JenaValve Trilogy for patients with pure native Aortic valve Regurgitation: The ARTEMIS Data Collection Study
Short Title: ARTEMIS

Artemis Protocol Version 1.0

Date: 15th April 2025

Promoter: **IRCCS Policlinico San Donato**
NCT 07075861

STATEMENT OF COMPLIANCE AND INVESTIGATOR SIGNATURE PAGE

Investigator Signature

I have read and understand the contents of this protocol. I agree to adhere to its requirements. I will ensure that the Study is conducted in compliance with the protocol, the EU Medical Device Regulation (EU) 2017/745 ("MDR"), the ISO 14155 for Good Clinical Practice in Clinical investigations of medical devices for human subjects; the EU General Data Protection Regulation (EU) 2016/679 (", GDPR"), Good Clinical Practice, Declaration of Helsinki, and all applicable regulatory requirements.

Table of Contents

Synopsis

Title	JenaValve Trilogy for patients with pure native Aortic valve Regurgitation: The ARTEMIS Data Collection Study
Trial Name	ARTEMIS Data Collection Study
Investigational Device	JenaValve Trilogy™ Heart Valve System
Data collection study Objective	To observe the safety and effectiveness of the JenaValve Trilogy™ Heart Valve System for transcatheter aortic valve replacement (TAVR) in subjects with severe native aortic regurgitation (AR) who are indicated for TAVR
Data collection study Design	A retrospective/prospective, single-arm, post-market study in patients with symptomatic, severe native aortic regurgitation to monitor the outcomes of Jena Valve Trilogy in a real-world clinical setting
Estimated Timeline	After enrollment is completed, patients are followed to 1 year (an amendment to extend the follow up to 5 years will be evaluated). Thereafter, the patient exits the data collection study and is to be followed per institutional standard of care for TAVR patients.
Data collection study Devices	The JenaValve Trilogy™ Heart Valve System contains the following sub-components: a prosthetic transcatheter porcine pericardial aortic valve, 20Fr Introducer Sheath System, transfemoral Delivery Catheter, and Loading Tool.
Indications for Use	The JenaValve Trilogy™ Heart Valve System is indicated for use in patients with clinically significant aortic regurgitation (AR) who are considered high risk candidates for surgical aortic valve replacement as deemed by the local multi-disciplinary heart team.
Principal Investigators	Luca Testa, MD, PhD
Number of Subjects	This is an investigator initiated study that will include 75 suitable patients according to the inclusion/exclusion criteria as per IFU.
Inclusion criteria	Patient with severe symptomatic aortic valve regurgitation in a native valve and: • Considered at high or prohibitive risk for surgical aortic valve replacement by the Heart Team • 18 years of age or older • Suitable anatomy according to the IFU • Absence of significant disease of the ascending aorta, including ascending aortic aneurysm (defined as maximal luminal diameter of 50mm or greater) or atheroma (especially if thick [>5mm], protruding or ulcerated)
Exclusion criteria	The JenaValve Trilogy Heart Valve System is contraindicated for use in patients who have known hypersensitivity or contraindication to Nitinol (titanium and/or nickel), an anti-coagulation/anti-platelet regimen or contrast medium that cannot be managed with premedication, or who have active bacterial endocarditis or other active infections. The JenaValve Trilogy Heart Valve System is contraindicated in those patients whose anatomy does not accommodate the System due to anatomical considerations outlined in the inclusion criteria.
Data collection study Duration	Expected data collection study duration: 36 months Enrolment completion: Approx. 24 months Follow-up Visits as per routine clinical practice: 30 days, and 12 Months
Population	The data collection study population will consist of subjects with pure native Aortic Valve Regurgitation

Schedule of Assessments:

For subjects included in the study, scheduled visits will be performed in the following order: Baseline, Index Procedure, Discharge, 30 days, 12 months (and annually thereafter, if required).

The study-required activities and standard of care data collection in the ARTEMIS Data Collection Data collection study are summarized in Table 1: Schedule of Assessments.

Table 1: Schedule of Assessments

Schedule of assessment	Screening/baseline	Procedure	Discharge	30d [-7/+21 days]	12 months [+45 days]
Demographics	X				
Medical History	X				
Physical Examination	X		x	x	x
Surgical Risk Assessment (STS & EuroSCORE II)	X				
NYHA Classification	X			x	x
Frailty Index	X				
Cardiovascular Medications Documentation	X		x	x	x
CT Angiography	X				
Modified Rankin Scale (mRS)	X		(x)	(x)	(x)
12 lead Electrocardiogram (ECG) [A,B]	X	x [B]	x [A, B]	x [A]	x [A]
2D Transthoracic Echocardiogram (TTE)	X	x	x	x	x
Angiogram		x			
CT Scan with Angiography of chest, abdomen and pelvis	X				
KCCQ (23 question questionnaire)	X			x	x
CBC and Platelet Count	X				
Creatinine	x	x	x		
INR (if subject is on Warfarin)	X			x	x
Troponin or CK-MB		x	x		
Adverse Event Assessment	X	x	x	x	x
Deviation	(x)	(x)	(x)	(x)	(x)
Device Deficiency		(x)	(x)	(x)	(x)
Withdrawal		(x)	(x)	(x)	(x)
Survival Status			(x)	(x)	(x)

[A] For subjects receiving a new permanent pacemaker, ECG should be completed showing the underlying rhythm

[B] Record a 12-lead ECG following the implant of the valve and daily until day of discharge.

(X) indicates if applicable

1.0 INTRODUCTION

The objective of this data collection study is to observe the ability of the JenaValve Trilogy™ Heart Valve System device to treat patients with pure native aortic regurgitation (AR) safely and effectively through the collection of data from the regular use of the CE-marked device in accordance with the medical standard of care and clinical practice.
The JenaValve Trilogy™ Heart Valve System device is used to treat symptomatic severe AR commercially in the EU under CE mark and is being evaluated in the ALIGN-AR IDE study and ALIGN-AR CAP protocol for patients at high-risk for surgery (1).
The data collection study is not being conducted to assess a new indication or to otherwise assess the JenaValve Trilogy Heart Valve System outside the scope of its intended purpose.

1.1 Aortic Regurgitation (AR) and Current Treatment Options

Aortic regurgitation (AR) occurs in approximately 0.4% of all adults, in 1% of individuals aged 65-74 years and 2% of individuals over 70 years of age.(2) Symptomatic patients with chronic severe AR have a poor prognosis and should therefore undergo open heart surgery per current guidelines. However, an increasing number of patients with symptomatic severe AR have excessive comorbidities or a clinical condition that contraindicates open heart surgery. Patients where open-heart surgery is not an option are often treated conservatively with medical management (3).

There are a host of factors involved in the Heart Team's assessment of eligibility for SAVR; the process involves evaluation of surgical risk using not only Society of Thoracic Surgeons (STS) scores, but also taking into account other technical and clinical factors. The AHA/ACC Guidelines for the Management of Patients with Valvular Heart Disease (4) details that surgical risk assessment should include consideration of STS risk estimate, frailty, major organ system dysfunction, and procedure-specific impediments. Evaluation of surgical risk includes but is not limited to:

- Advanced age
- Lung disease
- Cerebrovascular disease
- Severely impaired mobility
- Prior CABG
- Renal failure
- Severe pulmonary hypertension
- Peripheral vascular disease
- Low ejection fraction
- Obesity
- Immunosuppressive therapy
- Hematologic disorder
- Liver disease
- GI bleeding
- Low body mass index (BMI)
- Multiple pulmonary emboli
- Porcelain aorta
- Reconstructed sternum
- Chest wall radiation
- Chest wall deformity
- Other neurologic disease

Any combination of the above health factors may influence the categorization of a patient as high surgical risk and preclude referral for a SAVR procedure. The ALIGN-AR IDE trial was conducted to evaluate the safety and efficacy of the JenaValve Trilogy™ Heart Valve System for transcatheter aortic valve replacement (TAVR) in subjects clinically significant aortic regurgitation (AR) who are indicated for TAVR. Reported data from the study met the 30-day performance goal for safety outcomes (26.7%, p for noninferiority<0.0001), as

well as the 12-month performance goal for the efficacy outcome of all-cause mortality (7.8%, p for noninferiority <0.0001).

1.4 Mortality in AR Patients Treated Conservatively

The presence of NYHA functional class III/IV and congestive heart failure (CHF) are strong predictors of survival in AR. Dujardin et al. (2) found that in patients with moderate to severe AR, NYHA functional classification was the most powerful predictor of survival (Figure 1). When comparing symptomatic moderate to severe AR with asymptomatic moderate to severe AR, the yearly mortality rate was 9.4% vs. 2.4%. This association is observed also in patients with severe AR in whom symptoms seem to be major determinants of outcomes. In patients with LVEF>55%, but severe pure AR with CHF, reported a 2-year mortality rate of 88%.

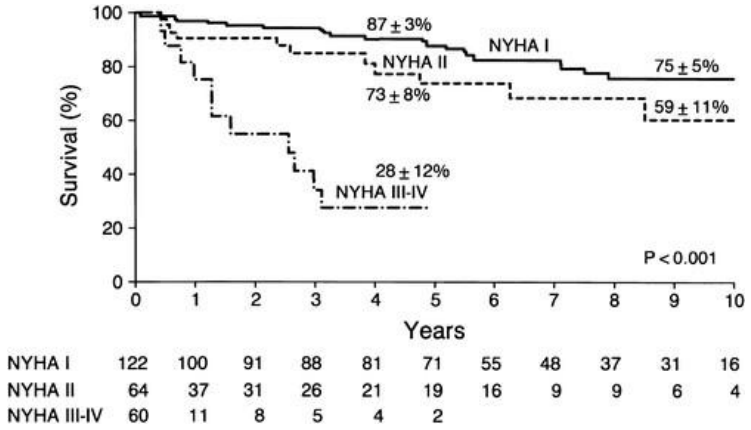

Figure 1: NYHA Functional Classification and Survival in Patients with Moderate-Severe Aortic Regurgitation. (Dujardin et al. 1999)[4]

Similarly, Dujardin et.al reported CHF as an important predictor of mortality in patients with AR. The yearly mortality rate was 24.5% in patients with NYHA functional class III/IV, but 5.8% in those with LVEF<55 compared to 2.0% in those with LVEF $\geq$ 55. Patients with symptoms present higher CHF event rates compared to those with LVEF <50 (Figure 2). Furthermore, in severe AR with LVEF>50%, LVEDD less than 70 mm, and LVESD less than 50 mm (for whom aortic valve replacement is not recommended according to ACC/AHA guidelines), mortality rates at 6 months was still as high as 21%(4). Thus, the presence of NYHA Functional Class III/IV symptoms and CHF are associated with higher mortality rates than LVEF<50.

