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

Statistical Analysis Plan

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 [1] and 11.9±4.3mmHg for the control prosthesis, [2] with a 1-sided type I error of 2.5% and a noninferiority margin of 3mmHg. The noninferiority margin was determined by the values of 15mmHg for AVMPG of clinically significant aortic stenosis [3] and 12mmHg for AVMPG of the control prosthesis. Fifty-six patents in each group were needed to complete the study cohort. Allowing for a 20% dropout rate during the 1-year follow-up, we determined that the recruitment of 70 patients in each group was 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): $\boldsymbol{\mu_1 - \mu_2 \geq \delta}$

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

(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

※ 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)

The primary endpoint of the PROVE-PERI trial is AVMPG on 1-year echocardiographic follow-up. The secondary endpoints are the EOA on 1-year echocardiographic follow-up and 1-year clinical outcomes including all-cause mortality, cardiac death and MAEs.

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, [4-6] 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 [7] 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 was necessary.

Statistical analyses will be performed using SPSS software (version 25.0; IBM, Armonk, NY) and SAS software (version 9.3; SAS Institute, Cary, NC). Data will be expressed as the mean ± standard deviation, median with IQRs or proportions. Comparisons between the 2 groups will be made using the chi-square test and Fisher's exact test for categorical variables and Student's t-test or the Mann–Whitney test for continuous variables, as appropriate. The null hypothesis is that the Avalus™ is 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 is presented with 97.5% one-sided confidence interval for mean difference between groups. The non-inferiority test will be performed using a t-test which compares 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 will be counted at postoperative 1 year, and comparisons between the 2 groups will be made using the chi-square test and Fisher's exact test. A P value of < .050 will be considered statistically significant. All outcomes will be compared with an intention-to-treat base. Per-protocol and as-treated analyses will be added for hemodynamic outcomes.

References

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