Supplementary Appendix

This supplement has been provided by the authors to give readers additional information about their work and contains the original and final protocol and also the original statistical analysis plan.

1. *Original protocol (English translation – Literal version), final protocol, summary of changes.*
2. *Original statistical analysis plan (single only version).*

RESEARCH PROTOCOL	**Treatment of Mitral Valve Bioprosthesis Dysfunction: Randomized Clinical Trial Comparing Transcatheter Valve-in-Valve Implantation versus Redo Mitral Valve Replacement Surgery**
VERSION	1.0
DATE	14/10/2019
SPONSOR	Instituto Dante Pazzanese de Cardiologia Brazilian Health United System (SUS)
AFFILIATED AUTHORITY	São Paulo State Health Secretariat – Brazil Brazilian Health United System (SUS)

Treatment of Mitral Valve Bioprosthesis Dysfunction: Randomized Clinical Trial Comparing Transcatheter Valve-in-Valve Implantation versus Redo Mitral Valve Replacement Surgery

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Protocol version: 1.0

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INVESTIGATOR COMMITMENT PAGE

The individuals responsible for conducting the study at this center agree to the following:

- We understand and will conduct the study in accordance with the protocol and its approved amendments, following the recommendations of Good Clinical Practice (GCP) and complying with all requirements of regulatory authorities and national laws.
- We will not deviate from the protocol without prior review and written approval from the Ethics Committees, both local and independent, except when necessary to avoid any immediate danger to the patient.
- We have sufficient time to adequately conduct and complete the clinical study within the agreed study period, and we have an adequate number of qualified personnel available, as well as appropriate facilities to conduct the trial properly and safely throughout the duration of the study.

Title	Treatment of Mitral Valve Bioprosthesis Dysfunction: Randomized Clinical Trial Comparing Transcatheter Valve-in-Valve Implantation versus Redo Mitral Valve Replacement Surgery
Coordination center	Instituto Dante Pazzanese de Cardiologia Av. Dr. Dante Pazzanese, 500 – Ibirapuera CEP: 04012090 São Paulo – SP, Brazil Phone: +55 (11) 50856000 Extension: 6325
Study design	Open-label, prospective, multicenter, randomized clinical trial
Methodological quality	Central randomization
Primary objectives:	To evaluate clinical outcomes (major cardiovascular events — all cause death and disabling stroke at12 months) following transcatheter implantation of a mitral prosthesis using the valve-in-valve (ViV) technique compared with redo mitral valve replacement surgery (rMVR).
Secondary objectives:	1. To analyze procedural complications at 30 days, including: • cardiovascular death • stroke • renal failure • atrial fibrillation • bleeding • vascular complications • left ventricular outflow tract obstruction • reoperation 2. To evaluate rehospitalization rates at 12 months.

	3. To study the incidence of prosthetic valve thrombosis as assessed by cardiac CT and transesophageal echocardiography at 3 and 12 months. 4. To evaluate the occurrence of structural valve deterioration during clinical follow-up up to 10 years.
Population:	Patients aged 18 years or older with symptomatic dysfunction of a mitral bioprosthesis and indication for redo mitral valve replacement surgery.
Follow-up:	Clinical follow-up at 7 days or hospital discharge (whichever occurs first), at 30 days, at 3 months, and annually up to 10 years after the procedure. Clinical follow-up with echocardiography and cardiac CT imaging at 3 and 12 months after the procedure. Annual clinical and echocardiographic follow-up until completion of 10 years post-procedure.
Outcomes (MVARC definitions)	1. Primary outcomes: Combined major adverse cardiac and cerebrovascular events (MACCE) at 12 months, defined as: • all-cause death • disabling stroke (neurological assessment) 2. Secondary outcomes: 2.1 Complications associated with ViV and redo surgery at 30 days: • all-cause mortality • cardiovascular mortality • disabling stroke • major vascular complications • life-threatening, extensive or major bleeding • new-onset atrial fibrillation • acute kidney injury (AKIN classification) • reoperation 2.2 Efficacy outcomes at 12 months:

	• Cardiovascular mortality • Rehospitalization for cardiac and non-cardiac causes • Change in New York Heart Association (NYHA) class • Quality of life measures (EuroQol 5D5L) 3. Mitral prosthesis thrombosis at 3 and 12 months as defined by echocardiography and cardiac CT. 4. Structural deterioration (as defined by echocardiography) and bioprosthetic valve failure (clinical follow-up) up to 10 years.
Sample size	150 patients randomized 1:1 to ViV implantation or redo surgery.

1. INTRODUCTION

Transcatheter implantation of balloon-expandable prostheses for the treatment of dysfunction of surgical valvular bioprostheses — a procedure termed "Valve-in-Valve" (ViV) — represents a therapeutic alternative to redo valve replacement surgery (rMVR). Initially applied to patients with biological prostheses in the aortic position[1,2], Cheung et al. were the first to report the transapical ViV procedure for the treatment of dysfunction of a mitral valve prosthesis[3]. Currently, mitral ViV has been performed in several centers worldwide, predominantly using the transseptal approach. Observational studies have demonstrated low rates of procedure-related complications, and initial echocardiographic parameters have been favorable[4-9]. However, randomized clinical trials comparing mitral ViV and redo mitral valve replacement surgery are not yet available[10,11], and there is also limited information regarding the cost-effectiveness and cost-utility of this new procedure. In particular, the long-term durability of transcatheter bioprostheses in the mitral position remains unknown, and clarification of this issue is required before expanding the indication of mitral ViV — especially in younger patients and those considered at low surgical risk.

