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ORIGINAL RESEARCH ARTICLE

Cardiac Allograft Vasculopathy Inhibition With Alirocumab: The CAVIAR Trial

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BACKGROUND: Cardiac allograft vasculopathy is an important cause of mortality after heart transplantation (HT). Dyslipidemia is a major contributor to the development of cardiac allograft vasculopathy. The safety and effectiveness of proprotein convertase subtilisin/kexin 9 inhibition to lower cholesterol and to prevent cardiac allograft vasculopathy early after HT are not well established.

METHODS: In this investigator-initiated, prospective, multicenter, double-blind randomized trial, participants were randomized early after HT to receive either alirocumab or placebo in addition to rosuvastatin. Before randomization and at 1 year, all participants underwent invasive coronary assessment, including angiography, fractional flow reserve, coronary flow reserve, the index of microcirculatory resistance, and intravascular ultrasound with near-infrared spectroscopy. Lipid values were assessed at baseline and at prespecified intervals. The primary end point was the change in coronary artery plaque volume from baseline to 1 year after HT based on serial intravascular ultrasound.

RESULTS: A total of 114 HT recipients were included (57 assigned to alirocumab and 57 assigned to placebo). Baseline characteristics were well matched between the 2 groups. The low-density lipoprotein cholesterol levels decreased significantly from baseline to 1 year in the alirocumab arm (72.7±31.7 to 31.5±20.7 mg/dL; $P<0.001$) and did not change with placebo (69.0±22.4 to 69.2±28.1 mg/dL; $P=0.92$). Plaque volume increased numerically in both groups from baseline to 12 months (alirocumab, 176.3±95.2 to 184.5±105.4 mm^3; $P=0.23$; placebo 173.7±96.7 to 183.1±109.8 mm^3; $P=0.15$). The change in plaque volume (mean difference in differences) did not differ between groups (1.01 [0.89–1.14]; $P=0.86$). Fractional flow reserve, coronary flow reserve, and the index of microcirculatory resistance did not change significantly with the addition of alirocumab. There were no significant adverse events related to alirocumab.

CONCLUSIONS: Proprotein convertase subtilisin/kexin 9 inhibition with alirocumab in addition to statin therapy early after HT safely lowers low-density lipoprotein cholesterol but did not reduce coronary artery plaque progression after 1 year compared with rosuvastatin alone in patients with a low baseline low-density lipoprotein cholesterol.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03537742.

Key Words: cholesterol ■ coronary artery disease ■ lipids ■ transplantation

Editorial, see p 18

Cardiac allograft vasculopathy (CAV) is a major contributor to morbidity and mortality after heart transplantation (HT).[1] Dyslipidemia occurs commonly after HT and contributes to the development of CAV.[2] Treatment with HMG-CoA reductase inhibitors (statins) improves dyslipidemia, reduces the incidence

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Clinical Perspective

What Is New?

- The proprotein convertase subtilisin/kexin 9 inhibitor alirocumab is generally safe when given early after heart transplantation.
- Alirocumab significantly lowers lipid values compared with placebo in heart transplant recipients receiving rosuvastatin.
- The addition of alirocumab to usual care including rosuvastatin early after heart transplantation did not significantly reduce coronary artery plaque volume progression, although in this study the placebo arm had little plaque progression.

What Are the Clinical Implications?

- Alirocumab can be used to treat dyslipidemia in heart transplant recipients.
- In heart transplant recipients, further lipid lowering with proprotein convertase subtilisin/kexin 9 inhibition did not significantly affect cardiac allograft vasculopathy in the short term and on top of effective statin therapy.

Nonstandard Abbreviations and Acronyms

CAV	cardiac allograft vasculopathy
CAVIAR	Cardiac Allograft Vasculopathy Inhibition With Alirocumab
CFR	coronary flow reserve
FFR	fractional flow reserve
HT	heart transplantation
IMR	index of microcirculatory resistance
IVUS	intravascular ultrasound
LAD	left anterior descending
LCBI	lipid core burden index
LDL-C	low-density lipoprotein cholesterol
NIRS-IVUS	intravascular ultrasound with near-infrared spectroscopy
PCSK9	proprotein convertase subtilisin/kexin 9

of CAV, and improves clinical outcomes after HT.[3] However, because of interactions between statins and immunosuppressive therapy and other concerns resulting in submaximal statin dosing, low-density lipoprotein cholesterol (LDL-C) values often are >70 mg/dL. Proprotein convertase subtilisin/kexin 9 (PCSK9) inhibition has been shown to dramatically reduce LDL-C levels and to decrease coronary atherosclerotic plaque progression in the non-HT population.[4,5] The safety and effectiveness of the PCSK9 inhibitor alirocumab for prevention of CAV early after HT have not been studied.

METHODS

Study Design

The CAVIAR trial (Cardiac Allograft Vasculopathy Inhibition With Alirocumab) was an investigator-initiated, National Institutes of Health–funded, multicenter, double-blind, placebo-controlled randomized study comparing the addition of alirocumab with standard therapy early after HT (NCT03537742). The study was designed following conventional approaches used in mechanistic transplantation trials, emphasizing surrogate imaging and physiological end points rather than clinical events, which would require large sample sizes in this population.

Study Population and Procedures

All participants included in the study were at least 18 years of age, underwent HT at Stanford University, and were followed up either at Stanford University or at Kaiser Permanente Santa Clara Medical Center. Those undergoing a repeat HT, who were undergoing >1 organ transplantation, or who were not eligible for a baseline coronary angiogram because of kidney disease, hemodynamic instability, or another medical condition prohibiting an invasive procedure were excluded from the study. All participants provided informed written consent, and the research protocol was approved by the relevant institutional review boards or ethics committees.

