The role of near-infrared spectroscopy in the detection of vulnerable atherosclerotic plaques

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Abstract

Coronary artery disease is the leading cause of mortality worldwide. Most acute coronary syndromes are caused by a rupture of a vulnerable atherosclerotic plaque which can be characterized by a lipid-rich necrotic core with an overlying thin fibrous cap. Many vulnerable plaques can cause angiographically mild stenoses due to positive remodelling, which is why the extent of coronary artery disease may be seriously underestimated. In recent years, we have witnessed a paradigm shift in interventional cardiology. We no longer focus solely on the degree of stenosis; rather, we seek to determine the true extent of atherosclerotic disease. We seek to identify high-risk plaques for improvement in risk stratification of patients and prevention. Several imaging methods have been developed for this purpose. Intracoronary near-infrared spectroscopy is one of the most promising. Here, we discuss the possible applications of this diagnostic method and provide a comprehensive overview of the current knowledge.

Key words: near-infrared spectroscopy, lipid-core plaque, vulnerable plaque.

Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide [1, 2]. It is known that most acute coronary syndromes (ACS) are caused by a rupture and subsequent thrombosis of an atherosclerotic plaque [3]. The term vulnerable atherosclerotic plaque (VP) was established in 1989 [4] to functionally define a lesion with a potential of rupture. Since then, much attention has been devoted to revealing the anatomical nature of VP. The goal is to identify VPs *in vivo* to prevent their rupture and thereby avert myocardial infarction and sudden cardiac death.

Autopsy studies have revealed that the most common non-thrombosed lesion that most resembles a ruptured plaque is the thin cap fibroatheroma (TCFA) [5]. This type of lesion is characterized by active inflammation and a large necrotic core of lipid and cellular debris with an overlying thin fibrous cap (measuring < 65 µm) that contains many macrophages and only a few smooth muscle cells [5]. Other lesions that are associated with acute coronary syndrome include plaque erosion (30–35% of cases) and calcified nodules (about 5%) [6]. This review deals only with the detection of TCFA. A number of diagnostic imaging

methods and numerous biomarkers for the identification of high-risk plaques *in vivo* have been tested [7–24].

Some of the imaging methods focus on the microanatomy of an atherosclerotic plaque [6–8]. Among the non-invasive methods, computed tomography (CT) coronary angiography (CTA) seems to exhibit the greatest potential. Some characteristics of atherosclerotic plaques detected by CTA (the presence of positive remodelling, low attenuation plaque and spotty calcification) are associated with the culprit lesions of ACS [9]. The invasive methods include intravascular ultrasound (IVUS), IVUS virtual histology and intravascular optical coherence tomography (OCT). Intravascular ultrasound is the method with the most solid evidence in VP detection, as only IVUS has large prospective studies that have proven its ability to identify lesions that cause future coronary events [10, 11]. Interestingly, these lesions were often angiographically mild and frequently harboured thin-cap fibroatheromas with a large plaque burden due to positive remodelling of the vessel [10]. A large plaque burden has recently been linked to the presence of lipid cores in lesions [12, 13]. A promising novel method is OCT. With a ten times greater resolution, it is the ideal tool for studying the microanatomy of a plaque [14, 15]. Much scientific attention is currently focused on OCT due to its great potential for VP identification [16, 17].

Some diagnostic methods are directed at measuring a plaque's metabolic activity and mechanical properties to predict the risk of its disruption (e.g., intravascular thermography, palpography and elastography). None of these methods have shown much promise thus far [6–8, 18–21].

Recently, intracoronary near-infrared spectroscopy (NIRS) was developed for the determination of the chemical composition of plaques with the intention of identifying lipid cores within lesions [6–8]. Lipid core plaques (LCP) are believed to be clinical correlates of VP [22]. The detection of LCP by NIRS not only provides us with the possibility of identifying VP but also has many other possible applications.

