The potential role of intracoronary imaging at the dawn of the fourth revolution in Interventional Cardiology

El rol potencial de las imágenes intracoronarias en la cuarta era de la revolución tecnológica en Cardiología Intervencionista

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ABSTRACT

Intracoronary imaging techniques, such as intravascular ultrasound (IVUS) and more recently optical coherence tomography (OCT), have been used intensively for research, treatment planning and guidance. During the last 2 decades they presented information concerning the process of atherosclerosis and the efficacy of new pharmaceutical and interventional treatment methods amongst which the bare metal stents, drug-eluting stents and now the bioabsorbable scaffolds. Intracoronary imaging methods have shown to be indispensable tools evaluating new therapies.
The question could be raised: what could be the potential role of the intracoronary imaging methods at the dawn of the so-called 4th revolution in interventional cardiology? Here it is important to select the most appropriate evaluation method(s) to observe the efficacy of these new platforms by studying the scaffold degradation, the bioabsorption process and ultimately vessel healing. Standard coronary angiography alone is not sufficient enough and thus intracoronary imaging methods such as IVUS and OCT are crucial additional imaging tools. Both IVUS and OCT have their particular advantages and disadvantages making them more complementary than competitors.

Keywords: *cardiovascular imaging, intravascular ultrasound, optimal coherence tomography, virtual histology.*

RESUMEN

Las técnicas de imagen coronaria intracoronaria, tales como el ultrasonido intravascular (IVUS) y más recientemente la tomografía de coherencia óptica (OCT) han sido utilizadas de manera intensiva para la investigación, tratamiento, planificación y guía. Durante las últimas dos décadas éstas técnicas permitieron presentar información acerca del proceso de la aterosclerosis y la eficacia de nuevos tratamientos farmacológicos e intervencionistas entre los cuales se encontraron los *stents* convencionales, lo liberadores de droga y aquellos con polímero biodegradable. Los métodos de imagen intracoronaria mostraron ser una herramienta indispensable para evaluar estas nuevas terapias.
La pregunta que puede realizarse es: ¿Cumplen los métodos de imágenes intracoronaria un rol en el amanecer de la llamada 4 revolución en la Cardiología Intervencionista? Es importante aquí elegir el método más apropiado para evaluar la eficacia de estas nuevas plataformas estudiando la degradación del polímero, el proceso de bioabsorción y, últimamente, la "cura" del vaso. La angiografía coronaria estándar por si sola no es suficiente, por lo que métodos de imagen intracoronaria como el IVUS y la OCT son cruciales herramientas adicionales. Ambos, IVUS y OCT, tienen sus ventajas y desventajas particulares, por lo que parecen complementarse y no competir entre sí.

Palabras clave: *ultrasonido intravascular, tomografía de coherencia coronaria, imágenes intravasculares, histología virtual.*

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INTRODUCTION

What is the additional value and potential role of intracoronary imaging within coronary interventions today? During the recent years we witnessed a sort of competition between different available cardiovascular imaging techniques to become the next reference method in diagnosis and treatment of coronary artery disease. The need to get a more in-depth understanding about the atherosclerotic process was one of the triggers of this competition as some of the imaging methods, and derived quantitative tools, promised to be able to identify coronary plaques at risk, of which results could contribute to optimize treatment.
While coronary angiography is still the gold standard in daily clinical practice, intracoronary imaging techniques such as intravascular ultrasound (IVUS) and more recently optical coherence tomography (OCT) brought great additional values making them extremely useful devices, sometimes even crucial, in making treatment decisions and for evaluation of the given treatment.
Coronary angiography presents the complete coronary artery tree including the tortuosity of the ves-

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TABLE 1. Intravascular detection of vulnerable plaque.

