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A Statement on Ethics From the HEART Group

Over the past several years, the editors of leading international cardiovascular journals have met to form the HEART group and to discuss areas of growing, common interest. Recently, the HEART group has developed a document that addresses general ethical principles in the conduct of the scientific process with which all of the editors concur. Published essentially simultaneously in all of the participating journals, including this journal, this document presents the ethical tenets accepted by all of the undersigned editors that will (continue to) guide their decisions in the editorial process.

These are the general principles on which the HEART Group is based and by which we, as a group, abide; however, please note that individual journal members and their respective societies may have their own rules and regulations that supersede the guidelines of the HEART Group.

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The following will be considered as parts of this process:

a. Disclosure of potential conflicts of interest for all involved in the performance of research and in the evaluation and publication process of a manuscript. Relevant relationships with commercial interests will be defined in terms of levels and nature of support. The nature of support will be listed as grants, supplies/equipment, type of employment, or personal income. Equity and royalty interests should be stated as well as any fiduciary relationship with the sponsor.

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Long-Term Results of Coronary Stenting with Different Duration of Clopidogrel (Plavix) Administration

Z.A. Aliguishieva, D.G. Iosseliani[1]

Moscow City Center of Interventional Cardioangiology, Moscow, Russia

INTRODUCTION

The introduction of intracoronary stents allowed to improve the results of percutaneous coronary interventions (PCI), but generally didn't resolve the restenosis problem, mainly due to smooth muscular cells proliferation. Creation of drug-eluting stents (DES) with various drug coatings was the reasonable continuation of searching effective ways to prevent restenosis. Generally, drugs with an inhibitory action on smooth muscular cells proliferation and migration are used for stent coating. However, in 2006 the question about long-term efficacy of coated stents came to the fore (3). The BASKET-LATE trial (2006-2007) has shown higher cumulative incidence of death and myocardial infarction after 18 months of DES use – 4.9% versus 1.3% in bare metal stent use; the obtained results were attributed to late stent thrombosis (4, 5, 6). Intracoronary ultrasonography data suggest that late unsatisfactory results are induced by impaired stent endothelization, fibrin deposits and inflammatory cell infiltration around stent struts (7). One of the most important predictors of in-stend stenosis /thrombosis can be inadequate duration of combined antithrombotic therapy (aspirin + clopidogrel) (8). The hypothesis that a longer (up to 6 months) combined antithrombotic therapy could improve long-term angiographic and clinical results in such patients, became a reason for this study conducting.

Objective of the study: To compare long-term clinical and angiographic results of stenting with different types of coronary stents depending on duration of treatment with platelet aggregation inhibitor (clopidogrel).

CLINICAL MATERIAL AND METHODS

Five hundred forty six patients with CAD aged from 38 to 70 years (mean age 56.7 ±9.4) were enrolled in this study and had 680 stents implanted: 396 BxSonic (Cordis, Johnson & Johnson) stents – in 306 patients, 178 Cypher (Cordis, Johnson & Johnson) stents – in 150 patients, and 106 Taxus stents (Boston Scientific Corporation) - in 90 patients, see Table. 4. All 546 patients were randomized to three groups according to the duration of further clopidogrel (Plavix) intake: the first group consisted of 180 patients who have taken Plavix 75 mg/day for a month, the second group included 182 patients who have taken Plavix 75 mg/day for three months, and the third group – 184 patients who have taken Plavix 75 mg/day for 6 months. Mainly there were male patients – 405 (74, 2%) with arterial hypertension – 476 (87, 2%) and different type of dyslipidemia. In most cases the reason of coronary angioplasty was effort angina of different functional classes (NYHA classification) – 397 (72.7%); functional class 1-2 unstable angina was diagnosed in 30 (16.6%), 26 (14.2%) and 33 (17.9%) patients; proportion of post-infarction angina patients was 15 (8.3%), 12 (6.5%), and 10 (5.45%), respectively. Patients with AMI and PCI in the first 24 hours from disease onset were excluded from the study (Table 1). There was no significant difference in main clinical and historical data between the investigated groups (p>0.05).

Table 1. Clinical characteristics of patients.

	I group N =180	II group N=182	III group N =184	P
Age (years)	56±7.4	54±6.2	55±4.2	>0.05
Male gender	137 (76.1%)	128 (70.3%)	140 (76%)	>0.05
History of MI	58 (32.2%)	55 (30.2%)	71 (38.5%)	>0.05
FC 1-4 effort angina	135 (75%)	128 (68.6%)	134 (72.8%)	>0.05
FC 1-2 unstable angina FC 3 unstable angina	30 (16.6%) 15 (8.3%)	26 (14.2%) 12 (6.5%)	33 (17.9%) 10 (5.4%)	>0.05 >0.05
Essential arterial hypertension	161 (89.4%)	157 (86.2%)	158 (85.8%)	>0.05
Cholesterol ⩾ 5.5 mmol/l	130 (72.2%)	110 (60.4%)	128 (69.5%)	>0.05
Triglycerides ⩾ 1.7 mmol/l	56 (31.1%)	68 (37.3%)	61 (33.1%)	>0.05
Diabetes mellitus	52 (28.8%)	60 (32.9%)	57 (30.9%)	>0.05
Ejection fraction ⩽40%	10 (5.5%)	14 (7.6%)	12 (6.5%)	>0.05
Smoking	58 (32.2%)	50 (27.4%)	44 (23.9%)	>0.05

The most frequent symptom-related arteries (SRA) were the left anterior descending artery (LAD) – 62.7%, 59.3% and 57.6% cases, then the right coronary artery (RCA) – 32.7%, 32.9% and 30.9% cases, and the left circumflex coronary artery (LCX) in 3.3%, 5.4% and 8.7% cases, respectively. There were no significant differences in coronary artery lesion and extent of lesion of coronary vessels between groups, no significant differences in type of vessel lesions (ACC/AHA classification) were revealed in examined groups as well. Class A/B1 – 31.4%, 30.3%, and 32.7%; class B2 – 46.2%, 43.4%, and 43.7%; C – 22.4%, 26.3%, and 23.6%.

[1]Moscow City Center of Interventional Cardioangiology
Russia, 101000, Moscow, Sverchkov per., 5
Phone: 007 495 624 96 36
Fax: : 007 495 624 67 33
e-mail: davidgi@mail.ru
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At baseline, the examined groups did not also differ in angiography findings. Angiographic characteristics of patients are summarized in Table 2.

Table 2. Baseline angiographic data.

	I group N =180	II group N=182	III group N =184	P
Number of affected arteries: One Two Three and more	 145 (80.5%) 27 (15%) 8 (4.4%)	 144 (79.1%) 30 (16.4%) 8 (4.3%)	 145 (78.8%) 33 (17.9%) 6 (3.2%)	 >0.05 >0.05 >0.05
LAD	113 (62.7%)	108 (59.3%)	106 (57.6%)	>0.05
LCX	6 (3.3%)	10 (5.4%)	16 (8.7%)	>0.05
RCA	59 (32.7%)	60 (32.9%)	57 (30.9%)	>0.05
OM (Obtuse marginal branch)	2 (1.1%)	4 (2.1%)	5 (2.7%)	>0.05
Class A/B1	70 (31.4%)	69 (30.3%)	75 (32.7%)	>0.05
Class B2	103 (46.2%)	99 (43.4%)	100 (43.7%)	>0.05
Class C	50 (22.4%)	60 (26.3%)	54 (23.6%)	>0.05
Reference artery diameter, mm	2.97± 0.52	2.96± 0.56	2.95± 0.46	>0.05
Mean percent stenosis, %	83± 16.7	85± 12	84± 16	>0.05
MLD (minimal lumen diameter) before the procedure, mm	0.71± 0.31	0.73± 0.35	0.7± 0.33	>0.05
Length of target lesion, mm	15.8± 6.1	14.7± 5.9	15.6± 6.4	>0.05
End size of balloon, mm	3.2± 0.7	3.0± 0.8	3.4± 0.5	>0.05
Maximum pressure, atm	13± 2.1	12± 2.2	14± 2.2	>0.05
Total number of stents:	**223**	**228**	**229**	

Selective coronary angiography (SCA) and left ventriculography in most cases were performed in accordance with M. Judkins technique. Heparin 10000 IU was administered as intravenous bolus before the invasive procedure. In order to reduce blood coagulation indices during the procedure, heparin was administered by intravenous drop infusion under control of activated clotting time (ACT). Activated clotting time was maintained at a level of 330 350 sec. Clopidogrel (Plavix) 150 mg was administered to the patients immediately before stenting. Platelet count, platelet aggregation time, mean aggregation and disaggregation percentage were determined in all patients before stenting, in patients of group 1 – in 1 month, in group 2 – in 3 months, in group 3 – in 6 months, in order to evaluate the efficacy of anti-aggregant therapy. The level of aggregation inhibition of 40 60% was considered as a therapeutic efficacy of clopidogrel. Percutaneous transluminal coronary angioplasty (PTCA) and stenting procedures were carried out using standard technique, aiming to achieve maximally complete luminal restoration. In the presence of anatomical and functional conditions (preservation of minimal artery lumen and antegrade blood flow TIMI 2-3; type A/B 1-2 vessel lesion) we used «direct» stenting, i.e. stenting without predilatation – 173 (77.5%), 168 (73.6%), and 175 (76.4%) cases, respectively (P>0.05). In other cases stenting was performed after balloon predilatation. Indications for stenting after balloon angioplasty were: 1) suboptimal result after PTCA (residual stenosis up to 50% with/without dissection A-B), and 2) acute occlusion or type C-F threatening dissection of vessel intima after PTCA. For optimum choice of prosthesis size we have calculated degree, lesion length and diameter of adjacent intact portion of the vessel using computer program for stenosis size calculation, provided by Siemens company, on Hicor computer of Coroscop angiographic unit (Siemens, Germany). Stent implantation was performed under the pressure, equal to or exceeding the nominal value according to the table of compliance to achieve necessary stent diameter and eliminate residual stenosis. Procedure was considered as successful if residual stenosis did not exceed 30% of the referent diameter of target segment, with antegrade blood flow TIMI 3, absence of threatening dissection and occlusion of significant side branch (diameter more than 2 mm). We assessed segment condition in the region of endovascular intervention and condition of coronary territory in general during control coronary angiography.

Table 3. Characteristics of used stents.

	I group N =180	II group N=182	III group N =184	P
BxSonic Cordis, Johnson & Johnson	128 (57.3%)	132 (57.8%)	136(59.3%)	>0.05
Cypher Cordis, Johnson & Johnson	60(26.9%)	62 (27.1%)	56(24.4%)	>0.05
Taxus Boston Scentific Corporation	35 (15.6%)	34(14.9%)	37 (16.1%)	>0.05
Stent diameter				
- 2.0 – 2.9 mm	120(53.8%)	132(57.8%)	135(58.9%)	>0.05
- 3.0 – 3.5 mm	96(43%)	87(38.1%)	91(39.7%)	>0.05
- 4.0 mm and more	7(3.1%)	9(3.9%)	3(1.3%)	>0.05
Stent length				
- 8-13 mm	101(45.2%)	93(40.7%)	97(42.3%)	>0.05
- 15-18 mm	99(44.3)	107(46.9%)	102(44.5%)	>0.05
- 23-28 mm	19(8.5%)	21(9.2%)	22(9.6%)	>0.05
- 28-33	4(1.8%)	7(3.1)	8(3.5%)	>0.05
Total number of stents:	**223**	**228**	**229**	**>0.05**

A total of 680 stents were implanted to 546 patients: in group 1 128 (57.3%) BxSonic bare metal stents, 60 (26.9%) sirolimus-eluting stents (SES) and 35 (15.6%) paclitaxel-eluting stents (PES), were implanted; in group 2 - 132 (57.8%) %) bare metal stents, 62 (27.1%) SES and 34 (14.9%) PES were implanted; and in group 3 – 136 (59.3%) bare metal stents, 56 (24.4%) SES and 37 (16.1%) PES were implanted (Table 3). The examined groups did not differ significantly in number and range of stents used.

In overwhelming majority of cases we used stents with a length of ≈18 mm (mean 18±7 mm) and diameter ≈3 mm (mean 3.2±0.8mm). Stent implantation was performed under pressure of 12±2.2 Atm. In case of optimal angiographic view of the stented vessel stent implantation procedure was completed,

otherwise repeated balloon inflations was performed until obtaining optimal result. In overwhelming majority of cases repeated inflations were performed with the same balloon. In all patients the artery lesion was fully covered by stent, vessel margins at the site of implantation were smooth and regular without stenotic changes. The result of stent implantation was visually assessed, and the vessel diameter was calculated before and after procedure. In case of multivessel lesion endovascular procedures were performed simultaneously on the other coronary arteries in addition to symptom-related artery stenting: in group 1 – in 81 (45%) patients, in group 2 – in 89 (48.9%) patients, and in group 3 – in 83 (45.1%) patients. Thus, total revascularization was carried out in 175 (97.2%) patients of the 1st group, in 180 (98.9%) patients of the 2nd group, and in 181 (98.3%) patients of the 3rd group.

All patients enrolled in the study underwent control examination including selective coronarography and left ventriculography during long-time follow-up (on average at 7.8±2.4 months). Such parameters as mortality, myocardial infarction (MI), stroke, incidence of angina in patients, incidence of restenosis and reocclusion of vessels and segments on which PCI was performed were assessed.

Narrowing of stent and adjacent segments (+5 mm) of more than 50% was considered as restenosis, total absence (TIMI 0) of antegrade blood flow below the target segment was considered as reocclusion. The number of clopidogrel-related complications was assessed as well.

For the statistical analysis of data the Spearmen rank correlation, Mann-Whitney test (nonparametric test for comparing means) and Wilcoxon test (nonparametric paired test for comparing means) were used in assessment of statistical significance of difference between the control and baseline parameters.

STUDY RESULTS

In-hospital period: Immediate angiographic success of stenting (residual stenosis less then 20%, absence of type C-F dissection and restoration of antegrade blood flow TIMI 3, absence of side branch occlusion and distal embolism) was observed in 299 (97.7%) cases with BxSonic stents (Cordis, Johnson & Johnson); in 148 (98.6%) cases with Cypher stents (Cordis, Johnson & Johnson), and in 88 (97.7%) cases with Taxus stents (Boston Scientific Corporation), P>0.05.

After procedure, antegrade blood flow TIMI 0-1 was observed in 2 cases: control CAG showed «no-reflow» phenomena with limited antegrade filling of target vessel and subsequent blood flow restoration to TIMI 2-3 in both patients after BxSonic and Cypher stents implantation while on massive therapy with anti-anginal drugs, platelet aggregation inhibitors and anticoagulants (Table 4).

After stenting minimal lumen diameter (MLD) was 3.05±0.31 mm, 3.01±0.35 mm and 3.02±0.29 mm, respectively (P>0.05); residual stenosis predominantly did not exceed 20%, the margins of vessel intima at the site of stenting were smooth and regular without stenotic changes; in 1.0%, 0.7% and 1.1% cases only threatening dissection developed at the distal end of the stent requiring additional prosthesis implantation. Clinical and angiographic results of stenting during in-hospital stage of follow-up are presented in Table 4.

Table 4. Immediate clinical and angiographic results.

	I group N =180	II group N=182	III group N =184	P
Mortality	-	-	-	
AMI: Q-wave Non-Q-wave	1(0,5%) 1(0.5%) 0	2(1,09%) 1(0.5%) 1(0.5%)	1(0,5%) 0 1(0.5%)	
Angina	3(1.6%)	2(1%)	3(1.6%)	
Complicated clinical course	4(2,2%)	4(2,1%)	4(2,1%)	
Acute stent thrombosis	2(1.1%)	1(0.5%)	1(0.5%)	
Repeated PCI - due to acute stent thrombosis - due to dissection	4(2.2%) 2(1.1%) 2(1.1%)	3(1.6%) 1(0.5%) 2(1%)	2(1.08%) 1(0.5%) 1(0.5%)	

Side branch occlusion was observed in 3 (10.3%) out of 29 patients with bifurcation lesions of target coronary artery: In 2 patients modular BxSonic stent was implanted, in another case paclitaxel-eluting stent was used. In all three cases diagonal branch (DB) and LAD occlusion was accompanied by pain syndrome and ECG changes. Recanalization of ostial occlusion of the side branch through stent struts and subsequent balloon dilatation without additional stent implantation were performed in all patients with subsequent consistent antegrade blood flow restoration to TIMI 3. One patient developed Q-wave AMI.

Uncomplicated clinical course after stenting was noted in 176 (97.7%) cases in the first group, in 178 (97.8%) in the second group, and 180 (97.8%) in the third group, P>0.05.

During in-hospital stage, acute stent thrombosis was observed in the first 4-6 hours after intervention in 4 (0.7%) cases: in three cases with BxSonic (Cordis, Johnson & Johnson) stent of 3.0 mm in diameter and 18-23 mm in length , and in another case with 2 Cypher (Cordis, Johnson & Johnson) stents measured 2.75x28 mm. Urgent mechanical recanalization of occluded artery with subsequent balloon dilatation and TIMI 2-3 blood flow restoration was performed in all four patients. Further these patients had stable course of the disease. However, despite the continued treatment and short period between the angina attack onset and repeated PCI, 3 out of 4 patients with stent thrombosis, and 3 patients with side branch occlusion and bifurcation lesion developed non-fatal acute myocardial infarction (Q-wave AMI in 2 cases and non-Q-wave AMI in another 2 cases); no lethal cases were observed (Table 4).

Complications at the site of arterial access (1.3%) included retroperitoneal haematoma requiring hemotransfusion in one case, pulsating haematoma in 5 cases (with surgery treatment needed in 1 case and repeated mechanical apposition at the puncture site in 4 cases).

Thus, there were no significant differences in the angiographic outcomes, number of acute stent thrombosis and major clinical events such as cardiac mortality, AMI, repeated interventions necessity when comparing the results obtained at in-hospital stage in different groups.

Late follow-up period (Table 5). As mentioned above, all 546 patients were randomized to 3 groups according to duration of further clopidogrel (Plavix) administration: the first group consisted of 180 patients who have taken Plavix 75 mg/day for a month, the second group included 182 patients who have taken Plavix 75 mg/day for three months, and the third group – 184 patients who have taken Plavix 75 mg/day for 6 months. Health state information, angiographic results in mid-term follow-up after 7.8 ±2.4 months were obtained from all 546 patients. Patients had no significant difference in clinical and historical data.

Table 5. Long-term clinical and angiographic results.

	I group N =180	II group N=182	III group N =184	P
ANGINA FREE	147 (81.6%)	158 (86.8%)	166 (90.2%)	P3-1< 0.05
REPEATED MI (non-fatal):	3 (1.7%)	1 (0.5%)	4 (2.2%)	>0.05
-due to p/o thrombosis (up to 30 days)	1 (0.5%)	-	2 (1.1%)	>0.05
-due to late thrombosis (after 30 days)	1 (0.5%)	-	1 (0.5%)	>0.05
-due to progressive atherosclerosis	1 (0.5%)	1 (0.5%)	1 (0.5%)	>0.05
MORTALITY	-	-	1 (0.5%)	>0.05
REPEATED PCI:	31 (17.2%)	20 (11.0%)	15 (8.1%)	P1-3<0.05
-Subacute thrombosis	2 (1.1%)	1 (0.5%)	2 (1.1%)	>0.05
-In-stent stenosis	26 (14.4%)	18 (9.9%)	12 (6.2%)	P1-3<0.05
-Late thrombosis	3 (1.7%)	1 (0.55%)	1 (0.5%)	>0.05
-PCI due to progressive atherosclerosis	30 (16.6%)	15 (8.2%)	21 (11.4%)	P1-2<0.05
CABG necessity	2 (1.1%)	1 (0.5%)	-	>0.05
Minor complications:	3 (1.6%)	5 (2.7%)	14 (7.6%)	P3-1.2< 0.05
-ecchymosis	2 (1.1%)	3 (1.6%)	9 (4.8%)	>0.05
-gingival and nasal bleeding	1 (0.5%)	2 (1.0%)	6 (3.2%)	>0.05
Allergic reactions	1 (0.5%)	-	-	>0.05
CLINICAL SUCCESS*	114 (63.3%)	145 (79.6%)	143 (77.7%)	P3-1.2< 0.05

* Absence of lethal cases, AMI, angina requiring PCI/CABG

In long-term follow-up, the rate of major cardiac events (such as mortality, AMI, repeated PCI/CABG necessity) was evaluated as well as long-term condition of stented segment and potential complication risk associated with the duration of Plavix treatment. Table 5 shows the outcomes of clinical course of CAD in examined groups after 30 days and after 7.8±2.4 months following coronary endoprosthesis implantation.

In mid-term follow-up the patients from group 3 were free from angina significantly more often – 90.2% versus 81.6% and 86.8% in groups 1 and 2, respectively. There were no significant differences in non-fatal MI rate (1.7%, 0.5% and 2%) and in cardiac mortality rate between the studied groups, only 1 patient (0.5%) from the group 3 died after Cypher (Cordis, Johnson & Johnson) stent implantation within the first 30 days after procedure prior to repeated examination due to self-sustained arrest of combined antiaggregant therapy (autopsy revealed stent thrombosis). Angina attacks, repeated MI, and death were observed mainly in patients with progressive atherosclerosis and failed PCI (restenosis or stent thrombosis).

Serious complications included 6 (1.1%) cases of subacute stent thrombosis within the first 30 days after stenting (1 case according to autopsy data): in 3 cases (1%) with BxSonic (Cordis, Johnson & Johnson) stent, in 2 cases (1.3%) after stenting with Cypher (Cordis, Johnson & Johnson) drug-eluting stent, and in 1 case (1.1%) after Taxus (Boston Scientific Corporation) stent implantation, P>0.05 (table 6). There were no significant difference in subacute stent thrombosis rate between the examined groups 1, 2 and 3 – 2 (0.9%), 1(0.4%) and 3 (1.3%); in 1 case (as shown above) subacute stent thrombosis was the reason of lethal outcome, and of non-fatal MI and unstable angina in other 3 (0.5%) and 2 (0.4%) patients, respectively. All five survived patients successfully underwent mechanical recanalization and balloon dilatation with TIMI 3 antegrade blood flow restoration.

Control selective coronary angiography data in mid-term follow-up showed that in-stent stenosis rate was maximal in patients who have taken Plavix for a month (in 26 (11.7%) cases) versus 19 (8.3%) and 12 (5.2%) cases (P<0.05); we revealed late stent thrombosis more frequently in group 1 – 2.2% cases versus 0.9% and 0.4% cases in the 2nd and the 3rd groups, however without significant differences (Table 6).

Table 6. In-stent stenosis rate depending on duration of Plavix treatment (P⩾0.05).

	I group N =180	II group N=182	III group N =184
P/o thrombosis	2 (0.9%)	1 (1.6%)	3 (1.3%)
In-stent stenosis	26 (11.7%)	19 (8.3%)	12 (5.2%)
Late thrombosis	5 (2.2%)	2 (0.9%)	1 (0.4%)

The worst mid-term angiographic results were revealed in patients who have taken Plavix for 1 month (1 group), determining significantly higher necessity of PCI performance in these patients – in 31 (17.2%) cases versus 20 (11.0%) and 15 (8.1%) cases in the 2nd and the 3rd groups. At that, coronary bypass grafting was recommended in 2 (1.1%) cases of the 1st group and in 1 (0.5%) cases of the 2nd group in patients with late stent thrombosis and concomitant lesions of other coronary arteries.

In-stent stenosis rate (by Mehran classification, 1999) in groups 1, 2, and 3 was 31 (17.2%), 21 (9.2%) and 13 (7.1%) cases, respectively (Table 7). In the examined groups (according to this classification) local stenosis (up to 10mm) was revealed

Table 6. In-stent stenosis rate depending on stent types and Plavix treatment duration.

	Stent number								
	Group 1 (N=223)			Group 2 (N=228)			Group 3 (N=229)		
	BxSonic n=128	Cypher n=60	Taxus n=35	BxSonic n=132	Cypher n=62	Taxus n=34	BxSonic n=136	Cypher n=56	Taxus n=37
p/o thrombosis	1 (0.8%)	-	1 (2.8%)	-	1 (1.6%)	-	2 (1.47%)	1 (1.8%)	-
Total:	2 (0.9%)			1 (0.4%)			3 (1.3%)		
In-stent стеноз	18 (14.2%)	5 (8.3%)	3 (8.6%)	15 (11.3%)	2 (3.2%)	2 (5.8%)	12 (8.8%)	0%	0%
Total:	26 (11.7%)			19 (8.3%)			12 (5.2%)		
Late thrombosis	3 (2.3%)	1 (1.7%)	1 (2.8%)	2 (1.5%)	0%	0%	1(0.7%)	0%	0%
Total:	5 (2.2%)			2 (0.9%)			1 (0.4%)		

*P<0.05

in 10 (19.6%), 4 (50%) and 3 (50%) cases; diffuse stenosis (more than 10mm) not extending beyond stent - in 20 (39.2%), 2 (25%) and 1 (16.6%) cases; diffuse proliferative stenosis (more than 10mm), extending beyond stent – in 15 (29.4%), 1 (12.5%) and 1 (16.6%) cases; total occlusion (late stent thrombosis) with antegrade blood flow TIMI 0 – in 6 (11.8%), 1 (12.5%) and 1 (16.6%) cases.

