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REVIEW

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## Invasive or non-invasive imaging for detecting high-risk coronary lesions?

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### ABSTRACT

**Introduction:** Advances in our understanding about atherosclerotic evolution have enabled us to identify specific plaque characteristics that are associated with coronary plaque vulnerability and cardiovascular events. With constant improvements in signal and image processing an arsenal of invasive and non-invasive imaging modalities have been developed that are capable of identifying these features allowing *in vivo* assessment of plaque vulnerability.

**Areas covered:** This review article presents the available and emerging imaging modalities introduced to assess plaque morphology and biology, describes the evidence from the first large scale studies that evaluated the efficacy of invasive and non-invasive imaging in detecting lesions that are likely to progress and cause cardiovascular events and discusses the potential implications of the *in vivo* assessment of coronary artery pathology in the clinical setting.

**Expert commentary:** Invasive imaging, with its high resolution, and in particular hybrid intravascular imaging appears as the ideal approach to study the mechanisms regulating atherosclerotic disease progression; whereas non-invasive imaging is expected to enable complete assessment of coronary tree pathology, detection of high-risk lesions, more accurate risk stratification and thus to allow a personalized treatment of vulnerable patients.

### ARTICLE HISTORY

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### KEYWORDS

Atherosclerosis; vulnerable plaque; intravascular ultrasound; optical coherence tomography; computed tomographic coronary angiography; positron emission tomography

## 1. Introduction

Coronary artery disease (CAD) is the main cause of death in the developing world [1]. Given the heavy burden that it imposes on society and an individual's health, it is imperative to optimize and tailor the treatment of patients with CAD based on their risk profile, prognosis, and comorbidities. Over the last few years, a considerable effort has been made to identify new treatments that have led to improvements in outcomes in this population [2–4]. Despite these advances, the incidence of recurrent events remains high [5]. To address the unmet need for an optimal management of these high-risk patients, new therapies have recently been developed and are currently undergoing preclinical or clinical evaluation that aim to reduce atherosclerotic disease progression and the risk of future events [6]. Accurate risk stratification is therefore essential these days for quantifying an individual's risk and tailoring management. However, existing clinical scores have a low accuracy at detecting high-risk patients [7,8]. To overcome this, efforts are made to understand the pathophysiology of CAD and the mechanisms associated with the formation of high-risk lesions that predispose to future cardiovascular events.

Pathological studies have demonstrated that acute coronary syndromes (ACSs) are caused either by plaque rupture,

plaque erosion, or thrombosis in calcific nodules [9,10]. Our understanding may be limited today about the morphological characteristics of the plaques that will erode, or the calcific nodules that will cause thrombosis, but we have extensively studied the phenotypic characteristics of the lesions that will rupture – which are responsible for 73% of all ACSs [11]. Majority of these lesions have specific morphological findings collectively termed thin-capped fibroatheromas (TCFA). These plaques exhibit an increased plaque burden, positive remodeling and have a large necrotic core that is covered by a thin fibrous cap (<65 μm) [12,13]. TCFA are also rich in macrophages, which can lead to plaque destabilization by secreting matrix metalloproteinases that readily degrade collagen and thin the fibrous cap leading to plaque rupture [11,12]. TCFA also contain cholesterol crystals that can penetrate and disrupt the fibrous cap and can promote the secretion of pro-inflammatory cytokines resulting in the activation of the immune system [14,15]. Other plaque features associated with increased vulnerability are intra-plaque hemorrhages and microcalcifications [12,16].

The fact that high-risk TCFA have specific morphological characteristics created hopes that their early identification would enable detection of vulnerable lesions and potentially identification of high-risk patients that would benefit from therapeutic strategies that would lead to the passivation of

these plaques [7]. Over the last few years, several invasive and noninvasive imaging modalities have been developed to study, with more accuracy, coronary anatomy, morphology, biology, and physiology. The aim of this review article is to describe the advantages and limitations of the invasive and noninvasive techniques, the evidence from their first applications in the study of atherosclerosis, and discuss their potential value in risk stratification and secondary prevention.

## 2. Invasive coronary imaging

### 2.1. Intravascular ultrasound

Intravascular ultrasound (IVUS) is the first imaging modality that enabled *in vivo* assessment of the luminal and outer vessel wall dimensions, evaluation of plaque burden, and characterization of its composition. This modality has been extensively used over the last 25 years to further our understanding about the atherosclerotic process. Preliminary IVUS studies showed that vulnerable plaques have focal manifestations and are mainly located proximally within the coronary arteries and at coronary bifurcations [17–19]. IVUS also enabled assessment of the effect of systemic and local factors on the progression of atherosclerosis [20–24], allowed morphologic comparison of symptomatic versus asymptomatic plaque rupture, serial assessment of plaque evolution [25], and the effect of different treatments on this process [26–28].

A preliminary IVUS-based study of coronary atherosclerosis provided promise that this modality may allow accurate assessment of the phenotypic characteristics of the plaque and detection of lesions that are likely to progress and cause major adverse cardiovascular events (MACE) [29]. However, three prospective studies of atherosclerotic evolution casted doubts about the accuracy of IVUS in detecting vulnerable lesions. The Prospective Natural-History Study of Coronary Atherosclerosis (PROSPECT) study was the largest study of its kind that utilized radiofrequency analysis of the backscatter IVUS signal and in particular IVUS-virtual histology (VH) to assess plaque morphology and vulnerability in 697 patients admitted with an ACS. All the studied patients had 3-vessel IVUS-VH imaging immediately after treatment of the culprit lesions and were followed up for a median of 3.4 years. On multivariate analysis, a plaque burden >70%, a minimal lumen area <4 mm<sup>2</sup>, and the presence of a TCFA phenotype were predictors of vulnerable plaques that caused MACE at follow-up. The positive predictive value of these three variables in detecting vulnerable lesions was 18.2% [30].

Similar results were reported in VH-IVUS in Vulnerable Atherosclerosis study, which included 170 patients admitted with stable angina or an ACS that were referred for PCI and underwent 3-vessel IVUS-VH imaging. The presence of TCFA as identified by IVUS-VH was the only predictor of non-culprit lesion-related MACE [31].

The Prediction of the Progression of Coronary Artery Disease and Clinical Outcomes Using Vascular Profiling of Shear Stress and Wall Morphology (PREDICTION) study was the only prospective study that examined the implications of the local hemodynamic forces on atherosclerotic disease progression. Five hundred and six patients with an ACS who had

PCI and 3-vessel grayscale IVUS imaging at baseline and 6–10 months follow-up were included in the analysis. The IVUS data at baseline were fused with the angiographic images to reconstruct coronary artery anatomy and blood flow simulation was performed in the baseline models. Low endothelial shear stress (ESS) at baseline was a predictor of plaque progression and of lesions that required revascularization at follow-up. An increased plaque burden and low ESS enabled prediction of lesions that will require revascularization with a positive predictive value of 41% [32].

