Statins for treating stable angina: can statins improve the plaque morphology and angina?

"...statins induce favorable changes in coronary plaque composition, as well as regression of coronary atherosclerosis."

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Coronary artery disease (CAD) is a major health problem worldwide. However, the age-adjusted death rate for CAD has substantially decreased during recent decades, with similar trends seen in many countries [1,2]. This decline is likely linked to lifestyle changes, risk factor modification and the widespread use of evidence-based therapies. Statins were introduced in 1987 and revolutionized the management of CAD. Landmark statin trials have established the key role of statins for both primary and secondary prevention, and statins now constitute the standard of care for patients with CAD [3]. The benefits of statin therapy are known to be greater than what can be explained by their effects on lipid levels alone [4,5] and imaging studies suggest that statin therapy may have a beneficial effect on both plaque volume and its composition. Our study assesses the available evidence regarding the effects of statins on plaque morphology and angina in patients with stable angina.

Plaque volume

The existence of atherosclerotic plaque regression is supported by a large body of evidence derived from both animal and human studies. In earlier studies, coronary angiography was used to assess plaque regression, revealing little change in the stenosis diameter after statin therapy [6,7]. A discrepancy existed between the clinical benefits of statin therapy and the changes seen on angiography. However, coronary angiography only visualizes the lumen, not the arterial wall, thus making it difficult to obtain information regarding the atherosclerotic plaque itself. By contrast, intravascular ultrasound (IVUS) visualizes not only the vessel lumen, but also the vessel wall, thus allowing accurate assessment of changes in the plaque volume.

The REVERSAL study was the first large, randomized trial to compare the effect of two different statins, both administered for 18 months, on coronary plaque [8]. Patients were randomized to receive either 40 mg/day pravastatin or 80 mg/day atorvastatin, and 502 evaluable IVUS examinations were obtained at baseline and 18 months. LDL cholesterol level decreased to 110 mg/dl in the pravastatin group and to 79 mg/dl in the atorvastatin group ($p < 0.001$). Compared with the baseline value, progression of the total atheroma volume occurred in the pravastatin group (2.7%; $p = 0.001$), but not in the atorvastatin group (-0.4%; $p = 0.98$). Intensive lipid-lowering treatment reduced the progression of coronary atherosclerosis compared with moderate lipid-lowering therapy, and thus demonstrates that coronary plaque progression can be halted by intensive statin therapy [8].

In the ASTEROID trial [9], patients were treated with 40 mg/day rosuvastatin, and 349 evaluable IVUS examinations were obtained at baseline and 24 months. LDL cholesterol levels decreased to 60.8 mg/dl and HDL cholesterol levels increased to 49.0 mg/dl. The change in percentage atheroma volume was -0.98% ($p < 0.001$) versus baseline and the change in total atheroma volume in the most diseased 10-mm subsegment was -6.1 mm^3 ($p < 0.001$) versus baseline. High-dose statin therapy resulted in the significant regression of coronary atherosclerosis, offering the first convincing evidence that statin therapy can cause regression of coronary atherosclerosis.

The SATURN study was the largest randomized trial comparing the effect of two potent statins on the progression of coronary atherosclerosis [10]. Serial IVUS was obtained in 1039 patients at baseline and after 104 weeks of

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treatment using either 80 mg/day atorvastatin or 40 mg/day rosuvastatin. The rosuvastatin group had lower levels of LDL cholesterol (62.6 vs 70.2 mg/dl; p < 0.001) and higher levels of HDL cholesterol (50.4 vs 48.6 mg/dl; p = 0.01) compared with those of the atorvastatin group. Percentage atheroma volume (primary end point) decreased by 0.99% with atorvastatin and by 1.22% with rosuvastatin (p = 0.17). Total atheroma volume (secondary end point) was more favorable with rosuvastatin than with atorvastatin (-6.39 vs -4.42 mm^3; p = 0.01). The SATURN trial demonstrated that maximum doses of atorvastatin and rosuvastatin resulted in significant regression of coronary atherosclerosis and with a similar degree of regression for both statins [10].

> "...statin therapy induces regression of coronary atherosclerosis in patients with mild-to-moderate coronary artery disease."

