First clinical trial of nitinol self-expanding everolimus-eluting stent implantation for peripheral arterial occlusive disease

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Background: **A novel self-expanding drug-eluting stent was designed to slowly release everolimus to prevent restenosis following peripheral arterial intervention. The purpose of the first-in-human Superficial Femoral Artery Treatment with Drug-Eluting Stents (STRIDES) trial was to evaluate the safety and efficacy of this device for the treatment of symptomatic superficial femoral and proximal popliteal arterial occlusive disease.**

Methods and Results: **One hundred four patients were enrolled at 11 European investigative centers in a prospective, nonrandomized, single-arm trial. The patients had severe symptomatic vascular disease, including a significant proportion of patients with critical limb ischemia (17%), diabetes (39%), and single-vessel outflow (26%). The mean lesion length was 9.0 ± 4.3 cm. Ninety-nine percent of patients were available for 12-month follow-up, including duplex imaging in 90% and arteriography in 83%. Clinical improvement, defined as a sustained decrease in Rutherford-Becker clinical category, was achieved in 80% of patients. Primary patency (freedom from ≥50% in-stent restenosis) was 94 ± 2.3% and 68 ± 4.6% at 6 and 12 months, respectively. Plain radiographic examination of 122 implanted devices at 12 months revealed no evidence for stent fracture.**

Conclusions: **The everolimus-eluting self-expanding nitinol stent can be successfully implanted in patients with severe peripheral arterial disease with favorable outcomes and clinical improvements observed in the majority of patients. (J Vasc Surg 2011;54:394-401.)**

Endovascular recanalization has become the preferred method of treatment for many patients with symptomatic femoropopliteal occlusive disease. It is the recommended approach for all ischemic patients with segmental disease ≤15 cm and for selected patients with more diffuse disease at prohibitive risk for open surgery.[1]

Despite its widespread popularity and applicability, however, the durability of endovascular intervention remains poor. Restenosis complicates up to 50% of procedures during the first year leading to high rates of therapeutic failure and reintervention.[2-5]

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Competition of interest: Drs Lammer, Bosiers, Zeller, and Schillinger serve on the Advisory Board of Abbott Vascular; Drs Lammer, Schillinger, and Zeller serve on the Steering Committee of the STRIDES Trial; Dr Lammer receives research support from Abbott Laboratories; Ms Boone, Ms Zaugg, Dr Verta, Ms Peng, Ms Gao, and Dr Schwartz are all full-time employees of Abbott Laboratories. The other authors report no conflicts.

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Given the significant impact that drug-eluting stents (DES) have had in reducing restenosis rates in the coronary circulation,[6] several methods of intravascular stent-based local drug delivery have been developed for peripheral interventions.[7-10] In this study, an everolimus-eluting peripheral stent system was designed with a relatively high drug load (225 μg/cm^2) and long elution profile (about 80% released during the first 3 months). The purpose of the first-in-human Superficial Femoral Artery Treatment with Drug-Eluting Stents (STRIDES) trial was to evaluate the safety and efficacy of this novel everolimus-eluting stent system for the treatment of symptomatic superficial femoral and proximal popliteal arterial occlusive disease.

METHODS

Study design. The STRIDES trial was a prospective, nonrandomized, single-arm, multicenter clinical study designed to evaluate the safety and performance of an everolimus-eluting self-expanding stent system for the treatment of atherosclerotic peripheral artery disease (PAD). The study was designed to enroll approximately 100 patients with chronic PAD in Rutherford-Becker clinical categories 2 to 5 (moderate to severe intermittent claudication, ischemic rest pain, or minor tissue loss) due to atherosclerotic de novo or restenotic occlusive lesions of the superficial femoral or proximal popliteal artery ≥3 and ≤17 cm in length. It was conducted in accordance with the International Conference on Harmonization Guidelines-Good Clinical Practices, Declaration of Helsinki, ISO 14155-1,

ISO 14155-2 and Ethics Committee requirements, and all patients gave written informed consent for participation. The trial was registered at http://www.clinicaltrials.gov with the identifier NCT00475566.

