ORIGINAL ARTICLE

STATINS AND THE RISK FOR CORONARY IN-STENT RESTENOSIS IN DIABETIC PATIENTS

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Abstract

Diabetes mellitus is considered to be an independent risk factor for the progression of coronary artery disease, due to the associated pro-atherosclerotic status, and also an important predictor of poor outcomes after both coronary artery bypass grafting and percutaneous coronary intervention. Even in the contemporary era of newer-generation stents and despite remarkable technological advances, in-stent restenosis is still a major problem. The aim of our study was to identify risk factors for restenosis in the first year after stent deployment in 95 diabetic patients with coronary heart disease. Our results suggest that a larger stent diameter and the use of statins positively influence the risk of in-stent restenosis in the first year after stent implantation. Systemic statin therapy should be considered in all interventional treated diabetic patients, in order to reduce the risk of in-stent restenosis, particularly in high-risk patients.

Rezumat

Diabetul zaharat este considerat a fi un factor de risc independent pentru progresia bolii coronariene ischemice (BCI), datorită statusului pro-aterosclerotic și, de asemenea, un predictor important al prognosticului terapiilor de reperfuzie coronariană. Chiar și în epoca contemporană, a stenturilor de „nouă generație" și în ciuda progreselor tehnologice remarcabile, restenozarea *in-stent* rămâne o problemă semnificativă. Scopul studiului nostru a fost identificarea factorilor de risc pentru restenoză în primul an după instalarea stentului la un grup de 95 de pacienți diabetici cu BCI. Rezultatele noastre sugerează că diametrul mai mare al stentului și utilizarea statinelor influențează favorabil riscul de restenozare *in-stent* în primul an după implantare. Terapia sistemică cu statine trebuie luată în considerare la toți pacienții diabetici cu intervenție, pentru a reduce riscul de restenozare *in-stent*.

Keywords: statins, coronary in-stent restenosis, diabetes mellitus

Introduction

Diabetes mellitus is considered to be an independent risk factor for coronary artery disease progression due to a pro-atherosclerotic status involving several physiopathological mechanisms [1]. Moreover, patients with diabetes have a significantly higher cardiovascular mortality rate in comparison with the general population [2]. Angiographic studies have indicated that diabetic patients frequently have diffuse vascular injury - with a higher plaque burden, smaller vessel reference diameter, poorly developed collateral circulation, and an increased incidence of multivessel or left main disease [1, 3]. In addition, diabetes is shown to be an important predictor of poor outcomes after both coronary artery bypass grafting and percutaneous coronary intervention [4, 5].
Even in the contemporary era of newer-generation stents and despite remarkable technological advances,

in-stent restenosis remains a significant problem [6, 7]. In-stent restenosis is angiographically defined as a recurrent stenosis greater than 50% in the previously treated vessel segment and is due to excessive tissue proliferation by neo-intimal accumulation or new-occurring atherosclerotic process called "neoathero-sclerosis" [7-9]. Several clinical, biological, angiographic, procedural or pharmacological parameters have been correlated with the presence or absence of restenosis in the coronary stents [7-12]. The emergence of drug-eluting stents (DES) with the concept of stents as local drug delivery platforms aims neointimal hyper-plasia, which is the main mechanism of restenosis during the first 12 months post-implantation [9]. This has reduced the need for target vessel revascularization to less than 50% compared to bare-metal stents (BMS) [6, 9].
However, diabetes remains the most robust clinical parameter correlated with clinical and angiographic

recurrences after percutaneous coronary intervention (PCI) [7, 8]. Hyperglycaemia produces endothelial dysfunction and a persistent proinflammatory status that can exaggerate the neointimal reaction in case of vascular injury, the incidence of restenosis and the need for repeated PCI [8, 13].

The aim of the present study was to identify the risk factors for restenosis in the first year after stent implantation in diabetic patients with coronary heart disease. Because our primary objective was to detect the effects of the main pharmacological classes on the risk of restenosis, this study was performed in bare-metal stents, thus eliminating the beneficial effect on smooth muscle cell proliferation and neointimal hyperplasia attributed to the pharmacologically active substance locally released by DES.

