Initial Results and Long-Term Clinical Follow-up of a Silicon Carbide Coated Stent

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Summary

Stenting is still limited by (sub-)acute thrombosis and restenosis. It is hypothesized that these problems are at least partly due to the limited bio- and hemocompatibility of the stent material, as determined by the physical and electrochemical properties of the stent surface. The aim of this study was to assess the feasibility, safety and efficacy of implantation of a stent coated with hydrogenated amorphous silicon carbide (a-SiC:H). Data were collected prospectively. The occurrence of cardiac adverse events and angina score were assessed at clinical follow-up. A total of 307 Tensum® (BIOTRONIK, Germany) stents were implanted in 288 patients. Two subgroups have been built: the first subgroup (114 patients, 114 stents) underwent elective stenting of single vessels, the second subgroup (174 patients, 193 stents) included all kinds of lesions and indications. The target lesion revascularization rate was 3.5% in the first subgroup and 15% in the second subgroup. The angiographic restenosis rates at the 6 month follow-up was 23% and 17%, respectively. In conclusion, the Tensum® coronary stent is a safe and efficacious device with a high primary success rate and favorable long-term clinical follow-up in elective stenting as well as daily practice. Compared to other trials (BENESTENT, STRESS) the low angiographic restenosis rate suggests that the silicon carbide coating may indeed play a role in reducing subacute thrombosis and restenosis.

Key Words

Stent, silicon carbide, coating, restenosis, target vessel revascularization

Introduction

Percutaneous transluminal coronary angioplasty (PTCA) is widely used and highly successful in the treatment of ischemic heart disease. The principal limitation of this technique is the relatively high rate of both angiographic and clinical restenosis. Little progress was made on reducing the incidence of restenosis until the development of intracoronary stents in 1986 [1]. Initially, only restenosis, severe dissection or threatened closure were indications for stent implantation. The major drawback of stent implantation was the risk of potentially lethal stent thrombosis. However, the use of intravascular ultrasound (IVUS) [2], high pressure inflation [3], and ticlopidine [4], has improved acute results and dramatically decreased the incidence of (sub-) acute stent thrombosis to 1-3%. After publication of the STRESS [5] and BENESTENT [6] trials, elective coronary stent implantation for prevention of restenosis became common clinical practice. Recoil [7] and negative remodeling [8] are prevented by stent implantation, and scaffolding the vascular wall results in improved lumen expansion over balloon dilatation alone. As a result of the larger lumen achieved with stenting, more lumen loss is tolerated before neointimal proliferation results in signifi-

cant restenosis. Although post-stent implantation restenosis rates are lower compared to balloon angioplasty, no effective, routine prevention for in-stent restenosis is available yet. The intravascular wound-healing process, resulting in neointima formation, is significantly affected by activated leukocytes and the local inflammatory response of the vessel wall. Thus, thrombosis and in-stent restenosis continue to be problems in stenting. Even in highly selected groups of patients the angiographic restenosis rate is between 22 and 32%. It is hypothesized that at least a part of these problems is due to the limited bio- and hemocompatibility of the stent material itself, which are determined by the physical and electrochemical properties of the stent surface [9]. Proteins are oxidized at the interface of incompatible materials, inducing thrombosis, platelet adhesion and cell proliferation. By coating a stent with amorphous hydrogenated silicon carbide, a semiconducting ceramic, protein oxidation is inhibited by a low density of unoccupied states in the energy range of the transfer level [10]. Furthermore, silicon carbide coated stents have reduced leukocyte binding properties compared to uncoated stainless steel stents [11], indicating an improved biocompatibility, which might cause a decreased inflammatory response. It is possible that coating a stent with silicon carbide can further reduce the risk of (sub-)acute stent thrombosis and might favorably influence long-term clinical outcome. To evaluate the efficacy, safety, and procedural outcome of a silicon carbide coated tantalum stent (Tensum®, BIOTRONK), an observational, multicenter study was performed. In order to provide more information about the mechanisms of thrombosis and restenosis, two subgroups have been built. The first group assessed the clinical performance following elective deployment of a single Tensum® stent in localized native coronary lesions. The second group was non-elective and included all indications for stenting in daily practice. By breaking the study into these two arms, the influence of the type of lesion and the stent material was assessed.

