Imaging

Imaging of coronary atherosclerosis: intravascular ultrasound

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Atherosclerosis is the main cause of coronary heart disease, which is today the leading cause of death worldwide and will continue to be the first in the world in 2030. In the formation of atherosclerotic coronary lesions, a critical primary step is the accumulation and oxidation of low-density lipoprotein (LDL) particles. Oxidized-LDL favours leucocyte recruitment and their activation, as well as cell death. This leads to generation of complex atherosclerotic plaques. These plaques have a high content of necrotic core, a thin inflamed fibrous cap (intense accumulation of macrophages) and scarce presence of smooth muscle cells (i.e. thin-capped fibroatheroma). At early stages of the formation of the atheroma, the remodelling of the vessel wall usually prevents plaque from encroaching on the lumen, thereby masking the presence of atheroma on angiography. In contrast, greyscale intravascular ultrasound can fully assess the extension of the disease axially and longitudinally. This intravascular imaging technique has played a vital role in advancing our understanding of the pathophysiology of coronary artery disease, and in the development of novel cardiovascular drugs and device therapies. This intravascular imaging technology and its clinical and research applications are discussed in more detail below.

Keywords Atherosclerosis • Imaging • Intravascular ultrasound

Background

Coronary angiography depicts arteries as a planar silhouette of the contrast-filled lumen. Importantly, angiography does not provide visualization of the vessel wall and is not suitable for assessment of atherosclerosis. Angiographic disease assessment is based on the comparison of the stenotic segment with the adjacent, ‘normal-appearing’ coronary, which is often an incorrect assumption due to the diffuse nature of atherosclerosis as shown by pathological and intravascular ultrasound (IVUS) studies1,2 (Figure 1).

Intravascular ultrasound

Imaging formation

The IVUS image is the result of reflected ultrasound waves that are converted to electrical signals and sent to an external processing system for amplification, filtering, and scan conversion. Greyscale IVUS imaging is formed by the envelope (amplitude) of the radio-frequency signal (Figure 2).

More recently, autoregressive spectral analysis of IVUS backscattered data has been incorporated into conventional IVUS systems to facilitate image interpretation of different tissue components. The first commercially available IVUS backscattering image analysis, named virtual histology™ (IVUS-VH), was built on the electronic 20 MHz IVUS platform. In contrast iMAP is an imaging modality for atherosclerotic plaque tissue characterization based on pattern recognition³ and integrated backscattered (IB) IVUS values are calculated as the average power, measured in decibels, of the ultrasound signal backscattered using a fast Fourier transformation⁴ (Figure 2). Lately, a rotational mechanical 45 MHz IVUS system has also integrated the classification tree for virtual histology tissue characterization (Figure 3).

Another approach is to assess the deformability of coronary plaque using also the analysis of radiofrequency signals at different diastolic pressure levels using palpography. This allows the construction of a ‘strain’ image, in which harder (low strain) and softer (high strain) regions of the coronary arteries can be identified, with radial strain values ranging between 0 and 2% (Figure 2). High strain regions have been associated with a necrotic core rich and inflamed plaques.⁵

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Catheter designs

The IVUS equipment consists of a catheter incorporating a miniaturized transducer and a console to reconstruct and display the image (Figure 4). Current catheters range from 2.6 to 3.2 French in size and can be introduced through conventional 6-French guide catheters. Rotational, mechanical IVUS probes rotate a single piezoelectric transducer at 1800 r.p.m. and operate at frequencies between 30 and 45 MHz while electronic phased-array systems operate at a centre-frequency of \( \approx 20 \) MHz. Higher ultrasound frequencies are associated with better image resolution; but increasing the frequency beyond 45 MHz has been limited because of decreased tissue penetration.\(^6,7\) Electronic systems have up to 64 transducer elements in an annular array that are activated sequentially to generate the cross-sectional image. In general, electronic catheter designs are slightly easier to set up and use, whereas mechanical probes offer superior image quality. Electronic IVUS catheters have the ability to display blood flow in colour to facilitate distinction between lumen and wall boundaries.

Combined intravascular imaging catheters

Another imaging modality able to characterize coronary atherosclerosis (i.e. lipid core) invasively is NIR spectroscopy (NIRS).\(^8\) To this aim, the 3.2F FDA-approved near infrared spectroscopy catheter is used. This catheter is compatible with a conventional 0.014” guidewire, contains a rotating (240 Hz) NIRS light source at its tip, and is pulled back by a motor drive unit at 0.5 mm/s.\(^9\) A newer catheter has been introduced. The 3.2F rapid exchange Apollo catheter combines a 40 MHz real-time IVUS catheter with a standard NIRS catheter (Figure 5). In the SPECTACL (SPEC-Troscopic Assessment of Coronary Lipid) trial, which was a parallel first-in-human multicentre study designed to demonstrate the
applicability of the lipid core plaques detection algorithm in 106 living patients, it has been confirmed that the intravascular NIRS system safely obtained spectral data in patients that were similar to those from autopsy specimens.\(^\text{10}\) Currently, an observational study of cholesterol in coronary arteries (COLOR registry, NCT00831116) is aimed at enrolling \(\approx 1000\) patients in 14 centres in the USA. In Europe, this imaging modality is being used in the IBIS 3 trial which is a study that will be able to assess the effects of rosuvastatin on the content of necrotic core (IVUS-VH) and lipid-containing regions (NIR spectroscopy) at 52 weeks.

**Figure 2** Intravascular ultrasound signal is obtained from the vessel wall (A). Greyscale intravascular ultrasound imaging is formed by the envelope (amplitude) (B) of the radiofrequency signal (C). By greyscale, atherosclerotic plaque can be classified into four categories: soft, fibrotic, calcified, and mixed plaques. (D) Shows a cross-sectional view of a greyscale image. The blue lines limit the actual atheroma. The frequency and power of the signal commonly differ between tissues, regardless of similarities in the amplitude. From the backscatter radiofrequency data different types of information can be retrieved: virtual histology (E), palpography (F), integrated backscattered (IB) intravascular ultrasound (G), and iMAP (H). Virtual histology is able to detect four tissue types: necrotic core, fibrous, fibrofatty, and dense calcium. Plaque deformability at palpography is reported in strain values, which are subsequently categorized into four grades according to the ROTterdam Classification (ROC). The tissues characterized by integrated backscattered (IB) intravascular ultrasound are lipidic, fibrous, and calcified; and iMAP detects fibrotic, lipidic, necrotic, and calcified.

