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TRANSCATHETER IMPLANTABLE DEVICES FOR MITRAL VALVE REPAIR IN ADULTS WITH CHRONIC MITRAL VALVE REGURGITATION

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Conflict of interest

All authors and reviewers involved in the production of this pilot assessment have declared that they have no conflicts of interest in relation to the technology assessed according to the EUnet-HTA Declaration of interest and confidentiality undertaking of interest (DOICU) statement form.

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LIST OF ABBREVIATIONS

6MWT	6-minute walk test
AATS	American Association for Thoracic Surgery
ACC	American College of Cardiology
ACCESS-EU	MitraClip Therapy Economic and Clinical Outcomes Study Europe
ACE	Angiotensin-converting-enzyme
AE	Adverse event
AF	Atrial fibrillation
AMADEUS	CARILLON Mitral Annuloplasty Device European Union Study
BCBS	Blue Cross Blue Shield Association
CCT	Comparative controlled trial
CE	Conformité Européene
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COAPT	Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation
CRD	Centre for Reviews and Dissemination
CRT	Cardiac resynchronisation therapy
CS	Coronary sinus
DMR	Degenerative mitral regurgitation
ePTFE suture	Expanded polytetrafluoroethylene suture
ERO	Effective regurgitant orifice
ESC-EACTS	European Society of Cardiology–-European Association for Cardio-Thoracic Surgery
EU	European Union
EVEREST II HRR	Endovascular Valve Edge-to-Edge Repair Study II High Risk Registry
FDA	United States Food and Drug Administration
FMR	Functional mitral regurgitation
GCV	Great cardiac vein
GDMT	Guideline-directed medical therapy
h	Hours
HAS	Haute Autorité de Santé
HealthPACT	Health Policy Advisory Committee on Technology
HF	Heart failure
HR	High risk
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICD	International Statistical Classification of Diseases and Related Health Problems
IE	Infective endocarditis
IHE	Institute of Health Economics

ISRCTN	International Standard Randomised Controlled Trial Number
LA	Left atrial
LBI-HTA	Ludwig Boltzmann Institute for Health Technology Assessment
LV	Left ventricular
LVD	Leaflet Verification Display
LVESD	Left ventricular end-systolic dimension
LVEF	Left ventricular ejection fraction
MACCE	Major cardiac and cerebrovascular events
MAE	Major adverse event
MATTERHORN	Multicenter, Randomized, Controlled Study to Assess Mitral Valve Reconstruction for Advanced Insufficiency of Functional or Ischemic Origin
MeSH	Medical Subject Headings
MI	Myocardial infarction
MITRA-FR	Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation
MR	Mitral regurgitation
MSAC	Medical Services Advisory Committee
MV	Mitral valve
NHC	National Health Committee
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NIIR	NeoChord International Independent Registry
NR	Not reported
NYHA	New York Heart Association
QoL	Quality of life
R-AMSTAR	Revised Assessment of Multiple Systematic Reviews
RCT	Randomised controlled trial
REA	Relative Effectiveness Assessment
REALISM	Real World Expanded Multicenter Study of the MitraClip® System
REDUCE FMR	CARILLON® Mitral Contour System® for Reducing Functional Mitral Regurgitation
RESHAPE-HF	Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation
RESHAPE-HF1-FU	Observational Study of Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation – Follow Up of the Former Participants in the RESHAPE-HF trial
SCAI	Society for Cardiovascular Angiography and Interventions
STS	The Society for Thoracic Surgeons
SF-36	Short-form 36 Health Survey
SGC	Steerable guide catheter
SOLVD	Studies Of Left Ventricular Dysfunction

STS	The Society for Thoracic Surgeons
TACT	Transapical Artificial Chordae Tendinae
TOE	Transoesophageal echocardiography
TITAN	Transcatheter Implantation of Carillon Mitral Annuloplasty Device
TMVR	Transcatheter mitral valve repair
TRAMI	Transcatheter Mitral Valve Interventions
TTE	Transthoracic echocardiography
U	Unit
VAD	Ventricular assist device

SUMMARY OF RELATIVE EFFECTIVENESS OF TRANSCATHETER IMPLANTABLE DEVICES FOR MITRAL VALVE REPAIR IN ADULTS WITH CHRONIC MITRAL VALVE REGURGITATION

Scope

The aim of the present rapid assessment was to summarise the information on the relative effectiveness and safety of transcatheter implantable devices for mitral valve repair in adults with chronic mitral regurgitation (MR). Details are listed in the Scope, Section 1.

Three different transcatheter therapeutic approaches and related devices were considered: leaflet repair with MitraClip® System (Abbott Vascular International), annulus repair with CARILLON® Mitral Contour System® (Cardiac Dimensions, Inc.), and chordal repair with NeoChord DS1000 (NeoChord, Inc.).

Comparators, which were dependent on device and population, were standard medical care with or without cardiac resynchronisation therapy (CRT) in high surgical risk or non-surgical candidates (for MitraClip® System and CARILLON® Mitral Contour System®) or surgery (for NeoChord DS1000).

Primary effectiveness outcomes were: mortality, cardiovascular mortality, need of cardiac transplantation, New York Heart Association (NYHA) class improvement, freedom from NYHA ≥ 3, 6-minute-walk test (6MWT), reduction in hospitalisation rate, cardiovascular hospitalisation, need for mitral valve surgery, and quality of life (QoL). Safety outcomes were: durability of the device, and short- and long-term adverse events (AEs).

Introduction

Description of technology

Three systems are considered in the present assessment: MitraClip® System for leaflet repair, CARILLON® Mitral Contour System® for annulus repair and NeoChord DS1000 for chordal repair.

MitraClip® is a first-of-its-kind transcatheter mitral valve repair (TMVR) system designed to reconstruct the insufficient mitral valve (MV). This transcatheter therapeutic option provides a solution for patients with moderate-to-severe and severe degenerative, or primary, mitral regurgitation (DMR) or functional, or secondary, MR (FMR) who are not considered suitable candidates for conventional mitral valve surgery. It is delivered without requiring median sternotomy or cardiopulmonary bypass and most patients can be discharged home after the post-procedure recovery period. The MitraClip® device is delivered to the heart through the femoral vein after transseptal puncture is performed and is implanted on the valve leaflets to create a double orifice valve that decreases the backflow of blood and allows the heart to pump blood more efficiently [**B0001**] [1-5]. In the EU, the MitraClip® System is intended for reconstruction of the insufficient MV through tissue approximation, but in the USA it is indicated for the percutaneous reduction of significant symptomatic MR (≥ 3+) due to primary abnormality of the mitral apparatus (DMR) in patients who have been determined to be at prohibitive risk for MV surgery by a “heart team” (including a cardiac surgeon experienced in MV surgery and a cardiologist experienced in MV disease), and for whom existing comorbidities would not preclude the expected benefit from reduction of the MR [**A0020**] [1, 2].

The CARILLON® Mitral Contour System® is a percutaneous coronary sinus (CS)-based mitral annuloplasty device, and the only transcatheter technology holding a Conformité Européene (CE) mark that was designed specifically to treat FMR. The approach incorporates a device implanted in the CS and great cardiac vein (GCV), which lie adjacent to the mitral annulus. The device imparts inward pressure on the mitral annulus, decreasing annular dimension, increasing anterior and posterior leaflet coaptation and reducing MR. The CARILLON® Mitral Contour System® is contraindicated for use in patients with existing devices in the CS/GCV and in patients who have had a MV replacement or a mitral annuloplasty ring implant [**B0001**] [3-7]. In the EU, the CARILLON® Mitral Contour System® is indicated for use in patients with FMR [**A0020**] [6, 7].

The NeoChord DS1000 is a single-use, handheld device designed to deploy commercially available expanded polytetrafluoroethylene (ePTFE) suture (labelled for use as artificial chordae tendineae) while the heart is beating, as an alternative to the conventional surgical approach for this type of MV repair. The NeoChord DS1000 consists of the handheld delivery instrument, into which an off-the-shelf ePTFE suture is loaded, and a needle, and includes a tethered Leaflet Verification Display (LVD), which enables confirmation of leaflet capture in the distal clamp of the device prior to deploying the suture and knot at the leaflet [**B0001**] [3-5, 8, 9]. In the EU, NeoChord DS1000 is indicated for use in patients with Grade 3+ or 4+ MR who are candidates for surgical mitral valve repair or replacement [**A0020**] [8, 9]. NeoChord DS1000 is the only-in-class product that provides a minimally invasive approach to expand access to patients with DMR, without cardiopulmonary bypass-associated risks [**B0002**].

Current therapeutic options for the treatment of MR include medical management, surgical repair or replacement of the MV, ventricular assist device implantation, heart transplantation, and CRT; in this assessment, comparators are chosen by type of MR, medical device indication, and clinical guidelines recommendations [**B0001**].

Health problem

MR is characterised by backward flow of blood from the left ventricle to the left atrium during systole, producing left atrial dilatation. Therefore, MR results in suboptimal blood delivery to the rest of the body, clinically known as decreased cardiac output. MR is due to primary abnormalities that affect the valve leaflets, the annulus, the chordae tendineae or papillary muscles, or the left ventricle [**A0002**]. The presentation of MR can be acute or chronic depending on the underlying pathology; accordingly, the cause could be primary (degenerative) MR and secondary (functional) MR [**A0002**] [1, 6, 10-14].

Primary/Degenerative MR

– caused by abnormalities in one or more components of the valve architecture, such as the leaflets, chordae or papillary muscles

– results in lack of coaptation of the valve leaflets, due to mitral valve prolapse (collapsing of the valve) or flail (outward bulging of the valve due to ruptured chord and/or papillary muscle)

Secondary/Functional MR

– occurs as a result of left ventricular (LV) dysfunction, which is typically caused by ischaemic heart disease or dilated cardiomyopathy

– dilation of the left ventricle because of dysfunction causes displacement of the papillary muscles and dilation of the mitral annulus resulting in tethering of the leaflets, thereby preventing coaptation of the MV leaflets

– the MV itself is usually structurally normal

The prevalence of MR is high among the general population, with approximately 19% having MR of at least mild severity. The prevalence of MR increases with age – clinically meaningful MR (moderate or greater in severity) is present in < 1% of people younger than 50 years, in but 11% of people over 70 years. MR accounts for the vast majority (97%) of all MV disease, and, in Europe, is the second most common type of heart valve disease requiring surgery, after aortic stenosis. The incidence of MR is high amongst patients with heart failure (HF), with almost 40% of patients with significant HF having more than mild MR [**A0006**] [1, 15, 16].

The target population in this assessment is adults with primary and secondary MR. In assessing the patient with chronic MR, it is critical to distinguish between chronic DMR and chronic FMR, as these 2 conditions have more differences than similarities. Correction of DMR is curative, whereas in FMR, restoration of MV competence is not by itself curative; as a result, the best therapy for chronic FMR is much less clear than it is for chronic DMR. Specific statistical data on target population size in Europe or other regions were not found [**A0007**, **A0023**] [1, 2, 6, 7, 9].

Methods

Submission files provided by the manufacturers were consulted initially to develop the assessment elements of the present pilot rapid assessment. When searches conducted by the manufacturers were not compliant with the strategy defined in the Project Plan, they were supplemented with further systematic searches using the Ovid MEDLINE, Embase, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Centre for Reviews and Dissemination (CRD) databases. In addition, clinical trials databases were searched to identify ongoing studies on the 3 devices included in the assessment.

No quality-assessment tool was used for the Description and Technical Characteristics of the Technology, and Health Problem and Current Use of Technology domains, however, multiple sources were used in order to validate individual, potentially biased, sources. Descriptive analysis was performed on different information sources.

For the Clinical Effectiveness and Safety domains, secondary and primary studies were considered for inclusion. Secondary studies (i.e. Health Technology Assessment [HTA] reports and systematic reviews published in peer-reviewed journals) were analysed first, and then, only where secondary studies were not available, primary studies were considered for inclusion.

Only studies with a comparative design (randomised controlled trials [RCTs] and comparative controlled trials [CCTs]) were accepted for inclusion in the Clinical Effectiveness domain, whereas case series were also considered for the Safety domain. The Revised Assessment of Multiple Systematic Reviews (R-AMSTAR) tool was designated for quality assessment of systematic reviews, the criteria from the Cochrane Handbook for Systematic Reviews of Interventions were chosen to assess the methodological quality of RCTs and CCTs, while the 18-items checklist developed by the Institute of Health Economics (IHE) was selected for assessing the quality of case series and cohort studies. The GRADE methodology was designated to qualitatively summarise results from the domains Clinical effectiveness and Safety.

Results

Available evidence

No comparative evidence was found for assessing effectiveness. Given the paucity of evidence, only secondary studies and non-comparative primary studies were used as best available evidence to attempt to summarise findings. For assessing safety, 1 systematic review and 20 primary studies were included (range of the number of patients: 20–803).

Clinical Effectiveness

MitraClip® System

One systematic review [17] was selected for update on the basis of year of publication, time range, scope, and population. Systematic searches covering the time period from the publication of the systematic review until May 2015 did not identify further relevant primary studies fulfilling the inclusion criteria defined in the scope of the present assessment.

The review [17] showed that survival at 1 year was reported by 6 of the 12 included studies and ranged from 75% to 90%. Long-term survival was not available [**D0001**, **D0003**].

Symptoms and severity of MR were assessed by the NYHA classification. A reduction (early, at 6 months or at 12 months of follow-up) in the number of patients in NYHA class III/IV was reported in 9 of the 11 studies that provided information on this outcome. Five of the included studies reported data at 12 months showing a reduction in the proportion of patients in NYHA class III/IV from 98% to 35%, from 88% to 27%, from 94% to 11%, from 98% to 22%, and from 90% to 26% [**D0005**].

After MitraClip® implantation, reduction of MR Grade to ≤ 2+ was shown in all 11 studies that reported this outcome, and ranged from 73% to100% of patients. In the studies that reported from 6 to 12 months of follow-up, 61–99% of patients presented an MR Grade ≤ 2+. LV volume, as well

as LV diameter, showed a reduction from baseline in all 6 studies that reported this outcome. Left ventricular ejection fraction (LVEF) was reported as improved or unchanged from baseline in 6 studies [**D0006**].

Only 3 of the included studies assessed functional status in exercise performance by the 6MWT, showing improvements for up to 6 months of follow-up: 194 ± 44 m to 300 ± 70 m ($p < 0.01$) [18]; 171 ± 99 to 339 ± 134 m ($p < 0.001$) [19]; and 300 ± 108 m to 339 ± 120 m ($p = 0.02$) [20] [**D0011**].

Changes in performing activities of daily living (e.g. dressing, showering, walking, doing housework) were reported by a general QoL assessment in only 2 of the included studies. This dimension is included within the 2 tools used in the studies: the Short-form (SF)-36 Health Survey Quality of Life Questionnaire and the Minnesota Questionnaire [**D0016**]. The SF-36 Health Survey Quality of Life Questionnaire showed improvements in the physical component from a baseline score of 31.6 ± 9.1 to 37.0 ± 9.7 at 1 month and 36.5 ± 10.6 at 12 months of follow-up ($p = 0.01$). The Minnesota Questionnaire also showed statistically significant improvement from 56.5 ± 21.9 pre-intervention to 39.4 ± 20.5 at 6 months of follow-up ($p < 0.001$) [**D0012**, **D0013**].

For all the 3 devices, patient satisfaction after the procedure was not assessed in any of the studies [**D0017**].

CARILLON® Mitral Contour System®

The only comparative study found was the Transcatheter Implantation of Carillon Mitral Annuloplasty Device (TITAN) trial, a prospective, non-randomised, non-blinded, multicentre study [21]. As the surgical risk was not formally assessed in the population observed, the study did not fulfil the inclusion criteria defined in the scope of the present assessment.

In the TITAN study [21], the 30-day mortality rate was 1.9% (1/53) in the non-implanted group, while the 1-year mortality rate was 22.2% (8/36) in the implanted group and 23.5% (4/17) in the non-implanted group [**D0001**, **D0003**].

The symptoms and severity of FMR were assessed, in both groups, by the NYHA classification. At baseline, NYHA class was 3.1 ± 0.23 in the implanted group (36 patients) and 2.9 ± 0.24 in the non-implanted group (17 patients) ($p = 0.105$). The implanted group was reassessed at 12 months and showed improvement in NYHA class from baseline to 2.1 ± 0.64 (25 patients). The improvement was maintained at the 24-month visit with NYHA class of 2.1 ± 0.74 (19 patients) ($p < 0.001$) [**D0005**].

FMR progression and changes in cardiac structure by echocardiographic measures were also presented. A statistically significant difference was noted between the 2 groups, with a continued decrease of FMR for up to 12 months noted in the implanted group: in 25 implanted patients, FMR reduction at 12 months ranged from 3 grades for 3 patients, 2 grades for 5 patients, 1 grade for 12 patients, and less than one grade for 5 patients. Statistically significant reduction of LV size was noted in the implanted group, compared with continued enlargement in the comparison group: the mean reduction in LV end-systolic volume was 19% at 12 months. Eight of 25 patients had a > 10% reduction in LV end-systolic volume at 12 months. The echocardiographic assessment also included the assessment of regurgitant volume, effective regurgitant orifice (ERO) area, vena contracta, FMR jet area relative to left-atrial area, and annular septal-lateral diameter: in the implanted group, all the measures were statistically significantly reduced from baseline at the 12-month follow-up [**D0006**].

Functional changes in exercise performance were observed by the 6MWT. Scores (distance walked, in metres) were reported at baseline and at 1, 6, and 12 months for both groups. In the implanted group, 6MWT scores were 302.5 ± 74 m at baseline (36 patients), 397.9 ± 152 m at 1 month (32 patients), 429.9 ± 209 m at 6 months (27 patients), and 406.0 ± 180 m at 12 months (23 patients). In the comparison group, 6MWT scores were 337.9 ± 83 m at baseline (17 patients), 351.0 ± 98 m at 1 month (14 patients), 322.2 ± 105 m at 6 months (10 patients), and 348.1 ± 138 m at 12 months (8 patients). There was a statistically significant difference between the 2 groups ($p = 0.005$) [**D0011**].

The assessment of changes in performing activities of daily living (e.g. dressing, showering, walking, doing housework) at baseline and at follow-up intervals was not reported separately in the study, but it is included within the tool used to assess QoL (i.e. the Kansas City Cardiomyopathy Questionnaire) [**D0016**]. Scores were reported at baseline and at 1, 6, and 12 months for both groups. In the implanted group, scores were 43.0 ± 18 at baseline (36 patients), 64.6 ± 19 at 1

month (31 patients), 63.4 ± 23 at 6 months (28 patients), and 61.2 ± 26 at 12 months (24 patients). In the comparison group, scores were 40.4 ± 19 at baseline (17 patients), 47.5 ± 25 at 1 month (14 patients), 49.6 ± 22 at 6 months (10 patients), and 51.0 ± 19 at 12 months (7 patients). There was a statistically significant difference between the two groups (p = 0.001) [**D0012**, **D0013**].

NeoChord DS1000

Only 2 case series with limited follow-up were available. Seeburger and colleagues [22] reported 1 patient death within 30 days due to post-cardiotomy syndrome and concomitant sepsis; whereas Colli and colleagues [23] observed no deaths at 30 days [**D0001**, **D0003**].

Colli et al. [23] reported that 87.3% (55/63) of patients were in NYHA class I at 30 days, compared to only 3 [5%] at baseline [**D0005**]. In the other study, 58.6% (17/29) of patients maintained performance success at 30 days, 70.5% (12/17) of whom maintained an MR Grade ≤ 1+ [22]. At the 30-day follow-up, Colli et al. found that 16% (10/63) of patients showed a reduction in MR of 2 grades, 25% (16/63) showed a reduction of 3 grades, 46% (29/63) showed a reduction of 4 grades, while 12.5% (8/63) patients were in MR Grade 3+ or 4+ [**D0006**].

The effects of the procedure on patients' body functions (**D0011**), generic and disease-specific health-related quality of life (HRQoL) [**D0012**, **D0013**], and activities of daily living [**D0016**] were not assessed.

Safety

MitraClip® System

The evidence available is not sufficient to exhaustively define how safe MitraClip® is in relation to the comparators. However, safety outcomes were reported in several case series and cohort studies. The largest series referred to the combined cohort from the Endovascular Valve Edge-to-Edge Repair Study II High Risk Registry (EVEREST II HRR) and the Real World Expanded Multicenter Study of the MitraClip® System (REALISM) HR studies [24], and to the German Transcatheter Mitral Valve Interventions (TRAMI) register [25].

Safety outcomes were reported at 30 days and 12 months for the 351 patients with high surgical risk in EVEREST II HRR and REALISM HR [24]. The mortality rate at 30 days was 4.8% (17/351) with no death related to device malfunctions. The rate of major adverse events (MAEs) was 18.8% (66/351) with blood transfusion ≥ 2 units as the most frequent event occurring at a rate of 13.4% (47/351). None of the reported strokes (9/351) was due to device or air embolisation. Twelve (3.4%) patients experienced major vascular complications. At 12 months, the mortality rate was 22.8% (80/351), while the rate of MAEs was 37.6% (132/351), with the most common event being blood transfusion (22.5%; 79/351); 3 additional strokes occurred (12/351). Events of single-leaflet device attachment, listed as the most frequent device-related complication, occurred at a rate of 2.3% (8/351), mostly in the early phase. A second MitraClip® procedure was necessary in 1.1% (4/351) of patients only within 30 days after the initial procedure. MV surgery was performed in 0.9% (3/351) of patients. No events of device embolisation occurred [**C0008**]. Safety outcomes were reported for in-hospital stay (mean duration: 10 days; range 6–17) and post-discharge follow-up (307 patients; mean duration 75 days; range, 42.0–172.0) in the 557 patients with high surgical risk in the TRAMI register [25]. The in-hospital mortality rate was 4.3% (24/554). Four (0.7%) stroke events were reported and no myocardial infarction (MI) events were reported. The rate of MAEs was 19.4% (108/557) with transfusion or severe bleeding being the most frequent events occurring at a rate of 13.7% (75/546). Major vascular complications were experienced in 2.2% (12/546) of patients. Respiratory insufficiency and psycho syndrome for 3 or more days, both listed as MAEs, were observed in 3.5% (19/547) and 2.4% (13/546) of patients, respectively. The mortality rate at post-discharge follow-up was 13.4% (41/307). The rate of major cardiac and cerebrovascular events (MACCE) was 13.4% (41/307), while 38.6% of patients (103/267) experienced re-hospitalisation for cardiac, cardiovascular, and other reasons. No device-related complications were reported. The rate of procedural complications was 8.9% (49/550) [**C0008**].

Patient selection and organisational settings have been identified as aspects affecting frequency and severity of harms. Frailty of patients, in particular NYHA class IV, has been associated with higher mortality rates in one study [26]. Effects of a learning curve have been acknowledged in a

series of 75 patients [27], whereas a later study, which analysed 496 procedures in 10 centres performing at least 50 procedures per year, showed that a learning curve does not appear to significantly affect procedural success [28] [**C0004**].

Subgroup analyses of specific subgroups were performed in the included studies. In particular, the impact of type II diabetes mellitus [29], anaemia [30], and NYHA classification [26] have been studied. No significant differences in terms of safety emerged from the study on patients with diabetes, however the study presented only short-term (3 months) results for a small population consisting of 19 patients with diabetes and 39 patients with no diabetes [29]. Similarly, peri-procedural MACCE and 1-year survival did not differ between patients with anaemia (n = 41) and those without anaemia (n = 39) [30]. In the other comparison [26], while in-hospital MACCE as well as re-hospitalisation rates were similar among groups in different NYHA classes, the 30-day mortality rate was significantly higher in NYHA class IV patients (8.0%; 11/137) compared with class III (3.2%; 17/526), and class II/I (4.8%; 4/83) ($p < 0.05$) [**C0005**].

Effects of a learning curve have not been addressed in any of the studies included for the present safety analysis. However, one of the included studies [25] referenced a previous study [27], in which a learning curve effect was acknowledged and significant differences between the earliest and latest procedures were observed. In the series of 75 patients, the median total procedure time (total time from puncture to closure of the femoral vein) decreased from 180 min to 95 min ($p < 0.005$); the median device time (total time from insertion of the SGC until removal of the clip delivery) decreased from 105 min to 55 min ($p < 0.005$); safety events decreased from 16 to 3 ($p = 0.0003$); acute procedural success (clip successfully placed and MR Grade ≤ 2+ at discharge) increased from 80% to 92% ($p = 0.46$). At 6 months, completeness of MV repair (MR ≤ 2+) was 89.4% for the latest patients and 65.0% for the earliest ($p = 0.03$). A more recent analysis from the German Mitral Valve Registry (496 patients in 10 centres) [28] investigated the impact of the learning curve on procedural success and complications in those centres performing at least 50 procedures per year. The analysis showed that a learning curve does not appear to significantly affect acute MR reduction, in-hospital mortality, or 30-day mortality [**C0007**].

CARILLON® Mitral Contour System®

The evidence available is not sufficient to exhaustively define how safe CARILLON® Mitral Contour System® is in relation to the comparator. In one study, all safety findings referred to the overall intention-to-treat population without distinguishing between the intervention and comparator cohorts, with the exception of the endpoint “death”, measured at 30 days and 12 months of follow-up [21]. The incidence of death was lower in the implanted group at 30 days (0% [0/36] patients vs 6% [1/17] patients), and at 12 months (22.2% [8/36] vs 23.5% [4/17] patients). Other safety findings were not analysed statistically in the 2 groups because of the small number of complications which occurred at the 30-day follow-up [**C0008**].

The evidence currently available is insufficient to address which aspects could affect frequency and/or severity of harms associated with the use of CARILLON® Mitral Contour System®. In one study [31], two MAEs (coronary sinus perforations) occurred early in the study (first and fourth patient) confirming that there is a learning curve to access the CS [**C0004**].

No evidence was found to define which patient groups are more likely to be harmed by the use of CARILLON® Mitral Contour System®. The cohorts of patients in the included studies were small (range 48–53 patients) and seemed to overlap. Moreover, subgroup analyses were not performed. One study [31] pointed out that neither demographic nor echocardiographic parameters were clearly predictive of procedural success. Rather, the procedural steps of placing the device further distal in the CS/GCV and applying more traction to plicate more tissue were associated with procedural success [**C0005**].

The same study [31] showed that there is a learning curve for safely accessing the CS; careful management of patients with high surgical risk, and acquisition of procedural skills are necessary to lower the risks associated with this device. Furthermore, experience-based skills related to the assessment of coronary arterial flow are crucial for recapturing and repositioning the device successfully and safely [**C0007**].

NeoChord DS1000

None of the included studies assessing NeoChord DS1000 was comparative [22, 23, 32]. The availability of "absolute" safety data, referring to the cohorts of patients who underwent MV repair using this specific device, does not allow for critical assessment of the NeoChord DS1000 safety profile in relation to the comparator (conventional surgery). In the included studies, MAEs ranged from 8% to 26.7% of patients at the 30-day follow-up [**C0008**].

The evidence currently available is insufficient to address which aspects could affect frequency and/or severity of harms associated with NeoChord DS1000. One study [22] reported that safety had improved significantly because of the introduction of procedural refinements and new criteria for patient selection [**C0004**].

No evidence was found to identify which patient groups are more likely to be harmed by the use of NeoChord DS1000. The included studies mostly featured small cohorts (range 13–62 patients), and analyses of subgroups for safety endpoints were not performed. One study observed that procedural success at 30 days was highly dependent on the morphological characteristics of the MV: patients with ideal MV anatomy were associated with a low risk of procedural failure (4%), patients with acceptable MV anatomy with a mild risk (8%), and patients with challenging MV anatomy were associated with a moderate risk (29%) [23] [**C0005**].

No evidence was found to help determine whether the use of NeoChord DS1000 is associated with user-dependent harms. In one study, the authors highlighted that special and extensive training for the operators is mandatory, because the determination of the exact positioning, length adjustment, and neo-chordae tensioning depends exclusively on the ability and training of the operator and echocardiographer, and affects the durability as well as the acute procedural success [22] [**C0007**].

Upcoming evidence

Several studies are ongoing on the MitraClip® System, and these studies will be crucial to define clear indications for the device, as well as criteria to identify the population that may benefit most from the procedure. In terms of the present assessment, 4 studies that feature guideline-directed medical therapy, instead of surgery, as a comparator are of particular relevance. These studies are: the Observational Study of Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation – Follow Up of the Former Participants in the RESHAPE-HF Trial (RESHAPE-HF1-FU; NCT02444286), with results expected in January 2017; the Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation (MITRA-FR) trial (NCT01920698) with results expected in October 2017; a multicentre, randomised trial (NCT02444338) with an estimated completion date of September 2019; and the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) study (NCT01626079) which is expected to be completed in 2020.

There is also one study ongoing on CARILLON® Mitral Contour System® – the CARILLON Mitral Contour System® for Reducing Functional Mitral Regurgitation (REDUCE FMR) trial (NCT02325830), which is a prospective, multicentre, randomised, double-blinded study. Results are expected by July 2017.

There is one study ongoing on NeoChord DS1000 – the NeoChord Transapical Artificial Chordae Tendineae (TACT) patient registry (NCT01784055). Results are expected by July 2016.

