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Study protocol for an internahaational prospective non-randomised trial evaluating the long-term outcomes of transcatheter aortic valve implantation versus surgical aortic valve replacement for aortic-valve stenosis in patients at risk to severe valve obstruction: the TAVISAR trial

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ABSTRACT

Background Aortic valve stenosis (AVS) represents the most prevalent primary valvular lesion necessitating surgical intervention or transcatheter intervention in Europe and North America. Its prevalence is increasing at a rapid rate as a consequence of the ageing population. A variety of mechanical interventions are available to determine the management of AVS; however, there is currently a paucity of robust data with which to perform a comparative analysis of the efficacy of surgical aortic valve replacement (SAVR) and that of conventional stented xenograft bioprostheses (BP) or sutureless aortic valves (SAV) and transcatheter aortic valve implantation (TAVI). The present study aims to compare the effectiveness and clinical outcomes of SAVR using BP or SAV technique and TAVI in patients with severe AVS.

Methods and analysis A collaboration between three cardiac surgery centres across two European countries has resulted in the conception of the Transcatheter Aortic Valve Implantation vs Surgical Aortic Valve Replacement trial. This prospective non-randomised trial is designed to evaluate the long-term outcomes of TAVI in comparison to SAVR for AVS in patients at risk of severe valve obstruction. The registry will enrol successive patients who have undergone mechanical intervention for AVS between January 2015 and December 2025. Investigators will assess the difference between replacement procedures for both the standard surgical approach and the transcatheter procedure. The principal clinical outcome under consideration will be the composite degree of all-cause mortality, ischaemic stroke or rehospitalisation at 10 years. The present study will also have a number of secondary endpoints, including all-cause mortality, followed by functional status, hospitalisation, neurocognition, physiological measures (echocardiographic assessment), adverse events and reoperation.

Ethics and dissemination It is hypothesised that the nature of the trials will serve to minimise bias related to institutional volume and surgical experience. Each participating centre is required to have an aortic valve programme that enables proper follow-up and management of any late aortic events following replacement surgery for the AVS. The data collected will provide valuable insight into the comparative effectiveness of various surgical approaches, both standardised and advanced, in aortic valve surgery and TAVI. This comprehensive

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The present study will be executed as an extensive international prospective registry, focusing on interventions to address severe aortic valve stenosis. This investigation will furnish clinicians with valuable insights regarding transcatheter and surgical techniques in the domain of aortic valve stenosis.
⇒ The primary outcome of this study is expected to facilitate a more precise estimation of a composite of all-cause mortality, stroke or rehospitalisation.
⇒ The present study will engender secondary outcomes that will offer significant insights, including crucial information on mortality from all causes, ischaemic stroke and the incidence of major adverse cardiac or cerebrovascular events.
⇒ The prospective study design is inherently constrained by the non-randomised nature of the study.

analysis will contribute significantly to the development of robust international guidelines.

Trial registration number Clinical Trial Gov.Com. ID: NCT05261204 IRB. ID: 2022011057

INTRODUCTION

Aortic valve (AV) stenosis (AVS) is a term used to describe a progressive, debilitating and life-threatening condition. If untreated, it can lead to significant complications and even death. The condition predominantly affects individuals above the age of 65. AVS has been identified as the most prevalent cardiac valve disease for which surgical intervention is necessary.[1–3] It has been demonstrated that the successful treatment of aortic valve dysfunction can lead to significant enhancements in patients' quality of life and survival outcomes.[4 5] Historically, surgical approaches for aortic valve replacement (AVR) have been limited to the selection between mechanical and biological prostheses. Notwithstanding recently achieved advances[6–8] and encouraging clinical outcomes associated with transcatheter aortic valve implantation (TAVI), surgical aortic valve replacement (SAVR) continues to be the preferred procedure for aortic valve stenosis in numerous clinical contexts.[2 3]

The increase in average life expectancy has resulted in an ageing population, which has led to an increase in the number of individuals afflicted with severe, symptomatic AVS. Although SAVR has been the prevailing treatment for patients diagnosed with the condition, a considerable number of elderly patients are too unwell to undergo AVR or possess significant comorbidities that render standard surgery inadvisable.[1–3] In light of the prevailing epidemiological and clinical conditions, significant progress has been made in the field of biological prosthetic valve design and implantation techniques.[1] These advancements have been instrumental in the management of AVS through the utilisation of novel platform technologies for the treatment of structural heart disease. These developments encompass transcatheter and minimally invasive approaches, marking a substantial evolution in the field.[9–12]

Treatment options prior to introduction of transcatheter aortic valve implant and sutureless aortic valve implant

Prior to the advent of TAVI, treatment modalities for patients afflicted with symptomatic AVS encompassed two primary approaches: palliation of symptoms without valve replacement (non-surgical standard treatment) or SAVR. The selection of a particular treatment modality was contingent on the patient's risk profile for postoperative morbidity or mortality as well as the patient's personal preference. A multitude of surgical intervention strategies, including balloon aortic valvuloplasty, has been examined. However, these approaches have not yielded sustained haemodynamic enhancement and have been associated with diminished quality of life and diminished life expectancy.[13 14] Patients deemed unsuitable for AVR frequently exhibit a considerable number of morbidities or anatomical limitations.[9] The decision to forgo surgical intervention may also be influenced by patient frailty. Surgical AVR has been shown to result in optimal long-term outcomes for patients with aortic valve stenosis, including those with high-risk characteristics, as indicated by Society of Thoracic Surgeons Predicted Risk of Mortality calculator (STS-PROM) scores greater than or equal to 10.[13–17]

The utilisation of TAVI in the management of patients afflicted with severe, symptomatic AVS has undergone an evolution, a development that has been substantiated by the findings from a series of clinical trials.[6–8 18–24] A series of randomised controlled trials (RCTs) have been conducted that compared the efficacy of TAVI with both balloon-expandable valves and self-expanding valves. These trials revealed that, in patients with intermediate or high risk for mortality following surgical intervention, TAVI demonstrated comparable or superior outcomes when compared with standard therapies, including SAVR. These findings have led to an expansion of guideline recommendations for TAVI.[2 3] Furthermore, technological advancements and procedural streamlining have collectively led to a significant increase in the utilisation of TAVI, with a consequent rise in the number of patients undergoing TAVI compared with isolated surgery for AVR in the USA.[25] However, the majority of individuals diagnosed with severe aortic stenosis are considered to be at low surgical risk.[26] Consequently, there was a paucity of evidence to support a direct comparison of TAVI with surgical intervention in this patient population.[27 28] In consideration of the aforementioned observations, the PARTNER (Placement of AoRTic TraNscathetER Valve) III trial was conducted. Among patients diagnosed with severe AVS and classified as low risk for surgical intervention, the incidence of the composite outcome of death, stroke or rehospitalisation within 1-year posttreatment was found to be significantly lower in the TAVR group compared with the surgical cohort (online supplemental material S1).

