On-X®

Prosthetic Heart Valve

CE 0459

Instructions for Use

English
Including Aortic Valve INR 1.5–2.0 Update

On-X® Aortic Heart Valve with Standard Sewing Ring - REF ONXA
On-X® Mitral Heart Valve with Standard Sewing Ring - REF ONXM
On-X® Aortic Heart Valve with Conform-X® Sewing Ring - REF ONXAC
On-X® Mitral Heart Valve with Conform-X® Sewing Ring - REF ONXMC
On-X® Aortic Heart Valve with Anatomic Sewing Ring - REF ONXAN
On-X® Aortic Heart Valve and Extended Holder - REF ONXAE
On-X® Aortic Heart Valve with Conform-X® Sewing Ring and Extended Holder - REF ONXACE
On-X® Aortic Heart Valve with Anatomic Sewing Ring and Extended Holder - REF ONXANE

On-X life technologies, inc.™ | designed for life

ON-X® PROSTHETIC HEART VALVE

INSTRUCTIONS FOR USE

On-X® Aortic Heart Valve with Standard Sewing Ring

On-X® Mitral Heart Valve with Standard Sewing Ring

On-X® Aortic Heart Valve with Conform-X® Sewing Ring

On-X® Mitral Heart Valve with Conform-X® Sewing Ring

On-X® Aortic Heart Valve with Anatomic Sewing Ring

On-X® Aortic Heart Valve and Extended Holder

On-X® Aortic Heart Valve with Conform-X® Sewing Ring and Extended Holder

On-X® Aortic Heart Valve with Anatomic Sewing Ring and Extended Holder

The current revision of all On-X LTI IFUs may be found at:
http://www.onxlti.com/ifu

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INSTRUCTION FOR USE

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician.

1. DEVICE DESCRIPTION

The On-X® Prosthetic Heart Valve (Figure 1) is a bileaflet mechanical heart valve, which consists of an orifice housing and two leaflets. The orifice inflow area has a flared inlet designed to reduce flow turbulence, and the outflow rim consists of leaflet guards designed to protect the leaflets while in the closed position. The leaflets rotate around tabs located within the inner circumference of the orifice ring. In the closed position, each leaflet forms a nominal angle of 40° relative to the plane of the orifice. In the open position, the plane of each leaflet forms a nominal angle of 90° relative to the plane of the orifice. The leaflets have a travel arc of 50° to the closed position.

The orifice is composed of graphite substrate coated with On-X® Carbon, a pure unalloyed form of pyrolytic carbon. The leaflets consist of On-X® Carbon deposited on a graphite substrate, which is impregnated with 10 weight% tungsten to provide radiopacity.

The sewing ring is constructed of polytetrafluoroethylene (PTFE) fabric mounted on the orifice using titanium retaining rings and 5-0 suture material. This form of sewing ring attachment to the orifice allows for rotation of the sewing ring in situ during implantation. Orientation reference marks are provided on the sewing ring for valve orientation.

The On-X® Prosthetic Heart Valve is available in 3 aortic and 2 mitral sewing ring configurations. All aortic configurations are available in sizes 19, 21, 23, 25, and 27/29 mm. The standard mitral sewing ring is available in sizes 23, 25, 27/29 and 31/33, while the mitral Conform-X® sewing ring is available in size 25/33 only.

Aortic valves, size 19 mm through 25 mm, are designed for intrasupra-annular sewing ring position, while the valve size 27/29 mm is designed for intra-annular sewing ring position. All mitral valve sizes are designed for the supra-annular sewing ring position.

2. INDICATIONS FOR USE

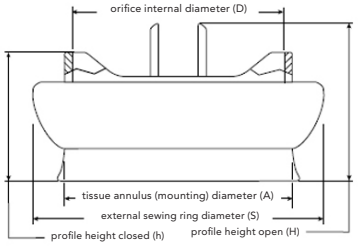
The On-X Prosthetic Heart Valve is indicated for the replacement of diseased, damaged, or malfunctioning native or prosthetic heart valves in the aortic and mitral positions.

3. CONTRAINDICATIONS

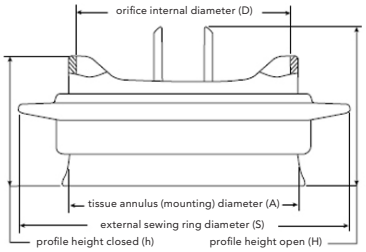
The On-X Prosthetic Heart Valve is contraindicated for patients unable to tolerate anticoagulation therapy.

Figure 1: Aortic and Mitral Profiles
(See Table 1 for corresponding dimensions)

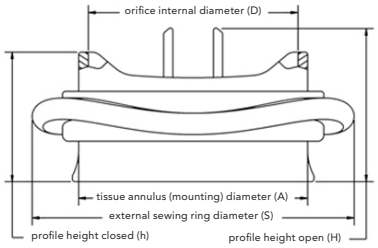
(A) AORTIC (ONXA, ONXAE)



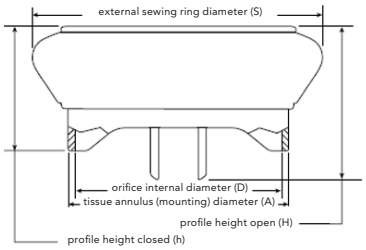
(B) AORTIC CONFORM-X® (ONXAC, ONXACE)



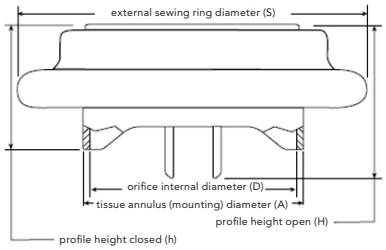
(C) AORTIC ANATOMIC (ONXAN, ONXANE)



(D) MITRAL (ONXM)



(E) MITRAL CONFORM-X® (ONXMC)



4. WARNINGS AND PRECAUTIONS

4.1 Warnings

FOR SINGLE USE ONLY.

DO NOT use the On-X Prosthetic Heart Valve if:

- **the prosthesis has been dropped, damaged, or mishandled in any way;**
- **the expiration date has elapsed;**
- **the tamper evident seal is broken;**
- **the serial number tag does not match the serial number on the container label.**

DO NOT pass a catheter, surgical instrument, or transvenous pacing lead through the prosthesis as this may cause valvular insufficiency, leaflet damage, leaflet dislodgment, and/or catheter/instrument/lead entrapment.

DO NOT resterilize the On-X Prosthetic Heart Valve.

4.2 Precautions

Handle the prosthesis with only On-X Life Technologies, Inc. (On-XLTI) On-X Prosthetic Heart Valve Instruments. Only On-XLTI On-X Prosthetic Heart Valve sizers should be used during the selection of the valve size; other sizers may result in improper valve selection.

Avoid contacting the carbon surfaces of the valve with gloved fingers or any metallic or abrasive instruments as they may cause damage to the valve surface not seen with the unaided eye that may lead to accelerated valve structural dysfunction, leaflet escape, or serve as a nidus for thrombus formation.

Avoid damaging the prosthesis through the application of excessive force to the valve orifice or leaflets.

5. POTENTIAL ADVERSE EVENTS

Adverse events potentially associated with the use of prosthetic heart valves (in alphabetical order) include, but are not limited to:

- angina
- cardiac arrhythmia
- endocarditis
- heart failure
- hemolysis
- hemolytic anemia
- hemorrhage
- myocardial infarction
- prosthesis leaflet entrapment (impingement)
- prosthesis nonstructural dysfunction
- prosthesis pannus
- prosthesis perivalvular leak
- prosthesis regurgitation
- prosthesis structural dysfunction
- prosthesis thrombosis
- stroke
- thromboembolism

It is possible that these complications could lead to:

- reoperation
- explantation
- permanent disability
- death

Mechanical prosthetic heart valves produce audible sounds as a normal function of their operation. In some patients, these sounds may be objectionable.

Risk of Re-Use Statement

In accordance with the EU Medical Device Directive, 93/42/EEC, Annex I, Section 13.6h, the device manufacturer must provide information on risks associated with re-use of a single use device. Therefore, the following statement is provided:

The implanted On-X prosthetic heart valve is designed for single use only. Do not re-use the device. In addition to the risks listed in Section 5, 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.

6. INDIVIDUALIZATION OF TREATMENT

Anticoagulation – Adequate anticoagulant or anticoagulant/antiplatelet therapy should be administered. Selection of an anticoagulant or anticoagulant/antiplatelet regimen is based on the particular needs of the patient and the clinical situation.

Patients with an On-X valve in the aortic valve position should be maintained on long-term warfarin anticoagulation which should achieve an International Normalized Ratio (INR) of 2.0 – 3.0 for the first 3 months after valve replacement surgery, after which the INR should be reduced to 1.5 – 2.0. Patients with an On-X valve in the mitral valve position or in multiple valve positions should be maintained at an INR of 2.5 – 3.5 continuously after valve replacement surgery. The addition of a daily aspirin at a dose from 75 to 100 mg is also recommended for patients with an On-X valve in any valve position, unless there is a contraindication to the use of aspirin.

Studies show that stable control of INR provides better clinical results and that patients should be regularly monitored. The use of home monitoring to accomplish stable INR control is recommended.

6.1 Specific Patient Population

The safety and effectiveness of the On-X Prosthetic Heart Valve has not been established for the following specific populations because it has not been studied in these populations:

- patients who are pregnant;
- nursing mothers;
- patients with chronic endocarditis;
- patients requiring pulmonary or tricuspid replacement.

7. PATIENT COUNSELING

- Prophylactic antibiotic treatment must be provided to all patients with prosthetic valves undergoing dental procedures or other potentially bacteremic procedures.
- Patients require anticoagulation or anticoagulant/antiplatelet therapy.
- Patients should be encouraged to complete the Patient ID card provided with the valve and carry it with them at all times.

8. HOW SUPPLIED

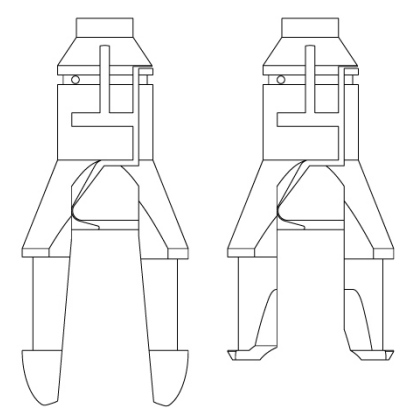
8.1 Available Models and Sizes

The On-X Prosthetic Heart Valve is available in 3 aortic and 2 mitral sewing ring configurations. All aortic configurations are available in sizes 19, 21, 23, 25, and 27/29 mm. The standard mitral sewing ring is available in sizes 23, 25, 27/29 and 31/33 mm, while the Mitral Conform-X sewing ring is available in size 25/33 only.

Aortic valves, size 19 mm through 25 mm, are designed for intrasupra-annular sewing ring position, while the valve size 27/29 mm is designed for intra-annular sewing ring position. All mitral valve sizes are designed for the supra-annular sewing ring position.

Aortic valves are available with either standard or extended valve holders (Figure 2).

Figure 2: Standard or Extended Aortic Valve Holders



The dimensional and model specifications for all available sizes of the On-X Prosthetic Heart Valve are shown in Table 1 and Figure 1. The symbol SZ mm on the box, container labels, and implant registration card refers to the tissue annulus diameter of the valve in millimeters.

