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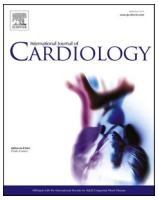

Généreux staging classification in predicting left ventricular reverse remodeling after intervention for severe aortic valve regurgitation

Annalisa Pasquini, MD, PhD [a,*], Andrea Pica, MD [a], Monica Filice, MD [a], Giuseppe De Carli, MD [b], Francesco Burzotta, MD, PhD [a], Carlo Trani, MD, PhD [a], Giovanni Alfonso Chiariello, MD, PhD [a], Daniela Pedicino, MD, PhD [a], Piergiorgio Bruno, MD, PhD [a], Natalia Pavone, MD, PhD [a], Maria Grandinetti, MD [a], Maria Lisa Nesta, MD, PhD [a], Francesca Graziani, MD, PhD [a], Antonella Lombardo, MD [a], Matteo Cameli, MD, PhD [b], Massimo Massetti, MD, PhD [a]

[a] Department of Cardiovascular Medicine, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Largo Agostino Gemelli 8 00168, Rome, Italy
[b] Department of Medical Biotechnologies, Division of Cardiology, University of Siena, Siena, Italy

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ABSTRACT

Aims: Severe native aortic regurgitation (AR) is characterized by a progressive left ventricular (LV) dysfunction and remodeling which, up to a certain degree, can be reversed by surgical aortic valve replacement (SAVR) or transcatheter aortic valve implantation (TAVI).
We aimed to investigate how Généreux staging classification could predict left ventricular reverse remodeling (LVRR).
Methods: This monocentric retrospective study analyzes data from 103 patients (29 % female) treated for pure chronic AR in whom echocardiographic examinations had been made before the procedure, in the early post-operative period (48-72 h), and at mid-term follow-up (6 months). The primary endpoint was the occurrence of LVRR defined as a significant reduction in left ventricle end systolic diameter and volume.
Results: Compared to patients in Généreux stage 1, we found that patients in Généreux stages ≥2 had a 77 % reduction in the likelihood of LVRR occurrence at early evaluation (OR 0.23; [CI 0.08–0.58; $p = 0.002$]) and a 74 % reduction in the likelihood of LVRR occurrence at mid-term evaluation (OR 0.26; [CI 0.10–0.60; $p = 0.002$]). A different course of LVRR was observed in the TAVI group, in which it was slower than SAVR group.
Conclusions: Généreux staging classification was found to be an independent prognostic factor for LVRR occurrence. Patients should be treated while being in Genereaux stage 1 since this results in a higher probability of LVRR occurrence.

1. Introduction

Aortic regurgitation (AR) represents 13 % of left-sided valvular heart diseases [1] and may cause debilitating symptoms, heart failure, and premature mortality.

In most patients, the disease course, chronic and slowly progressive, results in progressive volume and pressure overload to which the left ventricle (LV) adapts by dilation and eccentric hypertrophy. In the long term, this adaptation is no longer able to cope, and evolves in the decompensated phase which is characterized by systolic LV dysfunction [2] and/or symptoms such as exertional dyspnea. Surgery is recommended in patients with severe AR and symptoms or with LV dysfunction [3].

Until recently, the gold standard treatment was surgical aortic valve

Abbreviations: AR, Aortic regurgitation;; IQR, Interquartile range;; LV, Left ventricle;; LVRR, Left ventricular reverse remodeling;; NYHA, New York heart association;; ROC, Receiver operating characteristic;; SAVR, Surgical aortic valve replacement;; TAVI, Transcatheter aortic valve implantation..

* Corresponding author at: Department of Cardiovascular and Thoracic Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy.
E-mail address: annalisa.pasquini@policlinicogemelli.it (A. Pasquini).

