

The RESILIENT Trial Update: 6-Month Phase 1 Results

Encouraging data include no reinterventions,
100% clinical success, and no stent fractures.

BY JOHN R. LAIRD, JR, MD

It is estimated that more than 10 million Americans currently have some form of peripheral arterial disease. One of the largest peripheral arterial disease patient groups are those who suffer from lifestyle-limiting and limb-threatening disease of the superficial femoral artery (SFA). Stenting is now commonly employed as a treatment for stenoses and occlusions of the SFA. Two dedicated devices have been approved for this indication and several more are currently undergoing clinical investigation. To date, comparative data from randomized studies of SFA stenting versus percutaneous transluminal angioplasty (PTA) are limited and have failed to demonstrate the superiority of stenting over PTA in this vascular bed. In addition, there are many unanswered questions regarding the long-term durability of stents in this location, as well as the potential implications of stent fracture. The RESILIENT Trial, which began enrollment in July 2004, is a prospective, randomized, multicenter trial designed to evaluate the safety and efficacy of SFA stenting using a modern, self-expanding nitinol stent (Lifestent NT, Edwards Lifesciences, Irvine, CA) compared to balloon angioplasty alone. Phase 1 of the RESILIENT trial enrolled 20 patients, all of whom received the Lifestent NT. Enrollment in phase 2, the pivotal randomized arm of the trial, is ongoing. This article summarizes the preliminary findings from phase 1 of the RESILIENT Trial.

PHASE 1 DESIGN AND BASELINE CHARACTERISTICS

The feasibility phase of the prospective, multicenter RESILIENT Trial was designed to evaluate the safety of the LifeStent NT self-expanding stent in the treatment of stenoses or occlusions of the SFA and proximal popliteal artery. Twenty patients were enrolled and treated with the LifeStent NT System at six sites in the US. Inclusion criteria included

"Preliminary data from phase 1 of the RESILIENT Trial have been promising, with a 0% fracture rate at 6 months."

claudication (Rutherford category 1-3), *de novo* or restenotic (non-stented) stenoses or occlusions in the SFA or proximal one-third of the popliteal artery, lesion length <150 mm (single or tandem), and at least one patent runoff vessel to the foot.

Seventy-five percent of the patients were male, and the mean age was 70.5 ± 9.9 years. Ten patients (50%) had diabetes, and 80% were smokers. Ninety percent had hypercholesterolemia and 85% were hypertensive. All patients were either Rutherford category 2 (70%) or 3 (30%) at presentation. The target limb ankle-brachial index (ABI) was 0.76 ± 0.26 , and the mean lesion length was 83.7 ± 28.6 mm. Two-thirds of all lesions were calcified, and 23.8% were total occlusions. A mean of 1.8 stents per patient were implanted.

ACUTE AND MIDTERM RESULTS

There were no incidences of in-hospital death, stroke, myocardial infarction, emergent surgical revascularization, significant distal embolization, or thrombosis. At 30 days, the target limb ABI had improved to 0.97 ± 0.15 . Seventy-five percent of patients for which 30-day data were available (12 of 16) were asymptomatic (Rutherford category 0), and 25% (4 of 16) were classified as Rutherford category 1. Clinical success was 100%.

At 6 months, the target limb ABI was 0.94 ± 0.11 . Eighty per-

(Continued on page 36)

Subintimal Angioplasty for the Management of Chronic Total Occlusions

Subintimal angioplasty is an effective tool for the management of long-segment chronic total occlusions, particularly in higher Rutherford category patients.

BY LARRY HOESH, MD

Chronic total occlusions of the femoro-popliteal segments or infrapopliteal vessels are encountered more frequently with increasing patient longevity, bringing critical limb ischemia (CLI) to greater clinical attention. Surgical revascularization has been well documented for achieving limb salvage; however, the morbidity and mortality rate in this patient cohort can be significant.¹ Endovascular therapy has been shown to be equivalent to surgical revascularization in achieving limb salvage with a favorable patient survival.^{2,3} Bolia first described subintimal angioplasty and has outlined its main purposes for the treatment of chronic limb ischemia.⁴⁻⁶ The value of subintimal angioplasty in limb salvage, and even comparison to bypass grafting, suggests that subintimal angioplasty may be a good first-line approach to long-segment occlusions in CLI and higher Rutherford category patients who are at above average risk for surgery.^{7,8}

Bolia has described the subintimal angioplasty technique.⁹ This article describes the various techniques for subintimal angioplasty in more difficult applications used for 23 limbs in 20 patients for long-segment chronic total occlusion over the initial 9-month period the technique was started by a single operator. Indications primarily consisted of CLI (14 Rutherford category 5, four Rutherford category 4 and 5 for severe limiting claudication). Technical success was achieved in all cases. Four patients had flush occlusions, three patients had failed femoropopliteal bypass grafts, and only three patients required stent placement.

