Coronary Stenting using XIENCE V DES: General Problems, Perspectives (a Review)

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Endovascular methods of diagnostics and treatment have emerged already in mid-20th century, but only by the end of this century they rose to prominence in modern cardioangiology. With the advent of interventional methods of myocardial revascularization the possibilities of treatment of different forms of coronary artery disease were significantly extended (1). The development and the perfection of endovascular techniques allowed to replace one method of treatment by another due to the extension of indications for non-surgical treatment. From 1991 through 2001, the amount of interventional procedures for coronary artery disease in the USA has increased by 7 times, while of direct surgical interventions — by only 1,5 times(2).

Andreas R. Gruentzig can be named pioneer of angioplasty. In 1974 he was the first to invent a polymer balloon catheter with a fixed inflated diameter, and already by mid-1977 he has performed to first successful transluminal balloon angioplasty of a human coronary artery (3).

With the accumulation of experience, during the last decades, certain disadvantages of balloon angioplasty have been revealed. These disadvantages significantly influence the clinical course of the underlying disease.

In the last decade of the 20th century the leading place among all endovascular interventions on the coronary arteries went to coronary stenting.

The first implantation of an intracoronary stent in man was described by Sigwart et al. in 1987 (4). The use of high pressure during stent implantation in combination with antithrombotic pharmacological support has contributed to adequate blood flow restoration in the coronary arteries. Herewith the procedure of stenting was associated with low complication rate. Initially stenting was applied in cases with threatening coronary artery occlusion during transluminal balloon angioplasty (5). According to Garas S.M. et al. (6), the use of intracoronary stenting significantly decreased the rate of restenosis — from 50% to 20-30% — in comparison with balloon angioplasty. However it did not completely solve the problem of restenosis. Stent insertion has provided a high rate of immediate success and has allowed to avoid some serious complications proper to PTCA: marked dissections, acute coronary occlusions (7, 8, 9, 10). But the main advantage of stenting in comparison with balloon angioplasty consisted in a significant reduction of the rate of restenosis — recurrent narrowing of the lumen of a vessel previously subjected to angioplasty (11, 12). The reduction of restenosis rate by 10-15% after stenting as compared with balloon angioplasty was firstly proved in 1993-1994 in the STRESS (13) and BENESTENT (7) trials, that investigated the results of coronary stenting and balloon angioplasty. The trials have demonstrated an improvement of the results after stenting in comparison with balloon angioplasty. The authors concluded that after the procedure the diameter of a stented vessel was increased in a far greater degree than after PTCA, and in the long-term the stented coronary arteries preserved a bigger internal lumen; herewith the extension of their angiographic restenosis was decreased (31,6% vs. 42,1%, p=0,046 in the work of Fishman D., et al., and 26% p=0,02 — in the work of Serruys P. et al) (7, 13, 14).

Similar results were obtained by Rodriguez A. et al. (15), Versacci F. et al. (16) and Antoniocci D. et al. (17). The authors have demonstrated a decrease of the rate of late restenosis in the stented group, which, in its turn has contributed to a significant reduction of the need of repeated endovascular interventions (15, 16, 17).

Today coronary stenting is the most frequently used method of heart revascularization. However the damage of vascular endothelium and subsequent hyperplasia of the neointima developing mainly within the first 6 months after stent insertion often causes in-stent restenosis (18,19). According to most authors, a restenosis is considered hemodynamically significant if the vessel lumen in the site of dilatation is reduced by > 50% of the reference diameter or 75% of its surface area (20, 21, 22, 23).

In 1999, late in-stent stenosis was revealed in over 250.000 stented patients. For this reason worldwide trials are being conducted with the aim to study the causes of in-stent stenosis, the possibilities of its prevention and the development of an optimal tactics of treatment for the improvement of clinical prognosis (24, 25). The mechanism of restenosis is well known: it occurs due to a multitude of factors, such elastic recoil of the vessels, thrombosis, neointimal hyperplasia and negative remodeling of the vessels (26). Elastic recoil is caused to natural elastic properties of

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Manuscript received on June 20, 2011.
Accepted for publication of September 15, 2001

the blood vessels, manifested as a response to dilatation. It occurs immediately after percutaneous transluminal coronary angioplasty (PTCA). Thrombosis is a consequence of endothelial damage, rupture of the intima and damage of the middle layer of a vessel. These damages lead to the accumulation of platelets and the formation of a thrombus. The accumulated platelets represent a source of attractants and mitogens for smooth muscle cells (SMC). Besides, platelet-derived growth factor (PDGF), released by endothelial cells and macrophages, is considered as the main factor contributing to SMC migration. Inflammation plays an important role in restenosis, as leucocytes are found in the site of vascular damage early and in great amount (26). According to Hofma H. S., et al. (27), inflammation process plays a more important role in the healing of arterial wall after stenting, which can be explained by the presence of a foreign body (stent) in the arterial lumen (28). An important role is also played by neointimal hyperplasia. In the involved vessel, the SMC enter into the proliferation phase and move to the intima through the damaged internal elastic membrane. An important place in this process belongs to metalloproteinases. They continue to divide and to synthesize the extracellular matrix (ECM), which, In the end, forms the volume of restenotic lesion. The components of ECM — hyaluronan, fibronectin, osteopontin and vitronectin — also contribute to SMC migration. Moreover, the reorganization of ECM, as well as its replacement with collagen can lead to the contraction of the vascular wall. The adventitial myofibroblasts, playing an important role in intima supply with proliferative cell elements in restenosis, also divide and migrate in the neointima. The adventitial cells also participate in the process of vessel remodeling, as myofibroblasts are able to synthesize collagen and lead to tissue contraction (26). Rogers and Edelman (29), Edelman and Rogers (30) have demonstrated that the damage and, as a consequence, the interruption of the integrity of the internal elastic membrane is of key importance for intimal hyperplasia during the development of in-stent stenosis. During stent implantation, after primary balloon-induced injury of the vascular wall with the rupture of internal elastic membrane, one assists at an intensive proliferation of the intima. Its degree is proportional to the depth of stent insertion. Thus, it has been shown, that the hyperplasia of the intimal layer represents a response to an external impact (lumen dilatation with an inflated balloon and stent insertion) and is proportional to the degree of mechanical damage of the vascular wall's structures (29, 30). The feasibility of using stents as a reinforcing device became evident after experimental and clinical confirmation of an important role of early elastic recoil and negative remodeling of the vessels in the development of restenosis (31). Intravascular ultrasound (IVUS) allowed to understand that the late lumen loss and restenosis after PTCA are due not so much to intimal hyperplasia, as to negative remodeling of the vessel. Catala (32) has experimentally shown that the design and the material of stent produce a significant on the probability of restenosis development. An ideal stent design should maximally limit smoot muscle cells migration to the surface of the intima (32). Similarly, Topaz and Vetrovek (28) came to the conclusion that more dense, uniform reinforcement of the arterial lumen contributes to more effective prevention of neointimal growth.

