PERCEVAL
SUTURELESS AORTIC HEART VALVE
Instructions for Use

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

SYMBOLS

	CAUTION: SEE MANUAL FOR INSTRUCTIONS/WARNINGS
	CONTENTS STERILIZED USING ASEPTIC PROCESSING TECHNIQUE
	USE BY
	STORE BETWEEN 5°C AND 25°C
	SINGLE USE ONLY
	DO NOT RESTERILIZE
	CATALOGUE NUMBER
	SERIAL NUMBER
	SIZE
	MANUFACTURER
	QUANTITY INCLUDED IN PACKAGE
	DO NOT USE IF PACKAGE IS DAMAGED
	THIS WAY UP
	MR CONDITIONAL

1. DESCRIPTION

Perceval is a bioprosthetic valve designed to replace a diseased native or a malfunctioning prosthetic aortic valve via open heart surgery, with the unique characteristic of allowing sutureless positioning and anchoring at the implant site.

The choice of materials and configuration ensures the device biocompatibility and hemocompatibility.

The Perceval prosthesis consists of a tissue component made from bovine pericardium and a self-expandable Nitinol stent, which has the dual role of supporting the valve and fixing it in place.

Perceval tissue heart valve is supplied unmounted. Prior to implantation the prosthesis diameter is reduced to a suitable size for loading it on the holder. The valve is then positioned and released in the aortic root, where the stent design and its ability to apply a radial force to the annulus allow stable anchoring of the device.

2. AVAILABLE MODELS

The Perceval aortic model is available in four sizes: size S, size M, size L, and size XL. The prosthesis height is 31.0, 33.0, 35.5, and 37.5 mm, respectively. Each size is suitable for a range of aortic annuli and sinotubular junction (STJ) diameters. The characteristics of the patients aortic root anatomy for each size are described in the table below.

REF	SIZE	**AORTIC ANNULUS DIAMETER [A]** (mm)	**SINOTUBULAR JUNCTION DIAMETER [≤ 1.3 A]** (mm)
PVS21	S	19-21	≤ 24.7-27.3
PVS23	M	21-23	≤ 27.3-29.9
PVS25	L	23-25	≤ 29.9-32.5
PVS27	XL	25-27	≤ 32.5-35.1

Table 1: Patient anatomical characteristics

Each prosthesis is identified by a catalog number and a serial number. The catalog number consists of three letters (PVS) and two digits.

3. PACKAGING

The Perceval prosthesis is preserved in a buffered aldehyde-free sterile solution. Each is packaged individually in its own container.

A plastic tag with the prosthesis identification data is attached to the device. The prosthesis is mounted on a support that holds it into the jar.

The container is externally sealed with a transparent film, which should be removed just before preparing the prosthesis for implantation.

WARNING: The external surface of the container is not sterile and therefore must not come into contact with sterile instruments.

The container holding the prosthesis is packaged in a cube of insulating material to protect the device against temperature variations. Temperature indicators are also included in the package to monitor temperature exposure during transfer.

WARNING: Indicators are for transit only. They are not intended for monitoring temperatures during the shelf life of the product.

Remove the cube of insulating material and inspect each indicator immediately upon receipt. **Do not use the valve if either indicator has been activated.**

4. STORAGE

The Perceval prosthesis must be stored in an upright position at a temperature between +5°C and +25°C (41°F and 77°F). The lower limit is especially important because at temperatures near 0°C (32°F) the preserving solution will start to freeze, thus causing irreversible damage to the biological tissue.

Nevertheless, the device should be stored at a low temperature range, while remaining within the limits stated. If storeroom conditions do not allow for correct control of the temperature upper limit, the device must be kept refrigerated but never below +5°C (41°F). Avoid extreme changes in temperature.

Avoid exposure to heating or air conditioning units.

5. EXPIRATION DATE

The expiration date of the prosthesis is printed on the package label (Use By date).

Stock inspection and rotation at regular intervals are recommended to ensure that the valves are used before expiring.

6. STERILITY

The Perceval prosthesis is sterile if its packaging is sealed and undamaged. The external surface of the container is not sterile and therefore must not come into contact with sterile instruments.

WARNING: Valves removed from their container but not implanted are no longer sterile and must not be used. THE PROSTHESIS CANNOT BE RESTERILIZED. DO NOT USE THE VALVE IF ITS CONTAINER HAS BEEN OPENED OR DAMAGED.

7. ACCESSORIES AND MATERIALS FOR DEVICE PREPARATION AND IMPLANTATION

The accessories for implanting the Perceval prosthesis are:

- **Sizers**, designed to assist the physician in choosing the correct size of prosthesis.
- **Dual Holder**, indicated for the in situ positioning and deployment of the prosthesis. It is available in two models: one for sternal approaches (Dual Holder) and one specifically indicated for Minimally Invasive Cardiac Surgery (including minithoracotomy) (Dual MICS Holder).
- **Smart Clip**, mounted on Dual Holder/Dual MICS Holder, is intended to assist during assembly of the Perceval valve on the Dual Holder/Dual MICS Holder and to prevent its accidental release during in situ positioning and release of the prosthesis.
- **Dual Collapser**, designed to evenly reduce the diameter of the prosthesis thus allowing its mounting on the holder prior to implantation.
- **Dual Collapser base**, designed to allow proper positioning of the Dual Collapser and Dual holder (or Dual MICS Holder) thus simplifying the prosthesis preparation procedure.
- **Postdilation catheter**, a balloon catheter indicated for in situ dilation of the prosthesis after implantation. It is available in two models: one for sternal approaches (Postdilation catheter) and one specifically indicated for Minimally Invasive Cardiac Surgery (including minithoracotomy) (MICS Postdilation catheter).

  WARNING: Read the Instructions for Use enclosed in the packaging of the accessories.

	PVS21	PVS23	PVS25	PVS27
Sizers	ICV1219			
Dual Collapser	ICV1235		ICV1236	
Dual Collapser Base	ICV1232			
Dual Holder[(1)]	ICV1242		ICV1243	
Dual MICS Holder[(2)]	ICV1244		ICV1245	
Smart Clip	ICV1268			
Postdilation catheter[(1)]	ICV1148	ICV1149	ICV1170	ICV1234
MICS Postdilation Catheter[(2)]	ICV1216	ICV1217	ICV1218	ICV1241

(1) Indicated for sternal approaches

(2) Specifically indicated for Minimally Invasive Cardiac Surgery (including minithoracotomy)

Table 2: Perceval accessories

NOTE: The Perceval single-use accessories (Dual Collapser, Dual Holder/Dual MICS Holder with Smart Clip, Postdilation Catheter/MICS Postdilation Catheter) are also supplied as accessory kits (refer to **Table 16**).

Additional equipment/materials required for prosthesis preparation and implantation are:

- 1 sterile field for valve preparation
- 2 sterile bowls
- 2 bottles of sterile saline solution, one at room temperature, one at body temperature (37°C or 98.6°F)
- scissors
- 50 ml sterile Luer Lock syringe
- sterile inflation device (manometric syringe)
- atraumatic plastic forceps
- ruler (for aortotomy height measuring)
- scalpel

8. INDICATIONS FOR USE

The Perceval bioprosthesis is indicated for the replacement of diseased, damaged, or malfunctioning native or prosthetic aortic valves.

9. CONTRAINDICATIONS

Use of the Perceval prosthesis is contraindicated in the following cases:

1. Aneurysmal dilation or dissection of the ascending aortic wall;
2. Known hypersensitivity to nickel or cobalt alloys;
3. Anatomical characteristics outside the specification given in **Table 1**.

WARNING: It is strongly recommended that the Perceval valve not be used in children, adolescents, or young adults, in patients with chronic renal impairment or calcium metabolism disorders, or in patients receiving chronic drug treatment with preparations containing calcium, due to the increased risk of accelerated valve tissue calcification with such use.