Although these studies provided robust evidence that IVUS can detect vulnerable lesions, they also revealed significant limitations of intravascular imaging. First, in PROSPECT, IVUS was not able to study the entire coronary tree and thus, it assessed 53% of the lesions that caused events during the follow-up period. Second, 10.6% of the recruited patients were excluded from the PROSPECT and 33% from the PREDICTION because of incomplete data. Third, majority of the events in PROSPECT were unstable angina, rather than strong clinical end points such as cardiac death and myocardial infarction; whilst in PREDICTION, only 29% of the revascularizations were related to clinical events, as in most patients the decision to perform PCI was made based on the follow-up coronary angiography. Fourth, intravascular imaging was associated with a risk of complications – 1.6% of the patients in PROSPECT and 0.6% of patients in PREDICTION had a complication attributed to IVUS imaging [30–32]. Lastly, although IVUS was shown to be able to predict future events, its positive predictive value was quite low, 18.2% in PROSPECT and 41% in PREDICTION. As expected, these findings raised concerns about the role of imaging in detecting vulnerable lesions and created pessimism in the scientific community about the clinical potential of intravascular imaging to stratify cardiovascular risk [33,34].

### 2.2. Optical coherence tomography

Optical coherence tomography (OCT) with its high image resolution (10–20 vs. 150 μm for IVUS) enables more detailed assessment of vulnerable plaque morphology and visualization of plaque micro-characteristics that cannot be detected by IVUS imaging and are associated with increased vulnerability such as the presence of macrophages [35], neovascularization [36,37], and microcalcifications [38]. In addition, compared to IVUS, OCT allows more reliable characterization of plaque composition and estimation of fibrous cap thickness in fibroatheromas [39,40].

OCT not only allows assessment of plaque phenotype but it also enables evaluation of the effect of the local hemodynamic forces on vessel morphology. A computational fluid dynamic study that evaluated ESS in OCT-derived models showed that segments exposed to low ESS have a larger lipid burden, thinner fibrous caps, and higher prevalence of TCFA; findings that support evidence from experimental studies show that local hemodynamic forces contribute to the formation of vulnerable lesions [41].

Several studies used OCT to assess the prevalence and distribution of vulnerable plaques in different populations and in patients with different clinical presentations. Reports

have shown that patients with renal failure are more likely to have an increased lipid component, cholesterol crystals, calcific tissue, and vessel wall disruptions [42], while those with a history of diabetes and metabolic syndrome are more likely to have plaques with an increased necrotic core component compared to normal subjects [43]. Moreover, patients' social history and gender seem to also affect plaque morphology. A 3-vessel OCT imaging study showed that smokers were more likely to have lipid-rich lesions and plaque disruptions [44], while Kataoka et al. showed that female patients more often have lesions with lower cholesterol and calcium content but a higher incidence of plaque erosions [45]. Females also tend to have different TCFA distribution compared to males: in males TCFA were located in the proximal segments of the coronary arteries, whereas in females they were more evenly distributed, a finding that provides mechanistic insights about the higher incidence of revascularization and adverse events noted in female patients undergoing bypass operation compared to males [46].

In addition, patients admitted with a ST-elevation myocardial infarction (STEMI) are more likely to have more vulnerable plaques than those admitted with a non-ST-elevation myocardial infarction (NSTEMI) or stable angina symptoms [47,48].

Although OCT has been extensively used to assess plaque pathobiology, there is only one small study that investigated its efficacy in identifying lesions that are likely to progress and cause events. In this report, 53 patients were included; all the studied patients had OCT imaging at baseline and at 7 months follow-up. During this period, 13 non-flow limiting lesions exhibited disease progression. Lesions that progressed more often had vessel wall discontinuities (61.5% vs. 8.9%,  $P < 0.01$ ), neo-vessels (76.9% vs. 14.3%,  $P < 0.01$ ), lipid-rich plaques (100% vs. 60.7%,  $P = 0.02$ ), TCFA phenotype (76.9% vs. 14.3%,  $P < 0.01$ ), macrophages accumulations (61.5% vs. 14.3%,  $P < 0.01$ ), and intraluminal thrombi (30.8% vs. 1.8%,  $P < 0.01$ ) compared to those that remained unchanged. This analysis demonstrated for the first time the clinical implications of plaque micro-features, but it included a small number of patients that did not allow assessment of their additive value in predicting high-risk vulnerable plaques [49].

OCT may have allowed evaluation of plaque characteristics that are unseen by IVUS, but it also has significant limitations in assessing plaque morphology. These include its low penetration depth of 2–3 mm that restricts its reach to the internal elastic lamina in heavily diseased vessels, its limited accuracy to detect macrophages, its limited efficacy in differentiating deeply embedded lipid cores from calcific tissue, and the fact that it doesn't allow reliable assessment of the distribution of the plaque on vessel geometry [50,51].

### 2.3. Near-infrared spectroscopy

By analyzing the reflected infrared light from the coronary wall, near-infrared spectroscopy (NIRS) can identify the chemical signature of lipid cores. Preliminary validation studies in animal models have provided encouraging results, while the first validation study of NIRS in human histological data has showed that NIRS is able to detect lipid-rich lesions with high

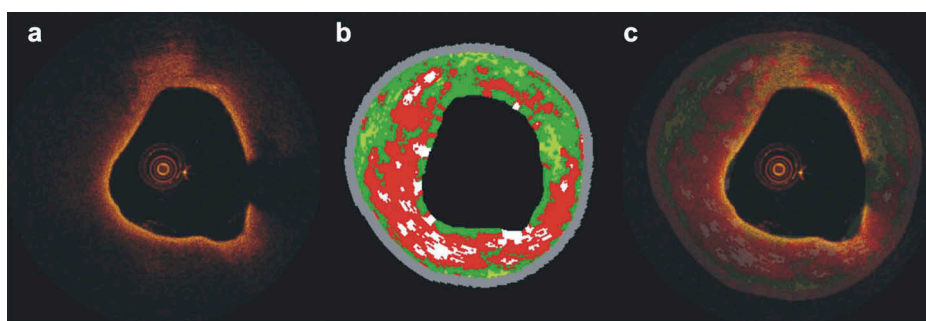
accuracy (area under the curve, AUC: 0.86) [52,53]. These findings were confirmed by more recent analyses showing that NIRS is the best invasive imaging modality for the detection of fibroatheromas [54–56].

Several reports validated the feasibility and reproducibility of NIRS *in vivo* [57,58], and prospective studies used this modality to examine the effects of interventional and pharmacological interventions on lipid burden [59,60]. However, stand-alone NIRS failed to dominate in the clinical arena and in the study of atherosclerosis as it has significant inherited limitations. First, it can only detect the lipid component and it cannot give information about the other plaque components. In addition, NIRS does not enable visualization and assessment of the lumen, outer vessel wall dimensions, and plaque burden and lacks image depth resolution that enables localization of the necrotic core within the plaque and differentiation of TCFA from thick cap fibroatheromas. To overcome these limitations, efforts were made to spectroscopically assess fibrous cap thickness and develop dual-probe imaging catheters that will provide simultaneous assessment of plaque characteristics from two imaging modalities with complementary strengths, thus enabling a more accurate characterization of plaque pathobiology [61,62].

