# In-Depth Investigation of the Interplay Between Native and Structural Mitral and Aortic Valve Degeneration

***Principal Investigator***: Roberto Lorusso
***Affiliation***: Maastricht University Medical Center
***Email***: roberto.lorussobs@gmail.com

***Background***:

Bioprosthetic heart valves (BHVs) composed of glutaraldehyde-pretreated heterograft tissue are increasingly used for cardiac valve replacements and in transcatheter valve implantation. While BHVs include a reduced risk of thrombosis, they might have a limited functional life because of structural valve degeneration (SVD)[1]. SVD includes permanent intrinsic changes of the valve leading to degeneration and/or dysfunction, which in turn may result in stenosis or intra-prosthetic regurgitation [1]. The mechanistic basis of SVD has been reported to be associated with leaflet calcium deposits in the majority of cases [2] and it can be clinically associated with young age [3], renal failure [4], diabetes mellitus [5], female sex, warfarin use, and stented BHVs (versus stentless) [6]. Moreover, both calcification and oxidative modifications are associated with progressive BHV dysfunction, indicating a role of patient´s metabolism in the SVD process. Notwithstanding, it is not clear if the same biochemical mechanism leading to native valve degeneration (such as in case of calcific valve stenosis or steno-regurgitation) can cause SVD in MHVs.

## ***Study Aim and Hypothesis:***

This study aims to investigate the rate of SVD in patients with different baseline valvular diagnoses classified on the presence of calcific deterioration of the native valve.

We hypothesize that patients receiving valve replacement surgery with BHVs for a diagnosis of calcific native valve disease will be affected by a higher rate of structural valve degeneration compared to patients receiving valve replacement surgery for a diagnosis of non-calcific valve disease. This hypothesis implies that patient´s metabolism is a determinant factor in both native and prosthetic valve degeneration with similar pathological patterns.

This study hypothesis will be tested in the overall population of patients who underwent cardiac valve replacement with a bioprosthetic valve and in two sub-populations, giving origin to two different sub-studies:

- Sub-study 1: Bioprosthetic valves in aortic position
- Sub-study 2: Bioprosthetic valves in mitral position

The following details of the study methodology will be applied in both studies.

## ***Primary End-Point***:

Primary end-point is the presence of structural valve deterioration defined as permanent intrinsic changes of the valve (i.e. leaflet tear, calcification, pannus deposition, flail, or fibrotic leaflet) leading to degeneration and/or dysfunction, which in turn may result in stenosis or intra-prosthetic regurgitation. Structural valve deterioration can be detected using imaging studies or at the time of reoperation or autopsy.

Structural valve deterioration will be classified as follows:

- Moderate haemodynamic SVD (any of the following)
    - Mean transprosthetic gradient >_20mmHg and <40mmHg
    - Mean transprosthetic gradient >_10 and <20mmHg change from baseline
    - Moderate intra-prosthetic aortic regurgitation, new or worsening (>1þ/4þ) from baseline
- Severe haemodynamic SVD (any of the following)
    - Mean transprosthetic gradient >_40mmHg
    - Mean transprosthetic gradient >_20mmHg change from baseline
    - Severe intra-prosthetic aortic regurgitation, new or worsening (>2þ/4þ) from baseline
- Morphological SVD (any of the following)
    - Leaflet integrity abnormality (i.e. torn or flail causing intra-frame
    - regurgitation)
    - Leaflet structure abnormality (i.e. pathological thickening and/or
    - calcification causing valvular stenosis or central regurgitation)
    - Leaflet function abnormality (i.e. impaired mobility resulting in
    - stenosis and/or central regurgitation)
    - Strut/frame abnormality (i.e. fracture)
    - Haemodynamic and morphological SVD

## ***Secondary End-Point***:

Secondary end points are the following:

- Overall mortality, Valve-related mortality

- Early and late adverse events: Thromboembolism, Stroke, Transient Ischemic Attack, Valve thrombosis, Hemolysis, Paravalvular leak, Endocarditis, Prosthesis explant, Mortality Valve-related
- Echocardiographic values: Valvular peak gradient, Valvular mean gradient, Valvular effective orifice area, Valvular effective orifice are index, Left ventricular mass index, Ejection fraction EF (%)

## *Expected Recruiting Time:*

Patients who underwent aortic or mitral valve replacement with surgical implantation of a bioprosthetic valve between 2000 and 2016 will be included in the study. The time frame has been chosen to guarantee a complete follow-up of at least 5 years for all participants.

