Update on Near-Infrared Spectroscopy/Intravascular Ultrasound

The fundamental aspects and current clinical roles.

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Intravascular imaging techniques such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are able to provide valuable insights on vessel size and structure, including plaque composition.[1,2] Unfortunately, both techniques miss the possibility of quantifying the amount of cholesterol content in the vessel wall, an essential piece of information to assess plaque vulnerability. The presence of a large lipid core covered by a thin fibrous cap with prominent inflammation within the shoulder region of the cap identifies plaques most likely to rupture.[1,3] Retrospective analysis of serial angiographies has suggested that in nearly two-thirds of patients presenting with acute coronary syndrome (ACS), a coronary angiogram obtained weeks or months before the acute episode revealed that the culprit lesion site had a noncritical (< 70%, mostly < 50%) diameter narrowing,[4,5] highlighting the importance of the different plaque features. A consequence of the excellent performance of second-generation drug-eluting stents is the prevalence of adverse events after ACS caused by lesions different from the stented culprit lesion. Techniques that empower clinicians to identify suspected vulnerable plaques offer clinically relevant information that can be used to escalate the aggressiveness of the new costly therapeutic agents targeted at reducing plaque vulnerability (PCSK9 inhibitors, SGLT2 inhibitors, etc.).[6,7]

BASIC PRINCIPLES OF NIRS SYSTEM

Near-infrared spectroscopy (NIRS) employs electromagnetic radiation with frequencies slightly lower than the visible spectrum (wavelength in the 800-2,500 nm range) to characterize the chemical structure of the surrounding tissues.[8] Because of its ability to distinguish between chemically different substances, it is widely used in biomedical sciences.[9] NIRS measurements are made by specific wavelengths of light onto a sample and measuring the ratio of reflected incident light.[10] Photons can be absorbed or dispersed by tissue, affecting the amount of light detected by the spectrometer. The chemical composition of organic bonds is responsible for most of the absorption of NIR light. The absorption pattern provides a unique chemical fingerprint that can be analyzed to yield qualitative and quantitative information about material composition. The chemical composition of the target zone can be determined using the unique spectral signals produced during this process.[9,10]

IN VITRO VALIDATION AND PATHOLOGIC CORRELATION

Cassis and Lodder used NIRS technology for the first time in animal research in 1993 to characterize low-density lipoprotein cholesterol (LDL-C) accumulation in the aortas of hypercholesterolemic rabbits.[11] Following that, researchers used diffuse reflectance NIRS to examine the lipid composition of human carotid plaques exposed during surgery.[12] Gardner et al used a novel catheter-based NIRS system to identify lipid burden in human coronary plaques and correlated them with histology findings at autopsy. In this double-blinded study, the lipid core burden index (LCBI) detected the presence or absence of fibroatheromas with an area under the curve of 0.86 (95% CI, 0.81-0.91).[13] In vivo studies were carried out to validate its accuracy for detecting lipid-core plaques (LCPs) in human vessels.[14-17] The initial clinical applications of the NIRS system indicated that the spectra acquired in the epicardial vessels of living patients

