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PhD THESIS

STUDY OF ANATOMIC AND LESION RELATED PREDICTIVE FACTORS OF IN STENT RESTENOSIS

Abstract

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THESIS CONTENT

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Key words: in-stent restenosis, bare metal stent, coronarography, lesions, prediction score

1.INTRODUCTION

Since the early 90's, the implantation of stents bare metal stent (BMS) became interventional treatment of choice for symptomatic coronary lesions [1]. This is due to the low risk of restenosis, as well as favorable clinical results when compared with conventional angioplasty. Introduction of drug eluting stent (DES) has brought an added benefit in terms of the risk of restenosis. Several randomized trials have demonstrated a reduction in first 12 months of ~ 30% to ~ 10%. Despite this advantage, the use of DES is associated with an increased risk of very late thrombosis due to delay the healing process [2, 3, 4]. Furthermore, it has assumed a prolonged antiplatelet therapy more than 12 months following stent implantation. Subsequent improvements in stent design, drug or polymer used were addressed to this incovenient. Long term results (more than 3-4 years) shows that all drug eluting stents reduce the need of revascularisation and proove to have more clinical efficacy when compared to bare metal stents [3, 5].

The benefit obtained by the use of DES is not universal, however. Their superiority in terms of the incidence of in stent restenosis becomes evident especially if the lesions are considered at high risk. For patients with low-risk of restenosis or for those with increased risk of stent thrombosis due to the premature discontinuation of dual antiplatelet therapy, BMS represents a feasible option [6, 7]. In fact, more research shows that using BMS constitutes a good alternative for noncompliant patients or with contraindications of long term dual antiplatelet therapy, large diameter coronary arteries, vein graft lesions or in case of acute coronary syndrome with ST segment elevation (STEMI) [6].

With all the progress made in recent decades, in-stent restenosis remains a problem incompletely solved. The need for re-revascularization in one year is 6.7% when DES is implanted and 11% when using BMS, often due to in-stent restenosis [8]. At the same time, BMS continues to be commonly used in many interventional cardiology centres, on clinical and especially economically arguments, using DES being limited due to the high price. In fact, cost/efficiency studies regarding DES, justify their implantation especially in patients at high risk

of restenosis. In United States of America reducing the use of DES with 50% in patients with a low risk of restenosis can lessen the costs in the national system of health insurance with 205 million dolars/year with a modest increase of only 0.5%, in terms of the need for re-revascularization [9].

Viewed in this context, all efforts to identify clinical and morphological variables and to create models of risk associated with restenosis in bare metal stents, in order to identify patients who would benefit most from DES implantation seems resonable. Thus, our study conducted in Army's Center for Cardiovascular Disease "Academician Vasile Cândea" it is justifiable and aimed to design a model for identification of patients at high risk of in-stent restenosis, as we encounter in our everyday practice.

2. AIM AND OBJECTIVES OF THE STUDY

Aim of the study: to indentify parameters associated with restenosis in bare metal stents and to develop a prediction model

Objectives of the study:

-to identify anatomic, clinical and lesion related factors with in-stent restenosis

-lesion quantification depending on Syntax score and association with in-stent restenosis

-conceiveing a prediction model and a prognostic score characteristic to the studied group

-comparative evaluation of existent prognostic scores with the new one

-evaluation of clinical presentation of patients with in-stent restenosis

-evaluation of angiographic presentation of stents with restenosis criteria

-identifying measures for prevention of restenosis in "bare metal"stents

3. MATERIAL AND METHODS

The study was conducted in the Department of Interventional Cardiology of Army's Center for Cardiovascular Disease "Academician Vasile Cândea" Bucharest on a group of patients who underwent angioplasty with bare metal stents for coronary heart disease. In our

department, a number of 2500 procedures are performed annually, 40% of these being therapeutic interventions.

The study is prospective with a retrospective component and control group. We consider this study reflects the "real world", because we proposed to study phenomenon of restenosis as shown in daily practice and experience of our department, without a planned coronary angiography.

The study group is formed from 512 patients treated percutaneously with BMS implantation, who were sent to our department from January 2005 to December 2013 with indication of repeat angiography based on clinical arguments.

