Association between LDL-C, Non HDL-C, and Apolipoprotein B Levels with Coronary Plaque Regression

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Abstract

Background: Previous reports have inferred a linear relationship between LDL-C and changes in coronary plaque volume (CPV) measured by intravascular ultrasound. However, these publications included a small number of studies and did not explore other lipid markers.

Objective: To assess the association between changes in lipid markers and regression of CPV using published data.

Methods: We collected data from the control, placebo and intervention arms in studies that compared the effect of lipid-lowering treatments on CPV, and from the placebo and control arms in studies that tested drugs that did not affect lipids. Baseline and final measurements of plaque volume, expressed in mm^3, were extracted and the percentage changes after the interventions were calculated. Performing three linear regression analyses, we assessed the relationship between percentage and absolute changes in lipid markers and percentage variations in CPV.

Results: Twenty-seven studies were selected. Correlations between percentage changes in LDL-C, non-HDL-C, and apolipoprotein B (ApoB) and percentage changes in CPV were moderate (r = 0.48, r = 0.47, and r = 0.44, respectively). Correlations between absolute differences in LDL-C, non-HDL-C, and ApoB with percentage differences in CPV were stronger (r = 0.57, r = 0.52, and r = 0.79). The linear regression model showed a statistically significant association between a reduction in lipid markers and regression of plaque volume.

Conclusion: A significant association between changes in different atherogenic particles and regression of CPV was observed. The absolute reduction in ApoB showed the strongest correlation with coronary plaque regression. (Arq Bras Cardiol. 2015; 105(1):11-19)

Keywords: Cardiovascular Diseases; Atherosclerosis/physiopathology; Cholesterol, LDL; Apolipoprotein B/therapeutic use; Lipoproteins, LDL.

Introduction

In the last twenty years, strong evidence from clinical studies demonstrated that the reduction of low-density lipoprotein cholesterol (LDL-C) with different lipid-lowering drugs, mainly HMG-CoA reductase inhibitors (statins), is critical in decreasing the incidence of coronary events[1,2]. Similarly, different studies showed an association between LDL-C reduction and regression of coronary plaque measured by intravascular ultrasound (IVUS)[3,4]. A recent meta-regression study has shown that pharmacologically induced regression of atherosclerotic plaque burden is associated with clinically significant reduction of myocardial infarction and revascularization[5].

Previous reports inferred a linear association between LDL-C and changes in coronary plaque volume (CPV) assessed by IVUS[6,7]. However, these publications included a small number of studies and did not explore the relationship with other lipid markers like non–high-density lipoprotein cholesterol (non-HDL-C) or apolipoprotein B (ApoB), which in several reports were related more closely to the risk of vascular disease than LDL-C itself[8,9].

In this context, the aim of our study was to assess the association between changes in plasma levels of lipid markers (LDL-C, non-HDL-C, and ApoB) and the regression of coronary atherosclerotic plaque measured by IVUS using published data.

Methods

Two reviewers independently searched the electronic databases PubMed/Medline, EMBASE and Cochrane Clinical Trials using the following terms: "intravascular ultrasound", "IVUS", "regression of atherosclerosis", and "statins". Studies were selected according to the following criteria: a) trials that explored the effect of one or more different lipid-lowering drugs (or different dosages) on the variation in CPV evaluated by IVUS (total atheroma volume), b) at least three months of follow-up, and c) availability of plaque volume measurements expressed

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in mm^3. In studies that tested drugs that did not affect lipids, only the placebo and control arms were used. In these circumstances, we did not consider the active arm due to potential bias related with extra-lipid mechanisms that could affect plaque regression. Mean values were considered for this analysis.

The quality of the studies was assessed with the Jadad scale. Potential publication biases were assessed with the Begg's test.

Changes in lipid measurements (LDL-C, non-HDL-C, ApoB, and HDL-C) between baseline and end of follow-up were calculated and expressed in percentages and absolute values (mg/dL). We collected data from the control, placebo, and intervention arms in studies that compared the effect of different lipid-lowering treatments, and only from the placebo and control arms in studies that tested drugs that do not modify lipid levels. Baseline and final measurements of the CPV (expressed in mm^3) were extracted and the percent changes were calculated using the formula: CPV Completion of Study - CPV Baseline/ CPV Baseline x 100.