Today two different tactics are being used for the fight against restenosis — it can be treated or prevented. The therapeutic tactics is based on the use of mechanical methods, while the prevention of in-stent stenosis formation is effectuated through the use of pharmacological agents and new technologies of stenting (including the use of new stents with antiproliferative properties) (33).

A drug-eluting stent (DES) usually contains a metal base, a polymer layer with a drug absorbed into or mixed with this layer, sometimes — a protective polymer layer preventing early drug washing out, and the drug, as such.

The pharmacological agent must be able to inhibit maximal amount of different components participating in complex process of restenosis (34, 35). All know anti-inflammatory and histochemical agents, immunomodulators, some antibiotics, as well as the medications used in oncology for the decrease of the intensity of cellular division in tumors, have been tested (36). The biggest effect was obtained with only two agents — Rapamycin (trade mark — Sirolimus) and Paclitaxel (trade mark — Taxol) (37, 38).

By its chemical composition, Rapamycin belongs to natural macrocyclic lactons and is a waste product of Streptomyces hydroscopicus bacteria. By its pharmacological properties Rapanycin is a cytostatic agent — immunosuppressor (39). Its action is based on the binding of cytozolic receptor FRBP 12, blocking of TOR enzyme, regulation of p27 level and deceleration of retinoblastoma protein phosphoration with the block of cell cycle development at G1-S transition (39). In vitro studies have demonstrated that Rapamycin can suppress the division and the migration of the SMC, and experimental models have proved its capacity to reduce neointima formation in the area of vascular wall damage (40, 41, 42).

Paclitaxel is an alkaloid derived from Taxus brevifolia, a well-known antitumoral agent producing a powerful antiproliferative effect. The combination of Paclitaxel and tubulin leads to cell blocking and division in the phases G0/G1 G2/M of the cellular cycle (43, 44). In vitro and animal studies have demonstrated the capacity of Paclitaxel to decelerate SMC division and migration, to prevent neointima formation after catheter angioplasty (45, 46). An active substance-containing polymer layer should possess an absolute biocompatibility, perform mechanical functions as well as provide necessary drug concentration. It means, that besides being non-toxic,

it should follow the changes of geometrical configuration during stent deployment and be resistant to mechanical influences caused by balloon inflation. Besides, local drug release must be maximally effective. The speed of drug release and its concentration in the due site should be predictable and controllable (41, 47). The first drug-eluting stents (DES) had been coated with a cytostatic agent only. Currently used DES possess a new important component — an additional coating made of biocompatible polymer. In the absence of polymer up to 40% of the drug is lost through the mechanical and chemical processes before stent implantation, and complete wash-out of the drug occurs before the occurrence of the expected restenosis; for this reason controlled endothelization does not occur and the rate of early thromboses increases (48). Biodegradable polymers are the most recent innovations in this field. Contacting with the biological environment of the living organism, these polymers can dissolve without changing their molecular mass, or get biodestructed under the impact of the following mechanisms: hydrolysis with the formation of oligomeric and monomeric products, enzymatic hydrolysis and cytophagous destruction (organism's protective cellular response) (49, 50). In first trials the stents with polymer coating did not only decrease proliferation, but even enhanced it due to their toxicity (51). Newer phosphoryl choline-based polymer coatings have demonstrated better biocompatibility and reduced the rate of DES thromboses (52), which allowed to consider these coatings as a transport mean for local delivery of drugs aimed to dosed release into the stented vascular wall area (53). Due to polymer coating, the drug is released in

Table 1.