Analysis of in-stent stenosis type showed that patients with bare metal stents BxSonic at 7.8±2.4 months had mainly diffuse and diffuse proliferative in-stent stenoses: 39.2% and 29.4% versus 25% and 12.5% with SES, 16.6% and 16.6% in patients with PES (P>0.05); patients with SES and PES more often had local in-stent stenosis: 50% and 50% versus 19.6% with self expandable metal stents, BxSonic, (P<0.05); after BX Sonic, Cypher and Taxus stent implantation, disseminated intravascular coagulation rate (in-stent stenosis + late thrombosis) was 51 (12.8%), 8 (4.5%) and 6 (5.6%) cases, respectively (P<0.05). Comparative analysis of the three stents (BX Sonic, Cypher and Taxus) revealed significant differences in incidence of in-stent stenosis and adjacent segments stenosis (+5 mm) – 45 (11.4%) versus 7 (3.9%) and 5 (4.7%) cases, respectively (P<0.05); late stent thrombosis was observed in 6 (1.5%), 1 (0.5%) and 1 (0.9%) cases, respectively (P<0.05).

Table 7. In-stent stenosis type according to Mehran classification (1999) at 7.8 ± 2.4 months.

	BxSonic n=51	Cypher n=8	Taxus n=6	P
Type I - local	10(19.6%)	4(50%)	3(50%)	<0.05
Type II - diffuse	20(39.2%)	2(25%)	1(16.6%)	NS
Type III – diffuse -proliferative	15(29.4%)	1(12.5%)	1(16.6%)	NS
Type IV – occlusion (late thrombosis)	6(11.8%)	1(12.5%)	1(16.6%)	NS

We performed the correlation analysis (Spearmen rank correlation) to determine baseline clinical, historical and angiography factors influencing on clinical course of disease in general, and on condition of stent and stented vessel in particular. In patients with bare metal BxSonic stents significant inverse correlation was found between unfavorable long-term outcomes of stenting (restenosis or occlusion) and vessel lumen diameter < 3mm (R=-0.302; p<0.03), diffuse and extended (more than 17 mm) coronary artery lesions (R=-0.292; p<0.04), stent implantation site in coronary artery (namely ostium and proximal segment of anterior descending branch of left coronary artery (R=0.280; p<0.04), initial morphologically complex lesion (C type of lesion) (R=0.270; p<0.04), length of prosthesis implanted (18 mm and more) (R=-0.295; p<0.05); among clinical and historical factors, diabetes mellitus, previous MI (PICS) and LVEF <40% influenced on development of in-stent stenosis (p<0.05). The most significant independent predictor of in-stent stenosis in patients with covered stents was placement of two and more stents in one artery. The correlation analysis revealed that clopidogrel intake for one and three months after stenting is significant independent predictor of in-stent stenosis.

Thus, following implantation of coated stents (Cypher and Taxus) significantly more preferable results were obtained in patients with a maximal duration of Plavix treatment (6 months) – 0% and 0% cases, whereas Plavix treatment for a 1 month was associated with the in-stent stenosis rate of 8.3% and 8.6%, and 3.2% and 5.8% in case of 3 months duration of Plavix intake, respectively (P<0.05) (Fig.1). However, Plavix treatment duration (1 month, 3 months or 6 months) did not influence significantly on in-stent stenosis rate with bare metal stents – 14.2% 11.3% and 8.8% cases; the only tendency towards in-stent stenosis rate reduction was revealed with increase of clopidogrel treatment duration (Table 6).

When assessing late stent thromboses, maximal number of thromboses was also revealed in patients with minimum Plavix treatment duration (1 month) – 2.2% versus 0.9% and 0.4% cases in groups 2 and 3; there were no significant differences in this parameter as well as in late thrombosis rate depending on stent types and duration of Plavix treatment; the only tendency towards late stent thrombosis rate reduction was revealed with increase of clopidogrel treatment duration (Table 6, Fig. 2).

DISSCUSION OF OBTAINED RESULTS

Over the last years significant advancement was achieved in endovascular treatment of coronary arteries. Implementation of drug-eluting stents in clinical practice reduced in-stent stenosis rate to acceptable 3-5% and extended indications for endovascular treatment. The use of angioplasty with stenting is feasible in treatment of patients with complicated and prognostically unfavourable anatomy of coronary stenosis (according to the coronary angiography data). However, due to high cumulative rate of cardiac mortality and recurrent MI (4.9%) revealed, Swiss scientists raised a question about long-term safety of drug-eluting stents (4.5). A problem of late thrombosis (after 30 days) is being investigated and

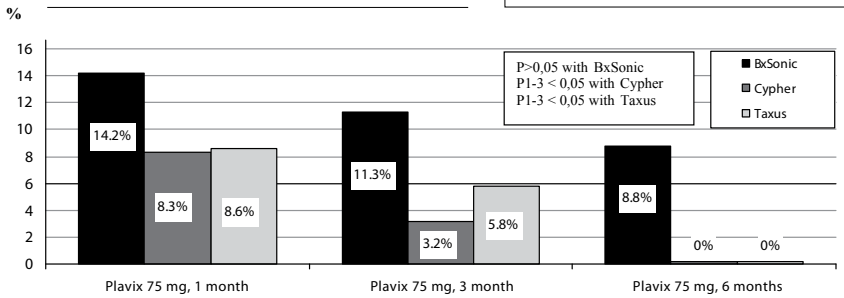

Figure 1. In-stent stenosis rate depending on Clopidogrel treatment duration.

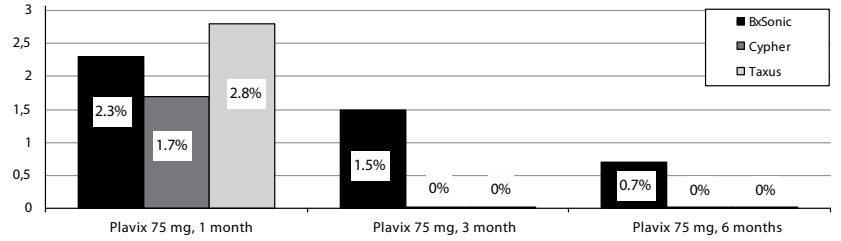

Figure 2. Stent thrombosis rate depending on Clopidogrel treatment duration (P>0.05).

discussed widely as a possible reason of unfavourable course of disease on the follow-up stage after use of «Cypher» and «Taxus» stents with antiproliferative coating. It is believed that the reasons of late unsatisfactory results are impaired DES endothelization, fibrin deposits and inflammatory cell infiltration around stent struts (7). The hypothesis that a longer (up to 6 months) combined antithrombotic therapy could improve long-term angiographic and clinical results in such patients, became a reason for this study conducting.

Five hundred forty six patients with CAD enrolled in this study had 680 stents implanted: 396 BxSonic (Cordis, Johnson & Johnson) stents, 178 Cypher (Cordis, Johnson & Johnson) stents and 106 Taxus (Boston Scientific Corporation) stents, Table 4. Further all 546 patients were randomized to three groups according to durations of subsequent clopidogrel treatment. the first group consisted of 180 patients who have taken Plavix 75 mg/day for a month, the second group included 182 patients who have taken Plavix 75 mg/day for three months, and the third group – 184 patients who have taken Plavix 75 mg/day for 6 months. Platelet count, platelet aggregation time, mean aggregation and disaggregation percents were determined in all patients before stenting, in patients of group 1 – in 1 month, in group 2 – in 3 months, in group 3 – in 6 months, in order to determine the efficacy of anti-aggregant therapy. The level of target aggregation inhibition of 40-60% was considered as a therapeutic efficacy of clopidogrel.

Analysis of in-hospital results of stenting with the use of different types of endoprosthesis (BxSonic, Cypher and Taxus) showed no significant differences in angiographic success (97.7%, 98.6% and 97.7%, respectively), number of major clinical events (mortality , MI, repeated interventions necessity) (Table 4). Main causes of complicated disease course after PCI were dissection at the distal end of the stent (1.0%, 0.7% and 1.1%, respectively), P> 0.05. Repeated endovascular interventions were performed successfully in all cases which is why there were no in-hospital lethal cases. Theoretically it could be possible to suppose increase in acute thrombosis rate with DES due to drug interaction with the coagulation system and homeostasis system (11). Meta-analysis of 14 clinical trials did not discover substantial increase in acute thrombosis rate with DES as compared to bare metal stents (0.5%), (10). This study showed higher absolute values of acute thrombosis -0, 7 -1, 0% vs. 0.44-0.5% in other clinical trial. In all 4 (0.7%) cases acute stent thrombosis was observed in the first 4-6 hours after intervention: in three cases – with BxSonic (Cordis, Johnson & Johnson) stent, diameter 3.0 mm and length 18-23 mm, and in another case with 2 Cypher (Cordis, Johnson & Johnson) stents measured 2.75?28 mm. Perhaps, the reason of this dangerous complication was latent (not diagnosed) dissection or inadequate anti-aggregation efficacy of clopidogrel saturating dose of 150 mg, with maximum effect in 6 hours only.

Analysis of late clinical angiographic results showed that patients who have taken Plavix 75 mg/day for a 6 months (3 group) -90.2% were significantly more often free from angina than patients in groups 1 and 2 - 81.6% and 86.8% cases. Respectively, patients who have taken Plavix 75 mg/day for the minimum period of time required repeated interventions repeatedly more often – 31 (17.2%) as compared to 20 (11.0%) and 15 (8.1%) in the 2nd and 3rd groups. At that, in 2 (1.1%) patients of the 1st group and in 1 (0.5%) patients of the 2nd group with late stent thrombosis and concomitant lesions of other coronary arteries coronary bypass grafting was recommended; but there were no significant differences in non-fatal MI rate and cardiologic mortality between the examined groups (Table 5). Progressive atherosclerosis and unsatisfactory result of stenting (restenosis and stent thrombosis) were the leading reasons of development of major clinical events in long-term follow-up.

Analysis of in-stent stenosis type showed that patients with bare metal stents had mainly diffuse and diffuse-proliferative in-stent stenosis types, whereas patients with DES had local in-stent stenosis type more often (P<0.05), Table 7. We observed the maximum rate of disseminated intravascular coagulation (in-stent stenosis + late thrombosis) with BX Sonic stents implantation – 51 (12.8%) versus 8(4.5%) and 6(5.6%) cases with Cypher and Taxus stent implantation (P<0.05); the same results were received from analysis of in-stent stenosis 45(11.4%) vs. 7 (3.9%) and 5(4.7%) cases, respectively (P<0.05), whereas the type of stent used did not influence significantly late (up to 6 months) thrombosis rate - 6(1.5%), 1(0.5%) and 1(0.9%), respectively (P>0.05).

Coronarography data analysis revealed unexpected results and showed that following SES and PES implantation only maximum duration of Plavix treatment (6 months) was accompanied by significant reduction of in-stent stenosis rate (but not late thrombosis) - 0% and 0% cases, whereas after 3 months duration of Plavix treatment (75 mg/day) these values were 3.2% and 5.8% and 8.3% and 8.6%, respectively ($P<0.05$). However, Plavix treatment duration (1 month, 3 months or 6 months) did not influence significantly on in-stent stenosis rate with bare metal stents – 14.2% 11.3% and 8.8% cases; we just revealed the tendency towards in stent stenosis rate reduction (Fig. 1, Table 6). Intracoronary ultrasonography data suggest that the causes of late unsatisfactory results are impaired stent endothelization, fibrin deposits and inflammatory cell infiltration around stent struts (7, 9). As is known, stent implantation fully excludes elastic vessel collapse and negative remodeling after PTCA, but on the other hand, intensity of the neointimal hyperplasia is strongly increased due to migration and proliferation of smooth muscle cells into intima through damaged internal elastic membrane with subsequent fission and synthesis of extracellular matrix. Moreover, loss of endothelium integrity, intima rupture and damage of the middle layer of the vessel trigger the mechanism of fibrin formation, as well as aggregation, adhesion of blood cells with clot development on rapamycine-eluting stent struts that may cause the late inflammatory reaction (as shown by Suzuki T. in test animals). Conglomerated platelets are the source of attractants and mytogens for bare metal stents. Moreover, platelet growth factor produced by endothelium cells and macrophages is regarded as the main factor facilitating SMC migration (13). Long-term combined anti-aggregant therapy could prevent clot formation until delayed DES epithelization will take place. This fact may explain decrease in the rate of diffuse in-stent stenosis drug-eluting stents, and subsequently the rate of late thrombosis while on long-term combined (A+C) therapy. Today the late thrombosis observed with «Cypher» and «Taxus» stents with antiproliferative coating is widely discussed. In our study we used only "determined" thrombosis concept. In our opinion late thrombosis definition proposed by FDA USA in 2006 is muzzy enough and could not demonstrate true rate of this event. Thus, only determined/confirmed thrombosis – acute coronary syndrome and thrombosis or stent occlusion, confirmed by angiography or autopsy data, – really could reflect true rate of this event. Use of definition of probable (sudden death in 30 days after stenting or infarction in the stented artery territory without angiographic confirmation) or possible (sudden death after 30 days following stenting) thrombosis could significantly overestimate the true rate of this event.

According to meta-analysis of the data from main randomized trials, the rate of very late thrombosis of «Cypher» and «Taxus» stents with antiproliferative coating that occurs within 1 to 4 years after implantation is about 0.2-0.6% per year; and today it is not clear enough, if this event can further persist, and if yes, what will be its incidence (10). It is considered that the main causes of late thrombosis besides the stent implantation technique peculiarities (full deployment with adhesion to vessel wall, absence of severe residual narrowing, absence of deformation and prolapse of stent struts into vessel lumen) are the violation of the regimen of dual anti-thrombotic therapy (late thrombosis risk due to aspirin and/or Plavix withdrawal is 60-70%) and clopidogrel resistance (4-30%) [10, 14]. In our study the therapeutic benefit (the level of aggregation reduction – 40-60%) was achieved in all cases of clopidogrel treatment; maximum number of cases of late thrombosis was observed in patients with minimum (1 month) clopidogrel therapy duration, however there were no significant differences in this parameter (Fig.2). Moreover, late stent thrombosis was the cause of MI only in 2 out of 8 cases. Therefore, cumulative rate of late thrombosis following implantation of stents with antiproliferative coating does not suggest increase in cardiac mortality and cardiac complications after their use.

Because of DES ability to decrease disseminated intravascular coagulation rate the question about DES role in CAD treatment became very important, i.e. should we absolutely refuse from «uncoated» stents or we could use them successfully in particular situations, with reasonable indications. This work showed that «uncoated» BX Sonic stent may be recommended in type A B1 lesions in RCA, LCX and the middle segment of LAD LCA, when vessel diameter is more than 3.0 mm with high immediate effect and good mid-term follow-up results (in-stent stenosis of 49.4%), while with the use of these stents in proximal LAD LCA lesions (type C) long-term results were not so optimistic (In-stent stenosis rate was 49.4%) that indicates the necessity of use of other stents, particularly drug-eluting stents. As known from some cooperative trials, in stent stenosis rate is approximately 6-9% in long-term follow-up after implantation (in our study we obtained the similar results). Therefore, results of bare metal stenting in patients with small risk of restenosis are comparable with that of DES use. It means that in some cases it is possible to use bare metal stent and to avoid the use of expensive DESs.

The issue of safety of long-term dual treatment (A+C) is very important. Better tolerability of clopidogrel as compared to ticlopidine was proved in the large clinical trial, CLASSICS, performed in patients following coronary stenting. In this trial the rate of major bleeding, neutropenia and thrombocytopenia as well as drug withdrawal due to extracardiac side effects with clopidogrel treatment was 2 times less than that with ticlopidine. However, in CREDO trial, where clopidogrel treatment duration was 11 months, there was increase in the rate of major bleeding in clopidogrel group 8.8% versus 6.7%

in placebo group; this difference was not statistically significant. In our study we obtained the similar results, tolerability of the drug was good, no serious side effects, requiring drug withdrawal, hospitalization or any specific interventions were observed (Table 5). The main hemorrhagic complication in our study was ecchymosis, which occurred in 1.1% in the first group, in 1.6% - in the second group and in 4.8% in the group of patients who have taken clopidogrel for 6 months; nasal and gingival bleeding (0.5%, 1% and 3.2%, respectively), which stopped spontaneously or after ascorbic acid administration. No gastrointestinal bleeding and skin reactions were observed in our study; clopidogrel did not cause any significant haematological disorder.

CONCLUSION

The data obtained in our study allow to draw the following conclusions: the tendency towards late stent thrombosis rate decreasing is observed with prolonged clopidogrel treatment. Patients who had received prolonged clopidogrel treatment had more stable clinical course of disease. The number of restenosis was less with 6 months clopidogrel treatment.

Today there is no alternative for the use of stents with antiproliferative drug coating in CAD treatment. Widely discussed data about possible late complications (late thrombosis) can not serve as a base for stopping their use, while they underline the importance of correct determination of indications and selection of patients for stenting, as well as thorough observance of all technical aspects of implantation, accurate compliance of dual anti-aggegant therapy regimen in long-term follow-up. Discussion about the efficacy of supportive drug therapy aiming to accelerate stenting segment epithelization after implantation of drug-eluting stent should be approached very seriously. In that respect, in view of new attitude to pleothropic effects of statins (anti-inflammatory effect and endothelium function improvement), it is very promising to investigate statins influence on DES endothelization. The possible prospect of radio endovascular surgery in CAD treatment is the implementation of new generations of stents with antiproliferative coating, polymeric bioabsorbable coating, and stent coated with the new drugs into clinical practice.

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Surgical and Endovascular Myocardial Revascularization in CAD Patients with Multivessel Coronary Lesion: Comparative Analysis of Immediate and Mid-Term Results.

D.G. Iosseliani[1], D.G. Gromov, O.E. Sukhorukov, E.Yu. Khotkevich, S.P. Semitko, I.V. Isaeva, J.-Ch. Vernhet, I.S. Arabadjian, Z.P. Ovesian, Z.A. Aliguishieva

Moscow City Center of Interventional Cardioangiology, Moscow, Russia

INTRODUCTION

Surgical and endovascular myocardial revascularization in CAD patients is used in the clinical practice for some decades. For many years cardiosurgery had the leading position in the treatment of multivessel coronary lesions (1-5), while percutaneous angioplasty was used in patients with isolated stenosis of one or two coronary arteries mainly. However, currently, due to improvement of the instruments and clinical experience accumulation, endovascular myocardial revascularization is used more frequently in patients with multivessel coronary disease (6-10). This tendency was shown after implementation of stents with antiproliferative drug coating in clinical practice that sharply decreased the restenosis rate in long-term follow-up (11 13). Today, percutaneous angioplasty is used actively in lesions of the main LCA, coronary bifurcation lesion, presence of continuous occluded coronary vessels and other complicated variants of the lesion (14-18). Meanwhile, surgical myocardial revascularization supporters believe that long-time disease prognosis after endovascular treatment is worse, restenosis and stenting arteries occlusion occur more frequently than after surgical treatment. Especially it concerns patients with diabetes mellitus, diffuse lesion of coronary circulation and severe left ventricle dysfunction. Despite multiple studies concerning comparative analysis of the results of surgical and endovascular CAD treatment there is no unequivocal opinion about benefits of any method. Some authors prefer endovascular treatment, while others choose surgical interventions. Both have enough argumentations. There are many reasons for this dissimilation including clinical heterogeneity of the investigated groups in some studies, absence of control coronary angiography and shuntography results in many of them. However, analysis of the precise angiography data shows real picture of shunts and stents state in mid-term and long-term follow-up, i.e. allows to asses objectively the results of surgical and endovascular interventions

During 10 years in Moscow City Center of Interventional Cardioangiology more than 28,000 patients with different forms of CAD were examined and treated, approximately in one third of them endovascular and surgical interventions were performed including approximately 11,000 PCIs and over 590 CABG operations. Total in-hospital mortality over these years was 1.2%. On average, the rates of in-hospital mortality after endovascular and surgical myocardial revascularization did not differ significantly, and in each group of patients did not exceed 0.5%. A wide experience of CAD treatment accumulated in the Center allowed us to perform our study (single- centre) aimed at comparative analysis of the efficacy of methods of direct surgical and endovascular myocardial revascularization in CAD patients with multivessel coronary disease. In this work, in contrast to majority of previous ones, we studied clinical and angiography results of the interventions in immediate and mid-term follow-up periods. Attending doctors, endovascular cardiologists and cardiosurgeons took part in this study for maximal objectivization of the conclusions.

STUDY DESIGN

Five hundred twenty nine CAD patients with multivessel coronary disease who underwent surgical or endovascular myocardial revascularization in the period from 2000 through 2006 were included in the retrospective study. While choosing the strategy of treatment we were guided by common criteria for both surgical and endovascular interventions. For maximal objectivization of the treatment method choice final decision was made after collective discussion of the examination result by cardiologists and cardiosurgeons.

Exclusion criteria for this study were as follows:

1. Repeated coronary artery bypass grafting (CABG);
2. PCI or CABG performed for urgent indications;
3. CAG, PCI or CABG performed in other medical hospital;
4. Simultaneous surgical interventions on vessels in other territories combined with CABG.

CLINICAL CHARACTERISTICS OF PATIENTS AND METHODS OF THE STUDY

All patients were divided into two groups depending on treatment method. The first group consisted of 280 patients after coronary artery bypass grafting; the second group consisted of 249 patients after

[1]Moscow City Center of Interventional Cardioangiology
Russia, 101000, Moscow, Sverchkov per., 5
Phone: 007 495 624 96 36
Fax: : 007 495 624 67 33
e-mail: davidgi@mail.ru
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coronary artery stenting procedure. When creating groups, special attention was given to study patients' similarity with regard to main historical, clinical and laboratory data (Table 1).

Table 1. Baseline clinical and historical data of patients.

	1 (n=280)	2 (n=249)	P
Age, years	56.9±7	57.7±7.4	NS*
Male sex	247 (88.2%)	205 (82.3%)	
CAD duration	4.6±5	47±62	
History of MI	199 (71%)	151 (60.6%)	
Angina FC I-IV	230 (82.1%)	196 (78.7%)	
Unstable angina	35 (12.5%)	38 (15.3%)	
MI	15 (5.4%)	15 (6%)	
Q-wave / non Q-wave MI	10(3.5%) / 2 (0.7%)	12 (4.8%) / 3 (1.2%)	
LV ejection fraction < 50%	39 (13.9%)	48 (19.3%)	
Diabetes mellitus	20 (7.1%)	31 (12.4%)	
Arterial hypertension	210 (75%)	203 (81.5%)	
Hypercholesterolemia	156 (55.7%)	143 (57.2%)	
Obesity	10 (3.6)	16 (6.4%)	
Multifocal	51(18.2%)	49 (19.7%)	

* – difference is not significant

As is evident from Table 1, groups had no significant differences by age, gender and CAD duration. Overwhelming majority of patients in both groups had clinical signs of stable angina. LV ejection fraction was lower than 50% (p>0.05) in 15% of patients in group 1 and in 20% of patients in group 2. In the second group diabetes mellitus was revealed quite more often than in group 1, 7% and 12%, respectively (p>0.05%).

Table 2. Baseline coronary angiography data.

	1 (n=280)	2 (n=249)	P
3 vessels lesion*	142 (50.7%)	104 (42%)	NS
Main LCA	24 (8.6%)	20 (8%)	
Proximal/3 LAD	145 (51.8%)	105 (55.6%)	
LAD	258 (92.1%)	155 (82%)	
CxB/OMB	193 (68.9%)	128 (67.7%)	
RCA	212 (75.7%)	137 (72.5%)	
Mean number of damaged vessels	2.5±0.5	2.4±.6	
Type B2/C lesion	259 (92.5%)	168 (89%)	
Occluding lesion	120 (42.8%)	66 (34.9%)	
Lesion of orifice	65 (23.2%)	41 (21.7%)	
Bifurcation lesion	140 (50%)	87 (46%)	
Diffuse lesion	67 (23.9%)	46 (18.5%)	

* main artery lesion > 70%. LCA – left coronary artery. LAD – left anterior descending coronary artery. CxB – circumflex branch. OMB - obtuse margin branch. RCA – right coronary artery.

According to selective coronary angiography results, lesions of three and more coronary arteries were revealed in 50% cases in group 1, and in 42% cases in group 2 (p>0.05). The groups did not differ significantly in number, localization and character of lesions, moreover in each group there was a clear predominance of type B2 and C coronary lesions (AHA/ACC classification). Main LCA lesion rate was 8.5% in group 1 and 8% in group 2 (p>0.05). Marked diffuse changes (with stenosis > 50%) of the distal part of major arteries were observed in 24% of patients in group 1 and in 18.5% of patients in group 2 (p>0.05) (Table 2).

Prior to intervention, all patients underwent complex examination including medical history, ECG, 24-hour ECG monitoring, echocardiography (stress echocardiography if necessary), and cycle ergometry (unless contraindicated).

Surgical interventions and endovascular procedures were performed by generally adopted methods. In CABG cases extracorporeal circulation through vena cava and aortic atrial cannulation under moderate hypothermia (30-33°C) was performed in all patients. In all cases antegrade cardioplegia with Custodiol solution was used.

The average amount of shunts in group 1 (distal anastomoses) was 2.87 + 0.87 per patient (range from 1 to 6). In 75 (26.8%) patients only arterial grafts were used, in 202 (72.1%) – arterial and venous grafts, and in 3 (1.1%) – only venous grafts were used. Mammaro-coronary bypass grafting was performed in 259 (92.5%) patients, among them bilateral in 23 (8.2%), bypass surgery with composite (sequential and/or Y-grafts) shunts – in 122 (43.6%) patients.

