



Serial intravascular ultrasound assessment of changes in coronary atherosclerotic plaque dimensions and composition: an update

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This manuscript reviews the use of serial intravascular ultrasound (IVUS) examination of coronary atherosclerosis in recent observational studies and randomized trials that revealed the effects of cholesterol-lowering and lipid-modifying therapies and offered novel insight into plaque progression and regression. We discuss the value of plaque progression–regression as complementary imaging endpoint and potential surrogate marker of cardiovascular event risk. In addition, the progress in serial assessment of coronary plaque composition and plaque vulnerability by radiofrequency-based analyses is reviewed. Finally, we report on the evaluation of true vessel remodelling in recent serial IVUS trials and discuss the future perspective of serial invasive imaging of coronary atherosclerosis.

Keywords

Coronary disease • Intravascular ultrasound • Radiofrequency • Serial studies • Progression–regression • Plaque vulnerability

Introduction

Coronary heart disease remains the leading cause of morbidity and mortality worldwide. Established preventive pharmacological therapies reduce cardiovascular event rates by only 30–40%. Given the significant residual cardiovascular risk, there is need to develop novel therapies to achieve even greater risk reduction.^{1–5} However, such novel anti-atherosclerotic therapies must be carefully evaluated, with ultimate proof of benefit in clinical endpoint studies. Increasingly, complementary imaging endpoint trials are used in comprehensive drug development programmes.

Intravascular ultrasound (IVUS) provides real-time, high-resolution, tomographic images of the lumen, and the atherosclerotic changes in the coronary vessel wall.^{4–7} The invasive nature of this imaging technique requires selective cannulation of the vessel by an IVUS imaging catheter that incorporates within its <1 mm diameter a miniaturized transducer that emits and receives high-frequency, 20–45 MHz, ultrasound depending on the system and type of catheter. Detection of the contours of the leading edge of the lumen and the media–adventitia interface permit direct measurements of

lumen and total vessel cross-sectional area and, therefore, calculation of absolute and percent plaque and media (or atheroma) area.^{6,7} In addition, morphology, severity, and composition of coronary atherosclerotic plaques can be determined. By using motorized pullback devices, volumetric data can be obtained which are particularly suitable when performing serial IVUS studies.^{4–11}

Recent trials have used serial IVUS imaging to investigate the effect of anti-atherosclerotic drugs on coronary plaque geometry and/or plaque composition (Table 1).^{12–30} IVUS is indeed a particularly suitable technique for the serial assessment of coronary atherosclerosis, given its relatively high image resolution, accurate measurements, high measurement reproducibility, and ability to early detect mild, angiographically silent atherosclerotic disease that can be a precursor of future coronary events.^{4–11} As a result, increasing attention has been focused on the appropriate role of serial IVUS imaging to study complementary surrogate endpoints during the development of novel pharmacological therapies (Figure 1).^{3–5,10,11} This review updates our current knowledge as obtained from both observational serial IVUS studies and randomized IVUS trials of pharmacological interventions.

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Table 1 Summary of pharmacological intervention trials with serial volumetric intravascular ultrasound endpoints

