Modified Prosthetic Vascular Conduits

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Abstract—Atherosclerosis in the form of peripheral arterial disease results in significant morbidity. Surgical treatment options for peripheral arterial disease include angioplasty, endarterectomy, and bypass grafting. For bypass grafting, vein remains the conduit of choice; however, poor quality and limited availability have led to the use of prosthetic materials. Unfortunately, because of a lack of endothelium and compliance mismatch, neointimal hyperplasia develops aggressively, resulting in high failure rates. To improve graft patency, investigators have developed surgical, chemical, and biological graft modifications. This review describes common prosthetic materials, as well as approaches currently in use and under investigation to modify and improve prosthetic conduits for bypass grafting in an effort to improve graft patency rates. (Circulation. 2008;117:1873-1882.)

Key Words: atherosclerosis ■ bypass ■ peripheral vascular disease ■ restenosis ■ revascularization

Prosthetic small-caliber conduits used to treat peripheral arterial disease and to create arteriovenous grafts for patients with end-stage renal disease currently have significant limitations because of their long-term durability. Although prosthetic materials are suitable conduits for large-caliber bypass grafting such as aortoiliac reconstructions, infrainguinal prosthetic graft patency is poor, with only 54% of below-knee grafts patent at 4 years.1 The present review discusses therapeutic strategies—both in clinical use and under investigation—to modify prosthetic bypass conduits for improved patency with less morbidity and limb loss. Although our focus is graft modification for the treatment of peripheral arterial disease, it must be acknowledged that graft-improving technologies certainly would be applicable in patients with coronary arterial disease and in end-stage renal failure patients. Currently, small-caliber prosthetic grafts are not used for coronary artery bypass grafting because of dismal patency rates. Arteriovenous prosthetic grafts for patients who require hemodialysis also have poor patency rates, which has led to the establishment of guidelines from the National Kidney Foundation to use autogenous fistulas instead of grafts whenever possible. Thus, it is clear that improvements in prosthetic graft technology will have a far-reaching impact on many different fields.

Prosthetic Bypass Grafting

When a vein is not available, it is necessary to use an alternative conduit (Table 1). The 2 most common prosthetic graft materials used today are polyethylene terephthalate, or Dacron, and polytetrafluorethylene (PTFE). Dacron was developed in Great Britain in 1941 by 2 chemists, J.R. Whinfield and J.T. Dickinson.14 Its high melting point makes it desirable for use in the textile industry. In 1952, Dr DeBakey made the first Dacron tube graft for aortic reconstruction on his wife’s sewing machine. Currently, Dacron is used most commonly for aortic replacement and large-diameter lower-extremity bypass surgery.2 PTFE was developed by a DuPont researcher, Dr Roy Plankett, in 1938, and it was first marketed under the Teflon trademark (DuPont) in 1945. Researchers at W.L. Gore & Associates, Inc (Newark, Del) developed expanded PTFE (ePTFE), which is much more compliant and porous compared with its nonexpanded counterpart. The first report of ePTFE used as a lower-extremity bypass conduit was published in 1976.3 Today, ePTFE is the most commonly used graft for lower-extremity and arteriovenous bypass grafting.2

Several studies have explored side-by-side comparisons of Dacron and ePTFE for above-knee applications and found no statistically significant differences in patency between the 2 conduits.4 5 However, when separated by location of distal anastomosis, the patency rate of ePTFE for infragenicular anastomoses tended to be better compared with Dacron (60% versus 46%, respectively); however, this difference was not statistically significant.5 Hobson et al9 also examined the difference between ePTFE and composite Dacron-autogenous vein grafts to the below-knee popliteal artery. Over a 30-month period, they found that in patients with poor arterial runoff, 45% of ePTFE grafts remained patent; however, all Dacron-autogenous vein grafts occluded within the first 10 months. Because of these poor outcomes, Dacron typically is not used for small-vessel anastomoses.

