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Percutaneous Mitral Valve Interventions in the Real World

Early and 1-Year Results From the ACCESS-EU, A Prospective, Multicenter, Nonrandomized Post-Approval Study of the MitraClip Therapy in Europe

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Objectives The purpose of this article is to report early and mid-term outcomes of the ACCESS-EU study (ACCESS-Europe A Two-Phase Observational Study of the MitraClip System in Europe), a European prospective, multicenter, nonrandomized post-approval study of MitraClip therapy (Abbott Vascular, Inc., Santa Clara, California).

Background MitraClip has been increasingly performed in Europe after approval; the ACCESS-EU registry provides a snapshot of the real-world clinical demographic data and outcomes.

Methods A total of 567 patients with significant mitral valve regurgitation (MR) underwent MitraClip therapy at 14 European sites. Mean logistic European System for Cardiac Operative Risk Evaluation at baseline was 23.0 ± 18.3; 84.9% patients were in New York Heart Association functional class III or IV, and 52.7% of patients had an ejection fraction ≤40%.

Results The MitraClip implant rate was 99.6%. A total of 19 patients (3.4%) died within 30 days after the MitraClip procedure. The Kaplan-Meier survival at 1 year was 81.8%. Intensive care unit and hospital length of stay was 2.5 ± 6.5 days and 7.7 ± 8.2 days, respectively. Single leaflet device attachment was reported in 27 patients (4.8%). There were no MitraClip device embolizations. Thirty-six subjects (6.3%) required mitral valve surgery within 12 months after the MitraClip implant procedure. There was improvement in the severity of MR at 12 months, compared with baseline ($p < 0.0001$), with 78.9% of patients free from MR, severity of >2+ at 12 months. At 12 months, 71.4% of patients had New York Heart Association functional class II or class I. Six-min-walk-test improved 59.5 ± 112.4 m, and Minnesota-living-with-heart-failure score improved 13.5 ± 20.5 points.

Conclusions In the real-world, post-approval experience in Europe, patients undergoing the MitraClip therapy are high-risk, elderly patients, mainly affected by functional MR. In this patient population, the MitraClip procedure is effective with low rates of hospital mortality and adverse events. (J Am Coll Cardiol 2013;62:1052–61) © 2013 by the American College of Cardiology Foundation

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MitraClip therapy (Abbott Vascular, Inc., Santa Clara, California) is a percutaneous treatment for mitral valve regurgitation (MR) based on edge-to-edge surgical technique pioneered by Alfieri et al. (1,2). MitraClip therapy has been successfully used to treat either functional (FMR) or degenerative mitral valve regurgitation (DMR) (3–7). The EVEREST trial (Endovascular Valve Edge-to-edge REpair STudy) compared safety and efficacy of percutaneous versus surgical therapy in a cohort of operable patients mainly with DMR (3). Because it only enrolled operable patients, the outcomes of the EVEREST trial could not be applicable to the current population being treated in Europe.

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To provide an up-to-date snapshot of the current practice in Europe, the ACCESS-EU study (ACCESS-Europe A Two-Phase Observational Study of the MitraClip System in Europe), a bi-phase European prospective, multicenter, nonrandomized post-approval study of MitraClip therapy was designed. The primary objective of the ACCESS-EU Phase I study was to gain information with regard to the use of the MitraClip system in Europe with respect to health economics and clinical care, to define demographic data of patients, and to provide further evidence of the safety and effectiveness of the MitraClip System in a real-world setting. In addition to the MitraClip device group, 2 standard therapy concurrent comparator groups (medically managed patients and patients who have undergone mitral valve surgery for MR) have been enrolled and evaluated primarily from a health economic perspective. No selection criteria to allocate patients in the MitraClip versus standard therapy groups were pre-specified, and the indication was based on individual clinical judgment. The present paper reports exclusively on patients who underwent percutaneous treatment with the MitraClip device.

Methods

The MitraClip System received CE Mark in March 2008, and commercialization was initiated in September 2008. The technical details of the device and of the procedure have been previously described (3). The ACCESS-EU Phase I study began enrolling patients in Europe in April 2009. Enrollment in ACCESS-EU Phase I was completed on April 13, 2011. This report includes baseline through 12-month clinical data collected as of June 15, 2012. Figure 1 presents patient accountability through 12 months.

Abbreviations and Acronyms

CI = confidence interval
DMR = degenerative mitral valve regurgitation
EF = ejection fraction
EuroSCORE = European System for Cardiac Operative Risk Evaluation
FMR = functional mitral valve regurgitation
MLHFQ = Minnesota Living with Heart Failure quality of life questionnaire
MR = mitral valve regurgitation
6MWT = 6-min walk test
NYHA = New York Heart Association
SLDA = single leaflet device attachment

Patient screening, enrollment, treatment, and follow-up. Indication to MitraClip therapy was given according to local institutional practice in consideration of current CE Mark approved labeling and the MitraClip System Instructions for Use. Eligible patients included those with symptomatic MR or asymptomatic moderate-to-severe (3+) or severe (4+) MR. Transthoracic and transesophageal echocardiogram studies were evaluated at baseline to assess patient eligibility. All patients provided written informed consent before their enrollment in the study (Fig. 2). Patients were evaluated at baseline through 12 months after enrollment. The Minnesota Living with Heart Failure quality of life questionnaire (MLHFQ) and 6-min walk test (6MWT) were administered at baseline and at 6 and 12 months. Enrollment in the study is complete.

