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Transcatheter Valve-in-Valve versus redo-Surgical Valve Replacement for Mitral Bioprosthetic Valve Dysfunction: Rationale and Design of the SURVIV randomised trial

Dimytri A. Siqueira[1]*, MD, PhD; Alexandre A. C. Abizaid[2], MD, PhD; Auristela A. Ramos[1], MD, PhD; Mario Issa[1], MD, PhD; Alberto C. Cervone[1], MD; Cristiano G. Bezerra[3], MD, PhD; Breno Alencar de Araripe Falcão[4], MD, PhD; Leandro A. Cortes[5], MD; Leonardo de Freitas C. Guimarães[6], MD, PhD; Luiz Eduardo K. São Thiago[7], MD, PhD; Mariana Rezende[1], MD; Tacianne Rolemberg Delamain[1], MD; Dorival Della Togna[1], MD, PhD; Jorge E. Assef[1], MD, PhD; Andrea A. Vilela[1], MD, PhD; Antonio Tito Paladino[1], MD, PhD; Ibraim M. Pinto[1], MD, PhD; Kleber Franchini[1], MD, PhD; Deepak L. Bhatt[8], MD, MPH, MBA; Fausto Feres[1], MD, PhD

*Corresponding author: Av. Dr. Dante Pazzanese, 500 Prédio III – 1o andar, São Paulo, Brazil, Postal Code: 04012-909
E-mail: dimytrisiqueira@gmail.com

ABSTRACT

Bioprosthetic mitral valves are prone to structural valve deterioration (SVD) over time, which can lead to bioprosthetic valve dysfunction (BVD) requiring reintervention. Redo-surgical mitral valve replacement (rMVR) is currently the standard treatment, although associated with a significant mortality in high-risk patients. Transcatheter mitral valve-in-valve (mViV) has emerged as an alternative to rMVR in patients with failed bioprostheses, but randomized studies comparing the two treatments are lacking. The SURVIV trial (ClinicalTrials.gov identifier NCT04402931) is an investigator-initiated, prospective, multicenter, open-label randomized controlled trial that will enroll 150 patients with mitral BVD suitable for rMVR or transcatheter mViV. Participants will be randomized 1:1 to transseptal mViV with a balloon-expandable transcatheter heart valve or to conventional surgical rMVR. Procedures will be performed according to local best practice with contemporary medical devices. The primary endpoint is the composite of all-cause of mortality or disabling stroke at 12 months. Key secondary endpoints are major complications (cardiovascular death, disabling stroke, life-threatening or major bleeding, acute kidney injury stage 2 or 3 and major vascular complications) at 30 days, according to Mitral Valve Academic Research Consortium criteria; rehospitalization for cardiovascular causes at 12 months; echocardiographic and/or tomographic signs of prosthetic valve thrombosis and early SVD at 3- and 12 months; and health-related quality of life (EQ-5D-5L) at 3 and 12 months. Clinical follow-up will continue up to 10 years. SURVIV is the first randomized trial to compare transcatheter mViV procedure with surgical rMVR for mitral BVD and may provide further clinical evidence to guide management of patients with failed mitral bioprostheses.

KEYWORDS: Transcatheter valve replacement, mitral valve disease, bioprosthetic valve dysfunction, randomized controlled trial, valve-in-valve, cardiac surgery, clinical outcomes

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[1] Instituto Dante Pazzanese de Cardiologia, São Paulo-SP, Brazil

[2] Instituto do Coração (INCOR), São Paulo-SP, Brazil

[3] Hospital Ana Nery, Salvador-BA, Brazil

[4] Hospital de Messejana, Fortaleza-CE, Brasil

[5] Instituto Nacional de Cardiologia (INC), Rio de Janeiro-RJ, Brazil

[6] Universidade Federal de São Paulo (UNIFESP), São Paulo-SP, Brazil

[7] Instituto de Cardiologia de Santa Catarina, São José-SC, Brazil

[8] Mount Sinai Fuster Heart Hospital, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Corresponding author:

Dimytri Alexandre Siqueira, MD, PhD

dimytrisiqueira@gmail.com

Av. Dr. Dante Pazzanese, 500 Prédio III – 1º andar

São Paulo, Brazil Postal Code: 04012-909

ABSTRACT

Bioprosthetic mitral valves are prone to structural valve deterioration (SVD) over time, which can lead to bioprosthetic valve dysfunction (BVD) requiring reintervention. Redo-surgical mitral valve replacement (rMVR) is currently the standard treatment, although associated with a significant mortality in high-risk patients. Transcatheter mitral valve-in-valve (mViV) has emerged as an alternative to rMVR in patients with failed bioprostheses, but randomized studies comparing the two treatments are lacking. The SURVIV trial (ClinicalTrials.gov identifier NCT04402931) is an investigator-initiated, prospective, multicenter, open-label randomized controlled trial that will enroll 150 patients with mitral BVD suitable for rMVR or transcatheter mViV. Participants will be randomized 1:1 to transseptal mViV with a balloon-expandable transcatheter heart valve or to conventional surgical rMVR. Procedures will be performed according to local best practice with contemporary medical devices. The primary endpoint is the composite of all-cause of mortality or disabling stroke at 12 months. Key secondary endpoints are major complications (cardiovascular death, disabling stroke, life-threatening or major bleeding, acute kidney injury stage 2 or 3 and major vascular complications) at 30 days, according to Mitral Valve Academic Research Consortium criteria; rehospitalization for cardiovascular causes at 12 months; echocardiographic and/or tomographic signs of prosthetic valve thrombosis and early SVD at 3- and 12 months; and health-related quality of life (EQ-5D-5L) at 3 and 12 months. Clinical follow-up will continue up to 10 years. SURVIV is the first randomized trial to compare transcatheter mViV procedure with surgical rMVR for mitral BVD and may provide further clinical evidence to guide management of patients with failed mitral bioprostheses.
Keywords: Transcatheter valve replacement, mitral valve disease, bioprosthetic valve dysfunction, randomized controlled trial, valve-in-valve, cardiac surgery, clinical outcomes