### 2.4. Multimodality imaging

Several histology-based studies have demonstrated that combined intravascular imaging provides more reliable characterization of plaque composition [54,55,63,64]. Sawada et al. were the first who used combined *in vivo* IVUS-VH–OCT imaging to study plaque morphology. They demonstrated significant discrepancies between the estimations of the two modalities about plaque phenotype that were attributed to the inherited limitations of each technique and concluded that combined intravascular imaging may enable more reliable evaluation of plaque characteristics (Figure 1) [65]. Since then, several other researchers have used combined intravascular imaging to study coronary atheroma and changed our understanding about plaque evolution. Diletti et al. used serial combined IVUS-VH–OCT imaging to study plaque characteristics in bifurcation lesions and found no difference in the fibrous cap thickness and necrotic core component at 6 months follow-up concluding that plaque evolution is a slow process and contradicted the findings of a previous report that used serial stand-alone IVUS to assess changes in plaque morphology at 1-year follow-up [25,66]. In another report, combined IVUS–OCT imaging was used to assess plaques that ruptured and caused events, plaques that had a silent rupture and non-ruptured TCFA. The authors showed that ruptured plaques had thinner fibrous caps – assessed by OCT – while the lesions that ruptured and caused events had a smaller lumen area and an increased plaque burden – identified by IVUS – compared to lesions that had a silent rupture. These findings indicate that combined IVUS–OCT not only detects morphological differences between these three groups but is also able to predict the natural course and the clinical implications of plaque evolution [67]. In another study from the same research group, multimodality IVUS–OCT imaging was used to assess plaque morphology in angiographically significant (diameter stenosis





**Figure 1.** Efficacy of combined OCT – IVUS-VH imaging in assessing plaque morphology. (a) OCT frame showing a lipid-rich plaque with a thin fibrous cap. The corresponding IVUS-VH frame is shown in panel (b). Fusion of these images enables complete assessment of plaque characteristics: OCT allows evaluation of plaque composition and fibrous cap thickness while IVUS-VH provides quantitative information about plaque composition, quantification of plaque burden and estimation of the remodeling pattern (c).

>70%) lesions, in intermediate (diameter stenosis: 50–69%), and in non-flow limiting lesions (diameter stenosis: 30–49%) and showed that significant stenoses had a more vulnerable phenotype with a higher prevalence of TCFA, thinner fibrous caps, and a greater plaque burden compared to mild or moderate stenoses [68]. These findings augmented the notion that lesions with severe stenoses are more likely to rupture and cause clinically significant events than mild or moderate stenoses [69,70] and questioned the results of angiographic studies conducted in 1980s suggesting that myocardial infarction is more likely to be caused by non-flow limiting lesions [71].

IVUS–OCT, but also IVUS–NIRS and IVUS–angioscopic imaging have been used to assess the effect of pharmacological treatments on plaque morphology [60,72–76]. In the Integrated Biomarkers Imaging Study (IBIS) 3 study, serial IVUS–NIRS was used to assess the implications of aggressive statin therapy (rosuvastatin 40 mg) on plaque characteristics in 164 patients undergoing coronary angiography for clinical purposes. Rosuvastatin therapy did not change the lipid component ( $P = 0.074$ ) but resulted in a decrease of the plaque volume at follow-up ( $P = 0.006$ ) [60]. These findings contradict the results of previous smaller IVUS–angioscopic-based studies which demonstrated that treatment with statins has an effect not only on the plaque burden but also on its phenotype and vulnerability [76,77]. In addition, the YELLOW study implemented serial NIRS–IVUS imaging to assess plaque characteristics in obstructive lesions at baseline and after 7 weeks of treatment with either rosuvastatin 40 mg or standard lipid therapy. A significant reduction in the lipid component was noted in patients receiving high-dose statin compared to standard dose statin therapy ( $P = 0.01$ ); this reduction however was not associated with changes in the atheroma burden ( $P = 0.86$ ) [74].

Although it is acknowledged that multimodality imaging enables more detailed assessment of plaque morphology, it is also a tedious and time-consuming process and there are concerns about its safety in the clinical arena. Taniwaki et al. were the first to explore the safety and feasibility of combined multivessel IVUS–OCT imaging. The authors presented data from the IBIS 4 which included 103 patients admitted and revascularized for a STEMI that underwent 3–vessel IVUS–VH–OCT imaging at baseline and at 13 months follow-up [78].

Multimodality imaging was feasible in the majority of the patients (at baseline IVUS–VH: 85.7%, OCT: 89.9%; and at follow-up IVUS–VH: 84.8%, OCT: 86.6%). The intravascular imaging-related complications rates were low: 1.9% at baseline and 1.1% at follow-up. When the authors compared 2-year follow-up outcomes between patients who had PCI with and without multimodality intravascular imaging, they found no difference in the incidence of MACE (16.7% vs. 13.3%,  $P = 0.39$ ). These findings suggest that multimodality intravascular imaging is feasible and safe, even in high-risk patients treated for STEMI.

Recently, industry has created hybrid catheters that combine two imaging probes which enable a more detailed and complete evaluation of coronary plaques. The TVC Imaging System (InfraReDx, Burlington, Massachusetts) is the first clinically available hybrid catheter and incorporates an IVUS and NIRS imaging probe enabling simultaneous data acquisition that is accurately co-registered in comprehensive images providing information about plaque composition and burden. Madder et al. used NIRS–IVUS to study 20 culprit lesions in patients presented with a STEMI and showed that an increased lipid component (lipid core burden index in a 4-mm segment,  $LCBI_{4\text{ mm}} > 400$ ) was able to differentiate the culprit from the non-ruptured plaques with a high accuracy (AUC: 0.90) [79]. These findings were echoed in a larger study that demonstrated a sensitivity of 64% and a specificity of 85% for  $LCBI_{4\text{ mm}} > 400$  in identifying culprit lesions that caused STEMI [80]. The same research group replicated the above study in patients who presented with a NSTEMI or unstable angina and showed that larger lipid cores were present in the culprit lesions of these patients as well, but in this setting,  $LCBI_{4\text{ mm}} > 400$  had a lower sensitivity and specificity (63.6% and 94.0% for NSTEMI and 38.5% and 89.8% for culprit lesion causing unstable angina, respectively) [81]. These results created hopes that hybrid imaging may enable accurate prediction of plaques that are likely to progress and cause events and currently, two prospective imaging studies, the PROSPECT II (NCT02171065) and Lipid Rich Plaque studies (NCT02033694), are recruiting patients and aim to examine the efficacy of NIRS–IVUS in detecting vulnerable, high-risk plaques.

