MitraClip™
EMEA VALUE DOSSIER
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ABBREVIATIONS

6MWT	Six-minute walk test	**LVEDD**	Left ventricular end diastolic diameter
ACC	American College of Cardiology	**LVEDV**	Left ventricular end-diastolic volume
AE	Adverse event	**LVEF**	Left ventricular ejection fraction
AF	Atrial fibrillation	**LVESD**	Left ventricular end-systolic diameter
AHA	American Heart Association	**LVESV**	Left ventricular end-systolic volume
AVSS	Abbott-sponsored study	**MACCE**	Major adverse cardiovascular and cerebrovascular event
BMI	Body mass index	**MDT**	Multidisciplinary team
CABG	Coronary artery bypass grafting	**MR**	Mitral regurgitation
CEC	Clinical Event Committee	**MV**	Mitral valve
CGA	Controlled Gripper Actuation	**NA**	Not applicable
CI	Confidence interval	**NHS**	National Health Service
CMR	Cardiovascular magnetic resonance	**NNT**	Number needed to treat
CRT	Cardiac resynchronisation therapy	**NYHA**	New York Heart Association
CT	Computed tomography	**OMT**	Optimal medical therapy
EACTS	European Association for Cardio-Thoracic Surgery	**OR**	Odds ratio
EACVI	European Association of Cardiovascular Imaging	**PMR**	Primary mitral regurgitation
EAPCI	European Association of Percutaneous Cardiovascular Interventions	**QALY**	Quality-adjusted life year
EHRA	European Heart Rhythm Association	**QoL**	Quality of life
EQ-5D	EuroQol-5 dimensions	**RCT**	Randomised controlled trial
EROA	Effective regurgitant orifice area	**RV**	Right ventricle
ESC	European Society of Cardiology	**SD**	Standard deviation
EuroSCORE	European System for Cardiac Operative Risk Evaluation	**SE**	Standard error
FDA	US Food and Drug Administration	**SF-12/-36**	12-/36-Item Short Form Survey
GDMT	Guideline-directed medical therapy	**SGC**	Steerable guide catheter
HF	Heart failure	**SMR**	Secondary mitral regurgitation
HFA	Heart failure association	**TAVI**	Transcatheter aortic valve implantation
HFrEF	Heart failure with reduced ejection fraction	**TEE**	Transoesophageal echocardiography
HR	Hazard ratio	**TEER**	Transcatheter edge-to-edge repair
ICER	Incremental cost-effectiveness ratio	**TMVr**	Transcatheter mitral valve repair
ISS	Investigator-sponsored study	**TMVR**	Transcatheter mitral valve replacement
KCCQ	Kansas City Cardiomyopathy Questionnaire	**TPY**	Total patient-years
LA	Left atrium	**TR**	Tricuspid regurgitation
LV	Left ventricle	**TTE**	Transthoracic echocardiography
LVAD	Left ventricular assist device		

- Mitral regurgitation (MR) occurs when the mitral valve leaflets fail to properly close during ventricular contraction (systole) so blood flows back into the left atrium, leading to inefficient pumping of blood around the body.[1, 2] MR can be classified into two main types, either primary (e.g., degenerative) mitral regurgitation (PMR), or secondary (functional) mitral regurgitation (SMR).[1]
- MR increases in prevalence with advancing age.[3] Approximately 10% of people over the age of 70 have clinically meaningful MR.[4]
- MR is associated with a substantial physical, emotional, and social burden to patients.[5] Severe symptoms may make everyday tasks and simple activities, such as getting out of bed, very difficult.
- If left untreated, MR can lead to heart failure (HF), or deterioration of pre-existing HF, resulting in an increased number of hospital admissions and a substantial cost burden to health systems (in 2020, the global cost of HF was estimated to be 346.17 billion USD annually and increasing).[6, 7,8, 9-13]
- Treatment options for MR include medical management, surgical repair or replacement, and transcatheter mitral valve repair (TMVr), or replacement (TMVR).
- MitraClip™ System is a first-in-class transcatheter edge-to-edge repair (TEER) solution with proven durable outcomes up to 5 years.[14, 15]
- MitraClip™ System is a proven technology with over 20 years of clinical experience, and 200,000+ patients treated in more than 75 countries. With an evidence base that includes the largest real-world dataset,[a] more than 3,200 scientific papers pertaining to MitraClip™ have been published and over 80,000 patients have been treated with the device in clinical trials. (Abbott data on file)
- MitraClip™ System received its first CE mark approval in 2008.[17] The latest generation device, MitraClip™ G4, was CE-marked in 2020[18] and was also approved under the Medical Device Regulation (MDR) in 2022 (CE British Standards Institution 2797) and features:
    - 4 clip sizes
    - Controlled Gripper Actuation to facilitate grasping of leaflets either simultaneously or independently
    - Left Atrial Pressure Steerable Guide Catheter facilitating continuous monitoring of left atrial pressure during the procedure.
- MitraClip™ is the only TEER device named in the latest international guidelines for the management of valvular heart disease (ESC/EACTS 2021):[19]
    - In PMR, TEER may be considered in symptomatic patients who fulfil the echocardiographic criteria of eligibility, are judged inoperable or at high surgical risk by the Heart Team and for whom the procedure is not considered futile (IIb B).
    - In SMR, TEER should be considered in selected symptomatic patients, not eligible for surgery and fulfilling criteria suggesting an increased chance of responding to the treatment (IIa B).
- The efficacy and safety of MitraClip™ Therapy has been extensively evaluated across randomised controlled trials (RCTs) spanning 5 years follow-up, national registries, and real-world studies.
- In 2018, two RCTs, COAPT™[20, 21] and MITRA-FR,[22, 23] published their results. Both studies compared MitraClip™ + guideline-directed medical therapy (GDMT) versus GDMT alone in patients with SMR.
- In COAPT™, 5 year outcomes showed that MitraClip™ + GDMT was safe, reduced the rate of HF hospitalisation, improved NYHA status, provided durable repair, and improved survival compared with GDMT alone.[15]
- EXPANDed is a pooled, patient level cohort combining EXPAND and EXPAND G4, and represents the largest core lab-assessed dataset from 2,000+ patients with MR. Of the 1,847 patients with echocardiographic data, 90% had MR severity ≤1+ at 30 days, with significant improvements in NYHA class and QoL.[16]
- MitraClip™ Therapy is associated with:
    - High acute procedural success rates (MR grade ≤2+)[20, 22, 24-27]
    - Low 30-day mortality and adverse event rates[20, 22, 24, 26-28]
    - Reduced long-term (up to 5 years) mortality versus medical therapy in patients with SMR[15, 20-23]
    - Significant and sustained reduction in MR severity for up to 5 years[14, 15, 20-22, 24-28]
    - Significant and sustained improvement in New York Heart Association (NYHA) functional status for up to 5 years[14, 15, 20-22, 24-27]
    - Improved quality of life (QoL)[20, 21, 29]
    - Positive impact on left ventricle remodelling[14, 20, 25, 28]

[a] EXPANDed is the largest real-world patient cohort (n=2,205) with echo-core lab-assessed outcomes to date.[16]

  - Reduction in HF hospitalisations in patients with PMR and SMR for up to 5 years[15, 25, 30]
  - Effective treatment of complex MV anatomies[25]
- MitraClip™ is likely to be cost-effective/cost-neutral over a 1–10-year period according to several studies due to improved clinical outcomes, QoL, and survival combined with reduced HF rehospitalisations and AE management costs.[31-40]
- Potential cost savings associated with the use of MitraClip™ can be attributed to the fact that:
  - The procedure is safe, effective, and achieves immediate MR reduction
  - The procedure is associated with minimised time spent under general anaesthesia, in the operating room, and in the ICU and general hospital ward, improving hospital capacity and resource use
  - Is associated with a rapid recovery with few (if any) complications, and most patients can be discharged directly home following the procedure, as opposed to a rehabilitation centre
  - The procedure results in improved patient functional status, meaning patients regain their independence, can resume daily activities, and are less reliant on caregivers (who may then return to work)
  - The procedure is associated with reduced risk of HF rehospitalisation and MV-related retreatment, minimising the costs associated with these.
- Abbott has developed an ambitious 2030 Sustainability Plan focusing on responsible data protection and management, building a diverse and innovative workforce, creating a resilient and responsible supply chain, and protecting the environment.

- **Mitral regurgitation (MR) occurs when the mitral valve leaflets fail to properly close during ventricular contraction (systole),[1, 2] and may be classified as either primary or secondary.[1]**
- **MR increases in prevalence with advancing age.[3] Approximately 10% of people over the age of 70 have clinically meaningful MR.[4] The relative prevalence of PMR versus SMR differs depending on the patient population investigated but SMR is generally more prevalent due to the growing HF population.[41-44]**
- **The severity of MR is graded from mild (grade 1) to severe (grade 4), usually determined by echocardiography.[45] There is a direct relationship between SMR severity and mortality, 1-year mortality rates range from 45–57% in patients with moderate to severe MR (grade 3+/grade 4+).[46]**
- **MR is associated with a substantial physical, emotional, and social burden to patients.[5] Severe symptoms may make everyday tasks and simple activities, such as getting out of bed, very difficult.**
- **If left untreated, MR can lead to heart failure (HF), or deterioration of pre-existing HF, resulting in an increased number of hospital admissions, increased deaths, and a substantial cost burden to health systems.[6, 7, 47] A 2020 study estimated the global overall economic cost of HF amounted to 346.17 billion USD annually,[8] and the economic burden of MR and HF is increasing.[9-13]**

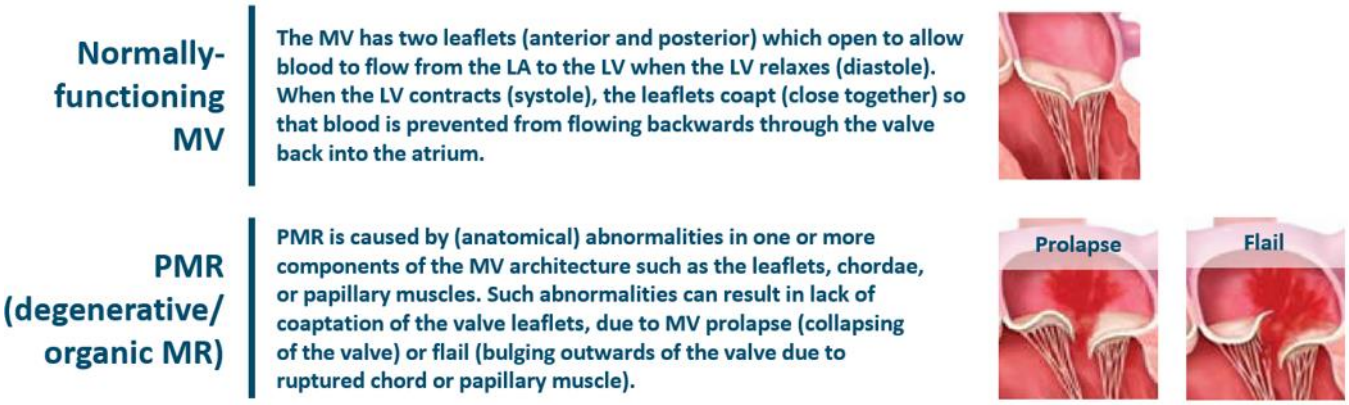
1.1 DISEASE DESCRIPTION – MITRAL REGURGITATION (MR)

- The mitral valve is located between the left atrium and left ventricle and maintains the blood flow in a single direction through the heart, so it is pumped forward out to the rest of the body.[2]
- MR, also known as mitral insufficiency or incompetence, occurs when the mitral valve no longer performs its function adequately, and backflow of blood from the left ventricle into the left atrium occurs.[1]
- As a consequence of MR, the heart is less able to efficiently pump blood around the body and, when the condition is severe, the patient experiences symptoms as a result of the backflow of blood, including shortness of breath, fatigue, light-headedness, palpitations, cough, excessive urination, and lower extremity swelling.[2, 48, 49]
- MR is a progressive disease, and patients may remain asymptomatic even when the condition has become severe, as compensatory mechanisms develop.[50] Often, patients are referred for treatment at a late stage of disease (particularly those with PMR).[23]
- Severe MR progression has an unfavourable prognosis leading to left ventricle failure, pulmonary hypertension, AF, stroke, and death.[1] If left untreated, severe MR can lead to an increase in the symptoms of HF which is associated with reduced survival.[6]
- The severity of MR is graded from mild (grade 1) to severe (grade 4) and is usually determined by echocardiography.[45] MR grading is demanding and quantifications require a multiparametric approach.[19, 51-53]
- MR may be acute (leaflet perforation, chordal rupture of the papillary muscle due to myocardial infarction) or chronic (long-term disorder associated with valvular or ventricular pathology) and according to aetiology may be classified as either primary (e.g. degenerative) mitral regurgitation (PMR), or secondary (functional) mitral regurgitation (SMR).[1]

1.1.1 PRIMARY MITRAL REGURGITATION (PMR)

- Primary mitral regurgitation (PMR) (e.g. degenerative or organic) is caused by abnormalities in one or more components of the mitral valve architecture, such as the leaflets, chordae, or papillary muscles.[54, 55]

Figure 1. The normal mitral valve and the mitral valve with PMR

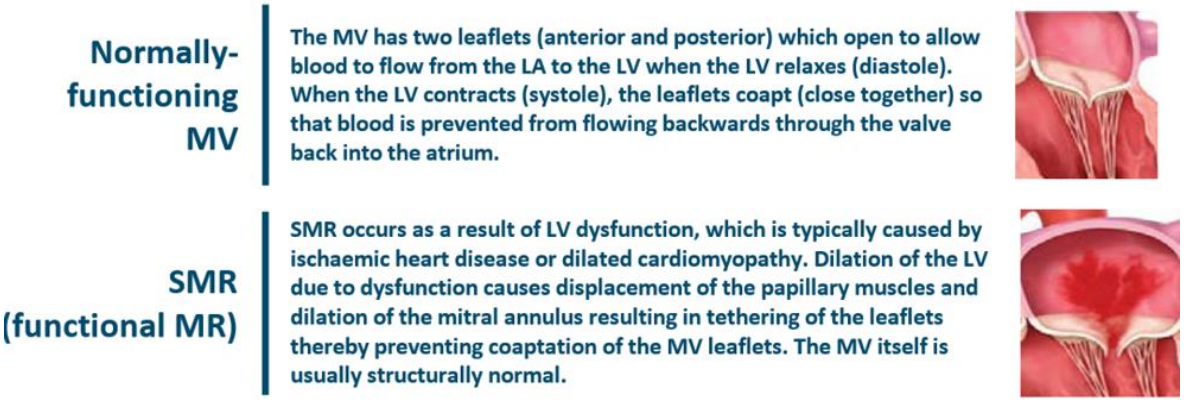


Abbreviations: LA, left atrium; LV, left ventricle; MR, mitral regurgitation; MV, mitral valve; PMR, primary mitral regurgitation.
Source: Sharma 2015[54] and McCarthy 2023.[55]

1.1.2 SECONDARY MITRAL REGURGITATION (SMR)

- Secondary mitral regurgitation (SMR), also referred to as functional mitral regurgitation occurs as a result of left ventricle dysfunction, which is typically caused by ischaemic heart disease or dilated cardiomyopathy.[54, 55]
- SMR is a dynamic condition, and its severity may vary depending on changes in loading conditions, including those arising from hypertension, medical therapy, or exercise.[56]

Figure 2. The normal mitral valve and the mitral valve with SMR



Abbreviations: LA, left atrium; LV, left ventricle; MR, mitral regurgitation; MV, mitral valve; SMR, secondary mitral regurgitation.
Source: Sharma 2015[54] and McCarthy 2023.[55]

1.1.2.1 HEART FAILURE (HF) WITHIN THE CONTEXT OF SMR

- SMR is commonly seen in patients with heart failure (HF) with reduced ejection fraction (HFrEF) and is a poor prognostic marker.[57]
- HF occurs when the heart muscle fails to pump blood efficiently. Certain conditions, such as narrowed arteries in the heart (coronary artery disease) or high blood pressure, gradually result in a heart that is weak (has poor contractility), and/or stiff (has difficulty relaxing), leading to inefficiency in filling and pumping blood to the body.
- Identification of the cardiac disease underlying HF is crucial for determining the most appropriate intervention (e.g., valve repair or replacement, specific pharmacological therapy for HF with reduced left ventricular ejection fraction [LVEF], reduction of heart rate in tachycardiomyopathy).[56]
- HF signs and symptoms are often non-specific, which can result in delayed diagnosis. They may include shortness of breath (dyspnoea), fatigue and weakness, swelling (oedema) in the legs, ankles, and feet, rapid or irregular heartbeat, reduced ability to exercise, persistent cough or wheezing with white or pink blood-tinged phlegm, increased need to urinate at night, swelling of the abdomen (ascites), rapid weight gain from fluid retention, lack of appetite and nausea, difficulty concentrating or decreased alertness, sudden severe shortness of breath, coughing up pink foamy mucus, and chest pain.[58]

Table 1. Origins of heart failure

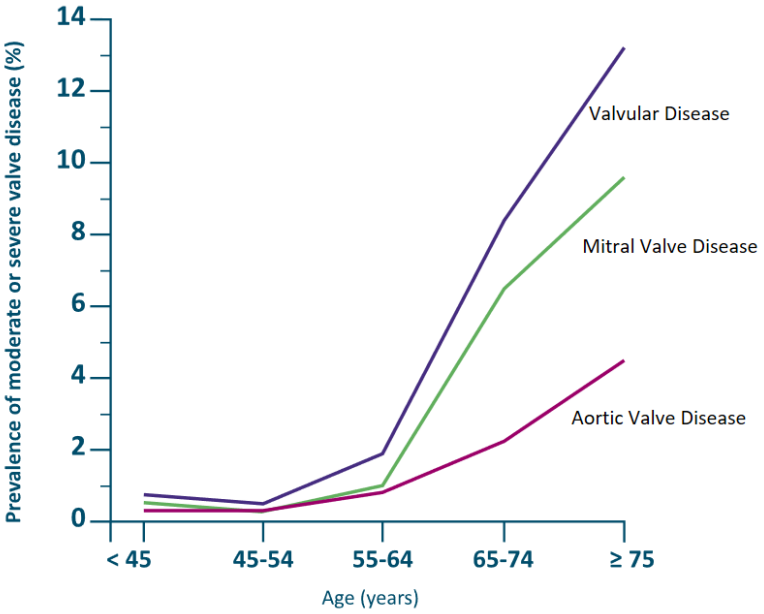
ISCHAEMIC ORIGIN	• HF of ischaemic origins is the most common aetiology. In an analysis of 24 multicentre HF trials, enrolling 43,568 HF patients, 62% of patients had an ischaemic aetiology.[59]
NON-ISCHAEMIC ORIGIN	• The causes and pathophysiological mechanisms in non-ischaemic HF are unknown or less well-defined than in HF of ischaemic origin.[60] • In non-ischaemic HF, a history of hypertension, diabetes and excessive alcohol intake may be present. Other identifiable causes of cardiomyopathy are hyperthyroidism, malnutrition, or cytotoxic drugs. In idiopathic dilated cardiomyopathy, up to 20% of patients may have a familial disease.[60]
HYPERTROPHIC CARDIOMYOPATHY	• Hypertrophic cardiomyopathy is also a prominent cause of HF. Profiles of advanced HF in hypertrophic cardiomyopathy are due to diverse pathophysiological mechanisms, including left ventricle outflow obstruction and diastolic or global systolic ventricular dysfunction. AF is the most common disease variable associated with progressive HF.[61]
OTHER	• HF may also be caused or exacerbated by other conditions, such as coronary artery disease, tissue damage (myocardial infarction with segmental loss of contraction), stress-induced ischaemia, myocardial hibernation or stunning, silent ischaemia in diabetic patients, or the development of AF.[62] Such conditions usually lead to ventricular remodelling resulting in geometric distortion and decreased contractile performance.

Abbreviations: AF, Atrial fibrillation; HF, heart failure.

1.2 EPIDEMIOLOGY OF MITRAL REGURGITATION

- MR accounts for the vast majority of all mitral valve diseases.[63] It has a prevalence of approximately 2% in the general population and is more common in the elderly population.[64, 65]
- Clinically meaningful MR (moderate or greater in severity) is present in <1% of people younger than 50 years but is found in nearly 1 in 10 people aged >75 years.[65]

Figure 3. Prevalence of valvular heart disease by age



Source: Nkomo 2006.[65]
Pooled data for 11,911 adults from several population-based studies

- The relative prevalence of PMR versus SMR differs depending on the patient population investigated.
  - In a US cohort study that enrolled 1,294 patients diagnosed with moderate or severe MR between 2000 and 2010, 44% of patients had PMR and 56% of patients had SMR.[41]
  - In a 2018 study that enrolled patients with moderate to severe or severe MR who underwent transthoracic echocardiography between 2011 and 2016 at a US tertiary medical centre (N=412), 40% had PMR and 60% had SMR.[42]
  - In a 2018 population-based study that enrolled all patients (N=63,463) across 19 European centres with a record of an echocardiogram during a 3-month period, 15,501 patients (24%) were found to have MR (any severity). Of patients with moderate or severe MR (N=3,309), 55% had PMR, 30% had SMR, and 14% had mixed forms.[43]
  - In a 2016 prospective analysis of 39,855 consecutive echocardiographic examinations performed at nine tertiary hospitals in Spain, MR was found to be present in 22% of cases. Of those found to have MR, 82.5% had mild MR, 11.7% had moderate MR, and 5.8% had severe MR. Among those with moderate and severe MR, PMR was more frequent than SMR (58.8% versus 23.5%). A third group of patients (17.8%) had mixed forms of MR.[44]
  - In a cohort of 4,009 subjects aged 65 years or older registered to a series of family medicine practices in England, 98 (2.4%) were found, upon clinical and echocardiographic assessment, to have MR. Of these, 83% had PMR and 17% had SMR.[64]
- The absolute prevalence of PMR has increased significantly over the past 20 years (by 70% between 1990 and 2017), driven by population aging, availability of imaging techniques and accessibility to diagnosis and treatment, and improvements in treatment meaning more patients with PMR remain alive for longer.[66]

1.3 COMORBIDITIES OF MITRAL REGURGITATION

- In general, morbidity and the proportion of people with multi-morbidity increases substantially with age.[3]
- Patients with MR often have at least one comorbidity[67, 68] which may influence the treatment that a patient can receive based on their risk-benefit profile (see Chapter 2).
- MR is not only highly prevalent in the older patient population, but it also appears more often in patients with certain comorbidities.

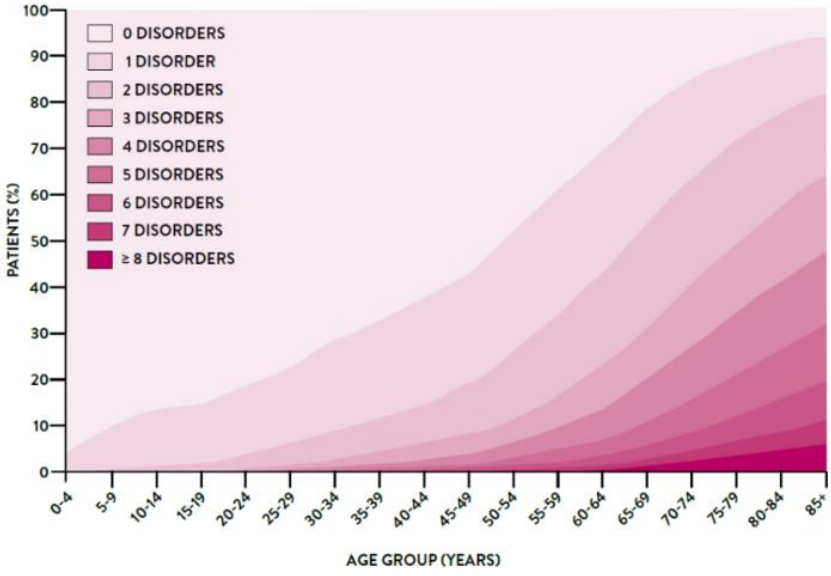
Table 2. Cardiac and non-cardiac comorbidities

CARDIAC COMORBIDITIES	• **Heart failure (HF):** Studies show that MR is detected in 70–80% of acute HF patients.[69-73]
	  ○ The prevalence of HF depends on the definition applied but is approximately 1–2% of the adult population in developed countries, increasing to >10% among people over 70 years of age.[56, 74]
	  ○ HF is one of the few heart conditions with an increasing prevalence, most likely due to improved survival following myocardial infarction and other chronic conditions, combined with an aging population and lifestyle factors.[75]
	• **Left ventricle systolic dysfunction (LVSD):** Up to 56.2% of patients with LVSD have MR.[76]
	• **Atrial fibrillation** occurs as a result of increased left atrial pressure associated with the backflow of blood in MR.[6, 77]
	• **Severe tricuspid regurgitation** is concomitant in up to 50% of patients with severe MR.[78]
	• **Ischaemic heart disease, history of myocardial infarction, and cardiomyopathy** are all a cause of SMR.[2, 68, 77, 79]

NON-CARDIAC COMORBIDITIES	• **Pulmonary hypertension** resulting from increased pressure in the pulmonary vasculature.[49] • **Renal dysfunction** along with its treatment, haemodialysis, may cause mechanical stress on the valves of the heart due to mitral annular calcification.[80] • **Chronic obstructive pulmonary disease** where chronic inflammation of the airways results in decreased tolerance to MR symptoms.[67, 77] • **Vasculopathy** where atherosclerosis of the peripheral or cerebral circulation increases the risk of stroke or embolic phenomenon.[81] • **Advanced stage malignancy** decreases life expectancy of the patient and immunosuppressive treatment a patient may undergo for this may increase the patient's risk potential for complications if treated for MR.[81]

Abbreviations: AF, atrial fibrillation; MR, mitral regurgitation; SMR, secondary mitral regurgitation.

