

METHOD OF SELECTIVELY MODIFYING THE ABLUMINAL SURFACE AND
COATING THE LUMINAL SURFACE OF POLYMERIC STENT GRAFTS

Cross-Reference To Related Application

5 [0001] This application claims the benefit of priority of Singapore Patent Application No. 10201800695U, filed 26 January 2018, the content of it being hereby incorporated by reference in its entirety for all purposes.

Technical Field

10 [0002] The present disclosure relates to a method of forming a biodegradable stent graft such that the abluminal surface and the luminal surface comprise an anti-proliferative agent and an anti-thrombotic agent, respectively. The present disclosure also relates to such a biodegradable stent graft and its uses.

15 **Background**

[0003] Stent grafts have been conventionally developed with a metallic stent body and struts with polymeric graft covers. Although the use of such stent grafts has demonstrated superiority over angioplasty, limitations of such stent grafts remain unresolved.

20 [0004] For example, restenosis may still occur within the stented segment, and future stent deployment in the restenotic segment may be impossible due to the stent graft that is already implanted. Stent graft thrombosis may also occur at a moderately high rate due to contact of blood with a foreign material surface. Conventional stent grafts that remain permanently in place, impede further surgical revisions or new access
25 creation. The risk of stent graft infection may also arise and the risk may be correlated to the long dwelling time of the implanted stent graft, which adversely provides ample time needed for bacterial colonization and biofilm formation on the graft surface.

[0005] Conventional biodegradable polymer-based stents that are expandable may have thin struts that are easily covered by neointima formation after implantation. For
30 biodegradable stents, this aspect is important for keeping any fracture or embolic debris from the degradation process from entering the bloodstream. This, however, implies that the mechanical strength of polymer-based materials is orders of

magnitude lower than those of metallic alloys. Hence, fabricating a polymer-based stent with sufficient radial and mechanical strength becomes a challenge.

[0006] Stents also often have one or more drug-eluting layers to deliver sustained doses of anti-proliferative and/or anti-thrombotic drugs, and the localized drug release from such layers may have benefits in reducing re-stenosis rates. To fabricate stents having such drug-eluting layers, the therapeutic agent may be dispersed in a polymer blend composition, followed by immersing the stent in the blend or by spray coating the blend onto the stent surface. Other drug deposition methods may include roll coating, vapor deposition, etc. Despite this, a limitation of conventional coating methods is that both luminal and abluminal surfaces of a stent tend to get coated with the same therapeutic agent, and drugs may be delivered from a stent surface into an undesired area. Moreover, conventional coating methods do not allow for chemical crosslinking of drugs, such as an anti-thrombotic therapeutic agent, and commercially available stent grafts or covered stents that incorporate drug coatings may be non-degradable, lack an anti-proliferative drug eluting function, or suffer from both of such limitations.

[0007] There is thus a need to provide for a solution that addresses one or more of the limitations mentioned above. The solution should at least resolve the issue with conventional coating methods that do not allow for selectively coating of a stent's surface and chemical crosslinking of drugs to the stent's surface.

Summary

[0008] In a first aspect, there is provided a method of forming a biodegradable stent graft having an abluminal surface and a luminal surface, wherein the abluminal surface comprises an anti-proliferative agent and/or an anti-restenotic agent, wherein the luminal surface comprises an anti-thrombotic agent and/or a vascular growth factor, the method comprising:

depositing a water soluble layer on the abluminal surface;

contacting the biodegradable stent graft with an alcohol-based solution

comprising a diamine to form amine functional groups on the luminal surface;

contacting the amine functional groups on the luminal surface with the anti-thrombotic agent and/or the vascular growth factor; and

coating the abluminal surface with the anti-proliferative agent and/or an anti-restenotic agent, wherein prior to coating the abluminal surface, the water soluble layer is removed from the abluminal surface.

[0009] In another aspect, there is provided for a biodegradable stent graft obtained according to the method of the first aspect, wherein the biodegradable stent comprises an abluminal surface and a luminal surface, wherein the abluminal surface comprises an anti-proliferative agent and/or an anti-restenotic agent, wherein the luminal surface comprises an anti-thrombotic agent and/or a vascular growth factor crosslinked to amine functional groups on the luminal surface.

[0010] In another aspect, there is provided for a biodegradable stent graft obtained according to the method of the first aspect for use in the manufacture of a drug delivery device for the treatment and/or prevention of a vascular disease.

[0011] In another aspect, there is provided for a method of treating and/or preventing a vascular disease, wherein the method comprises implanting the biodegradable stent graft obtained according to the first aspect in a blood vessel.

Brief Description of the Drawings

[0012] The drawings are not necessarily to scale, emphasis instead generally being placed upon illustrating the principles of the invention. In the following description, various embodiments of the present disclosure are described with reference to the following drawings, in which:

[0013] FIG. 1A is a photo of the poly(L-lactide-co-ε-caprolactone) (PLCL) stent graft, including the struts and stent graft cover. The abbreviations “PLCL” and “PLC” are used interchangeably in the present disclosure.

[0014] FIG. 1B illustrates a schematic of the cross-section of the biodegradable stent graft and the therapeutic coatings on the luminal and abluminal surfaces of the stent graft.

[0015] FIG. 2 illustrates the present method of selectively modifying the luminal surface with heparin by masking the abluminal surface with a water soluble polysaccharide (e.g. sucrose). After aminolysis with a diamine (e.g. 1,6-hexanediamine) in an alcohol-based solvent (e.g. isopropanol), the amine functional groups on the luminal surface are covalently bonded to heparin through (1) Schiff

base reaction between the aldehyde-terminated heparin and amine functional groups on the PLCL stent graft, and/or (2) via carbodiimide crosslinking between carboxyl-functional groups in the heparin and the amine functional groups on the PLCL stent graft.

5 [0016] FIG. 3A is a photo showing qualitative staining of heparin with toluidine blue on the surface of a stent graft segment (cut and unrolled) with and without masking of a water soluble polysaccharide.

[0017] FIG. 3B shows the whole blood clotting times (n=3). Specifically, FIG. 3B shows the whole blood clotting time of heparin-functionalized PLCL stent surfaces, 10 which is significantly longer than bare PLCL stent surfaces. The functionalization proceeded via aminolysis of 40 mins and 60 mins, followed by carbodiimide-based crosslinking with heparin. Blood was obtained from a healthy donor.