The number of stents implanted in group 2 varied from 1 to 5 and was on average 2.4+ 0.65 per patient. In overwhelming majority of cases matrix and modular prosthesis without drug coating were used. Antiproliferative drug-coated stents (mainly Cypher (Cordis, Johnson & Johnson) and Taxus (Boston Scientific)) were placed in 76 (30.5%) patients, in 31 (12.5%) out of them – together with bare metallic stents.

Complete myocardial revascularization (restoration of the territories of all major arteries and dominant side branches with lumen stenosis > 70%) was achieved in 171 (61.1%) of patients in group 1, and in 171 (68.6%) patients in group 2 (p>0.05). Diffuse lesion and/or occlusion of the distal segment of artery were the most common reasons for incomplete myocardial revascularization.

Statistics Data processing was performed by means of SPSS program for Windows 10.0.5 (russified version). The difference were considered as significant if p value was <0.05. All data concerning means are reported as M±m, where M is arithmetic mean of set sample, and m is standard error of means.

RESULTS AND DISCUSSION

Immediate (in-hospital) period

No intraoperative mortality was observed. During postoperative period there was 1 death (0.35%) in group 1, and 1 (0.4%) in group 2 (p>0.05) (Fig. 1). Thus,

intraoperative survival was 100% in both groups, survival in immediate postoperative period was 99.65% in group 1, and 99.6% in group 2 (p>0.05). In group 1 the death was caused by rapid progressive multiple organ failure and brain edema resulting from heart tamponade due to the failure of the distal anastomosis of shunt to the circumflex branch of the LCA. In group 2, the patient died from acute cardiovascular failure with concomitant transmural MI caused by subacute occlusion of two stents: in the LAD and the CxB.

In early postoperative period non-fatal Q-wave MI developed in 2 (0.7%) patients in group 1, and in 2 (0.8%) patients in group 2 (p>0.05) (Fig. 1). In group 1 localization of both myocardial infarctions corresponded to shunted RCA territory. Rethoracotomy for revision of shunts and coronary circulation was not performed (due to fast positive changes on ECG). After subsequent conservative therapy the patients' condition was stabilized, angina attacks did not recur. In mid-term follow-up these patients refused control examination due to absence of complaints and satisfactory tolerance of physical load. In group 2 one case of Q-wave MI developed due to acute stent thrombosis in the LAD and the CxB, in another other due to acute stent thrombosis in the LAD and the RCA. In each of the two cases urgent repeated endovascular procedures on syndrome-related arteries were performed with good angiographic effect. After that the patients' condition remained stable. In mid-term follow-up there were no signs of angina, moderate LV ejection fraction reduction was observed as compared to baseline, and control examination revealed good results of previous endovascular procedures.

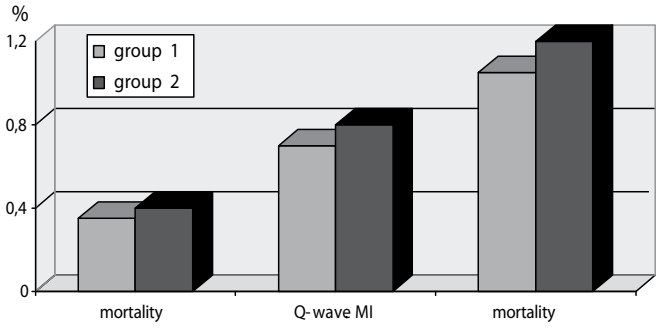

Figure 1. Mortality and non-fatal Q-wave MI rate in the studied groups during in-hospital stage.

Non Q-wave MI was observed in 1 patient of group 2, which corresponds to 0.4%. MI was caused by diagonal branch occlusion developed as a result of LAD stenting. Control examination performed at 6 months showed hypokinesis of antero-lateral segment of the LV and severe diffuse changes in the diagonal branch with antegrade blood flow TIMI III. In the same group angina recurrence was observed in early postoperative period in 1 (0.4%) case. Urgent coronary angiography revealed LAD dissection at the stent edge; second stent implantation was performed with good effect. The types of other complications are presented in Table 3.

Table 3. Types of complications in immediate postoperative period.

Groups	1 (n=280)	2 (n=249)
Rethoracotomy	16 (5.7%)	-
Heart tamponade	1 (0.35%)	1 (0.4%)
Stroke	1 (0.35%)	0
Brain edema	3 (1.1%)	1 (0.4%)
Delirium	8 (2.9%)	0
Multiple organ failure	2 (0.7%)	1 (0.4%)
Cardiovascular failure	2 (0.7%)	1 (0.4%)
Respiratory failure	6 (2.1%)	0
Renal failure	15 (5.4%)	2 (0.8%)
Mediastinitis	1 (0.35%)	0
Pneumonia	11 (3.9%)	0
Hydrothorax	45 (16.1%)	0
Wound complications*	8 (2.8%)	-
Complications at the site of vascular access	-	2 (0.8%)
Gastro-intestinal bleedings	6 (2.1%)	0
Atrial fibrillation	48 (17.1%)	2 (0.8%)

* soft tissues diastase, sternum ostheomyelitis

Smooth postoperative course (without complications) was observed in 161 (57.5%) patients in group 1, and in 235 (94.4%) patients in group 2 (p<0.05). The average duration of hospital stay was 15.33±7.8 days after surgical treatment, and 2.9±1.6 days after endovascular treatment (p<0.05).

Thus, in immediate period there were no differences between the groups in lethal outcome rate, Q-wave MI rate, while smooth clinical course was observed more often in stenting group.

Mid-term follow-up

In mid-term follow-up (8.1±4.6 months in group1 and 8.6±5.5 months in group 2), 185 (66.1%) and 180 (72.3%) patients, respectively, were examined. Other patients were questioned by telephone or examined in out-patient settings. In some cases the information on patient's health was obtained from their relatives or attending physicians. According to the data collected in such a way, survival in this group was 100%; overwhelming majority of patients refused from hospitalization due to absence of complaints and good physical tolerance. As complete objective analysis of the treatment results in these patients was not possible, only data on patients who underwent control examination including coronary angiography and shuntography is given below.

Survival rate in these patients was 100% in group 1, and 98.3% in group 2 (p>0.05). In group 2 there were 3 deaths (1.7%) (Fig. 2). In one case patient with chronic aneurism of the anterior wall of LV who underwent multiple LCA stenting died one week after the discharge. According to autopsy data his death was caused by recurrent transmural myocardial infarction due to the occlusion of stent in the CxB (no changes in the LAD stents were revealed). In

two other cases the death after endovascular procedure were caused by critical stenosis of the left main coronary artery. In each of these cases two stents had been in the left main by V-stenting technique involving the LAD and the CxB ostia. In immediate period patients' condition remained stable. The patients were hospitalized repeatedly with extensive acute anterior myocardial infarction in one month in one case, and in four months in another. Emergency coronary angiography showed signs of thrombosis of the previously placed stents with TIMI 2 antegrade blood flow in the LAD and the CxB. Despite successfully performed repeated endovascular procedures (PTCA of the of the left main and the ostia of the LAD and the CxB) and intra-aortic balloon pumping, both patients died of progressive cardiovascular failure in cardiological intensive care unit.

Non-fatal Q-wave MI was observed in 3 (1.6%) patients in group 1, and in 2 patients (1.1%) in group 2 ($p>0.05$) (Fig. 2). In group 1, MI was induced by occlusion of venous shunt to the LAD in one case, and by progression of native coronary artery lesion some months after the intervention in two other cases. In group 2 both cases of MI developed due to occlusion of LAD stent: in one case – in one month, in other – in 2 months after the discharge.

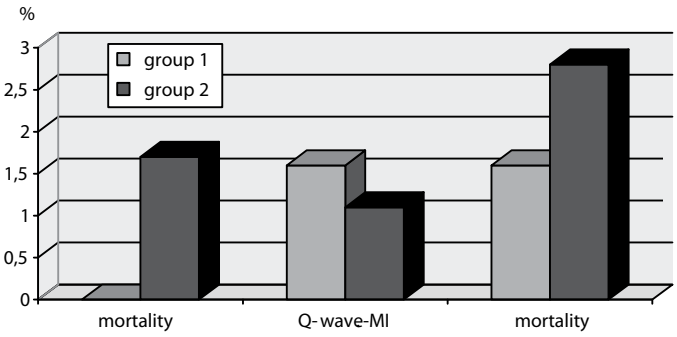

Figure 2. Mortality and Q-wave MI rate in investigated groups in mid-term follow-up.

Non Q-wave MI developed in 1 (0.5%) patient in each group due to progression of native coronary artery atherosclerotic lesion: in the RCA in group 1 and in the LAD in group 2 ($p>0.05$).

It should be noted that in six out of seven patients who have experienced myocardial infarction in mid-term follow-up, successful endovascular procedures on infarct-related arteries were performed during repeated hospitalization. In one out of these seven patients no repeated intervention was performed due to severe diffuse lesion of infarct-related artery and lack of evidence for ischemia of viable myocardium.

Signs of unstable angina were observed in 9 (4.9%) patients in group 1, and in 12 (8.7%) patients in group 2 ($p>0.05$), signs of exertional angina of FC I-III – in 32 (17.3%) and 48 (26.7%) patients, respectively ($p<0.2$). There were no cases of exertional angina of FC IV.

Thus, in mid-term follow-up there were no significant differences in rates of lethal outcome, myocardial infarction, unstable angina, effort angina between groups, while in view of all these cases, signs of angina were observed significantly more rarely in group 1 compared to group 2: in 45 (24%) and in 66 (37%) of patients, respectively ($p<0.05$) (Fig. 3).

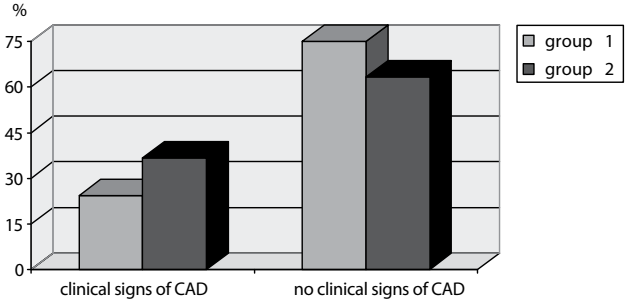

Figure. 3. Rate of recurrent angina signs in investigated groups of patients in mid term follow-up.

Improvement of clinical condition as compared to baseline was observed in 169 (91.3%) patients in group 1, and in 154 (85.6%) patients in group 2, no changes were revealed in 7 (3.8%) and 20 (11%) patients, the worsening – in 9 (4.9%) and 6 (3.3%) patients, respectively ($p> 0.05$), i.e. quality of life improved (complete disappearance of attacks or reduction of angina functional class) in overwhelming majority of patients, whereas impairment of quality of life was noted in less than 5% of patients.

Coronary angiography and shuntography revealed that angina recurrence was likewise caused by stenotic or occlusive changes in shunts or stents in 22 (12%) patients of group 1 and in 44 (24%) patients of group 2 ($p<0.05$). In other patients angina recurrence was probably caused by initially incomplete myocardial revascularization and/or progression of atherosclerotic lesion of coronary arteries. It is important to note that the analysis of the reasons of angina recurrence was performed with regard of data of 24-hours ECG monitoring, stress cycle ergometry and/or stress-echocardiography.

Physical tolerance

In mid-term follow-up stress cycle ergometry was performed in 161 patients in group 1, and in 135 patients in group 2. The criteria for load cessation were submaximal HR reached without occurrence of angina signs and/or ischemic ECG changes during examination in overwhelming majority of patients: in 137 (85%) patients in group 1 and in 92 (68%) patients in group 2 ($p<0.05$).

Physical exercise tolerance changes over time were assessed by comparative analysis of primary and control cycle ergometry in 116 patients in group 1, and in 90 patients in group 2. Increase in physical tolerance in comparison with the baseline was revealed in 87 (75%) cases in group 1, and in 52 (58%) cases in group 2 ($p<0.05$). In the majority of other patients physical exercise tolerance did not change.

Physical exercise tolerance value increased in average from 68±26 W to 99±27 W in group 1, and from 75±25 W to 92±31 W in group 2 ($p<0.05$) (Fig. 4).

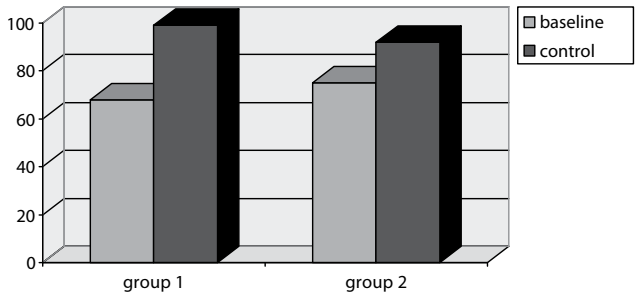

Figure 4. Change of physical exercise tolerance over time in groups, W.

Thus, after control examination an increase in physical exercise tolerance by one level as minimum in comparison with baseline was observed in all patients, but the increment of physical load tolerance in general was higher in group 1 compared to group 2.

Functional capacity of the myocardium

Control left ventriculography was performed in 166 patients in group 1, and in 130 patients in group 2. In 80% out of them LV EF increased by more than 5% or did not change substantially from baseline. LV EF increased on average from 60.4±10% to 63.2±10.1% in group 1, and from 60.7±12.8% to 62.8±11% in group 2, which amounted to less than 3% in both groups ($p<0.05$).

Significant growth of LV EF in each group was observed only in patients with initially low myocardial contractility and good angiographic results of interventions: from 51.5±6.6% to 58±10.2% in group 1, and from 46.7±8.5% to 55.3±12.6% in group 2 ($p<0.05$). No significant dependence of LV EF increase on myocardial revascularization method was revealed: 6.5% and 8.5%, respectively ($p>0.05$) (Fig. 5).

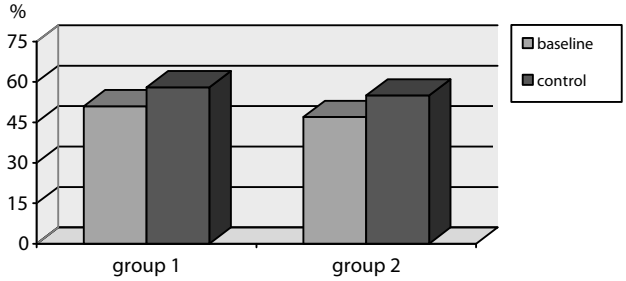

Figure 5. LV EF changes over time in groups of patients with initially low myocardial contractility and preserved angiographic results of the intervention .

In overwhelming majority of these patients the increase in LV EF was due to the improvement of anterior wall contractility that probably was caused by complete revascularization of this part of myocardium in 100% of cases, whereas revascularization of the LV posterior wall was incomplete in some of those cases. For example, distal occlusion of the RCA or the CxB persisted (Table 4).

Table 4. Changes in segmental LV EF over time in patients with initially low myocardial contractility and preserved angiographic results of the intervention.

Groups	1 (n=75)		2 (n=48)	
	baseline	control	baseline	control
Anterobasal segment	**42±11**	**49±15**	**38±12**	**48±13**
Anterolateral segment	**19±10**	**31±16**	**15±11**	**27±14**
Apical segment	5±8	6±8	4±7	7±7
Diaphragmatic segment	19±12	18±13	15±11	16±12
Inferobasal segment	22±12	22±11	18,5±11	20±9

Medical therapy

Changes in conservative treatment strategy in patients compared to baseline are presented by groups in Table 5.

Table 5. Change in medical therapy during follow-up period.

Groups	1		2	
	Baseline n=280	Control n=185	Baseline n=249	Control n=180
Nitrates	271 (96,8%)	33 (17,8%)	228 (91,6%)	81 (45%)
Calcium antagonists	68 (24,3%)	33 (17,8%)	68 (27,3%)	51 (28,3%)
Combination of drugs	94,6%	16,8%	88,7%	40,5%

As is evident from the Table 5, in mid-term follow-up incidence of prescribing nitrates, calcium antagonists and complex antianginal (nitrates together with calcium antagonists and/or beta blockers) treatment decreased significantly, however, the number of patients not requiring these drugs or their combination was significantly higher in group 1 compared to group 2.

Repeated myocardial revascularization

Repeated myocardial revascularization was performed in 25 (13.5%) patients in group 1 (PCI in all cases) and in 74 (41.1%) patients in group 2 (PCI in 67 (37.2%) patients and CABG in 7 (3.9%) patients) ($p<0.05$) (Fig. 6).

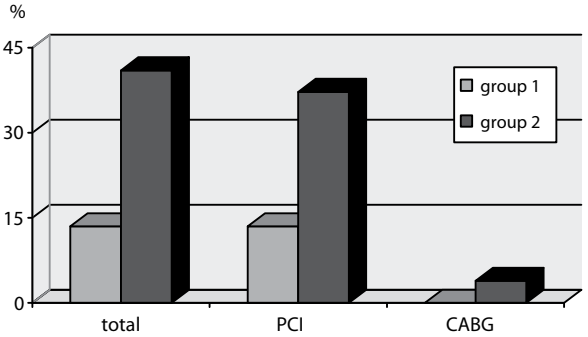

Figure 6. Repeated myocardial revascularization.

According to the data of coronary angiography and shuntography, unsatisfactory angiographic result (stenosis or shunt occlusion in group 1 and restenosis or stented segment occlusion in group 2) was the reason of repeated intervention in 14 (7.6%) and 52 (28.9%) patients, respectively ($p<0.05$) (Fig. 7).

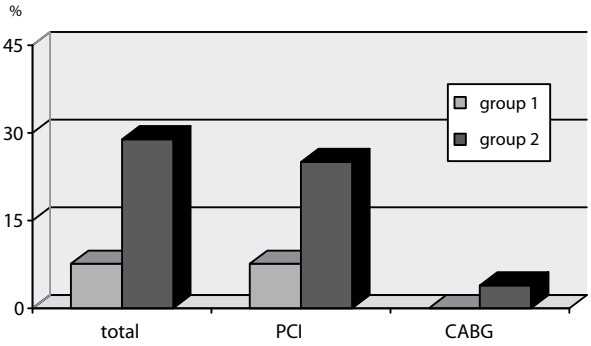

Figure 7. Repeated myocardial revascularization due to unsatisfactory angiographic result of previous intervention.

In other 11 (5.9%) patients of group 1 and in 22 (12.2%) patients of group 2 the indications for repeated intervention were initially present or newly developed coronary lesions.

Results of control angiography

Angiographic examination was performed in all patients who underwent control evaluation. When analyzing obtained data, stenosis more than 50% in stented segment or shunt was considered as unsatisfactory result.

Good angiographic result of previous interventions was revealed in 134 (72.4%) patients in group 1, and in 119 (66.1%) patients in group 2 ($p>0.05$). Shunt or stented coronary artery segment stenosis was revealed in 26 (14.1%) patients in group 1 and in 52 (28.9%) patients in group 2, occlusion – in 25 (13.5%) and 9 (5%) patients, respectively ($p < 0.05$) (Fig. 8).

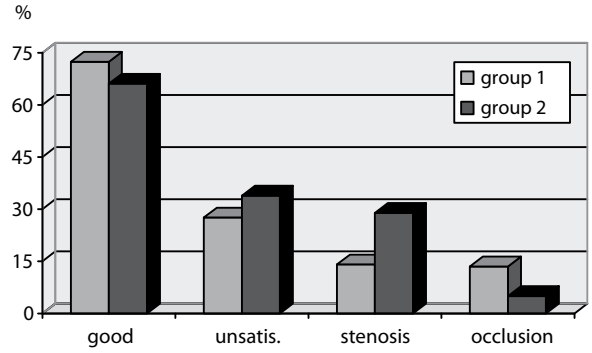

Figure 8. Patients' distribution according to intervention result.

Unsatisfactory angiographic result accompanied by clinical CAD manifestation was revealed in 20 (39.2%) out of 51 patients in group 1 and in 44 (72%) out of 62 patients in group 2 ($p<0.05$). The result was corrected by repeated interventions in 14 (27.4%) and 42 (68.9%) patients, respectively ($p<0.05$). In group 1 PCIs were performed in all cases, in group 2 PCI was performed in 35 cases and CABG – in 7 cases.

Thus, at the time of control examination there were no significant differences in number of patients with good and unsatisfactory angiographic result between groups. However, in group 2 unsatisfactory angiographic results were significantly more often associated with recurrence of angina and with the necessity in repeated medical interventions than in group 1.

Atherosclerotic lesion progression into haemodynamically significant lesion was revealed in 12 (6.4%) patients in group 1, and in 20 (11%) patients in group 2 ($p>0.05$). In group 1 progression of artery lesion proximal to anastomosis with shunt was assessed separately: occlusion of initially stenotic vessel was observed in 96 (52%) patients.

State of shunts and stented segments of the coronary arteries

As mentioned above, groups had no significant differences in number of patients with unsatisfactory angiographic result of interventions; however, when assessing the condition of each individual stented segment and shunt the following results were obtained. In 1 group 464 (89%) shunts (n=521) had no stenotic changes, in group 2 331 (80.7%) stented segments (n=410) were unchanged. Unsatisfactory angiographic result of interventions was observed in 58 (11%) and 79 (19.3%) cases, respectively ($p<0.1$). Stenosis rate was 32 (6%) in 1 group and 65 (16%) in 2 group ($p<0.05$), occlusion rate was 26 (5%) and 14 (3.4%), respectively ($p>0.05$) (Fig. 9).

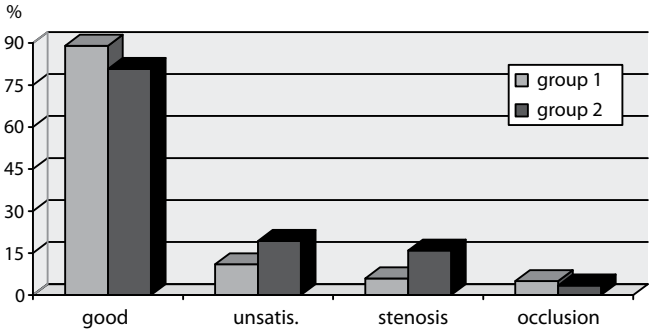

Figure 9. Angiographic results of interventions.

In group 1 good angiographic result was revealed more often after use of arterial grafts and sequential shunts, in particular, of the variants of "side-to-side" anastomoses, and in group 2 - after antiproliferative drug-coated stents implantation. In these cases stented segment restenosis rate was 6.1%, occlusion rate was 3%, in cases of bare metallic stents – 17.7% and 3.2%, respectively ($p<0.05$) (Table 6).

It is also evident from the Table 6, that the incidence of unsatisfactory angiographic results of interventions after antiproliferative drug-coated stents implantation did not differ from that in CABG, including arterial grafts use. It should be noted that antiproliferative drug-coated stents were mostly implanted in lesions with complex angiographic morphology.

Comparative analysis of the rate of unsatisfactory results of interventions in different subgroups

Significant benefit of CABG compared to PCI with regard to the rate of unsatisfactory angiographic result was revealed in subgroups of patients over 65 years, with diabetes mellitus and with initially low myocardial contractility (Table 7).

Table 6. The rate of unsatisfactory results of interventions depending on technique used .

Groups	n	group 1	group 2	P
Arterial grafts	346	31 (8.9%)	-	< 0.1
Venous grafts	175	27 (15.4%)	-	
MCS	249	23 (9.2%)		НД
CABG	272	35 (12.7%)	-	
Simple shunt (one distal anastomosis)	334	46 (13.8%)	-	< 0.1
Composite (several anastomoses)	187	12 (6.4%)	-	
Sequential	142	5 (3.5%)	-	< 0.05
Y-grafts	45	7 (15.5%)	-	
Side-to-side anastomosis	77	1 (1.3%)	-	< 0.05
End-to-side anastomosis	444	57 (12.8%)	-	
Bare metallic stents	344	-	73	< 0.05
Antiproliferative drug-coated stents	66	-	6 (9.1%)	

n – number of distal anastomoses (group 1) or stents (group 2).

Table 7. Clinical and historical factors unfavourably affecting results of stenting compared to CABG (p<0.05).

Groups	Group 1		Group 2	
	n	n*	n	n*
Age>65years	142	12 (8.5%)	126	31 (24.6%)
Diabetes mellitus	39	3 (7.7%)	52	11 (21.2%)
LV EF < 50%	59	4 (6.8%)	70	17 (24.3%)

n – number of shunts (group 1) or stents (group 2); n* - incidence of stenosis or occlusion of shunt (group 1) or stent (group 2).

The following types of localization and character of coronary lesions were potentially unfavourable factors related to PCI: left main coronary artery, proximal segment of the LAD, type B2/C according to AHA/ACC classification (including chronic occlusion, diffuse lesion, ostial and bifurcation lesions) (Table 8).

Table 8. Types of coronary arteries lesion unfavourably affecting results of stenting compared to CABG (p<0.05).

Groups	Group 1		Group 2	
	n	n*	n	n*
Left main lesion	56	6 (10.7%)	19	7 (36.8%)
Proximal LAD lesion	82	3 (3.7%)	98	27 (27.6%)
B2/C lesion	336	35 (10.4%)	239	63 (26.4%)
Occlusion (TIMI 0-1)	118	15 (13.6%)	53	22 (41.5%)
Ostial lesion	40	5 (12.5%)	44	17 (38.6%)
Bifurcation lesion	144	11 (7.6%)	101	26 (25.7%)
Diffuse lesion	49	11 (22.4%)	43	14 (32.6%)

n – number of shunts (group 1) or stents (group 2); n* - incidence of stenosis or occlusion of shunt (group 1) or stent (group 2).

