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ORIGINAL ARTICLE

MitraClip Treatment of Moderate-to-Severe and Severe Mitral Regurgitation in High Surgical Risk Patients

— Real-World 1-Year Outcomes From Japan —

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on behalf of the MitraClip Japan PMS Investigators

Background: The MitraClip NT System was approved for marketing in Japan on October 31, 2017, and a prospective, multi-center, single-arm Post-Marketing use Surveillance (PMS) study was launched in 2018. This is the first report of the Japan PMS study with 1-year subject outcomes.

Methods and Results: A total of 500 patients were registered between April 2018 and January 2019. Patients with symptomatic chronic moderate-to-severe (3+) or severe mitral regurgitation (MR; 4+), MR with a Society of Thoracic Surgery (STS) replacement score of ≥8%, or presence of 1 pre-defined risk factor were enrolled. Primary outcome measures included acute procedural success (APS), and rate of Single Leaflet Device Attachment (SLDA) at 30 days. The overall cohort was elderly (77.9±9.48 years) with functional MR etiology in 71.6% of the subjects. The majority of subjects were New York Heart Association (NYHA) class III/IV (68.9%), with mean STS replacement score of 11.95±9.66%. The APS rate was 91.13% and the 30-day SLDA rate was 1.21%. Durable MR reduction was achieved with 88.1% of subjects at MR ≤2+ at 1 year. Significant improvement in the functional capacity was observed, with 93% of subjects at NYHA class I/II at 1 year.

Conclusions: In the Japan PMS experience, the MitraClip procedure resulted in improvements in MR severity, with significantly improved functional outcomes. These results demonstrate safety and efficacy of MitraClip therapy in the eligible Japanese population.

Key Words: Mitral regurgitation; Mitral valve; Valvular diseases

Mitral regurgitation (MR) is the most common valvular abnormality that affects >2% of the elderly population aged >65 years.[1] The standard of care for these patients is either surgery or optimized medical therapy depending on whether the etiology of MR is degenerative (DMR) or functional (FMR).[2] However, many DMR patients do not undergo surgery due to increased perioperative risks or inclination to avoid surgery.[3] Also, FMR patients can continue to experience MR and its symptoms despite optimized medical therapy.[2,4] Subsequently, MR patients have limited alternative options for treatment of their condition.

MitraClip is the first commercially available device to treat MR through a minimally invasive transcatheter procedure. The device can be percutaneously delivered to grasp and coapt the mitral valve (MV) leaflets, resulting in fixed approximation of the leaflets throughout the cardiac cycle. This procedure mimics the surgical Alfieri stitch, first performed for MV insufficiency in 1983,[5] and is performed without the need for arresting the heart or cardiopulmonary bypass. The MitraClip System received CE approval in 2008, US Food and Drug Administration (FDA) approval in 2013, and is currently approved and commercially available in >80 countries. Over 100,000 patients have undergone the MitraClip procedure worldwide. This study presents the first report on the real-world experience of safety and efficacy of the MitraClip technology in a Japanese population.

Editorial p????

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Table 1. Baseline Demographics and Comorbidities

Characteristic	All subjects (N=500)	DMR only (N=126)	FMR only (N=358)	P value DMR vs. FMR
Age, mean ± SD (N)	77.92±9.48 (500)	82.48±9.17 (126)	76.19±9.10 (358)	<0.0001†
Patients aged >75 years, % (n/N)	65.2 (326/500)	86.5 (109/126)	57.3 (205/358)	<0.0001†
Male, % (n/N)	58.8 (294/500)	51.6 (65/126)	61.5 (220/358)	0.05†
BMI, mean ± SD (n)	21.01±3.22 (500)	20.70±2.96 (126)	21.14±3.33 (358)	0.17†
STS Replacement Score (%)	11.95±9.66 (500)	10.38±7.20 (126)	12.42±10.20 (358)	0.015†
Cardiovascular history, % (n/N)				
Dyslipidemia	43.4 (216/498)	34.4 (43/125)	47.1 (168/357)	0.014‡
Prior TIA	2.6 (13/492)	0.8 (1/124)	3.4 (12/352)	0.20§
Prior CVA	17.9 (89/496)	14.5 (18/124)	19.4 (69/356)	0.22‡
Prior MI	25.1 (124/494)	3.2 (4/124)	32.5 (115/354)	<0.0001‡
Atrial fibrillation	88.5 (316/357)	97.3 (72/74)	85.8 (230/268)	0.007‡
Cardiac intervention history, % (n/N)				
Prior cardiac surgeries	17.8 (89/500)	7.1 (9/126)	21.2 (76/358)	0.0004‡
Prior CABG	49.4 (44/89)	22.2 (2/9)	51.3 (39/76)	0.16§
PCI	28.8 (142/493)	10.6 (13/123)	35.3 (125/354)	<0.0001‡
CRT/CRT-D	17.3 (86/497)	1.6 (2/124)	22.7 (81/357)	<0.0001‡
Co-morbidity, % (n/N)				
Diabetes	28.9 (144/498)	11.9 (15/126)	35.4 (126/356)	<0.0001‡
Renal failure	49.1 (244/497)	36.3 (45/124)	53.2 (190/357)	0.001‡
Currently on dialysis	11.2 (27/242)	6.7 (3/45)	12.2 (23/188)	0.29‡
COPD	60.5 (46/76)	70.0 (14/20)	58.2 (32/55)	0.35‡
Home oxygen	9.2 (7/76)	10.0 (2/20)	9.1 (5/55)	1.00§
Peripheral arterial disease	11.3 (56/494)	12.1 (15/124)	11.3 (40/354)	0.81‡
Prior HFH within 1 year	64.1 (320/499)	51.6 (65/126)	68.3 (244/357)	0.0008‡
Echo characteristics, mean ± SD (N)				
EROA (cm^2)	0.40±0.26 (460)	0.53±0.33 (118)	0.36±0.21 (328)	<0.0001†
RV (mL/beat)	58.04±27.61 (461)	72.04±30.63 (114)	53.47±25.27 (333)	<0.0001†
LVEF (%)	46.10±14.93 (499)	63.40±8.90 (126)	39.84±11.45 (357)	<0.0001†
LVESV (mL)	93.54±64.43 (458)	46.69±24.73 (119)	111.68±66.10 (326)	<0.0001†
LVEDV (mL)	160.26±75.31 (451)	121.14±44.19 (119)	176.30±79.38 (319)	<0.0001†
NYHA functional class, % (n/N)				<0.0001§
I	0.6 (3/480)	2.5 (3/120)	0.0 (0/344)	
II	30.4 (146/480)	38.3 (46/120)	27.0 (93/344)	
III	51.0 (245/480)	53.3 (64/120)	50.3 (173/344)	
IV	17.9 (86/480)	5.8 (7/120)	22.7 (78/344)	