Soon after HT, participants underwent a baseline coronary angiogram, intravascular ultrasound (IVUS) with near-infrared spectroscopy (NIRS-IVUS) of their left anterior descending coronary artery (LAD); coronary physiological assessment with measurement of fractional flow reserve (FFR), coronary flow reserve (CFR), and the index of microcirculatory resistance (IMR) down the LAD; and lipid value determination. They were then randomized with a web-based system in a double-blind and 1:1 fashion to alirocumab or matching placebo, dispensed by an independent pharmacist. Participants administered the medication to themselves, and the used injection pens were counted at clinic visits to ensure compliance. Any adverse events related to treatment or leading to hospitalization were recorded. Alirocumab was provided by Regeneron, which had no role in the design, conduct, analysis, or reporting of the study. An independent data safety monitoring board periodically reviewed the data and conduct of the study. After 1 year, participants returned to the cardiac catheterization laboratory for repeat assessment.

Medical Therapy

All patients received 500 mg of IV methylprednisolone when coming off cardiac bypass. Selective induction with rabbit antithymocyte globulin (1 mg/kg [maximum dose, 125 mg] given on postoperative days 1, 2, and 3) was administered to patients who were allosensitized or to those with chronic kidney disease before transplantation or acute kidney injury immediately after transplantation at the discretion of the clinical team. Three additional doses of 125 mg of methylprednisolone were given over the next 24 hours. Intravenous corticosteroids were then tapered to 20 mg every 12 hours by postoperative day 5, and oral prednisone was started at 20 mg daily on day 6. This dose was maintained until week 3, after which prednisone was reduced by 5 mg daily after each negative rejection surveillance test, with the goal of prednisone discontinuation by month 3 after transplantation in the absence of acute rejection.

The daily maintenance immunosuppressive regimen included tacrolimus (months 1–3: trough level 10–12 if induction was given, 12–15 if no induction therapy; months 3–6: trough level 8–10 if induction was given, 10–12 if no induction; months 6–12: trough level 8–10) and mycophenolate mofetil (1000 mg twice daily). Dose adjustments were made as indicated by adverse effects or acute rejection.

For opportunistic infection prophylaxis, patients received cotrimoxazole (one single-strength tablet daily) for pneumocystis pneumonia prophylaxis except for patients with sulfa allergy, who received atovaquone instead of cotrimoxazole. For cytomegalovirus prophylaxis, patients received intravenous ganciclovir until they were able to take oral medications, at which time they initiated valganciclovir (starting dose, 900 mg daily) until 6 months and then acyclovir until 1 year. Last, patients received posaconazole for fungal prophylaxis until 3 months after transplantation.

Patients were seen in clinic and monitored for acute rejection by routine surveillance endomyocardial biopsy at weeks 2 and 3 after transplantation, after which they were switched to a primarily noninvasive surveillance strategy. They had donor-derived cell-free DNA testing (AlloSure, CareDx, Inc) at weeks 4 and 6 and then combined donor-derived cell-free DNA testing and gene expression profiling (AlloMap, CareDx, Inc) at months 2, 3, 4, 6, 8, 10, and 12. Patients had endomyocardial biopsies if noninvasive surveillance tests were abnormal or if they presented with symptoms or signs of allograft dysfunction. All patients had surveillance transthoracic echocardiograms at months 1, 2, 4, 6, and 12 after transplantation.

Lipid Management

The HMG-CoA reductase inhibitor rosuvastatin was initiated in all patients within 1 week of transplantation at 10 mg per day, regardless of plasma cholesterol or triglyceride concentration. If after 4 weeks, the patient was tolerating the rosuvastatin without any adverse effects, it was increased to 20 mg per day. Participants were then randomized to treatment with either alirocumab (initial dose, 150 mg SC every 2 weeks) or matching placebo on the day after their baseline coronary angiogram procedure. Total cholesterol, LDL-C, high-density lipoprotein, triglycerides, lipoprotein(a), apolipoprotein B, and high-sensitivity C-reactive protein were measured at 3, 6, and 12 months after HT. The dose of rosuvastatin was modified according to lipid testing results as follows: If the LDL-C was <20 mg/dL, the rosuvastatin dose was reduced by half, and a fasting lipid panel was rechecked after 1 month. With each follow-up result, if the LDL-C was still <20 mg/dL, the rosuvastatin dose was reduced by half. If the dose of rosuvastatin was 2.5 mg daily and LDL-C was still <20 mg/dL, then the study drug (alirocumab or placebo) was reduced to 75 mg every 2 weeks. Thereafter, if the LDL-C value remained <20 mg/dL, the statin was discontinued. Participants were closely monitored for any adverse effects of alirocumab or placebo.

Invasive Evaluation

All participants underwent coronary angiography with standard techniques. After intracoronary nitroglycerin and intravenous heparin administration, IVUS imaging of the LAD was performed with a motorized pullback at 0.5 mm/s. A 50-MHz extended-bandwidth NIRS-IVUS catheter (Dualpro, Infraredx) was used at Stanford University; a 40-MHz or 60-MHz IVUS catheter (Opticross or Opticross HD, Boston Scientific) was used at Kaiser Permanente. Images were analyzed offline in a blinded fashion by an independent core laboratory (Stanford Cardiovascular Core Analysis Laboratory) using validated quantitative IVUS analysis software (echoPlaque 4, Indec Systems).[6] End-diastolic cross-sectional areas were traced every 1 mm along the proximal 50 mm of the LAD, with automated interpolation for intermediate frames. Two-dimensional measurements included maximum and minimum vessel and lumen diameters and areas, maximum percentage cross-sectional narrowing, plaque area, and maximal intimal thickness. Three-dimensional volumetric analysis calculated vessel, lumen, and plaque volumes over the proximal 50 mm of the LAD with the Simpson method. NIRS data were displayed as a longitudinal chemogram, representing lipid distribution on a per-pixel basis using a 128-color scale from red (low lipid probability) to yellow (high lipid probability). Lipid content was quantified with the lipid core burden index (LCBI), calculated as the fraction of valid pixels with lipid probability >0.6 multiplied by 1000.[7] The maximum LCBI in any 4-mm region ($maxLCBI_{4mm}$) was defined as the highest LCBI value within any contiguous 4-mm segment of the scanned region.