Inclusion criteria:

-patients treated with bare metal stent (BMS) who underwent invasive angiographic evaluation within one year following the initial procedure

Exclusion criteria:

-patients had at least one drug eluting stent (DES), simoultaneously implanted

-patients with stents in coronary arterial or venous grafts

-patients with initial suboptimal postprocedural results

-patients with major cardiac events in the first month postprocedural

-patients who complete data aquisition of clinical and laboratory tests could not be performed due to various reasons

-de novo significant lesions

To achieve the purpose and objectives of our study we used a sequentially working protocol (Figure 5.1):

A) Identifying eligible patients for the study based on the indication of repeat angiography, its outcome and the criteria for inclusion and exclusion

B) Collection of retrospective data related to initial angiography (indication of invasive evaluation, coronary anatomy, location, complexity and morphological characteristics of the stented lesions), subsequent interventional treatment (indication, number of lesions and vessels treated interventional type, number and mplanted stents dimensions etc.); several angiographic parameters were collected (moderate or severe calcifications, stents located at the bifurcation

sites, presence of thrombus, chronic total occlusion etc.) as well as clinical and laboratory factors from patients' medical documents;

C) Collection of clinical and angiographic relevant data when assessing invasive control (timeframe initial procedure-control angiographic, presence of angiographic criteria of restenosis, clinical and angiographic presentation of patients with in-stent restenosis, adherence to medical treatment, etc.);

D) Data processing, conclusions.

We studied the association of clinical and angiographic variables for patients with or without in-stent restenosis, for coronary segments and for study groups. In-stent restenosis was angiographically defined as recurrent stenosis with a percentage diameter $\geq$ 50% witin the stent or its 5 mm proximal or distal edge. The length of the stent (stent length) was defined as its length specified by the manufacturer at the nominal inflation pressure of the balloon. When using several stents implanted in series for treatment of the same lesion ("overlapping stents"), this was defined as the sum of the individual lengths. The diameter of the stent was defined by its minimum diameter, specified by the manufacturer at the nominal inflation pressure. In case of postdilatation, it was defined as the diameter of the balloon used (at the nominal capacity specified by the manufacturer). The data related to diagnostic, clinical and paraclinical parameters were collected by medical history and patients medical records. All initial lesions treated with BMS implantation were morphologically quantified using SYNTAX score and ACC/AHA (American College of Cardiology/ American Heart Association) classification of coronary stenosis [10, 11]. For each patient we calculated the amount of SYNTAX scores /interventional treated segment, assuming that it correlates with clinical and angiographic post-procedural recurrences. We named the obtained score interventional SYNTAX score (SYNTAX i).

Statistical data processing. Bivariate analysis of continuous variables with normal distribution was performed using parametric tests (eg Student T) and nonparametric for those with non-Gaussian distribution (eg Kruskal Wallis). $p < 0.05$ was used as the threshold for statistical significance. Analysis of qualitative variables was conducted using Pearson chi square test (X^2), and if its assumptions were violated, Fisher's exact test was used. We calculated OR and 95% CI and was used to estimate relative risk assuming the fact that odds ratio over-estimate this risk.

Among the methods of multivariate analysis, applicable to our studied variables was logistic regression. This included only angiographic data. Based on logistic regression model obtained we create a new prognostic restenosis score.

4.RESULTS

During the study period were identified 512 eligible patients treated interventional for coronary heart disease ischemic implanting stents "bare metal". Based on data obtained by the control angiography, they were divided into two groups: patients with angiographic restenosis in at least one stent implanted (398 patients, 77.7%) and patients without invasive criteria of in-stent restenosis (permeability of the stent) (114 patients, 22.3%). The average time from initial procedure to invasive control evaluation was 210 (± 35) days for the first group and 280 (± 40) days for the second group.

In total, 808 segments were analyzed coronary angiography, 472 (58.42%) of them presenting imagistic criteria for in-stent restenosis. Instead, 336 (41.58%) of the segments examined submit stents without restenosis.

Bivariate analysis of demographic and clinical factors.

We analyzed a comparison of demographic and clinical parameters according to the presence or absence of in-stent restenosis at control angiography. The results are shown in table 1.

Clinical study of demographic factors revealed an average age of 60.2 ± 9.4 years for patients with in-stent restenosis and 58.9 ± 8.7 for those with stents without restenosis and a predominance of male patients.

It was found a statistically significant association between the presence of diabetes mellitus, prior percutaneous coronary angioplasty and in-stent restenosis (OR= 2,23; CI 95% 1,19-4,17; p=0,010 respectiv OR=4,01; CI 95% 1,173-4,56; p=0,014) (figure 1). Statins treatment seems to have protective effects (OR= 0,45; CI 95% 0,265-0,760; p=0,002).

