Results of Coronary Stenting using the Stents with Biodegradable Polymer and Antiproliferative (Biolimus A9) Coating

R.V. Zeynalov[1], D.A. Asadov, M.B. Matini, V.V. Mazurova., D.G. Gromov, O.V. Zakharova, A.G. Koledinsky, D.G. Iosseliani.
Moscow City Center of Interventional Cardioangiology, Moscow, Russia

The study comprised two groups of patients with coronary artery disease. Then patients from Group 1 received DES with biodegradable coating, and the patients from Group 2 – DES with permanent polymer coating. Baseline clinical, historic and angiographic characteristics were comparable in both groups. The rate of restenosis in the mid-term follow up was similar in both groups. The rate of thrombosis was reliably lower in the group of DES with biodegradable polymer coating.
Keywords: *DES, stents with biodegradable polymer coating, Biomatrix stents.*

Purpose of study: to determine the effectiveness of the use of drug-eluting stents (DES) with biodegradable polymer coating (Biomatrix) in comparison with DES with permanent polymer coating («Cypher») in patients with coronary artery disease (CAD).

Material and methods: the study comprised 117 patients in whom a total of 235 stents have been implanted. The patients were divided into 2 groups. The patients from Group 1 (n=51) received 110 Biomatrix stents. The patients from Group 2 (n= 66) received 125 Cypher stents. The final purpose of the study consisted in the comparison the rate of restenosis and thrombosis of the above stents in the mid-term follow-up.

Results: the rate of restenosis in the mid-term was 2,72% in the group with Biomatrix stents and 3,2% — in the group with Cypher ($p>0.05$). The rate of thrombosis in the studied groups was significantly different — 0% and 3,2%, respectively ($p< 0.05$)

Conclusions: the effectiveness of the stents with bidgradable polymer coating is comparable with the effectiveness of the stents with permanent polymer coating. At the same time the rate of thrombosis after the implantation of Biomatrix stents is significantly lower than with Cypher stents.

Introduction

Large-scale implementation of DES into the clinical practice has allowed to improve the results of stenting due to the reduction of the rate of restenosis. The first clinical trials demonstrated significant advantages of first-generation stents in comparison with balloon angioplasty and stenting with bare metal stents. However after mass introduction of DES into the practice, in particular, in multiple extended coronary lesions as well as in the presence of several risk factors, the increase of the rate of late restenoses and thromboses became evident. One of the main causes of these serious cardiac complications consist in the presence of permanent (non-soluble) polymer stent coating. The impact of this coating on the vascular wall contributes to the development of stent restenosis and thrombosis after the end of the drug action (1,2,3).

The introduction of DES with biodegradable (soluble) polymer coating represents an attempt to eliminate this side effect, thus decreasing the rate of unfavorable results of treatment. Such stents are made of a steel frame and polylactic biodegradable polymer coating impregnated with a medication — Biolimus A9. Due to the abluminal coating as well as to the polymer's capacity to get degraded within 6-9 months with the formation of water and carbon dioxide, these stents decrease the rate of late restenosis and thrombosis, thus contributing to full endothelization of the inner surface (4).

Methods

In conformity with the purpose and the tasks we present the data of examination and treatment of patients with coronary artery disease (CAD) in the Moscow City Center of Interventional Cardioangiology during the period from 2008 to 2010.

The patients have been selected for the study on the base of the following criteria:

– CAD diagnosed on the base of an extensive clinical and instrumental examination;

– documented painless ischemia or stable angina of effort assessed in conformity with ACC/AHA classification;

– primary, not restenotic character of coronary arterial narrowing without the signs of fresh parietal thrombi;

[1] Address for correspondence :
Dr. Rufat Zeynalov,
Moscow City center of Interventional Cardioangiology
Russia, 101000, Moscow,
Sverchkov per., 5
Phone: +7 495 624 96 36
Fax: +7 495 624 67 33
e-mail: zeynalovrufat@hotmail.com
Manuscript received on September 17, 2011
Accepted for publication on September 29, 2011

– lesions allowing for coronary stenting;

– hemodynamically significant (≥ 60% of the diameter) arterial lesion;

– diameter of the involved vascular segment 2,25 — 4 mm.