Figure 4. Number of chronic disorders by age group

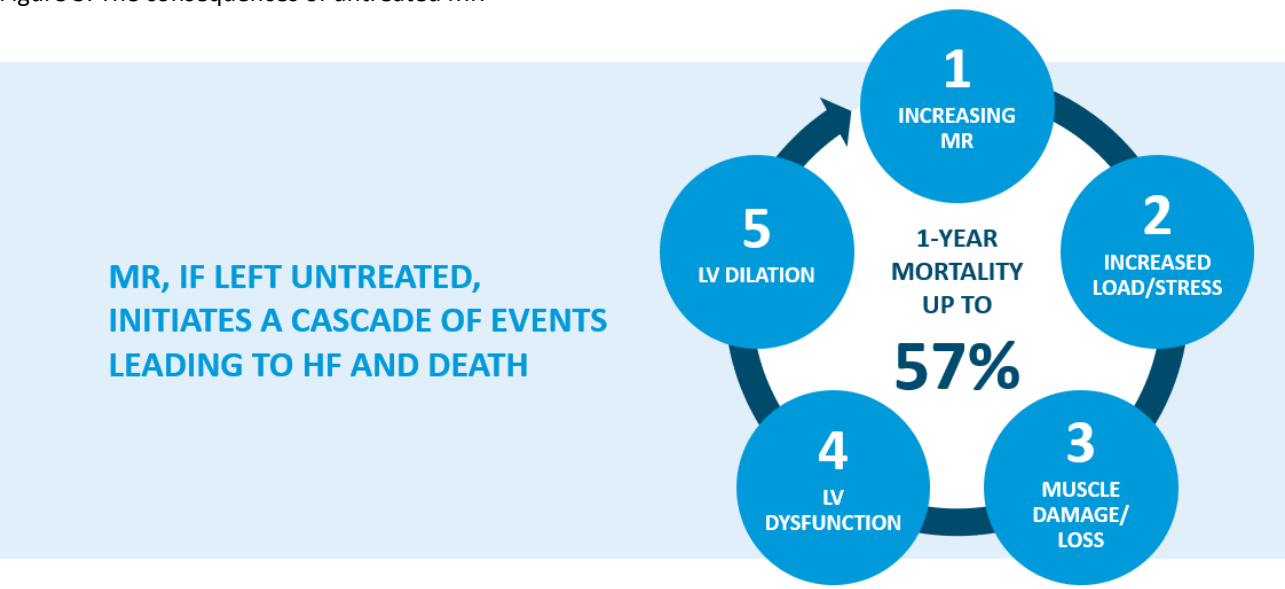


Source: Barnett 2012.[3]

1.4 MORTALITY ASSOCIATED WITH MITRAL REGURGITATION

- The risk of mortality is high if severe MR is left untreated; 1-year and 5-year mortality rates of 20% and 50% have been reported, respectively.[82]
- In a cohort of MR patients in France (N=107,412) who required hospitalisation between 2014 and 2015 and who were subsequently conservatively managed (i.e., did not undergo surgery), in-hospital and 1-year mortality rates were 4.1% and 14.3%, respectively.[83]
- MR is an independent predictor of all-cause 1-year death amongst patients with chronic HF[84] and an independent predictor of mortality in patients undergoing transcatheter aortic valve implantation (TAVI).[85]
- There is a direct relationship between SMR severity and mortality; 1-year mortality rates range from 45–57% in patients with moderate to severe MR (grade 3+/grade 4+).[46]
    - Severity of MR post-myocardial infarction correlates with worse outcomes; moderate or severe MR is associated with a 3.44 times greater risk of HF (p<0.001) and a 1.55 times greater risk of death (p=0.019) compared with no MR.[86]
    - The severity of MR among patients with ischaemic heart disease correlates with higher risk of cardiac mortality and total mortality (both p<0.001).[87]
    - Compared with healthy people of the same age and sex, patients with moderate SMR and patients with severe SMR have significantly increased rates of excess mortality (hazard ratio [HR]: 5.08; 95% confidence interval [CI]: 4.78–5.40; p<0.001 for moderate SMR, and HR: 7.53; 95% CI: 6.83–8.30; p<0.001 for severe SMR).[47]
- Patients with HF and SMR have a higher mortality rate than HF patients without SMR (7-year survival for patients with no SMR, mild-moderate SMR or severe SMR have been reported as 40%, 25%, and 7%, respectively).[88]
    - SMR is associated with an increased risk of all-cause mortality compared with patients without SMR (risk ratio 1.79; 95% CI: 1.47–2.18; p<0.001), as well as with an increased risk of cardiac mortality (risk ratio 2.62; 95% CI: 1.87–3.69; p<0.001).[89]
    - In a 2021 observational cohort study enrolling 13,223 patients with SMR across all HF subtypes, when compared with patients with HF with no/mild SMR, there was a stepwise increase in mortality risk for patients dependent on the severity of SMR, with an unadjusted HR of 1.29 (95% CI: 1.20–1.38; p<0.001) for moderate and SMR and 1.82 (95% CI: 1.64–2.02; p<0.001) for severe SMR.[47]

Figure 5. The consequences of untreated MR



Abbreviations: HF, heart failure; LV, left ventricle; MR, mitral regurgitation.
Sources: Cioffi 2005,[46] Enriquez-Sarano 2005,[90] Grigioni 2008.[91]
The 1-year mortality rate of 57% was recorded in a subgroup of patients with MR grade 4+.[46]

1.5 BURDEN TO PATIENTS OF MITRAL REGURGITATION

- MR confers a substantial physical, emotional, and social burden to patients.[5] Severe symptoms may make everyday tasks and simple activities, such as getting out of bed, very difficult.
- The inability to perform simple tasks can lead to feelings of loss of independence, distress, and depression. Patients feel like a burden to their family and worry about the future. Patients may need to make modifications to their house in order to cope with the condition, for example installing stair lifts or rails.
- The results of a survey of 419 patients with HF and SMR highlight the disease burden felt by patients. A quarter of patients indicated they were willing to undergo implantation of a transcatheter mitral valve repair (TMVr) device despite the risk of mortality or serious bleeding if it meant they would experience an improvement in physical functioning. Respondents indicated they would accept up to a 9.7% increase in risk of 30-day mortality with a TMVr device that could improve functioning from New York Heart Association (NYHA) class IV to III, or up to 2.0% for an improvement from NYHA class III to II.[92]
- Predictors of poor patient outcomes in PMR include:[93]
    - Advanced age
    - Atrial fibrillation (AF)
    - Symptoms of cardiac HF
    - Poor exercise capacity
    - Elevated brain natriuretic peptide (BNP)
    - Low ejection fraction (<60%)
    - Effective regurgitant orifice area (EROA) (>40mm^2)
    - Left atrial volume
    - Pulmonary hypertension
    - Abnormal left ventricle strain
- HF, an endpoint of progressed MR, is also associated with a substantial burden to patients, and despite new therapies becoming available in many countries, HF remains common with an unfavourable prognosis.[75]
    - Once a patient with HF becomes symptomatic, regardless of the aetiology of their HF, they have a worse QoL (physical, functional, and emotional) versus the general population, people without HF, and people with other chronic diseases including AF, angina, hypertension, and prior myocardial infarction (MI).[94, 95]
    - Severe HF symptoms may limit patient's daily physical and social activities; resulting in poor QoL. The inability to perform simple tasks may also lead to emotional distress and depression, and patients may feel like a burden to their family because of their physical symptoms.[96]

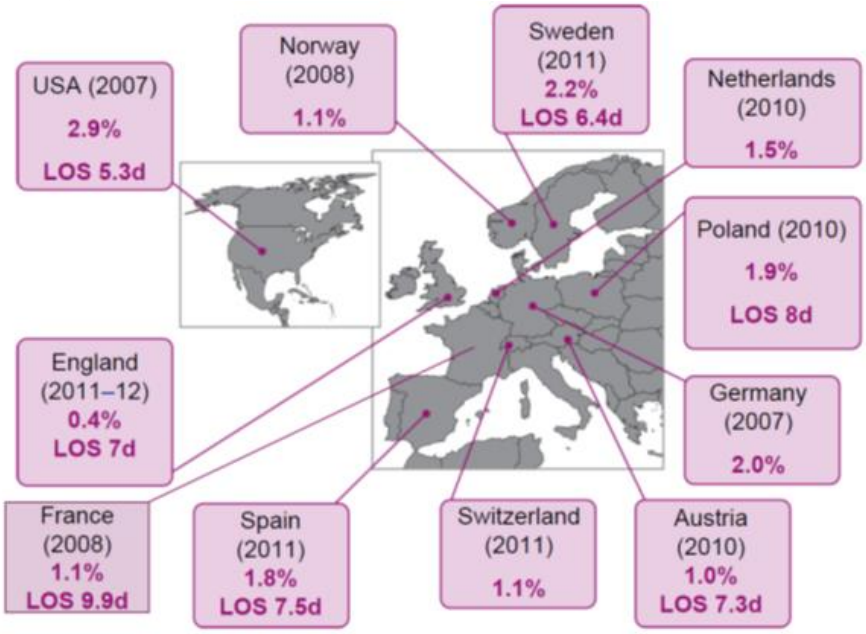
1.6 ECONOMIC BURDEN OF MITRAL REGURGITATION

- Results from a number of studies demonstrate that the economic burden of MR is increasing:
  - In a 2020 study of 107,412 MR patients in France who were admitted to hospital between 2014 and 2015 and were subsequently conservatively managed, readmission rates were high: 63% at least once and 37% at least twice. The mean costs of hospital admissions and of readmissions were €5,345 and €10,080, respectively.[83]
  - In a 2019 US study, medically managed HF patients with SMR had significantly more hospital days (1.91 versus 1.72; p=0.0096), greater annual expenditures (USD: 23,988 versus 21,530; p<0.0001), and an estimated 50% greater HF admissions rate (0.036 versus 0.024; p<0.0001) than HF patients without SMR.[97]
  - In 2015, the annual per patient costs for the treatment of MR in France were estimated at €24,871 (± 13,940) for patients receiving mitral valve surgery, and €12,177 (± 10,913) for patients receiving non-surgical management. The overall budget impact for the French healthcare system in 2009/2010 was €192 million for non-surgically treated MR patients and €100.8 million for MR patients receiving surgical treatment.[98]
  - A study conducted in the USA reported an increase in the number of hospitalisations due to valvular heart disease between 1983 and 2000, with a 1.5-fold greater increase of patients with mitral valve disease versus aortic valve disease (p<0.001).[9]

1.6.1 ECONOMIC BURDEN OF HF

- MR is often associated with HF, which presents a substantial cost burden for health systems. Up to 80% of patients hospitalised with HF have MR.[69, 70]
- A primary diagnosis of HF generally accounts for 1–3% of all hospital admissions globally (Figure 6), and 5% of all emergency hospital admissions in Europe and the USA are due to acute heart failure.[99, 100] In 2018 in Europe, HF was the leading cause of hospitalisation among people aged over 65 years.[101]

Figure 6. HF hospitalisation rates in Europe and the USA



Abbreviations: d, days; HF, heart failure; LOS, length of stay.
Percentages represent HF hospitalisations as a proportion of all hospitalisations.
Adapted from Cowie 2014.[99]

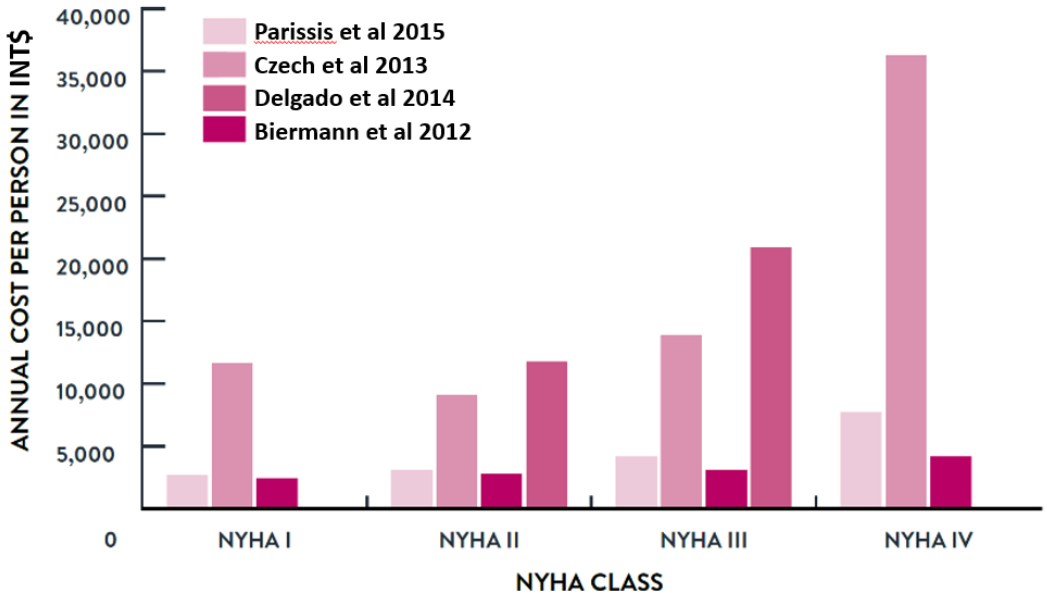
- The global overall economic cost of HF annually was 346.17 billion USD (2020 data).8
    - Direct costs comprise 60% of the economic burden of HF with increasing (re)hospitalisation being the predominant driver of cost; indirect costs include lost productivity and informal caregiving.[102]
    - Studies in Greece, Poland, Spain, and Germany show that patients with HF and a high NYHA functional class require greater levels of care and resource use which has a direct impact on per patient costs.[103-106]

Table 3. Direct and indirect costs of HF

DIRECT COSTS	Direct costs are responsible for 60% of the economic burden of HF with increasing (re-)hospitalisations being the main cost driver:[102] • **Germany:** between 2000 and 2013, the absolute number of HF-related hospitalisations increased by 65.4%.[10] • **Netherlands:** between 2000 and 2012, the absolute number of cardiovascular hospitalisations increased by 43%.[11] • **Spain:** between 2003 and 2011, the number of admissions for HF in patients aged >65 years increased by 26%.[12] • **Italy:** between 2001 and 2003, the number of HF-related hospitalisations increased by 8.6%.[13]
INDIRECT COSTS	• 40% of the economic burden of HF globally is caused by indirect costs such as lost productivity and informal caregiving.[102] • In 2010, the estimated annual informal caregiving cost in the US attributable to HF was $3 billion.[107]

Abbreviations: HF, heart failure.

Figure 7. Cost of HF by NYHA class



Abbreviations: HF, heart failure; Int$, international dollars; NYHA, New York Heart Association.
Source: Shafie 2018. [108]
Costs reported in the original studies were converted to 2014 international dollars (Int$).

- **Echocardiography is the basis for diagnosing valvular heart disease (VHD), including MR.[19] Following diagnosis, and guideline-directed medical treatment (GDMT) optimisation, early referral of patients with moderate or severe MR to a multidisciplinary heart team is recommended.[56]**
- **The best treatment approach for a given patient and their condition (whether it be PMR or SMR) is determined by a multidiscipliary heart team.[19] Treatment options include medical management, surgical mitral valve repair or replacement, or transcatheter mitral valve repair (TMVr) or replacement (TMVR):**
  - **Medical management:**
    - **GDMT may reduce the symptoms of MR, but does not directly address the underlying pathology/valvular dysfunction.[109]**
  - **Surgical treatment:**
    - **PMR: Surgery is the standard of care for PMR with evidence of LV dysfunction or dilation.[6, 19, 110] Surgery can provide substantial benefits for patients with PMR;[111] however, up to 50% of patients may not meet the eligibility criteria due to risks associated with age or the presence of comorbidities.[67]**
    - **SMR: Mitral valve surgery can acutely correct SMR, but has never clearly been demonstrated to alter the natural history of the primary disease or improve survival.[112]**
  - **Transcatheter edge-to-edge repair (TEER) is a minimally invasive TMVr option:**
    - **PMR: TEER may be considered in symptomatic patients who fulfil the echocardiographic criteria of eligibility, are judged inoperable or at high surgical risk by the Heart Team and for whom the procedure is not considered futile (IIb B).[19]**
    - **SMR: TEER with the MitraClip™ System is the best evidenced therapy in this indication. TEER should be considered in selected symptomatic patients, not eligible for surgery and fulfilling criteria suggesting an increased chance of responding to the treatment (IIa).[19]**
  - **Transcatheter mitral valve replacement (TMVR):**
    - **PMR: TMVR is an option in patients with severe PMR where leaflet pathology is limited to less than half the posterior leaflet and where TMVr has been attempted but was unsuccesful (3: B-NR)[110]**
    - **SMR: In patients with severe SMR undergoing MV surgery because of severe symptoms, chordal-sparing TMVR may be performed instead of downsized annuloplasty repair (2b; B-R)[110]**

2.1 DIAGNOSIS OF MITRAL REGURGITATION

- The diagnostic pathway of MR has changed over the past few years to align with new treatment options available with regard to transcatheter interventions. Besides evaluating clinical symptoms like nausea and fatigue, auscultation of the heart is key to diagnosing MR and a detailed pre-operative characterisation of the mitral valve is key to procedural success.[51]

Table 4. Mitral regurgitation diagnostic tools

ECHOCARDIOGRAPHY	Echocardiography is the basis for the diagnosis of valve diseases, including MR.[19] By visualising the central anatomic structures of the valve, it is possible to understand the pathology and the level of severity.[51] • **Transthoracic echocardiography (TTE) and transoesophageal echocardiography (TEE):** are tools which measure the severity of regurgitation by characterising the anatomy of the valve and its morphology (functional/secondary or primary/degenerative). Both are recommended by the ESC as a basic diagnostic tool for quantifying MR.[19] • **Stress-echocardiography:** As MR is a dynamic disease, diagnostics performed while the patient is in a resting state may underestimate the severity of the disease. Hence, stress-echocardiography is of value especially for patients in which symptoms do not correlate with the severity level of MR, helping to quantify the severity of the disease and to plan an intervention accordingly.[52] • **Handgrip-exercise echocardiography:** serves as a valuable tool to unmask dynamic MR.[53]

CARDIAC MAGNETIC RESONANCE	• **Cardiac magnetic resonance (CMR)** is a valuable diagnostic tool, especially in patients with limited echo quality, those whose MR severity is unclear, or those who require an evaluation of the myocardial anchoring of the atrioventricular valves.[51] • In patients with primary MR, CMR is indicated to assess left ventricle and right ventricle volumes and function and may help with assessing MR severity when there is a discrepancy between the findings on clinical assessment and echocardiography[110] • When echocardiographic parameters used to grade MR are inconsistent, CMR is a valid alternative to quantify the regurgitant volume and is the reference standard to quantify left ventricle and left atrium volumes. In addition, quantification of mitral regurgitation with CMR has shown prognostic implications.[19]
COMPUTED TOMOGRAPHY	• **Computed tomography (CT)** provides a detailed image of the valve anatomy, especially of the systolic and diastolic ventricle geometry. This information can be valuable for planning a catheter-based intervention.[51]

Abbreviations: CMR, cardiovascular magnetic resonance; CT, computed tomography; ESC, European Society of Cardiology; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

Table 5. Summary of guidelines for the diagnosis of MR

PMR	SMR
ESC/EACTS – GUIDELINES FOR THE MANAGEMENT OF VALVULAR HEART DISEASE (2021)[19]	
Evaluation • Echocardiography is the first choice of imaging technique. • EROA is strongly associated with all-cause mortality (starting from ≥20 mm^2 and increasing beyond 40 mm^2) • Evaluation of the specific lesion leading to MR has prognostic implications. • 3D TOE facilitates heart team discussion. • CMR is a valid alternative to quantify regurgitant volume when echocardiographic parameters are inconsistent. • Exercise echocardiography is particularly helpful in patients with discordant symptoms and regurgitation grade at rest. • BNP values can be useful during follow-up. • LV dimensions and ejection fraction should be considered to guide the management of patients with severe PMR. • The MIDA score has been proposed to estimate the risk of all-cause mortality in patients with severe PMR due to flail leaflet, who are under medical treatment or surgically treated. • Right heart catheterisation is used to confirm pulmonary hypertension diagnosed by echocardiography when this is the only criterion to refer the patient for surgery.	**Evaluation** • Echocardiographic criteria are the same as PMR. • Lower thresholds for EROA and regurgitant volume may be applied to define severe SMR (≥30 mm^2 likely corresponds to severe SMR, whether ≥20 mm^2 defines severe SMR remains controversial). • In HF patients, even mild MR is associated with poor prognosis; evidence suggests that surgical or transcatheter treatment of moderate SMR does not improve patient outcomes. Caution is therefore required when labelling severe SMR based solely on prognostic implications. • Other factors such as the extent of myocardial scar, as assessed with CMR, have been associated with poor prognosis. In addition, LVEF has been shown to be misleading in patients with severe SMR, while LV global longitudinal strain has been shown to have incremental prognostic value. • 3D echocardiography, CMR, and exercise echocardiography may help to identify patients with severe MR when 2D echocardiography at rest is inconclusive.
ACC/AHA – GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH VALVULAR HEART DISEASE (2020)[110]	
Initial diagnosis • In patients with known or suspected PMR, TTE is indicated for baseline evaluation of LV size and function, RV function, LA size, pulmonary artery pressure, and the mechanism and severity of primary MR (Stages A–D). (1; B-NR) • When TTE provide insufficient or discordant information, TEE is indicated for evaluation of the	**Diagnosis** • In patients with chronic SMR (Stages B–D), TTE is useful to establish the aetiology and to assess the extent of regional and global LV remodelling and systolic dysfunction, severity of MR, and magnitude of pulmonary hypertension. (1; B-NR) • In patients with chronic SMR (Stages B–D), non-invasive imaging (stress nuclear/PET, CMR, or stress echocardiography), coronary CT angiography, or

PMR	SMR
severity of MR, mechanism of MR, and status of LV function (Stages B–D). (1;C-EO) • CMR is indicated to assess LV and RV volumes and function and may help with assessing MR severity when there is a discrepancy between the findings on clinical assessment and echocardiography. (1; B-NR) • In patients with severe PMR undergoing mitral intervention, intraoperative TEE is indicated to establish the anatomic basis for PMR (Stages C and D) and to guide repair. (1; B-NR) **Changing signs or symptoms** • For PMR Stages B–D with new-onset or changing symptoms, TTE is indicated to evaluate the mitral valve apparatus and LV function. (1; B-NR) **Routine follow-up** • For asymptomatic patients with severe PMR (Stages B and C1), TTE is indicated every 6–12 months for surveillance of LV function (estimated by LVEF, LVEDD, and LVESD) and assessment of pulmonary artery pressure. (1; B-NR) • For asymptomatic patients with severe PMR (Stages B and C1), use of serum biomarkers and novel measurements of LV function, such as global longitudinal strain, may be considered as an adjunct to guide timing of intervention. (2b; B-NR) **Exercise testing** • In patients with PMR (Stages B and C), and symptoms that might be attributable to MR, haemodynamic exercise testing using Doppler echocardiography or cardiac catheterisation or cardiopulmonary exercise testing is reasonable. (2a; B-NR)	coronary arteriography is useful to establish aetiology of MR and to assess myocardial viability. (1;C-EO) • In patients with chronic SMR with severe symptoms (Stage D) that are unresponsive to GDMT who are being considered for transcatheter mitral valve interventions, TEE is indicated to determine suitability for the procedure. (1; B-NR) • In patients with chronic SMR undergoing transcatheter mitral value intervention, intraprocedural guidance with TEE is recommended. (1;C-EO)

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; BNP, brain natriuretic peptide; CMR, cardiovascular magnetic resonance; CT, computed tomography; EACTS, European Association for Cardio-Thoracic Surgery; EROA, effective regurgitant orifice area; ESC, European Society of Cardiology; GDMT, guideline-directed medical therapy; HF, heart failure; LA, left atrium; LV, left ventricle; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MIDA, Mitral Regurgitation International Database; MR, mitral regurgitation; OMT, optimal medical therapy; PET, positron emission tomography; PISA, proximal isovelocity surface area; PMR, primary mitral regurgitation; RV, right ventricle; SMR, secondary mitral regurgitation; TEE, transoesophageal echocardiography; TOE, transoesophageal echocardiogram; TR, tricuspid regurgitation; TTE, transthoracic echocardiography.

2.1.1 REFERRAL OF VALVULAR HEART DISEASE PATIENTS

- The 2021 ESC/EACTS guidelines for the management of VHD and the 2021 ESC guidelines for the diagnosis and treatment of HF state that:
  - Heart Valve Centres should promote timely referral of patients with VHD for comprehensive evaluation before irreversible damage occurs.[19]
  - Early referral of patients with HF and moderate or severe MR to a Multidisciplinary Heart Team, including HF specialists, is recommended for assessment and treatment planning.[56]
- The 2022 ACC/AHA guidelines for the management of HF and the 2020 ACC/AHA guidelines for the management of VHD state that:
  - Consultation with or referral to a Primary or Comprehensive Heart Valve Center is reasonable when treatment options are being discussed for 1) asymptomatic patients with severe VHD, 2) patients who may benefit from valve repair versus valve replacement, or 3) patients with multiple comorbidities for whom valve intervention is considered (Class 2a, Level C-LD[b]).[110]

[b] Class 2a: Moderate recommendation; Level C-LD: limited data.

2.2 TREATMENT OPTIONS FOR MITRAL REGURGITATION

- Treatment of MR is guided by the disease classification (primary/secondary) and severity. In SMR the approach to treatment is also guided by the nature of the patient's underlying heart disease.
- Current treatment options for MR include:[19, 56, 113-115]
  - Medical management
  - Surgical mitral valve repair or replacement
  - Transcatheter mitral valve repair (TMVr) or replacement (TMVR).

A number of country-specific MR treatment guidelines are summarised in the separate appendix document.

2.2.1 MEDICAL MANAGEMENT OF MITRAL REGURGITATION

- Traditional medical management of MR (both PMR and SMR) may, to an extent, relieve the symptoms of the condition, but is often insufficient at controlling the severity and progression of MR.[109]
- A study reported that 10-year survival with medical treatment for MR was significantly lower than what would be expected for the general population (p=0.016), with death from cardiac causes occurring at a rate of 21% at 5 years and 33% at 10 years.[111]

Table 6. Summary of guidelines for the medical management of MR

PMR	SMR
ACC/AHA – GUIDELINES FOR THE MANAGEMENT OF HEART FAILURE (2022)[116]	
NA.	• In patients with chronic severe secondary MR and HFrEF, optimisation of GDMT is recommended before any intervention for secondary MR related to LV dysfunction. (1; C-LD) • GDMT, including RAAS inhibition, beta blockers, and biventricular pacing, improves MR and LV dimensions in patients with HFrEF and secondary MR, particularly MR that is proportionate to LV dilatation. • A cardiologist with expertise in the management of HF is integral to shared decision-making for valve intervention and should guide optimization of GDMT to ensure that medical options for HF and secondary MR have been effectively applied for an appropriate time period and exhausted before considering intervention.
ESC/EACTS – GUIDELINES FOR THE MANAGEMENT OF VALVULAR HEART DISEASE (2021)[19]	

• In acute MR:
  ○ Nitrates and diuretics are used to reduce filling pressures.
  ○ Sodium nitroprusside reduces afterload and regurgitant fraction.
  ○ Inotropic agents and an intra-aortic balloon pump are of use in hypotension and haemodynamic instability.
• In chronic PMR with preserved LVEF, there is no evidence to support the prophylactic use of vasodilators.
• In patients with overt HF, medical treatment as per current HF guidelines applies.
	• Optimal GDMT for the management of HF, including replacement of ACEi or ARB with sacubitril/valsartan, sodium-glucose co-transporter 2 inhibitors and/or ivabradine, whenever indicated.
	• Indications for CRT should be evaluated in accordance with related guidelines.
	• If symptoms persist after optimisation of conventional HF therapy, options for mitral valve intervention should be promptly evaluated before further deterioration of LV systolic function or cardiac remodelling occur.

PMR	SMR
HFA/EACVI/EHRA/EAPCI/ESC JOINT POSITION STATEMENT ON THE MANAGEMENT OF SMR (2021)[117]	
NA.	• Optimisation of GDMT in symptomatic moderate or severe SMR. • Neurohormonal inhibitors, including ACEi, ARB, beta blockers, and mineralocorticoid receptor antagonists are mandatory in patients with HFrEF unless contraindicated or intolerable. • Further pharmacological options in patients who remain symptomatic include ivabradine and replacement of ACEi or ARB with sacubitril/valsartan. • Oral anticoagulation is essential in patients with AF.
ACC/AHA – GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH VALVULAR HEART DISEASE (2020)[110]	
• In symptomatic or asymptomatic patients with severe PMR and LV systolic dysfunction (Stages C2 and D) in whom surgery is not possible or must be delayed, GDMT for systolic dysfunction is reasonable. (2a; B-NR) • In asymptomatic patients with primary MR and normal LV systolic function (Stages B and C1), vasodilator therapy is not indicated if the patient is normotensive. (3; B-NR)	• Patients with chronic severe SMR (Stages C and D) and HF with reduced LVEF should receive standard GDMT for HF, including ACE inhibitors, ARBs, beta blockers, aldosterone antagonists, and/or sacubitril/valsartan, and biventricular pacing as indicated. (1; A) • In patients with chronic severe SMR and HF with reduced LVEF, a cardiologist expert in the management of patients with HF and LV systolic dysfunction should be the primary MDT member responsible for implementing and monitoring optimal GDMT. (1; C-EO)

Abbreviations: ACC, American College of Cardiology; ACEi, angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; AHA, American Heart Association; ARB, angiotensin receptor blocker; bpm, beats per minute; CRT, cardiac resynchronisation therapy; EACTS, European Association for Cardio-Thoracic Surgery; EACVI, European Association of Cardiovascular Imaging; EAPCI, European Association of Percutaneous Cardiovascular Interventions; EHRA, European Heart Rhythm Association; ESC, European Society of Cardiology; GDMT, guideline-directed medical therapy; HF, heart failure; HFA, Heart Failure Association; HFrEF, heart failure with reduced ejection fraction; LV, left ventricle; LVEF, left ventricular ejection fraction; MDT, multidisciplinary team; MR, mitral regurgitation; NA, not applicable; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation; VHD, valvular heart disease.