Table 1. Presentation of demographic and clinical factors, for the two groups of patients with or without restenosis

	Patients with restenosis (n=398)	**Pacienți without restenosis (n=114)**	**Student t (df)/Pearson chi square, X^2 (df)**	**P value**
Demographic factors				
Age (years)	60,2± 9,4	58,9± 8,7	1,346 (510)	0,179
Men	60,3± 10,8	58,8± 8,5	0,931 (227)	0,323
Women	60,1± 7,3	58,9± 9,1	0,989 (181)	0,353
Gender			0,735 (1)	0,391
Male	224 (56,3%)	59 (51,8%)		
Female	174 (43,7%)	55 (48,2%)		
Provenience			0,095 (1)	0,523
Rural	189 (47,5%)	58 (50,9%)		
Urban	209 (52,5%)	56 (49,1%)		
Studies level			0,504 (1)	0,777
Inferior	125 (31,4%)	34 (29,8%)		
Medium	153 (38,4%)	48 (42,1%)		
Superior	120 (30,2%)	32 (28,1%)		
Cardiovascular risk factors				
Diabetes mellitus	89 (22,4%)	13 (11,4%)	6,671 (1)	**0,010**
Arterial hypertension	159 (39,9%)	45 (39,5%)	0,008 (1)	0,927
Hypercholesterolaemia	251 (63,1%)	71 (62,3%)	0,023 (1)	0,878
History of smoking	164 (41,2%)	49 (43%%)	0,115 (1)	0,734
Heredocolateral antecedents and pathological personal history				
Family history of CHD	57 (14,3%)	14 (12,3%)	0,309 (1)	0,578
Peripheral artery disease	44 (11,1%)	14 (12,3%	3,411 (1)	0,065
Chronic kidney disease	9 (2,3%)	1 (0,9%)	-	0,300
Prior MI	29 (7,3%)	6 (5,3%)	0,570 (1)	0,450
Prior PTCA	39 (9,8%)	3 (2,7%)	6,046 (1)	**0,014**
Initial indication of PTCA				
STEMI	47 (11,8%)	11 (9,7%)	0,412 (1)	0,521
Non STEMI	37 (9,3%)	12 (10,5%)	1,254 (1)	0,504
Unstable angina	84 (21,1%)	17 (14,9%)	1,570 (1)	0,210
Acute coronary syndrome	168 (42,2%)	40 (35,1%)	1,431 (1)	0,232
Stable angina	198 (49,8%)	64 (56,1%)	1,874 (1)	0,171
Silent ischemia	32 (8%)	10 (8,8%)	0,298 (1)	0,585
Medication				
Beta-blockers	321 (80,7%)	90 (78,9%)	0,163 (1)	0,687
Calcium channel blockers	69 (17,3%)	15 (13,2%)	1,128 (1)	0,288
ACE/Sartans	251 (63,1%)	75 (65,8%)	0,284 (1)	0,594
Diuretics	68 (17,1%)	14 (12,3%)	1,512 (1)	0,217
Statin	270 (67,8%)	94 (82,5%)	9,213 (1)	**0,002**
Aspirin	385 (96,7%)	112 (98,2%)	0,712 (1)	0,399
Clopidogrel	342 (85,9%)	104 (91,2%)	2,216 (1)	0,137

ACE, angiotensin-converting enzyme inhibitors; MI, myocardial infarction; CHD, coronary heart disease ; PTCA, percutaneous transluminal coronary angioplasty;

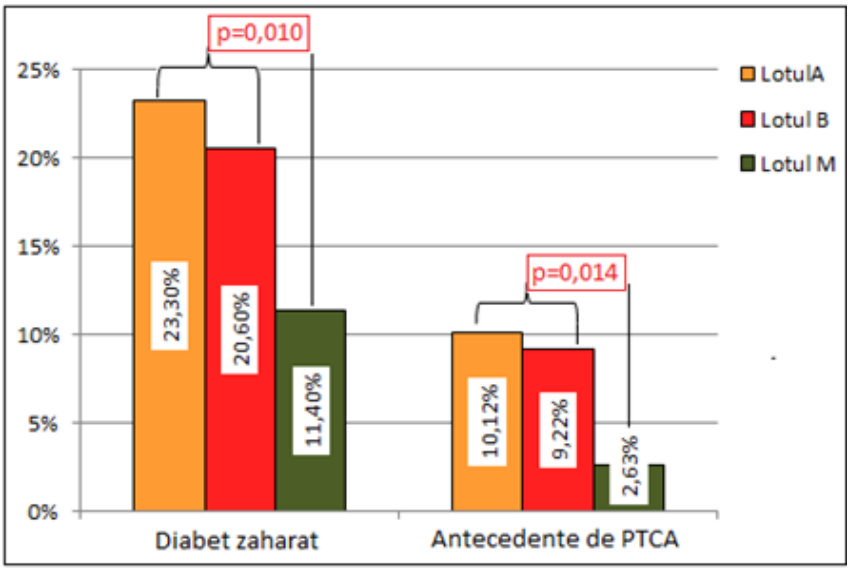

Figure 1: Clinical parameters associated with statistically significant in-stent restenosis

