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ORIGINAL RESEARCH ARTICLE

Alirocumab and Coronary Atherosclerosis in Asymptomatic Patients with Familial Hypercholesterolemia: The ARCHITECT Study

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BACKGROUND: The effect of alirocumab, a PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor, on coronary plaque burden in patients with familial hypercholesterolemia has not been addressed. Our aim was to assess changes in coronary plaque burden and its characteristics after treatment with alirocumab by quantification and characterization of atherosclerotic plaque throughout the coronary tree on the basis of a noninvasive analysis of coronary computed tomographic angiography in asymptomatic subjects with familial hypercholesterolemia receiving optimized and stable treatment with maximum tolerated statin dose with or without ezetimibe.

METHODS: This study is a phase IV, open-label, multicenter, single-arm clinical trial to assess changes in coronary plaque burden and its characteristics after 78 weeks of treatment with alirocumab in patients with familial hypercholesterolemia without clinical atherosclerotic cardiovascular disease. Participants underwent an initial coronary computed tomographic angiography at baseline and another at 78 weeks. Every patient received 150 mg of alirocumab subcutaneously every 14 days in addition to high-intensity statin therapy. The main outcome was the change on coronary plaque burden and its characteristics by quantification and characterization of atherosclerotic plaque throughout the coronary tree on the basis of analysis of coronary computed tomographic angiography.

RESULTS: The study was completed by 104 patients. The median age was 53.3 (46.2–59.4) years. Of these patients, 54 were women (51.9%). Median low-density lipoprotein cholesterol was 138.9 (117.5–175.3) mg/dL at entry and 45.0 (36.0–65.0) mg/dL at follow-up (P<0.001). Coronary plaque burden changed from 34.6% (32.5%–36.8%) at entry to 30.4% (27.4%–33.4%) at follow-up (P<0.001). A significant change in the characteristics of the coronary atherosclerosis was also found: an increase in the proportion of calcified (+0.3%; P<0.001) and mainly fibrous (+6.2%; P<0.001) plaque, accompanied by a decrease in the percentage of fibro-fatty (−3.9%; P<0.001) and necrotic plaque (−0.6%; P<0.001).

CONCLUSIONS: Treatment with alirocumab in addition to high-intensity statin therapy resulted in significant regression of coronary plaque burden and plaque stabilization on coronary computed tomographic angiography over 78 weeks in these groups of patients with familial hypercholesterolemia without clinical atherosclerotic cardiovascular disease. ARCHITECT (Effect of Alirocumab on Atherosclerotic Plaque Volume, Architecture and Composition) could link and explain ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) results.

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Key Words: alirocumab ■ computed tomography angiography ■ coronary artery disease ■ hypercholesterolemia ■ plaque, atherosclerotic

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Clinical Perspective

What Is New?

- This is the first study providing results regarding coronary plaque burden and its regression and characteristics secondary to intense lipid-lowering therapy in patients with familial hypercholesterolemia without previous cardiac events.
- This is the first study analyzing plaque burden in the complete coronary artery tree and not only in a segment as in previous studies.

What Are the Clinical Implications?

- Treatment with alirocumab in addition to high-intensity statin therapy may induce regression of coronary plaque burden and plaque stabilization in patients with familial hypercholesterolemia.
- ARCHITECT study (Effect of Alirocumab on Atherosclerotic Plaque Volume, Architecture and Composition) results show a mechanistic explanation that could link atherosclerotic plaques and clinical outcomes.
- Regression and stabilization of atherosclerotic plaque might reduce clinical events in patients with familial hypercholesterolemia.

