Long-term Israeli Single-Center Experience with the Percutaneous MitraClip Procedure

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ABSTRACT: **Background:** The MitraClip procedure is becoming an acceptable alternative for high-risk patients with mitral regurgitation (MR) due to functional (FMR) or degenerative (DMR) disease and suitable mitral anatomy.

Objectives: To evaluate the results of MitraClip at our institute in carefully selected patients.

Methods: We conducted a retrospective analysis of medical records and echocardiography data from January 2012 to December 2017.

Results: A total of 39 MitraClip procedures in 37 patients (aged 75 ± 12 years, 9 women) was performed. Twenty-four patients presented with FMR, 12 with DMR, and 1 with combined pathology. One-day post-procedure MR was reduced to moderate or lower in 86.1% of patients, with immediate device success in 88.8%. MR at 1 year was moderate or lower in 79%. Survival at 1 year was 86% and at 2 years 69.4%. Peri-procedural (< 1 week) death and MitraClip failure occurred in one and three patients, respectively. New York Heart Association score improved to class 1 or 2 in 37% of patients at 1 year vs. one patient at baseline. Post-procedural systolic pulmonary pressure was reduced from 53 (range 48–65) to 43 (range 36–52) mmHg at 1 month with a subsequent plateau at follow-up to 41 (34–57) mmHg at 6 months and 47 (38–50) at 12 months.

Conclusions: MitraClip in severe MR resulted in modest improvement in functional status and pulmonary pressure with a small risk of immediate procedural complications. Outcomes are encouraging considering the natural course of MR and the risks of surgical intervention.

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Mitral regurgitation is a significant source of cardiovascular death and morbidity. The prevalence of moderate-to-severe and severe mitral regurgitation is 2% to 3% of the general population, rising strikingly with advanced age to up to 9.3% in patients older than 75 years of age [1,2]. Although surgery is considered the mainstay treatment, it was denied in up to 50% of patients with severe mitral regurgitation due to impaired severe left ventricular dysfunction, older age, and co-morbidities [3]. The percutaneous edge-to-edge MitraClip System (Abbott Vascular, Menlo Park, CA, USA) is the only percutaneous mitral valve repair technique that has received both the European CE mark and U.S. Food and Drug Administration (FDA) approval. MitraClip received CE mark approval in 2008 for symptomatic patients with degenerative mitral regurgitation (DMR) and functional mitral regurgitation (FMR) [4] and FDA approval in 2013 for patients with moderate-to-severe degenerative mitral regurgitation who are deemed by a heart team to be at prohibitive risk for mitral valve surgery [5].

MitraClip therapy is gaining widespread acceptance for treatment of high-risk elderly patients, and physicians are gaining experience and expertise. Results have shown high immediate success, low complication rates, and sustained intermediate-term reduction of the severity of mitral regurgitation and improvement of clinical symptoms.

MitraClip was introduced in Israel in January 2011; however, the number of procedures performed is relatively small compared to other parts of the world. In this article, we summarize our own tertiary medical center's experience with this procedure, expanding on a prior preliminary report published 5 years ago [6].

PATIENTS AND METHODS

We performed a retrospective analysis of the medical records and echocardiography database of all patients who underwent a MitraClip procedure at our institution from January 2012 to December 2017, with follow-up until May 2018. Echocardiographic and clinical data were collected at baseline and at follow-up intervals of 1 day post-procedure and at 1, 3, 6, 12, and 24 months after the MitraClip procedure. All patients were approved for MitraClip after consideration by the local heart team, which included echocardiographers, interventional cardiologists, and cardiac surgeons.

All MitraClip procedures were performed by three highly experienced interventional cardiologists (H.V.A., A.A., R.K.)

under transesophageal echocardiography (TEE) guidance by an expert echocardiographer.

Procedural data were collected anonymously and analyzed retrospectively. Anatomical suitability for MitraClip was determined by pre-procedural TEE based on accepted recommendations [7,8], whereas valvular disease grading and other echocardiographic data were obtained through transthoracic echocardiography (TTE). Right ventricle function was coded as good (0), preserved (1), mildly reduced (2), and moderate/severe reduction (3).

