Ask the Experts:
What Is the Biggest Data Deficit in Dialysis Access Intervention? What Is the Solution?

ABIGAIL FALK, MD, FSIR, FASDIN

The largest deficit is the lack of true prospective randomized controlled trial data that provide an evidence-based approach to dialysis access intervention. There are only a few level I trials, most of which are company sponsored and thus have an inherent bias. Most published studies are single-center retrospective chart reviews that provide interesting observations, but do not test prespecified hypotheses or provide any real guidance or evidence-based treatment options.

However, several factors make these types of studies difficult to design and execute. First, the high mortality rate of patients with end-stage renal disease makes it difficult to design studies with long-term endpoints and follow-up. Second, primary access patency is clinically important, but there may be multiple target lesions, or if a target lesion is treated, another lesion may arise anywhere in the access circuit, confounding primary access patency. Finally, a great number of dialysis access interventions are done in outpatient access centers, where a profit motive may influence practice styles and skew outcomes.

More prospective randomized controlled trials are needed to provide data-driven treatment choices. As an adjunct, large registries established together with the key medical societies and specialties may help provide a greater understanding of what is required and may work best in dialysis access intervention.

ZIV J. HASKAL, MD, FSIR, FAHA, FACR

Dialysis access interventions are finally benefiting from a series of prospective controlled studies, in sharp contrast to a decade ago when manufacturers and regulatory agencies were under the solitary spell of the superficial femoral artery ("Dialysis? You want to place what where?!"). Still, successful interventional hemodialysis research has largely depended on the convergence of commercial and clinician-scientists' interests. Investigator-sponsored prospective studies have been rare, difficult to complete, and have closed early, such as studies of angioplasty versus stent grafts in cephalic arch stenosis or drug-eluting stents versus angioplasty. Hopefully, the rigor of regulatory and peer review, as well as data transparency, will offset the conflicts of interest that may accompany sponsored trials.

This work is currently active on several fronts, as shown in the 24-month results of the RESCUE, RENOVA, and REVISE trials. Notably missing is a study of primary stent graft placement in central vein stenosis or occlusions. Current devices are not mission specific, although existing expanded polytetrafluoroethylene stent grafts are suitable for evaluations. A dedicated toolkit of central vein devices is needed, as well as standardized reporting (and anatomic segmentation) of central vein interventions, as one size does not measure all. With this may come an increased focus on treating chronic undermanaged central venous hypertension and better natural history data for these lesions.

Arteriovenous fistulas (AVFs) may benefit from drug-coated balloons, and Bard Peripheral Vascular is conducting a controlled trial examining this potential benefit, which has rocketed through enrollment. Multiple other trials must be encouraged, as any results will bear replication, notwithstanding differing drug platforms. Drug-eluting stents have an untested value in the fistula from arm to arch.

Access modifiers, such as statins and other medications, drug-eluting implants placed at the fistula creation, balloon-assisted maturation and embolization, flow control devices, and devices for percutaneous fistula creation all warrant study. Whether any of these might reduce catheter use and catheter-related morbidities should remain a central focus. Careful study of alternate imaging and assessment tools (eg, intravascular ultrasound, optical coherence tomography, novel ultrasonic flow catheters) may better characterize which lesions to treat and perhaps improve long-term follow-up. The next 5 years should focus on a maturation of expectations in interventional access science from the embrace of retrospective research and assumptions of utility ("Look, a new hammer!"), to a demand for methodical assessments with meaningful functional and clinical outcomes.[1]

1. Haskal ZJ. Time to purposefully plan ahead: a call for quality in research. J Vasc Intervent Radiol. 2016;27:615-617.

ALEXANDER S. YEVZLIN, MD, FASN

The biggest conundrum in vascular access creation and maintenance happens to be the question for which there is arguably the least amount of available evidence. Although it is undoubtedly true that a mature AVF is superior to an arteriovenous graft (AVG) in terms of patency outcomes, this fact does not answer the question, "Which access should be created in which patient?" Quite simply, nearly 50% of all AVFs created in the United States fail to mature.