2.2.2 SURGICAL MITRAL VALVE REPAIR OR REPLACEMENT

2.2.2.1 PRIMARY MITRAL REGURGITATION

- Surgery is the standard of care for patients with symptomatic or asymptomatic PMR with evidence of left ventricle dysfunction or dilation,[6, 19, 110] with mitral valve repair generally preferred to replacement as evidenced by lower perioperative mortality, improved survival, better preservation of left ventricle function, and lower long-term morbidity.[28, 118, 119]
- A study that followed patients diagnosed with PMR associated with flail leaflet reported that death or the need for surgery was almost unavoidable within 10 years of diagnosis, supporting the claim that PMR is a progressive disease if left untreated.[111]
- Surgery can dramatically improve outcomes, with survival at 5 and 10 years reported at 97% and 100% of the expected survival for the general population, respectively (p=0.68).[111]
- Surgical repair by leaflet resection or chordal placement is the preferred technique for surgical repair of the mitral valve.[120] Annuloplasty is typically conducted in conjunction with mitral valve repair.[120] Annuloplasty refers to the implantation of a rigid or flexible ring surrounding the mitral valve to pull the leaflets together, restore coaptation and re-establish mitral valve function.[120, 121]
- Surgical replacement refers to the replacement of the existing mitral valve (if repair is not feasible), with a prosthetic valve (biological or mechanical). The type of valve used depends on various factors such as the patient's age, contraindication to warfarin therapy, medical condition, and medications. Generally, younger patients (≤65 years) are given mechanical valves as bio-prosthesis degrade more rapidly in these patients.[122]

2.2.2.2 SECONDARY MITRAL REGURGITATION

- Surgical options for patients with SMR and HF include surgical mitral valve repair and replacement, mechanical left ventricle assist devices, and orthotopic heart transplantation. Although SMR can be acutely corrected with mitral valve surgery, the surgery has never clearly been demonstrated to alter the natural history of the primary disease (dilated cardiomyopathy) or improve survival.[112] Moreover, whether the response to surgery is different in SMR due to ischaemic versus non-ischaemic cardiomyopathy has not been established.[112]
- In patients with moderate ischaemic MR undergoing coronary artery bypass grafting (CABG), simultaneous surgical mitral valve repair did not lead to significant differences in left ventricular reverse remodelling at 2 years when compared with patients who underwent CABG only.[123] Surgical mitral valve repair provided a more durable correction of MR but did not significantly improve survival or reduce overall adverse events (AEs) or readmissions and was associated with an early hazard of increased neurologic events and supraventricular arrhythmias compared with CABG only patients.[123]

Table 7. Summary of guidelines for the surgical management of MR

PMR	SMR
ESC – FOCUSED UPDATE OF THE 2021 ESC GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF ACUTE AND CHRONIC HF (2023)[124]	
NA.	• No amendments to the MR guidance provided in the 2021 ESC guidelines (see table entry below).
ACC/AHA – GUIDELINE FOR THE MANAGEMENT OF HEART FAILURE (2022)[116]	
NA.	• Patients with persistent severe secondary MR despite GDMT may benefit from either surgical or transcatheter repair, depending on clinical scenario. Thus, patient-centric conversation with a multidisciplinary cardiovascular team that includes a cardiologist with expertise in HF is essential when considering MV intervention.
ESC/EACTS – GUIDELINES ON THE MANAGEMENT OF VALVULAR HEART DISEASE (2021)[19]	
• Mitral valve repair is the recommended surgical technique when the results are expected to be durable. (I B). • Surgery is recommended in symptomatic patients who are operable and not high risk. (I B). • Surgery is recommended in asymptomatic patients with LV dysfunction (LVESD ≥40mm and/or LVEF ≤60%). (I B). • Surgery should be considered in asymptomatic patients with preserved LV function (LVESD <40 mm and LVEF >60%) and AF secondary to MR or pulmonary hypertension (SPAP at rest >50 mmHg). (IIa B). • Surgical mitral valve repair should be considered in low-risk asymptomatic patients with LVEF >60%, LVESD <40mm and significant LA dilatation (volume index ≥60 mL/m^2 or diameter ≥55 mm) when performed in a Heart Valve Centre and a durable repair is likely. (IIa B).	• Valve surgery/intervention is recommended only in patients with severe SMR who remain symptomatic despite GDMT (including CRT if indicated) and has to be decided by a structured collaborative Heart Team. (I B). • **Patients with concomitant coronary artery or other cardiac disease requiring treatment:** Valve surgery is recommended in patients undergoing CABG or other cardiac surgery. (I B). • **Patients without concomitant coronary artery or other cardiac disease requiring treatment:** Valve surgery may be considered in symptomatic patients judged appropriate for surgery by the Heart Team. (IIb C).
ESC – GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF ACUTE AND CHRONIC HF (2021)[56]	
NA.	• In patients with HF, severe SMR, and CAD who need revascularisation, CABG and mitral valve surgery should be considered. (IIa C).

PMR	SMR
HFA/EACVI/EHRA/EAPCI/ESC JOINT POSITION STATEMENT ON THE MANAGEMENT OF SMR IN PATIENTS WITH HF (2021)[117]	
NA.	• Decisions concerning treatments for MR, other than pharmacological therapy or circulatory support, should ideally be made in stable patients without fluid overload or the need for inotropic support. • Surgical treatment of severe SMR should be considered in operable patients with coronary artery disease requiring surgical revascularisation. • Circulatory support devices and cardiac transplantation should be considered as an alternative in patients with advanced left and/or right ventricular failure. • Interventions for MR should be avoided in patients with life expectancy <1 year due to conditions unrelated to the MR.
ACC/AHA – GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH VALVULAR HEART DISEASE (2020)[110]	
• In symptomatic patients with severe PMR (Stage D), mitral valve intervention is recommended irrespective of LV systolic function. (1; B-NR). • In asymptomatic patients with severe PMR and LV systolic dysfunction (LVEF ≤60%, LVESD ≥40 mm) (Stage C2), mitral valve surgery is recommended. (1; B-NR). • In patients with severe PMR for whom surgery is indicated, mitral valve repair is recommended in preference to mitral valve replacement when the anatomic cause of MR is degenerative disease, if a successful and durable repair is possible. (1; B-NR). • In asymptomatic patients with severe PMR and normal LV systolic function (LVEF ≥60% and LVESD ≤40 mm) (Stage C1), mitral valve repair is reasonable when the likelihood of a successful and durable repair without residual MR is >95% with an expected mortality rate of <1%, when it can be performed at a Primary or Comprehensive Valve Center. (2a; B-NR). • In asymptomatic patients with severe PMR and normal LV systolic function (LVEF >60% and LVESD <40 mm) (Stage C1) but with a progressive increase in LV size or decrease in EF on ≥3 serial imaging studies, mitral valve surgery may be considered irrespective of the probability of a successful and durable repair. (2b; C-LD). • In symptomatic patients with severe PMR attributable to rheumatic valve disease, mitral valve repair may be considered at a Comprehensive Valve Center by an experienced team when surgical treatment is indicated, if a durable and successful repair is likely. (2b; B-NR).	• In patients with severe SMR (Stages C and D), mitral valve surgery is reasonable when CABG is undertaken for the treatment of myocardial ischaemia. (2a; B-R). • In patients with chronic severe SMR from atrial annular dilation with preserved LV systolic function (LVEF ≥50%) who have severe persistent symptoms (NYHA class III or IV) despite therapy for HF and therapy for associated AF or other comorbidities (Stage D), mitral valve surgery may be considered. (2b; B-NR). • In patients with chronic severe SMR related to LV systolic dysfunction (LVEF<50%) who have persistent severe symptoms (NYHA class III or IV) while on optimal GDMT for HF (Stage D), mitral valve surgery may be considered. (2b; B-NR). • In patients with CAD and chronic severe SMR related to LV systolic dysfunction (LVEF<50%) (Stage D) who are undergoing mitral valve surgery because of severe symptoms (NYHA class III or IV) that persist despite GDMT for HF, chordal-sparing mitral valve replacement may be reasonable to choose over downsized annuloplasty repair. (2b; B-R).

Abbreviations: ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; AV, atrioventricular; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CRT, cardiac resynchronisation therapy; EACTS, European Association for Cardio-Thoracic Surgery; EACVI, European Association of Cardiovascular Imaging; EAPCI, European Association of Percutaneous Cardiovascular Interventions; EHRA, European Heart Rhythm Association; ESC, European Society of Cardiology; GDMT, guideline-directed medical therapy; HF, heart failure; HFA, Heart Failure Association; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; NA, not applicable; NYHA, New York Heart Association; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation; SPAP, systolic pulmonary artery pressure.

2.2.3 TRANSCATHETER MITRAL VALVE REPAIR

- Surgery can provide substantial benefits for patients with PMR;[111] however, up to 50% of patients may not meet the eligibility criteria due to risks associated with age or the presence of comorbidities.[67] Furthermore, surgery has not been shown to lower the rate of hospitalisation or death associated with SMR and confers a substantial risk of complications. Thus most patients with HF and SMR are treated conservatively.[20]
- Overall, many patients in need of valve reconstruction or replacement do not undergo surgery because of high perioperative risk. Transcatheter mitral valve repair (TMVr) provides an alternative minimally invasive technique for repair of the MR via a percutaneous approach, thus avoiding the need for (open heart) surgery.[6]
- Currently there are only a few CE-marked transcatheter interventions for mitral valve repair available. Clinical literature for transcatheter treatment of PMR comprises experience with TEER (MitraClip™ and PASCAL) and chordal repair (Harpoon and NeoChord). Clinical literature for transcatheter treatment of SMR comprises experience with TEER (MitraClip™, PASCAL) and annuloplasty (Carillon Mitral Contour System, Cardioband, and Mitralign).
- The latest (2021) ESC/EACTS guidelines for the treatment of valvular heart disease recommend using MitraClip™ System for TEER since, for any other repair systems, "clinical data are still limited."[19, 56]

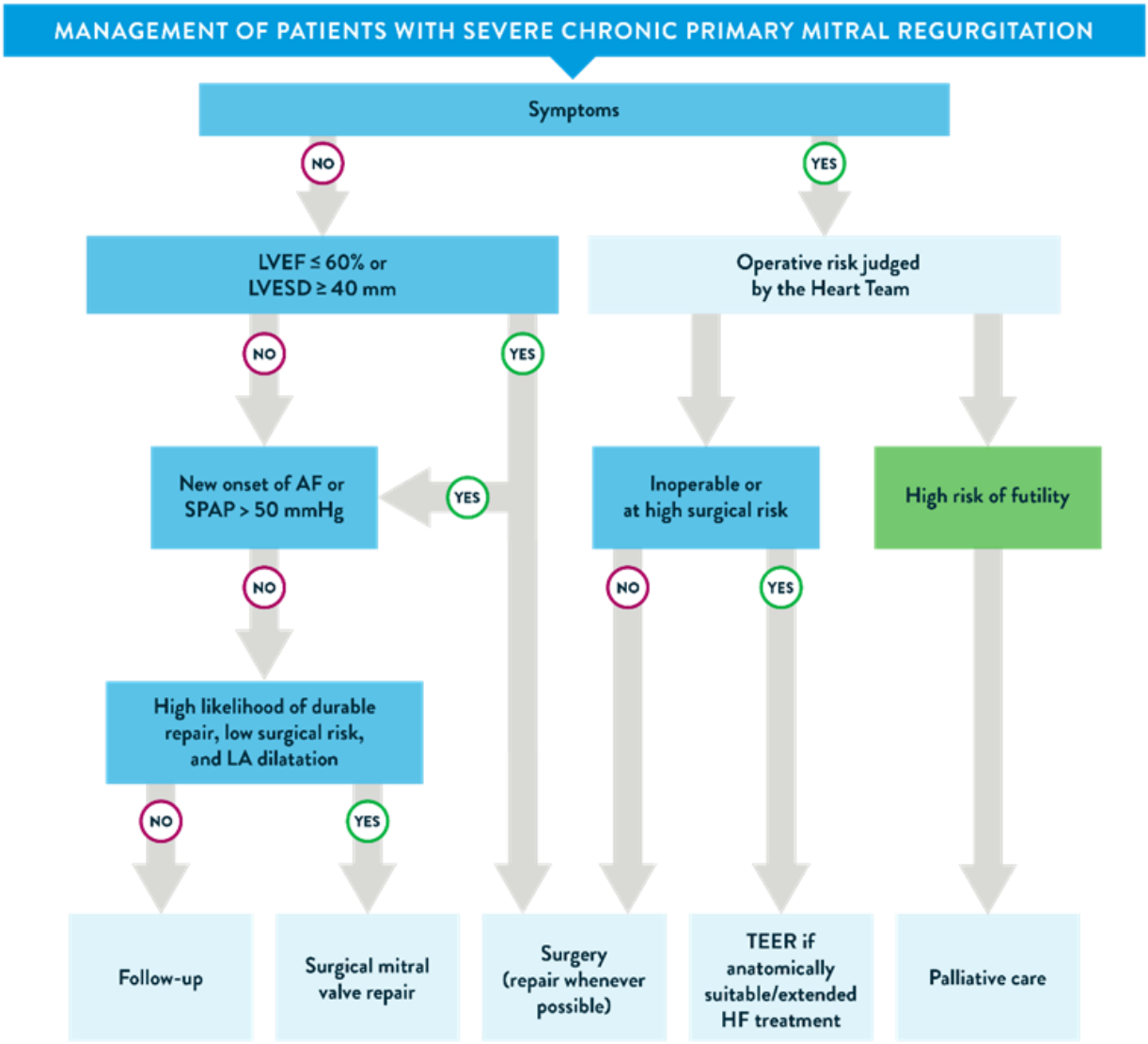
Table 8. Summary of guidelines for the TMVr management of MR

PMR	SMR
ESC – FOCUSED UPDATE OF THE 2021 ESC GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF ACUTE AND CHRONIC HF (2023)[124]	
NA.	• No amendments to the MR guidance provided in the 2021 ESC guidelines (see table entry below).
NA.	• Patients with persistent severe secondary MR despite GDMT may benefit from either surgical or transcatheter repair, depending on clinical scenario. Thus, patient-centric conversation with a multidisciplinary cardiovascular team that includes a cardiologist with expertise in HF is essential when considering MV intervention. • Specifically, MV TEER has been shown to be beneficial in patients with persistent symptoms despite GDMT, appropriate anatomy on transoesophageal echocardiography, LVEF between 20–50%, LVESD ≤70 mm, and pulmonary artery systolic pressure ≤70 mm Hg.
ACC/AHA – GUIDELINE FOR THE MANAGEMENT OF HEART FAILURE (2022)[116]	
NA.	• Patients with persistent severe secondary MR despite GDMT may benefit from either surgical or transcatheter repair, depending on clinical scenario. Thus, patient-centric conversation with a multidisciplinary cardiovascular team that includes a cardiologist with expertise in HF is essential when considering MV intervention. • Specifically, MV TEER has been shown to be beneficial in patients with persistent symptoms despite GDMT, appropriate anatomy on transoesophageal echocardiography, LVEF between 20–50%, LVESD ≤70 mm, and pulmonary artery systolic pressure ≤70 mm Hg.
ESC/EACTS – GUIDELINES FOR THE MANAGEMENT OF VALVULAR HEART DISEASE (2021)[19]	
• TEER may be considered in symptomatic patients who fulfil the echocardiographic criteria of eligibility, are judged inoperable or at high surgical	• **Patients with concomitant coronary artery or other cardiac disease requiring treatment:** In symptomatic patients, who are judged not appropriate for surgery by

PMR	SMR
risk by the Heart Team and for whom the procedure is not considered futile. (IIb B; see also Figure 8).	the Heart Team on the basis of their individual characteristics, PCI (and/or TAVI) possibly followed by TEER (in case of persisting severe SMR) should be considered. (IIa C). • **Patients without concomitant coronary artery or other cardiac disease requiring treatment:** TEER should be considered in selected symptomatic patients, not eligible for surgery and fulfilling criteria suggesting an increased chance of responding to the treatment. (IIa B). • In high-risk symptomatic patients not eligible for surgery and not fulfilling the criteria suggesting an increased chance of responding to TEER, the Heart Team may consider in selected cases a TEER procedure or other transcatheter valve therapy if applicable, after careful evaluation for ventricular assist device or heart transplant. (IIb C).
ESC GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF ACUTE AND CHRONIC HF (2021)[56]	
NA.	• Percutaneous edge-to-edge mitral valve repair should be considered in carefully selected patients with SMR, not eligible for surgery and not needing coronary revascularisation, who are symptomatic despite OMT and who fulfil criteria to achieve a reduction in HF hospitalisations. (IIa). • Percutaneous edge-to-edge mitral valve repair may be considered to improve symptoms in carefully selected patients with SMR, not eligible for surgery and not needing coronary revascularisation, who are highly symptomatic despite OMT and who do not fulfil criteria for reducing HF hospitalisation. (IIb).
HFA/EACVI/EHRA/EAPCI/ESC JOINT POSITION STATEMENT ON THE MANAGEMENT OF SMR IN PATIENTS WITH HF (2021)[117]	
NA.	• TEER is an evidence-based treatment option in patients with severe SMR who remain symptomatic despite GDMT (including CRT when indicated) and who have been carefully selected by a multidisciplinary Heart Team. • Interventions for MR should be avoided in patients with life expectancy <1 year due to conditions unrelated to the MR.
ACC/AHA – GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH VALVULAR HEART DISEASE (2020)[110]	
• In severely symptomatic patients (NYHA class III or IV) with primary PMR and high or prohibitive surgical risk, TEER is reasonable if mitral valve anatomy is favourable for the repair procedure and patient life expectancy is at least 1 year. (2a; B-NR)	• In patients with chronic severe SMR related to LV systolic dysfunction (LVEF <50%) who have persistent symptoms (NYHA class II, III, or IV) while on optimal GDMT for HF (Stage D), TEER is reasonable in patients with appropriate anatomy as defined on TEE and with LVEF between 20% and 50%, LVESD ≤70 mm, and pulmonary artery systolic pressure ≤70 mmHg. (2a; B-R).

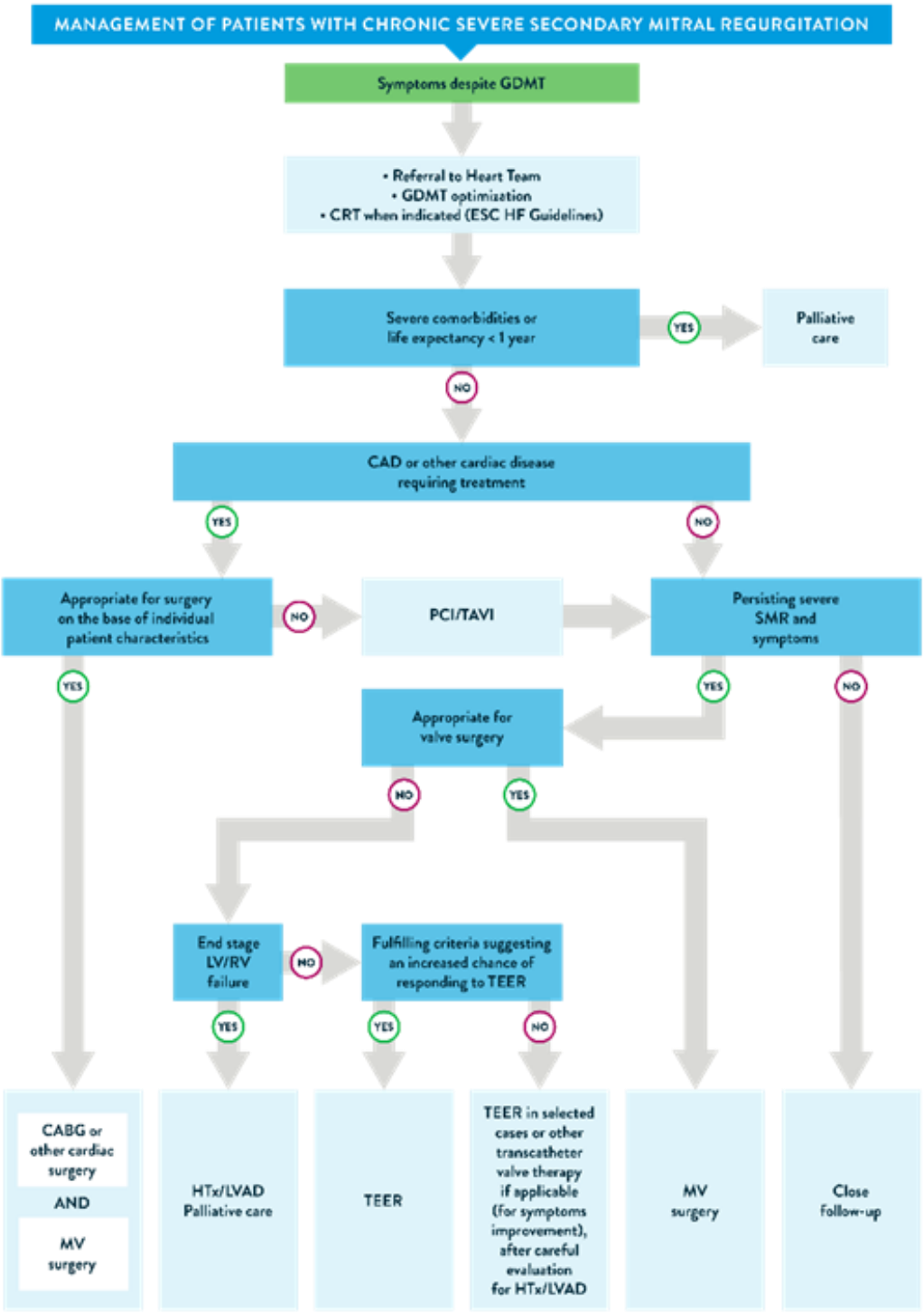
Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; CRT, cardiac resynchronisation therapy; EACTS, European Association for Cardio-Thoracic Surgery; EACVI, European Association of Cardiovascular Imaging; EAPCI, European Association of Percutaneous Cardiovascular Interventions; EHRA, European Heart Rhythm Association; ESC, European Society of Cardiology; GDMT, guideline-directed medical therapy; HF, heart failure; HFA, Heart Failure Association; LV, left ventricle; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; NA, not applicable; NYHA, New York Heart Association; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; PMR, primary mitral regurgitation; QoL, quality of life; SMR, secondary mitral regurgitation; TAVI, transcatheter aortic valve implantation; TEE, transoesophageal echocardiography; TEER, transcatheter edge-to-edge repair.

Figure 8. Proposed management of severe chronic PMR according to the 2021 ESC/EACTS guidelines



Abbreviations: AF, atrial fibrillation; EACTS, European Association for Cardio-Thoracic Surgery; ESC, European Society of Cardiology; HF, heart failure; LA, left atrium; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; PMR, primary mitral regurgitation; SPAP, systolic pulmonary arterial pressure; TEER, transcatheter edge-to-edge repair.
Source: Vahanian 2021.[19]

Figure 9. Proposed management of chronic severe SMR according to the 2021 ESC/EACTS guidelines



Abbreviations: CABG, coronary artery bypass grafting; CAD, coronary artery disease; CRT, cardiac resynchronisation therapy; EACTS, European Association for Cardio-Thoracic Surgery; ESC, European Society of Cardiology; GDMT, guideline-directed medical therapy; HF, heart failure; HTx, heart transplantation; LV, left ventricle; LVAD, left ventricular assist device; MV, mitral valve; PCI, percutaneous coronary intervention; RV, right ventricle; SMR, secondary mitral regurgitation; TAVI, transcatheter aortic valve implantation; TEER, transcatheter edge-to-edge repair.
Source: Vahanian 2021.[19]

2.2.4 TRANSCATHETER MITRAL VALVE REPLACEMENT

- Transcatheter mitral valve replacement (TMVR) is a new therapeutic option. To date, TMVR has generally been used in:
  - Surgical high-risk patients
  - Patients who are not candidates for TMVr as their mitral valve anatomy is not predictive of favourable outcomes[19]
  - Patients with severe mitral annular calcification (MAC)[125]
- Abbott's Tendyne™ Mitral Valve System is the first TMVR device, receiving CE-certification in January 2020 (CE British Standards Institution 2797).[126]
  - The Tendyne™ Mitral Valve System is a bioprosthesis valve designed for transapical implantation within the native mitral valve without the need for open heart surgery and without concomitant surgical removal of the failed native valve. Tendyne™ Mitral Valve System has the largest clinical experience to date of any transcatheter mitral valve replacement (TMVR) therapy, with over 1,600 procedures performed.
- As TMVR is a new therapeutic option, it is not yet accounted for in any treatment guidelines.[19, 56, 110]

Table 9. Summary of guidelines for the TMVR management of MR

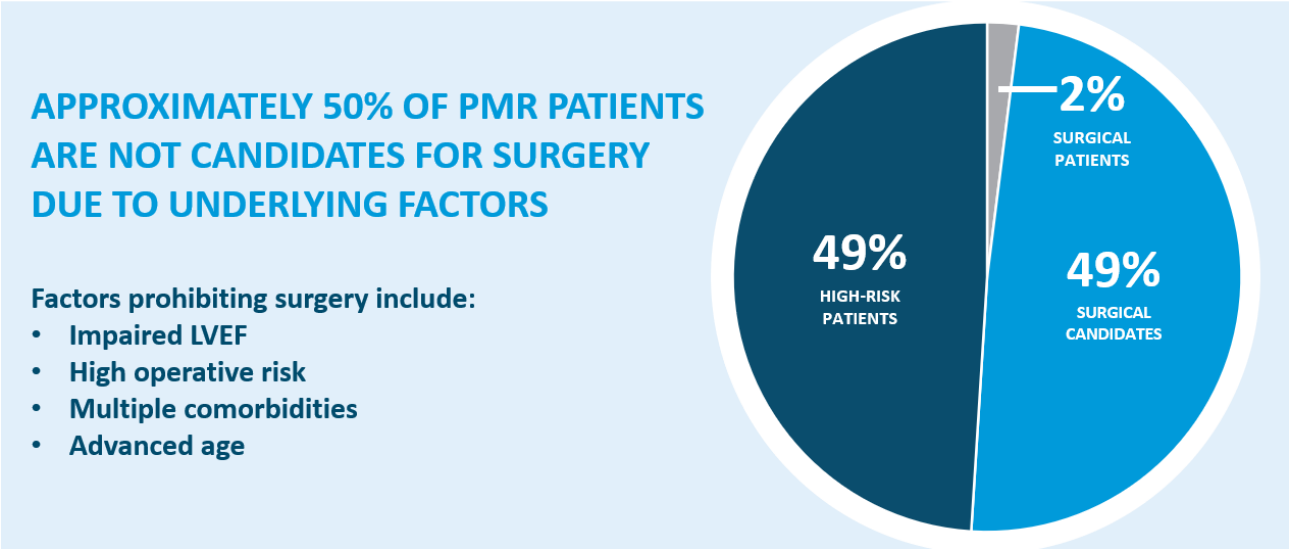
PMR	SMR
ESC – FOCUSED UPDATE OF THE 2021 ESC GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF ACUTE AND CHRONIC HF (2023)[124]	
NA.	• No amendments to the MR guidance provided in the 2021 ESC guidelines (see table entry below).
ESC/EACTS – GUIDELINES FOR THE MANAGEMENT OF VALVULAR HEART DISEASE (2021)[19]	
NA.	• TMVr systems other than TEER, as well as TMVR devices, are currently the subject of intense investigation but clinical data are still limited.
ESC GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF ACUTE AND CHRONIC HF (2021)[56]	
NA.	• TMVR is also emerging as a possible alternative option, but randomised trials are still lacking.
ACC/AHA – GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH VALVULAR HEART DISEASE (2020)[110]	
• In patients with severe PMR for whom surgery is indicated, TMVr is recommended in preference to TMVR when the anatomic cause of MR is degenerative disease, if a successful and durable repair is possible. (1; B-NR). • In patients with severe PMR where leaflet pathology is limited to less than one half the posterior leaflet, TMVR should not be performed unless TMVr has been attempted at a Primary or Comprehensive Valve Center and was unsuccessful. (3; B-NR).	• In patients with CAD and chronic severe SMR related to LV systolic dysfunction (LVEF <50%) (Stage D) who are undergoing MV surgery because of severe symptoms (NYHA class III or IV) that persist despite GDMT for HF, chordal-sparing TMVR may be reasonable to choose over downsized annuloplasty repair. (2b; B-R).

Abbreviations: CAD, coronary artery disease; EACTS, European Association for Cardio-Thoracic Surgery; ESC, European Society of Cardiology; GDMT, guideline-directed medical therapy; HF, heart failure; LV, left ventricle; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NA, not applicable; NYHA, New York Heart Association; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation; TEER, transcatheter edge-to-edge repair; TMVr, transcatheter mitral valve repair; TMVR, transcatheter mitral valve replacement.

2.3 UNMET NEEDS IN THE CURRENT MANAGEMENT OF MITRAL REGURGITATION

- Medical management of SMR aims to reduce left ventricle overload, reverse left ventricle remodelling, and reduce MR, but it is not effective in the treatment of severe SMR.[127]
- While medical management of MR may reduce symptoms and improve patient QoL,[15, 20-22, 28] it does not correct the defect resulting in MR.[109] Ultimately, the prognosis for medically-treated patients is poor.[109, 128]
- Surgical repair of the mitral valve is the gold standard treatment for patients with PMR,[19] but in practice, approximately 50% of patients cannot benefit from it because of clinical factors (e.g., advanced age, comorbidities, impaired LVEF, high operative risk) that render them ineligible for surgery.[63, 67, 129]
- As populations continue to age, the number of patients with MR who are considered unsuitable for surgery is likely to rise.[67, 130]
- Even when mitral valve surgery is an option, it remains associated with a high in-hospital mortality rate that increases with patient age and number of comorbidities.[131]

Figure 10. Factors precluding mitral valve surgical repair in patients with PMR



Abbreviations: PMR, primary mitral regurgitation; LVEF, left ventricular ejection fraction.
Sources: Iung 2003,[63] Rankin 2006,[129] Mirabel 2007.[67]

- There is no strong evidence supporting surgery in SMR patients unless they are low-risk, or require another intervention such as CABG.[19, 110]
- TEER with MitraClip™ is the guideline-recommended therapy for PMR patients not eligible for surgery as well as SMR patients who remain symptomatic despite GDMT (COAPT™ criteria).[19, 56]
- Transcatheter mitral valve replacement (TMVR) is a new treatment for both PMR and SMR, and more research is required to identify the patient population most likely to benefit from this approach.[19, 56, 110]
- There are multiple complex unmet needs in the treatment of patients with MR. In particular, there is a need for:
    - **Improved and timelier referral to Heart Centres for MR treatment** – MR is an underdiagnosed and undertreated condition[132] associated with significant clinical and economic burden and high mortality rates. Earlier diagnosis and treatment preserves cardiac function and increases life expectancy.[19]
    - A minimally invasive TMVr treatment option for patients with PMR that is as effective at treating MR as surgery.
    - Improved (real-time) imaging techniques to support TMVr procedures.