The incidence of unsatisfactory angiographic results with the use of antiproliferative drug-coated stents in subgroups with unfavourable factors related to PCI was comparable (Table 9).

Table 9. Incidence of unsatisfactory angiographic results in subgroups with potentially unfavourable factors affecting outcomes of PCI with the use of antiprolipherative drug-coated stents (p>0.05).

Groups	Group 1		Group 1	
	n	n*	n	n*
Age > 65 years	142	12 (8.5%)	19	0
Diabetes mellitus	39	3 (7.7%)	18	2 (11.1%)
LV EF < 50%	59	4 (6.8%)	14	1 (7.1%)
Proximal LAD stenosis > 70%	82	3 (3.7%)	21	1 (4.8%)
B2/C lesion	336	35 (10.4%)	42	5 (11.9%)

n – number of shunts (group 1) or stents (group 2); n* - incidence of stenosis or occlusion of shunt (group 1) or stent (group 2).

Significant PCI benefit in comparison with CABG in terms of the incidence of unsatisfactory angiographic results was revealed in subgroups with initial coronary artery stenosis < 70% only. The incidence of unsatisfactory angiographic results was 18 (23.1%) in group 1 and 5 (6.8%) in group 2 (p<0.05). In other cases there were no differences in the incidence of unsatisfactory angiographic results between groups (Table 10).

Table 10. Factors for which the incidence of unsatisfactory angiographic results was comparable in groups (p>0.05).

Groups	Group 1		Group 2	
	n	n*	n	n*
Age < 65 years	379	46 (12.1%)	284	48 (16.9%)
No diabetes mellitus	482	55 (11.4%)	358	68 (19%)
LV EF > 50%	446	50 (11.3)	261	51 (19.5%)
Lesion of the RCA	120	19 (15.8%)	117	19 (16.2%)
... CxB, OMB	131	20 (15.3%)	111	17 (15.3%)
... proximal/3 of the CxB	55	8 (14.5%)	38	8 (21.1%)
... proximal/3 ПКА	47	7 (14.9%)	37	8 (21.6%)
... middle/3 ПМЖВ	110	9 (8.2%)	53	8 (15%)
... middle /3 ОВ	45	1 (2.2%)	41	4 (9.8%)
... middle /3 ПКА	66	11 (16.7%)	67	10 (14.9%)
... distal/3 ПМЖВ	16	1 (6.2%)	4	0
... distal /3 ОВ	12	2 (16.7%)	12	2 (16.7%)
... distal /3 ПКА	32	2 (6.3%)	13	1 (7.7%)
Lesion of 2nd order branches	174	18 (10.3%)	28	3 (10.7%)
Stenosis > 70% (TIMI 3)	309	36 (11.7%)	349	55 (15.8%)
Lesion type A/B1	185	23 (12.4%)	171	16 (9.4%)

It should be noted, that no cases of the main LCA stenting with antiproliferative drug-coated stents were included in this report, probably due to this fact the incidence of main LCA restenosis in the endovascular treatment group was higher than that in the CABG group. Restenosis incidence with the use of bare stents varied from 20% in initial lesions of the left main and its ostium to 50% in bifurcation lesions.

CONCLUSIONS

1. This study results did not reveal differences in MACE rate between surgical and endovascular methods of myocardial revascularization in CAD patients with multivessel coronary disease both in immediate and mid-term follow-up. At in-hospital stage extracardiac complications were observed significantly more often after surgical treatment compared to endovascular treatment.
2. Overwhelming majority of patients had no CAD symptoms both after surgical and endovascular treatment. In the mid-term follow-up the absence of angina and no necessity in repeated myocardial revascularization were revealed more rarely in the CABG group. The main factor limiting clinical efficacy of PCI compared to CABG was development of coronary artery restenosis.
3. Control angiography results demonstrated more frequent development of stenosis at the site of intervention in the group receiving endovascular treatment compared to group treated surgically. There were no significant differences in occlusion incidence between groups.
4. Clinical and historical factors potentially unfavourable to PCI results compared to CABG were as follows: age of patient > 65 years, diabetes mellitus, and initially low myocardial contractility. Angiographic factors were as follows: lesion of the left main coronary artery, proximal segment of the LAD, type B2/C lesion according to AHA/ACC classification. Significant benefit of PCI compared to CABG was revealed in subgroups with initial coronary artery stenosis < 70%. In other cases there were no significant differences in incidence of unsatisfactory angiographic results between groups.
5. The incidence of unsatisfactory angiographic results in subgroups with potential unfavourable to PCI factors was comparable provided that antiproliferative drug-coated stents were used.

FINAL CONCLUSION:

Thus, in the majority of CAD patients with multivessel coronary disease the endovascular treatment may be an alternative to surgical treatment, including patients with potentially unfavourable factors for restenosis provided that antiproliferative drug-coated stents are used.

Moreover, the following data are supportive for the extension of indications for endovascular treatment in this category of patients: low possibility of extracardiac complications compared to that of more traumatic CABG, shorter hospital stay compared to surgical treatment, and possibility of relatively rapid, safe and effective restenosis treatment by repeated PTCA.

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Does Intracoronary Therapy with Metabolic Cytoprotector Limit Reperfusion Damage of the Myocardium After Endovascular Procedures in Patients with Acute Myocardial Infarction?

D.G. Iosseliani[1], A.G. Koledinsky, N.V. Kuchkina, M.V. Dyagileva, S.P. Semitko, Z.A. Aliguishieva
Moscow City Center of Interventional Cardioangiology, Moscow, Russia

Wide implementation of effective drugs in clinical practice, improvement of cardiac intensive care and strategy of early myocardial reperfusion allowed to achieve significant success in decreasing of mortality rate in patients with acute myocardial infarction (AMI) (1, 2). To our opinion, the primary role in the solution of this problem is to be played by early reperfusion with systemic thrombolysis and/or primary PTCA of the infarct-related artery (IRA) (3-6). Due to wide use of myocardial endovascular reperfusion (92-95% in patients hospitalized during the first six hours from AMI onset undergo this procedures), during the last ten years the hospital mortality from AMI at the Center decreased from 13-15% to 3-4%.

But together with significant therapeutic and prognostic effect of blood flow restoration in IRA there is an adverse effect of myocardial reperfusion damage, i.e. a certain part of the cells dies during perfusion restoration in the given segment of the left ventricle. It happens as a consequence of a complicated chain of pathological processes leading to Ca++ ions and anaerobic glycolysis products entering into ischemic cells because of energetic substrates deficiency. As a result the persistent contracture of muscle fibrils develops leading to cardiomyocytes necrosis (16-18). Production of free oxygen radicals, neutrophyls activation, endothelium and mypcytes edema, lost of antioxidative enzymes, and cardiomyocyte apoptosis promotes this process as well (19).

Experimental and clinical studies focused on different agents use for the prevention of myocardial reperfusion damage have shown that intravenous therapy is not effective from the viewpoint of damage zone limitation in AMI (11-15). To our opinion (11, 20,) the main reasons for the lack of treatment effect in these studies could be: inadequate and late drug entry into the infracted area due to its uptake by other organs, as well as an occlusion of coronary artery supplying this area. Intracoronary drug infusion during or immediately after infarct-related artery (IRA) angioplasty was deemed to be more encouraging, as it could produce a better effect on the myocardium and protect it from the reperfusion damage.

[1]Russia, 101000, Moscow, Sverchkov per., 5
Moscow City Center of Interventional Cardioangiology
Tel. 007 495 624-96-36
Fax 007 495 624-67-33
e-mail: koledant@mail.ru
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In this article we have analyzed the results of a study aimed at the investigation of the efficacy of two "metabolic" drugs, Neoton and Mexicor, administered intracoronary immediately during IRA recanalization to protect ischemic myocardium from reperfusion damage. Analysis of literature showed that there are no clinical studies on intracoronary administration of Neoton and Mexicor after vessel recanalization in AMI.

Neoton (Alfa Wassermann S.p.A., Italy) is an exogenous phosphocreatine – macroerg widely used by the myocardium as a reserve for fast ADP synthesis. The enzyme involved in this process, creatinkinase, rapidly and effectively converses phosphocreatine into creatine with ATP generation (fig. 1). Neoton delays the ischemic cardiomyocytes sarcolemma dysfunction and stimulates energetic metabolism by rapid ATP synthesis, thus decreasing necrosis and myocardial ischemia size. These Neoton properties were confirmed in experimental studies (21-23). However, clinical researches on intravenous drug administration in AMI did not show significant effect in preserving so-called "hibernating" myocardium, and thus limiting the damage area. We believe, that lack of efficacy of this drug in clinical setting would be induced by the mentioned above circumstances.

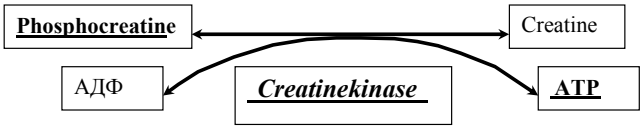


Figure 1. Scheme of biochemical action of exogenous phosphocreatine.

The second drug, Russian drug Mexicor (2-aethyl,6-methyl,3-hydroperidine succinate), (EkoPharmInvest, Russia), mexidol analogue, but containing increased amount of succinic acid (succinate) that covalently binds to potent antioxidant, emoxipine. Succinic acid goes to cardiomyocytes due to high penetrating properties of emoxipine molecule, after that, in cytosole, Mexicor dissociates into two components, each of them having a positive effect: emoxipine promotes the reduction of free radicals, while succinic acid allows to provide FAD-related ATP synthesis by fitting into tricarboxylic acid cycle on the concluding stage (as is known, no NADN-related ATP development occurs in acidosis, thus the Krebs (citric acid) cycle is inhibited, and ATP

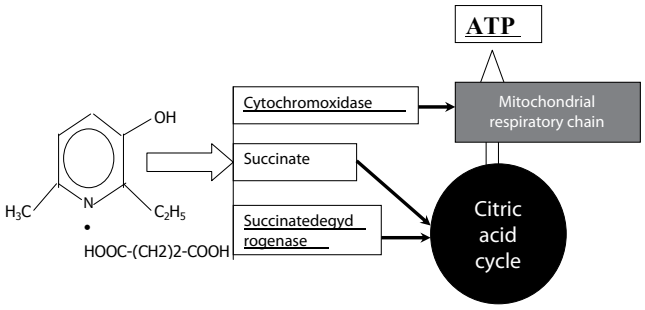
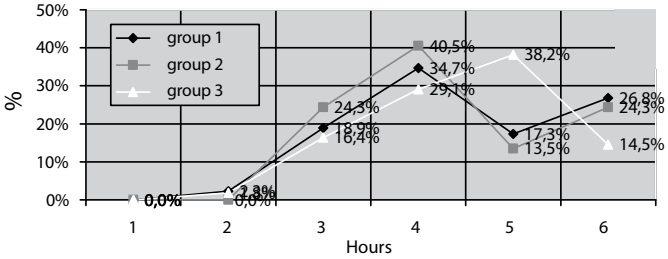


Figure 2. Scheme of biochemical action of Mexicor.



- Differences between the groups are not significant, (p>0.05).

Figure 3. Total time of myocardial ischemia (min), %.

is produced in glycolysis, allowing cardiomyocytes to receive more ATP) (fig. 2) (24, 25). Thus, Mexicor pharmacodynamics consists of stabilization of membrane structures in vascular wall, reduction of platelet aggregation, improvement of rheological blood properties and, what is mostly important, improvement of blood supply and metabolic processes activation in ischemic area of the myocardium leading to necrosis area reduction.

Thus, the purpose of this randomized study was to investigate the efficacy of intracoronary administration of Neoton and Mexicor in limiting damage to ischemic myocardium during endovascular reperfusion in AMI patients.

CLINICAL CHARACTERISTIC OF PATIENTS AND METHODS OF STUDY

From October 2004 through May 2006 we performed the randomized study including one hundred and forty eight patients with AMI within the first six hours after the onset of the disease. The randomization involved three group formation:

- the first group consisted of 45 patients who have received single intracoronary administration of phosphocreatine (Neoton) after antegrade blood flow restoration in IRA.

- the second group consisted of 49 patients who have received single intracoronary administration of Mexicor after antegrade blood flow restoration in IRA.

- the third group consisted of 49 patients who underwent only endovascular myocardial reperfusion by PTCA of IRA. These patients formed the control group.

Exclusion criteria for the study were: cardiogenic shock, systolic blood pressure below 90 mm Hg at the moment of admission; left ventricular ejection fraction below 25%; myocardial infarction of the right ventricle; severe arterial hypertension; pregnancy and breast-feeding; history of stroke with residual neurological symptoms; acute and chronic renal and hepatic failure; hemopoietic organ diseases; cancer; drug idiosyncrasy; pre-hospital and in-hospital use of fibrinolytic and thrombolytic drugs.

Standard 12-lead ECG was recorded and analyzed at baseline, immediately after endovascular procedures, on day 10 and 1 month after the procedure.

Patients received standard anti-aggregant therapy including 350 mg of acetylsalicylic acid and 75 mg of clopidogrel before and during endovascular procedure. All patients with systolic blood pressure higher than 100 mm Hg within the first day underwent intravenous infusion of nitroglycerine at a dose of 0.25-0.5 μg/kg/min.

Baseline clinical laboratory data of examined patients are shown in Table 1. As evident from the Table, at baseline there were no significant differences in majority of findings between compared groups.

Table 1. Baseline clinical historical and laboratory data in examined groups.

	Groups			
	1st group	2nd group	3rd group	P
Age (years)	52.3±8.5	55.7±9.2	59.4±11.6	NS
Gender, M	41 (91.1%)	37 (75.5%)	45 (83.3%)	0.03
Arterial hypertension	25 (55.6%)	31 (63.3%)	32 (59.3%)	0.05
Smoking	29 (64.4%)	34 (69.4%)	36 (66.7%)	NS
Duration of CAD (months)	4.8±1.9	5.4±2.3	7.2±3.1	NS
Hypercholesterolemia (%)	24 (53.3)	33 (67.3)	30 (55.6)	0.04
Diabetes mellitus	--	2 (4.1%)	3 (5.5%)	NS
MI (in anamnesis)	6 (13.3%)	9 (18.4%)	8 (14.8%)	NS
Acute left ventricular failure	17 (37.8%)	12 (24.5%)	16 (29.6%)	P=0.04

The majority of patients smoked, had arterial hypertension and lipid metabolism disturbances. Overwhelming majority of patients was hospitalized within 3-4 hours from angina attack onset (fig. 3). All patients had the typical ECG signs of acute ischemic phase of acute myocardial infarction. In 4 (8.8%) patients of the first group, in 3 (6.1%) patients of the second group and in 3 (5.6%) patients of the third group we revealed heart rhythm disturbances manifested as single and group ventricular extrasystoles. In three patients (6.7%) in the first group, and in three patients (6.1%) in the second group we noted intraventricular conduction disturbances (incomplete left anterior or posterior bundle branch block).

Selective coronary angiography (SCAG) and therapeutic percutaneous interventions (PCI) were performed according to standard methods by four specialists (experience of each is more than 300 interventions per year). In order to assess vessel's angiometric characteristics in the site of occlusion after recanalization procedure we performed predilation using balloon catheter with diameter of 1.5-2.0

mm with following lesion analysis by means of digital computer angiography. Only after that balloon and/or stent with appropriate length and diameter were chosen. In all examined cases PTCA procedure was successful: there was no threatening dissection, distal vessel embolization, antegrade blood flow deceleration. The amount of contrast administered in all three groups was approximately the same and did not exceed acceptable norms.

Intravenous heparin treatment was started with bolus infusion (70 units per kg body weight) with following drug infusion to achieve activated coagulation time (ACT) over 300 seconds. Cytoprotector administration was started immediately after mechanical recanalization of IRA. For this purpose we used special coronary mycrocatheters, Encatech multipurpos Coronary Catheter EUCA MCCU 4-5. Drug administration was realized within ten minutes, at flow rate up to 1.0 ml per second, total volume of administered solution was 50 ml.

While determining the dose of intracoronarly administered drug, we proceeded from the fact that normally coronary blood flow is about 80-120 ml/min, and volume blood flow is on average 0.5-1.5 ml/sec per coronary artery. Therefore, according to our calculations, intracoronary infusion of 0.1-0.5 ml/sec drug in isotonic saline solution should not induce any severe negative effect on patient's heart. In the first group, total dose of intracoronary phosphocreatine (Neoton, WASSERMANN) was 2.0 g, while total dose of Mexicor in the second group was 200 mg. Neoton was administered intracoronarly as a single dose, while administration of Mexicor was continued as intravenous infusions within the first 5 days at a daily dose of 600 mg with subsequent intramuscular drug administration within 9 days at a daily dose of 600 mg. Further patients received tablet formulation of drug at a daily dose of 300 mg (26, 27). No adverse effects of used drugs were observed in any case. During intracoronary drug infusion there was no significant changes in blood pressure and heart rate.

In order to control the state of coronary circulation and left ventricle function in dynamics, on day 10 and after six months from the onset of disease the patients underwent selective coronary angiography and left ventriculography; total and segmental contractility of the left ventricle was analyzed by means of digital quantitative image processing on Hicor computer, "Siemens".

Myocardial necrotic damage mass was assessed by means of quantitative analysis of cardiospecific enzymes, myoglobins and troponin I. Quantifications of myoglobin and troponin I was performed by enzyme-immunoassay using monoclonal antibody to myoglobin and cardiac troponin I isoform (diagnostic sets "Myoglobin ELISA", "Troponin I ELISA", DRG Instruments GmbH, Germany) on mycroplate-photometer ELISA Mat-3000 (DRG International Inc., USA) at wavelength 450 nm. The sensitivity of diagnostic sets used for myoglobin and troponin I was 5 ng/ml and 1 ng/ml, respectively. Biochemical criteria of myocardial necrotic damage were troponin I concentration > 1.5 ng/ml and myoglobin concentration > 90 ng/ml. Blood sampling and the analysis (5 ml from the cubital vein) according to existing recommendations were performed during recanalization, and 12 and 24 hours post-procedure (20). After 15-minites incubation at 25°C, blood was centrifuged at 4000 r.p.m for 10 minutes, and obtained serum samples were used for investigation.

We calculated 32-point Sylvester score (QRS sum) on the base of standard 12-lead ECG for the assessment of the extent of necrotic myocardial damage (28). As is known, QRS sum significantly correlates with myocardial damage volume in patients with AMI (29-31). It was calculated by means of analysis of absolute size and Q-, R-, and S- waves ratios. QRS sum was calculated before intervention with subsequent analysis of this value on day 10-11 of disease.

All patients were followed in the intensive care unit (ICU) within the first 1 2 days with subsequent transfer to cardiology department, where they underwent further examinations including ECG monitoring, heart ultrasonography, stress test with cycle ergometry on day 8, and selective coronary angiography and left ventriculography on day 10 of disease.

Mean in-hospital stay duration was 12.3±1.9 days.

One month later after the onsetof the disease, the information of examined patients' condition was collected by telephone call. According to the study protocol, six months after the discharge all patients were questioned by telephone with hospitalization proposal to perform the control coronary angiography and left ventriculography. Consent to hospitalization was given by 36 (80.1%) patients in the first group, 37 (75.6%) patients in the second group and 48 (88.9%) patients in the third group. The remaining patients refused from control examination due to sense of well-being, absence of CAD symptoms or occupation. However, with the help of telephone enquiry and the data of out-patient examination we obtained the information about all 148 patients participating in this study.

Statistical considerations: Statistical analysis was performed using SPSS statistical program (version 8.0). For an assessment of the quantitative parameters non-parametric and parametric Student and Wilcoxon tests were used. Analysis of signs correlations was performed by Pearson and Spearmen tests. The Fisher' test was used for evaluation of reliability of the qualitative data. All data concerning means are reported as M±m in tables and figures, where M is arithmetic mean of set sample, m – standard error of means. Differences were considered as significant at $P<0.05$.

STUDY RESULTS AND DISCUSSION OF THE OBTAINED DATA

The results of clinical trial aimed at the limitation of reperfusion myocardial damage by intracoronary administration of metabolic cytoprotectors are

reported in this study. The main difference between the performed study and known previous researches was 15 minutes-long infusion of the exogenous phosphocreatine, Neoton (group 1) or new Russian metabolic cytoprotector, Mexicor (group 2) in infarct-related coronary artery immediately after blood flow restoration. Considering that experimental reperfusion myocardial damage begins already in 5 minutes after blood flow restoration, drug infusion was performed simultaneously with antegrade blood flow restoration in IRA.

We consider such a method of Neoton and Mexicor administration as original since it has not been used until this study. This allowed the authors to obtain two invention patents on this treatment method.

The most complex problem encountered during the analysis of obtained data consisted in the assessment of necrotic damage mass. As is known, the sensitivity and specificity of existing clinical methods of myocardium mass assessment do not exceed 70%.

With regard to mentioned above, for better reliability of obtained data, we decided to use a set of several methods of assessment of necrotic damage mass including dynamic quantitative analysis of specific enzyme concentration in blood (myoglobin, troponin I), dynamic quantitative analysis of functional parameters of the left ventricle (total and segmental ejection fraction, left ventricle end-diastolic and end-systolic volumes); dynamic quantitative analysis of Sylvester score.

Starting discussion of obtained results we have to note that intracoronary administration of Neoton (2 g) and Mexicor (200 mg) in patients with AMI immediately after blood flow restoration in IRA was not associated with any severe complications (rhythm disturbances, hypotension, allergic reactions, patient's general condition worsening) in any case.

Main clinical and angiographic findings and endovascular data are shown in Tables №1, 2.

Table 2. Baseline clinical and angiographic findings and endovascular procedures data.

	Groups			
	1st group	2nd group	3rd group	P
Number of affected arteries	1.3±0.3	1.2±0.4	1.2±0.4	NS
Vessel diameter (mm)	3.5±0.3	3.4±0.3	3.3±0.4	NS
Occlusion length (mm)	23±6	21±7	24±6	NS
Presence of intra- and intersystemic collaterals (%)	7 (15.6)	6 (12.2)	9 (16.7)	NS
IRA stenting (%)	0	10 (20.4)	5 (9.3)	P=0,02
Severity of residual stenosis after procedure (%)	25±8.6	17±12.4	28±10.2	NS
Antegrade blood flow TIMI 2/3 prior to endovascular procedure performance	1/20	2/36	2/42	NS
Total time of ischemia (min)	318±35	288±24	294±24	NS
Interval "door-to-baloon" (min)	37±11	45±14	48±12	NS
Mortality (%)	0	0	0	NS

As one can see from the Tables, there were no significant differences in most baseline findings in compared groups; only in the first group we observed the LAD occlusion quite more often than in two other groups. Intra- and intersystemic collateral blood flow to occluded IRA in examined patients was absent in 85% cases.

In IRA occlusion mechanical recanalization and balloon angioplasty procedures were performed in overwhelming majority of cases. In all examined groups the LAD was the most frequent infracted-related artery (Fig. 4).

Dynamic examination of blood cardiospecific proteins showed that their concentration from the very beginning was increased significantly in all patients. This fact served to confirm the diagnosis of AMI. Cardiomarkers concentration achieved a peak approximately at 12 hours from the onset of disease. It should be noted that no significant statistical difference in these findings in examined groups of patients was observed at baseline, while after 12 hours from the onset of disease i.e. after endovascular procedures and intracoronary drug administration in the first two groups, serum protein concentrations differed significantly (fig. 5). Thus, at this moment troponin I serum concentration in the third group reached 543.3±35.4 ng/ml and was significantly higher compared to other two groups (253.7±31.9 ng/ml and 411.6±25.3 ng/ml, respectively). The same data were obtained when evaluating myoglobin dynamics (fig.6). Before endovascular myocardial reperfusion and intracoronary treatment with cytoprotectors, myoglobin level did not differ significantly in examined groups. Meanwhile, after 12 hours from the onset of disease and treatment performed this parameter was significantly lower in the first two groups of patients than that in the third group. Reported data clearly demonstrate the effectiveness of intracoronary cytoprotectors in myocardial cells protection from reperfusion damage. Baseline values of investigated findings in the examined groups, i.e. before treatment, had no significant differences, and such differences appeared during treatment, also confirming the reliability and credibility of obtained information.

The data obtained in evaluating Sylvester score may serve as confirmation of the possible beneficial influence of cytoprotectors on myocardial reperfusion damage limitation (Table 3). As evident from the table, baseline Sylvester score was significantly higher in the first group than that in other two groups, suggesting the greater myocardium damage mass in this group. On day 11 from the onset of disease a decrease in this parameter was observed in all examined groups, but in groups of patents treated intracoronary, decrease over time was substantially more pronounced, that could indirectly suggest more significant myocardium viability preservation in these groups.

Table 4 and fig. 7-9 show data of left ventriculography in examined groups at baseline and on day 10 of disease.

