Expanded Treatment Options With ePTFE Vascular Grafts Having CBAS Heparin Surface for Hemodialysis

Selection of best patient-centered dialysis access, using new and old technology, yields excellent outcomes: follow-up of 254 grafts.

BY INGEMAR DAVIDSON, MD, PHD; JOHN R. ROSS, MD; MICHAEL GALLICHIO, MD; AND DOUGLAS SLAKEY, MD, MPH

Disagreements surround the management of dialysis access patients, including proper selection of the dialysis modality (ie, hemodialysis [HD] vs peritoneal dialysis [PD]), type and surgical site selection, timing of access placement, and who places the access. The lack of and the difficulty of performing randomized studies with multiple confounding factors in a heterogeneous and rapidly changing end-stage renal disease (ESRD) population partly explains the dialysis access conundrum. The rapidly developing and competing technologies, socioeconomic forces, wide spectrum of the professional experience, and bias add to the multivariate and complex nature of dialysis access.[1]

INCONSISTENT OUTCOMES

In general, published dialysis access data are plagued by great variability. Reported outcome data are often influenced by study selection design bias and device variability. The large variability in outcomes is exemplified in Figure 1, in which dialysis graft function at 12 months after surgery varies from 10% to 78%.[2-15] This variability likely has many contributing components, such as the poorly defined but powerful "center effect," in which local system factors like dialysis access team training, technical skills, professional dedication, and bias and institutional support profoundly affect outcomes. Two recent blinded randomized studies by the Dialysis Access Consortium underscore the generally poor outcomes reported for both the grafts and native veins used for dialysis access.[14,15] One serious confounding bias in these studies is that PD is not considered or included in the selection process.

Graft thrombosis is the most common dialysis graft dysfunction. In 90% of thrombosed grafts, the underlying pathology leading to thrombosis is neointimal hyperplasia at the venous anastomosis associated with turbulent flow.[16] This phenomenon is largely prevented by an end-graft to end-vein anastomosis configuration. The end-graft to end-vein anastomosis can be accomplished by a new

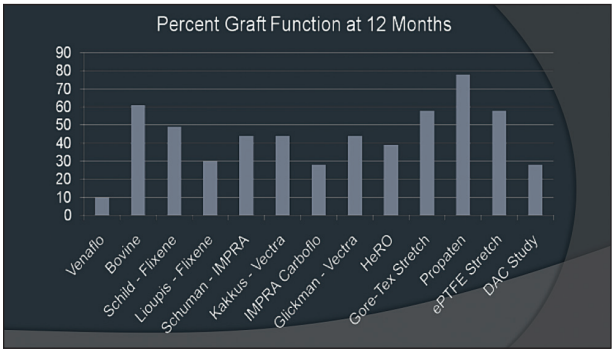

Figure 1. Published graft function outcome data at 1 year varies between 10% and 78%.

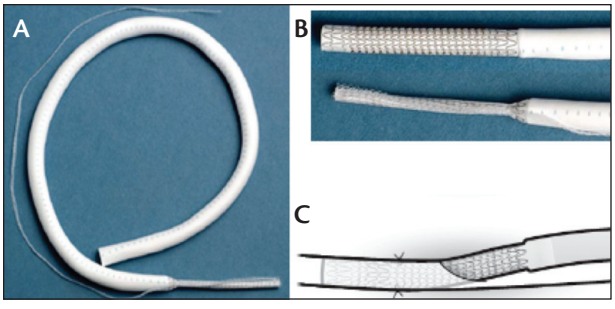

Figure 2. The GORE Hybrid Vascular Graft, with end-point attached heparin, has a 5 or 10 cm length nitinol-reinforced segment that is placed into a vein by pulling a deployment line (A). The nitinol segment (available in 6, 7, 8, and 9 mm diameters) is shown before and after deployment (B). End-graft to end-vein endoluminal anastomosis (C).

graft design in which the nitinol end is deployed into the vein (Figure 2).

