Effect of Aortic Regurgitation by Cardiovascular Magnetic Resonance After Transcatheter Aortic Valve Implantation

Alfredo N. Ferreira-Neto, MD[a], Constanze Merten, MD[b], Hans-Wilko Beurich, MD[b], Dirk Zachow, MD[b], Gert Richardt, MD[b], Eric Larose, MD[a], Leonardo Guimaraes, MD[a], Philippe Pibarot, PhD[a], Emilie Pelletier-Beaumont, MSc[a], Josep Rodés-Cabau, MD[a,**], and Mohamed Abdel-Wahab, MD[b,c,*]

Cardiovascular magnetic resonance (CMR) has demonstrated a high accuracy for evaluating the severity of aortic regurgitation (AR). However, scarce data exist on the impact of AR as evaluated by CMR on clinical outcomes following transcatheter aortic valve implantation (TAVI). The objective of this study was to evaluate the impact of AR as determined by CMR on clinical outcomes (mortality, heart failure [HF] hospitalization) post-TAVI. A total of 448 TAVI recipients from 2 centers (mean age: 80 ± 7 years, mean STS: 5.8 ± 5.4%) who survived the periprocedural period with no pacemaker implantation were included. A newer generation transcatheter valve system was used in 213 patients (48%). The CMR examination was performed at a median of 12 (IQR: 7 to 21) days post-TAVI. After a mean follow-up of 24 ± 19 months, a total of 94 patients (21%) had died and 72 patients (16%) had at least 1 hospitalization because of decompensated HF. The aortic regurgitation fraction (RF) as determined by CMR was an independent predictor of mortality (hazard ratio[HR]:1.06 for each increase of 10%, 95% confidence interval [CI]: 1.01 to 1.12, p = 0.03) and HF hospitalization (HR:1.15 for each increase of 10%, 95% CI:1.02 to 1.30, p = 0.02). The rate of moderate-severe CMR-AR defined as a RF ≥30% was 3%, and this was associated with an increased risk of mortality (HR: 2.63, 95% CI: 2.30 to 2.99, p <0.001) and HF hospitalization (HR: 2.96, 95% CI: 1.62 to 5.42, p <0.001). A stepwise increase in the risk of mortality and HF hospitalization was observed with an increase in AR severity, with a peak increase among patients with RF ≥30%. In conclusion, our results showed the clinical usefulness of evaluating AR severity by CMR post-TAVI. CMR would be particularly helpful in doubtful cases or those with discordances between echocardiography and clinical data. **(Am J Cardiol 2019;124:78−84)**

Transcatheter aortic valve implantation (TAVI) is a well-established therapy for patients with severe aortic stenosis and increased surgical risk.[1,2] The occurrence of post-procedural aortic regurgitation (AR), mainly secondary to paravalvular leaks (PVL), has been one of the most important limitations of TAVI. With early generation transcatheter valves (THV), up to 70% of patients had ≥mild PVL and close to 10% exhibited moderate or severe AR post-TAVI.[1,3,4] The arrival of newer generation THV (some with specific anti-PVL features) along with improvements in aortic annulus measurement and valve sizing, have translated into a significant reduction of residual AR after TAVI.[5,6] However, the current incidence of ≥mild AR of about 30% (moderate or severe AR: ∼3%) still remains greater than that observed after surgical aortic valve replacement.[5] Proper evaluation of post-TAVI AR by echocardiography may be difficult due to intrinsic characteristics of both the patient and the implanted prothesis.[7,8] Cardiovascular magnetic resonance (CMR) has emerged as an alternative for the diagnosis and quantification of AR after TAVI,[7−16] and several studies have shown that the severity of AR may be misclassified by transthoracic echocardiography (TTE) as compared to CMR.[7,8,10,12,14,16] However, scarce data exist on the clinical value of assessing AR severity post-TAVI by CMR.[17] The aim of our study was to evaluate, in a large cohort of patients, the clinical value of grading AR severity by CMR to determine clinical outcomes post-TAVI.

Methods

A total of 448 consecutive TAVI recipients without permanent pacemaker who survived the periprocedural period between October 2008 and October 2016 were included in the study. The study was performed in 2 centers and TAVI procedures (including valve type selection) were performed

[a]Quebec Heart and Lung Institute, Laval University, Quebec City, Quebec, Canada; [b]Heart Center, Bad Segeberg, Germany; and [c]Heart Center Leipzig at the University of Leipzig, Leipzig, Germany. Manuscript received January 12, 2019; revised manuscript received and accepted April 1, 2019.