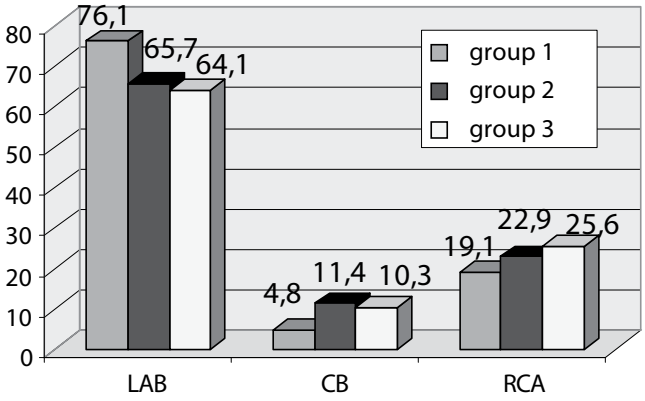


Figure 4. Incidence of EVP performance in different coronary vessels, (%).

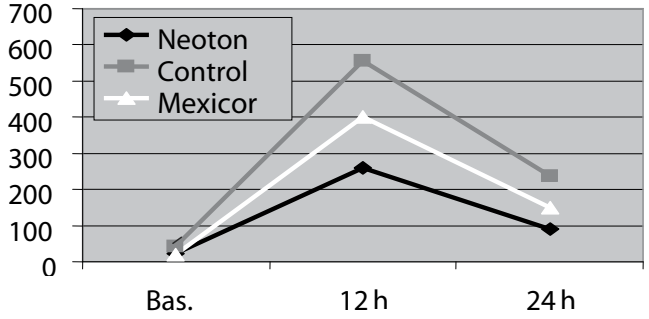


Figure 5. Change over time of the absolute Troponin I concentration in examined groups, ng/ml.

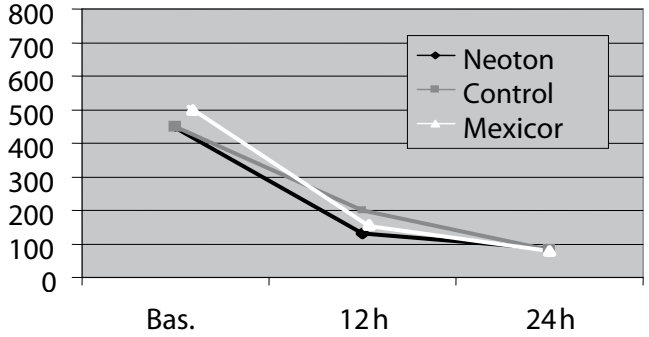


Figure 6. ДChange over time of the absolute myoglobin concentration changes in examined groups, ng/ml.

Table 3. Change over time of Sylvester score in examined groups on in-hospital stage.

	Baseline	Day 11	P
1st group	12.4	10.5	0.01
2nd group	8.7	7.1	0.008
3rd group	8.4	7.9	0.09

Table 4. Change over time of segmental contractility LV in examined groups.

Segmental contractility LV (%)					
			Baseline	Follow-up	P
I segment	1st group	Anterior	50.1±16.4	53.1±11.8	NS
		Posterior	--	--	
	2nd group	Anterior	35.4±19.1	55.7±27.1	<0.05
		Posterior	66.6±13.1	57.6±11.8	
	3rd group	Anterior	43.9±20.2	41.8±19.9	NS
		Posterior	68.2±13.2	66.4±5.8	NS
II segment	1st group	Anterior	1.2±22.1	20.2±21.7	<0.001
		Posterior	--	--	
	2nd group	Anterior	-6.8±18.6	21.4±38.5	<0.001
		Posterior	53.0±24.4	51.0±20.5	NS
	3rd group	Anterior	-2.8±20.4	11.5±17.6	NS
		Posterior	65.0±17.6	45.5±21.2	<0.05
III segment	1st group	Anterior	-2.4±6.4	17.8±13.2	<0.05
		Posterior	--	--	
	2nd group	Anterior	1.1±7.8	12.1±9.3	<0.05
		Posterior	23.4±11.9	27.0±9.4	
	3rd group	Anterior	1.4±8.6	5.2±10.4	NS
		Posterior	26.5±10.6	18.2±3.4	
IV segment	1st group	Anterior	42.3±23.0	35.9±21.8	<0.05
		Posterior	--	--	
	2nd group	Anterior	47.3±17.1	40.9±22.7	NS
		Posterior	13.0±16.7	29.6±5.12	<0.05
	3rd group	Anterior	50.2±22.5	38.2±18.7	<0.05
		Posterior	9.1±25.3	8.8±29.14	NS
V segment	1st group	Anterior	47.8±14.3	40.8±11.2	NS
		Posterior	--	--	
	2nd group	Anterior	43.7±21.5	43.7±21.5	NS
		Posterior	28.2±13.12	29.4±12.7	
	3rd group	Anterior	43.6±10.8	34.0±12.8	<0.05
		Posterior	31.57±13.7	32.6±10.1	

Left ventricle function on day 10 and in the long-term were improved in all three examined groups, however significant increase in the total left ventricular ejection fraction was observed only in the first two groups, while in the third group this parameter has changed insignificantly. It should be noted as well, that the incidence of postinfarction aneurism formation in the first and in the second groups was less than that in the third group (table 5). Thus, in groups 1, 2 and 3 postinfarction aneurism of the left ventricle was observed in 37.3%, 40.5% and 44.1% of cases, respectively. However, this difference was not statistically significant.

The fact that baseline values of LV EDV were the worst in the second group (intracoronary Mexicor administration) could indicate the beneficial influence of the intracoronary cytoprotector treatment ($p<0.05$), but after intracoronary treatment significantly more pronounced improvement of this parameter was observed exactly in this group compared to other two groups. This dependency was still observed on day 10 of disease, in groups 1 and 2 significant decrease in the left ventricular end-diastolic volume was observed at this time, while it in the third group it increased.

The analysis of left ventricle segmental contractility (on the base of left ventriculography data) demonstrated dominance of akinesis areas in the infarcted regions of the left ventricle, whereas in intact zones of the myocardium a hyperkinesis (probably of compensatory character) was observed practically in all cases. After 1-2 weeks (according to ultrasonography data) hyperkinetic zone in intact regions of the left ventricle recovered to normokinesis (34, 35). It should be noted as well, that significantly more pronounced improvement of segmental contractility in infarct-related segments was observed in the first two groups compared to control group.

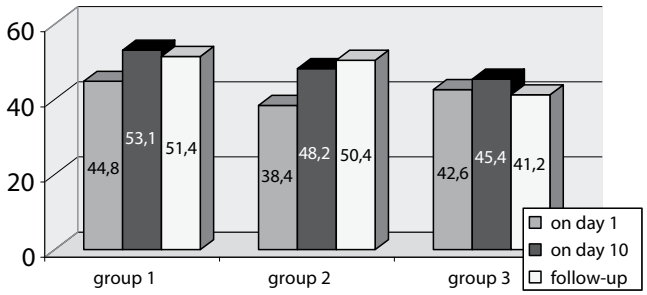


Figure 7. Change over time of the LV ejection fraction in anterior MI at baseline, on day 10 and in long-term follow-up, %.

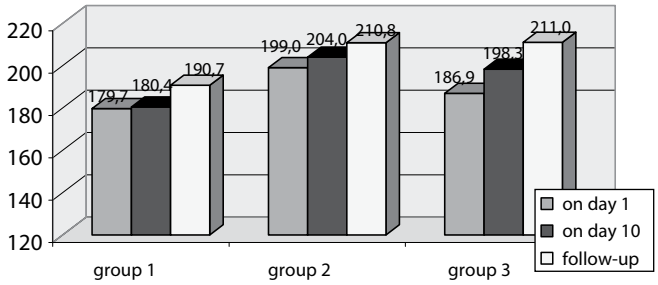


Figure 8. Change over time of the LV EDV in anterior MI at baseline, on day 10 and in long-term follow-up, ml.

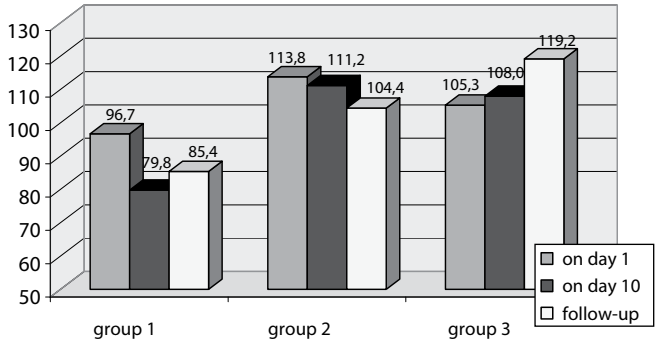


Figure 9. in anterior MI of the LV ESV in anterior MI at baseline, on day 10 and in long-term follow-up, ml.

Table 5. LV contractility according to echocardiography data in examined groups.

	Groups			
	1st group	2nd group	3rd group	P
EF LV (%)	46±8	49±8	39±6	<0.05
Aneurism of LV (%)	37.3	40.5	44.1	P=0.06

Thus, the study allows to confirm, that with intracoronary Neoton and Mexicor treatment performed immediately following mechanical recanalization of IRA, necrotic myocardium damage is significantly smaller than in similar group of patients who did not receive intracoronary treatment. In these groups, the left ventricle function restoration over time was better than in the control group. It can be a clear demonstration of the assumption that Neoton and Mexicor can contribute to the ischemic myocardium protection from reperfusion damage and Mexicor is superior to Neoton.

During in-hospital period no serious clinical complications were observed in the majority of patients in the groups of study. In the first group 1 patient (2.2%) was in need of intra-aortic balloon pumping within the first 24 hours of disease because of marked signs of acute left ventricular failure and extensive lesion of left ventricular myocardium. Later this patient's condition has stabilized, acute left ventricular failure regressed and intra-aortic balloon pump was removed. Hereafter, clinical course was stable. In the second group 1 patient (2.0%) also underwent intra-aortic balloon pumping within 24 hours because of marked acute left ventricular failure, thereafter condition has stabilized and intra-aortic balloon pumping procedure was terminated. In another case (2.0%) a patient with prostate adenoma developed acute urine retention leading to cystostomy. One patient (2.0%) from the same group had transient ischemic attack in vertebrobasilar territory with total symptoms regression in few days after treatment. In the third group, 3 patients (5.55%) died during in-hospital period: in one case (1.85%) patient with transmural AMI of the left ventricle anteroapical region and left ventricular ejection fraction of 26% died on the second day due to progressive left ventricular failure; in the second case (1.85%) the patient with posterolateral MI developed acute mental affection passing to coma on the second day, cerebrovascular accident in brainstem was diagnosed, the patient died on day 16 from disease onset; in the third case (1.85%) on day 9 from AMI development the patient developed acute ischemic stroke in the right mid-cerebral artery and was hospitalized in neurology department where he died on day 17. Two patients (3.7%) had gastrointestinal bleeding: one patient (1.85%) had erosive gastritis, another patient (1.85%) had Mallory-Weiss syndrome. In both cases esophagogastroduodenoscopia (EGDS) was urgently performed. In another case (1.85%) on day 4 after mechanical recanalization (MR) and transluminal balloon angioplasty (TLBA) recurrent MI with thrombosis in the proximal third of LAD developed in angioplasty site, and repeated MR and TLBA procedure were performed.

Thus, in the group 1 the incidence of serious complications on in-hospital stage was 2.2%, among these cardiac events were observed in 2.2%. No fatal outcomes were observed. In the second group complications were observed in 6.0% of cases, among these, cardiac events were observed in 2.0%. There were no deaths among the patients. In the third group, serious complications were observed in 11.1% of patients; among these, 3.7% were cardiac events. Mortality was 5.55%.

After six months 36 (80.1%) patients from the first group, 37 (75.6%) patients from the second group, and 48 (88.9%) patients from the third group were examined in hospital setting. Period of control examination after discharging from the hospital in the first group was on average 8.7 + 2.1 months, in the second group - 9.4 + 2.7 months, and in the third group - 7.9 + 1.6 months. Difference was not statistically significant.

In the first group selective coronary angiography and left ventriculography were performed in 32 (71.3%) patients, in the second group – in 36 (73.4%) patients and in the third group - in 44 (81.5%) patients. Thus, control angiography was performed in 112 patients that corresponds to 75.7% of the total amount of patients participating in the study (fig.10). Good result, i.e. absence of hemodynamically significant diameter stenosis (more than 50% of referent vessel diameter in angioplasty site) was revealed in the first group in 15 (46.9%) patients, in the second group - in 17 (47.2%) patients, and in the third group - in 21 (47.7%), i.e. good angiographic effect of previous endovascular intervention was observed in almost half of patients. Vessel stenosis in the angioplasty site was observed in 14 patients (43.7%) of the first group, in 16 patents (44.4%) of the second group and in 18 (40.9%) patients of the third group. Reocclusion was revealed in 3 patients (9.4%) of the first group, in 3 patients (8.3%) of the second group, and in 5 patients (11.4%) of the third group. Therefore, the result of conducted study showed that overwhelming majority of patients in all groups had functioning infarct-related artery. In the first group the vessel was patent in 90.6% cases, in the second group – in 91.6% cases and in the third group – in 88.6% cases. High rate of IRA restenosis in all examined groups may be explained by the fact that balloon angioplasty without subsequent stenting was performed in overwhelming majority of patients. Here we have to remark that repeated angioplasty with good angiographic results was performed in more than 70% of restenosis or reocclusion cases.

In long-term period the rate of recurrent acute infarction, cerebral vascular accident and lethal outcomes were also evaluated during observation period (Table 6).

In long-term period significant improvement of disease course was revealed in all examined groups (Table 7). There were no significant differences between examined groups.

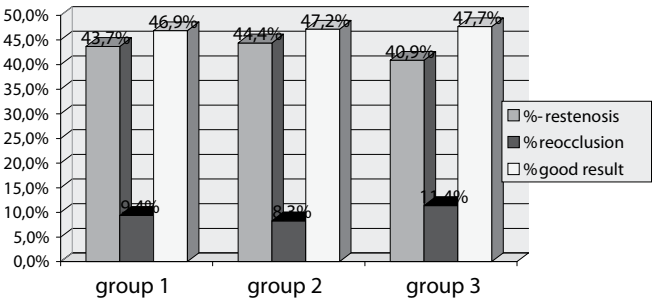
In the first group, 1 patient (2.2%) died from cerebral vascular accident during the observation period. Another patient (2.2%) underwent bypass graft surgery.

In the group 2, two patients died (4.1%) during long-term follow-up: one patient died of acute myocardial infarction, another had sudden death.

In group 3 two patients (3.7%) died of acute myocardial infarction during long term period.

As evident from Table 8, patients from all examined groups received approximately the same drug therapy. There was no significant difference in this parameter between groups.

During late follow-up, total LVEF in the control group was 41.2% and practically did not change, whereas in groups with intracoronary administration of metabolic cytoprotector substantial but not significant LV EF increase was observed: in the



- Differences in the examined groups are not significant, (p>0.05).

Figure 10. Restenosis rate in examined groups.

Table 6. Incidence of serious complications in long-term follow-up.

	Groups			
	1st group	2nd group	3rd group	P
Mortality	2.2%	4.1%	3.7%	NS
ACCD	2.2%	0%	0%	NS
Bypass graft surgery	2.2%	0%	0%	NS

Table 7. Clinical diagnosis distribution in long-term follow-up.

	Groups			
	1st group	2nd group	3rd group	P
Without CF	62.4%	71.2%	64.9%	NS
CF 1-4 FC	37.6%	28.8%	35.1%	NS

Table 8. Pharmaceuticals therapy in examined groups (%).

	Groups			
	1st group	2nd group	3rd group	P
Nitrates. %	100	100	100	NS
Beta-blockers, (%)	81	82	85	NS
IACF, %	91.4	86.5	88.6	NS
Calcium antagonists, %	13.5	13.5	13.6	NS
Glycosides, %	8.1	8.1	6.8	NS

first group this parameter increased from 44.6% to 51.4% (p=0.059), in the second group – from 38.4% to 50.4% (p=0.008).

Therefore, we can talk about higher parameters of left ventricle functional capacity in long-term follow up in groups of the patents who have treated by metabolic cytoprotectors.

Thus, as a result of the study performed we can make following conclusions:

Firstly, this study allows suggesting that intracoronary administration of cytoprotectors, Neoton and Mexicor, in used dosages does not lead to adverse side effects and is normally tolerated by patients. We can use that fact to state that wide opportunities in intracoronary treatment are opened for patients with different cardiovascular diseases.

Secondly, intracoronary administration of cytoprotectors, Neoton and Mexicor, simultaneously

with occluded IRA recanalization probably helps to prevent reperfusion damage to myocardial cells, and thus limits necrotic myocardium damage. It is shown by significantly lower parameters of myocardial cells death in the groups of patients who received intracoronary cytoprotector therapy, although at baseline there were no significant differences in these parameters between all investigated groups. The same is confirmed by the fact that in two groups after performed intracoronary cytoprotector treatment the functional capacity of the left ventricle in these groups became significantly better than in group of patients without such therapy (with approximately equal baseline parameters of total and segmental left ventricle functions. It should be noted especially that in approximately equal other conditions this regularity was observed on in-hospital stage and in mid-term follow-up (after 6 months) in these groups. Beneficial influence of metabolic cytoprotector on preserved viability of peri-infarction ischemic myocardium is confirmed by the fact that left ventricle postinfarction aneurism was observed more rarely in two groups of patients treated with intracoronary cytoprotectors than in patients without similar therapy.

However, small number of cases do not permit us to make the final conclusions about the importance of intracoronary cytoprotector treatment in reperfusion myocardium damage limitation within the first hours of acute myocardial infarction. It is necessary to accumulate further experience and to perform subsequent thorough analysis of obtained data.

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The Role of Acetyltransferase Activity in the Development of In-Stent Stenosis in Patients with Chronic Coronary Heart Disease after Coronary Stenting

S.P. Semitko, I.E. Kuznetsova*, D.T. Guranda**, Z.A. Aliguishieva*, D.G. Iosselian*[1]*

**Moscow City Center of Interventional Cardioangiology, Moscow*

***Laboratory of Biocatalysis and Biotransformation of A.N. Belozersky Scientific Research Institute of Physico-Chemical Biology of Moscow State University, , Moscow*

INTRODUCTION

Development of restenosis in the area of endovascular intervention, which impairs prognosis of disease and requires repeated revascularization, was and remains the main concern regarding arterial stenting. Implementation of stents with antiproliferative coating (DCS) into clinical practice permitted to significantly improve treatment results at the same time revealing a number of new problems. Thus, for example, stent polymeric coating and effect of pharmaceutical substance hinder the epithelization of the prosthetic device, thereby preserving conditions for development of stent thrombosis in long term period after stenting. This fact demanded correction of disaggregant therapy approach in favor of more prolonged (up to year and more) administration of aspirin and clopidogrel to patients. In turn, continued intake of two disaggregants is capable to increase the risk of development of both spontaneous hemorrhagic complications and complications related to different urgent extracardiac surgical interventions. On the other hand, about 10% of all patients are tolerant to standard dual disaggregant therapy, in case of which aspirin and clopidogrel intake in generally accepted doses doesn't provide the appropriate protection from possible thrombotic complications. Furthermore, in our opinion, the important problem is unwillingness of patient to thoroughly follow the recommendations of attending physician and to take expensive drug over a long period of time while feeling well, which, unfortunately, is not uncommon.

Thereby, in spite of evident advantages of DCS in respect of restenosis prevention, a diversity of problems remains, for solving of which using of bare metal prosthetic devices is justified and effective in a number of cases. Therefore, further searching for basic genetically determined mechanisms of in-stent restenosis development remains actual task of modern clinical medicine.

To date many factors which somehow or other are predictors or causes of in-stent restenosis development are known. Such factors as stent apposition due to its incomplete expansion or incorrect positioning; selection of inappropriate size of prosthetic device; development of edge dissection after stenting; complicated B2 and C types stenoses; "small" diameter of target artery; diffuse and calcified nature of coronary arteries lesion; ostial and proximal lesion of the anterior descending artery; diabetes mellitus and others may be emphasized.

The process of in-stent stenosis development may be briefly represented in the following way. Stent becomes covered with a thin layer of fibrin immediately after implantation, and the space between stent struts and the damaged artery wall is filled up with thrombotic deposits different by their thickness. Later on (within 6-12 weeks) stratified thrombus is replaced by extracellular matrix (which structure includes collagen, elastin, glycoproteins and proteoglycans) within which the number of smooth muscle cells increases, and foci of endothelial lining tending to fuse appear on the surface. Within 3 6 months, the surface of neointima is fully covered with a layer of endothelial cells; portion of extracellular matrix continues to increase reaching 90% of whole volume of the hyperplastic neointima, but the number of smooth muscle cells, on the contrary, decreases (1). Recently a number of articles in the field of abdominal surgery showed that synthesis and catabolism of extracellular component of connective tissue is directly dependent on the rate of acetylation processes.

People are divided into 2 groups depending on rate of acetylation. Persons metabolizing test-drugs at high rate belong to one of them (fast acetylation), the other one is distinguished by low rate of metabolism process (slow acetylation). Distribution of "slow" and "fast" acetylators is genetically determined, remains invariable lifelong, and does not depend on gender. Phenotype formation is completed by the age of six months. Biosynthesis of extracellular component of connective tissue prevails over its catabolism in people with the fast acetylation phenotype. And conversely, catabolism of extracellular component of connective tissue prevails over its biosynthesis in people with the slow acetylation phenotype. In 2000 S.A. Makarova et al. revealed significant correlation between phenotype of fast acetylation and risk of blood circulation insufficiency development in patients suffering from CHD. Namely, the "fast" acetylators are those in whom a process of patholog-

[1]Russia, 101000, Moscow, Sverchkov per., 5
Moscow City Center of Interventional Cardioangiology
Tel. 007 495 624-96-36
Tel. 007 495 624-67-33
e-mail: davidgi@mail.ru
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ic heart remodeling, which is underlain by morphological restructuring of the myocardium (increase in proportion of connective tissue), proceeds more aggressively. Moreover, data concerning significant correlation between "fast" acetyltransferase activity phenotype and unfavorable prognosis of myocardial infarction course were obtained (3).

Taking into consideration the important role of extracellular component of connective tissue in the in-stent stenosis development, we were interested to investigate possible dependence between the acetylation phenotype and in-stent stenosis occurrence.

CHARACTERISTICS OF PATIENTS AND METHODS OF THE STUDY

One hundred males suffering from chronic CHD with mean age of 56.8±6.1 years were included in the retrospective study; 116 single-type coronary matrix bare metal stents were implanted to patients with chronic CHD within the period from December of 2003 till January of 2007. Selection of patients for inclusion in the study was performed following control coronary arteriography that was performed on average in 7.2±2.2 months after the endovascular procedure. The main selection criterion was absence of any known clinical and angiographic risk factors of in stent stenosis development in respondents (Table 1). The first group consisted of patients with true in-stent stenosis (I group, n=50), patients without significant stent narrowing were included in the second group (II group, n=50). Clinical and angiographic characteristics of the patients included in the study are shown in Table 2.

Patients' baseline angiographic data, as well as immediate result of the endovascular procedure, were evaluated independently by two specialists. Drug therapy support of endovascular procedures was performed according to the protocol accepted in hospital: heparin IV at a dose of 120 IU/kg until ACT (Activated Clotting Time) is 300-350 sec.; initial loading dose of plavix – 300 mg, aspirin – 500 mg; maintenance dose of plavix – 75 mg/day (for 30 days), aspirin – 100 mg/day. Morphometric parameters of angiograms were processed using computer of angiographic unit, Axiom Artis FC (Siemens, Germany).

Original method of N-acetylation phenotype determination was developed on the base of the Laboratory of Biocatalysis and Biotransformation of A.N. Belozersky Scientific Research Institute of Physico-Chemical Biology of Moscow Stare University (5). Standard substance, sulfadimesine, was used as test drug. After single oral administration of 500 mg of sulfadimesine, urine was collected within 6 hours and proportions of metabolized (N-acetyl-sulfadimesine) and non-metabolized sulfadimesine were determined using high-performance liquid chromatography.

Statistical processing of obtained results was performed using SPSS software, version 10.0 for Windows.

Table 1. Patient inclusion criteria for this study.

Clinical and historical criteria	- male gender - age from 40 to 65 years - no history of diabetes mellitus or other endocrine pathology - stable angina of 1-3 FC - no history of intolerance of sulfonamides
Baseline angiographic criteria	- de novo type A-B1 stenoses except for lesion of LCA trunk, ostial localization and the proximal segment of LAD - reference artery diameter (in the lesion area) ⩾3.3 mm - lesion length up to 16 mm - no signs of calcification and thrombosis in the lesion area
Immediate result of the procedure	- implantation of the stent with diameter ⩾3.5 mm and length up to 18 mm - complete covering of the lesion area by stent - residual stenosis in the site of stent implantation ⩽5% - absence of edge dissection and slowing down the blood flow in the target artery after stent implantation
Long-term result of the procedure	- restenosis: lumen narrowing within stent ⩾50% or by 1.7 mm and more compared with reference diameter

Table 2. Clinical and angiographic characteristics of patients in the study groups.