**Characterization of atherosclerosis**

**Atheroma: pathological insights**

A detailed description of atherosclerosis development and composition is beyond the scope of this review. Nevertheless, we highlight here some important concepts that will support the use of tissue characterization imaging modalities for plaque typification.

In brief, an atheroma is formed by an intricate sequence of events, not necessarily in a linear chronologic order, that involves...
extracellular lipid accumulation, endothelial dysfunction, leucocyte recruitment, intracellular lipid accumulation (foam cells), smooth muscle cell migration and proliferation, expansion of extracellular matrix, neangiogenesis, tissue necrosis, and mineralization at later stages. The ultimate characteristic of an atherosclerotic plaque at any given time depends on the relative contribution of each of these features. Thus, in histological cross-sections, the pathologic intimal thickening is rich in proteoglycans and lipid pools, but no trace of necrotic core is seen. The earliest lesion with a necrotic core is the fibroatheroma (FA), and this is the precursor lesion that may give rise to symptomatic heart disease. Thin-capped fibroatheroma (TCFA) is a lesion characterized by a large necrotic core containing numerous cholesterol clefts. The overlying fibrous cap is thin and rich in inflammatory cells, macrophages, and T lymphocytes with a few smooth muscle cells.

Atheroma: linking pathology concepts and intracoronary imaging

Figure 6 outlines the virtual histology plaque and lesion types that are proposed based on the previous paragraph which describes pathologic data.

On the basis of tissue echogenicity (i.e. their appearance), not necessarily histological composition, atheromas have been classified in four categories by greyscale IVUS: (i) soft plaque (lesion echogenicity less than the surrounding adventitia), (ii) fibrous plaque (intermediate echogenicity between soft (echolucent) atheromas and highly echogenic calcified plaques), (iii) calcified plaque (echogenicity higher than the adventitia with acoustic shadowing), and (iv) mixed plaques (no single acoustical subtype represents >80% of the plaque) (Figure 1).

Description of the validation against pathology of the IVUS greyscale and the IVUS-based imaging modalities for plaque characterization is beyond the scope of this review. All available validation reports are to be found in the list of references.

Detection of calcification

The presence, depth and circumferential distribution of calcification are important factors not only for selecting the type of interventional device and estimating the risk of vessel dissection and perforation during PCI, but also in designing and conducting studies on progression/regression of coronary atheroma. Plaques with moderate to severe calcification showed no change or progression of atheroma size. Thus, careful selection of coronary segments to evaluate the effect of drugs on coronary atherosclerosis should be considered.

On IVUS, calcium appears as bright echoes that obstruct the penetration of ultrasound (acoustic shadowing) (Figure 1C). Therefore, IVUS detects only the leading edge of calcium and cannot determine its thickness. Using greyscale IVUS, a three-dimensional and quantitative analysis of atherosclerotic plaque composition by automated differential echogenicity has been developed to facilitate automatic detection of calcified areas.

Virtual histology, in comparison with histology, has a predictive accuracy of 96.7% for detection of dense calcium.

Coronary remodelling

Coronary remodelling refers to a continuous process involving changes in vessel size measured by the external elastic membrane (EEM) cross-sectional area (also called vessel cross-sectional area—CSA). ‘Positive remodelling’ occurs when there is an outward increase in EEM. ‘Negative remodelling’ occurs when the EEM decreases in size (shrinkage of the vessel). The magnitude and direction of remodelling can be expressed by the following index: EEM CSA at the plaque site divided by EEM CSA at the reference ‘non-diseased’ vessel. Positive remodelling will demonstrate an index >1.0, while negative remodelling has an index <1.0. Direct evidence of remodelling can only be demonstrated in serial studies showing changes in the EEM CSA over time, since remodelling may also be encountered at the ‘normal-appearing’ reference coronary segment.

Pathological studies have also suggested a relationship between positive vessel remodelling and plaque vulnerability. Vessel with positive remodelling showed increased inflammatory marker concentrations, larger lipid cores, paucity of smooth muscle cells, and medial thinning. Several IVUS studies have linked positive vessel remodelling with culprit and ruptured coronary plaques. Positive remodelling has been observed more often in patients with acute coronary syndromes than in those with...
stable coronary artery disease (CAD),\textsuperscript{34,35} and has been identified as an independent predictor of major adverse cardiac events in patients with unstable angina.\textsuperscript{36} Plaques exhibiting positive remodelling also had more often thrombus and signs of rupture.\textsuperscript{37} The pattern of remodelling has also been correlated with plaque composition; soft plaques are associated with positive remodelling while fibrocalcific plaques more often have negative or constrictive remodelling.\textsuperscript{38} Similar findings have been observed in studies.

\textbf{Figure 4} Intravascular ultrasound systems. The console of the Boston Scientific is iLab® ultrasound imaging system (A) and the iCross\textsuperscript{TM} is the coronary imaging catheter (B). The Console of the Volcano's s5\textsuperscript{TM} ultrasound imaging system and the Eagle Eye\textsuperscript{TM} platinum coronary imaging catheter are shown in (C and D). (E and F) The console of the Terumo Corporation Visiwave and the IVUS catheter ViewIT are shown.
utilizing virtual histology; positive remodelling was directly correlated with the presence and the size of the necrotic core, and inversely associated with fibrotic tissue (Figure 7).

