MitraClip™
EMEA VALUE DOSSIER APPENDICES

IMPORTANT NOTE TO USERS

- This document is the appendix to the MitraClip™ EMEA Value Dossier, and provides additional information on the clinical and economic value of MitraClip™ Therapy in the treatment of mitral regurgitation
- This appendix document is intended to accompany the MitraClip™ EMEA Value Dossier
- This appendix document **should not** be used independently of the main MitraClip™ EMEA Value Dossier

TABLE OF CONTENTS

APPENDIX 1 – COUNTRY-SPECIFIC MITRAL REGURGITATION TREATMENT GUIDELINES

1.1 POLAND

TRANSCATHETER MITRAL VALVE REPAIR AND REPLACEMENT. EXPERT CONSENSUS STATEMENT OF THE POLISH CARDIAC SOCIETY AND THE POLISH SOCIETY OF CARDIOTHORACIC SURGEONS (2021)[1]		
Approach	**PMR**	**SMR**
TMVr	TMVr is the first-choice treatment in patients with severe PMR and in patients with high or prohibitive surgical risk.	TMVr is a treatment option for patients with SMR and HF, provided medical therapy has already been dose-optimised and CRT-D has been implanted, if indicated.
	Determining patients' eligibility for edge-to-edge TMVr should be in alignment with the consensus recommendations developed in the treatment centre with expertise in both surgical and percutaneous treatment of mitral valve disease by an experienced multidisciplinary team.	
TMVI	TMVI is emerging as a promising alternative to edge-to-edge repair. TENDYNE™ valve is currently the only CE-approved and commercially available transcatheter mitral valve implant.	
Alternative uses of MitraClip™ (early stages of clinical testing)	Registry data, although limited, suggests MitraClip™ for the treatment of mitral regurgitation may be beneficial in the following patient groups: • Patients considered for OHT or implantation of an LVAD as a bridge procedure providing haemodynamic support • Patients with residual regurgitation jet after the surgical mitral valve repair • Patients with severe symptomatic mitral regurgitation related to obstructive hypertrophic cardiomyopathy to eliminate systolic anterior motion of the mitral valve • Patients in therapy-resistant cardiogenic shock related to decompensated HF and concomitant severe chronic mitral regurgitation • Patients with acute mitral regurgitation Decisions in such cases should be made by a multidisciplinary team.	

Abbreviations: CRT-D, cardiac resynchronisation therapy – defibrillator; HF, heart failure; LVAD, left ventricular assist device; OHT, orthotopic heart transplantation; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation; TMVI, transcatheter mitral valve implantation; TMVr, transcatheter mitral valve repair.

1.2 GERMANY

INTERVENTIONAL THERAPY FOR AV VALVE DISEASE – FOCUS ON MITRAL VALVE REGURGITATION. POSITION PAPER OF THE GERMAN CARDIAC SOCIETY (2018)[2]		
Approach	**PMR**	**SMR**
Surgical mitral valve repair or replacement	Mitral valve repair should be preferred in cases where a permanent result is to be expected (I C). Surgery is indicated in symptomatic patients with LVEF >30% (I B). Surgery is indicated in asymptomatic patients with left ventricle dysfunction (LVESD <45 mm and/or LVEF <60%) (I B).	Surgery is indicated in patients with severe SMR with concomitant aorto-coronary bypass surgery and LVEF >30% (I C). Surgery may be considered in symptomatic patients with severe SMR, LVEF <30%, but with the option of re-vascularising and the evidence of myocardial vitality (IIa C).
TMVr	The percutaneous edge-to-edge procedure may be considered in patients with symptomatic severe PMR, who meet the echocardiographic eligibility criteria and who are considered inoperable or high risk by a heart team ("avoiding futility") (IIb C).	In cases where revascularisation is not indicated, and the surgical risk is high, a percutaneous edge-to-edge procedure may be considered. Suitable patients include those with severe SMR and LVEF >30%, who remain symptomatic although being on OMT (including CRT if indicated) and who show compatible valve morphology via echocardiography, avoiding futility. (IIb C).

INTERVENTIONAL THERAPY FOR AV VALVE DISEASE – FOCUS ON MITRAL VALVE REGURGITATION. POSITION PAPER OF THE GERMAN CARDIAC SOCIETY (2018)[2]		
		Patients with severe SMR and LVEF <30%, who remain symptomatic although being on OMT (including CRT if indicated) and who do not have the option of revascularisation, may be considered for percutaneous edge-to-edge procedure based on their individual characteristics after a thorough evaluation bythe heart team (IIb C).

Abbreviations: AV, atrioventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; OMT, optimal medical therapy; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation; TMVr, transcatheter mitral valve repair.

1.3 MULTINATIONAL: SPAIN, PORTUGAL, AND ITALY

TRANSCATHETER MITRAL VALVE INTERVENTIONS FOR MITRAL REGURGITATION, WITH SPECIAL FOCUS ON MITRACLIP: THE POSITION OF SPANISH, PORTUGUESE AND ITALIAN INTERVENTIONAL SOCIETIES (2017)[3]		
Approach	**PMR**	**SMR**
TMVr	Among all CE-approved devices, only MitraClip™ has gained wide clinical use. With experience, more complex valve pathologies can be treated with MitraClip™ with acceptable results. High surgical risk or inoperable PMR is one of the main indications for MitraClip™. MitraClip™ has also been proved to be a useful tool for those patients with HF not responding to CRT therapy and small series have proved that MitraClip™ is a safe and effective alternative to surgical intervention in patients with acute MR following acute MI.	Among all CE-approved devices, only MitraClip™ has gained wide clinical use. With gains in experience, more complex valve pathologies can be treated with MitraClip™ with acceptable results. High surgical risk or inoperable PMR is one of the main indications for MitraClip™. MitraClip™ has also been proved to be a useful tool for those patients with HF not responding to CRT and small series have proved that MitraClip™ is a safe and effective alternative to surgical intervention in patients with acute MR following acute MI.

Abbreviations: CRT, cardiac resynchronisation therapy; HF, heart failure; MI, myocardial infarction; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation; TMVr, transcatheter mitral valve repair.

1.4 ITALY

TRANSCATHETER TREATMENT OF CHRONIC MITRAL REGURGITATION WITH THE MITRACLIP™ SYSTEM: AN ITALIAN CONSENSUS STATEMENT (2014)[4]		
Approach	**PMR**	**SMR**
Surgical mitral valve repair or replacement	Timing and indication for surgery should be driven by symptoms, LVEF, end-diastolic ventricular dimensions, AF, and pulmonary hypertension. Mitral valve repair with optimal haemodynamic result is superior to medical treatment alone in terms of survival and freedom from major adverse cardiac events. Annuloplasty is routinely carried out as part of mitral valve repair.	Consensus does not support surgery as an indication for SMR alone, however patients undergoing CABG who have concomitant moderate to severe secondary ischaemic MR should also undergo mitral valve surgery. Undersized annuloplasty is associated with lower mortality and is preferable to replacement (IIa C).
TMVr	MitraClip™ Therapy should be used for the treatment of patients with PMR or SMR who are symptomatic and who are refractory to medical therapy and at high surgical risk or inoperable. MitraClip™ should be used by surgeons proficient in mitral valve surgery and working in institutions with high-volume mitral surgical programmes.	

Abbreviations: AF, atrial fibrillation; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation; TMVr, transcatheter mitral valve repair.

APPENDIX 2 – SUMMARY OF MITRACLIP™ CLINICAL EVIDENCE

Table 1. Overview of MitraClip™ RCTs

STUDY	DESCRIPTION
EVEREST II (ASS)[5, 6] (completed) NCT00209274	• Randomised controlled trial of MitraClip™ versus conventional† mitral valve repair or replacement surgery • 279 patients with moderate-to-severe or severe PMR or SMR (≥3+) who are suitable for mitral valve surgery • US, Canada • Study period: 2005–2014
COAPT™ (ASS)[7-9] (follow-up ongoing) NCT01626079	• Randomised controlled trial of MitraClip™ + GDMT versus GDMT alone • 614 patients with moderate-to-severe or severe SMR (≥3+) and symptomatic HF who are unsuitable for mitral valve surgery • US, Canada • Study period: 2012–ongoing
REPAIR MR (ASS)[10] (recruitment ongoing) NCT04198870	• Randomised controlled trial of MitraClip™ versus conventional† mitral valve repair surgery • 500 severe PMR patients who are at moderate surgical risk and are suitable for mitral valve repair surgery • US, Canada, Germany, Switzerland • Study period: 2020–ongoing
MITRA-FR (ISS)[11, 12] (completed) NCT01920698	• Randomised controlled trial of MitraClip™ + GDMT versus GDMT alone • 307 patients with severe SMR[11] • France • Study period: 2013–2018
MATTERHORN (ISS) (status unknown) NCT02371512	• Randomised controlled trial of MitraClip™ versus surgery • 210 patients with PMR or SMR with left ventricle dysfunction • Germany • Study period: 2015–unknown
RESHAPE-HF2 (ISS) (ongoing) NCT02444338	• Randomised controlled trial of MitraClip™ + SoC versus SoC alone • 650 patients with moderate-to-severe or severe SMR and NYHA Class II–IV chronic HF • Czechia, Denmark, Germany, Greece, Italy, Poland, Portugal, Spain, UK • Study period: 2015–ongoing
MITRA-HR (ISS) (ongoing) NCT03271762	• Randomized controlled trial of MitraClip™ versus conventional† mitral valve repair or replacement • 330 patients with severe PMR eligible for anatomical repair with the MitraClip® or mitral valve surgery with high surgical risk • France, Monaco • Study period: 2018–ongoing
MITRADVANCE (ISS) (recruitment ongoing) NCT05292716	• Randomised controlled trial of MitraClip™ + optimal medical therapy for HF versus optimal medical therapy alone • 172 SMR patients with advanced HF on maximally tolerated SoC therapies for HF according to the most recent guidelines • Italy • Study period: 2021–ongoing

† Any mitral valve surgical repair approach/procedure that is not MitraClip™.
Abbreviations: ASS, Abbott-sponsored study; GDMT, guideline-directed medical therapy; ISS, investigator-sponsored study; MR, mitral regurgitation; PMR, primary mitral regurgitation; RCT, randomised controlled trial; SMR, secondary mitral regurgitation; SoC, standard of care.
Source: https://clinicaltrials.gov/.[13] Hyperlinks to trial entries are provided where such entries exist.

Table 2. Overview of contemporary MitraClip™ real-world evidence

CONTEMPORARY REAL-WORLD EVIDENCE	
EXPAND G4 (ASS)[14] (follow-up ongoing) NCT04177394	• Post-market, multi-centre, single-arm, prospective study to assess the safety and performance of MitraClip™ G4 • 1,064 patients scheduled to receive the MitraClip™ per the current approved indications for use • US, Canada, France, Germany, Israel, Italy, Japan, Netherlands, Saudi Arabia, Spain • Study period: 2020 – follow-up ongoing
COAPT™ PAS (ASS)[15] (follow-up ongoing)	• Prospective, single-arm, multicentre, observational, real-world surveillance study to evaluate the safety and effectiveness of MitraClip™ • 5,000 consecutive patients with SMR participating in the TVT registry • US • Study period: 2019 – follow-up ongoing
EXPAND (ASS)[16] (completed) NCT03502811	• A prospective study evaluating real-world experience of performance and safety of MitraClip™ (NTR, XTR) • 1,041 patients undergoing commercial procedures with MitraClip™ NTR/XTR • US, Germany, Israel, Italy, Netherlands, Spain, Switzerland, UK • Study period: 2018 – follow-up ongoing
TVT (ISS)[17] (ongoing) NCT02245763	• National surveillance system developed to track patient safety and real-world outcomes related to the TMVr procedure • 37,475 patients between 2014 – March 2020 TEER or TMVR • US • Study period: 2013 – ongoing

Abbreviations: ASS, Abbott-sponsored study; CRT, cardiac resynchronisation therapy; GDMT, guideline-directed medical therapy; HF, heart failure; ISS, investigator-sponsored study; MR, mitral regurgitation; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation; TMVr, transcatheter mitral valve repair.
Source: https://clinicaltrials.gov/.[13] Hyperlinks to trial entries are provided where such entries exist.