Comparative charateritics of drug-eluting stents

Manufacturer	Boston Scientific	Cordis	Abbot	Biosensors	Medtronic
Article	Taxus Liberte	Cypher Select	Xience V.	BioMatrix	Endeavor Resolute
Platform	Taxus Express	Bx Sonic	Multi Link Vision	S-stent	Driver
Stent material	Stainless steel	Stainless steel	Cobalt-chromium	Stainless steel	Cobalt-chromium
Primary coating	No	Parylene c	No	Parylene c	Нет
Third layer	No	Polybutyl methacrylate	No	No	Polivinil pirrolidinone
Polymer	Polyvinylidine fluoride hexa fluropropylyene (PVDF-HFP)	Poly ethylene co-vinyl Acetate	Polyvinylidine fluoride hexa fluropropylyene (PVDF-HFP)	Polylactic acid (PLA)	Biolinx three-layer coating: upper layer — hydrophilic polivinil pirrolidinone, middle layer– hydrophobic hexil methacrylate, hedrophilic venyl pirrolidinone and venyl acetate- medicinal diffuse barrier; hydrophobic butyl methacrylate- drug carrier
Dissolving polymer, term	No	No	No	Yes, up to 6-9 months	No
Hydrophile coating	No	No	No	Yes	Yes/no
Type of coating	Coated from all sides (including the surface facing the arterial lumen)	Coated from all sides (including the surface facing the arterial lumen)	Coated from all sides (including the surface facing the arterial lumen)	Applied at the surface facing the arterial wall	Coated from all sides (including the surface facing the arterial lumen)
Agent	Paclitaxel	Sirolimus	Everolimus	Biolimus A9	Zotarolimus ABT-578
Dose, μg/mm^2	1	140	100	15,6	10
Thickness of coating, μm	17,8	13,7	7,8	11	4,8

a homogenously dosed concentration and during a pre-determined period of time corresponding to the phases of vessel's healing (41). The system of drug delivery preserves its properties after sterilization, is able to change its geometrical form and volume following stent implantation and deployment and is resistant to mechanical influence caused by balloon inflation (52). The first prospective double blind multi-center trial (RAVEL) compared the results of angioplasty with Sirolimus-eluting stents and with bare metal stents (Bx Velocity) in 238 randomized patients with primary coronary lesions. At six months the rate of restenoses in the Sirolimus group was 0% vs. 26,6% in the control group. According to angiography data, late decrease of arterial lumen (so-called late lumen loss), as well as the number of MACE in the Sirolimus group were significantly lower (54). SIRIUS trial was the largest-scale study of Sirolimus-eluting stents. It was conducted in 53 centers throughout the USA and comprised 1101 randomly selected patients with primary coronary lesions. The patients received Sirolimus-eluting stents and bare metal stents. Final results of the trial have demonstrated a significant decrease of the rate of restenoses, late lumen loss and necessity of repeated revascularization in the Sirolimus group (55). Primary results of the use of Sirolimus-eluting stents for the treatment of in-stent stenosis are equally encouraging. A non-randomized study has shown the rate of restenosis below 10%. In comparison with the standard coronary stent, a Sirolimus-eluting stent offers better perspectives for the prevention of proliferation of the neointima, of restenosis and restenosis-related unfavorable clinical events (26). At present there are many various drug-eluting stents. Antiproliferative agents used in most available stents are Rapamycin and Paclitaxel. All stents without distinction are balloon-deployable, processed with polymer coating containing a cytostatic agent. The analogues of Rapamycin available at the present time include: Everolimus (stent Xience V, Abbot), Zotarolimus (stent Endeavor, Medtronic), Sirolimus (stent Cypher select, Cordis), Biolimus-A9 (stent Biomatrix, Biosensors). These agents are used in the coatings of second-generation stents. Comparative characteristics of the most widely used DES are presented in Table 1.

While the use of stents for PCI can be compared to a breakthrough resulting in a significant decrease of the rate of restenosis (20), the advent of stents with drug-eluting coating became a true revolution in the treatment of the coronary artery disease (56).

The stent Xience V (Abbott Vascular, USA), is one of the best second-generation stents. The safety and the effectiveness of Xience V have been statistically confirmed in numerous clinical trials comparing this stent with bare metal stents as well as with other second-generation stents.

Here is a brief summary of these trials

1. SPIRIT I. A 6-months (5 years) follow-up of 60 patients in comparison with a bare metal stent (Multi Link Vision) revealed that the rate of MACE, including death, myocardial infarction, emergency and elective CABG was 7,14% for Xience V, and 18,75% for Multi Link Vision (57, 58, 59).

2. SPIRIT II. The data of a clinical trial conducted in a group of 300 patients and comparing the Xience V stent with Paclitaxel-eluting stent Taxus Express2 / Taxus Liberte, have been presented by P. Serruys at 58th Annual session of the American College of Cardiology (ACC-2009). The rate of MACE at 6 months was 2,7% for Xience V vs. 6,5% for Taxus; at 2 years– 6,6% and 11,0%, respectively. (60).

3. SPIRIT III. (the results have been presented at PCR-2008 in Barcelona, Spain, on May 13, 2008): In a group of 1002 patients the rate of MACE decreased at 2 years by 45% in comparison with Taxus stent (6,0% for Xience V vs. 10,3% for Taxus) (61, 62, 63).

4. Meta-analysis of the data of SPIRIT II + SPIRIT III trials has shown the following key results for Xience V stent at 2 years follow-up: clinically significant decrease of the risk of ischemia, caused by target vessel failure by 31% in comparison with Taxus stent (10,4 % for Xience V vs.14,7% for Taxus). The risk of death from all causes decreased by 28% in comparison with Taxus stent (2,4% for Xience V vs.3,3% for Taxus). The risk of cardiac death decreased by 28% in comparison with Taxus stent (0,9% for Xience V vs. 1,3% for Taxus). Besides, the authors have noted clinically significant decrease of the risk of myocardial infarction (MI) by 45% in comparison with Taxus (3,1% for Xience V vs. 5,6% for Taxus); clinically significant decrease of the risk of ischemia caused by target lesion revascularization (TLR) by 1% in comparison with TAXUS (4,1% for Xience V vs. 6,8% for Taxus). Also a low rate of stent thrombosis between the years 1 and 2 was noted (0,5% for Xience V and 0,8% for Taxus) (64).