ABBREVIATIONS LIST

BVD - bioprosthetic valve dysfunction

BVF – bioprosthetic valve failure

rMVR - Surgical redo mitral valve replacement

mViV – Mitral valve-in-valve

SURVIV - Redo **SUR**gery vs transcatheter mitral **V**alve-**I**n-**V**alve

TEE – transesophageal echocardiography

CT – computed tomography

LVOT – left ventricular outflow tract

INTRODUCTION

Bioprosthetic valves are the device of choice for the majority of patients who undergo surgical mitral valve replacement, and their use has grown steadily as clinicians and patients seek to avoid lifelong anticoagulation [1]. Although multiple cohort studies have shown excellent survival and freedom from valve-related complications, all bioprosthetic valves are prone to progressive tissue deterioration - leading ultimately to structural bioprosthetic valve dysfunction (BVD). Surgical redo-mitral valve replacement (rMVR) remains the established therapy for BVD[2], but can be associated with high mortality rates, particularly in patients with advanced disease, comorbidities, or multiple previous cardiac surgeries [3-7]. Moreover, technical operative difficulties caused by tissue adhesions substantially increases the occurrence of bleeding complications, leading to significant morbidity, and increasing in-hospital length of stay.

Transcatheter valve-in-valve has emerged as a less-invasive alternative to redo surgery for older, high-risk patients with BVD. Applied initially for treating failed aortic bioprosthesis [8], nowadays transcatheter mitral valve-in-valve replacement (mViV) has been adopted worldwide. Contemporary registries report low rates of periprocedural morbidity and mortality in high- and intermediate-risk patients, coupled with favorable valve performance [9-11]. Recent meta-analysis comparing mViV and rMVR have shown equivalent mortality but lower incidences of stroke, major bleeding, and acute kidney injury with mViV [12-15]. Most available data are derived from observational studies subject to selection bias, heterogeneous follow-up, and incomplete adjustment for confounding [16-18]. Therefore, a head-to-head comparison of the results of mViV and rMVR is crucial to guide clinical recommendations (especially in younger, lower-risk patients). Additionally, careful imaging follow-up is required to detect complications such as leaflet

thrombosis, late transcatheter heart valve (THV) migration [19] and SVD; those answers are sometimes difficult to obtain from non-controlled trials. The SURVIV (Redo **SUR**gery vs Transcatheter mitral **V**alve-**I**n-**V**alve) study aims to compare the aforementioned treatments in patients of all-surgical risk spectrum with mitral BVD. Applying standardized end-point definitions, comprehensive echocardiographic and tomographic assessment, its primary aim is to determine whether mViV surpasses rMVR in safety and efficacy.

METHODS

Rationale and Study Design

The SURVIV study is an investigator-initiated, prospective, randomized, multicenter, controlled, open-label clinical trial designed to assess the safety and efficacy of transeptal mViV as compared to repeated-surgical MVR in patients with severe mitral BVD. Seven participating centers from different regions in Brazil (4 in southeast, 2 in northeast and 1 in southern) have been selected, with expertise in both transcatheter and surgical mitral valve interventions. Each center maintains a dedicated heart team comprising interventional cardiologists, cardiac surgeons, imaging specialists, and clinical coordinators to ensure optimal patient care and protocol adherence.

The trial is conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Ethical approval has been obtained from the Institutional Review Boards of all participating centers, and the study is registered at ClinicalTrials.gov (identifier: NCT04402931, date of registration 17 Feb 2020). All participants provide written informed consent before enrollment. The study flow is depicted in Figure 1.

Eligibility and Screening

Patients > 18 years-old with severe, symptomatic mitral BVD and requiring repeated mitral valve intervention will be screened for enrollment into the trial. Inclusion and exclusion criteria are depicted in table 1. A complete medical history, physical examination, NYHA functional class assessment, laboratory studies (complete blood count, metabolic panel, liver function tests, coagulation studies, BNP/NT-proBNP) and 12-lead electrocardiogram will be required. A comprehensive imaging assessment will be performed within 90 days before of the procedure, including transthoracic (TTE) and transesophageal echocardiography (TEE) and cardiac computed tomography (cardiac CT). A coronary CT scan to exclude concomitant coronary artery disease (CAD), and /or a right cardiac catheterization with invasive coronariography may be required to confirm pulmonary hypertension and associated CAD. As the available risk-stratification tools remain controversial in estimating outcomes after rMVR and mViV, STS-PROM or Euroscore II cut-off values will be waived during the screening phase, yielding a pragmatic local Heart Team-centred decision regarding eligibility. A committee comprised of investigators who are participants of the trial will review all screened cases to determine if the patient is an appropriate candidate for both treatments, with a focus on anatomical risk factors (e.g., valve sizing, risk of LVOT obstruction, porcelain aorta, hostile chest, intracardiac thrombus) or any other relevant clinical factors that could impact enrollment eligibility (such as associated valvular or myocardial diseases). The risk of left-ventricular outflow tract (LVOT) obstruction [20] will be predicted using a dedicated CT software (3Mensio®, Pie Medical Imaging, Maastricht, the Netherlands). Once deemed an appropriate candidate, the patient will be considered for enrollment in the study.

