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Science & Engineering

Instructions for Use -
HAART 300 Aortic Annuloplasty Device

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1. Device Labeling Symbols

Manufacturer

Do not use if package is damaged

Keep dry

MR Conditional

Use by date

Do not resterilize

Do not re-use

Consult Instructions for Use

LOT Batch code

EC REP Authorized European Rep

REF Catalog number

STERILE R Sterilized using irradiation

RX ONLY

CE Product complies with requirements of directive 93/42/EEC for medical devices

2. Indications

The HAART 300 Aortic Annuloplasty Device is intended to be used to correct annular dilatation and/or maintain annular geometry of the aortic valve in patients with tri-leaflet valve morphology with moderate to severe aortic insufficiency who are undergoing aortic valve repair due to symptoms or as part of a repair for an aortic root aneurysm. It is designed to return aortic annular geometry toward normal for a given leaflet size and to assist in producing adequate leaflet competence by recovering normal coaptation geometry and area.

3. Annuloplasty Device Description

3.1. Overview

The HAART 300 Aortic Annuloplasty Device (Figure 1) is a three dimensional annuloplasty ring designed to be implanted intra-annularly in the aortic valve in patients with tri-leaflet valve morphology. BioStable Science &

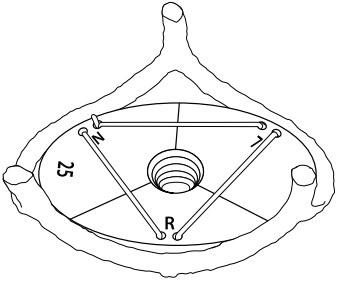


Figure 1. HAART 300 Aortic Annuloplasty Device on holder

Engineering developed the HAART 300 Aortic Annuloplasty Device to return aortic annular geometry toward normal for a given leaflet size and to assist in producing adequate leaflet competence by recovering normal coaptation geometry and area.

The Device consists of a titanium frame machined from medical grade Titanium 6AL-4V covered with medical grade polyester fabric affixed to the frame by suture. Twelve polyester pledgets are provided with the device for use during surgery.

3.2. Technological Characteristics

The HAART 300 Aortic Annuloplasty Device is comprised of three components: the implantable Annuloplasty Device, polyester Pledgets, and a Device Holder that is discarded during the procedure. Each of these components is briefly described below.

Annuloplasty Device

The HAART 300 Aortic Annuloplasty Device was developed from mathematical analyses of normal human computed tomography (CT) angiograms and exhibits 2:3 elliptical base geometry and 3 equidistant 10° outwardly flaring subcommissural posts. The annuloplasty Device consists of a titanium frame machined from medical grade Titanium 6AL-4V covered with medical grade polyester fabric affixed to the frame by suture. The Device materials and the manufacturing processes were specifically selected for use in an implantable medical device. The polyester fabric, ARF001, is manufactured for annuloplasty ring applications. HAART 300 Aortic Annuloplasty Devices are manufactured in 4 sizes ranging from 19mm to 25mm in 2mm increments. The HAART 300 Aortic Annuloplasty Device has a unique geometry that will bring aortic valve leaflets into normal approximation, helping to restore competency to the valve.

The titanium frame of the Device provides the stiffness to return the dilated aortic annulus to normal geometry while the polyester fabric provides material to support endothelialization and direct suturing of the subcommissural posts to the aortic valve annulus. The inner aspects of the Device posts have 2 layers of polyester fabric to facilitate suturing.

Polyester Pledgets

Polyester Pledgets are 3mm by 7mm and are made from the same ARF001 fabric used to cover the Device. The Pledgets are provided with the annuloplasty Device for use during surgery. They are supplied sterile in a separate package within the Device shelf box.

Holder

The HAART 300 Aortic Annuloplasty Device is supplied on a Holder that may be attached to a Handle to facilitate positioning the Device during the procedure (Figure 2). The Holder is machined from polyphenylsulfone and is attached to the annuloplasty Device using a single suture (Figure 1 on page 2). The Device can be removed from the Holder by severing the suture at any location along the face of the Holder.

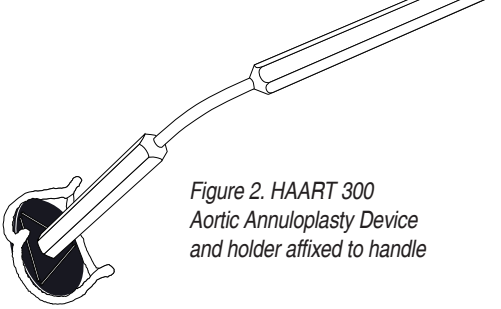


Figure 2. HAART 300 Aortic Annuloplasty Device and holder affixed to handle

3.3. Accessories

The HAART 301 Instrument Set (Figure 3) is comprised of two (2) Handles, four (4) Sizers and a Gage Sphere. The Handle is made from ASTM A276-05 stainless steel and the Sizers and Gage Sphere are fabricated from polyphenylsulfone.