Several linear regression analyses were performed. In the first model, we analyzed the relationship between percentage changes in LDL-C, non-HDL-C, and ApoB and percentage changes in CPV, comparing the baseline and final measurements in the same arm. These associations were adjusted for treatment time. In the second analysis, we assessed the relationship between absolute differences in lipid levels and percentage differences in CPV. For this analysis we calculated the absolute differences of the changes in lipid levels and the percentage differences of the variation in CPV measurements (follow-up - baseline values) between the intervention and control or placebo arms. Finally, we explored the association between LDL-C, non-HDL-C, and ApoB levels achieved at the end of follow-up (goal) and the percentage changes in CPV. To analyze the correlation, we used Pearson's correlation coefficient. To interpret the data within a clinical context, we tested associations between LDL-C, non-HDL-C, and ApoB levels below the goals recommended by most current guidelines and changes in CVP (< 70, < 100, and < 80 mg/dL, respectively).

Data analysis was performed using Stata 11.1 and Epidat 3.1. All statistical tests were two sided and the statistical significance level alpha was set at 0.05 for the analysis.

Results

Two independent authors searched the literature looking for studies compatible with the mentioned criteria. Of the 745 potential citations, 52 studies that evaluated any therapy on the regression of coronary plaque measured by IVUS were selected. Twenty-five studies were excluded due to the following main causes: absence of lipid values at the end of follow-up, quantification of plaque regression by another method, follow-up limitations, assessment of drugs not affecting lipids, or absence of a control/placebo arm. Most studies were randomized (77%) and two-thirds of them showed acceptable quality (3 or more points on the Jadad scale). We analyzed and discarded publication bias using the Begg's test ($p = 0.55$). Since not all studies reported ApoB values, more patients were included in the LDL-C and non-HDL-C analyses (4685) compared with the ApoB analysis (3065). A flow diagram of the study's screening process is shown in Figure 1. Most studies included patients with stable coronary heart disease. Two studies included patients with acute coronary syndromes, one study included individuals with diabetes

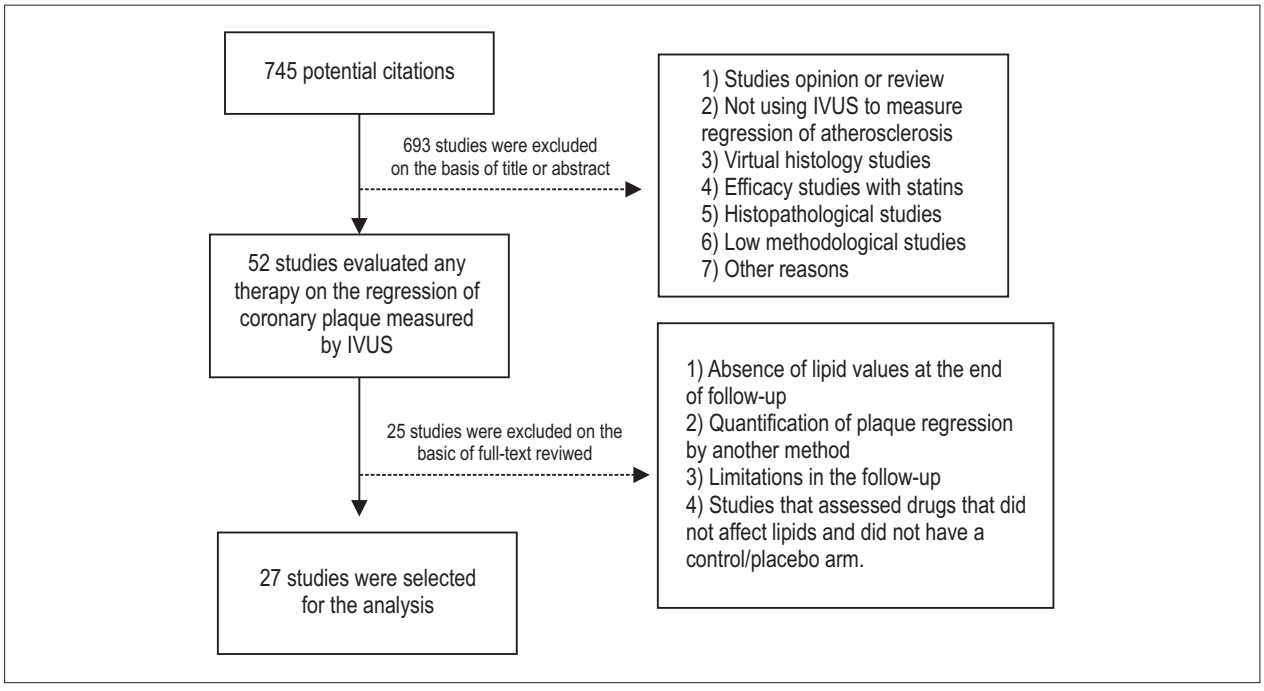

Figure 1 – *Flow diagram of the study screening process.*

and another included subjects with metabolic syndrome. In studies involving patients with acute ischemic syndromes, IVUS measurement in the target segment was determined in a non-percutaneous coronary angioplasty site.