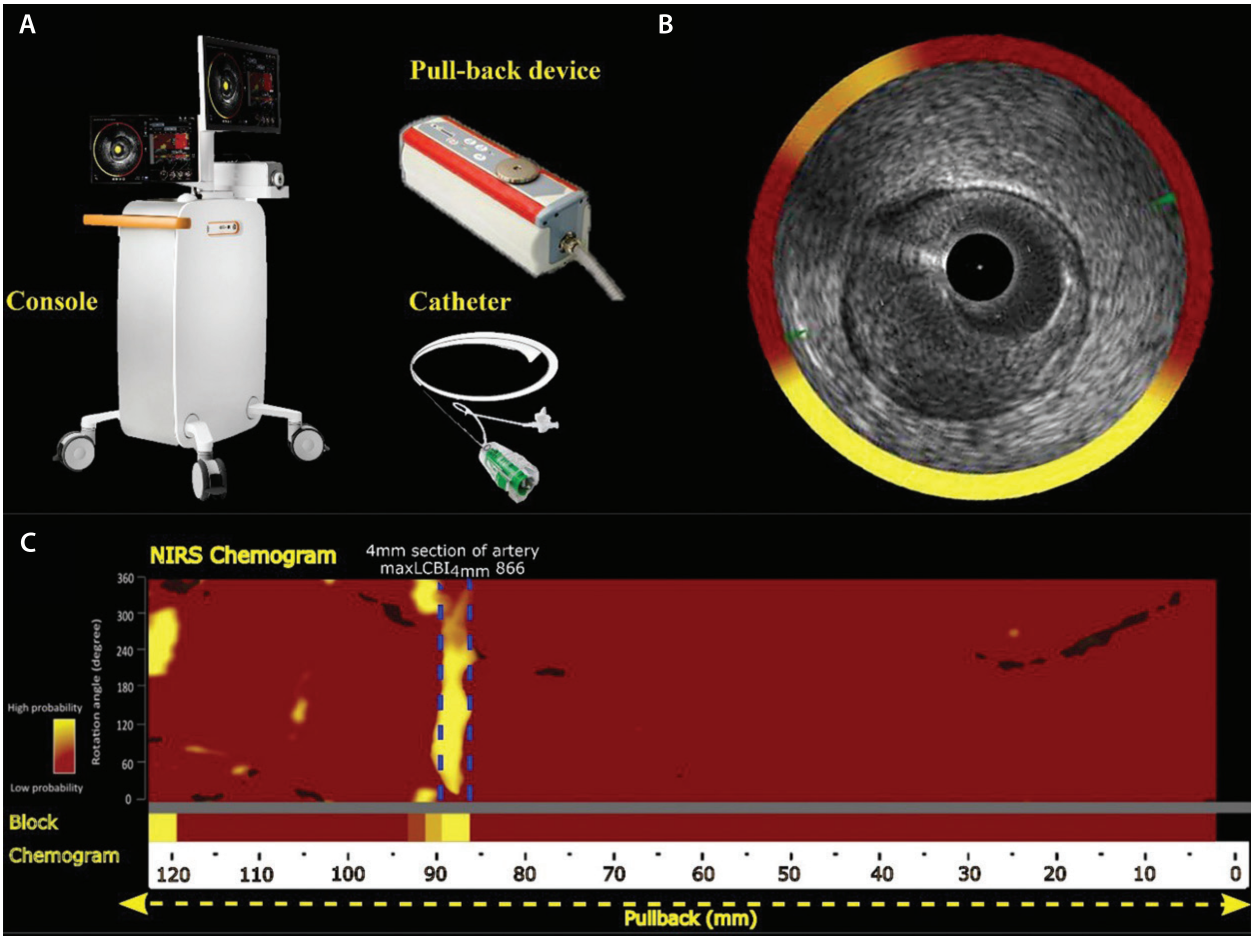

Figure 1. NIRS/IVUS imaging system (monitors, pull-back device, catheter) (A). NIRS/IVUS display during procedure (B). Interpretation of the NIRS chemogram and block chemogram (C). The X-axis indicates the pull-back position (mm) and the Y-axis represents the circumferential position of the measurement (degrees). Red regions of the chemogram correspond to locations having a low probability of lipid plaque. Yellow regions of the chemogram correspond to locations having a higher probability of lipid plaque. In this representative figure, NIRS has detected a large-size LRP in the mid-segment and a moderate in the proximal segment of the vessel. The LCBI, which is calculated as the number of yellow pixels divided by all valid pixels in the region of interest (red + yellow area) multiplied by 1,000, was 866. Upon selecting the region of interest, the application automatically identifies the maxLCBI4mm, defined as the 4-mm segment within the region of interest having the greatest LCBI (blue dash lines).

were similar to those obtained from previously verified spectra from postmortem specimens.[14,15]