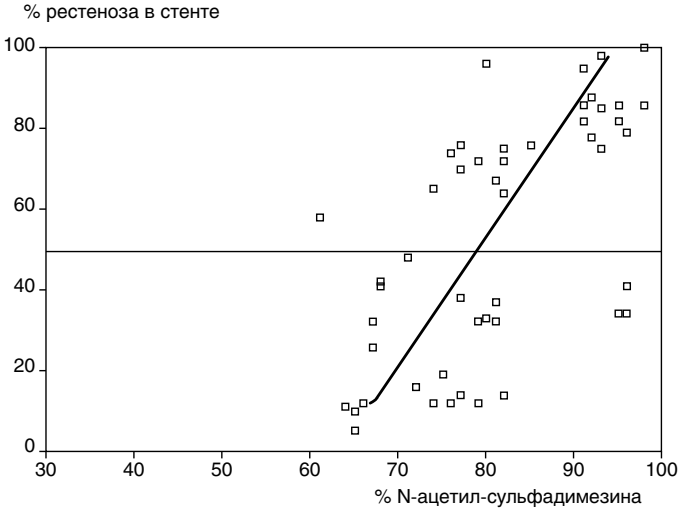
	Group 1 N=50	Group 2 N=50	P
Clinical and historical data			
Male gender	50 (100%)	50 (100%)	NS
Age	54,7±8,3	57,8±4,2	NS
Exertional angina pectoris of 1-3 FC	50 (100%)	50 (100%)	NS
Arterial hypertension	36 (72%)	42 (84%)	NS
Diabetes mellitus	0	0	NS
Previous myocardial infarction in the target artery territory	0	0	NS
Overweight	0	0	NS
Smoking	16 (32%)	22 (44%)	NS
Dislipoproteinemia	32 (64%)	30 (60%)	NS
Left ventricular ejection fraction ⩽ 40%	0	0	NS
Angiographic data			
Target artery			
LAD (middle third)	6	6	NS
LCX (middle third)	16	12	NS
RCA (middle and distal third)	28	32	NS
Reference diameter of the target segment	3,38±0,4 мм	3,21±0,6 мм	NS
Lesion type A-B1	50 (100%)	50 (100%)	NS
Immediate success of the procedure	50 (100%)	50 (100%)	NS
Residual stenosis after stent implantation	4,6±2,2%	5,1±1,8%	NS
Lumen narrowing during control angiography	78,6±11,1%	12,3±14,2%	0,0002

RESULTS OF THE STUDY

Proportion of metabolized test-drug, sulfadimesine (N-acetyl- sulfadimesine), during 6 hours varied from 32 to 98% in the pooled group, and was 80.14±12.61% on the average. However, this value was significantly (P=0.003) higher in group I (restenosis group) of patients amounting to 86.16±9.02%, whereas it was 74.12±12.83% in group II. Significant direct correlation between amount of metabolized

test-drug and rate of artery lumen narrowing within stent was revealed ($R=5.86\pm10^{-7}$; r = 0.641). As evident from Figure 1, trend line of positive correlation dependence of these parameters intersects the formal border of hemodynamically significant stent restenosis (⩾50%) at the point of 78.6% of metabolized test-drug. The data we obtained allow considering respondents, in whom percentage of test-drug acetylation during the first 6 hours was 78.6% and higher, as so-called "fast acetylators".

Figure 1. Distribution of the rate of sulfadimesine acetylation and lumen narrowing within stent in the pooled group of patients.



Division of the patients into two groups of "fast" (FA) and "slow" (SA) acetylators according to the main criterion – percentage of acetylated test-drug up to 80% and higher – allowed to clearly demonstrate significant difference between created groups of patients (Table 3).

Table 3. Results of follow-up angiography in groups of "fast" and "slow" acetylators.

	Fast acetylators	Slow acetylators	P
Mean in-stent loss, %	79,4±10,97	24,32±13,39	P<0,0001
In-stent stenosis	19(76%)	6(24%)	P=0,0003

CONCLUSION

An independent significant direct correlation between the rate of acetylation and degree of in stent stenosis after coronary artery replacement using bare stents in patients with chronic CHD was revealed. Using of developed method of the determination of amount of metabolized test-drug (sulfadimesine in our case) allows to reveal patients who have significantly higher risk of in-stent stenosis development when bare metal stents are used, which, in turn, opens up possibility of elective approach to selection of treatment policy for this patient group.

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Endovascular Myocardial Revascularization in Patients with Multivessel Coronary Disease with Objective Assessment of the Severity of Coronary Lesions using SYNTAX Scale

V.I. Ganiukov[1], R.S. Tarassov, N.I. Sussoev, I.N. Shigantzov, E.A. Levchenko, M.V. Demina, I.Yu. Bravve

Novosibirsk Regional Clinical Cardiology Dispensary, Novosibirsk, Russia

Objective: To assess the efficacy of endovascular myocardial revascularization in patients with objectively severe (SYNTAX score ⩾16) multivessel coronary disease.

Background: The optimal strategy of revascularization in patients with multivessel coronary disease is still a subject of debates. Over the last years, PCI has shown its efficacy in patients with multivessel coronary disease. The term "multivessel lesion" can comprise both two local stenoses in the second order coronary arteries, and lesion of the left main coronary artery associated with bifurcational stenosis of the LAD and occlusion of the right coronary artery. It is obvious that in such various groups of patients different outcomes of interventional treatment may be expected. SYNTAX scale was developed to objectively assess the severity of coronary lesions and to assess localization, number of stenotic segments, their length, and presence of occlusion and bifurcational stenosis. The use of this scale allows to form and to study the groups of patients with multivessel coronary disease identical by severity: moderate (score < 16), severe (score ⩾ 16) and extremely severe (score ⩾ 28).

Methods: The cases of multivessel lesions with SYNTAX score > 16 were considered as severe. The immediate and long-term outcomes of percutaneous coronary intervention (PCI) in 37 patients with multivessel coronary disease were analyzed.

Mean number of vessels with hemodynamically significant lesion was 2.48±0.5, occlusion of one or several coronary arteries was diagnosed in 20 patients (54%). Drug-eluting stents (DES) were used in 40.5% cases (n=15), bare metallic stents (BMS) were implanted in 29.7% patients (n=11), and combination of DES+BMS was used as well.

Results: The immediate success of the intervention was observed in 97.5% cases (successful revascularization was achieved in 116 out of 119 stenoses, recanalization of 3 chronic occlusions failed). There were no complications such as death, myocardial infarction or urgent coronary bypass surgery. Complete myocardial revascularization was achieved in 75.67% cases. During long-term follow-up (9.2±3.4 months after PCI) 70% of patients had no clinical signs of angina in combination with negative results of stress-test. The rate of repeated revascularization of the target stenosis was 3.7% (n=1). Control examination revealed clinical signs of unstable angina in one case only (3.7%), while at baseline this was seen in 32.4% ($p<0.05$).

Conclusions:

1. PCI is a safe and effective method of complete or partial myocardial revascularization in patients with severe (SYNTAX score ⩾16) multivessel coronary disease.
2. SYNTAX scale allows to assess adequately the efficacy of revascularization in the groups of patients IDENTICAL from the viewpoint of coronary stenosis severity.

Key words: percutaneous coronary intervention, multivessel lesion, objective assessment of the severity of coronary vessels stenosis, SYNTAX scale.

List of abbreviations:

CHD – coronary heart disease
MI – myocardial infarction
LV – left ventricle
EF – ejection fraction
FC – functional class
PCI – percutaneous coronary intervention
DES – drug eluting stent
BMS – bare metallic stent

INTRODUCTION

The optimal strategy of revascularization in patients with multivessel coronary disease is still a subject of debates.

Over the last years PCI has shown its efficacy in patients with multivessel coronary disease. According to published data, currently up to 75% out of total number of patients with multivessel coronary disease undergo endovascular revascularization (9-12). PCI with drug-eluting stents and CABG were shown to be comparably effective (4). PCI success rate and number of complications correlate with the

[1]Address for correspondence:
Russia, 630047, Novosibirsk,
Ul. Zalesskogo, 6, bld. 8,
Tel.(383) 216-55-37, Fax (383) 226-29-71,
e-mail : ganyukov@mail.ru
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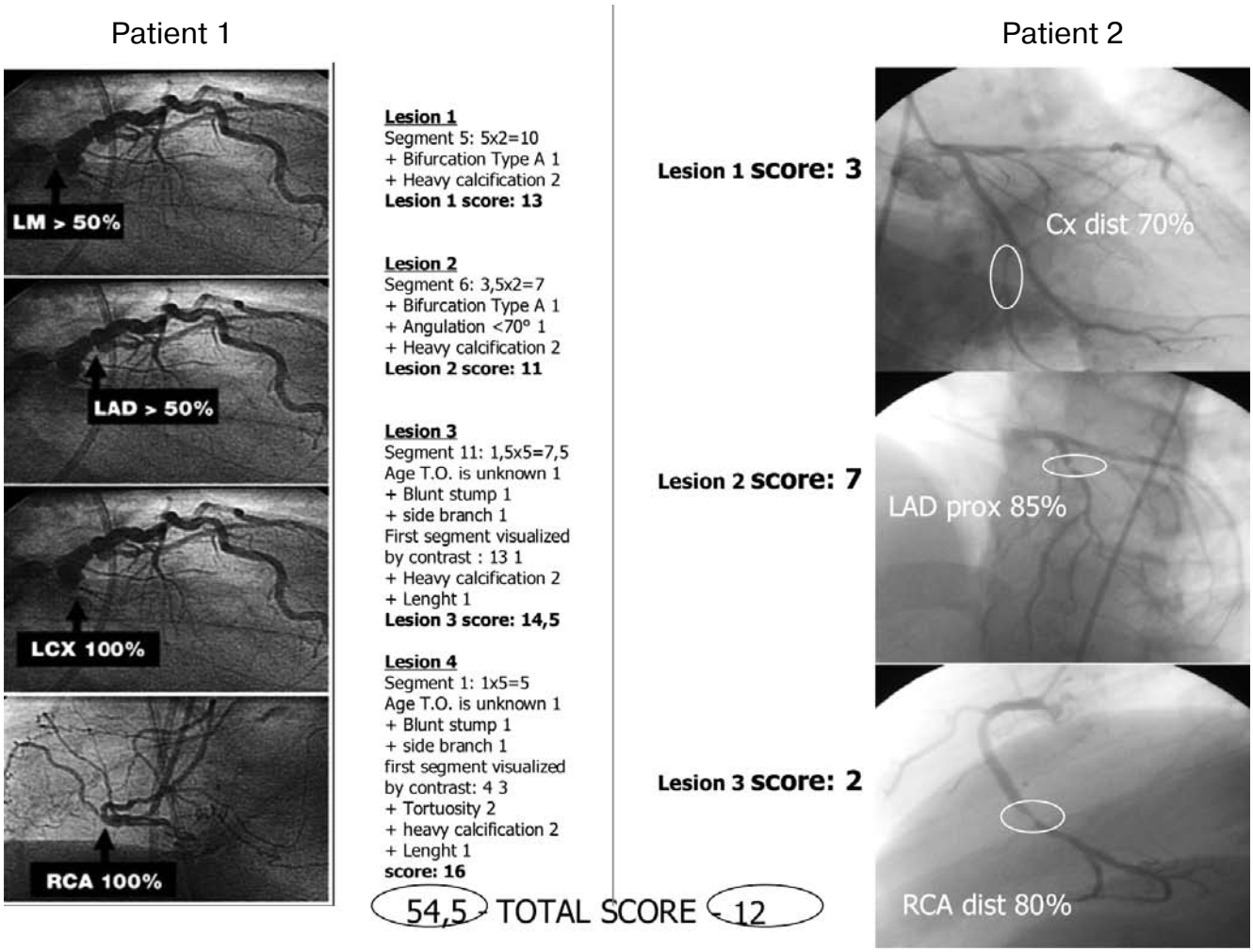

Figure 1. Comparison of severity of coronary lesions by SYNTAX scale in patients with multivessel lesion. Patient 1 - SYNTAX score 54.5; Patient 2 – SYNTAX score 12.

stenoses morphology; chronic total occlusions, C and B type stenoses are predictors of unfavorable results. The main objective of PCI in multivessel coronary disease is to improve the symptomatic status and physical tolerance in patients, which may be achieved by correction of several hemodynamically significant stenoses in the vessels supplying a significant area of viable myocardium (13). To date, the great amount of data based on the results of large multicenter studies evaluating the results of different revascularization methods in multivessel coronary disease is accumulated (14-19); however, it should be remembered that patients with multivessel coronary disease represent the extremely various population, and frequently they differ substantially both by the complexity and severity of coronary arteries stenosis. Figure 1 shows data of Patients 1 and 2, both with multivessel lesions. Nevertheless, it is clear that the lesion in Patient 1 is more severe. It is obvious that different results of interventional treatment may be expected in such various groups of patients. Syntax scale (1) was developed to objectively assess the severity of lesion of coronary vessels and to assess localization, number of stenotic segments, their length, and presence of occlusion and bifurcation stenosis. The use of this scale allows to form and to study the groups of patients with multivessel coronary disease identical by severity: moderate (score < 16), severe (score ⩾ 16) and extremely severe (score ⩾ 28). Assessment of the severity of the coronary vessels lesion using the SYNTAX scale in patients shown on Figure 1 revealed that Patient 1 has the score of 54.5, and Patient 2 has the score of 12 only. In the present study we have analyzed PCI results in patients with average SYNTAX coronary lesion severity score of 16.9 points that corresponds to severe multivessel lesion.

MATERIAL AND METHODS

The immediate and long-term results of PCI in 37 patients with multivessel coronary disease were analyzed. Coronary angiography was performed by Judkins method (5) using the biplane cardiovascular angiography equipment, “Integris BH 3000”, PHILIPS. The multivessel lesion was defined as the presence of hemodynamically significant stenosis (>50% of diameter) in two or three large epicardial arteries (the LAD, the right coronary artery and the left circumflex artery) (6, 7). The assessment of the complexity of coronary arteries stenoses by SYNTAX scale was judged as an objective criterion of the severity of coronary lesion. The following parameters were assessed: localization, number and length of the lesions, presence of occlusion and bifurcational

stenosis, calcification, and thrombosis. The score ⩾ 16 suggested presence of severe lesion. All patients underwent PCI with stenting. Main clinical characteristics of patients are shown in Table 1.

Table 1. Clinical characteristic of patients (n=37)

Variable	Absolute value, %
Age (years)	55,78±9,66
Male gender	34 (91,9%)
LVEF	52,37%±13,44
History of MI	24 (64,86%)
Unstable angina	12 (32,4%)
Arterial hypertension	29 (78,4%)
Diabetes mellitus	2 (5,4%)

Male patients prevailed in the presented sample (91.9%) The mean value of global myocardial contractive capacity was within the normal limits (52.37%±13.44). The majority of patients had history of MI (64.86%). The number of patients with signs of unstable angina was 32.4%; 78.4% patients had arterial hypertension; 5.4% patients had diabetes mellitus.

In addition to commonly accepted angiographic characteristics we have objectively assessed the severity of coronary lesion by SYNTAX scale in all patients (Table 2).

Table 2. Angiographic characteristic of patients (n=37).

Variable	Value, %
Number of vessels with "surgical grade" lesion	2,48±0,5
Lesion severity by SYNTAX scale	16,9±6,12
Vessel occlusion	20 (54%)
Number of implanted stents	2,94±0,9
Average length of the stented segments	61,4±19,6 (мм)
Average diameter of implanted stents	3,32±0,28 (мм)
DES alone implanted	15 (40,54%)
BMS alone implanted	11 (29,7%)
DES+BMS combination	11 (29,7%)

The average SYNTAX score in this sample of patients was 16.9±6.12, while the score ⩾16 allows to assign a patient to the group with severe lesion (1). The SYNTAX coronary stenosis severity score >20 points was revealed in 43.24% patients (n=16), which suggests objectively confirmed complexity of stenoses of the coronary arteries in this population. The number of vessels with hemodynamically significant lesion was 2.48±0.5; in more than half of cases - 54% (n=20) there was an occlusion of one or two coronary arteries. The average number of implanted stents was 2.94±0.9 per patient; drug- eluting stents were implanted in 40.5% of patients (n=15); bare metallic stents were implanted in 29.7% patients (n=11), and the combination of drug eluting and bare metallic stents was used in 29.7% patients.

The early results of PCI were assessed as follows: Immediate success of the intervention: residual stenosis less than 10% without such complications as death, MI and CABG.

The long-term outcomes were evaluated on the base of clinical data and the results of coronary angiography. Clinical status of patients and the results of stress-test were analyzed.

Statistical analysis was performed using ANOVA, correlation was assessed using Pearson's methods by means of STATISTICA for Windows, Stat. Soft, Inc., 1984-2001.

RESULTS AND DISCUSSION

PCI was successful in 97.5% of cases, 116 out of 119 stenoses were stented, recanalization of 3 chronic occlusions failed. The complete myocardial revascularization was achieved in 75.67% of cases; there were no death, MI and necessity in CABG during hospitalization.

The long-term follow-up after PCI (9.2±3.4 months) was achieved in 27 patients (72.9%). In the long-term after PCI 70% of patients (n=19) who had multivessel coronary disease at baseline, had no angina pectoris and the results of their stress-test were negative (Figure 2).

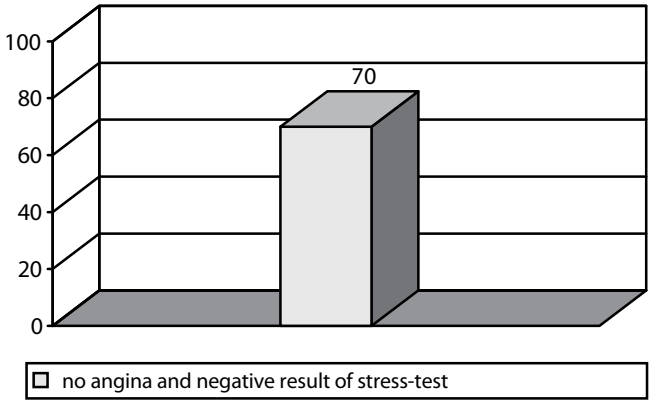

Figure 2. Long-term outcomes after PCI in patients with multivessel lesion.

The restenosis confirmed by angiography in the site of bare metallic stent implantation was observed only in 1 case (3.7%) that required the repeated intervention at the site of target stenosis; in other cases the signs of angina were caused by the incomplete myocardial revascularization. Thus, control examination revealed only one patient (3.7%) with unstable angina, while at baseline the clinical signs of this condition were noted in 32.4% of cases ($p<0.05$).

The reported data suggest that PCI performed in patients with multivessel coronary disease is a safe and effective method for myocardial revascularization.

Thus, the possibility of effective complete or partial myocardial revascularization in patients with objectively severe stenoses of coronary vessels is determined.

Clinical case

Elective coronarography was performed in a 70-year-old patient suffering from FC II exertional angina

(with no history of MI) and type II diabetes mellitus and having positive result of stress-test. The multivessel coronary disease achieving "surgical grade" was diagnosed (Figure 3).

The severity of lesion of the coronary vessels was assessed as SYNTAX score of 22, which corresponds to objectively severe lesion of the coronary vessels. The patient underwent PCI; 6 stents were simultaneously implanted (3 drug-eluting stents and 3 bare metallic stents). Angioplasty was successful, the complete myocardial revascularization was achieved; there were no complications.

Seven months after PCI the patient had no clinical signs of angina, the result of stress-test was negative. The conservative therapy is continued.

CONCLUSIONS

1. PCI is a safe and effective method of complete or partial myocardial revascularization in patients with severe (SYNTAX score ⩾16) multivessel coronary disease.
2. SYNTAX scale allows to assess adequately the efficacy of revascularization in the group of patients IDENTICAL by severity of coronary arteries stenosis.

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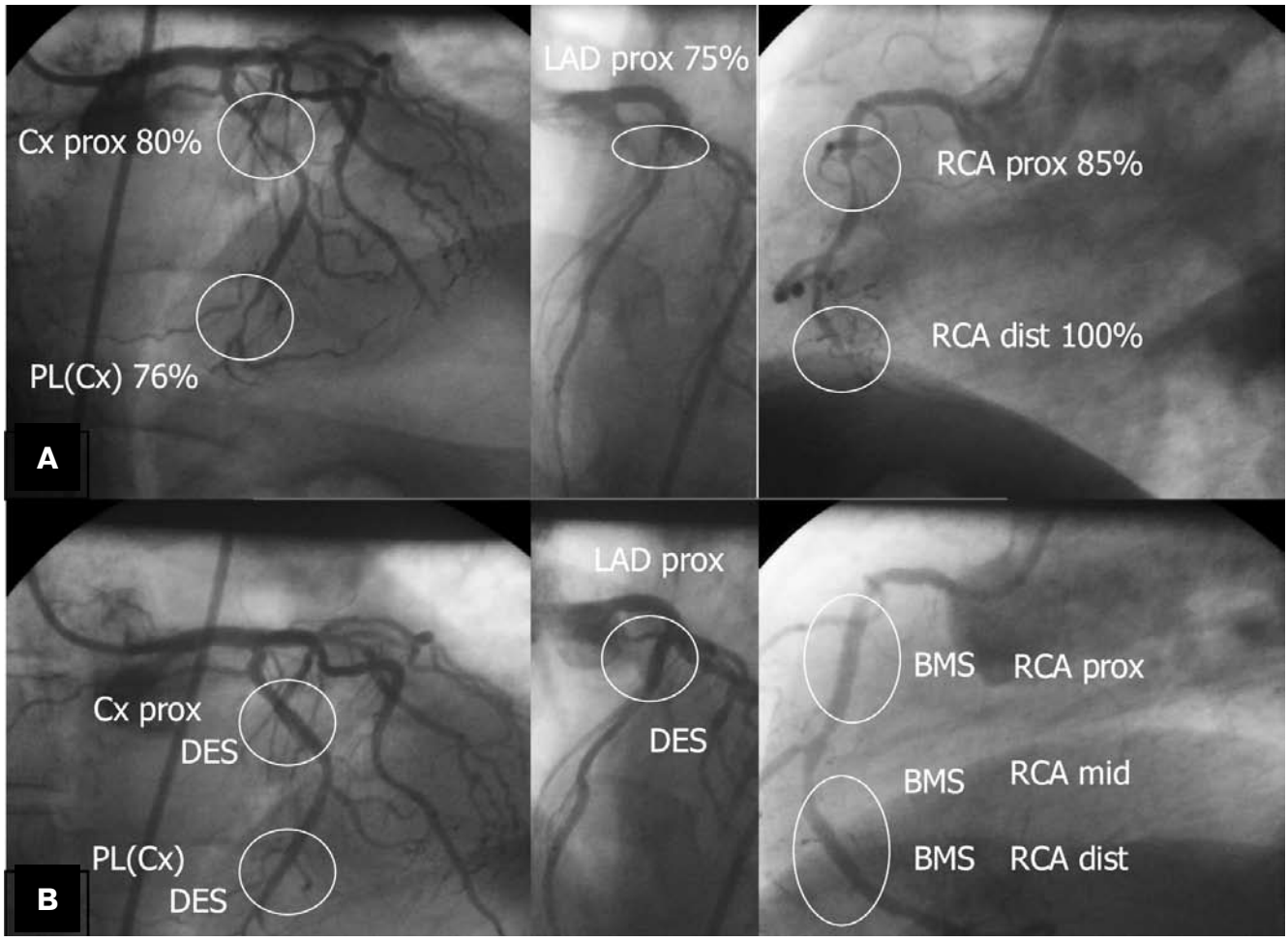

Figure 3. Clinical case, baseline coronarography data (A) and immediate PCI outcome (B).

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Year 2008. What Do We Know about Bifurcation Lesions (Review)

V.I. Ganiukov[1]

Novosibirsk Regional Clinical Cardiology Dispensary, Novosibirsk, Russia

According to Reimers et al. 2000 (1) a lesion can be defined as bifurcation if the stenosis is localized in a main branch in the immediate proximity to or at a place of a side branch origin, and coronary angioplasty may lead to occlusion of the latter. Taking into account Reimers's definition it becomes clear that not every bifurcation lesion (BL) requires special techniques of endovascular surgery to be used and in this case percutaneous coronary intervention (PCI) is the same as for the treatment of stenosis in the segment of vessel without side branch. Therefore, the definition given by Lefevre, 2007 (2) is better to be used for practical purposes: BL is a stenosis of a main branch with an involvement of a major side branch. What is a major side branch? Is it a vessel supplying the significant part of viable myocardium? Is it a branch measuring ⩾2 mm in diameter or a branch that is not large in diameter but lengthy? Maybe this is a small single vessel supplying the viable myocardium, while the main artery supplying it is occluded? Major side branch is a branch that you do not want to lose and wish to protect."

Percentage of PCIs performed for BL achieves 22% of the total number of the coronary interventions (3-6). The authors from Rotterdam (3) have noted the increase in the number of PCIs performed for BL from 8% up to 16% over one year due to introduction in the practice of the drug eluting stents (DES). Nevertheless, despite a progress in the interventional cardiology all authors continue to attribute BL interventions to one of the most technically demanding percutaneous coronary interventions, and restenosis rate in a side branch cannot be brought to less than 20% in the majority of the studies despite of DES use (2, 7, 8).

To date, some of the theoretic questions concerning BL classification and treatment are resolved, the great number of methods of bifurcation stenting is developed. The subjects remaining open to be settled are as follows: development of bifurcation stent, determination of the best method of elective use of two stents, determination of the best method of side branch stenting in bail-out case during "provisional T-stenting".

