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14/263,438 28 April 2014 (28.04.2014) US(71) Applicant: CONCIEVALVE LLC [US/US]; 2120 Ar-
gonne Drive Northeast, Minneapolis, Minnesota 55421
(US).(72) Inventor: RAJAMANNAN, Nalini M.; 25 East Superior,
#303, Chicago, Illinois 60611 (US).(74) Agent: WRIGLEY, Barbara A.; Oppenheimer Wolff &
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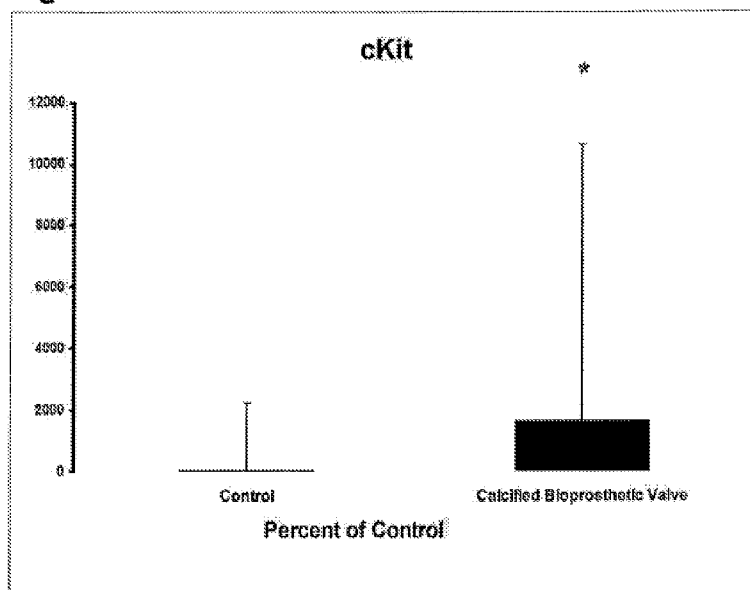
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- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

[Continued on next page]

(54) Title: METHODS FOR INHIBITING STENOSIS, OBSTRUCTION, OR CALCIFICATION OF A STENTED HEART VALVE OR BIOPROSTHESIS

Figure 14



(57) Abstract: The present invention relates to methods for inhibiting stenosis, obstruction, or calcification of a valve following implantation of a valve prosthesis which may involve disposing a coating composition which is a combination of two different drugs one to target inflammation and attachment of the target cell and the second drug to inhibit proliferation and calcification on an elastical stent, gortex graft or valve leaflet, the combination effect of the two drug therapies incorporated into the polymer to attach to the bioprosthesis will improve the efficacy of the inhibition of calcification and the improvement of the longevity of the prosthetic material including the stent, the valve, and the gortex covering. The valve prosthesis and or gortex graft is mounted on the elastical stent or prosthesis such that the elastical stent is in contact with the valve.

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**METHODS FOR INHIBITING STENOSIS, OBSTRUCTION, OR
CALCIFICATION OF A STENTED HEART VALVE OR
BIOPROSTHESIS**

INCORPORATION BY REFERENCE

[0001] All documents cited or referenced herein ("herein cited documents"), and all documents cited or referenced in herein cited documents, together with any manufacturer's instructions, descriptions, product specifications, and product sheets for any products mentioned herein or in any document incorporated by reference herein, are hereby incorporated herein by reference, and may be employed in the practice of the invention. More specifically, all referenced documents are incorporated by reference to the same extent as if each individual document was specifically and individually indicated to be incorporated by reference.

FIELD OF THE INVENTION

[0002] The invention relates to methods for inhibiting stenosis, obstruction, or calcification of heart valves and heart valve prostheses.

BACKGROUND OF THE INVENTION

[0003] The heart is a hollow, muscular organ that circulates blood throughout an organism's body by contracting rhythmically. In mammals, the heart has four-chambers situated such that the right atrium and ventricle are completely separated from the left atrium and ventricle. Normally, blood flows from systemic veins to the right atrium, and then to the right ventricle from which it is driven to the lungs via the pulmonary artery. Upon return from the lungs, the blood enters the left atrium, and then flows to the left ventricle from which it is driven into the systematic arteries.

[0004] Four main heart valves prevent the backflow of blood during the rhythmic contractions: the tricuspid, pulmonary, mitral, and aortic valves. The tricuspid valve separates the right atrium and right ventricle, the pulmonary valve separates the right atrium and pulmonary artery, the mitral valve separates the left atrium

and left ventricle, and the aortic valve separates the left ventricle and aorta. Generally, patients having an abnormality of a heart valve are characterized as having valvular heart disease.

[0005] A heart valve can malfunction either by failing to open properly (stenosis) or by leaking (regurgitation). For example, a patient with a malfunctioning aortic valve can be diagnosed with either aortic valve stenosis or aortic valve regurgitation. In either case, valve replacement by surgical means may be a possible treatment. Replacement valves can be autografts, allografts, or xenografts as well as mechanical valves or valves made partly from valves of other animals, such as pig or cow. Unfortunately, over time, the replacement valves themselves are susceptible to problems such as degeneration, thrombosis, calcification, and/or obstruction. Furthermore, the process of valve replacement may cause perforation in the surrounding tissue, leading also to stenosis, degeneration, thrombosis, calcification, and/or obstruction.

[0006] Thus, new methods for inhibiting stenosis, obstruction, or calcification of heart valves and heart valve prostheses are needed.

[0007] Citation or identification of any document in this application is not an admission that such document is available as prior art to the present invention.

SUMMARY OF THE INVENTION

[0008] The invention involves methods for inhibiting stenosis, obstruction, or calcification of a valve following implantation of a valve prosthesis in a patient in need thereof, which may comprise: disposing a coating composition on an elastical stent, gortex graft material, or valve leaflet, wherein the coating composition may comprise one or more therapeutic agents; and securing said valve prosthesis which may comprise a collapsible elastical valve which is mounted on the elastical stent at a desired position in the patient such that the elastical stent is in contact with the valve, or gortex graft material in contact with the prosthesis, thereby inhibiting stenosis, obstruction, or calcification of the valve or stent or surgical placement of a bioprostheses, following implantation of the valve prosthesis in a patient in need thereof.

[0009] Accordingly, it is an object of the invention to not encompass within the invention any previously known product, process of making the product, or method of using the product such that Applicants reserve the right and hereby disclose a disclaimer of any previously known product, process, or method. It is further noted that the invention does not intend to encompass within the scope of the invention any product, process, or making of the product or method of using the product, which does not meet the written description and enablement requirements of the USPTO (35 U.S.C. §112, first paragraph) or the EPO (Article 83 of the EPC), such that Applicants reserve the right and hereby disclose a disclaimer of any previously described product, process of making the product, or method of using the product.

[0010] It is noted that in this disclosure and particularly in the claims and/or paragraphs, terms such as "comprises", "comprised", "comprising" and the like can have the meaning attributed to it in U.S. Patent law; e.g., they can mean "includes", "included", "including", and the like; and that terms such as "consisting essentially of and "consists essentially of" have the meaning ascribed to them in U.S. Patent law, e.g., they allow for elements not explicitly recited, but exclude elements that are found in the prior art or that affect a basic or novel characteristic of the invention.

[0011] These and other embodiments are disclosed or are obvious from and encompassed by the following Detailed Description.

[0012] In further aspects, the invention may be set out in the following numbered clauses:

1. A method for inhibiting stenosis, obstruction, or calcification of a bioprosthetic valve following implantation of said bioprosthetic valve in a vessel having a wall, said method comprising:

providing a bioprosthetic valve for surgical replacement of a natural diseased valve, said bioprosthetic value including an elastical stent;

providing a coating composition on said elastical stent, bioprosthetic valve or both, wherein the coating composition comprises one or more therapeutic agents which inhibit cell proliferation and calcification

in combination with an effective amount of Atorvastatin which inhibits cell attachment by decreasing inflammation;

implanting said bioprosthetic valve into said vessel by surgically removing a natural valve and replacing said natural valve with said bioprosthesis or placing said bioprosthesis over said natural valve having valve leaflets thereby compressing said natural valve leaflets against the vessel wall;

eluting the said combination of therapeutic agents from said elastical stent, bioprosthetic valve or both; and

causing the inhibition of stenosis, obstruction, or calcification of the bioprosthesis or the natural valve or both following implantation of the bioprosthetic valve.

2. The method according to clause 1, wherein any one of the anti-restenotic agents for use with the stents, gortex grafts and bioprosthesis including: Anti-proliferative and anti-calcific agents including Sirolimus(and analog), Paclitaxel, Taxane, Dexamethasone, M-Prednisolone, Interferon gamma-1b, Leflunomide, Tacrolimus, Mycophenolic acid, Mizoribine, Cyclosporin, Tanilast, Biorest, Anti-proliferative Agents, Sirolimus(and analogs), Paclitaxol, Taxane, Actinomycin D, Methotrexate, Angiopeptin, Vincristine, Mitomycin, C Myc antisense, RestenASE, 2-Chloro-deoxyadenosine, PCNA ribozyme: Smooth Muscle Cell migration inhibitors, extracellular matrix modulators, Batimastat, Prolyl hydroxylase inhibitors, Halofuginone, C-proteinase inhibitors, Probucol, and a Mapkinase inhibitor MEK(5.0-10ug/ml), (Drug dosing for current drugs on the stents that are on the US market Sirolimus 140mcg/cm², Paclitaxel dosing 1 mcg/mm², Everolimus doing 100 mcg/cm², Zotarolimus 10 mcg/ 1 mm stent length, Biolimus 15.6 mcg/mm²) in combination with an effective amount of Atorvastatin is 80 mg.

3. The method according to clause 1, further comprising implanting said bioprosthetic valve by catheterization.

4. The method according to clause 1, wherein the bioprosthetic valve is an aortic bioprosthetic valve.

5. The method according to clause 1, wherein the bioprosthetic valve is a bioprosthetic mitral valve.
6. The method according to clause 1, wherein the bioprosthetic valve is a bioprosthetic pulmonic valve.
7. The method according to clause 1, wherein the bioprosthetic valve is bioprosthetic tricuspid valve.
8. The method according to clause 1, wherein the bioprosthetic valve comprises one or more cusps of biological origin.
9. The method according to clause 8, wherein the one or more cusps is porcine, bovine, or human.
10. The method according to clause 8, further comprising introducing a nucleic acid encoating a nitric oxide synthase into the one or more cusps.
11. The method according the clause 8, further comprising introducing a drug eluting treating encoating the one or more cusps on both sides with an anti-proliferative and anti-calcification treatment.
12. The method according to clause 1, wherein the elastical stent is substantially cylindrical.
13. The method according to clause 12, wherein the diameter of the elastical stent is about 15 mm to about 42 mm.
14. A valve prosthesis comprising:
 - an elastical stent;
 - a gortex graft;
 - a bioprosthetic valve having leaflets operably coupled to said elastical stent;

an effective amount of Atorvastatin in combination with wherein any one of the anti-restenotic agents for use with the stents, gortex grafts and bioprosthesis including Anti-proliferative and anti-calcific agents including Sirolimus(and

analog), Paclitaxel, Taxane, Dexamethasone, M-Prednisolone, Interferon gamma-1b, Leflunomide, Tacrolimus, Mycophenolic acid, Mizoribine, Cyclosporin, Tanilast, Biorest, Anti-proliferative Agents, Sirolimus(and analogs), Paclitaxol, Taxane, Actinomycin D, Methotrexate, Angiopeptin, Vincristine, Mitomycin, C Myc antisense, RestenASE, 2-Chloro-deoxyadenosine, PCNA ribozyme: Smooth Muscle Cell migration inhibitors, extracellular matrix modulators, Batimastat, Prolyl hydroxylase inhibitors, Halofuginone, C-proteinase inhibitors, Probucol, and a Mapkinase inhibitor MEK, in combination with atorvastatin deposited on the elastical stent, gortex graft, bioprosthetic valve on sides of the leaflets or both, said effective amount structured to elute from said elastical stent, gortex grafts, bioprosthetic valve leaflets or both;

wherein said bioprosthetic valve is structured to be implanted in vessel having a vessel wall to replace a natural diseased valve;

said bioprosthetic valve structured to inhibit stenosis, obstruction, or calcification of the bioprosthetic valve and natural valve following implantation of the bioprosthetic valve prosthesis.