5. SPIRIT IV. In September 2009, at TCT held in San-Francisco, G. W. Stone has presented the results of SPIRIT IV trial comprising 3690 patients, including 1185 patients with diabetes mellitus (32.2%). According to this study, the rate of MACE decreased by 39% in comparison with Taxus stent (4,2% for Xience V vs. 6,9% for Taxus). At 1 year there was a significant reduction of the target lesion failure in comparison with Taxus Express (Xience V 4.2% vs. Taxus 6.8%). Besides, with the use of Taxus the rate of ischemia-driven target lesion revascularizтion (ID-TLR), was higher than with the use of Xience V, with relative risk decrease by 46% (2,5% for Xience V vs. 4,6% for Taxus). Also the number of cases of cardiac death or target-vessel revascularization decreased by 31% in comparison with Taxus stent TAXUS (2,2% for XIENCE V vs.3,2% for TAXUS). The number of myocardial infarctions related to the target vessel decreased by 38% in comparison with Taxus (1,8% for Xience V vs. 2,9% for Taxus). The number of stent thromboses decreased by 80% in comparison with Taxus stent (0,17% for Xience V vs. 0,85% for Taxus); with the

use of Xience V the rate of thromboses in patients with diabetes mellitus decreased by 40% in comparison with Taxus Express stent (0.8% vs.1.33%), and in non-diabetic patients — by 94% (0.06% vs.1%). A decrease of Target Lesion Failure (TLF) was also noted in patients with small vessels — by 43% (3.9% vs. 6.8%), in patients with extended stenosis — by 35% (4.5% vs. 6.9%), and in patients with two and more involved coronary arteries — by 49% (5.1% vs. 10%) (65, 66).

6. Clinical trial Compare: on January 8, 2010 the on-line resource Lancet published the results of a large-scale clinical trial. P. C. Smits from Maasstad Ziekenhuis hospital (Rotterdam, the Netherlands) presented the results of comparison of Xience V and Taxus stents. Over 1800 complex cases have been randomized for this study in 1:1 ratio (60% — with acute coronary syndrome, 73% — with type B2/C lesions in the Taxus Liberte group and 74% — with type B2/C lesions in the Xience V group). The following data are of utmost interest: at 1 year the use of Xience V stent led to a significant reduction of MACE in comparison with Taxus Liberte (6,2 % for Xience V vs. 9,1 % for Taxus Liberte) — a decrease by 31%, as well as to the decrease of the rate of stent thrombosis (0,7 % for Xience V vs. 2,6 % for Taxus Liberte) — a decrease by 74% (67).

7. Clinical trial Lesson I, aimed at the evaluation of comparative effectiveness of Sirolimus-eluting stents Cypher (Cordis) and Everolimus-eluting stents Xience (Abbot). The authors have analyzed the data of 1532 patients who got Cypher stent during the period from 2004 to 2006, and of 1601 patients who received Xience stents from 2006 to 2009. They have identified 1342 pairs comparable by their baseline clinical parameters. Clinical outcomes were followed for up to 3 years. The results suggested a statistically reliable decrease of the number of MI and target vessel revascularization in the group of Xience (14,9% for Xience vs. 18,0% for Cypher). The number of deaths was not statistically different (6% for Xience vs. 6,5% for Cypher). The group of Xience demonstrated a decrease of the rate of definite and eventual stent thromboses (2,5% for Xience vs.4,0% for Cypher) (67) .

8. The Leaders trials have revealed a tendency towards the improvement of MACE with the implantation of Biolumus A9 -eluting stents (BES) in comparison with Sirolimus-eluting stents (SES). Major adverse cardiac events (MACE) have been noted in 15.7% patients with BES and in 19.0% with SES. In the subgroups of patients with a history of MI, there was a significant decrease of MACE among the patients with BES (9.6% vs. 20.7%). Another group of patients with BES, which comprised patients with Syntax score over 16, demonstrated a significant (by 57%) decrease of deaths in comparison with a group patients with SES (4.6% vs. 10.4%) (68).

9. Essence-Diabetes trial has shown that Xience V is more effective than Cypher for the treatment of coronary lesions in diabetic patients. The trial comprised 280 patients with diabetes mellitus and angina or confirmed ischemia and coronary arteries stenosis > 70% (with reference diameter of the vessel > 2,5 mm and lesion's length > 25 мм). Patients with the lesions of the left main coronary artery and coronary grafts, with chronic renal or hepatic failure and with bifurcation lesions requiring stenting of the side branch were excluded from the study. The patients were divided into 2 equal groups. In 8 months after the intervention control coronary angiography has been performed in all patients.

Maximal lumen loss in the Xience V group was lower than in the Cypher group (0,23 mm vs. 0,37 mm; P=0,02). Lumen loss inside the stent was 0,04 mm in the Xience V group and 0,18 mm in the Cypher group (P=0,015). Segmental lumen loss was 0,11 mm in the Xience V group and 0,20 mm in the Cypher group (P=NS). Restenosis over 50% was noted in 4,7% of patients from the Cypher group and in none patient from the Xience V group (P=0,029). Repeated intervention has been performed in 2,0% of patients from the Xience V group and in 5,3% in the Cypher group (P=0,085). During the follow-up there was 1 case of eventual stent thrombosis in each group (The results were presented by Young Hak Kim at TCT-2010).

