Kidney Medicine

Alirocumab and Lipid Levels, Inflammatory Biomarkers, Metabolomics, and Safety in Patients Receiving Maintenance Dialysis: The ALIrocumab in DIALysis Study (A Phase 3 Trial to Evaluate the Efficacy and Safety of Biweekly Alirocumab in Patients on a Stable Dialysis Regimen)

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Rationale & Objective: The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor alirocumab is used in the general population to treat dyslipidemia, but little is known about the effects of alirocumab on lipid levels, biomarkers, the metabolome, and safety in individuals receiving maintenance dialysis.

Study Design: Patients receiving maintenance dialysis for at least 3 months and with a low-density lipoprotein cholesterol level of >70 mg/dL were treated with alirocumab for 12 weeks. Laboratory measurements, drug levels, and safety assessments were obtained at baseline and every 4 weeks during the trial.

Setting & Participants: In an outpatient setting, 14 patients completed the trial.

Intervention: The patients were treated with alirocumab at a full dose of 150 mg every 2 weeks for 12 weeks. The patients were asked to report any adverse events every 2 weeks.

Outcomes: There were no unexpected adverse events or laboratory abnormalities in this population receiving dialysis. The drug levels were the same as those for a population not receiving dialysis.

Results: Alirocumab resulted in a 45% reduction in the low-density lipoprotein cholesterol level (P = 0.005) and a 35% reduction in the apolipoprotein B level (P = 0.06). There were no significant decreases in the levels of triglycerides, C-reactive protein, fibrinogen, or other inflammatory biomarkers tested. There were significant decreases in the levels of 7 ceramide, 5 sphingomyelin, and 5 cholesterol ester species.

Limitations: This study was performed in only 14 patients who were administered alirocumab for only 12 weeks. This study did not address alirocumab treatment in patients with chronic kidney disease not receiving maintenance dialysis.

Conclusions: Individuals receiving maintenance dialysis had a similar response to the PCSK9 inhibitor alirocumab as patients not receiving dialysis. The levels of inflammatory biomarkers were not clearly decreased by alirocumab, but the levels of ceramides, sphingomyelins, and cholesterol esters were significantly reduced.

Trial Registration: Clinical Trials.gov as NCT03480568.

Visual Abstract included

Complete author and article information provided before references.

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Kidney Med. 4(7):100483. Published online May 20, 2022.

doi: 10.1016/j.xkme.2022.100483

More than 660,000 Americans experience kidney failure, of whom 468,000 receive dialysis.[1] The cardiovascular disease mortality is 10-20 times higher than that in the general population.[2] Thus, there is a need for the prevention of atherosclerotic events in this population.

Although statins can be used, studies using statins have yielded mixed results. In observational studies of patients receiving hemodialysis, lower cholesterol levels were associated with higher mortality, which could have been due to long-standing atherosclerotic conditions or renal wasting syndrome.[3] In 3 randomized trials of 1,255-9,270 patients receiving dialysis treated with statins, the results were mixed and ranged from no effect in 2 trials to a 17% relative risk reduction in the third trial.[4-7] A retrospective, nonrandomized review of 65,000 patients receiving dialysis treated with statins showed a lower risk of all-cause mortality; so, cholesterol reduction may be beneficial in this patient population.[8]

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a protein that binds to and targets low-density lipoprotein (LDL) receptors for destruction. Alirocumab is a fully humanized monoclonal antibody that binds to PCSK9 in free plasma and removes it from circulation. Proprotein convertase subtilisin/kexin type 9 inhibitors reduce the destruction of LDL receptors and lower the levels of LDL cholesterol (LDL-C). Studies of PCSK9 inhibitors in patients at a high risk of atherosclerotic events have shown benefit.[9,10] However, alirocumab has not been studied for its effects on LDL-C, inflammatory biomarkers, and metabolomics in patients receiving maintenance dialysis.

METHODS

Study Design

Patients were recruited from outpatient nephrology practices between August 2018 and February 2019. The trial

PLAIN-LANGUAGE SUMMARY

Patients receiving maintenance dialysis have a high incidence of cardiovascular events even when blood pressure and diabetes are well controlled. Such patients may be treated with statins, but studies using statins have not shown a reduction in cardiovascular events. Proprotein convertase subtilisin/kexin type 9 inhibitors have a different mechanism of action for reducing low-density lipoprotein cholesterol levels. In this study, the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab was shown to be safe and effective in lowering the low-density lipoprotein cholesterol level in patients with a low-density lipoprotein cholesterol level of >70 mg/dL receiving dialysis. The drug levels were the same as those in patients not receiving dialysis, and there were no adverse events attributed to alirocumab. Alirocumab did not significantly affect inflammatory biomarkers in this small study but did reduce the levels of ceramides, sphingomyelins, and cholesterol esters, which are novel markers for cardiovascular risk.

complied with the Declaration of Helsinki, Baylor Scott & White Institutional Review Board approved the research protocol (IRB number, 018-038), and all patients provided informed consent.

Patients were eligible for the study if they had received maintenance hemodialysis or peritoneal dialysis for at least 3 months, without dialysis complications (Fig 1). For this pilot trial, the goal was to enroll 20 patients. Patients may or may not have had a previous diagnosis of atherosclerotic disease and were excluded if their LDL-C level was <70 mg/dL, they had a history of intolerance to alirocumab or drugs of the same class, they had a history of an atherosclerotic event within 3 months, or they had a history of malignant cancer within 3 years (except localized skin or cervical cancer). No patient had a known infection at the time of enrollment. No women of child-bearing potential were enrolled. Seven patients (50%) were being treated with a statin by their nephrologist at the time of enrollment, which was continued without change. No patients were on ezetimibe.