Apart from the NIRS–IVUS catheter, several other hybrid catheters have been designed and are currently undergoing

preclinical evaluation. These include (1) the combined IVUS-OCT, (2) the OCT-NIRS, (3) the OCT-near-infrared fluorescence catheter (NIRF), (4) the IVUS-NIRF, (5) IVUS-intravascular photoacoustic (IVPA), and (6) the IVUS-time resolved fluorescence spectroscopy catheter. Moreover, efforts are made to develop other invasive imaging techniques such as intravascular magnetic resonance imaging (MRI) or Raman spectroscopy [82,83]. These modalities are expected to enable not only more accurate evaluation of plaque morphology but also its biology and predict atherosclerotic evolution (Figure 2) [61,62].

### 3. Noninvasive imaging

#### 3.1. Computed tomographic coronary angiography

Computed tomographic coronary angiography (CTCA) has been recently introduced as an attractive alternative for the study of coronary atherosclerosis as it enables noninvasive assessment of atheroma characteristics. Several histology and intravascular-based imaging studies have shown that CTCA allows accurate evaluation of the luminal and outer vessel wall dimensions, assessment of plaque burden and remodeling pattern, and characterization of its composition [85–92]. Reports have demonstrated that CTCA enables detection of calcific tissue but it has a limited accuracy in differentiating lipid from fibrotic tissue component [86,87,89,91,92]; while recent histology-based studies have shown that CTCA – despite its limited imaging resolution – allows characterization of the phenotype of the plaque and detection of high-risk vulnerable lesions – which on CTCA exhibit a napkin-ring sign morphology – with high specificity but low sensitivity [93,94].

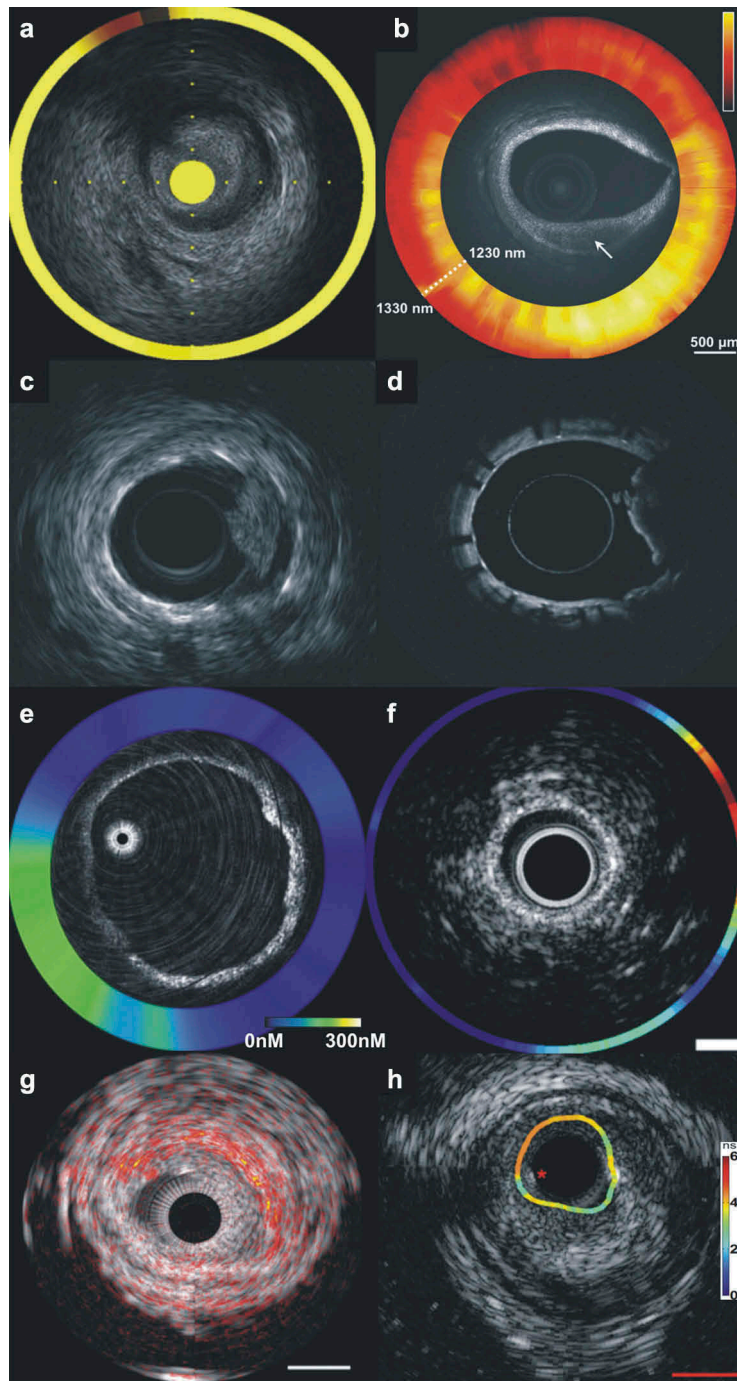
Despite the limited accuracy of CTCA in evaluating plaque morphology and composition, there is consistent evidence that this modality is able to identify lesions that are likely to progress and cause cardiovascular events [95–98]. Two retrospective studies conducted by Motoyama et al. that included 1059 and 3158 patients showed that the presence of attenuated plaques and positive remodeling indicated plaque vulnerability [95,98]. These findings were confirmed by Otsuka et al. in a retrospective analysis that included 895 patients who underwent CTCA for suspected CAD and were followed up for 2.3 years [96]. During this period, 24 ACSs occurred. Positive remodeling, low attenuated plaques, and a napkin-ring sign were predictors of vulnerable lesions. The sensitivity and specificity of the napkin-ring sign in detecting lesions that caused events was 41% and 97%, respectively, while the positive predictive value was 22%, which is slightly higher than the positive predictive value of IVUS-derived plaque characteristics reported in the PROSPECT study [30]. This is likely to be due to the different study design (e.g. retrospective vs. prospective design), the smaller follow-up period in the study of Otsuka et al. (2.3 vs. 3.4 years), and to the different clinical presentations and baseline characteristics of the patients recruited into these studies. The value of CTCA in detecting vulnerable lesions is also supported by a recent retrospective analysis which included 1650 patients with suspected CAD which showed that lesions that caused cardiovascular events had specific morphological characteristics on CTCA and in

particular increased plaque burden, lower attenuation, and a smaller lumen area compared to those that remained silent [97]. Nevertheless, all these studies were performed in patients with suspected CAD and not in those with established CAD who are likely to have extensive and advanced atherosclerotic lesions; therefore, the efficacy of CTCA to detect vulnerable lesions in this vulnerable population, who may be studied by invasive imaging techniques, remains unclear.

