IMPACT OF PRE-STENT IMPLANTATION PLAQUE BURDEN ON THE DEVELOPMENT OF STENT RESTENOSIS

STENT İMPLANTASYONU ÖNCESİNDEKİ PLAK YÜKÜNÜN STENT RESTENOZUNA OLAN ETKİSİ

PRE-STENT IMPLANTATION PLAQUE BURDEN AND RESTENOSIS

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Öz

Amaç: Biz bu çalışmamızda stent implantasyonu öncesinde kantitatif koroner anjiografi (QCA) ve Imaj J programını kullanarak hesapladığımız plak alanının stent restenozu gelişimi üzerine olan etkisini araştırmayı amaçladık. Gereç ve Yöntem: Mart 2008 ve Temmuz 2011 arasında uygulanan 5180 adet koroner anjiografi prosedürü çalışmada incelendi, 227 adet in-stent restenoz mevcut idi. Dışlama kriterlerinin ardından, yüz altmış dört adet stent implantasyonunun yapıldığı 121 hasta retrospektif olarak incelendi. Stentler hastaların klinik durumlarına göre; a) in-stent restenosis gelişen grup (n:77, 47%) ve b) in-stent restenosis gelişmeyen grup (n:87, 53%) olmak üzere iki gruba ayrıldı. Stent implantasyonundan en az 6 ay sonra koroner anjiografi ile 50% veya daha fazla daralmanın saptandığı durumlar in-stent restenoz oluşumu için pozitif olarak değerlendirildi. Plak alanı ölçümleri kantitatif koroner anjiografi (QCA) ve İmaj J programı kullanılarak yapıldı. Bulgular: Kantitatif olarak ölçülen plak alanlarında gruplar arasında istatistiksel olarak anlamlı farklılık saptanmadı (p>0.05). Ancak İmaj J ile ölçülen alanlarda gruplar arasında anlamlı düzeyde farklılık gözlendi (p<0.05). Gruplar arasında hipertansiyon, hiperlipidemi öyküsü, statin kullanımı, HDL değerleri ve lezyon tipleri (p<0.05) istatistiksel olarak anlamlı farklılık gösterirken, diyabet varlığı ve sigara kullanımı anlamlı düzeyde farklı saptanmadı (p>0.05). Stent restenoz gelişimi ile hipertansiyon, statin tedavisi kullanmama, HDL değerleri, kötü lezyon tipi ve İmaj J ile ölçülen plak alanı arasında ilişki mevcut idi. Tartışma: Hipertansiyon, statin tedavisi kullanmama, düşük HDL seviyeleri, kötü lezyon tipi ve İmaj J ile ölçülen geniş plak alanları in-stent restenoz gelişimi için önemli birer belirteçlerdir.

Anahtar Kelimeler

İmaj J; Plak Alanı; İn-Stent Restenoz

Abstract

Aim: In this study we have used quantitative coronary angiography (QCA) and the Image J program in order to investigate the influence of plaque area, as identified prior to stent implantation, on the development of stent restenosis. Material and Method: 5180 coronary angiography procedures were performed between March 2008 and July 2011. Of these, 227 presented with in-stent restenosis. After application of the exclusion criteria, 164 intracoronary stents implanted in 121 patients were retrospectively investigated. These stents were divided into two groups depending upon the clinical status of the patient: (a) those who developed in-stent restenosis (n: 77, 47%), and (b) those who failed to develop in-stent restenosis (n: 87, 53%). Narrowing by 50% or more, as identified during coronary angiography performed at least six months after the stent implantation, was considered as positive for development of in-stent restenosis. Plaque area measurement in the patients was performed using quantitative coronary angiography (QCA) and the Image J program. Results: Plaque area measurement when performed quantitatively revealed no statistically significant difference between the groups (p>0.05). However, significant difference in area was observed when Image J was used (p<0.05). Statistically significant differences were observed between groups in terms of history of hypertension and hyperlipidemia, use of statins, HDL values, and lesion type (p<0.05); the difference in terms of presence of diabetes or smoking status (p>0.05) was not significant. There was a relationship among the development of restenosis and hypertension, non-usage of statin therapy, HDL level, poor lesion type, and plaque area as measured with Image J. Discussion: Hypertension, non-usage statin therapy, low levels of HDL, poor lesion type, and larger plaque areas as measured with the Image J program were identified as important indicators for development of in-stent restenosis.