8.2 Packaging

The On-X Prosthetic Heart Valve is provided sterile, mounted on a holder, in a double-sealed plastic container. The package consists of the following items:

- Outer box
- Patient record card
- Plastic valve container
- Implant registration card
- Plastic valve holder
- Valve serial number tag
- Instructions for use (booklet or Website Reference Card)

Table 1: On-X Valve Specifications (millimeters)

Model Designator			Tissue Annulus (mounting) Diameter	Orifice Internal Diameter	External Sewing Ring Diameter	Profile Height (closed)	Profile Height (open)	Internal Orifice Area
Extended Holder	Standard Holder	Size/Type	(A)	(D)	(S)	(h)	(H)	(mm^2)
ONXAE-19*	ONXA-19	19 Aortic	19	17.4	23	10.8	13.3	228
ONXAE-21*	ONXA-21	21 Aortic	21	19.4	26	11.9	14.7	284
ONXAE-23*	ONXA-23	23 Aortic	23	21.4	29	13.1	16.1	344
ONXAE-25*	ONXA-25	25 Aortic	25	23.4	32	14.2	17.8	411
ONXAE-27/29*	ONXA-27/29	27/29 Aortic	27-29	23.4	34	14.2	17.8	411
ONXACE-19*	ONXAC-19*	19 Aortic Conform-X	19	17.4	27	10.8	13.3	228
ONXACE-21*	ONXAC-21*	21 Aortic Conform-X	21	19.4	30	11.9	14.7	284
ONXACE-23*	ONXAC-23*	23 Aortic Conform-X	23	21.4	33	13.1	16.1	344
ONXACE-25*	ONXAC-25*	25 Aortic Conform-X	25	23.4	34	14.2	17.8	411
ONXACE-27/29*	ONXAC-27/29*	27/29 Aortic Conform-X	27-29	23.4	36	14.2	17.8	411
ONXANE-19*	ONXAN-19*	19 Aortic Anatomic	19	17.4	27	10.8	13.3	228
ONXANE-21*	ONXAN-21*	21 Aortic Anatomic	21	19.4	30	11.9	14.7	284
ONXANE-23*	ONXAN-23*	23 Aortic Anatomic	23	21.4	33	13.1	16.1	344
ONXANE-25*	ONXAN-25*	25 Aortic Anatomic	25	23.4	34	14.2	17.8	411
ONXANE-27/29*	ONXAN-27/29*	27/29 Aortic Anatomic	27/29	23.4	36	14.2	17.8	411
	ONXM-23**	23 Mitral	23	21.4	31	13.1	16.1	344
	ONXM-25	25 Mitral	25	23.4	33	14.2	17.8	411
	ONXM-27/29	27/29 Mitral	27-29	23.4	34	14.2	17.8	411
	ONXM-31/33	31/33 Mitral	31-33	23.4	36	14.2	17.8	411
	ONXMC-25/33	Mitral Conform-X	25-33	23.4	39	14.2	17.8	411

* Not available in all markets ** Not available in the USA Refer to Figure 1 for location of measured dimensions. Values given are nominal within the tolerance band.

Instruments for implantation of the On-X Prosthetic Heart Valve are supplied separately, **NON-STERILE**, and must be cleaned and sterilized prior to use as outlined in section 8.5.

8.3 Storage

The sterility expiration date of the On-X Prosthetic Heart Valve is recorded on the outer package label. Appropriate inventory control should be maintained so that prostheses with earlier expiration dates are preferentially implanted and expiration is avoided. To protect the valve, it should be stored in its outer box until used. The storage environment should be clean, cool, and dry.

8.4 Accessories

The On-X Prosthetic Heart Valve is designed to be used only with On-XLTI On-X instruments. The instruments, supplied separately, are provided as a set, which includes sizers, rotators, an instrument handle, and a leaflet probe. The instruments are reusable.

CAUTION: Sizers and instrument handles have metallic regions that are bendable. Repeated bending of these metallic regions can lead to fatigue and fracture. To avoid instrument fracture during use, the stem should be inspected for surface cracks before and after each time it is bent. If metal fatigue surface cracks are present, the sizer and/or instrument handle should be discarded and replaced. Contact On-XLTI Customer Service to order replacements.

CAUTION: Leaflet probes and rotators are flexible, but are not intended to be bent to a permanently deformed state.

Sizer

The sizer is used to gauge the resulting tissue annulus diameter after the annulus is prepared for implant. The sizer has a bendable stem on each end. The sizers are cylindrical for size 19 mm through 25 mm valves and conical for size 27/29 mm and 31/33 mm valves (Figure 3a and 3b). To facilitate sizer selection, refer to Table 2.

Replica Sizers

Aortic replica sizers are provided for all aortic valve sizes (Figure 3a). They model the On-X standard aortic valve profile. They are used after sizing for standard, Conform-X, and Anatomic sewing ring configurations to assure fit of the aortic valve without obstruction of the coronary arteries. The size 19 through 25 aortic replica sizers shape is intended to model intrasupra-annular positioning. The size 27/29 aortic replica sizer is intended to model intra-annular positioning.

Figure 3a: Sizer and Replica Sizer

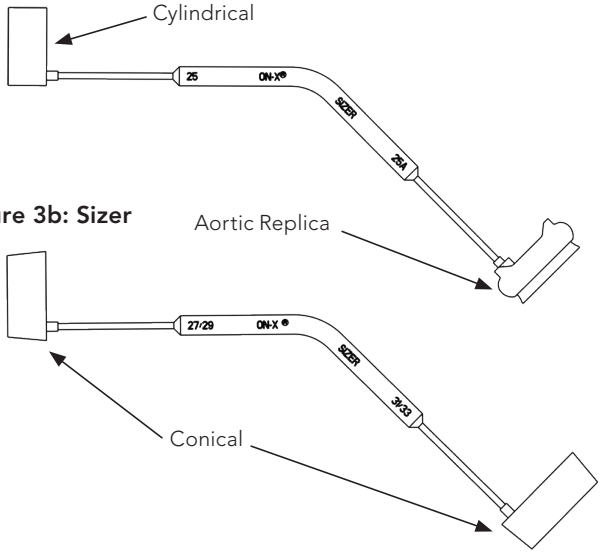


Figure 3b: Sizer

Table 2: Sizer Selections - Regardless of Aortic Holder Type

		Sizer Choice		Position of sewing ring
Size	**Valve Type**	**Sizer Type**	**Use Replicate Sizer**	
19	Aortic	Cylindrical	YES	Intrasupra-annular
21	Aortic	Cylindrical	YES	Intrasupra-annular
23	Aortic	Cylindrical	YES	Intrasupra-annular
25	Aortic	Cylindrical	YES	Intrasupra-annular
27/29	Aortic	Conical	YES	Intra-annular
19*	Aortic Conform-X	Cylindrical	YES	Intrasupra-annular
21*	Aortic Conform-X	Cylindrical	YES	Intrasupra-annular
23*	Aortic Conform-X	Cylindrical	YES	Intrasupra-annular
25*	Aortic Conform-X	Cylindrical	YES	Intrasupra-annular
27/29*	Aortic Conform-X	Conical	YES	Intra-annular
19*	Aortic Anatomic	Cylindrical	YES	Intrasupra-annular
21*	Aortic Anatomic	Cylindrical	YES	Intrasupra-annular
23*	Aortic Anatomic	Cylindrical	YES	Intrasupra-annular
25*	Aortic Anatomic	Cylindrical	YES	Intrasupra-annular
27/29*	Aortic Anatomic	Conical	YES	Intra-annular
23*	Mitral	Cylindrical	NO	Supra-annular
25	Mitral	Cylindrical	NO	Supra-annular
27/29	Mitral	Conical	NO	Supra-annular
31/33	Mitral	Conical	NO	Supra-annular
25/33	Mitral Conform-X	Cylindrical or Conical	NO	Supra-annular

* Not available in all markets

Instrument Handle
The instrument handle (Figure 4) facilitates holding the valve or the rotator during surgery. The instrument handle is comprised of a grip, a bendable stem, and a tip.

Rotator
The valve rotator (Figure 5) is used for reorienting an in situ valve and may be used to verify leaflet mobility. The rotator consists of a plastic head with a centrally located leaflet probe and an attached handle.

The rotator may be used with or without the instrument handle attached. To attach the rotator to the instrument handle, insert the instrument handle tip directly into the slot on the end of the rotator handle. The rotator snaps into place after the application of a light insertion force.

Leaflet Probe
The leaflet probe (Figure 6) is a flexible rod with tapered ends. The leaflet probe may be used to gently move the leaflets to verify that they open and close freely.

Figure 4: Instrument Handle

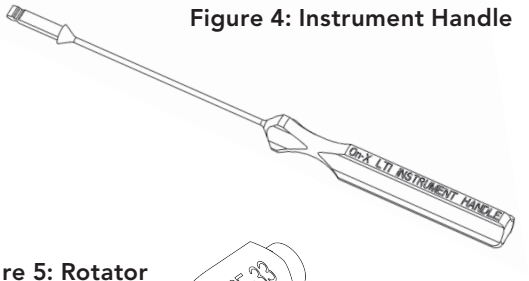
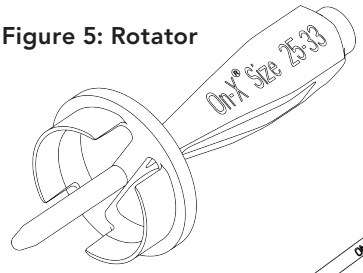


Figure 5: Rotator



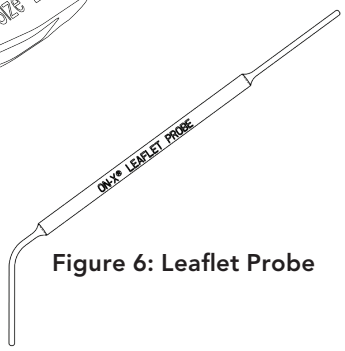


Figure 6: Leaflet Probe

8.5 Accessory Cleaning and Sterilization

Instruments for implantation of the On-X Prosthetic Heart Valve are supplied separately, NON-STERILE, and must be cleaned and sterilized prior to use. Standard hospital surgical instrument cleaning procedures must be used. Note: the metallic instruments are made of titanium. The plastic instruments are made of polyphenylsulfone. Materials used in these instruments can withstand standard steam and flash steam sterilization.

WARNING: These instruments are NOT provided sterile. They must be properly cleaned and sterilized prior to each use.

WARNING: DO NOT sterilize instruments with any method of sterilization other than steam. Damage to some items could result from use of other sterilization methods.

WARNING: The rotator must be removed from the handle after use and prior to cleaning. A force greater than the insertion force is required to remove the rotator from the instrument handle.

9. DIRECTIONS FOR USE

WARNING: DO NOT use the On-X Prosthetic Heart Valve if:

- **the prosthesis has been dropped, damaged, or mishandled in any way;**
- **the expiration date has elapsed;**
- **the tamper evident seal is broken;**
- **the serial number tag does not match the serial number on the container label.**

9.1 Physician Training

No special training is required to implant the On-X Prosthetic Heart Valve. The techniques for implanting this prosthesis are similar to those used for any mechanical heart valve prosthesis.

9.2 Sterilization and Resterilization

The On-X Prosthetic Heart Valve is provided sterile. If the sterility expiration date has passed or if upon removal from the outer box, the valve container is damaged or the sterility barrier is broken, do not use the valve. Call On-XLTI Customer Service and arrange to return the valve and receive a replacement.

WARNING: If during surgery the valve is removed from its container but not used, it must not be repackaged or resterilized. In this situation, the valve must be returned to On-XLTI. Call Customer Service for information before any return is made.

WARNING: Do not resterilize the On-X Prosthetic Heart Valve.

9.3 Handling and Preparation Instructions

CAUTION: Handle the prosthesis with only On-XLTI On-X Prosthetic Heart Valve Instruments. Only On-XLTI On-X Prosthetic Heart Valve sizers should be used during the selection of the valve size; other sizers may result in improper valve selection.