Table 3. Overview of additional MitraClip™ real-world evidence

STUDY	DESCRIPTION
GIOTTO (ISS)[18, 19] (completed)	• National, prospective patient registry • 1,659 consecutive patients undergoing TMVr with a MitraClip™ device according to current national and international guidelines • Italy • Study period: 2016–2021
SPANISH MITRACLIP™ REGISTRY (ISS)[20] (status unknown)	• National, prospective patient registry • 558 consecutive patients with PMR or SMR treated with MitraClip™ • Spain
MITRA SWISS (ISS)[21, 22] (ongoing)	• National, prospective patient registry • 1,212 patients with PMR or SMR treated with MitraClip™ • Switzerland • Study period: 2011–ongoing
TCVT EUROPEAN SENTINEL PILOT REGISTRY (ISS)[23] (completed)	• International, prospective, pilot patient registry • 628 consecutive patients with PMR or SMR who received MitraClip™ • Belgium, Denmark, Germany, Italy, Poland, Sweden, Switzerland, UK
TRAMI (ISS)[24, 25] (completed)	• National, multicentre, industry-independent, prospective, patient registry • 722 patients with PMR or SMR treated with MitraClip™ • Germany
FRENCH REGISTRY (ISS)[26] (completed)	• National, multicentre registry • 62 patients with PMR or SMR judged to be inoperable or at high surgical risk and treated with MitraClip™ • France
MULTICENTRE EXPERIENCE, 2015 (ISS)[27] (completed)	• Multicentre registry • 173 patients with PMR or SMR treated with MitraClip™ • Denmark, Sweden, UK

STUDY	DESCRIPTION
EVEREST II REALISM (ASS)[28] (completed) NCT01931956	• Prospective, continued access registry collecting additional real-world safety and effectiveness data for MitraClip™ • 965 patients with PMR or SMR divided into high risk and non-high risk arms • US • Study period: 2009–2018
GRASP (ISS)[29-31] (completed)	• Retrospective, multicentre registry with prospective collection of follow-up data • 304 consecutive patients with symptomatic moderate-to-severe or severe PMR or SMR treated with MitraClip™ • Italy
ACCESS-EU (ASS)[32] (completed) NCT01288976	• International, prospective, multicentre, observational registry • 567 patients with PMR or SMR who received MitraClip™ • Europe • Study period: 2008–2012
EVEREST II HRS (ASS)[33, 34] (completed) NCT01940120	• Prospective, multicentre, single-arm registry enrolling high surgical risk patients of the EVEREST II study • 78 patients with clinically significant PMR or SMR (≥3+) deemed to be high risk surgical candidates and treated with MitraClip™ • US • Study period: 2007–2013

Abbreviations: ASS, Abbott-sponsored study; GDMT, guideline-directed medical therapy; HRS, high risk study; ISS, investigator-sponsored study; MR, mitral regurgitation; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation; TCVT, transcatheter valve treatment.
Hyperlinks to the trial/registry entry on www.clinicaltrials.gov are provided where such entries exist.
Sources: https://clinicaltrials.gov/.[13]

APPENDIX 3 – ADDITIONAL CLINICAL EVIDENCE FOR MITRACLIP

3.1 BASELINE CHARACTERISTICS OF PATIENTS ENROLLED IN ADDITIONAL MITRACLIP™ REAL-WORLD EVIDENCE

Table 4. Baseline characteristics of patients enrolled in additional MitraClip™ real-world evidence

	ADDITIONAL REAL-WORLD EVIDENCE											
	EVEREST II HRS (PMR, SMR)	ACCESS-EU (PMR, SMR)	GRASP (PMR, SMR)	EVEREST II REALISM (PMR, SMR)		MULTICENTRE EXPERIENCE (PMR, SMR)	FRENCH REGISTRY (PMR, SMR)	TRAMI (PMR, SMR)	EUROPEAN SENTINEL (PMR, SMR)	MITRA SWISS (PMR, SMR)	SPANISH REGISTRY (PMR, SMR)	GIOTTO (PMR, SMR)
				HIGH RISK	NON-HIGH RISK							
PATIENTS, N	78	567	304	628	271	173	62	799	628	1,212	558	1,659
AGE, MEAN, Y	77	74	72	77	74	76	73	75	74	79‡	73	77‡
MALES, N (%)	49 (63)	362 (64)	194 (64)	375 (60)	144 (53)	109 (63)	(72)	485 (61)	(63)	733 (60)	392 (70)	1,061 (64)
PMR, N (%)	32 (41)	117 (23)	56 (22)	-	-	-	(23)	-	143 (23)	652 (54)	111 (20)	673 (41)
SMR, N (%)	46 (59)	393 (77)	-	(70)	(32)	94 (54)	(74)	495 (69)	452 (72)	560 (46)	364 (65)	986 (59)
NYHA III, N (%)	70 (90)	384 (70)	-	(81)	(51)	138 (80)	(81)	691 (89)	(69)	674 (58)	382 (68)	397 (20)
NYHA IV, N (%)		82 (15)	52 (17)			27 (16)			(17)	159 (14)	112 (20)	1,332 (80)
MR 3+, N (%)	-	230 (41)	-	-	-	(87)	(93)	705 (94)§	(86)§	199 (17)	130 (23)	343 (21)
MR 4+, N (%)	-	324 (57)	-	-	-					1,000 (83)	428 (77)	1,302 (79)

Abbreviations: HRS, high risk study; MR, mitral regurgitation; NR, not reported; NYHA, New York Heart Association; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation; Y, year.

‡ Median.

§ Severe (grading: mild, moderate, severe).

Sources: EVEREST II HRS, Kar 2018;[34] ACCESS-EU, Maisano 2013;[32] GRASP, Adamo 2019;[31] EVEREST II REALISM, Feldman 2015,[28] https://clinicaltrials.gov/;[13] Multicentre Experience, Estevez-Loureiro 2015;[27] French Registry, Armoiry 2013;[26] TRAMI, Kalbacher 2019;[25] European Sentinel, Nickenig 2014;[23] MITRA SWISS, Surder 2020;[21] Spanish Registry, Pascual 2020;[20] GIOTTO, Bedogni 2021.[18]

3.2 ACUTE PROCEDURAL SUCCESS

Table 5. Acute procedural success rate (MR grade ≤2+ post-implantation) across additional MitraClip™ real-world evidence

	ADDITIONAL REAL-WORLD EVIDENCE										
	EVEREST II HRS (PMR, SMR)	ACCESS-EU[32] (PMR, SMR)	GRASP (PMR, SMR)	EVEREST II REALISM (PMR, SMR)	MULTICENTRE EXPERIENCE (PMR, SMR)	FRENCH REGISTRY (PMR, SMR)	TRAMI (PMR, SMR)	EUROPEAN SENTINEL (PMR, SMR)	MITRA SWISS (PMR, SMR)	SPANISH REGISTRY (PMR, SMR)	GIOTTO (PMR, SMR)
ACUTE PROCEDURAL SUCCESS RATE, %†	71.8	91.2	100	89.0	98	88.2	96.5	95.4	91.5	93.9	97.2‡

Abbreviations: HRS, high risk study; MVARC, Mitral Valve Academic Research Consortium; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation.

† Defined as successful implantation resulting in MR severity ≤2+.

‡ MVARC device success, defined as: absence of procedural mortality or stroke; proper placement and positioning of the device; freedom from unplanned surgical or interventional procedures related to the device or access procedure; and continued intended safety and performance of the device, including: no evidence of structural or functional failure, no specific device-related technical failure issues and complications, reduction of MR to either optimal or acceptable levels (MR ≤2+) without significant mitral stenosis.[35]

Sources: EVEREST II HRS, Kar 2018;[34] ACCESS-EU, Maisano 2013;[32] GRASP, Grasso 2013;[36] EVEREST II REALISM, Feldman 2015;[28] Multicentre Experience, Estevez-Loureiro 2015;[27] French Registry, Armoiry 2013;[26] TRAMI, Kalbacher 2019;[25] European Sentinel, Nickenig 2014;[23] MITRA SWISS, Surder 2020;[21] Spanish Registry, Pascual 2020;[20] GIOTTO, Bedogni 2021.[18]

ADDITIONAL REAL-WORLD EVIDENCE	
EVEREST II HRS (PMR, SMR)	Acute procedural success rate, defined as successful implantation of the clip(s) with resulting MR severity ≤2+ as determined by a discharge echocardiogram, was 71.8%. In current practice, acute procedural success rate has improved in most reports to >95%, suggesting that the 5-year HRS results represent a 'worst case' for MR grade.[34]
ACCESS EU (PMR, SMR)	Most patients (91.2%) achieved MR grade ≤2+ at discharge, and 50.9% had MR grade ≤1+. The MitraClip™ device implantation rate was 99.6% with only two patients not successfully implanted with a MitraClip™ device.[32]
GRASP (PMR, SMR)	Acute device success was defined as residual MR ≤2+ after clip implantation. Acute device success was observed in all patients.[36]
EVEREST II REALISM (PMR, SMR)	Despite advanced age and burden of co-morbidities, 89% of all patients achieved MR reduction to ≤2+ post-procedure.[28]
MULTICENTRE EXPERIENCE (PMR, SMR)	Procedural success, defined as the reduction of the degree of MR to a 2+ or less, was obtained in 169 patients (98%).[27]
FRENCH REGISTRY (PMR, SMR)	At discharge, the proportion of implanted patients with residual MR ≤ grade 2 was 88.2%. Successful clip implantation was obtained in 95.2% of cases. [26]
TRAMI (PMR, SMR)	Procedural failure was recorded if one of the following criteria was reached: failure of clip placement, severe residual MR, conversion to surgery or operator-reported failure. Successful treatment was achieved in 96.5% of patients.[25]
EUROPEAN SENTINEL (PMR, SMR)	Acute procedural success, defined as a reduction in the degree of MR to equal to or less than moderate (≤2+) without complications, was high (95.4% overall, 93.7% in patients with PMR, and 95.8% in patients with SMR, p=0.304).[23]
MITRA SWISS (PMR, SMR)	Acute procedural success was achieved in the majority of patients (91.5%), with no differences between PMR and SMR groups (91.4% versus 91.7%, respectively; p=0.916).[21]

ADDITIONAL REAL-WORLD EVIDENCE	
SPANISH REGISTRY (PMR, SMR)	Procedural success was defined as the correct implantation of at least 1 clip and MR reduction to a grade less than or equal to moderate (2+). Procedural success was achieved in 93.9% of all enrolled patients, 96.4% in patients with PMR, and 92.4% in SMR patients, and 96.4% in patients with mixed aetiology (p=0.201).[20]
GIOTTO (PMR, SMR)	Device success† and acute procedural success‡ were evaluated using MVARC definitions.[35] Overall MVARC device success was achieved in 86.8% (SMR 86.6% versus PMR 87.1%; p=0.780) and MVARC procedural success in 84.0% (SMR 83.9% versus PMR 84.0%; p=0.902).[18]

† MVARC device success, defined as: absence of procedural mortality or stroke; proper placement and positioning of the device; freedom from unplanned surgical or interventional procedures related to the device or access procedure; and continued intended safety and performance of the device, including: no evidence of structural or functional failure, no specific device-related technical failure issues and complications, reduction of MR to either optimal or acceptable levels (MR ≤2+) without significant mitral stenosis.[35]
‡ MVARC procedural success, defined as: device success in the absence of major device or procedure related serious adverse events or any valve-related dysfunction, migration, thrombosis, or other complication requiring surgery or repeat intervention.[35]
Abbreviations: HRS, high risk study; MR, mitral regurgitation; MVARC, Mitral Valve Academic Research Consortium; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation.

