



- (51) International Patent Classification:
A61F 2/24 (2006.01)
- (21) International Application Number:
PCT/EP2015/070464
- (22) International Filing Date:
8 September 2015 (08.09.2015)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
62/047,077 8 September 2014 (08.09.2014) US
- (71) Applicant: MEDTENTIA INTERNATIONAL LTD OY
[FI/FI]; Upseerinkatu 1-3, Tower 1, FI-02600 Espoo (FI).
- (72) Inventors: O'CARROLL, Ger; Castlebaldwin, Co. Sligo (IE). PUGH, Mark; 44 Woodstream, Co. Sligo, Coolaney (IE). MORAN, Adrian; Ballinfull, Co. Sligo (IE). ZERKOWSKI, Hans-Reinhard; Auf der Bischoffhöhe 6, CH-4125 Reihen (CH). KERÄNEN, Olli; Anders Möllares väg 56, S-237 41 Bjärred (SE).
- (74) Agent: KIPA AB; P O Box 1065, S-251 10 Helsingborg (SE).
- (81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: ANNULOPLASTY IMPLANT

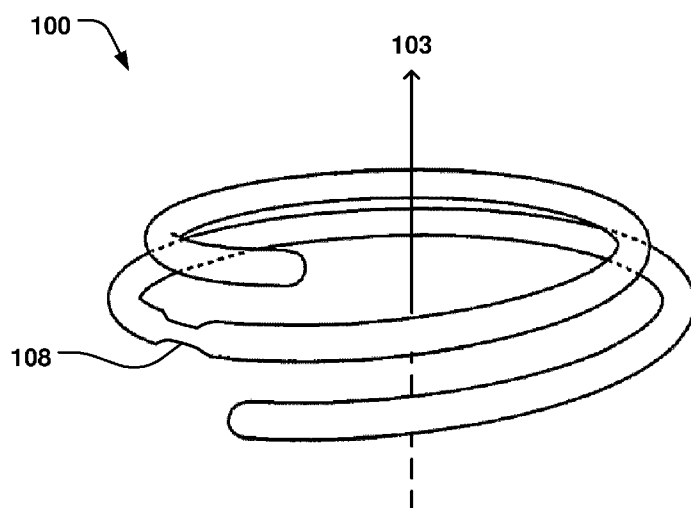


Fig. 7

(57) Abstract: An annuloplasty implant (100) comprising an inner core of a shape memory material, an outer covering arranged radially outside said inner core material to cover at least part of said inner core, wherein said outer covering is resilient to conform to said inner core during movement of said shape memory material, wherein said outer covering comprises a material having surface properties to promote endothelialization. Two portions of the implant may be joined by a recess (108) to be flexible with respect to each other by a bending motion at the recess. The two portions may also have a predefined breaking point at the recess.

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

Annuloplasty implant

Field of the Invention

5 This invention pertains in general to the field of cardiac valve replacement and repair. More particularly the invention relates to an annuloplasty implant, such as an annuloplasty ring or helix, for positioning at the heart valve annulus.

Background of the Invention

10 Diseased mitral and tricuspid valves frequently need replacement or repair. The mitral and tricuspid valve leaflets or supporting chordae may degenerate and weaken or the annulus may dilate leading to valve leak. Mitral and tricuspid valve replacement and repair are frequently performed with aid of an annuloplasty ring, used to reduce the diameter of the annulus, or modify the geometry of the annulus in any other way, or aid as a generally supporting structure during the valve replacement or repair procedure.

20 Annuloplasty rings devised for implantation are over time overgrown and encapsulated by tissue. The process of endothelialization, leading to the encapsulation of the implant by tissue, depends on the surface properties of the implant. Incomplete or delayed endothelialization can be a cause of embolism or thrombosis in a later stage after implantation.

30 A problem with prior art annuloplasty implants is the compromise between the functionality of the implant during the initial stages, such as during the implantation procedure, and the long term characteristics of the implant, for example with respect to the endothelialization process.

35 A further problem of prior art devices is the lack of flexibility of the implant in certain situations, which

impedes optimal functioning when implanted in the moving heart, or adaptability to varying anatomies.

An annuloplasty implant is intended to function for years and years, so it is critical with long term
5 stability. Material fatigue may nevertheless lead to rupture of the material, that may be unexpected and uncontrolled. This entails a higher risk to the patient and it is thus a further problem of prior art devices.

The above problems may have dire consequences for the
10 patient and the health care system. Patient risk is increased.

Hence, an improved annuloplasty implant would be advantageous and in particular allowing for improved properties during the initial implantation phase, and long
15 term functioning.

Summary of the Invention

Accordingly, embodiments of the present invention
20 preferably seeks to mitigate, alleviate or eliminate one or more deficiencies, disadvantages or issues in the art, such as the above-identified, singly or in any combination by providing a device according to the appended patent claims.

According to a first aspect of the invention an
25 annuloplasty implant is provided comprising an inner core of a shape memory material, an outer covering arranged radially outside said inner core material to cover at least part of said inner core, wherein said outer covering is resilient to conform to said inner core during movement of
30 said shape memory material, wherein said outer covering comprises a first material having surface properties to promote endothelialization.