Keywords

Image J; Plaque Area; In-Stent Restenosis.

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Introduction

Intracoronary stenting has emerged as one of the most commonly used therapeutic modalities for the treatment of coronary artery disease. However, one of the most serious problems encountered during the follow-up of patients who have received this treatment is the development of in-stent restenosis. It is difficult to determine the exact rate of restenosis because it depends on a number of different factors and variables. In the pre-stent era it ranged between 32-55% of all angioplasties, dropping to 17-41% [1-4] in the BMS era [5-7]. A further step to reduce restenosis was undertaken with the advent of DES, with a reduction to numbers <10% [8-9]. However, in one study, within a time frame of six months nearly 20-35% of patients with bare-metal stents and 5-10% of those with drug-eluting stents developed this complication [10].

Reports in the literature have pinpointed several factors suspected to be active in the development of restenosis [11-14]. These include advanced age, history of diabetes, long lesion, small vessel diameter, and poor lesion type. Some studies have suggested that monitoring the plaque area prior to the last stent implantation could help in predicting restenosis via using intravascular ultrasound (IVUS) [15-16]. As a result of this, interventions aimed at decreasing the plaque material are popularly considered to reduce restenosis as well; however, the expected results have not been obtained [17].

In this study we have used quantitative coronary angiography (QCA) and the Image J program to investigate the influence of plaque area, as measured prior to stent implantation, on the development of restenosis. We have also monitored and analyzed several clinical, biochemical, and angiography-related factors.

Material and Method

Study Population

The study included patients who had undergone coronary angiography at the Cardiology Department Coronary Angiography Unit between March 2008 and July 2011. This inclusion was irrespective of the presence or absence of in-stent restenosis. Of the 5180 coronary angiography procedures, 227 presented with in-stent restenosis whereas 383 did not develop the same. Medical records and prior history of these patients, as present in the database, were analyzed retrospectively. Only those patients who had undergone the stent implantation procedure at our clinic were enrolled in the study. Patients whose stent implantation procedure was performed elsewhere, patients whose files could not be accessed, and patients who presented with stent thrombosis were excluded from the study group. In total, 164 intracoronary stents implanted in 121 patients were found to match the inclusion criteria and hence were investigated retrospectively as part of the analysis procedure. These stents were divided into two groups depending upon the clinical status of the patient: (a) those who presented with in-stent restenosis (n: 77, 47%), and (b) those who failed to develop in-stent restenosis (n: 87, 53%).

Narrowing by 50% or more, as identified during coronary angiography performed at least six months after the stent implantation, was considered as positive for development of in-stent restenosis.

All characteristics of the patients that could potentially be related to the development of restenosis, including basic demographic characteristics such as age and gender, smoking status, hypertension, hyperlipidemia, diabetes, currently used drugs, and biochemical parameters, were meticulously recorded.

Angiographic Examination and Evaluation of the Plaque Burden

Records pertaining to the coronary angiography procedure performed during the stent implantation were obtained for each patient.

The plaque area present prior to the stent implantation was investigated semi-quantitatively using coronary angiography (QCA) and the Image J program.

The plaque area was calculated semi-quantitatively using the Siemens Axiom (Germany) coronary angiography instrument. Our analysis was based on the best possible view of the lesion-containing segment of the coronary artery into which the stent was implanted. Using the QCA method, calibration was performed based on the catheter diameter and the segment with stenosis was marked on the coronary angiography instrument. The margins of the lesion were adjusted manually and the plaque area was optimally calculated using the instrument (Figure 1). Plaque area calculations were done by two separate observers and the average of the results was used.

