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ORIGINAL ARTICLE

Characteristics of Coronary Atherosclerosis Related to Plaque Burden Regression During Treatment With Alirocumab: The ARCHITECT Study

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BACKGROUND: Intensive lipid-lowering therapy may induce coronary atherosclerosis regression. Nevertheless, the factors underlying the effect of lipid-lowering therapy on disease regression remain poorly characterized. Our aim was to determine which characteristics of atherosclerotic plaque are associated with a greater reduction in coronary plaque burden (PB) after treatment with alirocumab in patients with familial hypercholesterolemia.

METHODS: The ARCHITECT study (Effect of Alirocumab on Atherosclerotic Plaque Volume, Architecture and Composition) is a phase IV, open-label, multicenter, single-arm clinical trial to assess the effect of the treatment with alirocumab for 78 weeks on the coronary atherosclerotic PB and its characteristics in subjects with familial hypercholesterolemia without clinical atherosclerotic cardiovascular disease. Participants underwent a coronary computed tomographic angiography at baseline and a final one at 78 weeks. Every patient received alirocumab 150 mg subcutaneously every 14 days in addition to high-intensity statin therapy.

RESULTS: One hundred and four patients were enrolled. Median age was 53.3 (46.2–59.4) years and 54 were women (51.9%). The global coronary PB changed from 34.6% (32.5%–36.8%) at entry to 30.4% (27.4%–33.4%) at follow-up, which is −4.6% (−7.7% to −1.9%; $P<0.001$) reduction. A decrease in the percentage of unstable core (fibro-fatty+necrotic plaque; from 14.1 [7.9–22.3] to 8.0 [6.4–10.6]; −6.6%; $P<0.001$) was found. A greater PB (β, 0.36 [0.13–0.59]; $P=0.002$) and a higher proportion of unstable core (β, 0.15 [0.08–0.22]; $P<0.001$) were significantly related to PB regression.

CONCLUSIONS: Treatment with alirocumab in addition to high-intensity statin therapy might produce a greater PB regression in patients with familial hypercholesterolemia with higher baseline PB and in those with larger unstable core. Further studies are needed to corroborate the hypothesis raised by these results.

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Key Words: atherosclerosis ■ cholesterol ■ coronary vessels

There is wide scientific evidence showing the relationship between intense reduction of LDL (low-density lipoprotein) cholesterol (LDL-C) level and the improvement of cardiovascular outcomes and the decrease of coronary atherosclerosis.[1] Intensive lipid-lowering therapy (LLT) not only can halt the progression

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CLINICAL PERSPECTIVE

Intensive lipid-lowering therapy may induce coronary atherosclerosis regression, but response to treatment is, usually, heterogeneous, and the factors related to its effectiveness on disease regression remain poorly characterized. In the present study, we tried to determine which characteristics of atherosclerotic plaque are associated with a greater reduction in coronary plaque burden after treatment with alirocumab, an intensive lipid-lowering medication, in patients with familial hypercholesterolemia without previous clinical atherosclerotic disease. The main results show how treatment with alirocumab in addition to high-intensity statin therapy might produce a greater plaque burden regression in patients with higher baseline plaque burden and in those with larger unstable core, this last one represented by the sum of the fibro-fatty and necrotic components of the plaque. Although further studies are needed to corroborate the hypothesis raised by these results, these findings may have important clinical implications as can be a guide to reduce clinical coronary events in patients with familial hypercholesterolemia.

Nonstandard Abbreviations and Acronyms

ARCHITECT	Effect of Alirocumab on Atherosclerotic Plaque Volume, Architecture and Composition
CTA	computed tomographic angiography
FH	familial hypercholesterolemia
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LLT	lipid-lowering therapy
Lp(a)	lipoprotein (a)
PB	plaque burden
SAFEHEART	Spanish Familial Hypercholesterolemia Cohort Study

of atherosclerosis but also induces disease regression.[2] Furthermore, the relationship between coronary plaque burden (PB), plaque composition, and clinical outcomes is also well established.[3–5] Nevertheless, the factors underlying the effect of LLT on disease regression remain poorly characterized although favorable effects of intense LDL-C reduction on plaque composition have been suggested using intravascular imaging techniques.[6]

Invasive methods of analysis of the coronary arteries may have risk, and they allow the analysis of only a small arterial segment. New technological developments based on coronary computed tomographic angiography (CTA) provide an evaluation of the whole coronary tree.[7–9] Semiautomated plaque characterization is a diagnostic tool that provides information regarding coronary wall, including PB and its characterization, based on coronary CTA data.[7,10,11] In the recently published ARCHITECT study (Effect of Alirocumab on Atherosclerotic Plaque Volume, Architecture and Composition), the coronary arteries of asymptomatic subjects with familial hypercholesterolemia (FH) were analyzed to assess the changes in coronary PB and plaque characteristics of intensive treatment with alirocumab using coronary CTA.[12] The main results showed how treatment with alirocumab was associated with both, a reduction in PB and an improvement in the characteristics of coronary atherosclerosis.

