

Investigation of instent restenosis and stent thrombosis in patients after percutaneous coronary intervention

Doctoral Thesis

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INTRODUCTION

Cardiovascular diseases present the major cause of death in developed countries, but the incidence rapidly grows in developing regions as well. Unfortunately in our country together with the middle-European countries the prevalence and incidence is prominently high.

In the pathomechanism of cardiovascular diseases the atherosclerosis plays main role. In its treatment beside drug therapy the surgical and minimal invasive revascularisation of the coronary disease showed remarkable development in the last decades, decreasing significantly the mortality and morbidity of these diseases.

The first coronary intervention enriching the toolbar of cardiology was performed by Andreas Grünzig in 1977 which was a plain balloon angioplasty. The phenomenon of restenosis appeared with angioplasty in time, because the rate of occlusion and restenosis after balloon dilation together reached 40%. In the era of balloon angioplasty one of the major cause of restenosis was the elastic recoil, which means the restoration of the elastic fibre structure of the vessel wall after overextension. The other cause of restenosis was the intimal hyperplasia which developed due to the partial or complete rupture of intima and the consequential inflammatory response. The invasive treatment of restenosis or occlusion after balloon angioplasty was a big challenge, in many cases required bypass surgery.

The long-term efficacy was improved by the clinical use of two innovations: the uncoated metal endoprosthesis, bare metal stents (BMS) and the introduction of new, more effective antiplatelet drugs. BMS according to randomised trials almost halved (16-22%) the frequency of coronary restenosis compared to simple balloon angioplasty. The spread of bare metal stents the percutaneous coronary intervention (PCI)

became a recognized therapeutic option of ischemic heart disease due to the low rate of consequential occlusion and tolerable rate of restenosis. BMS owing to its durable radial force avoided both elastic recoil and the phenomenon of late negative remodelling. In pathomechanism of in-stent restenosis (ISR) the stent struts dilated by great pressure play important role by impressing the vessel wall which cause injury and provoke inflammation. Activated leucocytes increase the proliferation of media smooth muscle cells, their penetration into the intima and their production of extracellular matrix. Restenosis may appear in many clinical presentations ranging from stable angina to acute myocardial infarction.

Multicentre trials with high patient number verified many risk factors predisposing to restenosis: of comorbidities diabetes, renal insufficiency, and certain systemic diseases. There are certain lesion localisations at which occurrence of ISR is increased such as left main stem, ostium of right coronary, bifurcational lesions, in addition, chronic total occlusions and lesions requiring rotablation treatment due to their extreme calcification. It is a well-known fact that, the length of stenosis is directly proportional and the diameter of the dilated vessel is inversely proportional to the expected rate of ISR.

The challenge of ISR after BMS implantation launched the researches to get along cytostatic or immunosuppressive drugs to the place of intimal hyperplasia, inhibiting the development of ISR. This new stent type, the drug-eluting stent (DES) proved to be effective in prevention of ISR, the mid-term ISR rate remained under 10%. Its use despite its high price grow leaps and bounds, by their use the problem of patient with diabetes, long lesions, small vessel, total occlusions became solvable furthermore, by the invention of new bifurcational techniques the main stem stenosis is not the privilege of bypass surgery any longer. It showed good short- and mid-term results, in off-label indication of ISR treatment after BMS

implantation in comparison of the also effective intracoronary brachytherapy as well.

According to certain registries – in spite of significant spread of DES usage – the incidence of restenosis rather increased, as consequence of stent therapy of patients with significantly higher risk of restenosis and the use in even more complex lesions. As known, ISR in DES is presented in significant proportion as acute coronary syndrome, which enhances the problem of DES ISR. Still in current recommendations there is no clear guideline for DES ISR treatment.