Structures	IVUS	IVUS-VH	OCT
Fibrous cap	+	+	+++
Lipid core	+	++	+++
Inflammation	–	–	+
Calcium	+++	+++	+++
Thrombus	+	+	+++
Macrophages inflitration	–	–	+
Intimal tear	+	–	+++
Plaque rupture	+	+	+++
Positive remodelling	+++	+++	+

–: not applicable. +: poor. ++: good. +++: very good.

sels, however, its major limitations are possible foreshortening[1] of coronary lesions and the fact that it visualizes the lumen only, which could hide possible present problems within diffuse diseased arteries[2]. Coronary angiography is not a sufficient method to provide in-depth knowledge of coronary artery disease and to show in detail plaque progression or regression unlike the cross-sectional based intracoronary imaging modalities as IVUS[3,4] (**Figure 1**) or OCT[5,6]. These two modalities can be used for visualization and quantification of atherosclerotic lesions, plaque ruptures, presence of thrombosis and guidance of stent implantation[7]. The development of semi-automated analysis software tools for quantitative assessment[8] enhanced both IVUS and OCT into clinical studies evaluating new pharmaceutical therapies and new stent platforms as by example the recently introduced bioabsorbable vascular scaffolds (BVS)[9,10], sometimes referred to be the possible 4th treatment revolution in interventional cardiology.

In the era of the stents implantation with bioabsorbable polymers and the bioabsorbable scaffolds, which hopefully overcome the problems of drug-eluting stents (DES) with permanent polymers, there are a lot of questions that need to be addressed. Are bioabsorbable scaffolds a hope for treating vulnerable plaque?

Do bioabsorbable polymers for DES decrease the risks of very late stent thrombosis and the complexities of dual-antiplatelet therapy (DAPT) use in percutaneous coronary intervention (PCI) patients? Do the bioabsorbable scaffolds give long enough mechanical support to allow the vessel healing? Do they deliver their drugs efficiently to stop progression of disease at the treated segment? How long do they stay in the scaffolded lesion? Is there any residue in the vessel wall and if so, what kind and how does it interact with the vessel wall?

Some of these questions need to be addressed evaluating these particular interventional treatment methods. Both IVUS and OCT are playing an important role and this short review briefly discusses their potential in the rapidly evolving field of percutaneous coronary interventions and imaging.

INTRACORONARY IMAGING IN VULNERABLE PLAQUE DETECTION

Intracoronary imaging has opened new avenues of opportunity in the recognition and better understanding of the role of atherosclerotic lesions. All types of atherosclerotic plaques with high thrombotic risk and rapid progression should be treated as vulnerable plaques[11]. Different types of vulnerable plaques cause acute coronary events and sudden cardiac death. The vulnerable plaques could be differentiated based on morphology and activity imaging. Similar morphology plaques in diagnostic imaging might look very different using methods of detecting activity and physiology of these plaques. However, intracoronary imaging (IVUS and OCT) as a complementary techniques are very useful in identifying high risk plaques, by evaluating characteristic structures **(Table 1).** It is very important to better understand the evolution path of atherosclerosis toward a vulnerable state so that we can find out how long these plaques will stay vulnerable, how to protect plaques from becoming vulnerable and how to treat vulnerable plaque.

INTRACORONARY IMAGING IN RELATION TO NEW STENT- AND BIOABSORBABLE SCAFFOLD PLATFORMS.

The success of stenting vulnerable plaque depends on many variables: the stent type, its properties as platform, flexibility, and radial strength; the location, configuration and properties of target lesion, plaque morphology. As described-above, intracoronary imaging complements coronary angiography by presenting detailed information about the coronary vessel wall and plaque morphology. Furthermore, they are helpful during an intervention by assessing stent deployment, its expansion and by showing possible malapposition post-implantation. It has been reported that suboptimal stent/scaffold selection and deployment could be associated with increased risks of possible restenosis and thrombosis. Accurate stent/scaffold sizing, for which the quantitative analysis results of IVUS/OCT images can be used on-line, is thus very important, if not crucial, for the direct and long-term outcome of the provided treatment[12]. Proper sizing of the new bioabsorbable scaffolds is even more important as compared to permanent metallic platforms due to possible problems related to particular backbone materials used for the scaffolds such as scaffold elongation and even fractures if the selected scaffold is not of the "appropriate" size[13,14].

With respect to the scaffolds, both IVUS and OCT are capable to present information about the dimensional changes, strut covering by endothelization and

TABLE 2. Scaffolds measurements in different imaging modalities.

