Innovations in vascular access for hemodialysis

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Worldwide, hemodialysis remains the prevalent dialysis modality for more than 2 million patients who require well-functioning vascular access for this procedure. Creation of an arteriovenous fistula for long-term hemodialysis was the first innovation since the Scribner shunt and was followed by the development of an arteriovenous graft and catheter. Bioengineered vessels were developed during the last century, but this field has been energized by recent technology relating to the creation of human vessels. Novel endovascular techniques for creating an arteriovenous fistula may resolve some of the logistical issues involved in obtaining a timely arteriovenous fistula. Treatment of access stenosis, infection, and thrombosis has remained suboptimal, and innovative technologies are evolving. Many new approaches are now targeting the biological and mechanical aspects of vascular access, such as creation and maturation of arterial and venous anastomoses, development of a biological conduit for outflow, and negotiating the problems of central vein stenosis. Importantly, processes of access care that have long focused on arteriovenous fistulas are now recognizing the new paradigm, providing a complementary niche to arteriovenous grafts and dialysis catheters in the algorithm for individualized access placement. Cumulatively, to the credit of the multidisciplinary team approach, the long overdue focus on the very existential issue of vascular access for hemodialysis is being approached with newfound evidence-based enthusiasm as the vexing challenges related to regulations and reimbursement in hemodialysis persist. Patient choice and experience, often missed and ignored in the challenging management of an end-stage organ failure, need to stay central as we focus on patient-centered care of vascular access.

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During the past decade a steady increase has occurred in the prevalence of end-stage renal disease worldwide, with more than 2 million patients providing new challenges for physicians, researchers, and policy makers who are responsible for providing care to patients receiving dialysis.[1] Globally, hemodialysis (HD) is the major modality of renal replacement therapy in 70% to 90% of patients, with nearly half a million patients undergoing HD in the United States alone, and all requiring vascular access to perform this procedure. The health care expenditure to treat end-stage renal disease has increased to staggering levels, with approximately $34 billion spent in 2015 in the United States alone.[2] A significant portion of this expense is related to the establishment and maintenance of arteriovenous (AV) access. The costs of taking care of a patient undergoing HD are significantly greater for a patient using a central venous catheter (CVC) than for a patient using an AV graft (AVG) or an AV fistula (AVF), in that order. In resource-limited countries, creation of an ideal form of vascular access faces a multitude of challenges. The high cost of universal dialysis therapy prevents allocation of funds from the national health care budget, and even in countries with universal health coverage for dialysis, the cost of covering maintenance therapy for vascular access often remains the patient's responsibility. Thus innovative solutions to minimize the use of CVCs and improve the creation and utilization of a permanent form of AV access are urgently needed to tackle the growing chronic kidney disease epidemic. Irrespective of impending and future innovations, incorporation of experienced and dedicated vascular surgeons in collaboration with experienced and dedicated interventionalists will remain the key component of successful vascular access care.

A number of variables related to genetics, biology, anatomy, pathophysiology, social and demographic factors, economics, logistics, and regulatory policies and practice patterns play an overwhelmingly interlaced and extensively complicated role. Many of these factors have remained a subject of intense investigation, especially during the past 2 decades, although definitive solutions have not yet evolved because of the challenges of gaps in translational research, including agreement on patient-sensitive end points and regulatory hurdles. These factors not only make the process of achieving a seemingly simple and timely form of AV access extremely difficult but also render the process of developing innovative solutions into a maze (Figure 1). Some of these challenges have been discussed previously.[3] A multidisciplinary work

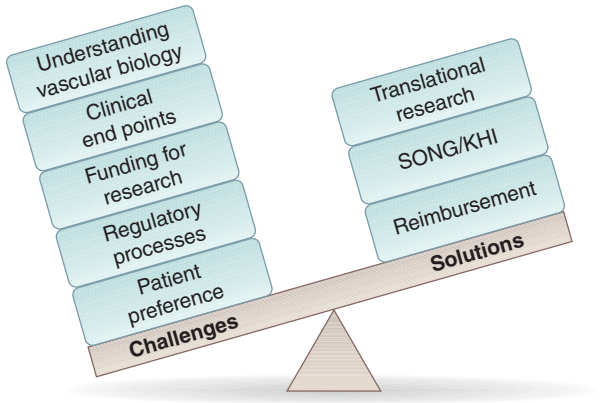

Figure 1 | Deficits in the understanding of all risk factors for vascular access maturation and dysfunction, along with challenges in trial design, research funding, and regulatory hurdles, currently outweigh potential solutions that might facilitate innovation. New coalitions, such as Standardized Outcomes in Nephrology (SONG) and the Kidney Health Initiative (KHI), may help tilt the balance in the future.

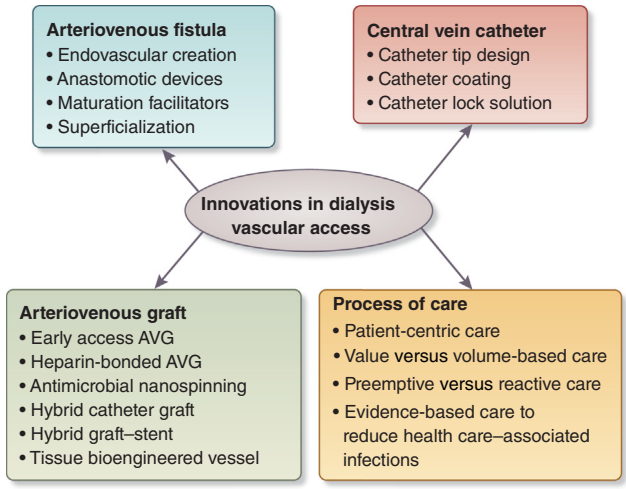

Figure 2 | Innovations in hemodialysis access based on the specific type of access and challenges in maturation and/or maintenance. AVG, arteriovenous graft.

group approach such as Standardized Outcomes in Nephrology and the Kidney Health Initiative will help advance our understanding of kidney health in the future, which might facilitate development of innovative therapies.[4,5]

To tackle the multitude and uniqueness of each potential etiologic factor leading to immaturity or dysfunction of vascular access, many recent innovations have focused on individual points of interest in dealing with challenges of various types of HD access, with variable success (Figure 2). Although no panacea to the puzzle of vascular access has emerged, each new step brings us closer to finding the solutions that might be applicable to individual specific challenges.

