Sustained Benefit at 2 Years of Primary Femoropopliteal Stenting Compared With Balloon Angioplasty With Optional Stenting

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Background—Primary stenting with self-expanding nitinol stents of the superficial femoral artery yielded improved morphological and clinical results compared with balloon angioplasty with optional stenting until 12 months in a randomized controlled trial. We now report 2-year data on restenosis and clinical outcomes of these patients.

Methods and Results—Of 104 patients with chronic limb ischemia and superficial femoral artery obstructions, 98 (94%) could be followed up until 2 years after intervention for occurrence of restenosis (>/=50%) by duplex ultrasound and for clinical and hemodynamic outcome by treadmill walking distance and ankle brachial index. Restenosis rates at 2 years were 45.7% (21 of 46) versus 69.2% (36 of 52) in favor of primary stenting compared with balloon angioplasty with optional secondary stenting by an intention-to-treat analysis (P=0.031). Consistently, stenting (whether primary or secondary; n=63) was superior to plain balloon angioplasty (n=35) with respect to the occurrence of restenosis (49.2% versus 74.3%; P=0.028) by a treatment-received analysis. Clinically, patients in the primary stent group showed a trend toward better treadmill walking capacity (average, 302 versus 196 m; P=0.12) and better ankle brachial index values (average, 0.88 versus 0.78; P=0.09) at 2 years, respectively. Reintervention rates tended to be lower after primary stenting (17 of 46 [37.0%] versus 28 of 52 [53.8%]; P=0.14).

Conclusions—At 2 years, primary stenting with self-expanding nitinol stents for the treatment of superficial femoral artery obstructions yields a sustained morphological benefit and a trend toward clinical benefit compared with balloon angioplasty with optional stenting. (Circulation. 2007;115:2745-2749.)

Key Words: arteriosclerosis | balloon | peripheral vascular disease | restenosis | stents

We followed up patients from the ABSOLUTE trial until 2 years after intervention for morphological, clinical, and hemodynamic outcome by duplex ultrasound, walking capacity on the treadmill, ankle brachial index at rest, and clinically driven target vessel revascularization.

Methods

Study design and inclusion and exclusion criteria have been reported.1 Briefly, we enrolled 104 patients with symptomatic peripheral artery disease (PAD) with severe intermittent claudication (Rutherford class 3) or chronic critical limb ischemia with either rest pain (Rutherford class 4) or ischemic ulcers (Rutherford class 5) and a >/=50% stenosis or occlusion of the ipsilateral SFA with a target lesion length >/=30 mm and at least 1 patent (<50% stenosis) tibioperoneal runoff vessel. Exclusion criteria were acute critical limb ischemia, previous bypass surgery, or stenting of the SFA;
untreated inflow disease of the ipsilateral pelvic arteries (>50% stenosis or occlusions); and known intolerance of study medications or contrast agent.

In patients randomized to stenting, primary stent implantation without predilation was anticipated. Predilation with undersized balloons was performed restrictively in patients with very tight stenosis or heavily calcified occlusions, which did not allow primary passage with the introducer device of the stents. Stents were implanted covering the margins of the target lesion for 10 mm proximal and distal. In case of multiple stents, the margins of the stents were overlapped for 10 mm. Postdilation after stenting was performed strictly within the stented segment with the balloon diameter corresponding to the proximal nondiseased vessel area with up to 10% oversizing.

In patients randomized to balloon angioplasty, the balloon diameter corresponded to the proximal nondiseased vessel area. The minimal time for each balloon inflation was 2 minutes at 10 to 12 atm. After dilation of the entire target segment, biplane control angiograms were obtained. In cases with a suboptimal primary result, inflation times exceeding 2 minutes. In patients with persistent limiting dissection in the worst-view angiogram, a second prolonged balloon dilation, without predilation was anticipated. Predilation with undersized balloons was performed restrictively in patients with very tight stenosis or heavily calcified occlusions, which did not allow primary passage with the introducer device of the stents. Stents were implanted covering the margins of the target lesion for 10 mm proximal and distal. In case of multiple stents, the margins of the stents were overlapped for 10 mm. Postdilation after stenting was performed strictly within the stented segment with the balloon diameter corresponding to the proximal nondiseased vessel area with up to 10% oversizing.