PROCEDURAL SUCCESS IN PMR VERSUS SMR PATIENTS	210 patients with severe symptomatic PMR (n=105) or SMR (n=105) received a MitraClip™ implant. Device success† and acute procedural success‡ were evaluated using MVARC definitions.[35] Device success was high in both groups (94.3% in PMR patients 93.3% in SMR versus patients). Procedural success was similar in both groups (87.8% in PMR and 88.6% in SMR).[37]

† MVARC device success, defined as: absence of procedural mortality or stroke; proper placement and positioning of the device; freedom from unplanned surgical or interventional procedures related to the device or access procedure; and continued intended safety and performance of the device, including: no evidence of structural or functional failure, no specific device-related technical failure issues and complications, reduction of MR to either optimal or acceptable levels (MR ≤2+) without significant mitral stenosis.[35]
‡ MVARC procedural success, defined as: device success in the absence of major device or procedure related serious adverse events or any valve-related dysfunction, migration, thrombosis, or other complication requiring surgery or repeat intervention.[35]
Abbreviations: MVARC, Mitral Valve Academic Research Consortium; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation.

3.3 30-DAY MORTALITY AND ADVERSE EVENT RATES

Table 6. 30-day mortality and adverse event rates across additional MitraClip™ real-world evidence

30-DAY OUTCOMES	ADDITIONAL REAL-WORLD EVIDENCE									
				EVEREST II REALISM (PMR, SMR)						
	EVEREST II HRS (PMR, SMR)	ACCESS-EU (PMR, SMR)	GRASP (PMR, SMR)	HIGH RISK	NON-HIGH RISK	FRENCH REGISTRY (PMR, SMR)	TRAMI (PMR, SMR)	EUROPEAN SENTINEL (PMR, SMR)	MITRA SWISS (PMR, SMR)	GIOTTO (PMR, SMR)
Death, % (N)	7.7 (6)	3.4 (19)	0.9 (1)	4.2	1.5	3.2 (2)†	4.5 (34)	2.9†	2.7 (33)	4.0 (57)
MAEs†, % (N)	26.9 (21)	-	3.4 (4)	-	-	-	3.1 (22)†	-	5.5 (67)	-
Hospitalisation, % (N)	-	-	-	-	-	-	-	-	1.9 (24)‡	-
MV reoperation, % (N)	0	-	0	-	-	(2)†	1.5 (11)†	-	0.9 (12)	-
MI, % (N)	2.6 (2)	0.7 (4)	0	-	-	0†	0	-	-	-
Stroke, % (N)	2.6 (2)	0.7 (4)	0.9 (1)	-	-	0†	0.8 (6)†	0.2†	-	-
CV reintervention, % (N)	0	-	0	-	-	-	-	-	-	-
SLDA, % (N)	(1)	4.8 (27)	-	-	-	-	0.7 (5)	-	-	-
Renal failure, % (N)	3.8 (3)	4.8 (27)	0	-	-	-	-	-	-	-

Abbreviations: AE, adverse event; HRS, high risk study; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation.
† In-hospital rather than 30 days.
‡ Heart failure hospitalisation.
Sources: EVEREST II HRS, Whitlow 2012;[33] ACCESS-EU, Maisano 2013;[32] GRASP, Grasso 2013;[36] EVEREST II REALISM, Feldman 2015;[28] French Registry, Armoiry 2013;[26] TRAMI, Puls 2016[24] European Sentinel, Nickenig 2014;[23] MITRA SWISS, Surder 2020;[21] GIOTTO, Bedogni 2021.[18]

ADDITIONAL REAL-WORLD EVIDENCE	
EVEREST II HRS (PMR, SMR)	Overall 30-day mortality rate in the HRS was 7.7%, significantly less than that predicted for open-heart MV surgery in this patient cohort.[33] MAEs included death, MI, reoperation for failed MV repair or replacement, urgent or emergent CV surgery for an AE, major stroke, renal failure, deep wound infection, mechanical ventilation >48 hours, GI complication requiring surgery, new onset of permanent AF, septicaemia, and transfusion of ≥2 units of blood. In total, 26.9% of patients experienced MAEs within 30 days of the MitraClip™ procedure; the most common were transfusion of ≥2 units of blood (17.9% of patients), death (7.7% of patients), and renal failure (3.8% of patients).[33]
ACCESS EU (PMR, SMR)	A total of 19 patients (3.4%) died within the 30 days after the MitraClip™ procedure.[32] MAEs were not defined. Despite the higher risk profile of patients enrolled in the ACCESS-EU study, the rate of adverse events remained low. Renal failure was the most common 30-day adverse event, occurring in 27 patients (4.8%).[32]

ADDITIONAL REAL-WORLD EVIDENCE	
GRASP (PMR, SMR)	One patient (0.9%) died within 30 days of receiving the MitraClip™ procedure.[36] MAEs included death, MI, reoperation for failed MV repair or replacement, urgent or emergent CV surgery for an AE, major stroke, renal failure, deep wound infection, mechanical ventilation >48 hours, GI complication requiring surgery, new onset of permanent AF, septicaemia, and transfusion of ≥2 units of blood. MAEs occurred in four patients at 30 days, all in the SMR subgroup.[36]
EVEREST II REALISM (PMR, SMR)	The mortality rate at 30 days was 4.2% in high risk patients and 1.5% in non-high risk patients.[28]
FRENCH REGISTRY (PMR, SMR)	In-hospital death occurred in two patients (3.2%), both of whom had SMR. The survival rate at 6-month follow-up was estimated at 83.1%.[26] MAEs were not defined. Non-fatal in-hospital AEs were observed in seven patients (11.3%).[26]
TRAMI (PMR, SMR)	Among the 749 enrolled patients, in-hospital mortality was 2.4% (18 patients) and 30-day mortality was 4.5% (34 patients).[24] MACCE included in-hospital death from any cause, stroke, and myocardial infarction. Intra-procedural death occurred in only one patient (0.1%), in-hospital mortality was 2.4% (n=18), and MACCE rate was 3.1% (stroke n=6, MI n=0).[24]
EUROPEAN SENTINEL (PMR, SMR)	Overall, in-hospital mortality was 2.9% (18 of 628 patients) and ranged between 4.9% (7 of 143 patients) in the PMR group and 2.0% (9 of 452 patients) in the SMR group (p=0.075).[23] MAEs were not defined. Overall, in-hospital mortality was 2.9%, and cardiac tamponade and stroke were infrequent (1.1% and 0.2% of patients, respectively).[23]
MITRA SWISS (PMR, SMR)	30-day mortality was 2.7% (n=33) overall, 2.1% (n=14) in patients with PMR, and 3.3% (n=19) in patients with SMR.[21] The MACE endpoint included all-cause mortality, hospitalisations for heart failure and mitral valve surgery due to failure of PMVR or redo-PMVR. The MACE rate was 5.5% overall, 5.2% in PMR, and 5.9% in SMR.[21]
GIOTTO (PMR, SMR)	Cumulative 30-day death rate was 4.0% (57 patients), of which 2.3% was for cardiovascular reasons (SMR 2.6% versus PMR 1.8%; p=0.317).[18]

Abbreviations: AE, adverse event; AF, atrial fibrillation; GI, gastrointestinal; HRS, high risk study; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse clinical event; MI, myocardial infarction; MV, mitral valve; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation.

LEARNING CURVE EVIDENCE	
GERMAN MITRAL VALVE REGISTRY (PMR, SMR)	The incidence of MACCE was not significantly different between the first and second groups of 25 consecutive patients (3.4% versus 5.6%; p=0.26).[38]

Abbreviations: MACCE, major adverse cardiovascular and cerebrovascular event; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation.

3.4 LONG-TERM MORTALITY RATES

Table 7. Long-term (≥1 year) mortality rates across additional MitraClip™ real-world evidence

		ADDITIONAL REAL-WORLD EVIDENCE									
					EVEREST II REALISM (PMR, SMR)						
		EVEREST II HRS (PMR, SMR)	ACCESS-EU (PMR, SMR)	GRASP (PMR, SMR)	HIGH RISK	NON-HIGH RISK	TRAMI (PMR, SMR)	EUROPEAN SENTINEL (PMR, SMR)	MITRA SWISS (PMR, SMR)	SPANISH REGISTRY[20] (PMR, SMR)	GIOTTO (PMR, SMR)
MORTALITY RATE, %	1Y	24.4	17.3	15.1†	23.0	10.0	19.7†	15.3†	-	14.0	17.5
	2Y	-	-	26.4†	-	-	31.9†	-	-	-	34.6
	3Y	-	-	25.5†	-	-	42.8†	-	-	-	-
	4Y	-	-	42.1†	-	-	53.1†	-	-	-	-
	5Y	53.8	-	47.3†	-	-	-	-	50.0	-	-

Abbreviations: HRS, high risk study; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation; Y, year.
† Kaplan–Meier estimate.
Sources: EVEREST II HRS, 1 year Whitlow 2012,[33] 5 years Kar 2018;[34] ACCESS-EU, Maisano 2013[32] GRASP, Adamo 2019;[31] EVEREST II REALISM, Feldman 2015;[28] TRAMI, Kalbacher 2019[25] European Sentinel, Nickenig 2014;[23] MITRA SWISS, Surder 2020;[21] Spanish Registry, Pascual 2020;[20] GIOTTO, Bedogni 2021.[18]

ADDITIONAL REAL-WORLD EVIDENCE	
EVEREST II HRS (PMR, SMR)	A total of 19 (24.4%) deaths were reported through 12 months. MitraClip™ Therapy improved the life expectancy of high surgical risk patients compared with standard of care. Kaplan–Meier estimated survival after 1 year was 75.4% for patients treated with MitraClip™ compared with 55.3% for control patients who met the high-risk criteria but did not receive surgery (p=0.047).[33] A total of 42 deaths were reported through 5 years.[34]
ACCESS-EU[32] (PMR, SMR)	A total of 98 (17.3%) deaths were reported within 12 months of the MitraClip™ procedure, 17.1% among PMR patients, and 17.0% among SMR patients.[32]
GRASP (PMR, SMR)	Cumulative incidence of all-cause mortality at 1, 2, 3, 4 and 5 years was 15.1%, 26.4%, 35.5%, 42.1% and 47.3% respectively.[31]
EVEREST II REALISM (PMR, SMR)	Mortality at 1 year was 23.0% in the high risk arm and 10.0% in the non-high risk arm.[28]
TRAMI (PMR, SMR)	Mortality rates, estimated by Kaplan–Meier method, were as follows: 19.7% (1-year), 31.9% (2-year), 42.8% (3-year) and 53.1% (4-year).[25]
EUROPEAN SENTINEL (PMR, SMR)	The Kaplan–Meier estimated 1-year mortality was 15.3%, without significant differences between groups (SMR 15.0% versus PMR 16.2%, p=0.650).[23]
MITRA SWISS (PMR, SMR)	At 5 years, a total of 265 patients had died, corresponding to a cumulative probability of death of 50%. The cumulative probability of death at 5 years was 45% in patients with PMR and 54% in patients with SMR (p<0.001).[21]
SPANISH REGISTRY (PMR, SMR)	All-cause mortality at 12 months among all enrolled patients was 14.0% (78 patients). Among patients with PMR, SMR, and mixed aetiology, the all-cause mortality rate at 12 months was 11.7% (n=13), 15.7% (n=57), and 9.6% (n=8), respectively (no significant differences among the three groups; p=0.728).[20]
GIOTTO (PMR, SMR)	At 1 year of follow-up, cumulative all-cause death rate was 17.5% (235/1340), while cardiovascular death rate was 10.2% (137/1340). At 2 years, all-cause and cardiovascular mortality were 34.6% (337/970) and 18.8% (183/975), respectively.[18]

Abbreviations: HRS, high risk study; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation.