[0018] FIG. 4 shows the compressive load of stent graph at 50% radial compression. Specifically, FIG. 4 is a graph showing the load taken to compress the stent grafts 15 radially by 50% in relation to stent grafts fabricated by different number of dip coatings.

[0019] FIG. 5 shows the cyclic compression of stent grafts. Specifically, FIG. 5 is a graph showing the cyclic compression testing of a stent graft (fabricated by 2 dip coatings), which also illustrates recoverability of over 80% after 10 compression 20 cycles.

[0020] FIG. 6A is a graph showing the change in mass of the PLCL copolymer during 24 weeks of degradation in saline at 37°C.

[0021] FIG. 6B is a graph showing the change in molecular weight of the PLCL copolymer during 24 weeks of degradation in saline at 37°C.

25 [0022] FIG. 7 is a graph showing that tensile modulus (E) of the PLCL copolymer is consistent over 3 months in saline at 37°C.

[0023] FIG. 8 is a graph showing that strain recovery of the PLCL copolymer is maintained over 70% after 3 months in saline at 37°C.

[0024] FIG. 9 illustrates a tapering edge at the end of the stent graft.

30 [0025] FIG. 10 is a graph showing the in vitro release of sirolimus from a PLCL stent with abluminal drug coating over a period of 28 days.

Detailed Description

[0026] The following detailed description refers to the accompanying drawings that show, by way of illustration, specific details and embodiments in which the invention may be practised. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention. Other embodiments may be utilized and changes may be made without departing from the scope of the invention. The various embodiments are not necessarily mutually exclusive, as some embodiments can be combined with one or more other embodiments to form new embodiments.

[0027] Features that are described in the context of an embodiment may correspondingly be applicable to the same or similar features in the other embodiments. Features that are described in the context of an embodiment may correspondingly be applicable to the other embodiments, even if not explicitly described in these other embodiments. Furthermore, additions and/or combinations and/or alternatives as described for a feature in the context of an embodiment may correspondingly be applicable to the same or similar feature in the other embodiments.

[0028] The present disclosure describes a method of forming a biodegradable stent graft, such that the abluminal surface and luminal surface of the stent graft comprise different therapeutic agents. The term “biodegradable” used herein refers to a material that can degrade naturally in a body, such as dissolving in body fluids without causing any harm to the body. A non-limiting example of a body fluid may be blood or a tissue fluid.

[0029] In the context of the present disclosure, a stent graft refers to a tubular device that is implantable into a blood vessel or an artificial vascular prosthesis for reinforcing and/or expanding a segment of the blood vessel lumen or prosthesis. The term “artificial vascular prosthesis” refers to a synthetic graft acting as a vessel substitute or conduit between blood vessels. The term “lumen” refers to the internal channel of a blood vessel or vascular prosthesis.

[0030] In the present disclosure, the term “stent graft” and “covered stent” are used interchangeably. The stent graft may comprise struts and a stent graft cover. An example of such a stent graft, which has struts and the stent graft cover, is shown in FIG. 1A and FIG. 1B. The stent graft cover may be termed a “stent cover” in the

present disclosure. The stent graft has an abluminal surface and a luminal surface. The abluminal surface refers to the surface of the stent graft that faces the blood vessel wall or wall of the vascular prosthesis, when the stent graft is implanted therein. Hence, the abluminal surface may be called the outer surface of the stent graft. The luminal surface refers to the surface that defines a channel for the blood to flow through when implanted in a blood vessel or vascular prosthesis, and hence may be called the inner surface of the stent graft.

[0031] The method of forming the stent graft, and the stent graft, as disclosed herein, are advantageous over conventional stent grafts, as the anti-thrombotic agent and/or the vascular growth factor are immobilized only on the luminal surface via chemical crosslinking, and only the abluminal surface is disposed with an anti-proliferative agent and/or an anti-restenotic agent. This localizes the therapeutic agents to the respective abluminal and luminal surfaces, and avoids any detrimental effects. For example, by chemically crosslinking an anti-thrombotic agent only to the luminal surface, the risk of bleeding at the wall of the blood vessels can be minimized, which may otherwise occur if the anti-thrombotic agent is deposited on the abluminal surface. Chemically crosslinking the anti-thrombotic agent only on the luminal surface also prevents blood clot formation in the blood vessel lumen more effectively, compared to anti-thrombotic agent deposited on the abluminal surface that suffers from poor delivery due to the abluminal surface hindering migration of anti-thrombotic agent into the lumen. The chemical crosslinking localizes the anti-thrombotic agent to the luminal surface of the stent graft, such as the stent graft cover, and this helps to delay thrombosis. The chemical crosslinking also mitigates the risk of bleeding arising from long term release of anti-thrombotic agent and complications relating to systemic administration of an anti-thrombotic agent, such as heparin.

[0032] In contrast to the present method and stent graft, conventional methods do not include chemical crosslinking of the anti-thrombotic agent selectively on the luminal surface. The abluminal and luminal surfaces from conventional coating methods and stent grafts tend to contain both drugs on each surface.

[0033] The anti-thrombotic agent and/or the vascular growth factor are formed only on the luminal surface, as the present method and stent graft advantageously coats the abluminal surface with a water soluble layer that renders poor solvation and poor

aminolysis rates of diamines. This is because the water soluble layer, which may be termed a “hydrophilic layer” in the present disclosure, prevents wetting of the abluminal surface by an alcohol-based solution, thereby preventing solvated diamines in the alcohol-based solvent from accessing the abluminal surface. In other words, this water soluble layer masks the abluminal surface from being functionalized with amine functional groups from the diamines, which can react and chemically crosslink with the anti-thrombotic agent and/or vascular growth factor. Once the luminal surface is functionalized with the amine functional groups, the anti-thrombotic agent and/or vascular growth factor can be chemically crosslinked to the luminal surface, as amine functional groups are absent from the abluminal surface. The abluminal surface is then coated with the anti-proliferative agent and/or anti-restenotic agent, and prior to coating, the water soluble layer may be removed from the abluminal surface.

[0034] The term “anti-proliferative agent” used herein refers to a drug that prevents narrowing of a lumen of a blood vessel or vascular prosthesis, wherein the narrowing is caused by growth of tissue around and/or through the struts of the stent graft, and the growth of tissue may result from proliferation of smooth muscle cells which are stimulated to proliferate due to vessel injury or a vascular disease.

