

Key Updates in AV Access Trials

A summary of the current status of AV access trials in 2018.

The everlinQ endoAVF Post Market Study (Europe and Canada)

Sponsor: TVA Medical, Inc.

Principal investigator(s): Nicholas Inston, MD (University Hospitals Birmingham, Birmingham, United Kingdom), and Thomas Schmitz-Rixen, MD (University of Frankfurt, Frankfurt, Germany).

Study population: Patients who are candidates for the placement of vascular access for chronic hemodialysis.

Rationale/need: This technology represents an option for patients in need of vascular access for dialysis, in addition to currently available surgical options or options resulting in the placement of temporary or permanent implanted device.

Key endpoints: Procedural success, primary patency, assisted primary patency, secondary patency, functional patency, time to maturation/usability, time to cannula-

tion, functional cannulation, central venous catheter exposure, interventions and secondary procedures, and adverse events.

Status: Currently enrolling.

Data: The data from this study have not yet been published. It is anticipated that the results of this trial will be published after the enrollment and 12 months of follow-up are completed. Enrollment is anticipated through the end of 2018, with follow-up through the end of 2019.

Principal investigator commentary: This study follows on the footsteps of the published FLEX and NEAT studies utilizing the everlinQ device.^{1,2}

1. Rajan DK, Ebner A, Desai SB, et al. Percutaneous creation of an arteriovenous fistula for hemodialysis access. *J Vasc Intervent Radiol.* 2015;26:484-490.

2. Lok CE, Rajan DK, Clement J, et al. Endovascular proximal forearm arteriovenous fistula for hemodialysis access: results of the prospective multicenter Novel Endovascular Access Trial (NEAT). *Am J Kidney Dis.* 2017;70:486-497.

The United States Pivotal Multicenter Trial of Ultrasound-Guided Percutaneous Arteriovenous Fistula Creation for Hemodialysis Access

Sponsor: Avenu Medical, Inc.

Principal investigator(s): Jeffrey Hull, MD (Richmond Vascular Center, North Chesterfield, Virginia).

Study population: Stage 4 and 5 end-stage renal disease (ESRD) patients within 6 months of dialysis at community dialysis centers.

Rationale/need: Safety and efficacy evaluation for US Food and Drug Administration (FDA) approval of the Ellipsys vascular access system for creation of proximal radial artery fistula.

Key endpoints: Device-related serious adverse events through 90 days. Fistula maturation at 90 days, defined as brachial artery flow volume of 500 mL/min and vein diameter of 4 mm compared against a performance goal derived from a meta-analysis of surgical literature.

Status: Presented and published.

Data: Percutaneous proximal radial artery fistulas were created in 107 patients at five sites in the United States. The fistulas were matured in subsequent procedures. Arteriovenous fistulas (AVFs) with fused anastomoses were created in 95% (102/107) of patients. Maturation procedures included proximal fistula balloon dilation

in 72% (77/107), brachial vein embolization in 32% (34/107), cubital vein ligation in 31% (33/107), and surgical transposition in 26% (28/107) of patients. Primary flow and diameter endpoints were achieved in 86% (92/107) of patients, exceeding the performance goal of 49% ($P < .0001$). No major adverse events were attributed to the device. Cumulative patency was 91.6%, 89.3%, and 86.7% at 90, 180, and 360 days, respectively. Target dialysis veins were cephalic, basilic, and brachial veins in 74% (73/99), 24% (24/99), and 2% (2/99) of patients, respectively. The mean time to two-needle cannulation was 100.2 ± 51.9 days (range, 34–224 days) for patients on dialysis at the start of the study. Functional patency was 98.4%, 98.4%, and 92.3% at 90, 180, and 360 days, respectively.¹

Principal investigator commentary: The pivotal trial of the Ellipsys vascular access system was the first and only evaluation of percutaneous fistula creation in the United States. The study shows that functional fistulas can be created in a minimally invasive procedure with ultrasound guidance in the office-based laboratory by interventional radiologists and nephrologists. Moving fistula creation out of the operating room and expanding the physician base that performs these procedures is an important paradigm shift for dialysis patients and the vascular access community. Another important aspect of this real-world study was that the patients were dialyzed at home or in community dialysis centers without the need for specialized training for fistula cannulation.

