IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

AORTIC INNOVATIONS LLC, Plaintiff, v. EDWARDS LIFESCIENCES CORPORATION, EDWARDS LIFESCIENCES LLC, and EDWARDS LIFESCIENCES (U.S.) INC., Defendants.	)	Case No. 1:23-cv-00158-JPM

REBUTTAL EXPERT CLAIM CONTRUCTION DECLARATION OF DAVID BROOKSTEIN, Sc.D.

Edwards v. Aortic Innovations
IPR2023-01325
Edwards Ex. 1151

I, David Brookstein, Sc.D, hereby declare as follows:

I. QUALIFICATIONS AND BACKGROUND INFORMATION

1. I provided an expert declaration in this matter, which I understand was served on October 27, 2023 ("Brookstein Opening Declaration"). I incorporate herein sections I and II of the Brookstein Opening Declaration, which set forth my qualifications, background information, and compensation.

II. MATERIALS CONSIDERED

2. In addition to the materials and information identified in my opening declaration, I have reviewed the declaration of Dr. Stephen J.D. Brecker Regarding Claim Construction dated October 27, 2023 ("Brecker Opening Declaration") and the materials attached to this Declaration as Appendix C.

III. CLAIM TERMS

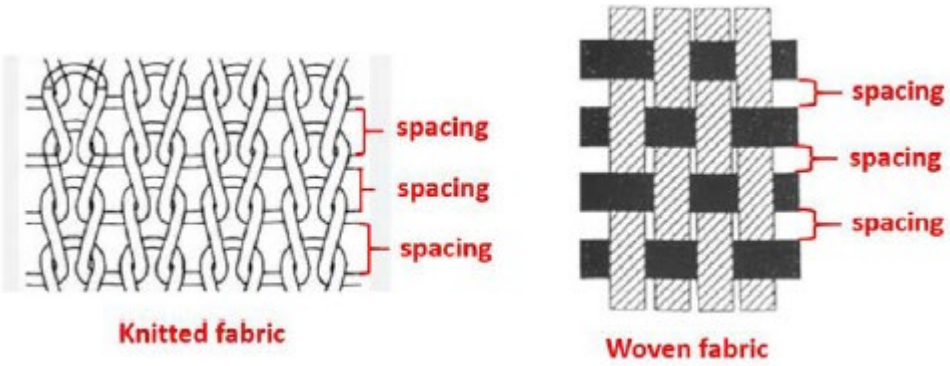
A. Spacings

3. Dr. Brecker opines that "[A]s is particularly clear in Figure 13 (but also present elsewhere), there are gaps and spaces between the fibers that extend to the frame. These gaps and spaces were, I believe, counterintuitive because a POSITA would have, at the time, favored a solid, non-porous, graft material to address PVL—like the ones seen in Walther, Spenser II, and Levi…." Brecker Opening Declaration at ¶88 (ellipses in original). I disagree with Dr. Brecker's characterization of the sealing materials in Walther, Spenser II, and Levi as "solid, non-porous, graft material." *See id.*[1]

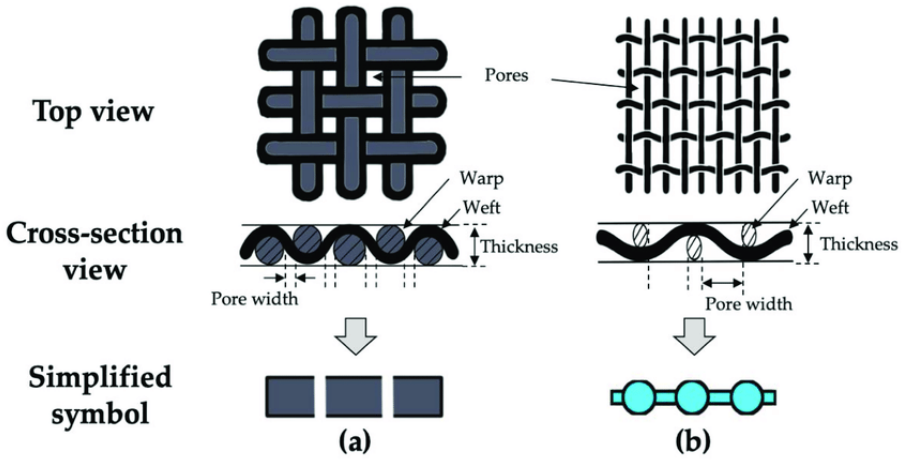
[1] I do not address every point or opinion raised in Dr. Brecker's Opening Declaration. This does not mean that I agree with any of the points or opinions raised in Dr. Brecker's Opening Declaration that are not specifically addressed herein. I reserve my right to comment on those additional points or opinions at another time should it become necessary.

4. Contrary to Dr. Brecker's characterization, a person of ordinary skill in the art ("POSA") would have recognized that the polyethylene terephthalate ("PET") cloths described and shown in Walther, Spenser II, and Levi are not "solid, non-porous, graft material" because each of those materials is described as a cloth or fabric made from yarns made from PET fibers. *See* Appendix C, Ex. 4 (Walther) at 1121, Figure 1; Appendix C, Ex. 5 (Spenser II) at [00145]; Appendix C, Ex. 10 (Levi) at 13:49-53. Based on my knowledge and experience in the field of medical textile engineering, a POSA would have known that all PET cloths or fabrics are porous, and therefore, a PET cloth or fabric cannot be a "solid, non-porous, graft material" as Dr. Brecker asserts.

5. The porosity of a PET cloth or fabric results from the way those materials are manufactured, which is most commonly by knitting or weaving yarns of PET material in a repeating pattern to form the cloth or fabric. The process of knitting or weaving PET yarns to produce a cloth or fabric necessarily results in "spacings" between the yarns that make up the cloth or fabric, as I explained and illustrated in the below figures from my Opening Declaration:



Brookstein Opening Declaration at ¶29. This is further illustrated in the figures below, which illustrate top and cross-sectional views of a woven fabric:



As illustrated above, a woven or knitted fabric always has pores where the fibers cross each other. Porosity is a measure of the "spacings" in the cloth or fabric. Thus, any spaces between the yarns means that the cloth or fabric is porous. As I explained in my Opening Declaration, the distance between the yarns in a cloth or fabric (i.e., the level of porosity) can vary based on several factors such as the width or density of yarns in the knit or weave. This is expressly acknowledged in the Levi reference, which explains that "the spacing between the woven fibers or yarns [in the skirt material] can be increased to facilitate elongation of the skirt in the axial direction." Appendix C, Ex. 10 (Levi) at 10:48-50. However, no matter the width or density of the yarns in a cloth or fabric, the cloth or fabric will always have "spacings" between the yarns/fibers that make up the material and be porous.

6. The porosity of PET cloths is reflected in the prior art medical literature describing PET cloths used in cardiovascular procedures. As reflected in the table below from the Mathisen article, which studies eight arterial prostheses used in cardiovascular procedures, every prosthesis made of a Dacron® (i.e., PET)[2] cloth was porous to water, meaning that the spacings between the yarns in the material were large enough to allow water to pass through the material:

[2] Dacron® is a brand name for PET fibers.

Table I. Physical characteristics

Graft	*Material*	*Construction*	*Prosthesis wall thickness (μm)*	*Compliance (C = ΔV/VΔp)*	*Water porosity (ml/cm²/min; 120 mm Hg)*
Gore-Tex	PTFE	Expanded	915	0.010-0.012	0
DeBakey Woven	Dacron	Woven	241	0.022-0.026	211
Cooley Woven	Dacron	Woven	210	0.019-0.020	152
Meadox Woven Double Velour	Dacron	Woven, double velour	343	0.041-0.049	309
Cooley Knitted Double Velour	Dacron	Warp-knit, double velour	610	0.050-0.054	1576
Microvel	Dacron	Warp-knit, double velour	708	0.057-0.073	2077
Vasculour II	Dacron	Warp-knit, internal velour	457	0.040-0.046	2104
Bionit II	Dacron	Warp-knit, external velour	514	0.049-0.057	1283

Appendix C, Ex. 2 (Mathisen) at Table 1. As shown above, the only tested prosthesis that did not have measurable water porosity was a prosthesis made from Gore-Tex® expanded polytetrafluoroethylene ("PTFE"), also known as ePTFE. *Id.* The differences in water porosity observed for the ePTFE graft and the PET cloth arise from the distinct structures of Gore-Tex® ePTFE grafts and PET cloths. Unlike PET cloths, Gore-Tex® ePTFE grafts are not comprised of yarns or fibers woven or knitted together. Instead, Gore-Tex® ePTFE grafts are formed by rapidly stretching a monolithic, non-porous tube of PTFE at high temperatures, which produces "circumferentially arranged nodes, about 5–10 μm wide by 5–100 μm long, interconnected by longitudinal fibrils of less than 0.5 μm in diameter." Appendix C, Ex. 11 (How) at 222-223. The process of producing ePTFE yields a "microporous" structure, which can be impermeable to the passage of fluids such as water due to pores that are smaller than a micron. *Id.*; *see also* Appendix C, Ex. 12 (Matsuda) at 519, Fig. 4. The microporous structure of ePTFE is a product of its unique structure and manufacturing methods, which are distinct from the weaving or knitting processes used to create medical textiles such as PET cloths. Thus, the water porosity results reported in the Mathisen article underscore the POSA's understanding that all cloths and fabrics are porous due to their woven or knitted structure.

7. A POSA would have understood that PET can be used to form a "solid, non-porous" sheet or film (*e.g.*, Mylar®). However, in contrast to a cloth or fabric, a PET sheet or film is formed from a single thin layer of PET material, rather than separate PET yarns knitted/woven together. The unitary structure of a film or sheet of PET would enable a POSA to produce a "non-porous" structure, which is not possible with a cloth or fabric made up of knitted or woven yarns. The only way to make a cloth or fabric "non-porous" is to coat the cloth/fabric with some other material, such as a layer of rubber or plastic, which would cover and fill the spacings between the yarns of the cloth/fabric. Notably, Walther and Spenser II do not mention of any such coating. *See* Appendix C, Ex. 4 (Walther) at 1121, Figure 1; Appendix C, Ex. 5 (Spenser II) at [00145]. A POSA would have expected that if such a coating was present on the cloth, it would have been described, or at least mentioned, in the references – particularly in a medical journal article such as Walther. The lack of any such coating informs a POSA that the described PET cloths cannot be "solid, non-porous, graft material" as Dr. Brecker suggests.

8. The POSA's understanding that all cloths and fabrics would be porous and have "spacings" between the fibers is also reflected by the prosecution histories of the Asserted Patents. As I noted in my Opening Declaration, Aortic Innovations acknowledged during prosecution of the '634 and '918 patents that "all fibers have some degree of being spaced-apart." Brookstein Opening Declaration at ¶32. Aortic Innovations also repeatedly distinguished the claimed "spacing(s)" from the spacings between the fibers in a "cloth," "sleeve," "graft," or "graft covering." *See id.* at ¶¶33-39. Aortic Innovations did not limit its arguments to "non-porous" materials. *See id.* To the contrary, for the reasons I explained above and in my Opening Declaration, a POSA would have understood Aortic Innovations' repeated statements distinguishing the claimed "spacings" from a "cloth," "sleeve," "graft," and "graft covering" to

encompass porous materials, such as cloths, which would be porous and have "spacings" between the yarns/fibers of the material.

9. I also disagree with Dr. Brecker's assertion that "a POSITA would have, at the time, favored a solid, non-porous, graft material to address PVL." Brecker Opening Declaration at ¶88. Dr. Brecker's position is contrary to Walther and Spenser II, which explain that the cloths reduced PVL by promoting tissue ingrowth and blood coagulation within the cloth. *See* Appendix C, Ex. 4 (Walther) at 1120; Appendix C, Ex. 5 (Spenser II) at [00145]. A POSA would have known that to promote tissue ingrowth, a material must be porous and have spacings for the tissue to grow into. The medical literature describing PET textile materials for use in cardiovascular devices emphasizes this point. As the Estridge article explains:

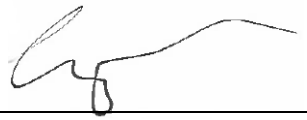
> The success or failure of porous soft tissue biomaterials is a result of porosity, bulk material properties, surface properties or chemistry, material configuration, implant location, implant function, and animal model used [1]. The most commonly used porous soft tissue biomaterial is Dacron® velour [2]. This material has been used extensively as an artificial vascular graft material and in percutaneous devices. Tissue vascularity has been cited as the key to long-term ingrowth. Therefore, pores of a size sufficient to allow vascular ingrowth are required. Most researchers suggest that 40 μm diameter pores or more are needed for soft tissue ingrowth, while others argue that pores of at least 100 μm are needed [1]. In either case, cells die due to lack of nutrition if removed by more than 100 μm from their blood supply [3]. Therefore, vascular ingrowth is critical to the success of soft tissue porous implants.

Appendix C, Ex. 1 (Eldridge) at 158; *see also* Appendix C, Ex. 2 (Hall) at 180-181 ("It is generally accepted that arterial grafts should be fashioned of a porous material to obtain a well-anchored, healthy inner lining. Such material permits the organization of the internal lining and invasion by surrounding connective tissue with further vascularization. . . . An impervious material used as an arterial substitute has no means to anchor the fibrin deposit and a consequence embolization occurs."). A "solid [and] non-porous" cloth or fabric would not have "pores of a size sufficient to allow vascular ingrowth," which is directly contrary to Walther and Spenser II. *See id.* The same

principle applies to blood coagulation. A POSA would have recognized that a PET cloth would promote blood coagulation by allowing blood to permeate the spacings between the yarns/fibers of the cloth. *See, e.g.*, Appendix C, Ex. 5 (Spenser II) at [00145] ("[T]he compressible material, and especially the fibers, may be adapted to encourage the coagulation of blood to further fill the gaps and prevent leakage."). A POSA would have known a "solid, non-porous, graft material" would not allow for blood to flow into the material and would result in much poorer blood coagulation than a porous material, such as a cloth or fabric.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on November 10, 2023, in Philadelphia, Pennsylvania.



David Brookstein, Sc.D.

APPENDIX C

EXHIBIT 10

US009393110B2

(12) **United States Patent**
Levi et al.

(10) **Patent No.: US 9,393,110 B2**
(45) **Date of Patent: Jul. 19, 2016**

(54) **PROSTHETIC HEART VALVE**

(75) Inventors: **Tamir S. Levi**, Moshav Ein HaEmek (IL); **Son V. Nguyen**, Irvine, CA (US); **Netanel Benichou**, D.N. Hof HaCarmel (IL); **David Maimon**, Haifa (IL); **Ziv Yohanan**, Yesud Hamaala (IL); **Nikolay Gurovich**, Hadera (IL); **Bella Felsen**, Haifa (IL); **Larisa Dadonkina**, Or Akiva (IL); **Ron Sharoni**, Hadera (IL); **Elena Sherman**, Ramat Hasharon (IL)

(73) Assignee: **Edwards Lifesciences Corporation**, Irvine, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 844 days.

(21) Appl. No.: **13/253,689**

(22) Filed: **Oct. 5, 2011**

(65) **Prior Publication Data**

US 2012/0123529 A1 May 17, 2012

Related U.S. Application Data

(60) Provisional application No. 61/390,107, filed on Oct. 5, 2010, provisional application No. 61/508,513, filed on Jul. 15, 2011.

(51) **Int. Cl.**
A61F 2/24 (2006.01)

(52) **U.S. Cl.**
CPC ..... ***A61F 2/2412*** (2013.01); ***A61F 2/2418*** (2013.01); ***A61F 2/2433*** (2013.01); (Continued)

(58) **Field of Classification Search**
CPC A61F 2/24; A61F 2/2412; A61F 2/2418; A61F 2/2427; A61F 2/243; A61F 2/2433; A61F 2/2469; A61F 2220/0075; A61F 2250/0036; A61F 2250/0039
USPC 623/2.11, 2.12, 2.17, 2.19, 1.11, 1.12, 623/1.24, 1.26
See application file for complete search history.

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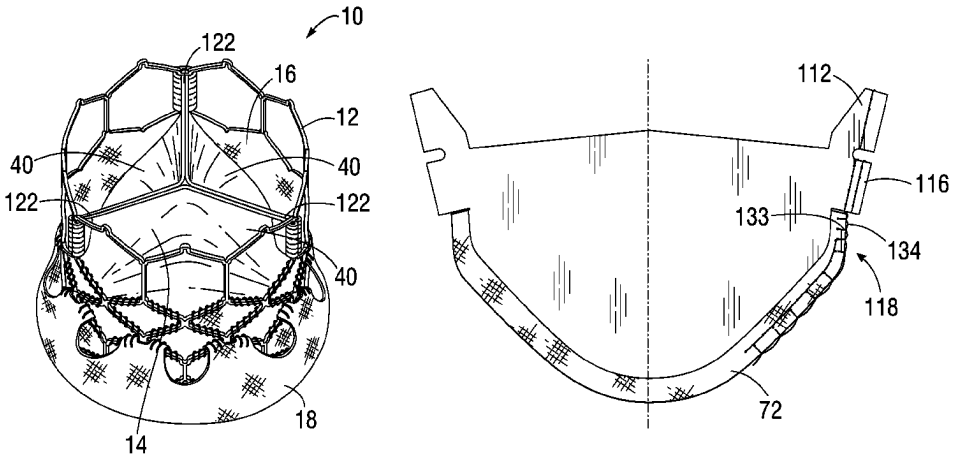
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Primary Examiner — Todd J Scherbel
(74) *Attorney, Agent, or Firm* — Klarquist Sparkman LLP; David L. Hauser; AnneMarie Kaiser

(57) **ABSTRACT**

Embodiments of a radially collapsible and expandable prosthetic heart valve are disclosed. A valve frame can have a tapered profile when mounted on a delivery shaft, with an inflow end portion having a smaller diameter than an outflow end portion. The valve can comprise generally V-shaped leaflets, reducing material within the inflow end of the frame. An outer skirt can be secured to the outside of the inflow end portion of the frame, the outer skirt having longitudinal slack when the valve is expanded and lying flat against the frame when the valve is collapsed. A diagonally woven inner skirt can elongate axially with the frame. Side tabs of adjacent leaflets can extend through and be secured to window frame portions of the frame to form commissures. The window frame portions can be depressed radially inward relative to surrounding frame portions when the valve is crimped onto a delivery shaft.

25 Claims, 26 Drawing Sheets



(52) **U.S. Cl.**
CPC . *A61F2220/0075* (2013.01); *A61F 2230/0054* (2013.01); *A61F 2250/0036* (2013.01); *A61F 2250/0097* (2013.01)

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FIG. 1

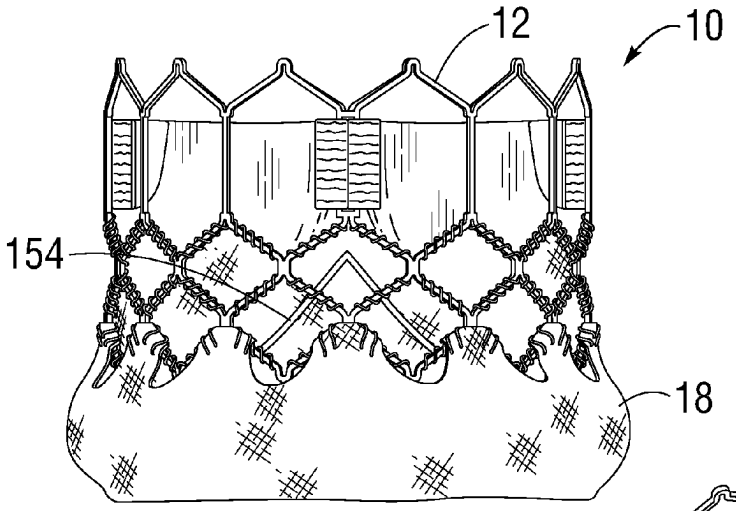


FIG. 2

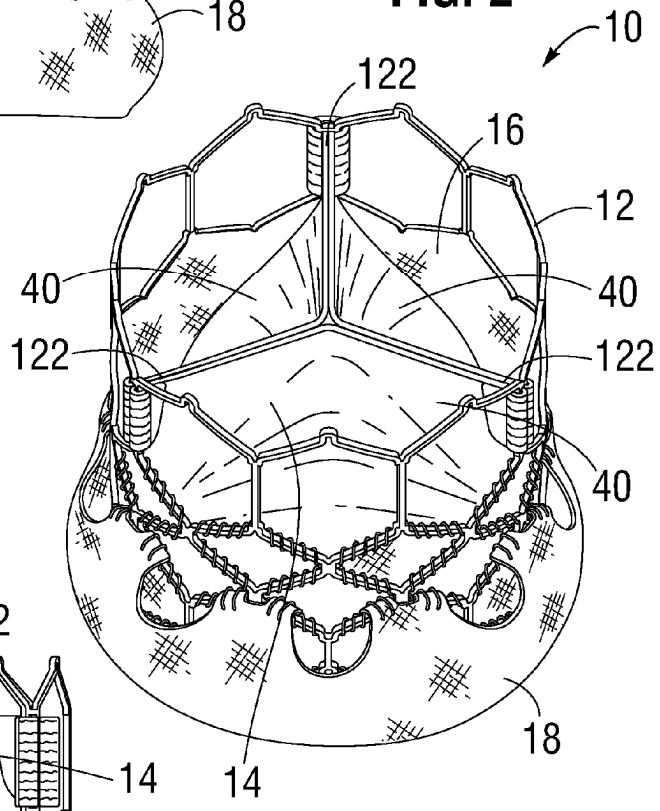
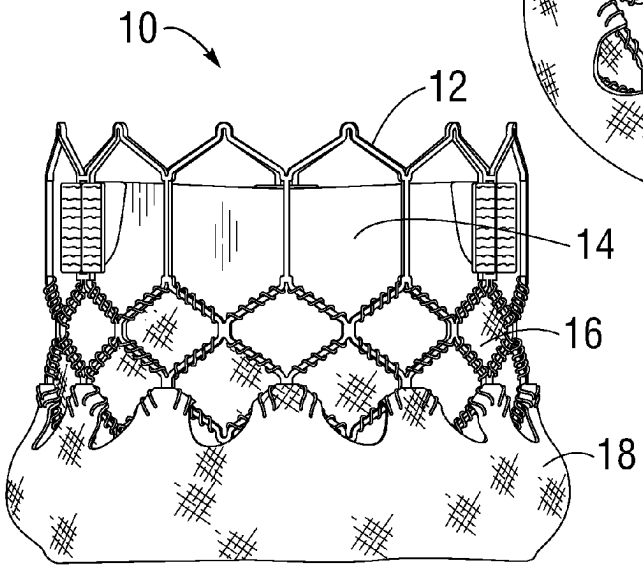


FIG. 3



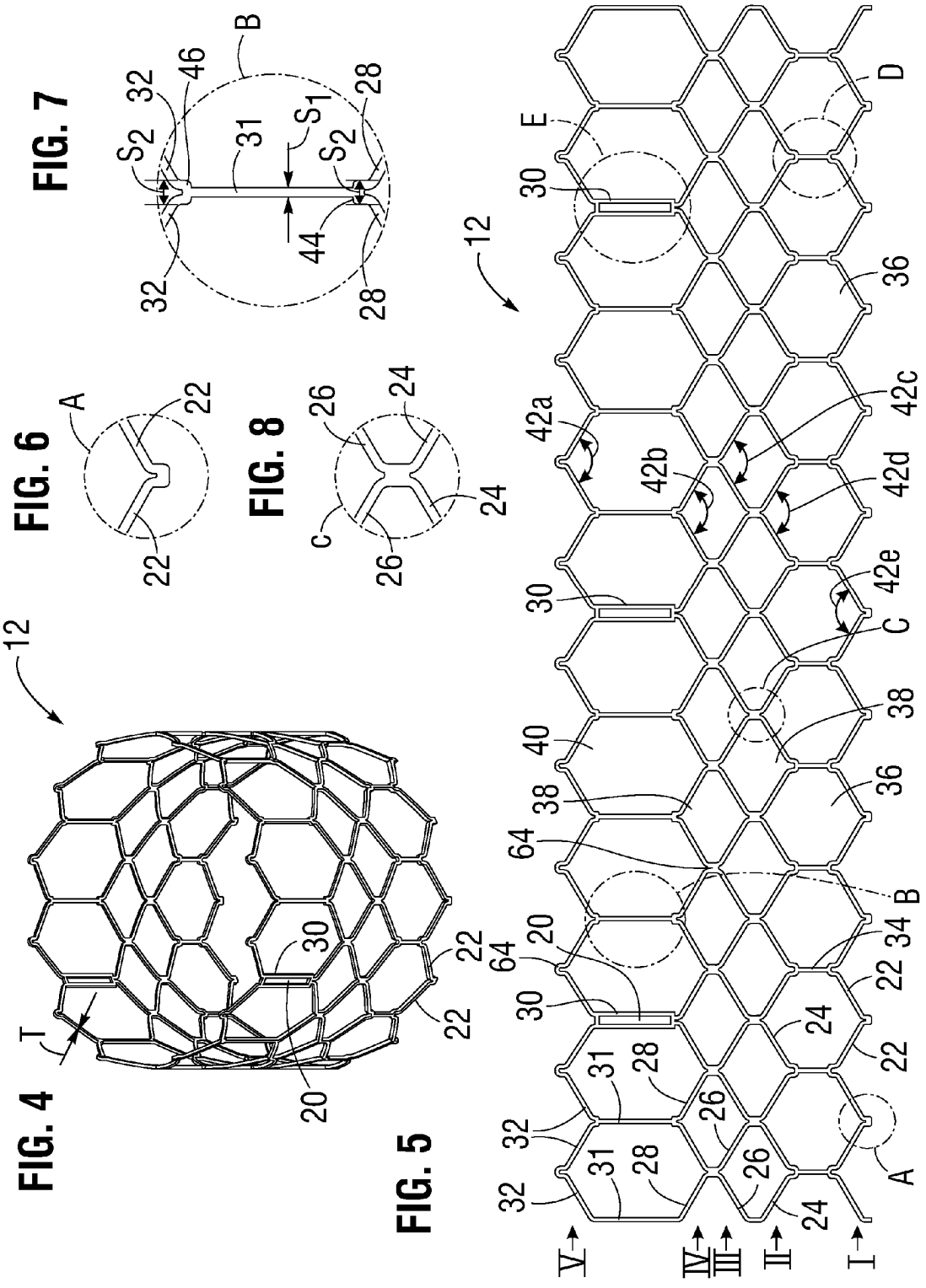

FIG. 4
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FIG. 5
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FIG. 6
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FIG. 8
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FIG. 9