1.1 Dysfunction and Failure of Surgical Mitral Bioprostheses

Bioprostheses are the preferred devices for the vast majority of patients with valvular heart disease requiring surgical valve replacement[12,13]. Several observational

studies have demonstrated excellent survival free from complications related to bioprostheses in both aortic and mitral positions[14-16].

Progressive tissue degeneration of bioprostheses constitutes the main cause of structural valve deterioration, occurring over the years following surgery. Structural deterioration encompasses permanent intrinsic leaflet alterations (rupture, calcification, pannus formation, or fibrosis), which may result in valvular stenosis or regurgitation. Other causes of prosthetic dysfunction may be potentially reversible, such as thrombosis and infective endocarditis[17-19]. Recently, the term bioprosthetic valve failure has been used to describe the association between significant hemodynamic impairment (important regurgitation or elevated transprosthetic gradients assessed by echocardiography) and resulting clinical events such as reintervention or death[20].

The need for reoperation after prior biological valve replacement is influenced by the patient's age at the time of the index surgery. Chan et al. demonstrated that in patients older than 60 years, survival free from reoperation after 15 years was 78% following aortic valve replacement and 62% following mitral valve replacement. Conversely, in patients younger than 40 years, survival free from reoperation was 34% and 36%, respectively[21]. Other studies indicate that up to 35% of patients undergoing mitral valve replacement require reoperation within the first 10 years[22]. In this context, North American data suggest that bioprosthetic valves have increasingly been indicated in patients younger than 65 years, which will likely result in a greater number of individuals with aortic and mitral bioprosthesis dysfunction in the near future[23,24].

In addition to age, other conditions are associated with increased risk of tissue deterioration of surgical bioprostheses, including: chronic kidney disease, calcium metabolism disorders, prosthesis–patient mismatch, mitral prosthesis position[18,25,26]. A possible explanation for the higher occurrence of dysfunction of mitral bioprostheses compared with aortic prostheses relates to the higher closing pressure exerted on mitral prosthetic leaflets, as well as their longer coaptation time during the cardiac cycle[27]. In mitral bioprostheses, the main mechanism of dysfunction is valvular regurgitation (49%), followed by mixed dysfunction (30%) and isolated stenosis (21%)[18].

From a clinical perspective, redo mitral valve replacement surgery is indicated in individuals with severe prosthetic dysfunction, defined according to echocardiographic criteria commonly used for native valve disease[13]. Redo surgery, even when performed electively, is associated with surgical mortality approximately two to three times higher than that of the index procedure, particularly in elderly individuals and those with comorbidities. Observational studies report mortality rates following redo mitral valve replacement ranging from 3% to 23%[28-33]. Advanced age, female sex, NYHA functional class > II, left ventricular dysfunction, renal failure, pulmonary disease, number of previous surgeries, and urgency of intervention are all predictors of higher surgical risk[34,35]. Additionally, thoracic adhesions resulting from previous surgery markedly increase the occurrence of bleeding, transfusions, infections, and other morbidities, prolonging hospital length of stay.

Analysis of the Society of Thoracic Surgeons (STS) database identified 11,973 patients undergoing mitral valve replacement, among whom 1,096 (9.7%) had a history of prior mitral surgery[36]. Compared with first-time surgery, redo procedures were associated

with higher mortality (11.1% vs. 6.5%, $p < 0.0001$). Independent predictors of 30-day mortality included: cardiogenic shock, tricuspid regurgitation, urgent surgery, concomitant coronary artery bypass grafting. Kwedar et al., in turn, found high mortality associated with rMVR in Medicare patients in the United States (n = 1,627): the mortality rate was 12%, with no differences according to sex, age (above or below 75 years), or type of prosthesis used (biological or mechanical). Mortality, however, was more frequent when surgery was performed on an urgent basis (15.6% vs. 5.5%, $p = 0.0001$) and in patients with heart failure (14.2% vs. 9.9%, $p = 0.008$). Cumulative survival was 58.6% at 5 years[37].

1.2 Transcatheter Mitral Valve Implantation (Valve-in-Valve)

The rapid development of transcatheter instrumentation and the extensive clinical experience acquired with transcatheter aortic valve implantation (TAVI) have enabled expansion of indications for transcatheter prosthesis implantation aimed at treating dysfunction of surgical bioprostheses in the aortic, mitral, tricuspid, or pulmonary positions. To date, however, scientific evidence derived from randomized studies comparing this strategy with redo valve replacement surgery remains unavailable.

The mitral Valve-in-Valve (ViV) implantation has emerged as a less invasive therapeutic alternative to reoperation in individuals at high surgical risk[38]. The procedure may be performed via transapical, transatrial, or transseptal approaches. The least invasive approach is the transseptal route. Through the femoral vein, transseptal puncture is performed and a sheath is positioned in the left atrium. After crossing the mitral prosthesis toward the left ventricle, a stiff guidewire is carefully positioned at the ventricular apex. The subsequent step consists of interatrial septal dilation (septostomy), allowing

advancement of the balloon-expandable prosthesis. Mounted on a balloon for anterograde deployment, the prosthesis is released slowly under ventricular pacing using a temporary pacemaker[39].

Initial experiences with mitral ViV have demonstrated satisfactory clinical and echocardiographic outcomes, despite the high surgical risk profile of patients included in early studies. A progressive shift in access strategy has been observed, with increasing preference for the transseptal approach. Data from the North American Transcatheter Valve Therapies (TVT) Registry showed that among 1,576 patients treated with mitral ViV between June 2015 and August 2019, the preferred access route was transseptal (n = 1,326; 84.1%), followed by the transapical approach (n = 203; 12.9%). The mean age of patients treated via the transseptal route was 73.4 years, 59.2% were female, and the mean STS score was 11 ± 8.5%. Mechanisms of prosthetic dysfunction were stenosis, regurgitation, or both in 55.6%, 24.9%, and 19.4% of patients, respectively. At 30 days, cardiovascular mortality rates were 2.1% in the transseptal group and 5.1% in the transapical group[40].

