Effect of Successful Edge-to-Edge Mitral Valve Repair on Ventricular Arrhythmic Burden in Patients With Functional Mitral Regurgitation and Implantable Cardiac Devices

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Significant mitral regurgitation (MR) may be present in up to half of patients with heart failure (HF) and it is associated with adverse cardiac remodeling and myocardial stretch. These are potential triggers for ventricular arrhythmias (VA) in patients with HF, and therefore MR may enhance electrical ventricular vulnerability. Our aim was to evaluate VA burden before and after percutaneous mitral valve repair (PMVR) in patients with implantable cardiac devices. We conducted a prospective registry of all consecutive patients (n = 34, age 69.0 ± 12.2 years, 77% male) with significant functional mitral regurgitation (FMR) who underwent MitraClip implantation in 2 centers between June 2014 and July 2018. VA burden was defined as the total number of events during device follow-up before and after PMVR. Among patients presenting VA during follow-up before or after PMVR, device success at hospital discharge was related to a significant reduction in the incidence of Nonsustained ventricular tachycardia (VT, p = 0.002) and any sustained VT or rapid VT/ventricular fibrillation (p = 0.034). Regarding implantable cardiac defibrillator (ICD) therapies, successful PMVR was related to a reduction in incidence of either antitachycardia pacing or appropriate shocks (p = 0.045) and in the occurrence of any defibrillation shocks (p = 0.045). Overall, effective repair lead to a significant reduction in the VA burden, with a significant decrease in the occurrence of any VA (p = 0.004) and any ICD therapies (p = 0.045). In conclusion, device success after PMVR was related to a reduction in overall arrhythmic burden and ICD therapies in our cohort. **(Am J Cardiol 2019;124:1113−1119)**

Moderate to severe mitral regurgitation (MR) may be present in up to half of patients with congestive heart failure (HF) and it is associated with poor outcomes.[1] From a pathophysiological perspective, MR implies a volume overload for the left cardiac chambers leading to left atrial (LA) and ventricular (LV) dilatation.[2] Cardiac remodeling[3] and myocardial stretch[4] are well identified as potential triggers for ventricular arrhythmias (VA) in patients with HF, and therefore MR may enhance electrical ventricular vulnerability.[5] Percutaneous mitral valve repair (PMVR) with MitraClip (Abbott Vascular, Santa Clara, CA) has proved to effectively reduced MR in patients at high risk for conventional surgery.[6] Furthermore, successful reduction of MR has translated into positive changes in cardiac hemodynamics and remodeling in different series. To the best of our knowledge, no data are available regarding the incidence of VA in patients undergoing PMVR. Our aim was to evaluate VA burden before and after PMVR in patients with implantable cardiac devices. We hypothesized that hemodynamic improvement after PMVR might have a positive impact in the frequency of VA.

Methods

We performed a prospective registry of all consecutive patients with functional MR (FMR) grade 3+ or 4+ who underwent PMVR in any of 2 centers (University Hospital of León [León, Spain] or University Hospital Puerta de Hierro [Madrid, Spain]) between June 2014 and July 2018. Only patients with an active implantable cardiac device (pacemaker, defibrillator or resynchronizer) were included for this report. Patients who fulfilled any of the following criteria were excluded for the analysis: time frame of follow-up less than 1 month from device implantation to PMVR or after PMVR (n = 3), effective VT ablation (n = 2) or upgrade procedure for cardiac resynchronization therapy

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(CRT) (n = 4) at any time after implantation of the first cardiac device.

Indication for PMVR was discussed in an interdisciplinary heart team including interventional and clinical cardiologists, cardiac surgeons, and specialists in cardiovascular imaging. All patients were at optimal medical therapy for HF at maximum tolerated doses at the time PMVR was performed. The procedure was performed according to standard practices under general anesthesia with fluoroscopic and transesophageal echocardiographic guidance.

Preprocedural demographic features as well as procedural outcomes were collected. Clinical and echocardiographic follow-up were performed addressing all-cause mortality, New York Heart Association (NYHA) functional class, N-terminal pro-Brain Natriuretic Peptide (NT-proBNP), and residual MR and LV ejection fraction. Medical therapies for HF were evaluated before and after PMVR, including doses of beta-blockers and amiodarone as potential antiarrhythmic confounders. For statistical purposes, dose of beta-blockers was classified in 2 levels (low and high) based on target daily recommended dose for each drug.