Additionally, a novel catheter system that aims to combine OCT with NIRS to provide an even better characterization of plaques has already been tested on the coronary arteries of human cadavers [25]. The advantages of all above-mentioned methods can be seen in Table I. An overview of the most important studies regarding vulnerable plaque are provided in Table II.

Near-infrared spectroscopy

Near-infrared spectroscopy is a technique that has been used for decades in the physical sciences to determine the chemical compositions of substances [26]. This method is based on the principle that different substances absorb near-infrared (NIR) light (wavelengths from 800 to 2,500 nm) to different degrees at various wavelengths when the light interacts with certain molecular bonds. Every substance has a characteristic pattern of absorbance that is analogous to a specific NIR fingerprint [26].

This method could obviously be used for the identification of lipid-rich and potentially vulnerable atherosclerotic plaques. The research in this field began in the early 1990s [27], but it took many years to ultimately develop an applicable NIRS catheter. In 2008, Gardner *et al.* [28] published a prospective study of coronary autopsy specimens that proved that the NIRS-IVUS system is capable of accurately detecting LCP through blood when compared to the gold standard of histological cross-sections [10, 28]. Subsequently, the feasibility of *in vivo* coronary LCP detection was demonstrated [29]. These findings launched extensive research in the field of NIRS IVUS, and the evidence supporting its capabilities is growing every day. Recently Gardner's results on the accuracy of NIRS to detect a plaque containing a large necrotic core rich in lipids was proven in a large study [30]. The results of the study proved the superiority of NIRS over the analysis of IVUS attenuation [30].

Table I. Characteristic properties of different intravascular imaging methods

Plaque characteristics	OCT	IVUS	NIRS	NIRS-IVUS	RF-IVUS
Resolution	10–20 µm	100 µm		100 µm	100 µm
Detection of lipid core	Yes	No	Yes	Yes	Yes
Plaque burden assessment	No	Yes	No	Yes	Yes
Positive remodelling	No	Yes	No	Yes	Yes
Cap thickness	Yes	No	No	No	No
Inflammation	Yes	No	No	No	No
Calcification	Yes	Yes	No	Yes	Yes
Thrombus detection	Yes	Yes	No	Yes	Yes

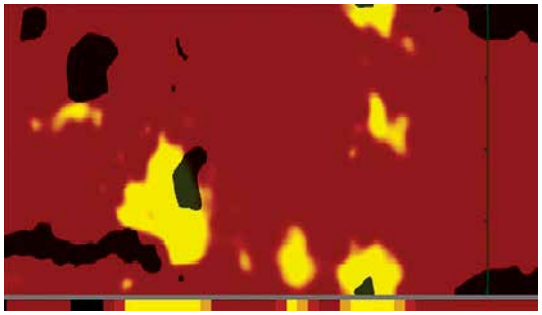

Figure 1. The results of NIRS are presented on a colour-coded probability map called a "chemogram". Every pixel represents the probability of lipid presence at the given location on a colour scale in which low probabilities of lipids are depicted as red, and high probabilities of lipids are shown as yellow. The X-axis of the chemogram indicates the pullback position in millimetres, and the Y-axis indicates the circumferential position in degrees as though the coronary vessel had been split open along its longitudinal axis

Intravascular near-infrared spectroscopy

A hybrid catheter that incorporates both NIRS and IVUS (TVC Imaging System, InfraReDx INC., Burlington, MA) is currently available. The combination of NIRS and IVUS in one system has the advantage of producing output that combines both the compositional information provided by NIRS and the structural information provided by IVUS that has the previously proven ability to detect certain properties of a vulnerable atherosclerotic plaque [10, 31].