The current NIRS/IVUS imaging catheter (Dualpro IVUS+NIRS catheter, Infraredx Inc.) consists of a 3.2-F rapid-exchange catheter compatible with 6-F guiding catheters, a pull-back and rotation device, and a console that houses the scanning laser, the computer that processes the spectral signals, and two monitors (Figure 1A).[2] The catheter tip produces and gathers light, which is then sent back to the system to be processed. The catheter imaging core is able to collect data rapidly by rotating at 960 rpm as it is pulled back at an automated speed of 0.5 mm/sec. IVUS images are acquired concurrently and are coregistered with NIRS data, and they are available in a variety of combined and individual displays (Figure 1B).[2,9] The software produces a color-coded graphical representation of the chemical composition of the interrogated tissue called a chemogram, which represents the probability of the presence of LCP over the scanned segment of the vessel. The chemogram is simply a map of the imaged vessel, with the X-axis representing axial position and the Y-axis showing circumferential position. The algorithm for LCP detection in humans was constructed, defining LCP as a fibroatheroma containing a lipid core ≥ 200 µm thick and > 60° angular extent on histologic analysis. In addition to the chemogram, there

TABLE 1. A SUMMARY OF NIRS STUDIES/TRIALS TO CHARACTERIZE ATHEROSCLEROTIC PLAQUES					
	First Author/ Study Name	Year	No. of Patients	Study Design	Main Findings
In Vivo-Ex Vivo Validation	SPECTACL[15]	2009	106	Multicenter, autopsy	NIRS system safely obtained spectral data in patients who were similar to those from autopsy specimens, and results demonstrated the feasibility of invasive detection of coronary LCP
In Vivo-Ex Vivo Validation	Puri et al[16]	2015	94	Single center	The pathologic study showed that the combination of NIRS-IVUS significantly improved the diagnostic accuracy of fibroatheroma compared with using IVUS-derived PB alone ($P < .01$). In vivo comparisons yielded similar associations
ACSs & Plaque Characterization	Goldstein et al[20]	2011	62	The COLOR registry substudy	NIRS imaging provided a rapid and automated means of LCP identification that can be used to identify large, stenotic, coronary LCPs, which in the study were found to be associated with a 50% risk of periprocedural MI when dilated during PCI
ACSs & Plaque Characterization	Madder et al[21]	2012	60	Single center	Target lesions responsible for ACS were frequently composed of LCP; LCP in culprit and NC lesions were more common in patients with ACS vs stable angina
ACSs & Plaque Characterization	Madder et al[22]	2013	20	Single center	The maxLCBI4mm > 400 detected in vivo by NIRS was a threshold for identification of STEMI culprit plaques
ACSs & Plaque Characterization	Madder et al[23]	2016	79	Two centers	The maxLCBI4mm ≥ 400 threshold detected STEMI culprit segments with high accuracy (sensitivity of 64% and specificity of 85%)
ACSs & Plaque Characterization	The LRP study[24]	2019	1,563	Multicenter, prospective, observational	The presence of LRP was associated with a fourfold higher NC MACE event rate (unadj. HR, 4.22; $P < .0001$). In addition, patients with maxLCBI4mm ≥ 400 were associated with a twofold higher NC MACE event rate (unadj. HR, 2.18; $P < .001$)
ACSs & Plaque Characterization	Torguson et al[25]	2021	1,552	The LRP substudy	PB of NC lesion and plaque composition in stable angina patients had a similar lipidic PB when comparing patients with ACS
ACSs & Plaque Characterization	Demola et al[26]	2021	1,266	The LRP substudy	Cholesterol-rich NC plaques determined by NIRS/IVUS showed a higher MACE in diabetic patients compared to nondiabetics
ACSs & Plaque Characterization	Bambagioni et al[27]	2021	1,551	The LRP substudy	LRPs were found more frequently in older patients and correlated to NC MACE over 2 years
ACSs & Plaque Characterization	PROSPECT II[28]	2021	805	Multicenter prospective	NC lesion-related MACE rates based on the NIRS-derived PB, those in the upper quartile of maxLCBI4mm ≥ 325, had a 10.1% risk of MACE compared with 4.8% among those with less PB
ACSs & Plaque Characterization	Shlofmitz et al[29]	2022	1,269	The LRP substudy	Proximal coronary segments had more LRPs than others. The proximal segment and maxLCBI4mm > 400 were found to be important risk factors for cardiovascular events
Stent Optimization	Dixon et al[30]	2012	69	Single center	Patients undergoing stent implantation could have LCP extended beyond angiographic margins of the initial target lesion using QCA alone
Stent Optimization	Maini et al[31]	2013	77	Single center	Plaque modification can be performed by invasive methods and evaluated with NIRS; axial plaque shifting was an acute prognostic marker for postprocedural myocardial infarction
Stent Optimization	Madder et al[32]	2021	500	Prospective, observational	The association between residual lipid content in the stented segment detected by NIRS and TLF was evaluated. A maxLCBI4mm > 200 was found in close relation to an increased risk of subsequent TLF (15.0% vs 3.1%; $P = .002$).