Follow-up ranged from 3 to 24 months. The main characteristics of the 27 studies selected are shown in Table 1.

Correlations between percentage changes in LDL-C, non-HDL-C, and ApoB with percentage changes in CPV were moderate ($r = 0.47$, $p = 0.0013$; $r = 0.46$, $p = 0.0016$; and $r = 0.43$, $p = 0.03$, respectively), whereas correlations between absolute differences in LDL-C, non-HDL-C, and ApoB with percentage differences in CPV were stronger ($r = 0.57$, $p = 0.015$; $r = 0.52$, $p = 0.03$; and $r = 0.80$, $p = 0.017$, respectively). Similarly, the correlation between LDL-C / HDL-C ratio and regression of atherosclerosis was moderate ($r = 0.47$, $p = 0.001$). However, the correlation between HDL-C and percentage changes in CPV was poor ($r = 0.24$, $p = 0.08$).

The linear regression model showed a significant association between percentage changes in LDL-C ($p = 0.002$), non-HDL-C ($p = 0.002$), and ApoB ($p = 0.04$) with percentage changes in CPV (Figures 2, 3, and 4). These associations remained significant even after adjustment for treatment time ($p = 0.006$, $p = 0.002$ and $p = 0.035$ for LDL-C, non-HDL-C, and ApoB, respectively). Also, a significant association between percentage changes in LDL-C / HDL-C ratio with percentage changes in CPV ($p = 0.002$) was demonstrated, but not with changes in HDL-C ($p = 0.09$). Similarly, significant associations were found between absolute reductions in LDL-C ($p = 0.02$), non-HDL-C ($p = 0.03$), and ApoB ($p = 0.02$) with percentage differences in CPV changes between groups. Figure 5 illustrates the association between the absolute reduction in ApoB and the percentage regression in CPV.

The correlation between the LDL-C goal and percentage change in CPV was moderate ($r = 0.48$, $p = 0.01$). However, this association was significant and continuous up to LDL-C levels close to 50 mg/dL (Figure 6). Similarly, the correlation between the non-HDL-C goal and percentage change in CPV was significant ($p = 0.01$) and continuous up to non-HDL-C levels close to 80 mg/dL. Finally, we found an almost significant association ($p = 0.056$) between ApoB goal and percentage change in CPV in values close to 60 mg/dL.

In a combined analysis of all treatment types, a 10% decrease in LDL-C, non-HDL-C, or ApoB was associated, respectively, with 2.7%, 2.9%, and 3% regressions in CPV.

Discussion

The regression of atherosclerosis is a surrogate of cardiovascular disease, and has been evaluated in research studies mainly by IVUS and carotid ultrasound. However, the independent predictive value of these methods is not similar. A recent meta-analysis found no significant association between LDL-C reduction and progression of atherosclerosis estimated by carotid intima-media thickness[35]. Furthermore, regression or slowed progression of carotid intima-media thickness induced by cardiovascular drug therapies do not reflect reductions in cardiovascular events[36].

In contrast, analyses that have included only a few studies have shown a significant association between LDL-C reduction and regression of coronary plaque measured by IVUS[3,4]. Also, the association between the regression of coronary atherosclerotic plaque measured by IVUS and the incidence of non-fatal cardiovascular events has been demostrated[5]. In our study, IVUS was chosen as the most robust method to detect plaque regression, and this was the first time that plasma levels of non HDL-C and ApoB were added to the analysis.

Large body of evidence supports a central role for LDL-C lowering in the prevention of atherosclerotic cardiovascular disease. However, the new guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults discourages the use of absolute values of LDL-C as a "goal" and makes virtually no reference to other markers more specific of atherogenic lipid particles, such as non-HDL-C or ApoB[37].

In our study, we found no threshold level of lipid reduction (absolute or percentage) associated with an interruption in plaque regression, suggesting that lower levels of atherogenic particles are associated with greater regression of plaque. In our analysis, we observed a significant, sustained, and continuous association between LDL-C, non-HDL-C, and ApoB levels at the end of follow-up with changes in CPV, suggesting that the respective goals of < 70, < 100, and < 80 mg/dL recommended by most guidelines is appropriate.[38,39] This finding does not conceptually agree with the latest guideline, which recommends that an approximate 50% reduction in LDL-C level is adequate regardless of the LDL-C goal achieved[40].

Another interesting finding to emphasize is that the regression of atherosclerosis in our study was independent of the lipid-lowering therapy (statins) and the dose used. When significant reductions in LDL-C, non-HDL-C, or ApoB were achieved, plaque regression was observed with different doses of statins. This finding also contrasts with the new guideline that recommends only intensive doses of rosuvastatin or atorvastatin. Finally, the significant association between the LDL-C / HDL-C ratio and regression of atherosclerosis indicates the importance of a balance between pro- and anti-atherogenic particles on vascular remodeling.