Vulnerable plaque and thrombi

Acute coronary syndromes are often the first manifestation of coronary atherosclerosis, making the identification of plaques at high risk of complication an important component of strategies to reduce casualties. Approximately 60% of clinically evident plaque ruptures originate within an inflamed TCFA.\(^{40,41}\)

Figure 5  Left anterior oblique view of the right coronary artery where the angiographic appearance of the Apollo catheter can be seen (A). The proximal near infrared spectroscopy (NIRS) optical core and distal ultrasound transducer (IVUS) are both clearly visible (B). A picture of the Apollo catheter tip indicating the relative positions to each other of the NIRS light source and IVUS probe (C). The combined intravascular ultrasound images and chemical information from a pullback through the right coronary artery obtained using the Apollo catheter. The chemogram obtained from the Apollo catheter pullback, with the stented area as indicated (D). The chemogram is a map of the measured probability of the lipid core plaque (LCP) from each scanned arterial segment; the yellow regions represent those with the highest probability for the presence of the LCP, while red regions represent those with the lowest. The chemogram displays the pullback position against the circumferential position of the measurement in degrees. The § represents a region of the coronary artery where insufficient NIRS signals were obtained to generate a chemogram. In this image the proximal end of the stent is located in an area with a high probability of the LCP (yellow). The block chemogram provides a summary of the raw data from the chemogram and displays the probability that an LCP is present for all measurements in a 2 mm block of coronary artery. The order of probability for the presence of the LCP from highest to lowest is yellow, light brown, brown, and red (E). The longitudinal IVUS pullback, with NIRS overlay (F). The lilac and blue lines mark the anatomical position on the IVUS, and the corresponding position on the chemogram during pullback, enabling simultaneous assessment of plaque structure and composition. (G) Shows a cross-sectional intravascular ultrasound image with the chemogram obtained from (D), demonstrating well opposed clearly identifiable stent struts (ss), highlighting the ability of the Apollo catheter to be used as a standalone IVUS catheter if required. The corresponding longitudinal IVUS image and chemogram is indicated by the lilac line on (D), (E), and (F). The chemogram indicates that there is a low probability of lipid present in the stented plaque. (H) A cross-sectional IVUS image distal to the stent demonstrates the presence of echolucent plaque between 1 and 7 o’clock. The chemogram displays a high probability of lipid in this plaque. The corresponding longitudinal IVUS image, and chemogram are indicated by the blue lines on (D), (E), and (F).

The definition of a VH-TCFA is a lesion fulfilling the following criteria in at least 3 frames: (i) plaque burden ≥ 40%; (ii) confluent necrotic core ≥ 10% in direct contact with the lumen (i.e. no visible overlying tissue).\(^{42}\) Using this definition of VH-TCFA, in patients with ACS who underwent IVUS of all three epicardial coronaries, on average, there were 2 VH-TCFA per patient with half of them showing outward remodelling.\(^{42}\)

Hong et al. reported the frequency and distribution of TCFA identified by virtual histology intravascular ultrasound in acute coronary syndrome (ACS = 105 patients) and stable angina pectoris (SAP = 107 patients) in a 3-vessel IVUS-VH study.\(^{43}\) There were
2.5 $\pm$ 1.5 in ACS and 1.7 $\pm$ 1.1 in SAP VH-TCFAs per patient, $P < 0.001$. Presentation of ACS was the only independent predictor for multiple VH-TCFA ($P = 0.011$). Eighty-three per cent of VH-TCFAs were located within 40 mm of the coronary.

The potential value of these VH IVUS-derived plaque types in the prediction of adverse coronary events was evaluated in an international multicentre prospective study, the Providing Regional Observations to Study Predictors of Events in the Coronary Tree study (PROSPECT study), which has been completed but not yet published.

Although plaque characteristics (i.e. tissue characterization) do not yet influence current therapeutic guidelines, the available clinical imaging modalities, IVUS and IVUS-based tissue characterization techniques such as virtual histology, integrated backscattered IVUS, and iMAP, have the ability to identify some of the pathological atheroma features described above and could help us to advance further our understanding on atherosclerosis

**Figure 2.**

**Figure 6** Virtual histology plaque types. FF, fibrofatty; FT, fibrous tissue; NC, necrotic core and DC, dense calcium.

Ruptured plaques may have a variable appearance in IVUS; the American College of Cardiology clinical expert consensus document recommended use of the following definitions: (i) Plaque ulceration: A recess in the plaque beginning at the luminal-intimal border, typically without enlargement of the EEM compared with the reference segment. (ii) Plaque rupture: plaque ulceration with a tear detected in a fibrous cap. Contrast injections may be used to prove and define the communication point.

The tear of the rupture (identified in $\sim 60\%$) occurs more often at the shoulder of the plaque than in the centre. $^{32,47,48}$ IVUS features of ruptured plaques are as follows: large in volume, eccentric, have mixed or soft composition and irregular surface, and are associated with positive vessel remodelling. $^{32,33,49,50}$ Ruptured plaques have less calcium, especially superficial calcium, but a larger number of small ($<90^\circ$ arc) calcium deposits, particularly deep calcium deposits.$^{51}$

Several IVUS studies have reported the frequency and distribution of ruptured plaques in the coronary arteries (Table 1).
Intravascular ultrasound has also been used to assess the natural evolution of ruptured plaques. Up to 50% of the ruptured plaques detected in a first ACS event heal with medical therapy, without significant change in plaque size. Another study revealed complete healing of plaque rupture in 29% of the patients treated with statins and incomplete healing in untreated patients.

Thrombus represents the ultimate pathological feature leading to ACS. Thrombus is usually recognized as an echolucent intraluminal mass, often with a layered or pedunculated appearance by IVUS. Fresh or acute thrombus may appear as an echodense intraluminal tissue, which does not follow the circular appearance of the vessel wall, while an older, more organized thrombus has a darker ultrasound appearance. However, none of these IVUS features are a hallmark for thrombus, and one should consider slow flow (fresh thrombus), air, stagnant contrast or black hole, an echolucent neointimal tissue observed after drug eluting stent and radiation therapy, as differential diagnoses. In addition, IVUS resolution is limited to precisely characterize thrombus. In a study in patients with acute myocardial infarction (AMI), intracoronary thrombus was observed in all cases by optical coherence tomography (OCT) and angioscopy but was identified in only 33% by IVUS.