Valvular regurgitation was determined according to guidelines [9], utilizing a four-group quantitative and qualitative scale mild (1), moderate (2), moderate-to-severe (3), and severe (4).

OUTCOMES

The immediate outcomes were procedural safety and success based on the Mitral Valve Research Consortium (MVARC) [10]. Technical success was defined as successful use of the device with no procedural mortality or emergency surgery. Device success was defined as proper placement of the device with no procedural mortality and with reduction in post-procedural mitral regurgitation by ≥ 1 grade from baseline and to an absolute level of ≤ moderate mitral regurgitation. Device time was defined as the time from guide catheter insertion to guide catheter removal.

STATISTICAL METHODS

Continuous variables are expressed as mean ± standard deviations, when normal distribution was observed, or as median (interquartile range [IQR] 25–75%) where the distribution was non-Gaussian. Categorical variables are expressed as numbers and percentages. Between-group differences were compared by unpaired *t*-test, Wilcoxon rank sum test, chi-square, or Fisher's exact test, as appropriate. Within-group differences were assessed by paired *t*-test. Survival univariate Cox proportional hazards ratio model was used to assess the independence of survival from prognostic factors.

A two-sided *P* value < 0.05 was considered to indicate statistical significance for all tests. Statistical analyses were performed using Statistical Package for the Social Sciences software version 18 (SPSS Inc., Chicago, IL, USA).

RESULTS

BASELINE CHARACTERISTICS

A total of 39 MitraClip procedures were performed in 37 patients (aged 75 ± 12 years). Twenty-four patients had FMR (13 with restricted posterior leaflet, 11 with bilateral leaflet tethering), 12 had DMR (9 flail P2 with concomitant flail P1 or P2 in 3 of them, one isolated flail A2, and 2 isolated flail P3), and 1 had combined DMR and FMR. All patients had baseline moderate-to-severe (grade 3) or severe (grade 4) MR. Post-procedural data were unobtainable for one patient who was excluded from analysis. As shown in Table 1, compared with DMR, patients with FMR were significantly younger: 74 years of age (range 67–81) vs. 84 (range 75–86). They had a significantly lower left ventricular ejection fraction (LVEF) %: 36 (30–45) vs. 60 (52–60). Cardiac dilatation was 60 (33–67) vs. 42 (42–50) mm for left ventricular end diastolic diameter (LVEDD), and showed worse right ventricle function. Interestingly, overall EuroSCORE and clinical characteristics (except ischemic heart disease, which is related to FMR) were not significantly different between FMR and DMR patient groups.

FOLLOW-UP DATA ANALYSIS

Peri-procedural (< 1 week) death occurred in one patient, and immediate MitraClip failure due to failed grasp/clip detachment occurred in three. Repeat MitraClip procedure was performed in one of the three patients with MitraClip failure 3 days after the initial failed MitraClip without significant amelioration of MR. The patient who died within 1 week from MitraClip encountered massive post-procedural gastric

Table 1. Baseline clinical and echocardiographic characteristics of patients who underwent MitraClip implantation

Variable	(N=36)	FMR (N=24)	DMR (N=12)	*P* value
Age, years	77 (69–83)	74 (67–81)	84 (75–86)	< 0.01
Female	9 (25%)	5 (20.8%)	4 (33.3%)	NS
NYHA class	4 (3–4)	4 (3–4)	4 (4–4)	NS
EuroSCORE	16 (9–33)	16 (9–33)	15 (8–35)	NS
Hypertension	29 (80.6%)	19 (79.2%)	10 (83.3%)	NS
Diabetes mellitus	11 (30.5%)	7 (29.2%)	4 (33.3%)	NS
CRF	20 (55.6%)	14 (58.3%)	6 (50%)	NS
CVA	6 (16.7%)	2 (8.3%)	4 (33.3%)	NS
IHD	24 (66.7%)	19 (79.2%)	5 (41.7%)	0.06
PVD	5 (13.9%)	2 (8.3%)	3 (2%)	NS
COPD	5 (13.9%)	3 (12.5%)	2 (16.7%)	NS
Atrial fibrillation	20 (55.6%)	15 (62.5%)	5 (41.7%)	NS
LVEF	45 (33–60)	36 (30–45)	60 (52—60)	< 0.01
Right ventricle function	1 (0–1)	2 (0–3)	0 (0–1)	< 0.01
LVEDD, mm	48 (44–45)	60 (53–67)	42 (42–50)	< 0.01
LVESD, mm	41 (31–54)	44 (39–55)	27 (21–32)	< 0.01
Mitral regurgitation grade	4 (4–4)	4 (3.25–4)	4 (4–4)	NS
TR grade	2 (1–2)	2 (1–2)	2 (1–2)	NS
SPAP (mmHg)	53 (47–65)	53 (49–64)	54 (42–67)	NS
MitraClip time (minutes)	81 ± 27	80 ± 26	83 ± 30	NS