In smaller-diameter conducting vessels, radial compliance is more important than strength for vascular conduits.2 In an attempt to meet this requirement, polyurethane, which has the highest elasticity among existing polymers, has been developed into vascular grafts. Despite this promising characteristic, 2 properties have limited the clinical application of virtually all polyurethane vascular grafts: poor biostability...
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<td>ePTFE [-(CF2-CF2)-]</td>
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<td>Soft-Wrap technology makes grafts softer and easier to handle</td>
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<td>Rapidax*</td>
<td>Trilaminar, self-sealing</td>
<td>Hemodialysis access 24 h after placement</td>
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(Continued)
and loss of compliance after implantation. To overcome this, Seifalian and coworkers developed a compliant poly(carbonate-urea)urethane vascular graft, MyoLink (CardioTech International Inc, Wilmington, Mass). Studies showed that it possessed a compliance profile similar to human arteries and was more resistant to biodegradation than earlier versions of polyurethane grafts. Currently, the only polyurethane graft available for use in the United States for vascular surgical procedures is the Vectra graft (Thoratec Corp, Pleasanton, Calif), which has been approved by the US Food and Drug Administration (FDA) for hemodialysis access.

Cause of Prosthetic Graft Failure

Most bypass graft failures occur secondary to the progression of atherosclerotic disease, thrombosis, or development of neointimal hyperplasia. With prosthetic grafts, a multitude of causes contribute to graft failure: the inherent thrombogenicity of the graft secondary to the lack of an endothelial cell lining, low-flow states when used in diameters <6 mm, and compliance mismatch between the graft and the native vessel. Compliance mismatch results in hemodynamic changes such as turbulent flow and shear stress, which result in the aggressive development of neointimal hyperplasia at the distal anastomosis. The ideal prosthetic vascular graft should be nonthrombogenic, should be compatible at high and low shear rates, and should have a compliance similar to that of native vessels. Additional desirable qualities include suturability, tensile strength, host incorporation, and resistance to infection.

Poor patency of prosthetic bypass grafts has led several researchers to concentrate efforts on improving available prosthetic materials. With these objectives in mind, a great deal of attention has been focused on surgical modifications, materials and coatings, protein modifications, endothelial cell seeding, and nitric oxide (NO) modifications of existing prosthetic grafts to improve graft patency and clinical outcomes (Table 2). Most of these modifications are designed to

### Table 1. Continued

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<td>LeMaitre</td>
<td>Expedial*</td>
<td>Polycarbonate urethane inner layer, heparin impregnated</td>
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<td>Other</td>
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<td>Fusion Graft*</td>
<td>Combined ePTFE graft fused to knitted polyester outer layer</td>
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The information included is intended to be representative rather than comprehensive.

*These products are currently available only in clinical trials.
improve thrombogenicity, to decrease the development of neointimal hyperplasia, and/or to improve host incorporation and healing. These approaches are not designed to effect graft compliance, suturability, or tensile strength, the former of which remains an important issue to date.

Surgical Modifications of Prosthetic Vascular Grafts

Because of the lower patency rates observed with prosthetic bypass grafting, surgical approaches have been developed to improve graft outcomes. These modifications are largely intended to decrease the compliance mismatch between the prosthetic graft and the native artery. They include vein cuffs, vein patches, vein boots, and arteriovenous fistulas at the distal anastomosis (Figure 1). Stonebridge et al9 conducted a prospective randomized trial to examine the efficacy of Miller vein cuffs in improving lower-extremity ePTFE graft patency. Cuffed below-knee popliteal artery grafts had a 45% 3-year patency rate compared with a 19% patency rate in uncuffed grafts \((P=0.018)\). Similarly, the use of vein patches such as those described by Taylor et al11 and Baston et al12 at the distal anastomosis has been shown to yield better long-term patency rates compared with prosthetic material alone in several retrospective reviews.11,12 No randomized prospective trials have been conducted to date. With respect to arteriovenous fistula modifications of ePTFE grafts as originally described by Ascher et al,13 Syrek et al14 retrospectively found that 2-year patency rates were significantly better for grafts with the arteriovenous fistula modification (23% versus 5% for the ePTFE alone grafts; \(P<0.05\)). Despite these surgical improvements, patency rates remain dismal, especially when the distal outflow is at or below the level of the popliteal artery.