**Clinical applications: diagnostic**

**Determination of severity and extent of atherosclerosis**

Determination of severity and extent of atherosclerosis remains one of the main diagnostic clinical applications of intravascular imaging, as angiography and non-invasive methods lack spatial or temporal resolution for accurate coronary disease assessment.

**Assessment of atheroma burden**

Quantification of atheroma or plaque area in cross-sectional IVUS images is performed by subtracting the lumen area from the EEM area. Hence, an IVUS-defined atheroma area is a combination of plaque plus media area. The atheroma area can be calculated in each frame (cross-sectional image), and total atheroma volume (TAV) can be calculated based on the pullback speed during imaging acquisition. Atheroma volume can be reported as the per cent of the volume of the EEM occupied by atheroma, namely per cent atheroma volume (PAV). Parameters commonly used to report the extent of the coronary atherosclerosis are shown in Figure 8.

![Figure 7](image-url)
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>IVUS/Other imaging modalities</th>
<th>Clinical presentation</th>
<th>n</th>
<th>Frequency/distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rioufol et al.</td>
<td>2002</td>
<td>IVUS</td>
<td>ACS</td>
<td>24</td>
<td>2 RP per patient and 12.5% of these patients had RP in the three major coronary arteries. Only 37.5% of the RP were located on the culprit lesion, and 79% of the patients had also an RP somewhere other than on the culprit lesion</td>
</tr>
<tr>
<td>Maehara et al.</td>
<td>2002</td>
<td>IVUS</td>
<td>SA/ACS</td>
<td>254</td>
<td>Multiple ruptures were observed in 39 of 254 patients (15%), 36 in the same artery.</td>
</tr>
<tr>
<td>Hong et al.</td>
<td>2004</td>
<td>IVUS</td>
<td>SA/AMI</td>
<td>235</td>
<td>(122 AMI and 113 SA) RP of infarct-related or target lesions occurred in 66% of AMI patients and in 27% of SA patients. Non-infarct-related or non-target artery RP occurred in 17% of AMI patients and 3% of SA patients. Multiple RP were observed in 20% AMI and 6% of SA patients</td>
</tr>
<tr>
<td>Tanaka et al.</td>
<td>2005</td>
<td>IVUS</td>
<td>AMI</td>
<td>45</td>
<td>RP was observed in 47% of patients at the culprit site and 17 additional RP were found at remote sites in 24% of patients</td>
</tr>
<tr>
<td>Hong et al.</td>
<td>2005</td>
<td>IVUS</td>
<td>SA/ACS</td>
<td>392</td>
<td>(231 ACS and 161 SA) 3-vessel IVUS imaging showed that RP occurred mainly in proximal segments of the LAD (83% of LAD RP), the proximal and distal segments of the RCA (48 and 32% of RCA RP, respectively), and the entire LCX</td>
</tr>
<tr>
<td>Tyczynski et al.</td>
<td>2005</td>
<td>IVUS</td>
<td>SA/ACS</td>
<td>16</td>
<td>(2 AMI, 13 UA and 1 SA) RP in the left main coronary artery (LMCA) were located in the distal portion and/or bifurcation of the LMCA (i.e. opposite to the flow divider) often did not compromise the lumen, and had an angiographic complex appearance</td>
</tr>
<tr>
<td>Pregowski et al.</td>
<td>2005</td>
<td>IVUS</td>
<td>SA/ACS</td>
<td>791</td>
<td>RP in saphenous vein grafts (SVGs) have a prevalence of 9.7%. These RP were found to be associated with complex angiographic characteristics and positive remodelling</td>
</tr>
<tr>
<td>Macias et al.</td>
<td>2006</td>
<td>IVUS</td>
<td>SA</td>
<td>104</td>
<td>patients with RP in the LAD; the majority were located within the proximal 30 mm of the artery</td>
</tr>
<tr>
<td>Rodriguez-Granillo et al.</td>
<td>2006</td>
<td>IVUS VH</td>
<td>SA/ACS</td>
<td>40</td>
<td>RP located in the left anterior descending were clustered in the proximal part of the vessel, whereas ruptures located in the right coronary artery were more distally located</td>
</tr>
<tr>
<td>Hong et al.</td>
<td>2008</td>
<td>IVUS VH</td>
<td>SA/ACS</td>
<td>212</td>
<td>(105 ACS and 107 SA) There were 76 RP (55 in ACS and 21 in SAP). 12 patients with ACS and 1 with SAP had multiple RP</td>
</tr>
<tr>
<td>Hong et al.</td>
<td>2010</td>
<td>IVUS</td>
<td>AMI</td>
<td>310</td>
<td>(125 STEMI and 185 NSTEMI patients) Culprit lesion PR, lipid-pool-like images, and thrombus were observed more frequently in patients with STEMI than in those with NSTEMI (46 vs. 29%, 39 vs. 25%, and 34 vs. 21%, respectively)</td>
</tr>
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</table>

IVUS, intravascular ultrasound; RP, ruptured plaque; ACS, acute coronary syndrome; SA, stable angina; AMI, acute myocardial infarction.
Research applications

Intravascular imaging has played an important role in the understanding of atherosclerosis disease in humans and translation of novel therapies to the clinical arena.