†From a t-test. ‡From a chi-squared test. §From Fisher's exact test when Cochran's rule is not met. BMI, body mass index; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CRT/CRT-D, cardiac resynchronization therapy/cardiac resynchronization therapy-defibrillator; CVA, cerebrovascular accidents; DMR, degenerative mitral regurgitation; EROA, effective regurgitant orifice area; FMR, functional mitral regurgitation; HFH, heart failure hospitalization; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; PCI, prior cardiac interventions; RV, regurgitant volume; SD, standard deviation; STS, Society of Thoracic Surgeons; TIA, transient ischemic attack.

Methods

Trial Design

MitraClip received marketing approval in Japan in 2017 after the results of the safety and efficacy of the AVJ-514 study[6] were presented to the Pharmaceuticals and Medical Devices Agency (PMDA), Japan (Marketing Approval No. 22900BZX00358000; October 31, 2017). The Japan Post-Marketing use Surveillance (PMS study) was launched immediately thereafter to collect efficacy and safety information for ongoing evaluation and reviewed by the PMDA, Japan.

Subject Population

A total of 500 patients were registered at 40 sites in the surveillance period from April 2, 2018 to January 25, 2019. All data presented in the report are based on the cut-off date of October 31, 2020. The surveillance consecutively registered patients with moderate-to-severe and severe MR (3+ and 4+ MR) in whom a MitraClip implant was attempted.

Subjects were screened to ensure they met all inclusion criteria and did not meet any exclusion criteria as per the approved instructions of use (IFU) of the MitraClip device. This included subject review by the multidisciplinary local heart team consisting of an interventional cardiologist, a cardiothoracic surgeon, and an echo-cardiologist. Echocardiographic evaluation, by transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE), was also performed to determine subject suitability and

Table 2. Procedural and Post Procedural Outcomes

	All subjects (N=500)	DMR only (N=126)	FMR only (N=358)	P value DMR vs. FMR
Number of MitraClips implanted per patient				
0	0.6 (3/500)	1.6 (2/126)	0.3 (1/358)	0.17§
1	54.8 (274/500)	51.6 (65/126)	57.0 (204/358)	0.29‡
2	42.8 (214/500)	46.0 (58/126)	40.5 (145/358)	0.28‡
3	1.8 (9/500)	0.8 (1/126)	2.2 (8/358)	0.46§
Total number of clips	729	184	518	
Mean±SD	1.46±0.54 (500)	1.46±0.55 (126)	1.45±0.55 (358)	0.81†
Implant rate	99.4 (497/500)	98.4 (124/126)	99.7 (357/358)	0.17§
Total device time (min)	94.11±51.17 (496)	95.85±50.99 (124)	92.85±51.45 (356)	0.57†
Procedure time (min)	134.80±60.48 (499)	134.02±57.87 (126)	134.25±61.73 (357)	0.97†
Total index procedure hospital stay (days)	20.46±22.64 (483)	17.10±28.63 (122)	21.48±19.76 (345)	0.12†
Post-procedure PACU/CCU/ICU duration (h)	76.97±346.58 (464)	78.57±316.20 (115)	77.44±363.33 (335)	0.97†

†Obtained by using a t-test. ‡Obtained by using a chi-squared test. §Obtained by using Fisher's exact test when Cochran's rule is not met. Data are presented as % (n/N), n or mean ± SD (n). CCU, cardiac/coronary care unit; DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation; ICU, intensive care unit; PACU, post anesthesia care unit; SD, standard deviation.

eligibility for the procedure in accordance with the device IFU. The subjects participating in the study represent the real-world use of MitraClip in eligible patients in Japan.

Statistical Analysis

The primary endpoints of this study are single leaflet device attachment (SLDA) rate at 30 days and acute procedural success (APS) at discharge based on site-reported assessments. The SLDA is defined as the loss of insertion of a single leaflet from the MitraClip device, with ongoing insertion of the opposing leaflet. APS is defined as achieving MR reduction to ≤2+ per echocardiographic assessment at discharge. If echocardiographic data at discharge were not available or non-evaluable, echocardiographic data at 30 days were used for analysis. APS was not achieved if a patient expired or received MV surgery before discharge. We report the endpoint success rates in the study, in addition to a learning curve analysis for the endpoint success rates and procedure times based on the first 250 vs. last 250 subject outcomes, and the first 6 vs. >6 subject outcomes at each site.

To evaluate the long-term outcomes, Kaplan-Meier (KM) analysis was performed to estimate the 1-year mortality and all-cause hospitalization rates of the enrolled subjects. Changes in MR and New York Heart Association (NYHA) functional class are reported through 1-year follow up. For the safety outcomes, 30-day adverse event (AE) rates were calculated to report all events occurring within 30 days of the index procedure. One-year AE rates were calculated to report KM event rates throughout the 365 days from the index procedure to account for the time of the event over a longer follow-up duration. Finally, the proportion of patients on different classes of medications and with FMR are reported at baseline and through 1-year follow up.