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*Corresponding author: Tel: +493418651428; fax:04551/802-4995.

**Corresponding author: Tel: (418) 656-8711; fax: (418) 656-8711.

E-mail addresses: josep.rodes@criucpq.ulaval.ca (J. Rodés-Cabau), mohamed.abdel-wahab@medizin.uni-leipzig.de (M. Abdel-Wahab).

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according to each center's standards. A TTE was performed in all patients at a median of 9 (IQR: 4 to 26) days post-TAVI. Qualitative and semiquantitative parameters were combined to achieve the grading of AR following the American and European Societies of Echocardiography[18] and the VARC-2 criteria.[19] The degree of AR by TTE was categorized as none/trace, mild, moderate, and severe. CMR studies were performed at a median of 12 (IQR: 7 to 21) days post-TAVI, and analyzed by experienced radiologists or cardiologists at the same center performing the TAVI procedure. Electrocardiogram-gated CMR exams were performed with dedicated phased-array cardiac coil, obtaining cine imaging of cardiac function by steady-state free precession sequence at 30 phases per cardiac cycle, in 8 to 14 parallel short-axis, 2 and 4-chamber as well as 2 orthogonal LVOT planes with slice thickness of 6 to 8 mm, during successive end-expiratory breath-holds. Through-plane phase-contrast imaging was performed both in the aorta and at the sino-tubular junction, with velocity encoding maximum value set to 200 cm/s. Flow from the entire cardiac cycle at a demarcated area in the aortic root was integrated as to obtain both the forward and regurgitant flow through the aortic valve. From this analysis, the left ventricular volumes, ejection fractions, outputs, and mass were obtained by the use of a semiautomated software. Total forward volumes as well as the regurgitant volumes and fractions were obtained. Arrhythmia-rejection algorithms within the CMR software were applied during image acquisition and reconstruction as to diminish the effect of cardiac rhythm irregularities. Three grades of AR were defined according to the RF value using the following thresholds: none/trace (RF < 15%), mild (RF 15% to <30%) and moderate/severe (RF ≥ 30%).[17,19] The patients were followed at 1 month, 12 months, and yearly thereafter. Clinical data was entered prospectively in a dedicated database and all clinical events were defined according to the VARC-2 criteria.[19] The primary endpoint was the occurrence of (i) all-cause mortality, and (ii) rehospitalization for heart failure (HF) during the follow-up period.

Continuous variables were tested for distribution normality with the Shapiro Wilk test and expressed as mean ± SD or median (interquartile range). Categorical variables were expressed as n (%). A proportional hazard model was used to compare clinical outcomes between groups. Uni and multivariable analysis were performed to determine the predictors of all-cause mortality and HF rehospitalization. Only variables with a probability value <0.10 through the univariable analysis were entered into the multivariable model. The agreement on AR grading by TTE and CMR was analyzed by the weighted kappa (k). Kaplan-Meier curves and log-rank tests of the time-to-event data were also used to evaluate the overall mortality and the HF rehospitalization. Results were deemed significant when a p value <0.05 was achieved. Analyses were conducted using the SAS statistical package, version 9.4 (SAS Institute Inc., Cary, North Carolina).

Results

The baseline and periprocedural characteristics of the overall population are shown in Table 1. Mean age of the study population was 80 ± 7 years, 56% were women, and the mean Society of Thoracic Surgeons predicted risk of mortality score was 5.8 ± 5.4%. Most procedures (92%) were performed through transfemoral approach, and the majority of patients (64%) received a balloon-expandable valve. A newer generation THV was used in 213 patients (48%). Post-TAVI echocardiography and CMR data are shown in Table 2. A total of 429 (96%) and 19 (4%) patients had ≤mild and moderate-severe AR as evaluated by echocardiography, respectively. By CMR assessment, 435 (97%) and 13 (3%) patients had ≤mild and moderate-severe AR, respectively. Although the mean RF was 7.4 ± 9.3% for the overall population, moderate-severe AR patients presented a mean RF of 43.5 ± 16.6%. The level of agreement between the 2 modalities (TTE and CMR)

