Evidence from intravascular ultrasound

Effects of intensive LDL lowering on coronary atherosclerosis

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Summary

Coronary atherosclerosis has been considered a chronic disease characterised by ongoing progression in response to systemic risk factors and local pro-atherogenic stimuli. As our understanding of the mechanisms implicated in atherogenesis and plaque progression evolved, effective treatment strategies have been developed that led to substantial reduction of the clinical manifestations and acute complications of coronary atherosclerosis. More recently, intracoronary imaging modalities have enabled detailed in vivo quantification and characterisation of coronary plaque, serial evaluation of atherosclerotic changes over time, and assessment of vascular responses to effective anti-atherosclerotic medication. The use of intracoronary imaging modalities has demonstrated that intensive lipid lowering can halt plaque progression and may even result in regression of coronary atheroma when the highest doses of the most potent statins are used. Although current evidence indicates the feasibility of atheroma regression, these changes in plaque size are modest and their clinical implications remain largely elusive. Growing interest has focused on achieving more pronounced regression of coronary plaque with use of novel anti-atherosclerotic medications and, more importantly, on elucidating ways to translate favourable changes of plaque anatomy into more favourable clinical outcomes.

Introduction

Atherosclerosis is a chronic disease advancing over time by accumulation of atheromatous lesions within the intimal layer of the vessel wall in response to systemic risk factors and the local haemodynamic environment [1]. Medical interventions, including lipid-lowering drugs and antihypertensive medications, have effectively reduced coronary atherosclerotic events [2–4]. However, understanding the change in the natural history of coronary atherosclerosis in response to these interventions has not been possible until recently. The advent of invasive imaging modalities allows us to quantify and morphologically characterise coronary atherosclerosis *in vivo* [5]. The effect of lipid-lowering therapies on coronary atherosclerosis has been an important focus during recent years and the modest regression in atheroma burden when high-lipid lowering agents are administered represents an important advance in cardiovascular medicine [6]. The present review summarises the accumulated data on the effect of lipid-lowering therapies on coronary atherosclerosis.

In vivo assessment of coronary atherosclerosis

The three intravascular imaging modalities most frequently used for the assessment and quantification of coronary atherosclerosis are greyscale intravascular ultrasound (IVUS), optical coherence tomography and near-infrared spectroscopy [5]. However, to date, no single invasive imaging modality is able to assess the full scope of coronary atherosclerosis. The gold standard for assessing the effect of lipid-lowering therapy on coronary atherosclerosis is IVUS, as it is the only imaging modality that accurately delineates the vessel contours in the presence of large necrotic cores or calcifications and thereby allows an accurate quantification of the atheroma burden. For the purpose of the present review, we therefore only summarised findings obtained with IVUS. The variability of core laboratory-based tracing of the outer vessel wall and lumen with IVUS (i.e., the measurements required for atheroma quantification) is negligibly low. For example, in the REVERSAL study [7], intra-observer and inter-observer variability was low for vessel area (–0.16 ± 0.68 mm^2, –0.07 ± 0.93 mm^2) and lumen area tracing (–0.02 ± 0.75 mm^2, –0.07 ± 0.93 mm^2) and linear regression analysis showed a close correlation with r values >0.98 for all comparisons.

Quantification of coronary atheroma volume with IVUS

IVUS is based on acoustic sound wave backscattering. The amplitude of the reflected ultrasound wave is used to create the grey-scale image, resulting in an axial resolution of 80–120 µm and a penetration depth of 4–8 mm. IVUS is the only invasive imaging modality

that allows the reproducible quantification of atheroma burden *in vivo*. IVUS performed serially at consecutive time points in the same vessel region is the gold standard for assessment of plaque progression or regression over time and provides the basis for an *in vivo* evaluation of the effect of anti-atherosclerotic medications. Plaque burden in a two-dimensional IVUS frame is expressed as the ratio of plaque plus media area divided by vessel area. Volumetric (three-dimensional) measures of disease burden include total atheroma volume (TAV: the sum of atheroma area measured in sequential cross-sectional frames) and percent atheroma volume (PAV: the percent of the vessel volume occupied by atheroma). PAV has been the primary endpoint in the majority of serial IVUS studies (fig. 1).