[1]Address for correspondence:
Russia, 630047, Novosibirsk,
Ul. Zalesskogo, 6, bld. 8,
Tel. 007 383 216-55-37
Fax 007 383 226-29-71,
e-mail: ganyukov@mail.ru
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SOLVED QUESTIONS (BASED ON SCIENTIFICALLY SOUND DATA OR EXPERT CONSENSUS)

1. Classification

European Bifurcation Club recommends classification given by Alfonso Medina et al., 2006 r. (9) for use in clinical practice and researches (Figure 1). According to the authors' conception, at first the proximal part of the main branch and the distal part of the main branch are subsequently assessed, then the side branch is analyzed. Stenosis degree at these bifurcation sites is classified as follows: stenosis <50% corresponds to the lesion degree of «0», stenosis >50% corresponds to the lesion degree of «1». Finally, bifurcation characteristics by Medina's classification looks like a set of three numbers. For example: combination 1, 0, 1 means that there is a BL with stenosis of the proximal part of the main branch and stenosis of the side branch more than 50% and simultaneously there is no stenosis or insignificant stenosis (<50%) of the distal part of the main branch. The advantages of Medina's classification are the simplicity of usage and a sufficiently comprehensive nature. Nevertheless, some features of BL require additional assessment after use of Medina's classification (angle of side branch, stenosis length and diameter of vessels involved in bifurcation, calcification).

Lefevre et al. (10) divide BL into Y-stenosis, when an angle between a side branch and the distal part of the main branch is <70° and T-stenosis, when this angle exceeds 70°. It is worth noting that after insertion of the guidewires T-shaped BL is often transformed into Y-shaped BL and it facilitates technical performance of this procedure. The differences between these two types of bifurcation are that in an Y-shaped BL the access to the side branch is relatively simple, but the risk of plaque dislocation is high, while in T-shaped BL the introduction of devices into the side branch is always difficult, and snow plough effect is less pronounced. Also, stent implantation into the side branch of T-shaped bifurcation allows to reinforce completely the ostium of the side branch, while stenting of Y-shaped BL is associated either with a necessity to place a part of stent in the lumen of the main vessel or with incomplete reinforcement of the part of the side branch ostium. Based on the TULIPE study data (11), Yves Louvard (2) insists that the value of angle mentioned above is a single predictor of side branch occlusion, rejecting such parameters as the side branch origin from the main artery stenosis, small diameter of the side branch, and ostial lesion of the side branch.

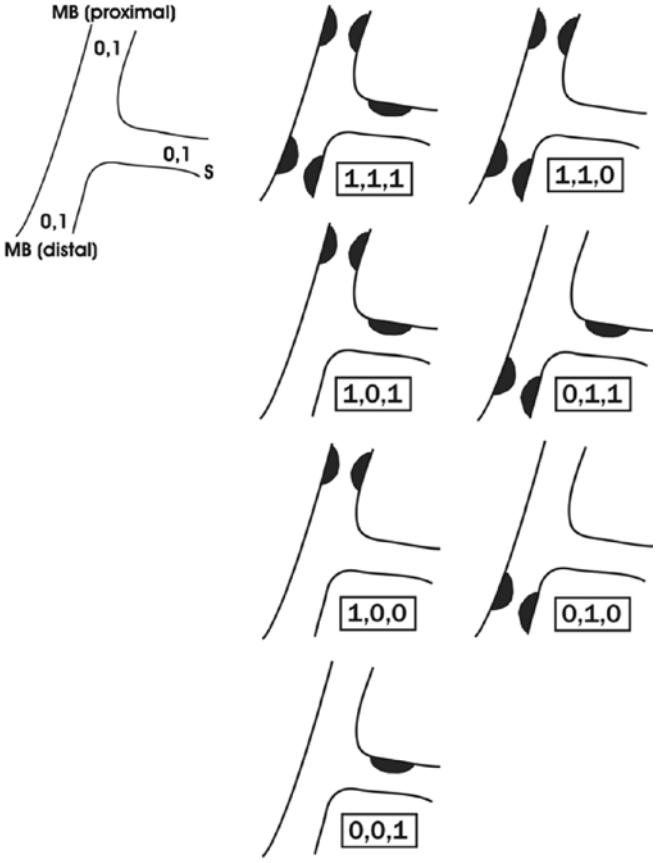

Figure 1. Medina's classification of bifurcation lesions MB (proximal) –proximal part of the main branch, MB (distal) –distal part of the main branch, SB – side branch. In BL the proximal part of the main branch and the distal part of the main branch are subsequently assessed, then the side branch is analyzed. Stenosis degree at these bifurcation sites is classified as follows: stenosis <50% corresponds to the lesion degree of «0», stenosis >50% corresponds to the lesion degree of «1». Finally, bifurcation characteristics by Medina's classification look like a set of three numbers. (Source: Medina A., Surez de Lezo J., Pan M. A new classification of coronary bifurcation lesions. Rev. Esp. Cardiol., 2006, 59, 149-153.)

2. Use of DES improved the outcomes in historical cohort of patients who received bare metal stents during BL interventions.

The first study analyzing the influence of the new stents on the outcomes of interventions in bifurcation stenosis was performed by Colombo et al., 2004 (12). In a group of patients with implantation of two drug-eluting stents the angiographic intervention success was 93.6%; at 6 months the total rate of restenosis in all segments of bifurcation was 25.7%, repeated target lesion revascularization was performed in 17.6% of cases. In conclusion, the authors emphasized that the obtained results improved the historical data of use of bare metal stents for BL. Hoye et al. (13) studied the results of different methods of bifurcation stenting in 248 patients. Sirolimus- and paclitaxel-eluting stents were used. At 6 months the rate of major adverse cardiac events (MACE) was 6.3% and 14.2% for each stent group, respectively, and TLR did not exceed 4.3% and 13.2%. The number of MACE shown in this study was significantly lower than that in historical cohort of patients implanted with bare metal stents during BL intervention.

Table 1. Comparative analysis of bifurcation stenting using bare metal stents (Yamashita et al.(14)) and drug-eluting stents (Ge et al.) (56)).

		Yamashita et al.(14)	Ge et al. (56)
One stent	MACE	38,0%	5,4%
	TLR	36,0%	5,4%
	Main branch restenosis	33,3%	4,8%
	Side branch restenosis	33,3%	4,8%
Two stents	MACE	51,0%	13,3%
	TLR	38%	8,9%
	Main branch restenosis	38,5%	9,6%
	Side branch restenosis	51,3%	13,5%

Taking into account the lack of information about randomized studies comparing drug-eluting stents with bare metal stents in BL intervention, let's appeal to analysis performed by Latib and Iakovou, 2007 (16) where the study by Yamashita, 2000 (14) was compared with the study by Ge, 2005 (15) (Table 1). Yamashita et al. (14) studied the outcomes of implantation of bare metal stents in 92 patients. The strategy of using one stent and dilatation of its strut into the side branch (n=39) and stenting of two branches (n=53) was implemented. Ge et al. (15) also used one (n=57) and two (n=117) drug-eluting stents in 174 patients. Table 6 demonstrates the advantages of drug-eluting stents. The long-term results after implantation of the new stents are better regarding both MACE number and number of restenosis and repeated target lesion revascularization.

Thus, the presented advantage of drug-eluting stents over bare metal stents in bifurcation stenting substantiates the conclusion about a necessity of routine use of the new generation stent for BL treatment.

3. Provisional T-stenting strategy (the main branch is stented, the endograft in the side branch is implanted only if necessary) must be used widely because the outcomes of implantation of one DES in BL is better than the use of two stents.

Pan et al., 2004 (17) studied the results of «simple» (n=47) and «complex» (n=44) strategy of the bifurcation stenting. Colombo et al., (12) randomized 86 patients into the group with two stents implantation (n=63) and into the group with one stent implantation (n=22) in bifurcation lesion. In the latest NORDIC trial Steigen et al., 2006 (18) compared the results of «complete stenting» (n=206) with stenting of the main branch only (n=207). Drug-eluting stent were used in all studies. None of authors showed the significant advantage of the strategy where two stents are used, neither by clinical outcomes nor by angiography data (Table 2). In NORDIC trail only the tendency towards the lower restenosis rate was reported for the first time when a «complete stenting» was used (16% versus 22.5%, p=0.15).

Table 2. Long-term outcomes of three studies (12, 17, 18) of drug-eluting stent use («complete stenting» strategy versus stenting of the main branch only in bifurcation lesion).*

Study	Strategy	MACE	Restenosis**	TLR
Colombo (12)	"Complete stenting"	19,0%	28,0%	9,5%
	One stent	13,6%	18,7%	4,5%
Pan (17)	"Complete stenting"	11,4%	20,0%	4,5%
	One stent	10,6%	7,0%	2,1%
Steigen (18)	"Complete stenting"	3,4%	16,0%	1,0%
	One stent	2,9%	22,5%	1,9%

* none of the studies revealed any significant differences between obtained parameters;
** main branch restenosis + side branch restenosis; MACE – major adverse coronary events; TLR – target lesion revascularization.

Thus, the results obtained from these studies substantiate the provisional T stenting method with implantation of one stent in the main branch when using drug eluting stent in majority of patients with BL. At the same time, in the opinion of experts of European Bifurcation Club (19), elective implantation of two drug eluting stents may be considered in case of true bifurcation stenosis (1,1,1; 1,0,1; 0,1,1), particularly, if the length of the side branch lesion exceeds 2-3 mm.

Nevertheless, the latest unpublished results of the CACTUS trial reported by A. Colombo in "Late breaking trials" section on PCR-2008 (20) differ from that presented above. In the CACTUS trial, patients with true bifurcation lesions were randomly assigned either to CRUSH group (n=177) or to provisional T-stenting group (n=173). Accordingly, the patients with BL from CRUSH group were implanted with two Cypher stents by Crush method, and the patients with BL from provisional T-stenting group were treated by provisional T-stenting method using one Cypher stent or two stents, if needed. The indication for implantation of the second stent in the provisional T-stenting group were the special angiographic findings related to the side branch: 1) TIMI <3; 2) residual stenosis >50%; 3) dissection more significant than type B. The second stent was implanted into the side branch in 31% cases. The long-term results were evaluated at 6 months. Binary restenosis rate was comparable in both groups (main branch restenosis 4.6% in CRUSH group and 6.7% in provisional T-stenting group, p=0.6; side branch restenosis 13.2% and 14.7%, respectively, p=0.9). Clinical results of treatment did not differ between groups. At the end of the follow-up period the number of myocardial infarction was 0.5% per group; the rate of death was 0% in CRUSH group and 0.5% in provisional T-stenting group, p=0.49; target lesion revascularization was performed in 6.2% and 6.8% of cases, respectively, p=0.83. In-stent thrombosis rate was 1.7% and 1.1%, respectively, p=0.62. In summary, A. Colombo concludes: the implantation of two stents has no advantages, however but it should not be punished and if you need to implant two stents you may do it with safety guaranteed. Despite of these encouraging statements by the author of the CRUSH method, a general practitioner who has "State mentality", of course, and knows arithmetic methods indeed, will undoubtedly choose less expensive approach out of two stenting methods leading to similar outcome. Thus, in my opinion, this study is an additional stimulating step towards the wide use of provisional T-stenting.

4. MADS classification of bifurcation stenting proposed by European Bifurcation Club (19) contains the most complete description of all current methods of bifurcation stenting.

The particular feature of this classification consists in the division of all technical methods of BL stenting into two categories: traditional stenting and inverted stenting (reverse stenting with changed sequence). With traditional stenting the first stent is implanted into the proximal part of bifurcation, or into the main branch with crossing of the side branch ostium, or in such a way that ensures free access to the main branch, while the access to the side branch is realized with crossong of stent strut. With the use of inverted stenting methods, the first stent is implanted through the proximal segment of the main branch into the side branch via ostium of the distal segment of the main branch or in such a way that ensures free access to the side branch, while the access to the main branch is realized via stent strut. Other principles of division of the BL stenting methods in the proposed classification are the number of implanted stents and the location of the first implanted stent.

In this review, it would be interesting to give more detailed information about technique and idea of two relatively new and currently widely used methods of bifurcation stenting: TAP (T and protrusion) and Minicrush. TAP is a T-stenting with a little protrusion of the second stent into a lumen of the first stent implanted into the main branch, and final "kissing balloon" dilatation should be performed in such a way that balloons would be blown off simultaneously to exclude a mashing of protruding part of the side branch stent into the side branch ostium. The principal idea of this method is ensuring of complete reinforcement of the side branch ostium. The method in the MADS classification is also proposed as an inverted TAP version (Fig. 2). Minicrush is a method where a stent is placed into the side branch in such a way that its proximal part protrudes into the main branch (as with standard CRUSH method). After implantation into the side branch the balloon catheter and guidewire are removed from the side branch. The next stage consists in the implantation of a stent into the main branch, with this stent crushing the part of stent protruding into the lumen of the main vessel. The difference between minicrush and standard CRUSH method is a degree of stent protrusion into the main branch. When CRUSH method is used, the proximal part of stent protrudes into the main branch more significantly than in minicrush method, where after crushing the protruding part of stent may not cover completely the ostium of the side branch.

Besides the general ideology of CRUSH methods family – complete reinforcement of the ostium of the side branch – minicrush method is intended for the easier access of the guide and then of the balloon catheter into the side branch via stent strut to perform a final "kissing balloon" dilatation.

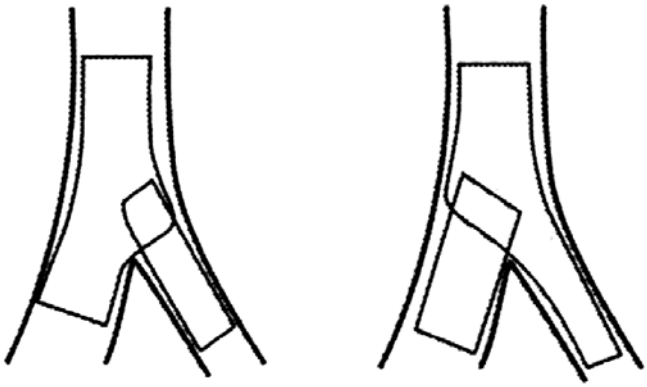

Figure 2. TAP bifurcation stenting (T and protrusion).

5. Bifurcation stenting by provisional T-stenting and any technical approach using two stents should be completed with kissing balloon dilatation.

Final "kissing balloon" dilatation is proposed for more reliable adherence of stents to the walls of bifurcation and for correction of possible deformation of stent implanted into the main branch. In spite of the fact that there are no randomized studies determining the place of final "kissing balloon" dilatation in PCI for BL, the experts of European Bifurcation Club recommend its use in stenoses 1,1,1; 1,0,1; 0,1,1 or in interventions where two or more stents are used (19).

The technical innovations concerning final "kissing balloon" dilatation involve the reports on the advantages of two-stage procedure over one-stage version (Figures 3 and 4).

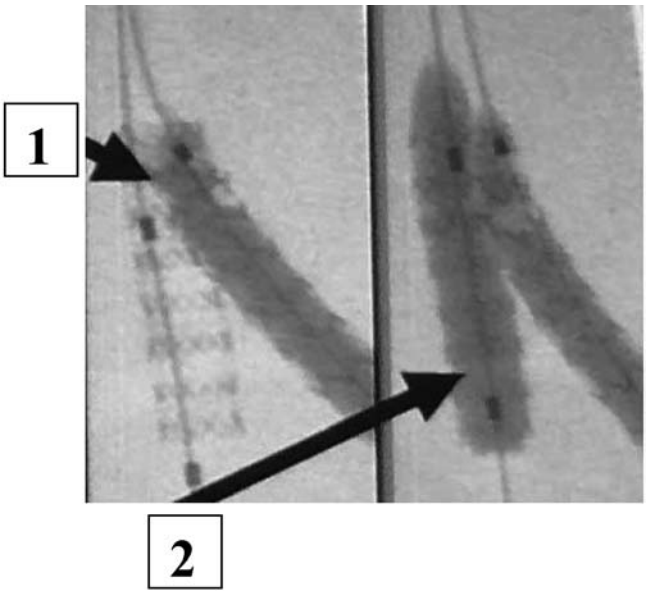

Figure. 3. Two-stage final "kissing balloon" dilatation. (After implantation of two stents, for example, by CRUSH method and placement of balloon trough the stent strut into the side branch the following steps are performed: firstly, 1 – dilatation of the stent strut with the balloon placed into the side branch, high-pressure balloon is used, inflation pressure is 20 atm. Then, 2 – inflation of balloons in the main and side branches is simultaneously performed at pressure of 10 atm).

Studies on vessel models (21) showed that the use of the two-stage final "kissing balloon" dilatation has an advantage over usual one-stage method due to provision of larger surface of entrance into the side branch (Figure 4).

OPEN SUBJECTS IN ENDOVASCULAR TREATMENT OF BIFURCATION LESIONS

1. Development of special bifurcation stents.

The disadvantages associated with BL stenting using bare metal stents dictate the necessity to develop bifurcation stents. Impossibility and difficulties of guidewire and balloon placement into the side branch through the stent strut; cylindrical form of usual stents

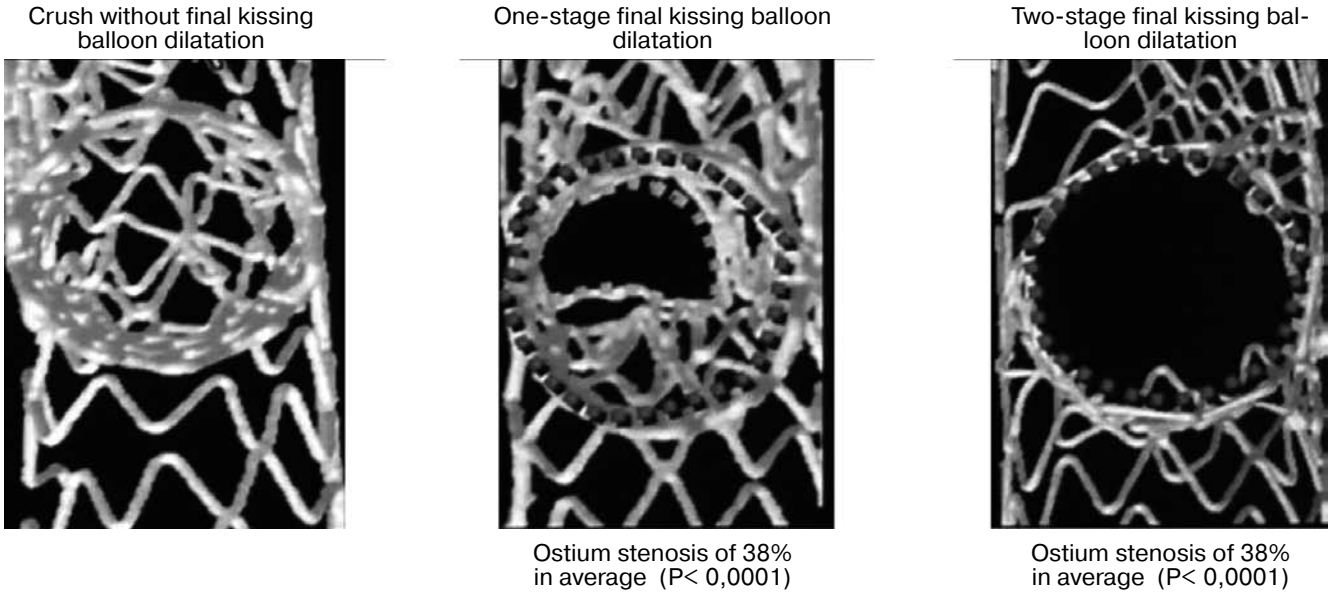

Figure 4. Comparative analysis of one-stage and two-stage final kissing balloon dilatation in vessel model studies.

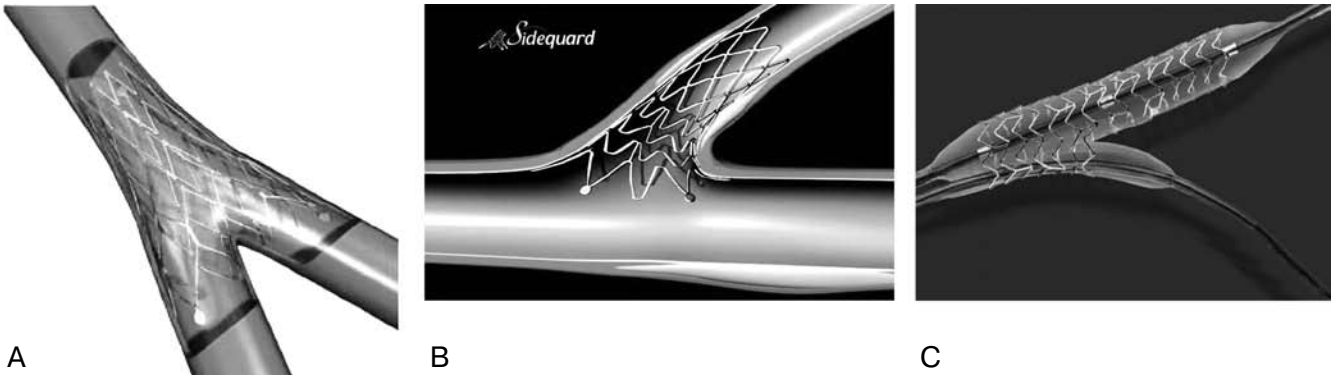

Figure 5. A. Axxess™ bifurcation stent (Devax, Inc.). (Source: Verheye S., Trauthen B. Axxess™ Biolimus A9® eluting bifurcation stent system. EuroIntervention, 2007, 2, 506.)
B. Sideguard™ stent (Cappella). (Source: Abizaid A., Costa J., Alfaro V. et al. Bifurcation stents: giving to Caesar what is Caesar's. EuroIntervention, 2007, 2,.518.)
C. Bifurcated stent Multilink Frontier (Abbot Corp.) (Source: Abizaid A., Costa J., Alfaro V. et al. Bifurcated stents: giving to Caesar what is Caesar's. EuroIntervention, 2007, 2,518.)

making difficult stent expansion in generally cone-shaped bifurcation; imposition of stents over each other with excessive "metallization" of the intervention site increasing restenosis risk are only a part of problems associated with the use of conventional reinforcement devices which persists in drug-eluting stents era as well. Taking into account the leading role of DES in bifurcation lesion interventions the development of drug-eluting stents seems to be perspective.

Axxess™ (Devax, Inc.) is the first nitinol self-expanding stent specially developed for bifurcation lesions and coated with bioabsorbable polymer eluting antiproliferative drug, Biolimus A9™. The indication for use of Axxess™ are Y-shaped BLs where angle B is <60˚ (22). The device is intended for implantation into the proximal part of bifurcation up to the carina and its V-shape guarantees the close adherence of the device to the vessel wall (Figure 5A).

Sideguard™ (Cappella) is a nitinol self-expanding stent intended for reinforcement of the side branch (23). Currently, it is a bare metal stent but in the future the metal surface of stent is planned to be coated with bioabsorbable polymer eluting an antiproliferative drug. The characteristic feature of this device and method of bifurcation stenting with Sideguard™ is the use of inverted stenting, when the stent is implanted firstly into the side branch and due to its design it closely fits to every part of the side branch ostium (Figure 5B).

The studies controlled by Abbot Vascular corporation are being carried out on animal models using SBAEECSS (side branch access everolimus-eluting coronary stent system) drug-eluting stent based on XIENCE V stent and using everolimus as an antiproliferative drug. The design and principle of use of the device are similar to that of Multilink Frontier stent (24) (Figure 5 C).

2. Determination of the best method of elective use of two stents.
T-stenting, T and protrusion, CRUSH, Culotte, Y-stenting, V-stenting and simultaneous "kissing" stents are discussed as a method of choice.

3. Determination of the best method of side branch stenting in case of bail-out when provisional T-stenting is used.
T-stenting, T and protrusion, Internal CRUSH, Culotte are discussed as a method of choice.

4. Whether use of DES for BL leads to the greater risk of in-stent thrombosis than BMS does? If yes, then how this risk may be reduced?
Bifurcation coronary lesions are an independent predictor of DES thrombosis (25, 26) in particular, if a stent is implanted during acute myocardial infarction (27). DES thrombosis rate depends on the number of the used stents. When one DES is implanted, this complication occurs in 0-1% of cases, if two DES are implanted, the incidence of this event is 0-5.5% (12, 13, 17, and 18). There are, and, probably, there will be no studies comparing correctly the number of in-stent thrombosis between BMS and DES patients, because of recently obtained data proving that the use of BMS in BL patients is unethical.

5. Accurate evaluation of significance of the ostial stenosis of the side branch by assessing fractional flow reserve (FFR).
Koo et al., 2005 (28) measured FFR by means of a guidewire placed into the side branch which was squeezed by a stent implanted into the main branch. After stent implantation in the main branch hemodynamical significance of the residual stenosis in the side branch was assessed. There was no lesion of the side branch with stenosis less than 75% and FFR value <0.75, and the functionally significant stenosis (FFR<0.75) was noted in 27% of cases only among the lesions with stenosis more than 75%. In the recent study, Koo et. al., 2008 (29) performed the treatment of residual stenosis in two groups of patients based on FFR assessment (FFR group, n=110) and angiography results (angiography group, n=110). In FFR group FFR assessment after provisional T stenting was performed in 91 patients. Twenty six patients with FFR<0.75 underwent balloon angioplasty after which FFR⩾0.75 was achieved

in 92% of them. At 9 months there was no difference in FFR values between patients who underwent balloon angioplasty and patients in whom this treatment option was not used (p=0.1). Functional restenosis (FFR <0.75) in FFR group was revealed in 8% of cases. Comparison of the number of unfavorable clinical outcomes in long-term follow-up between FFR and angiography groups has revealed the comparable results (3.7% and 4.6%, respectively, p=0.7). Authors' conclusion: the strategy of treatment of the residual stenosis of the side branch under the control of FFR levels leads to a good functional result. In spite of the presented encouraging data up to now there is no experts' consensus concerning the place of FFR in the assessment of significance of ostium stenosis of the side branch in PCI for BL.

