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Peripheral

Evaluation of the Biodegradable Peripheral Igaki-Tamai Stent in the Treatment of De Novo Lesions in the Superficial Femoral Artery

The GAIA Study

Martin Werner, MD,* Antonio Micari, MD, PHD,† Angelo Cioppa, MD,‡ Giuseppe Vadalà, MD,† Andrej Schmidt, MD,* Horst Sievert, MD,§ Paolo Rubino, MD,‡ Annalisa Angelini, MD,‖ Dierk Scheinert, MD,* Giancarlo Biamino, MD, PHD†

Leipzig and Frankfurt, Germany; and Palermo, Mercogliano, and Padua, Italy

Objectives This study sought to evaluate the safety and performance of the Igaki-Tamai (Igaki Medical Planning Company, Kyoto, Japan) biodegradable stent in patients with occlusive superficial femoral artery (SFA) disease.

Background Poly-L-lactic acid (PLLA) biodegradable stents have been shown to be effective in the coronaries, but no data are available regarding their efficacy in the femoral artery.

Methods A prospective, multicenter, nonrandomized study enrolled 30 patients with symptomatic de novo SFA disease undergoing implantation of Igaki-Tamai bioresorbable stents. Clinical examinations and duplex ultrasound were prospectively performed after 1, 6, 9, and 12 months. The main study endpoints were technical success, restenosis rate, rate of target lesion revascularization (TLR), changes in ankle-brachial index (ABI), and quality of life by evaluating the walking impairment questionnaire (WIQ). Safety was assessed by monitoring the occurrence of major adverse clinical events and serious adverse events.

Results The mean age of the patients was 67.7 years, and 77% were male. The mean lesion length was 5.9 cm. Mean diameter stenosis was reduced from 89.9% to 6.2%, after stent implantation. Technical success was 96.7%. Binary restenosis rate for the 6 and 12 months follow-up was 39.3% and 67.9%, respectively. The TLR rate was 25.0% after 6 months and 57.1% after 12 months. All TLR were successful; the secondary patency rate after 1 year was 89.3%. Between baseline and 12 months, ABI increased in 53.6% of patients. Functional endpoints (WIQ), even if affected by a relatively high reintervention rate, showed improvement in most of the patients.

Conclusions The GAIA (Evaluation of the Biodegradable Peripheral Igaki-Tamai Stent in the Treatment of De Novo Lesions in the Superficial Femoral Artery) study shows that when using biodegradable PLLA stents (Igaki-Tamai), the immediate angiographic results are comparable to the results of metal stents, achieving a high secondary patency rate after 1 year. Modifications of stent characteristics and technical modifications are needed with the goal to reduce the restenosis rate during the reabsorption period. (J Am Coll Cardiol Intv 2014;7:305–12) © 2014 by the American College of Cardiology Foundation

From the *Center for Vascular Medicine, Park Hospital Leipzig, Leipzig, Germany; †Cardiology Unit, GVM Care and Research, Maria Eleonora Hospital, Palermo, Italy; ‡Cardiology Unit, Montevergine Clinic, Mercogliano, Italy; §Cardiovascular Center Frankfurt, Frankfurt, Germany; and the ‖Department of Cardiac, Thoracic and Vascular Sciences, University of Padua, Padua, Italy. Drs. Werner, Angelini, and Biamino have worked as consultants for Kyoto Medical. Dr. Sievert has received honoraria, travel expenses, or consulting fees from Abbott, Access Closure, AGA, Angiomed, Aptus, Atrium, Avinger, Bard, Boston Scientific, Bridgepoint, Cardiac Dimensions, CardioKinetix, CardioMEMS, Coherex, Contego, Covidien, CSI, CVRx, EndoCross, ev3, FlowCardia, Gardia, Gore, Guided Delivery Systems, InSeal Medical, Lumen Biomedical, HLT, Lifetech, Lutonix, Maya

Endovascular therapy is 1 of the options endorsed by current guidelines (1,2) for the treatment of symptomatic femoropopliteal artery disease. Especially for longer (>5 cm) superficial femoral artery (SFA) lesions, there is some evidence that primary stenting yields higher patency rates than after balloon angioplasty (3). Balloon angioplasty alone is considered to be sufficient for short SFA lesions by many endovascular specialists (4,5). However, in case of suboptimal balloon angioplasty with flow-limiting dissection or a residual stenosis, a provisional stent implantation may be necessary to stabilize the vessel wall and prevent acute or subacute vessel reocclusion.