3.5 REDUCTION IN MR SEVERITY

Table 8. Pooled proportions of patients with MR ≤2+ post-procedure across additional MitraClip™ real-world evidence

		ADDITIONAL REAL-WORLD EVIDENCE							
		EVEREST II HRS (PMR, SMR)	ACCESS-EU (PMR, SMR)	GRASP		EVEREST II REALISM (PMR, SMR)	TRAMI (PMR, SMR)	SPANISH REGISTRY (PMR, SMR)	GIOTTO (PMR, SMR)
				PMR	SMR				
MR ≤2+ AT FOLLOW-UP, %	DC	71.8	91.2	-	-	-	97.7[†]	94.1[‡]	95.2[§]
	30d	73	-	96	92	-	-	-	93.4
	1Y	78	78.9	75	93	83	-	-	-
	2Y	88	-	-	-	-	-	-	-
	3Y	86	-	-	-	-	-	-	-
	4Y	87	-	-	-	-	-	-	-
	5Y	75	-	-	-	-	-	-	-

Abbreviations: DC, discharge; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation; Y, year.
[†] Percentage of patients with either "none/mild," or "moderate" (as opposed to "severe") MR on echocardiography.
[‡] Degree of mitral regurgitation after the clip. Time of follow-up not specified.
[§] Post-procedural MR.
Sources: EVEREST II HRS, Kar 2018;[34] ACCESS-EU, Maisano 2013[32] GRASP, Grasso 2013;[36] EVEREST II REALISM, Feldman 2015;[28] TRAMI, Puls 2016;[24] Spanish Registry, Pascual 2020;[20] GIOTTO, Bedogni 2020.[19]

ADDITIONAL REAL-WORLD EVIDENCE	
EVEREST II HRS (PMR, SMR)	Echocardiographic MR grade improved from baseline to ≤2+ in 73% of surviving patients at 30 days, which was maintained in 78% of survivors at 1 year. Subsequent follow-up demonstrated sustained MR reduction in 88% of survivors at 2 years, 86% at 3 years and 87% at 4 years, an 75% at 5 years.[34]
ACCESS-EU (PMR, SMR)	Most patients (91.2%) achieved MR reduction to 2+ or less at discharge. At 1 year from the procedure, 78.9% (258 of 327) of patients were free from MR severity of >2+.[32]
GRASP (PMR, SMR)	At 30 days, deterioration to MR grade ≥3+ was recorded in 4% of those with PMR and 8% of those with SMR. At 1 year, deterioration to MR grade ≥3+ was recorded in 25% of patients with PMR and 7% of those with SMR at 1 year.[36]
EVEREST II REALISM (PMR, SMR)	After 1 year post-MitraClip™ implantation 83% of surviving patients had MR ≤2+ in both the high risk and non-high risk arm.[28]
TRAMI (PMR, SMR)	MR at discharge was none/mild in 85.2% of patients, moderate in 12.6% of patients, and severe in 2.3% of patients.[24]
SPANISH REGISTRY (PMR, SMR)	The degree of MR after the clip was 0 in 4.5% of patients, I in 55.8% of patients, and II in 33.8% of patients.[20]
GIOTTO (PMR, SMR)	Post-procedure, 63.5% of patients had MR 1+ and 31.7% of patients had MR 2+. At 30 days, 57.5% of patients had MR 1+ and 35.9% of patients had MR 2+.[19]

Abbreviations: MR, mitral regurgitation; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation.

LEARNING CURVE EVIDENCE	
UNIVERSITY HOSPITAL GÖTTINGEN (PMR, SMR)	The first 75 patients to receive MitraClip™ in a single institution were stratified into three consecutive groups of 25 patients in order to assess the impact of the learning curve on outcomes. There was a significant difference in the proportion of patients with MR ≤2+ after 6 months between the first group of 25 patients (65.0%) and the third group of 25 patients (89.4%; p=0.03).[39]

Abbreviations: MR, mitral regurgitation; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation.

3.6 NYHA FUNCTIONAL STATUS

Table 9. Pooled proportions of patients in NYHA class I or II post-procedure across additional MitraClip™ real-world evidence

		ADDITIONAL REAL-WORLD EVIDENCE									
				EVEREST II REALISM (PMR, SMR)					MITRA SWISS (PMR, SMR)		
		EVEREST II HRS (PMR, SMR)	ACCESS-EU (PMR, SMR)	HIGH RISK	NON-HIGH RISK	FRENCH REGISTRY (PMR, SMR)	TRAMI (PMR, SMR)	EUROPEAN SENTINEL (PMR, SMR)	PMR	SMR	SPANISH REGISTRY (PMR, SMR)
NYHA CLASS I OR II (%)	6m	-	-	-	-	90.9	-	-	84.0	79.5	-
	1Y	74.1	92.0	85	91	-	63.3	74.2	84.4	77.7	75.1
	5Y	83.3	-	-	-	-	-	-	78.6	64.5	-

Abbreviations: m, month; NYHA, New York Heart Association; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation; Y, year. Sources: EVEREST II HRS, Kar 2018;[34] ACCESS-EU, Maisano 2013;[32] EVEREST II REALISM, Feldman 2015;[28] French Registry, Armoiry 2013;[26] TRAMI, Puls 2016;[24] European Sentinel, Nickenig 2014;[23] MITRA SWISS, Surder 2020;[21] Spanish Registry, Pascual 2020.[20]

ADDITIONAL REAL-WORLD EVIDENCE	
EVEREST II HRS (PMR, SMR)	At 1 and 5 years, 74.1% (p<0.0001) and 83.3% (p=0.0062) of treated patients had NYHA class I or II symptoms, respectively.[34]
ACCESS-EU (PMR, SMR)	At 12 months, 71.4% (245 of 343) of patients had NYHA functional class II or class I.[32]
EVEREST II REALISM (PMR, SMR)	At 1 year follow-up, 15% of patients in the high risk arm and 9% of patients in the non-high risk arm were in NYHA Class III/IV.[28]
FRENCH REGISTRY (PMR, SMR)	At 6 months' follow-up, 90.9% of patients were in class I or II NYHA.[26]
TRAMI (PMR, SMR)	At 1 year, 63.3% of patients had no or few symptoms of HF, pertaining to NYHA functional classes I or II (in contrast to 11.0% at baseline).[24]
EUROPEAN SENTINEL(PMR, SMR)	At 1 year, 26.9% of patients were in NYHA class I and 47.3% of patients were in NYHA class II.[23]
MITRA SWISS (PMR, SMR)	While more than 70% of patients were in NYHA class III/ IV before treatment in both cohorts, the rate remained consistently below 35%, with no difference between cohorts at follow-up (test for interaction p=0.963).[21]
SPANISH REGISTRY (PMR, SMR)	Improvement in NYHA class was maintained at 1 year, with 75.1% of the patients in NYHA class I or II.[20]

Abbreviations: NYHA, New York Heart Association; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation.

3.7 PATIENT QUALITY OF LIFE (QOL)

Table 10. QoL improvements from baseline post-procedure across additional MitraClip™ real-world evidence

		ADDITIONAL REAL-WORLD EVIDENCE					
			EVEREST II REALISM (PMR, SMR)			MITRA SWISS (PMR, SMR)	
		ACCESS-EU (PMR, SMR)	HIGH RISK	NON-HIGH RISK	TRAMI (PMR, SMR)	PMR	SMR
6MWT, m	**6m**	+56.4	-	-	-	+27	+37
	1Y	+59.5	-	-	-	-	-
MLWHFQ SCORE	**6m**	+12.3	-	-	-	-	-
	1Y	+13.5	-	-	-	-	-
SF-36 PCS	**1Y**	-	+5.0	+6.2	-	-	-
EQ-VAS	**1Y**	-	-	-	60.0 (vs 50.0 at baseline)	-	-

Abbreviations: EQ-VAS, EuroQol visual analogue scale; MLWHFQ, Minnesota Living with Heart Failure Questionnaire; PMR, primary mitral regurgitation; QoL, quality of life; SF-36, 36-Item Short Form Survey; SMR, secondary mitral regurgitation; 6MWT, six-minute walk test.
Sources: ACCESS-EU, Maisano 2013;[32] EVEREST II REALISM, Feldman 2015;[28] TRAMI, Puls 2016;[24] MITRA SWISS, Surder 2020;[21]

ADDITIONAL REAL-WORLD EVIDENCE	
ACCESS EU (PMR, SMR)	At 6 months, the 6MWT improved 56.4 ± 120.1 m (95% CI: 41.8 to 71.0; p=0.0006) as compared with baseline (322.0 ± 124.8 m vs 265.5 ± 120.0 m). MLWHFQ score went from 41.2 ± 19.1 at baseline to 28.9 ± 20 m at 6 months, representing an improvement of 12.3 ± 20.9 points (95% CI: 14.6 to 10.0; p<0.0001).[32] At 1 year, the improvement in mean ± SD 6MWT distance was 59.5 ± 112.4 m (95% CI: 44.5–74.6; p<0.0001) from 274.7 ± 118.7 m at baseline to 334.2 ±127.9 m at 1 year. The mean ± SD MLWHFQ score improved 13.5 ± 20.5 points (95% CI: 11.0–16.0; p<0.0001) from baseline (41.6 ± 18.9) to 1 year (28.1 ± 20.1).[32]
EVEREST II REALISM (PMR, SMR)	The change in SF-36 PCS from baseline at 1 year was +5.0 ± 9.9 points in the high risk arm and +6.2 ± 9.4 points in the non-high risk arm.[28]
TRAMI (PMR, SMR)	Patients' self-rated health status on the EQ VAS improved significantly from 50.0 [IQR 40.0–60.0] at baseline to 60.0 [IQR 50.0–70.0] at 1 year (p<0.0001).[24]
MITRA SWISS (PMR, SMR)	At 6 months, 6MWT increased significantly vs baseline in both the SMR (+37 m, 95%CI 18-56, p<0.001; from a median of 350 m to 372 m) and PMR cohort (+27 m, 95%CI 10-43, p=0.002; from a median of 370 m to 385 m).[21]

Abbreviations: EQ-VAS, EuroQol visual analogue scale; MLWHFQ, Minnesota Living with Heart Failure Questionnaire; PMR, primary mitral regurgitation; QoL, quality of life; SF-36, 36-Item Short Form Survey; SMR, secondary mitral regurgitation; 6MWT, six-minute walk test.

3.8 LEFT VENTRICLE REMODELLING

Table 11. Reverse left ventricle remodelling post-procedure across additional MitraClip™ real-world evidence

		ADDITIONAL REAL-WORLD EVIDENCE			
			EVEREST II REALISM (PMR, SMR)		
		EVEREST II HRS (PMR, SMR)	HIGHRISK	NON-HIGH RISK	EUROPEAN SENTINEL (PMR, SMR)
MEAN CFB IN LV MEASUREMENT, mL	**DC**	-	-	-	LVEDV: –4.6[†] LVESV: –0.6[†]
	1Y	-	LVEDV: –8	LVEDV: –13	-
	5Y	LVEDV: –38.2 LVESV: –14.6	-	-	-

Abbreviations: CFB, change from baseline; DC, discharge; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation; Y, year.
[†] Post-procedural.
Sources: EVEREST II HRS, 1 year Whitlow 2012,[33] 5 years Kar 2018;[34] EVEREST II REALISM, Feldman 2015;[28] European Sentinel, Nickenig 2014.[23]

ADDITIONAL REAL-WORLD EVIDENCE	
EVEREST II HRS (PMR, SMR)	At 12 months, LVEDV improved from 172 ml to 140 ml and LVESV improved from 82 ml to 73 ml (both p=0.001).[33] Outcomes were maintained after 5 years, with a mean reduction of –38.2 mL in LVEDV from baseline (p<0.0001) and –14.6 mL in LVESV from baseline (p=0.303).[34]
EVEREST II REALISM (PMR, SMR)	The change in LVEDV from baseline at 1 year was –8 ± 35 mL in the high risk arm and –13 ± 24 mL in the non-high risk arm.[28]
EUROPEAN SENTINEL (PMR, SMR)	LVEDV was 159.4 ± 86.1 pre-clip and 154.8 ± 86.3 post-clip (–4.6; p=0.119). LVESV was 103.0 ± 69.0 pre-clip and 102.4 ± 74.6 post-clip (–0.6; p=0.797). At 1 year, a nonsignificant reduction in LVEDV was observed (159.5 vs 157.7; p=0.646), with a significant reduction in left atrial volume (120.8 vs 105.6; p=0.001).[23]
MITRA SWISS (PMR, SMR)	Significant decreases from baseline to 6-month follow-up were observed for LVEDV (p=0.00022), LVESV (p=0.02), and LVEDD (p=0.03). A non-significant decrease in LVESD was also observed (p=0.06). The significant improvement in reverse LV remodelling was driven by the SMR subgroup.[22]

Abbreviations: EF, ejection fraction; LV, left ventricle; LVEDV, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation.

