Interventional procedure overview of off-pump minimal access mitral valve repair by artificial chordae insertion to treat mitral regurgitation

Contents

Table 1 Abbreviations

Abbreviation	Definition
ACC	American College of Cardiology
AHA	American Heart Association
AKI	Acute kidney injury
ARF	Acute renal failure
ASE	American Society of Echocardiography
COPD	Chronic obstructive pulmonary disorder
CPB	Cardio-pulmonary bypass
CVVH	Continuous veno-venous haemofiltration
EACVI	European Association of Cardiovascular Imaging
ECMO	Extracorporeal membrane oxygenation
ESC	European Society of Cardiology
IQR	Interquartile range
KM	Kaplan-Meier
LAVi	Left atrial volume index
LVEDVi	Left ventricular end-diastolic volume index
LVEF	Left ventricular ejection fraction
LVESVi	Left ventricular end-systolic volume index
LVESD	Left ventricular end-systolic diameter
MR	Mitral regurgitation
MRI	Magnetic resonance imaging
MVARC	Mitral valve academic research consortium
MV	Mitral valve
NYHA	New York Heart Association
PM	Pacemaker
PML	Posterior mitral leaflet
sPAP	Systolic pulmonary artery pressure
STS	Society of Thoracic Surgeons
STS-PROM	Society of Thoracic Surgeons-Predicted Risk of Mortality
TACT	Transapical artificial chordae tendineae
TIA	Transient ischaemic attack
TOE	Transoesophageal echocardiography
TOP-MINI	Transapical Off-Pump Mitral Valve Intervention with Neochord Implantation

The procedure, condition, current practice and unmet need

The procedure

This transcatheter (minimal access) procedure for mitral regurgitation is done on a beating heart with no need for cardiopulmonary bypass. With the person having treatment under general anaesthesia and using TOE, a left sided anterior thoracotomy is used to advance the device delivery system into the left side of the heart to the target mitral valve leaflet. Once it is correctly positioned, a needle is released with a synthetic chord which is anchored to the surface of the target mitral valve leaflet. The delivery system is removed, and the suture is tightened. Additional chordae can be placed if necessary. Typically, three to four are placed along the free edge of the mitral valve leaflet to re-suspend the prolapsed segment. The tension on the chord is adjusted under TOE guidance until there is improvement or elimination of the mitral regurgitation. Once confirmed on imaging, the endings of the chord sutures are secured to the pericardium. This procedure has a lower risk of compromising subsequent surgical mitral valve repair than some other transcatheter techniques for mitral regurgitation. It may also be suitable for people for whom open-heart surgery is not considered safe due to other health conditions.

The condition

The mitral valve allows blood to flow from the left atrium to the left ventricle. MR happens when the valve doesn't close properly, allowing blood to flow back into the atrium from the ventricle during systole (when the heart contracts). The heart must work harder, resulting in an enlarged left ventricle. If not treated, this can lead to problems including heart failure. MR can be degenerative (primary or structural) or functional (secondary). Degenerative MR is caused by 'wear and

tear' to the chords and leaflets in the valve. In functional MR the chords and leaflets are structurally normal but there is geometrical distortion of the subvalvular apparatus caused by idiopathic cardiomyopathy or weakening of the cardiac walls caused by coronary artery disease (ischaemic MR).

Current practice

Degenerative MR is typically managed with open-heart surgery to repair or replace the mitral valve. This procedure requires a sternotomy to access the heart and the use of cardiopulmonary bypass. Functional MR can be managed conservatively with medical therapy aimed at treating heart failure, but this approach is not curative. Surgical procedures such as undersized annuloplasty may also be an option. People with MR of either cause are usually older (typically over 70 years) and frail, with multiple comorbidities. This increases the perioperative risks of morbidity and mortality for open heart surgery. For these people, transcatheter mitral valve repair by artificial chordae may be an appropriate treatment option.

Unmet need

Open-heart surgery is the conventional approach for mitral valve repair or replacement. However, this approach may pose excessive risk for certain people, particularly those who are older, frail, or who have multiple or complex comorbidities. For people for whom open-heart surgery is excessively risky, minimally invasive surgical approaches have been developed, such as transcatheter artificial chordae insertion, which can often be performed through smaller incisions and without the need to stop the heart or use cardiopulmonary bypass. These options aim to reduce perioperative risk and improve recovery, although they may not be suitable for all anatomical presentations of mitral regurgitation.