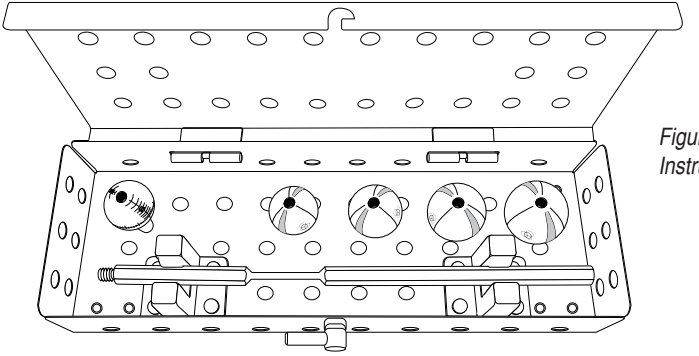


Figure 3. HAART 301 Instrument Set

The Handle may be threaded into the Sizers and Gage Sphere. The Handle may also be threaded into the face of the Holder to facilitate positioning the Device during the procedure (Figure 2 on page 3). The Handle may be bent in the narrowed section to present the Sizers, Gage Sphere, and Device to the surgical site in the desired manner.

Warning: The Sizers, Gage Sphere, and Handle are intended for multiple uses provided they are inspected before each use for signs of damage. A cleaning and steam sterilization process has been validated for these reusable instruments for use by the hospital. Instruments must be cleaned and sterilized before each use. Consult the HAART 301 Instrument Set IFU for detailed cleaning and sterilization instructions. Before each use, the Sizers and Gage Sphere should be visually inspected for crazing of polymer materials, cracks, signs of structural weakness, or unreadable markings. The Handle should be inspected for visible cracks or signs of structural weakness before each use and after bending. Replace any instrument that exhibits these faults as they may not function properly and could cause patient injury. For more information on instruments, see the HAART 301 Instrument Set IFU.

3.4. Size Designations

In patients with chronic aortic valve insufficiency or aortic root aneurysms, the three-dimensional anatomy of the aortic valve is typically distorted due to dilation of the aortic valve annulus. Consequently, direct measurements of annular diameter cannot be used to determine the size of the HAART 300 Aortic Annuloplasty Device needed to produce leaflet coaptation. The HAART 300 Aortic Annuloplasty Device was developed from mathematical analyses of normal human computed tomography (CT) angiograms and exhibits 2:3 elliptical base geometry and 3 equidistant 10° outwardly flaring subcommissural posts. Based upon CT angiographic analysis and empirical observations the leaflet free-edge length is approximately one half of the circumference of the elliptical valve annulus in normal aortic valves. The size designations for the HAART 300 Aortic Annuloplasty Device and the procedure used to determine the appropriate Device size are based upon the following mathematical relationships.

$$\mathbf{L} = \tfrac{1}{2}\,\mathbf{C} \text{ and } \mathbf{D} = 2\mathbf{L}/\pi \approx \mathbf{L}/1.5$$

L = the leaflet free-edge length **C** = the circumference of the elliptical valve annulus
D = diameter of the spherical Sizer (corresponds to the size designation of the Device)

The leaflet free-edge length is determined using the spherical Sizers. A Sizer is chosen so that the leaflet free-edge length approximately matches 180 degrees of the circumference of the Sphere at the equator. The diameter of that Sizer is recommended as the size of the Device required. The HAART 300 Aortic Annuloplasty Device chosen through this method will have an elliptical circumference at its base that is equal to twice the leaflet free-edge length.

Detailed procedures for determining the appropriate HAART 300 Aortic Annuloplasty Device size are provided in the Directions for Use Section.

4. Contraindications

- The Device is contraindicated in patients with a porcelain aorta.
- The Device is contraindicated in patients with evolving bacterial endocarditis.
- The Device is contraindicated in patients with heavily calcified valves.

5. Warnings

- The HAART 300 Aortic Annuloplasty Device is for Single Use Only. Do not re-use the Device. In addition to the risks listed under Complications, re-use may cause procedural complications including Device damage, compromised Device biocompatibility, and Device contamination. Re-use may result in infection, serious injury, or patient death.
- The decision to use an annuloplasty device must be made by the responsible physician on an individual basis after evaluation of the risks and benefits accrued to the patient in comparison to alternate treatment.
- Intraoperative and /or postoperative echocardiography should be used to eveluate the effectiveness of the valve repair.
- Hemolysis may occur even with mild regurgitation.
- Do not attempt to deform or reshape the annuloplasty Device as this could lead to device fracture, possible valve regurgitation or stenosis.
- The HAART 300 Aortic Annuloplasty Device has been sterilized by gamma irradiation methods and is provided sterile in a double packaged container. No steam sterilization cycle has been validated for the sterilization of the Device.
- Valve repair patients subjected to subsequent dental procedures or other surgical procedures should receive prophylactic antibiotic drug therapy to minimize the risk of systemic bacteremia and prosthetic endocarditis.
- Correct annuloplasty device sizing is an important element of successful valve repair. Significant undersizing can result in valve stenosis or ring dehiscence. Oversizing can result in valve regurgitation. The size of the HAART 300 Aortic Annuloplasty Device is selected using Sizers consistent with the design intent of the Device. Use only the HAART Sizers included in the HAART 301 Instrument Set to select the proper Device size. Do not use the Holder as a sizing tool.
- The HAART 300 Aortic Annuloplasty Device should not be used in combination with transcatheter aortic replacement (TAVR) devices as the device has not been tested as an anchor for valve-in-valve procedure.