COPD = chronic obstructive pulmonary disease, CRF = chronic renal failure, CVA = cerebrovascular accident, DMR = degenerative mitral regurgitation, FMR = functional mitral regurgitation, IHD = ischemic heart disease, LVEDD = left ventricular end diastolic diameter, LVEF = left ventricular ejection fraction, LVESD = left ventricular end systolic diameter, NYHA class = New York Heart Association class, PVD = peripheral vascular disease, SPAR = systolic pulmonary artery pressure, TR = tricuspid regurgitation

bleeding. Another patient died at 2 weeks post-MitraClip of unknown causes. Both patients who died within 2 weeks post MitraClip had a successful immediate post-procedure result with significant mitral regurgitation reduction to grade 1 and 2. There were no cases of pericardial tamponade post-MitraClip.

Overall, the mortality rate was 11 of 24 cases in the FMR group and 1 of 12 in the DMR group. Follow-up median time was 22.5 months (15–40 IQR). One-year survival rate was 86 ± 5.8% and 2-year survival rate was 69.4 ± 8.8%.

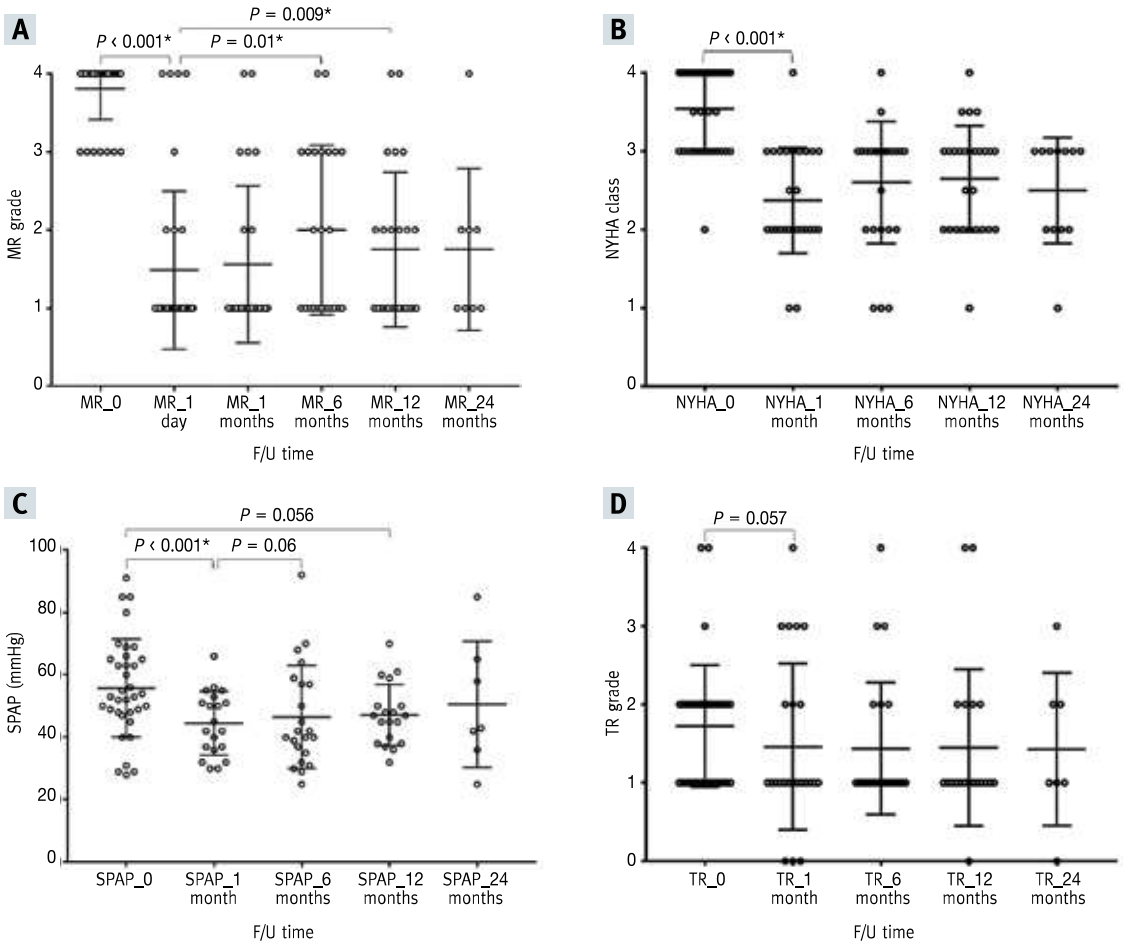
At the end of the MitraClip procedure, TEE assessment showed that mitral regurgitation was reduced to grade 1 (mild) or grade 2 (moderate) in 33/36 patients (91.7%), with 30/36 (83.3%) having grade 1 only. Device success and technical success were therefore calculated as 32/36 (88.8%) and 35/36 (97%), respectively.

