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**The predictive value of a modified Carpentier classification in patients with coincidental mitral regurgitation undergoing TAVI for severe aortic valve stenosis**

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# The predictive value of a modified Carpentier classification in patients with coincidental mitral regurgitation undergoing TAVI for severe aortic valve stenosis

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**Abstract**

**Introduction:** Concomitant mitral-regurgitation (MR) is frequently observed in patients undergoing trans-catheter aortic valve implantation (TAVI). The predictive value of MR etiology remains to be elucidated.

**Methods:** 600 patients with coincidental MR (≥ moderate) undergoing TAVI were categorized according to a modified Carpentier classification [Groups: no/mild MR, n=477; left atrial (LA) functional MR, n=18; MR due to left ventricular dilatation, n=29; degenerative MR, n=50; MR with restricted leaflet motion n=26]. MR improvement and patient outcome was compared among the groups in a retrospective analysis.

**Results:** MR regression was most pronounced in patients with restricted leaflet motion after 6 months, although a significant improvement was observed in all subgroups. MR relief was predominantly observed within the first 30 days after TAVI. Only patients with restricted leaflet motion experienced further improvement thereafter.

In the entire cohort a total of 15 strokes (2.5 %) during the first 30 days after TAVI were observed, with the highest incidence in the LA functional cohort (3 events, 17 %; p=0.008). In multivariate analysis, organic etiology was associated with an increased 1-year mortality.

In conclusion, despite significant MR regression in all MR groups, some individuals may require additional mitralvalve repair after TAVI. According to our data, the timing of these procedures should be based on the underlying MR etiology. The Carpentier classification in patients with coincidental MR undergoing TAVI for severe AS may also have prognostic implications as we found an increased incidence of strokes in our LA functional cohort and a worse mortality rate in organic MR.

Key words: Trans-catheter aortic valve implantation, TAVI, Carpentier classification, LA functional MR, functional mitral regurgitation, organic mitral regurgitation

## 1. Introduction

Transcatheter aortic valve implantation (TAVI) has become the treatment of choice in patients with severe aortic valve stenosis (AS) and high or prohibitive risk of cardiac surgery. Despite the significant reduction of morbidity and mortality after TAVI, several subgroups with reduced treatment response have been identified [1, 2].

The coincidence of significant mitral regurgitation (MR), which is present in about 30 % of the typical TAVI cohort, has been associated with worse outcome [3-8]. Therefore, significant mitral incompetency poses a substantial challenge in the management of the high surgical risk TAVI cohort.

Based on the etiology of MR, functional and organic MR are distinguished depending on whether left ventricular dysfunction and consecutive annular dilatation or intrinsic pathologies of the mitral valve itself ultimately cause valvular incompetency [9]. In previous studies, patients with degenerative MR showed less MR improvement and had a worse outcome compared to their functional counterparts [7].

However, functional MR etiology may be caused by a variety of pathologic conditions. For example, coronary artery disease, left ventricular hypertrophy, annulus dilatation due to increased left atrial or left ventricular volumes may cause significant regurgitation [9].

The Carpentier classification, which takes into account etiology, pathology and pathophysiology of MR, was introduced in the 1980s. It describes MR from the point of view of surgical repair, and is paramount when formulating a treatment strategy, since optimal management may differ depending on the underlying cause [10, 11].

We hypothesize, that MR etiology - as defined by a modified Carpentier classification - will provide addition information in terms of MR regression or the timing of additional procedures for MR correction and prognosis in patients with coincidental MR undergoing TAVI for severe AS.

## 2. Methods

### *2.1 Study design*

In this retrospective multicenter registry, a total of 600 patients with severe AS who underwent TAVI at 3 European University Hospitals (Charité Berlin – University Medicine, Campus Benjamin Franklin,

Berlin, Germany; University Hospital Zurich, Zurich, Switzerland; and Heart Hospital London, University College London, London, UK) were included. The availability of a transesophageal echocardiogram at baseline with sufficient image quality to determine the mechanism of MR was required for inclusion in the study.

