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CTA Evaluation of Bioresorbable Scaffolds versus Metallic Coronary Stents – a Feasibility Study

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ABSTRACT

Background: Computed tomography angiography (CTA) presents important limits in in-stent restenosis (ISR) evaluation in case of metallic coronary stents, due to the artifacts determined by stent struts, which alter in-stent plaque analysis. In case of bioresorbable scaffolds, stent strut resorption allows accurate evaluation of the vessel wall. Aim of the study: This study aims to compare the feasibility of CTA as a follow-up imaging method for ISR diagnosis following elective PTCA procedures, between bioresorbable scaffolds and metallic coronary stents. **Material and methods:** We conducted a prospective, observational study on 73 patients with elective PTCA procedures in their medical history, in whom 113 stents were assessed via CTA in order to diagnose ISR. Based on stent type, the patients were divided into two groups: Group 1 – patients with bioresorbable vascular scaffolds (BVS) (n = 30); and Group 2 – patients with bare metal stents (BMS) (n = 43). Plaque analysis was possible only in the BVS group with a post-processing research-dedicated software, Syngo.via Frontier, which identified plaque morphology and virtual histology composition. **Results:** After CTA evaluation, the BVS group presented a significantly higher incidence of severe coronary artery disease (CAD) (Group 1 – 73% vs. Group 2 – 30%, p <0.0001). The proximal part of the right coronary artery (RCA) presented a significantly higher percentage of metallic stents (14% BMS vs. 2% BVS, p = 0.0029). The comparative analysis of CTA sensibility for the visual evaluation of ISR identified a significantly higher percentage of diagnostic CT evaluations in the BVS group (Group 1 – 94% vs. Group 2 – 76.19%, p = 0.0006). CTA evaluation provided the most accurate results for the 3.0 and 3.5 mm devices. Regarding CTA sensibility for ISR diagnosis, the BVS group presented the smallest incidence of non-diagnostic CT evaluations. **Conclusions:** CTA evaluation of bioresorbable scaffolds is superior to metallic stent assessment, the latter being influenced by numerous sources of error dependent mainly on the presence of the metal structure.

Keywords: CTA, in-stent restenosis, bioresorbable scaffolds, metallic coronary stent

INTRODUCTION

In the last decades, percutaneous coronary angioplasty has become one of the most common interventions for the treatment of coronary artery disease (CAD).[1] However, restenosis, occuring at the site of treated injuries, and the possible need for repeated revascularization are the main drawbacks encountered in interventional cardiology.[2] Restenosis represents a complex phenomenon that starts immediately after vessel barotrauma, induced by coronary angioplasty.[3–5] Based on the moment of occurrence, in-stent restenosis (ISR) can be classified in early ISR – due to elastic recoil and in-lumen axial plaque relocation, characterizes balloon angioplasty primarily, and late ISR – the consequence of thrombus reorganization, neointima formation, vascular remodeling, and resolution of the inflammatory process.

The need for adequate follow-up of patients undergoing coronary angioplasty emerged since the first angioplasty, performed more than 40 years ago.[2] After percutaneous coronary intervention (PCI), the patient falls into the category of patients that must be followed regularly, being at risk for stent occlusion by thrombosis or restenosis.[6] The complete assessment of the type of occlusion is essential in order to choose the optimal revascularization strategy (DES vs. DEB). Thus, choosing an optimal imaging method to monitor stent permeability represents a priority in interventional cardiology. Identifying new, modern imaging techniques that can be applied as follow-up methods of implanted scaffolds represents an interest in interventional cardiology, knowing that the early identification of a significant restenosis simplifies the subsequent revascularization procedure.[7]

The CTA evaluation of metallic stents is based on contrast agent attenuation around the area of neointimal hyperplasia. However, this process presents major limitations due to metallic stent struts, which lead to significant artifacts and misinterpretations. Regarding post-implantation follow-up, bioresorbable scaffolds present the advantage of accurate evaluation via CTA in terms of luminal dimensions and plaque analysis. The accuracy and feasibility of multislice CTA in the evaluation of bioresorbable scaffolds, assessed in a multicentric study, may consolidate noninvasive imaging techniques as reference methods in this type of patient follow-up.[8,9]

CTA evaluation has become one of the most popular imaging techniques in cardiology, its relevance in vulnerable coronary plaque evaluation being widely accepted.[10–14] In a recent study, conducted on 238 patients enrolled in the ABSORB II trial with 258 coronary atherosclerotic lesions treated with bioresorbable scaffolds, subjects were evaluated via invasive angiography, intravascular ultrasound (IVUS), and CTA at the 3-year follow-up after PCI. After analyzing the results, CTA proved to have a similar diagnostic precision to conventional angiography in terms of identifying and quantifying the severity of ISR.[15]

In this regard, the accuracy of CTA evaluation represents another advantage of bioresorbable scaffolds in the interventional treatment of coronary atherosclerotic lesions.