15. The bioprosthetic valve of clause 14 wherein said bioprosthetic valve is coupled to a surgical sewing ring.

16. The bioprosthetic valve of clause 14, wherein the therapeutic agent is selected from paclitaxel, sirolimus, biolimus, everolimus, zotarolimus and combinations of the foregoing including wherein any one of the anti-restenotic agents for use with the stents, gortex grafts and bioprostheses including: Anti-proliferative and anti-calcific agents including Sirolimus(and analog), Paclitaxel, Taxane, Dexamethasone, M-Prednisolone, Interferon gamma-1b, Leflunomide, Tacrolimus, Mycophenolic acid, Mizoribine, Cyclosporin, Tanilast, Biorest, Anti-proliferative Agents, Sirolimus(and analogs), Paclitaxol, Taxane, Actinomycin D, Methotrexate, Angiopeptin, Vincristine, Mitomycin, C Myc antisense, RestenASE, 2-Chloro-deoxyadenosine, PCNA ribozyme: Smooth Muscle Cell migration inhibitors, extracellular matrix modulators, Batimastat, Prolyl hydroxylase inhibitors, Halofuginone, C-proteinase inhibitors, Probucol, and a Mapkinase inhibitor MEK will be used in combination with an effective dose of Atorvastatin.

17. The bioprosthetic valve of clause 14, said valve sized and constructed to be implanted by catheterization in a coronary valve of the patient.
18. The bioprosthetic valve of clause 14, wherein the valve is an aortic valve.
19. The bioprosthetic valve of clause 14, wherein the bioprosthetic valve comprises one or more cusps of biological origin.
20. The bioprosthetic valve of clause 19, wherein the one or more cusps are porcine, bovine, or human.
21. The bioprosthetic valve of clause 19 further comprising a nucleic acid encoating a nitric oxide synthases into one or more of the cusps.
22. The elastical stent of clause 14 sized, constructed and arranged in a substantially cylindrical configuration.
23. The valve prosthesis of clause 14 wherein a diameter of the elastical stent is about 15 mm to about 42 mm.
24. The method of clause 1 wherein the elastical stent has a surface constructed and arranged to reduce neointimal proliferation.
25. The valve prosthesis of clause 14 wherein the elastical stent has a surface constructed and arranged to reduce neointimal proliferation.
26. The method of clause 1 wherein the bioprosthetic valve has a surface constructed and wherein any one of the anti-restenotic agents for use with the stents, gortex grafts and bioprosthesis including: Anti-proliferative and anti-calcific agents including Sirolimus(and analog), Paclitaxel, Taxane, Dexamethasone, M-Prednisolone, Interferon gamma-1b, Leflunomide, Tacrolimus, Mycophenolic acid, Mizoribine, Cyclosporin, Tanilast, Biorest, Anti-proliferative Agents, Sirolmus(and analogs), Paclitaxol, Taxane, Actinomycin D, Methotrexate, Angiopeptin, Vincristine, Mitomycin, C Myc antisense, RestenASE, 2-Chloro-deoxyadenosine, PCNA ribozyme: Smooth Muscle Cell migration inhibitors, extracellular matrix modulators, Batimastat, Prolyl hydroxylase inhibitors, Halofuginone, C-proteinase inhibitors, Probucol, and a

Mapkinase inhibitor MEK(5.0-10ug/ml), (Drug dosing for current drugs on the stents that are on the US market Sirolimus 140mcg/cm², Paclitaxel dosing 1 mcg/mm², Everolimus doing 100 mcg/cm², Zotarolimus 10 mcg/ 1 mm stent length, Biolimus 15.6 mcg/mm²) in combination with an, in combination with an effective amount is 80 mg of Atorvastatin to improve the efficacy of the inhibition of calcification and the improvement of the longevity of the prosthetic material including the stent, the valve, and the gortex covering.

28. The bioprosthetic valve of clause 14, said valve is sized constructed and arranged to be implanted by catheterization in a coronary valve of the patient.

29. The bioprosthetic valve of clause 14, wherein the valve is an aortic valve.

30. The bioprosthetic valve of clause 14, wherein the bioprosthetic valve comprises one or more cusps of biological origin.

31. The bioprosthetic valve of clause 30, wherein the one or more cusps are porcine, bovine, or human.

32. The bioprosthetic valve of clause 14 and further comprising a nucleic acid encoating a nitric oxide synthases into one or more of the cusps.

33. The method of clause 1 further comprising providing a sewing ring operably coupled to said bioprosthetic valve, said sewing ring having a surface constructed and arranged to reduce neointimal proliferation.

34. The valve prosthesis of clause 14 further comprising a sewing ring operably coupled to said bioprosthetic valve, said sewing ring having a surface constructed and arranged to reduce neointimal proliferation and pannus formation.

35. The valve prosthesis of clause 14 wherein said bioprosthetic valve includes a Gortex graft upon which a portion of said of wherein any one of the anti-restenotic agents for use with the stents, gortex grafts and bioprosthesis including: Anti-proliferative and anti-calcific agents including Sirolimus(and analog), Paclitaxel, Taxane, Dexamethasone, M-Prednisolone, Interferon gamma-1b, Leflunomide, Tacrolimus, Mycophenolic acid, Mizoribine, Cyclosporin, Tanilast, Biorest, Anti-proliferative Agents, Sirolmus(and analogs), Paclitaxol, Taxane, Actinomycin D,

Methotrexate, Angiopeptin, Vincristine, Mitomycin, C Myc antisense, RestenASE, 2-Chloro-deoxyadenosine, PCNA ribozyme: Smooth Muscle Cell migration inhibitors, extracellular matrix modulators, Batimastat, Prolyl hydroxylase inhibitors, Halofuginone, C-proteinase inhibitors, Probucol, and a Mapkinase inhibitor MEK, in combination with an effective amount of Atorvastatin is deposited to improve the efficacy of the inhibition of calcification and the improvement of the longevity of the prosthetic material including the stent, the valve, and the gortex covering.

36. The valve prosthesis of clause 35 wherein said effective amount of Atorvastatin reduces pannus formation along a graft surface.

37. The method of clause 1 further comprising administering an oral amount of 80 mg Atorvastatin 80 mg a day and reducing stem cell attachment to the stent, the gortex graft and the valve.

38. The dosing range for the anti-proliferative agent (MAPKinase inhibitor) MEK inhibitor is 5 to 10 ug/ml which inhibited the mesenchymal interstitial valve cell proliferation induced by the PDGF concentration of 10 ug/ml. as per Figure 16.

39. The method of clause 37 further comprising administering aspirin 80 mg/day and an oral P2Y12 inhibitors selected from Clopidogrel 75 mg/day with a loading dose of 300 mg/day at the time of intervention, Prasugrel 60 mg/day and 10 mg/day for maintenance, and Ticagrelor 180 mg/day loading dose and 90 mg two times per day for maintenance.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] The following detailed description, given by way of example, but not intended to limit the invention solely to the specific embodiments described, may best be understood in conjunction with the accompanying drawings.

[0014] Figure 1 of the drawings is a front perspective view of a bioprosthetic aortic valve showing leaflet 16 and stent 10.

[0015] Figure 2 of the drawings is a front perspective view of another type of aortic valve showing the leaflets 26 and stent 28.

[0016] Figure 3 of the drawings is a front schematic view showing an aorta with the aortic valve of Figure 1 inserted therein at the time of initial implantation before any disease can develop in the aorta from the stent.

[0017] Figure 4 of the drawings is a front cut-away view of an aorta 32 showing the aortic valve of Figure 2 inserted therein at the time of initial implantation before any disease can develop in the aorta 32 from the stent 28.

[0018] Figure 5 of the drawings is a schematic view showing an aorta having the aortic valve of Figure 1 therein, in which the aorta surrounding the stent has been partially blocked by stenosis secondary to vascular smooth muscle cell proliferation and differentiation to bone forming cells after injury from the stent adjacent to the aorta, and c-kit stem cell proliferation and differentiation to bone formation cells secondary to inflammation and homing of c-kit stem cells to become bone forming cells.

[0019] Figure 6 of the drawings is a front cut-away view of an aorta showing the aorta surrounding the stent of Figure 2 partially blocked by stenosis secondary to vascular smooth muscle cell proliferation and differentiation to bone forming cells after injury from the stent adjacent to the aorta, and c-kit stem cell proliferation and differentiation to bone formation cells secondary to inflammation and homing of c-kit stem cells to become bone forming cells.

[0020] Figure 7 of the drawings is a top view of the mesh utilized in the stented aortic valve of Figure 2 of the drawings.

[0021] Figure 8 of the drawings is a top view showing the mesh of Figure 7 coated with an anti-proliferative coating to prevent stenosis in the stent surrounding the aorta to prevent the smooth muscle cell proliferation and calcification in the aorta, this is the treatment and the invention for this type of stent.

[0022] Figure 9 of the drawings is a photograph of insertion of the Portico™ valve prosthesis into the aortic artery of the patient using a catheter.

[0023] Figure 10 is a photograph showing a Portico™ transcatheter heart valve and an 18-F delivery catheter for insertion of the heart valve into the aorta.

[0024] Figure 11 is a drawing showing the treatment of the valve leaflet of Figure 1 with an anti-proliferative coating along the stent 10 and the valve leaflet 16.

[0025] Figure 12 is a drawing showing the treatment of the valve leaflet of Figure 2 with an anti-proliferative coating along the stent and the valve leaflet.

[0026] Figure 13 depicts pannus formation and calcification in the explanted valves from human patients at the time of surgical valve replacement of a failed bioprosthetic heart valve secondary to proliferating mesenchymal stem cells attaching to the valve and stent which calcifies and causes valve leaflet and stent destruction.

[0027] Figure 14 is a graph, which demonstrates the RNA expression of the ckit positive stem cell attachment to the calcified heart valve.

[0028] Figure 15 depicts the results of testing the anti-inflammatory drug atorvastatin at 80 mg per day.

[0029] Figure 16 depicts the results of the testing of the growth factor PDGF causing cell proliferation and the MEK inhibitor to block the cell proliferation.

[0030] Figure 17 depicts the two mechanisms for the two different agents which combined will have improved efficacy to inhibit the mesenchymal cell attachment and will inhibit mesenchymal cell proliferation and calcification to improve the stents, gortex grafts and valves to improve the longevity of these prosthesis by targeting the inflammation activated when introducing a foreign prosthesis into the human body.

DETAILED DESCRIPTION OF THE INVENTION

[0031] The invention provides a method for inhibiting stenosis, obstruction, or calcification of a stented aorta and valve leaflet or bioprosthesis with or without a

sewing ring, following implantation of a valve prosthesis in a patient in need thereof, which may comprise: disposing a coating composition on an elastical stent, gortex covering, and the bioprosthesis, wherein the coating composition may comprise one or more therapeutic agents to improve the efficacy of the inhibition of calcification and the improvement of the longevity of the prosthetic material including the stent, the valve, and the gortex covering.

[0032] ; securing a bioprosthetic collapsible elastical valve which is mounted on the elastical stent at a desired position in the patient such that the elastical stent is in contact with a natural valve that may or may not have been surgically removed, and optionally disposing a coating composition on both sides of the valve leaflets, the stent or a sewing ring to which the bioprosthetic valve is secured thereby inhibiting stenosis, obstruction, or calcification of the stented aorta following implantation of the stented valve prosthesis in a patient in need thereof or the surgical replacement of a bioprosthesis that replaces a native valve.

[0033] As used herein, the term "stenosis" may refer to the narrowing of a heart valve that could block or obstruct blood flow from the heart and cause a back-up of flow and pressure in the heart. Valve stenosis may result from various causes, including, but not limited to, scarring due to disease, such as rheumatic fever; progressive calcification; progressive wear and tear; among others. This is important not for the stented treatment but for the valve- is this flowing well with the rest of the patent.

[0034] As used herein, the term "valve" may refer to any of the four main heart valves that prevent the backflow of blood during the rhythmic contractions. The four main heart valves are the tricuspid, pulmonary, mitral, and aortic valves. The tricuspid valve separates the right atrium and right ventricle, the pulmonary valve separates the right atrium and pulmonary artery, the mitral valve separates the left atrium and left ventricle, and the aortic valve separates the left ventricle and aorta.

[0035] In an embodiment of the method, the bioprosthetic valve and the diseased valve may be an aortic valve, pulmonary valve, tricuspid valve, or mitral valve.

[0036] As used herein, the term "valve prosthesis" may refer to a device used to replace or supplement a heart valve that is defective, malfunctioning, or missing.