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replacement (SAVR); however, traditional surgical approaches may be contraindicated in patients with high or prohibitive surgical risk. More recently, transcatheter aortic valve implantation (TAVI) has been shown to be a viable alternative in such cases, with technological advances in next-generation devices having made TAVI safer and more effective [1]. In addition, the Valve-in-Valve technique using TAVI is a valuable alternative for the treatment of degenerated aortic bioprosthesis [4].

The effects of SAVR and TAVI on LV reverse remodeling (LVRR) have been extensively studied in patients with aortic stenosis (AS) [5,6]. In contrast, the post-operative LVRR process in patients with AR is less extensively studied [7]. Thus, the timing of the LVRR after SAVR is still unclear, and very little is known in the setting of TAVI.

It was demonstrated that LVRR was an independent prognostic predictor of survival and heart failure events [8,9]. Its occurrence could be predicted on the basis of echocardiographic parameters such as LV end systolic and diastolic diameters and volumes, LV ejection fraction and LV global longitudinal strain [10–15].

Généreux et al. identified a prognostic staging classification based on extra-aortic cardiac damage in asymptomatic patients with severe AS [16], with the potential to apply this classification to patients with other valvulopathies. We used this staging classification for patients with pure AR because it offers a finely tailored characterization of the extent of extra-valvular cardiac damage associated with valvulopathy. It includes all the known echocardiographic predictors of LVRR and has potential important prognostic implications for clinical outcomes (especially in elderly patients at high/prohibitive surgical risk and thus eligible for transcatheter aortic interventions).

The primary aim of the study was to evaluate the impact of Généreux staging classification on LVRR after SAVR and TAVI in patients treated for pure chronic AR. The secondary aim was to evaluate differences in the timing course of LVRR between SAVR and TAVI groups.

2. Methods

2.1. Study Population

In this retrospective monocentric cohort study patients with severe pure chronic AR treated by SAVR or transfemoral TAVI procedures at our institution (Fondazione Policlinico A. Gemelli IRCCS, Rome, Italy) were retrieved from interventional and surgical databases. Inclusion criteria were: patients with isolated pure chronic severe AR either for native valve disease or bioprosthetic degeneration with severe regurgitation, who had been treated by SAVR or TAVI according to ESC/EACTS guidelines [3]. The decision on the type of intervention in each case had been made by our Heart Team; other inclusion criteria were: the availability of complete echocardiographic examinations before the treatment, early after the procedure (24–72 h, early follow-up, T1) and at mid-term evaluation after hospital discharge (6 months, mid-term follow-up, T2); age > 18 years old. Exclusion criteria were: coexisting more than moderate aortic stenosis, infective endocarditis, coexisting aortopathies requiring ascending aortic surgery, surgical re-do, coexisting coronary artery disease (CAD) requiring intervention during the procedures.

The following data were collected:

- Clinical Data: Age, sex, weight, height, body surface area (BSA), cardiovascular risk factors and comorbidities, NYHA functional class, surgical risk scores, intraoperative complications.
- Laboratory Tests: Blood cells count, serum creatinine, N-terminal pro b-type natriuretic peptide (NT-proBNP).
- Echocardiographic Assessment: data from all transthoracic echocardiograms performed by experienced physicians from our heart valve clinic 24–48 h before the scheduled procedure, early after the procedure (24–72 h) and at mid-term follow-up (6 months after hospital discharge) were collected. The echocardiographic examinations were performed according to the European Association of Cardiovascular Imaging guidelines [17].

Each patient was assigned to Généreux classification stages according to the following criteria [16]: stage 0 – no cardiac damage; stage 1 – LV damage defined by the presence of LV hypertrophy (LV mass index >95 g/mq for women, > 115 g/mq for men), severe LV diastolic dysfunction (E/e' ratio > 14) or LV systolic dysfunction (LVEF <50 %); stage 2 – left atrial or mitral valve damage defined by the presence of enlarged left atrium (LAVi >34 ml/mq), atrial fibrillation or more than moderate mitral regurgitation; stage 3 – pulmonary artery vasculature or tricuspid valve damage defined as systolic pulmonary hypertension (sPAP ≥60 mmHg) or more than moderate tricuspid regurgitation; stage 4 – right ventricular (RV) damage defined by the presence of moderate or severe RV dysfunction (TAPSE <14 or s' < 7.2).

