Original Article

Randomized Intravascular Ultrasound Comparison between Endoprostheses with and without Amorphous Silicon-Carbide

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Objective

In-stent restenosis remains a major limitation following coronary stent implantation. Amorphous silicon-carbide (a-SiC) coating has been shown to improve stent biocompatibility, therefore, reducing local inflammation and thrombus generation. Due to the latter, a-SiC coating might have an impact on the prevention of neointimal hyperplasia (NIH) and restenosis.

Methods

This prospective, randomized, open-label trial compared a-SiC-coated (group A) versus uncoated (group B) stent implantation in de novo lesions. We included 100 patients (50 patients in each group) and the primary end-point was in-stent volume of NIH measured by intravascular ultrasound.

Results

All patients underwent successful stent deployment. Although absolute NIH volume was greater in A (51.2 mm³ SD 18.8 mm³ versus 41.9 mm³ SD 16.4 mm³; P = 0.014), relative (divided per mm of stent length) NIH volume was similar (2.9 mm³/mm stent SD 1.0 mm³/mm stent versus 2.5 mm³/mm stent SD 0.9 mm³/mm stent; P = 0.108). Late loss, restenosis, and major adverse cardiac events (MACE) were similar.

Conclusion

A-SiC-coated stents did not reduce either NIH or MACE at long-term follow-up.

Keywords

restenosis, coronary artery disease, percutaneous coronary intervention

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The superiority of coronary stent implantation over percutaneous transluminal balloon angioplasty in virtually all lesion subsets has led to the wide use of stents for the percutaneous treatment of coronary lesions [1,2]. However, in-stent restenosis remains as a major limitation [3,4].

Recent data suggest that neointimal proliferation, the cornerstone of in-stent restenosis [5,6], is related to the presence of thrombus and degree of inflammation at the stent site[7]. A potential approach for the prevention of neointimal proliferation is the use of amorphous silicon-carbide (a-SiC), an inactive substance known to have antithrombotic and anti-inflammatory properties [8,9]. By coating stents with a-SiC, hemo- and biocompatibility of stent prostheses is enhanced, potentially reducing neointimal proliferation.

Therefore, the purpose of the CERAMIC trial (randomized intravascular ultrasound Comparison between EndopRostheses with and without AMorphous sIlicon-Carbide for the prevention of coronary restenosis) was to determine whether a-SiC-coated stents prevent intrastent neointimal proliferation in humans.

Methods

The study was performed according to the Declaration of Helsinki. The study protocol was approved by the institutional ethical committee. Informed consent was obtained from each patient before enrollment.

The criteria for enrollment included the following: a single symptomatic or ischemia-driven *de novo* coronary lesion suitable for stent implantation in a native coronary artery. Exclusion criteria included: 1) acute coronary event within 72 hours prior to the intervention, 2) lesion located in the left main coronary artery, 3) ostial, bifurcated, or totally occluded lesions, 4) target artery < 3.0 mm or > 4.0 mm in size or > 15 mm in length.

Patients were randomized to either a-SiC-coated Teneo (Biotronik, Germany, group A) or bare Bx Velocity (Cordis, United States of America, group B) stent implantation. Teneo is a 316L stainless steel balloon-expandable tubular-slotted stent with a strut thickness of 0.08 mm and coated with a-SiC. The coating process with a-SiC is carried out by a plasma-enhanced chemical vapor deposition technique, which results in an a-SiC coating thickness of 0.08 mg. All Teneo stents were 15 or 20 mm in length and 3.0 or 3.5 mm in diameter, whereas all Bx Velocity stents used were 13 or 18 mm in length and 3.0 or 3.5 mm in diameter.

Stent implantation was performed using the conventional technique after balloon predilatation. Postdilatation was performed if necessary. Periprocedural intravenous heparin was given to maintain an activated clotting time >250 seconds, and all patients received aspirin (200 mg once daily) and clopidogrel (300 mg loading dose followed by 75 mg once daily) or ticlopidine (250 mg twice daily) for one month.

Clinical information was collected 30 days, 3 months, and 6 months after the procedure. Angiographic and intravascular ultrasound (IVUS) follow-ups were performed at the 6-month visit. Major adverse cardiac events (MACE) were defined as death, myocardial infarction, target vessel repeat percutaneous coronary intervention, or coronary artery bypass grafting.

