Methods and devices for improving biofixation of implantable vascular devices are provided. The methods and devices improve biofixation of implantable vascular devices by providing one or more thrombus-eliminating agents at a treatment site before and/or during and/or after vascular device implantation.
METHODS AND DEVICES FOR IMPROVING BIOFIXATION OF IMPLANTABLE VASCULAR DEVICES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. patent application Ser. No. 10/977,545, filed Oct. 28, 2004, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to methods and devices to improve biofixation of implantable vascular devices. More specifically, the present invention relates to methods and devices to eliminate or inhibit the formation of one or more thrombi at a vascular device implantation site.

BACKGROUND OF THE INVENTION

[0003] A variety of implantable vascular devices, including stent grafts and stents, have been developed to treat abnormalities of the vascular system. Stent grafts are used to treat aneurysms of the vascular system and have also emerged as a treatment for a related condition, acute blunt aortic injury, where trauma causes damage to an artery. Stents are used to treat areas of vessel narrowing or atherosclerosis.

[0004] Aneurysms arise when a thinning, weakening section of vessel wall balloons out and are often treated when the aneurysm diameter is more than its normal diameter. These thinned and weakened sections of vessel walls can burst, causing an estimated 32,000 deaths in the United States each year. Additionally, aneurysm deaths are suspected of being underreported because sudden unexplained deaths, about 450,000 in the United States alone, are often simply misdiagnosed as heart attacks or strokes while many of them may be due to aneurysms.

[0005] U.S. surgeons treat approximately 50,000 abdominal aortic aneurysms each year, typically by replacing or bypassing and/or bypassing the abnormal section of vessel with a plastic or fabric graft in an open surgical procedure. A less-invasive procedure that has more recently been used is the placement of a stent graft across the aneurysm site. Stent grafts are tubular devices that span the aneurysm site to provide support without replacing a section of the vessel. The stent graft, when placed within a vessel at an aneurysm site, acts as a barrier between blood flow and the weakened wall of a vessel, thereby decreasing pressure on the damaged portion of the vessel. This less invasive approach to treating aneurysms decreases the morbidity seen with conventional aneurysm repair. Additionally, patients whose multiple medical comorbidities make them excessively high risk for conventional aneurysm repair are candidates for stent grafting.

[0006] Stents are rigid, or semi-rigid, tubular scaffolds that are used to treat vessel narrowing or atherosclerosis, the leading cause of death in the United States. Specifically, atherosclerosis and other forms of vessel narrowing are treated with percutaneous transluminal angioplasty (“angioplasty”). The objective of angioplasty is to enlarge the lumen of an affected vessel by radial hydraulic expansion. The procedure is accomplished by inflating a balloon within the narrowed lumen of the affected vessel. After (or during) such an angioplasty procedure, stents are deployed at the treatment site within the vessel to reduce the risk of vessel reclosure. Stents are generally positioned across the treatment site, and then expanded to keep the passageway clear. The stent provides a scaffold which overcomes the natural tendency of the vessel walls of some patients to re-narrow, thus maintaining the openness of the vessel and resulting blood flow.

[0007] While stent grafts and stents (collectively referred to as “vascular devices”) represent improvements over previously-used vessel treatment options, there are still risks associated with their use. One of these risks is migration of the vascular device due to hemodynamic forces within the vessel. Stent graft migrations lead to endoleaks, a leaking of blood into the aneurysm sac between the outer surface of the graft and the inner lumen of the blood vessel which can increase the risk of vessel rupture. Stent migration can leave a treated area of a vessel more susceptible to reclosure. Such migrations of vascular devices are especially possible in curved portions of vessels where hemodynamic forces are asymmetrical placing uneven forces on the vascular device. Additionally, the asymmetrical hemodynamic forces can cause remodeling of an aneurysm sac which leads to increased risk of aneurysm rupture and increased endoleaks.

[0008] Based on the foregoing, one goal of treating aneurysms and vessel narrowings is to provide vascular devices that do not migrate. In an attempt to achieve this goal, vascular devices with stainless steel anchoring bars that engage the vessel wall have been developed. Additionally, endostaples that fix vascular devices more readily to the vessel wall have been developed. While these physical anchoring devices have proven to be effective in some patients, they have not sufficiently ameliorated vascular device migration associated with current treatment methods in all cases. Another method of preventing device migration is promoting the growth of surrounding vascular tissue into and around the device thereby forming a biological attachment of the device to the vessel wall. This biological attachment is referred to as biofixation, which can occur due to endothelialization as well as the proliferation of fibroblasts, smooth muscle cells and the growth of connective tissue matrices.