	QCA	IVUS	OCT
Stent length	+-	++	++
Stent area/diameters	+–	+	++
Lumen area/diameters	+–	++	++
Plaque burden	–	++	–
Stent apposition	–	++	++
Neointimal hyperplasia	–	+–	++
Stent restenosis	+	++	++
Thrombus	+	+-	++
Dissections	++	++	++
Calcification	+	++	++
Vessel remodeling	–	++	+

–: not applicable. +: poor. +–: good. ++: very good.

vessel remodeling over the time leading to a better understanding of the vessel response to the implanted scaffold[15,16]. An overview of the additional values of the IVUS and OCT are collected in **Table 2.**

Recently, several studies reported the use of IVUS as well as OCT to determine the influence of lesion preparation using different balloon sizes, e.g. pre-dilatation, on final stent expansion, where the selection of balloon and its size was based on IVUS or OCT assessment[17]. Stent expansion remains an important predictor of later possible restenosis and of sub-acute thrombosis[12]. It has been suggested that bioabsorbable scaffolds made of poly-l-lactic-acid (PLLA) have higher chances of adapting more gently to the vessel wall by allowing some deformation during implantation. Intracoronary imaging allows to address this by providing a comprehensive presentation of the stent geometry after implantation[18]. Azarnoush et al., used OCT to evaluate whether it could be applied for visualizing possible deformation of coronary vessels under the influence of the balloon inflation using it in a phantom model[19]. Muraoka et al., present the effects of IVUS-guided adjunctive high-pressure non-compliant balloon post-dilation after DES implantation in improving DES expansion safely[20], which implies that intracoronary imaging not only plays a role in stent or scaffold development but also in evaluating the treatment strategy. Taking into account that currently many different bioabsorbable scaffold platforms are under development, or have already entered the phase of clinical trials, it is crucial to appropriately investigate every aspect in the treatment procedure.

BIOABOSRBABLE SCAFFOLDS – TREATMENT STRATEGY SELECTION IN BIFURCATION LESIONS

Stent implantation in complex geometries, configurations as coronary bifurcations, is a challenging clinical problem, with a high rate of procedural complications[21]. The most common treatment strategy of atherosclerosis in coronary bifurcation is implantation a stent in the main branch and dilatation of the side branch passing through the struts of the stent at the bifurcation. Iakovou et al described different techniques of stenting a bifurcation[22]. Fusion of OCT and angiography and 3D vessel reconstruction could help cardiologist precisely assessing the size of side-branch, side-branch angles, lesion location what is important choosing treatment strategy. Bifurcation stenting techniques with metallic stents have been extensively studied but at the dawn of the 4th revolution, there are still no data how to treat bifurcations with bioabsorption scaffolds. The potential success of BVS implantation at side-branches is associated with disappearance of jailing struts. Dzavik and Colombo presented the feasibility of performing contemporary bifurcation techniques BVS[23]. Available stenting procedures (T-stenting, crush and culotte procedures) were performed in a synthetic arterial model. The study showed that BVS is recommended in provisional stenting with balloon inflation and 2-BVS, T-stent technique in a high-angle bifurcation. In other techniques, DES are preferable. Karanasos et al. demonstrated results of implanting BVS in ostial side-branch lesions[24]. In these cases, 3D vessel reconstruction based on fusion of OCT and Angiography was helpful to investigate the patterns of flow distribution at the follow up and their potential implications regarding 'neo-carina' formation. 'Neo-carina' formation could have adverse consequences by acting on flow distribution and possible protrusion in the main-branch. Presented cases suggest the possible contribution of bifurcation angle in determining the extent of 'neo-carina' formation and showed how important it is to investigate and understand the mechanism of neo-carina formation and its impact on treatment strategy selection in bifurcation lesions. Grundeken et al[25] in their study using 3D OCT reconstructions showed results of a new treatment strategy in complex bifurcation lesions with side branches > 2 mm using Tryton stent in combination with the BVS.

The above-mentioned examples showed the important role of intravascular imaging in studying stent platforms and new techniques. They also show that we still need to develop a new tool which will be able to optimize interventions. Gastaldi[26] demonstrated numerical models to analyze through the finite element method the stent behavior in applications involving coronary bifurcations. He showed promising results indicating the direction to developing novel computer methodologies, which will give the capability of analyzing different stenting techniques. In the future computer models, simulations will increase technical knowledge to allow stent designers to obtain information for the optimization of the devices used in bifurcations and clinicians to have some patients-specific proposal for intervention planning.