Pre- and postprocedural as well as follow-up angiographic data were analyzed offline using the Cardiovascular Angiographic Analysis System (CASS II, Pie Medical Imaging, Maastricht, The Netherlands) as described elsewhere. Following an intracoronary nitrate bolus, the angiographic view with the worst luminal diameter was selected for the analysis. IVUS images were acquired using motorized pull-back at a constant speed of 0.5 mm/s. Three segments were selected for angiographic and volumetric IVUS analysis: the stented segment and 2 edge segments that were axially 5 mm proximal and distal to the stent margins. IVUS volumetric analysis was performed with commercially available software (Echoplaque, Indec Systems, USA)

In an attempt to correct for occasional differences in stent length deployed between groups, not only absolute but also relative (per millimeter stent length) neointimal hyperplasia (NIH) volume was calculated. Volume obstruction was defined as the ratio of the volume of NIH to the volume of the stent, multiplied by 100.

The primary end-point was neointimal proliferation assessed by IVUS at 6-month follow-up catheterization. Secondary endpoints were 1) binary restenosis rate; 2) minimal luminal diameter (MLD) at 6-month follow-up angiography and late loss; 3) MACE at 6-month follow-up.

The size of the patient group required to test the hypothesis was calculated by the method already described by Armitage et al [10]. The expected NIH volume as measured by IVUS following Bx Velocity is 40.0 mm^3, with a standard deviation (SD) of 20.0 mm^3, a value that was determined by previous observations at six-month follow-up of patients who had received Bx-Velocity® stents. To detect a 30% reduction in NIH volume with a-SiC-coated stent treatment with 80% power at a 2-sided type I error rate (alpha) of 0.05, it was calculated that at least 34 patients in each group were necessary.

All statistical analyses were undertaken using SPSS (SPSS UK Ltd, Surrey, UK). Continuous variables are expressed as mean (SD) and were compared by the unpaired Student *t* test. Categorical variables were represented by percentages and absolute frequencies and compared by chi-square test with Fisher correction. P-value < 0.05 was considered statistically significant. Analysis was performed according to the intention to treat.

Results

As shown in table I, baseline clinical and angiographic characteristics were similar between groups.

All patients underwent successful stent implantation. No significant differences in postprocedural MLD or acute gain were found between groups. Stent size most commonly deployed was 3.5 mm (56% and 54%, for group A and B, respectively). Stent length was similar between groups (17.7 mm SD 4.0 mm versus 16.7 mm SD 4.3 mm; P = 0.231). Only 2% of the patients from the coated group, and 4% of the controls required additional stent implantation. No major in-hospital complications occurred.

No events occurred at 30 days. All patients underwent clinical follow-up at 6 months after catheterization. MACE rates were not significantly different between groups (20% versus 16%; for group A and B, respectively, P = 0.795). Target lesion revascularization was also similar between groups (14% for both groups). In group A, one patient suffered sudden death 3 months following stenting, whereas one in group A and 2 patients in group B suffered an acute myocardial infarction. Repeat target vessel revascularization was necessary in 16% and 14% of the patients (group A and B, respectively; P = 1.000). Only one patient (group A) required surgical revascularization due to a long proliferative in-stent restenosis of the left descending coronary artery.

At 6-month follow-up, 94% (n=47) of the cases in each group underwent angiographic assessment. No significant differences existed in in-stent restenosis rates [9 (19.1%) versus 8 (17.0%), for group A and B, respectively; P = 1.000]. In addition, the restenosis pattern was also similar: focal (44.4% group A versus 50.0% in group B; P = 1.000) and diffuse (56.6% group A versus 50.0% in group B; P = 1.000).

As table II shows, the in-stent follow-up MLD, late loss, loss index, net gain as well as follow-up MLD, and late loss values at both the proximal and the distal edges were not different between groups.

A total of 92% (n=46 and 45 for group A and B, respectively) of the patients in each group underwent IVUS assessment at 6-month follow-up.

