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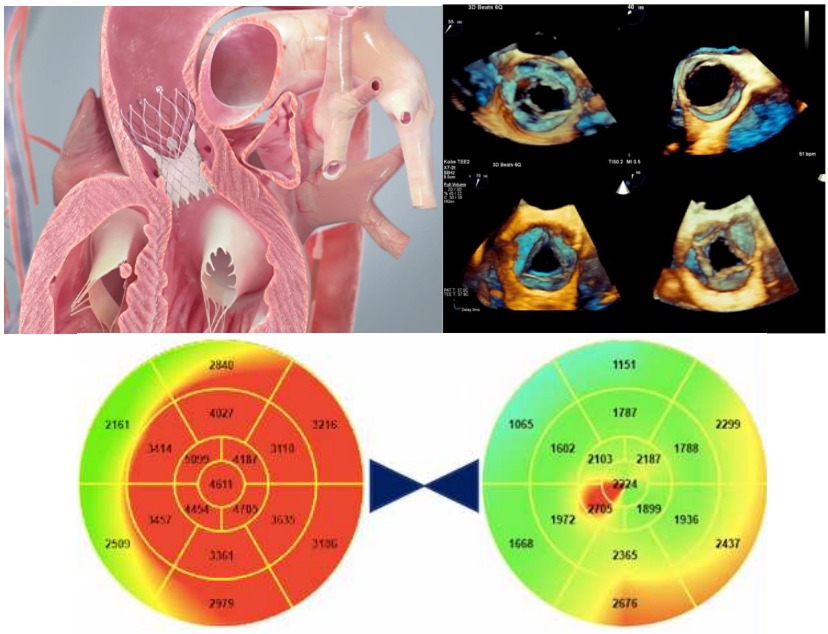

BEFORE AND AFTER TRANSCATHETER AORTIC VALVE IMPLANTATION: THE ROLE OF NEW ECHOCARDIOGRAPHIC TOOLS

PhD Thesis

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UNIVERSITÀ DEGLI STUDI DI NAPOLI "FEDERICO II"

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20/11/1990

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Contents

CHAPTER 1

General Introduction and outline of the thesis

Degenerative aortic stenosis (AS) is the most common heart valve disease among people >65 years in developed countries, with an increasing prevalence due to population ageing (1-2). AS leads to compensatory anatomical and physiological changes in the left ventricle (LV) culminating in detrimental effects including left ventricular hypertrophy (LVH), diastolic dysfunction and ultimately LV failure [3].

Transcatheter aortic valve implantation (TAVI) is an established therapy for patients with symptomatic severe aortic stenosis (AS), irrespective of operative risk (4). TAVI has been shown to improve symptoms, reduce progression of LV dysfunction and ultimately reduce mortality [5].

Transthoracic echocardiography (TTE) remains the investigation of choice for diagnosing and quantifying the severity of AS with several echocardiographic parameters being used. Historically, left ventricular ejection fraction (LVEF) has been the most commonly used measure to determine LV systolic function. More recently however deformation imaging has become an important method of determining clinical and subclinical assessment of heart chamber function. Deformation imaging

encompasses myocardial strain such as shortening, thickening and lengthening of myocardial fibres and includes global longitudinal strain (GLS) and peak atrial longitudinal strain (PALS) [6]. GLS is an important echocardiographic parameter that may be used as a predictor of cardiovascular outcomes and subclinical changes in LV function.

Deformation imaging also allows us to assess left atrial function and also can assess the different phases of left ventricular filling dynamics. In the left atrial (LA) reservoir phase, as the LA fills and stretches, there is deformation called peak left atrial longitudinal strain (PALS), which peaks in systole at the end of LA filling, before the opening of the mitral valve, and is reflective of LV systolic function.

There is an emerging data showing that LA function evaluated by PALS is more sensitive than LA volume to assess subtle LA reverse remodeling after TAVI (7).

In the recent years, myocardial work (MW) has emerged as an alternative tool for myocardial function assessment. This new parameter derives from GLS, with the advantage to incorporate information on afterload, through interpretation of strain in relation to dynamic non-invasive LV pressure. Russel et al. demonstrated that non-invasively pressure-strain loops (PSLs) could estimate LV performance deriving LV pressure curves during a cardiac cycle from non-invasively acquired

brachial artery cuff pressure (8-9). Myocardial work is approximatively calculated as the area of PSL. Experimental studies have shown a strong correlation of LV-PSL area with cardiac metabolism, assessed by fluorine 18 fluorodeoxyglucose-positron emission tomography (9). The clinical application of MW measurement has been shown in several pathological conditions, including LV dyssinchrony (10-11), ischemia (12-13), hypertrophic (14), hypertensive and dilated cardiomyopathy (15).

Among patients with moderate-to-severe AS, lower MW indices reflect a more advanced cardiac damage and are associated with increased mortality at long-term follow up (16).

Considering the increasingly wide availability of these new advanced techniques, which seem to be more sensible than traditional echocardiographic parameters, we have explored the feasibility, efficacy and prognostic role of these new diagnostic tools in the evaluation of TAVI patients, both before and after the procedure. Since the introduction of TAVI, the long-term durability of transcatheter heart valves (THV) has been debated. Most surgical aortic valves (SAV) degenerate within 10–20 years [17], whereas the performance of THVs in the very long term is currently unknown. These concerns remain

essential today because of the expansion of TAVI to low-risk and young patients with longer life expectancies [18].

A comprehensive echocardiographic examination should always include information on THV function and should immediately recognize possible prosthesis dysfunction. In this thesis we reported some review on echocardiography role in the assessment of prosthesis function, hemodynamic performance as well as cardiac function changes after TAVI with a special focus on the comparison between transcatheter and surgical aortic valves and between self-expandable and balloon-expandable valves.

We also analyzed a recently proposed AS staging classification based on LV structural and functional changes induced by AS (19) to assess the prognostic performance of this classification in a real-word cohort of patients undergoing TAVI and to investigate the impact of the procedure on the extent of extra-aortic valve cardiac damage.

Finally, we investigated the impact of coronavirus disease-2019 (COVID-19) pandemic on timing and early clinical outcomes of transcatheter aortic valve implantation.

This thesis is divided in three parts:

Part I. **Evaluation of cardiac damage and reverse remodeling in patients undergoing Transcatheter Aortic Valve Implantation.** The first part of the thesis is focused on the LV structural and functional changes induced by AS. We evaluated the impact of the extent of cardiac damage on survival among real-world patients treated with TAVI and the role of the newer, advanced echocardiographic parameters for detecting early reversal of cardiac dysfunction.

Part II. **After transcatheter aortic valve implantation: role of cardiovascular imaging to detect valve deterioration.** Since the introduction of TAVI, the long-term durability of THV has been debated. The expansion of TAVI to low-risk and young patients with longer life expectancies need for long-term assessment and durability. We provided an overview of the diagnostic tools to evaluate the hemodynamic performance of aortic prosthesis, with a special focus on the comparison between transcatheter and surgical aortic valves and between self-expandable and balloon-expandable valves. Moreover, we discussed how cardiovascular imaging can effectively detect long-term structural valve deterioration.

Part III. **TAVI in COVID-19 pandemic.** This part of the thesis is centered on the effects of COVID-19 pandemic on the management of patients with severe symptomatic aortic stenosis. We investigated the applicability and outcomes of a novel system to manage patients requiring TAVI at a tertiary level hospital during the COVID-19 pandemic.

PART I

Evaluation of cardiac damage and reverse remodeling in patients undergoing Transcatheter Aortic Valve Implantation.

Journal of
Clinical Medicine

MDPI

Article

Extent of Cardiac Damage and Mortality in Patients Undergoing Transcatheter Aortic Valve Implantation

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Abstract: (1) Aims: We sought to assess the impact of the extent of cardiac damage on survival among real-world patients with severe aortic stenosis (AS) undergoing transcatheter aortic valve implantation (TAVI). (2) Methods: A staging classification was applied to 262 patients from the EffecTAVI Registry at baseline and re-assessed within 30-days after TAVI. The primary endpoint of the study was all-cause mortality at 1-year. Secondary endpoints included cerebrovascular accident, myocardial infarction, permanent pacemaker implantation, endocarditis, and re-hospitalization for all causes. (3) Results: At baseline, 23 (8.7%) patients were in Stage 0/1 (no cardiac damage/left ventricular damage), 106 (40.4%) in Stage 2 (left atrial or mitral valve damage), 59 (22.5%) in Stage 3 (pulmonary vasculature or tricuspid valve damage) and 74 (28.3%) in Stage 4 (right ventricular damage). At 30-days after TAVI, a lower prevalence of advanced stages of cardiac damage than baseline, mainly driven by a significant improvement in left ventricular diastolic parameters and right ventricular function, was reported. At 1-year, a stepwise increase in mortality rates was observed according to staging at baseline: 4.3% in Stage 0/1, 6.6% in Stage 2, 18.6% in Stage 3 and 21.6% in Stage 4 ($p = 0.08$). No differences were found in secondary endpoints. (4) Conclusions: TAVI has an early beneficial impact on the left ventricular diastolic and right ventricular function. However, the extent of cardiac damage at baseline significantly affects the risk of mortality at 1-year after the procedure.

Keywords: transcatheter aortic valve implantation; staging; cardiac damage; mortality

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Citation: Avvedimento, M.; Franzone, A.; Leone, A.; Piccolo, R.; Castiello, D.S.; Ilardi, F.; Mariani, A.; Esposito, R.; Iapicca, C.; Angellotti, D.; et al. Extent of Cardiac Damage and Mortality in Patients Undergoing Transcatheter Aortic Valve Implantation. *J. Clin. Med.* **2021**, *10*, 4563. https://doi.org/10.3390/jcm10194563

Academic Editor: George N. Kouvelos

Received: 4 September 2021
Accepted: 29 September 2021
Published: 30 September 2021

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1. Introduction

Degenerative aortic stenosis (AS) is the most common heart valve disease among people $\geq$ 65 years in developed countries, with an increasing prevalence due to population ageing [1,2]. AS commonly leads to left ventricular (LV) pressure overload resulting in concentric hypertrophy that prevents symptom onset for a long time while yielding progressive left and right ventricular dysfunction and impaired survival [3,4]. Current guidelines recommend intervention in patients with AS according to the severity of the disease and the presence of the symptoms [5,6]. However, the benefits of valve replacement may be limited in patients with advanced functional and structural myocardial changes.

A recently proposed staging classification of AS is based on the assumption that there is a continuum in the pathophysiology of LV structural and functional changes induced by AS. Such a system showed prognostic ability among patients from the PARTNER 2 trial as well as in asymptomatic subjects with moderate to severe AS, thus challenging the current management of the disease [7,8].

The aim of our study was to assess the prognostic performance of this staging classification in a real-world cohort of patients undergoing transcatheter aortic valve implantation (TAVI) and to investigate the eventual impact of the procedure on the extent of extra-aortic valve cardiac damage.

2. Materials and Methods

2.1. Patient Population and Data Collection

All consecutive patients with severe symptomatic AS undergoing TAVI between 2014 and 2019 at our institution were enrolled in the EffecTAVI registry. Severe AS was defined according to current guidelines as a mean aortic valve gradient $\geq$ 40 mmHg and/or aortic valve area < 1.0 cm^2 (or an indexed aortic valve area < 0.6 cm^2/m^2) and/or a peak aortic jet velocity $\geq$ 4 m/s [9]. TAVI suitability was established by the local multi-disciplinary Heart Team. All patients in the registry (n = 275) received echocardiographic evaluation before TAVI. However, for the present analysis we only considered those with a complete dataset including variables needed for staging cardiac damage according to the system proposed by Gènèreux [7] et al. Clinical, procedural and follow-up data were anonymously entered in a web-based database (https://www.redcap.unina.it). The EffecTAVI registry has been approved by the local ethics committee and written informed consent was obtained for all patients for participation. All study-related procedures were carried out in accordance with the Declaration of Helsinki and this analysis was approved by the institutional review board.

2.2. Cardiac Damage Staging Classification

The following criteria for staging classification of cardiac damage were applied at baseline (within 1 month before TAVI) and after the procedure (within 30-days): Stage 0, no extra-aortic valve cardiac damage; Stage 1, LV damage as defined by the presence of LV hypertrophy (LV mass index > 95 g/m^2 for women, >115 g/m^2 for men) [10], severe LV diastolic dysfunction ($E/e' > 14$) [11] or LV systolic dysfunction (LV ejection fraction, LVEF < 50%); Stage 2, left atrial (LA) and/or mitral valve damage as defined by the presence of LA enlargement (LA volume > 34 mL/m^2) and/or moderate to severe mitral regurgitation and/or atrial fibrillation; Stage 3, pulmonary vasculature and/or tricuspid valve damage as defined by the presence of systolic pulmonary hypertension (systolic pulmonary arterial pressure, PAPS $\geq$ 60 mmHg) and/or moderate/severe tricuspid valve regurgitation [12,13]; and Stage 4, right ventricular (RV) damage as defined by the presence of moderate to severe RV systolic dysfunction (tricuspid annular systolic excursion, TAPSE < 17 mm) [10,11,14,15].

To improve the identification of subclinical LV dysfunction, we added the LV global longitudinal strain (GLS) to Stage 1, using a cutoff value of $<-20\%$ to define impaired LV-GLS [10]. Patients were hierarchically classified in a given stage (worst stage) if at least 1 of the proposed criteria was met within that stage (Figure S1).

2.3. Clinical Follow-Up and Endpoint Assessment

After hospital discharge, follow-up was performed by clinical or phone visits at 30-days and 1-year after TAVI. All adverse events were systematically collected and classified according to the definitions of the Valve Academic Research Consortium-2 [16]. The primary endpoint of the study was all-cause mortality at 1-year after TAVI. Secondary endpoints included cerebrovascular accident, myocardial infarction, permanent pacemaker implantation, endocarditis, and re-hospitalization for all causes.

2.4. Statistical Analysis

Continuous data are reported as mean $\pm$ standard deviation (SD) and categorical data are reported as frequencies and percentages. Kaplan–Meier curves were constructed to show the rate of mortality up to 1-year across the cardiac damage groups. The association between the extent of cardiac damage and the risk of all-cause mortality at 1-year was assessed by using a Cox-regression multivariable model including all variables associated

whose p-values were <0.10 in the univariable model. The univariable model was built by using the Student's t-test or Wilcoxon–Mann–Whitney test for continuous variables and the chi-square test or Fisher exact test for categorical variables as appropriate. Statistical analyses were performed with Stata software version 14.2 (StataCorp, College Station, Texas, TX, USA).

3. Results

3.1. Baseline Characteristics

Among patients included in the EffecTAVI registry between 2014 and 2019, 262 received a detailed echocardiographic assessment at baseline and were included in this analysis. Patients were categorized by the presence and extent of extra-aortic valvular cardiac damage. At baseline, 4 (1.4%) patients were in Stage 0 (no cardiac damage), 19 (7.2%) patients were in Stage 1 (LV damage), 106 (40.4%) patients were in Stage 2 (LA or mitral valve damage), 59 (22.7%) patients were in Stage 3 (pulmonary vasculature or tricuspid valve damage) and 74 (28.3%) patients were in Stage 4 (RV damage). Given the small number of patients in Stage 0 and Stage 1, they were merged in a single group, Stage 0/1. The prevalence of cardiac damage stages and the distribution of their individual components are presented in Figure 1 and Table S1. The baseline characteristics of the study population according to stage of myocardial damage are provided in Table 1. Patients in more advanced stages of cardiac damage were older and had higher STS score compared with those in lower levels. They also presented with a worse NYHA functional class status and had lower LVEF. Procedural characteristics are summarized in Table S2. In the majority of cases, TAVI was performed by the transfemoral approach (97.3%) and with self-expanding prosthesis (73.3%). Procedural success according to VARC2 criteria was 98.5% and 6.8% of patients experienced periprocedural complications.

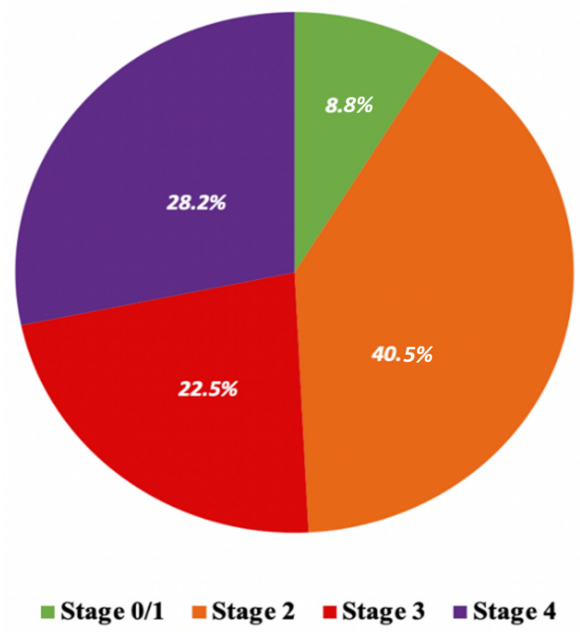

Figure 1. Distribution of stages of cardiac damage in the study population.

Table 1. Baseline characteristics of patient population according to the stage of cardiac damage.

	Stage 0/1 (*n* = 23)	Stage 2 (*n* = 106)	Stage 3 (*n* = 59)	Stage 4 (*n* = 74)
Age, years	77.3 ± 6.8	79.2 ± 6.7	81.1 ± 5.2	80.4 ± 5.7
Female sex	14 (60.9%)	67 (63.2%)	41 (69.5%)	40 (54.1%)
BMI (kg/m^2)	26.4 ± 4.3	27.1 ± 5.9	27.3 ± 5.7	28.1 ± 6
Hypertension	19 (82.6%)	94 (88.7%)	51 (86.4%)	65 (87.8%)
Diabetes mellitus	5 (21.7%)	41 (38.7%)	16 (27.1%)	25 (33.8%)
Dyslipidemia	12 (52.2%)	69 (65.1%)	34 (57.6%)	44 (59.5%)
Coronary artery disease	7 (30.4%)	49 (46.2%)	25 (42.4%)	36 (48.6%)
Previous myocardial infarction	1 (4.3%)	18 (17%)	12 (20.3%)	16 (21.6%)
Previous cerebrovascular accident	2 (8.7%)	11 (10.4%)	3 (5.1%)	12 (16.2%)
Peripheral artery disease	11 (47.8%)	57 (53.8%)	23 (39%)	45 (60.8%)
Chronic kidney disease	5 (21.7%)	34 (32.1%)	15 (25.4%)	21 (28.4%)
COPD	7 (30.4%)	26 (24.5%)	11 (18.6%)	27 (36.5%)
Dyspnea	11 (47.8%)	84 (79.2%)	43 (72.9%)	64 (86.5%)
Angina	5 (21.7%)	27 (25.5%)	16 (27.1%)	20 (27%)
Syncope	5 (21.7%)	15 (14.2%)	6 (10.2%)	7 (9.5%)
LVEF (%)	60.5 ± 8.9	55.9 ± 9.6	54.5 ± 11.7	49.3 ± 13.1
STS-PROM score (%)	3.5 ± 1.4	4.7 ± 3.1	5.2 ± 3.2	6.6 ± 4.8
Frailty scale				
0–1, *n* (%)	11 (47.8%)	41 (38.6%)	22 (37.3%)	21 (28.4%)
2–3, *n* (%)	12 (52.2%)	60 (56.6%)	36 (61%)	52 (70.3%)
4–5, *n* (%)	0 (0%)	5 (4.7%)	1 (1.7%)	1 (1.4%)
NYHA functional class				
I or II, *n* (%)	18 (78.3%)	48 (45.3%)	25(42.4%)	20 (27%)
III or IV, *n* (%)	5 (21.7%)	58 (54.7%)	34(57.6%)	54 (73%)

3.2. Echocardiographic Assessment at Follow-Up

The echocardiographic evaluation of the overall population is reported in Table S3. A complete echocardiographic assessment at baseline, discharge and at 30-days after the procedure was available for 130 patients, while 119 did not receive echocardiography at discharge or within 30 days and the evaluation was not complete for 13 patients. Re-assessment of the staging classification yielded more patients in Stage 0/1 and 2 compared with baseline (Table 2 and Figure 2). LVEF showed a marginally, non-significant improvement (55.3 ± 8.1% vs. 55.4 ± 7.3% vs. 58.4 ± 6.6% at baseline, discharge, and 30-days after TAVI; $p = 0.059$). Similarly, GLS significantly improved from baseline to follow-up (16.84 ± 1.8% vs. 19.6% ± 2.3 vs. 19.2 ± 3.5% at baseline, discharge, and 30-days after TAVI; $p = 0.044$). E/e′ ratio, a marker of diastolic dysfunction, showed a peculiar trend: from a mean value of 17.04 ± 4.4 at the baseline, it increased to 20.2 ± 5.7 at discharge and then decreased at 30-days after TAVI with a mean value of 12.19 ± 7.2 ($p = 0.192$). LA volume was significantly reduced (53.8 ± 5.1 mL/m^2 vs. 52.6 ± 13.9 mL/m^2 vs. 47.54 ± 11 mL/m^2 at baseline, discharge, and 30-days after TAVI; $p < 0.001$) as well as systolic pulmonary artery pressure (43.7 ± 8.2 mmHg vs. 41.7 ± 7.4 vs. 37.7 ± 11.1 mmHg, at baseline, discharge, and 30-days after TAVI; $p < 0.001$). Finally, improvement in RV function was demonstrated

by an increase in TAPSE (20.46 ± 4.3 mm vs. 20.38 ± 3.7 mm vs. 22.1 ± 5.1, at baseline, discharge, and 30-days after TAVI; $p = 0.085$).