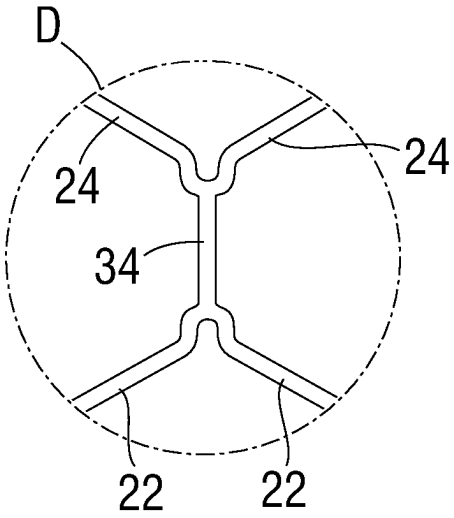


FIG. 10

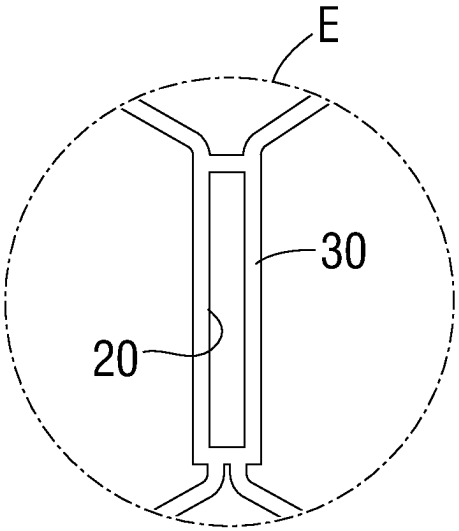


FIG. 11

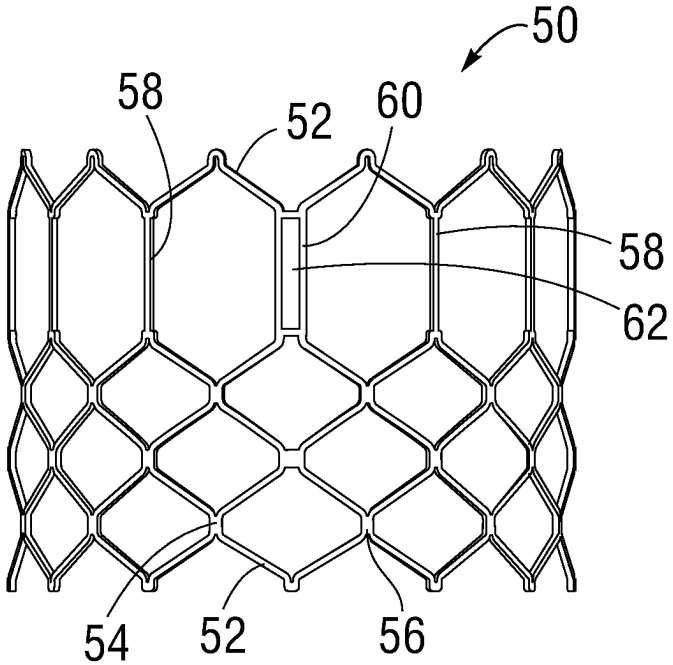


FIG. 12

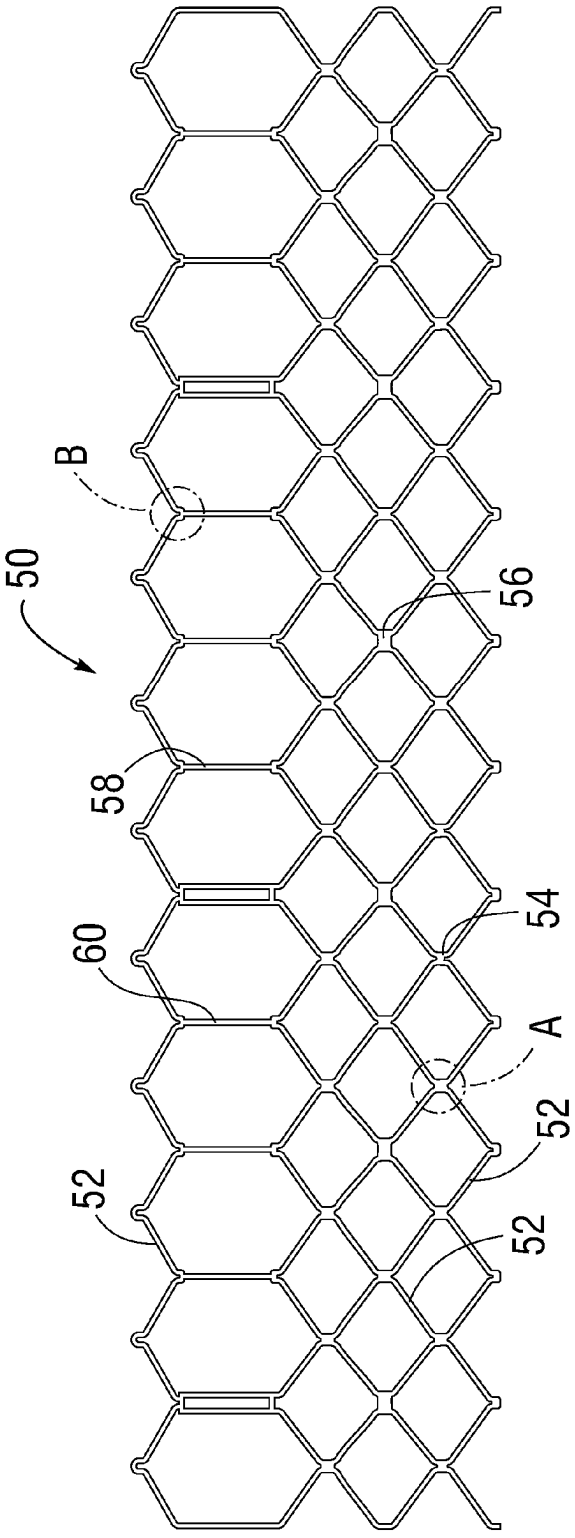


FIG. 15B

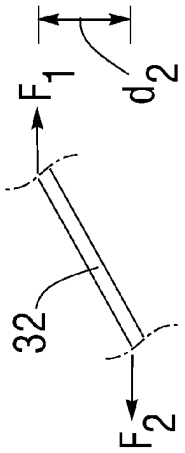


FIG. 15A

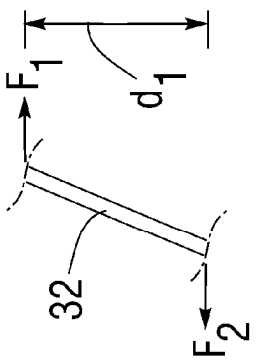


FIG. 14

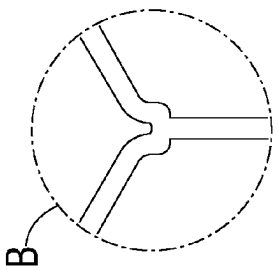


FIG. 13

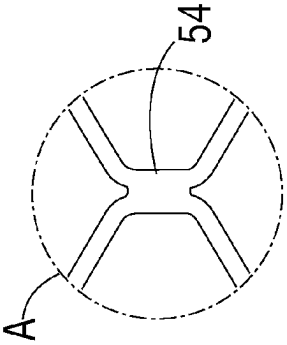


FIG. 16A

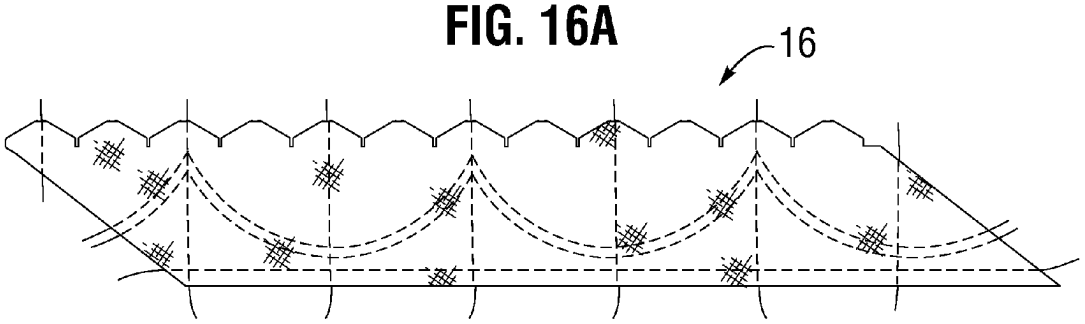


FIG. 16B

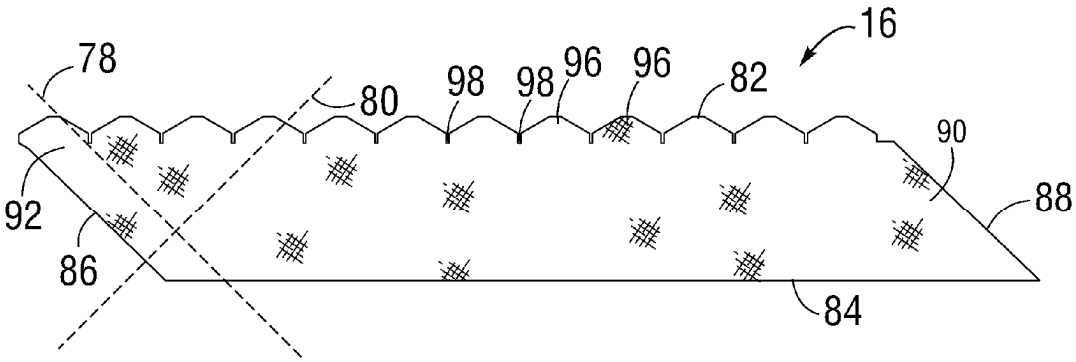


FIG. 17

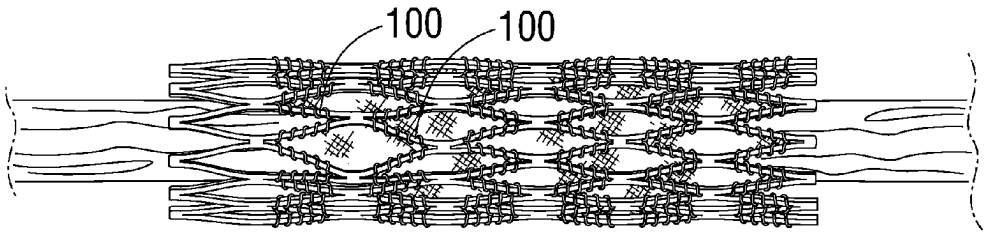


FIG. 18

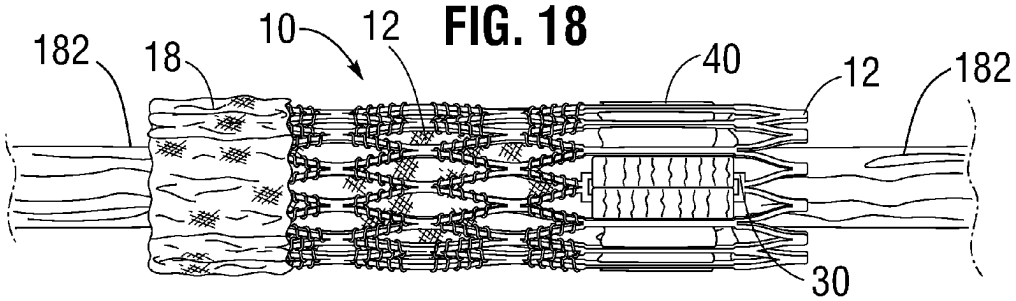


FIG. 19A

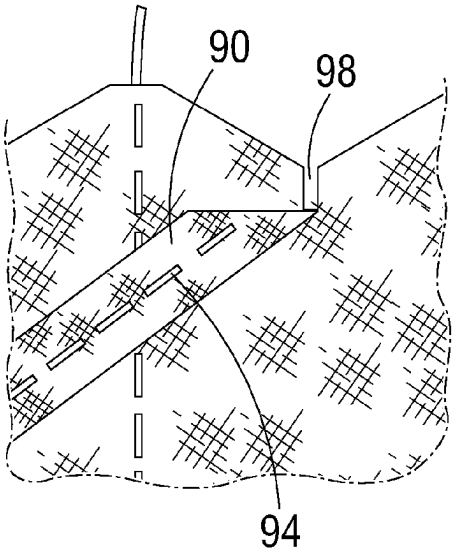


FIG. 19B

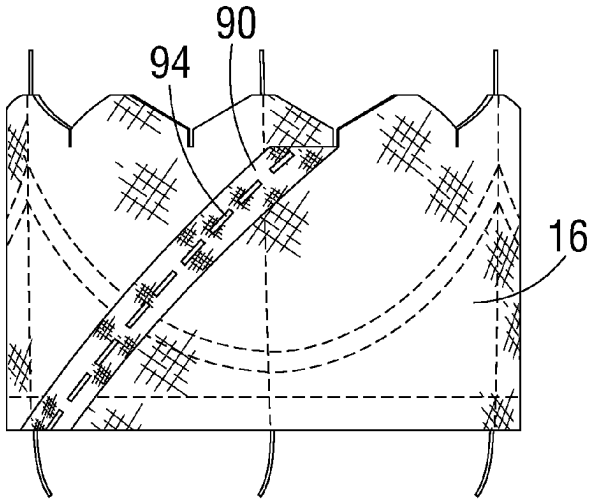


FIG. 20

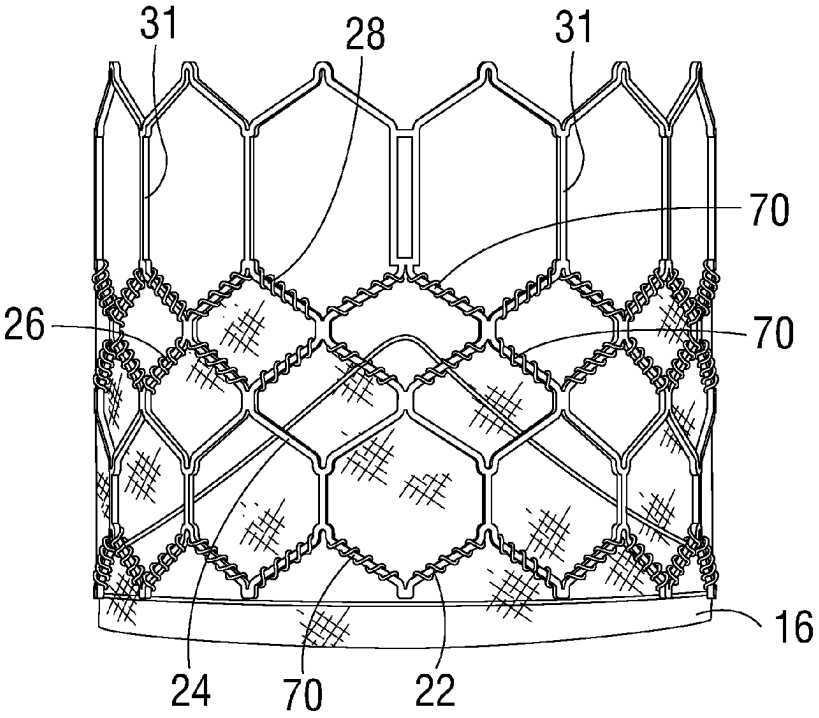


FIG. 21

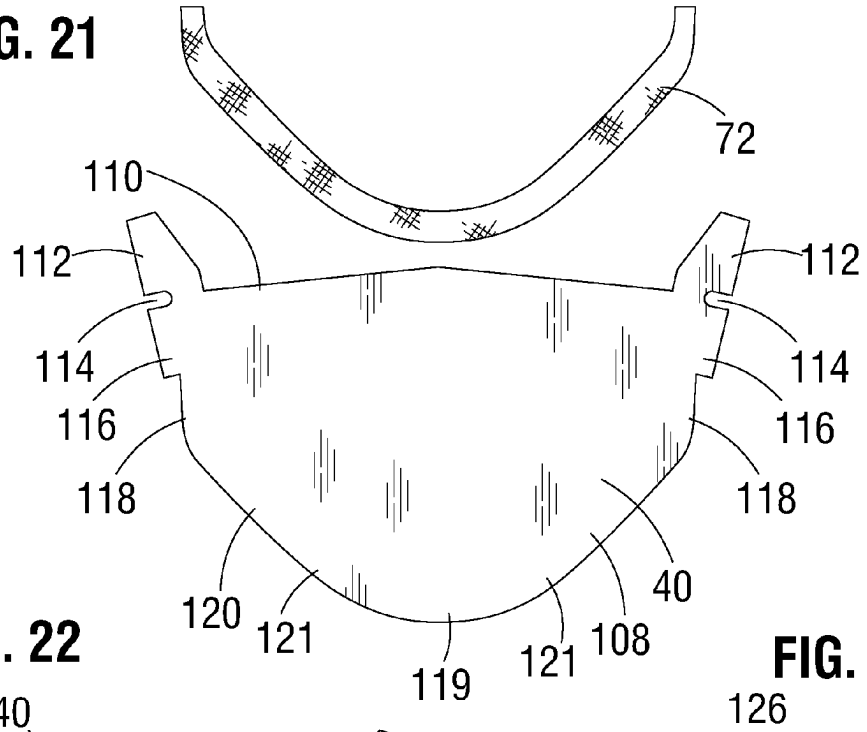


FIG. 22

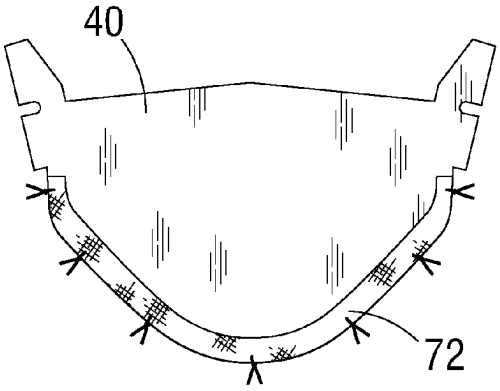


FIG. 23

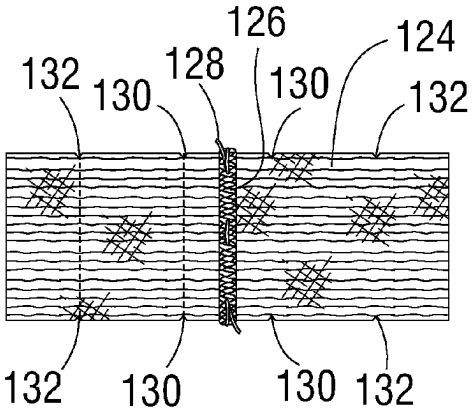