At 1 day post-MitraClip, TTE assessment showed that mitral regurgitation was reduced to grade 1 or 2 in 31/36 patients (86.1%), 27 of them having grade 1 only, with peak and mean mitral valve gradients of 9.1 ± 3.5 and 3.2 ± 2.1 mmHg, respectively. The two patients who had significant worsening of mitral regurgitation vs. immediate assessment at the end of the MitraClip procedure were found to have MitraClip detachment.

By comparing pre-procedural mitral regurgitation grade to its grade on the first post-procedural day, we noted a significant reduction: from grade 4 (4–4 IQR) to 1 (1–1 IQR), $P < 0.001$ [Figure 1A].

One clip was deployed in 12 patients (32.4%), two in 18 (48.6%), and three in 7 (18.9%). Procedure time did not differ between DMR and FMR. Procedure time was 81 ± 27 minutes.

Figure 1. Follow-up dotplot distributions for MR grade **[A]**, NYHA class **[B]**, SPAP **[C]**, and TR grade **[D]**. Follow-up times are marked as baseline (0), 1 month, 6 months, 12 months, and 24 months



MR = mitral regurgitation, NYHA class = New York Heart Association class, SPAR = systolic pulmonary artery pressure, TR = tricuspid regurgitation

Of the surviving patients, echo follow-up findings were available for 23/31 at 6 months follow-up, in 24/25 at 1 year follow-up, and in 8/13 at 2 years follow-up.

At 6 months, mitral regurgitation grade 1 or 2 was present in 15/23 (65.2%), whereas at 1 year of follow-up mitral regurgitation was grade 1 or 2 in 19/24 patients (79.2%), $P = 0.02$ and $P = 0.005$ for the respective paired comparison with mitral regurgitation grade at 1 day post-MitraClip [Figure 1A].

New York Heart Association (NYHA) class was reduced from 4 (3–4 IQR) at baseline to 2 (2–3) at 1 month follow-up ($P < 0.001$) with subsequent plateau at 3 (2–3) during later follow-up, as shown in Figure 1B.

Systolic pulmonary artery pressure (SPAP) was reduced from 53 (47-65) at baseline to 42 (34-52) mmHg at 1 month follow-up ($P < 0.001$), translating to a mean reduction of 13 mmHg, with subsequent plateauing at later follow-up [Figure 1C]. Ejection fraction, cardiac size, and tricuspid regurgitation (TR) grade did not change significantly with follow-up. TR grade trended toward reduction post-MitraClip, from 2 (1–2) at baseline to 1 (1–2) at 1 month ($P = 0.057$), as shown in Figure 1D.