The Ellipsys vascular access system has the unique ability to create a percutaneous fistula between the proximal radial artery and perforating vein. The use of the proximal radial artery has important immediate and long-term safety benefits. The radial artery is non-dominant, limits fistula flow, provides easy access to the fistula from the transradial approach, and has low risk of steal syndrome. The position of the anastomosis in the most superficial portion of the perforating vein and the proximal radial artery provided good outflow to the superficial veins while limiting the amount of deep flow (Figure 1).

The Ellipsys vascular access system met the primary safety and efficacy 90-day endpoints and achieved cumulative and functional patency rates comparable to the surgical literature.^{2,3} Secondary endpoints of time to two-needle dialysis, secondary procedures, and fistula-related complications were also comparable to surgical results.^{4,5} Surgeons in Europe have recently reported on their experience with percutaneous Ellipsys vascular access system; they reduced

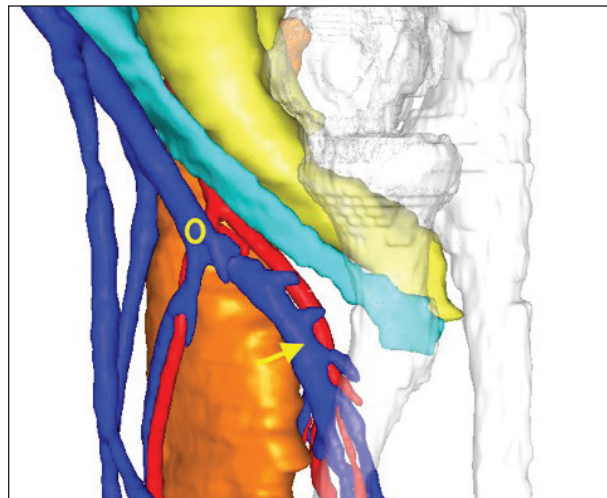


Figure 1. Three-dimensional reconstruction of antecubital fossa MRI demonstrates the site (yellow oval) of the Ellipsys vascular access system between the proximal radial artery and perforating vein. This site is close to the superficial system, above all the deep branches coming off the ulnar vein (yellow arrow).

maturation procedures to 20% by allowing the fistulas to have multiple outflow veins and varied cannulation sites. The time to first dialysis was reduced to 4 to 6 weeks due to the lack of surgical pain, swelling, and healing of dissection and incision. Patient acceptance of the procedure was improved by the minimally invasive approach.⁶

The current studies completed by interventional radiologists, nephrologists, and endovascular surgeons using the Ellipsys vascular access system suggest that it will be possible to improve upon the most significant problems with AVF creation for hemodialysis patients in the United States (pending FDA approval) including: (1) the 30% to 60% failure rate of surgical fistula, (2) the mean 136 days to achieve two-needle cannulation, and (3) the 80% of patients initiating dialysis on a catheter.^{5,7,8}

1. Hull JE, Jennings WC, Cooper RJ, et al. The pivotal multicenter trial of ultrasound-guided percutaneous arteriovenous fistula creation for hemodialysis access. *J Vasc Interv Radiol.* 2018;29:149-158.e5.
2. Wu CC, Jiang H, Cheng J, et al. The outcome of the proximal radial artery arteriovenous fistula. *J Vasc Surg.* 2015;61:802-808.
3. Huijbregts HJ, Bots ML, Wittens CH, et al. Hemodialysis arteriovenous fistula patency revisited: results of a prospective, multicenter initiative. *Clin J Am Soc Nephrol.* 2008;3:714-719.
4. Sidawy AN, Gray R, Besarab A, et al. Recommended standards for reports dealing with arteriovenous hemodialysis accesses. *J Vasc Surg.* 2002;35:603-610.
5. United States Renal Data System. 2016 USRDS annual data report: epidemiology of kidney disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2016.
6. Mallios A, Jennings WC, Boura B, et al. Early results of percutaneous arteriovenous fistula creation with the Ellipsys Vascular Access System [published online April 18, 2018]. *J Vasc Surg.*
7. Al-Jaishi AA, Oliver MJ, Thomas SM, et al. Patency rates of the arteriovenous fistula for hemodialysis: a systematic review and meta-analysis. *Am J Kidney Dis.* 2014;63:464-478.
8. Chan KE, Maddux FW, Tolkoff-Rubin N, et al. Early outcomes among those initiating chronic dialysis in the United States. *Clin J Am Soc Nephrol.* 2011;6:2642-2649.

