SUPPLEMENTAL MATERIAL

Table S1. VARC-3 definition of bleeding and transfusions

Overt bleeding that fulfils one of the following criteria*:
Type 1 • Overt bleeding that does not require surgical or percutaneous intervention, but does require medical intervention by a health care professional, leading to hospitalization, an increased level of care, or medical evaluation (BARC 2) • Overt bleeding that requires a transfusion of 1 unit of whole blood/red blood cells (BARC 3a) Type 2 • Overt bleeding that requires a transfusion of 2–4 units of whole blood/red blood cells (BARC 3a) • Overt bleeding associated with a haemoglobin drop of >3 g/dL (>1.86 mmol/L) but <5 g/d (<3.1 mmol/L) (BARC 3a) Type 3 • Overt bleeding in a critical organ, such as intracranial, intraspinal, intraocular, pericardial (associated with haemodynamic compromise/tamponade and necessitating intervention), or intramuscular with compartment syndrome (BARC 3b, BARC 3c) • Overt bleeding causing hypovolemic shock or severe hypotension (systolic blood pressure <90 mmHg lasting >30 min and not responding to volume resuscitation) or requiring vasopressors or surgery (BARC 3b) • Overt bleeding requiring reoperation, surgical exploration, or reintervention for the purpose of controlling bleeding (BARC 3b, BARC 4) • Post-thoracotomy chest tube output ≥2 L within a 24-h period (BARC 4) • Overt bleeding requiring a transfusion of ≥5 units of whole blood/red blood cells (BARC 3a) • Overt bleeding associated with a haemoglobin drop ≥5 g/dL (≥3.1 m mol/L) (BARC 3b). Type 4 Overt bleeding leading to death. Should be classified as: • Probable: Clinical suspicion (BARC 5a) • Definite: Confirmed by autopsy or imaging (BARC 5b)

*Overt bleeding is defined as any clinically obvious source of bleeding or bleeding source identified after appropriate investigation and diagnostic testing (e.g. imaging). Any procedural blood loss should be considered overt bleeding.

BARC, Bleeding Academic Research Consortium

Table S2. Rate of missing values

	All (N = 268)
Age	0
Sex male	0
BSA	0
Diabetes	0
Hypertension	0
Hypercholesterolemia	0
Smoking	81 (30.2)
COPD	0
eGFR	0
CAD	0
Prior MI	0
Prior PCI	0
Prior CABG	0
Prior stroke/TIA	0
Peripheral arteriopathy	47 (17.5)
Atrial fibrillation/flutter	0
Pacemaker	0
ICD/CRTD	0
COPD	0
EuroSCORE II	0
NYHA	0
Baseline echocardiography	
LVEF	0
Average AVG	0
Aortic valve area	0
Aortic valve area index	0
Paradoxical LFLG	0
Classical LFLG	0
Moderate-to-severe AR	0
BAV	0
sPAP	0
Right ventricular dysfunction	45 (16.8)
Procedural features	
Transfemoral approach	0
Pacing	0
Predilatation	0
Balloon-expandable prosthesis	0
Self-expandable prosthesis	0
Prosthesis size <23 mm	0
Postdilatation	1 (0.4%)
Pre-discharge echocardiography	
LVEF	0
Average AVG	0

Residual moderate-to-severe AR	0
sPAP	0

The rate of missing values is reported as N (%).
AVG, aortic valve gradient; AR, aortic regurgitation; BAV, bicuspid aortic valve; BSA, body surface area; CABG, coronary artery bypass graft surgery; CCS, chronic coronary syndrome; COPD, chronic obstructive pulmonary disease; CRT-D, Cardiac resynchronization therapy-defibrillator; eGFR, Estimated Glomerular Filtration Rate; EuroSCORE, European system for cardiac operative risk evaluation; ICD, Implantable cardioverter-defibrillator; LVEF, Left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association functional class; PCI, percutaneous coronary intervention; sPAP, Systolic pulmonary artery pressure; TIA, transient ischemic attack.