According to a second aspect of the invention an annuloplasty implant is provided comprising a shape memory
35 material, a recess along a portion of said implant to reduce the cross-sectional area thereof at said recess, wherein two portions of said implant are joined at said

recess and are flexible with respect to each other by a bending motion at said recess.

Further embodiments of the invention are defined in the dependent claims, wherein features for the second and subsequent aspects of the invention are as for the first aspect mutatis mutandis.

Some embodiments of the invention provide for improved endothelialization.

Some embodiments of the invention provide for prevention of late embolism or thrombosis.

Some embodiments of the invention provide for increased safety in case of material fatigue and rupture.

Some embodiments of the invention provide for a more flexible implant.

Some embodiments of the invention provide for a low-profile implant.

Some embodiments of the invention provide for facilitated delivery of the implant to the target site.

Some embodiments of the invention provide for minimized friction of the implant against the delivery catheter.

It should be emphasized that the term "comprises/comprising" when used in this specification is taken to specify the presence of stated features, integers, steps or components but does not preclude the presence or addition of one or more other features, integers, steps, components or groups thereof.

Brief Description of the Drawings

These and other aspects, features and advantages of which embodiments of the invention are capable of will be apparent and elucidated from the following description of embodiments of the present invention, reference being made to the accompanying drawings, in which

Fig. 1a is an illustration of an annuloplasty implant according to an embodiment of the invention;

Fig. 1b is an illustration of the annuloplasty implant in Fig. 1a in a cross-sectional view, according to
5 an embodiment of the invention;

Fig. 2 is an illustration of an annuloplasty implant according to an embodiment of the invention in a detail view from Fig. 1b;

Fig. 3 is an illustration of an annuloplasty implant
10 according to an embodiment of the invention in a detail view from Fig. 1b;

Fig. 4 is an illustration of an annuloplasty implant, in a helix or coil shape, according to an embodiment of the invention;

Fig. 5 is an illustration of an annuloplasty implant
15 according to an embodiment of the invention;

Fig. 6 is an illustration of an annuloplasty implant, in a detailed view, according to an embodiment of the invention;

Fig. 7 is an illustration of an annuloplasty implant
20 in a perspective view according to an embodiment of the invention;

Fig. 8 is an illustration of an annuloplasty implant, in a detailed view, according to an embodiment of the
25 invention; and

Fig. 9 is an illustration of an annuloplasty implant, in a detailed view, according to an embodiment of the invention.

30 **Description of embodiments**

Specific embodiments of the invention will now be described with reference to the accompanying drawings. This invention may, however, be embodied in many different
35 forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will be thorough and

complete, and will fully convey the scope of the invention to those skilled in the art. The terminology used in the detailed description of the embodiments illustrated in the accompanying drawings is not intended to be limiting of the invention. In the drawings, like numbers refer to like elements.

The following description focuses on an embodiment of the present invention applicable to cardiac valve implants such as annuloplasty rings. However, it will be appreciated that the invention is not limited to this application but may be applied to many other annuloplasty implants and cardiac valve implants including for example replacement valves, and other medical implantable devices.

Fig. 1a shows an annuloplasty implant 100 comprising an inner core 101 of a shape memory material, an outer covering 102 arranged radially outside said inner core material to cover at least part of said inner core, wherein the outer covering is resilient to conform to the inner core during movement of the shape memory material. Thus, the outer covering readily follows the movement of the inner core material, such when stretching the ring during delivery in a catheter, and subsequently, returning to the ring shape after released from the confinement of the catheter. The outer covering comprises a first material having surface properties to promote endothelialization. The first material may be a metal alloy. The material of the inner core material can thus be optimized for providing the desired shape memory properties, such as fast recovery to the predefined implanted shape, while the outer covering 102 is customized to promote the endothelialization process. This dual functionality removes the issue of having to compromise between the most desired shape memory properties in the initial stage and the long term characteristics desired to accelerate endothelialization and minimize the risk of late embolism. The latter functionality thus needs not to be dictated by the core

material, which may not provide for the most desired surface characteristics for endothelialization. Similarly, the shape memory effect would have been impeded if the annuloplasty implant would have been tailored for
5 endothelialization purely. Thus a synergetic effect is obtained by having such customized core material and covering. The core material may comprise a single wire or filament. The core material may also comprise a plurality of wires or filaments. The number of wires or filaments may
10 be varied as desired in order to provide the desired properties of the core material, such as the desired flexibility, shape memory effects, or cross-sectional dimension, that is preferred for the procedure. The annuloplasty implant may be both a helix or coil shape as
15 seen in Fig. 1a and 4, or a closed ring 200 as seen in Fig. 5. Any type of ring, such as open ring or C-shaped ring is also possible. Fig. 1b shows a cross-section of the implant 100 for illustrating the inner core 101 and the outer covering 102.

