Silicon Carbide Coating - a New Hybrid Design of Coronary Stents

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Summary

This paper describes some results of an open, non-randomized, multicenter, prospective, observational, feasibility study using a new type of coronary stent (alloplastic hybrid design consisting of tantalum coated with silicon-carbide) with respect to different risk for stent thrombosis. 413 stents were implanted consecutively in 298 patients with different risk for stent thrombosis, 247 of them in general accepted indications for coronary stenting and 166 stents in lesions with expected higher risk for stent thrombosis. Both groups were identically medicated postprocedural with aspirin/ticlopidine. The resulting acute and subacute thrombosis rates were 1.45% for both. After a mean follow-up of 6.5 months 26.8% of the implanted stents were restenosed. Focal in-stent (re)stenosis was the most common pattern (72.7%). A significant inverse relationship was documented between the stented vessel size and the in-stent (re)stenosis.

Key words

semiconducting coronary stent; hybrid stent design; stent thrombosis; hemocompatibility; clinical results

Introduction

The most significant progress in interventional cardiology has been the intracoronary stenting. This endovascular intervention technique has rapidly evolved and supplanted other interventional approaches (atherectomie, laser, long-term perfusion balloon-technique, cutting balloon) because of the excellent short and long term results. The intracoronary stent placement decreases the morbidity of acute and subacute closure, increases the safety of coronary intervention subsequently leading to a widespread of catheter based coronary intervention. In addition, coronary stenting reduces the restenosis rate, the „Achilles heel" of any coronary intervention [11]. The stenting accomplishes the criteria of a breakthrough technology [19]. Nowadays, stents are involved in more than 60 % of coronary interventions. This increasing clinical use - based on these convincing clinical experiences - is imbedded by a major limitation - the risk of stent thrombosis. The metallic stent surface is the trigger for stent coverage by thrombus. Subsequently, the common accepted indications for stent implantation are restricted to lesions with a primary low thrombotic risk. There are different approaches actually to reduce this stent thrombogenicity. A great contribution in preventing stent thrombosis has been the improvement in the stent deployment technique [8]. The complete apposition of stents to the arterial wall (high pressure balloon technique) allows a postprocedural therapy with antiplatelet agents alone (aspirin/ticlopidine) in lesions with low risk for stent thrombosis. Another approach was pursued by Serruys and Hardhammar [12][24. They documented preliminary data on the safety and

effectiveness of heparin - bonded polymer coated coronary stents. A third and new concept to address stent thrombosis directly is the improvement of the hemocompatibility of the stent surface itself [5] (so called active passivating).

Background:

The surface properties determine the hemocompatibility of alloplastic materials. Smooth surfaces are necessary in order to avoid the activation of the clotting process. Shear stress and turbulent flow conditions activate one important part of the coagulation cascade, the thrombocytes. In addition, thrombosis process is also caused by electrochemical interactions of blood coagulation proteins with the surface of endovascular implants [23]. Baurschmidt and Schaldach [2] documented that thrombogenesis at artificial surfaces is induced by an electron transfer from the protein solution (blood) to the metallic surface. Considering stenting, electrochemical interactions between fibrinogen and the surface layer can result in fibrinmonomer deposition on the stent surface. To avoid such start process for thrombus formation, alloplastic materials require empty electronic states at the transfer level. On one side this requires a semiconducting surface with an energetic difference between the Fermi level and the upper valence band edge of at least 1.4 eV. On the other side, the electronic transfer current must be minimized, which correlates with a reduced density of states in the band gap of the semiconductor. Thus, defined semiconductors with taylored electronic properties should exhibit superior thromboresistance, hemocompatible materials should be semiconductors. Due to the high brittleness of the known semiconductors the combination of mechanical stability and ductility combined with such high hemocompatibility can not be realized by one single material. As a solution, materials with well known and useful mechanical properties are coated with a thin semiconducting layer, resulting in a hybrid design. In this case, the basic material is selected to fulfill the mechanical requirements, whereas the surface material assures the improved hemocompatibility of the device.

Silicon carbide in an amorphous, doped and hydrogen-rich modification (a-SiC:H) represents the electronic requirements for such surface layer mentioned above. Consequently, BIOTRONIK (Berlin, Germany) realized a new principle of active passivating based on this knowledge and developed a metallic hybrid stent design using a-SiC:H as a semiconductor deposited on the surface of a slotted tube tantalum stent (TENSUM^{R}). Comprehensive in vitro (summarized in [1]) and experimental studies (normal porcine coronary arteries) formed the basis information for different clinical feasibility studies in order to evaluate the effectiveness of this new principle. TENSUM^{R}-stents were implanted under the conditions of the daily clinical practice in a cathlab in lesions with different risks for in-stent thrombosis but identical procedural and postprocedural treatment (aspirin/ticlopidine).