Statistical considerations. Baseline and demographic qualitative variables were expressed as percentages, and quantitative variables were expressed as mean ± SD or median (25th to 75th interquartile range). The MR severity was compared between baseline, discharge, and 6 and 12 months with Bowker's test. Changes in 6MWT distance and quality of life between baseline and 6 and 12 months were analyzed with paired *t* tests. Survival rates up to 12 months were presented as Kaplan-Meier curves. Differences were considered statistically significant at p values <0.05. The data were analyzed with SAS statistical software (version 9.1.3, SAS Institute, Inc., Cary, North Carolina).

Data collection. Demographic data, acute procedural results, and post-procedural follow-up data were collected by study personnel at investigational sites and entered onto electronic Case Report Forms. Echocardiographic studies and quantitative assessment of MR were performed by the study sites. Data management was performed by MedPass International–ACCESS-EU Data Coordinating Center.

Results

A total of 567 patients have been enrolled at 14 European sites. The baseline characteristics, including site-reported severity and etiology of MR are summarized in Table 1 (displaying also data from the EVEREST II and EVEREST high-risk studies for comparison). The mean logistic

Medinol, Medtronic, NDC, NMT, OAS, Occlutech, Osprey, Ovalis, Pathway, PendraCare, Percardia, pfm Medical, Recor, ResMed, Rox Medical, Sadra, Sorin, Spectranetics, SquareOne, Trireme, Trivascular, Velocimed, Veryan, and Vessix; he has received stock options from Cardiokinetix, Access Closure, Velocimed, Lumen Biomedical, Coherex, and SMT. Dr. Richardt is a member of an advisory board of Abbott Vascular. Dr. Schillinger has received lecture fees, study honoraria, and reimbursement for travel expenses from Abbott Vascular. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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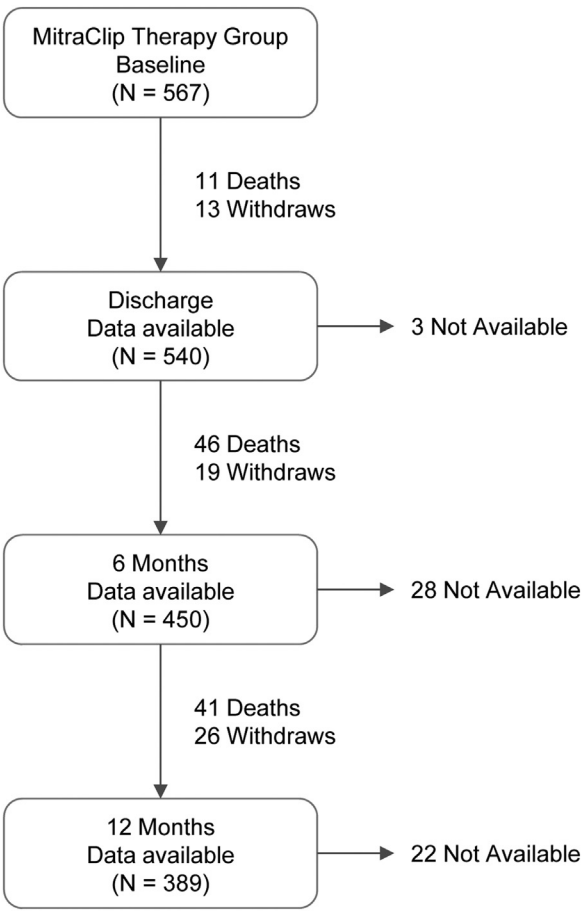

Figure 1 **Patient Enrollment and Follow-Up Status**

The ACCESS-EU Phase I study enrolled 567 patients between April 2009 and April 2011. Complete patient accountability from baseline through 12 months is shown. There were 58 patient withdrawals and 98 deaths through 12 months.