All patients were discussed in a multidisciplinary Heart Team meeting and TAVI was performed if patients were considered to be at high surgical risk or inoperable. Balloon-expandable and self-expandable transcatheter heart valves (EDWARDS Sapien, Edwards lifesciences or CoreValve, Medtronic Inc.) were implanted via trans-femoral, trans-subclavian, or trans-apical access. The Direct Flow valve (Direct Flow Medical, Santa Rosa, USA; n = 6), the Lotus valve (Boston scientific, Massachusetts, USA; n = 4), the Portico valve (St Jude Medical, Minnesota, USA; n = 31) and the Evolut R (Medtronic Inc.; n = 68) were used in a minority of patients. Technical details of the TAVI procedure with the used devices are described in detail elsewhere [12-14]. Patients after TAVI received Aspirin and Clopidogrel for six months and Aspirin thereafter. Individuals with an indication for oral anticoagulation were continued on this medication without additional Aspirin or Clopidogrel, except coronary/peripheral interventions were performed. OAC was discontinued for up to 7 days after the TAVI procedure, whereas Heparin was prescribed as a "bridging medication" during this period whenever possible.

**Table 1: Classification of Mitral valve pathology in patients with ≥ moderate MR**

| | **LA functional MR** | **Type I/IIIb** | **Type II** | **Type IIIa** | **Type IIIb** |
|---|---|---|---|---|---|
| **Pathology** | Unrestricted leaflet motion, dilated mitral annulus, normal LVEDd | Dilated Mitral annulus, dilated LV cavity, unrestricted leaflet mobility or tethering due to dilated LV<br><br>and/or<br>mitral leaflet perforation | Hypermobility of mitral leaflets due to prolapse, flail or Barlow | Thickened mitral leaflets and restricted opening | Normal annulus and LV diameter, restricted mitral leaflet mobility<br><br>and/or<br>systolic anterior motion (SAM) |
| **Number of individuals found in our cohort** | 18 | 29<br><br>Mitral leaflet perforation in 0 patients | 50 | 2<br>(excluded from the final analysis) | 26<br><br>SAM in 2 of 26 patients. |

LA left atrium, LVEDd left ventricular end diastolic diameter, LV left ventricle, SAM systolic anterior motion.

Transthoracic Echocardiography studies (TTE) were performed at baseline, at 30 days and 6 months after TAVI, using commercially available equipment (Philips iE33, Philips Healthcare, Andover, MA, USA; GE Vivid 7, GE Healthcare, Milwaukee, WI, USA). Two-dimensional images were acquired in parasternal and apical views, and analyzed by experienced echocardiographers. MR was quantified as none, mild, moderate, or severe, in accordance with the recommendations of the American Society of Echocardiography (ASE) and the European Association of Echocardiography (EAE) [15, 16]. LVEDd and mitral annular dimensions were considered normal in accordance to previous publications: LVEDd ≤ 59 mm in men and ≤ 53 mm in women. Mitral annulus parasternal long axis ≤ 41 mm in men and ≤ 34 mm in women. Mitral annulus diameter 4 chamber view ≤ 38 mm in men and ≤ 33 mm in women [17, 18].

AS severity was determined by mean trans-valvular pressure gradient, obtained by the modified Bernoulli equation and the AVA calculated by standard continuity equation [19]. Post-procedural aortic regurgitation (AR) was assessed based on intraprocedural angiograms or echocardiograms.

Based on the available literature [9-11, 20-22] we used a modified Carpentier classification to divide patients with ≥moderate MR according to the underlying mechanism (Table 1).

The periprocedural complications including major vascular complications, stroke, major bleeding, and postprocedural pacemaker implantation were classified according to the revised Valve Academic Research Consortium (VARC)-2 consensus document [23]. Furthermore, mean trans-valvular pressure gradients and postprocedural aortic regurgitation (AR) were reported.

Dyspnea was categorized according to the New York Heart Association (NYHA) functional class at baseline and at 6-months follow-up. All-cause mortality was also defined according to the revised VARC-2 standardized endpoint definitions [23].

*2.2 Statistical analysis*

Continuous variables are expressed as mean ± standard deviation (SD), categorical variables as number and percentages, respectively. Continuous variables following a normal distribution were compared by using a Student's t-test. Variables not following a normal distribution were compared with the Mann Whitney U-test or the Wilcox test as appropriate. A Chi-square or Fisher exact test was used to compare categorical variables. Cumulative survival was estimated with the Kaplan-Meier method, and comparisons between groups were made with the Log-rank test. Uni- and multivariate logistic- and cox-regression analyses were performed to define predictors of postprocedural MR reduction, stroke rate and all-cause mortality. Parameters for univariate analysis were selected according to the observed *p* values found in the intergroup-comparisons of baseline and procedure outcome variables. Based on these results, multivariate testing was performed including all parameters with a significant predictive value in univariate analysis (Table 4). The level of significance was set at $p<0.05$, with all reported *p*-values being 2-sided. All statistical analyses were performed using SPSS version 21 for Windows (Chicago, IL, USA).