3.9 HEART FAILURE HOSPITALISATIONS

Table 12. HF hospitalisation rates post-MitraClip™ implantation

		ADDITIONAL REAL-WORLD EVIDENCE					
		GRASP (PMR, SMR)	EUROPEAN SENTINEL (PMR, SMR)	MITRA SWISS (PMR, SMR)	SPANISH REGISTRY (PMR, SMR)	GIOTTO (PMR, SMR)	NATIONWIDE READMISSION DATABASE (PMR)
HF HOSPITALISATIONS, %	3M prior to TEER	-	-	-	-	-	5.3
	2M prior to TEER	-	-	-	-	-	6.8
	1M prior to TEER	-	-	-	-	-	6.8
	30d	-	-	1.9	-	3.7	4.0
	2 months	-	-	-	-	-	2.7
	3 months	-	-	-	-	-	1.8
	1Y	18.6	22.8	-	18.0	11.0	-
	2Y	24.5	-	-	-	15.6	-
	3Y	29.0	-	-	-	-	-
	4Y	32.5	-	-	-	-	-
	5Y	37.9	-	-	-	-	-

Abbreviations: d, day; HF, heart failure; M, month; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation; TEER, transcatheter edge-to-edge repair; Y, year.
Sources: GRASP, Adamo 2019;[31] European Sentinel, Nickenig 2014;[23] MITRA SWISS, Surder 2020;[21] Spanish Registry, Pascual 2020;[20] GIOTTO, Bedogni 2021;[18] Nationwide Readmission Database, Elkaryoni 2019.[40]

ADDITIONAL REAL-WORLD EVIDENCE	
GRASP (PMR, SMR)	Hospitalisation due to HF occurred in 18.6% of patients at 1 year, 24.5% at 2 years, 29% at 3 years, 32.5% at 4 years, and 37.9% at 5 years.[31]
TRAMI (PMR, SMR)	During the first year of follow-up, 14.1% of patients were re-hospitalized due to cardiac decompensation and 17.8% due to other cardiovascular reasons.[24]
EUROPEAN SENTINEL (PMR, SMR)	The estimated 1-year rate of rehospitalization because of heart failure was 22.8% and was significantly higher in the SMR group than the PMR group (25.8% vs. 12%, p=0.009).[23]
MITRA SWISS (PMR, SMR)	At 30 days, rehospitalisation for HF occurred in 1.9% of patients (n=24). Rate of rehospitalisation was the same in PMR patients (1.9%, n=13) and SMR patients (1.9%, n=11).[21]
SPANISH REGISTRY (PMR, SMR)	HF rehospitalisation rate at 12 months among all enrolled patients was 18% (101 patients); 11.7% (n=13) for PMR patients, 21.2% (n=77) for SMR patients, and 13.3% (n=11) for patients with mixed aetiology (p=0.047).[20]
GIOTTO (PMR, SMR)	Hospitalisation for HF occurred in 3.7%, 11.0%, and 15.6% of patients within 30 days, 1 year, and 2 years, respectively, of the MitraClip™ procedure.[18]
NATIONWIDE READMISSION DATABASE (PMR)	In a cohort of MitraClip™ recipients (N=2,567) registered in the Nationwide Readmission Database between 2014 and 2016, HF-related hospitalisation rates dropped from 5.3–6.8% in the 3 months prior to MitraClip™ implantation to 4.0%, 2.7%, and 1.8% 1, 2, and 3 months, respectively, post-procedure.[40]

Abbreviations: HF, heart failure; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation.

APPENDIX 4 – PUBLISHED ECONOMIC MODELS/COST STUDIES FOR MITRACLIP™

- Numerous economic models for MitraClip™ from the perspectives of various countries have been published, summaries of which are provided below.

Table 13: Overview of published economic models/cost studies for MitraClip™

AUTHOR	TITLE	COUNTRY	YEAR
ESTLER ET AL[53]	Cost-effectiveness of the MitraClip device in German heart failure patients with secondary mitral regurgitation	Germany	2023
REZAPOUR ET AL[41]	Cost-effectiveness analysis of mitral valve repair with the MitraClip delivery system for patients with mitral regurgitation: a systematic review.	NA	2021
CAPELLE ET AL[42]	Percutaneous mitral valve repair in severe secondary mitral regurgitation: Analysis of index hospitalization and economic evaluation based on the MITRA-FR trial.	France	2021
MAHDJOUB ET AL[43]	Is the MitraClip® procedure profitable in a high-volume French hospital?	France	2019
GUERIN ET AL[44]	MitraClip therapy in mitral regurgitation: a Markov model for the cost-effectiveness of a new therapeutic option.	France	2016
SAKAMAKI ET AL[45]	Cost-effectiveness analysis of percutaneous mitral valve repair with the MitraClip delivery system for patients with mitral regurgitation in Japan.	Japan	2019
ASGAR ET AL [46]	Clinical outcomes and economic impact of transcatheter mitral leaflet repair in heart failure patients.	Canada	2017
ARMENI ET AL[47]	Real-world cost effectiveness of MitraClip combined with Medical Therapy Versus Medical therapy alone in patients with moderate or severe mitral regurgitation.	Italy	2016
PALMIERI ET AL[48]	Impact of DRG billing system on health budget consumption in percutaneous treatment of mitral valve regurgitation in heart failure.	Italy	2015
COHEN ET AL[49]	Cost-effectiveness of transcatheter edge-to-edge repair in secondary mitral regurgitation.	UK	2022
WILLITS ET AL[50]	Safety, effectiveness and costs of percutaneous mitral valve repair: A real-world prospective study.	UK	2021
SHORE ET AL[51]	An analysis of the cost-effectiveness of transcatheter mitral valve repair for people with secondary mitral valve regurgitation in the UK.	UK	2020
MEALING ET AL[52]	EVEREST II high risk study based UK cost-effectiveness analysis of MitraClip® in patients with severe mitral regurgitation ineligible for conventional repair/replacement surgery.	UK	2013
INCLUDED IN THE MAIN DOSSIER			
BARON ET AL[54]	Cost-Effectiveness of Transcatheter Mitral Valve Repair versus Medical Therapy in Patients with Heart Failure and Secondary Mitral Regurgitation: Results from the COAPT Trial	US	2019

4.1 GERMAN PERSPECTIVE (ESTLER 2023)

- A cost-effectiveness analysis was developed, which combined a decision tree and a Markov model, to compare the clinical and economic consequences of MitraClip™ + OMT versus OMT alone from a German statutory health insurance (SHI) system perspective.[53]
- Clinical data were mainly based on the COAPT trial, supplemented by literature searches to identify further clinical and economic input data.
- Data on resource utilisation and cost were derived from German sources wherever possible. As no German utility data on NYHA classes were available, utility values were taken from the CARE-HF trial.
- In comparison with OMT alone, MitraClip™ resulted in an ICER of € 59,728/QALY (and costs per incremental life years gained of €42,360).
- The results were most sensitive to the probability of hospitalisation and the transition probabilities between NYHA classes, particularly between NYHA class II and III.
- At a willingness-to-pay threshold of €60,000/QALY, MitraClip™ had a 58% probability of being cost-effective compared with OMT alone, increasing to 88% at a threshold of €70,000/QALY.
- The authors conclude that, in the German context, MitraClip™ can be a cost-effective intervention for the treatment of secondary mitral regurgitation in patients with HF.

4.2 SYSTEMATIC REVIEW OF MITRACLIP™ COST-EFFECTIVENESS ANALYSES (REZAPOUR 2021)

- A systematic literature review of studies (published up to January 2020) reporting the cost-effectiveness of MitraClip™ for patients with mitral regurgitation and heart failure.[41]
- Study eligibility criteria were as follows:
  - Population: Patients with mitral regurgitation
  - Intervention: TMVr using MitraClip™
  - Comparator: Conventional medical treatment
  - Outcomes: Incremental cost-effectiveness ratio (ICER), incremental cost per quality-adjusted life year (QALY), net monetary benefit (NMB)
  - Study design: Model-based or trial-based full economic evaluations (cost-benefit analysis [CBA], cost-effectiveness analysis [CEA], cost-utility analysis [CUA])
- A total of seven studies met the eligibility criteria and were included in the systematic review.
- Each of the seven studies demonstrated that MitraClip™ reduces mortality and increases survival.
- The highest costs for the MitraClip™ device were in the USA, Canada, and Japan ($121,390, $78,619, and $70,887, respectively) and the lowest costs in Italy and France ($33,062 and $39,799, respectively).
- Total cost data (based on 2019 USD) showed that MitraClip™ system has the highest cost in the USA, Canada, and Japan
- In all countries covered by the included studies (UK, Canada, France, Italy, USA, and Japan), the cost per QALY was below the willingness to pay (WTP) threshold, meaning that MitraClip™ is a cost-effective treatment for patients with mitral regurgitation.

4.3 FRENCH PERSPECTIVE (CAPELLE 2021)

- A cost study based on patients randomised into the intervention (MitraClip™) arm of the MITRA-FR trial was conducted from a French hospital perspective.[42]
- Medical resource use was estimated using data collected from patients enrolled in the MITRA-FR study as well as non-specific data from national statistics.
- The study population comprised 144 patients who underwent MitraClip™ implantation across 33 different French hospitals.
- The mean number of hospital staff in attendance during a MitraClip™ implantation procedure was 7.9 (SD: 1.5), which included at least one interventional cardiologist, an echocardiographer, and an anaesthesiologist. The mean procedure duration was 154 minutes (SD: 68 minutes), increasing with the number of clips implanted. The median total hospital length of stay was 8 days.
- The occurrence of a serious adverse event (SAE) was not associated with an increased risk of admission to the critical care unit but was associated with an increased length of hospital stay.
- The mean (SD) total cost was €28,025 (3,424), which included €21,547 for the cost of the medical devices used during implantation and €6,478 (3,424) for other costs.
- The cost of MitraClip™ is substantial for patients with SMR, which advocates for further efforts to identify the patients with SMR who are likely to derive a clear clinical benefit from the procedure.

4.4 FRENCH PERSPECTIVE (MAHDJOUB 2019)

- Patients eligible for mitral valve repair with MitraClip™, and covered by the French National Health Service, were included in this retrospective single-centre study conducted between September 2016 and June 2018.[43]
- The study primary endpoint was the difference between per-patient hospital costs and revenues.
- Mean hospital cost and revenue were €30,039 ±2,476 and €30,331 ±2,720 per patient (N=22), respectively, resulting in a profit of €292 ±2,039 per patient.
- The total estimated profit was €6,429 for the whole study period. The largest benefits were observed for patients assigned to higher medico-economic severity levels.
- Profit increased following a reduction in the device cost (€1,136 ±2,415 per patient). The price of the device accounted for 78% of total costs.
- Percutaneous MitraClip™ implantation was evaluated to be a financially neutral procedure for a French university hospital.