The results of NIRS are presented on a colour-coded probability map called a "chemogram". Every pixel represents the probability of lipid presence at the given location on a colour scale in which low probabilities of lipids are depicted as red, and high probabilities of lipids are shown as yellow. The X-axis of the chemogram indicates the pullback position in millimetres, and the Y-axis indicates the circumferential position in degrees as though the coronary vessel had been split open along its longitudinal axis (Figure 1) [32]. Several parameters have been introduced for the quantification of lipid presence in the scanned region. The lipid-core burden index (LCBI) is defined as the fraction of yellow pixels on the chemogram multiplied by 1,000. The maximal lipid core burden index (mxLCBI) per 4 mm describes the region with the highest lipid burden. Additionally, the mean and maximal angles of the lipid core in the region of interest can be measured to better characterize the lesion's circumferential extent [28, 32–34].

Practical applications of near-infrared spectroscopy

Although NIRS was specifically developed for the identification of VPs, it seems to have many additional applications in clinical practice. Information about the lipid content of a plaque and the extent of the lipid core in combination with the structural information from IVUS provides clinicians with so-called true vessel characterization. True vessel characterization might aid in the risk stratification of patients prior to treatment for CAD, the optimization of percutaneous coronary interventions (PCI), the improvement of stenting and the reduction of the risk of periprocedural myocardial infarction (MI) [35]. The compositional information might also help with the adjustment of pharmaceutical therapy [36].

Prevention of distal embolization

In parallel with the fact that plaques that contain large lipid pools are prone to spontaneous rupture, these plaques also carry a greater risk of disruption during PCI [37, 38]. When such an event occurs, the lipid content of the plaque tends to embolize distally (Figure 2). This results in the obstruction of distal vessels, myocardial injury or periprocedural MI. A relationship between the pre-stenting level of LCBI and the post-procedural increase in cardiac biomarkers above the threshold for periprocedural MI has been observed in several small studies and case reports [39–43]. Goldstein *et al.* [42] published data that strongly supported the hypothesis that patients with a plaque with higher lipid content are at a significantly greater risk of periprocedural MI. In this study, 50% of the patients with mxLCBI values above the threshold of 500 suffered from periprocedural MI compared to only 4.2% of the patients with lower mxLCBI ($p < 0.001$) [42]. The above-mentioned findings seem to justify the use of protective devices in patients with high LCBI. This hypothesis was tested in the CANARY trial that was recently presented at the Transcatheter Cardiovascular Therapeutics (TCT) 2014 Congress (Coronary Assessment by Near-infrared of Atherosclerotic Rupture-prone Yellow, NCT01268319). The LCBI values of single native coronary artery lesions in 85 patients undergoing PCI were prospectively assessed. The study proved that marked reductions in the plaque's lipid contents, as determined by significant decreases in both LCBI and mxLCBI, followed PCI. The patients who developed periprocedural MI, as defined by at least three-fold elevations in cardiac biomarkers (i.e., cardiac troponin T, cardiac troponin I or creatine kinase-MB) above the normal limit, tended to have higher LCBI. Although this difference did not reach statistical significance in this small sample, the data suggest, in accordance with the above-mentioned trials, that high LCBI may be associated with periprocedural MI. A subgroup of 31 patients with mxLCBI ≥ 600 was then randomized to either PCI with a distal

Table II. An overview of important studies regarding vulnerable atherosclerotic plaque