[0035] The term “anti-restenotic agent” used herein refers to a drug that reduces and/or prevents restenosis. The term “restenosis” used herein refers to the narrowing of a blood vessel which has been subjected to a surgical procedure, such as an angioplasty procedure, and may include stenosis that occurs after stent implantation. In other words, restenosis is a wound healing process that reduces the cross-sectional area of the vessel lumen by, for example, extracellular matrix deposition, neointimal hyperplasia, and vascular smooth muscle cell proliferation, which may ultimately result in narrowing or even reocclusion of the lumen.

[0036] The term “anti-thrombotic agent” used herein refers to a drug that reduces and/or prevents formation of blood clot. The term “anti-thrombotic agent” may be used interchangeably with the term “anti-coagulant agent” in the present disclosure.

[0037] The term “vascular growth factor” used herein refers to any protein produced by a cell that stimulates the formation of blood vessels. The vascular growth factor disclosed herein includes, but is not limited to, vascular endothelial growth factor, which contributes to endothelial cell growth for a blood vessel.

[0038] The terms “chemically crosslinked”, “crosslinked”, or grammatical variants thereof, used herein, refer to a connection between two substances, such as two molecules or compounds, formed by chemical bonding. The chemical bonding may include, but is not limited to, covalent bonding.

5 [0039] The stent graft of the present disclosure may be used in the treatment of vascular aneurysms and stenoses in artificial vascular prosthesis or dialysis vascular access, e.g. arteriovascular fistula, arteriovascular graft, etc.

[0040] The present stent graft, obtained or obtainable from the present method, is also expandable. The present stent graft may be entirely made of a biodegradable polymer, and hence called a polymer (or polymeric) stent graft. The present polymer-based
10 stent graft may comprise a stent graft cover, which provides for adequate radial strength for expansion and holding the lumen/tubular prosthesis open. Moreover, the stent graft cover may help trap some debris against the arterial walls to prevent the debris from being released into the bloodstream. This is advantageous over
15 conventional routes that rely on neointimal formation to be promoted over a stent’s inner surface to keep embolic or fracture debris from being released into the bloodstream.

[0041] The word “substantially” does not exclude “completely” e.g. a composition which is “substantially free” from Y may be completely free from Y. Where
20 necessary, the word “substantially” may be omitted from the definition of the invention.

[0042] In the context of various embodiments, the articles “a”, “an” and “the” as used with regard to a feature or element include a reference to one or more of the features or elements.

25 [0043] In the context of various embodiments, the term “about” or “approximately” as applied to a numeric value encompasses the exact value and a reasonable variance.

[0044] As used herein, the term “and/or” includes any and all combinations of one or more of the associated listed items.

[0045] Unless specified otherwise, the terms "comprising" and "comprise", and
30 grammatical variants thereof, are intended to represent "open" or "inclusive" language such that they include recited elements but also permit inclusion of additional, unrecited elements.

[0046] Various embodiments and details of the present method, stent graft, and its uses, are described as follows.

[0047] In the present disclosure, there is provided for a method of forming a biodegradable stent graft having an abluminal surface and a luminal surface, wherein the abluminal surface comprises an anti-proliferative agent and/or an anti-restenotic agent, wherein the luminal surface comprises an anti-thrombotic agent and/or a vascular growth factor, the method comprising depositing a water soluble layer on the abluminal surface, contacting the biodegradable stent graft with an alcohol-based solution comprising a diamine to form amine functional groups on the luminal surface, contacting the amine functional groups on the luminal surface with the anti-thrombotic agent and/or the vascular growth factor, and coating the abluminal surface with the anti-proliferative agent and/or an anti-restenotic agent, wherein prior to coating the abluminal surface, the water soluble layer is removed from the abluminal surface.

[0048] In the present method, the water soluble layer is deposited only on the abluminal surface. As already mentioned above, the water soluble layer renders the abluminal surface unsuitable or poor for functionalization with amine groups that can undergo crosslinking with the anti-thrombotic agent and/or vascular growth factor. This selectively localizes, for example, the anti-thrombotic agent, to the luminal surface for more effective drug delivery and avoids detrimental bleeding at vessel wall at the abluminal surface. The functionalization of amine group utilizes a diamine which has poor solvation and poor aminolysis rate in the water soluble layer, and this ultimately hinders deposition of the antithrombotic agent and/or growth factor on the abluminal surface, or said differently, directs deposition of the antithrombotic agent and/or growth factor to the luminal surface.

[0049] In various embodiments, the water soluble layer may comprise a water soluble polymer or one or more water soluble saccharides. The water soluble polymer may comprise poly(vinyl alcohol), poly(acrylic acid), poly(methacrylic acid), polyethylene glycol, polyethylene oxide, or a copolymer thereof. The one or more water soluble saccharides may comprise a monosaccharide, an oligosaccharide, a polysaccharide, or a combination thereof.

[0050] Monosaccharide refers to the simplest unit of sugar which cannot be further hydrolyzed into another sugar unit, and examples of monosaccharide include glucose (dextrose), fructose (levulose), galactose, etc. A polysaccharide refers to a polymer composed of long chains of monosaccharide and/or oligosaccharide units bound together by glycosidic linkages, and on hydrolysis give the constituent monosaccharides or oligosaccharides. Examples include starch, glycogen, cellulose, chitin, etc. An oligosaccharide refers to a molecule that consists of fewer units of monosaccharide or oligosaccharide bound together by glycosidic linkages, which is in contrast to a "polysaccharide" where the number of monosaccharide or oligosaccharide units is significantly greater. An oligosaccharide includes a disaccharide, which is made of two units of monosaccharide.

[0051] The present method may further comprise drying the biodegradable stent graft after depositing the water soluble layer on the abluminal surface. While complete drying may not be necessary as long as the water soluble layer can limit diamine access to the abluminal surface, drying (or complete drying) can still be carried out to compact the water soluble layer, rendering access to the abluminal surface difficult for the diamine.