The major disadvantage of first generation DES was the higher rate of thrombotic occlusion of the stent, the stent thrombosis (ST) at very late follow-up, beyond one year after implantation. In order to avoid this event long-term administration of double antiplatelet therapy is recommended. ST presents as a myocardial infarction of the region according to the localisation of the stent. This emerged the need for long-term follow-up to measure the rare adverse events and the long-term prognosis. According to the currently known long-term trials the frequency of ST in DES is not exceeding those in BMS, only its distribution expands to a longer period after implantation, even to more years. Pathological examinations showed that beside the beneficial antiproliferative effect on neointima, the endothelisation of the surface of DES is also delayed or impaired which increases the thrombogenicity of the stent. The aim of improvement of new DES generations was to eliminate this adverse effect. The innovation of new stent types and appearing of drug-eluting balloons (DEB) together with other innovations resulted in the further improvement of interventional cardiology in the successful therapy of cardiovascular diseases.

OBJECTIVES

My objective was to investigate the patient population of the coronary stent registry at the Semmelweis University Heart Center.

The registry contains the data of 886 consecutive patients after DES implantation and same number of patient treated with BMS between 1 January 2003 and 31 October 2006. Moreover drug eluting balloon (DEB) registry contains the data of 82 patients treated with between 1 June 2009 and 28 February 2011.

My research aims were to determine:

1. The long-term efficacy and safety of DES compared to BMS. Safety endpoints were the stent thrombosis (ST) and all-cause mortality rate. Efficacy endpoint was the clinically-driven target lesion revascularisation (TLR).
2. The safety and efficacy of the first generation DES in the treatment of BMS ISR in aspect of the following endpoints: the rate of target lesion and target vessel revascularisation (TLR and TVR), ST, myocardial infarction, all-cause mortality and the composite endpoint of these.
3. Secondary restenosis rate following successful treatment of primary restenosis of DES implanted into BMS ISR.
4. The safety and efficacy of drug-eluting balloons in treatment of BMS ISR and DES ISR. Examined endpoints were: TLR, MACE, all cause mortality, ST and myocardial infarction.

METHODS

Establishment of stent registry in Városmajor

A prospective DES registry was initiated by Semmelweis University Heart Center at the start of usage of first generation DES from 1st January 2003 in order to have the long-term follow-up data of DES. The patients of the registry represent a real world population with high risk of restenosis and stent thrombosis. Important DES indication was the diffuse II and III type BMS restenosis according to Mehran classification.

The control group was built from patients treated with BMS implantation. The size of the control group was the same by choosing a BMS implanted patient to each DES-implanted patient on the same day, randomly. The type of the stent was not randomised but left to the operators' discretion according to characteristics of the patient and treated coronary lesion. By 31th October 2006 we enrolled and followed 886 patients in both groups, 1772 altogether.

Special groups of patients

The stent registry is suitable to examine special subgroups. Such subgroup was the patients with BMS-restenosis treated with DES implantation.

The occurrence of secondary restenosis after successful treatment of primary restenosis in the patient group mentioned above was not studied by this time.

Establishment of DEB registry in Városmajor

We started a prospective DEB registry from June 2009. DEB treatment was used in case of 82 patients with in-stent restenosis until March 2011. Every patient, presented with acute coronary syndrome or stable angina, were enrolled to the registry. There were no exclusion criteria.

The ethical approval was provided by the Local Ethical Committee for both the DES and DEB registry which satisfied the Declaration of Helsinki. All patients signed written informed consent to their participation in the registries.

Registered endpoints

The primary endpoint was the ischemia-driven target lesion revascularisation (TLR). Further clinical endpoints were: target vessel revascularisation (TVR) and the safety endpoints: definite and possible stent thrombosis (ST), myocardial infarction (MI) and all-cause mortality. The major adverse cardiac event (MACE) was the composite endpoint of TLR, ST, MI and all-cause mortality. The clinical endpoints were defined according to the Academic Research Consortium.

Follow-up

The first clinical follow-up was performed at two months after the index procedure then once every six months at our outpatient clinic. If the patient did not turn up, telephone visit was done. If a patient could not be reached the National Insurance Fund was contacted in order to receive information about mortality, owing to this the mortality data were 100% available.

Statistical analysis

The comparison of the groups in case of continuous variables Student t-test or Mann-Whitney U-test were used and in case of categorical variables chi square or Fischer's exact test was used as appropriate. Survival curves were constructed by the Kaplan-Meier method to compare them Log-rank test was performed.

Propensity score analysis was performed in order to compare the result of restenosis versus de novo groups balancing their significantly different baseline characteristics. Patient selection was done based on propensity score analysis, and then the formed quintiles were fitted into a Cox-regression model.