Lutonix AV Drug-Coated Balloon vs Standard Balloon for Treatment of Dysfunctional AV Fistulae (Lutonix AV IDE)

Sponsor: Lutonix Inc.

Principal investigator(s): Scott O. Trerotola, MD (University of Pennsylvania, Philadelphia, Pennsylvania); for the Lutonix AV Clinical Trial Investigators.

Study population: 285 subjects.

Rationale/need: First large, multicenter, prospective, randomized controlled trial (RCT) utilizing drug-coated balloon (DCB) in dysfunctional fistulas. Results led to FDA approval.

Key endpoints: The efficacy endpoint is target lesion primary patency (TLPP) at 6 months. The safety endpoint is freedom from any serious adverse event(s) involving the AV access circuit through 30 days.

Status: Enrollment completed.

Data: Six-month results have been accepted for publication in the *Clinical Journal of the American Society of Nephrology*. Interim 24-month results have been presented and show a mean time to target lesion reintervention for Lutonix at 318.7 days versus 198.4 days in the control, suggesting 120 additional intervention-free days (4 months).

Principal investigator commentary: In the 52 years since the AVF was described, plain old balloon angioplasty (POBA) has been the mainstay of fistula maintenance. Yet, with at best a 50% 6-month primary patency rate, there is substantial room for improvement over POBA in this space. Anything we can do to improve the quality of life for ESRD patients undergoing hemodialysis is strongly warranted, and prolonging the time until

the next access maintenance visit is needed and clearly meets that definition.

This trial builds on the existing set of small, single-center RCTs that have demonstrated superior patency for DCBs over POBA in AV access. It carries the additional weight of being an investigational device exemption (IDE) trial, including a large sample size and a multicenter, multidisciplinary investigative team as well as strict enrollment criteria, rigorous data collection and curation, well-established definitions, and data safety monitoring board/clinical events committee oversight. It was blinded in every way possible; only the investigator performing the index procedure was not blinded by necessity, as the DCBs are visibly different from POBA balloons.

Although not perfect, the results show a clear signal of superior patency using an approach of achieving good vessel preparation with high-pressure percutaneous transluminal angioplasty followed by DCB treatment when compared to a plain balloon of similar design. The TLPP in the DCB group exceeds Kidney Disease Outcomes Quality Initiative recommendations and, importantly, is consistent with previous studies; reproducibility is a great strength in medical research. As previously noted, the 6-month results should be online very soon and in print later this year; the 24-month results are being finalized now and will be submitted for publication along with subset analyses in the coming months.

Collectively, these contributions to the DCB literature will strengthen the weight of the evidence in favor of DCBs over POBA in AVF while we await additional studies of this and other DCBs that are presently underway. In addition, a Lutonix AV Post Approval Study will soon start enrolling 213 patients, further adding to the evidence regarding DCB in dysfunctional fistulas.

Lutonix Global AV Registry

Sponsor: Lutonix Inc.

Principal investigator(s): Dimitrios Karnabatidis, MD (Patras, Greece); for the Lutonix AV Global Registry Investigators.

Study population: 324 subjects.

Rationale/need: First large, multicenter, prospec-

tive study utilizing a DCB in dysfunctional fistulas and expanded polytetrafluoroethylene grafts in international sites in real-world clinical practice.

Key endpoints: The efficacy endpoint is TLPP at 6 months. The safety endpoint is freedom from any serious adverse event(s) involving the AV access circuit through 30 days.

Status: Enrollment completed.

Data: Interim 6-month results have been presented. Interim primary safety endpoint at 30 days was 99.4% (n = 156). Interim 6-month TLPP by Kaplan-Meier estimate was 74.9% (n = 77). Interim 6-month access circuit primary patency by Kaplan-Meier estimate was 70.9% (n = 74). The study is monitored and clinical events committee adjudicated.