## 3. Results

Baseline characteristics of the compared groups are depicted in Table 2. Patients with left atrial functional MR had the highest incidence of atrial fibrillation and the largest left atrial volumes. The Type I/IIIb MR cohort was significantly younger when compared to the other groups. Furthermore, significant differences between the groups were found with respect to LVEF, LVEDd, RWT and PAPs. NYHA functional class was also worst in patients with ≥ Type I/IIIb MR and unrestricted leaflet motion.

**Table 2: Baseline characteristics**

| Parameter | no/ mild MR n = 477 | LA functional MR n = 18 | Type I/IIIb MR n = 29 | Type II MR n = 50 | Type IIIb MR n = 26 | *p* |
|---|---|---|---|---|---|---|
| Age | 82.5 ± 7 † | 84 ± 5 † | 78 ± 8 § | 81 ± 10 | 84 ± 8 | 0.006 |
| Female gender | 51 % | 67 % | 38 % | 56 % | 54 % | 0.399 |
| Log Euroscore | 22 ± 12 | 22 ± 13 | 27 ± 16 | 21 ± 11 | 26 ± 15 | 0.120 |
| Previous cardiac surgery | 21 % | 18 % | 27 % | 21 % | 25 % | 0.429 |
| COPD | 25 % | 33 % | 38 % | 29 % | 38 % | 0.356 |
| eGFR | 54.2 ± 12.7 | 51.8 ± 17 | 50.1 ± 20.8 | 48.9 ± 18.3 | 47 ± 19 | 0.551 |
| CAD | 59 % | 67 % | 85 % | 55 % | 58 % | 0.112 |
| History of MCI | 10.6 % † | 16 % | 27.6 % ‡ | 8 % | 19 % | 0.019 |
| Atrial fibrillation | 118 (24. 7 %)*† | 12 (66.6 %)†‡§ | 11 (38 %) | 17 (34 %) | 7 (26 %) | 0.006 |
| EF | 56 ± 14 †§ | 52 ± 13 †‡ | 33 ± 12 ‡§ | 60 ± 11 § | 50 ± 13 | <0.001 |
| AVA | 0.7 ± 0.2 | 0.5 ± 0.1 | 0.7 ± 0.3 | 0.7 ± 0.2 | 0.6 ± 0.2 | 0.378 |
| AV dP-mean | 46 ± 15 | 44 ± 14.5 | 39 ± 17 | 39 ± 16 | 55 ± 19 | 0.107 |
| MR III | 0 *†‡§ | 14 (77.8 %) | 22 (83 %) | 43 (86 %) | 19 (73 %) | <0.001 |
| RWT | 0.52 ± 0.1 † | 0.48 ± 0.07 †§ | 0.38 ± 0.1‡§ | 0.49 ± 0.18 | 0.53 ± 0.11 | 0.002 |
| LVM | 251 ± 75 † | 274 ± 72 | 318 ± 97 ‡ | 229 ± 64 | 266 ± 73 | 0.008 |
| LVEDd | 47.7 ± 7 *† | 49.5 ± 5 † | 59.4 ± 4.9 ‡§ | 48 ± 6.4 | 50 ± 5.7 | <0.001 |
| LA vol | 75.3 ± 23 *† | 91 ± 23.4 ‡ | 89.7 ±25.6 ‡ | 69 ± 15 | 78 ± 30.8 | 0.004 |
| PAPs | 41 ± 14 † | 46 ± 11.6 | 52.3 ± 15 ‡ | 40 ± 14 | 48 ± 15 | 0.039 |
| NYHA III or IV | 309 (65 %) † | 14 (78 %) | 25 (86 %) ‡§ | 37 (74 %) | 15 (58 %) | 0.003 |

*significantly different to LA func. MR, †significantly different to Type I/IIIb MR, ‡significantly different to Type II MR, §significantly different to Type IIIb MR. CAD Coronary artery disease, MCI myocardial Infarction, EF left ventricular ejection fraction, RWT relative wall-thickness, LVM left ventricular mass in g, LVEDd left ventricular enddiastolic diameter, LA vol left atrial volume in ml, PAPs systolic pulmonary artery pressure as determined by TTE.