Descriptive analysis was performed to summarize baseline characteristics, APS, MR, and NYHA class data. For continuous variables, means, standard deviations, and the 95% confidence intervals for the mean by normal approximation were calculated. For categorical variables, counts, percentages, and 95% confidence intervals determined by using the Clopper–Pearson exact method were reported. Where applicable, P value comparisons were performed based on t-tests. All analyses were done for the overall subject population and by subject etiology.

Results

A total of 500 patients were consecutively enrolled at 40 Japanese sites (**Supplementary Table**). Of the 500 subjects that underwent the index procedure, 458 (91.6%) were available at the 30-day follow up, and 391 (78.2%) were available at the 1-year follow up (**Supplementary Figure**). **Table 1** presents the baseline demographics and comorbidities for the subjects enrolled and treated in the Japan PMS study. The overall cohort was elderly (77.9±9.5 years), with 65.2% of patients aged >75 years and 58.8% being of male gender. A majority of the subjects (>70%) had severe (4+) MR, with 25–30% at moderate-to-severe (3+) MR and <2% at moderate (2+) MR. The etiology of MR was functional in 71.6%, degenerative in 25.2% and mixed in 3.2% of the subjects.

The comorbidity profile of the subjects included atrial fibrillation (63.8%), renal failure (49.1%), prior myocardial infarction (MI) (25.1%), prior transient ischemic attack (TIA) (2.6%), myocardial ischemia (25.1%), and diabetes (28.9%). Eighteen percent (17.8%) of the subjects had prior cardiac surgery and 5.6% subjects had prior valve surgeries. The NYHA functional class profile showed that a majority of subjects were class III/IV (68.9%), whereas the remaining subjects (31.0%) were NYHA class I/II. Mean STS risk of mortality for replacement was 12.0±9.7%. The FMR and DMR subjects differed significantly for several baseline characteristics such as age, gender, STS replacement score, rates of prior heart failure hospitalization (HFH), MIs, cardiac interventions and cardiac surgeries, and incidence of dyslipidemia, diabetes, renal failure, and atrial fibrillation.

Of all the enrolled subjects, 3 did not receive MitraClip, representing a 99.4% implant rate. A majority of the subjects (n=274 or 54.8%) were implanted with 1 MitraClip device. Two-hundred and 14 (214) subjects (42.8%) received 2 MitraClip devices, and 9 subjects (1.8%) received 3 MitraClip devices. Mean procedure time was 134.8±60.5 min,

Table 3. Impact of Learning Curve on Procedural Outcomes: (A) Overall, (B) DMR Only, and (C) FMR Only

	First 250 subjects	Second 250 subjects	P value	First ≤6 subjects per site	First >6 subjects per site	P value
(A) Overall	(N=250)	(N=250)		(N=186)	(N=314)	
APS	91.09 (225/247) [86.83, 94.33]	91.16 (227/249) [86.93, 94.38]	0.98	92.35 (169/183) [87.50, 95.75]	90.42 (283/313) [86.60, 93.44]	0.46
30-day SLDA	1.21 (3/248) [0.25, 3.49]	1.20 (3/249) [0.25, 3.48]	1.00	1.63 (3/184) [0.34, 4.69]	0.96 (3/313) [0.20, 2.78]	0.67
Total device time (min)	100.02±52.18 (248) [93.50, 106.55]	88.19±49.54 (248) [81.99, 94.39]	0.01	112.05±54.52 (182) [104.08, 120.02]	83.71±46.11 (314) [78.59, 88.83]	<0.0001
Procedure time (min)	140.84±63.05 (250) [132.99, 148.70]	128.73±57.28 (249) [121.58, 135.88]	0.03	155.45±65.79 (185) [145.91, 164.99]	122.63±53.62 (314) [116.68, 128.59]	<0.0001
(B) DMR Only	(N=59)	(N=67)		(N=35)	(N=91)	
APS†,‡	91.23 (52/57) [80.70, 97.09]	80.30 (53/66) [68.68, 89.07]	0.09	87.88 (29/33) [71.80, 96.60]	84.44 (76/90) [75.28, 91.23]	0.78
30-day SLDA¶,‡	0.00 (0/58) [0.00, 6.16]	3.03 (2/66) [0.37, 10.52]	0.50	2.94 (1/34) [0.07, 15.33]	1.11 (1/90) [0.03, 6.04]	0.47
Total device time (min)§	102.05±45.53 (58) [90.08, 114.02]	90.41±55.11 (66) [76.86, 103.96]	0.20	116.58±62.11 (33) [94.55, 138.60]	88.34±44.35 (91) [79.10, 97.58]	0.021
Procedure time (min)§	135.69±54.35 (59) [121.53, 149.86]	132.54±61.17 (67) [117.62, 147.46]	0.76	154.31±72.40 (35) [129.44, 179.19]	126.21±49.49 (91) [115.90, 136.51]	0.04
(C) FMR Only	(N=184)	(N=174)		(N=144)	(N=214)	
APS†,‡	91.26 (167/183) [86.19, 94.92]	94.83 (165/174) [90.41, 97.61]	0.19	93.01 (133/143) [87.52, 96.60]	92.99 (199/214) [88.70, 96.02]	1.00
30-day SLDA¶,‡	1.09 (2/183) [0.13, 3.89]	0.00 (0/174) [0.00, 2.10]	0.50	1.40 (2/143) [0.17, 4.96]	0.00 (0/214) [0.00, 1.71]	0.16
Total device time (min)§	98.56±54.60 (183) [90.60, 106.53]	86.80±47.31 (173) [79.70, 93.90]	0.03	109.89±53.04 (142) [101.10, 118.69]	81.54±47.20 (214) [75.18, 87.90]	<0.0001
Procedure time (min)§	142.24±66.37 (184) [132.59, 151.89]	125.76±55.30 (173) [117.46, 134.06]	0.011	154.41±64.93 (143) [143.68, 165.15]	120.79±55.70 (214) [113.28, 128.29]	<0.0001

†The denominator is the total number of patients who have reached the point of assessment. ‡Obtained by using the Clopper-Pearson exact confidence interval. §Obtained by normal approximation. ¶The denominator is the total number of patients who have had successful implants. Data are presented as % (n/N) [95% CI] or mean ± SD (n) [95% CI]. APS, acute procedure success; CI, confidence interval; DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation; SLDA, single leaflet device attachment.