FIG. 24

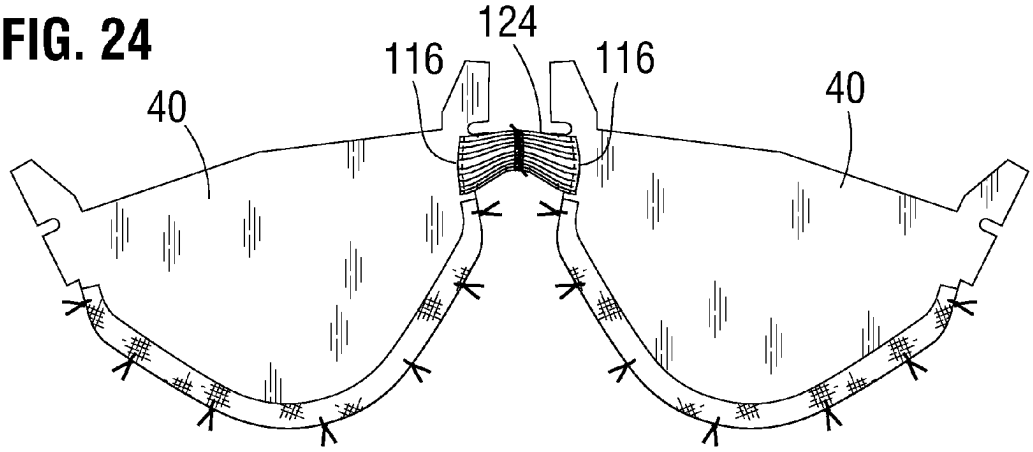


FIG. 25

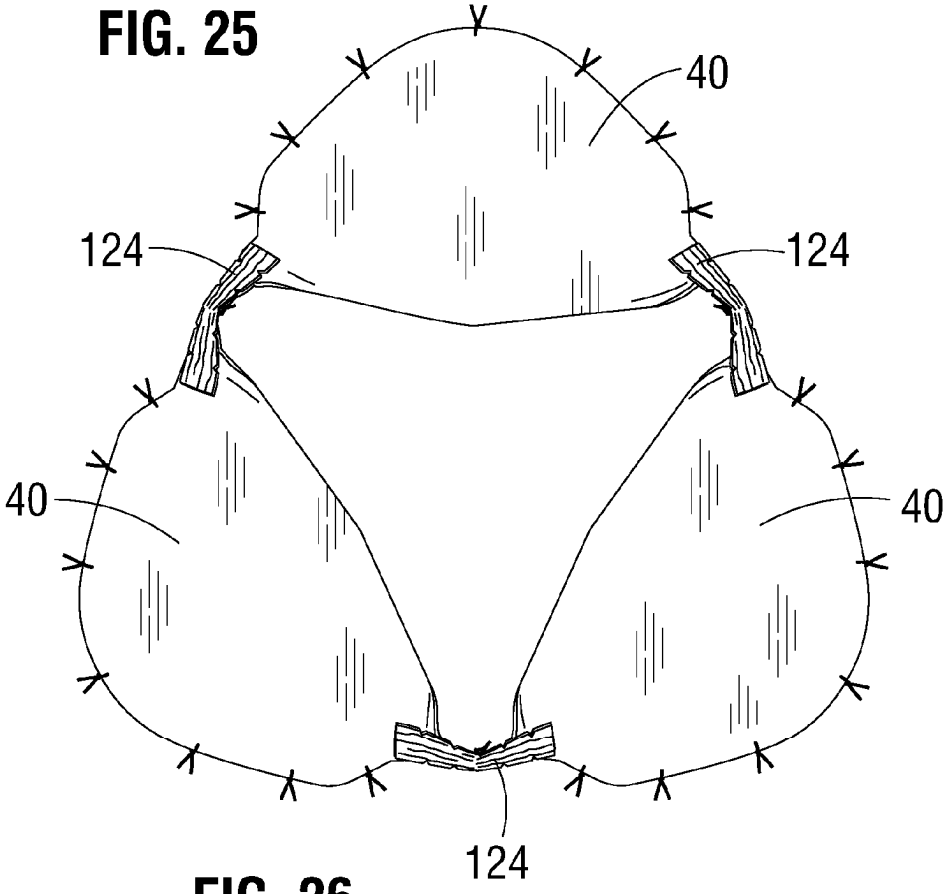


FIG. 26

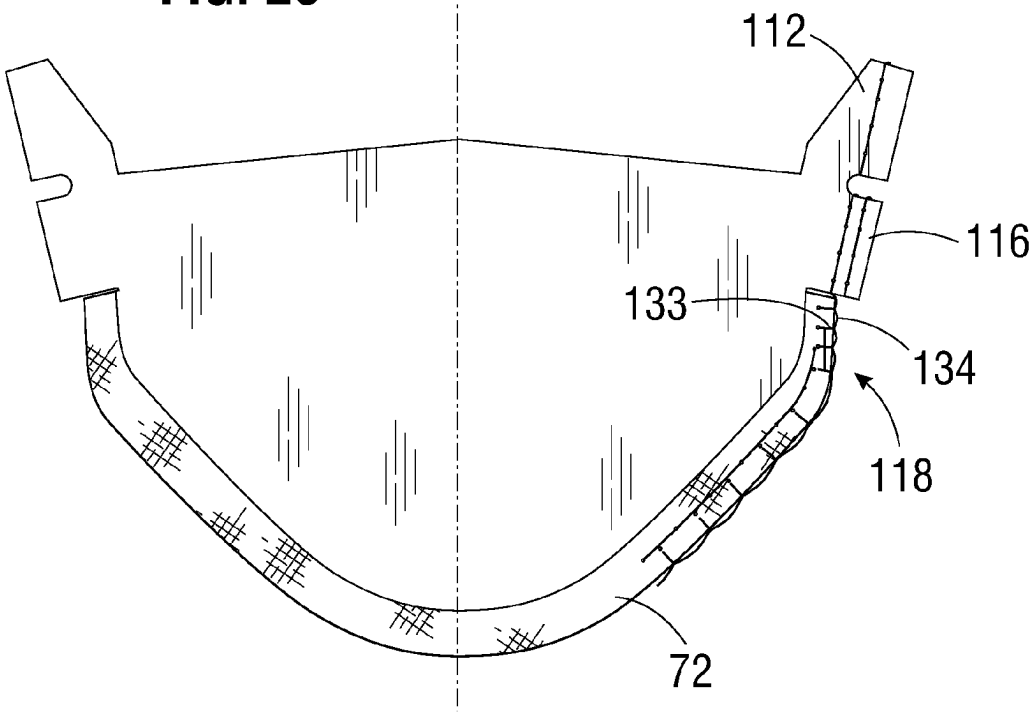


FIG. 27

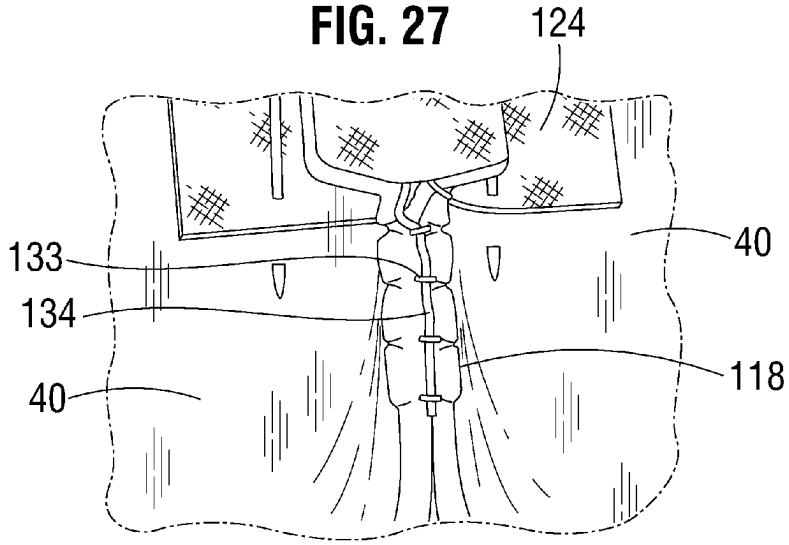


FIG. 28

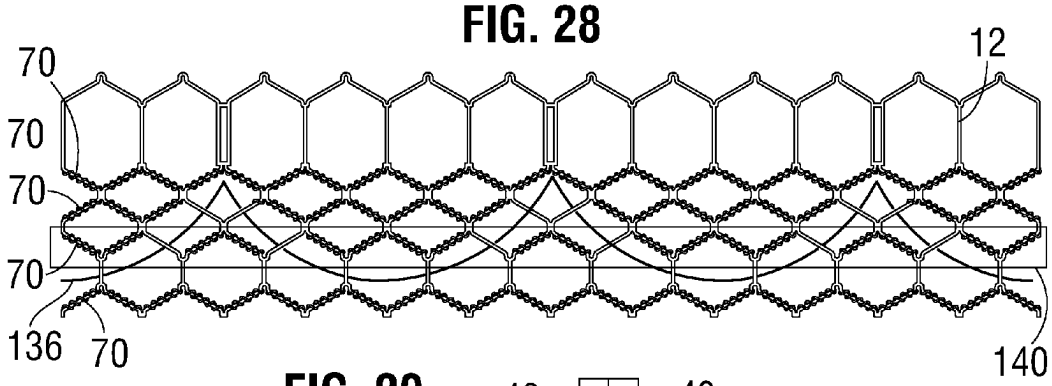


FIG. 29

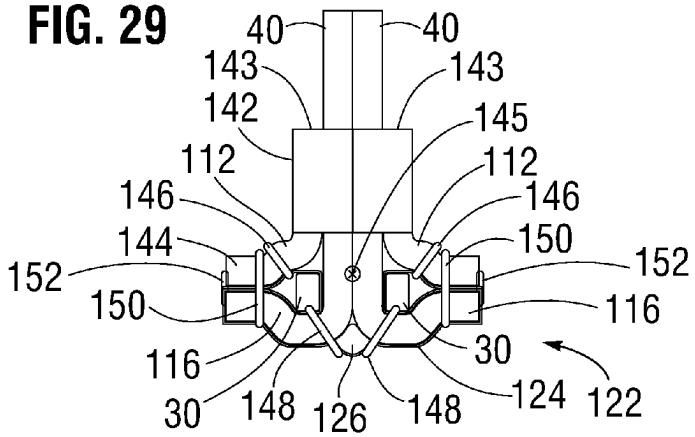


FIG. 30

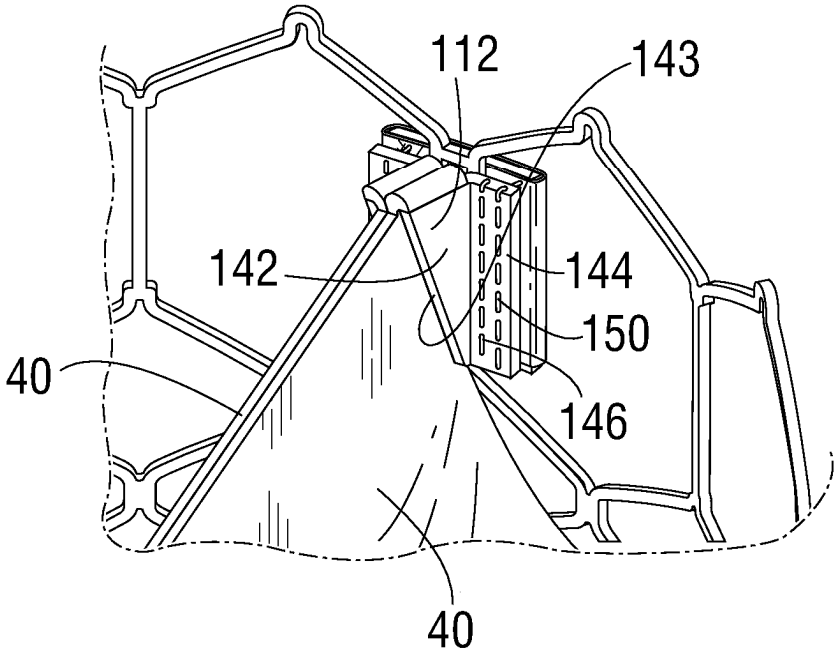


FIG. 31

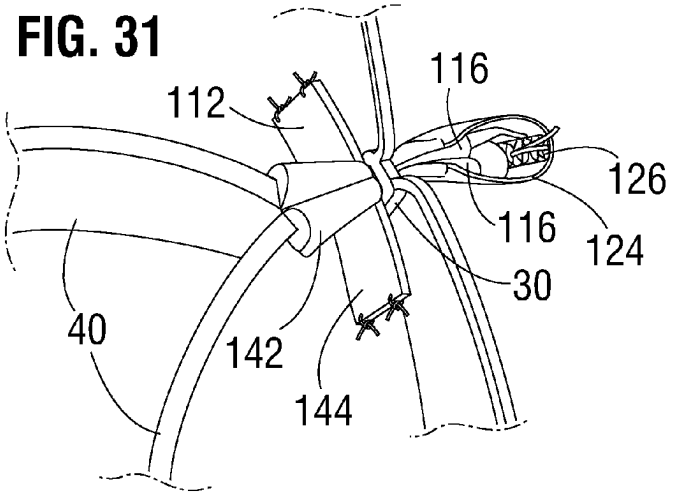


FIG. 32

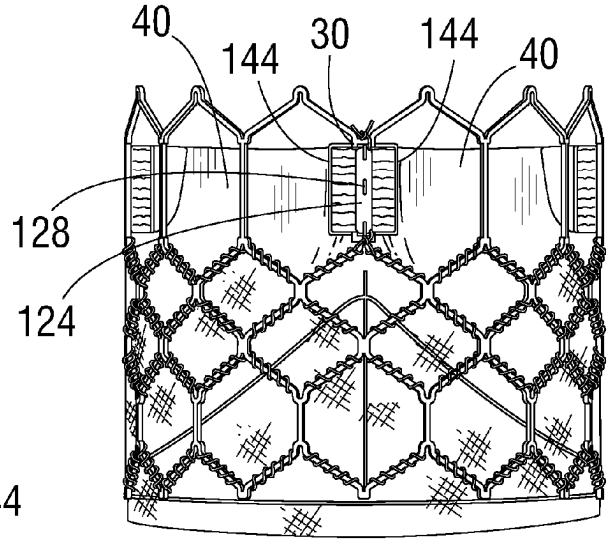


FIG. 33

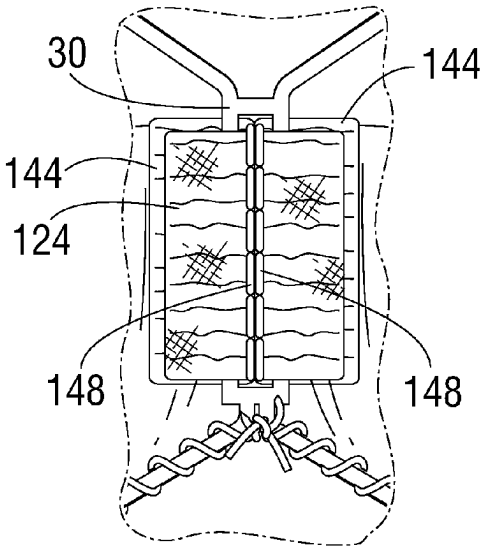


FIG. 34

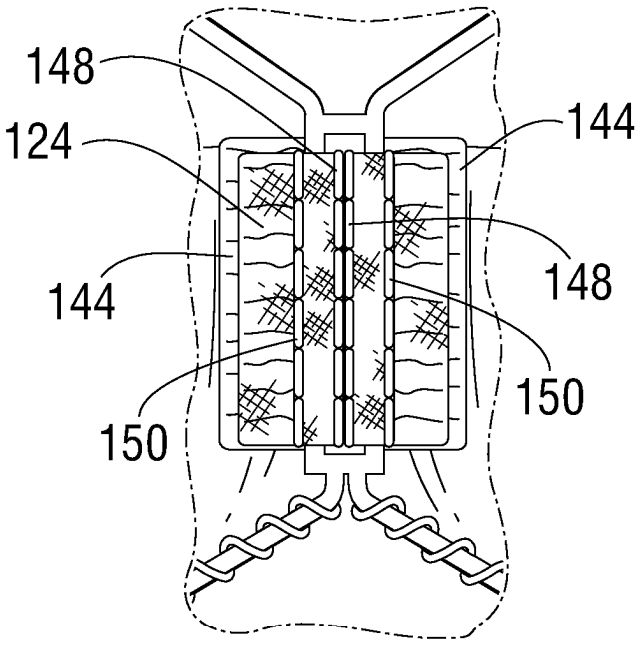


FIG. 35

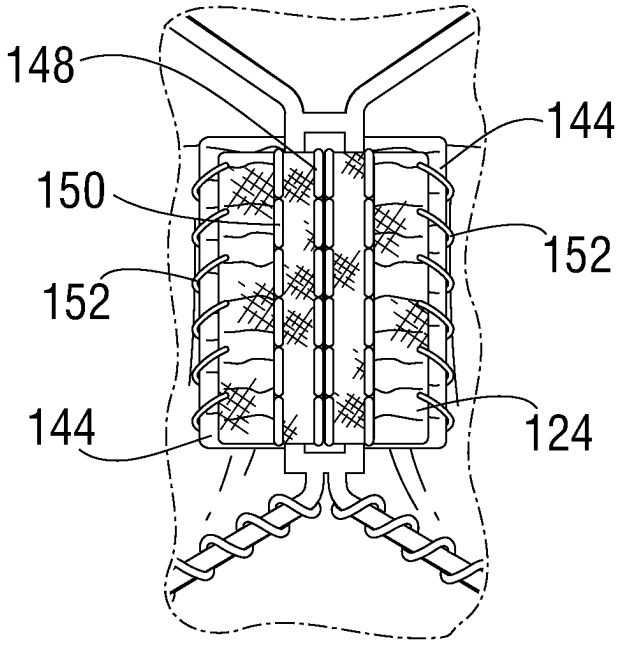


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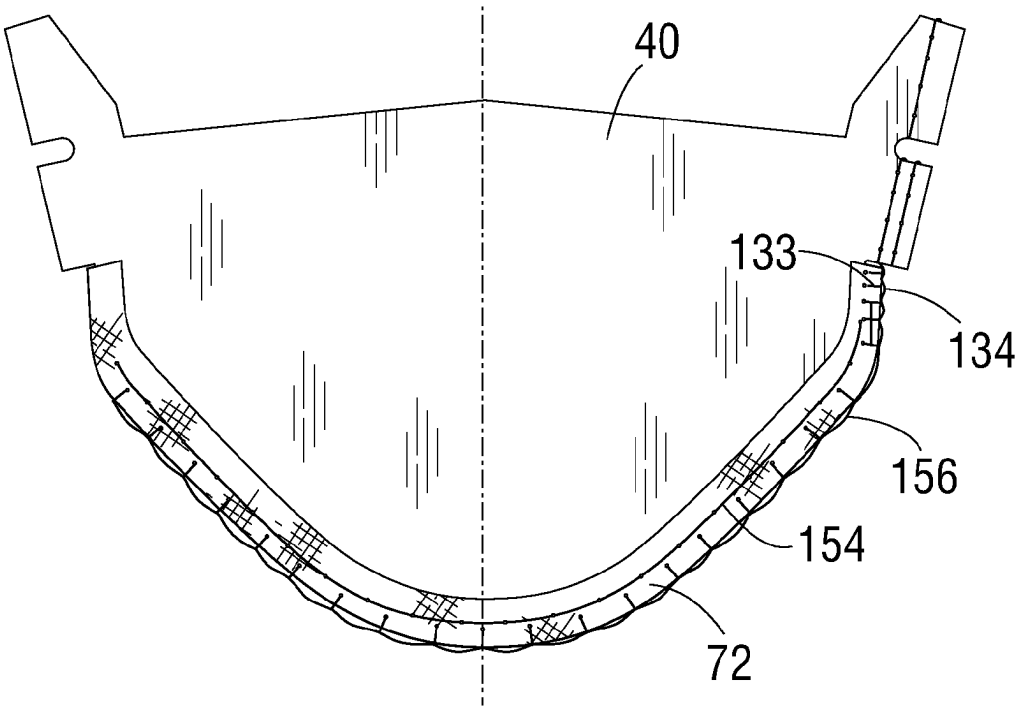


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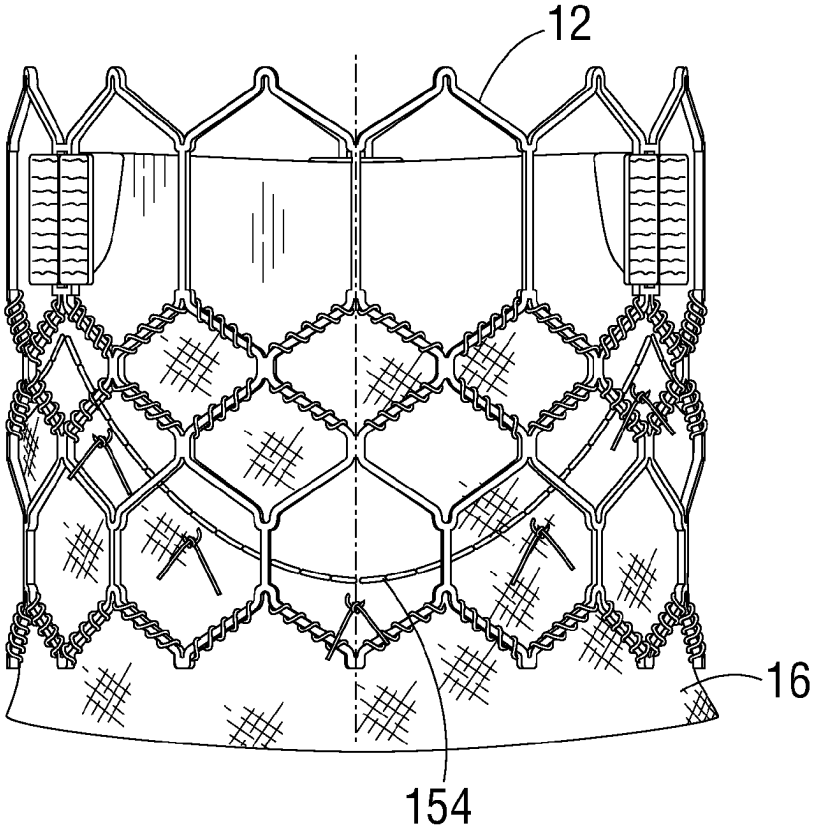


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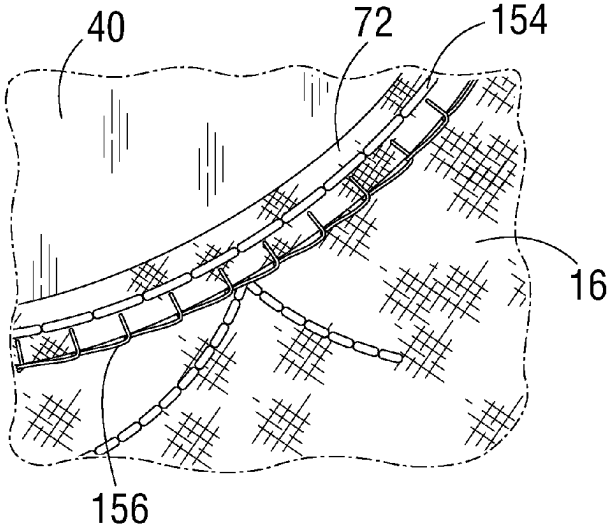