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The SFA represents a harsh environment for metallic stents, because mechanical forces such as bending, torsion, compression, and elongation occur during daily activities. Concerns exist about stent fractures and their clinical implications (6). Stents may also hamper potential surgical or endovascular future treatments. Thus, the use of biodegradable devices, which degrade over time and leave only the remodeled vessel, is a compelling concept: "leaving nothing behind lifelong." Therefore, the aim of this study was to evaluate the safety and performance of the biodegradable peripheral Igaki-Tamai stent (Kyoto Medical Planning Co., Kyoto, Japan) in the treatment of de novo SFA lesions.

Abbreviations and Acronyms

ABI = ankle-brachial index
CI = confidence interval
DUS = duplex ultrasound
PLLA = poly-L-lactic acid
SAE = serious adverse event(s)
SFA = superficial femoral artery
TLR = target lesion revascularization
WIQ = walking impairment questionnaire

Methods

Study design. A multicenter, prospective, nonrandomized study (GAIA) was designed to evaluate the efficacy and safety of the biodegradable Igaki-Tamai stent in patients with de novo atherosclerotic SFA disease. Subjects were evaluated through 12 months following the implant procedure. Table 1 presents the inclusion/exclusion criteria.

The study was conducted according to the Guidelines for Good Clinical Practices and has been approved by the local ethics committees. All patients provided written informed consent before the procedure. An independent clinical event committee was responsible for endpoint adjudication and safety monitoring.

Patient population. Thirty patients with atherosclerotic SFA disease were treated with balloon angioplasty followed by primary implantation of Igaki-Tamai bioresorbable stents. All patients underwent baseline physical examinations with a focus on manifestations of lower limb ischemia. The ankle-brachial index (ABI) was measured and duplex ultrasound (DUS) studies were performed, followed by selective angiography of the infrainguinal arteries to outline the vascular anatomy and define the lesion characteristics by visual estimation.

Stent characteristics. The stent used in this study was the peripheral Igaki-Tamai stent (Fig. 1A), which received CE certification in 2007 and has been available on the European market since 2009. It is the only biodegradable stent that is approved for the treatment of SFA lesions in Europe.

The Igaki-Tamai stent is made of a biodegradable polymer and marked with 2 radio-opaque markers, each one being set at 2.0 mm from each end (Fig. 1B). The polymer used is poly-L-lactic acid (PLLA), which is a bioabsorbable material already in widespread clinical use with applications such as resorbable sutures, soft-tissue implants, orthopedic implants, and dialysis media (7). Degradation of PLLA occurs predominantly via hydrolysis. The final degradation products of PLLA are eliminated from the body via the Krebs cycle (mainly as carbon dioxide) and excreted in the urine. For the first 6 months, the stent retains its radial strength and flexibility to potentially prevent restenosis; thereafter, the stent is bioabsorbed. A recent long-term follow-up report (8) suggested that the Igaki-Tamai stent required 3 years to disappear totally from human coronary arteries.

Delivery is performed with a balloon-expandable system, which is compatible with an 0.018-inch guidewire and a 7-F sheath. It is available in diameters of 5 to 6 mm and in lengths of 37.8 and 78.8 mm. The 37.8-mm stent is mounted on a 40-mm-long balloon, the 78.8-mm-long stent is mounted on an 80-mm-long balloon.

Stent procedure and medication regimens. After passing the lesions with conventional techniques, pre-dilation was performed at the discretion of the interventionist. The stent diameter was chosen to match the proximal reference vessel diameter in a 1-to-1 ratio to ensure deployment close to the stent's nominal diameter, where it exerts its optimal mechanical properties. When more than 1 stent was needed to cover the lesion, the stents overlapped by ≥0.5 cm. Focal post-dilation was performed in case of residual stenosis after stent deployment. The antithrombotic regimen was pre-defined as follows: periprocedural anticoagulation with heparin according to the usual