Sutureless aortic valve (SAV) implantation (SAVI) has been introduced as the next iteration of surgical aortic valves. This development embodies a combination of new technological armamentarium, with the objective of achieving two key outcomes. First, the precision of surgical implantation is combined with innovative elements similar to transcatheter technologies, thus serving to decrease the physiologic impact of surgical procedures. Second, these elements are combined to achieve a multifaceted approach. The present clinical experience evinces encouraging results with the use of SAV technologies, including a reduction in cardiac ischaemia and cardiopulmonary bypass times as well as the potential for simplified minimally invasive procedures.[9 29–31] The cardiovascular community has identified a need for an RCT to assess the safety and clinical efficacy of sutureless valve implantation versus sutured bioprostheses. This need has arisen in light of the growing use of rapid-deployment techniques (online supplemental material S1).

Table 1 Advice for patients who are suitable for SAVR or TAVI*

ACC/AHA recommendations	
COR 1 LOE A	In the case of patients suffering from severe AVS, both symptomatic and asymptomatic, who are below the age of 65, or for whom the life expectancy is above 20 years, and for whom there is an indication for aortic AVR, this is recommended.
COR 1 LOE A	For patients aged 65–80 with severe aortic stenosis who meet the criteria for TAVI, TAVI, SAVR or surgery is recommended. This decision is made after shared decision-making about longevity and durability.
COR 1 LOE A	For patients over 80 with severe aortic stenosis or those with less than 10 years to live and no anatomical contraindications, transfemoral TAVI is recommended over SAVR.
COR 1 LOE A	For patients with an indication for AVR for whom a bioprosthetic valve is preferred, but for whom transfemoral TAVI is not suitable, SAVR is recommended.
COR 1 LOE A	For patients of all ages with AVS where surgery is high risk, TAVI is recommended if the survival post-TAVI is>12 months and the quality of life is expected to be good.
ESC recommendations	
COR 1 LOE A	TAVI is recommended for older patients (aged>75 years) or those considered to be high risk (STS-PROM/ EuroSCORE IIf>8%) or for patients deemed unsuitable for surgery.

*The recommendations under discussion are supported by Class of Recommendation (COR) I and Level of Evidence (LOE) A. The latter is the highest level of recommendation available and implies both substantial safety and efficacy of the procedure.[2 3]
ACC/AHA, American College of Cardiology/American Heart Association; AVR, aortic valve replacement; AVS, aortic valve stenosis; SAVR, surgical aortic valve replacement; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality calculator; TAVI, transcatheter aortic valve implantation.

According to the established practice guidelines of ACC/AHA (American College of Cardiology/American Heart Association), in cases of symptomatic patients with severe aortic AVS who are between 65 and 80 years of age and possess no anatomical contraindications for TAVI or SAVR, both procedures are considered to be reasonable options. Following a mutual deliberation process focused on ascertaining the equilibrium between the patient's anticipated survival duration and the durability of the implanted valve, either TAVI or SAVR is recommended (class I recommendation, level of evidence (LOE): A). In the event that symptomatic patients with severe AVS who are above 80 years of age or younger patients with a life expectancy of less than 10 years and no anatomical contraindication to transfemoral TAVI have been considered, transfemoral TAVI is recommended in preference to SAVR (class I recommendation, LOE: A) (**table 1**).[3]

According to the latest ESC/EACTS (European Society of Cardiology/European Association of Cardiothoracic Surgeon) Guide to the Management of Valvular Heart Disease, TAVI is recommended for patients older than 75 years of age or those at high risk of mortality according to the STS-PROM/ EuroSCORE II >8% or who are deemed unsuitable for surgical intervention (class I recommendation, LOE: A). Conversely, SAVR is recommended for patients younger than 75 years of age who are deemed low risk for surgical intervention according to the STS-PROM/ EuroSCORE II <4%) or unsuitable for TAVI (class I recommendation, LOE A) (**Table 1**).[2] Furthermore, in this setting, the utilisation of SAVI is infrequently referenced within the guidelines. The preponderance of evidence for SAVI is predominantly supported by single-centre and retrospective analyses, with minimal long-term follow-up data. Nevertheless, there exist certain circumstances in which SAVI could potentially offer a theoretical advantage over conventional valves or TAVI.

The guidelines offer no specification as to whether SAVR, TAVI or SAVI should be employed in the treatment of AVS, owing to an absence of conclusive evidence, indicating the superiority of one of these interventions in the long term (ie, following surgery), with regard to survival and structural valve deterioration requiring reoperation. The Transcatheter Aortic Valve Implantation vs Surgical Aortic Valve Replacement (TAVISAR) protocol was designed to address this gap in evidence. The TAVISAR protocol is a prospective non-RCT designed to compare the SAVR using SAVI or conventional stented xenograft bioprosthetics and TAVI. This approach was undertaken to evaluate the long-term outcomes with or without concomitant coronary artery disease (CAD).

METHODS AND ANALYSIS

The TAVISAR is a prospective, non-randomised, controlled, multicentre study. Subjects will be enrolled in a 1:1 ratio to receive either the SAVR with a commercially available bioprosthetic valve, or SAVI and TAVI. Selected sites will enrol subjects into a CT substudy (online supplemental material S2). During the designated study period, a total of 2.040 qualified patients will be enrolled into the study at up to three investigative sites in European countries (two France and one Italy) that are actively enrolling patients (**box 1**).

A total of 200 eligible patients in each arm (SAVR and TAVI) will be enrolled in a CT substudy (online supplemental material S2). In the course of the study, a comprehensive review of patient data will be conducted. This

Box 1 Participating centres

1. Centre Cardiologique du Nord, Saint Denis, France.
2. Hôpital Henri Mondor, Assistance Publique—Hôpitaux de Paris, Créteil, France.
3. University of Genoa—UniGe, Genoa, Italy.

initiative aims to furnish a substantial set of data to inform future clinical research endeavours in this domain.

The data pertaining to consecutive patients with AVS will be meticulously compiled in a Microsoft Access datasheet (Redmond, Washington). This datasheet will encompass prespecified baseline, operative and outcome variables. The study commenced in 2014, and patient enrolment is scheduled to continue until 2025 (with the initial completion date set for 30 May 2025). This timeline is contingent on the findings of subsequent interim analyses. Approval to conduct this study will be sought from the institutional review board (IRB) or local ethical committee (IRB 2022011057), in accordance with local legislation. The study has been registered on ClinicalTrials.gov (NCT05261204) (online supplemental material S3).