2.2. Endpoint

The primary endpoint was LVRR occurrence, defined as a significant reduction (>15 %) in LV end systolic diameter and volume [18], at early (24–72 h) and mid-term (6 months) evaluations.

2.3. Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median [IQR], based on distribution. Categorical variables were shown as counts and percentages. Normality was tested with the Shapiro–Wilk test; $p < 0.05$ was considered significant. Categorical comparisons used Chi-squared or Fisher's exact test. Continuous variables were analyzed with the *t*-test or Mann–Whitney *U* test, as appropriate. Changes in echocardiographic measures over time were assessed using the Wilcoxon signed-rank test. Simple logistic regression evaluated the predictive value of the Généreux classification for LVRR. ROC curves and AUC assessed model discrimination. Each clinical and echocardiographic variable was tested for association with LVRR. The added value of the Généreux classification was evaluated by comparing models with and without it, using AUC, Likelihood Ratio Test (LRT), Net Reclassification Improvement (NRI), and Integrated Discrimination Improvement (IDI). Multivariable logistic models included the Généreux classification and other variables selected via stepwise forward selection, avoiding multicollinearity. To reduce selection bias in the comparison between TAVI and SAVR, a 1:1 propensity score matching (PSM) was performed by using the nearest neighbor method with a caliper of 0.1. This analysis was performed by including the variables age, comorbidities, STS mortality score, and EuroSCORE II, which were selected based on their association with treatment allocation. Covariate balance between groups was assessed by using standardized mean differences (SMD), values <0.1 being considered indicative of good balance and values <0.2 being considered acceptable [19]. Analyses were performed in R (v4.4.1). The study followed the Declaration of Helsinki and was approved by the ethics committee (CET Lazio Area 3); all patients gave written informed consent.

3. Results

3.1. Study population

One hundred-three patients (29.1 % female) with pure chronic severe AR who had undergone SAVR (79 patients, 77 %) or TAVI (24 patients, 23 %) between January 2017 and February 2025 were included in this study. No deaths occurred during hospitalization and in the first 6 months.

The type of valve implanted in the SAVR group, was a mechanical prothesis in two patients and a bioprothesis in all the other subjects; among the TAVI group, one patient received a balloon-expandable prothesis while a self-expandable protheses was used in the other

cases, as well as in the two 2 patients who underwent a Valve-in-Valve procedure.

Table 1, Table S1 and Table S2 show the baseline clinical and echocardiographic characteristics of our patient population and the differences between Généreux stages.

33 patients (32 %) were in Généreux stage 1, 47 patients (46 %) in stage 2, 18 patients (17 %) in stage 3 and 5 patients (5 %) in stage 4. No one was in Généreux stage 0.

Table 1
Baseline characteristics and differences between patients with and without left ventricular reverse remodeling (LVRR) at mid-term evaluation.