Table 1
Clinical, echocardiographic, and procedural characteristics of the overall population (n = 448)

Variable	Overall (n = 448)
Clinical	
Age (years)	80 ± 7
Men	199 (44%)
Body mass index (Kg/m^2)	27 ± 5
Coronary artery disease*	281 (63%)
Prior coronary artery bypass grafting	98 (22%)
History of atrial fibrillation	163 (36%)
Peripheral vascular disease	85 (19%)
Chronic obstructive pulmonary disease	75 (17%)
Chronic kidney disease	119 (27%)
Estimated glomerular filtration rate (ml/min)	68 ± 25
Society of thoracic surgeons predicted risk of mortality (%)	5.8 ± 5.4
Echocardiography pre-TAVI	
Left ventricle ejection fraction (%)	56 ± 12
Mean aortic gradient (mmHg)	43 ± 17
Aortic valve area (cm^2)	0.7 ± 0.3
Multiparametric aortic regurgitation grade	
None/trace	328 (73%)
Mild	74 (17%)
Moderate/severe	44 (10%)
Procedural characteristics	
Success	414 (92%)
Approach	
Transfemoral	410 (92%)
Nontransfemoral	38 (8%)
Prothesis type	
Self-expandable	163 (36%)
CoreValve	96 (21%)
Evolut R	25 (6%)
Other	42 (9%)
Balloon-expandable	285 (64%)
SAPIEN/SAPIEN XT	139 (31%)
SAPIEN 3	146 (33%)
Prothesis size (mm)	
≤23	109 (24%)
>23	339 (76%)
30-day clinical outcomes	
Major vascular complications	16 (4%)
Major bleeding	46 (10%)
Stroke	7 (2%)

* Presence of coronary lesions with diameter stenosis ≥50% or prior coronary revascularization.Values are presented as n (%) or mean ± standard deviation.

Table 2
Post-transcatheter aortic valve implantation echocardiography and cardiac magnetic resonance data (n = 448)

Variable	Overall (n = 448)
Echocardiography	
Time postprocedure (days)	9 (4–26)
Left ventricle ejection fraction (%)	58 ± 11
Mean aortic gradient (mmHg)	11 ± 6
Aortic valve area (cm^2)	1.75 ± 0.57
Pulmonary artery systolic pressure (mmHg)	35 ± 12
Moderate/severe mitral regurgitation	18 (4%)
Multiparametric aortic regurgitation grade	
None/trace	244 (55%)
Mild	185 (41%)
Moderate/severe	19 (4%)
Cardiac magnetic resonance	
Time postprocedure (days)	12 (7–21)
Mean heart rate (beats/min)	69 ± 13
Left ventricle end-diastolic volume (ml)	141 ± 46
Left ventricle end-systolic volume (ml)	65 ± 38
Left ventricle cardiac output (L/min)	5.1 ± 1.3
Left ventricle ejection fraction (%)	56 ± 13
Left ventricle mass (g)	145 ± 38
Total forward volume (ml)	73 ± 20
Regurgitant volume (ml)	5.5 ± 8.0
Regurgitant fraction (%)	7.4 ± 9.3
Aortic regurgitation grade according to cardiac resonance	
None/trace: regurgitant fraction <15%	386 (86%)
Mild: regurgitant fraction 15-<30%	49 (11%)
Moderate/severe: regurgitant fraction ≥30%	13 (3%)

Numbers represent n (%), mean ± standard deviation or median (interquartile range).

was modest (weighted k = 0.26; p <0.0001). A total of 79% of patients categorized as having moderate-severe AR by TTE had in fact a less severe AR by CMR assessment (Figure 1). The main baseline and procedural characteristics of patients according to AR severity by CMR are shown in Supplemental Table 1.

After a mean follow-up of 24 ± 19 months, 94 (21%) patients had died and 72 (16%) patients were rehospitalized because of HF decompensation. The factors associated with death and HF rehospitalization during the follow-up period are shown in Table 3. Greater RF as determined by CMR evaluation was independently associated with both all-cause mortality (p = 0.03), and HF rehospitalization (p = 0.02). Furthermore, when compared to RF < 30%, the presence of RF ≥ 30% was associated with significantly higher rates of mortality (p <0.001) and HF rehospitalization (p <0.001) (Table 4). The Kaplan-Meier estimates for all-cause mortality and HF rehospitalization up to 3-year follow-up according to the presence of moderate/severe AR by CMR evaluation (RF ≥ 30%) are shown in Figure 2. A RF ≥ 30% by CMR was associated with a higher mortality (p = 0.047) and HF rehospitalization (p = 0.007) at 3-year follow-up.