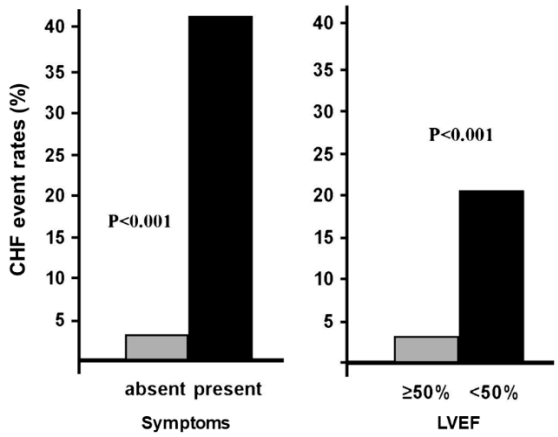

Figure 2: Event rates of congestive heart failure (CHF) in patients with or without symptoms and in patients with left ventricular ejection fraction (LVEF) <50% or LVEF≥55 (Detaint D et al. 2008)[12].

1.5 JenaValve Device Concept

The JenaValve Trilogy Heart Valve System is designed to allow a controlled valve release and deployment during the entire implantation procedure under beating heart conditions. The JenaValve Pericardial Transcatheter Heart Valve (THV) prosthesis includes three positioning Locators which are released in the first step during implantation. These Locators are intended to enable a correct positioning and re-positioning of the prosthesis into the cusps of the native aortic valve. After introducing the system via transfemoral access, the positioning Locators are released under fluoroscopic control. By gently advancing the delivery catheter towards the aortic root, the Locators are positioned in native aortic valve cusps. These three Locators are designed to precisely define the implantation plane of the valve stent in the aortic root below the coronary ostia. After correct anatomical positioning, the prosthesis is released and deployed. Once the valve is unfolded by the self-expanding mechanism of the nitinol stent, the native aortic valve leaflets are fixed in between the Locators and the rail (see Figure 5), thus defining correct height and position of the valve prosthesis.

1.6 JenaValve Device Preclinical Testing

JenaValve conducted acute and chronic preclinical animal studies using the ovine model. Acute animal studies have demonstrated the feasibility of successful delivery and implantation of the JenaValve Trilogy Heart Valve System with very good hemodynamic valve performance post procedure. Results of chronic animal implant studies revealed excellent long-term macroscopic/microscopic outcomes with no signs of valve degeneration or dislocation. Valve performance was evaluated by echocardiography at predefined time points throughout the studies and demonstrated durable long-term effectiveness of the valve.

1.7 Prior Clinical Experience with JenaValve Device

JenaValve has developed a lower profile system with transcatheter heart valve (THV) prosthesis that consists of porcine pericardial tissue mounted on a nitinol support frame. The tissue is sewn in place to secure the material to the frame and construct the valve leaflets. A transfemoral (TF) introducer-based delivery system has been developed to provide this alternative access approach. The first version of the TF delivery system was studied with the pericardial tissue valve prosthesis in a First-in-Man (FIM) clinical study in Europe (study number JV04FIM) which enrolled seven patients, with encouraging overall results. The delivery system has been modified since the conduct of JV04FIM; however, the results are relevant to the implant because that is the identical THV under investigation in this data collection study.

The JenaValve Trilogy Heart Valve system clinical program was conducted at sites in the US, Europe (Germany, The Netherlands) and New Zealand for two cohorts:

- Patients with symptomatic aortic regurgitation (AR) at high surgical risk
- Patients symptomatic, severe aortic stenosis (AS) at high surgical risk

In May 2021, the JenaValve Trilogy Heart Valve System received CE Mark approval for use in patients with symptomatic severe aortic stenosis (AS) or symptomatic severe aortic regurgitation (AR) who are considered by a Heart Team, including a cardiac surgeon, to be at increased risk for open surgery (STS-PROM ≥ 8% at 30 days, or if less than 8%, significant comorbidities are present that are not captured by STS-PROM), and eligible for the TAVR procedure.

The clinical program for AR is ongoing in the US under another protocol (IDE G150035). IDE G150035 was initially approved on October 22, 2015, and the pivotal HDE study was approved under G150035/S034 on May 22, 2020.

2.0 DEVICE DESCRIPTION

This data collection study is investigating the JenaValve Trilogy™ Heart Valve System when used to perform transcatheter aortic valve replacement (TAVR) for treatment of symptomatic, severe aortic regurgitation. The JenaValve Trilogy™ Heart Valve System consists of the following major components:

- JenaValve Trilogy™ Heart Valve (THV)
- JenaValve Trilogy™ Delivery System (comprising the 20Fr Introducer Sheath System, Delivery Catheter, and Loading Tool)

Intended Use/Indication or Use: The JenaValve Trilogy™ Heart Valve System is intended for use in patients with symptomatic, severe tri-leaflet aortic valve regurgitation (AR, not

due to acute endocarditis, rheumatic heart disease, or acute aortic dissection) who are assessed by a Heart Team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy.

The JenaValve Trilogy™ Heart Valve System is not intended for use in patients with congenital aortic valve disease (i.e., unicuspid, bicuspid, or quadricuspid valves), with acute conditions requiring surgical aortic valve replacement (i.e., acute endocarditis, acute aortic dissection), or patients who require concomitant cardiac surgery (e.g., ascending aortic aneurysm repair; aortic root replacement, coronary artery bypass grafting).

2.1 JenaValve Trilogy™ Heart Valve (THV)

The JenaValve Trilogy™ Heart Valve (Figure 3) is constructed from porcine pericardium that is attached to a self-expanding nitinol frame with polyester suture. The frame has a crown design that can collapse with the valve to be implanted using the JenaValve Trilogy™ Heart Valve System.

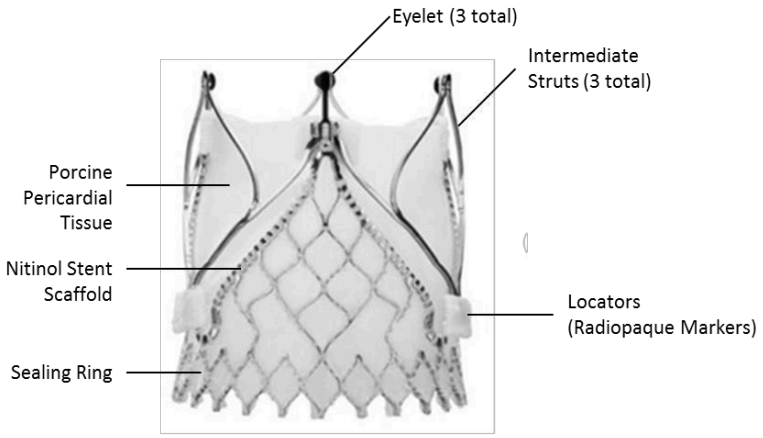

Figure 3: JenaValve Trilogy™ Heart Valve System

At the upper part the JenaValve Trilogy™ Heart Valve contains three eyelets designed to gear into the corresponding recesses at the crown of the delivery system enabling a firm attachment. The THV prosthesis has three positioning covered Locators that spread apart after the first step of the deployment process. The covers allow for safe positioning of the Locators within the native aortic valve cusps without perforating the cusps. At the base of THV is a nitinol sealing (‘rhombi’) ring that is covered by a pericardium skirt to seal with the native annulus and prevent paravalvular regurgitation. When placed into the native valve cusps, the Locators capture the native valve leaflets. This unique valve design anatomically aligns with the native commissures and fixes the transcatheter heart valve in place.

2.2 JenaValve Trilogy™ Heart Valve System

The JenaValve Trilogy™ Heart Valve System is designed to allow for a transfemoral approach using the JenaValve Introducer Sheath System and its compatible Delivery Catheter and Loading Tool. The delivery system is designed to implant the JenaValve THV using percutaneous access.

2.2.1 JenaValve Trilogy™ Delivery Catheter & Introducer Sheath

The JenaValve Trilogy™ Delivery Catheter (Figure 4 and Figure 5) delivers the THV transfemorally through the JenaValve Pre-Shaped 20Fr Introducer Sheath System (Figure 8). The Delivery Catheter features a tapered tip for crossing the valve, and a Catheter shaft which is controlled by three mechanisms: a Deflector (to centrally align the THV and its Locators above the native aortic cusps prior to alignment), a Controller (to rotate the THV above the native aortic cusps for alignment), and (3) a Deployer (to release the THV from the Catheter after the Locators are placed into the native cusps).

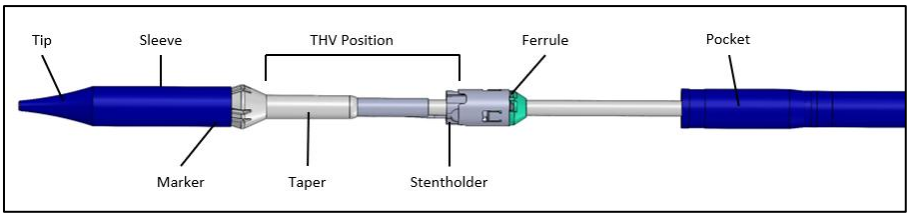

Figure 4: JenaValve *Trilogy™ Delivery Catheter THV Dock*

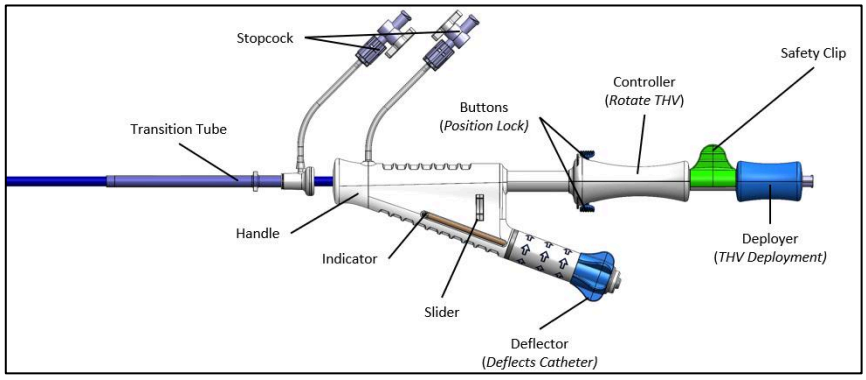

Figure 5: JenaValve Trilogy™ Delivery Catheter Handle

The JenaValve Trilogy™ Introducer Sheath System (Figure 6) is comprised of a polymeric shaft Dilator and a 20Fr Introducer Sheath (22Fr outer profile), with a pre-shaped distal end and a proximal housing with a hemostatic seal.