Study	Year	Design	Follow-up	Patients ^a	Treatment	Serial IVUS results
GAIN ¹²	2001	Randomized open-label multicentre	12 months	99	Atorvastatin vs. Usual care	Δ Atheroma volume (%): +2.5 ± 25 vs. +11.8 ± 31, <i>P</i> = 0.14 Δ Hyperechogenicity index (%) +42.2 ± 98 vs. +10.1 ± 69, <i>P</i> = 0.02
Nissen et al. ¹³	2003	Randomized placebo-controlled multicentre	5 weeks	47	r-ApoA-I Milano (ETC216) vs. Placebo	Δ Atheroma volume (%): -1.06 ± 3.17, <i>P</i> = 0.02 vs. baseline +0.14 ± 3.09, <i>P</i> = 0.97 vs. baseline
Jensen et al. ¹⁴	2004	Non-placebo-controlled single centre	15 months	40	Simvastatin	Δ Atheroma volume (%): +6.3 (95% CI 2.4–10.1), <i>P</i> = 0.002 vs. baseline
REVERSAL ¹⁶	2004	Randomized multicentre	18 months	502	Atorvastatin 80 mg vs. Pravastatin 40 mg	Δ Atheroma volume (%): -0.4 (95% CI -2.4 to 1.5) vs. +2.7 (95% CI 0.2–4.7), <i>P</i> = 0.02
ESTABLISH ¹⁵	2004	Open-label randomized single centre	6 months	48	Atorvastatin vs. Usual care	Δ Atheroma volume (%): -13.1 ± 12.8 vs. +8.7 ± 14.9, <i>P</i> < 0.0001
A-PLUS ¹⁷	2004	Randomized placebo-controlled multicentre	24 months	755	Avasimibe vs. Placebo	Δ Atheroma volume (%): +1.9 ± 14.6 vs. -0.1 ± 12.7, <i>P</i> = ns
CAMELOT ¹⁸	2004	Randomized placebo-controlled multicentre	24 months	274	Amlodipine 10 mg vs. Enalapril 20 mg vs. Placebo	Δ Atheroma volume (%): +0.5 ± 3.9, <i>P</i> = 0.31 vs. baseline +0.8 ± 3.7, <i>P</i> = 0.08 vs. baseline +1.3 ± 4.4, <i>P</i> < 0.001 vs. baseline
Yokoyama et al. ¹⁹	2005	Randomized single centre	6 months	59	Atorvastatin 10 mg vs. Usual care	Δ Atheroma volume (%): -3.2, <i>P</i> = 0.024 vs. baseline -2.9, <i>P</i> = 0.194 vs. baseline (+IVUS-backscatter endpoints)
Kawasaki et al. ²⁰	2005	Open-label randomized single centre	6 months	55	Atorvastatin 20 mg vs. Pravastatin 20 mg vs. Usual care	Δ Atheroma volume (%): +2, <i>P</i> = ns vs. baseline +1, <i>P</i> = ns vs. baseline 0, <i>P</i> = ns vs. baseline (+IVUS-backscatter endpoints)
ASTEROID ²¹	2006	Open-label blinded endpoints trial multicentre	24 months	349	Rosuvastatin 40 mg	Δ Atheroma volume (%): -0.98 ± 3.15, <i>P</i> < 0.001 vs. baseline
ACTIVATE ²²	2006	Randomized placebo-controlled multicentre	18 months	408	Pactimibe vs. Placebo	Δ Atheroma Volume (%): +0.59 ± 0.25 vs. +0.69 ± 0.25, <i>P</i> = 0.77
ILLUSTRATE ²³	2007	Randomized placebo-controlled multicentre	24 months	910	Atorvastatin monotherapy vs. Atorvastatin + Torcetrapib	Δ Atheroma volume (%): +0.19 ± 2.83 vs. +0.12 ± 2.99, <i>P</i> = 0.72
ERASE ²⁴	2007	Randomized placebo-controlled multicentre	6 weeks	136	Reconstituted HDL (CSL-111) infusion vs. Placebo (saline)	Δ Atheroma volume (%): -3.41 (IQR -6.55 to 1.88) vs. -1.62 (IQR -5.95 to 1.94), <i>P</i> = 0.48 (+Plaque characterization index endpoints)
STRADIVARIUS ²⁷	2008	Randomized placebo-controlled multicentre	18 months	676	Rimonabant vs. Placebo	Δ Atheroma volume (%): +0.25 (95% CI -0.04 to 0.54) vs. +0.51 (95% CI 0.22–0.80), <i>P</i> = 0.22
PERISCOPE ²⁸	2008	Randomized multicentre	18 months	360	Glimepiride vs. Pioglitazone	Δ Atheroma volume (%): +0.73 (95% CI 0.33–1.12) vs. -0.16 (95% CI -0.57–0.25), <i>P</i> = 0.002
IBIS-2 ²⁹	2008	Randomized placebo-controlled multicentre	12 months	239	Darapladib vs. Placebo	Δ Atheroma volume (mm ³): -5.0 ± 28.0 vs. -4.9 ± 32.7, <i>P</i> = 0.95 Δ Necrotic core volume (mm ³): -0.5 ± 13.9 vs. +4.5 ± 17.9, <i>P</i> = 0.012 (+Palpography endpoints)
ENCORE-II ³⁰	2009	Randomized placebo-controlled single centre	24 months	193	Nifedipine vs. Placebo	Δ Atheroma volume (%) +5.0 (95% CI -1.3 to 11.2) vs. +3.2 (95% CI -1.9 to 8.2), <i>P</i> = 0.66 (+Endothelial function test endpoints)

^aWith IVUS follow-up data; Δ, changes.

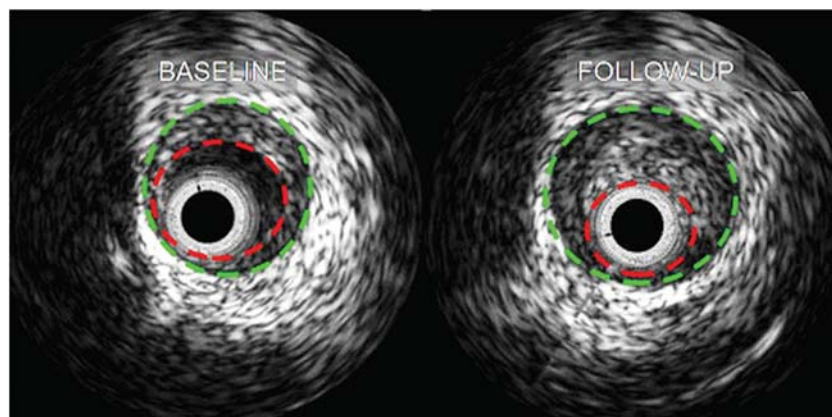


Figure 1 Serial IVUS assessment of coronary atherosclerosis progression.

