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Assessment of the Portico™ Transcatheter Aortic Valve for Valve-in-Valve Use

Version Number	[redacted]
Date	03June2021
Planned Number of Sites and Region(s)	[redacted]
Study Type	Multicenter, international, single arm, retrospective, data-collection study.
Abbott Medical Expert	[redacted]
Sponsor	Abbott [redacted]
Study Monitor	[redacted]
Electronic Data Capture Software	[redacted]
Core Laboratories	[redacted]
CIP Author of Current Version	[redacted]

[redacted]

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I have read and agree to adhere to the study plan and all regulatory requirements applicable in conducting this study.

Site Principal Investigator

Printed name:
Signature:
Date:

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CIP Synopsis

Title:	Retrospective Assessment of the Portico™ Transcatheter Aortic Valve for Valve-in-Valve Use
Acronym/Short Title:	Portico Valve-in-Valve Retrospective Registry
Purpose:	The purpose of this clinical study is to retrospectively evaluate the safety and performance of the Portico™ transthoracic aortic valve for the treatment of a failed surgical aortic valve bioprosthesis, Valve-in-Valve (ViV), in patients who were considered to be at increased risk for redo surgical aortic valve replacement. Primary endpoints, descriptive endpoints, and designated events of interest will be defined and adjudicated per the Valve Academic Research Consortium-2 (VARC-2) and VARC-3 criteria[1, 2].
Endpoints:	**Primary Safety Endpoint:** Composite of all-cause mortality, disabling stroke, life threatening bleeding requiring blood transfusion, acute kidney injury (AKI) requiring dialysis, and major vascular complications at 30 days. **Primary Performance Endpoint:** Composite of all-cause mortality or disabling stroke at 1 year.
	Descriptive Endpoints: 1. Procedure success defined as: • Absence of procedural mortality AND • Successful access, delivery of the valve, and retrieval of the delivery system 2. Evaluation of adverse event rates <u>At 30 days and one year:</u> • All-cause mortality • Cardiovascular-related mortality • All Stroke (by severity) • Transient Ischemic Attacks (TIA) • Myocardial infarction (MI) • New pacemaker implant (PPI) • Coronary obstruction <u>At 30 days:</u> • Minor, Major, and Life-threatening bleeding • Major vascular, major non-vascular access-related, or cardiac structure complication • Acute Kidney Injury (AKI) stages 1-4 3. Evaluation of adverse event rates annually through 5 years: • All-cause mortality • Cardiovascular-related mortality • All Stroke (by severity) • TIA

The following will be collected if standard of care or if available:

4. Echocardiographic assessment of valve performance at discharge, 30 days, 1 year, and annually through 5 years including:
- Transvalvular mean gradient
- Indexed Effective orifice area (iEOA)
- Doppler velocity index (DVI)
- Aortic Valve Area (AVA)
- Non-structural valve dysfunction:
  - Prosthetic patient mismatch (PPM) per body mass index (BMI)
  - Degree of aortic valve regurgitation (transvalvular and paravalvular leak (PVL)) as none/trace, mild, mild-moderate, moderate, moderate/severe, or severe per VARC-3; and per VARC-2 none/trace, mild, moderate, or severe).

5. Valve Integrity at 1 year and annually through 5 years as assessed by:
- Structural Valve Deterioration (SVD) (by hemodynamic valve deterioration (HVD) stages 1-3 per VARC-3)
  Confirmed intrinsic permanent changes to the prosthetic valve, including:
  - Wear and tear
  - Leaflet disruption
  - Flail leaflet
  - Leaflet fibrosis and/or calcification
  - Strut fracture or deformation

- Non-structural Valve Dysfunction other than PVL and PPM (HVD stages 1-3 per VARC-3)
  Any abnormality not intrinsic to the prosthetic valve resulting in valve dysfunction other than PVL and PPM, including:
  - Leaflet entrapment by pannus or tissue
  - Inappropriate positioning or sizing
  - embolization

- Clinically Significant Thrombosis
  Meeting either of the following criteria:
  - Clinical sequelae of thromboembolic event or worsening AS/transvalvular AR **and** HVD Stage 2-3 or confirmatory imaging of thrombosis
    Or
  - In the absence of clinical sequelae, **both** HVD Stage 3 **and** confirmatory imaging

- Endocarditis (by HVD stages 1-3 per VARC-3)
  Meeting at least one of the following criteria:

	○ Fulfilment of the Duke endocarditis criteria ○ Evidence of abscess, pus, or vegetation confirmed as secondary to infection by histological or microbiological studies during re-operation ○ Evidence of abscess, pus or vegetation confirmed on autopsy. The following definitions of HVD Stages (1-3) will be used when assessing valve integrity. • Stage 1 (Morphological Valve Deterioration): Evidence of SVD, non-structural valve dysfunction (other than paravalvular or PPM), 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 graded of intra-prosthetic 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 intra-prosthetic AR resulting in severe AR. • Any need for Portico TAVI re-intervention after implant through 5 years 6. Clinical benefit endpoints defined as improvement from baseline to 30 days, 1 year, and annually through 5 years from index procedure, including: • New York Heart Association (NYHA) functional classification
Design:	This is a multi-center, international, single-arm, retrospective data-collection study. [redacted] The study will enroll subjects who had a documented failed surgical aortic valve bioprosthesis (stenosed, insufficient, or combined etiology) considered to be at increased risk for redo surgical aortic valve replacement (SAVR) surgery that underwent an attempted Portico™ TAVR in any SAVR, referred to here as valve-in-valve (ViV).

	To participate in this study, patients must have been considered at increased risk for surgical aortic valve replacement and meet eligibility requirements. [redacted] An independent Clinical Events Committee (CEC) will adjudicate all specified safety endpoints according to standardized VARC-2 and VARC-3 criteria; CEC adjudicated adverse events will be presented when reporting study results; source documents will be requested for review by the CEC. An independent echocardiographic Core Laboratory will analyze available echocardiographic exams according to standardized guidelines. Aortic assessments will be based on current American Society of Echocardiography guidelines and VARC definitions. [redacted]
Devices used:	The devices to be used in this study include the Portico™ transthoracic aortic valve (23, 25, 27, and 29 mm sizes), Portico™ delivery system or the FlexNav™ delivery system, and the Portico loading system or the FlexNav loading system. Each has received approval from the Therapeutic Goods Administration (TGA) in Australia and CE Mark approval in Europe.
Study Population for the Primary Analysis Study Arm:	A patient becomes a subject in the study once he/she has been fully informed about the study, has agreed to participate and has signed and dated the Informed Consent Form (ICF). For deceased patients, all institutional/local legal and regulatory requirements for enrollment and use of the patient's medical records must be met prior to enrollment and data collection. Patients must meet all inclusion and none of the exclusion criteria during the screening assessment and must have undergone an attempted ViV procedure, defined by the Portico™ or FlexNav™ delivery systems entering his/her body.

	Inclusion Criteria 1. Subject had a degenerated surgical aortic bioprosthetic valve with severe aortic stenosis, severe regurgitation, or a combination of at least moderate stenosis with at least moderate regurgitation per EAPCI-ESC-EACTS standardized criteria. 2. Surgical bioprosthesis true inner diameter (true ID) was ≥ 19 mm and ≤ 27 mm and was confirmed by either CT or confirmed by the Valve in Valve Aortic App. Refer to the PCR website https://www.pcronline.com/PCR-Publications/PCR-mobile-apps/Valve-in-Valve-Aortic-app *Note: if CT was contraindicated and/or not possible to be obtained, a transesophageal echocardiogram (TEE) will be accepted for sizing.* 3. Prior to Portico ViV procedure, the patient was deemed at increased risk for surgery to replace the surgical aortic bioprosthetic valve. 4. Subject provided written informed consent prior to performing data collection for study specific visits. For patients that are deceased at the time of enrollment, all institutional/local legal and regulatory requirements for consent must be met prior to enrollment and data collection. 5. Subject is ≥ 18 years of age or legal age in host country at the time of consent. 6. Prior to the Portico ViV index procedure, the subject had New York Heart Association (NYHA) class II, III, or IV. 7. Subject had a minimum vessel diameter of 6.0 mm for Portico™ delivery system access or a minimum of 5.0 mm for the FlexNav™ delivery system. 8. Subject had the Portico or FlexNav delivery system enter their vasculature with the intent of replacing a failed aortic bioprosthetic valve. Exclusion Criteria from the time of the Portico ViV index procedure: 1. Subject had evidence of an acute MI, percutaneous intervention, or a peripheral intervention ≤30 days prior to Portico ViV index procedure (MI defined as: ST Segment Elevation as evidenced on 12 Lead ECG). 2. Subject had uncontrolled blood dyscrasias defined as: leukopenia (WBC<3,000 mm^3), acute anemia (Hb <9 g/dL), or thrombocytopenia (platelet count <50,000 cells/mm^3). 3. Subject was considered hemodynamically unstable at the time of the ViV procedure (requiring inotropic support or mechanical heart assistance) 4. Subject had severe ventricular dysfunction with left ventricular ejection fraction (LVEF) <20% as measured by resting echocardiogram. 5. Subject had imaging evidence of intracardiac mass, thrombus or vegetation.

	6. Subject had an active peptic ulcer or has/had upper gastrointestinal (GI) bleeding ≤3 months prior to ViV index procedure. 7. Subject had a documented history of a cerebrovascular accident (CVA) or a transient ischemic attack (TIA) ≤6 months prior to index procedure. 8. Subject had renal insufficiency (serum creatinine >3.0 mg/dL (265.5µmol/L)) and/or end stage renal disease requiring chronic dialysis. 9. Subject had active bacterial endocarditis or ongoing sepsis ≤ 6 months prior to the index procedure. 10. Surgical aortic bioprosthetic valve was unstable or rocking. 11. Subject had a vascular condition (i.e. stenosis, tortuosity, or severe calcification) that made insertion and endovascular access to the aortic valve impossible. 12. Subject was unable to tolerate antiplatelet or anticoagulant therapy.
Data Collection	Clinical and echocardiographic data will be collected, if available and standard of care (SOC), at baseline (pre-ViV implant), discharge, 30 days, 1 year, and annually through 5 years post-ViV index procedure.
Exploratory Registry Arm:	In addition, an exploratory registry arm will collect data for patients that were treated for a failed surgical aortic bioprosthetic valve true ID size of <19 mm or >27 mm at the time of the Portico ViV procedure. There is no enrollment limit for this registry arm. Outcomes for the exploratory registry arm will be descriptive and the patient data collected from these subjects will not be included in the primary analysis. For this arm of the study, the same follow-up timepoints and data will be collected. All above inclusion and exclusion criteria apply, with the exception of the following: **Inclusion Criteria #2:** Surgical bioprosthesis true inner diameter (true ID) was ≥ 19 mm and ≤ 27 mm) and was confirmed by either CT or confirmed by the Valve in Valve V Aortic App. Refer to the PCR website https://www.pcronline.com/PCR-Publications/PCR-mobile-apps/Valve-in-Valve-Aortic-app Note: if CT was contraindicated and/or not possible to be obtained, a transesophageal echocardiogram (TEE) will be accepted for sizing.

1 COMPLIANCE STATEMENT:

This clinical investigation will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki, ISO 14155:2011 standard and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the clinical investigation will be approved by the appropriate Ethics Committee (EC) of the respective clinical site and as specified by local regulations.

2 INTRODUCTION

This document is a study protocol for the Portico™ Valve-in-Valve (ViV) retrospective data-collection study. The objective of this study is to evaluate the safety and performance of the Portico™ transcatheter aortic valve in the treatment of a failed surgical aortic valve prosthesis ViV.

This clinical data-collection study will be conducted in accordance with this protocol. All parties involved in the conduct of this clinical study will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

2.1 Background and Justification for Study

Increased use of bioprosthetic valves, combined with increased life expectancy, is resulting in the need for treatment options for patients with failing bioprosthetic valves. Operative mortality for redo aortic valve surgery is generally low (2% to 7%) in suitable candidates. However, mortality risk can increase to more than 30%[1,4] in high-surgical risk patients. Implantation of a transcatheter aortic valve in a failed surgical aortic bioprosthesis to achieve adequate valvular function for symptom relief represents a minimally invasive alternative to conventional redo surgery.

The most common reasons for surgical bioprosthetic aortic valve replacement, or ViV treatment, is structural valve deterioration caused by 1) wear and tear, 2) calcific degeneration, 3) pannus, 4) endocarditis, and 5) thrombus[5].

Two types of commercially available transcatheter heart valves (THVs) are currently approved for ViV in Europe and the United States: the balloon expandable Edwards Sapien XT and Sapien 3 THVs (Edwards Lifesciences, Irvine, CA) and the self-expanding Medtronic CoreValve, Evolut R, and Evolut Pro THV (Medtronic, Dublin, Ireland).