Nonstandard Abbreviations and Acronyms

ARCHITECT	Effect of Alirocumab on Atherosclerotic Plaque Volume, Architecture and Composition
ASCVD	atherosclerotic cardiovascular disease
CTA	computed tomographic angiography
FH	familial hypercholesterolemia
LDL-C	low-density lipoprotein cholesterol
PB	plaque burden
SAFEHEART	Spanish Familial Hypercholesterolemia Cohort Study
SAPC	semiautomated plaque characterization

Familial hypercholesterolemia (FH) is an inherited genetic condition leading to elevated low-density lipoprotein cholesterol (LDL-C) levels from birth. The lifelong increased exposure to LDL-C is associated with premature atherosclerotic cardiovascular disease (ASCVD). Despite the use of statins and other lipid-lowering therapies, patients with FH continue to have a high prevalence of ASCVD.[1] PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors have shown a significant reduction in lipid levels in these patients.[2,3] Further-more, they have also shown regression of atherosclerotic plaque burden and a reduction in ASCVD events in subjects with previous coronary artery disease.[4] In recently published studies, our group demonstrated that patients with FH usually have an increased coronary atherosclerotic plaque burden (PB) despite the absence of clinical ASCVD.[5,6] Nevertheless, there are no data regarding coronary PB and its regression and characteristics secondary to lipid-lowering therapies in these patients.

Traditional methods of analysis of the coronary artery wall have allowed a very precise evaluation.[7] However, these are invasive methods, not without risk, and they allow the analysis of only a small arterial segment. New technological developments based on coronary computed tomographic angiography (CTA) allow the use automatic tools that provide a global evaluation of coronary wall characteristics.[8,9] Semiautomated plaque characterization (SAPC) is a diagnostic tool that incorporates medical image–processing algorithms for automatic coronary tree evaluation. It can provide information regarding the coronary wall, including PB and its characterization, on the basis of coronary CTA data.[6,8,10]

The aim of the ARCHITECT study (Effect of Alirocumab on Atherosclerotic Plaque Volume, Architecture and Composition) was to assess the changes in coronary PB and its characteristics of intensive lipid-lowering therapies with alirocumab by quantification and characterization of atherosclerotic plaque throughout the coronary tree on the basis of analysis of coronary CTA in asymptomatic subjects with FH receiving optimized and stable treatment with maximum tolerated statin dose with or without ezetimibe.

METHODS

Design and Population

This study was a phase IV, open-label, multicenter, single-arm clinical trial, Its aim was to assess the effect of alirocumab 78 weeks after initiation on the coronary atherosclerotic PB and its characteristics in subjects with molecularly determined FH without clinical ASCVD enrolled in the SAFEHEART registry (Spanish Familial Hypercholesterolemia Cohort Study). All of them were receiving optimized and stable treatment with maximum tolerated doses of statins with or without ezetimibe under clinical practice conditions. Patients were eligible for the study if LDL-C levels <100 mg/dL were not achieved, a global coronary PB >30% was present at baseline, and their treating physician prescribed alirocumab. Thus, the study treatment was the same as what patients would receive without participating in the study. Inclusion and exclusion criteria may be found in the Supplemental Material. It was estimated that a sample of 128 patients would be needed. Considering that 20% of the patients could discontinue the study prematurely, it was necessary to include 162 patients. The data that support the findings of this study are available from the corresponding author on reasonable request.

Patients were enrolled at 18 hospitals in Spain. Participants underwent a coronary CTA at baseline and a final one at 78 weeks. Every patient received 150 mg of alirocumab subcutaneously every 14 days. The study was approved by the Spanish Medicines Agency and the institutional review board at each site and was conducted in accordance with the Declaration of Helsinki principles of good clinical practice. All patients provided written informed consent before enrollment.

Biochemical Assessment

Blood samples were obtained at baseline and the end of the study. Blood samples were immediately processed and stored at −80°C locally and transferred to a central laboratory and biobank. Biochemical analyses were conducted by the lipid laboratory at the Hospital Reina Sofía, Universidad de Córdoba, Spain.

Coronary CTA Performance and Image Reconstruction

With the use of a tomographic scanner, 3-mm-thick slices were obtained during a breath-holding protocol. Coronary CTA was performed using 64−detector row scanners or higher with prospective or retrospective electrocardiographic gating. Eighty to 100 mL of intravenous contrast, followed by 50 to 80 mL of saline, was administered at a rate of 5 mL/s with a power injector through an antecubital vein. Optimal phase reconstruction was assessed by comparison of different phases, if available, and the phase with the least amount of coronary artery motion was chosen for analysis. Multiple phases were used for image interpretation if minimal coronary artery motion differed among the various arteries.