Randomization, Treatment and Follow-up

After informed consent, patients will be randomized 1:1 to receive either transcatheter mViV with Sapien 3® ou Sapien 3 Ultra® THV platforms (Edwards Lifesciences, Irvine CA) or rMVR with a surgical bioprosthetic valve. A sub-randomization in the surgical group will define which bioprosthetic valve to be used - providing that at a third of surgical patients will receive a Perimount® or Magna Ease® bioprosthesis (Edwards Lifesciences, Irvine CA) and two thirds will get other comercially-available surgical bioprosthesis. Randomization will be performed using a centralized, computer-generated allocation sequence with variable block sizes to ensure balanced treatment assignment while maintaining allocation concealment. The electronic randomization system will be accessible 24 hours a day through a secure web-based platform, ensuring rapid treatment allocation without delays that could compromise patient care. Randomization will occur only after all eligibility criteria have been verified and informed consent obtained. The allocation sequence will be concealed from investigators until the moment of randomization, preventing selection bias in patient enrollment. Given the nature of the interventions, blinding of patients, and treating physicians is not feasible. However, efforts will be made to minimize bias through blinded endpoint adjudication, standardized imaging protocols, and objective outcome measures. The clinical events committee will remain blinded to treatment allocation when analysing primary and secondary outcomes at 1 year follow-up.

The assigned treatment will be performed following treatment guidelines and according to local best practices**,** as described in the Supplementary Material. The choice of anticoagulants and duration of antithrombotic regimen after rMVR are left to physician discretion. Nevertheless, a specific protolol is advised and for patients in sinus rhythm,

anticoagulation with a vitamin K antagonist (warfarin) to achieve an INR of 2.5 or other direct oral anticoagulants (DOAC) are recommended for at least 3 months after surgery. At the time that the study is designed, the evidence base for the optimal antithrombotic strategy after mViV is not robust. Hence, the same protocol for rMVR is also recommended. The details about antithrombotic and antiplatelet therapy (including compliance and reason for interruption) and other cardiac medications will be recorded at each study visit.

The follow-up protocol includes clinical evaluation, laboratory testing, imaging studies, and quality of life questionnaires (EQ-5D-5L) at predefined intervals and are outlined in Figure 2. Echocardiographic (TEE) and cardiac CT examinations at 3 and 12 months will be performed and independently assessed by an imaging core lab to validate findings and provide useful imaging data for pre-specified sub-studies of bioprosthetic leaflet thrombosis and early signs of structural valve dysfunction. Echocardiographic variables include mean mitral transprothetic gradients, mitral valve area, Doppler velocity index, assessment of central and/or paravalvular regurgitation, plus other standard evaluations; CT variables cover predicted and post-procedure neo-LVOT area.

STUDY ENDPOINTS

The primary and secondary endpoints are listed in Table 2. The primary endpoint is defined as the incidence of a composite of all-cause mortality or stroke (intended as disabling) at 12 months post-procedure. Secondary endpoints include safety outcomes at 30 days, efficacy outcomes at 12 months and valve-related complications such as thrombosis and structural valve deterioration yearly. Clinical outcomes will be defined in accordance with the Mitral Valve Academic Research Consortium (M-VARC) [21], as this is the most current consensus document at the time of the study design and first enrolment.

Conversely, structural mitral bioprosthetic dysfunction and/or valve thrombosis will be classified accordingly to new proposed echocardiographic and cardiac CT definitions [22].

STATISTICAL ANALYSIS

Sample Size Calculation

The sample size calculation is based on the hypothesis of superiority of transcatheter mitral valve-in-valve (ViV) implantation compared to conventional mitral valve surgery with respect to the 12-month composite primary endpoint. Available evidence comparing both treatments were minimal at the time of the protocol design in 2018. Therefore, the mortality rates were estimated from descriptive studies published between 2012 and 2017 - which represented the most contemporary data available at the time of protocol development. These studies report on the 1-year follow-up after mViV or rSMVR separately [23-26,28]. Moreover, stroke rates beyond 30-days were not reported systematically in the literature, so historical data from participant centers were used. Accordingly, we assumed an estimated cumulative event rate of 8% in the ViV group and 25% in the surgical group. Considering these proportions, a two-sided significance level of 5%, and a statistical power of 80%, a total of 150 patients is estimated to be required. The calculation assumes a 1:1 randomization ratio between groups and is based on a time-to-event analysis using a Cox proportional hazards regression model.

Statistical Methods

Analysis populations will be conducted in the following populations set:

Intention-to-treat (ITT): Includes all randomized patients, analyzed according to their originally assigned treatment groups, regardless of the actual treatment received or any protocol deviations.

Modified intention-to-treat (mITT): Includes all randomized patients, analyzed according to their originally assigned treatment groups, but considering clinical outcomes from the date of the procedure (if performed) rather than from the date of randomization.

