Initial and 6-Month Results of Biodegradable Poly-L-Lactic Acid Coronary Stents in Humans

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Background—Although metallic stents are effective in preventing acute occlusion and reducing late restenosis after coronary angioplasty, many concerns still remain. Compared with metallic stents, poly-L-lactic acid (PLLA) stents are biodegradable and can deliver drugs locally. The aim of this study was to evaluate the feasibility, safety, and efficacy of the PLLA stent.

Methods and Results—Fifteen patients electively underwent PLLA Igaki-Tamai stent implantation for coronary artery stenoses. The Igaki-Tamai stent is made of a PLLA monomer, has a thickness of 0.17 mm, and has a zigzag helical coil pattern. A balloon-expandable covered sheath system was used, and the stent expanded by itself to its original size with an adequate temperature. A total of 25 stents were successfully implanted in 19 lesions in 15 patients, and angiographic success was achieved in all procedures. No stent thrombosis and no major cardiac event occurred within 30 days. Coronary angiography and intravascular ultrasound were serially performed 1 day, 3 months, and 6 months after the procedure. Angiographically, both the restenosis rate and target lesion revascularization rate per lesion were 10.5%; the rates per patient were 6.7% at 6 months. Intravascular ultrasound findings revealed no significant stent recoil at 1 day, and they revealed stent expansion at follow-up. No major cardiac event, except for repeat angioplasty, developed within 6 months.

Conclusions—Our preliminary experience suggests that coronary PLLA biodegradable stents are feasible, safe, and effective in humans. Long-term follow-up with more patients will be required to validate the long-term efficacy of PLLA stents. (Circulation. 2000;102:399-404.)

Key Words: angioplasty • stents • coronary disease

PTCA has been established as an alternative to coronary artery bypass grafting (CABG) to treat selected patients with coronary artery disease. However, the success of PTCA is limited by acute vessel occlusion and late restenosis. Stents were developed to overcome these issues, and the first clinical application with a metallic stent was conducted in 1986 by Sigwart et al.1 During the last 13 years, technological advances have led to the development of new stents. Although intravascular stents offer the promise of addressing both the problems of acute occlusion and late restenosis,2-3 many concerns must be addressed for long-term safety.4 Because all currently available stents are metallic, they induce a varying degree of thrombogenesis and significant intimal hyperplasia. Late thrombosis, especially after stent implantation followed by brachytherapy, may be another potential risk. The long-term development of stent malposition in cases of plaque shrinkage/positive vessel remodeling can also occur. Moreover, the long-term (>10 years) effects of metallic stents in human coronary arteries are still unknown. Finally, any metallic stents remaining in place may be obstacles to additional treatments (eg, repeat PTCA and CABG).

Intimal dissections that are tacked back in place are likely to heal rapidly. Restenosis commonly occurs within 3 to 6 months after coronary intervention, and it rarely occurs thereafter.5-7 Therefore, the clinical need for stent scaffolding is limited after this period. Considering the short-term need and the potential for long-term complications with metallic stents, stents made of biodegradable materials may be an ideal alternative. A biodegradable stent can also be useful for the local administration of pharmacological agents directly to the site of PTCA to prevent late restenosis. Zidar et al.4 reported a minimal
inflammatory reaction and minimal neointimal hyperplasia with the use of poly-\-
\-lactic acid (PLLA) stents in canine femoral arteries. Regarding coronary stenting, Van der
Giessen et al\textsuperscript{8} reported a marked inflammatory response after the implantation of 5 different polymer-loaded stents (polyglycolic acid/polyactic acid, polycaprolactone, polyhydroxybutyrate valerate, polyorthoester, and polyethyleneoxide/polybutylene terephthalate) in a porcine coronary
model. Although the biocompatibility of polymer stents in animal studies has been controversial, some reports suggest that high-molecular-weight PLLA is biocompatible in porcine coronary models.\textsuperscript{9,10} We report our preliminary experience of PLLA stent implantation in human coronary arteries.