Patients were eligible for enrollment in the STRIDES trial if they were suffering from symptomatic PAD due to a single de novo or restenotic lesion of the superficial femoral artery (SFA) or proximal popliteal artery located between the point 1 cm distal to the femoral bifurcation and the point 3 cm proximal to the proximal margin of the intercondylar fossa of the femur. Lesions with ≥50% diameter stenosis were considered eligible for the trial when their length was ≥3 cm and ≤17 cm, and they arose in target vessels with diameters ≥4.3 mm and ≤7.3 mm. Patients with significant inflow stenosis were eligible for inclusion if the stenosis had been successfully treated without complication. Patients were required to have a patent popliteal artery as well as at least one patent tibial artery that provided in-line circulation to the lower leg and foot. For patients with bilateral SFA lesions, the lesion referable to the limb with the highest Rutherford-Becker clinical category was treated.

Key exclusion criteria included prior placement of an intravascular stent in the SFA, prior bypass grafting in the extremity, the presence of major tissue loss (Rutherford-Becker clinical category 6), blind popliteal outflow, the presence of an active immunosuppressive disorder, active pharmacologic treatment with known inducers of CYP3A, prior or planned solid organ transplantation, severe hepatic insufficiency, or renal insufficiency defined by a serum creatinine >2.5 mg/dL.

Drug-eluting stent system. The everolimus-eluting peripheral stent was comprised of three components: the Dynalink nitinol self-expanding stent (Abbott Laboratories, Abbott Park, Ill), the antiproliferative drug everolimus, and an ethylene vinyl alcohol (EVAL, Kuraray Co, Ltd, Tokyo, Japan) copolymer.

The Dynalink .035 peripheral self-expanding stent is constructed of binary nickel-titanium, which is superelastic at body temperature. The 0.008-inch strut thickness design is based on a series of sinusoidal rings that are connected at six locations around the circumference such that the connections are aligned along the length of the stent and positioned 60 degrees from each other. The Dynalink and Absolute stents (Abbott) are identical, except that the Absolute stent contains radiopaque markers at its ends to facilitate deployment. The Dynalink/Absolute stent system has been shown to be safe and efficacious in several single-arm and randomized trials of endovascular therapy for PAD.[4,11,12]

The antiproliferative drug, everolimus, is a therapeutic agent originally developed for the prevention of organ transplant rejection but is also effective at inhibiting the growth of certain solid tumors (Certican and Afinitor; Novartis Pharmaceuticals Corporation, Basel, Switzerland).[13,14] It effectively inhibits experimental vascular smooth muscle cell proliferation and enhances vascular remodeling in animal models.[15,16] Lastly, everolimus has been shown to be safe and effective as the drug component of coronary DES.[17]

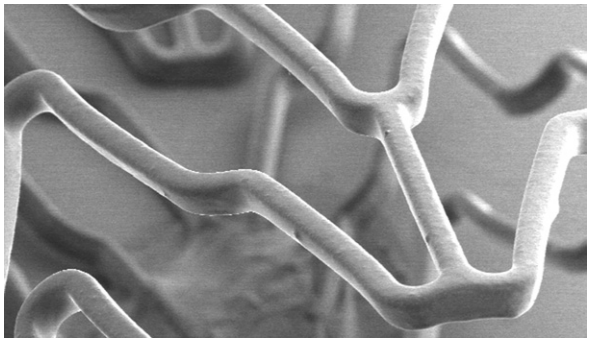


Fig 1. The Dynalink-E self-expanding everolimus-eluting stent.

The release of everolimus from the peripheral everolimus-eluting stent is controlled by an ethylene vinyl alcohol (EVAL) copolymer. EVAL is a semicrystalline polymer with a glass transition temperature of 55°C and melting point of 180°C. The chemical backbone is a C–C bond and the pendant group is –OH; neither contains hydrolytically or oxidatively labile chemical bonds. Owing to their biocompatibility, EVAL polymers are ubiquitous in medicine. They have been used as hemodialysis and apheresis membranes[18] and, more recently, have been formulated with dimethyl sulfoxide for use as embolic treatment for intracerebral aneurysms and arteriovenous malformations.[19] The STRIDES study is notable in that it represents the first clinical experience with EVAL as a polymer for intravascular drug elution. Other everolimus-eluting stents, most notable the Xience V device (Abbott), employ a fluorinated polymer drug carrier, poly(vinylidene fluoride-co-hexafluoropropylene) (PVDF-HFP) to control drug release.