The primary analysis will be assessed using both ITT and mITT population set. The primary composite endpoint of all-cause mortality or disabling stroke will be analyzed as a time-to-event outcome using Kaplan-Meier survival curves. Cox proportional hazards regression will be employed to estimate hazard ratios with 95% confidence intervals, adjusting forage. The proportional hazards assumption will be assessed using Schoenfeld residuals and graphical methods. If the assumption is violated, Greenwood-base z tests will be performed to compare the cumulated incidences in 3, 6 and 12 months.

Regarding secondary analyses, time-to-event endpoints will be analyzed using Kaplan-Meier survival Curves and Hazard Ratios will be estimated using Cox proportional hazards models adjusted for age. Proportional hazard supposition violation will be treated similarly as proposed in the primary endpoint analysis. Quality of life evaluation (EuroQOL) will be compared between groups using linear regression models adjusted for age and baseline EuroQOL values and presented as mean differences with 95% confidence intervals.

- Missing Data: All time-to-event analyses will be censored at the last visit performed for each participant or at the time of death (if death is not the event of

interest). No events will be imputed. Missing baseline or follow-up data will be handled using complete case analysis. No imputation methods are prespecified.

- Additional analyses: we will calculate the restricted mean survival time (RMST) at 1 year for the primary endpoint, and landmark analyses at 6 months will be presented to distinguish short- and long-term comparisons. Hazard ratios with 95% confidence intervals will be reported for each time window.

Continuous endpoints will be analyzed using t-tests or Wilcoxon rank-sum tests depending on data distribution. Categorical endpoints will be compared using chi-square or Fisher's exact tests as appropriate.

Quality Assurance

Statistical analysis will be conducted using R, R Core Team, version 4.4.1 or later, with all analyses pre-specified in a detailed statistical analysis plan finalized before database lock. All statistical code will be documented and archived to ensure reproducibility of results. Additional information regarding data collection and management is provided in the Supplementary Material.

Clinical Events Committee

An independent clinical events committee comprised of a cardiologist, an interventional cardiologist and a cardiovascular surgeon will review and adjudicates all primary and secondary endpoint events using predefined criteria. Committee members are blinded to treatment allocation and base their assessments on comprehensive clinical documentation and imaging studies.

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) provides ongoing oversight of study conduct, safety, and efficacy. The DSMB reviews unblinded safety data at regular intervals and has the authority to recommend study modification or termination if safety concerns arise.

DISCUSSION

Bioprosthetic heart valves have been increasingly preferred over mechanical valves in patients who require surgical aortic or mitral valve replacement. When structural BVD ensues, rMVR prevails as the treatment of choice, and studies have shown that – depending on patient age – a repeated surgical procedure can be required in up to 35% of patients after 10 years [29] and 50% at 20 years [30]. Early post-operative mortality ranges from 6% to 12% in recent series [3-6, 23-26], but can be significantly higher in patients with multiple surgeries [7], endocarditis or pulmonary hypertension [24].

The development of percutaneous treatment of aortic stenosis paved the way for a transcatheter approach for mitral BVD, and Cheung et al. were the first to report a valve-in-valve procedure using transapical access [27]. Initial studies have demonstrated acceptable clinical and hemodynamic results, despite the high-risk characteristics of patients selected for these procedures [28]. A progressive shift towards a higher use of the transseptal approach has been observed, and recent evidence revealed lower mortality and stroke rates [9]. Analysing a large cohort of 4243 high surgical-risk patients (STS score 9 ± 8%) treated from 2015 to 2022, Goel et al. [10] found mortality rates of 4.3% at 30 days and 13.4% at 1-year, with a high technical success rate and a low incidence of periprocedural complications, such as LVOT obstruction (0.4%) or valve migration (0.3%). In a prospective, observational study with carefully selected patients (n=50) and deemed at intermediate risk for rMVR, there were no deaths or strokes at a median follow-up of 758

days, and technical success was 98.0% [11]. By avoiding sternotomy and cardiopulmonary bypass, mViV should trigger less systemic inflammation and tissue trauma, hasten recovery, and improve clinical outcomes of patients with mitral SVD (Figure 3).

Several study-level meta-analyses revealed that - despite older age, more comorbidities, and a high-surgical risk profile -, patients undergoing mViV had a lower rate of periprocedural complications (including stroke, bleeding and acute kidney injury) and a shorter hospital length of stay[12-15]. Overall, no significant differences in mortality rates between rMVR and mViV were reported at 1-year, although few studies revealed a lower in-hospital mortality rate after mViV [14,15]. There are unsettled issues related to mViV procedure, as it can result in smaller effective orifice areas, raising concerns about higher transprosthetic gradients and patient–prosthesis mismatch. The incidence of leaflet thrombosis has not been clearly documented and late THV durability is largely unknown and need to be adressed before expanding indications to low-risk patients. In this regard, rheumatic valve disease is still a common indication for cardiac surgery in younger adults, representing a challenge to public health in low- and middle-income countries; management of heart valve disease in those countries requires long-term follow-up and is characterized by the need for subsequent operations, resulting in substantial impact on patient's quality of life and costs to healthcare systems.

CONCLUSIONS

SURVIV is the first randomized trial to compare mitral valve-in-valve to redo surgical replacement in patients with severe, symptomatic mitral bioprosthetic dysfunction. The results of this study can potentially provide evidence to impact treatment recommendations and support shared decisions for patients who need repeat mitral interventions.

