Intravascularmultimodality imaging: feasibility and role in the evaluation of coronary plaque pathology

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Abstract

Coronary artery disease remains the leading cause of death in the developed world. Over recent years, research has been focused on the development of diagnostic intravascular imaging techniques that enable assessment of plaque composition and morphology, and allow identification of vulnerable, high-risk lesions. Nevertheless recent studies of coronary atherosclerosis have shown that invasive modalities have a limited accuracy in detecting lesions that will progress and cause events, whilst histology-based studies also highlighted the limitations of invasive imaging in assessing plaque characteristics. To overcome these drawbacks, multimodality imaging has been proposed. Although it is apparent that coronary imaging with two or three imaging modalities is time consuming and is associated with a risk of complications, evidence from small clinical studies demonstrated that it provides incremental information about plaque pathology and biology and underscored the need to develop dual-probe hybrid imaging catheters that would enable complete and comprehensive assessment of plaque morphology. This paper reviews the current clinical evidence that supports the use of multimodality intravascular imaging in the study of atherosclerosis, summarizes the key findings of the first invasive imaging studies that utilize hybrid dual-probe catheters, and discusses the limitations of combined intravascular imaging that restrict its broad application in both the clinical and research arena.

Keywords: multimodality imaging • atherosclerosis • vulnerable plaque

Introduction

Coronary angiography has long been considered the gold standard imaging modality for the evaluation of coronary artery disease. Coronary angiography however, has significant limitations in the assessment of lesion pathology and biology. Whilst enabling two dimensional (2D) visualization of luminal silhouette, it does not permit the evaluation of the plaque characteristics, which appear to determine its natural course and vulnerability.

The in vivo assessment of plaque characteristics first became feasible in the beginning of nineties with the introduction of intravascular ultrasound (IVUS) imaging. The application of this technique in the clinical setting heightened our appreciation of the limitations of coronary angiography in assessing the severity of a lesion and plaque morphology, and emphasized the need to develop alternative imaging modalities for studying coronary plaque characteristics. Several intravascular imaging techniques have been developed over the past few years that have enhanced our understanding of atherosclerotic evolution. Some of these modalities have been validated and are currently part of daily clinical practice [e.g. optical coherence tomography (OCT), and near infrared spectroscopy (NIRS)], whilst others remain in the development phase and under pre-clinical evaluation (i.e. Raman spectroscopy, photoacoustic imaging, intravascular magnetic resonance imaging, near infrared fluorescence imaging, and fluorescence lifetime imaging). Histology-based and clinical studies have provided robust evidence about the clinical and research potential of the clinically applicable modalities but also revealed their limitations in the study of atherosclerosis (see Supplementary data online, Supplementary Data). To overcome the inherent drawbacks of the existing techniques, multimodality intravascular imaging was proposed in order to synergize their strengths for better assessment of plaque morphology and vulnerability (Figure 1). Today, several dualprobe catheters have been developed that enable combined intravascular imaging of plaque pathobiology.[1]

In this review article, we present the evidence from clinical studies that supports the value of multimodality intravascular imaging in the study of atherosclerosis (see Supplementary data online, Table S1), summarize the key findings of the first human studies that evaluated the use of dual-probe catheters to assess plaque morphology, and discuss the future perspectives of multimodality imaging.

Multimodality imaging in the study of atherosclerosis: feasibility and current evidence

Intravascular ultrasound and optical coherence tomographic imaging

Sawada et al. were the first to suggest the combined use of RF-IVUS and OCT to assess plaque pathology, advocating that imaging with two imaging modalities with complementary strengths would enable more reliable evaluation of plaque morphology.[2] One hundred and six coronary plaques in 56 patients who underwent coronary angiography for stable angina were included in the analysis. The authors found significant discrepancies between RF-IVUS and OCT and concluded that both modalities are necessary for an accurate assessment of the phenotype of plaque. In particular, the moderate resolution of RF-IVUS did not permit accurate differentiation between TCFA and FA, whereas OCT often failed to characterize the superficial necrotic core component in vessels with a larger lumen, likely due to the limited penetration of the optical signal. These results were confirmed by ex vivo histology-based studies which showed that the combination of both RF-IVUS and OCT permits more accurate identification of high-risk plaques.[3,4]

In another study, Gonzalo et al. focused on bifurcation lesions and used the origin of side branches as matching anatomical landmarks between IVUS and OCT.[5] The authors developed a methodology that takes into consideration plaque characteristics identified in both IVUS and OCT images to define the phenotype of the plaque and found that high-risk plaques with a thin fibrous cap are seen more often at the proximal rim of the bifurcation. The same research

group implemented serial combined IVUS-OCT imaging in 24 patients to study bifurcation lesions and found no difference in the fibrous cap thickness and necrotic core after 6 months follow-up.[6] These findings contradict a previous RF-IVUS-based study, which showed that the phenotype of the plaque rapidly changes with time with high-risks plaques regressing to stable forms and stable lesions progressing to high risk phenotypes.[7]

Recently, Tian et al. evaluated plaque characteristics using combined IVUS-OCT imaging in lesions with various degrees of severity and found that lesions with significant luminal stenoses (>70% diameter stenosis) had an increased plaque burden, were more often TCFAs, and exhibited neo-vessels and cholesterol crystals more frequently than the lesions with a mild (30–49%) or moderate stenosis (50–69%).[8] These results indicate that severely stenotic lesions have a vulnerable phenotype and are thus more likely to cause cardiovascular events compared to those with mild or moderate severity, contradicting the findings of angiographic-based studies, conducted in 1980s, that suggested that myocardial infarction is more likely caused by non-flow limiting lesions.[9]

In another study, the same research group used IVUS and OCT to investigate plaque characteristics of lesions that rupture and cause cardiovascular events.[10] One hundred and twenty six plaques with a TCFA phenotype (49 ruptured plaques that caused an event, 19 ruptured plaques that did not cause an event, and 58 non-ruptured plaques) in 82 patients were included in the analysis. There were no differences between the three groups in the incidence of macrophages, neo-vessels, calcifications, and cholesterols crystals. Ruptured plaques more often had thrombus, and a thinner fibrous cap compared to the non-ruptured TCFA. Ruptured plaques that caused an event had a smaller luminal area and increased plaque burden compared to the plaques that ruptured and did not cause an event. OCT-derived plaque characteristics and in particular cap thickness had higher predictive value for ruptured plaques, whilst the plaque burden assessed by IVUS had higher predictability to ruptured plaques which caused events (Figure 2). The findings of this study demonstrated the value of combined imaging in identifying lesions that are prone to progress, rupture and cause cardiovascular events, and questioned the argument that intravascular imaging cannot differentiate lesions that will silently rupture from those that will cause an event.