The trial comprised the patients with angina of effort of class I-IV (AHA/ACC) and painless myocardial ischemia, independently of the number of the involved coronary arteries and the function of left ventricular myocardium, with coronary lesions of types A, B and C.

The patients with a history of balloon angioplasty or stenting , with concomitant cardiovascular pathology (aortic aneurysm, valvular diseases) requiring surgical correction were excluded from the study.

The patients included in this study received only Cypher or Biomatrix stents. Only one type of stents could be implanted in each patient.

The study comprised 117 patients in whom a total of 235 DES have been implanted. Depending on the type of drug and polymer coating of the implanted stents the patients have been divided into 2 groups. Group 1 comprised 51 patients with Biomatrix stents with biodegradable polymer and antiproliferative coating — Biolimus A9. Group 2 (control) comprised 66 patients with Cypher stents with permanent polymer and antiproliferative coating — Sirolimus.

Mean age of patients in Group 1 was 58 ±8,2 years, in Group 2 — 53 ±6,7 years. 44 of 51 patients in Group 1 (86,3%) were males. In Group 2 there were 48 (72,7 %) males, i.e. male patients prevailed in both groups.

The analysis of risk factors in Group 1 revealed smoking in 18 patients (35,3%), family predisposition to CAD — in 8 (15,7%), arterial hypertension — in 12 (23,5%), dislipidemia — in 15 (29,4%), obesity — in 3 (5,9%), diabetes mellitus — in 10 patients (19.6 %). In Group 2 these risk factors were met in 22 (33,3 %), 11 (16,7 %), 13 (19,7%), 16 (24,4 %), 4 (6,1 %) and 11 patients (16.7%), respectively (p>0,05) (Table № 1).

The combination of 3 and more risk factors was met in 11 (21,56 %) patients from Group 1 and in 15 (22,7 %) patients from Group 2 (p>0,05).

Thus, the comparison of risk factors prevalence in the studied groups (including smoking, family history and arterial hypertension) did not reveal any significant difference. Neither was the rate of diabetes mellitus statistically different. The Table №2 shows patients' distribution according to the forms of CAD.

7 patients from Group 1 (13,7%) and 7 patients from Group 2 (9,0%) had a history of myocardial infarction, that is postinfarction cardiosclerosis (PICS) (p<0,05).

In Group 1 painless ischemia was seen in 3 patients (5,9 %) and angina of effort — in 35 (67,7%). Among them 5 patients (9,8 %) had heart failure of functional class I, 13 (25,5%) — of class II, 11

Table № 1.

The prevalence of risk factors for CAD in the studied groups

Risk factors	Group 1, n=51		Group 2, n=66		P
	abs.	%	abs.	%	
Smoking	18	35.3	22	33.3	>0.05
Family history	8	15.7	11	16.7	>0.05
Arterial hypertension	12	23.5	13	19.7	>0.05
Dislipidemia	15	29.4	16	24.2	>0.05
Obesity	3	5.9	4	6.1	>0.05
Diabetes mellitus	10	19.6	11	16.7	>0.05

Table № 2.

Patients' distribution by the forms of CAD

Form of CAD	Group 1, n=51		Group 2, n=66		P
	abs.	%	abs.	%	
Painless ischemia	3	5.9	5	7.6	>0.05
Angina of effort	36	70.6	48	72.7	>0.05
Unstable angina	6	11.8	8	12.1	>0.05
Myocardial infarction	7	13.7	5	7.6	>0.05
Non ST-elevation myocardial infarction	1	2.0	2	3.0	>0.05
ST-elevation myocardial infarction	6	11.8	3	4.5	**<0.05**