The aim of the present analysis was to determine which characteristics of atherosclerotic plaque, if any, are associated with a greater reduction in coronary PB after 18 months of treatment with alirocumab on top of statins in patients with FH enrolled in the ARCHITECT study.

METHODS

Design and Population

The data that support the findings of this study are available from the corresponding author upon reasonable request. The ARCHITECT study is a phase IV, open-label, multicenter, single-arm clinical trial to assess the effect of the treatment with alirocumab for 78 weeks on the coronary atherosclerotic PB and its characteristics in subjects with molecularly determined FH without clinical atherosclerotic cardiovascular disease under optimized and stable LLT and enrolled in the SAFEHEART registry (Spanish Familial Hypercholesterolemia Cohort Study).[13] Patients were eligible for the study if LDL-C levels were >100 mg/dL, a global coronary PB >30% was present at baseline, and alirocumab was prescribed by his/her treating physician. Inclusion and exclusion criteria may be found elsewhere.[12] Participants underwent a coronary CTA at baseline and a final one at 78 weeks. Every patient received alirocumab 150 mg subcutaneously every 14 days in addition to maximum tolerated and stable statin dose with or without ezetimibe. The study was approved by the Spanish Medicines Agency and the institutional review board at each site. It was conducted according to the principles of Good Clinical Practice of the Declaration of Helsinki. All patients provided written informed consent before enrollment.

Baseline Cardiovascular Risk Assessment

Cardiovascular risk was estimated by means of the SAFEHEART risk equation.[13] This equation calculates the likelihood to occur the first one of the following: 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) in patients with FH based on clinical and laboratory parameters including age, sex, history of atherosclerotic cardiovascular disease, blood

pressure, body mass index, smoking, and plasma LDL-C and Lp(a; lipoprotein[a]) levels.

Biochemical Assessment

Blood samples were obtained at baseline and at the end of the study. Blood samples were immediately processed and stored at −80 °C locally and transferred to a central laboratory and biobank where the analyses were performed.

Coronary CTA Performance and Image Reconstruction

Three-millimeter-thick slices were obtained during a breath-holding protocol using a tomographic scanner. 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 via 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 utilized for image interpretation if minimal coronary artery motion differed among the various arteries. Baseline and follow-up coronary CTA studies were performed using the same device, the same protocol, and the same technical procedures. In the Supplemental Material, an extensive description of the methods used can be found.

PB Quantification

Semiautomated plaque characterization (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. 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. PB was calculated as the proportion of the entire vessel wall occupied by atherosclerotic plaque, throughout the analyzed segments. Further details may be found elsewhere.[12]

Plaque Characterization

Semiautomated plaque characterization also provides plaque characterization. The plaque is divided into 4 components: fibrous, fibro-fatty, necrotic, and calcified. Unstable core was defined as the sum of the fibro-fatty and the necrotic components, since they are the components that confer instability to the plaque and most resemble the lipid-rich areas detected by other invasive imaging techniques.[4] The adaptive mode used for the analysis is a technique that modifies Hounsfield unit ranges based on 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 from the plaque. The different components of the plaque are described as a proportion of the total plaque volume. An extensive description of the method can be found elsewhere.[12]

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. Median and interquartile range were used for the quantitative variables and absolute number and percentage for qualitative variables. Paired sample analysis was used for comparing variables between the baseline visit and the final visit. Wilcoxon signed-rank test was used for quantitative variables and McNemar test was used in the case of qualitative ones. Univariate and multivariate linear regression analyses were conducted to determine which variables were related and in which magnitude to PB regression. Baseline PB, baseline unstable core (%), baseline type 2 diabetes, body mass index, and 10-year SAFEHEART risk equation score were tested based on the clinical relevance. A 2-sided $P<0.05$ was considered statistically significant.

RESULTS

Clinical and Biochemical Characteristics

The analyzed population consisted of 104 patients enrolled between June 2018 and October 2019. Main baseline characteristics may be found in Table 1. Median age was 53.3 (46.2–59.4) years and 54 were women (51.9%).