Some results from an open, non-randomized, prospective, observational, multicenter, feasibility study are demonstrated here.

Objectives

The primary endpoint was to determinate the rates of acute and subacute stent thrombosis in patients with different thrombogenic risk using identical postprocedural treatment with aspirin and ticlopidine.

The secondary endpoint was to estimate the in-stent (re)stenosis rate defined angiographically and/or clinically.

Methods

Device description

The TENSUM^{R}-stent used in this study is a slotted tube, balloon expandable design (80 µm strut diameter) made of tantalum (14 mm long with three segments 4.2 mm) connected by single struts with different lengths (1.0, 0.7 or 0.5 mm) (Fig.1). The foreshortening was < 10 % at 4 mm expansion. The unexpanded stent diameter was 1.6 mm, the metallic surface coverage after stent expansion was 13.7%, the elastic recoil was < 5 %.

The semiconductor silicon carbide was deposited on the stent surface using the plasma enhanced chemical vapor deposition technique [6].

Implantation procedure

Stents were manually crimed on a predilated balloon catheter. The high grade of radiopacifity (tantalum) allowed an exact positioning (particular important in case of side branches). 0.014 inch guide wires and 6-8 F guiding catheter were selected. Femoral (93 %), brachial (4 %) or radial approach (3 %) were used. Stent diameter ranged from 2.5 to 4.5 mm. After stent deployment, the diameter was optimized by successive dilatation at higher inflation pressures (12-16 bar)

and/or by using larger balloons. Criteria for optimal stent expansion were achieved when the within-stent diameter was angiographical or by intravascular ultrasound (IVUS) < 10% to the reference diameter of the vessel. The atrial sheath was removed immediately (low risk group), two hours after the procedure (high risk group) or 24 hours in all cases in one Center (Homburg/Saar). Homeostasis after sheath removal was accomplished with either conventional pressure bandages or the application of various hemostatic closure devices (VasoSeal, Peclose, AngioSeal).

All patients received heparin during the procedure, no oral anticoagulation but aspirin (300 mg p.d.) and ticlopidine (250-500 mg p.d.) over 1-2 month.

Events

Acute stent thrombosis was defined as angiographically documented total or subtotal occlusions or as any angiographically or IVUS visible thrombotic process within the stent(s) occurring within 24 hours after stent implantation. Subacute stent thrombosis (SAT) was defined as any angiographically documented total or subtotal occlusions with TIMI 0 or I flow throughout the stent occurring < 14 days after implantation.

Stents were considered restenotic if the angiographic diameter (caliper method or visual analysis) was < 50 % or if the IVUS - minimal lumen diameter was reduced > 50% compared to the result immediately after stent implantation.

Indications for stenting

298 patients were scheduled to undergo stenting consecutively [1] due to significant de novo lesions with distinct recoil (> 50 %) after conventional angioplasty [2], due to significant restenotic lesions (> 50 %) or dissections after predilataions [3] due to abrupt or threatened closure as the consequence of angiographically documented dissections [4] in vessels after recanalisation of chronic (> 1 year) occlusions [5] in case of recanalisation followed to acute complete thrombotic occlusions (acute myocardial infarction) [6], in patients with significant stenotic lesions of coronary arteries after heart transplantation (cardiac allograft vascular disease - CAVD) and [7] in significantly stenosed coronary venous bypass grafts. The feasibility study begun September 1995, the database with regard to stent implantation and the angiographic and clinical follow-up was closed April 1997.

For data analysis we devided the patient population in two subgroups with respect to (1) generally accepted indications for stent implantation (so-called normal thrombotic risk of coronary lesion - group A; n = 247 stents) and (2) high(er) expected risk for stent thrombosis (group B; n = 166 stents). This group B consisted of small vessels (reference diameter < 3 mm; n = 26 stents), implantation after recanalisation of chronic occlusions (n = 62 stents), total or subtotal thrombotic occlusion (acute myocardial infarction; infarct related artery, no thrombosis therapy, < 8 hours) (n = 27 stents), implantation in CAVD (n = 28 stents) and in disease vein grafts (n = 27 stents).