Currently, limited scientific evidence is available regarding clinical and echocardiographic outcomes of mitral ViV compared with redo mitral valve replacement surgery. In a retrospective study conducted at three institutions in the United States, 113 patients with degenerative mitral prostheses were analyzed. Sixty-two underwent ViV implantation with balloon-expandable prostheses (Sapien XT or Sapien 3, Edwards Lifesciences), and fifty-nine underwent redo surgery. Patients treated with ViV were older and presented higher surgical risk, as assessed by the STS score (74.9 ± 9.4 years vs. 63.7 ± 14.9 years; $p < 0.001$; STS 12.7 ± 8.0% vs. 8.7 ± 10.1%; $p < 0.0001$). The transseptal route was used in 77% of ViV procedures. Major bleeding and supraventricular

arrhythmias were significantly lower in the ViV group, as were ICU length of stay and total hospitalization duration. In these patients, rates of stroke, surgical conversion, and left ventricular outflow tract (LVOT) obstruction were 0%, 1.6%, and 3.2%, respectively. Thirty-day mortality was similar between groups (ViV 3.2% vs. surgery 3.4%). Hemodynamic outcomes assessed by echocardiography were also comparable (mean gradient 7.1 ± 2.5 mmHg with ViV vs. 6.5 ± 2.5 mmHg after surgery; p = 0.42). The occurrence of mitral regurgitation greater than moderate at 30 days was 3.8% with ViV and 5.6% with surgery (p = 1.00). At 12 months, no difference in survival between the two treatment strategies was observed (mortality 11.3% vs. 11.9%; p = 0.92)[41].

Important aspects of the procedure that still require clarification include: risk of LVOT obstruction[42-44], leaflet thrombosis, unknown medium- and long-term durability of transcatheter prostheses in the mitral position. It is known that subacute and late thrombosis of surgical bioprostheses occurs more frequently in the mitral than in the aortic position, and this phenomenon may also occur with transcatheter prostheses. Furthermore, the optimal antithrombotic regimen following mitral ViV implantation remains poorly defined. For all these reasons, scientifically comparing the results of mitral ViV with redo mitral valve replacement surgery is essential to guide and justify treatment recommendations — particularly in younger patients and/or those at lower surgical risk. Careful clinical and echocardiographic follow-up is required to detect late complications of the new procedure, such as: prosthesis migration, thrombosis, and structural leaflet degeneration. These outcomes are difficult to adequately assess in observational and uncontrolled studies[46].

In patients with deterioration and dysfunction of a previously implanted surgical bioprosthesis, the choice between redo surgery and ViV therefore requires comprehensive

multidisciplinary discussion regarding expected benefits and risks of short- and long-term complications with each technique. Such decision-making should involve a Heart Team composed of: clinical cardiologists, interventional cardiologists, cardiovascular surgeons, cardiovascular imaging specialists, and anesthesiologists. The opinions of patients and their families should also be respected in accordance with bioethical principles. Ultimately, any treatment must be evaluated from the patient perspective, promoting or restoring health (efficacy) without causing harm or complications (safety). It should also be as comfortable as possible for the patient without compromising safety or efficacy. From a public health perspective, treatment must also be cost-effective, ensuring appropriate allocation of limited healthcare resources.

1.3 Mitral Valve Surgery in Young Patients and Rheumatic Heart Disease

The epidemiology of valvular heart disease has changed over recent decades. The strong association between valvular disease and aging — amplified by population aging worldwide — has led many cardiologists to designate valvular heart disease as the "next epidemic" in the specialty. Despite this assertion, important differences remain in the prevalence and etiology of valvular diseases between developed and economically less favored countries. In developed nations, the most common valvular disease is aortic stenosis, generally related to senile degeneration and calcification of the aortic valve. Conversely, in less economically developed regions, the leading cause of morbidity and mortality attributable to valvular disease remains rheumatic heart disease. In these countries, valvular disease frequently requires long-term follow-up and multiple surgical interventions, resulting in substantial impact on patients' quality of life and significant costs to public healthcare systems.

Guidelines for prevention and treatment of acute rheumatic fever and rheumatic heart disease were originally published by the World Health Organization several decades ago[48]. Following these initiatives, several countries succeeded in reducing mortality related to rheumatic heart disease. Unfortunately, a high prevalence of rheumatic heart disease continues to be reported in many regions worldwide[49]. Watkins et al. conducted a systematic review of global and regional prevalence of rheumatic heart disease between 1990 and 2015. During this period, 319,400 deaths (95% uncertainty interval: 297,300 to 337,300) were attributed to rheumatic heart disease, with higher incidence observed in Oceania, Asia, and Central Africa[53].

Rheumatic fever remains a frequent cause of morbidity in Latin America, and valvular involvement represents a common indication for cardiac surgery in young adults[54]. In Brazil, the PROVAR study (Rheumatic Valve Disease Screening Program) demonstrated that echocardiographic prevalence of rheumatic heart disease was 42 per 1,000 children[55]. Data from the Brazilian Ministry of Health indicate that approximately 22,000 patients per year develop heart disease secondary to rheumatic fever, with disease prevalence ranging from 3% to 5% among children and adolescents[56,57]. Rheumatic fever affects approximately 7.9 per 1,000 inhabitants in La Paz (Bolivia) and 2.9 per 1,000 inhabitants in Cuba[58]. In conclusion, rheumatic fever and its associated complications — characterized by valvular disease and heart failure — remain a major public health challenge in many countries.