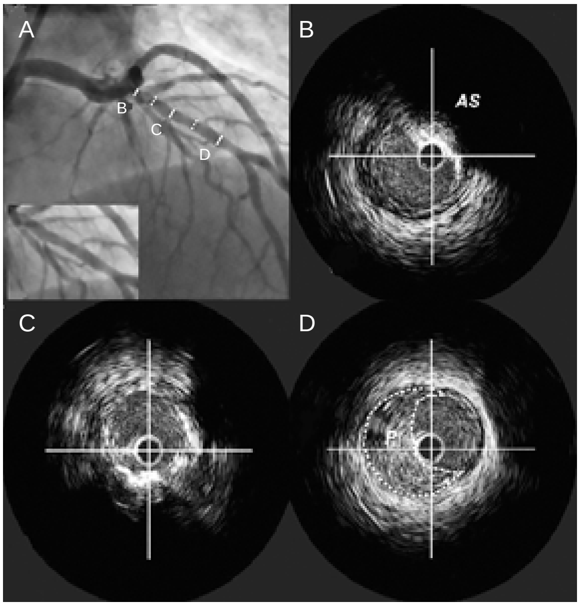

Figure 1. *Panel **A** shows the angiographic image of an LAD. The two dashed lines indicate an implanted stent. Panel **B**, proximal of the stent shows the presence of a calcified plaque which is identified by acoustic shadowing (AS). Panel **B** shows a cross-section acquired at the middle of the implanted stent. Finally panel **D**, shows a large plaque distal of the stent. On angiography these proximal and distal presence of disease is hidden by the fact that the lumen does not show a stenosis and is similar in size as within the stented segment.*

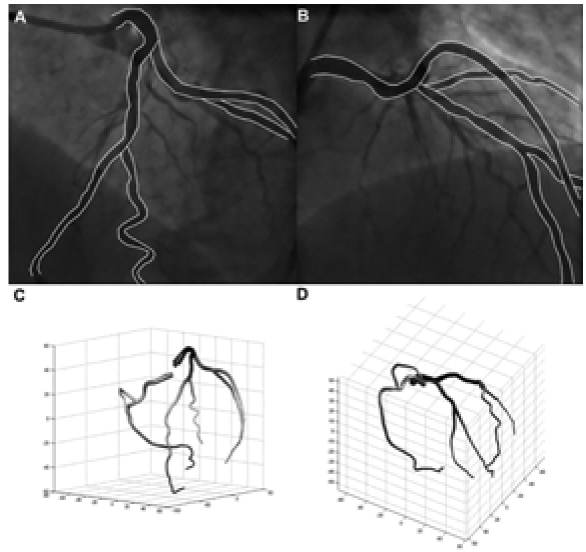

Figure 2. *Panels **A** and **B** are showing the left coronary artery detected by a software algorithm which used these detected arteries to create a true three-dimensional coronary artery tree showing the vessel tortuosity which is presented in panels **C** and **D**.*

IMAGE FUSION OF ANGIOGRAPHY AND IVUS/OCT

Intracoronary imaging is able to show tissue coverage of implanted devices. It is important to gain knowledge what exactly stimulates process of vessel healing. It has been shown that endothelial shear stress (ESS) is an important biomechanical parameter in the prediction of the localization of neointimal formation. Bourantas et al.[27] reported a study that applies a fusion between IVUS and/or OCT and coronary angiography to examine in-depth the effects of ESS on neointimal formation and showes that there is a correlation between ESS and neointimal thickness after BVS implantation. They found that, in contrast to the native segments, in scaffolded and stented segments a thick layer of tissue developed over lipid and calcific tissues making plaque more stable and in BVS the neointima developed slowly.
These types of studies are combining coronary lumen and plaque morphology information derived by intracoronary imaging and integrate that with coronary vessel tortuosity information derived from bi-plane angiography (or even rotational angiography), which allows to create a true three-dimensional (3D) reconstruction of the coronary vasculature **(Figure 2).**
Some of these studies in this area also provided information concerning the fact that the stent geometry and the shape of the struts, e.g. their thickness, determines local ESS[27 28]. Different local ESS resulted into an increased neointimal growth in-between the stent struts and a reduced neointimal coverage on top of the struts. It looks like that multi-modality imaging by integration of IVUS, OCT and angiography to assess the hemodynamic microenvironment in stented or scaffolded segments may be a very potential tool to investigate in-vivo the pro-restenotic and pro-thrombotic implications of different stent/scaffold designs[29].