Table 2. Re-assessment of cardiac damage at discharge and 30-days after TAVI.

	Baseline	Discharge	30-Days
Stage 0/1	12/130 (9.2%)	18/130 (13.8%)	46/130 (35.4%)
Stage 2	47/130 (36.2%)	75/130 (57.7%)	79/130 (60.8%)
Stage 3	32/130 (24.6%)	27/130 (20.9%)	4/130 (3.1%)
Stage 4	39/130 (30%)	10/130 (7.7%)	1/130 (0.7%)
LVEF,%	55.3 ± 8.1	55.4 ± 7.3	58.4 ± 6.6
GLS,%	−6.84 ± 1.8	−19.6 ± 2.3	−19.2 ± 3.5
E/e′ ratio	17.04 ± 4.4	20.2 ± 5.7	12.09 ± 7.2
LAVI, mL/m^2	53.83 ± 5.1	52.6 ± 13.9	47.54 ± 11
PAPS, mmHg	43.7 ± 8.2	41.7 ± 7.4	37.7 ± 11.1
TAPSE, mm	20.46 ± 4.3	20.38 ± 3.7	22.04 ± 5.1

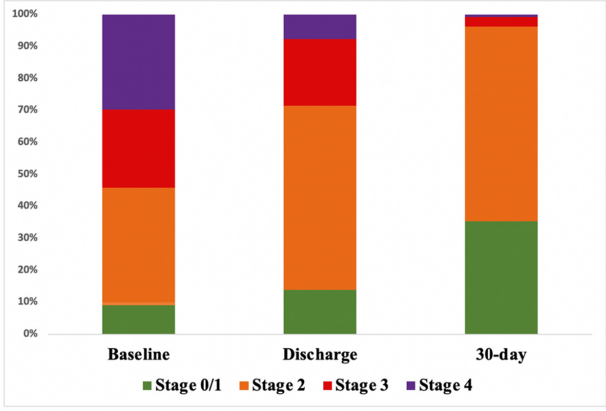

Figure 2. Re-assessment of cardiac damage at discharge and at 30-days after TAVI.

3.3. Clinical Outcomes

Clinical outcomes at 1-year after TAVI stratified by stage of cardiac damage are presented in Table 3. All-cause mortality progressively increased from Stage 0/1 (4.3%) to Stage 2 (6.6%), Stage 3 (18.6%) and Stage 4 (21.6%) ($p = 0.008$) (Figure 3). Death for cardiovascular causes occurred in 1 (4.3%) patient in Stage 0/1, 5 (4.7%) patients in Stage 2, 7 (11.9%) patients in Stage 3 and 11 (14.9%) patients in Stage 4 ($p = 0.012$).

Table 3. Clinical outcomes at 1-year after TAVI stratified by stage of cardiac damage.

	Stage 0/1 (*n* = 23)	Stage 2 (*n* = 106)	Stage 3 (*n* = 59)	Stage 4 (*n* = 74)	*p*-Value
All-cause death	1 (4.3%)	7 (6.6%)	10 (16.7%)	15 (20.3%)	0.008
Cardiovascular death	1 (4.3%)	5 (4.7%)	7 (11.9%)	11 (14.9%)	0.012
Stroke	0 (0%)	2 (1.9%)	2 (3.4%)	3 (4.1%)	0.67
Myocardial infarction	0 (0%)	2 (1.9%)	2 (3.4%)	5 (6.8%)	0.25
Permanent pacemaker implantation	6 (26.1%)	15(14.2%)	7 (11.9%)	16 (21.6%)	0.24
Endocarditis	1 (4.3%)	1 (0.9%)	0 (0%)	2 (2.7%)	0.38
Re-hospitalization	0 (0%)	10 (9.4%)	4 (6.8%)	9 (12.2%)	0.79

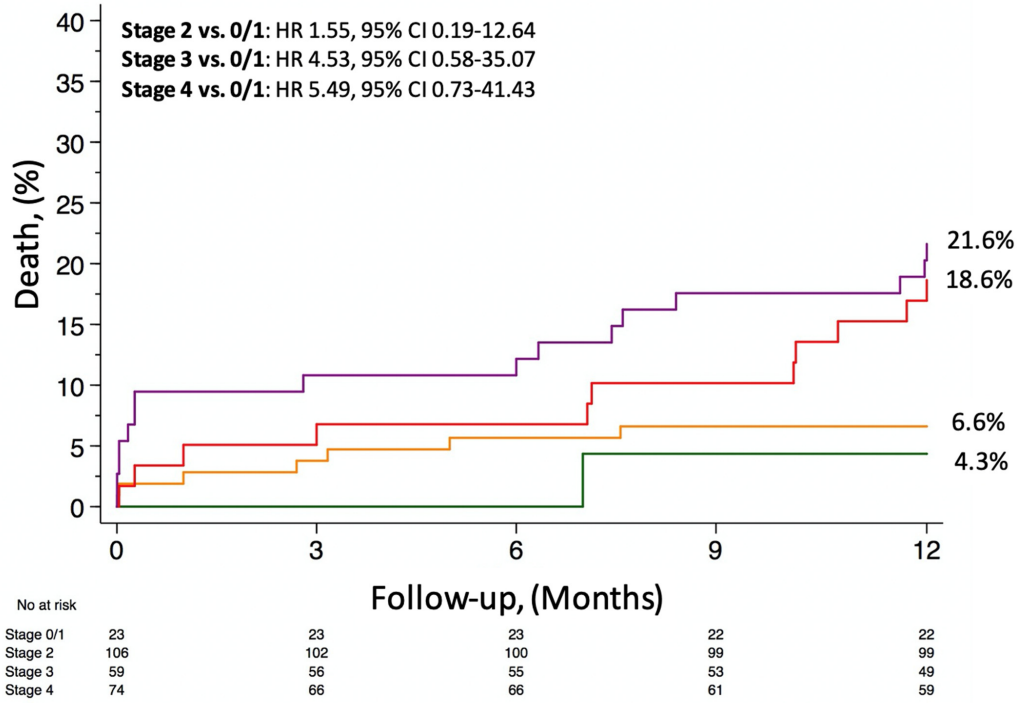

Figure 3. All-cause mortality according to the stage of cardiac damage.

No differences were found for secondary endpoints including cerebrovascular accident, myocardial infarction, permanent pacemaker implantation, endocarditis, and re-hospitalization for all causes at 1-year after the procedure. In addition, periprocedural complications did not increase the risk of major clinical outcomes.

In a multivariable model including cardiac damage, NYHA class III/IV, frailty class 4/5, STS score, hypertension, and dyslipidemia, only cardiac damage (HR 1.745, 95% CI 1.17–2.60, $p = 0.006$) and frailty class 4/5 (HR 6.16, 95% CI 1.78–21.37, $p = 0.004$) were significantly associated with all-cause mortality at 1-year follow-up (Supplementary Materials, Table S4).

4. Discussion

The main findings of the present analysis can be summarized as follows:

1. The staging classification of AS-related cardiac changes, derived from a randomized trial, maintains its prognostic performance in real-world TAVI patients;
2. TAVI triggers an early reversal of cardiac dysfunction, mainly driven by the amelioration of LV diastolic and RV function.

Nevertheless, the extent of extra-aortic valve cardiac damage at baseline significantly affects survival at 1-year after the procedure.

The identification of clinical and anatomic factors that affect clinical outcomes of patients with severe AS represents an important unmet need. Several scoring systems that account for baseline features and measures of frailty have been proposed for counselling AS patients [17,18]. However, their use in clinical practice is challenged by the lack or limited availability of all the required variables. In this context, the staging classification of cardiac damage proposed by Généreaux et al. features the unique advantage of being widely applicable as it is based on echocardiographic parameters that are routinely evaluated in patients with severe AS. This system was formulated by leveraging the data of 1661 patients from the PARTNER 2 trial and was proved to be a powerful predictor of mortality at 1-year after aortic valve intervention (either surgical or transcatheter) [7]. In our study, which included real-world patients, the system retains its prognostic ability as a greater extent of cardiac damage was associated with increased risk of all-cause mortality after TAVI. These findings are in line with prior studies that applied the staging classification system in larger populations. In a retrospective analysis of 1189 symptomatic, severe AS patients, stage of cardiac injury was independently associated with all-cause mortality and the combined endpoint of all-cause mortality, stroke, and cardiac-related hospitalization [19]. Among asymptomatic patients with moderate to severe AS, the staging was significantly associated with excess mortality in multivariable analysis adjusted for aortic valve replacement as a time-dependent variable (hazard ratio: 1.31 per each increase in stage; 95% CI: 1.06 to 1.61; $p = 0.01$) and demonstrated incremental value over other traditional risk markers [8]. Another study applied the staging system to TAVI patients and found a graded association between cardiac damage and all-cause mortality [20].

However, our analysis is the first to assess the impact of TAVI on the extent of extra-aortic valve cardiac damage. We found that the procedure triggers an early (within 30-days) re-classification of the stages owing to significant changes in measures of LV diastolic and RV function. LV hypertrophy and collagen abnormalities develop in patients with severe AS and impair diastolic function. Indeed, objective evidence of variable degrees of LV diastolic dysfunction has been reported in up to two-thirds of patients undergoing TAVI [21]. Similarly, RV dysfunction has been documented in up to 1 in 4 patients with severe AS Devereaux a consequence of transmission of elevated left-sided pressure back through the pulmonary vascular system. The suppression of pressure overload by TAVI ameliorates LV filling pressures (E/e' ratio), as suggested by the concomitant reduction in left atrial volume. Along the same line, a trend towards normalization of TAPSE may occur after TAVI [22,23]. as well as a reduction in pulmonary hypertension [24]. Nevertheless, these changes do not improve survival after TAVI as baseline conditions predominate in determining prognosis at 1-year. We consistently, observed an overall improvement in myocardial function suggested by changes in LV-GLS after TAVI with no relevant impact on mortality at 1-year.

The main clinical implication of the results of our study is the need to rethink the optimal timing of intervention in patients with AS. Multiple lines of evidence indicate that

the greater the extent of cardiac damage before TAVI, the higher the probability of worse outcomes after the procedure. Moreover, irreversible structural cardiac changes induced by longstanding AS neutralize the beneficial impact of TAVI on some functional parameters. From this perspective, anticipating the intervention might have the potential advantage of obtaining the full reversibility of cardiac function and improving survival to a greater extent.

Our study has several limitations. It is a retrospective analysis of data collected at a single center; thus, it is subject to inherent flaws related to that design and the sample size may not provide enough power to make definite conclusions. A comprehensive assessment of echocardiographic parameters after TAVI was not performed in the overall population, affecting the completeness of our observations. The parameters used for staging the extent of cardiac damage are those obtained in the context of the routine echocardiogram of TAVI patients and are potentially subject to measurement errors and variability. We did not assess the potential modifying effect of paravalvular aortic regurgitation on echocardiographic and clinical outcomes after TAVI. Moreover, we could not evaluate whether adding cardiac biomarkers might ameliorate the prognostic role of the staging classification as they are not routinely measured in our clinical practice.

5. Conclusions

The staging classification confirms its utility as an additive clinical tool to enhance risk stratification and therapeutic decision making in patients with AS. Timely intervention (either transcatheter or surgical) might reverse functional cardiac changes associated with AS; however, survival at medium-term is mainly related to the baseline grade of the extent of cardiac damage. Further and larger studies are needed to assess the value of the staging classification in the post-procedural setting.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/jcm10194563/s1, Figure S1: Staging of cardiac damage in patients with aortic stenosis, Table S1: Prevalence of cardiac damage stages and their individual components in study population, Table S2: Procedural data, Table S3: Echocardiographic parameters according to stage of cardiac damage at baseline, discharge and 30-days after TAVI, Table S4: Multivariable model.

Author Contributions: A.F., G.E., conceptualization, methodology, project administration, validation, writing—review and editing, supervision. M.A., A.L., F.I., C.I., D.A., D.S.C., investigation, data curation and writing—original draft preparation. R.P., statistical analysis. A.M., R.E., M.S., C.S., L.D.S., P.C., investigation and data curation. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the University of Naples Federico II (protocol code 231/18; date of approval 29/10/2018).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to firewalls to access our dataset from outside our Institution.

Acknowledgments: This paper is dedicated to the memory of our friend and colleague Maurizio Galderisi who died on March 2020 because of COVID-19.

Conflicts of Interest: C.I. and A.L. receive research grant support from the Cardiopath PhD program. Other authors have nothing to disclose.

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81° Congresso Nazionale SIC - Roma, 17-20 dicembre 2020

VALVULOPATIE *576*

VALUTAZIONE ECOCARDIOGRAFICA DELLE VALVOLE CARDIACHE ***(IMAGING CARDIOVASCOLARE)***
PATOLOGIA DELLA VALVOLA AORTICA ***(VALVULOPATIE)***
VALUTAZIONE ECOCARDIOGRAFICA DELLA FUNZIONE VENTRICOLARE ***(IMAGING CARDIOVASCOLARE)***

CORRELATION OF ATRIAL AND VENTRICULAR STRAIN IMPROVEMENT AFTER TRANSCATHETER AORTIC VALVE IMPLANTATION

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Background. Aortic stenosis (AS) is the most common heart valve disease encountered in clinical practice. The afterload increase imposed by severe AS creates concentric left ventricular (LV) remodeling and diastolic dysfunction, as well as progressive left atrial (LA) enlargement and dysfunction. There is emerging data showing that LA function evaluated by peak atrial longitudinal strain (PALS) is more sensitive than LA volume to assess subtle LA reverse remodeling after transcatheter aortic valve implantation (TAVI). The aim of this study was to assess the impact of TAVI on changes in LA size and phasic function by using comprehensive quantification of LA volumes and 2-dimensional speckle tracking imaging, in patients with symptomatic severe AS undergoing TAVI. We also sought to examine the correlation between PALS and other traditional and advanced echo parameters as left ventricular function using multilayer global longitudinal strain (GLS) by 2D speckle-tracking echocardiography (STE).

Methods: We prospectively enrolled 70 patients (mean age 80.5 ±5 years, male 40%) with severe symptomatic AS undergoing TAVI between 2018 and 2020. Exclusion criteria were prior valve surgery, severe mitral stenosis, permanent atrial fibrillation and poor ultrasound acoustic window. Echo-Doppler assessment, including GLS and PALS, was performed before and after 1-3 months to TAVI procedure. Changes (D) of the main echo parameters before and after intervention were computed. On the basis of changes in PALS, the study population was divided in two group: no improvement in PALS (NPALS) and improvement in PALS (IPALS).

Results: In the early follow-up after the procedure, a significant reduction of relative wall thickness (p=0.006), LA volume (p=0.036) E peak velocity (p=0.030) in the overall population was observed. Although LV volumes and ejection fraction didn't change, there was a significant improvement in PALS (P<0.001) and GLS (p=0.03) after TAVI. PALS improvement was observed in 50 patients (71%). The two group (IPALS and NPALS) were comparable for sex, age, risk factors, and for baseline echocardiographic parameters. In the IPALS group, a significant improvement of GLS after procedure was detected (ΔGLS 18.8 ± 21 in IPALS vs -4.1 ± 22 in NPALS, p=0.001). By a multiple linear regression analysis performed in the pooled population, after adjusting for baseline confounders, the association between ΔPALS and ΔGLS remained significant (beta=0.41, p=0.001).

Conclusion: Afterload reduction following TAVI induced relevant hemodynamic changes. In this study PALS was confirmed as an early echocardiographic marker of recovery of LA structure, and its improvement is correlated with GLS. Further study and a longer follow-up are needed to evaluate the impact of these finding on clinical outcomes.

Changes and prognostic impact of non-invasive myocardial work indices in patients undergoing transcatheter aortic valve implantation

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Running title: Myocardial work in TAVI

Total word count: (Abstract, Text, Figure Legends, Table Legends, References): 4338

Declarations of interest: none.

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List of abbreviations

AS = Aortic stenosis

EF = ejection fraction

GCW = Global constructive work

GLS = Global longitudinal strain

GWE = Global work efficiency

GWI = Global work index

GWW = Global wasted work

ICC = Intraclass correlation coefficient

LBBB = Left bundle branch block

LV = left ventricle

MW = Myocardial work

NYHA = New York Heart Association

TAVI = Transcatheter aortic valve implantation

Abstract

Background: Eventual changes and prognostic role of non-invasive myocardial work (MV) indices in patients undergoing transcatheter aortic valve implantation (TAVI) have not been adequately investigated.

Methods: We selected 88 consecutive patients (mean age 79.9±6.4 years, 35% males) with severe aortic stenosis scheduled for TAVI within the EffecTAVI registry. Exclusion criteria were prior valve surgery, atrial fibrillation, and left bundle branch block (LBBB) at baseline. Global work index (GWI), global constructive work (GCW), global wasted work (GWW) and global work efficiency (GWE) were measured by echocardiography at baseline and at 30-day after. Accuracy of non-invasive measures was assessed by invasive evaluation of MW. Adjusted Cox-regression analysis was performed to assess the impact of MV indices on 1-year clinical outcomes.

Results: In the overall population, at 30-day after TAVI, a significant reduction of GWI (2,406±567 vs. 1,908±479 mmHg% before and after TAVI respectively, p<0.001), GCW (2783±616 vs 2202±463 mmHg%, p<0.001) and GWW (238 ± 203 vs 172 ± 126 mmHg%, p= 0.002) was observed. GWE was improved only in patients that did not develop left ventricular (LV) dyssynchrony because of new onset LBBB or pacemaker implantation after TAVI. In a multivariable Cox-regression analysis, adjusted for confounders, GWE after TAVI (HR 0.892, 95% Confidence Intervals 0.81–0.97; p= 0.011) was the strongest predictor of adverse events (composite of all-cause death, endocarditis, worsening of dyspnea and re-hospitalization for cardiovascular events) at 1-year follow-up.

Conclusions: TAVI conveys significant changes of MV indices, consisting of an early reduction of GWI, GCW and GWW and an improvement of GWE only in patients without LV dyssynchrony. A value of GWE≤92% at 30-day predicts poor clinical outcomes after 1-year.

Key words: myocardial work; transcatheter aortic valve implantation; global work efficiency; speckle tracking; reverse remodeling.

Introduction

Transcatheter aortic valve implantation (TAVI) is an established therapy for patients with symptomatic severe aortic stenosis (AS), irrespective of operative risk (1). Through the reduction of afterload, TAVI is expected to trigger structural changes of the left ventricle (LV) that are ultimately associated with improved survival and clinical outcomes. LV reverse remodeling consists of regression of LV hypertrophy and amelioration of LV systolic function. These events occur over a period of several months whereas an early functional recovery of LV can be identified by measuring the global longitudinal strain (GLS) (2, 3). This parameter is more sensitive than LV ejection fraction (EF) in detecting changes in LV function; however, given its dependency from afterload, GLS can be misleading when assessing the true contractile status in patients undergoing TAVI (4).

Recently, echocardiographic assessment of myocardial work (MW), integrating strain measurement with pressure, emerged as a valuable tool to obtain a more objective evaluation of ventricular function. It overcomes the limitations of EF and GLS through the incorporation of loading conditions (5). We previously demonstrated that, among patients with moderate-to-severe AS, lower MW indices reflect a more advanced cardiac damage and are associated with increased mortality at long-term follow up (6). The aim of the present study was to assess the early impact of TAVI on non-invasive MW indices and their association with clinical outcomes at medium-term follow-up.