Enrolled participants were given alirocumab at a maximum dose of 150 mg at baseline and every 2 weeks for 6 injections total. For those treated with hemodialysis, the visits occurred on a nondialysis day for patient convenience. Those treated with peritoneal dialysis had visits during a time of stable dialysis. Electrocardiograms were obtained and the quality-of-life questionnaire EQ-5D-3L was administered at the baseline and at 12 weeks, and data on all adverse events were collected every 2 weeks. In this exploratory, single-drug study, all participants and staff were aware of drug assignment.

Laboratory Levels

Blood tests were performed after 10-12 hours of fasting. Data on cholesterol level, complete blood count, complete metabolic profile (safety laboratory tests), alirocumab and PCSK9 levels, antialirocumab antibody level, biomarkers, and metabolomics were obtained at the baseline visit and at 12 weeks. Safety laboratory tests were also performed at 4 and 8 weeks, and the trough alirocumab level was determined at 10.5 weeks. The end of treatment visit occurred at week 12, after the patients had received 6 injections.

If the LDL-C level fell <25 mg/dL for 2 consecutive measurements, the alirocumab dose was decreased to 75 mg every 2 weeks. If the LDL-C level fell <15 mg/dL for 2 consecutive measurements, alirocumab was discontinued.

The levels of lipids, apolipoprotein B, thyrotropin, hemoglobin A1C, troponin I, pro-brain natriuretic peptide, fibrinogen, and high-sensitivity C-reactive protein (hs-CRP) were measured in a commercial laboratory. Other biomarkers tested included fibroblast growth factor 23, tumor necrosis factor-α (TNF-α), interleukin 6, soluble vascular cell adhesion molecule, serum amyloid A, and soluble CD40 ligand, and these were analyzed using a multiplex, bead-based immunoassay on the Luminex platform (ImmunoAssay/ProteinCore/Baylor Scott & White Research Institute). A targeted metabolomic analysis of plasma was performed by liquid chromatography mass spectrometry using the Quant 500 metabolomic kit as previously described.[11] This analysis was able to detect and quantitate 542 metabolites, including 480 lipid species in 13 lipid classes.

The concentrations of alirocumab, total PCSK9, and antialirocumab antibodies were measured using enzyme-linked immunosorbent assay.[12]

Statistical Methods

Statistical analysis was conducted on all patient data. Summary tables were made of demographic characteristics, including age, sex, race, ethnicity, height, weight, body mass index, waist circumference, blood pressure, whether the patient was receiving hemodialysis or peritoneal dialysis, concomitant diagnoses, and baseline medications. Continuous variables were summarized using number, mean, standard deviation, median, minimum, and maximum. Categorical variables, including any adverse effects or serious adverse effect outcomes, were summarized using frequency and percentage.

Before examining changes in outcomes, the continuous variables were visually explored using a boxplot, a histogram, and an O-O plot. To formally test the normality of those variables, we further used the Kolmogorov-Smirnov and Shapiro-Wilk tests. Depending on the results, either the paired t test or the Wilcoxon rank sum test was applied for univariate comparison of continuous outcomes

between the baseline and end-of-study measurements. We used SAS, version 9.4, with a level of significance of 0.05.

The false discovery rate used for metabolomic analysis is the number of false positive results divided by the sum of the false positive plus total positive results.[13] It allows for the testing of multiple null hypotheses. The false discovery rate was analyzed using MetaboAnalyst 5.0, with a level of significance of 0.05.

RESULTS

Eighteen patients were screened, 16 patients were enrolled, and 14 patients completed the study (Table 1). The mean age was 59 years, and most were Black men. Of the patients receiving dialysis, 12 were receiving hemodialysis and 2 patients were receiving peritoneal dialysis. The patients had been receiving maintenance dialysis for a median duration of 3 years (range, 3 months to 8 years). As expected, the enrolled patients had a high prevalence of hypertension, diabetes, and hyperlipidemia. One-half of the patients were on a statin, one-third were on an angiotensin-converting enzyme inhibitor or angiotensin-converting enzyme receptor blocker, one-third were on a calcium-channel blocker, majority were on a beta blocker, and one-third were on aspirin.

Two patients had LDL-C levels <70 mg/dL and were excluded. One patient completed the study early because he had to undergo kidney transplantation, and 1 patient withdrew from the study. There were 27 adverse events, none of which were attributed to alirocumab and 1 of which was unexpected in a population receiving stable dialysis (new diagnosis of tuberculosis), and, specifically, no muscle side effects or injection-site reactions. There were 6 serious adverse events that required hospitalization (Table 2). There were no differences in the electrocardiograms or patient questionnaire EQ-5D-3L.

The safety laboratory tests, including complete blood count, complete metabolic profile, thyrotropin, troponin I,

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline

Sample Size, N	14
Age, y[a]	59.2 ± 7.4
Male sex, n (%)	10 (71%)
Race, n (%)	
White	1 (7%)
Black	10 (71%)
White/Hispanic	2 (14%)
Pacific Islander	1 (7%)
Height, in[a]	68 ± 4
Weight, lb[a]	171 ± 30
Body mass index[a]	27 ± 4
Waist circumference	39 ± 5
Blood pressure systolic (mm Hg)[a]	155 ± 19
Blood pressure diastolic (mm Hg)[a]	82 ± 11
Type of dialysis, n (%)	
Hemodialysis	12 (86%)
Peritoneal dialysis	2 (14%)
Time on dialysis, y[a]	3.4 ± 2.7
Concomitant diagnoses, n (%)	
Hypertension	8 (57%)
Hyperlipidemia	7 (50%)
Diabetes	6 (43%)
Baseline medications, n (%)	
Beta blocker	12 (86%)
Statin	7 (50%)
Calcium-channel blocker	5 (36%)
Aspirin	5 (36%)
ACEi/ARB	4 (29%)
Diuretic	3 (21%)
Anticoagulant	3 (21%)
Insulin	3 (21%)

Abbreviation: ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.
[a]Mean ± standard deviation.