Graft Materials and Coatings

An alternative material has recently been described for use in small-diameter (<6.0 mm) bypass grafting: the Aria graft (Thoratec). This graft is composed of 3 layers of Thoralon, a proprietary polyetherurethaneurea blended with a siloxane-based surface-modifying additive.15 Biocompatibility and durability of this graft have been demonstrated in sheep in both peripheral access and coronary artery bypass grafting.15 Furthermore, it has been successfully implanted into 27

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1PA indicates tissue plasminogen activator; FGF, fibroblast growth factor.
patients in Canada and Europe with no serious device-related injuries. On the basis of these results, a prospective, randomized, controlled clinical study, the Alternative Graft Investigational Study Trial (AEGIS), using the Aria graft for coronary artery bypass grafting is underway in Canada.

An approach for improving long-term graft outcomes is to use coatings to decrease thrombogenicity and neointimal hyperplasia. One such strategy is the use of carbon-impregnated ePTFE grafts. Carbon is biocompatible and has been used in other applications to reduce thrombogenicity. The Impra Carboflo graft (Bard Peripheral Vascular, Inc, Tempe, Ariz), a carbon-modified ePTFE graft, was evaluated in a prospective, randomized multicenter trial compared with standard ePTFE. All bypasses were to the anterior tibial artery, and a vein patch or cuff was used in each case. At 36 months, for the carbon and standard ePTFE groups, the primary patency (33% and 30%, respectively) and limb salvage (67% and 58%, respectively) rates were not statistically different.

Several additional graft coatings have undergone preliminary testing. Karrer et al coated ePTFE with polypropylene sulfide–polyethylene glycol (PEG) and tested these grafts in a porcine extracorporeal femorofemoral arteriovenous shunt. Grafts perfused for 3 and 9 minutes with and without heparin were assessed for cellular and microthrombi deposition with scanning electron microscopy. The polypropylene sulfide–PEG–coated ePTFE showed decreased thrombogenicity when used in combination with heparin. Yoneyama et al used the phospholipid polymer 2-methacryloyloxyethyl phosphorylcholine and polyurethane to form a 2-mm vascular graft. These grafts were anastomosed to rabbit carotid arteries and harvested at 8 weeks. Neither thrombus nor neointimal formation was observed. Jordan et al produced a membrane-mimetic film on the luminal surface of an ePTFE graft by in situ photopolymerization of an acrylate phospholipid. The grafts were assessed in vivo in a baboon femoral arteriovenous shunt model for 1 hour and demonstrated negligible platelet and fibrinogen deposition. Recently, this group of investigators coated ePTFE with an elastin protein polymer that showed decreased thrombogenicity in a primate ex vivo circuit model. San Roman et al coated Dacron grafts with hydrophilic acrylic polymers, which release salicylic acid, and tested these grafts in an ex vivo canine circuit. This coating appears to decrease the thrombogenicity of Dacron grafts. Yang et al coated the luminal surface of ePTFE grafts with a biodegradable elastomer poly(1,8-octanediol citrate) (POC) using a spin-shearing technique. The POC coating did not alter graft compliance and resulted in delayed plasma clotting in vitro compared with controls. Additionally, POC-ePTFE grafts supported attachment and proliferation of porcine endothelium-like cells (isolated from blood) in vitro; within 10 days, cells became confluent on POC-ePTFE grafts, whereas they were only in random clusters and patches on ePTFE controls. Although these and other polymeric applications to vascular grafts are preliminary, they certainly have potential to improve long-term vascular bypass graft outcomes.