This combination of the Dynalink nitinol self-expanding stent, the antiproliferative drug everolimus, and an ethylene vinyl alcohol (EVAL) copolymer has been referred to as the "Dynalink-E" stent (Fig 1). The total drug load is 225 $\mu g/cm^2$ stent surface area, a higher dose than coronary sirolimus-eluting (140 $\mu g/cm^2$) or everolimus-eluting stents (100 $\mu g/cm^2$).[20] The elution profile is prolonged as well with approximately 80% of the drug being released slowly over the first 90 days, as opposed to ~30 days in systems designed for use in the coronary arteries.[21]

Treatment strategy and follow-up procedures. Prior to the stenting procedure, patients received one of two antiplatelet regimens: (1) aspirin (75-100 mg daily) and either clopidogrel (75 mg daily) or ticlopidine (250 mg twice a day) for at least 3 consecutive days, or (2) a loading dose of 300 to 600 mg of clopidogrel or 500 mg of ticlopidine. Vascular access was achieved via the contralateral (crossover) or ipsilateral (antegrade) approach at the operators' discretion. Following diagnostic arteriography and systemic anticoagulation, lesions were traversed using wires and techniques most familiar to the operator. Successful wire traversal was an entry criterion for the study;

predilation prior to stent placement was allowed but not mandatory.

The drug-eluting stent was available in lengths of 28, 80, and 100 mm, with diameters of either 6 or 8 mm. The maximum allowable stent length per patient was 200 mm. Postdilation was mandatory to optimize stent strut apposition. Completion fluorography or a biplane X-ray was performed postdeployment to serve as a baseline for stent integrity evaluation at 12 months. Postprocedure, patients received a minimum daily dose of 75 mg of aspirin and either clopidogrel 75 mg or ticlopidine 250 mg daily for at least 6 months.

Follow-up patient visits, including duplex ultrasound examinations were performed at 1, 6, and 12 months. Clinical assessments included routine history and physical examination, as well as completion of Walking Impairment Questionnaires (WIQ).[22] Duplex examinations were aided by the use of a flexible centimeter tape affixed to the patient. Peak systolic velocity (PSV) measurements were obtained from a minimum of eight standard locations in the target vessel; in cases of stents exceeding 8 cm length, PSV measurements were obtained at 2-cm intervals. Duplex criteria used to determine the presence of an in-stent ≥50% stenosis included an increase of the intrastenotic PSV of 150% in reference to the proximal prestenotic PSV from the same vessel segment (PSV ratio ≥2.5). An independent core laboratory reviewed and verified the data by comparing the site-reported data with the actual recorded PSV measurements (Bioclinica BV, Leiden, The Netherlands). Follow-up diagnostic angiography was performed after 12 months using a standardized protocol and analyzed by an independent core laboratory (BioImaging Technologies, Leiden, The Netherlands). Follow-up plain radiography was performed after 12 months for the purposes of evaluating stent integrity. X-rays were obtained under two different projections separated by at least 45° using the highest available magnification then analyzed for strut fracture by an independent core laboratory (Bioclinica).

Endpoints, data collection, and statistical analysis. The primary endpoint of the STRIDES trial was the rate of in-stent binary restenosis (≥50% stenosis using duplex velocity criteria) at 6 months. Secondary endpoints included acute device success, change in Rutherford-Becker clinical category, improvement in walking capacity by WIQ, and rates of stent fracture, primary patency, target lesion revascularization, limb salvage, and survival after 12 months. Failure of primary patency was defined as the presence of ≥50% restenosis by duplex or angiogram, or at the first occurrence of one of the following: reintervention for the purpose of treating the target lesion, total occlusion of the target lesion, surgical bypass of the target lesion, or amputation of the extremity due to target lesion restenosis or occlusion.