Author	Journal	Publication year	Type of study	Number of patients	Results
Stone *et al.*	N Engl J Med	2011	Prospective	697	Thin-cap fibroatheroma, plaque burden > 70% and minimum luminal area < 4 mm associated with major adverse cardiovascular events
Calvert *et al.*	J Am Coll Cardiol Img	2011	Prospective	170	Thin-cap fibroatheroma, plaque burden > 70% and minimum luminal area < 4 mm associated with major adverse cardiovascular events
Dohi *et al.*	Eur Heart J Cardiovasc Imaging	2014	Prospective	87	Positive correlation between LCBI and plaque burden
de Boer *et al.*	Eur Heart J	2014	Observational	208	Hypercholesterolemia and male gender associated with higher LCBI
Kato *et al.*	Circ Cardiovasc Imaging	2012	Observational	104	Non-culprit lesions in patients with ACS had more VP characteristics (wider lipid arc, longer lipid length, larger lipid volume index, thinner fibrous cap, macrophage content and thrombus) compared to those with non-ACS according to OCT
Gardner *et al.*	J Am Coll Cardiol Img	2008	Observational	84	LCBI detected the presence or absence of any fibroatheroma with an area under the curve of 0.86 (95% CI: 0.81–0.91).
Waxman *et al.*	J Am Coll Cardiol Img	2009	Observational	89	Feasibility of NIRS in vivo, 83% success rate in demonstrating similar spectra to autopsy specimens
Kini *et al.*	J Am Coll Cardiol	2013	Prospective	87	Significantly greater reduction of mxLCBI in intensive statin therapy group at 6-month follow-up
Raghunathan *et al.*	Am J Cardiol	2011	Observational	30	Presence of LCP was associated with peri-procedural MI
Schultz	J Am Coll Cardiol	2010	Case report	1	Peri-procedural MI in a patient with a large LCP
Goldstein *et al.*	Circ Cardiovasc Interv	2011	Observational	62	50% incidence of peri-procedural MI in patients with large LCP (mxLCBI > 500) compared to 4.2% without large LCP ($p < 0.001$)
Saeed *et al.*	Eurointervention	2010	Case report	1	Slow flow and elevation of TnI after stenting of LCP
Waxman *et al.*	Circ Cardiovasc Interv	2010	Case report	1	DES failure due to progression of LCP after 15 months imaged by OCT
Jang *et al.*	J Am Coll Cardiol Interv	2014	Meta-analysis	24849	Lower incidence of major adverse cardiac events and all-cause mortality in IVUS-guided group
Oemrawsingh *et al.*	Circulation	2003	Prospective	144	IVUS-guided PCI was superior to angiography guidance in primary endpoints (minimal lumen diameter and the combined end point of death, myocardial infarction, and target-lesion revascularization) at 12-month follow-up
Stouffer	J Invasive Cardiol	2013	Case report	1	Stent length was optimized according to NIRS information
Dixon *et al.*	Am J Cardiol	2012	Observational	69	Target lesion length longer when determined by NIRS-IVUS guidance

Table II. Cont.

Author	Journal	Publication year	Type of study	Number of patients	Results
Papayannis *et al.*	Catheter Cardiovasc Interv	2013	Observational	9	Intra-stent thrombus formation was associated with a large LCP
Dohi *et al.*	J Am Coll Cardiol	2013	Observational	38	DES failure was associated with LCP presence
Madder *et al.*	Circ Cardiovasc Interv	2012	Observational	60	Target lesions in patients with ACS were more frequently composed of LCP than targets in patients with stable angina (84.4% vs. 52.8%, $p = 0.004$)
Madder *et al.*	J Am Coll Cardiol Interv	2013	Observational	40	A 5.8-fold higher mxLCBI in STEMI culprit segments. A threshold of mxLCBI > 400 distinguished STEMI culprit sites
Oemrawsingh *et al.*	Eur Heart J	2013	Prospective	203	A 4-fold higher risk of adverse cardiovascular events in patient with an LCBI above 46 at 1-year follow-up
Nissen *et al.*	JAMA	2006	Prospective	349	Significant decrease in LDL and increase in HDL and significant atherosclerosis regression in high-dose statin group
Serruys *et al.*	Circulation	2008	Prospective	330	Significant increase in necrotic core volume in placebo group
Takarada *et al.*	Atherosclerosis	2009	Prospective	40	Significantly greater increase in cap thickness in statin group at 9-month follow-up
Simsek *et al.*	Int J Cardiol	2012	Case report	1	Decrease of LCBI after 1 year of statin treatment

protection filter or PCI alone. Interestingly, the trial did not show any reduction in the risk of periprocedural MI between these groups. We hypothesize that periprocedural MI was caused by distal embolization of LCP. Since the lipid debris is semi-liquid, a protection filter might not provide sufficient protection against the distal embolization. A different type of protection might be needed. Further research is needed.