Statin side effects are dose-related and usual-dose statins are commonly prescribed in clinical practice [11]. However, little is known about whether this approach is as effective as high-dose statin therapy. The ARTMAP trial was designed to compare the effects of 20 mg/day atorvastatin versus 10 mg/day rosuvastatin on mild coronary atherosclerotic plaques [12]. Evaluable IVUS examinations were obtained for 271 patients at baseline and 6 months. At the 6-month follow-up, the percentage change in total atheroma volume (primary end point) was significantly less in the atorvastatin group than in the rosuvastatin group (-3.9 vs -7.4%; p = 0.018). By contrast, the change in percentage atheroma volume (secondary end point) did not differ between the two groups (-0.3 vs -1.1; p = 0.157). These findings demonstrate that usual doses of atorvastatin and rosuvastatin can also induce significant regression of coronary atherosclerosis, with a greater reduction caused by rosuvastatin.

Total atheroma volume and percentage atheroma volume (atheroma volume/vessel volume × 100) have been used as the IVUS parameters for plaque regression studies. Total atheroma volume was the primary end point in the REVERSAL and ARTMAP trials, both in the ASTEROID trial, and percentage atheroma volume in the SATURN trial. Percentage atheroma volume may reflect the dynamic remodeling response, but it has some limitations. If the vessel size increases due to the positive remodeling, percentage atheroma volume can decrease despite plaque progression. At present, it remains uncertain which index is the best surrogate corresponding to clinical outcomes. Taken together, the cumulative data strongly support the theory that statin therapy induces regression of coronary atherosclerosis in patients with mild-to-moderate CAD.

Plaque composition

The geometry of the vessel wall and the plaque volume can be accurately measured by IVUS, but characterization of the plaque composition remains difficult. New imaging modalities, including virtual histology IVUS and optical coherence tomography, have been developed in order to obtain more information regarding the composition of atherosclerotic plaques. To date, however, there are no ideal imaging tools that can delineate plaque composition, and only limited data are available.

Hong *et al.* evaluated the effects of statin treatments for each component of coronary atherosclerotic plaque using virtual histology IVUS [13]. A total of 100 patients were randomized to receive either 20 mg/day simvastatin or 10 mg/day rosuvastatin for 12 months. Virtual histology IVUS revealed that statin treatment was associated with significant changes in both the necrotic core and the fibrofatty plaque volume, and with little difference between the two statins. Nozue *et al.* investigated the effects of statin therapy on plaque composition using virtual histology IVUS [14]. A total of 164 patients were randomized to receive either 4 mg/day pitavastatin or 20 mg/day pravastatin, and virtual histology IVUS data were available for 119 patients at both baseline and 8 months. Both statins altered the coronary plaque composition by decreasing the fibrofatty plaque component and increasing the calcified plaque component. Despite the limitations of virtual histology IVUS, these findings support the supposition that statins rapidly stabilize vulnerable plaque by favorably changing the plaque composition.

> "Statins may reduce vascular inflammation, increase smooth muscle relaxation and improve endothelial function, all of which can contribute to better myocardial perfusion."

Takarada *et al.* used multiple imaging tools to perform a comprehensive analysis of vulnerable plaque in 82 patients with non-ST-segment elevation acute coronary syndrome [15]. The

percentage changes in total atheroma volume and in the corresponding fibrous cap thickness over the 9-month follow-up period were 3.1 ± 11% and 15 ± 17%, respectively. There was no correlation between the changes in plaque volume and those in the fibrous cap thickness. In a similar study by the same authors, the fibrous cap thickness was seen to increase 9 months after statin therapy in 40 patients with acute myocardial infarction [16]. A study using angioscopy also showed a significant decrease in yellow plaque after statin therapy [17]. These findings indicate that statin therapy beneficially affects plaque composition and induces plaque stabilization in patients with CAD.

Angina & ischemia

Despite controversial reports, statins appear to decrease the extent and severity of reversible ischemia in patients with CAD [18,19]. Statins may reduce vascular inflammation, increase smooth muscle relaxation and improve endothelial function, all of which can contribute to better myocardial perfusion [4].

Transient myocardial ischemia is not uncommon in patients with CAD and it increases the risk of coronary events. In the SAGE trial, statin therapy was associated with significant reductions in the total duration of myocardial ischemia, as measured by ambulatory electrocardiography monitoring [20]. The DUAAL trial investigated whether 24 weeks of atorvastatin therapy decreased ischemic episodes in patients with CAD [21]. Transient myocardial ischemia disappeared in >50% of the patients and there was a marked reduction in angina and nitroglycerin consumption. These findings indicate that statins may improve myocardial ischemia, as well as angina. in patients with CAD.