Examples of valve prostheses include, but are not limited to, bioprostheses; mechanical prostheses, and the like including, ATS 3fs® Aortic Bioprosthesis, Carpentier-Edwards PERIMOUNT Magna Ease Aortic Heart Valve, Carpentier-Edwards PERIMOUNT Magna Aortic Heart Valve, Carpentier-Edwards PERIMOUNT Magna Mitral Heart Valve, Carpentier-Edwards PERIMOUNT Aortic Heart Valve, Carpentier-Edwards PERIMOUNT Plus Mitral Heart Valve, Carpentier-Edwards PERIMOUNT Theon Aortic Heart Valve, Carpentier-Edwards PERIMOUNT Theon Mitral Replacement System, Carpentier-Edwards Aortic Porcine Bioprosthesis, Carpentier-Edwards Duraflex Low Pressure Porcine Mitral Bioprosthesis, Carpentier-Edwards Duraflex mitral bioprosthesis (porcine), Carpentier-Edwards Mitral Porcine Bioprosthesis, Carpentier-Edwards S.A.V. Aortic Porcine Bioprosthesis, Edwards Prima Plus Stentless Bioprosthesis, Edwards Sapien Transcatheter Heart Valve, Medtronic, Freestyle® Aortic Root Bioprosthesis, Hancock® II Stented Bioprosthesis, Hancock II Ultra® Bioprosthesis, Mosaic® Bioprosthetic, Mosaic Ultra® Bioprosthesis, St. Jude Medical, Biocor®, Biocor™ Supra, Biocor® Pericardia, Biocor™ Stentless, Epic™, Epic Supra™, Toronto Stentless Porcine Valve (SPV®), Toronto SPV II®, Trifecta, Sorin Group, Mitroflow Aortic Pericardial Valve®, Cryolife, Cryolife aortic valve®, Cryolife pulmonic valve®, Cryolife-O'Brien stentless aortic xenograft valve®.

[0037] Generally, bioprostheses comprise a valve having one or more cusps and the valve is mounted on a frame or stent, both of which are typically elastical. As used herein, the term "elastical" means that the device is capable of flexing, collapsing, expanding, or a combination thereof. The cusps of the valve are generally made from tissue of mammals such as, without limitation, pigs (porcine), cows (bovine), horses, sheep, goats, monkeys, and humans.

[0038] According to the method of the present invention, the valve may be a collapsible elastical valve having one or more cusps and the collapsible elastical valve may be mounted on an elastical stent.

[0039] In an embodiment, the collapsible elastical valve may comprise one or more cusps of biological origin.

[0040] In another embodiment, the one or more cusps are porcine, bovine, or human.

[0041] Examples of bioprotheses may comprise a collapsible elastical valve having one or more cusps and the collapsible elastical valve is mounted on an elastical stent include, but are not limited to, the SAPIEN transcatheter heart valve manufactured Edwards Lifesciences, and the CoreValve® transcatheter heart valve manufactured by Medtronic and Portico-Melody by Medtronic.

[0042] The elastical stent portion of the valve prosthesis used in the present invention may be self-expandable or expandable by way of a balloon catheter. The elastical stent may comprise any biocompatible material known to those of ordinary skill in the art. Examples of biocompatible materials include, but are not limited to, ceramics; polymers; stainless steel; titanium; nickel-titanium alloy, such as Nitinol; tantalum; alloys containing cobalt, such as Elgiloy® and Phynox®; and the like.

[0043] According to the method of the present invention, a coating composition which may comprise one or more therapeutic agents in combination is disposed on the elastical stent portion of the valve prosthesis. The process of disposing the coating composition which may comprise one or more therapeutic agents in combination may be any process known in the art. The coating compositions with the combination drugs may be prepared by dissolving or suspending a polymer and therapeutic agent in a solvent. Suitable solvents that may be used to prepare the coating compositions include those that may dissolve or suspend the polymer and therapeutic agent in solution. Examples of suitable solvents include, but are not limited to, tetrahydrofuran, methylethylketone (MEK), chloroform, toluene, acetone, isooctane, 1,1,1, trichloroethane, dichloromethane, isopropanol, and mixtures thereof. However, solvents are not required in many cases.

[0044] The coating compositions may be applied by any method to the surface of the elastical stent portion of the valve prosthesis or bioprotheses and sewing ring, known by one skilled in the art. Suitable methods for applying the coating compositions to the surface of the elastical stent portion of the valve prosthesis include, but are not limited to, spray-coating, painting, rolling, electrostatic

deposition, ink jet coating, and a batch process such as air suspension, pan-coating or ultrasonic mist spraying, or a combination thereof.

[0045] After the coating composition has been applied, it may be cured. As used herein, "curing" may refer to the process of converting any polymeric material into the finished or useful state by the application of heat, vacuum, and/or chemical agents, which application induces physico-chemical changes. The applicable time and temperature for curing are determined by the particular polymer involved and particular therapeutic agent used as known by one skilled in the art. Also, after the elastical stent is coated, it may be sterilized by methods of sterilization as known in the art (see, e.g., Guidance for Industry and FDA Staff - Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems <http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm071863.htm> and U.S. Patent No. 7,998,404 entitled "Reduced temperature sterilization of stents."

[0046] As used herein, the term "therapeutic agent" may refer to biologically active materials. The therapeutic agents named herein include their analogues and derivatives. Suitable therapeutic agents include, but are not limited to, microtubule stabilizing agents, such as paclitaxel, its analogues, and its derivatives; macrolide antibiotic agents, such as sirolimus (rapamycin) its analogues, and its derivatives; or combinations thereof. Bioliums or Everolimus Biolimus (see "Transcatheter Aortic Valve Replacement with St. Jude Medical Portico Valve", Journal of American College of Cardiology, Vol. 60., No. 7, 2012:581-6, 6 pages, dated August 14, 2012, which is hereby incorporated by reference.) The elastical stent portion of the valve prosthesis may be made to provide a desired release profile of the therapeutic agent.

[0047] There are also several other anti-proliferative drugs under investigation in human clinical trials. In general, these are analogues of sirolimus. Like sirolimus, these block the action of mTOR. Medtronic has developed zotarolimus; unlike sirolimus and paclitaxel, this sirolimus analogue designed for use in stents with phosphorylcholine as a carrier. Their ZoMaxx stent is a zotarolimus-eluting, stainless steel and tantalum—based stent; a modified phosphorylcholine slowly

releases the zotarolimus. The Medtronic Endeavor stent, which is a cobalt alloy, also uses phosphorylcholine to carry the zotarolimus was approved for use in Europe in 2005 is now close to U.S. FDA approval.

[0048] http://en.wikipedia.org/wiki/Drug-eluting_stent discloses a listing of current FDA approved and investigational drugs undergoing testing for treatment of stents.

[0049] Clinical trials are currently examining two stents carrying everolimus, an analog of sirolimus. Guidant, which has the exclusive license to use everolimus in drug-eluting stents, is the manufacturer of both stents. The Guidant vascular business was subsequently sold to Abbott. The Champion stent uses a bioabsorbable polylactic acid carrier on a stainless steel stent. In contrast, its Xience stent uses a durable (non-bioabsorbable) polymer on a cobalt alloy stent.

[0050] One alternative to drug-eluting stents is a stent surface constructed and arranged to reduce the neointimal proliferation. One such is the Genous bioengineered stent.

[0051] In place of the stainless steel (and now cobalt chrome) currently used in stents, various biodegradable frameworks are under early phases of investigation. Since metal, as a foreign substance, provokes inflammation, scarring, and thrombosis (clotting), it is hoped that biodegradable or bioabsorbable stents may prevent some of these effects. A magnesium alloy—based stent has been tested in animals, though there is currently no carrier for drug elution. A promising biodegradable framework is made from poly-L-lactide, a polymer of a derivative of L-lactic acid. One of these stents, the Igaki-Tamai stent, has been studied in pigs; tranilast and paclitaxel have been used as eluted drugs. Again none of these have been used suggested or implied for use in the aorta.

[0052] According to the method of the present invention, the valve prosthesis may be secured at a desired position in the heart of a patient such that the elastical stent is in contact with the valve or the walls of the valve. The desired position of the valve prosthesis may be easily determined using methods known to those of ordinary skill in heart valve replacement echo imaging, CT imaging, and catheterization. In an embodiment, the valve prosthesis may be configured to be

implanted by way of cardiac catheterization echo imaging, CT imaging, and catheterization. Catheter delivery of the valve prosthesis may be accomplished using methods well known to those skilled in the art, such as mounting the elastical stent portion on an inflatable balloon disposed at the distal end of a delivery catheter and expanding the valve prosthesis at the desired position.

[0053] The elastical stent portion of the valve prosthesis may be any shape cylindrical (final shape is cylinder may be funnel shaped original all required to contact the valve or walls of the valve where, without being bound to theory, the therapeutic agents are released and absorbed by the valve or walls of the valve, or the aorta including aortic valve, mitral valve, tricuspid valve, vena cava valve.

[0054] In an embodiment, the elastical stent portion may be substantially cylindrical so as to be able to contact the valve or walls of the valve upon securing.

[0055] In another embodiment, the diameter of the elastical stent portion may be about 15 mm to about 42 mm.

[0056] According to an embodiment of the present invention, the method further may comprise introducing a nucleic acid encoding a nitric oxide synthase into the one or more cusps of the valve prosthesis. Methods for introducing a nucleic acid encoding a nitric oxide synthase into the one or more cusps are described in U.S. Patent No. 6,660,260, issued December 9, 2003, and is hereby incorporated by reference in its entirety.

[0057] Although the present invention and its advantages have been described in detail, it should be understood that various changes, substitutions and alterations can be made herein without departing from the spirit and scope of the invention as defined in the appended claims. There is no method of treatment in the stents in their current form to prevent the stenosis that can develop from the stent injury to the aorta. This is the invention as described in this application to prevent stenosis that can develop in the vascular aorta from these stented valve therapy or in the valve leaflets attached to the stented valve.

[0058] The present invention will be further illustrated in the following Examples which are given for illustration purposes only and are not intended to limit the invention in any way.

[0059] For coronary stents see "Effect of Biolimus-Eluting Stents with Biodegradable Polymer vs. Bare-Metal Stents on Cardiovascular Events Among Patients with Acute Myocardial Infarction, The COMFORTABLE AMI Randomized Trial", JAMA: The Journal of the American Medical Association, Vol. 308, No. 8, August 22/29, 2012 is hereby incorporated by reference.

DETAILED DESCRIPTION

[0060] As best seen in Figure 1 of the drawings, an elastical stent 10 having a coating 12 disposed thereon, said coating composition comprising one or more therapeutic agents. The method comprises the steps of disposing the coating composition 12 on the elastical stent 10. A valve prosthesis 14 is mounted on the elastical stent 10. The valve prosthesis 14 is a collapsible elastical valve 16 which is mounted on the elastical stent 10 at a desired position 18 in the patient. The stent and valve are positioned within a coronary valve artery the aorta. The elastical stent 10 is in contact with the valve 16. The coating composition 12 inhibits stenosis, obstruction or calcification of the valve prosthesis 16 along with implantation of the valve prosthesis 14 in the patient.

[0061] The therapeutic agent referred to above may be selected from the group comprising paclitaxel, sirolimus, biolimus, and everolimus. Implantation of the valve is preferably performed using a catheter, as shown in the attached article from the Journal of the of the American College of Cardiology, Vol. 60, No. 7, 2012, August 14, 2012; 581-6 Figure 9, Transcatheter Aortic Valve Replacement with the St Jude Medical Portico Valve which is hereby incorporated by reference. An aorta 20 is shown in Figure 3 of the drawings with, a valve prosthesis 14 inserted therein. In one or more alternative embodiments of the invention the collapsible elastical valve 16 may have one or more cusps 22 of biological origin. The cusp 22 may be porcine, bovine, or human as is commonly known in the art. In an additional alternative embodiment of the invention nucleic acid 24 encoding a nitric oxide synthase may be introduced into one or more of the cusps 22 to

inhibit stenosis, obstruction or calcification of the valve. In a preferred embodiment the elastical stent 10 is substantially cylindrical and is from approximately 18 millimeters to about 29 millimeters in length. Although prevention of stenosis, calcification and obstruction of other valves other than the aorta was previously known it was not expected that an anti-proliferative agent would be required because of the size of the aorta, which is bigger than coronary valves. The aorta is 2 centimeters in diameter whereas coronary arteries are 4 millimeters in diameter. Most stents such as that shown in Figures 1-8 are constructed of titanium so as to avoid thrombosis. It has been previously known to utilize statins for coronary valves to prevent stenosis, obstruction or calcification but not with aortic valves. The statin utilized is 80 milligrams of Lipitor a day.