(21,5 %) — of class III and 7 (13,7 %) — of functional class IV. Unstable angina was seen in 6 (11,7%) patients. In Group 2 painless ischemia was observed in 5 patients (7,6%). In total, 48 patients in the control group (72,7%) were in heart failure. Among them 9 (13,6 %) had heart failure of functional class I, 20 (30,3%) — of class II, 12 (18,2 %) — of class III and 7 (10,6%) — of functional class IV. That is, both groups were highly homogenous by their functional class of angina, and statistical analysis did not reveal significant differences. A statistically significant difference have been revealed among patients with ST-elevation myocardial infarction (STEMI). In Group 1 there were 7 patients admitted with the diagnosis of MI. Among them 1 patient had non ST-elevation MI and 6 had STEMI. In Group 2, MI has been diagnosed at admission in 5 patients, 2 of them had non ST-elevation MI and 3 had STEMI.

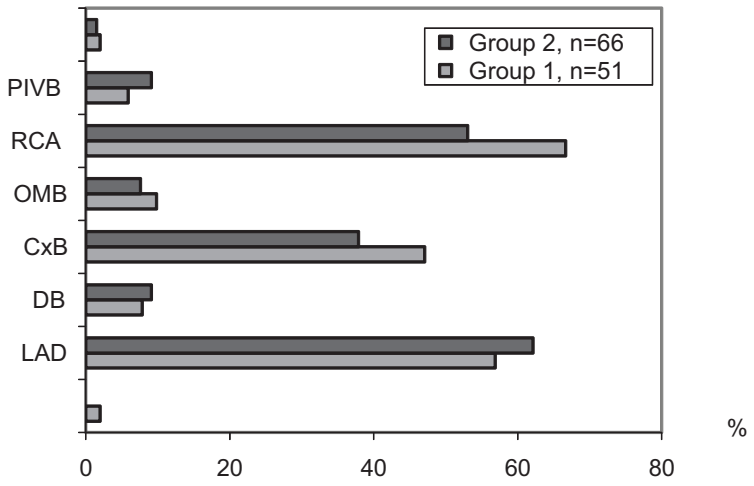

Diagram № 1. Involved (target) coronary arteries in the studied groups

The diagram № 1 shows the distribution of target arteries in the groups.

Statistical analysis

Statistical analysis of the quantitative data was carried out with the use of non-parametric methods — Wilcoxon-Mann-Whitney criterion and Wilcoxon signed-ranks test for matched pairs. If the amount of data in the compared groups was under 30 and in at least in one group it was under 5, the results have been compared using exact Fisher test (8, 9, 10).

Results

Early results. Final clinical success of the PCI as well as final optimal angiographic results have been obtained in 100 % of cases in both groups. In Group 1 (n=51) the complications occurred at different stages of the stenting procedure in 4 patients. In 1 case there was a dissection along the distal edge of the stent requiring an additional stent implantation. In another case the development of “no-reflow” phenomenon inhibited the antegrade filling of the vessel. «No-reflow» could be stopped by intracoronary nitroglycerin. The implantation of an additional stent was not necessary. Also 2 patients (3,92%) from this group had a subcutaneous hematoma at the puncture site, not requiring blood transfusion.

In Group 2 (n=66) the stenting-related complications developed in 3 patients. In one case the intimal damage distal to the target lesion in the territory of the stented artery, occurring during guidewire positioning, led to this artery thrombosis. After the administration of IIb/IIIa platelet receptors inhibitiors the thrombus was lysed and an additional stent has been implanted with good results (the MI did not develop). One patient had a subcutaneous hematoma with the signs of post-hemorrhagic anemia (not requiring blood transfusion). Another patient had a transient acute cerebrovascular accident, which was completely stopped in the intensive care unit in 2 hours after the procedure.

There were no other complications, including deaths, in the studied groups. The analysis of the immediate results revealed the absence of significant differences in the prevalence of complications between the groups (p>0,05) (table №3).

All patients were discharged in stable condition with the recommendations for further medical therapy.

Mid-term results of endovascular treatment.

The duration of mid-term follow-up in the studied groups was 8,4 ±1,4 months for Group 1 and 8,1 ±1,7 months for Group 2. The fate of all patients included into the study was known by the moment of control examination. According to the existing protocols the patients underwent exercise testing for the detection of eventual myocardial ischemia and coronary angiography (95 patients). The data are presented in Table № 4.