Table 2. Adverse Reactions: MedDRA System (Medical Dictionary for Regulatory Activities)

Eye Disorder	n (%)
Blurry vision	1 (7%)
Gastrointestinal disorders	
Constipation	1 (7%)
Diarrhea	1 (7%)
Nausea	1 (7%)
General disorders	
Dental caries	1 (7%)
Volume overload	1 (7%)
Hepatobiliary disorders	
Ascites	1 (7%)
Metabolism and nutrition disorders	
Very low-density lipoprotein	3 (21%)
Worsening hypertension	1 (7%)
Musculoskeletal and connective tissue disorders	
Finger pain	1 (7%)
Neck pain	1 (7%)
Spinal C2 fracture[a]	1 (7%)
Toe osteomyelitis[a]	1 (7%)
Nervous system disorders	
Dizziness	1 (7%)
Psychiatric disorders	
Adjustment disorder	1 (7%)
Renal and urinary disorders	
Uremia[a]	1 (7%)
Respiratory, thoracic, and mediastinal disorders	
Chronic cough	1 (7%)
Tuberculosis[a]	1 (7%)
Upper respiratory infection	3 (21%)
Skin and subcutaneous disorders	
Medication-induced rash	1 (7%)
Vascular disorders	
Thrombosis dialysis access	1 (7%)
Malfunction dialysis access	2 (14%)

[a]Serious adverse events requiring hospitalization.

Table 3. Effect of Alirocumab on Lipoproteins, Apolipoprotein B, C-Reactive Protein, and Fibrinogen Levels

	LDL-C	ApoB	HDL-C	Triglyceride	CRP	Fibrinogen
Before treatment	99.2 ± 27.1	89.8 ± 17.9	52.8 ± 19.8	100.2 ± 31.3	11.2 ± 18.8	410 ± 102
After treatment	54.9 ± 24.7	58.9 ± 2.3	57.8 ± 22.2	91.2 ± 47.1	4.5 ± 4.6	365 ± 79
P value	0.01	0.01	0.02	0.2	0.1	0.6

Note: Values indicate mean ± standard deviation, expressed in milligram per deciliter, except for CRP, which is represented as median ± standard deviation, expressed in milligram per deciliter. *P* value (paired *t* test).
Abbreviations: ApoB, apolipoprotein B, CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

pro-brain natriuretic peptide, and hemoglobin A1C, did not show significant differences between the baseline and final values. The baseline LDL-C levels ranged from 71 to 171 mg/dL, with a mean LDL-C level of 99 mg/dL (Table 3).

During the study, in 3 patients, the LDL-C levels fell <25 mg/dL, and the LDL-C level measurement was repeated and found to be >25 mg/dL; so, the study was completed as planned. For 1 patient, the LDL-C level fell <25 mg/dL, and upon repeating, it was <15 mg/dL. Alirocumab was never restarted, and the LDL-C levels never returned to the baseline values during the 12-week study.

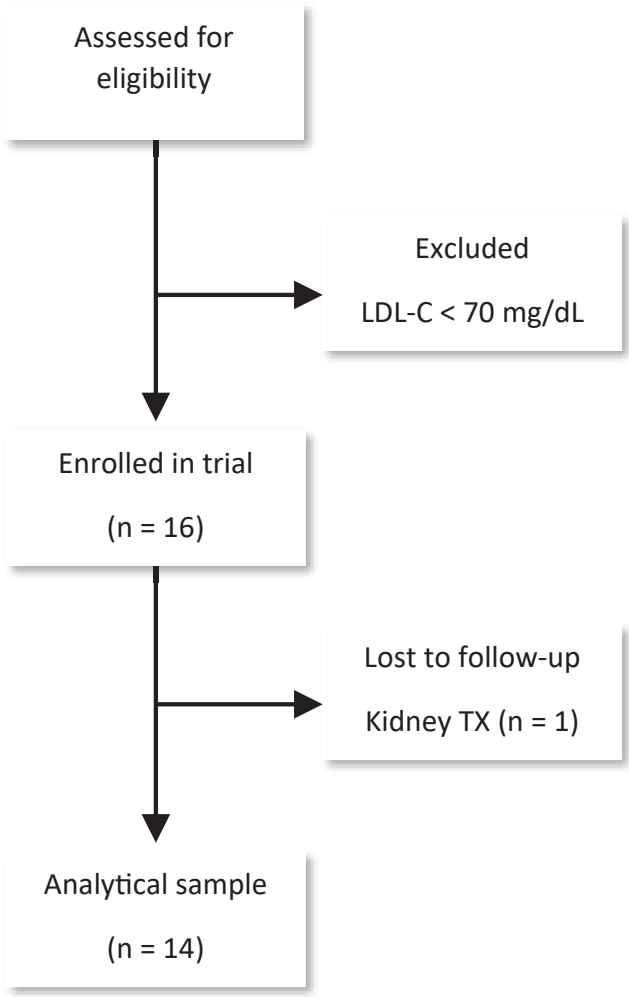

Figure 1. Study flow chart. Abbreviations: LDL-C, low-density lipoprotein cholesterol; TX, transplant.

Alirocumab lowered the LDL-C levels by 45% (P = 0.01) and apolipoprotein B levels by 35% (P = 0.01) (Fig 2). The triglyceride levels fell by 9% (P = 0.2), which was not significant, whereas the high-density lipoprotein cholesterol levels increased by 9% (P = 0.02). The hs-CRP levels fell by 11% (P = 0.1) because of large reductions in 2 patients. After treatment, the mean hs-CRP level was still high at 4.5 mg/dL. The levels of alirocumab and total PCSK9 were similar to those seen in patients not receiving dialysis (Figs 3 and 4). Antidrug antibodies developed in only 2 patients, neither of whom had any apparent clinical consequences, although the patients were treated for only 12 weeks.