6. Precautions

- Only surgeons having received appropriate training in aortic valve repair, including device implantation and sizing techniques, should use this Device.
- Only surgeons who have adequate training to determine whether incompetent heart valves are capable of being repaired, or if replacement is indicated, should use this Device.
- Only Surgeons who have adequate training to determine whether a stenotic valve is capable of being repaired via annuloplasty, or if valve replacement is required, should use this device.
- Do not use the Device after the expiration date printed on the label.
- To ensure the sterility and integrity of the Device, it should be stored in the outer cardboard box until needed for introduction into the sterile field. Do not use a Device that has been removed from the double packaging and dropped, soiled, or otherwise damaged.
- Do not use the HAART 300 Aortic Annuloplasty Device if the tamper-evident seal is damaged, broken or missing.
- Dispose of used Devices as biohazardous waste.
- To avoid damage to the fabric covering the Device, do not use suture needles with cutting edges during implantation.
- To prevent sutures from pulling through the native annular tissue, Pledgets should be used with the sutures as described in the Directions for Use along with a sufficient number of broad horizontal mattress sutures (at least 9) to support the tension associated with annular reduction.
- Do not place sutures in the circumflex coronary artery.
- Suture tails should be tied down to the lateral aspect of the annular Pledgets, as described in the Directions for Use, to prevent leaflet damage from long suture tails. The sutures should also be cut very short. Loose sutures or threads may be a source of thrombosis, thromboembolism, or hemolysis.
- The Device is not intended for use as sole therapy for correction of valvular insufficiency in patients with aortic root aneurysms. If aortic root diameter exceeds common standards for normal dimensions, aortic root replacement is indicated in addition to aortic valve repair.
- When postoperative anticoagulation therapy is used, the patient's antocoagulation status should be carefully monitored. The surgeon may desire that patients in atrial fibrillation remain on anticoagulation therapy until sinus rhythm is established.

- Provide careful monitoring of the patient's anticoagulation status when postoperative anticoagulation therapy is used. Surgeons who use the HAART 300 Aortic Annuloplasty Device should be current on anticoagulation regimens.

7. Magnetic Resonance (MR) Safety

MR Conditional

Non-clinical testing has demonstrated that the HAART 300 Aortic Annuloplasty Device is MR Conditional. A patient with this device can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 1.5 T and 3 T
- Maximum spatial field gradient of 4,000-G/cm (40 T/m)
- Maximum MR system reported, whole body average specific absorption rate (SAR) of 4.0 W/Kg (First Level Controlled Operating Mode) at 3 T.

RF Heating

Under the scan conditions defined above, the HAART Aortic Annuloplasty Device is expected to produce a maximum temperature rise of less than 3.0°C after 15 minutes of continuous scanning.

Caution: The RF heating behavior does not scale with static field strength. Devices that do not exhibit detectable heating at one field strength may exhibit high values of localized heating at another field strength.

MR Artifact

In non-clinical testing, the image artifact caused by the device extends approximately 10 mm from the HAART 300 Aortic Annuloplasty Device when imaged with a gradient echo pulse sequence and a 3 T MRI system.

8. Potential Adverse Events

Each prospective patient should be informed about the benefits and risks of valve repair and annuloplasty surgery before the procedure. Serious complications, including death, are possible with any open heart surgery procedure including the implantation of the HAART 300 Aortic Annuloplasty Device. These potential complications include those associated with open heart surgery in general and the use of general anesthesia. The potential complications associated with the HAART 300 Aortic Annuloplasty Device and its implantation procedure are listed in Table 1.

Table 1. Possible Complications Associated with the Device/Procedure

Abrasion of the natural valve	Infection – local, bacteremia, sepsis
Allergic reaction	Leaflet damage
Angina	Left Ventricular Outflow Tract Obstruction
Aortic insufficiency	Myocardial infarction
Arrhythmia	Neurological events (including TIA, stroke, and psychomotor deficit)
Complete heart block	Pain (patient discomfort)
Conduction defects	Pericardial effusion
Death	Permanent pacemaker
Device explant	Pleural effusion
Device fracture	Psychological problems
Device migration or malposition requiring intervention	Renal insufficiency / failure
Endocarditis	Reoperation
Extended surgery time or aborted procedure	Respiratory system disorders
Fever	Ring dehiscence
Gastrointestinal disorders	Stenosis
Heart Failure	Suture injury to coronary arteries
Hematoma	Thrombosis or thromboembolism
Hemolysis or hemolytic anemia	Syncope
Hemorrhage	Toxic reaction
Hypertension	Wound healing problems