This review will provide an overview of the advances and innovations in HD vascular access from the invention of surgical AVF to the most recent techniques in endovascular AVF creation, as well as innovations in AVGs and CVCs. Because of space constraints, this review will not address evolving technologies for treatment of AV access dysfunction, such as stent grafts and drug-coated angioplasty balloons. We also will provide brief suggestions for innovation in the process of care in this area of need.

Innovations in AVFs

The groundbreaking innovation in dialysis access occurred in 1966 when Brescia, Cimino, Appel, and Hurwich invented a new surgical procedure to connect an artery directly to a vein, resulting in a mature AVF that was capable of delivering optimal flow for HD.[6] This procedure revolutionized the delivery of HD therapy globally, and "end-stage renal disease patients from all over the world were flying into New York" (M.J. Brescia, oral communication, February 9, 2008, Salt Lake City, UT, with AA). The procedure was further innovated by changing a side-to-side AV anastomosis to an end-to-side AV anastomosis to avoid hand edema that occurred with the original procedure. A mature AVF continues to be the best type of access to date for most patients because it has the most favorable outcomes in terms of infection and number of procedures required to maintain patency.

Several other sites for AVF creation including (but not limited to) brachial artery, axillary artery, femoral artery, cephalic vein in the upper arm, basilic and brachial veins, and femoral and saphenous veins were later used.[7] In 1976, brachial artery to basilic vein was connected in the upper arm to benefit patients without suitable veins in the forearm for the creation of an AVF.[8] Next, to avoid injury to brachial artery and median nerve and reduce the depth of the vein to allow for cannulation, the basilic vein was transposed to the front of the upper arm.[9] In 1977, utilization of the perforating vein at the elbow to anastomose with the brachial artery allowed 2 outflow tracks (basilic vein and the cephalic vein) in the upper arm that could be used to provide dialysis.[10]

Although an upper arm AVF provides robust flow, it can result in hand ischemia. Several innovative procedures including banding of an AVF, insertion of a tapered graft, distal revascularization and interval ligation, and revision using distal inflow have been applied to ameliorate hand ischemia.[11–21] A percutaneous technique of minimally invasive limited ligation of AVF has been successful in controlling hand ischemia in patients with upper arm access.[18] A full discussion of these techniques is out of the scope of this review.

Endovascular AVF creation. Enthusiasm regarding AVF creation has been rekindled in the past 2 years as a result of meaningful advances in endovascular techniques that may well revolutionize how we create AVFs. Two important endovascular interventions have been approved recently by the Food and Drug Administration in the United States.[22–25]

The Novel Endovascular Access Trial investigated an endovascular technique by surgeons and interventional radiologists in nondialysis- and dialysis-dependent patients using

radiofrequency energy and catheter-based technology to create a proximal forearm AVF.[22] Preoperative vessel mapping was undertaken in these patients and conscious sedation was used to carry out the procedure on an outpatient basis. Figure 3 delineates the operative steps to create a 5 mm × 1 mm side-to-side anastomosis between the ulnar artery and the vein redirecting blood flow to the superficial veins. Briefly, the key steps of the procedure include puncturing the brachial vein with a 21-gauge needle and navigating a guidewire into the deep (ulnar) vein under fluoroscopic guidance. A 7-French sheath is then inserted over a guidewire. At this point, the brachial artery is punctured in an antegrade direction and a guidewire is navigated into the ulnar artery. A 6-French sheath is inserted. Then a venous magnetic catheter is advanced to the ulnar vein and an arterial magnetic catheter is introduced through the brachial artery. Magnetic catheters are aligned and the radiofrequency electrode is activated, creating the anastomosis between the ulnar artery and the ulnar vein. An angiogram is performed through the arterial sheath to confirm the fistula creation. To direct flow to the superficial veins, one brachial vein is embolized. Median cubital, cephalic, and basilic veins all serve as the outflow veins and can be accessed to provide dialysis therapy.

In this pivotal study, 59 percutaneous AVFs were successfully created in 60 patients (98%) using the everlinQ endoAVF system (TVA Medical, Austin, TX); 87% of AVFs were suitable for dialysis with a mean brachial artery flow of 918 ml/min and a fistula diameter of 5.2 mm. Using simple physical examination tools (look, listen, and feel), dialysis nurses assessed the fistula for cannulation and found that 64% of the fistulas were functionally usable at 2 months. Other fistulas took a longer time to mature. The mean time for fistula maturation was as long as 111 days. At 12 months, the primary and cumulative patency rates were 69% and 84%, respectively. Notably, 19 patients needed secondary interventions, including 5 basilic transposition procedures, 5