Outcome measures

The main outcomes included success endpoints, reduction in MR, functional outcomes, echocardiographic outcomes, mortality and complications. The measures used are detailed in the following paragraphs. A number of the included studies have performed additional analyses comparing endpoints among groups based on preoperative MV anatomy as follows: Type A, isolated central PML prolapse and/or flail; Type B, posterior multi-segment prolapse and/or flail; Type C, anterior or bileaflet prolapse and/or flail; Type D, paracommissural prolapse and/or flail or any type of disease with the presence of significant leaflet and/or annular calcifications.

MR grade

There are several classification systems of MR based on imaging. This is usually based on echocardiography, but angiography and MRI can also be used. In the included studies, MR grade was classified based on a range of objective guidelines including ASE, AHA, and ESC. Classification has 5 grades ranging from none to 1+ (mild MR), 2+, 3+, or 4+ (severe MR). A simplified 3 grade classification system is sometimes used (mild, moderate, or severe).

New York Heart Association (NYHA) functional class

The NYHA functional class is used to classify heart failure according to severity of symptoms and limitation of physical activity:

- Class 1 - no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, breathlessness, or palpitations.
- Class 2 - slight limitation of physical activity. Comfortable at rest but ordinary physical activity results in undue breathlessness, fatigue, or palpitations.

- Class 3 - marked limitation of physical activity. Comfortable at rest but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
- Class 4 - unable to carry out any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken discomfort is increased.

Echocardiographic outcomes

Some studies reported echocardiographic measurements, including linear dimensions and volumes. Other outcomes are described in the following paragraphs.

LVEF is the ratio of blood ejected during systole (stroke volume) to blood in the left ventricle at the end of diastole (end-diastolic volume). A normal range is typically between 50 and 70%. Values below 30% are considered a severe reduction.

LVEDVi is the volume of blood in the left ventricle at the end of diastole, just before the heart contracts (systole). It is indexed to adjust for a person's body surface area, enabling comparison across people of different sizes. The normal range is between 30 and 79 ml/m^2.

LVESVi is the volume of blood remaining in the ventricle after the heart contracts (systole). It is indexed to adjust for a person's body surface area, enabling comparison across people of different sizes. The normal range is between 9-31 ml/m^2.

LAVi is the volume of the left atrium at the end of systole. It is indexed to adjust for a person's body surface area, enabling comparison across people of different sizes. A normal value is 34ml/m^2 or lower.

sPAP is the pressure in the pulmonary artery during the systolic phase. The normal range is between 18 and 25mmHg.

MVARC endpoint definitions

Technical success (measured at exit from the catheterisation laboratory):

- Absence of procedural mortality
- Successful access, delivery, and retrieval of the device delivery system
- Successful deployment and correct positioning of the first intended device
- Freedom from emergency surgery or reintervention related to the device or access procedure.

Device success (measured at 30 days and at all later post-procedural intervals):

- Absence of procedural mortality or stroke
- Proper placement and positioning of the device
- Freedom from unplanned surgical or interventional procedures related to the device or access procedure
- Continued intended safety and performance of the device, including:
    - No evidence of structural or functional failure
    - No specific device-related technical failure issues and complications
    - Reduction of MR to either optimal or acceptable levels

Procedural success (measured at 30 days):

- Device success (either optimal or acceptable)
- Absence of major device or procedure related serious adverse events, including:

- Death
- Stroke
- Life-threatening bleeding
- Major vascular complications
- Major cardiac structural complications
- Stage 2 or 3 acute kidney injury (includes new dialysis)
- Myocardial infarction or coronary ischaemia requiring percutaneous coronary intervention or coronary artery bypass graft.
- Severe hypotension, heart failure, or respiratory failure requiring intravenous pressors or invasive or mechanical heart failure treatments
- Any valve-related dysfunction, migration, thrombosis, or other complication requiring surgery or repeat intervention

Patient success (measured at one year):

- Device success (either optimal or acceptable)
- Patient returned to the pre-procedural setting
- No rehospitalizations or reinterventions for the underlying condition
- Improvement from baseline in symptoms
- Improvement from baseline in functional status
- Improvement from baseline in quality-of-life

Clinical assessment tools

Most studies used a scoring system for assessing the risk of in-hospital mortality after cardiac surgery. The main ones are described below:

EuroScore II

EuroScore II is a validated and commonly used risk model for assessing the perioperative risk of mortality after major cardiac surgery. It is based on patient factors, such as age, sex and comorbidities, cardiac specific factors, such as NYHA class, and procedural factors, such as urgency. It is expressed as a percentage on a scale of 0 to 100%, with lower scores indicating a lower risk.