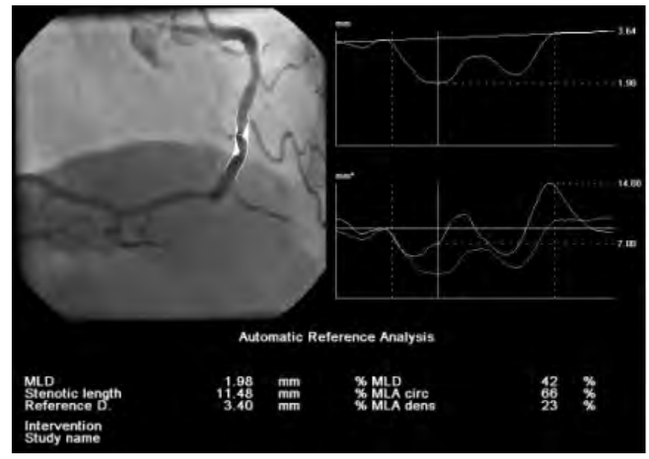

Figure 1. Plaque area calculation with QCA method

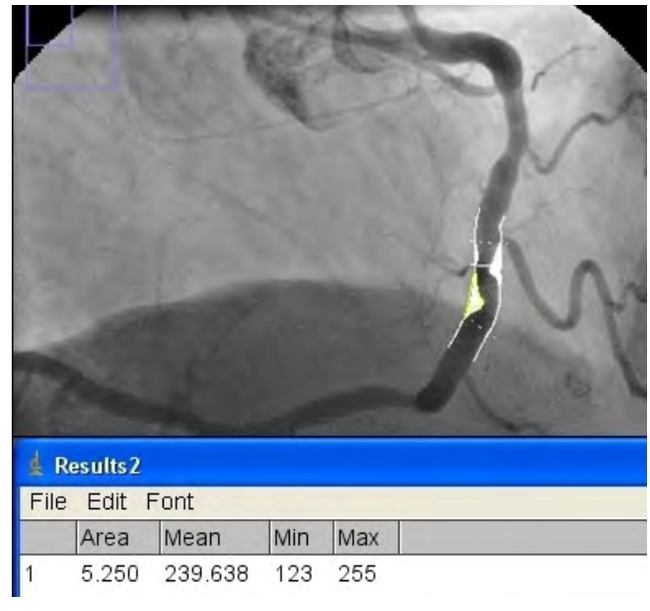

Figure 2. Plaque area calculation with Image J method

Plaque area calculation with both the methods was performed using the same image. An image of the plaque area, as calculated by the QCA method, was recorded in JPEG format and the plaque area was calculated using Image J.

The Image J program is easily accessed via the internet (http://rsbweb.nih.gov) and can be used to perform two-dimensional area calculation. Calibration is performed prior to area calculation. Then the area that needs be calculated is marked manually (Figure 2). In this study, we accepted the catheter diameter as a reference value with which the calibration was performed. ACC/AHA lesion classification was used for coronary lesion type [18]. The reproducibility of two-dimensional area calculation was assessed by coefficients of variation (standard deviation of differences between the repeated measurements divided by the mean value and expressed as a percentage) between measurements. The intra-observer variability was calculated in 34 randomly selected study participants (18 patients who presented with in-stent restenosis and 16 control patients who did not develop in-stent restenosis) by repeating the measurements under the same basal conditions. Intra-observer and inter-observer variation was found to be <5%.

Statistical analysis

SPSS (Statistical Package for Social Sciences) for Windows 16.0 program was used for all statistical analyses. The results obtained are presented as mean ±SD and frequency. Student's t test, Pearson's correlation analysis, chi-square test, and logistic regression analysis were performed for evaluation of data. A p-value less than 0.05 was considered statistically significant.

Results

A total of 164 stents were included as part of the study. Of these, 77 were found to have developed in-stent restenosis whereas 87 failed to do so. No significant differences were observed between the two groups with respect to age, gender, presence of diabetes mellitus, and smoking status (p> 0.05). However, the prevalence of hypertension and hyperlipidemia was statistically significantly higher in patients with in-stent restenosis (p<0.05).

When the current drug regimen was taken into account, a significant difference in the development of in-stent restenosis was observed for the use of statins (p< 0.05). It was observed that the risk for development of in-stent restenosis was lower in patients undergoing statin therapy as compared to those who were prescribed other medication. The development of in-stent restenosis was not found to be associated with the use of aspirin, clopidogrel, ticlopidine, or beta-blocker (p> 0.05, Table 1). When basic laboratory parameters for all the patients were analyzed, no single factor was seen to make a statistically significant difference between the two groups except for HDL, whose levels were lower in the patient group diagnosed with in-stent restenosis (p<0.05, Table 1).