[0009] One way to reduce the risk of vascular device migration is to administer to the treatment site, either before, during or relatively soon after implantation, a cell growth-promoting factor (also known as a biofixation factor). This administration can be beneficial because, normally, the endothelial cells that make up the portion of the vessel to be treated are quiescent at the time of vascular device implantation and do not multiply. As a result, the vascular device rests against a quiescent endothelial cell layer. If biofixation factors are administered immediately before, during or relatively soon after vascular device deployment and implantation, the normally quiescent endothelial cells lining the vessel wall, and in intimate contact with the vascular device, will be stimulated to proliferate. The same will occur with smooth muscle cells and fibroblasts found within the vessel wall. As these cells proliferate they can grow around the vascular device such that portions of the device becomes part of the vessel wall rather than merely pressing against its surface. This biofixation helps to prevent vascular device migration.
While the foregoing can provide a beneficial method to reduce the likelihood of vascular device migration, the presence or development of a thrombus at the treatment site can impair the effectiveness of the provided biofixation factor. A thrombus (blood clot) is the final product of blood coagulation and occurs within a vessel through the aggregation of platelets and the activation of the humoral coagulation system. The thrombus can impair the effectiveness of provided biofixation factors by acting as a barrier between the vessel wall and the vascular device, inhibiting the growth of tissue or cells on top of the thrombus. Alternatively, even when tissue or cell growth does occur on top of the thrombus, the presence of the thrombus can cause a weaker and/or ordinary link between the tissue or cells growing toward the surrounding vascular device and the vessel wall. Therefore, methods and devices to eliminate or inhibit the development of one or more thrombi present at treatment sites would be beneficial.

SUMMARY OF THE INVENTION

The present invention provides methods and devices to inhibit the development of thrombi at vascular device implantation sites and/or to eliminate thrombi that are present at a treatment site before vascular device implantation. (hereinafter collectively referred to as “elimination”). The elimination of one or more thrombi at vessel treatment sites can improve biofixation of a vascular device at the site. Improved biofixation can reduce the risk of vascular device migration. Reducing the risk of vascular device migration can improve the treatment outcomes associated with vascular devices.

One embodiment of the methods according to the present invention comprises providing a vascular device comprising a thrombus eliminating agent and positioning the vascular device at a treatment site wherein the vascular device releases the thrombus eliminating agent at the treatment site and wherein the thrombus eliminating agent eliminates one or more thrombi at the treatment site.

In another embodiment according to the methods of the present invention, the thrombus eliminating agent is an anti-coagulant. In another embodiment, the thrombus eliminating agent is selected from the group consisting of glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors, fibrinolytic agents (such as, without limitation, tissue plasminogen activator (tPA), tenecteplase and reteplase), flavixel, aspirin, heparin, unfractionated heparin (UFH), low molecular weight heparin, (LMWH), ultra-LMWH, pentasaccharide, direct anti-Xa, direct anti-IX/Xa, direct anti-IIa (thrombin), tissue factor pathway inhibitor (TFPI), hirudins, hirudin derivatives, anitithrombin (AT), activated protein C (APC), lipoproteins, sphingosine, thrombomodulin (TM), cellular Marcra protein, chloroplatinacine, diphtacinone, pindone, clopigroligase bisulfate, coumarin derivatives, coumadin, plasmin, microplasmins, fibrinolysin (without limitation, alitewinase), metalloproteinases and desmetasplase.

In another embodiment, the vascular device further comprises a release biofixation factor. In another embodiment, the biofixation factor is selected from the group consisting of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), platelet-derived epidermal growth factor (PDFGF), fibroblast growth factors (FGFs), transforming growth factor-beta (TGF-β), platelet-derived angiogenesis growth factor (PDAG), autologous platelet gel (APG) including platelet rich plasma (PRP), platelet poor plasma (PPP) and thrombin, and autologous platelet releasates.

In another embodiment, the treatment site is an aneurysm site or a site of vessel narrowing. In another embodiment, the biofixation site is within approximately 2 cm of the proximal and/or distal end of an aneurysm or site of vessel narrowing.

In yet another embodiment, the vascular device is a stent or a stent graft.