STS Score

The STS score is a risk stratification model, composed of up to 30 variables that predict short- and long-term mortality and morbidity after cardiac surgery. In general, an STS predicted risk of surgical mortality of 4 to 8% is considered intermediate risk and 8% or greater is considered high risk. Some studies report an STS-PROM MV score, which estimates the predicted risk of mortality at 30 days after isolated mitral valve repair (range, 0%-100%; a higher score indicates an increased risk).

Evidence summary

Population and studies description

This interventional procedures overview is based on 1,249 people from 7 prospective case series, 2 retrospective registry studies, 2 retrospective cohort studies and 1 retrospective case series. Of these 1,249 people, 1,070 people had the procedure. There is likely substantial overlap between these patient populations. This is a rapid review of the literature, and a flow chart of the complete selection process is shown in figure 1. This overview presents 12 studies as the key evidence in table 2 and table 3, and lists 9 other relevant studies in appendix B, table 5.

Colli (2016) conducted a prospective single centre case-series to evaluate the clinical outcomes of the TOP-MINI procedure using the NeoChord DS1000 system in the early postoperative period. This study was based in Italy and included 49 people with a median age of 72, with 34 males (69%). Acute procedural success was defined as implantation of at least 3 neochordae with residual MR of 2+ or greater. Primary efficacy outcomes were residual MR of 2+ or greater, freedom from reoperation for recurrence of severe MR and clinical improvement in NYHA functional class. Safety outcomes included hospital mortality, perioperative complications, major and minor adverse events. Patient outcomes were assessed at discharge and at 3 months post-procedure.

Colli (2015) conducted a multicentre prospective case series to evaluate the safety and efficacy of the TOP-MINI procedure in a consecutive cohort of symptomatic patients with severe mitral regurgitation (MR) due to leaflet flail or prolapse. The study was conducted across 2 sites in Italy and Lithuania between February 2013 and June 2014 and included 63 people with a median age of 66, with 42 males (67%). Early procedural success was defined as implantation of at least 2 neochordae with immediate reduction in MR to less than 2+. Primary efficacy outcomes were defined as reduction in MR to less than 2+ at the 30-day follow-up, freedom from reoperation for recurrence of severe MR and clinical improvement (NYHA functional class). Safety outcomes included perioperative complications, in-hospital and 30-day major and minor adverse events. Patient outcomes were assessed at discharge and at 30 days post-procedure.

Colli (2018a) conducted a prospective single centre case-series to evaluate the learning curve of surgeons performing the NeoChord procedure and monitor the performance of the procedure during the initial phase of its adoption. 112 consecutive patients who underwent the NeoChord procedure between November 2013 and March 2016 were included in the analysis. Participants included in the study had a median age of 68, with 82 males (73%). A composite

end-point was used based on MVARC definitions - the treatment was considered a success at 1 year follow up of the following criteria were met: (i) technical success including the placement of at least 2 neochordae and residual mitral regurgitation grade of mild or absent at the end of the procedure; (ii) freedom from major adverse events such as death, stroke, mitral regurgitation grade of greater than moderate, structural or functional valvular failure and/or unplanned interventions related to the procedure or device; (iii) freedom from a decline in baseline symptoms. Patient outcomes were assessed at discharge, 1 month, 3 months, 6 months and 1 year.

Colli (2018b) conducted a multicentre retrospective registry study to evaluate 1 year clinical results of the procedure using the NeoChord DS1000 device in a consecutive cohort of patients. 213 people were enrolled into the NeoChord Independent International Registry between February 2013 and July 2016. All participants presented with severe mitral regurgitation due to flail/prolapse of one or both leaflets, and they all completed postoperative echocardiographic assessment up to 1 year. Participants included in the study had a median age of 68, with 153 males (72%). The primary end-point was composed of (i) procedural success (defined as the placement of at least 2 neochordae and mild or less MR at the end of the procedure) and (ii) freedom from death, stroke, MR higher than moderate, unplanned interventions related to the procedure or device, cardiac-related rehospitalization or worsening NYHA functional class at 1 year and at each follow-up time. Patient outcomes were assessed at discharge, 1 month, 6 months and 1 year.