TABLE 1. A SUMMARY OF NIRS STUDIES/TRIALS TO CHARACTERIZE ATHEROSCLEROTIC PLAQUES (CONTINUED)					
	First Author/ Study Name	Year	No. of Patients	Study Design	Main Findings
Interventional and Antilipid Therapy Monitoring	The YELLOW I[33]	2013	87	Randomized	Significant reduction in maxLCBI4mm in the intensive statin group versus the standard of care group
	IBIS-3[34]	2016	103	Prospective observational	High-dose rosuvastatin therapy resulted in nonsignificant change in necrotic core, and a neutral effect was observed in LCBI
	The YELLOW II[35]	2017	85	Prospective observational	There was no significant change observed in plaque lipid content quantified using NIRS but a significant increase in FCT of obstructive NC lesions and enhancement of CEC in patients with stable CAD
	Ota et al[36]	2022	53	Prospective, open-label, single-center	PCSK9 inhibitors significantly reduced PB and lipid content in patients with CAD, and a significant correlation was found between the changes in LDL-C and maxLCBI4mm ($r = 0.318$; $P = .002$), alongside the reduction in plaque volume ($r = 0.386$; $P < .001$)
	PACMAN- AMI[37]	2022	300	Randomized, prospective, multicenter	In AMI patients with alirocumab (when comparing alirocumab + rosuvastatin with rosuvastatin alone), alirocumab resulted in a greater reduction in PB and plaque regression at 52 weeks in the NC vessel. For alirocumab versus placebo, the primary endpoint, mean change in percent atheroma volume from baseline, was -2.13% versus -0.92% ($P < .001$); patients with percent PAV regression was 84.6% versus 65.9% ($P < .001$); normalized total atheroma volume was -26.12 mm^3 versus -14.97 mm^3 ($P < .001$); total LCBI (by NIRS) was -29.3 versus -12.38 ($P = .004$); and change in LDL-C from baseline was -131.2 versus -76.5 mg/dL ($P < .001$)

Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; CAD, coronary artery disease; CEC, cholesterol efflux capacity; FCT, fibrous cap thickness; HR, hazard ratio; IVUS, intravascular ultrasound; LCP, lipid-core plaque; LCBI, lipid core burden index; LDL-C, low-density lipoprotein cholesterol; LRP, lipid-rich plaque; MACE, major adverse cardiovascular events; maxLCBI4mm, 4-mm segment with maximum lipid core burden index; NC, nonculprit; NIRS, near-infrared spectroscopy; PAV, percent atheroma volume; PB, plaque burden; QCA, quantitative coronary angiography; STEMI, ST-segment elevation myocardial infarction; TLF, target lesion failure.

is a block chemogram comprising 2-mm blocks spanning the axial length of the imaged vessel, which provides an easy-to-read visualization of the probability of LCP within corresponding sections of artery by attributing a color code of red (lowest probability), orange, tan, and yellow (highest probability, > 0.98) (Figure 1C).[18] The NIRS analysis generates a total LCBI measurement based on the amount of lipid in the investigated artery and detects the 4-mm segment with maximum LCBI (maxLCBI4mm).[19] All NIRS parameter measurements are fully automated, quantitative, and generated in real-time during catheter pull-back, enabling immediate integration into the catheterization laboratory workflow and clinical decision-making.