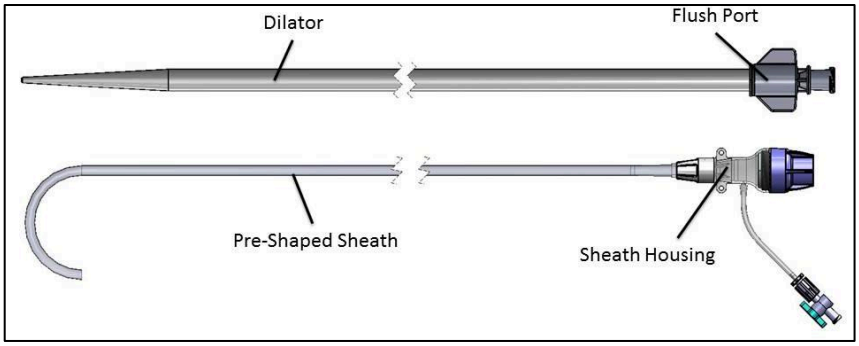

Figure 6: JenaValve Trilogy™ Introducer Sheath System: Dilator (bottom); Pre-Shaped Introducer Sheath (top)

The JenaValve Trilogy™ Heart Valve is crimped/loaded into the main Delivery Catheter at the time of the procedure using a dedicated Loading Tool.

2.2.2 JenaValve Trilogy™ Loading Tools

The Trilogy™ Loading Tool enables crimping and loading the THV into the same size Delivery Catheter (Figure 7).

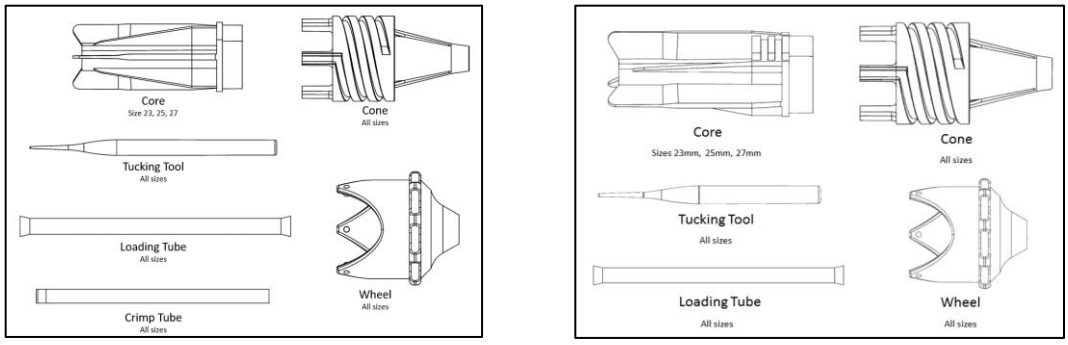

Figure 7: JenaValve *Trilogy™ Loading Tool Configurations*

3.0 DATA COLLECTION STUDY OBJECTIVE

This data collection study will observe the use of TAVR (Transcatheter Aortic Valve Replacement), using the JenaValve Trilogy™ Heart Valve System, in patients with clinically significant aortic regurgitation, deemed at high or prohibitive risk for surgery by the Heart Team.

4.0 DATA COLLECTION STUDY ENDPOINTS/OTHER DATA COLLECTION

4.1 Data Collection DATA COLLECTION STUDY Objective

Primary Efficacy Objective

Device Success at 12 Months according to Valve Academic Research Consortium (VARC)-3 definition (5) consisting of:

- Freedom from all-cause mortality
- Freedom from unsuccessful delivery of the device, and retrieval of the delivery system
- Freedom from incorrect positioning of a single prosthetic heart valve into the proper anatomical location
- Freedom from surgery or intervention related to the device or to a major vascular or access-related or cardiac structural complication
- Intended performance of the valve (i.e., no moderate or severe prosthetic valve regurgitation)

Rationale for primary efficacy objective

Ongoing Safety and Efficacy data collection to be assessed at 1yr. Assessed according to VARC 3 criteria.

5.0 DATA COLLECTION STUDY DESIGN

This is a retrospective and prospective, single-arm, data collection study in patients with severe native aortic regurgitation who are at high or prohibitive surgical risk according to the Heart Team, in a real-world clinical setting.

Subjects will provide informed consent for the collection of their clinical data.

Subjects participating in the Data collection study will initially be followed for 1 year (an amendment to extend the follow up to 5 years will be evaluated). Data collected will include the following visits: at screening/baseline, procedure, hospital discharge, and follow-up at 30 days, 12 months (annually thereafter if the follow up will be extended to 5 years).

5.1 Statistical analysis

Categorical variables will be shown as count and percentage, normal variables as mean±SD, non-normal variables as median and interquartile range. Normality assumption will be tested in continuous variable by visual inspection of qq-plot. Correlations between

continuous variables will be evaluated according to Pearson R or Spearman Rho, depending on the distribution. Paired T tests will be used to compare continuous variables. T test or Wilcoxon rank sum test will be used to compare unpaired means in normally or non-normally distributed variable, respectively. Fisher's exact test will be used to compare categorical data between groups. The null hypothesis will be refused with $p < 0.05$.
Device success on the study end points will be evaluated by Kaplan–Meier estimates of survival curves and their 95% confidence intervals.

According to the local experience in TAVR, the number of patients with severe AR deemed at prohibitive surgical risk is around 2/month. Considering a prospective enrollment of 2 years and historical patients collected data for 1 year, the final number of expected patients will be about 75. In fact, according to reference [1], a composite of all-cause mortality and heart failure rehospitalization at 1 year had cumulative incidence of about 17%. Therefore, considering an exponential distribution with event rate 0.17 (17 events per 100 person years), 75 patients amount to a total of 75-13*.5=68 person years. The resulting 95% confidence interval of the cumulative incidence will be 0.06; 0.24 [2].

[1] Poletti E, De Backer O, Scotti A, Costa G, Bruno F, Fiorina C, Buzzatti N, Latini A, Rudolph TK, van den Dorpel MMP, Brinkmann C, Patel KP, Panoulas V, Schofer J, Giordano A, Barbanti M, Regazzoli D, Taramasso M, Saia F, Baumbach A, Maisano F, Van Mieghem NM, Søndergaard L, Latib A, Amat Santos IJ, Bedogni F, Testa L. Transcatheter Aortic Valve Replacement for Pure Native Aortic Valve Regurgitation: The PANTHEON International Project. JACC Cardiovasc Interv. 2023 Aug 28;16(16):1974-1985. doi: 10.1016/j.jcin.2023.07.026. PMID: 37648345.

[2] Riley RD, Ensor J, Snell KIE, Harrell FE, Martin GP, Reitsma JB, et al. Calculating the sample size required for developing a clinical prediction model. BMJ (Clinical research ed). 2020

6.0 ELIGIBILITY CRITERIA

6.1 Inclusion Criteria

Patient with severe symptomatic aortic valve regurgitation in a native valve and:

- Considered at high or prohibitive risk for surgical aortic valve replacement by the Heart Team
- 18 years of age or older
- Suitable anatomy according to the IFU

- Absence of significant disease of the ascending aorta, including ascending aortic aneurysm (defined as maximal luminal diameter of 50mm or greater) or atheroma (especially if thick [>5mm], protruding or ulcerated)

6.2 Exclusion Criteria

The JenaValve Trilogy Heart Valve System is contraindicated for use in patients who have known hypersensitivity or contraindication to Nitinol (titanium and/or nickel), an anti-coagulation/anti-platelet regimen or contrast medium that cannot be managed with premedication, or who have active bacterial endocarditis or other active infections. The JenaValve Trilogy Heart Valve System is contraindicated in those patients whose anatomy does not accommodate the System due to anatomical considerations outlined in the inclusion criteria.

7.0 SUBJECT POPULATION

7.1 Subject Population

Adult subjects with pure native aortic regurgitation, as assessed by heart team, will be considered for inclusion if ineligible to surgical treatment.

7.2 Informed Consent Procedures

The study investigator(s) and support staff will approach patients being considered for TAVI with the JenaValve Trilogy Heart Valve System to assess their interest in participating in the data collection study. If patients are interested in participating, the subject will sign the Ethics Committee (EC)-approved informed consent form (ICF).
The general process for obtaining informed consent is as follows:

- Ensure that the principal investigator or his/her authorised designee conducts the informed consent process;
- Include all aspects of the data collection that are relevant to the subject's decision to participate throughout the clinical investigation;
- Avoid any coercion or undue improper influence on, or inducement of, the subject to participate;
- Not waive or appear to waive the subject's legal rights;
- Use native non-technical language that is understandable to the subject;
- Provide ample time for the subject to read and understand the informed consent form and to consider participation in the data collection study;

- Include personally dated signatures of the subject/subject's legal representative and the principal investigator/authorised designee responsible for conducting the informed consent process;
- Provide the subject with a copy of the informed consent form and any other written information; and,
- Ensure important new information is provided to new and existing subjects throughout the data collection process.

7.3 Subject Discontinuation/Withdrawal Criteria

Once the subject has been enrolled in the data collection study she/he may withdraw her/his consent to participate in the data collection study at any time without prejudice. Participation in this clinical investigation is entirely voluntary. Likewise, the Investigator may identify a reason that deems the subject no longer suitable for the data collection study. Reasons for discontinuation or withdrawal may include, but are not limited to, the following:

- Subject is uncooperative;
- Investigator determines that subject has developed a condition in which continued participation in the data collection study is considered potentially harmful to the subject;
- Subject withdraws their consent;
- Subject is lost to follow-up (missing scheduled consecutive follow-up visits);
- Subject incorrectly enrolled in the data collection study.

7.4 Data collection and Follow-Up for Discontinued/Withdrawn Subjects

All subjects in the data collection study are considered eligible for follow-up and will be followed per the assessment schedule outlined in **Table 1**. Subjects may withdraw at any time from the clinical trial without jeopardy or prejudice. If a subject terminates from the data collection study, the reason for data collection study termination will be recorded. If termination is a result of adverse event or death, an Adverse Event Form will also be completed. Every attempt will be made to conduct an exit/final visit prior to a subject terminating from the data collection study. The reason for early discontinuation will be documented in the source documents and electronic case report forms (eCRF).

7.5 Subjects Lost to Follow-Up

All reasonable efforts will be made to obtain complete data for all subjects, before they are considered lost to follow-up.