Materials and Methods

We retrospectively analysed PCI data using our interventional database from the Army's Centre for Cardiovascular Diseases from Bucharest, Romania, constituted along more than ten years; we identified 95 patients eligible for the study. The study obtained the approval of the local Ethical Committee.

Inclusion criteria: diabetic patients with "bare metal" stent implantation for coronary artery diseases who suffered an angiographic evaluation within one year following the initial procedure for clinical reasons.

Exclusion criteria: patients with initial sub-optimal post-procedural results, patients with major cardiac events in the first month after implantation, patients with incomplete data acquisition; patients with newly developed coronary lesions.

Coronary angiography was performed in agreement with the standard operating protocols and every lesion was analysed in minimum two orthogonal projections. We obtained the details regarding the length and diameter of the implanted stents from patients' medical records. Definition of in-stent restenosis according to angiographic criteria is recurrent restenosis with percentage diameter $\geq$ 50% within stent level or within its 5-mm proximal and distal edges.

We retrospectively collected data related to the initial angiography (indication for invasive evaluation, coronary anatomy, location, complexity and morphological characteristics of coronary lesions), subsequent interventional treatment (number of treated lesions and vessels, number and dimensions of implanted stents) as well as clinical and biological data relevant to the study. Thus, several angiographic parameters were evaluated as they were defined in the literature [14, 15].

Statistical analysis

For the statistical analysis IBM SPSS version 26 was used. Univariate data analysis was performed using *chi square* tests (Pearson Chi square, Fisher Exact Test) for categorical variables and *student t* test (normal distribution) for continuous ones. Multivariate analysis was performed using logistic regression (dichotomous dependent variable, continuous and categorical independent variables). The graphical representation of the data was realized through graphical columns, ROC and Forest. Statistically significant p value was $p \leq 0.05$.

Results and Discussion

We identified 95 diabetic patients eligible for the study - from which 82 patients (86.3%) with at least one in-stent restenosis, and 13 patients (13.7%) without in-stent restenosis. The mean period of time from the first procedure to the invasive re-evaluation was 220.6 ± 17.2 days for the restenosis group, respectively 277.5 ± 10.1 days for the group without restenosis. Baseline features of both studied groups are shown in Table I.

Table I

Baseline characteristics for the patients groups

	Restenosis (n = 82)	No restenosis (n = 13)	χ2/ t test	p value
Age	58 (IQR = 13)	56 (IQR = 17)	1.374	0.241
Sex				
Male	41 (50%)	8 (61.5%)	0.598	0.439
Female	41 (50%)	5 (38.5%)		
Clinical/paraclinical data				
High blood pressure	54 (65.9%)	7 (53.8%)	-	0.535
Hypercholesterolemia	52 (63.4%)	8 (61.5%)	-	0.990
Smoking	23 (28%)	6 (46.2%)	-	0.207
Peripheral arteries disease	25 (30.5%)	7 (53.8%)	-	0.120
Chronic kidney disease	4 (4.9%)	1 (7.7%)	-	0.529
Initial PCI indication				
Acute coronary syndrome	41 (50%)	6 (46.2%)	0.031	0.860
Stable angina	31 (37.8%)	4 (30.8%)	-	0.762
Silent cardiac ischemia	10 (12.2%)	3 (23.1%)	-	0.378
Diabetes treatment				
Oral hypoglycaemic medication	64 (78%)	8 (61.55)	-	0.293
Insulin	10 (12.2%)	2 (15.4%)	-	0.667