In contrast to intravascular imaging, CTCA enables complete assessment of coronary artery tree pathology, reconstruction of the coronary arteries, and generation of three dimensional (3D) geometries that can be processed with computational fluid dynamic techniques to estimate vessel wall biomechanics (Figure 3). Several reports used CTCA to examine the association between plaque morphology and local hemodynamic forces and studies examined the value of CTCA modeling in predicting atherosclerotic disease progression [99–101]. In the study of Bourantas et al. that included 32 patients admitted with an ACS who had CTCA imaging following complete revascularization and at 3 years follow-up, low baseline ESS was an independent predictor of lumen reduction ( $\beta = -0.47$  95% confidence interval:  $-0.78$  to  $-0.16$ ;  $P < 0.001$ ) and plaque burden increase ( $\beta = 0.11$ , 95% confidence interval:  $0.02$ – $0.21$ ;  $P = 0.018$ ) at follow-up [102]. These findings were confirmed by the analysis of Sakellarios et al. who simulated the LDL transport process into the vessel wall and showed that increased LDL accumulation was independently associated with a reduction in lumen area ( $\beta = -0.53$ , 95% confidence interval:  $-0.86$  to  $-0.20$ ;  $P = 0.002$ ) and an increase in plaque burden ( $\beta = 0.19$ , 95% confidence interval:  $0.08$ – $0.29$ ;  $P < 0.001$ ) [103]. The results of these two small scale studies are promising and support the use of CTCA-based modeling to assess vessel physiology; however, it is still unclear whether the ESS estimated by CTCA can improve prediction of high-risk plaques that will progress and cause cardiovascular events.

#### 3.2. Magnetic resonance imaging

Comparing to CTCA MRI has significant advantages in the study of atherosclerosis as it enables better evaluation of soft tissue characteristics, lacks of the blooming artifacts seen in the calcified plaques, and does not require radiation exposure. Although there is today convincing evidence about the efficacy of MRI in assessing plaque morphology in the carotids, its role in the study of coronary atherosclerosis is limited [104,105]. This should be attributed to the fact that coronary imaging requires increased imaging time to enhance spatial resolution and the need to reduce motion artefacts created during the cardiac cycle. The first studies investigating the efficacy of MRI in detecting obstructive CAD demonstrated a moderate accuracy [106] which however improved in recent reports [107,108] that implemented advanced imaging but remained inferior to CTCA [109]. Two studies compared the plaque burden estimations of black-blood MRI and IVUS and the first showed a good correlation between MRI and IVUS estimations while in the other report, there was a weak association between MRI and IVUS [110,111].

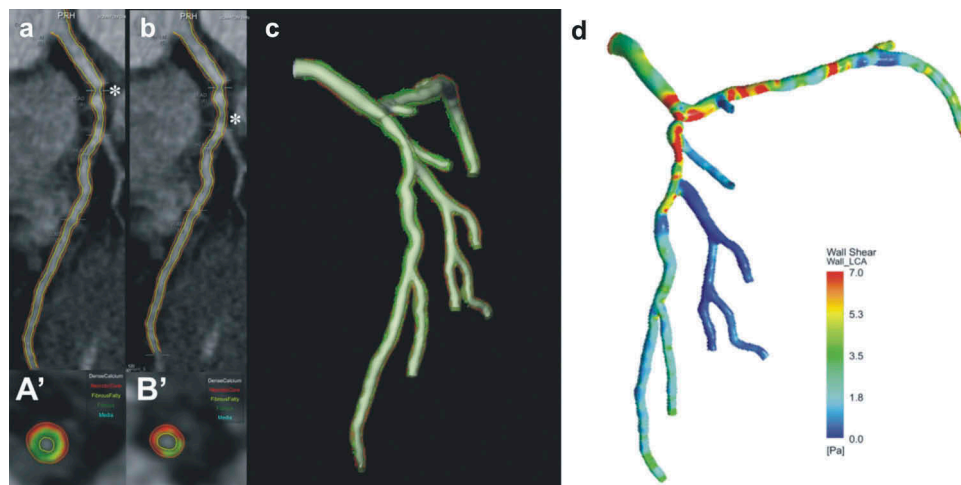


**Figure 2.** Output of the available hybrid imaging catheters: (a) combined NIRS-IVUS imaging, IVUS enables assessment of the lumen, outer vessel wall dimensions and plaque burden while NIRS allows detection of the lipid component indicated with a yellow-orange color; (b) a typical example of a combined OCT-NIRS image where spectroscopy enables reliable characterization of the composition of the plaque – the tissue extending from 4–7 o'clock could have been classified as calcific tissue according to standalone OCT, nevertheless NIRS demonstrates an increased lipid component – and classifies the plaque as fibroatheroma; (c, d) output of the combined IVUS-OCT catheter: (c) IVUS allows assessment of stent expansion and quantification of the lumen, stent, outer vessel wall dimensions and plaque burden behind the stent, while (d) OCT enables detailed assessment of stent apposition, strut endothelialisation, and detection and classification of the endoluminal thrombus; (e) hybrid OCT-NIRF imaging performed after injection of the Prosense VM110 activatable marker, OCT allows visualization of plaque characteristics while NIRF identifies the presence of cathepsin B which indicate increased protease activity and inflammation; (f) combined IVUS-NIRF imaging after injection of the indocyanin green tracer which indicates macrophages accumulation; (g) hybrid IVUS-IVPA imaging, IVPA allows reliable detection of lipid component – indicated with orange color – while IVUS allows assessment of the lumen and plaque morphology; and (h) hybrid IVUS-TRFS imaging. TRFS provides assessment of the superficial plaque components and detection of collagen (orange color), macrophages and lipid component (green color) while IVUS allows visualization of the lumen and quantification of the plaque burden. Images modified and obtained with permission from Bourantas et al [62] and Abran et al [84]. Full color available online.

Several reports have examined the efficacy of MRI in detecting plaque characteristics associated with increased vulnerability. The Multi-Ethnic Study of Atherosclerosis and the

Atherosclerotic Disease, Vascular Function, and Genetic Epidemiology study have shown that black-blood MRI imaging can detect positive remodeling [112,113]; while T1-weighted





**Figure 3.** A case example that highlights the role of CTCA in assessing plaque morphology and physiology. The raw CTCA data demonstrates two tight lipid-rich lesions in the ostium (a) and the proximal segment (b) of the left anterior descending artery. Panels (a') and (b') portray the cross sections with the minimal lumen area, their locations in panels (a) and (b) are indicated with asterisks. The annotated borders in the CTCA were used to reconstruct coronary artery anatomy, (c) assess the distribution of the plaque in the model (red indicates lipid tissue, green fibrotic, light-green fibrofatty and white calcific tissue) and perform blood flow simulation, estimate the local hemodynamic forces and their association with plaque morphology (d). Full color available online.