20 The outer covering 102 may comprise a spiral 103 wound around the inner core 101, as illustrated in the detailed view of Fig. 2, and in Fig. 4. The spiral may easily conform to the shape of the core material and follow movement thereof without affecting shape memory properties.
25 The spiral can provide for an increased surface roughness that ease the formation of endothelia cells over the surface and reduces the time for the endothelialization process and tissue overgrowth. At the same time, the surface of the outer covering is sufficiently smooth, with
30 a low friction coefficient, so that the implant slides into place easily and minimizes any interference with the tissue. As can be seen in Fig. 4, the coil may comprise a wire having a flattened cross-sectional profile, that can provide such smooth surface.

35 The outer covering may comprise a mesh or braiding 104 of strands, as illustrated in the detailed view of Fig. 3. The mesh may also easily conform to the shape of the core

material and follow movement thereof without affecting shape memory properties. The mesh can provide for an increased surface roughness that ease the formation of endothelia cells over the surface and reduces the time for the endothelialization process and tissue overgrowth. The implant 100, 200 may have any combination of spirals and mesh on different portions of the implant. Fig. 5 illustrates just a portion of the implant 200 having a covering 103, 104, for sake of clarity of presentation only.

The outer covering 102 may have a predefined surface porosity or roughness to start endothelialization within a set time period. Thus it is possible to customize the surface properties to attain the desired endothelialization process, to minimize embolism.

The outer covering 102 may cover substantially the entire core 101 in the longitudinal direction 107 of the implant 100, 200. This may provide for optimized endothelialization across the entire length of the implant. The covering may also have different properties on different parts of the implant 100, 200. In case having a coil shaped ring the ring placed towards the atrium or the ventricle may have different properties than the other ring.

The implant may comprise a catheter deliverable ring 100, wherein said ring has an elongated delivery configuration for advancement in a catheter and an implanted shape assuming a predefined configuration of said shape memory material for positioning at a heart valve annulus. Thus the ring in the implanted shape may comprise a first 105 and second 106 support members arranged in a coiled configuration, and being adapted to be arranged on opposite sides of native heart valve leaflets to pinch said leaflets.

The outer covering may cover the first and second support members. Alternatively, the covering may only be

provided at one of the rings, or have different properties for the rings as mentioned above.

The annuloplasty implant 100, 200, may comprise a recess 108 along a portion of the implant to reduce the cross-sectional area thereof at said recess, as illustrated in Figs. 6 and 7.

Two portions 109, 110 of the implant 100, 200 may thus be joined at said recess 108 and be flexible with respect to each other by a bending motion at the recess 108. The recess can thus serve to increase the flexibility of the implant, at defined locations where more movement is desired. The recess is provided in the inner core 101 of the shape memory material.

The two portions 109, 110, may also have a predefined breaking point at the recess 108. Thus since the amount of material is less at the reduced cross-section of the implant it is possible to define preferred breaking points of the implant, to avoid random breaking in case of material fatigue occurs after a long time. The location of the breaking point can thus be positioned to not cause any damage to the patient. Further, even if the core material is not broken, the material properties may change over time, e.g. becoming less flexible due to material hardening, and the recess will thus still provide flexibility to the implant.

The annuloplasty implant may comprise a plurality of said recesses 108, 108', along a longitudinal direction 107 of said implant, as seen in Fig. 6. A plurality of flexing or breaking points may thus be provided as desired where flexing, or possibly breaking, is preferred.

The covering may be arranged over said recess. In case of having a covering 102, there will also be an additional increase in safety since the covering will prevent any broken parts to be dislodged into the patient.

The first material may comprise a first metal alloy that is bio compatible, such as stainless steel, NiTiInol, or any other metal alloy that is suitable for formation of

endothelia. In addition of the advantageous properties of such metal alloy for the endothelialization process, the metal alloy covering over the inner core provides for reduced friction against a delivery catheter, compared to e.g. surfaces being more porous and/or having higher friction coefficients such as textile coverings. It is also conceivable to have a polymer covering that also has a very low friction coefficient, similar to that of the surface of a metal alloy. This may thus facilitate delivery of the implant, and allowing a more controlled delivery, since the implant moves more easily through the delivery catheter. It is thus possible to optimize the outer covering for providing advantageous formation of endothelia, while at the same time reducing friction, and further having the inner core optimized for the desired shape-memory properties as described above. The effect of having reduced friction can also be advantageously combined with having the recess 108, 108', in the core material, providing for the advantageous effects as described above with respect to the recess 108, 108'.

Having a metal alloy as outer covering provides also for a compact implant with a minimized cross-sectional dimension, while allowing for the optimization of the shape memory properties of the core material simultaneous as having the optimized properties of the covering with respect to endothelialization, as well as the low-friction properties described in the foregoing. The compact cross-sectional dimension allows for using a thinner catheter, that can be advantageous in some procedures, and/or facilitates the simultaneous use of additional instruments that can be inserted in parallel lumens of the catheter during the procedure.

The covering may comprise any polymer and is not limited to a metal alloy.

The inner core may comprise a second material such as a second metal alloy, different from said first material or first metal alloy, such as NiTiInol, or any other alloy that

provides for the desired shape memory effect. The inner core may comprise any polymer and is not limited to a metal alloy. Both metal alloys and polymers can be treated during manufacturing to have a desired heat-set shape, which is
5 the shape the implant strives towards when any restraining force is removed, i.e. the relaxed shape, such as when the implant is pushed out of the delivery catheter which forces the implant into an elongated shape. It is also possible that the implant assumes the desired implanted shape by
10 activation of the shape memory function of the material, such as by addition of energy, e.g. heating, electromagnetic energy etc, or by mechanical restructuring of the material.