- **The MitraClip™ System is a first-in-class TEER solution with proven outcomes up to 5 years,[14, 15] and is the only device that is cited in established guidelines for the treatment of MR.[19, 110, 116, 117]**
- **The MitraClip™ System has over 20 years of clinical experience with >200,000 patients treated in more than 75 countries. With an evidence base that includes the largest real-world dataset, more than 3,200 scientific papers pertaining to MitraClip™ have been published and over 80,000 patients have been treated with the device in clinical trials. (Abbott data on file)**
- **The MitraClip™ System received its first CE mark in 2008.[17] The latest generation device MitraClip™ G4 received CE approval in 2020 and was also approved under the Medical Device Regulation (MDR) in 2022 (CE British Standards Institution 2797).[18]**
- **The MitraClip™ G4 System includes four clip sizes (NT, XT, NTW, and XTW) to allow for tailored repairs based on the patient's mitral valve anatomy.[133] NTW and XTW are 50% wider than their respective NT and XT counterparts, enabling reduction of greater regurgitation volumes.[133]**
- **The MitraClip™ System allows for real-time positioning and repositioning to optimise MR reduction.**
- **It is recommended that patients with MR who are eligible to receive the MitraClip™ device are managed through a Multidisciplinary Heart Team.**
- **Abbott also operates an experienced field and training team and is committed to providing initial and ongoing training and support to those using the MitraClip™ System.**

3.1 THE MITRACLIP™ SYSTEM

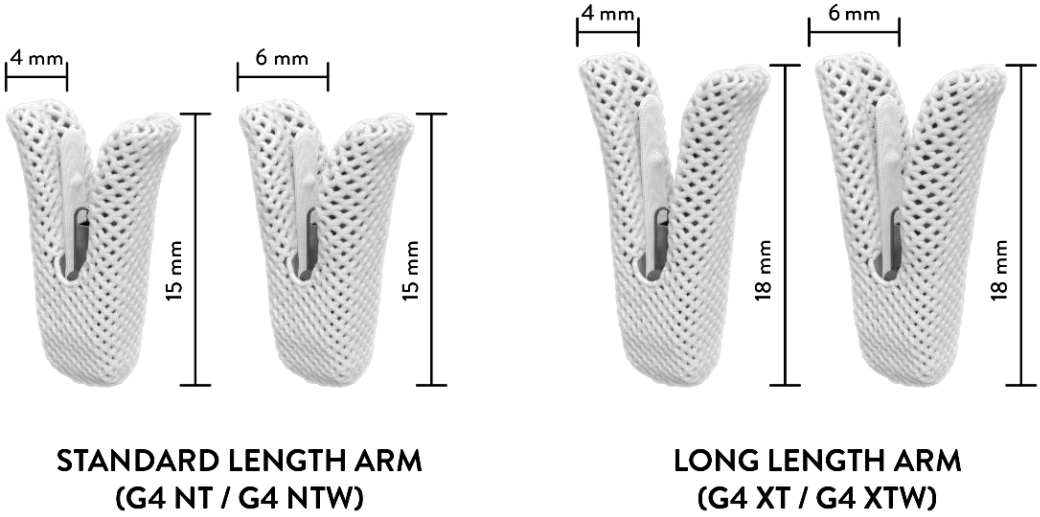
- MitraClip™ System is a first-in-class TEER solution with proven, durable outcomes up to 5 years.[14, 15]
- MitraClip™ System received its first CE mark in 2008.[17] The latest generation MitraClip G4 received CE approval in 2020 and was approved under the Medical Device Regulation (MDR) in 2022 (Œ British Standards Institution 2797).[18] US Food and Drug Administration (FDA) approval for MitraClip™ was granted in 2013 for PMR[134] and in 2019 for SMR.[135]
- In 2020, MitraClip™ System was the recipient of the prestigious Prix Galien Best Medical Technology award.[136], and in 2015, Abbott received a Chicago Innovation Award for MitraClip™ System.[137]
- MitraClip™ System is a proven technology with over 20 years of clinical experience, and 200,000+ patients treated in more than 75 countries. With an evidence base that includes the largest real-world dataset**Error! Bookmark not defined.** more than 3,200 scientific papers pertaining to MitraClip™ have been published and over 80,000 patients have been treated with the device in clinical trials. (Abbott data on file)
- MitraClip™ is the only device that is cited in established guidelines for the treatment of MR.[19, 110, 116, 117]
- The procedure is based on the Alfieri edge-to-edge surgical repair technique.[138]
- The MitraClip™ G4 System:
    - is intended for reconstruction of the insufficient mitral valve through tissue approximation[133]
    - intended patient population includes patients with symptomatic primary (degenerative) or secondary (functional) significant mitral regurgitation[133]
    - allows for real-time positioning and repositioning to optimise MR reduction
    - is specifically designed for mitral valve (MV) repair and provides precise steering to treat a variety of anatomies while achieving consistent outcomes

Figure 11. The MitraClip™ G4 System

Source: Abbott.

- The MitraClip™ G4 System, is the latest generation device that includes 4 clip sizes (NT/XT, NTW, and XTW) offering more options to physicians for tailored repairs based on the patient's mitral valve anatomy.
- The wider clips – NTW and XTW – are 50% wider than their respective NT and XT counterparts, enabling reduction of greater regurgitation volumes.[133]

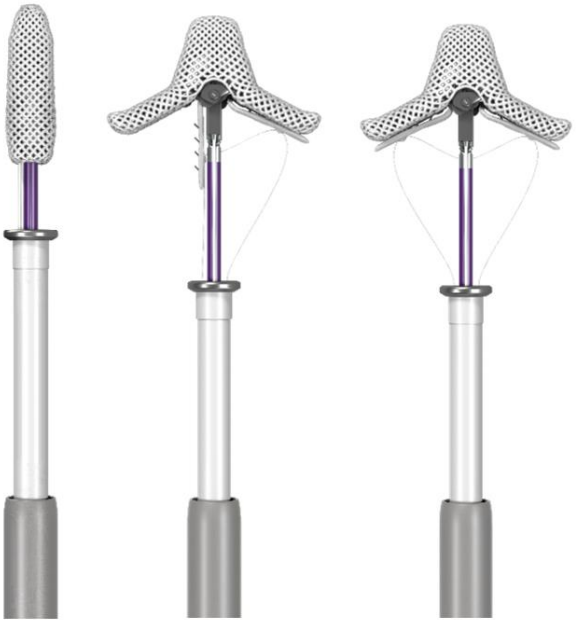
Figure 12. The MitraClip™ G4 4 clip sizes



Source: Abbott.

- MitraClip™ G4 increases procedure efficiency with:
  - A Controlled Gripper Actuation (CGA) feature that allows for simultaneous or independent grasping to facilitate optimal leaflet grasping and insertion.
  - A 40% reduction in system preparation steps and simplified deployment for procedure streamlining.
  - Integrated LAP pressure monitoring for MR assessment.

Figure 13. The MitraClip™ G4 Controlled Gripper Actuation (CGA)

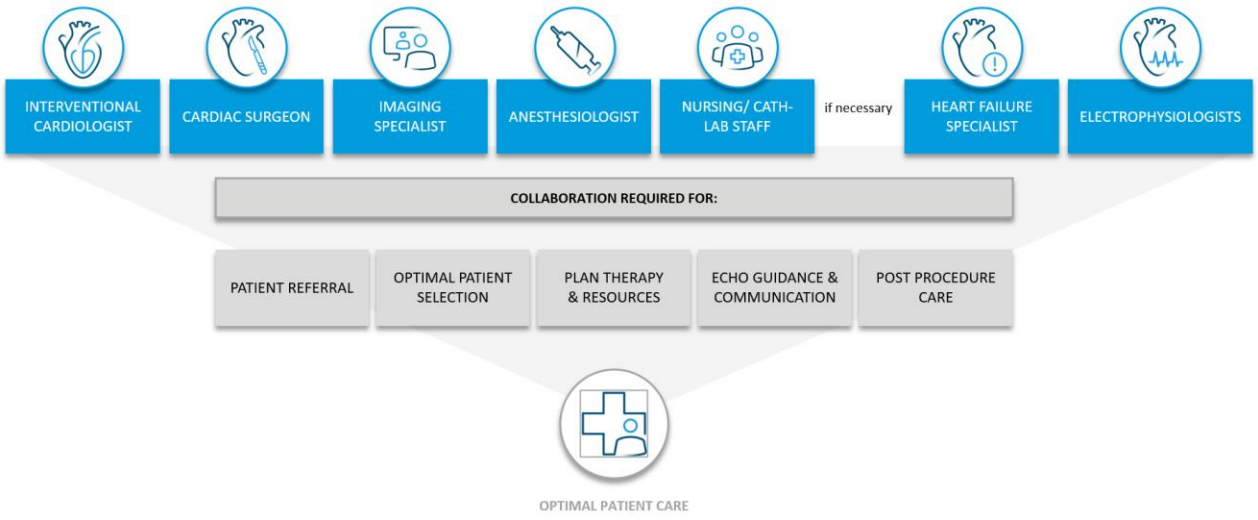


Source: Abbott.

3.2 MULTIDISCIPLINARY HEART TEAM APPROACH

- It is recommended that patients with MR who are eligible to receive the MitraClip™ device are managed through a Multidisciplinary Heart Team comprising clinical and interventional cardiologists, cardiac surgeons, imaging specialists with expertise in interventional imaging, cardiovascular anaesthesiologists, and other specialists if necessary (e.g. heart failure specialists or electrophysiologists).[19, 110, 139]
- In patients with HF, valvular heart disease should be managed in a multidisciplinary manner in accordance with clinical practice guidelines for valvular heart disease to prevent worsening of HF and adverse clinical outcomes.[116]
- A dedicated mitral valve Heart Team (as opposed to a general Heart Team) has been shown to be associated with better survival in patients with mitral valve disease, irrespective of treatment approach (surgery, MitraClip™, medica therapy).[140]

Figure 14. Multidisciplinary heart team approach



Source: Abbott.

3.3 MITRACLIP™ TRAINING

- Abbott is committed to providing initial and ongoing training and support to those using the MitraClip™ device and operate an experienced field and training team, some of whom have supported in over 500 mitral valve procedures.
- Mandatory and non-mandatory training courses are provided to physicians wanting to use MitraClip™.
- 'The Abbott Educational Network' offers a 1-day mandatory training course that covers MR pathology, echocardiography, patient screening and selection, and provides hands-on training with simulators. Additional to this course, there is a live webinar presented by experienced MitraClip™ implanters to which physicians are invited that covers procedural echo and MitraClip™ cases.
- A 3D-echo course (non-mandatory) teaches screening, procedural guidance, and post-procedural assessment in mitral valve structural heart disease. It also provides additional training in performing mitral and tricuspid valve interventions as well as those related to occlusions of the left atrial appendage, patent foramen ovale, and, and atrial septal defects. This course is aimed at echo cardiologists, interventional cardiologists, and cardiac surgeons and teaches the knowledge and skills necessary. As of 2020, the course can be hosted online via conference call.
    - A TEER module is included in the course that covers: the MitraClip™ device (clinical evidence, treatment guidelines), the anatomy, morphology, and pathomechanisms of MR (patient eligibility), how to use 3D echo, standardised echo guiding protocol for edge-to-edge repair, and post-procedural assessment of repair (leaflet insertion, quantification of residual MR).

3.4 SUMMARY OF THE MITRACLIP™ PROCEDURE

1. Preparation

The MitraClip™ System is prepared by removing all the air in the lumen of the Clip Delivery System and Steerable Guide Catheter. The MitraClip™ System is then tested prior to use.[133]

2. Transseptal crossing and guide insertion

The patient is placed under general anaesthetic so that transoesophageal echocardiography (TEE) can be performed. Transfemoral access is obtained and transseptal puncture performed to position the Steerable Guide Catheter in the left atrium. The Steerable Guide Catheter and Dilator are then carefully advanced into the left atrium over a wire. Once the Guide is in place and secured, the wire and Dilator are removed, leaving the Guide in the left atrium.[133]

3. Clip Delivery System insertion and steering in the left atrium

To introduce the Clip, the Clip Delivery System is advanced through the Guide into the left atrium. A series of steering manoeuvres and manipulations with the Guide and Clip Delivery System are required to align the Clip perpendicular to the mitral valve plane, and the Clip Arms perpendicular to the line of coaptation (this is done under echocardiographic and fluoroscopic guidance).[133]

4. Advancing into left ventricle and leaflet grasping

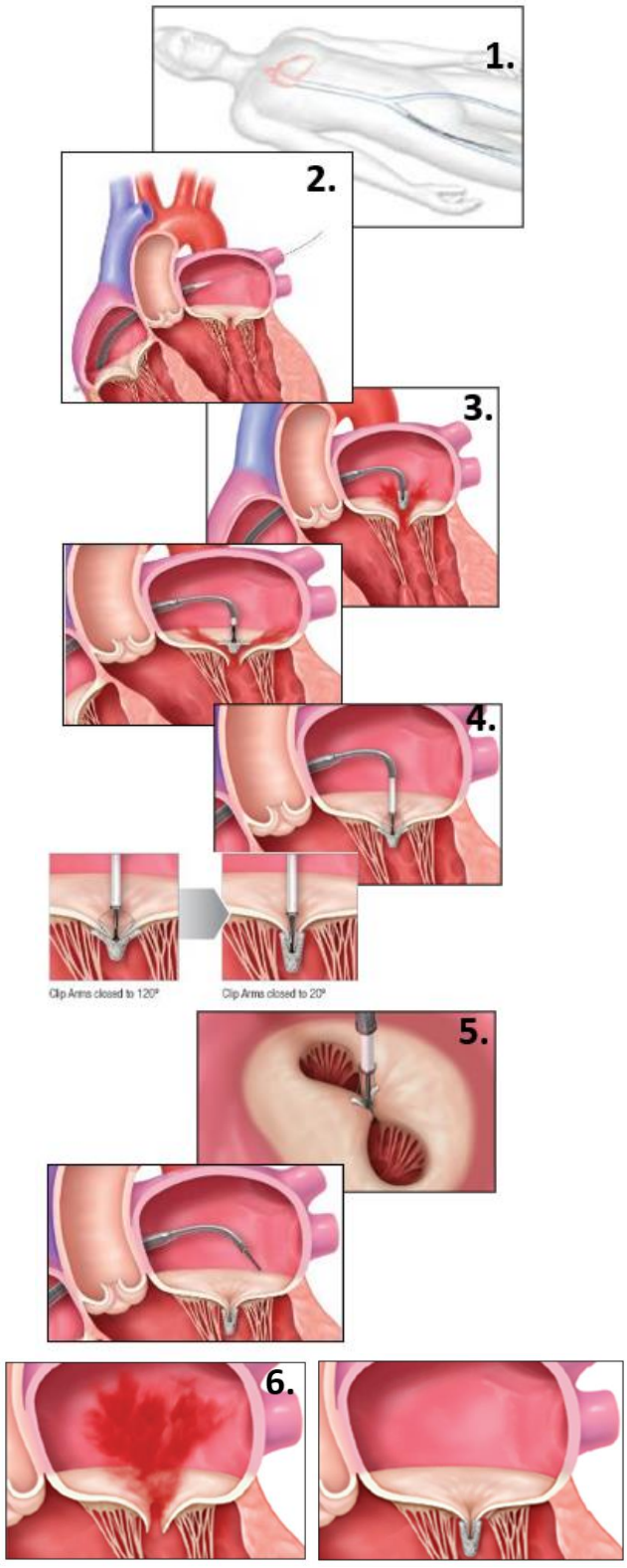
The mitral valve leaflets are grasped between the corresponding Arm and Gripper creating a double orifice valve. MR is assessed throughout the entire procedure using real-time TEE to confirm optimal positioning and sufficient reduction in MR.[133]

5. Leaflet insertion assessment and haemodynamic measurements

Prior to Clip closure and deployment, a leaflet insertion and haemodynamic assessment is performed. Following MR reduction, pressure gradients are assessed to ensure there is no induced mitral stenosis. Once the assessments are complete, the Clip is fully closed and deployed. Where necessary, the physician may also place a second Clip to optimise MR reduction.[133]

6. Deployment and System removal

The System is removed by releasing deflection on the catheter and slowly removing from the patient. Groin management and continued medical therapy are recommended per the institution's guidelines.[133]



3.5 MITRACLIP™ PATIENT PROFILE

- Patient and anatomic factors that determine suitability or non-suitability for MitraClip™ are outlined below. Whether or not a patient is deemed suitable to undergo TEER with MitraClip™ is also influenced by the experience and skill of the surgeon/surgical team.[141]

Table 10. Profile of patients that are suitable for MitraClip™

SIGNIFICANT CLINICAL BENEFITS HAVE BEEN REPORTED WITH MITRACLIP™ IN THE FOLLOWING PATIENT GROUPS:
Patients with PMR who have been declined for surgery[142]
Patients with severe left ventricle dysfunction who are refractory to medical therapy[143, 144]
Patients with severe HF, despite the use of OMT[145]
Patients who have MR that has not responded to CRT[146]
Patients in an unstable haemodynamic state[147-156]

Abbreviations: CRT, cardiac resynchronisation therapy; HF, heart failure; MR, mitral regurgitation; OMT, optimised medical therapy; PMR, primary mitral regurgitation.

Table 11. Profile of patients that are not suitable for MitraClip™

ANATOMIC AND PATIENT CHARACTERISTICS CONFERRING UNSUITABILITY FOR MITRACLIP™ INCLUDE:
Carpentier IIIa (chronic rheumatic disease, radiation heart disease, other chronic inflammatory conditions affecting the mitral valve)
Severe mitral annular calcification with mitral stenosis or calcium extension into the leaflets, or restricted leaflet motion
Severely calcified or fibrotic leaflet(s)
Prior surgical annuloplasty or ring with potential for stenosis
Prohibitively small mitral valve area (<3.5 cm^2)
Perforation from endocarditis (or other significant loss of leaflet tissue)
Active endocarditis
Mitral valve complexity that would preclude a successful mitral valve repair with an edge-to-edge device (i.e., severe Barlow's disease, commonly associated with multiple jets, excessive redundancy, calcification, or poor coaptation reserve in the leaflets that inhibits restoration of coaptation with TEER)
Short or restricted posterior mitral leaflet (<5 mm in the intended grasping location)
MR that is primarily due to clefts
Intracardiac thrombus that is mobile or may interfere with working in the cardiac chambers
Imaging limitations that preclude adequate mitral valve visualisation
Trans-septal or venous access issues that preclude placement of device
Patients without meaningful expected survival (12 months) or improvement in QoL due to non-mitral valve disease
Patients with <3+/4+ MR by quantitative echocardiographic assessment
Patients with inotropic requirement not thought to be related to mitral valve disease

Abbreviations: MR, mitral regurgitation; QoL, quality of life; TEER, transcatheter edge-to-edge repair.
Source: Lim 2021.[141]

3.6 THE CLIP SELECTION

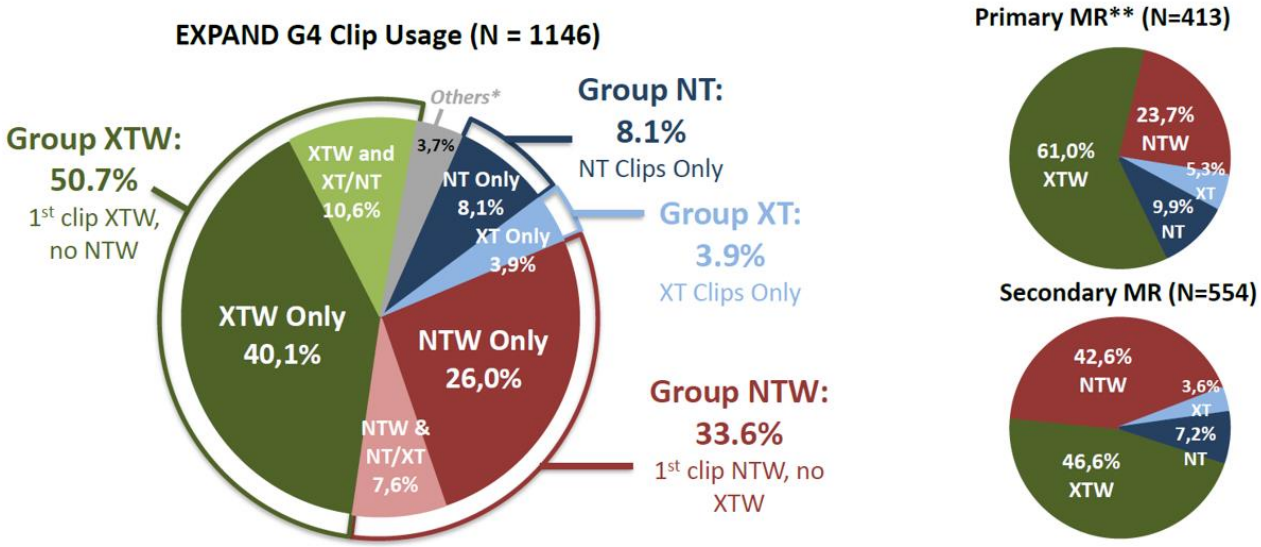
- MitraClip™ G4 clip selection is based on the clinical experience of expert physicians.
- The EXPAND G4 observational study evaluated adherence to clip size selection recommendations and their associated outcomes.
- The latest data from EXPAND G4 shows that the majority of patients are treated with the wider clips (NTW/XTW) as shown in Figure 15.[157, 158]

Table 12. Clip selection by mitral valve anatomy

ANATOMICAL CONSIDERATIONS	FAVOURS G4 NTW	FAVOURS G4 NT	FAVOURS G4 XTW	FAVOURS G4 XT
Leaflet length <9 mm	+	+		
Leaflet length ≥9 mm			+	+
Broad jet	+		+	
Smaller valve		+		
Larger valve	+		+	+

Source: Abbott data on file.

Figure 15. Distribution of MitraClip™ G4 clip size usage among subjects enrolled in EXPAND G4



Abbreviations: MR, mitral regurgitation; PMR, primary mitral regurgitation.
Source: Maisano 2022.[157]
* Others: XTW + NTW, NT/XT followed by XTW/NTW, NT/XT (N=42) were excluded from this analysis.
** PMR includes PMR only (n=405) and mixed aetiology patients (n=8).

3.7 MORTALITY PREDICTORS AFTER MITRACLIP™ IMPLANTATION

- The typical patient requiring MitraClip™ Therapy is older and has multiple comorbidities. Various clinical, anatomic, and procedural factors have been recognised as being predictors of adverse outcomes following MitraClip™ implantation.[159] For this reason, research has focused on identifying risk factors that predict the likelihood of mortality post-MitraClip™.[160]
- Some predictors of mortality post-MitraClip™ include: advanced age,[161] N-terminal-pro-B-type natriuretic peptide (NT-proBNP) >10,000 pg/mL,[161] NYHA class IV, [162] severe TR,[163], procedural failure,[164] and LV ejection fraction <30%.[164]
- An overview of predictors for mortality, as identified by COAPT™, following MitraClip™ implantation is provided in Table 13.

Table 13. Overview of predictors for mortality in SMR patients after MitraClip™ therapy

PREDICTORS FOR MORTALITY IN COAPT™ (HRS ARE VERSUS GDMT-TREATED PATIENTS)				
RVSP >45 mmHg†	2 years	HR 1.85, p<0.001	COAPT™[165]	N=614
TR grade ≥2+†	2 years	HR 1.42, p=0.028	COAPT™[165]	N=614
LVESD >5.5 cm†	2 years	HR 1.38, p=0.031	COAPT™[165]	N=614
NT-proBNP ≥ median‡ at baseline	2 years	HR 0.60, p=0.005 (vs 0.95 in MC patients with NT-proBNP < median)	COAPT™[166]	N=614

Abbreviations: GDMT, guideline-directed medical therapy; HR, hazard ratio; LVESD, left ventricular end-systolic diameter; MC, MitraClip™; NT-proBNP, N-terminal-pro-B-type natriuretic peptide; RVSP, right ventricular systolic pressure; SMR, secondary mitral regurgitation; TR, tricuspid valve regurgitation.

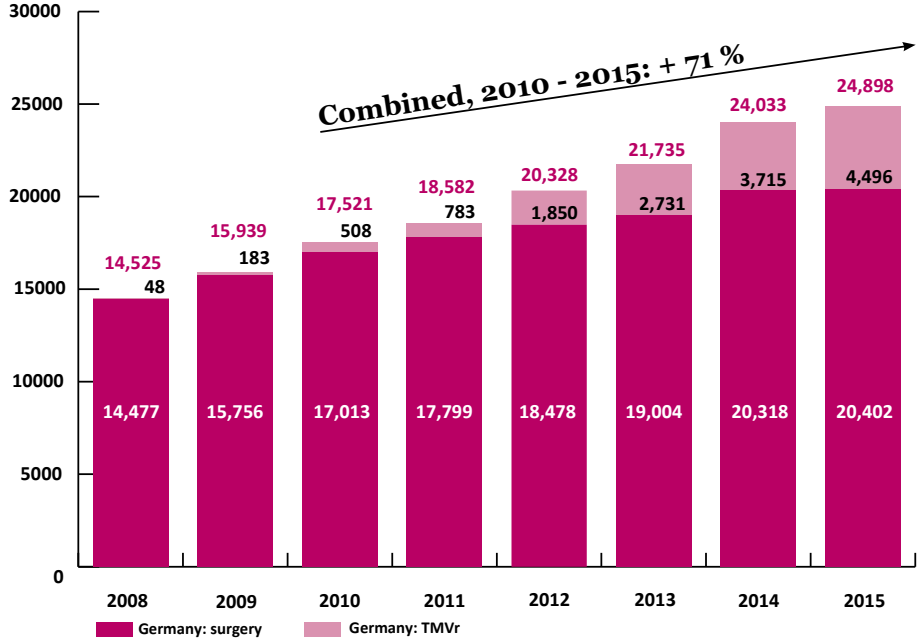
† HR is not specific to mortality but for a composite endpoint of mortality and hospitalisation for heart failure.

‡ The baseline median NT-proBNP (for all patients enrolled – both MC and GDMT-treated) was 3,089.

