Randomized comparison of carbon ion–implanted stent versus bare metal stent in coronary artery disease: The Asian Pacific Multicenter Arthos Stent Study (PASS) trial

Young-Hak Kim, MD,[a] Cheol Whan Lee, MD, PhD,[a] Myeong-Ki Hong, MD, PhD,[a] Seong-Wook Park, MD, PhD,[a] Seung-Jea Tahk, MD, PhD,[b] Joo-Young Yang, MD,[c] Shigeru Saito, MD,[d] Teguh Santoso, MD,[e] Lizhan Quan, MD,[f] Junbo Ge, MD,[g] Neil J. Weissman, MD,[h] Alexandra J. Lansky, MD,[c] Gary S. Mintz, MD,[i] and Seung-Jung Park, MD, PhD[a] ***Seoul, Suwon, and Ilsan, Republic of Korea, Kanagawa, Japan, Jakarta, Indonesia, Shenyang, and Shanghai, China, Washington, DC, and New York, NY***

Background Heavy metal ions can cause allergic and inflammatory reactions that might be associated with in-stent restenosis. This randomized multicenter clinical study was designed to determine if carbon ion–implanted stents reduce luminal late loss by blocking heavy metal ion diffusion into the surrounding tissue.

Methods A total of 225 patients with 230 native coronary lesions were randomly assigned to receive either a carbon ion–implanted Arthos^{Inert} stent (group 1, n = 113) or a bare metal Arthos stent (group 2, n = 117). The primary endpoint was in-stent luminal late loss at 6-month angiographic follow-up, and the secondary endpoints were the 6-month angiographic restenosis rate and the occurrence of the major adverse cardiac events (MACE) including death, nonfatal myocardial infarction, and target lesion revascularization at 12 months.

Results The baseline characteristics were similar in the 2 groups. In-hospital events did not occur in any patients. Angiographic follow-up at 6 months was obtained in 184 lesions (80%). At follow-up, the luminal late loss was similar in the 2 groups (0.91 $\pm$ 0.77 mm in group 1 vs 0.88 $\pm$ 0.80 mm in group 2, P = .79), and the angiographic restenosis rates were 11.0% in group 1 and 16.1% in group 2 (P = .31). The occurrence rates of MACE at 12 months were 9.1% in group 1 and 10.4% in group 2 (P = .73).

Conclusions The initial and long-term outcomes of the carbon ion–implanted stent were excellent. However, it did not improve long-term outcomes vs the bare metal stent. (Am Heart J 2005;149:336-41.)

Although coronary stenting has reduced the rate of coronary restenosis after balloon angioplasty, in-stent restenosis occurs in at least 10% of stented patients.[1] Numerous mechanical or pharmacological approach have been tried to reduce in-stent restenosis, and experimental and clinical studies have shown that stent design and materials are important factors in determining the risk of thrombosis and late restenosis.[2-4] Moreover, metal ions can evoke an inflammatory tissue response triggering cellular proliferation and thrombogenicity.[5-9] Therefore, attempts have been made to use a barrier coating on the metal surface to reduce metal ion release. Preliminary clinical studies have reported excellent clinical and angiographic results for Carbostents, a carbon film–coated stent.[10,11] The carbon ion–implanted Arthos^{Inert} stent (Amg, Raesfeld-Erle, Germany) is a new surface-treated balloon-expandable tubular stent, which involves carbon surface bombardment of stainless steel rather than a coating process. Theoretically, the carbon film of the Carbostent can easily crack during expansion exposing the bare metal substrate into the surrounding tissue because 2 different material layers with an adhesive boundary between