Bivariate and multivariate analysis of angiographic parameters

The main angiographic parameters studied are presented in table 2. In the study group we found a preponderance of patients with right dominant coronary system, single vessel significant lesions and localization in the anterior descending artery.

According to bivariate analysis we note that the angiographic parameters significantly associated with in-stent restenosis are: diameter ≤ 2,5mm (OR 2,56; CI 95% 1,85-3,55; p<0,001), stented length >28mm (OR 2,80; CI 95% 1,91-4,10; p<0,001), type C lesions (OR 2,22; CI 95% 1,65-3,00; p<0,001), ostial lesions (OR 2,77; CI 95% 1,44-5,34; p=0,002), initial restenotic lesions (OR 3,18; CI 95% 1,45-6,96; p=0,003) and total chronic occlusion (OR 4,13; CI 95% 2,13-8,01; p <0,001). According to multivariate analysis we have noticed that stent length > 28mm (OR 2.97; CI 95% 1,99-4,39; p<0.001), diameter≤ 2,5 mm (OR 2.50; CI 95% 1,78-3,45; p<0,001) ostial lesions (OR 8.36; CI 95% 4,09-16,94; p<0,001) and total chronic occlusion (OR 4.02; CI 95% 2,05-7,76; p<0.001) correlates independently with restenosis in BMS. Diameter ≥3,25 mm (OR 0.34; CI 95% 0,24-0,49; p <0.001), length ≤15 mm (OR 0.58; CI 95%0,420,81; p=0.001) represents parameters that are significantly correlated with the absence of in-stent restenosis.

Table 2. Presentation of angiographic factors on the basis of the presence or absence of restenosis at control angiography

	In-stent restenosis (472)	Fără restenoză în stent (336)	Pearson chi square X^2	P value
Stent location				
Anterior descending artery	217 (46%)	167 (49,7%)	0,949	0,329
Circumflex artery	104 (22%)	69 (20,5%)	0,180	0,671
Right coronary artery	151 (32%)	100 (29,8%)	0,357	0,549
Stent diameter				
≤ 2,5 mm	182 (38,6%)	66 (19,6%)	32,13	<0,001
2,5- 3,25 mm	213 (45,1%)	138 (41,1%)	1,15	0,282
≥ 3,25 mm	77 (16,3%)	132 (39,3%)	52,82	<0,001
Stent length				
≤ 15 mm	99 (21%)	125 (37,2%)	24,99	<0,001
15-28 mm	238 (50,4%)	169 (50,3%)	0,001	0,971
>28 mm	135 (28,6%)	42 (12,5%)	28,81	<0,001
Lesion type				
Type A+B	253 (53,6%)	242 (72%)	27,29	<0,001
Type C	219 (46,4%)	94 (28%)		
Ostial	44 (9,3%)	12 (3,6%)	9,19	0,002
Calcification	51 (10,8%)	28 (8,3%)	1,09	0,295
Chronic total occlusion	58 (12,3%)	11 (3,3%)	19,28	<0,001
Initial restenotic lesion	34 (7,2%)	8 (2,4%)	8,31	0,003
Thrombus	39 (8,3%)	26 (7,7%)	0,019	0,889
Bifurcation	16 (3,4%)	8 (2,4%)	0,387	0,533
Ulcerated plaque	18 (4%)	11 (3,3%)	0,41	0,597

Developing prediction score of restenosis. Based on the logistic regression model we designed a score prediction of angiographic restenosis who was appointed **CCUBCVA prediction score of restenosis (SPredRes).** It used the lowest estimated coefficient, in this case equal to 0.53 (for stent length <15 mm), to which was reported the estimated coefficient for each regressor (angiographic parameter). Thus depending on the importance of the coefficients we assigned a score to each variable. The constant 4 has been added to have a minimum score equal to 1. The formula by which we calculate the predictive score is:

SPredRes = 4+1.5D1-2D3-L1+2L3+2.5Cto+4Ost

For each parameter, multiplying factor was 0 or 1, depending on the its presence or absence. The average of SPredRes for stented lesions which will present angiographic restenosis

was 5.3 (± 1.8) compared to 3.6 (± 1.6) for those with no restenosis, the difference between the two being statistically significant (p <0.001). The 808 lesions were divided according to each predictive score in four quartiles according to table 3.