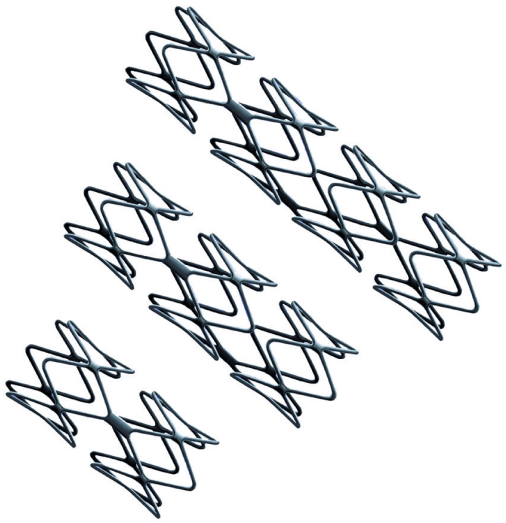

Figure 1. TENSUM^{R}-stent used for implantation in both patient groups (balloon expandable tantalum stent; three-segmented slotted tube connected by two single struts; coated with silicon carbide).

A comprehensive clinical follow-up was possible in one centre only, thus, we confined the data evaluation with respect to restenosis on this data base (Hanna). A complete clinical follow-up was eligible in 164 stents (90 %) and included exercise ECG, pharmacological or ergometric stress echocardiography only or angiography/IVUS in addition (n = 122 stents).

Statistics

Data were analysed using SPSS package (Version 6.01). Chi-square tests were used to compare the results between group A and B. Unpaired t-tests were used for comparison between restenosis rate and vessel diameter. Criterion for significance was $P < 0.05$.

Results

In hospital complications/overall success rate

The implantation success rate was 95 % altogether,

	Acute closure	Subacute thrombosis	Totals
Totals (413 stents)	6 (1.45%)	6 (1.45%)	12 (2.91%)
High risk (group B)*	4 (2.41%)	3 (1.81%)	7 (4.22%)
Low risk (group A)**	2 (0.81%)	3 (1.21%)	5 (2.02%)

* higher risk for stent thrombosis
Data presented are absolute numbers of stents (%)

** general accepted indications for stent implantation (lower risk for stent thrombosis)

Table 1. Acute (< 24 hours) and subacute (>24 hours < 14 days) stent thrombosis.

97 % in group A and 93 % in group B. The in-hospital mortality was 0.67 % (n = 2; stenting in setting of acute myocardial infarctions both, patient died in cardiogenic shock).

Non-emergency coronary artery bypass grafting was needed in one patient (0.34 %) 5 days after stenting because of uncovered long distal dissection of the right coronary artery in a three vessel disease.

5 patients (1.7 %) suffered on stent- related myocardial infarction, all of them with uncomplicated follow-up.

Major bleeding occurred in 4 patients (1.34 %), two required blood transfusions. The other two were surgically treated.

Stent-thrombosis

In 6 of 413 implanted stents (1.45 %) an acute thrombotic occlusion (< 24 hours after implantation) was documented. A subacute (> 24 hours < 14 days) stent thrombosis occurred in 6 implanted stents, in addition. There were no significant differences between both patients groups with respect to stent thrombosis rate (Table 1).

In-stent re(stenosis)

Defined as angiographic/IVUS > 50 % diameter stenosis within the stent and/or positive ergometric stress-tests (ECG and Echocardiography), 44 stents (26.8 % of eligible stents) were restenosed (Table 2).

	In-stent (re)stenosis (stents)	no in-stent (re)stenosis (stents)
Totals	44 (26.8%)	120 (73.2%)
Group A	27 (30.7%)	61 (69.3%)
Group B	17 (22.4%)**	59 (77.6%)

* defined as angiographic/IVUS > 50% diameter stenosis and/or positive ergometric stress tests (ECG and Echocardiography); follow-up time 3-12 months, mean follow-up 6.5±2.3 months

** stents implanted in CAVD excluded

Table 2. In-stent (re)stenosis rate.*

Distribution	Patients	Stents
Focal*	28 (71.8%)	32 (72.7%)
Diffuse	11 (28.2%)	12 (27.3%)
Totals	39	44

* Focal: articulations, proximal and/or diastal (2 mm) of the stent adjacent regions

Table 3.Distribution of the dominant in-stent hyperplastia.

Focal in-stent (re)stenosis was the most common pattern (Table 3). A diffuse in-stent (re)stenosis was seen in 27.3 %, a dominant focal intimal hyperplasia was observed in 72.7 % of restenosed stents. This focal intimal hyperplasia was localised mostly at the articulation points (connective bridges length 1 mm) between the slotted tube segments of the stent.