	Restenosis (n = 82)	No restenosis (n = 13)	χ2/ t test	p value
Other treatments				
Beta-blockers	72 (87.8%)	9 (69.2%)	-	0.097
Calcium channel blockers	10 (12.2%)	3 (23.1%)	-	0.378
Diuretics	8 (9.8%)	4 (30.8%)	-	0.057
ACEI/ARB	54 (65.9%)	8 (61.5%)	-	0.763
Statins	**49 (59.8%)**	**12 (92.3%)**	**-**	**0.028**
Aspirin	66 (80.5%)	11 (84.6%)	-	0.999
Clopidogrel	65 (79.3%)	11 (84.6%)	-	0.999
Nitrates	10 (12.2%)	2 (15.4%)	-	0.999
eGFR CKD-EPI (mL/min/m^2)	69.9 (IQR = 13)	78 (IQR = 26.7)	0.115	0.734
BMI (Kg/m^2)	30.4 (IQR = 4.5)	29.9 (IQR = 4.2)	0.479	0.489
HbA1c	7.4 (IQR = 0.8)	7.1 (IQR = 0.7)	2.108	0.147

% expressed in restenosis vs. no-restenosis group, ACEI= angiotensin converting enzyme inhibitors; ARB= angiotensin receptors blockers

There was a higher percentage, however statistically insignificant, of women in the group with in-stent restenosis (50% *vs.* 38.5%, p = 0.439). Also, risk factors for coronary heart disease (hypertension, dyslipidaemia and smoking) did not differ significantly between the two groups. We observed, instead, a higher percentage of patients undergoing statin treatment in the no-restenosis group (92.3% *vs*. 59.8%), a statistically significant result (p = 0.028). We mention that all our patients received statins at high doses: atorvastatin 40 - 80 mg/day or rosuvastatin 20 - 40 mg/day.

The oral hypoglycaemic treatment included metformin hydrochloride (1000 - 2000 mg/day) and/or gliclazide (60 - 120 mg/day).

A total of 154 stented lesions were analysed (136 in the group with restenosis, 18 in the group without restenosis) of which 110 (71.4%) presented angiographic criteria for restenosis and 44 (28.6%) stents without restenosis. Table II shows the baseline characteristics *per* lesion.

Table II
Baseline characteristics *per* lesion

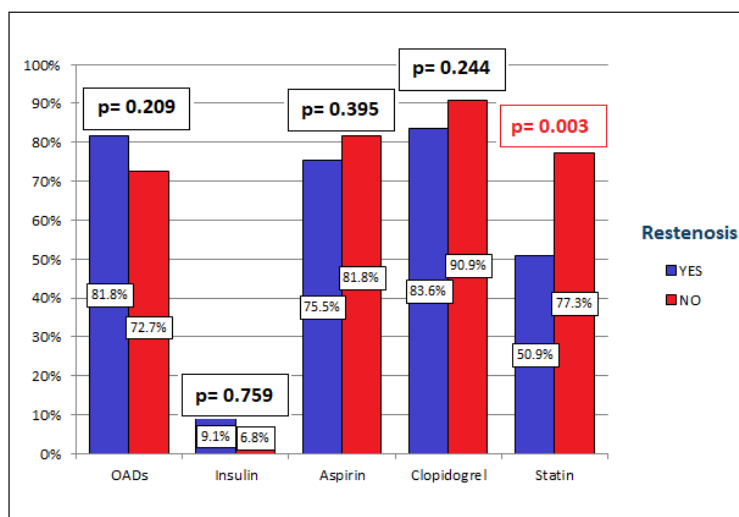|	Restenosis (n = 110)	No restenosis (n = 44)	χ2	p value
Sex				
Male	73 (66.4%)	23 (52.3%)	2.658	0.103
Female	37 (33.6%)	21 (47.7%)		
Clinical/paraclinical data				
High blood pressure	73 (66.4%)	32 (72.7%)	0.587	0.444
Hypercholesterolemia	72 (65.5%)	33 (75%)	1.320	0.251
Smoking	39 (35.5%)	19 (43.2%)	0.799	0.371
Peripheral arteries disease	41 (37.3%)	18 (40.9%)	0.176	0.675
Chronic kidney disease	5 (4.5%)	2 (4.5%)	-	1.000
Initial PCI indication				
Acute coronary syndrome	60 (54.5%)	25 (56.8%)	0.066	0.798
Stable angina	36 (32.7%)	16 (36.4%)	0.186	0.666
Silent cardiac ischemia	14 (12.7%)	3 (6.8%)	-	0.398
Diabetes treatment				
Oral hypoglycaemic medication	90 (81.8%)	32 (72.7%)	1.578	0.209
Insulin	10 (9.1%)	3 (6.8%)	-	0.759
Other treatments				
Beta-blockers	94 (85.5%)	36 (81.1%)	0.316	0.574
Calcium channel blockers	16 (14.5%)	7 (15.9%)	0.046	0.830
Diuretics	12 (10.9%)	10 (22.7%)	3.585	0.058
ACEI/ARB	79 (71.8%)	35 (79.5%)	0.976	0.323
Statins	**56 (50.9%)**	**34 (77.3%)**	**8.994**	**0.003**
Aspirin	83 (75.5%)	36 (81.8%)	0.725	0.395
Clopidogrel	92 (83.6%)	40 (90.9%)	1.358	0.244
Nitrates	15 (13.6%)	8 (18.2%)	0.511	0.475