IDENTIFYING CULPRIT LESIONS AND CLINICAL OUTCOME

Several studies have retrospectively correlated an increased LCBI at the site of culprit lesions with acute coronary events (Table 1).[15,16,20-37] Madder et al used NIRS to identify the culprit vessels in ST-segment elevation myocardial infarction (STEMI) patients. The maxLCBI4mm in STEMI culprit segments was 5.8-fold greater than in nonculprit (NC) segments of the culprit vessel. From the same laboratory, a larger lipid core burden has been shown to accurately differentiate between culprit and NC lesion in STEMI patients.[23] Similar, albeit less pronounced, evidence of lipid in culprit lesions determined by NIRS findings was observed in patients with non–ST-segment elevation myocardial infarction (NSTEMI).[21,38] In another study, NSTEMI culprit segments had a 3.4-fold greater maxLCBI4mm than NC segments, and unstable angina culprit segments had a 2.6-fold higher maxLCBI4mm than NC segments.[39] In aggregate, these studies report a stepwise increase in maxLCBI4mm from NC segments (< 130), to unstable angina (~380), to NSTEMI (~450), and finally to STEMI and cardiac arrest (~550). Because of these robust NIRS findings at the culprit locations, it was proposed that maxLCBI4mm > 400 is a marker of plaques causing STEMI.[22] These NIRS imaging findings are consistent with pathologic evidence showing that fibrotic lesions are more common in stable angina, whereas lipid-rich plaques (LRP) are more commonly observed as causes of NSTEMI, STEMI, and sudden death.[40] The close association of LCP with culprit lesions described previously can be helpful in cases of ACS or cardiac arrest in which it is difficult to identify a culprit lesion.