The complications of DES include intimal hemorrhages, incomplete healing, intimal inflammation and medial necrosis (63, 69). Aneurysms, false aneurysms, stent apposition, perforations, local vasculitis, thrombosis, accelerated progressing of atherosclerosis, fibrosis and systemic disturbances are potential complications associated with DES implantation (69). The IVUS-assisted studies of Colombo and Tobis (70) have demonstrated that many stents were under-deployed, which increased their blood-contacting surface area (70). These data suggested the necessity of more aggressive stent deployment during their implantation using high pressure (71). At the same time the studies of anticoagulant therapy have revealed that the combination of antiplatelet Aspirin agents with Ticlopidine, as well as the combination of Aspirin with Clopidogrel is several times more effective than Varfarin in the prevention of stent thrombosis (72). These two new practical approaches to stenting have significantly decreased the rates of stent thrombosis and bleeding.

On July 7, 2003, the company Cordis has appealed to interventionists with an advice to strictly follow the guidelines for the implantation of Cypher stents and for subsequent patients' care for the assurance of maximal safety of the procedure. And on October 29, 2003, FDA has announced an investigation of the causes of subacute thrombosis and related complications after Cypher implantation. As for 2005 (73), FDA did not recommend the use of Sirolimus-eluting stents in cases that were not definitely studied in randomized trials, up to the discovery of true causes of thrombosis (73). Antiproliferative agents do not stop the process of neointima formation, but just delay

it, and under their influence the process of endothelization does not end by 6 months, but continues further. Nevertheless this process leads to stepwise decrease of minimal lumen of the dilated segment of the artery. The growth of neointima does not stop even after 12 months (74). Karvouni et al. (73) have noted that by 15 months after Cypher (Sirolimus-eluting) implantation, the stent was not covered by the endothelium; at the same time BX Velocity (bare metal) stent was completely endothelized. In 2005, Waters (75) has presented 40 pathological cases after DES implantation: in 24 of these cases there was a thrombosis of the stented segment. It became evident, that the delay of endothelization after DES implantation prolong the time when the development of complications is possible. These complications include thrombosis — the most dangerous adverse event after DES implantation (76).

Long-term follow-up of 746 patients in whom Clopidogrel was stopped 6 months after stenting (Basket-Late trial) have been presented in March 2006, at the Annual session of ACC (77). The study revealed that within 1 year after the cessation of Clopidogrel intake the rate of complications in patients with DES was reliably higher than in those with BMS. Herewith in the group with DES there was a tendency towards lower need in repeated PCI for restenosis (78). Wenaweser at al. (77) have shown that an angiographically confirmed stent thrombosis was noted in 1,8% of cases. Almost one half of thromboses (41%) were late (on the average — in 453 days). The majority of late thromboses (59%) occurred more than one year after stenting (77).

One can suggest, that the obtained results, if they are not accidental and are not related to some particularities of the trial, favor more prolonged (over 6 months) administration of Clopidogrel after the implantation of DES. Eisenstein et al. (79) presented the results of their study of 4666 patients followed for 6, 12, and 24 months after stenting. In patients with bare metal stents prolonged Clopidogrel therapy had no impact on the rate of death and MI at 6-12 months after the procedure. On the contrary, in patients with DES the use of Clopidogrelfor 6, 12 and 24 months was associated with the decreased rate of mortality and MI in all time intervals.

At present we assist at the introduction of new techniques of stenting, including simultaneous use of DES and BMS, the so-called “hybrid” stenting. A group of Italian researchers headed by Varani has followed 2898 patients with coronary artery disease who underwent multiple coronary stenting, from July 2003 through December 2006 (81). BMS have been implanted in 1315 of these patients, DES — in 657, and 926 patients had “hybrid” stenting. Long-term results (2 years) suggest the absence of any significant difference between the outcomes with the use of DES and “hybrid” stenting. It has been shown that isolated use of DES is more cost-effective in comparison with the use of only BMS.

Bertand et al. (82) have compared two groups of patients: the patients from group 1 (n=161) received only DES, while the patients from group 2 (n=201) — a combination of DES and BMS. Long-term results of “hybrid” stenting were found to be comparable with the results of DES implantation. The authors have confirmed the effectiveness of isolated use of DES in coronary lesions with high risk of restenosis.

Conclusion: Sirolimus-eluting stents marked the advent of a new generation of intravascular devices. They have been followed by other stents with similar and essentially different types of coating. Their apparition can be considered as a logical evolutionary step in invasive cardiology, while the decrease of the risk of restenosis can mean the beginning of a new era in revascularization. Certainly, significant decrease of the rate of restenosis and TLR with the use of DES (in comparison with BMS) has been proved by multiple trials, and constitutes the main advantages of these stents. A representative of second generation of DES, Everolimus-eluting stent Xience V, is superior to Sirolimus-eluting, as well as to Paclitaxel-eluting stents. Today we assist at the development and successfully introduction of a third-generation DES — with PLA-based biodegradable coating, that has been shown to be safe and effective in early, as well as in long-term follow-up (68). However, the true innovation in this field was the advent of new stents, implanted into the thrombotic vessels. After the implantation they dissolve within about 2 years leaving the vessel patent in the absence of a permanent metallic implant (80).

References

1. Petrosian Yu.S., Zingerman L.S. Coronarography. Moscow, Meditzina, 1974. 150 p.

2. Rudd J.H.F. , Davies J. R., Weissberg P.L. Atherosclerotic Biology and Epidemiology of Disease. In Topol E.J. Textbook of cardiovascular medicine. Lippincott Williams & Wilkins, Philadelphia, 2002.