Frequency and characteristics of VA in all subjects and device antiarrhythmic therapies in patients with an implantable cardiac defibrillator (ICD) or ICD-CRT were determined by retrospective assessment of clinical and device follow-up records and local databases. Two cardiologists (T.B.G. and C.A.S.) independently analyzed all arrhythmic records and classified events according to prespecified criteria. Discrepancies between the reviewers were resolved by discussion. Data collection was approved by the local ethics committee of our institution and written informed consent was obtained.

VA burden was defined as the total number of events during device follow-up time frame presented on a per month basis before and after PMVR. Ventricular tachycardia (VT) was defined as a ventricular tachyarrhythmia with a cycle length between 300 and 400 ms and was classified as sustained or nonsustained depending on duration ≥ or <30 seconds, respectively. VT with a cycle length between 400 and 600 ms were also included if considered clinically relevant (documented symptoms, prompting hospital admission or ICD therapy). Ventricular fibrillation and rapid VT were defined as a sustained VT with a cycle length <300 ms. Antitachycardia pacing attempts and shocks were also collected in patients with ICD or ICD-CRT. Postprocedural events regarding PMVR were defined according to Mitral Valve Academic Research Consortium (MVARC) definitions.[7]

Continuous variables were summarized as mean ± standard deviation (SD) or as medians and interquartile range (IQR), and were compared using paired or unpaired Student *t* tests, or the nonparametric Wilcoxon rank sum tests if the normal distribution the variables could not be demonstrated. Derangement from the normal distribution was assessed with the Shapiro-Wilk test. Categorical variables were described as percentages and compared using Chi-square or Fisher exact tests accordingly to expected frequency over or below 5, respectively. McNemar's or exact binominal tests were used to compare before and after PMVR paired categorical variables depending sample size over or below 25. A p-value <0.05 was regarded as statistically significant. Statistical analyses were performed using STATA software version 14.2.

Results

Thirty-four patients with an implantable cardiac device and FMR grade 3+/4+ who underwent PMVR in one of the 2 recruiting centers within the specified period were included in this report.

Patients undergoing PMVR were severely symptomatic at the time of the procedure so that 94% of them had been admitted for HF within the previous year and/or were in advanced functional class NYHA III-IV. Prevalence of comorbidities was high in this cohort. Indications for implantable cardiac device are displayed in Table 1. Characteristics of studied population are summarized in Table 2.

PMVR was successfully performed in all patients (technical success 100%) and more than one clip was implanted in 14 (41%) cases. At discharge, all but 2 (94%) patients had a reduction in at least one degree in the severity of preprocedural MR, and 29 subjects presented MR ≤2+ (device success 85%). The median postprocedural transmitral valve gradient was 2.2 (IQR 2.0 to 2.5) mm Hg.

During a median clinical follow up of 438 (IQR 118 to773) days, 3 patients died from stroke, cancer, and chronic respiratory failure. Device success at discharge was related to a significant improvement in NYHA functional class ([I 0%,II 10%, III 77%, IV 14%] vs [I 15%,II 58%, III 15%, IV 12%], p = 0.0004) and to a nonsignificant reduction in NT-proBNP (3436.5 [IQR 2211 to 7187.5] vs 2246 [IQR 1406 to 4763], p = 0.094) and LV end-diastolic volume (184 [IQR 156 to 232] vs 173 [IQR 146 to 198], p = 0.093), with no changes in LV end-systolic volume (136 [IQR 104 to 174] vs 125 [IQR 99 to 146], p = 0.809) at last follow-up.

Overall, 19 (56%) patients presented VA at any time during follow-up. Differential features of included cohort are displayed in Table 2 grouped according to the occurrence of VA. Patients who presented VA were more frequently men (p = 0.011) with nonischemic cardiomyopathy (p = 0.037) and an ICD or CRT implanted rather than pacemaker (p = 0.018). Furthermore, they were in a more advanced NYHA functional class before PMVR (p = 0.053), had a higher prevalence of chronic kidney disease (p = 0.012) and presented higher procedural risk profiles according to Euroscore II (p = 0.009).

