Prospective Randomized comparison Of prosthetic Valve Effective orifice area: One-year analysis of two bovine PERIcardial valves (PROVE-PERI trial)

NCT 03796442

Trial Protocol v 1.4

Updated Dec 28, 2018

Protocol summary

Trial name and number	**Prospective Randomized comparison Of prosthetic Valve Effective orifice area: One-year analysis of two bovine PERIcardial valves (PROVE-PERI trial)** ClinicalTrial.gov 03796442
Objectives	This randomized controlled trial is designed to compare 1-year hemodynamic performances and clinical outcomes after aortic valve replacement (AVR) using a recently introduced and world-widely used bovine pericardial bioprostheses.
Design	Prospective randomized controlled trial
Study periods	IRB approval date ~ June 30, 2022
Subjects	Patients who are scheduled to undergo AVR
Sample size	Total 140 patients
Methods	Patients over 19 years of age who are scheduled to undergo AVR on a nonemergency basis and who are planned to undergo primary AVR using stented bioprostheses are assessed for eligibility for study enrollment. The exclusion criteria include (1) patients with concomitant mitral or tricuspid valve operation, (2) patients with infective endocarditis, (3) patients with severe left ventricular dysfunction (ejection fraction < 0.30), (4) patients with a medical history such as a malignant disease that might limit the possibility of mid-term follow-up and (5) patients who refuse study enrollment. Enrolled patients are randomly assigned to 1 of the 2 bioprostheses in a 1:1 manner. After surgery, early clinical and hemodynamic outcomes are evaluated following the protocol. After discharge, all patients undergo regular postoperative follow-up and are evaluated with echocardiography at 1-year follow-up.
Endpoints	The primary endpoint of the PROVE-PERI trial was mean pressure gradient across the aortic valve (AVMPG) on 1-year echocardiographic follow-up. The secondary endpoints were the effective orifice area (EOA) on 1-year echocardiographic follow-up and 1-year clinical outcomes including all-cause mortality, cardiac death and major adverse event (MAEs).
Safety	Postoperative complications including operative mortality, low cardiac output, bleeding reoperation, perioperative myocardial infarction, perioperative stroke, acute kidney injury, respiratory complications, postoperative atrial fibrillation, and mediastinitis were monitored for safety.
Expectations	This trial will provide the objective hemodynamic and clinical data for individual prosthesis, and help the patients and surgeons to choose optimal prosthesis for aortic valve replacement (AVR).

Study Protocol

1. Title

Prospective Randomized comparison Of prosthetic Valve Effective orifice area: One-year analysis of two bovine PERIcardial valves (PROVE-PERI trial)

2. Institutions

Seoul National University Hospital (101 Daehak-ro, Jongno-gu, Seoul, 03080, Korea)

Seoul National University Bundang Hospital (82, Gumi-ro 173 Beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do 13620, Korea)

3. Principal investigator and co-investigators

1) Principal investigators

Ho Young Hwang (Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital)

Cheong Lim (Department of Thoracic and Cardiovascular Surgery, Seoul National University Bundang Hospital)

2) Co-investigators

Yoonjin Kang (Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital)

Ji Seong Kim (Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital)

Jae Woong Choi (Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital)

Jae Hang Lee (Department of Thoracic and Cardiovascular Surgery, Seoul National University Bundang Hospital)

Jun Sung Kim (Department of Thoracic and Cardiovascular Surgery, Seoul National University Bundang Hospital)

3) Sub-investigator

Suk Ho Sohn (Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital)

4. Sponsor

none

5. Funding

none

6. Study period

IRB approval – June 30, 2022

7. Study subjects

Patients who are scheduled to undergo AVR

8. Background and Objectives

1) Background

Current guidelines demonstrate that aortic valve replacement ([AV]R) with a prosthetic valve is indicated for the patients with severe AV disease. [1] Many prosthetic valves have been introduced in the clinical practice, upgraded with their own characteristics, and contributed to the improved clinical outcomes after AVR. Among several types of prosthetic valves, bioprostheses have advantages in biocompatibility and in avoidance of long-term anticoagulation compared with mechanical valves, whereas they have disadvantages of limited durability and smaller effective orifice area (EOA).