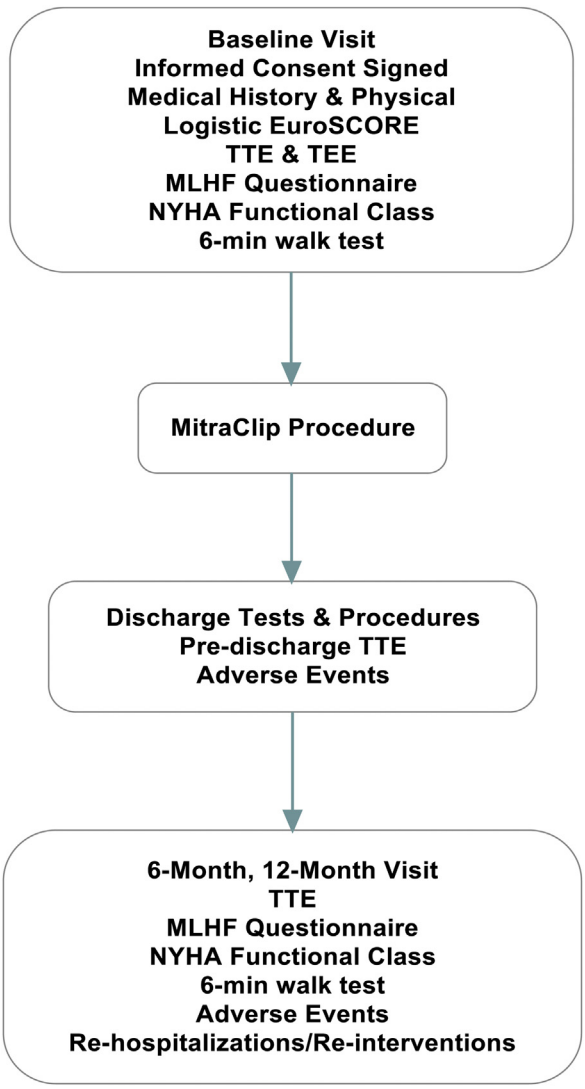

Figure 2 **Patient Screening, Enrollment, Treatment, and Follow-Up**

Patients enrolled in the ACCESS-EU study are a subset of patients treated under commercial use in Europe. Patients who signed the informed consent form and have attempted placement of the MitraClip device (Abbott Vascular, Inc., Santa Clara, California) were considered enrolled in the ACCESS-EU study. All enrolled patients were evaluated at baseline, discharge, 6 months, and 12 months. MLHF = Minnesota Living with Heart Failure questionnaire; NYHA = New York Heart Association; TEE = transesophageal echocardiogram; TTE = transthoracic echocardiogram.

European System for Cardiac Operative Risk Evaluation (EuroSCORE) at baseline was 23.0 ± 18.3 with 44.6% of patients having a baseline logistic EuroSCORE ≥20%. Patients with FMR tended to have more comorbidities and had a higher logistic EuroSCORE. Most ACCESS-EU Phase I patients had symptoms of heart failure at baseline, with 69.9% in New York Heart Association (NYHA) functional class III, and 14.9% in class IV. Many patients had some degree of left ventricular dysfunction, with a large proportion (52.7%) having a left ventricular ejection fraction (EF) ≤40%. Eleven percent had an EF ≤20%. Twenty-seven patients (4.9%) were in cardiogenic shock at the time of the index procedure.

The MitraClip device implant rate was 99.6% with only 2 patients not successfully implanted with a MitraClip device. One patient had a pre-existing patent foramen ovale and a severely dilated left atrium with a mobile septum and developed a large atrial septal defect as the consequence of the guide catheter manipulations. The defect was determined to be too large to treat with catheter-based techniques. The patient underwent successful surgical mitral valve replacement and atrial septal repair. The second patient did not receive a MitraClip device, due to an inability to adequately reduce MR. This patient also underwent a successful mitral valve surgery. In the remaining patients, 60.1% received 1 MitraClip device, 36.7% received 2 devices, and a very small proportion (<3%) received 3 or more devices. Procedural results, including procedure time, contrast volume, and fluoroscopy duration, are summarized in Table 2.

Safety. There was no incidence of death, stroke, or respiratory failure intra-procedurally and in the immediate post-operative period after the MitraClip procedure. Myocardial infarction was reported acutely in 1 patient, and a small proportion of patients experienced cardiac tamponade (0.9%) or the need for resuscitation (1.1%). Site-reported safety outcomes at 30 days are presented in Table 3. A total of 19 patients (3.4%) died within the 30 days after the MitraClip procedure. The site-reported causes of death for these patients were: cardiac (42%, 8 of 19); multi-organ failure (16%, 3 of 19); sepsis (11%, 2 of 19); pneumonia (5%, 1 of 19); respiratory failure (5%, 1 of 19); pulmonary embolism (5%, 1 of 19); cerebral (5%, 1 of 19); and unknown causes (11%, 2 of 19). Figure 3 shows the Kaplan-Meier freedom from mortality at 12 months post-procedure. The Kaplan-Meier estimate of freedom from mortality at 6 and 12 months is 88.2% (95% confidence interval [CI]: 85.1% to 90.6%) and 81.8% (95% CI: 78.1% to 84.8%), respectively. A total of 98 (17.3%) deaths were reported within 12 months of the MitraClip procedure.

The mean duration of time that patients spent in the intensive care unit after the MitraClip procedure was 2.5 ± 6.5 days with a median of 1.0 day. Patients were discharged from the hospital an average of 7.7 ± 8.2 days with a median of 6.0 days after the MitraClip procedure. The large majority of patients (79.2%) were discharged home without home health care, whereas 17.1% were discharged to a skilled nursing facility.

Single leaflet device attachment (SLDA), defined as the loss of insertion of a single leaflet from the MitraClip device with ongoing insertion of the opposing leaflet was reported in 27 patients (4.8%). All but 1 SLDA case were diagnosed within 6 months from the index procedure. Of the 27 patients that had SLDAs, 10 underwent a second MitraClip procedure, no action was taken in 11 patients, 6 patients had mitral valve repair or replacement surgery, and 1 patient had additional MitraClip devices implanted during the index procedure. There have been no reports of MitraClip device embolization in the ACCESS-EU Study.

Thirty-six subjects (6.3%) underwent a mitral valve surgery within 12 months after the MitraClip implant procedure. Nineteen patients (3.4%) underwent a second intervention to place an additional MitraClip device to reduce MR. Of the 19 attempts to further reduce MR with a second intervention to place a MitraClip device, 14 (74%) were successful.

Efficacy. Acute hemodynamic measurements obtained before MitraClip procedure and at least 10 min after MitraClip device deployment were available on a subset of patients. After the MitraClip procedure, mean cardiac output increased by 0.7 l/min, from 3.7 ± 1.5 l/min to 4.4 ± 1.9 l/min. Pulmonary Capillary Wedge Pressure V-wave decreased by 3.5 mm Hg, from 23.0 ± 10.8 mm Hg to 19.5 ± 9.1 mm Hg. All other hemodynamic parameters remained stable post-implant.