Table 1
Indications for implantation of cardiac devices before percutaneous mitral valve repair (n = 34)

Type of implantable cardiac device	Indication	N
Pacemaker	Advanced atrioventricular block	6 (18%)
	Sick sinus syndrome	0
Defibrillator	Primary prevention	18 (53%)
	Secondary prevention	1 (0.03%)
Resynchronizer	Left bundle brunch block	8 (24%)
	Other intraventricular conduction abnormalities	1 (0.03%)

Table 2
Baseline clinical characteristics of the included cohort. Preprocedural features among patients who presented or not any ventricular arrhythmic event during follow-up are displayed

All patients (n = 34)		Ventricular arrhythmic events		p Value
		Yes (n = 19)	No (n = 15)	
Age (years)	69.0 ± 12.2	70.8 ± 9.1	66.8 ± 15.3	0.170
Men	77%	95%	53%	0.011
Diabetes mellitus	24%	32%	13%	0.257
Ischemic heart disease	50.0%	32%	73%	0.037
Prior myocardial infarction	12/17 (71%)	5/6 (83%)	7/11 (64%)	0.600
Prior revascularization	15/17 (88%)	5/6 (83%)	10/11 (91%)	1.000
Atrial fibrillation	74%	79%	67%	0.462
Peripheral artery disease or stroke	24%	26%	20%	1.000
Chronic obstructive pulmonary disease	12%	16%	7%	0.613
Heart failure admissions (n/previous year)	1.8 ± 1.2	1.8 ± 1.3	1.7 ± 1.0	0.399
NYHA functional class IV	15%	26%	0.0	0.053
Implantable cardiac device				0.018
Pacemaker	18%	5%	33%	
Defibrillator	56%	53%	60%	
Resynchronizer	27%	42%	7%	
Chronic kidney disease GFR ≤ 60 mL/min	65%	84%	40%	0.012
EuroScore logistic	18.9 ± 12.0	21.8 ± 13.3	15.2 ± 9.3	0.054
EuroScore II	7.8 ± 4.2	9.3 ± 4.3	6.0 ± 3.2	0.009
Left ventricular ejection fraction	32.1 ± 11.2	30.5 ± 8.6	34.1 ± 13.9	0.183

Patients were followed up during a median of 32.1 (IQR 14.7 to 69.8) months from the implantation of a cardiac device until PMVR was performed. During this period of time, 18 (53%) patients presented VA in implantable cardiac device monitoring. Among them, 9 (27%) patients received ICD therapies. After MitraClip implantation, the cohort was followed for a median of 14.2 (IQR 3.8 to 25.4) months. During this time frame, 7 (21%) patients presented VA, including one patient who did not present VA before PMVR, and 3 (9%) subjects received ICD therapies. Overall, the number of patients who presented VA (53% vs 21%, p = 0.003) and ICD therapies (27% vs 9%, p = 0.070) was lower after PMVR (Figure 1). Furthermore, postprocedural VA were less frequent in patients with lower residual MR at discharge: grade 0+/1+ 6%, grade 2+ 27% and 60%, p = 0.013) (Figure 1).

Among patients who presented VA during follow-up (either before or after PMVR), device success at hospital discharge (16 of 19 [84%]) was related to a significant reduction in the incidence of nonsustained VT (p = 0.002) and any sustained ventricular tachycardia or rapid VT/VF (p = 0.034) (Table 3). Regarding ICD therapies, successful treatment with MitraClip was related to a significant reduction in incidence of either antitachycardia pacing or appropriate defibrillation shocks (p = 0.045) and in the occurrence of any defibrillation shocks (p = 0.045). Overall, effective transcatheter mitral valve repair lead to a significant reduction in the VA burden, with a significant decrease in the occurrence of any VA (p = 0.004) or any ICD therapies (p = 0.045). Changes in the incidence of VA events before and after PMVR in patients with device success are displayed in Figure 2.

No significant differences were observed regarding pharmacological treatment for HF at the time of PMVR and at last clinical follow-up among the subgroup of patients who were analyzed for VA events during follow-up (Table 4). Furthermore, no significant changes were observed in the dose of beta-blockers within this observation period. The use of amiodarone remained also unchanged before and after PMVR. No other antiarrhythmic drugs were administered in this cohort. A nonsignificant reduction in the dose of oral diuretics (p = 0.057) was noted at last follow-up.

Discussion

This study addressed the impact of MitraClip on the susceptibility for VA in patients with implantable cardiac devices. The main findings of our report were that successful PMVR was associated with a significant decrease in overall VA and ICD therapies. PMVR was performed in a cohort of patients with HF and moderate to severe or severe FMR who remained symptomatic despite medical therapy. Pharmacological treatment for HF was deemed to be as optimal as tolerated in each patient before PMVR and was not substantially changed during follow-up. Dosing of most commonly used antiarrhythmic drugs in this scenario were not either significantly increased during follow-up.