Correlations between the percentage reduction in different lipid markers and the CPV regression in our study were moderate, suggesting that the progression/regression of coronary atherosclerosis is multicausal. The correlation between the absolute change in ApoB and the percentage variation in plaque volume was higher, although this result emerges with the inclusion of a very small number of studies. This finding is consistent with the concept that ApoB level could be a better predictor of cardiovascular events than the LDL-C level, since it reflects more accurately the number of atherogenic particles[9].

Study limitations

Like all analyses of secondary data, there are many limitations related to the heterogeneity of the populations included, number of subjects analyzed and variability of

Table 1 – Studies included in the analysis (n = 4685)

Study	Intervention (mg/day)	n	Change in LDL-C (%)	Change in non- HDL-C (%)	Change in ApoB (%)	Change in coronary plaque volume (%)	Months of treatment exposure
REVERSAL[10]	Atorvastatin 80	253	-46.3	-42.9	-39.1	-0.4	18
REVERSAL[10]	Pravastatin 40	249	-25.2	-24.7	-22	2.7	18
ESTABLISH[11]	Atorvastatin 20	35	-41.7	-35.4	-27.9	-13.1	6
ESTABLISH[11]	Control	35	-0.7	-1.9	2.4	8.7	6
JAPAN-ACS[12]	Pitavastatin 4	125	-36.2	-30.5	-27.6	-16.9	8-12
JAPAN-ACS[12]	Atorvastatin 20	127	-35.8	-30.1	-27.6	-18.1	8-12
SATURN[13]	Atorvastatin 80	519	-41.5	-35.9	-28.4	-4.0	26
SATURN[13]	Rosuvastatin 40	520	-47.8	-40.2	-30.9	-5.8	26
Hong et al.[14]	Rosuvastatin 20	65	-49	-44	-36	-2.7	11
Hong et al.[14]	Atorvastatin 40	63	-40	-35.4	-34	-1.9	11
COSMOS[15]	Rosuvastatin 2,5-20	215	-38.6	-36.7	-31.3	-5.1	19
ASTEROID[6]	Rosuvastatin 40	346	-53.2	-47.2	-41.5	-6.7	24
ARTMAP[16]	Atorvastatin 10-20	143	-47	-43.4	-	-3.9	6
ARTMAP[16]	Rosuvastatin 20	128	-49	-45.9	-	-7.4	6
GAIN[17]	Atorvastatin 20-80	65	-42	-41	-	2.5	12
GAIN[17]	Usual care	66	-16	-15.9	-	11.8	12
Kawasaki et al.[18]	Control	17	-1.9	-1.1	-	0	6
Kawasaki et al.[18]	Pravastatin 20	17	-31.5	-28.6	-	-0.9	6
Kawasaki et al.[18]	Atorvastatin 20	18	-38.7	-39.2	-	-2.4	6
Jensen et al.[19]	Simvastatin 40	40	-46.3	-42.8	-	-6.3	3-12
Jensen et al.[19]	Diet	40	-2.4	-2.1	-	-0.4	3-12
Han et al.[20]	Rosuvastatin 20	21	-54.2	-44.6	-	-8.5	9-12
Han et al.[20]	Rosuvastatin 20/Ramipril 10	19	-47.2	-43.6	-	-11.6	9-12
STRADIVARIUS[21]	Placebo	341	-3.2	-3.8		0.5	18
A-PLUS[22]	Placebo	154	1.7	1.9	-4	-1.2	24
AQUARIUS[23]	Placebo	233	5.6	4.4	-	-1.1	26
Tani et al.[24]	Pravastatin 10-20	84	-11.3	-12.1	-6.4	-12.6	6
Nozue et al.[25]	Pitavastatin 4	58	-41	-37.9	-33	-2.2	8
Nozue et al.[25]	Pravastatin 20	61	-29	-26.4	-25.2	-1.4	8
Hirayama et al.[26]	Atorvastatin 10-20	20	-36.3	-36.4	-28.4	-18.9	20
HEAVEN [27]	Atorvastatin 80/Ezetimibe 10	42	-28.6	-32.3	-5.8	-2.9	12
HEAVEN[27]	Standard treatment	47	-1.9	-9.2	7.4	0.7	12
CART-2 [28]	Placebo	111	-6.9	-8.4	-	-0.3	12
ENCORE II[29]	Placebo	112	-11.8	-9.8	-	-0.3	18-24
Nasu et al.[30]	Fluvastatin 40	40	-32.3	-32.8	-27	-8.3	12
Nasu et al.[30]	Control	39	2.2	4	2.3	2.5	12
Yamada et al.[31]	Atorvastatin 10-20	26	-32.5	-29.8	-27.6	-1.9	12
Yamada et al.[31]	Usual care	32	0	-1.6	-2.2	11.5	12
Tani et al.[32]	Pravastatin 10-20	52	-14	-17.9	-	-14	6
Tani et al.[32]	Control	23	3.6	2.5	-	1.1	6
Yokoyama et al.[33]	Atorvastatin 10	29	-34	-30.5	-	-5.6	6
Yokoyama et al.[33]	Control	30	-4.4	-5.2	-	-3.5	6
Nakayama et al.[34]	Control	25	-7.1	-4.6	-	2.8	6