FIG. 39

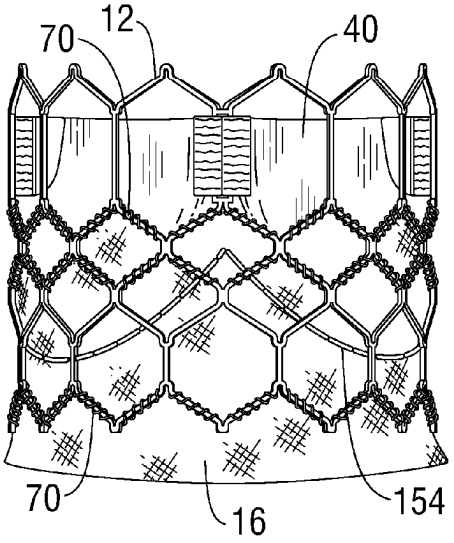


FIG. 40

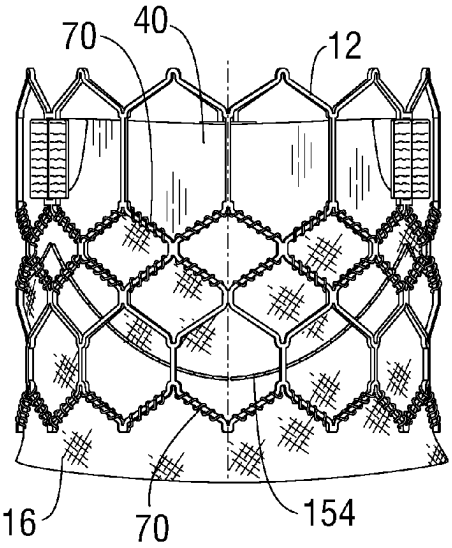


FIG. 41

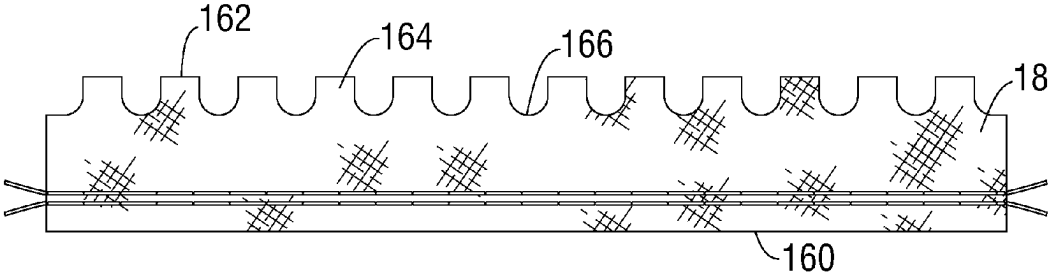


FIG. 43

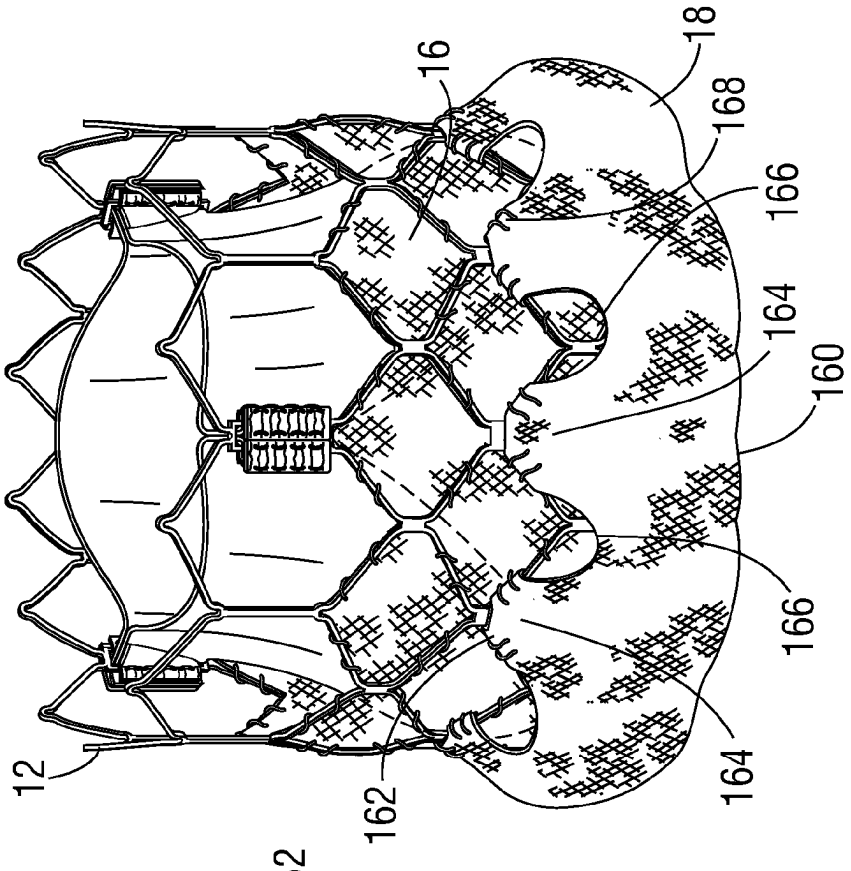


FIG. 42

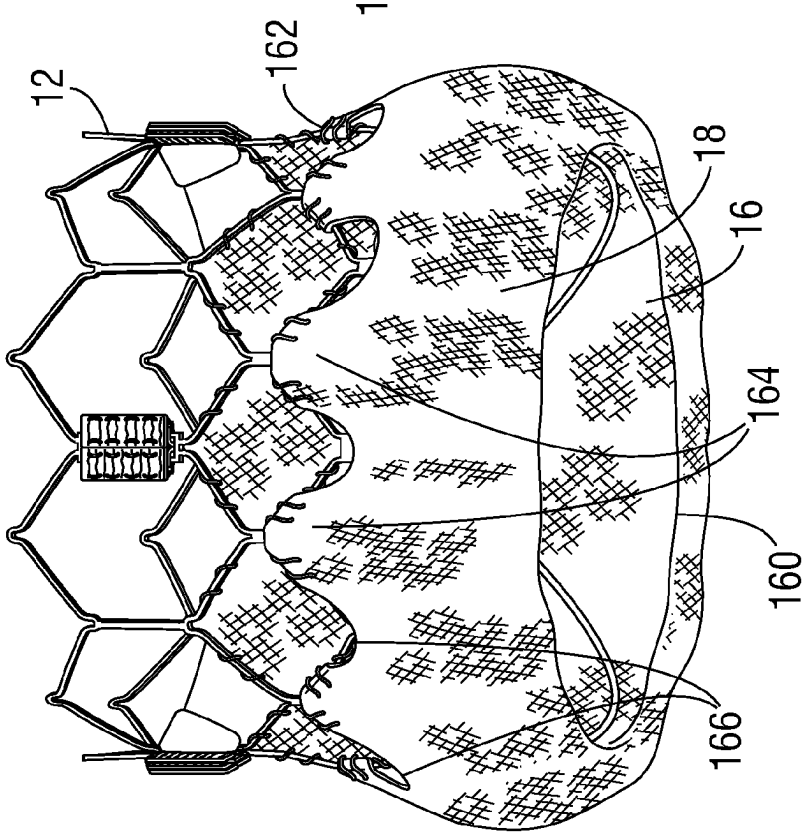


FIG. 44

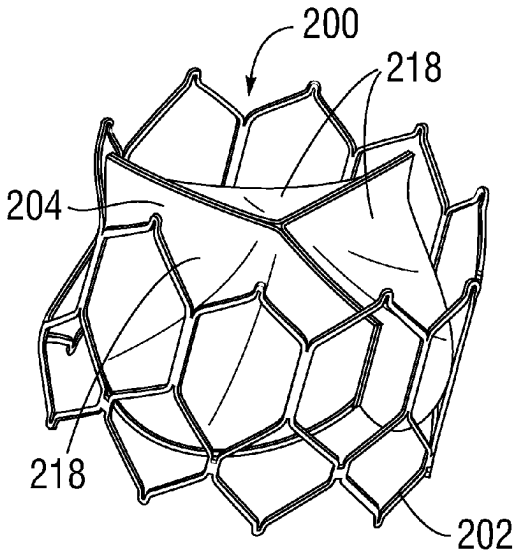


FIG. 45

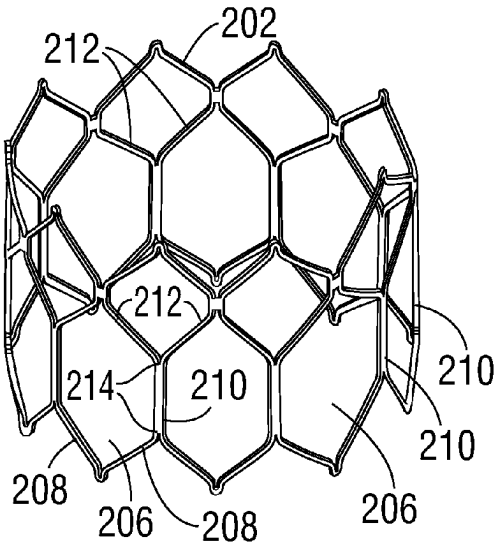


FIG. 46

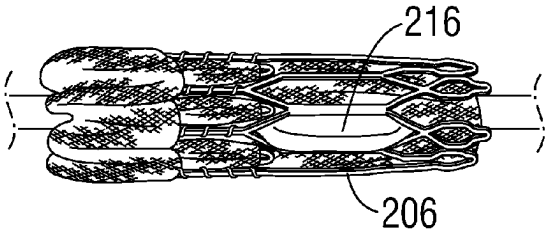


FIG. 47

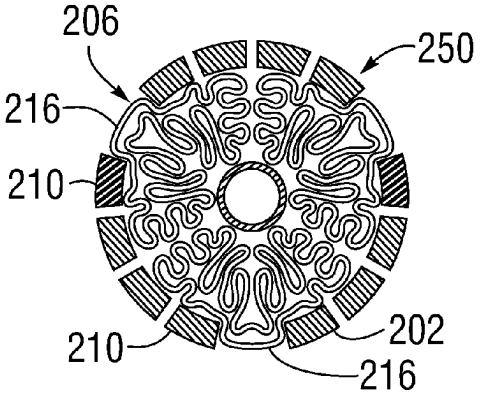


FIG. 48

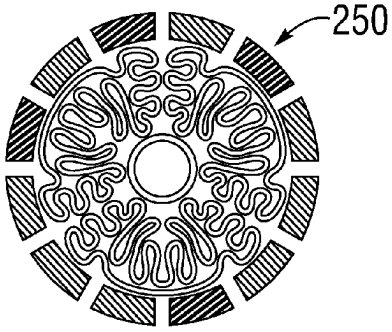


FIG. 49

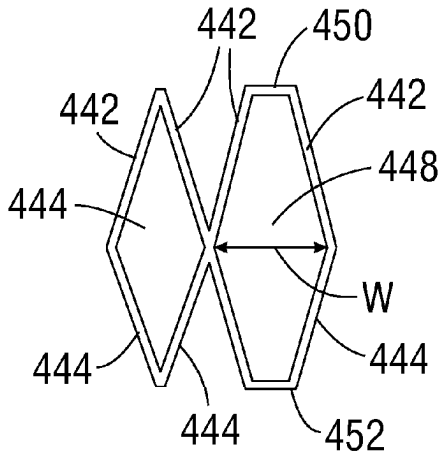


FIG. 50

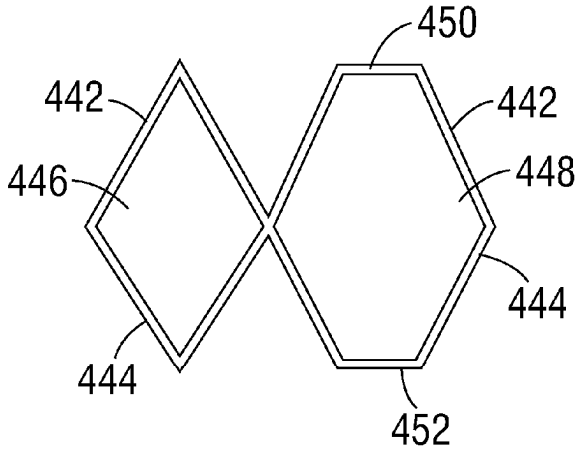


FIG. 51

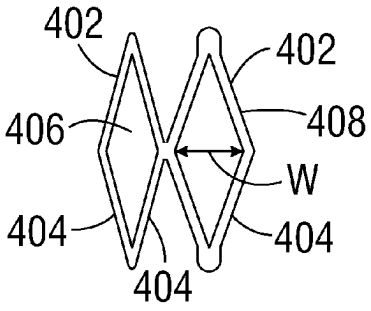


FIG. 52

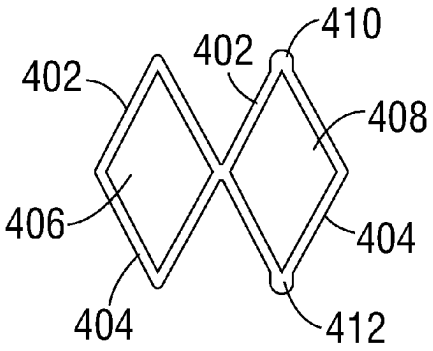


FIG. 53

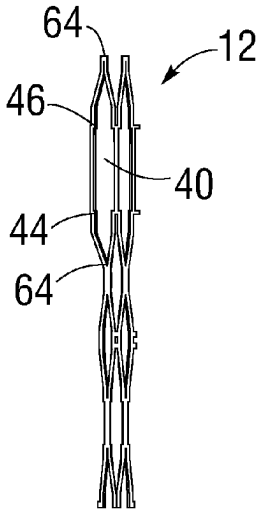


FIG. 54

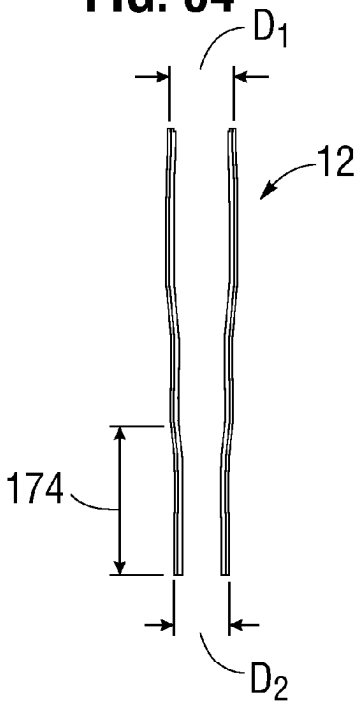


FIG. 55

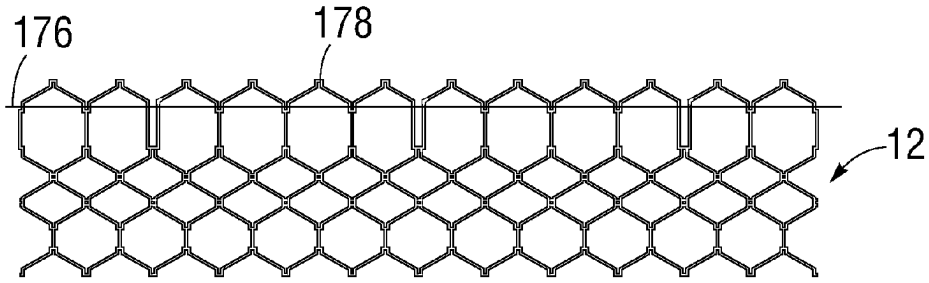


FIG. 56

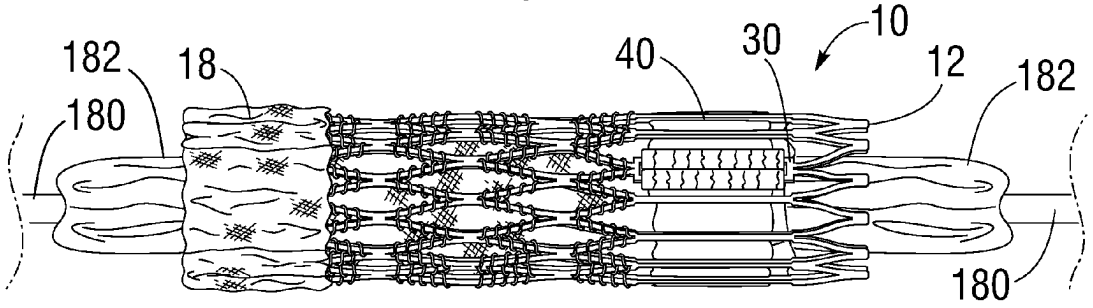


FIG. 57

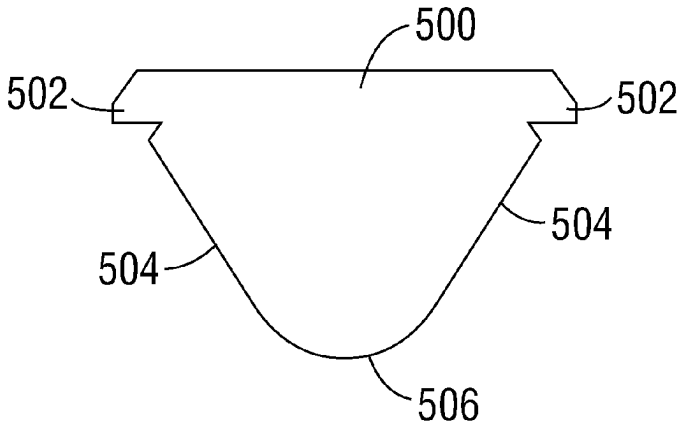


FIG. 58

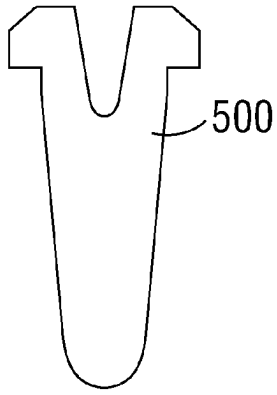


FIG. 59

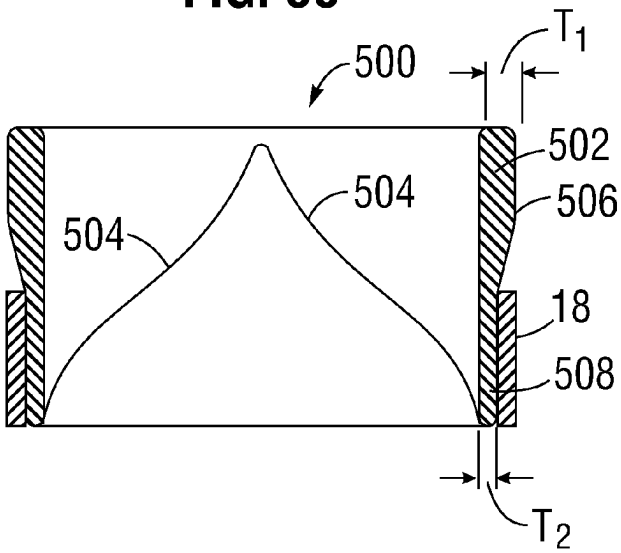


FIG. 60

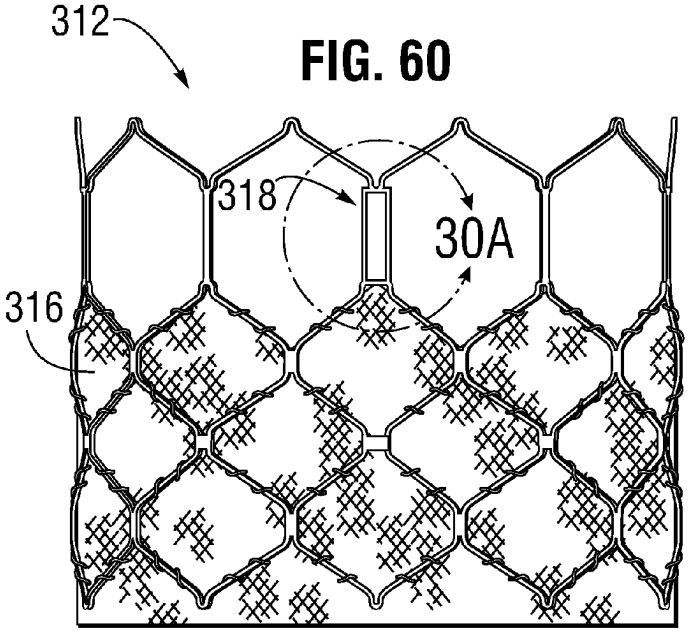


FIG. 60A

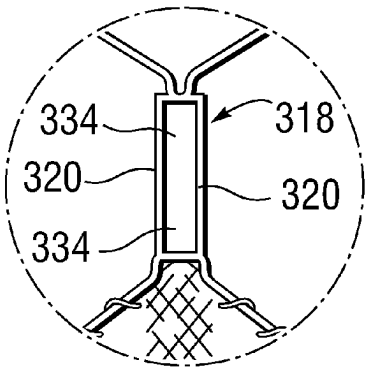


FIG. 61

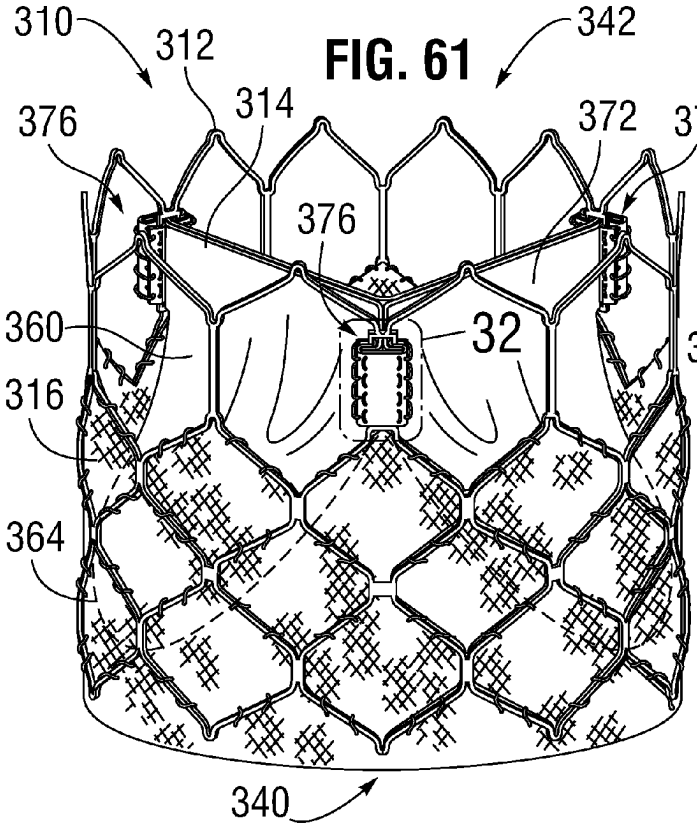


FIG. 62

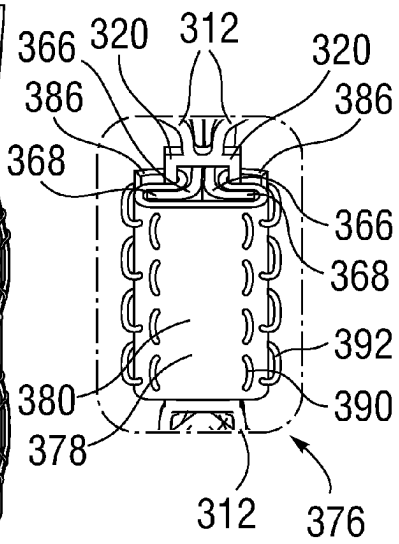


FIG. 63

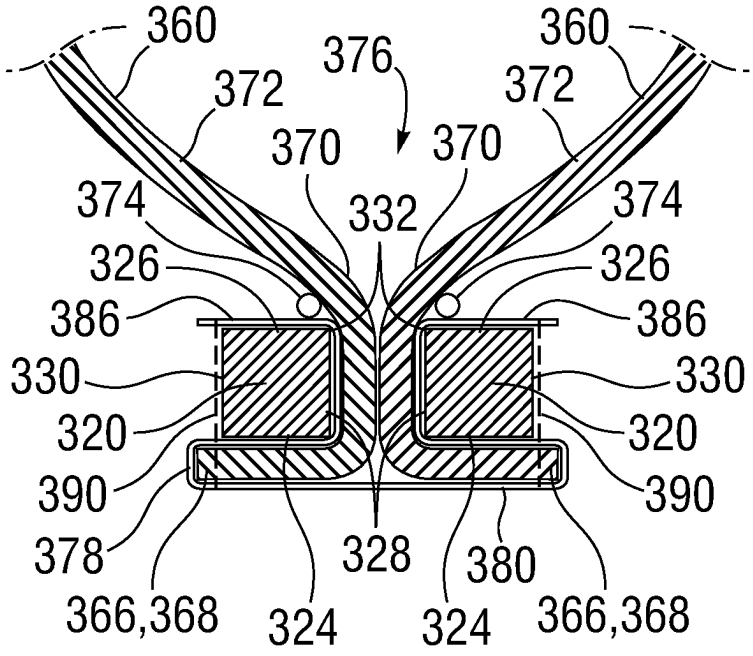

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FIG. 64

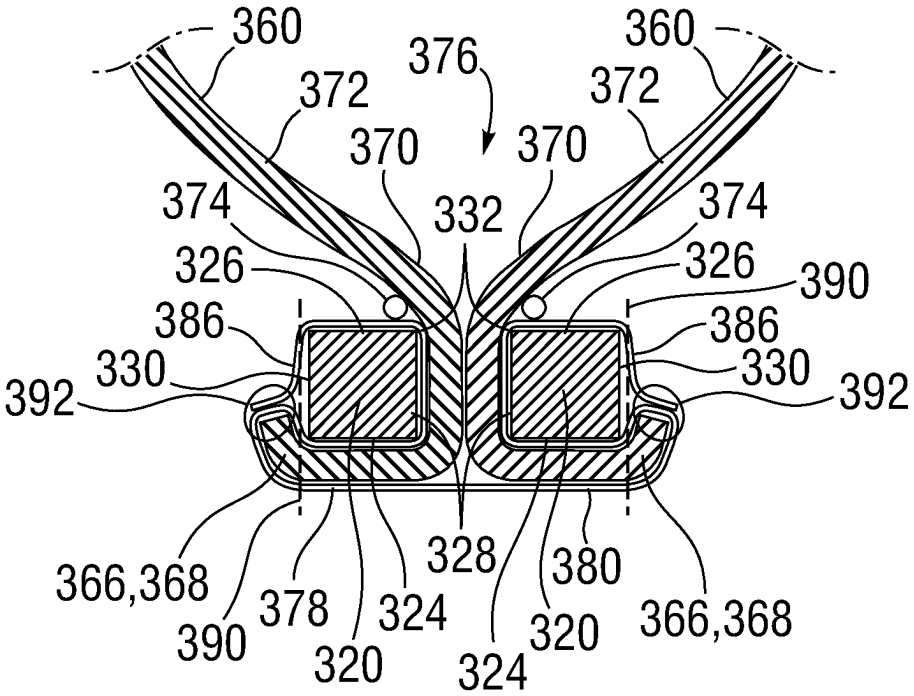

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FIG. 65

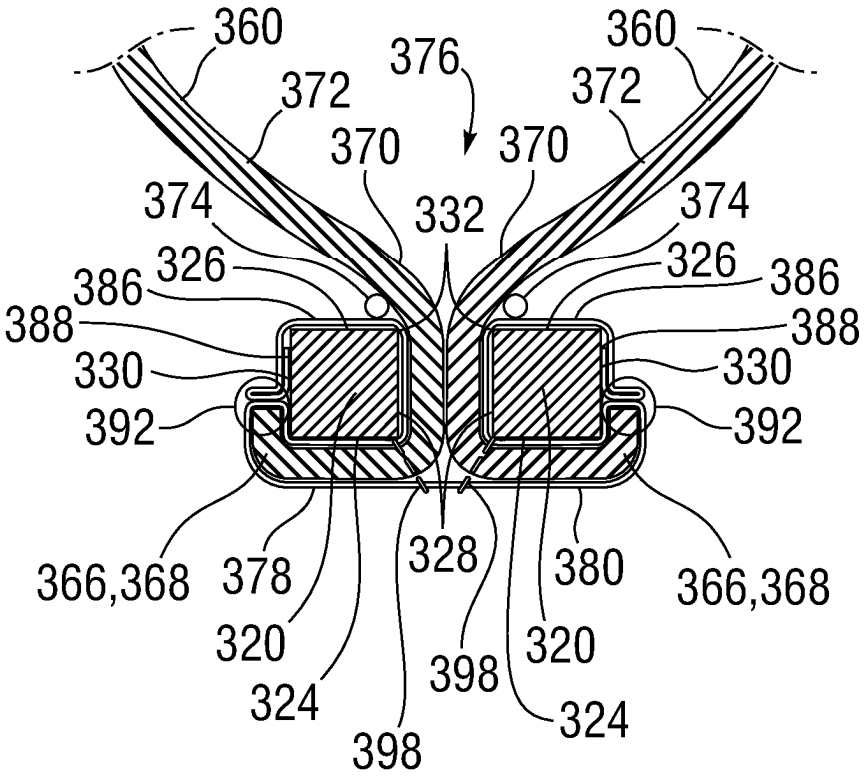

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FIG. 66

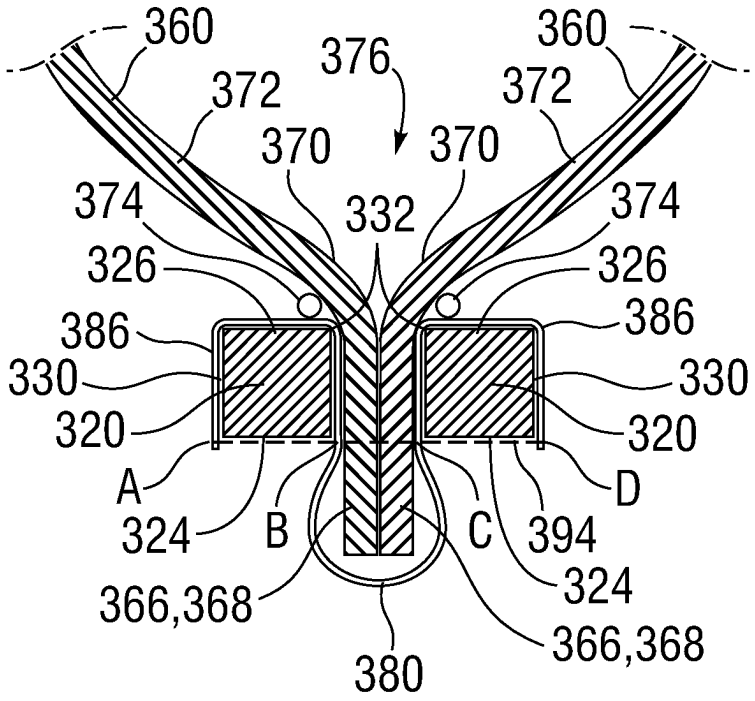

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FIG. 67

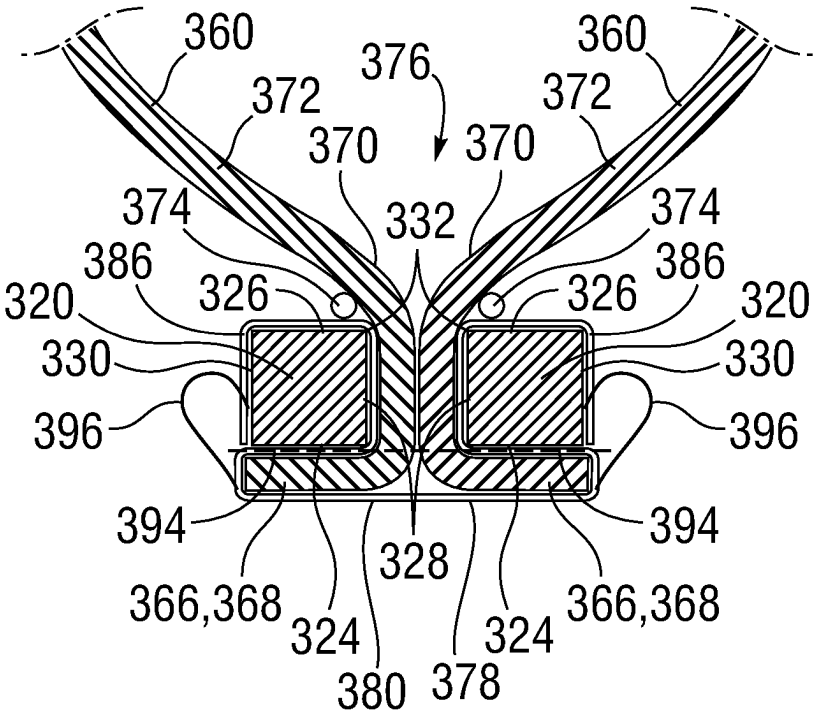

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FIG. 68

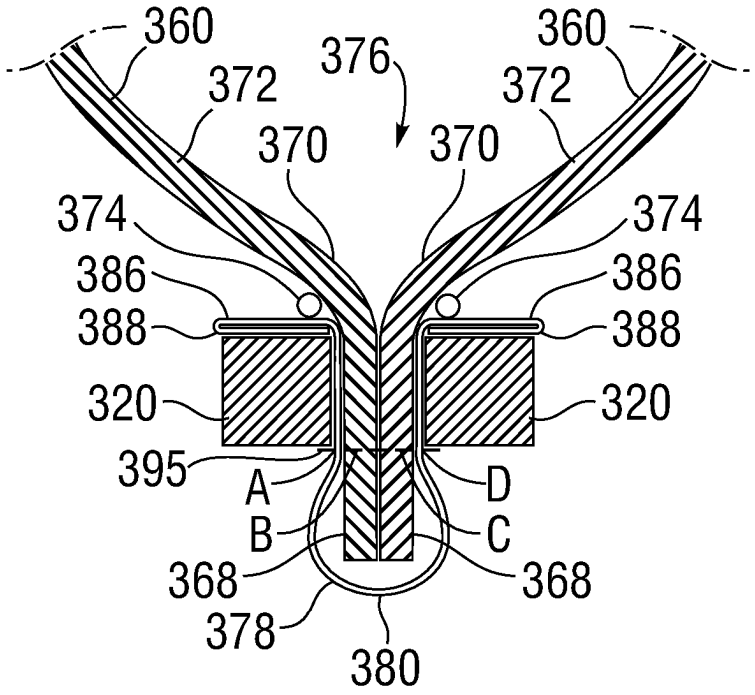

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FIG. 69

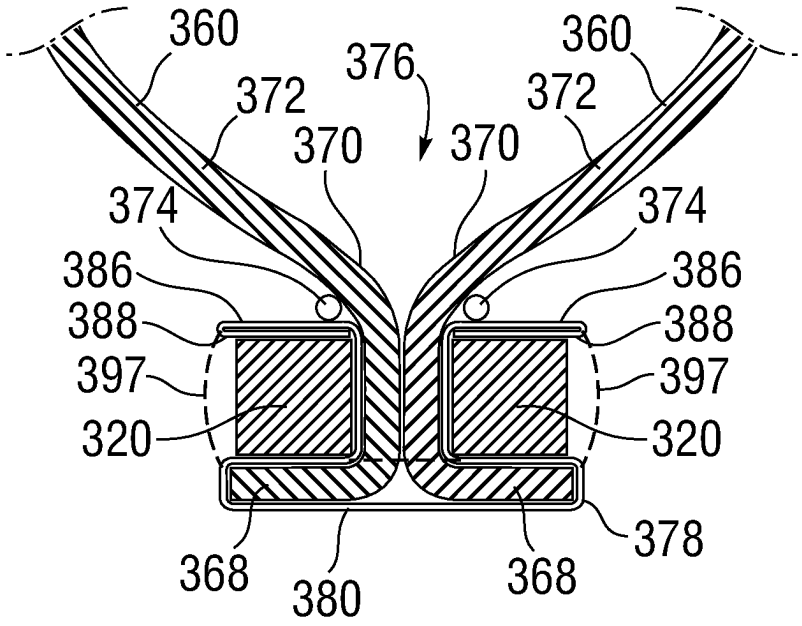

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FIG. 70

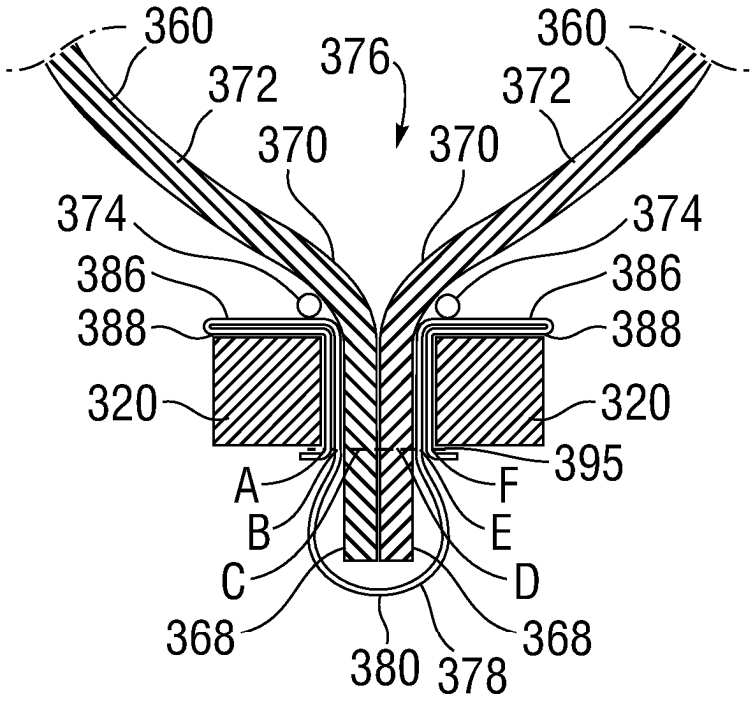

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FIG. 71

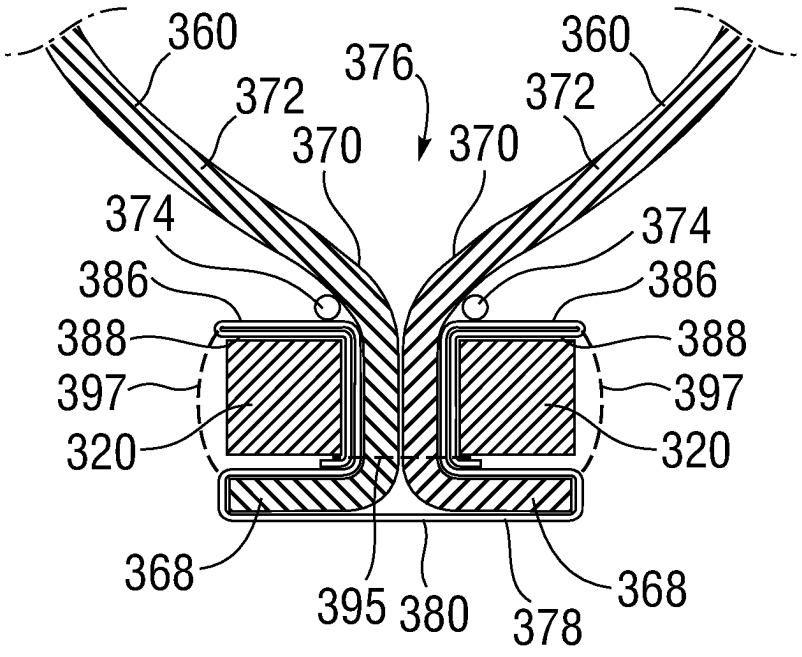

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FIG. 72

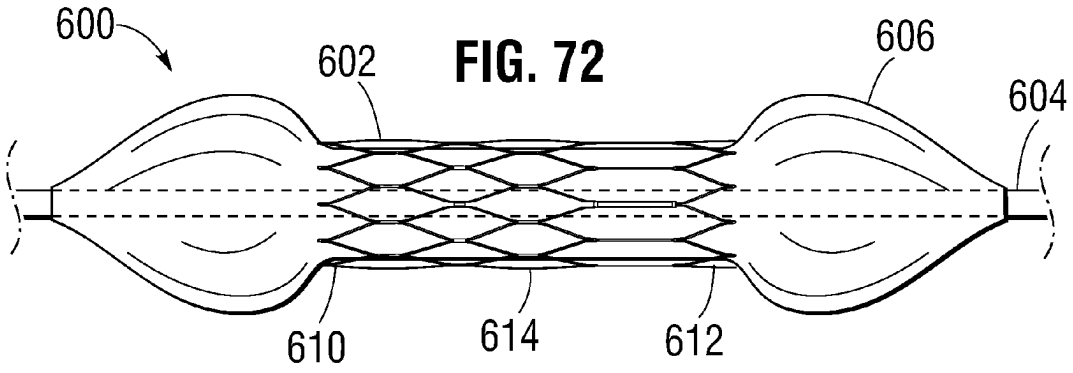


FIG. 73

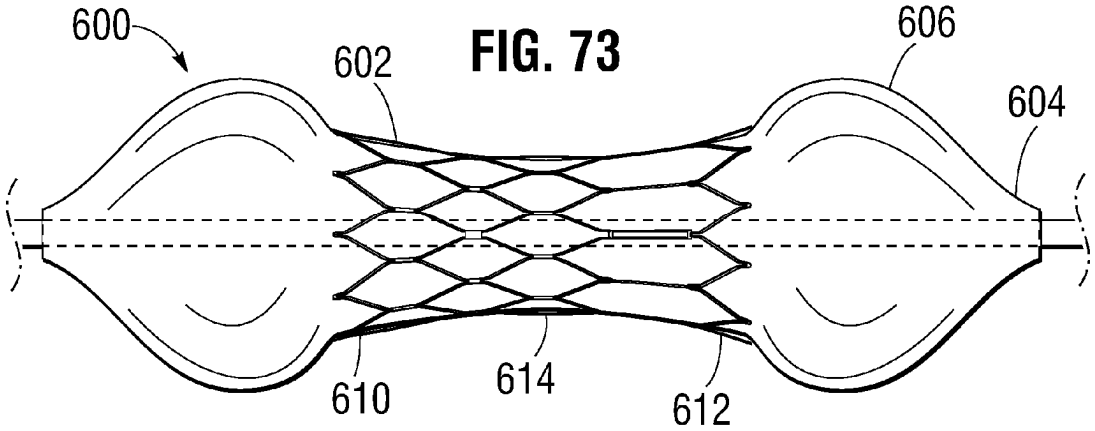
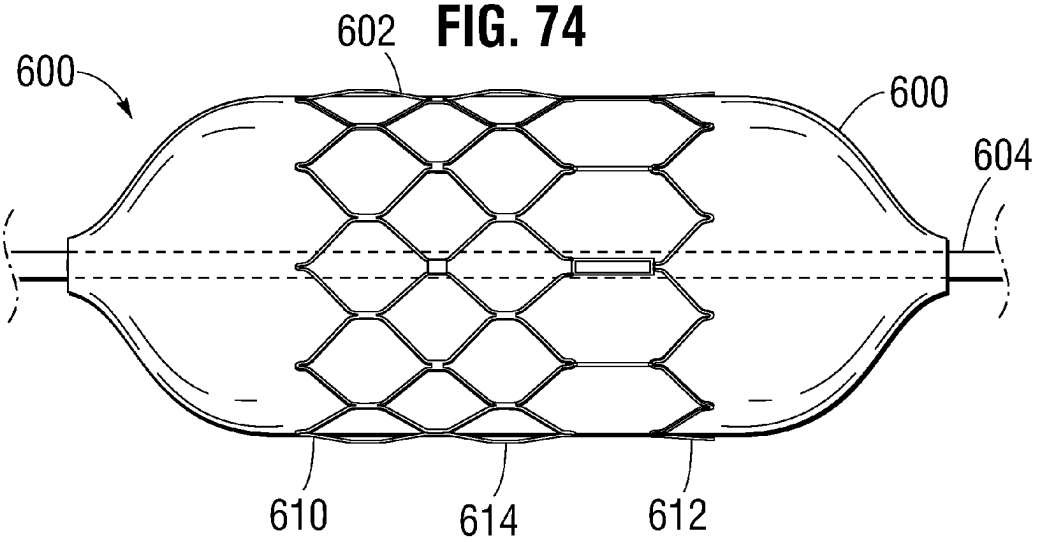


FIG. 74



PROSTHETIC HEART VALVE

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/390,107, entitled "COMMISSURE ATTACHMENT FOR PROSTHETIC VALVE," filed Oct. 5, 2010, and U.S. Provisional Application No. 61/508,513, entitled "PROSTHETIC HEART VALVE," filed Jul. 15, 2011, both of which applications are herein incorporated by reference.

FIELD

The present disclosure concerns embodiments of a prosthetic heart valve, and delivery systems for implanting heart valves.

BACKGROUND

The human heart can suffer from various valvular diseases. These valvular diseases can result in significant malfunctioning of the heart and ultimately require replacement of the native valve with an artificial valve. There are a number of known artificial valves and a number of known methods of implanting these artificial valves in humans.

Various surgical techniques may be used to replace or repair a diseased or damaged valve. Due to stenosis and other heart valve diseases, thousands of patients undergo surgery each year wherein the defective native heart valve is replaced by a prosthetic valve. Another less drastic method for treating defective valves is through repair or reconstruction, which is typically used on minimally calcified valves. The problem with surgical therapy is the significant risk it imposes on these chronically ill patients with high morbidity and mortality rates associated with surgical repair.

When the native valve is replaced, surgical implantation of the prosthetic valve typically requires an open-chest surgery during which the heart is stopped and patient placed on cardiopulmonary bypass (a so-called "heart-lung machine"). In one common surgical procedure, the diseased native valve leaflets are excised and a prosthetic valve is sutured to the surrounding tissue at the valve annulus. Because of the trauma associated with the procedure and the attendant duration of extracorporeal blood circulation, some patients do not survive the surgical procedure or die shortly thereafter. It is well known that the risk to the patient increases with the amount of time required on extracorporeal circulation. Due to these risks, a substantial number of patients with defective native valves are deemed inoperable because their condition is too frail to withstand the procedure. By some estimates, more than 50% of the subjects suffering from valve stenosis who are older than 80 years cannot be operated on for valve replacement.

Because of the drawbacks associated with conventional open-heart surgery, percutaneous and minimally-invasive surgical approaches are garnering intense attention. In one technique, a prosthetic valve is configured to be implanted in a much less invasive procedure by way of catheterization. For instance, U.S. Pat. Nos. 5,411,522 and 6,730,118, which are incorporated herein by reference, describe collapsible transcatheter heart valves that can be percutaneously introduced in a compressed state on a catheter and expanded in the desired position by balloon inflation or by utilization of a self-expanding frame or stent.

An important design parameter of a transcatheter heart valve is the diameter of the folded or crimped profile. The diameter of the crimped profile is important because it directly influences the physician's ability to advance the transcatheter heart valve through the femoral artery or vein. More particularly, a smaller profile allows for treatment of a wider population of patients, with enhanced safety.

SUMMARY

The present disclosure is directed toward methods and apparatuses relating to prosthetic valves, such as heart valves, delivery apparatuses, and assemblies of heart valves mounted on delivery apparatuses.

An exemplary embodiment of an assembly for implanting a prosthetic heart valve in a patient's body comprises a delivery apparatus comprising an elongated shaft and a radially expandable prosthetic heart valve mounted on the shaft in a radially collapsed configuration for delivery into the body. The prosthetic heart valve comprises an annular frame having an inflow end portion and an outflow end portion, and a leaflet structure positioned within the frame. The outer diameter of the inflow end portion of the frame is smaller than the outer diameter of the outflow end portion of the frame. The reduced diameter of the inflow end can be due to a reduce amount of materials positioned within the inflow end portion of the frame. The reduced diameter at the inflow end portion can make room for an outer skirt positioned around the inflow end portion.

In some embodiments, the heart valve can further comprise an outer skirt positioned around an outer surface of the inflow end portion of the frame such that an outer diameter of an inflow end portion of the prosthetic valve, inclusive of the outer skirt, is still less than or equal to an outer diameter of an outflow end portion of the prosthetic valve.

In some embodiments, the leaflet structure can comprise a plurality of leaflets that each comprises opposing side tabs on opposite sides of the leaflet. The side tabs can be secured to the outflow end portion of the frame. Each leaflet can further comprise a free outflow edge portion extending between the side tabs adjacent to the outflow end of the frame and an inflow edge portion extending between the side tabs adjacent to the inflow end of the frame. The inflow edge portion can comprise opposing axial edge portions that extend from the side tabs toward the inflow end in a generally axial direction and an intermediate edge portion that extends between the axial edge portions. The intermediate edge portion can comprise a curved apex portion adjacent to the inflow end of the frame and a pair of oblique portions that extend between the axial edge portions and the apex portion. The oblique portions can have a greater radius of curvature than the apex portion, forming a generally V-shaped leaflet.

In some embodiments, the frame comprises a plurality of angularly spaced commissure windows each comprising an enclosed opening between first and second axially oriented side struts. In these embodiments, the leaflet structure comprises a plurality of leaflets each comprising two opposing side tabs, each side tab being paired with an adjacent side tab of an adjacent leaflet to form commissures of the leaflet structure. Each commissure extends radially outwardly through a corresponding commissure window of the frame to a location outside of the frame and is sutured to the side struts of the commissure window. In some of these embodiments, the commissure windows of the frame are depressed radially inwardly relative to the portions of the frame extending between adjacent commissure windows when the prosthetic valve is in the collapsed configuration on the shaft.

In some embodiments, the frame comprises an inflow row of openings at the inflow end portion of the frame, an outflow row of openings at the outflow end portion of the frame, and at least one intermediate row of openings between the inflow row of openings and outflow row of openings. The openings of the inflow row of openings are larger than the openings of the at least one intermediate row of openings.

In some embodiments, portions of the leaflet structure protrude through openings in the frame while in the collapsed configuration on the shaft.

In some embodiments, the inflow end portion of the frame comprises a frame thickness that is less than a frame thickness of an intermediate portion of the frame between the inflow end portion and the outflow end portion.

Embodiments disclosed here can comprise an implantable prosthetic valve that is radially collapsible to a collapsed configuration and radially expandable to an expanded configuration. Such prosthetic valves can comprise an annular frame, a leaflet structure positioned within the frame, and an annular outer skirt positioned around an outer surface of the frame. The outer skirt can comprise an inflow edge secured to the frame at a first location, an outflow edge secured to the frame at a second location, and an intermediate portion between the inflow edge and the outflow edge. When the valve is in the expanded configuration, the intermediate portion of the outer skirt comprises slack in the axial direction between the inflow edge of the outer skirt and the outflow edge of the outer skirt, and when the valve is collapsed to the collapsed configuration, the axial distance between the inflow edge of the outer skirt and the outflow edge of the outer skirt increases, reducing the slack in the outer skirt in the axial direction.

In some of these embodiments, the outer skirt is not stretched in the axial direction when the valve is radially collapsed to the collapsed configuration and slack is removed from the intermediate portion of the outer skirt.

Some embodiments of an implantable prosthetic valve comprise an annular frame comprising a plurality of leaflet attachment portions, and a leaflet structure positioned within the frame and secured to the leaflet attachment portions of the frame. The leaflet structure comprises a plurality of leaflets, each leaflet comprising a body portion, two opposing primary side tabs extending from opposite sides of the body portion, and two opposing secondary tabs extending from the body adjacent to the primary side tabs. The secondary tabs are folded about a radially extending crease such that a first portion of the secondary tabs lies flat against the body portion of the respective leaflet, and the secondary tabs are folded about an axially extending crease such that a second portion of the secondary tabs extends in a different plane than the first portion. The second portion of each secondary tab is sutured to a respective primary tab and the secondary tabs are positioned inside of the frame.

In some of these embodiments, the first portion of each the secondary tab pivots about the axially extending crease and lays flat against the second portion of the secondary tab when the valve is collapsed to a radially collapsed configuration. The first portion of each secondary tab comprises an inner edge spaced radially from an inner surface of the frame, and the body portion of the leaflet articulates about the inner edges of the two secondary tabs of the leaflet in response to blood flowing through the valve when the valve is in operation within a patient's body.

Some embodiments disclosed herein comprise an implantable prosthetic valve that is radially collapsible to a collapsed configuration and radially expandable to an expanded configuration. The prosthetic valve comprises an annular frame having an inflow end portion and an outflow end portion, a leaflet structure positioned within the frame, and an annular inner skirt positioned within the frame. The inner skirt is secured to the inside of the frame and the inner skirt comprises a weave of a first set of strands with a second set of strands, both the first and second sets of strands being non-parallel with the axial direction of the valve. When the valve is collapsed from the expanded configuration to the collapsed configuration, the axial length of the frame increases and the both the first and second sets of strands rotate toward the axial direction of the valve, allowing the inner skirt to elongate in the axial direction along with the frame.

In some of these embodiments, the first set of strands are substantially perpendicular to the second set of strands when the valve is in the expanded configuration. In some embodiments, the first set of strands forms a first angle with the axial direction of the valve and the second set of strands forms a second angle with the axial direction of the valve, the first and second angles being substantially equal. In some of these embodiments, the first and second sets of strands comprise 20-denier yarn.

Some embodiments of an implantable prosthetic valve comprise a radially collapsible and expandable annular frame comprising a plurality of angularly spaced commissure windows each comprising an enclosed opening between first and second axially oriented side struts. The valve also comprises a leaflet structure positioned within the frame and comprising a plurality of leaflets each comprising two opposing side tabs. Each side tab is paired with an adjacent side tab of an adjacent leaflet to form commissures of the leaflet structure. Each pair of side tabs extends radially outwardly through a corresponding commissure window to a location outside of the frame, the portions of the tabs located outside of the frame extending circumferentially away from one another and along an exterior surface of the side struts. The valve further comprises a plurality of wedges, each wedge being positioned between the side struts of a commissure window and separating the pair of side tabs extending through the commissure window, the wedge being urged radially inwardly against the side tabs.