From the [a]Asan Medical Center, University of Ulsan College of Medicine Seoul, Republic of Korea, [b]Ajou University Hospital, Ajou University School of Medicine, Suwon, Republic of Korea, [c]NHIC Ilsan Hospital, Ilsan, Republic of Korea, [d]Shonan Kamakura General Hospital, Kanagawa, Japan, [e]University of Indonesia Medical School, Jakarta, Indonesia, [f]Liaoning Province People's Hospital, Shenyang, China, [g]Zhongshan Hospital, Fudan University, Shanghai, China, [h]Cardiovascular Research Institute, Washington Hospital Center, Washington, DC, and [i]Cardiovascular Research Foundation, New York, NY.
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Reprint requests: Seung-Jung Park, MD, PhD, Department of Medicine, College of Medicine, Asan Medical Center, University of Ulsan, 388-1 Poongnap-dong, Songpa-gu, Seoul 138-736, Republic of Korea.
E-mail: sjpark@amc.seoul.kr
0002-8703/$ - see front matter

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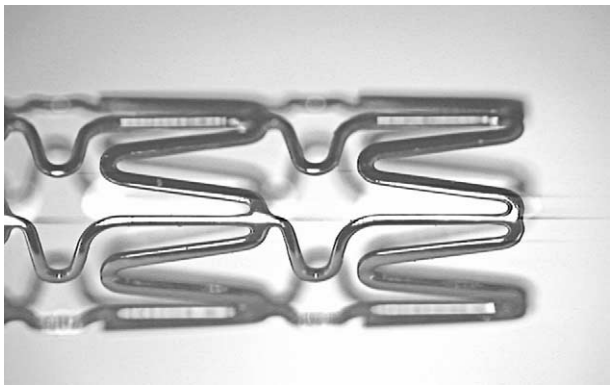
Figure 1



Design of Arthos and Arthos*Inert* stent. Both Arthos stent types use a 316L stainless steel stent substrate with laser-cut tube design.

them have their own unique modulus of elasticity. However, ion implantation creates a surface in which carbon ions are implanted directly into the stainless steel substrate of a stent. Therefore, the carbon ion implantation technique may seal the metal surface more effectively than the carbon coating technique.

The present study is the first international multicenter randomized study to assess the effects of the carbon ion–implanted Arthos*Inert* stent on initial and long-term clinical outcomes for a de novo coronary lesion.

Methods

Study design

Between June 2001 and May 2002, 225 consecutive patients with 230 lesions scheduled for elective stenting were enrolled at 7 Asian centers; the study is called PASS. At each center, ≥500 interventions are performed annually. The treated vessels were of 2.5 to 4.0 mm in diameter with ≥50% diameter stenosis that could be covered by a single stent (10-28 mm). The criteria for exclusion were contraindication to antiplatelet agents, heavily calcified lesions, left main coronary artery stenosis, chronic total occlusion, grafted lesions, primary angioplasty in acute myocardial infarction, left ventricular dysfunction (ejection fraction <40%), or an inability to follow the protocol. Eligible lesions were randomly assigned to receive either a carbon ion–implanted Arthos*Inert* stent (group 1, n = 113) or a bare metal Arthos stent (group 2, n = 117) according to computer-generated randomization lists. The ethics committee at each center approved the protocol, and all patients gave written informed consent.

Arthos*Inert* and Arthos stent

Both Arthos stent types use a 316L stainless steel stent substrate with laser-cut tube design (Figure 1). Both stents include 5 circumferential cells with 0.105-mm thickness (2.5 and 3.0 mm in diameter) and 6 circumferential cells with 0.115-mm thickness (3.5 and 4.0 mm in diameter). The thickness is similar to NIR stent (Boston Scientific, Natick, Mass) or S7 stent (A.V.E. Medtronic, Santa Rosa, Calif). The Arthos*Inert* stent uses the process of carbon ion implantation to change the surface characteristics of a stainless steel Arthos stent. By this technique, carbon atoms are emitted with a very high kinetic energy under vacuum and penetrate the internal and external stent surface (Figure 2). The carbon atoms occupy vacant positions in the metal lattice or displace other atoms from their sites on the metal surface.