CAUTION: Avoid contacting the carbon surfaces of the valve with gloved fingers or any metallic or abrasive instruments as they may cause damage to the valve surface not seen with the unaided eye that may lead to accelerated valve structural dysfunction, leaflet escape, or serve as a nidus for thrombus formation.

CAUTION: Avoid damaging the prosthesis through the application of excessive force to the valve orifice or leaflets.

Circulating Nurse

1. Check the expiration date on the outer box.

   WARNING: DO NOT use the On-X Prosthetic Heart Valve if the expiration date has elapsed. If a valve is unused, its plastic container is undamaged, and the sterility expiration date has passed, the valve should be returned to On-XLTI.

2. Remove the valve container and package inserts from the outer box. Inspect the container for damage.

   WARNING: DO NOT use the On-X Prosthetic Heart Valve if the prosthesis has been dropped, damaged, or mishandled in any way. If any damage is found, use another valve and arrange for a return through On-XLTI Customer Service.

3. Fill out the implant registration card as completely as local law allows and return to On-XLTI as soon as possible. This allows the patient to be entered into the tracking database, which could be important for future notices regarding the valve. Give the patient record card to the patient or place it in the patient's records.

4. Open the outer container

   Twist-off outer lid package design: Rotate the lid counter-clockwise until it stops, then lift the lid off off of the container (Figure 7a).

   Peel-off Tyvek® lid package design: Grasp the peel tab corner of the lid and pull back towards the center of the container (Figure 8a). Continue peeling until the lid is completely removed.

5. The scrub nurse may remove the sterile inner container from the outer container by gently lifting the pull tab attached to the top of the inner container (Figure 7b or Figure 8b). The inner container is then placed onto the instrument tray. Alternately, the inner container can be placed on the sterile field by gently inverting the outer container slightly above the sterile field (Figure 7c or Figure 8c) and allowing the inner container to slip out onto the sterile field.

Scrub Nurse/Surgeon:

1. Check the tamper evident seal of the inner container.

   WARNING: DO NOT use the On-X Prosthetic Heart Valve if the tamper evident seal has been broken. If the tamper evident seal has been broken, use another valve and arrange for return through On-XLTI Customer Service.

2. Open the inner container by gently twisting the lid to break the tamper-proof seals (Figure 9) and then lifting the lid off the base.

Twist-off Lid Design

Figure 7a. Twist-off outer lid

Figure 7b. Remove by pull tab...

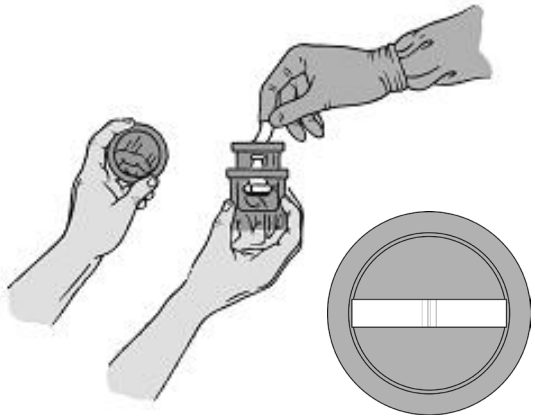
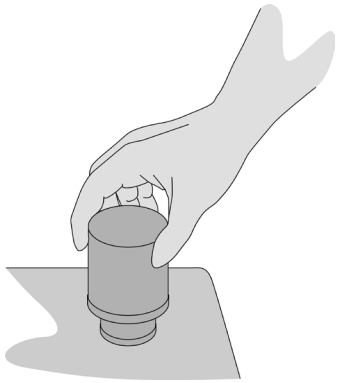


Figure 7c. ...or invert on sterile field



Peel-off Lid Design

Figure 8a. Peel-off outer lid

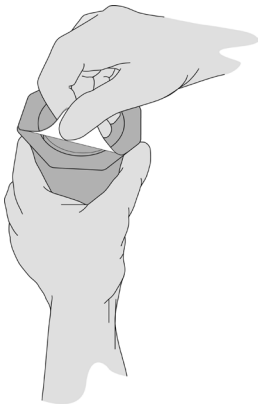


Figure 8b. Remove by pull tab...

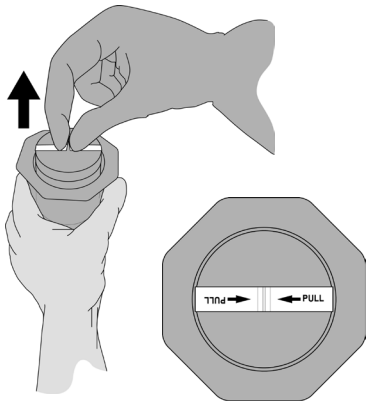
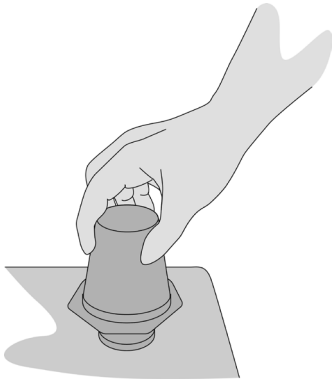


Figure 8c. ...or invert on sterile field



3. Press the instrument handle tip into the slot on the valve holder until it snaps firmly into position (Figure 10). Gently lift the valve out of the container and slide the holder plate off the holder.

   Carefully grasp the sewing ring with a gloved hand using a light grip and gently turn the instrument handle in either direction. The valve should easily rotate within the sewing ring. Stop rotation testing with an orientation mark aligned with the pivot axis.

   WARNING: DO NOT use the On-X Prosthetic Heart Valve if the valve does not rotate easily. Use another valve and arrange for return through On-XLTI Customer Service.

Figure 9. Opening the inner container

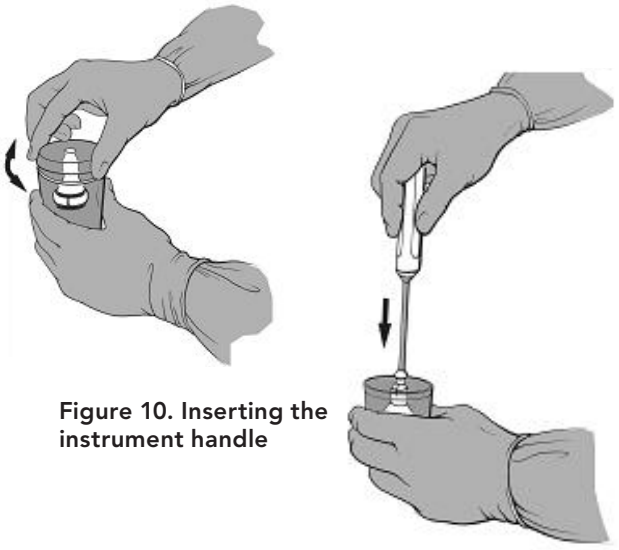


Figure 10. Inserting the instrument handle

4. Check the serial number tag against the label on the outer container.

   WARNING: DO NOT use the On-X Prosthetic Heart Valve if the serial number tag does not match the container label. Use another valve and arrange for a return through On-XLTI Customer Service.

5. Remove the serial number tag by cutting the suture that holds it on the valve. If desired, the tag can be used to check for sterility by standard culture techniques immediately after it is removed.

6. The valve is now ready for implantation. To ease positioning during implantation, the instrument handle stem can be bent by grasping the ends of the handle and the stem, then bending. Avoid grasping the valve.

   WARNING: DO NOT use the valve for leverage in bending the instrument handle. This could damage the valve and lead to mechanical failure.

9.4 Device Implantation

WARNING: All accessory instruments must be cleaned and sterilized prior to use according to the instrument instructions.

Sizing

Use only On-X Prosthetic Heart Valve sizers when sizing the annulus. Sizers contain cylindrical, conical, and aortic replica ends. Refer to Table 2 to facilitate sizer selection.

Cylindrical sizers correspond to the valve sizes 19 mm through 25 mm. Conical sizers correspond to the valve size 27/29 mm and 31/33 mm. These types of sizers may be used for both aortic and mitral valves.

The correct valve size is determined by obtaining a comfortable, not tight, fit of the sizer within the annulus. When a comfortable fit is found, the corresponding valve size is signified by the identification on the sizer. On-X Mitral Conform-X Prosthetic Heart Valves may be used when a comfortable fit is at or between size 25 and size 33.

Aortic replica sizers are provided for all aortic valve sizes. For size 19 mm through 25 mm aortic valves, the aortic replica sizers are used to verify that the aortic valve can be properly seated in the annulus and that the coronary arteries remain unobstructed. Size 19 mm through 25 mm aortic valves of standard, Conform-X, and Anatomic sewing ring configurations are designed to fit within the annulus at implant such that the exposed carbon flare rests in the annulus and the sewing ring is intrasupra-annular (Figure 11).

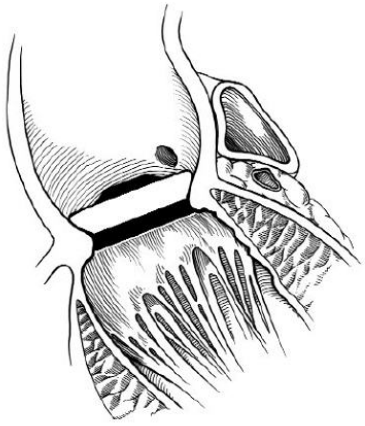
WARNING: DO NOT size the sewing ring of the size 19 mm through 25 mm aortic valve to fit within the annulus.

Size 27/29 mm aortic valves of standard, Conform-X, and Anatomic sewing ring configurations are designed to be placed in an intra-annular position and have a replica sizer to mimic this placement.

All mitral valves, including the On-X Mitral Conform-X Prosthetic Heart Valve, are designed to be placed in a supra-annular position (Figure 12).

CAUTION: Avoid oversizing the valve, as this could lead to interference with valve function.

Figure 11. Aortic replica sizers verify the aortic valve



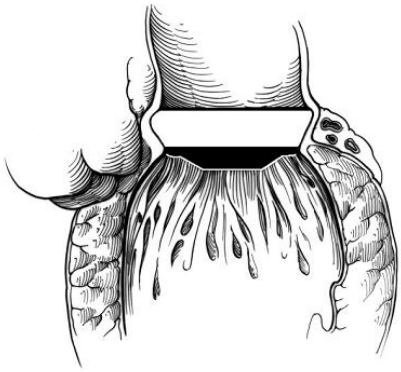
9.5 Suturing Techniques

The suturing techniques vary according to the preferences of the implanting surgeon and patient condition. The aortic valve is designed to have the tissue annulus abut the orifice flare. The general consensus among surgeons is that the non-everting interrupted mattress suture technique, with or without pledgets, provides the best conformation of the valve annulus to the outer surface of the flare.

The mitral valves have generally been implanted using a pledgetted or non-pledgetted everting mattress suture technique, although non-everting and continuous suture techniques have also been used with success.

CAUTION: When seating the valve, ensure that no suture material or anatomic structures interfere with leaflet motion. The valve's rotation capability may be helpful in avoiding abnormal residual pathology that could interfere with leaflet motion.