Principal investigator commentary: Since June 2016, the Lutonix Global AV Registry has recruited 324 patients from 25 international sites within 20 months. Interventional radiologists, vascular surgeons, and interventional nephrologists have been involved in recruitment, producing an interesting multidisciplinary outcome. This is the largest number of patients recruited thus far who have undergone DCB angioplasty for the treatment of dysfunctional vascular access. The Lutonix Global AV Registry adds a significant evidence contribution to our understanding of DCB function and use. What's more, about half of the cases are restenotic lesions (including in-stent restenosis). Symptomatic central venous stenoses account for 11% of cases, tandem

lesions were treated in one fifth of cases, and both AVFs and AV grafts (AVGs) are included in a 3:1 proportion. This is truly a real-world registry, as these are cases we come across in our everyday practice.

With 77 patients reaching the 6-month primary endpoint so far, TLPP is 74.9%. This is aligned with 6-month data from the Lutonix IDE trial announced by Dr. Trerotola in 2017 in which TLPP was 71.4%, as well as those published by Kitrou et al in a retrospective analysis published in 2016 in which TLPP was 72.2%.¹ Interestingly, in this study and the retrospective analysis, both AVFs and AVGs were included, showing not only consistency of results but also overall efficacy. Effectiveness of Lutonix DCB use in dysfunctional AV access is also underlined by the fact that circuit primary patency is 70.9% in this interim analysis, a figure similar to the TLPP.

Given the number of subjects and diversity of lesions in the Lutonix Global AV Registry, we could gain important insights on different aspects of this completely new drug-based approach of vascular access treatment.

1. Kitrou PM, Spiliopoulos S, Papadimitos P, et al. Paclitaxel-coated balloons for the treatment of dysfunctional dialysis access. Results from a single-center, retrospective analysis. *Cardiovasc Intervent Radiol*. 2017;40:50-54.

IN.PACT AV Access Study

Sponsor: Medtronic

Principal investigator(s): Robert A. Lookstein, MD (Mt Sinai Healthcare System, New York, New York); Andrew Holden, MD (Auckland University, Auckland, New Zealand); and Hiroaki Haruguchi, MD (Haruguchi Vascular Clinic, Tokyo, Japan).

Study population: Subjects with ESRD presenting with clinical and hemodynamic abnormalities in native AVFs located in the upper extremity.

Key endpoints: The primary efficacy endpoint is patency of dialysis fistulas through 6 months, and the primary safety endpoint is serious adverse events through 30 days.

Status: Enrollment complete.

Data: No published data are currently available.

SAVE-US (Surfacer System to Facilitate Access in Venous Occlusions–United States) Trial

Sponsor: Bluegrass Vascular Technologies, Inc.

Principal investigator(s): Mahmood Razavi, MD, FSIR, FSVM (St. Joseph's Hospital, Orange, California); Eric Peden, MD (Houston Methodist Hospital, Houston, Texas); Timothy Pflederer, MD

(Unity Point Health-Methodist, Peoria, Illinois); Monnie Wasse, MD, MPH (Rush University Medical Center, Chicago, Illinois); Ehab Sorial, MD (Santa Clara Medical Center, San Jose, California); and Ziv Haskal, MD (University of Virginia, Charlottesville, Virginia).

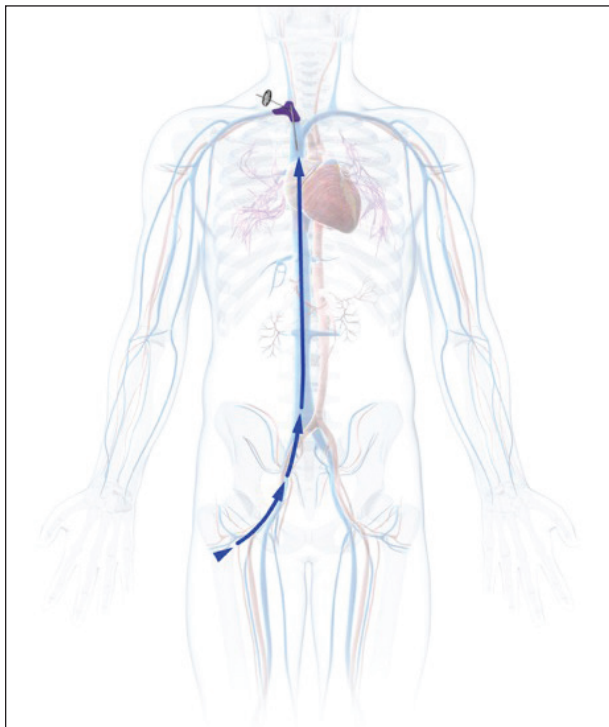


Figure 2. The Surfacr System's proprietary inside-out approach to gain central venous access in patients with obstructed veins.