The Avalus™ (Medtronic, Minneapolis, MN) is one of most recently introduced stented bovine pericardial bioprostheses. [2] A prospective observational study, which is called PERIGON (PERIcardial SurGical AOrtic Valve ReplacemeNt) Pivotal Trial, have reported favorable 5-year hemodynamic performance and clinical outcomes after AVR using the Avalus™ valve.4 However, there has been no study that prospectively compared results after AVR using the Avalus™ with those after AVR using other bovine pericardial valves.

To perform a comparative analysis for the efficacy and safety of this newly introduced bioprosthesis, a prospective randomized controlled trial (RCT) comparing the Avalus™ with the world-widely used Carpentier-Edwards PERIMOUNT Magna Ease (CEPME; Edwards Lifesciences, Irvine, CA) was designed by the authors.

2) Hypothesis and Objectives

The present study is conducted to compare 1-year hemodynamic performances after AVR using the Avalus™ valve with those using the CEPME.

We hypothesize that the Avalus™ was noninferior to the CEPME based on the mean pressure gradient across the aortic valve (AVMPG) at 1-year echocardiographic follow-up.

9. Inclusion criteria, Exclusion criteria and Sample size calculation

1) Inclusion criteria

① Patients who are scheduled to undergo AVR

② Over 19 years of age

③ Patients who are planned to receive a bioprosthetic valve for aortic valve substitute

④ Patients who or whose legal representative fill out a written consent form before the start of the clinical trial and patients who can comply with the clinical trial requirements

2) Exclusion criteria

① Patients with concomitant mitral or tricuspid valve operation

② Patients with severe left ventricular dysfunction (ejection fraction < 0.30)

③ Patients with infective endocarditis

④ Patients with a medical history such as a malignant disease that might limit the possibility of mid-term follow-up

⑤ Patients who refused study enrollment

3) Sample size calculation

The study is designed to have 80% power to detect 1-year AVMPG of 12.6±4.3mmHg for the study prosthesis [2] and 11.9±4.3mmHg for the control prosthesis, [3-5] with a 1-sided type I error of 2.5% and a noninferiority margin of 3mmHg. The noninferiority margin is determined by the values of 15mmHg for AVMPG of clinically significant aortic stenosis [6] and 12mmHg for AVMPG of the control prosthesis. Fifty-six patents in each group are needed to complete the study cohort. Allowing for a 20% dropout rate during the 1-year follow-up, we determine that the recruitment of 70 patients in each group is necessary.

(1) Level of significance (α) = 0.025

(2) Type II error (β) = 0.20, power of the test = 80%

(3) Drop out rate = 20%

(4) One-tailed test

H_0(null hypothesis): $\mu_1 - \mu_2 \geq \delta$

H_1(alternative hypothesis): $\mu_1 - \mu_2 < \delta$

(μ_1: mean AVMPG of the study group on $1-$year echocardiographic follow $-$ up ,
μ_2: mean AVMPG of the control group on $1-$year echocardiographic follow $-$ up
δ: noninferiority margin)

The calculation was performed using PASS Software(Power Analysis and sample size software: http://www.ncss.com), and the calculated formula is as follows.

$$n = \frac{(Z_\alpha + Z_\beta)^2 (\sigma_1{}^2 + \sigma_2{}^2)}{\left((\mu_1 - \mu_2) - \delta\right)^2}$$

μ_1 = mean AVMPG of the study group on $1-$year echocardiographic follow $-$ up
μ_2 = mean AVMPG of the control group on $1-$year echocardiographic follow $-$ up
σ_1 = standard deviation of AVMPG of the study group on $1-$year echocardiographic follow $-$ up
σ_2 = standard deviation of AVMPG of the control group on $1-$year echocardiographic follow $-$ up
δ: noninferiority margin

4) Subject recruitment plan

Subject recruitment will be performed for the patients who are scheduled to undergo AVR and who are hospitalized at Seoul National University Hospital and Seoul National University Bundang Hospital after providing sufficient explanation and informed consents. The subjects will be recruited competitively.