Table 3. Presentation of predictive score depending on its value and the presence of angiographic in-stent restenosis

Quartiles score PredRes	**Total (n=808)**	**Restenosis (n=472)**	**Non restenosis (n=336)**	**Chi square X^2**	**P value**
Quartile 1 =[1; 3)	133 (16,5%)	29 (6,2%)	104 (31%)	73,06	**<0,001**
Quartile 2=[3; 4,5)	262 (32,4%)	130 (27,5%	132 (39,3%)	12,25	**<0,001**
Quartile 3=[4,5; 6)	193 (23,9%)	130 (27,5%)	63 (18,7%)	8,26	**0,004**
Quartile 4 =[6; 10]	220 (27,2%)	183 (38,8%)	37 (11%)	67,83	**<0,001**

Values of SPredRes in quartile 1 were more commonly associated with the presence of stents without restenosis (31% versus 6,2%; p<0,001). The same situation we've encountered for those belonging to quartile 2 (39,3% versus 27,5%; p<0,001). Instead, for quartile 3 we observed a significant correlation with in-stent restenosis (27,5% versus 18,7%; p=0,004), which has been mantained also for quartile 4 (38,8% versus 11%; p<0,001) (figure 2).

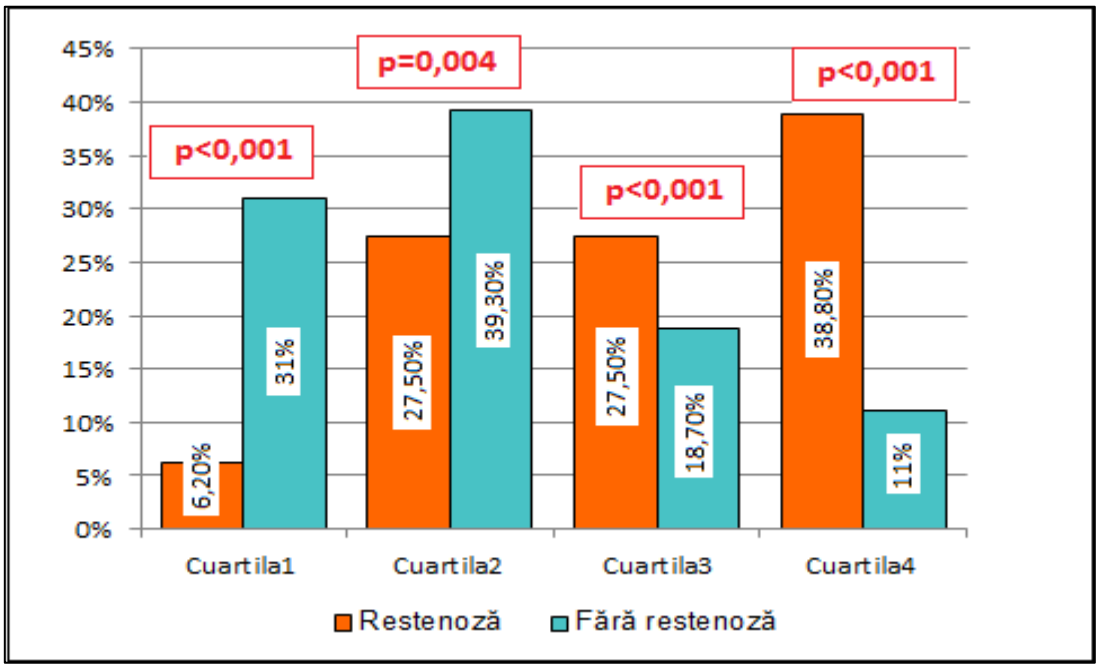

Figure 2. The distribution of stents with or without restenosis according to predictive score values

Syntax score analysis.