Protein and Drug Modifications

Protein coating or binding proteins to grafts is another approach for improving graft patency. Recently, several commercially available and FDA-approved grafts have used heparin-coating technologies to improve graft patency. Such products include the heparin-bonded Dacron graft called InterGard Heparin (InterVascular) and the Gore-Tex Proponent graft by W.L. Gore, which uses the Carmeda BioActive Surface modification. The Carmeda BioActive Surface technology involves covalent end-point linkage to retain heparin on the ePTFE surface. Bosiers et al conducted a prospective nonrandomized clinical study to examine outcomes of the Proponent graft. This study included 86 patients who underwent a total of 99 bypasses, 55 above-knee and 44 below-knee procedures, 21 of which were femorocrural procedures. The overall 1-year primary patency rate was 82%. Specifically, patency was 84% for above-knee, 81% for below-knee, and 74% for femororcrural bypass grafts. Although there was no control arm in this study, these data suggest better outcomes with the heparin-bonded Carmeda BioActive Surface–ePTFE graft compared with ePTFE alone; however, this would be better assessed through a prospective randomized controlled trial. Although these studies are promising, the risk of heparin-induced thrombocytopenia, which can be lethal, remains a drawback.

Another anticoagulant protein is thrombomodulin, an endothelial cell membrane–bound protein that complexes with thrombin and activates the protein C anticoagulation pathway. Tseng et al immobilized both thrombomodulin and heparin on the surface of membrane immitic films and demonstrated in a continuous-flow circuit that thrombin activity was significantly inhibited. The investigators found that combining thrombomodulin with heparin resulted in an additive effect compared with heparin alone or thrombomodulin alone. This material demonstrates great potential to improve the thrombogenic profile of blood-contacting devices.

Hirudin, a direct thrombin antagonist, is yet another anticoagulant under investigation. Wyers et al bound hirudin to Dacron using an albumin base coat. Treated Dacron patches were implanted into thoracic canine aortas and exposed to nonheparinized blood for 2 hours and showed less gross thrombus and less pseudoaneurmal development compared with control patches. Hirudin also has been bound to a carboxylated polyurethane with albumin to decrease polyurethane thrombogenicity. This material was shown to retain anti-thrombin properties in vitro; however, no in vivo studies have been conducted to date. Hirudin, in combination with iloprost, an inhibitor of platelet aggregation and promoter of vasodilation, has been used to modify ePTFE grafts. Heise et al used these 2 drugs, along with PEG, as the delivery mechanism to coat 4-mm ePTFE grafts. As PEG is hydrolyzed, there is a slow, continuous drug release over several weeks to months. These investigators found that the PEG-hirudin/iloprost group maintained nearly equivalent flow rates at 6 weeks compared with baseline, whereas the 2 control groups, untreated ePTFE and grafts coated with polylactide polymer alone, had markedly reduced flow. Furthermore, although neointimal hyperplasia developed at the
distal anastomosis in these grafts, the PEG-hirudin/iloprost grafts were noted to have less restenosis. An antithrombotic agent, tissue plasminogen activator, which degrades fibrin complexes, has been used to treat graft thrombosis. Greco et al\textsuperscript{28} implanted 1-mm tissue plasminogen activator–iloprost–modified ePTFE grafts into rat aortas and found that 4 of 10 control grafts were patent at 1 week and 9 of 10 treated grafts were patent. Fibroblast growth factor–modified ePTFE grafts have been studied in animal models. Greisler et al\textsuperscript{29} pretreated ePTFE grafts with \textsuperscript{125}I-labeled fibroblast growth factor-1/fibrin glue mixtures with heparin through pressure perfusion. When used as aortoiliac or thoracoabdominal bypass grafts in a canine model, the authors found that fibroblast growth factor-1/fibrin glue promoted greater endothelialization compared with control groups.\textsuperscript{29,30}

Another protein that has been applied to vascular grafts and studied in vivo is P15. This cell-binding peptide was discovered as the cell adhesion domain within type I collagen. The rationale for coating graft surfaces with P15 was that it would promote endothelial cell adhesion and result in a more biomimetic graft. These grafts were evaluated in a sheep model in which 2 P15-coated ePTFE grafts and 1 ePTFE graft were implanted as arteriovenous shunts into each of 2 sheep. At the end of the study, the P15-coated grafts showed a higher degree of endothelialization and significantly less neointimal hyperplasia at the venous anastomosis.\textsuperscript{31}