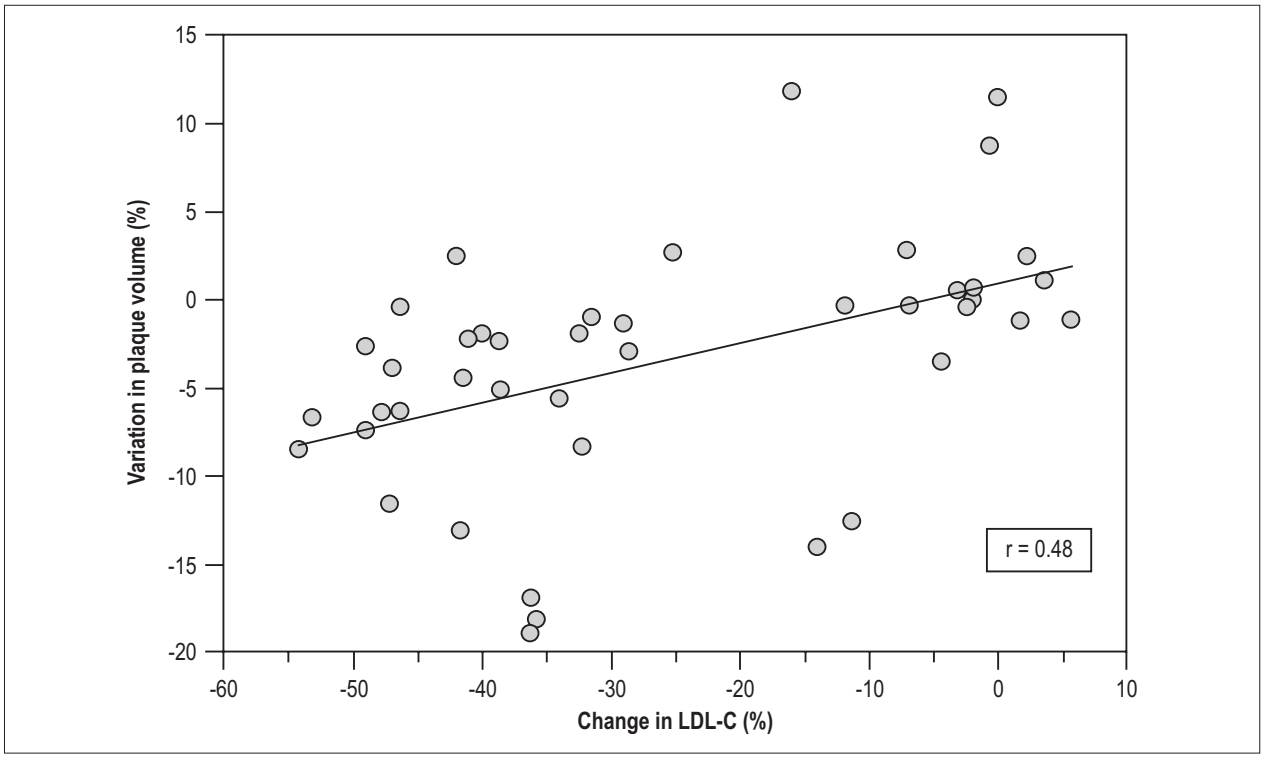

Figure 2 – *Relationship between changes in LDL-C plasma levels and variation in coronary plaque volume.*