Materials and Methods

Material

The Tensum® (BIOTRONIK, Germany) coronary stent was used for each stent procedure (Figure 1). The Tensum® stent has a slotted-tube design, made from tantalum and is coated with amorphous silicon carbide (a-SiC:H modification). Tantalum is a highly radiopaque material and is easily seen on fluoroscopy. Single tubular slotted segments, each 4.2 mm in length, are connected by 0.5 mm articulations. In this study, only stents consisting of three segments with a total stent length of 13.6 mm were used. The stent-to-vessel wall area ratio is 13.7% in the fully deployed state.

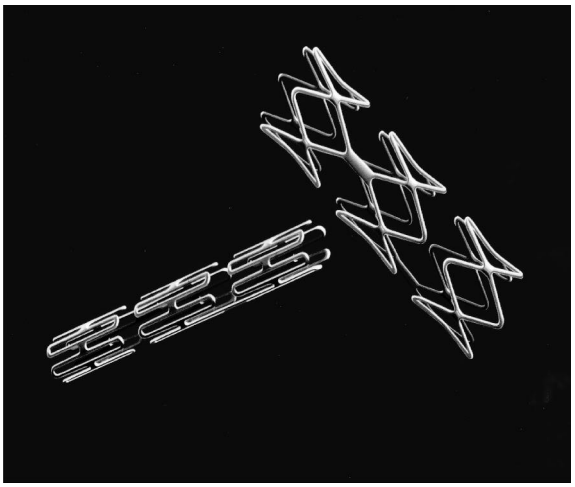

Figure 1. Tensum stent undeployed and deployed. The stent consists of tubular segments each of 4.2 mm and connected by 0.5 mm articulations.

Patients

Oral or written informed consent was obtained in all patients. The study was performed according to the declaration of Helsinki. The study protocol was approved by the institutional ethical committee. Patients were eligible for subgroup 1 if they were symptomatic with localized (< 15 mm lesion length) native coronary artery disease which was suitable for PTCA and intracoronary stent insertion. Only patients undergoing single vessel angioplasty (with no plans for further interventional procedures) were considered. Patients having stents deployed in a bailout situation were also excluded from subgroup one. Patient characteristics are summarized in Table 1.

Procedure

All procedures were performed by femoral approach using 6 or 8 French guiding catheters. At the beginning of the procedure, all patients received 10000 IU heparin intra-arterially. An additional 5000 IU of heparin was administered to some patients when required to maintain adequate anticoagulation. Predilatation was

	Subgroup 1 (elective)	Subgroup 2 (non-elect.)
Number of stents	114	193
Number of patients	114	174
male	88	125
female	26	49
mean age	57 ± 12 years	61.2 ± 10.3 years
Patient characteristics	**%**	**%**
Current smoker	32	36
Previous smoker	43	34
Hypercholesterolemia	14	48
Hypertension	26	34
IDDM	n.i.	5
NIDDM	n.i.	7
Positive family history	39	62
Previous myocardial infarction	25	31
Previous angioplasty	0	29
Previous CABG	0	21
Diabetes	4	12
Anginal score before intervention		
Stable angina	60	49
Unstable angina	30	45
Post myocardial infarction angina	10	6
Indication for stent implantation		
Severe dissection	0	53
Elective implantation	100	34
Restenotic lesion	0	13
Distribution of stent implantation		
Left anterior descending artery	55	36
Circumflex	13	22
Right coronary artery	32	35
Venous bypass grafts	0	17

Table 1. Patient and lesion characteristics for both subgroups.

performed by standard techniques. Following adequate predilatation the hand crimped Tensum® stents were deployed using standard high pressure techniques. The final result was assessed by angiography. In order to maximize the success of stent deployment it was attempted to reach a 1:1.1 vessel to stent ratio upon visual assessment. When necessary, on the basis of angiographic appearance, dilatation with a larger balloon or a higher pressure was performed. All patients received at least 80 mg/day of aspirin, ticlopidine at two daily doses of 250 mg for 30 days and, if indicated, subcutaneous heparin, 0.3 cc, for 3 days. Only patients on oral anticoagulants that could not be stopped for reasons other than coronary artery disease did not receive this antiplatelet regimen.