The wedges can be elongated in an axial direction and correspond in axial length with an axial length of the side struts of the commissure windows. The wedges can further restrict rotational movement of the pair of side tabs relative to the commissure window. Each wedge can be sutured to a flexible reinforcing sheet that is also sutured to each of the pair of side tabs, and each can be sutured to the pair of side tabs. The wedges can comprise a non-metallic material, such as suture material.

The foregoing and other objects, features, and advantages of the invention will become more apparent from the following detailed description, which proceeds with reference to the accompanying figures.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. **1-3** show an exemplary embodiment of a prosthetic heart valve.

FIGS. **4-10** show an exemplary frame of the heart valve of FIG. **1**.

FIGS. **11-15**B show another exemplary frame for use in a prosthetic heart valve.

FIGS. **16**A and **16**B show an exemplary inner skirt of the heart valve of FIG. **1**.

FIG. **17** shows another embodiment of a prosthetic heart valve in a compressed (crimped) condition with a deformed frame.

FIG. **18** shows the heart valve of FIG. **1** in a compressed state and mounted on an exemplary balloon catheter.

FIGS. **19-20** show the assembly of the inner skirt of FIG. **16**A with the frame of FIG. **4**.

FIGS. **21-28** show the assembly of an exemplary leaflet structure.

FIGS. **29-35** show the assembly of commissure portions of the leaflet structure with window frame portions of the frame.

FIGS. **36-40** show the assembly of the leaflet structure with the inner skirt along a lower edge of the leaflets.

FIG. **41** shows an exemplary outer skirt laid out flat.

FIGS. **42** and **43** show the exemplary prosthetic heart valve of FIG. **1**.

FIGS. **44-48** show an alternative embodiment of a prosthetic heart valve.

FIGS. **49-52** show portions of an alternative embodiment of a frame.

FIG. **53** shows a portion of the frame of FIG. **4** in a radially compressed state.

FIG. **54** shows a cross-sectional profile of the frame of FIG. **4**, showings a general tapering from the outflow end to the inflow end.

FIG. **55** shows the frame of FIG. **4** in an unrolled, flat configuration.

FIG. **56** shows the heart valve of FIG. **1** in a compressed state and mounted on an exemplary balloon catheter.

FIGS. **57** and **58** shows an embodiment of a leaflet have a generally V-shaped configuration.

FIG. **59** shows a cross-sectional view of an alternative embodiment of a prosthetic valve having a variable thickness frame.

FIG. **60** is a side view of an embodiment of a frame of a valve having commissure windows, prior to mounting a leaflet structure to the frame.

FIG. **60**A is an enlarged side view of one commissure window of FIG. **60**.

FIG. **61** is a perspective view of an embodiment of a prosthetic valve comprising the frame of FIG. **60** and a leaflet structure mounted to the valve.

FIG. **62** is an enlarged side view of one commissure of the valve of FIG. **61**.

FIGS. **63-71** are cross-sectional views of a commissure of the valve of FIG. **61** showing various techniques for suturing a pair of leaflet side tabs to a commissure window using a reinforcing sheet.

FIGS. **72-74** show balloon expansion of an alternative embodiment of a frame for a prosthetic valve having inflow and outflow end portions of reduced thickness.

DETAILED DESCRIPTION

FIGS. **1-3** show various views of a prosthetic heart valve **10**, according to one embodiment. The illustrated valve is adapted to be implanted in the native aortic annulus, although in other embodiments it can be adapted to be implanted in the other native annuluses of the heart. The valve **10** can have four main components: a stent, or frame, **12**, a valvular structure **14**, an inner skirt **16**, and an outer skirt **18**.

The valvular structure **14** can comprise three leaflets **40**, collectively forming a leaflet structure, which can be arranged to collapse in a tricuspid arrangement, as best shown in FIG. **2**. The lower edge of leaflet structure **14** desirably has an undulating, curved scalloped shape (suture line **154** shown in FIG. **1** tracks the scalloped shape of the leaflet structure). By forming the leaflets with this scalloped geometry, stresses on the leaflets are reduced, which in turn improves durability of the valve. Moreover, by virtue of the scalloped shape, folds and ripples at the belly of each leaflet (the central region of each leaflet), which can cause early calcification in those areas, can be eliminated or at least minimized. The scalloped geometry also reduces the amount of tissue material used to form leaflet structure, thereby allowing a smaller, more even crimped profile at the inflow end of the valve. The leaflets **40** can be formed of pericardial tissue (e.g., bovine pericardial tissue), biocompatible synthetic materials, or various other suitable natural or synthetic materials as known in the art and described in U.S. Pat. No. 6,730,118, which is incorporated by reference herein.

The bare frame **12** is shown in FIG. **4**. The frame **12** can be formed with a plurality of circumferentially spaced slots, or commissure windows, **20** (three in the illustrated embodiment) that are adapted to mount the commissures of the valvular structure **14** to the frame, as described in greater detail below. The frame **12** can be made of any of various suitable plastically-expandable materials (e.g., stainless steel, etc.) or self-expanding materials (e.g., Nitinol) as known in the art. When constructed of a plastically-expandable material, the frame **12** (and thus the valve **10**) can be crimped to a radially compressed state on a delivery catheter and then expanded inside a patient by an inflatable balloon or equivalent expansion mechanism. When constructed of a self-expandable material, the frame **12** (and thus the valve **10**) can be crimped to a radially compressed state and restrained in the compressed state by insertion into a sheath or equivalent mechanism of a delivery catheter. Once inside the body, the valve can be advanced from the delivery sheath, which allows the valve to expand to its functional size.

Suitable plastically-expandable materials that can be used to form the frame **12** include, without limitation, stainless steel, a nickel based alloy (e.g., a cobalt-chromium or a nickel-cobalt-chromium alloy), polymers, or combinations thereof. In particular embodiments, frame **12** is made of a nickel-cobalt-chromium-molybdenum alloy, such as MP35N™ (tradename of SPS Technologies), which is equivalent to UNS R30035 (covered by ASTM F562-02). MP35N™/UNS R30035 comprises 35% nickel, 35% cobalt, 20% chromium, and 10% molybdenum, by weight. It has been found that the use of MP35N to form frame **12** provides superior structural results over stainless steel. In particular, when MP35N is used as the frame material, less material is needed to achieve the same or better performance in radial and crush force resistance, fatigue resistances, and corrosion resistance. Moreover, since less material is required, the crimped profile of the frame can be reduced, thereby providing a lower profile valve assembly for percutaneous delivery to the treatment location in the body.

Referring to FIGS. **4** and **5**, the frame **12** in the illustrated embodiment comprises a first, lower row I of angled struts **22** arranged end-to-end and extending circumferentially at the inflow end of the frame; a second row II of circumferentially extending, angled struts **24**; a third row III of circumferentially extending, angled struts **26**; a fourth row IV of circumferentially extending, angled struts **28**; and a fifth row V of circumferentially extending, angled struts **32** at the outflow end of the frame. A plurality of substantially straight axially extending struts **34** can be used to interconnect the struts **22** of the first row I with the struts **24** of the second row II. The fifth row V of angled struts **32** are connected to the fourth row IV of angled struts **28** by a plurality of axially extending window frame portions **30** (which define the commissure windows **20**) and a plurality of axially extending struts **31**. Each axial strut **31** and each frame portion **30** extends from a location defined by the convergence of the lower ends of two angled struts **32** to another location defined by the convergence of the upper

ends of two angled struts **28**. FIGS. **6**, **7**, **8**, **9** and **10** are enlarged views of the portions of the frame **12** identified by letters A, B, C, D and E, respectively, in FIG. **4**.

Each commissure window frame portion **30** mounts a respective commissure of the leaflet structure **14**. As can be seen each frame portion **30** is secured at its upper and lower ends to the adjacent rows of struts to provide a robust configuration that enhances fatigue resistance under cyclic loading of the valve compared to known cantilevered struts for supporting the commissures of the leaflet structure. This configuration enables a reduction in the frame wall thickness to achieve a smaller crimped diameter of the valve. In particular embodiments, the thickness T of the frame **12** (FIG. **4**) measured between the inner diameter and outer diameter is about 0.48 mm or less.

The struts and frame portions of the frame collectively define a plurality of open cells of the frame. At the inflow end of the frame **12**, struts **22**, struts **24**, and struts **34** define a lower row of cells defining openings **36**. The second, third, and fourth rows of struts **24**, **26**, and **28** define two intermediate rows of cells defining openings **38**. The fourth and fifth rows of struts **28** and **32**, along with frame portions **30** and struts **31**, define an upper row of cells defining openings **40**. The openings **40** are relatively large and are sized to allow portions of the leaflet structure **14** to protrude, or bulge, into and/or through the openings **40** when the frame **12** is crimped in order to minimize the crimping profile.

As best shown in FIG. **7**, the lower end of the strut **31** is connected to two struts **28** at a node or junction **44**, and the upper end of the strut **31** is connected to two struts **32** at a node or junction **46**. The strut **31** can have a thickness S1 that is less than the thicknesses S2 of the junctions **44**, **46**. FIG. **53** shows a portion of the frame **12** in a crimped state. The junctions **44**, **46**, along with junctions **64**, prevent full closure of openings **40**. FIG. **18** shows the valve **10** crimped on a balloon catheter. As can be seen, the geometry of the struts **31**, and junctions **44**, **46** and **64** assists in creating enough space in openings **40** in the crimped state to allow portions of the leaflets to protrude (i.e., bulge) outwardly through openings. This allows the valve to be crimped to a relatively smaller diameter than if all of the leaflet material is constrained within the crimped frame.

The frame **12** is configured to prevent or at least minimize possible over-expansion of the valve at a predetermined balloon pressure, especially at the outflow end portion of the frame, which supports the leaflet structure **14**. In one aspect, the frame is configured to have relatively larger angles **42***a*, **42***b*, **42***c*, **42***d*, **42***e* between struts. The larger the angle, the greater the force required to open (expand) the frame. This phenomenon is schematically illustrated in FIGS. **15**A and **15**B. FIG. **15**A shows a strut **32** when the frame **12** is in its compressed state (e.g., mounted on a balloon). The vertical distance d_1 between the ends of the struts is greatest when the frame is compressed, providing a relatively large moment between forces F_1 and F_2 acting on the ends of the strut in opposite directions upon application of an opening force from inflation of the balloon (or expansion of another expansion device). When the frame expands radially, the vertical distance between the ends of the strut decreases to a distance d_2, as depicted in FIG. **15**B. As the vertical distance decreases, so does the moment between forces F_1 and F_2. Hence, it can be seen that a relatively greater expansion force is required as the vertical distance and the moment between the ends of the strut decreases. Moreover, strain hardening (stiffening) at the ends of the strut increases as the frame expands, which increases the expansion force required to induce further plastic deformation at the ends of the strut. As such, the angles between the struts of the frame can be selected to limit radial expansion of the frame at a given opening pressure (e.g., inflation pressure of the balloon). In particular embodiments, these angles are at least 110 degrees or greater when the frame is expanded to its functional size, and even more particularly these angles are at least 120 degrees or greater when the frame is expanded to its functional size.

In addition, the inflow and outflow ends of a frame generally tend to over-expand more so than the middle portion of the frame due to the "dog boning" effect of the balloon used to expand the valve. To protect against over-expansion of the leaflet structure **14**, the leaflet structure desirably is secured to the frame **12** below the upper row of struts **32**, as best shown in FIG. **1**. FIG. **55** shows a flattened view of the frame **12** similar to FIG. **5**, but showing a line **176** superimposed over the frame to indicate the position of the upper edges of the leaflets **40**. Thus, in the event that the outflow end of the frame is over-expanded, the leaflet structure is positioned at a level below where over-expansion is likely to occur, thereby protecting the leaflet structure from over-expansion.

In a known valve construction, the leaflets can protrude outwardly beyond the outflow end of the frame when the valve is crimped if the leaflets are mounted too close to the distal end of the frame. If the delivery catheter on which the crimped valve is mounted includes a pushing mechanism or stop member that pushes against or abuts the outflow end of the valve (for example, to maintain the position of the crimped valve on the delivery catheter), the pushing member or stop member can damage the exposed leaflets that extend beyond the outflow end of the frame. Another benefit of mounting the leaflets at a location spaced from the outflow end **178** of the frame is that when the valve is crimped on a delivery catheter, as shown in FIG. **56**, the leaflets **40** do not protrude beyond the outflow end **178** of the frame in the axial direction. As such, if the delivery catheter includes a pushing mechanism or stop member that pushes against or abuts the outflow end of the valve, the pushing mechanism or stop member can contact the end **178** of the frame, and not leaflets **40**, so as to avoid damage to the leaflets.