A multivariable Cox proportional-hazards model was used to identify independent predictors of TLR and MACE in patients with DES or BMS ISR. A stepwise multivariate analysis was performed with the variables of patient's demographic data and type of the drug-eluting balloon, type of the arterial approach, angiographic pattern of the ISR (focal or diffuse/occlusive), furthermore type of the stent (BMS or DES) in which the ISR developed.

A p value <0.05 was considered statistically significant. Statistica 8.0 (StatSoft Inc, Ok, USA) and PASW 18.0 (IBM Corporation New York, USA) statistical software were used for all statistical calculations.

RESULTS

1. Safety of the first-generation DES compared to BMS during long-term follow-up

We analysed the follow-up data of 1643 patients enrolled in the Városmajor stent registry who were on dual – aspirin and clopidogrel - antiplatelet therapy. The number of patients treated with DES or BMS implantation was almost equal. In DES group Cypher (Cordis Corporation, Miami Lakes, FL, USA), Taxus (Boston Scientific, Natick, MA, USA) and first-generation Endeavour (Medtronic, MN, USA) stents were used. The type of implanted stent was not randomized, that caused several differences between the two groups. The patients of the BMS group were older and more treated with STEMI. In DES group there were more patients with treated hyperlipidemia and had bypass surgery and even more PCI previously. Numerous risk factors for restenosis were represented in high rate in DES group, such as restenotic lesion, left main and bifurcation lesion. The duration of aspirin and clopidogrel treatment was recommended even beyond one year in this time at our Clinic in case of low bleeding risk and in patients without any planned surgery. The mean length of follow-up was 16.6 ± 10.1 months.

Significant difference developed in term of survival favouring DES already in the first 2 months. Afterwards, this difference remained (Log-rank $p=0.005$). (Table 1)

Table 1 – *Mortality rate in DES vs. BMS group*

	6 months	12 months	18 months	24 months
DES group	4.4%	5.9%	7.5%	8.8%
BMS group	8.1%	9.8%	11.6%	12.6%

The rate of ST did not differ in the two groups. At 18 months ST was 3.0% in DES group and 4.0% in BMS group. (Log-rank $p=0.206$). Important to notice that while late and very late ST did not occur in BMS group, 0.8% very late ST was registered in DES group beside long dual antiplatelet therapy. (Table 2)

Table 2 - ST rate in DES vs. BMS group

	6 months	12 months	18 months	24 months
DES group	2.2%	2.2%	3.0%	3.0%
BMS group	4.0%	4.0%	4.0%	4.0%

The ischemia-driven TLR tend to be lower in DES group in spite of high restenosis risk lesions - like left main, bifurcation and in-stent restenosis lesions - occurring more frequently in this group. TLR was 8.7% in DES group, while 11.1% in BMS group after 18 months of follow-up (Log-rank $p=0.06$). (Table 3)

Table 3 - TLR rate in DES vs. BMS group

	6 months	12 months	18 months	24 months
DES group	3.8%	5.4%	8.7%	9.9%
BMS group	7.3%	9.8%	11.1%	11.8%

2. The safety and efficacy of first generation DES in the treatment of BMS restenosis

The patients of our registry treated with Cypher (Cordis Corporation, Miami Lakes, FL, USA) and Taxus (Boston Scientific, Natick, MA, USA) first generation DES were examined. In the restenosis group DES were implanted in diffuse BMS restenosis lesions according to Mehran classification type II and III.

In the control group first generation DES were implanted into high restenosis risk de novo lesions.

Myocardial infarction with ST elevation and cardiogenic shock were exclusion criteria, just like the allergy against clopidogrel or acetyl salicylic acid.

Two hundred and one patients were enrolled to restenosis group and 313 to the de novo control group. After patient selection according to the propensity score analysis still 201 patients were followed in restenosis group, while 108 in the control group. Clinical follow-up data were available for 95,9% of the patient. The mean follow-up time was 45.6 ± 21.5 months. Differences between the two groups disappeared, except for the higher BMI in patients of restenosis group and the higher rate of insulin dependent diabetes mellitus in de novo group.

