Use of Stent Grafts in Dysfunctional Hemodialysis Accesses

Stent grafts have demonstrated superior patency rates compared to angioplasty for selected endovascular indications.

BY DHEERAJ RAJAN, MD, FRCPC, FSIR

Hemodialysis accesses, composed primarily of prosthetic grafts and autogenous fistulas, provide a relatively stable conduit for hemodialysis. However, as known to any interventionist and nephrologist, such conduits are prone to dysfunction and eventual failure. The primary causative pathology is intimal hyperplasia leading to venous stenosis, disruption in flow, and eventual thrombosis. Primary intervention-free patency from creation of arteriovenous (AV) prosthetic grafts at 1 year is 40%, with 60% for autogenous AV fistulas.[1]

Multiple studies have demonstrated that simple balloon angioplasty, also called *percutaneous transluminal angioplasty* (PTA), is successful at treating venous stenosis and prolonging the life span of the hemodialysis access. With interventions, cumulative patency rises modestly to 50% for AV grafts and 70% for AV fistulas at 1 year. However, patency is limited, and multiple reinterventions are required to maintain functionality of the access over time. In addition, it is not clear if PTA patency varies for locations of venous stenosis, different characteristics of stenosis (such as length of stenosis, number of previous interventions, and need for ultra-high-pressure balloons), and the types of accesses they are within. In general, although the Kidney Disease Outcomes Quality Initiative indicates that a 50% primary patency at 6 months is expected, this consensus statement was based on retrospective data.[2]

Two randomized prospective studies indicate that primary patency of angioplasty, at least within prosthetic grafts at the venous anastomosis, is actually much poorer. In studies by Vesely and Haskal et al, 6-month

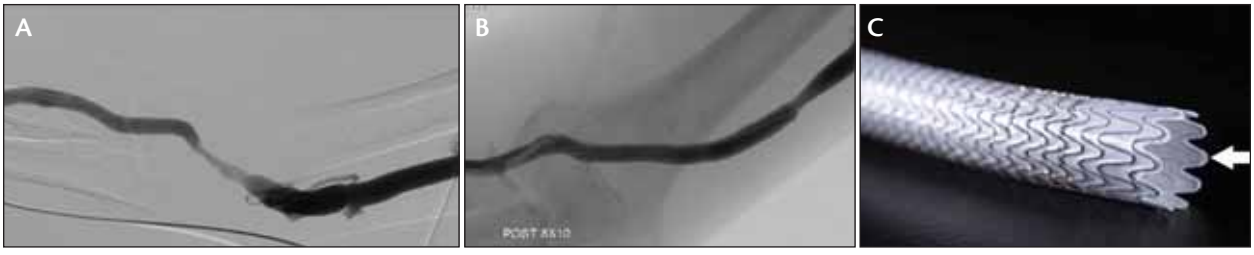

Figure 1. Venous anastomotic stenosis extending across elbow joint. The patient had undergone six PTAs of this stenosis and one declotting within 1 year (A). An 8- X 100-mm Viabahn stent graft (Gore & Associates, Flagstaff, AZ) was deployed, with a satisfactory result with no repeat interventions 6 months after deployment (B). The Viabahn device was used selectively due to the flexibility of the device to accommodate movement at the elbow joint. The Flair device was not used due to its increased rigidity and recommendations not to deploy the device across joint spaces. Note that the polytetrafluoroethylene (PTFE) extends to and covers the fluted ends of the stent graft (arrow) and no radiopaque markers (C).