Most patients (91.2%) achieved MR reduction to 2+ or less at discharge, and 50.9% had an MR severity rating of 1+ or less. There was improvement in the severity of MR at 12 months compared with baseline ($p < 0.0001$), with 79.8% (313 of 392) of patients free from MR severity of >2+ at 6 months (Fig. 4, Table 4). At 1 year from the procedure, 78.9% (258 of 327) of patients were free from MR severity of >2+ ($p < 0.0001$). Eighty-eight percent of patients experienced at least a 1-grade MR improvement from baseline to 12 months, 53% experienced 2-or-more-grade improvement, and finally, 16% of patients improved by 3 or more grades.

At 12 months, 71.4% (245 of 343) of patients had NYHA functional class II or class I.

The 6MWT (matched data available on 261 patients) (Fig. 5) improved 56.4 ± 120.1 m (95% CI: 41.8 to 71.0, $p = 0.0006$) at 6 months (322.0 ± 124.8 m) as compared with baseline (265.5 ± 120.0 m). At 12 months (matched data available on 216 patients), the improvement in 6MWT was 59.5 ± 112.4 m (95% CI: 44.5 to 74.6, $p < 0.0001$) from 274.7 ± 118.7 m at baseline to 334.2 ± 127.9 m at 12 months. There was no significant improvement in the distance walked during the 6MWT between 6 and 12 months.

The MLHFQ went from 41.2 ± 19.1 at baseline to 28.9 ± 20.7 at 6 months for patients with matched data ($n = 311$), representing an improvement of 12.3 ± 20.9 points (95% CI: 14.6 to 10.0, $p < 0.0001$). The MLHFQ score improved 13.5 ± 20.5 points (95% CI: 11.0 − 16.0, $p < 0.0001$) from baseline (41.6 ± 18.9) to 12 months (28.1 ± 20.1) in 264 patients with paired data. The MLHFQ score improved by 0.4 ± 16.2 points between 6 and 12 months ($p = 0.0002$).

Discussion

The ACCESS-EU study is the largest database of MitraClip therapy reported to date and demonstrates that most patients currently treated in Europe have a high surgical risk profile. Nonetheless, the procedure is safe, with low adverse-event rate at 30 days and 12 months. MitraClip therapy is effective in most patients, with sustained and meaningful improvement of hemodynamic and functional status at 12 months from the procedure.

The ACCESS-EU study offers a precious snapshot of the current population of patients undergoing transcatheter treatment of MR in Europe: the mean age was 74 years (45% of patients were older than 75 years); most patients had FMR (77%) and low EF (53% of patients with an EF ≤40%) and presented with multiple comorbidities, including coronary artery disease (63%), hypertension (76%), atrial fibrillation (68%), and renal disease (42%). Overall, 40% of patients had some form of heart rhythm management, although only 11% of patients had a biventricular-pacing device implanted before MitraClip procedure. The vast majority of patients were highly symptomatic (85% of patients were in NYHA functional class III or IV at baseline), a condition that has been associated with worse outcomes (4,8).

This population is different from the one treated in the EVEREST II RCT trial (EVEREST II Randomized