3.8 IMPACT OF MITRACLIP™ SYSTEM ON HEART VALVE CENTRES

- MitraClip™ offers a further treatment option for high-risk or inoperable MR patients; a 2015/16 survey conducted by the European Association of Percutaneous Cardiovascular Interventions (EAPCI) revealed that across 129 European heart centres, 91.8% had performed the MitraClip™ technique when treating MR with transcatheter procedure.[167]
- The availability of MitraClip™ initially raised concern that it would have a detrimental impact on mitral valve surgery volumes. However, analyses performed by single centres have demonstrated that the availability of MitraClip™ has resulted in an increase in mitral valve referrals and did not decrease the amount of mitral valve surgeries performed.
- In Germany between 2008 and 2015, overall mitral valve procedure volumes grew by 71%, driven by both TEER (9,267%) and surgical procedure growth (41%), as shown in Figure 16.[168]

Figure 16. TEER and non-TEER procedure volumes in Germany 2008–2015



Abbreviations: TEER, transcatheter edge-to-edge repair; TMVr, transcatheter mitral valve repair.
Source: Schaefer 2018.[168]

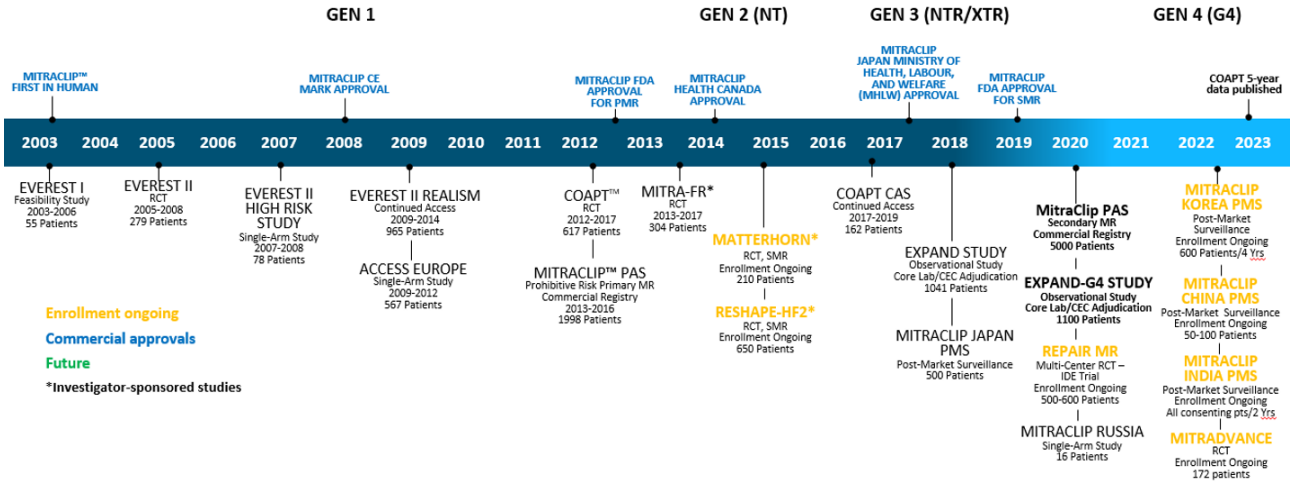
- There was a significant increase in the number of MitraClip implantations performed in Germany between 2011 and 2017. Patients treated in low throughput centres (≤10 procedures annually) had a greater risk of pulmonary embolism (odds ratio [OR]: 2.22 [95% CI: 1.19–4.13]; p=0.012) versus those treated in high-throughput centres. No association was found between centre procedure volume and in-hospital mortality (p=0.728).[169]
- A study of surgical and percutaneous mitral valve reconstructions performed in Germany between 2009 and 2015 revealed that annual overall procedural numbers more than doubled over the period, with a large increase in the percutaneous edge-to-edge technique and a slight increase in surgical mitral valve reconstructions. Patients undergoing the percutaneous approach tended to be older and at higher procedural risk than those undergoing surgical mitral valve repair, indicating that the availability of a percutaneous strategy has enabled the treatment of a previously untreated population.[170, 171] This trend was consistent across patient age groups.
- US single centre experience: Of 468 patients referred for MitraClip™ between 2007 and 2014, 33.3% received MitraClip™ whilst 17.5% (82 patients) underwent surgical interventions. The volume of isolated mitral valve operations increased by 80%.[172]

- **The efficacy and safety of the MitraClip™ System in the treatment of MR patients who are not considered suitable candidates for surgery has been consistently demonstrated.**
- **With an evidence base that includes the largest real-world dataset,[c] more than 3,200 scientific papers pertaining to the device have been published and over 80,000 patients have been treated with MitraClip™ in clinical trials spanning up to 5 years follow-up. (Abbott data on file)**
- **In COAPT™, 5 year outcomes showed that MitraClip™ + GDMT was safe, reduced the rate of HF hospitalisation, improved NYHA status, provided durable repair, and improved survival compared with GDMT alone.[15]**
- **EXPANDed is a pooled, patient level cohort combining EXPAND and EXPAND G4, and represents the largest core lab-assessed dataset from 2,000+ patients with MR. Of the 1,847 patients with echocardiographic data, 90% had MR severity ≤1+ at 30 days, with significant improvements in NYHA class and QoL.[16]**
- **MitraClip™ Therapy is associated with:**
  - **High acute procedural success rates (MR grade ≤2+)[20, 22, 24-27]**
  - **Low 30-day mortality and adverse event rates[20, 22, 24, 26-28]**
  - **Reduced long-term (up to 5 years) mortality versus medical therapy in patients with SMR[15, 20-23]**
  - **Significant and sustained reduction in MR severity for up to 5 years[20 14, 15, 20-22, 24-28]**
  - **Significant and sustained improvement in New York Heart Association (NYHA) functional status for up to 5 years[14, 15, 20-22, 24-27]**
  - **Improved quality of life (QoL)[20, 21, 29]**
  - **Positive impact on left ventricle remodelling[14, 20, 25, 28]**
  - **Reduction in HF hospitalisations in patients with PMR and SMR for up to 5 years[15, 25, 30]**
  - **Effective treatment of complex MV anatomies[25]**

4.1 SUMMARY OF THE CLINICAL EVIDENCE

- Evidence for the efficacy and safety of MitraClip™ is drawn from numerous clinical trials and real-world studies, with data available up to 5 years post-procedure,[14, 15] as well as a number of ongoing studies (Figure 17).
- A list of clinical trials and details of additional non-RCT clinical evidence for MitraClip™, as well as an overview of systematic reviews and network meta-analyses (NMAs) involving MitraClip™, are provided in the separate appendix document.

Figure 17. MitraClip™ clinical trial programme and global experience



Abbreviations: CAS, Continued Access Study; CEC, Clinical Endpoint Committee; FDA, Food and Drug Administration; IDE, investigational device exemption; MR, mitral regurgitation; PAS, Post Authorisation Study; PMR, primary mitral regurgitation; PMS, post-market surveillance; RCT, randomised controlled trial; SMR, secondary mitral regurgitation.

[c] EXPANDed is the largest real-world patient cohort (n=2,205) with echo-core lab-assessed outcomes to date.[16]

4.1.1 BASELINE CHARACTERISTICS OF PATIENTS ENROLLED IN MITRACLIP™ STUDIES

- The MR patients enrolled in MitraClip™ RCTs were generally elderly, with the majority in NYHA Class III and IV and MR 3+.[d]

Table 14. Baseline characteristics of patients enrolled in MitraClip™ RCTs

	COAPT™ (SMR)		MITRA-FR (SMR)		EVEREST II (PMR, SMR)	
	MITRACLIP™	GDMT	MITRACLIP™	GDMT	MITRACLIP™	SURGERY
PATIENTS, N	302	312	152	152	184	95
AGE, MEAN ± SD, YEARS	71.7 ± 11.8	72.8 ± 10.5	70.1 ± 10.1	70.6 ± 9.9	67.3 ± 12.8	65.7 ± 12.9
MALES, % (N)	66.6 (201)	61.5 (192)	78.9 (120)	70.4 (107)	62 (115)	66 (63)
PMR, % (N)	NA	NA	NA	NA	73 (135)	73 (69)
SMR, % (N)	100 (302)	100 (312)	100 (152)	100 (152)	27 (49)	27 (26)
NYHA CLASS III, % (N)	51.0 (154)	53.8 (168)	53.9 (82)	63.2 (96)	45 (82)	43 (41)
NYHA CLASS IV, % (N)	6.0 (18)[†]	10.6 (33)[†]	9.2 (14)	7.9 (12)	7 (12)	4 (4)
MR 3+, % (N)	49.0 (148)	55.3 (172)	-	-	71 (130)	71 (67)
MR 4+, % (N)	51.0 (154)	44.7 (139)	-	-	25 (46)	22 (21)

[†] IVa, ambulatory.
Abbreviations: GDMT, guideline-directed medical therapy; MR, mitral regurgitation; NA, not applicable; NYHA, New York Heart Association; PMR, primary mitral regurgitation; RCT, randomised controlled trial; SD, standard deviation; SMR, secondary mitral regurgitation.
Sources: COAPT™, Stone 2018;[20] MITRA-FR, Obadia 2018;[22] EVEREST II, Feldman 2011.[28]

- The MR patients enrolled in the latest registries were generally elderly, with the majority having NYHA CLASS III and IV.

Table 15. Baseline characteristics of patients enrolled in MitraClip™ contemporary registries

	EXPAND G4 (PMR, SMR)	EXPAND (PMR, SMR)	COAPT™ PAS (SMR)	TVT (PMR, SMR)	OCEAN-Mitral (PMR, SMR)
PATIENTS, N	1,164	1,041	5,000	33,878	2,150
AGE, MEAN ± SD, YEARS	77.5 ± 9.1	77.3 ± 9.7	73.1 ± 11.3	80[†]	80[†]
MALES, % (N)	55.8 (650)	54.9 (571)	57.6 (2,880)	53.68 (18,186)	56.2 (1,290)
PMR, % (N)	43.0 (424/986)	50.5 (422)	NA	72.03 (24,403)	29.7 (639)
SMR, % (N)	58.4 (580/993)	49.5 (413)	100 (5,000)	11.59 (3,925)	75.2 (1,617)
NYHA CLASS III, % (N)	-	78.6 (817)	85.7 (4,254/4,964)	61.27 (20,758)	48.7 (1,047)
NYHA CLASS IV, % (N)	-			21.22 (7,188)	14.5 (312)
MR 3+, % (N)	-	56.0 (509)	-	-	28.0 (601)
MR 4+, % (N)	-		75.8 (3,769/4,975)	-	61.0 (1,311)
TR 3+ or 4+, % (N)	8.1 (80/981)	21.5 (174)	-	-	-

[†] Median.
Abbreviations: MR, mitral regurgitation; NYHA, New York Heart Association; PAS, post-approval study; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation; TR, tricuspid regurgitation.
Sources: EXPAND G4, von Bardeleben 2023;[173, 174] EXPAND, Kar 2023;[25] COAPT™ PAS, Goel 2022;[26] TVT, Mack 2022;[175] OCEAN-Mitral, Kubo 2023.[176]

[d] NYHA Classification - The Stages of Heart Failure:
1. Class I - No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
2. Class II - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
3. Class III - Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20—100 m). Comfortable only at rest.
4. Class IV - Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.
5. No NYHA class listed or unable to determine.

4.1.2 OVERVIEW OF KEY RCT EVIDENCE

4.1.2.1 COAPT™

- COAPT™[15, 20, 21] enrolled 614 patients between 2012 and 2017 from 78 centres in the US and Canada. Patients had moderate-to-severe (3+) or severe (4+) SMR and remained symptomatic despite use of maximal doses of GDMT.
- Patients were randomised (1:1) to receive treatment with either MitraClip™ + GDMT (N=302) or GDMT alone (N=312).
- The primary efficacy outcome was all hospitalisations for HF within 2 years of follow-up, including recurrent events in patients with more than one event.
- Secondary efficacy outcomes included MR ≤2+, all-cause death, death or hospitalisation for HF, and all-cause hospitalisations at 1 and 2 years of follow-up.
- Five-year outcomes showed that MitraClip™ + GDMT was safe, reduced the rate of HF hospitalisation, improved NYHA status, provided durable repair, and improved survival compared with GDMT alone.[15]

Table 16. Key COAPT™ 1-, 2-, 3-, and 5-year results

		MITRACLIP™ (N=302)	GDMT (N=312)	HR (95% CI)
1 year	**All-cause death, KM % (events)**	19.1 (57)	23.2 (70)	0.81 (0.57–1.15; p<0.001)†
2 years	**All-cause death, KM % (events)**	29.1 (80)	46.1 (121)	0.62 (0.46–0.82; p<0.001)
	All-cause hospitalisation, annualised rate (events/TPY)	106.2 (474/446.5)	146.4 (610/416.8)	0.76 (0.60–0.96; p=0.02)
	HFH, annualised rate (events/TPY)‡	35.8 (160/446.5)	67.9 (283/416.8)	0.53 (0.40–0.70; p<0.001)
3 years	**All-cause death, KM % (events)**	42.8 (112)	55.5 (150)	0.67 (0.52–0.85; p=0.001)
	All-cause death or HFH, KM % (events)	58.8 (161)	88.1 (244)	0.48 (0.39–0.59; p<0.0001)
	HFH, annualised rate (events/TPY)	35.5 (220/619.7)	68.8 (378/549.5)	0.49 (0.37–0.63; p<0.0001)
5 years	**All-cause death, KM % (events)**	57.3 (162)	67.2 (189)	0.72 (0.58–0.89)
	All-cause death or HFH, % (events)	73.6 (213)	91.5 (266)	0.53 (0.44–0.64)
	All-cause hospitalisation, % (events)	88.3 (251)	94.9 (270)	0.75 (0.63–0.89)
	HFH, annualised rate (events)	33.1 (314)	57.2 (447)	0.53 (0.41–0.68)
	HFH, KM % (events)	61.0 (151)	83.0 (208)	0.49 (0.40–0.61)

† Tested for non-inferiority.
‡ Primary efficacy endpoint.
Abbreviations: CI, confidence interval; GDMT, guideline-directed medical therapy; HFH, heart failure hospitalisation; HR, hazard ratio; KM, Kaplan–Meier; TPY, total patient-years.
Sources: 1/2 years, Stone 2018;[20] 3 years, Mack 2021;[21] 5 years, Stone 2023.[15]

4.1.2.2 MITRA-FR

- MITRA-FR[22, 23] enrolled 304 symptomatic HF patients between 2013 and 2017 from 37 centres in France.
- Patients had severe SMR and were randomised (1:1) to receive treatment with either MitraClip™ + medical therapy (N=152) or medical therapy alone (N=152).
- The primary efficacy outcome was the composite of all-cause death and unplanned hospitalisation for HF at 1 year.
- Secondary efficacy outcomes included individual components of the primary outcome: cardiovascular death, and survival free from major cardiovascular events (death, stroke, myocardial infarction, or unplanned hospitalisation for HF) at 1 year.
- MitraClip™ + medical therapy did not result in significantly reduced risk of death or hospitalisation for HF at 1 year or 2 years compared with medical therapy alone. The cumulative incidence of all hospitalisations for HF within 2 years was lower among patients treated with MitraClip™ + medical therapy (88.3 per 100 patient-years) versus those who received medical therapy alone (106.9 per 100 patient-years; HR: 0.87; 95% CI: 0.56–1.35).

Table 17. Key MITRA-FR 1- and 2-year results

		MITRACLIP™ N=152	GDMT N=152	HR (95% CI)
1 year	**All-cause death and unplanned HFH, % (events)**	54.6 (83)	51.3 (78)	1.16 (0.73–1.84; p=0.53)
	All-cause death, % (events)	24.3 (37)	22.4 (34)	1.11 (0.69–1.77)
	CV death, % (events)	21.7 (33)	20.4 (31)	1.09 (0.67–1.78)
	Unplanned HFH, % (events)	48.7 (74)	47.4 (72)	1.13 (0.81–1.56)
	Major CV AE, % (events)	56.6 (86)	51.3 (78)	1.22 (0.89–1.66)
		N=109	N=137	
2 years	**All-cause death and unplanned HFH, % (events)**	64.2 (70)	68.6 (94)	1.04 (0.76–1.42)
	All-cause death, % (events)	33.9 (37)	35.0 (48)	0.99 (0.64–1.52)
	CV death, % (events)	31.2 (34)	32.1 (44)	0.99 (0.63–1.55)
	Unplanned HFH, % (events)	58.7 (64)	63.5 (87)	1.03 (0.74–1.43)
	Major CV AE, % (events)	66.1 (72)	68.6 (94)	1.09 (0.80–1.48)

Abbreviations: AE, adverse event; CI, confidence interval; CV, cardiovascular; GDMT, guideline-directed medical therapy; HFH, heart failure hospitalisation; HR, hazard ratio.
Source: 1 year Obadia 2018;[22] 2 years Iung 2019.[23]

4.1.2.3 MITRA-FR VERSUS COAPT™ – TWO DIFFERENT TRIALS, TWO DIFFERENT PATIENT POPULATIONS

- In addition to differences in trial design, the respective patient populations of the COAPT™ and MITRA-FR studies differed in their clinical characteristics, perhaps explaining why COAPT™ demonstrated statistically significant superiority of MitraClip™ (over GDMT) whereas MITRA-FR did not.[57]
- In COAPT, Clinical Event Committee (CEC) confirmed patients were failing maximally tolerated GDMT at baseline and few major changes were made during follow-up. In MITRA-FR, patients received HF medication at baseline and variable adjustments in each group were allowed during the follow-up per 'real-world' practice.

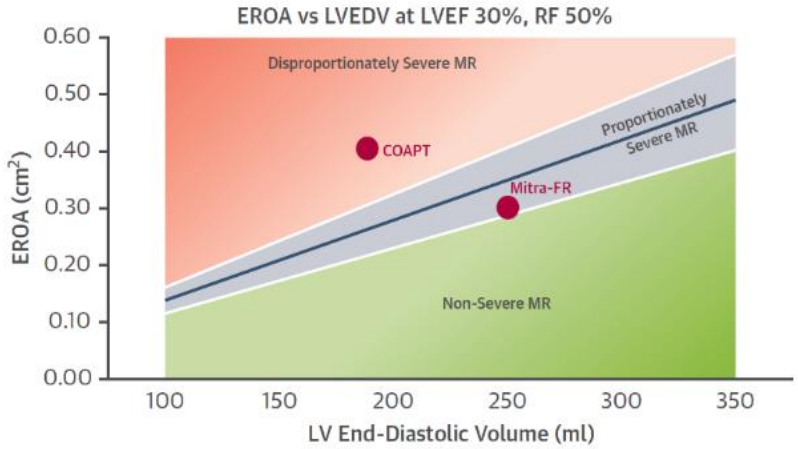
Table 18. Key differences between patients randomised to MitraClip™ in the COAPT™ and MITRA-FR trials

	COAPT™ (N=612)	MITRA-FR (N=304)
Primary efficacy endpoint	Hospitalisation for HF within 1 year (including recurrent events)	All-cause death and unplanned hospitalisation for HF at 1 year
Moderate to severe SMR entry criteria	US guidelines: EROA >30 mm^2 or RV >45 mL/beat	EU guidelines: EROA >20 mm^2 or RV >30 mL/beat
Patients randomised to MitraClip™	302	152
Age, mean ± SD, years	72 ± 12	70 ± 10
LVEF, mean ± SD, %	31 ± 10	33 ± 7
EROA, mean ± SD, mm^2	41 ± 15	31 ± 10
Indexed LVEDV, mean ± SD, mL/m^2	101 ± 34	135 ± 35
Prior HF hospitalisation within 1 year, %	58.3	100
Device implanted, % (events)	95.0 (293)	90.8 (138)
Implantation of multiple clips, % (events)	61.7 (181/293)	54.3 (75/138)
Complications, %†	8.5	14.6
Post-procedural MR grade ≤2+, %‡	95.0	91.9
MR grade ≤2+ at 1 year, %‡	94.8	83
Hospitalisation for HF at 1 year, %	35.8§	48.7
30-day mortality, %	2.3	3.3
1-year mortality, %	19.1	24.3

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; EACTS, European Association for Cardio-Thoracic Surgery; EROA, effective regurgitant orifice area; ESC, European Society of Cardiology; HF, heart failure; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; RV, regurgitation volume; SD, standard deviation.
† MITRA-FR definition: device implant failure, transfusion or vascular complication requiring surgery, atrial septal defect, cardiogenic shock, cardiac embolism/stroke, tamponade, urgent cardiac surgery.
‡ According to AHA/ACC guidelines in COAPT™ and ESC/EACTS guidelines in MITRA-FR.
§ Annualised HFH rate at 2 years.
Source: Pfister 2019;[177] Pibarot 2019,[178] Praz 2019;[57] COAPT™, Stone 2018; [20] MITRA-FR, Obadia 2018.[22]

- Patients with SMR represent a heterogeneous group that may be subdivided based on left ventricular end-diastolic volume (LVEDV) to inform treatment, with those patients with LVEDV that is proportionate to their MR volume likely to benefit from treatment that reduces LVEDV whereas those with disproportionate LVEDV/MR likely to benefit from interventions directed at the mitral valve.[179]
- MITRA-FR enrolled patients who had MR that was proportional to LVEDV and failed to demonstrate a significant difference in clinical outcomes (including LVEDV) between MitraClip™ versus GDMT-treated patients.[179]
- In comparison, patients enrolled in COAPT™ had an EROA ~30% higher but left ventricle volumes that were ~30% smaller, indicative of disproportionate MR. In these patients, TEER (MitraClip™) reduced the risk of death and hospitalisation for HF compared with conventional mitral valve surgery, and these benefits were paralleled by a meaningful decrease in LVEDV from baseline (Figure 18).[179]

Figure 18. Relationship between EROA and LVEDV, illustrating domains that define disproportionately severe, proportionately severe, and non-severe SMR



Abbreviations: EROA, effective regurgitant orifice area; LVEDV, left ventricular end-diastolic volume; RF, rheumatoid factors; SMR, secondary mitral regurgitation.
Source: Grayburn 2019.[179]

4.1.2.4 EVEREST II

- EVEREST II enrolled 279 patients between 2005 and 2008 in 37 centres in North America. Patients had grade 3+ or 4+ MR (PMR or SMR), and were randomised 2:1 to receive MitraClip™ (N=184) or mitral valve surgery (N=95).[14, 28]
- The primary efficacy outcome was freedom from death, surgery for mitral valve dysfunction, and 3+ and 4+ MR with patients followed-up for 5 years.
- Secondary efficacy outcomes included freedom from death, freedom from surgery for mitral valve dysfunction, and freedom from death and surgery for mitral valve dysfunction.
- At 5 years, 44.2% of MitraClip™ patients remained free from death, surgery for mitral valve dysfunction, and grade 3+/4+ MR compared with 64.3% of patients who underwent conventional surgery (p=0.01).
- Patients treated with MitraClip™ more commonly required surgery for residual MR during the first year after treatment. However, between 1 and 5-years of follow-up, comparably low rates of surgery for mitral valve dysfunction were observed in MitraClip™ and surgery arms.
- Overall, the final 5-year results from EVEREST II clearly support the long-term safety and durability of MR reduction with MitraClip™ TEER.

Table 19. Key EVEREST II 1- and 5-year results

		MITRACLIP™	SURGERY	P-VALUE
		N=181	N=89	
1 year	**Freedom from death, surgery for MV dysfunction, and 3+ and 4+ MR, % (N)**	55 (100)	73 (65)	p<0.007
	Death, % (N)	6 (11)	6 (5)	p=1.00
	MV surgery or reoperation, % (N)	20 (37)	2 (2)	p<0.001
	3+ or 4+ MR, % (N)	21 (38)	20 (18)	p=1.00
		N=154	N=56	
5 years	**Freedom from death, surgery for MV dysfunction, and 3+ and 4+ MR, % (N)**	44.2 (68)	64.3 (36)	p=0.01
	Death, % (N)	20.8 (32)	26.8 (15)	p=0.36
	MV surgery or reoperation, % (N)	27.9 (43)	8.9 (5)	p=0.003
	3+ or 4+ MR, % (N)	12.3 (19)	1.8 (1)	p=0.02

Abbreviations: MR, mitral regurgitation; MV, mitral valve. Source: Feldman 2011;[28] Feldman 2015.[14]

4.2 EFFICACY AND SAFETY OF MITRACLIP™ THERAPY

MitraClip™ Therapy is associated with:

- **High acute procedural success rates**
- **Low 30-day mortality and adverse event rates**
- **Reduced long-term (up to 5 years) mortality versus medical therapy in patients with SMR**
- **Significant and sustained reduction in MR severity for up to 5 years**
- **Significant and sustained improvement in NYHA functional status for up to 5 years**
- **Significant improvement in patient quality of life (QoL)**
- **Positive impact on left ventricle remodelling**
- **Reduction in HF rehospitalisations in patients with PMR and SMR for up to 5 years**
- **Effective treatment of complex anatomies**

4.2.1 ACUTE PROCEDURAL SUCCESS

MitraClip™ Therapy is associated with high acute procedural success rates across a range of different studies

- Acute procedural success is defined as a reduction in MR grade to ≤2+ immediately after MitraClip™ implantation, which corresponds to none (0), mild (1+), or moderate (2+) MR.[14]

Table 20. Acute procedural success rate (MR grade ≤2+ post-implantation) across key MitraClip™ studies

	RCT EVIDENCE					CONTEMPORARY REAL-WORLD EVIDENCE			
	COAPT™ (SMR)		MITRA-FR (SMR)		EVEREST II (PMR, SMR)	EXPAND G4 (PMR, SMR)	EXPAND (PMR, SMR)	COAPT™ PAS (SMR)	TVT (PMR, SMR)
	MITRACLIP™	GDMT	MITRACLIP™	GDMT					
Acute procedural success rate, %	95.0	NA	91.9	NA	NR	96.2	95.8	NR	92.9[†]

[†] Success rate in the third tertile of case experience (cases 52–482).
Abbreviations: NA, not applicable; NR, not reported; PAS, post-approval study; PMR, primary mitral regurgitation; RCT, randomised controlled trial; SMR, secondary mitral regurgitation.
Sources: COAPT™, Stone 2018;[20] MITRA-FR, Obadia 2018;[22] EXPAND G4, von Bardeleben 2023;[173] EXPAND, Kar 2023;[25] COAPT™ PAS, Goel 2022;[26] TVT, Chhatriwalla 2019.[27]

RCT EVIDENCE	
COAPT™ (SMR)	Among the 260 patients in whom echocardiography was performed at the time of discharge, the MR grade was 1+ or lower in 214 patients (82.3%), and 2+ in 33 patients (12.7%).[20]
MITRA-FR (SMR)	At the time of discharge from the hospital, assessments of the severity of MR were available for 123 patients in the intervention group. Of these patients, 117 (95.1%) had a reduction in MR of at least one grade, and 113 patients (91.9%) had reduction of MR to 2+ (mild to moderate) or lower.[22]

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

CONTEMPORARY REAL-WORLD EVIDENCE	
EXPAND G4 (PMR, SMR)	The acute procedural success rate was 96.2% (1,099 of 1,143).[173]
EXPAND (PMR, SMR)	Implantation success rate was 98.9% (1,030/1,041), and acute procedural success rate was 95.8% (985/1,028).[25]
TVT (PMR, SMR)	There was a small, but statistically significant, improvement in rates of acceptable procedural success (defined as MR grade ≤2, no mortality or need for cardiac surgery) with increasing institutional experience (1–18, 19–51, and 52–482 cases): 91.2%, 91.2%, 92.9%, respectively (p=0.006).[27] Increasing MitraClip™ case count (10, 50, 100, 150, and 200 cases) was associated with an increase in the adjusted proportions of patients achieving acceptable procedural success: 92.2%, 92.3%, 93.5%, 94.9%, and 96.1%, respectively.[27]

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

4.2.2 30-DAY MORTALITY AND ADVERSE EVENT (AE) RATES

MitraClip™ Therapy is associated with low 30-day mortality and adverse event rates across a range of different studies

- EVEREST II: Major AEs were defined as a composite of death, MI, reoperation for failed mitral valve surgery, nonelective cardiovascular surgery for adverse events, stroke, renal failure, deep wound infection, mechanical ventilation for more than 48 hours, gastrointestinal complication requiring surgery, new-onset permanent AF, septicaemia, and transfusion of 2 units or more of blood.[28]
- MITRA-FR: Major cardiovascular AEs were defined as a composite incorporating a number of events including death, MI, stroke and renal failure.[22]
- EXPAND G4: Major AEs were defined as all-cause death, MI, stroke, or non-elective cardiovascular surgery for device-related complications.[24]

Table 21. 30-day mortality and adverse event rates across key MitraClip™ studies

30-DAY OUTCOMES	RCT EVIDENCE						CONTEMPORARY REAL-WORLD EVIDENCE			
	COAPT™ (SMR)		MITRA-FR (SMR)		EVEREST II (PMR, SMR)					
	MITRACLIP™	GDMT	MITRACLIP™	GDMT	MITRACLIP™	SURGERY	EXPAND G4 (PMR, SMR)	EXPAND (PMR, SMR)	COAPT™ PAS (SMR)	TVT (PMR, SMR)
Death, % (N)	2.3 (7)	1.0 (3)	3.3 (5)	2.6 (4)	1 (2)	2 (2)	1.3 (15)	2.3	4.0	4.5 (1,398)
MAEs, % (N)	-	-	-	-	15 (27)	48 (45)	2.7 (31)	-	-	-
Hospitalisation, % (N)	13.0 (39)	12.6 (39)	-	-	-	-	-	-	-	-
MV reoperation, % (N)	1.0 (3)	0.3 (1)	-	-	0	1 (1)	-	-	-	1.1 (340)
MI, % (N)	1.0 (3)	0	-	-	0	0	0.2 (2)	0	-	-
Stroke, % (N)	0.7 (2)	0	-	-	1 (2)	2 (2)	0.5 (6)	0.5	-	1.3 (399)
CV reintervention, % (N)	0.3 (1)	1.0 (3)	-	-	2 (4)	4 (4)	0.9 (10)‡	1.1‡	-	-
SLDA, % (N)	-	-	-	-	-	-	1.0 (12)	1.7	-	1.3 (392)
Renal failure, % (N)	-	-	-	-	<1 (1)	0	-	-	-	0.9 (273)§

† Any complication occurring post-implantation (not specifically MAEs).
‡ Non-elective cardiovascular surgery for device-related complications.
§ Rate of dialysis at 30 days.
Abbreviations: AF, atrial fibrillation; CV, cardiovascular; GDMT, guideline-directed medical treatment; MAE, major adverse event; MI, myocardial infarction; MV, mitral valve; PAS, post-approval study; PMR primary mitral regurgitation; RCT, randomised controlled trial; SLDA; single leaflet device attachment; SMR, secondary mitral regurgitation; TVT, Transcatheter Valve Therapy.
Sources: COAPT™, Stone 2018;[20] MITRA-FR, Obadia 2018;[22] EVEREST II, Feldman 2011;[28] EXPAND G4 & EXPAND, von Bardeleben 2023;[173] COAPT™ PAS, Goel 2022;[26] TVT, Mack 2022.[175]

RCT EVIDENCE	
COAPT™ (SMR)	Among patients randomised to receive MitraClip™, the 30-day rate of death was 2.3% (n=7) compared with 1.0% (n=3) in the control group. The lower mortality predominantly emerged > 1 year after treatment, a delayed response consistent with long-term benefits from a durable decrease in the severity of left ventricular volume overload.[20] A total of 55 adverse events were reported within 30 days in the MitraClip™ arm versus 46 in the control arm. The most frequently reported adverse events within 30 days in the MitraClip™ arm were all-cause death, all-cause hospitalisation, unplanned mitral valve intervention, and myocardial infarction. The most frequently reported adverse events within 30 days in the GDMT control arm were all-cause death, all-cause hospitalisation, and LVAD implant. Except for non-HF-related hospitalisations (n=9 and n=3 for MitraClip™ and GDMT arms, respectively; p=0.08), differences in 30-day AE rates between the MitraClip™ and GDMT arms were not statistically significant.[20]
MITRA-FR (SMR)	The 30-day mortality rate was 3.3% (n=5) among patients randomised to receive MitraClip™ compared with 2.6% (n=4) among patients in the control group.[22] Major AE rate at 30 days in MITRA-FR is not reported for either treatment group; however, among patients randomised to receive MitraClip™ (N=152), a total of 21 (14.6%) periprocedural complications were reported during device implantation which included: device implantation failure (n=6), haemorrhage requiring surgical intervention (n=5), atrial septum lesion/defect and cardiogenic shock (both n=4), and cardiac embolism and tamponade (both n=2).[22]
EVEREST II (PMR, SMR)	Within 30 days of the procedure, two patients in the MitraClip™ group (1%) and two patients in the surgery group (2%) had died.[28] MitraClip™ Therapy was associated with significantly fewer major AEs (primary safety endpoint) than mitral valve surgery in the post-procedure period. The rate of major AEs, excluding transfusion at 30 days, was 5% in the MitraClip™ group versus 10% in the surgery group (p=0.23). The rate of any major AEs at 30 days was 15% versus 48% in the surgery group – a difference of 33% (p<0.001).[28]

Abbreviations: AE, adverse event; AF, atrial fibrillation; CI, confidence interval; GDMT, guideline-directed medical therapy; LVAD, left ventricular assist device; PMR, primary mitral regurgitation; RCT, randomised controlled trial; SMR, secondary mitral regurgitation.