The results of the other markers of inflammation, kidney disease, and vascular disease are shown in Table 4 and Fig 3. As with hs-CRP, 2 patients had very high levels of serum amyloid A, which fell dramatically, but none of these markers showed a significant difference before or after treatment, except for the levels of TNF-α. The TNF-α levels fell by 19% (P = 0.03), but the scatter gram suggested minimal significance.

The effect of alirocumab on the plasma metabolome is shown in Fig 5 and Table 5. There were 17 metabolite levels that were significantly decreased after treatment with alirocumab (false discovery rate paired t test, P < 0.05), which included 7 ceramide, 5 sphingomyelin, and 5 cholesterol ester species of the 480 species studied.

DISCUSSION

Atherosclerotic disease is a major cause of morbidity and mortality in individuals receiving maintenance dialysis, second only to dialysis complications. Blood pressure control is easier once the patient is receiving dialysis because the patient's volume status is finely tuned. Diabetes is better controlled via reduction in renal degradation of insulin. The ability to reduce the LDL-C levels to <70 mg/dL in this high-risk population could reduce some of the cardiovascular events that these patients may still experience.

Statins have yielded mixed results in patients receiving dialysis. In the Die Deutsche Diabetes Dialyse (4D) trial reported in 2004, 1,255 patients receiving hemodialysis

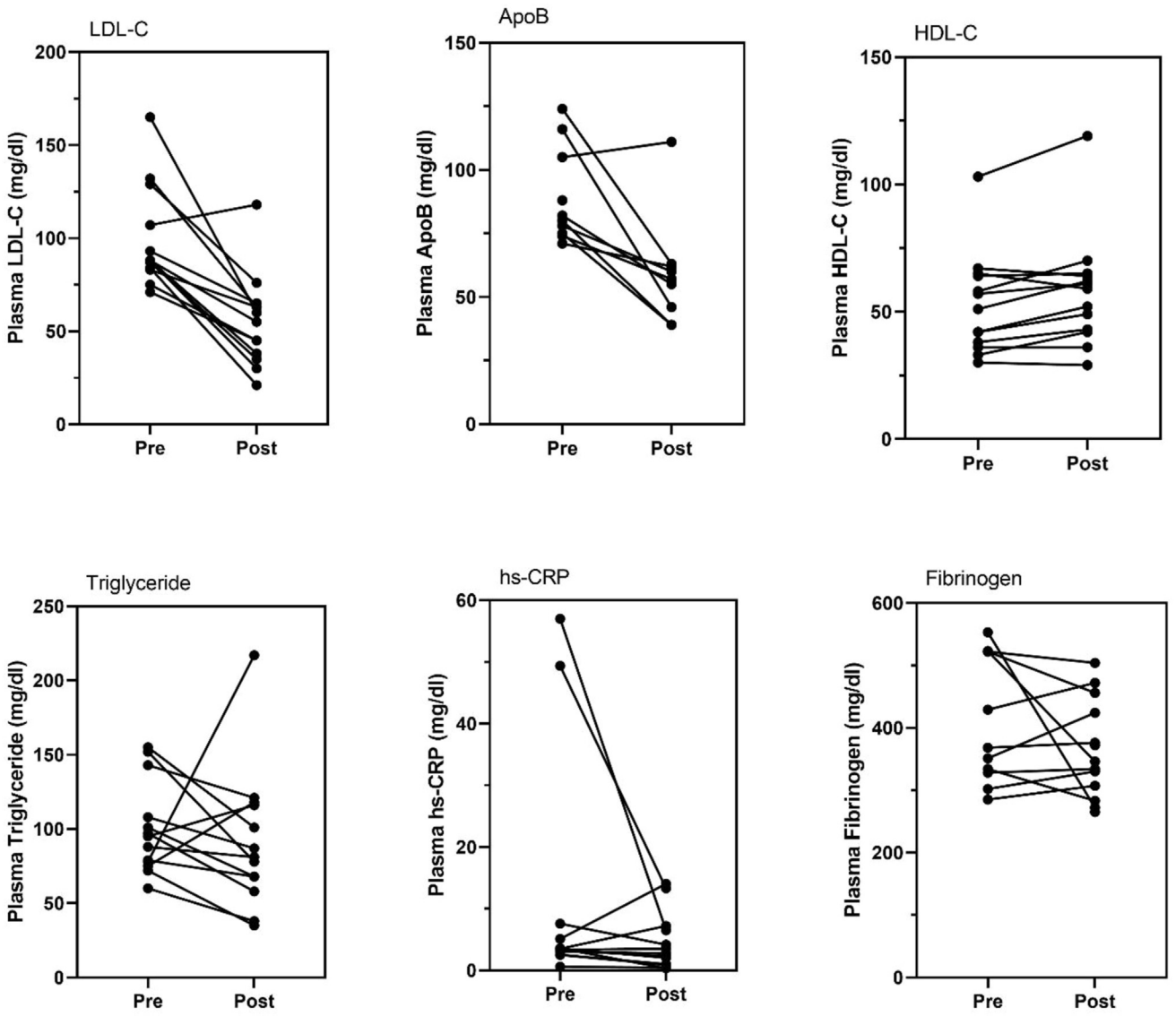

Figure 2. Effect of alirocumab on lipoproteins, apolipoprotein B, high-sensitivity C-reactive protein, and fibrinogen levels. Abbreviations: ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