Other etiologies occurring alone or in combination with intimal hyperplasia may contribute to graft thrombosis. These include poor arterial inflow caused by an arterial stenosis (atherosclerosis calcification plaques) commonly seen in patients with chronic kidney disease who also have diabetes, hypertension, and a history of cigarette smoking.[17]

Poor access inflow may also be seen in patients with impaired cardiac function, such as myocardial infarction, congestive heart failure, low blood pressure during and between the dialysis sessions, decreased blood volume, and dehydration, all of which may precipitate access thrombosis.[18,19]

Central venous and/or superior vena cava stenosis, uniformly caused by central venous catheters (CVCs), may not be associated with graft thrombosis but rather arm swelling. Cannulation difficulties then become a contributing factor to thrombosis from perigraft hematoma compression. A previous history of CVC placement is the most important risk factor for the development of central venous stenosis. Multiple CVCs and long dwell times increase the probability of stenosis.[20]

When no anatomical explanations are found, hypercoagulable states are investigated for increased platelet activity common in renal patients, as well as elevated serum fibrinogen, von Willebrand factor, factor VIII, C-reactive protein, and the presence of anticardiolipin antibodies and/or lupus antibodies.[21,22] In some cases, the patient may have one or more elevated clotting factors.[22]

CBAS HEPARIN SURFACE TECHNOLOGY

The proprietary CBAS Heparin Surface was developed by Carmeda AB, a company in Sweden that is a wholly owned subsidiary of W. L. Gore & Associates, Inc. Heparin, a polysaccharide anticoagulant, is bonded directly to the luminal surface of expanded polytetrafluoroethylene (ePTFE) grafts. The proprietary end-point attachment mechanism (CBAS Heparin Surface) serves to anchor heparin molecules to the luminal surface, allowing for prolonged retention of heparin's intrinsic bioactive properties. Antithrombin (AT), a coagulation inhibitor that circulates in the blood, serves as the mechanism of action and binds to the active site of the heparin molecule. Thrombin, a coagulation protein, binds to the AT and loses its ability to convert soluble fibrinogen into insoluble strands of fibrin. The CBAS heparin catalyzes (up to 1,000 fold) the inactivation of thrombin by antithrombin.[23] It is not consumed nor destroyed in this reaction. Controlled animal studies and isolated clinical explants demonstrate prolonged persistent heparin bioactivity.[24,25]

HEPARIN BONDED (CBAS HEPARIN SURFACE TECHNOLOGY) GRAFTS AND STENT-GRAFTS ON THE US MARKET

- GORE PROPATEN Vascular Graft 4 to 7 mm tapered configuration for dialysis and 6 mm straight for peripheral vascular surgery.
- Nitinol end-graft to end-vein (GORE Hybrid Vascular Graft).
- Stent-graft for peripheral and venous anastomosis revision stenting (GORE VIABAHN Endoprosthesis with Heparin BioActive Surface).
- GORE ACUSEAL Vascular Graft for early cannulation.

In vitro experiments have demonstrated the antithrombotic properties of CBAS Heparin Surface technology. For example, there is a > 80% platelet adhesion inhibition compared to the control.[25,26] Heparin has a potent antiproliferative effect on vascular smooth muscle cells. Animal studies have repeatedly confirmed that the CBAS Heparin Surface of the GORE PROPATEN Vascular Graft prevents neointimal hyperplasia in the ePTFE graft portion but not in the native vein distal to the graft-vein anastomosis.

There is a general consensus that the grafts having end-point attached heparin stay patent despite low flow secondary to stenosis and other pathology, partly explaining the higher intervention-free survival rate. This fact allows more time for interventions to take place, such as balloon angioplasty and stenting.

The available vascular grafts and stent-grafts having end-point attached heparin are depicted in the *Heparin Bonded (CBAS Heparin Surface Technology) Grafts and Stent-Grafts* sidebar. The 4 to 7 mm tapered GORE PROPATEN Vascular Graft is designed for hemodialysis access and has characteristics similar to the stretch graft. Clinical trials have demonstrated the enhanced patency of the GORE PROPATEN Vascular Grafts in peripheral surgery over the standard ePTFE. The unique, stable, proven CBAS Heparin Surface technology maintains the anticoagulant activity of heparin.[26]

THREE DATA SETS FROM ONE INSTITUTION

A prospective, nonrandomized, single-center study compared the 4 to 7 mm heparin bonded ePTFE vascular grafts (N = 73) (GORE PROPATEN Vascular Graft) to 4 to 7 mm standard ePTFE grafts (N = 67) between January 1, 2007, through October 1, 2009. Hospitals initially restricted graft use due to cost, and the GORE PROPATEN Vascular Grafts were selected only for difficult "high-risk" patients, most commonly with several past failed access procedures. At 12 months, 65% of the