Given the advances and improved clinical outcomes associated with percutaneous treatment of valvular disease and the high prevalence of mitral prosthesis dysfunction in our setting — particularly among young patients with prior rheumatic fever and multiple

previous cardiac surgeries — the performance of a specific randomized clinical trial evaluating the benefits, risks, and quality-of-life impact of the Valve-in-Valve procedure compared with standard redo mitral valve replacement surgery is justified.

2. PROTOCOL

Study Design

This study is a prospective, randomized clinical trial with analysis of clinical, echocardiographic, and computed tomography outcomes. Patients aged 18 years or older who have previously undergone mitral valve replacement with a biological prosthesis and who present with severe symptomatic prosthetic dysfunction (stenosis or regurgitation) and formal indication for treatment by either redo mitral valve replacement surgery or mitral Valve-in-Valve implantation will be eligible.

Procedures

The experimental group will undergo mitral Valve-in-Valve implantation using the least invasive strategy, namely the transseptal approach. The control group will undergo redo mitral valve replacement surgery, following the institution's standard procedural protocol.

Sample Size

A total of 150 patients will be included and allocated to mitral Valve-in-Valve implantation or redo mitral valve replacement surgery. With this sample size, it is expected

that appropriate data regarding clinical and echocardiographic outcomes, as well as quality-of-life analyses at one year, will be obtained.

Patients

Patients aged 18 years or older with severe symptomatic dysfunction of a mitral bioprosthesis and formal indication for redo mitral valve replacement within the Brazilian Unified Health system (Sistema Único de Saúde – SUS).

Prior Alignments

Not applicable.

Expected Contributions / Rationale for the Study

With increasing life expectancy and population aging — as highlighted in the Brazilian National Health Plan — there is a strong trend toward rising prevalence of valvular heart diseases. To date, relatively few patients in Brazil have been treated with mitral Valve-in-Valve implantation. This number is clearly lower than the potential population of patients eligible for the procedure, as described in Section 1.3 of the Introduction. Determining the clinical benefits and risks of mitral Valve-in-Valve implantation compared with standard surgical treatment is therefore essential to support appropriate and responsible indication of this new procedure.

3. OBJECTIVES

3.1 Primary Objective

To evaluate the safety and efficacy of transcatheter implantation of a balloon-expandable prosthesis for the treatment of mitral prosthetic dysfunction (Valve-in-Valve), compared with conventional redo mitral valve replacement surgery. The primary endpoint is the composite of all-cause death or disabling stroke.

3.2 Secondary Objectives

The study also has the following secondary objectives:

- To compare clinical outcomes of minimally invasive Valve-in-Valve implantation (transseptal technique) with those obtained with conventional redo mitral valve replacement surgery, by analyzing the occurrence of the following adverse events at 30 days, 12 months, and annually until completion of 10 years of follow-up: all-cause death, cardiovascular death, disabling stroke, major vascular complications, life-theatening, extensive and major bleeding, new-onset atrial fibrillation, renal failure (AKIN classification), and reoperation for any cause.
- To analyze the rates of cardiovascular and non-cardiovascular rehospitalization at 12 months and health status (change in NYHA class) and quality-of-life measures (EuroQol 5D- 5L) at 3 and 12 months.
- To evaluate the occurrence of mitral prosthetic thrombosis at 3 and 12 months, as defined by echocardiography and cardiac computed tomography.
- To investigate the occurrence of structural valve deterioration (as defined by echocardiography) and bioprosthetic valve failure (clinical follow-up) up to 10 years after the procedure.

4. METHODS

4.1 Study Design and Selected Population

This study is an open-label, multicenter, prospective, randomized clinical trial. Patients with severe symptomatic dysfunction of a mitral prosthesis, treated within the Brazilian Unified Health System (Sistema Único de Saúde – SUS), and with formal indication for either mitral Valve-in-Valve implantation or redo mitral valve replacement surgery will be selected.

Inclusion criteria

The following inclusion criteria will apply:

- Age ≥ 18 years.
- Presence of symptoms related to mitral bioprosthetic dysfunction, such as dyspnea with NYHA functional class > II.
- Structural deterioration of a mitral valve bioprosthesis with severe dysfunction (stenosis or regurgitation) as defined according to echocardiographic findings[59].
- Agreement among members of the multidisciplinary Heart Team (including a cardiovascular surgeon) regarding patient eligibility and confirmation that both proposed treatments (Valve-in-Valve or redo mitral valve replacement surgery) are indicated.
- Patient willingness to undergo redo mitral valve replacement surgery if randomized to the control group.
- Adequate anatomical parameters for transseptal Valve-in-Valve implantation, as defined by cardiac computed tomography.

- Prior agreement of the Heart Team regarding the treatment strategy for concomitant coronary artery disease, with SYNTAX score < 32.
- Patient agreement to remain under outpatient clinical follow-up for 10 years, attending protocol visits at 30 days, 3 months, 12 months, and annually until completion of follow-up.
- Provision of written informed consent by the patient or legal representative using a consent form approved by the Institutional Research Ethics Committee.

Exclusion criteria

The following exclusion criteria will apply:

- Patients considered inoperable by the multidisciplinary Heart Team.
- Myocardial infarction occurring within 30 days prior to the Valve-in-Valve or redo surgery procedure.
- Dysfunction of a mechanical mitral prosthesis.
- Presence of other significant valvular diseases (aortic, tricuspid, or pulmonary) requiring surgical treatment according to Heart Team decision.
- Complex coronary artery disease (SYNTAX score > 32).
- Leukopenia (white blood cell count < 3,000 cells/mL),
- anemia (hemoglobin < 8 g/dL), or
- thrombocytopenia (platelet count < 50,000 cells/mL).
- Hypertrophic cardiomyopathy, with or without obstruction.
- Predicted neoLVOT < 170 mm2, not amenable to septal reduction therapies.
- Severe left ventricular dysfunction (ejection fraction < 20%).

