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

Walter Masson1,2, Daniel Siniawski1,2, Martín Lobo1, Graciela Molinero1, Mariano Giorgi1, Melina Huerín1
Consejo de Epidemiología y Prevención Cardiovascular de la Sociedad Argentina de Cardiología1; Hospital Italiano de Buenos Aires2, Buenos Aires – Argentina

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...
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 CPV (< 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 change 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 ($p = 0.011$) 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. Furthermore, regression or slowed progression of carotid intima-media thickness induced by cardiovascular drug therapies do not reflect reductions in cardiovascular events.

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. Also, the association between the regression of coronary atherosclerotic plaque measured by IVUS and the incidence of non-fatal cardiovascular events has been demonstrated. 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.

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. 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.

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 declines in atherogenic plaques, whereas ApoB levels increase in atherogenic plaques.

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...
| 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 |
|------------|----------------------|-----|---------------------|------------------------|-------------------|---------------------------------|-----------------------------|
| REVERSAL18 | Atorvastatin 80      | 253 | -46.3               | -42.9                  | -39.1             | -0.4                            | 18                          |
| REVERSAL18 | Pravastatin 40       | 249 | -25.2               | -24.7                  | -22               | 2.7                             | 18                          |
| ESTABLISH11| Atorvastatin 20      | 35  | -41.7               | -35.4                  | -27.9             | -13.1                           | 6                           |
| ESTABLISH11| Control              | 35  | -0.7                | -1.9                   | 2.4               | 8.7                             | 6                           |
| JAPAN-ACS12| Pitavastatin 4       | 125 | -36.2               | -30.5                  | -27.6             | -16.9                           | 8-12                        |
| JAPAN-ACS12| Atorvastatin 20      | 127 | -35.8               | -30.1                  | -27.6             | -18.1                           | 8-12                        |
| SATURN13   | Atorvastatin 80      | 519 | -41.5               | -35.9                  | -28.4             | -4.0                            | 26                          |
| SATURN13   | 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                          |
| COSMOS13   | Rosuvastatin 2.5-20  | 215 | -38.6               | -36.7                  | -31.3             | -5.1                            | 19                          |
| ASTEROID15 | Rosuvastatin 40      | 346 | -53.2               | -47.2                  | -41.5             | -6.7                            | 24                          |
| ARTMAP16   | Atorvastatin 10-20   | 143 | -47                 | -43.4                  | -33               | -3.9                            | 6                           |
| ARTMAP16   | Rosuvastatin 20      | 128 | -49                 | -45.9                  | -7.4              | 6                               | 6                           |
| GAIN17     | Atorvastatin 20-80   | 65  | -42                 | -41                    | -                  | 2.5                             | 12                          |
| GAIN17     | 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                               | 6                           |
| Kawasaki et al.18| Atorvastatin 20     | 18  | -38.7               | -39.2                  | -                  | 6                               | 6                           |
| Jensen et al.19| Simvastatin 40     | 40  | -46.3               | -42.8                  | -                 | 3-12                           | 3-12                        |
| Jensen et al.19| Diet               | 40  | -2.4                | -2.1                   | -                 | 3-12                           | 3-12                        |
| Han et al.20| Rosuvastatin 20      | 21  | -54.2               | -44.6                  | -                 | 9-12                           | 9-12                        |
| Han et al.20| Rosuvastatin 20/Ramipril 10 | 19 | -47.2               | -43.6                  | -                 | 9-12                           | 9-12                        |
| STRADIVARIUS21| Placebo            | 341 | -3.2                | -3.8                   | -                 | 0.5                            | 18                          |
| A-PLUS22   | Placebo             | 154 | 1.7                 | 1.9                    | -4                | -1.2                           | 24                          |
| AQUARIUS23 | 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| Rosuvastatin 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                          |
| HEAVEN27   | Atorvastatin 80/Ezetimibe 10 | 42 | -28.6               | -32.3                  | -5.8              | -2.9                           | 12                          |
| HEAVEN27   | Standard treatment  | 47  | -1.9                | -9.2                   | 7.4               | 0.7                            | 12                          |
| CART-228   | Placebo             | 111 | -6.9                | -8.4                   | -                 | 0.3                            | 12                          |
| ENCORE II29| 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.
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 investigator: 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.
1. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al; Cholesterol Treatment Trialists’ (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366(9493):1267-78.

2. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, et al. Effects of statins on progression of coronary artery disease as measured by intravascular ultrasound. J Clin Hypertens (Greenwich). 2011;13(7):492-6.

3. D’Ascenzo F, Agostoni P, Abbate A, Castagno D, Lipinski MJ, Vetrovec GW, et al. Atherothrombosis and plaque regression and the risk of adverse cardiovascular events: a meta-regression of randomized clinical trials. Atherosclerosis. 2013;226(1):178-85.

4. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, et al; ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA. 2009;299(13):1556-65.

5. Nissen SE, Tardif JC, Nicholls SJ, Revkin JH, Shear CL, Duggan WT, et al; ILLUSTRATE Investigators. Effect of torcetrapib on the progression of coronary atherosclerosis. N Engl J Med. 2007;356(13):1304-16.

6. Boekholdt SM, Arnesaud BJ, Mora S, Pedersen TR, LaRosa JC, Nestel PJ, et al. Non-HDL cholesterol is a better predictor of cardiovascular events in patients treated with statins. JAMA. 2012;307(12):1302-9.

7. McQueen MJ, Hawken S, Wang X, Orampu S, Snieder A, Probstfield J, et al; INTERHEART Study Investigators. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. INTERHEART Study Investigators. Lancet. 2008;372(9634):224-33.

8. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Canz P, Vogel RA, et al; REVERSAL Investigators. Effect of intensified compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA. 2004;291(9):1071-80.

9. Okazaki S, Yokoyama T, Miyachi K, Shimada K, Kurata T, Sato H, et al. Effect of statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event; the ESTABLISH Study. Circulation. 2004;110(9):1061-8.

10. Hiro T, Kimura T, Morimoto T, Miyachi K, Nakagawa Y, Yamagishi M, et al; JAPAN-ACS Investigators. Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome: multicenter randomized trial evaluated by volumetric intravascular ultrasound using pitavastatin versus atorvastatin (JAPAN-ACS [Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome] study). J Am Coll Cardiol. 2009;54(4):293-302.

11. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P, et al. Effect of two intensive statin regimens on progression of coronary disease. N Engl J Med. 2011;365(22):2078-87.

12. Hong YJ, Jeong MH, Hachinohe D, Ahmed K, Choi YH, Cho SH, et al. Comparison of effects of rosuvastatin and atorvastatin on plaque regression in Korean patients with untreated intermediate coronary stenosis. Circ J. 2011;75(2):398-406.

13. Takayama T, Hiro T, Yamagishi M, Daida H, Hirayama A, Saito S, et al; COSMOS Investigators. Effect of rosuvastatin on coronary atheroma in stable coronary artery disease: multicenter coronary atherosclerosis study measuring effects of rosuvastatin using intravascular ultrasound in Japanese subjects (COSMOS). Circ J. 2009;73(11):2110-7.

14. Lee CW, Kang SJ, Ahn JM, Song HG, Lee Y, Kim WJ, et al. Comparison of effects of atorvastatin (20 mg) versus rosuvastatin (10 mg) therapy on mild coronary atherosclerotic plaques (from the ARTMAP trial). Am J Cardiol. 2012;109(12):1700-4.

15. Schartl M, Bocksch W, Koschky DH, Voelker W, Karsch KR, Kreuzer J, et al. Use of intravascular ultrasound to compare effects of different strategies of lipid-lowering therapy on plaque volume and composition in patients with coronary artery disease. Circulation. 2001;104(4):387-92.