VA are fairly common in patients with HF, especially among those with highly symptomatic end-stage disease.[8] In our cohort, VA occurred in over half of included patients and were more frequent in male and high-risk patients. Overall, prevalence of common comorbidities was higher in patients that presented VA during follow-up. At this regard, all patients in functional class NYHA IV before PMVR presented at least one VA event during follow-up. The incidence of VA was higher among patients with nonischemic cardiomyopathy, which might be due to the high rate of previous revascularization among patients with ischemic heart disease.

MR prompts a volume overload leading to progressive LV remodeling[2] and fibrosis, and myocardial stretch, which

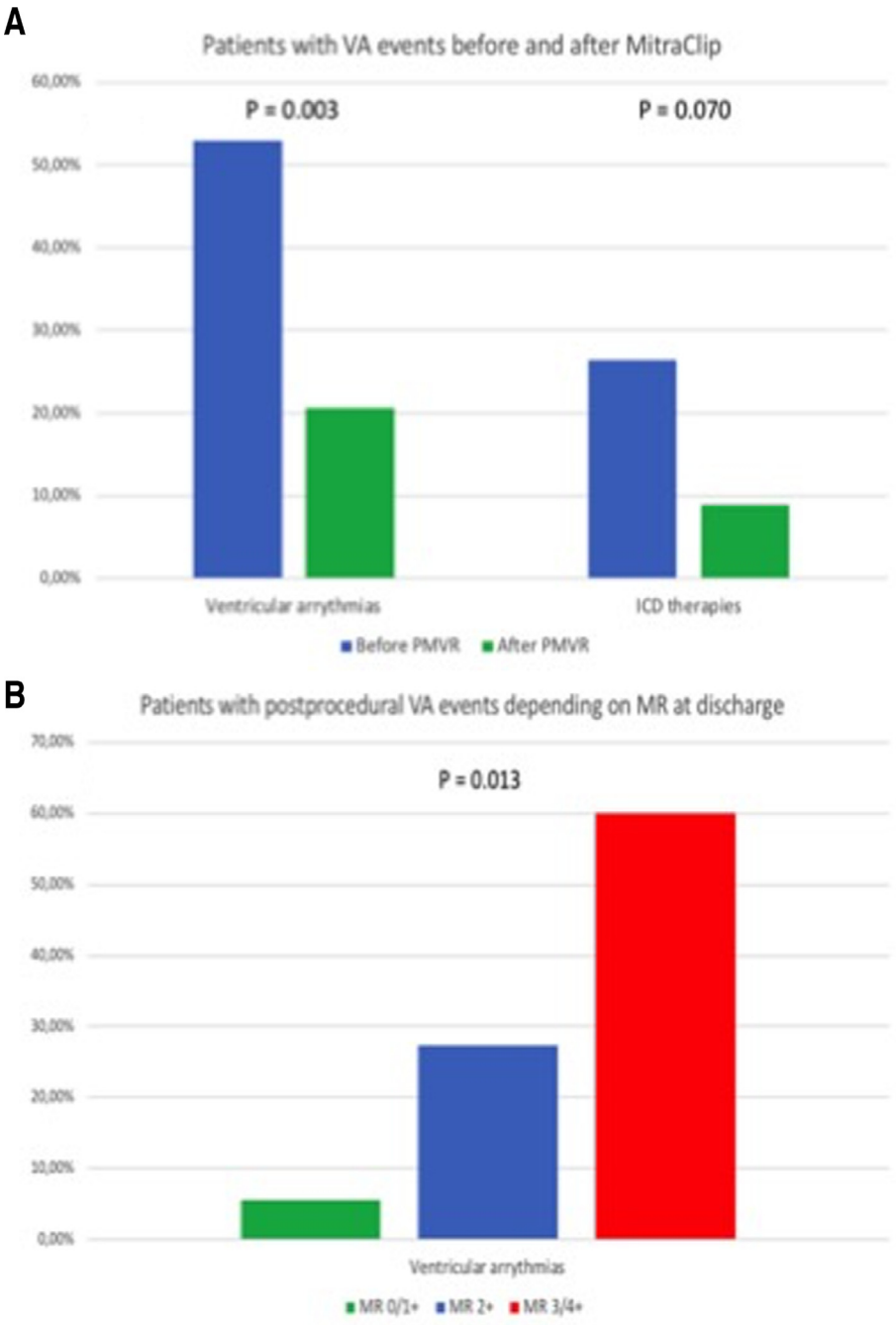

Figure 1. *(A)* Proportion of patients that presented VA and antitachycardia therapies before and after MitraClip. *(B)* Proportion of patients that presented VA after percutaneous mitral valve repair according to residual MR at discharge. MR = mitral regurgitation; VA = ventricular arrhythmias.