CONTEMPORARY REAL-WORLD EVIDENCE	
EXPAND G4 & EXPAND (PMR, SMR)	The EXPAND G4 study demonstrated unprecedented safety, with the lowest 30-day all-cause mortality reported to date and low major AE rates compared with EXPAND (all-cause death, 1.3% vs 2.3%; myocardial infarction, 0.2% vs 0%; stroke, 0.5% vs 1.2%; nonelective CV surgery for device-related complications, 0.9% vs 1.1%; and SLDA, 1.0% vs 1.7%).[173]
COAPT™ PAS (SMR)	Out of 4,116 patients with complete 30-day follow-up, there were a total of 165 deaths from discharge to 30 days (4%).[26]
TVT (PMR, SMR)	In-hospital mortality was 2.2% in the 33,878 MitraClip™ procedures recorded in the TVT registry to March 2020. 30-day mortality was 4.5% overall.[175] A total of 5,834 complications within 30 days reported in the TVT registry of 33,878 MitraClip™ procedures including death (n=1,398; 4.5%), stroke (n=399; 1.3%), mitral valve reintervention (n=340; 1.1%), AF (n=348; 2.9%), SLDA (n=392; 1.3%), ASD closure due to transseptal catheter (n=492; 1.6%), 30-day dialysis (n=273; 0.9%), acute kidney injury ([all stages] n=564; 1.7%), major vascular access site complications (n=161, 0.5%), in-hospital/30-day VARC major or life-threatening/disabling bleed (n=1,467; 4.7%).[175]

Abbreviations: AE, adverse event; ASD, atrial septal defect; PMR, primary mitral regurgitation; SLDA, single leaflet device attachment; SMR, secondary mitral regurgitation; TVT, Transcatheter Valve Therapy.

LEARNING CURVE EVIDENCE	
TVT (PMR, SMR)	A lower rate of procedural complications (13.6%, 12.0%, and 11.5%, respectively; p=0.013), less frequent blood transfusion (10.8%, 8.3%, and 7.5%, respectively; p<0.001), and fewer single-leaflet device detachments (1.3%, 0.9%, and 0.8%, respectively; p=0.05) were observed with increasing institutional case experience.[27]

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

4.2.3 LONG-TERM MORTALITY RATES

Long-term mortality rates favour MitraClip™ Therapy vs medical therapy in patients with SMR as demonstrated in COAPT™

- In COAPT™, the lower mortality predominantly emerged more than 1 year after treatment – a delayed response is consistent with long-term benefits from a durable decrease in the severity of left ventricular volume overload.[20]
- In COAPT™, nearly 99% of MitraClip™-treated patients remained free of device-specific complications, with no new events after 30 days.[15]

Table 22. Pooled long-term (≥1 year) mortality rates across key MitraClip™ studies

		RCT EVIDENCE						CONTEMPORARY REAL-WORLD EVIDENCE			
		COAPT™ (SMR)		MITRA-FR (SMR)		EVEREST II (PMR, SMR)					
		MITRACLIP™	GDMT	MITRACLIP™	GDMT	MITRACLIP™	SURGERY	EXPAND (PMR, SMR)	COAPT™ PAS (SMR)	TVT (PMR, SMR)	OCEAN-MITRAL REGISTRY (PMR, SMR)
Mortality rate, %	**1Y**	19.1	23.2	24.3	22.4	6.1	5.6	14.9	22.2†	23.1	12.3
	2Y	29.1	46.1	34.9	34.2	-	-	-	-	-	-
	3Y	42.8	55.5	-	-	-	-	-	-	-	-
	5Y	57.3	67.2	-	-	20.8	26.8	-	-	-	-

Abbreviations: GDMT, guideline-directed medical therapy; PAS, post-approval study; PMR, primary mitral regurgitation; RCT, randomised controlled trial; SMR, secondary mitral regurgitation.
† Inverse of freedom from all-cause mortality through 1 year.
Sources: COAPT™, 1/2 years Stone 2018,[20] 3 years Mack 2021;[21] 5 years Stone 2023.[15]; MITRA-FR, 1 year Obadia 2018,[22] 2 years Iung 2019;[23] EVEREST II, 1 year Feldman 2011,[28] 5 years Feldman 2015;[14] EXPAND, Kar 2023;[25] COAPT™ PAS, Goel 2022;[26] TVT, Mack 2022;[175] OCEAN-MITRAL Registry, Kubo 2023.[176]

RCT EVIDENCE	
COAPT™ (SMR)	MitraClip™ was superior in reducing all-cause mortality through 3 years, from 55.5% of patients in the control group to 42.8% in the MitraClip™ group (p=0.001). The NNT to save one life was 7.9 (95% CI: 4.6–26.1).[21] Death from any cause through 5 years occurred in 57.3% of patients in the MitraClip™ group and 67.2% in the control group (HR: 0.72; 95% CI: 0.58–0.89).[15] In follow-up analyses of subgroups of patients enrolled in COAPT™: • **Death within 2 years by baseline TR severity** occurred in 27.5% of MitraClip™ patients (versus 39.8% of GDMT patients) with ≤mild TR and in 34.1% of MitraClip™ patients (versus 63.6% of GDMT patients) with ≥moderate TR.[180] • **Death within 2 years by baseline ischaemic versus non-ischaemic cardiomyopathy status** occurred in 29.7% of MitraClip™ patients (versus 45.6% of GDMT patients) with ischaemic disease and in 25.7% of MitraClip™ patients (39.2% of GDMT patients) with non-ischaemic disease.[181] • **Death within 2 years by baseline LV function** occurred in 28.4% of MitraClip™ patients (versus 45.2% of GDMT patients) with HFrEF and in 22.8% of MitraClip™ patients (42.8% of GDMT patients) with HFpEF.[182]
MITRA-FR (SMR)	At both 1 and 2 years of follow-up, all-cause mortality with MitraClip™ plus GDMT was similar to GDMT alone.[22, 23]

RCT EVIDENCE	
EVEREST II (PMR, SMR)	After 1 year, 11 patients had died in the MitraClip™ group (6.2%) and 5 patients had died in the conventional surgery group (5.6%).[28] After 5 years, 20.8% of patients that received MitraClip™ and 26.8% of patients that received conventional surgery had died.[14]

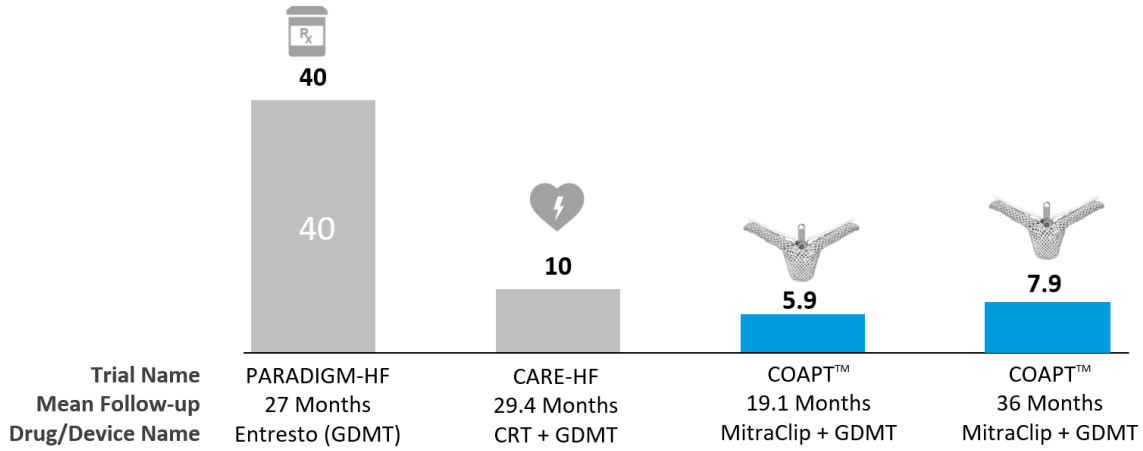
Abbreviations: CI, confidence interval; GDMT, guideline-directed medical therapy; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LV, left ventricle; NNT, number needed to treat; PMR, primary mitral regurgitation; RCT, randomised controlled trial; SMR, secondary mitral regurgitation; TR, tricuspid regurgitation.

CONTEMPORARY REAL-WORLD EVIDENCE	
EXPAND (PMR, SMR)	All-cause mortality at 1 year was 14.9% in the overall population, with a higher mortality rate in the SMR group.[25]
COAPT™ PAS (SMR)	Freedom from all-cause mortality through 1 year was 77.8%.[26]
TVT (PMR, SMR)	At 1 year post-MitraClip™ implantation, the mortality rate was 23.1% (n=4,791).[175]
OCEAN-MITRAL REGISTRY (PMR, SMR)	At 1 year of follow-up, a total of 255 patients (12.3%) had died, of which 159 (7.9%) were cardiovascular causes, and 96 (4.8%) were non-cardiovascular causes. Of the 255 patients that died, 71 (11.6%) had PMR and 184 (12.6%) had SMR.[176]

Abbreviations: PAS, post-approval study; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation.

- MitraClip™ sets a new standard in the treatment of mitral regurgitation, reducing the number needed to treat (NNT) to prevent one death from any cause to 5.9 over a 20-month period, and 7.9 over a 3-year period (Figure 19).[20, 21]

Figure 19. NNT to prevent one death from any cause



Abbreviations: CRT, cardiac resynchronisation therapy; GDMT, guideline-directed medical therapy; NNT, number needed to treat.
Data from different trials with similar follow up periods; incremental benefits due to test drug/device above background therapy.
Sources: McMurray 2014,[183] Cleland 2005,[184] Stone 2018,[20] Mack 2021.[21]

4.2.4 REDUCTION IN MR SEVERITY

Patients treated with MitraClip™ experience a significant sustained reduction in MR severity for up to 5 years

- MR is a progressive disease that increases in severity over time.[185, 186] As MR becomes more severe, morbidity and mortality risk increase.[72, 187] Earlier treatment with TEER is recommended[19, 56] and may improve outcomes.

Table 23. Pooled proportions of patients with MR ≤2+ across key MitraClip™ studies

		RCT EVIDENCE						CONTEMPORARY REAL-WORLD EVIDENCE				
		COAPT™ (SMR)		MITRA-FR (SMR)		EVEREST II (PMR, SMR)						
		MITRACLIP™	GDMT	MITRACLIP™	GDMT	MITRACLIP™	SURGERY	EXPAND G4 (PMR, SMR)	EXPAND (PMR, SMR)	COAPT™ PAS (SMR)	TVT (PMR, SMR)	OCEAN-MITRAL REGISTRY (PMR, SMR)
MR ≤2+, %	DC	-	-	91.9	-	-	-	-	-	93	93.5	96.3
	30d	-	-	-	-	-	-	98	97.8	91	-	-
	1Y	94.8	46.9	-	-	81.7	95.6	98.3	97.5	90.7	-	94.1
	2Y	99.4	46.0	-	-	-	-	-	-	-	-	-
	3Y	98.8	79.6	-	-	-	-	-	-	-	-	-
	5Y	95.0	-	-	-	81	97	-	-	-	-	-

Abbreviations: DC, discharge; GDMT, guideline-directed medical; PAS, post-approval study; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation.
Sources: COAPT™, 1 year Stone 2018;[20] 2/3 years Mack 2021;[21] 5 years Stone 2023;[15] MITRA-FR, Obadia 2018;[22] EVEREST II, 1 year Feldman 2011,[28] 5 years Feldman 2015;[14] EXPAND G4, 30d von Bardeleben 2023;[173] 1 year von Bardeleben 2023;[174] EXPAND, Kar 2023;[25] COAPT™ PAS, DC & 30d Goel 2022;[26] 1 year Goel 2023;[188] TVT, Chhatriwalla 2019;[27] OCEAN-MITRAL Registry, Kubo 2023.[176]

RCT EVIDENCE	
COAPT™ (SMR)	At 1 year, the proportion of patients with MR grade ≤2+ was significantly higher in the MitraClip™ + GDMT arm versus the GDMT alone arm (94.8% versus 46.8%; p<0.001).[20] High rates of MR grade ≤2+ (>90%) were maintained in patients treated with MitraClip™ up to 5 years.[15]
MITRA-FR (SMR)	At discharge, 91.9% of patients treated with MitraClip™ had MR grade ≤2+.[22]
EVEREST II (PMR, SMR)	At baseline, 2% of patients had MR grade ≤2+; 1-year post-MitraClip™ implantation, 81.7% of patients had MR grade ≤2+.[28] Reduction in MR grade was sustained over 5 years – 81% of patients that received MitraClip™ had MR grade ≤2+ at 5 years post-procedure.[14]

Abbreviations: GDMT, guideline-directed medical therapy; MR, mitral regurgitation; PMR, primary mitral regurgitation; RCT, randomised controlled trial; SMR, secondary mitral regurgitation.

CONTEMPORARY REAL-WORLD EVIDENCE	
EXPAND G4 (PMR, SMR)	TEER with the fourth-generation system resulted in significant reduction in MR severity at 30 days compared with baseline (≤1+ in 91%, ≤2+ in 98%; p<0.0001 versus baseline).[173] At 1 year follow-up, 92.9% of patients were ≤1+ (i.e. none/trace or mild MR) and 98.3% were MR ≤2+ (p<0.0001 versus baseline).[174]

CONTEMPORARY REAL-WORLD EVIDENCE	
EXPAND (PMR, SMR)	At 30 days and 1 year of follow-up, respectively, 97.8% and 97.5% of patients had MR grade ≤2+.[25]
COAPT™ PAS (SMR)	At 30 days and 1 year of follow-up, respectively, 93% and 91% of patients had MR grade ≤2+.[26] At 1 year of follow-up, 90.7% of patients remained in MR grade ≤2+.[188]
TVT (PMR, SMR)	Prior to MitraClip™ implantation, the vast majority (93.0%) of patients (N=12,334) had 3+ or 4+ MR. Post-implantation, 93.5% of patients had MR ≤2+.[27]
OCEAN-MITRAL REGISTRY (PMR, SMR)	Upon discharge, 18.8% of patients (405/2,150) had MR 0+ (none to trace), 57.0% (1,225/2,150) had MR 1+ (mild), and 20.5% (440/2,150) had MR 2+. At 1 year of follow-up, 94.1% of patients remained in MR grade ≤2+.[176]

Abbreviations: MR, mitral regurgitation; NYHA, New York Heart Association; PAS, post-approval study; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation; TEER, transcatheter edge-to-edge repair.

4.2.5 NYHA FUNCTIONAL STATUS

Patients treated with MitraClip™ Therapy experience significant and sustained improvement in NYHA functional status for up to 5 years

- Improved patient functional status after MitraClip™ has clear value for patients. They regain their independence and can resume daily activities where previously these would have been inhibited by MR symptoms including fatigue, palpitations, and shortness of breath. In addition, patients will likely be less reliant on caregivers (who may then be able to return to employment) and may have a reduced likelihood of requiring nursing or care home admission in the future.
- Patients who had received treatment with MitraClip™ reported they *"could walk again, climb the stairs again"* and that they felt their *"life had started again."* (Abbott data on file).

Table 24. Pooled proportions of patients in NYHA class I or II across key MitraClip™ studies

		RCT EVIDENCE						CONTEMPORARY REAL-WORLD EVIDENCE				
		COAPT™ (SMR)		MITRA-FR (SMR)		EVEREST II (PMR, SMR)						
		MITRACLIP™	GDMT	MITRACLIP™	GDMT	MITRACLIP™	SURGERY	EXPAND G4 (PMR, SMR)	EXPAND (PMR, SMR)	COAPT™ PAS (SMR)	TVT (PMR, SMR)	OCEAN-MITRAL REGISTRY (PMR, SMR)
NYHA class I or II, %	30d	-	-	-	-	-	-	83	80.1	77	80.4	96.7
	1Y	72.2	49.6	NR	NR	99.0	92.5	82.1	80.3	77	-	95.0
	2Y	59.2	39.3	-	-	-	-	-	-	-	-	-
	3Y	49.0	30.2	-	-	-	-	-	-	-	-	-
	5Y	24.1	15.7	-	-	91.4	97.5	-	-	-	-	-

Abbreviations: GDMT, guideline-directed medical therapy; NYHA, New York Heart Association; PAS, post-approval study; PMR, primary mitral regurgitation; RCT, randomised controlled trial; SMR, secondary mitral regurgitation.
† Based on 112 patients.
Sources: COAPT™, 1 year Stone 2018,[20] 2/3 years Mack 2021,[21] 5 years Stone 2023;[15] MITRA-FR, Obadia 2018;[22] EVEREST II, 1/5 years Feldman 2015;[14] EXPAND G4, 30d von Bardeleben 2023;[173] 1 year von Bardeleben 2023;[174] EXPAND, Kar 2023;[25] COAPT™ PAS, Goel 2022;[26] TVT, Mack 2022;[175] OCEAN-MITRAL Registry, Kubo 2023.[176]

RCT EVIDENCE	
COAPT™ (SMR)	At 1 year, 72.2% of MitraClip™ patients were in NYHA class I or II compared with 49.6% of patients in the control arm (p<0.001).[20] At 2 years, 59.2% of MitraClip™ patients had NYHA class I or II compared with 39.3% of patients in the control arm (p<0.0001). At 3 years, 49.0% of MitraClip™ patients had NYHA class I or II compared with 30.2% of patients in the control arm (p=0.001).[21] At 5 years, 24.1% of MitraClip™ patients had NYHA class I or II compared with 15.7% of patients in the control arm.[15]
EVEREST II (PMR, SMR)	99.0% of MitraClip™ patients were NYHA class I or II after 1 year compared with 92.5% of patients in the surgery group (p=0.03). Improvement in NYHA functional status was maintained over 5 years – 91.4% of patients that received MitraClip™ were NYHA functional class I or II after 5 years compared with 97.5% of patients in the conventional surgery group (p=0.19).[14]

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

CONTEMPORARY REAL-WORLD EVIDENCE	
EXPAND G4 (PMR, SMR)	At 30 days follow-up, 83% of patients were in NYHA class I or II, a significant improvement from baseline (p<0.0001).[173]

CONTEMPORARY REAL-WORLD EVIDENCE	
	At 1 year follow-up, 82.1% of patients remained in NYHA class I or II (p<0.0001 versus baseline).[174]
EXPAND (PMR, SMR)	A total of 80.2% of patients at 30 days and 80.3% of surviving patients at 1 year were in NYHA functional class I/II, in comparison to only 21.5% at baseline (both p<0.0001).[25]
COAPT™ PAS (SMR)	At 30 days post-procedure, 77% of patients were in NYHA class I or II compared with 14% at baseline (p<0.0001).[26]
TVT (PMR, SMR)	At 30 days post-procedure, 80.4% of patients were in NYHA class I or II.[175]
OCEAN-MITRAL REGISTRY (PMR, SMR)	Among the 1,010 patients with complete data, 96.7% and 95.0% had NYHA class I or II at 30 days or 1 year post-procedure, respectively.[176]

Abbreviations: NYHA, New York Heart Association; PAS, post-approval study; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation.

4.2.6 PATIENT QUALITY OF LIFE (QOL)

MitraClip™ Therapy is associated with significant improvements in patient QoL as measured by multiple scoring systems, including KCCQ, 6MWT, and SF-36

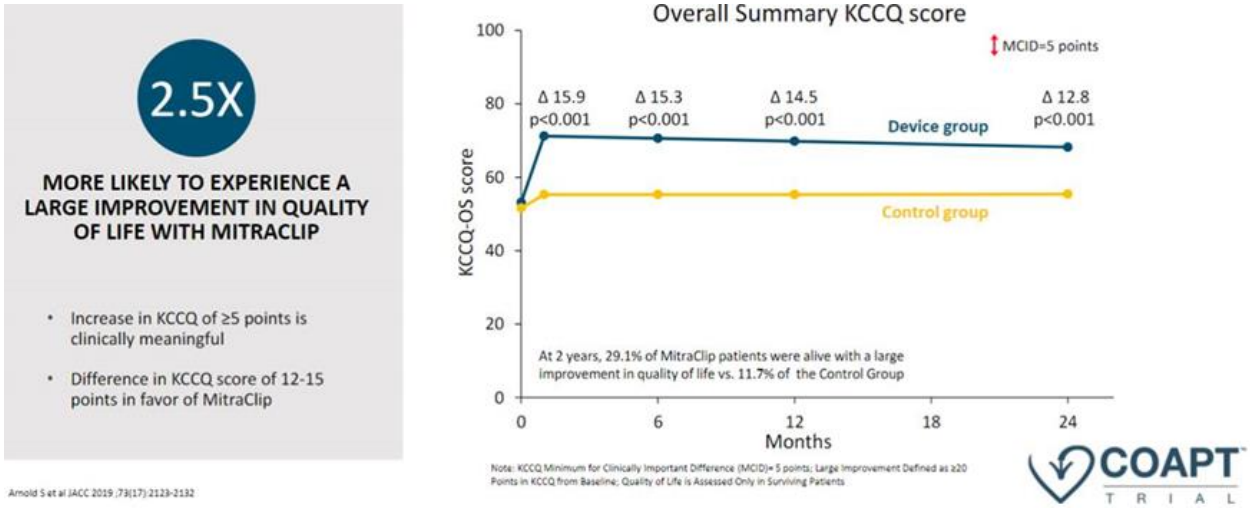
- The KCCQ measures symptoms, physical and social limitations, and QoL in patients with HF. The KCCQ is scored from 1 to 100, with a lower score representing more severe symptoms. The 20-point difference in KCCQ scores observed at 2 years between the two treatment groups in COAPT™ is classified as a very large clinical change.[189]
- The 6MWT is a submaximal exercise test in which the distance a subject can walk over the span of 6 minutes is used as a measure of functional capacity and exercise tolerance.[190, 191] In patients with cardiopulmonary conditions, the 6MWT is a useful tool for assessing prognosis and response to treatment.[191]
- The SF-36 is a generic, easily administered, QoL measure that assesses physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. The measure also includes a single item that provides an indication of perceived change in health.[192]

Table 25. QoL improvements from baseline post-MitraClip™ implantation in COAPT™

		COAPT™ (SMR)			
		Change from baseline		Between group difference	p-value
		MITRACLIP™	GDMT		
6MWT distance, mean ± SD, m	**1Y**	–2.2 ± 9.1	–60.2 ± 9.0	-	p<0.001
	2Y	–55.0 ± 10.8	–93.5 ± 10.9	-	p=0.01
KCCQ overall score, mean (95% CI)	**1Y**	+17.0 (13.6 to 20.3)	+5.1 (1.5 to 8.6)	14.5 (10.9–18.1)	p<0.001
	2Y	+18.4 (13.7 to 23.2)	+5.8 (0.2 to 11.4)	12.8 (7.5–18.2)	p<0.001
SF-36 physical summary score, mean (95% CI)	**1Y**	+5.0 (3.6–6.4)	+0.6 (–0.6–2.2)	4.5 (3.0–6.0)	p<0.001
	2Y	+4.9 (3.1–6.8)	+1.6 (–0.7–3.8)	3.6 (1.4–5.8)	p=0.001
SF-36 mental summary score, mean (95% CI)	**1Y**	+4.3 (2.5–6.1)	+1.9 (–0.0–3.8)	4.4 (2.6–6.2)	p<0.001
	2Y	+4.2 (1.6–6.8)	–0.5 (–3.3–2.2)	3.6 (0.8–6.4)	p=0.011

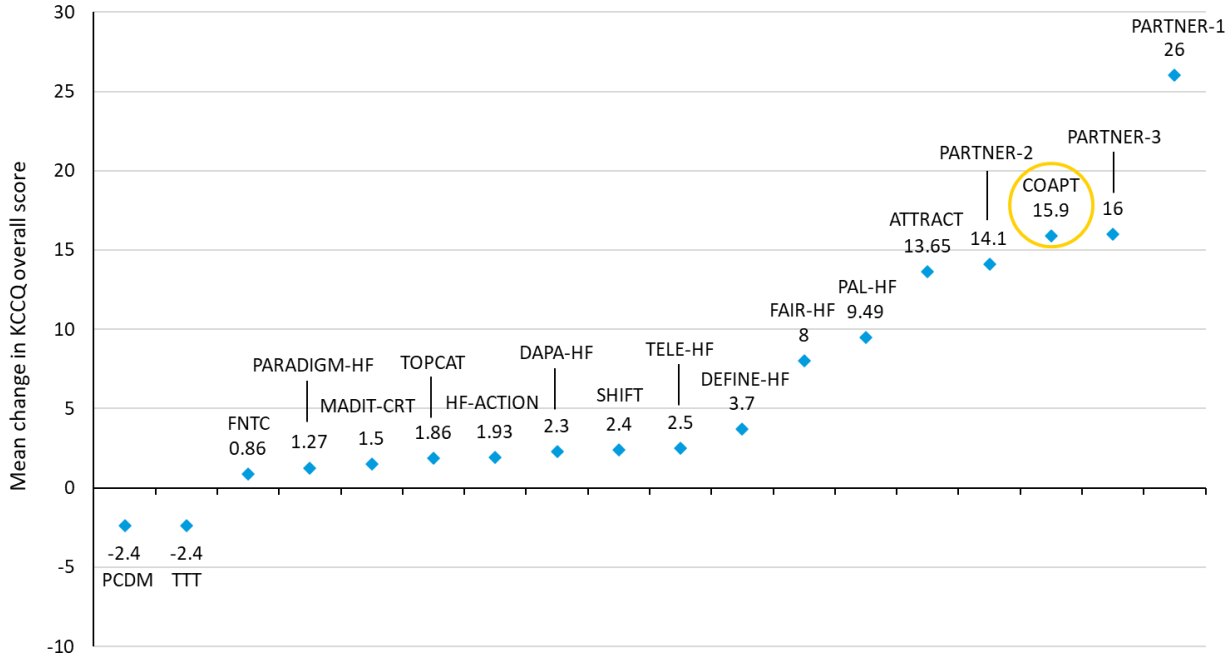
Abbreviations: GDMT, guideline-directed medical therapy; KCCQ, Kansas City Cardiomyopathy Questionnaire; QoL, quality of life; SF-36, 36-Item Short Form Survey; SMR, secondary mitral regurgitation; 6MWT, six-minute walk test.
Sources: 6MWT, 1 year Stone 2018,[20] 2 years Mack 2021;[21] KCCQ/SF-36, Arnold 2019.[29]

Figure 20. Change from baseline in overall summary KCCQ score with MitraClip™ + GMDT versus GDMT alone



Abbreviations: GDMT, guideline-directed medical therapy; KCCQ, Kansas City Cardiomyopathy Questionnaire; MCID, minimal clinically important difference.
Source: Arnold 2019.[29]

Figure 21. Change in KCCQ score in HF therapy trials



Data are not from head-to-head studies. Data provided are for informational purposes only.
PCDM: Patient-Centered Heart Failure Trial (NCT00461513); TTT: Train the trainer (a teaching course for doctors); FNTC: Family Nursing Therapeutic Conversations in Heart Failure Outpatient Clinics in Denmark; PARADIGM-HF: Study Evaluating the Efficacy and Safety of LCZ696 (sacubutril/valsartan) Compared to Enalapril on Morbidity and Mortality of Patients With Chronic Heart Failure (NCT01035255); MADIT-CRT: Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy (NCT00180271); TOPCAT: Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function (NCT00094302); HF-ACTION: Exercise Training Program to Improve Clinical Outcomes in Individuals With Congestive Heart Failure (NCT00047437); DAPA-HF: Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (NCT03036124); SHIFT: Systolic Heart Failure Treatment with the I(f) Inhibitor Ivabradine Trial; TELE-HF: Yale Heart Failure Telemonitoring Study (NCT00303212); DEFINE-HF: Dapagliflozin Effect on Symptoms and Biomarkers in Patients With Heart Failure (NCT02653482); FAIR-HF: Ferinject® Assessment in patients with IRon deficiency and chronic Heart Failure; PAL-HF, Palliative Care in Heart Failure (NCT01589601); ATTRACT, Asian neTwork for Translational Research and Cardiovascular Trials (NCT02791009); PARTNER, Placement of AoRTic TraNscathetER Valve Trial (NCT00530894); COAPT, Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (NCT01626079); PARTNER-2, Placement of AoRTic TraNscathetER Valves II - XT Intermediate and High Risk (NCT01314313); PARTNER-3: Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients With Aortic Stenosis (NCT02675114).