Table 1 Baseline Characteristics

Characteristic*	ACCESS-EU Phase I			EVEREST II Randomized Clinical Trial	EVEREST II High Risk Study
	All Patients (N = 567)	FMR Patients (n = 393)	DMR Patients (n = 117)	MitraClip Patients (n = 184)	MitraClip Patients (n = 78)
Age, yrs	73.7 ± 9.6 (567)	73.0 ± 8.9 (393)	75.6 ± 12.1 (117)	67.3.0 ± 12.8 (184)	76.7 ± 9.8 (78)
Patients over 75 yrs of age	45.1% (256/567)	40.7% (160/393)	61.5% (72/117)	29.9% (55/184)	61.5% (48/78)
Sex					
Female	36.2% (205/567)	32.1% (126/393)	49.6% (58/117)	37.5% (69/184)	37.2% (29/78
Male	63.8% (362/567)	67.9% (267/393)	50.4% (59/117)	62.5% (115/184)	62.8% (49/78)
Comorbidities					
Congestive heart failure	70.1% (397/566)	70.7% (277/392)	62.4% (73/117)	90.8% (167/184)	100.0% (78/78)
Coronary artery disease	62.7% (354/565)	68.2% (267/391)	41.0% (48/117)	47.0% (86/183)	84.2% (64/76)
Myocardial infarction	32.0% (175/547)	35.0% (132/377)	21.6% (25/116)	21.9% (40/183)	55.8% (43/77)
Atrial fibrillation	67.7% (356/526)	69.3% (248/358)	58.8% (67/114)	33.9% (59/174)	61.6% (45/73)
Cerebrovascular disease	12.9% (73/566)	13.8% (54/392)	10.3% (12/117)	7.6% (14/184)	17.9% (14/78)
Cardiomyopathy	46.2% (259/561)	54.4% (212/390)	22.6% (26/115)	17.9% (33/184)	51.3% (40/78)
Hypertension	76.1% (429/564)	76.2% (298/391)	75.0% (87/116)	72.3% (133/184)	89.7% (70/78)
Diabetes	29.6% (168/567)	34.1% (134/393)	14.5% (17/117)	7.6% (14/184)	41.0% (32/78)
Renal disease	41.6% (236/567)	48.1% (189/393)	25.6% (30/117)	3.3% (6/184)	23.1% (18/78)
Peptic ulcer disease	5.1% (29/565)	6.6% (26/391)	2.6% (3/117)	6.0% (11/183)	9.1% (7/77)
Cardiogenic shock	4.9% (27/554)	5.4% (21/386)	2.6% (3/116)	—	—
Chronic pulmonary disease	19.0% (107/562)	20.3% (79/389)	14.7% (17/116)	14.8% (27/183)	34.7% (27/78)
Previous coronary artery bypass grafting	28.9% (164/567)	33.3% (131/393)	17.1% (20/117)	20.7% (38/184)	55.1% (43/78)
Previous percutaneous intervention	38.2% (213/558)	40.4% (156/386)	27.6% (32/116)	24.0% (44/183)	38.5% (30/78)
Cardiac rhythm device implant					
CRT	10.7% (59/552)	12.8% (49/382)	1.7% (2/115)	N/A	N/A
ICD	16.7% (92/552)	20.2% (77/382)	3.5% (4/115)	7.2% (13/181)	13.0% (10/77)
Pacemaker	12.7% (70/552)	13.1% (50/382)	12.2% (14/115)	4.4% (8/181)	22.1% (17/77)
Logistic EuroSCORE	23.0 ± 18.3 (567)	24.8 ± 18.9 (393)	15.5 ± 13.3 (117)	—	—
Logistic EuroSCORE ≥20%	44.6% (253/567)	48.4% (190/393)	28.2% (33/117)	—	—
STS mortality risk	—	—	—	5.0 ± 4.0 (184)	14.2 ± 8.2 (78)
STS mortality risk ≥12%	—	—	—	6.0% (11)	61.5% (48)
LVEF					
10%–20%	11.0% (62/562)	13.4% (52/388)	3.4% (4/117)	—	—
20%–30%	23.3% (131/562)	30.9% (120/388)	0.9% (1/117)	—	—
30%–40%	18.3% (103/562)	21.9% (85/388)	5.1% (6/117)	—	—
>40%	47.3% (266/562)	33.8% (131/388)	90.6% (106/117)	—	—
Mean ± SD (n)	—			60.0 ± 10.1 (182)	54.4 ± 13.7 (78)
NYHA					
I	1.3% (7/549)	0.3% (1/379)	5.2% (6/115)	9.2% (17/184)	0.0% (0/78)
II	13.8% (76/549)	12.4% (47/379)	20.9% (24/115)	39.7% (73/184)	10.3% (8/78)
III	70.0% (384/549)	70.7% (268/379)	67.0% (77/115)	44.6% (82/184)	60.3% (47/78)
IV	14.9% (82/549)	16.6% (63/379)	7.0% (8/115)	6.5% (12/184)	29.5% (23/78)

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Table 1 Continued

Characteristic*	ACCESS-EU Phase I			EVEREST II Randomized Clinical Trial	EVEREST II High Risk Study
	All Patients (N = 567)	FMR Patients (n = 393)	DMR Patients (n = 117)	MitraClip Patients (n = 184)	MitraClip Patients (n = 78)
MR					
2+: Moderate	2.3% (13/567)	1.5% (6/393)	3.4% (4/117)	4.3% (8/184)	1.3% (1/78)
3+: Moderate-to-severe	40.6% (230/567)	39.5% (155/393)	37.6% (44/117)	70.7% (130/184)	76.9% (60/78)
4+: Severe	57.1% (324/567)	59.0% (232/393)	59.0% (69/117)	25.0% (46/184)	21.8% (17/78)
LV internal dimensions, systole (cm)	4.6 ± 1.5 (322)	5.1 ± 1.4 (208)	3.5 ± 0.9 (94)	3.7 ± 0.9 (181)	3.9 ± 1.1 (78)
MR etiology					
Functional	77.1% (393/510)	100% (393)	—	26.6% (49/184)	59.0% (46/78)
Degenerative	22.9% (117/510)	—	100% (117)	73.4% (135/184)	41.0% (32/78)

Values are mean ± SD (n) or % (n/N). *Sample sizes smaller than 567,393 (functional mitral valve regurgitation [FMR]) or 117 (degenerative mitral valve regurgitation [DMR]) for the ACCESS-EU Phase I study, 184 for the EVEREST II RCT study, or 78 for the EVEREST II High Risk Study reflect missing data.

CRT = cardiac resynchronization therapy; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral valve regurgitation; N/A = not available; NYHA = New York Heart Association functional class.

Clinical Trial), who were slightly younger (71 years, on average), less symptomatic (52% patients in class III to IV), had the opposite MR etiology distribution (73.4% DMR), had mostly preserved EF (average 60.0 ± 10.1%), and presented less comorbidities: coronary disease in 47%; atrial fibrillation in 34%, while renal insufficiency was a protocol exclusion criterion. Two ACCESS-EU contributing centers have recently demonstrated that exclusion criteria for the EVEREST II trial would have been met in 73% (9) and 80% (10) of patients, respectively, predominantly because of ventricular dysfunction.

The difference in the respective patient populations treated with the MitraClip device in the ACCESS-EU and EVEREST II RCT studies is not unexpected, because conventional surgery is very effective in DMR, and the main unmet need for low-risk procedures is for patients with FMR, with low EF, and multiple comorbidities. As a result, the average logistic EuroSCORE was 23.0 ± 18.3, and 45% of patients had a EuroSCORE >20%.