Data were collected on electronic case report forms (InForm; PhaseFoward, Waltham, Mass) and adjudication for prespecified study endpoints was provided by an independent Clinical Events Committee (Harvard Clinical Research Institute, Boston, Mass). An independent Data Safety Monitoring Board reviewed the study at prespecified intervals (coordinated by Harvard Clinical Research Institute, Boston, Mass).

Table I. Clinical demographics of 104 patients enrolled in the STRIDES trial

	Mean ± SD or %
Age (years)	69 ± 8.9
Male gender	57%
Current smoker	37%
Diabetes mellitus	39%
Hypertension	78%
Hypercholesterolemia	57%
Coronary artery disease	42%
Cerebrovascular disease	18%
Prior ipsilateral lower extremity intervention	19%
Contralateral peripheral vascular disease	60%
Rutherford-Becker classification	
II (moderate claudication)	34%
III (severe claudication)	49%
IV (ischemic rest pain)	8.7%
V (ulceration)	8.7%
Limb salvage indication (CLI)	17%
Baseline ankle-brachial index	0.64 ± 0.19

CLI, Critical limb ischemia; *STRIDES,* Superficial Femoral Artery Treatment with Drug-Eluting Stents.

All patients that received study stents were included in the analysis (intent-to-treat). Endpoint values are summarized descriptively at baseline and at follow-up with mean, median, or percentage. Primary patency, freedom from target lesion revascularization (TLR), and limb salvage rates are reported using Kaplan-Meier methods according to recommendations by the *Society for Vascular Surgery Ad Hoc Committee* for reports dealing with lower extremity ischemia[23] as well as the DEFINE Group's recommendation for reporting of clinical endpoints in peripheral endovascular revascularization trials.[24] The protocol-defined time windows for clinical and radiographic evaluations were ±14 days for 6-month evaluations and ±28 days for 12-month evaluations.

RESULTS

One hundred four patients (with 106 lesions) were enrolled at 11 European investigative centers between May 2007 and January 2008. The patients' clinical and lesional demographics are given in Table I. As expected, the population had severe disease, including a significant proportion of patients with coronary artery disease (42%), diabetes mellitus (39%), and critical limb ischemia (17%).

Lesional demographics are given in Table II. The target lesions were complex, including a mean lesion length of 9.0 ± 4.3 cm, with significant proportions of TransAtlantic Inter-Society Consensus (2000) C lesions (78%), total occlusions (45%), lesions ≥10 cm (39%), and restenoses (9.4%).

Details of the 104 interventional procedures are given in Table III. Predilation of lesions prior to stent placement was optional and was performed in 63% of cases. Postdila-

Table II. Demographics of the 106 lesions treated in the STRIDES trial

	Mean ± SD or %
Lesion origin	
De novo	91%
Restenotic	9.4%
Calcification	
Moderate	51%
Severe	27%
Reference vessel diameter (mm)	5.3 ± 0.6
Lesion length (cm)	9.0 ± 4.3
Total occlusion (%)	45%
TASC (2000) lesion classification	
A	5%
B	17%
C	78%
D	0%
TASC (2007) lesion classification	
A	42%
B	45%
C	13%
D	0%
Patent crural outflow vessels	
One	26%
Two	27%
Three	47%

STRIDES, Superficial Femoral Artery Treatment with Drug-Eluting Stents; *TASC,* Trans-Atlantic Inter-Society Consensus.

Table III. Procedural details of 104 endovascular interventions in the STRIDES trial

	Mean ± SD or %
Predilation	
% of cases	63%
Maximum balloon pressure (atm)	9.2 ± 2.3
Postdilation	
% of cases	98%
Maximum balloon pressure (atm)	10.3 ± 2.6
Number of stents implanted per patient	
One	58%
Two	36%
Three or more	6.7%
Device success (per device), %	98%
Procedure duration, median min (range)	53 (35-820)
Hospital stay, median days (range)	2 (1-35)

STRIDES, Superficial Femoral Artery Treatment with Drug-Eluting Stents.

tion was required to ensure optimal stent expansion and apposition; it was performed for 98% of stented lesions. The majority of patients had either one (58%) or two (36%) stents implanted.