Effect of statin therapy on coronary atherosclerosis

In the last decade, serial IVUS studies assessed the progression of coronary atherosclerosis in response to statins. The REVERSAL study [7] compared the impact of moderate lipid lowering with pravastatin 40 mg versus intensive lipid lowering with atorvastatin 80 mg on coronary atherosclerosis in stable coronary artery disease patients. In patients treated with atorvastatin, lower low-density lipoprotein cholesterol (LDL-C) levels (79 ± 30 mg/dl) were associated with prevention of plaque progression (ΔPAV +0.2%), whereas in pravastatin treated patients higher on-treatment LDL-C levels (110 ± 26 mg/dl) resulted in continuous plaque progression (ΔPAV + 1.6%), measured with IVUS over an 18-month follow-up. ASTEROID [8] was the first large-scale serial IVUS study in which plaque regression was observed in the coronary artery tree. In stable coronary artery disease patients treated with the highest dose of rosuvastatin (40 mg) over 24 months, reduction of LDL-C to 61 ± 20 mg/dl and increase of high-denstiy lipoprotein cholesterol (HDL-C) to 49 ± 13 mg/dl were associated with a median PAV reduction of 0.8% (1.2 to 0.5, p <0.01). The SATURN [9] study subsequently compared rosuvastatin 40 mg with atorvastatin 80 mg and documented a similar extent of plaque regression – 1.2% (1.2 to 0.6%) versus 1.0% (1.5 to 0.9%) – with the two high-intensity statin regimens.

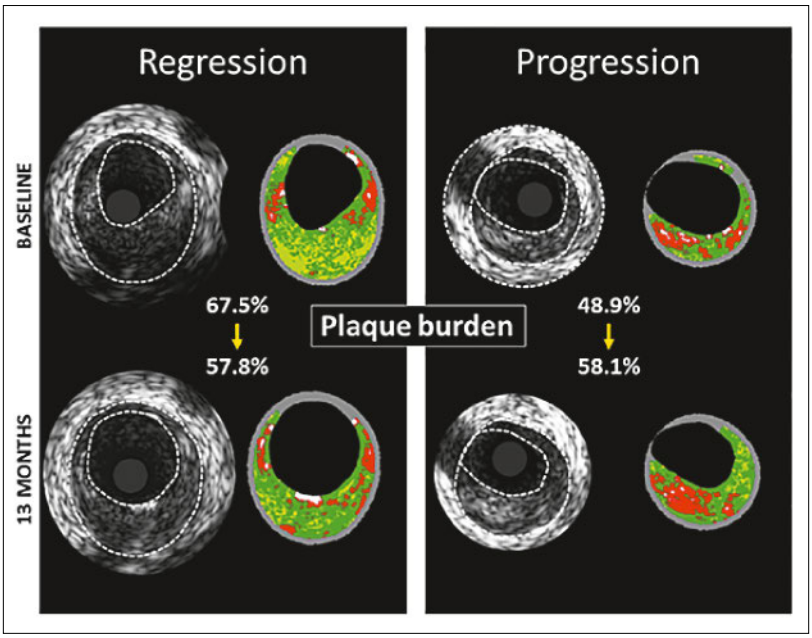

Figure 1: Representative example of a lesion showing regression (left panel) and progression (right panel). The left cross-sections indicate the grayscale-IVUS findings and the coloured cross-sections on the right indicate radiofrequency IVUS analysis. (Adapted with permission from Raber et al. [6]).

Effect of ezetimibe on coronary atherosclerosis

The PRECISE IVUS study [10] investigated on the effect of ezetimibe on top of atorvastatin on PAV reduction in acute coronary syndrome (ACS; 60%) and stable coronary artery disease (CAD; 40%) patients presenting for coronary angiography. The plaque burden at the time of enrolment was higher, as noted in previous IVUS studies, without difference between treatment groups (ezetimibe 10 mg + atorvastatin 51.3% ± 10.8% vs placebo + atorvastatin 50.9% ± 11.4, p = 0.80). Dual lipid-lowering strategy with ezetimibe and atorvastatin resulted in a more intense PAV reduction (–1.4%, –3.4 to 0.1%) as compared with placebo and atorvastatin (–0.3%, –1.9 to 0.9; p = 0.001), an effect that was much more pronounced in ACS than in stable CAD patients. A second study (OCTIVUS [11]) investigated the efficacy of ezetimibe in addition to atorvastatin 80 mg versus placebo and atorvastatin 80 mg in a non-infarct related lesion of patients with ST elevation myocardial infarction. In contrast to the previous study, no significant PAV reduction was observed between the two groups (–0.9% ± 2.6 vs –1.1% ± 3.7, p = 0.67), most likely because of the lack of adequate power.