Moreover, a recent report used combined IVUS-OCT imaging to compare plaque characteristics in 133 patients admitted with an ACS because of plaque rupture and plaque erosion.[11] Ruptured plaques had increased plaque burden and necrotic core component, exhibited more often positive remodelling, had a TCFA phenotype and were located either proximally or distally to the minimum lumen area site. On the other hand, lesions with plaque erosion had more often negative remodelling, exhibited modest plaque burden, were fibrotic-rich and half of the them were located proximally to the minimum lumen area site, a quarter of them in the minimum lumen area site and another quarter distally to the minimum lumen area site. These findings indicate the different patho-biological mechanisms involved in formation and destabilization of plaques that will erode from those that determine the natural evolution of plaques that will rupture and cause cardiovascular events.

Three prospective studies used combined IVUS and OCT imaging to examine the effect of statin therapy on the compositional characteristics of the plaque, with the Integrated Biomarkers Imaging Study 4 (IBIS 4), being the largest study of its kind (see Supplementary data online, Table S1). IBIS 4 used combined 3-vessel RF-IVUS and OCT imaging to assess plaque morphology and characteristics in patients with a ST-elevation myocardial infarction (STEMI).[12] It included 103 patients treated with high intensity rosuvastatin 40 mg od who had serial imaging at baseline and 13 months follow-up. The results from the IVUS analysis–the OCT analysis has not been presented yet–showed a regression in the percent atheroma volume at 13 months follow-up (–0.9%, P=0.007).[13] OCT and RF-IVUS imaging was feasible in the vast majority of the cases at both baseline (OCT: 89.9%, RF-IVUS: 85.7%) and follow-up (OCT: 86.6%, RF-IVUS: 84.8%). The complications rates were low: 1.9% at baseline and 1.1% at follow-up. When the authors compared outcomes between patients who had PCI with and without multimodality intravascular imaging they found

no difference in the incidence of acute kidney injury (1.0% vs. 1.9%, P= 0.72), or the incidence of major adverse cardiovascular events after 2 years follow-up (16.7% vs. 13.3%, P = 0.39). Considering that the advancement of the IVUS or OCT catheters could cause endothelial injury, the authors compared the incidence of revascularization in the non-infracted arteries and found no statistical differences between patients who had intravascular imaging compared to those who had not (9.0% vs. 4.8%, P= 0.20). These findings suggest that multimodality intravascular imaging is feasible and safe, even in high-risk patients treated for STEMI.

Intravascular ultrasound–near infrared spectroscopic imaging

The first IVUS-NIRS studies focused on the comparison of RF-IVUS and NIRS in assessing the composition of the plaque and demonstrated a weak correlation in the estimation of the two modalities with regards to the lipid burden.[14,15] Similar were the findings of a small scale study that compared NIRS and OCT.[16] These discrepancies between different imaging modalities are due to the limitations of each modality and underscore the potential additive value of multimodality imaging for more accurate plaque characterization. This hypothesis was confirmed by histology-based studies which showed that combined IVUS-NIRS imaging allows more accurate identification of high-risk, vulnerable plaques.[17,18]

The Reduction in Yellow Plaque by Intensive Lipid Lowering Therapy (YELLOW) was the first study that used combined IVUS and NIRS imaging to assess the effect of aggressive lipid lowering treatment in flow limiting lesions.[19] In this study, IVUS and NIRS imaging was performed at baseline and at 7 weeks follow-up in lesions with a fractional flow reserve<0.80 in 87 patients who were randomized to aggressive or standard of care lipid therapy. Anatomical landmarks and angiographic images were used to co-register the IVUS and the NIRS data acquired at the two time points.Within 2 months there was a 24% reduction in the lipid component and an increase in the elastic membrane area by 9% in the intensive treatment group, whilst in the standard of care group the change in the lipid component was increased by 5.4% and the external elastic membrane by 3%. Concerns were raised that these ambiguous results (i.e. the excessive reduction in lipid component, which was much greater than had been reported in other studies, and the increase in the outer vessel wall area) could have been caused by inaccurate co-registration of the two imaging modalities at baseline and follow-up, and highlighted the need to develop hybrid dual-probe catheters that would allow accurate co-registration of the acquired data.[20]

Combined RF-IVUS and NIRS imaging was also used to assess the effect of aggressive lipid lowering treatment with rosuvastatin on the plaque burden and composition in the Integrated Biomarkers Imaging Study 3 (IBIS 3) which included 164 patients who underwent coronary angiography for clinical purposes and had serial single vessel RF-IVUS imaging at baseline and 6 or 12 months follow-up.21 One hundred three of these patients also had serial NIRS imaging. In contrast to the YELLOW study, IBIS failed to demonstrate a treatment effect on the lipid component and there was an increase in the percentage atheroma volume at follow-up (see Supplementary data online, Table S1). Further information about the implications of lipid lowering treatment on plaque characteristics are expected to be provided by the Reduction in Coronary Yellow Plaque, Lipids and Vascular Inflammation by Aggressive Lipid Lowering (YELLOW II) study which is actively enrolling patients with lipid rich lesions that will have serial IVUS-NIRS and OCT imaging at baseline and 8–12 weeks follow-up (NCT01837823).

Hybrid intravascular imaging: first human studies of dual-probe catheters

The miniaturization of medical devices and advances in imaging processing has enabled the construction of dual-probe catheters which provide comprehensive visualization and complete assessment of plaque pathophysiology. Several prototypes are currently under development including the combined IVUS-OCT, NIRS-OCT, IVUS-near infrared fluorescence (NIRF), IVUS-photoacoustics and IVUS-fluorescence lifetime imaging and have recently been tested in histology studies and animal studies providing promising results (Figure 3). However technical limitations (i.e. relatively large catheters, poor imaging quality, increased time for data acquisition, need for blood removal) have not allowed their application in the clinical arena yet.[1]

Today two catheters, the combined NIRS-IVUS and the OCT-NIRF have been used in the clinical setting (see Supplementary data online, Table S2).