[0062] In a preferred embodiment the coating 12 on elastic stent 10 is paclitaxel, which is a mitotic inhibitor, previously used in cancer chemotherapy. It previously was sold as dissolved in cremafor EL and etheynol as a delivery agent. A newer formulation has paclitaxel bound to albumin sold under the trademark Abraxane. It is known to use paclitaxel to prevent restenosis. Paclitaxel is used as an anti-proliferative agent for the prevention of restenosis (recurring narrowing) of coronary stents locally delivered to the wall of the coronary artery. A paclitaxel coating limits the growth of neointima (scar tissue) within stents. The article Paclitaxel footnote 39. Paclitaxel stent coating inhibits neointima hyperplasia at four weeks and a poor sign model of coronary restenosis PMID 11342479. "Paclitaxel", Wikipedia, the free encyclopedia, <http://en.wikipedia.org/wiki/Paclitaxel>, 10/4/2012 is hereby incorporated by reference. In an alternative embodiment biolimus, and equipotent sirolimus analog from biodegradable polylactic acid was not inferior and potentially better than sirolimus eluding stents in terms of major adverse clinical events, in a large clinical trial with follow-up of four years.

[0063] As noted above the elastical stent 10 shown in Figures 1-6 may comprise any biocompatible material known to those of ordinary skill in the art. Examples of bio compatible materials include but are not limited to ceramics; polymers; stainless steel, titanium; nickel-titanium alloy such as Nitinol; tantalum; alloys containing cobalt such as elgioloy and finox® and the like.

[0064] As best seen in Figure 8, according to the method of the present invention, a coating composition 12 which may comprise one or more therapeutic agents is disposed on the elastical stent 10 portion of the valve prosthesis 14. The process of disposing the coating composition 12, which may comprise one or more therapeutic agents, may be any process known in the art. The coating compositions 12 may be prepared by dissolving or suspending a polymer and therapeutic agent in a solvent. Suitable solvents that may be used to prepare the coating compositions 12 include those that may dissolve or suspend the polymer and therapeutic agent in solution. Examples of suitable solvents include, but are not limited to, tetrahydrofuran, methylethylketone (MEK), chloroform, toluene, acetone, isooctane, 1,1,1, trichloroethane, dichloromethane, isopropanol, and mixtures thereof.

[0065] The coating compositions 12 may be applied by any method to the surface of the elastical stent 10 portion of the valve prosthesis 14 known by one skilled in the art. Suitable methods for applying the coating compositions 12 to the surface of the elastical stent 10 portion of the valve prosthesis 14 include, but are not limited to, spray-coating, painting, rolling, electrostatic deposition, ink jet coating, and a batch process such as air suspension, pan-coating or ultrasonic mist spraying, or a combination thereof.

[0066] After the coating composition 12 has been applied, it may be cured. As used herein, "curing" may refer to the process of converting any polymeric material into the finished or useful state by the application of heat, vacuum, and/or chemical agents, which application induces physico-chemical changes. The applicable time and temperature for curing are determined by the particular polymer involved and particular therapeutic agent used as known by one skilled in the art. Also, after the elastical stent is coated, it may be sterilized by methods of sterilization as known in the art (see, e.g., Guidance for Industry and FDA Staff - Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems <http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm071863.htm> and US Patent No. 7,998,404 entitled "Reduced temperature sterilization of stents."

[0067] As used herein, the term "therapeutic agent" may refer to biologically active materials. The therapeutic agents named herein include their analogues and derivatives. Suitable therapeutic agents include, but are not limited to, microtubule stabilizing agents, such as paclitaxel, its analogues, and its derivatives; macrolide antibiotic agents, such as sirolimus (rapamycin) its analogues, and its derivatives; or combinations thereof Bioliums or Everolimus Biolimus (see "Transcatheter Aortic Valve Replacement with St. Jude Medical Portico Valve", Journal of American College of Cardiology, Vol. 60., No. 7, 2012:581-6, 6 pages, dated August 14, 2012 which is hereby incorporated by reference. The elastical stent portion of the valve prosthesis may be made to provide a desired release profile of the therapeutic agent.

[0068] Implantation of a Portico trans catheter heart valve may be seen in Figure 10, attached. In a preferred embodiment the heart valve 16 transverses the aortic arch 24. The trans catheter heart valve is flared in a left ventricular outflow tract 26. The trans catheter heart valve is in functional during positioning. The valve when open may be seen in Figure 1. Transcatheter aortic valve replacement with the St. Jude Medical Portico valve: first-in-human experience. Willson AB, Rodes-Cabau J, Wood DA, Leipsic J, Cheung A, Toggweiler S, Binder RK, Freeman M, DeLarochelliere R, Moss R, Nombela-Franco L, Dumont E, Szummer K, Fontana GP, Makkar R, Webb JG. J. Am Coll Cardiol. 2012 Aug 14;60(7):581-6. Epub 2012 May 30. Willson AB, Rodes-Cabau J, Wood DA, Leipsic J, Cheung A, Toggweiler S, Binder RK, Freeman M, DeLarochelliere R, Moss R, Nombela-Franco L, Dumont E, Szummer K, Fontana GP, Makkar R, Webb JG. J. Am Coll Cardiol. 2012 Aug 14;60(7):581-6. Epub 2012 May 30.

[0069] As seen in Figure 2 the Medtronic core valve 26 is disclosed within a coated stent 28. The Edwards LifeSciences Sapien Valve, New techniques for the treatment of valvular aortic stenosis—transcatheter aortic valve implantation with the SAPIEN heart valve. Thielmann M, Eggebrecht H, Wendt D, Kahlert P, Ideler B, Kottenberg-Assenmacher E, Erbel R, Jakob H. Minim Invasive Ther Allied Technol. 2009;18(3):131-4. Geometry and degree of apposition of the CoreValve ReValving system with multislice computed tomography after implantation in patients with aortic stenosis. Schultz CJ, Weustink A, Piazza N, Otten A, Mollet

N, Krestin G, van Geuns RJ, de Feyter P, Serruys PW, de Jaegere P. J Am Coll Cardiol. 2009 Sep 1;54(10):911-8.

[0070] As seen in Figure 3, an Edwards Sapien valve 30 is disclosed contained within an aorta 32, which is without disease. Similarly, in Figure 4, the Medtronic Core Valve 26 within stent 28 is positioned with aorta 32. Both in Figures 3 and 4 the aortas are shown without disease. As best seen in Figure 5 of the drawings aorta 32 has the Edwards Sapien valve 30, also numbered 16, is fixedly positioned within stent 10. However, in this case the stent and valve are not coated with the present invention's anti proliferative agent. Accordingly, stenosis, obstruction and calcification have occurred. Similarly, in Figure 6, the Medtronic core valve 26 positioned within stent 28 is contained within aorta 32. Again, without the anti-proliferative agents of the present invention stenosis, obstruction, and calcification have occurred. The leaflets or cusps 22 shown in Figures 1-6 may be constructed of tissue from mammal. The stents may be constructed also of biodegradable polymers providing controlled drug release or alternatively biological leaflets can be porcine or human cells. Alternatively, any non murine species having heart valve tissue including, without limitation, mammals such as pigs, cows, horses, sheep, goats, monkeys, and humans can be utilized for the leaflets. U.S. Patent No. 6,660,260 which describes such heart valve cells is hereby incorporated by reference.

[0071] As seen in Figures 7 and 8, a stent 10 is disclosed without any coating 12 thereon. In Figure 8, the same stent 10 is shown having a coating 12 thereon which is an anti-proliferative agent such as paclitaxel, sirolimus, everolimus or biolimus.

[0072] Figure 11 and Figure 12 are the treated valves and stents is shown having a coating 12 thereon which is an anti-proliferative agent such as paclitaxel, sirolimus, everolimus or biolimus.

[0073] The inventor has found that a particular regime of dosing is effective for any prosthetic heart valve and for the vasculature which contains a gortex graft covering by applying the anti-proliferative drug to any device that is covered with gortex as part of the anti-proliferative therapy to reduce pannus formation around

the gortex. These include Gore-Tex Vascular Grafts by Gore Medical, Gore-Tex Stretch Vascular Grafts, Gore Propaten Vascular Graft, Annuloplasty Rings manufactured by St. Jude, Medtronic and Edwards Lifesciences which contain the gortex covering and any type of gortex including gor-tex with expanded polytetrafluorethylene surgical material.

[0074] Figure 13 depicts the pannus formation and calcification process in the explanted valves from human patients at the time of surgical valve replacement of a failed bioprosthetic heart valve. Control bioprosthetic valve versus explanted bioprosthetic valve from humans. Panel (a1) Ventricular surface of the control valve, (a2) ventricular surface of the diseased valve with the pannus and calcification process via a stem call attachment to the heart valve. Figure 14 is a graph which demonstrates the RNA expression of the ckit positive mesenchymal stem cell attachment to the calcified heart valve, causing the calcification process to occur on the valve as expressed by the well known bone transcription factor cbfa1(core binding factor a1) and opn(osteopontin) and extracellular matrix protein. The results are expressed as a percent of control with the control being 0 for all of these markers. GAPDH is a house keeping gene used as a control for the experiment.

[0075] The dosing for any one of the anti-restenotic agents for use with the stents, gortex grafts and bioprosthesis including: Anti-proliferative and anti-calcific agents including Sirolimus(and analog), Paclitaxel, Taxane, Dexamethasone, M-Prednisolone, Interferon gamma-1b, Leflunomide, Tacrolimus, Mycophenolic acid, Mizoribine, Cyclosporin, Tanilast, Biorest, Anti-proliferative Agents, Sirolimus(and analogs), Paclitaxol, Taxane, Actinomycin D, Methotrexate, Angiopeptin, Vincristine, Mitomycin, C Myc antisense, RestenASE, 2-Chlorodeoxyadenosine, PCNA ribozyme: Smooth Muscle Cell migration inhibitors, extracellular matrix modulators, Batimastat, Prolyl hydroxylase inhibitors, Halofuginone, C-proteinase inhibitors, Probucol, and a Mapkinase inhibitor MEK(5.0-10ug/ml), (Drug dosing for current drugs on the stents that are on the US market Sirolimus 140mcg/cm², Paclitaxel dosing 1 mcg/mm², Everolimus doing 100 mcg/cm², Zotarolimus 10 mcg/ 1 mm stent length, Biolimus 15.6 mcg/mm²) in combination with an, in combination with an effective amount is 80

mg of Atorvastatin to improve the efficacy of the inhibition of calcification and the improvement of the longevity of the prosthetic material including the stent, the valve, and the gortex covering.

[0076] An experimental animal was developed to test for the dosing of the atorvastatin to reduce the inflammation and also the pannus formation on the valve leaflet. The experimental procedure is as follows, Male New Zealand white rabbits weighing 2.5-3.0 kg were assigned to a control (N=10) or 0.5% cholesterol-fed group (N=10) or to a cholesterol-fed and atorvastatin group (N=10). All animals were fed ad libitum for 12 weeks. Control rabbits were fed a standard diet. Cholesterol-fed animals received a diet supplemented with 0.5% (w/w) cholesterol (Purina Mills, Woodmont, IN), and the cholesterol-fed and atorvastatin group were given atorvastatin 3.0 mg/kg daily orally for the statin treatment arm¹. Prior to the initiation of the diet the rabbits underwent surgical implantation of bovine pericardial bioprosthetic valve tissue (Perimount, Edwards, Irvine CA) using intramuscular ketamine /xylazine (40/5 mg/kg). Following this 12-week period, the rabbits were anesthetized using intramuscular ketamine/xylazine (40/5 mg/kg) and then underwent euthanasia with intracardiac administration of 1 ml of Beuthanasia. Immediately after removal from the subcutaneous implantation site the bioprosthetic valves were fixed in 4% buffered formalin for 24 hours and then embedded in paraffin. Paraffin embedded sections (6µm) were cut and stained with Masson Trichrome stain for histopathologic exam.