In another embodiment, when the treatment site is a site of vessel narrowing, the vascular device further comprises and releases one or more anti-restenosis agents. In another embodiment, the anti-restenosis agent is selected from the group consisting of paclitaxel, rapamycin, tacrolimus, actinonycin D, vincristine, sirolimus, everolimus, biolimus, mycopropholic acid, ABT-578, cervistatin, simvastatin, methylprednisolone, dexamethasone, angiopentin, L-arginine, estradiol, 17-β-estradiol, tranilast, methotrexate, batimastat, halofuginone, BCP-671, OX-2, lantruculin D, cytochalasin A and nitric oxide. In another embodiment, when the treatment site is a site of vessel narrowing, the vascular device further comprises and releases one or more reverse cholesterol transport (RCT) agents or reverse lipid transport agents (hereinafter collectively referred to as “RCT agents”). In another embodiment, the RCT agents are released and selected from the group consisting of surface constitutents of plasma lipoproteins (including, without limitation, apolipoprotein A1 (apo-A1), apo-A1’s mutation apo-A1-milano, apoA1 and cholesterol ester transport protein (CETP)), liver X receptors and the AIP binding cassette (ABC) superfamily of transporter proteins (including, without limitation, ABCA1 and ABCG1).

In another embodiment, the method comprises administering a thrombus eliminating agent at a treatment site, providing a vascular device comprising a biofixation factor, and implanting the vascular device at the treatment site wherein the administered thrombus eliminating agent eliminates a thrombus at the treatment site and wherein the biofixation factor stimulates cell growth at the treatment site.

In another embodiment, the method comprises administering a thrombus eliminating agent at a treatment site, providing a vascular device comprising a thrombus eliminating agent and/or a biofixation factor and positioning the vascular device at the treatment site wherein the administered thrombus eliminating agent eliminates a thrombus at the treatment site and wherein the biofixation factor stimulates cell growth at the treatment site.

Embodiments according the present invention also include devices. In one embodiment, the device comprises a thrombus eliminating agent. In another embodiment, the thrombus eliminating agent is an anti-coagulant. In another embodiment, the thrombus eliminating agent is selected from the group consisting of glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors, fibrinolytic agents (such as, without limitation, tPA, tenecteplase and reteplase), flavixel, aspirin, heparin, unfractionated heparin (UFH), low molecular weight heparin, (LMWH), ultra-LMWH, pentasaccharide, direct anti-Xa, direct anti-IX/Xa, direct anti-IIa (thrombin), tissue factor pathway inhibitor (TFPI), hirudins, hirudin
derivatives, antithrombin (AT), activated protein C (APC), lipoproteins, sphingosine, thrombomodulin (TM), cellular Marcks protein, chlorophucinone, diphacinone, pindone, clopidogrel bisulfate, coumarin derivatives, coumadin, plasmins, microplasmins, fibrolases (without limitation, alfilm-prase), metalloproteinases and desmetaplas.

[0021] In another embodiment, the vascular device further comprises a biofixation factor. In another embodiment, the biofixation factor is selected from the group consisting of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), plate-derived epidermal growth factor (PDEGF), fibroblast growth factors (FGF's), transforming growth factor-beta (TGF-β), platelet-derived angio genesis growth factor (PDGF), autologous platelet gel (APG) including platelet rich plasma (PRP), platelet poor plasma (PPP) and thrombin, and autologous platelet releasates.

[0022] In another embodiment, the vascular device further comprises an anti-restenosis agent. In another embodiment, the anti-restenosis agent is selected from the group consisting of paclitaxel, rapamycin, tacrolimus, actinonycin D, vincristine, sirolimus, everolimus, biolimus, mycophenolic acid, AY7-578, cervistatin, simvastatin, methylprednisolone, dexamethasone, angiotepin, L-arginine, estradiol, 17β-estradiol, tranilast, methotrexate, batimastat, halofuginone, BCP-671, QP-2, lanturnulin D, cytochalasin A and nitric oxide. In another embodiment, when the treatment site is a site of vessel narrowing, the vascular device further comprises and releases RCT agents. In another embodiment of methods, the RCT agents are selected from the group consisting of surface components of plasma lipoproteins (including, without limitation, apolipoprotein A1 (apo-A1), apo-A1's mutation apo-A1-milano, apoE and cholesterol ester transport protein (CETP)), liver X receptors and the ATP binding cassette (ABC) superfamily of transporter proteins (including, without limitation, ABCA1 and ABCG1).

[0023] In another embodiment, the thrombus-eliminating agent is found within a coating on the vascular device. In another embodiment, the coating is a polymer coating, a collagen coating or a fibrin coating.