10. POTENTIAL ADVERSE EVENTS

The risks or potential adverse events (in alphabetical order) associated with cardiac valve replacement with a bioprosthesis include, but may not be limited to: angina, cardiac arrhythmia, cardiac tamponade, endocarditis, heart failure (acute cardiac failure), hemolysis, hemolytic anemia, hemorrhage (bleeding), infection other than endocarditis, myocardial infarction, nonstructural valve dysfunction (entrapment by pannus or suture, inappropriate sizing or positioning, or other), pericardial effusion, paravalvular leak, prosthesis transvalvular regurgitation, prosthesis stenosis, prosthesis thrombosis, stroke or any related neurologic disorders, structural valve deterioration (SVD) (calcification, leaflet tear or perforation, or other), thromboembolism, tissue dehiscence, or stent distortion due to thoracic compression (i.e., from cardiopulmonary resuscitation) or trauma.

The previously mentioned adverse events and other adverse events may arise in response to the individual patient reactions to the implanted prosthesis.

Other potential adverse events may include, but not be limited to, dislodgment or migration of the prosthesis, or new or worsened conduction system disturbances (e.g., atrioventricular block, left bundle branch block, or asystole) which may require a permanent cardiac pacemaker implant.

It is possible that these adverse events may lead to death, permanent disability, reoperation, explantation, or other forms of re-interventions.

11. DIRECTIONS FOR USE

Personnel training

Perceval implantation shall be performed only by physician and associated staff trained on Perceval preparation and implantation technique. An “Inservice Guide” with a detailed and illustrated description of the valve preparation and implantation steps is provided as training material.

Implant site preparation

The device implant is performed under surgery using an access allowing exposure of the aortic valve (i.e., median sternotomy, upper ministernotomy, or right minithoracotomy). The choice of the surgical approach is left to the surgeon according to his or her practice and selection criteria. Appropriate accessories are to be used according to the surgical approach chosen.

1. Expose the aortic valve via transverse aortotomy.

WARNING: Oblique aortotomy is not recommended since release of the device at the implant might result in aortotomy suture difficulties.

2. Perform the aortic incision distal to the sinotubular junction, to preserve a segment of ascending aorta above the upper limit of the prosthetic valve. A transverse aortotomy located at least 3.5 cm above the aortic annulus or at least 0.5 cm above the sinotubular junction is considered optimal (a ruler is helpful). The incision point is typically at the level of the pericardial reflection. In any case, make sure the length of the prosthesis does not extend beyond the aortotomy and that a small rim is still available for the aorta closure. Aortotomy extension depends on the surgeon’s preference; it is not recommended to overextend the incision.

3. Remove the native leaflets and calcium residues in order to regularize the annulus profile. If replacing a previous implant, remove it taking care to avoid damage to the aortic wall.

WARNING: Complete intra-annular decalcification of the annulus is not necessary, but eccentric/bulky protruding intra-luminal calcifications must be removed.

Sizing procedure and prosthesis selection

Check via preoperative echo that patient anatomical characteristics are within specifications given in **Table 1**.

WARNING: Check that at the preoperative echo the ratio between the sinotubular junction and the annulus diameter is ≤ 1.3. A ratio greater than 1.3 indicates a condition of aortic root dilation for which Perceval implant is contraindicated.

Prior to implant, use the supplied sizers (in Fig. 1a there is an example for size M) to determine the best suited prosthesis size.

Each sizer has a transparent obturator identified with a tick symbol (✓) and a white obturator identified with a cross symbol (**×**). When the transparent obturator (✓) passes through the annulus and the white obturator (**×**) does not, the valve size identified on the sizer handle must be chosen (see **Table 3** and **Figures 1b** and **1c**).

Sizer	Obturator	Sizing outcome	Valve size
Sizer S	(✓) - transparent	DOESN’T PASS through	**No** Perceval valve
	(✓) - transparent	PASSES through	Perceval **size S**
	(**×**) - white	DOESN’T PASS through	
Sizer M	(✓) - transparent	PASSES through	Perceval **size M**
	(**×**) - white	DOESN’T PASS through	
Sizer L	(✓) - transparent	PASSES through	Perceval **size L**
	(**×**) - white	DOESN’T PASS through	
Sizer XL	(✓) - transparent	PASSES through	Perceval **size XL**
	(**×**) - white	DOESN’T PASS through	
	(**×**) - white	PASSES through	**No** Perceval valve

Table 3: Sizing Specifications

WARNING: Use only the sizers supplied with the prosthesis. The use of any other instrument may invalidate the correct prosthesis sizing and function.

WARNING: Do not under or oversize the prosthesis. This could result in possible migration, excessive compression/rupture of the aorta, or stent folding that may lead to fatal arrhythmia or hemorrhage, regurgitation, or altered hemodynamics.

WARNING: Ensure that the sizers are measuring the aortic annulus and not the Left Ventricular Outflow Tract (LVOT).

Prosthesis preparation

The valve and preserving solution are sterile and do not require further treatment.

Examine the valve container for integrity. Check that the transparent seal is preserved and that the container has not been opened, since this would result in a loss of sterility. If there is any evidence of leakage of the solution, either as visible liquid or dried residual salts, do not implant the valve.

WARNING: Check the “Use by” date on the labels. Do not use the valve after the date printed on the packaging.

After having examined the package, tear off the transparent film and open the container by unscrewing the cover.

Simplified procedure before implant

The prosthesis does not contain free glutaraldehyde, so it is not necessary to rinse the valve three times before implantation.

The following procedure is suggested to keep the valve moist and assist the aseptic handling:

- prepare a bowl containing sterile saline solution at room temperature and place the valve into the bowl during the procedure;
- remove the valve from the container, cut the green suture, and remove the holding collar (Fig. 2a);
- remove the identification tag attached to the prosthesis;
- **to free the prosthesis from the holding support simply cut the suture at the three points marked in Fig.2b. The device is now ready to be mounted on the holder.**

Before implanting the valve check that the identification data on each label and tags match. Do not implant the valve if data do not match.

Prosthesis mounting on the Holder

1. A Dual Collapser of size consistent with the size of the selected prosthesis must be chosen (see **Table 2**).
2. Mount the Dual Collapser (Fig. 3a) on its base and fix it (Fig. 3b). Place the lever in the open position.
3. A Dual Holder model indicated for the selected surgical approach of size consistent with that of the prosthesis must be chosen (see **Table 2**) and prepared according to the Instructions for Use given with the device.
4. Prepare the holder by rotating the control button clockwise (opened-lock arrow) and sliding the sheath back.
5. Fix the holder to the base by aligning the groove on the handle with the notch on the support. IMPORTANT: The holder must be positioned so that its logo points upwards.
6. Holding the valve from the inflow portion (pericardium), align it (suture line on the inflow ring must be above) to the Dual Collapser and insert it (Fig. 4) in the collapsing area.

   WARNING: Check valve leaflets while pushing to make sure they allow holder tip crossing.

   When correctly loaded the valve is firmly held in place (axial and rotational displacement are prevented) and valve straight struts are aligned to holder angular markers.
7. Collapse the valve by turning the lever of the Dual Collapser.

   WARNING: Check that the struts are evenly collapsed and their elements are not overlapped.
8. Still securing the holder in place, push the sliding sheath forward, and position the Smart Clip between the sheath and the handle of the holder as indicated in Figure 5, slightly pressing the Smart Clip itself, until the Smart Clip is completely inserted in the slot; the Smart Clip will automatically push forward the sheath, that will partially cover and grip the collapsed outflow ring. Keep the lever in closed position.
9. Turn the knob counterclockwise (closed-lock arrow) until it stops, paying attention not to dislodge the holder, thus allowing the inflow cap to grip the inflow ring maintaining it in a collapsed position (Fig.6) .
10. By turning the lever in the open position release the Dual Collapser (Fig.7); the Smart Clip will automatically push forward the sheath that will completely cover the outflow ring of the prosthesis.

    WARNING: Pay attention not to accidentally remove the Smart clip.

    WARNING: An incomplete grip on the prosthesis may cause expulsion of the prosthesis. Never collapse the valve more than twice.

    WARNING: Do not press the Smart Clip more than twice.

11. A prosthesis correctly mounted on the holder is shown in Figure 8. Before implant the collapsed prosthesis should be kept in warm sterile saline solution.