Three stroke events occurred post-MitraClip, two within 1 month of the procedure in two FMR patients, and one in the mixed-etiology case in 6 months.

SURVIVAL COX REGRESSION ANALYSIS

Univariate survival Cox regression analysis is shown in Table 2.

Of the different demographic and echocardiography characteristics we examined, we found that worse mitral regurgitation at 1 month and 6 months post-MitraClip were significantly associated with reduced remaining survival: hazard ratio (HR) 1.9 and 2.9; and 95% confidence interval (95%CI) 1.05–3.43 and 1.29–6.44, respectively. Higher EuroSCORE trended but was not associated with reduced survival. For the DMR subgroup analysis, a higher EuroSCORE was significantly associated with slightly reduced survival HR 1.058, 95%CI 1.01–1.12; whereas, mitral regurgitation was not.

Table 2. Univariate Cox regression survival analysis in all patients. All variables represent baseline parameters

Parameter	Hazard ratio	95% Confidence interval	*P* value
Age	1.037	0.97–1.09	0.16
Ejection fraction, %	0.98	0.93–1.02	0.31
LVEDD, mm	1.05	0.99–1.12	0.11
LVESD, mm	1.013	0.97–1.0057	0.66
Left atrium diameter, mm	0.97	0.9–1.05	0.49
TR	0.78	0.38–1.6	0.49
SPAP, mmHg	0.99	0.96–1.03	0.72
Mitral regurgitation	1.34	0.77–2.3	0.3
Mitral regurgitation (1 month)	1.9	1.053–3.44	0.033*
Mitral regurgitation (6 months)	2.9	1.29–6.44	0.01**
NYHA class	0.9	0.31–2.6	0.85
EuroSCORE	1.043	0.997–1.09	0.065

*Mitral regurgitation 1 month post-MitraClip

**Mitral regurgitation grade at 6 months post-MitraClip

LVEDD = left ventricular end diastolic diameter, LVESD = left ventricular end systolic diameter, NYHA class = New York Heart Association class, SPAR = systolic pulmonary artery pressure, TR = tricuspid regurgitation

DISCUSSION

We compared the results of our study with five large similar European registries that included both FMR and DMR [11-15], as presented in Table 3. Similar to the other studies, our patients were elderly and predominantly male; the majority presented with FMR. With regard to NYHA classes, all our patients had a low baseline functional class of 3 or 4 (except for one patient in class 2). The transcatheter mitral valve interventions (TRAMI) [14], Transcatheter Valve Treatment Sentinel Pilot Registry (TCVT) [12], and ACCESS-EU [14] registries found 11%, 15.9%, and 15.1% of patients, respectively, at NYHA class 1 or 2.

Compared to the other registries, mitral regurgitation severity in our cohort was significantly reduced to grade ≤ 2 in a similar proportion of patients at the end of the MitraClip procedure (91.7% vs. 91–97% in the other registries). We used more than one clip in 67% of patients vs. 37–62% in the other registries.

Device procedure time (81 ± 27 minutes) compared favorably with most registries, aside from the Dutch registry, in which

Table 3. Comparison of baseline characteristics and 1-year outcomes in different registry studies of patients who underwent MitraClip

	Present study	TRAMI [14]	TCVT [11]	ACCESS-EU [14]	GRASP-IT [15]	MC-Dutch [13]
Patient number	36	749	628	567	304	1151
Age, years	77 (69–83)	76 (71–81)	74.2 ± 9.7	73.7 ± 9.6	72 ± 10	76 (69–82)
Gender: male	75%	61.4%	63%	63.8%	63.8%	59%
EuroSCORE	16 (9–33)	20 (12–31)	20.4 ± 16.7	23 ± 18.3	6 (3–11)	N/A
NYHA class ≤ 2	2.7%	11%	14.5%	15.1%	N/A	N/A
FMR	67%	71%	72%	77%	79%	72%
DMR	33%	29%	–	23%	–	17%
≥ 2 clips	67%	N/A	37.5%	N/A	37.8%	42%
MitraClip time, minute	81 ± 27	103 ± 54	138 ± 68	100	156 ± 67	66 (42–103)
Device success	88.8%	97%	95.4%	91%	92%	91%
Peri-operation mortality	2.7%	2.4%	2%	0%	0%	0.3%
MR ≤ 2 at discharge	86.1%	97%	98.2%	91%	N/A	92%
1 year survival	86%	79.7%	84.7%	83%	86.2%	N/A
1 year NYHA class ≤ 2	37%	(63%)	(74.2%)	(71.4%)	N/A	N/A