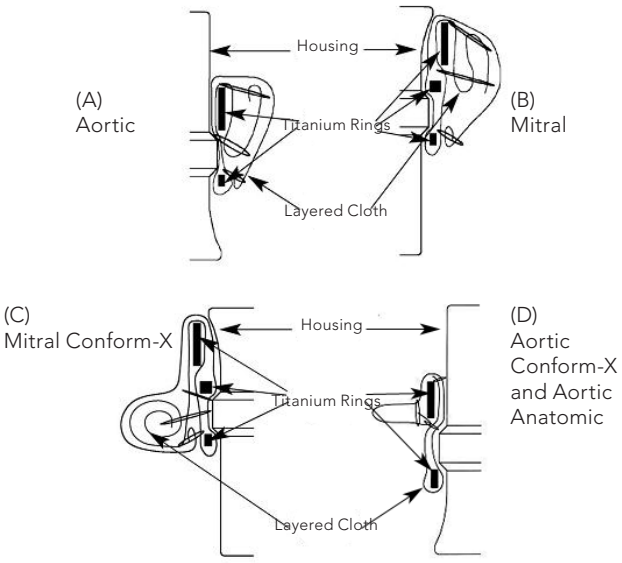
Figure 12. Supra-annular valve positioning



The sutures should be passed through the mid-point of the sewing ring. This allows the sewing ring to remain flexible and conform to the annulus. It also prevents the suture needle from contacting the titanium rings that lie within the sewing ring (Figure 13). The orientation marks on the sewing ring may be used to aid in suture placement.

CAUTION: For the Anatomic sewing ring, the sutures at the three valve commissures must correspond to the three orientation marks on the sewing ring.

Figure 13. Sewing ring cross-sections

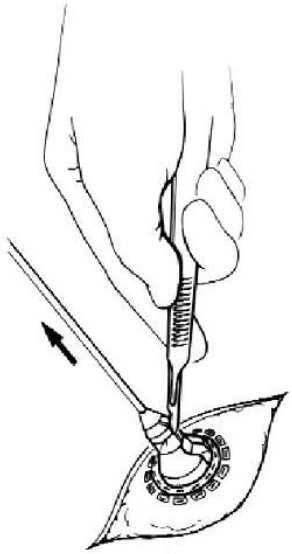


When all the sutures are in place, the valve is advanced into the annulus and the sutures are tied down. For aortic valves, it is suggested that the first 3 knots be tied equidistant to one another and midway between the commissures to stabilize the valve in the annulus. The holder is removed from the valve by carefully cutting the retaining suture as shown in Figure 14, then gently lifting the valve holder with handle out of the valve.

WARNING: Do NOT attempt to reinsert the valve holder into the valve once it has been removed.

CAUTION: Suture ties should be cut short to avoid any potential interference with leaflet motion.

Figure 14. Removing the valve holder



9.6 Leaflet Motion Assessment and Valve Rotation

Leaflet Motion Testing
Once the valve is in place, free motion of the leaflets must be tested. To test leaflet mobility, use the rotator probe or the leaflet probe to gently move the leaflets to verify that they open and close freely.

WARNING: Test the leaflet mobility only with the On-XLTI On-X leaflet probe or the leaflet probe on the end of the rotator.

Rotation
If the leaflets do not move freely, gently rotate the valve in either direction until it reaches a position where leaflet interference is not encountered.

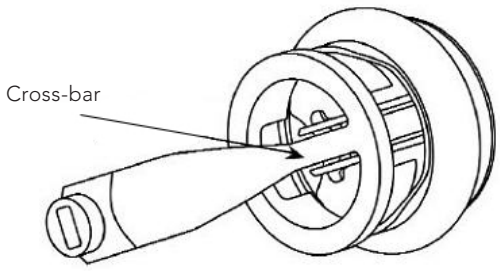
CAUTION: Do not attempt to rotate the valve if any significant resistance to rotation is encountered. The torque required to rotate the valve in situ should be about the same as that required when testing rotation before implantation. If noticeably greater torque is required to rotate, stop attempting rotation. If rotation is necessary and cannot be performed, remove the valve.

The rotator may be used with or without the instrument handle attached. As needed, attach the instrument handle to the rotator by inserting the instrument handle tip into the slot on the end of the rotator handle until it snaps firmly into position.

WARNING: Use only the On-XLTI On-X rotator to rotate the valve in situ. Use only the correspondingly sized rotator. Use of the wrong size rotator could damage the valve.

With the rotator leaflet probe between the leaflets and the cross-bar aligned with the leaflet pivot axis of the valve, carefully insert the valve rotator into the valve until it seats easily in place (Figure 15).

Figure 15. Insert valve rotator



CAUTION: No resistance should be experienced when inserting the rotator. If resistance is encountered, stop, remove, and realign the rotator before attempting to insert the rotator again.

Retest leaflet motion after rotation. If free leaflet motion cannot be achieved, remove the valve.

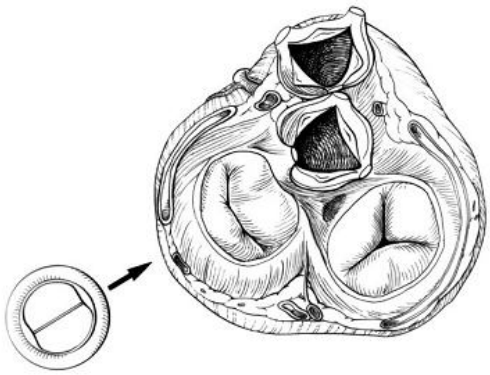
9.7 Valve Orientation

Aortic:
Based on clinical studies, there is no preferred orientation for the Aortic On-X Prosthetic Heart Valves with the standard, Conform-X, or Anatomic sewing ring configurations.

CAUTION: Once the valve is implanted, visually confirm that the coronary ostia are free from potential interference.

Mitral:
Literature suggests that the pivot axis of the mitral valve should be positioned anti-anatomically. Refer to Figure 16.

Figure 16. Pivot axis of the mitral valve positioned anti-anatomically



Mitral Standard and Conform-X

10. POSTOPERATIVE INFORMATION

10.1 Magnetic Resonance Imaging (MRI) Compatibility

MR Conditional: MR
The On-X Prosthetic Heart Valve, Mitral Conform-X Heart Valve Prosthesis, Size 25-33*, was determined to be MR-conditional according to the terminology specified in the American Society for Testing and Materials (ASTM) International, Designation: F2503-08. Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment. ASTM International, 100 Barr Harbor Drive, PO Box C700, West Conshohocken, Pennsylvania.

Non-clinical testing demonstrated that the On-X Mitral Conform-X Heart Valve Prosthesis, Size 25-33, is MR Conditional. A patient with this device can be scanned safely immediately after placement under the following conditions:

Static Magnetic Field:
- Static magnetic field of 3-Tesla or less

- Maximum spatial gradient magnetic field of 720-Gauss/cm or less

MRI-Related Heating:
In non-clinical testing, the On-X Prosthetic Heart Valve, Mitral Conform-X Heart Valve Prosthesis, Size 25-33, produced the following temperature rise during MRI performed for 15-min of scanning (i.e., per pulse sequence) in the 3-Tesla (3-Tesla/128-MHz, Excite, HDx, Software 14X.M5, General Electric Healthcare, Milwaukee, WI) MR system:

Highest temperature change +1.6˚C

Therefore, the MRI-related heating experiments for the On-X Mitral Conform-X Heart Valve Prosthesis, Size 25-33, at 3-Tesla, using a transmit/receive RF body coil at an MR system reported whole body averaged SAR of 2.9-W/kg (i.e., associated with a calorimetry measured whole body averaged value of 2.7-W/kg), indicated that the greatest amount of heating that occurred in association with these specific conditions was equal to or less than +1.6˚C.

Artifact Information:
MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the On-X Mitral Conform-X Heart Valve Prosthesis, Size 25-33. Therefore, optimization of MR imaging parameters to compensate for the presence of this device may be necessary.

*The MRI findings apply to this specific largest heart valve prosthesis and all other smaller sizes which are made from similar materials.

Pulse Sequence	Signal Void Size (mm2)	Plane Orientation
T1-SE	1,090	Parallel
T1-SE	686	Perpendicular
GRE	1,478	Parallel
GRE	1,014	Perpendicular

10.2 Returned Goods
Prior authorization from On-XLTI Customer Service is required for the return of any product. For any questions regarding the valve or for return authorization, please contact Customer Service.

Licensed under U.S. Patent Nos. 5,308,361; 5,137,532; 5,545,216; 5,772,694; 5,641,324; 5,908,452; 5,284,676; 5,305,554; 5,328,713, 5,332,337; 5,336,259; 5,514,410; 5,677,061; 6,096,075; Serial No. 09/010,449 allowed; Serial No. 09/224,816 allowed; and other permits and patents pending.

11. PATIENT INFORMATION

11.1 Patient Registration
In each valve package, there is a Patient Record Card and an Implant Registration Card. On-XLTI requests that the Implant Registration Card be filled out immediately and that the mailing copy be returned to On-XLTI Customer Service. For multiple valve implants, please fill out a card for each valve. On-XLTI will use these data for notification purposes and to help with inventory restocking in the hospital. All patient information remains strictly confidential, and the release of patient-identifying information can be refused if allowed by law.

11.2 Patient Record Card
A Patient Record Card is provided with the prosthesis. Patients should be encouraged to complete the card and carry it with them at all times.

11.3 Patient Information Booklet
On-XLTI has made available a patient information booklet that the physician may choose to provide to the patient prior to discharge. Copies of this booklet are available on request from your On-XLTI sales representative.

12. DISCLAIMER OF WARRANTIES
Because of the complications listed previously that may occur with the use of any heart valve prosthesis and the possibilities of damage, also noted previously, before, during or after implantation, On-XLTI warrants only that the product shall conform to On-XLTI's standard specifications. No other warranty is made by On-XLTI concerning the function of the product in use, and On-XLTI assumes no risk whatsoever as to the results of the use of this product. The entire risk with use of the product is that of the buyer. On-XLTI disclaims all other warranties, respecting the product, expressed or implied, including but not limited to those related to the product's merchantability or fitness for a particular purpose. On-XLTI shall not be liable for any direct, special, consequential or incidental loss, damage or expense related to the use of the product. No person has any authority to alter any of these conditions or to bind On-XLTI to any additional responsibility or warranty in connection with the use of the product.

APPENDIX A

Clinical information as required by FDA (USA)

1. ADVERSE EVENTS

In the European premarket study a total of 184 aortic On-X Prosthetic Heart Valves were implanted in 184 patients at 11 centers. The mean follow-up was 2.2 years (range of 0 to 4.0 years) with a total of 411.8 patient-years. In the mitral position 229 valves were implanted in 229 patients at 16 centers. Mean mitral follow-up was 1.8 years (range of 0 to 4.5 years) with a total of 417.9 patient-years.

In aortic patients, a total of 7 deaths occurred during the study and 2 of these were characterized as valve-related. The causes of the aortic valve-related deaths were early thromboembolism (1 patient) and sudden, unexplained death (1 patient). In mitral patients, a total of 18 deaths occurred during the study and 3 of these were characterized as valve-related. The causes of the mitral valve-related deaths were early, uncontrolled bleeding (1 patient) and sudden, unexplained death (2 patients).

1.1 Observed Adverse Events

Adverse events were reported in the clinical study as shown in Tables 3 and 4

2. CLINICAL STUDIES

2.1 Premarket Trials

The On-X Prosthetic Heart Valve premarket clinical trials were designed to study the safety and effectiveness of the valve in aortic and mitral valve replacement. Patients requiring isolated aortic heart valve replacement were enrolled from 1996 to 2000 at 11 centers in an international multicenter, prospective, non-randomized study with retrospective controls. Patients requiring isolated mitral heart valve replacement were enrolled from 1996 to 2001 at 16 centers in an international multicenter, prospective, non-randomized study with retrospective controls.