Methods

Patient population and data collection

All consecutive patients with severe symptomatic AS undergoing TAVI at our institution were enrolled in the EffecTAVI registry. Severe AS was defined according to current guidelines as a mean aortic valve gradient ≥40 mmHg and/or aortic valve area <1.0 cm^2 (or an indexed aortic valve

area <0.6 cm^2/m^2) and/or a peak aortic jet velocity ≥ 4 m/s (7). TAVI suitability was established by the local multi-disciplinary Heart Team. Patients with a complete echocardiographic evaluation at baseline and at 30-day follow up were considered eligible for the present analysis. Exclusion criteria were: prior valve surgery, atrial fibrillation, left bundle branch block (LBBB) at baseline and suboptimal image quality. Clinical, procedural and follow-up data were anonymously entered in a web-based database (https://www.redcap.unina.it/redcap/). The EffecTAVI registry has been approved by the local ethic committee and all study-related procedures were carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained for all patients for participation in this registry.

Echocardiographic measurements

Transthoracic echocardiograms were performed using a Vivid ultrasound (E95, iQ) System (GE Healthcare, Horten, Norway) and stored on a dedicate workstation for off-line analysis (EchoPAC, GE Healthcare, Version 203). For each echocardiographic measurement, at least two cardiac cycles were averaged. Conventional echocardiographic measurements were performed in accordance with the guidelines (7,8).

Strain analysis was based on speckle-tracking approach and measured by an experienced cardiologist, as previously described (9). The acquisitions for the measurement of LV global longitudinal strain (GLS) were performed in apical long-axis, 4- and 2-chamber views (frame rate 60-90 frame/s).

Myocardial work indices

Quantification of MW was performed using commercially available software package (Echopac Version 203, GE Healthcare). As described in previous works (5,10), MW was estimated as the area of the pressure-strain loops , which were calculated by integrating LV GLS data with non-invasive LV pressure curves. In patients with AS, peak systolic LV pressure was estimated as the sum of

systolic blood pressure and mean transaortic pressure gradient, as previously validated (11, 12). In order to confirm the accuracy of the method, in twelve patients peak systolic LV pressure was measured invasively before TAVI procedure, and MW indices derived with invasive LV pressure were correlated to those echocardiography-based. In post-TAVI population, mean transaortic pressure gradient is assumed to be negligible, therefore peak systolic LV pressure was only derived from the brachial systolic blood pressure measure with a cuff manometer. The opening and closing timings were set by pulse-wave Doppler recordings at mitral valve and aortic valve level and then confirmed by two-dimensional echocardiographic evaluation of the apical long-axis view, to define the different phases of the cardiac cycle. Then, the patient-specific, non-invasive pressure curve was obtained using a normalized reference curve, adjusted to the valvular event times. The following MW indices were calculated:

- global work index (GWI): total work within the area of the pressure-strain loop, calculated from mitral valve closure to mitral valve opening;
- global constructive work (GCW): work performed during shortening in systole adding negative work during lengthening in isovolumetric relaxation;
- global wasted work (GWW): negative work performed during lengthening in systole adding work performed during shortening in isovolumetric relaxation;
- global work efficiency (GWE): constructive work divided by the sum of constructive and wasted work, expressed as percentage.

Clinical follow-up and endpoint assessment

After hospital discharge, follow-up was performed by clinical or phone visits at 30-day and 1-year after TAVI. All adverse events were systematically collected and classified according to the definitions of the Valve Academic Research Consortium-3 (13). The primary endpoint of the study was the composite of all-cause mortality, endocarditis, worsening of dyspnea (New York Heart Association [NYHA] class ≥ 3) and re-hospitalization for cardiovascular events at 1-year after

TAVI. Occurrence of ventricular dyssynchrony after TAVI was defined as electrical dyssynchrony induced by development of left ventricular bundle branch block (LBBB) or ventricular pacing.

Statistical analysis

Data are reported as mean ± standard deviation for continuous variables or percentages of individuals for categorical variables. Group comparisons were performed using two-sample t-test and Chi-square test for continuous and categorical variables. Echocardiographic parameters and MW indices were compared pre and post-TAVI using either a paired t-test or Wilcoxon signed rank test. Multivariable Cox proportional hazards model adjusted for diabetes mellitus, peak aortic velocity pre-TAVI, tricuspid valve gradient pre-TAVI, LV end-systolic volume pre-TAVI, ventricular dyssynchrony, LVEF post-TAVI GWI, GWW and GWE post-TAVI was used to determine the independent association with composite endpoint. The selection of the variables for the multivariable analysis was based on their significant association (P-value <0.1) with composite endpoint in univariable analysis. Three models were generated to avoid collinearity between MW parameters. Receiver-Operator Characteristics (ROC) curves was generated and the Youden's J statistic used to estimate the best cut-off value that predicted composite endpoint. The Kaplan-Meier method was used for cumulative survival analysis with the log-rank test for assessing statistical differences between curves.

Intraclass correlation coefficient (ICC) was used to investigate the agreement between LV MW indices estimated with invasively-measured versus echocardiography-derived LV systolic pressures. To assess intraoperator reproducibility, MW measurements of fifteen random individuals were re-evaluated by the same operator blinded to the previous results using ICCs analysis. A second observer was blinded to the measurements of the first observer for interobserver measurements. The ICC chosen was of single measures and absolute agreement with random effect. A good agreement was defined by an ICC between 0.75 and 0.9, whereas an excellent agreement was defined by a

value above 0.9. Statistical analyses were performed using IBM-SPSS, version 23 (SPSS Inc, Chicago, IL, USA). A P-value <0.05 was considered significant.

Results

Baseline characteristics

Among patients included in the EffectTAVI registry between 2016 and 2021, 88 consecutive patients with symptomatic severe AS scheduled for TAVI fulfilled the inclusion criteria and were included in this analysis. Baseline demographic and clinical characteristics of the study cohort are presented in **Table 1**. The population was predominantly female, elderly, hypertensive, dyslipidemic and at high risk of surgery. TAVI procedures were mostly performed via a transfermoral approach, and the implanted prostheses were predominantly self-expandable.

Echocardiographic assessment before and after TAVI

Echocardiographic assessment at baseline and at 30-day after the procedure of the overall population is reported in **Table 2**. As expected, after TAVI a significant improvement in transaortic mean pressure gradient, peak aortic velocity and aortic valve area was observed. Already at 30 day-follow up, initial signs of reverse remodelling were detected, such as a significant reduction of LV relative wall thickness and left atrial volume. Despite no difference in diastolic parameters and right chambers was observed, systolic pulmonary artery pressure significantly reduced after the procedure. LV GLS improved whereas non-significant changes in LV EF were observed. The analysis of non-invasive MW showed that, one month after the procedure, GWI (2,406 ± 567 vs. 1,908 ± 479 mmHg% before and after TAVI respectively, p<0.001), GCW (2783 ± 616 vs 2202 ± 463 mmHg%, p<0.001) and GWW (238 ± 203 vs 172 ± 126 mmHg%, p= 0.002) significantly reduced, with no change in GWE (90 ± 6 vs 91 ± 5%, p=0.113).

Validation of LV MW indices by invasive measurement

The ICC for LV myocardial work indices calculated with invasive versus echocardiography-derived LV systolic pressures showed a strong agreement for GWI and GCW (0.88 and 0.86, respectively), and excellent agreement for GWW (0.98) (**Supplementary Table 1S**). The ICC for intra-observer variability of echocardiography-derived LV myocardial work indices was 0.83 for LV GWI, 0.81 for GCW, 0.79 for GWW and 0.89 for GWE, demonstrating strong agreement. Similarly, the ICC for inter-observer variability was 0.85 for LV GWI, 0.81 for GCW, 0.83 for GWW and 0.83 for GWE, indicating strong agreement (**Supplementary Table 2S**).

Impact of LV dyssynchrony on myocardial work

After TAVI, 32 patients (36.4%) developed LV dyssynchrony (59% due to pacemaker implantation, 41% due to new onset LBBB). When the population was divided according to the presence or absence of LV dyssynchrony at 30-day follow-up, GWI and GCW dramatically reduced after intervention in both groups ($p<0.001$). Conversely, a significant reduction in GWW was found only in the those without dyssynchrony (242 ± 230 vs. 142 ± 104 mmHg% before and after TAVI, $p<0.001$), whereas no change in GWW was observed in those with LV dyssynchrony (231 ± 142 vs. 233 ± 147 mmHg%, $p=0.958$). Consistently, GWE significantly improved after TAVI in patients with normal QRS duration (90 ± 7 vs. 93 ± 5%, $p=0.001$), while a trend of GWE reduction was observed in patients who developed dyssynchrony after TAVI (91 ± 5 vs. 89 ± 5%, $p=0.110$) (**Figure 1**).

Prognostic value of MW indices

After a median follow-up of 12 months (interquartile range:12-23 months), 5 patients (6%) died, 5 (6%) suffered for worsening dyspnea (NYHA class ≥ 3), 2 (2%) developed endocarditis and 4 (5%) were re-hospitalized for cardiovascular events. In the univariable Cox-regression analysis, patients who experienced events were predominantly diabetics ($p=0.079$), had lower peak aortic velocity ($p=0.093$), lower tricuspid valve gradient and increased LV end-systolic volume at baseline

(p=0.047). Moreover, patients with events developed more often ventricular dyssynchrony (p=0.093), had lower LVEF (p=0.066), GWI (p=0.069) and GWE (p=0.003) but increased GWW (p=0.049) after TAVI (**Table 3**). For the other clinical, demographic, and echocardiographic parameters, no significant correlations with the outcomes were found (P>0.1 for all, data not shown). On multivariable Cox-regression analysis, only GWE emerged as independently associated with composite endpoint (HR 0.905; 95% CI: 0.832-0.984, p=0.020). A GWE value of 92% was associated with outcomes with a sensitivity of 87%, and a specificity of 56% (AUC = 0.760, p=0.002) (**Figure 2**). The cumulative event rate for the composite endpoint (all-cause death, worsening dyspnea endocarditis, and rehospitalization for CV events) was significant higher in patients with more impaired GWE (≤92%) compared to those with higher GWE (>92%) after TAVI (29.5% vs. 4.8% at 1-year follow-up, respectively; log-rank p=0.003) (**Figure 3**).

Discussion

The main findings of the present study can be summarized as follows: (i) in patients undergoing TAVI a significant reduction of LV GWI, GCW and GWW was observed at 30-day follow- up; (ii) GWE was improved only in patients without LV dyssynchrony; (iii) lower GWE at 30-day after TAVI was independently associated with worse subsequent clinical outcomes. We also showed that calculation of MW indices by echocardiography in patients with severe AS is accurate and has a good correlation with invasively based measures.

Impact of TAVI on MW indices

In patients with AS, LV hypertrophy develops as initial compensatory adaptation to the increased afterload with the aim to maintain LV systolic function and reduce wall stress. However, disease progression further increases wall stress leading to systolic and diastolic LV dysfunction, subendocardial ischemia and fibrosis, pulmonary hypertension, and right ventricular failure (9,14,15). TAVI improves symptoms, quality of life and promotes regression of LV mass.

Nevertheless, functional recovery of the LV and regression of LVH do not invariably occur in all patients (14,16). In addition, the rate and extent of reverse LV remodeling may differ according to baseline stage of cardiac damage and cardiovascular risk profile (17). In this context, non-invasive MW indices proved to effectively mirror the changes in myocardial contractility at different stages of AS severity (6). In the present study, we extended these findings, showing that assessment of MW by echocardiography is more sensitive than other parameters to detect improvement of contractile LV performance early after TAVI. By corroborating prior results from Jain et al. (11) and Fortuni et al (12), we found a close correlation between the MW indices derived with estimated LV systolic pression and those measured invasively. This supports the correction of peripheral blood pressure values with mean transaortic gradient as a valuable method to calculate LV myocardial work by echocardiography in AS patients.

Beyond the initial reduction of GWI and GCW immediately after TAVI, described as an effect of the immediate relief from the obstructed valve and the increased afterload (11,18), we found a significant reduction of GWW, probably related to the reduction of wall stress associated with the reverse myocardial remodeling at one month after the procedure.

More interestingly, the beneficial effects of TAVI on myocardial performance were greatest in patients who maintained a spontaneous rhythm without conduction disorders. Indeed, in this group, GWW reduction was even more prominent than GCW, resulting in a significant improvement of GWE. Conversely, in patients who developed ventricular dyssynchrony after TAVI, the reduction of GWI and GCW was not accompanied by a consistent reduction of GWW, with consequent reduction of MWE (**Figure 4**). This finding is consistent with studies in patients undergoing cardiac resynchronization therapy (CRT), showing large amount of WW in dyssynchronous ventricular septum, that reduces after response to CRT with concomitant increase of GWI and LV performance (19).

Myocardial work efficiency after TAVI: clinical implications

Reduced myocardial efficiency reflects impairment of ventricular performance and may provide additional information in failing ventricles, as seen in postinfarct patients (20,21) and in heart failure with reduced EF (22,23). In heart failure with preserved EF, lower resting values of GWE have been associated with lower exercise capacity and blunted LV contractile reserve during effort, suggesting an early subclinical myocardial damage, not detectable by the simple LV EF measurement (10). In the current study, we demonstrated for the first time that also in AS patients undergoing TAVI measuring GWE has clinical impact, since values lower than 92% were independently associated with worse prognosis at 1-year. We can then speculate that among patients with severe AS, anticipating the time of intervention prior that irreversible myocardial damage has occurred, is associated with higher probability of success in terms of reverse remodeling. In this perspective, LV myocardial work evaluation may improve the assessment of LV systolic function at baseline and during the follow-up, perhaps identifying patients that could benefit from an earlier intervention or from adjunctive therapies as CRT.

Study Limitations

Our study is a retrospective analysis of data collected at a single center; thus, it is subject to inherent flaws related to that design and the sample size may not provide enough power to make definite conclusions. Another limitation is that, although most of the echocardiographic examinations were performed close to the TAVI procedure, difference in loading conditions and blood pressure between the two assessment may have affected our results. Finally, we limited the analysis to only patients with native aortic disease, thus results are not applicable to valve-in-valve procedures.

Conclusions

In patients AS undergoing TAVI, non- invasive MW indices inform about reverse remodeling and myocardial contractility improvement that occur early after the procedure. While GWI and GCW decrease in all subjects after TAVI as an immediate effect of afterload reduction, a significant

reduction of GWW and improvement of GWE can be detected only in those who do not develop LV dyssynchrony. In this setting, GWE≤92% early after TAVI is associated with poor outcome. Thus, MW efficiency could represent an alternative tool for myocardial function assessment and prognostic evaluation in patients receiving TAVI. The role of these measures in detecting the extent of reversibility of LV dysfunction post TAVI and in predicting long-term outcomes needs to be addressed in prospective studies.

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Figure legend

Figure 1. Comparison of myocardial work indices before and 30-days after TAVI according to the presence or absence of LV dyssynchrony. GWI = global work index; GCW = global constructive work; GWW = global wasted work; GWE = global work efficiency.

Figure 2. Receiver operator characteristics (ROC) curve analysis for GWE as predictor of cardiovascular events (composite of all-cause death and rehospitalization for heart failure).

Figure 3. Kaplan-Meier survival curves of patients with reduced GWE after TAVI (GWE ≤92%, red line), and those with higher GWE (>92%, blue line), at 1-year follow-up.

Figure 4. Examples of estimated LV myocardial work indices before and 30-days after TAVI in a patient without LV dyssynchrony (upper panel) and in one who developed LV dyssynchrony after the procedure (lower panel). GCW = global constructive work; GWW = global wasted work; GWE = global work efficiency.

Table 1. Baseline demographic and clinical characteristics

Variables	***n = 88***
Males, n (%)	35 (39.8)
Age, years	79.9 ± 6.4
Body mass index, kg/m^2	26.0 ± 5.3
Body surface area, m^{2,7}	1.7 ± 0.2
Risk factors	
Hypertension, n (%)	80 (90.9)
Current smoker, n (%)	6 (6.8)
Diabetes mellitus, n (%)	23 (26.1)
Obesity, n (%)	10 (11.4)
Dyslipidemia, n (%)	51 (58)
History of CAD, n (%)	29 (33)
Risk scores	
STS score	3.9 ± 2.0
EuroSCORE II	5.3 ± 6.0
Logistic EuroSCORE	14.5 ± 12.4
Type of prosthesis	
Self-expandable, n (%)	61 (69.3)
Balloon-expandable, n (%)	27 (30.7)

Values are n (%) or mean ± SD.

CAD = coronary artery disease; STS = Society of Thoracic Surgeons.

Table 2. Echocardiographic characteristics before and after TAVI

Parameters	Before-TAVI (n=88)	After-TAVI (n=88)	*p-value*
Aortic valve severity			
Mean Pressure Gradient, mmHg	49.3 ± 12.5	10.8 ± 5.6	<0.0001
Peak aortic Velocity, m/s	4.4 ± 0.5	2.2 ± 0.5	<0.0001
Aortic Valve Area, cm^2	0.7 ± 0.2	1.8 ± 0.5	<0.0001
Indexed Stroke Volume, ml/m^2	44.2 ± 10.8	44.8 ± 10.1	0.694
LV characteristics			
Interventricular septum, mm	12.2 ± 1.6	11.9 ± 1.7	0.072
LV posterior wall, mm	10.8 ± 1.6	11.3 ± 4.3	0.317
LV end-diastolic diameter, mm	47.7 ± 6.8	48 ± 6.9	0.612
LV end-systolic diameter, mm	30.5 ± 6.9	30 ± 7.5	0.597
LV mass indexed, $g/m^{2,7}$	55.4 ± 15.9	54.1 ± 13.9	0.294
Relative wall thickness	0.48 ± 0.09	0.46 ± 0.08	0.007
LV end-diastolic volume, ml	88.9 ± 31.4	90 ± 26.8	0.668
LV end-systolic volume, ml	37.9 ± 17.9	37 ± 16.2	0.527
LV EF, %	58.2 ± 8.5	59.4 ± 7.5	0.091
GLS, %	18.4 ± 4.2	19.5 ± 4.2	0.006
Indexed left atrial volume, ml/m^2	47 ± 14.3	44.1 ± 13.1	0.014
Mitral E/A ratio	0.8 ± 0.4	0.8 ± 0.4	0.412
DT, ms	275.2 ± 82.4	270.4 ± 81.5	0.613
E/e', average	15.6 ± 5.8	15.7 ± 6.3	0.887
TAPSE, mm	22.4 ± 3.7	22.3 ± 3.6	0.900
RV basal diameter, mm	36.7 ± 5	36.4 ± 5.3	0.680
Indexed right atrial volume, ml/m^2	22.8 ± 6.9	24.3 ± 7.0	0.067
Tricuspid valve velocity (m/s)	2.9 ± 0.4	2.8 ± 0.4	0.106
sPAP (mmHg)	39.5 ± 9	37.4 ± 8.6	0.021

Myocardial work			
GWI, mmHg%	2406 ± 567	1908 ± 479	<0.0001
GCW, mmHg%	2783 ± 616	2202 ± 463	<0.0001
GWW, mmHg%	238 ± 203	172 ± 126	0.002
GWE, %	90 ± 6	91 ± 5	0.113

LV = left ventricle; EF = ejection fraction ; GLS = global longitudinal strain; DT = deceleration time; RV = right ventricle; sPAP = pulmonary artery systolic pressure; GWI = global work index; GCW = global constructive work; GWW = global wasted work; GWE = global work efficiency.

Table 3. Univariable and multivariable predictors of composite events at 1-year follow up

Parameters	Univariate		Multivariate	
	HR (95% CI)	***P-value***	**HR (95% CI)**	***P- value***
Diabetes mellitus	2.425 (0.902-6.519)	0.079	2.488 (0.854 – 7.252)	0.095
Peak aortic Velocity – pre	0.411 (0.146-1.160)	0.093	-	-
Tricuspid valve gradient - pre	0.941 (0.877-1.010)	0.093	0.937 (0.870-1.010)	0.088
LV end-systolic volume - pre	1.022 (1.000-1.045)	0.047	-	-
Ventricular dyssynchrony	2.335 (0.869-6.271)	0.093	-	-
LVEF - post	0.954 (0.908-1.003)	0.066	-	-
GWI - post	0.999 (0.998-1.000)	0.069	-	-
GWW - post	1.003 (1.000-1.006)	0.049	-	-
GWE - post	0.897 (0.836-0.964)	0.003	0.905 (0.832-0.984)	0.020

LV = left ventricle; LVEF = left ventricular ejection fraction; GWI = global work index; GWW = global wasted work; GWE = global work efficiency.