The in-stent (re)stenosis data with respect to the stent design used in this study (different length of connective bridges) revealed a tendency to a slightly but not significant higher restenosis rate in the group of stents with a bridge length of 1 mm compared to the bridge lengths 0.7 or 0.5 mm independently of the thrombotic risk (group A or group B), as shown in Table 4 (angiographic/IVUS controls only).

A significant relationship is documented between the stented vessel size and the in-stent (re)stenosis (Fig. 2).

Discussion

A new type of coated stent (semiconductor hybrid design) was implanted in lesions with normal and higher local thrombotic risk for stent thrombosis without

	1 mm		0.7 / 0.5 mm	
	n	%	n	%
Totals	24	40.0	20	32.3
Group A	16	41.0	11	47.8
Group B	8	38.1	9	23.1

angiographic/IVUS analysis (biased group of patients with respect to restenosis);

mean follow-up 6.0±2.1 months (range 3-12 months);

restenosis defined as > 50% diameter reductin in comparison to postprocedurale diameter

Table 4. In-stent (re)stenosis rate with respect to the length of the connective bridges.

post-procedural anticoagulation. The acceptable results even in the risk-situations for coronary stenting suggest that this new stent design is safe and acceptable effective in the interventional therapy of coronary obstruction in patients with normal and higher thrombotic risk, too.

Considering the results of a six months follow-up there is no compelling evidence for a reduction of intimal hyperplasia within the coated stent. For the risk of in-stent (re)stenosis the stent design, particular the length of intersegmental struts and the stented vessel size may be more important than the stent surface characteristics.

Hemocompatibility/Stent thrombosis

Although advances in stent deployment technique, stent design and new types of antiplatelet therapy (ticlopidine) achieved low thrombosis rates (1 to 4 %), these outcomes are related to selected cases mostly (20). These data are not transferable in the „real-clinical life" conditions in the daily routine. In many clinical situations, such as unstable angina pectoris, acute myocardial infarction, bailout situations after conventional balloon dilatation (abrupt closure), small vessels, identifiable lesion thrombus, recanalized chronic total occlusions, the risk of stent thrombosis is increased till more than 10 % using conventional (uncoated) stents [3][10][17][20]. In addition, the peak in incidence of subacute stent thrombosis appears two days to two weeks after implantation, consequently after hospital discharge and causes myocardial infarction or death in the majority of patients who experience it [4][11]. Thus, to reduce this existing risk of stent thrombosis remains an important task for clinicians and producer when stenting should be used for indications with higher local thrombotic risk in addition. New stent designs with active type of surface passivation might have a major impact. Such a new concept is the improvement of hemocompatibility of the materials used. The only way to solve the material-related problems in implant technology is to use a well-known engineering material with good mechanical performance, disregarding its hemocompatibility, and to coat it with a hemocompatible coating (so-called alloplastic hybrid design) [7]. Surface properties determine the hemocompatibility of alloplastic materials [22]. The surface potential of the metal used is the initial trigger for stent coverage by thrombus. This thrombogenesis is induced by an electronic transfer from the protein to the metallic surface layer [2]. This fast electron transfer induces an atomic relaxation

Figure 2. Distribution of in-stent (re)stenosis rates in stents implanted in vessels with different size.

(Franck-Condon principle). The resulting relaxation energy (each participating amino acid releases approximately 2 eV) is large enough to break the bonds of the fibrinopeptides when the amino acids are located directly adjacent to the interface. For perpendicular adsorption of fibrinogen coupled solitons move through the helix to the fibrinopeptides where they dissipate and cleave the peptide bonds of the fibrinopeptides. Once the peptides have been removed, the fibrin monomers polymerize and form a thrombus [6]. To avoid such fibrinogen-activation, metallic surfaces should have empty electronic states at the transfer level and minimized densities of states in the band gap of the semiconductor used [5]. This electronic requirements are fulfilled by alloy of silicon and carbon (a-SiC:H). This semiconductor can be deposited on any substrate material which is resistant to temperatures of about 250 °C and thus it is suitable as hybrid coating for metallic stents (7): As a great practical advantage for any stents, thus, can be subsequently applicated using 6 F guiding catheters (important for transradial approach).