9. How Supplied

9.1. Packaging

The HAART 300 Aortic Annuloplasty Device is available in 19, 21, 23 and 25 mm sizes. Each HAART 300 Aortic Annuloplasty Device shelf box contains Pledgets and a single annuloplasty Device assembly consisting of the Device sutured onto its corresponding Holder. The assembled Device and Holder are packaged within nested, sealed trays. Pledgets are packaged separately within nested pouches. The packaging system is designed to ease placement of the Device into the sterile field. The components within the packaging are sterile if the pouches, trays, and lids are undamaged and unopened. The surfaces of the outer packaging are NONSTERILE and must not be placed in the sterile field.

9.2. Storage

Store the product in its original packaging, including the outer shelf box, in a clean, cool, and dry area to protect the product and minimize the potential for contamination. Stock rotation is recommended at regular intervals to ensure usage before the expiration date printed on the box label. Do not use the Device after the expiration date printed on the label.

10. Directions for Use

10.1. Sizing

The HAART 300 Aortic Annuloplasty Device size should be selected based on the free-edge lengths of the valve leaflets. The free-edge length is determined using the Sizers provided in the HAART 301 Instrument Set. Sizers are provided in 19, 21, 23, and 25 mm diameters to correspond to the four HAART 300 Aortic Annuloplasty Device sizes. The listed Device size refers to the diameter of a circle with equivalent circumference to the elliptical ring.

Correct annuloplasty device sizing is an important element of successful valve repair. The appropriate HAART 300 Aortic Annuloplasty Device size is selected by threading each individual Sizer onto the Handle and inserting it behind the valve leaflet such that the leaflet free-edge length between commissural insertions lies smoothly along the circumference of the Sizer. The appropriate Sizer for a given leaflet has been selected when the distance from one stippled area to the other matches the leaflet free-edge length from one commissure to the other (Figure 4 on page 11). If the leaflet free-edge length is between two sizes, choose the smaller of the two size options. The size number on the corresponding Sizer indicates the appropriate Device size based on the leaflet measured.

All 3 leaflet free-edge lengths should be checked with the Sizers before selecting the final HAART 300 Aortic Annuloplasty Device size. If leaflet sizes differ by one size, the smaller Device size should be selected. If leaflet sizes differ by more than one size, an intermediate size is considered, or more advanced techniques, such as leaflet replacement, may be appropriate.

10.2. Handling and Preparation Instructions

Each Device is supplied mounted on a Holder and is packaged in nested, sealed trays to ease transfer of the Device into the sterile field. Pledgets are packaged within nested pouches. The inner pouches and sealed trays should be inspected for damage prior to opening. Do not use the Device if the sterile packaging has been compromised.

The Holder should be attached to the Handle contained within the HAART 301 Instrument Set to facilitate placement of the Device within the aortic root. For ease of orientation, the face of the Holder is marked in 3 segments (Figure 5). The segment marked R should face the Right coronary cusp. The segment marked L should face the Left coronary cusp and the N segment should face the Noncoronary cusp. The post between the N and L segments should be placed into the aorta adjacent to the mitral valve.

10.3. Device Implantation

Post Sutures

Insertion is begun by suturing all three posts of the Device to the three subcommissural areas using

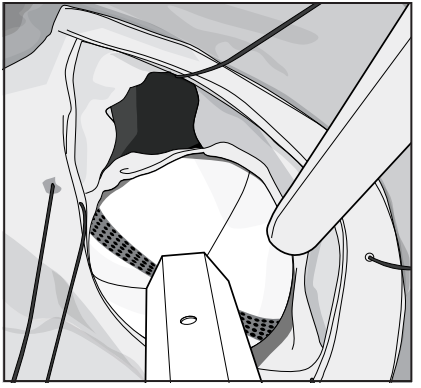


Figure 4. Proper sizing of leaflet free-edge length using the sizer

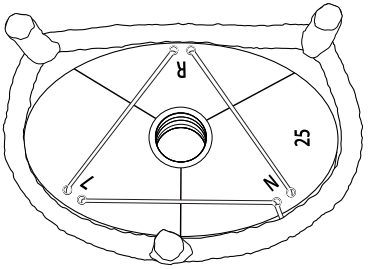


Figure 5. HAART 300 Aortic Annuloplasty Device on holder

"Cabrol-like" configurations with generous bites taken in the aortic wall, using 4-0 Prolene horizontal mattress sutures supported by Pledgets above the annulus (Figure 6). Prolene suture is recommended for suturing the posts to facilitate easy tightening of the sutures and passage of the Device below the valve.

The post sutures are placed with the HAART 300 Aortic Annuloplasty Device on the Holder above the valve (Figure 7). The post on the posterior minor axis diameter should be first sutured to the subcommissural space of the left/non-coronary commissure, adjacent to the center of the anterior mitral leaflet, before suturing either of the other two posts into place.