Initiating the subintimal plane can easily be performed at occluded stumps or at the level of a large shelf-like plaque by pointing a catheter eccentrically away from the midline lumen. At times, a stiffer catheter (braided JR4, C.R. Bard Inc., Murray Hill, NJ, or other catheters) can be used, or heavy-duty straight wires such as the Newton wire (Boston Scientific



Figure 1. Diffuse vascular calcifications with more focal high-grade left external iliac artery stenosis. Flush occlusion of the left superficial femoral artery (SFA) (A,B). Correction of focal left external iliac artery stenosis with placement of a Smart stent (Cordis Corporation, a Johnson & Johnson company, Miami, FL) (C). Subintimal channel with .035-inch Spectranetics support catheter (Spectranetics Corporation, Colorado Springs, CO) in the subintimal plane (D). Final subintimal recanalized left SFA demonstrating a widely patent SFA, popliteal artery, and proximal trifurcation (E-G).

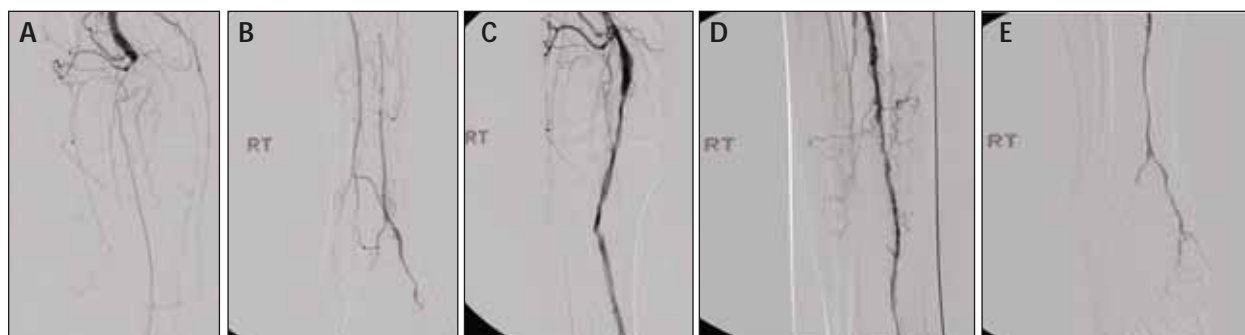


Figure 2. Occlusion of the popliteal artery at the knee joint level, with distal reconstitution of the posterior tibial artery near the ankle and of the peroneal artery in the distal calf (A,B). The proximal fibrous portion of the occlusion required a Smart nitinol stent. The rest of the subintimal angioplasty to the posterior tibial artery demonstrates rapid antegrade flow (C-E).

Corporation, Natick, MA) can be used to initiate the subintimal plane. Once the subintimal plane is entered, a Glidewire (Terumo Corporation, distributed by Boston Scientific Corporation) is passed, forming a loop. The loop is preserved, and re-entry often can occur effortlessly, with the loop entering the expected location of healthier artery distally. If re-entry is not achieved at the desired level, small contrast injections may show small “holes” in the intima communicating with the true lumen, allowing lower-profile torqueable wires to be passed through these holes achieving true lumen entry.

CASE STUDIES

Case 1

A 48-year-old woman with a 60 pack-year history of cigarette smoking had undergone two previous coronary bypass operations. The last operation was performed 6 months prior to this case. The inferior aspect of her left leg saphenous vein graft harvest site failed to heal and had deepened and worsened. She had undergone left femoral-popliteal bypass 7 years previously, which failed early. Arteriography demonstrated that she had diffuse vascular calcifications but with more focal stenosis of the left external iliac artery corrected with angioplasty and stenting (Figure 1). She had a flush occlusion of the left SFA, with the bypass stump apparent. The popliteal artery reconstituted at Hunter's canal with a two-vessel runoff.