10. Methods

1) Detailed process of the study

Patients over 19 years of age who are scheduled to undergo AVR on a nonemergency basis and who are planned to undergo primary AVR using stented bioprostheses at 2 institutions are assessed for eligibility for study enrollment. After excluding the patients who meet the exclusion criteria and who refuse to participate, enrolled patients are randomly assigned to 1 of the 2 bioprostheses in a 1:1 manner.

Surgeries are performed under median sternotomy or upper partial sternotomy under cardiopulmonary bypass with cold cardioplegic arrest. After the diseased AV is excised, the annulus is prepared for landing the prosthesis, and the proper valve sizes for both types of

prostheses are decided before randomization. Then, randomization is performed with a web-based block randomization method with randomly determined block sizes of 4 and 6. After randomization, the assigned prosthesis is implanted with non-everting transverse mattress sutures. The knot-tying is performed manually or by using an automated knot-fastener.

Patients are evaluated with early clinical outcomes and early echocardiographic measurements. After discharge, all patients undergo regular postoperative follow-up through the outpatient clinic at 3- to 6-month intervals and are interviewed by telephone for confirmation of their condition if the last clinic visit has not been conducted as scheduled. At postoperative 1-year, clinical outcomes and echocardiographic measurements are evaluated as scheduled.

※ Randomization : Patients who meet the inclusion criteria and the exclusion criteria are randomly assigned to 1 of the 2 bioprostheses in a 1:1 manner. Randomization is performed with a web-based block randomization method (https://mrcc.snuh.org/) with randomly determined block sizes of 4 and 6, considering the institution as a stratification factor.

2) Outcome measures

1) Demographics: age, sex, height, weight, BMI, BSA, diagnosis, operation name

2) Preoperative data

- Risk factors: DM, HTN, smoking, dyslipidemia, stroke, COPD, CKD, chronic liver disease, coronary disease, peripheral vascular disease, history of cardiac surgery, New York Heart Association functional class, STS mortality risk, EuroSCORE II
- Echocardiographic measurements: Effective orifice area, mean pressure gradient, peak pressure gradient, LA dimension, LV ejection fraction, LV end diastolic dimension, LV end systolic dimension, pulmonary artery systolic pressure, TR severity, etc.
- Electrocardiography
- Laboratory tests: CBC, routine chemistry, NT-proBNP, CRP, ABGA, lactate, PT, aPTT
- CT scan (thoracoabdominal CT angio)
- Pulmonary function test

3) Operative data: CPB time, ACC time, concomitant procedures, operative findings

4) Postoperative data

- Early clinical outcomes: op mortality, op morbidities (low cardiac output, bleeding reoperation, perioperative myocardial infarction, perioperative stroke, acute kidney injury, respiratory complications, postoperative atrial fibrillation, and mediastinitis)

- Echocardiographic measurements: Effective orifice area, mean pressure gradient, peak pressure gradient, LA dimension, LV ejection fraction, LV end diastolic dimension, LV end systolic dimension, pulmonary artery systolic pressure, TR severity, etc.
- Electrocardiography: 1st, 2nd and 3rd AV block, bundle branch block

5) 1-year follow-up data

- Clinical outcomes: all-cause mortality, cardiac death and major adverse events (valve-related mortality, structural valve deterioration, nonstructural dysfunction, thromboembolic and bleeding events, prosthetic valve endocarditis, AV reintervention or the need for a new permanent pacemaker or defibrillator within 14 days after the index operation), last follow-up date, New York Heart Association functional class
- Echocardiographic measurements: Effective orifice area, mean pressure gradient, peak pressure gradient, LA dimension, LV ejection fraction, LV end diastolic dimension, LV end systolic dimension, pulmonary artery systolic pressure, TR severity, etc.
- Electrocardiography: 1st, 2nd and 3rd AV block, bundle branch block

※ Primary clinical endpoint

mean pressure gradient across the aortic valve (AVMPG) on 1-year echocardiographic follow-up

※ Secondary clinical endpoint

the effective orifice area (EOA) on 1-year echocardiographic follow-up

operative mortality, operative morbidities

1-year clinical outcomes (all-cause mortality, cardiac death and major adverse events)

3) Differences from previous treatments and studies

When compared with previous treatments, the operative strategies and perioperative management are identical, but only the bioprostheses used in the treatments are different.