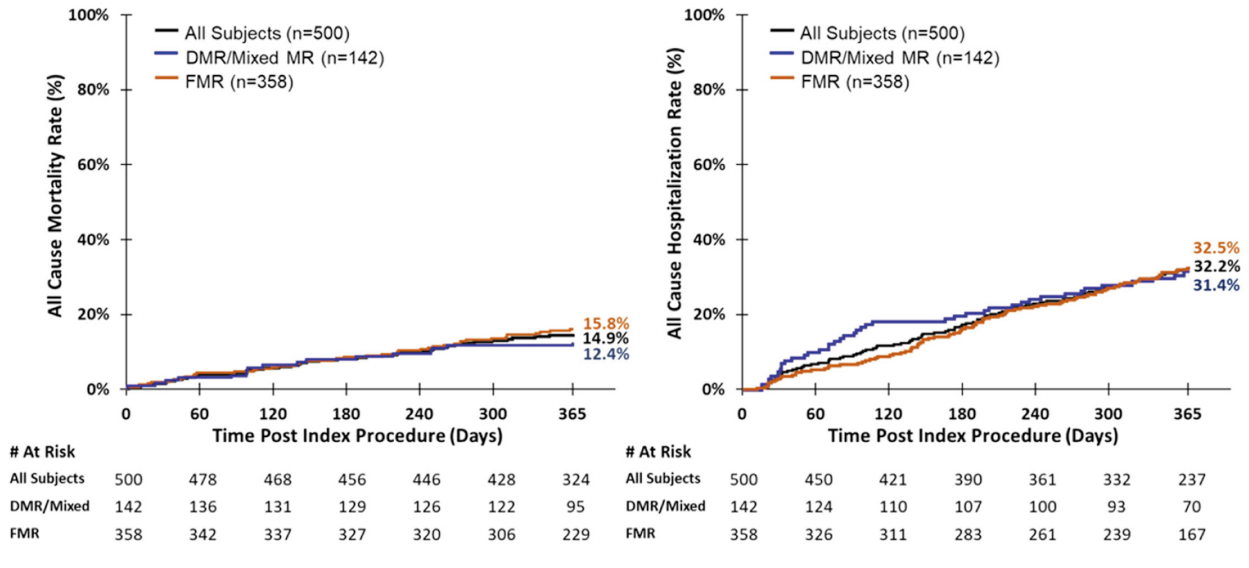

Figure 1. Kaplan-Meier estimates of 1-year mortality and all-cause hospitalization.

