High coronary plaque load: a heavy burden

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This editorial refers to ‘Coronary atheroma volume and cardiovascular events during maximally intensive statin therapy’1, by R. Puri et al., on page 3182

Hydroxymethylglutaryl (HMG) CoA-reductase inhibitors, or statins, play an important role in the primary and secondary prevention of coronary heart disease. By inhibiting the enzyme HMG-CoA reductase, statins lower the production of cholesterol in the liver, resulting in lower LDL cholesterol levels. Besides lowering cholesterol levels, statin therapy slows down plaque progression and in some patients even causes plaque regression.

In the beginning of the 1990s, the first trials were initiated to assess the effect of statin therapy on plaque dynamics. Randomized trials, such as MARS and REGRESS, used (qualitative) invasive coronary angiography (ICA) to assess luminal stenosis characteristics. Since ICA only allows assessment of the coronary lumen, differences in minimal lumen diameters (MLD) and mean segment diameters (MSD) between baseline and follow-up were assessed as a measurement of coronary plaque change.1,2 These early studies demonstrated that moderate dose statin therapy on average reduces plaque progression. Importantly, this was associated with a reduction of major adverse cardiovascular events (MACEs). Of note, it was shown that the beneficial effect of statin therapy is more pronounced in more severe lesions.1

A relative shortcoming of these studies was the inability of ICA to visualize true coronary atherosclerotic burden. Around the same time as the first angiographic studies with statin therapy were executed, a novel method for the assessment of coronary plaque burden was designed: intracoronary ultrasound (ICUS), nowadays known as intravascular ultrasound (IVUS). This invasive method uses ultrasound to create two-dimensional tomographic images of the coronary lumen and vessel wall morphology.3 Since then IVUS is frequently used for coronary plaque assessment and has been widely validated for serial plaque imaging.4 IVUS is able to visualize true atherosclerotic burden with a high resolution and could be of value, not only for prognostic implications, but also to provide novel insights into the mechanisms of plaque dynamics in patients receiving statin therapy. In the future, non-invasive, serial assessment of coronary atherosclerosis could be feasible using quantitative computed tomography coronary angiography (QCT).5 Figure 1 demonstrates the difference in coronary plaque assessment between ICA, IVUS, and QCT.

Puri et al. have now presented the results of a novel substudy of the SATURN trial.6 In this study, 1039 patients underwent serial IVUS before and after 24 months of statin therapy. Patients were randomized to the highest dose of either rosuvastatin (40 mg) or atorvastatin (80 mg), which is currently the most intensive statin regimen used in clinical practice. Serial IVUS was performed in a single coronary artery, without significant luminal stenosis or previous revascularization. The authors investigated the prognostic influence of baseline percentage atheroma volume (PAV) on: (i) MACEs; (ii) lipid levels at baseline and follow-up; and (iii) coronary plaque progression. It was demonstrated that PAV at baseline is associated with the occurrence of MACEs during 2 years of follow-up. The incidence of MACEs in patients in the lowest quartile of PAV was 5.1% and was significantly increased stepwise per PAV quartile (5.1, 5.7, 7.9, and 12%, respectively, \( P = 0.001 \)). This relationship remained significant after correction for baseline risk factors. Of particular interest, neither LDL cholesterol levels at baseline nor those after high dose statin treatment could independently predict MACEs. Thereafter, the correlation between PAV at baseline and plaque progression on IVUS was assessed. As expected, patients with PAV above the median demonstrated a greater reduction in PAV at 12 months follow-up. Accordingly, in these patients, lumen volume was significantly more increased after therapy compared with patients with PAV below the median. However, no significant differences in vessel wall volume were observed between the two groups. Thus, patients with heavy disease burden at baseline benefit relatively more from aggressive/high dose statin therapy with regard to plaque regression, compared with patients with a light disease burden, confirming the older ICA results with modest dose statin therapy.

One of the most striking results of this study is the fact that LDL levels at baseline or after statin treatment showed no predictive value for MACEs. This could lead to doubt about the beneficial effect of LDL-lowering therapy. However, as also discussed by the authors, there is overwhelming evidence for the beneficial effects
of statin therapy on plaque progression and MACEs. As demonstrated by IVUS in the REVERSAL trial, there is a significant association between the amount of LDL cholesterol reduction due to statin therapy and slowed progression of atherosclerosis (as assessed by PAV). Currently, statin therapy is so fundamentally established in daily practice that its beneficial effect is beyond doubt. Even though it has been demonstrated that in patients receiving statin therapy LDL cholesterol levels have no additional prognostic value, further lowering of LDL cholesterol levels with novel PCSK9 monoclonal antibodies could further reduce the residual risk in these patients. These drugs are currently being investigated in a trial to assess safety and efficacy.

Recently, evidence has become available suggesting that the effect of statin therapy on prognosis is not solely mediated through lowering of LDL cholesterol but that so-called ‘pleiotropic effects’ also play an important role. These molecular mechanisms seem to be in part independent of LDL lowering. Examples of these pleiotropic effects are: improvement of endothelial function, stabilization of

![Figure 1](https://academic.oup.com/eurheartj/article-abstract/34/41/3168/518054)
atherosclerotic plaques, and a decrease in oxidative stress and inflammation. Indeed, recent studies have demonstrated that in addition to a decrease in PAV, statin therapy leads to stabilization of coronary atherosclerosis. Nozue et al. performed IVUS virtual histology (IVUS-VH) in 39 patients during percutaneous coronary intervention (PCI) and after 8 and 48 months of statin therapy. An increase in negative remodelling and calcified plaque was observed during follow-up, suggesting stabilization of coronary plaque.11 This was further confirmed by Taguchi et al. in 120 patients with acute coronary syndrome (ACS) receiving statin therapy who underwent serial IVUS. In patients showing either plaque progression or regression, the amount of necrotic core, associated with plaque vulnerability, was significantly decreased after 8–10 months of statin therapy.12 In the SATURN substudy, Puri et al. demonstrated that plaque regression was most pronounced in patients with PAV above the median. These patients presented with an unfavourable risk profile at baseline. It seems that the most diseased patients benefit the most from aggressive therapy. This was in line with a recent study that compared plaque regression by statin therapy in patients with stable coronary artery disease (CAD) and ACS, and demonstrated the greatest benefit of statin therapy in ACS patients.13 Unfortunately, the study by Puri et al. lacks further insight into the prognostic value of PAV changes by statin therapy. This would be an interesting topic, worth further investigation.

In conclusion, statin therapy lowers PAV and, as a result, improves prognosis. These beneficial effects are more pronounced in patients with a PAV above the median. Despite aggressive/high dose statin therapy, a high atherosclerotic plaque burden still remains a heavy burden, and novel treatment modalities should be developed to reduce residual risk further.

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