TEVISAR study patient entry criteria

Characterisation of patient populations

The following inclusion criteria have been established for the trial: patients must have severe, calcific, symptomatic AVS, with or without the need for concomitant coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI), who are at low operative risk for SAVR. Furthermore, patients must have undergone either of the following surgical approaches: an open surgical approach with the use of a conventional stented xenograft bioprosthesis or a sutureless prosthesis (Perceval, LivaNova plc, London, United Kingdom); or transcatheter aortic valve implantation with either a balloon or a self-expanded transcatheter heart valve (THV). Participants of any gender, race or ethnicity are eligible for inclusion in the study.

Criteria for determining severity of aortic valve stenosis

The pathological underpinnings of AVS are marked by an elevated afterload, accompanied by progressive hypertrophy of the left ventricle, valve obstruction and a subsequent decline in systemic and coronary blood flow. Typically, patients afflicted with AVS remain asymptomatic (eg, angina, syncope and/or heart failure) until a late stage in the progression of the disease. Nevertheless, once clinical manifestations become apparent, the prognosis remains unfavourable in the absence of intervention. The construction of survival curves has enabled the demonstration that the time elapsed between the onset of symptoms and death is approximately 2 years in patients with heart failure, 3 years in those with syncope and 5 years in those with angina.[32] Furthermore, it has been documented that among patients afflicted with moderate-to-severe AVS who have received medical treatment, the mortality rate following the onset of symptoms amounts to approximately 25% within a period of 1 year and 50% over a period of 2 years. It is of additional note that more than 50% of the documented fatalities were of a sudden nature.[33]

Table 2 Standard operating procedures for evaluating the severity of aortic valve stenosis

Key	Mild	Moderate	Severe
Mean gradient (mm Hg)	< 25	25–40	> 40
Jet velocity (m/s)	< 3.0	3.0–4.0	> 4.0
Valve area (cm^2)	> 1.5	1.0–1.5	< 1.0
Valve area index (cm^2/m^2)	- -	- -	< 0.6

The evaluation of AVS severity is informed by a range of haemodynamic and natural history data. As outlined in the ACC/AHA guidelines, AVS can be conceptualised as a continuous spectrum.[2] The amelioration of AV obstruction often leads to a diminution of symptoms and enhancements in haemodynamic parameters, global left ventricle systolic function and a reversal of left ventricular (LV) hypertrophy.[13 34] The following table (table 2) presents the echocardiographic indicators for assessing the severity of AVS, as outlined in the 2021 published practice guidelines of the joint ACC/AHA Task Force.[3]

Inclusion criteria

- Individuals who have reached the age of 65 years or older at the time of consent.
- The heart team has reached a consensus that the patient's operative mortality risk is less than 2% (eg, STS <4). It is imperative that the heart team evaluation encompasses risk calculators such as the STS, in addition to the overall clinical status and comorbidities that are not fully addressed by the STS risk score. These elements must be thoroughly reviewed during the case review process.
- The patient exhibits symptoms consistent with severe calcific aortic stenosis, as indicated by the following thorough transthoracic echocardiogram (TTE) criteria.
  - Jet velocity ≥4.0 m/s or mean gradient ≥40 mm Hg.
  - Aortic valve area (AVA) ≤1.0 cm^2 or AVA index ≤0.6 cm^2/m^2.
  - According to the established criteria, qualifying echocardiograms must be conducted within the specified 90-day period prior to the enrolment process.
- The aortic valve annulus ranges from 273 mm^2 to 683 mm^2, as measured through three-dimensional imaging techniques, including CT, transoesophageal echocardiography (TEE) and MRI.
- For patients undergoing TAVI, adequate iliofemoral access is imperative. The minimum average vessel diameter for this procedure is 5.5 mm (20, 23, 26 mm) and 6.0 mm (29 mm). Furthermore, acceptable levels

of vessel calcification and tortuosity are necessary for the safe implantation process.
- New York Heart Association (NYHA) Functional Class ≥II (online supplemental table 1).
- The study participant has received exhaustive information regarding the objectives of the study, consented to its provisions, and provided written informed consent, as stipulated by the IRB of the respective clinical site.

Exclusion criteria

- Candidates exhibiting any of the following conditions will be excluded from the study:
- Estimated life expectancy <24 months.
- The patient has indicated a refusal to undergo an SAVR procedure.
- A minimum of one-quarter of the patients must exhibit signs of frailty; however, a maximum of 0.25 of those who are frail may be enrolled in the trial.
- The AV is characterised by its congenital state, with the presence of either a unicuspid or a bicuspid configuration. Additionally, it may be non-calcified, further contributing to its distinct characteristics.
- Severe aortic valve regurgitation (>3+).
- Severe mitral valve regurgitation (>3+).
- Aortic coarctation.
- The presence of a pre-existing mechanical or bioprosthetic valve, irrespective of position, is to be noted. It is noteworthy that the inclusion of the mitral ring does not constitute an exclusion.
- The presence of one or more of the following criteria serves to diagnose an acute myocardial infarction ≤1 month (30 days) prior to enrolment, with evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia (online supplemental table 2).

Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and with at least one of the following:
Presentation of symptoms indicative of myocardial ischaemia.
Observation of new or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block on ECG.
Development of pathological Q waves on ECG (Electrocardiogram).
Presence of imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
Identification of an intracoronary thrombus by angiography.

- The following constitutes exclusionary criteria: any therapeutic invasive cardiac procedure performed within 30 days of the valve implant (VI) procedure. Preplanned PCI performed within 2 weeks prior to valve procedure or implantation of a permanent pacemaker or implantable cardioverter defibrillator is not considered exclusionary.
- Ventricular dysfunction with LVEF <45%.
- Hypertrophic cardiomyopathy with or without obstruction.
- The patient demonstrated an inability to maintain tolerance for antithrombotic and anticoagulation therapy during and following the VI procedure.
- The presence of active bacterial endocarditis within 180 days following the VI procedure is documented.
- Renal insufficiency, defined as an eGFR (Estimated glomerular filtration rate) of less than 40 mL/min according to the Cockcroft-Gault formula, and/or the presence of renal replacement therapy at the time of screening is documented.
- Chronic liver disease (MELD (End-Stage Liver Disease) Score ≥10 or Child-Pugh Class B or C).
- Severe lung disease (FEV1 <50% predicted) or currently on home oxygen.
- The occurrence of a stroke or transient ischaemic attack within 180 days following the VI procedure is a potential complication that should be noted.
- The presence of an intracardiac mass, thrombus or vegetation is indicated by cardiac imaging (echocardiogram, CT and/or MRI) findings.
- The patient exhibited haemodynamic or respiratory instability, necessitating inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of the initial screening visit.
- The necessity of any planned surgical or peripheral procedure to be performed within the 30-day follow-up period following valve implantation is to be determined.
- A series of emergency interventional and surgical procedures were performed within 30 days of the valve implantation procedure.
- The patient has indicated a refusal to receive blood products.