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Table 1. Patient Selection Criteria

Inclusion Criteria:

1. Age > 18 years;
2. Symptoms of heart failure NYHA class > II.
3. Severe mitral bioprosthetic dysfunction defined by echocardiography;
4. Heart team agree on eligibility including assessment that mViV and rMVR are suitable;
5. The study patient or the study patient's legal representative informed of the nature of the study, agreed to its provisions and provided written informed consent as approved by the Institutional Review Board (IRB) center;
6. The study patient agreed to comply with all required post-procedure follow-up visits including annual visits through 10 years;
7. Heart team agreed on treatment strategy for concomitant coronary disease (if present);
8. Patient agreed to undergo rMVR if randomized to control treatment.

Exclusion Criteria:

1. Heart Team assessment of inoperability (including examining cardiac surgeon);
2. Hostile chest;
3. Acute myocardial infarction < 1 month before the intended treatment [WHO definition];
4. Concomitant, severe valvular disease (aortic, tricuspid or pulmonic) requiring surgical intervention;
5. Mitral mechanical prosthesis or valve rings;
6. Preexisting mechanical or bioprosthetic valve dysfunction in other position;
7. Complex CAD: unprotected LM, Syntax > 32 (in the absence of prior revascularization);
8. Any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days of the index procedure (unless part of planned strategy for treatment of concomitant CAD). Implantation of a permanent pacemaker is not an exclusion criteria;
9. Patients with planned concomitant surgical or transcatheter ablation for atrial fibrillation;
10. Leukopenia (WBC < 3000 cell/mL), acute anemia (Hgb< 9 g/dL), thrombocytopenia (Pht< 50,000 cell/mL);
11. Hypertrophic cardiomyopathy with or without obstruction (HOCM);
12. Predicted neo-LVOT area <170 mm^2 without feasible augmentation strategies;
13. Severe ventricular dysfunction with left-ventricular ejection fraction (LVEF) < 20%;
14. Echocardiographic evidence of a mobile intracardiac mass, thrombus or vegetation;
15. Active upper gastrointestinal (GI) bleeding within 3 months (90 days) prior to procedure;
16. A known contraindication or hypersensitivity to all anticoagulation regimens, or inability to be anticoagulated for the study procedure;
17. Clinically or neuroimaging confirmed stroke or TIA within 3 months of the procedure;
18. Renal insufficiency (creatinine > 3.0 mg/dL) and/or renal replacement therapy at screening;
19. Estimated life expectancy < 12 months due to activity malignancies, severe hepatic dysfunction (Child-Pugh class C), severe COPD (FEV_1 <30% predicted) or others;
20. Currently participating in an investigational drug or another device study;
21. Active bacterial endocarditis within 6 months of procedure;
22. Current pregnancy or intention to become pregnant during study period.

Abbreviations: CAD, coronary artery disease; LM, left main; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; LV, left ventricular; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; ViV, valve-in-valve.

Table 2. Primary and major secondary endpoints.

PRIMARY ENDPOINT
. All-cause death or disabling stroke at 12 months
SECONDARY ENDPOINTS
Safety endpoints at 30 days:
. All-cause mortality
. Cardiovascular mortality
. Disabling Stroke
. Major vascular complications
. Life-threatening or major bleeding (BARC 3-5)
. Acute kidney injury (AKIN stage 2-3)
. New-onset atrial fibrillation
. Reoperation for any cause
. Left ventricular outflow obstruction
Efficacy endpoints at 12 months:
. Individual components of the primary endpoint
. Cardiovascular death
. Rehospitalization for heart failure
. Change in NYHA functional class
Valve-related complications (yearly):
. Prosthetic valve thrombosis
. Structural valve deterioration
. Bioprosthetic valve failure
. Endocarditis
Long-term endpoints (annualy up to 10 years):
. All-cause mortality
. Cardiovascular mortality
. Disabling Stroke
. Myocardial infarction