PB Quantification

The global coronary PB changed from 34.6% (32.5%–36.8%) at entry to 30.4% (27.4%–33.4%) at follow-up, which is −4.6% (−7.7% to −1.9%; $P<0.001$) reduction. Ninety-one patients (87.5%) showed coronary PB regression. Table 2 depicts plaque volumes and volumes of each component and PB as proportion of the total vessel volume.

Plaque Characterization

A significant change in the characteristics of the coronary atherosclerosis was found at follow-up when compared with baseline characteristics (Figure). Table 2 depicts the percentage of each plaque component as a proportion of total plaque volume. An increase in the proportion of calcified plaque (from 3.4 [1.2–11.0] to 5.5 [2.2–10.31]; +0.3%; $P<0.001$) and fibrous plaque (from 76.4 [67.9–81.6] to 85.4 [77.6–89.8]; +6.2%; $P<0.001$) was found. On the other hand, a decrease in the percentage of fibro-fatty plaque (from 11.4 [7.0–16.7] to 7.0 [5.5–8.4]; −3.9%; $P<0.001$) and necrotic plaque (from 4.1 [1.3–8.9] to 1.0 [0.4–2.0]; −0.6%; $P<0.001$) was found.

Plaque Regression Predictors

Table 3 shows the association between baseline PB and the different components of the atherosclerosis in

Table 1. Baseline Clinical and Biochemical Characteristics of the ARCHITECT Cohort

	Median (IQR)/n (%)
n	104
Female	54 (51.9%)
Age, y	53.3 (46.2–59.4)
Type 2 diabetes	10 (9.6%)
Hypertension	15 (9.3%)
Active tobacco smoker	19 (18.3%)
BMI, kg/m^2	27.8 (24.3–31.2)
Total cholesterol, mg/dL	209.0 (189.0–249.0)
LDL-C, mg/dL	138.9 (117.5–175.3)
HDL-C, mg/dL	51.0 (45.0–59.0)
TG, mg/dL	89.0 (69.0–117.0)
Lp(a), mg/dL	29.9 (10.5–83.0)
Patients on statins	104 (100%)
Patients on high-potency, high-dose statins*	96 (92.3%)
Patients on ezetimibe	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)

10-y SAFEHEART-RE: 10-y risk estimated by means of the SAFEHEART risk equation, which estimates the likelihood to occur the first one of the following: 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). ARCHITECT indicates Effect of Alirocumab on Atherosclerotic Plaque Volume, Architecture and Composition; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C: low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); SAFEHEART, Spanish Familial Hypercholesterolemia Cohort Study; SAFEHEART-RE, Spanish Familial Hypercholesterolemia Cohort Study risk equation; and TG, triglyceride.

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

Table 2. Plaque Characteristics Changes

Plaque	Baseline, median (interquartile range)	Follow-up, median (interquartile range)	Median difference,* median (interquartile range)	*P* value
n	104	104	…	…
Total plaque volume, mm^3	1028.6 (721.3 to 1238.5)	819.4 (618.5 to 1016.6)	−133.4 (−44.4 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, mm^3	19.5 (3.5 to 85.2)	21.2 (8.2 to 57.3)	0.03 (−8.3 to 11.6)	0.95
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, mm^3	383.4 (271.8 to 509.2)	296.2 (207.3 to 399.3)	−67.0 (−174.7 to 35.12)	<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, mm^3	55.1 (31.7 to 98.7)	27.3 (18.0 to 41.7)	−28.1 (−69.2 to −5.1)	<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, mm^3	24.0 (6.4 to 64.2)	3.1 (1.3 to 9.9)	−18.5 (−66.1 to −2.1)	<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
Unstable core, mm^3	84.7 (38.6 to 168.3)	30.9 (20.4 to 55.6)	−47.6 (−145.4 to −13.3)	<0.001
Unstable core, %‡	14.1 (7.9 to 22.3)	8.0 (6.4 to 10.6)	−6.6 (−14.4 to 0.3)	<0.001

*Follow-up−baseline.
†Proportion of total vessel volume.
‡Proportion of total plaque volume.

the baseline CTAs and PB regression after treatment with alirocumab. As can be seen, a greater PB, a higher proportion of fibro-fatty plaque and a higher proportion of necrotic plaque, and, consequently, a higher proportion of unstable core are related to PB regression. On the other hand, a higher percentage of fibrous plaque is associated with PB progression. The percentage of calcified plaque was not related to PB regression. Furthermore, the coronary calcium score, was also not related to PB. Univariate linear regression analysis also showed that baseline age, male sex, LDL-C, Lp(a), and C-reactive protein were not associated to PB regression. On the other hand, baseline body mass index was significantly related to PB regression in univariate analysis.