In participants undergoing evaluation at Stanford University, a coronary pressure wire (Certus, Abbott Vascular) was calibrated outside of the body and advanced so that the sensor was positioned at the tip of the guide catheter and pressures were equalized. The wire was then advanced to the distal two-thirds of the LAD. Care was taken to position the wire in the same location at baseline and at the 1-year follow-up. Three intracoronary injections of ≈3 mL room-temperature saline were performed, and the resting mean transit time was calculated as previously described.[8] Intravenous adenosine (140 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was then administered. Once maximal hyperemia was achieved, 3 injections of ≈3 mL room-temperature saline were performed, and the hyperemic mean transit time was measured. CFR was calculated as the resting mean transit time divided by the hyperemic mean transit time; IMR was calculated as the hyperemic mean transit time multiplied by the hyperemic distal coronary pressure; and FFR was calculated as the mean distal pressure divided by the mean proximal pressure during maximal hyperemia, as previously described.[8]

Study End Points

The primary end point of the study was a comparison of change in plaque volume from baseline to 1 year in the 2 randomized groups as assessed by core laboratory analysis of NIRS-IVUS. Secondary end points included differences in LDL-C and other lipid particle values between the 2 arms at 3, 6, and 12 months; differences in coronary physiology (FFR, CFR, and IMR); and differences in other NIRS-IVUS parameters.

Statistical Analysis

Baseline characteristics were summarized as means, medians, SDs, and interquartile ranges for continuous variables and as counts with percentages for categorical variables. For comparisons between groups at baseline, continuous variables were compared with the Student *t* test or Welch *t* test as appropriate or the Mann-Whitney *U* test for nonnormally distributed data. Categorical variables were compared with the Pearson χ^2 test or Fisher exact test as appropriate.

The primary analysis, conducted according to the intention-to-treat principle, evaluated changes in end points under a

linear mixed-effects model framework. The model included fixed effects for treatment arm, days since randomization (time), and their interaction, with a subject-specific random intercept to account for within-subject correlation. The treatment-by-time interaction was the primary parameter of interest, representing the differential progression in $\log_{10}$ plaque volume between treatment groups over 1 year.

The sample size was determined from empirical IVUS data from 96 previous HT recipients evaluated in our Stanford core laboratory. In that cohort, the SD of change in $\log_{10}$ plaque volume from baseline to 1 year was ≈0.10. We considered a treatment effect of 0.06 on the $\log_{10}$ scale to be clinically meaningful and consistent with previous lipid-lowering IVUS trials. With 52 subjects per arm, the study was calculated to provide >85% power at a 2-sided α of 0.05 to detect this effect size. The mixed-effects model allowed inclusion of all available repeated measurements under the missing-at-random assumption. As a prespecified secondary analysis, we also compared the within-patient change in plaque volume from baseline to 1 year between the 2 treatment groups with an independent-sample *t* test. This analysis, corresponding to a modified intention-to-treat approach restricted to patients with paired baseline and 1-year imaging data, was included as a supportive assessment to complement the model-based estimates.

Statistical inference was based on 2-sided Wald tests at the 0.05 level of significance. All analyses were performed in R version 4.4.1 (R Foundation, Vienna, Austria). The protocol, statistical analysis plan, and participant data can be accessed by contacting the corresponding author.

RESULTS

Between 2019 and 2024, a total of 114 patients were enrolled, with 57 randomized to alirocumab and 57 to placebo (Figure 1; Figure S1). Baseline recipient and donor characteristics were well matched between the 2 arms, as shown in Table 1. The baseline LDL-C was similar between the alirocumab and placebo arms (72.7±31.7 mg/dL versus 69.0±22.4 mg/dL, respectively). Medical therapy at baseline and 1 year is displayed in Table 2. Two participants in each arm were not taking rosuvastatin at baseline. In the alirocumab arm, the first participant enrolled in the study was mistakenly started on 40 mg of pravastatin daily and within 3 months switched to rosuvastatin, maintained at 20 mg daily. The other was on atorvastatin because of insurance reasons, which was ultimately reduced to 5 mg daily. In the placebo arm, one participant was started on 40 mg of pravastatin daily and switched within 3 months to atorvastatin, maintained at 40 mg daily. The second was on 10 mg of atorvastatin daily throughout. Both were because of insurance issues. The atorvastatin dosing was adjusted in the same fashion as rosuvastatin. When analyzed across patients taking a mammalian target of rapamycin inhibitor, overall exposure, expressed as the proportion of days covered during the first post-transplantation year, was low and did not differ significantly between those randomized to alirocumab and those randomized to placebo (0.37 days [0–0.72] versus 0.53 days [0.28–0.75]; P=0.18). The LDL-C level was reduced to a significantly greater extent by alirocumab compared with placebo at every time point after the baseline measurement, as shown in Table 3 and Figure 2, so that at 1 year, the average LDL-C was significantly lower in the alirocumab group compared with the placebo group (31.5±20.7 mg/dL versus 69.2±28.1 mg/dL; P<0.001). Lipoprotein(a) and apolipoprotein B levels were also significantly