Reimbursement

The reimbursement status of the 3 medical devices under assessment in European Union (EU) countries is decided at the national or regional level, with or without restrictions (see Table 20 and Table 21). All 3 medical devices are reimbursed in Austria (partially covered) and Germany. MitraClip® is reimbursed (with or without restrictions) in many other EU countries; in addition to Austria and Germany, CARILLON® Mitral Contour System® is reimbursed in Italy and Turkey and NeoChord DS1000 is reimbursed in Lithuania [**A0021**].

Discussion

As no comparative studies were available for inclusion, a summary of relative effectiveness could not be produced within the present rapid assessment. Given that the body of evidence was limited to the Safety domain and acknowledging the limitations in the design of all the included studies (case series and cohort studies), the authors of the present report agreed to not perform any assessment of the quality of the body of evidence as this would only give a partial overview without allowing to reach further conclusion on the relative assessment of the 3 devices.

Positive results were observed with MitraClip® System vs medical therapy in a small comparative series: the EVEREST II HRR study enrolled only 78 patients and compared the outcomes with a retrospective cohort of 36 patients receiving medical therapy or surgery. This study formed the basis for the recommendations of national institutions and scientific societies, even if these recommendations were often driven by the lack of an alternative for such subgroups of patients. Results from the 4 ongoing studies comparing MitraClip® with optimal medical management (NCT02444286, NCT01920698, NCT02444338, and NCT01626079) are particularly anticipated.

Despite the existence of a comparative study on the use of CARILLON® Mitral Contour System®, some critical issues can be highlighted: the comparison group was created by implanting and acutely recapturing the device for clinical indications in a subgroup of the initially enrolled patients. How this procedure impacted on the outcomes observed in the comparison group is unknown. Moreover, the non-device-related mortality in this sick patient population affected the number of patients followed at 12 and 24 months; in the implanted group, follow-up was not feasible for 30.5% and 47.2% patients at 12 and 24 months, respectively. The ongoing REDUCE FMR study aims to assess the safety and efficacy of CARILLON® Mitral Contour System® in treating FMR associated with HF, compared to a randomised control group that is medically managed according to HF guidelines. The study does not state to formally assess the surgical risk of the candidates, but sets a LVEF ≤ 40% as an inclusion criterion. Results from REDUCE FMR are anticipated as they may be helpful in answering the research questions posed in the present assessment, and may provide further information for defining the role of the procedure within the clinical pathway.

The use of NeoChord DS1000 for the treatment of DMR is in its infancy. Non-comparative studies presented results as first-in-human experiences, with several limitations in terms of sample size and duration of follow-up. The ongoing NeoChord TACT study aims to observe procedural success at Day 1 (i.e. reduction in MR ≤ 2+), therefore, comparative studies with larger cohorts and long-term follow-up will still be necessary to define the use of NeoChord DS1000 in comparison to the standard of care (i.e. surgery).

Safety data related to MitraClip® were retrieved from large series and registries that, overall, showed comparable rates. Effects of a learning curve have been acknowledged in a series of 75 patients, whereas an analysis of 496 procedures in 10 centres performing at least 50 procedures per year showed that a learning curve does not appear to significantly affect procedural success. In terms of clinical effectiveness, the evidence of safety for CARILLON® Mitral Contour System® and NeoChord DS1000 is still limited to small series, and little can be concluded on the transferability of the results. Available data appear encouraging and both technologies have been acknowledged to be relatively safe within the studies identified. However, the fact that the effects of a learning curve have not been explored is an issue that should be considered carefully.

Conclusion

The available evidence did not allow any final statement to be reached on the relative effectiveness and safety of transcatheter implantable devices for mitral valve repair in adults with moderate-to-severe and severe chronic MR. As recognised by most of the authors, comparative analyses with longer durations of follow-up are believed necessary to clarify the benefits–harms ratio of the 3 procedures.

Two of the devices assessed, NeoChord DS1000 and CARILLON® Mitral Contour System®, can be considered still at an early stage of development and show small levels of diffusion. Different is the MitraClip® case that is not at early stages, counting around 23,000 patients implanted worldwide before results from studies comparing the MitraClip therapy to its claimed comparator (i.e. optimal medical therapy) have been published.

Ongoing studies on CARILLON® Mitral Contour System® and MitraClip® will, in the near future, help to determine whether they are more effective and/or safe than the comparators. For NeoChord DS1000, thorough research, including controlled trials, needs to be conducted to determine whether this device is more effective and/or safe than the comparators, and to verify how long the effects of the treatment remain.

Summary table of relative effectiveness of transcatheter implantable devices for mitral valve repair in adults with chronic mitral valve regurgitation

For MitraClip®, AEs are listed as "major" (MAEs) on the basis of the systematic review by Munkholm-Larsen [17] (Table 1). The AEs related to CARILLON® Mitral Contour System® and NeoChord DS1000 were listed as "major" or "other" depending on how they were defined within the studies included (Table 2 and Table 3). If MAEs were not defined explicitly or clearly in a study, we have listed them according to the definition provided from the other studies. Safety outcomes for which no AEs occurred within the studies were not reported in the summary table. Only data reported as a percentage of study populations were tabulated. Details of safety results are tabulated in Appendix 1 (Table 12, Table 13, Table 14).

Table 1: Summary table of relative effectiveness of the MitraClip® System for MV repair in adults with chronic MR

	Health benefits*				**Harms**	
	Mortality (all-cause and cardiovascular mortality)	**Morbidity** (need for cardiac transplantation, NYHA functional status improvement, freedom from NYHA class ≥ 3)	**Function** (6MWT score, changes in performing activities of daily living)	**Health related QoL**	**MAEs**	**Other AEs**
MitraClip® System	-	-	-	-	Mortality (range 3.2–4.2% in-hospital; 1.7–6% at 30 days; 9.3–23.1% at 12 months) *[17, 24-26, 29, 30, 33-39]* Early need for surgery (range 0.7–3.2% at 30 days; 0.9–7.4% at 12 months) *[17, 24, 29, 33, 34, 39]* Cerebrovascular accident (range 0–6% at 30 days; 0% at 12 months) *[17, 39]* Cardiac tamponade (range 0–2% at 30 days; 1% at 24 months) *[17, 35]* Transseptal complications (range 1.2–3% at 30 days) *[17]* Partial clip detachment (range 0–12.5% at 30 days; 10% at 24 months) *[17, 35]* Transfusion of ≥ 2 U blood product (range 7.3–8.1% intra-procedural; 0–17.1% at 30 days; 22.5% at 12 months) *[17, 24, 26, 33, 34]* Stroke (0% in-hospital; 2.6% at 30 days;3.4% at 12 months; 0% at 24 months) *[24, 33, 35]* MI (0% in-hospital; 3.4% at 12 months) *[33, 39]* Major bleeding (8% at 24 months; 18.8% at 30 days; 5.8% at 12 months) *[24, 35, 39]* MAEs/MACCE§ (range 4.9–12% in-hospital; 4.7–18.8% at 30 days; 5–41% at 12 months) *[24, 25, 30, 34, 36, 37, 39, 40]* Major complications§ (2.5–4% intra-procedural; 17.2–19.4% in-hospital) *[25, 30, 35, 38]*	Non-fatal AEs/ Minor complications* (range 11.3–13.8% in-hospital; 17.8% at 72 days) *[25, 33]* Sepsis (1.4% at 30 days) *[34]* Prolonged intubation (0.7% at 30 days) *[34]* Partial clip detachment (2.28% at 12 months; 10% at 24 months) *[24, 35]* MV stenosis (0.9% at 12 months) *[24]* TIA (2.1% at 30 days) *[26]* > 5 days' hospitalisation (20% at about 7 months) *[41]*

	Health benefits*				Harms	
	Mortality (all-cause and cardiovascular mortality)	**Morbidity** (need for cardiac transplantation, NYHA functional status improvement, freedom from NYHA class ≥ 3)	**Function** (6MWT score, changes in performing activities of daily living)	**Health related QoL**	**MAEs**	**Other AEs**
Comparator	Lacking	Lacking	Lacking	Lacking	Lacking	Lacking
Assessment Elements	**D0001**, **D0003**	**D0005**, **D0006**	**D0011**, **D0016**	**D0012**, **D0013**	**C0008**	**C0008**
Quality of body of evidence*	NA	NA	NA	NA	NA	NA

Abbreviations: 6MWT = 6-minutes walk test; AE = adverse event; AF = atrial fibrillation; h = hours; MAE = major adverse event; MACCE = major cardiac adverse and cerebrovascular event; MI = myocardial infarction; NYHA = New York Health Association; TIA = Transient ischaemic attack; U = units; NA = not assessed.

* *As no comparative studies were available for inclusion, no summary of relative effectiveness could be produced. See Effectiveness domain for details.*

** *Given that the body of evidence was limited to the Safety domain and acknowledging the limitations in the design of all the included studies (case series and cohort studies), the authors of the present report agreed to not perform any assessment of the body of evidence as this would only give a partial overview.*

§ *These items include miscellaneous harms not necessarily described in the studies (See Appendix 1, Table 12 for more details).*

Table 2: Summary table of relative effectiveness of CARILLON® Mitral Contour System® for MV repair in adults with chronic MR

	Health benefits*				Harms	
	Mortality (all-cause and cardiovascular mortality)	**Morbidity** (need for cardiac transplantation, NYHA functional status improvement, freedom from NYHA class ≥ 3)	**Function** (6MWT score, changes in performing activities of daily living)	**Health related QoL**	**MAEs**	**Other AEs**
CARILLON® Mitral Contour System®	-	-	-	-	Mortality (0 vs 16% at 30 days; 22.2% vs 23.5% at 12 months) *[21]* MI (range 0–6.5% at 30 days; 4% at 12 months) *[21, 31]* Cardiac perforation (range 0–6.5% at 30 days; 0% at 12 months) *[21, 31]*	-
Comparator	Lacking	Lacking	Lacking	Lacking	Lacking	Lacking
Assessment Elements	**D0001**, **D0003**	**D0005**, **D0006**	**D0011**, **D0016**	**D0012**, **D0013**	**C0008**	**C0008**
Quality of body of evidence	NA	NA	NA	NA	NA	NA

Abbreviations: 6MWT = 6-minutes walk test; AE = adverse event; AF = atrial fibrillation; h = hours; MAE = major adverse event; MI = myocardial infarction; NYHA = New York Health Association; U = units; NA = not assessed.

* *As no comparative studies were available for inclusion, no summary of relative effectiveness could be produced. See Effectiveness domain for details.*

** *Given that the body of evidence was limited to the Safety domain and acknowledging the limitations in the design of all the included studies (case series and cohort studies), the authors of the present report agreed to not perform any assessment of the body of evidence as this would only give a partial overview.*

Table 3: Summary table of relative effectiveness of NeoChord DS1000 for MV repair in adults with chronic MR

	Health benefits*				Harms	
	Mortality (all-cause and cardiovascular mortality)	**Morbidity** (need for cardiac transplantation, NYHA functional status improvement, freedom from NYHA class ≥ 3)	**Function** (6MWT score, changes in performing activities of daily living)	**Health related QoL**	**MAEs**	**Other AEs**
NeoChord DS1000	-	-	-	-	Mortality (range 0–3% at 30 days) *[22, 23]* Stroke (range 0–3% at 30 days) *[22, 23]* MI (range 0–2% at 30 days) *[22, 23]* Intraoperative conversion to conventional surgery (range 8–20% at 30 days) *[23, 32]* Re-operation for NeoChord DS1000 failure (range 13–20% at 30 days) *[22, 23]* Septicaemia (range 0–3% at 30 days) *[22, 23]* Conversion to standard care (8% at 6 months) *[32]*	Dehiscence (range 2–8% at 30 days to 0% at 6 months) *[23, 32]* Transfusion of > 2 U blood product (range 5–17% at 30 days) *[22, 23]* Procedural ventilation > 48 h (3% at 30 days) *[22]* Ventricular fibrillation (5% at 30 days) *[23]* Severe pericardial effusion (3% at 30 days) *[23]* Onset of persistent AF (21% at 30 days) *[23]* Onset of permanent AF (2% at 30 days) *[23]* Pacemaker implantation (3% at 30 days) *[23]*
Comparator	Lacking	Lacking	Lacking	Lacking	Lacking	Lacking
Assessment elements	**D0001**, **D0003**	**D0005**, **D0006**	**D0011**, **D0016**	**D0012**, **D0013**	**C0008**	**C0008**
Quality of body of evidence **	NA	NA	NA	NA	NA	NA

Abbreviations: 6MWT = 6-minutes walk test; AE = adverse event; AF = atrial fibrillation; h = hours; MAE = major adverse event; MI = myocardial infarction; NYHA = New York Health Association; U = units; NA = not assessed.

** As no comparative studies were available for inclusion, no summary of relative effectiveness could be produced. See Effectiveness domain for details.*

*** Given that the body of evidence was limited to the Safety domain and acknowledging the limitations in the design of all the included studies (case series and cohort studies), the authors of the present report agreed to not perform any assessment of the body of evidence as this would only give a partial overview.*

1 SCOPE

Description	Project scope*
Population	Indication: • MR; International Statistical Classification of Diseases and Related Health Problems (ICD)-10: I34.0 mitral (valve) insufficiency • Adults with: – moderate-to-severe and severe DMR or FMR who are at high surgical risk or non-surgical candidates (i.e. MitraClip® and CARILLON® Mitral Contour System® populations) – moderate-to-severe and severe DMR who are surgical candidates (i.e. NeoChord DS1000 population) The interventions assessed are proposed to treat the condition.
Intervention	Transcatheter MV repair by device implantation in adults with chronic MR. Three systems will be considered within the present assessment: • MitraClip® System for leaflet repair • CARILLON® Mitral Contour System® for annulus repair • NeoChord DS1000 for chordal repair
Comparison	In patients without HF, with DMR, who are at high surgical risk or are non-surgical candidates, MitraClip® will be compared to: • Standard medical care In patients with HF, with DMR, who are at high surgical risk or are non-surgical candidates, MitraClip® will be compared to: • Standard medical care with pharmacological treatment for HF In patients with FMR who are at high surgical risk or are non-surgical candidates, MitraClip® System or CARILLON® Mitral Contour System® will be compared to: • Pharmacological treatment (with or without CRT) In patients with DMR who are surgical candidates, NeoChord DS1000 will be compared to: • Surgery
Outcomes	Primary effectiveness outcomes: • Mortality (all-cause) • Cardiovascular mortality • Need for cardiac transplantation • NYHA functional status improvement • Freedom from NYHA class ≥ 3 • 6MWT • Reduction in rate of hospitalisation • Cardiovascular hospitalisation • Need for MV surgery • QoL Secondary effectiveness outcomes: • Improvements in echocardiographic outcomes (e.g. reduction in LV volumes, improvement in LVEF) • Procedural success rate Safety : • Durability of the device • Short- and long-term AEs (device-related as well as procedure-related): 1) Any AE; 2) serious AEs; 3) most frequent AEs Outcomes were selected based on the recommendations from the clinical guidelines for treatment of MR [12, 13] and the EUnetHTA Guidelines on Clinical and Surrogate Endpoints and Safety [42-44] and amended following comments from dedicated reviewers and external experts.

Study design	Effectiveness: • Systematic reviews; • Health Technology Assessment (HTA) reports; • Randomised controlled trials (RCT); • Controlled clinical trials (CCT). Safety (other than the designs already listed): • Case series; • Medical devices adverse events registries.

2 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY

2.1 Research questions

Element ID	Research question
B0001	What are the MitraClip® System, CARILLON® Mitral Contour System®, and NeoChord DS1000, and what are the comparators?
A0020	For which indications have the MitraClip® System, CARILLON® Mitral Contour System®, and NeoChord DS1000 received marketing authorisation or a CE mark?
B0002	What are the claimed benefits of the MitraClip® System, CARILLON® Mitral Contour System®, and NeoChord DS1000 in relation to the comparators?
B0004	Who administers the MitraClip® System, CARILLON® Mitral Contour System®, NeoChord DS1000, and the comparators, and in what context and level of care are they provided?
B0008	What kind of special premises are needed for the MitraClip® System, CARILLON® Mitral Contour System®, NeoChord DS1000, and the comparators?
B0009	What supplies are needed for the MitraClip® System, CARILLON® Mitral Contour System®, NeoChord DS1000, and the comparators?
A0021	What is the reimbursement status of the MitraClip® System, CARILLON® Mitral Contour System® and NeoChord DS1000?

2.2 Results

[B0001] – What are the MitraClip® System, CARILLON® Mitral Contour System®, and NeoChord DS1000, and what are the comparators?

Three systems are considered within the present assessment: MitraClip® System for leaflet repair; CARILLON® Mitral Contour System® for annulus repair; NeoChord DS1000 for chordal repair.

Table 4: Features of the technologies [1, 2, 6-9]

Device	Proprietary name	Manufacturer	Reference codes	GMDN code
MitraClip	MitraClip® System	Abbott Vascular International	MitraClip kit: SK01ST; Clip delivery system: CDS02ST; Steerable guide catheter: SGC01ST	56280
CARILLON	CARILLON® Mitral Contour System®	Cardiac Dimensions, Inc.	NA	59101
NeoChord DS1000	NeoChord DS1000	NeoChord, Inc.	NA	NA

Abbreviations: NA = not applicable; SGC = steerable guide catheter.

The data provided below, on the 3 technologies under assessment (MitraClip® System, CARILLON® Mitral Contour System® and NeoChord DS1000) were sourced from the submission files provided by the manufacturers [1, 6, 8], instructions for use [2, 7, 9] and 3 further references [3-5].

MitraClip® System

MitraClip® System is a first-in-kind TMVR system designed to reconstruct the insufficient MV. This transcatheter therapeutic option provides a solution for patients with severe DMR or FMR who are not considered suitable candidates for conventional MV surgery. It is delivered without requiring median sternotomy or cardiopulmonary bypass and most patients can be discharged directly home after the post-procedure recovery period. The MitraClip® System device is delivered to the heart through the femoral vein after transseptal puncture is performed and is implanted on the valve leaflets to create a double orifice valve that decreases the backflow of blood and allows the heart to pump blood more efficiently.

The MitraClip® System is contraindicated in DMR patients who: cannot tolerate procedural anticoagulation or post-procedural antiplatelet regimen; have active endocarditis of the MV; have rheumatic MV disease; show evidence of intracardiac, inferior vena cava, or femoral venous thrombus. According to the instructions for use [2], evaluable data regarding safety or effectiveness is not available for prohibitive risk DMR patients with a LVEF < 20% or a left-ventricular end-systolic dimension (LVESD) > 60 mm. The MitraClip® System should be used only when criteria for clip suitability for DMR have been met. The procedure is recommended to be performed when an experienced heart team has determined that reduction of MR to ≤ 2+ is expected following MitraClip® System implantation. Procedures should be performed under general anaesthetic by physicians trained to carry out invasive endovascular and transseptal procedures and those trained in the proper use of the system. The device should be implanted with sterile techniques using fluoroscopy and echocardiography (transoesophageal echocardiography [TOE] and transthoracic echocardiography [TTE]) in a facility with on-site cardiac surgery and immediate access to a cardiac operating room. Short-term anticoagulant therapy may be necessary after MV repair with the MitraClip® System.

The MitraClip® System consists of 2 major parts: the clip delivery system, which includes the implantable clip, a steerable sleeve and a delivery catheter; and the steerable guide catheter (SGC), which includes a dilator. Several accessories are used in conjunction with the MitraClip® delivery system including: a stabiliser, a lift, a silicone pad, a support plate, and fasteners.

The MitraClip® System procedure can be described as follows: while the patient is under general anaesthetic (so that TOE can be performed safely in order to visualise the MV leaflets), transfemoral transvenous access is obtained and transseptal puncture is performed at the interatrial fossa to position the SGC in the left atrium. The clip delivery system is then introduced through the SGC to orient the clip perpendicular to the MV leaflets' line of coaptation. The MV leaflets are grasped between the corresponding arm and gripper resulting in reduction in MR, coaptation of the leaflets, and creation of a double orifice valve. MR is assessed throughout the entire procedure using real-time TOE (2D and/or 3D) to confirm optimal positioning and sufficient reduction in MR. The procedure does not require cardiac arrest or cardiopulmonary bypass, thereby permitting real-time evaluation of the impact of the clip implantation on MR. If reduction in MR is not sufficient, the clip can be taken safely off the leaflets, repositioned, and re-implanted, or can be removed completely from the anatomy according to the implanting physician's judgement. Standard surgical options are preserved in patients after percutaneous repair with the MitraClip® System – successful surgical repair is feasible in the majority of patients after the MitraClip® procedure, in both the acute and delayed setting. The MitraClip® System instructions for use [2] includes step-by-step detailed instructions.

CARILLON® Mitral Contour System®

The CARILLON® Mitral Contour System® is a percutaneous CS-based mitral annuloplasty device and the only transcatheter technology holding a CE mark that was designed specifically to treat FMR. It is a class III medical device and consists of the following components: a proprietary implant intended for permanent placement in the CS/GCV, and a catheter-based delivery system consisting of a custom curved 9F (3.0 mm outer diameter) delivery catheter and a handle assembly. The implant is attached to the handle assembly and is delivered through the delivery catheter to the coronary vein along the posterolateral aspect of the mitral annulus. The implant is designed to re-shape the mitral annulus in order to reduce annular dilation and MR.

The procedure typically takes 40 minutes or less. Real-time echocardiography and angiography can be conducted during the procedure to help evaluate efficacy and safety aspects of the procedure. Since the device is placed in the venous system (right side of the heart), blood thinners or anticoagulants are typically not required. The procedure can be conducted using conscious sedation or general anaesthetic. The device can be recaptured, providing the physician with significant control over the procedure, and effectively allowing him/her to reposition the device, if necessary.

The CARILLON® Mitral Contour System® is contraindicated for use in: patients with existing devices in the CS/GCV and patients who have had a MV replacement or a mitral annuloplasty ring implant.

There are approximately 30 different device sizes (lengths and anchor diameters) that allow for the placement of the device in a variety of different patient anatomies (details on appropriate selection can be found in the instructions for use [6]). In brief, available vein length is determined by total vein length, vein diameters, geometry, and relevant arterial anatomy: if available vein length is ≤ 12 cm, a 60 or 70 mm length implant should be used for the first attempt; if available vein length is ≥ 13 cm, an 80 mm length implant should be used for the first attempt; if additional implant attempts are made, either length may be chosen (implants with 13 or 14 mm distal anchors are available only in 70 or 80 mm lengths). The venogram determines the size of the device that should be placed. In the packaging itself, both the CARILLON® delivery catheter and CARILLON® handle assembly are provided. Given the placement of the device in the CS/GCV and the inward pressure placed on the mitral annulus, the device is designed to re-shape the mitral annulus in order to reduce annular dilation and MR. If an additional implant procedure attempt is planned, the implant procedure should be repeated with a new delivery catheter, handle assembly, and implant. Components of the CARILLON® Mitral Contour System® are single use only.

NeoChord DS1000

NeoChord DS1000 is a single-use, handheld device designed to deploy commercially available ePTFE suture, labelled for the use as artificial chordae tendineae, while the heart is beating, as an alternative to the conventional surgical approach for this type of MV repair. The NeoChord DS1000 consists of the handheld delivery instrument, in which an off-the-shelf ePTFE suture will be loaded, a needle, and includes a tethered LVD, which enables confirmation of leaflet capture in the distal clamp of the device prior to deploying the suture and knot at the leaflet.

NeoChord DS1000 is contraindicated in heavily calcified valves; valvular retraction with severely reduced mobility; active bacterial endocarditis; complex mechanism of MR (leaflet perforation, etc.); significant tethering of leaflets; inflammatory valve disease. CAUTION: The NeoChord DS1000 has not been studied in a FMR patient population. The NeoChord DS1000 has not been studied in patients with anterior leaflet prolapse.

Comparators

Current therapeutic options for the treatment of MR, some of them defined as comparators in this assessment, include medical management, surgical repair or replacement of the MV, ventricular assist device implantation, heart transplantation, or CRT.

Medical management: Medical management may relieve symptoms, but does not reverse the underlying pathology of MR, so disease progression is not prevented. There is no evidence to support the use of angiotensin-converting-enzyme (ACE) inhibitors, beta-blockers, spironolactone, diuretics, aldosterone antagonists, and nitrates in chronic MR without HF, and these agents are, therefore, not recommended in this group of patients. When HF has developed, ACE inhibitors are beneficial and should be considered in patients with advanced MR and severe symptoms who are not suitable for surgery or when residual symptoms persist following surgery. Beta-blockers and spironolactone should also be considered for relief of symptoms because no medicine is indicated for MR. These drugs are approved in all European countries [12, 13, 45-47].

MV surgery: MV surgery is the guideline recommended standard of care for patients with symptomatic severe DMR or asymptomatic severe DMR with an evidence of LV dysfunction or dilation, with MV repair generally preferred to replacement as evidenced by lower perioperative mortality, improved survival, better preservation of LV function, and lower long-term morbidity. MV repair is

the preferred surgical treatment for severe DMR with significant advantages over MV replacement, using different techniques according to the type and location of the mitral lesion(s) (leaflet resection, implantation of artificial chordae, chordal transposition/transfer, edge-to-edge technique, and annuloplasty using a prosthetic ring or band). According to the literature, more than 95% of degenerative MV lesions could be successfully repaired in expert centres. Freedom from re-operation is more than 90% at 10 years and more than 80% at 20 years [12, 13, 46, 48-53].

Surgical outcomes depend on factors like pre-operative status, mechanism of MR, technique of repair, and experience of the centre and the surgeon; centres with extensive experience in MV repair achieve hospital mortality rates less than 1%, very low rates of MAEs and good long-term results. After timely MV repair, long-term survival and QoL are the same as in the age-matched general population. Late survival is reduced in patients with congestive HF, reduced LVEF (≤ 30%), pulmonary hypertension, or AF [51-60].

Despite the benefits offered by surgical intervention, approximately 50% of patients may not be considered suitable candidates for surgery, with surgery denied more frequently in certain groups. In older patients, surgery was denied in 58% of patients aged 70–80 years and in 85% of patients aged > 80 years. In patients with a high comorbidity score, surgery was denied in 70% of patients with a Charlson Comorbidity Index of 3, and in 65% of patients with a score of > 3. (The Charlson Comorbidity Index is used to assess whether a patient will live long enough to benefit from a specific screening measure or medical intervention). Among patients with reduced LVEF, surgery was denied in 62% of patients with LVEF of 30–40%, and in 86% of patients with LVEF < 30% [1].

CRT, ventricular assist device implantation, and heart transplantation: CRT and heart transplantation are options that are recommended for patients with HF who suffer from severe symptoms, are too high risk for MV surgery, and have failed on optimal medical management. For patients with HF and prolonged QRS duration, especially if associated with left bundle branch block, CRT has been shown to improve mortality, HF hospitalisation, QoL, functional capacity, and induce reverse remodelling [61-66].

In this assessment, comparators were chosen based on CE mark, specific indications, information in published clinical guidelines for treatment of MR [12, 13] and EUnetHTA guidelines, and were amended following comments from dedicated reviewers and external experts:

In patients with DMR who are surgical candidates, the use of the NeoChord DS1000 device was compared to surgery.

In patients without HF, with DMR who are at high surgical risk or are non-surgical candidates, the MitraClip® System was compared to no pharmacological treatment.

In patients with HF, with DMR who are at high surgical risk or are non-surgical candidates, the MitraClip® System was compared to pharmacological treatment.

In patients with FMR who are at high surgical risk or are non-surgical candidates, the MitraClip® System or the CARILLON® Mitral Contour System® was compared to pharmacological treatment (with or without CRT).

[A0020] – For which indications have the MitraClip® System, CARILLON® Mitral Contour System®, and NeoChord DS1000 received marketing authorisation or a CE mark?

MitraClip® System [1, 2]

The first use of MitraClip® System in man occurred on 27 June, 2003, in Caracas, Venezuela. The MitraClip® System was granted a CE mark in March 2008, and the product was commercialised for the first time in Europe in September 2008. The United States Food and Drug Administration (FDA) approval was granted in October 2013. As of 28 February, 2015, more than 20,000 patients worldwide have undergone the MitraClip® procedure. The indication for the MitraClip® System in Europe is much broader than in the USA:

EU: The MitraClip® System is intended for the reconstruction of the insufficient MV through tissue approximation.

USA: The MitraClip® System is indicated for the percutaneous reduction of significant symptomatic MR (≥ 3+) due to primary abnormality of the mitral apparatus (DMR) in patients who have been determined to be at prohibitive risk for MV surgery by a heart team, which includes a cardiac surgeon experienced in MV surgery and a cardiologist experienced in MV disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the MR.

CARILLON® Mitral Contour System® [6, 7]

The CARILLON® device was granted a CE mark in Europe in August 2011; in Australia, the authorisation status is ongoing.

EU: The CARILLON® Mitral Contour System® is indicated for use in patients with FMR.

NeoChord DS1000 [8, 9]

The NeoChord DS1000 device was granted a CE mark in Europe in 2012. The intended use of the device is the repair of chordal elongation and rupture resulting in MV prolapse.

EU: Indicated for use in patients with MR grade 3+ or 4+ who are candidates for surgical MV repair or replacement.

CAUTION: The NeoChord DS1000 has **not been studied in a FMR** patient population. The NeoChord DS1000 has **not been studied in patients with anterior leaflet prolapse**.

Details on the regulatory status of the 3 devices can be found in Appendix 1 (Table 19).