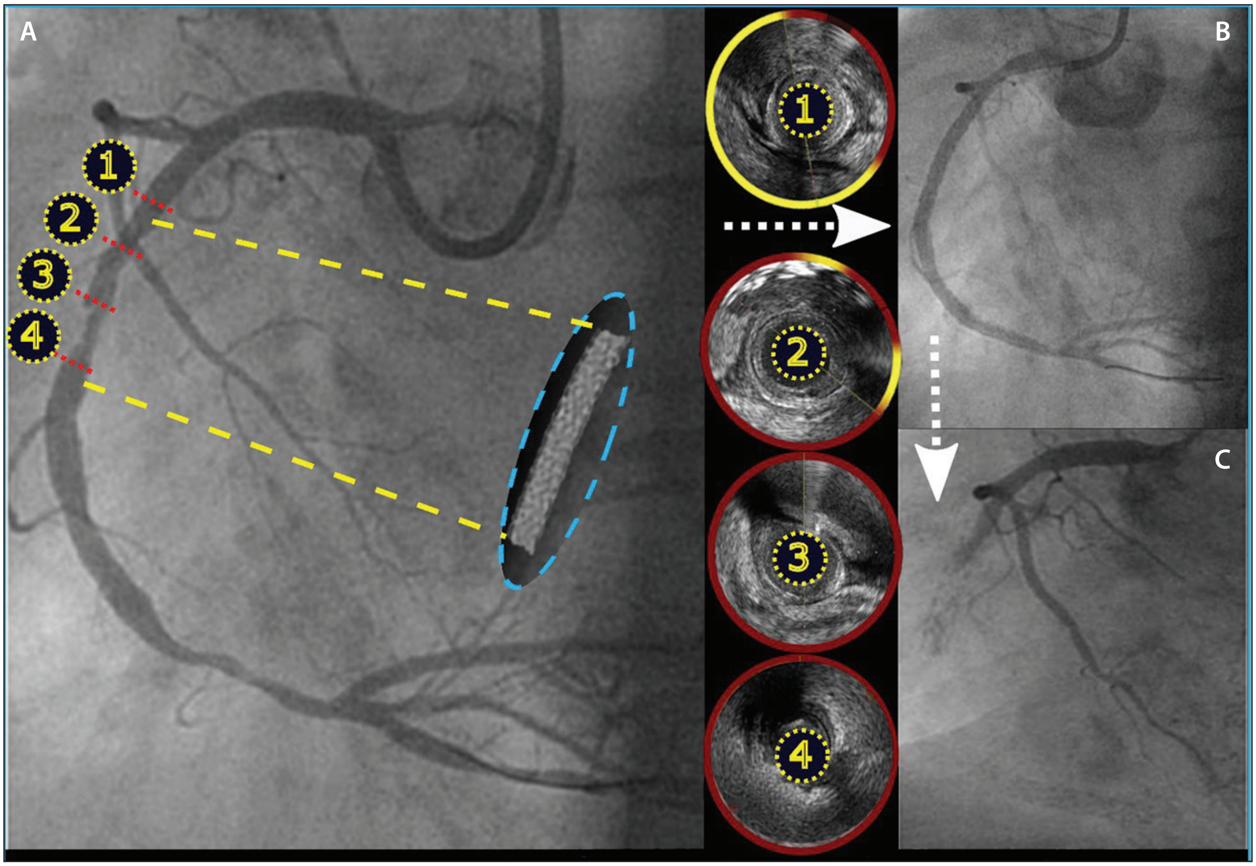

Figure 2. A patient with unstable angina. Initial coronary angiography showed a long and severe lesion in the middistal portions of the right coronary artery (A). Four cross-sections (1-4) demonstrating a cross-sectional chemogram superimposed on IVUS image from the distal to proximal portion of the midright coronary artery that show LCP in the proximal site. Coronary angiography after successful revascularization (B). Necrotic-core lipid plaque rupture and thrombus formation months after stent implantation, either in-stent or at the edge of a stent placed over an incompletely covered LCP (yellow dashed line shows the proximal and distal edge of stent when it has been placed; white dashed arrows show the timeline) (C).

The presence of an LCP with a high plaque burden on NIRS/IVUS shows that the lesion is a culprit. Another analysis in NC segments (those having a large LRP with a maxLCBI4mm ≥ 400 at an NC site) had a 10-fold increased risk of future patient-level major adverse cardiovascular events (MACE).[41]

Another NIRS study from Sweden included 144 patients with coronary artery disease (CAD) and showed that a maxLCBI4mm ≥ 400 and an LCBI ≥ the median assessed by NIRS in NC segments of a culprit artery were significantly associated with MACE at the end of 1-year follow-up.[42] The more recent PROSPECT II study identified 3,629 NC lesions in 898 patients by NIRS/IVUS. MACE within 4 years occurred in 112 of 898 patients, with 66 arising from 78 untreated NC lesions.[28] Lesions with both large plaque burden determined by IVUS and LRP determined by NIRS had a 4-year MACE rate of 7%.[28] The potential of NIRS/IVUS to predict future coronary events based on LCBI values in NC segments provides a unique diagnostic utility, as well as a risk-stratification tool.[9]

Anecdotal reports of LRP progressing to acute occlusion have been repeatedly published. Multiple recent prospective studies confirmed that a high LCBI is a predictor of plaque destabilization.[24-27,29] The largest of them, the multicenter, prospective, cohort LRP study collected NIRS/IVUS images of multiple arteries in 1,562 patients undergoing coronary angiography and/or angioplasty with stable or unstable coronary syndromes. The study demonstrated that non–flow-limiting plaques, which did not undergo percutaneous coronary intervention (PCI) but were shown to be lipid rich by NIRS, were associated with increased NC segment-related MACE.[24] Multiple substudies from this large observa-