Table 4 shows multivariable linear regression analysis. In this model, only PB and unstable core (%) were found as independent predictors of PB regression. No other clinical or biochemical variables were related to PB regression.

DISCUSSION

The results of the present study show how, by analyzing the PB and the characteristics of coronary atherosclerosis, its response to the intense reduction of LDL-C by the use of alirocumab for 18 months can be predicted in patients with FH without clinical atherosclerotic cardiovascular disease. A large PB and a predominance of unstable components, represented in this study by what we named as unstable core, which represents the sum of the fibro-fatty and necrotic components, predict a greater reduction in coronary atherosclerosis when treated with alirocumab on top of long-term maximum tolerated treatment with statins and ezetimibe.

The recently published ARCHITECT study demonstrated that 18 months of treatment with alirocumab was associated with both a reduction in coronary PB and an improvement in the characteristics of coronary atherosclerosis in asymptomatic subjects with FH.[12] By adding the results of the present study, we think we amplify the importance of the previous results and provide new insights into coronary atherosclerosis not only for patients with FH, for whom the ARCHITECT study is unique, but also for the whole group of patients with or at risk of

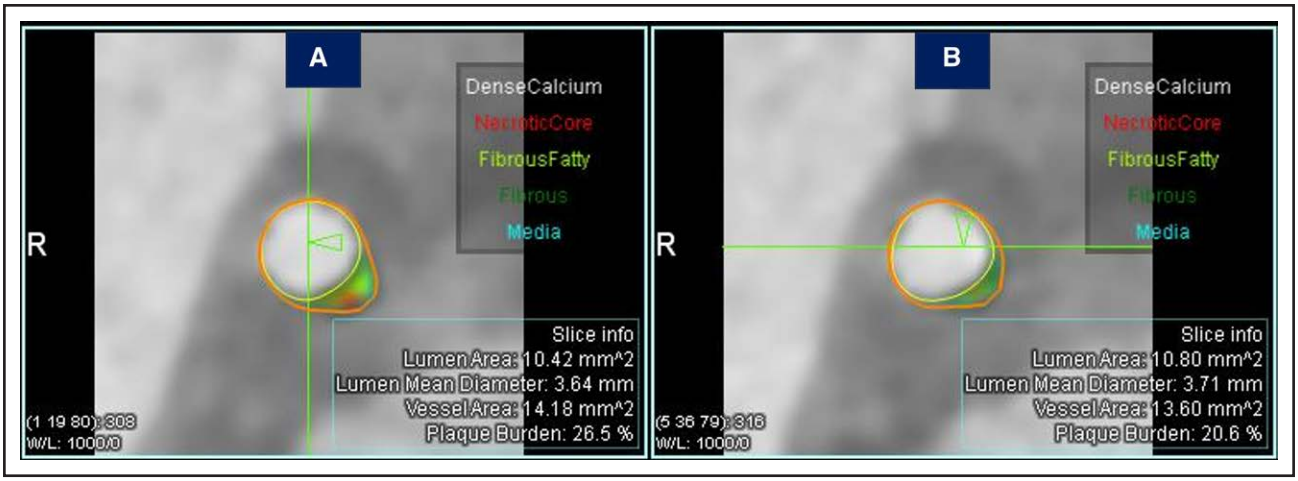

Figure. Example of plaque burden reduction and composition change in the left anterior descending artery of a patient with familial hypercholesterolemia.
Before (**A**) and after (**B**) 78 weeks of alirocumab treatment (right-hand side). The cross-sections have been obtained immediately proximal to the origin of the first diagonal branch. At this level, coronary plaque burden was reduced from 26.5% to 20.6%. Furthermore, in the follow-up image, an evident change in plaque composition can be seen: when compared with the baseline image, the fibro-fatty (light green) and necrotic (red) components have almost disappeared and the fibrous plaque (dark green) is the main component. See text for more details.

experiencing coronary atherosclerosis and its life-limiting consequences. Although the PB reduction might seem modest, it is similar to previous reports.[4] Furthermore, in a recent publication, it has been shown that a 1% reduction in mean PB as induced by LLT is associated with a 20% reduction in the odds of cardiovascular events.[14]

The present study introduces several novel aspects in the analysis of coronary atherosclerosis, such as the use of a noninvasive technique the coronary CTA, the analysis of the whole coronary artery tree, and the fact that the population studied is a cohort of patients with FH who had not presented clinical atherosclerotic coronary artery disease. It is of note that the present study is the first one that analyzes coronary atherosclerosis in patients with molecularly diagnosed FH and the first one that enrolled patients without previous clinical atherosclerotic disease.