. Heart failure hospitalization

Figures

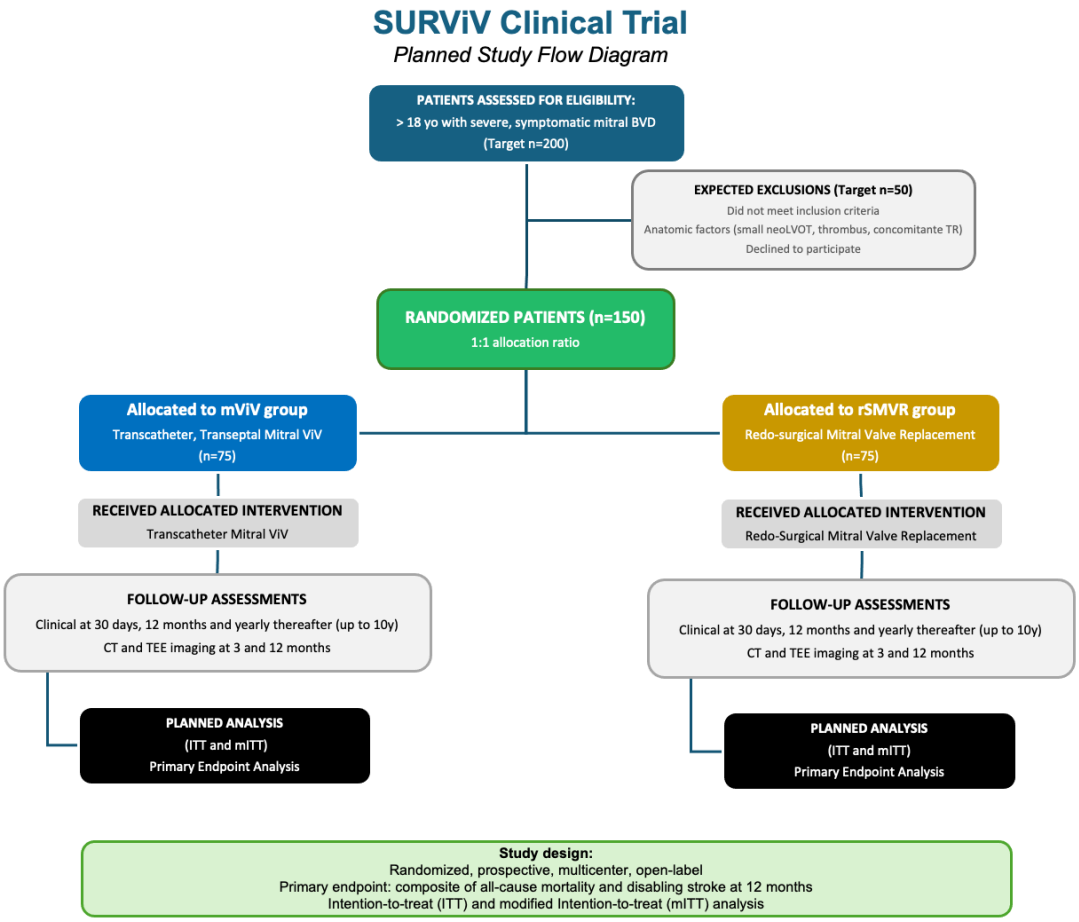

Figure 1. Planned Study Flow Diagram for the SURVIV trial

This CONSORT flow diagram illustrates the planned recruitment, randomization, intervention, and follow-up strategy for the SURVIV trial. The study targets enrollment of 200 patients with severe, symptomatic mitral bioprosthetic valve dysfunction (BVD) requiring reintervention, with an anticipated exclusion rate of approximately 50 patients who do not meet inclusion criteria, decline participation, or have other contraindications. The remaining 150 eligible patients will undergo 1:1 randomization to either mViV (n=75) or rMVR) (n=75). Randomization will be performed using a centralized, computer-generated allocation sequence with variable block sizes to ensure balanced treatment assignment and allocation concealment. All randomized patients will receive their allocated intervention according to standardized protocols, followed by comprehensive clinical assessments at predetermined intervals including 3 months, 12

months, and annually through 10 years. The follow-up protocol encompasses clinical evaluation, multimodality imaging, and quality of life assessments designed to capture both acute safety outcomes and long-term efficacy endpoints. The primary analysis will follow the intention-to-treat principle, analyzing all 150 randomized patients according to their assigned treatment group regardless of protocol deviations or crossover.

Abbreviations: ITT, intention-to-treat; QoL, quality of life; rMVR, redo mitral valve replacement; STS, Society of Thoracic Surgeons; ViV, valve-in-valve.