[B0002] – What are the claimed benefits of the MitraClip® System, CARILLON® Mitral Contour System®, and NeoChord DS1000 in relation to the comparators?

MitraClip® System

The MitraClip® System is a first-of-its-kind TMVR solution, providing a therapeutic option for HR or inoperable symptomatic patients.

The MitraClip® procedure is delivered via a minimally invasive approach, thereby eliminating the need for cardiopulmonary bypass and surgical incisions, which can include sternotomy or thoracotomy [1].

CARILLON® Mitral Contour System®

The CARILLON® Mitral Contour System® is a percutaneous CS-based mitral annuloplasty device, and the only transcatheter technology holding a CE mark that was designed specifically to treat FMR. FMR is a common condition that can occur secondary to systolic HF and dilated left ventricular cardiomyopathy. The primary method of clinical management is medical therapy as surgical valve replacement or repair is frequently not preferred in patients with advanced HF and contraindications to surgery [6].

NeoChord DS1000

The device is the only-in-class product that provides a minimally-invasive approach to expand access to patients with DMR, without cardiopulmonary bypass- associated risks [8, 9].

[B0004] – Who administers the MitraClip® System, CARILLON® Mitral Contour System®, NeoChord DS1000, and the comparators, and in what context and level of care are they provided?

The 3 technologies under assessment are provided in secondary healthcare, in both public and private settings. According to the European Society of Cardiology-European Association for Cardio-Thoracic Surgery (ESC-EACTS) guidelines [12] and latest position statement from the ESC Working Groups on Cardiovascular Surgery and Valvular Heart Disease [46], decision-making should ideally be made by a multidisciplinary "heart team" with a particular expertise in valvular heart disease, including cardiologists, cardiac surgeons, imaging specialists, HF specialists, anaesthetists, and, if needed, general practitioners, geriatricians, or intensive care specialists. This "heart team" approach is particularly advisable in the management of HR patients and is also important for other subgroups, such as asymptomatic patients, where the evaluation of valve reparability is a key component in decision-making. Risk assessment is fundamental to decision-making; the risk-benefit ratio should be assessed for each possible option, keeping in mind relevant comorbidities and individualised life expectancy [46].

As stated by the manufacturer, the decision to use the MitraClip® System is aligned with the European guidelines and is usually made by a "heart team". According to the manufacturer, the adoption of CARILLON® Mitral Contour System® requires hospitals to have expertise in the areas of interventional cardiology, echocardiography, and HF. Cardiologists typically make recommendations regarding the application of CARILLON® Mitral Contour System®, provide information to potential patients and their family members, and perform the procedure within a catheterisation lab. As a fully implantable, non-active, non-electronic device, once the device is in place, there is no administration work required for patients or their caregivers. As stated by the manufacturer, only physicians thoroughly trained in the use of NeoChord DS1000 should use the device. Use of the device requires a minimum of one trained physician/operator and one trained member of the operating room staff [1, 2, 6-9].

Comparators

Surgery is performed in high-level care with expertise from multiple disciplines, offering all available options for diagnosis and management; surgical procedures require anaesthesia and cardiopulmonary bypass. The optimal care for patients with complex heart disease is best performed in Heart Valve Centres of Excellence that offer all available treatment options and surgical techniques. Decisions about intervention should be dependent on the centres publicly available data on mortality rates and operative outcomes [13].

Pharmacological treatment (with or without CRT) is provided by cardiologists in secondary care.

[B0008] – What kind of special premises are needed for the MitraClip® System, CARILLON® Mitral Contour System®, NeoChord DS1000, and the comparators?

[B0009] – What supplies are needed to use the MitraClip® System, CARILLON® Mitral Contour System®, NeoChord DS1000, and the comparators?

The data provided below are based on the submission files provided by the manufacturers [1, 6, 8] and the instructions for use of the 3 devices [2, 7, 9].

MitraClip® System

The MitraClip® System can be used in a standard catheterisation lab or in a hybrid room with the following equipment: fluoroscopy; general anaesthesia; slave monitors (one for fluoroscopy, one for echocardiography); echocardiography machine equipped with TOE probe; sterile system preparation station. The MitraClip® device should be implanted with sterile techniques using echocardiography (e.g. TOE and TTE) and fluoroscopy. The MitraClip® System is generally performed under general anaesthetic and should be performed according to local institutional guidelines.

CARILLON® Mitral Contour System®

The CARILLON® Mitral Contour System® is deployed in a catheterisation lab utilizing standard catheterisation techniques. The implantable device is deployed via percutaneous means with access via the jugular vein, with the device being delivered into the CS/GCV. The delivery catheter used for device deployment is 9F. No transseptal puncture is required. The device is deployed under fluoroscopic guidance. Echocardiography may also be used during the procedure as a diagnostic tool (either TOE or TTE). The procedure can be conducted under general anaesthetic or conscious sedation.

NeoChord DS1000

In addition to the standard equipment used for lateral thoracotomy, anaesthesia and procedural patient monitoring, the NeoChord DS1000 procedure requires the following: TOE; commercially available ePTFE suture indicated for chordae tendineae repair or replacement with a mean diameter of 0.307 mm (GORE™ CV-4) or 0.246 mm (GORE™ CV-5); standard prolene suture; pledget. Additional recommended ancillary equipment includes a saline rinse tray and rubber-shod clamps. Patients who receive at least one NeoChord using the NeoChord DS1000 should be managed according to the normal standard of care for cardiac implants. As such, a standard anticoagulation regimen for similar cardiac implants (e.g. an annuloplasty ring) is recommended. Antibiotic administration is recommended according to institutional protocol for cardiovascular implant procedure. Patient monitoring via telemetry should be continued as necessary.

The step-by-step procedures for all 3 technologies are described in detail in their respective instructions for use documents [2, 7, 9].

According to the Society for Cardiovascular Angiography and Interventions (SCAI), the American Association for Thoracic Surgery (AATS), the American College of Cardiology (ACC), and The Society for Thoracic Surgeons (STS) [67, 68], several key components are required for the establishment of a structural heart disease intervention therapy programme. Comprehensive multidisciplinary teams are required for transcatheter valve therapies and structural interventional programmes. The institution should have an active valvular heart disease surgical programme with at least 2 institutionally based cardiac surgeons experienced in valvular surgery, as well as a full range of diagnostic imaging and therapeutic facilities including a cardiac catheterisation laboratory or hybrid operating room/catherisation laboratory; a non-invasive imaging system; physical space – minimum room size of 800 square feet (74.3 m^2) to accommodate echocardiographic equipment, sonographers, anaesthesia equipment, the emergency cardiothoracic surgical team, and cardiopulmonary bypass equipment (e.g. surgeon, assistant, surgical technicians, pump technicians), if needed; equipment (e.g. access kits, endovascular sheaths, interventional catheters, vascular closure devices, drainage catheters, etc.); post-procedure intensive care facility; expert consensus document on cardiac catheterization laboratory standards update has outlined the specifications for a hybrid catherisation laboratory [68, 69].

For the comparators, please see assessment element [**B0004**]**.**

[A0021] – What is the reimbursement status of the MitraClip® System, CARILLON® Mitral Contour System®, NeoChord DS1000, and comparators?

The data provided below are based on the submission files provided by the manufacturers [1, 6, 8], and according reimbursement information provided by EUnetHTA JA2 WP5 Strand B members.

The 3 medical devices under assessment are reimbursed with different strategies across Europe; at national or regional level (Italy, Spain), with (e.g., in Austria, the Czech Republic, France and Switzerland) or without restrictions (see Appendix 1, Table 21). In some countries, a specific reimbursement fee has been set for the MitraClip® System; in other countries, the 3 devices are reimbursed, together with more generic procedures, as the reimbursement system is not device specific. In Austria, the 3 devices are partially covered by the LKF reimbursement system.

In France, HAS recommends limiting implantations of the MitraClip® System to patients with severe degenerative mitral insufficiency which is symptomatic despite optimal medical treatment, who are not eligible for valve replacement or repair surgery and who meet the echocardiographic eligibility

criteria. In Spain, the MitraClip® System is within the list of reimbursed devices in the National list of Health Services. In Switzerland, trans-catheter mitral valve repair is reimbursed under certain restrictions (only in patients with a risk > 10% of dying within the next year; collaborating in the Swiss MItra Registry). In Germany, the CARILLON® Mitral Contour System® is approved under the New Diagnostic and Treatment Methods (NUB) regulation for usage in the indication described in the CE mark approval (as indication in the Instructions for Use). It is recommended that the technology is funded as a new innovation, and individual hospitals can apply for this coverage. At present, 115 hospitals in Germany have been approved to negotiate reimbursement under this coverage. Usage should initially be concentrated in centres of innovation. In Italy, this medical device is approved for a National Classification of Medical Devices (CND) code that maps to minimally invasive cardiac surgery; reimbursement is derived from this code on a regional basis. In Turkey, it is approved for reimbursement in public hospitals.

NeoChord DS1000 is reimbursed in Germany and Lithuania; in other EU countries, reimbursement applications are in process.

Details on the reimbursement status are given in Appendix 1 (Table 20, Table 21).

2.3 Discussion

The 3 technologies considered in the present assessment address the treatment of MR, either of degenerative/primary or functional/secondary aetiology. Different access strategies have been implemented: mini-thoracotomy for NeoChord DS1000, jugular vein for CARILLON® Mitral Contour System®, femoral vein for MitraClip® System. The 3 devices provide the intended effect by acting on different MV anatomic structures. NeoChord DS1000 is specifically designed to address DMR by providing artificial chords; CARILLON® Mitral Contour System® only addresses FMR by re-shaping annulus geometry from the CS/GCV; MitraClip® System is designed to reduce MR by clipping the leaflets of the MV to each other, thereby replicating the suture placed in the Alfieri technique.

The 3 devices are available in the European market under the CE mark regulation. The only device that is also available in the USA is the MitraClip® System. Differences have been noted between indications for use in Europe and the USA, as FDA approval was granted only for a subset of the population. In light of this, the authors of this assessment discussed the parameters for assessing these 3 medical devices, and whether they should be based on broad CE mark indication or narrow indications and manufacturers' positioning of the device. The authors noted that the CE mark indications were much broader than the FDA indication or clinical guidelines recommendations and the manufacturers' positioning of their device. A decision on the reimbursement status in different EU countries is already made or will be made according to the CE mark Instructions for Use, the intended use, and indications. Clinical guidelines are not mandatory and providing recommendations only, which may, or may not, be followed by clinicians.

3 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY

3.1 Research questions

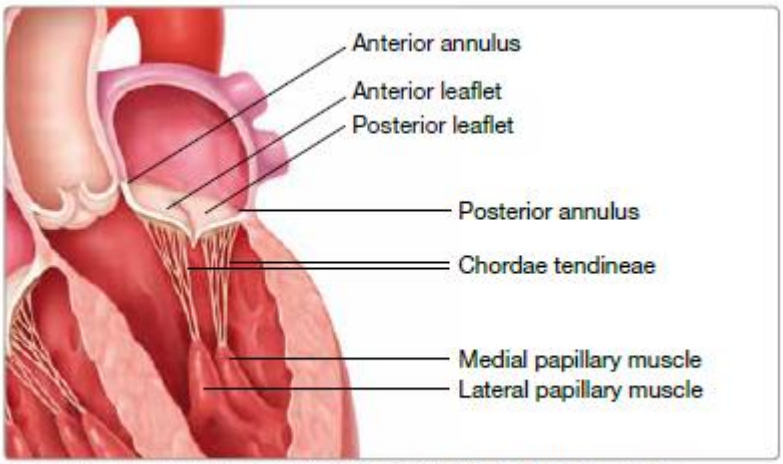
Element ID	Research question
A0002	What is the disease in the scope of this assessment?
A0003	What are the known risk factors for developing chronic MR?
A0004	What is the natural course of chronic MR?
A0005	What are the symptoms and the burden of chronic MR for the patient?
A0006	What are the consequences of chronic MR for society?
A0024	How is chronic MR currently diagnosed according to published guidelines and in practice?
A0025	How is chronic MR currently managed according to published guidelines and in practice?
A0007	What is the target population of this assessment?
A0023	How many people belong to the target population?
A0011	How much are the MitraClip® System, CARILLON® Mitral Contour System®, and NeoChord DS1000 used?

3.2 Results

[A0002] – What is the disease in the scope of this assessment?

MR is characterised by backward flow of blood from the left ventricle to the left atrium during systole, producing left atrial dilatation. It also causes the left ventricle to become enlarged because of the additional workload required to maintain normal blood flow. MR can occur because of abnormalities of the mitral valve leaflets, the annulus, the chordae tendineae or papillary muscles, or the left ventricle (see Figure 1).

Figure 1: Mitral valve anatomy [1]



The mitral valve apparatus consists of the annulus, the leaflets, the chordae tendineae, and papillary muscles.

MR can be acute (leaflet perforation, chordal rupture, rupture of the papillary muscle due to MI) or chronic (long-term disorder associated with valvular or ventricular pathology) and, according to the aetiology, primary (degenerative) or secondary (functional) (see Table 5). DMR refers to abnormalities of the leaflets and is most commonly caused by myxomatous degeneration, especially in

developed countries. With FMR, the leaflets are usually normal, and the regurgitation occurs as a consequence of adverse LV remodelling, with papillary muscle displacement, leaflet tethering, and annular dilatation. FMR due to ischaemic heart disease or non-ischaemic dilated cardiomyopathy, resulting in HF. The most frequent causes of MR are degenerative (myxomatous) disease, ischaemic heart disease, rheumatic heart disease, and infectious endocarditis [1, 6, 10-14].

Table 5: Aetiologies of MR and their characteristics

Primary /Degenerative (DMR)
• Caused by abnormalities in one or more components of the valve architecture, such as the leaflets, chordae, or papillary muscles • Results in lack of coaptation of the valve leaflets, because of MV prolapse (collapsing of the valve) or flail (outwards bulging of the valve due to ruptured chord and/or papillary muscle)
Secondary/Functional (FMR)
• Occurs as a result of LV dysfunction, which is typically caused by ischaemic heart disease or dilated cardiomyopathy • Dilation of the left ventricle because of dysfunction causes displacement of the papillary muscles and dilation of the mitral annulus, resulting in tethering of the leaflets thereby preventing coaptation of the MV leaflets • The MV itself is usually structurally normal

Abbreviations: DMR = degenerative mitral regurgitation; FMR = functional mitral regurgitation; LV = left ventricular; MV = mitral valve.

The severity of MR is graded from mild to severe (numerically: mild, 1+; severe, 4+) and is usually determined by echocardiography (see Table 6, Table 7) [13]. The classification of MR severity used in the USA and in much of the clinical and epidemiological literature, which assigns 4 grades (mild, moderate, moderate-to-severe, and severe), is different to the system used most frequently in Europe, which assigns 3 grades (mild, moderate, and severe).

Table 6: Stages of DMR

Grade	Valve anatomy	Valve haemodynamics*	Haemodynamic consequences	Symptoms
A – ***At risk*** of MR	- Mild MV prolapse with normal coaptation - Mild valve thickening and leaflet restriction	- No MR jet or small central jet area < 20% LA on Doppler - Small vena contracta < 0.3 cm	None	None
B – ***Progressive*** MR	- Severe MV prolapse with normal coaptation - Rheumatic valve changes with leaflet restriction and loss of central coaptation - Prior IE	- Central jet MR 20%–40% LA or late systolic eccentric jet MR - Vena contracta < 0.7 cm - Regurgitant volume < 60 ml - Regurgitant fraction < 50% - ERO < 0.40 cm^2 - **Angiographic grade 1–2+**	- Mild LA enlargement - No LV enlargement - Normal pulmonary pressure	None
C – ***Asymptomatic severe*** MR	- Severe mitral valve prolapse with loss of coaptation or flail leaflet - Rheumatic valve changes with leaflet restriction and loss of central coaptation - Prior IE - Thickening of leaflets with radiation heart disease	- Central jet MR > 40% LA or holosystolic eccentric jet MR - Vena contracta ≥ 0.7 cm - Regurgitant volume ≥ 60 ml - Regurgitant fraction ≥ 50% - ERO ≥ 0.40 cm^2 - **Angiographic grade 3–4+**	- Moderate or severe LA enlargement - LV enlargement - Pulmonary hypertension may be present at rest or with exercise - **C1**: LVEF > 60% and LVESD < 40 mm - **C2:** LVEF ≤ 60% and LVESD ≥ 40 mm	None

Grade	Valve anatomy	Valve haemodynamics*	Haemodynamic consequences	Symptoms
D – ***Symptomatic severe*** MR	- Severe mitral valve prolapse with loss of coaptation or flail leaflet - Rheumatic valve changes with leaflet restriction and loss of central coaptation - Prior IE - Thickening of leaflets with radiation heart disease	- Central jet MR > 40% LA or holosystolic eccentric jet MR - Vena contracta ≥ 0.7 cm - Regurgitant volume ≥ 60 ml - Regurgitant fraction ≥ 50% - ERO ≥ 0.40 cm^2 - **Angiographic grade 3–4+**	- Moderate or severe LA enlargement - LV enlargement - Pulmonary hypertension present	- Decreased exercise Tolerance - Exertional dyspnoea

* ***Several valve haemodynamic criteria*** *are* ***provided*** *for* ***assessment of MR severity****, but not all criteria for each category will be present in each patient.* ***Categorisation of MR severity as mild, moderate, or severe depends on data quality and integration of these parameters in conjunction with other clinical evidence.***

Abbreviations: DMR = degenerative mitral regurgitation; ERO = effective regurgitant orifice; IE = infective endocarditis; LA = left atrium/atrial; LV = left ventricular; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension; MR = mitral regurgitation.

Source: Nishimura et al., 2014 [13]

Table 7: Stages of FMR

Grade	Valve anatomy	Valve haemodynamics*	Associated cardiac findings	Symptoms
A – ***At risk*** of MR	- Normal valve leaflets, chords, and annulus in a patient with coronary disease or cardiomyopathy	- No MR jet or small central jet area < 20% LA on Doppler - Small vena contracta < 0.3 cm	- Normal or mildly dilated LV size with fixed (infarction) or Inducible (ischaemia) regional wall motion abnormalities - Primary myocardial disease with LV dilation and systolic dysfunction	- Symptoms due to coronary ischaemia or HF may be present that respond to revascularisation and appropriate medical therapy
B – ***Progressive*** MR	- Regional wall motion abnormalities with mild tethering of mitral leaflet - Annular dilation with mild loss of central coaptation of the mitral leaflets	- Regurgitant volume < 30 ml - ERO < 0.20 cm^2 - Regurgitant fraction < 50%	- Regional wall motion abnormalities with reduced LV systolic function - LV dilation and systolic dysfunction due to primary myocardial disease	- Symptoms due to coronary ischaemia or HF may be present that respond to revascularisation and appropriate medical therapy
C – ***Asymptomatic severe*** MR	- Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet - Annular dilation with severe loss of central coaptation of the mitral leaflets	- Regurgitant volume ≥30 mL - ERO ≥ 0.20 cm^2 - Regurgitant fraction ≥ 50%	- Regional wall motion abnormalities with reduced LV systolic function - LV dilation and systolic dysfunction due to primary myocardial disease	- Symptoms due to coronary ischaemia or HF may be present that respond to revascularisation and appropriate medical therapy
D – ***Symptomatic severe*** MR	- Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet - Annular dilation with severe loss of central coaptation of the mitral leaflets	- Regurgitant volume ≥ 30 ml - ERO ≥ 0.20 cm^2 - Regurgitant fraction ≥ 50%	- Regional wall motion abnormalities with reduced LV systolic function - LV dilation and systolic dysfunction due to primary myocardial disease	- HF symptoms due to MR persist even after revascularisation and optimisation of medical therapy - Decreased exercise tolerance - Exertional dyspnoea

* ***Several valve haemodynamic criteria*** *are* ***provided for assessment of MR severity****, but not all criteria for each category will be present in each patient.* ***Categorisation of MR severity as mild, moderate, or severe depends on data quality and integration of these parameters in conjunction with other clinical evidence.***

The measurement of the proximal isovelocity surface area by 2D TTE in patients with FMR underestimates the true ERO due to the crescentic shape of the proximal convergence.

Abbreviations: ERO = effective regurgitant orifice; FMR = functional mitral regurgitation; HF = heart failure; LA = left atrium; LV = left ventricular; MR = mitral regurgitation; TTE = transthoracic echocardiogram.

Source: Nishimura et al., 2014 [13]

The closest ICD-10 classification of MV disorders for MR is I34.0:

Table 8: ICD-10 classification of MV disorders

I05	RHEUMATIC MITRAL VALVE DISEASES
I05.1	Rheumatic mitral insufficiency (incompetence or regurgitation)
I34	NON RHEUMATIC MITRAL VALVE DISORDERS
I34.0	Mitral valve insufficiency (incompetence or regurgitation)
I34.1	Mitral valve prolapse (Floppy mitral valve syndrome) (excludes Marfans syndrome)
I34.8	Other non-rheumatic mitral valve disorders
I34.9	Non-rheumatic mitral valve disorders, unspecified
I39.0*	Mitral valve disorders in diseases classified elsewhere
Q23.3	Congenital mitral insufficiency

Source: Submission File Abbott Vascular [1]; ICD-10 Version: 2010 [70]

[A0003] – What are the known risk factors for developing chronic MR?

The known risk factors for developing chronic MR are age, hypertension, low body mass index, coronary systolic blood pressure, increased left atrium size and LV diastolic diameter, low LVEF, and female gender. In addition to HF being a complication of MR, HF is a major risk factor for the development of MR, having been detected in 56% of patients with LVEF < 40% and clinical HF (70% mild, 30% moderate/severe) in a US cohort [1, 6, 10, 11, 71].

[A0004] – What is the natural course of chronic MR?

MR can be present many years before any symptom occurs. If untreated, moderate-to-severe MR can cause progressive congestive HF, and lead, eventually, to death. The risk of mortality for those with severe MR that is left untreated is higher than for the general population: 1-year and 5-year mortality rates of 20% and 50%, respectively, have been reported. According to further evidence on asymptomatic severe chronic MR, the estimated 5-year rates of death from any cause, death from cardiac causes, and cardiac events (death from cardiac causes, HF, or new AF with medical management) have been reported to be 22.3%, 14.3%, and 33.3%, respectively. In addition to symptoms, age, AF, severity of MR (particularly ERO area, pulmonary hypertension, LA dilatation, increased LVESD, and low LVEF were all found to be predictors of poor outcome [1, 10-12, 72, 73].

[A0005] – What are the symptoms and the burden of chronic MR for the patient?

Symptoms

Symptoms of chronic MR include palpitation, dyspnoea, orthopnoea, fatigue, lethargy, cardiac cachexia, thromboembolism, and subacute infective endocarditis. MR confers a substantial physical, emotional, and social burden to patients. Severe symptoms may prevent patients from performing everyday tasks and simple activities, such as getting out of bed. The inability to perform activities of daily of living and be independent can lead to feelings of loss of independence, distress, and depression. Patients feel like they are a burden to their family and they worry about the future. Patients may need to adjust their houses in order to cope with the condition, for example installing a

stairlift or rails. Given the statements above, HF can impact upon all aspects of a patient's QoL. Patients with HF have significant impairments in all aspects of their health compared with the general population, and have significantly greater physical QoL impairment than patients with chronic lung disease or arthritis [1, 6, 10, 11, 74].

Hospitalisation

A study of patients with severe MR who were not considered suitable for valve surgery reported that hospitalisations due to HF exacerbations rose from 41% in the first year to 90% after 5 years; another study showed that a greater proportion of hospitalisations in patients with MR before surgery were associated with congestive HF compared to the period after surgical intervention ($p < 0.001$) [1, 75]. Baskett et al. performed a retrospective analysis of mortality and hospitalisation for HF in 301 patients from the Studies Of Left Ventricular Dysfunction (SOLVD). The authors concluded that the presence of mitral insufficiency in patients with LV dysfunction is independently associated with adverse outcomes, including death and hospitalisations for HF [6, 76].

Comorbidities

Approximately 40% of patients with MR have at least 1 comorbidity including, but not limited to, advanced age, frailty, and prior cardiac surgery. The presence of comorbidities may influence the treatment that a patient can receive based on the impact of the surgical risk–benefit profile. Cardiac comorbidities include: HF (almost 40% of patients with significant HF have MR), AF (occurs as a result of increased LA pressure associated with the backflow of blood in MR), ischaemic heart disease/history of MI (a cause of FMR), LV dysfunction (a cause of FMR), cardiomyopathy (a cause of FMR), concomitant valvular heart disease, and atherosclerosis. Non-cardiac comorbidities include: pulmonary hypertension (a consequence of increased pressure in the left atrium, resulting in increased pressure in the pulmonary vasculature), renal dysfunction (along with haemodialysis, may cause mechanical stress on the valves resulting in mitral annular calcification), chronic obstructive pulmonary disease (chronic inflammation of the airways resulting in decreased tolerance of symptoms secondary to MR), vasculopathy (atherosclerosis of the peripheral or cerebral circulation increases the risk of stroke or embolic phenomenon), malignancy (advanced stage malignancy decreases life expectancy of the patient and immunosuppressive treatment may increase the patient's risk potential for complications if treated for MR), neurological impairment (prior history of stroke or transient ischaemic attack may increase the risk for complications and increase mortality risk associated with cardiac surgery), and frailty (will affect the patient's morbidity and mortality risks associated with surgery because of the postoperative recovery needed) [1, 12, 77].

[A0006] – What are the consequences of chronic MR for society?

The prevalence of MR is high among the general population, with approximately 19% having MR of at least mild severity. The prevalence of MR increases with age: clinically meaningful MR (moderate or greater in severity) is present in < 1% of people younger than 50 years, but in 11% of people over 70 years. MR accounts for the vast majority (97%) of all MV diseases and, in Europe, is the second most common type of heart valve disease requiring surgery, after aortic stenosis. The incidence of MR is high amongst patients with HF: almost 40% of patients with significant HF have MR [1, 15, 16].

In France, the annual cost-per-patient for the treatment of MR has been estimated at € 24,581 for patients receiving surgery, and € 12,177 for patients receiving non-surgical management. MR is often associated with HF, with recurrent hospitalisations and need for multiple medications for management placing a substantial cost burden on the health system: in the UK, the cost of managing HF accounts for 2% of the total (NHS) budget (£625 million), of which 61% of which is accounted for by inpatient hospital stays [1, 78, 79].

The cost of HF in the USA was also estimated to account for 2% of the total healthcare budget ($32.9 billion), with hospitalisations accounting for 60% of this cost. The burden of MR is increasing; a study conducted in the USA reported an increase in the number of hospitalisations due to valvular heart disease from 1983 to 2000, with a 1.5-fold greater increase among patients with MV disease compared with aortic valve disease ($p < 0.001$) [1, 80].

[A0024] – How is chronic MR currently diagnosed according to published guidelines and in practice?

An overview of the latest guidelines for the diagnosis of chronic MR is presented in Appendix 1, Table 10.

According to the most recent US Guideline from 2014 [13], further steps should be performed to diagnose and assess the severity of chronic MR:

"A careful history, a detailed physical examination should be performed to diagnose and assess the severity of valve lesions based on a compilation of all findings made by inspection, palpation, and auscultation. The use of an electrocardiogram (ECG) to confirm heart rhythm and use of a chest x-ray to assess the presence or absence of pulmonary congestion and other lung pathology may be helpful in the initial assessment of patients with known or suspected valvular heart disease (VHD). A comprehensive transthoracic echocardiogram (TTE) with 2–dimensional (2D) imaging and Doppler interrogation should then be performed to correlate findings with initial impressions based on the initial clinical evaluation. The TTE will also be able to provide additional information, such as the effect of the valve lesion on the cardiac chambers and great vessels, and to assess for other concomitant valve lesions. Other ancillary testing such as transoesophageal echocardiography (TOE, computed tomography (CT) or cardiac magnetic resonance (CMR) imaging, stress testing, and diagnostic haemodynamic cardiac catheterisation may be required to determine the optimal treatment for a patient with VHD. An evaluation of the possible surgical risk for each individual patient should be performed if intervention is contemplated, as well as other contributing factors such as the presence and extent of comorbidities and frailty. Follow-up of these patients is important and should consist of an annual history and physical examination in most stable patients."

Steps that should be performed to diagnose and assess the severity of chronic MR (with recommendation and levels of evidence) [13]:

CLASS I

1. TTE is indicated for baseline evaluation of LV size and function, right ventricular function and left atrial size, pulmonary artery pressure, and mechanism and severity of primary MR (stages A to D) in any patient suspected of having chronic primary MR. (Level of Evidence: B)

CLASS I

2. Chronic MR is indicated in patients with chronic DMR to assess LV and right ventricular volumes, function, or MR severity, and when these issues are not satisfactorily addressed by TTE. (Level of Evidence: B)

CLASS I

3. Intraoperative TOE is indicated to establish the anatomical basis for chronic DMR (stages C and D) and to guide repair. (Level of Evidence: B)

CLASS I

4. TOE is indicated for evaluation of patients with chronic DMR (stages B to D) in whom non-invasive imaging provides non-diagnostic information about the severity of MR, mechanism of MR, and/or status of LV function. (Level of Evidence: C)

CLASS IIa

1. Exercise haemodynamics with either Doppler echocardiography or cardiac catheterisation is reasonable in symptomatic patients with chronic DMR where there is a discrepancy between symptoms and the severity of MR at rest (stages B and C). (Level of Evidence: B)

CLASS IIa

2. Exercise treadmill testing can be useful in patients with chronic DMR to establish symptom status and exercise tolerance (stages B and C). (Level of Evidence: C)

Abbreviations: DMR = degenerative mitral regurgitation; LV = left ventricular; MR = mitral regurgitation; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.