CHAPTER 2

Extent of cardiac damage and mortality in patients undergoing Transcatheter Aortic Valve Implantation

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Review

Echocardiographic Evaluation after Transcatheter Aortic Valve Implantation: A Comprehensive Review

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Abstract: Transcatheter aortic valve implantation (TAVI) is an increasingly popular treatment option for patients with severe aortic stenosis. Recent advancements in technology and imaging tools have significantly contributed to the success of TAVI procedures. Echocardiography plays a pivotal role in the evaluation of TAVI patients, both before and after the procedure. This review aims to provide an overview of the most recent technical advancements in echocardiography and their use in the follow-up of TAVI patients. In particular, the focus will be on the examination of the influence of TAVI on left and right ventricular function, which is frequently accompanied by other structural and functional alterations. Echocardiography has proven to be key also in detecting valve deterioration during extended follow-up. This review will provide valuable insights into the technical advancements in echocardiography and their role in the follow-up of TAVI patients.

Keywords: echocardiography; follow-up; TAVI

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Citation: Angellotti, D.; Manzo, R.; Castiello, D.S.; Immobile Molaro, M.; Mariani, A.; Iapicca, C.; Nappa, D.; Simonetti, F.; Avvedimento, M.; Leone, A.; et al. Echocardiographic Evaluation after Transcatheter Aortic Valve Implantation: A Comprehensive Review. *Life* **2023**, *13*, 1079. https://doi.org/10.3390/life13051079

Academic Editors: Egidio Imbalzano and Marco Vatrano

Received: 6 March 2023
Revised: 19 April 2023
Accepted: 23 April 2023
Published: 24 April 2023

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1. Role of Echocardiography in TAVI Patients

Echocardiography plays a key role in the evaluation of patients undergoing transcatheter aortic valve implantation (TAVI) because it is essential for determining eligibility for the procedure and evaluating its efficacy during the follow-up. Transthoracic echocardiography (TTE) enables accurate noninvasive evaluation of valve anatomy and hemodynamics, as well as of cardiac chambers function and morphology prior to intervention. Current guidelines recommend echocardiographic follow-up after TAVI before hospital discharge or within thirty days, six months, one year, and annually thereafter [1]. A comprehensive echocardiographic examination should always include information on transcatheter heart valve (THV) function and should immediately recognize possible prosthesis dysfunction. Moreover, aging is associated with altered left ventricle (LV) diastolic filling and LV hypertrophy. Consequently, the elderly status of TAVI patients, along with additional comorbidities, might negatively affect LV structural and functional recovery after the procedure. Therefore, a complete evaluation of TAVI-induced changes in the LV and right ventricle (RV) function, as well as in the degree of mitral regurgitation (MR) severity, is essential for providing prognostic data and defining the correct therapeutic strategy.

2. Impact of TAVI on Cardiac Function and Structure

TTE is the most commonly used method for evaluating LV structural and functional changes during the pre- and post-procedural stages of TAVI. The availability of advanced echocardiographic techniques has allowed for a more thorough assessment of the impact of TAVI on the left heart chambers and concomitant heart valve disorders.

2.1. TAVI and Reverse Remodeling

LV pressure unloading following TAVI is a significant driver for LV mass (LVM) regression [2]. Moreover, because TAVI reduces LV wall stress and intra-cavitary pressures, an improvement in diastolic subendocardial perfusion resulting in enhanced LV longitudinal function can be observed shortly after the procedure [3]. Consequently, when the reason for LV dysfunction is the afterload mismatch rather than irreversible myocardial damage (due to fibrosis or coexisting coronary artery disease), functional improvement is anticipated almost immediately following the procedure. Reverse remodeling is a continuous process that occurs over time, with the largest LVM index (LVMi) regression occurring during the first year but still present at a three-year follow-up, with comparable effects in both sexes [4]. An early decrease in LV mass may be due to the regression of myocyte hypertrophy, whereas a late LV remodeling may be due to the regression of fibrosis [3]. Puls et al. demonstrated that myocardial fibrosis was associated with a higher extent of baseline pathological LV remodeling (higher LVMi and larger left ventricle) and with delayed but not inhibited reverse remodeling at a six-month follow-up [5]. Baseline LVMi, relative wall thickness, and moderate or severe aortic regurgitation (AR) at 30 days were independently associated with LVMi regression at one year, with AR being associated with a smaller LVMi decrease [4]. Inconsistent data exist regarding the relationship between factors linked to increased afterload (systolic blood pressure, patient-prosthesis mismatch, and high residual transvalvular gradient) and LVM regression: some authors support the hypothesis that these indexes have a negative correlation with reverse remodeling, whereas others do not find an association [4,6–8].

Reverse remodeling has been linked to a substantial impact on clinical outcomes. Lindman and her colleagues showed that in a population of patients with severe symptomatic aortic stenosis (AS) and severe LV hypertrophy, a greater decrease in LVM 30 days after TAVI was associated with lower hospitalization rates at one-year follow-up [9]; Chau and his colleagues described a 5–6% reduction in the risk of all-cause mortality, cardiovascular mortality, or re-hospitalization between 1 and 5 years for each 10% decrease in LVMi from baseline to one year. A greater LVMi regression was associated with a better quality of life at a two-year follow-up. Moreover, residual severe LV hypertrophy one-year post-TAVI was associated with a 71% increased risk of all-cause and cardiovascular mortality and an 89% increased risk of re-hospitalization [4].

In analogy with the LV, also the left atrium (LA) undergoes adaptive remodeling in AS. There is a functional connection between LV and LA: LV hypertrophy leads to LA decreased compliance and impaired relaxation with increased filling pressures; this, over time, induces LA dilation and progressive fibrosis [10]. Similar to the LV, structural and functional recovery occurs in the LA following the elimination of the aortic obstruction. This is reflected by decreased LA volume and increased peak atrial longitudinal strain (PALS) occurring relatively soon after TAVI, with the severity of AS being the key determinant of improvement [11]. In addition, LA speckle-tracking analysis has a predictive value: a PALS < 21% has been observed to predict major adverse cardiovascular events after TAVI [12].

2.2. Impact on LV Systolic Function

An early improvement in LV ejection fraction (EF) after TAVI occurs in approximately 50% of cases, but its prognostic significance remains controversial [13,14]. Several studies reported a lower risk of major adverse cardiac and cerebrovascular events and lower rates of one-year mortality, while other studies did not report an association between LV functional improvement and long-term outcomes at one-year follow-ups [13–16]. Greater LV mass, absence of hypertension, and a higher baseline transvalvular gradient are among the independent predictors of immediate post-procedural functional recovery [15]. Conversely, LV-EF $\leq$ 35%, a history of percutaneous coronary intervention, myocardial infarction, permanent pacemaker, and higher baseline EF are all predictors of lack of LV function

improvement [13,14,16]. Data on the relationship between baseline moderate or severe AR with EF improvement are inconsistent [13,15].

Global longitudinal strain (GLS) has been proven to be one of the most effective methods for assessing subclinical LV dysfunction. Indeed, GLS proved to detect a significant improvement in LV function shortly after the procedure, even in the absence of significant changes in EF and irrespective of the THV type implanted [3]. Moreover, the lower the baseline LV systolic function, the better the improvement of both EF and GLS [16–20]. Patients with preserved LV-EF at baseline do not experience a decline or significant change in LV systolic function [17,20].

The analysis of layer-specific strain has provided further insight into the evaluation of LV function in AS patients undergoing TAVI, showing a more prominent impairment of the endocardial longitudinal strain in the advanced phases of the disease, with the occurrence of symptoms [21]. After TAVI, a significant improvement in all the myocardial layers has been reported, especially in the subendocardial one [22]. However, Cimino et al. showed a significant improvement in endocardial longitudinal strain early after TAVI only in patients with concentric hypertrophic remodeling [23].

Recently, noninvasive measurement of LV myocardial work (MW) has proven to be a valuable method for estimating myocardial performance in AS patients undergoing TAVI [24]. This tool incorporates echocardiographic strain data, cardiac events timing (from aortic and mitral valve opening and closure), and estimation of LV pressure (derived from systolic blood pressure) in order to derive global work index (GWI), global constructive work (GCW), global wasted work (GWW) and global work efficiency (GWE). In the specific setting of AS patients, LV pressure estimation is obtained by adding the mean aortic transvalvular gradient to the aortic systolic pressure. Jain et al. found that myocardial work indices decreased significantly following TAVI as a direct result of the acute relief of the aortic obstruction and decreased afterload. However, global work indices remained abnormal after the procedure, suggesting an incomplete recovery of the LV function after TAVI [25] (Figure 1). Moreover, lower values of GCW and GWI at baseline in AS patients have been associated with advanced stages of myocardial disease and with a worse prognosis even after aortic valve replacement [24].

In evaluating functional recovery during the follow-up, the presence of post-procedural AR plays a key role, as it can negatively impact LV remodeling and mimic an acute AR. Poulin et al. evaluated patients with new post-TAVI mild AR or moderate or severe AR (pre-existing or new) in contrast to non-important post-TAVI AR. The authors reported the absence of LV GLS improvement or positive remodeling in the presence of significant AR [20]. Moreover, moderate or severe AR was associated with a lack of LV end-diastolic volume index decrease after TAVI and represented the only independent correlate of survival at one-year follow-up in the study population of Sato and colleagues [26].

2.3. Impact on LV Diastolic Function

The LV hypertrophic response to the increased afterload results in the development of LV diastolic dysfunction (LVDD), which worsens progressively as the pressure overload persists. In a large cohort of AS patients undergoing TAVI, LVDD was found in about 70% of cases; among these patients, advancing stages of LVDD at baseline were independent predictors of all-cause mortality at one-year follow-up, with grade III as the strongest one. Moreover, one-year all-cause mortality increased progressively with worsening LVDD, with a higher risk among patients with grade III LVDD, irrespective of LV function. This incremental risk emerged as early as 30 days after the procedure, being mainly driven by cardiovascular death. Advanced stages of LVDD were also associated with prolonged hospitalization. After TAVI, no change in LVDD grade was documented in up to 50% of patients [27]. Blair et al. showed that there was a significant post-procedural improvement in several, but not all, diastolic parameters, including E-wave velocity, lateral e-velocity, E/lateral e, and left atrium volume index; they also demonstrated that improvement in LVDD grade was not significantly associated with improved outcomes after TAVI [28].

Conversely, Muratori et al. documented no association between baseline LVDD and survival, despite an improvement in LVDD during follow-up [29]. Moreover, in the presence of LVDD, the LV could not be able to increase compliance in response to an acute onset of paravalvular leak (PVL), leading to high elevation in LV end-diastolic pressures. There are discordant findings relative to the effect of LVDD in association with PVL on the risk of death: two studies reported an additive effect on one-year mortality [30,31], contrary to the results reported by Asami et al. showing that PVL did not further increase the risk of one-year mortality, beyond the effect of LVDD [27].

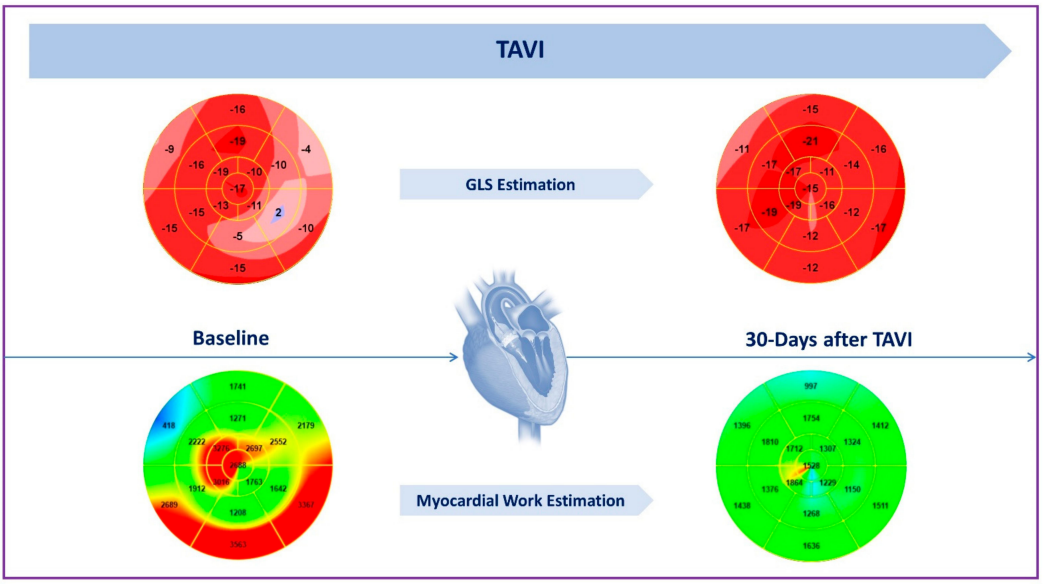

Figure 1. Global longitudinal strain (GLS), global work index (GWI), and global work efficiency (GWE) before and 30 days after TAVI.

2.4. Impact on Mitral Regurgitation

MR often coexists with aortic stenosis: in patients undergoing TAVI, moderate or severe concomitant MR has a prevalence ranging from 11.5% to 36.8%, and degenerative MR is the underlying etiology in up to two-thirds of patients [32]. The impact of baseline MR on outcomes after TAVI has not been formally evaluated since severe MR represented an exclusion criterion in most of the main TAVI trials [33]. However, baseline moderate-to-severe MR increased the rates of re-hospitalization after 30 days as well as the rates of all-cause mortality after 30 days and one-year follow-up compared to non-mild MR, irrespective of the MR etiology [34–37]. In addition, primary MR showed to be associated with increased 30-day, two-year, and three-year mortality rates compared with secondary MR [37,38]. The rate of MR regression ranges from 47 to 78% as described in previous studies [32,35,36]. Mitral regurgitation tends to improve more likely and with a higher degree of regression in patients receiving a balloon-expandable valve [39]; indeed, it has been suggested that the longer stent frame of self-expanding valves (SEV) may anatomically and functionally interfere with the anterior mitral leaflet, especially in cases of lower implantation [40]. This finding was not confirmed in a subsequent study by Bedogni et al. including a large Core Valve cohort [41]. Furthermore, SEV implantation is associated with a higher incidence of PVL, left bundle-branch block, and pacemaker implantation that could lead to volume overload and adverse effects on LV remodeling, thus contributing to a reduced likelihood of MR improvement [39]. Furthermore, there are conflicting data on

the impact of residual MR on outcomes after TAVI, with some but not all studies reporting a positive relationship between improved MR and higher survival rates [35,36,42–44]. Different mechanisms of post-procedural MR regression have been reported, mainly related to the hemodynamic changes occurring after the relief of the aortic obstruction: the reduced LV afterload decreases the trans-mitral pressure gradient. Consequently, reduced driving force results in MR grading improvement. Conversely, in the case of functional MR, the reduced LV-LA pressure gradient could sometimes lead to the persistence of MR due to a reduction in mitral valve closing forces [34]. On the other hand, reverse remodeling plays a role in functional MR improvement by reducing LV end-diastolic volumes and mitral valve tethering forces [45]. Mitral-aortic curtain compression, secondary to prosthetic valve deployment, has been proposed as an additional mechanism by which TAVI could impact mitral regurgitation severity [46,47]. Above all, besides the understanding of MR regression mechanisms, identifying clinical and echocardiographic predictors of MR improvement or MR persistence after TAVI is a matter of interest and this evaluation plays a key role in the pre-procedural phase [27,29,31,32,35,37,43,48] (Table 1). The identification of patients with the lowest or the highest probability of MR reduction is essential for defining the best management strategy and selecting the population that might more likely benefit from double-valve interventions [42]. Currently, a recent approach is to first perform TAVI, and, then, in the presence of suitable anatomical features, staged mitral percutaneous procedures can be scheduled for patients without significant MR regression [42]. In this context, MR re-assessment will represent one of the most critical steps of the echocardiographic follow-up program. Severity assessment should be performed by integrating different echocardiographic methods, with quantitative measurements always required in clinical practice.

Table 1. Suggested predictors of MR improvement and MR persistence after TAVI.

Factors Predicting MR Improvement	Factors Predicting MR Persistence or Worsening	
Functional etiology	Organic etiology	PPM
LV dilatation	Baseline severe MR	Use of SEV
Low ejection fraction	Permanent AF	Deep valve implantation
Coronary artery disease	Pulmonary hypertension	Calcified mitral valve disease
High transvalvular aortic gradient	Moderate or severe PVL	Mitral annular diameter > 35.5 mm

AF: atrial fibrillation; LV: left ventricle; MR: mitral regurgitation; PPM: patient-prosthesis mismatch; PVL: paravalvular leak; SEV: self-expandable valves.

3. TAVI and Right Heart

Cardiac damage in severe AS is not limited to the aortic valve and LV but is a systemic disease characterized by a significant alteration of the right heart as a result of ventricular interdependence. Severe AS is associated with chronic pressure overload of the LV, which elevates LA pressure, which is conveyed through the pulmonary vasculature and results in remodeling and dysfunction of the right heart [49,50]. This pathophysiological phenomenon presents with clinical and echocardiographic markers including pulmonary hypertension (PH), tricuspid regurgitation (TR), and right ventricular systolic dysfunction (RVSD) with a prevalence estimated to be about 30%, 20%, and 25%, respectively [51–53]. Their presence at baseline has been shown to have a negative prognostic impact on patients with AS undergoing TAVI with poor outcomes and more than a two-fold increased risk of cardiovascular death one year after TAVI, with a gradient of risk according to the recovery of RV dysfunction [49,54–57].

3.1. Impact on Right Ventricle Function

RV function has been evaluated using several parameters. Among them, the most used and clinically validated are tricuspid annular plane systolic excursion (TAPSE), tissue Doppler-derived tricuspid lateral annular systolic velocity (S′), percent RV fractional area

change (FAC) and RV-EF [58,59]. According to current guidelines, RVSD is defined as at least one of the following: TAPSE < 17 mm, S′ < 9.5 cm/s, and RV FAC < 35% [60,61]. All these echocardiographic parameters have been shown to predict adverse outcomes and one-year mortality after TAVI [56].

A significant improvement in RV function has been described as early as 24 h after TAVI [62] and confirmed at mid-term follow-up with the increase in TAPSE and FAC values [63].

In a population of 144 patients undergoing TAVI, Leclercq et al. showed that, at six-month follow-up, at least one RVSD parameter (including TAPSE, S′, and FAC) significantly improved in 63.4% of patients, whereas a completely recovered normal RV function (with no TR) was achieved in 24.5% of patients [64]. RV recovery after TAVI seems to be closely related to the baseline RV systolic function, with no changes in the majority of patients with normal RV parameters at baseline, whereas in those with RVSD before TAVI, 50% experienced recovery of RV function during follow-up, showing better outcomes than those with persistent RVSD [57]. Similarly, an analysis of 226 patients undergoing TAVI with RVSD at baseline revealed that only 26% of patients with severe RVSD (defined as TAPSE < 10 mm) experienced an improvement in RV function, whereas patients with moderate RVSD (TAPSE between 10 and 16 mm) experienced an improvement more frequently (41%). In addition, this improvement is more likely to occur in the absence of atrial fibrillation, severe PH, or severe renal failure. Despite this, the improvement in RV function does not appear to be associated with improved survival [65]. Another essential issue is whether the RV function changes differently after TAVI vs. surgical aortic valve replacement (SAVR). A recent meta-analysis indicated that TAPSE and S′ were unchanged post-TAVI but decreased by 12 months following SAVR. Furthermore, both post-procedure TAPSE and △TAPSE were considerably better in the transfemoral-TAVI group compared to the SAVR group [54]. These data support the hypothesis that TAVI improves RV function and may be preferred to SAVR in patients with baseline RVSD. Hence, the RV function should be included in risk-scoring algorithms for patient selection.

3.2. Impact on Tricuspid Regurgitation and Pulmonary Hypertension

Echocardiography is the preferred tool for TR grading and PH evaluation [59,66,67]. In the majority of TAVI patients, TR is functional and the result of right-sided chamber remodeling (dilation, hypertrophy, and dysfunction). PH, a common finding in this patient population, may also contribute to worsening TR and differentiating adaptive RV remodeling with poor leaflet coaptation from advanced hemodynamic stress burdens that are secondary to long-standing AS. In the majority of patients undergoing TAVI, the suppression of pressure overload by TAVI reduces LV filling pressures in conjunction with a decrease in left atrial volume, pulmonary artery systolic pressure (PASP), and TR grading. TR evolution after TAVI is highly variable. Barbanti et al. showed that at 30 days after TAVI, TR response was unchanged in most of the patients (68%), while 15% experienced TR improvement and 17% had TR worsening, including 8% without significant TR before TAVI [52].