Stent implantation

After predilation, the stents were deployed by inflating the stent delivery balloon to nominal pressure; if necessary, adjunctive high-pressure balloon dilation was performed to achieve angiographic optimization. Procedural success was defined as successful stenting at the desired position (diameter stenosis ≤30%) in the absence of death, Q-wave myocardial infarction, or emergency bypass surgery. During the procedure, patients received a 10 000-U bolus of heparin with a repeat bolus of 5000 U to maintain an activated clotting time of ≥250 seconds. All patients received 200 mg/d of aspirin and 75 mg of clopidogrel once daily (or 250 mg of ticlopidine twice daily) 48 hours before the procedure. Therapy with clopidogrel or ticlopidine was continued for 4 weeks, and aspirin continued indefinitely.

Quantitative coronary angiography analysis

Cineangiograms were sent to the angiographic core laboratory (Cardiovascular Research Foundation, New York, NY), and 2 experienced angiographers, unaware of the study purpose, analyzed the angiographic results. Quantitative coronary angiography was performed using the CMS-GFT algorithm (MEDIS, Leiden, the Netherlands). Angiographic measurements were obtained during diastole after intracoronary nitroglycerin administration using a guiding catheter for magnification calibration. Single matched views of the worst diameter stenosis were compared.

Follow-up

Clinical data were obtained upon all 225 patients included in the trial. Clinical events were recorded during the 12-month follow-up. Angiographic follow-up was performed at 6 months or earlier if a patient showed symptoms of recurrence. The primary endpoint was in-stent luminal late loss defined as the difference between the minimal luminal diameter immediately after the procedure and the diameter at 6 months. Secondary endpoints were the angiographic restenosis rate defined as >50% diameter stenosis at 6 months and the occurrence of the major adverse cardiac events (MACE) including death, nonfatal myocardial infarction, and target lesion revascularization at 12 months.

Statistical analysis

The sample size of 230 lesions was calculated to give the study a power of 80% to detect a statistically significant difference ($P < .05$) in a mean in-stent late luminal loss of 0.2 mm, assuming an SD of 0.5 mm in each group. Analysis was made on an intent-to-treat basis. Data are expressed as means ± 1 SD for continuous variables and as frequencies for

Figure 2

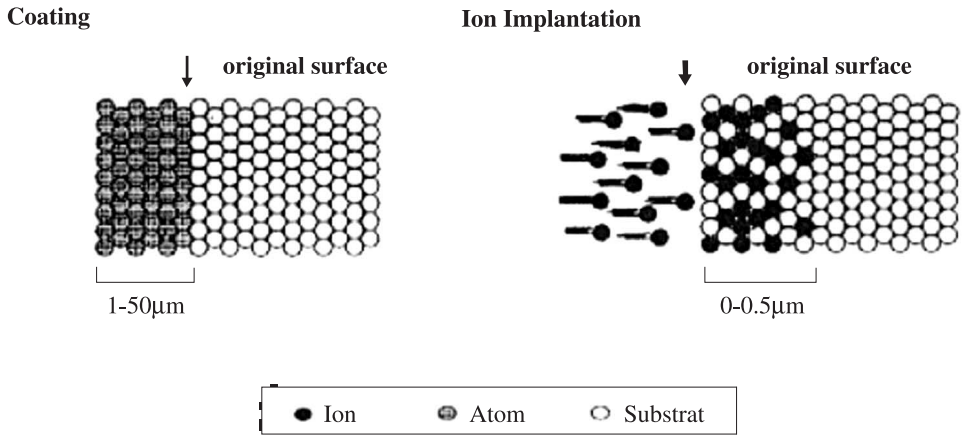


Illustration of the difference to the surface after the coating process and the ion implantation. Although carbon atoms are covered on the metal surface by the coating technique (coating), carbon ions are emitted with a very high kinetic energy under vacuum and penetrate the internal and external stent surface by the ion implantation technique (ion implantation). By ion implantation technique, the carbon ions occupy vacant positions in the metal lattice or displace other atoms from their sites on the metal surface.