All patients were treated with either clopidogrel or ticlopidine prior to the procedure as specified in the protocol; 83% of patients received continuous thienopyridine treatment through the first 6 months. Thienopyridine treatment beyond 6 months was left to the discretion of the treating physician; at the end of 12 months, 61% of patients remained on therapy. Low-dose aspirin therapy (75-100 mg per day) was continuously maintained in 87% of patients during the first 6 months; at the end of 12 months, 92% were taking aspirin.

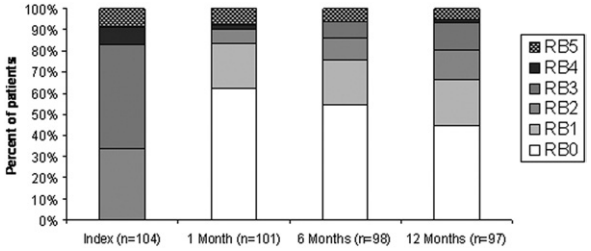


Fig 2. Clinical results of the Superficial Femoral Artery Treatment with Drug-Eluting Stents (STRIDES) trial as assessed by Rutherford-Becker clinical category (*RB*). The number of patients evaluated at each interval is shown in parentheses.

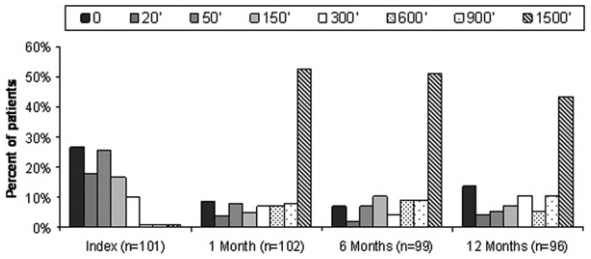


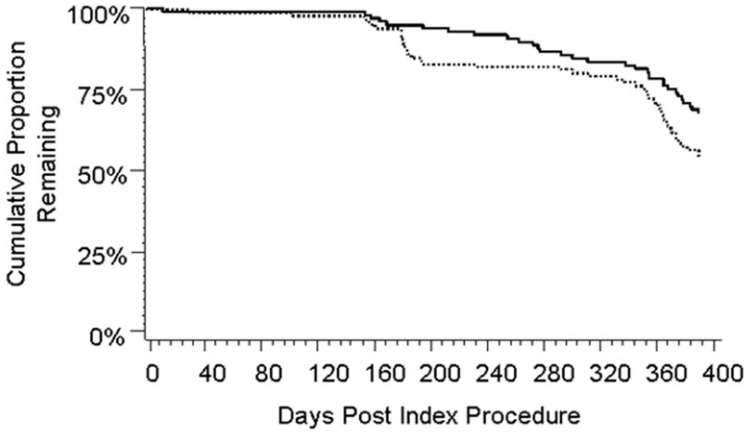
Fig 3. Improvement in ambulation following endovascular intervention in the Superficial Femoral Artery Treatment with Drug-Eluting Stents (STRIDES) trial. Patients' ability to ambulate was measured at prespecified time intervals by the Walking Improvement Questionnaire (WIQ). The figure shows, at each interval of study, the percentage of patients that were able to ambulate the stated distances.

Ninety-eight patients (94%) underwent duplex imaging at 6 months for assessment of in-stent restenosis, the trial's primary endpoint. The rate of restenosis at 6 months was 14% (95% confidence interval, 7.8%-22.2%).

Patient follow-up at 12 months was 99%. Mean resting ankle-brachial index (ABI) increased from a preprocedure level of 0.64 ± 0.19 to 0.92 ± 0.16 postprocedure, then remained elevated at 0.98 ± 0.14, 0.91 ± 0.17, and 0.89 ± 0.20 at 1, 6, and 12 months, respectively.