The distribution of the implanted prostheses, route of implantation, TAVI related pacemaker rate, major vascular complications and paravalvular AR were not significantly different between the groups. The

incidence of 30-day strokes was 2.7 % in the total population, whereas the highest rate was observed in the LA functional cohort (16.6 %). The mean time to cerebrovascular event was 5.7 ± 4.2 days in the latter group (Table 3). Age and LA functional MR were both identified as independent predictors of stroke within 30 days in uni- and multivariate analysis. Neither AF itself nor LA volume in the total cohort or in patients with AF (OR: 0.996, CI: 0.966 – 1.026; $p = 0.783$) were associated with a higher incidence of strokes (Table 4). There was no association between vascular complications or need for pacemaker implantation and the occurrence of strokes.

**Table 3: Procedure characteristics and outcome**

| **Parameter** | **no/ mild MR n = 477 ⎪ n = 2552 ‖ n = 1763 $** | **LA functional MR n = 18 ⎪ n = 16 ‖ n = 14 $** | **Type I/IIIb MR n = 29 ⎪ n = 25 ‖ n = 24 $** | **Type II MR n = 50 ⎪ n = 35 ‖ n = 38 $** | **Type IIIb MR n = 26 ⎪ n = 19 ‖ n = 23 $** | ***p*** |
|---|---|---|---|---|---|---|
| Valve type | | | | | | 0.078 |
| Edwards Sapien | 186 (39 %) | 4 (22.2 %) | 10 (34.5%) | 18 (36 %) | 6 (23 %) | |
| Corevalve | 204(43 %) | 10 (55.6 %) | 14 (48 %) | 25 (50 %) | 14 (54 %) | |
| Other | 87 (18 %) | 4 (22.2 %) | 5 (17.5 %) | 7 (14 %) | 6 (23 %) | |
| Access | | | | | | 0.987 |
| Femoral | 427 (89.5 %) | 16 (89 %) | 26 (89.6 %) | 43 (86 %) | 23 (88.5 %) | |
| Axillar | 10 (2 %) | 0 | 0 | 1 (2 %) | 0 | |
| Transapical | 40 (8.5 %) | 2 (11 %) | 3 (10.4 %) | 6 (12 %) | 3 (11.5 %) | |
| Pacemaker | 80 (16.8%) | 3 (16.7 %) | 3 (10.3 %) | 4 (8 %) | 3 (11.3 %) | 0.510 |
| Stroke (30 days) | 10 (2 %) * | 3 (16.6 %) § | 1 (3.5 %) | 2 (4 %) | 0 | 0.008 |
| Days until stroke | 2.5±4.2 | 5.7±4.2 | 1 | 1±1.4 | - | 0.556 |
| Maj. Vasc. comp | 38 (7.9 %) | 1 (5.5 %) | 2 (6.9 %) | 4 (8 %) | 3 (11.3 %) | 0.964 |
| ≥ Moderate AR | 35 (7.3 %) | 4 (22.2 %) | 9 (31 %) | 8 (16 %) | 7 (27 %) | 0.004 |
| ≥ moderate MR discharge | 46 (18 %) *†‡§ | 13 (81 %) | 18 (72 %) | 30 (86 %) § | 12 (63 %) | <0.001 |
| MR ≥ grade I improvement | 9 (3.5 %) *†‡§ | 12 (75 %) ‡ | 13 (52 %) | 18 (51.4%) | 12 (63 %) | <0.001 |
| ≥ moderate MR 6 months | 45 (25.5%) *†‡§ | 11 (78.5%) § | 18 (75%) § | 33 (87 %) § | 11 (48 %) | <0.001 |
| MR ≥ grade 1 improvement | 13 (7.4 %) *†‡§ | 8 (57 %) | 12 (50 %) | 21 (55 %) § | 17 (73 %) | <0.001 |
| NYHA III or IV 6 months | 37 (21 %) *† | 1 (7 %) † | 10 (42 %) § | 10 (26 %) | 3 (13 %) | 0.018 |
| ≥ 1 NYHA class improvement | 128 (73 %) | 12 (86 %) | 15 (63 %) | 28 (74 %) | 14 (61 %) | 0.312 |

*significantly different to LA func. MR, † significantly different to Type I/IIIb MR, ‡ significantly different to Type II MR, § significantly different to Type IIIb MR. ⎪Number of patients with TTE at baseline. ‖ Number of patients with TTE available at 30 days. $ Number of Patients with TTE at 6 months. AR aortic regurgitation.