Table S3. Medications at admission

	Overall (N=268)	MR ≤ 2+ (N= 211)	MR > 2+ (N=57)	P value
ACEi, N (%)	85 (31.7)	66 (31.3)	19 (33.3)	0.751
ARB, N (%)	41 (15.3)	32 (15.2)	9 (15.8)	1.000
ACEi/ARB, N (%)	126 (47)	98 (46.4)	28 (49.1)	0.766
Dihydropyridine CCB, N (%)	37 (13.8)	30 (14.2)	7 (12.3)	0.830
Diuretic, N (%)	190 (70.9)	144 (68.2)	46 (80.7)	0.072
β-blocker, N (%)	84 (31.3)	63 (29.9)	21 (36.8)	0.336
Aspirin, N (%)	169 (63.1)	133 (63)	36 (63.2)	1.000
$P2Y_{12}$ inhibitor, N (%)	90 (33.6)	73 (34.6)	17 (29.8)	0.531
VKA, N (%)	23 (8.6)	17 (8.1)	6 (10.5)	0.595
DOAC, N (%)	56 (20.9)	44 (20.9)	12 (21.1)	1.000
Statin, N (%)	161 (60.1)	121 (57.3)	40 (70.2)	0.094

ACEi, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; calcium-channel blocker, CCB; VKA, Vitamin K antagonist; DOAC, Direct acting Oral Anticoagulant.

Table S4. Medications at discharge

	Overall (N=266)	MR ≤ 2+ (N= 210)	MR > 2+ (N=56)	P value
ACEi, N (%)	75 (28.2)	52 (24.8)	23 (41.1)	0.020
ARB, N (%)	48 (18)	31 (14.8)	17 (30.4)	0.011
ACEi/ARB, N (%)	123 (46.2)	83 (39.5)	40 (71.4)	<0.001
Dihydropyridine CCB, N (%)	61 (22.9)	50 (23.8)	11 (19.6)	0.594
Diuretic, N (%)	225 (84.6)	175 (83.3)	50 (89.3)	0.404
β-blocker, N (%)	96 (36.1)	74 (35.2)	22 (39.3)	0.639
Aspirin, N (%)	210 (78.9)	167 (79.5)	43 (76.8)	0.713
$P2Y_{12}$ inhibitor, N (%)	165 (62)	134 (63.8)	31 (55.4)	0.279
VKA, N (%)	19 (7.1)	15 (7.1)	4 (7.1)	1.000
DOAC, N (%)	59 (22.2)	46 (21.9)	13 (23.2)	0.857
Statin, N (%)	164 (61.7)	126 (60)	38 (67.9)	0.354

ACEi, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; calcium-channel blocker, CCB; VKA, Vitamin K antagonist; DOAC, Direct acting Oral Anticoagulant.

Table S5. Adverse events at one year according to baseline MR severity

	All (N = 268)	**MR≤2+ (N = 211)**	**MR>2+ (N = 57)**	***P***
Primary outcome*, N (%)	55 (20.5)	23 (10.9)	32 (56.1)	<0.001
All-cause death, N (%)	29 (10.8)	10 (4.7)	19 (33.3)	<0.001
Cardiac death, N (%)	21 (7.8)	5 (2.4)	16 (28.1)	<0.001
Non-cardiac death, N (%)	6 (3.0)	5 (2.4)	3 (5.3)	0.373
HF rehospitalization, N (%)	34 (12.7)	13 (6.2)	21 (36.8)	<0.001

HF, heart failure; MR, mitral regurgitation. *Composite of all-cause death and HF rehospitalization.

Table S6. Baseline demographic and clinical features according to MR improvement.