Medical, Medtronic, NDC, Occlutech, Osprey, Ostial, PendraCare, Pfm Medical, Recor, ResMed, Rox Medical, SentreHeart, Spectranetics, SquareOne, Trireme, Trivascular, Venus Medical, Veryan, and Vessix; has received grant research support from Cook, St. Jude Medical; and has stock options with Cardiokinetix, Access Closure, Velocimed, Lumen Biomedical, Coherex, and SMT. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Table 1. Study Inclusion and Exclusion Criteria

Inclusion criteria
Age ≥18 yrs
Quality-of-life–limiting peripheral artery disease in combination with a resting ABI of <0.8.
De novo SFA lesion with a diameter stenosis of >70%
Lesion length of ≤13 cm
Target vessel reference diameter ≥5 mm and ≤6 mm
Distal runoff defined as minimal 1 patent infrapopliteal artery
Exclusion criteria
Minor or major tissue ulceration
Prior stenting in the intended target lesion
Impossibility to cross the target lesion
Acute or subacute occlusion of the target lesion
Treatment of ipsilateral lesions during the index procedure or planned treatment after the index procedure
Any known allergies and/or intolerances to the following: ASA, clopidogrel, heparin, contrast agents (that could not be adequately pre-medicated)
Woman with childbearing potential without a negative pregnancy test
Life expectancy of <12 months
Any planned surgery within 30 days after the study procedure
Patient currently participating in another investigational drug or device study
Severe renal failure (serum creatinine >2.5 mg/dl)
Myocardial infarction or stroke within 4 weeks before the procedure

ABI = ankle-brachial index; ASA = aspirin; SFA = superficial femoral artery.

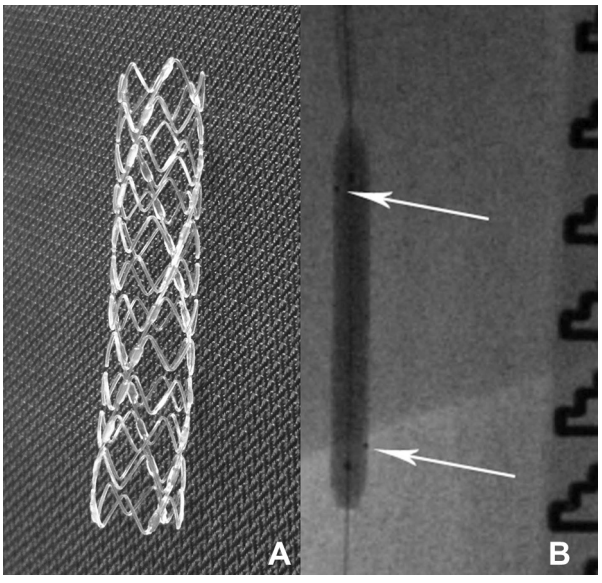

Figure 1. The Igaki-Tamai Stent

(A) The Igaki-Tamai stent is made of poly-L-lactic acid (PLLA) monofilament with a zigzag helical design. **(B)** A fluoroscopic image of the Igaki-Tamai stent during implantation. The **arrows** indicate the proximal and distal gold markers.

institutional practices (≥5,000 U), and dual antiplatelet therapy with clopidogrel and aspirin for 6 months after the procedure, with the recommendation to continue aspirin lifelong.

Follow-up and study endpoints. All patients were evaluated before their discharge from the hospital, and were scheduled to return for ambulatory follow-up visits at 1, 6, 9, and 12 months after the index procedure. At the follow-up visits, patients underwent physical examinations, assessment for any adverse events, ABI measurements, and DUS for the detection of restenoses.

The primary endpoint of this study was the in-stent binary restenosis rate using DUS, performed by an independent operator, at 1-, 6-, 9-, and 12-month follow-up visits. A peak systolic velocity ratio ≥2.4, corresponding to a ≥50% decrease in vessel diameter (9), was used for the diagnosis of binary restenosis. Secondary endpoints were:

1. Technical success defined as the ability to cross the target lesion with the device and deploy the stent as intended at the treatment site.
2. Improvement in ABI at rest of ≥0.15 compared with the baseline assessment.
3. Changes in quality of life by comparing the walking impairment score at 6 and 12 months follow-up with the score at baseline.
4. The occurrence of target lesion revascularization (TLR), serious adverse events (SAE), and major adverse clinical events up to 12 months follow-up.