MRI imaging studies have shown that this technique can identify the presence of thrombus and high-risk plaques [114,115]. T1-weighted imaging can also provide useful prognostic information: in a study that included 568 patients with suspected CAD, an increased coronary plaque intensity in T1-weighted imaging was independent predictor of future adverse cardiovascular events at 55 months follow-up (hazard ratio: 3.96; 95% confidence interval: 1.92–8.17;  $P < 0.001$ ); nevertheless, there is no data today about the efficacy of MRI in detecting lesions that are likely to progress and cause cardiovascular events [116].

### 3.3. Positron emission tomography

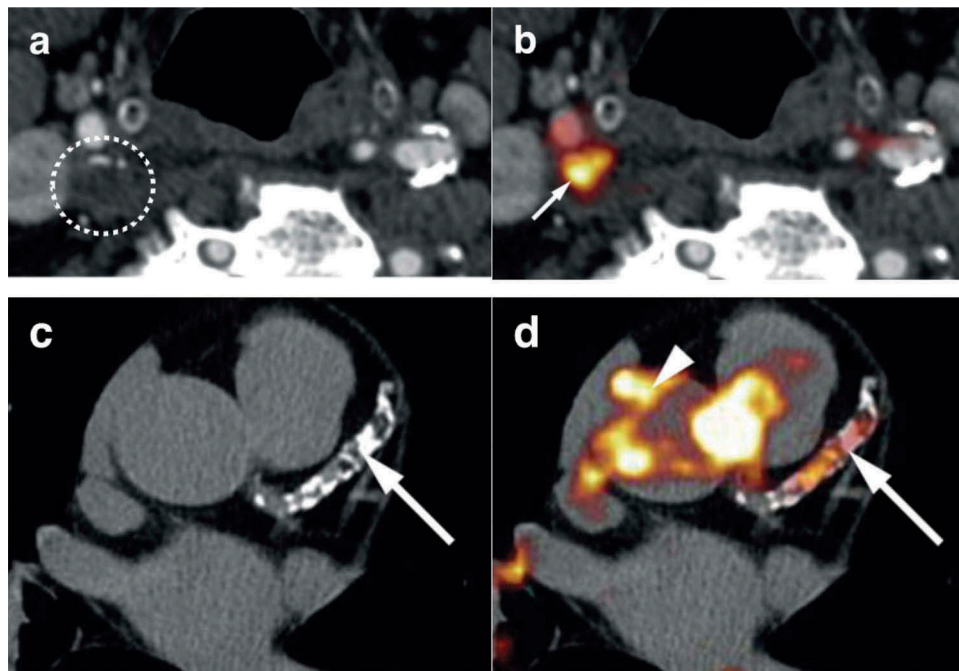
Molecular imaging using positron emission tomography (PET) can be applied to detect inflammation and metabolic processes occurring within atherosclerotic plaques, including microcalcification, hypoxia, and neo-angiogenesis. PET is a highly sensitive noninvasive nuclear imaging technique that involves intravenous injection of radio-labeled tracers with a range of molecular targets. PET scanners detect annihilation events that occur as a result of beta-decay of the positron-emitting radio-isotope and use this data to generate 2D or 3D tomographic maps displaying the distribution of the radio-ligand within the body at specific time points. As the spatial resolution of PET is limited (roughly 5 mm), PET images are typically fused with CT or MRI for accurate anatomical signal localization.

Several PET ligands with established roles in clinical cancer imaging have been repurposed for use in atherosclerosis research. Of these PET tracers,  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) is the most well studied in atherosclerosis.  $^{18}\text{F}$ -FDG signals within atherosclerotic plaques reflect the metabolic activity of macrophages and therefore plaque inflammation. Indeed, *in vivo*  $^{18}\text{F}$ -FDG uptake is strongly correlated with macrophages density within excised carotid plaques, as well as gene expression associated with vascular inflammation

[117,118]. Vascular  $^{18}\text{F}$ -FDG signals have also been shown to be significantly correlated with presence of traditional cardiovascular risk factors (e.g. older age, smoking, hypertension, diabetes mellitus, and hyperlipidemia) and are elevated in patients with systemic inflammatory conditions conferring increased cardiovascular risk, such as rheumatoid arthritis and psoriasis [119–121]. Data from the prospective Dublin Carotid Atherosclerosis Stroke Study showed that increased carotid artery  $^{18}\text{F}$ -FDG uptake can identify patients with increased risk of early stroke recurrence, independent of age and stenosis severity (Figure 4a,b) [122]. Moreover, a retrospective study of imaging from 513 cancer-free patients examined over a 4-year period found that aortic  $^{18}\text{F}$ -FDG uptake strongly predicted risk of cardiovascular events independent of traditional risk factors (hazard ratio: 4.71,  $P < 0.001$ ), with nearly 30% net reclassification improvement over Framingham risk score in the highest risk group [123].

Although  $^{18}\text{F}$ -FDG PET has well-established, evidence-based roles for imaging vascular inflammation, there are several limitations to this technique in atherosclerosis. First, as most metabolically active cells take up glucose, it is unclear how much of the observed signal is influenced by cells other than macrophages within plaques, including neutrophils, lymphocytes, endothelial cells, and vascular smooth muscle cells. Vascular  $^{18}\text{F}$ -FDG signal intensity is also significantly influenced by plaque hypoxia and therefore might not be purely representative of inflammation *per se* [125]. Perhaps most importantly, using  $^{18}\text{F}$ -FDG to image the coronary vasculature is particularly difficult because of high background myocardial uptake of  $^{18}\text{F}$ -FDG, even with strict dietary manipulation or prolonged fasting [126]. Nonetheless, in a feasibility study of coronary  $^{18}\text{F}$ -FDG imaging, increased tracer uptake was observed in proximal culprit coronary lesions in patients with ACS compared to non-culprit lesions in patients with stable angina [127]. Several other PET tracers have been tested for use in atherosclerosis imaging, which might offer more specific markers of inflammation than  $^{18}\text{F}$ -FDG or provide better





**Figure 4.** Representative images of vascular PET-CT imaging of disease activity in patients with atherosclerosis. Top: CT (a) and  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) PET-CT (b) images from a patient with recent transient ischemic attack resulting from a symptomatic right internal carotid artery stenosis (circle) demonstrating an intense focal inflammatory signal (arrow) on PET imaging. Bottom: CT (c) and  $^{18}\text{F}$ -sodium fluoride (NaF) PET-CT (d) images from a patient with stable angina showing high tracer uptake representing micro-calcification in relation to left anterior descending artery atherosclerosis (arrows), as well as the ascending aorta (arrowhead). Figure adapted from Tarkin et al [124].

methods for coronary artery imaging owing to inherently low myocardial tracer activity. These include  $^{18}\text{F}$ -fluorodeoxymanose, the somatostatin receptor subtype-2 PET ligand  $^{68}\text{Ga}$ -DOTATATE,  $^{11}\text{F}$ -fluorocholine, and transient receptor protein receptor tracers, including  $^{11}\text{C}$ -PK11195 [128–131].