Positioning and release of the prosthesis

For the positioning and release of the prosthesis proceed as follows:

- position a suture thread (preferably mono-ply 3/0, twin needle) in each valve sinus, 2-3 mm under the leaflet hinge point, perpendicular to the annulus; start from the leaflet corresponding to the left ostium and proceed placing the next two stitches so that at the end of the procedure they are approximately 120° equidistant. The LVOT extremity of each guiding suture must be positioned 2-3 mm under the leaflet hinge point. The aortic extremity of each guiding suture must be positioned 2-3 mm above the leaflet hinge point. At each step, once the guiding suture has been passed, cut off the needle of the extra luminal thread, and secure both threads with a clamp.

WARNING: Should there be a hypoplastic coronary ostium, the first guide thread should be positioned in the corresponding sinus.

WARNING: Should there be any traction suture, these must be released prior to valve deployment.

- Take the holder in the left hand with the Smart Clip on top. Pass each thread through one of the eyelets on the prosthesis inflow ring. It is recommended to start from the posterior eyelet first (left coronary leaflet), then the one corresponding to the right coronary and lastly through the non-coronary one. Check with the forceps that the guiding sutures are not trapped within the valve struts, taking care not to touch the struts during this operation.
- Keeping the three guiding sutures straight with a gentle pull (maintaining alignment with respect to the aorta), parachute the holder containing the valve into the aorta sliding on the threads until it is stopped at the insertion point of the threads themselves;

WARNING: Check that the commissural struts are correctly aligned with the native commissures.

- Proceed to release the inflow section: without moving the dual holder or releasing the sutures, rotate the holder control button clockwise (opened-lock arrow) until you hear a click and also “feel” the valve inflow ring being released;
- Ensure that the sinusoidal struts of the prosthesis correspond with the sinuses of Valsalva and that the metallic stent does not obstruct the coronary ostia;
- Proceed to release the outflow section: remove the Smart Clip and then withdraw the sliding sheath of the Holder, avoiding rotational movements and taking care to keep the Holder in an axial position with respect to the aorta;
- Remove the Holder gently ensuring it does not catch or distort the valve as it is removed:

WARNING: Check visually for the following: coronary ostia patency, proper valve alignment, no paravalvular leaks, leaflet coaptation (note that the presence of a limited spacing between the leaflet is intrinsic to the valve design, provided that it is symmetrical and limited in extension), no visible annulus below and above the valve inflow ring and well-developed anterior mitral leaflet.

WARNING: Check visually that sinusoidal struts are juxtaposed at the Valsalva sinuses. Full apposition of the outflow ring to the aortic wall at the level of the STJ is not required. Post-dilation of the outflow ring is not recommended.

Postdilation

A postdilation of the inflow ring is to be carried out after the total deployment of the prosthesis. A postdilation catheter model indicated for the selected surgical approach of size consistent with that of the prosthesis must be chosen (see **Table 2**) and prepared according to the Instructions for Use given with the device.

The deflated postdilation catheter must be carefully inserted across the prosthesis avoiding any interference with the prosthetic metallic and biological components. Once the blue positioning marker present on the proximal side of the balloon is located at the level of the free edges of the prosthetic cusps, the balloon can be inflated at the required pressure (4 atm) for 30 seconds. Warm sterile saline (at +37°C or 98.6°F) must then be poured within the aortic root, as the balloon is inflated, to ensure the optimal valve sealing and optimized anchoring. During the balloon dilation, the catheter must be kept absolutely steady, in order to avoid any misplacement or damage to the prosthesis. As the balloon is deflated, the catheter can be removed from the operative field.

WARNING: IF DURING OR AFTER PROSTHESIS RELEASE THERE IS ANY SIGN OF POOR SEATING THAT COULD IMPAIR PROPER VALVE FUNCTIONING, REMOVE THE PROSTHESIS FOLLOWING THE INSTRUCTIONS GIVEN UNDER “PROSTHESIS REMOVAL PROCEDURE”.

Probing and prosthesis position verification

Verify that the prosthesis is well-anchored to the aortic root and that there is no lack of contact between the prosthesis and aortic annulus, potentially responsible for para-prosthetic leaks. Aortic root filling may be done at the physician’s discretion (hydraulic testing). Remove the guiding sutures. To remove the guiding sutures they must be cut right above the level of the aortotomy. The guiding sutures must not be tied.

WARNING: Avoid touching the prosthesis with any sharp or cutting surgical instruments, because it could impair the prosthesis integrity.

Implant site closure

Close the aortotomy ensuring the outflow ring of the stent is not captured with the suture.

Confirm hemostasis and valve integrity with TEE prior to surgical access closure.

Prosthesis removal procedure

If it should prove necessary to remove the prosthesis from the implant site, proceed as follows:

- Introduce crushed ice obtained from sterile physiological solution in the surgical area, ensuring that the ice comes into contact with the prosthesis;
- Wet the prosthesis with iced physiological solution and at the same time clamp the outflow section of the prosthesis with three surgical forceps positioned at around 120°;
- Acting on the forceps, encourage radial compression of the prosthesis in order to reduce its diameter;
- After detachment of the prosthesis from the aortic wall, extract the forceps and prosthesis as if they were a single device, taking care not to damage the surrounding tissue.

WARNING: A removed Perceval prosthesis MUST NOT BE RE-IMPLANTED, because its integrity is no longer assured.

Post-operation management

Some medical professional societies recommend anticoagulant therapy, unless contraindicated, during the first 3 months after bioprosthetic aortic valve implantation. Such postoperative anticoagulant therapy should be determined on an individual basis.

Long-term low dose aspirin, unless contraindicated, is recommended for all patients with bioprosthetic valves. Long-term anticoagulant therapy, unless contraindicated, is recommended for all patients with bioprosthetic valves who have risk factors for thromboembolism.

It is recommended that prophylactic antibiotic therapy be given to patients undergoing dental or other procedures which are potentially bacteremic in order to minimize the risk of endocarditis.

All recipients of bioprosthetic heart valves should be advised to receive follow-up medical evaluation on a regular basis to assess valve performance. The frequency of the follow-up evaluation should follow general guidelines (e.g., AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease), hospital-specific guidelines, and individual surgeon/cardiologist practices. Decisions regarding the frequency and type of follow-up should also consider specific patient factors that might lead to an increased risk of accelerated calcification and structural valve deterioration (see Specific Patient Populations).

12. PRECAUTIONS

- In case of elongated, pear-shaped aortic root Perceval implantation should be avoided if aortic root height (distance from annulus to sinotubular junction) is greater than 21, 22.5, 24, and 25 mm for prosthesis size S, M, L, and XL respectively.
- Data from clinical or in vitro testing are not available to establish the safe use of the Perceval valve in patients with congenital bicuspid aortic valve. Therefore, careful consideration of its use is recommended in such cases, especially when the depth of the 2 sinuses in the LVOT is unequal.
- Data from clinical or in vitro testing are not sufficient to establish the safe use of the Perceval valve in patients with pure aortic insufficiency. The use of the Perceval valve in these cases is not recommended.
- Data from clinical or in vitro testing are not available to establish the safe use of the Perceval valve in patients with a valve prosthesis or annuloplasty ring in the mitral, pulmonic, or tricuspid position. Therefore, careful consideration of its use is recommended in such cases.
- In case of concomitant procedures these must be performed as much as possible prior to Perceval implantation.
- After Perceval implantation, manipulation of the heart and/or of the ascending aorta, if required, should be done gently; should an atrial retractor be placed, take care not to compress the ascending aorta. These maneuvers may lead to unknown effects on the implanted valve, including displacement and folding.
- Patients with an implanted Perceval valve may experience valve deformation when emergency cardiovascular procedures, such as cardiopulmonary resuscitation (CPR), are administered post-implant. In such cases, an echocardiographic exam post-procedure is recommended, in order to verify the preserved position and function of the valve.
- The Perceval prosthesis is designed for single use only.
- Valves from containers found to be damaged or opened must not be used for implantation.
- Valves removed from their container and not implanted should be considered no longer sterile and must not be used for implantation.
- The Perceval prosthesis should not come into contact with linen, gauze, or any material that may give off lint or fibers that could adhere to the valve and cause embolism or adverse reactions with the blood.
- When handling the valve follow indications provided under “Prosthesis Preparation”; be careful not to touch the tissue leaflet or deform unevenly the prosthesis.
- Avoid using sharp or cutting surgical instruments that could damage the integrity of the prosthesis.
- Do not add drugs, chemical substances, antibiotics, or anything else to the storage or rinsing solutions. Foreign substances may cause damage to the tissue.
- Keep the prosthesis moist. If allowed to dry, even partially or briefly, the tissue will be irreversibly damaged. For this reason, both sides of the prosthesis must be irrigated with physiological solution every two minutes during implantation.
- Use only sterile procedures to handle the Perceval prosthesis. The storage solution is not adequate for resterilizing a contaminated valve.
- Store the valve in an upright position at temperatures between +5°C and +25°C (41°F and 77°F). Avoid freezing. Valves exposed to temperatures below +5°C (41°F) must not be used for implantation.
- Do not try to resterilize the valve or its container using gas, steam, or irradiation procedures.
- Use only the supplied sizers (**Table 2**) to determine the appropriate valve size. The use of other sizers could result in over or undersizing leading to serious malfunction of the prosthesis.
- Use only accessories listed in **Table 2** to prepare and release the prosthesis. The use of other accessories could result in failure to implant and impair the prosthesis integrity.
- Surgery training is mandatory for the correct prosthesis positioning and implant.