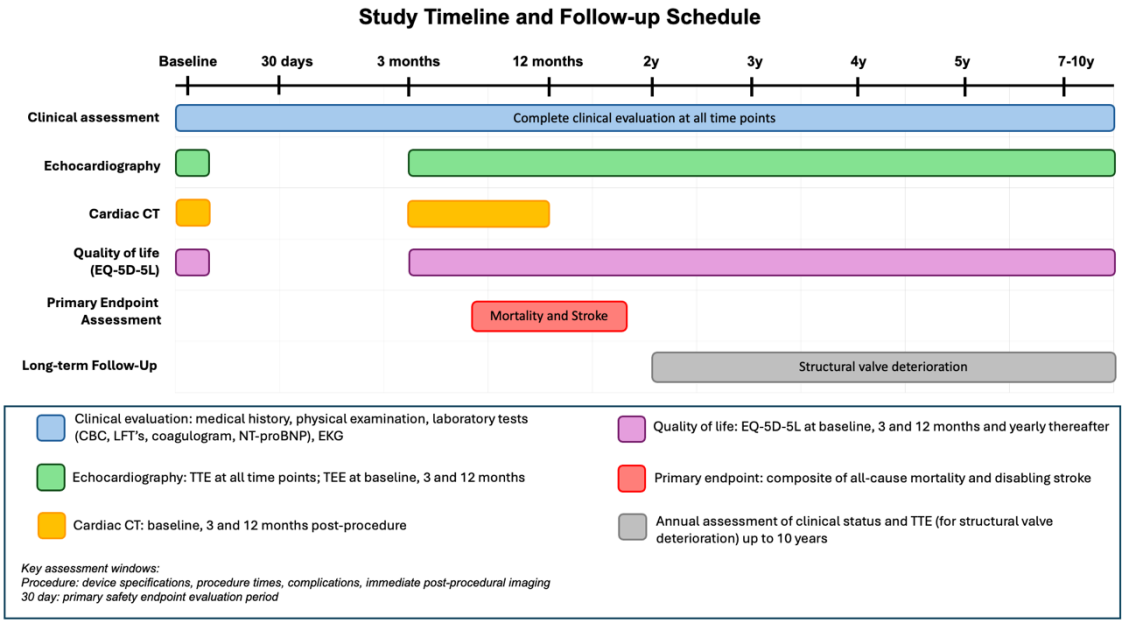

Figure 2. Study Timeline and Follow-up Schedule

This comprehensive follow-up schedule illustrates the timing and scope of clinical assessments designed to capture both acute and long-term outcomes while minimizing patient burden and ensuring high retention rates. Clinical assessment (blue bars) includes complete medical history, physical examination, laboratory studies (complete blood count, comprehensive metabolic panel, liver function tests, coagulation studies, BNP/NT-proBNP), and 12-lead electrocardiography at all timepoints. Echocardiographic evaluation (green bars) consists of transthoracic echocardiography at baseline, 3 months, 12 months, and annually thereafter, with transesophageal echocardiography performed at baseline, 3 and 12 months for comprehensive anatomical assessment. Cardiac CT (orange bars) is performed at baseline, 3 months, and 12 months to evaluate anatomical suitability, for procedural planning, and post-procedural complications (such as THV thrombosis or signs of early bioprosthetic deterioration). Quality of life assessment (pink bars) using the EQ-5D-5L questionnaire is administered at baseline, 3 months, and 12 months to assess sustained functional improvements and yearly thereafter. The primary endpoint assessment (red bar) occurs at 12 months and evaluates the composite outcome of all-cause mortality or disabling stroke. Long-term follow-up (grey bar) continues annually from 2 to 10 years, focusing on structural valve deterioration, valve-related complications, and long-term durability outcomes. This structured approach ensures comprehensive data collection for both primary safety and efficacy endpoints while maintaining feasibility for long-term patient follow-up.

Abbreviations: BNP, B-type natriuretic peptide; CT, computed tomography; EQ-5D-5L, EuroQol 5-Dimension 5-Level questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

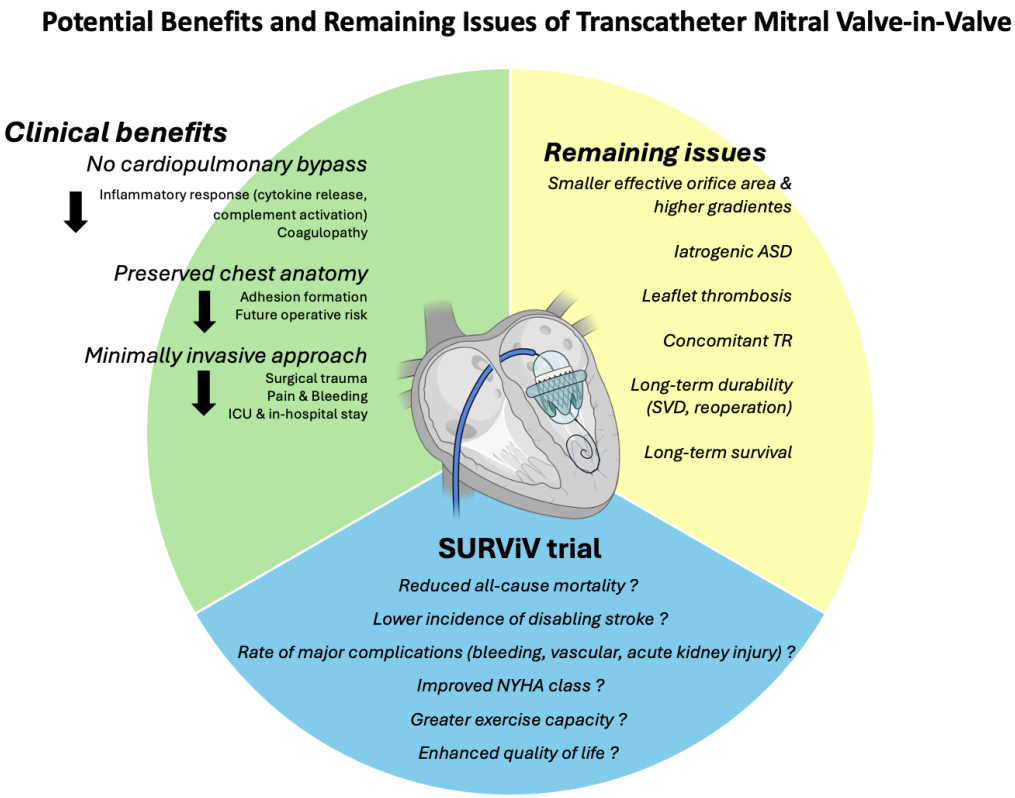

Figure 3. Mechanistic Rationale and Hypothesized Clinical Benefits of Transcatheter Valve-in-Valve Approach.

This conceptual framework illustrates the mechanistic rationale underlying the study hypothesis that transcatheter mViV may demonstrate clinical benefits as compared to rMVR for the 12-month composite primary endpoint. The transseptal ViV approach avoids sternotomy and cardiopulmonary bypass, theoretically providing key mechanistic advantages: reduced inflammatory response through decreased cytokine release and complement activation; elimination of cardiopulmonary bypass-related complications including coagulopathy; minimally invasive technique resulting in reduced surgical trauma, pain, and bleeding; and preservation of chest wall anatomy with decreased adhesion formation and lower future operative risk. These mechanistic benefits are hypothesized to accelerate patient recovery through faster mobilization, shorter intensive care unit stays, and earlier hospital discharge. The improved recovery profile is expected to translate into superior clinical outcomes across multiple domains: enhanced 30-day safety profile with reduced all-cause mortality, stroke incidence, life-threatening bleeding, and acute kidney injury; improved functional outcomes including better New York Heart Association functional class, greater exercise capacity, enhanced quality of life scores, and superior symptom relief; and achievement of the primary composite endpoint of reduced all-cause mortality and stroke with sequelae at 12 months. Remaining issues related to transcatheter treatment that need to be addressed include the role of

iatrogenic atrial septal defect (ASD) and concomitant tricuspid regurgitation (TR) after the procedure and rates of leaflet thrombosis, structural valve deterioration, reintervention and long-term durability at 10 years as compared to redo-surgical mitral valve replacement.