on 20 mg of atorvastatin versus a placebo were followed up for a median duration of 4 years.[4] There was no significant effect on the primary endpoint. An 11-year follow up of this study still did not observe a significant effect.[5] Similarly, in the 2010 AURORA study (A study to evaluate the use of rosuvastatin in subjects on regular hemodialysis: An assessment of survival and cardiovascular events), which used 10 mg of rosuvastatin versus a placebo in 2,776 patients receiving dialysis for a mean duration of 3.8 years, the statin had no effect on the primary endpoint.[6] A third study published in 2011, the SHARP trial, included 9,270 patients with chronic kidney disease (not necessarily receiving dialysis, with a mean estimated glomerular filtration rate of 27 mL/min/1.73 m^2) and aged ≥40 years who were treated with 20 mg of simvastatin plus 10 mg of ezetimibe daily versus a placebo and followed up for 4.9 years.[7] There was no effect on myocardial infarction, acute coronary syndrome, or the need for coronary revascularization, although there was a decrease in nonhemorrhagic stroke. A registry by Jung et al,[8] reported in 2020, was a retrospective review of 65,404 patients from the Health Insurance and Assessment Service database in Korea who were receiving hemodialysis and statin therapy versus those receiving no statin therapy. This study showed a lower risk of all-cause mortality (risk ratio, 0.48; confidence interval, 0.47-0.50; $P < 0.001$). This was, however, not a randomized, controlled trial.

PCSK9 inhibitors are serine protease enzymes predominantly produced in the liver. The physiologic role of PCSK9 is to bind to the LDL-C receptor on the surface of hepatocytes, targeting the LDL receptors for destruction in lysosomes. Inhibitors of this enzyme lead to increased

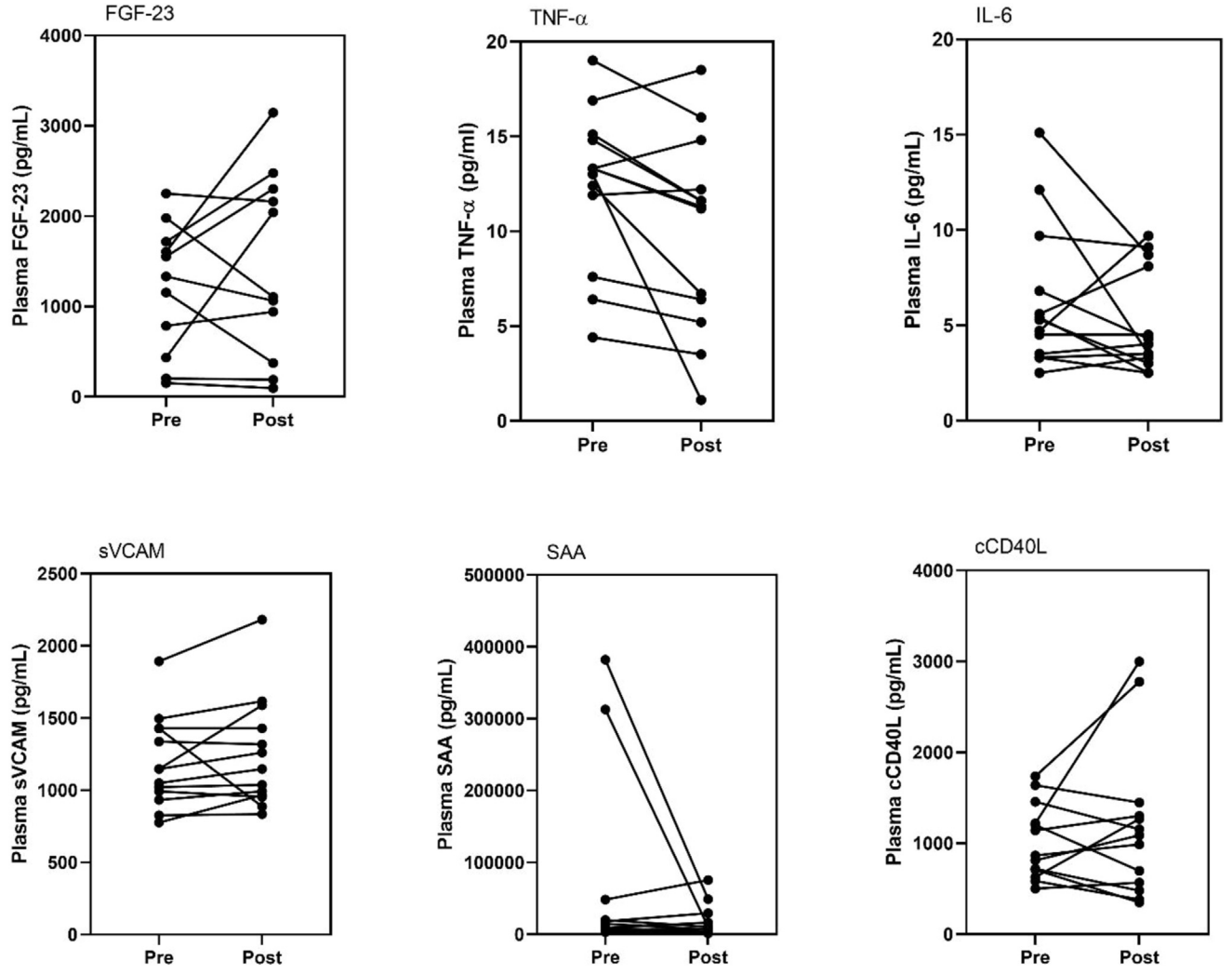

Figure 3. Plasma biomarkers in participants receiving maintenance dialysis: before versus after treatment with alirocumab. Abbreviations: FGF-23, fibroblast growth factor 23; TNF-α, tumor necrosis factor α; IL-6, interleukin 6; SAA, serum amyloid A; sCD40L, soluble CD40 ligand; sVCAM, soluble vascular cell adhesion molecule.

levels of LDL receptors and lower levels of LDL-C. Because PCSK9 inhibitors are a different molecule with a different mechanism of action compared with statins, they could possibly have off-target effects on biomarkers of inflammation. It is also important to assess the safety of a PCSK9 inhibitor in patients receiving dialysis when patients cannot tolerate statins because the PCSK9 inhibitor is given as a subcutaneous injection every 2 weeks and is not removed by dialysis.