[A0025] – How is chronic MR currently managed according to published guidelines and in practice?

An overview of the latest guidelines for the management of chronic MR is presented in Appendix 1, Table 10.

According to the most recent US Guideline from 2014 [13], further treatment is recommended that differs for chronic DMR and chronic FMR.

Chronic DMR

Medical therapy: Recommendations

CLASS IIa

1. Medical therapy for systolic dysfunction is reasonable in symptomatic patients with chronic DMR (**stage D**) and LVEF < 60% in **whom surgery is not contemplated**. (**Level of Evidence: B**)

CLASS III: No Benefit

1. Vasodilator therapy is not indicated for normotensive asymptomatic patients with chronic DMR (**stages B and C1**) and normal systolic LV function. (**Level of Evidence: B**)

According to the EU Guideline from 2012 [12], there is no evidence to support the use of vasodilators, including ACE inhibitors, in chronic MR **without HF,** and they are therefore not recommended in this group of patients. However, when **HF has developed**, ACE inhibitors are beneficial and should be considered in patients with advanced MR and severe symptoms, who **are not suitable for surgery or when there are still residual symptoms following surgery**. Beta-blockers and spironolactone should also be considered as appropriate.

Intervention: Recommendations

CLASS I

1. **MV surgery** is recommended for **symptomatic patients** with **chronic severe** DMR (**stage D**) and LVEF > 30%. (**Level of Evidence: B**)

CLASS I

2. **MV surgery** is recommended for **asymptomatic patients** with **chronic severe** DMR and LV dysfunction (LVEF 30–60% and/or LVESD ≥ 40 mm, **stage C2**). (**Level of Evidence: B**)

CLASS I

3. **MV repair** is recommended in preference to MV replacement when **surgical treatment is indicated** for patients with chronic severe DMR **limited to the posterior leaflet**. (**Level of Evidence: B**)

CLASS I

4. **MV repair** is recommended in preference to MV replacement when surgical treatment is indicated for patients with **chronic severe DMR** involving the **anterior leaflet or both leaflets** when a successful and durable repair can be accomplished. (**Level of Evidence: B**)

CLASS I

5. **Concomitant MV repair or MV replacement** is indicated in patients with chronic **severe DMR undergoing cardiac surgery for other indications**. (**Level of Evidence: B**)

CLASS IIa

1. **MV repair** is reasonable in **asymptomatic patients with chronic severe** DMR (**stage C1**) with preserved LV function (LVEF > 60% and LVESD < 40 mm) in whom the likelihood of a successful and durable repair without residual MR is greater than 95% with an expected mortality rate of less than 1% when performed at a Heart Valve Centre of Excellence. (**Level of Evidence: B**)

CLASS IIa

2. **MV repair** is reasonable for asymptomatic patients with **chronic severe nonrheumatic DMR** (**stage C1**) and preserved LV function (LVEF > 60% and LVESD < 40 mm) in whom there is a high likelihood of a successful and durable repair with: 1) new onset of AF, or 2) resting pulmonary hypertension (pulmonary artery systolic arterial pressure > 50 mm Hg). (**Level of Evidence: B**)

CLASS IIa

3. **Concomitant MV repair** is reasonable in patients with chronic moderate DMR (**stage B**) when **undergoing cardiac surgery for other indications**. (**Level of Evidence: C**)

CLASS IIb

1. **MV surgery** may be considered in symptomatic patients with chronic severe DMR and LVEF ≤ 30% (**stage D**). (**Level of Evidence: C**)

CLASS IIb

2. **MV repair** may be considered in patients with rheumatic MV disease when surgical treatment is indicated if a durable and successful repair is likely **or** when the reliability of long-term anticoagulation management is questionable. (**Level of Evidence: B**)

CLASS IIb

3. **TMVR** may be considered for **severely symptomatic patients (NYHA class III to IV)** with chronic severe DMR (**stage D**) who have favourable anatomy for the repair procedure and a reasonable life expectancy, but who have a **prohibitive surgical risk because of severe comorbidities and remain severely symptomatic despite optimal guideline-directed medical therapy (GDMT) for HF**. (**Level of Evidence: B**)

CLASS III: Harm

1. MVR should not be performed for the treatment of isolated severe DMR limited to less than one half of the posterior leaflet unless MV repair has been attempted and was unsuccessful. (**Level of Evidence: B**)

Chronic FMR

Medical Therapy: Recommendations

CLASS I

1. Patients with chronic FMR (**stages B to D**) and HF with reduced LVEF should receive **standard GDMT therapy for HF, including ACE inhibitors, angiotensin II receptor blockers, beta blockers, and/or aldosterone antagonists** as indicated. (**Level of Evidence: A**)

CLASS I

2. **CRT with biventricular pacing** is recommended for symptomatic patients with chronic severe FMR (**stages B to D**) who **meet the indications for device therapy**. (**Level of Evidence: A**)

Intervention: Recommendations

CLASS IIa

1. MV **surgery** is reasonable for patients with chronic severe FMR (**stages C and D**) who are **undergoing coronary artery bypass grafting or aortic valve replacement**. (**Level of Evidence: C**)

CLASS IIb

1. **MV repair or replacement** may be considered for severely symptomatic patients (NYHA class III to IV) with chronic severe FMR (**stage D**) who **have persistent symptoms despite optimal GDMT for HF**. (**Level of Evidence: B)**

CLASS IIb

2. MV **repair** may be considered for patients with chronic moderate FMR (**stage B**) who are **undergoing other cardiac surgery**. (**Level of Evidence: C**)

[A0007] – What is the target population of this assessment?

The target population of this assessment is adults with chronic DMR or FMR. More specifically, according to the Project Plan, the target population is defined as adults with moderate-to-severe and severe DMR who are surgical candidates (i.e. NeoChord DS1000 population) and adults with moderate-to-severe and severe DMR or FMR who are at high surgical risk or are non-surgical candidates (i.e. CARILLON® Mitral Contour System® and MitraClip® System populations); the current CE mark indication is broader and can be found in Appendix 1 (Table 19) [1, 2, 6, 7, 9].

MitraClip® System

According to the CE mark indication (reconstruction of the insufficient MV through tissue approximation), the target population is patients with chronic DMR or FMR.

Manufacturer positioning: the MitraClip® System is indicated for patients suffering from moderate-to-severe and severe MR with a high risk or contraindication for surgery [1].

Patients are thus candidates for the MitraClip® System treatment when they have severe **DMR or FMR** (according to the ESC-EACTS guidelines classification), they are refractory to medical treatment, and when their risk for surgery is judged to be too high or when surgery is contraindicated.

CARILLON® Mitral Contour System®

The CE mark indication states that: The CARILLON® Mitral Contour System® is indicated for use in patients with FMR.

According to the manufacturer, the clinical focus of the treatment modality is patients with advanced systolic HF due to dilated ischaemic or non-ischaemic cardiomyopathy and **FMR** of grades 2+, 3+, or 4+ [6].

NeoChord DS1000

According to the CE mark indication, the target population for NeoChord DS1000 comprises patients with Grade 3+ or 4+ MR who are candidates for surgical MV repair or replacement [9].

[A0023] – How many people belong to the target population?

Specific statistical data on the size of the target population were not found. The MR severity classification used in the USA, and extensively in the clinical and epidemiological literature, assigns 4 grades (mild, moderate, moderate-to-severe, and severe), which differs from the ESC-EACTS classification used predominantly in Europe, which assigns 3 grades (mild, moderate, and severe). Part of the “moderate-to-severe” group in the USA classification system will, therefore, be included in the “severe” group in the European classification, while the remaining part will form part of the “moderate” group. A correlation table to correct this was not found [1, 12].

MitraClip® System

Specific statistical data for Europe or other geographical regions on the prevalence/incidence of the target group, i.e. patients suffering from severe symptomatic MR with high surgical risk or with contraindications for surgery that could be candidates for MitraClip® System, were not found.

CARILLON® Mitral Contour System®

The size of the target population from a prevalence perspective can be estimated based on evaluating proportions of the HF population that present with: advanced HF symptoms (NYHA class III or IV), dilated cardiomyopathy, FMR of Grades 2+, 3+, or 4+. From this group of patients, the following should be excluded: patients with contraindications (including resident coronary sinus lead, mitral annuloplasty ring/artificial MV, significant mitral calcification, or significant degenerative leaflet pathology), patients who have not been optimised on a HF regimen, and patients who are deemed to be at low risk for surgery. Giving consideration to each of these inclusions and exclu-

sions, the estimated size of the target population can be projected to be between 15% and 30% of the HF population. Given the growing prevalence of HF worldwide, the number of candidates for this procedure is likely to increase over time [6].

NeoChord DS1000

Specific statistical data on the size of the target population were not found.

[A0011] – How much are the MitraClip® System, CARILLON® Mitral Contour System®, and NeoChord DS1000 used?

MitraClip® System

The manufacturer stated that, by December 2014 and including clinical trials, MitraClip® was implanted in 16,327 patients in Europe, and a total of 19,148[1] patients worldwide. The procedure is performed in 312 centres in Europe (464 centres worldwide) [1].

CARILLON® Mitral Contour System®

The manufacturer stated that, to date, there have been approximately 300 patients implanted with CARILLON® Mitral Contour System® in 10 countries, and this is anticipated to grow to more than 550 patients before the end of 2015 [6].

NeoChord DS1000

The manufacturer stated that, to date, the experience with NeoChord DS1000 is based on 200 patients (30 patients from TACT trial and 170 patients from post-marketing) [8].

3.3 Discussion

MR is a complex condition with two different aetiologies present in patients with a plethora of comorbidities. The burden of MR is very high and impacts on patients as well as on society. In assessing patients with chronic MR, it is critical to distinguish DMR from FMR as the two conditions have more differences than similarities. While the correction of DMR is curative, the restoration of MV competence in FMR is not by itself curative. Because of that, the best therapy for FMR is less clear than it is for DMR. Specific statistical data on the target population size in Europe or other regions were not found.

The 3 devices considered in the present assessment have distinct utilisation rates: while NeoChord DS1000 and CARILLON® Mitral Contour System® appear to be in their infancy with hundreds of patients treated worldwide, the MitraClip® System has been implanted in approximately 23,000 patients, mainly in Europe.

[1] Initially, Abbott Vascular stated in the Submission file that their device was implanted in 19,148 patients worldwide. This number was updated to approx. 23,000 by Abbott Vascular during the review of the draft assessment.

4 CLINICAL EFFECTIVENESS

4.1 Methods

Domain framing

No deviation was required from the general scope of the project, according to the final Project Plan.

Research questions

Element ID	Research question
D0001	What is the expected beneficial effect of the technologies on mortality?
D0003	What is the effect of the technologies on the mortality due to causes other than the target disease?
D0005	How do the technologies impact on symptoms and severity of chronic MR?
D0006	How do the technologies affect progression (or recurrence) of chronic MR?
D0011	What is the effect of the technologies on patients' body functions?
D0016	How does the use of the technologies affect activities of daily living?
D0012	What is the effect of the technologies on generic HRQoL?
D0013	What is the effect of the technologies on disease-specific QoL?
D0017	Was the use of the technologies worthwhile?

Sources

Submission files provided by the manufacturers [1, 6, 8] were initially consulted to develop the assessment elements of the present domain. As searches conducted by the manufacturers were not compliant with the strategy defined in the Project Plan, they were performed *de novo* (Appendix 1, page 70).

Literature searches were performed in the following databases:

- Ovid MEDLINE
- Embase
- Cochrane Library
- CINAHL
- CRD databases (DARE, NHS EED, HTA).

In addition, the following clinical trials databases were searched to identify ongoing studies on the 3 devices included in the assessment:

- ClincalTrials.gov
- ISRCTN
- EU Clinical Trials Register
- metaRegister of Controlled Trials (mRCT)
- International Clinical Trials Registry Platform (ICTRP).

Analysis of secondary and primary studies was performed, for each device, in two different phases: secondary studies (i.e. HTA reports and systematic reviews published in peer-reviewed journals) were screened as a first step and then, only where secondary studies were not available, primary studies were considered for inclusion.

Secondary studies were retrieved in full-text version. A cross-reference search was also performed. To allow a broader overview, searches were extended to include HTA reports published in non-English languages but having a summary in English. HTA reports were extracted and tabulated in ascending chronological order. Only the most recent reports were discussed qualitatively. Systematic reviews were assessed according to year of publication, time range, scope, and population to identify the most recent review that overlapped with the scope of the present assessment. Searches from such reviews were then extended to include May 2015, to identify further, more recent, primary studies fulfilling the inclusion criteria of the present assessment. The R-AMSTAR tool was used for quality assessment of systematic reviews while the criteria from the Cochrane Handbook for Systematic Reviews of Interventions were selected to assess the methodological quality of RCTs and CCTs.

4.2 Results

Included studies

The search produced 372 records (see Appendix 1, page 72). The reference list was screened by title and abstract to identify potentially relevant studies. Among the 155 potentially relevant studies, 15 were secondary studies (i.e. HTA reports and systematic reviews published in peer-reviewed journals), whereas 140 were primary studies. A cross-reference search identified a further 10 HTA reports.

Selection of studies

A total of 14 HTA reports were included. Among these were 3 updated versions of previous reports and 1 horizon scanning report without any literature review, leaving 10 HTA reports for full-text analysis and extraction (Table 9). Three reports focused on CARILLON® Mitral Contour System®, and the rest focused on MitraClip® System. Links to the full-text documents are provided in Table 11.

A total of 11 systematic reviews were identified, all of which were on MitraClip® System. The review by Munkholm-Larsen et al. [17] was selected for update within the present assessment, on the basis of year of publication, time range, scope, and population. Primary studies in the period 2013–2015 were screened to identify new evidence on the use of MitraClip®. As no new comparative studies were found among the 44 records identified, no further studies were included within the present assessment. Therefore, for MitraClip®, assessment elements were answered using the findings from the review by Munkholm-Larsen et al. [17].

To find evidence on NeoChord DS1000 and CARILLON® Mitral Contour System®, the whole list of primary studies was screened. No comparative studies were found on the use of NeoChord DS1000; in all, only 3 case series were available [22, 23, 32]. Given the paucity of studies, even if not used for any quantitative analysis, these non-comparative studies were described briefly and used to attempt to answer the assessment elements for NeoChord DS1000. One comparative study on the use of CARILLON® Mitral Contour System® was identified [21], but it did not meet the inclusion criteria of the present assessment because no formal surgical risk assessment was performed on the study population. In light of the scarcity of studies, and although not used for any quantitative analysis, the study was described briefly and used to attempt to answer the assessment elements for CARILLON® Mitral Contour System®.

MitraClip® System

Secondary studies

MitraClip® was assessed by 8 different institutions, from 2009 to 2015 (Table 9). In Europe, recommendations from the earliest assessments [81, 82] were restrictive in use because of the lack of comparative studies with adequate comparators and low quality observational studies. The latest report, published by Haute Autorité de Santé (HAS) in April 2015 [83], considered the series

from the EVEREST II HRR study and a further 9 non-comparative cohort studies. HAS highlighted the following critical issues: implanted patients have multiple aetiologies of MR with heterogeneous baseline characteristics and therapeutic strategies that are not identical; complications at 1 year of follow-up are not systematically described in the studies; evidence is limited to small numbers and short follow-up periods; efficacy cannot be assessed by type of MR; the definition of "high surgical risk" varies depending on the study; the learning curve of the technique is not considered in the studies.

Despite these issues – but in line with the latest ESC-EACTS and AHA-ACC Guidelines [12, 13] – HAS recommended the use of the MitraClip® System in patients with severe DMR who are symptomatic despite optimal medical treatment, ineligible for surgery, and meet the echocardiographic eligibility criteria. The lack of alternatives for this population and the potential benefit of the MitraClip® System was considered crucial by HAS. They stated that, for other indications (e.g., FMR or mixed aetiologies) and/or for patients at lower surgical risk, the role of MitraClip® remains undetermined.

The review by Munkholm-Larsen et al. [17] was focused on the assessment of safety, success rate, clinical efficacy, and survival outcomes of MitraClip® System implantation in managing patients with severe DMR and/or FMR and high surgical risk candidates. The review covered the time frame from January 2000 to March 2013. All 12 studies included were prospective observational studies from specialised tertiary referral centres (no comparative studies were identified). The review did not identify any RCTs comparing MitraClip® vs non-surgical therapies. Only 3/12 studies involved multiple centres [84-86], and only 3/12 studies had 100 or more patients (n = 202 [87]; n = 117 [88]; and n = 100 [85]); the rest of the studies included fewer than 100 patients (range 16–85). Most of the studies (7/12) had a median follow-up of 1 year; 3/12 studies had a median follow-up of 6 months, and only one study reported outcomes beyond 12 months. Immediate procedural success ranged from 72% to100%; 30-day mortality ranged from 0% to 7.8%. One-year survival ranged from 757 to 90%.

The authors of the review highlighted a series of issues [17]:

1) DMR and FMR are often combined (in 9/12 included studies);
2) data on long-term outcomes and durability of device beyond 3 years are limited;
3) inclusion and exclusion criteria, patient selection, and the definition of high risk varied significantly between the included studies;
4) the available literature on high surgical risk patients is of low quality, with the majority being either registries or observational studies. They concluded that *"before further convincing evidence becomes available, the use of MitraClip® implantation should be considered only within the boundaries of clinical trials with special arrangements for clinical governance, consent, and audit or research. MitraClip® interventions should only take place in centres with appropriate cardiothoracic surgical support to manage the potential intraoperative complications"*.

The review [17] was considered to be of good quality (R-AMSTAR score: 30/44; page 92).

Primary studies

No new comparative studies were identified by updating the review by Munkholm-Larsen et al. Assessment elements were developed using findings from this review [17].

CARILLON® Mitral Contour System®

Secondary studies

CARILLON was assessed by the NICE (UK) in 2010 [89], by HealthPACT (Australia) in 2012 (update of an earlier assessment [90]), and by the NHC (New Zealand) in 2013 [91]. The evidence of safety and efficacy, based only on a few case series, was judged inadequate in quality and quantity from the 3 institutions; 2 of them recommended this procedure should be used only in the context of research [89, 91].

Primary studies

No new studies have been identified on the use of CARILLON® Mitral Contour System®. The study mentioned in the most recent HTA report [91] presented the results of the TITAN trial [21]: a prospective, non-randomised, non-blinded, multicentre study designed on the basis of an earlier feasibility study (CARILLON Mitral Annuloplasty Device European Union Study [AMADEUS] [31]) to assess safety and functional changes at 24 months. The population was composed of 53 patients with dilated ischaemic or non-ischaemic cardiomyopathy, at least moderate (2+) FMR; LVEF < 40%, NYHA class II–IV, 6MWT150–450 m, and stable HF medication regimen. Of those 53 patients, 36 underwent permanent device implantation, and 17 had the device implanted and acutely recaptured due to clinical indications (i.e. 8 due to transient coronary compromise and 9 due to < 1 Grade MR reduction). Two groups were then observed: patients with a permanent implant (at 1, 6, 12, and 24 months) and patients with a recaptured implant (comparison group; followed at 1, 6, and 12 months). Follow-up at 12 months was not completed for all patients; depending on the outcome measure, up to 25 patients in the implanted group were followed and up to 8 in the comparison group. This was also related to the mortality in this sick patient population that was adjudicated to be not device related. Follow-up at 24 months was limited to 19 patients in the implanted group (only for patients who had paired data at both 6 and 12 months). Echocardiographic measures assessed changes in FMR and cardiac structure.

NeoChord DS1000

Secondary studies

No secondary studies were found on the use of NeoChord DS1000.

Primary studies

No comparative studies were found on the use of NeoChord DS1000. The only evidence came from 3 case series [22, 23, 32], which were non-comparative, and hence, did not meet the inclusion criteria set to assess clinical effectiveness within the present assessment.

Two studies [22, 32] seem to report on the same cohort of patients. The study by Rucinskas et al. presented a subset of the 30 patients described in the TACT study (NCT01777815) by Seeburger et al. [22, 32]. A total of 30 patients were enrolled at 7 centres across Europe (Leipzig, Turin, Aarhus, Munich, Bad Nauheim, Milan, and Vilnius). All patients presented with severe MR (Grade 3+ or 4+) due to isolated prolapse of the posterior mitral leaflet (i.e. DMR patients) and were candidates for surgery according to guidelines. Patients were seen at 30 days to assess whether the reduction of MR was maintained. Early procedural success was defined as placement of at least 1 chord and reduction of MR to ≤ 2+.

The study by Colli et al. [23] reported on 62 patients, treated in 2 centres (Padua and Vilnius), within the prospective data collection for the NeoChord International Independent Registry (NIIR). All patients presented with severe MR (Grade 3+ or 4+ due to isolated prolapse or flail of the posterior, anterior or both MV leaflets) or were under medical treatment. All patients were candidates for conventional MV repair surgery, according to current guidelines. The rate of patients maintaining MR reduction (≤ 2+) at 30 days was assessed. Early procedural success was defined as placement of at least 2 neo-chordae with immediate reduction in MR ≤ 2+.

Table 9: HTA reports on the 3 devices considered in the present assessment (MitraClip® System, CARILLON® Mitral Contour System®, and NeoChord DS1000) in ascending chronological order

Year	Institution	Country	Title	Device	Population assessed	Studies considered for recommendations (n = number of patients)	Recommendations
2009	NICE	UK	Percutaneous mitral valve leaflet repair for MR	MitraClip®	Patients with MR	1 case series (n = 107)	*"Evidence on the safety and efficacy of percutaneous mitral valve leaflet repair for MR is currently inadequate in quality and quantity.* *Therefore, this procedure should only be used:* • *with special arrangements for clinical governance, consent and research for patients who are well enough for surgical mitral valve leaflet repair to treat their MR, or* • *in the context of research for patients who are not well enough for surgical mitral valve leaflet repair to treat their MR"*
2010	NICE	UK	Percutaneous mitral valve annuloplasty	CARILLON® Mitral Contour System®	Patients with MR	1 case series (n = 48)	*"Current evidence on the safety and efficacy of percutaneous mitral valve annuloplasty is inadequate in quality and quantity. Therefore this procedure should only be used in the context of research, which should clearly describe patient selection, concomitant medical therapies and safety outcomes. Both objective measurements and clinical outcomes should be reported"*
2012 (2010 update)	HealthPACT	Australia	CARILLLON® mitral contour system® for mitral regurgitation	CARILLON® Mitral Contour System®	Patients with FMR	1 comparative study (n = 53); 1 case series (n = 14)	*"The evidence base for the Carillon mitral contour system is limited, and there is still uncertainty around the uptake of this and other comparator technologies for the treatment of mitral valve disease in Australian clinical practice. Therefore, HealthPACT have recommended that no further assessment of this technology is warranted."*
2012 (2011 update)	LBI-HTA	Austria	Percutaneous repair of mitral regurgitation with the MitraClip®	MitraClip®	Patients with moderate-to-severe or severe MR. Patients eligible for surgery as well as for those at high surgical risk	1 RCT (n = 279); 1 uncontrolled before-after study (n = 107)	*"Overall, the available evidence is currently insufficient to assess the efficacy and safety of MitraClip in comparison to the respective standard therapy for patients with MR. Therefore, the inclusion into the hospital benefit catalogue is not recommended, either for operable or for inoperable patients"*
2012	HTA Centre of Stockholm County Council	Sweden	MitraClip® for the treatment of severe mitral insufficiency*	MitraClip®	Patients with severe mitral insufficiency.	1 RCT (n = 279); 11 observational uncontrolled (n = 31– 202)	*"Without any study with an adequate control group and due to low quality of the assessed observational studies ... the questions could not be answered whether intervention with MitraClip, compared with medical treatment of patients with severe mitral insufficiency, results in improved quality of life and heart function or reduced hospitalisation and mortality. More research is necessary for further evaluation of MitraClip."*

Year	Institution	Country	Title	Device	Population assessed	Studies considered for recommendations (n = number of patients)	Recommendations
2013	FDA	USA	MitraClip® Clip Delivery System – SSED	MitraClip®	The intended population for these studies was patients with significant symptomatic MR (≥ 3+) of either FMR or DMR aetiology that were determined to be too high risk to undergo mitral valve surgery based upon the STS predicted procedural mortality replacement score or judgment of a cardiothoracic surgeon	1 single-arm registry (n = 78); 2 continued access registries (n = 581; n = 272) *Final recommendations were based on a cohort of 127 patients determined to be at prohibitive risk for surgical mortality*	*"In conclusion, ... the data support that for the percutaneous reduction of significant symptomatic MR (≥ 3+) due to primary abnormality of the mitral apparatus (DMR) in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team ... and in whom existing comorbidities would not preclude the expected benefit from reduction of the MR, the probable benefits outweigh the probable risk"*
2013	NHC	New Zealand	Percutaneous interventions for MR	CARILLON® Mitral Contour System®; MitraClip®	Patients with MR	CARILLON® Mitral Contour System®: 3 case series (n = 9; n= 48; n = 53) MitraClip®: 1 RCT (n = 279); 11 others (n = NR)	*On CARILLON® Mitral Contour System®:* *"The Australia New Zealand Horizon Scanning Network review in the same year also found a lack of high quality evidence supporting the device. What evidence there is suggests the approach risks coronary artery compression, mitral annulus calcification, and has a relatively high device insertion failure rate"* *On MitraClip®:* *"Current evidence suggests the procedure is safe, but less effective than surgery, cost-ineffective, and potentially significantly cost increasing. Accordingly, it is recommended that the procedure is not publicly funded in New Zealand. This is consistent with MSAC's recent decision in Australia"*
2014	BCBS	USA	Percutaneous mitral valve repair	MitraClip®	Patients with DMR considered at high risk of surgical mortality	5 case series (n = 15–127)	*"The evidence for evaluating the MitraClip in patients with degenerative MR who are at high surgical risk is limited to case series.* *Based on the uncertainty of the mortality outcomes of patients receiving MitraClip compared with their natural history, no conclusion can be reached about the device's effect on net health outcomes"*

Year	Institution	Country	Title	Device	Population assessed	Studies considered for recommendations (n = number of patients)	Recommendations
2014 (2012 update)	MSAC	Australia	The reduction of severe MR through tissue approximation using transvenous/ transseptal techniques	MitraClip®	Patients considered to be high risk for surgery and currently treated by medical management	20 non-comparative series (n = NR)	*"After considering the strength of the available evidence in relation to safety, effectiveness and cost-effectiveness, MSAC did not support public funding for the reduction of MR through tissue approximation using transvenous/ transseptal techniques because of uncertain comparative safety, effectiveness and cost-effectiveness due to limited direct comparative data"*
2015	HAS	France	Assessment of an edge-to-edge mitral valve repair clip and its implantation	MitraClip®	Patients with mitral insufficiency	1 single-arm registry (n = 78); 9 non-comparative series (n = 51–1002)	*"In the current state of knowledge, HAS recommends limiting implantations of the MitraClip device to patients with severe degenerative mitral insufficiency which is symptomatic despite optimal medical treatment, who are not eligible for valve replacement or repair surgery and who meet the echocardiographic eligibility criteria. In this indication, HAS believes that there is no alternative and that the need is not covered. In this indication, the improvement in treatment is substantial in relation to the lack of alternatives.* *In the other indications (functional or mixed mitral insufficiency) and/or for lower surgical risks, the role of the MitraClip edge-to-edge mitral valve repair clip in the therapeutic strategy remains undetermined"*

Abbreviations: BCBS = Blue Cross Blue Shield Association; DMR = degenerative mitral regurgitation; FDA = US Food and Drug Administration; FMR = functional mitral regurgitation; HAS = Haute Autorité de Santé; HealthPACT = Health Policy Advisory Committee on Technology; LBI-HTA = Ludwig Boltzmann Institute for Health Technology Assessment; MR = mitral regurgitation; MSAC = Medical Services Advisory Committee; NHC= National Health Committee; NICE = The National Institute for Health and Care Excellence; NR = not reported; RCT = randomised controlled trial; SSED = Summary of Safety and Effectiveness Data; STS = The Society for Thoracic Surgeons.

** Title translated from the original language.*

[D0001] – What is the expected beneficial effect of the technologies on mortality?

[D0003] – What is the effect of the technologies on the mortality due to causes other than the target disease?

MitraClip® System

The review by Munkholm-Larsen et al. [17] showed that survival at 1 year was reported by 6 of the 12 included studies and ranged from 75% to 90%. Long-term survival data were not available.

CARILLON® Mitral Contour System®

In the study by Siminiak et al. [21], the 30-day mortality rate was 1.9% (1/53 patients from the non-implanted group) while the 1-year mortality rate was 22.2% (8/36) in the implanted group and 23.5% (4/17) in the non-implanted group. The earlier feasibility study (AMADEUS [31]) reported a 30-day mortality rate of 2.2% (1/46).

NeoChord DS1000

In the study by Seeburger et al. [22], 1 patient died within 30 days due to post-cardiotomy syndrome and concomitant sepsis. No death at 30 days has been observed in the study by Colli et al. [23].

[D0005] – How do the technologies impact on symptoms and severity of chronic MR?