Aside from inflammation, several other pathogenic mechanisms of atherosclerosis can be imaged using PET, including microcalcification, hypoxia, neo-angiogenesis, hematopoiesis, and HDL accumulation [126,132–135]. For example, early vascular calcification occurring in response to intense plaque inflammation, and below the resolution of CT, can be detected using  $^{18}\text{F}$ -sodium fluoride (NaF) PET. In carotid plaques,  $^{18}\text{F}$ -NaF binding takes place in areas of pathological mineralization and is related to the surface area of exposed hydroxyapatite (Figure 4c,d) [136]. Increased vascular  $^{18}\text{F}$ -NaF accumulation has also been shown to occur during early stages of neointima thickening, while a prospective clinical study showed that plaque microcalcification detected by  $^{18}\text{F}$ -NaF PET enabled accurate identification of culprit coronary lesions in patients with a myocardial infarction [126,137]. The ongoing multicenter Prediction of Recurrent Events With  $^{18}\text{F}$ -Fluoride (PREFFIR, NCT02278211) study aims to evaluate the prognostic value of coronary  $^{18}\text{F}$ -NaF PET-CT imaging in 700 patients with myocardial infarction and proven multivessel CAD followed up over 2 years.

#### 4. Expert commentary

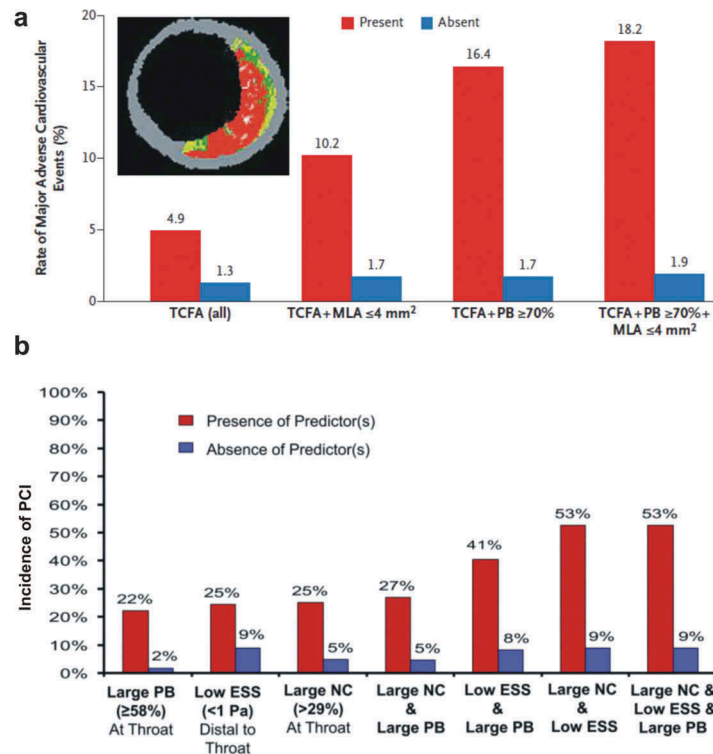
Imaging of coronary atherosclerosis has provided unique insights about atherosclerotic evolution and has enabled *in vivo* identification of vulnerable, high-risk plaques (Table 1).

Prospective invasive imaging-based studies have shown that IVUS has a low accuracy in detecting these lesions, but this increases considerably when the local hemodynamic patterns are included in the prediction model (Figure 5) [138]. These findings highlight the need for a complete and detailed evaluation of plaque morphology, physiology, and biology to predict its evolution. Invasive imaging – with its high resolution – and in particular hybrid intravascular imaging appears as the ideal approach to study atherosclerotic disease progression and detect vulnerable plaques. Emerging hybrid dual-probe catheters are anticipated to allow precise assessment of plaque characteristics and evaluation of the interplay between plaque micro-features that are unseen by stand-alone IVUS – such as neovessels (given by IVPA), inflammation (provided by NIRF), macrophages (detected by IVPA), or cholesterol crystals detected by OCT – and established markers of plaque vulnerability, such as plaque burden, lipid component, and ESS and their synergistic effect on the formation of high-risk lesions. Hybrid intravascular imaging is also anticipated to shed light into the pathophysiological mechanisms that are involved in plaque erosion and allow us to appreciate the role of microcalcification and cholesterol crystals on plaque destabilization. Finally, hybrid intravascular imaging may also enable prediction of the clinical implications of plaque rupture and differentiation of the lesions that will rupture and cause cardiovascular events from those that will sustain a clinically silent rupture. Considering the limitations of intravascular imaging that restricts its broad use – i.e., the increased time required for the processing of the acquired data, the fact that it can be used only in symptomatic patients undergoing coronary angiography for clinical purposes and that it does not

**Table 1.** Prospective and retrospective studies investigating the efficacy of invasive and noninvasive imaging in detecting vulnerable lesions.

Study	Design	Objective	Modality used	Studied patients	FU period	Findings
<b>Invasive imaging studies</b>						
Sano et al. [29]	Prospective single-center study	To examine the ability of IB-IVUS in detecting lesions that will cause MACE	IB-IVUS	140 patients admitted with stable angina	30 months	Comparing to lesions that did not cause events, the vulnerable plaques exhibited an increased plaque burden (60% vs. 52%) and lipid tissue component (percent lipid area: 72% vs. 50%), positive remodeling (remodeling index: 1.30 vs. 1.16), and low fibrotic tissue component (percent fibrotic area 23% vs. 47%)
PROSPECT [30]	Prospective multicenter observational study	To investigate the efficacy of IVUS-VH in predicting lesions that will progress and cause cardiovascular events	IVUS-VH	697 patients admitted with an ACS who had 3-vessel IVUS-VH	3.4 years	A plaque burden > 70%, MLA < 4 mm <sup>2</sup> , and TCFA phenotype were able to predict lesions that will cause MACE with a positive predictive value of 18.2%
VIVA [31]	Prospective single-center observational study	To investigate the efficacy of IVUS-VH in identifying vulnerable, high-risk plaques	IVUS-VH	170 patients with stable angina or ACS that had 3-vessel IVUS-VH	1 year	A TCFA phenotype (HR: 8.13; 95% CI: 1.63–40.56; <i>P</i> = 0.011) was an independent predictor of lesions that caused MACE
PREDICTION [32]	Prospective multicenter observational study	To investigate the ability of plaque characteristics and hemodynamic forces in predicting disease progression and cardiovascular events	Grayscale IVUS	506 patients admitted with an ACS that underwent 3-vessel IVUS	6–10 months	An increased plaque burden and low ESS enabled prediction of lesions that required revascularization with a positive predictive value of 41%
Uemura et al. [49]	Single-center observational study	To identify plaque characteristics in nonsignificant lesions associated with rapid disease progression	OCT	53 patients with established CAD treated with PCI had OCT in a nonsignificant lesion	7 months	Comparing to lesions that remained unchanged those that progressed had more often vessel wall discontinuities (61.5% vs. 8.9%), neo-vessels (76.9% vs. 14.3%), a lipid component (100% vs. 60.7%), TCFA phenotype (76.9% vs. 14.3%), macrophages accumulations (61.5% vs. 14.3%), and thrombi (30.8% vs. 1.8%)
<b>Noninvasive imaging studies</b>						
Motoyama et al. [95]	Retrospective analysis	To identify CTCA-derived plaque characteristics associated with future events	CTCA	1059 consecutive patients who underwent CTCA for clinical reasons	2.3 years	Positive remodeling and/or low attenuated coronary plaques were seen in 73% of the lesions that caused ACS
Otsuka et al. [96]	Retrospective analysis	To determine the value of CTCA plaque characteristics in predicting cardiovascular events	CTCA	895 patients undergoing CTCA for clinical purposes	2.3 years	Positive remodeling (HR: 5.25, 95% CI: 2.17–12.69, <i>P</i> < 0.001), low attenuated plaques (HR: 3.75, 95% CI: 1.43–9.79, <i>P</i> = 0.007), and plaques with a napkin-ring morphology (HR: 5.55, 95% CI: 2.10–14.70, <i>P</i> < 0.001) were independent predictors of lesions that caused cardiovascular events
Versteylen et al. [97]	Retrospective analysis of registry data	To examine the value of CTCA-derived plaque characteristics in detecting vulnerable plaques	CTCA	1650 patients undergoing CTCA for clinical purposes	26 months	Comparing to silent lesions, culprit lesions had an increased plaque burden (39% vs. 29%), lower attenuation (287 HU vs. 468 HU), and increased remodeling index (1.4 vs. 1.3)