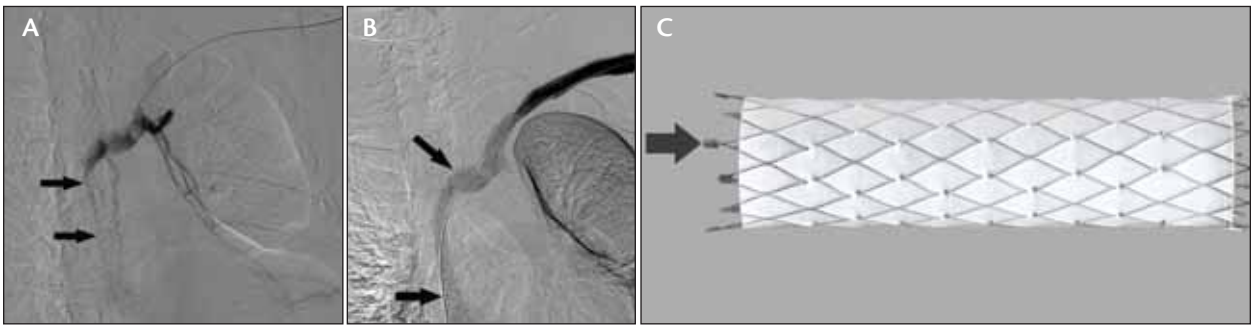

Figure 2. Critical superior vena cava stenosis (arrows) with monthly angioplasties to prevent superior vena cava syndrome. The patient has a left brachiocephalic fistula, and the right innominate and internal jugular veins are occluded (A). A 10- X 80-mm Fluency stent graft (Bard Peripheral Vascular, Inc., Tempe, AZ) was placed, with subsequent decompression of collaterals and resolution of chest, neck, and facial swelling (B). The patient remained asymptomatic since placement 7 months earlier (tantalum markers [arrows]). Tantalum markers to improve visualization are present at both ends of the device (arrow), and the distal 2 mm of the device on either end is uncovered and slightly flared to enhance anchoring (C).

primary patency ranged from 23% to 40%.[3,4] Given relatively poor patency of PTA and the associated attendant costs, multiple devices have been investigated to improve patency and capitalize on the multibillion-dollar market of hemodialysis interventions.

ANGIOPLASTY IS THE GOLD STANDARD

Despite the relatively poor patency of PTA, angioplasty remains the gold standard for treating venous stenoses within dysfunctional hemodialysis access circuits. There are many reasons for angioplasty remaining the standard of care despite no tangible change in practice during the last couple of decades.

Multiple devices have been developed, tested, and subsequently investigated, with results that are either equivalent to PTA or inferior to PTA. In a randomized prospective study, the Peripheral Cutting Balloon (Boston Scientific Corporation, Natick, MA) was found to be as equally effective as PTA.[5] In a small retrospective study, the PolarCath (Boston Scientific Corporation) had poorer outcomes compared to PTA, with 19% patency at 6 months.[6] Brachytherapy demonstrated initial promise; however, the initial randomized trial was halted due to lack of funding.[7]

Self-expanding stents were initially considered to be superior to angioplasty, and many interventionists are currently placing them despite the lack of good evidence regarding efficacy. In fact, previous randomized and retrospective studies using older stent designs have failed to show any superiority over PTA at the venous anastomosis, with one recent retrospective study actually demonstrating poorer outcomes compared to PTA.[8-12] Part of the confusion lies in variability of reporting standards and uses based on lesion location and access type. The studies completed do show improved initial or primary patency. However, overall access patency is unchanged compared to maintenance PTA. In addition, there are no definitive large randomized studies that have compared bare-metal stents (BMS) to PTA.

COVERED STENTS AND STENT GRAFTS

Covered stents are essentially a covering over an inner skeleton represented by the stent platform. The inner support structure, or the stent itself, is composed of a variety of metals. The most common metal used is nitinol, which is composed of 50% nickel and 50% titanium. This unique metal is capable of different shapes at different temperatures, is flexible, and returns to its predetermined shape when surrounding structures allow it to.

The stent skeleton itself is a supporting structure to the covering material and, depending on the manufacturer, it can reside outside the covering, be sandwiched within it, reside external to the covering material, or a combination of any of these. A covered stent is a device where the covering material resides over the stent but is not integrated with the inner stent. An example would be the Wallgraft (Boston Scientific Corporation), in which the outer Dacron covering is separate from the stent and can be peeled off. Stent grafts are devices in which the covering material is integrated with the stent structure. The Flair stent graft (Bard Peripheral Vascular, Inc.) is an example of the nitinol stent imbedded within a PTFE sandwich.