Data collection

During the procedure pre- and post-treatment angiograms were made in two orthogonal views after intracoronary injection of 0.2 mg nitroglycerin. Following the procedure, offline quantitative coronary angiography (QCA) analysis of 35 mm cine-angiograms was performed using the MEDIS QCA system in most patients [12,13]. Catheter calibration and computer-assisted edge detection were used. The Reference Diameter (RD), Minimal Lumen Diameter (MLD) and

		Subgroup 1	Subgroup 2
Proximal reference diameter	pre-	3.26 ± 0.46 mm	3.13 ± 0.49 mm
	post-	3.38 ± 0.49 mm	3.29 ± 0.48 mm
	6 month follow-up	3.46 ± 0.57 mm	n.i.
Minimal luminal diameter	pre-	0.88 ± 0.38 mm	0.76 ± 0.57 mm
	post-	3.21 ± 0.48 mm	3.06 ± 0.48 mm
	6 month follow-up	2.17 ± 0.79 mm	n.i.

Table 2. Quantitative angiographic data.

Percentage Diameter Stenosis (%DS) were determined in two pre-procedural orthogonal views. In two final orthogonal views the Reference Diameter, MLD in stent, %DS in stent and Mean Stent Diameter (MSD) were determined. Follow-up was performed by interviewing patients, family physicians and referring cardiologists. The primary endpoint of this study was the occurrence of target vessel revascularization or angiographic evidence of stent restenosis. However, additional information on angina score and cardiac events, including hospital admissions, myocardial infarction, unstable angina, coronary angiogram and revascularization, was collected. Myocardial infarction was defined as Creatinine Kinase (CK) elevation to above twice the normal upper limit (> 240 U/L).

Procedural results

In subgroup 1 the final balloon size used was 3.26 ± 0.39 mm. The maximum pressure used for stent deployment was 15.4 ± 2.6 atmospheres. Procedural success was achieved in 99% of the lesions (113/114). In the one failure the stent dislodged from the balloon when trying to access a calcified proximal left anterior descending artery lesion. The stent was subsequently deployed proximal to the lesion without any clinical sequelae. Quantitative angiographic data for the primary procedure is shown in Table 2. The MLD of the target site increased from 0.88 ± 0.38 mm pre-procedure to 3.21 ± 0.48 mm post-procedure with a reference diameter of 3.38 ± 0.49 mm. The lesion length was 11.4 ± 3.8 mm. In subgroup 2 QCA was performed only on the first 100 patients. At pre-procedure views, the RD was 3.13 ± 0.49 mm and the MLD was 0.76 ± 0.57 mm. In 12% the treated lesion was a total occlusion with TIMI 0 flow. In the final views the MLD increased to 3.07 ± 0.48 mm, an acute gain of 2.31 mm. The %DS improved from 76.48 ± 20.56% pre-procedure to 6.05 ± 12.72% after stent implantation. The data are summarized in Table 2.

In-hospital Complications

In subgroup 1, there were no deaths or need for Coronary Artery Bypass Graft (CABG) in the first week. Subacute stent thrombosis (SAST) occurred in one patient at 48 hrs (SAST rate 1/114 = 0.8%). The patient was treated with thrombolysis and subsequently underwent repeat PTCA for what was felt to be a sub-optimally deployed stent. In subgroup 2, fifteen patients (8%) experienced an adverse event before hospital discharge. One patient died on the third day post-intervention. Despite subcutaneous heparin post-intervention, at autopsy massive pulmonary embolism was found as the cause of death. No clinical signs of venous thrombosis were seen prior to the death, nor was the patient known to have coagulation abnormalities. Acute stent thrombosis occurred in one patient suffering from homo-cysteinuria, two hours post-stent-implantation. The stent was opened successfully and the remaining hospital stay was uncomplicated. In the laboratory test, no elevation of cardiac enzymes after the stent occlusion was seen. This thrombosis might be due partly to the hypercoagulable state present in homocysteinuria patients, who have decreased antithrombin III and protein C levels and increased levels of factor V and factor X [14]. Elective CABG was performed in one patient. After stent implantation a suboptimal result was obtained. Repeat angiography was scheduled prior to discharge, showing a dissection proximal of the stent extending into the left main stem. Although the patient was free of anginal complaints, elective CABG was performed the ninth day post-stent-implantation. The patient recovered uneventfully