In the selected patient groups the difference regarding the indication of the stent implantation has become equalized but the rate of left main and bifurcation lesions remained still higher in the de novo group. The average total length of the implanted DES was higher in the restenosis group compared to the de novo group.

The rate of the TLR was 10.4% versus 12.4% in the restenosis versus de novo group, respectively ($p=0.490$). The all-cause mortality rate was lower in the restenosis group (7.4% vs. 14.7%; $p=0.032$) while the rates of definite and probable stent thrombosis (1.9% vs. 1.6%; $p=0.708$) and myocardial infarction (7.9% vs. 7.8%; $p=0.551$) were not different between the two groups. Need to highlight, that no stent thrombosis have occurred after two years of follow-up. See detailed in Table 4.

Due to the probable bias of the two types of first generation DES it was important to investigate whether there was a different in aspect of clinical endpoints. No differences were found in either endpoint.

Table 4 - *Clinical outcome in the selected patients groups*

Endpoint	1 year		2 years		3 years		4 years		p
	ISR	de novo	ISR	de novo	ISR	de novo	ISR	de novo	
Mortality	1 (0.5)	2 (1.9)	11 (5.3)	6 (5.8)	14 (6.8)	11 (10.6)	15 (7.4)	15 (14.7)	0.032
ST	2 (0.7)	1 (0.7)	5 (1.9)	2 (1.6)	5 (1.9)	2 (1.6)	5 (1.9)	2 (1.6)	0.708
TLR	9 (4.5)	6 (6.4)	17 (8.7)	8 (8.7)	20 (10.4)	9 (9.8)	20 (10.4)	11 (12.4)	0.490
TVR	17 (8.8)	8 (8.0)	26 (13.7)	12 (12.3)	31 (16.7)	13 (13.4)	32 (17.6)	17 (18.2)	0.274
MI	6 (3.2)	3 (2.7)	12 (6.6)	7 (6.8)	14 (7.9)	8 (7.8)	14 (7.9)	8 (7.8)	0.551
MACE	26 (13.0)	16 (15.4)	42 (21.3)	22 (21.3)	51 (26.4)	25 (24.3)	52 (27.2)	32 (31.7)	0.777

The values are in format: n (%)

3. Development of secondary restenosis after successful treatment of primary restenosis of first generation DES implanted for BMS restenosis

In the patient population of Városmajor registry mentioned above the ischemia-induced TLR at 4 years of follow-up was 10.4% in the restenosis group of 201 persons and 12.4% in the de novo group of 108 persons. Repeated revascularisation was needed in case of 17 patients in restenosis group and in case of 9 patients of de novo group due to restenosis. The pattern of restenosis was not different in the two groups. After the successful treatment of ischemia-inducing restenosis the patients were followed for further 35.1±24.0 months. During

follow-up secondary DES restenosis causing ischemia developed in 29.5% of patients in restenosis group, while only in 16.7% in de novo group. The difference by low number of cases was not significant ($p=0.919$). ST had not developed in the second follow-up period.

4. The safety and efficacy of drug-eluting balloons in the therapy of instent restenosis

The 82 patients enrolled to the DEB registry had high cardiovascular risk: 36.6% had diabetes, 70.7% had previous myocardial infarction and 19.5% was presented with acute coronary syndrome. Restenosis developed 42.7% of the cases in DES and 57.3% of the cases in BMS. The most frequent pattern of ISR in 35.4% was diffuse intrastent restenosis. Diffuse intrastent, diffuse-proliferative restenosis and restenosis causing total occlusion was presented in 46.4% altogether. Successful dilatation was performed with drug-eluting balloons in 97.6% of cases. In 2.4% (2 cases) premature balloon rupture occurred. In additional 3 cases the angiographic result was not satisfactory: stent implantation was necessary due to dissection on the edge in 2 cases, and high pressure repeated balloon dilation was required due to significant residual stenosis in 1 case. Thus, the total success rate was 93.9%. In 73.2% of cases Pantera Lux balloon, 18.3% of cases Dior balloon, and 18.3% of cases SeQuent Please balloon were used. The follow-up length was 28.0 (25.0-30.3) months.