TTE / CMR	None/ Trace	Mild	Moderate/ Severe	Total
None/ Trace	238 (97%)	143 (77%)	5 (26%)	386
Mild	5 (2%)	34 (19%)	10 (53%)	49
Moderate/ Severe	1 (1%)	8 (4%)	4 (21%)	13
Total	244	185	19	276/448 (62%)

Figure 1. Comparison of the aortic regurgitation grade as determined by a multiparametric echocardiographic approach (TTE) versus cardiac magnetic resonance (CMR) post-TAVI.
Grey = number of patients (%) well categorized by TTE when compared to CMR assessment; White = number of patients (%) miscategorized by TTE when compared to CMR assessment.

Discussion

Whereas first generation THV were associated with up to 70% and ~10% of mild and moderate/severe AR, respectively,[1,3,4,20,21] rates of ~30% and ~3% of mild and moderate/severe AR, respectively, have been reported with the use of newer generation THV.[5,6,22,23] These results coincide with the echocardiographic data obtained in our study, in which newer generation valves were used in about half of the patients, with rates of 41% and 4% of mild and moderate-severe AR, respectively. However, proper diagnosis and grading of AR by TTE may be challenging after TAVI mainly due to the presence of multiple and eccentric regurgitant jets often obscured by the Doppler weakening caused by the prosthesis and calcification present in the aortic leaflets and left ventricular outflow tract.[7–10,12,16,24]

More recently, CMR has been shown to be an accurate and reproducible tool for the assessment of AR in patients with native aortic valve disease[25–27] and in TAVI recipients.[7–17] However, longer procedural/image acquisition times, the possibility of artefacts and interference of arrhythmias in image acquisition and interpretation are known caveats of such exam.[27] Although 36% of our patients had a previous history of atrial fibrillation, such rhythm was not necessarily present during the CMR exam. Additionally, the mean heart rate during these exams (69 ± 13 beats/min) was satisfactory and the use of arrhythmia-rejection algorithms present in the acquisition and reconstruction software of CMR exams further reduced the impact of occasional cardiac rhythm irregularities. Differences in agreement between echocardiography and CMR, as that observed in the present study, have been extensively reported, with echocardiographic evaluation typically under- or overestimating the severity of post-TAVI AR in a significant proportion of cases.[7–10,12,16,24] The difficulties in accurately grading post-TAVI AR by echocardiography may partially explain some of the differences between studies regarding the clinical impact of residual AR (>none/trace).[12,20,28,29] In fact, the observed discrepancy in AR grading, where 79% of patients with moderate-severe AR by TTE exhibited a less severe AR by CMR, may partially explain why this cohort had an unexpected lower mortality risk in the presence of moderate-severe AR by TTE assessment. Also, the relatively low number of patients with moderate-severe AR along with the presence of multiple noncardiac comorbidities may have influenced the results.