D'Onofrio (2022) conducted a single centre, retrospective study comparing outcomes of the NeoChord procedure and conventional surgical mitral valve repair. Data of patients who underwent isolated mitral valve repair with the NeoChord procedure or conventional surgery from January 2010 to December 2018 were collected. After 1:1 propensity matching, 176 people were included

(88 in each group), with a median age of 68 with 77% males in the NeoChord group, and a median age of 64 with 73% males in the conventional surgery group. The primary end point was overall all-cause mortality. Secondary end points were freedom from reoperation, freedom from moderate (2+) and severe (3+) MR and NYHA functional class in the overall population and in patients with isolated P2 prolapse (type A anatomy). Median follow up was 3.4 years in the NeoChord group, and 6.6 years in the conventional group.

D'Onofrio (2023) conducted a single centre retrospective case-series to evaluate clinical and echocardiographic 5 year outcomes of people who underwent the NeoChord procedure. All patients who underwent the procedure from November 2013 to March 2016 were included. Indications were severe symptomatic degenerative mitral regurgitation due to leaflet prolapse/flail. 100 consecutive patients were included in the analysis, with a median age of 66 and 73% male. Device success was defined by the absence of procedural mortality or stroke, proper placement and positioning of the device, freedom from unplanned surgical or interventional procedures related to the device or access procedure, no evidence of structural or functional failure, no specific device-related technical failure issues and complications, and reduction of MR to either optimal or acceptable levels without significant mitral stenosis. Follow up occurred at 1, 3, 6, 12 months, and annually thereafter for 5 years.

Gerosa (2021) conducted a single centre retrospective registry study to evaluate the mid-term outcomes of people who underwent the NeoChord procedure. 203 consecutive people with severe symptomatic MR due to prolapse or flail of one or both mitral leaflets that underwent the NeoChord procedure between November 2013 and June 2019 were included (78% male; median age: 64 years). Clinical outcomes and the composite primary endpoint (patient success) were defined according to MVARC criteria. Mitral regurgitation (MR) severity was graded as absent, mild, moderate and severe according to ASE and ESC guidelines.

Median follow-up was 24 months, patients underwent clinical and echocardiographic follow-up at 1, 3, 6, 12 months and annually thereafter for 3 years.

Kurnicka (2019) conducted a prospective case-series to evaluate early results of the NeoChord procedure in the first group of consecutive patients operated on in Poland. 21 people with severe MR due to posterior leaflet prolapse (81% male; mean age: 61, SD 12.7 years) underwent MV repair with the NeoChord DS1000 system between October 2014 and August 2017. 6 month echocardiographic results including MR grade and parameters of the left ventricle and left atrium geometry and function were evaluated. Patient outcomes were assessed at discharge, and 6 months post-procedure.

Samalavicius (2017) conducted a prospective case-series to describe the anaesthetic management and procedural success of patients undergoing the NeoChord procedure. 76 people (68% male; mean age: 60, SD 13 years) who underwent mitral valve repair with the NeoChord system between December 2011 and December 2016 were included in the study. Perioperative safety data were collected, along with reduction in MR post-procedure.

Seeburger (2014) conducted a multicentre prospective case-series called the 'TACT' trial to evaluate the safety and performance of the NeoChord DS1000 system. 30 people (60% male; mean age: 64, SD 11.9 years) across 7 centres with severe MR due to isolated posterior prolapse were included in this trial. All participants underwent off-pump transapical implantation of neochordae. The primary performance endpoint was the rate of patients maintaining an MR grade of 2+ or less at 30 days. The safety endpoint was major adverse events such as death, reoperation, and cardiovascular events.

Wrobel (2019) conducted a prospective case series to evaluate early outcomes of a single-centre experience with transapical beating heart mitral valve repair

with the NeoChord system. 37 people (78% male; mean age: 62.3, SD 3.4 years) with severe symptomatic MR were treated with the NeoChord procedure between September 2015 and December 2018. Transapical chordal implantation was considered suitable for patients if severe MR was present due to prolapse or flail of 1 leaflet and had the potential for good coaptation without requiring a prosthetic annuloplasty. Early surgical success defined as the reduction of MR to less than moderate by implantation of at least 2 neochordae was evaluated. Standard cardiac surgery perioperative complications and those related directly to the NeoChord technique were also presented.

Zorinas (2019) conducted a retrospective cohort study to compare early postoperative outcomes of conventional mitral valve repair surgery with the NeoChord procedure in people with degenerative MR. 169 people who underwent mitral valve repair between 2011 and 2018 were included. 78 people were in the NeoChord group (67.9% male; mean age: 59.5, SD 12.8 years) and 91 were in the conventional surgery group (57.1% male; mean age: 54.2 ±11.1 years). STS and EuroScore II risk scores did not differ between the groups. Performance and safety outcomes were assessed post-operatively, and at 30 days post-procedure.