MitraClip® System

The review by Munkholm-Larsen et al. [17] presented an assessment of symptoms and severity of MR by the NYHA classification. A reduction (early, at 6 months or at 12 months of follow-up) of the number of patients in NYHA class III/IV was reported in 9/11 studies that provided information on this outcome. Five of the included studies reported data at 12 months showing a reduction in proportion of patients in NYHA class II/IV from 98% to 35%, from 88% to 27%, from 94% to 11%, from 98% to 22%, and from 90% to 26%.

CARILLON® Mitral Contour System®

The study by Siminiak et al. [21] presented an assessment of symptoms and severity of FMR, in both groups, according to NYHA classification. At baseline, NYHA class was 3.1 ± 0.23 in the implanted group (36 patients) and 2.9 ± 0.24 in the comparison group (17 patients) ($p = 0.105$). The implanted group was reassessed at 12 months and showed improvement in NYHA class from baseline to 2.1 ± 0.64 (25 patients). The improvement was maintained at the 24-month visit with NYHA class 2.1 ± 0.74 (19 patients) ($p < 0.001$).

NeoChord DS1000

In the study by Colli et al. [23], 87% (55/63) of the patients were in NYHA class I at 30 days, whereas at baseline, only 3 (5%) patients were in NYHA class I.

[D0006] – How do the technologies affect progression (or recurrence) of chronic MR?

MitraClip® System

The review by Munkholm-Larsen et al. [17] reported that, after MitraClip® implantation, reduction of MR Grade to ≤ 2+ was observed in all 11 studies that reported this outcome, and ranging from 73% to 100% of patients. In the studies that reported from 6 to 12 months of follow-up, 61–99% of patients showed an MR grade ≤ 2+. LV volume as well as LV diameter showed a reduction from baseline in all the 6 studies that reported this outcome. LVEF was reported as improved or unchanged from baseline in 6 studies.

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The study by Siminiak et al. [21] presented an assessment of FMR progression and changes in cardiac structure by echocardiographic measures. A statistically significant difference was noted between the two groups, with a continued decrease of FMR up to 12 months noted only in the implanted group. Among 25 implanted patients, the reduction in FMR at 12 months was 3 grades in 3 patients, 2 grades in 5 patients, 1 grade in 12 patients, and less than 1 grade in 5 patients. A statistically significant reduction of LV size was noted in the implanted group, compared with continued enlargement in the comparison group: the mean reduction in LV end-systolic volume was 19% at 12 months. Eight of 25 patients had a > 10% reduction in LV end-systolic volume at 12 months. The echocardiographic assessment included also the assessment of regurgitant volume, ERO area, vena contracta, FMR jet area relative to left atrial area, and annular septal-lateral diameter; in the implanted group at 12-months' follow-up, all of the measures were statistically significantly reduced from baseline.

NeoChord DS1000

In the study by Seeburger et al. [22], at 30 days, 17/29 patients (58.6%) maintained performance success (defined as MR graded ≤ 2+ on early echocardiography). Of these patients, 12 (71%) have maintained an MR Grade ≤ 1+. In the study by Colli et al. [23], at the 30-day follow-up, 10 (16%) patients showed a reduction in MR by 2 grades, 16 (25%) patients by 3 grades, and 29 (46%) patients by 4 grades, while 8 (12.5%) patients were in MR Grade 3+ or 4+.

[D0011] – What is the effect of the technologies on patients' body functions?

MitraClip® System

The review by Munkholm-Larsen et al. [17] reported that only 3 studies assessed functional status in exercise performance by the 6MWT showing improvements for up to 6 months of follow-up: 194 ± 44 m to 300 ± 70 m ($p < 0.01$) [18]; 171 ± 99 to 339 ± 134 metres ($p < 0.001$) [19]; and 300 ± 108 m to 339 ± 120 m ($p = 0.02$) [20].

CARILLON® Mitral Contour System®

Functional changes in exercise performance were observed in the study by Siminiak et al. [21] by the 6MWT. Scores (distance walked, in metres) were reported at baseline and at 1, 6, and 12 months for both groups. In the implanted group, 6MWT scores were 302.5 ± 74 m at baseline (36 patients), 397.9 ± 152 m at 1 month (32 patients), 429.9 ± 209 m at 6 months (27 patients), and 406.0 ± 180 m at 12 months (23 patients). In the comparison group, 6MWT scores were 337.9 ± 83 m at baseline (17 patients), 351.0 ± 98 m at 1 month (14 patients), 322.2 ± 105 m at 6 months (10 patients), and 348.1 ± 138 m at 12 months (8 patients). There was a statistically significant difference between the two groups ($p = 0.005$).

NeoChord DS1000

The effects of NeoChord DS1000 on patients' body functions were not assessed in the 2 studies [22, 23].

[D0016] – How does the use of the technologies affect activities of daily living?

MitraClip® System

Only 2 studies of those included in the review by Munkholm-Larsen et al. [17] assessed changes in performing activities of daily living (e.g. dressing, showering, walking, doing housework) within a general QoL assessment. This dimension is included within the 2 tools used in the studies (the SF-36 Health Survey Quality of Life Questionnaire and the Minnesota questionnaire). Refer to [**D0012**] and [**D0013**].

CARILLON® Mitral Contour System®

The assessment of changes in performing activities of daily living (e.g. dressing, showering, walking, doing housework) at baseline and at follow-up intervals was not reported separately in the study by Siminiak et al. [21], but it is included within the tool used to assess QoL (i.e. the Kansas City Cardiomyopathy Questionnaire). Refer to [**D0012**] and [**D0013**].

NeoChord DS1000

The effects of NeoChord DS1000 on activities of daily living were not assessed in the 2 studies [22, 23].

[D0012] – What is the effect of the technologies on generic HRQoL?

[D0013] – What is the effect of the technologies on disease-specific QoL?

MitraClip® System

The review by Munkholm-Larsen et al. [17] reported that QoL was assessed in 2 studies using different questionnaires. The SF-36 Health Survey Quality of Life Questionnaire (score range 0–100) showed improvements in the physical component from a baseline score of 31.6 ± 9.1 to 37.0 ± 9.7 at 1 month and 36.5 ± 10.6 at the 12-month follow-up ($p = 0.01$). The Minnesota questionnaire (score range 105–0) also showed statistically significant improvement from 56.5 ± 21.9 pre-intervention to 39.4 ± 20.5 at the 6-month follow-up ($p < 0.001$).

CARILLON® Mitral Contour System®

In the study by Siminiak et al. [21], QoL was assessed using the Kansas City Cardiomyopathy Questionnaire (score range 0–100). Scores were reported at baseline and at 1, 6, and 12 months for both groups. In the implanted group, scores were 43.0 ± 18 at baseline (36 patients), 64.6 ± 19 at 1 month (31 patients), 63.4 ± 23 at 6 months (28 patients), and 61.2 ± 26 at 12 months (24 patients). In the comparison group, scores were 40.4 ± 19 at baseline (17 patients), 47.5 ± 25 at 1 month (14 patients), 49.6 ± 22 at 6 months (10 patients), and 51.0 ± 19 at 12 months (7 patients). There was a statistically significant difference between the two groups ($p = 0.001$).

NeoChord DS1000

The effects of NeoChord DS1000 on generic HRQoL or disease-specific QoL were not assessed in the 2 studies [22, 23].

[D0017] – Was the use of the technologies worthwhile?

MitraClip® System

Patient satisfaction was not assessed in the review by Munkholm-Larsen et al. [17].

CARILLON® Mitral Contour System®

Patient satisfaction was not assessed in the single study [21].

NeoChord DS1000

Patient satisfaction was not assessed in the either of the studies [22, 23].

4.3 Discussion

MitraClip® System

There is a lack of comparative evidence on the use of MitraClip® in high surgical risk patients with moderate-to-severe and severe MR vs standard care (either no treatment or pharmacological therapy). However, positive results from small comparative series (the EVEREST II HRR study enrolled only 78 patients and compared the outcomes with a retrospective cohort of 36 patients receiving medical therapy or surgery), case series, and national registries led some institutions to recommend the procedure in a specific subset of the potential population (patients with severe DMR who are symptomatic despite optimal medical treatment, and are ineligible for surgery [83]). The latest European guidelines, even recognising an evidence level of "C" *(consensus of opinion of the experts and/or small studies, retrospective studies, registries)* give the same recommendations (*"may be considered in patients with symptomatic severe secondary MR despite optimal medical therapy – including CRT if indicated, who fulfil the echo criteria of eligibility, are judged inoperable or at high surgical risk by a team of cardiologists and cardiac surgeons, and who have a life expectancy greater than 1 year"*) [12]. It is not possible to make any conclusion, based on current evidence for patients with FMR.

Evidence published to date, reporting data up to 4 years [92], has been focusing on the framework defined by the EVEREST trials in which the MitraClip® System was compared to surgery. In this context, surgery proved to be more effective in terms of reduction of MR and reintervention rate. The MitraClip® System indications have since been updated, making high surgical risk or nonsurgical patients the target population for this therapy. For such a subset of patients, surgery is no longer the best option and medical therapy solely aims to reduce symptoms. The comparator in the present assessment has been defined using such considerations and taking into account the manufacturer's positioning of the device. Several registered studies are ongoing and will, in the near future, be crucial for defining clear indications of MitraClip® and identifying criteria to select the population that may benefit most from the procedure (see Appendix 1, Table 15).

For the present assessment, 4 ongoing studies are particularly relevant because they do not consider any surgical option as comparator:

- The RESHAPE-HF1-FU study (NCT02444286) is an observational cohort aimed to enrol 42 FMR patients in NYHA class III/IV with chronic HF, who had previously participated in the RESHAPE-HF trial. MitraClip® System outcomes will be compared with outcomes from optimal standard of care therapy. Results are expected in January 2017.
- In October 2017, results from the MITRA-FR trial (NCT01920698) are expected to be available. MITRA-FR is a multicentre, randomised study comparing treatment with MitraClip® implantation in addition to optimal standard medical therapy vs optimal medical therapy alone in 288 patients with severe FMR.
- Another multicentre, randomised trial (NCT02444338) is expected to be completed by September 2019; 380 patients with chronic HF and clinically significant FMR (NYHA class II–IV) will be randomised to MitraClip® plus optimal standard of care therapy or standard of care therapy alone.
- The largest trial, the COAPT multicentre, randomised study (NCT01626079), will be completed in 2020 and expects to enrol 430 symptomatic HF subjects, treated with the standard of care, who have been deemed by the site's local heart team as being unsuitable for MV surgery. Percutaneous MV repair using MitraClip® System will be compared to no intervention (non-surgical management based on standard hospital clinical practice).

Another ongoing study that deserves to be mentioned despite the surgical comparator (reconstructive MV surgery) is the Multicenter, Randomized, Controlled Study to Assess Mitral Valve Reconstruction for Advanced Insufficiency of Functional or Ischemic Origin (MATTERHORN) trial (NCT02371512), aimed to assess MV repair with the MitraClip® System in the context of a multicentre, randomised study enrolling 210 high surgical risk patients with clinically significant MR of primarily functional pathology. Results are expected by December 2017.

CARILLON® Mitral Contour System®

There is a lack of comparative evidence on the use of CARILLON Mitral Contour System® in adults with moderate-to-severe and severe FMR who are at high surgical risk or are non-surgical candidates. The only comparative study identified [21] reported on a population of patients in which the surgical risk was not assessed, thus ruling out the study from formal inclusion within the present assessment. Nevertheless, the study was described in the absence of any other evidence. Results refer to the TITAN trial, a prospective, non-randomised, non-blinded, multicentre study designed to assess the safety and functional changes for up to 24 months of follow-up. Although improvements have been observed in terms of FMR reduction, NYHA classification, exercise performance, and QoL measures, some critical issues can be highlighted in this study. The comparison group was created by implanting and acutely recapturing the device for clinical indications (i.e. transient coronary compromise or reduction in MR Grade < 1) in 17/53 patients initially enrolled for treatment. How this procedure impacted on the outcomes observed in the comparison group or whether this group of patients differed clinically given that the intervention had been unsuccessful for them, is unknown.

Moreover, the mortality noticeably affected the number of patients followed at 12 and 24 months: in the implanted group, in the best case (and depending on the outcome assessed), only 25/36 patients were observed at 12 months, and 19 patients at 24 months (follow-up was not feasible in 30.5% and 47.2% of patients, respectively). In the comparison group, follow-up was limited to 12 months and, in the best case, was achieved in 8/17 patients (follow-up was not feasible in 52.9% of patients).

In conclusion, results from the TITAN trial, even if promising, need to be confirmed by randomised blinded studies comparing patients receiving treated with CARILLON® Mitral Contour System® with a medically managed control group with higher rates of follow-up.

The only ongoing registered study is the REDUCE FMR (NCT02325830) that plans to enrol 180 patients and provide results by July 2017. It is a prospective, multicentre, randomised, double-blind study aimed to assess the safety and efficacy of CARILLON® Mitral Contour System® in treating FMR associated with HF, compared to a randomised control group that is medically managed according to HF guidelines (see Appendix 1, Table 16). REDUCE FMR does not state to formally assess the surgical risk of the candidates but set a LVEF ≤ 40% among the inclusion criteria. Results from REDUCE FMR are anticipated, as they may helpful to answer the research questions of the present assessment and provide further information for defining the role of the procedure within the clinical pathway.

NeoChord DS1000

The use of NeoChord DS1000 for the treatment of DMR is in its infancy. Early results on patients who were candidates for surgery are promising in terms of procedural success (chordae implantation and reduction of MR). However, no comparative studies are available and no definitive conclusions can be drawn from the few case series available (a total of 62 patients have been observed in the largest cohort and follow-up did not exceed 30 days).

The only ongoing registered study is the NeoChord TACT trial (NCT01784055) that is expected to enrol 100 patients and to provide results by July 2016. However, such results will not be sufficient to produce final recommendations, as the NeoChord TACT study is a patient registry aimed to observe procedural success at Day 1 (i.e. reduction in MR ≤ 2+) (see Appendix 1, Table 17). Comparative studies with a larger number of patients and adequate long-term follow-up will be necessary to define the use of NeoChord DS1000 in comparison to the standard of care (i.e. surgery).

5 SAFETY

5.1 Research questions

Element ID	Research question
C0008	How safe are the technologies in relation to the comparators: • What is the frequency of AEs (any) of the TMVR (technology and procedure) in relation to comparators? • What is the frequency of serious AEs of the TMVR (technology and procedure) in relation to comparators? • What is the frequency of serious AEs leading to death for the TMVR (technology and procedure) in relation to comparators? • What are the most frequent AEs of the TMVR (technology and procedure) in relation to comparators?
C0004	Which aspects may affect the frequency and/or severity of harms?
C0005	Which patient groups are more likely to be harmed by the use of the technologies?
C0007	Are the technologies and comparators associated with user-dependent harms?

5.2 Results

Included studies

Among 372 records yielded from the literature search, 21 studies (1 secondary study and 20 primary studies) were included to assess the safety of the 3 TMVR devices: MitraClip® System, CARILLON® Mitral Contour System®, and NeoChord DS1000. The inclusion process is graphically represented as a PRISMA flow diagram on page 72.

Secondary studies

The same secondary studies used in the Clinical Effectiveness domain were assessed for inclusion in the Safety domain: the justification for their exclusion is explained in detail in the chapter on Clinical Effectiveness (see section 4.2). We included 1 systematic review [17] on MitraClip® in the assessment of safety, which was the most recently published systematic review that met our inclusion criteria. The review was updated within the present assessment. No secondary studies were included for CARILLON® Mitral Contour System® and for NeoChord DS1000.

Primary studies

The studies screened for their inclusion in the safety analysis were the same as those considered in the Clinical Effectiveness domain, but they did not meet the inclusion criteria for the assessment of effectiveness in the present assessment. Additional cohort, case series, and registry studies were reviewed to see whether they met the inclusion criteria for the Safety domain. The included systematic review on the MitraClip® System [17] was updated; so primary studies published from 2013 to 2015 were screened to identify new evidence on the use of the MitraClip® System. In total, 44 studies were identified as potentially relevant, 15 of which were included [24-26, 29, 30, 33-41, 93].

All 155 potentially relevant records were screened to identify evidence for CARILLON® Mitral Contour System® and NeoChord DS1000 system. Two studies on CARILLON® Mitral Contour System® [21, 31] and 3 studies on NeoChord DS1000 were included (as described in the chapter on Clinical Effectiveness) [22, 23, 32]. In conclusion, 20 primary studies that met our inclusion criteria were included to provide evidence on the safety of TMVR technologies.

All included studies were prospective, case series and cohort studies in which all patients underwent the TMVR procedure with MitraClip® System, CARILLON® Mitral Contour System® or NeoChord DS1000. Ten studies assessing MitraClip® were analyses of registries. Subgroup analyses assessing safety and clinical outcomes of TMVR devices in groups of patients with different clinical characteristics were performed in 10 studies (MitraClip® System: 8 studies; NeoChord DS1000: 2 studies). Twelve studies were multicentre (MitraClip®: 8 studies; CARILLON® Mitral Contour System®: 2 studies; NeoChord: 2 studies) and the remaining study was from a single centre.

Safety results reported in the included studies were extracted and tabulated in Appendix 1 (Table 12, Table 13, Table 14) and are described below.

MitraClip® System

Secondary studies

We included 1 systematic review [17] that met our inclusion criteria. Twelve prospective observational studies assessing MitraClip® System in high surgical risk patients with significant MR were included. No RCTs were identified. With the exception of 3 studies that had 202, 117, and 100 patients, respectively, all other studies included fewer than 100 patients (range 16–85). Seven studies had a median follow-up of 1 year. Three studies had a median follow-up of 6 months. Only 1 study reported outcomes beyond 12 months. Safety outcomes, following implantation of MitraClip® System for high surgical risk patients, across studies included 30-day mortality; cerebrovascular accident; need for early mitral surgery; cardiac tamponade; transseptal complications; partial clip detachment; and transfusion of ≥ 2 units of packed red blood cells. MitraClip® System implantation is an option for managing selected high surgical risk patients with severe MR.

Primary studies

In the non-comparative study by Alegria-Barrero et al. [38], 43 consecutive patients with severe DMR or FMR (MR 3+ or 4+) and high surgical risk (as defined by logEuroSCORE) ineligible for conventional MV repair underwent MitraClip® System implantation. MAEs at 12 months were defined as a composite of cardiovascular mortality, MI, unplanned cardiac surgery, transfusion of more than 2 U of blood, and hospitalisation for HF.

In the multicentre cohort study by Armoiry et al. [33], short- and mid-term safety and efficacy results in 62 patients with FMR (73.8%), DMR (23.0%) or mixed MR (3.2%) who underwent a MitraClip® System procedure in 7 French centres between 2010 and 2012 were reported. All patients were judged ineligible for surgery or at high surgical risk by a heart team. Patient data were collected and recorded in a multicentre national registry. Safety was evaluated and described by the occurrence of in-hospital deaths, in-hospital surgical MV repairs, and other non-fatal AEs, as well as by the proportion of per procedural blood transfusions. In-hospital events corresponded to events occurring during the hospital stay for the MitraClip® System procedure. The 6-month survival rate was also estimated.

In the non-comparative, non-randomized study by Attizzani et al. [36], 171 patients with severe MR (3+ or 4+) at high surgical risk (as judged by an interdisciplinary medical team) undergoing MitraClip® System implantation in 1 Italian centre (University hospital) between 2008 and 2013 as part of the ongoing GRASP (Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation) registry were investigated. The primary safety endpoint was the incidence of MAEs at 30 days defined as the composite of death, MI, reoperation for failed MitraClip® implantation, non-elective cardiovascular surgery for AEs, stroke, renal failure, deep wound infection, mechanical ventilation for > 48 h, gastrointestinal complication requiring surgery, new onset of permanent AF, septicaemia, and transfusion of 2 U of blood.

The single-centre study by Bozdag-Turan et al. [39], investigated a cohort of 121 patients with severe MR (≥ 3+) at high surgical risk according to logEuroSCORE and the STS mortality risk calculation, undergoing MitraClip® implantation. Clinical data and outcomes of patients were collected and recorded in a prospective single-centre registry. Evaluation of the clinical and safety endpoint was carried out at the 12-month follow-up. In particular, data concerning re-interventions and MACCE were reported.

In the study by Braun et al. [93], 119 patients, with symptomatic MR at high surgical risk or who declined surgery, were enrolled to undergo percutaneous edge-to-edge repair of MV with the MitraClip® System between 2009 and 2012. The outcomes of patients with DMR (n = 72) compared to patients with FMR (n = 47) were analysed. In both groups, more than 50% of patients did not meet the eligibility criteria of the EVEREST II trial representing a real-world sample. In terms of safety, data on MV re-intervention and death after 12 months following MitraClip implantation were recorded.

The study by Glower et al. [24] was a prospective, multicentre evaluation of the safety and effectiveness of MitraClip® System in 351 patients with symptomatic MR (MR grades 3+ to 4+) at high surgical risk (≥ 12%, estimated using the STS calculator or by a surgeon co-investigator according to prespecified criteria) with 12-months' follow-up. Analyses included patient data from both the EVEREST II prospective registries of high surgical risk patients: EVEREST II HRR and REALISM HR.

A study by Hellhammer et al. [29] reported on a subanalysis of the MitraClip® Registry (NCT02033811) concerning high surgical risk patients with diabetes mellitus. Among 58 patients with symptomatic severe and moderate-to-severe MR enrolled, 19 (32.8%) had diabetes mellitus II. Primary safety endpoints comprised clip implantation, in-hospital complications, and 30-day mortality.

Another study by Hellhammer et al. [30] aimed to assess the impact of anaemia on peri-procedural MACCE and mortality in patients undergoing treatment of severe MR using MitraClip® System. A total of 80 patients were included in the study, all of whom were at high surgical risk (logEuroSCORE ≥ 20% or pre-existing conditions). Anaemia was assessed at baseline and 2 groups were defined: 41 (51.3%) patients presented with anaemia, whereas 39 (48.7%) had normal erythrocyte levels.

The study by Koifman et al. [41] reported a single-centre experience in Israel. From 2011, 20 high surgical risk patients with at least moderate-to-severe MR with HF symptoms were considered eligible for MitraClip® implantation.

The study from Reichenspurner et al. [37] reported on the results of a sub-group of patients within the MitraClip Therapy Economic and Clinical Outcomes Study Europe (ACCESS-EU) study, a post-approval study designed to gain information on the use of MitraClip® in the EU with respect to health economics and clinical care, and to provide further evidence on the safety and effectiveness of MitraClip® in a real-world setting. The subgroup limited to moderate-to-severe (MR 3+) or severe (MR 4+) DMR patients consisted of 117 of the overall 567 patients in the ACCESS-EU study. Those patients were then stratified according to LogEuroSCORE of high and low surgical risk.

The study by Rudolph et al. [26] presented a subgroup analysis of patients from the German TRAMI registry (only prospectively enrolled), stratified by NYHA functional class. Among the 803 patients enrolled, 143 (17.8%) had NYHA class IV, 572 (71.2%) NYHA class III, and 88 (11.0%) NYHA class I or II.

The study by Toggweiler et al. [35] reported on 74 patients included in the Swiss MitraSWISS registry between 2009 and 2011. All patients had moderate-to-severe (MR 3+) or severe (MR 4+) FMR and DMR and were considered at high surgical risk defined by a logEuroSCORE > 15% and/or additional surgical risk factors.

The study by Vandendriessche et al. [40] reported on the prospective Belgian registry aimed to collect data on the use of MitraClip® in high surgical risk patients with HF and severe MR. A total of 41 patients were treated from 2010 to 2013. All patients had FMR and cardiomyopathy or annular dilatation; one patient presented with mixed aetiology.

The study by Wiebe et al. [25] reported on the non-randomised German TRAMI Registry, fed by 15 centres retrospectively from 2009 to 2010 and prospectively up to 2013. Outcomes of a total of 1,002 patients were reported. Baseline echocardiographic data indicated 627 patients with FMR, however, it is noteworthy that the missing data rate for this criterion was 13%. A clustered analysis by surgical risk assessed on the logEuroSCORE (high risk if ≥ 20) indicated 557 patients (55.6%) were at high surgical risk.

The study by Yeo et al. [34] reported on the MitraClip Asia-Pacific Registry (MARS). The data were collected retrospectively. The series comprised high surgical risk DMR patients and symptomatic FMR patients treated from 2011 to 2013 in 5 countries. A total of 142 patients were observed.

Among 15 studies, 8 resulted to be above the threshold of "acceptability quality" whereas the last 7 studies were not (see Appendix 1, page 93).

CARILLON® Mitral Contour System®

Primary studies

In a prospective, multicentre, single-arm study, Schofer et al. [31] assessed patients with dilated ischaemic or non-ischaemic cardiomyopathy and moderate-to-severe FMR. Thirty of the 48 patients enrolled into the AMADEUS study received the CARILLON® Mitral Contour System® device. No implantation was attempted in 5 patients for varying clinical reasons and the implant was recaptured in 13 patients. Safety was evaluated according to the 30-day rate of MAEs defined as the composite endpoint of death, MI, cardiac perforation requiring catheter-based or surgical intervention, device embolisation, or the occurrence of surgery or percutaneous coronary intervention related to device failure.

The study by Siminiak et al. [21] presented results of the TITAN trial designed on the basis of the previously described feasibility study [31]. The detailed description of the study is reported in the Clinical Effectiveness section (see Section 4.2). Safety was defined as the 30-day composite of death, MI, cardiac perforation, device embolisation, or surgery for device failure. The safety findings at the 30-day and 12-month follow-up referred to the overall intent-to-treat population (53 patients) without distinguishing between intervention or comparison groups, except for the death endpoint that was estimated either for the implanted cohort (36 patients) or for the comparison cohort (17 patients). The only safety data at 24 months refers to the number of deaths in the implanted cohort.

Both studies were funded by Cardiac Dimensions, Inc. and are equal or above the threshold of "acceptable quality" (see Appendix 1, page 93).

NeoChord DS1000

Primary studies

In the prospective study by Rucinskas et al. [32], safety outcomes (not explicitly defined by the authors) were recorded at 30 days and 6 months after the procedure. According to the authors, the 1- and 2-year follow-ups are ongoing.

The study by Seeburger et al. [22] reported the primary safety endpoints during the first 30 days after the procedure in all patients enrolled. Safety endpoints comprised MAEs and were measured mostly as a ratio between the number of observed events compared to the number of patients in the cohort.

In the study by Colli et al. [23], safety outcomes included perioperative complications, in-hospital and 30-day major and minor AEs.

The quality of included studies was evaluated using the IHE 18-item checklist. The detailed quality scores are reported in Appendix 1, page 93.

[C0008] How safe are the technologies in relation to the comparators:

- **What is the frequency of AEs (any) of the TMVR (technology and procedure) in relation to comparator(s)?**
- **What is the frequency of serious AEs of the TMVR (technology and procedure) in relation to comparator(s)?**
- **What is the frequency of serious AEs leading to death for the TMVR (technology and procedure) in relation to comparator(s)?**
- **What are the most frequent AEs of the TMVR (technology and procedure) in relation to comparator(s)?**

MitraClip® System

Given the lack of studies with proper comparisons, an assessment of safety could not be performed in relation to the comparators defined. The largest series referred to the combined cohort from the EVEREST II HRR and the REALISM HR studies [24], and to the German TRAMI register [25].

For the 351 high surgical risk patients in the EVEREST II HRR and REALISM HR [24], safety outcomes were reported at 30 days and 12 months. Mortality rate at 30 days was 4.8% (17/351) with no death related to device malfunctions. The MAE rate was 18.8% (66/351) with blood transfusion ≥ 2 units being the most frequent event occurring at a rate of 13.4% (47/351). None of the reported strokes (9/351) was due to device or air embolisation. Major vascular complications were experienced in 12 (3.4) patients. The mortality rate at 12 months was 22.8% (80/351). The MAE rate was 37.6% (132/351), with the most common event being blood transfusion (22.5%; 79/351), and 3 additional strokes occurred (12/351). Events of single-leaflet device attachment, listed as the most frequent device-related complication, occurred at a rate of 2.3% (8/351), mostly in the early phase. A second MitraClip® procedure was necessary in 1.1% of patients (4/351) only within 30 days after the initial procedure. Mitral valve surgery was performed in 0.9% of patients (3/351). No events of device embolisation occurred (see Appendix 1, Table 12).

For the 557 high surgical risk patients in the TRAMI register [25], safety outcomes were reported at in-hospital (mean hospital stay: 10 days; 6–17) and post-discharge follow-up (307 patients; mean: 75 days; 42.0–172.0). In-hospital mortality rate was 4.3% (24/554). Four events of stroke were reported (0.7%) and no event of myocardial infarction. MAE rate was 19.4% (108/557) with transfusion or severe bleeding as the most frequent events occurring at a rate of 13.7% (75/546). Major vascular complications were experienced in 2.2% of patients (12/546). Respiratory insufficiency and psycho syndrome for 3 or more days, both listed among MAEs, were observed in 3.5% (19/547) and 2.4% (13/546) of patients, respectively. Mortality rate at post-discharge follow-up was 13.4% (41/307). Rate of MACCE was 13.4% (41/307) while 38.6% of patients (103/267) experienced rehospitalization for cardiac, cardiovascular, and other reasons. Device-related complications were reported: partial detachment of the clip from one of the leaflets was seen in 2% of patients. Procedural complications rate was 8.9% (49/550) (see Appendix 1, Table 12).