Cardiac allograft disease

Most clinical adverse events in transplant patients occur after 1 year. Cumulative incidence of cardiac events per patient year was 0.9% within the first year, increasing to 1.9% by 5 years. Cardiac events accounted for 38.8% of the deaths by the end of the first year, rising to 18% of total mortality by 7 years after heart transplantation. After the first year of transplantation, 36% (20/55) of the patients died because of sequelae of CAD.55 Death is usually silent because heart is denervated. Therefore, there is a need for screening in order to detect coronary atherosclerosis early. The presence of obstructive coronary disease in angiography is a predictor of any cardiac event [odds ratio (OR) 3.44, P = 0.05], as well as a predictor of cardiac death (OR 4.6, P < 0.05). However, a pathological study reported 10 patients who died or underwent retransplantation within 2 months of coronary angiography. One quarter of the patients had intermediate lesions or atheromatous plaques. Fresh or organizing thrombus was most often associated with discrete lesions and accounted for all complete occlusions. Authors concluded that transplant CAD has a heterogeneous histologic and angiographic appearance, with angiographic underestimation of disease in some patients. Accordingly, many active transplant centres incorporated IVUS imaging into their post-transplant surveillance, but there is no consensus on how frequent IVUS should be performed. The predictive value of IVUS has been explored in a study that included 143 patients who underwent 3-vessel IVUS investigation at 13 and 12 months after transplantation. The change in intimal thickness was calculated (≥0.5 mm was defined as rapidly progressive vasculopathy). At 1 year, rapid progression was demonstrated in 37% of the patients and in 47% of them a new lesion was found. At 5.9 years, patients with rapid progression died more than their counterparts (26 vs. 11%, P = 0.03). The combined endpoint of death and MI was also more frequently seen in patients with rapid progression (51 vs. 16%, P < 0.0001).56

Intravascular ultrasound has been also used to assess novel therapies in heart transplantation recipients. Eisen et al. randomized 634 patients to receive 1.5 mg of everolimus per day (209 patients), 3.0 mg of everolimus per day (211 patients), or 1.0–3.0 mg of azathioprine per kilogram of body weight per day (214 patients), in combination with cyclosporine, corticosteroids, and statins. The primary efficacy endpoint was a composite of death, graft loss or retransplantation, loss to follow-up, biopsy-proved acute rejection of grade 3A, or rejection with haemodynamic compromise. At 1 year, IVUS showed that the average increase in maximal intimal thickness was significantly smaller in the two everolimus groups than in the azathioprine group.57

Drug effects on atherosclerosis

The initial observations about a positive continuous relationship between coronary heart disease risk and blood cholesterol levels led to the conduction of a number of IVUS-based studies to evaluate the effect of different lipid lowering drugs on atheroma size. The efficacy of lowering low-density lipoprotein cholesterol (LDL-C) with inhibitors of hydroxymethylglutaryl-coenzyme A reductase (statins) is unequivocal; however, the change in atheroma size by statins is not constant across all IVUS studies (Table 2). There are many potential explanations for these discrepancies in IVUS studies such as drug properties, dose, and duration of treatment. In early studies like the GAIN study,58 atheroma volume was not reduced by atorvastatin despite the reduction in LDL-C (86 vs. 140 mg/dL) at 12 months. In contrast, the REVERSAL study59 showed that LDL-C levels were further lowered by atorvastatin vs. pravastatin (110 vs. 79 mg/dL) which was associated with an increase of 2.7% of the atheroma volume in pravastatin-treated patients and in a 0.4% reduction in the

\[
\text{Volumetric quantification of the extent of atherosclerosis in coronary arteries}
\]

\[
\text{TAV} = \left( \text{EEM}_{\text{CSA}} - \text{LUMEN}_{\text{CSA}} \right)
\]

\[
\text{TAV}_{\text{norm}} = \sum \frac{\text{EEM}_{\text{CSA}} - \text{LUMEN}_{\text{CSA}}}{\text{number of analysed frames per patient}} \times \frac{\text{mean/median no. of analysed frames in the population}}{100}
\]

\[
\% \text{ change in TAV} = \frac{\text{TAV (follow-up)} - \text{TAV (baseline)}}{\text{TAV (baseline)}} \times 100
\]

\[
\text{PAV} = \frac{\sum (\text{EEM}_{\text{CSA}} - \text{LUMEN}_{\text{CSA}})}{\sum \text{EEM}_{\text{CSA}}} \times 100
\]