Table I. Baseline clinical characteristics

Characteristics	Group 1 (n = 110)	Group 2 (n = 115)	*P*
Age (y)	60.1 ± 9.8	60.0 ± 9.2	.87
Male	85 (77%)	85 (74%)	.64
Current smoker	48 (44%)	49 (43%)	.88
Diabetes mellitus	37 (34%)	30 (26%)	.22
Hypercholesterolemia (>200 mg/dL)	38 (35%)	45 (39%)	.49
Previous myocardial infarction	14 (13%)	19 (17%)	.42
Previous percutaneous coronary intervention	17 (16%)	16 (14%)	.76
Left ventricular ejection fraction (%)	63.9 ± 10.3	63.8 ± 9.5	.95
Acute coronary syndrome	73 (66%)	77 (67%)	.93
Multivessel coronary disease (≥2)	57 (47%)	64 (56%)	.56

Table II. Angiographic characteristics

Characteristics	Group 1 (n = 113)	Group 2 (n = 117)	*P*
Coronary artery dilated			.29
Left anterior descending	60 (53%)	50 (43%)	
Left circumflex	25 (22%)	31 (26%)	
Right	28 (25%)	36 (31%)	
Type B2, C	40 (35%)	50 (44%)	.21
Ostial lesion	4 (4%)	4 (3%)	.97
Bifurcation lesion	6 (5%)	8 (7%)	.62
Lesion length (mm)	14.44 ± 5.34	15.07 ± 5.02	.35
Stent length (mm)	17.17 ± 4.79	17.73 ± 4.66	.37
Balloon-to-artery ratio	1.14 ± 0.26	1.13 ± 0.24	.49
Maximal inflation pressure (atm)	12.5 ± 3.1	12.2 ± 3.4	.51
Reference vessel diameter (mm)	3.21 ± 0.39	3.23 ± 0.43	.75
Minimal lumen diameter (mm)			
Baseline	0.81 ± 0.53	0.80 ± 0.42	.82
Final	3.23 ± 0.44	3.22 ± 0.43	.86
Follow-up	2.32 ± 0.78	2.34 ± 0.84	.84
Diameter stenosis (%)			
Baseline	74.80 ± 15.60	75.47 ± 11.69	.71
Final	−0.62 ± 8.20	−0.13 ± 9.68	.68
Follow-up	28.07 ± 23.02	28.07 ± 24.53	.99
Acute gain (mm)	2.42 ± 0.57	2.42 ± 0.50	.95
Late loss (mm)*	0.91 ± 0.77	0.88 ± 0.80	.79
Loss index	0.39 ± 0.35	0.37 ± 0.35	.63
Binary angiographic restenosis	10/91 (11.0%)	15/93 (16.1%)	.31

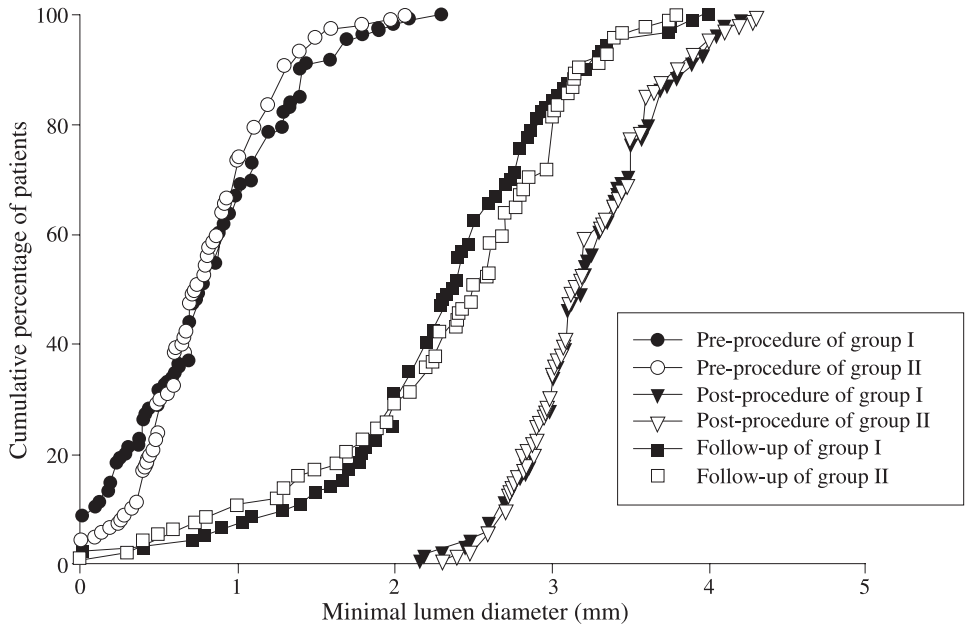
*Late loss/acute gain.