Also, as can be seen in FIG. **5**, the openings **36** of the lowermost row of openings in the frame are relatively larger than the openings **38** of the two intermediate rows of openings. As shown in FIG. **54**, this allows the frame, when crimped, to assume an overall tapered shape that tapers from a maximum diameter D_1 at the outflow end of the valve to a minimum diameter D_2 at the inflow end of the valve. When crimped, the frame **12** has a reduced diameter region extending along a portion of the frame adjacent the inflow end of the frame, indicated by reference number **174**, that generally corresponds to the region of the frame covered by the outer skirt **18**. The diameter of region **174** is reduced compared to the diameter of the upper portion of the frame (which is not covered by the outer skirt) such that the outer skirt **18** does not increase the overall crimp profile of the valve. When the valve is deployed, the frame can expand to the cylindrical shape shown in FIG. **4**. In one example, the frame of a 26-mm valve, when crimped, had a diameter D_1 of 14 French at the outflow end of the valve and a diameter D_2 of 12 French at the inflow end of the valve.

FIGS. **11** and **12** show an alternative frame **50** that can be incorporated in the valve **10**. The frame **50** comprises multiple rows of circumferentially extending, angled struts **52** that are connected to each other at nodes, or connecting portions, **54** and **56**. The uppermost row of struts **52** are connected to an adjacent row of struts by a plurality of axially extending struts **58** and commissure window frame portions **60**. Each commissure frame portion **60** defines a slot, or

commissure window, **62** for mounting a respective commissure of the valvular structure, as described in greater detail below. In particular embodiments, the thickness T of the frame **50** is about 0.45 mm or less. FIGS. **13** and **14** are enlarged views of the portions of the frame **50** identified by letters A and B, respectively, in FIG. **12**.

The main functions of the inner skirt **16** are to assist in securing the valvular structure **14** to the frame **12** and to assist in forming a good seal between the valve and the native annulus by blocking the flow of blood through the open cells of the frame **12** below the lower edge of the leaflets. The inner skirt **16** desirably comprises a tough, tear resistant material such as polyethylene terephthalate (PET), although various other synthetic or natural materials can be used. The thickness of the skirt desirably is less than 6 mil, and desirably less than 4 mil, and even more desirably about 2 mil. In particular embodiments, the skirt **16** can have a variable thickness, for example, the skirt can be thicker at its edges than at its center. In one implementation, the skirt **16** can comprise a PET skirt having a thickness of about 0.07 mm at its edges and about 0.06 mm at its center. The thinner skirt can provide for better crimping performances while still providing good perivalvular sealing.

The skirt **16** can be secured to the inside of frame **12** via sutures **70**, as shown in FIG. **39**. Valvular structure **14** can be attached to the skirt via one or more thin PET reinforcing strips **72** (which collectively can form a sleeve), discussed below, which enables a secure suturing and protects the pericardial tissue of the leaflet structure from tears. Valvular structure **14** can be sandwiched between skirt **16** and the thin PET strips **72** as shown in FIG. **38**. Sutures **154**, which secure the PET strip and the leaflet structure **14** to skirt **16**, can be any suitable suture, such as an Ethibond suture. Sutures **154** desirably track the curvature of the bottom edge of leaflet structure **14**, as described in more detail below.

Known fabric skirts comprise a weave of warp and weft fibers that extend perpendicular to each other and with one set of fibers extending perpendicularly to the upper and lower edges of the skirt. When the metal frame, to which the fabric skirt is secured, is radially compressed, the overall axial length of the frame increases. Unfortunately, a fabric skirt, which inherently has limited elasticity, cannot elongate along with the frame and therefore tends to deform the struts of the frame and prevents uniform crimping.

FIG. **17** shows an example of a crimped valve where the struts have been deformed in several places, as indicated by reference number **100**, by a skirt having fibers that extend perpendicular to the upper and lower edges of the skirt. Moreover, the fabric tends to bunch or create bulges of excess material in certain locations, which limits the minimum crimping profile and prevents uniform crimping.

Referring to FIG. **16**B, in contrast to known fabric skirts, the skirt **16** desirably is woven from a first set of fibers, or yarns or strands, **78** and a second set of fibers, or yarns or strands, **80**, both of which are non-perpendicular to the upper edge **82** and the lower edge **84** of the skirt. In particular embodiments, the first set of fibers **78** and the second set of fibers **80** extend at angles of about 45 degrees relative to the upper and lower edges **82**, **84**. The skirt **16** can be formed by weaving the fibers at 45 degree angles relative to the upper and lower edges of the fabric. Alternatively, the skirt can be diagonally cut from a vertically woven fabric (where the fibers extend perpendicular to the edges of the material) such that the fibers extend at 45 degree angles relative to the cut upper and lower edges of the skirt. As further shown in FIG. **16**B, the opposing short edges **86**, **88** of the skirt desirably are non-perpendicular to the upper and lower edges **82**, **84**. For example, the short edges **86**, **88** desirably extend at angles of about 45 degrees relative to the upper and lower edges and therefore are aligned with the first set of fibers **78**. Therefore the overall shape of the skirt is that of a rhomboid.

FIGS. **19**A and **19**B shows the skirt **16** after opposing edge portions **90**, **92** have been sewn together to form the annular shape of the skirt. As shown, the edge portion **90** can be placed in an overlapping relationship relative to the opposite edge portion **92**, and the two edge portions can be sewn together with a diagonally extending suture line **94** that is parallel to edges **86**, **88**. The upper edge portion of the skirt **16** can be formed with a plurality of projections **96** that define an undulated shape that generally follows the shape of the fourth row of struts **28** immediately adjacent the lower ends of axial struts **31**. In this manner, as best shown in FIG. **20**, the upper edge of skirt **16** can be tightly secured to struts **28** with sutures **70**. Skirt **16** can also be formed with slits **98** to facilitate attachment of the skirt to the frame. Slits **98** are dimensioned so as to allow an upper edge portion of skirt to be partially wrapped around struts **28** and reduce stresses in the skirt during the attachment procedure. For example, in the illustrated embodiment, skirt **16** is placed on the inside of frame **12** and an upper edge portion of the skirt is wrapped around the upper surfaces of struts **28** and secured in place with sutures **70**. Wrapping the upper edge portion of the skirt around struts **28** in this manner provides for a stronger and more durable attachment of the skirt to the frame. The skirt **16** can also be secured to the first, second, and third rows of struts **22**, **24**, and **26**, respectively, with sutures **70**.

Referring again to FIG. **16**B, due to the orientation of the fibers relative to the upper and lower edges, the skirt can undergo greater elongation in the axial direction (i.e., in a direction from the upper edge **82** to the lower edge **84**).

Thus, when the metal frame **12** is crimped (as shown in FIG. **18**), the skirt **16** can elongate in the axial direction along with the frame and therefore provides a more uniform and predictable crimping profile. Each cell of the metal frame in the illustrated embodiment includes at least four angled struts that rotate towards the axial direction (i.e., the angled struts become more aligned with the length of the frame). The angled struts of each cell function as a mechanism for rotating the fibers of the skirt in the same direction of the struts, allowing the skirt to elongate along the length of the struts. This allows for greater elongation of the skirt and avoids undesirable deformation of the struts when the valve is crimped.

In addition, the spacing between the woven fibers or yarns can be increased to facilitate elongation of the skirt in the axial direction. For example, for a PET skirt **16** formed from 20-denier yarn, the yarn density can be about 15% to about 30% less than a conventional PET skirt. In some examples, the yarn spacing of the skirt **16** can be from about 155 yarns per inch to about 180 yarns per inch, such about 160 yarns per inch, whereas in a conventional PET skirt the yarn spacing can be from about 217 yarns per inch to about 247 yarns per inch. The oblique edges **86**, **88** promote uniform and even distribution of the fabric material along inner circumference of the frame during crimping so as to minimize bunching of the fabric to facilitate uniform crimping to the smallest possible diameter. Additionally, cutting diagonal sutures in a vertical manner may leave loose fringes along the cut edges. The oblique edges **86**, **88** help minimize this from occurring. As noted above, FIG. **17** shows a crimped valve with a conventional skirt that has fibers that run perpendicular to the upper and lower edges of the skirt. Comparing FIGS. **17** and **18**, it is apparent that the construction of skirt **16** avoids

undesirable deformation of the frame struts and provides more uniform crimping of the frame.

In alternative embodiments, the skirt can be formed from woven elastic fibers that can stretch in the axial direction during crimping of the valve. The warp and weft fibers can run perpendicular and parallel to the upper and lower edges of the skirt, or alternatively, they can extend at angles between 0 and 90 degrees relative to the upper and lower edges of the skirt, as described above.

The inner skirt **16** can be sutured to the frame **12** at locations away from the suture line **154** so that the skirt can be more pliable in that area (see FIG. **28**). This can avoid stress concentrations at the suture line **154**, which attaches the lower edges of the leaflets to the skirt **16**.

As noted above, the leaflet structure **14** in the illustrated embodiment includes three flexible leaflets **40** (although a greater or fewer number of leaflets can be used). As best shown in FIG. **21**, each leaflet **40** in the illustrated configuration has an upper (outflow) free edge **110** extending between opposing upper tabs **112** on opposite sides of the leaflet. Below each upper tab **112** there is a notch **114** separating the upper tab from a corresponding lower tab **116**. The lower (inflow) edge portion **108** of the leaflet extending between respective ends of the lower tabs **116** includes vertical, or axial, edge portions **118** on opposites of the leaflets extending downwardly from corresponding lower tabs **116** and a substantially V-shaped, intermediate edge portion **120** having a smooth, curved apex portion **119** at the lower end of the leaflet and a pair of oblique portions **121** that extend between the axial edge portions and the apex portion. The oblique portions can have a greater radius of curvature than the apex portion. Each leaflet **40** can have a reinforcing strip **72** secured (e.g., sewn) to the inner surface of the lower edge portion **108**, as shown in FIG. **22**.

The leaflets **40** can be secured to one another at their adjacent sides to form commissures **122** of the leaflet structure. A plurality of flexible connectors **124** (one of which is shown in FIG. **23**) can be used to interconnect pairs of adjacent sides of the leaflets and to mount the leaflets to the commissure window frame portions **30**. The flexible connectors **124** can be made from a piece of woven PET fabric, although other synthetic and/or natural materials can be used. Each flexible connector **124** can include a wedge **126** extending from the lower edge to the upper edge at the center of the connector. The wedge **126** can comprise a non-metallic material, such as a rope or a piece of Ethibond 2-0 suture material, secured to the connector with a temporary suture **128**. The wedge **126** helps prevent rotational movement of the leaflet tabs once they are secured to the commissure window frame portions **30**. The connector **124** can have a series of inner notches **130** and outer notches **132** formed along its upper and lower edges.

FIG. **24** shows the adjacent sides of two leaflets **40** interconnected by a flexible connector **124**. The opposite end portions of the flexible connector **124** can be placed in an overlapping relationship with the lower tabs **116** with the inner notches **130** aligned with the vertical edges of the tabs **116**. Each tab **116** can be secured to a corresponding end portion of the flexible connector **124** by suturing along a line extending from an outer notch **132** on the lower edge to an outer notch **132** on the upper edge of the connector. Three leaflets **40** can be secured to each other side-to-side using three flexible connectors **124**, as shown in FIG. **25**.

Referring now to FIGS. **26** and **27**, the adjacent sub-commissure portions **118** of two leaflets can be sutured directly to each other. In the example shown, PTFE-6-0 suture material is used to form in-and-out stitches **133** and comb stitches **134** that extend through the sub-commissure portions **118** and the reinforcing strips **72** on both leaflets. The two remaining pairs of adjacent sub-commissure portions **118** can be sutured together in the same manner to form the assembled leaflet structure **14**, which can then be secured to the frame **12** in the following manner.

As noted above, the inner skirt **16** can be used to assist in suturing the leaflet structure **14** to the frame. As shown in FIG. **28**, the skirt **16** can have an undulating temporary marking suture **136** to guide the attachment of the lower edges of each leaflet **40**. The skirt **16** itself can be sutured to the struts of the frame **12** using sutures **70**, as noted above, before securing the leaflet structure **14** to the skirt **16**. The struts that intersect the marking suture **136** desirably are not attached to the skirt **16**. This allows the skirt **16** to be more pliable in the areas not secured to the frame and minimizes stress concentrations along the suture line that secures the lower edges of the leaflets to the skirt. The portion of the skirt **16** demarcated by rectangle **140** initially is left unsecured to the frame **12**, and is later secured to the frame after the leaflet structure **14** is secured to the skirt, as further described below. As noted above, when the skirt is secured to the frame, the fibers **78**, **80** of the skirt (see FIG. **16**B) generally align with the angled struts of the frame to promote uniform crimping and expansion of the frame.

FIG. **29** is a cross-sectional view of a portion of the frame and leaflet structure showing the adjacent tab portions of two leaflets secured to a corresponding window frame portion **30**. FIGS. **30-36** show one specific approach for securing the commissure portions **122** of the leaflet structure **14** to the commissure window frame portions **30** of the frame. First, as shown in FIG. **30**, the flexible connector **124** securing two adjacent sides of two leaflets is folded widthwise and the upper tab portions **112** are folded downwardly against the flexible connector. As best shown in FIGS. **30** and **31**, each upper tab portion **112** is creased lengthwise (vertically) to assume an L-shape having an inner portion **142** folded against the inner surface of the leaflet and an outer portion **144** folded against the connector **124**. The outer portion **144** can then be sutured to the connector **124** along a suture line **146**. Next, as shown in FIG. **31**, the commissure tab assembly (comprised of a pair of lower tab portions **116** connected by connector **124**) is inserted through the commissure window **20** of a corresponding window frame portion **30**. FIG. **32** is a side view of the frame **12** showing the commissure tab assembly extending outwardly through the window frame portion **30**.

As best shown in FIGS. **29** and **33**, the commissure tab assembly is pressed radially inwardly at the wedge **126** such that one of the lower tab portions **116** and a portion of the connector **124** is folded against the frame **12** on one side of the window frame portion **30** and the other lower tab portion **116** and a portion of the connector **124** is folded against the frame **12** on other side of the window frame portion **30**. A pair of suture lines **148** are formed to retain the lower tab portions **116** against the frame **12** in the manner shown in FIG. **29**. Each suture line **148** extends through connector **124**, a lower tab portion **116**, the wedge **126**, and another portion of connector **124**. Then, as shown in FIGS. **29** and **34**, each lower tab portion **116** is secured to a corresponding upper tab portion **112** with a primary suture line **150** that extends through one layer of connector **124**, the lower tab portion **116**, another layer of connector **124**, another layer of connector **124**, and the upper tab portion **112**. Finally, as shown in FIGS. **29** and **35**, the suture material used to form the primary suture line **150** can be used to further form whip stitches **152** at the edges of the tab portions **112**, **116** that extend through two layers of connector **124** sandwiched between tab portions **112**, **116**.

As shown in FIGS. **29** and **30**, the folded down upper tab portions **112** form a double layer of leaflet material at the commissures. The inner portions **142** of the upper tab portions **112** are positioned flat abutting layers of the two leaflets **40** forming the commissures, such that each commissure comprises four layers of leaflet material just inside of the window frames **30**. This four layered portion of the commissures can be more resistant to bending, or articulating, than the portion of the leaflets **40** just radially inward from the relatively more rigid four layered portion. This causes the leaflets **40** to articulate primarily at inner edges **143** of the folded-down inner portions **142** in response to blood flowing through the valve during operation within the body, as opposed to articulating about the axial struts of the window frames **30**. Because the leaflets articulate at a location spaced radially inwardly from the window frames **30**, the leaflets can avoid contact with and damage from the frame. However, under high forces, the four layered portion of the commissures can splay apart about a longitudinal axis **145** (FIG. **29**) adjacent to the window frame **30**, with each inner portion **142** folding out against the respective outer portion **144**. For example, this can occur when the valve **10** is compressed and mounted onto a delivery shaft, allowing for a smaller crimped diameter. The four layered portion of the commissures can also splay apart about axis **145** when the balloon catheter is inflated during expansion of the valve, which can relieve some of the pressure on the commissures caused by the balloon and so the commissures are not damaged during expansion.

After all three commissure tab assemblies are secured to respective window frame portions **30**, the lower edges of the leaflets **40** between the commissure tab assemblies can be sutured to the inner skirt **16**. For example, as shown in FIGS. **36-38**, each leaflet **40** can be sutured to the skirt **16** along suture line **154** using, for example, Ethibond thread. The sutures can be in-and-out sutures extending through each leaflet **40**, the skirt **16** and each reinforcing strip **72**. Each leaflet **40** and respective reinforcing strip **72** can be sewn separately to the skirt **16**. In this manner, the lower edges of the leaflets are secured to the frame **12** via the skirt **16**. As shown in FIG. **38**, the leaflets can be further secured to the skirt with blanket sutures **156** that extend through each reinforcing strip **72**, leaflet **40** and the skirt **16** while looping around the edges of the reinforcing strips **72** and leaflets **40**. The sutures **156** can be formed from PTFE suture material. FIGS. **39** and **40** show the frame **12**, leaflet structure **14** and the skirt **16** after securing the leaflet structure and the skirt to the frame and the leaflet structure to the skirt.

FIG. **41** shows a flattened view of the outer skirt **18** prior to its attachment to the frame **12**. The outer skirt **18** can be laser cut or otherwise formed from a strong, durable piece of material, such as woven PET, although other synthetic or natural materials can be used. The outer skirt **18** can have a substantially straight lower edge **160** and an upper edge **162** defining a plurality of alternating projections **164** and notches **166**. As best shown in FIG. **42**, the lower edge **160** of the skirt **18** can be sutured to the lower edge of the inner skirt **16** at the inflow end of the valve. As shown in FIG. **43**, each projection **164** can be sutured to the second rung II of struts **24** of the frame **12**. The corners **162** of the projections **164** can be folded over respective struts of rung II and secured with sutures **168**.

As can be seen in FIGS. **1**, **3** and **43**, the outer skirt **18** is secured to the frame **12** such that when the frame is in its expanded state, there is excess material or slack between the outer skirt's lower and upper edges **160**, **162** that does not lie flat against the outer surface of the frame **12**. In other words, the outer skirt is configured with excess material which causes the outer skirt to bulge outwardly as the frame foreshortens (i.e., shortens in length) during radial expansion. Accordingly, when the valve **10** is deployed within the body, the excess material of the outer skirt **18** can fill in gaps between the frame **12** and the surrounding native annulus to assist in forming a good fluid-tight seal between the valve and the native annulus. The outer skirt **18** therefore cooperates with the inner skirt **16** to avoid perivalvular leakage after implantation of the valve **10**. In another advantageous feature, the slack between the lower and upper edges of the outer skirt **18** allows the frame **12** to elongate axially during crimping without any resistance from the outer skirt and the outer skirt does not substantially affect the outer diameter of the prosthetic valve in the crimped condition.

FIG. **56** shows the valve **10** of FIGS. **1-3** and **42-43** mounted on an elongated shaft **180** of a delivery apparatus, forming a delivery assembly for implanting the valve **10** in a patient's body. The valve **10** is mounted in a radially collapsed configuration for delivery into the body. The shaft **180** comprises an inflatable balloon **182** for expanding the balloon within the body, the crimped valve **10** being positioned over the deflated balloon. The frame **12** of the valve **10**, when in the radially compressed, mounted configuration, comprises an inflow end portion **174** (see FIG. **54**) that has an outer diameter D_2 that is smaller than the outer diameter D_1 of the outflow end portion of the frame. The tapering of the frame can be at least partially due to the V-shaped leaflets **40**, as the V-shaped leaflets have less leaflet material within the inflow end portion of the frame **12** compared to a more rounded, U-shaped leaflet. Due to the tapered shape of the frame **12** in the mounted state, even with the additional thickness of the outer skirt **18** positioned around the inflow end portion **174** of the frame **12** the overall outer diameter of the inflow end portion of the valve **10** can be about equal to, or less than, the overall outer diameter of the outflow end portion of the valve.

Furthermore, as shown in FIG. **56**, the valve **10** comprises commissure portions of the leaflets extending radially outwardly through corresponding window frame portion **30** to locations outside of the frame and sutured to the side struts of the commissure window frame. To minimize the crimp profile of the valve, the window frame portions **30** can be depressed radially inwardly relative to the surrounding portions of the frame, such as the frame portions extending between adjacent commissure windows, when the valve is radially compressed to the collapsed configuration on the shaft. For example, the commissure windows **30** of the frame can be depressed inwardly a radial distance of between 0.2 mm and 1.0 mm relative to the portions of the frame extending between adjacent commissure windows when the valve is radially collapsed. In this way, the outer diameter of the outflow end portion the valve comprising the commissure portions can be generally consistent, as opposed to the commissure portions jutting outward from the surrounding portions of the valve, which could hinder delivery of the valve into the body. Even with the radially depressed commissure window frames **30**, the outer diameter of the inflow end portion of the frame can still be smaller than, or about equal to, the outer diameter of the outflow end portion of the frame when the valve is radially collapsed on the shaft, allowing for a minimal maximum overall diameter of the valve. By minimizing the diameter of the valve when mounted on the delivery shaft, the assembly can contained within a smaller diameter catheter and thus can be passed through smaller vessels in the body and can be less invasive in general.

FIG. **44** illustrates a prosthetic heart valve **200**, according to another embodiment. The heart valve **200** includes a frame, or stent, **202** and a leaflet structure **204** mounted on the stent.

The leaflet structure **204** can include a plurality of leaflets **218** (e.g., three, as depicted), which can be sutured to each other and to the frame **202** using suitable techniques and/or mechanisms. The frame **202** can be adapted to include commissure frame portions **30** (as shown in FIG. **4**) to assist in suturing the leaflets to the frame.

The frame **202** shares some design features of the frame **12** described above. In particular, like frame **12**, the frame **202** has relatively large frame openings **206** along the area of the frame that supports the leaflet structure, as shown in FIG. **45**. The openings **206** are defined by a row of angled struts **208** at the outflow end of the frame, a plurality of axially extending, circumferentially spaced struts **210**, and an intermediate row of angled struts **212**. As shown, the axial struts **210** desirably are thinner than the junctions **214** connecting the opposite ends of the axial struts **210** to the convergence of two struts **212** and to the convergence of two struts **208**. By virtue of this configuration, the width of openings **206** remain large enough when the valve is radially compressed to a delivery configuration to allow portions of the leaflet structure **204** to protrude outwardly through the openings, as indicated at **216** in FIGS. **46** and **47**. This allows the valve to be crimped to a relatively smaller diameter than if all of the leaflet material is constrained within the crimped frame.

For purposes of comparison, FIG. **48** is a cross section of a known prosthetic valve **250** showing the valve in its crimped state. When the valve is radially compressed, the spacing between adjacent struts is relatively small and does not allow portions of the leaflet structure to protrude outwardly through the frame. Consequently, the presence of all of the leaflet material being constrained within the inside of the frame limits the crimping diameter of the valve.

FIGS. **49** and **50** show a flattened section of an alternative frame construction that can allow portions of the leaflets to protrude outwardly through the frame in the crimped state. This frame construction can be implemented in the valve **10** described above. FIG. **49** shows the frame section in the radially compressed state while FIG. **50** shows the frame section in the radially expanded state. The frame (only a portion of which is shown) includes a first, circumferentially extending row of angled struts **442** and at least a second, circumferentially extending row of angled struts **444**. Some openings in the frame are diamond shaped openings **446** formed by adjacent struts **442** connected to each other at their upper ends and adjacent struts **444** connected to each other at their lower ends. The frame also includes larger openings **448** that are formed by adjacent struts **442** connected at their upper ends to respective ends of a horizontal strut **450** and by adjacent struts **444** connected at their lower ends to respective ends of a horizontal strut **452**. When the frame is radially compressed, the horizontal struts **450**, **452** maintains the width W of openings **448** large enough to permit portions of the valve's leaflets to protrude outwardly through the frame. Thus, the width of openings **448** is greater than the width of openings **446** when the frame is crimped. The frame can be formed with openings **446**, **448** alternating around the circumference of the frame. Alternatively, openings **448** can be located at selected positions along the frame's length and circumference to correspond to areas where the leaflet material tend to bunch up within the frame, such as between the commissures.

FIGS. **51** and **52** show a flattened section of another frame construction that can allow portions of the leaflets to protrude outwardly through the frame in the crimped state. This frame construction can be implemented in the valve **10** described above. FIG. **51** shows the frame section in the radially compressed state while FIG. **52** shows the frame section in the radially expanded state. The frame (only a portion of which is shown) includes a first, circumferentially extending row of angled struts **402** and at least a second, circumferentially extending row of angled struts **404**. Some openings in the frame are diamond shaped openings **406** formed by adjacent struts **402** connected to each other at their upper ends and adjacent struts **404** connected to each other at their lower ends. The frame also includes openings **408** that are formed by adjacent struts **402** connected at their upper ends to an enlarged node or junction **410** and by adjacent struts **404** connected at their lower ends to an enlarged node or junction **412**. The junctions **410**, **412** add rigidity to the frame at those locations such that when the frame is radially compressed, the width W of openings **408** remains large enough to permit portions of the valve's leaflets to protrude outwardly through the frame. Thus, the width of openings **408** is greater than the width of openings **406** when the frame is crimped. The frame can be formed with openings **406**, **408** alternating around the circumference of the frame. Alternatively, openings **408** can be located at selected positions along the frame's length and circumference to correspond to areas where the leaflet material tend to bunch up within the frame, such as between the commissures.

FIG. **57** shows a leaflet **500** for a prosthetic valve (e.g., valve **10** or **200**), according to another embodiment. The leaflet **500** has an overall V-shape, similar to leaflets **40** described above. The leaflet **500** has two tab portions **502** on opposite sides of the leaflets which are secured to adjacent tab portions of other leaflets to form the commissures of the leaflet structure. The sub-commissure portion of the leaflet **500** (the portion below the tabs **502**) include two substantially straight edges **504** that extend from respective locations just below the tabs **502** to a curved lower edge **506**. FIG. **58** shows the general shape of the leaflet **500** when the valve is crimped. The frame (not shown in FIGS. **57-58**) slightly elongates when crimped, causing the leaflet **500** to become slightly elongated.

The tapered profile of the sub-commissure portion of the leaflet reduces the amount of leaflet material in the lower half of the crimped valve to minimize the crimp diameter of that portion of the valve. Thus, if additional components are mounted to that portion of the valve, such as an outer skirt **18**, the reduced profile of that portion of the valve can help offset or minimize the increase in diameter caused by the additional component. Additionally, the commissure tabs **502** are relatively short and require less sutures for forming the commissures of the leaflet structure than known leaflet designs (such as T-shaped and scalloped leaflets), which better distributes and reduces the bulkiness of the leaflet material when the valve is crimped.

FIG. **59** shows a cross-sectional view of a valve **500**, according to another embodiment. The valve **500** comprises a frame **502**, leaflets **504**, and an outer skirt **18** mounted (e.g., by sutures) to the outer surface of the frame **502**. The frame **502** has a thickness that varies along its length to optimize strength where needed, yet minimize material (and therefore crimp profile) at selected regions of the frame. In the embodiment shown, the outflow end portion **506** of the frame has a maximum thickness T_1 (measured from the inside diameter to the outside diameter of that portion of the frame) and the inflow end portion **508** of the frame has a minimum thickness T_2 (measured from the inside diameter to the outside diameter of that portion of the frame). It should be noted that the struts of the frame **502** (which are not shown in FIG. **59**) that form the outflow end portion **506** have a thickness T_1 and the struts that form the inflow end portion **508** have a thickness T_2. The frame **502** can have an identical construction to the frame **12**

described above, except for the variable thickness of the frame. The areas of reduced thickness can be formed using a variety of manufacturing techniques, such as electro-polishing selected portions of the frame (the non-polished portions can be masked), grinding selected portions of the frame, wire cutting, or other suitable techniques.

