Computed tomography coronary angiography : from quantification of coronary atherosclerosis to risk stratification of patients

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Chapter 3

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" by Puri et al. pusblished in European Heart Journal in November 2013

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 cause plaque regression.

In the beginning of the 90's the first trials were initiated to assess the effect of statin therapy on plaque dynamics. Randomized trials, like MARS and REGRESS, used (quantitative) 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 (MACE). 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 in 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.

In this issue of the European Heart Journal Puri *et al.* present the results of a novel sub-study of the SATURN trial. 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 (40mg) or atorvastatin (80mg), which is currently the most intensive statin regiment used in clinical practice. Serial IVUS was performed in a

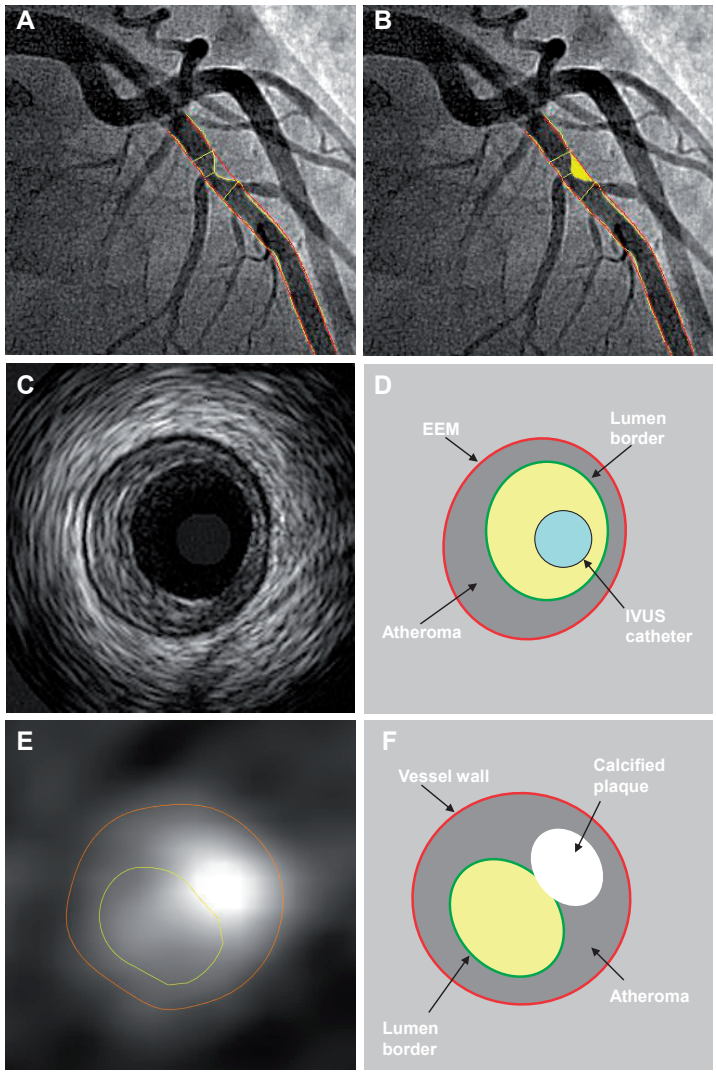

Figure 1. Difference in coronary plaque assessment between IVUS , invasive coronary angiography (ICA) and quantitative computed tomography coronary angiography (QCT).
Panel A demonstrates quantitative coronary angiography (Qangio XA version 7, Medis medical image systems B.V.). After delineation of the contrast-filled lumen the percentage stenosis can be calculated. The yellow area in Panel B represents the coronary plaque. However, since the vessel wall cannot be depicted on ICA this is a derived parameter. Panel C demonstrates a cross-sectional IVUS image of a coronary artery. This view allows assessment of coronary atherosclerosis. After segmentation of the EEM and lumen contours as demonstrated in Panel D, the plaque burden can be assessed. Panel E represent a cross-section of a QCT analysis of a coronary artery (Qangio CT research edition version 1.3.6., Medis medical image systems B.V.). In a similar fashion as IVUS, the lumen and vessel wall are segmented (Panel F). Thereafter, coronary plaque burden can be calculated. In addition, QCT allows for characterization of coronary atherosclerosis.
Abbreviations: EEM: external elastic membrane, IVUS: Intravascular Ultrasound

single coronary, without significant luminal stenosis or previous revascularization. The authors investigated the prognostic influence of baseline percentage atheroma volume (PAV) on: a) MACE b) lipid levels at baseline and follow-up and c) coronary plaque progression. It was demonstrated that PAV at baseline is associated with the occurrence of MACE during 2 years follow-up. The incidence of MACE 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 relation remained significant after correction for baseline risk factors. Of particular interest, neither LDL cholesterol levels at baseline or after high dose statin treatment could independently predict MACE. Thereafter, the correlation between PAV at baseline and plaque progression on IVUS was assessed. As expected, patients with PAV above 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 to patients with PAV below 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 to 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 MACE. 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 MACE.[6] 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, 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[7, 8] These drugs are currently investigated in trial to assess the safety and efficacy.

Recently, evidence has become available suggesting that the effect of statin therapy on prognosis in not solely mediated through lowering of LDL-cholesterol but also so-called “pleiotropic effects” 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 atherosclerotic plaques and decreasing oxidative stress and inflammation.[9] Indeed, recent studies have demonstrated that in addition to decrease in PAV, statin therapy leads to stabilization of

coronary atherosclerosis. Nozue *et al* performed IVUS Virtual Histology (IVUS-VH) in 39 patients during PCI and after 8 and 48 months of statin therapy. An increase in negative remodeling and calcified plaque was observed during follow-up suggesting stabilization of coronary plaque.[10] This was further confirmed by Taguchi *et al,* in 120 ACS patients receiving statin therapy who underwent serial IVUS. Both in patients showing plaque progression or regression, the amount of necrotic core, associated with plaque vulnerability, was significantly decreased after 8 to 10 months of statin therapy.[11] In the SATURN sub-study, Puri *et al.* demonstrated that plaque regression was most pronounced in patients with PAV above the median. These patients presented with an unfavorable 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 comparing plaque regression by statin therapy in patients with stable CAD and ACS demonstrated the most benefit of statin therapy in ACS patients.[12] Unfortunately, the study by Puri *et al.* lacks further insight in 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 further reduce residual risk.

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