Statistical analysis. Descriptive statistics were used to present: 1) mean values and SD for continuous variables; 2) median values (range); and 3) counts and percents for categorical variables. Binary restenosis, TLR, and patency rates are presented as percents of sample size (numerator/denominator). Mean ABI and walking impairment questionnaire (WIQ) were compared using the Student *t* test for dependent samples. Analyses were performed using SPSS software, version 20 (SPSS, Chicago, Illinois).

Results

Thirty patients were enrolled in the study, at 4 different sites. Most patients were male (76.7%), and mean age was 67.7 ± 8.8 years. The baseline clinical characteristics are shown in Table 2. Cardiovascular risk factors were highly prevalent, including hypertension in 90.0%, current or former smoking in 60.0%, and diabetes in 56.7% of patients. The mean ABI at rest before intervention was 0.71 ± 0.10.

Angiographic and procedural characteristics and immediate results. Lesion and lesion treatment characteristics are presented in Table 3. The target lesions were mainly situated

Table 2. Baseline Patient Demographics (N = 30)

Height, cm	30 (168.9 ± 8.7)
Weight, kg	30 (79.1 ± 9.6)
Age, yrs	30 (67.7 ± 8.8)
Male	23 (76.7)
Smoking history	
Never smoked	12 (40)
Previous smoker	11 (36.7)
Current smoker	7 (23.3)
Diabetes mellitus	17 (56.7)
No treatment	4 (23.5)
Oral medication	5 (29.4)
Insulin	7 (41.2)
Oral medication and insulin	1 (5.9)
Hypertension	27 (90.0)
Dyslipidemia	18 (60.0)
Renal failure*	6 (20.0)
Previous cerebrovascular event	3 (10)
Previous coronary artery disease	20 (66.7)
Previous MI	4 (20)
Angina pectoris	3 (15)
History of valve disease	2 (6.7)
Present or recurrent arrhythmias	5 (16.7)

Values are n (mean ± SD) or n (%). *Serum creatinine >2.5 mg/dl.
MI = myocardial infarction.

Table 3. Lesion and Lesion Treatment Characteristics (N = 30)

Treatment side	
Left	18 (60.0)
Right	12 (40.0)
Target lesion location	
Proximal SFA	5 (16.7)
Mid SFA	13 (43.3)
Distal SFA	11 (36.7)
Mid and distal SFA	1 (3.33)
Target lesion occlusion	3 (10.0)
Pre-dilation performed	25 (83.3)
Lesion crossed with the device	30 (100)
Stent deployed at intended site	29 (96.7)
Post-dilation after stent implantation	5 (16.7)
Number of implanted stents:	39 (100)
5.0 mm/37.8 mm	3 (7.7)
5.0 mm/78.8 mm	8 (20.5)
6.0 mm/37.8 mm	8 (20.5)
6.0 mm/78.8 mm	20 (51.3)
RVD, mm	30 (5.3 ± 0.4)
Diameter stenosis pre-procedure, %	30 (89.9 ± 11.1)
Stenosis length, cm	30 (5.9 ± 3.6)
Diameter stenosis post pre-dilation, %	25 (39.4 ± 22.6)
Maximal stent inflation pressure, atm	30 (9.6 ± 2.3)
Stent inflation duration, s	29 (95.0 ± 54.0)
2nd stent maximal inflation pressure, atm	9 (10.0 ± 1.0)
2nd stent inflation duration, s	9 (116.7 ± 57.0)
Diameter stenosis post–stent implantation, %	30 (6.2 ± 12.0)

Values are n (%) or n (mean ± SD).
RVD = reference vessel diameter; SFA = superficial femoral artery.

in the mid (46.7%) and distal (40.0%) SFA. On average, the reference vessel diameter was 5.3 ± 0.4 mm. The lesions presented on average a diameter stenosis of 89.9 ± 11.1% and a length of 5.9 ± 3.6 cm. In 25 subjects, pre-dilation was performed, resulting in an mean diameter stenosis of 39.4 ± 22.6% after pre-dilation.