Medtronic's CoreValve was the first to obtain CE Mark and FDA approval in 2014 and 2015 respectively for ViV with data from the Global ViV registry used to support the expanded indication. The Global Valve-in-Valve Registry[6] was initiated in December 2010 and designed to collect retrospective and prospective data from centers worldwide that had ViV experience with either CoreValve or Edwards Sapien devices, used off-label at that time. A total of 202 patients with degenerated bioprosthetic valves from 38 centers across Europe, North America, Australia, New Zealand and the Middle East contributed data to the registry. Of these 202 patients (mean age 77.7±10.4 years; 52.5% men, 42% with stenosis as primary mode of failure), 124 underwent Valve-in-Valve with a CoreValve THV and 78 with an Edwards SAPIEN THV. At 30 days, 185 patients had survived, 17 patients died (8.4%). There were no differences between the CoreValve and Edwards SAPIEN patients with respect to mortality, major vascular complication, stroke, or need for a permanent pacemaker. At 30 days, mortality and stroke rate (8.4% and 2%, respectively) are comparable to the rates in other transcatheter aortic valve replacement cohorts. At 1 year, freedom from all-cause mortality was 85.8%.

Edwards Lifesciences Sapien XT and Sapien 3 THVs are both currently approved for Valve-in-Valve use. The Sapien XT valve received CE Mark and FDA approval in 2015 based on data from the PARTNER 2 ViV nested registry. The PARTNER 2 (Placement of Aortic Transcatheter Valves) trial was a prospective, multicenter study that enrolled patients with symptomatic aortic stenosis. The nested ViV registry included 100 patients with a degenerated surgical aortic bioprostheses who were at high risk of complications during reoperation and eligible to receive a 23mm or 26mm Sapien XT valve. Following enrollment of the 100 patients in the nested registry, additional patients were enrolled as part of a continued access registry. Data from the PARTNER 2 ViV nested registry and continued access registry were published[5] and showed that in high-risk patients, ViV for treatment of bioprosthetic aortic valve failure is associated with relatively low mortality and complication rates, improved hemodynamics, and excellent functional and quality-of-life outcomes at 30 days and 1 year.

Early in 2017, Edwards Lifesciences obtained FDA approval for the third-generation Sapien 3 valve for ViV use based on unpublished real-world data collected from the Society of Thoracic Surgeons (STS)/American College of Cardiology (ACC) Transcatheter Valve Therapy (TVT) Registry. The STS/ACC TVT registry is a joint initiative of the STS and the ACC and is designed to provide important information on characteristics and outcomes of TAVR in contemporary U.S. clinical practice. Overall, 2,893 ViV procedures have been entered into the database from 2012 to 2015.

Given the growing body of competitive clinical data in support of ViV as a safe and effective alternative treatment option for patients with a failed surgical bioprosthetic valve, physicians have occasionally been using Portico in a ViV application at their own discretion in a commercial setting. Abbott is interested in analyzing safety and performance of patients that have undergone a Portico TAVI ViV procedure.

The Abbott (previously St. Jude Medical) family of CE Marked Portico transcatheter aortic valves (size range 23-29mm) is currently approved in Europe and Australia for treatment of patients with symptomatic, severe native aortic stenosis who are considered high or extreme surgical risk. First-in-human experiences of ViV with the Portico valve indicate the procedure is may be a safe and effective option for the treatment of a degenerated surgical bioprosthesis due to severe stenosis or severe central aortic regurgitation[7, 8].

A propensity-matched analysis from the ViV International Data (VIVID) registry which includes prospective data on patients who have undergone a commercial ViV procedure from 55 centers across Europe, the Americas, Australia, New Zealand demonstrated Valve-in-Valve with the Portico™ valve (n=54) is procedurally safe, associated with good clinical outcomes at 30 days and results in comparable hemodynamic performance at 1 year to ViV with CoreValve (n=102).[9]

In a large nation-wide study recently published from France, 44,218 of patients were analyzed by propensity score matching from a hospital discharge database after undergoing TAVI for aortic stenosis or TAVI ViV for failed aortic bioprosthesis between 2010 and 2019.[10] The mean follow-up was 516 days and 2,749 patients were analyzed in each arm. The combined endpoint of cardiovascular death, all-cause stroke or rehospitalization for heart failure was not different between the valve-in-valve TAVI and native TAVI groups (RR 1.03, 95% CI 0.94–1.13; p=1.00). The TAVI ViV patients had good short-term and long-term outcomes and there was no

significant difference observed compared to native valve TAVI. Therefore, ViV procedures may be a viable alternative to redo surgeries for patients at increased risk.

2.2 Rationale for Conducting this Study

The purpose of this clinical study is to evaluate the safety and performance of the Portico™ transthoracic aortic valve for the treatment of a failed surgical aortic valve bioprosthesis (ViV) in patients considered to be at increased surgical risk due to the need for a redo surgical aortic valve replacement. [redacted]

3 STUDY OVERVIEW

3.1 Study Objective

The objective of this data-collection study is to evaluate the safety and clinical performance of the Portico transthoracic aortic valve (sizes 23-29 mm) for ViV treatment of a failed aortic surgical bioprosthetic valve in patients who are considered at increased surgical risk for a redo surgical aortic valve replacement.

This is a multi-center, international, single arm, retrospective, data-collection study. [redacted] Patients must have met the sizing requirements of the Portico™ transthoracic aortic valve sizing specification (≥19 mm and ≤27 mm). Patients must meet all inclusion and exclusion criteria to be eligible for enrollment.

[redacted]

[redacted]

3.2 Exploratory Registry Arm

In addition, an exploratory registry arm will collect data for patients that were treated for a failed surgical bioprosthetic aortic valve true inner diameter size of <19 mm or >27 mm. [redacted] Outcomes for the exploratory registry arm will be descriptive and the data collected from these subjects will not be included in the primary analysis. For this arm of the study, the same follow-up timepoints and data will be collected.

3.2.1 Device(s) in this Study Description of the Devices

The device that will be studied includes the full family of Portico transthoracic aortic valve, Portico delivery system, and FlexNav™ delivery system and loading systems. Information provided below is referenced from the current market labeling.

The Portico valve model number and reference dimensions for the annulus treatment range are provided in **Table 1**. Model numbers for equivalent devices may vary based on respective geographies.

Table 1. Valve Model Number and Treatment Range

Device Name	Model Number	Manufacturer	Intended to Treat Aortic Annulus Diameter (mm)	Ascending Aorta Diameter (mm)
Portico Valve	PRT-23	Abbott	19 – 21	26-36
Portico Valve	PRT-25	Abbott	21 – 23	28-38
Portico Valve	PRT-27	Abbott	23 – 25	30-40
Portico Valve	PRT-29	Abbott	25 – 27	32-42

The model numbers and reference dimensions of the Portico™ transfemoral delivery and loading systems associated with the Portico™ valve are provided in **Table 2**.

Table 2. Model Numbers of Portico Valve, Delivery, and Loading Systems

Device Name	Model/Type	Manufacturer	Region
Portico	PRT-23	SJM	Europe and Australia
Portico	PRT-25	SJM	Europe and Australia
Portico	PRT-27	SJM	Europe and Australia
Portico	PRT-29	SJM	Europe and Australia
Portico Delivery System	PRT-DS-TF/18F	SJM	Europe and Australia
Portico Delivery System	PRT-DS-TF/19F	SJM	Europe and Australia
Portico Loading System	PRT-LS-TF/ALT-18F	SJM	Europe and Australia
Portico Loading System	PRT-LS-TF/ALT-19F	SJM	Europe and Australia

Device Name	Model/Type	Manufacturer	Region
FlexNav Loading System	FN-LS-SM	SJM	Europe and Australia
FlexNav Loading System	FN-LS-LG	SJM	Europe and Australia
FlexNav Delivery System	FNAV-DS-SM	SJM	Europe and Australia
FlexNav Delivery System	FNAV-DS-LG	SJM	Europe and Australia

3.2.2 Indication for Use

The Portico™ TAVI system includes the Portico valve, the Portico loading system, Portico delivery system, the FlexNav™ delivery system, and the FlexNav loading system. The Portico system evaluated in this data-collection study will include the following:

- The Portico valve is indicated for transcatheter delivery in patients with symptomatic severe native aortic stenosis who are considered at high or extreme surgical risk.
- The Portico delivery system is indicated for transfemoral or subclavian/axillary access delivery of the Portico valve.
- The Portico loading system is indicated for loading the Portico valve.
- The FlexNav delivery system is indicated for transfemoral or subclavian/axillary delivery of the Portico valve.
- The FlexNav loading system is indicated for loading the Portico valve.

3.2.3 Device Description

The Portico transthoracic aortic valve (**Figure 1**) is designed to be implanted in an aortic annulus without open heart surgery and without concomitant surgical removal of the failed valve. The Portico transthoracic aortic valve in this study has been implanted without surgery or removal the existing aortic surgical bioprosthetic valve.

Figure 1. Portico Transcatheter Aortic Valve

3.2.4 Delivery Systems

The Portico™ Delivery System is an over-the-wire, 0.035”-compatible system with an outer diameter ranging between 18 French (Fr) and 19 Fr depending on valve size.

[redacted]

[redacted]

4 STUDY DESIGN

This is a multi-center, international, single-arm, retrospective data-collection study. The study will use a Core Laboratory for echocardiogram analysis and a Clinical Events Committee (CEC). [redacted]

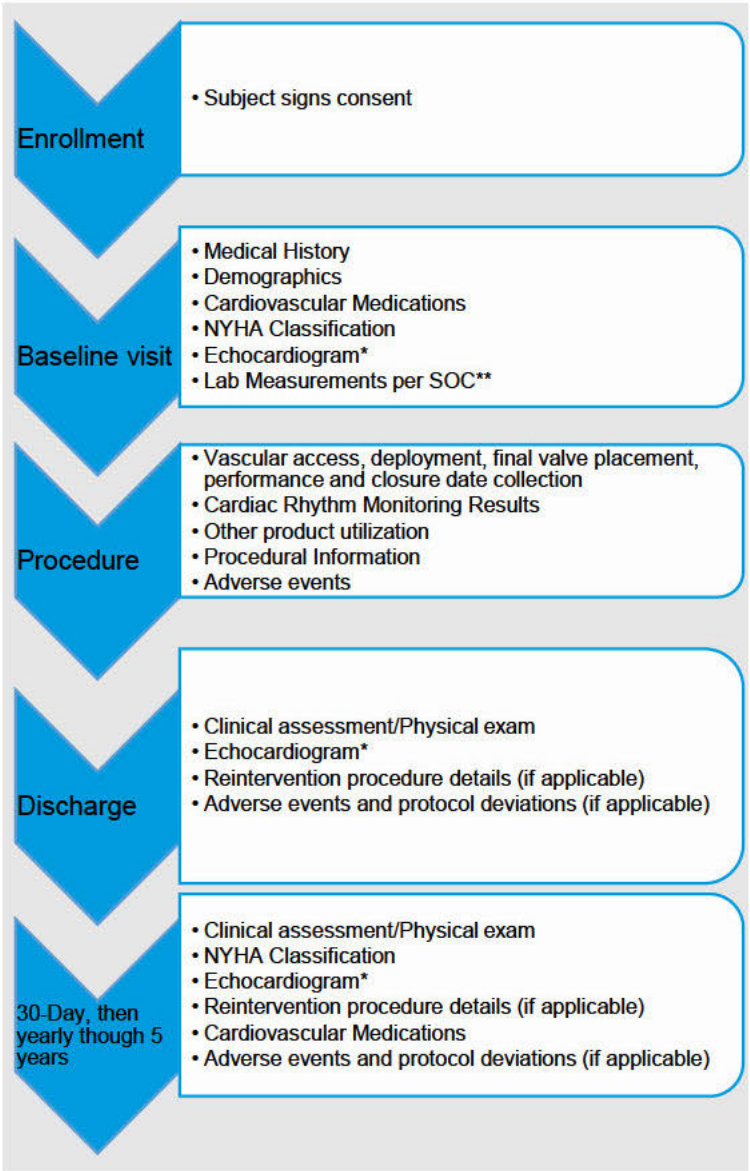
4.1 Data-Collection Timepoints

The study timepoints for collecting data is provided below in **Figure 2**. Data collection timepoints will be based on the hospital's standard of care (SOC). The Baseline, Procedure, and Hospital Discharge data will be recorded from information already in the subject's medical records from previous hospital/clinic visits.

Additional data-collection timepoints and windows are provided below:

- 30-Day timepoint [redacted]
- 1-Year timepoint
- 2-Year timepoint
- 3-Year timepoint
- 4-Year timepoint
- 5-Year timepoint

Figure 2: Study Flow Chart



*Echocardiogram imaging to include comprehensive TTE or TEE 2D echocardiogram, including, at minimum, assessment of aortic valve gradients (mean gradient, peak jet velocity, or doppler velocity index (DVI), aortic valve area (AVA), indexed effective orifice area (EOA), indices, degree of regurgitation- paravalvular leak (PVL), cardiac output and cardiac index, left ventricle systolic function (global and segmental). Echocardiogram imaging studies must be submitted to Abbott when available. If not available, echocardiogram imaging reports may be acceptable.
**Including CBC, Platelet count, BUN, creatinine and/or estimated GFR

4.2 Additional echocardiogram and data available

In the event that more than 1 echocardiogram or required data point is performed and available within a specific study data collection timepoint, the data closest to the study timepoints will be used for the primary analysis. However, all available data should be collected in additional applicable CRFs. Additional echocardiograms should be submitted to the echocardiogram core lab for analysis.