The patients with and without in-stent restenosis were investigated with respect to the type of percutaneous coronary intervention (PCI) associated with the stent implantation procedure. Of the 77 stents that were diagnosed with in-stent restenosis, 66 (85.7%) were implanted using elective PCI, nine (11.7%) using primary PCI, and two (2.6%) with rescue PCI. Of the 87

Table 1. Baseline characteristics and laboratory parameters of the study population

Variables	Without Restenosis (n=87)	With Restenosis (n=77)	P value
Age	58,6 ± 11	57,5 ± 11	0,890
Gender, male	71 (%81,6)	58 (%75,3)	0,669
Hypertension	63 (%75)	69 (%89,6)	0,022
Diabetes mellitus	29 (%33,3)	26 (%33,8)	0,557
Dyslipidemia	21 (%24,1)	34 (%44,2)	0,028
Smoking	24 (%27,6)	31 (%40,3)	0,129
Acetylsalicylic acid	70 (%86,4)	66 (%89,2)	0,883
Klopidogrel	20 (%26)	11 (%15,9)	0,065
B-blocker	66 (%82,5)	62 (%82,7)	0,560
Statin	53 (%67,9)	33 (%45,8)	0,036
Glucose (mg/dL)	123,7 ± 52,7	126,6 ± 51,5	0,850
Creatine (mg/dL)	0,98 ± 0,35	1,08 ± 0,69	0,450
Total cholesterol (mg/dL)	183,1 ± 47,9	180,6 ± 50,3	0,850
Triglyceride (mg/dL)	166,9 ± 112,6	179,1 ± 83,3	0,450
HDL (mg/dL)	39,8 ± 10,0	36,4 ± 10,1	0,045
LDL (mg/dL)	109,2 ± 39,7	106,4 ± 40,4	0,750
Hemoglobin (g/dL)	13,7 ± 1,9	13,5 ± 1,9	0,850
Platelet (thousand/uL)	235 ± 54	255 ± 79	0,095
MPV (fL)	8,6 ± 1,0	8,5 ± 0,9	0,910

Abbrevations: HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; MPV, mean platelet volume

Table 2. Evaluation and Measurement of Coronary Angiograpy Image

Variables	Without Restenosis (n=87)	With Restenosis (n=77)	P value
PCI Type			
Elective PCI	81 (%93,1)	66 (%85,7)	0,075
Primer PCI	4 (%4,6)	9 (%11,7)	
Rescue PCI	2 (%2,3)	2 (%2,6)	
Lesion type			
A	10 (%11,5)	1 (%1,3)	0,001
B1	47 (%54)	24 (%31,2)	
B2	23 (%26,5)	33 (%42,8)	
C	7 (%8)	19 (%24,7)	
Stent Localization			
LAD	41 (%47,2)	39 (%50,6)	0,890
D1	2 (%2,3)	2 (%2,6)	
LCX	15 (%17,2)	14 (%18,2)	
RCA	29 (%33,3)	22 (%28,6)	
Stent Type			
BMS	67 (%73)	68 (%88,3)	0,910
DES	20 (%27)	9 (%11,7)	
Plaque Area Quantitative	4,22 ± 2,61	4,67 ± 2,39	0,664
Plaque Area İMAGE J	7,68 ± 4,45	11,03 ± 6,17	0,025

Abbrevations: PCI, percutaneous coronary interventions; LAD, left anterior descending coronary artery; RCA, right coronary artery; LCX, left circumflex coronary artery; D1, first diagonal coronary artery; BMS, Bare metal coronary stent; DES, drug-eluting coronary stent

Table 3. Logistic regression analysis associated with the risk for development of in-stent restenosis

Variables	BETA (ß)	O.R.	%95 CI	P value
Hypertension	1,50	4,49	1,26-15,93	0.035
Hyperlypidemia	0,82	2,28	0,89-5,80	0.861
Non usage Statin	1,51	4,52	1,75-11,67	0.028
HDL	-0,47	0,95	0,91-0,99	0.042
Stent length	-0,11	0,89	0,76-1,04	0.783
Plaque areaμ	0,10	1,11	1,02-1,21	0.025
Type -B1 Lesion	2,36	10,62*	0,90-124,39	0.036
Type -B2 Lesion	3,60	36,91*	2,83-480,15	0.042
Type –C Lesion	5,40	222,26*	5,79-8528,71	0.037

Abbrevations: HDL, high density lipoprotein cholesterol.
μ Plaque area calculation with Image J method
* Risk increase with respect to Type-A Lesion

stents that did not present with in-stent restenosis, 81 (93.1%) were implanted with elective PCI, four (4.6%) with primary PCI and two (2.3%) with rescue PCI. There was no significant difference between the two groups in terms of the type of percutaneous coronary intervention (p>0.05, Table 2).