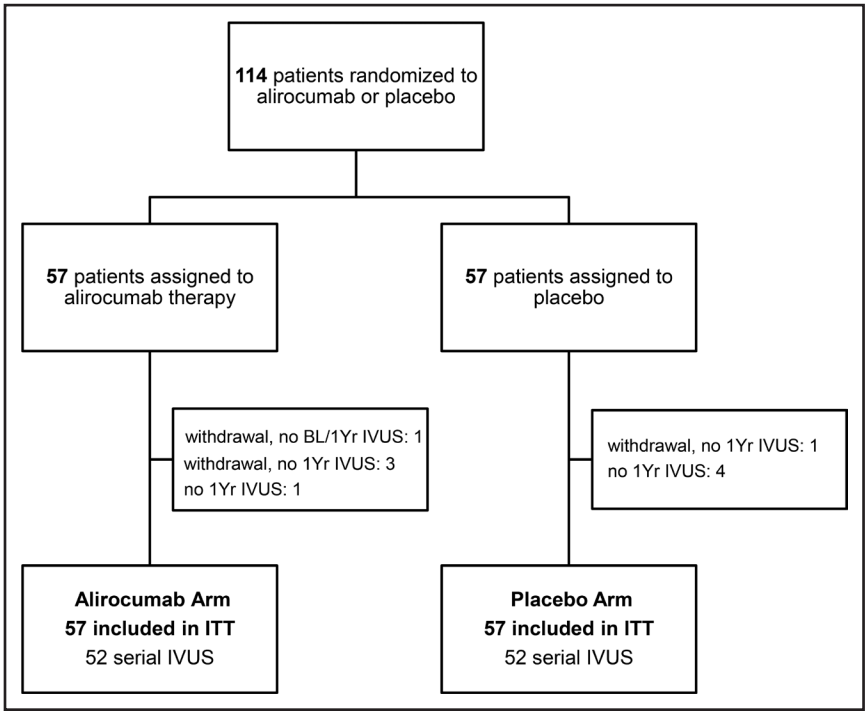

Figure 1. Patient flowchart.
BL indicates baseline; ITT, intention to treat; and IVUS, intravascular ultrasound.

Table 1. Baseline Recipient and Donor Clinical Characteristics

Variable	Alirocumab (n=57)	Placebo (n=57)
Recipient characteristics		
Age, y	51.4±16.4	55.2±10.8
Male, n (%)	47 (82.5)	45 (78.9)
Race and ethnicity, n (%)		
Black	4 (7.0)	7 (12.3)
White	27 (47.4)	28 (49.1)
Hispanic or Latino	15 (26.3)	10 (17.5)
Asian	7 (12.3)	9 (15.8)
Other/unknown	4 (7.0)	3 (5.3)
Body mass index, kg/m^2	26.1±4.0	26.1±4.5
Comorbidities, n (%)		
CMV IgG positive	36 (63.2)	34 (59.6)
Diabetes	25 (43.9)	27 (47.4)
Hypertension	45 (78.9)	48 (84.2)
Hypercholesterolemia*	36 (63.2)	37 (64.9)
Ischemic cardiomyopathy	13 (22.8)	6 (10.5)
Laboratory data		
Total cholesterol, mg/dL	157.8±36.0	150.4±30.6
LDL-C, mg/dL	72.7±31.7	69.0±22.4
HDL cholesterol, mg/dL	64.6±20.7	59.8±17.5
Triglycerides, mg/dL	153.2±69.3	155.9±109.2
Lipoprotein(a), mg/dL	43.5±52.3	54.4±64.6
Apolipoprotein B, mg/dL	73.8±20.8	68.2±17.3
C-reactive protein, mg/L	5.8±15.1	3.8±7.6
Donor characteristics		
Age, y	35.4±12.1	35.5±12.8
Male, n (%)	40 (71.4)	42 (76.4)
Sex mismatch, n (%)	17 (30.4)	9 (16.4)
Blood type mismatch, n (%)	11 (19.6)	8 (14.3)
CMV IgG mismatch, n (%)	28 (50.9)	27 (49.1)
Total ischemic time, min	230.8±96.7	243.4±82.5

Values are mean±SD or number (percentage).

CMV indicates cytomegalovirus; HDL, high-density lipoprotein; IgG, immunoglobulin G; and LDL-C, low-density lipoprotein cholesterol.

*Hypercholesterolemia was defined as patient either taking statin or diagnosed as hypercholesterolemia by a treating physician before heart transplantation.

Table 2. Medical Therapy at Baseline and 1 Year

Variable	Alirocumab (n=57)	Placebo (n=57)	*P* value
At baseline			
Statin type			1.0
Rosuvastatin, n (%)	54 (96.4)	54 (96.4)	
Atorvastatin, n (%)	1 (1.8)	1 (1.8)	
Pravastatin, n (%)	1 (1.8)	1 (1.8)	
Average dose, mg/d	10.0±4.7	10.4±4.8	0.65
γ-Antithymocyte globulin, n (%)	28 (49.1)	27 (47.4)	0.85
Tacrolimus, n (%)	56 (98.2)	56 (98.2)	1.0
Sirolimus, n (%)	0 (0.0)	2 (3.5)	0.50
Everolimus, n (%)	0 (0.0)	0 (0.0)	1.0
Cyclosporine, n (%)	1 (1.8)	0 (0.0)	1.0
Mycophenolate mofetil, n (%)	50 (87.7)	52 (91.2)	0.54
Mycophenolic acid, n (%)	6 (11.5)	4 (7.1)	0.52
At 1 y			
Statin type			0.36
Rosuvastatin, n (%)	51 (98.1)	48 (92.3)	
Atorvastatin, n (%)	1 (1.9)	4 (7.7)	
Pravastatin, n (%)	0 (0.0)	0 (0.0)	
Average dose, mg/d	6.9±6.9	13.8±9.4	<0.001
Tacrolimus, n (%)	50 (96.2)	52 (94.5)	1.0
Sirolimus, n (%)	13 (25.0)	19 (34.5)	0.28
Everolimus, n (%)	8 (15.4)	8 (14.5)	0.90
Cyclosporine, n (%)	1 (1.9)	2 (3.6)	1.0
Mycophenolate mofetil, n (%)	30 (57.7)	31 (56.4)	0.89
Mycophenolic acid, n (%)	1 (2.0)	1 (1.8)	1.0

Values are mean±SD or number (percentage).

reduced by alirocumab compared with placebo. Because some lipid values were skewed, the median values, their geometric mean ratios, and the 95% CIs from log-transformed analyses are displayed in Table S1. There were no significant adverse events related to alirocumab therapy, as shown in Table S2. There was no significant difference in acute cellular rejection (grade 2R or higher, diagnosed by right ventricular biopsy) between the alirocumab and placebo arms (5.3% versus 15.8%, respectively; *P*=0.07). There was also no difference in the development of de novo donor-specific antibodies in each group (12.3% versus 16.4%, respectively; *P*=0.54). There was no significant difference in significant cytomegalovirus infections in each group (8.8% versus 10.5%, respectively; *P*=0.75).