Study population: 30 patients from up to 10 centers in the United States.

Rationale/need: To evaluate the safety and efficacy of the Surfacr Inside-Out Access Catheter System to facilitate the entry and placement of central venous catheters (CVCs) in patients with limited or diminishing upper body venous access.

Key endpoints: Primary endpoints include rate of successful transient CVCs created across venous occlusions (success is defined as placement of patent operational CVCs); acute device safety, defined as the absence of procedural complications at discharge and 7 days postprocedure; and overall device- and procedure-related anticipated adverse events compared to historical safety data from central venous placement procedures. Secondary endpoints

include assessment of whether the device able to advance from the femoral vein to subclavian exit to facilitate catheter placement and the technique conversion rate.

Status: Currently enrolling for phase 2 (expanded sites and enrollment).

Available data: No data have been published to date. The study will be completed in the next year and results will be published at that point.

Principal investigator commentary: The Surfacr Inside-Out Access Catheter System is designed to reliably, efficiently, and repeatedly gain central venous access, allowing for the placement and maturation of permanent AV access options and eliminate the progression of central venous occlusions. The Surfacr system is a novel device allowing physicians to insert a guidewire through the femoral vein in the groin area and, using fluoroscopy, navigate it up through the torso with an exit point in the jugular vein (Figure 2).

Dr. Peden notes that because patients with chronically occluded veins have limited treatment options available, it is important to have a reliable and repeatable way to gain central venous access while patients are awaiting fistula placement or maturation. This also may greatly reduce catheter-related infections and costs.

Dr. Razavi adds that an advantage of participating in trials that involve innovative technologies is that patients are able to access therapies that they would otherwise not have, such as the Surfacr system. Loss of internal jugular access in patients who need chronic indwelling catheters can be more than just an inconvenience. The Surfacr system enables physicians to secure right neck venous access, even in absence of patent internal jugular or brachiocephalic veins through a relatively straightforward procedure.

CE Mark approval of the Surfacr system was secured in 2016, and Bluegrass Vascular Technologies, Inc. is also currently wrapping up enrollment of patients in its postmarket SAVE registry in Europe, a prospective, multicenter, postmarket clinical follow-up study designed to confirm clinical performance and safety of the Surfacr system.

Fist Assist Efficacy Study

Sponsor: Fist Assist Devices, LLC

Principal investigator(s): Sanjay Desai, MBBS, MS, FEVS (Ramaiah Medical Center, Bangalore, India).

Study population: Patients with stage 5 renal failure requiring AVFs with demographics similar to the United States population and a body mass index smaller than the United States population.

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Rationale/need: To evaluate whether an external, noninvasive pneumatic device (Fist Assist device) can help with AVF vein dilation and assess the safety of the Fist Assist device on the arms to prevent fistula thrombosis and skin issues.

Key endpoints: Vein size dilation compared to sham controls at 1 and 3 months.

Status: Completed.

Available data: After 3 months, the mean percentage increase in vein diameter in the forearm treatment group was significantly larger than those in the upper arm treatment group at proximal distances of 5, 10, and 15 cm from the anastomosis ($P < .05$). Patients in the forearm treatment group also had significantly larger mean percentage increases in vein diameter as compared to controls at proximal locations of 5 and 10 cm ($P = .008$ and $P = .006$, respectively). All fistulas treated

with the device were functional with no reported thrombosis, extravasations, or other adverse effects.

Commentary: The Fist Assist device is a safe, external device for vein dilation. It can be applied on fistulas after surgery and is safe and easy to wear. Application of this novel intermittent pneumatic compression device may be more effective at assisting long-term forearm fistula dilation (3 months) as compared to upper arms. Forearm fistulas are associated with lower risks of infection, distal ischemia, and steal syndrome. Thus, efficiently dilating forearm fistulas is extremely important because this may decrease costs associated with vascular access, reduce complications, and preserve upper arm veins for future use in vascular access. This study is now closed and data are being evaluated. One manuscript has recently been published in *Journal of Vascular Access*, and another manuscript is expected to be published this summer. ■