Thus, there may exist a group of patients who are high risk for failure to mature who should not have an AVF created. When one compares the patency outcomes of AVGs and AVFs prior to maturity, most studies, which unfortunately are small and retrospective in nature, suggest that there is no difference between the two. The solution to this conundrum is to acquire more robust prospective data that can help identify those who are at high risk for AVF failure to mature and to create an algorithm for access creation based on these data.

CHRISTOPHER OWENS, MD, MSc

In my mind, the timing of a referral for permanent vascular access in patients with chronic kidney disease (CKD) is the biggest data deficit in vascular access intervention. We either put fistulas in too soon or too late, and the consequence of this single source of clinical imprecision is that 80% of patients initiating hemodialysis do so with a central venous catheter.

There seems to be a disconnect between the vascular access surgeons and the referring nephrologists. Although it is better than it was, the nephrologists take the patients as far as they can go in their CKD before determining that the patient needs dialysis and, thus, a need to refer them to the surgeon. This model of unilateral decision making relegates the access surgeon to the end of the food chain, so to speak, without any control over what happens to the patient in, for example, the year prior to hemodialysis.

Some solutions to this issue would be to transition clinics with providers from multiple specialties, working together to identify and save the vein, create a renal replacement plan including peritoneal dialysis, and provide patient education. The latter is particularly important, as I have had patients referred to me who did not know why they were at a surgeon's office, were already on dialysis, or didn't really understand what a fistula was! Patients want education. We are currently piloting a nurse practitioner–led transition clinic, and the reviews from participants have been overwhelmingly positive. Among many other benefits, this gives back some control to the patient during a life-changing event for them.

Modeling the rate of progression through the advanced stages of CKD is the other key piece of missing data that is needed to better predict who is likely to survive to hemodialysis among the many advanced CKD patients. Of course, this is a model of competing risk, with death being that risk. We used a large Veterans Affairs dataset to demonstrate that over a 4-year period, only about 14% of patients with stable stage 4 CKD (mean estimated glomerular filtration rate, 30 mL/min/1.73 m^2) required hemodialysis. Remarkably, nearly 50% died over that same interval, which is a very sobering figure. Outcome prediction with prospective validated models would allow an earlier focus of resources that could lead to more successful access creation in a timely fashion and fewer access interventions.

TED SAAD, MD

Routine periodic AV access surveillance (typically monthly access flow measurement) has become standard in dialysis practice in the United States. Abnormal surveillance data prompt referrals for radiographic imaging of the access, with percutaneous interventions performed as deemed clinically necessary. This practice has been driven in large part by the Centers for Medicare & Medicaid Services mandate, supported by the Kidney Disease Outcomes Quality Initiative guidelines, and embraced by both dialysis and interventional programs. At the same time, we have seen significant developments in the techniques and tools available to treat AV access dysfunction, including high-pressure angioplasty balloons, stent grafts, and thrombectomy devices. More tools are in the pipeline, including drug-coated balloons and stent grafts specifically developed for the treatment of native AVF stenosis.

The clinical paradigm of surveillance-based intervention is built largely upon old, underpowered, and fundamentally flawed studies; these have not consistently demonstrated significant outcome benefits from surveillance-based preemptive interventions in terms of dialysis effectiveness, access thrombosis rate, access longevity (secondary patency), or more general clinical outcomes such as mortality and hospitalization rates. Furthermore, no study to date has clearly demonstrated cost-effectiveness of the surveillance-intervention paradigm. This has become increasingly important as the United States health care system changes (for better or for worse), with increased emphasis on "value," shifts in reimbursement structure away from the traditional fee-for-service model, and shared risks between payers and providers.

We need a well-designed prospective study of both AVFs and AVGs, examining the impact of surveillance-based interventions on clinically relevant access and/or patient outcomes; this must incorporate "real-world," rigorous cost-benefit analysis. In particular, how will the use of novel, higher-cost devices improve outcomes, and how will those costs translate into "value" for the patient, payer, and health care delivery system?

LEE KIRKSEY, MD, MBA

An AVF remains the gold standard for hemodialysis access. Unfortunately, many fistulas fail to mature and become a usable vascular access or thrombose, resulting in prolonged catheter use with the attendant morbidity and mortality risk.[1] To date, efforts to address nonmaturation have been directed at endovascular devices. In my opinion, the "holy grail" of innovation in this space will address blood vessel wall biology. Anecdotally, I have the occasional patient who repeatedly develops diffusely aneurysmal pathologic megafistulas at each of their reconstructions. Clearly, there is wall biology that we do not completely understand.