3. Gruentzig A. Transluminal dilatation of coronary-artery stenosis. Lancet, 1978, 1, 263.

4. Sigwart U., Puel J., Mirkovitch V., et al. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N. Engl. J. Med., 1987, 326, 701-6.

5. Gianturco C, Wright KC, Wallace S, et al. Percutaneous endo-vascular stents: An experimental evaluation. Radiology, 1985, 156 (1), 69-72 .

6. Garas SM, Huber P, Scott NA. Overview of therapies for prevention of restenosis after coronary interventions. Pharmacol. Ther., 2001, 92(2-3), 165-78.

7. Serruys P.W., de Jaegere P., Kiemeneij F., et al. A comparison of balloon-expandable stent implantation with balloon angioplasty in patients with coronary artery disease: BENESTENT study group. N. Engl. J. Med., 1994, 331, 489–509.

8. Serruys P.W., Van Hout B., Bonnier H. et al. Effectiveness, costs and cost-effectiveness of a strategy of elective heparin-coated stenting compared with balloon angioplasty in selected patients with coronary artery disease: the BENESTENT II Study. Lancet, 1998, 352, 673.

9. Zakharova O.V., Arablinsky A.V., Iosseliani D.G. Endovascular methods of treatment of CAD patients with restenosis after primary balloon angioplasty. Klinicheskaya meditzina, 2004, 82(10), 22-6.

10. Babunashvili A.M., Ivanov V.A. Use of coronary stenting depending on clinical presentation of IHD and the type of atherosclerotic lesion of the coronary arteries. Moscow, 2000, 77 p.

11. ACC/AHA Percutaneous Coronary Intervention in United States. J. Am. Coll. Cardiol., 2002, 23, 2, 1881-2137.

12. Serruys P.W. ARTS I — the rapamycin eluting stent; ARTS II — the rosy prophecy. Eur. Heart J., 2002, 23, 757.

13. Fishman D.L., Leon M.B., Baim D.S., et al. A randomized comparison of coronary-stent placement and balloon angioplasty in treatment of coronary artery disease. Stent Restenosis Study Investigators. N. Engl. J. Med., 1995, 332 (8), 536;

14. Serruys PW, Sousa E, Belardi J et al. BENESTENT-n Trial: subgroup analysis of patients assigned either to angiographic and clinical follow-up or clinical follow-up alone. Circulation, 1997, 96, 653.

15. Rodrigues A., Ayala F., Bernardi V., et al. Optimal coronary balloon angioplasty with provisional stenting versus primary stent (OCBAS). J. Am. Coll. Cardiol., 1998, 32, 1351-7.

16. Versaci F., Gaspardone A., Tomai F., et al. A comparison of coronary artery stenting with angioplasty for isolated stenosis of the proximal left anterior descending coronary artery. N. Engl. J. Med., 1997, 12, 817.

17. Antoniucci D., Santoro G., Bolognese L., et al. A clinical trial comparing primary stenting of the infarct-related artery with optimal primary angioplasty for acute myocardial infarction (FRESCO). J. Am. Coll. Cardiol., 1998, 31,1234-9.

18. Iosseliani D.G., Arablinsky A.V., Chernysheva I.E. Immediate results of direct stenting of the coronary arteries. Kardiologia, 2002, 42 (2), 8-10.

19. Hoffmann R., Mintz G.S., Mehran R., et al. Tissue proliferation within and surrounding Palma-Schatz stents in dipendent on the aggressiveness of stent implantation technique. Am. J. Cardiol., 1999, 83, 1170-4.

20. Block P., Petch M.C., Letouzey J.P. Manpower in cardiology in Europe. Eur. Heart J., 2000, 21, 14, 1135-40.

21. Gensini GG. Coronary arteriography: role in myocardial revascularization. Postgrad Med., 1978, 63(1), 121-8, 133-8

22. Sawada Y., Nokasa H., Kimura T., et al. Initial and six months outcome of Palmaz-Schatz stent implantation: STRESS/BENESTENT equivalent vs non- equivalent lesions. J. Am. Coll. Cardiol., 1996, 27 (suppl A), 252A.

23. Varnauskas E. Twelve-year follow-up of survival in the randomized European Coronary Surgery Study. N. Engl. J. Med., 1988, 319, 332-7.

24. Grossman W., Baim D. Coronary angiography. In: Cardiac Catheterization, Angiography and Intervention. Eds Grossman W, Baim D. Lea&Febiger, 1991: 185-214.

25. Sharma SK, Karakala V, Dangas G, D. et al. In-stent restenosis after Palmaz-Schatz stent implantation. Eur. Heart J., 1998, 20, 352.

26. Lee C.H., Serruys P.W, An overview of drug-eluting stent. International Journal of interventional Cardioangiology, 2003, 1, 9

27. Hofma H.S., Whelan D.M. van Beusekom HM. et al. Increasing arterial wall injury after long-term implantation of two types of stents in a porcine coronary model. Eur. Heart J., 1998, 19, 601.

28. Topaz O., Vetrovek G. The stenotic stent: mechanism and revascularization options. Cathet. Cardiovasc. Diagn., 1996, 37,293-9.

29. Rogers C., Edelman E.R. Endovascular stent design dictates experimental restenosis and thrombosis. Circulation, 1995, 91, 2995-3001.

30. Edelman E.R.., Rogers C. Hoop Dreams. Stent without restenosis. Circulation, 1996, 94(6), 1199-202.

31. Sousa J.E., Costa M.A., Abizaid A.C., et al. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. Circulation, 2001, 104, 2007.