The two groups were also compared with respect to the type of lesion into which the stent implantation were performed. Of the 77 stents with in-stent restenosis, one (1.3%) was implanted into a type A lesion, 24 (31.2%) into type B1 lesion, 33 (42.9%) into type B2 lesion, and 19 (24.7%) into type C lesion. Of the 87 stents without in-stent restenosis, 10 (11.5%) were implanted into type A lesion, 47 (54.0%) into type B1 lesion, 23 (26.4%) into type B2 lesion, and seven (8.0%) into type C lesion. The type of lesion differed significantly between the two groups (p<0.01). It was observed that the risk for in-stent restenosis increased as the type of lesion progressed from A to C (Table 2). It was identified that, of the 77 stents that presented with in-stent restenosis, 39 (50.6) were implanted in the left anterior descending (LAD), two (2.6%) in the diagonal, 14 (18.2%) in the circumflex, and 22 (28.6%) in the right coronary artery (RCA). For the 87 stents that did not develop in-stent restenosis, 41 (47.2) were implanted in the LAD, two (2.3%) in the diagonal, 15 (17.2%) in the circumflex, and 29 (33.3%) in the RCA. When the patients with open and stenotic stents were compared, no statistically significant difference with respect to the artery into which the PCI had been performed was noticed (p>0.05, Table 2).

Amongst the 77 stents with in-stent restenosis, it was observed that 68 (88.3%) were bare-metal stents (BMS) and nine (11.7%) were drug-eluting stents (DES). Of the 87 stents without in-stent restenosis, 67 (77.0%) were BMS and 20 (23.0%) were DES. When the correlation between type of implanted stent and development of restenosis was evaluated, a statistically non-significant difference was determined (p=0.091). However, it can be stated that the use of drug-eluting stents was more frequent in the group that failed to develop in stent restenosis (Table 2).

The performance of percutaneous transluminal coronary angioplasty (PTCA) prior to the stent implantation was also compared for the two groups. Of the 77 stents that presented with in-stent restenosis, 38 (49.4%) were observed to have undergone PTCA whereas 39 (50.6%) did not due to decisions related to coronary by-pass operation and medical treatment. In the 87 stents that did not develop in-stent restenosis, 40 (46.0%) were noted to have undergone PTCA because of thrombus burden of the lesion whereas 47 (54.0%) did not. Upon comparison, groups with and without in-stent restenosis did not demonstrate any statistically significant difference with respect to the performance of the PTCA (p>0.05).

The two groups were compared with respect to the performance of post-dilatation after stent implantation. Of the 77 stents with in-stent restenosis, ten (13.0%) underwent post-dilatation and 67 (87.0%) did not. Of the 87 stents that did not develop in-stent restenosis, ten (11.5%) underwent post-dilatation and 77 (88.5%) did not. Statistically there was no significant difference between the two groups (p>0.05).

The stents implanted in the two groups were compared in terms of stent size and diameter. Statistically significant difference was observed for difference in stent size (p<0.05) but not for stent diameter (p>0.05).

There was no statistically significant difference between the two groups with respect to the quantitative plaque area determined during follow-up coronary angiography (p>0.05); importantly, the plaque area as examined with Image J displayed no difference between the groups (p<0.05).

There was a moderately positive correlation between the quantitative measurement of the plaque area and the measurement of plaque area done with Image J ($r = 0.60$, $p < 0.001$).

Considering the aforementioned evaluations, the factors that were found to make a difference between stents that did and did not develop restenosis included the presence of hypertension, presence of hyperlipidemia, non-usage statin therapy, lower HDL levels, longer stent size, type of lesion, and plaque area as calculated by Image J. Logistic regression analysis was performed with factors associated with the risk for development of in-stent restenosis (Table 3).

Although a significant difference was observed between the groups with and without in-stent restenosis in terms of hyperlipidemia and stent size, logistic regression analysis revealed that these variables were not influential for the development of in-stent restenosis (p>0.05).