after bypass surgery. One patient developed unstable angina before discharge. At repeat angiography the stent implanted in the circumflex artery was patent, with TIMI 3 flow and no evidence of thrombus in the stent was present. However the mid-left anterior descending (LAD) coronary artery stenosis, which initially was considered not to be significant, was judged significant and was successfully dilated. The further hospital stay was uneventful. In 21 patients, CK elevation to above twice the local normal value was seen post-procedure. In 10 patients (5.8%) stent implantation was performed during rescue PTCA. In these patients CK elevation post intervention was not considered as an adverse event. Eleven patients (6%) experienced myocardial infarction post-intervention with a mean maximal CK of 413 (range 298 - 900) U/L.

Follow-up

In subgroup 1 one patient (1/114) died after six months. This patient had an acute fatal myocardial infarction in the same territory as the stent 5 months following the index procedure. The target lesion revascularization rate was 4/113 (3.5%). Three patients required repeat PTCA and 1 patient had CABG . Follow up angiography was performed in 73 of 114 and the results are shown in Table 2. The minimal lumen diameter at follow-up was 2.17 ± 0.79 mm with a reference diameter of 3.46 ± 0.57. Angiographic restenosis, defined as a minimal lumen diameter of < 50% of the proximal reference diameter, was found in 17/73 (23%). In subgroup 2 follow-up was obtained in 172 out of 174 patients. At a mean follow-up of 454 ± 181 days, 97% of the patients were alive. Cause of death was unknown in 1 patient (558 days post-intervention). One patient died due to leukemia (508 days post-intervention), 1 patient died several hours post-CABG (316 days post-intervention), one patient died due to ventricular septum rupture post-non-target-vessel-myocardial-infarction (287 days post-intervention), and, as described above, one patient died due to pulmonary embolism the third day post-intervention. Eighty-one percent of the patients were free from clinical evidence of target-vessel restenosis. A total of 30 patients had angiographically-visualized target-vessel restenosis (i.e. 17%), including the 2 patients undergoing target-vessel revascularization before hospital discharge for stent thrombosis and dissection extending proximal of the stent, as described above. Of the remaining 28 patients, 14 underwent re-angioplasty, 10 patients underwent CABG of the target-vessel, and four were treated with medication only. Non-target-vessel revascularization was performed in 3.6% of the patients. One patient experienced a non-target-vessel-related myocardial infarction after discharge from the hospital. Angina scores showed a significant improvement compared with the angina scores before stenting. Seventy-one percent of the patients said that they were entirely free from chest pain at follow-up, 20% had anginal complaints conforming to Canadian Cardiac Society (CCS) class I or II, and 9% of the patients had angina CCS class III or IV.

Discussion

The aim of this study was to investigate the effect of the stent material on stent thrombosis and restenosis. For that purpose a tantalum stent with a hemocompatible silicon carbide coating (Tensum®) was implanted in an elective subgroup and a non-elective group representing daily practice. The Tensum® stent is made of tantalum, a highly radioopaque material, easily seen on fluoroscopy. Due to the first generation stent design and the high radioopacity of the stent, quantitative coronary angiography with automatic contour detection is hindered by interference of the stent struts, often demanding manual correction. However, in cases where precise stent placement is mandatory, such as ostial or bifurcation lesions, the high radioopacity of the stent is an advantage. A low (sub-)acute thrombosis rate of 0.8% (group 1) and 0.6% (group 2) was found and long-term clinical follow-up showed favorable results. Due to the heterogeneity of the patient data found in literature, reliable comparison of the Tensum® data with other stents is difficult. However, the BENESTENT and STRESS trials were performed on a highly selective patient population, which represents only a small section of the population undergoing PTCA [15] and is very similar to the group 1 population of this study. For example, the angiographic restenosis rate of the "gold standard" (STRESS study, stainless steel stent, articulated, unstable angina patients eligible) was 31.6% compared to 23% in group 1. Target lesion revascularization in the STRESS study was 16.1% compared to 3.5% with a silicon carbide coated stent in this study. In addition, even in the non-elective group 2 similar results have been obtained. Restenosis rate was 17% and target vessel revascularization was