The outflow end portion **502** generally corresponds to the region of the frame that supports the commissures of the leaflets **504** and typically experiences the greatest loading on the valve. Therefore the outflow end portion **502** of the frame has a greater thickness T_1 selected to provide the required strength under anticipated loads. The inflow end portion **508** supports an additional layer of material by virtue of the outer skirt **18**. The reduced thickness of the inflow end portion **508** allows the inflow end portion to be crimped to a smaller diameter than the outflow end portion. This offsets or minimizes the increase in the crimp diameter caused by the addition of the outer skirt **18**.

FIGS. **60-62** show an another embodiment of an implantable prosthetic valve **310** that comprises a leaflet structure **314** and a radially collapsible and expandable frame **312** (similar to the frame **50** shown in FIG. **11**) having a plurality of radially spaced commissure windows **318** that are used to secure the leaflet structure within the frame. The valve **310** also comprises a skirt **316** secured between the inner surface of the frame **312** and the curved lower edges **364** of the leaflet structure **314**. The valve **310** has a lower, inflow end **340** and an upper, outflow end **342**.

As shown in FIG. **60**A, each window **318** comprises an enclosed opening **334** between two axially extending side struts **320**, respectively. Each side strut comprises a generally rectangular, e.g. square, cross-sectional profile, as shown in FIG. **63**. Each rectangular side strut **320** comprises four surfaces: an exterior surface **324** on a radially outward facing side, and interior surface **326** on a radially inward facing side, a medial surface **328** on a side facing the other side strut, and a lateral surface **330** on a side facing away from the other side strut. In other embodiments, side struts can comprise other cross-sectional shapes, such circular or hexagonal.

The leaflet structure comprises a plurality of leaflets **360**, each comprising a pair of side tabs **366** secured to the frame **312**, a curved lower edge **364** secured to the skirt **316**, and an articulation portion **372** between the side tabs and the lower edge. Each side tab **366** is paired with an adjacent side tab of another leaflet **360** to form commissures **376** of the leaflet structure **314**. Each pair of side tabs **366** extends radially outwardly through a corresponding commissure window **318** to a location outside of the frame **312** and is secured to the side struts **320** of the window, such as with sutures, as shown in FIG. **62**. In some embodiments, each side tab **366** comprises an end portion **368** (see FIG. **64**) and the two side tab end portions **368** of each commissure **376** extend circumferentially away from one another and along the exterior surfaces **324** of respective side struts **320** of the window **318**.

In some embodiments, each commissure **376** further comprises at least one non-rigid reinforcing sheet **378** sutured to the side tabs **366** and to the side struts **320**. The sheets **378** can comprise a flexible, tear resistant material, including a variety of natural and/or synthetic biocompatible materials. Exemplary synthetic materials can include polymers such as nylon, silicone, and polyesters, including PET. In one example, the sheets **378** comprise a woven PET fabric.

Each reinforcing sheet **378** can be generally rectangular (when laid flat) and can comprise a middle portion **380** and opposing end portions **386**. In some embodiments, a first end portion **386** of the sheet is secured to a first side strut **320** and a second end portion **386** of the sheet is secured to the second side strut **320**, as shown in FIG. **64**. The sheet **378** separates the side tabs **366** from the side struts **320** such that side tabs do not contact the side struts. For example, each end portion **386** of the sheet can be wrapped completely around a respective side strut **320**, as shown in FIG. **64**.

The side tabs **366** and the reinforcing sheet **378** can be secured to the side struts **320** in multiple stages. For example, FIG. **63** shows an exemplary first suturing stage wherein the sheet is positioned such that the middle portion **380** of the sheet extends circumferentially across outer surfaces of the end portions **368** of the side tabs **366** and each end portion **386** of the sheet extends between a respective side tab **366** and the exterior, medial and interior surfaces **324**, **328**, **326**, respectively, of a respective side strut **320**. The sheet **378** surrounds the side tabs **366** and protects the side tabs from edges of the side struts **320**. A pair of in-and-out sutures **390** can secure each side tab **366** and one end of the sheet **378** to a respective strut **320**. As shown in FIG. **63**, each suture **390** can be oriented generally perpendicularly to the circumference of the frame **312** along the lateral surfaces **330** of the side struts **320** and can pass radially back and forth through the commissure **376** at a plurality of difference longitudinal positions. Each suture **390** can intersect a first layer of the sheet **378**, a side tab end portion **368**, a second layer of the sheet, and a third layer of the sheet, in that order moving radially inward. The sutures **390** secure the sheet **378** to the side tab end portions **368** and tighten the sheet end portions **386** around the side struts **320**, thereby securing the side tabs **366** to the side struts **320** and securing the leaflet structure **314** to the frame **312**.

FIG. **64** shows an exemplary second suturing stage wherein a second pair of sutures **392** are used to tie down loose portions of the reinforcing sheet **378**. For example, the second sutures **392** can intersect the portions of the middle portion **380** and the end portions **386** of the sheet that extend laterally beyond the first sutures **390**. The second sutures **392** can be helical whip stitches that intersect the commissures **376** at a plurality of different longitudinal positions, as shown in FIG. **62**, and secure the loose portions of the sheet **378** tightly against the lateral surfaces **330** of the side struts.

Both the first sutures **390** and the second sutures **392** can be positioned adjacent to the lateral surfaces **330** of the struts **320** and spaced away from the window opening **334**. This placement of the sutures can reduce the stress on the sutures caused by movement of the articulation portions **372** of the leaflets. Instead, much of this stress is transferred from flex hinges **370** of the leaflets to the side struts **320** near interior-medial edges **332** of the struts.

The reinforcing sheet **378** protects the flex hinges **370** from damage caused by the interior-medial edges **332** of the struts **320** as the leaflets articulate between open and closed positions, as shown in FIG. **64**. In addition, some embodiments can also include longitudinally extending cushion strips **374** positioned between the flex hinges **370** and the struts **320**, such as adjacent to the interior-medial edges **332**, as shown in FIG. **64**, to further protect the flex hinges from damage caused by the struts. The cushion strips **374** can comprise a flexible, compressible material, such as PET fabric, pericardial tissue, or various other biocompatible materials. In some embodiments, the cushion strips can comprise a tube filled with a resilient material. For example, the cushion strip can comprise a PET tube filled with pericardial tissue. In other embodiments, the outer tubular covering of the cushion strips can be formed from sheet **378** and can be filled with a resilient material. The sheet can be secured around the resilient material with sutures to retain the cushioning strips properly located as shown in FIG. **64**. In other embodiments, separate

cushion strips **374** can be sutured to the reinforcing sheet **378**. The cushion strips **374** can have a thickness similar to the bars **62** to provide a radial clearance between the side struts **320** and the articulating portions **372** of the leaflets to prevent or minimize contact between the leaflets and the inner surface of the frame during the cardiac cycle.

FIG. **65** shows an embodiment similar to FIGS. **63** and **64** but with a different suturing pattern. In FIG. **65**, the sutures **390** are replaced with sutures **398** that secure the sheet **378** around the end portions **368** of the side tabs. Each suture **398** intersects the middle portion **380** of the sheet, one of the side tabs **366**, and a second layer of the sheet adjacent to the medial-exterior edge **324** of each side strut. The sutures **398** can comprise in-and-out stitches that intersect the commissures at a plurality of different longitudinal positions. Each end portion of the sheet **378** can comprise a folded portion **388** that is folded under to form a double layer of the sheet **378** along the surface of the respective side strut **320**. The sutures **392** secure the end portions **386** of the sheet and the end portions **368** of the side tabs tightly around the lateral surfaces **330** of the side struts.

FIGS. **66** and **67** show an alternative method for suturing the side tabs **366** and the sheet **378** to the side struts **320**. FIG. **66** shows suture line **394** positioned along the exterior surfaces **324** of the side struts and generally perpendicular to the radius of the frame. The suture **394** intersects both side tabs **366** and both end portions **386** of the sheet **378**. The suture **394** secures each end portion **386** of the sheet tightly around the medial, interior, and lateral surfaces **328**, **326**, **330**, respectively, of the respective side strut **320**, and also secures the middle portion **380** of the sheet loosely around the end portions **368** of the side tabs **366**. In the embodiment shown in FIG. **66**, the suture **394** intersects a first sheet layer A, a second sheet layer B, the two side tabs **366**, a third sheet layer C, and a fourth sheet layer D, in that order.

After the first suture **394** is in place, the end portions **368** of the side tabs are spread apart and positioned adjacent to the exterior surfaces **324** of the side struts **320**, as shown in FIG. **67**. This tightens the loose middle portion **380** of the sheet around the end portions **368** of the side tabs. A pair of sutures **396** can then secure the middle portion **380** of the sheet tightly to the end portions **386** of the sheet to hold the end portions **368** of the side tabs in place, as shown in FIG. **67**. The sutures **396** can be looping whip stitches that intersect the commissure **376** at a plurality of different longitudinal positions, similar to the sutures **392** in FIG. **64**.

FIGS. **68** and **69** show another alternative method for suturing the side tabs **366** and the sheet **378** to the side struts **320**. FIG. **68** shows a suture line **395** positioned along the exterior side of the window opening and oriented generally perpendicular to the radius of the frame. The suture **395** intersects both side tabs **366** and two portions of the sheet **378**. The suture **395** secures the middle portion **380** of the sheet which extends loosely around the end portions **368** of the side tabs **366**. In the embodiment shown in FIG. **68**, the suture **395** intersects a first sheet layer A, a first side tab B, a second side tab C, and a second sheet layer D, in that order.

After the first suture **395** is in place, the end portions **368** of the side tabs are spread apart and positioned adjacent to the exterior surfaces **324** of the side struts **320**, as shown in FIG. **69**. This tightens the loose middle portion **380** of the sheet around the end portions **368** of the side tabs. A pair of sutures **397** can then secure the middle portion **380** of the sheet tightly to the end portions **386** of the sheet to hold the end portions **368** of the side tabs in place, as shown in FIG. **69**. The end portions **386** of the sheet can comprise a folded under portion **388**, creating a double layer of sheet material to reinforce the sutures **397**. The sutures **397** can be looping whip stitches that intersect the commissure **376** at a plurality of different longitudinal positions, similar to the sutures **392** in FIG. **62**.

FIGS. **70** and **71** show yet another alternative method for suturing the side tabs **366** and the sheet **378** to the side struts **320**. FIG. **70** shows the suture line **395** positioned along the exterior side of the window opening and oriented generally perpendicular to the radius of the frame. The suture **395** intersects both side tabs **366** and four portions or layers of the sheet **378**. Each end portion **386** of the sheet comprises a folded portion **388** that forms a double layer of sheet material between the side tabs **366** and the medial surfaces **328** of the side struts. The suture **395** secures the middle portion **380** of the sheet loosely around the end portions **368** of the side tabs **366**. As shown in FIG. **70**, each stitch of the suture **395** intersects a first pair of sheet layers comprising layers A and B, a first side tab C, a second side tab D, and a second pair of sheet layers comprising layers E and F, in that order.

After the first suture **395** is in place, the end portions **368** of the side tabs are spread apart and positioned adjacent to the exterior surfaces **324** of the side struts **320**, as shown in FIG. **71**. This tightens the middle portion **380** of the sheet around the end portions **368** of the side tabs. A pair of sutures **397** can then secure the middle portion **380** of the sheet tightly to the end portions **386** of the sheet to hold the end portions **368** of the side tabs in place, as shown in FIG. **71**. The folded portions **388** of the sheet create a double layer of sheet material to reinforce the sutures **397**. The sutures **397** can be looping whip stitches that intersect the commissure **376** at a plurality of different longitudinal positions, similar to the sutures **392** in FIG. **62**.

The commissure various configurations for attaching the leaflet structure **314** to the window frames **318** shown in FIGS. **61-71** can also be used as alternative ways to attach the leaflet structure **14** of the valve **10** of FIGS. **1-3** to the window frame portions **30** of frame **12**.

FIGS. **72-74** show a prosthetic heart valve assembly **600** comprising an embodiment of a frame **602** for a prosthetic valve mounted on a balloon **606** of a delivery shaft **604**. The frame **602** can be similar in shape to the frame **12** and can comprise in inflow end portion **610**, an outflow end portion **612** and an intermediate portion **614**. For clarity, the other components of the valve, such as the leaflets and the skirts, are not shown. The frame **602** can have a reduced thickness at the inflow end portion **610** and at the outflow end portion **612**, relative to the thickness of the intermediate portion **614**. Due to the thinner end portions, when the balloon **606** is inflated the end portions **610**, **612** offer less resistance to expansion and expand faster than the intermediate portion **614**, as shown in FIG. **73**. Because the end portions expand faster than the intermediate portion, the frame **602** becomes confined on the balloon **606**, inhibiting the frame from sliding towards either end of the balloon and reducing the risk of the frame sliding off the balloon prematurely. As shown in FIG. **74**, further inflation of the balloon can cause the intermediate portion **614** of the frame to expand to the same final diameter as the end portions **610**, **612** for implantation, after which the balloon can be deflated and removed. Controlling the position of the valve on the balloon can be important during delivery, especially with frames that foreshorten during expansion and move relative to the balloon. In the embodiment shown in FIGS. **72-74**, the intermediate portion **614** of the frame can be held constant relative to the balloon while the two end portions foreshorten towards the intermediate portion due to the "dog-bone" effect of the balloon. Any conventional means can be used to produce the frame **602** with reduced thickness at the end portions **610**, **612**, such as sanding down the end

portions with sand paper or the like. In one embodiment, the end portions **610**, **614** of the frame have a thickness of about 0.37 mm while the intermediate portion **614** has a thickness of about 0.45 mm.

In view of the many possible embodiments to which the principles of the disclosed invention may be applied, it should be recognized that the illustrated embodiments are only preferred examples of the invention and should not be taken as limiting the scope of the invention. Rather, the scope of the invention is defined by the following claims. We therefore claim as our invention all that comes within the scope of these claims.

We claim:

1. An assembly for implanting a prosthetic heart valve in a patient's body comprising:

a delivery apparatus comprising an elongated shaft; and

a radially expandable prosthetic heart valve adapted to be mounted on the shaft in a radially collapsed configuration for delivery into the body, the prosthetic heart valve comprising an annular frame having an inflow end portion defining an inflow end of the frame that is configured to receive antegrade blood flow into the prosthetic heart valve when implanted, and the annular frame also having an outflow end portion defining an outflow end of the frame opposite the inflow end of the frame, the prosthetic heart valve also comprising a leaflet structure positioned within the frame, an inner fabric skirt positioned along an inner surface of the frame, and an outer fabric skirt extending from the inflow end of the frame along an outer surface of the frame to a frame attachment location;

wherein the frame is adapted to shorten axially during radial expansion of the prosthetic valve, thereby increasing axial slack in the outer fabric skirt; and

wherein the outer fabric skirt comprises an edge defining a plurality of alternating projections and notches that is attached to the frame at the frame attachment location.

2. The assembly of claim **1**, wherein an outer diameter of the inflow end portion of the frame is smaller than an outer diameter of the outflow end portion of the frame.

3. The assembly of claim **1**, wherein the leaflet structure comprises a plurality of leaflets, wherein each of the leaflets comprises:

opposing side tabs on opposite sides of the leaflet, the side tabs being secured to the outflow end portion of the frame;

a free outflow edge portion extending between the side tabs adjacent to the outflow end of the frame; and

an inflow edge portion extending between the side tabs adjacent to the inflow end of the frame, the inflow edge portion comprising opposing axial edge portions that extend from the side tabs toward the inflow end of the frame in a generally axial direction and an intermediate edge portion that extends between the axial edge portions, the intermediate edge portion comprising a curved apex portion adjacent to the inflow end of the frame and a pair of oblique portions that extend between the axial edge portions and the apex portion, the oblique portions having a greater radius of curvature than the apex portion.

4. The assembly of claim **1**, wherein the frame comprises three angularly spaced commissure windows each comprising an enclosed opening between first and second axially oriented side struts; and

the leaflet structure comprises a plurality of leaflets each comprising two opposing side tabs, each side tab being paired with an adjacent side tab of an adjacent leaflet to form commissures of the leaflet structure, and wherein each commissure extends radially outwardly through a corresponding commissure window of the frame to a location outside of the frame and is sutured to the side struts of the commissure window.

5. The assembly of claim **4**, wherein the commissure windows of the frame are depressed radially inwardly relative to the portions of the frame extending between adjacent commissure windows when the prosthetic valve is in the radially collapsed configuration on the shaft.

6. The assembly of claim **1**, wherein the frame comprises an inflow row of openings at the inflow end portion of the frame, an outflow row of openings at the outflow end portion of the frame, and at least one intermediate row of openings between the inflow row of openings and the outflow row of openings;

wherein the openings of the inflow row of openings are larger than the openings of the at least one intermediate row of openings.

7. The assembly of claim **1**, wherein the frame has a plurality of openings and portions of the leaflet structure protrude through the openings while the prosthetic valve is in the radially collapsed configuration.

8. The assembly of claim **1**, wherein the inflow end portion of the frame comprises a frame thickness that is less than a frame thickness of an intermediate portion of the frame between the inflow end portion and the outflow end portion.

9. The valve of claim **1**, wherein the outer fabric skirt extends from the inflow end of the frame along the outer surface of the frame to a plurality of outer skirt attachment locations on the outer surface of frame, and wherein distances from the inflow end of the frame to the plurality of outer skirt attachment locations become smaller when the prosthetic heart valve is radially expanded.

10. The valve of claim **9**, wherein when the prosthetic heart valve is radially expanded, the plurality of outer skirt attachment locations and the inflow end of the frame are at substantially the same radial distance from a longitudinal center axis of the prosthetic heart valve.

11. The valve of claim **1**, wherein the projections at the edge of the outer skirt are attached to the frame and the notches in the edge of the outer skirt are not attached to the frame.

12. An assembly for implanting a prosthetic heart valve in a patient's body comprising:

a delivery apparatus comprising an elongated shaft;

a radially expandable and collapsible prosthetic heart valve mounted on the shaft in a radially collapsed configuration for delivery into the body, the prosthetic heart valve comprising an annular frame and a leaflet structure within the frame;

wherein the frame comprises a plurality of angularly spaced commissure windows each comprising an enclosed opening between first and second axially oriented side struts, and the frame further comprises intermediate side struts that are axially oriented and positioned angularly between the commissure windows, and the leaflet structure comprises a plurality of commissure portions that extend outwardly through respective commissure windows to locations outside of the frame; and

wherein the commissure windows are depressed radially inwardly relative to the intermediate side struts when the prosthetic heart valve is radially collapsed on the shaft, such that an outermost surface of each commissure portion of the leaflet structure outside of the frame is at substantially the same radial distance from a longitudi-

nal center axis of the prosthetic heart valve as outer surfaces of the intermediate side struts.

13. The valve of claim **12**, wherein the commissure windows of the frame are depressed inwardly a radial distance of between 0.2 mm and 1.0 mm relative to the intermediate side struts when the valve is radially collapsed.

14. The valve of claim **12**, wherein an outer diameter of an inflow end portion of the frame is smaller than an outer diameter of an outflow end portion of the frame when the valve is radially collapsed on the shaft.

15. The assembly of claim **12**, wherein an outer surface of the frame defines radial depressions in regions proximate the commissure windows, and outer portions of the commissure portions of the leaflet structure are located in the radial depressions along the outside of the frame.

16. The assembly of claim **12**, wherein the commissure portions of the leaflet structure are sutured to the axially oriented side struts of the commissure windows.

17. An implantable prosthetic valve that is radially collapsible to a collapsed configuration and radially expandable to an expanded configuration, the prosthetic valve comprising:

an annular frame having a longitudinal axis extending between an inflow end of the frame and an outflow end of the frame and defining an axial direction, the inflow end of the frame being configured to receive antegrade blood flow into the prosthetic valve when implanted;

a leaflet structure positioned within the frame; and

an annular outer skirt positioned around an outer surface of the frame, the outer skirt comprising an inflow edge positioned at a first location at the inflow end of the frame, an outflow edge defining a plurality of spaced apart axial projections that are secured to the frame at a second location axially spaced from the inflow edge, and an intermediate portion extending between the inflow edge and the outflow edge and positioned outside of the frame;

wherein when the valve is in the expanded configuration, the intermediate portion of the outer skirt comprises slack in the axial direction between the inflow edge of the outer skirt and the outflow edge of the outer skirt, and when the valve is collapsed to the collapsed configuration, the distance between the inflow edge of the outer skirt and the outflow edge of the outer skirt increases, reducing the slack in the outer skirt in the axial direction.

18. The valve of claim **17**, wherein the outflow edge of the outer skirt comprises a plurality of alternating projections and notches, the projections being secured to the frame at the second location, the outer skirt being unsecured to the frame at the notches.

19. The valve of claim **17**, wherein the outer skirt is not stretched in the axial direction when the valve is radially collapsed to the collapsed configuration and slack is removed from the intermediate portion of the outer skirt.

20. An implantable prosthetic valve comprising:

an annular frame comprising a plurality of leaflet attachment portions; and

a leaflet structure positioned within the frame and secured to the leaflet attachment portions of the frame, the leaflet structure comprising a plurality of leaflets, each leaflet comprising a body portion having a free outflow edge, two opposing primary side tabs extending from opposite sides of the body portion, and two opposing secondary tabs, each secondary tab extending from the body portion adjacent to a respective primary side tab, the secondary tabs extending from the body portion at opposite ends of the free outflow edge;

wherein the secondary tabs are folded about radially extending creases that extend radially from the opposite ends of the free outflow edge, such that a first portion of the secondary tabs lies flat against the body portion of the respective leaflet, and the secondary tabs are folded about axially extending creases such that a second portion of the secondary tabs extends in a different plane than the first portion, wherein the radially extending creases and the axially extending creases are non-parallel.

21. The valve of claim **20**, wherein the second portion of each secondary tab is sutured to a respective primary tab.

22. The valve of claim **20**, wherein the secondary tabs are positioned inside of the frame.

23. The valve of claim **20**, wherein the first portion of each the secondary tab pivots about the axially extending crease and lays flat against the second portion of the secondary tab when the valve is collapsed to a radially collapsed configuration.

24. The valve of claim **20**, wherein the first portion of each secondary tab extends radially inwardly from the frame and comprises an inner edge spaced radially from an inner surface of the frame, and the body portion of the leaflet articulates about the inner edges of the two secondary tabs of the leaflet in response to blood flowing through the valve when the valve is in operation within a patient's body.

25. The valve of claim **20**, wherein the plurality of leaflet attachment portions comprises window frame portions each comprising an enclosed opening between first and second axially oriented side struts, and wherein the primary side tabs extend radially outwardly through respective window frame portions to a location outside of the frame and are sutured to the secondary tabs to secure the leaflets around the side struts.

* * * * *

EXHIBIT 11

8

Vascular implants for peripheral arterial bypass and aortic aneurysm repair

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Abstract: Prosthetic vascular grafts have been used to treat occlusive arterial disease for over six decades with good results for large diameter arterial reconstructions. Less invasive endovascular procedures in the form of angioplasty and stenting are considered when the pattern of disease is suitable. For the treatment of aortic aneurysms, endovascular repair with a remotely introduced stent-graft is firmly established. This chapter describes the prosthetic grafts, the modifications made to improve their patency as well as newly developed tissue engineered small diameter artery analogs. The principles of aortic aneurysm repair, the developments in device design and their clinical performance are also discussed.

Key words: vascular grafts, Dacron grafts, expanded polytetrafluoroethylene (PTFE) grafts, intimal hyperplasia, tissue engineered vascular grafts, endovascular procedures, stent-grafts.

8.1 Introduction

Vascular implants are widely used to treat both occlusive and aneurysmal diseases. Arterial occlusive disease is mainly associated with atherosclerosis producing symptomatic stenotic lesions and reduced perfusion of distal tissues. Restoration of blood flow is achieved through several methods, ranging from minimally invasive endovascular procedures, such as angioplasty and stenting, through to major surgical arterial reconstruction using bypass grafts. The success of surgical intervention relies on maintaining graft patency, and numerous parameters and adjuvant techniques have been explored to optimise patency.

An aneurysm or a localised dilatation of a segment of artery may result in rupture, haemorrhage and death if untreated. The majority of aneurysms occur in the abdominal aorta below the renal arteries. Conventional treatment involves replacement of the affected aorta with a prosthetic graft segment. This major open abdominal surgery is associated with significant

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respiratory, renal and cardiac complications precluding the elderly and patients with significant co-morbidities. Endovascular aneurysm repair is a minimally invasive procedure introduced in the 1990s to exclude the aneurysm from the circulation and prevent rupture while the aneurysm sac and its contents remained *in situ*. This is achieved by means of a device consisting of a fabric graft and a metal stent structure. The device, called a 'stent-graft', is introduced through one of the femoral arteries and guided to the aneurysm where it is anchored in place. The procedure is performed under X-ray fluoroscopy.

The aim of this chapter is to review the vascular implants currently used in open vascular surgical reconstructions and endovascular procedures for treating infrainguinal arterial disease and aortic aneurysm repair.

8.2 Vascular stents

Stents are classified as either balloon-expandable or self-expanding according to their method of deployment. The choice of materials for both types of stents is dependent on several factors, e.g. mechanical and physical properties, availability of fabrication techniques, good resistance to corrosion and fatigue, biocompatibility and non-thrombogenicity.

Balloon-expandable stents require materials that can be deformed plastically through the inflation of a balloon. The ideal material should therefore have a low yield stress so that expansion of the stent can be achieved at acceptable balloon pressure. On the other hand it should have high elastic modulus so as to achieve high radial strength with low profile stent struts and minimal recoil after the stent is fully deployed. Stainless steel 316 L is the standard material for balloon-expandable stents since it fulfils these requirements well. Cobalt–chromium-based alloys which have higher elastic modulus, tensile strength but similar yield stress to 316 L are also commonly used.

Self-expanding stents are fabricated in their expanded size then compressed into a delivery system. As they are released from the delivery system, they self-expand to the preset size, relying on the elastic properties of the material. These stents undergo large strains which should be fully recoverable and the material that is most suited for this purpose is superelastic nickel–titanium alloy, nitinol.

The required properties such as high radial strength, low recoil, good flexibility and trackability are derived not only from the material used but also the dimensions of the stent struts, the geometry (number of cells or repeating units in the circumferential and longitudinal directions) and the manufacturing process used to produce the stents.

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8.2.1 Drug eluting stents

Drug eluting stent technology based on a thin film polymeric drug carrier that slowly releases an anti-proliferative agent has been demonstrated to be effective in reducing restenosis rates in coronary artery stenting. However, there has been concern about the increased rate of late thrombosis over that seen in bare metal stents. Stent fracture has been reported as a complication of drug-eluting coronary stenting, in particular sirolimus-eluting stents (Lee *et al.*, 2007). When used in peripheral arteries, drug eluting stents have not shown significant improvements in restenosis rates compared with bare metal stents (Duda *et al.*, 2006). It is thought that the polymer used as the carrier for the drug delivery may provoke vessel irritation, endothelial dysfunction and chronic inflammation, thereby inhibiting the healing response. Current research is being carried out to develop novel coatings with surface properties designed to promote selective adhesion and growth of endothelial cells (EC) leading to rapid endothelialisation of the arterial wall and stent (Nickson *et al.*, 2008).

