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Study design of the prospective non-randomized single-arm multicenter evaluation of the durability of aortic bioprosthetic valves with RESILIA tissue in subjects under 65 years old (RESILIENCE trial)

Pibarot P, Borger MA, Clavel MA, Griffith B, Bavaria JE, Svensson LG and Thourani VH.

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Key points

- The RESILIENCE trial is the first prospective study to use both clinical and imaging SVD definitions to assess long-term bioprosthetic valve durability.
- The multicentre trial will assess a primary endpoint of time from AVR to RESILIA tissue valve failure due to SVD.
- The secondary outcomes are the volume of valve leaflet calcification (measured by CT) and the occurrence of Stage 2 or 3 haemodynamic SVD (measured by TTE).

Background information

- SVD is the main cause of bioprosthetic valve failure.
- Patient- and prosthesis-related factors contributing to SVD include severe PPM, younger age, hypertension and valve design flaws.
- Historically, SVD has been defined according to the need for valve reintervention.
  - This underestimates its incidence because it only captures the most severe cases of SVD associated with heart failure symptoms, and many elderly patients with the condition do not undergo reoperation.
- Recently proposed SVD definitions have focused on haemodynamic and/or morphological valve deterioration, as analysed by TTE or CT.
  - While an absolute mean gradient of at least 20 mmHg (SVD Stage 2) or 40 mmHg (SVD Stage 3) during TTE follow-up has been proposed, this incorrectly classifies patients with PPM as having SVD.
  - The RESILIENCE trial requires both morphological and haemodynamic valve deterioration to confirm SVD (see Methods).
- RESILIA tissue is treated to minimise free aldehydes and protect and preserve the tissue.
- In juvenile sheep, bioprosthetic valves with RESILIA tissue had significantly reduced leaflet calcification and improved haemodynamic performance compared with the Carpentier-Edwards PERIMOUNT mitral valve.

Aim

- To investigate the time to failure (due to SVD) and predictors of durability in valves with RESILIA tissue.

Type of study

- A multicentre, prospective, non-randomised, single-arm, observational trial (RESILIENCE trial: NCT03680040).

Endpoints

- Primary:
  - Time from AVR to valve failure due to SVD (defined as the subject requiring valve reintervention or study valve-related death).

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- Secondary:
  - Volume of valve leaflet calcification
  - SVD Stage 2 or 3.

Methods

Patient

- The study will enrol up to 250 adults aged under 65 years, who have previously undergone SAVR with a RESILIA tissue valve, at up to 15 centres in Europe and the US.
- Exclusion criteria include: pregnancy or desire to become pregnant; previous bioprosthetic valve reintervention; endocarditis; life expectancy less than 2 years; renal failure requiring dialysis; altered mineral metabolism (hyperparathyroidism, parathyroid tumours); or organ transplant recipient or candidate.
- Twenty-eight patients were enrolled between 21 November 2018 and 10 May 2019.
- An enrolment period of 3 years is anticipated.

Follow-up and monitoring

- The first follow-up visit will take place at 5 years post valve implantation.
  - Retrospective data from the time of implant will be collected, including medical history, STS score, demographic, valve implant and comorbidity information
  - The TTE completed 3–6 months post valve implantation will be used as the post-implant baseline measurement.
- Subsequent follow-up visits will take place at 7, 9 and 11 years post valve implantation.
- Valve failure due to SVD is defined as the patient requiring valve reintervention, or confirmed study valve-related death.
- For the secondary outcomes, Stage 2 and 3 SVD will be defined by:
  - Onset or exacerbation of transvalvular aortic regurgitation (Stage 2: ≥1 grade with final moderate regurgitation; Stage 3: ≥2 grades with final severe regurgitation), and/or
  - An increase in transprosthetic gradient (Stage 2: ≥10 mmHg; Stage 3: ≥20 mmHg) with a simultaneous decrease in EOA (Stage 2: >0.3 cm^2; Stage 3: >0.6 cm^2).

Echocardiographic and computed tomography measurements

- Two-dimensional echocardiography will be used to examine bioprosthetic valve leaflet morphology and mobility.
- Data from continuous-wave Doppler interrogation will be used to calculate EOA, and mean and peak transprosthetic gradients.
- Calcification of the valve leaflet will be measured via non-contrast CT.

Statistical analysis

- The enrolled population will include all patients who met the enrolment criteria and gave informed consent.
  - Summaries of procedural and baseline data will be based on the enrolled population.
- The analysis population will include all enrolled patients who have at least one follow-up assessment.
  - Primary and secondary observations will be assessed in the analysis population.
- The Kaplan–Meier method will be used to estimate survival probabilities and standard errors in the primary and secondary outcomes.
- Standard error for time to AVR will be reported in accordance with the Greenwood algorithm.
- Landmark Cox proportional hazard analyses will be used to assess valve leaflet calcification and SVD stage at 5, 7 and 9 years.

Limitations

- A comparative arm with non-RESILIA tissue is lacking.
- TTE may not be sensitive enough to assess leaflet morphology changes.

Conclusion

The RESILIENCE trial will be the first to assess the association between long-term durability of bioprosthetic valves and clinical and imaging SVD definitions. This will provide a thorough description of SVD stages and establish the long-term durability (11 years) of RESILIA tissue valves.

This document is a summary of the Pibarot P et al. *paper and covers key information including aim, type of study, methods, limitations and conclusions.*

The full publication is available at:
http://bit.ly/pibarot

Abbreviations

AVR: aortic valve replacement
CT: computed tomography
EOA: effective orifice area
PPM: patient–prosthesis mismatch
SAVR: surgical aortic valve replacement
STS: Society of Thoracic Surgeons
SVD: structural valve degeneration
TTE: transthoracic echocardiography

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