The physicians in charge of analyzing the coronary CTA were in no case responsible for the clinical management of the patients and were unaware of their clinical characteristics. The coronary CTA scans were received in the core laboratory as a pool without the possibility of identifying which study corresponded to each patient or whether it was an initial or final study.

PB Quantification

SAPC (QAngio CT [Research Edition V2.1.16.1; Medis Specials]) was used for coronary atherosclerotic plaque quantification and its characterization. This tool incorporates medical image−processing algorithms for automatic coronary tree extraction, as well as lumen and vessel contour detection. SAPC provides information regarding vessel morphology, intensities, and PB and characterization in coronary CTA data. The analysis workflow allows a fully automatic extraction of the complete coronary tree, semiautomatic editing of coronary tree, automatic labeling of the segments in the coronary tree with anatomical names, a 2-step contour detection approach per vessel for both lumen and vessel contour: longitudinal detection, transversal detection, and edit contour in longitudinal and transversal images simultaneously. This method is insensitive to differences in attenuation values between data sets and independent of window and level settings. Following the guidelines of the Society of Cardiovascular Computed Tomography, 17-segment coronary artery model vessels were assessed. Only vessels >1.5 mm were evaluated. This software has been widely validated[8,11,12] and recently used in clinical trials aimed at assessing the effect of lipid-lowering drugs on atherosclerotic plaque.[13] PB was calculated as the proportion of the entire vessel wall occupied by atherosclerotic plaque throughout the analyzed segments.

Plaque Characterization

SAPC also provides an adaptive thresholding for plaque characterization. In this way, the plaque is divided into 4 components: fibrous, fibro-fatty, necrotic, and calcified. Noncalcified plaque was defined as the sum of fibrous, fibro-fatty, and necrotic components. The adaptive mode used for the analysis that modifies Hounsfield unit ranges on the basis of the measured intensities in the lumen was used to balance for different kilo voltages on the plaque analysis. Media border exclusion was used to subtract a fixed region from the outer border of the plaque. An extensive description of the method can be found in the Supplemental Material.

Statistical Analyses

Statistical analyses were performed using SPSS version 22.0. Variables were analyzed for a normal distribution with the Kolmogorov-Smirnov test. A descriptive analysis was performed for the intention-to-treat population (consisting of all patients included in the study, excluding those who did not have the main measure of efficacy evaluable at the 18-month visit). Median and interquartile range were used for the quantitative variables and absolute number and percentage for the qualitative variables. Paired sample analysis was used for comparison of the variables between the baseline visit and the final visit. Wilcoxon signed-rank test was used for quantitative variables, and the McNemar test was used in the case of qualitative variables. A multivariate forward linear regression analysis was conducted to determine whether LDL-C decrease was associated with PB regression. To evaluate intraobserver and interobserver variability of coronary PB measurement, 15 randomly chosen studies were analyzed twice by the same observer and once more by a second observer. Interobserver and intraobserver agreement was evaluated by means of the intraclass correlation coefficient. A 2-sided P value <0.05 was considered statistically significant.

RESULTS

Clinical and Biochemical Characteristics

The analyzed population consisted of 104 patients (Figure S1) enrolled between June 2018 and October 2019. Of these patients, 54 were women (51.9%). The median age was 53.3 (46.2–59.4) years. Although the estimated sample size was 128 patients, only 110 were enrolled because of the exhaustion of human and material resources due to the COVID-19 pandemic. Of the 110 patients enrolled, 6 patients were not analyzed because of the lack of follow-up SAPC (Figure S1). Main baseline characteristics are shown in Table 1. All subjects were receiving statin treatment. Ninety-six (92.3%) were on high-potency statins. Use of other lipid-lowering therapies is also depicted in Table 1. During the follow-up period, the responsible physicians decided to stop treatment