In the PARTNER II trial cohort B, among one-year survivors with nonsignificant TR at baseline, 19% had progression to significant TR [55]. Muraishi et al. showed a TR worsening from baseline mild or less TR to a moderate or severe grade in 87 patients (5.4%) with 3 independent predictors of TR progression: atrial fibrillation, transaortic mean pressure gradient < 40 mmHg on pre-TAVI TTE, and PASP > 40 mmHg [68].

The impact of TAVI on PH is another important aspect. In many AS patients, the pulmonary vasculature undergoes remodeling because of chronic pulmonary venous congestion; hence, PH is likely irreversible and persists following TAVI. Indeed, a significant decrease in PASP > 15 mmHg within one month of TAVI is observed in only a minority of patients (up to 35%) and more commonly in those without atrial fibrillation, severely depressed LV-EF, and severe MR [69]. On the other hand, a multicenter study showed significant changes in PASP after TAVI. Of 617 patients enrolled, 16% of patients without PH at baseline, PASP remained unchanged. In the remaining 84% of patients, a reversible

PH was observed in 46%, with a change of PASP category of >1, from severe to mild-to-moderate or normal. In this cohort, LV-EF > 40%, baseline PASP > 46 mmHg, absence of moderate-to-severe TR, and logistic EuroSCORE < 25% were independent predictors of PASP reduction at discharge. Furthermore, the severity of PH at baseline does not predict post-procedural early or late mortality and therefore should not be considered a contraindication for TAVI [70].

Along the same line, Avvedimento et al. found a substantial decrease in PASP 30 days after TAVI [63]. A similar finding was reported from a two-center study: in this cohort, TAVI resulted in a significant and sustained reduction in PASP in the majority of survivors at follow-up after three months, which translated into a survival benefit compared to patients with persisting or new onset of severe PH [71].

In conclusion, the right heart, frequently described as the forgotten side of the heart, plays a key role in prognosis after TAVI, and its echocardiographic evaluation, in terms of RVSD, PH, and TR should be considered to stratify patients prior to TAVI and to evaluate cardiac damage evolution post-TAVI.

4. Endocarditis

Prosthetic valve endocarditis (PVE) is a rare but extremely serious complication that occurs in 0.3–2.3% of TAVI patients [72]. In the VARC-2 consensus document, PVE is defined as any of the following: fulfillment of the Duke criteria, evidence of abscess/paravalvular leak/pus/vegetation on reoperation or during autopsy [73,74].

Echocardiography plays a key role in PVE diagnosis, and it should be performed if PVE is suspected [74]. Bacterial proliferation can cause valve dehiscence, identified with TTE as PVL, with or without the rocking motion of the prosthesis [75]. Other echocardiographic findings included in Duke's major criteria to diagnose endocarditis are vegetation, abscess, and pseudoaneurysm [74]. Endocarditis may also cause endocardium perforation, and consequently the communication of two cavities known as fistula, with color Doppler flow detected by TTE. If none of these findings is shown, TTE and/or transesophageal echocardiography (TEE) should be executed within five-seven days if clinical suspicion of endocarditis is high. Nonetheless, even in the case of TTE positivity or when it is not diagnostic, TEE should be performed to obtain a better characterization of the lesions and to exclude local complications [75]. The role of echocardiography is pivotal during the diagnostic phase as well as during follow-up. Uncomplicated PVE is conservatively managed and treated with medical targeted therapy; in this situation, TTE and/or TEE are performed to monitor vegetation dimensions, to rule out silent evolution, or in the case of clinical findings to suggest new complications (fever persistence, embolism, heart failure, etc.). Finally, at the end of medical therapy, TTE is repeated to assess valve morphology and function. Nonetheless, in the case of uncontrolled infection, refractory heart failure, and high embolic risk, patients should undergo surgical treatment. Noteworthy, intraoperative echocardiography is recommended in each of the aforementioned instances [75].

5. Thrombosis

Valve thrombosis is considered any thrombosis unrelated to infection, attached to or in close proximity to the valve that occludes part of the blood flow path, interfering with valve function or sufficiently large to warrant treatment [76]. It affects 0.6% of patients undergoing TAVI, particularly within the first year [77]. Various risk factors are involved in thrombus formation, including patient-related comorbidities (i.e., obesity, diabetes mellitus, chronic kidney disease) and valve implantation itself, which may cause endothelial damage and blood flow turbulences that represent predisposing factors for localized thrombogenesis. Clinical presentation of THV thrombosis is highly heterogeneous and includes patients with no symptoms, or conversely acute heart failure, embolic event, and most commonly progressive dyspnea [78]. Thus, echocardiography is the first step in assessing the presence of a thrombus. TTE should detect hypo-attenuated leaflet thickening (HALT) with relatively normal leaflet motion, HALT with reduced leaflet motion but

normal gradients, and clinical valve thrombosis with elevated trans-prosthetic gradients [1]. Thrombus is identified as a mobile and globular mass with a soft echo density (comparable to that of the myocardium) which can cause, besides the above-mentioned abnormalities, central regurgitation, anomalous trans-prosthetic flow detected by color Doppler as aliasing, effective orifice area reduction [79]. Noteworthy, thrombosis may occur at the same time as pannus formation, determined by fibroblast proliferation and extra-cellular matrix deposition as a response to valve implantation. It is essential to differentiate between thrombus and pannus to guide patient management. Differential diagnoses can be obtained by means of imaging, firstly by means of echocardiography. Pannus is identified by TTE as a small mass with a bright echo density, different from the bigger and soft thrombus, and it tends to be fixed. Finally, it is less involved in leaflet motion reduction than thrombus and it is not responsive to anticoagulation, given its fibrotic nature [80,81].

6. Strengths and Pitfalls of Echocardiography after TAVI

Echocardiography is the key imaging modality for the evaluation of THVs, but there are some relevant challenges to recognize. For example, peak aortic jet velocity is highly flow dependent. This may lead to a significant overestimation in the case of a high-flow state. Any error in aortic jet velocity will inevitably result in an even larger overestimation of the mean transaortic pressure gradient. PVL severity evaluation can also be challenging. Therefore, measurements should always be interpreted in the clinical context as part of an integrative approach. In patients with poor acoustic windows, new onset severe PVL and valve dysfunction, or contradicting parameters, the use of other imaging modalities may be reasonable.

As well as with post-procedural complications (PVL, valve dysfunction, endocarditis, and thrombosis), TTE also has high sensitivity in detecting intraprocedural complications (prosthesis dislocation and limited anterior mitral leaflet mobility).

TEE performed during transcatheter structural cardiac interventions may result in greater complications than those performed in the nonoperative setting. In a study including 1249 patients requiring TEE guidance during TAVI, an incidence of 0.9% of overall complications was observed (among those, the most frequent were gastrointestinal bleeding, dysphagia, and odynophagia). Absolute contraindications to TEE include esophageal stricture, diverticulum, tumor, and recent esophageal or gastric surgery. Relative contraindications include cervical spine disease, hiatal hernia, coagulopathy, prior chest radiation, and facial or airway trauma [82,83].

7. Conclusions

Echocardiography is pivotal in the assessment of prosthesis function as well as cardiac function changes after TAVI. In particular, LVMi and PALS are useful tools recently implemented in clinal practice that are able to detect reverse remodeling early after TAVI. Similarly, GLS and MW estimation represent valuable methods for detecting an early recovery of LV systolic function. Moreover, TTE allows us to reassess MR severity after TAVI and to define the best management for patients with significant MR and persistent symptoms. In addition, RSVD, PH, and TR measurements enable us to evaluate the right heart function after TAVI and to estimate the patients' prognoses. TEE is better than TTE at detecting endocarditis and valve thrombosis, two rare but potentially life-threatening complications. In conclusion, technical improvements and the implementation of new diagnostic tools have consolidated the main role of echocardiography in clinical outcomes evaluation after TAVI.

Author Contributions: Writing, D.A., R.M., D.S.C., M.I.M., A.M., C.I. and D.N.; conceptualization, F.S., M.A., A.L. and M.E.C.; supervision, C.A.M.S. and G.E.; review and editing, F.I., A.F. and R.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: All data underlying this article will be shared on reasonable request to the corresponding author.

Conflicts of Interest: Piccolo reports personal fees from Abbott Vascular, Biotronik, Terumo, Amgen, Boehringer Ingelheim, and Daiichi-Sankyo, outside the submitted work. Esposito reports personal fees from Abbott Vascular, Amgen, Boehringer Ingelheim, Edwards Lifesciences, Terumo, and Sanofi, outside the submitted work and research grants to the institution from Alvimedica, Boston Scientific, and Medtronic. The other authors have no conflicts of interest to declare.

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Review

Hemodynamic Performance of Transcatheter Aortic Valves: A Comprehensive Review

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Abstract: Transcatheter aortic valve implantation (TAVI) is a widely adopted treatment option for patients with severe aortic stenosis. Its popularity has grown significantly in recent years due to advancements in technology and imaging. As TAVI use is increasingly expanded to younger patients, the need for long-term assessment and durability becomes paramount. This review aims to provide an overview of the diagnostic tools to evaluate the hemodynamic performance of aortic prosthesis, with a special focus on the comparison between transcatheter and surgical aortic valves and between self-expandable and balloon-expandable valves. Moreover, the discussion will encompass how cardiovascular imaging can effectively detect long-term structural valve deterioration.

Keywords: hemodynamic; performance; TAVI; durability

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Citation: Angellotti, D.; Manzo, R.; Castiello, D.S.; Immobile Molaro, M.; Mariani, A.; Iapicca, C.; Nappa, D.; Simonetti, F.; Avvedimento, M.; Leone, A.; et al. Hemodynamic Performance of Transcatheter Aortic Valves: A Comprehensive Review. *Diagnostics* **2023**, *13*, 1731. https://doi.org/10.3390/diagnostics13101731

Academic Editor: Jan Poelaert

Received: 26 March 2023
Revised: 3 May 2023
Accepted: 10 May 2023
Published: 13 May 2023

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1. How to Assess THV Function

Since the introduction of transcatheter aortic valve implantation (TAVI), the long-term durability of transcatheter heart valves (THV) has been debated. Most surgical aortic valves (SAV) degenerate within 10–20 years [1], whereas the performance of THVs in the very long term is currently unknown. These concerns remain essential today because of the expansion of TAVI to low-risk and young patients with longer life expectancies [2].

After TAVI, transthoracic echocardiography (TTE) provides baseline parameters to be used as a benchmark for all the echocardiographic evaluations the patient will undergo during the follow-up [3]. A comprehensive approach to fully assess THV function integrates several valve morphology and hemodynamics parameters. It includes the use of multiple views with attention to determine the type of prosthesis, confirm the good valve leaflet morphology and mobility, and identify the presence of calcification or abnormal structures on the THV. Color Doppler evaluation discriminates physiologic from pathologic flows and between intra- and/or para-valvular leaks (PVL). Quantitative parameters of the THV function include transprosthetic flow velocity and pressure gradients, effective orifice area (EOA), and Doppler velocity index (DVI). The transvalvular gradients are measured with the use of the Bernoulli formula. The EOA should be calculated by the continuity equation method that requires the measurement of three variables: the left ventricle outflow tract (LVOT) diameter and the LVOT and transprosthetic flow velocities [4]. When assessing balloon-expandable valves (BEV), LVOT diameter and pulsed-wave Doppler should be obtained just apical to the proximal edge of the stent to avoid flow acceleration within the stented valve. This method provides more accurate measures by eliminating potential errors due to reverberations and acoustic shadowing in the case of in-stent measures. Even if not validated, the same method should be used for self-expanding valves (SEV). In both cases, in the presence of low implantation, with the stent protruding into the left ventricle

(LV) cavity, stroke volume could be obtained from LV volumes [3]. The DVI can be helpful when a reliable measure of the LVOT diameter cannot be obtained. This index is less dependent on valve size and is calculated as the ratio of the proximal peak flow velocity in the LVOT to the transprosthetic peak flow velocity [4].

2. Hemodynamic Performance of Transcatheter vs. Surgical Aortic Bioprosthesis

Bioprosthetic valves degenerate over time: durability is determined by several physical factors including valve design and transvalvular gradients and clinical factors. In the best scenario, a SAV can last 20 years but in the real world, many fail much earlier. The choice of SAV is a crucial determinant of successful replacement and postoperative outcomes [5]. In large sample size studies, with echocardiographic follow-up extending for two decades beyond surgery, the mean gradient was 20 mmHg for Perimount and 18 mmHg for Mitroflow pericardial aortic valves [6,7]. Aortic valve gradients showed early variability and a gradual late-rising phase. Higher early postoperative gradients were associated with an increased risk of future explant. Mean gradients varied according to valve size across time and remained almost stable at 20 years with a progression of 3.8%. The EOA showed an annualized reduction of 0.06 cm^2. Late deterioration is well described for SAV, which showed 10-year freedom from valvular failure in the range of 60% to 90%, with younger patients predisposed toward premature deterioration.

Unlike surgical valves, THVs expand to fulfill the annular space and offer better hemodynamics. Multiple lines of evidence suggest that, for a given annulus size as determined by echocardiography, better orifice areas may be achieved with THVs than SAVs. A five-year follow-up from pivotal trials investigating the first-generation TAVI devices showed good hemodynamic performance and low rates of valve reintervention. The randomized PARTNER 1 study documented significantly better valve areas and lower gradients with THV: data from 473 echocardiograms at five-year follow-ups of all patients enrolled in the trial with successful TAVI or surgical aortic valve replacement (SAVR) were analyzed: Douglas et al. report a very favorable hemodynamic profile with no significant valve deterioration during study follow-up, a clear demonstration of the excellent longitudinal durability of both types of prostheses over this time [8]. Hemodynamic data trends showed two phases in mean gradient and EOA after TAVI, suggesting early favorable changes in the first months with minimal longitudinal changes at five years. In the SAPIEN 3 observational study, 1077 patients assigned to receive TAVI were compared with those treated with SAVR in the PARTNER 2A trial. Mean transaortic gradients at 30 days did not differ between the two groups and remained low at a one-year follow-up (11.4 vs. 10.9 mmHg at 30 days and 11.4 vs. 11.5 mmHg at one year). The TAVI group mean gradient trend revealed small changes, including a 12.1 to 9.2 mmHg reduction in the first month post implantation with a slight increase to 10 mmHg thereafter [9]. Moreover, in high-risk patients from the PARTNER trial, TAVI showed to have less prosthesis-patient mismatch (PPM) than SAVR, a result that could impact long-term outcomes [10]. A recent analysis pooled data from the CoreValve US High-Risk Pivotal and SURTAVI trials and found a lower rate of structural valve deterioration (SVD) in patients undergoing TAVI vs. surgery at five years (TAVI 2.2% vs. surgery 4.38%) [11]. Sutureless aortic valve replacement is an alternative to conventional SAVR. A comparison between Perceval sutureless valves and THVs showed that the latter are associated with a better hemodynamic performance and lower trans-prosthetic mean gradients (13 ± 6 vs. 11 ± 4 mmHg, respectively) [12]. These results have been confirmed by Muneretto et al. in a multicenter study: lower gradients were observed in the TAVI group in comparison to both conventional and sutureless surgical valves (14 ± 7 vs. 22 ± 11 vs. 19 ± 12 mmHg, respectively) [13]. Even when compared with other sutureless devices such as 3F Enable Valves, TAVI showed a better hemodynamic performance with larger effective orifice areas indexed (1.0 ± 0.3 vs. 0.76 ± 0.22 cm^2/m^2) [14]. Better hemodynamics with TAVI was confirmed in patients with small aortic annulus [15]. Conversely, available data report a higher incidence of PVL post TAVI, compared to SAVR with sutureless valves [12–14,16].

3. Hemodynamic Performance of Transcatheter Aortic Bioprosthesis

As TAVI continues to improve due to increasing experience, patient selection, and technical improvements, device success predominantly depends on anatomic factors and implantation technique. As the procedure indications broaden to younger patients, long-term durability becomes increasingly essential. Relevant differences exist between types of SAV and THV; for both, the assessment of valve function is complicated by the lack of standardization in device sizing and measurements. A complete evaluation of prosthetic valve function by echocardiography requires an understanding of the construct and appearance of each device and the normal function of each type and size of implanted valve. A longitudinal echocardiographic follow-up is an essential tool for lifetime management through the assessment of valve function over the years. An analysis from the multicenter OBSERVANT registry reported a reduction of the mean pressure gradients of 40.7 mmHg and an increase in EOA of 1.1 cm^2 at one-year after TAVI [17]; these results remained stable over the three years of follow-up [18]. In another cohort of 1077 TAVI patients, a mean gradient of 10 mmHg was reported after the procedure. A slight increase to 12 mmHg after three years was observed, corresponding to an average annualized increase of 3.8%; the calculated EOA increased to 1.70 cm^2 after the procedure. There were reductions in the mean area at 12 months (1.5 cm^2) and 36 months (1.4 cm^2) representing an annualized decrease of 0.06 cm^2. In a recent multicenter registry including 1521 patients, the annualized increase in mean transprosthetic gradient post TAVI was 0.3 mmHg/year [19]. In the Canadian multicenter experience, 339 patients were followed for a mean follow-up of 45 months, and a similar trend was found: from 11.4 mmHg at discharge to 12.4 mmHg at three-year follow-up [20]. Similarly, Toggweiler et al. reported five-year outcomes of 88 patients undergoing TAVI: mean transprosthetic gradients increased, on average, by 0.27 mmHg/year [21]. In all the reports, the common factor always associated with increased transvalvular gradient progression was small-size prosthesis (<23 mm).

4. Balloon- vs. Self-Expandable THV

As with SAVs, the durability of all THVs could not be equivalent for all valve types. Two devices have been considered the leading characters in TAVI since the first years of use: BEV and SEV. The position of functioning leaflets is intra-annular for BEV and may be supra- or intra- annular for SEV. Despite the differences in stent design, for expansion mode and leaflet position, which affect hemodynamic performance and EOA, both device types have been refined uninterruptedly to improve deliverability and decrease complications. Many observational, randomized studies, and meta-analyses compared BEV and SEV, showing larger EOAs and lower mean gradients in favor of SEV. In the multicenter randomized CHOICE trial, investigators compared the early generation of SEV and BEV. Echocardiographic outcomes at five years showed that the mean pressure gradient was two-fold higher in the BEV group compared with the SEV one (12 vs. 6.9 mmHg). In contrast, EOA was significantly smaller (1.6 vs. 1.9 cm^2) [22]. The results of the SCOPE I trial indicated that the SEV Acurate neo valve did not meet the criteria for noninferiority compared with the BEV Sapien 3 valve among intermediate to high surgical risk patients undergoing transfemoral TAVI, despite a lower mean gradient (8 vs. 12 mmHg) and a larger EOA at three years follow-up [23]. In the SOLVE-TAVI trial, the SEV Evolut R slightly outperformed BEV Edwards Sapien S3 in terms of hemodynamic performance (mean gradient $\geq$ 20 mmHg at one month: 2.0% vs. 3.3% and mean gradient 6 vs. 10 mmHg at one year) with equivalent clinical outcomes [24]. More recently, in the FRANCE-TAVI registry, the most extensive observational study comparing SEV and BEV in 7820 patients, the mean transprosthetic gradient and rate of patients with a mean gradient > 20 mmHg were higher in patients receiving BEV [25].