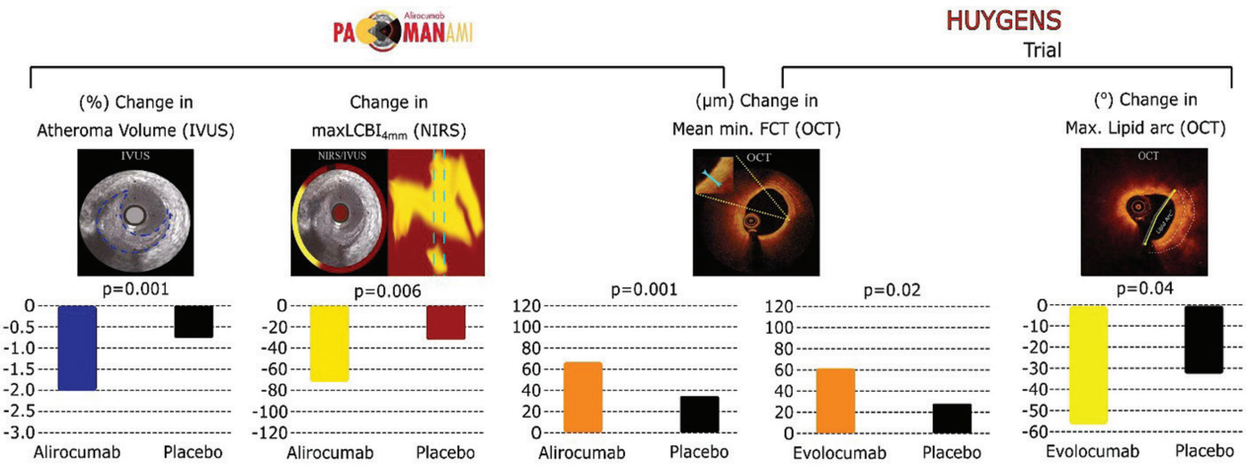

Figure 3. Main results, including primary and secondary endpoints, of the PACMAN-AMI and HUYGENS trials comparing alirocumab to the placebo and evolocumab to the placebo, respectively. FCT, fibrous cap thickness.

tional trial have been recently published and provide additional knowledge on the value of NIRS/IVUS in specific lesion subsets. In a post hoc subanalysis of the LRP study, Torguson et al examined the plaque burden and plaque composition of NC lesions by comparing patients with stable angina or silent ischemia versus ACS. They found a similar lipidic plaque burden in both groups.[25] Another recent substudy analyzed LRP patients to determine proximal versus nonproximal LRP distribution and the impact on NC MACE and found that the proximal segments have more LRPs than other segments. Additionally, having a maxLCBI4mm > 400 in a proximal segment was found to be an important predictor for future cardiovascular events.[29] Demola et al focused on diabetic patients and showed that cholesterol-rich NC plaques determined by NIRS/IVUS showed a higher MACE in diabetic patients when compared to nondiabetic patients.[26] Moreover, LRPs were more frequently found in older patients and were related to NC MACE at > 2 years in another substudy.[27]

STENT OPTIMIZATION

The subanalysis from the COLOR registry found a link between NIRS-evaluated plaque morphology and the degree of coronary artery stenosis in a prospective study of 62 patients. It demonstrated that an increasing degree of stenosis seen by angiography was associated with more vulnerable plaque morphology as assessed by NIRS/IVUS.[20]

Furthermore, NIRS imaging of target lesions before and after stenting has shown a decrease in lipid burden after PCI. The phenomenon underlying this lipid reduction is multifactorial but, at least in some cases, is attributable to lipid particle liberation and downstream embolization.[31,43]

Aside from the potential risk of no-reflow and periprocedural myocardial infarction, outcomes linked with changes in target lesion lipid burden or the quantity of retained lipid underlying the implanted stent have yet to be defined.[43,44] The use of NIRS/IVUS may improve stent placement by accurately identifying the margins of the lipid-laden segment and thereby avoiding any geographic miss of high lipid burden.[45]

Neoatherosclerosis is an essential contributor of in-stent restenosis[46] and may possibly lead to late stent thrombosis. Histologically, it is characterized by the accumulation of lipid-laden macrophages within the neointima with or without the necrotic core formation and/or calcification and can occur months to years after stent placement.[6,47,48] In the study by Ali et al, the prevalence of LCP within neointimal hyperplasia segments was 89% using NIRS versus 62% using OCT. Additionally, they found an association between significantly reduced minimal cap thickness and plaque rupture occurring in segments with neoatherosclerosis.[49] Several studies had found that when struts penetrated LCP rather than a fibrous plaque, there was a higher risk of stent thrombosis after drug-eluting stent implantation (Figure 2).