	MR not improved (N = 32)	**MR improved (N = 24)**	***P***
Age, years	82 (78-87)	83 (78-85)	0.708
Sex female, N (%)	18 (56.3)	12 (50.0)	0.788
BSA, m^2	1.7±0.1	1.7±0.1	0.999
Diabetes, N (%)	10 (31.3)	7 (29.2)	1.000
Hypertension, N (%)	30 (93.8)	23 (95.8)	1.000
Hypercholesterolemia, N (%)	28 (87.5)	17 (70.8)	0.176
Smoking, N (%)	1 (4.8)	1 (5.3)	1.000
COPD, N (%)	9 (28.1)	7 (29.2)	1.000
eGFR, mL/min	56 (41-68)	69 (42-85)	0.685
CCS, N (%)	15 (46.9)	8 (33.3)	0.412
Prior MI, N (%)	4 (12.5)	3 (12.5)	1.000
Prior PCI, N (%)	15 (46.9)	6 (25.0)	0.162
Prior CABG, N (%)	4 (12.5)	3 (12.5)	1.000
Prior stroke/TIA, N (%)	1 (3.1)	0 (0)	1.000
Peripheral arteriopathy, N (%)	9 (37.5)	5 (23.8)	0.356
Atrial fibrillation/flutter, N (%)	11 (34.4)	9 (37.5)	1.000
Pacemaker, N (%)	5 (15.6)	2 (8.3)	0.686
ICD/CRT-D, N (%)	1 (3.1)	4 (16.7)	0.153
EuroSCORE II, %	4.4 (3.0-8.0)	8.0 (4.0-12.0)	0.071
NYHA I, N (%)	0 (0.0)	0 (0)	
NYHA II, N (%)	11 (34.4)	8 (33.3)	0.447
NYHA III, N (%)	19 (59.4)	12 (50.0)	
NYHA IV, N (%)	2 (6.3)	4 (16.7)	
LVEF, %,	43 (36-55)	35 (30-57)	0.659
Average AVG, mmHg	33 (26-37)	30 (24-33)	0.153
Aortic valve area, cm^2	0.6±0.1	0.6±0.2	0.401
Aortic valve area index, cm^2/m^2	0.3±0.1	0.4±0.1	0.535
Paradoxical LFLG, N (%)	14 (43.8)	10 (41.7)	1.000
Classical LFLG, N (%)	18 (56.3)	14 (58.3)	1.000
Moderate-to-severe AR, N (%)	1 (3.1)	3 (12.5)	0.303
BAV, N (%)	1 (3.1)	0 (0.0)	1.000
sPAP, mmHg	50 (43-60)	40 (32-55)	0.126
Right Ventricular dysfunction, N (%)	12 (42.9)	7 (33.3)	0.564
Transfemoral approach, N (%)	27 (84.4)	24 (100.0)	0.064
Pacing, N (%)	29 (90.6)	20 (83.3)	0.447
Predilatation, N (%)	16 (50.0)	7 (29.2)	0.171
Balloon-expandable prosthesis, N (%)	5 (15.6)	10 (41.7)	0.037
Self-expandable prosthesis, N (%)	27 (84.4)	14 (58.3)	0.037
Prosthesis size <23 mm, N (%)	4 (12.5)	4 (16.7)	0.713
Postdilatation, N (%)	6 (18.8)	5 (20.8)	1.000
LVEF, %,	48 (36-55)	49 (34-57)	0.861
Average AVG, mmHg	6 (4-8)	6 (5-9)	0.113

Residual moderate-to-severe AR, N (%)	0 (0.0)	0 (0.0)	1.000
sPAP, mmHg	50 (40-65)	40 (35-50)	0.147

Continuous normally distributed variables are expressed as mean ± SD. Categorical variables are expressed as N (%). Continuous non-normally distributed variables are expressed as median (interquartile range).