The ACCESS-EU patients presented in this report have more in common with the MitraClip patients treated in the EVEREST II High Risk Study (11). These patients were indeed older (mean age of 77), presented with multiple comorbidities, and were determined to be at high surgical risk on the basis of a Society of Thoracic Surgeons score ≥12% or on the basis of the estimate of mortality of a surgeon. The EVEREST II High Risk Study patients were also more often symptomatic (90% had class III to IV) and were predominantly FMR (59%).

Despite the higher risk profile of patients enrolled in the ACCESS-EU study, the rate of adverse events remained low: 30-day mortality was 3.4%, with main cause being cardiac and low cardiac output state resulting in multi-organ failure, sepsis, and respiratory failure.

Compared with early reports (5), length of stay was longer, likely reflective of baseline high-risk status and standard treatment practices in Europe. However, a significant proportion of patients have been discharged home without the need for home health care. The data suggest that patients undergoing the MitraClip procedure tolerated and recovered quickly from the procedure.

Although not prospectively specified in the ACCESS-EU study, procedural success (defined as successful implantation of the MitraClip device and MR reduction to 2+ or less in the EVEREST trials) was obtained in 91% of patients. The rate of patients with MR ≥3+ at discharge in the current registry was 9%, an improvement from earlier reports reflecting group learning and accumulated experience. A recent publication from a single center cohort of 75 patients has examined the effects of learning curve and has demonstrated a substantial effect of learning on safety as well as on acute and mid-term efficacy of the procedure (9). Fluoroscopy time (29 min) was a relatively small percentage (24.9%) of the overall procedure time. In approximately two-thirds (68.3%) of ACCESS patients, no contrast was used, which might be reflective of the high risk profile

Table 2 Procedure Time, Contrast Volume, and Fluoroscopy Duration

	ACCESS-EU Phase I		
	All Patients (N = 567)	FMR Patients (n = 393)	DMR Patients (n = 117)
Procedure time*	100.0 (15.0, 390.0)	93.0 (20.0, 342.0)	100.0 (15.0, 390.0)
Contrast volume (ml)	0.0 (0.0, 308.0)	0.0 (0.0, 308.0)	0.0 (0.0, 280.0)
Fluoroscopy duration	25.0 (0.0, 152.0)	26.0 (0.0, 152.0)	22.0 (5.0, 83.0)

Values are median (minimum, maximum). *Procedure time is defined as the time from start of the transseptal procedure until the time the steerable guide catheter is removed.
Abbreviations as in Table 1.

and high rate of renal disease observed in this patient population.

There were 27 cases (4.8%) of SLDA reported at 12 months in the ACCESS-EU study. Most SLDA occurred early (within 6 months from the index procedure), reflecting the relationship with intra-procedural factors. Interestingly, one-half of the patients with SLDA were treated percutaneously with another clip implant (12): either within the index procedure (n = 1) or at a later stage (n = 10). The SLDA was the main cause leading to repeat MitraClip implantation due to residual or recurrent MR. Overall, the second MitraClip procedure was successful in approximately 3 of 4 patients. Only 6 of 27 patients with SLDA required valve surgery (13). The SLDA is primarily related to the challenge of assessing leaflet insertion at the time of the procedure, and it is more often seen in patients with more complex anatomy and EVEREST II exclusion criteria. With experience and improved imaging guidance, the risk of SLDA might become less probable. In particular, 3-dimensional echocardiography (14), with x-plane features, allows appropriate scanning of the clip area in multiple planes to better analyze leaflet insertion.

The rate of valve surgery at 12 months for failed MitraClip repair was 6.3%, lower than that reported in the EVEREST II RCT (20% in the intention to treat analysis). However, this rate might underestimate the proportion of patients with recurrent/residual MR, due to the risk of surgery.

In the EVEREST II trial, MitraClip was inferior to surgery in the overall population comparison of the primary efficacy endpoint (freedom from death, mitral valve surgery, and recurrent MR ≥3+). However, in an exploratory intention-to-treat analysis, surgery was nonsuperior in patients who were older than 70 years (p = 0.009) and in patients with FMR, as compared with DMR (p = 0.02). Interestingly, these patients are the most commonly treated in the ACCESS-EU study.

The European study demonstrated a clinically meaningful improvement of MR, functional status, and quality of life at 6 and 12 months after the procedure in the overall population. Four of 5 patients treated had MR ≤2+ at 12 months from the index procedure. Improvement of MR obtained at 6 months remained stable at 12 months, suggesting stability of results. Improvement of at least 1 degree of MR was observed in 88% (289 of 327) of patients, and at least 2 degrees reduction was observed in 53% (173 of 327) of patients. Unfortunately, the ACCESS-EU study echocardiographic data were not assessed by a core laboratory. In addition, the challenge of grading MR after a double orifice repair makes the MR reduction endpoint a weak measure of the efficacy of the procedure. Functional MR is known to be fluctuant and load-dependent, therefore its measure is difficult to standardize.