Hybrid near infrared spectroscopy-intravascular ultrasound catheter

The NIRS-IVUS catheter (TVC, InfraReDx, Inc., Burlington, Massachusetts) incorporates a rotational IVUS transducer with a NIRS probe on a single 3.2Fr catheter and provides cross sectional images of the coronary arteries where the IVUS and NIRS information is co-registered allowing assessment of the lumen and outer vessel wall morphology, and evaluation of plaque distribution and composition. The catheter is commercially available and has received FDA approval for the study of the composition of the plaque. Several reports used this modality to assess plaque characteristics and vulnerability. Roleder et al. used OCT as gold standard to assess the efficacy of NIRS-IVUS in evaluating plaque phenotype and demonstrated that combined NIRS-IVUS imaging allows detection of OCT-derived TCFA with a high sensitivity and specificity (100% and 91%, respectively).[22] A limitation of this analysis however, was the fact that the authors used OCT as a reference instead of using the information by all the three imaging modalities to more accurately characterize plaque morphology.[20]

Madder et al. used NIRS-IVUS to assess plaque characteristics in 20 patients admitted with STEMI and showed that culprit lesions have specific morphological characteristics i.e. an increased plaque burden and lipid component that allow their differentiation from the non-culprit lesions with a high accuracy [area under the curve (AUC): 0.90].[23] A larger scale, two centre study including 75 patients admitted with a STEMI has confirmed the above findings demonstrating that the maximum lipid plaque burden index in a 4 mm segment was able to differentiate culprit from the non-culprit lesions with a sensitivity and specificity of 64% and 85%, respectively.[24] The same research group has reported similar findings in patients admitted with non-STEMI and unstable angina: NIRS-IVUS imaging enabled identification of culprit lesions with high accuracy in both studied groups (AUC: 0.87 and 0.79, respectively).[25] Nevertheless, there is no prospective data today about the predictive value of the combined NIRS-IVUS imaging to detect high-risk prone to rupture plaques. To answer this questions two studies, the Prospective Natural History Study Using Multimodality Imaging in Patients With Acute Coronary Syndromes (PROSPECT II, NCT02171065) and the Lipid Rich Plaque (NCT02033694), have recently commenced and are anticipated to provide further insights about the value of hybrid-intravascular imaging in vulnerable plaque detection.

Combined IVUS-NIRS-OCT imaging has also been used to evaluate the effect of sex on plaque morphology in patients with stable angina.[26] In the study of Bharadwaj et al., 128 patients (95 men and 33 women) with stable angina had combined IVUS-NIRS and OCT imaging of the culprit lesions. There were no significant differences between groups in the thickness of the fibrous cap, the incidence of TCFA, macrophage accumulation, microvessels and the calcific and lipid burden–assessed by NIRS. Male patients had an increased plaque burden compared to females but this difference was not statistically significant when patient clinical characteristics were taken into account.

Hybrid optical coherence tomography near infrared fluorescence imaging catheter

NIRF involves the injection of activatablemarkers that have the ability to bind molecules associated with plaque vulnerability and fluoresce when they are irradiated with near infrared light. Combined OCT-NIRF imaging provides unique opportunities for studying plaque pathophysiology as OCT is able to assess luminal dimensions and plaque morphology while NIRF–depending on the activatable marker that is used for imaging–appears able to detect molecules associated with increased inflammation such as matrix metalloproteinases or cathepsins.[27] Today two OCT-NIRF catheters are available that incorporate an OCT probe and a NIRF transducer into a dual clad catheter (diameter: 2.4–2.6Fr) that acquire 24.5–100 frames/s and are pulled-back at a constant speed by an automated pull-back device. Several experimental studies in animal models that used numerous activatable markers have provided robust evidence about the feasibility of combined OCT-NIRF imaging and showed that NIRF enables detection of macrophages accumulation and fibrin deposition[28,29]; but none of these markers have been used in the clinical setting yet.

In a recent report, Wang et al. showed that necrotic-rich plaques have the ability to fluoresce (near infrared autofluoresnce imaging–NIRAF) when they are excited with NIRF light at 633 nm.[30] The safety and the efficacy of OCT-NIRAF in the characterization of atherosclerosis was been tested in a small study involving 12 patients undergoing PCI.31 The acquired NIRAF emission intensities were co-registered offline with the OCT imaging data. A strong NIRAF signal was seen in regions of plaque with high-risk features such as lipid containing plaques, thin-fibrous caps, macrophages and ruptured plaques with overlaying thrombus. The authors observed that not all the plaques with high-risk features (i.e. macrophages, lipid-rich lesions) had increasedNIRAF signal and speculated that an increasedNIRAF signal may be a new imaging marker associated with increased plaque vulnerability (Figure 4). Histological evidence has showed that NIRAF may allow detection of inflamed plaques with oxidized lipid component and neo-vessels32; further research is required towards this direction in order to better understand the pathobiological implications and clinical relevance of an increased NIRAF signal.

Discussion–Conclusions

The first multimodality imaging studies of coronary atherosclerosis have provided robust evidence that multimodality intravascular imaging is feasible and enables more detailed evaluation of the composition of the plaque, more accurate characterization of its phenotype and assessment of plaque features associated with increased vulnerability. More importantly these studies eradicated false beliefs about the morphology of vulnerable plaques, furthered our understanding of plaque vulnerability and demonstrated that a complete assessment of plaque pathobiology may enable more accurate identification of the lesions that will progress, rupture and cause cardiovascular events. Finally, serial multimodality imaging studies have allowed us to better understand atherosclerotic evolution and have a complete assessment of the effect of treatments on plaque burden, morphology, and vulnerability.

However, although it is apparent that multimodality intravascular imaging is superior to standalone imaging its applications in the study of atherosclerosis is limited. This is attributed to the risk–despite being minimal–of complications, to the increased cost and time required for multimodality intracoronary imaging of the coronary arteries, as well as the fact that co-registration and analysis of the acquired data is a tedious and time consuming process. Some of these limitations are expected to be overcome by hybrid dual-probe catheters, whilst others such as the increased cost, the partial sampling of the coronary tree and the risk of complications will remain considerable pitfalls for intravascular imaging.

Today several ongoing large scale prospective hybrid-invasive imaging-based studies of coronary atherosclerosis have commenced and are expected to provide us with more information on the potential value of hybrid intravascular imaging in understanding the mechanisms involved in atherosclerotic plaque development and destabilization and in detecting lesions that are prone to progress and cause events. The advent of new hybrid imaging modalities is anticipated to provide further opportunities to study plaque pathobiology and allow reliable detection of vulnerable plaques and patients that are at high risk to sustain future cardiovascular events. Preliminary uni-modality intravascular imaging studies have provided proof of the latter concept[33] and showed that a complete assessment of coronary morphology is likely to enable more accurate risk stratification which would justify the implementation of individualized secondary prevention strategies using aggressive pharmacological or interventional treatments targeting atherosclerotic process in selected populations.

Conflict of interest: None declared.