- Echocardiographic or tomographic evidence of tumor mass, thrombus, or vegetation.
- Gastrointestinal bleeding within 30 days prior to the procedure.
- Contraindication or hypersensitivity to antithrombotic or antiplatelet medications.
- Stroke or transient ischemic attack within 3 months prior to the procedure.
- Severe renal dysfunction (creatinine > 3.0 mg/dL) or need for hemodialysis.
- Life expectancy < 12 months due to conditions such as malignancy, chronic liver disease with cirrhosis, dialysis-dependent renal failure, or advanced chronic obstructive pulmonary disease requiring supplemental oxygen.
- Bacterial endocarditis within 6 months prior to the procedure.
- Porcelain aorta or hostile chest.
- Pregnancy.

Selected patients will have their data collected and stored in an electronic platform provided by the Dante Pazzanese Institute of Cardiology (REDCap — Research Electronic Data Capture). The randomization list will be generated electronically using appropriate software. Confidentiality of the randomization list will be maintained through an automated central randomization system available 24 hours per day.

The treatment allocation group will only be disclosed after patient information has been entered into the electronic system, preventing investigators and the clinical care team from predicting treatment assignment.

4.2 Follow-Up

Patients will be followed according to the schedule below during hospitalization, at 30 days, 3 months, and 12 months, and annually thereafter up to 10 years, preferably through clinical visits including echocardiographic assessment according to institutional routine.

	Screening	**Procedure**	**Pos-procedure/Discharg**	**30days (± 7days)**	**3 months (± 14 days)**	**12 months (± 30 days)**	**Annually up to 10 years (± 60 days)**
Visits							
Clinical Assessment							
Informed Consent	X						
Clinical History, Physical examination	X				X	X	X
NYHA class	X			X	X	X	X
STS score	X						
Euroscore II	X						
SYNTAX score *(if applicable)*	X						
Quality of live (EQ-5D-5L)	X					X	
Lab tests	X		X				
Medications	X		X	X	X	X	X
Adverse events assessment			X	X	X	X	X
Examination							
EKG	X		X			X	X
Transthoracic echocardiography	X		X				
Transesophageal echocardiography	X				X	X	
Cardiac CT	X				X	X	
Computed coronary tomography, coronary angiogram	X						
Elegibility							
Heart Team discussion	X						
Randomization	X						
Procedure							
Mitral Valve-in-valve or redo surgery		X					

4.3 Clinical Endpoints

The variables to be assessed during follow-up visits include:

- all-cause death
- cardiovascular death
- disabling stroke
- major vascular complications
- bleeding and need for transfusion
- atrial fibrillation
- renal failure
- use of healthcare services (emergency department visits, hospitalizations, surgeries, procedures)
- assessment of health-related quality of life using the EuroQOL-5D-5L questionnaire.

Clinical endpoints will be defined according to Mitral Valve Academic Research Consortium (MVARC).

4.4 Sample Size

We estimate that a sample size of 150 patients will allow demonstration of superiority of mitral Valve-in-Valve implantation over surgery with respect to the primary endpoint at 12 months, with 80% statistical power. For this calculation, we assumed Kaplan–Meier event rate estimates of 8% in the Valve-in-Valve group and 25% in the surgical group.

4.5 Risks and Benefits

This study may involve known potential risks related to the procedures performed. In general, risks associated with Valve-in-Valve implantation and mitral valve replacement surgery include:

- vascular access site injury or complications (groin)
- air embolism
- allergic reaction to contrast
- arrhythmias
- bleeding at puncture site
- cardiac arrest
- cardiac tamponade
- cardiovascular injury including cardiac perforation or aortic dissection
- electrical conduction disturbances requiring permanent pacemaker implantation
- death
- prosthesis embolization requiring emergency surgery
- prosthesis migration
- emergency cardiac surgery
- fever
- heart failure
- hemolysis
- intrathoracic hemorrhage
- arterial hypertension

- hypotension
- infection, including endocarditis, thoracic inflammation or infection
- myocardial infarction
- cardiogenic shock
- paravalvular or intravalvular (central) leaks
- pleural effusion
- worsening renal function
- respiratory complications
- septicemia
- stroke
- venous thrombosis and thromboembolism
- impaired wound healing

Information obtained from this study will contribute to determining whether this new procedure should be incorporated into the Brazilian public healthcare system (SUS) and may help other patients in the future.

5. STUDY TIMELINE AND RELATED ACTIVITIES

5.1 Deliverables and Related Activities

The proposal is to complete the clinical study with patient randomization, treatment, and follow-up (for 12 months) by December 2023.

We anticipate that patient inclusion and performance of procedures will require a period of 22 months (until October 2021), with an expected recruitment rate of

approximately 7 patients per month. The additional 14 months of the three-year period will be dedicated to: post-procedural clinical follow-up; database cleaning; interim analysis; preparation of the primary manuscript.

The study timeline includes the following phases:

Macro Timeline of Activities

	2020				2021				2022				2023- 2031
	1T	2T	3T	4T	1T	2T	3T	4T	1T	2T	3T	4T	
Regulatory maintenance activities													
Patient screening and enrollment													
Follow-up													
Data management													
Interim statistical analysis													
Writing of the manuscript													
Database lock, final statistical analysis													

Long-term clinical follow-up is planned until 2031.