Table 1. Baseline Characteristics of the ARCHITECT Cohort

Characteristic	Value
n	104
Female, n (%}	54 (51.9)
Age, y	53.3 (46.2–59.4)
Type 2 diabetes, n (%}	10 (9.6)
Hypertension, n (%}	15 (9.3)
Active tobacco smoker, n (%)	19 (18.3)
Body mass index, kg/m²	27.8 (24.3–31.2)
Total cholesterol, mg/dL	209.0 (189.0 – 249.0)
Low-density lipoprotein cholesterol, mg/dL	138.9 (117.5–175.3)
High-density lipoprotein cholesterol, mg/dL	51.0 (45.0–59.0)
Triglycerides, mg/dL	89.0 (69.0–117.0)
Lipoprotein (a), mg/dL	29.9 (10.5–83.0)
Apolipoprotein A1, mg/dL	131.0 (117.3–146.0)
Apolipoprotein B, mg/dL	91.0 (81.0–110.8)
High-sensitivity C-reactive protein, mg/dL	0.07 (0–1.9)
Patients on statins, n (%)	104 (100)
Patients on high-potency, high-dose statins,* n (%}	96 (92.3)
Patients on ezetimibe, n (%}	89 (85.6)
Years on statins	18.6 (9.6–26.6)
Years on ezetimibe	8.6 (1.8–13.6)
10-y SAFEHEART-RE,† %	0.68 (0.35–1.02)

Values shown are median (interquartile range) or n (%).

*High-dose, high-potency statins: atorvastatin, 40 or 80 mg/d, or rosuvastatin, 20 or 40 mg/d.

†10-y SAFEHEART-RE: 10-year risk estimated by means of the SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study) risk equation, which estimates the likelihood of one of the following to occur first: fatal or nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, coronary revascularization, peripheral artery revascularization and cardiovascular death (any death related to cardiovascular disease or derived of cardiovascular therapeutic procedures not described in the previous definitions).

with statins in 7 patients (6.7%) and change the type of high-potency statin in 2 (1.92%). Median LDL-C was 138.9 (117.5–175.3) mg/dL at entry and 45.0 (36.0–65.0) mg/dL at follow-up (P<0.001), which is a 67.6% median relative percentage reduction. Median total cho-

lesterol was 209.0 (189.0–249.0) mg/dL at entry and 118.0 (103.0–138.1) mg/dL at follow-up (P<0.001). Median high-density lipoprotein cholesterol was 51.0 (45.0–59.0) mg/dL at entry and 53.0 (45.0–63.0) mg/dL at follow-up (P=0.267). Patients receiving alirocumab demonstrated significantly greater reductions in triglycerides, lipoprotein (a), and high-sensitivity C-reactive protein (Table 2). Median 10-year cardiovascular risk according to the SAFEHEART risk equation[14] at enrollment and after follow-up was 0.68% (0.35%–1.02%) and 0.22% (0.09%–0.35%), respectively (P<0.001).

One patient discontinued the study due to acute coronary syndrome requiring percutaneous coronary revascularization, although the patient continued treatment with alirocumab. The reason for discontinuation was that after the patient had been revascularized and stents were implanted, we could not evaluate the entire coronary tree using CTA. No other patient prematurely discontinued the study. Four patients started with 75 mg of alirocumab subcutaneously every 14 days on the basis of the preference of their treating physician, but the dose was increased to 150 mg subcutaneously every 14 days after 2 months. One patient temporarily (4.5 months) suspended administration of alirocumab due to logistical problems of supply to the hospital due to the COVID-19 pandemic during the first semester after enrollment. One patient required hospital admission for SARS-CoV-2 infection and discontinued alirocumab administration for 6 weeks.

PB Quantification

Table 3 shows the coronary PB quantification results. The analyzed coronary tree length was 330.6 (229.6–403.8) mm and 336.8 (252.9–432.8) mm at entry and at follow-up, respectively (P=0.209). Total plaque volume was 1028.6 (721.3–1238.5) mm³ and 819.4 (618.5–1016.6) mm³ at entry and at follow-up, respectively (P<0.001). Regarding the main end point of the study, the global coronary PB, it changed from 34.6% (32.5%–36.8%) at entry to 30.4% (27.4%–33.4%) at follow-up, which represents a −4.6% (−7.7% to −1.9%) statistically significant regression (P<0.001; Figure). Univariate

Table 2. Absolute Change in Biochemical Measures from Baseline to 78 Weeks Follow-Up