The vertical level of the post in each subcommissural area should be gauged to bring the bottom of the Device into apposition with the bottom of the leaflets, and to keep the Device posts below the commissural aspects of the leaflets. Aligning the posts first, both vertically and horizontally, brings the Device into initial proper position with the valve, and prevents skewed insertion with resultant leaflet distortion. Again, the sutures should be placed so that the posts are positioned well down into the subcommissural space to prevent abrasive contact between the leaflets and the polyester fabric.

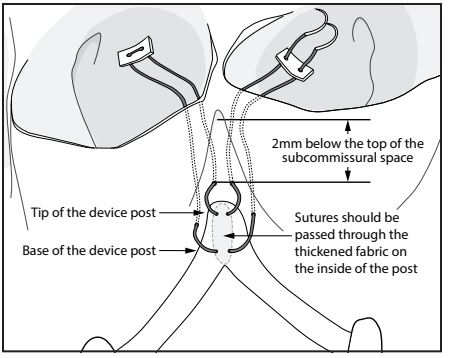


Figure 6. Suturing technique for the HAART 300 Aortic Annuloplasty Device Posts

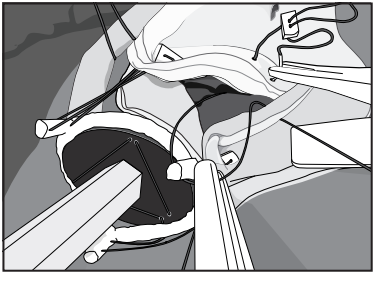


Figure 7. Placing the post sutures

The HAART 300 Aortic Annuloplasty Device is covered with polyester fabric, which allows endothelialization. Horizontal mattress post sutures are used primarily to correctly position the Device prior to placement of additional looping sutures around the leaflet sections of the Device. Only the horizontal mattress post sutures

should catch the fabric and then only just on the inside of the posts (Figure 6 on page 12). Extra fabric has been added in those areas to allow needle passage, but only very superficial bites are required.

After all three post sutures are placed, the Device is lowered below the native valve, and the suture attaching the Device to the Holder is cut. The HAART 300 Aortic Annuloplasty Device must be removed gently from the Holder, primarily by pushing the Device off the Holder at opposite ends of the major and minor axis of the Holder. Only after the Device has been pushed off the Holder should the Holder be removed from beneath the valve.

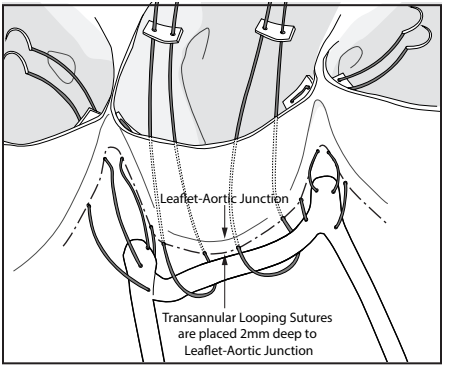


Figure 8. Leaflet section looping sutures

Leaflet Section Sutures

Two looping sutures are placed around each leaflet segment of the Device and up through the annulus, again taking deep bites into the aorta and emerging above the valve onto fine Pledgets (Figures 8 and 9). Use of 4-0 Prolene suture is recommended to allow the complex horizontal mattress sutures to be pulled tightly at the ends.

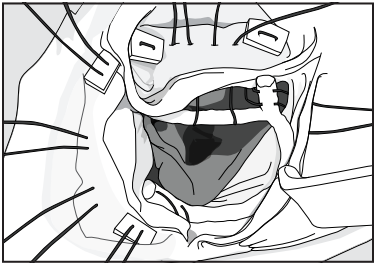


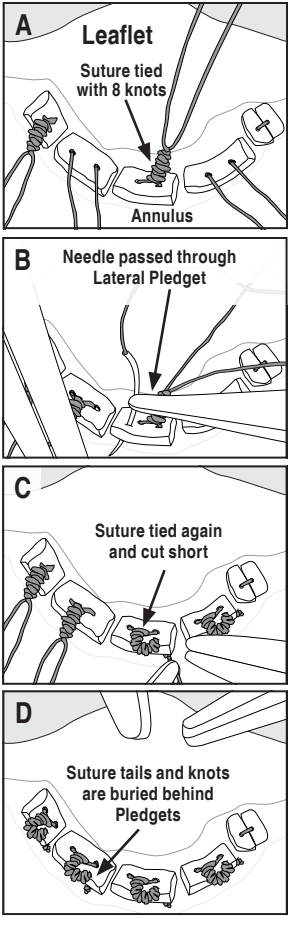
Figure 9. Suturing of the leaflet sections with the device below the valve leaflets.

Suture Management

After all nine sutures are placed, each is tied firmly over the Pledget with 8 knots, ensuring that the leaflet posts are buried back into the subcommissural regions and the Device fabric is kept below leaflet tissues. The knots should be thoroughly tightened to prevent the sutures from coming untied.