When compared with previous studies, all studies previously performed were prospective single-arm designs or retrospective studies. To the best of our knowledge, the present study is the first prospective randomized controlled trial comparing results of AVR using the Avalus™ valve with those using another bovine pericardial valve that has been used worldwide.

4) Risks associated with the study

*** Predicted risks**

Because both prostheses have proved their efficacy and safety by prospective pivotal trials

and many related studies, the predicted risks associated with the present study will be comparable to routinely performed aortic valve replacement.

If any adverse event or risk occurs, providing the standard management for them will be sufficient.

5) Criteria for suspension and dropout

Patients who decline to participate in the trial are suspended or drop-out

6) Safety

Safety outcomes will be a composite of death from any cause and individual major postoperative complications including low cardiac output, bleeding reoperation, perioperative myocardial infarction, perioperative stroke, acute kidney injury, respiratory complications, postoperative atrial fibrillation, and mediastinitis.

All safety outcome measures will be assessed and recorded at designated time intervals by research personnel at each individual center. Data regarding every event will be reviewed and adjudicated centrally by the principal investigator and sub-investigator.

7) Efficacy

Efficacy analysis will be performed for ITT(Intention to treat) group, and supplemental analysis will be performed for PP(Per protocol) and As treated group. The primary endpoint will be concluded as 'noninferior' if both ITT and PP analyses confirm the noninferiority.

ITT group includes all study population. PP group is constituted from the ITT group after excluding the patients with major violation of the study protocol.

The null hypothesis was that the Avalus^{TM} was inferior to the CEPME based on the AVMPG at 1-year echocardiographic follow-up, with a non-inferiority margin of 3mmHg. The result for the primary endpoint was presented with 97.5% one-sided confidence interval for mean difference between groups. The non-inferiority test was performed using a t-test which compared mean difference between groups with the non-inferiority margin under the one-sided significance level of 0.025.

For analysis of 1-year clinical outcomes including all-cause mortality, cardiac death, and MAEs, events were counted at postoperative 1 year, and comparisons between the 2 groups were made using the chi-square test and Fisher's exact test. A P value of < .050 was considered statistically significant.

8) Schedules

① Study planning : October 1, 2018 – November 31, 2018

② Enrollment : January 1, 2019 (or after IRB approval) – June 30, 2022

③ Data analysis and reporting : January 1, 2022 – December 31, 2022

11. Data monitoring and Safety committee

1) Monitoring committee

Ho Young Hwang (Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital)

Suk Ho Sohn (Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital)

2) Data and Safety Monitoring List

Operative mortality, low cardiac output, bleeding reoperation, perioperative myocardial infarction, perioperative stroke, acute kidney injury, respiratory complications, postoperative atrial fibrillation, and mediastinitis

3) Data and Safety Monitoring Periods

Safety outcomes will be monitored every 6 months.

4) Reporting drug adverse events, non-compliance, or unpredicted events

If any drug adverse event, non-compliance, or unpredicted event occurs, they must be reported within 15 working days from the date of recognition.

5) Withdrawal of the trial

If critical adverse events or complications associated with the trial occur and it is impossible to keep the trial going on, the trial will be withdrawed.

12. Ethics

The Investigators and all parties involved will conduct this study in adherence to the ethical principles based on Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements. Relevant study documentation will be submitted to Ethics Committees of participating centers, according to local/national requirements, for review. Written

approval of the study must be obtained locally before the study commences at each participating center. Once protocol amendments or consent form modifications are approved and implemented at the lead center, updated documents will be provided to participating centers. On completion of the study, the regulatory authorities will be notified that the study has ended.

13. References

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[3] Fiegl K, Deutsch MA, Rondak IC, Lange R, Guenzinger R. Matched Comparison of Two Different Biological Prostheses for Complete Supra-annular Aortic Valve Replacement. Thorac Cardiovasc Surg. 2015;63:459-66.

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