categorical variables. Differences among groups were assessed by using the χ^2 test for categorical variables and Student *t* test for continuous variables. A *P* value <.05 was considered statistically significant.

Results

Baseline clinical and angiographic characteristics are summarized in (Tables I and II). No significant differences were found between the 2 groups with respect to baseline characteristics. Stents were successfully deployed in all lesions. Abciximab was administered to 2 patients (one patient in each group). Debulking coronary atherectomy before stenting was performed in 2 lesions of group 1 and in 4 lesions of group 2

Figure 3



Comparison of the cumulative distribution of the minimal lumen diameter of group 1 (carbon ion–implanted Arthos^{Inert} stent) and group 2 (bare metal Arthos stent). No statistical differences were found between the 2 groups in minimal lumen diameter before the procedure, immediately after the procedure, and at the 6-month follow-up.

(P = .45). Rotablator atherectomy was performed in one calcified lesion of group 2. The procedural success rate was 99.1% in group 1 and 98.3% in group 2. For the treatment of major dissections (≥NHLBI [National Heart, Lung, and Blood Institute] classification grade C) at the stent edges,[12] additional stent implantation was required in 2 lesions (1.8%) of group 1 and in 2 lesions (1.7%) of group 2. Two Arthos^{Inert} stents and 2 Arthos stents were used to treat dissections in group 1 and group 2, respectively. In-hospital events including stent thrombosis, Q-wave myocardial infarction, emergency bypass surgery, or death did not occur. Postprocedural creatinine kinase-MB ≥3 times the upper normal limit developed in 4 patients (3.6%) of group 1 and in 3 patients (2.6%) of group 2 (P = .72).

Quantitative angiographic data are listed in Table II and cumulative frequency distribution curves of the minimal lumen diameter in Figure 3. At baseline and postprocedure, no difference was observed between the 2 groups in the minimal lumen diameter of the target vessel and the reference artery diameter (Table II). Angiographic follow-up was obtained in 182 patients (81%) with 184 lesions (80%), including 91 lesions (81%) in group 1 and 93 lesions (79%) in group 2. At follow-up, minimal lumen diameter of the target vessel was not different in the 2 groups. Likewise, the luminal late loss was similar in the 2 groups (0.91 ± 0.77 mm in group 1 vs 0.88 ± 0.80 mm in group 2, P = .79), and the angiographic restenosis rates were 11.0% in group 1 and 16.1% in group 2 (P = .31).

A 12-month clinical follow-up was available in all patients. There was one cardiac death (one in group 2) and one nonfatal myocardial infarction (one in group 2). During 14.8 ± 3.8 months of follow-up, target lesion revascularization was required in 21 (9.3%) patients (20 repeated interventions, 1 bypass surgery). The rates of target lesion revascularization were similar in the 2 groups [10 (9.1%) patients in group 1 vs 11 (9.6%) patients in group 2, P = .90]. The occurrence rates of MACE were 9.1% in group 1 and 10.4% in group 2 (P = .73).