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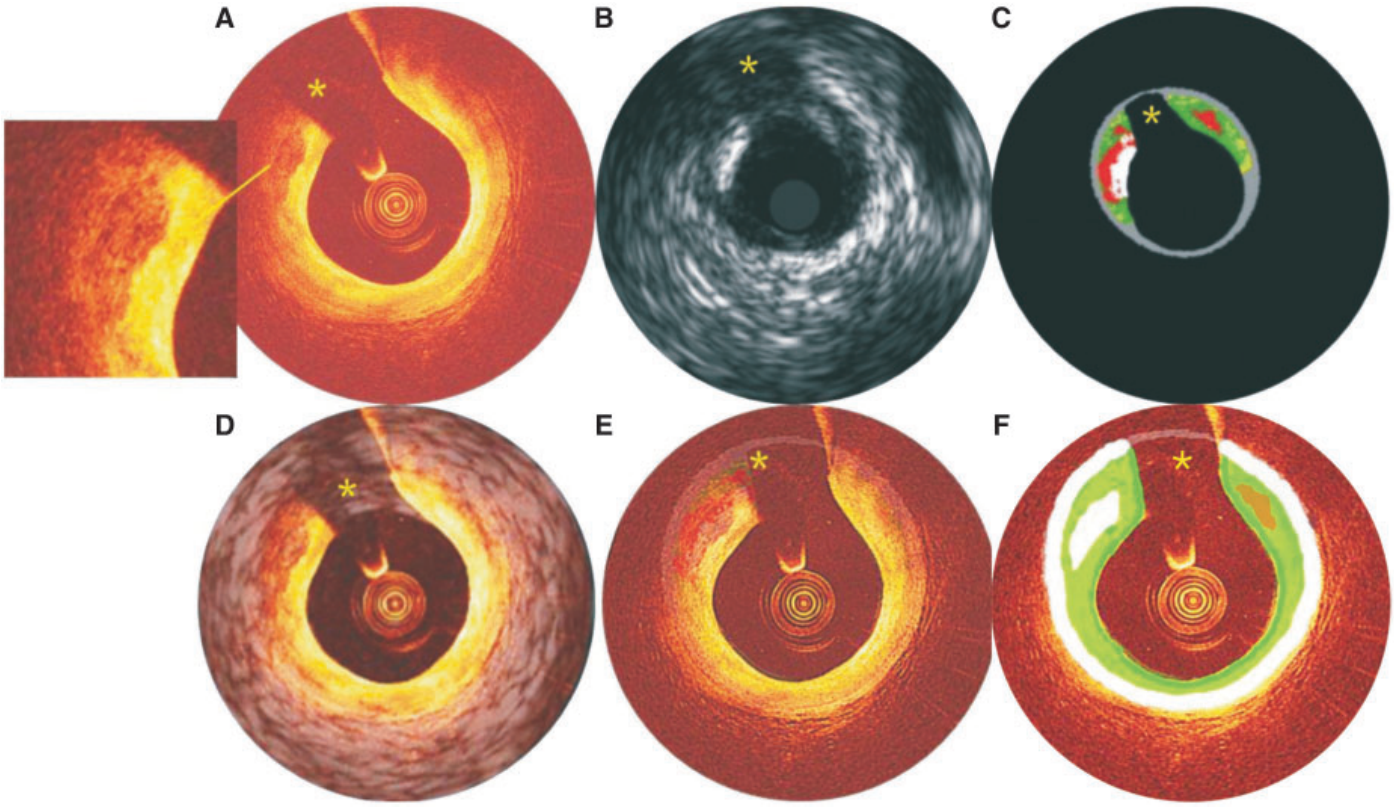

Figure 1 Combined OCT–virtual histology IVUS (IVUS-VH) imaging for more reliable assessment of plaque morphology and burden. Corresponding OCT (**A**), grayscale IVUS (**B**), and IVUS-VH (**C**) images–the * indicates the origin of side branch. Calcific tissue is detected by both OCT and IVUS-VH images at 11 o' clock (magnified views). Co-registered OCT–grayscale IVUS (**D**) and OCT –IVUS-VH (**E**) images. OCT confirms the necrotic core tissue detected in IVUS-VH at 2 o' clock, but not the necrotic core tissue behind the calcific plaque at 11 o' clock which appears to be a false estimation and is due to artefact. Panel **F** portrays the final plaque morphology derived by the combined information provided by OCT and IVUS-VH.

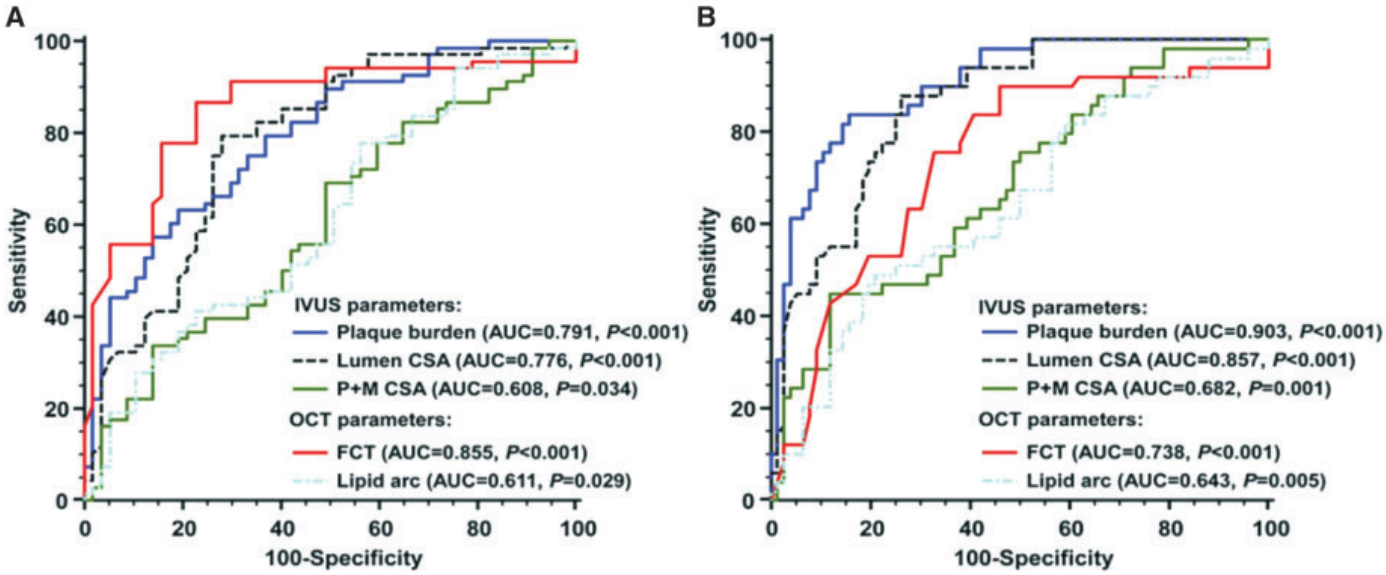

Table 1 Best Cutoff Values of Plaque Characteristics for Differentiating Ruptured Plaque (RCP and RNCP) From TCFA