13. SUMMARY OF PRIMARY CLINICAL STUDIES

The safety and performance of the Perceval prosthesis has been investigated in three clinical studies:

- the Perceval Pilot Trial (V10601);
- the Perceval Pivotal Trial (V10801); and
- the Perceval CAVALIER Trial (TPS001).

The Pilot trial (V10601) was aimed at demonstrating the 30-days safety of the Perceval valve in 30 subjects aged 75 years or older, with NYHA class III and IV and Logistic EuroSCORE > 5%, without aortic dilatation, requiring aortic valve replacement due to stenosis or steno-insufficiency. This prospective and non-randomized study was conducted at 3 European investigational centers. The first patient was enrolled on April 24, 2007, and the last patient on February 8, 2008. Clinical and echocardiographic examinations were carried out at 1, 3, 6, and 12 months after surgery and then annually until 5 years post implant. The primary endpoint was the assessment of the safety of the Perceval prosthesis in terms of mortality and morbidity at 30 days correlated to prosthetic valve performance, while the secondary endpoints were the evaluation of mortality and morbidity indexes at 3, 6, and 12 months, the evaluation of the clinical status according to the New York Heart Association (NYHA) functional classification, and the evaluation of the hemodynamic performance through echocardiography examination at 30 days and at 3, 6, and 12 months from implantation.

The outcome of this first clinical experience suggested an extremely secure valve positioning (all prostheses were easily deployed and successfully implanted) with no problems of diminished blood flow to the coronary ostia. In addition, the incidence of paravalvular leakage was minimal. In 46.7% of the cases simultaneous coronary artery bypass grafting (CABG surgery) was performed without adding any risk to the patients. The aortic cross-clamp time, as well as the cardiopulmonary bypass time(pump time), was significantly reduced when compared to historical controls both for isolated and complex AVR procedures.

Based on the Pilot trial results, Sorin designed a Pivotal trial (V10801), aimed at confirming the safety and performance results of the first trial in a larger patient population. In particular, the target patient population of the Pivotal trial included subjects aged 75 years or older, with NYHA class III and IV, Logistic EuroSCORE > 5%, without aortic dilatation (same criteria as for the Pilot study). In this trial, 150 patients were enrolled in 9 European investigational centers. The first patient was enrolled on January 9, 2009 and the last one on January 19, 2010. The clinical and echocardiographic follow-up was planned at discharge (or at 30 days, if the patient was still hospitalized), at 3-6 months, and 12 months after surgery and then annually until 5 years post implant. The primary endpoint was the evaluation of the safety and the performance (in terms of improvement of clinical status and hemodynamic performance) of the Perceval prosthesis at 3-6 months after implant. The secondary endpoints were the assessment of mortality and morbidity rates and of the performance at discharge (or at 30 days, if the patient was still hospitalized) and 12 months after implant.

On the basis of the Pilot study results and interim results of the Pivotal study, Sorin planned the CAVALIER Trial (TPS001) designed to evaluate the safety and effectiveness of the Perceval valve with extended indications in terms of age (≥ 65 years) and valve sizes S (PVS21), M (PVS23), L(PVS25), and XL (PVS27).

CAVALIER STUDY DESIGN

The CAVALIER study was a prospective, non-randomized, multicenter trial of the Perceval heart valve implanted in patients requiring native or prosthetic aortic valve replacement. Out of 26 European sites that were initiated, 25 sites contributed patients for the analysis, whereas one site did not contribute to the implanted populations and was discontinued. All sites in the study followed a common protocol including patient selection and inclusion/exclusion criteria, and obtained an informed consent.

Adverse Event (AE) rates as compared to a set of Objective Performance Criteria (OPC) and to literature-based control data were used for the design and analysis of this study. NYHA functional classification status and hemodynamic performance of the valve by echocardiography were evaluated using a comparison to literature-based control data.

STUDY INCLUSION CRITERIA

Patients considered for enrollment in the study were those patients who met the following inclusion criteria:

1. Patients of age ≥ 65 years;
2. Patients with aortic valve stenosis or steno-insufficiency;
3. Patients in which a preoperative evaluation indicated the need for native or prosthetic aortic valve replacement with a biological prosthesis;
4. Patients willing to sign the informed consent;
5. Patients willing to undergo all the medical follow-ups and echocardiography examinations and laboratory tests in the study protocol.

STUDY EXCLUSION CRITERIA

Subjects were not enrolled in the study if any of the exclusion criteria listed below was met:

1. Patients involved in any other clinical study for drugs or devices;
2. Patients with a previously implanted Perceval prosthesis, within the clinical study, that required replacement;
3. Patients with previous implantation of valve prostheses or annuloplasty ring not being replaced by the study valve;
4. Patients that required simultaneous cardiac procedures, apart from septal myectomy and/or coronary bypass;

5. Patients who required double or multiple valve replacement or repair in whom the mitral, tricuspid, or pulmonic valve would be replaced with a non-Perceval valve or repaired;
6. Patients with aneurysmal dilation or dissection of the ascending aortic wall;
7. Patients needing non-elective intervention;
8. Patients with active endocarditis;
9. Patients with active myocarditis;
10. Patients with congenital bicuspid aortic valve;
11. Patients with aortic root enlargement, where the ratio between the diameter of the sino-tubular junction and the annulus diameter, assessed by TTE, is > 1.3;
12. Patients with an aortic root height (measured from aortic annulus to sino-tubular junction) ≥ 21 mm for size S/21, ≥ 22.5 mm for size M/23, ≥ 24 mm for size L, and ≥ 25 mm for size XL/27;
13. Patient with myocardial infarction ≤ 90 days before the planned valve implant surgery;
14. Patients with known hypersensitivity to nickel alloys;
15. Patients with a documented history of substance (drug or alcohol) abuse;
16. Patients who were a prison inmate, institutionalized, or unable to give informed consent;
17. Patients with a major or progressive non-cardiac disease that, in the investigator's experience, results in a life expectancy of less than 12 months, or in whom the implant of the device would create an unacceptable risk to the patient;
18. Patients undergoing renal dialysis for chronic renal failure or suffering from hyperparathyroidism;
19. Patients with an acute preoperative neurological deficit, myocardial infarction, or cardiac event that had not returned to baseline or stabilized ≥ 30 days prior to the planned valve implant surgery.

FOLLOW-UP SCHEDULE

Subjects were evaluated at each of the following time intervals:

- Preoperatively;
- at implant;
- in the early postoperative period (at hospital discharge or within 30 days postoperatively);
- in the late postoperative period (between 3 and 6 months postoperatively);
- at 12 months (between 11 and 13 months postoperatively); and
- annually until study completion (i.e., 5 years).