It is also disclosed an annuloplasty implant without a
15 covering according to one embodiment of the invention. Such annuloplasty implant comprises a shape memory material and a recess 108 along a portion of said implant to reduce the cross-sectional area thereof at said recess, wherein two portions 109, 110 of said implant are joined at said
20 recess and are flexible with respect to each other by a bending motion at said recess. This provides for the above mentioned advantages.

The present invention has been described above with
25 reference to specific embodiments. However, other embodiments than the above described are equally possible within the scope of the invention. The different features and steps of the invention may be combined in other combinations than those described. The scope of the
30 invention is only limited by the appended patent claims. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials,
35 and/or configurations will depend upon the specific application or applications for which the teachings of the present invention is/are used.

Claims

1. An annuloplasty implant (100, 200) comprising
an inner core (101) of a shape memory material,
5 an outer covering (102) arranged radially outside said
inner core material to cover at least part of said inner
core, wherein said outer covering is resilient to conform
to said inner core during movement of said shape memory
material, wherein said outer covering comprises a first
10 material having surface properties to promote
endothelialization.

2. Annuloplasty implant according to claim 1, wherein
said outer covering comprises a spiral (103) wound around
15 said inner core.

3. Annuloplasty implant according to claim 1, wherein
said outer covering comprises a mesh or braiding (104) of
strands.

20 4. Annuloplasty implant according to any of claims 1-3,
wherein said outer covering has a predefined surface
porosity or roughness to start endothelialization within a
set time period.

25 5. Annuloplasty implant according to any of claims 1-4,
wherein said outer covering covers substantially the entire
core in the longitudinal direction (107) of the implant.

30 6. Annuloplasty implant according to any of claims 1-5,
wherein said implant comprises a catheter deliverable ring
(100), wherein said ring has an elongated delivery
configuration for advancement in a catheter and an
implanted shape assuming a predefined configuration of said
35 shape memory material for positioning at a heart valve
annulus.

7. Annuloplasty implant according to claim 6, wherein said ring in the implanted shape comprises a first (105) and second (106) support members arranged in a coiled configuration, and being adapted to be arranged on opposite
5 sides of native heart valve leaflets to pinch said leaflets.

8. Annuloplasty implant according to claim 7, wherein said outer covering covers the first and second support
10 members.

9. Annuloplasty implant according to any of claims 1-8, comprising a recess (108) along a portion of said implant to reduce the cross-sectional area thereof at said recess.
15

10. Annuloplasty implant according to claim 9, wherein two portions (109, 110) of said implant are joined at said recess and are flexible with respect to each other by a bending motion at said recess.
20

11. Annuloplasty implant according to claim 10, wherein said two portions has a predefined breaking point at said recess.

25 12. Annuloplasty implant according to any of claims 9-11, comprising a plurality of said recesses (108, 108') along a longitudinal direction (107) of said implant.

30 13. Annuloplasty implant according to any of claims 9-12, wherein said covering is arranged over said recess.

14. Annuloplasty implant according to any of claims 1-13, wherein said first material comprises a first metal alloy.
35

15. Annuloplasty implant according to any of claims 1-14, wherein said inner core comprises a second material,

different from said first material, and wherein said second material comprises a second metal alloy such as NiTiInol.

16. An annuloplasty implant (100, 200) comprising
5 a shape memory material,
a recess (108) along a portion of said implant to
reduce the cross-sectional area thereof at said recess,
wherein two portions (109, 110) of said implant are joined
at said recess and are flexible with respect to each other
10 by a bending motion at said recess.