Optimization of percutaneous coronary intervention

Although angiograms are still considered to be the gold standard for the identification of coronary anatomy, angiograms are merely negative images of the vessel lumen [44]. Coronary angiography does not provide thorough information about the vessel wall or about the structure of a plaque that is indicated for PCI. Thus, various imaging modalities have been tested to improve the pre-interventional characterization of lesions. The intention is to prevent procedural complications, such as early and late in-stent thrombosis, dissection, or restenosis [45–50]. In a study by Dixon *et al.* [51], the NIRS-IVUS system exhibited potential in the optimization of stent length to cover the entire LCP. Furthermore, an association between the extent of LCP pre-stenting as detected with NIRS and thrombus formation post-stenting as determined with OCT has been observed in a small study [52]. It has previously been proposed that the extent of LCP might predict DES failure [53]. These results suggest that NIRS might aid the accurate placement of stents via more precise determination of the plaque's extent. This increased accuracy might help to prevent adverse events such as acute thrombosis or dissection. Obviously, larger studies are needed to support this hypothesis.

Detection of vulnerable plaques

The main purpose of NIRS is to identify lesion with high lipid contents that indicate probable sites of future coronary events. Although much research remains to be performed, we have already achieved several important milestones on this long journey. The fact that the lesions responsible for ACS more frequently harbour lipid cores has been proven in a study that compared ACS culprit sites with lesions responsible for stable CAD [54]. The same authors subsequently published another study that established characteristic NIRS images of ST-elevation myocardial infarction (STEMI) culprit lesions. These images are characterized by large lipid contents and mxLCBI above a certain threshold [55]. Thus, it seems that we have already identified a possible suspect. The more difficult part of this quest is to prove the suspect guilty, and this goal remains to be accomplished.