Table 3
Predictors of mortality or HF rehospitalization post-TAVI

	Univariable model		Multivariable model	
	HR (95% CI)	p Value	HR (95% CI)	p Value
All-cause mortality (n = 94, 21%)				
Men	1.39 (1.23−1.57)	<0.001	1.41 (1.27−1.58)	<0.001
Coronary artery disease	1.03 (1.01−1.05)	0.002	0.95 (0.83−1.08)	0.42
Chronic obstructive pulmonary disease	1.41 (1.05−1.88)	0.021	1.40 (0.96−2.04)	0.08
Regurgitation fraction*	1.12 (1.02−1.24)	0.024	1.06 (1.01−1.12)	0.03
Diabetes	0.90 (0.87−0.94)	<0.001	0.78 (0.68−0.91)	0.001
Left ventricle ejection fraction	0.99 (0.99−0.99)	<0.001	1.00 (0.99−1.00)	0.68
Estimated glomerular filtration rate <60 ml/min	0.99 (0.99−0.99)	<0.001	1.68 (1.35−2.08)	<0.001
New York Heart Association III-IV	1.66 (0.97−2.86)	0.067	1.49 (0.91−2.41)	0.11
Stroke	2.46 (2.15−2.81)	<0.001	3.00 (2.74−3.30)	<0.001
Major bleeding	1.66 (1.40−1.97)	<0.001	1.60 (1.12−2.29)	0.009
Rehospitalization for HF (n = 72, 16%)				
Men	1.93 (1.58−2.36)	<0.0001	1.69 (1.54−1.85)	<0.0001
Coronary artery disease	1.70 (1.33−2.16)	<0.0001	1.45 (1.19−1.78)	0.0003
Regurgitation fraction*	1.21 (1.08−1.36)	0.0008	1.15 (1.02−1.30)	0.02
Diabetes	1.09 (1.06−1.13)	<0.0001	0.95 (0.86−1.04)	0.26
Stroke	0.82 (0.77−0.88)	<0.0001	0.86 (0.69−1.07)	0.18

* For each increase of 10%.

Previous studies using CMR have reported a rate of moderate-severe AR post-TAVI ranging from 13% to up to 50%.[7,8,14,17] These differences may be explained by the use of different classifications for grading the severity of AR. The lower rate of moderate-severe AR observed in our study (3%) may be explained by the use of newer generation THV in a significant proportion of patients (all previous CMR studies in the TAVI field were performed in patients receiving older generation THV), as well as by the strict criteria used for defining moderate-severe AR. The RF cut-off of 30% determining clinically significant AR was first described in the evaluation of AR severity in native aortic valves,[26] and Ribeiro et al[17] showed, in a cohort of 135 patients, that a RF ≥30% was the best threshold for identifying patients at increased risk of major cardiovascular events within 2 years post-TAVI. Our study confirms, by analyzing the largest cohort of patients with post-TAVI CMR to date, that the 30% RF cut-off appropriately determined an increased risk of mortality and HF hospitalization.

The added value of implementing CMR examinations in the evaluation of TAVI results observed in our study may have important clinical implications. However, the systematic use of CMR in all TAVI patients would translate into a major increase in costs, and could also be associated with logistic issues due to the more restricted access to CMR. Also, the incidence of clinically significant AR appears to be rather low (3%) with the use of newer generation THV. Thus, CMR assessment may be reserved to cases with doubtful or borderline echocardiography data, or to cases with a discordance between clinical presentation and echocardiographic findings (i.e. patients with HF symptoms despite ≤mild AR as evaluated by echocardiography, or patients with good early outcomes despite of a moderate-severe AR). In these cases, CMR may play an important role in accurately quantifying AR post-TAVI, thus helping

Table 4
Clinical outcomes according to aortic regurgitant fraction as determined by cardiac magnetic resonance and transthoracic echocardiography

Cardiac magnetic resonance	Overall (n = 448)	Regurgitant fraction <30% (n = 435)	Regurgitant fraction ≥30% (n = 13)	Regurgitant fraction ≥30% vs <30%	
				HR (95% CI)	p Value
All-cause mortality	94 (21%)	87 (20%)	7 (54%)	2.63 (2.30−3.00)	<0.001
Rehospitalization for HF	72 (16%)	66 (15%)	6 (46%)	2.96 (1.62−5.42)	<0.001
Transthoracic echocardiography	**Overall (n = 448)**	**Aortic regurgitation ≤Mild (n = 429)**	**Aortic regurgitation >Mild (n = 19)**	**Aortic regurgitation > Mild vs ≤ Mild**	
				HR (95% CI)	p Value
All-cause mortality	94 (21%)	92 (21%)	2 (11%)	0.46 (0.45−0.47)	<0.001
Rehospitalization for HF	72 (16%)	69 (16%)	3 (16%)	0.93 (0.81−1.07)	0.327

Results are shown as n (%).