Effect of PCSK9 inhibition as addition to statins in coronary atherosclerosis

The use of statins has successfully decreased the risk of cardiovascular events and its effect on coronary atheroma has been summarised above. However, despite successful LDL-C reduction with statin therapy, there still exists an unmet need for an additional/alternative LDL-C lowering therapy for further risk reduction. Examples include patients with familial hyper-

cholesterolaemia for whom even with the maximal dose of highly potent statins do not achieve goal LDL-C concentrations, and other patients with statin intolerance or those who tolerated only small doses of statins as a result of side effects, myalgia being the most frequent. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a new class of drug that has been shown to further decrease LDL-C levels in patients on and off statin therapy [12]. The GLAGOV (Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound) trial [13] assessed the effect of an additional PCSK9 inhibition on top of moderate or high intensity statin therapy on progression of coronary atherosclerosis in patients with stable CAD. Evelocumab further decreased on-treatment LDL-C levels by –56.5 mg/dl (–59.7 to –53.4 mg/dl) to a mean level of 36.6 mg/dl (34.5 to 38.8 mg/dl) which resulted in a reduction of PAV by –1.0% (–1.3 to –0.6%, p <0.01) and total atheroma volume (–4.9 mm^3, –7.3 to –2.5 mm^3, p <0.01).

Factors associated with coronary plaque regression or progression

One important lesson learned from serial IVUS studies is the close link between LDL-C levels and the occurrence of plaque progression or regression (fig. 2), thus confirming at the level of intracoronary plaque imaging previous clinical observations that closely related LDL-C levels and adverse cardiac events. An observational study by von Birgelen et al. [14]. showed that serial changes of cross-sectional plaque area in left main stem lesions of patients treated with usual-care statin regimens were linearly related to LDL-C levels, and that plaque progression was halted at an LDL-C threshold of 1.94 mmol/l (75 mg/dl) within the overall cohort. Serial IVUS studies examining the effects of various (statin and non-statin) anti-atherosclerotic strategies affirm a linear relation between changes of atheroma volume and on-treatment LDL-C levels (fig. 2). Interestingly, a reduction of atherosclerosis burden occurred only when guideline recommended on treatment LDL-C levels of <1.8 mmol/l were achieved. Further, LDL-C levels were independent predictors of plaque regression in both ASTEROID and SATURN [15]. This linear relation between on-treatment LDL-C levels and change in atheroma volume was also confirmed in studies investigating non-statin treatment regimens such as the PRECISE IVUS study (ezetimibe) [7] and the GLAGOV study (evolocumab s.c.) [13].

Notwithstanding the clear mechanistic role of LDL-C in atherogenesis and the robust association with serial plaque imaging investigations, a notable proportion of patients who achieved very low LDL-C levels failed to show coronary plaque regression. Atheroma continued to progress in 34% of patients in the SATURN trial and in a strikingly similar 36% of patients in ASTEROID, despite low on-treatment LDL-C levels and overall atheroma regression [8, 9]. In a pooled analysis of seven serial IVUS trials examining the vascular effects of statins and non-statin regimens, disease progression was observed in 20% of patients with LDL-C <70 mg/dl [14]. Increasing atheroma burden despite LDL-C levels below guideline-recommended thresholds was associ-

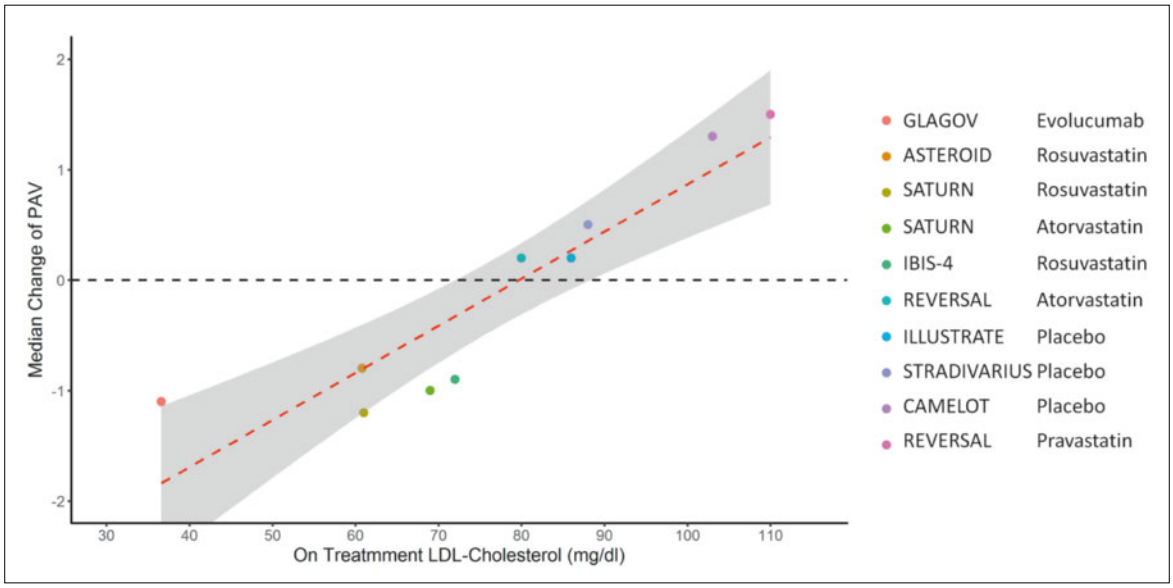

Figure 2: Median changes of percent atheroma volume (PAV) show a close correlation with average on-treatment low-density lipoprotein cholesterol levels.