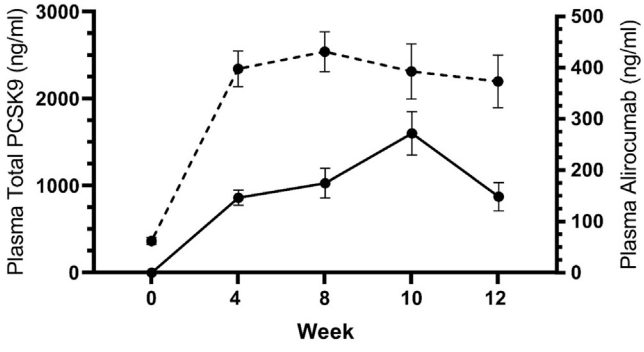

Figure 4. Levels of alirocumab and free PCSK9. Solid line, plasma alirocumab levels; dashed line, total plasma proprotein convertase subtilisin/kexin type 9 levels. Abbreviation: PCSK9, proprotein convertase subtilisin/kexin type 9.

PCSK9 inhibitors have been studied for secondary prevention in large studies. Sabatine et al[9] studied 24,081 patients who had had a prior myocardial infarction, cerebrovascular accident, or established coronary artery disease plus additional risk factors and added evolocumab to a high dose of statin, which resulted in an absolute risk reduction of 1.5% in the primary endpoint. The ODYSSEY OUTCOMES study assessed 18,924 patients with a previous acute coronary syndrome who received high-intensity statin therapy.[10] There was an absolute risk reduction of 1.6% in the primary endpoint, with a decrease in death of 0.6%.

In this study, as expected, the levels of LDL-C and apolipoprotein B fell significantly and the levels of high-

Table 4. Plasma Biomarkers in Subjects With End-Stage Renal Disease: Before Versus After Treatment With Alirocumab

	FGF-23	TNF-α	IL-6	sVCAM	SAA	sCD40L
Before treatment	1,500 ± 1,251	12.4 ± 4.1	6.3 ± 3.8	1,190 ± 314	69,590 ± 131,221	1,017 ± 412
After treatment	1,339 ± 1,049	10.0 ± 5.1	5.1 ± 2.7	1,247 ± 382	18,244 ± 22,736	1,192 ± 837
P value	0.03	0.03	0.03	0.04	0.4	0.3

Note: Values indicate mean ± standard deviation, expressed in pictogram per milliliter. *P* value (paired *t* test).
Abbreviations: FGF-23, fibroblast growth factor 23; TNF-α, tumor necrosis factor α; IL-6, interleukin 6; SAA, serum amyloid A; sCD40L, soluble CD40 ligand; sVCAM, soluble vascular cell adhesion molecule.

density lipoprotein cholesterol increased significantly. Alirocumab had a lowering effect on the hs-CRP levels in those with high levels of hs-CRP at the time of the initiation of the study (mg/dL, baseline range, 0.6-57.03), but the overall change was not significant, and the hs-CRP levels remained high (range, 0.36-14.05). Other biomarkers were also assessed in our study, but only the TNF-α levels decreased significantly, with questionable importance.

Biomarkers were assessed in a larger study of 543 patients with stage 5 chronic kidney disease over 21 months.[14] Although the levels of most biomarkers were elevated (albumin, ferritin, hs-CRP, insulin-like growth factor 1, interleukin 6, orosomucoid, troponin T, TNF-α, soluble vascular cell adhesion molecule, platelets, and white blood cell counts), only interleukin 6, soluble vascular cell adhesion molecule, and albumin could independently classify the patients as having cardiovascular disease, and only interleukin 6, white blood cell count, and TNF-α independently predicted all-cause mortality.

Ceramides and sphingomyelins may be better able to predict incident cardiovascular events. Ceramides were shown to be a novel predictor of cardiovascular events