Small annulus, defined as an annuli area <4.0 cm^2 or a perimeter < 72 mm, is a challenging anatomy associated with worse outcomes and higher mean gradients after TAVI. Data from the TAVI-SMALL registry, which focused on this set of patients, suggested that SEV seemed to slightly outperform BEV in terms of transvalvular gradients [26]. In a

multicenter, propensity score-matched study comparing hemodynamics and early clinical outcomes in 246 patients with the small aortic annulus, indexed EOA was significantly larger in SEV patients versus BEV at one-year follow-up with mean gradients of 9.3 vs. 14.0 mmHg [27]. Large annulus (area > 5.75 cm^2, perimeter > 85 mm) was once considered a contraindication for TAVI due to the potential risks of severe PVL and valve embolization. A retrospective analysis from a multicenter cohort of 7425 patients with large annuli showed that, at one year, both SEV and BEV had stable hemodynamic performance: low mean gradient (7.0 mmHg for SEV versus 9.0 mmHg for BEV) and similar valve areas. In another analysis among patients with large annuli, a small difference in mean gradient in favor of the SEV group was found [28]. Compared with tricuspid aortic stenosis (AS), bicuspid AS patients often have larger annular dimensions, a more extensive calcification burden, and an asymmetric orifice. An increased risk of significant PVL, device embolization, and annular rupture has been reported after TAVI. BEV performs better than SEV due to the greater radial force which allows more uniform expansion in asymmetric anatomy, resulting in a higher device success rate at the expense of worse hemodynamic performance. A significantly higher mean gradient has been reported for BEV (11.3 vs. 9.6 mmHg), although the proportion of patients with mean aortic valve (AV) gradient $\geq$ 20 mmHg was similar between groups [29,30]. The current TAVI technology involves tissue leaflets that are adapted but not specifically designed for the procedure. Benchtop analyses and flow simulation studies showed that prosthesis leaflets may face damage during crimping and deployment on nodular valve calcifications, potentially reducing valve durability. Consequently, while there is a competition to create lower profile valves through crimping, this approach is not without its problems related to damaging the tissue leaflets. To design future TAVI devices that can overcome these limitations, it is crucial to study the potential obstacles and underlying mechanisms that cause various TAVI failure modes [31].

5. Valve-in-Valve

An increased prevalence of valve deterioration requiring reintervention is expected due to the aging of the population previously treated with SAVR and the rising number of TAVI procedures. Although valve-in-valve (ViV)-TAVI is an attractive option to avoid reoperation in failed SAVs, it hides some pitfalls, particularly in small SAV. The risks of elevated post-procedural transvalvular gradients after ViV are more frequent in patients with small THV. In this setting, the initial implantation of the prosthesis with the best hemodynamic performance is crucial for an optimal outcome. The VIVID registry indicated that TAVI ViV in small THVs was associated with decreased survival. Elevated ($\geq$20 mmHg) post-procedural mean gradients were observed in 26.8% of patients. The authors reported a time to intervention for bioprosthetic valve failure of only nine years [32]. On the contrary, an assessment of longitudinal hemodynamics from the PARTNER trial showed that, at a median follow-up of three years, no significant hemodynamic changes were seen in this population [8]. Higher transvalvular gradients are more frequently seen in ViV for failed SAV than for failed THV. In a recent small randomized multicenter study that compared BEV and SEV for patients with failed small surgical valves, the mean echocardiographic gradient was significantly lower with SEV than with BEV (15 mmHg vs. 23 mmHg) [33]. Bioprosthetic valve fracture (BF) is a technique to reduce gradients in ViV-TAVI procedures by fracturing the sewing ring of the SAV with high-pressure non-compliant balloon inflation. In a small study to evaluate the outcome of bioprosthetic fracture, 81 cases of BF ViV-TAVI (BF group) were compared to 79 cases of ViV-TAVI without BF (control group). The mean transvalvular gradient decreased from 37 $\pm$ 13 mmHg to 10 $\pm$ 5 mmHg in the BF group and from 35 $\pm$ 16 mmHg to 15 $\pm$ 6 mmHg in the control group, with a significantly higher final gradient in the latter. In both groups, the mean gradient remained stable over time (BF group: 10 $\pm$ 5 mmHg at discharge, 12 $\pm$ 6 mmHg at follow-up; control group: 15 $\pm$ 6 at discharge, 18 $\pm$ 9 mmHg at follow-up) [34]. However, a mean gradient of such magnitude implied that many patients present with a mean gradient $\geq$ 20 mmHg, which could be considered a device failure. In these patients in particular the risk of reintervention

increased over time. Supra-annular positioning compared to intra-annular bioprostheses seemed to allow a larger effective orifice, resulting in severe PPM risk reduction and better hemodynamic outcomes. In this setting, ViV's success in reducing mean gradient and increasing the valve area of a degenerated surgical valve depends on a pre-, intra-, and post-procedural analysis of both SAV and THV.

Despite the high procedural success of ViV-TAVI, several concerns have been raised about coronary obstruction (CO) during the procedure. Compared to TAVI on the native valve, ViV-TAVI has a higher risk of CO (0.1% vs. 3.1%), especially in failed surgical prostheses. Indeed, the incidence of this complication is much higher in stentless and externally mounted leaflets valves (such as Mitroflow and Trifecta) [35,36]. In a recent study, Malvidini et al. showed the failure modalities of Trifecta valves: a total of 1228 patients received Trifecta prosthetic and among them, 44 patients (3.5%) underwent aortic valve reintervention. Trifecta failed due to the development of leaflets calcification, fibrofatty circumferential pannus, and leaflets tear or dehiscence. In particular, the occurrence of leaflets tears was the main mechanism leading to an early reintervention up to five years from the implantation [37]. Consequently, longitudinal echocardiographic follow-up after ViV is pivotal to assessing valve function and addressing long-term durability questions. The hemodynamic performance of THVs reported within the text is resumed in Figure 1.

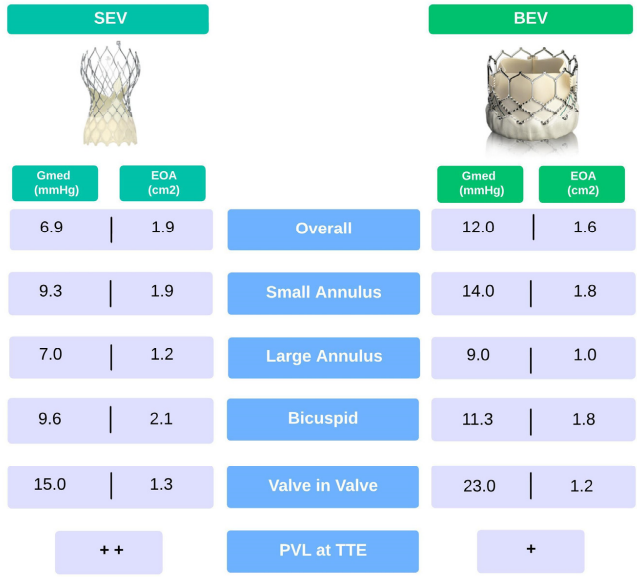

Figure 1. Hemodynamic performance of SEV and BEV in different settings. Small annulus: area < 4.0 cm^2 or perimeter < 72 mm; large annulus: area > 5.75 cm^2 or perimeter > 85 mm. BEV: balloon-expandable valves; EOA: effective orifice area; Gmed: mean transvalvular gradient; PVL: paravalvular leak; SEV: self-expanding valves; TTE: transthoracic echocardiography.

6. Structural Valve Deterioration

SVD is a type of bioprosthetic valve dysfunction (BVD), and it is defined as a deterioration of the leaflets or supporting structures resulting in the thickening, calcification, tearing, flailing or disruption of the prosthetic valve materials, eventually associated with valve hemodynamic dysfunction, manifested as stenosis or regurgitation of different grades [38]. This phenomenon is a gradual process and takes place over the years, with the most reliable pathophysiologic mechanism that hypothesizes an accelerated and progressive calcification of the prosthesis due to the interaction of free aldehyde groups coming from

glutaraldehyde, a compound used to mask antigens of the bioprosthesis, with circulating calcium ions [39–41]. Hence, it can be classified into three different stages that represent the progressive worsening of bioprosthetic valve function: stage 1 is defined as any evidence from computed tomography (CT) and/or TTE or transesophageal (TEE) of structural deterioration without any significant hemodynamic changes; stage 2 is defined as the presence of moderate stenosis and/or regurgitation evaluated with TTE; and stage 3 is defined as the presence of severe stenosis and/or regurgitation assessed with TTE [39,40]. However, for bioprosthetic valve with a high native mean transvalvular gradient, it should be considered an increase of at least 10 mmHg in the mean gradient and/or a mean gradient > 20 mmHg, as well as an increase of >1 grade of intraprosthetic regurgitation resulting in at least moderate aortic regurgitation (AR), to correctly diagnose stages 2 and 3. Thus, assessing EOA, maximal velocity, and transvalvular mean gradient must be assessed before hospital discharge or during the first 30 days after TAVI. This way, the patients control themselves and, through regular follow-up echocardiography, SVD could be easily identified. Another critical point to note is that follow-up intervals should be adapted to the severity of SVD, with more considerable intervals in lower stages and vice versa [30,38,40].

An additional critical definition encountered in the EAPCI consensus and VARC-3 paper is bioprosthetic valve failure (BVF) that integrates any BVD (SVD, non-structural valve disease, thrombosis, and endocarditis) with its clinical consequences. It should be considered as the main outcome of interest in studies assessing the long-term performance of TAVI and SAVR, thereby avoiding over-interpretation of valve-related outcomes in asymptomatic patients with no clinical impact. BVF can be classified into three stages, as follows: stage 1, any BVD with clinically expressive criteria (new-onset or worsening symptoms, LV dilatation/hypertrophy/dysfunction, or pulmonary hypertension) or irreversible stage 3 SVD; stage 2, aortic valve reintervention (i.e., valve-in-valve, paravalvular leak closure or SAVR); stage 3, valve-related death (any death caused by BVD). In addition, BVF could be further classified as definite (i.e., autopsy, reintervention, severe hemodynamic SVD) or probable (i.e., valve-related death), and early (up to 30 days) or late (>30 days) according to the timing of onset after valve implantation [38,40].

The cumulative incidence of SVD in patients undergoing TAVI has decreased over the years, reaching about 1–2% for severe SVD, thanks to the evolution of TAVI technology and to the improvement of the technical skills and knowledge of interventional cardiologists who perform the implant procedure [42–44].

In the literature, several patients- and prosthesis-related risk factors that can influence the onset of SVD are described. Younger age, female sex, hypertension, and pathologies involving calcium and phosphorus metabolism (i.e., end-stage renal disease or hyperparathyroidism) are among the most reported patient-related risk factors. Through lipid-mediated inflammation, cardiovascular risk factors such as diabetes mellitus, metabolic syndrome, and dyslipidemia could also favor SVD. Among prosthesis-related factors, the implantation of smaller (i.e., <26 mm diameter) or under-expanded devices, as well as the over-expansion mainly when balloon post-dilatation is performed, may result in different mechanical stresses, potentially facilitating SVD [39,41,45–48].

As abovementioned, echocardiography is considered the gold standard for assessing BVD and it allows for both morphologic and hemodynamic valvular assessment, making it a cornerstone in TAVI patients' follow-up. Multi-detector CT has a higher spatial resolution than echocardiography. Still, it is unable to assess valve hemodynamics and should not be systematically performed in the routine follow-up of patients with SAVR or TAVI unless valve thrombosis or pannus is suspected [38,39].

7. Paravalvular Regurgitation

Despite technological improvements, AR remains a common finding after TAVI [49]. It may consist of central and paravalvular regurgitation; the latter infrequently includes multiple small jets. BEVs are generally associated with less paravalvular regurgitation than SEV [50]. Studies have shown the feasibility of measuring AR in native valves and post

TAVI. Two-dimensional imaging and Doppler echocardiography are the cornerstone of PVL assessment of any valvular prosthesis and correlate very well with invasive hemodynamic data. It is paramount to use windows that avoid acoustic shadowing and image the regurgitant jets parallel to the insonation beam. In general, parasternal, apical, and subcostal windows are better for TTE, mid-esophageal 120 degrees, and deep transgastric for TEE [51]. The primary is the assessment of prosthesis position, stent, and leaflet morphology. In general, for the BEV platform, recommended position is with the ventricular side of the stent 2 to 4 mm below the aortic annulus; the position is slightly lower for the self-expanding valve system (4 to 6 mm for the first-generation system, 3 to 5 mm for the second generation self-expanding transcatheter aortic valve) [52]. It is essential to confirm that all the prosthetic cusps are moving well and that the valve stent has assumed a circular shape (using two- or three-dimensional views). Color Doppler enables evaluation of the circumferential extent of PVL, jet number, location, direction, and eccentricity. Since color Doppler is essential in localizing and assessing PVL severity, it is important to recognize that shadowing the prosthetic valve may affect the detection of paravalvular regurgitation by either TTE or TEE: TTE may not optimally display posterior paravalvular regurgitation, whereas TEE may not optimally display anteriorly located defects. The American Society of Echocardiography guidelines propose that for paravalvular jets, the proportion of the short-axis annular circumference occupied by the jet provides a semi-quantitative guide to severity: <10% of the circumference suggests mild, 10–20% suggests moderate, and >20% suggests severe PVL. However, this assumes continuity of the jet which may not be the case for transcatheter valves and, therefore, may overestimate the severity when there are multiple small jets with variable severity. This approach also does not consider that the radial extent of paravalvular jets may vary on the plane of interrogation and, in the case of transcatheter valves, may be very small. The circumferential extent of PVL is best not to be used alone but in combination with vena contracta width and vena contracta area and flow convergence. A large flow convergence in the aorta is indicative of a severe AR. Continuous wave Doppler (CWD) of the AR jet should also be routinely recorded but only utilized if a complete signal is obtained. Two parameters from CWD recordings have been used in the evaluation of AR: velocity waveform density and the deceleration rate (pressure half-time, PHT). These may have limited applicability in the TAVI population because the common occurrence of multiple PVL jets limits the utility of CWD spectral density from a single jet and PHT is highly heart rate dependent; nevertheless, a very dense velocity waveform recording may signal at least moderate AR. Quantitative parameters are also employed in determining PVL such as regurgitant volume, regurgitation fraction, and less often, effective regurgitant orifice area. The regurgitant volume may be estimated by calculating the difference between the left and right ventricle stroke volumes, providing that there is no significant pulmonary regurgitation. Secondary sign involving the diagnosis of PVL includes excessive diastolic flow reversal in the descending aorta (pulsed-wave Doppler from the suprasternal notch) and/or abdominal aorta (subcostal view). This latter is useful if new (relative to baseline) and holodiastolic, consistent with at least moderate AR. However, diastolic flow reversal as well as CWD parameters of jet density and pressure half-time lack specificity because of the influence of other hemodynamic parameters such as ventricular or aortic compliance. An in-depth description of the multiparametric assessment of PVL severity at TTE is reported in Figure 2. Lately, Yokoyama et al. demonstrated that patients with mild PVL, as well as known moderate or severe PVL, had a 1.4-fold increased risk of mortality five years after TAVI compared with those with none or trace PVL [53]. Accurately measuring this complication is an essential means; thus, an integrative multiwindow and multiparametric approach remains the best choice to assess PVL [54]. Previous studies tried to support a unifying grading scheme that included five classes for every quantitative, semi-quantitative, and qualitative parameter [55]. However, we reckon that this results in significant variability in grading PVL. Thus, we support considering the parameters proposed in the guidelines for the classification of PVL severity according to the three-class grading scheme. Prosthetic valve size and implantation depth play a key role in terms

of PVL and permanent pacemaker implantation incidence after TAVI [56]. Notably, a higher aortic anatomical implantation of the TAVI prosthesis leads to better hemodynamic performance both with BEV and SEV.

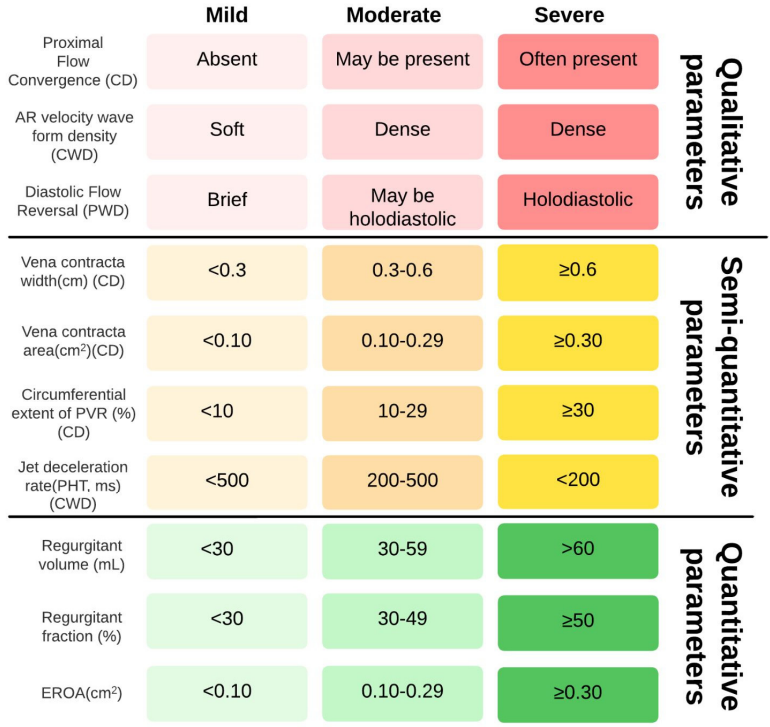

Figure 2. Multiparametric assessment of PVL severity at TTE. CD: color Doppler; CWD: continuous wave Doppler; EROA: effective regurgitant orifice area; PHT: pressure half-time; PVR: paravalvular regurgitation; PWD: pulsed wave Doppler.

In a recent study, Wendt et al. found no or mild PVL in 99.1% of patients with a modified higher aortic implantation of the Edwards Sapien 3. Despite the high implantation, with almost 80% of the device within the aorta, no valve embolization or dislodgement was observed [57]. Along the same line, Breitbart et al. reported better outcomes with higher SEV implantation. This study enrolled 104 patients undergoing computed tomography angiography post-TAVI with Evolut R: in patients with an implantation depth lower than 4 mm, a higher incidence of new-onset conduction disturbances was observed, while no influence on the PVL incidence and severity was reported [58].

8. Patient Prosthesis Mismatch

PPM occurs significantly less often after TAVI than SAVR, especially in patients with small aortic annuli, and impacts survival [59]. In addition, patients with PPM have less regression of LV hypertrophy after TAVI. The severity of PPM is graded using EOA indexed to body surface area (BSA) with absence defined as >0.85 cm^2/m^2, moderate as $\geq$0.65 and $\leq$0.85 cm^2/m^2, and severe as <0.65 cm^2/m^2. Although patients with BSA > 1.83 m^2 had a significantly lower incidence of PPM with SEV compared with BEV, there was no significant difference in patients with BSA $\leq$ 1.83 m^2 [60]. The PARTNER trial demonstrated that EOA and indexed EOA were significantly larger in TAVI at each follow-up time and that EOA

was a predictor of decreased mortality [61]. Hahn et al. showed significant differences in mean gradient and EOA between valve sizes for each iteration in BEV and SEV and presented a table of expected normal values [3]. The European Association of Cardiovascular Imaging guidelines suggest using an increased reduction of EOA > 25% to indicate probable stenosis [4]. The EOA is calculated as the ratio between Doppler stroke volume and aortic velocity time integral, and the cover index was determined as the ratio between the difference of prosthesis diameter and annular diameter, and prosthesis diameter. Left ventricular stroke volume is calculated by pairing the neo-LVOT diameter with the appropriate pulsed-wave spectral Doppler measurement of the velocity time integral assessed preferentially using the outer-to-outer border of the stented valve diameter and with the sample volume just apical to the proximal edge of the stent. Importantly, the methodology used by the echocardiography core lab for measuring the EOA for each valve type could be different. In the setting of low valve implantation, the outer-to-outer measurements could not be accurately assessed; thus, measurements are performed at the mid-stent level. Furthermore, if the image quality is poor, the stroke volume can be measured by the two-dimensional (2D) method, unless there is significant mitral regurgitation. Long-term echocardiographic follow-up provides integrative information about hemodynamic improvements that more frequently occur in patients undergoing TAVI, rather than in patients undergoing SAVR, with a slight increase in the LVOT diameter at one year in the self-expandable valves and of the EOA at five years post implantation [8,62].

9. Conclusions

Bioprosthetic valve deterioration recognition becomes fundamental as TAVI indication is shifting toward younger patients. At the longest follow-up available, THVs were found to be better than surgical prostheses in terms of hemodynamic performance and PPM incidence, while demonstrating comparable durability. Among THVs, SEV showed to have lower transprosthetic mean gradients and larger EOA compared to BEV, and this data is confirmed across almost all clinical settings. However, BEVs outperform SEVs in terms of PVL incidence and severity. Studies of bioprosthetic valve durability utilizing modern-era serial echocardiography assessments will be critical for the management of patients with an extended expected lifespan and for making comparative decisions among next-generation THV.

Author Contributions: Writing, D.A., R.M., D.S.C., M.I.M., A.M., C.I. and D.N.; conceptualization, F.S., M.A., A.L. and M.E.C.; supervision, C.A.M.S. and G.E.; review and editing, F.I., A.F. and R.P. All authors have read and agreed to the published version of the manuscript.