The aortic cohort included 184 patients (121 men, 63 women), aged from 20 to 80 years (mean of 60.2 years). The cumulative follow-up was 411.8 patient-years with a mean follow-up of 2.2 years (SD = 0.8 years, range = 0 to 4.0 years). The mitral cohort included 229 patients (86 men, 143 women), aged from 21 to 78 years (mean of 59.2 years). The cumulative follow-up was 417.9 patient-years with a mean follow-up of 1.8 years (SD = 1.3 years, range = 0 to 4.5 years). Tables 5 and 6 present preoperative and operative patient demographics. Chart 1 shows the number of patients implanted versus duration of follow-up. Table 7 presents implant information by valve size, including the number of patients implanted and the number of patient-years.

Safety endpoints captured in the studies were complications; blood analyses were used to confirm the absence or presence of certain complications. Safety results are provided in Tables 3 and 4. Effectiveness endpoints were New York Heart Association (NYHA) classification and echocardiographic assessments. NYHA and blood data were obtained pre-operatively, intra-operatively, and post-operatively at 3 to 6 months, at one year, and annually thereafter. Hemodynamic data were obtained at discharge and at one year. Tables 8 and 9 present these effectiveness results.

2.2 Postmarket Trial of Lower Target Anticoagulation

The Prospective Randomized On-X Anticoagulation Clinical Trial (PROACT) was designed to evaluate whether it is safe and effective to treat patients implanted with the On-X Prosthetic Heart Valve with less aggressive anticoagulant therapy than currently recommended by the American College of Cardiology/American Heart Association (ACC/AHA) or American College of Chest Physicians (ACCP) guidelines for patients receiving a bileaflet mechanical valve prosthesis. The first cohort to complete enrollment and analysis was used to compare standard anticoagulant therapy versus international normalized ratio (INR) goal of 1.5 to 2.0 in high-risk patients requiring aortic valve replacement (AVR).

Study Design and Patient Selection

The high-risk AVR arm of the PROACT study was a prospective, randomized, unblinded, controlled trial comparing the outcomes after AVR with the On-X valve. It was a multicenter trial consisting of 36 centers in North America, of which 35 centers were in the United States and 1 center was in Canada. A total of 425 patients were recruited in this cohort for AVR in patients at high risk for valve thrombosis and thromboembolism. Enrollment began in June 2006 and was closed for the high-risk AVR group in October 2009. Follow-up data through September 1, 2014 were available for this report. The primary endpoints were the rates of valve thrombosis, thromboembolism, bleeding, reoperation, explant and all-cause and valve-related mortality, as defined by the Society of Thoracic Surgeons/American Association for Thoracic Surgery (STS/AATS) guidelines for valve studies. Non-inferiority between the 2 groups was to be evaluated using the composite of valve thrombosis, thromboembolism, and bleeding rate, and a non-inferiority margin of 1.5% (absolute). The sample size estimation was determined using a 1-sided proportion test with a type I error of 0.05 and power of 80% to test the non-inferiority hypothesis.

Patient Inclusion Criteria

The patient inclusion criteria were as follows:

1. Patients with a clinical indication for isolated AVR

2. Patients with the following conditions, which place a patient in the "high-risk" group: chronic atrial fibrillation, left ventricular ejection fraction < 30%, enlarged left atrium > 50 mm in diameter, spontaneous echocardiographic contrasts in the left atrium, vascular pathologic features, neurologic events, hypercoagulability (defined below), left or right ventricular aneurysm, lack of a platelet response to aspirin or clopidogrel, and women receiving estrogen replacement therapy.

3. Concomitant cardiac surgery, including coronary artery bypass grafting, mitral or tricuspid valve repair, ascending aortic replacement, and maze procedure, was allowed

4. Adult patients (at least 18 years old)

Patient Exclusion Criteria
The key patient exclusion criteria were as follows:

1. Right-sided valve replacement

2. Double (aortic plus mitral) valve replacement

3. Patients with active endocarditis at the time of implantation

4. Previous confirmed or suspected thromboembolic event or thrombophlebitis occurring or resolving within the last year prior to enrollment

5. Patients who are in an emergency state

Hypercoagulability in the AVR patients was defined by the following blood tests done preoperatively and before the initiation of warfarin therapy: activated protein C resistance (factor V Leiden mutation), prothrombin mutation, antithrombin III activity, protein C activity, protein S activity, factor VIII activity, and low-density lipoprotein cholesterol. Resistance to aspirin or clopidogrel in AVR patients was defined from clinical laboratory test results: urine 11-dehydro-thromboxane B2 (later changed to blood thromboxane A2) for aspirin and inhibition of P2Y12 for clopidogrel.

Randomization to Test and Control Groups
All patients received routine warfarin with a target INR of 2.0 to 3.0, plus aspirin 81 mg daily for the first 3 postoperative months. At 90 days postoperatively, randomization was performed using a standard randomization Mersenne Twister algorithm through an on-line randomization module.

Test group: For the first 3 postoperative months, warfarin at an INR target of 2.0 to 3.0 with aspirin 81 mg/day was used. After 3 months, the warfarin dose was reduced to an INR target of 1.5 to 2.0, with aspirin 81 mg/day.

Control group: Postoperatively, warfarin at an INR target of 2.0 to 3.0 with aspirin 81 mg/day was used throughout the study period.

Any patient in the test group who experienced a thromboembolism event was crossed over to standard anticoagulation therapy (INR, 2.0 - 3.0 plus aspirin 81 mg/day), although such patients remained in the test group by intention-to-treat.

Primary Endpoints
The primary endpoints included major bleeding events, minor bleeding events, transient ischemic attack (TIA), ischemic stroke, peripheral thromboembolism, valve thrombosis, the composite of these events, reoperation, explant, and all-cause and valve-related mortality.

Secondary Endpoints
The secondary endpoints included endocarditis, hemolysis, hemolytic anemia, paravalvular leak, structural and nonstructural dysfunction, postoperative New York Heart Association functional class, and echocardiographic hemodynamics (peak gradient, mean gradient, effective orifice area, and valvular regurgitation).

Follow-up Schedule
The patients were followed up by in-person visits to the study sites at 3 months, 6 months, and 1 year after surgery and then annually for 2 to 5 and as much as 8 postoperative years to accrue the necessary 800 patient-years of follow-up mandated by the FDA. During these visits, electrocardiography or echocardiography was performed as required by the protocol and as clinically indicated. All patients maintained with warfarin therapy were followed up using weekly home INR testing through a central telephone or online database. The follow-up period was through September 1, 2014 and was complete in 98% of patients.

INR Management
All patients received a home INR monitor at randomization. The INR control was maintained using weekly home testing, with warfarin dose adjustments made by the clinical sites to minimize INR variability and maximize the time in the INR target range. Compliance to home monitoring was determined by the frequency of the tests conducted monthly.

Statistical Analysis
The descriptive statistics, including mean and standard deviation, were reported for the numeric measures. Early adverse events were those occurring before randomization and were calculated as percentages. Late (post-randomization) linearized adverse event rates in %/patient-year (pt-yr) were calculated based on the safety population including all patients who had received at least 1 dose of the study drug. Kaplan-Meier life table curves were calculated for time to event data, from the point of randomization to the first event The analyses

were performed using Statistical Analysis Systems statistical software, version 9.2 (SAS Institute, Cary, NC).

RESULTS

From June 2006 to October 2009, 425 patients were enrolled in the high-risk AVR arm of the PROACT trial. Of these 425 patients, 185 were randomized after 3 postoperative months to the test group and 190 were randomized to the control group. The follow-up period averaged 3.82 years through September 1, 2014 (878.6 pt-yrs for the control group and 766.2 pt-yrs for the test group). The remaining 50 patients were removed from the trial before randomization for the following reasons: death (n = 8), adverse event exclusion by protocol (n = l0), different or no surgery performed (n = 14), withdrawal by patient or physician (n = 11), protocol criterion exclusion (n = 3), explantation (n = 1), and lost to follow-up (n = 3). The mean age at surgery was 55.8 ± 12.0 years (range, 22 - 85) for the control group and 54.1 ± 13.0 years (range, 20 - 83) for the test group (p = .187). In the control and test groups, 81% and 80% of the patients were men, respectively (p = .898).

Comparisons between the 2 groups for native valve pathologic features, valve lesion, preoperative New York Heart Association functional classification, clinical risk factors, and abnormal laboratory test results are listed in Table 10. No statistically significant differences were found.

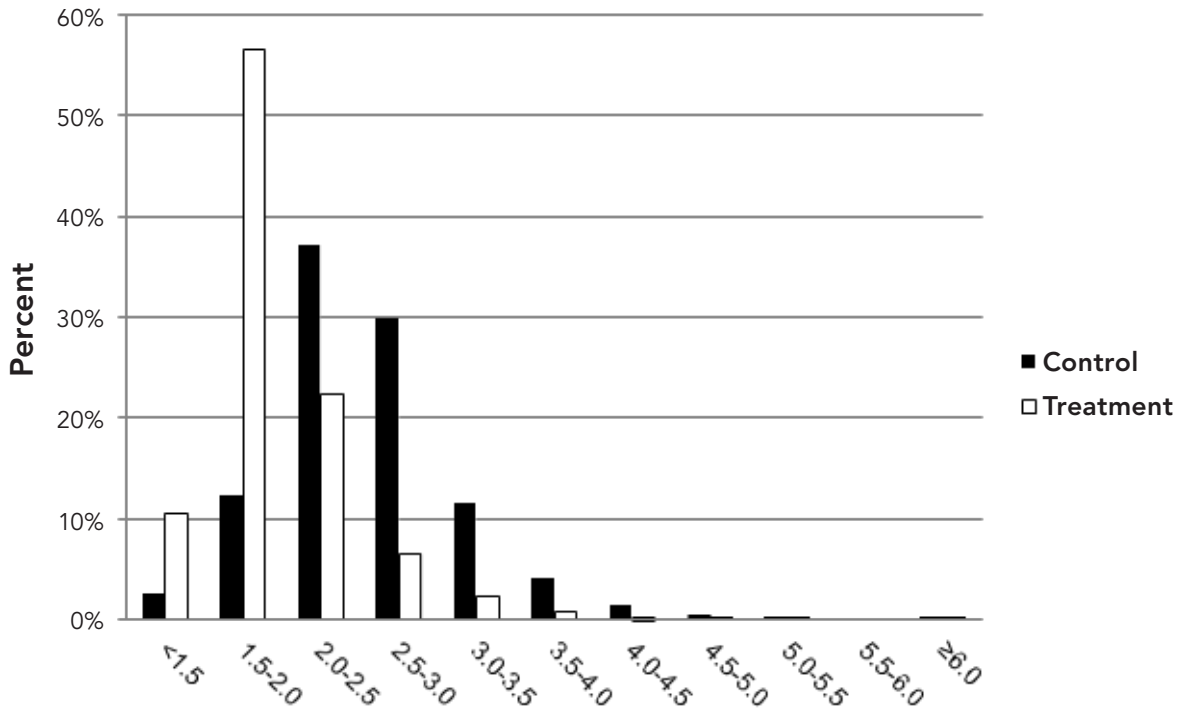
The patients were considered minimally compliant if their frequency of testing was at least twice monthly, approximately twice as often as conventional INR monitoring in a clinician outpatient office. The patients were considered fully compliant when their frequency of testing was 2 - 3 times monthly. Ideal home monitoring would have resulted in an average interval between the tests of 7 days. In the present study, the average interval between tests was 9 days in both groups. More than 80% of the patients were minimally compliant with the home monitoring procedures, >20% were ideally compliant, and 96% of all patients at least attempted to conduct home testing once. Finally, 4% of patients refused home INR monitoring altogether and were monitored by their local physicians at clinic visits. The mean INR was l.89 ± 0.49 (median 1.80) for the test patients (target, 1.5 – 2.0) and 2.50 ± 0.63(median 2.40) for the control patients (target, 2.0 – 3.0).