In the event that an absolute contraindication to the administration of iodinated contrast exists, or in the event that an allergy to iodinated contrast exists that cannot be premedicated.

Trial design and endpoints

The schematic of the trial design is documented in the online supplemental material (see online supplemental figure 1).

Endpoint definitions and measurement

Primary endpoint

The primary endpoint of the study will assess the safety and effectiveness of the procedure. The composite endpoint of all-cause mortality, stroke and readmission due to any cause at 1, 5 and 10 years after the procedure will be utilised. At baseline and at 30 days, as well as during scheduled follow-up periods, neurological examinations

of all patients will be performed. Neurological examinations, including assessments using the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS), were carried out at 90 days for any patient showing signs of stroke following the procedure. The definition of a readmission to hospital includes any event related to this study, the valve or heart failure. The endpoint will be evaluated as a non-inferiority analysis based on a relative non-inferiority margin of 35%.

Secondary endpoints

Key secondary outcomes have been predetermined in order to manage type 1 error and implement a hierarchical approach to testing. Secondary endpoints of particular pertinence are to be determined, including death, stroke and the emergence of new-onset atrial fibrillation within 30 days, 1, 5 and 10 years as well as the duration of the primary admissions and the presence of poor treatment outcomes. The secondary endpoint was also a composite of major adverse cardiac or cerebrovascular events (rate of death, stroke, subsequent aortic valve surgery, hospitalisation for heart failure or an increase in New York Heart Association class of ≥1) at 30 days, 1, 5 and 10 years. The Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score was also analysed. This score ranges from 0 to 100, with higher scores indicating fewer physical limitations and a greater sense of well-being. The analysis covered the 30-day period as well as the 1-year, 5-year and 10-year periods. At 30 days, 1 year and each scheduled follow-up, changes in NYHA functional class, 6 min walk distance and KCCQ summary score were also assessed. An overview of all secondary safety and efficacy endpoints and how they are defined are provided in online supplemental table 3.

Study procedure

Screening phase

The screening phase is conceived with the objective of obtaining patient consent, ascertaining their compatibility for participation in the study and submitting the presentation for case scrutiny for the Heart Teen scared decision-making. The screening procedures are scheduled to take place within the 30 days preceding the VI procedure, unless specified otherwise in the following sections. Patients who provide their consent will be entered into the electronic database (EDC) and assigned a unique subject identifier. The patient's status will be designated as 'Discontinued' in the event that the patient withdraws consent prior to or following the conclusion of the case discussion and on initiation of all screening procedures (which include the case discussion call) and subsequent non-approval of the case discussion by the heart team.

The following information will be gathered during the screening process:

Operability

The operability of the subject is to be assessed by determining the STS Risk Score, Logistic EuroSCORE and EuroSCORE II. The calculation of Logistic EuroSCORE will be conducted using the following reference: http://www.euroscore.org/calcold.html. Similarly, the calculation of EuroSCORE II will be conducted using the following reference: http://www.euroscore.org/calc.html.

Medical histories and physical assessments

Comprehensive medical histories and physical assessments, incorporating parameters such as height, weight, blood pressure and heart rate. The system will also encompass all medications administered for cardiovascular indications, along with all antithrombotic and anticoagulant medications.

Assessment of cardiopulmonary status

The evaluation of the cardiovascular and respiratory systems is ensured by means of the following:

- The Canadian Cardiovascular Society status of angina should be documented, along with a 12-lead ECG (online supplemental table 2).
- NYHA classification should also be included (online supplemental table 1).
- A TTE is conducted, encompassing an evaluation of aortic valve gradients (mean and peak), areas, indices and the extent of regurgitation. This comprehensive assessment should also include a determination of left ventricle systolic function (global and segmental). Notably, this preliminary echocardiogram must be undertaken within 90 days prior to the enrolment process.
- The requisite cardiac imaging, in the form of TEE, CT or cardiac MRI with three-dimensional reconstruction, is imperative for the determination of the area of the aortic valve annulus. Qualifying cardiac imaging must be performed within 1 year prior to enrolment unless there is a clinical indication to the detriment of this procedure.
- In order to perform the required iliofemoral CT, CT angiography is necessary, incorporating both thoracic and abdominal scans for the purpose of visualising the iliac and femoral arteries. This procedure must be carried out no later than 1 year prior to enrolment.
- In order to assess the severity of aortic stenosis and the severity of CAD, if applicable, left and right heart catheterisation is required. Unless there is a clinical indication to the detriment of the patient, cardiac catheterisation must be undertaken within 1 year prior to enrolment.
- The SYNTAX (Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score is a mandatory component for the assessment of significant native CAD.
- For patients with a documented medical history of pulmonary diseases, the performance of a comprehensive pulmonary function evaluation serves as an indispensable diagnostic procedure.

Neurological assessment and evaluation

The Mini Mental State Examination, the NIHSS and the mRS are three well-established tools used to assess

cognitive function and the severity of neurological impairment in patients with stroke.

Functional assessment and evaluation

- The 6 min walk test is a clinical evaluation used to assess functional mobility and frailty in patients. The test involves a 5 min walk, grip strength assessment and a series of activities of daily living to evaluate the patient's autonomy and independence. Additionally, laboratory parameters such as albumin levels are monitored to provide a comprehensive health picture.
- Quality of life assessments play a pivotal role in evaluating the impact of health conditions on patients' well-being. The KCCQ is a patient-reported outcome measure that focuses on symptoms, functionality and quality of life.
- The EuroQol-5D-5L (EQ-5D-5L) is a well-established tool that quantifies health-related quality of life, providing a standardised metric for comparing health states across different populations. The Short Form 36 (SF-36) is a health survey that assesses physical and mental health, providing a comprehensive assessment of health status.

Clinical laboratory tests

A complete compendium of clinical laboratory tests is provided below. These include white blood cells, haemoglobin and platelet count. Other tests comprise prothrombin time or international normalised ratio and creatine kinase (CK)/CK-MB and/or troponin. The maximum time frame for these tests is 72 hours prior to the VI procedure.

Verification of eligibility

Informed consent

The study's investigator(s) and support staff will approach patients suffering from symptomatic, severe AVS to ascertain their interest in participating in the study. They will provide an overview of the study, including the background, risks, benefits and study procedures. If patients are interested in participating in the study, including the CT substudy, if applicable, they will be required to sign the IRB-approved informed consent form prior to undergoing any study-specific procedures. On completion of the requisite formalities, patients who have consented to participate in the study will be entered into the study's EDC. This will be meticulously compiled in a Microsoft Access datasheet (Redmond, Washington).