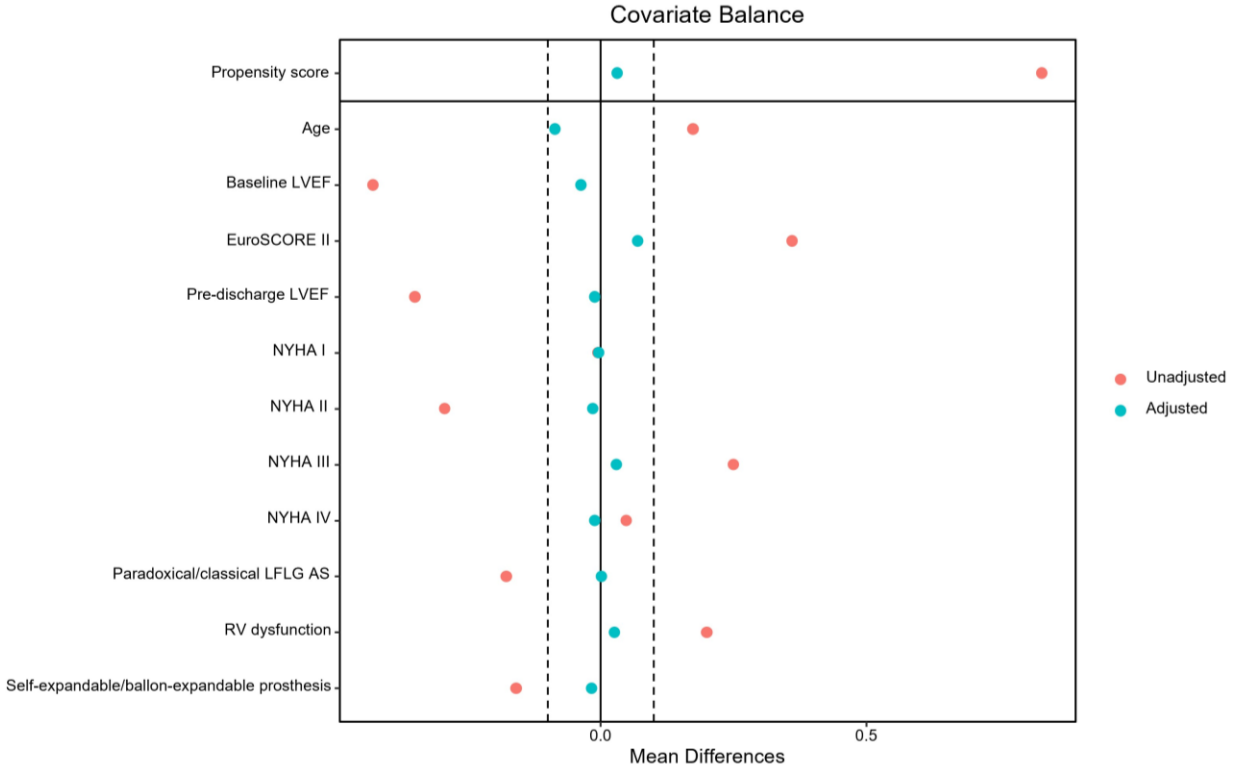
AVG, aortic valve gradient; AR, aortic regurgitation; BAV, bicuspid aortic valve; BSA, body surface area; CABG, coronary artery bypass graft surgery; CCS, chronic coronary syndrome; COPD, chronic obstructive pulmonary disease; CRT-D, Cardiac resynchronization therapy-defibrillator; eGFR, Estimated Glomerular Filtration Rate; EuroSCORE II, European system for cardiac operative risk evaluation; ICD, Implantable cardioverter-defibrillator; LVEF, Left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association functional class; PCI, percutaneous coronary intervention; sPAP, Systolic pulmonary artery pressure; TIA, transient ischemic attack.

Table S7. Adverse events at one year in patients with MR>2+ with or without improvement after TAVR

	All (N = 56)	**MR not improved (N = 32)**	**MR improved (N = 24)**	***P***
Primary outcome*, N (%)	31 (55.4)	22 (68.8)	9 (37.5)	0.030
All-cause death, N (%)	18 (32.1)	14 (43.8)	4 (16.7)	0.044
Cardiac death, N (%)	15 (26.8)	12 (37.5)	3 (12.5)	0.065
Non-cardiac death, N (%)	3 (5.4)	2 (6.3)	1(4.2)	1.000
HF rehospitalization, N (%)	21 (37.5)	16 (50.0)	5 (20.8)	0.030