OBJECTIVES

CTA presents important limitations in ISR evaluation in case of metallic coronary stents due to the artifacts determined by stent struts, which alter in-stent plaque analysis.

In case of bioresorbable scaffolds, stent strut resorption allows the accurate evaluation of the vessel wall. This study aims to analyze the utility of CTA in the follow-up evaluation of bioresorbable scaffolds versus metallic coronary stents, in order to diagnose ISR after PCI.

MATERIAL AND METHODS

We conducted a prospective, observational study, which included 73 patients, treated by implanting one or more stents for coronary artery disease, in the CardioMed Medical Center Tîrgu Mureș, according to ESC guidelines, between January 2015 and March 2017. Based on stent type, the study subjects were divided into two groups: Group 1 – 30 patients with 50 implanted bioresorbable scaffolds (ABSORB 1.1/Abbott Vascular) and Group 2 – 43 patients with 63 metallic (MULTI-LINK ULTRA/Abbot Vascular, Tsunami Gold/Terumo, Guidant MULTI-LINK PLUS/Abbot Vascular) and drug-eluting stents (Resolute Integrity/Medtronic, XIENCE/Abbot Vascular).

Patients with PTCA and stent placement in their medical history were included in this study. Other inclusion criteria were age over 18 years, BMI <40 kg/m^2, signed written informed consent. Exclusion criteria were ST-elevation myocardial infarction or non-ST-elevation myocardial infarction as diagnosis of PCI indication, electric and hemodynamic instability at admission, allergy to iodine contrast material, indication for oral anticoagulation therapy à la longue, acute renal failure or terminal-stage chronic kidney disease, pregnancy or lactation, active malignancy/end-stage disease with life expectancy under 1 year, or refusal to provide written informed consent for study enrollment.

Each patient underwent invasive angiography and CTA evaluation, between 12 and 24 months after PTCA, in order to evaluate the stent's degree of permeability. After PTCA, each subject performed the 1-, 6-, 12-, and 18-month follow-up visit with major adverse cardiovascular events (MACE) rate evaluation.

CT scanning protocol

Each CTA evaluation was performed using a 64- and 128-slice dual-source CT scanner (SOMATOM Definition, Siemens Healthcare) available in the Laboratory of Advanced Research in Cardiac Multimodal Imaging of the Cardio Med Medical Center of Tîrgu Mureş, with 64 detector rows × 0.5 mm and 128 × 0.6 mm respectively, 330 ms rotation time, and a table feed of 0.2–0.4 mm per rotation.

The scanning protocol involved a 4–6 h fasting period, avoidance of smoking, caffeine use, and intense physical exercises 24 h prior to the CT examination; a heart rate below 60 bpm during image acquisition, using a bradycardization protocol with Metoprolol 25–50 mg or Ivabradine 5 mg orally, 1 h prior to the CT scan. The scanning protocol was explained to each patient, the study subjects being instructed to follow audio instructions regarding respiration. The Ultravist 370 mg I/ml contrast agent (Bayer Healthcare, Germany) was administered through a peripheral venous catheter (16–22 G) placed in the antecubital vein, followed by 50 ml of 0.9% NaCl solution. The dose of the contrast agent was adjusted according to body weight and scan time, based on the formula: contrast agent volume (mL) = (scan time + 10) × preset flow rate, at a flow rate of 5 mL/s, a tube voltage of 120 kV, and a tube current of 400 mAs.

The CT scanning protocol included a topography in antero-posterior and lateral incidence, in order to frame the acquisition territory from the base of the sternum to the apex of the heart. "Automatic bolus tracking" technique was used to detect the contrast reaching the descending aorta. The region of interest was placed in the descending aorta and the median region of the heart, and image acquisition was performed after the audio command of breathing, at 10 seconds after the beginning of contrast material injection.