8.0 PRE-INDEX PROCEDURE METHODOLOGY

The following baseline data must be collected prior to the index procedure for all subjects meeting the inclusion / exclusion criteria:

- Subject Interview
- Signed Informed Consent
- Medical History
- Targeted Physical Exam (including vital signs)
- Surgical Risk Assessment (STS & EuroScore II)
- Cardiovascular Medications Documentation
- 12 lead Electrocardiogram (ECG)
- Laboratory Tests (Complete blood count (CBC): WBC with differential, RBC with HCT and Hb, platelet count, coagulation panel (PT, PTT and an INR for subjects on vitamin-K antagonist), serum creatinine, serum albumin, C-reactive protein, plasma-free Hb, serum LDH, haptoglobin and cardiac biomarkers (troponin I or T or CK/CK-MB)
- Pregnancy test for women of childbearing age within 72 hours of Index procedure
- 2D Transthoracic Echocardiogram (TTE)
- Multi-detector CT Scan Imaging
- NYHA Functional Class
- Modified Rankin Scale (mRS)
- Kansas City Cardiomyopathy Questionnaire (KCCQ)

The procedures required for screening/baseline may be conducted during more than one visit.

9.0 INDEX PROCEDURE- GENERAL DESCRIPTION

The TAVR procedure will be performed according to the IFU. Additionally, the physician will follow standard of care regarding administration of concomitant medication, antibiotics and anticoagulation therapy before and during the procedure.

The following data should be collected during the index procedure assessment period:

- Procedural details
- Adverse Event Assessment
- Anticoagulation/antiplatelet therapy administered intra-procedure

10.0 INDEX PROCEDURE THROUGH DISCHARGE

10.1 Antithrombotic Therapy

As per local routine practice: IV unfractionated heparin with a target ACT ≥ 250 seconds

10.1.2 Post-Index TAVR Procedure

As per local routine practice: Aspirin, clopidogrel, anticoagulant, based on presence/absence of any concomitant disease

10.2 Implantation Procedure

*A*ccording to the IFU

10.2.1 THV Prosthesis Assessment

After deployment the valve function is assessed by angiography and echocardiography.

10.3 Post-Index Procedure/ Prior to Leaving Hospital

The following items will be recorded once (except as specified) post–index procedure or prior to discharge.

- Cardiovascular medications
- Targeted Physical Exam (including vital signs)
- 12 lead ECG / rhythm strip
- Laboratory Tests
    - (coagulation panel (PT, PTT and an INR for subjects on vitamin-K antagonist),
    - serum creatinine, Hb, and platelet count (daily during index hospitalisation - up to 7 days post-index procedure or discharge) and
    - cardiac biomarkers (troponin I or T or CK/CK-MB)
- Echocardiographic assessment of THV function
- NYHA Functional ClassAdverse Events
- Modified Rankin Scale (mRS)

11.0 FOLLOW-UP EVALUATIONS

Follow-up evaluations will be scheduled for 1 month and 12 Months after the index procedure. Thereafter, the patient exits the data collection study and is to be followed per institutional requirements for patients with transcatheter aortic valves.

11.1 1-Month Post-Index Procedure Follow-Up Evaluation

A follow-up evaluation will be scheduled for 30 days post-index procedure (-7 /+21 days). The following assessments will be performed:

- Targeted Physical Exam (including vital signs)
- NYHA Functional Class
- Cardiovascular Medications
- Adverse Events
- 12 lead ECG
- Modified Rankin Scale (mRS)
- Echocardiography (TTE or TEE) including assessment of THV function
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- INR (if subject is on Warfarin)
- Adverse Events Assessment
- IF Applicable:
    - Deviation
    - Device Deficiency
    - Withdrawal
    - Survival Status

If the subject reports any adverse events that are potentially serious during the follow-up evaluation period, the subject should return to the investigator's facility for further evaluation of the event.

11.4 12 Month (1 Year) Post-Index Procedure Follow-Up Evaluation

A follow-up evaluation will be scheduled for 12 Month post-index procedure (± 45 days). The following assessments will be performed:

- Targeted Physical Exam (including vital signs)
- NYHA Functional Class
- Cardiovascular Medications
- Modified Rankin Scale (mRS) in the event of a stroke
- 12 lead ECG (per schedule of tests)
- Echocardiography (TTE or TEE) including assessment of THV function
- INR (if subject is on Warfarin)
- Adverse Events
- Kansas City Cardiomyopathy Questionnaire (KCCQ)

If the subject reports any adverse events that are potentially serious during the follow-up evaluation period, the subject should return to the investigator's facility for further evaluation of the event.

11.5 Data collection study Exit

If the patient exits the study prior to completing the required assessments, the data collection study exit CRF must be completed.

12.0 SCHEDULE OF ASSESSMENTS & SUBJECT EVALUATIONS

Evaluation of subjects enrolled in this data collection study will include all tests and procedures listed in the Schedule of Assessments as outlined in Table 1.

Pre-procedural echocardiography (TEE or TTE) and a baseline multi-detector CT scan are used to determine anatomical suitability for TAVR. Following ethics committee approval and patient written informed consent, the patient will be screened for eligibility by heart teams. After the procedure, enrolled patients are to be followed immediately post-procedure, at hospital discharge, and then at 1 month and 1 year as in Schedule of Assessments Table 1.

13.0 ADVERSE EVENTS

TAVR procedures to treat aortic regurgitation are well described in the literature. Risks to the subjects will be clearly explained in the Clinical Risk/Benefit Analysis Section (see **Appendix 1- Clinical Risk/Benefit Analysis**).

13.1 General Adverse Event Definitions

Adverse Event: is defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device (See **Appendix 2 – Adverse Event Definitions**).

Adverse Event Identification: a condition that is one of the following:

a) A unique symptom or event that is a change from the patient's baseline status
b) A series of symptoms or events that can be categorized as a single entity based on definitions found herein
c) A specific diagnosis responsible for a clinical change
d) A worsening or exacerbation of a pre-existing condition

Serious Adverse Event: A serious adverse event (SAE) is any untoward medical occurrence that**:**

- Results in death
- Led to serious deterioration in the health of the subject, that either resulted in:
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function, or
    - in-patient or prolonged hospitalisation, or

- medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- Led to fetal distress, fetal death or a congenital abnormality or birth defect

Serious Adverse Device Effect (SADE)
An adverse device effect that has resulted in any of the consequences characteristics of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE)
A serious adverse device effect which by its nature, incidence, severity, or outcome, has not been identified in the current version of the risk analysis report.

13.2 Adverse Event Classification

Adverse events will be assigned an attribution according to the Investigator's believed primary cause. Events will be categorized as follows:

Device Related Adverse Event: An adverse event, which in the judgment of the Investigator, results from use of the JenaValve Trilogy™ Heart Valve System.

Procedure Related Adverse Event: An adverse event which, in the judgment of the Investigator, results as a consequence of the procedure.

Concomitant Medication-Related Adverse Event: an adverse event is considered to be concomitant medication related when, in the judgment of the Investigator, it is reasonable to believe that the event is associated with concomitant medications used in conjunction with the investigational device and is not otherwise specific to the investigational device (e.g. bleeding associated with anticoagulation medication).

Pre-Existing Condition-Related Adverse Event: an adverse event is considered to be related to a pre-existing condition when, in the judgment of the Investigator, it is reasonable to believe that the event is associated with the patient's pre-existing condition and is not specific to the investigational device or index procedure. Pre-existing conditions that are aggravated or become more severe during or after the index procedure should be evaluated on a case-by-case basis to determine if the event may be more appropriately classified as device or index procedure-related.

Intercurrent Condition: It is reasonable to believe that the event is directly associated with an intercurrent condition/co-morbidity.

Intercurrent Intervention: It is reasonable to believe that the event is directly associated with an intercurrent intervention which was performed for reasons other than to address a device- or index procedure-related complication.
Unknown: The adverse reaction cannot be judged because information is insufficient or contradictory and cannot be supplemented or verified.

The Investigator, will assess all serious adverse events considered device-related for potential reportability as an Unanticipated Adverse Device Effect (UADE).

The Investigator should follow all unresolved serious adverse events until the events are resolved, the subject is lost to follow-up, the subject has withdrawn consent, or the adverse event is otherwise explained.

13.3 Events Expected to Occur with Index-Procedure

For purposes of this data collection study, the following events are not considered reportable adverse events because they are normally expected to occur in conjunction with treatment of Aortic Regurgitation or structural heart interventional procedures, or are associated with customary, standard care of subjects undergoing minimally invasive cardiovascular intervention:

- Chest pain without associated enzyme/ECG changes.
- Post-operative pain.
- Post-anesthesia emesis, nausea, or headache (within 48 hours of procedure).
- Electrolyte imbalance without clinical sequelae following procedure, even if requiring correction.
- Low grade temperature increase ($\leq$38.5°C).
- Dizziness: Imprecise term commonly used to describe various symptoms such as faintness, giddiness, imbalance, lightheadedness, unsteadiness or vertigo.
- Elevated White Blood Count, outside the standard laboratory normal value, without signs and symptoms of infection.
- Minor, localized tenderness, swelling, induration, oozing, etc. at surgical site.
- Sinus bradycardia/tachycardia that does not require treatment or intervention.
- Systolic or diastolic blood pressure changes that do not require treatment or intervention.
- Any blood transfusions during preplanned operative procedure and unrelated to an adverse event.
- Thrombocytopenia: does not become an AE until treatment is administered.
- Hyperglycemia: The use of insulin in the post op period does not constitute hyperglycemia if during the same hospitalisation. An elevated blood sugar of less than 250 mg/dl during the first 48 hours post op does not constitute hyperglycemia.
- Expected, non-clinically significant events such as non-significant lab variances.

13.4 Adverse Event Reporting Requirements

13.4.1 General Reporting Requirements (Non-Serious Adverse Events)

All adverse events must be recorded on the Adverse Event Electronic Case Report Form (eCRF) by the Investigator (or designee). The report should include: severity, duration, action taken, treatment outcome and relationship of the adverse experience to the data collection study device, procedure, concomitant medications, pre-existing condition, etc. (i.e., unrelated, related or relationship unknown).

The Investigator must also adhere to the following criteria:

- Use separate Adverse Event Form(s) to document each series of events.
- The Adverse Event Form(s) causality must be assessed by the Investigator or co-Investigator or sub-investigator.
- It is the responsibility of the Investigator to inform their IRB/EC of serious adverse events as required by their IRB/EC procedures.