Methods

Description of the Stent
The Igaki-Tamai stent (Igaki Medical Planning Co, Ltd) is a coil stent made of PLLA monofilament (molecular mass, 183 kDa) with a zigzag helical design (Figure 1). The thickness of the stent strut is 0.17 mm (0.007 inch). The length of the stent is 12 mm and, in its expanded state, the stent covers 24\% of the vessel area. Because the PLLA stent is self-expanding and springy, radial force measurements were estimated using percent compression strain/compressive stress. This method was a modification of that described in International Standardization Organization 604:1993 (Plastics: Determination of compressive properties). The radial force of the PLLA stent was 11.9%/0.006 MPa and is comparable that of 15.4%/0.006 MPa with the self-expanding Radius stent (Scimed Life Systems, Inc) (unpublished data). The stent has 2 radiopaque gold markers to facilitate the identification of both ends of the prosthesis. Denudation of foreign protein from the stent is done with alcohol, and the stents are mounted on standard angioplasty balloon catheters that are the same size as the stent (manufacturer-specified balloon diameter, 3.0, 3.5, and 4.0 mm).

Deployment of the stent is currently done with a balloon-expandable covered sheath system through an 8 French guiding catheter. Our preliminary study showed the PLLA stent expanded by itself to its original size in 0.2 seconds when heated to 70°C, in 13 seconds at 50°C, and in 20 minutes at 37°C. The stent delivery balloon inflation is performed with a heated dye at 80°C (almost 50°C at the stent site, as estimated by the in vitro experiment) using a 30-second inflation at 6 to 14 atm. This temperature ensures adequate stent expansion within 30 seconds and may minimize vessel injury caused by a heated balloon. The stent continues to expand gradually to its original size after deployment in vivo. When the stent is implanted in a vessel smaller than that of the unconstrained stent diameter, the residual radial force in the prosthesis will tend to dilate the artery. Dilatation will continue until equilibrium is attained between the circumferential elastic resistance of the arterial wall and the dilating force of the PLLA stent.

Patient Population
A protocol for implants in humans was approved by the hospital ethics committee, and written informed consent (according to the Helsinki Declaration) was obtained from all patients before PLLA stent implantation. The indications for stent implantation were (1) the prevention of restenosis in a de novo lesion, (2) restenosis of a major coronary artery after previous balloon angioplasty, and (3) suboptimal results after balloon dilatation.

Implants
A total of 25 stents were implanted in 19 lesions in 15 patients during 17 procedures. All stent implantations were elective. All patients received 10 000 U of intravenous heparin at the beginning of the procedure. Patients also received nifedipine, nitroglycerin, and dextran during the procedure. Before stent implantation, the lesions were dilated by optimally sized balloons or debulked by directional atherectomy (n=2) or rotational atherectomy (n=2) as needed. After pretreatment, the balloon catheter was exchanged for the stent delivery system over a 0.014-inch (0.036-cm) guidewire. The diameter of the stent was chosen visually to be 10\% to 20\% greater than the reference vessel diameter. Multiple stenting was performed, depending on lesion length, to cover the entire lesion. The stent delivery balloon inflation was performed with a heated dye at 80°C. A 30-second inflation at 9 to 14 atm was repeated to obtain optimal results. Postdilatation, higher balloon pressure was used in cases of inadequate stent expansion. The maximum inflation pressure used was 10.8±1.5 atm.

According to local practice, intravenous heparin (~10 000 to 15 000 U/day) was continued postoperatively for 3 days. Poststent medical management included ticlopidine (200 mg/day for 1 month; this is the usual dose in Japan) and aspirin (81 mg/day for 6 months). Calcium antagonists and nitrates were also administered if needed.

Quantitative Coronary Angiography Analysis
Coronary angiography and intravascular ultrasound (IVUS) were performed before, immediately after, 1 day after, and 3 and 6 months after the procedure. Quantitative coronary angiography (QCA) was analyzed using the Cardiovascular Measurement System (Medical Imaging Systems), referenced to the known diameter of the angiographic catheter. The minimal lumen diameter (MLD) of the treated coronary segments, the reference diameter, and the percent diameter stenosis on the baseline angiogram were determined in the view that demonstrated the lesion to be most severe and not foreshortened. Baseline and follow-up cineangiograms were evaluated in the same view. The procedure was considered successful if residual stenosis <50\% with TIMI grade 3 flow was achieved. Angiographic restenosis was defined as a follow-up diameter stenosis ≥50\%.

Quantitative IVUS Analysis
The IVUS system (Boston Scientific Corporation) uses a 40-MHz transducer with a 2.6-French monorail imaging sheath. After the IVUS catheter was passed into and beyond the lesion, a motorized pull-back with a constant speed of 0.5 mm/s was started to obtain IVUS imaging. To evaluate the self-expanding ability of PLLA stents, 5 segments were identified and analyzed: 3 were within the stent and 2 were in the reference segments proximal and distal to the stent. The 3 segments within the stent were the proximal edge of the stent, the central body of stent, and the distal edge of the stent. The stent and lumen cross-sectional areas (CSAs) were measured, and the results were averaged among the 3 averaged segments. A quantitative IVUS analysis was performed with the Manual Measure computer system (Goodman Co).