4.5 FRENCH PERSPECTIVE (GUERIN 2016)

- The efficacy of the MitraClip™ strategy versus medical management was assessed using a 4-state Markov model based on MR grade. The model analysed a fictional population of 1,000 patients over a 5-year period from a national health insurance perspective.[44]
- The primary endpoint was the number of deaths avoided. Data from EVEREST II HRS patients were used along with a literature review.
- At 5 years, among 1,000 patients, 276 deaths were found to be prevented with the MitraClip™ strategy. The mean ICER was calculated to be €20,720 per death avoided.
- MitraClip™ constitutes an attractive therapeutic alternative, for both the patient and the payer. Over time, re-hospitalisations are avoided due to improved MR grades.

4.6 JAPANESE PERSPECTIVE (SAKAMAKI 2019)

- The cost-effectiveness of MitraClip™ compared with propensity score-matched medical therapy in patients with symptomatic severe MR at high surgical risk was evaluated using a Markov model.[45]
- Hospitalisation costs for mitral valve surgery, congestive HF hospitalisation, and for major adverse event hospitalisation and treatment were calculated based on a claims database (Medical Data Vision).
- The analysis was conducted from the perspective of a public healthcare payer with a discount rate of 2% for both cost and effectiveness.
- Total cost and QALY gained were 7,541,151 JPY and 3.23 QALYs (3.85 LYs) for MitraClip™ group versus 4,699,692 JPY and 1.79 QALYs (2.43 LYs) for medical therapy.
- The ICER for MitraClip™ versus medical therapy was 1.97 million JPY/QALY (US: $18,570/QALY) which was deemed to be cost-effective.

4.7 CANADIAN PERSPECTIVE (ASGAR 2017)

- Clinical outcomes and economic impact of MitraClip™ Therapy versus medical management in HF patients with moderate to severe symptomatic MR was assessed using a decision model.[46]
- An observational study was used to estimate parameters for the decision model which estimated costs and benefits in a cohort of MitraClip™-treated patients propensity-matched to a population of medically-managed patients.
- At a mean follow up of 22 months, all-cause mortality was 21% in the MitraClip™ cohort compared with 42% in the medical management cohort (p=0.007).
- The decision model demonstrated that MitraClip™ increased life expectancy from 1.87 to 3.60 years and QALYs from 1.13 to 2.76.
- The incremental cost was $52,500 Canadian dollars, corresponding to an ICER of $32,300 per QALY gained.
- In HF patients with symptomatic moderate to severe MR, MitraClip™ Therapy is associated with superior survival and is cost-effective compared with medical therapy.

4.8 ITALIAN PERSPECTIVE: FIRST REAL-WORLD ECONOMIC EVIDENCE (ARMENI 2016)

- Clinical records of patients with moderate to severe SMR treated with MitraClip™ + medical therapy (n=232) or with medical therapy only (n=151) were collected, propensity-matched, and analysed from a payer's perspective.[47]
- The cost of MitraClip™ Therapy in the Italian setting was estimated to be €23,069 ±2,397 while the total cost over 1 year was €25,272 ±3,400.
- Hospitalisation costs after MitraClip™ Therapy were statistically significant lower compared with patients treated with only medical therapy (6 months: €455 ±1,322 versus €1,374 ±2,353, p<0,01; 1 year: €495 ±1,353 versus €2,388 ±3,965; p<0.01).
- The cost-effectiveness of MitraClip™ Therapy is in line with or superior to non-pharmaceutical strategies for HF.

4.9 ITALIAN PERSPECTIVE (PALMIERI 2015)

- The economic impact of MitraClip™ Therapy for patients with MR and HF was determined from the perspective of the Italian public healthcare system.[48]
- Cost estimates were obtained using the diagnosis-related group billing system and hospitalisation costs for 2012–

2013. QoL was measured before and after MitraClip™ therapy.

- MitraClip™ Therapy was associated with a significant improvement in QoL from baseline (0.48) to 2-years follow-up (0.78; p <0.01).
- Total costs were estimated at €25,500, including device costs of €21,000 and hospitalisation costs of €4,500 (assuming a 9-day hospital stay).
- Based on a cost per case of €25,500, the cost per QALY of MitraClip™ was estimated at €16,350 over a 2-year follow up.
- MitraClip™ Therapy may represent a cost-effective treatment option for HF patients with MR who are predicted to achieve a good outcome over a sufficiently long follow-up period.

4.10 UK PERSPECTIVE (COHEN 2022)

- Patient-level data from COAPT™ were used to inform a cost-effectiveness analysis of MitraClip™ plus GDMT versus GDMT alone from the perspective of the NHS.[49]
- Procedure costs were based on costs of the MitraClip™ device and English tariffs. Subsequent costs were based on data acquired during the COAPT™ trial. Health utilities were estimated using SF-6D.
- Costs for the index procedural hospitalisation were £18,781, of which £16,218 were for the MitraClip™ device.
- Over 2-years of follow-up, MitraClip™ reduced subsequent costs compared with GDMT (£10,944 versus £14,932; p=0.006), driven mainly by reductions in heart failure hospitalisations; nonetheless, total 2-year costs remained higher with MitraClip™ (£29,165 versus £14,932; p<0.001).
- Projecting survival, health utilities, and costs over a lifetime, MitraClip™ plus GDMT increased life expectancy by 1.57 years and quality-adjusted life expectancy by 1.12 QALYs at an incremental cost of £21,980 versus GDMT alone, resulting in an ICER of £23,270 per QALY gained (after discounting).
- The ICER improved to £12,494 per QALY if the benefits of MitraClip™ observed in the first 2 years were maintained.
- For patients with HFrEF and severe SMR, MitraClip™ in addition to GDMT increases life expectancy and quality-adjusted life expectancy at an ICER representing good value for the NHS.

4.11 UK (ENGLAND) COST STUDY (WILLITS 2021)

- A prospective, single-armed registry with a follow-up of 2 years that received data for 199 mainly elective patients with mixed mitral regurgitation aetiology at four centres in England.[50]
- A MitraClip™ device was implanted in 187 patients (94%), with a procedural success rate of 86%.
- MitraClip™ implantation reduced hospital admissions from 470 in the year prior to MitraClip™ implantation, to 251 in the year post-implantation (rate ratio: 0.57, 95% CI: 0.49–0.67; p < 0.001).
- MitraClip™ reduced total days in hospital and associated aggregated costs, from approximately 1,267,000 GBP pre-procedure to 890,000 GBP post-procedure.
- Reduction in healthcare resource use was mainly related to a reduction in admissions due to cardiac reasons, and in particular heart failure indications.

4.12 UK PERSPECTIVE (SHORE 2020)

- An economic model (partitioned survival model combined with a "proportion in state" model) from the NHS perspective assessed the cost-effectiveness of MitraClip™ plus GDMT versus GDMT alone for the treatment of patients with mitral regurgitation.[51]
- The model had a lifetime time horizon and was based on extrapolated survival data and patient-level NYHA data from COAPT.
- Compared with GDMT alone, MitraClip™ combined with GDMT was associated with an additional 1.07 QALYs and an increase in costs of £32,267 per patient over a lifetime time horizon.
- The estimated incremental cost per QALY gained was £30,057 (i.e. on the threshold of cost-effectiveness at £30,000 per QALY).
- From the UK reimbursement perspective, MitraClip™ added to GDMT is likely to be a cost-effective treatment option (compared with GDMT alone) in patients with severe SMR at high risk of surgical mortality or deemed ineligible for conventional surgery.

4.13 UK PERSPECTIVE (MEALING 2013)

- A Markov model was developed to determine the cost-effectiveness of MitraClip™ compared with medical management in patients with severe MR who were ineligible for surgery.[52]
- Clinical data were extracted from the EVEREST II HRS, utility data were derived from a representative sample of the UK population, and cost data were taken from the British National Formulary and NHS reference costs (from 2011).
- The model results were most sensitive to variations in the time horizon, with the ICER for MitraClip™ versus medical management falling as the time horizon increased (at 5 years: ICER of £22,500).
- Using a 10-year time horizon, there was a 95% probability that MitraClip™ would be cost-effective at a WTP threshold of £20,000 per QALY gained.
- The majority of costs associated with MitraClip™ are incurred when the procedure is performed, with benefits of the intervention being accrued over time.
- This economic analysis demonstrates that patients accrue enough additional benefit for MitraClip™ Therapy to be considered a cost-effective treatment option.

APPENDIX 5 – SYSTEMATIC REVIEWS AND NETWORK META-ANALYSES INVOLVING MITRACLIP™

- Numerous systematic reviews and network meta-analyses (NMAs) involving MitraClip™ have been published, an overview of which is presented in the table below.

AUTHOR, YEAR	TITLE	NUMBER OF STUDIES INCLUDED	NUMBER OF PATIENTS INCLUDED
SYSTEMATIC REVIEWS			
ILIADIS ET AL 2017[55]	Functional status and quality of life after transcatheter mitral valve repair: a prospective cohort study and systematic review	37	NR
MUNKHOLM-LARSEN ET AL 2014[56]	A systematic review on the safety and efficacy of percutaneous edge-to-edge mitral valve repair with the MitraClip™ system for high surgical risk candidates	12	MitraClip™: 878
VAKIL ET AL 2014[57]	Safety and Efficacy of the MitraClip® System for Severe Mitral Regurgitation: A Systematic Review	16	MitraClip™: 2,980
PHILIP ET AL 2014[58]	MitraClip for Severe Symptomatic Mitral Regurgitation in Patients at High Surgical Risk: A Comprehensive Systematic Review	21	MitraClip™: 3,198 Surgery: 3,265
(NETWORK) META-ANALYSES			
KHADER ET AL 2021[59]	Does the clinical effectiveness of Mitraclip compare with surgical repair for mitral regurgitation?	12	MitraClip™: 1,210 Surgery: 3,009
KUMAR ET AL 2020[60]	Percutaneous mitral valve repair for secondary mitral valve regurgitation: A systematic review and meta-analysis	4	MitraClip™: 564 OMT: 566
VALLAKATI ET AL 2020[61]	Transcatheter Mitral Valve Repair in Patients with Heart Failure: A Meta-Analysis	4	MitraClip™: 746 Medical therapy: 675
BARROS DA SILVA ET AL 2020[62]	Stroke after transcatheter edge-to-edge mitral valve repair: a systematic review and meta-analysis	10	MitraClip™: 1,087 Control: 1,069†
BENITO-GONZÁLEZ ET AL 2020[63]	Percutaneous Mitral Valve Repair Vs. Stand-Alone Medical Therapy in Patients with Functional Mitral Regurgitation and Heart Failure	5	MitraClip™: 696 Managed conservatively: 717
MARMAGKIOLIS ET AL 2019[64]	Clinical outcomes of percutaneous mitral valve repair with MitraClip for the management of functional mitral regurgitation	7	MitraClip™: 1,174 Medical therapy: 1,015
BERTAINA ET AL 2019[65]	Prognostic impact of MitraClip in patients with left ventricular dysfunction and functional mitral valve regurgitation: A comprehensive meta-analysis of RCTs and adjusted observational studies	8	MitraClip™: 1,207 OMT: 1,048
GOEL ET AL 2019[66]	Mitraclip Plus Medical Therapy Versus Medical Therapy Alone for Functional Mitral Regurgitation: A Meta-Analysis	5	MitraClip™: 796 Medical therapy: 717
GIANNINI ET AL 2018[67]	A meta-analysis of MitraClip combined with medical therapy vs. medical therapy alone for treatment of mitral regurgitation in heart failure patients	6	MitraClip™: 833 Conservative therapy: 1,288

AUTHOR, YEAR	TITLE	NUMBER OF STUDIES INCLUDED	NUMBER OF PATIENTS INCLUDED
TAKAGI ET AL 2017[68]	A review of comparative studies of MitraClip versus surgical repair for mitral regurgitation	7	MitraClip™: 574 Surgery: 441
CHIARITO ET AL 2017[69]	Outcome after percutaneous edge-to-edge mitral repair for functional and degenerative mitral regurgitation: a systematic review and meta-analysis	9	MitraClip™: 2,615
SANNINO ET AL 2017[70]	Survival and Cardiovascular Outcomes of Patients With Secondary Mitral Regurgitation A Systematic Review and Meta-analysis	53	45,900
BENITO-GONZALEZ ET AL 2017[71]	Survival Advantage of MitraClip® Over Medical Treatment in Patients with Mitral Regurgitation: A Meta-Analysis	5	MitraClip™: 720 Conservative management: 551
BAIL 2015[72]	(Meta)-analysis of safety and efficacy following edge-to-edge mitral valve repair using the MitraClip system	26	MitraClip™: 3,821
D'ASCENZO ET AL 2015[73]	Meta-Analysis of the Usefulness of MitraClip in Patients With Functional Mitral Regurgitation	9	MitraClip™: 875

Abbreviations: NMA, network meta-analysis; OMT, optimal medical therapy; RCT, randomised controlled trial.
† Surgery or OMT.