DMR = degenerative mitral regurgitation, FMR = functional mitral regurgitation, GRASP-IT = Getting Reduction of mitrAl inSufficiency by Percutaneous clip implantation in ITaly registry, MC = MitraClip, MR = mitral regurgitation, NYHA class = New York Heart Association class, TCVT = Transcatheter Valve Treatment Sentinel Pilot Registry, TRAMI = transcatheter mitral valve interventions

multiple clips were used less often. Technical success was similarly high in our patients (97%). At 1-day post procedure, mitral regurgitation was reduced to none or mild (grade 1) in 73% of the patients, similar to the rate reported in the TCVT study, whereas reduction to ≤ grade 2 was achieved in only 81% of our patients vs. 91–98% in ACCESS-EU, MC Dutch, TCVT, and TRAMI reports. This result translated in a lower device success in our study (88.8%) vs. higher rates in other studies (91–97%). Our lower procedural success can be attributed to the learning curve experience involved with adopting a new technique. Early mitral clip detachment 1-day post-MitraClip with significant mitral regurgitation worsening despite a good initial result in the catheterization laboratory was observed in 2/36 patients, underscoring the importance of early post-procedural repeat assessment. Post-procedural stroke was rare (only three cases).

We observed long-term clinical and echocardiography improvement post-MitraClip compared to baseline characteristics. At 1 year follow-up, grade 1 mitral regurgitation was present in 54.1% of the patients, which is in the same range as the TCVT registry (58.6%) and better than the ACCESS-EU (30.6%). SPAP was reduced significantly at 1 month post-MitraClip, with a subsequent trend toward a slight increase at later follow-up. The TCVT registry also showed a significant reduction in SPAP following MitraClip (5.8 mmHg, $P < 0.001$ post-discharge). In that study, in contrast to ours, a significant decrease in SPAP persisted at 1 year follow-up. Tricuspid regurgitation trended to decrease post-MitraClip, without reaching statistical significance.

NYHA class 1 and 2 was observed in 37% of the patients at 1 year follow-up compared to none of the patients at baseline. Better results were reported in TCVT (74.2% of the patients were in class 1 and 2 at 1 year follow-up), but in that study patients featured better baseline NYHA class than in our study (14.5% exhibited NYHA class 1 or 2 vs. none in class 1 and only one patient in class 2 at baseline in our study, whereas only 16.3% were in class 4 at baseline in TCVT vs. 51.4% in our study). Similarly, in TRAMI, 11% of patients who underwent MitraClip were in baseline NYHA class 1 or 2, and consequently at 1 year of follow-up 63% of the MitraClip patients improved to NYHA class 1 or 2. In ACCESS-EU, 15.1% were in baseline NYHA class 1 or 2 vs. 71.4% at 1 year.

The cumulative incidence of 1 year survival in our study was 86%, similar to the 1-year survival reported in the GRASP-IT study (Getting Reduction of mitrAl inSufficiency by Percutaneous clip implantation in ITaly registry) (86.2%) [15], TCVT (84.7%), ACCESS-EU (83%), and TRAMI (79.7%).

We found on univariate analysis that worse mitral regurgitation at 1 month and 6 months post-MitraClip was associated with increased mortality, but we could not verify the independent value of these predictors due to the relatively small number of patients in our registry. Nonetheless, our findings are in agreement with the TCVT, GRASP-IT, and TRAMI studies that found that device procedural success (which, by definition, entails mitral regurgitation reduction to grade 2 or less) was significantly associated with decreased 1-year mortality. In contrast to our study, TCVT and TRAMI also found that a higher baseline NYHA class predicted 1-year mortality, a discrepancy that can be attributed to the fact that these studies also included patients with low NYHA class, whereas we performed MitraClip only in patients with a high NYHA class.