Sirolimus- and paclitaxel-eluting stents have been used successfully in coronary interventions and have been shown to reduce the incidence of restenosis. Cagiannos et al\textsuperscript{32} coated 6-mm ePTFE grafts with sirolimus for 1 cm at each end of the graft and used a porcine iliac artery bypass model to examine efficacy. The authors found a statistically significant reduction in percent of cross-sectional narrowing in the sirolimus group compared with untreated and adhesive-treated ePTFE grafts (28.5% and 16.2%; \textit{P}=0.007). Lee et al\textsuperscript{33} examined paclitaxel-coated ePTFE grafts using a porcine model for arteriovenous grafting. Although the hemodynamics are not the same as an arterial bypass graft, the authors found that the mean percent of luminal stenosis in the paclitaxel-coated ePTFE graft was 10.4% compared with 60.5% in the control ePTFE graft (\textit{P}<0.05).

**Endothelial Cell Seeding**

Endothelial cells secrete several substances that inhibit both thrombosis and neointimal hyperplasia and are critical for homeostasis and maintenance of vascular integrity in the circulation. Because of their vasoprotective properties, researchers have attempted to modify prosthetic grafts by seeding endothelial cells onto the luminal surface, thereby creating a biologically active graft. There are 2 types of seeding techniques: 2-stage and 1-stage procedures.

Two-stage seeding techniques involve procuring vein or artery from the patient, harvesting the endothelial cells, and expanding them in culture before seeding them onto the graft. Several groups have shown success with 2-stage seeding in animal models and in clinical trials. Magometschnig et al\textsuperscript{34} harvested venous endothelial cells, seeded them onto ePTFE, and used the grafts for crural reconstruction. They showed a 30-day graft patency of 92% compared with 53% in the control ePTFE group. Deutsch et al\textsuperscript{35} reported their results with this procedure for infringuinal bypasses in a 2-phase study. Phase I involved 27 endothelial cell–seeded ePTFE grafts and 17 unseeded ePTFE grafts. The 9-year patency rate was significantly better for the experimental group (65% versus 16%; \textit{P}=0.002). Phase II did not have a control arm, but of the 86 endothelial cell–lined ePTFE grafts, 68% were patent at 5 years. Laube et al\textsuperscript{36} reported this technique for coronary artery revascularization using 4-mm ePTFE seeded with venous endothelial cells. Of 21 coronary grafts, 91% remained patent after a mean follow-up time of 28 months. Although 2-stage procedures clearly have impressive results, there are also significant limitations. Because of the several-week cell culture delay, these grafts cannot be used in an emergency situation. The processes of culture and seeding are labor intensive and costly and carry the risk of infection. Additionally, endothelial cell growth requires several growth factors that may cause unwanted effects after the grafts are implanted.\textsuperscript{37}

In contrast to 2-stage procedures, 1-stage procedures can be completed during 1 surgical procedure. One-stage procedures involve isolating endothelial cells, usually from venipuncture. Herring et al\textsuperscript{38} first successfully introduced the concept of single-stage seeding in 1978 using a canine model. Subsequently, their group, along with others, reported clinical results in which venous endothelial cells were seeded on preclotted grafts, but results were mostly disappointing.\textsuperscript{39–41} A randomized multicenter prospective trial compared seeded femoropopliteal grafts with saphenous vein grafts.\textsuperscript{40} The 30-month patency rates were 38% and 92%, respectively (\textit{P}=0.006). Possible reasons for failure included low endothelial cell seeding density, lack of endothelial cell attachment, and lower propensity for endothelialization compared with the canine model.

More recently, investigators have used endothelial progenitor cells (EPCs) isolated from peripheral blood or bone marrow to seed prosthetic vascular grafts. In 1999, Fujita et al\textsuperscript{42} seeded 4-mm Dacron grafts with preclotted autologous bone marrow blood and implanted them into the canine carotid circulation. At 4 weeks, treated grafts exhibited 80% coverage with endothelium-like cells, whereas control grafts had no coverage. Others have seeded Dacron or ePTFE grafts with bone marrow–derived CD34+ EPCs and have demonstrated 40% to 92% graft endothelialization at 4 weeks in canine and rabbit models.\textsuperscript{43,44} The challenges of using EPCs include cell culture and the associated time, cost, and infection risks that are inherent to that process. Furthermore, whether these cells will function as true endogenous endothelial cells instead of taking on the characteristics of fibroblasts, smooth muscle cells, or myofibroblasts remains to be determined. An exciting alternative approach that deserves mention is the approach used by Rotmans et al.\textsuperscript{45} This group coated ePTFE grafts with anti-CD34 antibodies to capture circulating EPCs to the grafts in vivo. Implanted grafts demonstrated enhanced endothelialization at 72 hours; however, intimal hyperplasia still developed at the distal anastomosis. Refinements in this technique may help to recruit
EPCs to prosthetic grafts to enhance endogenous endothelialization.