Funding: Dr. Leone is supported by a research grant provided by the CardioPath PhD program.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: All data underlying this article will be shared on reasonable request to the corresponding author.

Conflicts of Interest: Piccolo reports receiving personal fees from Abbott Vascular, Biotronik, Terumo, Amgen, Boehringer Ingelheim, and Daiichi-Sankyo, outside the submitted work. Esposito reports receiving personal fees from Abbott Vascular, Amgen, Boehringer Ingelheim, Edwards Lifesciences, Terumo, and Sanofi, outside the submitted work, and research grants to the institution from Alvimedica, Boston Scientific, and Medtronic. The other authors have no conflicts of interest to declare.

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PART III

TAVI in COVID-19 pandemic

Acta Cardiologica

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/tacd20

Impact of COVID-19 pandemic on timing and early clinical outcomes of transcatheter aortic valve implantation

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To cite this article: Domenico Angellotti, Rachele Manzo, Domenico Simone Castiello, Raffaele Piccolo, Marisa Avvedimento, Attilio Leone, Federica Ilardi, Andrea Mariani, Cristina Iapicca, Luigi Di Serafino, Plinio Cirillo, Anna Franzone & Giovanni Esposito (2022): Impact of COVID-19 pandemic on timing and early clinical outcomes of transcatheter aortic valve implantation, Acta Cardiologica, DOI: 10.1080/00015385.2022.2119660

To link to this article: https://doi.org/10.1080/00015385.2022.2119660

Published online: 05 Oct 2022.

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ACTA CARDIOLOGICA
https://doi.org/10.1080/00015385.2022.2119660

ORIGINAL SCIENTIFIC PAPER

Impact of COVID-19 pandemic on timing and early clinical outcomes of transcatheter aortic valve implantation

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ABSTRACT

Background: We sought to investigate the applicability and outcomes of a novel system to manage patients requiring transcatheter aortic valve implantation (TAVI) at a tertiary level hospital during the coronavirus disease-2019 (COVID-19) pandemic.

Methods: To analyse the impact of hospitalisation pathways during the pandemic on clinical outcomes of TAVI patients, the study population was divided into two groups (pre-pandemic and pandemic groups) and all perioperative/follow-up data were compared. The primary endpoint was all-cause mortality at 30 days; secondary endpoints included procedural success and short-term complications.

Results: A total of 315 patients received TAVI during the study period. Pandemic group ($n = 77$) showed a more complex baseline clinical profile (NYHA class III-IV, 70.1% vs. 56.3%; $p = 0.03$). The overall time to procedure was significantly longer during pandemic (56.9 ± 68.3 vs.37.7 ± 25.4; $p = 0.004$) while intensive care unit stay was shorter (2.2 ± 1.4 vs. 3.7 ± 3.9, $p < 0.05$). Hospitalisation length was similar in both groups as well as all-cause mortality rate and the incidence of major periprocedural complications. No case of infection by COVID-19 was reported among patients during the hospital stay.

Conclusions: Comparative analysis of early clinical outcomes showed that COVID-19 pandemic did not affect the safety and effectiveness of TAVI as similar rates of procedural complications and all-cause mortality were reported than before February 2020. Despite the increased time lag between diagnosis and procedure and a more complex clinical profile of patients at baseline, the revised pathway of hospitalisation allowed to resume inpatient procedures while not affecting patients' and healthcare workers' safety.

ARTICLE HISTORY
Received 29 November 2021
Revised 22 August 2022
Accepted 26 August 2022

KEYWORDS
TAVI; COVID-19 pandemic; management; outcomes

Introduction

The coronavirus disease-2019 (COVID-19) pandemic has challenged the management of patients with severe symptomatic aortic stenosis. In this population, delayed intervention is associated with an increased risk of cardiac events [1]. At the same time, age and comorbidities make these patients particularly vulnerable to complicated and fatal forms of COVID-19 [2]. In the pandemic peak, elective procedures such as transcatheter aortic valve implantation (TAVI) have been deferred or performed only in urgent cases with the aim to save and divert healthcare resources [3]. In the subsequent months and prior to the implementation of vaccines, guidelines for optimal management of patients requiring structural heart interventions were proposed by major cardiac societies [4]. However, the applicability of such recommendations in practice has not been adequately investigated and the impact on clinical outcomes of the re-organisation of pathways for the management of patients requiring TAVI is only partially explored [5]. The present study was designed to evaluate timing of intervention and early clinical outcomes of TAVI at a tertiary care hospital in Italy that adapted the system for triaging patients during the COVID-19 outbreak with the aim to treat patients with severe symptoms while minimising their exposure to the infection.

Methods

Study design and participants

This is a single-centre retrospective study including 315 patients with symptomatic severe aortic stenosis

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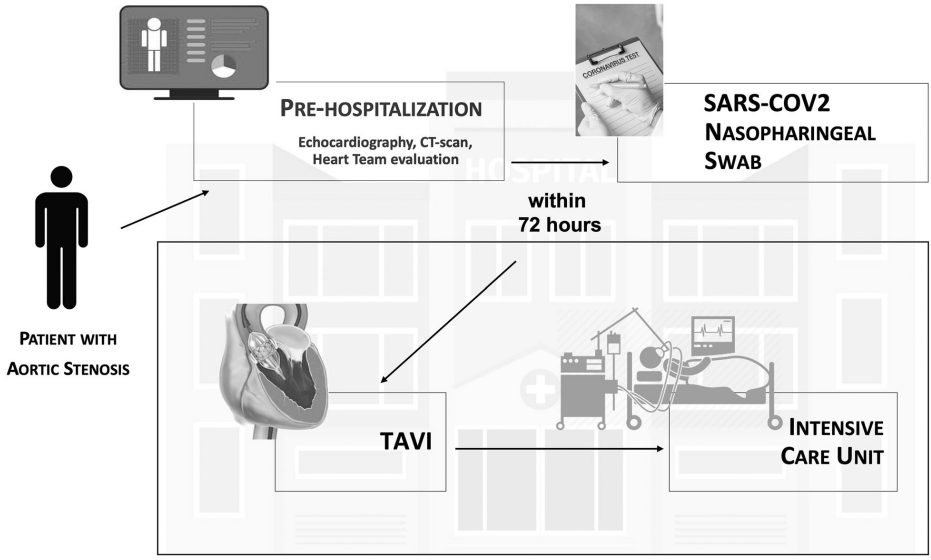

Figure 1. Readapted system for the management of TAVI patients during COVID-19 pandemic.

receiving TAVI between April 2017 and June 2021 at our centre and included in the prospective EffecTAVI Registry.

Based on the date in which the World Health Organisation declared the COVID-19 as a Pandemic Disease (30th January 2020), overall population was divided into two groups: (1) Pre-pandemic group: patients receiving TAVI from 1st April 2017 to 30th January 2020; and (2) Pandemic group: patients receiving TAVI from 30th January 2020 to 30th June 2021.

All clinical and periprocedural data, as well as any clinical event that occurred during the hospital stay and at the follow-up, were recorded in a dedicated online database (Redcap™ at https://www.redcap.unina.it/redcap/). The study complies with the principles of the Declaration of Helsinki and of Good Clinical Practice; the registry was approved by the local Ethics Committee and all patients provided written informed consent to participate.

Patient pathway to TAVI

Prior to the pandemic, patients with severe symptomatic aortic stenosis were screened for TAVI during hospitalisation. Admission to regular ward to undergo was scheduled to perform echocardiography, coronary angiography and gated CT scan. Patient was then discharged and re-admitted for TAVI, according to the waiting list, after multidisciplinary evaluation. Because of the pandemic, the system for managing patients referred for TAVI, at our institution, was adapted, as follows (Figure 1): after telephone screening for COVID-19 symptoms and/or direct contact with confirmed cases, they were admitted to the hospital for one day in which clinical visit, laboratory evaluation, transthoracic echocardiography, and gated CT scan were performed. Active infection by COVID-19 testing with polymerase chain reaction (PCR) was also investigated. Interventional and clinical cardiologists evaluated screening exams and planned the procedural aspects of the intervention within 24 h. Patients with active COIVD-19 infection were temporary suspended from the waiting list and reassessed after full recovery. Patients tested negative for COVID-19 were hospitalised within 72 h and received TAVI on the next day. Access of patients with severe symptoms and/or worsening clinical conditions was prioritised. This pathway was implemented at the end of the first lockdown period. Procedures were performed under conscious sedation and following institutional protocol and according to international standards. Access site, type of valve prosthesis and other procedural details were left at operator's discretion. After the intervention, patients were transferred to the intensive care unit for 24–48 h and discharged from standard ward at the

Table 1. Clinical characteristics at baseline.

	Overall population ($n = 315$)	Pre-pandemic group ($n = 238$)	Pandemic group ($n = 77$)	% Difference (95% CI)	*p*-Value
Female sex, *n* (%)	195 (61.9%)	146 (61.3%)	49 (63.6%)	2.3% (−10.3%; 14.9%)	0.79
Age, m ± SD	79.7 ± 6.3	79.7 ± 6.2	79.7 ± 6.5	−0.0 (−1.7; 1.6)	0.96
Dyspnoea, *n* (%)	246 (78.1%)	189 (79.4%)	57 (74.0%)	−5.4% (−16.1%; 5.3%)	0.34
Angina, *n* (%)	71 (22.5%)	59 (24.8%)	12 (15.6%)	−9.2% (−20.0%; 1.6%)	0.11
Syncope, *n* (%)	42 (13.3%)	29 (12.2%)	13 (16.9%)	4.7% (−4.1%; 13.5%)	0.33
Heart failure, *n* (%)	92 (29.3%)	65 (27.4%)	27 (35.1%)	7.6% (−4.1%; 19.4%)	0.25
NYHA III–IV Class, *n* (%)	188 (59.7%)	134 (56.3%)	54 (70.1%)	13.8% (1.2%; 26.4%)	0.03
Hypertension, *n* (%)	277 (87.9%)	207 (87.0%)	70 (90.9%)	3.9% (−4.5%; 12.4%)	0.42
Dyslipidemia, *n* (%)	205 (65.1%)	145 (60.9%)	60 (77.9%)	17.0% (4.8%; 29.2%)	0.006
Diabetes, *n* (%)	108 (34.3%)	80 (33.6%)	28 (36.4%)	2.8% (−9.5%; 15.0%)	0.68
Coronary artery disease, *n* (%)	131 (41.6%)	102 (42.9%)	29 (37.7%)	−5.2% (−17.9%; 7.5%)	0.50
Previous MI, *n* (%)	56 (17.8%)	38 (16.0%)	18 (23.4%)	7.4% (−2.4%; 17.3%)	0.17
Previous CABG, *n* (%)	28 (8.9%)	23 (9.7%)	5 (6.5%)	−3.2% (−10.5%; 4.2%)	0.49
Previous valvular surgery, *n* (%)	15 (4.8%)	14 (5.9%)	1 (1.3%)	−4.6% (−10.1%; 0.9%)	0.13
Peripheral artery disease, *n* (%)	150 (47.6%)	124 (52.1%)	26 (33.8 %)	−18.3% (−31.1%; −5.6%)	0.006
COPD, *n* (%)	94 (29.8%)	66 (27.7%)	28 (36.4%)	8.6% (−3.2%; 20.4%)	0.15
CKD, *n* (%)	88 (27.9%)	63 (26.5%)	25 (32.5%)	6.0% (−5.6%; 17.6%)	0.31
Previous cerebrovascular events, *n* (%)	33 (10.5%)	28 (11.8%)	5 (6.5%)	−5.3% (−13.2%; 2.6%)	0.28
Previous malignancy, *n* (%)	58 (18.4%)	47 (19.7%)	11 (14.3%)	−5.5% (−15.5%; 4.5%)	0.31
Liver disease, *n* (%)	22 (7.0%)	16 (6.7%)	6 (7.8%)	1.1% (−5.5%; 7.7%)	0.80
Sinusal rythm, *n* (%)	239 (75.9%)	178 (74.8%)	61 (79.2%)	4.4% (−6.6%; 15.5%)	0.54
Atrial fibrillation, *n* (%)	74 (23.5%)	58 (24.4%)	16 (20.8%)	−3.6% (−14.6%; 7.4%)	0.64
STS-PROM score (%), m ± SD	5.0 ± 3.2	5.0 ± 3.0	5.0 ± 3.6	0.0 (−0.8; 0.8)	0.94
BMI (kg/m^2), m ± SD	27.6 ± 5.8	27.7 ± 6.0	27.4 ± 5.3	−0.3 (−1.8; 1.2)	0.71
Systolic BP (mmHg), m ± SD	131.9 ± 19.3	131.0 ± 19.6	134.7 ± 18.4	3.7 (−1.3; 8.7)	0.14
Diastolic BP (mmHg), m ± SD	71.4 ± 10.8	71.1 ± 10.9	72.5 ± 10.6	1.4 (−1.4; 4.2)	0.32
Heart rate (bpm), m ± SD	72.2 ± 12.7	72.1 ± 12.9	72.3 ± 12.2	0.2 (−3.1; 3.6)	0.89
Haemoglobin (g/dL), m ± SD	11.8 ± 1.7	11.8 ± 1.7	11.8 ± 1.7	0.0 (−0.4; 0.5)	0.92
Creatinine (mg/dL), m ± SD	1.2 ± 0.9	1.2 ± 0.9	1.2 ± 1.0	0.0 (−0.2; 0.3)	0.74
Peak gradient (mmHg), m ± SD	78.7 ± 24.7	79.7 ± 24.9	75.5 ± 23.9	−4.3 (−10.8; 2.2)	0.19
Mean gradient (mmHg), m ± SD	48.6 ± 16.4	49.4 ± 16.3	46.4 ± 16.4	−2.9 (−7.2; 1.3)	0.17
AVAi (cm^2/m^2), m ± SD	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.2	0.0 (−0.0; 0.1)	0.16
Left ventricle EF (%), m ± SD	54.5 ± 11.2	54.4 ± 11.4	54.5 ± 10.9	0.1 (−2.8; 3.0)	0.95
SPAP (mmHg), m ± SD	44.0 ± 11.8	44.7 ± 11.9	41.6 ± 11.4	0.0 (−5.8; 0.49)	0.09
BNP (pg/mL), m ± SD	523.1 ± 103.5	436.7 ± 121.2	598.1 ± 83.3	0.0 (−15.6; 8.0)	0.17

AVAi: aortic valve area indexed; BMI: body mass index; BP: blood pressure; CABG: coronary artery bypass grafting; CI: confidence intervals; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; EF: ejection fraction; MI: myocardial infarction; NYHA: New York Heart Association functional class; SPAP: systolic pulmonary arterial pressure; BNP: brain-type natriuretic peptide.

completion of clinical monitoring. Outpatient control visit was performed at 30 days after the procedure.

Outcomes

The primary endpoint of the study was all-cause mortality at 30 days. Secondary endpoints included procedural success, acute kidney injury, vascular complications, permanent pacemaker implantation, and any rehospitalisation (including all-cause and cardiac-related rehospitalisation). Events were adjudicated according to the standardised Valve Academic Research Consortium-2 (VARC-2) criteria. We also evaluated the number of days from diagnosis to procedure (time to procedure), the length of total hospitalisation and intensive care unit stay.

Statistical analysis

Continuous variables were reported as mean ± standard deviation and compared with the use of the Student's *t*-test or the Wilcoxon rank-sum test. Categorical variables were reported as number and percentage and compared with the use of Fisher's exact test or the Wilcoxon rank-sum test. Each variable and outcome were analysed with the *p*-value test and a value <0.05 was considered statistically significant. Statistical analyses were performed with Stata software version 14.2 (StataCorp, College Station, Texas, USA).

Results

Clinical characteristics at baseline

Demographic and clinical characteristics at baseline are shown in Table 1. Pre-pandemic group included 238 patients whereas 77 patients were in the pandemic group. No relevant differences were found between the two groups in terms of mean age, sex and main cardiac risk factors. Patients in the pandemic group presented more often with dyspnoea and a higher prevalence of NYHA functional class III or IV. Laboratory values as well as echocardiographic measurements at baseline were similar in both groups.

Table 2. Procedural characteristics.

	Overall population ($n = 315$)	Pre-pandemic group ($n = 238$)	Pandemic group ($n = 77$)	% Difference (95% CI)	p-Value
Elective procedure, *n* (%)	256 (81.3%)	199 (83.6%)	57 (74.0%)	−9.6% (−19.6%; 0.5%)	0.066
Femoral access, *n* (%)	307 (97.5%)	231 (97.1%)	76 (98.7%)	1.6% (−2.4%; 5.7%)	0.69
Balloon valvuloplasty, *n* (%)	108 (34.5%)	84 (35.4%)	24 (31.6%)	−3.9% (−16.2%; 8.5%)	0.58
Balloon expandable valve, *n* (%)	72 (22.9%)	49 (20.6%)	23 (29.9%)	9.3% (−1.5%; 20.1%)	0.12
Self-expanding valve, *n* (%)	243 (77.1%)	189 (79.4%)	54 (70.1%)	−9.3% (−20.1%; 1.5%)	0.12
Post-dilation, *n* (%)	35 (11.1%)	25 (10.5%)	10 (13.0%)	2.5% (−5.6%; 10.6%)	0.54
Concomitant PCI, *n* (%)	28 (8.9%)	22 (9.2%)	6 (7.9%)	−1.3% (−8.8%; 6.1%)	0.82
Moderate-severe para-valvular leak, *n* (%)	9 (2.9%)	9 (3.8%)	0 (0.0%)	−3.8% (−8.1%; 0.5%)	0.12
Procedural success, *n* (%)	297 (97.1%)	233 (97.9%)	64 (94.1%)	−3.8% (−8.3%; 0.8%)	0.11

CI: confidence intervals; PCI: percutaneous coronary intervention.

Procedural volume and characteristics

In the pre-pandemic era, a mean rate of 9.3 TAVI per month were performed compared with 3.7 per month during COVID-19 outbreak. As reported in Table 2, in the latter period, a lower number of procedures were performed in an elective setting. TAVI was preferentially performed with transfemoral access in both cohorts and the use of self-expanding than balloon-expandable prosthesis was more common.

Procedural success, defined as absence of intra-procedural mortality, prosthetic valve correct positioning and normal valve function once in place, was high and comparable between study groups. Patients in the pandemic group spent less time in the intensive care unit (2.2 ± 1.4 days vs 3.7 ± 3.9 days, $p < 0.05$).

Timing of intervention and clinical outcomes at 30 days

Time from diagnosis to the procedure was longer in the pandemic group compared with the pre-pandemic group (56.9 ± 68.3 days vs. 37.7 ± 25.4 days; $p < 0.05$). Hospitalisation length was similar in the two cohorts; Table 3). All-cause mortality at 30 days was not different between the study groups. Similarly, rates of major periprocedural complications including acute kidney injury, permanent pacemaker implantation, vascular complications and any rehospitalisation were comparable. No cases of infection with COVID-19 were reported during hospital stay and within 30-day after the procedure.

Discussion

The main findings of our study can be summarised as follows:

- In the acute phase of the COVID-19 outbreak, TAVI procedures were reduced by 80% compared with the pre-pandemic period;
- a revised pathway for procedure planning was adopted early after the first lockdown; however, overall time from diagnosis to procedure was longer than pre-COVID-19 era;
- patients treated during the pandemic presented with more severe symptoms but spent less time in the intensive care unit after the procedure;
- the pandemic did not affect the rates of all-cause mortality and other early clinical outcomes after TAVI.

The COVID-19 pandemic forced healthcare systems around the world to a profound reorganisation of activities and spaces to face the acute and severe depletion of hospital resources associated with the unexpected need for admissions to intensive care of patients requiring respiratory support. The deferral of elective procedures was one of the main measures to prioritise COVID-19 patients. However, it resulted in an unprecedent drop of life-saving interventions: in our region, the volume of PCI for acute coronary syndromes was reduced by up to 50% [6]. Along the same line, a significant delay for the treatment of structural heart diseases has been accumulated with approximately 80% less interventions than before pandemic in Italy [7]. We also experienced the interruption of elective TAVI and no procedure was performed, at our centre, in March 2020.

This was a worldwide phenomenon with clinical consequences that were particularly severe in some contexts. In a study of 77 patients undergoing evaluation for TAVI at Mount Sinai Hospital, 10% had a cardiac event during the first month of waiting list; later, during the follow-up, 24 patients required urgent TAVI and 3 died before intervention [1]. On the other hand, a continued TAVI program has been associated with an increased risk of nosocomial COVID-19 exposure and related mortality [8]. In this context, to balance the challenges related to the pandemic with the risk of delayed interventions, we remodelled our system to screen and prepare patients for TAVI, based on local

Table 3. Timing of intervention and clinical outcomes at 30 days.