[0052] After drying, the biodegradable stent graft that has the water soluble layer formed on the abluminal surface may be contacted with an alcohol-based solution that contains a diamine for forming amine functional groups on the luminal surface. Contacting the biodegradable stent graft with an alcohol-based solution may comprise immersing the biodegradable stent graft into the alcohol-based solution, according to various embodiments. The alcohol-based solution acts as a solvent for the diamine and solubilizes the diamine. As the alcohol-based solution is able to access the hydrophobic domains of the polymer forming the stent graft, and hence the hydrophobic domains at the luminal surface, the diamine can then access the luminal surface. The polymer forming the stent graft may be a polyester. The alcohol-based solution also does not damage the polymer stent graft or surfaces of the polymer stent graft. Advantageously, the alcohol-based solution aids in the solvation of diamine for aminolysis of the diamine at a polymeric luminal surface which may contain hydrophobic domains that hinder wetting of diamine to the luminal surface. Moreover, as already discussed above, the water soluble layer at the abluminal surface

prevents wetting of an alcohol-based solution onto the abluminal surface, hence allowing selectively access of the diamine to the luminal surface. The alcohol-based solution may comprise methanol, ethanol, or isopropanol. Forming of the amine functional groups on the luminal surface may occur by aminolysis. During aminolysis, a nucleophilic attack on the carbonyl carbon ($-\text{C}(=\text{O})\text{O}$) of the polymeric luminal surface, e.g. an ester bond of a PLCL stent graft, by a primary amine (NH_2) of the diamine ($\text{H}_2\text{N}-\text{R}-\text{NH}_2$) occurs. One end of the diamine then forms an amide bond with the PLCL luminal surface. Meanwhile, the other end of the diamine that does not participate in the nucleophilic attack provides for a free amine functional group for chemical crosslinking the anti-thrombotic agent and/or vascular growth factor to the luminal surface. This luminal surface containing the free amine functional group may be referred to as a PLCL-R- NH_2 surface.

[0053] In the context of the present disclosure, the term "amine" refers to groups of the form $-\text{NR}_y\text{R}_z$, wherein R_y and R_z may be individually selected from the group including but not limited to hydrogen and an optionally substituted alkyl. The nitrogen atom may bear a lone pair of electrons.

[0054] The term "alkyl" used herein as a group or part of a group refers to a straight or branched aliphatic hydrocarbon group, including but not limited to, a C_1 - C_{10} alkyl, a C_1 - C_9 alkyl, C_1 - C_8 alkyl, C_1 - C_7 alkyl, C_1 - C_6 alkyl, C_1 - C_5 alkyl, a C_1 - C_4 alkyl, a C_1 - C_3 alkyl, and a C_1 - C_2 alkyl. Examples of suitable straight and branched C_1 - C_6 alkyl substituents include methyl, ethyl, n-propyl, 2-propyl, n-butyl, sec-butyl, t-butyl, hexyl, and the like.

[0055] The term "diamine" used herein refers to a compound that has two amine groups. In various embodiments, the diamine may comprise ethylenediamine, trimethylenediamine, 1,4-diaminobutane, 1,5-pentanediamine, or 1,6-hexanediamine.

[0056] After the luminal surface has been functionalized with the amine functional groups, chemical crosslinking of the anti-thrombotic agent and/or the vascular growth factor to the luminal surface may be carried out. As only the luminal surface has been functionalized with the amine, the crosslinking selectively occurs on the luminal surface and not the abluminal surface. Advantages of crosslinking the anti-thrombotic agent and/or the vascular growth factor to the luminal surface have already been explained above. For instance, the anti-thrombotic agent and/or the vascular growth

factor localized on the luminal surface renders delivery of the anti-thrombotic agent and/or the vascular growth factor more effective, such that the anti-thrombotic agent and/or the vascular growth factor are already disposed in the lumen of a blood vessel or vascular prosthesis when the stent graft is implanted. This prevents blood clot from forming in the lumen more effectively. This also prevents unwanted bleeding that may occur in cases where the anti-thrombotic agent and/or the vascular growth factor are attached to the abluminal surface. With crosslinking of the anti-thrombotic agent and/or the vascular growth factor at the luminal surface, migration of the anti-thrombotic agent and/or the vascular growth factor into the lumen are not hindered by the vessel wall or vascular prosthesis wall.

[0057] Functionalizing of the luminal surface with amine groups for chemical crosslinking with the anti-thrombotic agent and/or the vascular growth factor helps to form covalent bonding between the amine groups and the anti-thrombotic agent and/or the vascular growth factor. With covalent bonding, the anti-thrombotic agent and/or the vascular growth factor are immobilized to the luminal surface and do not migrate to other sites. Covalent bonding may be formed as the anti-thrombotic agent and/or the vascular growth factor may comprise a carboxyl functional group and/or an aldehyde.

[0058] The term “carboxyl functional group” used herein refers to the group of COOH . In the context of the present disclosure, the term “aldehyde” refers to an organic compound containing the structure -C(=O)H , wherein the carbon atom forms the carbonyl center (a carbon double-bonded to oxygen) with the carbon atom also bonded to hydrogen. The aldehyde may be termed an “alkanal” if it forms part of an organic compound, such as being positioned at the terminal end of a carbon chain, an example of which may be $\text{-CH}_3\text{CH}_2\text{C(=O)H}$.

[0059] Prior to coating the abluminal surface with the anti-proliferative agent and/or the anti-restenotic agent, the water soluble layer may be removed. The water soluble layer may be removed at any time before the anti-proliferative is coated onto the abluminal surface. In various embodiments, the water soluble layer may be removed by dissolving the water soluble layer in an aqueous solution or water. Removal of the water soluble layer may also comprise washing the water soluble layer off the abluminal surface using an aqueous solution or water. Advantageously, the water

soluble layer circumvents use of an organic solvent for removal. Being water soluble, the water soluble layer can be conveniently removed by dissolving away in the aqueous solution or water. In other words, no physical removal means, such as peeling or centrifugation is required.

- 5 [0060] In various embodiments, coating the abluminal surface with the anti-proliferative agent and/or the anti-restenotic agent may comprise spray coating the anti-proliferative layer and/or the anti-restenotic agent on the abluminal surface or spray coating a biodegradable polymer on the abluminal surface, wherein the biodegradable polymer comprises the anti-proliferative agent and/or the anti-
- 10 restenotic agent. In other words, the anti-proliferative layer and/or the anti-restenotic agent can be coated onto the abluminal surface, or mixed in a polymer blend that is then coated onto the abluminal surface to form a layer of biodegradable polymer that is capable of eluting the anti-proliferative layer and/or the anti-restenotic agent. This layer of biodegradable polymer may be termed a biodegradable polymer matrix.
- 15 Advantageously, the layer of biodegradable polymer can provide for controlling release of the anti-proliferative layer and/or the anti-restenotic agent from the abluminal surface by a diffusion-controlled mechanism and/or a degradation-controlled mechanism. The release of a drug, e.g. sirolimus, from such a layer, is shown in FIG. 10.
- 20 [0061] In various embodiments, the biodegradable polymer may comprise a poly(L-lactide), poly(D-lactide), poly(D,L-lactide), polycaprolactone, poly(L-lactide-co-glycolide), poly(D,L-lactide-co-glycolide), poly(L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone), a polymer with ester linkages, or a combination thereof.
- 25 [0062] Advantageously, coating the anti-proliferative layer and/or the anti-restenotic agent on the abluminal surface helps to render the anti-proliferative layer and/or the anti-restenotic agent more effective for reducing and/or preventing narrowing of the lumen that arises from tissue growth at the vessel wall or vascular prosthesis wall. If the anti-proliferative layer and/or the anti-restenotic agent were to be attached to the
- 30 luminal surface, this may decrease the effectiveness of the anti-proliferative layer and/or the anti-restenotic agent.