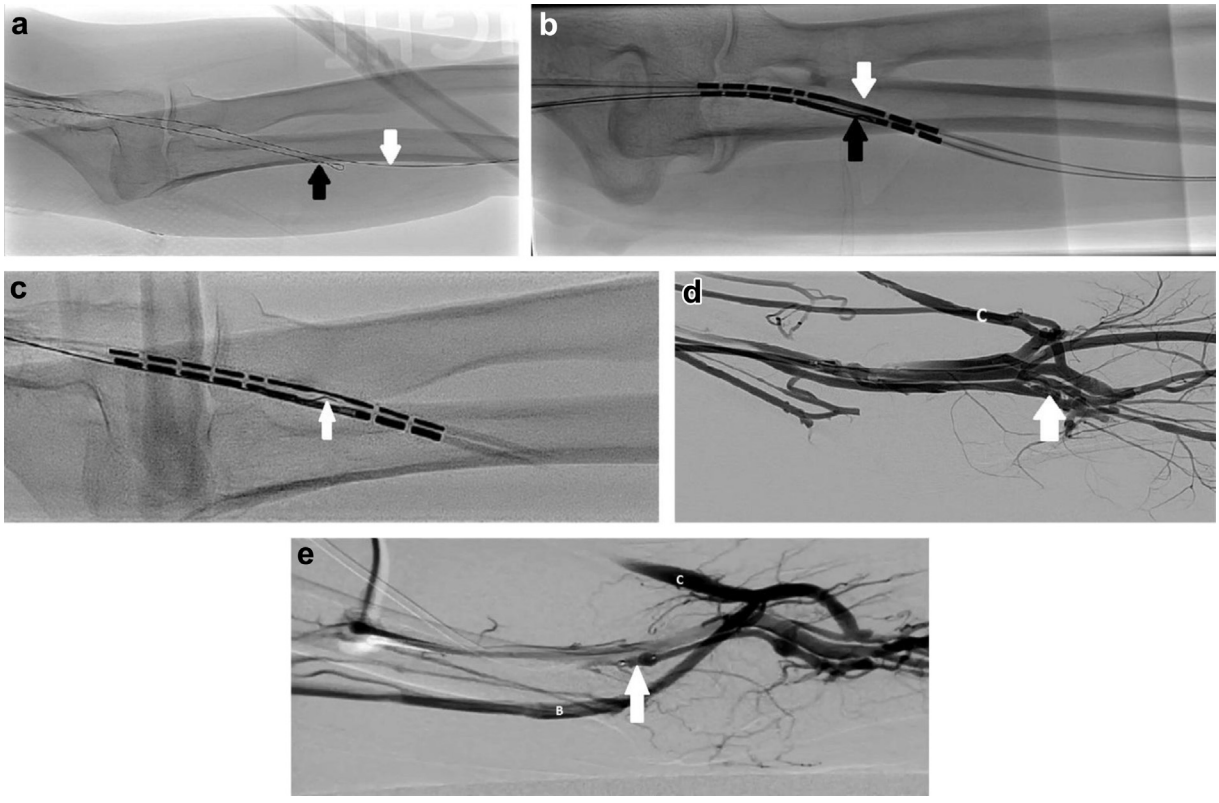

Figure 3 | Endovascular arteriovenous fistula (endoAVF) procedure steps. (**a**) After entering the brachial vein with a 21-gauge needle, a 0.018-inch guidewire is advanced through the needle to the ulnar vein (black arrow) under fluoroscopy, and a 7-French sheath is inserted. The white arrow indicates the wire in the ulnar artery. (**b**) Next, access to the brachial artery is similarly achieved; a guidewire is advanced to the ulnar artery, and a 6-French sheath is inserted. The everlinQ venous catheter is advanced to the ulnar vein (black arrow) and the arterial catheter to the ulnar artery (white arrow) under fluoroscopy. (**c**) Magnetic catheters align and then the radiofrequency electrode is deployed (white arrow). (**d**) After removing catheters, the endoAVF (white arrow) is confirmed with brachial artery contrast injection. (**e**) One brachial vein is embolized to divert flow to superficial veins (arrow; Amplatzer plug in embolized brachial vein). Finally, the arterial sheath is removed and hemostasis is attained per institutional practice. B, basilic vein; C, cephalic vein. Note: If the operator did not use a vascular closure device during the procedure to attain hemostasis, participants held manual compression over the puncture sites for 15 to 20 minutes and then the sites were covered with a simple adhesive bandage. Additional use of adhesive dressings, bandages, and supportive wrappings was discouraged. Reprinted from *American Journal of Kidney Diseases,* volume 70, 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), pages 486–497, Copyright © 2017, with permission from Elsevier.[22]

coil embolizations, 3 fistula ligations, 2 angioplasties, and 2 surgical repairs of the artery. The study demonstrated that a radiofrequency magnetic catheter–based system could be used successfully to create an endovascular AVF. The technique not only bypasses the need for open surgical exploration and general anesthesia but also provides another site for AVF creation using the ulnar artery and vein. Additional experience is needed to conclusively establish the success of this procedure on a larger scale.

Another endovascular technique utilizes a thermal resistance anastomosis device (TRAD) to create an AVF.[23–25] TRADs use pressure and thermal resistance energy to create an elliptical AV anastomosis that can withstand dilatation by balloon angioplasty to augment and direct flow into the fistula. The entire procedure can be performed with use of local anesthesia, with or without a regional block. The procedure uses a standard micropuncture needle to cannulate the cubital or brachial vein in a retrograde direction, navigating the needle and a guidewire under real-time ultrasonography into the proximal radial artery. Via a sheath, the TRAD is advanced into the artery, with its jaws capturing the walls of the artery and the vein. The device activation fuses and establishes a durable anastomosis. Percutaneous balloon angioplasty and embolization of accessory veins can be performed immediately to augment the flow into the AVF (Figure 4).[24] Surgical ligation of veins, valvulotomy, and transposition procedures also can be performed as needed.