ated with the following findings: presence of diabetes mellitus, higher systolic blood pressure and smaller increase in HDL-C [14]. These insights corroborate the multifactorial nature of atherosclerosis and reinforce the need for intensive modification of global risk and the potential benefits of introducing anti-inflammatory treatment strategies (e.g., cannakinumab investigated in the CANTOS trial) in addition to the reduction of LDL-C in coronary artery disease patients.

The strongest multivariable predictor of PAV regression in SATURN was increased baseline PAV [9], suggesting that plaque regression under intensive statin therapy is more successful in patients carrying a high coronary atheroma burden.

ACS patients show a more intense reduction in coronary atheroma burden as compared to stable CAD patients, a finding that is probably related to a higher plaque burden at baseline [6]. For example, in the PRECISE IVUS study [10], PAV reduction after 12 months of atorvastatin + ezetimibe therapy reached 2.3% in ACS patients and 1.2% in stable CAD patients.

The important role of inflammation in atherosclerosis has also been reflected in serial IVUS studies. In REVERSAL [3], reduction of C-reactive protein (CRP) emerged as an independent predictor of a reduction in plaque size. Consistently, in SATURN [16] stable levels of CRP after 24 months of intensive statin therapy were associated with greater atheroma regression as compared with patients with increasing levels of high-sensitivity CRP values, suggesting that the favourable impact of high-dose statins is probably mediated by pleiotropic effects beyond the reduction of LDL-C.

Association between plaque regression and clinical outcomes

The clinically relevant question is whether a condition of plaque stabilisation or regression as defined by serial IVUS translates into improved clinical outcomes.

Plaque burden at baseline

Plaque burden obtained at a single point in time correlates with established clinical risk factors and may predict subsequent clinical events [17]. In PROSPECT [18], high plaque burden (>70%) at the index procedure was associated with major adverse cardiovascular events over a 3-year follow-up; however, clinical event rates were low overall, and the impact of the change of plaque burden on clinical outcomes could not be assessed because serial intravascular imaging was not available. The low specificity (9.6%) of increased plaque burden as a predictor of major adverse cardiac and cerebrovascular events (MACCE) is also noteworthy, as it limits the clinical implications for routine patient evaluation and decision making. The association between increased plaque burden and future events was also consistently demonstrated in the VIVA study [19] and in noninvasive imaging studies using multidetector computed tomography [20]. The PREDICTION study [21], a natural history study that was not limited to anatomic, but also assessed local haemodynamic plaque characteristics, corroborated the predictive impact of increased plaque burden at baseline. In addition, this study demonstrated the incremental value of low shear stress for identification of lesions that subsequently required percutaneous coronary intervention (PCI). The baseline percent atheroma volume has also been linked to subsequent clinical events. In the SATURN study [9], each standard deviation increase of baseline PAV was correlated with a 28% increase in major adverse cardiovascular events.

Clinical implications of serial changes of coronary plaque burden

Our understanding of the clinical implications of serial changes of plaque burden is based mostly on indirect evidence and on *post hoc* analyses. Von Birgelen et al. [14] reported in an observational study that plaque progression detected with IVUS was associated with more frequent adverse clinical events. In a pooled analysis of six serial IVUS studies, Nicholls et al. [22] found that PAV progression was an independent predictor of major adverse cardiovascular events over a mean follow-up of 21 months. The majority of events were repeat revascularisation procedures, and an impact of plaque progression on mortality was not reported. From that pooled analysis, however, it remains unclear whether repeat revascularisation procedures were performed within the arterial regions where PAV progression occurred, thus leaving the question of a causative relation between PAV progression and subsequent events open.

In summary, the association between serial reduction of atheroma burden (which has been consistently quantified around only 1%) and major cardiovascular events (which are reduced by over one-fifth per 40 mg/dl LDL-C reduction per year) appears to be modest and remains mostly inferential.

Conclusion

In-vivo imaging modalities allow assessment of the progression of coronary atherosclerosis in response to lipid-lowering therapy, and the modest regression in atheroma burden when high-intensity lipid lowering agents are administered represents an important pro-

gress in cardiovascular medicine. However, our current invasive imaging modalities may capture only in part the complex biology of atheroma progression, stabilisation or regression. Given the complementary information provided by different modalities separately, efforts should continue to focus on combined use of these techniques and, perhaps, more sophisticated tools to better elucidate mechanisms of statin-mediated changes of coronary plaques.

Disclosure statement

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