In aspect of clinical endpoints there were no differences between the types of balloons: TLR ($p=0.467$), MACE ($p=0.633$).

After DEB treatment of BMS and DES restenosis the need for repeated revascularisation in the treated lesion was 11.8% vs. 13.3% independently of the type of DEB. However, the follow-up data at 28 months show the continuous, linear increase of TLR after one year, as well, 21.1 % in BMS group and 29.0% in DES group. Though, there was no significant difference, the tendency of TLR was higher after DES ISR treatment at 28 months of follow up. (Table 5)

Table 5 - Results of clinical follow up at 12 and 28 months

	BMS-ISR (n=47)	DES-ISR (n=35)	BMS-ISR (n=47)	DES-ISR (n=35)	p
	12 months	12 months	28 months	28 months	
Mortality	4 (8.5)	1 (2.9)	6 (12.9)	4 (11.4)	0.828
ST	1 (2.1)	1 (2.9)	2 (4.5)	1 (2.9)	0.724
AMI	2 (4.4)	0 (0.0)	4 (9.5)	2 (8.8)	0.620
TLR	6 (13.3)	4 (11.8)	9 (21.1)	9 (29.0)	0.687
MACE	11 (23.4)	5 (14.3)	16 (34.7)	13 (40.8)	0.994
Control angio	14 (29.8)	14 (40.0)	24 (51.1)	18 (51.4)	0.211

The values are in format: n (%)

Two independent predictors of MACE and TLR was identified by multivariate Cox analysis. Diffuse or occlusive type of restenosis was a significant predictor of TLR with a hazard ratio of 2.070 (95% CI 1.047-4.093); p=0.036 and a significant predictor of MACE with a hazard ratio of 2.056 (95% CI 1.101-3.838); p=0.024. Renal insufficiency predicted independently a higher rate of TLR: hazard ratio 9.618 (95% CI 1.710-54.094); p=0.010 and a higher rate of MACE: hazard ratio 7.810 (95% CI 2.691-22.667); p<0.001.

CONCLUSIONS

First generation DES is safe beside dual antiplatelet therapy, the total number of stent thrombosis is not increased compared to BMS treatment. However, need to calculate on stent thrombosis after one year, which is quite rare in case of BMS. The consequential myocardial infarction and all-cause mortality rate was not higher than those registered in case of BMS treatment. First generation DES is safe and effective in the therapy of diffuse BMS restenosis. In case of prolonged administration of dual antiplatelet therapy the rate of stent thrombosis is not higher even at long-term follow-up, either is the rate of myocardial infarction and all-cause mortality compared to high restenosis risk de novo lesions. The rate of repeated ischemia-driven revascularisation in previously treated lesion or in the same vessel is just slightly higher, but difference is not significant. Altogether, the rates of adverse cardiac events are the same in both groups.

The rate of secondary restenosis after successful implantation of first generation DES into BMS restenosis is slightly higher than the rate of secondary restenosis in DES implanted into de novo lesions.

The use of paclitaxel-eluting balloon provide satisfactory result at 1 year in restenosis therapy both in BMS and in DES; the need for repeat revascularisation in the treated lesion was around 13%, in all DEB types. Nevertheless, follow-up data at 28 months show the continuous, linear increase of TLR after one year as well. The results may conclude that the long-term effectiveness of DEB is not enough in prevention of restenosis. Further clinical investigations are necessary with higher patient number and longer follow-up length.

LIST OF OWN PUBLICATIONS

Papers related to the dissertation:

1. **Berta B**, Jambrik Z, Kohar K, Szabo Gy, Ruzsa Z, Molnar L, Barczy Gy, Geller L, Becker D, Merkely B. (2014) Efficacy of Drug-Eluting Balloon in Patients with Bare Metal or Drug-Eluting Stent Restenosis. *Hellenic J Cardiol*, 55: 369-377. **IF: 0,785**
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1. Merkely B, Jambrik Z, **Berta B**. In-Stent Restenosis in Drug-Eluting Stents. In: Tintoiu IC, Popma JJ, Bae J-H, Rivard A, Galassi AR, Christian G (editors), Coronary Stent Restenosis. Romanian Academy Publishing House, Bukarest, 2011: 523-531.

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