In the pivotal prospective single-arm study, 102 of the 107 patients included in the study underwent successful TRAD-assisted percutaneous AVF creation using the Ellipsys Vascular Access System (Avenu Medical, San Juan Capistrano, CA).[24] Primary end points of the study included brachial artery flow volume of 500 ml/min and target vein diameter of 4 mm and were achieved in 86% (92/107) of the patients. It is worth mentioning that a great majority of the patients (77/107) required a balloon angioplasty procedure to augment maturation. Additionally, 34 and 33 of the 107 patients needed brachial vein embolization and cubital vein ligation, respectively. None of the patients demonstrated any major device-related adverse events. The cumulative patency at 90, 180, and 360 days was 91.6%, 89.3%, and 86.7%, respectively. Importantly, 2-needle dialysis was achieved in 88% (71/81) of patients undergoing HD. In another study utilizing the TRAD to create 33 endovascular AVFs in 34 patients (with a technical success rate of 97%), similar results were noted.[25] Taken together, these studies demonstrate that the TRAD technique is a viable endovascular option to create an AVF by interventionalists with no requirement of general anesthesia or surgery on an outpatient basis.

Located at the proximal forearm, these 2 novel techniques create a so-called endoAVF with a minimal risk of hand ischemia. It is conceivable that the lack of surgical manipulation of the juxta-anastomotic region as in traditional surgery is a contributory factor to prompt maturation. It is extremely important to note that these techniques create additional anatomic locations for creation of AVFs when creation of a distal radial artery AVF is not possible and the surgical option would be to move to the upper arm. If feasible surgically, a distal radial AVF would still be a preferred first AVF before moving to the proximal forearm to use these techniques. Because of their simplicity, these techniques will likely gain popularity among numerous specialists, including interventional nephrologists, interventional radiologists, and surgeons. Further experience is needed to conclusively establish the utility and role of Ellipsys and everlinQ in clinical practice. In reality, these techniques will provide a complementary approach in carefully selected cases to the traditional surgical approach in AVF creation. Pivotal studies have demonstrated safety and efficacy in the short term, but the long-term implications remain to be seen.

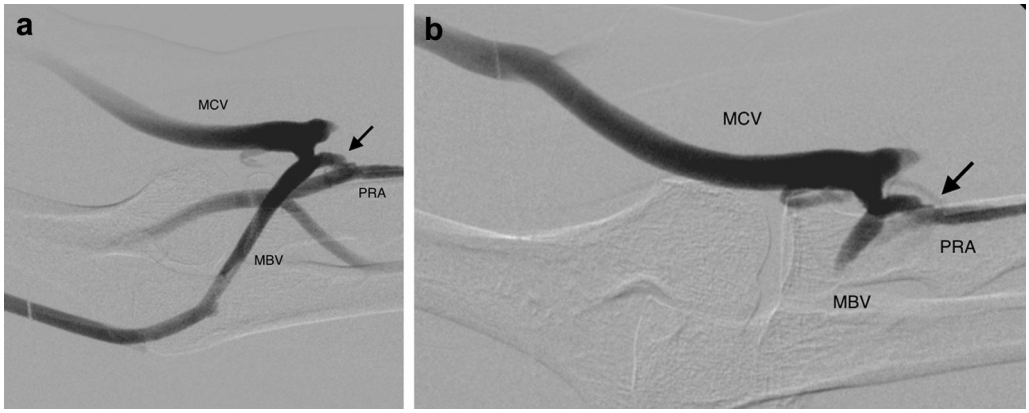

Figure 4 | A fistulogram demonstrates successful modification in access outflow to the targeted median cephalic vein (MCV) by ligation of the median basilic vein (MBV). (**a**) The thermal resistance anastomosis device percutaneous arteriovenous fistula (AVF) anastomosis between the perforating vein (arrow) and proximal radial artery (PRA) is shown with substantial outflow into the competing MBV, hindering access maturation. (**b**) Image obtained after MBV ligation shows all AVF flow now into the MCV, with the targeted cephalic vein now palpable and easy to cannulate. Reprinted from *Journal of Vascular and Interventional Radiology*, volume 29, Hull JE, Jennings WC, Cooper RI, et al. The pivotal multicenter trial of ultrasound-guided percutaneous arteriovenous fistula creation for hemodialysis access, pages 149–158, Copyright © 2018, with permission from Elsevier.[24]

Facilitating AV anastomosis creation and maturation in AVFs. A recent study showed that pre-existing arterial intima hyperplasia did not play a role in subsequent AVF blood flow, diameter, or stenosis.[26] However, AV anastomosis is subjected to oscillatory and transverse wall shear stresses that lead to maladaptive neointimal hyperplasia. Preformed or sutureless devices can be designed to provide smooth flow through computational flow techniques to facilitate the patency of these locations. Optiflow (Bioconnect Systems, Ambler, PA) is a sutureless anastomotic device that uses an intraluminal flange connected to a conduit to provide optimum anastomotic configuration. Clinical trials have shown promise, although it can be utilized only with arteries at least 3 mm in diameter.[27,28]

Disruption of neointimal hyperplasia process is another potential target. Perivascular single topical application of Vonapanitase (Proteon Therapeutics, Inc., Waltham, MA; a recombinant human chymotrypsin-like elastase) at the time of surgery can disrupt elastin and also exhaust peptides that may later attract proliferating cells. Initial clinical trial results have shown a trend toward longer median primary patency. Larger clinical trials—PATENCY-1 and PATENCY-2—are designed to evaluate primary and secondary patencies, respectively.[29]

The use of CorMatrix (CorMatrix Cardiovascular Inc., Sunnyvale, CA) is yet another technology that has shown promising results in animal experiments where the carotid artery of mice was connected to the ipsilateral jugular vein to create an AVF. The multilamellar sheet of decellularized, non–cross-linked, lyophilized matrix derived from porcine small intestine submucosa is wrapped around the outflow vein. It provides a scaffolding that has shown decreased neointimal hyperplasia and improved luminal diameter.[30]

Far infrared therapy is another commonly used technique that has been studied primarily in the Taiwanese population for AVF maturation. Far infrared waves are invisible electromagnetic waves that can improve cutaneous blood flow and potentially improve endothelial function. Many plausible mechanisms of action include thermal effects, activation of the L arginine nitric oxide pathway, suppression of inflammation, and a decrease in oxidative injury and neointimal hyperplasia. The far infrared wave is applied to the site of AV anastomosis of an AV fistula using a far infrared wave emitter with wavelengths between 5 and 25 μm from a height of 20 cm above the AVF. Patients receive this therapy for 40 minutes during HD for a period ranging from few weeks up to 12 months.[31] This technique has shown promising results, including decreased thrombosis and better luminal diameter, flow, and primary patency of AVF.[32] Application of this therapy needs to be studied in large and diverse populations.