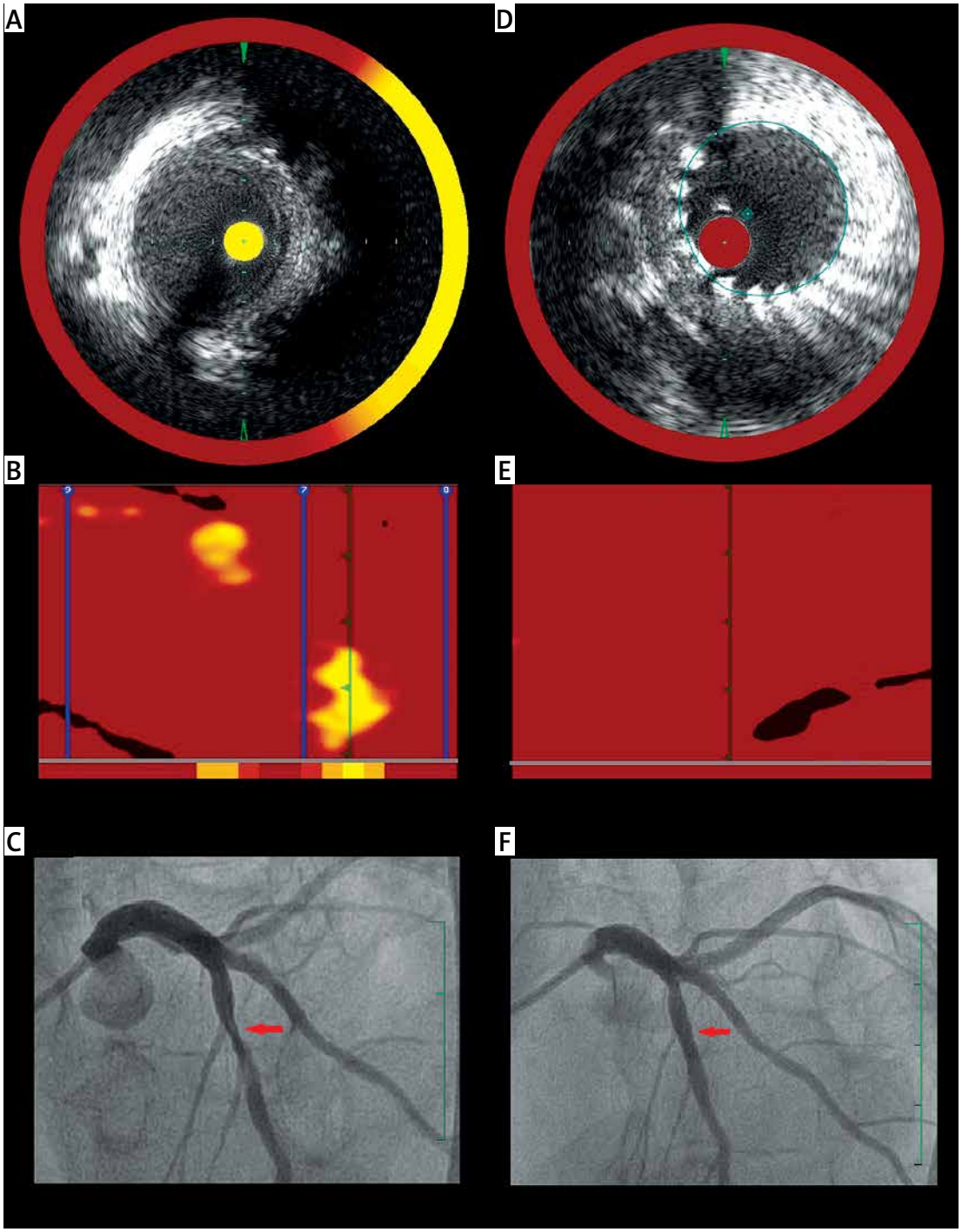

Figure 2. Panel **A** reveals the intravascular ultrasound (IVUS) image of a lesion in the left anterior descending artery prior to percutaneous coronary intervention (PCI). The near-infrared spectroscopy (NIRS) chemogram obtained before PCI reveals two lipid cores (**B**). A coronary angiogram of the lesion is provided (**C**). A second IVUS image acquired after the PCI shows good apposition of the stent (**D**). The second NIRS chemogram documented complete disappearance of the lipid cores during the dilation of the lesion (**E**). A good angiographic result is shown in panel **F**

To achieve this goal, large clinical trials capable of meeting clinical endpoints are needed. A pilot study recently published by Oemrawsingh *et al.* [56] evaluated the prognostic value of NIRS. In this prospective observational study, non-culprit vessels of 203 patients with either stable CAD or ACS who were referred for PCI were examined by NIRS. The primary endpoint of the study (i.e., a composite of all-cause mortality, non-fatal ACS, stroke and unplanned coronary revascularization) occurred 4 times more often in the patients with LCBI values that were equal to or above the me-

dian value of 43 during a 1-year follow-up. Much larger prospective studies are already in the process of patient recruitment. In the PROSPECT II trial (NCT02171065), 900 ACS patients will undergo three-vessel imaging during PCI for the initial culprit lesion in a protocol similar to that of the PROSPECT I trial. The difference between the trials is that the NIRS-IVUS catheter will be used instead of simple IVUS in the PROSPECT II trial. With the additional information provided by NIRS, the authors plan to build upon the already known IVUS results (i.e., plaque burden is associated with a higher event rate) and determine the lipid contents of the high-risk sites. The Lipid-Rich Plaque study (LRP) (NCT02033694) is a large, prospective, observational, case-control study that is presently in the process of enrolling 9,000 patients who will undergo PCI. The study's primary endpoint is non-culprit lesion-related major adverse cardiac events (NC-MACE), which are defined by a composite of cardiac death, cardiac arrest, non-fatal MI, ACS, revascularization by coronary artery bypass graft (CABG) or PCI, and/or rehospitalization for progressive angina related to the non-culprit lesion. The study aims to compare the incidence of NC-MACE between the case (large LCP as defined by NIRS-IVUS) and control (small or no LCP detected by NIRS-IVUS) groups at 2 years of follow-up. The study is expected to yield results in December of 2018.