Although absolute NIH volume was significantly higher in the coated group (51.2 mm^3 SD 18.8 mm^3 versus 41.9 mm^3 SD 16.4 mm^3; P = 0.014), no differences existed in relative NIH volume between the groups (2.9 mm^3/mm stent SD 1.0 mm^3/mm stent versus 2.5 mm^3/mm stent SD 0.9 mm^3/mm stent, for group A and B; P = 0.108). Volume obstruction was also similar between groups (36.4% SD 11.1% in group A versus 37.9% SD 10.9% in group B; P = 0.505). Moreover, proximal and distal edge volumes were not different between groups (tab. III). Late incomplete apposition was not observed in our study.

Discussion

The occurrence of in-stent restenosis limits long-term results following percutaneous interventions [3,4,11]. In the ARTS trial,[11] which compared surgical versus percutaneous revascularization in a multivessel diseased population, no significant differences in death, stroke, or myocardial infarction were found at long-term follow-up. However, one-year repeat revascularization rates were much higher in the nonsurgical group (21% versus 4%; P < 0.001), mostly due to in-stent restenosis. In addition, despite the economical advantage observed in that study by selecting a percutaneous approach, this advantage narrowed down considerably at long-term follow-up when compared with that in the in-hospital phase.

Recent data suggest that neointimal proliferation is strongly

Table I – Baseline clinical and angiographic characteristics

	a-SiC-coated stent (N = 50 P)	Standard stent (N = 50 P)	P valuep
Age (years)	56.7 SD 10.2a	57.8 SD 9.7a	0.569
Male	37 (74%)	27 (54%)	0.061
Ever smoked	26 (52%)	29 (58%)	0.688
Diabetes mellitus	4 (8%)	7 (14%)	0.523
Hypertension	29 (58%)	26 (52%)	0.688
Hyperlipidemia	35 (70%)	37 (74%)	0.824
Previous MI	9 (18%)	11 (22%)	0.803
Clinical presentation			0.981
Stable angina	20 (40%)	21 (42%)	
Unstable angina	16 (32%)	14 (28%)	
Recent MI	10 (20%)	10 (20%)	
Silent ischemia	4 (8%)	5 (10%)	
Target-vessel			0.185
LAD (%)	16 (32%)	24 (48%)	
RCA (%)	22 (44%)	24 (48%)	
Circumflex	12 (24%)	6 (12%)	
ACC/AHA lesion class			0.686
A / B1	23 (46%)	27 (54%)	
B_2 / C	27 (54%)	23 (46%)	
Reference diameter (mm)	2.8 DP 0.3	2.8 DP 0.4	0.870
Diameter stenosis (%)	71.0 DP 6.0	68.2 DP 9.7	0.085

SD- standard deviation; MI- myocardial infarction; LAD- left anterior descending; RCA- right coronary artery; ACC/AHA- American College of Cardiology/American Heart Association.

related to the degree of inflammation and thrombus generated at the stent site [12,13]. In a clinical study utilizing the immunofluorescence technique [9], local coronary artery wall changes were evaluated following balloon and stent implantation. In that study, late loss and restenosis rates were associated with thrombus formation and inflammation, only after stent implantation. In addition, several studies have reported that organized thrombus serves as a nidus for cytokine and growth factor release, which contribute to the process of neointimal formation [12-14].

So far, the use systemic antithrombotic or antiproliferative drugs has not consistently been shown to be efficacious in preventing neointimal proliferation [15,16]. Due to the latter, a new alternative therapeutic approach has emerged, the utilization of inert substances like a-SiC, an amorphous ceramic semiconductor material as stent coating, in an attempt to reduce the stent metallic thrombogenic predisposition [16]. This material prevents electron transfer usually taking place from the stainless steel to circulating peptides, especially fibrinogen [8,9]. When electron transfer occurs, fibrinogen changes its tertiary structure, which accelerates thrombus formation. Indeed, in vitro data have confirmed this hypothesis [9]. Moreover, immunofluorescence studies have also established its anti-inflammatory potential. Thus, by improving stent bio- and hemocompatibility, a-SiC coating could interfere with the organic reaction cascade that leads to NIH [8,9,16]. In the present study, the use of a-SiC-coated stents did not reduce either neointimal growth or revascularization rates at 6-month follow-up. In addition, IVUS analysis at the edges was also similar between groups. Up until now, scant data were available regarding a-SiC-coated stents. Although single center experience with a-SiC-coated stents has been reported, the lack of angiographic follow-up in those reports precludes any definitive conclusion [16-19]. In the TRUST study [20], patients with unstable angina were randomized to a-SiC-coated or uncoated stent implantation, showing a reduction in target vessel revascularization at 6-month follow-up only in patients with unstable angina class IIIB (4.7% versus 15.3%). In our study, where the predominant clinical presentation was stable angina, the latter results were not reproduced.