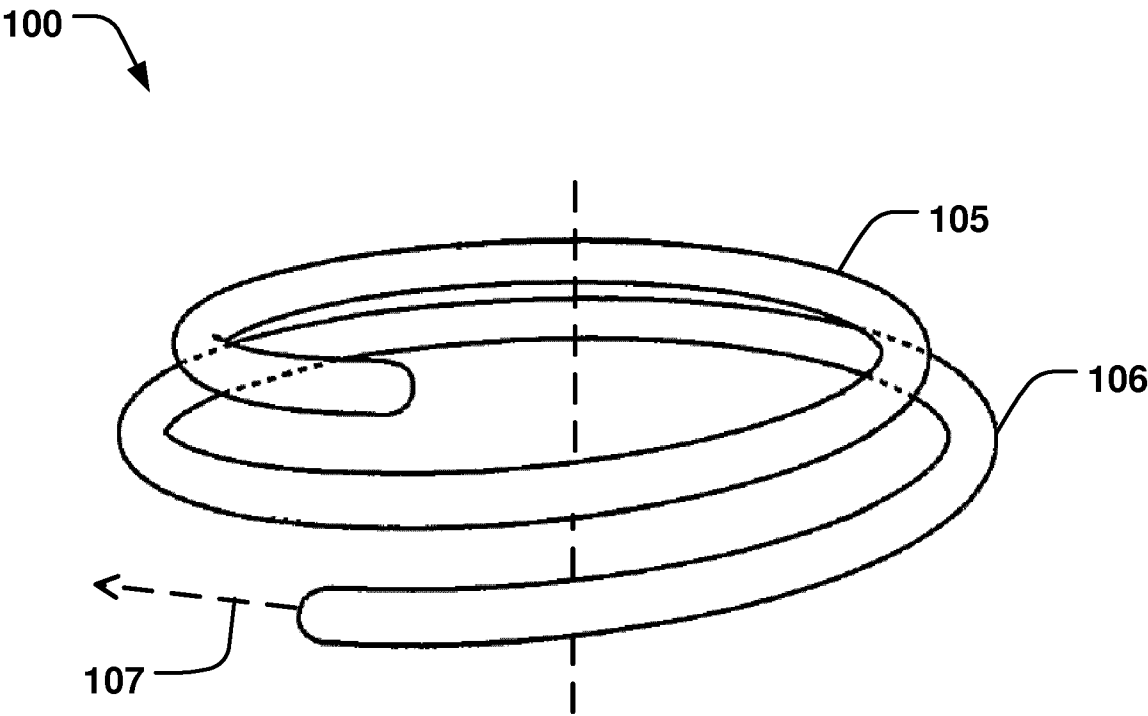


Fig. 1a

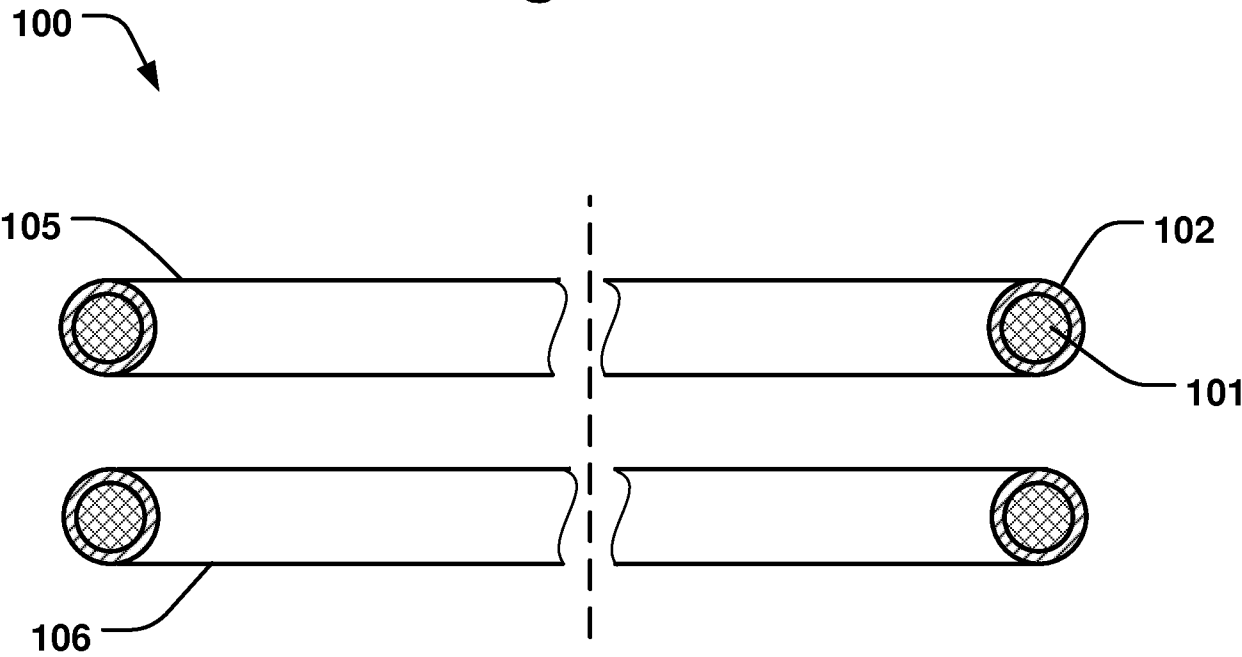
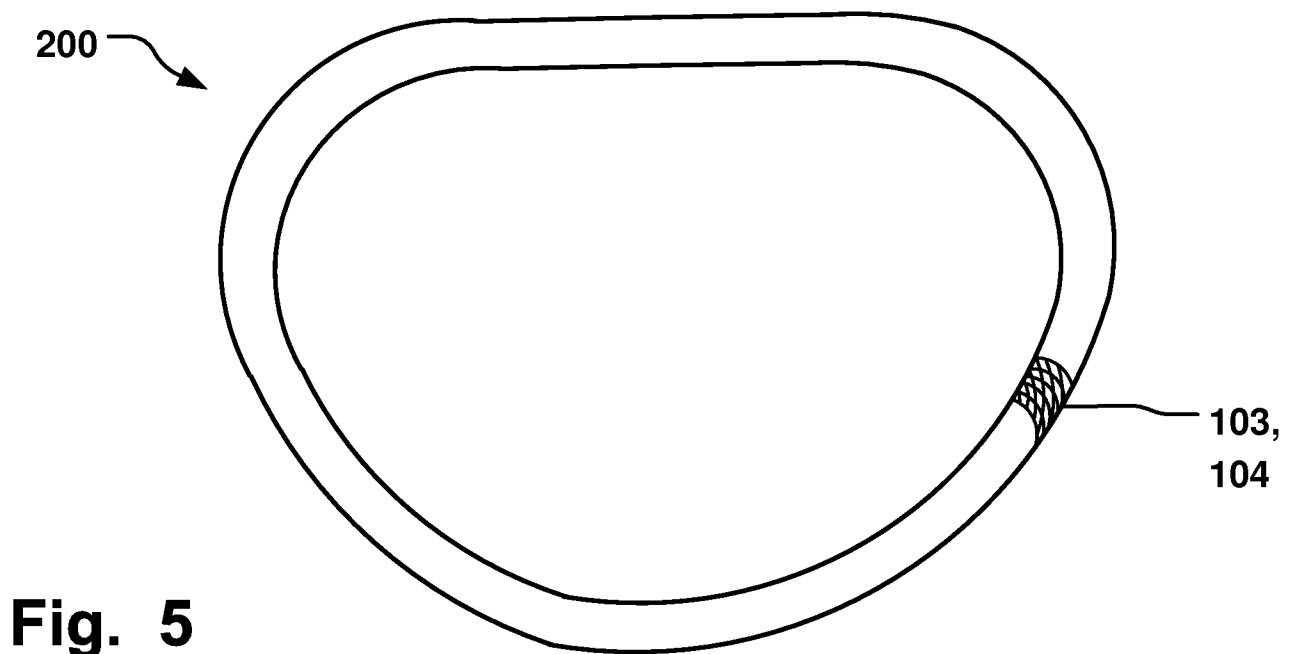