In the mid-term follow-up 51 patients (100%) from Group 1 and 65 patients (98,48%) from Group 2 underwent clinical examination. The evaluation of myocardial perfusion by the means of stress-testing did not reveal clinical signs of angina in 47 patients (92,15%) from Group 1 and in 61 (93,8 %) patients from Group 2. Clinical signs of angina with confirmed myocardial ischemia has been noted in 4 (7,84%) patients from the Group 1 and in 3 (4,54%) patients from the control group. All patients with clinical signs of angina underwent coronary angiography.

Control coronary angiography in the mid-term follow-up has been performed in 42 patients (82 %) from Group1, who received 94 stents (85,5%), and in 53 patients (80,3%) from Group 2, in whom 76 stents (79,2%) had been implanted. The results of coronary angiography allowed for the assessment of such pa-

rameters as restenosis, thrombosis and progressing of atherosclerotic process.

In-stent restenosis was determined as the lumen loss > 50%, and also at 5 mm distal and proximal to the stent

Restenosis was revealed in 2 patients from Group 1. In one case clinical picture of angina resumed within 5 months, in another — within 7 months after the discharge.

In Group 2 there were 4 patients with in-stent restenosis. One of then had painless ischemia, 2 had angina of effort of functional class II. Clinical signs of angina resumed at 5 and 6 months after the discharge. The 4th patient with in-stent restenosis had angina of the III functional class in 5 months after stenting. In all cases restenosis involved only one stent. The frequency of restenosis was not statistically different between the groups (p>0.05).

The progressing of atherosclerotic process was noted in 2 (3,92%) patients from Group 1. As their lesions were hemodynamically significant, both of them underwent coronary stent implantation. The progressing of atherosclerotic process in 1 (1,5%) patient from Group 2 also required coronary stent implantation. The evaluation of atherosclerosis progression in the coronary arteries during the period of follow-up did not reveal significant differences between the groups (p>0,05).

The frequency of stent thrombosis in the studied groups was statistically different. In Group 1 there were no cases of stent thrombosis during the whole period of the follow-up. In group 2 (control) thrombosis was revealed in 4 stents (3,2%) of 3 patients (4,54%) (Table №5).

One patient from Group 2 had a subacute thrombosis in the area of the implanted stent and developed a Q-wave MI at day 17 after stenting. The patient with subacute thrombosis has been brought to the Center of Interventional Cardioangiology and underwent mechanical recanalization and balloon angioplasty in the area of thrombotic stent (with good effect).

Both patients with late thromboses revealed in the mid-term follow-up were from the control group. Both of them were admitted in emergency. The first patient was admitted at day 45 after stenting with the diagnosis of a Q-wave MI. He underwent mechanical recanalization, thrombextraction and balloon angioplasty of the stent. The second patients was admitted in 8 months after the discharge with clinical picture of unstable angina. He underwent mechanical recanalization and balloon angioplasty in two stents.

The analysis of factors influencing the development of restenoses and thromboses in stents did not

Table №3.

Immediate clinical and angiographic results of stenting in the studied groups

	Group 1	Group 2	P
Successful procedure, n (%)	51 (100%)	66 (100%)	>0.05
Vessel's dissection, n (%)	1 (1,96%)	1 (1,5%)	>0.05
Myocardial infarction, n (%)	0	0	>0.05
Cerebrovascular complications, n (%)	—	1 (1,5%)	>0.05
Hematoma at the puncture site, n (%)	2 (3,92%)	1 (1,5%)	>0.05
Total number of patients with complications (%)	4 (7,84%)	3 (4,54%)	>0.05

p>0,05 non-significant differences; n – number of patients

Table № 4.