She underwent left external iliac artery stent-assisted angioplasty and subintimal recanalization of the left SFA. A 6-F Balkin sheath (Cook Incorporated, Bloomington, IN) was placed over the bifurcation into the left common femoral artery. A relatively stiff braided JR4 catheter was placed in the common femoral artery and, with use of a Newton wire, the area between the bypass stump and profunda was vigorous-

ly probed entering the SFA. The JR4 catheter was then advanced into the superior SFA and exchanged for a Glidewire, which was advanced with a loop to the location of expected “healthy” popliteal artery. The loop, however, did not enter the popliteal artery. Contrast injection demonstrated a trickle of contrast entering the popliteal artery in an antegrade fashion. A torqueable Choice PT Extra Support (Boston Scientific Corporation) was then advanced across this intimal “hole” into the popliteal artery, and standard percutaneous transluminal angioplasty with a 5-mm X 8-cm Meditech Ultra-thin SDS balloon (Boston Scientific Corporation) was performed, achieving patency. The patient's wound rapidly healed in a 4-week period.

Case 2

A 78-year-old man had diabetes mellitus and significant coronary arterial disease with recent myocardial infarction presenting with a nonhealing, 2-cm wound on the right third toe. Angiography demonstrated occlusion of the popliteal artery above the knee joint level, with reconstitution of the posterior tibial artery at the ankle and of the peroneal artery in the distal calf (Figure 2).

He underwent subintimal recanalization to the posterior tibial artery. An antegrade approach was selected for all long-segment infrapopliteal occlusions. A braided JR4 catheter was placed at the occlusion eccentrically, and a Glidewire was utilized to start the subintimal plane forming a loop with the JR4 catheter advanced over to the tibioperoneal trunk location. The JR4 catheter was pointed toward the posterior tibial artery, and this area was probed with a Glidewire entering the subintimal channel in the posterior tibial artery. A .035-inch Spectranetics support catheter was required for the stiff subintimal plane in the posterior tibial artery. A Glidewire was still utilized to dissect this plane; how-

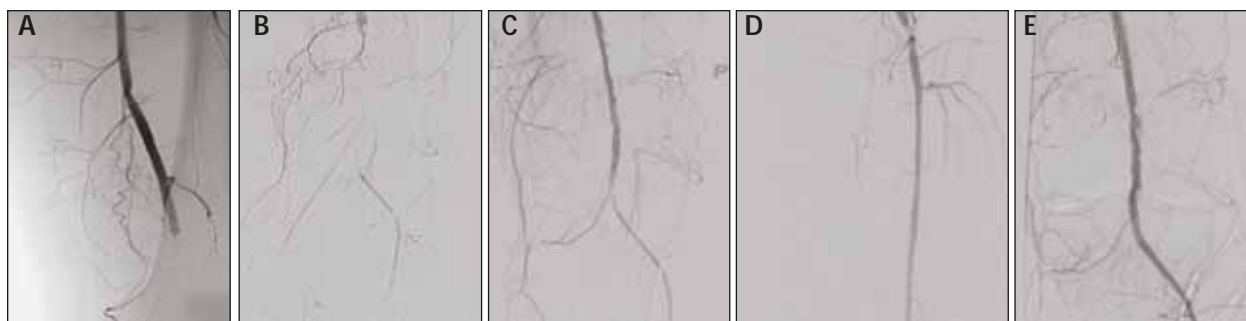


Figure 3. The popliteal artery is occluded above the knee, with collateral reconstitution of the proximal variant anterior tibial artery. The anterior tibial artery further distally is occluded, with no dorsalis pedis in the foot; however, collaterals supplying the plantar arteries and dorsal arch were noted (A,B). Initially, the subintimal channel did not directly communicate with the anterior tibial artery; however, with a JR4 catheter placed at the origin of the anterior tibial artery, a Glidewire was advanced across the intima into the anterior tibial artery (C-E).

ever, as with other infrapopliteal trifurcation subintimal dissections, care is taken to avoid a large loop and often the loop is removed from the Glidewire. Eventually, a relatively healthy portion of the posterior tibial artery was entered. Standard angioplasty with a 2.5-mm Symmetry (Boston Scientific Corporation) balloon was performed in steps in the posterior tibial artery, and 5-mm angioplasty was performed in the popliteal artery. The rigid superior fibrous cap required a 6-mm X 4-cm Smart stent to achieve adequate patency. A palpable pulse was achieved and maintained without other intervention until healing occurred in a 4-month period.

Case 3

A 52-year-old woman had large embolic events to her left middle cerebral artery and left popliteal artery with distal emboli in the runoff vessels (Figure 3). She presented with strict contraindication for thrombolytic therapy. Attempts at Angiojet thrombectomy (Possis Medical Inc, Minneapolis, MN) were unsuccessful. A subintimal plane was created into the variant high anterior tibial artery takeoff. The subintimal recanalization provided limb salvage and allowed the patient to pursue rehabilitation, moving her past her acute event. A JR4 catheter was placed eccentrically at the occlusion, and a Glidewire was passed into the occluded tibioperoneal trunk. The JR4 catheter was then pulled back to the anterior tibial origin, as demonstrated by roadmap images, and a Glidewire was advanced in the anterior tibial artery. After the JR4 catheter was advanced into the true lumen anterior tibial artery origin, the Glidewire was exchanged for a V-18 (Boston Scientific Corporation), and support wire and standard angioplasty was performed. A Smart stent was required at the superior edge to stabilize thrombus at this location.