To reduce the time needed for data collection, previously collected data will be used to partially fulfil the new dataset. These data will be retrieved, if possible, from a previous study published by the same research group (Lorusso R, Gelsomino S, Luca F, De Cicco G, Bille G, Carella R, et al. Type 2 diabetes mellitus is associated with faster degeneration of bioprosthetic valve: results from a propensity score-matched Italian multicenter study. Circulation. 2012;125:604-14.) [5].

It is expected to complete the data collection within December 2022.

## *Statistical Plan:*

Data will be collected from patient charts for preoperative, operative, and hospital admittance details, or in the case of patients hospitalized for any cause after surgery, through direct or telephone interview with survivors, with relatives, general physicians, or hospital doctors. Patients will be followed up according to each individual institutional protocol. All collected data will be sent to a core laboratory for statistical analysis.

Main analysis of the clinical outcomes will include all patients who will enter the study. Results will be considered statistically significant at the 5% level. All the continuous variables will be evaluated in order to test the distribution. Normally distributed variables will be analysed with the T-test method for independent samples. Non-normally distributed variables will be analysed with non-parametric tests. Categorical variables will be compared using Chi-square. Fisher's exact tests with a statistical significance level at 5% will be applied if at least one of the expected counts is less than

5. Kaplan–Meier survival analysis will be used to evaluate time related outcomes and produce plots, which will be compared by the log-rank test. A multistate analysis and competing outcomes analysis (death vs. re-operation for SVD vs. survival free from re-operations) will be performed. Factors influencing survival will be explored with a Cox regression.

A propensity score (PS) matched analysis will be considered based on the results of the previous analysis to match patients with a diagnosis of calcific native valve disease and those a diagnosis of non-calcific valve disease. The PS will be calculated via non-parsimonious multivariable logistic regression model. Patients will be matched 1:1 using a greedy matching algorithm (nearest match without replacement) based on the PS of each patient with a caliper width of 10% of the standard deviation of the logit of the PS.

## *Limitations:*

This study retains the obvious limitations related to the multicenter and retrospective format of data collection. In particular, the clinical evaluation and procedures are performed at different centers by different surgeons. However, the main limitation of the present study is its retrospective nature.

## *Strenght Points:*

This will be the first and largest study addressing the above-mentioned knowledge gap, opening the chances of multiple future studies to further investigate the topic from clinical and pre-clinical point of view.

Moreover, in order to minimize the bias related to the retrospective nature of the study, we will use the PS analysis, a technique that has been used in other recent clinical studies and validated by other previous large cohort studies with cardiovascular end points. Moreover, a multistate analysis and competing outcomes analysis will provide a robust statistical approach to the outcomes analysis.

## *Funding and Costs:*

None

## *External funding support (public or private):*

None

## *Sample size (if prospective):*

Based on a previous study published by the same research group [5] which included 6184 patients with data refer to bioprosthetic implantations performed from November 1988 to December 2009, we expect to recruit at least 5000 patients.

## *Minimal number of enrolled patients per centre to participate:*

N/A

## *References:*


1. Capodanno D, Petronio AS, Prendergast B, Eltchaninoff H, Vahanian A, Modine T, et al. Standardized definitions of structural deterioration and valve failure in assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves: a consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) endorsed by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2017;38:3382-90.
2. Schoen FJ, Kujovich JL, Webb CL, Levy RJ. Chemically determined mineral content of explanted porcine aortic valve bioprostheses: correlation with radiographic assessment of calcification and clinical data. Circulation. 1987;76:1061-6.
3. Saleeb SF, Newburger JW, Geva T, Baird CW, Gauvreau K, Padera RF, et al. Accelerated degeneration of a bovine pericardial bioprosthetic aortic valve in children and young adults. Circulation. 2014;130:51-60.
4. Washiyama N, Shiiya N, Yamashita K, Terada H, Ohkura K, Takahashi K. Etiology of renal failure influences the outcome of heart valve replacement in chronic dialysis patients. J Artif Organs. 2011;14:39-42.
5. Lorusso R, Gelsomino S, Luca F, De Cicco G, Bille G, Carella R, et al. Type 2 diabetes mellitus is associated with faster degeneration of bioprosthetic valve: results from a propensity score-matched Italian multicenter study. Circulation. 2012;125:604-14.
6. Salaun E, Mahjoub H, Girerd N, Dagenais F, Voisine P, Mohammadi S, et al. Rate, Timing, Correlates, and Outcomes of Hemodynamic Valve Deterioration After Bioprosthetic Surgical Aortic Valve Replacement. Circulation. 2018;138:971-85.