MR regression was significant in all groups at 30 days, as well as 6 months after TAVI. The extent of MR improvement ( ≥ 1 grade of MR reduction) after 6 months was most pronounced in patients with ≥ moderate MR and restricted leaflet motion and was statistically significant when compared to patients with organic MR (Table 3). A significant change in MR between the 30 days and the 6 months follow up was observed in the type IIIb cohort only (Figure 1). As depicted in Table 4, paravalvular AR was inversely and LVEDd directly associated with MR regression in multivariate analysis. In this analysis there was also a non-significant trend towards worse MR improvement in the organic MR cohort (Table 4, $p = 0.054$).

**Table 4: Uni- and multivariate analysis of MR regression, mortality and stroke after TAVI**

| | **Univariate analysis** | | **Multivariate analysis** | |
|---|---|---|---|---|
| **Parameters** | **HR/ OR (95% CI)** | ***p* value** | **HR/ OR (95% CI)** | ***p* value** |
| *Predictors of MR improvement at 6-months follow-up in patients with ≥ moderate MR* | | | | |
| Type II MR* | 0.46 (0.15 - 1.44) | 0.184 | 0.18 (0.03 - 1.03) | 0.054 |
| Age | 1.01 (0.96 - 1.06) | 0.695 | | |
| Log Euroscore | 1.04 (0.99 – 1.09) | 0.128 | | |
| AF | 0.75 (0.31 – 1.81) | 0.525 | | |
| RWT | 0.16 (0 – 16.22) | 0.440 | | |
| LVM | 1.0 (0.99 – 1.01) | 0.419 | | |
| LVEDd* | 1.08 (1.01 – 1.15) | 0.020 | 1.13 (1.03 – 1.24) | 0.009 |
| EF baseline | 1.0 (0.98 – 1.03) | 0.746 | | |
| Baseline LA volume | 1.0 (0.98 – 1.2) | 0.921 | | |
| PAPs baseline | 0.99 (0.95 – 1.03) | 0.562 | | |
| ≥ moderate post-procedural AR* | 0.45 (0.27 – 0.75) | 0.002 | 0.46 (0.26 – 0.75) | 0.002 |
| *Predictors of 1-year all-cause-mortality* | | | | |
| Type II MR* | 1.66 (0.88 - 3.15) | 0.119 | 3.17 (1.12 – 8.94) | 0.029 |
| Age | 1.01 (0.98 - 1.05) | 0.430 | | |
| Log Euroscore* | 1.02 (1.0 - 1.03) | 0.031 | 1.02 (1.0 – 1.03) | 0.030 |
| AF* | 1.93 (1.16 – 3.21) | 0.012 | 1.88 (0.71 – 5.0) | 0.207 |
| RWT* | 18.63 (1.3 – 267.4) | 0.031 | 3.1 (0.24 – 40.9) | 0.309 |
| LVM | 1.0 (1.0 – 1.003) | 0.204 | | |
| LVEDd | 0.98 (0.94 – 1.03) | 0.508 | | |

| | | | | |
|---|---|---|---|---|
| EF baseline | 0.99 (0.98 – 1.01) | 0.197 | | |
| Baseline LA volume | 1.0 (0.97 – 1.03) | 0.447 | | |
| PAPs baseline | 1.01 (0.98 – 1.04) | 0.724 | | |
| ≥ moderate post-procedural AR | 1.48 (0.83 – 2.66) | 0.187 | | |
| *Predictors of stroke within 30 days after TAVI* | | | | |
| LA functional MR* | 9,36 (2.33 - 37.54) | 0,020 | 7.96 (1.95 – 32.55) | 0.040 |
| Age* | 1,11 (1.0 - 1,22) | 0.045 | 1.11 (1.0 – 1.22) | 0.047 |
| Log Euroscore | 1.03 (0.99 – 1.06) | 0.110 | | |
| AF | 1.52 (0.31 – 7.42) | 0.607 | | |
| RWT | 2.38 (0.02 – 363) | 0.736 | | |
| LVM | 1.0 (0.99 – 1.01) | 0.796 | | |
| LVEDd | 0.97 (0.85 – 1.12) | 0.723 | | |
| EF baseline | 0,99 (0.96 - 1.03) | 0.663 | | |
| LA vol baseline | 1.02 (0.99-1.05) | 0.161 | | |
| PAPs baseline | 1.05 (0.99 – 1.10) | 0.094 | | |
| ≥ moderate post-procedural AR | 0.72 (0.27 – 1.87) | 0.493 | | |

*Parameters included in multivariate analysis. AF atrial fibrillation, EF left ventricular ejection fraction, RWT relative wall-thickness, LVM left ventricular mass, LVEDd left ventricular enddiastolic diameter, LA vol left atrial volume in ml, PAPs systolic pulmonary artery pressure as determined by TTE. AR aortic regurgitation.