Innovations in AVGs

The incidence and prevalence of AVG is in flux around the world. The Dialysis Outcomes and Practice Patterns Study (DOPPS) demonstrated significant variability in the use of AVG—between 2% and 18%—among different countries in DOPPS 1 (1996–2001) to DOPPS 5 (2012– 2015). AVGs constituted 12% to 13% of all created AV accesses in DOPPS phases 4 to 5 in Europe, Australia, New Zealand, and Japan versus 25% in the United States.[33] In 2017 the Australian and New Zealand Dialysis and Transplant Registry Report showed about 5% prevalence of AVGs in Australia and New Zealand, whereas a review of the European Renal Association–European Dialysis and Transplant Association Registry showed a decreasing trend in utilization of AVFs, an increasing trend in the use of CVCs, and only a minority of patients using AVGs. In some countries like Denmark and the French-speaking part of Belgium, AVGs were not used at all.[34] The advent of a major national initiative in the early 21st century in the United States to increase the prevalence of AVFs resulted in a significant decline in the number of AVGs.

Although the "fistula first" strategy remains a valid dictum in principal for most patients undergoing HD for the reasons mentioned earlier, it may not be universally applicable either because of nonsuitable veins or the maturation issues in AVFs leading to long CVC exposure. Paradigm innovation has resulted in modification of "fistula first" into "fistula first, catheter last" in which AVGs find a reentry as an important tool in a select group of patients undergoing HD, which includes elderly persons and patients with certain comorbidities that render AVF creation or maturation unlikely to be successful. Evidence suggests that AVG outcomes are similar to AVF outcomes in selected circumstances and AVGs can be used in carefully chosen populations (especially elderly persons) to mitigate the ever-present dangers of CVCs.[35,36] Further, in a prospective observational study of 79,545 patients undergoing dialysis, investigators found that changing from a catheter to a fistula or a graft was associated with significantly improved survival and concluded that the risks of AVGs approached those of AVFs, providing an alternative to prolonged catheter exposure.[37]

It must be remembered that the traditional AVG material, mostly expanded polytetrafluoroethylene (ePTFE), and the technology used in the aforementioned studies may have had many disadvantages, leading to frequent thrombosis and the need for interventions. Recent innovations have resulted in the advent of new generations of AVGs, such as early cannulation AVGs (eAVGs), hybrid AVGs, and heparin and drug-eluting AVGs, although their superiority over the traditional AVG is not established.

eAVGs. eAVGs have a tri-layer design that incorporates an elastomeric "self-sealing" membrane that allows cannulation soon after implantation of the AVG. Different commercially available eAVGs for HD access have demonstrated an improved performance to obviate the need for CVCs for dialysis. A review of 15 studies utilizing eAVGs for HD showed that early cannulation of Flixene (Getinge US Sales, LLC, Wayne, NJ), AVflo (Nicast Ltd., Global Park Lod, Israel), Rapidax (Vascutek, Glasgow, UK), and Acuseal (W. L. Gore & Associates, Inc., Flagstaff, AZ) grafts within 72 hours was possible and had no significant difference in patency or complication rates compared with ePTFE grafts.[38] Further, a

study of 121 patients requiring urgent HD who were randomly assigned to either eAVG or tunneled CVC concluded that the use of eAVG decreased the rate of bacteremia and mortality compared with tunneled CVC and was cost neutral.[39] The eAVGs are currently underutilized, and increasing awareness of this strategy has the potential to reduce CVC use in appropriate cases of patients who need urgent-start HD.

AVG surface modification. AVG surface modification is an emerging technology to reduce the complications of thrombosis and infection. Heparin coating, intuitively, should be thrombus retardant. Propaten (W. L. Gore & Associates, Inc.) is the only drug-eluting heparin-bonded AVG available in the United States. A prospective randomized trial of 160 patients compared a heparin-bonded graft with a standard ePTFE graft.[40] A lower incidence of early thrombosis during the first 5 months and a trend toward prolonged patency were found, but the results were not replicated in further randomized trials.

Electrospinning of biologic material onto a mandrel can facilitate endothelial cell attachment to graft layers, resulting in a more biocompatible conduit.[41] Outer wall modification with electrospinning, nanotopography, lithography, or plasma treatment can alter the graft for early use and biocompatibility.[42] Three-dimensional blood vessel printing is already being used in aortic grafts and remains a possible future strategy for vascular access.[43]

Hybrid AVG stent. The Gore Hybrid Vascular Graft System (W. L. Gore & Associates, Inc.) consists of a heparin-coated ePTFE graft with a nitinol-reinforced stent-graft at its venous end. In a retrospective study, 25 patients undergoing dialysis who were not candidates for AVFs or standard graft placement and had exhausted peripheral veins received the Gore Hybrid grafts, and outcomes were compared with those of contemporaneous 35 patients who had standard ePTFE grafts.[44] Successful placement was achieved in all patients. Compared with the standard ePTFE grafts, at 24 months, the primary and secondary patency outcomes were similar, although it was not possible to establish noninferiority of this device. Significantly, this device allows easier AVG placement in persons with minimal availability of the axillary vein. Recently, this product has been discontinued.