4.3 Measures Taken to Avoid Bias

In order to avoid bias, a Clinical Events Committee (CEC) will be used to review and adjudicate events of interest noted in the Safety Reporting and Committees section. The CEC adjudication (including relationship to procedure and device) will be used for the primary analysis. An Echocardiogram Core Lab will be used to assess echocardiographic data points. Echocardiogram assessments will be used for the primary analysis. Physicians and staff involved with the study CEC and core lab will not be participating as Primary Investigators in this study. All patients that underwent a Portico ViV procedure will be screened for eligibility and enrollment as study subjects, regardless of procedure success. All eligible subjects, regardless of their outcome or survival should be considered for screening and enrollment.

5 ENDPOINTS

5.1 Primary Safety Endpoint

Composite of all-cause mortality, disabling stroke, life threatening bleeding requiring blood transfusion, acute kidney injury (AKI) requiring dialysis, and major vascular complications at 30 days.

5.2 Primary Performance Endpoint

Composite of all-cause mortality or disabling stroke at 1 year.

5.3 Descriptive Endpoints

Descriptive Endpoints:

1. Procedure success defined as:
   - Absence of procedural mortality AND
   - Successful access, delivery of the valve, and retrieval of the delivery system

2. Evaluation of adverse event rates
   At 30 days and one year:
   - All-cause mortality
   - Cardiovascular-related mortality
   - All Stroke (by severity)
   - Transient Ischemic Attacks (TIA)
   - Myocardial infarction (MI)
   - New pacemaker implant (PPI)
   - Coronary obstruction

At 30 days:

- Minor, Major, and Life-threatening bleeding
- Major vascular, major non-vascular access-related, or cardiac structure complication
- Acute Kidney Injury (AKI) stages 1-4

3. Evaluation of adverse event rates annually through 5 years:
   - All-cause mortality
   - Cardiovascular-related mortality
   - All Stroke (by severity)
   - TIA

The following will be collected if standard of care or if available:

4. Echocardiographic assessment of valve performance at discharge, 30 days, 1 year, and annually through 5 years including:
   - Transvalvular mean gradient
   - Indexed Effective orifice area (iEOA)
   - Doppler velocity index (DVI)
   - Aortic Valve Area (AVA)
   - Non-structural valve dysfunction:
     - Prosthetic patient mismatch (PPM) per body mass index (BMI)
     - Degree of aortic valve regurgitation (transvalvular and paravalvular leak (PVL)) as none/trace, mild, mild-moderate, moderate, moderate/severe, or severe per VARC-3; and per VARC-2 none/trace, mild, moderate, or severe).

5. Valve Integrity at 1 year and annually through 5 years as assessed by:
   - Structural Valve Deterioration (SVD) (by hemodynamic valve deterioration (HVD) stages 1-3 per VARC-3)
     Confirmed intrinsic permanent changes to the prosthetic valve, including:
     - Wear and tear
     - Leaflet disruption
     - Flail leaflet
     - Leaflet fibrosis and/or calcification
     - Strut fracture or deformation

   - Non-structural Valve Dysfunction other than PVL and PPM (HVD stages 1-3 per VARC-3)
     Any abnormality not intrinsic to the prosthetic valve resulting in valve dysfunction other than PVL and PPM, including:
     - Leaflet entrapment by pannus or tissue
     - Inappropriate positioning or sizing
     - embolization

   - Clinically Significant Thrombosis
     Meeting either of the following criteria:
     - Clinical sequelae of thromboembolic event or worsening AS/transvalvular AR **and** HVD Stage 2-3 or confirmatory imaging of thrombosis
       Or
     - In the absence of clinical sequelae, **both** HVD Stage 3 **and** confirmatory imaging

- Endocarditis (by HVD stages 1-3 per VARC-3)
  Meeting at least one of the following criteria:
  - Fulfilment of the Duke endocarditis criteria
  - Evidence of abscess, pus, or vegetation confirmed as secondary to infection by histological or microbiological studies during re-operation
  - Evidence of abscess, pus or vegetation confirmed on autopsy.

The following definitions of HVD Stages (1-3) will be used when assessing valve integrity.

- Stage 1 (Morphological Valve Deterioration):
  Evidence of SVD, non-structural valve dysfunction (other than paravalvular or PPM), 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 graded of intra-prosthetic 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 intra-prosthetic AR resulting in severe AR.

- Any need for Portico TAVI re-intervention after implant through 5 years

6. Clinical benefit endpoints defined as improvement from baseline to 30 days, 1 year, and annually through 5 years from index procedure, including:
- New York Heart Association (NYHA) functional classification

6 SUBJECT SELECTION AND WITHDRAWAL

6.1 Study Population

This study will enroll subjects of all genders from the general population of patients that have had a failed surgical bioprosthetic aortic valve procedure with a subsequent Portico™ ViV attempted implant. Patients must meet all general eligibility criteria and provide written informed consent prior to be being included in this retrospective data-collection study.

For the exploratory registry arm, patients that had an inner aortic diameter <19 mm or >27 mm of the surgical aortic bioprosthetic valve will be included in this registry arm. Data collected in this registry arm will not be included in the primary analyses.

6.2 Subject Recruitment and Screening

A member of the site's study team trained to the protocol must evaluate patients for the general study eligibility criteria, and if applicable, will enter the patients into a site-specific recruitment/screening log. A patient who does not satisfy all general eligibility criteria prior to informed consent is considered a recruitment failure and should not be enrolled in the study.

Sites will ask patients meeting general inclusion criteria and no general exclusion criteria to sign an Informed Consent Form (ICF) following the established Informed Consent process if they wish to participate in this data-collection study. Sites will enter these patients into the recruitment/screening log. Once a duly dated and signed ICF is obtained, sites will begin the protocol data collection assessments as part of the study screening process.

Subjects who do not meet the study eligibility criteria are considered a screen failure and should not be enrolled in the study. The Principal Investigator or the delegated study personnel will record the screen failure in the hospital records and on a recruitment/screening log as required.

6.3 Informed Consent

Patients that have had a failed surgical aortic bioprosthetic valve and underwent a Portico ViV Implant procedure may be identified and screened as potential study subjects. Patients may be identified from their study site's procedure records for potential study enrollment. Once identified, each patient must complete the informed consent process prior to study participation.

The Principal Investigator or his/her authorized designee will conduct the Informed Consent process, as required by applicable regulations and the center's local Ethics Committee (EC). This process will include a verbal discussion with the patient on all aspects of the study which are relevant to the patient's decision to participate, such as details of data being collected, any potential benefits and potential risks of participation. During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the patient and will respect the patient's legal rights. The patient must be provided with the Informed Consent Form (ICF) written in a language that is understandable to the subject and has been approved by the center's local EC. The patient must have adequate time to review, ask questions and consider participation.

If the patient agrees to participate and signs the ICF, the ICF must be signed and dated by the subject and by the person who obtained the subject's consent. The signed original form will be filed in the subject's hospital or research charts, and a copy will be provided to the subject by the Investigator or his/her authorized designee.

The Principal Investigator or his/her authorized designee will document the informed consent process in the subject's hospital/clinic and/or research charts. The date of signature will be entered on an applicable Case Report Form (CRF).

Failure to obtain the ICF from a subject prior to study enrollment should be reported to the Sponsor within 5 working days and to the study site's EC according to their reporting requirements.

If, during the study, new information becomes available that can significantly affect a subject's future health and medical care, the Principal Investigator or his/her authorized designee will

provide this information to the subject. If relevant, the subject will be asked to confirm their continuing informed consent in writing.

6.4 Informed Consent and Enrollment of the Deceased

For patients that are deceased at enrollment time but underwent a previous Portico ViV procedure to replace a failed surgical bioprosthetic valve, all institutional/local legal and regulatory requirements must be met prior to enrollment and data collection.

7 ELIGIBILITY CRITERIA

7.1 Inclusion Criteria

1. Subject had a degenerated surgical aortic bioprosthetic valve with severe aortic stenosis, severe regurgitation, or a combination of at least moderate stenosis with at least moderate regurgitation per EAPCI-ESC-EACTS standardized criteria.
2. Surgical bioprosthesis true inner diameter (true ID) was ≥ 19 mm and ≤ 27 mm and was confirmed by either CT or confirmed by the Valve in Valve Aortic App. Refer to the PCR website https://www.pcronline.com/PCR-Publications/PCR-mobile-apps/Valve-in-Valve-Aortic-app Note: if CT was contraindicated and/or not possible to be obtained, a transesophageal echocardiogram (TEE) will be accepted for sizing.
3. Prior to Portico ViV procedure, the patient was deemed at increased risk for surgery to replace the surgical aortic bioprosthetic valve.
4. Subject provided written informed consent prior to performing data collection for study specific visits. For patients that are deceased at the time of enrollment, all institutional/local legal and regulatory requirements for consent must be met prior to enrollment and data collection.
5. Subject is ≥ 18 years of age or legal age in host country at the time of consent.
6. Prior to the Portico ViV index procedure, the subject had New York Heart Association (NYHA) class II, III, or IV.
7. Subject had a minimum vessel diameter of 6.0 mm for Portico™ delivery system access or a minimum of 5.0 mm for the FlexNav™ delivery system.
8. Subject had the Portico or FlexNav delivery system enter their vasculature with the intent of replacing a failed aortic bioprosthetic valve.

7.2 Exclusion Criteria

Exclusion criteria is from the time of the Portico ViV index procedure:

1. Subject had evidence of an acute MI, percutaneous intervention, or a peripheral intervention ≤30 days prior to Portico ViV index procedure (MI defined as: ST Segment Elevation as evidenced on 12 Lead ECG).
2. Subject had uncontrolled blood dyscrasias defined as: leukopenia (WBC<3,000 mm3), acute anemia (Hb <9 g/dL), or thrombocytopenia (platelet count <50,000 cells/mm³).
3. Subject was considered hemodynamically unstable at the time of the ViV procedure (requiring inotropic support or mechanical heart assistance)
4. Subject had severe ventricular dysfunction with left ventricular ejection fraction (LVEF) <20% as measured by resting echocardiogram.
5. Subject had imaging evidence of intracardiac mass, thrombus or vegetation.
6. Subject had an active peptic ulcer or has/had upper gastrointestinal (GI) bleeding ≤3 months prior to ViV index procedure.
7. Subject had a documented history of a cerebrovascular accident (CVA) or a transient ischemic attack (TIA) ≤6 months prior to index procedure.
8. Subject had renal insufficiency (serum creatinine >3.0 mg/dL (265.5µmol/L)) and/or end stage renal disease requiring chronic dialysis.
9. Subject had active bacterial endocarditis or ongoing sepsis ≤ 6 months prior to the index procedure.
10. Surgical aortic bioprosthetic valve was unstable or rocking.
11. Subject had a vascular condition (i.e. stenosis, tortuosity, or severe calcification) that made insertion and endovascular access to the aortic valve impossible.
12. Subject was unable to tolerate antiplatelet or anticoagulant therapy.