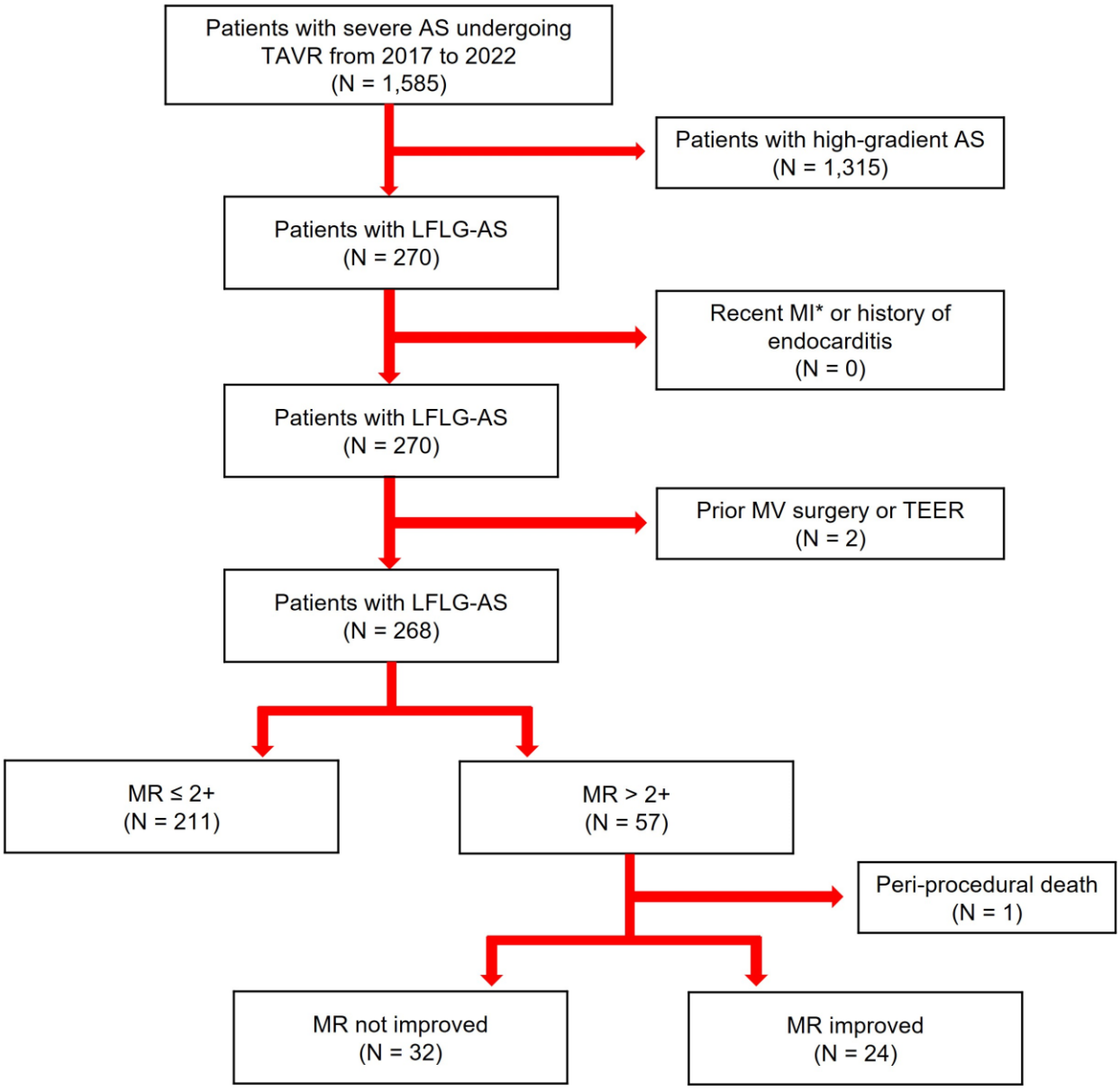
HF, heart failure; MR, mitral regurgitation. *Composite of all-cause death and HF rehospitalization.