% expressed in groups (restenosis *vs*. no restenosis), ACEI= angiotensin converting enzyme inhibitors; ARB= angiotensin receptors blockers

We observed that there were no statistically significant differences between the two groups regarding the treatment with insulin, oral hypoglycaemic medication, beta-blockers, ACEIs/ARBs, diuretics, calcium channel blockers or nitrates. Although there was a more frequent association of permeable stents with aspirin (81.8%

vs. 75.5%) or clopidogrel (90.9% *vs.* 83.6%), this correlation was not significant (p = 0.395 and p = 0.244, respectively). On the contrary, there was a significant correlation between statin treatment and stents without restenosis (p = 0.003, OR 0.305, 95% CI 0.137–0.677) (Figure 1).

Regarding angiographic characteristics among the two studied groups (Table III), lesion length > 28 mm were correlated with restenosis (p = 0.002, OR 6.114, 95% CI 1.769 - 21.129) and diameter ≥ 3.5 mm with stents without restenosis (p = 0.014, OR 0.365, 95% CI 0.160 - 0.834).

Figure 1.
Stents distribution according to the hypoglycaemia/antiplatelet/statin treatment and restenosis/no-restenosis
(OADs = oral antidiabetic drugs)

Table III

Baseline angiographic characteristics *per* lesion

	Restenosis (n = 110)	No restenosis (n = 44)	χ2	p value
Stent location				
LAD	51 (46.4%)	22 (50%)	0.167	0.683
LCX	24 (21.8%)	10 (22.7%)	0.015	0.902
RCA	35 (31.8%)	12 (27.3%)	0.306	0.580
Stent diameter				
≤ 2.5 mm	46 (41.8%)	13 (29.5%)	2.003	0.157
2.5 – 3.5 mm	48 (43.6%)	17 (38.6%)	0.322	0.570
≥ 3.5 mm	**16 (14.5%)**	**14 (31.8%)**	**5.978**	**0.014**
Stented length				
≤ 15 mm	26 (23.6%)	15 (34.1%)	1.758	0.185
15 - 28 mm	50 (45.5%)	26 (59.1%)	2.338	0.126
> 28 mm	**34 (30.9%)**	**3 (6.8%)**	**9.993**	**0.002**
Lesion type				
Type A + B	60 (54.5%)	31 (70.5%)	3.291	0.070
Type C (ACC/AHA)	50 (45.5%)	13 (29.5%)		
Ostial lesion	6 (5.5%)	1 (2.3%)	-	0.674
Calcification	18 (16.4%)	5 (11.4%)	0.618	0.432
Chronic total occlusion	12 (10.9%)	3 (6.8%)	-	0.557
Thrombus	9 (8.2%)	2 (4.5%)	-	0.730
Bifurcation	2 (1.8%)	0 (0%)	-	-