Figure 17 shows the distribution of INR measurements by group, demonstrating the lower INR levels maintained in the test group. The percentage of INR measurements in the target range was 64.1% for the test group and 70.4% for the control group. The test group in-range percentage was similar to that of the control group, despite the narrower target range. The mean and median INR were within the target range for both groups. The percentage of readings >3.0 or <l.5 was 17.3% in the control group and 13.5% in the test group, respectively.

The results of the primary endpoint events are presented in Table 11. The linearized late event rates showed that the test group experienced lower event rates in both major and minor bleeding.

The rates of thrombotic events between the 2 groups

Figure 17. INR Distributions



appeared to be similar. The difference in bleeding events between the 2 groups was noticeably in favor of the test group. Also, the mortality rates between the 2 groups were similar; the rates of other secondary valve-related events not shown in Table 11 were all <1 %/pt-yr and were also similar between the 2 groups.

Before randomization, 4 patients had died within the first 30 days and 4 more had died between 30 and 90 days. The 4 early deaths were from cardiogenic shock, multiorgan failure, biventricular failure, and atheroembolic shower leading to renal failure; all occurred within 2 days of surgery. The 4 deaths occurring at 30 to 90 postoperative days were from sudden death of unknown cause, prosthetic endocarditis, cerebral hemorrhage, and arrhythmia.

After randomization, the incidence of sudden death was similar in both groups (3 in each group). There were 3 cardiac deaths in the control group and none in the test group. Valve-related deaths included 2 cerebral bleeding events and 1 gastrointestinal bleeding event in the control group and 1 ischemic stroke and 1 cerebral bleeding event in the test group. The remaining late deaths were determined by independent adjudication to be not valve-related and there were 7 in each group.

A qualitative evaluation of reoperation and explants revealed that the types and causes of the reoperations and explants were similar between the 2 groups. Before randomization, the most common surgical procedure was re-exploration for perioperative bleeding, which occurred 22 times (5.2% of 425 patients, or about one half of all perioperative bleeding events). New pacemaker insertion within 14 days was the second most common procedure and occurred in 19 patients (4.5% of 425 patients). Other early procedures were for gastrointestinal bleeding, prosthetic endocarditis, sternal rewiring, and an occult pregnancy; each occurred once. After randomization, valve-related reoperations were related to prosthetic endocarditis, paravalvular leak, thrombosis, peripheral thrombectomy, bleeding, and heart transplantation. Overall, the rate of post-randomization reoperations was 0.46%/pt-yr for the control group and 0.91%/pt-yr for the test group), and the rate of explants was 0.34% in the control group and 0.91% in the test group The types and numbers of reoperations and explants are similar between groups.

TIA was defined as a neurologic deficit lasting ≤3 days. Seven (7) TIAs occurred in the control group, with an average duration of 1.6 days, and 11 in the test group, averaging 1 day in duration. These were all short-duration blindness, numbness, weakness, or tingling in patients whose computed tomography or magnetic resonance imaging scans showed no circulation abnormality or new cerebral infarction. Seven (7) ischemic strokes occurred in the control group and 6 occurred in the test group. Of these, 3 each in the control and test groups had resolved within 3 days but the computed tomography and magnetic resonance imaging results were positive. Four (4) control patients and 2 test patients experienced a permanent neurologic deficit, and 1 test patient died of stroke on the second postoperative day. The incidences of neurologic thromboembolism events in the 2 groups were similar as shown in Table 11.

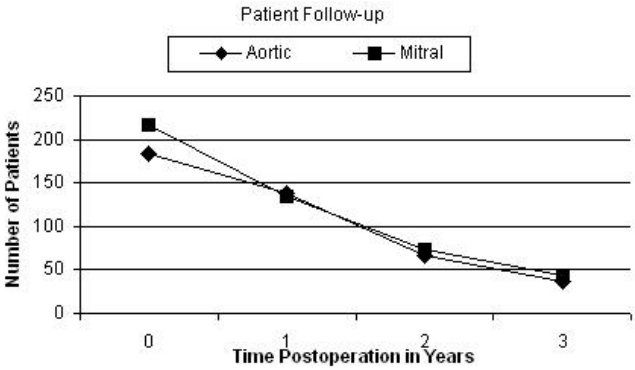
Valve thrombosis was qualitatively different from thromboembolism in that all 4 valve thrombosis events occurred in patients who had stopped taking warfarin against medical advice. These cases were managed by valve explantation (1 control and 1 test), 1 thrombectomy, and 1 spontaneous resolution with the re-administration of warfarin. All 4 patients recovered.

Of the primary endpoint events in the control and test groups combined, 46 were major bleeding events, 44 were minor bleeding events, 13 were ischemic strokes, and 18 were TIAs. Major bleeding events were further classified into 5 cerebral bleeding events, 27 gastrointestinal bleeding events, 3 hematomas, 2 nosebleeds, and 9 other bleeding events. Cerebral bleeding events resulted in 3 deaths and 2 permanent deficits. Ischemic strokes resulted in 1 death and 6 permanent deficits; 6 patients recovered fully within <3 days. Table 11 stratifies the bleeding and cerebral events into those in the control group and those in the test group.

To test the study hypotheses, analyses of non-inferiority were conducted and are shown in Table 12. These analyses establish that the test group is non-inferior to the control group with a non-inferiority margin of 1.5% applied. Comparisons to Objective Performance Criteria (OPC) were also required by the protocol and are shown in Table 13. The study was considered successful if the OPC event rates must be less than twice the corresponding OPC, which can be seen in the table.

Chart 1: Patient Follow-up Over Time

Aortic patients implanted N = 184,
Cumulative follow-up = 411.8 patient-years
Mitral patients implanted N = 229,
Cumulative follow-up = 417.9 patient-years



Patients Followed, Nf		Discharge	1 Year Postoperative	2 Year Postoperative	3 Year Postoperative
	Aortic	184	138	66	37
	Mitral	216	134	74	44

Table 3: Aortic Replacement Observed Adverse Event Rates[1]

All patients implanted, N = 184, Cumulative follow-up = 411.8 patient-years

Complication	Early Events		Late Events[2]		Freedom from Event[3], % [SE]	
	n	% (n/N)[4]	n	%/pt-yr	1 Year Postoperative (n=138)	3 Year Postoperative (n=37)
Mortality (all)	4	2.2%	3	0.7%	97.8% [1.1]	96.0% [1.5]
Mortality (valve-related)	1	0.5%	1	0.2%	99.4% [0.5]	98.8% [0.9]
Endocarditis	0	0.0%	2	0.5%	99.4% [0.6]	98.9% [0.8]
Explant	1	0.5%	2	0.5%	98.4% [0.9]	97.8% [1.1]
Hemolysis[5]	**0**	**0.0%**	**0**	**0.0%**	**100.0% [0]**	**100.0%[0]**
Hemorrhage6 (all)	1	0.5%	3	0.7%	99.4% [0.5]	97.3% [1.4]
Hemorrhage (major)	1	0.5%	1	0.2%	100.0% [0]	99.1% [0.9]
Perivalvular Leak (all)	4	2.2%	3	0.7%	96.7% [1.3]	96.7% [1.3]
Perivalvular Leak (major)	1	0.5%	0	0.0%	100.0% [0]	100.0% [0]
Nonstructural Valve Dysfunction	0	0.0%	0	0.0%	100.0% [0]	100.0% [0]
Reoperation (valve-related)	2	1.1%	3	0.7%	97.8% [1.1]	97.2% [1.2]
Structural Valve Dysfunction	0	0.0%	0	0.0%	100.0% [0]	100.0% [0]
Thromboembolism	1	0.5%	7	1.7%	97.8% [1.1]	93.9% [2.5]
Thrombosis	0	0.0%	0	0.0%	100.0% [0]	100.0% [0]

Notes:
1. Data does not include results from double valve replacement.
2. Late events calculated as linearized rates based on total patient-years.
3. Freedom from event was calculated based on the method of Kaplan-Meier. SE = Standard Error.
4. n = number of patients in each category; N = total number of study patients.
5. Blood studies conducted at a core laboratory established that the valve creates a low level of fully compensated hemolysis typified by an increase in SLDH with a mean within normal range, a decrease in haptoglobin to below normal in 69% Aortic Valve Replacement (AVR) and 65% Mitral Valve Replacement (MVR) patients at 1-year, and all other analytes within normal range.
6. The anticoagulant agents used were reported. The target International Normalized Ratio was 2.5 to 3.5 in AVR and 3.0 to 4.5 in MVR.

Table 4: Mitral Replacement Observed Adverse Event Rates[1]

All patients implanted, N = 229, Cumulative follow-up = 417.9 patient-years

Complication	Early Events		Late Events[2]		Freedom from Event[3], % [SE]	
	n	% (n/N)[4]	n	%/pt-yr	1 Year Postoperative (n=134)	3 Year Postoperative (n=44)
Mortality (all)	9	3.9%	9	2.2%	95.4% [1.4]	89.2% [2.7]
Mortality (valve-related)	1	0.4%	2	0.5%	99.5% [0.5]	97.2% [1.7]
Endocarditis	0	0.0%	3	0.7%	99.0% [0.7]	99.0% [0.7]
Explant	1	0.4%	3	0.7%	98.0% [1.0]	98.0% [1.0]
Hemolysis[5]	**0**	**0.0%**	**0**	**0.0%**	**100.0% [0]**	**100.0%[0]**
Hemorrhage[6] (all)	4	1.8%	6	1.4%	96.4% [1.3]	94.4% [2.0]
Hemorrhage (major)	4	1.8%	2	0.5%	97.0% [1.2]	97.0% [1.2]
Perivalvular Leak (all)	2	0.9%	3	0.7%	98.0% [1.0]	97.1% [1.2]
Perivalvular Leak (major)	1	0.4%	1	0.2%	99.4% [0.6]	99.4% [0.6]
Nonstructural Valve Dysfunction	0	0.0%	1	0.2%	100.0% [0]	99.1% [0.9]
Reoperation (valve-related)	3	1.3%	5	1.2%	97.0% [1.2]	97.0% [1.2]
Structural Valve Dysfunction	0	0.0%	0	0.0%	100.0% [0]	100.0% [0]
Thromboembolism	2	0.9%	7	1.7%	97.0% [1.2]	96.3% [1.4]
Thrombosis	0	0.0%	0	0.0%	100.0% [0]	100.0% [0]

Notes:
1. Data does not include results from double valve replacement.
2. Late events calculated as linearized rates based on total patient-years.
3. Freedom from event was calculated based on the method of Kaplan-Meier. SE = Standard Error.
4. n = number of patients in each category; N = total number of study patients.
5. Blood studies conducted at a core laboratory established that the valve creates a low level of fully compensated hemolysis typified by an increase in SLDH with a mean within normal range, a decrease in haptoglobin to below normal in 69% AVR and 65% MVR patients at 1-year, and all other analytes within normal range.
6. The anticoagulant agents used were reported. The target International Normalized Ratio was 2.5 to 3.5 in AVR and 3.0 to 4.5 in MVR.

Table 5: Preoperative Patient Demographics

Aortic Preoperative Patient Demographics

All patients implanted, N = 184,
Cumulative follow-up = 411.8 patient-years

Patient Characteristic		N	% (n/N)1
Age at implant in years		**60.2 ± 8.4**	
Gender:	• Male	121	65.8%
	• Female	63	34.2%
NYHA Classification:	• I	9	4.9%
	• II	91	49.5%
	• III	79	42.9%
	• IV	5	2.7%
	• Unknown	0	0.0%
Valve Lesion:	• Stenosis	86	46.7%
	• Insufficiency	39	21.2%
	• Mixed	59	32.1%
	• Other	0	0%

Notes: 1. n = number of patients in each category; N = total number of study patients.