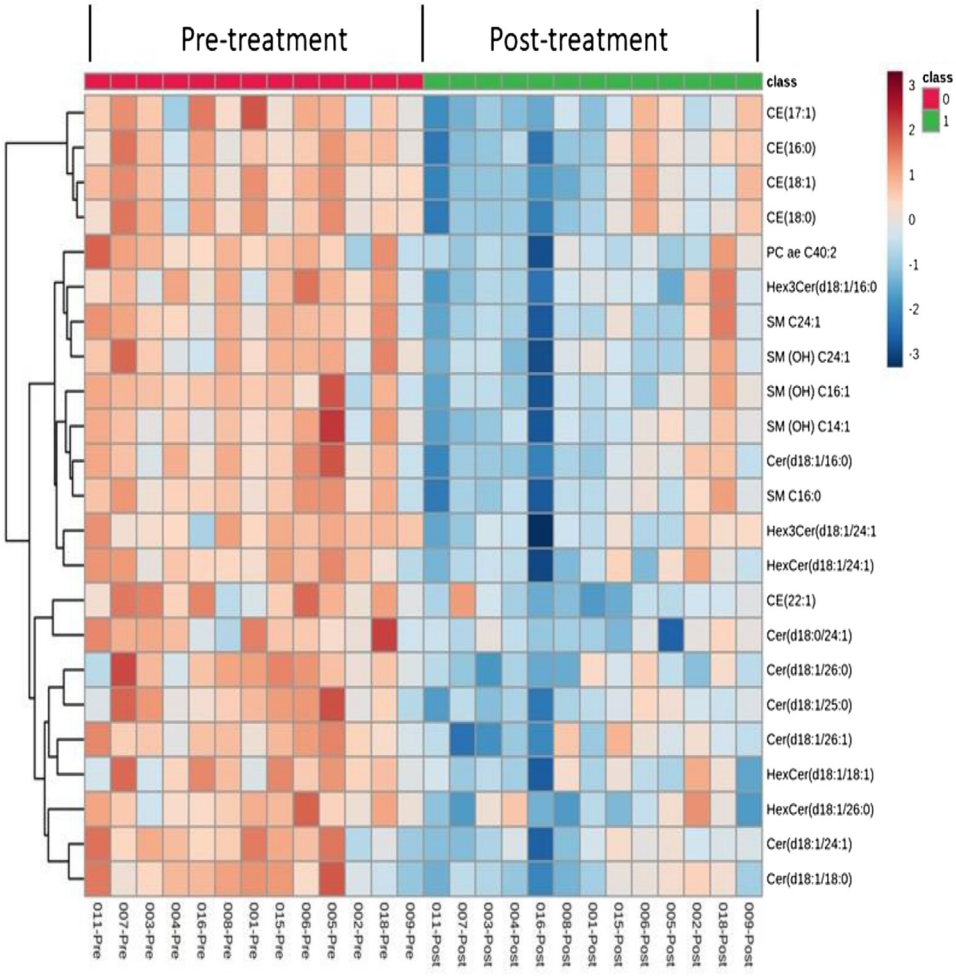

Figure 5. Heat map of 23 plasma metabolites significantly decreased in participants receiving maintenance dialysis after treatment with alirocumab, expressed as micromoles per liter.

Table 5. Concentration of Plasma Lipids Species Significantly Different (Paired *t* Test; False Discovery Rate) After Treatment With Alirocumab, Expressed in Micromoles per Liter

	Plasma Lipid Species, μM	Mean ± SEM		95% CI of Mean		Mean % Change	FDR q value
		Before	After	Before	After		
Cholesterol esters	CE(16:0)	107.0 ± 6.1	73.7 ± 7.3	93.9-120	57.8-89.7	−31.1	0.05
	CE(17:1)	9.7 ± 0.7	6.5 ± 0.6	8.2-11.3	5.3-7.7	−33.1	0.03
	CE(18:0)	7.5 ± 0.5	5.0 ± 0.5	6.5-8.5	4.0-6.1	−33.0	0.03
	CE(18:1)	505 ± 27	324 ± 34	445-564	251-397	−35.8	0.03
	CE(22:1)	0.25 ± 0.02	0.17 ± 0.11	0.22-0.29	0.15-0.20	−31.3	0.03
Ceramides	Cer(d18:0/24:1)	0.35 ± 0.02	0.26 ± 0.01	0.312-0.393	0.237-0.289	−25.4	0.03
	Cer(d18:1/16:0)	1.34 ± 0.07	0.92 ± 0.06	1.18-1.50	0.78-1.06	−31.3	0.03
	Cer(d18:1/18:0)	0.40 ± 0.02	0.31 ± 0.02	0.36-0.44	0.26-0.36	−22.3	0.03
	Cer(d18:1/24:1)	1.03 ± 0.07	0.74 ± 0.07	0.86-1.19	0.60-0.89	−27.8	0.03
	Cer(d18:1/25:0)	3.96 ± 0.26	2.71 ± 0.15	3.41-4.52	2.39-3.03	−31.6	0.03
	Cer(d18:1/26:0)	0.86 ± 0.06	0.54 ± 0.39	0.73-1.00	0.46-0.62	−37.4	0.03
	Cer(d18:1/26:1)	0.33 ± 0.02	0.21 ± 0.02	0.29-0.38	0.16-0.26	−37.0	0.03
Sphingomyelins	SM (OH) C14:1	5.92 ± 0.34	4.26 ± 0.27	5.18-6.66	3.68-4.85	−28.0	0.03
	SM (OH) C16:1	3.52 ± 0.18	2.52 ± 0.17	3.13-3.91	2.14-2.89	−28.4	0.03
	SM (OH) C24:1	2.12 ± 0.18	1.49 ± 0.11	1.87-2.38	1.25-1.73	−29.7	0.03
	SM C16:0	151 ± 6	110 ± 8	137-164	92-128	−26.7	0.03
	SM C24:1	78 ± 3	56 ± 5	71-85	46-66	−27.2	0.03

Abbreviations: CI, confidence interval; FDR, false discovery rate; SEM, standard error of the mean.

(myocardial infarction, percutaneous intervention, coronary artery bypass surgery, stroke, and death) in 265 patients with coronary artery disease over 4 years, with the hazard ratio ranging from 1.42 to 1.58 for different ceramide species.[15] In another study, the use of PCSK9 inhibitors and the ceramide risk score—composed of the ceramide species Cer(16:0), Cer(18:0), and Cer(24:0)—in 24 patients showed that the ceramide risk score was associated with cardiovascular mortality independent of other cardiovascular risk factors.[11] Sphingomyelins were also shown to increase the risk of progression to kidney failure and the risk of coronary heart disease (hazard ratio, 1.24; confidence interval, 1.01-1.52; $P = 0.038$) in 1,087 patients in the Finnish Diabetic Nephropathy study.[12] In this study, there were significant changes in the levels of ceramides and sphingomyelins after treatment with alirocumab. The significant changes in the cholesterol ester levels mirrored the changes in the LDL-C levels.

In conclusion, individuals receiving maintenance dialysis had a similar response to the PCSK9 inhibitor alirocumab as patients not receiving dialysis. There were no unexpected adverse events, and the alirocumab drug levels were similar to those of patients not receiving dialysis. Alirocumab can be expected to reduce LDL-C levels when these levels are still >70 mg/dL when patients are on medium or high doses of statins. The levels of inflammatory biomarkers were not clearly decreased by alirocumab, but the levels of ceramides, sphingomyelins, and cholesterol esters were significantly reduced; furthermore, metabolomic analysis may provide a novel way to assess cardiovascular risk in these high-risk patients.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Fig S1: Plasma ceramides significantly different (false discovery rate $P < 0.05$, paired *t* test) in participants receiving maintenance dialysis: before versus after alirocumab.