The composition of atherosclerosis has been shown to have prognostic significance in studies based on invasive techniques.[15] Coronary plaques that are prone to rupture and cause adverse cardiac events are characterized by large PB, large lipid content, and thin fibrous cap.[4,16] It would be of great interest to be able to predict, based on the characteristics of coronary atherosclerosis, which patients will respond better or worse in terms of reduction

Table 3. Linear Regression Univariate Analysis Showing Association Between Baseline Atherosclerotic Characteristics and Plaque Burden Regression/Progression (Positive β Values Mean Plaque Burden Regression)

Variable	β-Coefficients	95% CI	*P* value
Total plaque burden, %*	0.473	0.253 to 0.692	<0.001
Necrotic plaque, %†	4.824	0.177 to 0.425	<0.001
Fibro-fatty plaque, %†	0.263	0.058 to 0.352	0.007
Unstable core, %†	0.373	0.08 to 0.22	<0.001
Fibrous plaque, %†	−0.310	−0.195 to −0.049	0.001
Calcified plaque, %†	−0.078	−0.137 to 0.057	0.429
Coronary calcium score (Agatston)	−0.043	−0.010 to 0.007	0.736
Age, y	−0.008	−0.15 to 0.07	0.427
Male sex	−0.97	−2.77 to 0.83	0.288
BMI, kg/m²	0.234	0.006 to 0.063	0.019
LDL-C, mg/dL	−0.083	−0.026 to 0.011	0.4
Lp(a), mg/dL	0.17	−0.004 to 0.033	0.112
CRP, mg/dL	0.121	−0.048 to 0.17	0.27

BMI indicates body mass index; CRP, C-reactive protein; LDL-C, low-density lipoprotein cholesterol; and Lp(a), lipoprotein (a).
*Proportion of total vessel volume.
†Proportion of total plaque volume.

Table 4. Linear Regression Multivariate Analysis Showing Association Between Baseline Atherosclerotic Characteristics and Plaque Burden Regression/Progression (Positive β-Values Mean Plaque Burden Regression)

Variable	β-Coefficients	95% CI	*P* value
Total plaque burden, %*	0.36	0.13 to 0.59	0.002
Unstable core, %†	0.15	0.08 to 0.22	<0.001
Type 2 diabetes	−0.17	−4.26 to 1.92	0.46
10-y SAFEHEART-RE, %	−0.03	−1.03 to 0.98	0.96
BMI, kg/m²	0.03	−0.004 to 0.06	0.09

10-y SAFEHEART-RE: 10-y risk estimated by means of the SAFEHEART risk equation, which estimates the likelihood to occur the first one of the following: 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). BMI indicates body mass index; SAFEHEART, Spanish Familial Hypercholesterolemia Cohort Study; and SAFEHEART-RE, Spanish Familial Hypercholesterolemia Cohort Study risk equation.
*Proportion of total vessel volume.
†Proportion of total plaque volume.

of coronary PB to intensive LLT. The ARCHITECT study was not specifically designed for this purpose, so the results should be considered as merely hypotheses generators, but the results obtained are plausible if we take current scientific knowledge into account.[3] Although related results can be found in the scientific literature,[17,18] to our knowledge, this is the first report regarding patients with FH without previous clinical event treated with a proprotein convertase subtilisin/kexin type 9 inhibitor in addition to statin to intensely reduce LDL-C.