[0063] The present disclosure also provides for a biodegradable stent graft obtained according to the method described in various embodiments of the first aspect, wherein the biodegradable stent graft comprises an abluminal surface and a luminal surface, wherein the abluminal surface comprises an anti-proliferative agent and/or an anti-restenotic agent, wherein the luminal surface comprises an anti-thrombotic agent and/or a vascular growth factor crosslinked to amine functional groups on the luminal surface.

[0064] Embodiments and advantages described in the context of the present method are analogously valid for the biodegradable stent graft described herein, and vice versa. For instance, embodiments and advantages of crosslinking the anti-thrombotic agent and/or a vascular growth factor only to the luminal surface have already been described above. Chemical crosslinking of anti-thrombotic agent and/or vascular growth factor to the luminal surface having the amine functional groups has the clinical effect of delaying thrombosis. Otherwise, there may be an increase risk of bleeding and complications relating to systemic administration of heparin (an anti-thrombotic agent) if attached to the abluminal surface.

[0065] Chemical crosslinking of the amine functional groups and the anti-thrombotic agent and/or the vascular growth factor may be in the form of covalent bonding. The covalent bonding may be formed from reaction of the amine functional groups on the luminal surface with carboxyl functional group and/or aldehyde of the anti-thrombotic agent and/or the vascular growth factor. The anti-thrombotic agent and/or the vascular growth factor may comprise a carboxyl functional group and/or an aldehyde, according to various embodiments.

[0066] The carboxyl functional group forms a crosslinkage with two of the amine functional groups, wherein the crosslinkage comprises a carbodiimide. This means each -COOH group reacts with two amine groups, such that a carbon becomes covalently bonded to two nitrogen, forming a carbodiimide. The term "carbodiimide" refers to a group of the form -N=C=N-.

[0067] The aldehyde forms a crosslinkage with one of the amine functional groups, wherein the crosslinkage comprises an imine. This means each -COOH group reacts with one amine, such that a carbon is covalently bonded to one nitrogen. This reaction leading to an imine may be referred to herein as a Schiff base reaction. The term

“imine” includes within its meaning the reaction product of an amine and an aldehyde, wherein the resultant product is a molecule having at least one “C=N” group, wherein the nitrogen atom in “C=N” is already attached to the luminal surface.

[0068] The biodegradable stent graft may further comprise a tapered edge at one or both ends of the biodegradable stent graft, wherein the tapered edge is defined by a vertex where the abluminal surface meets the luminal surface, and wherein the vertex has an acute angle which is more than 0° and up to 45°, e.g. 10° to 45°, 20° to 45°, 30° to 45°, 40° to 45°, 10° to 20°, 10° to 35°, 10° to 40°. These angles help to reduce turbulent blood flow in a lumen. The tapered edge reduces turbulent blood flow and improves laminar flow of blood in a vessel, so as to avoid flow alteration and/or pockets of flow stagnation at the edges of the stent graft, especially the stent graft cover, which in turn reduces/prevents undesired stenosis or thrombosis at these regions. Hence, tapering the edges of the stent graft, for example, the stent graft cover, advantageously promotes laminar flow and reduces deleterious effects from flow disruption and turbulence.

[0069] The biodegradable stent graft may further comprise a biodegradable polymer coated on the abluminal surface, wherein the biodegradable polymer comprises the anti-proliferative agent and/or the anti-restenotic agent. Embodiments and advantages of this biodegradable polymer have already been mentioned above and shall not be iterated for brevity.

[0070] In various embodiments, the biodegradable polymer may comprise a poly(L-lactide), poly(D-lactide), poly(D,L-lactide), polycaprolactone, poly(L-lactide-co-glycolide), poly(D,L-lactide-co-glycolide), poly(L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone), a polymer with ester linkages, or a combination thereof.

[0071] As already mentioned above, the biodegradable stent graft disclosed herein may comprise a stent cover having struts disposed thereon as shown in FIG. 1A. The stent cover and struts may be made from or comprised of a biocompatible polymer. The term “biocompatible” used herein refers to a material that, upon implantation in a body, does not elicit a detrimental response sufficient to result in the rejection of the the material or harm the body, and includes a biodegradable material. The biodegradable stent graft disclosed herein may be termed a biodegradable polymeric

stent graft as the entire stent graft can be composed from biocompatible polymer, including the stent graft cover and strut.

[0072] In various embodiments, the biocompatible polymer may comprise a biodegradable polyester, or a blend of different polyesters. The polyester may
5 comprise, for example, poly(L-lactide), poly(D-lactide), poly(D,L-lactide), polycaprolactone, poly(L-lactide-co-glycolide), poly(D,L-lactide-co-glycolide), poly(L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone), a copolymer thereof, or a combination thereof. Any other polymer or copolymer with ester linkages, or a combination thereof, can be used.

10 [0073] The present disclosure further provides for a biodegradable stent graft obtained according to the method described in various embodiments of the first aspect for use in the treatment and/or prevention of a vascular disease. The present disclosure further provides for a biodegradable stent graft obtained according to the method described in various embodiments of the first aspect for use in the manufacture of a
15 drug delivery device for the treatment and/or prevention of a vascular disease. The present disclosure further provides for a method of treating and/or preventing a vascular disease, wherein the method comprises implanting the biodegradable stent graft obtained according to the method described in various embodiments of the first aspect in a blood vessel.

20 [0074] Embodiments and advantages described in the context of the method of forming the stent graft and the stent graft as disclosed herein, are analogously valid for uses of the present stent graft described herein, and vice versa. Such embodiments and advantages have already been described above and shall not be iterated for brevity.

25 [0075] In various embodiments, the vascular disease may include vascular aneurysm, thrombosis, peripheral artery disease, Buerger's disease, disseminated intravascular coagulation, stenosis, renal artery stenosis, and/or cerebrovascular disease.