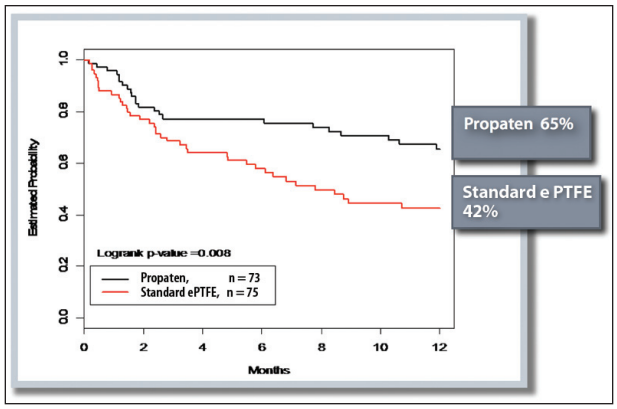

Figure 3. Heparin bonded ePTFE grafts (Propaten) had a 23% clot-free (intervention-free) survival benefit over the standard ePTFE grafts.

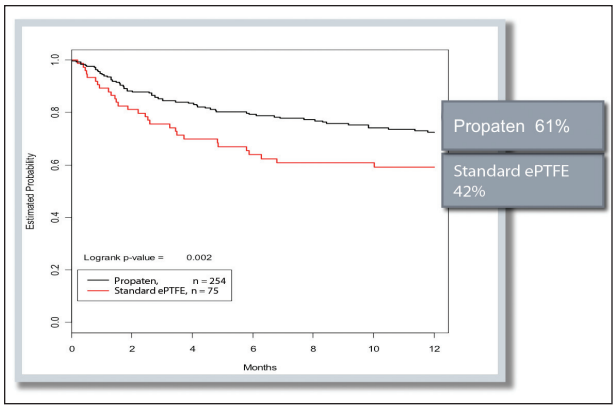

Figure 4. Clot-free (intervention-free) survival at 12 months for 254 heparin bonded ePTFE grafts (Propaten) had a 19% benefit (*P* = .002) over the standard stretch ePTFE graft.

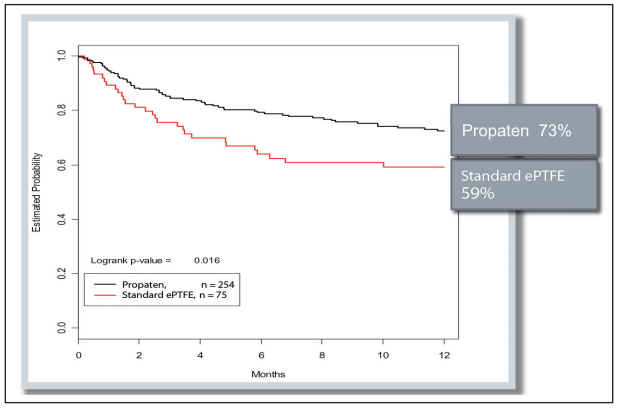

Figure 5. Graft survival at 12 months for 254 heparin bonded ePTFE grafts (Propaten) had a 14% benefit (*P* = .016) versus 75 control patients receiving a standard ePTFE graft.

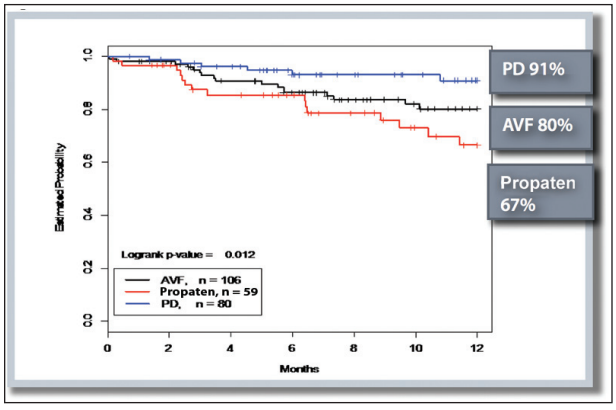

Figure 6. The clot-free (intervention-free) survival rates for peritoneal dialysis, AVF, and heparin bonded ePTFE grafts (Propaten) were 91%, 80%, and 67%, respectively.

GORE PROPATEN Vascular Grafts (Propaten) remained clot-free compared to 42% of the standard ePTFE grafts, a 23% benefit (*P* = .008) (Figure 3).[2]

Since mid 2008, the GORE PROPATEN Vascular Graft was made freely available, explaining the recent larger GORE PROPATEN Vascular Graft cohort. With the larger GORE PROPATEN Vascular Graft cohort of 254 implants, intervention-free and graft survival continued to show a 19% (*P* = .002) and 14% (*P* = .016) benefit over the historic control, respectively (Figures 4 and 5).