	Cutoff	YI	Sensitivity	Specificity	PPV	NPV
IVUS parameters						
Plaque burden	>72%	0.46	79 (63-85)	71 (51-76)	75 (63-85)	71 (57-82)
Lumen CSA	<3.7 mm^2	0.48	79 (68-88)	69 (56-81)	75 (63-85)	74 (60-85)
P+M CSA	>7.2 mm^2	0.20	78 (66-87)	41 (29-55)	61 (50-71)	62 (43-76)
OCT parameters						
FCT	<52 μm	0.64	87 (76-94)	78 (65-88)	82 (71-90)	83 (71-92)
Lipid arc	>197°	0.22	78 (66-87)	44 (31-57)	62 (51-73)	63 (46-77)

Table 2 Best Cutoff Values of Plaque Characteristics for Differentiating RCP From RNCP and TCFA

	Cutoff	YI	Sensitivity	Specificity	PPV	NPV
IVUS parameters						
Plaque burden	>76%	0.72	84 (70-93)	88 (79-95)	82 (69-91)	90 (80-95)
Lumen CSA	<2.6 mm^2	0.64	84 (70-93)	81 (70-89)	73 (60-84)	89 (79-95)
P+M CSA	>12 mm^2	0.33	45 (31-60)	87 (77-94)	71 (52-86)	72 (61-80)
OCT parameters						
FCT	<38 μm	0.44	45 (31-60)	88 (79-95)	71 (52-86)	72 (61-80)
Lipid arc	>247°	0.28	47 (33-61)	80 (70-89)	61 (43-76)	70 (59-80)

Figure 2 Receiving operator characteristics (ROC) curve analysis of the IVUS and OCT plaque characteristics associated with plaque rupture (**A**) and with plaques that ruptured and cause a cardiovascular event. **Table 1** and **Table 2** provides the cut-off, the Youden index, the sensitivity, specificity, the positive and the negative predictive value of the plaque characteristics that differentiate ruptured from non-ruptured TCFA and of the variables that differentiate the culprit from the non-culprit ruptured TCFA, respectively. Images were obtained and modified with permission from Tian et al.[8]