[0076] The drug delivery device, in various embodiments, may include the biodegradable stent graft and an expansion means for expanding the stent graft. The
30 expansion means may be a balloon catheter. The drug delivery device may also include one or more guide wires for directing the stent and/or catheter to a target segment of the blood vessel or vascular prosthesis.

[0077] In summary, the present disclosure provides for a method of fabricating a stent graft for implantation in a blood vessel, the method may comprise the steps of masking an abluminal surface of the stent with a water soluble layer, introducing amine functional groups to a luminal surface of the stent, removing the water soluble layer from the abluminal surface, attaching anti-thrombotic and/or anti-coagulant molecules containing a carboxyl functional group to the luminal surface of the stent, and applying anti-proliferative drug to the abluminal surface of the stent.

[0078] The water soluble layer may be a water soluble saccharide (mono-, di-, oligo- or polysaccharide) or a water soluble polymer. The water soluble polymer may be selected from the group consisting of poly(vinyl alcohol), poly(acrylic acid), poly(methacrylic acid), polyethylene glycol, polyethylene oxide, or a copolymer thereof.

[0079] The amine functional groups may be introduced to the polymeric luminal surface by immersing the stent graft into a solution of diamine compounds in an alcohol-based solvent. The diamine compound may be an aliphatic diamine selected from the group consisting of ethylenediamine, trimethylenediamine, 1,4-diaminobutane, 1,5-pentanediamine, and 1,6-hexanediamine. The alcohol-based solvent may be selected from the group consisting of methanol, ethanol, and isopropanol.

[0080] The anti-thrombotic agent may comprise heparin, heparin derivatives, heparan sulfate, heparin mimicking polymers, sulfated polysaccharides, and/or negatively charged (acidic) polysaccharides.

[0081] The anti-proliferative and/or anti-restenotic agent may comprise actinomycin D, or analogs and/or derivatives thereof, taxoids (e.g. taxols, docetaxel, paclitaxel, paclitaxel derivatives), limus drugs, or functional and/or structural analogs thereof, (e.g. rapamycin, sirolimus derivatives, tacrolimus, everolimus, everolimus derivatives, zotarolimus), macrolides, cytotoxic protein drugs, and/or a combination thereof.

[0082] While the methods described above are illustrated and described as a series of steps or events, it will be appreciated that any ordering of such steps or events are not to be interpreted in a limiting sense. For example, some steps may occur in different orders and/or concurrently with other steps or events apart from those illustrated and/or described herein. In addition, not all illustrated steps may be required to

implement one or more aspects or embodiments described herein. Also, one or more of the steps depicted herein may be carried out in one or more separate acts and/or phases.

Examples

[0083] The present disclosure relates to a method of forming a polymeric stent graft or covered stent, which has a luminal surface in contact with blood and an abluminal surface in contact with the vessel wall when the stent graft is implanted in the vessel for treatment. The terms “stent graft” and “covered stent” are used interchangeably in the present disclosure.

[0084] The present method involves selective masking of the abluminal surface with a water soluble layer, wherein the water soluble layer protects the abluminal surface from modification via an aminolysis reaction. The present method also modifies the luminal surface for immobilization with an anti-thrombotic/anti-coagulant agent by covalent crosslinking. The crosslinking may be carried out before or after removal of the water soluble layer, as the crosslinking depends on the availability or presence of $-NH_2$ groups on the luminal surface. The abluminal water soluble layer can be washed off and a spray nozzle can be used to coat the abluminal surface with a polymeric layer that is capable of eluting one or more anti-proliferative compounds.

The present fabrication methodology creates a trilayer anti-thrombotic agent/polymer matrix/anti-proliferative coating configuration for the stent graft.

[0085] The present disclosure also relates to a self-expandable stent graft coated with at least one layer of a biodegradable polymer matrix on its outer (abluminal) surface, from which at least one anti-proliferative drug can be released. The stent graft is also immobilized with at least one anti-thrombotic drug coating on its inner (luminal) surface. The anti-proliferative drug can be released over a period of time. The entire stent graft can be composed of one or more biodegradable (i) polymers, (ii) copolymers, or (iii) a polymer blend, which maintain(s) the radial strength and radial strength recoverability of the stent graft without losing the ability to degrade over a given period of time.

[0086] Details of the present method and stent graft are discussed, by way of non-limiting examples, as set forth below.

[0087] Example 1: Present Method

[0088] An example of the present method is illustrated in FIG. 2. The stent graft formed by the present method includes a stent cover (i.e. stent graft cover) and struts.

[0089] The stent graft cover of the present method disclosed herein can be fabricated by electrospinning, melt extrusion, or dip coating, wherein the number of coating may be 1 to 3. The resulting thickness of the stent graft cover can be 100 mm to 350 mm, 150 mm to 350 mm, 200 mm to 350 mm, 250 mm to 350 mm, 300 mm to 350 mm, 100 mm to 300 mm, 150 mm to 300 mm, 200 mm to 300 mm, 250 mm to 300 mm, 100 mm to 250 mm, 150 mm to 250 mm, 200 mm to 250 mm, 100 mm to 200 mm, 150 mm to 200 mm, 100 mm to 150 mm, etc. The thickness of the stent graft cover may depend on the diameter of the blood vessel in which the stent graft is to be implanted. The force leading to 50% radial compression of the stent graft, including the cover, can be any value ranging from 0.5 N to 4 N.

[0090] The polymer stent graft used in the present method can be composed of a biodegradable polyester, or a blend of different polyesters, for example, poly(L-lactide), poly(D-lactide), poly(D,L-lactide), polycaprolactone, poly(L-lactide-co-glycolide), poly(D,L-lactide-co-glycolide), poly(L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone), a copolymer thereof, or a combination thereof. Any other polymer or copolymer with ester linkages, or a combination thereof, can be used.

[0091] The present method involves a step of immobilizing the luminal surface of the stent graft with an anti-thrombotic agent.

[0092] The abluminal surface was first masked with a water soluble layer. This water soluble masking layer may be comprised of one or more water soluble saccharides (mono-, di-, oligo- or poly-saccharides) or a water soluble polymer. The water soluble saccharide or polymer was coated onto the stent graft's abluminal surface and allowed to dry.

[0093] Examples of the water soluble polymer may include poly(vinyl alcohol), poly(acrylic acid), poly(methacrylic acid), polyethylene glycol, polyethylene oxide, or a copolymer thereof.