Mitral Preoperative Patient Demographics

All patients implanted, N = 229,
Cumulative follow-up = 417.9 patient-years

Patient Characteristic		N	% (n/N)1
Age at implant in years		**59.2 ± 10.6**	
Gender:	• Male	86	37.6%
	• Female	143	62.4%
NYHA Classification:	• I	5	2.2%
	• II	68	29.7%
	• III	134	58.5%
	• IV	18	7.9%
	• Unknown	4	1.7%
Valve Lesion:	• Stenosis	29	12.7%
	• Insufficiency	111	48.5%
	• Mixed	87	38.0%
	• Other	2	0.9%

Notes: 1. n = number of patients in each category; N = total number of study patients.

Table 6: Operative Patient Demographics[1]

Operative Aortic Patient Demographics

All patients implanted, N = 184,
Cumulative follow-up = 411.8 patient-years

Variable	Category[1]	n	% (n/N)2
Etiology[3]	Calcific	92	50.0%
	Degenerative	51	27.7%
	Rheumatic	24	13.0%
	Congenital	18	9.8%
	Endocarditis	8	4.4%
	Prosthetic Valve Dysfunction	0	0.0%
	Other	6	3.3%
Concomitant Procedures[3]	None	141	76.7%
	Coronary Artery Bypass Graft	21	11.4%
	Myotomy	10	5.4%
	Mitral Repair	5	2.7%
	Aorta Repair or Replacement	4	2.2%
	Tricuspid Repair	1	0.5%
	Muscle Bridge	1	0.5%
	Tricuspid Replacement	0	0.0%
	Explant of Annuloplasty Ring	0	0.0%
	Maze Procedure	0	0.0%
	Closure of Atrial Appendage	0	0.0%
	Ventricular Aneurysm Repair	0	0.0%
	Other	0	0.0%
Pre-existing Conditions[3]	Systemic Hypertension	90	48.9%
	Hyperlipidemia	83	45.1%
	Angina	42	22.8%
	Coronary Artery Disease	42	22.8%
	Diabetes Mellitus	33	17.9%
	Atrial Arrhythmias	25	13.6%
	Left Ventricular Dysfunction	23	12.5%
	Congestive Heart Failure	22	12.0%
	Myocardial Infarction	12	6.5%
	Cerebrovascular Accident	10	5.4%
	Carotid Artery Disease	7	3.8%
	Endocarditis	4	2.2%
	Cardiomyopathy	3	1.6%
	Pacemaker Implant	2	1.1%
	Coronary Artery Bypass Graft	1	0.5%
	Previous Aortic Valve Replacement	1	0.5%
	Previous Mitral Valve Replacement	0	0.0%
	Other	27	14.8%
Valve Size	19 mm	17	9.2%
	21 mm	35	19.0%
	23 mm	70	38.0%
	25 mm	38	20.6%
	27/29 mm	24	13.0%

Operative Mitral Patient Demographics

All patients implanted, N = 229,
Cumulative follow-up = 417.9 patient-years

Variable	Category[1]	N	% (n/N)2
Etiology[3]	Rheumatic	86	37.6%
	Degenerative	62	27.1%
	Calcific	36	15.7%
	Endocarditis	16	7.0%
	Prosthetic Valve Dysfunction	6	2.6%
	Congenital	4	1.8%
	Other	38	16.6%
Concomitant Procedures[3]	None	130	56.8%
	Coronary Artery Bypass Graft	44	19.2%
	Tricuspid Repair	22	9.6%
	Closure of Atrial Appendage	12	5.2%
	Mitral Repair	12	5.2%
	Maze Procedure	12	5.2%
	Septal Defect Closure	8	3.5%
	Ventricular Aneurysm Repair	3	1.3%
	Muscularization	2	0.9%
	Tricuspid Replacement	1	0.4%
	Explant of Annuloplasty Ring	1	0.4%
Pre-existing Conditions[3]	Atrial Arrhythmias	137	59.3%
	Pulmonary Hypertension	108	46.8%
	Systemic Hypertension	88	38.1%
	Hyperlipidemia	88	38.1%
	Congestive Heart Failure	80	34.6%
	Other	77	33.3%
	Coronary Artery Disease	67	29.0%
	Cigarette Smoker	64	27.7%
	Left Ventricular Dysfunction	47	20.4%
	Cerebrovascular Accident	43	18.6%
	Diabetes Mellitus	40	17.3%
	Angina	38	16.4%
	Myocardial Infarction	30	13.0%
	Hyperthyriodism	27	11.7%
	Chronic Obstructive Pulmonary Disease	25	10.8%
	Endocarditis	18	7.8%
	Gastroinestinal Ulcer	18	7.8%
	Chronic Kidney Failure	13	5.6%
	Carotid Artery Disease	12	5.2%
	Coronary Artery Bypass Graft	10	4.4%
	Cancer	10	4.4%
	Previous Mitral Valve Replacement	9	3.9%
	Cardiomyopathy	8	3.5%
	Pacemaker Implant	6	2.6%
Valve Size	25 mm	33	14.4%
	27/29 mm	131	57.2%
	31/33 mm	65	28.4%

Notes:
1. Ordered by frequency of occurrence, except for valve size.
2. n = number of patients in each category; N = total number of study patients.
3. May be more than one per patient.

Table 7: Number Implanted and Years by Valve Size

Number of Aortic Patients Implanted and Number of Patient-years by Valve Size

All patients implanted, N = 184,
Cumulative follow-up = 411.8 patient-years

	Numbers by Valve size					
	19 mm	21 mm	23 mm	25 mm	27/29 mm	Total
Number of Patients Implanted	17	35	70	38	24	184
Number of Patient-years	36.9	82.2	151.5	85.9	55.3	411.8

Number of Mitral Patients Implanted and Number of Patient-years by Valve Size

All patients implanted, N = 229,
Cumulative follow-up = 417.9 patient-years

	Numbers by Valve size				
	25 mm	27/29 mm	31/33 mm		Total
Number of Patients Implanted	33	131	65		229
Number of Patient-years	60.2	239.1	118.6		417.9

Table 8: Valve Effectiveness Outcomes

Aortic Effectiveness Outcomes, Functional New York Heart (NYHA) Classification[1]

All patients implanted, N = 184,
Cumulative follow-up = 411.8 patient-years

NYHA Class	Preoperative Assessment (Nd = 184)		Postoperative Assessments					
			1 Year (10-14 Months) (Nf = 138, Nd = 129)[2]		2 Year (22-26 Months) (Nf = 66, Nd = 66)		3 Year (34-38 Months) (Nf = 37, Nd = 36)	
	N[3]	% (n/Nd)	n	% (n/Nd)	n	% (n/Nd)	n	% (n/Nd)
I	9	4.9	83	64.3	48	72.7	20	55.6
II	91	49.5	35	27.1	12	18.2	10	27.8
III	79	42.9	4	3.1	6	9.1	4	11.1
IV	5	2.7	0	0	0	0	0	0
Undetermined[4]	0	0	7	5.4	0	0	2	5.6
Missing[5]	0	N/A	9	N/A	0	N/A	1	N/A

Notes:
1. Data does not include results from double valve replacement.
2. Nf = number of patients followed (reproduced from Figure 2); Nd = number of patients for which NYHA data were collected (not including missing).
3. n = number of patients in each category.
4. Undetermined means data were collected but Class could not be determined during exam
5. Missing refers to the difference between the number of patients followed, Nf, and the number of patients for which NYHA data were collected, Nd.

Mitral Effectiveness Outcomes, Functional New York Heart (NYHA) Classification[1]

All patients implanted, N = 229,
Cumulative follow-up = 417.9 patient-years

NYHA Class	Preoperative Assessment (Nd = 229)		Postoperative Assessments					
			1 Year (10-14 Months) (Nf = 134, Nd = 127)[2]		2 Year (22-26 Months) (Nf = 74, Nd = 69)		3 Year (34-38 Months) (Nf = 44, Nd = 42)	
	n[3]	% (n/Nd)	N	% (n/Nd)	n	% (n/Nd)	N	% (n/Nd)
I	5	2.2	85	66.9	35	50.7	14	33.3
II	68	29.7	29	22.8	24	34.8	22	52.4
III	134	58.5	5	3.9	5	7.2	6	14.3
IV	18	7.9	0	0	1	1.4	0	0
Undetermined[4]	4	1.7	8	6.3	4	5.8	0	0
Missing[5]	0	N/A	7	N/A	5	N/A	2	N/A

Notes:
1. Data does not include results from double valve replacement.
2. Nf = number of patients followed (reproduced from Figure 2); Nd = number of patients for which NYHA data were collected (not including missing).
3. n = number of patients in each category.
4. Undetermined means data were collected but Class could not be determined during exam
5. Missing refers to the difference between the number of patients followed, Nf, and the number of patients for which NYHA data were collected, Nd.

Table 9: Effectiveness Outcomes, Hemodynamic Results

Effectiveness Outcomes, Aortic Hemodynamic Results[1]

All patients implanted, N = 184,
Cumulative follow-up = 411.8 patient-years

Hemodynamic Parameter	Results by Valve Size									
	19 mm		21 mm		23 mm		25 mm		27/29 mm	
Early Postoperation (< 30 days), N_f[2] = 184										
Mean Gradient[3]	N_d[4] = 20		N_d = 31		N_d = 58		N_d = 33		N_d = 20	
•Mean ± SD	11.6 ± 4.5		9.4 ± 3.6		8.4 ± 4.3		7.5 ± 3.8		6.1 ± 2.9	
•Min, max	5.6, 21.5		4.0, 18.4		2.0, 26.4		2.1, 18.6		1.0, 11.5	
EOA[5]	N_d = 19		N_d = 31		N_d = 57		N_d = 33		N_d = 20	
•Mean ± SD	1.4 ± 0.2		1.8 ± 0.3		2.1 ± 0.5		2.5 ± 0.8		2.8 ± 0.4	
•Min, max	1.1, 1.9		1.3, 2.4		1.0, 3.6		0.9, 4.3		1.9, 3.5	
Regurgitation[6]	N_d = 22		N_d = 40		N_d = 72		N_d = 38		N_d = 24	
	n[7]	% (n/N_d)	n	% (n/N_d)	n	% (n/N_d)	N	% (n/N_d)	n	% (n/N_d)
•0	9	40.9%	14	35.0%	31	43.1%	19	50.0%	9	37.5%
•1-2+	12	54.6%	25	62.5%	37	51.4%	19	50.0%	13	54.2%
•3+	0	10.0%	0	0.0%	2	2.8%	0	0.0%	0	0.0%
•4+	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
•Not available	1	4.6%	1	2.5%	2	2.8%	0	0.0%	2	8.3%
1 Year Postoperation, N_f = 138										
Mean Gradient	N_d = 13		N_d = 22		N_d = 55		N_d = 24		N_d = 16	
•Mean ± SD	9.7 ± 2.6		7.7 ± 2.8		6.6 ± 3.0		3.7 ± 2.2		5.6 ± 2.9	
•Min, max	5.7, 14.3		3.1, 15.2		2.0, 16.0		0.5, 11.3		1.0, 10.8	
EOA	N_d = 13		N_d = 22		N_d = 54		N_d = 25		N_d = 16	
•Mean ± SD	1.4 ± 0.3		1.9 ± 0.4		2.3 ± 0.6		2.8 ± 0.8		2.8 ± 0.6	
•Min, max	0.9, 1.8		1.2, 2.9		1.0, 4.1		0.8, 4.2		2.0, 4.1	
Regurgitation	N_d = 16		N_d = 28		N_d = 60		N_d = 30		N_d = 21	
	n	% (n/N_d)	n	% (n/N_d)	n	% (n/N_d)	N	% (n/N_d)	n	% (n/N_d)
•0	4	25.0%	6	21.4%	24	40.0%	12	40.0%	5	23.8%
•1-2+	11	68.8%	21	75.0%	33	55.0%	16	53.3%	15	71.4%
•3+	0	0.0%	0	0.0%	2	3.3%	2	6.7%	1	4.8%
•4+	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
•Not available	1	6.2%	1	3.6%	1	1.7%	0	0.0%	0	0.0%
> 1 Year Postoperation, N_f = 103 (total of 2 yr (66) and 3 yr (37) follow-up)										
Mean Gradient	N_d = 17		N_d = 29		N_d = 61		N_d = 30		N_d = 18	
•Mean ± SD	9.0 ± 3.2		8.1 ± 3.2		6.6 ± 3.1		4.2 ± 2.5		5.5 ± 3.0	
•Min, max	2.2, 14.3		3.5, 16.6		2.0, 14.1		0.8, 12.8		1.0, 10.8	
EOA	N_d = 17		N_d = 29		N_d = 60		N_d = 31		N_d = 18	
•Mean ± SD	1.5 ± 0.2		1.8 ± 0.5		2.3 ± 0.7		2.7 ± 0.8		2.9 ± 0.8	
•Min, max	0.9, 1.9		0.7, 2.9		1.4, 4.7		0.8, 4.2		2.0, 4.3	
Regurgitation	N_d = 20		N_d = 37		N_d = 68		N_d = 36		N_d = 25	
	n	% (n/N_d)	n	% (n/N_d)	n	% (n/N_d)	N	% (n/N_d)	n	% (n/N_d)
•0	5	25.0%	9	24.3%	27	39.7%	17	47.2%	7	28.0%
•1-2+	12	60.0%	25	67.6%	37	54.4%	16	44.4%	17	68.0%
•3+	2	10.0%	0	0.0%	3	4.4%	2	5.6%	1	4.0%
•4+	0	0.0%	0	0.0%	0	0.0%	1	2.8%	0	0.0%
•Not available	1	5.0%	3	8.1%	1	1.5%	0	0.0%	0	0.0%