Figure 8 Parameters commonly used to report the extent of the coronary atherosclerosis are the total atheroma volume (TAV) and the percent atheroma volume (PAV). EEM, external elastic membrane; CSA, cross-sectional area.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Year</th>
<th>Treatment</th>
<th>n</th>
<th>FU</th>
<th>Primary endpoint</th>
<th>Results (mean ± SD)</th>
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<tr>
<td>Statin trials</td>
<td></td>
<td></td>
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<tr>
<td>GAIN58</td>
<td>RCT</td>
<td>2001</td>
<td>Atorvastatin</td>
<td>48</td>
<td>12 months</td>
<td>Plaque volume</td>
<td>2.5 ± 24.9 mm³</td>
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<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>51</td>
<td></td>
<td></td>
<td>11.8 ± 31 mm³</td>
</tr>
<tr>
<td>ESTABLISH84</td>
<td>RCT</td>
<td>2004</td>
<td>Atorvastatin</td>
<td>24</td>
<td>6 months</td>
<td>% Change in plaque volume</td>
<td>13.1 ± 12.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>24</td>
<td></td>
<td></td>
<td>8.7 ± 14.9%</td>
</tr>
<tr>
<td>REVERSAL59</td>
<td>RCT</td>
<td>2004</td>
<td>Atorvastatin</td>
<td>253</td>
<td>18 months</td>
<td>% Change in plaque volume</td>
<td>4.1 ± 29.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pravastatin</td>
<td>249</td>
<td></td>
<td></td>
<td>5.4 ± 20.1%</td>
</tr>
<tr>
<td>Jensen et al.85</td>
<td>Non-RCT</td>
<td>2004</td>
<td>Simvastatin</td>
<td>40</td>
<td>12 months</td>
<td>% Change in plaque volume</td>
<td>6.30%</td>
</tr>
<tr>
<td>Petronio et al.86</td>
<td>RCT</td>
<td>2005</td>
<td>Simvastatin</td>
<td>36</td>
<td>12 months</td>
<td>Plaque volume</td>
<td>−2.5 ± 3.0 mm³/mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>35</td>
<td></td>
<td></td>
<td>1.0 ± 3.0 mm³/mm</td>
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<td>Nishioka et al.87</td>
<td>Non-RCT</td>
<td>2004</td>
<td>Pravastatin, atorvastatin, simvastatin, and fluvastatin</td>
<td>22</td>
<td>6 months</td>
<td>Plaque Volume</td>
<td>30.9 ± 15.6 mm³</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>26</td>
<td></td>
<td></td>
<td>35.5 ± 12.7 mm³</td>
</tr>
<tr>
<td>Tani et al.88</td>
<td>RCT</td>
<td>2005</td>
<td>Pravastatin</td>
<td>52</td>
<td>6 months</td>
<td>% Change in plaque volume</td>
<td>−14.4 ± 23%</td>
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<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>23</td>
<td></td>
<td></td>
<td>1.1 ± 4.6%</td>
</tr>
<tr>
<td>ASTEROID89</td>
<td>Non-RCT</td>
<td>2006</td>
<td>Rosuvastatin</td>
<td>349</td>
<td>24 months</td>
<td>Change in PAV</td>
<td>−0.98 ± 3.15%</td>
</tr>
<tr>
<td>Takashima et al.90</td>
<td>Non-RCT</td>
<td>2007</td>
<td>Pitavastatin</td>
<td>41</td>
<td>6 months</td>
<td>% Change in plaque volume</td>
<td>−10.6 ± 9.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>41</td>
<td></td>
<td></td>
<td>8.1 ± 14.0%</td>
</tr>
<tr>
<td>COSMOS91</td>
<td>Non-RCT</td>
<td>2009</td>
<td>Rosuvastatin</td>
<td>126</td>
<td>18 months</td>
<td>Change in PAV</td>
<td>−5.1 ± 14.1%</td>
</tr>
<tr>
<td>JAPAN-ACS92</td>
<td>RCT</td>
<td>2009</td>
<td>Atorvastatin</td>
<td>127</td>
<td>8–12 months</td>
<td>% Change in plaque volume</td>
<td>−18.1 ± 14.2%</td>
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<td></td>
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<td>Pitavastatin</td>
<td>125</td>
<td></td>
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<tr>
<td>Hirayama</td>
<td>Non-RCT</td>
<td>2009</td>
<td>Atorvastatin</td>
<td>28</td>
<td>28 weeks</td>
<td>% Change in plaque volume</td>
<td>−9.4 ± 10.3%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80</td>
<td>weeks</td>
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<td>−18.9 ± 14.1%</td>
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<td>ACAT (acyl-coenzyme A cholesterol acyltransferase) inhibitor trials</td>
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<tr>
<td>A-PLUS93</td>
<td>RCT</td>
<td>2004</td>
<td>Avasimibe 50 mg</td>
<td>108</td>
<td>24 months</td>
<td>Change in PAV</td>
<td>0.7 ± 0.4%</td>
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<td>Avasimibe 250 mg</td>
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<td>0.8 ± 0.4%</td>
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<td></td>
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<td>Avasimibe 750 mg</td>
<td>117</td>
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<td>1.0 ± 0.3%</td>
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<td></td>
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<td></td>
<td>Placebo</td>
<td>109</td>
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<td>0.4 ± 0.4%</td>
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<tr>
<td>ACTIVATE64</td>
<td>RCT</td>
<td>2006</td>
<td>pactimibe</td>
<td>206</td>
<td>18 months</td>
<td>Change in PAV</td>
<td>0.69 ± 0.25%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>202</td>
<td></td>
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<td>−0.59 ± 0.25%</td>
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<tr>
<td>Increasing high-density lipoprotein therapies</td>
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<td>ApoA-I Milano94</td>
<td>RCT</td>
<td>2003</td>
<td>ApoA-I Milano 15 mg/kg</td>
<td>21</td>
<td>5 weeks</td>
<td>Change in PAV</td>
<td>−1.29 ± 3.5%</td>
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<td>ApoA-I Milano 45 mg/kg</td>
<td>15</td>
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<td>−0.74 ± 2.8%</td>
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<td></td>
<td></td>
<td>Placebo</td>
<td>11</td>
<td></td>
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<td>0.14 ± 3.09%</td>
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<tr>
<td>ERASE62</td>
<td>RCT</td>
<td>2007</td>
<td>CSL-111 (reconstituted HDL infusion)</td>
<td>89</td>
<td>4 weeks</td>
<td>% change in plaque volume</td>
<td>−3.41 (IQR, −6.55 to 2.25)</td>
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<td>Placebo</td>
<td>47</td>
<td></td>
<td></td>
<td>−1.62 (IQR, −5.95 to 1.94)</td>
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<td>CART-295</td>
<td>RCT</td>
<td>2008</td>
<td>Succinobucol (AGI-1067)</td>
<td>183</td>
<td>12 months</td>
<td>Absolute change in plaque volume</td>
<td>−3.4 ± 14.5 mm³</td>
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<td>Placebo</td>
<td>49</td>
<td></td>
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<td>−0.6 ± 13.4 mm³</td>
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<td>Other therapies</td>
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<td>Study</td>
<td>Intervention</td>
<td>Study Duration</td>
<td>End Point</td>
<td>Change (95% CI)</td>
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<td><strong>CAMELOT</strong></td>
<td>Amlodipine, Enalapril, Placebo</td>
<td>2004</td>
<td>Change in PAV</td>
<td>0.5 ± 3.9%</td>
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<tr>
<td><strong>Waseda</strong></td>
<td>Losartan, Non-ARB</td>
<td>2006</td>
<td>Change in PAV</td>
<td>−9.9 ± 3.1 mm²</td>
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<tr>
<td><strong>ILLUSTRATE</strong></td>
<td>Torcetrapib + atorvastatin, Atorvastatin</td>
<td>2007</td>
<td>Change in PAV</td>
<td>0.12 ± 2.99%</td>
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<tr>
<td><strong>PERSPECTIVE</strong></td>
<td>Perindopril, Placebo</td>
<td>2007</td>
<td>Change in PAV</td>
<td>0.19 ± 2.83%</td>
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<tr>
<td><strong>PERISCOPE</strong></td>
<td>Pioglitazone, Glimepiride</td>
<td>2008</td>
<td>Change in PAV</td>
<td>−0.16% (95% CI −0.57 to 0.25%)</td>
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<tr>
<td><strong>STRADIVARIUS</strong></td>
<td>Rimonabant, Placebo</td>
<td>2008</td>
<td>Change in PAV</td>
<td>0.25% (95% CI −0.04 to 0.54%)</td>
<td></td>
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<tr>
<td><strong>ENCELE II</strong></td>
<td>Nifedipine</td>
<td>2009</td>
<td>% change in plaque volume</td>
<td>5.0 (95% CI −1.3, 11.2)</td>
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<tr>
<td><strong>APPROACH</strong></td>
<td>Rosiglitazone, Glipizide</td>
<td>2010</td>
<td>Change in PAV</td>
<td>−0.21% (95% CI −0.86, 0.44)</td>
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</table>