7.3 Exploratory Registry Arm Inclusion and Exclusion Criteria

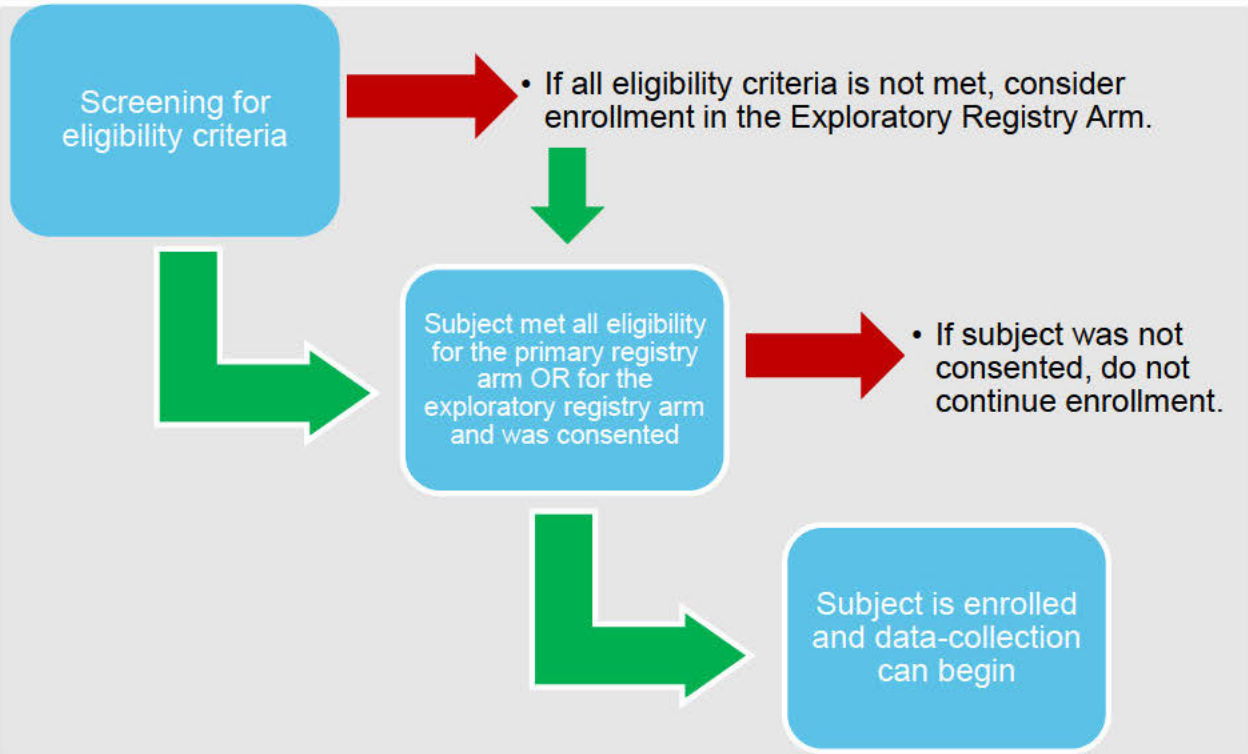
For inclusion in the Exploratory Registry Arm, the eligibility required is the same as listed above, with the exception of the following:

Inclusion Criteria #2:
Surgical bioprosthesis true ID was ≥ 19 mm and ≤ 27 mm and was confirmed by either CT or confirmed by the ViV Aortic App. Refer to the PCR website https://www.pcronline.com/PCR-Publications/PCR-mobile-apps/Valve-in-Valve-Aortic-app
Note: if CT was contraindicated and/or not possible to be obtained, a transesophageal echocardiogram (TEE) will be accepted for sizing.

8 SUBJECT ENROLLMENT

Patients must first meet all inclusion criteria and none of the exclusion criteria. Patients must also have had the Portico™ or FlexNav™ delivery system enter their body with the intent to implant the Portico transcatheter aortic valve via ViV procedure. In order for patients to be enrolled as study subjects, the above must be met and the subject (or legally authorized representative/next of kin) must sign the approved study ICF and any required forms designated by the study site/local/national authorities, based on geographic regulations. Patients deceased at the time of study screening may be enrolled per local and national regulations. The enrollment process is outlined below in **Figure 3**.

Figure 3: Flowchart of Screening and Enrollment



8.1 Point of Enrollment

Subjects will be considered enrolled into the study after completing the following:

- Signed Informed Consent is obtained (as applicable from the patient, legally authorized representative, or next of kin)
- The subject met all of the inclusion and none of the exclusion criteria for one of the study arms.
- Subject had the Portico™ or FlexNav™ delivery system enter his/her vasculature.
- If the subject is deceased, then all local and national requirements for consenting and/or enrollment must be met prior to enrollment and data collection in the study database.

If a patient is enrolled but then subsequently is found to not meet all eligibility criteria, the patient would be excluded and a Protocol Deviation CRF would be completed for not meeting eligibility. Patients who are deemed screening failures are not considered enrolled and are not part of the study analysis population.

The Principal Investigator or delegated study personnel will record enrollment information (name of the study, date of consent and inclusion/exclusion information) in the medical records and the screening/consent study database forms within one week of consenting. The Principal Investigator must document in the enrollment note that the patient met eligibility criteria and was deemed to be at increased risk for surgery to replace the original failed aortic surgical bioprosthetic valve.

Notification of subject enrollment to the Sponsor is considered to have occurred once the patient met all eligibility criteria, the required consent process and forms were completed (with documentation of enrollment in the medical records), and when the screening/consent study database forms have been completed.

8.2 Subject Lost to Follow-up and Withdrawal

Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled. Withdrawal from the study will not jeopardize the subject's future medical care or relationship with the study site Principal Investigator. Subjects will be requested to provide the reason for the request to withdraw from the study. The Principal Investigator must make all reasonable efforts to retain the subject in the study until completion of the study.

A study subject that has been withdrawn from the study will not be replaced. All data collected up to the point of their study withdrawal will be reported and included in the data analysis as applicable.

If a subject cannot be reached and review of their medical records does not provide sufficient information to assess the status and performance of their ViV, the site should make every effort to reach the subject and their local or referring physician. The efforts undertaken to contact the subject, referring physicians, including internists as well as cardiologists, family members, or other alternate contacts must be noted in the subject's records. These efforts must include at least two attempts of telephone contact on separate dates, and a registered letter before considering the subject lost-to-follow-up.

Reasons for early termination include, but are not limited to:

1. Subject refuses to continue participating in the study, withdraws consent
2. Subject is 'lost to follow-up': Site personnel should at all times make all reasonable efforts to locate and communicate with the subject in order to achieve subject compliance to the scheduled follow-up visits:
    - A subject will be considered 'lost to follow-up' after one missed visit, and a minimum of two phone calls from the investigational site to the subject or listed contact of the subject. These two phone calls need to be documented in the subject's hospital records.
    - If these two attempted phone calls are unsuccessful, a letter should be sent to the subject's last known address or general practitioner and a copy of this letter should be maintained in the subject's hospital records.

Note: If a subject missed one or more of the scheduled follow-up visits (inclusive of the assigned visit windows), this will be considered as a missed visit. The subject may therefore still return for subsequent follow-up visits and will not be withdrawn from the study.

If a subject withdraws from the clinical study, the site will record the subject's reasons for withdrawal, on a Withdrawal CRF.

The status of the subject's condition should be documented at the time of withdrawal on any ongoing adverse event forms.

8.3 Total Expected Study Duration

It is anticipated that all subject data would be collected from the Portico ViV procedure and through the following 5 years post-procedure.

9 DATA COLLECTION AND EVALUATION OF ENDPOINTS

The Principal Investigator is responsible for ensuring all study data is collected as required per the protocol scheduled time points. In addition to accessing the subject's medical records, data collection may also occur remotely by phone contact, mail, in-person, or through email. The clinical study will be conducted in accordance with the protocol. All parties participating in the conduct of the study will be qualified by education, training and/or experience to perform their tasks. This training will be documented appropriately. The data collection elements required for each follow-up are listed below and in **Table 3** below.

9.1 Baseline

The following baseline (pre-ViV implant procedure) data will be collected from medical records for all enrolled subjects:

1. Medical History
2. Demographics
3. Cardiovascular medications
4. New York Heart Association (NYHA) Classification (based on symptoms of any limitations)
5. Echocardiography to include comprehensive transthoracic (TTE) or transesophageal (TEE) 2D echocardiogram, including, at minimum, assessment of aortic valve gradients (mean gradient, peak jet velocity, or doppler velocity index (DVI), aortic valve area (AVA), indexed effective orifice area (EOA), indices, degree of regurgitation, cardiac output and cardiac index, left ventricle systolic function (global and segmental).
   For all data-collection timepoints, echocardiogram reports may be acceptable if imaging study is not available to be submitted to Abbott.
6. Lab Measurements per SOC (including CBC, Platelet count, BUN, creatinine and/or estimated GFR)
7. Protocol deviations related to informed consent process or, inclusion/exclusion criteria (if applicable)

9.2 Procedure

The following data will be collected from the medical records of the ViV implant procedure:

1. Vascular access, deployment, final valve placement, performance and closure data collection
2. Other product utilization (e.g. introducer sheaths, guide wires, balloon catheters)
3. Cardiac rhythm and any rhythm changes throughout the duration of the procedure
4. Procedural information (e.g. number of valves used, cerebral protection device use, fluoroscopy time, balloon dilatation used, stent size, implant depth, final disposition of the subject, etc.)
5. Adverse events and protocol deviations related to safety reporting (if applicable)

All the required information must be recorded on the applicable CRF.

9.3 Follow-up Data Collection

9.3.1 Discharge [redacted]

The discharge data-collection will be from hospital discharge or up to 7 days after the procedure, whichever occurs first. If the subject was discharged over the weekend, the data collection for discharge may be based on the last weekday prior to discharge. The discharge data will be collected from medical records and includes:

1. Clinical assessment with physical exam
2. Echocardiogram (within the first 48 hours post-procedure), including parameters noted above in Baseline.
3. If applicable, reinterventions procedure details (eg. Surgery or TAVR)
4. Adverse events and protocol deviations related to safety reporting (if applicable)

9.3.2 30-Day Data Collection [redacted]

The following data collection will occur at 30 days post index procedure:

1. Clinical assessment with physical exam
2. NYHA classification (based on symptoms of any limitations)
3. Echocardiogram, including parameters noted above in Baseline.
4. If applicable, reintervention procedure details
5. Lab Measurements (CBC, Platelet count, and Creatinine)
6. Cardiovascular medications
7. Adverse events and protocol deviations related to safety reporting (if applicable)

9.3.3 1-Year Data Collection [redacted]

The following data collection will occur at 1 year post-index procedure:

1. Clinical assessment with physical exam
2. NYHA classification
3. Echocardiogram, including parameters noted above in Baseline.
4. If applicable, reintervention procedure details
5. Cardiovascular medications
6. Adverse events and protocol deviations related to safety reporting (if applicable)

9.3.4 2-Year Data Collection [redacted]

The following data collection will occur at 2 years post-index procedure:

1. Clinical assessment with physical exam
2. NYHA classification
3. Echocardiogram, including parameters noted above in Baseline.
4. If applicable, reintervention procedure details
5. Cardiovascular medications
6. Adverse events and protocol deviations related to safety reporting (if applicable)

9.3.5 3-Year Data Collection [redacted]

The following data collection will occur at 3 years post-index procedure:

1. Clinical assessment with physical exam
2. NYHA classification
3. Echocardiogram, including parameters noted above in Baseline.
4. If applicable, reintervention procedure details
5. Cardiovascular medications
6. Adverse events and protocol deviations related to safety reporting (if applicable)

9.3.6 4-Year Data Collection [redacted]

The following data collection will occur at 4 years post-index procedure:

1. Clinical assessment with physical exam
2. NYHA classification
3. Echocardiogram, including parameters noted above in Baseline.
4. If applicable, reintervention procedure details
5. Cardiovascular medications
6. Adverse events and protocol deviations related to safety reporting (if applicable)

9.3.7 5-Year Data Collection [redacted]

The following data collection will occur at 5 years post-index procedure:

1. Clinical assessment with physical exam
2. NYHA classification
3. Echocardiogram, including parameters noted above in Baseline.
4. If applicable, reintervention procedure details
5. Cardiovascular medications
6. Adverse events and protocol deviations related to safety reporting (if applicable)

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Table 3: Data Collection Overview

Visit Activity or Information Collected	Initial Data Collection			Follow-Up Data Collection					
	Baseline	Procedure	Discharge	30-Day	1 Year	2 Year	3 Year	4 Year	5 Year
Demographics	X								
Medical History	X								
Lab measurements*	X			X					
Clinical Assessment with physical exam^			X	X	X	X	X	X	X
Cardiovascular Medications (examples: cardiac medications and blood thinners)	X			X	X	X	X	X	X
NYHA Classification$^{\beta}$	X			X	X	X	X	X	X
Transthoracic Echocardiography (TTE) or Transesophageal Echocardiography (TEE)$^{\lambda}$	X		X	X	X	X	X	X	X
Procedure details		X							
Adverse Events, Device Deficiency, and Withdrawal$^{\Sigma}$		X	X	X	X	X	X	X	X
Reintervention Procedure (if applicable)			X	X	X	X	X	X	X
Protocol Deviations related to informed consent process or inclusion/exclusion criteria, or safety reporting requirements (if applicable)	X	X	X	X	X	X	X	X	X

*Blood tests that are standard of care; βNYHA will be determined from signs and symptoms observed attributed to heart function and can be calculated from medical records. ^Clinical assessment will assess general health and information on any new diagnostics, treatments, or tests since the last visit. ∑If applicable; ϟEchocardiograms submitted to the Echo Core Lab should be imaging medium but may be provided as a report if imaging is not available to submit to the core lab.

Note: Neurologic assessments will be collected for any neurologic event (if applicable) and may be assessed from available medical records.

In the event that more than 1 echocardiogram or required data point is performed and available within a specific study data collection timepoint, the data closest to the study timepoints will be used for the primary analysis. However, all available data should be collected in additional applicable CRFs. Additional echocardiograms should be submitted to the echocardiogram core lab for analysis. Data may be collected based on availability from SOC and protocol deviations for out of window/missed visit or out of window/missed data will not be required.