These outcome data are further supported by a recent dialysis access experience for the calendar year of 2012, including 393 access procedures. PD and HD accounted for 81 (33%) and 166 (67%) of new dialysis access cases, respectively. Revisions accounted for 38% of the procedures. Of the HD cases, 106 (65%) were native vein arteriovenous fistulas (AVFs), and 59 (35%) were GORE PROPATEN Vascular Grafts in a loop configuration.

One year patient survival was similar for PD and native vein AVFs (98%) and PTFE grafts (92%; [NS]). Patients receiving grafts were, on average, 6 years older (or 58 years of age) compared to 52 years of age for the PD and AVF patients. The freedom from intervention survival rates for PD, native vein AVFs, and GORE PROPATEN Vascular Grafts were 91%, 80%, and 67%, respectively (Figure 6). Although PD provided the highest access function survival rate of 91%,[27] the relative ease of revisions and thrombectomy of the grafts provided similar or slightly better graft survival (85%) at 1 year compared with native vein AVFs (81%; [NS]) (Figure 7).

SUMMARY

With the selection philosophy of doing the right thing for every patient at all times, dialysis access treatment outcomes are optimized for each patient. Access function at 1 year in excess of 90% was achieved with PD, followed by GORE PROPATEN Vascular Grafts of 85%, and native vein AVFs of 81%. GORE PROPATEN Vascular Grafts had an approximate 20% improvement in clot-free (intervention-free) survival over standard ePTFE grafts at 1 year. ■

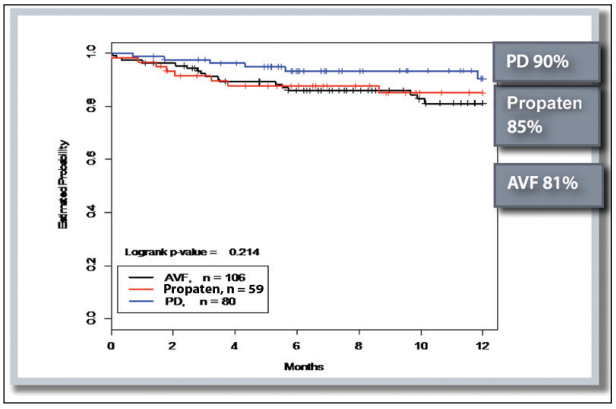

Figure 7. One year dialysis access function was highest for PD at 90%. Because of the relative ease to re-establish function of thrombosed grafts compared to native vein AVFs, the heparin bonded ePTFE grafts (Propaten) had similar or slightly better graft function at 1 year compared to AVFs of 85% and 81%, respectively.

Ingemar Davidson, MD, PhD, is with Tulane University in New Orleans, Louisiana. He has disclosed that he has given presentations on this subject at events sponsored by W. L. Gore & Associates, Inc. Dr. Davidson may be reached at drd@ingemardavidson.com.

John R. Ross, MD, is Medical Director of the Dialysis Access Institute in Orangeburg, South Carolina. He has disclosed that he receives research funding from W. L. Gore & Associates, Inc. Dr. Ross may be reached at jrrsurgery@aol.com.

Michael Gallichio, MD, practices at the Orangeburg Regional Medical Center in Orangeburg, South Carolina. He has disclosed that he has no financial interests related to this article.

Douglas Slakey, MD, MPH, is with Tulane University in New Orleans, Louisiana. He has disclosed that he has no financial interests related to this article.