Clinical results as assessed by Rutherford-Becker clinical category and Walking Distance are given in Figs 2 and 3, respectively. There was sustained clinical benefit in the majority of patients, with improvements in Rutherford-Becker clinical category observed in 80% after 12 months. Endovascular intervention afforded significant improvements in ambulation such that the percentage of patients that could ambulate 1500′ (457 m) increased from 1% preprocedure to 53%, 51% and 43% at 1, 6, and 12 months, respectively.

Observed rates of primary patency (freedom from restenosis) and freedom from TLR by Kaplan-Meier analysis are shown in Fig 4. Note that the abscissa extends to 393 days to account for the 28-day window around the 365-day



Freedom from target lesion revascularization					
Days post index procedure	0	(0, 30]	(30, 180]	(180,365]	(365,393]
#at Risk	104	104	103	99	82
#Censored	0	0	0	1	72
#Events	0	1	4	16	10
%Event Free	100±0%	99±1.0%	95 ±2.1%	80±3.8%	70±4.5%
Primary patency					
Days post index procedure	0	(0, 30]	(30, 180]	(180,365]	(365,393]
#at Risk	104	103	103	96	69
#Censored	1	0	1	1	55
#Events	0	0	6	26	14
%Event Free	100±0%	100±0%	94±2.3%	68 ±4.6%	55±5.0%

Fig 4. Freedom from target lesion revascularization (*solid line*) and primary patency (*dashed line*) in the Superficial Femoral Artery Treatment with Drug-Eluting Stents (STRIDES) trial.

endpoint. Freedom from TLR after 6 and 12 months was 95 ± 2.1% and 80 ± 3.8%, respectively. Primary patency after 6 and 12 months was 94 ± 2.3% and 68 ± 4.6%, respectively.

There was no limb loss in claudicants (100% limb salvage in 86 patients). The 12-month rate of limb salvage in patients with critical limb ischemia was 89 ± 7% (16/18 patients with salvaged limbs). The first case of ipsilateral major amputation occurred in a 78-year-old woman with tissue loss in the left foot (Rutherford-Becker 5) and an ABI of 0.21. Following uneventful stent placement, her course was complicated by heparin-induced thrombocytopenia and thrombosis requiring below-knee amputation 12 days following the procedure. The second case was that of an 83-year-old female with congestive cardiomyopathy and prior revascularization of the left leg who presented with ischemic tissue loss in the right foot and underwent uneventful stent placement in the distal right SFA. Unfortunately, her course was complicated by recurrent pneumonia, gastrointestinal bleeding requiring colectomy, and poor wound healing eventually requiring below-the-knee amputation after multiple toe and transmetatarsal amputations failed to heal. She succumbed to multisystem organ failure 10 months following the procedure. Other serious adverse events (SAEs) are given in Table IV.

Table IV. SAEs in the STRIDES trial

	N (%)
Access site	
Hematoma	1 (1.0%)
Pseudoaneurysm	2 (1.9%)
Non-access site bleeding	
Hematoma	1 (1.0%)
Other	1 (1.0%)
Cardiac/hemodynamic	
Angina	4 (3.9%)
Congestive cardiomyopathy	2 (1.9%)
Other	8 (7.7%)
Pulmonary	
Pneumonia	5 (4.8%)
Pulmonary edema	2 (1.9%)
Pulmonary embolism	1 (1.0%)
Other	3 (2.9%)
Stroke	1 (1.0%)
Carcinoma	6 (5.8%)
Gastrointestinal	3 (2.9%)
Infectious	4 (3.8%)
Miscellaneous	
Back pain	1 (1.0%)
Fever	1 (1.0%)
Peripheral neuropathy	1 (1.0%)
Joint pain	1 (1.0%)

SAEs, Serious adverse events; *STRIDES,* Superficial Femoral Artery Treatment with Drug-Eluting Stent.

Stent integrity was examined radiographically after 12 months in 122 devices. There was no evidence for strut fracture in any device.