Variables	Baseline	Follow-up	Median absolute change	P values
n	104	104	–	–
Total cholesterol, mg/dL	209.0 (189.0 to 249.0)	118.0 (103.0 to 138.1)	−92.4 (−72.0 to −126.0)	<0.001
Low-density lipoprotein cholesterol, mg/dL	138.9 (117.5 to 175.3)	45.0 (36.0 to 65.0)	−92.4 (−69.8 to −123.5)	<0.001
High-density lipoprotein cholesterol, mg/dL	51.0 (45.0 to 59.0)	53.0 (45.0 to 63.0)	0 (−4.9 to 5.7)	0.267
Triglycerides, mg/dL	89.0 (69.0 to 117.0)	75.5 (51.3 to 108.8)	−11 (−36.3 to −4.3)	<0.001
Lipoprotein (a), mg/dL	29.9 (10.5 to 83.0)	14.1 (9.4 to 55.6)	−6.9 (−0.8 to −20.7)	<0.001
High-sensitivity C-reactive protein, mg/dL	0.07 (0 to 1.9)	0 (0 to 1.1)	0 (−0.6 to −0.5)	<0.001

Values shown are median (interquartile range). Paired-sample analysis was used for comparison of the variables. Wilcoxon signed-rank test was used for quantitative variables, and the McNemar test was used for qualitative variables.

Table 3. Plaque Burden and Characteristics Changes

Plaque	Baseline	Follow-up	Median difference*	P values
n	104	104	–	–
Measured coronary tree length, mm	330.6 (229.6 to 403.8)	336.8 (252.9 to 432.8)	11.7 (−57.2 to 71.4)	0.209
Total plaque volume, mm³	1028.6 (721.3 to 1238.5)	819.4 (618.5 to 1016.6)	−133.4 (−444.4 to 62.2)	<0.001
Total plaque burden, %	34.6 (32.5 to 36.8)	30.4 (27.4 to 33.4)	−4.6 (−7.7 to −1.9)	<0.001
Calcified plaque, %	3.4 (1.2 to 11.0)	4.5 (2.2 to 10.3)	0.3 (−1.9 to 2.7)	<0.001
Fibrous plaque, %	76.4 (67.9 to 81.6)	85.4 (77.6 to 89.8)	6.2 (−0.07 to 14.5)	<0.001
Fibro-fatty plaque, %	11.4 (7.0 to 16.7)	7.0 (5.5 to 8.4)	−3.9 (−7.8 to 0.2)	<0.001
Necrotic plaque, %	4.1 (1.3 to 8.9)	1.0 (0.4 to 2.0)	−0.6 (−3.8 to 7.4)	<0.001

Values shown are median (interquartile range). Paired-sample analysis was used for comparison of the variables. Wilcoxon signed-rank test was used for quantitative variables, and McNemar test was used for qualitative variables.

*Follow-up − baseline.

linear regression analysis showed that LDL-C decrease and PB regression were not related (Hazard ratio: 0.004 [95% CI, −0.014 to 0.021]; P=0.662). An example of coronary PB regression can be seen in Figure S2. Ninety-one patients (87.5%) showed coronary PB regression. Intraobserver and interobserver intraclass correlation coefficients for PB were 0.94 (95% CI, 0.85–0.97) and 0.88 (95% CI, 0.52–0.97), respectively.

Plaque Characterization

A significant change in characteristics of the coronary atherosclerosis was found at the end of follow-up. As can be seen in Table 3, an increase in the proportion of calcified (+0.3%; P<0.001) and mainly fibrous (+6.2 %; P<0.001) plaque was found, accompanied by a decrease in the percentage of fibro-fatty (−3.9%; P<0.001) and necrotic plaque (−0.6%; P<0.001).

Adverse Events

Fifteen patients (14%) reported at least one adverse event related to treatment administration, although none

of these events were severe. Six patients experienced mild and transient myalgia, 5 patients experienced mild and transient allergic reactions, 2 patients reported injection site reaction, and 2 patients reported flu-like syndrome. None of these events were a reason for discontinuation of the study or medication.