Anti-neointimal hyperplasia therapy in AVGs. Ongoing research is being conducted to examine interventions to curb neointimal hyperplasia, a major factor causing graft dysfunction and failure. Drugs including sirolimus and paclitaxel suppress neointimal hyperplasia and are being utilized in clinical trials. A study of 12 patients undergoing HD who underwent placement of 13 ePTFE grafts with perivenous anastomosis Coll-R (Vascular Therapies, LLC, Cresskill, NJ), a biodegradable sirolimus-eluting perivascular wrap that is placed intraoperatively around graft vein anastomosis of AVGs, showed encouraging results.[45] No technical failures, infections, or impaired vascular anastomotic or wound healing problems were reported. Sirolimus levels were subtherapeutic. The unassisted patency of these grafts with Coll-R was 76% at 1 year and 38% at 24 months, and the thrombosis rate was 0.37 per patient-year. In a preclinical study in pigs of grafts with the luminal surface coated with paclitaxel, inhibition of neointimal hyperplasia was shown when compared with the control group, and no signs of infection or bacterial contamination were seen.[46] No further data are available about these technologies.

A number of similar therapies have either been tried or are in progress. Vascugel wrap (Pervasis Therapeutics, Cambridge, MA) utilizes allogeneic endothelial cell implants embedded in gel foam that is applied at the graft vein or AV anastomosis and showed feasibility and encouraging results in the initial clinical study without local adverse events.[47] An increase in panel reactive antibodies did occur in a small percentage of patients.

Anastomotic devices for AVGs. Graft anastomosis to artery or vein is especially prone to neointimal hyperplasia and consequent stenosis. Computational studies of hemodynamic changes in blood flow after AV anastomosis have the potential to create an optimal shear stress conducive to proper maturation with avoidance of abnormal remodeling. These studies also may provide insight into better AVG, anastomosis, and cannulation needle configuration.

Use of sutureless devices to facilitate patency of these locations has resulted in development of the InterGraft Anastomotic Connector System (Phraxis, Inc., St. Paul, MN). It is minimally invasive, sutureless, and has venous and arterial connectors, which are intravascularly deployed and decrease the incidence of AVG stenotic lesions. In the first pilot study in humans, 9 AVGs were placed with a 100% success rate. Three subjects left the study for unrelated reasons, and the remaining 6 subjects had patent grafts, which were cannulated within 17 days, with blood flow >1 L/min and no dilatations or aneurysm formation. Further clinical evaluation is ongoing.[48]

Hybrid AVG devices for central venous stenosis or occlusion. A variety of surgical techniques have been used to bypass central vein stenosis by using vein mobilization, long AVG, or nontraditional CVC sites. These procedures for end-stage vascular access are lifesaving, although the results of these interventions are generally sobering.

The Hemodialysis Reliable Outflow device (HeRO, Merit Medical Systems, South Jordan, UT) combines an AVG with a tunneled CVC to negotiate central vein stenosis or occlusion without external exposure. It is also an alternative to thigh grafts in patients with severe upper extremity central vein stenosis or occlusion. In a retrospective study, 60 HeRO device placements in 59 patients undergoing dialysis with a mean of 6.3 previous tunneled CVC insertions and 3.1 previous AVG/AVF placements were compared with 22 lower extremity AVGs in 21 patients who had a mean of 4.1 previous tunneled CVCs and 2.6 previous AVG/AVF placements.[49] It was concluded that in patients with complicated vascular access, patients with HeRO and lower extremity AVGs have similar secondary patency, infection, and all-cause mortality but that the HeRO group required more interventions to maintain access patency. In selected cases, HeRO can provide a life-saving vascular access.

Analysis of data from published studies and unit cost from the National Health System (United Kingdom; 2014–2015

reference costs), comparing HeRO devices patients with AVG to those with a tunneled CVC found in the base case that a 100-patient cohort with HeRO devices underwent 6 fewer failed devices, 53 fewer access-related infections, and 67 fewer thrombosis compared with patients with a tunneled CVC.[50] It was concluded that compared with patients with a tunneled CVC, patients with a HeRO device have a marginal net positive cost because of lesser complications in this challenging vascular access subgroup. Another retrospective study of 41 patients with 15,579 HeRO days found secondary patency of 81.6% at 6 months and 53.7% at 12 months but a higher rate of interventions—2.84 per 1 year—with the HeRO device.[51] It was concluded that the use of HeRO devices should be judicious, with outcome expectations reduced.

It is important to remember that the current treatment of central vein stenosis remains suboptimal and prevention is key by avoiding CVCs and devices. To this end, development of leadless electrophysiologic devices is likely to greatly benefit the end-stage renal disease population that needs such devices.[52]

Bioengineered vessels as AVGs. Advances in research have resulted in the creation of tissue bioengineered vessels to replace prosthetic grafts during the past several decades. These techniques involve chemical treatment of allogeneic blood vessels to decrease immunogenicity, such as Artegraft collagen vascular grafts (Artegraft, North Brunswick Township, NJ) and CryoVein cadaver saphenous vein allografts (CryoLife, Kennesaw, GA) or the growing of human vascular cells on biodegradable scaffolds, which are later decellularized, such as Humacyl, the acellular vessel by Humacyte (Humacyte, Durham, NC). Biohybrid technology takes advantage of the combining of human endothelial cells and progenitor cells with synthetic material to grow vessels around a template.