Statistical Analysis
Continuous variables are expressed as mean±SD. Univariate analysis was performed with the paired t test for continuous variables. P<0.05 was considered significant.
Between September 1998 and January 1999, 25 biodegradable Igaki-Tamai stents were implanted in 19 lesions from 15 patients during 17 procedures. Eleven stents were implanted in 8 left anterior descending coronary arteries, 9 stents in 6 circumflex coronary arteries, and 5 stents in 3 right coronary arteries. Baseline clinical and angiographic characteristics of patients and lesions are shown in Table 1. Subjects included 14 men and one woman with a mean age of 60 ± 15 years. All target lesions were American Heart Association/American College of Cardiology type B or C. A single stent was implanted in 14 lesions, double stents in 4 lesions, and triple stents in one lesion. Debulking before stenting was done in 4 procedures (2 directional atherectomy and 2 rotational atherectomy). All stents were successfully delivered, and angiographic success was achieved in all procedures.

The mean reference vessel diameter was 2.85 mm (range, 2.12 to 3.41 mm), and the mean lesion length was 13.4 mm (range, 6.4 to 26.9 mm) by QCA (Table 2). The percent diameter stenosis decreased from 64% before stenting to 12% after stenting. The MLD increased from 1.02 mm before stenting to 2.59 mm after stenting. The percentage of acute stent recoil, which was defined as \((\text{maximal inflated balloon diameter} - \text{final MLD})/\text{maximal inflated balloon diameter} \times 100\), was 22 ± 7% by QCA.

At the 1-day angiographic follow-up, the percent diameter stenosis was 13% and the MLD was 2.58 mm. One-day angiographic follow-up revealed no further recoil of the stented segment compared with that immediately after stenting (mean recoil, −3 ± 9%). IVUS findings also showed that no significant difference existed in stent CSA immediately after stenting and at 1 day (7.42 versus 7.37 mm²; Table 3).

### Results

Between September 1998 and January 1999, 25 biodegradable Igaki-Tamai stents were implanted in 19 lesions from 15 patients during 17 procedures. Eleven stents were implanted in 8 left anterior descending coronary arteries, 9 stents in 6 circumflex coronary arteries, and 5 stents in 3 right coronary arteries. Baseline clinical and angiographic characteristics of patients and lesions are shown in Table 1. Subjects included 14 men and one woman with a mean age of 60 ± 15 years. All target lesions were American Heart Association/American College of Cardiology type B or C. A single stent was implanted in 14 lesions, double stents in 4 lesions, and triple stents in one lesion. Debulking before stenting was done in 4 procedures (2 directional atherectomy and 2 rotational atherectomy). All stents were successfully delivered, and angiographic success was achieved in all procedures.

### Table 1. Baseline Demographic, Clinical, and Angiographic Characteristics of the Study Population

<table>
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<th>Procedure No.</th>
<th>Lesion No.</th>
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<th>Sex</th>
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<th>CCS Class</th>
<th>Vessel</th>
<th>De Novo/Restenosis</th>
<th>Lesion</th>
<th>AHA/ACC Type</th>
<th>Stent Size, mm</th>
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<td>Hypertension, hyperlipidemia, smoking</td>
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<td>Hyperlipidemia, smoking</td>
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</table>

* and †, Same person.

CCS indicates Canadian Cardiovascular Society; AHA/ACC, American Heart Association/American College of Cardiology; AP, angina pectoris; OMI, old myocardial infarction (MI > 2 weeks); RMI, recent myocardial infarction (MI ≤ 2 weeks); LAD, left anterior descending coronary artery; LCX, circumflex coronary artery; RCA, right coronary artery; DCA, directional coronary atherectomy; and DM, diabetes.