Preoperative demographic and baseline data including NHYA functional classification were collected before surgery. Postoperative data, including blood values, NYHA functional class, and echocardiography data were collected at each follow-up. All echoes were sent to the Echocardiography Core Laboratory for interpretation. Adverse event data were collected at the time of occurrence or site notification using the definitions from the "*Guidelines for Reporting Morbidity and Mortality after Cardiac Valve Interventions*" approved by the Council of the Society of Thoracic Surgery and published in 2008[1].

CLINICAL ENDPOINT

The objectives of this clinical investigation were to demonstrate:

1) the complication and survival rates for the Perceval valve are comparable to appropriate historical controls manifested as Objective Performance Criteria (OPCs), and to that reported in the literature for other stentless and stented bioprostheses;
2) the hemodynamic performance of the Perceval valve is comparable to that reported in the literature for other stentless and stented bioprostheses; and
3) clinically significant improvement in overall patient condition by comparison of preoperative and postoperative NYHA functional classifications.

ACCOUNTABILITY OF PMA COHORT

The CAVALIER study cohort consisted of 658 patients with aortic valve replacement, for which the Perceval implantation was performed or attempted from February 23, 2010, through September 30, 2013. The cut-off for data included in this report was November 5, 2014. Database was prepared based on the snapshot and locked on December 5, 2014.

Among the 658 attempted patients, there were:

- 30 patients who experienced failure to implant
- 628 implanted patients who were followed from the implantation (early exposed patients)
- 599 implanted patients who were followed from the 31th day after implantation (late exposed patients) (with 1444.44 late patient-years of cumulative follow-up)

[1]Akins CW. et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg 2008;135:732-8

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The mean follow-up was 829.7 ± 453.9 days (2.3 ± 1.2 years), with range 0 to 1,624 days (0 to 4.4 years). The total cumulative follow-up for the 628 implanted patients was 1494.77 patient-years.

Table 4 summarizes the study compliance.

Table 4: Study Compliance

Visit interval	**Possible N (100%)**	**Clinical visit or phone call n (%)**	**Clinical visit n (%)**	**Phone call n (%)**	**Missed n (%)**
Preoperative	658 (100.0%)	658 (100.0%)	658 (100.0%)	-	-
Discharge (or 30 days)	615 (100.0%)	614 (99.8%)	614 (99.8%)	-	1 (0.2%)
3-6 Months	580 (100.0%)	541 (93.3%)	512 (88.3%)	29 (5.0%)	39 (6.7%)
12 Months	554 (100.0%)	537 (96.9%)	498 (89.9%)	39 (7.0%)	17 (3.1%)
2 Years	453 (100.0%)	435 (96.0%)	396 (87.4%)	39 (8.6%)	18 (4.0%)
3 Years	318 (100.0%)	308 (96.9%)	279 (87.7%)	29 (9.1%)	10 (3.1%)
4 Years	83 (100.0%)	83 (100.0%)	77 (92.8%)	6 (7.2%)	-

STUDY POPULATION DEMOGRAPHICS AND BASELINE PARAMETERS

The study cohort consisted of 658 patients in whom the Perceval heart valve implant was attempted. **Table 5** presents the patient preoperative characteristics including the demographic profile of the study cohort. The mean age at implant was 78.3 years old and 40% were octogenarians. There were 64.4% females and 35.6% males. The majority of the patients were in NYHA class II and III. Mean STS score was 7.2%, and 19.3% of the patients had previous cardiovascular intervention or interventions.

Table 5: CAVALIER Study Preoperative Patient Characteristics

Patients	658	%
Mean age ± SD (range)	78.3 ± 5.6 (61.6 ; 92.6)	
Age		
< 65	7	1.1%
65-69	41	6.2%
70-74	138	21.0%
75-79	209	31.8%
80-84	186	28.3%
85-89	70	10.6%
≥ 90	7	1.1%
Sex		
Female	424	64.4%
Male	234	35.6%
Mean BSA ± SD (range)	1.8 ± 0.2 (1.0 - 2.4)	
NYHA		
I	22	3.3%
II	198	30.1%
III	386	58.7%
IV	32	4.9%
Not available	20	3.0%
Mean EuroScore ± SD (range)	10.2 ± 7.8 (1.2 - 75.3)	
Mean STS Score ± SD (range)	7.2 ± 7.4 (0.8 - 50.0)	
Cardiac Rhythm[1]		
Sinus Atrial Fibrillation Paced Other	559 52 21 22	85.5% 8.0% 3.2% 3.4%

Previous Cardiovascular Intervention[2]		
None **Previous intervention**	531 (80.7%) 127 (19.3%)	
Valve replacement	10	1.5%
CABG surgery	13	2.0%
PCI[3]	78	11.9%
Valve repair with annuloplasty ring	1	0.2%
Pacemaker	33	5.0%
Other	10	1.5%

1. Missing data for 4 patients.
2. Patients may have more than one previous intervention.
3. PCI = Percutaneous Coronary Intervention (with or without stents)

SAFETY AND EFFECTIVENESS RESULTS

A. Safety Results

The analysis of safety was based on the implanted patient cohort of 628 patients over the course of 1,494.77 total patient-years and 1,444.44 late patient-years. The key safety outcomes and adverse event rates for aortic valve replacement for this study are presented in **Table 6**. The data are presented as percentages for early events, linearized late rates for late events, and "freedom from event" (actuarial analysis) at year 1, 2, 3, and 4 post-implant.

Table 6: Observed Adverse Event Rates

Adverse event	**Early events[1]**		**Late events[2]**		**Freedom From Event [95% CI][3]**			
	N	**%**	**N**	**%/pt-yr**	**1 year**	**2 years**	**3 years**	**4 years**
All mortality	23	3.7	74	5.1	91.7 [88.6 – 93.9]	88.7 [86.1 – 91.3]	83.2 [79.9 – 86.5]	77.4 [72.5 – 82.4]
Valve-related and valve- and procedure-related death	8	1.3	24	1.8	97.2 [95.9 – 98.5]	96.2 [94.6 – 97.8]	94.4 [92.4– 96.5]	89.5 [85.1– 93.8]
Valve reintervention	5	0.8	14	1.0	98.0 [96.9 – 99.1]	97.4 [96.1– 98.7]	97.1 [95.7 – 98.5]	95.2 [92.3 – 98.2]
Explant[4]	5	0.8	13	0.9	98.0 [96.9 – 99.1]	97.4 [96.1– 98.7]	97.1 [95.7 – 98.5]	95.2 [92.3 – 98.2]
All bleeding	28	4.5	37	2.6	87.5 [84.8 – 90.1]	86.6 [83.9 – 89.4]	85.2 [82.2 – 88.2]	84.1 [80.5 – 87.7]
Major bleeding	22	3.5	28	1.9	89.1 [86.6– 91.6]	88.5 [85.9 – 91.0]	87.6 [84.9 – 90.3]	86.5 [83.1 – 89.9]
Major anticoagulation-related bleeding	11	1.8	16	1.1	94.6 [92.8 – 96.5]	94.3 [92.4 – 96.1]	93.7 [91.6 – 95.7]	92.6 [89.6 – 95.5]
Thromboembolism[5]	27	4.3	29	2.0	94.3 [92.4 – 96.1]	92.8 [90.7 – 94.9]	91.7 [89.3 – 94.0]	89.4 [86.0 – 92.9]
Stroke	14	2.2	12	0.8	96.7 [95.3 – 98.1]	95.9 [94.3 – 97.5]	95.1 [93.2 – 96.9]	94.1 [91.4 – 96.7]
Endocarditis	1	0.2	17	1.2	98.5 [97.5– 99.5]	97.7 [96.4 – 98.9]	97.4 [96.0 – 98.8]	93.7 [89.2 – 98.1]
Valve thrombosis	0	0	0	0	100 [100 - 100]	100 [100 - 100]	100 [100 - 100]	100 [100 - 100]
Structural valve deterioration[6]	0	0	9	0.6	100 [100 - 100]	99.8 [99.4 – 100]	99.8 [99.4 – 100]	95.5 [91.0 – 100]

Adverse event	Early events[1]		Late events[2]		Freedom From Event [95% CI][3]			
	N	%	N	%/pt-yr	1 year	2 years	3 years	4 years
Nonstructural valve dysfunction[7]	7	1.1	10	0.7	97.9 [96.7 – 99.0]	97.5 [96.2 – 98.7]	97.5 [96.2 – 98.7]	93.4 [88.7 – 98.0]
All paravalvular leak	4	0.6	5	0.3	98.9 [98.0 – 99.7]	98.6 [97.7 – 99.6]	98.6 [97.7 – 99.6]	97.2 [95.0 – 99.5]
Major paravalvular leak	2	0.3	3	0.2	99.3 [98.7 – 99.9]	99.1 [98.4 – 99.9]	99.1 [98.4 – 99.9]	98.2 [96.1 – 100]
All hemolysis	4	0.6	5	0.3	98.6 [97.7 – 99.6]	98.4 [97.3 – 99.5]	98.4 [97.3 – 99.5]	98.4 [97.3 – 99.5]
Adverse events leading to pulse generator implant[8]	46	7.3	29	2.0	84.8 [81.9 – 87.6]	83.9 [81.0 – 86.9]	83.3 [80.3 – 86.4]	81.6 [77.1 – 86.1]

1. Early valve-related events include postoperative events occurring 1-30 days post implant. Early events rates are calculated as the percentage of events on total number of patients (628evaluable patients).