Long annular suture tails in the coronary sinus can cause leaflet injuries. As a final step of annular suturing, one or both needles from the tied annular suture should be passed downward through the

Figure 10. Management of Annular Sutures



center of the lateral aspect of the Pledget, and the suture should be again tied down to the Pledget with 6 more knots. This maneuver directs the suture tails down and away from the leaflets. Figure 10 illustrates the procedure for proper management of the suture tails.

Panel A: The 4-0 Prolene horizontal mattress sutures that hold the Device firmly up under the annulus emerge above the annulus and are supported by fine polyester Pledgets. The sutures are tied tightly with 8 knots over the Pledgets (arrow). These suture lines are reducing annular size significantly, and therefore, can be associated with significant tension. Thus, extra care should be taken with tying good 8-throw knots that will not come untied.

Panel B: Each suture is passed down through the lateral Pledget (arrow) and tied again with 6 knots. This step positions the final knot and suture tails laterally and under the Pledget.

Panel C: The suture tails are cut very short beneath the Pledgets (arrow).

Panel D: The double knot prevents each suture from coming untied, and with the second knot beneath the Pledget, the suture tails are directed laterally and down into the annulus, preventing contact with the leaflets.

At the end of the Device implant procedure, all annular sutures should be carefully inspected by the surgeon, and if any question exists about the position of a given suture tail, the knot tower should again be sutured down and away from the leaflet with a fine 6-0 Prolene suture.

Assessment of Valve Repair

After completing the Device implantation, the valve should be inspected to ensure that the leaflets are vertical with good effective

height and surface of coaptation. The leaflets should meet in the midline with no evidence of central gaps or leaflet prolapse.

Effective height and leaflet length may be assessed using the Gage Sphere provided in the HAART 301 Instrument Set (Figure 11). The Gage Sphere has two different vertical scales marked on the surface. One scale originates at the apex of the Sphere and is intended for estimating the vertical effective height of the valve leaflet from the leaflet base to the free-edge margin (Figure 12). For a successful repair, leaflet effective height should be approximately 8 to 10 mm. Thus, as the Gage Sphere is gently pressed down into the leaflet-sinus complex, a successful repair will be associated with the leaflet free-edge being at the level of the Gage Sphere equator. The second scale may be used to assess leaflet geometric lengths, when desired, for further evaluation of leaflet size and symmetry after the overall valve repair.

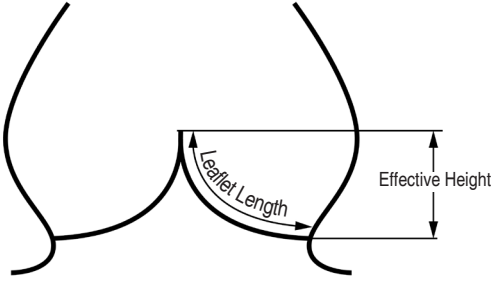


Figure 11. Diagram of leaflet length and effective height

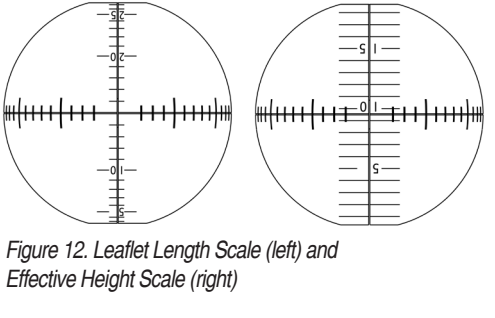


Figure 12. Leaflet Length Scale (left) and Effective Height Scale (right)

Any necessary leaflet reconstruction is performed after annuloplasty Device insertion. When significant leaflet prolapse is encountered, leaflet free-edge plication or other techniques should be performed, at the surgeon's discretion, to achieve an effective height of 8 to 10mm. Similarly, structural leaflet defects should be corrected using pericardial reconstruction or other methods consistent with the surgeon's training and preferences.

10.4. Sterilization

The HAART 300 Aortic Annuloplasty Device is provided sterile on the Holder and must not be resterilized. Devices that have been damaged or contaminated should not be used. Pledgets are provided sterile and must not be resterilized. Pledgets that have been damaged or contaminated from patient contact should not be used.

11. Clinical Results

A prospective, multi-centered, open-label, clinical investigation was conducted to provide evidence of safety and efficacy of aortic valve annuloplasty using the HAART 300 Aortic Annuloplasty Device during surgical valve repair for aortic insufficiency (AI) with or without root or ascending aortic aneurism. Clinical evaluations were scheduled at baseline and following the procedure at discharge/14 days, 3 months, 6 months, 1 year and 2 years. The 6-month evaluation was used for the primary safety and efficacy analyses. Subjects served as their own controls in pretreatment vs posttreatment comparisons. Adverse event information was collected at the time of occurrence, during follow-up visits, or upon notification of the site. Hemodynamic performance of the valve was assessed with echocardiography by an independent echocardiography core laboratory. Heart failure was classified with the NYHA Functional Capacity classification system.