13.4.2 Reporting Requirements (Serious & Unanticipated Adverse Events)

All serious and any unanticipated adverse device effects must be reported by the Investigator (or designee) by submitting the Adverse Event Electronic Case Report Form within 24 hours of learning of the adverse event.

The Investigator (or designee) shall send a written report including a narrative description of the serious and/or unanticipated adverse event to the EC or its designee within ten (10) working days of the initial report.

13.5 Patient Death

Patient death during the data collection must be reported via written documentation within 24 hours of Investigator's knowledge of the death. Notification can be made by entering the CRF in the database. Patient death must be reported to the EC in accordance with EC requirements.

14 Treatment Failures & Device Malfunctions

All reported device observations, malfunctions or failures for the JenaValve Trilogy™ Heart Valve System are required to be documented on the Procedure / Device Observation Case Report Form and reported to the EC. In the event of a suspected observation or device problem, the device shall be returned to the manufacturing company for analysis. Instructions for returning the investigational device are included in the Instructions for use (IFU).

15.0 ADMINISTRATIVE RESPONSIBILITIES

The ARTEMIS data collection study will be performed in accordance with Good Clinical Practice Guidelines, the MDR 2017/745, and ISO 14155.

15.1 Ethics Committee (EC) Approval

The Clinical Investigational Plan shall be reviewed and approved by the Ethics Committee prior to patient enrollment.

15.2 Informed Consent

The Heart Team will determine whether the patient should be treated with the JenaValve device as being at high/prohibitive surgical risk. After that determination, if the patient meets all clinical eligibility criteria, the patient (and/or their authorised legal representative) will be approached to obtain written informed consent. The background of the proposed data collection study and the benefits and risks of the procedures and data collection study should be explained to the patient or the patient's legally authorised representative. The patient or patient's legally authorised representative must sign the consent form prior to enrollment. Failure to obtain signed informed consent renders the patient ineligible for the data collection study. All enrolled subjects will complete the appropriate consent form that has been approved by ethics committee (EC). Copies of the signed informed consent shall be kept in the patient's medical records and data collection study files. A copy of the informed consent form must be given to each patient (or their authorised legal representative) enrolled in the data collection study.

Modifications to the data collection study Informed Consent must have approval from the EC.

Retrospective arm
The information relating to the processing of personal data will be made available to participants through the publication of the Information form on the Promoter's website.

15.3 Confidentiality

All data used in the analysis and reporting of this observational data collection study will be used in a manner without identifiable reference to the patient.

The investigator must assure that the subject's anonymity will be maintained and that the confidentiality of records and documents that could identify subjects will be protected,

respecting the privacy of and confidentiality rules in accordance with applicable regulatory requirements, including all applicable provisions of the GDPR and its current regulations.

- Subjects must be identified only by their assigned data collection study number and initials on all CRFs and other records and documents submitted to the EC, and other authorised parties.
- The investigator will keep a Patient Identification List with complete identification information (name, address, contact number, informed consent version number) on each subject.
- Documents such as subject written informed consent forms should be maintained by the investigator in strict confidence.

The subject should also be informed about the use of his/ her health information collected during the data collection study(data collection study data).

15.4.1 Electronic Case Report Forms

Electronic Case Report Forms (eCRF) will be used to collect all patient data during the course of the data collection study. The eCRF must be fully completed for each subject and electronically signed by the Investigator when complete.

MDR Regulations and Good Clinical Practice Guidelines require that Investigators maintain information in the data collection study patient's medical records that corroborate data collected on the eCRF. To comply with these regulatory requirements, the following information should be maintained:

- Medical history/physical condition of the data collection study patient before involvement in the data collection study sufficient to verify protocol entry criteria
- Dated and signed notes on the day of entry into the data collection study including the data collection study investigator, data collection study
- name, patient number assigned and a statement that consent was obtained
- Dated and signed notes from each data collection study patient visit with reference to the CRFs for further information, if appropriate (for specific results of procedures and exams)
- Information related to adverse events
- Data collection study patient's condition upon completion of or withdrawal from the data collection study
- Discharge summaries/procedure reports

15.4.3 Data Reporting

The Investigator or designated individual shall be responsible for recording all data collection study data on the electronic case report forms (eCRF).

The Investigator is required to electronically sign the eCRF to verify that he/she has reviewed and agrees with the recorded data. All protocol deviations shall be documented and a justification for any missed assessments shall be provided on the Protocol Deviation Case Report Form.

The Investigator will allow any regulatory body to review and inspect the data collection study files, patient eCRF, patient medical records and other related data collection study documents as required.

15.5 Record Maintenance

15.5.1 Records

The following records must be maintained in designated ARTEMIS Data collection study administrative files:

- Clinical data collection protocol and all amendments
- Ethics Committee Approval Letter(s) including EC-approved informed consent(s) (including any revisions)
- CV for all investigators
- Correspondence with the EC
- EC membership list and/or assurance number
- Investigational site authorised data collection study personnel signature list
- Device Instructions for Use
- Printed copy of blank set of CRFs
- Patent Screening & Enrollment Log
- Adverse Event Log
- Reports (includes Adverse Event reports and final reports from Investigator)

The following records must be maintained for each patient enrolled in the data collection study:

- Signed patient consent forms
- Copy of final completed CRFs
- All lab and testing results
- Record of any complications, adverse events, device problems and/or malfunctions, with supporting documentation
- Procedure reports, progress notes, physician and/or nursing notes, and patient office files

- Records pertaining to patient deaths throughout the course of the data collection study (including death records, death certificate and autopsy report, if performed)

16. Publication Policy

The result of the study will be published in peer-reviewed publications and other different forms such as abstracts, oral communications or posters.
All data and results are property of the Promoter.

APPENDIX 1: CLINICAL RISK / BENEFIT ANALYSIS

1.0 SUMMARY

The objective of this data collection study is to evaluate the "real world" safety and effectiveness of the JenaValve Trilogy™ Heart Valve System for transcatheter aortic valve replacement (TAVR) in subjects with pure native aortic regurgitation (AR) who are indicated for TAVR as being at high/prohibitive risk for surgery. There is no specific risk of participation as the indication to proceed to TAVR using the JenaValve Trilogy device is taken independently from and prior to the participation to the study. General risks to subjects undergoing the TAVR procedure are listed below.

2.0 POTENTIAL BENEFITS of TAVR

The potential benefit to data collection study subjects outweighs the risks of participation in this data collection study. The benefits may include but are not limited to, the following:

- Clinical Improvement (e.g. fewer heart failure hospitalisations, reduction in need for or high doses of cardiac medications including diuretics)
- Functional improvement (e.g. NYHA Functional Class, KCCQ)
- Unique device design features that may enhance safety of valve deployment/implantation as compared to other available non-dedicated TAVR devices
- Overall advancement of medical and scientific knowledge that may benefit future patients with similar conditions may be gained through this clinical data collection study.
- Subjects may also benefit indirectly from increased medical attention from participating in an data collection study.

There may also be other benefits that are unforeseen at this time.

3.0 POTENTIAL RISKS of TAVR

Adverse events that may be anticipated in this clinical data collection study are believed to be consistent with those associated with other minimally invasive surgical and catheter-based procedures, including TAVR procedures. Complications may occur at any time during the procedure, post-procedure or follow-up period.

Potential adverse events (AE) which may be associated with the ancillary procedures including cardiac catheterization, aortic balloon valvuloplasty and local and/or general anaesthesia include but are not limited to the following:

- Vascular damage (e.g. perforation, dissection, contrast media extravasation)
- Vascular access (femoral entry site) complications (e.g. bleeding, hematoma, arteriovenous fistula, arterial occlusion, pseudo aneurysm, wound healing disorder, pain)
- Peripheral nerve injury and/or ischemia

- Cardiovascular injury (e.g. damage of ventricle, ventricular septal perforation, myocardium or valvular structures including annulus rupture)
- Hypotension, Hypertension
- Cardiogenic tamponade or pericardial effusion
- Arrhythmias and conduction system disorders (e.g. ventricular tachycardia or fibrillation; AV block) which may require permanent pacemaker implantation
- Heart murmur
- Hemodynamic compromise or cardiogenic shock
- Heart failure or low cardiac output
- Cardiac arrest
- Angina pectoris
- Myocardial infarction
- Thrombus formation
- Embolization (e.g. air, calcific material, thrombus)
- Cerebrovascular event (e.g. TIA, Stroke, neurologic changes)
- Pulmonary embolism
- Pulmonary edema
- Pleural effusion
- Respiratory compromise or respiratory failure
- Renal compromise or renal failure
- Allergic reaction/hypersensitivity to contrast media, medication, or device materials
- Inflammation
- Infection (e.g. endocarditis, access site infection) and sepsis
- Fever
- Pneumonia
- Hemorrhage or bleeding, possibly requiring intervention or transfusion
- Retroperitoneal bleeding
- Restenosis
- Syncope
- Anemia
- Abnormal laboratory values (e.g. electrolyte imbalance)
- Exercise intolerance or weakness
- Paralysis, permanent disability, or other comorbid condition (new onset or worsening)
- Death

Potential adverse events (AE) that may be specifically associated with the TAVR procedure and the use of the investigational device include but are not limited to the following:

- Anemia including hemolytic anemia
- Coronary obstruction/transvalvular flow disturbance
- Mitral valve injury
- Device thrombosis
- Device embolization, malposition, or deployment in unintended location
- Device endocarditis
- Valve explantation
- Mechanical failure of delivery system and/or accessories
- Structural valve deterioration (intrinsic damage of valve integrity e. g. cusps tear, suture line disruption, stent breakage, wear, calcification) or device degeneration

- Non-structural valve dysfunction (e.g., regurgitation- paravalvular or transvalvular)
- Conversion into an open cardiac surgery including an extracorporeal circulation
- Implantation of second TAVR device
- Re-operation or emergency cardiac surgery
- Aortic valve stenosis

The above risks may require intervention to address the condition. There may also be other risks that are unforeseen at this time.

3.1 Alternatives to participation

Patients with severe AR who are candidates for TAVR because at high/prohibitive surgical risk have no good treatment alternatives. If patients cannot be treated by means of TAVR, the medical therapy has poor results and is the last and least effective treatment.

4.0 CONCLUSION

Patients with severe aortic regurgitation who cannot be treated surgically, can nowadays be succesfully treated by means of TAVR with the JVT device.
This study could objectively add useful “real world” information to the current evidence from the literature.