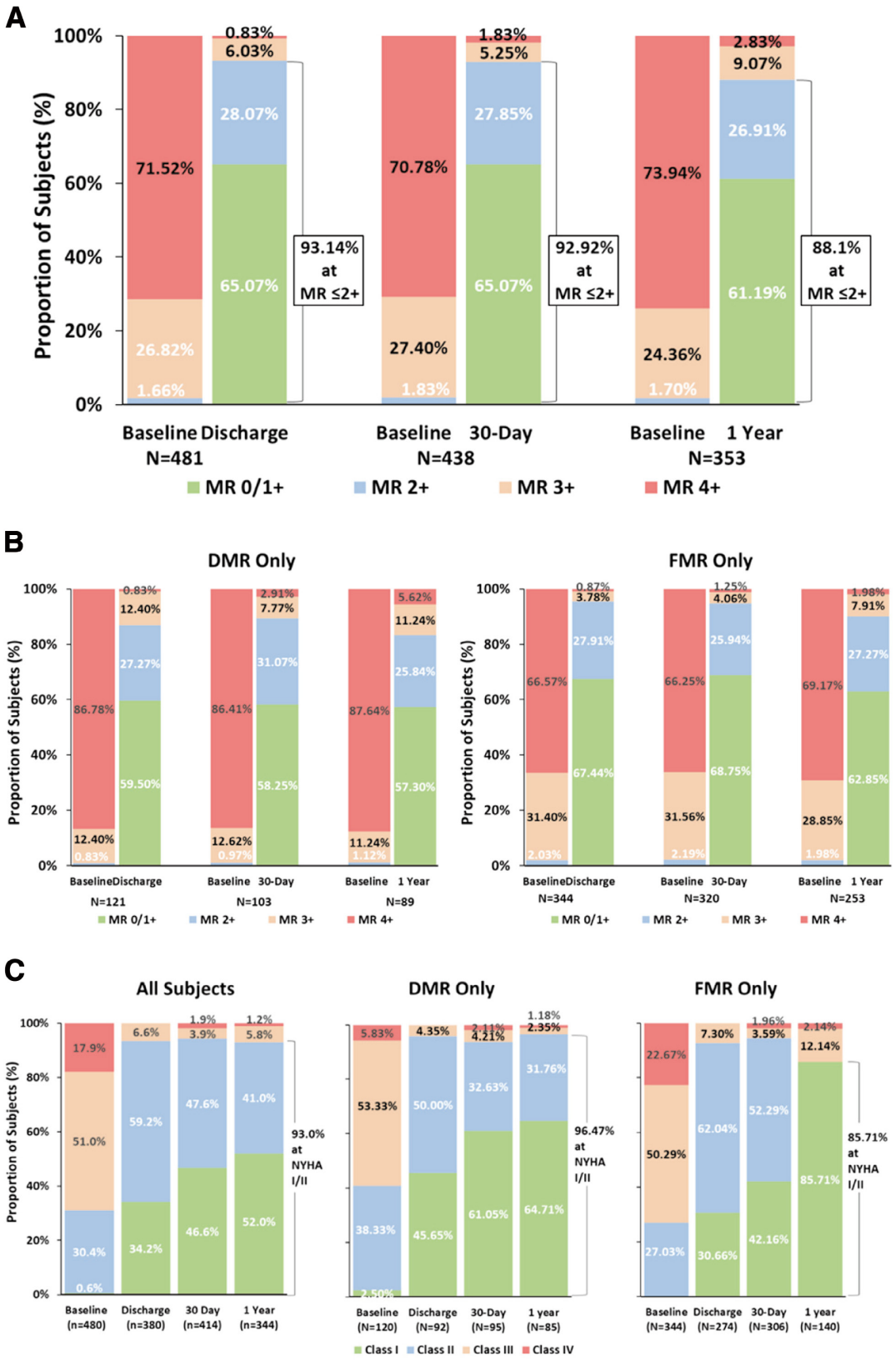

Figure 2. Mitral regurgitation (MR) and New York Heart Association (NYHA) class change through study follow up. (**A**) MR at follow-up timepoints for all subjects relative to the baseline MR (paired analysis). (**B**) Paired analysis of MR relative to baseline by subject etiology. (**C**) NYHA class change through study follow up.

Table 4. Major AEs Through 30-Day and 1-Year Follow up Across All Enrolled Subjects

	All subjects (N=500)	DMR only (N=126)	FMR only (N=358)	P value†† (DMR vs. FMR)
30 day				
Death†	1.6 (8/497)	1.6 (2/124)	1.7 (6/357)	1.00
MI	0.0 (0/497)	0.0 (0/124)	0.0 (0/357)	1.00
Stroke	1.2 (6/497)	1.6 (2/124)	1.1 (4/357)	0.65
MV re-intervention‡	1.0 (5/497)	0.0 (0/124)	1.4 (5/357)	0.33
Other surgery§	0.8 (4/497)	0.0 (0/124)	1.1 (4/357)	0.58
MV re-intervention‡ for device-related events¶	0.6 (3/497)	0.0 (0/124)	0.8 (3/357)	0.57
Other surgery§ for device-related events	0.2 (1/497)	0.0 (0/124)	0.3 (1/357)	1.00
1 year				
Death†	14.9 (73)	11.6 (14)	15.8 (56)	0.26
MI	0.0 (0/497)	0.0 (0/124)	0.0 (0/357)	
Stroke	2.0 (10/497)	2.4 (3/124)	1.7 (6/357)	0.60
MV re-intervention‡	3.8 (19/497)	2.4 (3/124)	3.9 (14/357)	0.36
Other surgery§	2.8 (14/497)	0.8 (1/124)	3.4 (12/357)	0.13
MV re-intervention‡ for device-related events¶	1.8 (9/497)	2.4 (3/124)	1.4 (5/357)	0.61
Other surgery§ for device-related events	0.4 (2/497)	0.0 (0/124)	0.3 (1/357)	0.56

†AE-led-to-death recorded on AE form. ‡MV re-intervention includes additional MitraClip procedure and MV surgery. §Other surgery includes CABG surgery and other non-MV surgery. ¶Event identified as possibly being related to the device by the site. ††For the 30-day section, P values were calculated from Fisher's exact tests. For the 1-year section, P values were calculated from log-rank tests. Data are presented as % (n/N). Note: The 30-day AE rates report all events occurring within 30 days of the index procedure. 1-year AE rates report Kaplan-Meier event rates through 365 days from the index procedure. Note: Event rates excludes 3 subjects who were terminated before discharge. AE, adverse event; CABG, coronary artery bypass graft; DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation; MI, myocardial infarction; MV, mitral valve.

and mean device time was 94.1±51.2 min across all attempted procedures (**Table 2**). The procedural and post-procedural outcomes were comparable across DMR and FMR subjects and did not differ significantly across etiologies.

The endpoints were successfully met. The APS rate was 91.1%; where 452 out of 496 subjects achieved MR ≤2+ at discharge without death or re-intervention. This analysis excludes 3 subjects who were terminated before discharge, and 1 subject who did not have a MR grade assessment at discharge or at 30 days follow up. The SLDA rate at 30 days was 1.2% across the 497 subjects who had at least 1 implanted clip. The outcomes were relatively better for FMR subjects compared to the DMR subjects, with APS and SLDA rates at 93.0% and 0.6% compared to 85.4% and 1.6% for DMR subjects respectively. Learning curve analysis showed no significant difference in the success rate of primary endpoints in the subjects treated earlier vs. later, although duration of the procedure was observed to decrease with experience (**Table 3**). Similar learning curve trends were seen for both DMR and FMR subjects.

One-year mortality and all-cause hospitalization rates were evaluated at 14.9% and 32.2% respectively (**Figure 1**). MR reduction was durable throughout follow up, with paired analysis relative to baseline showing 93.1%, 92.9% and 88.1% of subjects at MR ≤2+ at discharge, 30-day and 1-year timepoints respectively for the overall population (**Figure 2A**,**B**). Significant and durable improvement was observed in the functional capacity of the subjects, with 93% at NYHA class I/II at 1 year compared to 31% at baseline (**Figure 2C**).

The AE rates were low. It is to be noted that 1 subject died on the day of the 1-year visit, so although 72 events are reported with hierarchical rank of visit completion before death is accounted for, all 73 deaths are accounted for in the KM analysis for mortality, as shown in **Table 4**. Seventy-three subjects suffered death at 1 year, with an estimated KM event rate of 14.9%, and 10.0 (2%) suffered stroke. There was MV reintervention for 19 (3.8%) subjects at 1 year, though the number of reinterventions related to the device, as identified by the site, was only 9 (1.8%). No MI was observed throughout the 1-year follow up. All 30-day and 1-year major AEs are listed in **Table 4**. The AE rates did not differ significantly across the MR etiologies.