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In patients randomized to balloon angioplasty, the balloon diameter corresponded to the proximal nondiseased vessel area. The minimal time for each balloon inflation was 2 minutes at 10 to 12 atm. After dilation of the entire target segment, biplane control angiograms were obtained. In cases with a suboptimal primary result, defined as a residual stenosis >30% or the presence of a flow-limiting dissection in the worst-view angiogram, a second prolonged balloon dilation of the entire target segment was performed with inflation times exceeding 2 minutes. In patients with persistent suboptimal results after the second prolonged balloon dilation, secondary stenting was performed.

For all stent implantations in both groups, self-expandable nitinol stents (Dynalink/Absolute, Guidant, Santa Clara, Calif) with a nominal diameter of 6 mm were used.

All patients received acetylsalicylic acid 100 mg daily continuously and clopidogrel 75 mg daily for 3 months after intervention. Acetylsalicylic acid and clopidogrel were initiated at least 2 days before the intervention; otherwise, a loading dose of 300 mg clopidogrel was given during the intervention.

Patients were followed up until 2 years after intervention. Twenty-four months (±1 month) after the index procedure, systematic reexaminations could be performed in 98 of 104 patients (4 patients died, 2 refused or were unable to participate in the follow-up examinations), including staging of PAD according to the Rutherford classification,7 measurement of resting ankle brachial index, treadmill walking exercise testing (3.2 km/h at 12° slope), and color-coded duplex sonography for determination of restenosis.8 The degree of restenosis by duplex ultrasound in the femoropopliteal segment was classified using the peak velocity ratio. Peak velocity ratio was derived by dividing the peak systolic velocity in the stenotic segment by the peak systolic velocity in the preceding normal segment or, in patients with multiple stenoses, in the adjacent distal segment. A peak velocity ratio >2.4 was predefined as >50% stenosis.8 Within the ABSOLUTE trial, agreement for binary restenosis between duplex ultrasound and angiography at 6 months was excellent (κ=0.91; 95% CI, 0.85 to 0.97). Clinically driven target vessel revascularization until 24 months was recorded.

**Statistical Methods**

Metric data are given as mean±SD or, in the case of nonnormal distributions or censored data sets, as medians and interquartile range (IQR; range from the 25th to the 75th percentile) and were analyzed by Mann-Whitney U tests. Proportions were compared by χ² statistics using Yates’ corrections. Multivariable logistic regression analysis was applied to assess the association between treatment group and restenosis at 24 months and to adjust for potentially confounding factors. Multiplicative interaction terms and log-likelihood ratio tests were used to test for interactions. We converted the odds ratios derived from the multivariate model to risk ratios with 95% confidence intervals. Time-dependent outcomes were analyzed by the Kaplan-Meier method and compared by log-rank tests. Calculations were performed with Stata release 8.0 (Stata Inc, College Station, Tex).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

Demographic data and clinical and interventional characteristics of the 98 patients with complete 2-year data are shown.
By an intention-to-treat analysis, restenosis rates at 2 years were 45.7% (21 of 46) versus 69.2% (36 of 52) in favor of primary stenting compared with balloon angioplasty with optional stenting \((P/H_{11005}0.03)\). Figure 1 shows the occurrence of restenosis in both treatment groups until 24 months after intervention. Multivariable analysis confirmed a significantly reduced risk for restenosis at 2 years for primary stenting \(\text{(adjusted risk ratio, 0.52; 95% confidence interval, 0.24 to 0.93)}\) after adjustment for age, gender, diabetes mellitus, smoking, PAD stage, and lesion length. No interaction between treatment group, restenosis, and PAD stage or length of the lesion was observed, indicating that the benefit of stenting did not vary by these strata.

Ultrasound data other than binary restenosis showed no significant difference between the 2 groups. In patients with restenosis, median peak systolic velocity levels after primary stenting versus balloon angioplasty were 3.3 (IQR, 2.7 to 5.5) versus 3.6 (IQR, 2.9 to 6.3), respectively \((P=0.60)\). Lengths of the restenotic segments in the 2 groups also were comparable \((median, 50 \text{ mm [IQR, 10 to 100 mm]} \text{ versus } 50 \text{ mm [IQR, 20 to 100]}; P=0.83)\).