Stabilisation of a plaque

Obviously, when we succeed in identifying VP *in vivo*, some means of stabilising them will be needed to prevent adverse events. While the apparent solution is pharmacotherapy, preventive interventions will probably also be necessary.

Many trials have already studied the effects of various medications on different characteristics of VP. These include studies with IVUS, angioscopy, OCT and even NIRS [35, 57–61]. In the ASTEROID trial, high-dose rosuvastatin (40 mg daily) was found to induce significant reductions in IVUS-defined plaque extents at 2 years of follow-up, although the net reductions were very small [56]. A different study with OCT demonstrated that statin therapy significantly increased the coronary fibrous-cap thickness during 9 months of follow-up in patients with ACS compared to patients who discontinued statin therapy [59]. Changes in NIRS-determined plaque compositions after one year of high-dose statin therapy were described in a case study [60]. In the prospective YELLOW trial, 87 diabetes patients with multivessel CAD, a lesion indicated for PCI and one other significant stenosis were randomized to aggressive (rosuvastatin 40 mg daily) or standard-of-care lipid-lowering therapy. The non-target lesions were evaluated for lipid content and plaque morphology with NIRS-IVUS during the first PCI and at 7 weeks of follow-up. Significant changes in both the NIRS and IVUS parameters were observed in the high-dose statin group. These results suggest that statin therapy reduces the lipid contents of lesions and potentially reduces the vulnerability of those lesions [36]. However, this study had some limitations, the most important of which was that the baseline characteristics of the patients in the two randomized arms were considerably different. The results of the better-designed YELLOW II trial (NCT01837823) are expected to be available in March 2015. Importantly, although the changes in the parameters observed in the above-mentioned studies were statistically significant, the absolute changes were very minor. A much larger study will be needed to prove the clinical endpoints.

Whether preventive PCI of possible VP sites will provide some benefits remains unknown. Presently, we do not have evidence supporting this hypothesis. A large substudy of the PROSPECT II trial called the PROSPECT ABSORB (NCT02171065) seeks to answer this question. In this trial, which is currently recruiting participants, patients with an angiographically and fractional flow reserve (FFR)-insignificant lesion will be randomized to two groups. In one group, the lesions will be treated with a bioresorbable vascular scaffold (BVS) and a guideline-directed medical therapy, and the second group will be treated with medical therapy alone. This study aims to determine whether the BVS safely increases the minimal lumen diameter at 2 years of follow-up.

Conclusions

In recent years, interventional cardiologists have accepted the fact that improved characterization of coronary atherosclerosis is needed. We have shifted our attention from the simple determination of the degree of arterial stenosis to the study of the anatomy and composition of atherosclerotic plaques. Much progress has been achieved, but the larger portion of the task remains to be completed. Our ultimate goals are the ability to estimate the risk of atherosclerotic disease in a specific patient and to identify vulnerable lesions to tailor coronary heart disease treatment accordingly. Coronary near-infrared spectroscopy paired with intravascular ultrasound appears to be very promising tool to achieve these goals. This diagnostic method has already yielded important evidence that is sufficient to raise our hopes. Spectroscopy seems to have identified a possible correlate of VP *in vivo* and appears to be useful for the optimization of coronary interventions. It is important to note that the studies

that have been performed to date have not been sufficiently large to prove any clinical endpoints. Thus, we are still at the very beginning of this research. Large clinical trials are needed to determine whether this method will prove valuable or be condemned to oblivion.

Conflict of interest

The authors declare no conflict of interest.

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