[0024] In another embodiment, the vascular device is a stent graft or a stent.

BRIEF DESCRIPTION OF THE FIGURES

[0025] FIG. 1 depicts a schematic diagram of a representative stent graft that can be used in accordance with the present invention deployed at a treatment site.

[0026] FIG. 2 depicts a distal end of an injection and delivery catheter that can be used in accordance with the present invention.

[0027] FIG. 3 depicts a schematic diagram of an injection catheter that can be used in accordance with the present invention at a treatment site after stent graft deployment.

DEFINITION OF TERMS

[0028] Prior to setting forth embodiments according to the present invention, it may be helpful to an understanding thereof to set forth definitions of certain terms that will be used hereinafter. Unless otherwise explained, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The singular terms “a,” “an,” and “the” include plural referents unless context clearly indicates otherwise. Similarly, the word “or” is intended to include “and” unless the context clearly indicates otherwise. The term “comprises” means “includes.”

[0029] Abdominal aortic aneurysm: As used herein “abdominal aortic aneurysm” shall include a weak section of an artery wall in the abdominal section of an animal.

[0030] Animal: As used herein “animal” shall include mammals, fish, reptiles and birds. Mammals include, but are not limited to, primates, including humans, dogs, cats, goats, sheep, rabbits, pigs, horses and cows.

[0031] Drug(s): As used herein “drug” shall include any bioactive agent or composition having a therapeutic effect in an animal. Exemplary, non-limiting examples include small molecules, peptides, proteins, protein constructs (including, without limitation, HDL and RCT agents), hormones, DNA or RNA fragments, genes, cells, genetically-modified cells, biofixation factors, matrix metalloproteinase inhibitors and autologous platelet gel.

[0032] Stent graft: As used herein “stent graft” shall include a fabric (metal, composite, and/or derivations and combinations of these materials) tube that reinforces a weakened portion (in one instance, an aneurysm) of a vessel.

[0033] Stent: As used herein “stent” shall include a structure that can be implanted in a vessel to help maintain patency of the vessel.

[0034] Eliminating: As used herein the phrase “eliminate a thrombus” (and other similar phrases including “eliminating a thrombus”, “eliminating thrombi” or “elimination of a thrombus”) includes reducing the number of, presence of, thickness or size of one or more thrombi at a treatment site so that the interference the thrombus or thrombi might otherwise cause in the biofixation of a vascular device is reduced. Eliminating a thrombus also includes inhibiting the formation of one or more thrombi that could develop at a treatment site after vascular device implantation.

[0035] Endoleak: As used herein “endoleak” refers to the presence of blood flow past the seal between the end of a stent graft and the vessel wall (i.e., commonly known as a Type 1 endoleak), and into the aneurysmal sac, when all such flow should be contained within the stent graft’s lumen.

[0036] Migration: As used herein “migration” refers to displacement of a vascular device from its original implanted location.

[0037] Placed or implanted vascular device: As used herein “placed vascular device” or “implanted vascular device” shall include a surgically placed or implanted vascular device, either by invasive or non-invasive techniques. A vascular device can include, without limitation, a stent graft or a stent.

[0038] Thrombus-eliminating agents: As used herein “thrombus-eliminating agent” shall include, without limitation, glycoprotein Ib/IIa (GP Ib/IIa) inhibitors, fibrinolytic agents (such as, without limitation, tPA, tenecteplase and reteplase), clopidogrel bisulfate, flaxidex, aspirin, heparin, unfractionated heparin (UFH), low molecular weight...
Biofixation Factors: As used herein, "biofixation factors" include any agent that can promote coagulation and includes, without limitation, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), platelet-derived epidermal growth factor (PDEGF), fibroblast growth factors (FGF's), transforming growth factor-beta (TGF-β), platelet-derived angiogenesis growth factor (PDGF), autologous platelet gel (APG) including platelet rich plasma (PRP), platelet poor plasma (PPP) and thrombin, and autologous platelet releasates. Biofixation factors include, but are not limited to, endothelialization factors.

Anti-Restenosis Agents: As used herein, "anti-restenosis agents" include any agent that can reduce the risk of vessel reocclusion after an angioplasty procedure. Non-limiting examples of anti-restenosis agents include paclitaxel, rapamycin, tacrolimus, actinomycin D, vincristine, sirolimus, everolimus, biolimus, mycophenolic acid, ABT-578, cerivastatin, simvastatin, methylprednisolone, dexamethasone, angiotensin I-arginine, estradiol, 17β-estradiol, tranilast, methotrexate, batimatim, halofuginone, BCP-671, PQ-2, lantronculin D, cytochalas A and nitric oxide.