15%. In conclusion, despite treatment of a high number of high-risk patients, the Tensum® coronary stent was shown to be a safe and efficacious device with a high primary success rate and a favorable long-term clinical follow-up. The Tensum® stent exhibited a better clinical outcome than comparable stents studied in comparable patient groups. Some of the observed difference might be attributed to modern procedures, but it is unlikely that such a dramatic difference could be realized by a half-decade of technique improvement alone. These initial results with a first generation design of a stent using the amorphous silicon carbide coating suggest that this coating may indeed play a role in reducing both SAST and restenosis. This may be particularly important for lesions at high risk, such as thrombotic lesions or small vessels. The next generation of silicon carbide coated stent (Tenax®, BIOTRONIK, Germany) is a stainless steel slotted tubular stent with no articulation coated with the same compound [16]. The absence of articulation should improve the restenosis rates and results of similar studies along with randomized trials in high-risk lesions conducted with this stent are awaited with interest.

References

[1] Sigwart U; Puel J, Mirkovitch V, Joffre F, Kappenberg L. Intravascular stents to prevent occlu-sion and restenosis after transluminal angioplasty. N Eng J Med 1987; 316: 701-706.

[2] von Birgelen C; Gil R, Ruygrok P, et al. Optimized expansion of the Wall stent compared with the Palmaz Schatz stent: on-line observations with two and three dimensional intracoronary ultrasound after angiographic guidance. Am Heart J 1996; 131: 1067-1075.

[3] Colombo A; Hall P, Makamura S, et al. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. Circulation 1995; 91: 1676-1688.

[4] Schomig A; Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary artery stents. N Eng J Med 1996; 334: 1084-1089.

[5] Fischman DL; Leon MB, Baim DS, et al. A randomized comparison of coronary stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Eng J Med 1994; 331: 496-501.

[6] Serruys P; 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 Eng J Med 1994; 331: 489-495.

[7] Haude M; Erbel R, Issa H, Meyer J. Quantitative analysis of elastic recoil after balloon angioplasty and after intracoronary implantation of balloon expandable Palmaz Schatz stent. J Am Coll Cardiol 1993; 21: 26-34.

[8] Glagov S; Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Eng J Med 1987; 316: 1371-1375.

[9] Liu MW; Voorhees WD III, Agrawal S, Dean LS, Roubin GS. Stratification of the risk of thrombosis after intracoronary stenting for the threatened or acute closure complicating coronary balloon angioplasty: a Cook registry study. Am Heart J. 1995; 130: 8-13.

[10] Bolz A; Schaldach M. Amorphous silicon carbide: A semiconducting coating with superior hemocompatibility. Artif Organs 1991; 14 Suppl. 4: 151-160.

[11] Van Oeveren W; Tigchelaar I, Monnink SHJ, van Luyn MJA, Haan J. Biocompatibility of BIOTRONIK Tensum 3 stents. Unpublished data.

[12] Reiber JHC; Serruys PW, Kooijman CJ, et al. Assessment of short-, medium- and long-term varia-tions in arterial dimensions from computer assisted quantification of coronary cineangiograms. Circulation 1985; 71: 280-288.

[13] Haase J; DiMario C, Slager CJ, et al. In vivo validation of online and off-line geometric coronary measurements using insertion of stenosis phantom in porcine coronary arteries. Cathet Cardiovasc Diagn 1992; 27:16-27.

[14] Mayer EL; Jacobsen DW, Robinson K, Homocysteine and coronary atherosclerosis. J Am Coll Cardiol 1996; 27: 517-527.

[15] Tilli FV; Aliabadi D, Kinn JW, Kaplan BM, Benzuly KH, Safian R. Real life stenting: a comparison of target vessel revascularization in BENESTENT-STRESS lesions to Non BENESTENT-STRESS lesions (Abstr.) Circulation 1996; 94: I-332.

[16] Bolz A; Harder C, Unverdorben M, Schaldach M. Development of a new hybrid coronary stent design with optimized biocompatible properties. In Press: Wise DL. Biomaterials Engineering and Devices: Human Applications. Humana Press (1999).