CT image reconstruction and data analysis

Post-processing of CT acquisitions was performed using a dedicated software, Syngo.via Frontier with a Siemens workstation (Siemens AG, Erlangen, Germany) and QCTA RE (Medis, Leiden, Holland).

In order to reconstruct images of the coronary arteries, cardiac cycles with minimal movement or frequency artefacts were selected. Stents were evaluated via curved multiplanar reconstructions, defining the following imagistic patterns:

- permeable stent without signs of neointimal hyperplasia: homogeneous opacification of the vascular lumen;
- permeable stent with insignificant neointimal hyperplasia: longitudinal attenuation of the contrast agent, with a lumen reduction <50%;
- significant ISR: longitudinal and transverse attenuation of the contrast agent, with a lumen reduction >50%;
- ISR with occlusion: complete lack of lumen opacity.

The analyzed stent was considered correctly evaluated if its lumen was visible in all its length and contrast attenuation was not significantly altered by artifacts caused by metals struts or motion. In the situation of getting a low-quality, blurry and unequally acquired image with a series of artifacts, the CT evaluation was considered non-diagnostic. Together with the stented coronary artery segment, 5 mm before and after the scaffold were evaluated with maximum intensity projection in order to define restenosis in the stent ends.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 7 software (GraphPad Software, Inc., San Diego, USA). A two-tailed p value of <0.05 was considered statistically significant. The D'Agostino Pearson normality test was used to test the normality of distribution of numerical data, continuous data was shown as mean ± standard deviation and median respectively, and categorical variables were expressed as percentages and integer values. Pearson and Spearman coefficients were used for correlation analysis.

Ethics

This study was conducted according to the current revised edition of the Declaration of Helsinki. The study was performed under the approval of the Ethics Committee of the University of Medicine and Pharmacy of Tîrgu Mureș (approval no. 338/17.11.2017) and the Ethics Committee of the CardioMed Medical Center (approval no. 29/28.12.2017). Written informed consent was obtained from each patient.

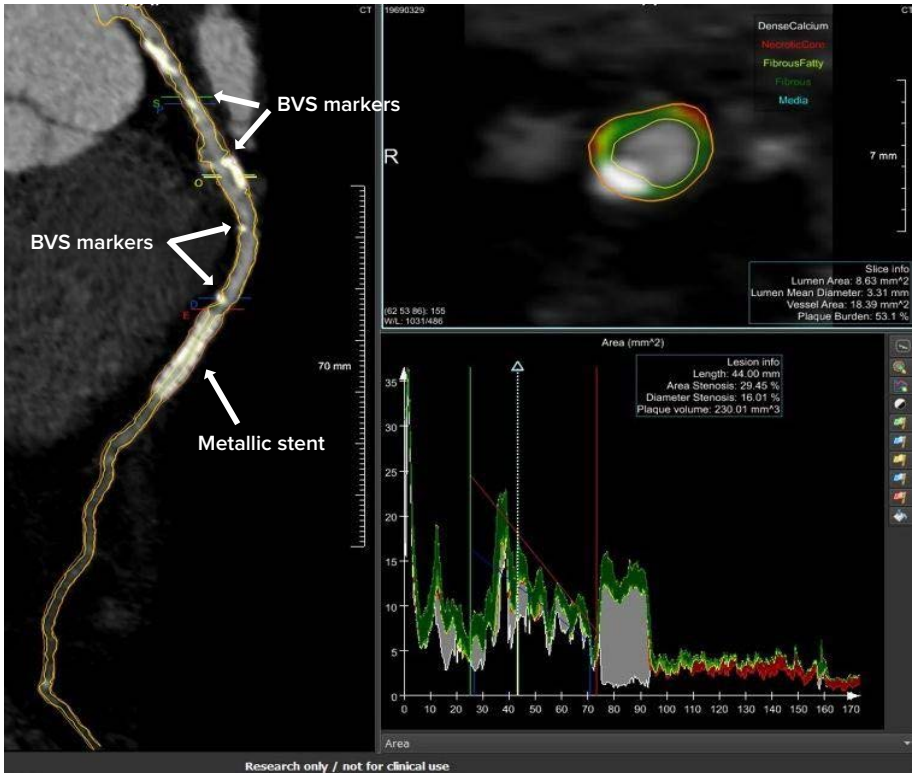

FIGURE 1. CTA of the left anterior descending artery at 12 months after PTCA with 3 BVS and 1 DES – QAngio-CT RE post-processing software (Medis, Leiden, the Netherlands)

RESULTS

General characteristics of the study population

General characteristics and the main cardiovascular risk factors in the two study groups are summarized in Table 1.