32. Catala L. Is stent design affecting the biologic response? In: «Endovascular Therapy Daily», at the «Eight complex coronary angioplasty», Paris, May 23-28, 1997, p.2.

33. Dangas G., Mehran R., Lansky A.J., et al. Acute and long-term results of treatment of diffuse in-stent restenosis in aortocoronary saphenous vein grafts. Am. J. Cardiol., 2000, 86, 777.

34. Mohacsi P.J., Tuller D., Hulliger B., et al. Different inhibitory effects of immunosuppressive drugs on human and rat aortic smooth muscle and endothelial cell proliferation stimulated by platelet-derived growth factor or endothelial cell growth factor. J. Heart Lung Transplant., 1097, 16, 484-92.

35. Suzuki T., Kopia G., Hayashi S., et al. Stent-based delivery of sirolimus reduces neointimal formation in a porcine coronary model. Circulation, 2001, 104, 1188-93.

36. Van Giesen W.J., Lincoff M., Schwartz R.S., et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. Circulation, 1996, 94, 1690–7.

37. Poon M., Marx S.O., Gallo R., et al. Rapamycin inhibitis vascular smooth muscle cell migration. J. Clin. Invest,. 1996, 98, 2277-83.

38. Heldman A.W., Cheng L., Jenkins G.M.. et al. Paclitaxel stent coating inhibitis neointimal hyperplasia at 4 weeks in a porcine model of coronary restenosis. Circulation, 2001, 103, 2289-95.

39. Beyar R., Roguin A. The sirolimus-coated stent: will the Achilles heel of interventional cardiology finally be cured? Eur. Heart J., 2001, 22, 2054-7.

40. Bruke S.E., Labbers N.L., Chen Y.W. et al. Neointimal formation after balloon-induced vascular injury in Yucatan minipigs is reduced by oral rapamycin. J. Cardiovasc. Pharm., 1999, 33, 829-35.

41. Hwang C.W., Wu D., Edelman E.R. Physiological transport forces govern drug distribution for stent-based delivery. Circulation, 2001,104, 600-5.

42. Wahl A.F., Donaldson K.L, Fairchild C, et al. Loss of normal P53 function confers sensitization to Taxol by increasing G2/m arrest and apoptosis. Nat. Med., 1996, 2, 72-9.

43. Donaldson K.L., Goolsby G.L., Kiener P.A., Wahl A.F. Activation of p34cdc2 coincident with taxol-induced apoptosis. Cell Growth Differ., 1994, 5, 1041-50.

44. Heldman A.W., Cheng L., Jenkis G.M., et al. Paclitaxel stent coating inhibits neointimal hyperplasia at 4 weeks in a porcine model of coronary restenosis. Circulation, 2001,103, 2289-95.

45. Farb A., Heller P.F., Shroff S., et al. Pathological analysis of local delivery of paclitaxel via a polimer-coated stent. Circulation, 2001,104, 473-9.

46. Whelan D.M., van Beusekom H.M., van Giessen W.J. Mechanisms of drug loading and release kinetics. Semin. Interv. Cardiol., 1998, 3, 127-31.

47. Heldman G.P. Internal testing of DES. Circulation, 2001, 103, 2289-95.

48. Grenadier E., Roguin A., Hertz I., et al. Stenting very small coronary narrowings (< 2 mm) using the biocompatible phosphoryl-choline-coated coronary stent. Catheter Cardiovasc. Interv., 2002, 55, 303-8.

49. Seldinger S.I. Catheter replacement of the needle in percutaneous arteriography: a new technique. Acta Radiol., 1953. 39, 368.

50. Volova T.G., Sevastianov V.I., Shishatskaya. Polyhydrooxyalkoanates — biodegradable polymers for medicine. Krasnoyarsk, Platina, 2006, 287 p.

51. Hofma S.H., Beusekom H.M., Serruys P.W., Giessen W.J. Recent developments in coated stents. Curr. Intervent. Cardiol. Rep., 2001, 3, 28–36.

52. Malik N., Gunn J., Shepherd L., et al. Phosphorylcholine-coated stents in porcine coronary arteries: in vivo assessment of biocompatibility. J. Invasive Cardiol., 2001, 13, 193-201.

53. Whelan D.M., Van Giessen W.J., Krabbendam S.C., et al. Biocompatibilrty of phosphorylcholine coated stents in normal porcine coronary arteries. Heart, 2000, 83, 338-45.

54. Regar E., Serruys P.W., Bode S., et al. Angiographic findings of the multicenter randomized study with the sirolimus-eluting Bx velocity balloon-expandable stent (RAVEL): sirolimus-eluting stents inhibit restenosis irrespective of the vessel size. Circulation, 2002, 90, 937-41.

55. Moses J.W., O'Schaughnessy C., Caputo R., et al. The U.S. multicenter, randomized, double-blind study of the sirolimus-eluting stent in coronary lesions: safety outcomes at 9 months. Eur. Heart J., 2002;23:264.

56. Serruys P.W., Ong A.T., Piek J.J., et al. A randomized comparison of a durable polymer Everolimus-eluting stent with a bare metal coronary stent: The SPIRIT first trial.. EuroIntervention, 2005, 1, 58-65.

57. Garg S., Serruys P., Onuma Y., et al. 3-Year Clinical Follow-Up of the XIENCE V Everolimus-Eluting Coronary Stent System in the Treatment of Patients With De Novo Coronary Artery Lesions The SPIRIT II Trial. J.Amer.Coll. Cardiol., 2009, 2, (12), 1190-8.