[0094] Amine functional groups were then introduced to the luminal surface by immersing the stent graft into a solution of diamine compounds in an alcohol-based

solvent. The diamine compounds can be an aliphatic diamine such as, but not limited to, ethylenediamine, trimethylenediamine, 1,4-diaminobutane, 1,5-pentanediamine, 1,6-hexanediamine. The alcohol-based solvent may include, for example, methanol, ethanol or isopropanol. An aminolysis reaction selectively occurs on the luminal surface of the stent graft to form an amine-functionalized surface. This amine-functionalization occurs only at the luminal surface of the stent graft. As already discussed above, the water soluble layer restricts contact of the diamine in the alcohol-based solution with the stent surface, and hence the reaction does not proceed.

[0095] The masking layer was then removed by washing with water.

[0096] The anti-thrombotic or anti-coagulant molecules containing a carboxyl-functional group were then covalently attached to the luminal surface, which is functionalized with amine groups, via carbodiimide crosslinking. To introduce the anti-thrombotic or anti-coagulant molecules, the stent graft can be immersed into a solution comprising the anti-thrombotic or anti-coagulant molecules (e.g. heparin) and the crosslinker (e.g. 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) / N-hydroxysuccinimide (NHS), or derivatives thereof.) The anti-thrombotic molecule may have one or more carboxyl-functional groups located either at the terminal ends and/or side chains of the polymer. The anti-thrombotic molecule may be selected from the group consisting of heparin, heparin derivatives, heparan sulfate, heparin mimicking polymers, sulfated polysaccharides, or negatively charged (acidic) polysaccharides.

[0097] The anti-thrombotic molecules can also be immobilized onto the luminal surface by attachment via aldehyde functional groups located either at the terminal ends or side chains of the anti-thrombotic molecule. When aldehyde functional groups are present, a Schiff base reaction can occur between the aldehyde groups and the amine functional groups of the aminolysed luminal surface of the stent graft.

[0098] The final trilayer configuration of the stent graft was achieved by spray coating the abluminal surface of the stent graft with an anti-proliferative drug or a blend of an anti-proliferative drug and a biodegradable polymer.

[0099] In certain instances, the luminal surface can be immobilized with vascular growth factors with heparin-binding domains through binding to heparin, or heparin derivatives, on the luminal surface. In such instances, the internal luminal surface

promotes endothelial cell growth and migration instead of being anti-thrombotic. The growth factors can include protein factors of the vascular endothelial growth factor (VEGF) family, fibroblast growth factor (FGF) family, and/or the heparin-binding EGF-like (HB-EGF) family.

- 5 [00100] The abluminal surface of the stent graft can have a polymer-based biodegradable drug coating comprised of a polymer and one or more anti-proliferative and/or anti-restenotic agents, wherein the anti-proliferative agent and anti-restenotic agent are selected from the group consisting of actinomycin D, or analogs and derivatives thereof, taxoids (taxols, docetaxel, paclitaxel, paclitaxel derivatives), limus
10 drugs, functional or structural analogs thereof (e.g. rapamycin, sirolimus derivatives, tacrolimus, everolimus, everolimus derivatives, zotarolimus), macrolides, cytotoxic protein drugs, and a combination thereof.

[00101] In certain examples, the stent graft cover has a tapered edge at one or both ends. The taper angle can be more than 0° and up to 45°.

- 15 [00102] Example 2: Stent Graft of the Present Method

[00103] The present disclosure relates to a dual drug-coated, radially self-expandable cylindrical device that is implantable into a blood vessel or artificial vascular prosthesis to reinforce or expand a segment of the lumen/prosthesis. A “stent” or covered stent referred to as a “stent graft” are examples of such device. The
20 expression “artificial vascular prosthesis” refers to a synthetic graft acting as a vessel substitute or conduit between native blood vessels.

[00104] The present stent grafts can be used in the treatment of vascular aneurysms and stenoses in artificial vascular prosthesis or dialysis vascular access e.g. arteriovascular fistula and arteriovascular graft.

- 25 [00105] The present stent graft can also be coated or immobilized with therapeutic agents on both the inner (luminal) and outer (abluminal) surfaces of the stent graft.

[00106] The present stent graph is a biodegradable self-expandable stent graft, wherein the stent graft body comprises a biodegradable polymer blend or copolymer, and wherein the stent graft may be in a crimped state that expands radially to a
30 deployed state in saline or body fluid at 37°C. The outer surface of the stent graft in contact with the wall of the vessel/vascular prosthesis can be coated with a biodegradable polymer matrix capable of releasing at least one anti-proliferative or

anti-restenotic drug, wherein the amount and rate of release can be tuned through the amount of drugs loaded, polymer formulation, and matrix thickness. The internal surface of the stent graft in contact with the blood is immobilized with an anti-thrombotic drug layer through chemical crosslinkages.

5 [00107] The stent graft, which includes the struts and the stent graft cover, may be composed of a biodegradable polymer. The biodegradable polymer may be a copolymer of poly(L-lactide) and polycaprolactone, a copolymer of poly(D-lactide) and polycaprolactone, a mixture of poly(L-lactide) and polycaprolactone, a mixture of poly(D-lactide) and polycaprolactone, or a combination thereof. For instance, non-
10 limiting examples of copolymers of polycaprolactone (PCL) and poly(L-lactide) or poly(D-lactide) may have a lactide content of about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95%.

[00108] The present stent graft may have a stent graft cover that is 100 mm to 350 mm thick and the force required for 50% radial compression of the stent graft may be
15 0.5 N to 4 N.

[00109] The outer surface of the stent graft may have a polymer-based biodegradable drug coating comprising a polymer and one or more anti-proliferative and/or anti-restenotic agents selected from the group comprising of actinomycin D, or analogs and derivatives thereof, taxoids (taxols, docetaxel, paclitaxel, paclitaxel derivatives),
20 limus drugs, functional or structural analogs thereof (e.g. rapamycin, sirolimus derivatives, tacrolimus, everolimus, everolimus derivatives, zotarolimus), macrolides, cytotoxic protein drugs, and a combination thereof.

[00110] The internal surface of the stent graft can be chemically conjugated with an anti-thrombotic agent selected from the group consisting of heparin, heparin
25 derivative, low-molecular weight heparin, anti-adhesive proteins, anti-adhesive peptide sequences, factor X-inhibiting peptide sequences, and other anti-thrombotic polysaccharides. The internal surface may alternatively be immobilized with vascular growth factors with heparin-binding domains through binding to heparin or heparin derivatives on the internal surface. In such instances, the internal surface promotes
30 endothelial cell growth and migration instead of being anti-thrombotic. The growth factors can include protein factors of the vascular endothelial growth factor (VEGF)

family, fibroblast growth factor (FGF) family, and/or the heparin-binding EGF-like (HB-EGF) family.