9.4 Subject Study Completion

Subject participation in the study will conclude when:

1. The subject completes the 5-year data collection time point.
2. When consent is withdrawn (by the subject or legal authorized representative).
3. When the subject is deceased at the time of enrollment or dies during the study, their study completion will occur after their last study follow-up was available, including details of what led up to death and the cause of death.
4. When the subject is lost to follow-up, their study completion will occur after their last study follow-up.
5. For subject's where the Portico delivery system entered their body but was not successfully implanted, they will complete the study after 30 days from the attempted procedure.

Upon completion of subject participation in this data-collection study, the subject will continue to receive follow-up as per standard of care.

9.5 Description of Activities Performed by Sponsor Representatives

Trained Sponsor personnel may provide guidance to ensure compliance to the protocol. If applicable, they may provide technical expertise and technical guidance related to the protocol. While Sponsor representatives may perform these activities, the Principal Investigator remains responsible for ensuring all study data is collected as required per the protocol.

10 CORE LABORATORY

10.1 Echo Core Laboratory

Echocardiographic examinations will be forwarded to an independent Echocardiographic Core Laboratory for interpretation. It is the responsibility of each study site to perform the local interpretation of the echocardiogram for clinical assessment. The Echocardiographic Core Laboratory will not be responsible for notifying the site of any abnormal findings that are identified as part of participation in the study.

The responsibility of the Echocardiographic Core Laboratory is to complete the data collection forms and provide the study required interpretation and documentation of each echocardiogram submitted to the Sponsor. Data obtained from the Core Laboratory evaluation will be used for study purposes only and not for clinical treatment of the subject.

11 SAFETY REPORTING

To comply with worldwide standards and guidelines on clinical investigation adverse event reporting, the Sponsor has adopted uniform and worldwide applicable standard definitions and reporting timelines to be used and adhered to by the investigators.

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device under investigation.

As part of ISO14155 Section 3.2, the Adverse Event definition includes notes outlined below.

Note 1: This definition includes events related to the medical device under investigation or the comparator.
Note 2: This definition includes events related to the procedures involved.
Note 3: For users or other persons, this definition is restricted to events related to medical devices under investigation.

11.2 Serious Adverse Event (SAE)

If the AE meets any of the criteria below, it is regarded as a serious adverse event.

1. Led to a death,
2. Led to a serious deterioration in health of the subject, that either resulted in
   a. a life-threatening illness or injury, or
   b. a permanent impairment of a body structure or a body function, or
   c. in-patient hospitalization or prolongation of existing hospitalization, or
   d. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
   e. chronic disease
3. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: A planned hospitalization for a pre-existing condition, or a procedure required by the protocol without a serious deterioration in health, is not considered to be an SAE.

11.3 Device Deficiency

During the clinical study, the Principal Investigator will be responsible for reporting all device deficiencies on the applicable case report forms (CRFs) in the electronic data capture system.

A device deficiency is defined as an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling. This includes the failure of the device to meet its performance specifications or otherwise perform as intended. Note: performance specifications include all claims made in the labeling of the device.

A device malfunction is the failure of a device to meet its performance specifications or otherwise perform as intended, when used in accordance with the instructions for use or protocol.

11.4 Device Relationship

Determination of whether there is a reasonable possibility that an investigational product or device under investigation caused or contributed to an AE is to be **determined by the Investigator** and recorded on the appropriate CRF form. Determination should be based on the assessment of temporal relationships, evidence of alternative etiology, medical/biologic plausibility and patient condition (pre-existing condition).

11.5 Unanticipated (Serious Adverse) Device Effect (USADE)

Unanticipated serious adverse device effect (USADE) refers to 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 of 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.

11.6 Adverse Event and Device Deficiency/Device Malfunction Reporting

Safety surveillance and reporting starts as soon as the patient met all enrollment requirements for the study. Adverse events will not be collected for screen failure subjects. Safety surveillance and reporting will continue until sites perform the last follow-up visit, the subject concludes participation in the clinical investigation, or the subject withdraws from the clinical investigation. Sites will collect all adverse event data, including deaths and device deficiency data throughout the period defined above and will report these events to the Sponsor on a CRF. Sites should update additional information regarding an adverse event on the appropriate CRF.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be reported.

The Sponsor will provide an offline form to allow the investigator to report SAEs in the event the entry cannot be made in the electronic data capture (EDC) system. This does not replace the EDC reporting system. Sites must still enter all information in the EDC system as soon as feasible.

Non-cardiac related laboratory values collected in the study that are abnormal will not be considered AEs unless:

1. the investigator determined that the value is clinically significant,
2. the abnormal lab value required intervention, or
3. the abnormal lab value required subject withdrawal from the clinical investigation.

Clinical Site	Reporting timelines
All Sites	Sites must report SAE and Device Deficiency/Device Malfunction events to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined. Note: SAEs that occur prior to the subject's Portico ViV procedure are not required to be submitted/reported (refer to **Table 3**).

Sites must record the date the site staff became aware that the event met the criteria of an SAE in the source document. The Investigator will further report the SAE to the local EC according to the institution's EC reporting requirements.

All data including deaths and device deficiency data will be collected throughout the clinical study and will be reported to the Sponsor through the Electronic Data Capture (EDC) system. The Principal Investigator will record all reportable adverse events and device deficiencies on the appropriate CRFs. The Principal Investigator will report the event to the EC per their reporting requirements.

The List of Reportable Events include:

1. Endpoint VARC-2 and VARC-3 events:
    - Death (all-cause and cardiovascular-related)
    - Myocardial Infarction
    - Major Vascular complications
    - Major non-vascular access-related complications
    - Stroke/TIA
    - Bleeding
    - Acute kidney Injury
    - New permanent pacemaker implantation
    - Coronary obstruction
    - Cardiac structural complication
    - Portico valve endocarditis
    - Portico valve thrombosis
    - Need for reintervention (conversion to surgery or repeat TAVR ViV)
    - Portico valve structural deterioration

2. All non-serious device or procedure related Adverse Events.

3. All Serious Adverse Events (SAEs) regardless of device or procedure relationship

4. All Cardiovascular and Neurological events regardless of device or procedure relationship

5. Device Deficiencies (DDs)/Device Malfunctions

Sites must report SAEs and DDs to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

Sites must record the date the study staff became aware that the event met the criteria of an SAE in the source document. The Investigator will further report the SAE to the local EC according to the institution's EC reporting requirements.

11.6.1 Additional Considerations

However, if the Portico delivery system entered the patient's body but was not successfully implanted, the patient should continue to be followed-up until 30 days.

12 STATSTICAL CONSIDERATIONS

The following section describes the statistical methods for the clinical investigation. A separate Statistical Analysis Plan will provide additional details on statistical analyses, including justification of clinical investigation design and analysis of descriptive endpoints.

12.1 Analysis Population

Subjects who are enrolled in the study will be included in the analysis population. Subjects that are enrolled in the Exploratory Arm of the study will not be included in the primary arm of the study.

12.2 Statistical Analyses

12.2.1 Primary Safety Endpoint Analyses

The primary safety composite endpoint is all-cause mortality, disabling stroke, life threatening bleeding requiring transfusion, AKI requiring dialysis, and major vascular complications at 30 days, as adjudicated by the CEC. The proportion of subjects experiencing a primary safety endpoint will be estimated from the binomial model. The 95% confidence intervals will be calculated using the exact Clopper–Pearson method.

12.2.2 Primary Performance Endpoint Analyses

The primary performance composite endpoint is all-cause mortality or disabling stroke at 1 year, adjudicated by the CEC. The proportion of subjects experiencing a primary performance endpoint will be estimated using the Kaplan-Meier (KM) method, and the standard error of KM estimate will be calculated with Greenwood method.

12.2.3 Descriptive Endpoints Analyses

Descriptive endpoints are listed in Section 5.3. Study results will be summarized using descriptive statistics including mean, standard deviation, median and range for continuous data and count and percentage for categorical data.

12.3 Sample Size Calculation

It is anticipated that up to [redacted] subjects may be enrolled in the primary analysis population. Additional subjects that have undergone an attempted Portico ViV implant may be analyzed. The exploratory registry arm will have no limit on the number of enrolled subjects.

12.4 Timing of Analysis

The analyses will be conducted on datasets locked after approximately [redacted] subjects completed their 1-year follow-up excepting deaths, withdrawals and loss to follow-up before 1-year or crossed the 1-year visit window without a visit (missed visit).

12.5 Subgroup Analysis

Subjects that were treated with adjunctive therapies during the ViV procedure (eg. snorkel, basilica, or chimney techniques), will be analyzed for study primary endpoints.

12.6 Pooling Strategy

Additional information regarding the planned pooling strategy in this clinical study will be maintained in a separate Statistical Analysis Plan (SAP).

12.7 Procedures for Accounting for Missing Data

This is a retrospective study collecting data that is available per the site standard of care (SOC) and the majority of subjects will be followed for at least 1 year. Therefore, there is no plan to impute missing data.

12.8 Planned Interim Analysis

No interim analyses are planned for this clinical study.

12.9 Deviations from Statistical Plan

The Sponsor will document any major changes to the statistical plan in an amendment to the statistical plan and any less significant changes to the planned analyses in the final report.

12.10 Exploratory Registry Arm

Subjects enrolled that had a true inner surgical bioprosthetic aortic valve diameter of < 19 mm or > 27 mm will be included in a separate exploratory analysis. The data collected from these subjects will not be included in the primary analysis and will be analyzed using descriptive statistics. Data from this analysis may be used to explore future research, specifically on valve sizing and echocardiogram measurements (eg. PVL, TVL, etc.).

13 ACCESS TO SOURCE DATA AND DOCUMENTS

The Investigator and study site institution will permit direct access to source data/documents for performing study-related monitoring, audits, EC review, and regulatory inspections or audits.

Subjects (or legally authorized representatives) providing informed consent are agreeing to allow study monitors or regulatory authorities, including foreign countries, to review in confidence any records identifying the subjects in this study. This information may be shared with regulatory agencies; however, the Sponsor undertakes not to otherwise release the subject's personal and private information.

14 QUALITY ASSURANCE

14.1 Selection of Clinical Sites and Investigators

The Sponsor will select Investigators qualified by training and experience to participate in the study. Sites will be selected based upon review of a recent site assessment, if applicable, and the qualifications of the investigators who will participate in the study.

14.2 Study Finances and Agreements

Abbott will finance the study and will compensate investigational sites for participation in the study per the conditions of agreement between Abbott and the investigational site.

14.3 Protocol Amendments

The Sponsor will provide approved protocol amendments to the Investigators prior to implementing the amendment. The Principal Investigator is responsible for notifying the EC or equivalent committee of the protocol amendment (administrative changes) or obtaining EC's approval of the protocol amendment (changes in subject care or safety), according to the instructions provided by the Sponsor with the protocol amendment.

Sites must provide documentation of acknowledgement and approval of the protocol amendment by the EC prior to implementation of the protocol amendment. Sites must also provide copies of this documentation to the Sponsor.

14.4 Training

All Investigators and study personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit, or other appropriate training sessions. Over-the-phone or self-training may take place as required. Training of Investigators and study personnel will include, but is not limited to, the protocol requirements, electronic case report form completion, and study personnel responsibilities. All Investigators and study personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Prior to signing the training log, Investigators and study personnel must not perform any protocol related activities that are not considered standard of care at the site.

14.5 Monitoring

Sponsor and/or designee will monitor the study over its duration according to the protocol specific monitoring plan which will include the planned extent of source data verification.

Prior to initiating any procedure, the Sponsor monitor (or delegate) will ensure that the following criteria are met:

- The investigator understands and accepts the obligation to conduct the study according to the protocol and applicable regulations and has signed the Clinical Trial Agreement.
- The Investigator and his/her staff should have sufficient time and facilities to conduct the study and should have access to an adequate number of appropriate subjects to conduct the study.
- Sites must have source documentation (including original medical records) to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information.
- The Investigator/site will permit access to such records and will maintain a monitoring visit sign-in log at the site. The Investigator will agree to dedicate an adequate amount of time to the monitoring process. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator will provide the monitor with a suitable working environment for review of study-related documents.

14.6 Protocol Compliance and Deviations from the Protocol

A protocol deviation must be reported for:

- Any deviation to the informed consent process
- Any deviation in the inclusion or exclusion criteria disqualifying patient eligibility
- Any deviation in the safety reporting requirements outlined above in section 9.

The Principal Investigator must maintain accurate, complete, and current records, including documents showing the date of and reason for each deviation from the protocol. Relevant information for each deviation will be documented as soon as possible on the applicable CRF.

The Principal Investigator is required to adhere to local regulatory requirements for reporting deviations to their local EC.

The Sponsor will not grant any waivers for protocol deviations. Sites must report the above noted deviations to the Sponsor using the Deviation CRF. The Sponsor will monitor the occurrence of protocol for evaluation of investigator compliance to the protocol and regulatory requirements and handle according to written procedures. Investigators will inform their EC or equivalent committee of all protocol deviations in accordance with their specific EC or equivalent committee reporting policies and procedures.