	Overall 103	No LVRR 66 (64 %)	LVRR 37 (36 %)	*p value*
Age, y	66 [54, 73]	68 [54, 75]	61 [54, 70]	*0.252*
Female sex, n (%)	30 (29.1 %)	13 (19.7 %)	17 (45.9 %)	*0.010*
Diabetes, n (%)	19 (18.4 %)	16 (24.2 %)	3 (8.1 %)	*0.078*
Arterial hypertension, n (%)	73 (70.9 %)	48 (72.7 %)	25 (67.6 %)	*0.744*
Atrial fibrillation (AF), n (%)	24 (23.3 %)	15 (22.7 %)	9 (24.3 %)	*1.000*
NYHA pre-intervention, n (%)				*0.821*
I	17 (16.5 %)	10 (15.2 %)	7 (18.9 %)	
II	45 (43.7 %)	28 (42.4 %)	17 (45.9 %)	
III	29 (28.2 %)	19 (28.8 %)	10 (27.0 %)	
IV	12 (11.7 %)	9 (13.6 %)	2 (8.1 %)	
Coronary artery disease (CAD), n (%)	19 (18.4 %)	17 (25.8 %)	2 (5.4 %)	*0.022*
NTproBNP, pg/ml	828.00 [384.00, 4446.00]	1317.50 [469.00, 6540.00]	540.00 [259.00, 1220.00]	*0.009*
Left ventricle end diastolic diameter (LVEDD), mm	58.00 [55.00, 62.00]	57.00 [54.25, 62.00]	59.00 [56.00, 63.00]	*0.063*
Left ventricle end systolic diameter (LVESD), mm	39.35 ± 9.19	38.33 ± 9.69	41.26 ± 8.03	*0.135*
Left ventricle end diastolic volume (LVEDV), ml	155.00 [126.00, 207.00]	154.50 [116.25, 199.75]	158.00 [140.00, 215.00]	*0.228*
Left ventricle end systolic volume (LVESV), ml	72.00 [55.50, 95.50]	71.75 [52.25, 95.75]	75.00 [60.00, 93.00]	*0.409*
Left ventricle ejection fraction (LVEF), %	55.12 [49.07, 61.92]	54.63 [48.22, 62.43]	55.88 [49.65, 60.87]	*0.799*
Left atrial volume indexed (LAVi), ml/m2	39.00 [32.63, 49.49]	40.14 [35.60, 46.66]	33.42 [31.86, 52.87]	*0.229*
Systolic pulmonary artery pressure (sPAP), mmHg	30.00 [25.00, 37.50]	30.00 [25.00, 38.75]	30.00 [25.00, 35.00]	*0.911*
Tricuspid annular plane systolic excursion (TAPSE), mm	23.00 [20.00, 25.12]	23.00 [19.25, 25.54]	23.00 [20.00, 25.00]	*0.712*
Généreux staging pre, n (%)				*0.015*
0	0 (0 %)	0 (0 %)	0 (0 %)	
1	33 (32 %)	14 (21.2 %)	19 (51.4 %)	
2	47 (46 %)	36 (54.5 %)	11 (29.7 %)	
3	18 (17 %)	13 (19.7 %)	5 (13.5 %)	
4	5 (5 %)	3 (4.5 %)	2 (5.4 %)	
Cardiac surgery, n (%)	79 (77 %)	51 (77.3 %)	28 (75.7 %)	*1.000*
NYHA at mid-term follow-up, n (%)				*0.001*
I	40 (38.8 %)	11 (16.7 %)	29 (78.4 %)	
II	40 (38.8 %)	32 (48.5 %)	8 (21.6 %)	
III	23 (22.3 %)	23 (34.8 %)	0 (0 %)	
IV	0 (0 %)	0 (0 %)	0 (0 %)	

Table 1 shows the differences between patients with LVRR and patients without LVRR, at mid-term evaluation. Continuous variables are expressed by mean ± standard deviation or median [interquartile range], qualitative and ordinal variables by counts and percentages.
LVRR = Left ventricular reverse remodeling.

Patients in advanced stages were older, with higher surgical risk scores and worst NYHA class, and showed lower levels of hemoglobin and higher levels of natriuretic peptides.

3.2. Left ventricular reverse remodeling occurrence after SAVR or TAVI

LVRR was observed in 37 patients (35.9 %), and it appeared to be more prevalent among patients in the lowest stage, since it occurred in 19 of 33 patients (57.6 %) in Généreux stage 1, in 11 of 47 patients (23.4 %) in stage 2, in 5 of 18 patients (27.8 %) in stage 3 and in 2 of 5 patients (40 %) in stage 4.