RCT EVIDENCE	
COAPT™ (SMR)	Functional capacity, measured using the 6MWT, was preserved with a change from baseline of –2.2 m in the MitraClip™ arm versus –60.2 0 m in the GDMT arm at 1 year (p<0.001),[20] and -55.0 m in the MitraClip™ arm versus –93.5 m in the GDMT arm (p=0.01) at 2 years.[21] Quality of life improvements for KCCQ overall score and SF-36 physical and mental scores were significantly greater in the MitraClip™ arm than the GDMT arm at 1 and 2 years of follow-up.[29]
MITRA-FR (SMR)	At 1 year, mean ± SD 6MWT distance was 339 ± 151 m in the MitraClip™ arm (a mean improvement from baseline of 25 m) and 363 ± 157 m in the GDMT arm (a mean improvement from baseline of 19 m).[22] At 1 year, mean ± SD EQ-5D score was 60.8 ± 20.3 in the MitraClip™ arm (compared with 51.5 ± 19.2 at baseline) and 58.6 ± 18.2in the GDMT arm (compared with 53.2 ± 16.6 at baseline).[22]
EVEREST II (PMR, SMR)	Patients treated with MitraClip™ experienced a significant improvement in both physical and mental QoL from as early as 30 days after the procedure (both p<0.001 versus baseline) as measured using the SF-36 questionnaire, whereas patients who underwent conventional surgery experienced a decrease from baseline to 30 days in their physical QoL (p=0.004 versus baseline). Patient QoL was maintained after 1 year in the MitraClip™ group (physical and mental components: p<0.001 versus baseline) and improved significantly in the conventional surgery group following the initial transient decrease (physical and mental components p=0.006 versus baseline).[28]

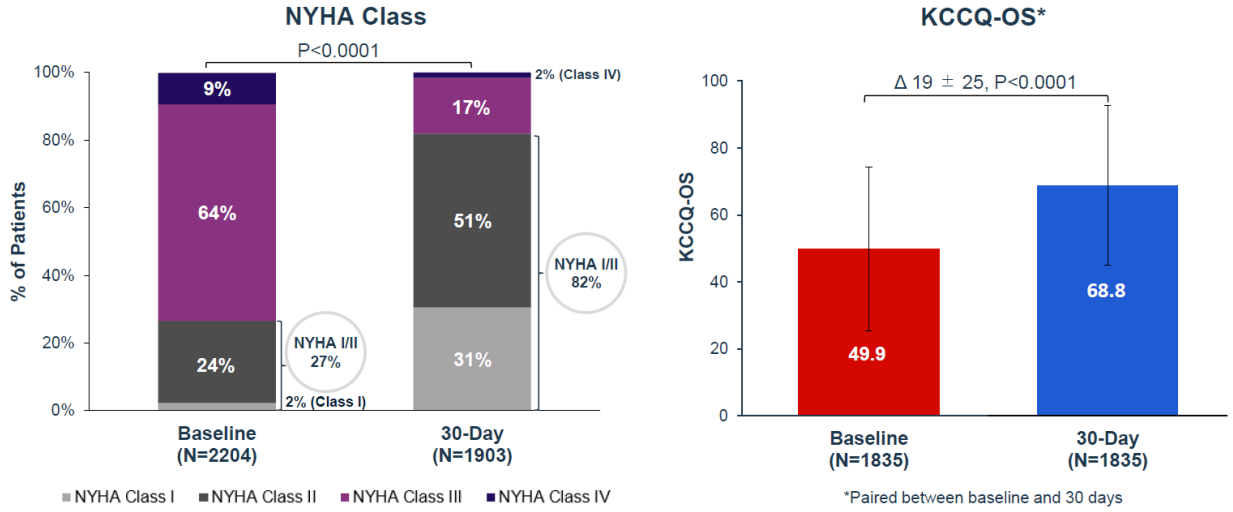
Abbreviations: EQ-5D, EuroQol-5 dimensions; GDMT, guideline-directed medical therapy; KCCQ, Kansas City Cardiomyopathy Questionnaire; PMR, primary mitral regurgitation; QoL, quality of life; RCT, randomised controlled trial; SD, standard deviation; SF-36, 36-Item Short Form Survey; SMR, secondary mitral regurgitation; 6MWT, six-minute walk test.

REAL-WORLD EVIDENCE	
EXPAND G4 (PMR, SMR)	Patients experienced a significant improvement in KCCQ score, from 52 at baseline to 70 at 30 days post-MitraClip™ (Δ +18; p<0.0001).[173] At 1 year follow-up, the mean KCCQ score was 72.5 (Δ +18.5; p<0.0001 versus baseline).[174]
EXPAND (PMR, SMR)	KCCQ overall summary scores improved significantly for the entire population, from 47.0 at baseline to 67.0 at 30 days (Δ +19.3; p<0.0001) and 70.2 at 1 year (Δ +21.6; p<0.0001).[25]
COAPT™ PAS (SMR)	At 30 days post-procedure, KCCQ scores were significantly improved versus baseline, from 38.3 points to 67.8 points (Δ +29.2; p<0.0001). At 1 year post-procedure, KCCQ scores were significantly improved versus baseline from 41 points to 74 points (Δ +28; p<0.0001).[26]

Abbreviations: KCCQ, Kansas City Cardiomyopathy Questionnaire; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation.

- In a paired analysis of the EXPANDed dataset, combining patients from EXPAND and EXPAND G4, at 30 days there was a significant increase versus baseline in the proportion of patients in NYHA functional class I/II (82% vs 27%; p<0.001) and KCCQ overall score (68.8 vs 49.9; p<0.001).[16]

Figure 22. Functional and QoL Outcomes from the EXPANDed patient cohort combining EXPAND and EXPAND G4



Abbreviations: KCCQ-OS, Kansas City Cardiomyopathy Questionnaire overall score; NYHA, New York Heart Association.

4.2.7 LEFT VENTRICLE REMODELLING

MitraClip™ Therapy has a positive impact on left ventricle remodelling as demonstrated in a number of studies

- MR imposes an important volume overload on the left heart, which causes progressive adverse LV remodelling. The negative impact of MR on prognosis has been at least partially linked to this progressive adverse LV remodelling as a result of ongoing volume overload.[193]

Table 26. Reverse left ventricle remodelling post-MitraClip™ across MitraClip™ studies

		RCT EVIDENCE				CONTEMPORARY REAL-WORLD EVIDENCE
		COAPT™ (SMR)		EVEREST II (PMR, SMR)		EXPAND (PMR, SMR)
		MITRACLIP™	GDMT	MITRACLIP™	SURGERY	
Mean CFB in LV measurement, mL	1Y	LVEDV: –3.7	LVEDV: +17.1	LVEDV: –25.3 LVEDD: –0.4 LVESV: –5.5 LVESD: –0.1 LVEF: –2.8	LVEDV: –40.2 LVEDD: –0.6 LVESV: –5.6 LVESD: 0.0 LVEF: –6.8	LVEDV: –19.3 LVESV: –9.4
	5Y	LVEDV: –20.0 LVEDD: –0.08 LVESV: –6.5 LVESD: +0.03 LVEF: –3.0	LVEDV: –24.4 LVEDD: –0.22 LVESV: –15.0 LVESD: –0.15 LVEF: +0.9	LVEDV: –5.2† LVESV: +0.4† LVEF: –1.8†	LVEDV: –0.9† LVESV: –1.2† LVEF: +0.7†	-

Abbreviations: CFB, change from baseline; GDMT, guideline-directed medical therapy; LV, left ventricle; LVEDD, left ventricular end diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; PMR, primary mitral regurgitation; RCT, randomised controlled trial; SMR, secondary mitral regurgitation.
Sources: COAPT™, 1 year Stone 2018,[20] 5 years Stone 2023;[15] EVEREST, 1 year Feldman 2011,[28] 5 years Feldman 2015;[14] EXPAND, Kar 2023.[25]
† Values are the change from 1 year to 5 years.

RCT EVIDENCE	
COAPT™ (SMR)	A positive trend of reverse left ventricle remodelling at 1 year was observed. LVEDV change from baseline was –3.7 mL for MitraClip™ versus +17.1 mL in the GDMT arm (p=0.004).[20] At 5 years, LVEDV change from baseline was –20.0 mL for MitraClip™ and –24.4 mL in the GDMT arm.[15]
EVEREST II (PMR, SMR)	After 1 year, patients treated with MitraClip™ had significant reductions in LVEDV, LVEDD, LVESV, and LVEF from baseline (all p<0.001). There was a non-statistically significant reduction in LVESD from baseline (p=0.06). A similar pattern of results was seen in the surgery group (p=0.19) and reductions in LVEDV, LVEDD and LVEF were significantly greater than in the MitraClip™ group (p≤0.04).[28] LVEDV continued to improve between 1 and 5 years after MitraClip™. LVEF decreased slightly beyond 1 year after MitraClip™, but the overall decrement in LV systolic function was comparable between arms and largely attributable to greater reduction in LVEDV versus LVESV.[14]

Abbreviations: GDMT, guideline-directed medical therapy; LVEDD, left ventricular end diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; PMR, primary mitral regurgitation; RCT, randomised controlled trial; SMR, secondary mitral regurgitation.

CONTEMPORARY REAL-WORLD EVIDENCE	
EXPAND (PMR, SMR)	The MitraClip™ procedure was associated with significant reduction in LVESV and LVEDV reduction from baseline through 1 year (both p<0.0001).[25]

Abbreviations: LVEDD, left ventricular end diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation.

4.2.8 HEART FAILURE HOSPITALISATIONS

MitraClip™ Therapy is associated with significantly lower rates of hospitalisation for HF compared with GDMT alone in patients with SMR

- Despite medical advances, HF hospitalisation is a worsening epidemic. Due to population growth, ageing, and the increasing prevalence of comorbidities, the absolute number of hospital admissions for HF is expected to increase considerably in the future, perhaps by as much as 50% in the next 25 years.[56]

- MitraClip™ treatment resulted in a significant reduction in hospitalisation rates in the 1 year after treatment relative to the 1 year before treatment in both patients with SMR and patients with PMR.[25, 30] In COAPT™, the NNT to prevent one HF hospitalisation was 3.0 at 3 years.[21]

Table 27. HF hospitalisation rates post-MitraClip™ implantation

		RCT EVIDENCE				CONTEMPORARY REAL-WORLD EVIDENCE		
		COAPT™ (SMR)		MITRA-FR (SMR)				
		MITRACLIP™	GDMT	MITRACLIP™	GDMT	EXPAND (PMR, SMR)	COAPT™ PAS (SMR)	TVT (PMR, SMR)
Heart failure hospitalisation rate, % (N)	**30d**	-	-	-	-	-	-	4.7 (80)
	1Y	-	-	48.7 (74)	47.4 (72)	18.9	24.9	20.2 (254)
	2Y	35.7 (92)	56.7 (151)	55.9 (85)	61.8 (94)	-	-	-
	3Y	46.5 (114)	81.5 (196)	-	-	-	-	-
	5Y	50.0 (151)	66.7 (208)	-	-	-	-	-

Abbreviations: D, day; GDMT, guideline-directed medical therapy; PMR, primary mitral regurgitation; PY, patient-years; RCT, randomised controlled trial; SMR, secondary mitral regurgitation; Y, year.
Sources: COAPT™, 2 years Stone 2018,[20] 3 years Mack 2021,[21] 5 years Stone 2023;[15] MITRA-FR, 1 year Obadia 2018,[22], 2 years Iung 2019;[23] EXPAND, 1 year Kar 2023;[25] COAPT™ PAS, 1 year Goel 2022;[26] TVT, Sorajja 2017.[194]

RCT EVIDENCE	
COAPT™[20, 21] (SMR)	At 2 years, the HFH rate was 35.7% among MitraClip™-treated patients versus 56.7% among patients who received GDMT alone (HR: 0.52; 95% CI: 0.40–0.67; p<0.001). Annualised HFH rates at 2 years were 35.8% per year for MitraClip™-treated patients versus 67.9% per year for patients who received GDMT (HR: 0.53; 95% CI: 0.40–0.70; p<0.001).[20] At 3 years, the HFH rate was 46.5% among MitraClip™-treated patients versus 81.5% among patients who received GDMT alone (HR: 0.43; 95% CI: 0.34–0.54; p<0.0001). Annualised HFH rates at 3 years were 35.5% per year for MitraClip™-treated patients versus 68.8% per year for patients who received GDMT (HR: 0.49, 95% CI: 0.37–0.63; p<0.0001). The NNT to prevent one HFH within 3 years was 3.0 patients.[21] At 5 years, one or more hospitalisations from HF during follow-up occurred in 151 patients (50.0%) in the MitraClip™ group and in 208 patients (66.7%) in the control group. The annualised HFH rate was 33.1% per year in the MitraClip™ group and 57.2% per year in the control group (HR:0.53; 95% CI: 0.41–0.68).[15]
MITRA-FR (SMR)	At 1 year, the rate of unplanned HFH was 48.7% (74 of 152 patients) in the MitraClip™ group and 47.4% (72 of 152 patients) in the control group (hazard ratio, 1.13; 95% CI, 0.81 to 1.56).[22] At 2 years, unplanned HFH had occurred in 55.9% of patients (85/152) in the MitraClip™ group and 61.8% (94/152) in the control group.[23] In an analysis of the MITRA-FR trial, the cumulative HFH rate between 12 and 24 months among patients was 27.6 events per 100 patient-years in the MitraClip™ arm versus 60.0 events per

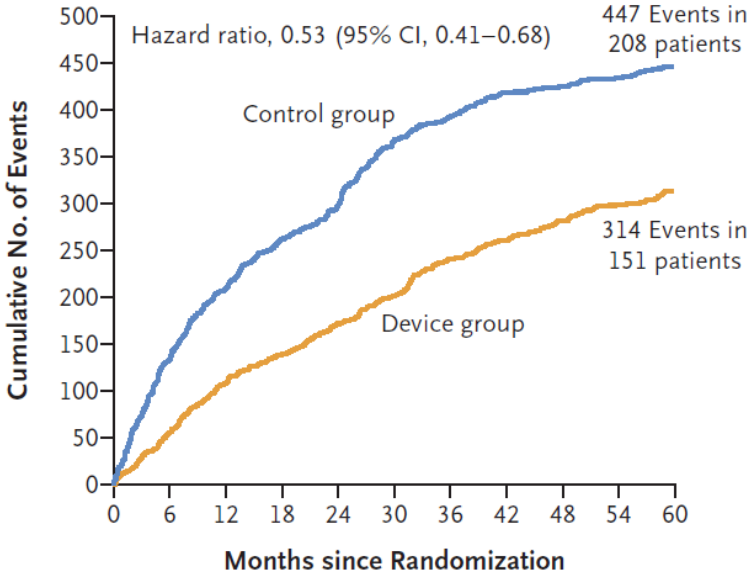
RCT EVIDENCE	
	100 patient-years in the GDMT arm (HR 0.45, 95% CI: 0.20–1.02; p=0.057). The difference did not reach statistical significance due to the low total number of events.[195]

Abbreviations: GDMT, guideline-directed medical therapy; HF, heart failure; HR, hazard ratio; NNT, number needed to treat; SMR, secondary mitral regurgitation.

CONTEMPORARY REAL-WORLD EVIDENCE	
EXPAND (PMR, SMR)	HFH rate at 1 year was 18.9% for the overall population. HFH was less frequent in PMR than SMR patients. In the 1 year before the MitraClip™ procedure the annualised HFH rate was 80% (745 events per 934 patient-years) versus 28% (251 events per 887 patient years) at 1-year post-MitraClip™ (RR: 0.37; p<0.001). The reduction in the annualised HFH rate was consistent across both PMR and SMR.[25]
TVT (PMR, SMR)	The 30-day rate of rehospitalisation for HF was 4.9%. At 1-year post-procedure, the rate of rehospitalisation for HF was 20.2% in the overall cohort.[194] Significant differences in the 1-year outcomes were present according to the mitral pathology treated. The cumulative incidences of mortality (24.7%), rehospitalisation for HF (20.5%), and the combined endpoint for both of these 2 outcomes (35.7%) were lower for patients with PMR, in comparison to those observed with SMR (31.2%, 32.6%, and 49.0%, respectively).[194]

Abbreviations: CI, confidence interval; HF, heart failure; PMR, primary mitral regurgitation; RR, relative risk; SMR, secondary mitral regurgitation.

Figure 23. Hospitalisations due to HF in COAPT™



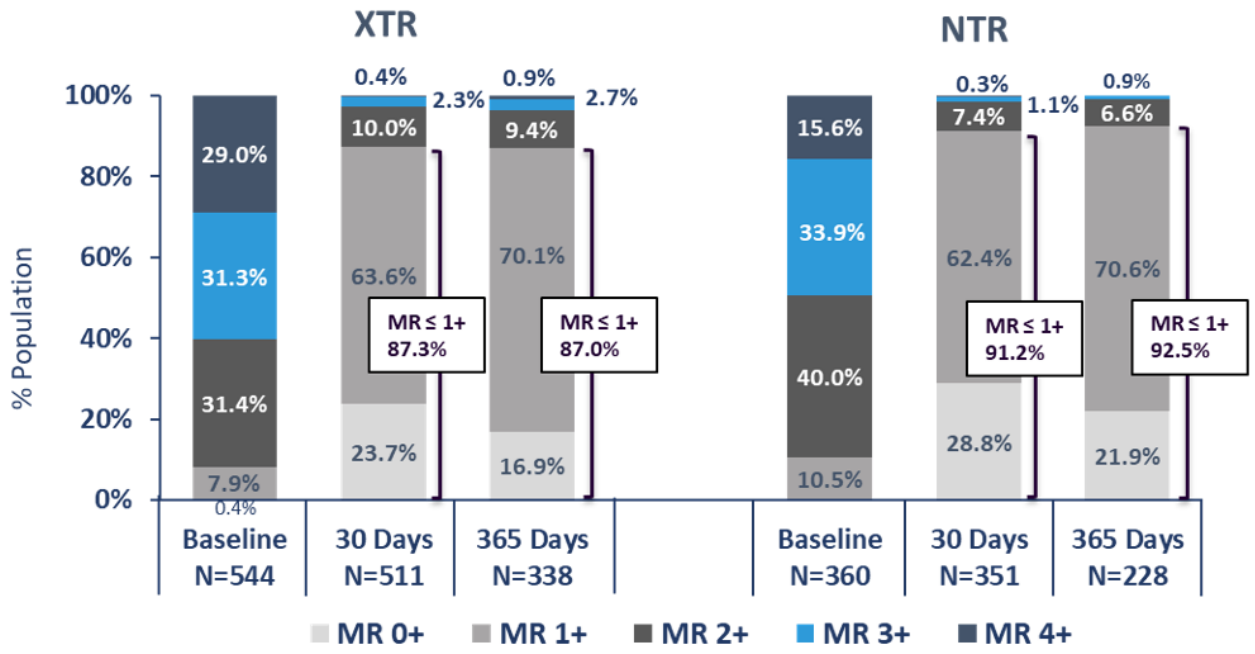
Abbreviations: CI, confidence interval; GDMT, guideline-directed medical therapy; HF, heart failure; HR, hazard ratio; NNT, number needed to treat.
Source: Mack 2021.[21]

4.2.10 COMPLEX MITRAL VALVE ANATOMIES

MitraClip™ Therapy achieves significant MR reduction in both simple and complex mitral valve anatomies

- MV anatomy was determined to be complex if at least 1 of the following features were observed on baseline TEE: PMR jet outside of A2-P2 coaptation zone, more than 1 significant MR jet, an extremely wide MR jet (requiring multiple implants), MV orifice area <4 cm2, calcification in the intended landing zone of the implant, minimal leaflet tissue for attachment (coaptation length <2 mm), severely degenerative leaflets or wide flail gaps (>10 mm) or widths (>15 mm).[25]
- In the EXPAND registry, 18.2% of subjects enrolled had complex mitral valve anatomy, 28.3% of patients with PMR and 10.1% of patients with SMR.[25]
- Following MitraClip™ placement, 87.0% of subjects with severe baseline MR, large prolapse gaps, or complex mitral valve anatomy achieved MR reduction to MR grade ≤1+ at 1 year (when using the XTR clip; the rate was 92.5% among patients fitted with the NTR clip) (Figure 24).[25]
- In PMR patients, XTR achieved more favourable MR reduction (at least 2 grades) in patients with more severe baseline MR, large prolapse gaps, and complex MR anatomies. In SMR patients, there was no advantage of clip selection strategy to improve MR reduction.[25]

Figure 24. MR reduction with MitraClip™ among subjects with severe baseline MR, large prolapse gaps, or complex mitral valve anatomy



Abbreviations: MR, mitral regurgitation.
Source: Kar 2023.[25]

- **MitraClip™ Therapy may be considered a cost-effective therapy compared with surgery or medical therapy:**
  - **MitraClip™ is likely to be cost-effective/cost-neutral over a 1–10 year period according to several studies[31-40] as a result of improved clinical outcomes, QoL, and survival combined with reduced HF rehospitalisations and AE management costs.**
- **The minimally invasive nature of the MitraClip™ Therapy procedure may translate into improved efficiency in the use of healthcare resources. MitraClip™ Therapy may be considered a cost-saving therapy due to the fact that the procedure:**
  - **is safe, effective, and achieves immediate MR reduction**
  - **is associated with minimised time spent under general anaesthesia, in the operating room, and in the ICU and general hospital ward, improving hospital capacity and resource use**
  - **is associated with a rapid recovery with few (if any) complications, and most patients can be discharged directly home following the procedure, as opposed to a rehabilitation centre**
  - **results in improved patient functional status, meaning patients regain their independence, can resume daily activities, and are less reliant on caregivers (who may then return to work)**
  - **is associated with reduced risk of HF rehopsitalisation and mitral valve-related retreatment, thus reducing the hospital resource use and costs associated with their management**
  - **is associated with durable MR reduction and sustained patients safety up to 5 years**

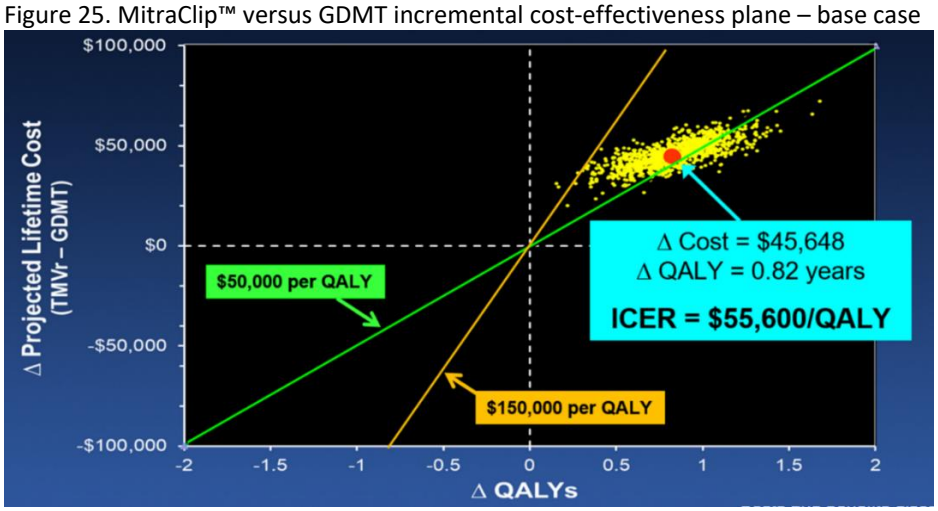
5.1 COST-EFFECTIVENESS

- MitraClip™ is likely to be cost-effective/cost-neutral over a 1–10-year period according to several studies due to improved clinical outcomes, QoL, and survival combined with reduced HF rehospitalisations and AE management costs.[31-40]
- MitraClip™ has been evaluated to be a cost-effective intervention in US,[31] UK,[32, 33] Italian,[34, 35] French,[36] Japanese,[37] and Canadian[196] cost studies. Overviews of numerous published economic models for MitraClip™ from the perspectives of various countries are provided in the separate appendix document.

5.1.1 2019 COAPT™ IN-TRIAL ECONOMIC ANALYSES: US PERSPECTIVE

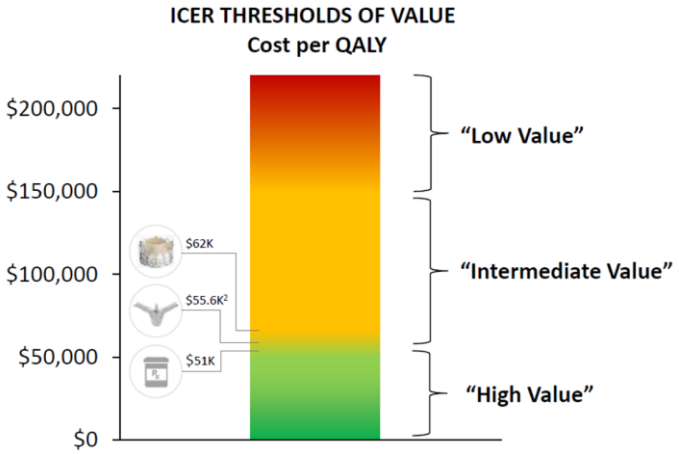
- A cost-effectiveness analysis evaluating the long-term costs of MitraClip™ Therapy + GDMT versus GDMT alone in patients with HF and grade ≥3+ SMR from the perspective of the US healthcare system (costs in 2018 USD).[31] The analysis featured patient-level, lifetime projections of survival, quality-adjusted life expectancy, and costs derived from COAPT™.[20, 21]
- The analysis was based on the intention-to-treat population of COAPT™ (MitraClip™ + GDMT: N=302, GDMT: N=312). Future costs and benefits were discounted at 3% per year.
- The model base case scenario assumed that survival, QoL, and economic benefits of MitraClip™ decrease in a linear fashion between years 2–5 of follow-up, such that no benefit of MitraClip™ + GDMT over GDMT would be seen beyond year 5.[31] The model best case scenario assumed that the observed in-trial benefits of MitraClip™ + GDMT over GDMT alone would remain constant over the patient's lifetime. The model worst case scenario assumed that there would be no benefit of MitraClip™ + GDMT over GDMT alone beyond 2 years.
- MitraClip™ Therapy + GDMT reduced 2-year follow-up costs by >$11,000/patient compared with GDMT alone.[31] Cumulative 2-year costs remained higher (~$35,000/patient) for MitraClip™ + GDMT patients versus GDMT alone due to the upfront cost of the MitraClip™ index hospitalisation.
- Over a lifetime horizon, MitraClip™ Therapy + GDMT was predicted to be associated with a 0.82 QALY gain compared with GDMT alone at an incremental cost of $45,648 and a lifetime ICER of $55,600 per QALY gained (which is within the range of cost-effectiveness in the US).
- By increasing both life expectancy and QoL in this patient population, MitraClip™ Therapy is cost-effective.