Van Rosendael et al[17] demonstrated an association of statin use with greater transformation of coronary atherosclerosis into high-density calcium and that it was related to a slower plaque progression, supporting the concept of reduced atherosclerotic risk with increased densification of calcium. The same concept may be seen in the results of the present study: after treatment, a numerical nonstatistically significant increase in the volume of calcium was seen, which represented a percentual increase in the proportion of calcium. In other work derived from data of the SATURN study (The Study of Coronary Atheroma by Intravascular Ultrasound: The effect of Rosuvastatin vs. Atorvastatin), the authors aimed to characterize clinical factors that associate with differing measures of coronary atheroma volume following potent statin therapy. Their main conclusion was that higher risk patients, particularly those with greater baseline coronary atheroma volume, are more likely to experience less disease progression with potent statin therapy.[19] These results also agree with the results of the ARCHITECT study although the estimation of cardiovascular risk with the SAFEHEART risk equation score was not an independent predictor of PB regression. Zeb et al also studied PB plaque regression induced by statins but, in this case, using coronary CTA instead of intravascular ultrasound. For this purpose, they enrolled 100 consecutive patients without known prior heart disease or revascularization. They concluded that statin therapy resulted in significantly lower progression of plaques compared with non–statin users, reinforcing the evidence of the relationship between LLT and PB regression.[20]

Recently, the PACMAN-AMI study (Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction)—a randomized clinical trial—has been published. The aim was to determine the effects of alirocumab on coronary atherosclerosis using 3 different invasive imaging techniques: intravascular ultrasound to analyze the change in PB (in this work named as percent atheroma volume), near-infrared spectroscopy to assess the maximum lipid core burden index within 4 mm ,and optical coherence tomography to measure fibrous cap thickness. The authors concluded that the use of alirocumab on top of high-intensity statin therapy compared with placebo resulted in significantly greater coronary plaque regression.[4] In a second publication of the PACMAN-AMI study, the authors assessed the effects of alirocumab on coronary atherosclerosis including PB, plaque composition, and fibrous cap thickness in patients after an acute myocardial infarction. The results showed a triple regression occurred in one-third of patients and related to treatment with alirocumab and higher baseline lipid content.[6]

The findings of our study are consistent with the findings of the PACMAN-AMI study. In both with different samples and clinical situations, the drug used is alirocumab, and in both, there is a regression of the plaque and its stabilization, reducing the components associated with instability such as the thickness of the fibrous cap or the lipid content. In PACMAN-AMI, a high lipid content of the plaque is associated with its regression. The same happens in ARCHITECT, if we establish a similarity between lipid content and unstable core, the parameter used in this work. However, in PACMAN-AMI, baseline plaque load or baseline percent atheroma volume was not associated with triple regression, while in ARCHITECT, the PB was associated with plaque regression. It is possible that the invasive nature of the techniques used in PACMAN-AMI is responsible for this difference since coronary CTA allows a complete evaluation of the coronary tree. An important difference is that our patients were treated with high-intensity oral therapy for a long time before the start of the study, which was not the case in PACMAN-AMI. Furthermore, in ARCHITECT, the treatment with alirocumab was longer, the median age was younger, and there were 52% women; in PACMAN-AMI, there was a higher proportion of patients with hypertension, smokers, and few women. LDL-C was not related to PB regression in our study probably due to the design (single arm) and the mild dispersion of the LDL-C values in our intensively treated population.

Limitations

ARCHITECT is not a randomized clinical trial. However, the design of the study is well adapted to study the quantitative and qualitative changes in coronary atherosclerosis by evaluating the entire coronary tree after the administration of alirocumab.

Conclusions

These findings show how treatment with alirocumab in addition to high-intensity statin therapy might produce a greater PB regression in patients with FH with higher baseline PB and in those with higher fibro-fatty and necrotic components (unstable core). These findings may have important clinical implications and could reduce clinical coronary events in patients with FH. Further studies are needed to corroborate the hypothesis raised by our results.

ARTICLE INFORMATION

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Disclosures

Dr Pérez de Isla reports research grants, speaker fees, and consultant fees from Sanofi and Amgen. Dr Díaz-Díaz reports research grants, speaker fees, and consultant fees from Sanofi, Amgen, and Daiichi Sankyo. Dr Romero reports research grants, speaker fees, and consultant fees from Sanofi and Amgen. Dr Muñiz-Grijalvo reports speaker fees from Sanofi and Amgen. Dr Argüeso reports research grants, speaker fees, and consultant fees from Sanofi and Amgen. Dr Fuentes reports research grants, speaker fees, and consultant fees from Sanofi and Amgen. Dr Sánchez Muñóz-Torrero reports research grants, speaker fees, and consultant fees from Sanofi and Amgen. Dr Suárez Gutierrez reports speaker fees from Sanofi and Amgen. Dr Saltijeral Cerezo reports research grants, speaker fees, and consultant fees from Sanofi and Amgen. Dr Mata reports research grants from Sanofi and Amgen. The other authors report no conflicts.

Supplemental Material

Supplemental Methods
SAFEHEART Study Investigators

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