Case examination committee

The Case Examination Committee (CEC) is a select review committee made up of investigators who are participating in the trial. The role of the CEC is to review the referred cases in order to determine if the patient is an appropriate candidate for the trial, with a focus on confirming patient the patient's surgical risk, valve size, appropriate vascular access and any relevant clinical factors affecting factors affecting eligibility. Before a case is submitted for review, the principal investigator and the heart team will assess the patient for surgical risk and basic eligibility criteria. It is required that at least one site investigator personally examines the patient to determine surgical risk. Once the patient has been fully screened and approved, the site will submit the case for review and approval by the Case Review Committee. Once a case is approved by the Case Review Committee, the patient is eligible for enrolment and valve implantation.

Enrolment

The patient is eligible for enrolment once all screening procedures have been completed, all inclusion/exclusion criteria have been confirmed and the case review has been completed and approved. Recruitment is centralised. To register a patient, the site enters the subject into the electronic system and receives the treatment assignment (SAVR or SAVI or TAVI). Once the assignment is made and the subject is informed of the treatment assignment of the treatment allocation, the subject is considered enrolled in the trial. The intent-to-treat (ITT) population includes all recruited patients.

Recruited patients are considered to be enrolled in the trial. Patients are considered to have withdrawn from the study if they were prospectively assigned to an ITT cohort and withdrew consent prior to the valve procedure. All assessments and the reason for withdrawal are recorded in the EDC. Patients who have been enrolled in the TAVI procedure but have subsequently undergone SAVR will remain in the study and undertake all subsequent study visits. The rationale for the conversion from TAVI to SAVR will be documented in the EDC. In the event of a patient being lost to follow-up or withdrawing early, the CEC may elect to conduct a search of the Social Security Death Index and/or other death registries. In the event that the patient is confirmed to be deceased, the CEC may elect to convene a discussion with the heart team.

Therapeutic interventions

Valve implantation should take place before 14 and 21 days after enrolment for prospective allocation and no later than 30 days after informed consent. The date of valve implantation will be considered as day 0. The preliminary encounter (day 0) is designated for the scheduling of all subsequent encounters and the calculation of visit windows. Patients who undergo SAVR or TAVI will remain enrolled in the study and will complete it through year 10, in accordance with the visits and events delineated in the study procedure and schedule of procedures. On the initial day (day 0) of the VI procedure, a comprehensive evaluation of the patient's cardiovascular system will be conducted. This evaluation will encompass the administration of medications designed to regulate cardiovascular function and antithrombotic/anticoagulant therapies. It will also include an assessment of potential adverse events (AEs). The evaluation will be further supplemented by a TTE or TEE as well as a supra-aortic angiogram or TEE, as deemed necessary by the attending medical team. It is recommended that patients participating in the study should receive prophylactic treatment against endocarditis in line with recommendations issued by the American Heart Association.[35 36]

As illustrated in table 3, the recommended anticoagulation/antithrombotic regimen is presented.

Standard AVR procedure

Replacement of a faulty aortic valve typically involves the insertion of a synthetic graft prosthesis, a conventional stented xenograft bioprosthesis or a rapid-deployment sutureless prosthesis. Concomitant surgical interventions, such as CABG, the treatment of atrial fibrillation, septal myotomy and aortic root enlargement, are deemed permissible in such cases. Further details on the procedure are consulted in online supplemental material S1.

- *AV replacement using conventional stented xenograft bioprosthesis*

For patients undergoing SAVR, the standard of care as outlined by the institution dictates the usage of a bioprosthetic surgical valve and associated components that are commercially available.

- *AV replacement using SAVI*

The Perceval sutureless prosthesis (manufactured by LivaNova plc, a United Kingdom-based company) will be implanted in patients diagnosed with severe symptomatic AVS (online supplemental figure 2). In order to minimise the impact of selection bias, a CT scan was performed during the enrolment phase prior to the implantation of the SAVI. This scan confirmed the eligibility for the current sutureless valve implantation, the suitability for the proposed surgical access (full sternotomy or mini-sternotomy) and the decision regarding an isolated or concomitant procedure. The use of a right anterior minithoracotomy was precluded due to the variable experience of the centres with this procedure as well as its unsuitability for the purpose of serving as a comparator to the standard valve. Further elucidation on the sutureless valve and implantation procedure may be found in the supplementary material (online supplemental material S1).

Transcatheter aortic valve implantation

The utilisation of both the balloon and the self-expanding THV is contingent on the Edwards SAPIEN Transcatheter Heart Valve (Edwards Lifesciences LLC One Edwards Way Irvine, CA 92614 USA)[6 7 18–23] and the CoreValve (US CoreValve Clinical Investigators trial, Medtronic) being the preferred choice.[8 23 24] The SAPIEN 3 THV (PARTNER consortium—Placement of AoRTic TraNscathetER Valve Trial, Edwards SAPIEN Transcatheter Heart Valve) is a catheter-delivered heart valve that combines a balloon-expandable stent and bioprosthetic valve technology. Transcatheter delivery of the study valve is facilitated via transfemoral access. The device's composition is delineated below: first, a radiopaque, cobalt-chromium alloy balloon-expandable frame, second, a trileaflet bovine pericardial tissue valve, third, a polyethylene terephthalate (PET) internal fabric skirt; and fourth, a PET external sealing ring. The utilisation of self-expanding, supra-annular bio-protheses, such as the CoreValve, Evolut R or Evolut PRO models is to be employed. The transcatheter bioprosthesis consists of a self-expanding nitinol frame and a porcine trileaflet pericardial valve. For an in-depth exploration of the TAVI procedure, including implantation, please refer to the online supplemental material S1, online supplemental figures 3–5 provided in the online resource.

Perioperative measures and potential risks during procedures

The following parameters are to be measured: operative time, cardiopulmonary bypass time, cross-clamp time, blood loss and transfusions. It should be noted that TAVR is not without its risks.

Cardiopulmonary bypass parameters

The collection of data will encompass the duration of myocardial ischaemia, cardiopulmonary bypass and retrograde or antegrade cardiac cardioplegia perfusion.

Blood loss and transfusions

The number of red blood cell units transfused will be documented. A streamlined iteration of the E-CABG perioperative bleeding classification will be adopted,[37] which has been demonstrated to be commensurate with the Universal Definition of Perioperative Bleeding[38] in terms of predicting early mortality.[39] Major bleeding is delineated as the transfusion of a minimum of four units of red blood cells during and after the procedure and/or reoperation due to excessive intrathoracic bleeding (online supplemental table 4).

Reoperation for bleeding

The term 'reoperation for bleeding' is used to denote any instance in which the sternum has been left open and subsequent surgery is required in order to deal with severe bleeding. It is imperative to note that reopening the chest for haemodynamic instability without excessive bleeding, and pericardial or pleural puncture or chest tube placement for retention of blood, are not classified as reoperations for bleeding.

Potential risks associated with the procedures

TAVI are not without their potential risks. The overall procedures themselves carry with them certain inherent risks, including complications associated with standard cardiac catheterisation, balloon valvuloplasty and local and/or general anaesthesia. In addition to these, there are risks unique to the use of the study valve and its delivery systems. The reader is referred to online supplemental table 5, where the potential risks associated with anaesthesia and interventional procedures are reported.