CONCLUSION

Interventions in bifurcation coronary lesions still are one of the most technically challenging percutaneous coronary interventions.

On the up-to-date stage of development of interventional cardiology the postulates based on expert consensus and evidences obtained from research studies may be used in cardiologic practice as follows:

- Today Medina's classification is recognized as the simplest, easiest and the most comprehensive for use in clinical practice and research studies.
- The majority of bifurcation lesions may be treated by provisional T-stenting using one stent implanted into the main branch, but implantation of two stents should be planned according to the indications only (true bifurcation stenosis, side branch lesion length more than 2-3 mm).
- Bifurcation stenting by provisional T-stenting and any technical approach using two stents should be followed by final "kissing balloon" dilatation.
- Bifurcation stenoses should be routinely treated with drug eluting stents.
- MADS classification of bifurcation stenting proposed by European Bifurcation Club (19) contains the fullest description of all current methods of bifurcation stenting.

Introduction in the clinical practice of specially developed bifurcation stents with antiproliferative coating is believed to be very hopeful.

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THIRD RUSSIAN CONGRESS OF INTERVENTIONAL CARDIOANGIOLOGY
(Information Statement)

D.P. Dundua
Center of Endosurgery and Lythotripsy, Moscow, Russia

Third Russian Congress of Interventional Cardioangiology under the chairmanship of eminent scientists, physicians and organizers of healthcare Professors D.G. Iosseliani, A.F. Tzyb, A.P.Seltzovsky and V.A. Ivanov was held on March 24-26, 2008, in the Congress Hall of Moscow World Trade Center. The program of the Congress included sectional sessions on all main trends of modern interventional cardiology and angiology. In accordance with the tradition, each section was preceded by a plenary session with a summarizing lecture delivered by the leading specialists in the field of interventional cardiology and angiology, therapy and medical imaging. As previously, the priority was given to the problem of coronary angioplasty in patients with coronary heart disease. However, unlike the previous Congresses, this forum gave a broader coverage of recent achievements in endovascular treatment of congenital and acquired heart diseases, aneurysms of thoracic and abdominal aorta, peripheral and visceral arteries. Several sectional sessions and satellite symposia addressed the most thrilling topics of oncology, neuroradiology, obstetrics and gynecology, hepatology, nephrology and cell therapy.

Cochairman of the Organizing Committee of the Congress Professor David Iosseliani

About one thousand of specialists took part in the work of the 3rd Russian Congress of Interventional Cardioangiology. One hundred seventy seven presentations from over 60 cities of Russia and other countries were read within the framework of scientific program of the forum. The geography of countries and regions represented significantly enlarged. The specialists working in all parts of Russia and abroad, from the Far East to South America, brought the results of their work to the attention of colleagues.

Most papers were presented by the teams of Moscow City Center of Interventional Cardioangiology (director – Professor David Iosseliani) and Moscow Center of Endosurgery and Lythotripsy (director – Professor Alexander Bronshtein).

Greetings from the First Vice-Mayor of Moscow Liudmila Shvetzova

Well-known specialists from different countries delivered lectures on the most relevant topics of interventional cardioangiology. After the opening ceremony of the Congress the participants listened to the lecture of Academician E.I. Chazov dedicated to 35th anniversary of first intracoronary thrombolysis in a patient with acute myocardial infarction. The lecture of Jean Fajadet from France, presented the same day, seemed to bridge over the decades and was dedicated to of the the most relevant problems of today's interventional cardiology – the choice of drug-eluting stent during coronary interventions. A comprehensive review of the evolution of the methods of treatment of acute coronary syndrome was presented in the lecture by the outstanding American cardiologist C. Richard Conti. The lecture of a brilliant speaker, physician and researcher David R. Holmes, Jr. (USA) addressed the problem of interaction between atrial fibrillation, stroke and new methods of prevention of this dangerous complication. American interventional angiologist Barry Katzen gave the most impressive review of the history of percutaneous treatment of thoracic and abdominal aortic aneurysms. Alec Vahanian from France made a thorough analysis of different aspects of percutaneous aortic valve replacement.

Very interesting papers were presented by Andrejs Erglis (Latvia), Alexandre Abizaid (Brazil), W. Haberbosch (Germany), Augusto Pichard (USA), Rainer Rienmueller(Austria), Jan Kovac (Great Britain).

Dr. Andrejs Erglis (Riga, Latvia) during the break between the sessions

Department of Cardiovascular Surgery,
Center of Endosurgery and Lythotripsy.
Russia, 111123, Moscow,
Shosse Entiziastov, 62
Tel.+7 (495) 305-34-04
Fax +7 (495) 305-69-35
e-mail : david.doundoua@gmail.com

The sessions of the Congress addressed the most burning questions of endovascular surgery, such as the treatment of patients with multivessel and occlusive lesions of the coronary arteries, the technique of bifurcation stenting. The session dealing with the comparison of surgical and percutaneous methods of treatment of coronary heart disease passed in the spirit of collegiality. Russian and foreign colleagues shared their experiences with percutaneous angioplasty and stenting of the left main coronary artery, with the treatment of in-stent restenoses. There were fruitful discussions of the problems of carotid angioplasty, endovascular interventions for critical leg ischemia, vasorenal hypertension, endografting of aortic aneurysms, use of the newest methods of invasive and non-invasive heart and vessels imaging.

The lecture by Academician Evgueny Chazov

Medical companies – manufacturers of instruments and equipment – held their satellite symposia within the frames of the Congress: "Innovative Technologies in DES: New Horizons of Biocompatibility" (Medtronic); "Endovascular Closure of Pathologic Communications between Cardiac Chambers and Vessels" (EGAMed), "New Technologies with EPC Coating - Genous Stent. MoMa System for Proximal Protection" (RayMed); "New Generation DES: The Science is in Basis of Leadership" (Abbott Vascular), "The Newest Siemens Technologies for Interventional Radiology: Angiographic Computer Tomography" (Siemens AG). The representatives of the leaders of pharmacological industry, such as Bayer, Boehringer Ingelheim, B.Braun, General Electric Healthcare Nycomed, Merck Sharp & Dohme, Sanofi-Aventis, Tyco, SchwarzPharma organized issue-related satellite symposia for the discussion of different aspects of pharmacological therapy of atherosclerosis, arterial and venous thrombosis, heart failure, hypotensive and antianginal therapy, comparative safety of the use of contrast materials.

As mentioned above, the first plenary session had been opened by Academician Evgueny Chazov. In his lecture he described the first successful percutaneous intervention in a patient with acute myocardial infarction. Academician Chazov spoke about the evolution in the understanding of pathogenesis of acute coronary syndrome, about colossal changes which occurred during the last 35 years in the treatment of acute myocardial infarction. He emphasized that the success in the treatment of acute coronary syndrome depends equally on the appropriate organization of medical care, as well as on the use of the newest technologies and medications.

Sectional session held after this lecture in the same hall was entirely dedicated to the treatment of acute myocardial infarction and acute coronary syndrome. Dr. A. Erglis presented Latvian experience with the treatment of acute myocardial infarction. Modern approach to the problem allowed to perform revascularization during the acute stage of MI available virtually in all regions of the country. The participants listened with great interest to the presentations of A. Koledinsky from Moscow City Center of Interventional Cardioangiology on the use of cytoprotectors during mechanical revascularization in patients with AMI, S. Kozlov from Yekaterinburg comparing the outcomes of myocardial infarction depending on revascularization method. Interventional cardiologists from Krasnodar Regional Center, Samara, Khanty-Mansisk, Ivanovo, Moscow shared their experience with the treatment of acute coronary syndrome.

Dr. Alexandre Abizaid (Sao Paolo, Brazil) gives his view on the problems of modern cardiology

The nest session addressed the subject of coronary stenting and was called: «Drug-Eluting Stents: Comparative Evaluation of Long-term Results with the Use of Different Drug-Eluting Stents ». Dr. A.Abizaid (Brazil) spoke on the most burning problem of prevention of late stent thromboses. He emphasized that despite low rate of late thromboses after DES implantation their clinical consequences can be catastrophic. This life-threatening complication can be prevented by several means: through the optimization of stenting procedure, the use of second generation DES, the prolongation of the period of compulsory double antiaggregant therapy from 3-6 months to 1-2 years, more selective approach to the use of DES. In his lecture on long-term results of the use of drug-eluting stents Professor W. Haberbosch (Germany) showed that due to these stents the problem of restenosis is no more pressing. World experience suggests that the survival with the use of DES is not worse than that observed with bare metal stents. The results of a comparative analysis of long-term results obtained with different stents were presented in the talk of A. Babuhashvili from Moscow CELT clinic. The advantages of drug-eluting stents as compared to bare metal stents were demonstrated in the works from the leading Russian interventional centers headed by D. Iosseliani, A. Krylov, V. Kucherov, A. Mizin, I. Zyrianov, A. Samko.

In his lecture Jean Fajadet from Toulouse addressed the problem of the choice of drug-eluting stent. Basing on huge personal experience and extensive literature data the speaker demonstrat-

ed the advantages of drug-eluting stents over the «ordinary" ones, while emphasizing, that taking into account the high price of DES their use is justified in cases when these advantages are the most obvious. The speaker pointed out, that the design of metal stents is permanently being improved and the rate of restenosis with the use of contemporary stents is steadily declining, technical and pharmacodynamical features of new drug-eluting stents compare favorably with the first generation stents. All these, in the opinion of Dr. Fajadet, allow for the great optimism in what concerns the future of interventional cardiology.

The interview of Dr. Jean Fajadet (Toulouse, France)

The participants of a sectional session on coronary bifurcations stenting considered different approaches to bifurcation stenting. In their presentations Drs. A. Babunashvili (Moscow), V. Ganiukov (Novosibirsk), S. Kozlov (Yekaterinburg) emphasized that due to the use of drug-eluting stents and the improvements of the techniques of stenting it became possible to treat the lesions which recently were not even considered for percutaneous treatment. Different techniques of bifurcation stenting have been presented in the talks by D. Gromov (Moscow) and F. Mustafaoglu (Voronezh). The physicians from Orenbourg center headed by V. Demin described their experience with the use of bifurcation stent under IVUS control.

Recanalization of chronic coronary occlusions is one of the most urgent problems of interventional cardiology. Recanalization through retrograde approach is being used in the world for few years only. During the sectional session on this subject Russian interventional cardiologists A. Babunashvili (Moscow), A. Ossiev (Novosibirsk), Yu. Shamitov (Cheboksary), M. Maliukov (Lipetzk) and P. Lopotovsky (Moscow) spoke of their experience. It is delightful to note that our cardiologists successfully overcame the "last barrier" in interventional cardiology – chronic occlusion.

Sectional session dedicated to the treatment of in-stent restenoses was opened by Professor Augusto Pichard from Washington University. His highly informative and brilliantly presented lecture addressed different approaches to the treatment of in-stent restenoses after DES implantation. He noted that the arsenal of modern interventional cardiology allows to achieve success in this, seemingly dead-end situation. In their presentations A. Fedorchenko from Krasnodar Regional Center of Cardiology, A. Kononov from Moscow City Center of Interventional Cardioangiology considered different aspects of prevention, prognostics and treatment of in-stent restenoses.

The discussion of the treatment of patients with multivessel coronary lesions conducted with the participation of cardiac surgeons, was marked by the spirit of collegiality. The specialists from leading Russian centers – Cardiological Scientific and Production Clinical Complex, Moscow City Center of Interventional Cardioangiology, Multiprofile CELT clinic, Institute of Transplantology and Artificial Organs, Novosibirsk Institute of Cardiovascular Surgery – noted in their presentations that for a long time already the treatment of patients with multivessel coronary lesions stopped to be an exclusive surgical prerogative. Early and long-term results of percutaneous coronary interventions and surgery are generally comparable, however for certain categories of patients surgical or endovascular option may be preferable. The speakers emphasized that with the accumulation of experience and improvement of percutaneous methods it will be possible to offer radical treatment without surgical intervention to more patients.

Endovascular approach is more preferable in the treatment of patients with acute coronary syndrome, high surgical risk, with aortocoronary shunts lesions.

The program of the session on angioplasty of "unprotected" left main coronary artery included six presentations from several leading medical centers (A. Babunashvili with coauthors, Moscow; D. Iosseliani with coauthors, Moscow; A. Erglis, Riga, Latvia; T. Kislukhin with coauthors, Samara; T. Batyraliev, I. Pershukov, Voronezh; V. Chestukhin with coauthors, Moscow). According to the data of Russian specialists, at present cumulative experience of our invasive cardiologists exceeds 1000 such procedures. Active introduction of drug-eluting stents into clinical practice allowed to enlarge the indications for the stenting of the left main coronary artery. Good long-term results are achieved today with such complex lesions as bifurcation stenoses of the left main, combined lesions of the left main and two or three other coronary arteries. The lesion of the left main coronary artery is not always a target for coronary surgery. High effectiveness of drug coating in the prevention of intimal hyperplasia allows for a substantial improvement of clinical results of stenting and for a decrease of the necessity of repeated interventions.

Ending the review of talks on percutaneous coronary interventions, one has to mention several papers presented during the sections "Miscellaneous". Joint presentation from Moscow and Yekaterinburg contained comparative analysis of informational significance of the left ventricular ejection fraction and the indices of mechanical heart asynchrony in the evaluation of the effectiveness of revascularization. V. Ganiukov from Novosibirsk with his coauthors presented their view on the role of coronary angioplasty in patients with acute myocardial infarction with developing heart aneurysm. A Fedorchenko analyzed the influence of the factor of time interval from the onset of AMI to percutaneous revascularization on the state of left ventricular contractility. E. Sharabrin and coau-

thors from Nijny Novgorod spoke of high effectiveness of PTCA in patients with coronary artery disease and complex heart rhythm disturbances. Several speakers discussed the results of coronary interventions in elderly patients (V. Sukhov and coauthors, St. Petersburg), in patients with type 2 diabetes mellitus (N. Borovkov, N. Dezortseva , Nijny Novgorod) and metabolic syndrome (N. Solovieva and coauthors, St. Petersburg). The authors emphasized that invasive cardiology is the method of choice for myocardial revascularization for certain groups of patients. In the era of dominance of stents with antiproliferative or cytostatic coating it was interesting to listen the presentations on successful use of bare metal stents (N. Kobeshavidze, Moscow; T. Batyraliev, Voronezh), stents of cobalt-chromium alloy and dexamethazone-eluting stents (A. Panin, I. Zyrianov, Tiumen). The work of Yu. Artamonova and coauthors form Moscow Multiprofile CELT clinic, dedicated to randomized comparison of radial and femoral approaches for the achievement of active hemostasis during PTCA procedures deserves special mention. The authors highlighted the advantages and disadvantages of each approach, which in general are of equal value, and pointed out that the choice of approach has to be left to the operator.

Several sectional sessions as well as satellite symposium of EGAMed company addressed the problem of transcatheter management of acquired and congenital heart diseases. Professor Alec Vahanian highlighted the subject of endovascular treatment of aortic stenosis with his usual brightness and emotionality. It is really enjoying that the experience with endovascular closure of anomalous communications in adults and children is being actively adopted in Russia, which has been shown in the presentations from Volgograd, Yekaterinburg, Ivanovo, Moscow, Samara, St. Petersburg.

Dr. Augusto Pichard (Washington, DC, USA) and Dr. David R. Holmes, Jr (Rochester, USA) listen the lecture of Academician Evgueny Chazov

The authors of two presentations spoke about endovascular treatment of hypertrophic obstructive cardiomyopathy. A. Ossiev and his colleagues from Novosibirsk presented their large experience with successful transcatheter management of HOCM, with a special emphasis made of technical aspects of the intervention. B. Shukurov from Volgograd spoke about his group's experience with the treatment of this rare disease.

It is worth mentioning the most interesting lecture of Professor David Holmes, Jr from Rochester (USA) containing a comprehensive analysis of cause-effect relation between atrial fibrillation, stroke and transcatheter occlusion of left atrial appendage as a method of prevention of this severe complication. The speaker brightly and convincingly demonstrated the danger and social significance of atrial fibrillation complication and presented a really impressive potential of endovascular methods of its treatment.

A large part of the Congress agenda was dedicated to endografting of thoracic and abdominal aortic aneurysms. An acknowledged leader of endovascular surgery Barry Katzen from Maiami (USA) in his hour-long lecture presented a detailed overview of the history of aortic aneurysms endografting, making a special emphasis on the changing views on the method, the improvement of technology and technique of endografting. To date the indications for transcatheter treatment of aortic aneurysms are clearly defined. Long-term results of surgical and endovascular management are comparable, and in the group of elderly patients with high surgical risk endografting has real advantages over surgery. During the sectional session which took part after B. Katzen's lecture, five Russian specialists presented their experience. Z. Kavteladze and his colleagues from Moscow have the largest experience with the treatment of endovascular treatment of aneurysms in Russia. They considered different aspects of endografting of thoracic and abdominal aortic aneurysms. Two papers from Yekaterinburg presented by S. Chernyshev and colleagues are suggestive of a stepwise accumulation of experience in this field in our country.

The biggest amount of presentations made during the sectional sessions on angioplasty and stenting of peripheral, visceral and extracranial arteries came from Moscow Multiprofile CELT clinic. Along with already traditional works addressing endovascular treatment of the lesions of iliac, femoral and popliteal arteries, several talks (Z. Kavteladze, Moscow; I. Eroshkin, Odintzovo) were dedicated to the treatment of critical lower limb ischemia, of diabetic foot. The authors emphasized that critical ischemia of the lower extremities is a destiny of the severest category of patients with a lot of comorbidities, and sometimes suffering from polyorgan disfunction. All this, along with technical difficulties, related to the performance of the intervention, complicates the treatment and requires a perfectly organized team work of specialists in different fields. Angioplasty and stenting of iliac and femoral arteries were considered in the papers from Moscow Multiprofile CELT clinic ЦЭЛТ (S. Drozodv, K. Bylov). Z. Kavteladze spoke about the use of drug-eluting stents for the management of superficial femoral artery. O. Karakulov from Perm, A. Mizin from Khanty-Mansisk, A. Troitzky from Khimki, V. Demin from Orenburg, A. Karpenko from

Barnaul presented their own experience with endovascular treatment of the lesions of leg's arteries. Interesting presentations were issued from Moscow Multiprofile CELT clinic: Z. Kavteladze with his colleagues addressed the problem of vascular filters use for the prevention of embolic complications during peripheral angioplasty; A. Babunashvili spoke about the possibilities of recanalization of an occluded radial artery, and D. Kartashov presented the experience with endografting of iliac arteries aneurysms. A. Troitzky spoke about late complications of angioplasty of the iliac arteries.

The session on interventional phlebology generated a great interest. Ten presentations delivered during this session addressed different problems – from the prevention and treatment of deep veins' thromboses and pulmonary artery thromboembolism to endovascular management of bleedings, varicocele. Two papers (A. Zlatovratsky from Moscow and A. Mizin from Khanty-Mansisk) were dedicated to the use of rheolythic thrombectomy for the treatment of deep veins' thrombosis. S. Kapranov and his colleagues presented their view on the possibilities of endovascular treatment of Padget-Schroetter syndrome. O. Karakulov described the possibilities of interventional radiology in the treatment of massive pulmonary arterial thromboembolism.

A sectional session held during the first day of the congress addressed the problems of invasive radiology use in oncology. Within the framework of this session 15 papers from different hospital of Moscow, St.Petersburg, Vladikavkaz, Irkutsk have been presented. The presentation of A. Granov was dedicated to endovascular interventions used for the management of malignant tumors, while B. Dolgushin spoke about extravascular interventions in oncology. Other talks presented during this sessions addressed particular problems of oncourology, hepatology, gastroenterology, oncogynecology.

The subjects of high significance have been discussed during the sessions on neuroradiology (chaired by G. Belozerov, Moscow and V. Bondar, Khabarovsk), the methods of interventional invasive radiology in obstetrics and gynecology (chaired by S. Kapranov and B. Toloknov), cell therapy in cardiology (chaired by V. Mazaev and A. Konopliannikov).

Dr. Rainer Rienmueller (Graz, Austria) talks to the journalists

Two sectional sessions and one satellite symposium were dedicated to non-invasive imaging in cardiology and angiology. Informative lectures delivered by A. Pichard (Washington) and R. Rienmueller (Graz, Austria) were given over to the possibilities of multispiral computer and magnetic resonance tomography in the diagnostics of cardiovascular diseases, as well as in the evaluation of the results of coronary stenting. The speakers have pointed out, that the new diagnostic tools can significantly broaden the capabilities of early diagnostics of coronary artery disease, cardiac and vascular diseases. Equally important, newly developed methods permit to assess not only anatomical peculiarities of cardiovascular system, but also functional capacities of the heart, coronary blood flow and myocardial perfusion. In his lecture Professor Rienmueller drew the audience's attention to the possibilities of multispiral computer tomography in the evaluation of stenting results and emphasized that despite significant successes in primary diagnostics of coronary artery disease, the evaluation of coronary bed state after stenting is connected with certain difficulties, necessitates special staff training and special software. Basing on their own clinical material V. Glagolev and Z. Kavteladze demonstrated the capabilities of x-ray computer tomography in diagnostics and determination of the tactics of treatment of coronary artery disease, peripheral arterial and aortic lesions. The papers, presented by the groups of V. Ganiukov and N. Abramova, addressed different aspects of the use of multispiral computer coronary angiography.

The Congress' proceedings are published in the 14th issue of International Journal of Interventional Cardioangiology.

On March 26 the scientific program of the Congress was closed by a Plenary Session dedicated to the report of the Board of Russian Scientific Society of Interventional Cardiangiology and the election of new governing bodies of the Society. The President of the Society Vladimir Ivanov reported the results of 3-years activities and made his suggestions for the improvement of eventual work. The election resulted in the formation of a new Society Board which includes the leading specialists from all regions of Russia.

Zaza Kavteladze (Moscow) was elected new President of the Society.

The Vice-Presidents of the Society are: David Iosseliani (Moscow, Editor-in-Chief of International Journal of Interventional Cardioangiology, Alexander Arablinsky (Moscow) and Victor Demin (Orenburg).

Board members:

1. Abugov S. (Moscow)
2. Arablinsky A. (Moscow)
3. Babunashvili A. (Moscow)
4. Biriukov A. (Riazan)
5. Bobkov Yu. (Moscow)
6. Buzaev V. (Ufa)
7. Chebotar E. (Nijny Novgorod)
8. Chernyshov S. (Yekaterinburg)
9. Chestukhin V. (Moscow)
10. Demin V. (Orenburg)
11. Dolgushin B. (Moscow)
12. Dundua D. (Moscow)
13. Fedorchenko A. (Krasnodar)
14. Ganiukov V. (Novosibirsk)

15. Gromov A (Moscow)
16. Iosseliani D. (Moscow)
17. Ivanov V. (Krasnogorsk)
18. Kapranov S. (Moscow)
19. Karakulov O. (Perm)
20. Kavteladze Z. (Moscow)
21. Khamidullin A. (Kazan)
22. Kokov L. (Moscow)
23. Koledinsky A. (Moscow)
24. Kozlov S. (Yekaterinburg)
25. Krylov A. (Tomsk)
26. Kucherov V. (Moscow)
27. Kuzmenko V. (Kaliningrad)
28. Lopotovsky P. (Moscow)
29. Maltzev A. (Moscow)
30. Mazaev V. (Moscow)
31. Melnik A. (Irkutsk)
32. Mironkov B. (Moscow)
33. Mizin A. (Khanty-Mansisk)
34. Morozova E. (Penza)
35. Osiev A. (Novosibirsk)
36. Perevalov A. (Ijevsk)
37. Pershukov I. (Voronezh)
38. Plekhanov V. (Ivanovo)
39. Poliaev Yu. (Moscow)
40. Prokubovsky V. (Moscow)
41. Protopopov A. (Krasnoyarsk)
42. Samko A. (Moscow)
43. Semitko S. (Moscow)
44. Shakhov B. (Nijny Novgorod)
45. Sharabrin E. (Nijny Novgorod)
46. Shebriakov V. (Kupavna)
47. Shipovsky V. (Moscow)
48. Shukurov B. (Volgograd)
49. Sukhorukov O. (Moscow)
50. Sukhov V. (St. Petersburg)
51. Terekhin S (Krasnogorsk)
52. V.Volynsky (Moscow)
53. Yarkov S. (Moscow)
54. Zakharov S. (Moscow)
55. Zyrianov I. (Tiumen)

The next congress is scheduled to be conducted in 2011 in Moscow.

Record №7
Jubilee Session of Moscow Scientific Society of Cardioangiology marking the 65th anniversary of the President of the Society David G. Iosseliani
June 06, 2008

Chairmen: D.G. Iosseliani, L.S. Wann, V.S. Chekanov

The following presentations have been read over:

1. Coronary CT Angiography Should be the First Test Performed on Stable Patients with New Onset Chest Pain. L. Samuel Wann, Milwaukee, USA
2. Coronary Atherosclerosis and Pacing (Experimental and Clinical Trials). Valery S. Chekanov, Milwaukee, USA
3. Questions and discussion

Attendance: 321 persons.

Secretary of the MSSC N.A. Lonskaya