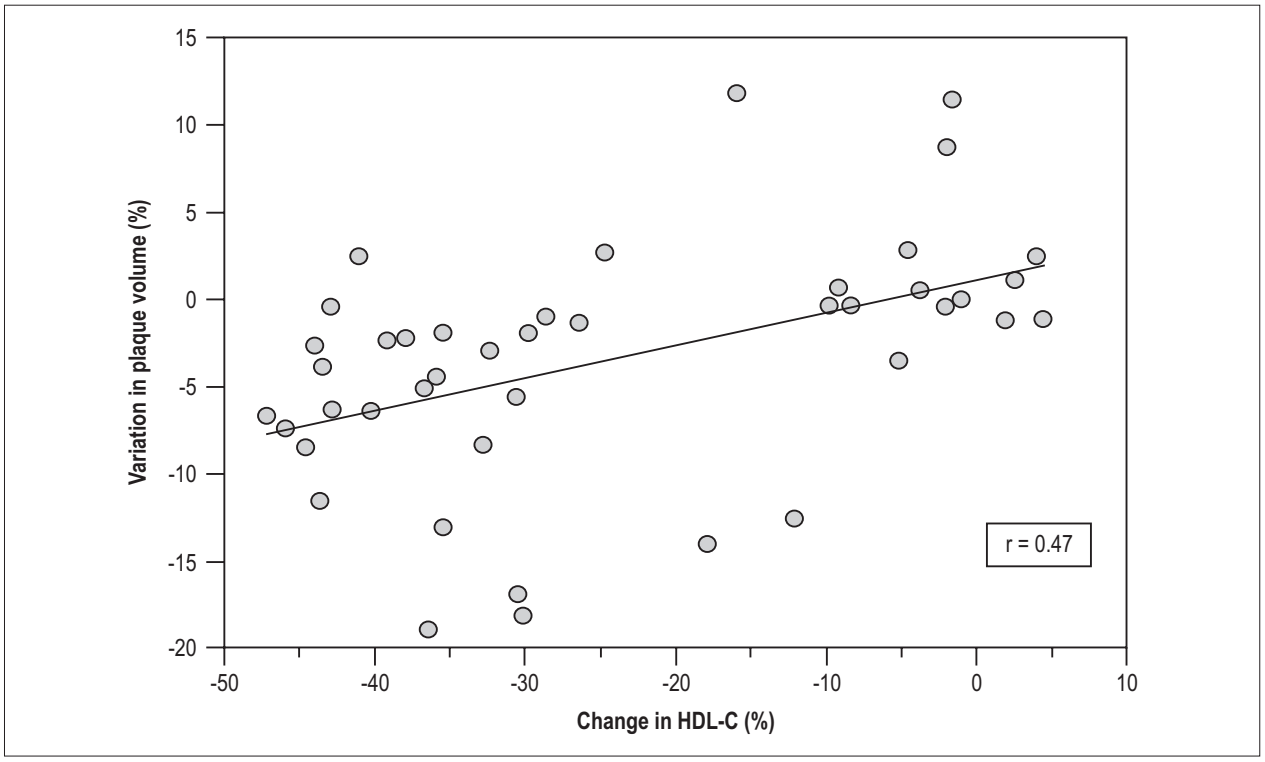

Figure 3 – *Relationship between changes in non-HDL-C plasma levels and variation in coronary plaque volume.*