Other sources for seeding have included microvascular endothelial cells derived from fatty tissue such as subcutaneous fat or omentum. The advantages of these cells include ease of obtaining them in large quantities and the lack of required cell culture. However, results with seeding of these cells also have been disappointing to date.46,47 Overall, endothelial cell seeding of prosthetic grafts remains a very attractive approach. The problems of cell attachment and obtaining a sufficient number of cells to seed the grafts remain challenges that must be overcome.

**NO Modifications**

Prosthetic graft modifications incorporating NO to improve patency are the subject of current and active focus. NO is produced constitutively from endothelial cells and is vital in the regulation of vascular tone, prevention of platelet aggregation, and inhibition of vascular smooth muscle cell proliferation and migration.48 These properties of NO contribute to the maintenance of a healthy vasculature and prevent neointimal hyperplasia after vascular intervention. Most NO-based graft modifications have focused on the use of 2 classes of NO donors: diazeniumdiolates and S-nitrosothiols (Figure 2).

Diazeniumdiolates are NO donors formed by the reaction of secondary amine structures with NO under high pressures. The major advantages of diazeniumdiolates are that they are stable solids, that the half-life of NO release can be tailored to the need, and that NO release is easily triggered in an aqueous environment.49 Smith et al50 were the first to use the combination of a diazeniumdiolate and a polymer (polyethyleneamine) incorporated into vascular grafts. These grafts produced NO for several weeks in vitro. Using a baboon arteriovenous shunt model, these investigators demonstrated that after 1 hour, NO-releasing grafts showed significantly less platelet deposition compared with untreated grafts. Unfortunately, the coating process altered graft architecture, and the resultant compliance mismatch may have created long-term biocompatibility issues. To address the issues of compliance mismatch, Pulfer et al51 incorporated polymeric diazeniumdiolate polyethyleneamine/NO microspheres into the pores of an ePTFE graft in an attempt to release NO but not alter the compliance of the graft. They showed that these grafts retained their physical properties and released NO in vitro for >150 hours.

Although these studies provided efficient methods for delivering NO, it was subsequently shown that some of the diazeniumdiolate polymers leach out of the polymer matrixes and form measurable levels of nitrosamines, a well-known class of carcinogens.52 To address this issue, Batchelor et al53 reported the preparation of a more lipophilic, discrete diazeniumdiolate species that is resistant to leaching. Polyurethane vascular grafts (5 mm, Vectra) were coated with this new diazeniumdiolate dispersed in a polyvinyl chloride matrix. Using a sheep arteriovenous shunt model, these investigators reported that the NO-coated grafts were patent at 21 days and had a mean luminal thrombus-free surface area of 95%, whereas the control grafts had all occluded.

Recently, NO-producing polyurethanes were created by covalently binding diazeniumdiolates to a polyurethane backbone.54,55 This approach eliminates the need for reaction additives, thus avoiding leaching of undesired byproducts. Jun et al54 showed that NO production by these polyurethane films occurred for ~2 months under physiological conditions in vitro and that mechanical properties of the material were suitable for vascular graft applications. Furthermore, platelet adhesion was greatly diminished, vascular smooth muscle cell growth was inhibited, and endothelial cell growth was stimulated across the polyurethane graft. To date, there are no published in vivo studies using these grafts.