APPENDIX 2: ADVERSE EVENT DEFINITIONS

Definitions in table below are adapted from VARC-3:

ACUTE KIDNEY INJURY (VARC-3 Definition)

Stage 1: AKI that fulfills at least one of the following criteria:

- Increase in serum creatinine to 150–200% (1.5–2.0× increase) within 7 days compared with baseline
- Increase of ≥0.3 mg/dL (≥26.4 mmol/L) within 48 h of the index procedure

Stage 2: AKI that fulfills the following criterion:

- Increase in serum creatinine to 200–300% (2.0–3.0× increase) within 7 days compared with baseline

Stage 3: AKI that fulfills at least one of the following criteria:

- Increase in serum creatinine to ≥300% (>3× increase) within 7 days compared with baseline
- Serum creatinine of ≥4.0 mg/dL (≥354 mmol/L) with an acute increase of ≥0.5 mg/dL (44 mmol/L)

Stage 4: AKI requiring new temporary or permanent renal replacement therapy

ACUTE VESSEL OCCLUSION

State of complete luminal obstruction with no antegrade blood flow.

ADVERSE EVENT DEFINITIONS

- **Adverse Event (AE)** An adverse event is any undesirable experience (sign, symptom, illness, or other medical event) occurring to the patient, and that appears or worsens during the clinical data collection study, whether or not associated with the investigational product or related procedures.
- **Serious Adverse Event (SAE)** Adverse event that: a) led to a death, b) led to a serious deterioration in health that either: 1) resulted in a life-threatening illness or injury, or 2) resulted in a permanent impairment of a body structure or a body function, or 3) required in-patient hospitalisation or prolongation of existing hospitalisation, or 4) resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function. c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

This definition includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if

circumstances had been less fortunate. These are handled under the SAE reporting system.
A planned hospitalisation for pre-existing condition, or a procedure required by the data collection study protocol without a serious deterioration in health, is not considered to be a serious adverse event.

- **Adverse Device Effect (ADE)** Adverse event related to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE: This includes any event that is a result of a use error or intentional misuse.
- **Serious Adverse Device Effect (SADE)** Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
- **Unanticipated Adverse Device Effect (UADE)** Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree if incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.
- **Unanticipated Serious Adverse Device Effect (USADE)** Serious adverse device effect which by its nature, incidence, severity, or outcome has Unanticipated Serious Adverse Device Effect (USADE) Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. NOTE: Anticipated: an effect which by its nature, incidence, severity, or outcome has been previously identified in the risk analysis report.

ALL-CAUSE MORTALITY (VARC-3 Defined)

- **Cardiovascular mortality**

  Death meeting one of the following criteria:
  - Related to heart failure, cardiogenic shock, bioprosthetic valve dysfunction, myocardial infarction, stroke, thromboembolism, bleeding, tamponade, vascular complication, arrhythmia or conduction system disturbances, cardiovascular infection (e.g. mediastinitis, endocarditis), or other clear cardiovascular cause
  - Intraprocedural death
  - Sudden death
  - Death of unknown cause

- **Valve Related Mortality**

  Cardiovascular mortality adjudicated to be associated with bioprosthetic valve dysfunction (BVD).

- **Non-cardiovascular mortality**

  Death clearly related to a non-cardiovascular cause: such as respiratory failure not related to heart failure (e.g. pneumonia), renal failure, liver failure, infection (e.g. urosepsis), cancer, trauma, and suicide.

BLEEDING (VARC-3 Defined)

Overt bleeding that fulfils one of the following criteria:

Type 1

- Overt bleeding that does not require surgical or percutaneous intervention, but does require medical intervention by a health care professional, leading to hospitalisation, an increased level of care or medical evaluation (BARC 2)
- Overt bleeding that requires a transfusion of 1 unit of whole blood/red blood cells (BARC 3a)

Type 2

- Overt bleeding that requires a transfusion of 2-4 units of whole blood/red blood cells (BARC 3a)
- Overt bleeding associated with a hemoglobin drop of >3 g/dL (>1.86 mmol/L) but <5 g/d (<3.1 mmol/L) (BARC 3a)

Type 3

- Overt bleeding in a critical organ, such as intracranial, intraspinal, intraocular, pericardial (associated with hemodynamic compromise/tamponade and necessitating intervention), or intramuscular with compartment syndrome (BARC 3b, BARC 3c)
- Overt bleeding causing hypovolemic shock or severe hypotension (systolic blood pressure <90 mmHg lasting >30 min and not responding to volume resuscitation) or requiring vasopressors or surgery (BARC 3b)
- Overt bleeding requiring reoperation, surgical exploration, or re-intervention for the purpose of controlling bleeding (BARC 3b, BARC 4)
- Post-thoracotomy chest tube output ≥2 L within a 24 h period (BARC 4)
- Overt bleeding requiring a transfusion of ≥5 units of whole blood/red blood cells (BARC 3a)

- Overt bleeding associated with a hemoglobin drop ≥5 g/dL (≥3.1 mmol/L) (BARC 3b)

Type 4

- Overt bleeding leading to death. Should be classified as:
  - *Probable*: Clinical suspicion (BARC 5a)
  - *Definite*: Confirmed by autopsy or imaging (BARC 5b)

CARDIAC STRUCTURAL COMPLICATIONS (VARC-3 Defined)

Major - One of the following:

- Cardiac structure perforation, injury, or compromise resulting in death, VARC type ≥2 bleeding, hemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention
- New pericardial effusion resulting in death, VARC type ≥2 bleeding, hemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention
- Coronary obstruction resulting in death, hemodynamic compromise, myocardial infarction, or unplanned surgical or percutaneous intervention. Coronary obstruction may be acute (during the procedure) or delayed (after completion of the procedure).
- Coronary artery access difficulties for needed coronary angiography or intervention, resulting in death, hemodynamic compromise, myocardial infarction, coronary or aortic root injury, compromise in aortic valve prosthesis integrity, unplanned surgical or percutaneous intervention, or the inability to perform the intended procedure.

- Minor - One of the following:
  - Cardiac structure perforation, injury, or compromise not resulting in death, VARC type ≥2 bleeding, hemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention
  - New pericardial effusion not resulting in death, VARC type ≥2 bleeding, hemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention
  - Coronary obstruction not resulting in death, hemodynamic compromise, myocardial infarction, or unplanned surgical or percutaneous intervention
  - Coronary artery access difficulties for needed coronary angiography or intervention, not resulting in death, hemodynamic compromise, myocardial infarction, coronary or

aortic root injury, compromise in aortic valve prosthesis integrity, unplanned surgical or percutaneous intervention, or the inability to perform the intended procedure.

CARDIOGENIC SHOCK

Acute decreased pumping ability of the heart and/or LVAD that causes a shock-like state.

CONDUCTION DISTURBANCES AND ARRHYTHMIAS (VARC-3 Defined)

New-onset conduction disturbance: **defined as a new conduction disturbance relative to baseline.**

- Timing of occurrence:
  - **Procedural**: ≤24 h after the index procedure
  - **Delayed**: > 24 h after the index procedure
- Conduction disturbances
  - 1st-, 2nd-, 3rd-degree AV block
  - Left bundle branch block
  - IVCD with QRS ≥120 ms
- Duration:
  - **Transient**: resolved before discharge or ≤7 days after the index procedure in case of prolonged hospitalisation
  - **Persistent**: present at hospital discharge or >7 days after the index procedure in case of prolonged hospitalisation
  - **Permanent**: present >30 days after the index procedure
- Permanent pacemaker
  - **Type**: single, dual, biventricular, defibrillator, leadless
  - **Timing**: No. of days after the index procedure
  - **Indication**: including AV Block, SSS
- Atrial fibrillation (or flutter)

New-onset arrhythmia: defined as any arrhythmia that was not present at baseline that has the ECG characteristics of atrial fibrillation (or flutter) and lasts sufficiently long to be recorded on a 12-lead ECG or at least 30 s on a rhythm strip.
Timing of occurrence:

- **Periprocedural:** ≤30 days after the index procedure
- **Late/spontaneous:** >30 days after the index procedure
- **Paroxysmal:** atrial fibrillation that terminates spontaneously or with intervention ≤7 days of onset.
- **Persistent:** Continuous atrial fibrillation that is sustained >7 days.

- **Long-standing persistent:** Continuous atrial fibrillation >12 months in duration.
- **Permanent:** Used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm.

CONGESTIVE HEART FAILURE

Re-hospitalisation for signs or symptoms of right or left sided volume overload. Diagnosis must be confirmed by at least one of the following:

- Chest x-ray report confirming pulmonary vascular congestion,
- Unplanned treatment of diagnosed new or worsening HF requiring the use of intravenous diuretics, inotropes, or vasodilators during any hospital admission or overnight stay in a healthcare facility.
- Hemodynamic assessment showing elevated right or left sided increased pressures.

CONVERSION TO OPEN SURGERY (VARC-3 Defined)

Conversion to open sternotomy or thoracotomy using cardiopulmonary bypass secondary to any procedure-related complication or failed intended transcatheter approach. Should be classified as:

- Intraprocedural conversion: during the index procedure
- Periprocedural conversion: ≤30 days after the index procedure
- Delayed conversion: >30 days after the index procedure

ENDOCARDITIS (VARC-3 Defined)

Meeting at least one of the following criteria: (i) Fulfillment of the Duke endocarditis criteria (ii) Evidence of abscess, pus, or vegetation confirmed as secondary to infection by histological or microbiological studies during re-operation; and (iii) Evidence of abscess, pus, or vegetation confirmed on autopsy.

MITRAL REGURGITATION

Echocardiographic and Doppler parameters used in grading mitral regurgitation (MR) severity, according to the current American Society of Echocardiography Guidelines for Non-invasive Evaluation of Native Valve Regurgitation[21].