Several ongoing drug development efforts aim to address this problem by enhancing fistula outward remodeling or inhibiting intimal hyperplasia, one commonly present underlying culprit for fistula nonmaturation and patency loss. The most advanced of these programs is Proteon Therapeutics' vonapanitase, a recombinant human elastase, which is applied to the outside of the exposed vessels at the time of AVF creation in the phase 3 PATENCY-1 and PATENCY-2 trials. A previous phase 2 trial demonstrated statistically significant increases in fistula maturation by ultrasound criteria and a strong trend for improved patency, particularly in patients undergoing the creation of radiocephalic fistulas.[2] Results of PATENCY-1 are expected in December 2016. Vascular Therapies' sirolimus-eluting collagen implant[3] is being applied to the fistula in a phase 3 trial, and Enceladus Pharmaceuticals' liposomal prednisolone is being administered intravenously after fistula creation in a phase 2 trial.

Two additional devices are in development, including BioConnect Systems' Optiflow and Laminate Medical Technologies' VasQ System, which aim to improve the fistula's anastomotic angle and hemodynamic profile. Other companies are developing endovascular and percutaneous approaches to creating fistulas, including TVA Medical's everlinQ and Avenu Medical's Ellipsys. All of these technologies aim to increase the proportion of patients with mature, usable, and patent fistulas.

Finally, there is increasing activity in tissue-engineered blood vessels as an alternative to traditional AVGs in those unable to have a fistula. The durability of prosthetic bridge grafts continues to be limited by intimal hyperplasia at the graft to vein interface that results from compliance mismatch. The most advanced of these technologies is Humacyte's Humacyl, which in a recent publication of data from 60 patients showed an improvement in graft survival compared with a historical control. A phase 3 trial is being initiated.[4]

Each of these innovations represents the potential to significantly improve clinical outcomes in this challenging patient group. Moreover, significant reduction

in health care expenditure related to fistula and graft failure, maintenance interventions, and catheter exposure times may be a secondary benefit. ■

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Abigail Falk, MD, FSIR, FASDIN
Interventional Radiologist
Advanced Imaging and Interventional Institute
New York, New York
abigail.falk@gmail.com
Disclosures: Consultant, Bard Peripheral Vascular, Inc.

Ziv J. Haskal, MD, FSIR, FAHA, FACR
Professor of Radiology
Editor-In-Chief, *JVIR*
University of Virginia School of Medicine
Charlottesville, Virginia
ziv2@mac.com
Disclosures: Clinical events committee chair, C.R. Bard Lutonix Balloon AV Fistula trial; Principal Investigator, RENOVA trial.

Alexander S. Yevzlin, MD, FASN
Associate Professor of Medicine (CHS)
Director of Acute Dialysis
Director of Interventional Nephrology
VA Nephrology Chief
University of Wisconsin, Madison
Madison, Wisconsin
asy@medicine.wisc.edu
Disclosures: None.

Christopher Owens, MD, MSc
Associate Professor of Vascular and Endovascular Surgery
University of California, San Francisco
Chief, Section of Vascular Surgery
Associate Chief, Surgery (Systems Improvement and Innovation)
San Francisco VA Medical Center
Director
Vascular Integrated Physiology and Experimental Therapeutics Laboratory
San Francisco, California
christopher.owens@ucsf.edu
Disclosures: None.

Ted Saad, MD
Nephrology Associates, PA
Newark, Delaware
tsaad@delawarekidney.com
Disclosures: Consultant, WL Gore; consultant and clinical investigator, CR Bard Peripheral Vascular; partner/owner, Nephrology Associates Vascular Access Centers.

Lee Kirksey, MD, MBA
Department of Vascular Surgery
The Heart and Vascular Institute
The Cleveland Clinic Foundation
Associate Professor
The Lerner School of Medicine/Case Western
Cleveland, Ohio
kirksel@ccf.org
Disclosures: None.