Functional outcomes are a more appropriate way of assessing the value of MitraClip therapy in the FMR population, where standardization of echo assessment is not feasible. Besides NYHA functional class improvement, more objective outcomes included the increased distance of the 6MWT and the improved MLHFQ score at 6 and 12 months from MitraClip implant. Functional improvement

Table 3 Site-Reported Safety Outcomes at 30 Days and 12 Months

	ACCESS-EU Phase I					
	30 Days			12 Months		
Safety Outcomes	All Patients (N = 567)	FMR Patients (n = 393)	DMR Patients (n = 117)	All Patients (N = 567)	FMR Patients (n = 393)	DMR Patients (n = 117)
Death	3.4% (19/567)	2.8% (11/393)	6.0% (7/117)	17.3% (98/567)	17.0% (67/393)	17.1% (20/117)
Stroke	0.7% (4/567)	0.5% (2/393)	0.9% (1/117)	1.1% (6/567)	1.0% (4/393)	0.9% (1/117)
Myocardial infarction	0.7% (4/567)	0.8% (3/393)	0.9% (1/117)	1.4% (8/567)	1.8% (7/393)	0.9% (1/117)
Renal failure	4.8% (27/567)	5.1% (20/393)	2.6% (3/117)	8.6% (49/567)	9.4% (37/393)	6.0% (7/117)
Respiratory failure	0.7% (4/567)	1.0% (4/393)	0% (0/117)	0.9% (5/567)	1.0% (4/393)	0.0% (0/117)
Need for resuscitation	1.8% (10/567)	2.3% (9/393)	0.9% (1/117)	2.1% (12/567)	2.8% (11/393)	0.9% (1/117)
Cardiac tamponade	1.1% (6/567)	1.0% (4/393)	0.9% (1/117)	1.2% (7/567)	1.0% (4/393)	0.9% (1/117)
Bleeding complications	3.9% (22/567)	3.8% (15/393)	3.4% (4/117)	4.8% (27/567)	4.6% (18/393)	3.4% (4/117)

Values are % (n/N).
Abbreviations as in Table 1.

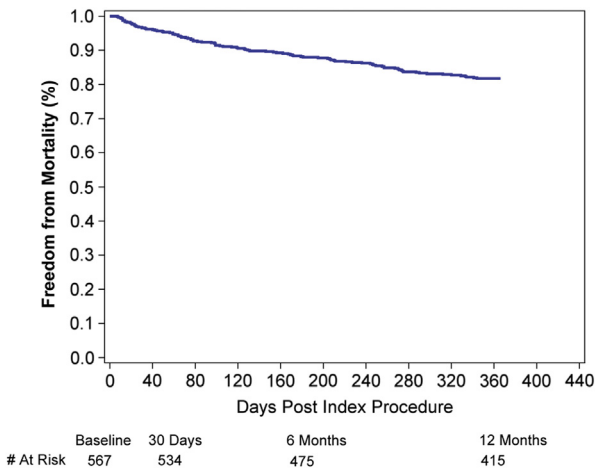

Figure 3 Kaplan-Meier Freedom From All-Cause Mortality at 12 Months

A total of 98 (17%) deaths were reported within 12 months of the MitraClip procedure. The Kaplan-Meier estimate of freedom from mortality at 12 months is 81.8% (95% confidence interval: 78.1% to 84.8%).

was also associated with favorable 12-month survival of 81.8% (95% CI: 78.1% to 84.8%); however, in absence of a relevant comparator group, any survival benefit is difficult to estimate and will require properly designed studies randomized against optimal medical therapy. In the DMR patients, residual MR is usually related to an untreated lesion, mainly residual prolapsing tissue, at risk of disease progression. Therefore, residual MR in the DMR population could be a more meaningful outcome to monitor, particularly in the younger population.

Study limitations. The ACCESS-EU phase I registry has several limitations, which will be addressed by the phase II study. The main limitation is the lack of a core-laboratory adjudication of echocardiographic parameters. Details with regard to morphological evaluation (number of segments involved, annular dimensions, jet geometry) were not recorded. These data would have great impact on defining anatomical risk factors for success. In addition, echocardiographic data on baseline and follow-up ventricular dimensions were insufficient to prove favorable geometrical remodeling in this high-risk population. Another limitation of the study, which is related to the post-market nature of the study, is that there were no pre-defined enrollment criteria: indication

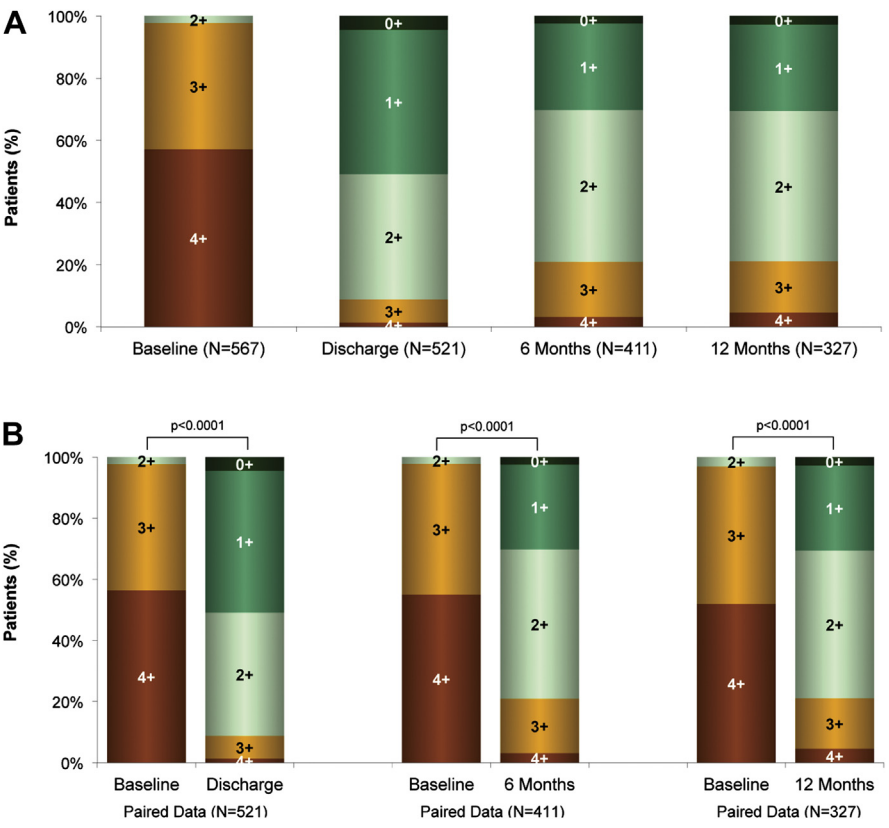

Figure 4 Severity of Mitral Regurgitation at Baseline, Discharge, 6 and 12 Months