In the event of repeated non-compliance, as determined by the Sponsor, a Sponsor's monitor or company representative will attempt to secure compliance by one or more of the following (and not limited to):

- Visiting the Investigator and/or delegate
- Telephoning the Investigator and/or delegate
- Corresponding with the Investigator and/or delegate

Repeated non-compliance with the signed agreement, the protocol, or any other conditions of the study may result in further escalation in accordance with the Sponsor's written procedures, including securing compliance or, at its sole discretion, the Sponsor may terminate the Investigator's participation in the study.

14.7 Quality Assurance and Audits

A Sponsor representative or designee may request access to all study records, including source documentation, for inspection during a Quality Assurance audit.

If an Investigator is contacted by a Regulatory Agency in relation to this study, the Investigator will notify Sponsor immediately. The Investigator and Research Coordinator must be available to respond to reasonable requests and audit queries made during the audit process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current study (e.g., Form FDA 483, Inspectional Observations, Warning Letters, Inspection Reports, etc.). The Sponsor may provide any needed assistance in responding to regulatory audits.

The Sponsor may also prepare an audit plan and conduct an audit. The designated Sponsor auditors will be different than those engaged in the site monitoring activities. The auditor shall

prepare an audit report documenting the matters confirmed in the audit to certify and verify that the audit has been conducted and submit them to the Sponsor.

14.8 Study Committees

[redacted]

14.8.2 Clinical Events Committee (CEC)

An independent Clinical Events Committee (CEC), (consisting of, at a minimum, an interventional cardiologist and a neurologist) will adjudicate adverse events related to primary and secondary endpoint criteria according to the Valve Academic Research Consortium (VARC-2 and VARC-3) definitions.[1, 25] The CEC will have final adjudication responsibilities for subject outcomes related to primary and secondary endpoints. Members of the CEC cannot be investigators of the Portico ViV data-collection study. A charter that is agreed upon by both the Sponsor and the independent CEC governs the event adjudication process. The primary function, responsibilities and membership of the CEC will be described in detail in a CEC charter.

15 DATA HANDLING AND RECORD KEEPING

Sponsor and/or its affiliates will maintain documentation of the systems and procedures used in data collection for the duration of the clinical investigation.

CRF data collection will be performed through a secure web portal and only authorized personnel will access the EDC system using a unique username and password to enter, review or correct data. Passwords and electronic signatures will be strictly confidential.

The data will be subjected to consistency and validation checks within the electronic data capture (EDC) system and supplemental review by the Sponsor.

At the end of the clinical investigation, completed CRF images with the date-and-time stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be provided to the investigational sites, if requested

For the duration of the clinical investigation, the Investigator will maintain complete and accurate documentation including, but not limited to, medical records, clinical investigation progress records, laboratory reports, CRFs, signed ICFs, device accountability records (if applicable), correspondence with the EC and clinical investigation monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical investigation.

15.1 Protection of Personally Identifiable Information

The Sponsor respects and protects personally identifiable information collected or maintained for this study. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data. Confidentiality of data will be observed by all parties involved at all times throughout the study. All data will be secured against unauthorized access.

The Principal Investigator or institution will provide direct access to source data during and after the clinical study for monitoring, audits, Ethics Committee review and regulatory authority inspections. As required, the Principal Investigator or institution will obtain permission for direct access to source documents from the subject, hospital administration, and local/national r[redacted]

[redacted] of the clinical investigation. The Sponsor will track and document control all revisions.

15.3 Document and Data Control

15.3.1 Recording Data

The CRF will be reviewed by the authorized site personnel. An appropriate comment will be provided to explain changes to subject data reported on the CRF. Required CRFs will be signed by authorized site personnel.

15.4 Monitoring

It is the responsibility of the Sponsor to ensure the study is conducted, recorded and reported according to the approved protocol subsequent amendment(s), applicable regulations and guidance documents.

Monitoring will be conducted according to the Sponsor's Clinical Monitoring work instruction. A study-specific Monitoring Plan will be created in accordance with the Sponsor's procedures. This monitoring plan will be updated as appropriate.

Prior to beginning the study, the Sponsor will contact the Principal Investigator or designee to discuss the study and data requirements. A designated monitor will periodically review the subject records and associated source documents, which may occur on-site or remotely. The Principal Investigator shall make subject and study records available to the clinical monitor for monitoring.

Centralized monitoring will occur through routine internal data review. This monitoring is designed to identify missing and inconsistent data, data outliers, and potential protocol deviations that may be indicative of site non-compliance.

15.5 Source Records

Source documents will be created and maintained by the investigational site team throughout the study. The data reported on the case report forms (CRFs) will be derived from, and be

consistent with, these source documents, and any discrepancies will be explained in writing. Anonymized source documents must be uploaded to the database on request of the Sponsor. The Principal Investigator will ensure accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor on the CRFs and in all required reports.

15.6 Records Retention

The Sponsor and the Principal Investigator will maintain the study documents as required. Measures will be taken to prevent accidental or premature destruction of these documents. The Principal Investigator or the Sponsor may transfer custody of records to another person/party and document the transfer at the investigational site or the Sponsor's facility, as appropriate.

These documents must be retained by the investigational site for a period of at least two years after the conclusion of the study and made available for monitoring or auditing by the Sponsor's representative or representatives of the applicable regulatory agencies.

All original source documents must be stored for the maximum time required by the regulations at the hospital, research institute, or practice in question. If original source documents can no longer be maintained at the site, the Principal investigator will notify the Sponsor.

16 ETHICAL CONSIDERATIONS

The Principal Investigator at each investigational site will obtain EC approval for the protocol and ICF/other written information provided to the patient prior to consenting and enrolling patients in this study. The site must receive the approval letter prior to the start of this study and provide a copy to the Sponsor.

Sites will submit any amendments to the protocol as well as associated ICF changes to the EC and written approval obtained prior to implementation, according to each institution's EC requirements.

No changes will be made to the protocol or ICF or other written information provided to the patient without appropriate approvals, including EC, the Sponsor, and the regulatory agencies (if applicable).

Until the study is completed, the Investigator will advise his/her EC of the progress of this study, per EC requirements. Written approval must be obtained from the EC on an annual basis to continue the study, or according to each institution's EC requirements.

[redacted]

[redacted]

[redacted]

19.1 [redacted]

19.2 [redacted]

19.3 [redacted]

20 STUDY CONDUCT COMPLIANCE

In addition to applicable regional or local laws and regulations, this study will be conducted in compliance with the most current version of the World Medical Association (WMA) Declaration of Helsinki, ISO14155. In the event of any conflict, local laws and regulations will have precedence, and in such cases, good faith efforts will be made to adhere to the intent of the other documents.

The Principal Investigator will sign a Clinical Trial Agreement and agrees to be compliant with it. The Principal Investigator will not start enrolling subjects or requesting informed consent from any subject prior to obtaining EC approval and relevant Regulatory Authority approval, if applicable, and authorization from the Sponsor in writing for the study.

If additional requirements are imposed by the EC or relevant Regulatory Authority, those requirements will be followed. If any action is taken by an EC or a relevant Regulatory Authority with respect to the study, that information will be forwarded to the Sponsor.

The Sponsor has taken up general liability insurance in accordance with the requirements of the applicable local laws. An appropriate Sponsor's country representative will be utilized to understand the requirements for the type of insurance that will be provided for subjects, and

such information will be incorporated into the site informed consent, as applicable. If required, additional subject coverage or a study specific insurance will be provided by the Sponsor.

Investigators are required to adhere to the protocol, signed investigator agreement and any conditions required by the EC. If a site has long-standing, open monitoring findings or challenges with compliance, the monitor or study management shall consider developing a corrective and preventative action plan.

21 SUSPENSION OR PREMATURE TERMINATION OF THE STUDY

The Sponsor reserves the right to terminate the study at any stage, with appropriate written notice to the Investigators, local EC, and relevant regulatory authorities, if required.

An Investigator, EC, or regulatory authority may suspend or prematurely terminate participation in a study at the investigational sites for which they are responsible. The Principal Investigators will follow the requirements specified in the Clinical Trial Agreement.

If suspicion of an unacceptable risk to subjects arises during the study or when so instructed by the EC or regulatory authority, the Sponsor may suspend the study while the risk is assessed. The Sponsor will terminate the study if an unacceptable risk is confirmed. If the Sponsor completes an analysis of the reasons for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, the Sponsor will inform the Principal Investigator, EC, or regulatory authority, where appropriate, of the rationale, providing them with the relevant data supporting this decision. Approval from the Ethics Committee or regulatory authority, where appropriate, will be obtained before the study resumes. If subjects have been informed of the suspension, the Principal Investigator or authorized designee will inform them of the reasons for resuming the study.

If the Sponsor suspends or prematurely terminates the study at an individual investigational site in the interest of safety, the Sponsor will inform all other Principal Investigators.

If suspension or premature termination occurs, the Sponsor will remain responsible for providing resources to fulfill the obligations from the protocol and existing agreements for following up the subjects enrolled in the study, and the Principal Investigator or authorized designee will promptly inform the enrolled subjects at his/her investigational site, if appropriate.

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Appendix A. **Abbreviations**

Abbreviation	Term
ADE	Adverse Device Effect
AE	Adverse Event
AKI	Acute Kidney Injury
AR	Aortic Regurgitation
AS	Aortic Stenosis
ASADE	Anticipated Serious Adverse Device Effect
ATS	American Thoracic Society
AV	Aortic Valve
AVR	Aortic Valve Replacement
BARC	Bleeding Academic Research Consortium
BAV	Bicuspid Aortic Valve
CAD	Coronary Artery Disease
CBC	Complete Blood Count
CE	Communauté Européenne (European Community)
CEC	Clinical Events Committee
CK	Creatine Kinase
CRF	Case Report Form
CW Doppler	Continuous Wave Doppler
CVA	Cerebrovascular Accident
DD	Device Deficiency
DMP	Data Management Plan
DRK	Device Return Kit
EC	Ethics Committee
ECG	Electrocardiogram
Echo	Echocardiography
EDC	Electronic Data Capture
EF	Ejection Fraction
EOA	Effective Orifice Area
EU	European Union
Hg	Mercury
HOCM	Hypertrophic cardiomyopathy with or without obstruction
ID	Identification
IDE	Investigational Device Exemption
IFU	Instructions for Use
Kg	Kilogram
LBBB	Left Bundle Branch Block

Abbreviation	Term
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
LVO	Left Ventricular Output
MI	Myocardial Infarction
mRS	Modified Rankin Scale
No	Number
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
QoL	Quality of Life
PCI	Percutaneous Coronary Intervention
PVL	Paravalvular Leak
PW Doppler	Pulsed Wave Doppler
RA	Right Atrium
RBC	Red Blood Cell
RV	Right Ventricular
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAVR	Surgical Aortic Valve Replacement
SSC	Subject Selection Committee
STS	Society of Thoracic Surgeons
TAVI	Transcatheter Aortic Valve Implantation
TAVR	Transcatheter Aortic Valve Replacement
TEE	Transesophageal Echocardiogram (same as TOE)
TF	Trans Femoral
THV	Transcatheter Heart Valve
TIA	Transient Ischemic Attack
TTE	Transthoracic Echocardiogram
TVT	Transcatheter Valve Therapy
UADE	Unanticipated Adverse Device Effect
UCB	Upper Confidence Bound
URL	Upper Reference Limit
US	United States (same as USA)
USA	United States of America (same as US)
USADE	Unanticipated Serious Adverse Device Effect
VARC-2 or 3	Valve Academic Research Consortium – 2 or-3
ViV	Valve-in-Valve
VIVID	Valve-in-Valve International Data
WBC	White Blood Cell

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Appendix B. **Definitions**

Study Specific Definitions

Cardiovascular Mortality **(VARC-2)**	**Any 1 of the following criteria:** • Death due to proximate cardiac cause (e.g., myocardial infarction, cardiac tamponade, worsening heart failure) • Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease • All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure • All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related adverse events • Sudden or unwitnessed death • Death of unknown cause
Myocardial Infarction **(VARC-2)**	**Periprocedural MI (less than or equal to (≤) 72 h after the index procedure)** New ischemic symptoms (eg, chest pain or shortness of breath), or new ischemic signs (eg, ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, or imaging evidence of new loss of viable myocardium or new wall motion abnormality), ***AND*** Elevated cardiac biomarkers within 72 h after the index procedure consisting of at least 1 sample post procedure with a peak value exceeding 15x upper reference limit (URL) (troponin) or 5x for CK-MB. If cardiac biomarkers are increased at baseline (>99th percentile), a further increase of at least 50% post procedure is required AND the peak value must exceed the previously stated limit. **Spontaneous MI (greater than 72 h after the index procedure)** Any 1 of the following criteria: • Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least 1 value above the 99th percentile URL, together with evidence of myocardial ischemia with at least 1 of the following: o Symptoms of ischaemia o ECG changes indicative of new ischemia [new ST-T changes or new Left Bundle Branch Block (LBBB)] o New pathological Q waves in at least 2 contiguous leads o Imaging evidence of new loss of viable myocardium or new wall motion abnormality • Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST-segment elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/ or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. • Pathological findings of an acute myocardial infarction.
Stroke **(FDA/VARC-2)**	This study is following the FDA's definition of Stroke per FDA's Current Thinking Regarding Neurological Assessments for Transcatheter aortic valve Trials (Revised: 25 Aug 2011). *Definitions:* a. Stroke: Stroke is an acute symptomatic episode of neurological dysfunction attributed to a vascular cause. Stroke Disability (consistent with VARC-2 Definitions):