Reverse Cholesterol Transport (RCT) Agents and Reverse Lipid Transport Agents: As used herein, reverse cholesterol transport (RCT) agents and reverse lipid transport agents (hereinafter "RCT agents") include agents that draw cholesterol and/or lipids from the blood and atheromas and transport them into HDL constructs. The HDL constructs then fill up with the cholesterol and lipids and transport them to the liver (via the blood) where the liver dumps it into the bile. Thus, while these agents are not classic anti-restenosis agents, they can reduce plaque burden and hyperlipidemia. Reverse cholesterol transport (RCT) agents and reverse lipid transport agents include, without limitation, surface constituents of plasma lipoproteins (including, without limitation, apolipoprotein A1 (apo-A1), apo-A1’s mutation apo-A1-milano, apoE and cholesterol ester transport protein (CETP)), liver X receptors and the ATP binding cassette (ABC) superfamily of transporter proteins (including, without limitation, ABCA1 and ABCG1).

DETAILED DESCRIPTION

Embodiments according to the present invention include methods and devices that are useful in reducing the risk of implantable vascular device migration. More specifically, methods and devices that promote implantable vascular device attachment to blood vessel luminal walls are provided. One embodiment provides methods and devices useful for minimizing post-implantation stent graft migration following deployment at an aneurysmal treatment site and is also useful in preventing or minimizing post-implantation endoleak following stent-graft deployment at an aneurysmal treatment site. Another embodiment provides methods and devices useful for minimizing post-implantation stent migration following deployment at a vessel narrowing site and is useful for preventing the reclosure of such vessels as a result of stent migration. In another embodiment, methods and devices are provided to eliminate thrombosis at a vascular device implantation site. Embodiments of methods and devices are hereinafter exemplified using stent grafts as an example though they may be applicable to all types of implantable vascular devices.

As discussed briefly above, an aneurysm is a swelling, or expansion of a vessel lumen at a defined point and is generally associated with a vessel wall defect. Aneurysms are often a multi-factorial asymptomatic vessel diseases that if left unchecked can result in spontaneous rupture, often with fatal consequences. One method to treat aneurysms involves a highly invasive surgical procedure where the affected vessel region is removed and replaced or bypassed in-situ with a synthetic graft that is sutured in place. However, this procedure is extremely risky and generally only employed in otherwise healthy vigorous patients who can be expected to survive the associated surgical trauma. Elderly and more feeble patients are not candidates for these aneurysm surgeries, and, before the development of stent grafts, remained untreated and at continued risk for sudden death.

In contrast to the described invasive open surgical procedures, stent grafts can be deployed with a cut down procedure or percutaneously using minimally invasive procedures. Essentially, a catheter having a stent graft compressed and fitted into the catheter’s distal tip is advanced through an artery to the aneurysmal site. The stent graft is then deployed within the vessel lumen juxtaposed to the weakened vessel wall forming an inner liner that insulates the aneurysm from the body’s hemodynamic forces thereby reducing the risk of rupture. The size and shape of the stent graft is matched to the treatment site’s lumen diameter and aneurysm length. Moreover, bifurcated grafts are commonly used to treat abdominal aortic aneurysms that are located near the iliac branch.

While stent grafts provide a number of benefits, stent graft migration can cause problems, and fixation of the stent graft to the vessel wall has been proposed as one method to reduce this risk. One method of affixing a vascular device to a vessel wall involves promoting the growth of the surrounding vascular tissue into and around the device thereby forming a biological attachment of the device to the vessel wall. This biological attachment is referred to as biofixation which includes endothelialization. For example, biofixation may be stimulated by induced angiogenesis resulting in formation of new capillaries in the interstitial space and surface endothelialization. This has led to modification of vascular devices with vascular endothelial growth factor (VEGF) and fibroblast growth factors 1 and 2 (FGF-1, FGF-2). The discussion of these factors is for exemplary purposes only, as those of skill in the art will recognize that numerous other growth factors have the potential to induce cell-specific endothelialization. Co-pending U.S. patent application Ser. No. 10/977,545, filed Oct. 28, 2004 which is hereby incorporated by reference, discloses injecting autologous platelet gel (APG) into the aneurysmal sac and/or between an implanted stent graft and the vessel wall to induce biofixation of the stent graft to prevent stent graft migration and resulting endoleak. The development of
genetically-engineered growth factors also is anticipated to yield more potent endothelial cell-specific growth factors. Additionally it may be possible to identify small molecule drugs that can induce endothelialization.