The interval between transplantation and the baseline angiogram was 85±36 days in the placebo group and 78±29 days in the alirocumab group (*P*=0.27). The interval between baseline and the annual angiogram was 356±20 days in the placebo group and 362±34 days in the alirocumab group (*P*=0.31). All NIRS-IVUS analyses were performed by experienced and qualified core laboratory analysts according to standard protocols to ensure consistency. Measurement reproducibility was assessed with randomly selected pullback images; the intraclass correlation coefficient for plaque volume, the primary end point, was 0.96. Plaque volume increased numerically in both groups from baseline to 12 months (alirocumab, 176.3±95.2 to 184.5±105.4 mm^3; *P*=0.23; placebo, 173.7±96.7 to 183.1±109.8 mm^3; *P*=0.15). The primary end point, change in plaque volume (mean difference in differences) from baseline to 1 year, was not significantly different (1.01 [0.89–1.14]; *P*=0.86) in the alirocumab arm compared with

Table 3. Change in Lipid Values From Baseline to 1 Year in Both Study Groups

Variable	Baseline	1 y	Difference* (95% CI)	*P* value
Alirocumab				
Total cholesterol, mg/dL	157.8±36.0	94.2±26.3	−54.3 (−64.5 to −44.2)	<0.001
LDL-C, mg/dL	72.7±31.7	31.5±20.7	−33.6 (−41.2 to −26.1)	<0.001
HDL cholesterol, mg/dL	64.6±20.7	48.2±13.4	−15.8 (−19.6 to −12.0)	<0.001
Triglycerides, mg/dL	153.2±69.3	123.1±69.3	−25.8 (−54.6 to 3.0)	0.08
Lipoprotein(a), mg/dL	43.5±52.3	27.9±39.9	−11.9 (−17.6 to −6.2)	<0.001
Apolipoprotein B, mg/dL	73.8±20.8	39.6±17.4	−28.6 (−34.4 to −22.8)	<0.001
hs-CRP, mg/L	5.8±15.1	8.3±27.4	1.5 (−3.6 to 6.5)	0.57
Placebo				
Total cholesterol, mg/dL	150.4±30.6	140.1±41.3	−8.3 (−18.0 to 1.4)	0.09
LDL-C, mg/dL	69.0±22.4	69.2±28.1	0.37 (−6.9 to 7.6)	0.92
HDL cholesterol, mg/dL	59.8±17.5	46.3±10.9	−12.1 (−15.7 to −8.5)	<0.001
Triglycerides, mg/dL	155.9±109.2	160.0±171.4	6.0 (−21.4 to 33.5)	0.67
Lipoprotein(a), mg/dL	54.4±64.6	49.2±56.2	−7.7 (−13.4 to −2.1)	0.008
Apolipoprotein B, mg/dL	68.2±17.3	70.1±25.3	2.2 (−3.6 to 8.0)	0.46
hs-CRP, mg/L	3.8±7.6	3.4±3.1	−0.45 (−5.4 to 4.5)	0.86

Values are mean±SD.
HDL indicates high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein.
*Based on linear mixed-effect model between day 365 and day 0 within each arm.

the placebo arm (Figure 3). The NIRS-IVUS measurements at baseline and 1 year in the 2 groups are displayed in Table 4 and showed that the maximal intimal thickness increased from baseline to 1 year in both groups and to a similar degree. Plaque volume did not increase significantly from baseline to 1 year in either arm; however, vessel volume decreased significantly in both arms to a similar degree, resulting in significant changes in percent plaque volume and lumen volume. In participants who underwent NIRS-IVUS, NIRS-derived LCBI and maxLCBI$_{4mm}$ did not change significantly from baseline to 1 year in either arm. A modified intention-to-treat analysis including only those participants with complete serial data revealed similar findings and is displayed in Figure S2.

An exploratory subgroup analysis evaluating any interaction based on being above or below the median value for baseline age, sex, plaque volume, baseline maximal intimal thickness, baseline LDL-C, or baseline lipoprotein(a) value showed significant interactions with greater plaque progression in older patients and those with higher baseline LDL-C randomized to placebo compared with alirocumab (Figure S3). Cumulative distribution plots of plaque volume change and stratified by LDL-C are displayed in Figure S4.

Baseline coronary physiological assessment was performed in 38 participants randomized to alirocumab and 40 participants assigned to placebo. Changes in coronary physiology parameters from baseline to 1 year are shown in Table 5. In the alirocumab group, there were no significant changes in FFR, CFR, or IMR from baseline to 1 year. In the placebo arm, CFR increased significantly as a result of a slower resting coronary flow at 1 year compared with baseline.

DISCUSSION

The primary findings in this study are that the PCSK9 inhibitor alirocumab can be safely administered to HT recipients early after HT and results in significant reductions in total cholesterol, LDL-C, lipoprotein(a), and apolipoprotein B compared with statin therapy alone. Despite these favorable improvements in the lipid profile, alirocumab did not significantly reduce the change in plaque volume from baseline to 1 year compared with statin therapy alone, nor did alirocumab significantly affect the lipid burden of plaque, as assessed with NIRS-IVUS, or coronary physiology, as assessed with FFR, CFR, and IMR.