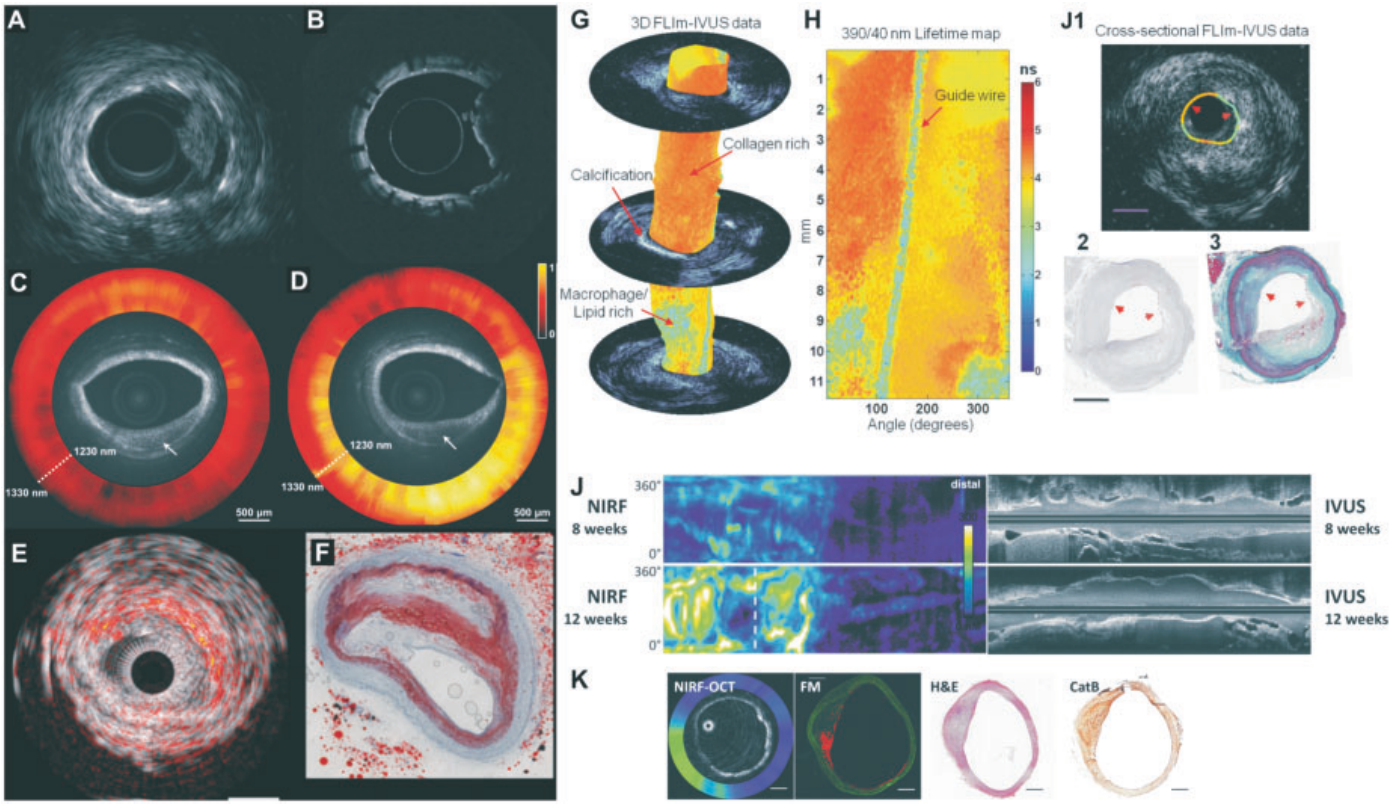

Figure 3 Output of different hybrid intravascular imaging catheters. Co-registered IVUS (**A**) and OCT images (**B**) produced by an IVUS-OCT catheter, showing a stented vessel with thrombus (indicated with an *). Output of the combined OCT-NIRS catheter (**C, D**): the plaque detected on OCT images at 6 o' clock in panel (**C**) does not correspond to lipid tissue–as it is shown by NIRS–and it has been classified as fibrocalcific while in panel (**D**) a plaque with same morphological characteristics has significant NIRS absorption and thus it has been classified as lipid-rich plaque. IVUS photoacoustic image (**E**) produced by a hybrid IVUS-photoacoustic catheter and corresponding histological section (Oil Red O stained, **F**). Photoacoustic imaging at 1710nm wavelength enables identification of the lipid tissue, detected between 10 and 3 o' clock in histological section, and is shown with red-orange colour in grayscale IVUS. Co-registered IVUS-fluorescence lifetime imaging (FLIm) using a hybrid IVUS-FLIm catheter (**G**). FLIm at 390/40nm wavelength band enables detection of calcific, collagen and lipid tissue/macrophages (**H**). IVUS-FLIm cross-sectional images (**H1**) with corresponding histological sections stained with CD68 (**2**) and elastin-Masson's Thichrome (**3**). IVUS-FLIm appears able to accurately identify collagen rich tissue (indicated with red arrow, high lifetime values) and a thin-cap fibroatheroma (yellow arrow, low lifetime values) with macrophages (CD68fl). Scale bars 1mm. (**J**) NIRF and IVUS imaging of a rabbit aorta 8 weeks and 12 weeks after mechanical injury with a balloon. A ProSenseVM110, a molecular sensor injected 24 h before imaging was used to detect for cathepsin protease activity. Atheroma was induced in the rabbit aorta by mechanical balloon injury and hypercholesterolaemic diet. (**K**) Cross-sectional OCT-NIRF image (yellow/white indicates high and blue/black low NIRF signal) at the location of the white dotted line in (**J**). Matched fluorescence microscopy (red corresponds to ProSense VM110; green to autofluorescence) and histological cross sections demonstrates increased ProSense VM110 NIRF signal in a fibrofatty plaque (H&E staining) associated with cathepsin B immunostain. Scale bars, 1mm. Images obtained with permission by Bourantas et al.[1]

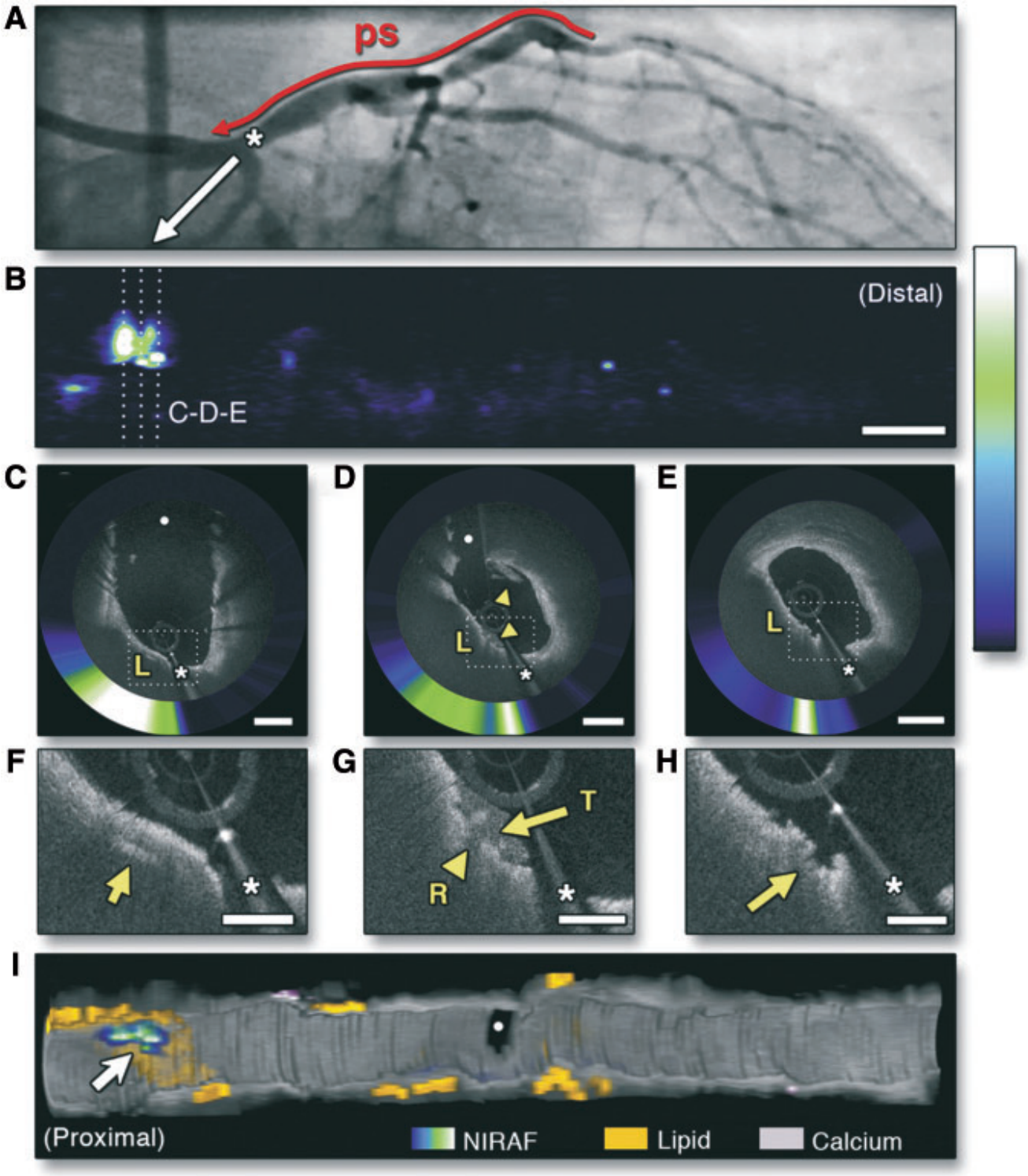

Figure 4 (**A**) Angiographic image showing a left anterior descending artery assessed by OCT-NIRAF imaging (ps, indicates the studied segment). (**B**) Spread out plot of the NIRAF signal; increased signal is noted in the distal left main stem–proximal left anterior descending artery. OCT-NIRAF cross-sections in this segment shows a lipid-rich plaque (**C–E**) with a cholesterol crystal (**F**), and evidence of plaque rupture (G, H) with superimposed thrombus (**I**). Longitudinal reconstruction of the studied segments from the OCT-NIRAF data shows several lipid rich plaques, while increased NIRAF activity (indicated with an arrow) was restricted only in the area with a large lipid pool and evidence of plaque rupture. Scale bar in (**B**) is 5mm while in OCT images and magnified views is 1mm and 0.5mm, respectively. (*) indicates the guidewire shadow, (*L*) lipid tissue, (*R*) plaque rupture, (*T*) thrombus and (TCFA) thin cap fibroatheroma. Image was obtained with permission from Ughi et al.[31]

Supplementary data

The unmet need to assess plaque pathophysiology – limitations of existing imaging modalities