DISCUSSION

Subintimal angioplasty was first used in 1987 and gained popularity, initially in Europe.¹⁰ The technique was adopted a decade later by US centers, with reports appearing from the departments of surgery and radiology at Montefiore Medical Center.¹¹ More recently, various cases with the use of re-entry catheters have been described in the US experience.¹² Many US endovascular specialists have been reluctant to adopt the technique given the counterintuitive nature of starting a subintimal plane intentionally for fear of being unable to gain re-entry. The technique, however, is relatively easy and inexpensive because it does not rely on stents or various atherectomy devices. In fact, the success of re-entry can be better than intentional true lumen passage for long-segment CTOs.

Subintimal angioplasty is technically successful in 70% to 90% of cases, as described in the literature. Limb salvage is achieved in approximately 80% to 90% of patients, and clinical worsening has rarely been described. Primary patency rates range from 60% to 80% at 6 months and 60% to 70% at 12 months.¹³⁻¹⁵ In this patient series, secondary interventions were quick and easy, with wire passage readily into the prior subintimal plane achieving overall excellent secondary patency at 1 year. The approach does not interrupt bypass options and may, in fact, preserve options better than stent placement, which may lead to a greater loss of collaterals upon occlusion, making more distal reconstructions necessary. Often, after a subintimal infrainguinal plane is created, new collaterals are observed, and it is likely that multiple tiny "holes" are present in the subintimal channel supplying greater collaterals. When the subintimal channels start to fail, often portions with collaterals remain patent, and overall perfusion benefit may substantially exceed even patency rates.¹⁵⁻¹⁷

CONCLUSION

Endovascular therapy is replacing surgical revascularization in the management of CLI without compromising limb salvage or subsequent vascular intervention. CLI patients represent a subset of patients with high mortality rates similar to myocardial infarction and stroke patients. The mortality risks of infrapopliteal surgical revascularization can approach the risks of abdominal aortic surgery. An initial endovascular approach achieves limb salvage rates equivalent to surgical bypass. Subintimal angioplasty is a relatively easy technique to master and can be applied to long-length occlusions as a first-line treatment option for CLI. Subintimal angioplasty should be in the armamentarium of all endovascular specialists. ■

Larry Horesh, MD, is from the Department of Interventional Radiology, Jackson-Madison County General Hospital, Jackson, Tennessee. He has disclosed that he has no financial interest in any product or manufacturer mentioned herein. Dr. Horesh may be reached at (731) 935-8854; lhoresh@yahoo.com.