[0077] Figure 15 depicts the results of testing the anti-inflammatory drug atorvastatin at 80 mg per day equivalent to human dosing and shows the percent reduction of stem cell RNA expression on the valves treated with Atorvastatin and the reduction of stem cell mediated pannus formation.

[0078] Figure 15 demonstrates the RNA gene expression for the control, cholesterol and cholesterol plus atorvastatin experimental assays. There was an increase in the Sox9, osteoblast transcription factor, Cyclin, and cKit in the leaflets of the cholesterol-fed animals as compared to the control and atorvastatin groups ($p<0.05$). Table 1, is the RTPCR data from the experimental model. The serum cholesterol levels were significantly higher in the cholesterol fed compared

to control assays ($1846.0 \pm 525.3 \text{ mg/dL}$ vs. $18.0 \pm 7 \text{ mg/dL}$, $p < 0.05$). Atorvastatin treated experimental arm manifested lower cholesterol levels than the cholesterol diet alone ($824.0 \pm 152.1 \text{ mg/dl}$, $p < 0.05$). There was an increase in hsCRP serum levels in the cholesterol fed compared to control assays (13.6 ± 19.7 vs. 0.24 ± 0.1 , $p < 0.05$), which was reduced by atorvastatin (7.8 ± 8.7 , $p < 0.05$). These assays were tested in a rabbit model of experimental hypercholesterolemia with and without atorvastatin at a dose equivalent to 80 mg a day for humans. Previous experiments were performed to test the lower dosing ranges at 20 mg a day and 40 mg a day of Atorvastatin and there was zero therapeutic benefit at the lower dosing ranges.

[0079] Figure 16 demonstrates an in vitro assay testing the role of a cell proliferation with a known growth factor platelet derived growth factor that stimulates interstitial cell valve proliferation and an inhibitor MEK(PD0325901). Mesenchymal valve cells were isolated from the cardiac aortic valves by collagenase digestion. Cells were cultured in medium 199 with 10% (v/v) heat-inactivated fetal bovine serum at 37C in a humidified atmosphere of 5% CO₂ in air. Cells were utilized between the 3rd and 7th passage. Mesenchymal cells were grown to confluence in 24-well plates and then growth-arrested by incubation in serum-free medium for 24 hours. The test materials were added to the wells and incubated for 18 hours. Test materials include PDGF at concentrations (10-40 ug/ml) PDGF Sigma in combination with a MEK inhibitor(PD0325901 Mek Inhibitor) (2.5-10ug/ml). The wells were pulsed for 4 hours with 1μCi/well of tritiated thymidine. Newly synthesized DNA will be then identified by incorporation of radioactivity into acid-precipitated cellular material. All samples were assayed in quadruplicate wells. The positive control wells were given PDGF (10 ug/ml) Sigma (St. Louis, MO), the negative control wells received serum-free medium. Figure 16, Panel A, is the results of the mesenchymal stem cells proliferating with the dose response treatment of platelet derived growth factor, Panel B, is the effect of the MEK inhibitor with a dosing range of (2.5 ug/ml to 10 ug/ml) with a inhibition effect at a dosing range of (5ug/ml to 10 ug/ml), Panel C, is the p42/44 protein expression by western blot demonstrating an increase in the p42/44 protein expression in the presence of PDGF indicating active cell proliferation and an inhibition of the p42/44 expression with the MEK inhibitor with a dose response effect with the higher doses of MEK.

[0080] Drug eluting stents may also incorporate a dual antiplatelet therapy to inhibit future thrombus formation including Aspirin 80 mg/ day and Oral P2Y12 Inhibitors: 1) Clopidogrel 75 mg/day with a loading dose of 300 mg/day at the time of intervention or 2) Prasugrel 60 mg/day then 10 mg/day for maintenance or 3) Ticagrelor 180 mg/day loading dose and 90 mg BID maintenance.

[0081] Mechanisms of action for the role of statin as anti-inflammatory agent and antiproliferative and anticalcific agent in combination will mediate the inhibition of calcification and stem cell attachment. Atorvastatin reduces the ckit stem cell from adhering to the valve to reduce further destruction of the valve by activating endothelial nitric oxide synthase in the valves in combination with the anti-proliferative agents. There was a 95% reduction in the myofibroblast proliferation and extracellular matrix production in the two models inhibiting calcification in these tissues.

WHAT IS CLAIMED IS:

1. A method for inhibiting stenosis, obstruction, or calcification of a bioprosthetic valve following implantation of said bioprosthetic valve in a vessel having a wall, said method comprising:

providing a bioprosthetic valve for surgical replacement of a natural diseased valve, said bioprosthetic value including an elastical stent;

providing a coating composition which is a combination of two agents on said elastical stent, bioprosthetic valve or both, wherein the coating composition comprises an effective amount of Atorvastatin at 80 mg dosing in combination with any one of the anti-restenotic agents for use with the stents, gortex grafts and bioprosthesis including: Anti-proliferative and anti-calcific agents including Sirolimus(and analog), Paclitaxel, Taxane, Dexamethasone, M-Prednisolone, Interferon gamma-1b, Leflunomide, Tacrolimus, Mycophenolic acid, Mizoribine, Cyclosporin, Tanilast, Biores, Anti-proliferative Agents, Sirolimus(and analogs), Paclitaxol, Taxane, Actinomycin D, Methotrexate, Angiopeptin, Vincristine, Mitomycin, C Myc antisense, RestenASE, 2-Chloro-deoxyadenosine, PCNA ribozyme: Smooth Muscle Cell migration inhibitors, extracellular matrix modulators, Batimastat, Prolyl hydroxylase inhibitors, Halofuginone, C-proteinase inhibitors, Probucol, and a Mapkinase inhibitor MEK(5.0-10ug/ml), (Drug dosing for current drugs on the stents that are on the US market Sirolimus 140mcg/cm², Paclitaxel dosing 1 mcg/mm², Everolimus doing 100 mcg/cm², Zotarolimus 10 mcg/ 1 mm stent length, Biolimus 15.6 mcg/mm²) and an effective dose of Atorvastatin 80 mg to improve the efficacy of the inhibition of calcification and the improvement of the longevity of the prosthetic material including the stent, the valve, and the gortex covering;

implanting said bioprosthetic valve into said vessel by surgically removing a natural valve and replacing said natural valve with said bioprosthesis or placing said bioprosthesis over said natural valve having valve leaflets thereby compressing said natural valve leaflets against the vessel wall;

eluting said therapeutic agents from said elastical stent, gortex graft, bioprosthetic valve or both; and

causing the inhibition of stenosis, obstruction, or calcification of the bioprosthesis or the natural valve or both following implantation of the bioprosthetic valve.

2. The method according to claim 1, wherein said effective amount of Atorvastatin is 80 mg in combination with an anti-proliferative agent including MEK Inhibitor and other agents .
3. The method according to claim 1, further comprising implanting said bioprosthetic valve by catheterization.
4. The method according to claim 1, wherein the bioprosthetic valve is an aortic bioprosthetic valve.
5. The method according to claim 1, wherein the bioprosthetic valve is a bioprosthetic mitral valve.
6. The method according to claim 1, wherein the bioprosthetic valve is a bioprosthetic pulmonic valve.
7. The method according to claim 1, wherein the bioprosthetic valve is bioprosthetic tricuspid valve.
8. The method according to claim 1, wherein the bioprosthetic valve comprises one or more cusps of biological origin.
9. The method according to claim 8, wherein the one or more cusps is porcine, bovine, or human.
10. The method according to claim 8, further comprising introducing a nucleic acid encoating a nitric oxide synthase into the one or more cusps.
11. The method according the claim 8, further comprising introducing a drug eluting treating encoating the one or more cusps on both sides with an anti-proliferative and anti-calcification treatment.
12. The method according to claim 1, wherein the elastical stent is substantially cylindrical.

13. The method according to claim 12, wherein the diameter of the elastical stent is about 15 mm to about 42 mm.

14. A valve prosthesis comprising:

an elastical stent;

a bioprosthetic valve having leaflets operably coupled to said elastical stent;

an effective amount of Atorvastatin in combination with wherein any one of the anti-restenotic agents for use with the stents, gortex grafts and bioprosthesis including: Anti-proliferative and anti-calcific agents including Sirolimus(and analog), Paclitaxel, Taxane, Dexamethasone, M-Prednisolone, Interferon gamma-1b, Leflunomide, Tacrolimus, Mycophenolic acid, Mizoribine, Cyclosporin, Tanilast, Biorest, Anti-proliferative Agents, Sirolimus(and analogs), Paclitaxol, Taxane, Actinomycin D, Methotrexate, Angiopeptin, Vincristine, Mitomycin, C Myc antisense, RestenASE, 2-Chloro-deoxyadenosine, PCNA ribozyme: Smooth Muscle Cell migration inhibitors, extracellular matrix modulators, Batimastat, Prolyl hydroxylase inhibitors, Halofuginone, C-proteinase inhibitors, Probucol, and a Mapkinase inhibitor MEK(5.0-10ug/ml), (Drug dosing for current drugs on the stents that are on the US market Sirolimus 140mcg/cm², Paclitaxel dosing 1 mcg/mm², Everolimus doing 100 mcg/cm², Zotarolimus 10 mcg/ 1 mm stent length, Biolimus 15.6 mcg/mm²) in combination with an equivalent Atorvastatin at 80 mg deposited on the elastical stent, bioprosthetic valve on sides of the leaflets or both, said effective amount structured to elute from said elastical stent, bioprosthetic valve leaflets or both to improve the efficacy of the inhibition of calcification and the improvement of the longevity of the prosthetic material including the stent, the valve, and the gortex covering;

wherein said bioprosthetic valve is structured to be implanted in vessel having a vessel wall to replace a natural diseased valve;

said bioprosthetic valve structured to inhibit stenosis, obstruction, or calcification of the bioprosthetic valve and natural valve following implantation of the bioprosthetic valve prosthesis.

15. The bioprosthetic valve of claim 14 wherein said bioprosthetic valve is coupled to a surgical sewing ring.

16. The bioprosthetic valve of claim 14, wherein the therapeutic agent is selected from wherein any one of the anti-restenotic agents for use with the stents, gortex grafts and bioprosthesis including: Anti-proliferative and anti-calcific agents including Sirolimus(and analog), Paclitaxel, Taxane, Dexamethasone, M-Prednisolone, Interferon gamma-1b, Leflunomide, Tacrolimus, Mycophenolic acid, Mizoribine, Cyclosporin, Tanilast, Biores, Anti-proliferative Agents, Sirolimus(and analogs), Paclitaxol, Taxane, Actinomycin D, Methotrexate, Angiopeptin, Vincristine, Mitomycin, C Myc antisense, RestenASE, 2-Chloro-deoxyadenosine, PCNA ribozyme: Smooth Muscle Cell migration inhibitors, extracellular matrix modulators, Batimastat, Prolyl hydroxylase inhibitors, Halofuginone, C-proteinase inhibitors, Probucol, and a Mapkinase inhibitor MEK(5.0-10ug/ml), (Drug dosing for current drugs on the stents that are on the US market Sirolimus 140mcg/cm², Paclitaxel dosing 1 mcg/mm², Everolimus doing 100 mcg/cm², Zotarolimus 10 mcg/ 1 mm stent length, Biolimus 15.6 mcg/mm²) in combination with a paclitaxel, sirolimus, biolimus, everolimus, zotarolimus and combinations of the foregoing with Atorvastatin at an effective dose of 80 mg to improve the efficacy of the inhibition of calcification and the improvement of the longevity of the prosthetic material including the stent, the valve, and the gortex covering.

17. The bioprosthetic valve of claim 14, said valve sized and constructed to be implanted by catheterization in a coronary valve of the patient.

18. The bioprosthetic valve of claim 14, wherein the valve is an aortic valve.

19. The bioprosthetic valve of claim 14, wherein the bioprosthetic valve comprises one or more cusps of biological origin.

20. The bioprosthetic valve of claim 19, wherein the one or more cusps are porcine, bovine, or human.

21. The bioprosthetic valve of claim 19 further comprising a nucleic acid encoating a nitric oxide synthases into one or more of the cusps.