LAD = left anterior descendant artery; LCx = left circumflex artery; RCA = right coronary artery

Table IV

Corelation between stented length > 28 mm, stent diameter and in-stent restenosis

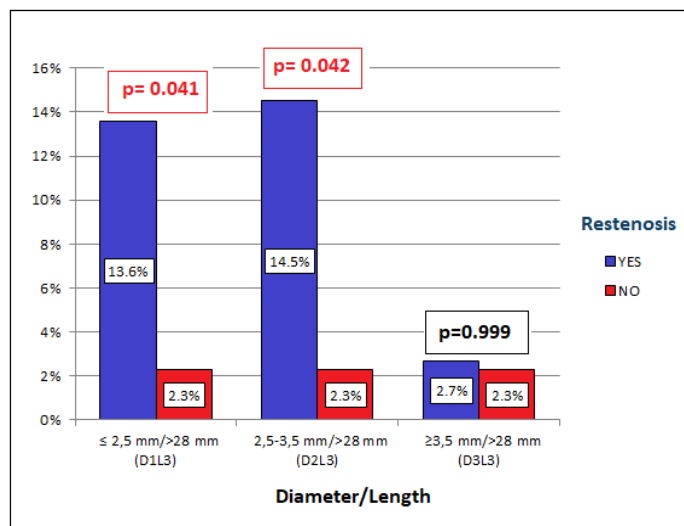|	Restenosis (n = 110)	No restenosis (n = 44)	p value	OR [CI 95%]
≤ 2.5 mm/>28 mm	**15 (13.6%)**	**1 (2.3%)**	**0.041**	**[0.735 - 33.798]**
2.5 - 3.5 mm/> 28 mm	**16 (14.5%)**	**1 (2.3%)**	**0.042**	**[0.940 - 56.983]**
≥ 3.5 mm/> 28 mm	3 (2.7%)	1 (2.3%)	0.999	[0.122 - 11.193]

Figure 2.
Stents distribution based on stent diameter/ length >28 mm and restenosis/no-restenosis

We also studied the relationship between stented length > 28 mm, stent diameter and the presence or absence of in-stent restenosis. Thus, we noticed a significantly higher proportion of stents with length > 28 mm and diameter ≤ 2.5 mm or 2.5 - 3.5 mm in the restenosis group (13.6% *vs.* 2.3%, p = 0.041, respectively 14.5% *vs.* 2.3%, p = 0.042) (Table IV, Figure 2).

All the 3 parameters with statistical significance resulting from the univariate analysis (stent diameter ≥ 3.5 mm, stented length > 28 mm and statin treatment) were introduced in the logistic regression model. All 3 parameters retain their statistical significance (Table V).

Diameter ≥ 3.5 mm (p = 0.030, OR 0.370, 95% CI 0.151 - 0.911) and statins (p = 0.002, OR 0.271, 95% CI 0.117 - 0.630) reduce the probability of restenosis while stented length > 28 mm (p = 0.006, OR 5. 944, 95% CI 1.669 - 21.164) favours restenosis (Figure 3).

Table V
Independent risk factors for restenosis (multivariate analysis)