Mean follow-up time was 461 ± 357 days. All-cause-mortality after 1 year was not significantly different in patients with no/mild MR and those with ≥ moderate MR at baseline ($p$ = 0.087). Furthermore, according to our Kaplan Meier analysis no significant differences were observed within the compared subgroups after 30 days ($p$ = 0.127) and 1 year (Figure 2). One-year all-cause-mortality did not differ between patients with and those without MR improvement (≥ 1 grade) at 30 days after TAVI ($p$ = 0.667). In multivariate Analysis, organic MR was identified as an independent predictor of 1-year all-cause mortality (Table 3).

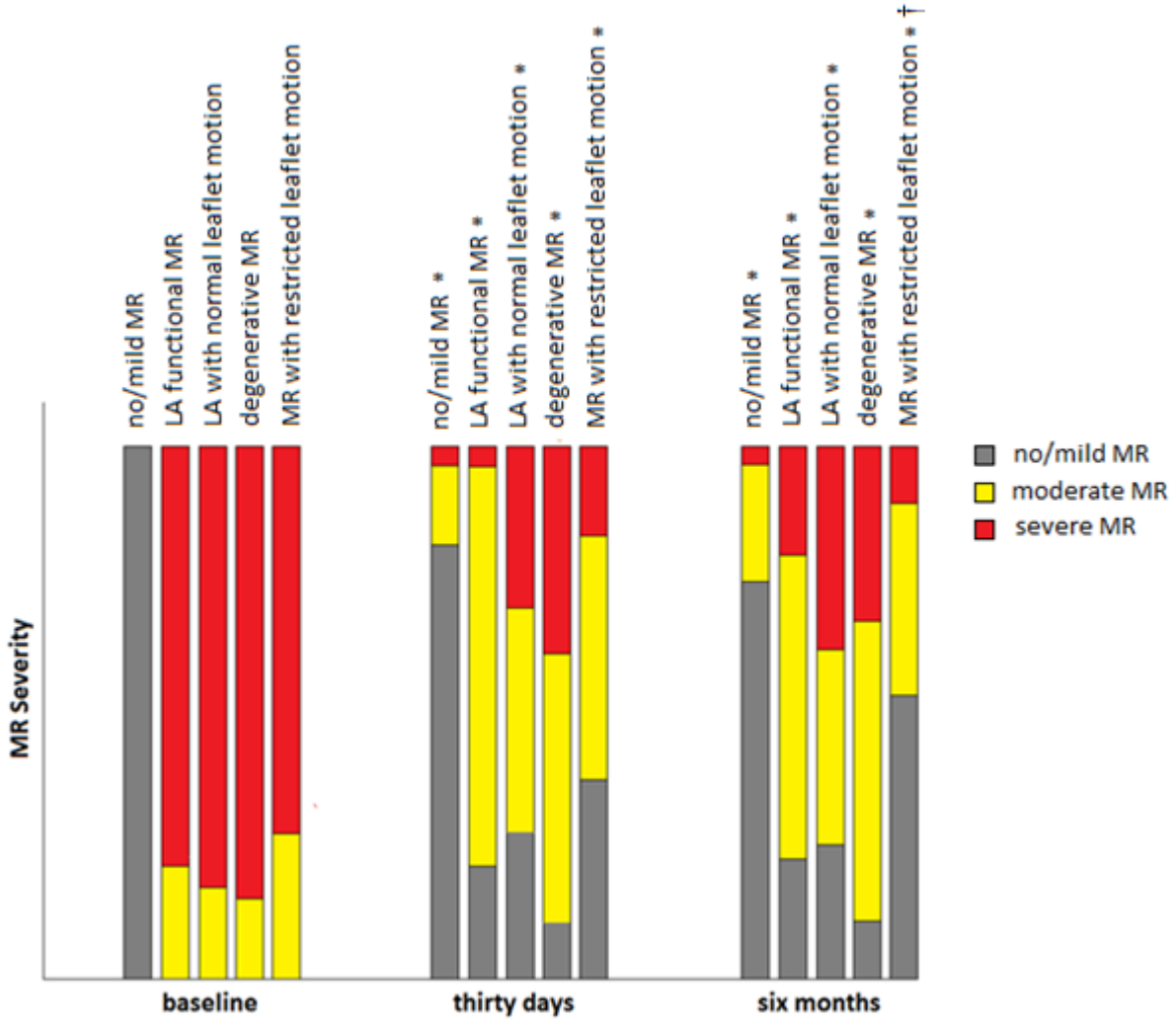


Figure1: Course of MR with respect to the investigated groups. *Significantly different compared to baseline. † significantly different compared to 30 days.

## 4. Discussion

To the best of our knowledge, this is the first study investigating the predictive value of a modified Carpentier classification in patients with coincidental MR undergoing TAVI for severe AS.

Most importantly, MR pathophysiology based on this classification may determine the timing of additional mitralvalve-repair in patients with inadequate MR regression after TAVI. Furthermore, an increased incidence of embolic strokes following the procedure was apparent in patients with LA functional MR, a subgroup characterized by dilated left atrial cavities and the presence of atrial fibrillation [20-22].

In our modified Carpentier classification we defined three subgroups of functional MR: LA functional MR, MR associated with left ventricular dilatation (Type I/IIIb) and MR with restricted leaflet motion due to papillary muscle dysfunction (Type IIIb).