Clinically, Rutherford stages of PAD at 2 years were almost identical in the 2 groups: In the primary stent versus balloon angioplasty groups, 40.0% and 39.6% were asymptomatic, 56.5% and 56.3% had intermittent claudication, and 4.4% and 4.2% had critical limb ischemia, respectively \((P=0.74)\). However, patients in the primary stent group showed a trend toward better walking capacity on the treadmill \([302 \text{ m (IQR, 99 to 700)} \text{ versus } 196 \text{ m (IQR, 77 to 355)}; P=0.12]\) and better ankle brachial index values \([0.88 (SD, 0.18) \text{ versus } 0.78 (SD, 0.17); P=0.09]\).

Reinterventions included 12 balloon angioplasties, 2 stent implantations, and 3 bypass operations in the primary stent group compared with 20 balloon angioplasties, 8 stent implantations, and 0 bypass operations in patients who underwent initial balloon angioplasty with optional stenting. Overall, reintervention rates tended to be lower after primary stenting compared with balloon angioplasty with optional secondary stenting \(17 \text{ of 46 [37.0%]} \text{ versus } 28 \text{ of 52 [53.8%]; } P=0.14\). Figure 2 gives an overview of clinically driven target vessel revascularization during the course of the study. At 2 years, freedom from restenosis, including target vessel revascularization, was nonsignificantly different with 78.3% (36 of 46) in the primary stent group versus 65.4% (34 of 52) in the balloon angioplasty with optional secondary stenting group \((P=0.24)\), respectively. One minor amputation had to be performed in a patient treated within the balloon angioplasty group. Stent fractures were not systematically

| TABLE 2. Baseline Angiographic and Interventional Data of 98 Patients Randomized to Primary Stenting or Balloon Angioplasty With Optional Secondary Stenting of Atherosclerotic Obstruction in the SFA |
|---------------------------------|----------------|----------------|
| Length of the target lesion, mm | 112 (77)       | 93 (65)        |
| Degree of stenosis, %           | 90 (10)        | 90 (10)        |
| Occlusions, n (%)               | 19 (41)        | 16 (31)        |
| Target lesion calcification, n (%)* | 9 (20)      | 7 (13)         |
| No. of crural runoff vessels, n (%) | 26 (56)   | 30 (58)        |
| No. of stents used, n (%)       | 46 (100)       | 17 (33)        |
| No. of stents used, n (%)       | 0              | 0              |
| Length of the treated segment, mm | 138 (71)    | 117 (56)       |

PTA indicates balloon angioplasty with optional secondary stenting. Data are given as mean (SD) when appropriate.

*By fluoroscopy.
assessed at 24 months; however, no new stent fractures were detected in patients undergoing reinterventions between months 12 and 24.

By a treatment-received analysis, stent implantation (whether primary or secondary) was superior to plain balloon angioplasty with respect to the occurrence of restenosis at 2 years (31 of 63 [49.2%] versus 26 of 35 [74.3%]; \( P = 0.03 \)).

Clinically, Rutherford stages of PAD at 2 years were not significantly different between the 2 groups: In the stent versus balloon groups, 43.3% and 33.3% were asymptomatic, 51.7% and 63.6% had intermittent claudication, and 5.0% and 3.0% had critical limb ischemia, respectively (\( P = 0.53 \)). Similarly, patients in the stent group showed no significant difference in walking capacity on the treadmill (268 m [IQR, 89 to 700] versus 189 m [IQR, 79 to 329]; \( P = 0.25 \)) and ankle brachial index values (0.84 [SD, 0.19] versus 0.77 [SD, 0.16]; \( P = 0.36 \)) compared with patients after plain balloon angioplasty. Reintervention rates tended to be lower after stenting compared with balloon angioplasty, but this also was not statistically significant (26 of 63 [41.3%] versus 19 of 35 [54.3%]; \( P = 0.30 \)).