	Severity i. Disabling (Major): an mRS score of 2 or more at 90 days and an increase of at least 1 mRS category from an individual's prestroke baseline ii. Non-disabling (Minor): an mRS score of <2 at 90 days or 1 that does not result in an increase of at least 1 mRS category from an individual's prestroke baseline c. Transient Ischemic Attack (TIA): A transient (less than 24 hrs) episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction. No evidence of infarction if imaging performed.
Bleeding **(VARC-2)**	**Life-threatening or disabling bleeding** • Fatal bleeding (BARC type 5) **OR** • Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) **OR** • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) **OR** • Overt source of bleeding with drop in hemoglobin of greater than or equal to 5 g/dl or whole blood or packed red blood cells (RBCs) transfusion greater than or equal to 4 U (BARC type 3b). *Given 1 U of packed RBC typically will raise blood hemoglobin concentration by 1 g/dL, an estimated decrease in hemoglobin will be calculated.* **Major bleeding (BARC type 3a)** • Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery **AND** • Does not meet criteria of life-threatening or disabling bleeding **Minor bleeding (BARC type 2 or 3a, depending on the severity)** • Any bleeding worthy of clinical mention (eg, access site hematoma) that does not qualify as life-threatening, disabling, or major
Acute Kidney Injury *(AKIN Classification)* **(VARC-2)**	Change in serum creatinine (up to 48 h) compared with baseline **Stage 1** Increase in serum creatinine to 150% to 199% (1.5 to 1.99 X increase compared with baseline) or increase of greater than or equal to 0.3 mg/dL (26.4 mmol/L) or Urine output <0.5 mL/kg per hour for >6 but <12 hours **Stage 2** Increase in serum creatinine to 200% to 299% (2.0 to 2.99 X increase compared with baseline) or Urine output <0.5 mL/kg per hour for >12 but <24 hours **Stage 3** Increase in serum creatinine to greater than or equal to 300% (3 X increase compared with baseline) or serum creatinine of ≥ 4.0 mg/dL (354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) or Urine output <0.3 mL/kg per hour for ≥24 hours or anuria for ≥12 hours. *Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.*

Coronary obstruction	Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary ostium, either by the valve prosthesis itself, the native leaflets, calcifications, or dissection, occurring during or after the TAVI procedure
Vascular Access Site and Access-Related Complications (VARC-2)	**Major vascular complications** • Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm or • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) ***leading to*** death, life-threatening or major bleeding*, visceral ischaemia or neurological impairment or • Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage or • The use of unplanned endovascular or surgical intervention ***associated*** with death, major bleeding, visceral ischaemia or neurological impairment or • Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram or • Surgery for access site-related nerve injury or • Permanent access site-related nerve injury **Minor vascular complications** • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula, pseudoaneuysms, hematomas, percutaneous closure device failure) ***not leading to*** death, life-threatening or major bleeding*, visceral ischaemia or neurological impairment or • Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage or • Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication or • Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft) **Percutaneous closure device failure** Failure of a closure device to achieve haemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)
New Permanent Pacemaker	New permanent pacemaker implantation, with precision of the indication and the number of days postimplant of the placement of the new permanent pacemaker. Type of permanent pacemaker should be recorded (eg, defibrillator, single vs dual chamber, biventricular).

Prosthetic Valve Stenosis Criteria ***In conditions of normal or near normal stroke volume (50–70***

Parameter	Normal	Mild Stenosis	Moderate/severe Stenosis
Peak velocity (m/s)	less than 3	3–4	greater than 4
Mean gradient (mm Hg)	less than 20	20–40	greater than 40
Doppler velocity index	greater than or equal to 0.35	0.35–0.25	less than 0.25

ml). **(VARC-2)**	Effective orifice area (cm^2)	greater than 1.1*	1.1–0.8	less than 0.80
Prosthetic Valve Regurgitation Criteria (Central and Paravalvular) **(VARC-2)**	**Parameter**	**Mild**	**Moderate**	**Severe**
	Valve structure and motion	Usually normal	Usually abnormal	Usually abnormal
	Left ventricular size	Normal	Normal/mildly dilated	Dilated
	Doppler parameters *(qualitative or semiquantitative)*			
	Jet width in central jets (% LVO diameter): color	Narrow (less than or equal to 25%)	Intermediate (26%–64%)	Large (greater than or equal to 65%)
	Jet density: CW Doppler	Incomplete or faint	Dense	Dense
	Jet deceleration rate (PHT, ms): CW Doppler	Slow (greater than 500)	Variable (200–500)	Steep (less than 200)
	LV outflow vs. pulmonary flow: PW Doppler	Slightly increased	Intermediate	Greatly increased
	Diastolic flow reversal in the descending aorta (semi-quantitative parameters)			
	PW Doppler	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic
	Circumferential extent of paraprosthetic AR	less than 10%	10–29%	greater than or equal 30%
	Doppler parameters *(quantitative)*			
	Regurgitant volume (ml/beat)	less than 30%	30–59%	greater than or equal 60%
	Regurgitant fraction	less than 30%	30–49%	greater than or equal 50%

VARC-3 Protocol Definitions:

Acute Kidney Injury (AKI) VARC-3	Stage 1: At least one of the following: • Increase in serum creatinine ≥150-200% (≥1.5-2.0x increase) within 7 days compared with baseline • Increase of ≥0.3mg/dl (≥26.4 µmol/L) within 48 h of the index procedure Stage 2:

* Effective orifice area (EOA) used in this CIP is 1.0 cm^2 for Portico valve of 23 mm diameter.

	• Increase in serum creatinine >200-300% (>2.0-3.0x increase) within 7 days compared with baseline Stage 3: At least one of the following: • Increase in serum creatinine > 300% (> 3.0x increase) within 7 days compared with baseline • Serum creatinine ≥4.0 mg/dl (≥354 µmol/L) with an acute in-crease of ≥0.5 mg/dl (≥44 µmol/L) Stage 4: • AKI requiring new temporary or permanent renal replacement therapy Given practical challenges with the use of urine output criteria in daily practice, AKI should be solely defined based on serum creatinine values. Acute kidney in-jury defined by urine output using the following criteria might be used in the con-text of a dedicated AKI study: AKI Stage 1: Urine output <0.5 mUkg/h for >:6 but <12 h; AKI stage 2: Urine output <0.5 mUkg/h for >:12 but <24 h; AKI stage 3: Urine output <0.3 mUkg/h for >:24 h or anuria for >: 12 h.
Bleeding and Tranfusions[a] (VARC-3)	Overt bleeding that fulfills 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 hospitalization, 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 haemoglobin drop of >3 g/dl (>1.86 mmoVL) but <5 g/d (<3.1 mmoVL) (BARC 3a). Type 3: • Overt bleeding in a critical organ, such as intracranial, intraspinal, intraocular, pericardia! (associated with haemodynamic 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)[c] • Overt bleeding associated with a haemoglobin 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) [a]The timing, indication, and number of transfused blood products should be collected and reported specifically during the index procedure, during the entire index hospitaliza-tion, and during follow-up after discharge, whether or not overt bleeding is identified. [b]Overt bleeding is defined as any clinically obvious source of bleeding or bleeding source identified after appropriate investigation and diagnostic testing (e.g. imaging). Any procedural blood loss should be considered overt bleeding. [c]Total number of transfusions should be reported separately for (i) within 48 h of the index procedure, (ii) the total duration of the index procedure hospitalization, and (iii) during any subsequent repeat hospitalization.
Cardiac Structural Complication (VARC-3)	Major One of the following: • Cardiac structure[a] perforation, injury, or compromise resulting in death, VARC type ≥2 bleeding, haemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention • New pericardial effusion resulting in death, VARC type ≥2 bleeding, haemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention • Coronary obstruction[b] resulting in death, haemodynamic 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, haemodynamic 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, haemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention • New pericardial effusion not resulting in death, VARC type ≥2 bleeding, haemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention • Coronary obstruction not resulting in death, haemodynamic compromise, myocardial infarction, or unplanned surgical or percutaneous intervention • Coronary artery access difficulties for needed coronary angiography or intervention, not resulting in death, haemodynamic 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 [a]Aortic annulus, left ventricular outflow tract, ventricular septum, left or right ventricle, atrial septum, left or right atrium, mitral valve apparatus, tricuspid valve apparatus, coronary artery, and coronary sinus. Also includes any new intercardiac cavity communication (e.g. VSD), and new left-to-right or right-to-left shunt. [b]Angiographic or echocardiographic evidence of a new partial or complete ob-struction of a coronary ostium or an epicardial coronary artery, either by the valve prosthesis itself, the native leaflets, embolized material (e.g. calcification, thrombus, and/or tissue), external device

	compression, or the consequence of coronary artery instrumentation (e.g. dissection, occlusion, embolization), occur-ring during or after the procedure, and with objective evidence of ischaemia (i.e. new ST-segment deviation on electrocardiogram) or symptoms. Excludes coron-ary complications due to a concomitant or subsequent planned percutaneous intervention for significant coronary artery disease.
Clinically Significant Valve Thrombosis (VARC-3)	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 3 • Confirmatory imaging (CT evidence of hypo-attenuated leaflet thickening (HALT) or TEE findings) In the absence of clinical sequelae, both • Haemodynamic valve deterioration Stage 3 and • Confirmatory imaging (CT evidence of HALT or TEE findings) Certainty of diagnosis: • Definite: Histopathological confirmation • Probable: Haemodynamic changes and imaging findings com-patible with valve thrombosis, with resolution of haemodynamic changes and imaging findings following anticoagulation therapy • Possible: Imaging demonstrated findings compatible with leaflet thrombosis formation, but either haemodynamic changes or imaging findings persist following anticoagulation therapy or anticoagulation therapy is not (yet) administered 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
Endocarditis (VARC-3)	Meeting at least one of the following criteria: (i) Fulfilment 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.

Mortality ➢ Cardiovascular	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 • Intra-procedural death • Sudden death • Death of unknown cause
➢ Non-cardiovascular	Death clearly related to a non-cardiovascular cause: such as re-spiratory failure not related to heart failure (e.g. pneumonia), renal failure, liver failure, infection (e.g. urosepsis), cancer, trauma, and suicide
Myocardial Infarction (VARC-3)	Type 1: • 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 ischaemia ➢ New ischaemic 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 ischaemic etiology 0 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 haemorrhage, meets the type 1 MI criteria regardless of cTn values Type 2: • 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 ischaemia ➢ ECG changes indicative of new ischaemia (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: • Patients who suffer cardiac death, with symptoms suggestive of myocardial ischaemia accompanied by presumed new ischaemic 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:

- In patients with normal baseline CK-MB: The peak CK-MB measured within 48 h of the procedure ≥10x the local laboratory ULN or CK- MB ≥5 x ULN with one or more of the following:
  - New pathologic Q-waves in ≥2 contiguous leads
  - New persistent LBBB[c]
  - 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 c T n, a c T n (I or T) level measured within 48 h of the procedure rises to ≥70x 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[c]
  - 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 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:
- In patients with normal baseline CK-MB: The peak CK-MB measured within 48 h of the procedure ≥10x the local laboratory ULN or CK-MB ≥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 c T n, a c T n (I or T) level measured within 48 h of the procedure rises to ≥70x the local laboratory ULN or ≥35 x ULN with one or more of the following:
- New pathologic Q-waves in c2 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 described.