The number of patients examined in the mid-term follow-up

	Group 1 n=51 (100 %)	Group 2 n=66 (100%)	P
Mid-term follow-up, months	8,4 ± 1,4	8,2 ±1,7	>0.05
The patients with available information, n (%)	51 (100%)	66 (100 %)	>0.05
Examined in the mid-term follow-up, n(%)	51 (100%)	65 (98,48%)	>0.05
Control CAG in the mid-term follow-up, n (%)	42 (82 %)	53 (80,3%)	>0.05

p>0,05 non-significant differences; n – number of patients

reveal statistically reliable relation between any factor and the development of these complications.

The analysis of the influence of the stent length on the frequency of restenosis revealed statistically significant differences in Group2: the implantation of stents longer than 23 mm was related to higher frequency of restenosis in comparison with shorter stents ($p<0.05$).

The analysis of the influence of the stent diameter on the frequency of restenosis did not reveal any significant inter-, or intragroup differences. Small diameter of stent had no statistically reliable impact on the frequency of restenosis ($p>0.05$).

The study of the influence of stent's diameter and length on the development of late stent thrombosis has shown that in all three cases of stent thrombosis in the control group the diameter of endoprosthesis was < 2,75 mm, while its length was > 18 mm .

After stenting all patients received double antiplatelet therapy. The Table № 6 shows different regimens of antiplatelet therapy in the mid-term follow-up.

The Table shows that the number of patients receiving double atniplatelet therapy in the mid-term follow-up was not statistically significant between the studied groups. A patient from Group 2 with subacute stent thrombosis received Plavix (75 mg/day) by the moment of thrombus formation. One of two patients with late thrombosis has stopped to take Plavix in 4 months after the implantation of Cypher. Another patient received Plavix (75 mg/day) by the moment of late stent thrombosis development.

Thus, the comparison of the results revealed that in the mid-term follow-up the rate of restenosis was somewhat higher in the group of stents with permanent polymer coating. However this difference between the groups was statistically insignificant.

The analysis of the obtained results did not reveal any correlation between the rates of restenosis, progressing of atherosclerotic process and any clinical risk factor in the studied groups.

The analysis of the influence of the stent's diameter and length has shown that in Group 2 patients the rate of thrombosis was significantly higher in the presence of stents longer than 18 mm in comparison with Group1.

Total rate of thrombosis was statistically different between the groups ($p<0,05$). In Group 1 it was 0%, while in Group 2 — 3.2%. ($p<0,05$). The analysis of the obtained data revealed a correlation between the stent's dimensions and the rate of late thrombosis. Statistical analysis has shown that the probability of thrombus formation in Group 2 increased with the implantation of stents with diameter < 2.75 mm and length > 18 mm.

Discussion

The introduction of drug-eluting stents with biodegradable polymer coating into the practice has opened new possibilities of influencing the rate of stent restenosis and thrombosis. Herewith, due to drug-eluting coating these stents decrease the rate of restenosis, and their dissolving polymer coating contribute to the decrease of the rate of stent thrombosis.

The LEADERS trial comprised the patients with Biomatrix and Cypher stents. According to this trial's data, the rate of MACE in the mid-term follow-up

Table №5.

Analysis of the frequency of stent thrombosis in two groups

Type of thrombosis	Group 1, n=110 (100%)	Group 2, n=125 (100%)	P
Acute	—	—	—
Subacute	—	1 (0.8%)	>0.05
Late	—	3 (2,4%)	< 0.05
Thromboses, in total	—	4 (3,2%)	< 0.05

p>0,05 non-significant differences; n – number of stents

Table № 6.

Antiplatelet therapy in the studied groups in different periods of follow-up

Antiplatelet regimen	Up to 3 months			3 – 6 months			6 – 9 months			> 9 months		
	Gr.1	Gr.2	P	Gr.1	Gr.2	P	Gr.1	Gr.2	p	Gr.1	Gr.2	p
Plavix + Aspirin	51	66	p>0,05	49	63	p>0,05	45	57	p>0,05	38	49	p>0,05
Only Plavix	—	—		—	—		—	—	—	—	—	
Only Aspirin	—	—		2	3	p>0,05	4	6	p>0,05	10	13	p>0,05
No antiplatelet therapy	—	—	—	—	—		2	3	p>0,05	3	4	p>0,05