have been associated with the incidence of VA.[4,9,10] At this regard, Aleong et al reported that LV end-diastolic diameter was independently associated to defibrillator shocks beyond LVEF[11] and moderate to severe MR was found to be an independent factor for the incidence VA in patients with dilated cardiomyopathy.[12]

PMVR has proved to effectively reduce MR, which leads to a hemodynamic enhancement that has translated into a significant clinical improvement in different contemporary series.[13–15] Symptomatic relief may have an impact on the VA burden, since, as it occurred in our cohort, patients with and advanced NYHA functional class have shown a much higher incidence of VA.[8] At this regard, Boccalandro et al reported a strong relationship between worse clinical status and repolarization abnormalities that constitute a cornerstone trigger for VA.[16] Furthermore, Ishikawa et al published that unloading of left cardiac chambers was related to a reduction in myocardial stress and arrhythmic burden in a preclinical model.[17] Improvement of LV hemodynamic conditions after successful PMVR might therefore lead to a reduced myocardial electrical vulnerability.

Decreasing left cardiac chambers volume overload after PMVR was associated with a reduction in neurohormonal activation[12] and to an inverse positive remodeling and to an

Table 3
Ventricular arrhythmic burden in patients with successful reduction of MR ≤2+ after percutaneous mitral valve repair (events per patient per month)

n = 16			
Ventricular arrhythmic events	Before PMVR	After PMVR	p Value*
Nonsustained ventricular tachycardia	0.06 [0.01-0.42] 0.28 ± 0.43	0 [0-0.01] 0.05 ± 0.13	0.003
Sustained ventricular tachycardia	0 [0-0.02] 0.08 ± 0.25	0 [0-0] 0.01 ± 0.01	0.062
Rapid sustained ventricular tachycardia or ventricular fibrillation	0 [0-0.02] 0.04 ± 0.12	0 [0-0] 0.01 ± 0.04	0.126
Any sustained ventricular arrhythmia	0 [0-0.05] 0.12 ± 0.37	0 [0-0] 0.01 ± 0.06	0.034
Any ventricular arrhythmia	0.18 [0.05-0.42] 0.41 ± 0.74	0 [0-0.01] 0.06 ± 0.14	0.004
Anti-tachycardia pacing†	0 [0-0.01] 0.13 ± 0.33	0 [0-0] 0 ± 0.01	0.062
Appropriate ICD shock†	0 [0-0.03] 0.06 ± 0.14	0 [0-0] 0.01 ± 0.06	0.126
Inappropriate ICD shock†	0 [0-0] 0.03 ± 0.09	0 [0-0] 0	0.157
Any ICD shock†	0 [0-0.05] 0.08 ± 0.18	0 [0-0] 0.01 ± 0.06	0.070
Anti-tachycardia pacing or Appropriate ICD shock†	0 [0-0.05] 0.19 ± 0.45	0 [0-0] 0.02 ± 0.07	0.045
Any ICD therapy†	0 [0.-0.08] 0.21 ± 0.51	0 [0-0] 0.02 ± 0.07	0.045
Any ventricular arrhythmic event (ventricular arrhythmia or ICD therapy)	0.21 [0.06-0.55] 0.61 ± 1.12	0 [0-0.01] 0.08 ± 0.18	0.005

* Wilcoxon matched-pairs signed-ranks test.
† Among patients with ICD or ICD-CRT.

improved LA and LV function in most reports.[18] Worthy of mention, these changes seemed to be directly related to the grade of reduction in MR.[19] In patients with end-stage HF, cardiac reverse remodeling related to other HF therapies (such as CRT) was associated with a significant reduction in the risk of subsequent life-threatening VA.[20] Similarly, inverse LV remodeling after correction of MR might contribute to the reduction of VA after PMVR. At this regard, device success in our cohort was related to an improved NYHA functional class and a strong trend to reduce NT-proBNP levels and LV dimensions during follow-up.