The relationship between LDL-C and coronary artery plaque progression in noncardiac transplantation recipients has been recognized for many years.[9] In this population, the reduction of plaque progression by lowering LDL-C either with statin therapy or PCSK9 inhibition has been well documented.[10] Previous studies have also demonstrated a relationship between LDL-C levels and plaque progression after HT.[11,12] Lowering LDL-C after HT with statin therapy has been shown to reduce plaque progression by as much as 50%.[3,13] However, in these studies, LDL-C levels were relatively high at baseline. More recent data suggest that there may be a threshold

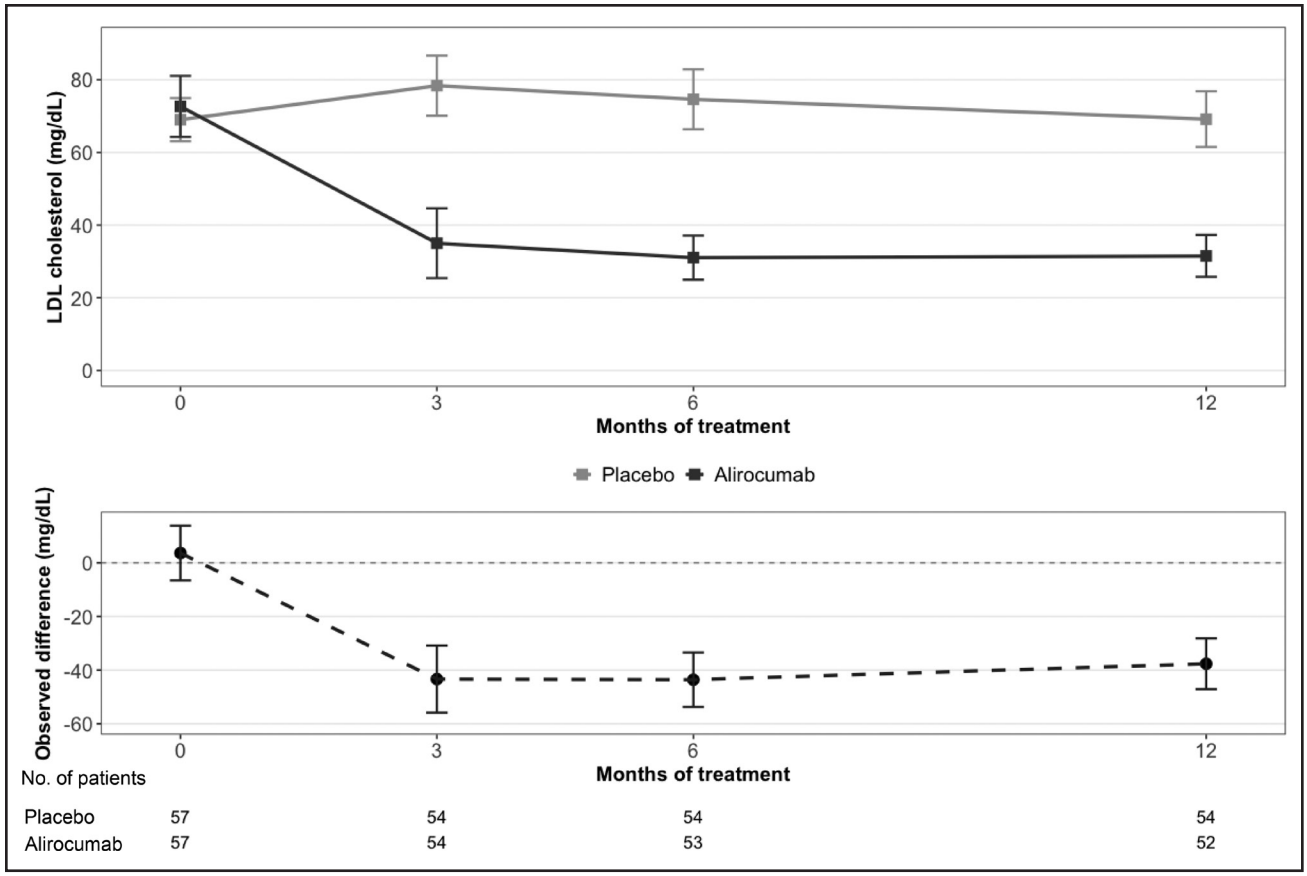

Figure 2. LDL cholesterol levels at each time point in the 2 arms.
LDL indicates low-density lipoprotein.

LDL-C level ≈70 mg/dL, above which there is a significant effect on plaque progression, but below which there is not.[14] A recent study in HT recipients, which suggested no relationship between LDL-C and plaque progression, included patients with baseline LDL-C lower than in previous studies.[15] One possible explanation for the lack