22. The elastical stent of claim 14 sized, constructed and arranged in a substantially cylindrical configuration.
23. The valve prosthesis of claim 14 wherein a diameter of the elastical stent is about 15 mm to about 42 mm.
24. The method of claim 1 wherein the elastical stent has a surface constructed and arranged to reduce neointimal proliferation.
25. The valve prosthesis of claim 14 wherein the elastical stent has a surface constructed and arranged to reduce neointimal proliferation.
26. The method of claim 1 wherein the bioprosthetic valve has a surface constructed and arranged to reduce neointimal proliferation and calcification.
27. The valve prosthesis of claim 14, wherein said effective amount is 80 mg of Atorvastatin in combination with wherein any one of the anti-restenotic agents for use with the stents, gortex grafts and bioprosthesis including: Anti-proliferative and anti-calcific agents including Sirolimus(and analog), Paclitaxel, Taxane, Dexamethasone, M-Prednisolone, Interferon gamma-1b, Leflunomide, Tacrolimus, Mycophenolic acid, Mizoribine, Cyclosporin, Tanilast, Biorest, Anti-proliferative Agents, Sirolimus(and analogs), Paclitaxol, Taxane, Actinomycin D, Methotrexate, Angiopeptin, Vincristine, Mitomycin, C Myc antisense, RestenASE, 2-Chloro-deoxyadenosine, PCNA ribozyme: Smooth Muscle Cell migration inhibitors, extracellular matrix modulators, Batimastat, Prolyl hydroxylase inhibitors, Halofuginone, C-proteinase inhibitors, Probucol, and a Mapkinase inhibitor MEK(5.0-10ug/ml), (Drug dosing for current drugs on the stents that are on the US market Sirolimus 140mcg/cm², Paclitaxel dosing 1 mcg/mm², Everolimus doing 100 mcg/cm², Zotarolimus 10 mcg/ 1 mm stent length, Biolimus 15.6 mcg/mm²) in combination with an Atorvastatin 80 mg.
28. The bioprosthetic valve of claim 14, said valve is sized constructed and arranged to be implanted by catheterization in a valve of the patient.
29. The bioprosthetic valve of claim 14, wherein the valve is an aortic valve.

30. The bioprosthetic valve of claim 14, wherein the bioprosthetic valve comprises one or more cusps of biological origin.

31. The bioprosthetic valve of claim 30, wherein the one or more cusps are porcine, bovine, or human.

32. The bioprosthetic valve of claim 14 and further comprising a nucleic acid encoating a nitric oxide synthases into one or more of the cusps.

33. The method of claim 1 further comprising providing a sewing ring operably coupled to said bioprosthetic valve, said sewing ring having a surface constructed and arranged to reduce neointimal proliferation.

34. The valve prosthesis of claim 14 further comprising a sewing ring operably coupled to said bioprosthetic valve, said sewing ring having a surface constructed and arranged to reduce neointimal proliferation and pannus formation.

35. The valve prosthesis of claim 14 wherein said bioprosthetic valve includes a Gortex graft upon which a portion of said effective amount of Atorvastatin is deposited.

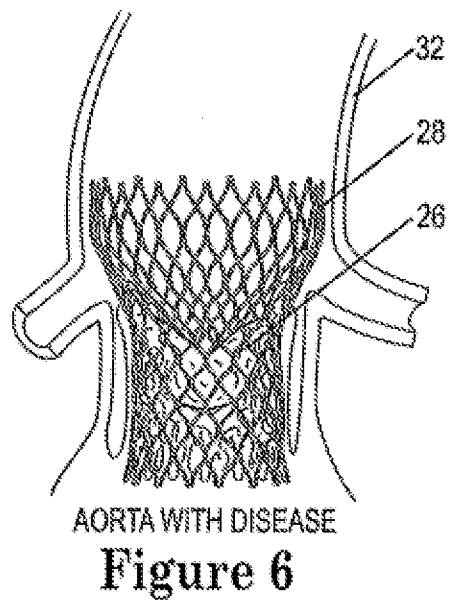
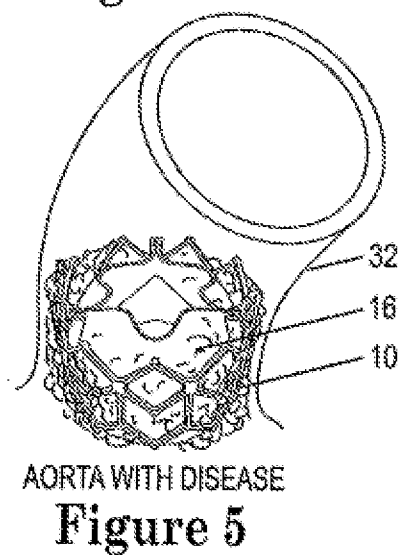
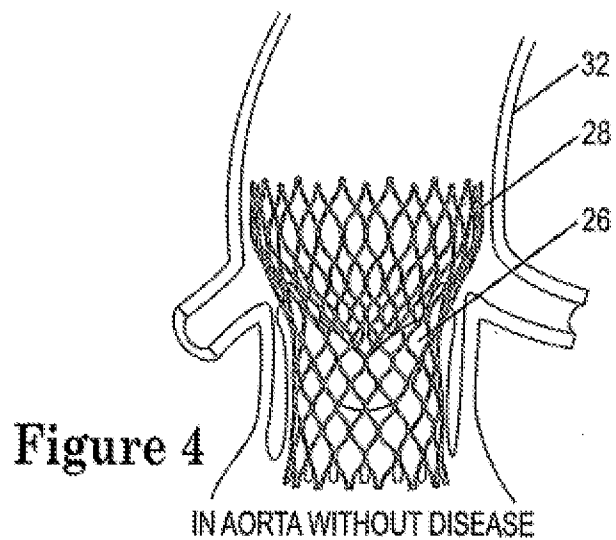
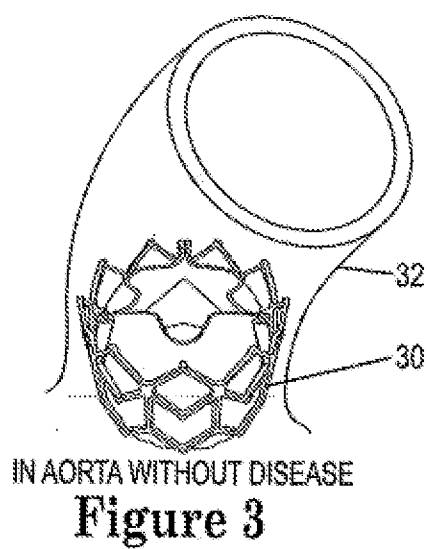
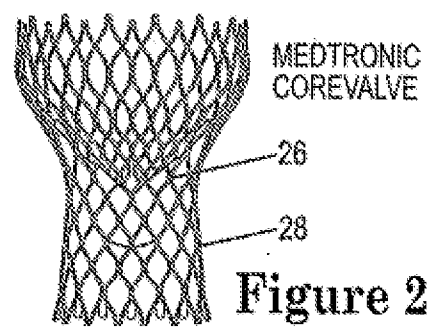
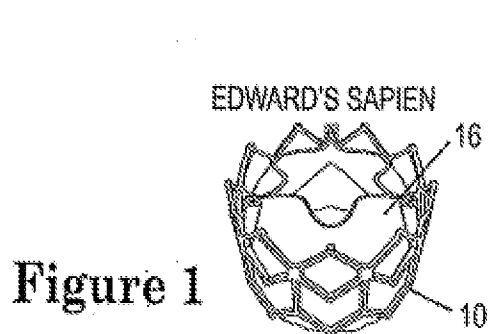
36. The valve prosthesis of claim 35 wherein said effective amount of Atorvastatin reduces pannus formation along a graft surface.

37. The method of claim 1 further comprising administering an oral amount of 80 mg Atorvastatin 80 mg a day and reducing stem cell attachment to the stent and the valve by inducing endothelial nitric oxide and inhibiting cell proliferation with the combination anti-proliferative agents wherein any one of the anti-restenotic agents for use with the stents, gortex grafts and bioprosthesis including: anti-proliferative and anti-calcific agents including Sirolimus(and analog), Paclitaxel, Taxane, Dexamethasone, M-Prednisolone, Interferon gamma-1b, Leflunomide, Tacrolimus, Mycophenolic acid, Mizoribine, Cyclosporin, Tanilast, Biorest, Anti-proliferative Agents, Sirolimus(and analogs), Paclitaxol, Taxane, Actinomycin D, Methotrexate, Angiopeptin, Vincristine, Mitomycin, C Myc antisense, RestenASE, 2-Chloro-deoxyadenosine, PCNA ribozyme: Smooth Muscle Cell migration inhibitors, extracellular matrix modulators, Batimastat,

Prolyl hydroxylase inhibitors, Halofuginone, C-proteinase inhibitors, Probucol, and a Mapkinase inhibitor MEK(5.0-10ug/ml), (Drug dosing for current drugs on the stents that are on the US market Sirolimus 140mcg/cm², Paclitaxel dosing 1 mcg/mm², Everolimus dosing 100 mcg/cm², Zotarolimus 10 mcg/ 1 mm stent length, Biolimus 15.6 mcg/mm²) in combination with an effective dose of Atorvastatin 80 mg.

38. The method of claim 37 further comprising administering aspirin 80 mg/ day and an oral P2Y₁₂ inhibitors selected from Clopidogrel 75 mg/day with a loading dose of 300 mg/day at the time of intervention, Prasugrel 60 mg/day and 10 mg/day for maintenance, and Ticagrelor 180 mg/day loading dose and 90 mg two times per day for maintenance.

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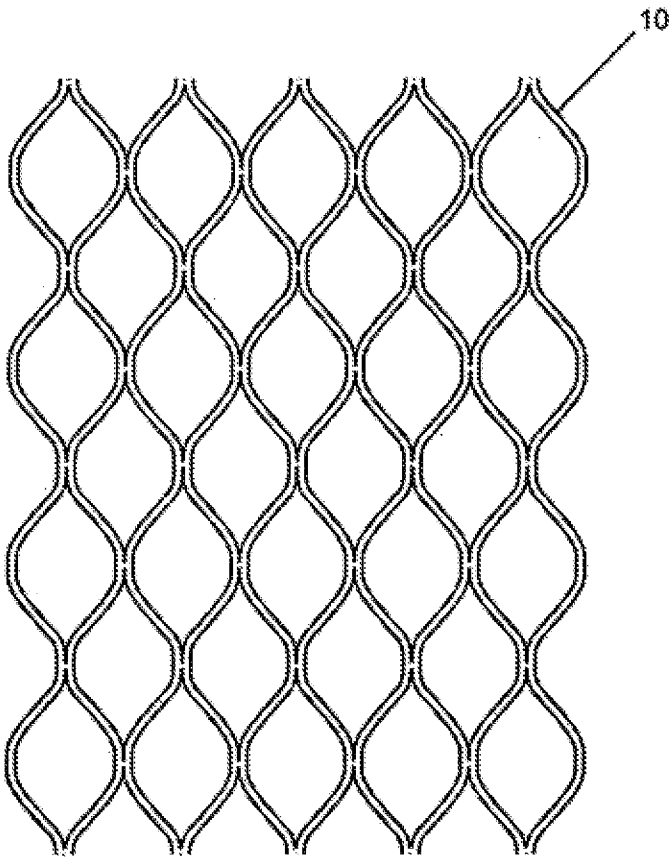