Figure S1. Covariate balance for baseline MR severity before and after weighting



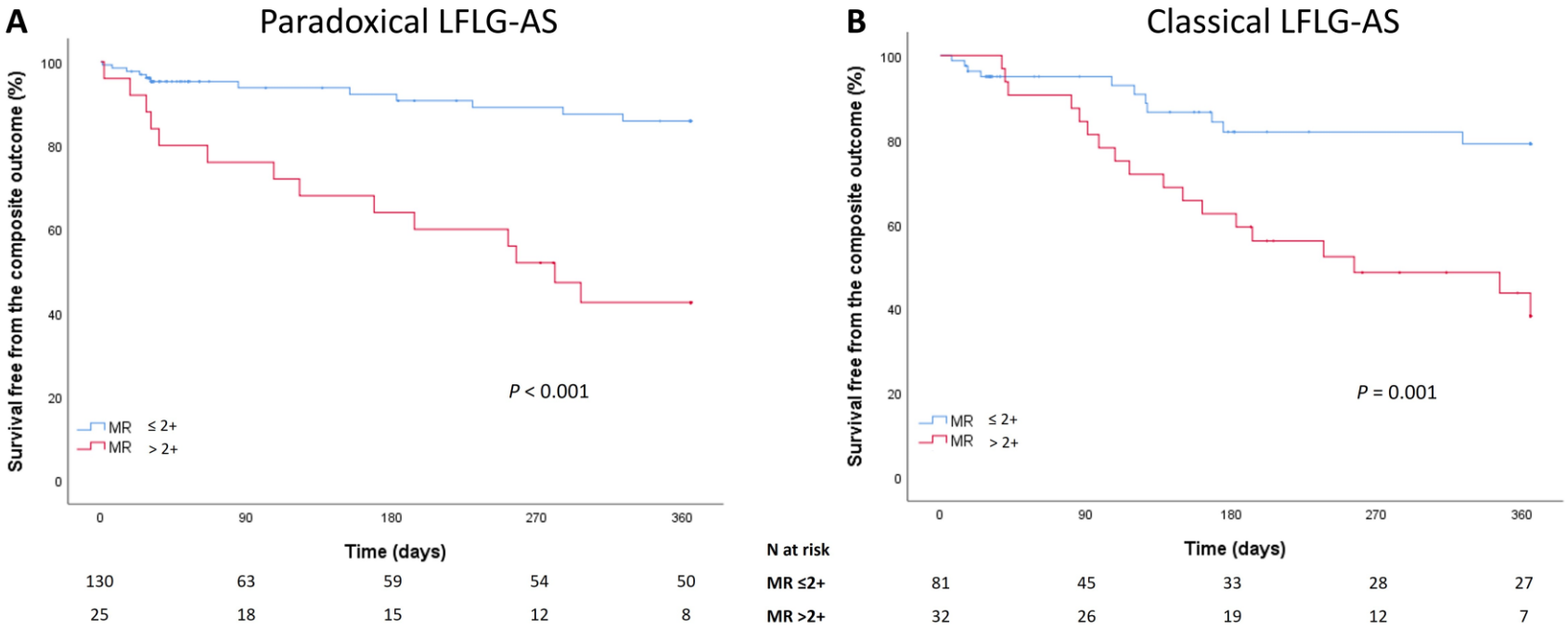
Love plot showing the unadjusted (red circles) and adjusted (blue circles) values of the mean difference before and after weighting. The dotted line represents the threshold value of 0.1, conventionally considered an index of optimal balance achieved after weighting.
EuroSCORE II, European system for cardiac operative risk evaluation; LFLG-AS, low flow low gradient aortic stenosis; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; RV, right ventricular.

Figure S2. Study selection process



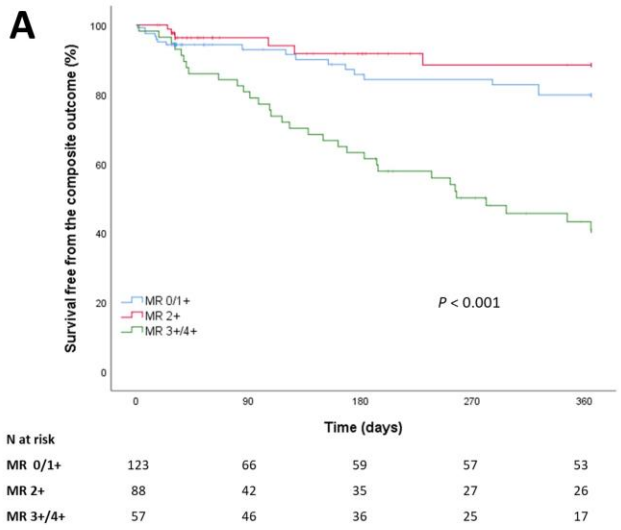
AS, aortic stenosis; LFLG-AS, low flow, low gradient aortic stenosis; MI, myocardial infarction; MR, mitral regurgitation; MV, mitral valve; TEER, transcatheter edge-to-edge repair.
* Defined as MI occurred within 90 days from the TAVR procedure.

Figure S3. Survival free from the primary outcome according to baseline MR severity in patients with paradoxical (panel A) or classical (panel B) LFLG-AS forms

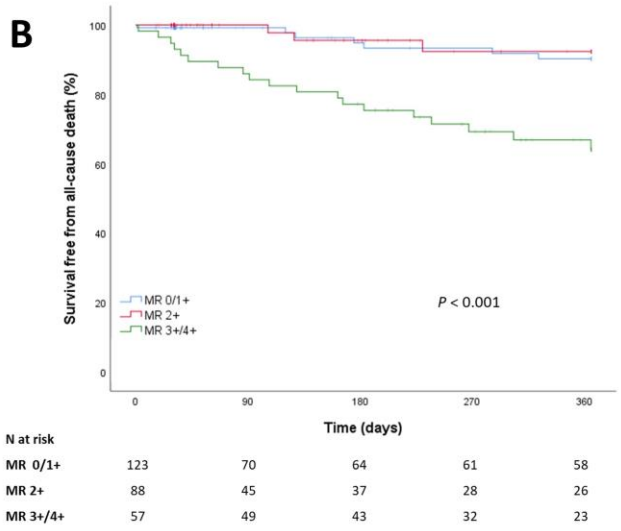


LFLG-AS, low flow, low gradient aortic stenosis; MR, mitral regurgitation.