The covering itself is commonly composed of PTFE, or polyethylene terephthalate (PET), also known as *Dacron*. These coverings can be of varying thickness and porosity. PTFE is structurally composed of fibrils and nodes. Although many consider all coverings to be

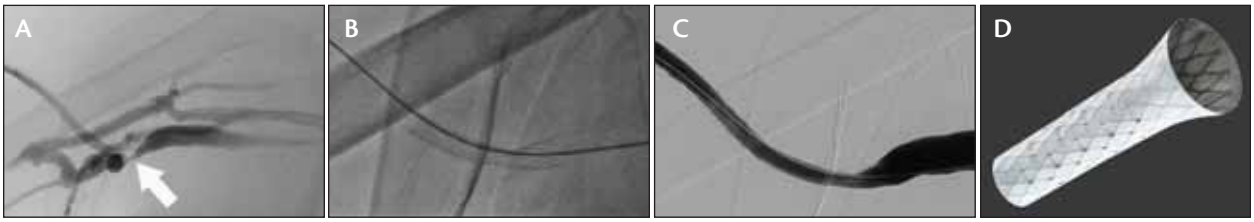

Figure 3. Typical venous anastomotic stenosis (arrow) in a patient with a brachial-basilic prosthetic graft (A). A flared 8- X 50-mm Flair stent graft deployed across the stenosis (B). Completion fistulogram demonstrated no residual stenosis and decompression of venous collaterals (C). The distal end of the device is flared with no exposed nitinol ends and no radiopaque markers. Note the inner carbon-impregnated surface (D).

equivalent, this is not the case. Dacron incites an inflammatory reaction and is considered less ideal than PTFE.[13] The optimal type and design of coverings to date remains expanded PTFE (ePTFE).

Intranodal distance determines porosity of the PTFE material and therefore affects potential tissue ingrowth and vessel incorporation, with increased porosity leading to faster endothelialization. A shortened intranodal distance reduces porosity of the PTFE but also increases its rigidity and thickness. One animal study examined three different PTFE materials consisting of different porosity. This study found that medium- to large-porosity PTFE resulted in reduced intimal hyperplasia than low-porosity PTFE and BMS.[14] In addition, the inner side or the intravascular luminal side of the covering itself can be impregnated or coated. Common substances used include carbon and heparin. Carbon-impregnated stent grafts fill in intranodal gaps, thereby supposedly decreasing platelet adhesion and risk of thrombosis. Heparin bonding to the covering prevents platelet adhesion as well.

WHY DO STENT GRAFTS POTENTIALLY WORK BETTER THAN PTA AND OTHER DEVICES?

Compared to all other previous devices, stent grafts may work simply because they exclude areas of pathology (ie, intimal hyperplasia), whereas previous devices only partially treat intimal hyperplasia without fully treating it or excluding it. The covering, a relatively inert polymeric covering, acts as a barrier to migration of smooth muscle cells and the potentially diseased and/or thrombogenic wall from luminal blood flow.[15] This exclusion is obtained nontraumatically as compared to surgery in which surgical manipulation of vessels themselves is thought to be the trigger for intimal hyperplasia and future stenoses. This characteristic also confines blood flow within the lumen of the device, which is very useful in cases of vascular rupture. With the Flair device, the flared portion of the stent graft has been found to promote laminar flow within an in vitro model, whereas the common end-to-side venous anastomosis of dialysis grafts was associated with turbulent flow within the region of the anastomosis.