Intravascular ultrasound

IVUS is currently the most widely used intravascular imaging modality. It provides cross sectional images of the vessel which allow identification of the luminal and media-adventitia borders, evaluation of the plaque burden and characterization of its composition[1-2]. This modality has been extensively used to study atherosclerotic evolution and the effect of new therapies on plaque progression[3]. Developments in signal processing have led to the development of three methods for the radiofrequency analysis of the backscattered IVUS signal (RF-IVUS), namely virtual histology IVUS (VH-IVUS), iMAP-IVUS and integrated backscatter analysis[4]. These techniques have enabled more reliable characterization of plaque composition and assessment of its phenotype[5]. However, in contrast to what it has shown in preliminary histology and small scale clinical studies,[6] prospective large scale studies of atherosclerosis demonstrated that RF-IVUS has a low accuracy in the prediction of lesions that are likely to progress and cause future cardiovascular events[7-8]. The limited accuracy of RF-IVUS was attributed to its moderate radial imaging resolution (70-150μm), which does not allow detection of micro-features associated with plaque vulnerability (e.g. macrophages, micro-calcifications, neo-vascularization, plaque erosion), and to the fact that RF-IVUS does not provide accurate assessment of plaque type within stented segments and in plaques with a complex pathology[9-10].

Optical coherence tomography

OCT was introduced 14 years ago in the clinical arena. This modality provides high resolution images (12-18μm) that permit visualization of all vessel wall layers (provided that there is no disease in the intima), and assessment of micro-features that cannot be detected by other imaging modalities, such as macrophages, neo-vessels, micro-calcifications, characterisation of the type of thrombus, and estimation of the thickness of the fibrous cap over lipid-rich plaques[11]. A recent study has shown that OCT enables detection of lesions that are likely to progress and cause events[12] and histology studies have shown that OCT is superior to IVUS in assessing the composition of the plaque[13]. However, more extensive validation has raised concerns about the efficacy of this modality in assessing plaque morphology and its ability to discriminate between deeply embedded calcific and lipid tissue, and identifying the presence of macrophages[14-15]. Additional limitations include an inability to penetrate lipid-rich cores and its limited tissue penetration (range 2-3mm), which often prevents optimal atheroma visualization.

Near infrared spectroscopy

NIRS is an intravascular imaging modality that relies on the spectral analysis of the reflected NIR light emitted by a catheter that is advanced in the coronary arteries. Histology-based studies suggest that NIRS is able to accurately assess the plaque composition and detect lipid cores[16]. Recent advances in the analysis of the NIRS signal have permitted assessment of the thickness and composition of the fibrous cap over lipid-rich plaques and differentiation of thin (TCFA) from thick cap fibroatheromas (FA)[17].

Nevertheless, a more extensive validation suggested that NIRS may be superior to IVUS in the detection of plaques with an increased necrotic core component, but it also has limited accuracy in the characterization of the phenotype of the plaque[18]. Other significant limitations of NIRS technology include the lack of image depth resolution, the fact that it does not enable quantification of plaque burden, visualization of the lumen and outer vessel wall, and assessment of plaque micro-characteristics associated with increased vulnerability such as plaque erosion, neo-vascularization and microcalcification.

Table 1. Multimodality imaging studies examining the value of combined intravascular imaging in the study of atherosclerosis.

Study	Aim	Num of patients	Num of studied segments	Imaging modality	Results
Sawada et al[19]	To assess the efficacy of RF-IVUS and OCT in detecting TCFA (defined as plaques that met both the RF-IVUS and OCT criteria)	56	126	RF-IVUS and OCT	1. RF-IVUS had only 46% positive ratio in detecting TCFA. Its limited accuracy was due to its moderate resolution which did not allow accurate assessment of the fibrous cap thickness 2. OCT had a higher positive ratio of 78% in detecting TCFA; the cause of failure for OCT was the erroneous detection of lipid cores
Gonzalo et al[20]	To evaluate the distribution of different plaque types in bifurcations using multimodality imaging	30	103	RF-IVUS and OCT	1. Lipid rich plaques (FA, TCFA) were seen in 43.7% of the studied lesions 2. The necrotic core percentage was decreasing from the proximal to the distal rim of the ostium of the side branch while the cap thickness showed an inverse tendency 3. Lipid rich plaques were seen more often in the proximal rim and in-bifurcation site than the distal rim of the bifurcation
Diletti et al[21]	To assess changes in the phenotype of the plaque in bifurcations	24	56	RF-IVUS and OCT at baseline and 6-month follow-up	1. Most of the lipid-rich plaques (81%) did not change their phenotype at 6 months follow-up 2. No differences were noted in the necrotic core component and fibrous cap thickness at follow-up
Tian et al[22]	To indentify morphological characteristics of asymptomatic TCFA, ruptured non-culprit plaques and ruptured culprit plaques	82	126	Grayscale IVUS and OCT	1. Cap thickness was smaller in ruptured plaques 2. Plaque burden was increased and the lumen area was smaller in ruptured plaques that cause events 3. Combined IVUS-OCT imaging enabled prediction of plaques that will rupture (OCT-derived cap thickness was the best predictor of plaque rupture) and cause events (IVUS-derived plaque burden was the best predictor of ruptured plaques that caused events)
Tian et al[23]	To investigate the association between lesion severity and plaque morphology	255	643	Grayscale IVUS and OCT	1. TCFA were seen more often in lesions that had a significant (>70%) stenosis on angiography 2. Severely (>70%) stenotic lesions had a thinner fibrous cap and exhibited more often plaque features associated with plaque vulnerability (i.e., micro-vessels and cholesterol crystals)
Kwon et al[24]	Compared morphological characteristics in plaques that rupture and those that erode and cause events	133 patients; 90 with plaque rupture and 43 with plaque erosion	133; 90 with plaque rupture and 43 with plaque erosion	RF-IVUS and OCT	1. IVUS showed that plaques that erode had lower plaque burden, exhibited often negative remodelling, and were rich in fibrotic tissue 2. OCT showed that plaques that erode had more often white thrombus and in 25% of the cases were located at the site of the minimum lumen area, whereas the ruptured plaques were seen only in the proximal or distal shoulder of the lesion