2. Late postoperative events (> 30 days). Linearized late rates calculated using 1444.44 late patient-years.

3. Freedom from first event (early or late) rates were calculated using the Kaplan-Meier method. In brackets the 95% lower and upper limits are reported.

4. There was 1 additional explant which was perioperative on Day 0.

5. There was 1 additional thromboembolic event which was a perioperative transient ischemic attack on Day 0.

6. The Kaplan-Meier rates are calculated considering only the 7 cases out of 9, adjudicated by the CEC as SVD.

7. Includes paravalvular leak. Also includes 2 cases of late tricuspid regurgitation reported as nonstructural valve dysfunction (NSVD) but reclassified as non-NSVD by the CEC.

8. There were 27 additional adverse events leading to pulse generator implant which were perioperative on Day 0.

According to the study protocol, the results of the CAVALIER study were compared to the OPC as recommended in the ISO 5840 requirements. The results in the **Table 7** refer to the valve-related events.

Table 7: Linearized hazard rates (%/late patient-year) based on CEC adjudicated valve-related events and follow-up greater than 30 days after surgery). Total patients N = 628.

Adverse event	Linearized Hazard Rates for >30 days post-op (All patients= 599) (1444.44 late patient-years; mean= 829.7 days; max=1624 days)			
	Number of patients	Number of events	one-sided 95% CI [Poisson distribution]	2 x OPC[1]
Bleeding	20	22	2.1%	2.8
Major Bleeding	15	16	1.6%	1.8
Thromboembolism	19	21	2.1%	5
Non structural valve dysfunction PVL	3	3	0.5%	2.4
Major PVL	2	2	0.4%	1.2
Endocarditis	15	16	1.6%	2.4
Valve thrombosis	0	0	-	0.4

[1] FDA Objective Performance Criteria.

Table 8 presents the results of the Clinical Event Committee (CEC) adjudication for the 102 new or worsened cardiac conduction disturbances and other adverse events, occurring in 100 patients, leading to pulse generator implantation in the CAVALIER study. One (1) patient had 2 different early arrhythmia events and a second patient had 2 late events.

Table 8: CEC-Adjudicated Cardiac Conduction Disturbances and Other Adverse Events Leading to Pulse Generator Implantation in CAVALIER Study [1, 2]

Adverse Event Leading to Pulse Generator Implant	Perioperative [Day 0]	Early [1-30 Days]	Late [> 30 Days]	Overall
Device-Related				
Cardiac Arrhythmia	1	2	0	3
3rd Degree AV Block	1	0	0	1
Bradycardia	0	1	0	1
Other Arrhythmias	0	1	0	1
Total	1	2	0	3
Device- and Procedure-Related				
Cardiac Arrhythmia	25	36	1	62
3rd Degree AV Block	24	25	0	49
2nd Degree AV Block	0	2	0	2
1st Degree AV Block	0	1	0	1
Atrial Fibrillation	1	2	0	3
Left Bundle Branch Block	0	2	1	3
Right Bundle Branch Block	0	1	0	1
Bradycardia	0	1	0	1
Other Arrhythmias	0	2	0	2
Total	25	36	1	62
Procedure-Related				
Cardiac Arrhythmia	1	4	0	5
3rd Degree AV Block	0	1	0	1
Atrial Fibrillation	0	2	0	2
Ventricular Fibrillation	1	0	0	1
Asystole	0	1	0	1
Heart Failure [3]	0	1	0	1
Total	1	5	0	6
Unrelated to Device or Procedure				
Cardiac Arrhythmia	0	3	24	27
3rd Degree AV Block	0	0	11	11
2nd Degree AV Block	0	1	3	4
Atrial Fibrillation	0	1	4	5
Left Bundle Branch Block	0	0	1	1
Bradycardia	0	0	2	2
Asystole	0	1	1	2
Other Arrhythmias	0	0	2	2
Heart Failure	0	0	2	2
Myocardial Infarction	0	0	1	1
Total	0	3	27	30
TOTAL	27	46	28	101

1. N = 628 implanted
2. Table presents 102 events in 100 patients, with 1 patient having 2 different early arrhythmia events and a second patient having 2 late events.
3. The event worsening of heart failure was not adjudicated by the CEC.

B. Effectiveness Results

Effectiveness of the Perceval heart valve was evaluated by NYHA functional class and echocardiographic assessment of the hemodynamic performance of the study valve.

The differences between the NYHA class at 12 months and the baseline were calculated. The data are presented in **Table 9.** In total, 77.5% of patients (362 over 467) showed a decrease of NYHA equal of at least one class, whereas 19.7% of patients remained stable over the time. Only 2.8% of patients showed a worsened clinical status.

Reduction in mean gradients and increase in EOA were observed at one year follow-up.

Table 9: Effectiveness Outcome, NYHA Functional Classification

	NYHA class change at 12 months vs. baseline													
	NYHA improved						**NYHA Stable**		**NYHA worsened**					
NYHA class at baseline	**-3**		**-2**		**-1**		**No change**		**+1**		**+2**		**+3**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
NYHA I (N = 15)	-	-	-	-	-	-	8	53.3	7	46.7	-	-	-	-
NYHA II (N = 160)	-	-	-	-	97	60.6	57	35.6	6	3.8	-	-	-	-
NYHA III (N = 277)	-	-	152	54.9	98	35.4	27	9.7	-	-	-	-	-	-
NYHA IV (N = 15)	8	53.3	7	46.7	-	-	-	-	-	-	-	-	-	-
Total (N = 467)	8	1.7	159	34.0	195	41.8	92	19.7	13	2.8	-	-	-	-

In **Table 10** all of the main non-regurgitation hemodynamic data obtained at the 1 year follow-up echocardiographic exams are presented. Reduction in mean gradients and increase in EOA compared to pre-implant were observed at 1 year follow-up.

Table 10: Effectiveness Outcome at 1 Year Follow-up Visit: Hemodynamic Results

Hemodynamic parameter	**All sizes**	**S/21 mm**	**M/23 mm**	**L/25 mm**	**XL/27 mm**
Mean Gradient [mmHg]	N[1] = 362	n = 46	n = 156	n = 143	n = 17
Mean ± SD	9.1 ± 5.0	10.1 ± 4.2	9.4 ± 5.5	8.5 ± 4.6	9.7 ± 4.7
EOA [cm^2]	N[1]= 300	n=31	n=131	n=123	n=15
Mean ± SD	1.5 ± 0.4	1.3 ± 0.3	1.5 ± 0.4	1.5 ± 0.4	1.6± 0.4

[1] N=number of subjects with available hemodynamic parameter.

Valvular regurgitation data obtained at the echocardiographic exams at 1 year through 3 years follow-up are presented in **Tables 11** to **13**.