CLINICAL USES

Most stent grafts are currently being used for off-label indications within North America. Only the Flair stent graft has on-label approval for use at the venous anastomosis with prosthetic grafts. Stent grafts have been used off-label throughout hemodialysis access circuits for recurrent venous stenosis, failure of angioplasty, venous rupture, exclusion of venous aneurysms within fistulas and pseudoaneurysms within grafts, to exclude clot within accesses, in-stent stenosis, and occasionally as a bridging device from the occluded access venous outflow to an adjacent venous collateral.

DEVICES AVAILABLE

Within North America, multiple stent graft platforms exist, many without on-label approval for interventions within hemodialysis access circuits. The Viabahn stent graft is composed of reinforced ePTFE attached to an external nitinol stent structure and an internal heparin-bonded surface. The nitinol structure does not extend beyond the ePTFE. The nitinol structure is more flexible than most other stent grafts available (Figure 1). There are no radiopaque markers on the device to enhance visibility. The device is indicated for use within the United States for treatment of iliac and superficial femoral artery lesions.

The Fluency stent graft is composed of an inner nitinol skeleton and is encapsulated within two layers of ePTFE. The nitinol skeleton extends beyond the covering by 2 mm on either side, with tantalum markers for increased visibility (Figure 2). The luminal surface is impregnated with carbon. The device has on-label indications within North America for tracheobronchial strictures. The Flair stent graft is also composed of a nitinol skeleton fully encapsulated between two layers of ePTFE, with no nitinol extending beyond the cover-

ing. The inner lumen of the device is impregnated with carbon, and the device comes with a distal flared end configuration, which is roughly 4 mm larger in diameter than the main body section, and a straight, nonflared configuration. There are no markers on the device. Within the United States, the device has an on-label indication for primary treatment of stenosis at the venous anastomosis of synthetic arteriovenous access grafts instead of angioplasty alone (Figure 3).

There are anecdotal reports of interventionists using the 12-mm Viatorr stent graft (Gore & Associates) for central venous lesions. The Viatorr device, composed of ePTFE and a nitinol skeleton with 2 cm uncovered, is specifically designed and has on-label indication for transjugular intrahepatic portosystemic shunt creation. Uses outside this indication are off-label with no published reports. The Wallgraft is composed of an inner metal woven skeleton of Elgiloy with an outer covering of Dacron, also known as *polyethylene terephthalate*. The two components are not bound to each other. The stent component is more radiopaque than nitinol and does not extend beyond the covering material. The current on-label indication is for treatment of biliary strictures.

This list is not exhaustive and is restricted to devices that have been used within hemodialysis access circuits. There are multiple devices currently undergoing study for arterial indications or that have been developed in markets outside North America where use within hemodialysis access sites is unknown.

WHAT IS THE EVIDENCE?

Do stent grafts work for all stenoses and areas of occlusion within hemodialysis grafts and fistulas? This has yet to be determined. There are now multiple studies indicating their utility for specific indications, with multiple ongoing studies. In perhaps the most recognized recent study examining the outcomes of stent grafts, a specifically constructed stent graft (the Flair device) used for primary treatment of stenosis at the venous anastomosis of prosthetic hemodialysis grafts was associated with a significantly higher primary patency rate than angioplasty at 6 months (50% vs 23%). This study was a randomized, prospective, multicenter study with 190 patients enrolled.[3] This study differs from many studies, with an objective measure of mandatory 2- and 6-month angiographic follow-up.

In another randomized, prospective, single-center study of questionable statistical design and a small study population, stent grafts versus stents were used to treat stenosis exclusively at the cephalic arch in autogenous fistulas. Stent grafts were found to have significantly better primary patency than stenting (82% vs 39% at 6 months).[16] Interestingly, BMS patency was equivalent to previously published patency rates for PTA in this location.[17] This outcome also suggests that stents do not have any improved patency over PTA in this location.