LDL-cholesterol and IVUS plaque progression

A relation between low-density lipoprotein (LDL) cholesterol levels *in vivo* and the postmortem extent of coronary atherosclerosis was established by histopathological studies that were—by nature—studies at a single point in time.³¹ Angiographic studies of progression-regression of coronary atherosclerosis were limited by the fact (i) that angiography showed the opacified silhouette of the lumen only and (ii) that the variability of vascular remodelling prevented any reliable prediction of the dimensions of plaques that form the basis of lumen narrowing. Using coronary calcium scoring as an indirect measure of atherosclerotic burden, serial electron beam tomography examinations showed in 2002 that lipid-lowering therapy significantly decreased the progression of coronary calcification.³²

Nevertheless, the relation between LDL-cholesterol levels and the progressive enlargement of coronary plaques was not demonstrated until 2003.^{33,34} In that observational study with IVUS cross-sectional area measurements at baseline and 18 ± 9 months of follow-up, 60 patients treated by usual care including statins showed a direct linear relation between LDL-cholesterol levels and changes of plaque area in the left main stem. Despite some methodological limitations, this study suggested that an LDL-cholesterol value of 75 mg/dL could be the threshold below which—for the entire patient population assessed—no increase of atherosclerotic plaque dimensions may occur (Figure 2).^{33,34}

Modification of lipid profile by statins and IVUS plaque progression

Subsequently, two large-scale pharmacological intervention trials with serial volumetric IVUS were published, studying the effect of statin therapy on coronary plaque progression-regression (Figure 2).^{16,21} The *Reversal of Atherosclerosis with Aggressive Lipid Lowering* (REVERSAL) trial tested in a prospective, randomized

manner the effect of 18 months of intensive vs. moderate lipid-lowering therapy on coronary plaque progression.¹⁶ The REVERSAL trial demonstrated that atorvastatin (80 mg) treatment to a mean LDL-cholesterol level of 78 mg/dL stopped progression of plaque volume.¹⁶ Our serial cross-sectional IVUS data and the volumetric IVUS data of the REVERSAL trial are in good agreement with clinical trials that found an additional effect of intensive cholesterol-lowering therapy in high-risk patients.^{35,36} Several smaller pharmacological intervention studies confirmed the impact of LDL-cholesterol lowering with statins on plaque progression as assessed with serial IVUS.^{12,14,15}

In 2006, the *Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden* (ASTEROID) demonstrated for the first time that very high-intensity statin therapy with 40 mg rosuvastatin to a mean LDL-cholesterol level of 60.8 mg/dL resulted in significant regression of atherosclerotic plaque volume as assessed with serial IVUS.²¹ However, the ASTEROID trial had no control group.²¹ Therefore, the ongoing *Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin vs. Atorvastatin* (SATURN) compares the two statins in a randomized double blind multicentre design.³⁷

Non-statin modification of lipid profile and IVUS plaque progression

Besides statins, other novel cholesterol modifying agents have been evaluated in serial IVUS studies.^{17,22,23} Cholesterol esterification by the enzyme acyl-coenzyme-A cholesterol acyltransferase (ACAT) plays an important role in atherosclerotic plaque formation; inhibition of ACAT may therefore influence atherosclerosis progression.²² However, two serial IVUS studies showed no significant difference in plaque progression between patients treated with ACAT inhibitors vs. placebo.^{17,22} This is an example of how negative serial IVUS studies avoided further large-scale clinical endpoint trials in drug-development programmes. However, additional outcome-driven trials may be necessary to