6. FINANCING OF THE RESEARCH, PUBLICATION OF RESULTS, AND ADDITIONAL INFORMATION

6.1 Funding

This is an investigator-initiated study, with treatment costs covered by the Brazilian Unified Health System (Sistema Único de Saúde – SUS) through resources from the São

Paulo State Health Secretariat and Fundação Adib Jatene. The study will receive financial support from Edwards Lifesciences, which will provide a research grant to the research organization at the Dante Pazzanese Institute of Cardiology. The company will also provide devices and/or equipment for study conduct as established by contract:

- 75 Sapien 3 prostheses (Edwards Lifesciences) for the Valve-in-Valve group
- 25 Perimount or Magna Ease surgical prostheses (Edwards Lifesciences) for the surgical group

Surgical treatment of the remaining patients will be performed using prostheses already available through the public healthcare system.

The contract with the company is expected to end once the 12-month endpoint is reached and results up to this stage are published. Patient follow-up will continue according to the study protocol.

6.2 Key Personnel

The multidisciplinary clinical staff of participating hospitals will be responsible for performing procedures and patient follow-up, including: cardiovascular surgeons, interventional cardiologists, clinical cardiologists, echocardiographers, anesthesiologists, and intensivists.

6.3 Dissemination of Results

The study Steering Committee commits to publishing study results regardless of outcome.

As this is a randomized study addressing a topic of national and international relevance, the main publications will be submitted to high-impact journals.

Proposals for sub-studies and secondary publications, as well as inclusion of individual data in meta-analyses, must be submitted by investigators to the Steering Committee, which will evaluate proposals and may approve, suggest improvements, or reject them. Evaluation will be based on scientific merit and investigator contribution to the success of the main study.

The study database is intended to be made accessible to other researchers. During the first two years after publication of the primary manuscript, investigators will prioritize analyses of sub-studies proposed by members of the collaborative group. During this phase, the database will remain under custody of the study coordinators, and access by third parties will only be permitted with explicit authorization from the Steering Committee, following evaluation of a proposal accompanied by a statistical analysis plan. The Steering Committee should grant access to requested data provided that the proposal does not conflict with planned or ongoing sub-studies. After a period of two years, all data collected in the study will be made publicly available on an open platform. No information allowing future patient identification (such as initials, date of birth, etc.) will be publicly available after this period. Any individual requesting access to the database must formally commit to notifying the Steering Committee of any information that could allow patient identification.

6.4 Risks Related to Study Execution

Among risks to be considered in study conduct, the following should be highlighted:

- The study is expected to require approximately 2 years for completion, considering analysis of 12-month primary outcomes.
- Long-term follow-up of 10 years is planned.
- During this period, evidence from other studies may be published, potentially affecting study conduct. For example, similar randomized studies may be conducted demonstrating benefit of one treatment strategy over the other. Results from such studies will be evaluated together with the Data Monitoring Committee before any decisions are made.

7. REFERENCES

1. Wenaweser P, Buellesfeld L, Gerckens U, Grube E. Percutaneous aortic valve replacement for severe aortic regurgitation in degenerated bioprosthesis: the first valve-in-valve procedure using the CoreValve Revalving system. Catheter Cardiovasc Interv. 2007;70:760-764.
2. Walther T, Falk V, Dewey T, et al. Valve-in-a-valve concept for transcatheter minimally invasive repeat xenograft implantation. J Am Coll Cardiol. 2007;50:56-60.
3. Cheung A, Webb JG, Wong DR, et al. Transapical transcatheter mitral valve-in-valve implantation in a human. Ann Thorac Surg. 2009;87:e18-20.

4. Seiffert M, Conradi L, Baldus S, et al. Transcatheter mitral valve-in-valve implantation in patients with degenerated bioprostheses. JACC Cardiovasc Interv. 2012;5:341-349.
5. Bouleti C, Fassa AA, Himbert D, et al. Transfemoral implantation of transcatheter heart valves after deterioration of mitral bioprosthesis or previous ring annuloplasty. J Am Coll Cardiol Intv. 2015;8:83-91.
6. Søndergaard L, Brooks M, Ihlemann N, et al. Transcatheter mitral valve implantation via transapical approach: an early experience. Eur J Cardiothorac Surg. 2015;48:873-877.
7. Coylewright M, Cabalka AK, Malouf JA, et al. Percutaneous mitral valve replacement using a transvenous, transseptal approach. JACC Cardiovasc Interv. 2015;8:850-857.
8. Eleid MF, Cabalka AK, Williams MR, et al. Percutaneous transvenous transseptal transcatheter valve implantation in failed bioprosthetic mitral valves, ring annuloplasty, and severe mitral annular calcification. JACC Cardiovasc Interv. 2016;9:1161-1174.
9. Seiffert M, Conradi L, Baldus S, et al. Transcatheter mitral valve-in-valve implantation in patients with degenerated bioprostheses. JACC Cardiovasc Interv. 2012;5:341-349.
10. Baldizon I, Espinoza A, Kuntze T, Girdauskas E. Early transcatheter valve dysfunction after transapical mitral valve-in-valve implantation. Interact Cardiovasc Thorac Surg. 2016;22:501-503.