We found no significant differences regarding mean age in the study groups (Group 1 – 65 ± 7 years vs. Group 2 – 58.07 ± 7.75 years, p = 0.71).

With regard to the incidence of cardiovascular risk factors, there were no statistically significant differences regarding the prevalence of diabetes mellitus (Group 1 – 38% vs. Group 2 – 20%, p = 0.56), male gender (Group 1 – 82% vs. Group 2 – 86.66%, p = 0.56), or chronic tobacco use (Group 1 – 40% vs. Group 2 – 43.33%, p = 1.0).

However, dyslipidemia had a higher incidence among patients from Group 1 (Group 1 – 73% vs. Group 2 – 30%, p <0.0001).

TABLE 1. General characteristics and cardiovascular risk factors

	BMS, n	BMS, %	BVS, n	BVS, %	p value
Age (years)	65 ± 7	–	58.07 ± 7.75	–	0.71
Male gender	37	82%	26	86.66%	0.56
Body mass index (kg/m^2)	23.7 ± 2.0	–	24.5 ± 2.3	–	0.78
Diabetes mellitus	17	38%	6	20%	0.56
Dyslipidemia	33	73%	9	30%	<0.0001
Chronic tobacco use	18	40%	13	43.33%	1.0
Diseased vessels					
1 vessel	26	60.46%	13	43.33%	0.0051
2 vessels	12	27.9%	8	26,66%	0.0051
3 vessels	5	11.62%	9	30%	0.0051

TABLE 2. Stent type and characteristics

Model	Stent material	Strut thickness (μm)	Stent, n
BMS			
MULTI-LINK VISION/Abbott Vascular	Cobalt	81.28	2
Resolute Integrity DES/Medtronic	Cobalt	91.44	11
XIENCE PRO DES Everolimus/Abbott Vascular	Cobalt	81.28	28
Tsunami Gold BMS/Terumo Europe	Stainless steel	78.74	13
MULTI-LINK PLUS/Guidant	Stainless steel	55.88	9
BVS			
ABSORB Bioresorbable Vascular Scaffold 1.1, Abbott Vascular, Santa Clara, California	Poly-L-lactic acid	150	50

In terms of CAD severity, Group 1 presented a significantly higher incidence of severe atherosclerotic involvement (Group 1 – 11.62% vs. Group 2 – 30%, p <0.0051).

Characteristics of the implanted stents

The type and main characteristics of implanted stents are presented in Table 2.

Revascularized coronary segments with metallic and bioresorbable scaffolds are presented in Table 3.

Regarding the revascularized coronary segment, the proximal part of the right coronary artery (RCA) presented a significantly higher percentage of metallic stents compared to BVS (14% BMS vs. 2% BVS, p = 0.0029). The middle (9.52% BMS vs. 10% BVS, p = 1.0) and distal parts of the RCA (9.52% BMS vs. 4% BVS, p = 0.25) presented no significant differences in terms of the type of implanted device.

CTA performance in the evaluation of BVS vs. BMS

The comparative analysis of CTA sensitivity in terms of visual evaluation of ISR in the two study groups identified a significantly higher percentage of diagnostic CT evaluations in the BVS group (Group 1 – 94% vs. Group 2 – 76.19%, p = 0.0006). The diagnostic sensitivity analysis of CTA in ISR is presented in Table 4.

Plaque analysis was possible only in the BVS group with a post-processing research-dedicated software, Syngo.via Frontier, which identified the vulnerability markers presented in Table 5.

Patients from Group 1 presented in a greater percentage 1 (38.29%) or 2 (25.53%) vulnerability markers (Figure 2).

Morphological and virtual histology aspects of the analyzed coronary plaques in the BVS group are presented in Table 6.