Regarding the control group, late loss (about 1.0 mm) and NIH (about 40.0 mm^3) values were similar to those of the RAVEL bare stent group [21]. However, higher binary restenosis (26.6% versus 17.0%) and target-vessel revascularization (22.8% versus 14.0%) rates were found in the RAVEL control group when compared with ours. The latter might be due to a greater proportion of patients with diabetes (22.0% versus 14.0%) and lower preprocedural reference diameter values (2.6mm versus 2.8 mm) in RAVEL, which increase the risk for development of in-stent restenosis [15,22].

Another significant difference between the 2 groups was the degree of strut thickness, which is higher in the Bx Velocity® group. A recent study [23] comparing stents with different strut thicknesses showed that higher strut thickness, using as a model the Bx Velocity® stent, was associated with greater restenosis and revascularization rates when compared with thinner strut stents. The latter might be due to greater endothelial damage.

Limitations - As mentioned above, a major difference between the 2 stent groups besides the a-SiC coating was the strut thickness. Nevertheless, in spite of the latter, no differences in NIH occurred. In addition, because patients with complex lesions were excluded, no

Table II – Quantitative coronary angiography results.

	a-SiC-coated stent (N = 50 P) mean (SD)	Standard stent (N = 50 P) mean (SD)	P value
In-stent segment			
Preprocedure MLD (mm)	0.8 (0.2)	0.9 (0.4)	0.085
Postprocedure MLD (mm)	2.8 (0.3)	2.8 (0.3)	0.366
Early lumen gain (mm)	2.0 (0.3)	1.9 (0.3)	0.319
Follow-up MLD (mm)	1.9 (0.7)	1.8 (0.6)	0.552
Late loss (mm)	0.9 (0.6)	1.0 (0.6)	0.567
Loss index	0.5 (0.3)	0.5 (0.4)	0.340
Net gain (mm)	1.1 (0.7)	0.9 (0.6)	0.184
Proximal edge			
- Postprocedure MLD (mm)	2.9 (0.4)	2.9 (0.4)	0.998
- Follow-up MLD (mm)	2.3 (0.8)	2.6 (0.4)	0.507
- Late loss (mm)	0.6 (0.8)	2.3 (0.6)	0.279
Distal edge			
- Postprocedure MLD (mm)	2.6 (0.4)	2.4 (0.6)	0.666
- Follow-up MLD (mm)	2.2 (0.7)	0.5 (0.5)	0.786
- Late loss (mm)	0.4 (0.7)	0.3 (0.3)	0.172

a-SiC- amorphous silicon-carbide; SD- standard deviation; MLD- minimal luminal diameter.

Table III - Edge IVUS measurements at 6-month follow-up.

	a-SiC-coated stent (N = 46 P) mean (SD)	Standard stent (N = 45 P) mean (SD)	P value
Proximal edge			
Vessel volume (mm^3)	84.6 (40.5)	82.4 (41.5)	0.799
Plaque volume (mm^3)	38.1 (17.4)	40.4 (26.0)	0.620
Lumen volume (mm^3)	46.6 (38.7)	41.7 (23.3)	0.467
Distal edge			
Vessel volume (mm^3)	68.5 (22.6)	61.7 (23.3)	0.161
Plaque volume (mm^3)	35.1 (19.1)	32.0 (21.8)	0.472
Lumen volume (mm^3)	33.4 (12.2)	29.5 (13.4)	0.150

IVUS- intravascular ultrasound; SD- standard deviation.

conclusions could be drawn regarding the performance of the a-SiC-coated stent in that patient subgroup. Although MACE rates were similar between the 2 groups, we can not conclude that these 2 stents are clinically similar due to the size of the study population.