DISCUSSION

As significant enhancements in stented arterial patency have been achieved in the coronary circulation through the use of DES,[6] it was inevitable that this technology would eventually be applied to the peripheral circulation. Several small series have been published that suggest that drug-eluting stents designed for the coronary arteries might also be efficacious in limiting restenosis and improving patency in the infrapopliteal arteries.[9] Similarly, the hypothesis that drug-eluting stents might also be efficacious in the larger and more complex SFA was first addressed by the SIROCCO (SIROlimus Coated Cordis SMART Nitinol Self-expandable Stent for the Treatment of Obstructive Superficial Femoral Artery Disease) studies, which were published in 2002 and 2005.[7,8,10] The SIROCCO self-expanding drug-eluting stent (Cordis, a Johnson and Johnson Company, Miami Lakes, Fla) utilized the nitinol SMART (Shape Memory Alloy Recoverable Technology) stent as its platform, was loaded with 90-μg sirolimus/cm^2 stent area using a 5- to 10-μm copolymer matrix (total drug load ~1 mg per 80-mm stent) and delivered its drug load over a period of about 7 days.[8] A total of 93 patients were enrolled in the combined SIROCCO I and SIROCCO II clinical trials. Unfortunately, neither trial achieved a significant reduction in restenosis and, even after 4 years, there was no difference in any metric comparing patients treated with the bare SMART stent vs the sirolimus-eluting SIROCCO stent.[10]

In retrospect, some have hypothesized that the failure of the SIROCCO stent design was in its inadequate drug delivery. As stated, the SIROCCO stent was loaded with 90-μg sirolimus/cm^2 stent area, which was considerably lower than the successful sirolimus-eluting coronary stent (Cypher [Cordis], 140 μg sirolimus/cm^2 stent area).[20] Moreover, the SIROCCO stent released sirolimus over about 7 days, considerably more rapidly than the ~30-day release profile of the Cypher stent. Lastly, an unexpected finding in the SIROCCO trial and a possible reason for its failure, was the observation that the stent platform was prone to fracture. Of the 93 patients enrolled, stent fracture was found in 18% at 6 months, including single strut fractures in eight patients, multiple strut fractures in four patients, complete transverse linear stent separations in two patients, and transverse linear fractures with stent displacement in two patients.[25] It has been suggested that stent fracture may create a nidus for restenosis, given the documented association between strut fracture, restenosis, and therapeutic failure.[26] Indeed, the reported frequency of strut fracture following peripheral stenting is surprisingly high,[11,27] including one retrospective clinical study demonstrating a fracture rate of 65%.[28]

The everolimus-eluting self-expanding nitinol stent utilized in the STRIDES trial was designed to address and potentially overcome these shortcomings of prior peripheral DES by providing (1) a higher level of drug delivery to the target tissue, (2) a longer profile of elution leading to sustained suppression of proliferation, and (3) resistance to stent fatigue and fracture due to its flexible design. The everolimus-eluting self-expanding stent was loaded with relatively high overall drug content (225 μg everolimus/cm^2 stent area) compared with coronary stents that elute its analogs (eg, Xience V [Abbott] 100 μg everolimus/cm^2, Cypher 140 μg sirolimus/cm^2, Endeavor [Medtronic, Minneapolis, Minn] ~160 μg zotarolimus/cm^2). The dose of 225 μg everolimus/cm^2 stent area was chosen as this roughly corresponds to a twofold increase in dose/mm^2 arterial area compared with coronary DES formulations. Equally important as the total bulk dose is its release profile. Using an ethylene vinyl alcohol copolymer system, the everolimus-eluting peripheral DES was designed to release drug over a period of approximately 3 months, compared with coronary DES, which release drug over only about 30 days. The comparatively prolonged release rate of the everolimus-eluting peripheral DES was intended to roughly match the kinetics of nitinol stent expansion, as oversized self-expanding nitinol stents continue to enlarge to their nominal diameter and potentially remodel the human arterial wall for at least 6 months.[29]