11. Cheung A, Webb JG, Barbanti M, et al. Five-year experience with transcatheter transapical mitral valve-in-valve implantation for bioprosthetic valve dysfunction. J Am Coll Cardiol. 2013;61:1759-1766.
12. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease. J Am Coll Cardiol. 2017;70:252-289.
13. Baumgartner H, Falk V, Bax JJ, et al. ESC/EACTS Guidelines for the Management of Valvular Heart Disease. Eur Heart J. 2017;38:2739-2791.
14. Ribeiro AHS, Wender OCB, de Almeida AS, et al. Comparison of clinical outcomes in patients undergoing mitral valve replacement with mechanical or biological substitutes: a 20-year cohort. BMC Cardiovasc Disord. 2014;14:146-158.
15. Poirier NC, Pelletier LC, Pellerin M, et al. Fifteen-year experience with the Carpentier-Edwards pericardial bioprosthesis. Ann Thorac Surg. 1998;66:S57-61.
16. Johnston DR, Soltesz EG, Vakil N, et al. Long-term durability of bioprosthetic aortic valves: implications from 12,569 implants. Ann Thorac Surg. 2015;99:1239-1247.
17. Piazza N, Bleiziffer S, Brockmann G, et al. Transcatheter aortic valve implantation for failing surgical aortic bioprosthetic valve. JACC Cardiovasc Interv. 2011;4:721-732.

18. Paradis JM, Del Trigo M, Puri R, et al. Transcatheter valve-in-valve and valve-in-ring for treating aortic and mitral surgical prosthetic dysfunction. J Am Coll Cardiol. 2015;66:2019-2037.
19. Vesey JM, Otto CM. Complications of prosthetic heart valves. Curr Cardiol Rep. 2004;6:106-111.
20. Capodanno D, Petronio AS, Prendergast B, et al. Standardized definitions of structural deterioration and valve failure in assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves. Eur J Cardiothorac Surg. 2017;52:408-417.
21. Chan V, Malas T, Lapierre H, et al. Reoperation of left heart valve bioprostheses according to age at implantation. Circulation. 2011;124:S75-S80.
22. Hammermeister K, Gulshan KS, Henderson WG, et al. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve. J Am Coll Cardiol. 2000;36:1152-1158.
23. Gammie JS, Sheng S, Griffith BP, et al. Trends in mitral valve surgery in the United States. Ann Thorac Surg. 2009;87:1431-1437.
24. Barnett SD, Ad N. Surgery for aortic and mitral valve disease in the United States. J Thorac Cardiovasc Surg. 2009;137:1422-1429.
25. Mahjoub H, Mathieu P, Larose E, et al. Determinants of aortic bioprosthetic valve calcification assessed by multidetector CT. Heart. 2015;101:472-477.
26. Ruel M, Kulik A, Rubens FD, et al. Late incidence and determinants of reoperation in patients with prosthetic heart valves. Eur J Cardiothorac Surg. 2004;25:364-370.

27. Schoen FJ, Levy RJ. Calcification of tissue heart valve substitutes. Ann Thorac Surg. 2005;79:1072-1080.
28. Castillo-Sang M, Guthrie TJ, Moon MR, et al. Outcomes of repeat mitral valve surgery in patients with pulmonary hypertension. Innovations (Phila). 2015;10:120-124.
29. Balsam LB, Grossi EA, Greenhouse DG, et al. Reoperative valve surgery in the elderly. Ann Thorac Surg. 2010;90:1195-1200.
30. Chikwe J, Chiang YP, Egorova NN, et al. Survival and outcomes following bioprosthetic vs mechanical mitral valve replacement in patients aged 50-69 years. JAMA. 2015;313:1435-1442.
31. Maganti M, Rao V, Armstrong S, et al. Redo valvular surgery in elderly patients. Ann Thorac Surg. 2009;87:521-525.
32. Vohra HA, Whistance RN, Roubelakis A, et al. Outcome after redo mitral valve replacement in adult patients: a 10-year single-centre experience. Interact Cardiovasc Thorac Surg. 2012;14:575-579.
33. Bourguignon T, Bouquiaux-Stablo AL, Loardi C, et al. Very late outcomes for mitral valve replacement with the Carpentier-Edwards pericardial bioprosthesis. J Thorac Cardiovasc Surg. 2014;148:2004-2011.e1.
34. Jones JM, O'Kane H, Gladstone DJ, et al. Repeat heart valve surgery: risk factors for operative mortality. J Thorac Cardiovasc Surg. 2001;122:913-918.
35. Akins CW, Buckley MJ, Daggett WM, et al. Risk of reoperative valve replacement for failed mitral and aortic bioprostheses. Ann Thorac Surg. 1998;65:1545-1551.

36. Mehaffey HJ, Hawkins RB, Schubert S, et al. Contemporary outcomes in reoperative mitral valve surgery. Heart. 2018;104:652-656.
37. Kwedar K, McNeely C, Zajarias A, et al. Outcomes of early mitral valve reoperation in the Medicare population. Ann Thorac Surg. 2017;104:1516-1521.
38. Dvir D, Webb J. Mitral valve-in-valve and valve-in-ring: technical aspects and procedural outcomes. EuroIntervention. 2016;12:Y93-Y96.
39. Urena M, Himbert D, Brochet E, et al. Transseptal transcatheter mitral valve replacement using balloon-expandable valves: a step-by-step approach. JACC Cardiovasc Interv. 2017;10:1905-1919.
40. Guerrero M. TVT Registry. Presented at TCT 2019. Available from: https://www.tctmd.com/news/transseptal-transcatheter-mitral-valve-valve-ups-survival-high-risk-patients
41. Kamioka N, Babaliaros V, Morse MA, et al. Comparison of clinical and echocardiographic outcomes after surgical redo mitral valve replacement and transcatheter mitral valve-in-valve therapy. JACC Cardiovasc Interv. 2018;11:1131-1138.
42. Wang DD, Eng M, Greenbaum A, et al. Predicting LVOT obstruction after TMVR. JACC Cardiovasc Imaging. 2016;9:1349-1352.
43. Guerrero M, Wang DD, O'Neill W. Percutaneous alcohol septal ablation to reduce LVOT obstruction induced by TMVR. Catheter Cardiovasc Interv. 2016;88:e191-e197.