Supporting this observation, previous postmortem observations have linked the implantation of stent struts into a lipid core with the occurrence of stent thrombosis.[50-52] Dixon et al used NIRS imaging to examine coronary lesions and found that in 16% of cases, LCP expanded beyond the angiographic borders of the initial target lesion.[30] Madder et al evaluated the association between residual lipid content in the stented segment detected by NIRS and target lesion failure (TLF). They found a maxLCBI4mm > 200 as a threshold with an increased risk of subsequent TLF.[32,53]

EVIDENCE OF LIPID PLAQUE REGRESSION AFTER PHARMACOLOGIC THERAPY

NIRS/IVUS has the potential to monitor the effect of treatment. The YELLOW study was a randomized clinical trial that enrolled patients with multivessel CAD who were undergoing PCI.[33] The nontarget lesions in both groups were examined at baseline and after 7 weeks of therapy using fractional flow reserve and NIRS/IVUS. A comparison of baseline and follow-up results for nontarget lesions revealed a reduction in maxLCBI4mm significantly higher in the group with intensive statin treatment group as compared to the standard statin treatment group.[33]

Studies using NIRS/IVUS imaging have shown that lipid-lowering therapy can reduce volume and vulnerability of coronary plaques.[40,54]

The subsequent YELLOW II trial explored the effects of high-dose statin therapy on alterations in plaque morphology (by OCT) and plaque lipid characteristics (by NIRS) in obstructive NC lesions.[35] The mean baseline NIRS-derived maxLCBI4mm was > 400, and the study found no significant change in plaque lipid content by NIRS, but there was a substantial change in fibrous cap thickness after about 12 weeks of statin medication.[35] In parallel, the IBIS-3 trial demonstrated that high-dose rosuvastatin therapy had a neutral effect on LCP in nonstenotic NC lesions after 6- and 12-month follow-up intervals, despite a lower mean baseline maxLCBI4mm.[34] In another lipid-lowering therapy study, Ota et al reported that PCSK9 inhibitors significantly reduced plaque volume and lipid content in patients with CAD, and a significant correlation was found between the changes in LDL-C and maxLCBI4mm, alongside the reduction in plaque volume.[36]

The most recent PACMAN-AMI randomized clinical trial evaluated the effect of early administration of 150 mg alirocumab twice a month in addition to a high dose of rosuvastatin therapy in acute myocardial infarction patients with successful PCI of a culprit vessel with NC lesions between 20% to 50% diameter stenosis. Three hundred patients were randomly assigned 1:1 to receive alirocumab and rosuvastatin or rosuvastatin alone. NC lesions were examined by NIRS/IVUS and OCT at baseline and at 52-week follow-up. Regarding primary and secondary endpoints, a more significant reduction in plaque burden and regression in NC lesions were found in the alirocumab group compared to placebo.[37] PACMAN-AMI also found a significantly greater increase in minimal fibrous cap thickness with alirocumab compared to placebo, which is consistent with the findings of the HUYGENS OCT trial that also randomized NSTEMI patients to evolocumab and placebo, demonstrating at 52 weeks a mean increase in minimal fibrous cap thickness, and showed again significant decrease in lipid arc after antilipid therapy when evolocumab therapy was compared to placebo in 135 patients (Figure 3).[55]

LIMITATIONS

The main limitation of NIRS/IVUS is its invasiveness, preventing application in the primary prevention of asymptomatic patients with preclinical illness. Other limitations of NIRS are the lack of information regarding the vascular lumen, plaque anatomy, and status of the fibrous cap or its features.

CONCLUSION

NIRS/IVUS system is a novel intracoronary imaging modality that proved to be a diagnostically useful tool for the detection of vulnerable plaques. Early identification and stabilization of these types of plaques are crucial and can identify patients at risk of future coronary events. A new randomized trial has shown that aggressive lipid-lowering treatment can lead to a reduction in cholesterol content and an increase in fibrous cap thickness. It remains uncertain whether prophylactic revascularization of non–flow-limiting vulnerable plaques might improve patient prognosis. ■

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