1. Wojakowski W, Chmielak Z, Widenka K, Pręgowski J, Perek B, Gackowski A, et al. Transcatheter mitral valve repair and replacement. Expert consensus statement of the Polish Cardiac Society and the Polish Society of Cardiothoracic Surgeons. Kardiologia Polska (Polish Heart Journal). 2021;79(10):1165-77.
2. Baldus S, Kuck KH, Rudolph V, Nef H, Eggebrecht H, Boekstegers P, et al. Interventionelle Therapie von AV-Klappenerkrankungen – Fokus Mitralklappeninsuffizienz Positionspapier der Deutschen Gesellschaft für Kardiologie. Der Kardiologe. 2018;12:128–44.
3. Estevez-Loureiro R, Freixa X, Arzamendi D, Perez de Prado A, Campante-Teles R, Melica B, et al. Transcatheter mitral valve interventions for mitral regurgitation, with special focus on MitraClip: The position of Spanish, Portuguese and Italian interventional societies. Int J Cardiol. 2017;243:169-73.
4. Maisano F, Alamanni F, Alfieri O, Bartorelli A, Bedogni F, Bovenzi FM, et al. Transcatheter treatment of chronic mitral regurgitation with the MitraClip system: an Italian consensus statement. J Cardiovasc Med (Hagerstown). 2014;15(3):173-88.
5. Abbott Vascular. Press release. 13th January 2020. Abbott to initiate trial to study MitraClip as an option for moderate surical risk patients. Available at: https://abbott.mediaroom.com/2020-01-13-Abbott-to-Initiate-Trial-to-Study-MitraClip-as-an-Option-for-Moderate-Surgical-Risk-Patients (last accessed: 15 Dec 2021).
6. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, et al. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. N Engl J Med. 2018;379(24):2307-18.
7. Stone GW, Abraham WT, Lindenfeld J, Kar S, Grayburn PA, Lim DS, et al. Five-year follow-up after transcatheter repair of secondary mitral regurgitation. New England Journal of Medicine. 2023.
8. Mack MJ, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, et al. 3-Year Outcomes of Transcatheter Mitral Valve Repair in Patients With Heart Failure. J Am Coll Cardiol. 2021;77(8):1029-40.
9. Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, et al. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. N Engl J Med. 2018;379(24):2297-306.
10. Iung B, Armoiry X, Vahanian A, Boutitie F, Mewton N, Trochu JN, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation: outcomes at 2 years. European journal of heart failure. 2019;21(12):1619-27.
11. Feldman T, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, et al. Percutaneous Repair or Surgery for Mitral Regurgitation. New England Journal of Medicine. 2011;364(15):1395-406.
12. Feldman T, Kar S, Elmariah S, Smart SC, Trento A, Siegel RJ, et al. Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation: 5-Year Results of EVEREST II. J Am Coll Cardiol. 2015;66(25):2844-54.
13. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/home. Accessed on: 05 April 2023.
14. Rodriguez E, Denti P, Bedogni F, Mahoney P, Williams MR, Price MJ, et al. Contemporary Outcomes with the MitraClip™ G4 System: Preliminary Results based on the EXPAND G4 Study. Presented at: CRF TCT, 4–6 November 2021.
15. Goel K, Makkar R, Naik H, Atmakuri S, Mahoney P, Morse A, et al. Contemporary, real-world outcomes of 5000 patients with secondary mitral regurgitation treated with MitraClip™: Results from the COAPT Post Approval Study. Presented at ESC Congress 2022; 26–29 August; Barcelona.
16. Kar S, von Bardeleben RS, Rottbauer W, Mahoney P, Price MJ, Grasso C, et al. Contemporary outcomes following transcatheter edge-to-edge repair: 1-year results from the expand study. Cardiovascular Interventions. 2023;16(5):589-602.
17. Makkar RR, Chikwe J, Chakravarty T, Chen Q, O'Gara PT, Gillinov M, et al. Transcatheter Mitral Valve Repair for Degenerative Mitral Regurgitation. JAMA. 2023;329(20):1778-88.
18. Bedogni F, Popolo Rubbio A, Grasso C, Adamo M, Denti P, Giordano A, et al. Italian Society of Interventional Cardiology (GIse) registry Of Transcatheter treatment of mitral valve regurgitaTiOn (GIOTTO): impact of valve disease aetiology and residual mitral regurgitation after MitraClip implantation. European journal of heart failure. 2021.
19. Bedogni F, Testa L, Rubbio AP, Bianchi G, Grasso C, Scandura S, et al. Real-world safety and efficacy of transcatheter mitral valve repair with MitraClip: thirty-day results from the Italian Society of

Interventional Cardiology (GIse) Registry Of Transcatheter Treatment of Mitral Valve RegurgitaTiOn (GIOTTO). Cardiovascular Revascularization Medicine. 2020;21(9):1057-62.
20. Pascual I, Arzamendi D, Carrasco-Chinchilla F, Fernández-Vázquez F, Freixa X, Nombela-Franco L, et al. Transcatheter mitral repair according to the cause of mitral regurgitation: Real-life data from the Spanish MitraClip registry. Revista Española de Cardiología (English Edition). 2020;73(8):643-51.
21. Sürder D, Klersy C, Corti R, Biasco L, Gaemperli O, Maisano F, et al. Impact of mitral regurgitation aetiology on MitraClip outcomes: the MitraSwiss registry. EuroIntervention. 2020;16(2):e112-e20.
22. Surder D, Pedrazzini G, Gaemperli O, Biaggi P, Felix C, Rufibach K, et al. Predictors for efficacy of percutaneous mitral valve repair using the MitraClip system: the results of the MitraSwiss registry. Heart. 2013;99(14):1034-40.
23. Nickenig G, Estevez-Loureiro R, Franzen O, Tamburino C, Vanderheyden M, Luscher TF, et al. Percutaneous mitral valve edge-to-edge repair: in-hospital results and 1-year follow-up of 628 patients of the 2011-2012 Pilot European Sentinel Registry. J Am Coll Cardiol. 2014;64(9):875-84.
24. Puls M, Lubos E, Boekstegers P, von Bardeleben RS, Ouarrak T, Butter C, et al. One-year outcomes and predictors of mortality after MitraClip therapy in contemporary clinical practice: results from the German transcatheter mitral valve interventions registry. Eur Heart J. 2016;37(8):703-12.
25. Kalbacher D, Schafer U, RS VB, Eggebrecht H, Sievert H, Nickenig G, et al. Long-term outcome, survival and predictors of mortality after MitraClip therapy: Results from the German Transcatheter Mitral Valve Interventions (TRAMI) registry. Int J Cardiol. 2019;277:35-41.
26. Armoiry X, Brochet E, Lefevre T, Guerin P, Dumonteil N, Himbert D, et al. Initial French experience of percutaneous mitral valve repair with the MitraClip: a multicentre national registry. Arch Cardiovasc Dis. 2013;106(5):287-94.
27. Estevez-Loureiro R, Settergren M, Winter R, Jacobsen P, Dall'Ara G, Sondergaard L, et al. Effect of gender on results of percutaneous edge-to-edge mitral valve repair with MitraClip system. The American journal of cardiology. 2015;116(2):275-9.
28. Feldman T, Lim S, Fail P, Whisenant B, Rinaldi M, Grayburn P, et al. EVEREST II REALISM - A CONTINUED ACCESS STUDY TO EVALUATE THE SAFETY AND EFFECTIVENESS OF THE MITRACLIP DEVICE: ANALYSIS OF RESULTS THROUGH 1 YEAR. Journal of the American College of Cardiology. 2015;65(10_Supplement):A1983-A.
29. Attizzani GF, Ohno Y, Capodanno D, Cannata S, Dipasqua F, Imme S, et al. Gender-related clinical and echocardiographic outcomes at 30-day and 12-month follow up after MitraClip implantation in the GRASP registry. Catheter Cardiovasc Interv. 2015;85(5):889-97.
30. Scandura S, Capranzano P, Caggegi A, Grasso C, Ronsivalle G, Mangiafico S, et al. Percutaneous mitral valve repair with the MitraClip system in the elderly: One-year outcomes from the GRASP registry. Int J Cardiol. 2016;224:440-6.
31. Adamo M, Grasso C, Capodanno D, Rubbio AP, Scandura S, Giannini C, et al. Five-year clinical outcomes after percutaneous edge-to-edge mitral valve repair: Insights from the multicenter GRASP-IT registry. Am Heart J. 2019;217:32-41.
32. Maisano F, Franzen O, Baldus S, Schafer U, Hausleiter J, Butter C, et al. 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. J Am Coll Cardiol. 2013;62(12):1052-61.
33. Whitlow PL, Feldman T, Pedersen WR, Lim DS, Kipperman R, Smalling R, et al. Acute and 12-month results with catheter-based mitral valve leaflet repair: the EVEREST II (Endovascular Valve Edge-to-Edge Repair) High Risk Study. J Am Coll Cardiol. 2012;59(2):130-9.
34. Kar S, Feldman T, Qasim A, Trento A, Kapadia S, Pedersen W, et al. Five-year outcomes of transcatheter reduction of significant mitral regurgitation in high-surgical-risk patients. Heart. 2018.
35. Mitral Valve Academic Research Consortium (MVARC). Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 1: Clinical Trial Design Principles a Consensus Document from the Mitral Valve Academic Research Consortium. Journal of the American College of Cardiology. 2015;66(3):278-307.
36. Grasso C, Capodanno D, Scandura S, Cannata S, Imme S, Mangiafico S, et al. One- and twelve-month safety and efficacy outcomes of patients undergoing edge-to-edge percutaneous mitral