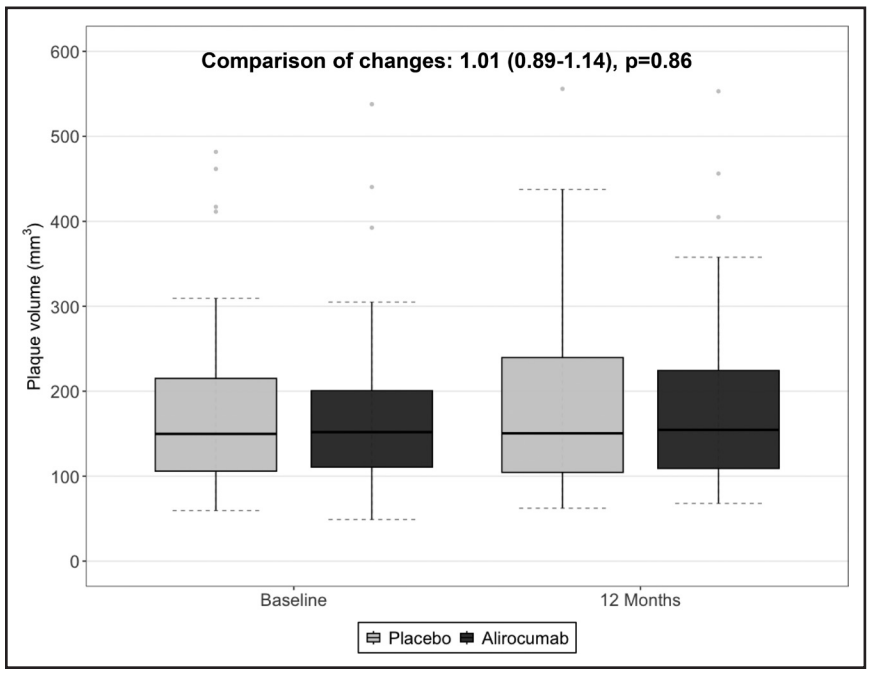

Figure 3. Comparison of trajectory of change in plaque volume from baseline to 1 year in each arm.

Table 4. Baseline and 1-Year IVUS Indices

Variable	Baseline	1 y	GMR* (95% CI)	*P* value
Alirocumab				
Maximal intimal thickness, mm	0.90±0.50	1.1±0.53	1.25 (1.11–1.42)	<0.001
Plaque volume, mm^3	176.3±95.2	184.5±105.4	1.05 (0.97–1.15)	0.23
Average plaque area, mm^3/mm†	3.8±1.9	4.0±2.1	1.05 (0.97–1.15)	0.24
Percent plaque volume	22.7±9.4	26.3±12.0	1.16 (1.05–1.27)	0.002
Lumen volume, mm^3	591.3±152.8	513.1±146.1	0.86 (0.81–0.90)	<0.001
Average lumen area, mm^3/mm	12.6±2.8	10.9±2.5	0.86 (0.81–0.90)	<0.001
Vessel volume, mm^3	767.7±192.3	697.6±177.1	0.91 (0.88–0.94)	<0.001
Average vessel area, mm^3/mm	16.4±3.3	14.9±2.8	0.91 (0.88–0.94)	<0.001
NIRS LCBI	2.3±6.8	1.9±6.5	1.10 (0.23–5.31)	0.90
NIRS $maxLCBI_{4mm}$	21.0±64.2	19.3±69.4	1.17 (0.23–6.03)	0.84
Placebo				
Maximal intimal thickness, mm	0.87±0.49	1.1±0.62	1.29 (1.14–1.47)	<0.001
Plaque volume, mm^3	173.7±96.7	183.1±109.8	1.07 (0.98–1.16)	0.15
Average plaque area, mm^3/mm	3.6±1.9	3.8±2.2	1.06 (0.97–1.16)	0.16
Percent plaque volume	21.9±9.3	24.8±11.5	1.13 (1.03–1.24)	0.01
Lumen volume, mm^3	598.0±144.3	539.6±158.8	0.89 (0.84–0.94)	<0.001
Average lumen area, mm^3/mm	12.4±2.9	11.1±3.0	0.89 (0.84–0.94)	<0.001
Vessel volume, mm^3	771.8±184.6	722.7±190.1	0.94 (0.91–0.97)	<0.001
Average vessel area, mm^3/mm	16.0±3.4	14.9±3.5	0.94 (0.91–0.97)	<0.001
NIRS LCBI	4.6±15.8	1.7±3.5	0.69 (0.25–1.87)	0.44
NIRS $maxLCBI_{4mm}$	36.1±76.4	19.6±40.0	0.93 (0.34–2.58)	0.89

Values are mean±SD.

GMR indicates geometric mean ratio; IVUS, intravascular ultrasound; NIRS LCBI, near-infrared spectroscopy-derived lipid core burden index; and NIRS $maxLCBI_{4mm}$, highest NIRS LCBI within any contiguous 4-mm segment of the scanned region.

*Based on linear mixed-effect model between day 365 and day 0 within each arm.

†Plaque, lumen, and vessel volumes were standardized for analyzed longitudinal length (mm^3/mm).

of benefit of alirocumab on plaque progression in the CAVIAR trial is that the LDL-C levels were already very low (≈70 mg/dL) at baseline after initiation of therapy with rosuvastatin. Our subgroup analysis demonstrating a possible interaction based on the median LDL-C at baseline, with those participants with higher LDL-C

Table 5. Serial Coronary Physiology Data in the 2 Study Groups

Variable	Baseline	1 y	Difference* (95% CI)	*P* value
Alirocumab				
FFR	0.90±0.03	0.90±0.04	−0.00 (−0.02 to 0.02)	0.89
CFR	4.5±1.9	4.6±2.0	0.16 (−0.62 to 0.95)	0.68
IMR	15.6±6.6	15.4±8.9	−0.01 (−2.74 to 2.72)	1.00
Resting T_{mn}	1.0±0.36	1.1±0.40	0.06 (−0.09 to 0.21)	0.45
Hyperemic T_{mn}	0.25±0.09	0.24±0.12	0.00 (−0.04 to 0.04)	0.97
Placebo				
FFR	0.90±0.04	0.89±0.05	−0.01 (−0.03 to 0.01)	0.22
CFR	4.2±1.8	5.1±2.3	0.97 (0.18 to 1.76)	0.02
IMR	14.6±5.9	15.4±7.5	1.16 (−1.63 to 3.94)	0.41
Resting T_{mn}	0.89±0.35	1.1±0.34	0.19 (0.04 to 0.34)	0.01
Hyperemic T_{mn}	0.24±0.10	0.25±0.13	0.01 (−0.03 to 0.05)	0.55

Values are mean±SD.

CFR indicates coronary flow reserve, FFR, fractional flow reserve, IMR, index of microcirculatory resistance, T_{mn}, mean transit time.