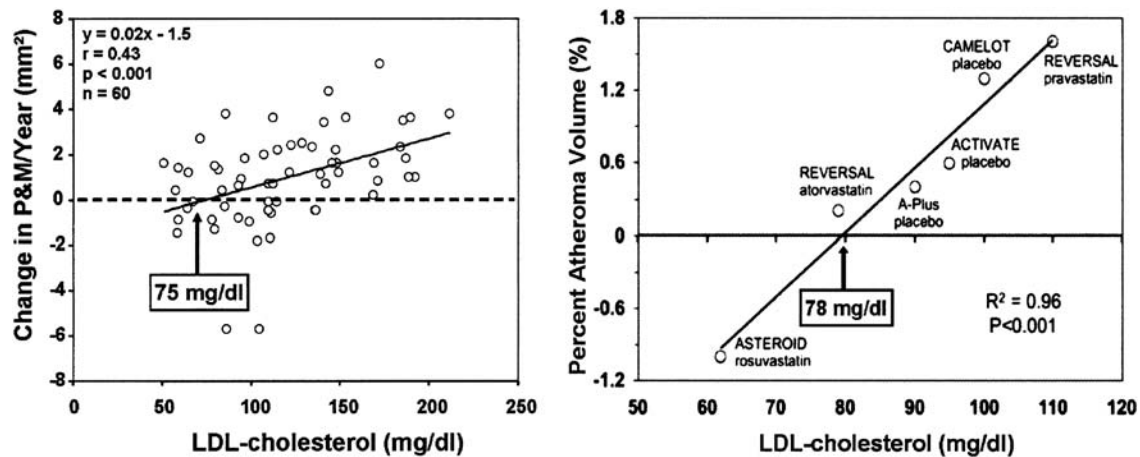


Figure 2 Low-density lipoprotein (LDL) cholesterol vs. coronary plaque progression—regression as assessed with serial intravascular ultrasound (image reproduced with permission from⁵). Demonstration of the positive significant relation between coronary plaque cross-sectional area progression and LDL-cholesterol levels in a first observational study (left graph, modified from³³). Relation between LDL-cholesterol and mean change in coronary atheroma volume by data derived from several large multicentre trials (right graph, modified from²¹). Of note, as IVUS is unable to distinguish between plaque (atheroma) and media, plaque measurements actually represent plaque + media.

clearly show effects on morbidity and mortality. Our above-mentioned observational study suggested a significant negative linear relation between high-density lipoprotein (HDL) cholesterol and atherosclerotic plaque progression; low HDL-cholesterol was on average associated with greater plaque progression.³³ A small, randomized serial IVUS trial suggested that 5-week infusions of a HDL-mimic drug (Apo-A1 Milano) induced significant regression of plaque volume in patients with acute coronary syndrome.¹³ A larger randomized, multicentre, serial IVUS trial found no significant regression of coronary atherosclerosis in response to infusions of another HDL-mimetic drug.²⁴ Other novel cardiovascular drugs, such as the cholesteryl-ester-transfer-protein-inhibitor torcetrapib achieved a substantial increase in HDL-cholesterol levels, but no significant decrease in coronary plaque progression as determined with serial IVUS.²³ The lack of efficacy of this drug may be related either to its mechanism of action or to specific adverse effects, such as an increase in arterial hypertension.²³ Nevertheless, therapeutic increase in HDL-cholesterol remains a valid target of preventive medicine and further research on how to achieve this goal is certainly warranted.³⁸

Metabolic regulation and IVUS plaque progression

Using serial IVUS, the *Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes* (PERISCOPE) trial compared pioglitazone vs. glimepiride during 18 months of treatment with regard to their effect on plaque progression—regression.²⁸ Patients on the insulin-sensitizer pioglitazone showed no further plaque progression while glimepiride-treated patients had unequivocal progression of atherosclerosis (change in percent plaque volume; $P = 0.002$).²⁸

Another trial that investigated the effect of improving metabolic regulation on coronary plaque progression was the *Strategy to*

Reduce Atherosclerosis Development Involving Administration of Rimobant—The Intravascular Ultrasound Study (STRADIVARIUS).²⁷ This randomized, double-blinded, placebo-controlled trial investigated the effect of the selective cannabinoid type-1 receptor antagonist rimobant (that has positive metabolic effects in obese patients with metabolic syndrome) on coronary arterial progression—regression in patients with abdominal obesity, metabolic syndrome, and coronary atherosclerosis.²⁷ After 18 months rimobant failed to show an effect on changes in percent plaque volume ($P = 0.22$), the primary endpoint, but showed a favourable effect on changes in total atheroma volume ($P = 0.03$), a secondary endpoint.²⁷ However, to date the drug has been withdrawn because of concerns over the risk of psychiatric disorders.