The second class of NO donors that have been used in developing NO-releasing polymers is S-nitrosothiols. S-nitrosothiols serve as a reservoir and transporter of NO within physiological systems.56 Examples of endogenous S-nitrosothiols include S-nitrosoalbumin, S-nitrosoglutathione, and S-nitrosoyocysteine (Figure 3), which are present in circulating blood and within cells.57 Several polymers have been developed by covalently linking S-nitrosothiols to a polymer to prevent leaching of reaction byproducts. Bohl and West58 created NO-releasing hydrogels that showed decreased smooth muscle cell proliferation and decreased platelet adhesion on collagen-coated slides. They speculated that these materials could be used to coat vascular grafts to provide local, sustained NO delivery.

**Figure 2.** Generic structures of 2 NO donors: A, diazeniumdiolate; B, S-nitrosothiol.

**Figure 3.** Examples of endogenous NO donors: A, S-nitrosoalbumin; B, S-nitroso-L-glutathione (GSNO); and C, S-nitroso-L-cysteine.
An exciting property of S-nitrosothiols is their ability to release NO when exposed to visible light, which provides an opportunity to control the timing of NO release. To test this property, Frost et al.\(^5^9\) anchored the NO donor S-nitroso-N-acetylpenicillamine to fumed silica particles, which were then sandwiched between layers of silicone rubber and polyurethane films. They demonstrated that S-nitroso-N-acetylpenicillamine released NO in the presence of light but not when exposed to a physiological solution (ie, blood). They concluded that this represented an external on/off trigger for NO release and that this material has the potential to be made into intravascular devices that are biocompatible.

The main limitation to using polymers loaded with either S-nitrosothiols or diazeniumdiolates is the finite reservoir of NO that exists within these materials.\(^6^0\) New materials are being developed that rely on S-nitrosothiols and/or nitrates that are already circulating in blood. Gappa-Fahlenkamp et al.\(^6^1\) immobilized L-cysteine on Dacron and polyurethane surfaces. This yields a free thiol group that can undergo NO exchange reactions to release NO. The potential advantage of this type of material is the essentially unlimited source of NO that could be generated locally when in contact with circulating blood.

### Challenges for Clinical Development

The development of drug-eluting grafts is a relatively new field, and many questions must be answered before they become commercially available. One issue is how these products will be regulated by the FDA. Should they be regulated as drugs or as devices? Fortunately, 2 products serve as a precedent: drug-eluting stents and heparin-bonded vascular grafts. The more pertinent example is the heparin-bonded grafts. Currently, there are 2 FDA-approved heparin-bonded grafts: the InterGard Knitted Heparin-Bonded Vascular Prosthesis (InterVascular) and the Propaten Vascular Graft (W.L. Gore). Both are classified as medical devices under the Cardiovascular Review Panel, just as their non–drug-eluting counterparts. The precedence set suggests that new drug-eluting vascular grafts should be regulated as medical devices.

Other questions that must be considered and for which there are currently no set precedents include how much drug should be incorporated into the graft and how long it should be available in vivo. Furthermore, an additional question that must be addressed is the adverse effects that could result from the drug-releasing nature of these grafts. If the drug were covalently bonded to the grafts, little systemic effects would be anticipated because the drug would not be released into the circulation. If the drug were not covalently attached to the backbone of the graft, side effects of the drug would need to be considered. With respect to adverse events, drug-eluting stents may serve as a precedent. Despite early enthusiasm for the decreased restenosis rates of both the sirolimus and paclitaxel drug-eluting stents, the stents have recently been shown to have increased rates of late in-stent thrombosis.\(^6^2\)\(^6^3\)

The drug-eluting stents inhibit endothelial cell proliferation; therefore, they remain thrombogenic.\(^6^4\) FDA approval was based on short-term (<1 year) trials; however, most late in-stent thromboses occurred >1 year after implantation. This finding underscores the importance of extensive preclinical evaluation.

### Conclusions

Standard prosthetic grafts have considerable limitations with respect to patency. Because so many patients require bypass grafting with prosthetic conduits, it is imperative to develop good alternatives to vein bypass grafting. Currently available modified prosthetic grafts have shown improvements in outcome; however, the work of many researchers shows significant promise for even better bypass graft materials. The upcoming years will likely prove an exciting time for both investigators and vascular surgeons alike as new methods and materials are used in an effort to improve patient care.

### Disclosures

None.

### References

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