- Bertele V, Roncaglioni MC, Pangrazzi J, et al. Clinical outcome and its predictors in 1560 patients with critical limb ischaemia. Chronic Critical Leg Ischaemia Group. Eur J Vasc Endovasc Surg. 1999;18:401-410.
- Wolf GL, Wilson SE, Cross AP. Percutaneous transluminal angioplasty versus open surgery for peripheral arteriosclerosis: report of a prospective randomized trial in a selected group of patients. J Vasc Surg. 1989;9:1-9.
- Holm J, Arvidsson B, Jivegard L, et al. Chronic lower limb ischaemia: a prospective randomized controlled study comparing the 1-year results of vascular surgery and percutaneous transluminal angioplasty (PTA). Eur J Vasc Surg. 1991;5:517-522.
- Bolia A, Brennan J, Bell PR. Recanalization of femoro-popliteal occlusions: improving success rate by subintimal recanalisation. Clin Radiol. 1989;40:325.
- Bolia A, Miles KA, Brennan J, et al. Percutaneous transluminal angioplasty of occlusions of the femoral and popliteal arteries by subintimal dissection. Cardiovasc Intervent Radiol. 1990;13:357-363.
- London NJ, Srinivasan R, Naylor AR, et al. Subintimal angioplasty of femoropopliteal occlusions: the long-term results. Eur J Vasc Surg. 1994;8:148-155.
- Hynes N, Yousaf A, Manning B, et al. Subintimal angioplasty as a primary modality in the management of critical limb ischemia: comparison to bypass grafting for aortoiliac and femoropopliteal occlusive disease. J Endovasc Ther. 2004;11:460-471.
- Tisi PV, Mirnesami A, Baker S, et al. Role of subintimal angioplasty in the treatment of chronic lower limb ischaemia. Eur J Vasc Endovasc Surg. 2002;24:417-422.
- Reekers JA, Bolia A. Percutaneous intentional extraluminal (subintimal) recanalization: how to do it yourself. Eur J Radiol. 1998;28:192-198.
- Bolia A, Brennan J, Bell PR. Recanalisation of femoro-popliteal occlusions: improving success rate by subintimal recanalisation. Clin Radiol. 1989;40:325.
- Lipsitz EC, Ohki T, Veith FJ, et al. Does subintimal angioplasty have a role in the treatment of severe lower extremity ischemia? J Vasc Surg. 2003;37:386-391.
- Saketkhoo RR, Razavi MK, Pakidar A, et al. Percutaneous bypass: subintimal recanalization of peripheral occlusive disease with IVUS guided luminal re-entry. Tech Vasc Interv Radiol. 2004;7:23-27.
- Ingle H, Nasim A, Bolia A, et al. Subintimal angioplasty of isolated infragenicular vessels in lower limb ischemia: long-term results. J Endovasc Ther. 2002;9:411-416.
- Reekers JA. Percutaneous intentional extraluminal (subintimal) revascularization (PIER) for critical limb ischemia: too good to be true? [commentary] J Endovasc Ther. 2002;419-421.
- Lipsitz EC, Ohki T, Veith FJ, et al. Fate of collateral vessels following subintimal angioplasty. J Endovasc Ther. 2004;11:269-273.
- Lazaris AM, Tsiamis AC, Bolia A, et al. Clinical outcome of primary infrainguinal subintimal angioplasty in diabetic patients with critical lower limb ischemia. J Endovasc Ther. 2004;11:447-453.
- Green JS, Newland C, Fishwick G. Positive outcome following unsuccessful subintimal angioplasty. Eur J Vasc Endovasc Surg. 1998;16:266-270.

(Continued from page 29)

cent of patients (12 of 15) were Rutherford category 0, 13.3% (2 of 15) were category 1, and 6.7% (1 of 15) were category 2. Clinical success remained 100%, and primary patency by duplex ultrasound was 93.3% (14 of 15). There have been no reinterventions, and very importantly, no stent fractures have been identified (0 of 17) on radiographic follow-up.

Quality-of-life assessments such as the Walking Impairment Questionnaire and SF-8 also showed significant improvement at 6 months. Pain indices, walking distances, stair climbing, and walking speed scores all improved approximately twofold from baseline. SF-8 tests showed marked improvement in physical and mental scores, which increased from 40.5±9.1 to 50.0±9.5 ($P=.0016$) and 47.0±11.7 to 50.7±8.6 ($P=.3228$), respectively.

RESILIENT PHASE 1 IN CONTEXT

Results from the SIROCCO trials have generated much interest in SFA stenting. Although the long-term restenosis rates in the drug-eluting stent arm of the SIROCCO trial were not as low as the investigators had hoped, the results observed in the bare-metal control arm were surprisingly good with 6-month angiographic restenosis rates in SIROCCO I and II of 23.5% and 7.7%, respectively. A problem that was brought to light in the SIROCCO trial was the frequent occurrence of stent fracture when multiple nitinol stents are implanted into the SFA and popliteal artery. The magnitude of this problem was further supported by the findings from the European FESTO trial. Preliminary data from phase 1 of the RESILIENT Trial have been promising in this regard, with a 0% fracture rate at 6 months versus 6.9% in the SIROCCO II DES arm and 10.7% in its bare-metal control arm. The 6-month duplex derived restenosis rate of 6.7% in RESILIENT phase 1 also compares favorably with the 6-month angiographic restenosis rate from the bare-metal control arm of SIROCCO II.

The acute and 6-month data from RESILIENT's feasibility phase are encouraging. Longer-term data and forthcoming results from the pivotal phase 2 randomized portion of this trial will provide us with much needed information about the effectiveness of nitinol stents in the SFA compared to balloon angioplasty alone. Important additional data regarding the risk of stent fracture with this newer, more flexible nitinol stent design will be generated. ■

John R. Laird, Jr, MD, is Director of Peripheral Vascular Interventions at the Cardiovascular Research Institute, and is Assistant Clinical Professor of Medicine at Georgetown University Medical Center, Washington, DC. He is also the Co-Director of the Center of Vascular Care at the Washington Hospital Center, Washington, DC. Dr. Laird may be reached at (202) 877-5975; John.R.Laird@medstar.net.