Beyond being a frequent finding in this population, the incidence of VA is related to progression of pump failure[21] and increased rates of rehospitalizations for HF and death.[22] Furthermore, VA and sudden cardiac death are a frequent cause of mortality in patients with advanced HF[23] and the incidence of either appropriate and inappropriate ICD shocks does also impair prognosis.[24] From a theoretical point of view, we may expect that the reduction of the VA burden and ICD shocks after successful PMVR translates into an increased survival in this setting. Different observational series including mainly patients with FMR have pointed out a reduction in all-cause mortality in patients who underwent PMVR compared with those treated consevatively.[25] To date 2 randomized control trials have addressed potential survival benefit of MitraClip implantation over standalone medical treatment in the setting of FMR. MITRA-FR[26] trial did not show significant differences in survival at 1-year follow-up among patients with FMR that received MitraClip compared with those treated medically. On the contrary, the recently published COAPT[27] trial analyzed a larger population and did robustly show an overall 38% relative reduction in all-cause mortality at 2-years follow-up, including cardiovascular mortality and death related to HF. A higher device success rate, cohort size and follow-up period, and an accurate documentation of concomitant HF medications in this study, alongside with differences in enrolled populations may explain these results. At this regard, reduction in VA, as found in this study, might account as a major underlying mechanism for improved survival after PMVR.

This is the first study to address VA in patients with FMR undergoing PMVR. Nevertheless, this report presents several limitations. First, the study population was small. Second, the nonrandomized before and after design might have precluded the introduction of some variables related the incidence of VA. At this regard, patients undergoing VT ablation and those who receive a CRT device as an upgrade procedure, which have proved to reduced VA burden, were not included in the analysis. Furthermore, concomitant antiarrhythmic drugs and HF therapies, which have also been related to a decrease in the frequency of VA, were overall not significantly modified after PMVR. Due to the retrospective device follow-up, differences in device programming and/or initiation of antiarrhythmic drug therapies occurring as a result of a documented VA were not evaluated. Incidence of new ischemic cardiac events or revascularization procedures in patients with coronary artery disease was neither addressed. Patients from 2 different centers were included in the present report, assuming similar characteristics, and therefore multilevel analysis was not performed.