Table 11: Postoperative valvular regurgitation by valve size at 1 year in CAVALIER Study [1]

Size	21 mm	23 mm	25 mm	27 mm
Severity				
None	12 (24.5%)	99 (51.3%)	73 (43.2%)	10 (45.5%)
Trace	13 (26.5%)	34 (17.6%)	46 (27.2%)	2 (9.1%)
Mild	20 (40.8%)	46 (23.8%)	43 (25.4%)	5 (22.7%)
Moderate	2 (4.1%)	5 (2.6%)	4 (2.4%)	0 (0%)
Severe	1 (2.0%)	1 (0.5%)	1 (0.6%)	0 (0%)
Not Evaluable	1 (2.0%)	8 (4.1%)	2 (1.2%)	5 (22.7%)
Total Number	49	193	169	22
Location				
None	12 (24.5%)	99 (51.3%)	73 (43.2%)	10 (45.5%)
Central	29 (59.2%)	70 (36.3%)	68 (40.2%)	5 (22.7%)
Paravalvular	3 (6.1%)	6 (3.1%)	9 (5.3%)	1 (4.5%)
Both	3 (6.1%)	10 (5.2%)	7 (4.1%)	0 (0%)
Not Evaluable	2 (4.1%)	8 (4.1%)	12 (7.1%)	6 (27.3%)

Total Number	49	193	169	22

1. N = 628 implanted. 433 patients with available regurgitation data at 1 year post-implant. Data updated to 7/2/15.

Table 12: Postoperative valvular regurgitation by valve size at 2 years in CAVALIER Study [1]

Size	21 mm	23 mm	25 mm	27 mm
Severity				
None	5 (12.2%)	54 (33.3%)	48 (34.5%)	5 (55.6%)
Trace	10 (24.4%)	36 (22.2%)	30 (21.6%)	1 (11.1%)
Mild	16 (39.0%)	48 (29.6%)	45 (32.4%)	3 (33.3%)
Moderate	5 (12.2%)	14 (8.6%)	8 (5.8%)	0 (0%)
Severe	1 (2.4%)	2 (1.2%)	0 (0%)	0 (0%)
Not Evaluable	4 (9.8%)	8 (4.9%)	8 (5.8%)	0 (0%)
Total Number	41	162	139	9
Location				
None	5 (12.2%)	54 (33.3%)	48 (34.5%)	5 (55.6%)
Central	32 (78.0%)	79 (48.8%)	65 (46.8%)	4 (44.4%)
Paravalvular	0 (0%)	7 (4.3%)	7 (5.0%)	0 (0%)
Both	2 (4.9%)	12 (7.4%)	8 (5.8%)	0 (0%)
Not Evaluable	2 (4.9%)	10 (6.2%)	11 (7.9%)	0 (0%)
Total Number	41	162	139	9

1. N = 628 implanted. 351 patients with available regurgitation data at 2 year post-implant. Data updated to 7/2/15.

Table 13: Postoperative valvular regurgitation by valve size at 3 years in CAVALIER Study [1]

Size	21 mm	23 mm	25 mm	27 mm
Severity				
None	4 (12.9%)	24 (21.1%)	28 (23.5%)	-
Trace	7 (22.6%)	33 (28.9%)	21 (17.6%)	-
Mild	13 (41.9%)	37 (32.5%)	45 (37.8%)	-
Moderate	5 (16.1%)	13 (11.4%)	9 (7.6%)	-
Severe	1 (3.2%)	0 (0%)	1 (0.8%)	-
Not Evaluable	1 (3.2%)	7 (6.1%)	15 (12.6%)	-
Total Number	31	114	119	0
Location				
None	4 (12.9%)	24 (21.1%)	28 (23.5%)	-
Central	22 (71.0%)	68 (59.6%)	58 (48.7%)	-
Paravalvular	0 (0%)	4 (3.5%)	9 (7.6%)	-
Both	4 (12.9%)	12 (10.5%)	12 (10.1%)	-
Not Evaluable	1 (3.2%)	6 (5.3%)	12 (10.1%)	-
Total Number	31	114	119	0

1. N = 628 implanted. 264 patients with available regurgitation data at 3 year post-implant. Data updated to 7/2/15.

ANALYSIS OF GENDER RELATED DIFFERENCES

Among the attempted implant (N=658), there were 424 females (64.4%) and 234 males (35.6%) patients in the CAVALIER study cohort.

Analyses were performed on the 628 patients who were successfully implanted (females = 404; males = 224). The results do not include the 30 patients who were classified as failure to implant (for whom the Perceval valve implant was not implanted and a non-study prosthetic valve was ultimately implanted).

Valve-related adverse events and outcomes were evaluated by gender (see **Table 14**). There were no considerable differences between males and females for any safety endpoints.

Effectiveness endpoints were compared for both males and females. The two groups exhibited improvement in NYHA classification at 12 months. However, there was a potential observed difference in the 12-month NYHA distribution between males and females (see **Table 15**).

Table 14: Early Mortality and Survival Comparisons by Gender

Parameter	**Total (N = 628)**	**Female (N = 404)**	**Male (N = 224)**
Early (≤ 30-day) mortality	3.5%	3.2%	4.0%
Percent Survival at 48 months (95% Confidence interval)			
All mortality	77.43 (72.47 – 82.39)	76.39 (69.65 – 83.13)	78.93 (71.81 – 86.04)
Cardiac-related death	88.32 (84.19 – 92.45)	88.86 (83.6 – 94.11)	87.45 (80.91 – 94.0)
Valve-related death	89.45 (85.07 – 93.83)	89.32 (83.48 – 95.17)	89.60 (83.18 – 96.03)

Table 15: Comparison of 12-Month NYHA Functional Classification by Gender

Postoperative NYHA (12 months)	**All (N = 476)**		**Female (N = 303)**		**Male (N = 173)**	
	N	**%**	**N**	**%**	**N**	**%**
CLASS I	271	56.9%	155	51.2%	116	67.1%
CLASS II	171	35.9%	131	43.2%	40	23.1%
CLASS III	34	7.1%	17	5.6%	17	9.8%
CLASS IV	-	-	-	-	-	-

Although the study population included a greater proportion of female patients, the comparisons of safety and effectiveness data by gender support the conclusion that the results of the overall study can be applied equally well to males and females. Patients of both genders demonstrated excellent hemodynamic outcomes and improvement in functional status.

14. PATIENT INFORMATION

Registration Form and Identification card

A Patient Registration Form is enclosed in each valve carton. The registration form must be completed and returned to the manufacturer by the implanting surgeon/hospital. Upon receipt of the form, the manufacturer will prepare and forward an identification card with patient and valve information to the patient.

Patient's card

Every artificial heart valve is supplied with a patient's card that identifies the bearer. This system enables the surgeon to give the patient a document containing concise but comprehensive data about the operation and the implanted valve, which can be used whenever this information needs to be produced immediately.

15. MAGNETIC RESONANCE IMAGING (MRI) SAFETY INFORMATION

MR Conditional

Non-clinical testing demonstrated that the Perceval is MR Conditional. A patient with this device can be scanned safely immediately after placement under the following conditions:

- Static magnetic field of 1.5 Tesla or 3.0 Tesla only
- Maximum spatial gradient magnetic field of 2500 Gauss/cm or less
- Maximum whole-body averaged specific absorption rate (SAR) of 4 W/kg in the First Level Controlled Mode for the MR system

MRI-Related Heating

In non-clinical testing and modeling at 1.5 T, the device produced a maximum temperature rise less than 3.0^{o}C during 15 minutes of continuous MR scanning in the First Level Controlled Mode at a maximum whole body averaged SAR of 4.0 W/kg.

In non-clinical testing and modeling at 3.0 T, the device produced a maximum temperature rise less than 2.7^{o}C during 15 minutes of continuous MR scanning in the First Level Controlled Mode at a maximum whole body averaged SAR of 4.0 W/kg.

Artifact Information

The maximum artifact size (i.e., as seen on the gradient echo pulse sequence) extends approximately 5 mm relative to the size and shape of the device. Therefore, optimization of MR imaging parameters to compensate for the presence of this device may be necessary.