According to our data and also in accordance with other studies, patients with left atrial functional MR were characterized by large atrial volumes and an increased incidence of atrial fibrillation [20-22]. We did not identify individuals with leaflet perforation in our unrestricted leaflet cohort, which therefore represents the typical functional MR cohort with dilated cardiomyopathy.

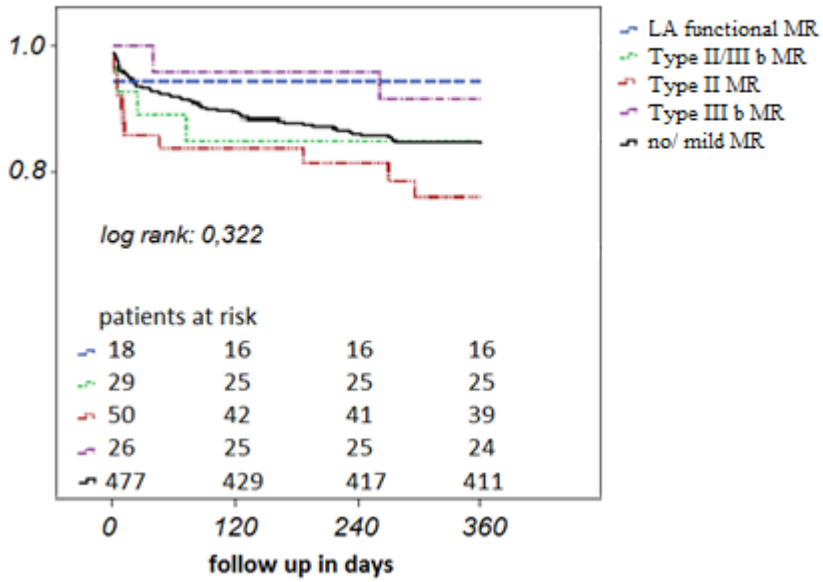


Figure 2: Cumulative 1-year survival according to the investigated groups.

As mentioned in the literature, restricted leaflet motion is typically caused by coronary artery disease resulting in papillary muscle dysfunction [9-11]. However, the incidence of coronary artery disease and also the incidence of myocardial infarction was not increased in these patients when compared to the other groups in our study. Alternatively, left ventricular hypertrophy combined with reduced coronary perfusion - both in context of AS - may also cause papillary muscle dysfunction and consequently significant MR. This phenomenon has already been reported by Roberts et al. in 1972 and is again supported by our finding of significantly increased relative wall-thickness (representing concentric hypertrophy) in this cohort [9].

Since inverse left ventricular remodeling is frequently observed after surgical aortic valve replacement or TAVI, papillary muscle dysfunction and MR are also expected to improve [24]. In fact, according to our data the Type IIIb MR cohort showed the greatest extent of MR reduction after 6 months.