Artegraft (Artegraft, North Brunswick, NJ), a bovine carotid artery processed to improve its flexibility and patency, was the first vascular HD conduit approved by the US Food and Drug Administration. In a study, 17 Artegrafts were placed in 17 patients undergoing HD who had a challenging vascular access history, including recurrent ePTFE and CVC infections and compromised hand vasculature. Results showed an 18-month primary patency of 73.3%, a primary assisted patency of 67%, and a secondary patency of 89%.[53] The 1-year patency of these grafts was superior to reported ePTFE graft patency. In another single-institution retrospective study of 120 consecutive bovine carotid artery graft placements in 98 patients, bovine carotid artery grafts had a superior 1-year secondary patency of 67% versus 48% for ePTFE grafts and a 2-year patency of 67% versus 38%.[54]

Other bioengineered options include the ProCol vascular bioprosthesis (LeMaitre Vascular, Inc., Burlington, MA), which is derived from bovine mesenteric vein and treated with glutaraldehyde. It is approved for vascular access after a previously failed attempt of prosthetic access.[55] The CryoVein (CryoLife, Kennesaw, GA) cadaver saphenous vein allograft, a cryopreserved femoral vein, was studied when 48 femoral vein grafts were placed in 44 patients with infection or multiple previous graft failures.[56] It showed 1-year primary patency of 49% and secondary patency of 75%. Similarly, a single-center cohort study of 20 patients who received cryopreserved arterial allografts because of failed or failing vascular access and 53 patients who received prosthetic grafts demonstrated the ability to access the allograft soon after placement without the maturation or healing process and similar primary and assisted primary patency compared with prosthetic grafts.[57] Omniflow II (LeMaitre Vascular, Inc., Burlington, MA) is a biosynthetic vessel with a unique composite structure of cross-linked bovine biocompatible collagen and reinforcing polyester mesh. It is approved for human use in several countries, including the United States. Omniflow II grafts were implanted in 38 patients undergoing dialysis who were not candidates for other forms of AVGs.[58] The primary patency was 92% at 6 months, 80% at 12 months, and 60% at 24 months. The cumulative 38-month patency was 70%, and no infections related to the vascular access were detected.

The recent excitement in the field of bioengineered vessels stems from two phase 2 single-arm trials utilizing bioengineered human acellular vessels for the creation of HD vascular access in 60 patients with a mean follow-up of 16 months at 6 centers in the United States and Poland.[59] The study showed that these vessels are safe and have a good potential to provide long-term vascular access. These acellular vessels had no dilatation, rare postcannulation bleeding, and a 1-year primary patency of 28%, a primary assisted patency of 38%, and a secondary patency of 89%.

Because of these encouraging results, a phase 3 clinical trial of Humacyl was begun in May 2016 to compare the safety and efficacy of these vessels with ePTFE in patients undergoing HD who are not candidates for AVF placement. In September 2017, the study had recruited 350 patients at 40 centers in the United States, Europe, and Israel. It was expected that data regarding the implants would be available by the end of 2018.

Many of the aforementioned innovative treatment approaches, including antineointimal therapies and bioengineered vessels, have yet to demonstrate convincing evidence of clinical benefits compared with the available conventional therapies.

Innovations in CVCs

CVC use continues to remain universally prevalent, with predominant use in incident HD patients.[60,61] The ease of placement and ability to use them immediately give CVCs a definite advantage over AVFs and AVGs, even though CVC use is associated with higher morbidity and mortality.[62] CVC use is often complicated by dysfunction, infection, and central vein stenosis.[63,64] These complications vary depending on the type and duration of the CVC being used. Despite the current recommendation from various professional societies to using CVC as a "bridge access" to a definitive AVF or AVG, there seems to be a growing consensus that CVC as a primary access may be acceptable in a select subgroup of patients. Furthermore, from a patient perspective, use of a CVC avoids painful needle sticks, provides relatively less time in the dialysis chair on a daily basis, and offers better quality of life compared with AVFs and AVGs.

Table 1 | Innovations in dialysis catheters

Catheter characteristic	Innovation
Catheter tip design	Step tip, split tip, symmetric tip, self-centering
Coating	Heparin, silver
Catheter material	Carbothane, polyurethane
Lock solution	Anticoagulation versus antibiotic versus antiseptic

A broad categorization of dialysis CVCs generally refers to differentiating between nontunneled and tunneled catheter design. A nontunneled CVC is chosen for emergent and short-term use, whereas a tunneled CVC is used for relatively long-term maintenance HD therapy. CVC design has improved over the years to provide maximal blood flow, reduce recirculation, and minimize endothelial injury. The innovations have mainly resulted in different lumen and tip designs and modifications in the side holes, catheter material, surface coatings, and lock solutions to improve catheter function, biocompatibility, and infectious complications (Table 1).

Catheter design. The commonly used dialysis CVC has 2 lumens. The nontunneled CVC has a conical tip to facilitate placement, and very little design innovation has occurred in recent years. In contrast, in the tunneled CVC, significant changes have been made both to the luminal shape and tip design. The inner luminal shape has evolved from twin cylinders to a double-D design with varying internal diameters to guarantee better flows during HD. The tip design has evolved from a step tip to a split tip to a symmetric tip, with side holes varying from small multiple round holes to rhomboid-shaped slots to minimize recirculation and prevent thrombosis-related dysfunction.[65,66] More recently a self-centering superior vena cava catheter has been introduced in clinical practice.[66]

Despite these innovations, *in vitro* testing data and clinical data on catheter functionality remain inconclusive. A single-center randomized clinical trial compared symmetric tip versus split-tip dialysis catheters in 302 patients. No difference was found in mean primary assisted patency between the symmetrical tip catheter and the split-tip catheter.[67] Other commonly encountered complications such as thrombolytic use were lower with the symmetric tip, whereas catheter-related bloodstream infection was no different between the 2 tip designs. Similar results were reported from a large multicenter randomized prospective study comparing symmetric tip and split tip design in 601 patients.[68]