1. Davidson I, Gallieni M, Saxena R, Dolmatch B. A patient centered decision making dialysis access algorithm. *J Vasc Access*. 2007;8:59-68.
2. Davidson I, Hackerman C, Kapadia A, Minhajuddib A. Heparin bonded hemodialysis e-PTFE grafts result in 20% clot free survival benefit. *J Vasc Access*. 2009;10:153-156.
3. Kennealey PT, Elias N, Hertl M, et al. A prospective, randomized comparison of bovine carotid artery and expanded polytetrafluoroethylene for permanent hemodialysis vascular access. *J Vasc Surg*. 2011;53:1640-1648.
4. Schild AF, Baltodano NM, Alfieri K, et al. New graft for low friction tunneling in vascular access surgery. *J Vasc Access*. 2004;5:19-24.
5. Schild AF, Schuman ES, Noicely K, et al. Early cannulation prosthetic graft (Flixene) for arteriovenous access. *J Vasc Access*. 2011;12:248-252.
6. Lioupis C, Mistry H, Rix T, et al. Comparison among transposed brachiobasilic, brachiobrachial arteriovenous fistulas and Flixene vascular graft. *J Vasc Access*. 2011;12:36-44.
7. Schuman ES, Standage BA, Ragsdale JW, Gross GF. Reinforced versus nonreinforced polytetrafluoroethylene grafts for hemodialysis access. *Am J Surg*. 1997;173:407-410.
8. Kakkos SK, Topalidis D, Haddad R, et al. Long-term complication and patency rates of Vectra and IMPRA Carboflo Vascular Access Grafts with aggressive monitoring, surveillance and endovascular management. *Vascular*. 2011;19:21-28.
9. Glickman MH, Stokes GK, Ross JR, et al. Multicenter evaluation of a polyurethaneurea vascular access graft as compared with an expanded polytetrafluoroethylene vascular access graft in hemodialysis applications. *J Vasc Surg*. 2001;34:465-473.
10. Cinat ME, Hopkins J, Wilson SE. A prospective evaluation of PTFE graft patency and surveillance techniques in hemodialysis access. *Ann Vasc Surg*. 1999;13:191-198.
11. Ko PJ, Hsieh HC, Chu JJ, et al. Patency rates and complications of Exxcel yarn-wrapped polytetrafluoroethylene grafts versus Gore-Tex stretch polytetrafluoroethylene grafts: a prospective study. *Surg Today*. 2004;34:409-412.
12. Glickman MH. HeRO Vascular Access Device. *Semin Vasc Surg*. 2011;24:108-112.
13. Katzman HE, McLafferty RB, Ross JR, et al. Initial experience and outcome of a new hemodialysis access device for catheter-dependent patients. *J Vasc Surg*. 2009;50:600-607.
14. Dember L, Beck GJ, Allon M, et al. Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis: a randomized controlled trial. *JAMA*. 2008;299:2164-2171.
15. Dixon BS, Beck GJ, Vazquez MA, et al. Effect of dipyridamole plus aspirin on hemodialysis graft patency. *N Engl J Med*. 2009;360:2191-2201.
16. Roy-Chaudhury P, Kelly BS, Melhem M, et al. Vascular access in hemodialysis: issues, management, and emerging concepts. *Cardio Clinics*. 2005;23:249-273.
17. Asif A, Ravani P, Roy-Chaudhury P, et al. Vascular mapping techniques: advantages and disadvantages. *J Neph*. 2007;20:299-303.
18. Ritz E, Koch M. Morbidity and mortality due to hypertension in patients with renal failure. *Am J Kidney Dis*. 1993;21(5 supplement 2):113-118.
19. Davenport A. Intradialytic complications during hemodialysis. *Hemodial Int*. 2006;10:162-167.
20. Agarwal AK. Central vein stenosis: current concepts. *Adv Chronic Kidney Dis*. 2009;16:360-370.
21. Ecder T. Do hematologic reasons play a role in early failures? Presented at: the VAS 7th International Congress; May 5–7, 2011; Istanbul, Turkey.
22. O'Shea SI, Lawson JH, Reddan D, et al. Hypercoagulable states and antithrombotic strategies in recurrent vascular access site thrombosis. *J Vasc Surg*. 2003;38:541-548.
23. Björk I, Lindahl U. Mechanism of the anticoagulant action of heparin. *Mol Cell Biochem*. 1982;48:161-182.
24. Lin PH, Chen C, Bush RL, et al. Small-caliber heparin coated ePTFE grafts reduce platelet deposition and neointimal hyperplasia in a baboon model. *J Vasc Surg*. 2004;39:1322-1328.
25. Lin PH, Bush RL, Yao Q, et al. Evaluation of platelet deposition and neointimal hyperplasia of heparin-coated small-caliber ePTFE grafts in a canine femoral artery bypass model. *J Surg Research*. 2004;118:45-52.
26. Begovac PC, Thomson RC, Fisher JL, et al. Improvements in GORE-TEX Vascular Graft performance by Carmeda bioactive surface heparin immobilization. *European J Vasc Endovasc Surg*. 2003;25:432-437.
27. Singh N, Davidson I, Minhajuddin A, et al. Risk factors associated with peritoneal dialysis catheters survival: a nine year single center study in 315 patients. *J Vasc Access*. 2010;11:316.