In the open randomized multicenter study reviewed here, this new type of coated coronary stent was implanted in patients with different risks for local stent thrombosis. The rates for acute or subacute stent thrombosis were acceptable low altogether and not dif-

ferent between the two groups using the analogue postprocedural medication without anticoagulation (more detailed information with respect to that topic in [14]). The data are encouraging and demonstrate that these stents can be implanted with favorable results even when using postprocedural conventional (aspirin/ticlopidine) antithrombotic medication in patients with higher risk for stent thrombosis, too. Additionally, the incidence of significant bleeding complications and other in-hospital events were similar between the two groups and remarkably low as well. Therefore, based on the character of this study design, we can not make a scientific statement on the specific merits of the thromboresistance properties of this hybrid-stent. But, the favorable impact of these results allows further randomized comparative studies in situations with higher local thrombotic risk for stent thrombosis. Such studies are under the way now.

In-stent (re)stenosis

In this study, stent placement was performed frequently in complex lesion anatomy and different risk for stent-thrombogenicity without „positive" selection of patients. The follow-up results are not comparable with those reported for elective stent deployment in randomized selected patient groups. A higher restenosis rate could be expected. In addition, our preliminary results considering these data contain some selection bias, particularly because of asymptomatic patients were predominantly excluded from the angiographic and IVUS follow-up (see also in [15]). Thus, the data documented in Table 2 have no compelling evidence for a positive effect of the semiconductor hybrid principle on postprocedural intimal hyperplasia. On the other hand, a positive influence of stent-surface on the in-stent (re)stenosis rate might be expected with respect to the reported relationship between local thrombogenicity and growth-factor induced intimal hyperplasia [18][24]. Thus, this approach warranted for a preliminary long-term assessment of outcome. Considering these limitations, our preliminary data suggest, that 30.7 % stents in group A and 22.4 % stents in group B are restenosed, considering the > 50 % criterion and excluding the stent implanted in CAVD. (As we know now the stent implanted in CAVD needs a special consideration because the restenosis rate in such patients is obviously distinct minor in comparison to stented vessels/lesions in native coronary artery disease [13]). The difference in in-stent (re)stenosis rate between the both patient groups was not significant. But, as expected, a tendency ($p < 0.5$) between restenosis rate and the length of the connective bridges was documented independent of thrombosis risk (Table 4). This supports the data from Ikari [16], Dusaillant [9] and Penn [21]. These authors reported, that the articulation site, due to the lack of mechanical support and more sever injury, should be the main locus of excess intima hyperplasia. They found in IVUS follow-up studies that the lumen dimensions were significantly smaller at the articulation both acutely and at follow-up. Three reasons may be involved in this process,

1. a small amount of acute tissue prolapse through the articulation region,
2. a superimposed chronic neoinitimal tissue accumulation and
3. a late vessel remodeling as the result of weaker mechanical support.

The basic stent design used in this study consists of three identical tube segments connected by two single struts with different length (1 mm or 0.7/0.5 mm). Especially, the 1.0 mm articulation gap potentially prevents complete endoluminal coverage of the injured area allowing tissue prolapse into the vessel lumen just in slightly angulated artery segments providing a focus for early „restenosis". These observations (in combination with the data contained in Table 3) lead to the question, what is more important with respect to restenosis, stent design or the surface characteristics? However, any statement based on these data has some limitations:

1. Using the tantalum based TENSUM^{R}-stent, any intimal protrusion through bridges can be detected reliable only by IVUS control, especially in vessels < 3mm. But, the open character of this study did not allow an IVUS 6 months follow-up control in more than 10% of the implanted stents.
2. The distribution of stents with different design is not symmetrical leading to different statistical weights.
3. The observed increased incidence of focal hyperplasia at the articulation may be due to the fact that this articulations frequently cover central areas of stenosis. Thus, without IVUS control, the higher incidence at this stent location may be due to a smaller minimal lumen diameter immediately after implantation. Nevertheless, also these preliminary data support development of stent designs without central open articulation.

With respect to the restenosis data given above it has to

take into consideration, that in contrast to previous studies, we included stent placements and their follow-up data of so-called small vessel stenting in this feasibility study. As shown in Fig. 2 a clear significant inverse relationship between the size of the reference segment and the restenosis rate was documented. These date are in agreement with the published data from Dussaillant et al [9]. These authors demonstrated that the stent volume was smaller in restenotic than in non-restenotic stents regardless of the pattern and location of in-stent (re)stenosis, using IVUS data.

Conclusions

Silicon-carbide coated coronary stents are suitable in standard as well as in high risk situations. The incidence of acute or subacute stent thrombosis are acceptable low even when using postprocedural conventional antithrombotic medication in patients with high risk for stent thrombosis. Considering preliminary one-center data, there is no compelling evidence for a simultaneous reduction of the stent induced intimal hyperplasia. For the risk of in-stent (re)stenosis the stent design and the stented vessel size may be more important than the semiconductor surface characteristics.

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