Comparing the differences between patients with and without LVRR, we found a higher prevalence of men with previous CAD in the group without LVRR occurrence (Table 1).

Interestingly we found that patients in whom LVRR occurred showed a lower NYHA functional class, as evaluated post-operatively, than patients in whom LVRR did not occur.

In 13 patients, LVRR occurred later and was detected only at the mid-term evaluation. They showed higher levels of creatinine and NT-pro-BNP, lower levels of hemoglobin, and a greater hemodynamic impact as indicated by higher levels of sPAP (Table S3) and there was a higher prevalence of TAVI interventions. This trend was confirmed by analyzing the differences in variables between the TAVI and SAVR groups at baseline and after the interventions: although TAVI patients had more advanced cardiac damage at baseline than SAVR patients (Table S4), LVRR occurred in both groups, but with a slower time course in TAVI patients (Table S5). TAVI patients were older and with more comorbidities than SAVR patients (Table S4).

3.3. Prognostic value of Généreux staging classification

When assessing the prognostic value of the Généreux staging classification for LVRR, as LVRR rates across stages 2 to 4 were relatively close (suggesting a not strictly linear trend and a potential threshold effect), a grouped modeling approach (Stage 1 vs Stage ≥2) was considered for the simple logistic regression models. Compared to patients in Stage 1, among patients in Stages ≥2 there was a 77 % reduction in the likelihood of LVRR occurrence at early evaluation (OR 0.23; [CI 0.08–0.58; $p = 0.002$]) and a 74 % reduction in the likelihood of LVRR occurrence at mid-term evaluation (OR 0.26; [CI 0.10–0.60; $p = 0.002$]). Disaggregated logistic regression analyses were also performed and reported in Supplementary data (Table S10 and Table S11).

The Généreux staging classification showed better and additional prognostic value than echocardiographic and clinical variables in assessing LVRR: by comparing the simple logistic regression models fitted for each variable to assess their association with LVRR, the incremental predictive value of the Généreux classification over these models was demonstrated by the improvement in NRI and IDI, with significant LRTs (Tables S6 and S7).

This staging classification was associated with a statistically significant reduction in the likelihood of LVRR after TAVI and SAVR, independently of age, sex, kind of intervention (surgical or percutaneous), comorbidities (CAD, arterial hypertension, diabetes, dyslipidemia, chronic obstructive pulmonary disease) and NYHA class, both at early and mid-term follow-up, as demonstrated by multiple logistic regression models (Tables S8 and S9). ROC curves and AUC are reported in Fig. 1. Adding Généreux staging classification to the other covariates improved the predictive value of the models, as demonstrated by NRI, IDI and LRT (Table S6 and S7).

3.4. SAVR vs TAVI complications

Intraoperative complications in the SAVR group were two cardiac tamponades, while in the TAVI group the following complications were observed: device migration/embolization in three patients and a second valve (in-valve) in one patient; minor vascular complications in two