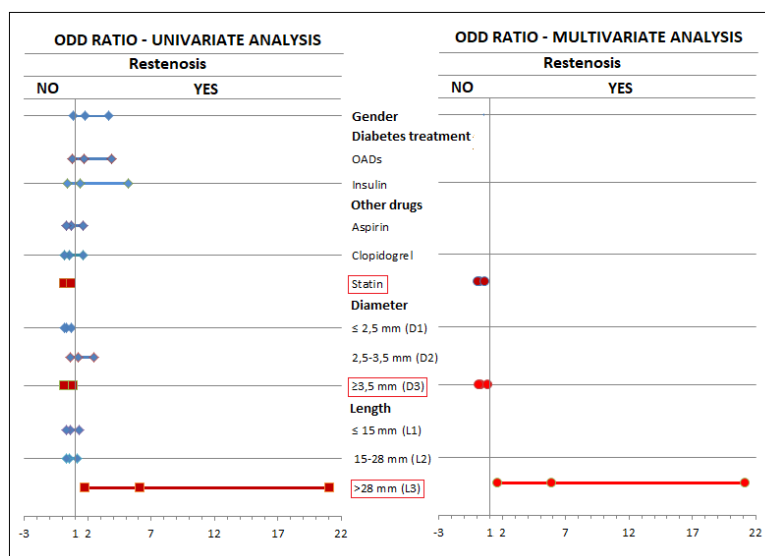|	Estimated coefficient				[95% CI]	
		Test Wald (df)	p value	Odd ratio	Lower	Upper
≥ 3.5 mm	-0.994	4.682 (1)	0.030	0.370	0.151	0.911
> 28 mm	1.789	7.566 (1)	0.006	5.944	1.669	21.164
Statins	-1.305	9.194 (1)	0.002	0.271	0.117	0.630

Figure 3.
Risk factors for restenosis (uni- and multivariate analysis)

The predictive power of the logistic regression model was also evaluated by using the analysis of the receiver operating characteristic (ROC) curve which showed an area-under-curve (AUC) of 0.749 (good predictability) (Figure 4).
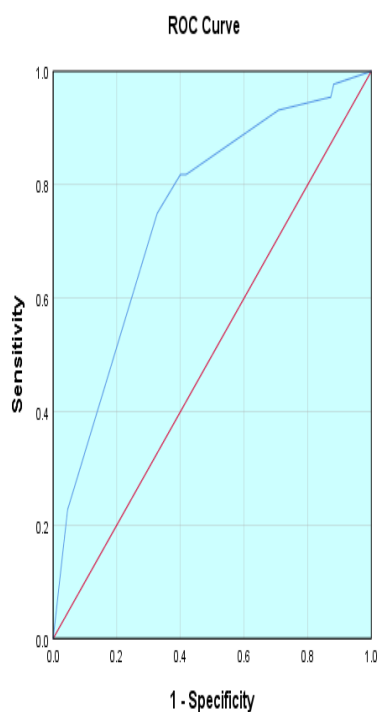
Figure 4.
ROC curve for the logistic regression model

Coronary heart disease displays some gender differences, regarding clinical manifestations, outcome and pharmacological treatment, in particular regarding the statin therapy [16]. Even though without statistical significance, there was a higher percentage of women in the group with in-stent restenosis (50% *vs.* 38.5%, p = 0.439). Studies show that women have a poor adherence to statin treatment because of the side effects, so that they usually receive a lower dose of medication [17].

Most elderly patients (more than 60 - 65 years old, according to World Health Organization) with dys-lipidaemia are at increased risk of coronary events and stroke, so the benefits of statins outweigh their unexpected secondary effects. However, treatment with high doses of statins in elderly needs close monitoring for safety [18].

Coronary lesions in diabetic patients are characterized by a diffuse form of atherosclerosis – generating longer, more complex lesions, with an underlying biological status that promotes neointimal hyperplasia and high rates of subsequent restenosis after stent deployment [19-21].

It has been suggested that the duration of diabetes may be a cardiovascular disease risk factor. In our study the mean duration of diabetes was 8.6 years, ranging from 1 to 22 years.

Moreover, interventional coronary revascularization is characterized by an increased incidence of in-stent restenosis and the risk of major cardiac events compared to non-diabetic patients [20, 22]. For example, in a series of patients enrolled in 16 studies, angiographic recurrence at 6 months was found in 31.1% of patients with diabetes and only in 20.6% of those without diabetes (p < 0.001) [22].