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Beyond these two prospective studies, there have been a few recent retrospective studies. One study looked at salvaging fistulas that were unsalvageable with traditional endovascular techniques. The study population included clotted fistulas and aneurysms but did not contain any central venous stenoses/occlusions. Primary patency was 88% at 6 months.[18] Another study examined use of stent grafts for central venous occlusions in 14 patients with autogenous fistulas. Primary patency was found to be 100% at 12 months.[19] However, patency was assessed with Doppler ultrasound in a majority of cases, with no objective measure used. Despite this significant deficiency, this study suggests improved patency for central lesions that surpasses that seen with PTA and bare-metal stenting. In one retrospective study specifically examining angioplasty-induced rupture salvaged with stent grafts, 21 patients were salvaged with a primary access circuit patency of 20% at 6 months.[20] For the three aforementioned retrospective studies, the Fluency stent graft was inserted and used off-label. In one retrospective study, Viabahn stent grafts were used to successfully exclude prosthetic graft pseudoaneurysms where there was concern for rupture. Primary patency was 20% at 6 months.[4]

Given increased patency over PTA for venous anastomotic stenosis in prosthetic grafts and superior salvage rates in other cases, one may infer an overall cost savings per patient access over the cumulative access life span. However, the financial costs/benefits have yet to be ascertained or properly quantified.

PATTERNS OF FAILURE

Despite the advantages of stent grafts, they are also still prone to failure due to intimal hyperplasia. The most common pattern of failure is edge stenosis that occurs within 5 mm of each end of the stent graft. Theories include the stent graft edges acting as points of friction or endothelial disruption subsequently leading to a thrombotic cascade that ultimately results in a

late intimal hyperplastic response. Early thrombus formation has been found to have a direct correlation with late neointimal proliferation.[21,22] In addition, initial animal work has shown that patterns of stenosis are reflective of neointima formation at the ends of the covered stents and extends inward centrally, the pattern now commonly seen in clinical practice.[23]

ONGOING STUDIES AND FUTURE DIRECTIONS

There are multiple ongoing studies examining the utility of stent grafts within dialysis accesses. The RENOVA study is a randomized, multicenter, prospective postapproval study of the Flair stent graft versus PTA (1:1 randomization) assessing superiority of access circuit primary patency at 12 months, days between interventions to assess patency of the intervention and safety of the Flair device compared to PTA. Patients will also be followed to 24 months, and there is no required angiographic follow-up. Assessment of patency is based on clinical evaluation. Study patients are restricted to those having arm prosthetic grafts, with a study population size of 270 patients. The study has recently completed enrollment, with 12-month follow-up on the last enrolled patient to be completed this year. None of the patients from the original FLAIR study who had placement of the stent grafts were rolled into this study.

The REVISE trial is also a multicenter randomized trial using the Propaten (heparin) bioactive surface Viabahn stent graft. The study is comparing primary patency between the device and PTA in patients with venous anastomotic stenosis in prosthetic grafts. This study is ongoing and expected to complete recruitment this year. The primary endpoint is target lesion patency at 6 months with time-to-event analysis. Randomization is 1:1, with an expected enrollment of 280 patients. There is no mandated follow-up beyond each center's normal follow-up practice. In addition, there are no restrictions to placing the device across joint spaces.

The RESCUE study, also actively enrolling, addresses the clinical concern of in-stent stenosis. Despite inconclusive evidence of BMS advantages over PTA, a significant number of dialysis patients within the United States have had stents placed within their access circuits. Unsurprisingly, in-stent stenosis is a frequent and recurring problem for these patients, and there is no Food and Drug Administration–approved device to treat in-stent stenosis. The RESCUE trial is a randomized, prospective, multicenter study that is comparing use of the Fluency stent graft to angioplasty for in-stent stenosis within the venous outflow circuit within patients with autogenous fistulas and prosthetic grafts. This study has just begun actively enrolling.

Another investigator-initiated, prospective, randomized, multicenter study by me and Abigail Falk, MD, compares outcomes between PTA and the Viabahn stent graft for cephalic arch stenosis and central venous stenosis/occlusions. Patency of the treated lesion and access circuit patency will be assessed at 3 and 6 months.[24] The study has also recently begun enrolling patients.