The medications taken by all subjects stayed fairly consistent from baseline through 1-year follow up in FMR subjects. The few medications that showed significant change included: (a) β-blockers and angiotensin-converting enzyme inhibitors, which had a sharp increase post procedure. This is often seen with the MitraClip procedure, which then allows for upregulation of HF mediations due to reduction in severity of MR; (b) aspirin showed significant decrease post procedure; and (c) statins, P2Y12 and anticoagulants were adjusted for patient condition throughout the follow up (**Table 5**).

Discussion

The principal findings of the present investigation are: (1) in Japan, transcatheter MV repair is being performed predominantly for patients with severely symptomatic, and prohibitive surgical risk in accordance with the approved labeled indications for use; (2) the MitraClip procedures are performed successfully with acute reduction in MR to a grade of ≤2 achieved in 91.13% of patients with low incidences of AEs; (3) significant improvement is observed in enrolled subjects at 1-year follow up, with a death rate of 14.9%, hospitalization rate of 32.2%, and 93.0% of subjects at NYHA class I/II.

Patients suffering from severe MR have poor prognosis in addition to increased risk of heart failure and impaired

Table 5. Proportion of FMR Subjects on Different Classes of Medications at Baseline and Through 1-Year Follow up

	Baseline	Discharge	30 day	1 year	P value
HF medications	96.9 (347/358)	99.4 (343/345)	99.1 (329/332)	98.9 (274/277)	0.02
ACE inhibitor	38.3 (133/347)	41.1 (141/343)	38.9 (128/329)	42.7 (117/274)	0.04
Angiotensin II receptor blocker	24.2 (84/347)	25.4 (87/343)	24.6 (81/329)	23.0 (63/274)	0.34
β-blocker	76.4 (265/347)	80.2 (275/343)	80.9 (266/329)	78.1 (214/274)	0.009
Diuretics – loo/thiazides	87.3 (303/347)	87.5 (300/343)	86.3 (284/329)	85.0 (233/274)	0.15
Diuretics – tolvaptan	45.5 (158/347)	45.8 (157/343)	45.3 (149/329)	48.2 (132/274)	0.11
Mineralocorticoid receptor antagonist	44.1 (153/347)	42.6 (146/343)	44.1 (145/329)	41.6 (114/274)	0.36
Digitalis	7.5 (26/347)	5.8 (20/343)	6.1 (20/329)	7.3 (20/274)	0.44
Cardiac medications	52.0 (186/358)	54.5 (188/345)	55.4 (184/332)	56.3 (156/277)	0.23
Vasodilators	32.8 (61/186)	31.4 (59/188)	30.4 (56/184)	24.4 (38/156)	0.27
Antiarrhythmic	54.8 (102/186)	55.3 (104/188)	53.8 (99/184)	51.9 (81/156)	0.26
Other	33.3 (62/186)	38.8 (73/188)	38.0 (70/184)	45.5 (71/156)	0.20
Anticoagulants	69.3 (248/358)	73.0 (252/345)	72.6 (241/332)	72.2 (200/277)	0.048
Warfarin	53.6 (133/248)	52.8 (133/252)	53.9 (130/241)	53.0 (106/200)	0.85
NOAC	46.8 (116/248)	48.0 (121/252)	46.1 (111/241)	47.0 (94/200)	0.99
Anti-platelets	44.4 (159/358)	51.9 (179/345)	50.9 (169/332)	46.2 (128/277)	0.001
Aspirin	80.5 (128/159)	73.7 (132/179)	73.4 (124/169)	68.0 (87/128)	0.02
P2Y12 inhibitors	40.3 (64/159)	48.0 (86/179)	49.1 (83/169)	43.0 (55/128)	0.04
Statins	46.1 (165/358)	48.1 (166/345)	46.1 (153/332)	44.0 (122/277)	0.02

Data are presented as % (n/N). Note: For the P values, a GEE model (or generalized linear model with repeated measures) is utilized to test whether variable visit is significant over binary medication usages. The P values were calculated by performing a type III GEE analysis. ACE, angiotensin-converting enzyme; GEE, generalized estimating equation; HF, heart failure; NOAC, novel oral anticoagulant.

long-term survival.[7] Particularly, patients with prohibitive surgical risk, have limited therapeutic options, and transcatheter MV repair is an important advancement for these patients.[8] The MitraClip device is shown to be very effective in these patients in reducing MR, decreasing symptoms of heart failure leading to reduced mortality and hospitalizations, and improving functional capacity in day-to-day activities.[8,9]

The enrolled subjects in the Japan PMS study meet the approved indications. The subjects are elderly (mean age of 78 years, with 65.2% subjects aged >75 years) and have a high STS replacement score, which fits the prohibitive risk criteria. In addition, the enrolled subjects have higher comorbidities (higher rates of prior HFH, renal failure and active dialysis, and more dilated ventricles), compared to EXPAND and TVT registry subjects (**Table 6**). Although they are largely comparable to AVJ-514 subjects,[6] the STS scores and proportions of subjects who have NYHA class III/IV in this study are still higher in the Japan PMS study. These differences may be influenced by the regional factors (i.e., healthcare financing model and cultural characteristics), as well as the scope of the study (i.e., trial with controlled inclusion/exclusion criteria such as COAPT vs. a post-market study [EXPAND, Japan PMS] or commercial device use registry [TVT registry]). Overall, it can be inferred that the patients undergoing transcatheter MV repair in Japan, as part of the PMS study, were treated in accordance with the labeled indications for use, with a relatively higher prevalence of severe comorbidities, and prohibitive surgical risk compared to other contemporary studies.