[0046] As stated earlier, the presence of one or more thrombi at a treatment site may impede the biofixation of a stent graft. Therefore, embodiments according to the present invention provide methods and devices to eliminate thrombi at treatment sites in order to reduce the biofixation impedance they might otherwise cause. In one embodiment, thrombi can be eliminated by administering thrombus-eliminating agents before vascular device implantation. In this embodiment, the thrombus-eliminating agent can be administered to the treatment site by any medically acceptable method, including, without limitation, injection, infusion, or by direct application (i.e., at the time of a surgical procedure, prior to the placement of the stent graft).

[0047] In another embodiment, thrombi can be eliminated by including one or more thrombus-eliminating agents on the vascular device to be implanted such that the device releases the one or more thrombus-eliminating agents at the treatment site. The elimination of thrombi at treatment sites can allow for better adherence of the vascular device to the vessel wall at the treatment site through improved biofixation. The field of medical device coatings is well established and methods for coating stent grafts with drugs, with or without added polymers, are well known to those of skill in the art. Non-limiting examples of coating procedures include spraying, dipping, waterfall application, heat annealing, etc. The amount of coating applied to the stent graft can vary depending upon the desired effect of the agents contained within the coating. The coating may be applied to the entire stent graft or to a portion of the stent graft.

[0048] In one embodiment, coated stent grafts can release, without limitation, both thrombus-eliminating agents and biofixation factors. In the case of a stent, the stent can release, without limitation, thrombus-eliminating agents and/or biofixation factors and/or anti-restenosis agents and/or RCT agents. Therefore embodiments according to the present invention provide coatings for stent grafts that incorporate these drugs. Drugs that can be incorporated into the stent graft coatings are not limited to these provided examples and can include any beneficial drug of choice in combination with the delivery of a thrombus-eliminating agent (either through administration before stent graft deployment as described above and/or through release from the vascular device itself).

[0049] As stated, the coating applied to the stent graft releasably includes one or more thrombus-eliminating agents. These agents, when contacting a thrombus, eliminate the thrombus so that improved biofixation can occur (as compared to tissue growth in the presence of thrombus/thrombi). This improved tissue growth allows cells and tissue to grow into, on and/or around a placed stent graft thereby increasing its fixation in its intended location.

[0050] The thrombus-eliminating agents may be released from the carrier via any pharmaceutically known release profile, including, but not limited to, immediate release, controlled release and/or delayed release. Further, in one embodiment, different drugs can be provided in layers on the vascular device. For example, in one embodiment, the outermost layer can be adapted to release one or more thrombus-eliminating agents. A layer closer to the vascular device than the outermost layer can be adapted to release one or more biofixation factors. In this example, the thrombus-eliminating agent(s) would be released first to eliminate one or more thrombus at the treatment site before the biofixation factor(s) are released. Alternatively, different layers on the vascular device can include different concentrations of drugs. For example, an outermost layer could include one ratio of thrombus-eliminating agent(s) to biofixation factors while an inner layer could have a different ratio of thrombus-eliminating agent(s) to biofixation factors. Alternatively, different layers on the vascular device could include different combinations of drugs. For example, an outer layer could include a thrombus-eliminating agent and a biofixation factor while an inner more layer could include one or more biofixation factors and one or more anti-restenosis or RCT agents. While layers are described in these embodiments, discrete layers are not required and, in one embodiment, one layer can include different concentrations of different drugs in different portions.

[0051] In one embodiment, a stent graft comprising one or more thrombus-eliminating agents and/or one or more biofixation factors and/or one or more anti-restenosis agents and/or one or more RCT agents is provided "pre-loaded" into a delivery catheter. In normal stent graft deployment protocols, the vascular stent graft 100 is fully deployed through the right common iliac artery 114 to an aneurysm site 104 and 104 (FIG. 1). Stent graft 100 has a distal end 102 and an iliac leg 108 to anchor the stent graft in the common iliac artery 116. Stent graft 100 is deployed first in a first delivery catheter and the iliac leg 108 is deployed in a second delivery catheter. The stent graft 100 and iliac leg 108 are joined with a 2 cm overlap of the two segments 106. Note that while a particular stent graft design is depicted in FIG. 1, it is representative only, and any stent graft design can be used.