As outlined in the Instructions for Use and training manual, the handling of products and implant procedures is to be conducted in accordance with the stipulated guidelines, with the objective of mitigating risks associated with device utilisation. Furthermore, endeavours will be undertaken to reduce risks through meticulous site and investigator selection, in addition to their effective management. Initially, a set of criteria are established for the selection of sites and investigators, with the aim of ensuring that the study personnel and their respective institutions possess the necessary qualifications to screen, perform and manage study procedures, in addition to providing support for the associated research requirements. The second element to be considered is the design

Table 3 Recommended anticoagulation/antithrombotic regimen

	AVR	TAVI
Drive access	Sternotomy or mini-sternotomy	Femoral vascular access
Anaesthesia	General	General/conscious sedation
The following protocol is to be observed prior to the implantation of the valve		
	The recommended daily dosage of acetylsalicylic acid is between 81 and 100 milligrams.	The recommended daily dosage of acetylsalicylic acid is between 81 and 100 milligrams.
	► BMS patients within 1 month or those with a DES within 12 months should continue their Clopidogrel/prasugrel therapy before their implant. ► Patients with AF prescribed warfarin should undergo bridging with LMWH or UFH before an implant. ► TEE is not mandatory for patients with atrial fibrillation before an implant. If TEE during AVR reveals a clot, the procedure will be aborted and delayed until the patient has been on warfarin or dabigatran for at least 30 days. For surgical patients with LA clot as revealed by TEE, the implant procedure may proceed as standard.	► BMS patients within 1 month or those with a DES within 12 months should continue their Clopidogrel/prasugrel therapy before their implant. ► If patients have atrial fibrillation and are prescribed warfarin, they should undergo bridging with LMWH or UFH before an implant. ► TEE isn't necessary to rule out a left atrial thrombus before TAVR in patients with persistent or paroxysmal atrial fibrillation and no anticoagulation. However, if the TEE procedure during TAVR reveals a clot, the TAVR will be aborted and delayed until 30 days on warfarin or dabigatran. TAVR can only proceed once the clot is eliminated. ► In addition to ASA, the following measures are recommended for patients undergoing TAVR/PCI. ► In transfemoral TAVR, the loading dose of clopidogrel is 300 or 600 mg, given before the implant.
The following protocol is to be observed intraprocedural.		
	Heparin will be given to achieve or maintain an ACT greater than 250 s.	Heparin will be given to achieve or maintain an ACT greater than 250 s
	AVR	**TAVI**
The following protocol is to be observed post valve implant procedure		
Category I for stroke risk No atrial fibrillation, no recent stents	► ASA 81 mg qd ► Clopidogrel 75 mg was initiated within 24 hours of surgery for 1 month, contingent on its clinical safety and the surgical team's discretion. Clopidogrel is contraindicated in centres using warfarin post-surgical AVR anti-coagulation.	► ASA 81 mg qd ► A 300 mg loading dose of Clopidogrel is recommended 6 hours before or after implantation. ► Take 75 mg of clopidogrel once a day for at least 1 month after the procedure.
Category II for stroke risk No atrial fibrillation, recent stents	► ASA 81 mg qd ► Discontinue clopidogrel before surgery in cases of BMS within 1 month or DES within 12 months. ► Clopidogrel 75 mg was given 24 hours after surgery if appropriate, for at least 1 month after SAVR in patients with BMS and 12 months in those with DES.	► ASA 81 mg qd ► Take Clopidogrel 75 mg once daily for 1 month before and after the implant procedure, without interruption.

Continued

Table 3 Continued

	AVR	TAVI
Category III for stroke risk Atrial fibrillation, no recent stents	► ASA 81 mg qd ► If appropriate, patients should be initiated on warfarin or dabigatran 24 hours after PCI, continuing for a minimum of 1 month or until their condition stabilises. If the patient's condition permits, warfarin therapy should be preceded by a bridging phase of unfractionated or LMWH until the INR reaches a therapeutic level. ► If patients are deemed unsuitable for warfarin or dabigatran, an alternative is Clopidogrel 75 mg once-daily (in addition to ASA 81 mg).	► ASA 81 mg qd ► After TAVR, start warfarin or dabigatran if safe. Keep taking this anticoagulation therapy for at least 1 month, or longer if possible. If warfarin is safe, use bridging with unfractionated or low-molecular weight heparin until the INR reaches the right level. ► If patients are unsuitable for warfarin or dabigatran, clopidogrel (75 mg once daily) is an alternative.

AF, atrial fibrillation; ASA, aspirin; BMS, bar metal stent; DES, drug-eluting stent; INR, international normalised ratio; LA, left atrium; LMWH, low-molecular weight heparin; UFN, unfractionated heparin.

of the trial management structure. This is established to provide disciplined oversight of trial activities, including close monitoring of site and personnel performance, as well as to provide opportunities for investigators and study personnel to share best practices through investigator meetings, ongoing education and case reviews.

Postprocedure follow-up visit

The postimplantation period is defined as the 48 hours after the patient leaves the catheterisation laboratory/operating room. Study patients will be continuously monitored clinically, haemodynamically and electrocardiographically during catheterisation for all local, systemic AEs and complications. After completion of the implantation procedure, all study patients will be monitored in accordance with the institution's standard of care and will be subjected to follow-up in accordance with the institution's standard of care. During the postoperative period, which includes discharge, postoperative follow-up visits at 30 days, 6 months, 12 months and 2 to 10 years postoperatively, the following information (box 2) is collected.

Abbreviations: BNP, brain or B-type natriuretic peptide; Hgb, haemoglobin (PT; prothrombin time; WBCs white blood)

Discharge is defined as the exact date and time that the patient is released from care. For patients who are discharged within 48 hours of leaving the catheterisation laboratory or surgical suite, there is no requirement to repeat tests collected during the postprocedure period that are also mandatory for the discharge visit. If the patient is discharged over a weekend or public holiday, the discharge assessments may be conducted on the previous weekday prior to discharge. The 30-day postprocedure visit window is defined as the period starting from the day of valve implantation. The designated visit period commences 7 days subsequent to the initial procedure, while the 6-month follow-up visit is scheduled to take place from the initial visit date. This visit window extends for a period of +14 days. For the 12-month postoperative follow-up evaluation, the visit window is set at +30 days. This is calculated from the VI date on the initial visit.

Adverse event

AEs are defined as any medically undesirable incident, unintended disease or injury, or aberrant clinical symptom (including atypical laboratory findings) in patients, users, or other subjects, regardless of their association with the investigational medical device. AEs may be reported by patients, prompted by the Investigator or designee, or collected through observation by the Investigator, the

Box 2 Postprocedure follow-up visit

Systems
- Physical assessment including weight, blood pressure and heart rate.
- All drugs used for cardiovascular effects and all antithrombotic/anticoagulant drugs.
- Evaluation of adverse events.