### Table 2. Results of QCA Analysis

<table>
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<tr>
<th>Lesion number</th>
<th>Reference vessel diameter, mm</th>
<th>MLD, mm</th>
<th>Percent diameter stenosis, %</th>
<th>Loss index</th>
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<tr>
<td>19</td>
<td>2.85 ± 0.34</td>
<td>1.02 ± 0.36</td>
<td>64 ± 11</td>
<td>0.44 ± 0.30</td>
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<td>19</td>
<td>2.95 ± 0.35</td>
<td>2.59 ± 0.35</td>
<td>12 ± 8</td>
<td>0.48 ± 0.32</td>
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<tr>
<td>19</td>
<td>2.00 ± 0.40</td>
<td>2.58 ± 0.32</td>
<td>13 ± 11</td>
<td>0.48 ± 0.32</td>
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No stent thrombosis and no major cardiac events (death, Q-wave myocardial infarction, and repeat PTCA or CABG) developed within 30 days. Two patients showed a mild creatine kinase elevation (>2× but <3× upper normal limit) after debulking procedures. All patients were discharged and followed-up clinically and angiographically for >6 months. No deaths, myocardial infarctions, or CABGs occurred in any of the 15 patients within 6 months. Only one patient underwent repeat PTCA (2 lesions were successfully dilated).

Follow-up coronary angiograms suitable for QCA were obtained in all 15 patients within 6 months. The mean MLD at 3 months was 1.88 mm, and the mean percent diameter stenosis was 33%. At 6 months, the mean MLD was 1.84 mm and the mean percent diameter stenosis was 33% (Table 2). The angiographic restenosis rate per lesion was 10.5% (2 of 19), and that per patient was 6.7% (1 of 15) at 3 months (Table 4). The 3-month target lesion revascularization rate per lesion was 5.3% (1 of 19), and the per-patient rate was 6.7% (1 of 15). At 6 months, both the angiographic restenosis rate and the target lesion revascularization rate per lesion were 10.5% (2 of 19), and these rates per patient were 6.7% (1 of 15). Finally, the loss index, which was defined as late loss divided by initial gain, was 0.44 at 3 months and 0.48 at 6 months.

The 3-month IVUS record for one non-restenotic lesion was missing. One restenotic lesion was treated by repeat angioplasty at 3 months and it was not available for the analysis at 6 months. Therefore, IVUS imaging was analyzed in 18 lesions at 3 months and in 18 lesions at 6 months. IVUS showed the presence of stent struts at 6 months. The mean stent CSA tended to be larger both at 3 months and 6 months than immediately after stenting (8.18 and 8.13 mm² versus 7.42 mm²; \( P = 0.086 \) and 0.091); arteries also tended to have a mild layer of neointimal hyperplasia at these follow-up times (2.51 and 2.50 mm², respectively; Table 3). The mean stent CSA was similar at 3 and 6 months (8.18 and 8.13 mm²; \( P = 0.30 \)). This difference suggests that the Igaki-Tamai stent continues to expand for ≥3 months. Lumen CSA was similar at 3 and 6 months (5.67 mm² versus 5.63 mm²; \( P = 0.15 \)), and neointimal area was also similar (2.51 mm² versus 2.50 mm²; \( P = 0.65 \)). This result may imply that the Igaki-Tamai stent does not significantly stimulate intimal hyperplasia within the stent between 3 and 6 months after the procedure.

Serial coronary angiograms of a representative case are shown in Figure 2. The percent diameter stenosis was 30% immediately after stenting, 20% at 1 day, 17% at 3 months, and 16% at 6 months. Serial IVUS findings of the case are shown in Figure 3. Stent CSA was 7.60 mm² immediately after stenting, 8.32 mm² at 1 day, 10.95 mm² at 3 months, and 9.78 mm² at 6 months. Neointimal area was 3.70 mm² at 3 months and 3.82 mm² at 6 months, and no restenosis occurred in this case.

### Discussion

The current study is the first to demonstrate the feasibility and safety of coronary biodegradable polymer stents in humans. Neither stent thrombosis nor early stent recoil in the 25 PLLA stents was observed during this period. No major clinical events related to PLLA stent implantation occurred in the 15 patients within 30 days. The 6-month follow-up of all patients showed acceptable restenosis and target lesion revascularization rates, and no deaths, myocardial infarctions or CABGs were recorded. Although the number of patients was limited and the follow-up period was relatively short because of our desire to evaluate the biodegradation of the stents, the initial and 6-month results were quite encouraging.

### Table 3. Results of Quantitative IVUS Analysis

<table>
<thead>
<tr>
<th>Lesion</th>
<th>After Stenting</th>
<th>1 Day After Stenting</th>
<th>3-Month Follow-Up</th>
<th>6-Month Follow-Up</th>
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<tr>
<td>Stent CSA, mm²</td>
<td>7.42±1.51</td>
<td>7.37±1.44</td>
<td>8.18±2.42*</td>
<td>8.13±2.52*</td>
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<td>Neointimal area, mm²</td>
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<td>Lumen CSA, mm²</td>
<td>7.42±1.51</td>
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<td>5.67±2.42†</td>
<td>5.63±2.70‡</td>
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*\( P < 0.1 \) vs after stenting; † \( P < 0.005 \) vs after stenting; ‡ \( P < 0.001 \) vs after stenting.