(9 months) was 9,2% and 10,5%, respectively. Herewith the indices of cardiac death (1,6% vs. 2,5%), Mi (5,7% vs.4,6%), target vessel revascularization (4.4% vs.5.5%), in-stent stenosis (20,9% vs.23,3%) were lower in the group with Biomatrix stents (5,6). The comparison of these data with our results reveals some divergences. Probably, the main cause of these divergences is a more complex contingent of patients included in the LEADERS trial. The rate of extended stenoses, as well as of small coronary arteries in this trial was higher (6). However, despite higher indices of restenosis in the trial, they are lower than in the group with Cypher stents, which was also confirmed by our study.

The thrombosis of the stented coronary arteries is still the main cause of cardiac complications, including cardiac death. Recent long-term trials conducted in large populations of patients have revealed the problem of late thrombosis, primarily related to the delay of vessel healing and to the inflammatory reaction of its wall to the polymer coating of DES.

Awata M. et al. (7) have evaluated the endothelization of stents with biodegradable and permanent coating using angioscopy. The coating of the stent's struts was evaluated with a special score, where 0 corresponded to a visible strut, and 3 — to a completely endothelized strut. After 9 months the surface of stents with biodegradable coating was more homogenous in comparison with the stents with permanent coating. (80% vs. 56% p = 0.035).

Conclusion

Optimal immediate angiographic results of PCI and absence of recurrent angina at in-hospital stage are seen in the vast majority of patients after the implantation of stents with biodegradable (Biolimus A9), as well as with permanent polymer coating (Sirolimus). The rate of restenosis in the mid-term follow-up in both groups was not statistically different. However the rate of stent thrombosis in the mid-term follow-up was significantly lower in the group of stents with biodegradable polymer coating in comparison with the stents with permanent coating. Also, in the group of stents with biodegradable polymer coating we did not reveal factors influencing the results of stenting in the mid-term, while the use of stents with diameter < 2,75 mm and length > 18 mm was a risk factor fo thrombosis in the group of stents with permanent coating.

References

1. Mauri L., O'Malley A.J., Popma J.J. et al. Comparison of thrombosis and restenosis risk from stent length of sirolimus-eluting stents versus bare metal stents. Am. J. Cardiol., 2005, 15, 95(10), 1140-5.

2. Hwang C.W., Levin A.D., Jonas M., et al. Thrombosis modulates arterial drug distribution for drug-eluting stents.. Circulation, 2005, 111 (13), 1619–26.

3. Virmani R., Guagliumi G., Farb A. et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? Circulation, 2004, 109 (6), 701–5.

4. Grube E., Buellesfeld E.L. BioMatrix Biolimus A9-eluting coronary stent: A next-generation drug-eluting stent for coronary artery disease. Expert. Rev..Med. Devices, 2006, 3, 731-41.

5. Wykrzykowska J.J., Ruber L., de Vries T. Biolimus-eluting biodegradable polymer versus sirolimus-eluting permanent polymer stent performance in long lesions: results from the LEADERS multicentre trial substudy. EuroIntervention, 2009, 5(3), 310-7.

6. Chevalier B., Serruys P.W., Garcia E. et al. Randomized comparison of Nobori™, Biolimus A9-eluting coronary stent with a Taxus®, paclitaxel-eluting coronary stent in patients with stenosis in native coronary arteries: the Nobori trial. EuroIntervention, 2007, 2, 426–34.

7. Awata M., Uematsu M., Sera F. Angioscopic assessment of arterial repair following biodegradable polymer-coated biolimus A9-eluting stent implantation. — Comparison with durable polymer-coated sirolimus-eluting stent. Circ. J., 2011, 25, 75(5), 1113-9.

8. Conover W. J. Practical Nonparametric Statistics, 2nd ed. Wiley, New York, 1980.

9. Glantz S. Medical and biological statistics (transl. From English). Moscow, Praktika, 1999, p.459.

10. Gubler E.V., Genkin A.A. Use of non-parametric statistical criteria in medical and biological studies. Leningrad, Meditzina, 1973, 140 p.