Fig S2: Plasma cholesteryl esters significantly different (false discovery rate $P < 0.05$, paired *t* test) in participants receiving maintenance dialysis: before versus after alirocumab.

ARTICLE INFORMATION

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Support: This study was funded by Regeneron Pharmaceuticals and the Baylor Scott & White Foundation.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Acknowledgments: The authors would like to thank Janet Jackson, who performed the data collection for analysis. The authors would also like to thank Joel Bakian, David Stein, and Rowland Robinson for support.

Disclaimer: All work, including writing, was performed only by the authors, and Regeneron and Sanofi had access to the data only once the manuscript was completed.

Peer Review: Received November 30, 2021. Evaluated by 2 external peer reviewers, with direct editorial input by the Statistical Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form March 13, 2022.

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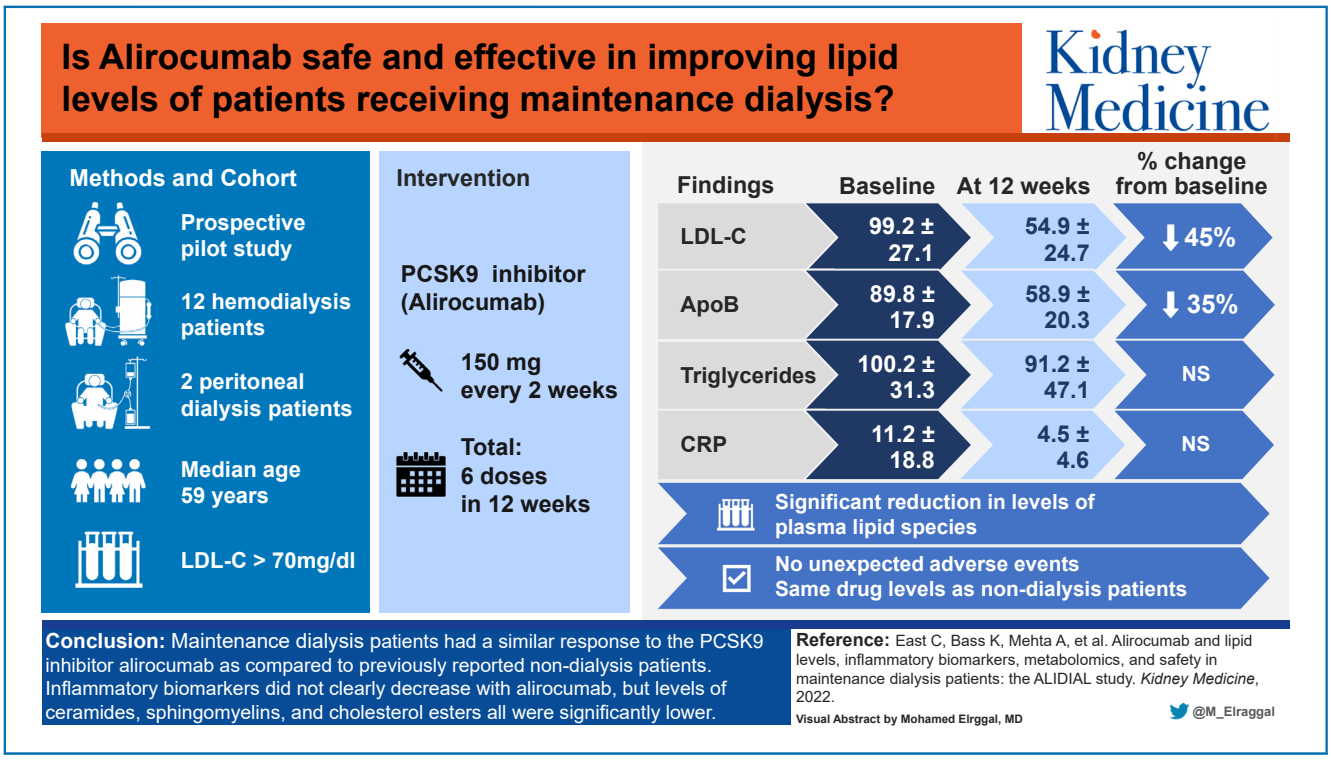
Is Alirocumab safe and effective in improving lipid levels of patients receiving maintenance dialysis?
Kidney Medicine
Methods and Cohort
Prospective pilot study
12 hemodialysis patients
2 peritoneal dialysis patients
Median age 59 years
LDL-C > 70mg/dl
Intervention
PCSK9 inhibitor (Alirocumab)
150 mg every 2 weeks
Total: 6 doses in 12 weeks
Findings
Baseline
At 12 weeks
% change from baseline
LDL-C
99.2 ± 27.1
54.9 ± 24.7
45%
ApoB
89.8 ± 17.9
58.9 ± 20.3
35%
Triglycerides
100.2 ± 31.3
91.2 ± 47.1
NS
CRP
11.2 ± 18.8
4.5 ± 4.6
NS
Significant reduction in levels of plasma lipid species
No unexpected adverse events
Same drug levels as non-dialysis patients
Conclusion: Maintenance dialysis patients had a similar response to the PCSK9 inhibitor alirocumab as compared to previously reported non-dialysis patients. Inflammatory biomarkers did not clearly decrease with alirocumab, but levels of ceramides, sphingomyelins, and cholesterol esters all were significantly lower.
Reference: East C, Bass K, Mehta A, et al. Alirocumab and lipid levels, inflammatory biomarkers, metabolomics, and safety in maintenance dialysis patients: the ALIDIAL study. Kidney Medicine, 2022.
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