Mitral regurgitation grading according to the American Society of Echocardiography (4)			
	MR Severity*		
	Mild MR	Moderate MR	Severe MR
Structural			
MV morphology	**None or mild leaflet abnormality** (e.g., mild thickening, calcifications or prolapse, mild tenting)	Moderate leaflet abnormality or moderate tenting	**Severe valve lesions** (primary: flail leaflet, ruptured papillary muscle, severe retraction, large perforation; secondary: severe tenting, poor leaflet coaptation)
LV and LA size†	Usually normal	Normal or mild dilated	Dilated‡
Qualitative Doppler			
Color flow jet area§	**Small, central, narrow, often brief**	Variable	Large central jet (>50% of LA) or eccentric wall-impinging jet of variable size
Flow convergence‖	**Not visible, transient or small**	Intermediate in size and duration	**Large throughout systole**
CWD jet	Faint/partial/parabolic	Dense but partial or parabolic	Holosystolic/dense/**triangular**
Semiquantitative			

Mitral regurgitation grading according to the American Society of Echocardiography (4)			
	MR Severity*		
	Mild MR	Moderate MR	Severe MR
VCW (cm)	<0.3	Intermediate	≥0.7 (>0.8 for biplane)¶
Pulmonary vein flow#	**Systolic dominance** (may be blunted in LV dysfunction or AF)	Normal or systolic blunting#	Minimal to no systolic flow / **systolic flow reversal**
Mitral inflow∗∗	**A-wave dominant**	Variable	E-wave dominant (>1.2 m/sec)
Quantitative††,‡‡			
EROA, 2D PISA (cm2)	<0.20	0.20-0.29	0.30-0.39

Bolded qualitative and semiquantitative signs are considered specific for their MR grade.
∗ All parameters have limitations, and an integrated approach must be used that weighs the strength of each echocardiographic measurement. All signs and measures should be interpreted in an individualized manner that accounts for body size, sex, and all other patient characteristics;† This pertains mostly to patients with primary MR; ‡ LV and LA can be within the "normal" range for patients with acute severe MR or with chronic severe MR who have small body size, particularly women, or with small LV size preceding the occurrence of MR; § With Nyquist limit 50-70 cm/sec.
‖ Small flow convergence is usually <0.3 cm, and large is ≥ 1 cm at a Nyquist limit of 30-40 cm/sec; ¶ For average between apical two- and four-chamber views; # Influenced by many other factors (LV diastolic function, atrial fibrillation, LA pressure); ∗∗ Most valid in patients >50 years old and is influenced by other causes of elevated LA pressure; †† Discrepancies among EROA, RF, and RVol may arise in the setting of low or high flow states; ‡‡ Quantitative parameters can help subclassify the moderate regurgitation group.

MYOCARDIAL INFARCTION (VARC-3 and 4th Universal Definition(6) Defined

Type 1 (Spontaneous MI) (>48 h after the index procedure)

- Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL with at least one of the following:
  - Symptoms of acute ischemia
  - New ischemic ECG changes (new ST-segment or T-wave changes or new LBBB)
  - New pathologic Q-waves in ≥2 contiguous leads
  - Imaging evidence of a new loss of viable myocardium or new wall motion abnormality in a pattern consistent with an ischemic etiology
  - Identification of a coronary thrombus by angiography or autopsy
- Post-mortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large, circumscribed area of necrosis with or without intramyocardial hemorrhage, meets the type 1 MI criteria regardless of cTn values

Type 2 (Imbalance between myocardial oxygen supply and demand)

- Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following:
  - Symptoms of ischemia
  - ECG changes indicative of new ischemia (new ST-segment or T-wave changes or new LBBB)
  - New pathologic Q-waves in ≥2 contiguous leads
  - Imaging evidence of a new loss of viable myocardium or new wall motion abnormality

Type 3 (MI associated with sudden cardiac death)

- Patients who suffer cardiac death, with symptoms suggestive of myocardial ischemia accompanied by presumed new ischemic ECG changes or ventricular fibrillation but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.

Type 4A (Criteria for PCI-related MI ⩽48 h after the index procedure)

- **In patients with normal baseline CK-MB:** The peak CK-MB measured within 48 h of the procedure ≥10 x

the local laboratory ULN or CKMB≥5 x ULN with one or more of the following:

- New pathologic Q-waves in ≥2 contiguous leads
- New persistent LBBB
- Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch
- Substantial new loss of viable myocardium on imaging related to the procedure

- In the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the procedure rises to ≥70 x the local laboratory ULN or ≥35 x ULN with one or more of the following:
  - New pathologic Q-waves in ≥2 contiguous leads
  - New persistent LBBB
  - Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch
  - Substantial new loss of viable myocardium on imaging related to the procedure
- **In patients with elevated baseline CK-MB (or cTn):** The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level plus new ECG changes as described.

Type 4B (Stent thrombosis)

- Stent thrombosis as documented by angiography or autopsy using the same criteria utilized for type 1 MI.
- Acute: 0 to 24 h
- Subacute: >24 h to 30 days
- Late: >30 days to 1 year
- Very late: >1 year after stent implantation

Type 5 Periprocedural (post-SAVR, TAVR or CABG) MI (⩽48 h after the index procedure)

- **In patients with normal baseline CK-MB:** The peak CK-MB measured within 48 h of the procedure ≥10 x the local laboratory ULN or CKMB ≥5 x ULN with one or more of the following:
  - New pathologic Q-waves in ≥2 contiguous leads
  - New persistent LBBB
  - Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch
  - Substantial new loss of viable myocardium on imaging related to the procedure

- In the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the procedure rises to ≥70x the local laboratory ULN or ≥35x ULN with one or more of the following:
  - New pathologic Q-waves in ≥2 contiguous leads
  - New persistent LBBB
  - Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch
  - Substantial new loss of viable myocardium on imaging related to the procedure
- **In patients with elevated baseline CK-MB (or cTn):** The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level plus new ECG changes as described.

NEW YORK HEART ASSOCIATION CLASSIFICATION (NYHA)

Classification system for defining cardiac disease and related functional limitations into four categories:

Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

PULMONARY INSUFFICIENCY

Post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) ratio [FEV1/FVC] less than 70% Post-bronchodilator FEV1 less than 80% predicted, with or without chronic symptoms (i.e., cough or sputum production)

STROKE (VARC-3 Defined)

Stroke classification

- **Ischemic:** Acute onset of focal neurological signs or symptoms conforming to a focal or multifocal vascular territory within the brain, spinal cord, or retina (NeuroARC[23] Type 1a or 1aH) and fulfilling one of the following criteria:
  - Signs or symptoms lasting ≥24 h or until death, with pathology or neuroimaging evidence of CNS infarction, or absence of other apparent causes
  - Symptoms lasting <24 h, with pathology or neuroimaging confirmation of CNS infarction in the corresponding vascular territory
- **Hemorrhagic:** Acute onset of neurological signs or symptoms due to intracranial bleeding from intracerebral or subarachnoid hemorrhage not due to trauma (NeuroARC[23] Types 1b or 1c)
- **Stroke, not otherwise specified:** Acute onset of neurological signs or symptoms persisting ≥24 h or until death but without sufficient neuroimaging or pathology evidence to be classified (NeuroARC[23] Type 1d).

Stroke Grading

- Acute stroke severity
  - **Mild** neurological dysfunction: NIHSS 0-5
  - **Moderate** neurological dysfunction: NIHSS 6-14
  - **Severe** neurological dysfunction: NIHSS ≥15

Stroke Disability

- **Fatal stroke**: death resulting from a stroke
- **Stroke with disability**: mRS score of ≥2 at 90 days and increase of ≥1 from pre-stroke baseline
- **Stroke without disability**: mRS score of 0 (no symptoms) or 1 (able to carry out all usual duties and activities) at 90 days or *no* increase in mRS category from pre-stroke baseline

SURGERY OR INTERVENTION RELATED TO THE DEVICE OR A MAJOR VASCULAR OR ACCESS RELATED OR CARDIAC STRUCTURAL COMPLICATION

Surgery or intervention related to the device involves dysfunction of the valve requiring AVR (e.g. implantation of another THV or SAVR) or intervention that does not require replacement (e.g. BAV or paravalvular leak closure) will be collected and reported as separate secondary endpoints. Both surgery or interventions that require AVR or non replacement intervention on the device are considered events resulting in technical and device failure, and are components of the primary safety endpoint at 30 days.

Surgery or intervention will be adjudicated by the CEC as related to device, implant procedure, both. Surgery or intervention adjudicated by the CEC as related to the device or implant procedure will be reported as surgery or intervention related to the device but unrelated procedures unrelated will not. Cardiac structural complications and vascular or access related complications, as defined by VARC-3, fulfill the criteria as well as device failure.

TRANSPLANTATION

- **Planned Transplantation:** Patient undergoes the transplantation procedure as an event unrelated to the THV or THV procedure
- **Unplanned Transplantation:** Patient undergoes the cardiac transplantation procedure on an urgent basis within 30 days of THV implant as a consequence of THV implantation or the THV implant procedure.

TRICUSPID REGURGITATION

Echocardiographic and Doppler parameters used in grading tricuspid regurgitation (TR) severity, according to the current American Society of Echocardiography Guidelines for Non-invasive Evaluation of Native Valve Regurgitation [21].

Tricuspid regurgitation grading according to the American Society of Echocardiography (4)			
Parameters	**Mild TR**	**Moderate TR**	**Severe TR**
Structural			
TV morphology	Normal or mildly abnormal leaflets	Moderately abnormal leaflets	Severe valve lesions (e.g., flail leaflet, severe

Tricuspid regurgitation grading according to the American Society of Echocardiography (4)			
Parameters	**Mild TR**	**Moderate TR**	**Severe TR**
			retraction, large perforation)
RV and RA size	Usually normal	Normal or mild dilatation	Usually dilated∗
Inferior vena cava diameter	Normal < 2 cm	Normal or mildly dilated 2.1- 2.5 cm	Dilated > 2.5 cm
Qualitative Doppler			
Color flow jet area†	Small, narrow, central	Moderate central	Large central jet or eccentric wall-impinging jet of variable size
Flow convergence zone	Not visible, transient or small	Intermediate in size and duration	Large throughout systole
CWD jet	Faint/partial/parabolic	Dense, parabolic or triangular	Dense, often triangular
Semiquantitative			
Color flow jet area (cm^2)†	Not defined	Not defined	>10
VCW (cm)†	<0.3	0.3-0.69	≥0.7
PISA radius (cm)‡	≤0.5	0.6-0.9	>0.9
Hepatic vein flow§	Systolic dominance	Systolic blunting	Systolic flow reversal
Tricuspid inflow§	A-wave dominant	Variable	E-wave >1.0 m/sec
Quantitative			
EROA (cm^2)	<0.20	0.20-0.39	≥0.40
RVol (2D PISA) (mL)	<30	30-44	≥45

∗ RV and RA size can be within the "normal" range in patients with acute severe TR;† With Nyquist limit >50-70 cm/sec; ‡ With baseline Nyquist limit shift of 28 cm/sec; § Signs are nonspecific and are influenced by many other factors (RV diastolic function, atrial fibrillation, RA pressure); ‖ There are little data to support further separation of these values.

VALVE DYSFUNCTION - Aortic Bioprosthetic Valve Dysfunction (BVD) (VARC-3 Defined)

Unintended Performance of the Valve

Standard VARC-3 criteria are mean gradient <20 mmHg, peak velocity <3 m/s, Doppler velocity index >_0.25, and less than moderate aortic regurgitation. hemodynamic criteria. The intended use of the THV is to avoid aortic regurgitation, As such this definition is modified to the presence of moderate or greater aortic regurgitation.