**IVUS-based tissue characterization studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Study Duration</th>
<th>End Point</th>
<th>Change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yokoyama et al.</td>
<td>Atorvastatin</td>
<td>2005</td>
<td>Overall plaque size and tissue characterization by IB IVUS</td>
<td>Atorvastatin reduced plaque size and changed plaque composition</td>
</tr>
<tr>
<td>Kawasaki et al.</td>
<td>Pravastatin, Atorvastin Diet</td>
<td>2005</td>
<td>Overall tissue characterization by IB IVUS</td>
<td>Statins reduced lipid without changes in plaque size</td>
</tr>
<tr>
<td><strong>IBIS 2</strong></td>
<td>Darapladib, Placebo</td>
<td>2008</td>
<td>Necrotic core volume by IVUS VH</td>
<td>Darapladib reduced significantly necrotic core</td>
</tr>
<tr>
<td><strong>Nasu et al.</strong></td>
<td>Fluvastatin, Control</td>
<td>2009</td>
<td>Overall tissue characterization by IVUS VH</td>
<td>Fluvastatin reduced plaque volume and fibrofatty</td>
</tr>
<tr>
<td><strong>Hong et al.</strong></td>
<td>Simvastatin</td>
<td>2009</td>
<td>Overall tissue characterization by IVUS VH</td>
<td>Both reduced necrotic core and increased in fibrofatty volume</td>
</tr>
<tr>
<td><strong>Toi et al.</strong></td>
<td>Rosuvastatin, Atorvastin, Pivastatin</td>
<td>2009</td>
<td>Overall tissue characterization by IVUS VH</td>
<td>Pitavastatin reduced plaque volume and fibrofatty</td>
</tr>
<tr>
<td><strong>Miyagi et al.</strong></td>
<td>Statin (pravastatin, pitavastatin, atorvastatin, fluvastatin, simvastatin)</td>
<td>2009</td>
<td>Overall tissue characterization by IB IVUS</td>
<td>Statins reduced lipid and increased fibrous</td>
</tr>
</tbody>
</table>

**Notes:** IVUS, intravascular ultrasound; IB, integrated backscatter; VH, virtual histology; FU, follow-up; SD, standard deviation; CI, confidence interval; RCT, randomized controlled trial; IB, integrated backscattered.
atheroma volume in atorvastatin-treated patients. The clinical significance and the accuracy of IVUS for such measurements are still debatable, but these results were statistically significant. The PROVE-IT study,\(^6\) showed that the lower the LDL-C and C-reactive protein values, the greater the reduction in clinical events and atheroma progression.

The first study showing regression of plaque size was the ASTEROID trial.\(^6\) At 24 months treatment with rosvastatin 40 mg daily resulted in lowering of LDL-C to 60.8 mg/dL and elevation of high-density lipoprotein cholesterol (HDL-C) by 14.7%. These lipid effects were associated with statistically significant, albeit small reductions in PAV (0.79%) and the TAV (6.8%).

Intravascular ultrasound studies have also demonstrated coronary plaque modification in HDL-treated patients. The infusion of synthetic HDL-C particles containing the variant apolipoprotein, apoA-I Milano, complexed with phospholipids (ETC-216) reduced the PAV by \(-1.06\%\) (3.17\% \(P = 0.02\) compared with the baseline) in the combined ETC-216 group at 5 weeks. On the contrary, in the placebo group, the PAV increased by \(0.14\%\) (3.09\%; \(P = 0.97\) compared with the baseline). In the ERASE study,\(^6\) 60 patients were randomly assigned to receive 4 weekly infusions of placebo (saline), 111 to receive 40 mg/kg of reconstituted HDL (CSL-111), and 12 to receive 80 mg/kg of CSL-111. The latter was discontinued due to liver function test abnormalities. Within the treated group, the percentage change in the atheroma volume was \(-3.4\%\) with CSL-111 (\(P < 0.001\) vs. baseline), while for the placebo group it was \(-1.6\%\) (\(P = 0.48\) between groups). It is still unclear what the future holds for these therapeutic agents.

Patients with human deficiency of cholesterylester transfer protein (CETP) have elevated circulating levels of HDL-C. This has led to investigation on CETP inhibition as a novel and potentially effective approach to elevate HDL-C. In the ILLUSTRATE trial, the PAV (the primary efficacy measure) increase was similarly low in patients receiving atorvastatin monotherapy vs. in those receiving the combined torcetrapib–atorvastatin therapy after 24 months (0.19 vs. 0.12\%, respectively).\(^6\)

The enzyme acyl-coenzyme \(A\) cholesterol acyltransferase (ACAT) esterifies cholesterol in a variety of cells and tissues. Inhibition of ACAT1, by blocking the esterification of cholesterol, could prevent the transformation of macrophages into foam cells and slow the progression of atherosclerosis, while inhibition of ACAT2 would be expected to decrease serum lipid levels. In the ACTIVATE study, the change in the PAV was similar in the placebo group (0.69 and 0.59\%, respectively; \(P = 0.77\)).\(^6\)

Systolic blood pressure has been shown to be an independent predictor of plaque progression by IVUS.\(^6\) A randomized study of patients with CAD and a diastolic blood pressure <100 mmHg treated with placebo or antihypertensive therapy using either amlodipine 10 mg daily or enalapril 20 mg daily showed that patients treated with amlodipine had a reduction in plaque size and also a reduction in cardiovascular events when compared with placebo at 24 months.\(^6\) The PERSPECTIVE study,\(^6\) a substudy of the EUROPA trial, evaluated the effect of perindopril on coronary plaque progression in 244 patients. There were no differences in changes in IVUS plaque measurements detected between the perindopril and placebo groups.