58. Piek J.J., Neumann F.J., Giessen W.J., et al. One-year results of a durable polymer everolimus-eluting stent in de novo coronary narrowings (The SPIRIT FIRST Trial).. EuroIntervention 2005, 1, 266-72.

59. Tsuchida K., Garcia-Garcia H.M., Ong A.T., et al. Revisiting late loss and neointimal volumetric measurements in a drug-eluting stent trial: analysis from the SPIRIT FIRST trial. Catheter Cardiovasc. Interv., 2006, 67,188-97.

60. Onuma Y., Tanimoto S., Ruygrok P., et al. Efficacy of everolimus eluting stent implantation in patients with calcified coronary culprit lesions: two-year angiographic and three-year clinical results from the SPIRIT II study. Catheter Cardiovasc. Interv., 2010, 76 (5), 634-42.

61. Applegate R.J., Hermiller J.J., Sanz M., et al. Comparison of everolimus-eluting and paclitaxel-eluting coronary stents in patients with two treated vessels: 2-year results from the SPIRIT III randomised trial. EuroIntervention, 2010, 6, 437-46.

62. Stabile E., Escolar E., Weigold G., et al. Marked malposition and aneurysm formation after sirolimus-eluting coronary stent implantation. Circulation, 2004, 110(5), 47-8.

63. Stone G.W., Midei M., Newman W . Randomized comparison of everolimus-eluting and paclitaxel-eluting stents: two-year clinical follow-up from the Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions (SPIRIT) III trial. Circulation, 2009, 119, 680-6.

64. Nikolsky E., Lansky A.J., Sudhir K., et al. SPIRIT IV trial design: a large-scale randomized comparison of everolimus-eluting stents and paclitaxel-eluting stents in patients with coronary artery disease. Am. Heart J., 2009,158, 520-6.

65. Kedhi E., Joesoef K.S., McFadden E., et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet, 2010, 375,201-9.

66. Stone G.W., Rizvi A., Newman W., et al. Everolimus-eluting versus paclitaxel-eluting stents

in coronary artery disease. N. Engl. J. Med., 2010, 362,1663-74.

67. Raber L., Juni P., Nuesch E., et al. Long-term comparison of everolimus-eluting and sirolimus-eluting stents for coronary revascularization. J. Am. Coll. Cardiol., 2011, 57(21), 2143-51.

68. Udupi K. et al. Next generation Endeavor Resolute Stent: role of the BioLinx polymer system. Medtronic Cardiovascular, Santa Rosa, CA 95-403, USA.

69. Vik-Mo H., Wiseth R., Hegbom K. Coronary aneurysm after implantation of a paclitaxel-eluting stent. Scand. Cardiovasc. J., 2004, 38(6), 349-52.

70. Colombo A., Tobis J. Techniques in Coronary Artery Stenting. London, Martin Dunitz Ltd. 2000, 422.

71. Waksman R., Ajani A.E., White R.L., et al. Prolonged antiplatelet therapy to prevent late thrombosis after intracoronary gamma radiation in patients with in-stent restenosis: Washington Radiation for In-Stent Restenosis Trial plus 6 months of clopidogrel (WRIST PLUS). Circulation, 2001, 103, 2332–5.

72. Waksman R., Bhargava B., Taafe M., et al. Prolonged antiplatelet therapy to reduce late thrombosis after intracoronary gamma radiation in patients with in-stent restenosis: “plavix-wrist” Circulation, 2000, 102, II, 570. (abstract).

73. Karvouni E. 17 months after SES implantation — despite ASA continuation (clopidogrel stoped at 12 months). Heart, 2005, 8, 64-71.

74. Alt E., Haehnel I., Beilharz C. et al. Inhibition of neointima formation after experimental coronary stenting. Circulation, 2000, 101, 1453–8.

75. Waters R.E. 3 cases following DES for in-stent-restenosis (at 16, 20, 43 months) — shortly after interruption of antiplatelet Tx. Catheter Cardiovasc. Interv., 2005, 4, 107-15.

76. Camenzind E., Steg P.G., Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. Circulation, 2007, 115 (11), 1440-55;

77. Wenaweser P., Hess O. Stent thrombosis is associated with an impaired response to antiplatelet therapy. J. Am. Coll. Cardiol., 2005, 46(5), CS5-6.

78. Pfisterer M.E., Kaiser C.A., Bader F., et al. Late clinical events related to late stent thrombosis after stopping clopidogrel: prospective randomized comparison between drug-eluting versus bare-metal stenting. Program and abstracts from the American College of Cardiology 55th Annual Scientific Session, March 11-14, 2006, Atlanta, Georgia. Abstract 422-411.

79. Eisenstein E.L., Anstrom K.J., Kong D.F.,et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. JAMA, 2006, E1–E10.

80. Zilberman M., Eberhart R.C.. Expandable bioresorbable endovascular stent. I. Fabrication and properties. Annu. Rev. Biomed. Eng., 2006, 8, 153-80.

81. Varani E., Guastaroba P., Di Tanna G.L. et al. Long-term clinical outcomes and cost-effectiveness analysis in multivessel percutaneous coronary interventions: comparison of drug-eluting stents, bare-metal stents and a mixed approach in patients at high and low risk of repeat revascularisation.EuroIntervention, 2010, 5 (8), 953-61

82. Bertand O.F., Faurie B., Larose E. et al. Clinical outcomes after multilesion percutaneous coronary intervention: comparison between exclusive and selective use of drug-eluting stents. J. Invasive Cardiol., 2008, 20 (3), 99-104.