Conclusion

There is growing evidence that statins induce favorable changes in coronary plaque composition, as well as regression of coronary atherosclerosis. These changes may be related to plaque stabilization and serve as protection against a heart attack. Statins are also able to improve myocardial ischemia and angina in patients with CAD. Given their well-established and beneficial effects, statins should be considered as the first-line therapy for all patients with CAD.

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References

1. Wijeysundera HC, Machado M, Farahati F *et al.* Association of temporal trends in risk factors and treatment uptake with coronary heart disease mortality, 1994–2005. *JAMA* 303, 1841–1847 (2010).
2. Smolina K, Wright FL, Rayner M, Goldacre MJ. Determinants of the decline in mortality from acute myocardial infarction in England between 2002 and 2010: linked national database study. *BMJ* 344, d8059 (2012).
3. Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 380, 581–590 (2012).
4. Liao JK, Laufs U. Pleiotropic effects of statins. *Annu. Rev. Pharmacol. Toxicol.* 45, 89–118 (2005).
5. Lee CW, Park CS, Hwang I *et al.* Expression of HMG-CoA reductase in human coronary atherosclerotic plaques and relationship to plaque destabilisation. *Heart* 97, 715–720 (2011).
6. Waters D, Higginson L, Gladstone P *et al.* Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography. The Canadian Coronary Atherosclerosis Intervention Trial. *Circulation* 89, 959–968 (1994).
7. Jukema JW, Bruschke AV, van Boven AJ *et al.* Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. The Regression Growth Evaluation Statin Study (REGRESS). *Circulation* 91, 2528–2540 (1995).
8. Nissen SE, Tuzcu EM, Schoenhagen P *et al.* Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA* 291, 1071–1080 (2004).
9. Nissen SE, Nicholls SJ, Sipahi I *et al.*; ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA* 295, 1556–1565 (2006).
10. Nicholls SJ, Ballantyne CM, Barter PJ *et al.* Effect of two intensive statin regimens on progression of coronary disease. *N. Engl. J. Med.* 365, 2078–2087 (2011).
11. Armitag J. The safety of statins in clinical practice. *Lancet* 370, 1781–1790 (2007).
12. Lee CW, Kang SJ, Ahn JM *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.* 109, 1700–1704 (2012).
13. Hong MK, Park DW, Lee CW *et al.* Effects of statin treatments on coronary plaques assessed by volumetric virtual histology intravascular ultrasound analysis. *JACC Cardiovasc. Interv.* 2, 679–688 (2009).
14. Nozue T, Yamamoto S, Tohyama S *et al.* Statin treatment for coronary artery plaque composition based on intravascular ultrasound radiofrequency data analysis. *Am. Heart J.* 163, 191–199 (2012).
15. Takarada S, Imanishi T, Ishibashi K *et al.* The effect of lipid and inflammatory profiles on the morphological changes of lipid-rich plaques in patients with non-ST-segment

elevated acute coronary syndrome: follow-up study by optical coherence tomography and intravascular ultrasound. *JACC Cardiovasc. Interv.* 3, 766–772 (2010).

16. Takarada S, Imanishi T, Kubo T *et al.* Effect of statin therapy on coronary fibrous-cap thickness in patients with acute coronary syndrome: assessment by optical coherence tomography study. *Atherosclerosis* 202, 491–497 (2009).
17. Takano M, Mizuno K, Yokoyama S *et al.* Changes in coronary plaque color and morphology by lipid-lowering therapy with atorvastatin: serial evaluation by coronary angioscopy. *J. Am. Coll. Cardiol.* 42, 680–686 (2003).
18. Zoghbi GJ, Dorfman TA, Iskandrian AE. The effects of medications on myocardial perfusion. *J. Am. Coll. Cardiol.* 52, 401–416 (2008).
19. Sdringola S, Gould KL, Zamarka LG, McLain R, Garner J. A 6 month randomized, double blind, placebo controlled, multi-center trial of high dose atorvastatin on myocardial perfusion abnormalities by positron emission tomography in coronary artery disease. *Am. Heart J.* 155, 245–253 (2008).
20. Deedwania P, Stone PH, Bairey Merz CN *et al.* Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE). *Circulation* 115, 700–707 (2007).
21. Deanfield JE, Sellier P, Thaulow E *et al.* Potent anti-ischaemic effects of statins in chronic stable angina: incremental benefit beyond lipid lowering? *Eur. Heart J.* 31, 2650–2659 (2010).