16. Kazuaki M, Sano K, Okubo M, Yokomaki H, Ito Y, Murata I, et al. Volumetric quantitative analysis of tissue characteristics of coronary plaques after statin therapy using three-dimensional integrated backscatter intravascular ultrasound. J Am Coll Cardiol. 2005;45(12):1946-53.

17. Jensen LO, Thyssen P, Pedersen KE, Stender S, Haghtfeld T. Regression of coronary atherosclerosis by simvastatin: a serial intravascular ultrasound study. Circulation. 2004;110(3):265-70.

18. Han SH, Chung WI, Kang WC, Lee K, Park YM, Shin MS, et al. Rosuvastatin combined with ramipril significantly reduced atheroma volume by anti-inflammatory mechanism: comparative analysis with rosuvastatin alone by intravascular ultrasound. Int J Cardiol. 2012;158(2):217-24.

19. Nicholls SJ, Westlake A, Folkerts G, Kastelein JJ, Menon V, Williams B, Armbrecht J, et al; STRADIVARIUS Investigators. Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease: the STRADIVARIUS randomized controlled trial. JAMA. 2008;299(13):1547-60.

20. Tardif JC, Grégoire J, L’Allier PL, Anderson TJ, Bertrand O, Reeves F, et al; Avasimibe and Progression of Lesions on Ultrasound (A-PULS) Investigators. Effects of the acyl coenzyme A: cholesterol acyltransferase inhibitor avasimibe on human atherosclerotic lesions. Circulation. 2004;110(21):3377-2.
32. Tani S, Watanabe I, Anazawa T, Kawamata H, Tachihana E, Furukawa K, et al; Surugadai Atherosclerosis Regression Investigators. Effect of pravastatin on malondialdehyde-modified low-density lipoprotein levels and coronary plaque regression as determined by three-dimensional intravascular ultrasound. Am J Cardiol. 2005;96(8):1089-94.

33. Yokoyama M, Komiyama N, Courtney BK, Nakayama T, Namikawa S, Kuriyama N, et al. Plasma low-density lipoprotein reduction and structural effects on coronary atherosclerotic plaques by atorvastatin as clinically assessed with intravascular ultrasound radio-frequency signal analysis: a randomized prospective study. Am Heart J. 2005;150(2):287.

34. Nakayama T, Komiyama N, Yokoyama M, Namikawa S, Kuroda N, Kobayashi Y, et al. Pioglitazone induces regression of coronary atherosclerotic plaques in patients with type 2 diabetes mellitus or impaired glucose tolerance: a randomized prospective study using intravascular ultrasound. Int J Cardiol. 2010;138(2):157-65.

35. Huang Y, Li W, Dong L, Li R, Wu Y. Effect of statin therapy on the progression of common carotid artery intima-media thickness: an updated systematic review and meta-analysis of randomized controlled trials. J Atheroscler Thromb. 2013;20(1):108-21.

36. Costanzo P, Perrone-Filardi P, Vassallo E, Paolillo S, Cesarano P, Brevetti G, et al. Does carotid intima-media thickness regression predict reduction of cardiovascular events? A meta-analysis of 41 randomized trials. J Am Coll Cardiol. 2010;56(24):2006-20.

37. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;63(25 Pt B):2889-934.

38. Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, et al. ESC/EAS guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011;32(14):1769-818.

39. Anderson TJ, Grégoire J, Hegele RA, Couture P, Mancini GB, McPherson R, et al. 2012 Update of the Canadian Cardiovascular Society Guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol. 2013;29(2):151-67.

40. Ray KK, Kastelein JJ, Boekholdt SM, Nicholls SJ, Khaw KT, Ballantyne CM, et al. The ACC/AHA 2013 guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: the good the bad and the uncertain: a comparison with ESC/EAS guidelines for the management of dyslipidaemias 2011. Eur Heart J. 2014;35(15):960-8.