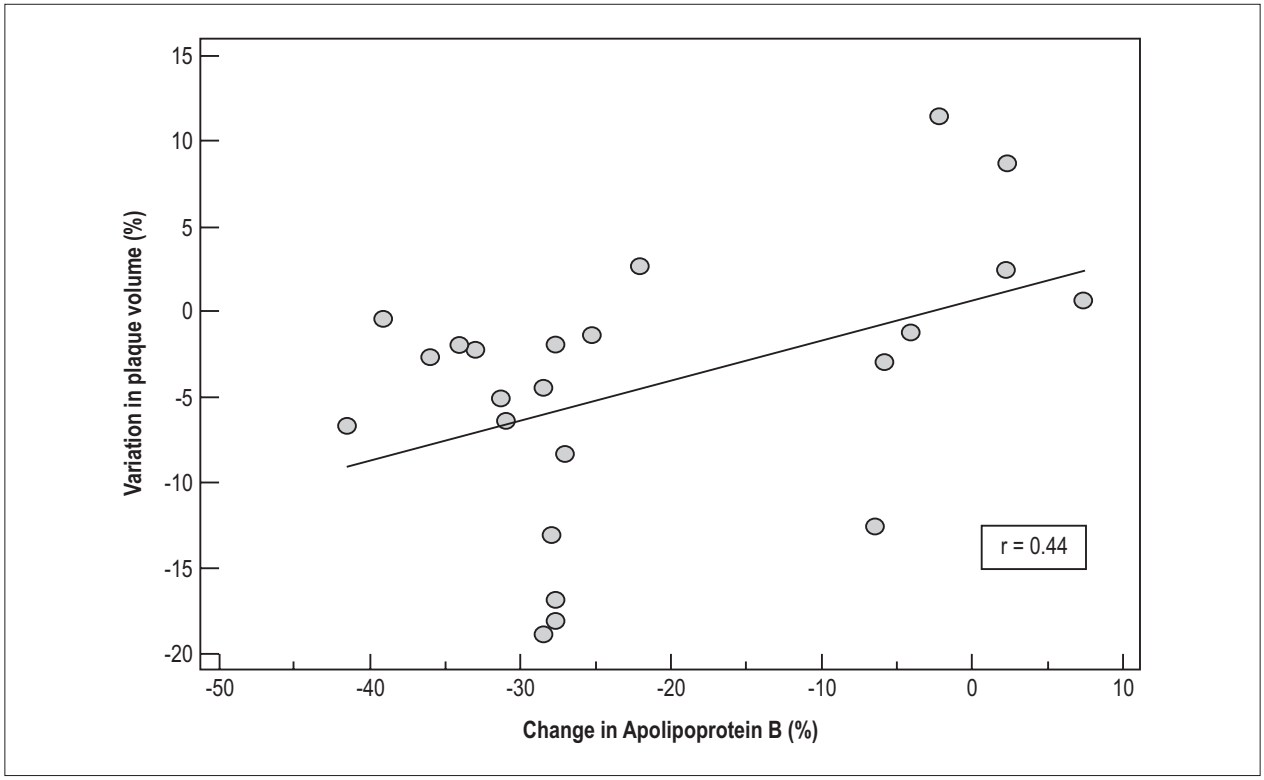

Figure 4 – *Relationship between changes in apolipoprotein B plasma levels and variation in coronary plaque volume.*

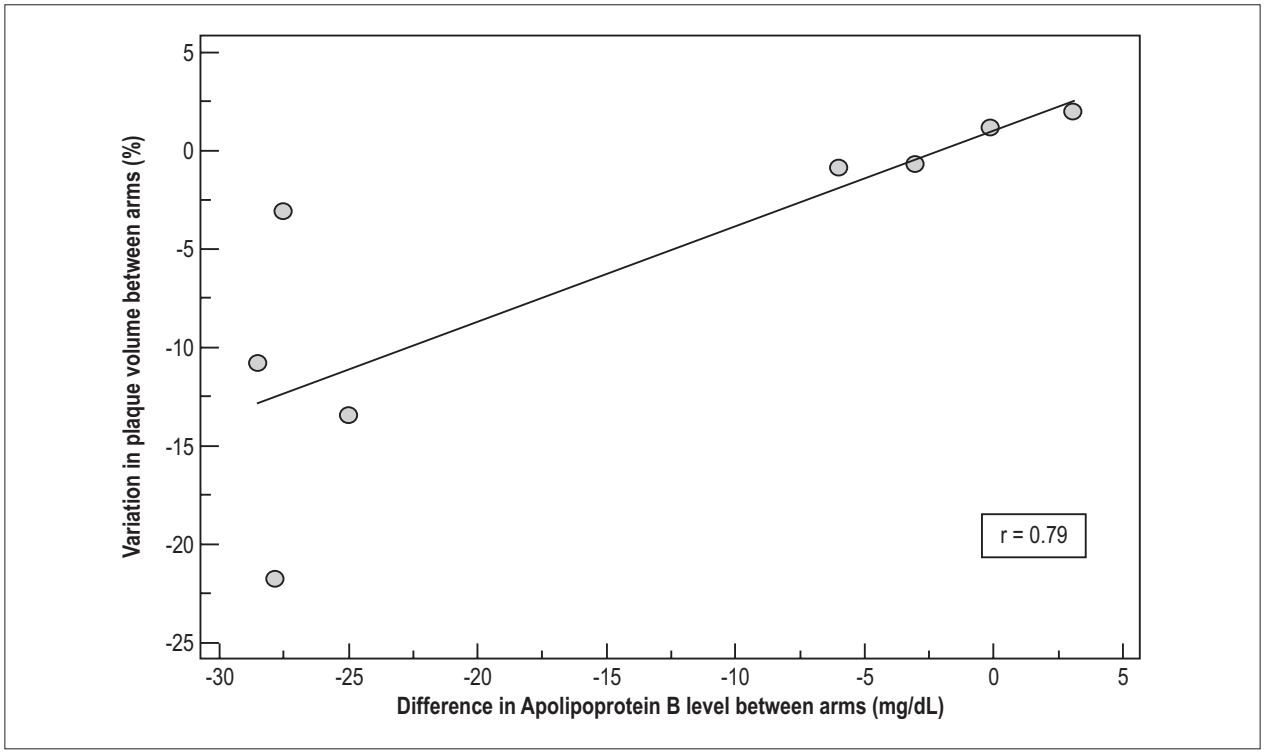

Figure 5 – *Relationship between the absolute difference in apolipoprotein B plasma levels and the percentage difference of the variation in coronary plaque volume.*