Cardiopulmonary
- 12-lead ECG.
- New York Heart Association classification.
- Comprehensive transthoracic echocardiogram.
- CT scan (only for those patients in the CT substudy).

Clinical lab testing
- White blood cells, haemoglobin and platelet count.
- Prothrombin time or international normalised ratio.
- Creatinine.
- Brain or B-type natriuretic peptide.

Neurological evaluations
- Mini Mental State Examination.
- National Institutes of Health Stroke Scale.
- Modified Rankin Scale.

Functional evaluations
- 6 min walk test.
- Quality of Life Questionnaires.
- Kansas City Cardiomyopathy Questionnaire.
- EuroQol 5D-5L.
- Short Form 36.

Box 3 Adverse event

Serious adverse event (SAE)

An adverse event is deemed to be serious if the events are associated with

⇒ Death.

⇒ Serious health deterioration in the study patient, including life-threatening illness or injury, permanent impairment to body structure or function, prolonged hospitalisation or the need for medical or surgical intervention to prevent permanent impairment to body structure or function.

⇒ Fetal distress, fetal death, congenital abnormality or birth defect.

⇒ Medically significant incident.

Serious medical events not meeting the above criteria may still be SAEs if they endanger the patient and require immediate medical or surgical intervention to prevent one of the above outcomes.

Pre-existing medical conditions or symptoms reported before enrolment will not be recorded as an AE. Record an AE if the pre-existing condition or symptoms worsen due to the device, or if study symptoms are due to the device or trial-related procedure. Do not record death as an AE, but only as a consequence of another specific AE.

Anticipated adverse events

Anticipated adverse events (AEs) are defined as such events which have been identified as potentially occurring in connection with the investigational device or implant procedure.

Unanticipated adverse device effect

An unanticipated adverse device effect (UADE) is defined as any serious adverse effect on health or safety, or any life-threatening issue or fatality, caused by, or associated with, a device, if that effect, problem or death was not previously identified in the investigational plan or application (including a subsidiary plan or additional application) or any other unanticipated serious issue related to the rights, safety or welfare of subjects.

It is imperative that all UADEs are reported to CEC without delay. Completion of the AE Form of the CEC is also mandatory for all UADEs. In addition, the Investigator is obliged to inform his/her EC/IRB of all UADEs occurring at his/her site no later than 10 days after the Investigator first becomes aware of the effect (and any additional information as required by EC/IRB or local regulations).

All AEs associated with UADEs are subjected to close monitoring until either resolution or a stable clinical endpoint is achieved. Essential treatments and outcomes must be documented.

CEC, safety team or monitoring team. The Investigator will assess all AEs to determine their relation to the device and/or implant procedure and categorise them as related or unrelated to serious criteria based on their seriousness. In the event that an AE is deemed to have occurred, the Investigator must obtain all the information required to complete the AE form. Furthermore, it is of the utmost importance that patients contact both the investigator and/or the study coordinator should they encounter significant AEs occurring between scheduled study visits (**box 3**).

Implications for treating patients undergoing transcatheter versus standard surgical aortic valve operation for severe aortic valve stenosis

The analysis of data collected during this prospective trial has the capacity to yield contemporary results for a substantial number of patients suffering from severe AVS, benefitting from an extended follow-up period. The potential for bias associated with institutional volume and surgical expertise is anticipated to be minimised by the multicentre design of this prospective trial. To participate in this study, centres are required to demonstrate an annual minimum of 200 procedures for aortic valve stenosis, in addition to having in place a programme that facilitates effective follow-up and management of any late aortic events following replacement surgery. This replacement surgery must have been performed using conventional stented xenograft bioprosthesis, or a rapid deployment SAVI or TAVI procedure.

The primary focus of the present study is the compilation of data that is expected to furnish insights into the repercussions of divergent surgical interventions on standard aortic valve surgery and transcatheter aortic valve implantation. This will be achieved by means of an evaluation of the long-term mortality, stroke incidence and readmission rates of patients who have undergone either SAVR or TAVI. In addition, the report will shed light on ventricular remodelling in the long-term follow-up and recovery of normal quality of life using the KCCQ, EuroQol 5D-5L and SF-36 questionnaires. It will also provide definitive results on the comparative effectiveness of standard AV surgical strategies in contrast to THV therapy.

A comprehensive synthesis of the outcomes from the analytical investigation, which drew parallels across two distinct surgical procedures – SAVR and TAVI for AVS—is presented below. This is facilitated through the prospective study's multicentre approach, which enabled a comprehensive evaluation.

- The study sets out to ascertain whether there are any differences in mortality rates from all causes and incidence of stroke between cohorts at 10 years following SAVR or TAVI.
- Specifically, it seeks to identify which procedure leads to the optimal outcome for LV remodelling and improved LVEF over a 10-year period.
- Whether patients with improved LVEF also exhibit improved HF symptoms.
- Which of the two procedures (SAVR and TAVI) achieves an immediate reduction in LV mass and what percentage of patients can benefit from this in the long term. Furthermore, a subgroup analysis comparing SAVI and TAVI is of paramount importance, as there is a lack of robust data on these two approaches in long-term follow-up.
- Which of the two cohorts, defined by the percentage of patients who experienced residual aortic AV regurgitation progression during follow-up, will demonstrate more severe HF symptoms.

The absence of reliable evidence in extant guidelines was the motivation for this study

Since Cribier's first TAVI procedure in 2002,[40] over 1.500.000 patients have received TAVI worldwide.[41] The

development of international guidelines recommending TAVI over conventional surgery for the treatment of severe AVS has been supported by robust research findings.[6–8 18–25] A comprehensive and rigorous programme of studies, involving multiple randomised, multicentre trials, has provided substantial evidence in support of this recommendation. These recommendations are supported by Class of Recommendation (COR) I, LOE A, which is the highest level of recommendation available and implies the substantial safety and efficacy of the procedure.[2 3] By contrast, with the number of valves implanted set to reach 75 000 by 2022, the figure of patients who have undergone SAVI since the first Percevalve sutureless valve implantation in 2007 is considerably lower.[42] Additionally, a notable discrepancy exists in the robustness of results between the smaller number of SAVI and TAVI implants, with the former supported by a limited number of multicentre RCTs.[43–45] The implications of these observations are significant for the safety and efficacy recommendations outlined in international guidelines and supported by COR 1, LOE A.[2 3]

In meta-analyses of observational data, sutureless valves appear to demonstrate certain benefits in comparison with both conventional SAVR and TAVR. Similar to TAVR, the midterm outcomes of sutureless valves are deemed satisfactory; however, the long-term results remain pending.[46 47]