Several studies have reported that smaller vessel reference diameter, smaller minimal luminal diameter after stenting and greater stented length are important predictors of stent restenosis in diabetic patient [22-24]. Moreover, the progressive increase of stented length or the progressive reduction of the post-intervention luminal diameter progressively increases the subsequent risk of angiographic recurrence [23]. There are several explanations for this phenomenon. First, the extent of vascular injury and subsequent neo-intimal response correlates with stent length [8, 25]. Second, for a certain degree of neo-intimate accumulation, the possibility of a reduction over 50% of the luminal diameter is dependent on that of the implanted stent [26]. Similarly, in our study, the stent length > 28 mm is an independent predictor of restenosis in the coronary stent. When we analysed the stent length > 28 mm in combination with the stent diameter we found a significant association with stent restenosis in diameters < 3.5 mm. In contrast, diameter ≥ 3.5 mm represent a protective factor and are significantly correlated with the presence of permeable stents in diabetic patients. This is also in accordance with the early observations which suggest that in large vessels (> 3.0 mm diameter) the rate of in-stent restenosis is not significantly different between diabetic and non-diabetic patients [27].

It is proven that premature discontinuation of double antiplatelet therapy is associated with an increased risk of major cardiac events and of stent thrombosis [9, 28]. In our study compliance with double anti-platelet therapy was good, with no statistically significant differences between patients with or without stent angiographic restenosis. Information on the possible protective effect of anti-diabetic medication on stent restenosis is inconsistent and inconclusive [11, 29-32]. Several studies have suggested that some oral anti-diabetics, such as thiazolidinediones, lower the risk of stent restenosis and major post-procedural cardiac events [11, 29]. On the other hand, although pre-clinical studies have indicated that insulin administration reduces intimal hyperplasia, the incidence of in-stent restenosis does not appear to be influenced when comparing insulin therapy with usual care with oral hypoglycaemic agents [30]. In our study we did not find a significant association between the anti-diabetic medication and the presence or absence of in-stent restenosis.

According to our results, the only class of drugs that favourably influences in-stent restenosis is represented by statins. This is in accordance with several previous studies showing that statins have many attributes that can reduce the development of post-angioplasty restenosis [10, 33-39]. Moreover, data provided by the Lescol Intervention Prevention Study (LIPS) sub-study show that statins reduce the impact of diabetes on long-term outcome after coronary intervention and also decrease the risk of major adverse cardiovascular events in diabetic patients by over 50% [33]. The efficacity of statins is mainly due to their pleiotropic effects rather than their lipid-lowering success [34, 40, 41]. In addition to lowering cholesterol, they have many other effects (anti-inflammatory, antithrombotic, antioxidant, lowering the level of C-reactive protein, antimitotic – inhibiting the proliferation of smooth muscle cells, increasing the synthesis of nitric oxide and stimulating the expression and activity of endothelial nitric oxide synthase) [10]. In diabetic patients, high intensity statin therapy increases endothelial progenitor cell levels and decreases in-stent neointima volume [36].

Moreover, the administration of statins before the coronary angioplasty procedure is associated with a reduction in myocardial necrosis peri- and post-per-cutaneous transluminal coronary angiography (PTCA) and also decreases the need for repeated revascularization [38]. In addition, there is evidence that statin-releasing stents inhibit the restenosis process in animal models [39].

These observations are supported by our study results, which conclude that statins represent an independent factor for stents' permeability first year post-implantation in diabetic patient.

The main limitation of our research is its retrospective design, being a "real world", not a randomized study; also, data related to procedural or genetic factors, proven to be related to in-stent restenosis were not been evaluated.

Conclusions

In-stent restenosis in patients with diabetes remains a problem still incompletely solved, even in the era of new generation stents. Our results suggest that larger stent diameter and the use of statins have a positive impact on the risk of in-stent restenosis in the first 12-months after stent implantation - when the main restenosis mechanism is represented by neointimal hyperplasia. Systemic statins therapy should be considered in all interventional treated diabetic patients, in order to decrease the risk of in-stent restenosis and athero-sclerotic plaque progression, especially in those with multiple risk factors. Further and larger studies will be useful, regarding the potential additive effect of statins to the anti-proliferative impact of drug-eluting stents.

Conflict of interest

The authors declare no conflict of interest.

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