Figure 25. MitraClip™ versus GDMT incremental cost-effectiveness plane – base case



Abbreviations: GDMT, guideline-directed medical therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TMVr, transcatheter mitral valve repair (MitraClip™).
Source: Baron 2019.[31]

Figure 26. MitraClip™ Therapy provides high-intermediate economic value



Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.
Sources: Anderson 2014;[197] Baron 2019.[31]

5.2 POTENTIAL COST SAVINGS

5.2.1 PROCEDURE TME

MitraClip™ Therapy is likely associated with minimised time spent under general anaesthesia, in the operating room, and in the ICU and general hospital ward, improving hospital capacity and resource use

- There is a learning curve when MitraClip™ is introduced at an institution as reflected in decreasing procedure times with increasing institutional experience.
- In the TVT registry, procedure time decreased with increasing institutional experience even as the number of clips deployed per case increased. Mean procedure time decreased significantly with increasing case experience:
  - 139 minutes for cases 1–18.
  - 116 minutes for cases 19–51.
  - 94 minutes for cases 52–482.[27]
- In EXPAND G4, use of the fourth-generation system resulted in similar implantation rates compared with the third generation studied in EXPAND (98.0% vs 98.9%) and acute procedural success rates (96.2% vs 95.8%), with a 24% reduction in median device time (35.0 minutes vs 46.0 minutes).[173]
- This improved procedural efficiency and the lowest device time reported to date may be attributed to the use of fewer clips per procedure (1.4 vs 1.5) and/or advances in operator experience and imaging techniques. In EXPAND G4, more patients were treated with only 1 clip compared with EXPAND (65% vs 55%), 87.8% of which included wide clips (NTW or XTW or both).[173]

Table 28. MitraClip™ procedure and device times (definitions varied across studies)

	RCT EVIDENCE		REAL-WORLD EVIDENCE								
	COAPT™ (SMR)	EVEREST II (PMR, SMR)	EXPAND G4 (PMR, SMR)	EXPAND (PMR, SMR)	TVT (PMR, SMR)	TRAMI (PMR, SMR)	ACCESS-EU (PMR, SMR)	GRASP (PMR, SMR)	WILLITS 2021 (PMR, SMR)	SPANISH MITRACLIP™ REGISTRY	OCEAN-MITRAL REGISTRY (PMR, SMR)
Procedure time, mean, mins	162.9[†]	AF: 177 No AF: 183[‡]	77.0	80[††]	115[††]	102.8	100[‡,††]	156	180[††]	135[††,‡‡]	87
Device time, mean, mins	82.7[§]	AF: 130 No AF: 141[§]	35.0[§]	46[††]	-	-	-	80	-	-	-

Abbreviations: AF, atrial fibrillation; mins, minutes; PMR, primary mitral regurgitation; RCT, randomised controlled trial; SD, standard deviation; SMR, secondary mitral regurgitation; SGC, Steerable Guide Catheter; TEE, transoesophageal echocardiography.
[†] COAPT™: Procedure time was defined as the time from the first of any of the following – intravascular catheter placement, anaesthesia or sedation, or TEE – to the removal of the last catheter and the TEE probe.
[‡] COAPT™/EVEREST II/ACCESS-EU: MitraClip™ procedure time was defined as the time from the start of the transseptal procedure until the time the SGC was removed.
[§] COAPT™/EVEREST II/EXPAND G4: Device time was defined as the time from when the SGC was placed in the intra-atrial septum to the time the clip delivery system was retracted into the SGC.
[††] Median.
[‡‡] Spanish MitraClip™ registry: Procedure time was defined as the time from anaesthetic induction to the end of the procedure.
Definitions for procedure/device time were not provided for EXPAND, TVT, TRAMI, GRASP, or Willits 2021.
Sources: COAPT™, Stone 2018;[20] EVEREST II, Herrmann 2012;[198] EXPAND G4, von Bardeleben 2023;[173] EXPAND, Kar 2023;[25] TVT, Chhatriwalla 2019;[27] TRAMI, Puls 2016;[164] ACCESS-EU, Maisano 2013;[199] GRASP, Capodanno 2015;[200] Willits 2021;[39] Spanish MitraClip™ registry, Pascual 2020;[201] OCEAN-MITRAL Registry, Kubo 2023.[176]

5.2.2 HOSPITAL LENGTH OF STAY (LOS)

MitraClip™ Therapy is likely associated with cost savings as a result of minimised lengths of hospital/ICU/CCU stay following the procedure

- In the GRASP registry, the procedure-related LOS was reduced with increasing MitraClip™ experience. A total of 25.9% of patients were discharged within 72 hours (early discharge) in 2008/2009, compared with 59.1% of patients in 2014/2015.[202]
- In European countries, hospital LOS following a MitraClip™ procedure may vary from that seen in the US as a result of differing reimbursement systems and practice pathways, rather than differences in procedure or patient complexity.[25]
- Following the MitraClip™ procedure, the majority (>85%) of patients can be discharged directly home as opposed to a cardiac rehabilitation centre.[194]
- A 2021 case series (N=6) in the US demonstrated that it is safe to discharge patients on the same day of their MitraClip™ procedure provided they have stable HF symptoms, are at low bleeding risk, and did not experience any intraprocedural complications.[203]

Table 29. Hospital length of stay post-MitraClip™ implantation

	RCT EVIDENCE				REAL-WORLD EVIDENCE							
	COAPT™ (PMR, SMR)		EVEREST II (PMR, SMR)									
	MITRACLIP™	GDMT	MITRACLIP™	SURGERY	EXPAND G4 (PMR, SMR)	EXPAND (PMR, SMR)	TVT (PMR, SMR)	TRAMI (PMR, SMR)	ACCESS-EU (PMR, SMR)	EVEREST II REALISM (PMR, SMR)	MITRA SWISS (PMR, SMR)	WILLITS 2021 (PMR, SMR)
Country/region	US				Europe, US†		US	DE	Europe‡	US	CH	UK
Mean LOS, days	2.5	-	AF: 2.4 No AF: 1.6	AF: 9.6 No AF: 6.6	3.0	5	2§	9§	7.7	2.9	5§	5§
Mean ICU/CCU LOS, days	0.6	-	AF: 34 h No AF: 24 h	AF: 150 h No AF: 55 h	-	-	-	-	2.5	1.4	2§	-

Abbreviations: CH, Switzerland; CCU, cardiac care unit; DE, Germany; GDMT, guideline-directed medical therapy; h, hours; ICU, intensive care unit; LOS, length of stay; PMR, primary mitral regurgitation; RCT, randomised controlled trial; SMR, secondary mitral regurgitation
† Canada, France, Germany, Israel, Italy, Japan, Netherlands, Saudi Arabia, Spain, Switzerland, US, UK.[204]
‡ 14 European sites.
§ Median.
Sources: COAPT™, Baron 2019;[31] EVEREST II, Hermann 2012;[198] EXPAND G4, von Bardeleben 2023;[173] EXPAND, Kar 2023;[25] TVT, Sorajja 2017;[194] TRAMI, Puls 2016;[164] ACCESS-EU, Maisano 2013;[199] EVEREST II REALISM, Lim 2014;[205] MITRA SWISS, Sürder 2020;[206] Willits 2021.[39].

CONTEMPORARY REAL-WORLD EVIDENCE	
TVT (PMR, SMR)	In a cohort of MitraClip™ patients (N=2,952) from the TVT registry, 85.9% were discharged directly home following MitraClip™ implantation.[194]
TRAMI[164, 207, 208] (PMR, SMR)	Overall, 89.3% of patients were discharged to their normal social environment.[164] A similar proportion of elderly (aged ≥76 years) (81.8%) and younger patients (aged <76 years) (86.2%) were discharged home following the MitraClip™ procedure (p=0.06).[208] Patients in NYHA class IV at baseline were less frequently discharged to home (80.0%) than patients in NYHA class III (90.4%) or NYHA class I/II at baseline (95.3%; p<0.01).[207]

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

5.2.3 MITRAL VALVE REINTERVENTIONS

MitraClip™ Therapy is associated with low rates of mitral valve-related reinterventions, therefore reducing the costs associated with these

Table 30. Mitral valve-related retreatment rate post-MitraClip™ implantation

		RCT EVIDENCE				CONTEMPORARY REAL-WORLD EVIDENCE				
		COAPT™ (SMR)		EVEREST II (PMR, SMR)						
		MITRACLIP™	GDMT	MITRACLIP™	SURGERY	TVT (PMR, SMR)	TRAMI (PMR, SMR)	ACCESS-EU (PMR, SMR)	EVEREST II REALISM (PMR, SMR)	OCEAN-MITRAL REGISTRY (PMR, SMR)
Mitral valve related retreatment rate, %	30d	1.0	0.3	0	1.0	1.7	-	-	0.3/1.1†	-
	1Y	-	-	-	-	8.3	8.5	6.3	-	2.4
	2Y	4.0	9.0	-	-	-	-	-	-	-
	3Y	3.8	49.2	-	-	-	-	-	-	-
	5Y	4.5	52.0	27.9	8.9	-	-	-	-	-

Abbreviations: GDMT, guideline-directed medical therapy; PMR, primary mitral regurgitation; RCT, randomised controlled trial; SMR, secondary mitral regurgitation.

† 0.3% needed a further mitral valve surgery, 1.1% required a second MitraClip™.

Sources: COAPT™, 30 days/2 years Stone 2018;[20] 3 years Mack 2021,[21] 5 years Stone 2023;[15] EVEREST II, 1 year Feldman 2011,[28], 5 years Feldman 2015;[14] TVT, Sorajja 2017;[194] TRAMI, Puls 2016;[164] ACCESS-EU, Maisano 2013;[199] EVEREST II REALISM, Lim 2014;[30] OCEAN-MITRAL Registry, Kubo 2023.[176]

RCT EVIDENCE	
COAPT™ (SMR)	Mitral valve-related retreatment within 30 days of follow-up was required in 1.0% of patients treated with MitraClip™ + GDMT versus 0.3% of GDMT-treated patients,[20] 4.0% versus 9.0%,[20] respectively at 2 years of follow-up, 3.8% versus 49.2%, at 3 years of follow-up.[21] At 5 years of follow-up, the rate of unplanned mitral valve intervention or surgery was 4.5% in the MitraClip™ + GDMT group vs 52.0% in the GDMT alone group (48.7% TEER, 4.3% mitral valve surgery, and 1.7% mitral valve replacement).[15]
EVEREST II (PMR, SMR)	Mitral valve-related retreatment within 30 days of follow-up was not required in any patients treated with MitraClip™ versus 1.0% of patients who underwent surgery.[28] However, at 5 years, MV surgery or reoperation was more frequent with MitraClip™ than in those receiving surgery (27.9% vs. 8.9%; p=0.003).[14] The EVEREST II trial was performed early during the global experience with this first-in-class new technology, and both the acute procedure success rates and SLDA rates improved significantly in subsequent registry experiences. Clinical failures primarily occurred within the first 6 months, most of which were caused by inadequate MR reduction during the index procedure or early SLDA.[14]

Abbreviations: CI, confidence interval; GDMT, guideline-directed medical therapy; HR, hazard ratio; LVAD, left ventricular assist device; RCT, randomised controlled trial; SMR, secondary mitral regurgitation; TEER, transcatheter edge-to-edge repair.

REAL-WORLD EVIDENCE	
TVT (PMR, SMR)	At 30 days follow-up, 1.7% of patients had required an additional mitral valve procedure (surgery in 0.4% and a second MitraClip™ procedure in 1.3%). At 1 year, 8.3% of patients had required an additional procedure (surgery in 2.1% and a second MitraClip™ procedure in 6.2%).[194]

REAL-WORLD EVIDENCE	
TRAMI (PMR, SMR)	During the first year of follow-up, an additional mitral valve procedure was necessary in 8.5% of patients (surgery in 2.3%, a percutaneous procedure in 5.2%, and an alternative procedure in the remaining 1%).[164]
ACCESS-EU (PMR, SMR)	Thirty-six subjects (6.3%) required mitral valve surgery within 12 months after the MitraClip implant procedure.[199]
EVEREST II HRS & REALISM (PMR, SMR)	Of 327 MitraClip™ patients, 0.3% needed a further mitral valve surgery within 30 days of their index procedure. A second MitraClip™ procedure was necessary in 1.1% of patients within 30 days.[30]
OCEAN-MITRAL REGISTRY (PMR, SMR)	At 1 year of follow-up, a total of 24 patients from the total cohort (2.4%) required a mitral valve reintervention (32 with PMR, 64 with SMR).[176]

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

5.2.4 HEART FAILURE HOSPITALISATIONS

MitraClip™ Therapy reduces the frequency of HF hospitalisations and therefore their associated costs

- MitraClip™ Therapy is associated with significantly lower rates of hospitalisation for HF compared with GDMT alone in patients with SMR.[15, 20, 21]
- MitraClip™ treatment also resulted in a significant reduction in hospitalisation rates in the 1 year after treatment relative to the 1 year before treatment in both patients with SMR and patients with PMR.[25, 30]
- Despite medical advances, HF hospitalisation is a worsening epidemic. Due to population growth, ageing, and the increasing prevalence of comorbidities, the absolute number of hospital admissions for HF is expected to increase considerably in the future, perhaps by as much as 50% in the next 25 years.[56]

Table 31. HF hospitalisation rates post-MitraClip™ implantation

		RCT EVIDENCE				CONTEMPORARY REAL-WORLD EVIDENCE			
		COAPT™ (SMR)		MITRA-FR (SMR)					
		MITRACLIP™	GDMT	MITRACLIP™	GDMT	EXPAND (PMR, SMR)	COAPT™ PAS (SMR)	TVT (PMR, SMR)	OCEAN-MITRAL REGISTRY (PMR, SMR)
Heart failure hospitalisation rate, % (N)	**30d**	-	-	-	-	-	-	4.7 (80)	-
	1Y	-	-	48.7 (74)	47.4 (72)	18.9	24.9	20.2 (254)	15.0 (297)
	2Y	35.7 (92)	56.7 (151)	55.9 (85)	61.8 (94)	-	-	-	-
	3Y	46.5 (114)	81.5 (196)	-	-	-	-	-	-
	5Y	50.0 (151)	66.7 (208)	-	-	-	-	-	-

Abbreviations: d, days; GDMT, guideline-directed medical therapy; HFH, heart failure hospitalisation; PMR, primary mitral regurgitation; PY, patient-years; RCT, randomised controlled trial; SMR, secondary mitral regurgitation; Y, year(s).
Sources: COAPT™, 2 years Stone 2018,[20] 3 years Mack 2021,[21] 5 years Stone 2023;[15] MITRA-FR, 1 year Obadia 2018,[22], 2 years Iung 2019;[23] EXPAND, 1 year Kar 2023;[25] COAPT™ PAS, 1 year Goel 2022;[26] TVT, Sorajja 2017;[194] Armeni 2016;[35] OCEAN-MITRAL Registry, Kubo 2023.[176]

RCT EVIDENCE	
COAPT™ (SMR)	At 2 years, the HFH rate was 35.7% among MitraClip™-treated patients versus 56.7% among patients who received GDMT alone (HR: 0.52; 95% CI: 0.40–0.67; p<0.001). Annualised HFH rates at 2 years were 35.8% per year for MitraClip™-treated patients versus 67.9% per year for patients who received GDMT (HR: 0.53; 95% CI: 0.40–0.70; p<0.001).[20] At 3 years, the HFH rate was 46.5% among MitraClip™-treated patients versus 81.5% among patients who received GDMT alone (HR: 0.43; 95% CI: 0.34–0.54; p<0.0001). Annualised HFH rates at 3 years were 35.5% per year for MitraClip™-treated patients versus 68.8% per year for patients who received GDMT (HR: 0.49, 95% CI: 0.37–0.63; p<0.0001). The NNT to prevent one HFH within 3 years was 3.0 patients.[21] At 5 years, one or more hospitalisations from HF during follow-up occurred in 151 patients (50.0%) in the MitraClip™ group and in 208 patients (66.7%) in the control group. The annualised HFH rate was 33.1% per year in the MitraClip™ group and 57.2% per year in the control group (HR: 0.53; 95% CI: 0.41–0.68).[15]
MITRA-FR (SMR)	At 1 year, the rate of unplanned HFH was 48.7% (74 of 152 patients) in the MitraClip™ group and 47.4% (72 of 152 patients) in the control group (HR: 1.13; 95% CI, 0.81 to 1.56).[22] At 2 years, unplanned HFH had occurred in 55.9% of patients (85/152) in the MitraClip™ group and 61.8% (94/152) in the control group.[23] In an analysis of the MITRA-FR trial, the cumulative HFH rate between 12 and 24 months among patients was 27.6 events per 100 patient-years in the MitraClip™ arm versus 60.0 events per 100 patient-years in the GDMT arm (HR: 0.45, 95% CI: 0.20–1.02; p=0.057). The difference did not reach statistical significance due to the low total number of events.[195]
EVEREST II HRS & REALISM (PMR, SMR)	In a subgroup analysis of high-risk patients (grades 3 to 4+ MR and a surgical mortality risk of ≥12%†) from EVEREST II and REALISM, annual HFH rate decreased significantly from 0.79% in the 12 months before the MitraClip™ procedure to 0.41% in the 12 months after the procedure (p<0.0001). The proportion of patients hospitalised for HF was reduced from 42.5% (149 of 351) to 19.8% (67 of 338).[30]

Abbreviations: GDMT, guideline-directed medical therapy; HF, heart failure; HR, hazard ratio; NNT, number needed to treat; SMR, secondary mitral regurgitation.

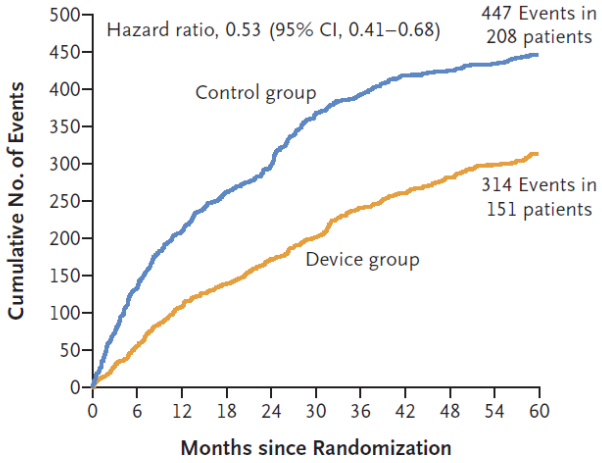
CONTEMPORARY REAL-WORLD EVIDENCE	
EXPAND (PMR, SMR)	HFH rate at 1 year was 18.9% for the overall population. HFH was less frequent in PMR than SMR patients. In the 1 year before the MitraClip™ procedure the annualised HFH rate was 80% (745 events per 934 patient-years) versus 28% (251 events per 887 patient years) at 1 year post-MitraClip™ (RR: 0.37; p<0.001). The reduction in the annualised HFH rate was consistent across both PMR and SMR.[25]
TVT (PMR, SMR)	The 30-day rate of rehospitalisation for HF was 4.9%. At 1-year post-procedure, the rate of rehospitalisation for HF was 20.2% in the overall cohort.[194] Significant differences in the 1-year outcomes were present according to the mitral pathology treated. The cumulative incidences of mortality (24.7%), rehospitalisation for HF (20.5%), and the combined endpoint for both of these 2 outcomes (35.7%) were lower for patients with PMR, in comparison to those observed with SMR (31.2%, 32.6%, and 49.0%, respectively).[194]
OCEAN-MITRAL REGISTRY (PMR, SMR)	At 1 year of follow-up, 15.0% (297/2,150) required a HF hospitalisation, 54 with PMR and 243 with SMR.[176]

Abbreviations: CI, confidence interval; HF, heart failure; PMR, primary mitral regurgitation; RR, relative risk; SMR, secondary mitral regurgitation.

PROPENSITY-SCORE MATCHED ANALYSIS ARMENI (SMR)	Clinical records of patients with moderate to severe SMR treated with MitraClip™ (n=232) or with medical therapy (n=151) were collected and analysed using propensity-score matching. Compared with medical therapy, patients treated with MitraClip™ experienced fewer re-hospitalisations at 30 days (0.05 versus 0.07; p=0.30), 6 months (0.13 versus 0.40; p<0.01) and 1 year (0.16 versus 0.70; p<0.01) of follow-up.[35]
US PERSPECTIVE: HEALTH CLAIMS DATA ANALYSIS	Patients with SMR and PMR at high surgical risk in the EVEREST II HRS and REALISM Continued Access Study (n=403) were linked to Medicare claims data. All-cause hospitalisation decreased from 1,854 to 1,435/1,000 person-years (p<0.001) and HF-related hospitalisations decreased from 749 versus 332/1,000-person years, p<0.001) following the MitraClip™ procedure. Overall mean Medicare costs per patient were similar pre-and post-MitraClip™ procedure though there was a significant decrease in mean costs among those who survived a full year after MitraClip™ ($18,131 pre-MitraClip™ versus $11,679 post-MitraClip™; p=0.02).[209]

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

Figure 27. Hospitalisations due to HF in COAPT™



Abbreviations: CI, confidence interval; GDMT, guideline-directed medical therapy; HF, heart failure; HR, hazard ratio; NNT, number needed to treat.
Source: Mack 2021.[21]

5.3 REIMBURSEMENT AND FUNDING

- Reimbursement and funding systems differ by country. Examples of MitraClip™ Therapy reimbursement and funding are provided in Table 32.
- In some countries, DRG tariffs can be completed by other sources of funding.
- For more information about reimbursement of MitraClip™ Therapy, contact the Abbott regional and country HE&R team.

Table 32. MitraClip™ reimbursement and funding status in select s EMEA countries

COUNTRY	DRG/REIMBURSEMENT	RATE
Austria	Procedure including device - DRG MEL08.03 (LG146) FP A: Interventions on the heart valves and ascending aorta with heart-lung machine	EUR 16,646
Belgium	Device - One or more implants and accessories for the percutaneous restoration of the coaptation of the mitral valve leaflets for patients with severe symptomatic MR with a high surgical risk or surgical contraindication	EUR 15,000
Bulgaria	Device - C14140040000001 MitraClip G4 System/Clip Delivery System XT, NT, NTW, XTW/ Steerable Guide Catheter	BGN 69,000
Czech Republic	Device - VZP17707 & VZP17708 MitraClip™ G4	CZK 638,550
Denmark	Procedure including device - DRG 05MP09 Percutaneous insertion of MitraClip™	DKK 201,480
England	The device (in PMR indication) is reimbursed through the 'High-Cost Tariff-Excluded Devices' Program on top of HRG EY22C (HRG with most activity)	GBP 3,838 + device
France	Device - LPPR 3139483 (3180770) Percutaneous Clip System for Mitral Valve, Abbott, MitraClip™	EUR 21,100
Germany	Procedure including device - DRG F98C Complex, minimally invasive surgery at cardiac valve without minimally invasive surgery at several valves	EUR 30,791
Israel	Procedure including device - MitraClip™ procedure is included in the National Health Basket	NA
Italy	**Italy:** Procedure including device - DRG 104 Intervention on heart valves and other major cardiothoracic surgery with cardiac catheterization **Emilia Romagna:** dedicated tariff for MitraClip procedure including device **Lombardi:** dedicated tariff for MitraClip procedure including device	EUR 24,675 EUR 31,493 EUR 34,122
Netherlands	Procedure including device - DBC 979001188 Transcatheter heart valve implantation	EUR 36,870
Norway	Procedure including device – DRG 104D Catheter-based implantation of heart valve	NOK 311,421
Poland	Procedure including device	PLN 108,574
Slovakia	Device - Kód MZ SR X03770 Mitral valve reconstruction system MitraClip™	EUR 20,000

COUNTRY	DRG/REIMBURSEMENT	RATE
Spain 	Global hospital budget system	NA
Sweden 	Procedure including device - DRG E04E Operation on single heart valve, not complicated	SEK 280,788
Switzerland 	Procedure including device - DRG F98C Endovascular implantation of heart valve replacement, age >15 years	CHF 47,747

Source: Abbott data on file.

- **Abbott, as part of its Corporate Social Responsibility efforts, has developed an ambitious 2030 Sustainability Plan focusing on the following targets:[210].**
  - **Build the diverse, innovative workforce of tomorrow.**
  - **Responsibly connect data, technology and care.**
  - **Create a resilient, diverse and responsible supply chain.**
  - **Protect a healthy environment.**
- **Abbott has received recognition for their excellence in a number of areas, including industry leadership, workplace leadership, scientific innovation, and sustainability.**

- Abbott demonstrates its commitment to corporate social responsibility through various initiatives. Among others Abbott focuses on sustainability, aiming to reduce their environmental impact through responsible manufacturing practices and initiatives to minimise waste and conserve resources. Furthermore, the company invests in research and development to advance medical science and improve patient outcomes, while promoting ethical business practice and transparency in its operations. Overall, Abbott corporate social responsibility efforts reflect their dedication to making a positive impact on society and improving the well-being of individuals worldwide.

6.1 2030 SUSTAINABILTY PLAN

- Abbott is building a more resilient supply chain, including working with suppliers to expand opportunities for, including working with suppliers to expand opportunities for diverse and small businesses, and actively engaging with suppliers to meet our high-quality standards. The targeted goals in this area are:
  - Certify that 80% of newly contracted direct material spends are linked to contracts that incorporate social responsibility requirements.
  - Ensure ethical sourcing from all suppliers with high-risk sustainability factors through 100% auditing.
  - Ensure an inclusive environment by increasing spending with diverse and small businesses 50% by 2030, and Black- and women-owned businesses 150% by 2025, from a 2020 baseline.
- Abbott is willing to be a trusted healthcare leader securing responsible data collection, use, management and privacy, in order to protect our patients and customers, empower them to make better, more complete decisions about their health and drive innovation through insights and analytics.
- Abbott is working across all manufacturing sites and with key suppliers to sustainably manage water use and address climate change by reducing carbon emissions and expanding renewable energy. This will contribute to reducing the environmental impact of product packaging and minimise waste through reuse and recycling programmes across the company. The targeted goals in this area are:
  - Reduce absolute Scope 1 and Scope 2 carbon emissions by 30% from 2018 baseline by the end of 2030, consistent with the objectives of the Science Based Targets initiative.[211]
  - Work with key carbon-intensive suppliers to implement sustainable programmes to reduce Scope 3 carbon emissions.
  - Achieve water stewardship certification at all high-water-impact manufacturing sites in water-stressed areas.
  - Implement accredited water stewardship management practices in more than 75% of all manufacturing sites operating in water-stressed areas.
  - Work with 50 key suppliers in high water-stressed areas to reduce water quality and quantity risks to Abbott and the community.
  - Address 50 million pounds of packaging through high-impact sustainable design programmes that:
    - Employ circularity principles through smart design and material selection
    - Eliminate and reduce materials
    - Improve the energy efficiency of Abbott's products

        - Optimise packaging, pallet and truckload efficiency.
    - Reduce waste impacts using a circular economy approach to achieve and maintain at least a 90% waste diversion rate.
    - Engage with key suppliers to reduce the environmental impact of materials sent to Abbott that become waste in our operations and develop and track supplier waste diversion initiatives.
- Abbott's 2022 Global Sustainability Report [212] revealed that progress against the 2030 Sustainability Plan had so far resulted in:
    - A 5% absolute reduction in Scope 1 and 2 emissions in 2022 (vs 2018 baseline)
    - 27 million kwh annual energy savings across Abbott sites and approximately 7,000 metric tonnes of $C0_2$ emissions reduced
    - 6,800 megalitres of water saved
    - 1,100 metric tonnes of waste eliminated

6.2 HONOURS

- Industry leadership: Abbott has been recognised as a world leader, advancing practices in medicine, science and technology:
    - Abbott was named Fast Company's World Changing Company of 2020 and has been included on its World Changing Ideas list for three consecutive years.
    - Abbott has led its industry sector for 10 years on the Dow Jones Sustainability Index for strong environmental, social and governance performance.
- Workplace leadership: Abbott strive to be recognised as a best place to work throughout the world.
    - Abbott is certified as a 'Great Place to Work' in the US and has twice been honoured by Fortune as one of 19 'best workplaces' with 100,000 or more employees.
    - Abbott has been named on DiversityInc's list of Top Companies for Diversity for 20 consecutive years (2004–2023), ranking ninth on the list in 2023.
    - Abbott has been named as a Seramount '100 Best Company' for 22 years in a row and recognised as a Top Company for Executive Women and Best Company for Multicultural Women.
- Scientific innovation: when developing healthcare solutions for people around the globe, Abbott set our sights beyond our reach.
    - Two Abbott technologies were included in TIME Magazine's 100 'Best Inventions of 2021.'
    - Prix Galien honoured Abbott's MitraClip™ as the 'Best Medical Technology' at its 2022 International Awards, and its 2020 USA Awards.
    - Abbott technologies have been awarded the 2022 Gold Edison Award as well as silver awards for 'human-centered' design and innovation.
    - Five Abbott healthcare innovations were recognised at the 2022 Consumer Electronics Show where Abbott also made history as the first healthcare company to keynote in the annual event.

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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 cm^2 et un volume télédiastolique indexé du ventricule gauche ≤ 96 mL/m^2.
Les patients ayant un ventricule gauche fortement dilaté (défini par un volume télédiastolique indexé du ventricule gauche > 96 mL/m^2) et une insuffisance mitrale modérée ou moindre, démontré par un orifice régurgitant de la valve mitrale ≤ 0,3 cm^2, 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)

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