valve repair (from the GRASP Registry). The American journal of cardiology. 2013;111(10):1482-7.
37. Seeger J, Muller P, Gonska B, Scharnbeck D, Markovic S, Walcher D, et al. Percutaneous Mitral Valve Repair With the MitraClip in Primary Compared With Secondary Mitral Valve Regurgitation Using the Mitral Valve Academic Research Consortium Criteria. The Journal of invasive cardiology. 2017;29(4):145-50.
38. Ledwoch J, Franke J, Baldus S, Schillinger W, Bekeredjian R, Boekstegers P, et al. Impact of the learning curve on outcome after transcatheter mitral valve repair: results from the German Mitral Valve Registry. Clin Res Cardiol. 2014;103(11):930-7.
39. Schillinger W, Athanasiou T, Weicken N, Berg L, Tichelbacker T, Puls M, et al. Impact of the learning curve on outcomes after percutaneous mitral valve repair with MitraClip and lessons learned after the first 75 consecutive patients. European journal of heart failure. 2011;13(12):1331-9.
40. Elkaryoni A, Chhatriwalla AK, Kennedy KF, Saxon JT, Cohen DJ, Arnold SV. Change in Hospitalization Rates Following Transcatheter Mitral Valve Repair: A Nationwide Cohort Sample. Circ Cardiovasc Interv. 2019;12(12):e008342.
41. Rezapour A, Azari S, Arabloo J, Pourasghari H, Behzadifar M, Alipour V, et al. Cost-effectiveness analysis of mitral valve repair with the MitraClip delivery system for patients with mitral regurgitation: a systematic review. Heart Fail Rev. 2021;26(3):587-601.
42. Capelle A, Obadia J-F, Iung B, Messika-Zeitoun D, Vahanian A, Guerin P, et al. Percutaneous mitral valve repair in severe secondary mitral regurgitation: Analysis of index hospitalization and economic evaluation based on the MITRA-FR trial. Archives of Cardiovascular Diseases. 2021;114(12):805-13.
43. Mahdjoub I, d'Acremont F, Mauduit N, Grimandi G, Rondeau F, Letocart V, et al. Is the MitraClip(R) procedure profitable in a high-volume French hospital? Arch Cardiovasc Dis. 2019;112(11):691-8.
44. Guerin P, Bourguignon S, Jamet N, Marque S. MitraClip therapy in mitral regurgitation: a Markov model for the cost-effectiveness of a new therapeutic option. J Med Econ. 2016;19(7):696-701.
45. Sakamaki H, Nakao K, Matsumoto T, Inoue S. Cost-effectiveness analysis of percutaneous mitral valve repair with the MitraClip delivery system for patients with mitral regurgitation in Japan. J Med Econ. 2019:1-9.
46. Asgar AW, Khairy P, Guertin MC, Cournoyer D, Ducharme A, Bonan R, et al. Clinical outcomes and economic impact of transcatheter mitral leaflet repair in heart failure patients. J Med Econ. 2017;20(1):82-90.
47. Armeni P, Boscolo PR, Tarricone R, Capodanno D, Maggioni AP, Grasso C, et al. Real-world cost effectiveness of MitraClip combined with Medical Therapy Versus Medical therapy alone in patients with moderate or severe mitral regurgitation. Int J Cardiol. 2016;209:153-60.
48. Palmieri V, Baldi C, Di Blasi PE, Citro R, Di Lorenzo E, Bellino E, et al. Impact of DRG billing system on health budget consumption in percutaneous treatment of mitral valve regurgitation in heart failure. J Med Econ. 2015;18(2):89-95.
49. Cohen DJ, Wang K, Magnuson E, Smith R, Petrie MC, Buch MH, et al. Cost-effectiveness of transcatheter edge-to-edge repair in secondary mitral regurgitation. Heart. 2022;108(9):717-24.
50. Willits I, Keltie K, de Belder M, Henderson R, Linker N, Patrick H, et al. Safety, effectiveness and costs of percutaneous mitral valve repair: A real-world prospective study. PLoS One. 2021;16(5):e0251463.
51. Shore J, Russell J, Frankenstein L, Candolfi P, Green M. An analysis of the cost-effectiveness of transcatheter mitral valve repair for people with secondary mitral valve regurgitation in the UK. J Med Econ. 2020;23(12):1425-34.
52. Mealing S, Feldman T, Eaton J, Singh M, Scott DA. EVEREST II high risk study based UK cost-effectiveness analysis of MitraClip(R) in patients with severe mitral regurgitation ineligible for conventional repair/replacement surgery. J Med Econ. 2013;16(11):1317-26.
53. Estler B, Rudolph V, Seleznova Y, Shukri A, Stock S, Müller D. Cost-effectiveness of the MitraClip device in German heart failure patients with secondary mitral regurgitation. The European Journal of Health Economics. 2023;24(3):349-58.
54. Baron SJ, Wang K, Arnold SV, Magnuson EA, Whisenant B, Brieke A, et al. Cost-Effectiveness of Transcatheter Mitral Valve Repair Versus Medical Therapy in Patients With Heart Failure and

Secondary Mitral Regurgitation. Circulation. 2019;140(23):1881-91.
55. Iliadis C, Lee S, Kuhr K, Metze C, Matzik AS, Michels G, et al. Functional status and quality of life after transcatheter mitral valve repair: a prospective cohort study and systematic review. Clin Res Cardiol. 2017;106(12):1005-17.
56. Munkholm-Larsen S, Wan B, Tian DH, Kearney K, Rahnavardi M, Dixen U, et al. A systematic review on the safety and efficacy of percutaneous edge-to-edge mitral valve repair with the MitraClip system for high surgical risk candidates. Heart. 2014;100(6):473-8.
57. Vakil K, Roukoz H, Sarraf M, Krishnan B, Reisman M, Levy WC, et al. Safety and efficacy of the MitraClip(R) system for severe mitral regurgitation: a systematic review. Catheter Cardiovasc Interv. 2014;84(1):129-36.
58. Philip F, Athappan G, Tuzcu EM, Svensson LG, Kapadia SR. MitraClip for severe symptomatic mitral regurgitation in patients at high surgical risk: a comprehensive systematic review. Catheter Cardiovasc Interv. 2014;84(4):581-90.
59. Khader AA, Allaf M, Lu OW, Lazopoulos G, Moscarelli M, Kendall S, et al. Does the clinical effectiveness of Mitraclip compare with surgical repair for mitral regurgitation? Journal of cardiac surgery. 2021;36(3):1103-19.
60. Kumar A, Al-Khafaji J, Shariff M, Vaz IP, Adalja D, Doshi R. Percutaneous mitral valve repair for secondary mitral valve regurgitation: A systematic review and meta-analysis. European journal of internal medicine. 2020;78:107-12.
61. Vallakati A, Hasan AK, Boudoulas KD. Transcatheter Mitral Valve Repair in Patients with Heart Failure: A Meta-Analysis. Cardiology. 2021;146(1):42-8.
62. Barros da Silva P, Sousa JP, Oliveiros B, Donato H, Costa M, Goncalves L, et al. Stroke after transcatheter edge-to-edge mitral valve repair: a systematic review and meta-analysis. EuroIntervention. 2020;15(16):1401-8.
63. Benito-González T, Estévez-Loureiro R, Villablanca PA, Armeni P, Iglesias-Gárriz I, Minguito C, et al. Percutaneous Mitral Valve Repair Vs. Stand-Alone Medical Therapy in Patients with Functional Mitral Regurgitation and Heart Failure. Cardiovascular revascularization medicine : including molecular interventions. 2020;21(1):52-60.
64. Marmagkiolis K, Hakeem A, Ebersole DG, Iliescu C, Ates I, Cilingiroglu M. Clinical outcomes of percutaneous mitral valve repair with MitraClip for the management of functional mitral regurgitation. Catheter Cardiovasc Interv. 2019;94(6):820-6.
65. Bertaina M, Galluzzo A, D'Ascenzo F, Conrotto F, Grosso Marra W, Frea S, et al. Prognostic impact of MitraClip in patients with left ventricular dysfunction and functional mitral valve regurgitation: A comprehensive meta-analysis of RCTs and adjusted observational studies. International Journal of Cardiology. 2019;290:70-6.
66. Goel S, Pasam RT, Wats K, Chava S, Gotesman J, Sharma A, et al. Mitraclip Plus Medical Therapy Versus Medical Therapy Alone for Functional Mitral Regurgitation: A Meta-Analysis. Cardiology and therapy. 2019.
67. Giannini C, D'Ascenzo F, Fiorelli F, Spontoni P, Swaans MJ, Velazquez EJ, et al. A meta-analysis of MitraClip combined with medical therapy vs. medical therapy alone for treatment of mitral regurgitation in heart failure patients. ESC Heart Fail. 2018;5(6):1150-8.
68. Takagi H, Ando T, Umemoto T, Group A. A review of comparative studies of MitraClip versus surgical repair for mitral regurgitation. Int J Cardiol. 2017;228:289-94.
69. Chiarito M, Pagnesi M, Martino EA, Pighi M, Scotti A, Biondi-Zoccai G, et al. Outcome after percutaneous edge-to-edge mitral repair for functional and degenerative mitral regurgitation: a systematic review and meta-analysis. Heart. 2018;104(4):306-12.
70. Sannino A, Smith RL, 2nd, Schiattarella GG, Trimarco B, Esposito G, Grayburn PA. Survival and Cardiovascular Outcomes of Patients With Secondary Mitral Regurgitation: A Systematic Review and Meta-analysis. JAMA Cardiol. 2017;2(10):1130-9.
71. Benito-González T, Estevez-Loureiro R, Iglesias-Garriz I, Gualis J, Pérez de Prado A, Garrote C, et al. Survival Advantage of MitraClip® Over Medical Treatment in Patients with Mitral Regurgitation: A Meta-Analysis. The Journal of heart valve disease. 2017;26:651-8.
72. Bail DH. (Meta)-analysis of safety and efficacy following edge-to-edge mitral valve repair using the

MitraClip system. Journal of interventional cardiology. 2015;28(1):69-75.
73. D'Ascenzo F, Moretti C, Marra WG, Montefusco A, Omede P, Taha S, et al. Meta-analysis of the usefulness of Mitraclip in patients with functional mitral regurgitation. The American journal of cardiology. 2015;116(2):325-31.

Abbott Vascular International BVBA

Park Lane, Culliganlaan 2B, B-1831 Diegem, Belgium, Tel: +32 2 714 14 11
All drawings are artist's representations only and should not be considered as an engineering drawing or photograph. Photo(s) on file at Abbott . Data on file at Abbott.

Abbott Sponsored Studies (EVEREST I, EVEREST II, REALISM, ACCESS-EU, COAPT™, EXPAND, and EXPAND G4)
Product is subject to prior training requirement as per the Instruction for Use. This product is intended for use by or under the direction of a physician.

Prior to use, it is important to read the package insert thoroughly for instructions for use, warnings and potential complications associated with use of this device.

Information contained herein is for distribution in Europe, Middle East and Africa ONLY.

Prior to use, reference the Instructions for Use provided inside the product carton (when available) or at eifu.abbottvascular.com for more detailed information on Indications, Contraindications, Warnings, Precautions and Adverse Events.

For MitraClip Family of products, the following needs to be considered by French healthcare professionals only:
Clip de réparation mitrale MitraClip G4. Dispositif médical de classe lll, organisme notifié BSI 2797. Fabriqué par Abbott Vascular, mandataire européen Abbott Vascular International BVBA. Se référer aux informations de la notice d'instructions qui décrivent les informations de bon usage du dispositif. Le système MitraClip G4 est conçu pour la réparation de la valve mitrale par rapprochement des tissus en cas d'insuffisance mitrale.
Pris en charge par l'assurance maladie. Indication de prise en charge :
Patients avec insuffisance mitrale sévère d'origine dégénérative, symptomatique malgré une prise en charge médicale optimale, non éligibles à la chirurgie de réparation ou de remplacement valvulaire et répondant aux critères échocardiographiques d'éligibilité. Patients avec une insuffisance mitrale secondaire de grade 3+/4+ symptomatique malgré une prise en charge médicale optimale et remplissant les critères suivants :
• non éligibles à la chirurgie de réparation ou de remplacement valvulaire, • ayant eu une hospitalisation pour insuffisance cardiaque dans les 12 mois précédant l'intervention,
• ayant une fraction d'éjection ventriculaire gauche comprise entre 20 et 50%,
• et une surface de l'orifice régurgitant > 0,3 cm2 et un volume télédiastolique indexé du ventricule gauche ≤ 96 mL/m2.
Les patients ayant un ventricule gauche fortement dilaté (défini par un volume télédiastolique indexé du ventricule gauche > 96 mL/m2) et une insuffisance mitrale modérée ou moindre, démontré par un orifice régurgitant de la valve mitrale ≤ 0,3 cm2, ne sont pas éligibles à la technique (non indication). Les critères cliniques et échocardiographiques doivent être validés par une équipe multidisciplinaire ad hoc. Les patients ayant une espérance de vie inférieure à 1 an compte tenu de comorbidités extracardiaques ne sont pas éligibles à la technique (non- indication).
Code LPPR: 3128048 (MitraClip G4 NT), code LPPR 3191785 (MitraClip G4 NTW), code LPPR 3172820 (MitraClip G4 XT), code LPPR 3111421 (MitraClip G4 XTW)

™ Indicates a trademark of the Abbott Group of Companies.
For more information, visit our website at www.structuralheart.abbott.