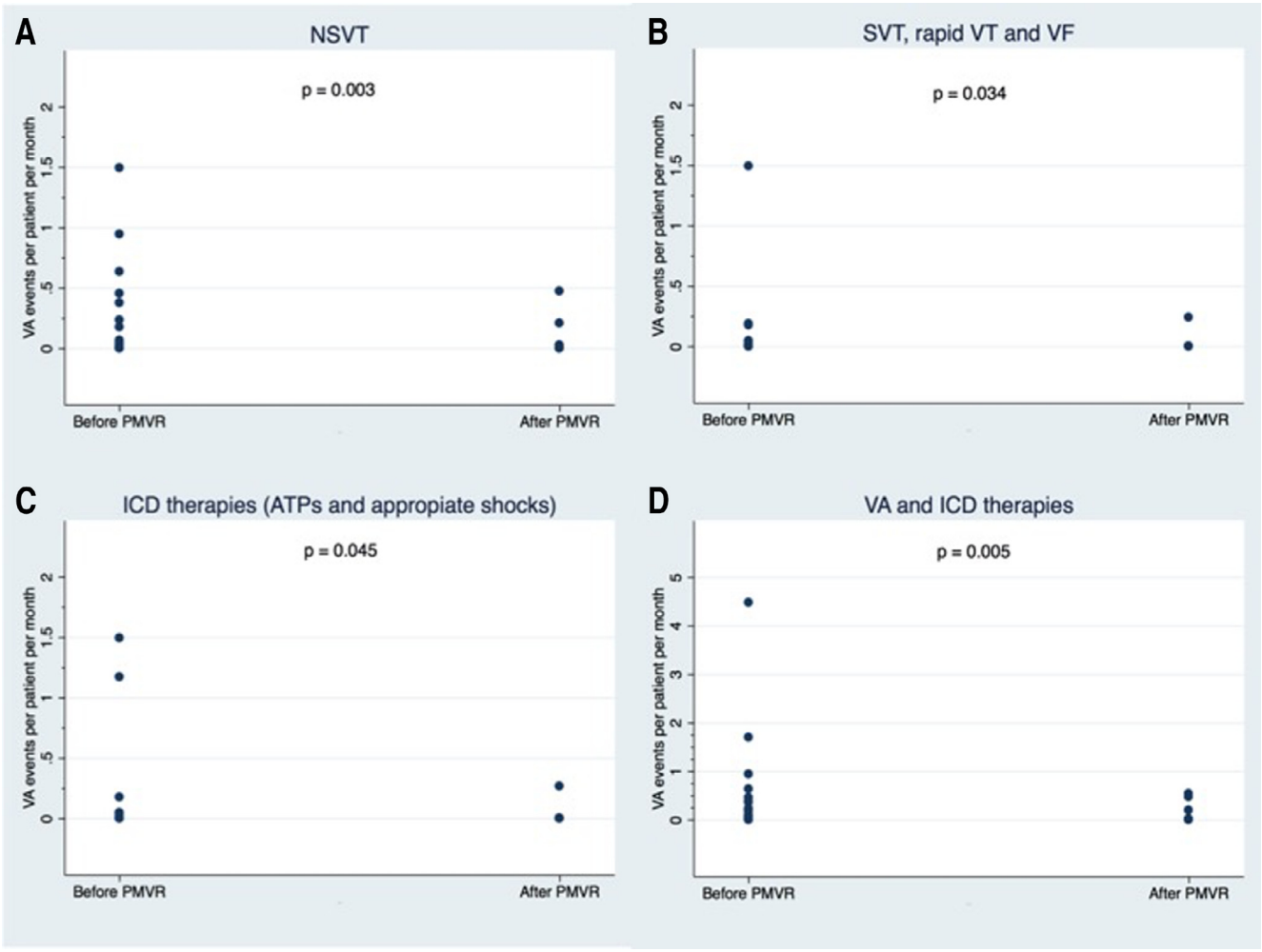

Figure 2. Incidence (episodes per patient per month) of ventricular arrhythmias before and after percutaneous mitral valve repair. *(A)* Nonsustained ventricular tachycardia. *(B)* Sustained ventricular tachycardia (including rapid ventricular tachycardia or ventricular fibrillation). *(C)* Antitachycardia pacing and appropriate defibrillation shocks. *(D)* Ventricular arrhythmias and anti-tachycardia therapies. ATP = antitachycardia pacing; ICD = implantable cardiac defibrillator; NSVT = nonsustained ventricular tachycardia; SVT = sustained ventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia.

Table 4
Pharmacological treatment for heart failure and antiarrhythmic drugs at the time percutaneous mitral valve repair was performed and at last clinical follow up among patients who were compared for the incidence ventricular arrhythmias (n = 16)

	Baseline	Follow up	p Value
Beta-blockers	94%	94%	1.000
None	6%	6%	
Low dose (mg per day) [carvedilol ≤25, metoprolol ≤100, bisoprolol ≤5]	38%	25%	0.500
High dose (mg per day) (carvedilol >25, metoprolol >100, bisoprolol >5)	56%	69%	
ACE/Angiotensin II /Neprilysin inhibitors	81%	88%	1.000
Mineralocorticoid receptor antagonists	75%	81%	1.000
Amiodarone (mg per day)	0 [0-200]	0 [0-200]	0.157*
	100 ± 126.5	75 ± 100	
Furosemide (mg per day)	80 [50-120]	80 [40-80]	0.057*
	91.3 ± 46.7	76.3 ± 49.1	

* Wilcoxon matched-pairs signed-ranks test.

Third, differences in device follow-up time before and after PMVR might limit detection of events after Mitraclip implantation and, therefore, magnified differences in VA burden. However, patients were followed up over a median of one year after transcatheter mitral valve repair and the incidence of events was time-adjusted. Furthermore, an increase in the incidence of VA might be expected over time due to progression of underlying LV disease, which might have

impaired postprocedural outcomes. Given stated limitations, the results reported in this publication should be interpreted with caution. In conclusion**,** device success after PMVR was related to a reduction in overall arrhythmic burden and ICD therapies in our cohort. Further studies should be performed to confirm these findings and address its potential impact on clinical outcomes.

Disclosure

Dr. Estévez-Loureiro is consultant for Abbott vascular and proctor for MitraClip. The rest of authors have nothing to disclose.

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