	Overall population ($n = 315$)	Pre- pandemic group ($n = 238$)	Pandemic group ($n = 77$)	% Difference (95% CI)	p-Value
Time to procedure (days), m ± SD	42.8 ± 42.1	37.7 ± 25.4	56.9 ± 68.3	19.2 (6.4; 32.0)	0.004
ICU stay (days), m ± SD*	3.3 ± 3.5	3.7 ± 3.9	2.2 ± 1.4	−1.4 (−2.3; −0.5)	0.002
Hospitalisation length (days), m ± SD	10.8 ± 7.7	10.8 ± 7.9	10.7 ± 6.7	−0.1 (−2.2; 1.9)	0.897
All-cause mortality, *n* (%)	15 (4.8%)	14 (5.9%)	1 (1.3%)	−4.6% (−10.1%; 0.9%)	0.129
Acute kidney injury, *n* (%)	7 (2.2%)	6 (2.5%)	1 (1.3%)	−1.2% (−5.0%; 2.6%)	1
Permanent pacemaker implantation, *n* (%)	44 (14.0%)	38 (16.0%)	6 (7.8%)	−8.2% (−17.1%; 0.8%)	0.09
Any rehospitalisation, *n* (%)	4 (1.3%)	4 (1.7%)	0 (0.0%)	−1.7% (−4.6%; 1.2%)	0.58
Vascular complications, *n* (%)	70 (22.2%)	54 (22.7%)	16 (20.8%)	−1.9% (−12.7%; 8.8%)	0.88

*ICU: intensive care unit

capacities and relying upon the general recommendations of scientific societies [4]. A pathway consisting of a single-stop hospital admission to collect all the exams to plan TAVI and to exclude active infection by Sars-CoV2 allowed us to resume inpatient procedures while not affecting patients' and healthcare workers' safety. By this approach, our TAVI program was maintained without interruption during the subsequent pandemic waves. There is evidence, indeed, that deferral of intervention is detrimental even in patients with a valve disease that might be classified as not requiring urgent treatment based on prespecified criteria. In the AS DEFER study, patients with aortic stenosis were triaged with an algorithm based on recommendations similar to those coming from the American College of Cardiology and Society for Cardiovascular Angiography and Interventions consensus statement [2,3]. Postponement of surgical or transcatheter aortic valve replacement resulted in higher rates of rehospitalisation for valve-related symptoms or worsening heart failure, especially in patients with multivalvular disease [2]. Despite the novel system, an overall longer time to procedure was observed in our cohort because of two main reasons: first, we had to resume procedures that were not performed during the lockdown; second, in the context of the pandemic asset of the hospital, we could only schedule a limited number of elective procedures per week.

The higher prevalence of severe symptoms among patients admitted for TAVI during the pandemic might be related to the following conditions: there were several logistic challenges for patients with severe aortic stenosis to be referred to a TAVI centre because of the restrictions and the closure of follow-up outpatient visits; limitation of daily life activities might have exacerbated the poor functional capacity of the subjects with severe aortic stenosis.

Despite a more complex clinical profile, length of ICU stay was shorter than before pandemic. This occurred as consequence of a revised approach to the hospitalisation with the main objective to optimise resources utilisation. Indeed, we faced the daily need to allocate personnel and beds to COVID patients. In addition, shortening the length of ICU was intended to mitigate the exposure to the infection. A continued TAVI program has been associated with an increased risk of nosocomial COVID-19 exposure and related mortality [8,9]. Our strategy proved effective as TAVI patients spent less time in hospital without a significant impact on clinical outcomes.

Comparative analysis of early clinical outcomes showed that COVID-19 pandemic did not affect the safety and effectiveness of TAVI as similar rates of procedural complications and all-cause mortality were reported than before February 2019. Along the same line, the feasibility of the procedure was confirmed by other reports from Israel [10], UK [11] and the Netherlands [8].

Our study has several limitations including a small sample size from a single-centre and the lack of a comprehensive evaluation of clinical events that eventually occurred in patients while in the waiting list. However, by reporting the experience of one of the main TAVI centre of a country that has been severely hit by the pandemic, it represents a real snapshot of the difficult times that we are facing. Patients with more advanced disease received priority to the intervention during the pandemic and this could represent a possible bias.

Conclusions

The treatment of patients with severe AS represented a very hard challenge during the COVID-19 pandemic. Our experience shows that, despite the increased time lag between diagnosis and procedure and a more complex clinical profile of patients at baseline, TAVI can be safely performed during the pandemic and hospitalisation can be simplified by a more pragmatic pre-hospital pathway. The implementation of vaccines and the growth of immunised population might allow a further streamlining of the procedure and an important step towards the return to a routinary delivery of life-saving cares.

Acknowledgements

Dr. Leone is supported by a research grant provided by the CardioPath PhD program.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Discussion

Part I. **Evaluation of cardiac damage and reverse remodeling in patients undergoing Transcatheter Aortic Valve Implantation.**

In patients with AS, LV hypertrophy develops as initial compensatory adaptation to the increased afterload with the aim to maintain LV systolic function and reduce wall stress. However, disease progression further increases wall stress leading to systolic and diastolic LV dysfunction, subendocardial ischemia and fibrosis, pulmonary hypertension, and right ventricular failure (20,21). TAVI improves symptoms, quality of life and promotes regression of LV mass. Nevertheless, functional recovery of the LV and regression of LVH do not invariably occur in all patients (20,22). The identification of clinical and anatomic factors that affect clinical outcomes of patients with severe AS represents an important unmet need. Several scoring systems that account for baseline features and measures of frailty have been proposed for counselling AS patients (23,24). However, their use in clinical practice is challenged by the lack or limited availability of all the required variables. In this context, the staging classification of cardiac damage proposed by Généreaux et al. features the unique advantage of being widely applicable as it is based on echocardiographic parameters that are routinely evaluated in patients with severe AS. This system was

formulated by leveraging the data of 1661 patients from the PARTNER 2 trial and was proved to be a powerful predictor of mortality at 1-year after aortic valve intervention (either surgical or transcatheter) (19). In our study, which included real-world patients, the system retains its prognostic ability as a greater extent of cardiac damage was associated with increased risk of all-cause mortality after TAVI. These findings are in line with prior studies that applied the staging classification system in larger populations. In a retrospective analysis of 1189 symptomatic, severe AS patients, stage of cardiac injury was independently associated with all-cause mortality and the combined endpoint of all-cause mortality, stroke, and cardiac-related hospitalization (25). Among asymptomatic patients with moderate to severe AS, the staging was significantly associated with excess mortality in multivariable analysis adjusted for aortic valve replacement as a time-dependent variable (hazard ratio: 1.31 per each increase in stage; 95% CI: 1.06 to 1.61; p = 0.01) and demonstrated incremental value over other traditional risk markers (26). Another study applied the staging system to TAVI patients and found a graded association between cardiac damage and all-cause mortality (27). However, our analysis is the first to assess the impact of TAVI on the extent of extraaortic valve cardiac damage. We found that the procedure triggers an early (within 30-days) re-classification of the

stages owing to significant changes in measures of LV diastolic and right ventricle (RV) function. LV hypertrophy and collagen abnormalities develop in patients with severe AS and impair diastolic function. Indeed, objective evidence of variable degrees of LV diastolic dysfunction has been reported in up to two-thirds of patients undergoing TAVI (28). Similarly, RV dysfunction has been documented in up to 1 in 4 patients with severe AS Devereaux a consequence of transmission of elevated left-sided pressure back through the pulmonary vascular system. The suppression of pressure overload by TAVI ameliorates LV filling pressures (E/e0 ratio), as suggested by the concomitant reduction in left atrial volume. Along the same line, a trend towards normalization of tricuspid annular plane excursion (TAPSE) may occur after TAVI (29,30). as well as a reduction in pulmonary hypertension (31).

In this context we showed that assessment of MW by echocardiography is more sensitive than other parameters to detect improvement of contractile LV performance early after TAVI. By corroborating prior results from Jain et al. (32) and Fortuni et al (33), we found a close correlation between the MW indices derived with estimated LV systolic pression and those measured invasively. This supports the correction of peripheral blood pressure values with mean transaortic gradient as a

valuable method to calculate LV myocardial work by echocardiography in AS patients.

Beyond the initial reduction of global work index (GWI) and global constructive work (GCW) immediately after TAVI, described as an effect of the immediate relief from the obstructed valve and the increased afterload (32,34), we found a significant reduction of global wasted work (GWW), probably related to the reduction of wall stress associated with the reverse myocardial remodeling at one month after the procedure.

More interestingly, the beneficial effects of TAVI on myocardial performance were greatest in patients who maintained a spontaneous rhythm without conduction disorders. Indeed, in this group, GWW reduction was even more prominent than GCW, resulting in a significant improvement of global work efficiency (GWE). Conversely, in patients who developed ventricular dyssynchrony after TAVI, the reduction of GWI and GCW was not accompanied by a consistent reduction of GWW, with consequent reduction of myocardial work efficiency (MWE). This finding is consistent with studies in patients undergoing cardiac resynchronization therapy (CRT), showing large amount of wasted work (WW) in dyssynchronous ventricular septum, that reduces after response to CRT with concomitant increase of GWI and LV performance (35).

Reduced myocardial efficiency reflects impairment of ventricular performance and may provide additional information in failing ventricles, as seen in postinfarct patients (36,37) and in heart failure with reduced LVEF (38,39). In heart failure with preserved LVEF, lower resting values of GWE have been associated with lower exercise capacity and blunted LV contractile reserve during effort, suggesting an early subclinical myocardial damage, not detectable by the simple LVEF measurement (40). In the current study, we demonstrated for the first time that also in AS patients undergoing TAVI measuring GWE has clinical impact, since values lower than 92% were independently associated with worse prognosis at 1-year. We can then speculate that among patients with severe AS, anticipating the time of intervention prior that irreversible myocardial damage has occurred, is associated with higher probability of success in terms of reverse remodeling. In this perspective, LV myocardial work evaluation may improve the assessment of LV systolic function at baseline and during the follow-up, perhaps identifying patients that could benefit from an earlier intervention or from adjunctive therapies as CRT.

Part II. **After transcatheter aortic valve implantation: role of cardiovascular imaging to detect valve deterioration.**

As TAVI continues to improve due to increasing experience, patient selection, and technical improvements, device success predominantly depends on anatomic factors and implantation technique. As the procedure indications broaden to younger patients, longterm durability becomes increasingly essential.

Echocardiography is pivotal in the assessment of prosthesis function as well as cardiac function changes after TAVI. In particular, left ventricular mass index (LVMi) and PALS are useful tools recently implemented in clinal practice that are able to detect reverse remodeling early after TAVI (41, 42). Similarly, GLS and MW estimation represent valuable methods for detecting an early recovery of LV systolic function (43, 44). Moreover, TTE allows us to reassess MR severity after TAVI and to define the best management for patients with significant MR and persistent symptoms. Transesophageal echocardiography (TEE) is better than TTE at detecting endocarditis and valve thrombosis, two rare but potentially life-threatening complications (45).

Bioprosthetic valve deterioration recognition becomes fundamental as TAVI indication is shifting toward younger patients. At the longest follow-up available, THVs were found to be better than surgical prostheses in terms of hemodynamic performance and prosthesis-patient mismatch (PPM) incidence, while demonstrating comparable durability.

Among THVs, self-expanding valves (SEV) showed to have lower transprosthetic mean gradients and larger effective orifice area (EOA) compared to balloon-expandable valves (BEV), and this data is confirmed across almost all clinical settings. However, BEVs outperform SEVs in terms of para-valvular leaks (PVL) incidence and severity.

In conclusion, technical improvements and the implementation of new diagnostic tools have consolidated the main role of echocardiography in clinical outcomes evaluation after TAVI.

Part III. **TAVI in COVID-19 pandemic**

The COVID-19 pandemic forced healthcare systems around the world to a profound reorganization of activities and spaces to face the acute and severe depletion of hospital resources associated with the unexpected need for admissions to intensive care of patients requiring respiratory support. The deferral of elective procedures was one of the main measures to prioritize COVID-19 patients. However, it resulted in an unprecedent drop of life-saving interventions: in our region, the volume of percutaneous coronary intervention (PCI) for acute coronary syndromes was reduced by up to 50% (46). Along the same line, a significant delay for the treatment of structural heart diseases has been accumulated with approximately 80% less interventions than before

pandemic in Italy (47). We also experienced the interruption of elective TAVI and no procedure was performed, at our centre, in March 2020**.**

In this context, to balance the challenges related to the pandemic with the risk of delayed interventions, we remodelled our system to screen and prepare patients for TAVI.

The higher prevalence of severe symptoms among patients admitted for TAVI during the pandemic might be related to the following conditions: there were several logistic challenges for patients with severe aortic stenosis to be referred to a TAVI center because of the restrictions and the closure of follow-up outpatient visits; limitation of daily life activities might have exacerbated the poor functional capacity of the subjects with severe aortic stenosis.

Despite a more complex clinical profile, length of intensive care unit (ICU) stay was shorter than before pandemic. This occurred as consequence of a revised approach to the hospitalisation with the main objective to optimize resources utilisation. Indeed, we faced the daily need to allocate personnel and beds to COVID patients. In addition, shortening the length of ICU was intended to mitigate the exposure to the infection.

Comparative analysis of early clinical outcomes showed that COVID-19 pandemic did not affect the safety and effectiveness of TAVI as similar

rates of procedural complications and all-cause mortality were reported than before February 2019. Along the same line, the feasibility of the procedure was confirmed by other reports from Israel (48), UK (49) and the Netherlands (50).

Conclusions

The main findings of this research path can be summarized as follows: (a) the staging classification of AS-related cardiac changes, derived from a randomized trial, maintains its prognostic performance in real-world TAVI patients; (b) TAVI triggers an early reversal of cardiac dysfunction, mainly driven by the amelioration of LV diastolic and RV function; (c) in patients with AS undergoing TAVI, non- invasive MW indices inform about reverse remodeling and myocardial contractility improvement that occur early after the procedure. Thus, MW efficiency could represent an alternative tool for myocardial function assessment and prognostic evaluation in patients receiving TAVI; (d) technical advancements and the implementation of new diagnostic tools echocardiography have consolidated the main role of echocardiography in the follow-up of TAVI patients; (e) studies of bioprosthetic valve durability utilizing modern-era serial echocardiography assessments will be critical for the management of patients with an extended expected lifespan and for making comparative decisions among next-generation THV.

List of abbreviations

AS = aortic stenosis

BEV = ballon-expandable valves

COVID-19 = coronavirus disease-2019

CRT = cardiac resynchronization therapy

EF = ejection fraction

EOA = effective orifice area

GCW = global constructive work

GLS = global longitudinal strain

GWE = global work efficiency

GWI = global work index

GWW = global wasted work

ICU = intensive care unit

LA = left atrial

LV = left ventricle

LVMi = left ventricle mass index

MW = myocardial work

MWE = myocardial work efficiency

PALS = peak atrial longitudinal strain

PPM = prosthesis-patient mismatch

PSL = pressure-strain loops

PVL = paravalvular leak

RV = right ventricle

SAV= surgical aortic valve

SEV = self-expanding valves

TAPSE = tricuspid annular plane excursion

TAVI = transcatheter aortic valve implantation

TEE = transesophageal echocardiography

THV = transcatheter heart valves

TTE = transthoracic echocardiography

WW = wasted work

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ADDITIONAL INFORMATION

PUBLICATIONS

Echocardiographic evaluation after transcatheter aortic valve implantation: A comprehensive Review

- 2023

Transcatheter aortic valve implantation (TAVI) is an increasingly popular treatment option for patients with severe aortic stenosis. Recent advancements in technology and imaging tools have significantly contributed to the success of TAVI procedures. Echocardiography plays a pivotal role in the evaluation of TAVI patients, both before and after the procedure. This review aims to provide an overview of the most recent technical advancements in echocardiography and their use in the follow-up of TAVI patients. In particular, the focus will be on the examination of the influence of TAVI on left and right ventricular function, which is frequently accompanied by other structural and functional alterations. Echocardiography has proven to be key also in detecting valve deterioration during extended follow-up. This review will provide valuable insights into the technical advancements in echocardiography and their role in the follow-up of TAVI patients.

doi: 10.3390/life13051079. PMID: 37240724; PMCID: PMC10221682.

Hemodynamic Performance of Transcatheter Aortic Valves: A Comprehensive Review - 2023

Transcatheter aortic valve implantation (TAVI) is a widely adopted treatment option for patients with severe aortic stenosis. Its popularity has grown significantly in recent years due to advancements in technology and imaging. As TAVI use is increasingly expanded to younger patients, the need for long-term assessment and durability becomes paramount. This review aims to provide an overview of the diagnostic tools to evaluate the hemodynamic performance of aortic prosthesis, with a special focus on the comparison between transcatheter and surgical aortic valves and between self-expandable and balloon-expandable valves. Moreover, the discussion will encompass how cardiovascular imaging can effectively detect long-term structural valve deterioration.

DOI: 10.3390/diagnostics13101731

Impact of COVID-19 pandemic on timing and early clinical outcomes of transcatheter aortic valve implantation

- 2022

Background: We sought to investigate the applicability and outcomes of a novel system to manage patients requiring transcatheter aortic valve implantation (TAVI) at a tertiary level hospital during the coronavirus disease-2019 (COVID-19) pandemic.

Methods: To analyse the impact of hospitalisation pathways during the pandemic on clinical outcomes of TAVI patients, the study population was divided into two groups (pre-pandemic and pandemic groups) and all perioperative/follow-up data were compared. The primary endpoint was all-cause mortality at 30 days; secondary endpoints included procedural success and short-term complications.

Results: A total of 315 patients received TAVI during the study period. Pandemic group (n = 77) showed a more complex baseline clinical profile (NYHA class III-IV, 70.1% vs. 56.3%; p = 0.03). The overall time to procedure was significantly longer during pandemic (56.9 ± 68.3 vs.37.7 ± 25.4; p = 0.004) while intensive care unit stay was shorter (2.2 ± 1.4 vs. 3.7 ± 3.9, p < 0.05). Hospitalisation length was similar in both groups as well as all-cause mortality rate and the incidence of major periprocedural complications. No case of infection by COVID-19 was reported among patients during the hospital stay.

Conclusions: Comparative analysis of early clinical outcomes showed that COVID-19 pandemic did not affect the safety and effectiveness of TAVI as similar rates of procedural complications and all-cause mortality were reported than before February 2020. Despite the increased time lag between diagnosis and procedure and a more complex clinical profile of patients at baseline, the revised pathway of hospitalisation allowed to resume inpatient procedures while not affecting patients' and healthcare workers' safety.

DOI: 10.1080/00015385.2022.2119660

Extent of Cardiac Damage and Mortality in Patients Undergoing Transcatheter Aortic Valve Implantation

- 2021

(1) Aims: We sought to assess the impact of the extent of cardiac damage on survival among real-world patients with severe aortic stenosis (AS) undergoing transcatheter aortic valve implantation (TAVI). (2) Methods: A staging classification was applied to 262 patients from the EffecTAVI Registry at baseline and re-assessed within 30-days after TAVI. The primary endpoint of the study was all-cause mortality at 1-year. Secondary endpoints included cerebrovascular accident, myocardial infarction, permanent pacemaker implantation, endocarditis, and re-hospitalization for all causes. (3) Results: At baseline, 23 (8.7%) patients were in Stage 0/1 (no cardiac damage/left ventricular damage), 106 (40.4%) in Stage 2 (left atrial or mitral valve damage), 59 (22.5%) in Stage 3 (pulmonary vasculature or tricuspid valve damage) and 74 (28.3%) in Stage 4 (right ventricular damage). At 30-days after TAVI, a lower prevalence of advanced stages of cardiac damage than baseline, mainly driven by a significant improvement in left ventricular diastolic parameters and right ventricular function, was reported. At 1-year, a stepwise increase in mortality rates was observed according to staging at baseline: 4.3% in Stage 0/1, 6.6% in Stage 2, 18.6% in Stage 3 and 21.6% in Stage 4 (p = 0.08). No differences were found in secondary endpoints. (4) Conclusions: TAVI has an early beneficial impact on the left ventricular diastolic and right ventricular function. However, the extent of cardiac damage at baseline significantly affects the risk of mortality at 1-year after the procedure.

DOI: 10.3390/jcm10194563