[0052] In another embodiment, a stent graft comprising one or more thrombus-eliminating agents and/or one or more biofixation factors and/or one or more anti-restenosis agents and/or one or more RCT agents is pre-loaded into a delivery catheter such as that the distal end of which is depicted in FIG. 2. Stent graft 100 is radially compressed to fill the stent graft chamber 218 in the distal end 202 of delivery catheter 200. The stent graft 100 is covered with a retractable sheath 220. In one embodiment, catheter 200 has two delivery ports 208 and 210 (and associated lumens) for delivering drugs of choice to the treatment site. In these embodiments, drugs such as, without limitation, one or more thrombus-eliminating agents and/or one or more biofixation factors and/or one or more anti-restenosis agents and/or one or more RCT agents can be controllably released through either or both of delivery ports 208 and/or 210 directly to the treatment site.

[0053] FIG. 3 depicts an alternative injection catheter 302 that can be used to deliver drugs at a treatment site. The injection catheter 302 has been placed along the side of a deployed stent graft 100. In this embodiment, the injection catheter 302 is independent of the catheter that delivered and deployed the stent graft 100. Delivery ports 304 and 306 are positioned along a portion of the vessel where biofixation would be advantageous near the distal end 102 of the stent graft 100. An evacuation or drain port 305 positioned within the aneurismal sac 104 is also found on this injection
A method includes providing a vascular device having a thrombus-eliminating agent; and positioning the vascular device at a treatment site wherein said vascular device releases the thrombus-eliminating agent at the treatment site and where the thrombus-eliminating agent eliminates one or more thrombi at the treatment site. The treatment site is selected to be a site within 2 cm of an aneurysm site.

Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques. Notwithstanding that the numerical ranges and parameters are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

The terms "a" and "an" and "the" and similar referents used are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context.

Groupings of alternative elements or embodiments disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated that one or more members of a group may be included in, or deleted from, a group for reasons of convenience and/or patentability. When any such inclusion or deletion occurs, the specification is herein deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

Embodiments according to this invention are described herein, variations of those embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description.

Furthermore, numerous references have been made to patents and printed publications throughout this specification. Each of the above cited references and printed publications are herein individually incorporated by reference in their entirety.

What is claimed is:

1. A method comprising:
   - providing a vascular device comprising a thrombus-eliminating agent; and
   - positioning said vascular device at a treatment site wherein said vascular device releases said thrombus-eliminating agent at said treatment site and wherein said thrombus-eliminating agent eliminates one or more thrombi at said treatment site.

2. The method according to claim 1, wherein said thrombus-eliminating agent is an anti-coagulant.

3. The method according to claim 1, wherein said thrombus-eliminating agent is selected from the group consisting of glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors, fibrinolytic agents, tPA, tissue plasmin, reteplase, fludexid, aspirin, heparin, unfractionated heparin (UFH), low molecular weight heparin, (LMWH), ulirana-MW, pentasaccharide, direct anti-Xa, direct anti-IX/Xa, direct anti-IIa (thrombin), tissue factor pathway inhibitor (TFPI), hirudins, hirudin derivatives, antithrombin (AT), activated protein C (APC), lipoproteins, sphingosine, thrombolodulin (TM), cellular Marcks protein, chlorophacinone, diprophacinone, pinodone, clogpodogrel bisulfate, coumarin derivatives, coumadin, plasmins, microplasmins, fibrinolases, allimepnoise, metallocproteinases and desmetophase.

4. The method according to claim 1, wherein said vascular device further comprises and releases a biofixation factor.

5. The method according to claim 4, wherein said biofixation factor is selected from the group consisting of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), platelet-derived epidermal growth factor (PDGEF), fibroblast growth factors (FGFs), transforming growth factor-beta (TGF-β), platelet-derived angiogenesis growth factor (PDAGF), autologous platelet gel (APG) including platelet rich plasma (PRP), platelet poor plasma (PPP) and thrombin, and autologous platelet leukocytes.

6. The method according to claim 1, wherein said treatment site is selected from the group consisting of an aneurysm site, a site of vessel narrowing, within 2 cm of an aneurysm site and within 2 cm of a site of vessel narrowing.

7. The method according to claim 6, wherein said treatment site is within 2 cm of an aneurysm site or within 2 cm of a site of vessel narrowing.

8. The method according to claim 6, wherein when said treatment site is a site of vessel narrowing, said vascular device further comprises and releases one or more agents selected from the group consisting of anti-restenosis agents and RCT agents.