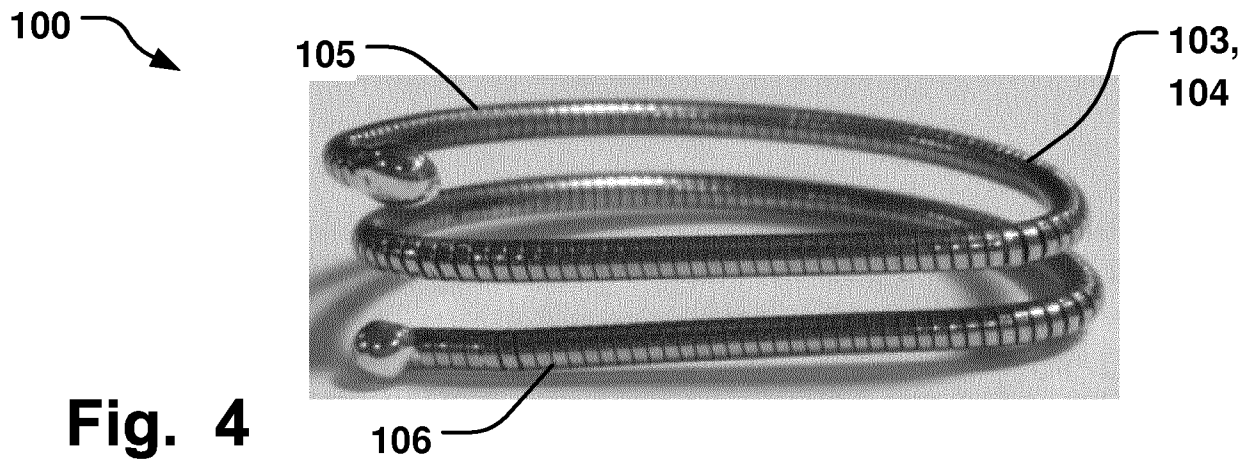
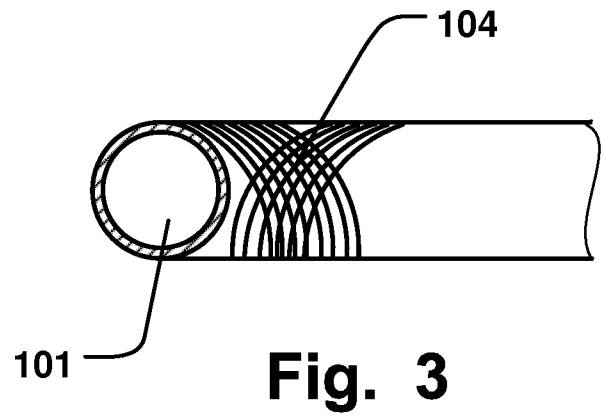
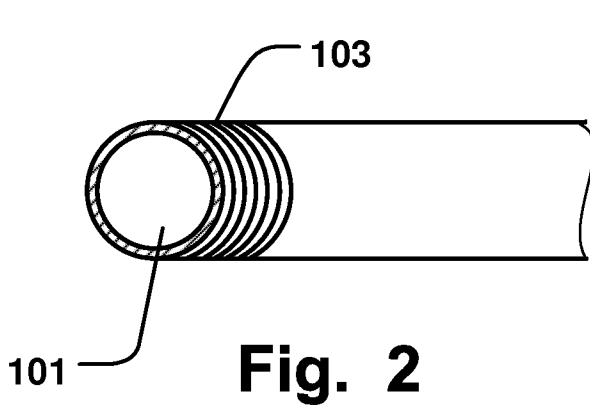