Antihypertensive treatment and IVUS plaque progression

Serial IVUS studies have also been used to investigate potential effects of antihypertensive drugs on coronary plaque progression—regression. In the *Norvasc for Regression of Manifest Atherosclerotic Lesions by Intravascular Sonographic Evaluation* (NORMALISE) substudy of the *Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis* (CAMELOT) trial, 274 patients were examined with serial IVUS during a follow-up interval of 20 months.¹⁸ Compared with baseline, IVUS showed progression in the placebo group ($P < 0.001$), a trend towards progression in the enalapril group ($P = 0.08$), and no progression in the amlodipine group ($P = 0.31$).¹⁸ In a pooled analysis of several IVUS trials ($n = 1115$, follow-up 18–24 months), Sipahi et al²⁶ demonstrated that beta-blocker treatment can slow progression of coronary atherosclerosis (change in atheroma volume: $-2.4 \pm 0.5 \text{ mm}^3/\text{year}$ in treated patients vs. $-0.4 \pm 0.8 \text{ mm}^3/\text{year}$ in untreated patients; $P = 0.034$). A randomized study on the *Effect*

of Nifedipine on Coronary Endothelial Function and Plaque Formation in Patients with Coronary Artery Disease (ENCORE II) demonstrated that calcium channel blockade with nifedipine improved coronary endothelial function on top of statin treatment, but did not show an effect of nifedipine on plaque volume.³⁰

Potential of plaque progression by serial IVUS as surrogate marker of cardiovascular risk

The assessment of morbidity and mortality as primary endpoints in conventional large-scale clinical trials of established and novel agents is associated with a substantial financial burden.^{2–5} Complementary surrogate imaging endpoint studies may allow smaller study sample size and shorter study duration to expedite the process of drug development and testing to evaluate the potential benefits of novel anti-atherosclerotic drugs much before necessary clinical endpoint data are available—an approach that may reduce cost and inefficient (or even harmful) treatment. However, an important pre-requisite of complementary surrogate endpoint studies is evidence that the surrogate endpoint (i.e. imaging) reflects clinical outcome: in the case of coronary atherosclerosis, this is cardiovascular events. Quantitative coronary angiographic studies have shown that progressive obstruction of the coronary lumen (i.e. indirect evidence of plaque progression) is associated with an increased risk of adverse cardiovascular events.^{39–41} Therefore, it may be extrapolated that plaque progression, as quantified with serial IVUS (i.e. direct evidence of plaque progression) should show (a similar or even) stronger association with cardiovascular event risk. In the absence of a clear proof by a randomized study that directly address this question, there is evidence from several IVUS studies that supports this thesis.⁵

First, in a non-serial IVUS study by Ricciardi *et al.*⁴² angiographically silent atherosclerosis of the left main coronary artery as detected by IVUS was an independent predictor of future adverse cardiac events. In 102 studied patients, major adverse cardiac events occurred in 38% during a follow-up of 29 months; by multivariate analysis only IVUS assessed minimum lumen area and diabetes mellitus were independent significant predictors of these events.⁴²

Second, data obtained by our group suggested that plaque progression as measured by IVUS was associated with a significantly increased risk of clinical events as predicted by established risk scores.⁴³ During follow-up of that small observational study, actual adverse cardiovascular events occurred predominantly in patients with the greatest rate of plaque progression ($P < 0.001$, Figure 3).⁴³

Third, large prospective trials have also provided evidence that supports this hypothesis. In pharmacological intervention trials with clinical endpoints, IVUS was used in subgroups as a secondary endpoint to assess changes in atherosclerotic plaque dimensions.^{18,25} A trial evaluating intensive antihypertensive therapy with amlodipine reported concordant reduction in adverse clinical cardiovascular events and reduced coronary plaque progression as assessed with serial IVUS.¹⁸ Patients with coronary artery disease and normal blood pressure ($n = 1991$) were randomized to

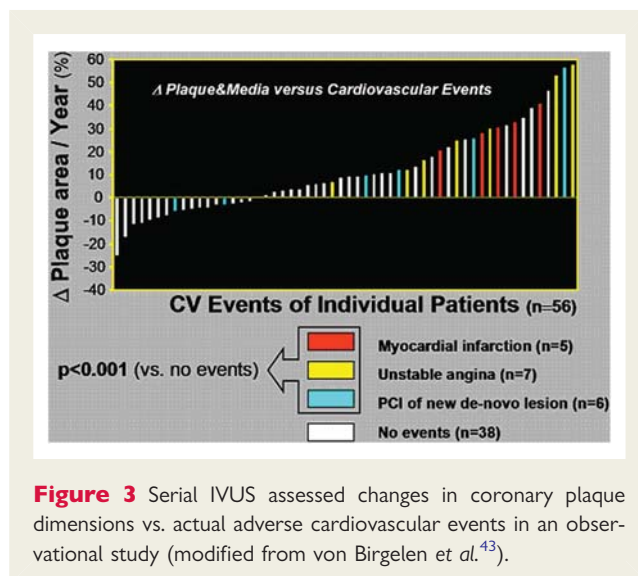


Figure 3 Serial IVUS assessed changes in coronary plaque dimensions vs. actual adverse cardiovascular events in an observational study (modified from von Birgelen *et al.*⁴³).