UNDERSTANDING THE BIOABSORPTION PROCESS OF CORONARY SCAFFOLDS

Bioabsorbable scaffolds are a novel addition to the treatment options for the interventionist and have been developed with the intention to provide temporary lumen scaffolding without the disadvantages of a permanent implanted metallic device. Ideally, degradable implants should offer a better biocompatibility, a limited permanent longitudinal and radial straightening effect onto the coronary vessel and the possibility for vessel growth and late positive remodeling. Currently, there are two types of the main backbone components used for bioabsorbable scaffolds: 1) polymer-based, such as the PLLA; and 2) metallic-based scaffolds applying magnesium[30].
The exact nature of the degradation and the bioresorption process is still not yet fully understood, especially in the clinical setting. This process shows a difference in duration and "behavior" between the two most used backbone materials being polymers or magnesium. To evaluate these differences in-vivo only imaging can be applied, histology is obviously out of the question, and this novel task showed to be very challenging as the two materials do appear visually very much different in all possible applied imaging methods[31-33]. Both the magnesium and the polymeric based scaffolds are

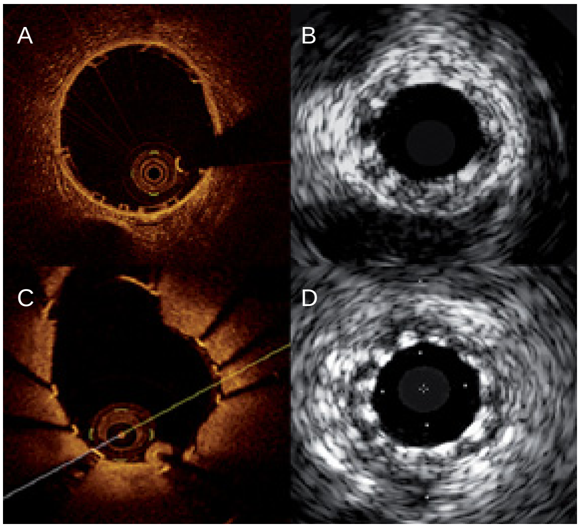

Figure 3. *Panel **A** shows a cross-sectional OCT image of a PLLA scaffold (BVS stent) and in panel **B** the same scaffold at approximately the same location but now acquired by IVUS. Panels **C** and **D** show the equivalent but now from a magnesium based scaffold.*

radiolucent and therefore not visible on angiography, performing quantitative coronary angiography is thus a difficult task[34]. The magnesium struts are visualized in IVUS images as bright structures at post-implant, almost similar to those of "regular" metallic based stents. In OCT images they appear as bright highly reflective structures with a shadow trail, an appearance often used by semi-automated quantitative computer algorithms for detection[35]. In contrast, polymeric struts in IVUS show, at post-implant, two thick lines indicating when 40MHz catheters are applied and one big bright spot when a 20MHz catheters is used due to an echogenic "blooming" effect. OCT visualizes polymeric struts, also at post-implant, as a light scattering box with a black central core, without the typical shadowing as observed behind metallic stent struts[10, 36] (Figure 3). Over time these visual appearances are changing drastically due to the degradation of the material and the further bioresorption process in both the IVUS images as well as within the of OCT. Some of these changes can be quantified and could possibly shed some light into the behavior of the scaffolds in-vivo post-implantation and could perhaps be the link between the ex-vivo bench degradation results[37].

An automated quantitative differential echogenicity analysis software tool was applied to quantify the changes in IVUS image properties of both the PLLA as well as the magnesium based scaffold platform, showing promising results[37,38]. In this method the adventitia, known to contain fibrotic tissue components, is used as a discriminator between hypo- and hyperechogenic tissue components found between the lumen-intima and the external elastic membrane area (e.g. the plaque). After scaffold implantation the amount of hyperechogenic tissue components within the scaffolded plaque area immediately increases.