Pulse sequence	T1-SE	T1-SE	GRE	GRE
Signal Void Size	1,446 mm^2	1,049 mm^2	2,026 mm^2	1,600 mm^2
Plane Orientation	Parallel	Perpendicular	Parallel	Perpendicular

16. RETURN OF EXPLANTED DEVICES

For return of any product contact Sorin Group USA, Inc. Customer Service at 1.800.289.5759 to obtain a Returned Goods Authorization number and the explant kit including packaging needed for shipping returned valves. Any explanted valve should be placed in 10% formalin (4% formaldehyde) and packaged in the explant kit provided prior to shipment.

17. WARRANTIES

SORIN GROUP CANADA INC. WARRANTS THAT REASONABLE CARE WAS USED IN THE MANUFACTURE OF THIS DEVICE. SORIN GROUP CANADA INC. WARRANTS THAT THIS DEVICE WAS MANUFACTURED ACCORDING TO STRICT SPECIFICATIONS. NO OTHER WARRANTY, INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR PURPOSE, IS EITHER EXPRESSED OR IMPLIED SINCE HANDLING, STORAGE, AND CLEANING OF THIS DEVICE AS WELL AS FACTORS RELATING TO THE PATIENT, DIAGNOSIS, TREATMENT, SURGICAL PROCEDURES AND OTHER MATTERS BEYOND SORIN GROUP CANADA INC.'S CONTROL DIRECTLY AFFECT THIS DEVICE AND THE RESULTS OBTAINED FROM ITS USE. SPECIFICALLY DISCLAIMED ARE ANY AND ALL WARRANTIES OR CONDITIONS TO THE EXTENT THAT SUCH MAY BE IMPLIED UNDER THE PROVISIONS OF THE SALE OF GOODS ACT OF BRITISH COLUMBIA. NO REPRESENTATIVE OF THE COMPANY MAY MODIFY ANY OF THE FOREGOING AND THE PURCHASER AND/OR USER ACCEPTS THE PRODUCT SUBJECT TO ALL TERMS HEREIN STATED.

PRODUCT AVAILABILITY

Manufactured by:
Sorin Group Canada Inc.
5005 North Fraser Way
Burnaby, BC
CANADA V5J 5M1
Tel: (604) 412-5650
Fax: (604) 412-5690

Distributed in U.S.A. by:
Sorin Group USA, Inc.
14401 West 65th Way
Arvada, Colorado 80004 USA
Tel: (800) 289-5759
Fax: (877) 657-3605
www.sorin.com

SINGLE-USE ACCESSORY KIT TABLE

Table 16: Perceval Single Use Accessory Kits

Single Use Accessory Kits REF	Single Use Accessory Kits Content	PVS21	PVS23	PVS25	PVS27
ICV1345(1)	ICV1235 Dual Collapser ICV1242 Dual Holder ICV1148 Post-dilation Catheter	X			
ICV1346(1)	ICV1235 Dual Collapser ICV1242 Dual Holder ICV1149 Post-dilation Catheter		X		
ICV1347(1)	ICV1236 Dual Collapser ICV1243 Dual Holder ICV1170 Post-dilation Catheter			X	
ICV1348(1)	ICV1236 Dual Collapser ICV1243 Dual Holder ICV1234 Post-dilation Catheter				X
ICV1349(2)	ICV1235 Dual Collapser ICV1244 Dual MICS Holder ICV1216 MICS Post-dilation Catheter	X			
ICV1350(2)	ICV1235 Dual Collapser ICV1244 Dual MICS Holder ICV1217 MICS Post-dilation Catheter		X		
ICV1351(2)	ICV1236 Dual Collapser ICV1245 Dual MICS Holder ICV1218 MICS Post-dilation Catheter			X	
ICV1352(2)	ICV1236 Dual Collapser ICV1245 Dual MICS Holder ICV1241 MICS Post-dilation Catheter				X

(1) Indicated for sternal approaches
(2) Specifically indicated for Minimally Invasive Cardiac Surgery (including minithoracotomy)

FIGURES

Fig 1a Example of a Sizer

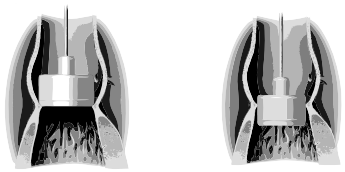

Fig 1b White obturator not passing through the annulus
Fig 1c Transparent obturator passing through the annulus

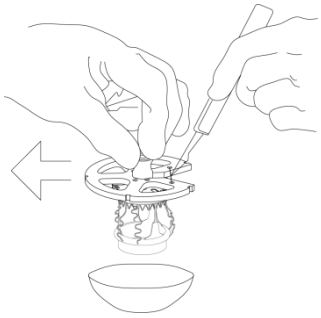

Fig 2a Removal of the holding collar

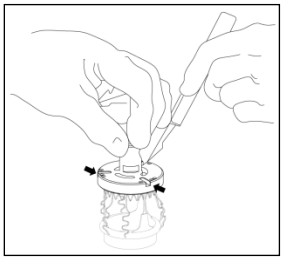

Fig. 2b Removal of the holding support

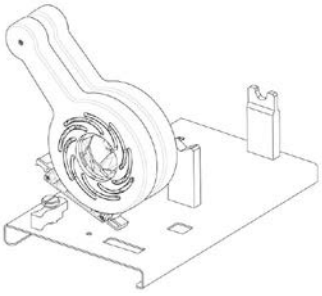

Fig. 3a Mounting the dual collapser on its base

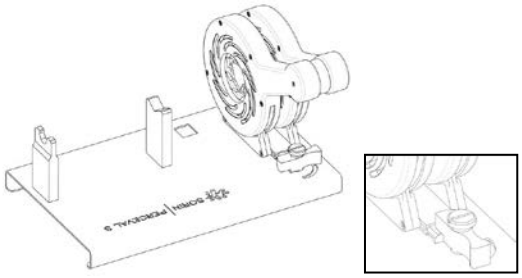

Fig. 3b Fixing the dual collapser on its base

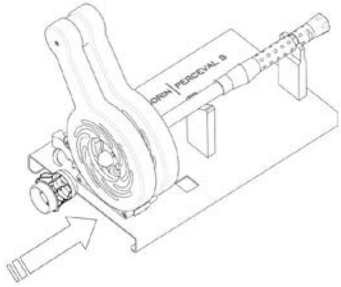

Fig. 4 Inserting the valve in the collapsing area

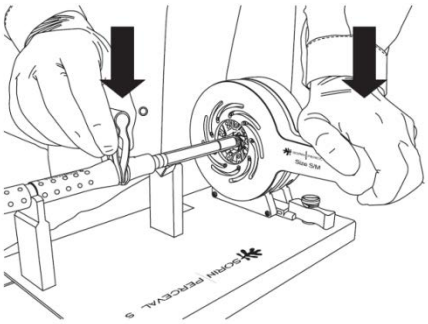

Fig. 5 Sliding the sheath on the holder, position the Smart Clip between the Sheath and the handle of the holder

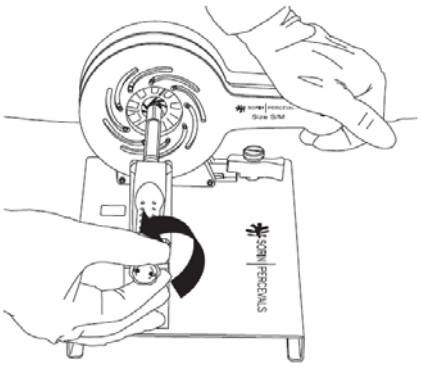

Fig. 6 Turn the knob counterclockwise allowing the inflow cap to grip the inflow ring

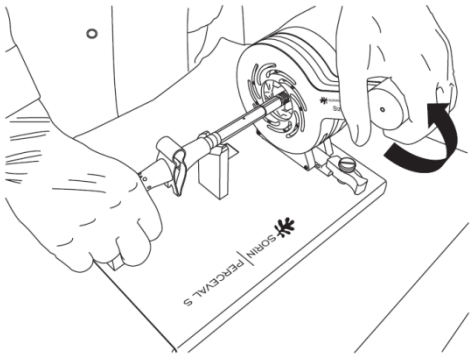

Fig. 7 Turn the lever in the open position to release the Dual Collapser; the Smart Clip will automatically push forward the sheath

Fig. 8 Prosthesis correctly mounted on the holder

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