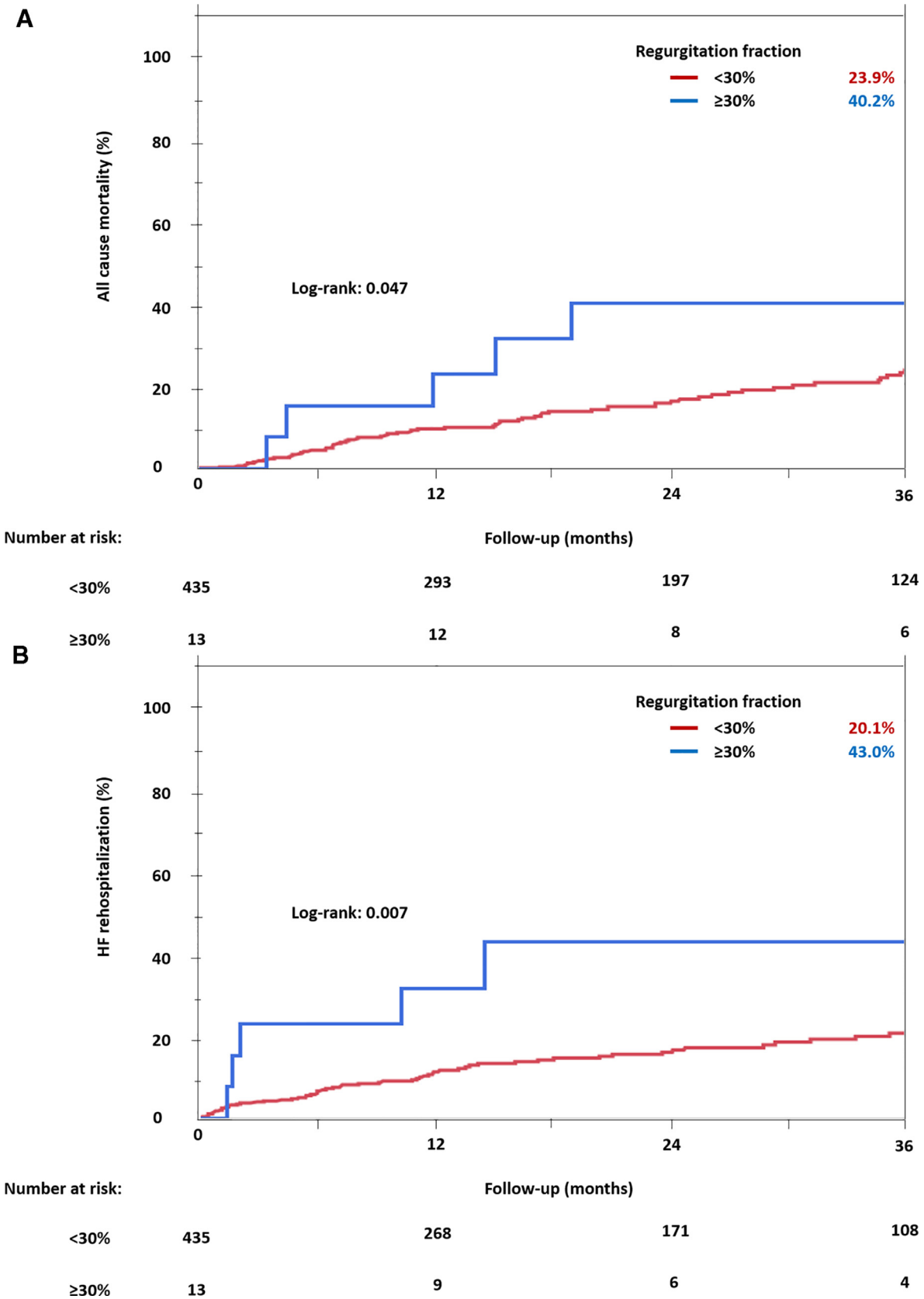

Figure 2. Kaplan-Meier estimates for mortality and HF hospitalization according to the presence of moderate/severe aortic regurgitation (RF ≥ 30%) as determined cardiovascular magnetic resonance.
A. All-cause mortality. B. Rehospitalization due to decompensated HF.

to improve patient treatment. Importantly, our data strongly suggest that the presence of a RF ≥30% should trigger the implementation of additional interventions to reduce AR severity.

This study has some limitations. While clinical and CMR data were entered prospectively in a dedicated database, the analyses of this study were of retrospective nature and limitations associated to this methodology must be considered. The interpretation of CMR was performed by experienced cardiologists or radiologists, but there was no central CMR lab for the study.

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Supplementary materials

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