Thiazolidinediones increase insulin sensitivity in peripheral tissues, thereby lowering glucose, and also lower blood pressure and inflammatory markers, and improve lipid profile, endothelial function, and carotid IMT. Thiazolidinediones (i.e. rosiglitazone and pioglitazone) may therefore reduce progression of coronary atherosclerosis compared with other antidiabetic drugs. Two studies have addressed this question. The APPROACH (Rosiglitazone study)\(^6\) and the PERISCOPE (Pioglitazone study) trials.\(^6\) A change in PAV in the APPROACH study was not different in patients allocated to glipizide or rosiglitazone \([-0.64\%, 95\%\text{ confidence interval (CI)} -1.46, 0.17; P = 0.12\)], while in the PERISCOPE study pioglitazone vs. gliclazide was associated with favourable effects on the change of PAV \([-0.16 \pm 0.21\text{ vs. } 0.73 \pm 0.20\%, P = 0.002\]). Rosiglitazone significantly reduced the normalized TAV by 5.1 mm\(^3\) (95% CI \(-10.0, -0.3\); \(P = 0.04\)) when compared with glipizide, whereas pioglitazone just failed to achieve a statistically significant change in the TAV \((-5.5 \pm 1.6\text{ vs. } -1.5 \pm 1.5\text{ mm}^3, P = 0.06\)) when compared with gliclazide. Pioglitazone resulted in comparable plaque size reduction (i.e. TAV) as rosiglitazone, but this reduction was associated with an almost double reduction in vessel size. The formula of change in the PAV has as a numerator change in atheroma volume and as denominator change in vessel volume; this may mask the specific directional changes in its numerator and denominator when used as primary endpoint to compare two pharmacological agents.

There are several recent reports showing serial changes of plaque composition in patients treated with various statin treatments. In one of them, patients with stable angina pectoris \((n = 80)\) treated with fluvastatin for 1 year had significant regression of the plaque volume, and changes in the atherosclerotic plaque composition with a significant reduction of the fibrofatty volume \((P < 0.0001)\). This change in the fibrofatty volume had a significant correlation with change in the LDL-cholesterol level \((r = 0.703, P < 0.0001)\) and change in the hsCRP level \((r = 0.357, P = 0.006)\).\(^6\) Of note, the necrotic core did not change significantly.

In a second study, Hong et al. randomized 100 patients with stable angina and ACS to either rosvastatin 10 mg or simvastatin 20 mg for 1 year. The overall necrotic core volume significantly decreased \((P = 0.010)\) and the fibrofatty plaque volume increased \((P = 0.006)\) after statin treatments. Particularly, there was a significant decrease in the necrotic core volume \((P = 0.015)\) in the rosvastatin-treated subgroup. By multiple stepwise logistic regression analysis, they showed that the only independent clinical predictor of decrease in the necrotic core volume was the baseline HDL-cholesterol level \((P = 0.040, OR: 1.044, 95\%\text{ CI }1.002–1.089)\).\(^6\)

The IBIS 2 study compared the effects of 12 months of treatment with darapladib (oral Lp-PLA2 inhibitor, 160 mg daily) or placebo in 330 patients.\(^7\) This study failed to demonstrate the treatment effect of darapladib on the two co-primary endpoints (i.e. density of high strain values by palpography and change in hsCRP). Other endpoints included changes in the necrotic core size (IVUS-VH) and atheroma size (IVUS-greyscale). Background therapy was comparable between groups, with no difference in the LDL-cholesterol at 12 months. In the placebo-treated group, however, the necrotic core volume increased significantly, whereas darapladib halted this increase, resulting in a significant
treatment difference of $-5.2 \text{ mm}^3$ ($P = 0.012$). These intraplaque compositional changes occurred without a significant treatment difference in the TAV.

Nevertheless, there is no a single report describing a clear direct association between reduction in the plaque size and/or the plaque composition with reduction in clinical events. This is in part due to the fact that clinical outcome studies are expensive since they have to include a large population (that should be imaged at least at two different time points) that has to be followed up for a long period of time to collect the number of events (which are becoming scarce due to improvement in the standard of care) needed to assess the treatment effect.

**Future directions**

In the future, integration of multiple image technologies in a single catheter is likely to provide a more comprehensive assessment of the coronary vasculature.

IVUS-VH has a limited axial resolution ($100–200 \mu m$) not allowing a precise measurement of the fibrous thin cap; on the contrary OCT is a high-resolution imaging technique ($10–20 \mu m$) that can be used in the assessment of microstructure, but only using OCT in plaque-type characterization can be a source of misclassification. The OCT signal has in fact a low penetration, limited to $1–2 \text{ mm}$, and could not detect lipid pools or calcium behind thick fibrous caps, thus producing inaccurate detection of signal-poor areas.\(^7\)\(^3\)\(^7\)\(^4\) The combined use of IVUS-VH analysis and OCT seems to improve the accuracy for TCFA detection.\(^7\)\(^3\)\(^7\)\(^4\)

Intravascular ultrasound guidance during the treatment of chronic total occlusions, in which the most exacting parts of the procedure are to enter into the proximal part of the occlusion and to keep the guidewire within the limits of the vessel to avoid coronary perforations, with a forward-looking intravascular ultrasound (FL-IVUS) holds promise because it is able to visualize the vessel, plaque morphology, and true and false lumens in front of the imaging catheter. The Preview catheter is currently undergoing preclinical and early clinical evaluation. It is a single-use, over-the-wire imaging catheter, and the distal imaging tip is shown in Figure 9.

**Conflict of interest:** M.A.C. is a consulting speaker (\(<10,000 \text{ USD threshold}\)) and received research grants (through the University and/or core lab) from Boston Scientific and Lightlab, and is a consulting speaker for the drug companies: Sanofi and Eli Lilly (\(<10,000 \text{ USD per year}\)).

**References**