For all patients, the lesion could be crossed with the device for stent deployment. In 1 patient, the stent could not be deployed (the balloon did not inflate). The stent could be retrieved, and another stent was implanted successfully. Thus, the technical success rate was 96.7%. Twenty-two subjects had 1 stent implanted, and 8 patients had 2 stents implanted. Nine patients were treated with the 5-mm-diameter stent, and 21 subjects received the 6-mm-diameter stent. After stent implantation, the mean diameter stenosis was reduced to 6.2%. Figure 2 shows the fluoroscopic images of a patient treated with the Igaki-Tamai stent for SFA stenosis.

Safety assessment. Twenty-nine patients completed the 1-month follow-up, and 28 patients completed the 6-month, 9-month, and 12-month follow-up. One patient was not willing to undergo the follow-up examination and withdrew from the study; 1 patient died 57 days post-procedure due to heart failure and pneumonia. The clinical event committee adjudicated this mortality as not related to the procedure nor to the device. No other major adverse clinical events were recorded during the observational period.

Until the 12 months follow-up, 34 SAE were recorded. Sixteen SAE were not related to the device or procedure. Eighteen TLR were classified as SAE. They have been performed in 16 patients (2 patients received a TLR twice), resulting in a 57.1% TLR rate after 1 year (Fig. 3). Table 4 lists the type of TLR.

Performance analysis. Until the 1-month follow-up, DUS showed that in 2 patients (6.9%, 95% confidence interval [CI]: 0% to 17.2%), binary restenosis was present. At 6 months, there were 9 new cases with restenosis or reocclusion, resulting in a binary restenosis rate of 39.3% (95% confidence interval: 20.7% to 55.2%). Restenosis rates for the 9 and 12 months follow-up were 60.7% (95% CI: 41.4% to 75.9%) and 67.9% (95% CI: 48.3% to 82.8%), respectively (Fig. 3). Primary patency and secondary patency rates after 1 year were 32.1% and 89.3%. In all cases of restenosis or reocclusion, it was possible to navigate a guidewire through the obstructed stent without problems so that all TLR were successful.

Mean ABI increased from 0.71 (±0.10) at baseline to 0.93 (±0.16) following treatment. ABI at the 1-month follow-up was 0.89 (±0.19). ABI at the 6-, 9-, and 12-month follow-up was 0.77 (±0.21), 0.78 (±0.19), and

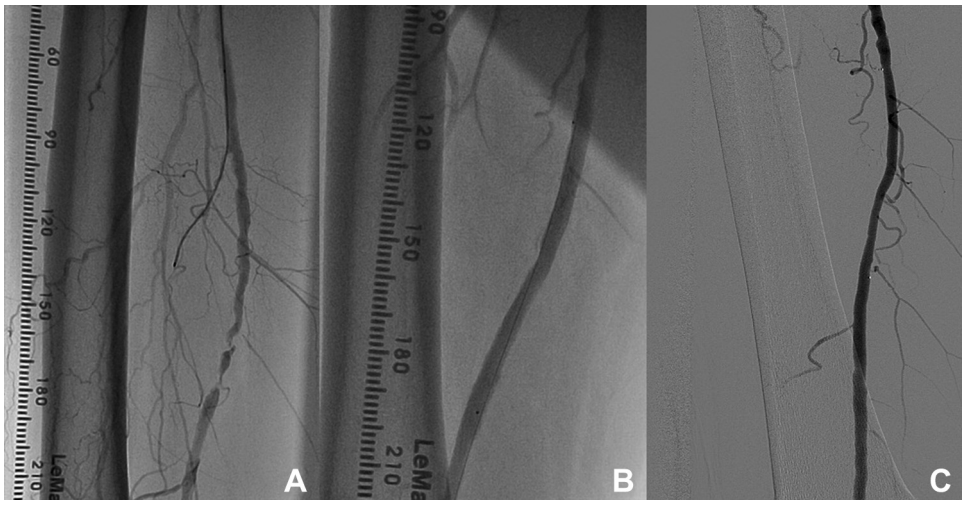

Figure 2. Treatment With an Igaki-Tamai Stent

(A) Angiographic image of a high-grade stenosis of the superficial femoral artery right leg. **(B)** Angiographic image obtained after implantation of an Igaki-Tamai stent. **(C)** Angiographic image obtained after 2 years showing no restenosis.