44. Khan JM, Rogers T, Schenke WH, et al. Intentional laceration of the anterior mitral leaflet to prevent LVOT obstruction during TMVR. JACC Cardiovasc Interv. 2016;9:1835-1843.
45. Bapat VV, Khaliel F, Ihleberg L. Delayed migration of Sapien valve after mitral valve-in-valve implantation. Catheter Cardiovasc Interv. 2014;83:e150-e154.
46. Makkar R, Chakravarty T. Early leaflet thrombosis. JACC Cardiovasc Interv. 2018;11:1172-1174.
47. Coffey S, Cairns BJ, Iung B. The modern epidemiology of heart valve disease. Heart. 2016;102:75-85.
48. World Health Organization. Rheumatic fever and rheumatic heart disease. Geneva: WHO; 1988. (Technical Report Series No. 764).
49. Nulu S, Bukhman G, Kwan GF. Rheumatic heart disease: the unfinished global agenda. Cardiol Clin. 2017;35:165-180.
50. Weinberg J, Beaton A, Aliku T, et al. Prevalence of rheumatic heart disease in African school-aged population. Int J Cardiol. 2016;202:238-239.
51. Paar JA, Berrios NM, Rose JD, et al. Prevalence of rheumatic heart disease in children and young adults in Nicaragua. Am J Cardiol. 2010;105:1809-1814.
52. Rothenbühler M, O'Sullivan CJ, Stortecky S, et al. Active surveillance for rheumatic heart disease. Lancet Glob Health. 2014;2:e717-e726.
53. Watkins DA, Johnson CO, Colquhoun SM, et al. Global burden of rheumatic heart disease, 1990-2015. N Engl J Med. 2017;377:713-722.
54. Bocchi EA, Arias A, Verdejo H, et al. The reality of heart failure in Latin America. J Am Coll Cardiol. 2013;62:949-958.

55. Nascimento BR, Beaton AZ, Nunes MC, et al. Echocardiographic prevalence of rheumatic heart disease in Brazilian schoolchildren: PROVAR study. Int J Cardiol. 2016;219:439-445.
56. Ministério da Saúde. Incidence of rheumatic fever in Brazil. Brasília: Ministério da Saúde; 2003.
57. Reis G, Motta MS, Barbosa MM, et al. Dobutamine stress echocardiography for risk stratification in rheumatic mitral stenosis. J Am Coll Cardiol. 2004;43:393-401.
58. Hernández-Leiva E. Epidemiology of acute coronary syndrome and heart failure in Latin America. Rev Esp Cardiol. 2011;64(Suppl 2):34-43.
59. Lancellotti P, Pibarot P, Chambers J, et al. Recommendations for imaging assessment of prosthetic heart valves. Eur Heart J Cardiovasc Imaging. 2016;17:589-590.

Questionário de saúde

Versão em português para o Brasil

(Portuguese version for Brazil)

Versão do responsável pelo paciente do EQ-5D-5L: 2

(pedir ao responsável pelo paciente como ele ou ela
(ou seja o responsável) acredita que o paciente classificaria a sua própria saúde se
pudesse nos dizer)

Abaixo de cada título, por favor marque O quadrado que (*escreva o nome da pessoa cuja saúde será avaliada, por ex. Sr. Silva ou Maria*) escolheria para descrever a sua própria saúde HOJE se pudesse nos dizer.

MOBILIDADE

Sem problemas em andar ❑
Problemas leves em andar ❑
Problemas moderados em andar ❑
Problemas graves em andar ❑
Incapaz de andar ❑

CUIDADOS PESSOAIS

Sem problemas para se lavar ou se vestir ❑
Problemas leves para se lavar ou se vestir ❑
Problemas moderados para se lavar ou se vestir ❑
Problemas graves para se lavar ou se vestir ❑
Incapaz de se lavar ou se vestir ❑

ATIVIDADES HABITUAIS *(ex. trabalho, estudos, atividades domésticas, atividades em família ou de lazer)*

Sem problemas em realizar as suas atividades habituais ❑
Problemas leves em realizar as suas atividades habituais ❑
Problemas moderados em realizar as suas atividades habituais ❑
Problemas graves em realizar as suas atividades habituais ❑
Incapaz de realizar as suas atividades habituais ❑

DOR / MAL ESTAR

Sem dores ou mal-estar ❑
Dores ou mal-estar leves ❑
Dores ou mal-estar moderados ❑
Dores ou mal-estar fortes ❑
Dores ou mal-estar extremos ❑

ANSIEDADE / DEPRESSÃO

Não ansioso/a ou deprimido/a ❑
Levemente ansioso/a ou deprimido/a ❑
Moderadamente ansioso/a ou deprimido/a ❑
Muito ansioso/a ou deprimido/a ❑
Extremamente ansioso/a ou deprimido/a ❑

- Nós gostaríamos de saber o quão boa ou ruim você acredita que (*escreva o nome da pessoa cuja saúde será avaliada, por ex. Sr. Silva ou Maria*) diria que está a sua própria saúde HOJE se pudesse nos dizer.
- Esta escala é numerada de 0 a 100.
- 100 significa a melhor saúde que você possa imaginar.
  0 significa a pior saúde que você possa imaginar.
- Marque um X na escala para indicar quão boa ou ruim (*escreva o nome da pessoa cuja saúde será avaliada, por ex. Sr. Silva ou Maria*) diria que está a sua própria saúde HOJE se pudesse nos dizer.
- Agora, por favor escreva no quadrado abaixo o número que você marcou na escala.

O paciente classificaria a sua PRÓPRIA SAÚDE HOJE COMO: ☐