The average score $Syntax_i$ for group A+B (patients with in-stent restenosis) was 8.6 (+ 4.6) compared with 7.5 (± 3.5) of group M (only patients with stents permeable), the difference being statistically insignificant (p = 0,098). $Syntax_i$ score values were divided into quartiles according to table 4. Comparative analysis of patients with or without restenosis based on the $Syntax_i$ score values belonging to quartile 1 and 2, shows that there are no statistically significant differences (18.6% versus 14.9%; p = 0,365; 21.9% versus 26.3%; p = 0,318). Instead, the values in quartile 3 were noticed more frequently in patients with stents without restenosis (42.1% vesus 31.6%; p = 0,038). Those belonging to quartile 4 were predominantly in the group with in-stent restenosis (27.9% versus 16.7%; p = 0.015).

Tabel 4. Comparative presentation of patient population depending on Syntaxi score' s quartiles

Cuartilă Scor $Syntax_i$	**Total (n=512)**	**Restenoză (n=398)**	**Fără restenoză (n=114)**	**Chi square X^2**	**Valoare p**
Cuartila 1= [2; 5)	91 (17,8%)	74 (18,6%)	17(14,9%)	0,821	0,365
Cuartila 2= [5; 7)	117 (22,8%)	87 (21,9%)	30 (26,3%)	0,998	0,318
Cuartila 3= [7; 12)	174 (34%)	126 (31,6%)	48 (42,1%)	4,311	**0,038**
Cuartila 4= [12; 25,5]	130 (25,4%)	111 (27,9%)	19 (16,7%)	5,892	**0,015**

Comparative analysis of the two scores.

It has been observed that the predictive power of the predictive score is higher than that of the Syntax/lesion score, which is relatively low (AUC = 0,750 new score compared to the AUC = 0,524 Syntax score calculated per lesion). There is an important difference between ROC curves drawn for the two scores (table 5, figure 3).

Table 5.Parameters of ROC curve for PredRes score and Syntax score per lesion

ROC curve	**AUC** CI, 95%	**Index Youden**	**Sensibility**	**Specificity**
SPredRes	0.750 [0.741;0.768]	$S_1 = 4.8$	$P(S > S_1 \mid \mathbf{Rest} = 1)$ =0.591	$P(S < S_1 \mid \mathbf{Rest} = 0)$ =0.785
Syntax score per lesion	0.524 [0.506;0.543]	$S_2 = 7.8$	$P(S > S_2 \mid \mathbf{Rest} = 1)$ =0.185	$P(S < S_2 \mid \mathbf{Rest} = 0)$ =0.884

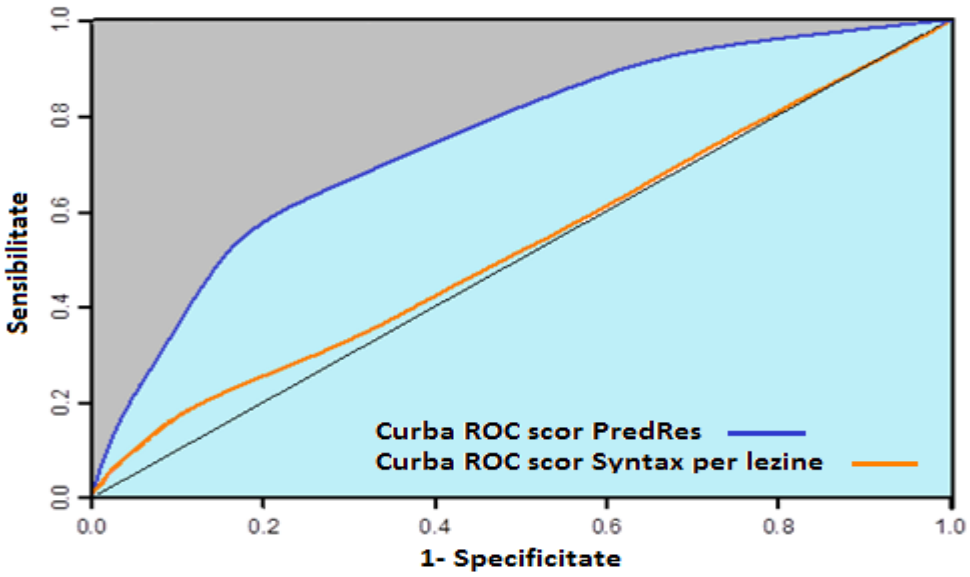

Figure 3. Comparative presentation of ROC curves for Syntax score/lesion and SPredRes score

The method of the clinical presentation of patients with in-stent restenosis

At the time of the control angiography most patients presented clinical symptoms of stable angina (206; 51,8%), followed by those with unstable angina (92; 23,1%) and those asymptomatic (64; 16.1%). Less frequently we have noticed patients with acute myocardial infarction (36; 9%). A comparative analysis was made between the subgroup of 128 patients with acute coronary syndrome (myocardial infarction and unstable angina) with 270 patients with stable angina or asymptomatic. Parameters associated significantly with acute coronary syndrome, as clinical form of presentation of patients with restenosis in stent are smoking status (OR=2,878; CI 95% 1,865-4,440; p<0,001) and the presence of prior myocardial infarction (OR=3,853; CI 95% 1,762-8,426; p<0,001).