In conclusion, the results of the CERAMIC trial indicate that the a-SiC-coated stent in this broad, comprehensive population was not superior to the bare stent as far as the long-term clinical, angiographic, and IVUS findings are concerned.

References

1. Serruys PW, Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994; 331: 489-95.
2. Ruygrok PN, Serruys PW. Intracoronary stenting. From concept to custom. Circulation 1996; 94: 882-90.
3. Till FV, Aliabadi D, Kinn JW, et al. Real life stenting: a comparison of target vessel revascularization in Benestent-Stress lesions to non Benestent-Stress lesions. [Abstract] Circulation 1996; 94(Suppl. I): I-332.
4. Lowe HC, Oesterle SN, Khachigian LM. Coronary in-stent restenosis: current status and future strategies. J Am Coll Cardiol 2002; 39: 183-93.
5. Dussaillant GR, Mintz GS, Pichard AD, et al. Small stent size and intimal hyperplasia contribute to restenosis: a volumetric intravascular ultrasound analysis. J Am Coll Cardiol 1995; 26: 720-4.
6. Hoffmann R, Mintz GS, Dussaillant GR, et al. Patterns and mechanisms of in-stent restenosis: a serial intravascular ultrasound study. Circulation 1996; 94: 1247-54.
7. Inoue T, Sohma R, Miyazaki T, et al. Comparison of activation process of platelets and neutrophils after coronary stent implantation versus balloon angioplasty for stable angina pectoris. Am J Cardiol 2000; 86: 1057-62.
8. Bolz A, Amon M, Osbek C, et al. Coating of cardiovascular stents with a semi-conductor to improve their hemocompatibility. Tex Heart Inst J 1996; 23: 162-6.
9. Monnink SHJ, Van Boven AJ, Peels HJ, et al. Silicon-carbide coated coronary stents have low platelet and leukocyte adhesion during platelet activation. J Investig Med 1999; 47: 304-10.
10. Armitage P, Berry G. The planning of statistical investigations. In: Armitage P, Berry G, ed. Statistical Methods in Medical Research. Oxford: Blackwell, 1994: 175-206.
11. Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001; 344: 1117-24.
12. Lincoff AM, Topol EJ, Ellis SG. Local drug delivery for the prevention of restenosis. Fact, fancy and future. Circulation 1994; 90: 2070-84.
13. Chandrasekar B, Tanguay JF. Platelets and restenosis. J Am Coll Cardiol 2000; 35: 555-62.
14. Schwartz RS, Holmes DR, Topol EJ. The restenosis paradigm revisited: an alternative proposal for cellular mechanisms. J Am Coll Cardiol 1992; 20: 1284-93.
15. Hoffmann R, Mintz GS. Coronary in-stent restenosis – predictors, treatment and prevention. Eur Heart J 2000; 21: 1739-49.
16. Babapulle MN, Eisenberg MJ. Coated stents for the prevention of restenosis: part II. Circulation 2002; 106: 2859-66.
17. Heublein B, Ozbek C, Pethig K. Silicon carbide-coated stents: clinical experience in coronary lesions with increased thrombotic risk. J Endovasc Surg 1998; 51: 32-6.
18. Hanekamp CEE, Bonnier HJRM, Michels RH, et al. Initial results and long-term clinical follow-up of an amorphous hydrogenated silicon-carbide coated stent in daily practice. Int J Cardiovasc Interv 1998; 1: 81-6.
19. Heublein B, Pethig K, Elsayed AM. Silicon carbide coating: a semiconducting hybrid design of coronary stents. A feasibility study. J Invas Cardiol 1998; 10: 255-62.
20. Hamm CW, Hugenholtz PG. Silicon carbide coated stents in patients with acute coronary syndrome (Trust study). Catheter Cardiovasc Interv 2003; 60: 375-81.
21. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002; 346: 1773-80.
22. Elezi S, Kastrati A, Neumann FJ, et al. Vessel size and long-term outcome after coronary stent placement. Circulation 1998; 98: 1875-80.
23. Pache J, Kastrati A, Mehilli J, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (Isar-Stereo-2) trial. J Am Coll Cardiol 2003; 41: 1283-8.