receive either 10 mg amlodipine, 20 mg enalapril, or placebo. The cardiovascular event-rate was significantly lower in amlodipine-treated patients compared with placebo-treated patients (16.6 vs. 23.1%, $P = 0.003$), while it did not differ significantly between enalapril-treated patients and placebo group (20.3 vs. 23.1%, $P = 0.16$).¹⁸ A subgroup of these patients ($n = 274$) had serial IVUS with a follow-up after 2 years. In parallel with the clinical endpoints, there was no change in plaque volume in the amlodipine group ($P = 0.31$), while plaque volume increased non-significantly in the enalapril group ($P = 0.08$) and significantly in the placebo group ($P < 0.001$).¹⁸

Finally, the REVERSAL study used the same treatment regimen as the clinical *Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) trial*, which reported a significantly greater reduction in cardiovascular events in patients with acute coronary syndromes after treatment with 80 mg/day atorvastatin for 2 years.^{16,36} REVERSAL and PROVE IT were distinct studies, but when considered together their results provide inferential evidence that atherosclerotic progression measured by IVUS may be predictive of an increased risk of cardiovascular events.^{16,36}

Serial IVUS assessment of plaque composition

Both, progression of the size of the atherosclerotic plaque and its unfavourable tissue composition contribute to the risk of cardiovascular events.^{39–41,44–46} As outlined above, progression–regression studies with serial IVUS reported a beneficial effect of anti-atherosclerotic pharmacological therapies on the progression of atherosclerotic plaque size—a geometrical measure.^{12–16,18,21,26–28} However, there appears to be a discordance between the highly significant clinical benefit of certain pharmacological interventions and their quite limited effect on plaque size that perhaps could be explained by a stabilizing effect on plaque composition.^{5,12,19,20,24}

Schartl *et al.*¹³ used a straightforward computer-aided grey-scale IVUS analysis method to detect changes of plaque echogenicity that

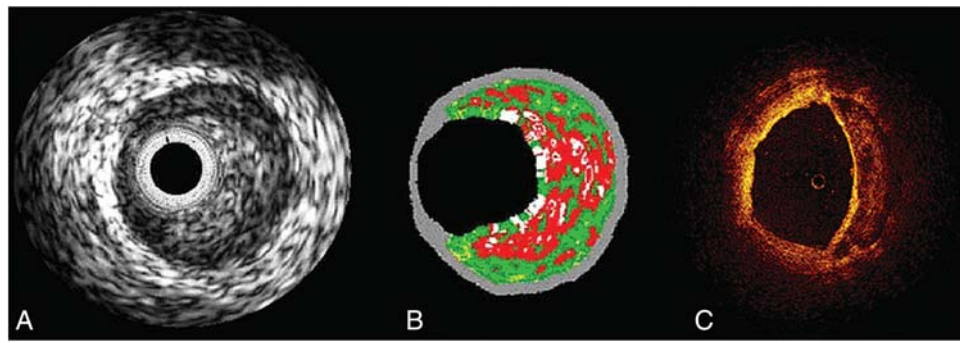


Figure 4 Technical progress may lead to the development of imaging catheters which may integrate grey-scale IVUS (A), radiofrequency-based IVUS (B), and optical coherence tomography (C, not the same plaque as in A or B).

may reflect plaque composition. Lipid-lowering to LDL-cholesterol levels below 100 mg/dL with atorvastatin (compared with usual care) led to a significantly larger increase in plaque hyperechogenicity which was thought to reflect an increase in fibrous tissue indicating plaque stabilization.¹³ Conventional grey-scale IVUS (Figure 4A) permits accurate geometric quantification of lumen and plaque dimensions, but it has significant limitations in the assessment of plaque composition.^{4–7,47,48} Therefore, spectral analysis of IVUS radiofrequency (RF) data has been developed (Figure 4B) that quantifies coronary plaque components (e.g. the necrotic core) with a high predictive accuracy as demonstrated *in vitro* and *in vivo*.^{47–50} Non-serial RF-IVUS studies provided interesting insights in the pathology of coronary atherosclerosis and demonstrated the ability to detect features of plaque vulnerability (e.g. necrotic core and thin-capped fibro-atheromas) in patients with unstable clinical presentation.^{51–53} Given its relatively good measurement reproducibility,^{54,55} RF-IVUS seems to be a suitable image modality for the serial assessment of plaque composition during pharmacological interventions.^{19,20,29} Kawasaki *et al.*²⁰ demonstrated plaque stabilization (decrease in necrotic and increase in fibrous tissue) with statin therapy in a serial RF-IVUS study. Recently, the first multicentre, randomized, placebo-controlled pharmacological intervention trial *Integrated Biomarker And Imaging Study-2* (IBIS-2) used changes of RF-IVUS-derived volumetric data as an endpoint to test the effect of inhibition of the enzyme lipoprotein-associated phospholipase-A₂ with darapladib on plaque geometry and composition.²⁹ In addition, serial palpography—an IVUS method that assesses the local mechanical properties of plaque tissue based on deformation caused by the intraluminal pressure—was used to assess changes in local plaque strain (high-strain regions at the lumen–plaque interface had a high predictive value for the detection of vulnerable plaques).^{29,56} There was no significant difference in changes in plaque strain between groups, but the RF-IVUS data showed that the necrotic core volume—a key determinant of plaque vulnerability—continued to increase among patients receiving placebo while this was not the case in patients with darapladib treatment.²⁹