Discussion

Detailed analysis performed during the course of our study revealed no significant difference between patients with and without in-stent restenosis with respect to the plaque area calculated through QCA, whereas plaque area as measured with Image J was larger in those with restenosis. Correlation analysis revealed a significant correlation between QCA and the plaque area as measured through Image J. Regression analysis determined that the plaque area measured with Image J was a significant determinant for the development of in-stent restenosis. Every 1 mm2 increase in the plaque area as measured with Image J was found to cause a 1.11-fold increase in the development of restenosis. Although popularly used in the research arena, QCA is unable to replace visual assessment in clinical practice because it is both time-consuming as well as technologically intensive. Another disadvantage is that finalizing the square and segment for which measurement will be performed is a subjective matter and hence is known to vary among people

who perform this measurement using the QCA method. Therefore, Image J is a more practical and serviceable alternative method.

Intracoronary stent implantation, an invasive revascularization method, has become the therapy of choice for coronary artery disease and its popularity is increasing on a daily basis. Unfortunately, in spite of advancements in the materials used and an increase in the rate of procedural success, no concordant improvement in terms of in-stent restenosis, the main problem affecting percutaneous coronary interventions, has yet been achieved. A meta-analysis of 11 studies that included a total of 5103 patients showed that the prevalence of angiographic in-stent restenosis was 5-10% in case of DES and 20-35% in case of BMS [10].

Some previously published studies have identified pre-procedural plaque burden as a predictor of restenosis. Although the mechanism underlying the relationship between plaque burden and restenosis are not clear, plaque burden has emerged as a potential indicator. A high pre-procedural plaque burden could hinder optimal dilatation of the stent. To overcome this problem, balloon angioplasty with higher pressure could be performed but doing so would increase the trauma effect on the vascular walls which in turn would increase the risk of restenosis. Another study advanced the explanation that atherosclerotic plaque burden could be the source for cells involved in the intimal hyperplasia process [15]. Hoffman et al. investigated various predictors for development of restenosis following stent implantation and also tried to address the question of whether plaque burden was influential in the process. In their study they examined the plaque burden before stent implantation using intravascular ultrasound (IVUS) and found that the plaque burden was correlated with development of restenosis [15]. Similarly, a study by Shiran et al. showed that the pre-procedural plaque area as measured using IVUS was a strong predictor for restenosis [16]. Considering that the real-life data show that IVUS is not commonly used by interventional cardiologists, Image J can be developed as a useful and convenient process to assess the plaque burden. Subsequent comparative studies with IVUS would give better information about the usefulness of this method.

Previous studies have suggested that factors such as gender and age can function as predictors of in-stent restenosis development, but their impact still needs to be conclusively assessed. A study by Gupta et al. revealed that female gender is a risk factor for restenosis [19]. A study by Bainey et al. reached the same conclusion [20]. Other sources have defined gender and advanced age as predictors of restenosis [21]. In our study, no significant difference could be uncovered between the two groups with respect to gender and age.

When the two groups were compared, hypertension emerged as a clinical factor that was capable of influencing the development of in-stent restenosis; patients with hypertension were at a 4.5-fold greater risk for developing the complication. Similar to our study results, a report by Kastrati et al. also definitively identified hypertension as a risk factor for restenosis [22].

In our study, the prevalence of diabetes was 33.8% in the group with restenosis and 33.3% in the group without stenosis. There was no significant difference between the groups and the presence of diabetes did not appear to increase the risk for in-stent restenosis. Our results are in direct contradiction to several previously published studies that have reported contrary results [23-26]. One factor that can account for the lower incidence of restenosis in the diabetic pool of our study could be the more frequent use of DES and the relatively limited number of patients.

Study Limitations

The number of enrolled patients and the study design were entirely based on the retrospective analysis of patient files; therefore the database can be presented as a major limitation of our study. The data of the patients who underwent second coronary angiography in another clinic or who did not require coronary angiography were unavailable.

Conclusions

No correlation was observed between QCA measured plaque area and the development of restenosis. However, a significant link was observed between plaque area measured with Image J and the development of restenosis. The presence of a correlation between the two methods indicates that the latter methodology can potentially prove useful in cardiology practice, furnishing clinicians with sensitive and significant findings. Intra-procedural techniques aimed at reducing the plaque burden could prove effective for decreasing restenosis development but more extensive research on this subject needs to be conducted and better methodology needs to be developed for the purpose.

Competing interests

The authors declare that they have no competing interests.

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