IB-IVUS: integrated backscatter intravascular ultrasound; IVUS-VH: intravascular ultrasound virtual histology; MACE: major adverse cardiovascular events; MLA: minimum lumen area; TCFA: thin-cap fibroatheroma; ACS: acute coronary syndrome; OCT: optical coherence tomography; CAD: coronary artery disease; PCI: percutaneous coronary intervention; CTCA: computed tomographic coronary angiography; HR: hazard ratio; CI: confidence interval.



**Figure 5.** Efficacy of plaque characteristics and vessel physiology in detecting lesions prone to progress. (a) In the PROSPECT study an increased plaque burden, a TCFA phenotype and a minimum lumen area  $< 4$  mm<sup>2</sup> were able to detect lesions that will progress and cause events with a positive predictive value of 18.2%. (b) In the PREDICTION study the positive predictive value of the model built from the plaque burden and ESS was 41% and increased considerably to 53% after including information about the composition of the plaque. Panels a and b were obtained with permission from Stone et al [30] and Papafaklis et al [138].

enable complete assessment of coronary artery tree – future intravascular imaging studies assessing vulnerable lesions are anticipated to include small number of patients and focus on the mechanisms regulating atherosclerotic disease progression.

On the other hand, CTCA overcomes these limitations and carries a unique potential for the conduction of large scale outcome studies. Several software have been developed for the fast processing of CTCA imaging data, coronary reconstruction, and blood flow simulation [85,87,139] and evidence supports the use of CTCA in detecting vulnerable plaques in low risk patients [95–98]; nevertheless, there is lack of prospective data, and the efficacy of CTCA in identifying vulnerable lesions in patients with established CAD and extensive atherosclerotic burden remains unclear. Future studies are anticipated to explore the efficacy of CTCA in detecting vulnerable lesions in high-risk patients and the additive value of PET imaging in this challenging setting. Positive results are likely to change clinical practice and justify the focal treatment of vulnerable lesions not only with novel endovascular devices with a better safety profile, but also with nanotechnology-based therapies that target high-risk plaques and modify vulnerable plaque physiology [7,140,141].

Irrespective of the potential value of invasive and noninvasive imaging in detecting lesions that will progress and cause events, cumulative evidence has demonstrated that imaging of atherosclerosis may also be useful in stratifying cardiovascular risk and detecting high-risk patients that are likely to suffer a cardiovascular event. Angioscopic, IVUS, and NIRS-based studies have shown that plaque imaging can provide useful prognostic information

[142–145]. However, the above studies included a small number of patients and therefore, the number of events reported was too small to allow us to examine the additive predictive value of intravascular imaging over clinical or angiographic variables.

In parallel, several retrospective analyses have demonstrated that CTCA-based imaging provides useful prognostic information and enables detection of patients that are likely to suffer a cardiovascular event amongst individuals with suspected CAD [95–98,146,147]. In patients with established CAD, a small scale study showed that CTCA-derived variables were predictors of MACE at 5-year follow-up and improved considerably the prognostic accuracy of the model developed from the clinical variables (from 0.68 to 0.76) [148]. However, the small number of the reported events and the fact that this analysis did not take into account the angiographic variables associated with clinical outcomes (i.e. the Syntax score, or the residual Syntax score) did not allow us to draw safe conclusions about the additive prognostic value of CTCA in this population [149–152].

The accurate risk stratification and identification of high-risk individuals has recently attracted attention as several new therapies have been introduced that appear capable of modifying atherosclerotic disease progression [6,153]. Nevertheless, all these new therapies have significant limitations either from administration route (intravenous or subcutaneous), from side effects (bleeding, infection, or bone marrow suppression), or cost. Invasive or noninvasive imaging may have a role in this setting and

facilitate accurate risk stratification and detection of high-risk patients that would benefit from an individualized, aggressive treatment for coronary atherosclerosis.

## 5. Five-year view

Future hybrid intravascular imaging-based studies are expected to shed light into the mechanisms regulating atherosclerotic evolution and predict more accurately lesions that will progress and cause cardiovascular events. Noninvasive imaging and in particular CTCA or combined PET-CTCA imaging are anticipated to have increased applications in the study of atherosclerosis and used to identify noninvasively vulnerable plaques and stratify more accurately cardiovascular risk. Future studies sought also investigate the clinical feasibility and cost-effectiveness of noninvasive imaging in identifying vulnerable patients and guiding treatment in patients with established CAD.

## 6. Key issues

- Intravascular imaging modalities enable assessment of plaque characteristics and can identify with low accuracy lesions that are likely to progress and cause cardiovascular events
- Combined intravascular imaging appears able to overcome limitations of standalone imaging modalities and provide detailed and complete assessment of plaque pathobiology
- CTCA can assess atherosclerotic disease burden in the entire coronary tree, identify plaque features related with increased vulnerability and provide useful prognostic information in low risk-individuals
- PET imaging provides complementary information to CTCA as it enables non-invasive assessment of plaque inflammation and biology
- Future studies sought to evaluate the value of CTCA, MRI or PET-CTCA imaging in stratifying cardiovascular risk in patients with established CAD

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