OUTSTANDING CONCERNS

Questions that remain and require more defined answers beyond trial outcomes are the need for prophylactic antibiotics, use of antiplatelet agents before and after placement of these devices, and safety/outcomes from puncturing across stent grafts within AV accesses. There are concerns for infection of these devices and risk factors for infection; actual risk has yet to be determined for indications not yet investigated.[25,26] Prophylactic antibiotics are recommended for stent grafts placed across pseudoaneurysms and aneurysms because chronic clot within them has been found to be colonized by bacteria.[27,28] Also, there are anecdotal reports of safe needle punctures through stent grafts, but there are no specific studies addressing this practice. Long-term durability and fatigability of these devices in certain locations has not been assessed. Stent fractures are common at the cephalic arch and within the subclavian vein where it is compressed between the first rib, clavicle, and costoclavicular ligament.[29] Are stent grafts also at risk for fracture at these locations?

CONCLUSION

Stent grafts in both randomized and retrospective studies have shown superior outcomes compared to PTA for multiple specific lesions within autogenous fistulas and prosthetic grafts. These superior outcomes may also translate into overall cost savings. However, universal improved outcomes have not been completely assessed. Many questions remain, including technical issues, the need for further technical refinements of current technology, long-term outcomes, and overall costs. Despite these issues, stent grafts have the potential to surpass and, in some cases, have already surpassed PTA as the gold standard for treating venous stenoses within dysfunctional AV accesses. ■

Dheeraj Rajan, MD, FRCPC, FSIR, is the Head and Associate Professor, Division of Vascular & Interventional Radiology, Department of Medical Imaging, at the University of Toronto in Canada. He has disclosed that

he is a paid consultant to Bard Peripheral Vascular, Inc. Dr. Rajan may be reached at dheeraj.rajan@uhn.on.ca.