Specific RF-IVUS plaque characteristics are related to known risk factors of sudden cardiac death.⁵⁷ Nevertheless, the relation between serial changes of plaque composition as assessed with RF-IVUS and clinical endpoints has still to be demonstrated.^{47,48,58}

The natural history study *Providing Regional Observations to Study Predictors of Events in the Coronary Tree* (PROSPECT) found a relation between some RF-IVUS plaque characteristics and subsequent cardiac events, which may in the future potentially help to identify high-risk patients before adverse cardiac events occur.⁵⁸ Histopathological studies demonstrate that vulnerable plaques are generally characterized by a necrotic core and a thin fibrous cap (cap thickness <65 μm).^{44–46} RF-IVUS can visualize and measure the necrotic core, but is unable to visualize such a thin fibrous cap because of its image resolution of approximately 100 μm .^{47,48} Nevertheless, that thin fibrous cap is a defining feature of plaques 'prone to rupture'.^{44–46} Optical coherence tomography (OCT, Figure 4C) provides images of intimal structures including the accurate visualization of thin fibrous caps (resolution approximately 10 μm).^{59–61} For instance, serial OCT imaging demonstrated a significant increase in fibrous cap thickness during statin therapy.⁶¹ However, OCT is unable to reliably detect a large and deep necrotic core, because its penetrance is limited.^{11,60} Recently, Sawada *et al.*⁶⁰ demonstrated a more effective detection of vulnerable plaques by combined use of the two complementary imaging modalities: OCT plus IVUS.

Serial IVUS investigation of coronary vessel remodelling

Arterial remodelling, as first described by Glagov *et al.*,⁶² describes characteristic changes of arterial size during plaque progression–regression. Expansive arterial remodelling is defined as an increase in vessel size during progression and is associated with inflammation, and unstable clinical presentation.^{63–66} Based on these observations, expansive remodelling is recognized as a characteristic of unstable-vulnerable lesions. These findings have generated the hypothesis that plaque stabilizing, pharmacological intervention may be associated with constrictive remodelling. Serial IVUS observations confirmed a broad spectrum of remodelling responses in mild-to-moderate atherosclerotic coronary lesions by assessing changes of the total vessel size over time.^{67–69}

Reanalysis of serial IVUS data from trials that tested the effect of anti-atherosclerotic drugs on plaque size (progression–regression)