Fig. 1b



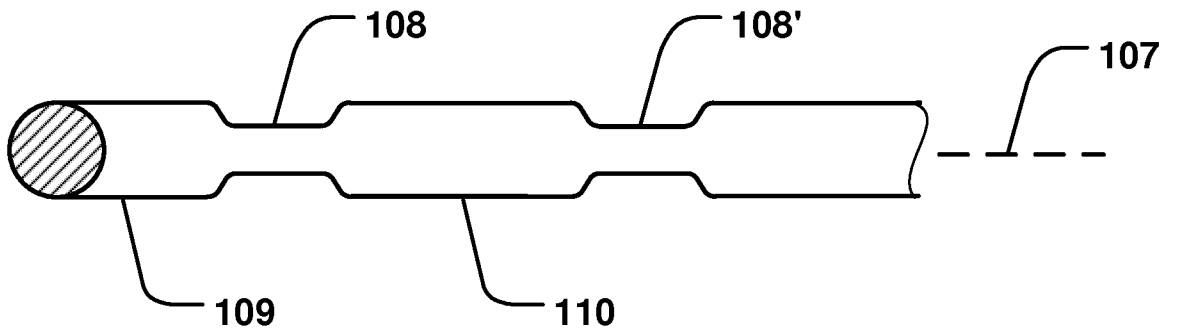


Fig. 6

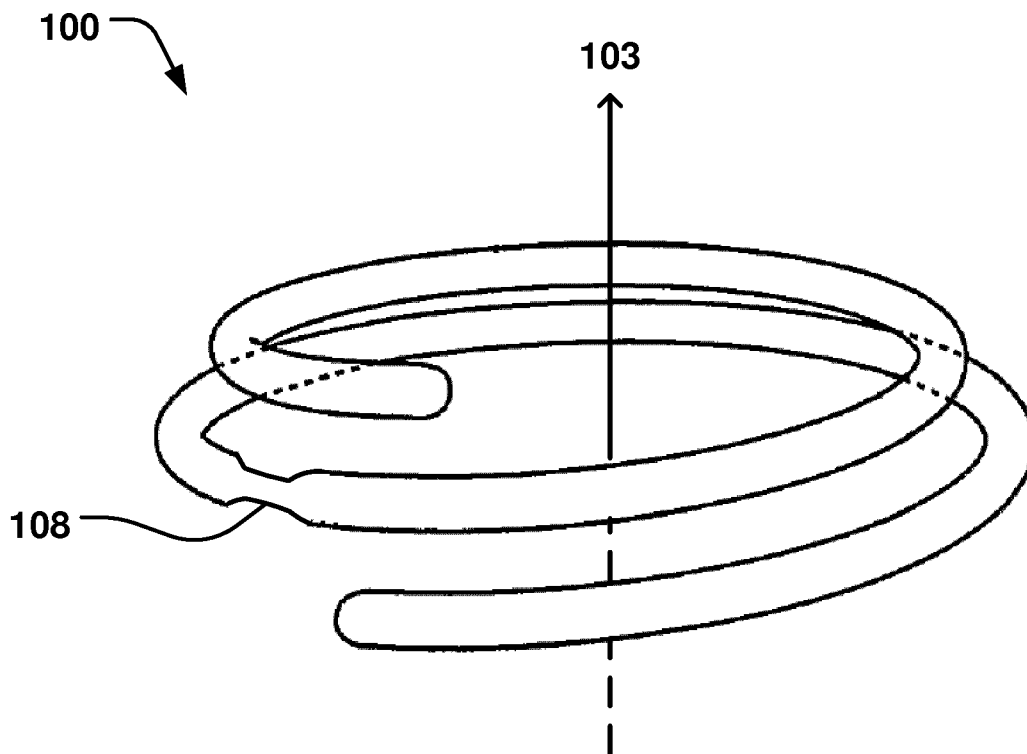


Fig. 7

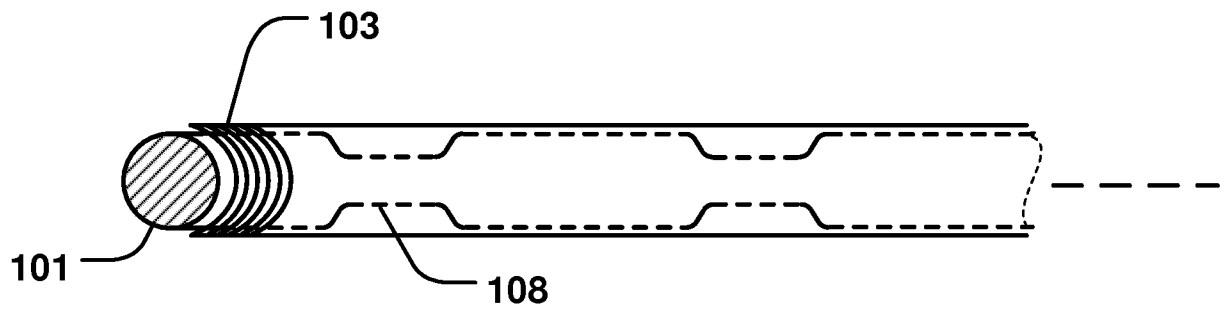


Fig. 8

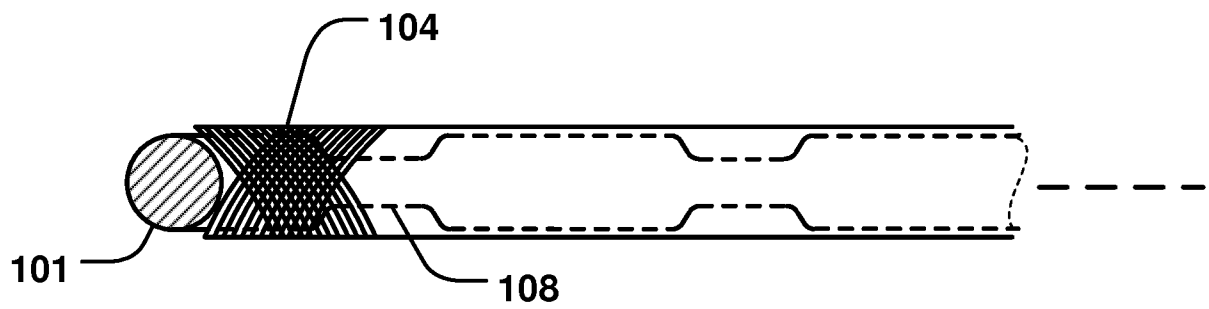


Fig. 9

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/070464

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61F2/24
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/121433 A1 (BOLLING STEVEN F [US] ET AL) 13 May 2010 (2010-05-13)	1-15
Y	paragraphs [0172] - [0183], [0202] - [0204]; figure 18	14,15
X	US 5 628 790 A (DAVIDSON JAMES A [US] ET AL) 13 May 1997 (1997-05-13) column 6, line 64 - column 7, line 10; figures 1-5	1,3-15
X	US 2005/256569 A1 (LIM JYUE B [US] ET AL) 17 November 2005 (2005-11-17)	1,3-5, 9-13,15, 16
Y	paragraphs [0014], [0017], [0027], [0032]; figures 3, 4	7,8,11
	----- -/--	



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

26 October 2015

Date of mailing of the international search report

04/11/2015

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Prechtel, A

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2015/070464

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2008/077235 A1 (KIRSON E D [US]) 27 March 2008 (2008-03-27)	1,2,4-6, 14,15
Y	paragraphs [0026] - [0030]; figure 6 -----	7,8
Y	US 2011/060401 A1 (HOERSTRUP SIMON-PHILIPP [CH] ET AL) 10 March 2011 (2011-03-10) paragraphs [0062] - [0064], [0076]; figures 2B, 2C, 2D -----	11