A common dogma with symmetric tip catheters is that the recirculation rate is lower despite reversing the ports. The recirculation rate with usual and reversed connections was studied in a subset of 206 patients at blood flow rates of 350 ml/min, 400 ml/min, and 450 ml/min at 1, 5, and 11 weeks after CVC placement and was found to be statistically insignificant (3.2% vs. 3.8%) at all 3 blood flow rates.[68] However, when recirculation rate was measured with 425 ml/min blood flow and reversed connection was collected using an *in vitro* testing model, the result was 0% for the symmetric tip catheter compared with 22.3% to 39.2% for the split-tip catheter and 8.7% to 16.3% for the step-tip catheter.[69]

More recently, a single-center retrospective study reported improved catheter patency at 1, 3, and 6 months with a self-centering catheter compared with a split-tip catheter.[70] Another multicenter observational study using a self-centering catheter in 75 patients reported 87% patency at 26 months while achieving blood flow of >300 ml/min.[71]

Catheter coating. Catheters can be surface coated externally and internally to minimize the formation of biofilm and reduce the risk of activating the coagulation cascade, fibrin sheath formation, and infection. Surface-coated CVCs have been studied extensively in intensive care settings with marginal benefit when used over a 2-week period.[72] Surface coating of tunneled dialysis CVCs with heparin, silver, or an antimicrobial agent has not been proven to be beneficial thus far. A single randomized trial reported 2 decades ago using a silver-coated tunneled dialysis catheter failed to report any benefit against clinical infection with a mean patency of 92 days.[73] No further innovations or studies have been published since then.

Catheter material. The materials used for dialysis catheters have evolved. Early catheters were made of silicone, but the more recent CVCs are made of polyurethane and polycarbonate copolymers such as carbothane. The copolymer catheters have several properties that are advantageous to manufacturing a tunneled dialysis CVC. These catheters are strong, soft, flexible, and have thin walls, thus increasing the inner luminal diameter, but they still maintain rigidity in the longitudinal axis, which helps prevent luminal collapse at high negative pressures.[65]

Catheter lock solutions. Catheter lock solutions can function as antibacterial, antiseptic, and anticoagulant solutions. Conventionally, heparin- or citrate-based solutions are used to lock the lumen after each dialysis session. A recent meta-analysis of 30 studies by the Cochrane group evaluated the role of antimicrobial lock solution in preventing catheter-related bloodstream infection in both tunneled and non-tunneled dialysis catheters.[74] The authors concluded that antibacterial lock solution decreased the incidence of catheter-related bloodstream infection compared with standard lock solution, although with a low to very low certainty of evidence. On the other hand, various types of antibiotic lock solutions are used to treat catheter-related bloodstream infection, primarily to salvage the catheter and preserve the venous access site. The response to this treatment strategy depends on the type of bacteria and whether the initial clinical presentation is complicated or uncomplicated. Broadly, gram-negative microorganisms respond better to a combination of systemic antibiotics and antibiotic lock solution compared with gram-positive organisms.[75] Our knowledge has not increased since the last guidelines for treatment of catheter-related bloodstream infection were published by the Infectious Diseases Society of America in 2009.[76] More recently, 75 patients undergoing HD were studied in a double-blind randomized trial comparing either 30% citrate, heparin, or minocycline ethylenediamine tetraacetic acid. The incidence of hydraulic resistance as a measure of poor blood flow was lower with the

citrate and minocycline-ethylenediamine tetraacetic acid groups compared with the heparin group.[77] A perfect catheter lock remains elusive in the prevention and treatment of catheter dysfunction and infection.

Innovations in processes of care

Dialysis access care has evolved in recent years from being fragmented to being a multidisciplinary complex process.[78] The implementation of the Fistula First Breakthrough Initiative by the Centers for Medicare and Medicaid Services in the United States in the early 2000s helped practitioners understand and overcome some of the barriers in improving the AVF rate in the prevalent dialysis population. Subsequent adoption of the policy by major professional societies as a recommendation has highlighted some of the fallacies in this dictum.[79,80] However, a clear positive outcome from this change in practice in the early 2000s has helped practitioners recognize the need for a multidisciplinary approach toward providing ideal vascular access care.[81]

The quality of care provided between high-income countries and resource-limited countries can be variable. However, the focus of care should remain patient centered. In high-income countries, traditionally a "fee for service" model has been the norm, leading to unnecessary interventions and procedures without an emphasis on quality. A shift toward quality-based care is needed with accountability for performance and outcomes. These innovations in processes of care currently are being piloted by the Centers for Medicare and Medicaid Services and, it is hoped, will help improve quality of care with simultaneous reduction in health care costs.[82] In resource-limited countries, the focus needs to be on education, identifying workforce expertise, and utilizing resources efficiently and effectively.[83] The notion of merely imitating the practices of high-income countries is certainly not wise. Because available resources may vary in different regions across the globe, creating a process that provides appropriate care using the right tools and expertise and at the lowest possible cost remains a challenge moving forward.

Summary

Numerous innovations have occurred in the field of HD vascular access, but the solutions developed are largely piecemeal, and no comprehensive or universal approach to develop a perfect access has been attained thus far. With newer knowledge and technology, the field is still ripe for groundbreaking innovations. A novel strategic approach will need to take into account all potential etiologic factors and availability of local resources, along with consideration of patient-related outcomes. These considerations will form the basis for future innovations to improve the life of patients undergoing HD. Notwithstanding the focus on the amalgam of clinical factors operative in vascular access issues, coordination of care with an organized and well-defined process of care will perhaps reveal the road map to navigate this difficult territory.

DISCLOSURE

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