Effectiveness Outcomes, Mitral Hemodynamic Results[1]

All patients implanted, N = 229,
Cumulative follow-up = 417.9 patient-years

Hemodynamic Parameter	Results by Valve Size					
	25 mm		27/29 mm		31/33 mm	
Early Postoperation (< 30 days), N_f[2] = 216						
Mean Gradient[3]	N_d = 31		N_d = 117		N_d = 59	
•Mean ± SD	4.3 ± 1.3		4.3 ± 1.6		4.5 ± 2.2	
•Min, max	1.7, 7.5		1.2, 10.0		1.0, 11.7	
EOA5	N_d = 25		N_d = 97		N_d = 53	
•Mean ± SD	2.4 ± 0.8		2.2 ± 0.6		2.2 ± 0.8	
•Min, max	0.9, 4.2		1.0, 4.3		0.8, 4.4	
Regurgitation[6]	N_d = 28		N_d = 104		N_d = 56	
	n	% (n/N_d)	N	% (n/N_d)	N	% (n/N_d)
•0	20	71.4%	73	70.2%	40	71.4%
•1-2+	4	14.3%	25	24.0%	16	28.6%
•3+	0	0.0%	0	0.0%	0	0.0%
•4+	0	0.0%	0	0.0%	0	0.0%
•Not available	4	14.3%	6	5.8%	0	0.0%
1 Year Postoperation, N_f = 134						
Mean Gradient	N_d = 18		N_d = 79		N_d = 30	
•Mean ± SD	3.7 ± 2.0		4.4 ± 1.8		4.0 ± 1.5	
•Min, max	1.7, 7.5		1.7, 10.0		2.0, 7.1	
EOA	N_d = 15		N_d = 70		N_d = 28	
•Mean ± SD	2.1 ± 0.6		2.1 ± 0.6		2.1 ± 0.6	
•Min, max	1.2, 3.1		0.9, 4.0		1.4, 4.3	
Regurgitation	N_d = 15		N_d = 66		N_d = 29	
	n	% (n/N_d)	n	% (n/N_d)	N	% (n/N_d)
•0	11	73.3%	53	80.3%	23	79.3%
•1-2+	3	20.0%	11	16.7%	6	20.7%
•3+	1	6.7%	1	1.5%	0	0.0%
•4+	0	0.0%	0	0.0%	0	0.0%
•Not available	0	0.0%	1	1.5%	0	0.0%

Notes:

1. Hemodynamic evaluations were performed using transthoracic echocardiography (TTE) and in some cases, transesophageal echocardiography (TEE). Data does include results from double valve replacement.
2. N_f = number of patients followed (reproduced from Figure 2).
3. Mean gradient represents the pressure drop measured across the valve in mmHg.
4. N_d = number of patients for which hemodynamic data were collected.
5. EOA = effective orifice area measured in cm2.
6. Regurgitation represents the valvular backflow of blood due to normal leakage and perivalvular leakage; 0 = none, 1+ = mild, 2+ = moderate, 3+ = moderate/severe, 4+ = severe.
7. n = number of patients in each category.

Table 10: Preoperative characteristics of test and control groups for high-risk AVR group

Class/test	Test (n=185)	Control (n=190)	*P* value
Valve pathologic findings (etiology)			
Rheumatic	3 (2)	3 (2)	.71
Calcific	121 (65)	130 (68)	.61
Congenital	69 (37)	72 (38)	.93
Endocarditis	8 (4)	5 (3)	.81
Degenerative/Myxomatous	31 (17)	32 (17)	.89
Prosthetic valve			
dysfunction	8 (4)	9 (5)	.79
Valve lesion			.24
Stenosis	95 (51)	97 (51)	
Regurgitation	46 (25)	34 (18)	
Mixed	39 (21)	54 (28)	
NYHA class			.45
I	39 (21)	36 (19)	
II	73 (39)	73 (38)	
III	50 (27)	51 (27)	
IV	7 (4)	16 (8)	
Unknown	16 (9)	14 (7)	
Clinical risk factors			
Atrial fibrillation	3 (2)	11 (6)	.06
Ejection fraction < 30%	9 (5)	7 (4)	.75
Estrogen therapy	4 (2)	2 (1)	.66
Left atrial diameter > 50			
mm	15 (8)	22 (12)	.34
Neurologic events	6 (3)	9 (5)	.63
Spontaneous			
echocardiographic contrasts	0(0)	2 (1)	.46
Ventricular aneurysm	1 (0.5)	1 (0.5)	.46
Abnormal laboratory tests			
AT-III activity	28 (15)	24 (13)	.58
Factor VIII activity	1 (0.5)	1 (0.5)	.46
Factor V Leiden mutation	5 (3)	3 (2)	.71
Protein C activity	9 (5)	9 (5)	.88
Prothrombin mutation	4 (2)	3 (2)	.96
Protein S activity	3 (2)	3 (2)	.68
P2Y12 inhibition	42 (23)	52 (27)	.35
Urine thromboxane	84 (45)	69 (36)	.09

Data presented as n (%). Incidence rates by disease etiology and comparison of test and control groups using a chi-square test of significance (including Yates' correction for continuity for small sample sizes). AVR, Aortic valve replacement; NYHA, New York Heart Association; AT-III, antithrombin III. All p-values are tests of the proportions except the valve lesion and NYHA class distributions which are chi-square tests of the distributions.

Table 11: Post-Randomization Linearized Late Adverse Event Rates For High-Risk AVR Group

Event	Control (pt-yr=878.6) (INR 2.0 – 3.0)		Test (pt-yr=766.2) (INR 1.5 – 2.0)	
	N	Rate (%/pt-yr)	N	Rate (%/ pt-yr)
Major Bleed	34	3.87	12	1.57
Cerebral Bleed	4	0.46	1	0.13
Minor Bleed	35	3.98	9	1.17
Total Bleed	*69*	*7.85*	*21*	*2.74*
Ischemic Stroke	7	0.80	6	0.78
TIA	7	0.80	11	1.44
Neurologic Event TE	*14*	*1.59*	*17*	*2.22*
Peripheral TE	1	0.11	4	0.52
Total TE	*15*	*1.70*	*21*	*2.74*
Valve Thrombosis	2	0.23	2	0.26
Major Bleed, TE, and Valve Thrombosis	*51*	*5.80*	*35*	*4.57*
Composite Primary Endpoint	*86*	*9.79*	*44*	*5.74*
Sudden Death	3	0.34	3	0.39
Valve-Related Death	3	0.34	2	0.26
Total Mortality	16	1.82	12	1.57

TE = Thromboembolism; Composite Primary Endpoint = Composite of Total Bleed, Neurologic Event TE, Peripheral TE, and Valve Thrombosis

Table 12: Non-Inferiority Analyses

Complications from Categories	Event Count Control	Rate (%/pt-yr)	Event Count Treatment	Rate (%/pt-yr)	Difference (Treatment-Control)	95% CI of Difference [1]	Non Inferiority Indicator (1.5% MI) [2]
Total Patient-Years	878.6		766.2				
Composite Primary Endpoint	86	9.79	44	5.74	-4.05	-6.77- -1.32	Non-Inferior
Major Bleed, TE, Valve Thrombosis	51	5.80	35	4.57	-1.23	-3.45 -0.98	Non-Inferior

Composite Primary Endpoint = Composite of Total Bleed, Neurologic Event TE, Peripheral TE, and Valve Thrombosis; TE = Thromboembolism; CI = Confidence Interval; MI = Margin of Inferiority [1] CI values are calculated using Poisson distribution, test. [2] Non-Inferiority is calculated under the null hypothesis of Treatment Rate - Control ≤1.5%. Consistent with the March 2010 FDA Guidance, non-inferiority is concluded if the upper bound of the two-sided confidence interval is less than 1.5%

Table 13: Objective Performance Criteria Analyses for Treatment Group

Complications from Categories	Event Count	Rate (%/pt-yr)	One-Sided Upper Limit of 95% CI	FDA OPC Rate (2* OPC Rate)	P-Value [1]
Total Patient-Years	766.2				
Thromboembolism	21	2.74	3.92	3.0 (6.0)	<0.001
Valve Thrombosis	2	0.26	0.84	0.8 (1.6)	0.005
Major or Minor Bleed	21	2.74	3.92	3.5 (7.0)	<0.001
Major Bleed	12	1.57	2.52	1.5 (3.0)	0.012

CI = Confidence Interval

[1] CI values are calculated using Poisson distribution the Poisson regression with an offset log total follow-up time. P-values represent tests on the null hypothesis of Treatment Rate ≥ 2X FDA OPC Rate using 1993 values.

Table 14: Definitions

EC REP	AUTHORISED REPRESENTATIVE IN THE EUROPEAN COMMUNITY		DO NOT USE IF PACKAGE IS DAMAGED
	MANUFACTURER	2	DO NOT REUSE
	CONSULT INSTRUCTIONS FOR USE		USE BY
WWW.ONXLTI.COM/IFU/HV	CONSULT INSTRUCTIONS FOR USE	SN	SERIAL NUMBER
REF	CATALOGUE NUMBER		DATE OF MANUFACTURE
STERILE	STERILIZED USING STEAM	2 STERILIZE	DO NOT RESTERILIZE
MR	MR CONDITIONAL		

On-X Life Technologies, Inc.
1300 East Anderson Lane, Bldg. B Austin, Texas 78752 U.S.A.
TEL: (512) 339-8000 FAX: (512) 339-3636
WEB: www.onxlti.com EMAIL: onx@onxlti.com

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