Clinical Presentation

Subclinical: Any bioprosthetic valve dysfunction associated with absent or mild hemodynamic changes, AND absent symptoms or sequelae

Structural valve deterioration (SVD)

Intrinsic permanent changes to the prosthetic valve, including wear and tear, leaflet disruption, flail leaflet, leaflet fibrosis and/or calcification, or strut fracture or deformation.

Non-structural valve dysfunction (NSVD)

Any abnormality, not intrinsic to the prosthetic valve, resulting in valve dysfunction. Examples include residual intra- or paraprosthetic aortic regurgitation; leaflet entrapment by pannus, tissue, or suture; inappropriate positioning or sizing; dilatation of the aortic root after stentless prostheses or aortic valve sparing operations; prosthesis-patient mismatch; and embolization.

Hemodynamic Changes

Stage 1: Morphological valve deterioration

- Evidence of structural valve deterioration, non-structural valve dysfunction (other than paravalvular regurgitation or prosthesis-patient mismatch), thrombosis, or endocarditis *without significant hemodynamic changes*.

Stage 2: Moderate hemodynamic valve deterioration

- Increase in mean transvalvular gradient ≥10 mmHg resulting in mean gradient ≥20 mmHg with concomitant decrease in EOA ≥0.3 cm^2 or ≥25% and/or decrease in Doppler velocity index ≥0.1 or

≥20% compared with echocardiographic assessment performed 1–3 months post-procedure, OR new occurrence or increase of ≥1 grade of intraprosthetic AR resulting in ≥moderate AR.

Stage 3: Severe hemodynamic valve deterioration

- Increase in mean transvalvular gradient ≥20 mmHg resulting in mean gradient ≥30 mmHg with concomitant decrease in EOA ≥0.6 cm^2 or ≥50% and/or decrease in Doppler velocity index ≥0.2 or ≥40% compared with echocardiographic assessment performed 1–3 months post-procedure, OR new occurrence, or increase of ≥2 grades, of intraprosthetic AR resulting in severe AR.

Bioprosthetic valve failure (BVF)

- ***Stage 1:*** Any bioprosthetic valve dysfunction associated with clinically expressive criteria (new-onset or worsening symptoms, LV dilation/ hypertrophy/dysfunction, or pulmonary hypertension) or irreversible Stage 3 hemodynamic valve deterioration (HVD)
- ***Stage 2:*** Aortic valve reoperation or re-intervention
- ***Stage 3:*** Valve-related death

Prosthetic Aortic Valve Regurgitation (VARC-3 Defined)

Prosthetic aortic valve regurgitation						
Three-class grading	None/ Trace	Mild		Moderate		Severe
Five-class grading	None/ Trace	Mild	Mild-moderate	Moderate	Moderate-severe	Severe
Doppler parameters (qualitative or semi-quantitative)						
Jet features						
Extensive/ wide jet origin	Absent	Absent	Absent	Present	Present	Present
Multiple jets	Possible	Possible	Often present	Often present	Usually present	Usually present
Jet path visible along the stent	Absent	Absent	Possible	Often present	Usually present	Present
Proximal flow convergence	Absent	Absent	Absent	Possible	Often present	Often present
E/A ratio	<1.0	<1.0	<1.0	≥1.5	≥1.5	≥1.5
Vena contracta width (mm)	N.Q.	<2	2 to <4	4 to <5	5 to <6	≥6
Vena contracta area (mm^2)	N.Q.	<5	5 to <10	10 to <20	20 to <30	≥30
Jet width at its origin	Narrow (<5)	Narrow (5 to <15)	Intermediate (15 to <30)	Intermediate (30 to <45)	Large (45 to <60)	Large (≥60)
Jet density	Faint	Faint	Variable	Dense	Dense	Dense
Jet deceleration rate	Slow	Slow	Variable (200 to <500)	Variable (200 to <500)	Variable (200 to <500)	Steep (<200)

Prosthetic aortic valve regurgitation						
Three-class grading	None/ Trace	Mild		Moderate		Severe
Five-class grading	None/ Trace	Mild	Mild-moderate	Moderate	Moderate-severe	Severe
Diastolic flow reversal in descending aorta	Absent	Absent or brief	Intermediate	Intermediate	Holodiastolic	Holodiastolic
Circumferential extent of PVR	N.Q.	<5	5 to <10	10 to <20	20 to <30	≥30
Doppler parameters (quantitative)						
Regurgitant volume	<15	<15	15 to <30	30 to <45	45 to <60	≥60
Regurgitant orifice area	<5	<5	5 to <10	10 to <20	20 to <30	≥30
Regurgitant fraction	<15	<15	15 to <30	30 to <40	40 to <50	≥50
CMR regurgitant fraction	<15	<15	15 to <30	30 to <40	40 to <50	≥50

VALVE MALPOSITIONING (VARC-3 Defined)

Should be classified as:

- *Valve migration:* After initial correct positioning, the valve prosthesis moves upward or downward, within the aortic annulus from its initial position, without valve embolization
- *Valve embolization:* The valve prosthesis moves either upward or downward after final deployment such that it loses contact with the aortic annulus
- *Ectopic valve deployment:* Irretrievable deployment of a valve prosthesis at a site other than the intended position because of valve embolization or inability to deliver the prosthesis to the desired location

VALVE THROMBOSIS (VARC-3 Defined)

Clinical sequelae of a thromboembolic event (e.g., stroke, TIA, retinal occlusion, other evidence of systemic thromboembolism) or worsening valve stenosis/regurgitation (e.g., signs of heart failure, syncope) and:

- Hemodynamic valve deterioration Stage 2 or 3a or
- Confirmatory imaging (CT evidence of HALT or TEE findings)

In the absence of clinical sequelae, both:

- Hemodynamic valve deterioration Stage 3a and
- Confirmatory imaging (CT evidence of HALT or TEE findings)

    - Timing
        - Acute: Within 0–24 h of the index procedure
        - Subacute: >24 h and ≤30 days after the index procedure
        - Late: >30 days and ≤1 year after the index procedure
        - Very late: >1 year after the index procedure

Response to anticoagulant therapy (≥3 months)

- Resolved: Partial or complete resolution of symptoms, imaging findings, and HVD
- Persistent: No improvement in symptoms, imaging findings, or HVD
- Recurrent: Recurrence of symptoms, imaging findings, or HVD

- Certainty of diagnosis

  - Definite: Histopathological confirmation
  - Probable: Hemodynamic changes and imaging findings compatible with valve thrombosis, with resolution of hemodynamic changes and imaging findings following anticoagulation therapy
  - Possible: Imaging demonstrated findings compatible with leaflet thrombosis formation, but either hemodynamic changes or imaging findings persist following anticoagulation therapy or anticoagulation therapy is not (yet) administered.

VASCULAR AND ACCESS-RELATED COMPLICATIONS (VARC-3 Defined)

- Vascular complications
  - Major - One of the following:
    - Aortic dissection or aortic rupture
    - Vascular (arterial or venous) injury (perforation, rupture, dissection, stenosis, ischemia, arterial or venous thrombosis including pulmonary embolism, arteriovenous fistula, pseudoaneurysm, hematoma, retroperitoneal hematoma, infection) or compartment syndrome resulting in death, VARC type ≥2 bleeding, limb or visceral ischemia, or irreversible neurologic impairment.
    - Distal embolization (non-cerebral) from a vascular source resulting in death, amputation, limb or visceral ischemia, or irreversible end-organ damage
    - Unplanned endovascular or surgical intervention resulting in death, VARC type ≥2 bleeding, limb or visceral ischemia, or irreversible neurologic impairment. Planned initial vascular access via surgical cutdown is not considered a vascular complication, while complications of this form of access are.
    - Closure device failure resulting in death, VARC type ≥2 bleeding, limb or visceral ischemia, or irreversible neurologic impairment
  - Minor – One of the following:
    - Vascular (arterial or venous) injury (perforation, rupture, dissection, stenosis, ischemia, arterial or venous thrombosis

including pulmonary embolism, arteriovenous fistula, pseudoaneurysm, hematoma, retroperitoneal hematoma, infection) not resulting in death, VARC type ≥2 bleeding, limb or visceral ischemia, or irreversible neurologic impairment
    - Distal embolization treated with embolectomy and/or thrombectomy, not resulting in death, amputation, limb or visceral ischemia, or irreversible end-organ damage
    - Any unplanned endovascular or surgical intervention, ultra-sound guided compression, or thrombin injection, not resulting in death, VARC type ≥2 bleeding, limb or visceral ischemia, or irreversible neurologic impairment
    - Closure device failure not resulting in death, VARC type ≥2 bleeding, limb or visceral ischemia, or irreversible neurologic impairment
- Access-related non-vascular complications
    - Major – One of the following:
        - Non-vascular structure, non-cardiac structured perforation, injury, or infection resulting in death, VARC type ≥2 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention.
        - Non-vascular access site (e.g., trans-apical left ventricular) perforation, injury, or infection resulting in death, VARC type ≥2 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention.

    - Minor – One of the following:
        - Non-vascular structure, non-cardiac structure perforation, injury, or infection *not* resulting in death, VARC type 2, irreversible nerve injury, or requiring unplanned surgery or percutaneous intervention
        - Non-vascular access site (e.g. trans-apical left ventricular) perforation, injury, or infection *not* resulting in death, VARC type 2 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention.

BIBLIOGRAPHY

1. Vahl, Torsten P et al. Transcatheter aortic valve implantation in patients with high-risk symptomatic native aortic regurgitation (ALIGN-AR): a prospective, multicentre, single-arm study. The Lancet, Volume 403, Issue 10435, 1451 – 1459.
2. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based . *Lancet* 2006; **368**(9540): 1005-11.
3. Dujardin KS, Enriquez-Sarano M, Schaff HV, Bailey KR, Seward JB, Tajik AJ. Mortality and morbidity of aortic regurgitation in clinical practice. A long-term follow-up study. *Circulation* 1999; **99**(14): 1851-7.
4. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2021; **143**(5): e72-e227.
5. Généreux P, Piazza N, Alu MC, et al. Valve Academic Research Consortium 3: Updated Endpoint Definitions for Aortic Valve Clinical Research. *Journal of the American College of Cardiology* 2021; **77**(21): 2717-46.
6. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). *Circulation* 2018; **138**(20): e618-e51.