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Although the study by Siminiak [21] assessed the safety outcomes in 2 cohorts of patients, one with successfully implanted with CARILLON® Mitral Contour System® and one with patients in whom the implanted device was recaptured for clinical indications, the evidence available is not sufficient to answer this research question exhaustively. All safety findings reported refer to the overall intention-to-treat population without distinguishing between the intervention and comparator cohorts, except for the endpoint “death” measured at 30 days and 12 months of follow-up. The incidence of deaths was lower in the implanted group at 30 days, with 0% (0/36 patients) vs 6% (1/17 patients), as well as at 12 months, with 22.2% (8/36) vs 23.5% (4/17 patients) (see Appendix 1, Table 13). However, the different safety findings in the 2 groups were not statistically analysed because of the small number of complications that occurred at 30-days’ follow-up.

NeoChord DS1000

All the included studies assessing NeoChord DS1000 were not comparative. The availability of "absolute" safety data, referring to the cohorts of patients who underwent MV repair using this specific device, does not allow a critical assessment of the safety profile of NeoChord DS1000 in relation to the comparator (conventional surgery). Taking into account the safety data related to the implantation of neo-chordae, MAEs ranged from 8% to 26.7% of patients at the 30-day follow-up (see Appendix 1, Table 14). It is important to note that MAEs were not defined exhaustively in all the studies and did not include the same safety endpoints.

[C0004] – Which aspects may affect the frequency and/or severity of harms?

MitraClip® System

Patient selection and organisational settings have been identified as aspects affecting frequency and severity of harms. Frailty of patients, in particular NYHA class IV, has been associated with higher mortality rates [26]. A learning curve effect has been documented previously [27]. It is likely that high-volume centres, with a proper heart team experienced in patient selection and with the specific technology, are able to perform the procedure with the lowest harm rate for the patients [28].

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Two studies [21, 31] on this novel device did not address specifically this research question. However, 1 study [31] highlighted that 2 MAEs (CS perforations) occurred early in the study (first and fourth patient) confirming that there is a learning curve to access the CS. Therefore, risks associated with this therapy are expected to decrease with improved procedural skills and experience. In addition, careful assessment of coronary arterial flow is important to successfully recapture or reposition the system when a compromised coronary artery was observed.

NeoChord DS1000

The evidence currently available is insufficient to address which aspects could affect frequency and/or severity of harms associated with NeoChord DS1000. The infancy of this device along with the fact that all included studies were performed in the same setting (University hospitals) with a short term follow-up (30 days apart one study [32] reporting safety data about two outcomes at 6 months) do not allow to evaluate how harms are affected by time or different settings. One study [22] reported that safety significantly improved because of the introduction of 2 procedure refinements: the use of multiple neo-chordae per procedure to equally distribute the mechanical stress on mitral valve leaflet and polytetrafluoroethylene sutures, and the revision of the left ventricular access to a posterolateral approach to reduce mechanical stress due to the posterolateral fixation of neo-chordae. Also patient's selection based on mitral valve leaflet morphology was refined during the study; patients with a wide prolapse achieved better results than patients with narrow prolapsing segments (considered to be the most suitable at the beginning of the trial).

[C0005] – Which patient groups are more likely to be harmed by the use of the technologies?

MitraClip® System

Subgroup analyses on specific populations were performed in the included studies. In particular, the impact of type II diabetes mellitus [29], anaemia [30], and NYHA class [26] were studied.

No significant differences in terms of safety and effectiveness emerged from the study on diabetic patients [29] even though only short-term (3 months) results for a small population (19 with type II diabetes and 39 with no diabetes) were presented. Similarly, peri-procedural MACCE and 1-year survival did not differ between patients with anaemia (n = 41) and those without anaemia (n = 39) [30]. In the other comparison [26], while in-hospital MACCE and re-hospitalisation rates were similar between groups in different NYHA classes, the 30-day mortality rate was significantly higher in NYHA class IV patients: 8.0% in NYHA IV (11/137), 3.2% in NYHA III (17/526), and 4.8% in NYHA II/I (4/83) ($p < 0.05$).

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The available evidence does not allow us to analyse this research question. The cohort size in the 2 included studies were small (range 48–53 patients) and seemed to overlap. Moreover, subgroup analyses were not undertaken. One study [31] pointed out that neither demographic nor echocardiographic parameters were clearly predictive of procedural success. Instead, the procedural steps of placing the device further distal in the CS/GCV and applying more traction to plicate more tissue were associated with procedural success.

NeoChord DS1000

No evidence was found to answer this research question. The cohorts of patients were mostly small in all the included studies (range 13–62 patients), and subgroup analyses for safety issues were not undertaken. One study observed that procedural success at 30 days was highly dependent on the morphological characteristics of the MV [23]. Patients with ideal MV anatomy were associated with a low risk of procedural failure (4%), patients with acceptable MV anatomy with a mild risk (8%), and patients with challenging MV anatomy were linked to a moderate risk (29%) [23].

[C0007] – Are the technologies and comparators associated with user-dependent harms?

MitraClip® System

Effects of a learning curve have not been addressed in any of the studies included for the present safety analysis. However, one of the included studies [25] referenced a previous study in which a learning curve effect was acknowledged and significant differences between the earliest and latest procedures were observed [27]. In the series of 75 patients, the median total procedure time (total time from puncture to closure of the femoral vein) decreased from 180 min to 95 min ($p = 0.0001$); the median device time (total time from insertion of the SGC until removal of the clip delivery) decreased from 105 min to 55 min ($p = 0.002$); safety events decreased from 16 to 3 ($p = 0.0003$); acute procedural success (clip successfully placed and MR Grade ≤ 2+ at discharge) increased from 80% to 92% ($p = 0.46$). At 6 months, completeness of MV repair (MR ≤ 2+) was 89.4% for the latest patients and 65.0% for the earliest ($p = 0.03$) [27]. The manufacturer, Abbott Vascular International, highlighted a more recent analysis from the German Mitral Valve Registry (496 patients in 10 centres) that investigates the impact of the learning curve on procedural success and complications [28]. The analysis, which is limited to centres performing at least 50 procedures per year, showed that a learning curve does not appear to significantly affect acute MR reduction in-hospital and 30-day mortality.

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The analysis of the available evidence [31] showed that there is a learning curve for accessing the CS safely; careful management of high surgical risk patients and acquisition of procedural skills are necessary to lower the risks associated with this device. Furthermore, experience-based skills related to the assessment of coronary arterial flow are crucial for recapturing and repositioning the device successfully and safely. No other evidence was found to answer the research question.

NeoChord DS1000

The TACT trial [22] showed that procedural refinements, arising from the learning curve, resulted in an improvement in safety. In addition, the authors highlighted that special and extensive training for the operators is mandatory. In fact, the determination of the exact positioning, length adjustment, and neo-chordae tensioning depends exclusively on the ability and training of the operator and echocardiographer, and affects the durability as well as the acute procedural success. No other evidence was found to answer the research question.

5.3 Discussion

Safety data related to the MitraClip® System were retrieved from large series and registries that, overall, showed comparable rates. However, as recognised by most of the authors, comparative analyses with longer follow-ups are deemed necessary to clarify the benefits/harms ratio of the procedure.

Effects of a learning curve have been acknowledged in a series of 75 patients [27] while the analysis of 496 procedures in 10 centres performing at least 50 procedures per year, showed that a learning curve does not appear to significantly affect acute MR reduction, in-hospital and 30-day mortality [28].

As for clinical effectiveness, the evidence of safety for CARILLON® Mitral Contour System® and NeoChord DS1000 is still limited to small series, and little can be concluded on the transferability of the results. Available data are encouraging and both technologies have been acknowledged to be relatively safe within the studies identified. However, the fact that the effects of a learning curve have not been explored is an issue that should be considered carefully.

6 POTENTIAL ETHICAL, ORGANISATIONAL, SOCIAL, AND LEGAL ASPECTS

6.1 Research questions

Research questions

Element ID	Research question
F0100	At what severity level of the disease are the technologies directed?
G0001	What kind of work flow and patient flow processes are needed?
G0003	What processes are required to ensure proper education and training for staff?

6.2 Results

[F0100] – At what severity level of the disease are the technologies directed?

Information about the severity level of MR and extent to which the patient would be considered at high risk for conventional surgery could be important to define whether TMVR by device implantation should be considered. According to both European and American guidelines, surgical risk needs to be assessed by a “heart team” with a particular expertise in valvular diseases, including cardiologists, cardiac surgeons, imaging specialists, anaesthetists and, if needed, general practitioners, geriatricians, or intensive care specialists [12, 13]. The ideal tools for the risk classification *of such a subset of patients are still debated: some authors [25] pointed out that the* logEuroSCORE may be inadequate in reflecting decisions based on valve morphology or aetiology of MR, and suggested the EuroSCORE II as a more suitable tool, while still acknowledging that neither of the scores apply specifically to minimally invasive cardiovascular interventions.

[G0001] – What kind of work flow and patient flow processes are needed?

In small countries, setting up a service requires consideration of how many procedures there are likely to be in relation to the number required to ensure reasonable outcomes.

[G0003] – What processes are required to ensure proper education and training for staff?

Training programmes are provided in different modalities and duration by the manufacturers of the devices. Details have been provided from the manufacturers but, recently, they have been deemed confidential.

6.3 Discussion

At present, and given their complex profile characterised by high comorbidity, the “heart team” approach for the assessment of severity level seems to be a crucial element in the decision-making chain of moderate-to-severe and severe MR patients.

Considerations on volume/outcome relationships are needed to ensure proper service provision.

Training programmes are provided in different modalities and duration from the manufacturers of the devices.

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APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

OVERALL DESCRIPTION OF METHODS

Pilot team

Deviations from the original Project Plan concerned the distribution of work within the pilot team and were believed necessary due to overlapping of other projects' workload among several authors, and given the stringent timelines of the present rapid assessment.

- The Agenzia Nazionale per i Servizi Sanitari Regionali (AGENAS, Italy) developed the domains EFF and SAF and the chapter on potential ethical, organisational, social and legal aspects;
- The Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ, Croatia) developed the domains CUR and TEC; according to the final Project Plan, AAZ was originally listed as author of the EFF domain in collaboration with AGENAS. Differences in terms of the actual scope of the assessment (relating to the population and comparators assessed) occurred between AAZ and AGENAS. AAZ stressed that, according to the 9 published EUnetHTA Guidelines on Rapid Relative Effectiveness Assessment, the joint assessment should be inclusive enough to allow its adaptation at national level by a majority of EU countries to make national recommendations for further national evidence-based decision-making. Since no agreement could be reached, the pilot team agreed on this deviation from the Project Plan;
- The Section of European Programmes and Projects (Ministry of Health of the Slovak Republic) reviewed the domain TEC.

Search

The search strategy did not differ from the one described in the original Project Plan. Details are given below in the present appendix.

Quality rating of studies

The R-AMSTAR tool, developed by Kung et al. at the UCLA School of Dentistry, Los Angeles, California, was used for systematic reviews; the 18-items checklist developed by the IHE (Canada) was used for case series and cohort studies.

Source of assessment elements

A preliminary working version of the HTA Core Model® for Rapid Relative Effectiveness Assessment, based on the "HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals 3.0", was the primary source for selecting the assessment elements. Additionally, assessment elements from other EUnetHTA Core Model Applications were screened and included when believed relevant to the present assessment. The REA Model Checklist was used for potential ethical, organisational, social, and legal aspects.

Deviations from project plan

As no comparative studies were included, a summary of relative effectiveness could not be produced within the present rapid assessment. Given that body of evidence was limited to the Safety domain and acknowledging the limitations in the design of all the included studies (case series and cohort studies), the authors of the present assessment agreed to not perform any assessment of the quality of the body of evidence as this would only give a partial overview without allowing to reach further conclusion on the relative assessment of the 3 devices.

No further deviations from the original Project Plan occurred.

DOCUMENTATION OF THE SEARCH STRATEGIES

Language: English.

PubMed (1st Jan 2005 – 16th May 2015)

"Mitral Valve Insufficiency" MESH term OR [Title/Abstract] "Mitral Valve Incompetence" OR "Failed Mitral valve" OR "Mitral Regurgitation" OR "Mitral Valve Insufficiency" OR "Mitral Valve Regurgitation" OR "Mitral Valve Incompetence" OR "Mitral Insufficiency" OR " mitral valve repair" OR "Mitral Incompetence" OR "leaflets repair" OR "percutaneous edge-to-edge repair" OR " transcatheter edge-to-edge repair" "percutaneous annulus repair" OR "transcatheter annulus repair" OR "transapical chordal repair" OR "Transcatheter mitral valve" OR "mitral valve repair" OR "transapical mitral valve repair" OR "transapical chordal replacement" OR " percutaneous chordal repair" OR "transcatheter chordal repair"	AND	(Carillon* AND "annulus repair") OR ("MitraClip System" AND leaflets) OR (NeoChord*" AND chordal) OR neochord OR MitraClip OR Carillon	AND	"Safety" MESH term OR "Comparative Effectiveness Research" MESH term OR "quality of life" MESH term OR "Return to work" MESH term OR "Patient Satisfaction" MESH term OR "Hospitalization MESH term OR "Patient discharge" MESH term OR Survival Rate MESH term OR Treatment Outcome MESH term OR "Follow-Up Studies" MESH term OR "Quality of life" MESH term [Title/Abstract] "Length of stay OR "Duration of inotropic support" OR "Exercise capacity" OR Safety OR Mortality OR Effectiveness OR "return-to-work" OR "Back-to-Work" OR Complication* OR pain OR "Adverse events" OR "side effects" OR morbility OR survival
"mitral valve" and transcatheter	AND		AND	

EMBASE (1st Jan 2005 – 17th May 2015)

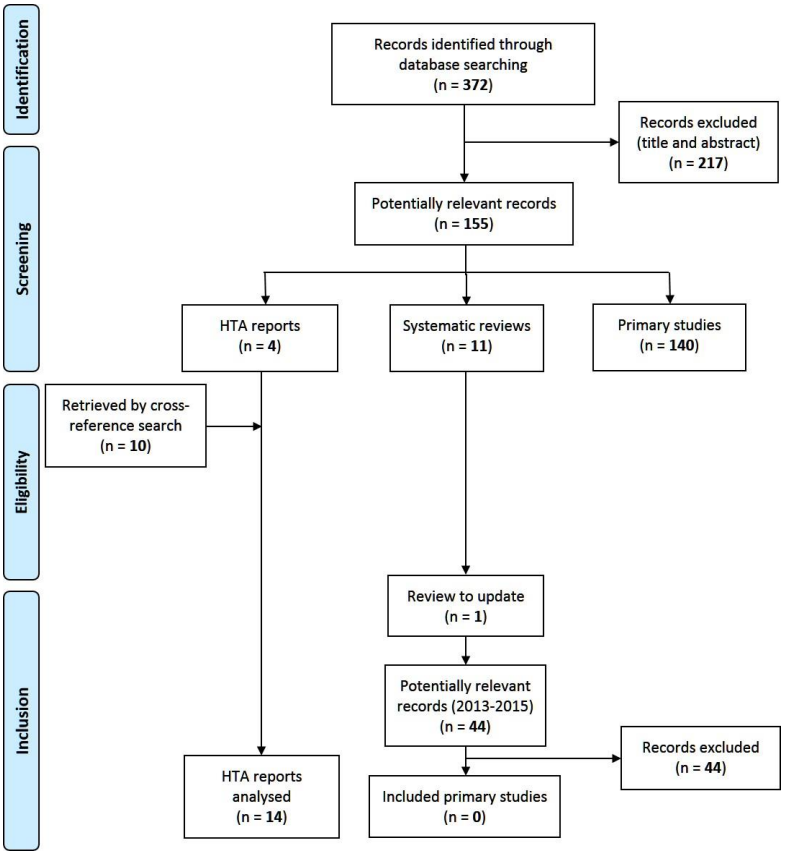
'mitral valve repair'/exp EMTREE term OR "mitral valve disease"/exp EMTREE term OR 'mitral valve regurgitation'/exp EMTREE term OR "Mitral Valve Incompetence" OR "Failed Mitral valve" OR "Mitral Regurgitation" OR "Mitral Valve Insufficiency" OR "Mitral Valve Regurgitation" OR "Mitral Valve Incompetence" OR "Mitral Insufficiency" OR " Miitral valve repair" OR "Mitral Incompetence" OR "leaflets repair" OR "percutaneous edge-to-edge repair" OR " transcatheter edge-to-edge repair" "percutaneous annulus repair" OR "transcatheter annulus repair" OR "transapical chordal repair" OR "Transcatheter mitral valve" OR "mitral valve repair" OR "transapical mitral valve repair" OR "transapical chordal replacement" OR " percutaneous chordal repair" OR "transcatheter chordal repair"	AND	'annuloplasty ring'/exp EMTREE term OR 'implantable clip'/exp EMTREE term OR "Transcatheter mitral valve repair " OR (Carillon AND "annulus repair") OR ("MitraClip System" AND leaflets) OR ("CARILLON Mitral Contour System" AND annulus) OR (NeoChord*" AND DS1000 AND chordal) OR neochord OR MitraClip OR Carillon	AND	EMTREE TERM: 'quality of life'/exp OR EMTREE TERM:"clinical effectiveness" OR EMTREE TERM: "comparative effectiveness" OR EMTREE TERM: 'device safety'/exp OR EMTREE TERM: 'program effectiveness'/exp OR EMTREE TERM: 'program evaluation'/exp OR EMTREE TERM: 'risk assessment'/exp OR EMTREE TERM: Mortality/exp OR EMTREE TERM: "return-to-work"/exp OR EMTREE TERM: "Back-to-Work"/exp OR EMTREE TERM: 'program acceptability'/exp OR EMTREE TERM: Safety/exp OR EMTREE TERM: 'heart failure'/exp EMTREE TERM: Ventricular Function, Left" OR EMTREE TERM:" Ventricular Dysfunction" OR "Length of stay" OR " "Exercise capacity" OR Complications OR pain OR 'device failure analysis'/exp OR Effectiveness OR "Comparative Effectiveness Research" Survival Rate OR Treatment Outcome OR "Postoperative Complications" "Adverse events" OR "side effects" OR

				"quality of life" OR QoL OR "Right Ventricular failure"OR survival OR morbility OR effectiveness
"mitral valve" and transcatheter	AND		AND	

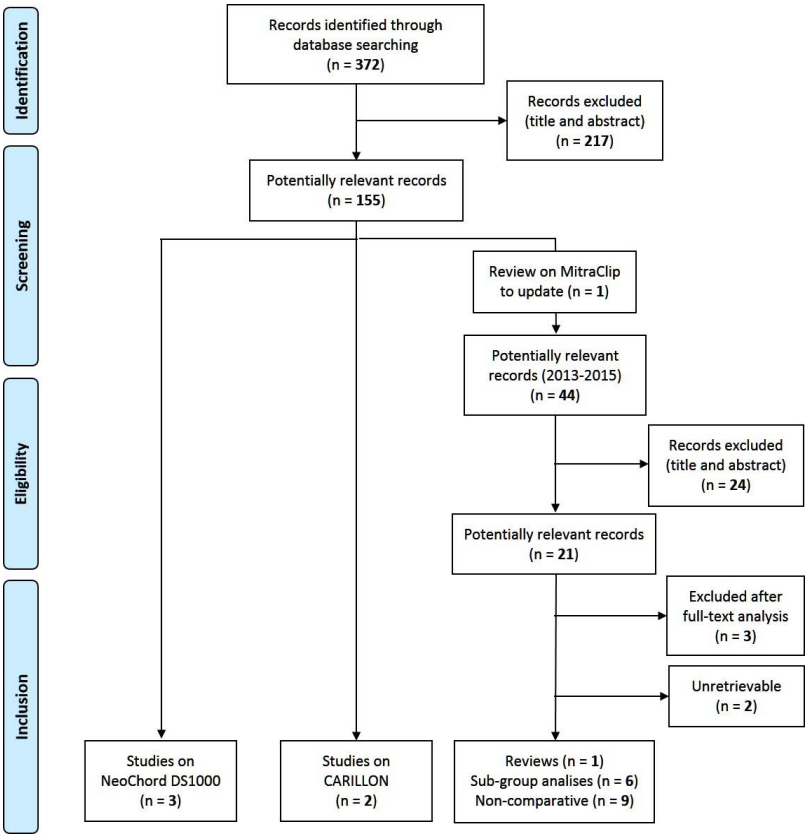
Cochrane Library (1st Jan 2005 – 18th May 2015)

"Mitral Valve Insufficiency" MESH term OR [Title/Abstract] "Mitral Valve Incompetence" : ti,ab,kw OR "Failed Mitral valve" : ti,ab,kw OR OR "Mitral Regurgitation" : ti,ab,kw OR OR "Mitral Valve Insufficiency" : ti,ab,kw OR "Mitral Valve Regurgitation" : ti,ab,kw OR "Mitral Valve Incompetence" : ti,ab,kw OR "Mitral Insufficiency" : ti,ab,kw OR " mitral valve repair" : ti,ab,kw OR "Mitral Incompetence" : ti,ab,kw OR "leaflets repair" : ti,ab,kw OR "percutaneous edge-to-edge repair" : ti,ab,kw OR " transcatheter edge-to-edge repair" : ti,ab,kw OR "percutaneous annulus repair" : ti,ab,kw OR "transcatheter annulus repair" : ti,ab,kw OR "transapical chordal repair" : ti,ab,kw OR "Transcatheter mitral valve" : ti,ab,kw OR "mitral valve repair" : ti,ab,kw OR "transapical mitral valve repair" : ti,ab,kw OR "transapical chordal replacement" : ti,ab,kw OR " percutaneous chordal repair" : ti,ab,kw OR "transcatheter chordal repair" : ti,ab,kw	AND	neochord OR MitraClip OR Carillon	AND	MESH descriptor: Safety OR MESH descriptor: Comparative Effectiveness Research OR MESH descriptor: "quality of life" OR MESH descriptor: "Return to work" OR MESH descriptor: "Patient Satisfaction" OR MESH descriptor: "Hospitalization OR MESH descriptor:"Patient discharge" OR MESH descriptor: Survival Rate OR MESH descriptor: Treatment Outcome OR MESH descriptor: "Postoperative Complications" OR MESH descriptor: "Follow-Up Studies" OR MESH descriptor: "Heart Failure" OR MESH descriptor:"Ventricular Function, Left" OR MESH descriptor:" Ventricular Dysfunction "Length of stay " : ti,ab,kw OR "Duration of inotropic support" : ti,ab,kw OR "Exercise capacity" : ti,ab,kw OR Safety: ti,ab,kw OR Mortality: ti,ab,kw OR Effectiveness: ti,ab,kw OR "return-to-work" " : ti,ab,kw OR "Back-to-Work" " : ti,ab,kw OR Complication: ti,ab,kw OR Complications: ti,ab,kw OR pain: ti,ab,kw OR "Adverse events" : ti,ab,kw OR "side effects" : ti,ab,kw OR morbility" : ti,ab,kw OR survival : ti,ab,kw OR morbility: ti,ab,kw OR effectiveness : ti,ab,kw
"mitral valve" and transcatheter" : ti,ab,kw				

PRISMA flow-chart – Evidence for Clinical Effectiveness domain



PRISMA flow-chart – Evidence for Safety domain



DESCRIPTION OF THE EVIDENCE USED

Guidelines for diagnosis and management

Table 10: Overview of guidelines

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Class of recommendations/Level of evidence
ESC/EACTS Guidelines on the management of valvular heart disease (version 2012) [12]	2012	Europe	• Percutaneous edge-to-edge procedure may be considered in patients with symptomatic severe primary MR who fulfil the echo criteria of eligibility, are judged inoperable or at high surgical risk by a 'heart team', and have a life expectancy greater than 1 year • The percutaneous mitral clip procedure may be considered in patients with symptomatic severe secondary MR despite optimal medical therapy (including CRT if indicated), who fulfil the echo criteria of eligibility, are judged inoperable or at high surgical risk by a team of cardiologists and cardiac surgeons, and who have a life expectancy greater than 1 year	IIb, C
ESC ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 [47]	2012	Europe	• In patients with an indication for valve repair but judged inoperable or at unacceptably high surgical risk, percutaneous edge-to-edge repair may be considered in order to improve symptoms.	Not mentioned
European Association of Echocardiography. Recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease) [94]	2010	Europe	• TTE (Transthoracic Echocardiography) is recommended as the first-line imaging modality for mitral valve analysis. • TEE (Transoesophageal Echocardiography) is advocated when TTE is of non-diagnostic value or when further diagnostic refinement is required. • 3D-TEE or TTE is reasonable to provide additional information in patients with complex mitral valve lesion. • TEE is not indicated in patients with a god-quality TTE except in the operating room when a mitral valve surgery is performed.	Not mentioned
German Society for Thoracic and cardiovascular Surgery on treatment of mitral valve insufficiency [95]	2014	Germany	• DMR: Percutaneous intervention (only MitraClip has sufficient evidence) may be considered in patients with advanced stage MR, high age or pronounced comorbidities. • MitraClip shows promising results for the treatment of secondary MR, particularly in elderly patients with ischemic MI or a distinctive risk profile, such as after coronary artery bypass surgery and represents a therapeutic alternative in selected patients.	Not mentioned
Consensus Paper from the focus group 'Interventional mitral valve therapy' (Arbeitskreis Interventionelle Mitralklappentherapie) of the working group 'Interventional Cardiology of the German Society for Cardiology' (Arbeitsgemeinschaft Interventionelle Kardiologie (AGIK)) and Senior Hospital Consultants (Deut-	2013	Germany	The indication to interventional treatment of mitral valve regurgitation should always be determined on an individual basis as currently there are no established guidelines for this therapy. During this decision making process, the following factors should be considered: 1.The recommendations from the current guidelines by the German and European societies for cardiology on the treatment of cardiac valve disease. 2. The morphology of the mitral valve. 3. The cause and the severity of the MR. 4. The left ventricular function.	Not mentioned

schen Gesellschaft für Kardiologie und der Leitendenden Krankenhausärzte (ALKK) [96]			5. The operative risk. Indications for the MitraClip therapy Ideal for MitraClip treatment: • Severe MR and • Optimal valve morphology and • Secondary MR with LV-EF\30 % • Or Primary MR (with operation-indication following guidelines) • and • A high operative risk or other risk constellations **MitraClip to be considered**: • Moderate to severe MR and • Optimal valve morphology and • SMR or PMR (with operation-indication following guidelines) and • High operative risk, very high age or other risk-constellations **MitraClip not recommended or only in exceptional cases**: • Moderate to severe MR and • Conditionally suitable valve morphology • or Life expectancy\12 months • or LV-EF\15 % or cardiothoracic operation planned due to other indications • or previously operated mitral valve • or as surgical/interventional hybrid procedure • or at low operative risk.	
ACC/AHA 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease [13]	2014	USA	**Chronic Primary MR** Transcatheter MV Repair may be considered for severely symptomatic patients (NYHA class III/IV) with chronic severe primary MR (stage D0 who have a reasonable life expectancy but a prohibitive surgical risk because of severe comorbidities **Chronic secondary MR** Not reported	IIb, B

Abbreviations: ESC/EACTS: European Society of Cardiology and the European Association for Cardio-Thoracic Surgery (EACTS); ACC/AHA: the American College of Cardiology/American Heart Association; MR: mitral regurgitation; DMR: degenerative mitral regurgitation
Source: Submission File Abbott Vascular [1]

Evidence tables of individual studies included for clinical effectiveness and safety

Table 11: HTA reports on the 3 devices considered in the present assessment (MitraClip® System, Carillon® Mitral Contour System® and NeoChord DS1000); ascending chronological order

Year	Agency	Country	Title	Device	Link to full-text
2009	NICE	UK	Percutaneous mitral valve leaflet repair for MR	MitraClip	http://www.nice.org.uk/guidance/ipg309
2010	NICE	UK	Percutaneous mitral valve annuloplasty	Carillon	www.nice.org.uk/ipg352
2012 (2010 update)	HealthPACT	Australia	Carillon mitral contour system for mitral regurgitation	Carillon	https://www.health.qld.gov.au/healthpact/docs/briefs/WP089.pdf
2012 (2011 update)	LBI-HTA	Austria	Percutaneous repair of mitral regurgitation with the Mitra-Clip	MitraClip	http://eprints.hta.lbg.ac.at/967/
2012	HTA Centre of Stockholm County Council	Sweden	[MitraClip for the treatment of severe mitral insufficiency]	MitraClip	http://www.vardgivarguiden.se/Global/04_Utbildning%20och%20utveckling/HTA/HTA_Rapport_MitraClip_2012_5.pdf
2013	FDA	USA	MitraClip Clip Delivery System – SSED	MitraClip	http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100009b.pdf
2013	NHC	New Zealand	Percutaneous interventions for MR	Carillon; MitraClip	http://nhc.health.govt.nz/system/files/documents/publications/percutaneous-interventions-for-mrt.pdf
2014	BCBS	USA	Percutaneous mitral valve repair	MitraClip	http://www.bcbs.com/blueresources/tec/vols/
2014 (2012 update)	MSAC	Australia	The reduction of severe MR through tissue approximation using transvenous/transseptal techniques	MitraClip	http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1387C0671D63E5CCCA257C70001948F3/$File/1192.1-%20MSACPSD%20-%20Mitraclip.pdf
2015	HAS	France	Assessment of an edge-to-edge mitral valve repair clip and its implantation	MitraClip	http://www.has-sante.fr/portail/jcms/c_2028913/fr/rapport-d-evaluation-mitraclip