*Based on linear mixed-effect model between day 365 and day 0 within each arm.

having less change in plaque volume with alirocumab compared with placebo, supports this hypothesis, although this was a post hoc exploratory analysis and needs to be confirmed.

Another possible explanation for the lack of benefit of alirocumab on plaque progression after HT is that CAV may be less related to LDL-C level and more related to inflammation or immune-mediated factors. Some studies have suggested that the beneficial effects of statins on development of CAV after HT are related to their anti-inflammatory effects.[16] Although PCSK9 inhibition has been associated with beneficial effects on inflammation, whether these effects prevent CAV, particularly in the presence of statins, is unknown.

There was no significant plaque progression in the placebo arm of the CAVIAR trial. This was an unexpected finding because a previous study we performed testing the effect of the angiotensin-converting enzyme inhibitor ramipril on the development of CAV after HT showed significant plaque progression from baseline to 1 year.[17] There are a number of possible reasons for this finding, including the more potent statin prescribed and improved immunosuppression in the placebo arm of the CAVIAR trial (compared with our previous ramipril study), resulting in less plaque progression, thereby making it more difficult to demonstrate a benefit with alirocumab. Because of this slower plaque progression, longer-term therapy and follow-up may have been necessary to demonstrate a benefit of alirocumab.

Other possible explanations for the lack of benefit of alirocumab on plaque progression, short of an actual lack of therapeutic benefit, include issues with our study design and execution. Although they were not significant, there were numerical differences in baseline characteristics such as recipient age and comorbidities. Because some participants in the alirocumab arm developed very low LDL-C values, the rosuvastatin dose was significantly lower at 1 year in the alirocumab arm. Although high-sensitivity C-reactive protein values were not significantly different between the 2 groups from baseline to 1 year, there was a numerical increase in the inflammatory marker in the alirocumab arm. Last, the short follow-up relative to other lipid-lowering studies, which generally have 2- to 5-year follow-up and the use of the highly potent rosuvastatin, may have impaired our ability to detect a difference in plaque progression.

The findings in this study build on a recent trial evaluating the addition of the PCSK9 inhibitor evolocumab to usual care early after HT.[18] That trial also demonstrated substantial reductions in LDL-C with PCSK9 inhibition but no significant effect on CAV development as assessed by IVUS. The CAVIAR trial distinguishes itself through several key methodological differences, including: (1) the use of alirocumab, another PCSK9 inhibitor of current interest in the cardiovascular field; (2) a more comprehensive primary end point examining 3-dimensional IVUS–derived plaque volume compared with the 2-dimensional maximal intimal thickness assessed with a 20-MHz IVUS; (3) the use of high-definition, extended-bandwidth NIRS-IVUS for enhanced IVUS resolution and plaque lipid content quantification; and (4) a more aggressive statin regimen with rosuvastatin, which achieved lower LDL-C levels in the placebo arm than the pravastatin-based regimen in the previous trial. It is important to note that now 2 randomized trials have failed to demonstrate a significant effect of 2 different PCSK9 inhibitors on the development of CAV early after HT.

One of the unique aspects of the CAVIAR trial is that in a subset of patients, we performed detailed coronary physiological assessment of the epicardial vessel with FFR and the microvasculature with CFR and IMR at both baseline and the 1-year follow-up. We did not find any significant change in FFR, CFR, or IMR from baseline to 1 year in the alirocumab group. This may be attributable to less acute microvascular dysfunction soon after HT in this study, as demonstrated by the normal CFR and IMR at baseline. In a previous study, both CFR and IMR were more abnormal at baseline and improved during the first year, and as a result of the increased hyperemic flow, FFR decreased.[19] In the placebo arm of this study, CFR increased from baseline to 1 year. However, the 1-year CFR in the placebo arm was similar to the CFR in the alirocumab arm. The change in CFR in the placebo group appears to be attributable to a lower baseline CFR as a result of a relatively faster resting mean transit time at baseline. IMR, which is a reflection of the minimum achievable microvascular resistance and a reflection of the health of the microvasculature, did not change in the placebo arm and was similar in the alirocumab arm. The high resting transit time at baseline in the placebo group that drove the lower baseline CFR may have been the play of chance. The increase in CFR seen in the placebo group over 1 year may not reflect an important change in microvascular function.

The main limitation of this study is the relatively small sample size, although detailed and serial invasive analyses in the HT patient population are difficult to perform on a large scale. The relatively short follow-up time, in conjunction with the lower-than-expected plaque progression in the placebo arm, contributed to reduced power to detect differences between the study groups. It may be that longer treatment duration and follow-up are necessary for the significant reductions in lipid levels seen with alirocumab to result in reduced development of CAV and clinical events. Use of an IVUS-derived primary end point as a surrogate for CAV and ultimately clinical events is another limitation of this study. Ideally, we would have enrolled a larger

cohort and followed up participants for a longer time period to evaluate the impact of alirocumab on clinical events. However, logistically, this type of study is very challenging. Other studies evaluating therapies for CAV have also used IVUS-derived parameters.[20] Moreover, changes in IVUS plaque volume between baseline assessment soon after HT and 1 year later have been shown to predict CAV and clinical events during long-term follow-up.[21] Interrogation of only the LAD may have missed differences in CAV development in other coronary arteries, but multivessel invasive assessment can be challenging and increases risk.

Conclusions

PCSK9 inhibition with alirocumab early after HT safely and significantly reduces total cholesterol, LDL-C, lipoprotein(a), and apolipoprotein B levels when added to rosuvastatin therapy but did not reduce the development of CAV compared with treatment with rosuvastatin alone after 1 year. The lack of significant plaque progression in the placebo arm reduced the power of the study to detect a difference with alirocumab. Longer-term therapy in HT recipients with higher baseline LDL-C levels might still be beneficial for reducing CAV and clinical events.

ARTICLE INFORMATION

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Supplemental Material

Tables S1 and S2
Figures S1–S4

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