The primary safety measure was survival, using an all-cause mortality endpoint, through the 6-month time point. Survival through the 2-year extended follow-up was examined as a secondary measure. Adverse events were categorized and summarized and two secondary safety measures (implant success through discharge/14 days and freedom from clinical cardiovascular events through 6 months) were defined based on the presence or absence of particular adverse events.

The primary efficacy measure was change in AI and aortic valve function from preoperative baseline to the 6-month study endpoint based on aortic valvular regurgitation (AI grade) assessed by transthoracic echocardiography (TTE). Change in AI grade from baseline to 2 years was examined as a secondary measure. Change in the NYHA Functional Capacity classification from preoperative baseline to the 6-month study endpoint and to 2 years of follow-up were evaluated as secondary efficacy outcomes.

Sixty-five (65) subjects were implanted with the HAART 300 Aortic Annuloplasty Device between February 2, 2012 and November 8, 2013 at nine (9) European heart centers. Mean age was 62.7 years (standard deviation (SD) 12.9 years, range 28 to 83 years) and 69.2% of subjects were male. Twenty-

five (25, 38.5%) subjects had isolated AI, eighteen (18, 27.7%) had AI and associated ascending aortic aneurism, and twenty-two (22, 33.8%) had AI and associated aortic root aneurism. Expected follow-up was 98.3% at the 6-month primary evaluation time point and 100% at the final 2-year evaluation.

Safety Results

One subject death, unrelated to the device, occurred prior to the 6-month evaluation resulting in survival of 98.4% (89.3%-99.8%, 95% confidence interval) using all-cause mortality as the endpoint. Two other deaths unrelated to the device occurred after the subjects' study participation had ended but prior to the 2-year evaluation resulting in a 2-year end of study survival of 94.7% (84.4%-98.3%, 95% confidence interval). Implant procedure success evaluated through discharge/14 days by the absence of specific adverse events was 96.9% (89.3%-99.6%, 95% confidence interval). Cardiovascular event-free survival was 92.1% (85.2%-99.0%, 95% confidence interval) at 6 months and was 82.8% (69.0%-96.5% confidence interval) at the 2-year end of study.

There were 249 adverse events reported from 57 subjects (Table 2 on page 18 and Table 3 on page 19). Fifty serious adverse events were reported from 31 subjects. Four adverse events in 4 subjects were considered serious adverse device effects and all were related to surgical technique errors. There were no unanticipated adverse events or device effects. Most adverse events occurred in the interval between the procedure and discharge (Table 4 on page 21).

Efficacy Results

Statistical comparisons of baseline condition with 6-month and 2-year condition were conducted using Wilcoxon Signed-Rank tests and paired t-tests for primary and secondary efficacy endpoints. Missing values were imputed using a modified last observation carry forward methodology that permanently penalized reoperation. Distributions and changes for AI Grade and NYHA Functional Class are presented in Table 5 on page 23 and Table 6 on page 24, respectively.

Table 2: Summary of Adverse Event Types

	Implanted N=65		
	Events	**NSE[1]**	**%[2]**
Adverse Events	249	57	87.7
Serious Adverse Events	50	31	47.7
Adverse Device Effect	4	4	3.1
Serious Adverse Device Effect	4	4	1.5
Unanticipated Adverse Device Effect	0	0	0.0
Deaths	3	3	4.6

[1] NSE = Number of Subjects with Event.

[2] % = NSE divided by Total subjects (65).

Table 3: All Adverse Events by Category

Adverse Event Category *Subcategory*[1]	Implanted N=65		
	Events	NSE[2]	%[3]
Neurologic event (including TIA, stroke and psychomotor deficit)	12	11	16.9
Stroke	1	1	1.5
Angina	2	2	3.1
Bleeding event	9	8	12.3
Reoperation for bleeding	1	1	1.5
CHF	5	5	7.7
Conduction defects	1	1	1.5
Infection (including Endocarditis)	20	18	27.8
Endocarditis	1	1	1.5
Aortic insufficiency	14	13	20.0
Syncope	6	5	7.7
Arrhythmia	38	31	47.7
Hematoma	3	3	4.6
Hypertension	1	1	1.5
Pericardial effusion	17	17	26.2
Hemorrhagic/Vascular event	3	3	4.6
Allergic reaction to contrast or medication	1	1	1.5
Fever	1	1	1.5
Renal insufficiency	1	1	1.5

Table 3: All Adverse Events by Category (cont)

Adverse Event Category *Subcategory*[1]	Implanted N=65		
	Events	NSE[2]	%[3]
Renal failure	1	1	1.5
Pleural effusion	23	23	35.4
Abnormal lab values	21	18	27.8
Respiratory event	32	28	43.1
Gastrointestinal event	4	3	4.6
Musculoskeletal	25	18	27.8
Wound healing problem	5	4	6.2
Ophthalmic disorder	1	1	1.5
Psychological problem	3	3	4.6
Total	249	57	87.7

[1] Subcategory numbers (italicized) are included in the Category totals.
[2] NSE = Number of Subjects with Event.
[3] % = NSE divided by Total subjects (65).