Table 12: Safety findings from included primary studies – MitraClip® System

Study [ref.]	Number of patients	Follow up	Main safety findings		Limitations of the study (as acknowledged by study authors)	Authors' conclusions
			Safety outcomes reported	***n/N (%)***		
Alegria-Barrero et al. [38]	43 *(40 successfully implanted: 21 with 1 clip, group A; 19 with ≥2 clips, group B)*	30 days;12 months	*Mortality rate at 12 months*	*A: 1/21 (4.7)* *B: 3/19 (15.8)*	*Relatively small number of patients recruited.*	*"MitraClip was shown to be a safe treatment for patients with severe functional and degenerative MR"*
			Major procedural complications	*A: 0/21 (0)* *B: 1/19 (5.3)*		
Armoiry et al. [33]	62	In-hospital	*In-hospital mortality rate*	*2/62 (3.2)*	*Missing data corresponding to variables not reported from each centre; mid-term follow-up data available for a limited number of patients.*	*"The preliminary data of our registry are encouraging in terms both efficacy and safety and may solve the unmet need in patients who are ineligible for conventional surgery". However "randomized control trials are mandatory to confirm these preliminary data"*
			Surgical mitral valve repairs after the MitraClip procedure	*2/62 (3.2)*		
			Other non-fatal AEs (wrong clip positioning, deep venous thrombosis, bleeding at puncture site, new-onset of atrial arrhythmia, acute febrile respiratory illness, false aneurysm at venous puncture site and tamponade)	*7/62 (11.3)*		
			Procedural blood transfusion	*5/62 (8.1)*		
			Stroke	*0/62 (0)*		
			Myocardial infarction	*0/62 (0)*		
Attizzani et al. [36]	171 *(78 not fulfilling echocardiographic eligibility criteria of EVEREST I and II studies, EVEREST$_{OFF}$ group; 93 meeting these criteria, EVEREST$_{ON}$ group)*	30 days; 12 months	*MAEs (including death) at 30 days (P=0.204)*	*EVEREST$_{OFF}$: 2/78 (2.6)* *EVEREST$_{ON}$: 6/93 (6.5)*	*No randomized control group, small sample size with limited follow-up, 12 month follow up echocardiographic parameters could have been influenced by survival bias, 12 month follow-up data were available for 90% of enrolled patients, study setting was a centre performing high volume of Mitraclip implantation per year.*	*"Favorable safety rates previously demonstrated for this relatively novel procedure could be reproduced in more complex settings"* suggesting *"a potential room for expanding the indication of MitraClip implantation in high risk surgical patients beyond the EVEREST studies' eligibility criteria; nevertheless, additional research with longer follow-up an larger sample sizes are mandatory before any formal recommendation"*
			Mortality rate at 30 days (P=0.566)	*EVEREST$_{OFF}$: 1/78 (1.3)* *EVEREST$_{ON}$: 2/93 (2.2)*		
			Mortality rate at 12 months (P=0.358)	*EVEREST$_{OFF}$: 11/70 (15.7)* *EVEREST$_{ON}$: 9/84 (10.7)*		
			Surgery for mitral valve dysfunction at 12 months (P=n.r.)	*EVEREST$_{OFF}$: 0* *EVEREST$_{ON}$: 0*		
Bozdag-Turan et al. [39]	121 *(38 with EF≤30; 83 with EF>30)*	12 months	*MACCE at 12 months (P=0.38)*	*EF≤30: 14/38 (36.8)* *EF>30: 24/83 (28.9)* *All: 38/121(31.4)*	*N.r.*	*"Percutaneous edge- to-edge repair could be safely performed with good clinical and echocardiographic results in surgical high risk patients with or without severe impaired systolic left ventricular function"*
			Mortality rate 12 months (P=0.051)	*EF≤30: 13/38 (34.2)*		

				EF>30: 15/83 (18.1) *All: 28/121(23.1)*		
			Myocardial infarction at 12 months (P=0.18)	*EF≤30: 2/38 (5.3)* *EF>30: 1/83 (1.2)* *All: 3/121(3.4)*		
			Cerebro-vascular accident at 12 months (P=n.r.)	*EF≤30: 0/38 (0)* *EF>30: 0/83 (0)* *All: 0/121(0)*		
			Major bleeding at 12 months (P=0.13)	*EF≤30: 4/38 (10.5)* *EF>30: 3/83 (3.6)* *All: 7/121(5.8)*		
			MV surgery total at 12 months (P=0.035)	*EF≤30: 0/38 (0)* *EF>30: 9/83 (10.8)* *All: 9/121(7.4)*		
Braun et al. [93]	119 *(72 with DMR, 47 with FMR)*	12 months	*Conventional mitral surgery after Mitraclip procedure at 12 months*	*DMR: 10/n.c.* *FMR: 0/n.c.*	*Relatively small patient population, lack of follow-up data, subjectivity of echocardiographic MR quantification after clip implantation.*	*"Percutaneous edge- to-edge repair of mitral valve is feasible in patients with degenerative as well as functional MR". However "Randomized controlled trial comparing MitraClip therapy in high risk patients to medical therapy as well as mitral valve surgery are necessary to clarify the future role of this novel method".*
			Second mitral valve clipping at 12 months	*DMR: 4/n.c.* *FMR: 1/n.c.*		
			Procedural deaths	*DMR: 0/n.c.* *FMR: 0/n.c.*		
			Post-procedural deaths	*DMR:1/n.c.* *FMR: 1/n.c.*		
			Procedure related complications	*DMR: 1/n.c.* *FMR: 1/n.c.*		
Glower et al. [24]	351 *(105 with DMR and 246 with FMR)*	30 days; 1 year	*Mortality rate at 30 days*	*All: 17/351 (4.8)* *DMR: 7/105 (6.7)* *FMR: 10/246 (4.1)*	*Patient group was narrowly defined, short term data, no surgical or medical control group, possibly placebo effect due to medical therapy prior to device implantation.*	*"Mitral valve device is feasible and relatively safe and is effective (…) in this high-risk group of patients who are unlikely to receive surgery and essentially have no other option to reduce MR".*
			MAEs at 30 days	*All: 66/351 (18.8)* *DMR: 19/105 (18.1)* *FMR: 47/246 (19.1)*		
			*Stroke at 30 days**	*All: 9/351 (2.6)*		
			Major bleeding complications at 30 days	*DMR: 19/105 (18.1)* *FMR: 47/246 (19.1)*		
			*Blood transfusions ≥2U at 30 days**	*All: 47/351 (13.4)*		
			Mortality rate at 1 year	*All: 80/351 (22.8)* *DMR: 25/105 (23.8)* *FMR: 55/246*		

				(22.4)		
			MAEs at 1 year	*All: 132/351 (37.6)* *DMR: 38/105 (36.2)* *FMR: 94/246 (38.2)*		
			*Stroke at 1 year**	*All: 12/351 (3.4)*		
			*Blood transfusions ≥2U at 1 year**	*All: 79 /351 (22.5)*		
			*Single leaflet device attachment rate (device related complication) at 1 year**	*All: 8/351 (2.28)*		
			*Mitral valve surgery (device related complication) at 1 year**	*All: 3/351 (0.9)*		
			*Second Mitraclip procedure (device related complication) at 1 year**	*All: 4/351 (1.1)*		
			*Mitraclip embolization (device related complication) at 1 year**	*All: 0/351 (0)*		
			*Mitral valve stenosis (device related complication) at 1 year**	*All: 3/351 (0.9)*		
Hellhammer et al. [29]	58 *(19 with diabetes mellitus II, 39 without diabetes mellitus II)*	30 days; 3 months	*Mortality rate at 30 days (P=0.672)*	*Diabetes: 0/19 (0)* *No diabetes: 1/39 (2.6)*	*Short follow-up, small size population, no randomized study.*	*"MitraClip system is safe and event rates are low." However "a prospective randomized study with more patients and longer follow follow-up time was necessary".*
			Successful clip implantation rate (P=0.672)	*Diabetes: 19/19 (100)* *No diabetes: 38/39 (97.4)*		
			In-hospital complications (MACCE, peripher vascular complications, stroke, pacemaker damage, sepsis, ventilation>24 h, acute kidney injury stage III, major bleeding)	*Diabetes: 1/19 (5.3)* *No diabetes: 9/39 (23.1)*		
			Mitral valve surgery (P=0.672)	*Diabetes: 0/19 (0)* *No diabetes: 1/39 (2.6)*		
Hellhammer et al. [30]	80 *(41 with anaemia, group A; 39 with normal erythrocyte levels, group B)*	Up to 12 months	*Mortality rate at 30 days (P = 0.611)*	*A: 1/41 (2.4)* *B: 2/39 (5.1)*	*Limited number of patients and unequal follow-up times.*	*"Mitral valve repair with the MitraClip system can be performed safely and efficiently in patients with anemia. Anemia does not affect clinical outcome and quality of life in patients undergoing mitral valve repair."*
			MACCE rate (including death, myocardial infarction, stroke, and procedure related re-operation; P = 0.959)	*A: 2/41 (4.9)* *B: 2/39 (5.1)*		
Koifman et al. [41]	20	231 days (mean)	*Abortion of the procedure*	*1/20 (5)*	*Small sample size and relatively short follow-up duration.*	*"Mitral valve repair using the MitraClip percutaneous*
			Patients hospitalised for more than 5 days	*4/20 (20)*		

			Mortality at 7 months	*2/20 (10)*		*technique is feasible and safe in high risk, mainly inoperable, highly symptomatic patients with significant MR."*
Reichenspurner et al. [37]	117 *(33 high surgical risk, group A; 84 low surgical risk, group B)*	30 days; 12 months	*Adverse events rate at 30 days* *Mortality rate at 30 days* *Adverse events rate at 12 months* *Mortality rate at 12 months*	*21/117 (17.9)* *A: 9/33 (27.3)* *B: 12/84 (14.3)* *7/117 (6.0)* *A: 3/33 (9.1)* *B: 4/84 (4.8)* *48/117 (41.0)* *20/117 (17.1)* *A: 8/33 (24.2)* *B: 12/84 (14.3)*	*Lack of a protocol for patient selection and determination of aetiology.*	*"Primarily for DMR patients who are inoperable or at exceedingly high risk for surgical MVR, MitraClip therapy represents an attractive and less-invasive treatment option. The majority of patients thus treated benefit significantly regarding the severity of MR as well as clinically, regarding NYHA functional class and improvements in physical capacities and quality of life."*
Rudolph et al. [26]	803 *(143 NYHA class IV, 572 NYHA class III, 88 NYHA class I or II)*	30 days	*Mortality* *Procedural (P = 0.59)* *At 30 days (P < 0.05)* *Transfusions/severe bleeding* *Procedural (P < 0.01)* *At 30 days (P = 0.19)* *Transient ischaemic attacks (TIA)* *Procedural (P < 0.01)* *At 30 days (P < 0.01)*	*Procedural* *1/803 (0.1) – NYHA III* *At 30 days* *NYHA IV: 11/137 (8.0)* *NYHA III: 17/526 (3.2)* *NYHA I/II: 4/83 (4.8)* *Procedural* *NYHA IV: 19/140 (13.6)* *NYHA III: 35/554 (6.3)* *NYHA I/II: 3/87 (3.4)* *At 30 days:* *NYHA IV: 15/98 (15.3)* *NYHA III: 38/387 (9.8) NYHA I/II: 4/57 (7.0)* *Procedural* *NYHA IV: 5/140 (3.6)* *NYHA III:3/555*	*Inhomogeneous population (but still reflecting real-life practice) and need of randomised studies to clarify the real therapeutic value and optimal time point of MitraClip implantation in severely diseased group of patients (e.g., those in NYHA IV).*	*"Our data indicate that percutaneous mitral valve repair with the MitraClip is feasible and safe, and leads to relevant clinical improvement even in critically ill, not fully recompensated patients, but is associated with an elevated 30-day mortality. The decision to perform the procedure in this group of patients has therefore to be individualized. While awaiting further studies addressing this topic, aggressive medical management of acute HF should be considered prior to MitraClip therapy in this patient group."*

				(0.5) *NYHA I/II: 0/88 (0)* *At 30 days* *NYHA IV: 6/91 (6.6)* *NYHA III: 5/380 (1.3)* *NYHA I/II: 0/55 (0)*		
			≥3 days until mobilisation (P < 0.05)	*NYHA IV: 16/137 (11.7)* *NYHA III: 35/546 (6.4)* *NYHA I/II: 2/88 (2.3)*		
Toggweiler et al. [35]	74	2 years	*Intra-procedural complications making procedure unfeasible*	*3/74 (4)*	*Low number of patients and limited experience of the centres.*	*"In the light of these results, the definition of procedural success may need to be re-evaluated. In future, improved patient selection, experience and maybe concomitant utilisation with non-surgical mitral annuloplasty devices may lead to even better outcomes and a wider application of the MitraClip procedure."*
			Bleeding requiring transfusion	*6/74 (8)*		
			Pericardial tamponade after rupture of the left atrium	*1/74 (1)*		
			Strokes at 24 months	*0/74 (0)*		
			In-hospital mortality	*3/74 (4)*		
			Partial clip detachment at 24 months	*7/74 (10)*		
			Repeated procedure due to persistent 3+ or 4+ MR	*5/74 (6.8)*		
Vandendriessche et al. [40]	41	Up to 12 months	*In-hospital MAEs (death, additional major bleeding need to undergo urgent cardiac surgery).*	*5/41 (12)*	*Small sample size.*	*"In the light of these results, the definition of procedural success may need to be re-evaluated. In future, improved patient selection, experience and maybe concomitant utilisation with non-surgical mitral annuloplasty devices may lead to even better outcomes and a wider application of the MitraClip procedure."*
Wiebe et al. [25]	557	72 days (median)	*In-hospital MACCE rate (mortality, stroke, and myocardial infarction)*	*27/546 (4.9)*	*Inadequacy of the logEuroSCORE in reflecting decisions based on valve morphology or aetiology of MR, and absence of post-procedural results and longer terms durability data.*	*"Percutaneous mitral valve repair with the MitraClip system is feasible in patients with a logEuroSCORE ≥ 20. Procedural results were similar, despite a significant higher intra-hospital MACCE rate compared to patients with lower predicted cardiac operative risk. Although mortality was four times higher than in patients with a*
			Major in-hospital complications rate	*108/557 (19.4)*		
			Minor in-hospital complications rate	*77/557 (13.8)*		
			Other complications rate	*97/546 (17.8)*		

						logEuroSCORE < 20, mortality in high risk patients was lower than predicted by the logEuroSCORE. In patients with a logEuroSCORE ≥ 20, moderate residual mitral valve regurgitation is more frequent."
Yeo et al. [34]	142	Up to 30 days	*Mortality rate at 30 days*	*8/142 (5.6)*	*Non-comparative nature of the study and short duration of follow-up.*	*"MitraClip therapy is a safe and efficacious therapeutic option for patients with either FMR or DMR. In the Asia-Pacific region. The significant proportion of DMR. In comparison to the commercial experience in Europe, deserves further examination."*
			In-hospital mortality rate	*6/142 (4.2)*		
			MAE rate at 30 days	*18/142 (12.7)*		
			Patients underwent mitral valve reoperation	*1/142 (0.7)*		
			Blood transfusion of ≥2 units	*5/142 (3.5)*		
			Sepsis	*2/142 (1.4)*		
			Prolonged intubation	*1/142 (0.7)*		
			Patients readmitted for HF	*1/142 (0.7)*		

*Data are reported for all patients without distinguishing between DMR and FMR patients.
Abbreviations: AEs, adverse events; MAE, major adverse events; n.r., not reported; n.c., not clear; EF, Ejection fraction; DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation; MV, mitral valve; NYHA, New York Heart Association; HF, heart failure; MACCE, major adverse cardiac and cerebrovascular events; MR, mitral regurgitation; Tot, total.

Table 13: Safety findings from included primary studies – Carillon® Mitral Contour System®

Study [ref.]	**Number of patients**	**Follow up**	**Main safety findings**		**Limitations of the study (as acknowledged by study authors)**	**Authors' conclusions**
			Safety results	***n/N (%)***		
Schofer et al. (AMADEUS trial) [31]	48 patients	30 days	*Death*	*1/46 (2.2)*	*First-in-human feasibility and safety trial, lack of a randomised, blinded control group.*	*"Percutaneous reduction in FMR with a novel coronary sinus–based mitral annuloplasty device is feasible in patients with heart failure, is associated with a low rate of major adverse events, and is associated with improvement in quality of life and exercise tolerance. Further studies are required to define the long-term efficacy of the therapy, optimal timing for intervention, and effects on survival."*
			Myocardial infarction§	*3/46 (6.5)*		
			Cardiac perforation necessitating catheter based or surgical intervention§	*3/46 (6.5)*		
			Device embolization	*0/46 (0)*		
			Device failure requiring surgical or percutaneous coronary intervention	*0/46 (0)*		
			Total major adverse events	*7/46 (15.2)*		
Siminiak et al. (TITAN Trial) [21]	53 *(36 with permanent implant, group A; 17 with device recaptured, group B)*	30 days; 12 months; 24 months	*Death (30 days)*	*A: 0/36 (0)* *B: 1/17 (16)*	*Lack of a randomised and blinded comparator.*	*"This study demonstrates that percutaneous CS-based mitral annuloplasty can significantly and safely reduce FMR severity in HF patients, resulting in significant LV reverse remodelling over 12*
			Death (12 months)	*A: 8/36 (22.2)* *B: 4/17 (23.5)*		
			Death (24 months)*	*A: 3/n.r. (n.a.)* *B: n.a.*		

			Myocardial infarction *(30 days)* *(12 months)*	 *0/53 (0)* *2/53 (4)*		*months and improved measures of clinical outcome over 24 months. The lack of a randomized and blinded comparator remains the primary limitation of the study. As such, a randomized trial comparing intervention with a medically managed control group is warranted."*
			Cardiac perforation *(30 days)* *(12 months)*	 *0/53 (0)* *0/53 (0)*		
			Device embolization *(30 days)* *(12 months)*	 *0/53 (0)* *0/53 (0)*		
			Surgery due to device *(30 days)* *(12 months)*	 *0/53 (0)* *0/53 (0)*		
			Overall MAE rate *(30 days)* *(12 months)*	 *1/53 (1.9)* *14/53 (26.4)*		

§: not specified if the adverse event is caused by the procedure or by the device.
*Safety data at 24 months follow up refer only to the intervention group
Abbreviations: FMR, functional mitral regurgitation; n.r., not reported; n.a., not applicable; CS, coronary sinus; HF, heart failure; LV, left ventricular

Table 14: Safety findings from included primary studies – NeoChord DS1000

Study [ref.]	Number of patients	Follow up	Main safety findings		Limitations of the study (as acknowledged by study authors)	Authors' conclusions
			Safety outcomes reported	***n/N (%)***		
Rucinskas et al. [32]	13	30 days; 6 months	*Intraoperative conversion to conventional surgery*	*1/13 (8)*	*Long-term durability of the NeoChord procedure remains to be proved and target population and pathology for use of this device has to be found (patients who are 'too healthy" for conventional procedures or patients "too sick" for surgery or both).*	*"In our patient group, trans apical NeoChord implantation under beating-heart conditions was feasible, could be performed safely, and resulted in a relatively short procedure time. Additional questions remain regarding this promising repair technique. The long-term durability of the NeoChord procedure remains to be proved. The target population and pathology for use of this device has to be found."*
			Dehiscence *(30 days)* *(6 months)*	 *1/13 (8)* *0/13 (0)*		
			Conversion to standard care *(30 days)* *(6 months)*	 *0/13 (0)* *1/13 (8)*		
			Total serious adverse events	*2/13 (15)*		
Seeburger et al. [22]	30	30 days	*Death*	*1/30 (3)*	*First-in-man clinical experience. Determination of exact positioning, length adjustment, and neo-chordae tensioning depends exclusively on ability and training of operator and echocardiographer.*	*"Mitral Valve repair for PML prolapse with off-pump transapical implantation of neo-chordae is safe and feasible from a procedural point of view. Further investigation is needed to assess durability*
			Myocardial infarction	*0/30 (0)*		
			Reoperation for failed surgical repair	*6/30 (20)*		
			Nonelective cardiovascular surgery	*0/30 (0)*		
			Procedural ventilation >48h	*1/30 (3)*		
			Procedure-related transfusion of >2 U	*5/30 (17)*		

			blood product			*and long-term outcome."*
			Stroke (transient)	*1/30 (3)*		
			Renal failure	*0/30 (0)*		
			Deep wound infection	*0/30 (0)*		
			New onset of permanent atrial fibrillation	*0/30 (0)*		
			Septicemia	*0/30 (0)*		
			Any Major adverse event§	*8/30 (26.7)*		
Colli et al. [23]	62	30 days	**Perioperative complications**		*Need to improve mitral valve morphological characterisation by echocardiographic measurements to allow proper patient selection.*	*"Top mini allows successful treatment of degenerative MR with a safety profile and good clinical results. Future detailed echocardiographic evaluations will identify its precise anatomical indications. A larger number of patients and adequate long term of follow up is also needed to assess the definitive value of this therapeutic approach."*
			Ventricular fibrillation	*3/63 (5)*		
			Haemodynamic instability needing extra-corporeal membrane oxygenation	*1/63 (2)*		
			Bleeding requiring >2 blood units	*3/63 (5)*		
			Surgical revision for bleeding	*0/63 (0)*		
			Apex bleeding or rupture	*0/63 (0)*		
			Conversion to conventional surgery	*0/63 (0)*		
			Major adverse events			
			Death	*0/63 (0)*		
			Stroke	*0/63 (0)*		
			Acute myocardial infarction	*1/63 (2)*		
			Septicaemia	*2/63 (3)*		
			Minor adverse events			
			Severe pericardial effusion	*2/63 (3)*		
			Wound dehiscence	*1/63 (2)*		
			Gastrointestinal complications needing surgery	*0/63 (0)*		
			Acute renal failure needing CWH	*0/63 (0)*		
			Onset of persistent AF	*13/63 (21)*		
			Onset of permanent AF	*1/63 (2)*		
			Pace-maker implantation	*2/63 (3)*		
			Reoperation for NeoChord failure at 30 days	8/63 (13)		
			Total major adverse events	*3/63 (17)*		

§: different to all the other safety outcomes (measured as number of events/number of procedures performed), this outcome was estimated as number of patients reporting at least one adverse event/number of procedures performed.

Abbreviations: MR, mitral regurgitation; DMR, degenerative mitral regurgitation; PML, posterior mitral leaflet.

Safety findings from the 15 studies on MitraClip® System

Alegria-Barrero et al. [38] observed that 40 patients of 43 enrolled were successfully implanted (overall procedural success of 93%) with 21 receiving one clip (group 1) and 19 receiving more than one clip (group 2). MAEs occurred in 5 patients of forty (12%) with successful MitraClip implantation. One patient in group 2 with previous mitral valve repair underwent surgical bailout mitral valve repair after the MitraClip was unable to reduce the degree of MR. No other MAEs periprocedurally nor 30-day mortality were recorded. Three patients in group 2 and 1 patient in group 1 died at 12 months follow-up because of HF related to dilated cardiomyopathy (all patients had FMR).

Armoiry et al. [33] reported that in-hospital death occurred in 2 patients with FMR (3.2%). Two other surgical mitral valve repairs were required after the MitraClip procedure (patients with FMR). Other non-fatal AEs were observed in 7 patients (11.3%): 1 clip was implanted in the wrong position in the subvalvular apparatus, 1 deep venous thrombosis, 1 bleeding at puncture site, 1 new-onset atrial arrhythmia, 1 acute febrile respiratory illness, 1 false aneurysm at venous puncture site and 1 tamponade. Peri-procedural blood transfusion was necessary in 5 patients (8.1%). No cases of stroke or myocardial infarction were reported. After 6 months, the survival rate was estimated to be 83.1%.

In the study by Attizzani et al. [36], patients were divided in 2 groups: 78 patients that did not fulfill echocardiographic eligibility criteria of EVEREST I and II studies formed the investigational group (i.e. $EVEREST_{OFF}$ group) whereas 93 patients that met these criteria represented the control group (i.e. $EVEREST_{ON}$ group). Thirty-day follow-up data were available for all enrolled patients; MAEs were reported in 8 patients, 2 patients (2.6%) in the $EVEREST_{OFF}$ group and 6 (6.5%) in the $EVEREST_{ON}$ group (p=0.204) including 1 death (1.3%) in the first group and 2 deaths (2.2%) in the latter one (p=0.566). At 12 months, follow-up data from 154 patients (90%) were available and safety data related to the number of deaths and mitral valve surgery were reported. No surgical valve repair intervention was required while 11 (15.7%) patients died in the $EVEREST_{OFF}$ group and 9 (10.7%) in the $EVEREST_{ON}$ group (p=0.358).

Bozdag-Turan et al. [39] reported that 38 patients (31.4%) experienced a MACCE 12 months after the procedure while 9 patients (7.4%) underwent mitral valve surgery. During the follow-up period 28 patients died, 4 of them at 30 days after the procedure. No patient died during the procedure despite the high surgical risk level. Patients were allocated in 2 groups according to their left ventricular functionality (patients with LVEF ≤30 and patients with LVEF >30), and a stratified analysis of the outcomes was performed.

In the study by Braun et al. [93], outcome data were available for 113 patients (95%) at follow-up. Ten patients (all from DMR group) underwent conventional mitral surgery while 5 patients (4 from DMR group and 1 from FMR group) underwent second clipping. No procedural death was observed. However, 2 patients died within a few days after successful clipping (1 from FMR group while it is not clear if the other patient was from FMR or DMR group. Two patients experienced complications related to the procedure: gastrointestinal bleeding occurred in 1 patient with DMR and myocardial infarction in 1 patient with FMR.

In the study by Glower et al. [24], among 351 patients enrolled in both the EVEREST II HRR and REALISM HR, 342 patients (97.4%) had 30-day follow-up available and 327 patients (93.2%) had 1-year follow-up available. Death occurred in 4.8% (17/351) patients at 30 days with no death related to a device malfunction. MAEs occurred in 66 patients of 351 (18.8%) mostly consisting of blood transfusions ≥2U occurring in 13.4% of patients (47/351). Nine strokes were reported none of which was due to device or air embolization. Major vascular complications were infrequent, occurring in 12 patients (3.4%). At 1 year 80 patients had died (22.8%), MAE rate was 37.6% (132/351), with the most common event being blood transfusions (79 patients among 351, 22.5%), and 3 additional strokes occurred. The rate of device-related complications was low through 12 months: single-leaflet device attachment occurred in 8 patients, with most (6) in the early phase (<30 days); mitral valve surgery occurred in 3 patients while a second MitraClip procedure was performed in 4 patients during 30 days after the first procedure. No device embolization occurred.

Hellhammer et al. [29] reported that MitraClip has been implanted successfully in all 19 patients with diabetes (100%) and in 38 of 39 no diabetic patients (97.4%). In-hospital complications occurred in 10 patients (1 with diabetes mellitus II and 9 non-diabetic patients). No patient died in

the diabetes group while 1 death occurred in the non-diabetes group during 30 days after the procedure. No death was reported in either group during 3 months after the implantation procedure. Thus, due to a low mortality (at 30 days and 3 months) and few overall complications, the safety of the procedure was demonstrated even in the diabetes patients group.

In the study by Hellhammer et al. [30] mortality at 30 days did not show a statistically significant difference (2.4% in patients with anaemia and 5.1% in patients without anaemia; P = 0.611). Groups did not differ in terms of in-hospital complication rates. MACCE rate (including death, myocardial infarction, stroke, and procedure related re-operation) was 4.9% (n = 2) and 5.1% (n = 2) in the two groups (P = 0.959). The need for preoperative and postoperative transfusion did not differ between groups.

The study by Koifman et al. [41] reported the abortion of the procedure in 1 patient due to inability to achieve MR reduction, leaving 19 patients successfully implanted. Patients were discharged at a mean of 2.8 ± 3.5 days post-implantation, 13 (65%) were discharged on the day after the procedure, but a number of patients had longer hospitalisation periods. Notably, 4 patients were hospitalized for more than 5 days (2 patients developed fever; 1 patient had a large femoral artery pseudo-aneurysm; 1 patient continued to suffer from intractable HF and thrombocytopenia and died following a massive stroke 2 weeks after clip implantation). Among 18 patients with successful reduction of MR surviving to discharge, 2 patients died, 1 due to HF 7 months post-procedure and the other to non-cardiac causes 6 months post-procedure.

Reichenspurner et al. [37] reported that within 30 days, the overall incidence of AEs was 17.9% (21/117), with 27.3% (9/33) and 14.3% (12/84) for high- and low-risk subgroups, respectively. This included 3 patients requiring valve re-intervention. Mortality at 30 days was 6.0% (7/117) with 9.1% (3/33) and 4.8% (4/84) for high- and low-risk subgroups, respectively. Causes of death were classified as cardiac in 42.9% (3/7) of cases as determined by the sites. At 12 months, the overall incidence of AEs in the entire cohort was 41.0% (48 of 117). This included 13 patients undergoing repeated valve intervention. Mortality at 12 months was 17.1% (20 of 117) for the entire cohort and 24.2% (8/33) and 14.3% (12/84) for high-risk and low-risk subgroups, respectively. Causes of death were classified as cardiac in 45% (9/20) cases as determined by the sites.