9. The method according to claim 8, wherein said anti-restenosis agent is selected from the group consisting of paclitaxel, rapamycin, tacrolimus, actinomycin D, vincristine, sirolimus, everolimus, biolimus, mycophenolic acid, ABT-578, cestavarina, simvastatin, methylprednisolone, dexamethasone, angiotopien, L-arginine, estradiol, 17-β-estradiol, tranilast, methotrexate, batimistat, halofuginone, BCP-671, QP-2, lanrunculin D, cytchalasin A and nitric oxide and said RCT agent is selected from the group consisting of surface constituents of plasma lipoproteins, apolipoprotein A1 (apo-A1), apo-A1's mutation apo-A1-milano, apoE, cholesterol ester transport protein (CETP), liver X receptors, the ATP binding cassette (ABC) superfamily of transporter proteins, ABCA1 and ABCG1.
10. The method according to claim 1, wherein said vascular device is a stent graft or a stent.

11. A method comprising:
   administering a thrombus-eliminating agent at a treatment site;
   providing a vascular device comprising a biofixation factor; and
   implanting said vascular device at said treatment site;
   wherein said administered thrombus-eliminating agent eliminates a thrombus at said treatment site and
   wherein said biofixation factor stimulates cell growth at said treatment site.

12. A method comprising:
   administering a thrombus-eliminating agent at a treatment site;
   providing a vascular device comprising a thrombus-eliminating agent and/or a biofixation factor; and
   positioning said vascular device at said treatment site;
   wherein said administered and provided thrombus-eliminating agent eliminates a thrombus at said treatment site and/or wherein said biofixation factor stimulates cell growth at said treatment site.


14. The vascular device according to claim 13, wherein said thrombus-eliminating agent is an anti-coagulant.

15. The vascular device according to claim 14, wherein said thrombus-eliminating agent is selected from the group consisting of glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors, fibrinolytic agents, tPA, tenectplase, reteplase, flaxidel, aspirin, heparin, unfractionated heparin (UFH), low molecular weight heparin, (LMWH), ultra-LMWH, pentasaccharide, direct anti-Xa, direct anti-Xa/Xa, direct anti-IIa (thrombin), tissue factor pathway inhibitor (TFPI), hirudins, hirudin derivatives, antithrombin (AT), activated protein C (APC), lipoproteins, sphingosine, thrombomodulin (TM), cellular Marcks protein, chloroprocainone, diphenacine, pindone, clopidogrel bisulfate, coumarin derivatives, coumadin, plasmins, microplasmins, fibrolases, alteimeprase, metalloproteinases and desmetoplasce.

16. The vascular device according to claim 13, wherein said vascular device further comprises a biofixation factor.

17. The vascular device according to claim 16, wherein said biofixation factor is selected from the group consisting of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), plasmin-derived epidermal growth factor (PDEGF), fibroblast growth factors (FGFs), transforming growth factor-beta (TGF-β), platelet-derived angiogenesis growth factor (PDAF), autologous platelet gel (APG) including platelet rich plasma (PRP), platelet poor plasma (PPP) and thrombin, and autologous platelet releasates.

18. The vascular device according to claim 13, wherein said vascular device further comprises one or more anti-restenosis agents or RCT agents.

19. The vascular device according to claim 18, wherein said anti-restenosis agent is selected from the group consisting of paclitaxel, rapamycin, tacrolimus, actinomycin D, vincristine, sirolimus, everolimus, biolimus, mycophenolic acid, ABT-578, cervatin, simvastatin, methylprednisolone, dexamethasone, angiopeptin, L-arginine, estradiol, 17-β-estradiol, tranilast, methotrexate, batimastat, halofuginone, BCP-671, QP-2, lanrunculin D, cytochalasin A and nitric oxide and said RCT agent is selected from the group consisting of surface constituents of plasma lipoproteins, apolipoprotein A1 (apo-A1), apo-A1’s mutation apo-A1-milano, apoE, cholesterol ester transport protein (CETP)), liver X receptors, the ATP binding cassette (ABC) superfamily of transporter proteins, ABCA1 and ABCG1.

20. The vascular device according to claim 13, wherein said thrombus-eliminating agent is found within a coating on said vascular device.

21. The vascular device according to claim 20, wherein said coating is a polymer coating, a collagen coating or a fibrin coating.

22. The vascular device according to claim 13, wherein said vascular device is a stent graft or a stent.