0.89 (±0.15), respectively. At 12 months, ABI was improved ≥0.15 compared with baseline in 15 cases (53.6%).

At screening, 29 patients completed the WIQ, whereas at 6 and 12 months, 28 subjects answered the questions. At 6-month follow-up, 23 patients (82.1%) had an improved walking capacity compared with baseline, and 20 patients (71.4%) had improved their walking speed. The majority of patients (26 patients, 92.9%) could climb stairs with less trouble. At 12 months, all patients showed improvements in walking distance compared with baseline capacity. Twenty-four patients (85.7%) showed improvement in walking speed, and 23 patients (82.1%) could climb stairs with less trouble.

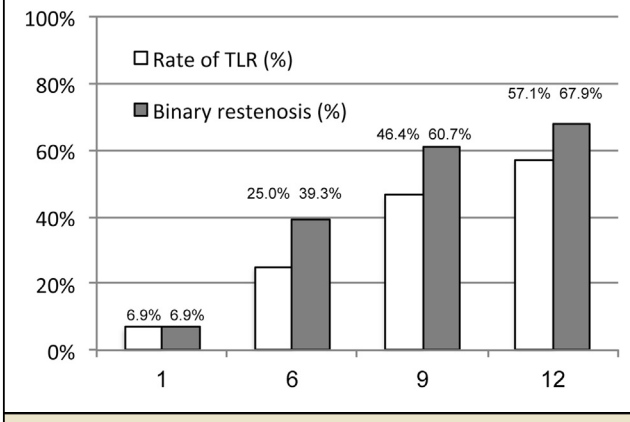

Figure 3. Graphic Display of the Binary Restenosis Rate and the Rate of TLR

Shown are the rates at 1, 6, 9, and 12 months. TLR = target lesion revascularization.

Histopathologic analysis of restenosis. Specimens of the tissue that caused in-stent restenosis were retrieved by atherectomy in 8 cases. The histological analysis (Fig. 4) showed hyperplastic tissue, characterized by stellate or fusate myofibroblasts, embedded in myxoid extracellular matrix. Remnants of stent struts were found within the restenotic tissue in 3 cases (37.5%). Inflammatory cells were present in 4 cases (50.0%), 2 of them with a foreign body reaction (giant cells surrounding the struts), 1 with polymorphonucleated cells. Thrombus was present in 4 cases (50.0%), and minimal microcalcification was present in 1 case (12.5%).

Discussion

The concept of a biodegradable stent gained attention 1 decade ago, as the first biodegradable stents were used in the clinical setting. The Igaki-Tamai stent was the first in-human, fully biodegradable stent. Despite the first promising results in the coronary field (10), the advent of drug-eluting stents diverted attention from biodegradable stents. However, the shortcomings of metallic stents are evident in the coronaries as well as in the peripheral arteries. The efficacy of metallic stents in the coronaries is limited because of the risk of late stent thrombosis, hampered vascular remodeling, and impaired vasomotor function distal to the implanted stent (7). For the peripheral arteries, especially the SFA, major problems after implantation of nitinol stents are the risk of stent fracture and the high risk of recurrent in-stent stenosis caused by intima hyperplasia. Treatment of SFA in-stent restenosis is still a

Table 4. TLR

Type of TLR	n = 18 (in 16 Patients)
Atherectomy	6
Balloon angioplasty	5
Stent	3
Atherectomy + stent	2
Thrombolysis	1
Thrombolysis + atherectomy	1

TLR = target lesion revascularization.

challenge for endovascular therapy. A recent study (11) has shown recurrent obstructions after restenosis in nitinol stents in 50% to 85% of lesions at 2 years, depending on the pattern of restenosis. On the basis of these limitations, bioabsorbable stents came into focus again for coronary as well as peripheral arteries (7).

Recently, the long-term (>10 years) clinical outcomes after implantation of Igaki-Tamai stents in the coronaries have been published (8). The study reported a high survival rate free of cardiac death (98% at 10 years), demonstrating the long-term safety of this stent. After 10 years, the TLR rate was 28%.