DISCUSSION

This study shows how, in patients with FH without previous clinical ASCVD on statin treatment with or without ezetimibe and the PCSK9 inhibitor, alirocumab resulted in a significant regression of the coronary atherosclerotic burden. Alirocumab was tested at 150 mg every 14 days for 78 weeks, added to high-intensity statin therapy, and PB was assessed by noninvasive coronary CTA imaging in both men and women. In addition, a change in the characteristics of coronary atherosclerosis was also present, with a reduction in the proportion of fibro-fatty and necrotic plaque. To our best knowledge, this is the first single-arm clinical trial regarding coronary atherosclerotic plaque regression with a PCSK9 inhibitor (alirocumab) in asymptomatic patients with FH.
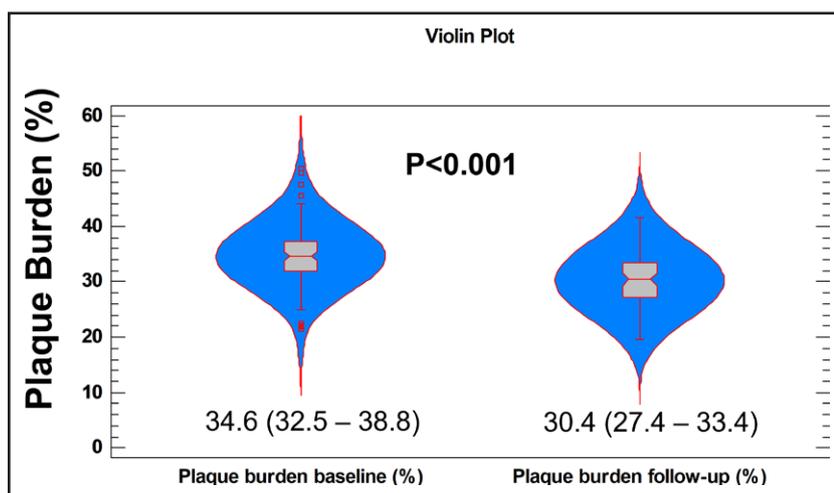
Figure. Violin-plot chart showing coronary plaque burden changes (baseline and follow-up) by means of semiautomatic plaque characterization (QAngio CT) in patients with familial hypercholesterolemia treated with alirocumab.
Results are shown as median value (interquartile range).

Studies published in the scientific literature show the relationship between intense reduction of LDL-C levels and decrease of coronary atherosclerosis.[4,15–19] However, the present work had a series of novel aspects that differentiate it from previous ones. First, in this study, a noninvasive technique was used, the coronary CTA, unlike most previous studies that use invasive techniques. Second, it was the first study to evaluate the entire coronary tree. In a recent trial using the same technique, icosapent ethyl was shown to reduce and modify coronary atherosclerosis, but the evaluation was limited to bulging atherosclerotic plaques in the coronary lumen.[20] Third, the population studied is a cohort of patients with molecularly proven FH who had not presented clinical atherosclerotic coronary artery disease. This population is very different from populations of other studies in which the patients included, in general, are subjects in secondary prevention and are older. This fact is of crucial relevance as we can show results of a type of patient with elevated LDL-C levels from birth that had not been analyzed until now. Finally, half of the patients included are women, unlike most studies in which there is a predominance of men.[4,18]

In previous studies with statins, ezetimibe, and PCSK9 inhibitors, the reduction in atherosclerosis was less intense than in the present one,[15,16,18,21–23] but we must always bear in mind the different characteristics of the patients, and that the technique used in our study analyzes the entire coronary tree and is not limited to a small segment. It is also important to emphasize that the percentage of patients who experienced plaque regression in our study was similar to that of the recently published PACMAN-AMI trial (Vascular Effects of Alirocumab in Acute MI-Patients), which analyzed the efficacy of alirocumab in secondary prevention.[4] Furthermore, a parallel between coronary PB regression and SAFEHEART-RE (SAFEHEART risk equation) score was found.[14]

In addition to the burden of atherosclerosis, the composition of atherosclerosis has been shown to have prognostic significance. Coronary plaques that are prone to rupture and cause adverse cardiac events are characterized by large PB, large lipid content, and thin fibrous caps. Therefore, if a clear association between plaque regression and reduction of cardiovascular events emerges, it may become possible to directly image plaque treatment responses to guide management decisions.[24] Although the first studies that tried to evaluate changes in the characteristics of atherosclerosis yielded ambiguous results,[25] more recently, with the use of alirocumab and evolocumab, qualitative changes have been demonstrated that suggest a stabilization of the atherosclerotic plaque.[4,26] Calcium plaques are not very prone to instability and, consequently, are not often responsible for an acute atherosclerotic event. However, a predominance of lipid and necrotic content is associated with a greater probability of experiencing one of these events.