### Table 4. Restenosis Rate and Target Lesion Revascularization Rate at Follow-Up

<table>
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<tr>
<th>Lesion</th>
<th>3-Month Follow-Up</th>
<th>6-Month Follow-Up</th>
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<tbody>
<tr>
<td>Restenosis rate, %</td>
<td>10.5 (2/19)</td>
<td>10.5 (2/19)</td>
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<tr>
<td>TLR rate, %</td>
<td>5.3 (1/19)</td>
<td>10.5 (2/19)</td>
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</table>

<table>
<thead>
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<th>Patient</th>
<th>3-Month Follow-Up</th>
<th>6-Month Follow-Up</th>
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<td>Restenosis rate, %</td>
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<td>6.7 (1/15)</td>
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<tr>
<td>TLR rate, %</td>
<td>6.7 (1/15)</td>
<td>6.7 (1/15)</td>
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</table>

TLR indicates target lesion revascularization.

### Figure 2

by Van der Giessen et al,8 and less inflammatory neointimal formation was less than that seen in a previous study. However, the degree of high-molecular-weight, knitted design in porcine coronary artery model8,11; however, Lincoff et al9 found that high-molecular-weight PLLA was well tolerated in the porcine coronary model. We also reported the biocompatibility of the PLLA drug delivery stent with a knitted polymer stents injured the vessel wall more severely than that seen in a previous report by Van der Giessen et al,8 and less inflammatory response was noted.

Thrombotic occlusion of polymeric stents have been reported in animal experiments.4,8,9 Zidar et al10 reported reduced platelet adherence and reduced thrombogenicity of the PLLA stent compared with slotted-tube stainless steel metallic stents in vitro. This property may be one advantage of PLLA stents for clinical use. In the present study, no PLLA stent thrombosis occurred under the aspirin and ticlopidine regimen.

To reduce vessel wall injury by stent implantation, we changed the stent design from knitted to coil using the same polymer, because our preliminary study showed that the knitted polymer stents injured the vessel wall more severely on implantation because of the uneven thickness of the stent struts (this study was done in porcine coronary arteries). In our animal experiment, 14 new PLLA coil stents used in the current study were implanted in 6 pigs, and no stent thrombosis and no late restenosis were recorded within 6 weeks.13 No significant neointimal hyperplasia within PLLA coil stents was found in this study compared with 9 Palmaz-Shatz half-stents in 9 pigs. PLLA coil stents also showed biocompatibility with a minimal inflammatory response in porcine coronary arteries at up to 16 weeks.

One concern with a biodegradable stent is whether stent degradation occurs in a reasonable time period. To reduce restenosis in humans, stents must maintain their scaffolding strength for >6 months to overcome late vessel remodeling.14–16 PLLA has been used for orthopedic applications in humans and has generally been found to be biocompatible for at least the first few weeks to months after implantation.17–20 Therefore, we selected PLLA from among several biodegradable polymers for the human coronary stent. According to the IVUS analysis at follow-up, the PLLA stents used in this study seemed to maintain their scaffolding properties at 6 months. It was not possible to identify signs of biodegradation. We could not show the dissolution time and whether intimal hyperplasia or other problems might develop late when the stent begins to break down; this is the major limitation of the study. Long-term follow-up using IVUS is scheduled to clarify the lifetime of this stent in human coronary arteries for this cohort.

We reported the initial and 6-month results of PLLA biodegradable coronary stents in humans. Our preliminary experience suggests the feasibility, safety, and efficacy of PLLA stents within a 6-month time frame. If the restenosis rate is comparable with metallic stents in larger numbers of patients over a longer time frame, PLLA stents can be an attractive alternative to metallic stents and serve as a useful vehicle for locally administered drugs. Because of the biodegradable feature of this stent, longer-term studies are necessary to investigate the interaction between the postulated disappearance of the stent strut and the restenosis mechanism. Follow-up studies past 6 months in this cohort are now underway. Finally, we plan to conduct further studies with larger numbers of patients to determine the long-term safety and efficacy of PLLA stenting for human coronary arteries.

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References


Initial and 6-Month Results of Biodegradable Poly-l-Lactic Acid Coronary Stents in Humans
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