X	US 2005/049698 A1 (BOLLING STEVEN F [US] ET AL) 3 March 2005 (2005-03-03) paragraphs [0041], [0042]; figures 6A, 6B -----	1,16
X	WO 2006/091163 A1 (MEDTENTIA AB [SE]; KERAENEN OLLI [SE]; WIERUP PER [SE]) 31 August 2006 (2006-08-31)	1,3-8
Y	pages 13, 16; figure 8 -----	14,15
A		11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2015/070464

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2010121433 A1	13-05-2010	CA 2756028 A1 EP 2408400 A1 EP 2412316 A2 US 2010121433 A1 WO 2010108079 A1	23-09-2010 25-01-2012 01-02-2012 13-05-2010 23-09-2010
US 5628790 A	13-05-1997	NONE	
US 2005256569 A1	17-11-2005	EP 1761209 A1 US 2005256569 A1 WO 2005112828 A1	14-03-2007 17-11-2005 01-12-2005
US 2008077235 A1	27-03-2008	US 2008077235 A1 US 2010049315 A1	27-03-2008 25-02-2010
US 2011060401 A1	10-03-2011	EP 1958598 A1 EP 2117477 A1 US 2011060401 A1 WO 2008098776 A1	20-08-2008 18-11-2009 10-03-2011 21-08-2008
US 2005049698 A1	03-03-2005	AT 539704 T CA 2467766 A1 EP 1443877 A1 JP 4235554 B2 JP 2005508702 A US 2003093148 A1 US 2005049698 A1 US 2008097593 A1 WO 03041617 A1	15-01-2012 22-05-2003 11-08-2004 11-03-2009 07-04-2005 15-05-2003 03-03-2005 24-04-2008 22-05-2003
WO 2006091163 A1	31-08-2006	CN 101340861 A CN 102247225 A EP 1853199 A1 EP 2649964 A1 JP 4740963 B2 JP 5390479 B2 JP 2008531185 A JP 2010253287 A US 2008208330 A1 US 2010318183 A1 WO 2006091163 A1	07-01-2009 23-11-2011 14-11-2007 16-10-2013 03-08-2011 15-01-2014 14-08-2008 11-11-2010 28-08-2008 16-12-2010 31-08-2006