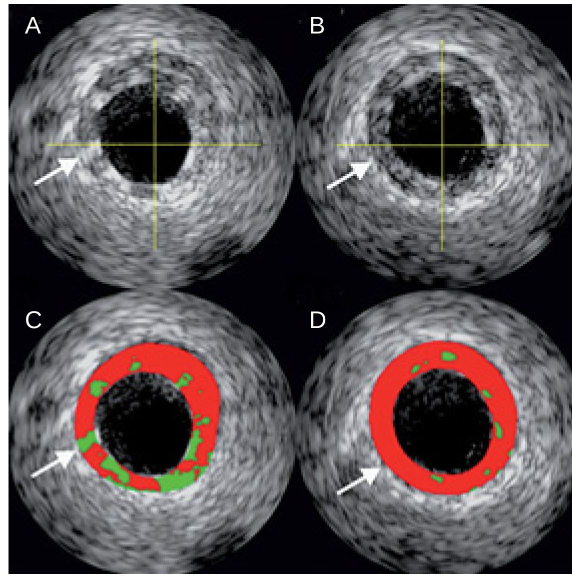

Figure 4. *In panels **A, B, C** and **D** an IVUS cross-sectional image is presented of a BVS stent imaged at post-implantation **(A)** and at 6 months follow-up **(B)**. It can be appreciated that the scaffold struts are showing a diminished appearance in the grey-scale images. This change in the so-called echogenicity can be quantified by measuring it. An in-house developed automated algorithm identified hyper- and hypoechogenic structures and color-coded them by green (hyper) and red (hypo). At 6 months follow-up scaffolds struts are less visible in IVUS (panel **B, white arrows**). In echogenicity (panels **C, D**) green areas present hyperechogenic tissue components including scaffolds struts, red areas are hypoechogenic tissue components. In echogenicity absorption process is showed as disappearing green areas.In panel **D** it can be appreciated that the level of green shows a significant reduced appearance.*

During the degradation and bioresorption process the morphology of the struts changes, which ultimately results in a diminishing gray-level intensity of the struts within the IVUS images[36] (Figure 4). It looks like that quantitative differential echogenicity could so be applied as a possible surrogate to quantify the bioresorption process in-vivo, assuming that the decrease in echogenicity parallels stent degradation. The same method was also applied to evaluate the resorption process of the magnesium scaffold platform[39].

Another study proposes to quantify the bioabsorption process by applying the commercially available IVUS-Virtual Histology (IVUS-VH, Volcano Corporation, Rancho Cordova, CA, USA) analysis tool, exploring more in-depth the raw IVUS radiofrequency data, using the so-called Shin's method[40]. This method classifies the scaffold struts as calcium surrounded by a layer of necrotic core, which is expected to diminish both over time during the strut degradation. These longitudinal changes in necrotic core and dense calcium content could perhaps also be used as surrogates to monitor the bioabsorption process in-vivo[41]. Nevertheless, to date it seems that differential echogenicity could be the most promising method to observe the bioabsorption process of scaffolds in humans[41]. An automated quantitative resorption analysis tool for OCT has not been proposed yet. However, as this field is still in its infancy, further studies linking the bench identified degradation details to the in-vivo bioabsorption measurements is highly desirable.

FUTURE PERSPECTIVES OF INTRACORONARY IMAGING

Currently, there are IVUS and OCT systems available with incorporated analysis tools for semi-automated quantification of dimensional parameters. Although, there are still promising developments announced such as higher ultrasound frequencies (>50MHz) theoretically improving the IVUS image resolution and second-harmonic imaging[42], in the era of the bioabsorbable scaffolds there is a strong need for new and improved additional software tools which might enhance the clinical value of intracoronary imaging techniques in daily practice.

3D MODELING

Recent study demonstrated that true quantitative 3D analysis of coronary angiography more reliably assessed segment lengths and diameters[43]. However, it still has the same limitations in assessing early stages of coronary plaque development and is not able to identify possible vulnerable plaques or locations. Three-dimensional computational methods to evaluate the distribution and growth of in-stent neointimal tissue applying OCT imaging, might be an interesting and useful tool[44] and, if in real-time, could even be helpful for on-line guidance of complex interventional procedures.

AUTOMATED PLAQUE CHARACTERIZATION

Quantitative automated tools to assess plaque composition by IVUS have been proposed of which some are commercially available as earlier described. These tools have been applied to quantify the degradation process of the bioresorbable scaffolds by assessing plaque compositional changes which could be used as a surrogate to identify the degradation of the scaffolds. With respect to OCT, the identification of the coronary plaque morphology is mostly performed qualitatively. This time consuming process, including possible inter- and intra-observer related deviations, could be overcome by application of automated tools, of which methods one was recently proposed[45]. In addition to this development, automated or semi-automated algorithms assessing neoatheroslerosis in bioabsorbable scaffolds could be another valuable additional tool.

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