Table 4: Time Course of Adverse Events

Adverse Event Category Subcategory[1]	Implanted N=65						
	Onset/Discovery Interval						
	Proc	Proc-Disch	Disch-3 Mo	3 Mo-6 Mo	6 Mo-1 Yr	1 Yr-1.5 Yr	1.5 Yr-2 Yr
Neurologic event (including TIA, stroke and psychomotor deficit)	---	5	1	---	1	2	3
Stroke						1	
Angina	---	---	---	---	---	1	1
Bleeding event	1	5	---	---	1	1	1
Reoperation for bleeding		1					
CHF	---	---	1	2	1	1	---
Conduction defects	---	---	1	---	---	---	---
Infection (including Endocarditis)	---	11	3	2	2	2	---
Endocarditis			1				
Aortic insufficiency	---	3	---	1	4	2	4
Syncope	---	---	2	2	---	1	1
Arrhythmia	1	24	6	2	1	1	3
Hematoma	---	---	2	---	---	---	1
Hypertension	---	---	---	---	---	1	---
Pericardial effusion	---	10	6	1	---	---	---
Hemorrhagic/Vascular event	---	---	2	---	---	---	1
Allergic reaction to contrast or medication	---	---	---	---	---	---	1

Table 4: Time Course of Adverse Events (cont)

Adverse Event Category Subcategory[1]	Implanted N=65						
	Onset/Discovery Interval						
	Proc	Proc-Disch	Disch-3 Mo	3 Mo-6 Mo	6 Mo-1 Yr	1 Yr-1.5 Yr	1.5 Yr-2 Yr
Fever	---	---	---	1	---	---	---
Renal insufficiency	---	1	---	---	---	---	---
Renal failure	---	1	---	---	---	---	---
Pleural effusion	---	18	5	---	---	---	---
Abnormal lab values	---	10	7	3	---	1	---
Respiratory event	---	16	8	3	2	3	---
Gastrointestinal event	---	2	1	---	---	1	---
Musculoskeletal	---	---	5	3	9	5	3
Wound healing problem	---	---	---	2	2	---	1
Ophthalmic disorder	---	---	---	---	1	---	---
Psychological problem	---	1	1	---	1	---	---
Total	2	107	51	22	25	22	20

[1] Subcategory numbers (italicized) are included in the Category totals.

Table 5: Change in AI grade at the 6-month primary analysis time point and at 2-year end of study using imputed data.

	AI Grade	Implanted N=65					
		Baseline		6 Months		2 Years	
		n	%	n	%	n	%
0	None/Trace	---	---	15	23.1	6	9.2
1+	Mild	3	4.6	32	49.2	37	56.9
2+	Moderate	16	24.6	11	16.9	14	21.5
3+	Moderate-to-Severe	31	47.7	7	10.8	8	12.3
4+	Severe	15	23.1	---	---	---	---
	Total	65[1]	100	65[2]	100	65[3]	100
	Median	3.0		1.0		1.0	
	Mean (SD)	2.9 (0.8)		1.2 (0.9)		1.4 (0.8)	
	Change from Baseline						
	Median	---		-2.0		-2.0	
	Mean (SD)	---		-1.7 (1.0)		-1.5 (1.0)	
				p<0.0001[4]		p<0.0001[4]	

[1] *6 imputed values*
[2] *9 imputed values*
[3] *17 imputed values*
[4] *Wilcoxon Signed-Rank Test on paired differences (Follow-up – Baseline)*

Table 6: Change in NYHA Functional Capacity Classification at the 6-month primary analysis time point and at 2-year end of study using imputed data.

NYHA Class	Implanted N=65					
	Baseline		6 Months		2 Years	
	n	%	n	%	n	%
I	11	16.9	44	67.7	39	60.0
II	35	53.8	21	32.3	25	38.5
III	19	29.2	---	---	1	1.5
IV	---	---	---	---	---	---
Total	65[1]	100	65[2]	100	65[3]	100
Median	2.0		1.0		1.0	
Mean (SD)	2.1 (0.7)		1.3 (0.5)		1.4 (0.5)	
Change from Baseline						
Median	---		-1.0		-1.0	
Mean (SD)	---		-0.8 (0.8)		-0.7 (0.7)	
			p<0.0001[4]		p<0.0001[4]	

[1] 0 imputed values
[2] 8 imputed values
[3] 16 imputed values
[4] Wilcoxon Signed-Rank Test on paired differences (Follow-up – Baseline)

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Patents

Patents: US8,163,011; US8,425,594; US9,161,835; CA 2,665,626; JP5881653; JP5877205; other applications pending.

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Science & Engineering

BioStable Science & Engineering, Inc.
2621 Ridgepoint Drive
Suite 100
Austin, TX 78754 USA