(A) Mitral regurgitation severity at baseline, discharge, 6 and 12 months (unpaired data). **(B)** Change in mitral regurgitation severity from baseline to discharge, baseline to 6 months, and baseline to 12 months (paired data).

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Table 4 MR Severity at Baseline, Discharge, 6 and 12 Months

	ACCESS-EU Phase I									
	All Patients (N = 567)				FMR Patients (n = 393)			DMR Patients (n = 117)		
MR Severity	Baseline	Discharge	6 Months	12 Months	Baseline	Discharge	6 Months	12 Months	Baseline	Discharge	6 Months	12 Months
0	—	4.4% (23/521)	2.4% (10/411)	2.8% (9/327)	—	5.0% (18/361)	2.6% (7/271)	1.4% (3/219)	—	3.8% (4/106)	3.2% (3/94)	8.5% (6/71)
1+	—	46.4% (242/521)	27.7% (114/411)	27.8% (91/327)	—	47.9% (173/361)	27.3% (74/271)	30.6% (67/219)	—	52.8% (56/106)	35.1% (33/94)	23.9% (17/71)
2+	2.3% (13/567)	40.3% (210/521)	48.9% (201/411)	48.3% (158/327)	1.5% (6/393)	38.8% (140/361)	48.7% (132/271)	46.6% (102/219)	3.4% (4/117)	32.1% (34/106)	39.4% (37/94)	42.3% (30/71)
3+	40.6% (230/567)	7.5% (39/521)	17.8% (73/411)	16.5% (54/327)	39.4% (155/393)	7.8% (28/361)	19.6% (53/271)	18.3% (40/219)	37.6% (44/117)	7.5% (8/106)	13.8% (13/94)	16.9% (12/71)
4+	57.1% (324/567)	1.3% (7/521)	3.2% (13/411)	4.6% (15/327)	59.0% (232/393)	0.6% (2/361)	1.8% (5/271)	3.2% (7/219)	59.0% (69/117)	3.8% (4/106)	8.5% (8/94)	8.5% (6/71)

Values are % (n/N). Unmatched data. Sample sizes smaller than 567, 393, or 117 reflect missing data.
Abbreviations as in Table 1.

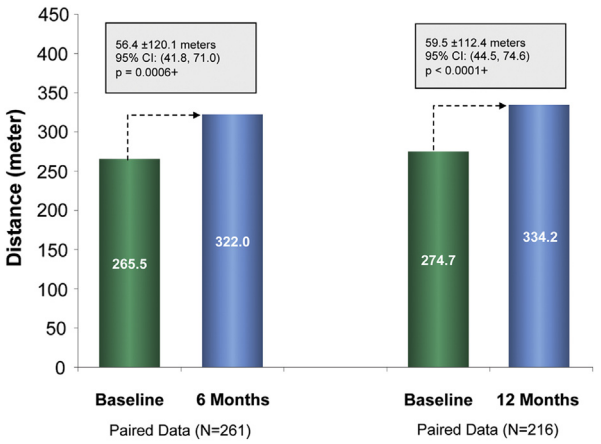

Figure 5 Change in 6-Min Walk Distance From Baseline to 6 and 12 Months

Change in 6-min walk test distance from baseline to 6 months and baseline to 12 months (paired data).

for MitraClip therapy as well as anatomical eligibility were left to the individual centers, according to their experience. However, this limitation adds value to the data presented, because outcomes reflect the real-world application of the therapy. Finally, because there was no pre-specified medical therapy strategy, changes in medical therapy during the conduction of the study might have affected outcomes.

Conclusions

In the real-world, post-approval experience in Europe, patients undergoing the MitraClip therapy are high-risk, elderly patients, mainly affected by FMR. This has represented a significant shift from the population originally investigated in the EVEREST II RCT study and is in line with the patients enrolled in the EVEREST II High Risk Study and treated in the REALISM study (EVEREST II Continued Access Study). The unmet need for a safer solution in high-risk patients has driven this change in practice, although not supported by published evidence. The ACCESS-EU study is the first large database reporting outcomes of the MitraClip in a high-risk population of patients with prevalence of FMR. In this patient population, the MitraClip procedure is safe, with low rates of hospital mortality and adverse events. Most patients have been treated successfully, which might be attributed in part to improved learning curve. As a result, meaningful clinical improvement has been observed in most patients in the mid-term, with objective improvement of quality of life and functional status. Longer-term follow-up and more in-depth analysis of the data will provide useful insights of the MitraClip therapy in the real world. The inferences from this study are fundamental for designing future trials

for both the FMR and DMR pathologies and support the indication to MitraClip therapy in high-risk patients with either FMR or DMR.

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Key Words: double orifice repair ▪ MitraClip ▪ mitral regurgitation ▪ mitral valve ▪ percutaneous mitral valve repair.