TABLE 3. Stent location

Segment	BMS, n	BMS, %	BVS, n	BVS, %	p value
RCA proximal	9	14.29	1	2	0.0029
RCA mid	6	9.52	5	10	1.0
RCA distal	6	9.52	2	4	0.25
LAD proximal	9	14.29	11	22	0.66
LAD mid	14	22.22	13	26	0.61
LAD apical	1	1.59	2	4	0.36
LCX proximal	3	4.76	4	8	0.37
LCX mid	3	4.76	6	12	0.06
D1 proximal	6	9.52	3	6	0.59
D1 mid	0	0	1	2	–
MO1 proximal	3	4.76	0	0	–
MO2 mid	3	4.76	0	0	–
Intermediate	0	0	1	2	–
Left main	0	0	1	2	–
TOTAL	63	100	50	100	

TABLE 4. ISR detection sensitivity of CTA

	Diagnostic CT		Non-diagnostic CT		p value
	n	%	n	%	
BVS	47	94	3	6	0.0006
BMS	48	76.19	15	23.8	0.0006

TABLE 5. CTA features of vulnerable plaques

	%
Positive remodeling	46.8
Spotty calcification	65.95
Napkin-ring	4.25
Low attenuation	19.14

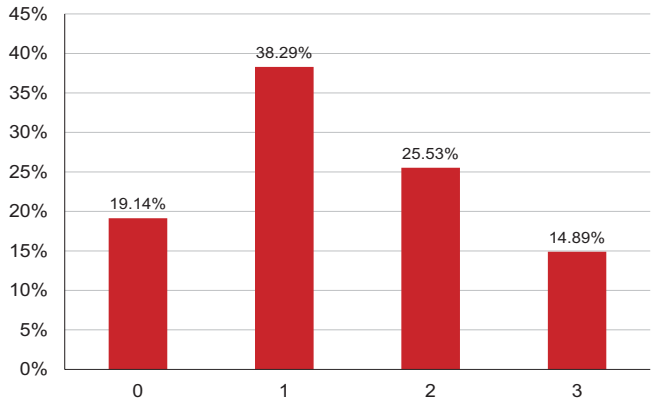

FIGURE 2. Incidence of CTA markers of vulnerability

In terms of significant hemodynamic ISR, CTA evaluation provides the most accurate results for the 3.0 and 3.5 mm devices. In 2.5 and 4.0 mm devices, the number of significant ISR diagnoses was zero. Regarding the sensitivity of CTA for ISR identification, the BVS group presented the smallest incidence of non-diagnostic CT evaluations (Figure 3).

DISCUSSIONS

Following the feasibility of CTA in diagnosing ISR in BMS vs. BVS as a primary endpoint, this study demonstrated a significant difference in the specificity of this imaging method, showing a higher accuracy for bioresorbable scaffolds compared with metallic coronary stents. The major advantage of BVS derives from its radiolucency properties. Moreover, the inclusion of the bioresorbable matrix in the vascular wall at 12–24 months after PTCA results in the loss of the initial mechanical resistance and lumen remodeling, with an increase in size.[16] Regarding metallic stents, it is a well-known fact that ISR is more common in small-diameter devices, the more so as the metallic struts are greater.

These findings are in line with data published by Oncel *et al.*, which has shown that the visual CT analysis of 39 coronary stents, based on two independent radiologists, had a sensitivity of 89%, a specificity of 95%, and a positive predictive value of 90% compared to standard invasive angiography, these values being even much lower in case of devices with diameters below 2.75 mm.[17] In a study conducted on 25 patients revascularized with metallic stents of 2.5 and 3.0 mm diameter, Rist *et al.* have shown that in this class of patients, the follow-up evaluation via CTA failed to detect the presence of asymptomatic intrastent occlusion in 17% of the cases.[18] However, another study, led by Graaf *et al.*, using 320-slice CTA evaluation in 53 patients with 89 metallic stents in vessels with diameter under 3 mm and strut dimensions above 140 microns, demonstrated a reduced specificity of this method in assessing the incidence of ISR, due to significant reduction of image quality through metal artifacts.[19]

The most common causes for reconstruction errors in the CTA evaluation of metallic stents include the following: heart rate >65 bpm, which results in a larger number of cardiac cycles, a higher dose of irradiation in a time unit, and a loss of optimal spatial resolution due to motion artifacts, requiring the extension of acquisition over a larger number of cardiac cycles;[20,21] the so-called "blooming effect" of contrast reflection, which is more evident in small