The method of angiographic presentation of in-stent restenosis lesions

The 472 lesions with restenosis control angiography were divided according to Mehran classification as follows: pattern I those with focal restenosis (159; 33.68%), pattern II those with diffuse restenosis (197; 41.74%) , pattern III lesions with diffuse proliferative restenosis Extented beyond the margins of the stent (79; 16.74%) and type IV those with complete occlusion (37, 7.84%).

We analyzed the group composed of focal restenosis lesions (pattern I) compared to the group with diffuse restenosis lesions (pattern II+ pattern III). In the first group there were 159 lesions (36.6%) and in the second 276 lesion (63.4%).

Table 6. Presentation angiographic parameters depending on the presence of diffuse or focal restenosis

	Focal restenosis (n=159)	**Diffuse restenosis (n=276)**	**Chi square X^2**	**P value**
Stent diameter				
≤ 2,5 mm	58 (36,5%)	113 (40,9%)	0,666	0,414
2,5-3,25 mm	71 (44,7%)	123 (44,6%)	0	0,986
≥3,25 mm	30 (18,9%)	40 (14,5%)	1,125	0,289
Stent length				
≤ 15 mm	61 (38,3%)	29 (10,5%)	46,028	**<0,001**
15-28 mm	82 (51,6%)	134 (48,6%)	0,257	0,612
> 28 mm	16 (10,1%)	113 (40,9%)	44,644	**<0,001**
Type C lesion	48 (30,2%)	155 (56,2%)	26,305	**<0,001**
Chronic total occlusion	19 (11,9%)	34 (12,3%)	0,013	0,910
Average score Syntax/ lesion	5,1 (±3)	5,6 (±3,4)	1,205	0,272
Average score PredRes	4,8 (±1,9)	5,6 (±1,2)	20,310	**<0,001**
Platform				
Cobalt-chromium	94 (59,1%)	162 (58,7%)	0,246	0,694
Stainless steel	65 (40,9%)	114 (41,3%)	0,293	0,687

It was noted that the length> 28mm and type C lesions were associated with diffuse restenosis and length <15 mm with the focal lesions. Also, it was noted that SPredRes distinguishes between lesions with focal restenosis and those with diffuse restenosis.

5. DISCUSSIONS

Our observations are consistent with many research which show that diabetes mellitus, prior coronary angioplasty, longer length and small stent diameter, certain lesion characteristics (type C ACC/AHA, ostial lesions or chronic total occlusions) represents factors correlated with in-stent restenosis [12, 13, 14, 15].

It was shown that the risk of clinical and angiographic events correlates with morphological complexity and severity of atherosclerotic disease [15, 16, 17]. For example, when using DES LEADERS trial (Limus Eluted from A Durable versus ERodable Stent coating) shows that a score ≥16 Syntax is a good predictor of major adverse cardiac events and the need for re-revascularization at one year [17]. In the studied group, for each patient, we calculated interventional Syntax scores ($Syntax_i$) as the sum of the individual scores assigned to each lesion treated by stent placement. We started from the hypothesis that it is correlated with angiographic post-procedural recurrences. The average of $Syntax_i$ score calculated for patients with in-stent restenosis was 8.6 (± 4.6) compared with 7.5 (± 3.5) for those with permeable stents, but the difference was not statistically significant ($p = 0.098$). Analysing the score in relation with the presence of in-stent restenosis score we observed a significant association with scores in quartile 4 (≥12) (OR 1.93; 95% CI 1.12 to 3.31; $p = 0.015$). We found and that a majority of patients with single or three vessel coronary heart disease present $Syntax_i$ score values in this quartile, suggesting that the extent of atherosclerotic lesions can be considered an indicator of angiographic recurrences. Incidentally, this is one of the information provided recently by Cassese S et al. showing that multivessel coronary heart disease is one of the factors significantly correlated with BMS or DES in-stent restenosis [15].