The main limitation of our study was that it is observational and included a relatively small number of patients, compared with large-scale European studies, some of which included a multicenter population base. Incomplete echocardiographic follow-up data at any point could have created a selection bias. For example, the apparent higher percentage of patients with grade 1 or 2 mitral regurgitation at 12 months vs. 6 months post-MitraClip procedure is because not all patients had 6 and 12 month echocardiographic examinations. When restricting echocardiography comparisons to patients who had echocardiographic examinations at both time points, mitral regurgitation grade at 12 month seemed slightly worse than at 6 months (9/17 patients [52.9%] with grade 1 mitral regurgitation at 12 months vs. 11/17 [64.7%] with grade 1 at 6 months).

Due to the small number of patients and mortality cases, we were unable to evaluate multivariate analysis for mortality predictors to confirm independent value of potential predictors. In particular, the small number of patients with DMR etiology and the low mortality observed in this latter group preclude the possibility of direct comparison with the larger FMR group or of subgroup analysis.

Nonetheless, our study reflects real-life single-center experience, and was not sponsored by industry. Our results show a significant overall positive experience, which is remarkable considering the more extensive experience of our European colleagues with MitraClip, reinforcing the notion that a rigorous patient selection process and skilled operators are a good basis for MitraClip program implementation in tertiary hospitals. Furthermore, the fact that we found a less favorable 1-year functional class improvement compared with other MitraClip registry studies in which a significantly higher proportion of patients had initial good functional capacity implies that we performed MitraClip at a relatively late stage. Referral of patients to MitraClip earlier (when in NYHA class 2 or 2-3) might have yielded better clinical results.

This finding is consistent with the well-established fact that waiting for mitral surgery in severe mitral regurgitation until symptoms become pronounced (NYHA class 3 or 4) is associated with increased hospital mortality and reduced long-term survival [16-19]. Indeed, careful selection of patients with FMR for MitraClip, only after optimizing medical treatment and excluding extremely sick patients, has recently been shown to improve overall survival in the recent COAPT trial [20], and could potentially be applicable to our patients as well.

CONCLUSIONS

MitraClip in severe mitral regurgitation resulted in modest improvement in functional status and pulmonary pressure with a small risk of immediate procedural complications. Outcomes appear encouraging considering the natural course of MR or of surgical intervention in similar patients.

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Capsule

Effect of anti-CD4 antibody UB-421 on HIV-1 rebound after treatment interruption

Administration of a single broadly neutralizing human immunodeficiency virus (HIV)-specific antibody to HIV infected individuals leads to the development of antibody-resistant virus in the absence of antiretroviral therapy (ART). It is possible that monotherapy with UB-421, an antibody that blocks the virus-binding site on human CD4+ T cells, could induce sustained virologic suppression without induction of resistance in HIV-infected persons after analytic treatment interruption. **Wang** et al. conducted a nonrandomized, open-label, phase 2 clinical study evaluating the safety, pharmacokinetics, and antiviral activity of UB-421 monotherapy in HIV-infected persons undergoing analytic treatment interruption. All the participants had undetectable plasma viremia (< 20 copies of HIV RNA per ml) at the screening visit. After discontinuation of ART, participants received eight intravenous infusions of UB-421, at a dose of either 10 mg per kilogram of body weight every week (cohort 1) or 25 mg per kilogram every 2 weeks (cohort 2). The primary outcome was the time to viral rebound (≥ 400 copies per ml). A total of 29 participants were enrolled, 14 in Cohort 1 and 15 in Cohort 2. Administration of UB-421 maintained virologic suppression (< 20 copies per ml) in all the participants (94.5% of measurements at study visits 2 through 9) during analytic treatment interruption, with intermittent viral blips (range, 21 to 142 copies per ml) observed in 8 participants (28%). No study participants had plasma viral rebound to more than 400 copies per milliliter. CD4+ T-cell counts remained stable throughout the duration of the study. Rash, mostly of grade 1, was a common and transient adverse event. One participant discontinued the study drug due to a rash. A decrease in the population of CD4+ regulatory T cells was observed during UB-421 monotherapy.

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