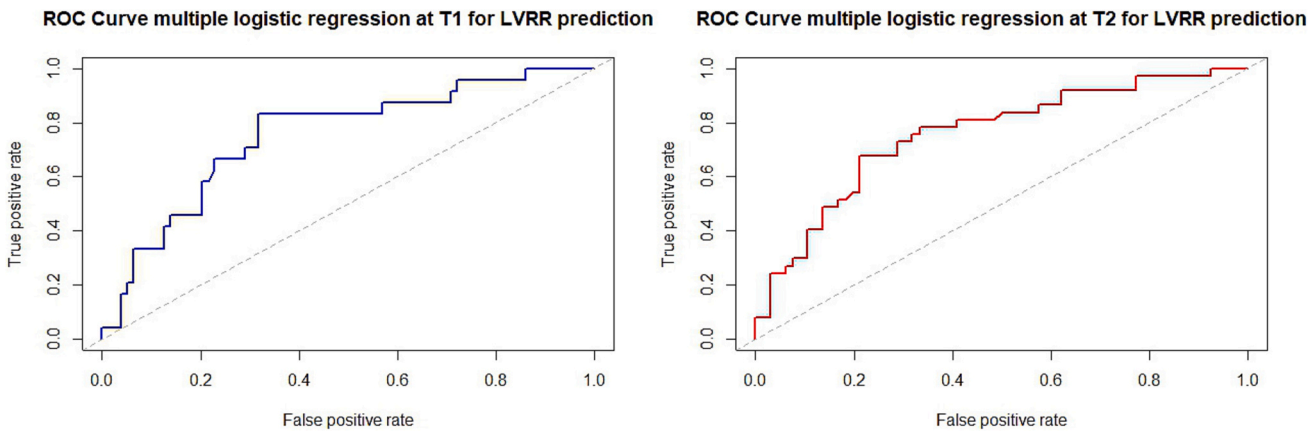

Fig. 1. ROC curve of multiple logistic regression models.
ROC curves for multiple logistic regression models. At T1 (early follow-up): AUC 0.75 [CI 0.64–0.87]. At T2 (mid-term follow-up): AUC 0.76 [CI 0.66–0.86].

patients; permanent pacemaker implantation required in three patients (two patients received a cardiac resynchronization therapy with a 99 % pacing stimulation percentage while one patient received a bicameral pace-maker with a 99 % pacing stimulation percentage).

Paravalvular regurgitation was mild in three patients (2 TAVI patients and 1 SAVR patient) and mild to moderate in one TAVI patient.

3.5. Bias control in SAVR vs TAVI comparison

To disentangle treatment effect (SAVR vs TAVI) from patient selection bias, we made a Propensity Score Matching (PSM) analysis (including age, comorbidities, STS score mortality and EuroScore II). This analysis showed a good balancing of the covariates (with a SMD $<$ 0.1), except for age for which the SMD value was 0.144 and thus still below the 0.2 threshold recommended for judging the balance as acceptable [19]. To deeply reinforce the analysis, a post-matching logistic regression analysis adjusted for age and kind of intervention to predict LVRR was performed. In this model, both kind of intervention ($p = 0.757$) and age ($p = 0.169$) were not predictors of LVRR, thus confirming the robustness of the results.

4. Discussion

Our study demonstrated that Généreux staging classification could be used as an independent predictor of LVRR in patients undergoing SAVR and TAVI for pure AR: patients classified as stage more than 1 had a lower likelihood of experiencing LVRR.

Originally developed for asymptomatic patients with severe AS, the Généreux staging classification was designed to assess the prognostic impact of extra-valvular cardiac damage.

Our study suggests that this staging classification may also be useful in the context of chronic pure AR, potentially carrying prognostic significance in this population. Compared with other predictors of LVRR, the Généreux staging classification improved the accuracy in predicting this process, likely due to its detailed characterization of extra-valvular cardiac damage. Stage 1 patients could thus represent an optimal window of intervention. Because of the inclusion criteria (considering only chronic severe AR patients with indication to intervention) we had no patient in stage 0 (without cardiac damage).

The volume overload related to chronic severe AR is known to alter ventricular geometry and to raise LV volume and mass, this causing diastolic and systolic dysfunction. Both preoperative low LVEF and increased LV dimensions are associated with high mortality in AR patients undergoing SAVR [20–22], while the reduction of LV dimensions and mass is associated with better prognosis after surgery [23]. Recently, it was reported that LV end systolic volume index was an independent predictor of overall mortality [24].

LVRR was an independent prognostic predictor of survival and heart failure events [8,9]; as higher stages have been shown to be less likely to have LVRR, patients may be treated prior to the progression of extra-valvular heart damage in order to achieve a higher incidence of LVRR and thus a better prognosis after intervention. Despite not demonstrating its value as a predictor of survival and heart failure events, we found that this process could have an impact on NYHA functional class after interventions and thus on relevant clinical outcomes.