The study confirms that the procedure has been translated well and is being performed successfully and safely at Japanese sites, as demonstrated by the rates of study endpoints and AEs. A MR ≤2+ at discharge with APS is achieved for 91.13% subjects, and only 1.12% SLDA events are observed through 30 days. The APS and the SLDA rates are comparable to other contemporary studies, as shown in **Table 6**, as well as to the APS rates of the German TRAMI study (94%)[10] and MitraSwiss study (85%).[11] The procedural outcomes were excellent, with 99.4% implant rate and 1.46±0.54 average number of clips. This is in alignment with the MitraClip experience worldwide in the EXPAND,[12] TVT Registry,[13] COAPT,[4] and the AVJ-514 trials,[6] as shown in **Table 6**. The procedure duration does not vary with etiologies within Japan PMS subjects; however, it differs across studies and is likely to have regional influences and variability across different subject demographics (**Table 6**). In addition, the procedure durations are also significantly influenced by the experience at the site. This is demonstrated in the much higher device and procedure times for the AVJ-514 trial[6] (127 min and 285 min respectively;**Table 6**), which decreased in the PMS study during the initial subjects/sites (100 min and 141 min for the first 250 subjects, and 112 min and 155 min for the first 6 subjects at sites respectively), and decreased further as more experience is accumulated at a given site or with overall subjects to 88 min and 129 min for the last 250 subjects, and 84 min and 123 min for more than 6 subjects at the sites respectively (**Table 3**). However, it is worth noting that although procedures may take longer for earlier cases at a site, the APS and SLDA outcomes were not affected by the experience at the site (**Table 3**), and excellent patient outcomes were achieved irrespective of the site experience. These trends were preserved for analysis within both MR etiologies (**Table 3**). Looking at the safety profile of MitraClip procedures, major AE (MAE) rates at 30 days were 4.6% overall, comprising 1.6% death, 1.2% stroke and 1% MV re-intervention (**Table 4**). The 30-day mortality rates are considerably lower than those reported in the TVT

Table 6. Comparison of Key Baseline Characteristics Across Studies and Outcomes Other Relevant/Contemporary

	Japan PMS (n=500)	AVJ-514[6] (n=30)	EXPAND[12] (n=1,041)	TVT Registry[13] (n=2,952)	COAPT[4] (MitraClip Arm, n=302)	MARS[14] (n=142)
MR etiology, % (n/N)		FMR: 46.7 (14/30) DMR: 53.3 (16/30)	FMR: 49.6 (414/835) DMR: 45.6 (381/835)	FMR: 8.6 (254/2,952) DMR: 85.9 (2,536/2,952)	FMR only	FMR: 53.5 (76/142) DMR: 45.8 (65/142)
Baseline characteristics						
Age (years)	77.92±9.48	80.4±7.0	77.3±9.7	82 (74–86)	71.7±11.8	71.4±11.9
Male (%)	58.8	76.7	54.9	55.8	66.6	64.1
BMI	21.01±3.22	21.8±3.8	25.9±5.1	–	27.0±5.8	24.8±4.6
STS replacement score	11.95±9.66	10.3±6.59	8.0±6.4	9.2 (6.0–14.1)	7.8±5.5	7.4±8.1
Atrial fibrillation (%)	63.8	66.7	59.3	63.7	57.3	45.1
Diabetes (%)	28.9	20.0	25.4	25.0	35.1	28.9
Renal failure (%)	49.1	–	36.1	–	–	28.4
Currently on dialysis (%)	11.2	–	–	4.1	–	2.8
Prior HFH within 1 year (%)	64.1	–	53.7	–	58.3	–
Prior MI (%)	25.1	26.7	24.2	27.2	51.7	25.4
EROA (cm^2)	0.40±0.26	–	0.35±0.18	0.40 (0.30–0.60)	0.41±0.15	
LVEF (%)	46.10±14.93	50.2±12.8	51.4±16.0	55 (40–60)	31.3±9.1	47±17
LVESV (mL)	93.54±64.43	–	78.8±61.5	–	135.5±56.1	–
LVEDV (mL)	160.26±75.31	–	148.1±71.3	–	194.4±69.2	–
LVESD (cm)	4.5±1.3	4.1±1.18	–	3.6 (3.0–4.5)	5.3±0.9	4.5±1.3
LVEDD (cm)	5.8±1.0	5.7±0.9	–	5.2 (4.6–5.8)	6.2±0.7	6.0±1.0
NYHA class III/IV (%)	69.0	36.4	78.5	84.0	57	68.3
Endpoint success rates (%)						
APS	91.13	86.7	92.9	91.8	–	93.7
SLDA rates	1.21	None	1-year rate=1.7	Procedural rate=1.5	1-year rate=0.7	Procedural rate=4.2
Procedural outcomes						
Implant rate (%)	99.4	100	98.9	–	98	–
Average number of clips	1.46±0.54	~1.77	1.5±0.6 (1,030)	66.5% with 1 clip	1.7±0.7 (293)	–
Device time (min)	94.11±51.17 (496)	126.6±79.57	56.8±41.8	–	82.7±80.8	–
Procedure time (min)	134.80±60.48 (499)	284.6±90.67	89.1±49.6	–	162.9±118.1	130±98
Total index procedure hospital stay (days)	20.46±22.64 (483)	14.4±8.5	6.5±7.0	Median 2.0 days (1.0–5.0)	–	6.0±7.8
Post procedure PACU/CCU/ICU duration (h)	76.97±346.58 (464)	36.8±36.3	48.74±79.86 (666)	–	–	–
Adverse event rates (%)						
Death	2.4	0.0	2.3	5.2	2.3	5.6
MI	0.0	–	0.0	0.2	–	–
Stroke	1.2	–	0.8	1.4	0.7	–
MV re-intervention (surgery or repeat MitraClip)	1.0	–	~1.1	1.7	~1.4	0.7