In Rudolph et al. [26], with only 1 fatal event observed, procedural mortality was judged as very low, with no differences between groups. The number of transfusions/severe bleeding increased significantly with NYHA functional class (NYHA IV, 13.6% vs. NYHA III, 6.3% vs. NYHA I/II, 3.4%; P <0.01), as did the number of transient ischaemic attacks (NYHA IV, 3.6% vs. NYHA III, 0.5% vs. NYHA I/II, 0.0%; P < 0.01). Moreover, duration of ventilation and intensive care unit stay were longer in patients with high NYHA class. A higher percentage of patients in NYHA IV required ≥3days until mobilisation (NYHA IV, 11.7% vs. NYHA III, 6.4% vs. NYHA I/II, 2.3%; P <0.05). Patients in NYHA class IV were less frequently discharged (80.0% vs. 90.4% vs. 95.3%; P < 0.001). In-hospital mortality did not differ between groups.

Toggweiler et al. [35] reported intra-procedural complications in 3 patients (4%) making clip implantation unfeasible. Six patients (8%) had bleeding requiring transfusion, and 1 (1%) patient had a pericardial tamponade after rupture of the left atrium. No strokes occurred at 2 years post-procedure. Overall, in-hospital mortality was 4.1% (3/74). At 2 years, partial clip detachment had occurred in 7 (10%) patients (within the first 30 days in 4 patients; between 30 days and 1 year in 2 patients; 1 patient had clip detachment 2 years post procedure). In 5/7 (71%) patients, partial clip detachment resulted in 3+ or 4+ MR and the procedure was repeated in 5 patients, whereas the remaining 2 were treated medically. The re-do procedure reduced MR to moderate in 2/5 (40%) patients while the remaining 3 patients had persistent moderate-to-severe or severe MR.

In-hospital MAEs occurred in 5 patients (12%) in the study by Vandendriessche et al. [40]. One in-hospital death due to intracranial bleeding was observed, 2 additional major bleeding (1 requiring urgent surgery), and 2 patients needed to undergo urgent cardiac surgery.

Wiebe et al. [25] reported an in-hospital MACCE rate (including mortality, stroke, and myocardial infarction) of 4.9% (27/546) in high surgical risk patients. The Major in-hospital complications rate was 19.4% (108/557) while the minor in-hospital complications rate was 13.8% (77/557). Other complications were observed in 17.8% of cases (97/546). Days at Intensive Care Unit ranged from 1–2 while the mean hospital stay was 10 days (6–17).

Yeo et al. [34] observed that the 30-day mortality rate was 5.6% (n = 8), of which 4.2% (n = 6) was in-patient mortality. The 30-day MAE rate was 12.7% (18/142). One patient (0.7%) underwent a mitral valve reoperation, 5 patients (3.5%) had blood transfusion of ≥2 units, 2 patients (1.4%) developed sepsis, 1 patient (0.7%) had prolonged intubation, and 1 patient (0.7%) was readmitted for HF. No cases of device embolization were observed. No statistically significant difference was observed in MAE rate between FMR (6.2%, 7/76) and DMR (15.4%, 10/65) patients (P = 0.306).

Safety findings from the 2 studies on Carillon® Mitral Contour System®

In the study by Schofer et al. [31], safety outcomes were measured as the number of AEs in the total intention-to-treat patient population (46 patients; 2 patients withdrew from the study before the 30-day follow-up). Six patients experienced a total of 7 MAEs including one patient who was dead at 30-day follow-up. Durability of the device was not assessed.

In the study by Siminiak et al. [21], all safety endpoints were measured as ratio of number of AEs and intent-to-treat population. The 30-day MAE rate in the overall intent-to-treat population was 1.9%. At 12 months there were 8 deaths in the implanted group (22.2%) and 4 deaths in the device recaptured group (23.5%). Between 12 and 24 months further, 3 not device related deaths occurred.

Safety findings from the 3 studies on NeoChord DS1000

In Rucinskas et al. [32], safety findings were expressed as the number of adverse events (AEs) per number of patients observed at follow-up. The authors highlighted that there were no major adverse events (MAEs) related to the implantation of the chords other than intraoperative conversion to conventional surgery. Another patient was converted to standard care (not defined) before the 6 months follow-up assessment. Durability of the implanted chords was not assessed within the study.

Seeburger et al. [22] reported that 8 patients (26.7%) experienced at least 1 MAE at 30 days follow-up; one patient died within 30 days (post-cardiotomy syndrome with concomitant sepsis and 1 experienced perioperative stroke with full recovery at 30-day follow up. The permanent implantation rate was not assessed within the study.

In Colli et al. [23], safety findings were measured as the percentage of the number of AEs per number of procedures performed. Total serious AEs, considering only all MAEs estimated at 30-day follow-up, amounted to 5% (3/63). Eight reoperations (13%) due to device failure were carried out, 5 resulted into conversions to conventional surgery (repair or replacement) and 3 in new NeoChord implantation (1/63) or NeoChord re-tensioning (2/63). The permanent implantation rate was not evaluated.

List of ongoing and planned studies

Table 15: List of ongoing studies with MitraClip® System

Study Identifier	Estimated completion date [status]	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT01626079 COAPT	Aug 2020 [recruiting]	Interventional. Multicentre randomised with parallel assignment.	430	Percutaneous mitral valve repair using MitraClip System	No Intervention (non-surgical management based on standard hospital clinical practice).	Symptomatic heart failure subjects who are treated per standard of care and who have been determined by the site's local heart team as not appropriate for mitral valve surgery.	***Primary outcomes:*** Composite of Single Leaflet Device Attachment (SLDA), device embolizations, endocarditis requiring surgery, Echocardiography Core Laboratory confirmed mitral stenosis requiring surgery, LVAD implant, heart transplant, and any device related complications requiring non-elective cardiovascular surgery (12 months); Recurrent heart failure (HF) hospitalizations (24 months). ***Secondary outcomes:*** A composite of all-cause death, stroke, MI, or non-elective cardiovascular surgery for device related complications in the Device group (30 days) All-cause mortality (12 months) MR severity (12 months) Change in distance walked on the 6MWT (12 months) Change in quality of life (QoL) as measured by the KCCQ (12 months) Change in Left Ventricular End Diastolic Volume (LVEDV) (12 months) New York Heart Association (NYHA) Functional Class I/II (12 months) Recurrent hospitalizations - all cause (12 months) Hierarchical composite of death and recurrent HF

							hospitalization hospitalization (12 months)
NCT02444338	Sep 2019 [recruiting]	Interventional. Multi-centre randomised.	380	MitraClip device plus optimal standard of care therapy	Standard of care therapy	Patients with chronic heart failure and clinically significant functional MR (NYHA II to NYHA IV).	***Primary outcomes:*** Cardiovascular death ***Secondary outcomes:*** MR severity reduction (24 months) Change in 6MWT (6, 12 and 24 months) cardiovascular hospitalizations and cardiovascular death (24 months) Quality of Life (QoL) overall score (12 months) New York Heart Association (NYHA) Functional Class (6, 12 and 24 months) Patient-reported Global Assessment (PGA) (6, 12 and 24 months)
NCT02371512 MATTERHORN	Dec 2017 [recruiting]	Interventional. Multi-centre randomised with parallel assignment.	210	Valve repair with the MitraClip system	Reconstructive mitral valve surgery	Advanced insufficiency of functional or ischemic origin in patients with moderate-to-severe MR of primarily functional pathology and reduced left ventricular function considered to be at high surgical risk.	***Primary outcomes:*** Composite of death, rehospitalisation for heart failure, reintervention (repeat operation or repeat intervention), assist device implantation and stroke (whatever is first) (12 months) ***Secondary outcomes:*** Recurrence of grade 3 or 4 MR (12 months) Change in 6MWT distance (12 months) Change in NYHA functional class (12 months) Change in MLHFQ score (12 months) Echocardiographic assessment of left ventricular remodelling (12 months) Change in serum BNP (12 months) Length of stay ICU / hospital Number of patients in whom operative or interventional mitral valve repair can not be performed (need for mitral valve replacement) (12 months)

NCT02033811 MitraClip® Registry	Jan 2020 [recruiting]	Observational (Patient Registry). Cohort study.	200	percutaneous mitral valve repair (PMVR) with the MitraClip® system	NA	Patients undergoing percutaneous mitral valve repair (PMVR) with the MitraClip® system.	***Primary outcomes:*** Major cardiac adverse events (30 days) ***Secondary outcomes:*** Mortality (12 months)
NCT01920698 MITRA-FR	Oct 2017 [recruiting]	Interventional. Multi-centre randomised with parallel assignment.	288	Percutaneous MitraClip device implantation in addition to optimal standard medical therapy	Optimal medical therapy alone	Patients with severe FMR.	***Primary outcomes:*** All-cause mortality and unplanned hospitalizations for heart failure (12 months). ***Secondary outcomes:*** All-cause mortality, cardiac mortality (30 days, 6 months, 12 months, and 24 months) Survival with no major cardiovascular events (30 days, 6 months, 12 months, and 24 months) Serious Adverse Events (30 days, 6 months, 12 months, and 24 months) Change in Quality of Life score as measured by the European Quality of Life-5 Dimensions instrument (6 and 12 months) Change in functional evaluation (12 months) Change in echocardiographic evaluation (6, 12 and 24 months) Change in biomarkers (BNP levels, creatinine) (6 and 12 months) Cost-effectiveness of each strategy (12 months)
NCT02444286 RESHAPE-HF1-FU	Jan 2017 [recruiting]	Observational. Cohort study	42	MitraClip device plus optimal standard of care therapy	Optimal standard of care therapy alone	Follow-up of patients treated for clinically significant FMR with New York Heart Association (NYHA) Functional Class III or IV chronic heart failure, former participants in the RESHAPE-HF Trial.	***Primary outcomes:*** Cardiovascular death (24 months) ***Secondary outcomes:*** MR severity reduction (12 and 24 months) 6MWT (6, 12 and 24 months) Cardiovascular hospitalizations and cardiovascular death (24 months)

							Quality of Life (QoL) (12 months) New York Heart Association (NYHA) Functional Class (6, 12 and 24 months) Patient-reported Global Assessment (PGA) (6, 12 and 24 months)

Abbreviations: 6MWT: Six minutes walk test; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVAD: left-ventricular assist device; MI: myocardial infarction; MR: mitral regurgitation; NA = not applicable.
Source: https://clinicaltrials.gov (accessed on 21st May 2015).

Table 16: List of ongoing studies with Carillon® Mitral Contour System®

Study Identifier	Estimated completion date [status]	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT02325830 REDUCE FMR	Jul 2017 [recruiting]	Interventional. Multicentre randomised with parallel assignment.	180	Percutaneous mitral valve repair with CARILLON Mitral Contour System	No Intervention (medical management according to heart failure guidelines)	Diagnosis of dilated ischemic or non-ischemic cardiomyopathy; Functional MR: 2+ (Moderate), 3+ (Moderate/Severe), or 4+ (Severe); New York Heart Association (NYHA) II, III, or IV Six Minute Walk distance of at least 150 meters and no farther than 450 meters Left Ventricular Ejection Fraction ≤ 40% LV end diastolic dimension (LVEDD) > 55mm or LVEDD/Body Surface Area (BSA) > 3.0cm/m^2 Stable heart failure medication regimen for at least three (3) months prior to index procedure.	***Primary outcomes:*** Change in regurgitant volume associated with the CARILLON device relative to the Control population (at 12 months). ***Secondary outcomes:*** Document the difference in the rate of major adverse events between Treatment (CARILLON) and Control groups (30 days and 12 months) Assess rate of heart failure hospitalizations between Treatment (CARILLON) and Control groups (12 months) Assess the change in six-minute walk distance between Treatment (CARILLON) and Control groups (12 months) Assess the change in left ventricular volumes between Treatment (CARILLON) and Control groups (12 months)

Source: https://clinicaltrials.gov (accessed on 20th May 2015).

Table 17: List of ongoing studies with NeoChord DS1000

Study Identifier	Estimated completion date [status]	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT01784055 NeoChord TACT	July 2016 [recruiting]	Observational (Patient Registry). Cohort study.	100	Artificial chordae placement using DS1000 System	NA	Patients with Grade 3+ or 4+ mitral valve regurgitation who are candidates for surgical mitral valve repair or replacement	Procedure Success (1 day).

Abbreviations: NA = not applicable.
Source: https://clinicaltrials.gov (accessed on 20th May 2015).

Risk of bias tables

Quality assessment of systematic reviews

Munkholm-Larsen et al., 2014 [17]	**R-AMSTAR items**									
	(1)	**(2)**	**(3)**	**(4)**	**(5)**	**(6)**	**(7)**	**(8)**	**(9)**	**(10)**	**(11)**
	4	3.5	4	2.5	3.5	4	2	2	1.5	1	2

Adapted from: Kung J, Chiappelli F, Cajulis OO, Avezova R, Kossan G, Chew L, Maida CA. From Systematic Reviews to Clinical Recommendations for Evidence-Based Health Care: Validation of Revised Assessment of Multiple Systematic Reviews (R-AMSTAR) for Grading of Clinical Relevance. The Open Dentistry Journal, 2010, 4, 84-91).

Total score*: 30/44 (final score calculated from judgments provided by 2 independent assessors)

** the R-AMSTAR total score has a range of 11 to 44, 11 signifying that none of the AMSTAR criteria were satisfied, and a score of 44 revealing that all of the criteria of systematic review excellence were verified.*

List of R-AMSTAR items: *(1) Was an 'a priori' design provided? (2) Was there duplicate study selection and data extraction? (3) Was a comprehensive literature search performed? (4) Was the status of publication (i.e. grey literature) used as an inclusion criterion? (5) Was a list of studies (included and excluded) provided? (6) Were the characteristics of the included studies provided? (7) Was the scientific quality of the included studies assessed and documented? (8) Was the scientific quality of the included studies used appropriately in formulating conclusions? (9) Were the methods used to combine the findings of studies appropriate? (10) Was the likelihood of publication bias assessed? (11) Was the conflict of interest included?*

Quality assessment of included primary studies by the IHE 18-items checklist

The quality is "acceptable" if the study has 14 or more positive answers (i.e. "Yes").*

Item #	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12	#13	#14	#15	#16	#17	#18	Yes
MitraClip																			
Alegria-Barrero, 2014	Y	Y	N	Y	Y	Y	Y	na	Y	Y	Y	Y	Y	N	N	Y	Y	Y	**14**
Armoiry, 2013	Y	Y	Y	N	N	Y	Y	na	Y	Y	Y	Y	Y	N	Y	Y	Y	N	**13**
Attizzani, 2015	Y	Y	N	Y	Y	Y	Y	na	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	**15**
Bozdag-Turan, 2014	Y	Y	N	Y	N	Y	Y	na	Y	Y	Y	Y	Y	N	N	Y	Y	N	**12**
Braun, 2014	Y	Y	nr	Y	Y	Y	Y	na	Y	Y	Y	Y	Y	Y	N	Y	Y	N	**14**
Glower, 2014	Y	Y	Y	Y	N	Y	Y	na	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	**15**
Hellhammer, 2014	Y	Y	N	Y	N	Y	Y	na	Y	Y	N	Y	Y	Y	N	Y	Y	N	**12**
Hellhammer, 2015	Y	Y	N	Y	Y	N	Y	na	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	**14**
Koifman, 2014	Y	Y	N	Y	Y	N	Y	na	Y	Y	Y	Y	Y	Y	N	Y	Y	N	**13**
Reichenspurner, 2013	Y	Y	Y	Y	Y	N	Y	na	Y	Y	Y	Y	Y	N	N	Y	Y	N	**13**
Rudolph, 2014	Y	Y	Y	Y	N	N	Y	na	Y	Y	Y	Y	Y	na	N	Y	Y	Y	**13**
Toggweiler, 2014	Y	Y	Y	Y	Y	N	Y	na	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**16**
Vandendriessche, 2014	Y	Y	Y	Y	Y	Y	Y	na	Y	Y	Y	Y	Y	Y	N	Y	Y	N	**15**
Wiebe, 2014	Y	Y	Y	N	N	N	Y	na	Y	Y	Y	Y	Y	N	N	Y	Y	Y	**12**
Yeo, 2014	Y	Y	Y	Y	Y	N	Y	na	Y	Y	Y	Y	Y	na	Y	Y	Y	N	**14**
CARILLON																			
Schofer, 2009	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	**16**
Siminiak, 2012	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	**14**
NeoScord DS1000																			
Rucinskas, 2014	Y	Y	N	N	N	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	Y	N	**11**
Seeburger, 2014	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N	N	**13**
Colli, 2015	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y	Y	N	**14**

Abbreviations: nr= not reported; na= not applicable, Y= Yes, N= No.

**Adapted from: Moga C, Guo B, Schopflocher D, Harstall C. Development of a quality appraisal tool for case series studies using a modified Deplhi technique. Methodology Paper. Edmonton AB: Institute of Health Economics, 2012. The threshold of ≥14 was chosen based on the threshold set by the Delphi panel in Moga et al.*

List of items: *1. Is the hypothesis/aim/objective of the study clearly stated in the abstract, introduction or methods section? 2. Are the characteristics of the participants included in the study described? 3. Were the cases collected in more than one centre? 4. Are the eligibility criteria (inclusion and exclusion criteria) to entry the study explicit and appropriate? 5. Were participants recruited consecutively? 6. Did participants enter the study at a similar point in the disease? 7. Was the intervention clearly described in the study? 8. Were additional interventions (co-interventions) clearly reported in the study? 9. Are the outcome measures clearly defined in the introduction or methodology section? 10. Were relevant outcomes appropriately measured with objective and/or subjective methods? 11. Were outcomes measured before and after intervention? 12. Were the statistical tests used to assess the relevant outcomes appropriate? 13. Was the length of follow-up reported? 14. Was the loss to follow-up reported? 15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes? 16. Are adverse events reported? 17. Are the conclusions of the study supported by results? 18. Are both competing interest and source of support for the study reported?*

Applicability tables

Table 18: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	***MitraClip*** Patients enrolled had DMR or FMR with a grade of severity ≥ 2+. Analysis was often presented by combining both DMR and FMR, and definition of high risk varied between studies. ***CARILLON*** Patients enrolled had dilated ischaemic or non-ischaemic cardiomyopathy, at least moderate (2+) FMR, LVEF < 40%, were in NYHA class II–IV, and stable HF medication regimen. Even if surgical risk was not formally assessed, the low LVEF suggests that these patients do not suit surgery. ***NeoChord DS1000*** Patients enrolled in the studies had severe DMR (grade 3+ or 4+) and had an indication for surgery confirmed according to guidelines. This is in line with the scope of the present assessment.
Intervention	The procedure was clearly described, for all the 3 devices, in terms of pre-procedural assessment, equipment, and interventional phases.
Comparators	***MitraClip*** No studies comparing the intervention to its claimed comparator (optimal medical therapy) were available. ***CARILLON*** In the only comparative study available (not included as it did not present surgical risk assessment of the patients) the comparison group was created by implanting and acutely recapturing the device for clinical indications in a subset of the initially enrolled patients. ***NeoChord DS1000*** No comparative studies were available.
Outcomes	The most frequently reported outcomes were: mortality, NYHA class improvement, reduction in MR grade, reduction in ventricular size, change in 6MWT score, change in the score used for assessing QoL (the Kansas City Cardiomyopathy Questionnaire for CARILLON; SF-36 Health Survey Quality of Life Questionnaire and the Minnesota questionnaire for MitraClip). Reported outcomes were in line with those defined in the scope of the present assessment. For none of the devices a post-procedural assessment of patients' satisfaction was performed in the studies.
Setting	The procedures were mainly performed in specialised tertiary referral centres. Given the status of the 3 technologies and the open issues on patient selection, learning curve, patients flow (i.e., number of procedures required to ensure reasonable outcomes), and education and training of the staff (i.e., case load for training, case load for maintenance of skill) this setting is likely to be the most appropriate to provide the treatment. Moreover, as highlighted by studies' authors and international guidelines, the presence of a heart team remains a prerequisite to the technology.

Abbreviations: DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; HF, heart failure; QoL, quality of life.

Regulatory and reimbursement status

Table 19: Regulatory status of MitraClip® System, Carillon® Mitral Contour System® and NeoChord DS1000

Country	Institution (EMA, FDA, TGA etc)	Approved yes/no/on-going	Verbatim wording of the (anticipated) indication	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include potential date of launch
MitraClip® System					
Europe	Notified Body DEKRA	Yes	**The MitraClip System** is intended for reconstruction of the insufficient mitral valve through tissue approximation.	March 2008 – CE Certificates renewed an	Yes As of October 2008
USA	FDA	Yes	This device is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR ≥ 3+) due to primary abnormality of the mitral apparatus [degenerative MR] in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation.	October 24, 2013	Yes As of October 2013
Japan	PMDA	On-going	To be determined.	To be determined	To be determined
Australia	SGA	Yes	The MitraClip System is intended for reconstruction of the insufficient mitral valve through tissue approximation	There were three registrations: November 18, 2010 (CDS/SGC); September 24, 2011 (CDS only); September 24, 2010 (Accessories)	Yes - 2011
Carillon® Mitral Contour System®					
European Countries	CE Mark	Yes, approved.	The Carillon® Mitral Contour System® is indicated for use in patients with functional mitral regurgitation.	August, 2011	Yes
Australia	TGA	Ongoing. Anticipated by Q3 2015	The Carillon® Mitral Contour System® is indicated for use in patients with functional mitral regurgitation.	N/A	Anticipated for Q3 2015
USA	FDA	No	N/A	N/A	N/A
Japan	MHLW	No	N/A	N/A	N/A
NeoChord DS1000					
EU	CE Mark	Yes	Indicated for use in patients with Grade 3+ or 4+ mitral valve regurgitation who are candidates for surgical mitral valve repair or replacement.	2012	Yes

Abbreviations: CE: Conformité Européenne; N/A: Not applicable
Sources: Submission files of manufacturers [1, 6, 8]

Table 20: Reimbursement status of Carillon® Mitral Contour System® and NeoChord DS1000

Carillon® Mitral Contour System®				
Country and issuing organisation e.g. G-BA, NICE	**Technology specific or indication specific reimbursement decision**	**Status of recommendation (positive/ negative/ongoing)**	**Date of decision**	**If positive, level of reimbursement**
Germany, InEK	Approved under NUB regulation for use under indication described with CE Mark approval – indication in IFU.	Positive – Status 1 approval at 94 hospitals in Germany.	January 2015	Level of reimbursement is hospital specific as negotiated between the hospital and the hospital's sickness fund.
Italy	Approved under Italian Device Classification CND Code: C03900101 KIT PER ACCESSI CARDIO-CHIRURGICI MINI-INVASIVI A VISIONE DIRETTA CARDIOSURGERY KITS, MINI-INVASIVE ACCESS, DIRECT VISION in certain Italian regions. It is approved for use under its CE Mark indication for use as stated in the IFU.	Positive – noted in previous column.	July 2013	Level of reimbursement is negotiated at a regional level.
Turkey	Approved under device register for public institutions. Approved for use according to CE Mark labelling as stated in the IFU.	Positive	2014	Level of reimbursement differs by institution.
NeoChord DS1000				
France, Italy, Netherlands		In process		
Lithuania		Approved via national tender		

Sources: Submission files of manufacturers [6, 8]

Table 21: Reimbursement information of MitraClip® System, Carillon® Mitral Contour System® and NeoChord DS1000 provided by EUnetHTA JA2 WP5 Strand B members

Country	Reimbursement status
Austria	The products and related interventions are partially covered by the LKF reimbursement system. As they are innovative products/an innovative benefit, they are treated similar to a comparable *previous* intervention and are, therefore, temporarily represented in the MEL catalogue of benefits (the related code begins with an XN, indicating the preliminary nature; the relevant code would be XN050 "Implantation of a mitral valve clip - transdermal"). As soon as better evidence is available, the intervention/benefit is transferred to a *normal* code and the reimbursement is newly calculated.
Czech Republic	These technologies are not yet in the list of medical performances, which are reimbursed by law, issued by Ministry of Health of the Czech Republic. But currently there is an ongoing pilot project. Based on this, only two cardiosurgical centers have a contract with public insurance company which guarantee full reimbursement of technologies. To conclude this, there is a limited access to reimbursed technologies in the Czech Rep.
France	MitraClip System: technology assessment in 2015: HAS recommends limiting implantations of the MitraClip device to patients with severe degenerative mitral insufficiency which is symptomatic despite optimal medical treatment, who are not eligible for valve replacement or repair surgery and who meet the echocardiographic eligibility criteria. In this indication, HAS believes that there is no alternative and that the need is not covered. In this indication, the improvement in treatment is substantial in relation to the lack of alternatives. In the other indications (functional or mixed mitral insufficiency) and/or for lower surgical risks, the role of the MitraClip edge-to-edge mitral valve repair clip in the therapeutic strategy remains undetermined. This role needs to be assessed with trials comparing it to standard treatments. The treatment of functional mitral insufficiency is under clinical research in several national and international trials, and HAS encourages the inclusion of patients in these studies. HAS recommends the establishment of a registry, carried out with the participation of the involved healthcare professionals, to document, at minimum, in all patients who undergo implantation in France. Carillon® Mitral Contour System®: not reimbursed, no technology assessment. NeoChord DS1000: not reimbursed, no technology assessment.
Germany	For mitral valve clipping, a German hospital gets 32.227,99 € (DRG F98C). For this DRG amount, the patient needs to stay in hospital 4-26 days.
Hungary	The HTA Department of the National Institute of Pharmacy and Nutrition (OGYEI) didn't get a reimbursement submission in relation to the mentioned products (MitraClip System, Carillon® Mitral Contour System® and NeoChord DS1000).
Italy	In Italy there is a Regional Health care system, so each Italian region has own rules of reimbursement. In particular all regions adopt the DRG System but each region could consider a different fee and could consider an extra fee for particular procedure in order to reimburse a high cost device for example. Regarding Transcatheter implantable devices for mitral valve repair in adults with chronic mitral valve regurgitation: In The Lazio (a region in the center of the Italy) the stated DRG is 104 Cardiac Valve and Other Major Cardiothoracic Procedures with Cardiac Catheterization with a fee of €24.675. In the Lombardy (in the north) each implant of TAVI is reimbursed with a specific fee that consider the cost of implant + 20% for a total amount of € 28.235,41.
Netherlands	In the Netherlands each individual device/retrievers/etc are not assessed. In the Netherlands, products for mitral valve repair are reimbursed but only for patients with severe stenosis who cannot undergo surgery (due to a high risk for complications).
Russian Federation	Neither "Carillon" nor "NeoChord" are being reimbursed in the Russian Federation at the moment. So far, both of these transcatheter implantable devices for mitral valve repair in adults are not being used in Russia at all. As far as we know at the moment, the situation with MitraClip in the Russian Federation is the same as for two previ-

	ous transcatheter implantable devices for mitral valve repair in adults.
Slovenia	The Health Insurance Insitute of Slovenia does not reimburse medical devices which are built-in to the body. They are included in regular medical services.
Spain	The MitraClip system is within the list of reimbursed devices in the National list of Health Services. The other two (Carillon and NeoChord) are not explicitly mentioned in the National list, so the Regional Services could reimburse but only under regional agreements.
Switzerland	In general, there is no positive list for reimbursement of devices applied in medical procedures (implants, catheters, etc.); reimbursement is regulated on the level of the procedures. Only medical products which are applied by patients themselves (such as glucose monitoring devices) are listed in the “Mittel- und Gegenständeliste”. Trans-catheter mitral valve repair is reimbursed in under certain restrictions (only in patients with a risk > 10% of dying within the next year; collaborating in the Swiss MItra Registry). The reimbursement rules (imposed 3 years ago after evaluation by the “Leistungs- und Grundsatzkommission”) do not restrict the type of devices. The procedures are reimbursed under the Swiss DRG system, so Hospitals are free to choose the products they use as long as they are CE marked. They choose the products based on the recommendations of the clinicians who use the products and on the prices and conditions they can negotiate with the producers.

APPENDIX 2: CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, SOCIAL AND LEGAL ASPECTS

1. Ethical	
1.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any new ethical issues?	Yes
1.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be ethically relevant?	Yes
Information about the severity level of the disease and extent to which the patient would be considered at high risk from conventional surgery could be important to decision-makers when making decisions about whether or not to implement a technology. ***F0100:*** *At what severity level of the disease are the technologies directed?*	
2. Organisational	
2.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparator(s) require organisational changes?	Yes
Organisational aspects are likely to play a relevant role for those settings that will provide transcatheter mitral valve repair for MR. Whatever is the comparator of choice (pharmacological therapy or surgery), the technology will completely reshape the clinical pathway for both the provider and patients. Proper analyses need to be developed to assess, for example, the impact of the technology on patient flow and the need of specialised human resources and their training. ***G0001:*** *What kind of work flow and patient flow processes are needed?* ***G0003:*** *What processes are required to ensure proper education and training for staff?*	
2.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences which may be organisationally relevant?	No
3. **Social**:	
3.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences which may be socially relevant?	No
4. **Legal**:	
4.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences which may be legally relevant?	No