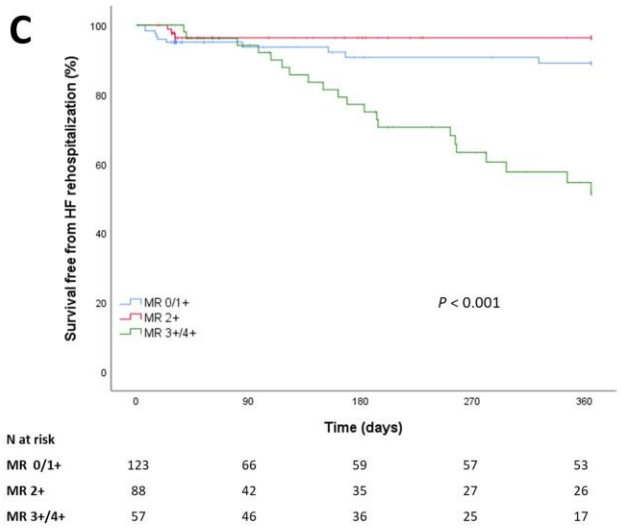
Figure S4. Survival free from the primary outcome (panel A), all-cause death (B), and HF hospitalization (C) in patients with MR 0/1+, 2+ and >2+



N at risk					
MR 0/1+	123	66	59	57	53
MR 2+	88	42	35	27	26
MR 3+/4+	57	46	36	25	17



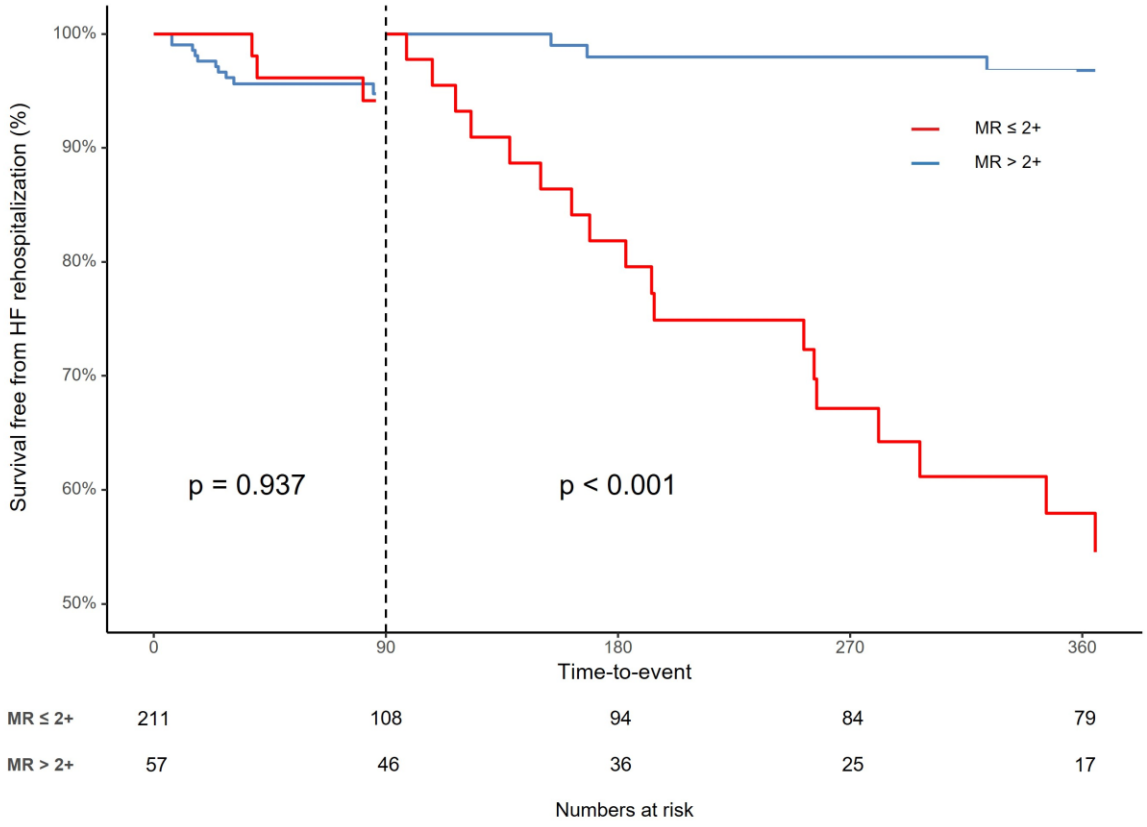
N at risk					
MR 0/1+	123	70	64	61	58
MR 2+	88	45	37	28	26
MR 3+/4+	57	49	43	32	23