Abbreviations: CPB, cardiopulmonary bypass; ICU, intensive care unit; NYHA, New York Heart Association; ViV, valve-in-valve; EOA, effective orifice area; ASD, atrial septal defect; TR, tricuspid regurgitation

SUPPLEMENTARY MATERIAL

METHODS (continued)

Treatment description

1) Transcatheter Mitral Valve-in-Valve procedure

Comprehensive imaging assessment is performed within 90 days of the procedure, including transthoracic and transesophageal echocardiography, cardiac computed tomography, and coronary angiography if indicated. The cardiac CT images will be analyzed using dedicated software 3-Mensio Structural Heart module (Pie Medical Imaging, Maastricht, the Netherlands to determine optimal valve sizing, predict neo-LVOT dimensions, and plan the procedural approach.

The transcatheter mitral ViV procedure will be performed in a hybrid operating room or cardiac catheterization laboratory equipped with advanced imaging capabilities including high-resolution fluoroscopy and transesophageal echocardiography. The procedure will be conducted under general anesthesia with endotracheal intubation to ensure patient comfort and optimal imaging quality.

Femoral venous access will be established using vascular ultrasound, and a transseptal puncture will be held under fluoroscopic and echocardiographic (TEE) guidance. An ideal transseptal puncture site (posterior and inferior, 2.5 to 4 mm in height to the mitral bioprosthetic plane) is advisable to optimize the delivery angle and minimize difficulties in navigating the THV to the deteriorated surgical valve. After full anticoagulation with intravenous administration of 100 UI/Kg of heparin, a balloon atrial septostomy with a 12 -14 mm semi-compliant or non-compliant balloon will be performed to facilitate delivery system passage.

The balloon-expandable transcatheter heart valve (SAPIEN 3® or SAPIEN 3 Ultra®, Edwards Lifesciences, Irvine CA) will be advanced mounted upsize-down in the delivery system and positioned within the degenerated surgical bioprosthetic valve under real-time imaging fluoroscopic guidance. Valve sizing will be based on the stent internal diameter of the surgical bioprosthesis specified in previous surgical report or according to cardiac CT measurements, with appropriate oversizing to ensure adequate sealing and prevent

migration. The THV will be deployed under rapid ventricular pacing to minimize cardiac motion and ensure precise positioning, using wire-pacing technique or standard, right-ventricular pacemaker lead. Pre- and postdilation will be performed according to physician discretion. Post-deployment assessment will include evaluation of THV position and function and the occurrence of paravalvular or central regurgitation or LVOT obstruction using TEE and hemodynamic measurements. Iatrogenic atrial septal defect closure will be indicated if a significant right-toleft shunting with hypoxemia is observed during the procedure or if signs of right ventricular overload ensue during clinical and echocardiographic follow-up. Depending on clinical status, patients will transferred to the ward or to an intensive care unit for monitoring.

2) Surgical Redo Mitral Valve Replacement

Pre-procedure imaging assessment will include chest computed tomography to evaluate mediastinal anatomy, identify patent grafts, and plan surgical approach. Cardiac catheterization will be performed to address concomitant coronary artery disease. Blood products will be made available given the increased bleeding risk associated with redo valve surgery.

The redo-mitral valve replacement operation procedure will follow established techniques for cardiovascular surgery with modifications based on individual patient anatomy and previous surgical history. The procedure will be performed by experienced cardiac surgeons with expertise in complex mitral valve surgery and redo operations. The standard approach involves median sternotomy with careful dissection of adhesions and identification of vital structures. Alternative approaches including right thoracotomy may be considered based on patient anatomy and surgeon preference. Cardiopulmonary bypass can be established using peripheral cannulation strategies when central cannulation is not feasible.

The mitral valve is accessed through the left atrium, typically via the interatrial groove or transseptal approach. The degenerated bioprosthetic valve is carefully excised, preserving the annular structure, and avoiding injury to surrounding tissues. A new bioprosthetic valve will be implanted using standard suturing techniques.

After mitral valve surgeries, patients are usually weaned from cardiopulmonary bypass with appropriate hemodynamic support as needed, and intraoperative

transesophageal echocardiography confirms adequate valve function and excludes complications. Patients are transferred to the intensive care unit for postoperative monitoring and typically remain hospitalized for 5-10 days depending on recovery.

STATISTICAL ANALYSIS (continued)

Data Collection and Management

Data collection will follow Good Clinical Practice standards with electronic case report forms designed to capture comprehensive clinical, procedural, and follow-up information. The data management system will include built-in quality checks, range validations, and consistency algorithms to ensure data integrity and completeness.

Source Document Verification

Regular monitoring visits will be conducted to verify source document accuracy, protocol compliance, and data quality. A risk-based monitoring approach will focus resources on critical data elements and high-risk sites while maintaining overall study integrity.

Core Laboratory Services

Centralized core laboratories will provide standardized analysis of echocardiographic and computed tomography imaging to ensure consistent endpoint assessment across participating sites. The imaging core laboratory is staffed by experienced cardiologists and radiologists with expertise in valvular heart disease and transcatheter interventions.