLHIV. Evolocumab was well tolerated, with 97.7% of patients completing treatment. The incidences of TEAEs and laboratory abnormalities were comparable across treatment groups. Evolocumab-binding antibodies were rarely detected in our trial; no neutralizing antibodies developed.

STUDY LIMITATIONS AND STRENGTHS. The BEIJERINCK study has some limitations. First, the study was not designed to evaluate the effect of evolocumab on CVD events. One study has completed its enrollment in assessing the benefit of pitavastatin in PLHIV without ASCVD (37). The short study duration (24 weeks) in the present trial in patients needing life-long treatment could limit the results for long-term tolerance. However, all patients included in the present study will continue in an open-label, 24-week trial, and all will receive evolocumab providing more data on tolerance and safety. The strengths of this study include an international and double-blind placebo-controlled phase, inclusion of "real-world" intermediate-to-high ASCVD risk HIV population, and stringent criteria of statin intolerance.

CONCLUSIONS

Evolocumab therapy resulted in more than 56% reduction of LDL-C, compared with placebo, in PLHIV on maximally-tolerated statin therapy; the placebo-corrected percentages of patients achieving an LDL-C <70 mg/dl and an LDL-C reduction of ≥50% at week 24 were 65.4% and 71.9%, respectively. Treatment with evolocumab also reduced triglycerides, atherogenic lipid parameters (non-HDL-C, ApoB, total cholesterol, VLDL-C, and Lp[a]), and increased HDL-C compared with placebo. Evolocumab was well tolerated and safe in PLHIV. Based on the results of this study, the administration of evolocumab in PLHIV has a favorable benefit-to-risk profile and effectively reduces LDL-C.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Evolocumab is generally well tolerated and effective for lowering LDL-cholesterol in HIV-infected patients at high risk of developing atherosclerosis when statin drugs are insufficient.

TRANSLATIONAL OUTLOOK: Further studies are needed to evaluate the effect of PCSK9 inhibitors on vascular inflammation, endothelial function, and clinical ischemic events.

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KEY WORDS cardiovascular disease, hypercholesterolemia, low-density lipoprotein cholesterol (LDL-C), people living with HIV (PLHIV), proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor

APPENDIX For a complete list of the BEIJERINCK Study investigators, please see the online version of this paper.