1. Huber TS, Carter JW, Carter RL, et al. Patency of autogenous and polytetrafluoroethylene upper extremity arteriovenous hemodialysis accesses: a systematic review. J Vasc Surg. 2003;38:1005-1011.
2. Vascular Access 2006 Work Group. Clinical practice guidelines for vascular access. Am J Kidney Dis. 2006;48 (suppl) 1:S176-247.
3. Haskal ZJ, Trerotola S, Dolmatch B, et al. Stent graft versus balloon angioplasty for failing dialysis-access grafts. N Engl J Med. 2010;362:494-503.
4. Vesely TM. Use of stent grafts to repair hemodialysis graft-related pseudoaneurysms. J Vasc Interv Radiol. 2005;16:1301-1307.
5. Vesely TM, Siegel JB. Use of the peripheral cutting balloon to treat hemodialysis-related stenoses. J Vasc Interv Radiol. 2005;16:1593-1603.
6. Gray RJ, Varma JD, Cho SS, Brown LC. Pilot study of cryoplasty with use of PolarCath peripheral balloon catheter system for dialysis access. J Vasc Interv Radiol. 2008;19:1460-1466.
7. Misra S, Bonan R, Pflederer T, et al. BRAVO I: A pilot study of vascular brachytherapy in polytetrafluoroethylene dialysis access grafts. Kidney Int. 2006;70:2006-2013.
8. Beathard GA. Gianturco self-expanding stent in the treatment of stenosis in dialysis access grafts. Kidney Int. 1993;43:872-877.
9. Kariya S, Tanigawa N, Kojima H, et al. Peripheral stent placement in hemodialysis grafts. Cardiovasc Intervent Radiol. 2009;32:960-966.
10. Quinn SF, Schuman ES, Demlow TA, et al. Percutaneous transluminal angioplasty versus endovascular stent placement in the treatment of venous stenoses in patients undergoing hemodialysis: intermediate results. J Vasc Interv Radiol. 1995;6:851-855.
11. Hoffer EK, Sultan S, Herskowitz MM, et al. Prospective randomized trial of a metallic intravascular stent in hemodialysis graft maintenance. J Vasc Interv Radiol. 1997;8:965-973.
12. Vogel PM, Parise C. SMART stent for salvage of hemodialysis access grafts. J Vasc Interv Radiol. 2004;15:1051-1060.
13. Dolmatch BL, Dong YH, Trerotola SO, et al. Tissue response to covered Wallstents. J Vasc Interv Radiol. 1998;9:471-478.
14. Dolmatch B, Dong YH, Heeter Z. Evaluation of three polytetrafluoroethylene stent-grafts in a model of neointimal hyperplasia. J Vasc Interv Radiol. 2007;18:527-534.
15. Sick PB, Brosteanu O, Niebauer J, et al. Nointima formation after stent implantation in an experimental model of restenosis: polytetrafluoroethylene-covered versus uncovered stainless steel stents. Heart Dis. 2002;4:18-25.
16. Shemesh D, Goldin I, Zaghal I, et al. Angioplasty with stent graft versus bare stent for recurrent cephalic arch stenosis in autogenous arteriovenous access for hemodialysis: a prospective randomized clinical trial. J Vasc Surg. 2008;48:1524-1531.
17. Rajan DK, Clark TW, Patel NK, et al. Prevalence and treatment of cephalic arch stenosis in dysfunctional autogenous hemodialysis fistulas. J Vasc Interv Radiol. 2003;14:567-573.
18. Bent CL, Rajan DK, Tan K, et al. Effectiveness of stent-graft placement for salvage of dysfunctional arteriovenous hemodialysis fistulas. J Vasc Interv Radiol. 2010;21:496-502.
19. Kundu S, Modabber M, You JM, et al. Use of PTFE stent grafts for hemodialysis-related central venous occlusions: intermediate-term results. Cardiovasc Intervent Radiol. 2010 Nov 12. [Epub ahead of print]
20. Dale JD, Dolmatch BL, Duch JM, et al. Expanded polytetrafluoroethylene-covered stent treatment of angioplasty-related extravasation during hemodialysis access intervention: technical and 180-day patency. J Vasc Interv Radiol. 2010;21:322-326.
21. Farb A, Sangiorgi G, Carter AJ, et al. Pathology of acute and chronic coronary stenting in humans. Circulation. 1999;99:44-52.
22. Rogers C, Edelman ER. Endovascular stent design dictates experimental restenosis and thrombosis. Circulation. 1995;91:2995-3001.
23. Dolmatch BL, Tio FO, Li XD, Dong YH. Patency and tissue response related to two types of polytetrafluoroethylene-covered stents in the dog. J Vasc Interv Radiol. 1996;7:641-649.
24. National Institute of Mental Health; University Health Network, Toronto. Covered Stents to Treat Hemodialysis Access Stenoses in the Cephalic Arch and Central Veins. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2011 May 18]. Available from: http://clinicaltrials.gov/ct2/show/NCT01200914?term=NCT01200914&rank=1 Identifier: NCT01200914.
25. Asif A, Gadalean F, Eid N, et al. Stent graft infection and protrusion through the skin: clinical considerations and potential medico-legal ramifications. Semin Dial. 2010;23:540-542.
26. Kim CY, Guevara C, Gage SM, et al. Assessment of graft infection risk following covered stent deployment in polytetrafluoroethylene (PTFE) arteriovenous hemodialysis access (abstract no. 227). J Vasc Interv Radiol. 2011;22:S97.
27. Ayus JC, Sheikh-Hamad D. Silent infection in clotted hemodialysis access grafts. J Am Soc Nephrol. 1998;9:1314-1317.
28. Delorme JM, Guidoin R, Canizales S, et al. Vascular access for hemodialysis: pathologic features of surgically excised ePTFE grafts. Ann Vasc Surg. 1992;6:517-524.
29. Meier GH, Pollak JS, Rosenblatt M, et al. Initial experience with venous stents in exertional axillary-subclavian vein thrombosis. J Vasc Surg. 1996;24:974-981.