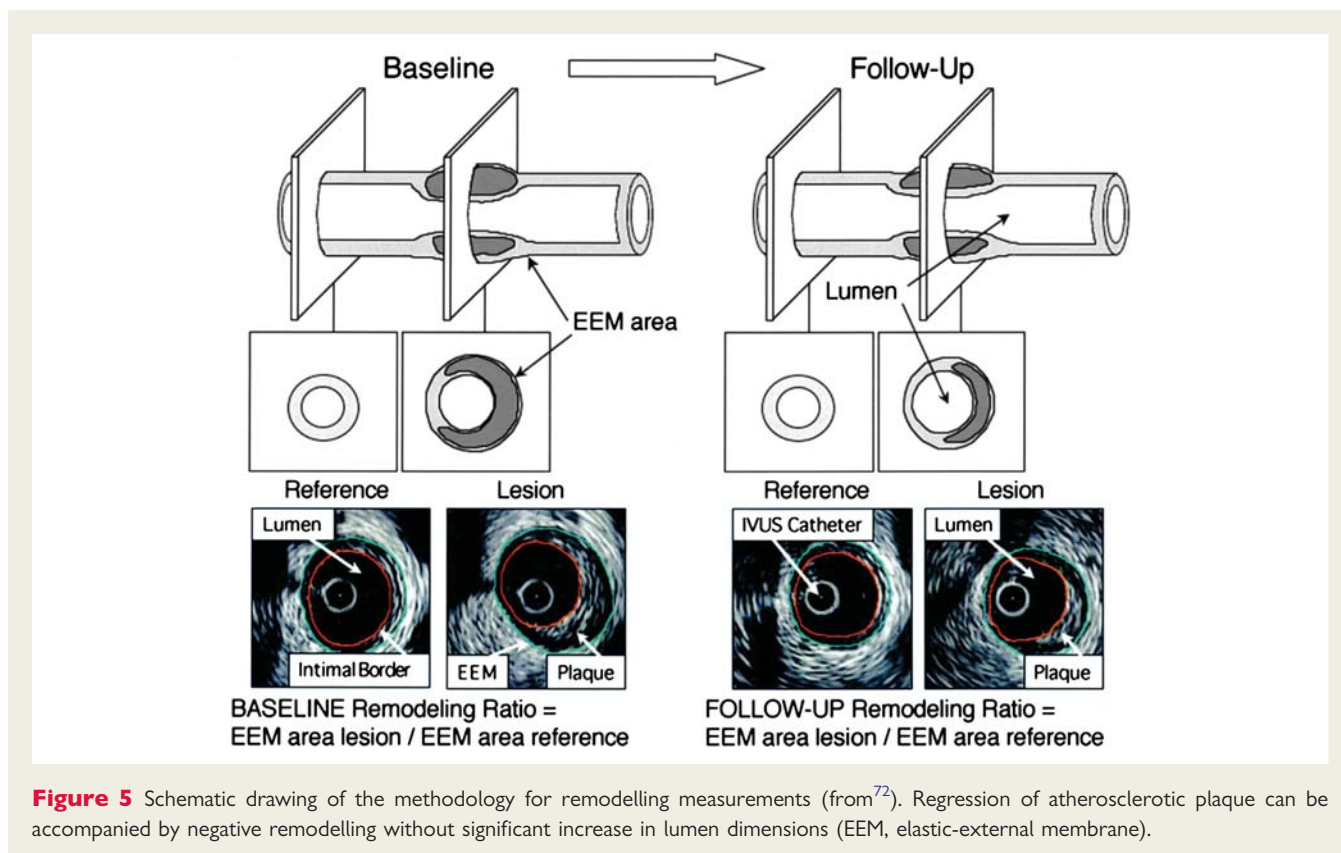


Figure 5 Schematic drawing of the methodology for remodelling measurements (from⁷²). Regression of atherosclerotic plaque can be accompanied by negative remodelling without significant increase in lumen dimensions (EEM, elastic-external membrane).

revealed interesting insights into the serial remodelling behaviour during pharmacological intervention.^{70–74} Schoenhagen *et al.*⁷² observed negative remodelling of the coronary vessel wall during plaque stabilizing therapy with statins that appeared to be related to their anti-inflammatory effects (Figure 5). Schartl *et al.*⁷⁰ showed that the positive remodelling process is diminished in patients with plaque progression despite intense lipid-lowering therapy. Based on their serial IVUS findings, Tardif *et al.*⁷¹ concluded that regression of atherosclerotic plaque is generally accompanied by negative remodelling without an increase in lumen dimensions ('reverse vascular remodelling'). Rodriguez-Granillo *et al.*⁷⁴ reported arterial remodelling data from an imaging substudy of the EUROPA study, which demonstrated that the angiotensin-converting enzyme inhibitor perindopril reduced clinical events in patients with stable coronary artery disease. Imaging sub-studies, found no effect on angiographic luminal diameter or plaque burden assessed by IVUS.²⁵ In contrast there was more frequent constrictive remodelling during follow-up.⁷⁴

These data demonstrate that, beside the reduction in plaque size (regression), a shift of the remodelling pattern towards negative remodelling may be considered as a sign of plaque stabilization.^{70–74} However, the role of the remodelling state or behaviour as an independent complementary surrogate endpoint in serial IVUS trials has not yet been defined.⁷⁵

Conclusion

As the global burden of cardiovascular disease increases, there is need for complementary surrogate endpoints to maximize efficacy

in the evaluation of new anti-atherosclerotic therapies.^{4,5,76} Most coronary events are associated with complex interaction between both progression of plaque size and changes of atheroma composition.^{39–41,44–46} As current non-invasive imaging techniques still have significant limitations for the serial assessment of coronary atherosclerosis, invasive imaging with IVUS remains for the time being the gold standard.^{11,76} RF-based IVUS analysis permits quantitative assessment of atherosclerotic plaque composition. As a consequence, serial RF-IVUS data are increasingly incorporated in pharmacological intervention trials.^{19,20,29,47,48} The development of a single image catheter that permits simultaneous imaging with both IVUS (including RF-analysis) and OCT during a single pullback is currently underway. In the future, such technical advances will provide additional insights into the natural history of coronary atherosclerosis and may allow further improvement of complementary surrogate endpoints for trials that aim at further reduction in cardiovascular morbidity and/or mortality.

Conflict of interest: G.S.M. has acted as a consultant for Volcano and Boston Scientific and received grants and honoraria from both. The other authors reported no conflict.

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