Figure 7

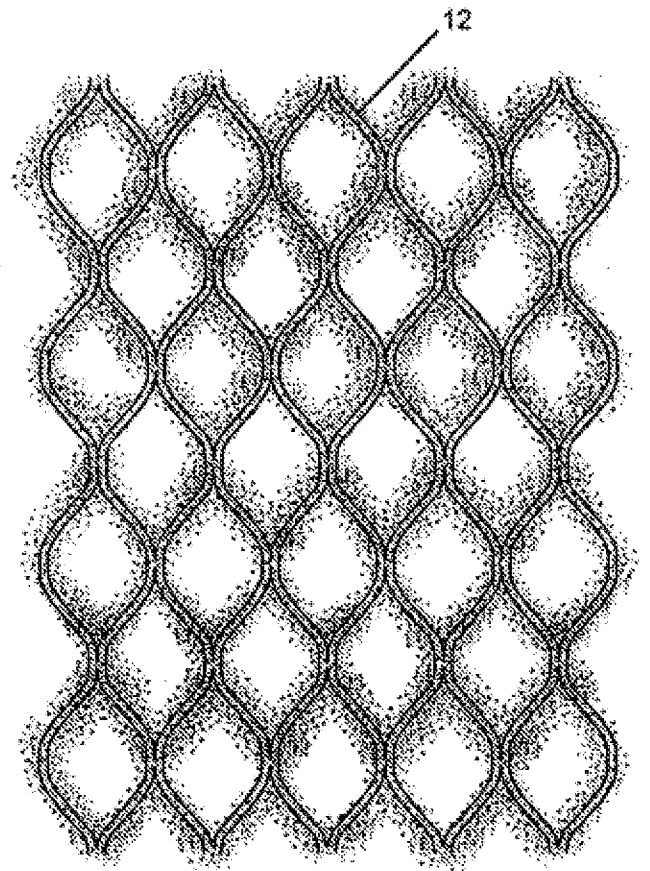


Figure 8

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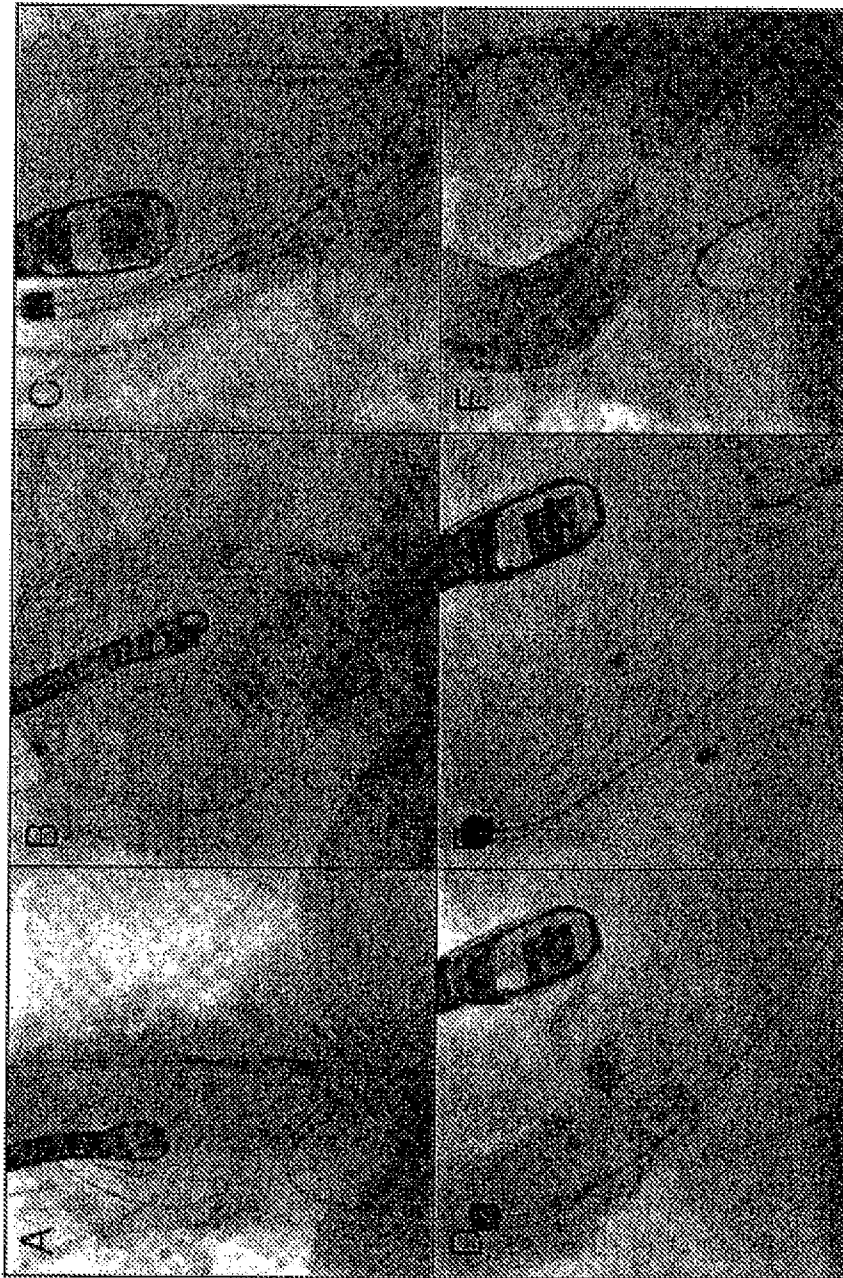


FIG. 2 | DELIVERY AND DEPLOYMENT OF PORTICO THV

(A) THE FULLY SHEATHED TRANSCATHETER HEART VALVE (THV). (B) TRANSVERSING THE AORTIC ARCH. (C) THE THV IS FLARED IN THE LEFT VENTRICULAR OUTFLOW TRACT. (D) THE THV IS FUNCTIONAL DURING POSITIONING. (E) RECAPTURE IS POSSIBLE IF REQUIRED. (F) POST-DEPLOYMENT ANGIOGRAPHY DEMONSTRATES A COMPETENT VALVE AND PATENT LEFT CORONARY ARTERY.

Figure 9

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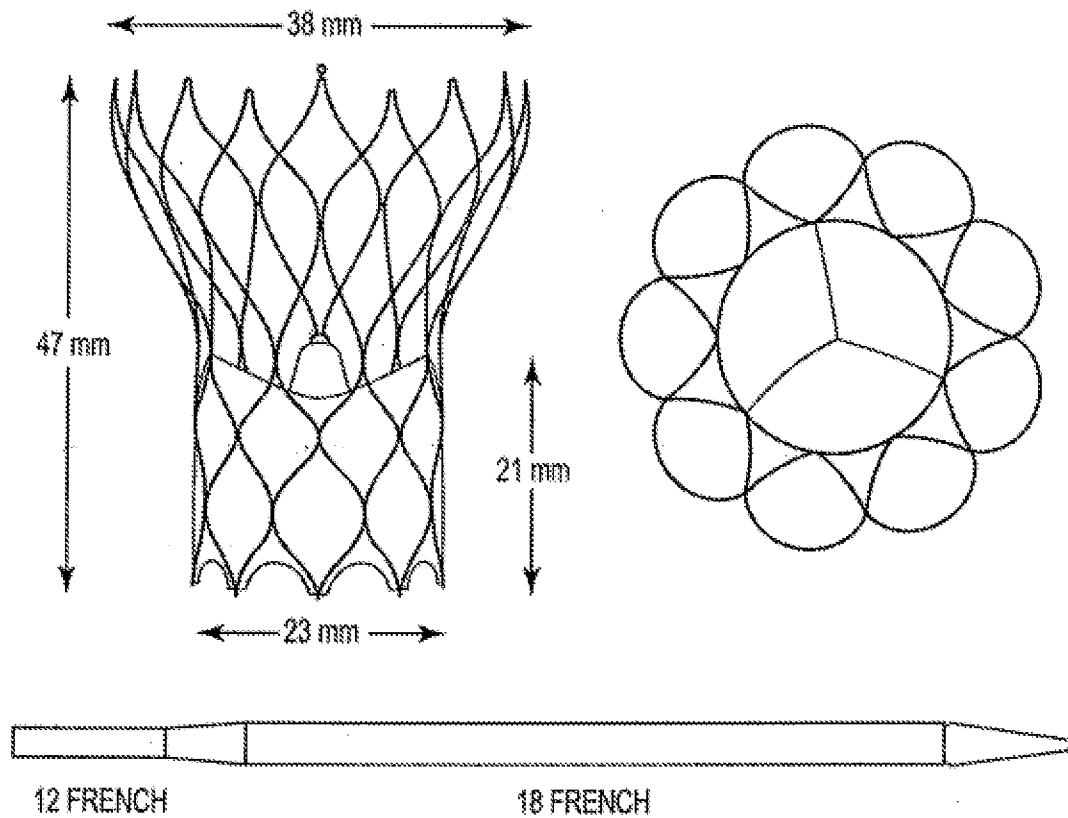


FIG. 1 | PORTICO | TRANSCATHETER HEART VALVE

THE 23-mm TRILEAFLET PORTICO TRANSCATHETER HEART VALVE CONSISTS OF A NITHINOL SELF-EXPANDABLE STENT AND BOVINE PERICARDIAL LEAFLETS, WITH AN 18-F DELIVERY CATHETER.

Figure 10

Edward's Sapien

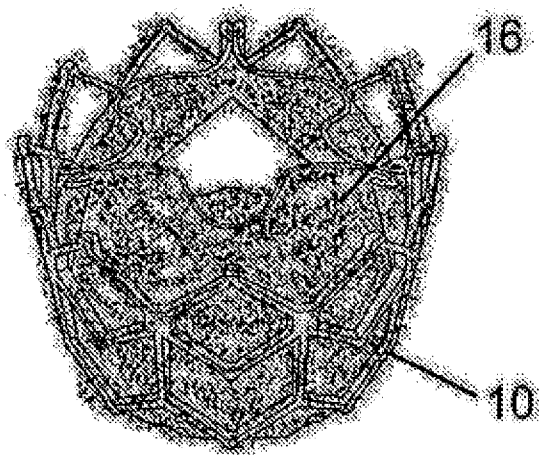


Figure 11

Medtronic Corevalve
and Corevalve Evolut

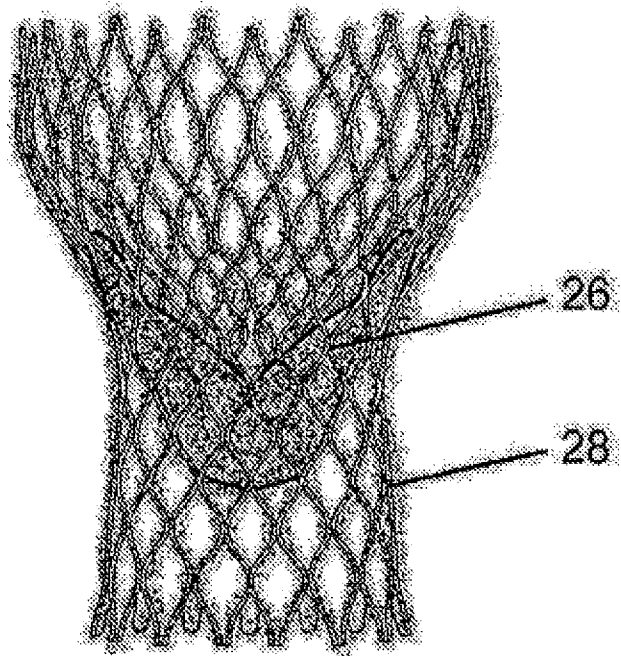
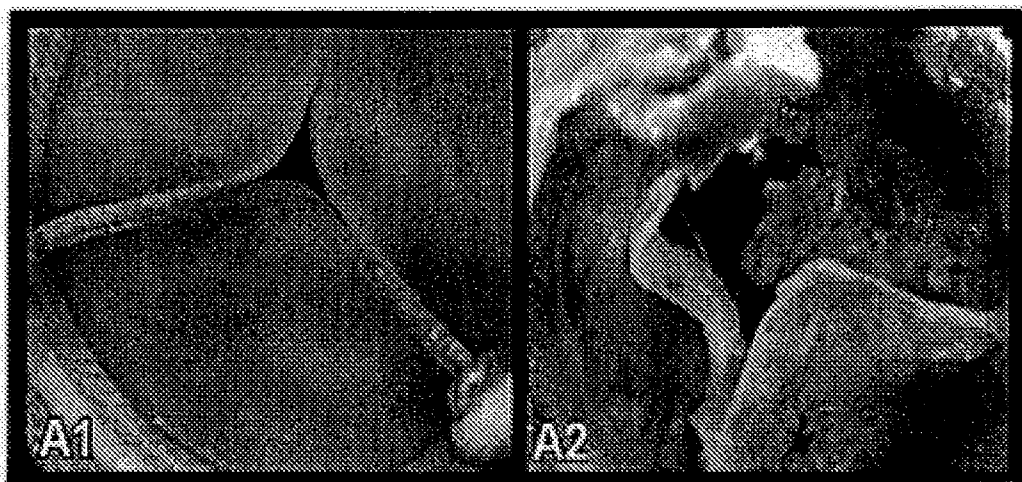