This study is the first report, to our knowledge, on the efficacy and safety of a PLLA bioabsorbable stent in the SFA. Similar to the results in the coronaries, the treatment of symptomatic SFA lesions with the biodegradable Igaki-Tamai stent was safe and effective in achieving favorable acute angiographic results. Functional endpoints (WIQ), even if affected by a relatively high reintervention rate, were acceptable, showing improvement in most of the patients in walking distance and speed, because of the high secondary patency rate.

In fact, a high rate (67.9%) of recurrent obstruction of the treated arterial segment was observed after 1 year. Subsequently, repeat revascularization of the target lesion was performed in 57.1% of cases within the observation period, resulting in a secondary patency rate of 89.3%.

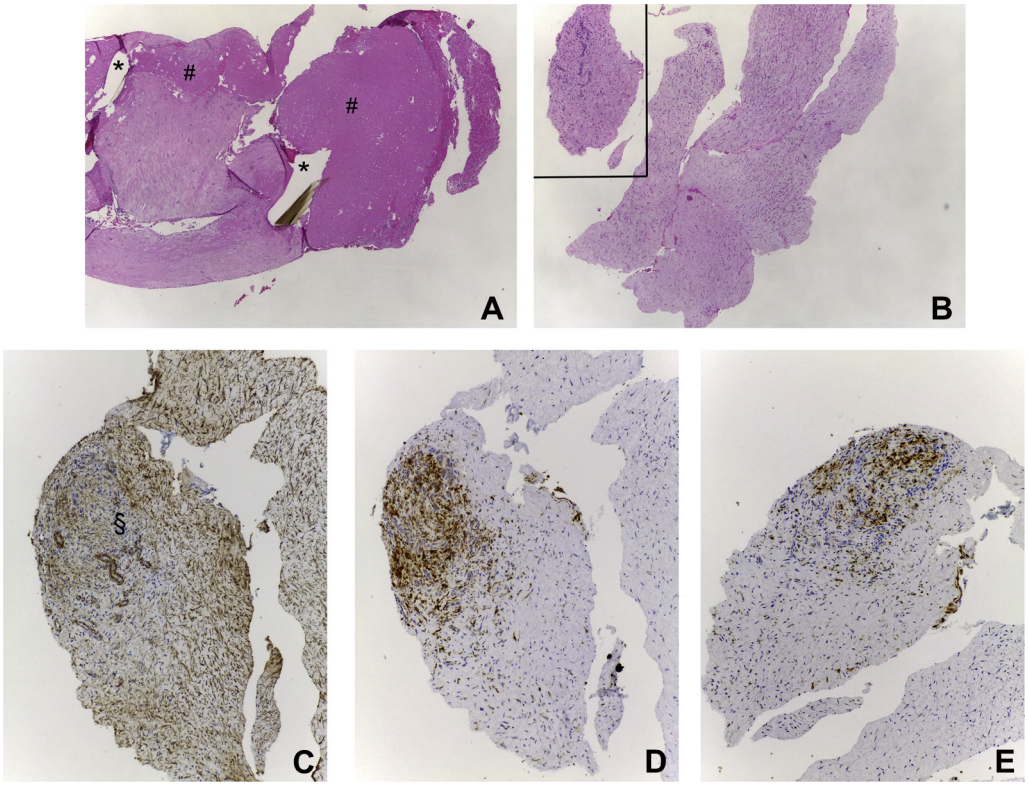

Figure 4. Histopathology of the Restenotic Lesions

The retrieved material was excised by atherectomy after Igaki-Tamai stent implantation. **(A)** Multiple fragments composed mainly of hyperplastic tissue and thrombotic material **(#)** close to stent remnants **(*)**. Hematoxylin-eosin stain, original magnification ×5. **(B)** Multiple fragments of hyperplastic tissue rich in myofibroblasts and with an area of inflammation and neovascularization **(inset)** Hematoxylin-eosin stain, original magnification ×5. **(C, D, E)** High-power views of the inflamed area from **B (inset)**. **(C)** Immunohistochemical staining showing myofibroblasts positive for smooth muscle cell actin (SMA) embedded in myxoid material with neoangiogenesis (§). Anti-SMA antibody staining, original magnification ×10. **(D)** Immunohistochemical staining for macrophages. Anti-CD68 antibody staining, original magnification ×10. **(E)** Immunohistochemical staining for leukocyte common antibody (LCA). Anti-CD45 antibody staining, original magnification ×10.