The Dynalink/Absolute stent platform utilized in the present study has previously been shown to resist fracture when implanted in the SFA. For example, in a comparative retrospective study of three different peripheral stents, radiographic strut fracture within the Dynalink/Absolute (Abbott Laboratories) stent was observed in only 1.8% of cases after a mean follow-up of 15 ± 9 months, while fractures of SMART (Cordis) and Wallstents (Boston Scientific, Natick, Mass) were observed in 28% and 19% of cases, respectively (mean follow-up of 32 ± 16 months and 43 ± 24 months, respectively).[11] Similarly, in a randomized, prospective, single-center study of percutaneous transluminal angioplasty (PTA) alone vs PTA with Absolute stent placement, stent fracture was observed in only 2% of patients.[4,12] Taken together, the results of these studies suggest that the Dynalink/Absolute nitinol stent pattern is well-suited to the environment of the SFA and that chronic implantation is not associated with high rates of fracture.

Thusly designed, clinical testing of the everolimus-eluting peripheral DES was undertaken in the STRIDES trial. In STRIDES, successful device placement was achieved in 98% of cases, and 99% of patients were available for 12-month follow-up, which included repeat duplex imaging in 90% and arteriography in 83%. Clinical improvement (sustained decrease in Rutherford-Becker clinical category) was achieved in 80% of patients. Primary patency (freedom from ≥50% in-stent restenosis) was 94 ± 2.3% and 68 ± 4.6% at 6 and 12 months, respectively, and plain radiographic examination of 122 implanted devices revealed no evidence for stent fracture. Clearly, the results of this initial clinical trial suggest that this device is safe and effective for the treatment of this disease.

It must be noted, however, that the everolimus-eluting peripheral DES tested in the STRIDES trial appeared to be far less effective at preventing restenosis than typical coronary DES. Each of the Cypher, Taxus (Boston Scientific), and Endeavor coronary DES have been shown to have profound effects on coronary neointimal hyperplasia, reducing restenosis from 24%-35% to 3.2%-9.4% in pivotal clinical trials.[20,30,31] In contrast, the 68 ± 5% patency rate observed in the current trial appears to be only a modest improvement in outcome compared with historical results. For example, in a cohort of 51 patients with similar demographics and lesion characteristics treated with the bare metal Dynalink/Absolute stent, a 12-month primary patency rate of 63 ± 7% was observed.[4,12] Similarly, although lesion complexity and reporting methods vary widely, contemporary reports of patency rates using other bare nitinol or covered stents in the current era range from 50% to 81%.[2-5,32-35] Given these results, it is difficult to conclude that the everolimus-eluting peripheral DES represents a significant advance in currently available interventional technology.

The results of the STRIDES trial are also noteworthy given the large number of restenotic events that were observed during months 7 to 12. As seen in Fig 4, the favorable primary patency rate of 94% that was observed at 6 months had decreased to a disappointing 68% by 1 year. Interestingly, this phenomenon was also observed in the SIROCCO trial wherein the impressive 5% restenosis rate noted at 6 months had increased to 19% at 18 months, which was no different than bare nitinol controls.[7,8,10] This suggests, perhaps, that neither DES was formulated with a long enough elution profile to overcome the continued interaction between stent and SFA.

In conclusion, the everolimus-eluting self-expanding nitinol stent can be safely and successfully implanted in patients with severe PAD, with favorable outcomes and clinical improvements observed in the majority of patients. Neointimal hyperplasia appeared to be inhibited and patency enhanced during the first 6 months. The effect was not sustained, however, as primary patency had decreased to 68% by 12 months.

AUTHOR CONTRIBUTIONS

Conception and design: JL, MB, TZ, MS, EB, MZ, LS
Analysis and interpretation: JL, MB, TZ, MS, EB, MZ, PV, LP, XG, LS
Data collection: JL, MB, TZ, MS, EB, MZ, PV, LP, XG, LS
Writing the article: JL, MB, TZ, MS, EB, MZ, PV, LP, XG, LS
Critical revision of the article: JL, MB, TZ, MS, EB, MZ, PV, LP, XG, LS
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Statistical analysis: JL, EB, MZ, PV, LP, XG, LS
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Overall responsibility: JL, LS

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APPENDIX

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