The primary benefit of sutureless valve technology as perceived by researchers is the reduction in ischaemic surgical time when compared with conventional sutured valves.[48] However, there is an absence of compelling data to suggest that the decrease in aortic cross-clamp time, facilitated by the use of the sutureless valve, may result in improvements in morbidity or mortality.[46 47 49–53] A recent study has revealed that cross-clamp times were found to be significantly reduced in the SAVI group when compared with the full sternotomy SAVR group. However, no significant differences were observed in terms of cumulative CPB time or clinical outcomes.[45] These findings were derived from the CADENCE-MIS trial,[45] a randomised study that compared minimally invasive SAVI with rapid deployment valves with full sternotomy SAVR. Nonetheless, an association between prolonged cross-clamp or CPB times and an increased risk of postoperative complications, including renal failure, respiratory failure, low-output syndrome, postoperative atrial fibrillation, higher transfusion requirements, longer postoperative hospital stays and trends in mortality, has been suggested by several retrospective observational studies.[54–56–] A systematic review and meta-analysis of randomised and propensity-matched comparative studies was conducted with the objective of investigating the impact of diminished operative times on clinical outcomes. The analysis demonstrated that equivalent 1-year survival outcomes were observed; however, diminished postoperative complications, such as atrial fibrillation and blood product transfusions, were observed in the SAVI group. In contrast, augmented PMK implantation was noted.[57]

This study explores the contemporary interest among surgeons in the use of the SAVI system. It is challenging to ascertain whether the inclination towards SAVI is predominantly influenced by the simplicity of implantation and the surgeon's perception of diminished operative time in high-risk patients, as opposed to its tangible effect on clinical outcomes. This inquiry necessitates the execution of ad hoc studies. However, it is plausible to hypothesise that SAVI could offer a potential advantage in terms of postoperative complications for selected high-risk patients requiring multiple or extensive procedures.

Statistical methods

Sample size calculations

The sample size for the trial has been calculated on the basis of attaining a minimum of 85% power in order to pass the 1, 5 and 10-year safety and effectiveness endpoint. The event rate estimates for the primary safety and effectiveness endpoint have been derived using data from prior studies. Given that the current study population is a lower risk cohort and in order to account for both procedural refinement over time in both groups and changes in definitions for components of the endpoint, the rates have been adjusted.

The sample size is based on the composite primary endpoint, which assumes an event rate of 16.6% in the SAVR arm and 14.6% in the TAVR cohort. An enrolled sample size of 1.757 patients with 10-year data would produce 85% power for passing the endpoint. The calculation of this sample size is predicated on the utilisation of a one-sided Score test (Farrington & Manning), with a significance level of alpha=0.025, and incorporating the stipulated non-inferiority margin of a relative 35%.

The primary sample size estimation was derived through a pure frequency analysis; however, the endpoint analysis will use the Kaplan-Meier estimates. Given the equivalence of the two methodologies in the absence of censoring and the anticipated sufficiency of uncensored patients, the sample size is expected to be adequate. However, given the highly uncertain feasibility assumptions associated with this previously unstudied population, an actual sample size of 2.020 has been determined, representing a 15% increase over the minimum size deemed statistically justified. This augmented sample size is intended to not only meet the requirements of the study but also to provide additional flexibility in case of contingencies, such as withdrawals or losses to follow-up, which are inherent in clinical trials. Furthermore, this selected size is expected to enhance the precision of analysis for various unpowered secondary endpoints.

Analysis populations

The ITT population constitutes all randomised patients, whereas the As Treated (AT) population is a subset of the ITT population consisting of all patients for whom the index procedure is initiated, irrespective of whether the index procedure is completed. In instances where multiple procedures are undertaken, the final procedure

that involved the deployment of the study valve will be designated as the index procedure. This procedure will then be utilised to determine the AT trial allocation, and the date of the index procedure will be employed in the determination of all subsequent follow-up visits and associated assessments.

The VI population constitutes the subset of the AT population consisting of all patients who receive and retain the intended valve during the index procedure. Patients who receive a valve in VI will thus be part of the VI population. Furthermore, patients who are converted from TAVI to SAVR during the procedure will also be part of the VI population. The AT population is to be used as the primary population for trial endpoint analysis. The VI population will be used for analysis of echocardiographic data and related endpoints, while selected sensitivity analyses will be performed using the ITT population.

Endpoint analysis

The composite endpoints to be evaluated include all-cause mortality, total stroke and rehospitalisation rates at 1, 5 and 10 years following procedure completion. These endpoints will undergo a non-inferiority analysis with a relative non-inferiority margin set at 35%, as outlined in the study protocol. The components of the composite endpoint will be methodically analysed by the CEC. Patients will be classified as having experienced the endpoint once any component of that endpoint is documented. In the absence of such an event, the patient will be considered to be free of the endpoint and censored for the subsequent analysis, which will be based on the last known date on which the patient was alive and free of events.

In conducting the event rate difference endpoint test, the non-inferiority margin of a relative 35% will be utilised. A one-sided non-inferiority test at an α-level of 0.025 will be performed, which involves the computation of the two-sided 95% confidence limit for the event rate ratio (TAVI/SAVR). It is imperative to note that the acceptance criterion necessitates the upper confidence limit to be no greater than 1.35. Should the non-inferiority analysis demonstrate a satisfactory outcome, the subsequent superiority analysis will be conducted. The type I error rate for this analysis is protected by the non-inferiority analysis, thereby precluding the necessity for an alpha adjustment.

The secondary endpoints will be categorised into two groups. For the key secondary endpoints, testing for superiority will be conducted in a prespecified hierarchical order, with the use of a gatekeeping method to control for multiple comparisons. P values will be presented alongside claims of significance. Conversely, for other secondary endpoints, analyses will be conducted without the application of a correction for multiple comparisons. Consequently, HRs and 95% CIs will be presented without p values or claims of significance. It is important to note that inferences derived from these 95% CIs may lack reproducibility.

The comparison of continuous variables, which will be presented as means with SD or medians with interquartile ranges, will be conducted using Student's t-test or the Wilcoxon rank-sum test. Categorical and ordinal variables, which are presented as proportions, will be compared using Fisher's exact test or the Wilcoxon rank-sum test. Following the implementation of a baseline, continuous variables will be analysed through the utilisation of an analysis of variance, with adjustment for the baseline measurement. Time-to-event analyses will be performed using Kaplan-Meier estimates and then compared using a log-rank test. Median survival time and area under the Kaplan-Meier curve were used to estimate life expectancy and valve durability. Risk factors were identified using univariate and multivariate Cox proportional hazards regression. Echocardiographic analyses will be conducted on the VI population, comprising patients in whom the intended valve was inserted. Statistical analyses will be conducted utilising R software (R Foundation for Statistical Computing, Vienna, Austria).

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