Discussion

With the widespread use of coronary stents, in-stent restenosis is a major problem in coronary intervention. Although several mechanical and pharmacological therapies have been developed to decrease restenosis, only drug-eluting stents have proven successful.[13,14] However, there is some debate about the advisability and practicality (especially the cost) of making extensive use of a drug-eluting stent. In-stent restenosis

results from excessive fibroproliferative and inflammatory responses related, in part, to insults to the arterial wall.[5,6] Growth factors, cytokines, and vasoregulatory molecules trigger the proliferation of vascular smooth muscle cells, and these responses finally lead to in-stent restenosis.[15] Moreover, metallic stents containing copper and nickel ions have an impact on the movement of neutrophils.[16] Patients with allergic reactions to nickel and molybdenum were found to show a higher frequency of in-stent restenosis than those without such hypersensitivity because of inflammatory responses after allergic triggering.[17] Recent population-based study for 1141 adults showed that the incidence of positive patch test to nickel was exhibited by 13% of subjects.[18] Therefore, there were a lot of efforts to manufacture stents that cause no inflammatory reaction at the arterial wall by coating the stent surface.[19] Several experimental studies have reported that carbonized prostheses provoke little inflammatory change and show excellent tissue integration without thrombus formation.[8,9,20-22]

A recent study showed that a stent coated with Carbofilm (Carbostent) might prevent stent thrombosis in those treated with aspirin alone, because of the antithrombotic activity of the carbon coating.[23] Another recent open-label nonrandomized clinical study obtained excellent angiographic outcomes from Carbostent implantation, that is, an 11% angiographic restenosis rate and a 10% target lesion revascularization rate.[10] The carbon ion–implanted stent studied in the present study has theoretical advantages over the stent coated with Carbofilm. Although a carbon coating automatically creates an adhesive boundary among the different materials, this can fail mechanically and result in breaks and tears. In the Arthos*Inert* stent, carbon ions are implanted directly into the stainless steel substrate of a stent; adhesion problems and mechanical failure are minimized. The current study, which is the first large international multicenter randomized trial undertaken to estimate the efficacy of a carbon ion–implanted stent, found similar excellent initial and long-term outcomes to the study using Carbostent.[10] A large mean reference diameter (3.22 $\pm$ 0.41 mm) in the present study subjects may in part explain the low restenosis rate. On the other hand, the results of the present study are impressive when one considers the high proportion of complex lesions—39% of type B2 or C—which carry a high risk of restenosis.

Regardless of the good clinical and angiographic results, this study did not show a restenosis preventing effect of the carbon ion–implanted stent vs the bare metal stent. The angiographic late luminal loss, the restenosis rate, and the combined clinical endpoint were not different between the 2 stent groups. One recent laboratory report studied the effect of a carbon-coated Carbostent on the antithrombotic and antiinflammatory activity after implantation.[24] This study involved serial measurement of the plasma concentrations of C-reactive protein, fibrinogen, and several cytokines (tumor necrosis factor, interleukin [IL]-1β, IL-6, and IL-8) for 2 days after stent implantation to investigate the effect of stent carbon coating. This study failed to show lower levels of up-regulation of potential biomarkers in the carbon-coated stent vs the bare metal stent and suggested that the carbon coating had no beneficial effect on early inflammatory response after stent implantation. Their observations coincide with the results of our study regardless of different manufacturing process implying that the carbon barrier is not effective for reducing neointimal growth after stenting.

In conclusion, the present study showed good clinical and angiographic long-term results for the carbon ion–implanted stent. However, the carbon ion–implanted stent was not statistically beneficial vs the bare metal stent in the in-stent late luminal loss.

Study limitations

The current study might not be powered adequately to show statistical differences in the late luminal loss of the 2 stents. In addition, the small proportion of complex coronary lesions occurring during the course of this study might induce similar favorable outcomes for the bare metal stent vs the carbon ion–implanted stent. This limitation might warrant further studies including lesions that are more complex.

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