The use of high-sensitivity (hs}-troponins is recommended for diagnosis of spontaneous MI, but has not been studied for assessment of periprocedural MI. Standard troponin assays are therefore recommended for evaluation of periprocedural MI. Periprocedural

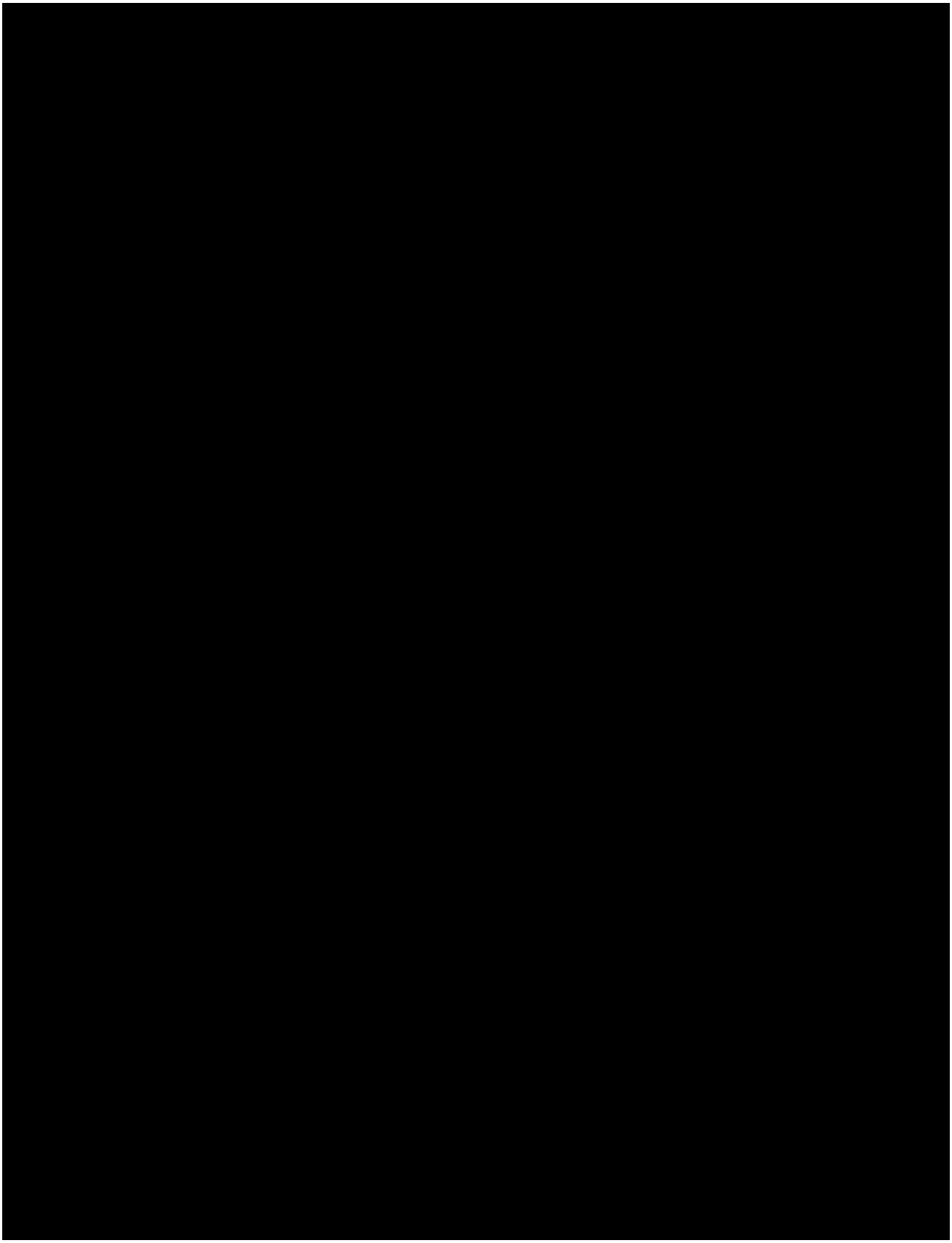
	biomarker elevation >ULN not meeting the criteria for MI should be categorized as 'myocardial injury not meeting MI criteria'. CK-MB, creatine kinase-MB; cTn, cardiac troponin; ECG, electrocardiogram; LBBB, left bundle branch block; MI, myocardial infarction; SAVR, surgical aortic valve replacement; T AVR, transcatheter aortic valve replacement; ULN, upper limit of normal; URL, upper reference limit.
Neurologic Events (VARC-3)	Ischemic Stroke: • Acute onset of focal neurological signs or symptoms conforming to a focal or multifocal vascular territory within the brain, spinal cord, or retina (NeuroARC 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.[c] Haemorrhagic Stroke: • Acute onset of neurological signs or symptoms due to intracranial bleeding from intracerebral or subarachnoid haemorrhage not due to trauma (NeuroARC 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 Type 1 d). **Covert CNS infarction[c] or haemorrhage** • Neuroimaging or pathological evidence of CNS focal or multifocal ischaemia (NeuroARC Type 2a or 2aH) or haemorrhage (NeuroARC 2b) without acute neurological symptoms consistent with the lesion or bleeding location. **Neurologic dysfunction (acutely symptomatic) without CNS injury (NeuroARC Type 3):** • **TIA:** Transient focal neurological signs or symptoms lasting <24 h presumed to be due to focal brain, spinal cord, or retinal ischaemia, but without evidence of acute infarction by neuroimaging or pathology, or with no imaging performed (NeuroARC Type 3a or Type 3aH). • **Delirium without CNS injury:** Transient non-focal neurological signs or symptoms, typically of variable duration, without evidence of infarction on neuroimaging or pathology, or with no imaging performed (NeuroARC Type 3b). Acute Stroke Severity[d]: • Mild neurological dysfunction: NIHSS 0-5 • Moderate neurological dysfunction: NIHSS 6-14 • Severe neurological dysfunction: NIHSS ≥15 Stroke Disability[e]: • Fatal Stroke: death resulting from a stroke • Stroke with disability: mRS score of ≥2 at 90 days[e] 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.

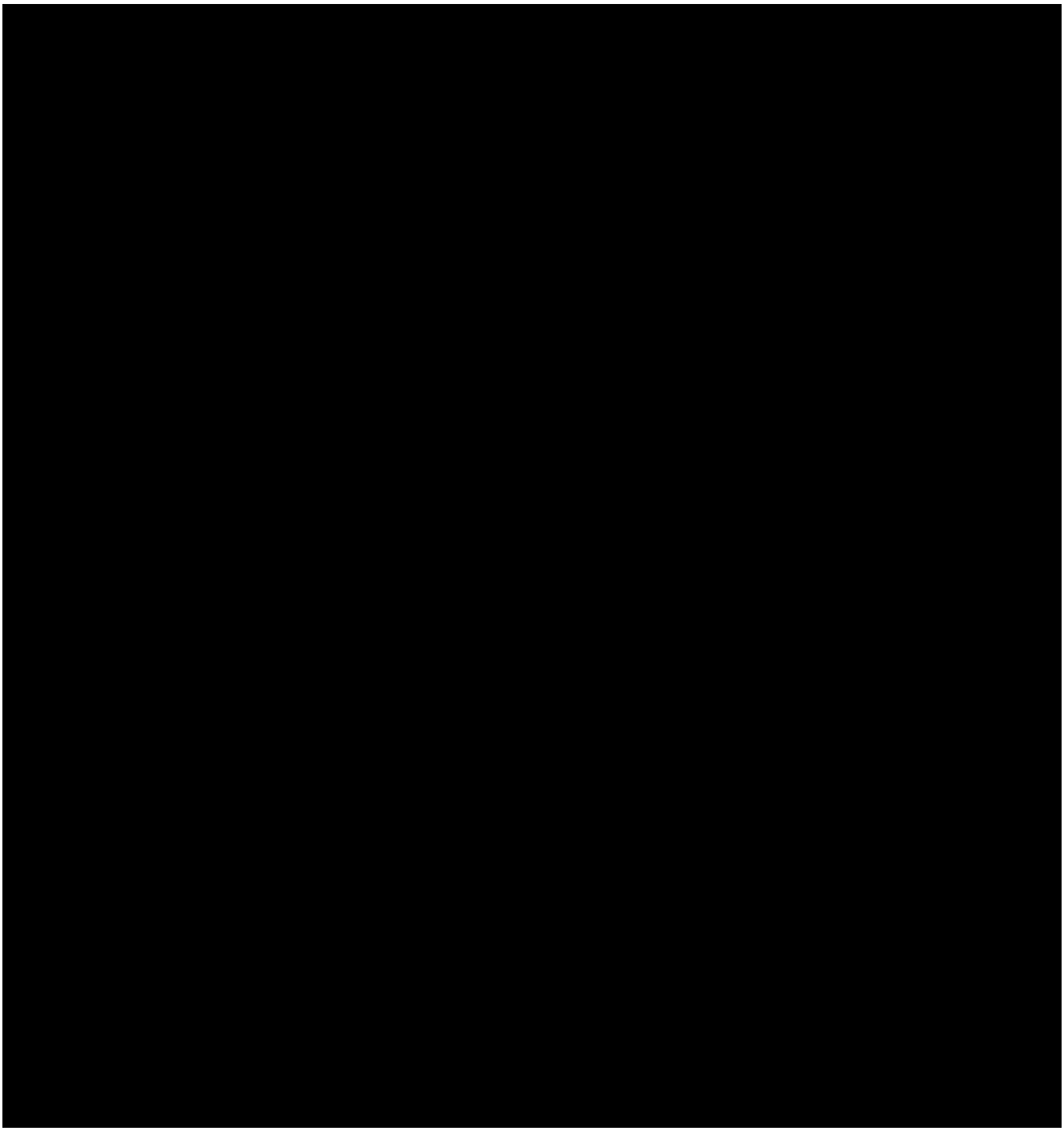
	CNS, central nervous system; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; TIA, transient ischaemic attack. [a]in general, all studies should report at a minimum all stroke and stroke disability. [b]Includes haemorrhagic conversions when ischaemic infarction is the primary mechanism. [c]When CNS infarction location does not match transient (<24h) symptoms, the event should be classified as covert CNS infarction (NeuroARC Type 2a) and TIA (NeuroARC Type 3a), not as an ischaemic stroke. [d]Severity assessment should be performed at the time of stroke diagnosis using the NIHSS. [e]Disability assessment using the mRS should be performed between 30 and 90 days with 90 days being optimal.
Permanent Pacemaker	Type of permanent pacemaker should be recorded (e.g. single chamber, dual chamber, biventricular, defibrillator) • Type: single, dual, biventricular, defibrillator, leadless • Timing: No. of days after the index procedure • Indication: including AV Block, SSS
Vascular and Access-Related Complications (VARC-3)	Major Vascular Complications One of the following: • Aortic dissection or aortic rupture • Vascular (arterial or venous) injury (perforation, rupture, dissection, stenosis, ischaemia, arterial or venous thrombosis including pulmonary em-bolism, arteriovenous fistula, pseudoaneurysm, haematoma, retroperitoneal haematoma, infection) or compartment syndrome resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment • Distal embolization (non-cerebral) from a vascular source resulting in death, amputation, limb or visceral ischaemia, or irreversible end-organ damage • Unplanned endovascular or surgical intervention resulting in death, VARC type ≥2 bleeding. limb or visceral ischaemia, or irreversible neurologic impairment • Closure device failure[c] resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment Minor Vascular Complications One of the following: • Vascular (arterial or venous) injury (perforation, rupture, dissection, stenosis, ischaemia, arterial or venous thrombosis including pulmonary em-bolism, arteriovenous fistula, pseudoaneurysm, haematoma, retroperitoneal haematoma, infection) not resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment • Distal embolization treated with embolectomy and/or thrombectomy, not resulting in death, amputation, limb or visceral ischaemia, 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 ischaemia, or irreversible neurologic impairment • Closure device failure[c] not resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment

	Major Access-Related Non-Vascular Complications 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 Access-Related Non-Vascular Complications One of the following: • Non-vascular structure, non-cardiac structured 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 [a]Any complication related to the device insertion. delivery, and complete removal of all its components (delivery catheter, sheath, guide wire). excluding the actual implantation in the heart. [b]Any device-related vascular access site and any other accessory access sites (venous or arterial) used during procedure. [c]A failure to achieve haemostasis at the access site, resulting in alternative treatment (other than manual compression or planned adjunctive endovascular balloon inflation). [d]Including, but not limited to, the lung (e.g. pneumothorax), direct nerve injury, access site or wound infection, mediastinitis, sternal instability, wound dehiscence, and inability to close the chest.

Appendix C. **NYHA Functional Classification**

Class I	Patient has cardiac disease but without resulting limitations of ordinary physical activity. Ordinary physical activity (eg, walking several blocks or climbing stairs) does not cause undue fatigue, palpitation, dyspnea, or anginal pain. Limiting symptoms may occur with marked exertion.
Class II	Patient has cardiac disease resulting in slight limitation of ordinary physical activity. Patient is comfortable at rest. Ordinary physical activity such as walking more than 2 blocks or climbing more than 1 flight of stairs results in limiting symptoms (eg, fatigue, palpitation, dyspnea, or anginal pain).
Class III	Patient has cardiac disease resulting in marked limitation of physical activity. Patient is comfortable at rest. Less than ordinary physical activity (eg, walking 1 to 2 level blocks or climbing 1 flight of stairs) causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patient has dyspnea at rest that increases with any physical activity. Patient has cardiac disease resulting in inability to perform any physical activity without discomfort. Symptoms may be present even at rest. If any physical activity is undertaken, discomfort is increased.





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