N at risk					
MR 0/1+	123	66	59	57	53
MR 2+	88	42	35	27	26
MR 3+/4+	57	46	36	25	17

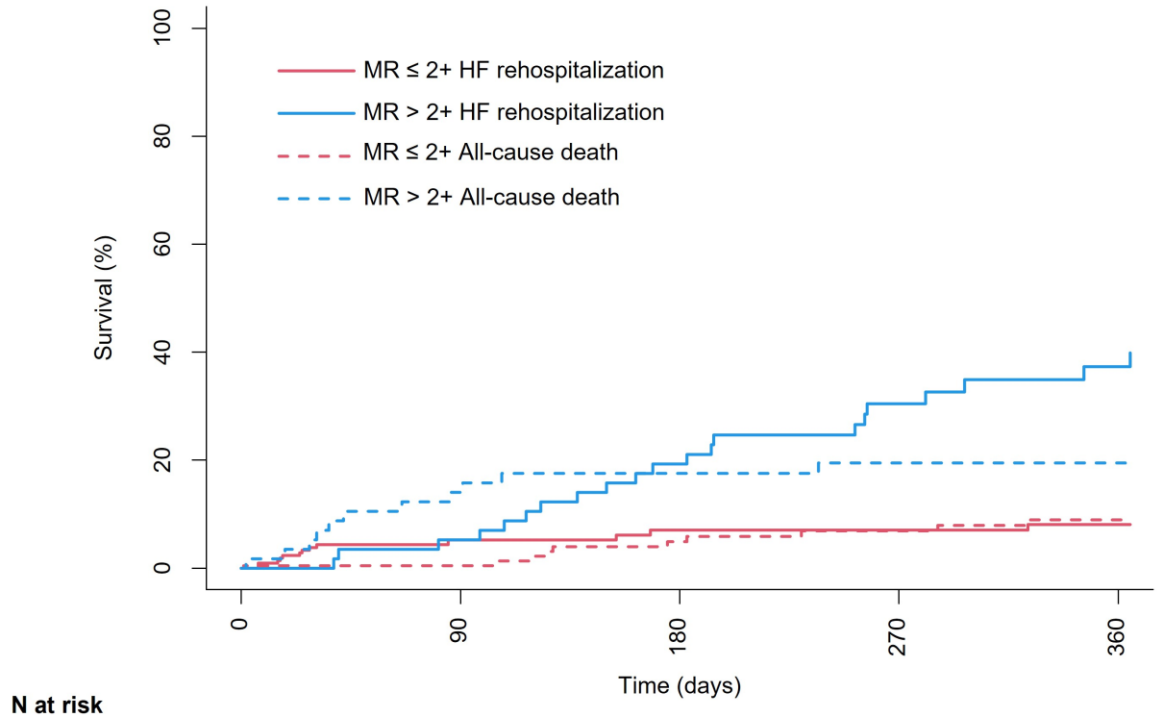
HF, heart failure; MR, mitral regurgitation.

Figure S5. Landmark analysis for HF hospitalization in patients with MR ≤2+ vs. those with MR >2+



HF, heart failure; MR, mitral regurgitation.

Figure S6. Cause-specific risk curves for HF hospitalization (solid curves) and competing risk of death (dotted curves) in patients with MR ≤2+ vs. those with MR >2+



N at risk					
MR ≤2+	211	108	94	84	79
MR >2+	57	46	36	25	17

HF, heart failure; MR, mitral regurgitation.