TABLE 6. Plaque morphology and virtual histology composition – Group 1

	Mean value ± SD
Plaque length (mm)	17.45 ± 4.97
Stenosis (%)	22.37 ± 12.73
Eccentricity index	0.43 ± 0.26
Remodeling index	1.03 ± 0.29
Vascular volume (mm^3)	273.2 ± 87.42
Lumen volume (mm^3)	119.8 ± 46.45
Plaque volume (mm^3)	153.6 ± 65.0
Dense calcium (mm^3)	17.48 ± 20.43
Dense calcium (%)	10.55 ± 11.92
Necrotic core (mm^3)	136.4 ± 52.76
Necrotic core (%)	89.45 ± 11.92
Fibro-fatty (mm^3)	11.07 ± 10.38
Fibro-fatty (%)	6.83 ± 5.66
Fibrous (mm^3)	125.1 ± 48.53
Fibrous (%)	82.56 ± 12.63
Calcium score – local	73.79 ± 80.19
Calcium score – target coronary artery	186.9 ± 207.5

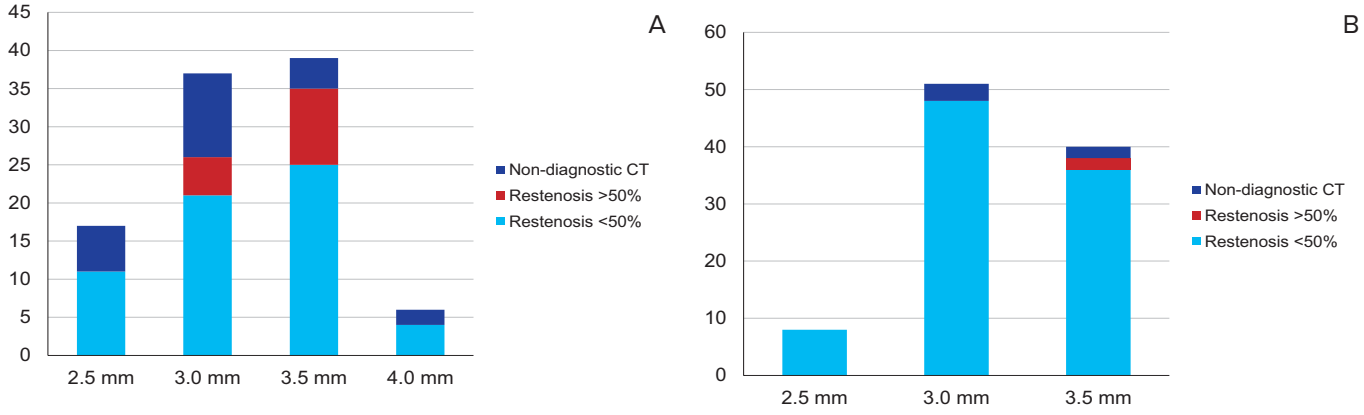

FIGURE 3. **A** – ISR detection sensitivity of CTA in BMS of different dimensions; **B** – ISR detection sensitivity of CTA in BVS of different dimensions

diameter and large strut stents and is dimmed in stents with diameter above 3 mm;[22,23] stent composition: gold or gold-coated stents, as well as tantalum stents involve rough artifacts compared with steel or cobalt metallic stents.[20] Proximal stent distribution on LDA, LCX, or RCA allows a better visualization of contrast material in the lumen of the stent compared to more distal segments such as diagonal or obtuse marginal branches and distal LCX.[23]

A series of these technical obstacles disappear in bioresorbable scaffold reconstructions. Moreover, their diameter increases at 12–24 months after PTCA due to vascular remodeling as a result of matrix resorption and loss of rigidity, characteristic for these devices.

CONCLUSIONS

The CTA evaluation of bioresorbable scaffolds is superior to metallic stent assessment, the latter being influenced by numerous sources of error dependent mainly on the presence of the metal structure. Noninvasive CT assessment is a fast and effective method compared to conventional invasive coronary evaluation, which is not a suitable screening technique due to the risks associated with the invasive nature of the procedure and the additional costs related to the need for post-interventional hospitalization for at least 24 hours.

CONFLICT OF INTEREST

Nothing to declare.

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