There isn't a univocal echocardiographic definition of LVRR, and several studies defined it as a significant increase in LVEF [25]. We preferred not to consider LVEF as a definition of LVRR, because of the transient and reversible myocardial stunning due to cardioplegia and long aortic clamp time, with a potential transitory LV and RV impairment [26]. Moreover, aortic regurgitation itself could lead to overestimation of LVEF before intervention, not reflecting myocardial contractility [27].

The occurrence of LVRR even after TAVI (even though with a slow time course) is an additive prognostic benefit that could lead to consider this intervention also for patients at high or prohibitive surgical risk. In the percutaneous population we observed a more advanced degree of valvular heart disease, and for this reason, the hemodynamic compensation after the procedure was slower than the surgical group. This doesn't seem to be related to procedural factors, kind of valve implanted or periprocedural hemodynamic status: TAVI patients were older with more comorbidities than SAVR patients; moreover, they had a prolonged history of severe aortic regurgitation with a more advanced valvular heart disease. They had been excluded from surgical correction due to high or prohibitive operative risk. Only recently has TAVI become an alternative treatment to medical therapy for these patients.

It must also to be considered that the occurrence of LVRR was not related to the kind of intervention itself (SAVR vs TAVI), being the treatment effect disentangled from potential patient selection bias.

5. Conclusions

The main novelty of our study is that the Généreux staging classification could be used as an independent predictor of LVRR at early and mid-term evaluation, and this is the first study applying this classification in patients with AR. Further studies are needed to confirm these results and to evaluate the prognostic impact on overall survival and hospitalization for acute decompensated heart failure. Considering that the probability of LVRR occurrence decreased for patients in higher Généreux stages, performing interventions when patients are in lower stages could be a reasonable option to improve long-term outcomes. As LVRR also occurred in patients with severe AR treated with TAVI in our

study, this treatment may be increasingly used in patients at high surgical risk, given the potential survival benefits. However, SAVR remains the gold standard for most patients with severe AR, including those at high risk, especially when the ascending aorta is involved while TAVI is a valuable option in AR patients deemed at too high risk for conventional surgery, although more challenging.

6. Limitations

The relatively small sample size, with LVRR observed in only 37 individuals limits the generalizability of our study findings. The number of patients in Stage 4 was low, limiting confidence in conclusions for this subgroup and the relatively high LVRR rate in this group may reflect sampling variability. Our results also need to be confirmed by other imaging techniques, such as cardiac magnetic resonance, and by advanced echocardiographic techniques, such as speckle-tracking analysis. Moreover, other studies are needed to determine the long-term stability of the condition.

CRediT authorship contribution statement

Annalisa Pasquini: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Andrea Pica:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Monica Filice:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Giuseppe De Carli:** Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Francesco Burzotta:** Validation, Supervision, Methodology, Investigation, Conceptualization. **Carlo Trani:** Visualization, Validation, Supervision, Methodology, Conceptualization. **Giovanni Alfonso Chiariello:** Visualization, Validation, Data curation, Conceptualization. **Daniela Pedicino:** Visualization, Validation, Supervision, Conceptualization. **Piergiorgio Bruno:** Writing – review & editing, Visualization, Validation, Supervision, Investigation, Data curation, Conceptualization. **Natalia Pavone:** Visualization, Investigation, Data curation, Conceptualization. **Maria Grandinetti:** Writing – original draft, Supervision, Methodology, Data curation, Conceptualization. **Maria Lisa Nesta:** Writing – original draft, Validation, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Francesca Graziani:** Visualization, Validation, Supervision, Formal analysis, Conceptualization. **Antonella Lombardo:** Visualization, Validation, Supervision, Conceptualization. **Matteo Cameli:** Writing – review & editing, Visualization, Supervision, Methodology, Investigation, Conceptualization. **Massimo Massetti:** Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

Nothing to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2025.133770.

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