### Discussion

At 2 years, we found a sustained benefit of primary stent implantation with self-expanding nitinol stents for the treatment of symptomatic SFA obstructions compared with plain balloon angioplasty with optional stenting. Restenosis occurred significantly less often after primary implantation of nitinol stents and translated into a tendency for better clinical outcomes. These data favor the use of nitinol stents for endovascular revascularization of long SFA lesions. Nevertheless, a 45% restenosis rate in stented patients at 2 years underlines the need for further improvement of the devices.

In patients with critical limb ischemia, endovascular and surgical revascularization revealed equal outcomes with respect to limb salvage at 2 years in the Bypass Surgery Versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial.9 Putting together these findings and our recent observation, long-segment SFA disease in patients with critical limb ischemia seems an acceptable indication for stent implantation because stenting is suggested to further improve the clinical results of plain balloon angioplasty observed in the BASIL trial.

In patients with intermittent claudication, occurrence of restenosis in 45% of the patients at 2 years remains problematic. Nevertheless, in the primary stent group, freedom from restenosis at 2 years after reinterventions could be achieved in 78%. Endovascular treatment of long-segment SFA disease therefore seems a reasonable treatment option for patients with disabling claudication. If treated by endovascular means, primary stenting seems to be the therapy of choice to improve the durability of interventional success and to reduce the need for reinterventions.

The rates of restenosis observed in the ABSOLUTE trial seem high compared with the midterm findings from the Sirolimus Coated Cordis SMART Nitinol Self-expandable Stent for the Treatment of Obstructive Superficial Femoral Artery Disease (SIROCCO) trial.10 Duda et al10 reported only 21% restenoses at 24 months in the bare metal stent group of SIROCCO using the SMART self-expanding nitinol stent (Cordis, Johnson & Johnson, Miami Lakes, Fla). However, average lesion length in SIROCCO was 83 mm,10 shorter than in the ABSOLUTE trial. Furthermore, in the present study, only 6-mm stents were used; reduced restenosis rates might have been achieved by the use of larger stents, particularly in patients with large arteries. A direct, nonrandomized comparison of the 2 devices at our institution revealed no significant differences in patency and clinical outcome in SFA lesions >100 mm long.11 Nevertheless, randomized head-to-head
comparisons between different products are deemed necessary to assess whether different stents yield different restenosis rates.

With regard to the timing of restenosis, it seems remarkable that the vast majority of restenoses occurred during the initial 12 months after treatment. In the stent and angioplasty groups, the incidences of late restenosis from months 12 to 24 were only 9% and 6%, respectively. This suggests that after endovascular treatment of peripheral arteries, the activity of the restenotic process may decrease with increasing time from the initial injury.

Covered stent grafts, an alternative to bare stents, seem to be a promising endovascular treatment option. Kedora and colleagues recently reported findings of a randomized comparison of percutaneous Viabahn stent grafts versus prosthetic femoropopliteal bypass in 86 patients. At 12 months, primary (74% versus 74%) and secondary (84% versus 84%) patency rates were identical in the endovascular and surgical groups. Particularly for treatment of long SFA lesions, stent graft implantation may be worth considering, as long as adequate outflow can be obtained to minimize the risk for stent graft thrombosis.

Some limitations of the present study have to be recognized. The number of restenoses occurring from 12 to 24 months was quite low in both groups (4 and 3 events in the stent and balloon groups, respectively). Therefore, the limited power of the comparative analysis has to be acknowledged. Furthermore, at the 2-year follow-up, biplane x-ray investigations for evaluation of stent fractures were not available; therefore, the frequency and potential impact of material fatigue remain indeterminate. However, at least clinically, adverse events other than restenosis were not observed during the second year of follow-up.

Conclusion

At 2 years, primary stenting with self-expanding nitinol stents for treatment of SFA obstructions yields a sustained morphological and a trend toward clinical benefit compared with balloon angioplasty with optional stenting.

Disclosures

Dr Schillinger is on the speakers’ bureau for Guidant, Boston Scientific, and Cordis J&J, and is a consultant and on the advisory board for Guidant. Dr Minar is on the speakers’ bureau for Guidant, Boston Scientific, and Sanofi-Synthelabo. Dr Cejna is on the speakers’ bureau for Boston Scientific and is a consultant and on the advisory board for Cordis J&J. Dr Lamar is on the speakers’ bureau for Guidant. The other authors report no conflicts.

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