8.2.2 Bioresorbable stents

Stents are designed to resist the compressive forces due to remodelling of the arterial wall following angioplasty. Permanent metallic stents exert elevated forces and potential mechanical trauma on the vessel wall over long periods but it may only be required to provide radial support for a limited time after deployment. Stents based on degradable polymers and co-polymers of lactic acid (PLLA) and corrodible magnesium alloys have been proposed as a means of providing the initial temporary support to the vessel wall without the long-term complications of permanent metallic stents. PLLA-based stents which can also be loaded with antiproliferative drugs are currently under development (e.g. Abbott BVS everolimus-eluting and Igaki–Tamai which are both self-expanding). However, because of the relatively low elastic modulus of polymer materials, these stents tend to have lower radial strength, higher immediate recoil and the stent struts are more bulky than metallic stents. The Reva medical stent is made from tyrosine-derived polycarbonate and has a unique construction that is designed to prevent recoil during deployment. Magnesium alloy has similar mechanical properties to stainless steel but will corrode completely over time after implantation. Unlike other metallic materials, the corrosion products of magnesium stents are not harmful and may actually have cardiovascular benefits (Bo and Pisu 2008). Short-term trials of Biotronik magnesium balloon-expandable stents have been conducted in lower limb and coronary arteries (Peeters *et al.*, 2005; Erbel *et al.*, 2007).

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In patients with lower-limb occlusive disease balloon angioplasty and stenting are commonly applied in the iliac, femoral and infrapopliteal arteries depending on the pathology and morphology of the lesions. Since stenotic lesions are usually localised and short, angioplasty or primary stenting with a self-expanding stent perform well. Femoropopliteal lesions tend to be long and diffuse and the results are therefore worse than bypass surgery with a suitable autologous vein (Ruef *et al.*, 2004; Beard, 2008). Stents placed in the femoropopliteal segment are exposed to large repetitive mechanical stresses that can lead to stent compression, distortion and fracture (Kroger *et al.*, 2004; Schillinger and Minar, 2007). These mechanical stresses are associated with high restenosis rates and the transient nature of a bioresorbable stent may potentially overcome some of these problems (Peeters *et al.*, 2005).

8.3 Bypass grafts

The materials and techniques used for bypass vary with anatomical site, availability and the surgeons' preference. Clinical evidence acquired over several decades demonstrates that polyethylene terepththalate (PET or more commonly known as Dacron) and expanded polytetrafluoroethylene (ePTFE) perform well when used to replace large diameter vessels. These materials are stable and inert and are resistant to chemical degradation and mechanical failure (van Damme *et al.*, 2005). The main complication is infection, accounting for between 1 and 6% of cases (Mussa *et al.*, 2007; Zetrenne *et al.*, 2007). However, when it occurs, it is extremely challenging to treat and with aortic graft infection, mortality rates range from 25 to 88%.

For peripheral arterial bypass where the graft used is 6 mm or less in diameter, the overwhelming evidence identifies autologous vein as the gold standard in achieving optimum graft patency, but, if unavailable, prosthetic alternatives are available although the results are considerably poorer. This chapter will focus on the characteristics of materials for lower limb peripheral arterial bypass.

8.3.1 Critical limb ischaemia

Throughout the western world critical limb ischaemia (CLI) has become a progressively more common manifestation of atherosclerosis, which places the limb at imminent risk, especially in the presence of diabetes and tissue necrosis. The outcome of CLI can be summarised by the data presented by Wolfe (1986), whose one year estimates were that 25% of patients would have at least one leg amputated, 55% would retain both legs, and 20% would have died. Its financial demands on the health service are profound, and

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have led to close appraisal of the cost-effectiveness of the management of CLI, which has been the subject of much debate. In limbs that are not irretrievably ischaemic, a policy of aggressive arterial reconstruction has been shown to improve the patients' quality of life.

The bypass conduit is one of the most important factors determining long-term patency, with autologous vein remaining the preferred choice since its introduction by Kunlin in 1949. Vein, however, is absent or of insufficient quality in up to one-third of patients necessitating the use of prosthetic material (e.g. ePTFE, Dacron) and biological prosthetic (e.g. modified human umbilical vein, HUV) (Tilanus *et al.*, 1985). A study by Kumar *et al.* (1995) demonstrated no significant difference in patency rates between ePTFE and Dacron, but further randomised trials reported significantly higher patency rates in HUV grafts compared with ePTFE (Eickhof *et al.*, 1987; McCollum *et al.*, 1991; Aalders and van Voonhoven, 1992; see Table 8.1). Long-term follow-up, however, revealed graft dilatation and aneurysm formation in up to 30% of HUV bypasses and its popularity has diminished subsequently (Aalders and van Voonhoven, 1992).

The superiority of vein over ePTFE has been established through randomised trials summarised in Table 8.2 (Bergan *et al.*, 1982; Tilanus *et al.*, 1985; Veith *et al.*, 1986; Kumar *et al.*, 1995). Tilanus *et al.* (1985) reported a significant difference in long-term patency rates between ePTFE, 37%, and autologous vein, 70% ($p < 0.001$). The data reported by Bergan *et al.* (1982) do not entirely corroborate with this, identifying a difference between the two grafts only when anastomosed to infrapopliteal vessels. However, this

Table 8.1 Trials comparing the patency in HUV and ePTFE infrainguinal above-knee (AK) and below-knee (BK) femoropopliteal bypass grafts

Author	Distal vessel	Bypass material	Follow-up (years)	Primary patency (%)	Secondary patency (%)
Eickhoff *et al.* (1987)* ($n = 105$)	BK	HUV	4		42**
	BK	ePTFE			22
McCollum *et al.* (1991)* ($n = 191$)	AK	HUV	3	57	66**
	AK	ePTFE		48	49
Aalders and van Voonhoven (1992)* ($n = 85$)	AK	HUV	5	65	73**
	AK	ePTFE		32	41

* Randomised controlled trial; ** statistical significance $p < 0.05$.

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Table 8.2 Trials of vein vs. ePTFE/Dacron grafts for infrainguinal bypass

Author	Distal vessel	Bypass material	*n*	Follow-up (years)	Primary patency (%)	Secondary patency (%)
Bergan *et al.* (1982)	AK pop	Vein	41	2.5	70	
	AK pop	ePTFE	33		72	
	BK pop	Vein	50		76	
	BK pop	ePTFE	46		62	
	Infra pop	Vein	57		50**	
	Infra pop	ePTFE	58		20	
Tilanus *et al.* (1985)	Fempop	Vein	85	5		70**
	Fempop	ePTFE	91			37
Veith *et al.* (1986)	AK pop	Vein	85	4	61	
	AK pop	ePTFE	91		38	
	BK pop	Vein	62		76**	
	BK pop	ePTFE	80		54	
	Combined pop	Vein	147		68**	
	Combined pop	ePTFE	171		38	
	Infrapop	Vein	106		49**	
	Infrapop	ePTFE	98		12	
Kumar *et al.* (1995)	AK pop	Vein	50	4	73	90**
	AK pop	ePTFE	49		47	47

** Statistically significant results ($p < 0.05$).
pop: popliteal; fempop: femoropopliteal.

study only reported patency rates up to 30 months follow-up, whereas the benefit of vein grafts becomes more evident with time. It is generally accepted that autologous vein achieves the optimum patency, particularly in bypass to crural vessels performed for critical limb ischaemia, and that ePTFE should be reserved for arterial reconstruction only in the absence of vein.

8.3.2 Expanded polytetrafluoroethylene

Expanded PTFE grafts are made by extrusion of PTFE resin mixed with a lubricant. The microporous structure of ePTFE is obtained by a process that involves rapid stretching of the extruded tube at high temperature. The structure is characterised by circumferentially arranged nodes, about 5–10 μm wide by 5–100 μm long, interconnected by longitudinal fibrils of less than 0.5 μm in diameter. Porosity is an important factor that determines the healing and incorporation of a prosthetic graft to the surrounding tissue.

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The degree of porosity of an ePTFE graft is controlled by the distance between the nodes. In clinically used grafts this is of the order of 30 μm although experimental studies have shown that grafts with larger internodal distance are associated with higher degree of endothelialisation (Hirabayashi *et al.*, 1992). Expanded PTFE grafts are usually provided with an external support coil to improve their resistance to kinking. They may in addition have a thin reinforcing layer of low porosity ePTFE on the external surface.

Carbon and heparin coated ePTFE grafts have been introduced in order to reduce the thrombogenicity of the base biomaterial and thereby improve the patency of infrainguinal bypass. Prospective randomised multicentre trials have shown that carbon coated grafts produced a small benefit but the results did not show statistical significance (Barcourt, 1997; Kapfer *et al.*, 2006). Covalent bonding of heparin to the luminal surface of ePTFE grafts has been shown to provide patency rates comparable to the autologous saphenous vein at one and two years for above and below-knee femoropopliteal and femorocrural bypass (Bosiers *et al.*, 2006; Dorrucci *et al.*, 2008; Daenens *et al.*, 2009). These studies were non-randomised. However, a prospective randomised multicentre trial was reported in the Gore Propaten® Instructions for Use document (W. L. Gore & Associates, 2006), involving 200 patients requiring above-knee femoropopliteal bypass. The study compared the heparin bonded Gore Propaten® graft against the standard Gore-Tex Stretch graft (W. L. Gore & Associates, Inc., Flagstaff, Arizona, USA). The primary and secondary patency rates and limb salvage were similar and the heparin did not appear to confer a significant advantage over the standard ePTFE graft.

8.3.3 Polyethylene terepthalate (Dacron) grafts

Polyethylene terepthalate (PET) fibres are used to manufacture fabric grafts in two basic constructions: woven or knitted. The woven graft consists of yarns of PET fibres running alternately over and under each other, resulting in a tight and strong structure with relatively low porosity. Knitted grafts are produced by looping yarns around needles. The number and size of the needles and the diameter of the yarns determine the spacing between the yarns and consequently the porosity of the fabric. Since the yarns of knitted grafts are less tightly packed, knitted grafts are more conformable and are easier to handle than woven grafts. Knitted grafts are much more porous and require preclotting with the patient's blood prior to implantation. However, the need for preclotting is obviated by the use of grafts pre-impregnated with gelatine, albumin and collagen. Both woven and knitted grafts are provided with circumferential crimps which are usually circular but sometimes helical in order to improve their surgical handling and

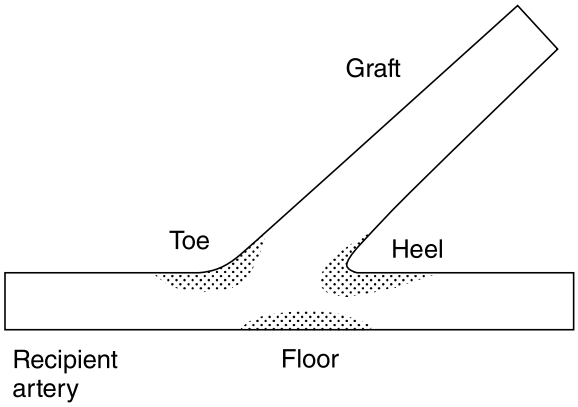
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flexibility. Some fabric grafts also incorporate an external support coil to resist kinking as well as external compression, a desirable feature in extra-anatomical bypass such as axillofemoral bypass. These grafts are usually not crimped.

8.4 Intimal hyperplasia

Early failure of vascular prostheses, within days of surgery, occurs mainly because of technical errors, especially when the recipient artery is very small and friable, or thrombosis. After the initial post-operative period, graft failure commonly occurs as a result of intimal hyperplasia (IH) development, normally at critical points within the distal end-to-side (ETS) anastomosis. These points correspond to the graft heel, toe and recipient artery floor (Fig. 8.1), where areas of separation and flow division occur resulting in abnormally low wall shear stress (WSS), an important factor in the development of hyperplasia (Sottiurai, 1990; Sottiurai *et al.*, 1994).

The intima of an artery consists of an endothelial monolayer covering the internal elastic lamina, which, in turn is surrounded by smooth muscle cells (SMC) and the outermost loose connective tissue of the adventitia. The intimal response to trauma is well documented, whereby a thick neo-intima develops due to the proliferation of EC in conjunction with the migration of SMC from the underlying media through the elastic lamina. The subsequent proliferation of these cells with secretion of a tough extra-cellular collagenous matrix creates a characteristic histological appearance of an intimal layer of SMC within an abundant stroma, resulting in an overall reduction in lumen and increase in wall thickness. Such cellular activity in response to local trauma has important implications in the genesis of both atheromatous plaques and IH. The aetiology and mechanisms by



8.1 The distribution of IH in the ETS distal anastomosis (after Sottiurai, 1990).

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which this response is induced are multifactorial and complex. Studies into distal anastomotic IH after arterial bypass have elucidated some of the important causes.

8.4.1 Trauma

The arteriotomy and anastomosis of a graft to the native vessel during a bypass procedure elicit a healing response. Re-growth of endothelium and development of underlying hyperplasia is an integral part of this; however, once intimal integrity has been restored there appears to be the potential for continued thickening. Only relatively subtle trauma is required to provoke such a response and studies have shown that simple endothelial denudation through desiccation or balloon angioplasty induces re-endothelialisation and IH (Zollikofer *et al.*, 1984; Davies *et al.*, 1993, 1996; More *et al.*, 1994).

8.4.2 Compliance mismatch

The term compliance mismatch describes the discrepancy in physical properties between autologous tissue and prosthetic materials and has generated much interest as a cause of IH and subsequent graft occlusion (Walden *et al.*, 1980). Expanded PTFE and Dacron, the two most commonly used prosthetic bypass conduits, may be considered to be almost non-compliant when perfused with a pulsatile waveform (Table 8.3).

In creating an anastomosis between such a graft and the inherently elastic artery one generates a compliance mismatch which influences some of the haemodynamic forces in the juxta-anastomotic regions. Stewart and Lyman (1992) and Miyawaki *et al.* (1990) described flow disturbances at regions of compliance mismatch in straight tube models, with microscopic zones of flow separation and stagnation at the wall. They speculated that

Table 8.3 Compliance measurements of bypass graft conduit materials (Walden *et al.*, 1980)

Conduit material	Compliance (% radial change/mmHg $\times 10^{-2}$)
Human femoral artery	5.9 ± 0.5
Saphenous vein	4.4 ± 0.8
Human umbilical vein	3.7 ± 0.5
Bovine heterograft	2.6 ± 0.3
Dacron	1.9 ± 0.3
ePTFE	1.6 ± 0.3

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this might contribute to the development of IH. In an attempt to clarify the influence of compliance mismatch, Ballyk *et al.* (1998) utilised a mathematical model to calculate the stress along the suture line of end-to-end (ETE) and ETS anastomoses. They found that the presence of a suture line increased the mean stress compared with an undisturbed artery, irrespective of geometry or conduit compliance. They also reported greater stress in ETS than in ETE models, and significantly higher mean stress with a compliance mismatch in an ETS model. They speculated that the concentration of stress at the toe might correlate with the known propensity for intimal deposition at the toe of an ETS anastomosis. Bassiouny *et al.* (1992) investigated the location and severity of distal anastomotic hyperplasia in 13 dogs and found increased suture line hyperplasia in ePTFE grafts compared with vein. They accept, however, that caution must be applied in attributing such findings solely to compliance mismatch. Trubel *et al.* (1994) compared elasticity and IH in venous grafts and vein grafts constricted with an external Dacron mesh implanted into 12 sheep. Elasticity was significantly lower and distal anastomotic IH significantly greater in the mesh-constricted group, a finding they attributed to the compliance mismatch between graft and native vessel.

The confounding issues of previous studies, however, were recognised by Wu *et al.* (1993) as ambiguous definition of IH, pharmacological influences, poor control groups and short follow-up periods. They designed an *in vivo* study to examine the direct and sole effect of compliance mismatch. They discerned between 'true' IH and intimal thickening as a result of mural thrombus organisation. In addition, they recognised the undesirable influence of anticoagulant and antiplatelet agents used in other studies, since these compounds, such as heparin and aspirin, are known to inhibit IH (Bush *et al.*, 1988; Clowes and Clowes, 1989). They created ETE and ETS carotid bypass grafts in opposing arteries of 11 dogs using pre-clotted 5 mm supported Dacron grafts. A group of autologous carotid artery grafts interposed end-to-end into a section of femoral artery served as a control. Flow rates in all vessels were equal, no anticoagulant or antiplatelet agents were administered, and follow-up was performed at 6 and 12 months. They found that compliance in the Dacron graft was 1/300 that in the arterial conduit; however, there was no difference between the two groups in terms of thickness of anastomotic neointima. The neointimal thickness did not significantly change between 6 and 12 months. This important and well-conducted study indicates that compliance mismatch alone is not sufficient to explain the development of neointimal hyperplasia at the anastomotic interface. Similar conclusions were reported by Okuhn *et al.* (1989) who compared virgin and externally banded iliac arteries in dogs and found no difference in intimal thickness when such a compliance mismatch was applied.

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8.4.3 Haemodynamic factors

The endothelium has the capacity to transduce the physical stimuli of flowing blood. The mechanical forces experienced by the vessel wall may be classified into fluid and solid dynamic forces, represented by wall shear and tensile stress respectively. Tensile stress forces are a function of blood pressure and arterial wall radius. WSS has been previously defined as the product of velocity gradient and blood viscosity. The biological response within the arterial wall attempts to restore the physiological equilibrium within the vessel, and it is this adaptive property that is believed to play an important role in the pathophysiology of IH. Endothelium remains quiescent when exposed to WSS within physiological parameters (1–2 N/m^2 in aorta, 2–4 N/m^2 in popliteal artery, 0.15–0.6 N/m^2 in vein) (Ando *et al.*, 1991). Abnormally low or high stress, however, imposes a hostile environment upon the endothelium, resulting in IH. The resultant reduction in lumen diameter will serve to increase low WSS, while the deposition of IH in pathologically high WSS is likely to be a result of the healing process due to mechanical trauma.

There is substantial evidence for the inverse relationship between WSS and the development of IH. One of the first studies demonstrating an inverse relationship was reported by Rittgers *et al.* (1978) who found focal deposition of IH in ilio-iliac vein grafts in dogs corresponding to areas of flow separation and therefore reduced shear rate. Kraiss *et al.* (1991) implanted tandem aorto-aortic and bilateral aorto-iliac ePTFE grafts into baboons and confirmed the luminal WSS in the proximal graft to be double that in the distal grafts. They reported that the corresponding intimal thickness after 12 weeks was significantly greater in the distal grafts compared with the proximal one, affirming an inverse relationship between WSS and intimal thickness. Further studies have added veracity to this conclusion which is now widely accepted and has influenced subsequent research (Kohler *et al.*, 1991; Sho *et al.*, 2002). Intimal thickening is also a feature of early atherosclerotic lesions and its development was studied by Pedersen *et al.* (1999) using high-resolution magnetic resonance *in vivo*. They also found that intimal thickness showed a linear decrease with mean and maximum WSS, but interestingly a linear increase with oscillating shear index. The oscillating shear index (OSI) is defined as:

$$\mathrm{OSI} = \frac{|A_{\mathrm{neg}}|}{|A_{\mathrm{neg}}| + |A_{\mathrm{pos}}|}$$

where $|A_{\mathrm{neg}}|$ and $|A_{\mathrm{pos}}|$ are the absolute numerical areas under the WSS versus time curve. By convention WSS is considered negative when flow is directed towards the heart. The OSI therefore describes the degree of deviation of WSS from the antegrade flow direction. These findings are

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corroborated in a study by Keynton *et al.* (2001) who reported that OSI within ePTFE bypass grafts in carotid arteries of mongrel dogs provided a stimulus for the development of anastomotic IH. An anastomosis with high outflow resistance may have significant retrograde flow during the diastolic phase of the cardiac cycle. The resultant OSI would be high, and the anastomosis at risk of IH and subsequent occlusion. Such a scenario may be observed in the clinical situation.

The patterns of flow within the distal anastomosis are responsible for the haemodynamic profile, with areas of low flow, turbulence and flow separation associated with low WSS or high OSI. Bassiouny *et al.* (1992) studied the distribution of IH within the distal anastomosis of explanted ePTFE and vein grafts to the ilio-femoral arterial segments of dogs. Equal quantities of IH were found along the arterial floor irrespective of conduit material; however, increased hyperplasia was reported in the anastomotic suture line of ePTFE grafts. Flow visualisation studies in models recreating the morphological features of each anastomosis identified secondary flow patterns within a sinus created along the suture line. They speculated that such a flow phenomenon might interact with other biomechanical and humoral factors to modulate suture line intimal thickness. They further postulated that this process might be self-limiting and abate once the remodelling has eliminated the morphological anomalies that generate the flow patterns. The non-compliant ePTFE may be expected to create a more pronounced anastomotic sinus than autologous vein, resulting in the increased degree of observed IH. In addition, however, flow patterns may directly contribute to endothelial trauma and result in IH. Sottiurai (1990) described the 'shingle effect' whereby the distal aspect of an endothelial cell overlaps the adjacent downstream cell. Flow separation as seen at the heel and toe of an ETS distal anastomosis may lift this overlapping process, exposing the underlying sub-endothelium and facilitating access of blood-borne elements known to influence the formation of IH, such as platelets.

The presence and nature of distal anastomotic IH in ETS anastomoses has led to theories describing different types of IH with differing aetiologies and sequelae (Fortunato *et al.*, 1999). Suture line IH may represent a combination of vascular healing and remodelling in response to mechanical injury, local haemodynamics and compliance mismatch. As it is a ubiquitous and potentially self-limiting feature of any anastomosis, it may not represent a poor prognostic factor (Sottiurai *et al.*, 1989; Bassiouny *et al.*, 1992). Conversely, a more sinister form may be the juxta-anastomotic IH seen at the toe, heel and along the recipient artery floor, which may be attributed to the haemodynamic forces and blood-borne products. When considering arterial reconstruction to crural vessels of 3 mm diameter or less the accumulation of only small amounts of hyperplasia at these critical points will

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serve to stenose the outflow. This diminishes blood flow below the thrombotic threshold velocity of the graft resulting in thrombosis.

The location of IH at the heel, toe and recipient artery floor has been linked to areas of flow separation and division and regions of low WSS found in standard ETS anastomoses (How *et al.*, 2000). This potential causal link between IH and local haemodynamics has stimulated further work into the effect of anastomotic geometry on flow, and cuffed anastomoses have been shown to modify flow patterns with the formation of a vortex, improving WSS at the critical points in the anastomosis (Da Silva *et al.*, 1997; How *et al.*, 2000; Fisher *et al.*, 2001). Clinical studies have confirmed the modulation of IH away from the recipient artery in cuffed anastomoses with a benefit in terms of outcome in below knee bypasses when compared with standard ETS grafts (Stonebridge *et al.*, 1995; Tyrrell and Wolfe, 1997). While minimising technical error at the anastomosis has long been known to influence outcome, these studies pioneered the future of anastomotic engineering, whereby geometry was explored in an attempt to optimise flow and the haemodynamics, with the intention of inhibiting the accretion of IH.

8.5 Tissue engineering of vascular grafts

In the quest to develop better small diameter vascular grafts, attention has focused, over the past decade, on tissue engineering approaches. Ideally, the engineered graft should be non-thrombogenic. It should also possess mechanical properties to match those of the native vessel; the wall should have the ability to be vascularised and exhibit vasoactivity without inducing inflammatory response and neointima proliferation and perhaps it should also grow in concert with the changing needs of the body over time. In order to achieve the first requirement, the engineered graft should contain a confluent, adherent endothelial layer. To achieve the latter objectives, it should have a well-organised extracellular matrix, which confers the bulk of the mechanical properties, while resident cells perform metabolic and biochemical functions that are similar to native vessels.

An early approach to render the surface non-thrombogenic was to seed EC on non-biodegradable synthetic grafts (e.g. Herring 1991; Williams *et al.*, 1994; Zilla and Greisler, 1999). However, problems related to cell retention, synthetic materials and non-matching mechanical properties, recognised as important in the pathogenesis of graft failures, remained unresolved. The second approach moves towards using more natural materials to engineer the wall closer to that of native vessels. Weinberg and Bell (1986) were the first to create a multilayered vascular structure by seeding EC, SMC and fibroblasts (FC) in collagen gel, but the graft was limited by poor mechanical integrity despite being reinforced with Dacron mesh. This

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concept of a hybrid graft was further pursued by using cell-seeded gel of Type I collagen and dermatan sulphate to create an artificial basement membrane supported by polyurethane (Miwa and Matsuda, 1994), the media supported by silicone tube (Kanda and Matsuda, 1994), and the whole graft supported by knitted Dacron (Ishibashi and Matsuda, 1994). To achieve a more realistic vascular architecture, L'Heureux *et al.* (1998) used cell sheets assembly method, wrapping SMC sheets to form the media of the vessel, upon which a sheet of FC was wrapped around to serve as the adventitia, and EC were seeded in the lumen. The resulting three-layered organisation with extracellular matrix proteins such as elastin was found to withstand up to 2000 mmHg.

The third approach, which is perhaps the most widely reported and most commonly adopted tissue engineering approach, is to seed cells in biodegradable polymeric scaffold and subject them to biophysical and chemical stimulations provided by a bioreactor. Using this approach, Niklason *et al.* (1999) demonstrated the engineered graft obtained from polyglycolic acid (PGA) scaffold seeded with SMC and EC exhibited good mechanical properties (able to withstand more than 2000 mmHg) and desirable histological characteristics. This approach has also been used to develop large diameter conduits, e.g. for replacement of pulmonary artery (e.g. Shinoka *et al.*, 1998) and abdominal aorta (e.g. Sum-Tim *et al.*, 1999). In addition to biodegradable polymers, decellularised matrices are also being widely pursued as a scaffold to support cells and tissue development. For example, seeding decellularised porcine aortas with human EC and myofibroblasts (Teebken *et al.*, 2000), or using decellularised small intestinal submucosa without cell seeding (Badylak *et al.*, 1989; Huynh *et al.*, 1999), an idea first reported some 30 years ago (Egusa, 1968; Lawler *et al.*, 1971). There are also attempts to use de-endothelialised cryopreserved allograft vein and re-endothelialised with recipient EC as a possibility of producing a vascular graft (Lamm *et al.*, 2001).

Tissue engineering may have significant potential to meet the demand of tissue/organ shortage and reduce organ replacement. Although much progress has been made, no real breakthrough has occurred thus far in the development of a viable tissue-engineered vascular graft. Most of the tissue-based vascular grafts have been developed *ex vivo* and demonstrated in animal models. It is worth noting, however, that Shinoka *et al.*, (2001) reported the first human reconstruction of pulmonary artery using a tissue-engineered graft constructed from cells isolated and expanded from the 4-year-old patient's own peripheral veins and seeded in tubular scaffold of polycaprolactone–polylactide copolymer reinforced with woven PGA. The patient was reported to be clinically well after 7 months but how the graft will perform in her developing years is yet to be seen. In almost all tissue engineering approaches, there are impending issues related to immuno-

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