Hou et al[25]	To quantify the effect of statin therapy on plaque progression	46; 27 patients treated with 60mg and 19 with 20 mg atorvastatin	66; 36 in the high intensity and 30 in the low intensity statin group	Grayscale IVUS and OCT at baseline, 6 and 12 months follow-up	Higher dose atorvastatin resulted in: 1. Greater increase in fibrous cap thickness (% change: 139±161% vs. 68±84%, P=0.040) at 6 months follow-up 2. A increased reduction in the maximum lipid arc (% change: -10±18 vs 3.8±31, P=0.041) and macrophages accumulation (% change: -19% vs. -3%) at 6 months follow-up No difference in the changes in plaque between groups
Gin et al[26]	To assess the effect of statin therapy on plaque characteristics in patients with stable angina and an acute coronary syndrome	69; 14 with stable angina, 55 with an acute coronary syndrome	97; 23 in the stable angina and 74 in the acute coronary syndrome group	Grayscale IVUS and OCT at baseline, 6 months and 12 months follow-up	1. Fibrous cap thickness increased in both groups at 12 months follow-up; in patients with an acute coronary syndrome this increase was higher (193 vs. 128, P=0.018) comparing to those with stable angina 2. In patients with an acute coronary syndrome reduction of the microvessels was also noted at follow-up (45 at baseline vs. 27 at 12 months follow-up; P=0.039) 3. There were no differences in plaque burden between baseline and follow-up in both groups
Taniwaki et al[27]	To examine the safety and feasibility of multimodality imaging in the 3 epicardial coronary arteries	103 patients admitted with STEMI	103 culprit and 204 non-culprit vessels	RF-IVUS and OCT at baseline and 13 months follow-up	1. Multi-modality serial intravascular imaging was feasible in the vast majority of the culprit and non-culprit vessels 2. Multimodality imaging was safe (complication rate 1.9% at baseline and 1.1% at follow-up)
Kini et al[28]	To examine in obstructive lesions the effect of aggressive lipid lowering treatment (rosuvastatin 40mg od) on plaque characteristics	87; 44 patients randomized to intensive and to 43 standard of care lipid lowering therapy	87; 44 allocated to intensive and 43 to standard lipid lowering therapy	Grayscale IVUS, NIRS and FFR at baseline and 7 weeks follow-up	1. In contrast to the standard of care group, patients treated with intensive lipid lowering therapy had a significant reduction in the lipid component at follow-up(change in the $maxLCBI_{4mm}$ −149.1 [−210.9 to −42.9] vs. 2.4 [−36.1 to 44.7]; P=0.01) 2. There were no differences in the plaque burden and FFR measurements at baseline and follow-up in both groups.
Oemrawshingh et al[29]	To examine the implications of aggressive lipid lowering treatment (rosuvastatin 40mg) on the composition of the plaque	103	103	NIRS and RF-IVUS imaging at baseline and 6 or 12 months follow-up	1. Aggressive lipid lowering therapy had no effect in the lipid component assessed by either NIRS (LCBI: 44.9±51.1 at baseline vs. 46.1±43.2 at follow-up, P=0.80; $maxLCBI_{4mm}$: 201.9±163.8 at baseline vs. 206.8±154.5 at follow-up, P=0.72) or RF-IVUS imaging (necrotic core component: 29.1±31.9mm^3 at baseline vs. 27.7±31.2mm^3 at follow-up, P=0.074) 2. An increase in the percentage atheroma volume was noted at follow-up(40.7±10.2% at baseline vs. 41.6±9.7%, P=0.001)

Table footnote: RF-IVUS, radiofrequency analysis of the intravascular ultrasound data; OCT, optical coherence tomography; TFCA, thin cap fibroatheroma; FA, fibrotatheroma; NIRS, near infrared spectroscopy; FFR, fractional flow reserve; STEMI, ST-elevation myocardial infarction, $maxLCBI_{4mm}$, maximum lipid core burden index in 4mm segment.

Table 2. Design and findings of studies that utilize dual-probe imaging catheters.

Study	Aim	Num of patients	Num of studied segments	Imaging modality	Results
Roleder et al [30]	To assess the accuracy of NIRS-IVUS imaging in detecting OCT-defined TCFA	60	76	NIRS-IVUS and OCT	1. OCT-defined TCFA had positive remodelling, increased plaque burden and smaller lumen area on IVUS and increased lipid component in NIRS 2. Combined NIRS-IVUS imaging had a higher accuracy (sensitivity: 100%, specificity: 91%) in detecting OCT-derived TCFA than IVUS (sensitivity: 100%, specificity: 69%) or NIRS (sensitivity: 100%, specificity: 78%)
Madder et al [31]	To examine the value of NIRS-IVUS in differentiating culprit from non-culprit lesions in patients admitted with a STEMI	20	20 culprit vessels	NIRS-IVUS	1. Culprit plaques had an increased lipid component on NIRS and plaque burden on IVUS 2. The lipid burden estimated by NIRS was the only independent predictor of culprit lesions and had an high accuracy in detecting these lesions (AUC: 0.90)
Madder et al [32]	To prospectively assess the value of NIRS-IVUS in detecting culprit from non-culprit lesions in patients with a STEMI	75	75 culprit vessels	NIRS-IVUS	1. A $maxLCBI_{4mm}$>400 was able to identify culprit from non-culprit lesions with high accuracy (c-statistic: 0.83) 2. An increased plaque burden (>50%) and the presence of calcification were able to identify culprit lesions (c-statistic: 0.81 and 0.67 respectively) 3. In multivariate analysis $maxLCBI_{4mm}$>400 and plaque burden were the only variables that were associated with culprit lesions
Madder et al [33]	To assess using NIRS-IVUS morphological differences between culprit and non-culprit lesions in patients with non-STEMI and unstable angina	81; 43 non-STEMI and 38 unstable angina patients	81; 43 in non-STEMI and 38 in unstable angina patients	NIRS-IVUS	1. Compared to non-culprit plaques the culprit lesions had an increased lipid burden in both non-STEMI (3.4-fold higher) and unstable angina patients (2.6-fold higher) 2. The lipid burden estimated by NIRS allowed with a high accuracy detection of culprit lesions in both groups (AUC: 0.87 in the non-STEMI, and 0.79 in the unstable angina group)
Bharadwaj et al [34]	To examine sex differences in plaque morphology in patients with stable angina	128; 95 male, 33 female	128	IVUS-NIRS and OCT	1. There were no differences in plaque morphology, cap thickness, macrophages accumulation and calcific burden between males and females 2. Men had increased plaque burden (44.4% vs. 39.3%, P=0.031) in the reference segment compared to women but not in the minimum lumen site 3. After adjusting for baseline characteristics sex was not a predictor of an increased plaque burden at the reference segment
Ughi et al[35]	To examine the safety and feasibility of OCT-NIRAF imaging	12	17	OCT-NIRAF	1. Image acquisition was successful in all the studied segments 2. There was an excellent reproducibility of the NIRAF signal in 4 segments that had repeated pull-backs 3. An increased NIRAF signal was noted in ruptured plaques and in lesions with a high-risk phenotype

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