Decreasing left ventricular pressures, as observed immediately after relief of AS, is likely to influence MR severity, which is highly afterload dependent. These considerations may explain why significant improvement of MR was observed in all groups, even in patients with organic MR (Type II MR) early (30 days) after TAVI. However, in multivariate analyses Type II etiology was inversely related with MR regression following AS intervention, underlining the presence of a structural defect of the mitralvalve. Interestingly, larger left ventricular diameters were directly associated with the amount of

MR improvement. This finding possibly reflects the burden of afterload mismatch in patients with dilated cardiomyopathy, which, according to Laplace´s law, is expected to improve following TAVI.
Overall, 60 % of the patients with significant coincidental MR at baseline, still suffered from ≥ moderate MR after TAVI and may therefore benefit from additional mitralvalve intervention. According to our data, the timing of mitral valve repair after TAVI may be crucial with respect to the mitral-pathophology. We found a prolonged MR regression over a 6 months period in patients with Type IIIb MR, whereas the remaining groups showed no further reduction beyond 30 days after TAVI.

Patients with atrial functional MR had a significantly increased incidence of clinical apparent strokes within 30 days after TAVI. This is an important finding as procedure related cerebrovascular events still pose an unsolved issue in the TAVI field. However, the mean time from procedure to event was 6 days in this group of patients, indicating that there was no direct relation between strokes and the intervention. Since atrial functional MR was associated with a high prevalence of atrial fibrillation, we believe that inadequate anticoagulation after TAVI may be the reason for this finding. Unfortunately, our database does not contain data on medical treatment, but discontinuation of anticoagulation for up to one week after TAVI was a common practice in our cohort. As vascular complications or the necessity of a pacemaker implantation may prompt physicians to discontinue anticoagulation, it is important to note that the stroke rate was not increased in these patients.
It is also important to mention that AF and atrial volumes itself were not found to predict the occurrence of strokes in uni- and multivariate analysis. Therefore, the combination of AF, large atrial volumes and MR, causing turbulent atrial flow, may explain a hyper-coagulate state and therefore the increased stroke rates. These results may encourage a discussion about the optimal periprocedural antithrombotic management in these patients.

We also investigated mortality rates at 30 days and 1 year and observed a significantly worse outcome in patients with Type II MR in multivariate analysis. These results are in line with a previous study [7]. However, despite the reduced treatment response in terms of MR reduction, which itself was not associated with worse outcome, additional risk factors and comorbidities – not considered in this investigation - may account for this result. For example, Type II MR as a degenerative disease may be a consequence of other cardiovascular risk factors like arterial hypertension, connective tissue disorders, kidney disease, and many more. It is therefore likely that this group of patients is highly heterogeneous.

Some limitations need to be noted. First, the study is limited by the retrospective observational design and the rather small number of patients with more than mild MR. This may have affected the validity of the regression analysis. Second, clinical and echocardiographic follow-up data were not available in all patients included in the registry and the results may therefore be biased. Echocardiographic follow up was also only available for 6 months after TAVI. Therefore, we may have missed later MR regression

or worsening. Furthermore, our database did not retain data on anticoagulation, which would have been crucial to explain the increased incidence of strokes in our LA functional MR cohort. However, our study represents a well-characterized, contemporary "real-world" patient population undergoing TAVI in 3 European countries, Germany, the UK and Switzerland.

In conclusion, according to our data not moderate to severe MR itself, but the etiology of MR as determined by a modified Carpentier classification has prognostic impact in patients undergoing TAVI for severe AS. Mortality was increased in patients with organic MR and an increased incidence of postprocedural strokes was observed in the LA functional MR cohort, most likely due to anticoagulation issues. Our data may therefore encourage physicians to restart anticoagulation as soon as possible after TAVI, especially in patients with LA functional MR.
Despite significant MR regression in all MR groups, nearly 60 % of our MR cohort were left with moderate or severe MR after TAVI. Since some of these patients may benefit from additional mitral-valve repair, the timing of these procedures remains an important question. According to our data, ongoing MR regression may be expected for 6 months after TAVI in patients with Type IIIb MR, whereas no further improvement was found in the remaining groups after 30 days. Larger studies are needed to confirm these results.

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**Conflicts of interest**
U. Landmesser: Received lecture or advisory fees from Amgen, Sanofi, MSD, Berlin-Chemie, Medicines Company, Abbott.

## 5. References


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