Data are presented as mean±SD (n) or n (range), unless otherwise stated. APS, acute procedural success; BMI, body mass index; CCU, cardiac/coronary care unit; EROA, effective regurgitant orifice area; HFH, heart failure hospitalizations; ICU, intensive care unit; LVDD, left ventricular diastolic dysfunction; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; MV, mitral valve; NYHA, New York Heart Association; PACU, post anesthesia care unit; SLDA, single leaflet device attachment; STS, Society of Thoracic Surgeons.

registry[13] (5.2%) and the MARS trial[14] (5.6% overall), and are comparable to the EXPAND[12] and COAPT[4] studies (2.3% for both). The KM estimates of 1-year MAE rates (14.9% mortality, 0% MI, 2.0% stroke, and 3.8% MV reintervention), also compare well with EXPAND[12] (14.9% mortality, 1.2% MI, 1.7% stroke, 1.9% MV reintervention), and are significantly lower than those reported in the TVT registry[13] (25.8% death, 2.5% MI, 3.3% stroke and 8.3% MV reintervention).

The benefits of the MitraClip procedure are seen across the spectrum with MR reduction, reduced follow-up mortality and hospitalization rates, and improved functional class of the enrolled subjects. The MR severity was reduced significantly post procedure, with 93.14%, 92.92% and 88.1% of subjects at MR ≤2+ at discharge, 30 day and 1 year respectively. This is comparable or better than the contemporary experience with the TVT registry[13] (93.0% at MR ≤2+ at discharge), COAPT[4] (94.8% at MR ≤2+ in the MitraClip arm at 1 year), MARS registry[14] (76.8% at MR ≤2+ at 30 days) and AVJ-514 trial[6] (86.7% at MR ≤2+ at discharge and 30 days). The EXPAND study, however, shows relatively higher improvement rates, with ~98% of subjects at MR ≤2+ at 1 year. The factors leading to higher reported rates in the EXPAND study can be 2-fold: (1) the EXPAND study used a newer generation of the device (MitraClip NTR/XTR), as opposed to the 1st generation MitraClip NT used in the other studies compared here); and (2) the EXPAND echocardiographic data are adjudicated by a central core laboratory. The assessment of MR, especially post MitraClip implantation, is known to be challenging due to acoustic shadowing from TMVR, multiple potential regurgitant orifices, and the eccentric nature of post-procedural regurgitation in these patients.[13,15] Hence, variability in the methodology of MR assessment from site-reported data vs. a standardized core laboratory evaluation (as in COAPT and EXPAND studies) can affect the MR assessment results. The excellent clinical and functional outcomes in the Japan PMS subjects confirm equivalent or greater effectiveness of the treatment of MR compared to the EXPAND study, and indicates a non-standardized assessment of MR across sites as the more likely reason for this difference.

Mortality and hospitalization outcomes at 1 year (**Figure 1**) show overall all-cause mortality of 14.9% and compare well to the 1-year mortality rate of the COAPT[4] study at 18.8% and the EXPAND[12] study at 14.9%. This is considerably lower than the 1-year mortality rate in the TVT registry[13] at 25.8%. Given that just HF hospitalizations in the prior year were 64.1% in this population (**Table 1**), all-cause hospitalizations also show significant improvement at 32.2% during 1-year follow-up post procedure. In alignment with the reduction in mortality and hospitalizations, significant NYHA functional class improvements were seen in the present study (**Figure 2C**), with 93.4% and 93.0% at NYHA I/II at 30 days and 1 year respectively. These rates are much higher than the NYHA I/II rates reported in the COAPT study[4] (72.2% at 1 year), EXPAND study[12] (with 80.3% at 1 year) and the MARS study[14] (82.1% at 30 days), and are comparable to AVJ-514 trial[6] results of 96.7% at NYHA I/II at 30 days (n=30). The persistent risks of death and hospitalization is attributed, at least in part, to untreated comorbidities. For example, Sorajja et al found a significant correlation between severe tricuspid regurgitation at baseline and subsequent poorer outcome after transcatheter MV repair.[13] Similarly, concomitant lung disease and renal failure are also important variables associated with 1-year outcomes.[13] Hence, achieving comparable or better mortality, hospitalization and functional capacity outcomes despite a more aged population with higher comorbidities in the Japan PMS study, speaks to the successful execution of the MitraClip procedure, and superior effectiveness of the MitraClip in the Japanese population.

Study Limitations

First, data about heart failure medication dosages were not collected in this trial. Current guidelines recommend medical therapy as a class I indication for patients with severe FMR and HF with reduced left ventricular ejection fraction (LVEF).[2,16] Therefore, further studies will be necessary to evaluate serial change of heart failure medication dosages after MitraClip therapy. Second, the clinical impact of MitraClip therapy on patients with low LVEF was not evaluated because this trial enrolled only patients with a LVEF ≥30%.

Conclusions

The MitraClip procedure is being performed in Japan for severely symptomatic MR patients at significant prohibitive surgical risk in accordance with the approved indications of use. The Japan PMS study subjects experience marked improvement in their clinical and functional outcomes, which are comparable or better than the contemporary experience of MitraClip from other key studies including MARS, AVJ-514, COAPT, EXPAND and the TVT registry. These results demonstrate the successful introduction of the MitraClip device in Japan. Further, the results add to the growing evidence of safety and efficacy of the MitraClip, and bolster the overall global experience with patient selection and MitraClip procedure use in the Japanese population for both degenerative and functional MR etiologies.

Disclosures

All authors are from the training faculty at Abbott Medical Japan.

IRB Information

Sendai Kosei Hospital IRB (Reference number: 29-87) approved this study.

Data Availability

The deidentified participant data can be shared on a request basis. Additionally, related documents can also be made available, including study protocol, statistical analysis plan, etc. The requested data will be transferred to the requesting party with access based on the terms of an agreed upon data sharing contract. Please contact the corresponding author directly to request data sharing.

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Supplementary Files

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