In another previously mentioned study, icosapent ethyl also produced a stabilization of plaque components.[27]

In view of the results of the present study and those of previously published studies, we can say that treatment with alirocumab is associated with a very intense reduction in LDL-C levels, which made it easier for these patients to reach the more stringent goals recommended by the main guidelines.[28,29] In addition, the present study suggests an explanation linking this intense lowering and the reduction in atherosclerotic cardiovascular events seen with alirocumab in ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab),[30] the decrease in the coronary PB and its stabilization.

In a recent study, the combination of statin and evolocumab after a non−ST-segment−elevation myocardial infarction for 52 weeks produced favorable changes in coronary atherosclerosis consistent with stabilization and regression. This demonstrated a potential mechanism for the improved clinical outcomes observed achieving very low LDL-C levels after an acute coronary syndrome.[26]

Several reasons can justify the lack of statistical correlation between LDL-C level reduction and changes in coronary atherosclerotic plaque in the present study: (1) the study design was not dedicated to analyze this relationship; (2) the sample size is relatively small; (3) the PB reduction may be based on multiple mechanisms and not only on LDL-C levels (other lipid fractions and inflammatory phenomena may play a role); and (4) patients enrolled were on intensive lipid-lowering treatment for a very long time, which can modify the baseline characteristics of atherosclerotic plaques and their potential modifications when using alirocumab.

The findings of our study suggest that vulnerable plaques might regress and be stabilized in patients with FH. This should further motivate both patients and health care professionals to strive for early implementation of the most effective lipid-lowering regimens to lower their high risk of future cardiovascular events. We still do not have a long enough follow-up of these patients to draw conclusions, but we must consider the parallelism that exists in other population groups between the effect of alirocumab and evolocumab on coronary plaques (regression) and the reduction in clinical events. Therefore, we believe that we can anticipate a clinical benefit in the future follow-up of these patients.

Study Strengths and Limitations

The main limitation of the present study is that it is not a randomized clinical trial design, but, rather, a study in which each patient is evaluated individually before and after a therapeutic intervention; it lacks a comparison group and is of an open-label nature. However, the design of the study is well adapted to the need stated in the objectives, which can be summarized as the evaluation of the quantitative

and qualitative changes in coronary atherosclerosis by evaluating the entire coronary tree after the administration of alirocumab. On the other hand, because all patients had to have an LDL-C >100 mg/dL to be included in the study, the fact of not treating them with PCSK9 inhibitors could create an ethical conflict in this high-risk population. Another limitation of this study is that the follow-up time is relatively short, although similar to other imaging-based studies,[4,18] and does not allow a direct correlation to be established with either clinical events or biochemical parameters. However, all the patients in this study belong to the SAFEHEART registry, so they will be followed up annually and will probably provide important data in the future. Other limitations are the premature termination of the study due to operational reasons, which limits inference, and the median age of the enrolled patients, which may have implications for external validity.

Conclusions

This study shows how treatment with PCSK9 inhibitor alirocumab, in addition to high-intensity statin therapy, resulted in significant regression of coronary PB and plaque stabilization on coronary CTA over 78 weeks in patients with FH without clinical ASCVD. ARCHITECT provides crucial mechanistic clues on coronary plaque behavior under the use of alirocumab, and its results could link and explain ODYSSEY OUTCOMES results. Further studies in this high-risk population are needed to demonstrate the hypothesis raised by our results.

Supplemental Material

Inclusion criteria

Exclusion criteria

Sample size calculation method

Description of the method used for coronary plaque assessment

Correlations between lipid fractions changes and plaque burden changes

Figures S1 and S2

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