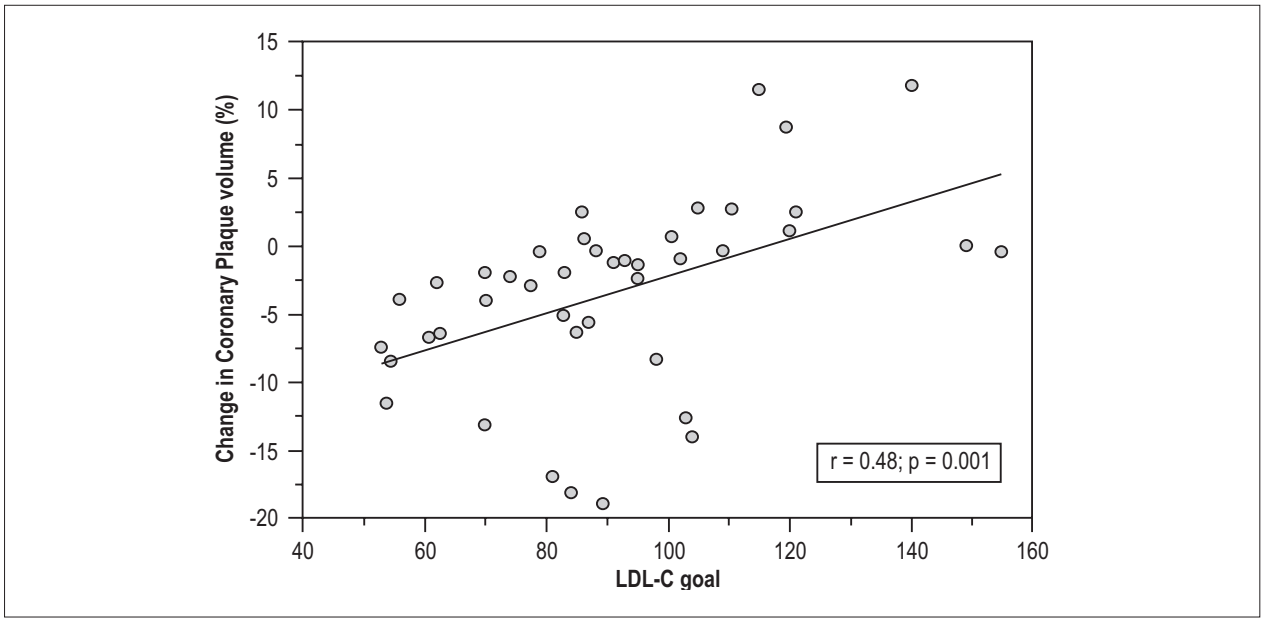

Figure 6 – *Relationship between LDL-C levels achieved at the end of the follow-up (LDL-C goal) and percentage changes in coronary plaque volume.*

follow-up. We found heterogeneity when we analyzed the L'Abbé and Galbraith plots, but not all studies could be analyzed, since the data required for the analysis were not always published. We understand that whereas there may be "statistical heterogeneity", we have not seen a marked clinical heterogeneity. Then, the fundamental objective of our work was to show the linear relationship between the changes in lipid levels and regression of atherosclerotic plaque, and not force a summary measure.

In previous analysis, C-reactive protein level was an important determinant of plaque regression. Our study did not analyze this biomarker. Also, the percentage atheroma volume (PAV) is a more stable measurement of the coronary plaque than the total atheroma volume. However, we decided to choose the percentage change in total atheroma volume as the end point because the PAV was only reported in 15 of the 27 studies included in this analysis. Finally, this analysis was performed with data imported from the studies and not with individual patient data; therefore, the results are not entirely accurate.

Conclusion

We found in our analysis significant associations between changes in LDL-C, non-HDL-C, and ApoB levels and regression of coronary plaque measured by IVUS. These results are aligned with the concept "lower LDL-C is better" and expand this assumption to other atherogenic lipid markers.

Author contributions

Conception and design of the research: Masson W, Siniawski D, Huerín M. Acquisition of data: Masson W, Lobo M, Molinero G, Huerín M. Analysis and interpretation of the data: Masson W, Siniawski D, Lobo M, Giorgi M, Huerín M. Statistical analysis: Masson W, Lobo M. Writing of the manuscript: Masson W, Siniawski D, Molinero G, Huerín M. Critical revision of the manuscript for intellectual content: Masson W, Siniawski D, Lobo M, Molinero G, Giorgi M, Huerín M. Supervision / as the major investigador: Masson W.

Potential Conflict of Interest

Dr. Giorgi reported receiving an educational grant from Pfizer and BMS.

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There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

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