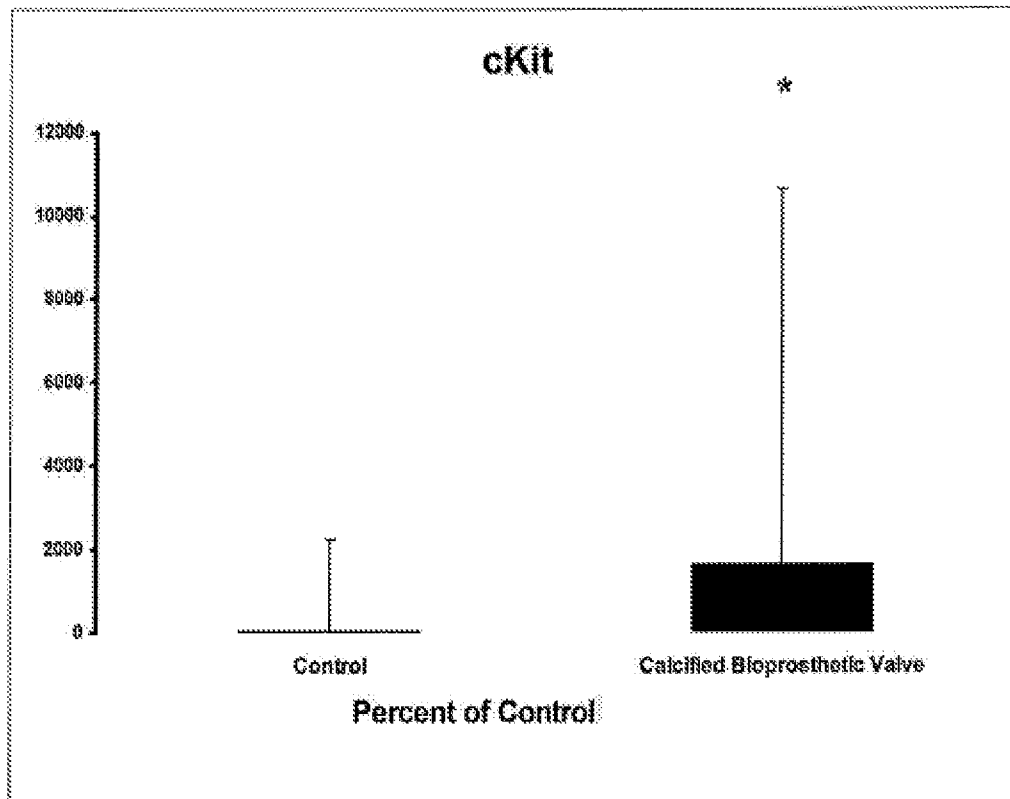
Figure 12

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Figure 13



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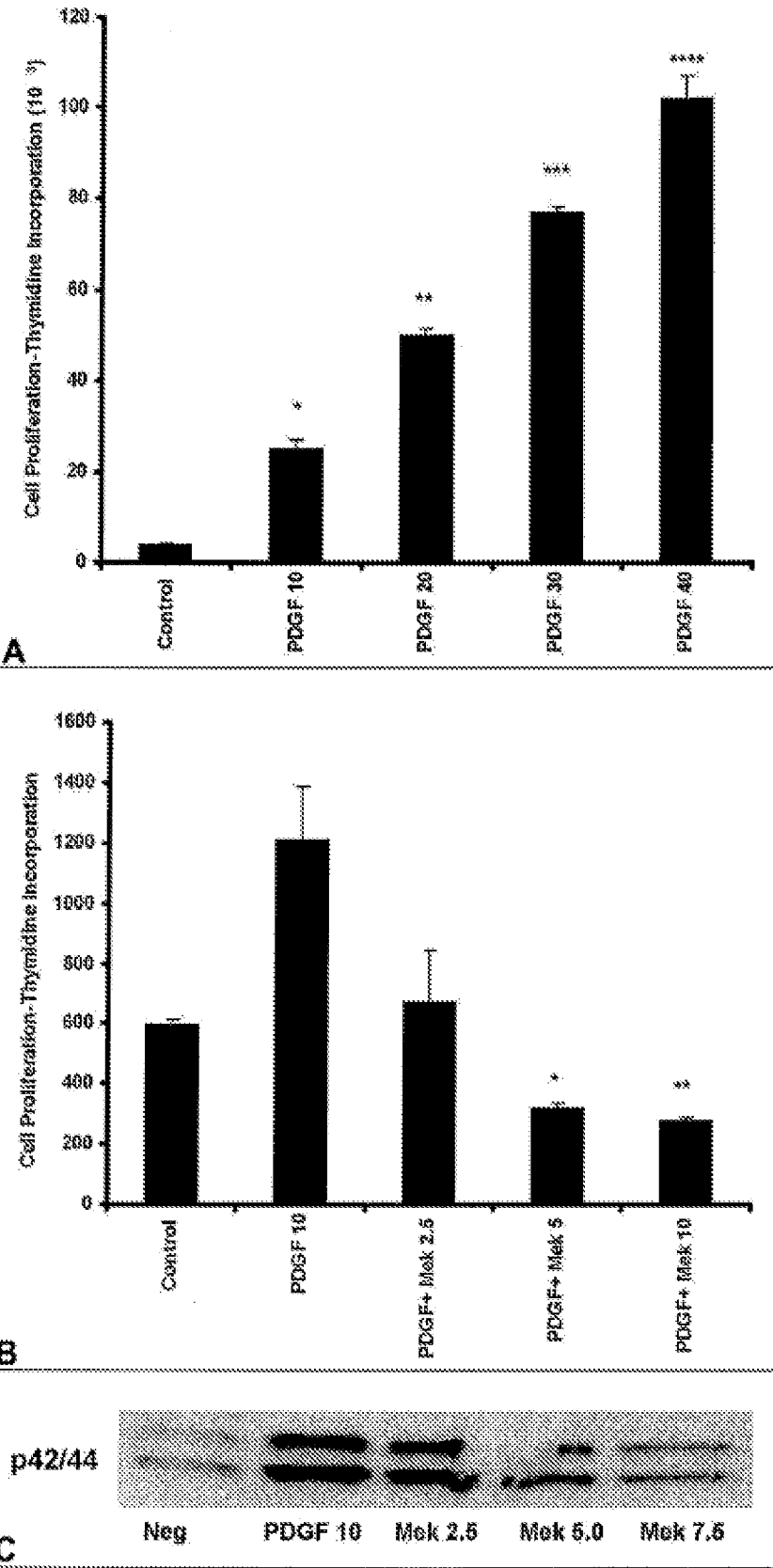
Figure 14

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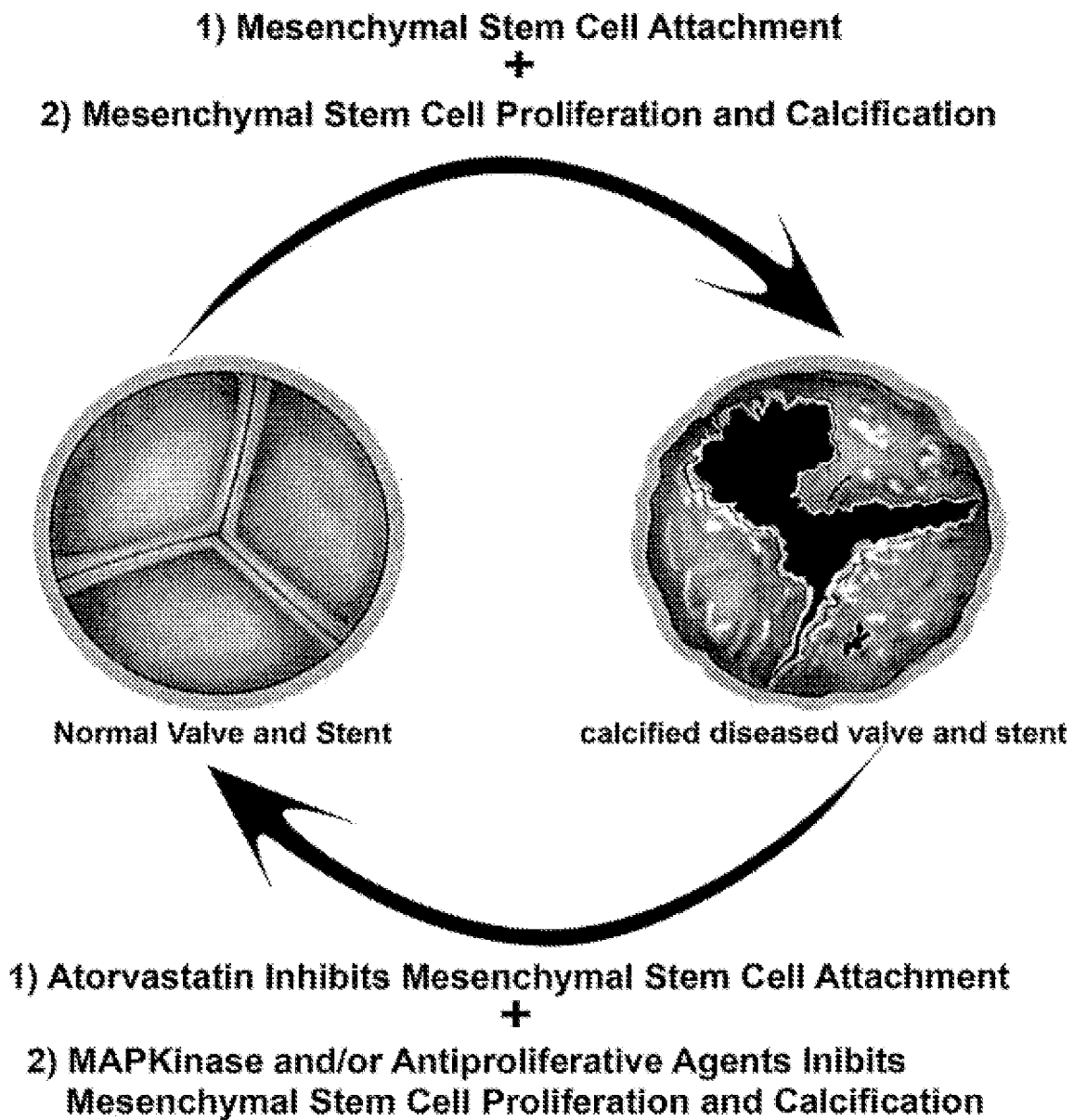
Figure 15

Table 1	Control	Cholesterol	Chol+ Atorv
Cholesterol	18 ± 7	1846.3 ± 525.3*	842 ± 152.1**
Triglycerides	102.3 ± 16.9	323.25 ± 274.6*	97 ± 27.1**
HDL	4.6 ± 5.1	21.3 ± 7.5*	24.7 ± 16.7
hsCRP	0.24 ± 0.1	13.6 ± 19.7*	7.82 ± 8.7**
cKit	681 ± 618	978 ± 1217	302 ± 290**
OPN	1373 ± 1216	1662 ± 1491	1483 ± 1501
Cyclin	1461 ± 1339	2988 ± 3451*	984 ± 970**
Sox9	580 ± 459	910 ± 554*	168 ± 102**
GAPDH	2233 ± 2887	2553 ± 3013	2456 ± 3158
Morphometric	++	+++++*	+++

Figure 16



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Figure 17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/061745

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61F 2/24 (2014.01)

CPC - A61F 2/24 (2014.12)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - A61F 2/06, 2/24, 2/82, 2/86 (2014.01)

CPC - A61F 2/24, 2/2412, 2/2418, 2/2436, 2220/0008; A61L 31/10, 31/16, A61L 2300/416 (2014.12)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 427/2.24, 2.25, 623/1.11, 1.26, 2.1, 2.13, 2.14, 2.18, 2.38 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, Google Patents, Google Scholar

Search terms used: stent, heart valve, expandable, atorvastatin, statin, stenosis, prosthetic, bioprosthetic, coating, TAVI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/002228 A1 (TERUMO KABUSHIKI KAISHA) 05 January 2012 (05.01.2012) see machine translation	1-38
A	US 2012/0283822 A1 (ZHAO JR) 08 November 2012 (08.11.2012) entire document	1-38
A	US 2007/0239269 A1 (DOLAN et al) 11 October 2007 (11.10.2007) entire document	1-38
A	US 2006/0165752 A1 (PATHAK et al) 27 July 2006 (27.07.2006) entire document	1-38
A	WO 2004/087214 A1 (SHANLEY et al) 14 October 2004 (14.10.2004) entire document	1-38
A, P	US 2014/0114407 A1 (CONCIEVALVE LLC) 24 April 2014 (24.04.2014) entire document	1-38

☐ Further documents are listed in the continuation of Box C.

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

09 January 2015

Date of mailing of the international search report

05 FEB 2015

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Authorized officer:

Blaine R. Copenheaver

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774