[00111] The present stent graft may have a stent graft cover with tapered edges at both ends, wherein the taper angle is more than 0° and up to 45°.

5 [00112] In certain examples, the graft cover and/or struts may comprise or consist of other biodegradable polymers. Non-limiting examples of such other biodegradable polymers may include, but are not limited to a polylactide, such as poly(L-lactide) (PLLA), a polycaprolactone (PCL), a copolymer of polycaprolactone (PCL) and polylactic acid (PLA), or a copolymer of poly(lactide) and poly(glycolide) (PLGA).

10 [00113] Example 3: Discussion on Advantages of Present Method and Present Stent Graft

[00114] The present method of fabricating a trilayer stent graft, wherein the trilayer stent graft includes the luminal surface immobilized with the anti-thrombotic agent and the abluminal surface immobilized with the anti-proliferative agent eluting
15 coating, advantageously prevents thrombosis and recurrence of stenosis. The present stent graft hence has an advantageous dual drug coating (anti-thrombotic agent-immobilized surface and anti-proliferative agent eluting coating) to prevent thrombosis and recurrence of stenosis.

[00115] In the present method, the water soluble masking layer is removable by
20 washing with an aqueous solution, or even water, after incorporating amine functional groups on the luminal surface. This circumvents the use of organic solvents which can adversely react with the amine functional groups and hinder subsequent attachment of the anti-thrombotic agent or other drugs at the luminal surface. This also circumvents the use of certain organic solvents that may damage the polymeric stent graft.

25 [00116] The present method does not require the stent graft to be constructed of a non-biodegradable material in order to coat different drugs at the abluminal and luminal surfaces. Even if biodegradable materials are used for forming the stent graft, the present method does not compromise the mechanical strength and expansion of the stent graft.

30 [00117] The present method advantageously allows for a stent graft having a tapered edge at one or both ends of the graft cover to be coated with different drugs, wherein the tapered edge(s) reduces turbulent blood flow and improves laminar flow.

[00118] The present method serves as a chemical based coating method for selective immobilization of anti-thrombotic agent on the luminal surface of a stent graft, and coating of the abluminal surface with an anti-proliferative agent. This is designed to improve patency rates encountered with conventional devices, by allowing at least two different therapeutics to be localized, such that the therapeutics are more targeted at and directed to the tissues where their effects are most efficacious.

[00119] The biodegradable stent graft derived from the present method can dissolve away completely without leaving a permanent fixture within the area of treatment, allowing future stent deployment or surgical revision if needed.

[00120] The biodegradable stent graft can be made from polymeric struts and polymeric cover, wherein the polymeric cover not only improves the radial strength which is required for in-stent application, but also renders the stent graft expandable without using an expanding means, such as a balloon catheter. The present stent graft is also resistant to external compression.

[00121] In addition, the present stent grafts have an added benefit of increased material and drug contact area to the lumen/prosthesis.

[00122] The stent graft is designed to have a tapered edge at one or both ends of the stent graft to reduce the disruption to the blood flow when implanted. The use of a graft cover may increase the overall thickness of the stent graft, and this may disrupt laminar flow of blood in a vessel, thereby resulting in flow alteration and/or pockets of flow stagnation at the edges of the stent graft, especially the stent graft cover. This may in turn promote stenosis or thrombosis at these regions. Hence, tapering the edges of the stent graft, particularly the stent graft cover, advantageously promotes laminar flow and reduce deleterious effects of the flow disruption or turbulence.

[00123] While the invention has been particularly shown and described with reference to specific embodiments, it should be understood by those skilled in the art that various changes in form and detail may be made therein without departing from the spirit and scope of the invention as defined by the appended claims. The scope of the invention is thus indicated by the appended claims and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced.

CLAIMS

1. A method of forming a biodegradable stent graft having an abluminal surface and a luminal surface, wherein the abluminal surface comprises an anti-proliferative agent and/or an anti-restenotic agent, wherein the luminal surface comprises an anti-thrombotic agent and/or a vascular growth factor, the method comprising:
 - depositing a water soluble layer on the abluminal surface;
 - contacting the biodegradable stent graft with an alcohol-based solution comprising a diamine to form amine functional groups on the luminal surface;
 - contacting the amine functional groups on the luminal surface with the anti-thrombotic agent and/or the vascular growth factor; and
 - coating the abluminal surface with the anti-proliferative agent and/or an anti-restenotic agent, wherein prior to coating the abluminal surface, the water soluble layer is removed from the abluminal surface.
2. The method of claim 1, wherein the water soluble layer comprises a water soluble polymer or one or more water soluble saccharides.
3. The method of claim 2, wherein the water soluble polymer comprises poly(vinyl alcohol), poly(acrylic acid), poly(methacrylic acid), polyethylene glycol, polyethylene oxide, or a copolymer thereof.
4. The method of claim 2 or 3, wherein the one or more water soluble saccharides comprise a monosaccharide, an oligosaccharide, a polysaccharide, or a combination thereof.
5. The method of any one of claims 1 to 4, further comprising drying the biodegradable stent graft after depositing the water soluble layer on the abluminal surface.

6. The method of any one of claims 1 to 5, wherein contacting the biodegradable stent graft with an alcohol-based solution comprises immersing the biodegradable stent graft into the alcohol-based solution.

5 7. The method of any one of claims 1 to 6, wherein the alcohol-based solution comprises methanol, ethanol, or isopropanol.

8. The method of any one of claims 1 to 7, wherein the diamine comprises ethylenediamine, trimethylenediamine, 1,4-diaminobutane, 1,5-pentanediamine, or
10 1,6-hexanediamine.

9. The method of any one of claims 1 to 8, wherein the water soluble layer is removed by dissolving the water soluble layer in an aqueous solution or water.

15 10. The method of any one of claims 1 to 9, wherein the anti-thrombotic agent and/or the vascular growth factor comprise a carboxyl functional group and/or an aldehyde.

11. The method of any one of claims 1 to 10, wherein coating the abluminal
20 surface with the anti-proliferative agent and/or the anti-restenotic agent comprises spray coating the anti-proliferative layer and/or the anti-restenotic agent on the abluminal surface or spray coating a biodegradable polymer on the abluminal surface, wherein the biodegradable polymer comprises the anti-proliferative agent and/or the anti-restenotic agent.

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