The results obtained shows that the proposed model has a good power of prediction, accurately identifying leasions treated with BMS stent placement, which will subsequently develop restenosis. Representation of the ROC curve of predictive score for restenosis supports this statement indicating an AUC of 0.75, in contrast, for example, only 0.63 calculated in PRESTO trial [13]. Several arguments make this predictive score to be very useful in daily practice. First, the predictive score of restenosis CCUBCA can identify lesions at high risk to develop restenosis in BMS and that could benefit from DES placement. We believe that its power of prediction it is a result of the calculation method because, unlike the proposed models in EVENT and PRESTO trials, it incorporates both risk factors for restenosis in stent and those for protection. Last but not least, utility derives from the fact that its parameters can be easily quantified by visual estimation, like Syntax score, which is a common practice in catheterization angiography laboratories .

Depending on angiographic appearance, Mehran et al. classified in-stent restenosis as diffuse or focal [18]. This division has prognostic value, the risk for repeated revascularization is

increased for diffuse restenosis compared with focal [18, 19]. The 472 restenotic lesions included in our study were more frequently the diffuse type compared to the focal pattern (33,68% pattern I, 41,74% pattern II, 16,74% pattern III and 7,84% pattern IV). These observations are consistent with several published studies demonstrating that BMS restenosis is often diffuse [18, 19, 20, 21]. Interestingly, the average predictive score of restenosis is higher for stents with diffuse restenosis as compared with the focal [5,6 (±1,2) versus 4,8 (±1,9); $p<0,001$]. It follows that an elevated SPredRes value is not only predictive but also a more aggressive form of restenosis presentation.

6.CONCLUSIONS

1. Diabetes mellitus represents a clinical factor strongly associated with presence of in-stent restenosis. According to bivariate analysis, the estimated risk of restenosis in bare metal stents is greater in his presence. The presence of prior percutaneous angioplasty and history of restenosis significantly increases the risk of recurrence.

2. Dual antiplatelet therapy with aspirin and clopidogrel has minimal influence on the restenosis phenomenon. Statin treatment seems to have a protective effect.

3. According to multivariate analysis stent length > 28mm, diameter ≤ 2,5 mm, ostial lesions and chronic total occlusion are independently correlated with restenosis in bare metal stents. These characteristics identify a subset of lesion involving a higher risk of restenosis when BMS are implanted and of which DES placement would be much more effective for prevention of clinical and angiographic recurrences within the first post-procedural first year.

4. Diameter ≥3,25 mm, stent length ≤15 mm are parameters that correlate significantly with subsequent absence of further in-stent restenosis.

5. $SYNTAX_i$ score (sum of individual scores assigned to each lesion treated percutaneously with stent implantation) correlates significantly with the presence of in-stent restenosis at values ≥12, the lesion complexity quantified by this score represents a risk factor associated with clinical and angiographic events in the first year after bare metal stent placement.

8. The score proposed in this study, predictive score of restenosis CCUBCVA, demonstrate a good ability to distinguish coronary lesions which will subsequently develop restenosis. Values ≥ 4.5 correlates significantly with the presence of in-stent restenosis. The

estimated risk of restenosis increases remarkably when calculated predictive score has a value >6. This is a morphological score based on lesional characteristics, and stents size, which proves its prediction power even in patients known to be at increased risk of in-stent restenosis such as diabetic patients and can be easily calculated by visual estimation.

9. The clinical method of presentation of patients with in-stent restenosis is represented by stable angina pectoris in more than half of the cases (51.8%). Approximately one third of patients were hospitalized in order to perform control angiography with the diagnosis of acute coronary syndrome, of which clinical predictors are smoking and the presence of prior acute myocardial infarction.

10. The diffuse form constitutes angiographic presentation of restenosis within the first 12 months for more than 50% of the lesions treated with bare metal stents.

Original part of thesis:

A) Identification of the clinical or angiographic variables associated with and description of in-stent restenosis phenomenon characteristic of daily activity in a tertiary center for Interventional Cardiology that treats with a broad spectrum of coronary artery disease, from stable forms up to acute coronary syndromes with ST elevation.

B) Designing a pattern and a predictive score that proves a good accuracy in identifying coronary artery lesions with increased risk of developing post-procedural angiographic in-stent restenosis.

Study limitations :

-the main limitation consists in the fact that the study is descriptive, single-centre, non-randomized, enrolling consecutive patients who were sent to our department.

-inference data for presented subgroups (bifurcation lesions, prior percutaneous coronary intervention) is affected by the reduced number of patients, which may represent a factor of confusion

-absence of data relating to techniques or genetic factors which have not been assessed

-patients in the control group have not been selected on the basis of clinical or angiographic characteristics of the patients from the main lot

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