Compared with recently published trials, the Igaki-Tamai stent did not match the patency rates of third-generation nitinol stents. For example, the Edwards RESILIENT (Randomized Study Comparing the Edwards Self-Expanding Lifestent versus Angio-plasty Alone in Lesions INvolving the SFA and/or Proximal Popliteal Artery) trial (12) reported a 37% restenosis rate for the LifeStent (Bard Peripheral Vascular, Tempe, Arizona), and the Astron trial (13) reported a 1-year 34.4% restenosis rate for the Astron stent (Biotronik, Berlin, Germany).

To further understand the pathophysiological mechanism of in-stent restenosis in this cohort, we have investigated the obstructive tissue that was obtained by atherectomy in 8 patients. The data of the histopathologic analyses supported a hyperplastic restenotic response with a partial thrombotic phenomenon in 50% of the cases.

Concerns have been raised about the possible induction of an inflammatory response by PLLA or its degradation products. van der Giessen et al. (14) reported a marked inflammatory response after the implantation of 5 different polymer stents, including lactic acid, in a porcine coronary model. These concerns have not been supported by other authors: Zidar et al. (15) reported a minimal inflammatory reaction and minimal neointimal hyperplasia with the use of PLLA stents in canine femoral arteries. Atherectomy of a restenotic coronary lesion after treatment with the Igaki-Tamai stent did not show any significant inflammatory response (8). These findings go along with the current histopathologic analysis that showed the typical pattern of smooth muscle cell proliferation (16) in the absence of significant inflammatory infiltration. Only in 2 of the 8 assessed cases could we observe a localized minimal foreign body reaction, confined to only some strut remnants.

The role of thrombus in restenosis is unclear. Schwartz et al. (17) suggested that mural thrombus assumes a major role in restenosis by providing an absorbable matrix into which smooth muscle cells proliferate. Thrombus was in fact observed in 4 of 8 specimens (50.0%) in the present cohort and thus cannot be excluded as a factor contributing to the genesis of SFA restenosis in the Igaki-Tamia stent. Thrombolysis was used in 2 cases to recanalize an occluded stent, which raises the question whether prothrombotic properties of either the device or its degradation products might play a role.

Another factor influencing long-term patency is the stent's radial force, which is needed to withstand compression from outside, caused by, for example, calcified plaques. Compared with cobalt chromium, nitinol, and other materials that are currently being used in stent fabrication, bioabsorbable candidates are substantially inferior from a mechanical strength perspective (18). In our study, however, relevant recoil after stent implantation was not observed, with an mean diameter stenosis post-stenting of only 6.2%. This suggests that the mechanical properties of the Igaki-Tamai stents were sufficient to withstand compression in this cohort without extreme calcification.

This study is the first report on the treatment of atherosclerotic SFA lesion with a bioabsorbable stent. There has been 1 published work (19) evaluating an absorbable magnesium-alloy stent (AMS, Biotronik, Berlin, Germany) in the infrapopliteal arteries. Although the study indicated that the AMS technology can be safely applied, it did not demonstrate efficacy, with a binary restenosis rate of 68.2% for the magnesium alloy stent after 6 months.

Study limitations. Limitations of the current study are related to its nonrandomized design, which makes a direct comparison to other treatment modalities impossible. Additionally, the systematic DUS may have led to a higher TLR rate, because some cases of TLR may have been driven by DUS results and not by ischemia problems. Finally, this study shows that the biodegradable Igaki-Tamai stent can achieve an immediate angiographic result similar to the result of other metal stents. Modifications of stent characteristics (e.g., drug-eluting properties) or combination with other treatment modalities (e.g., atherectomy, drug-coated balloons) are needed to optimize the results, while leaving nothing behind.

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Reprint requests and correspondence: Dr. Martin Werner, Center for Vascular Medicine, Park Hospital Leipzig, Strümpellstrasse 41, 04289 Leipzig, Germany. E-mail: office@drwerner.eu.

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Key Words: biodegradable stent ■ GAIA study ■ Igaki-Tamai ■ peripheral artery disease ■ PLLA stent(s) ■ superficial femoral artery.