Table 2 presents study details.

Figure 1 Flow chart of study selection

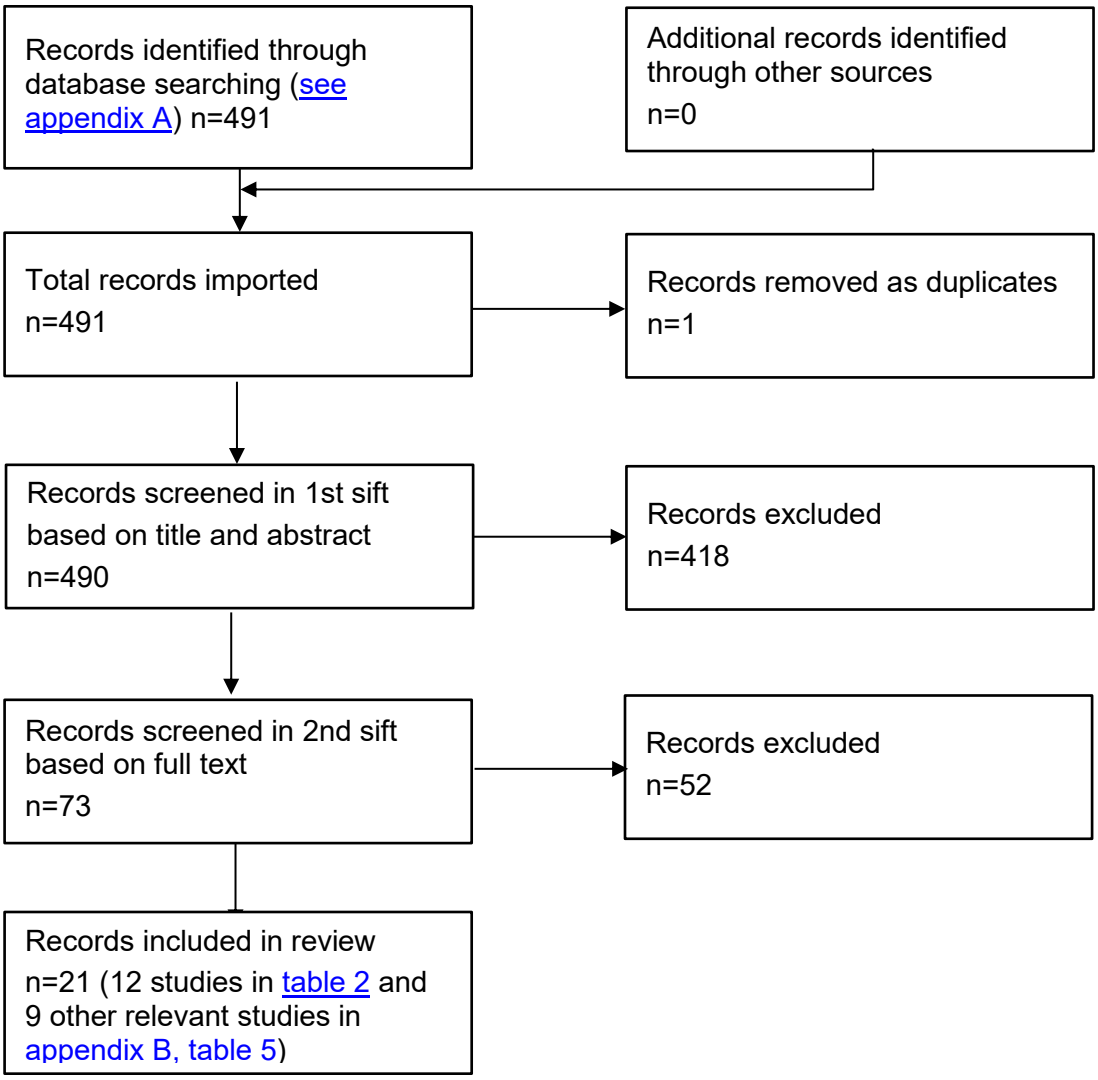

Table 2 Study details

Study no.	First author, date Country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
1	Colli, 2018b, Italy (3 centres), Germany (2 centres), Lithuania (1 centre), Poland (1 centre)	**n=213** **Age, median (IQR)** 68 (IQR 56-77) **Male sex, n (%)** 153 (71.8) **EuroScore II (%), mean (±SD)** 1.8 (±2.5) **STS-PROM MV repair score (%), mean (±SD)** 1.5 (±2.1) **NYHA functional class, n (%)** I: 14 (6.6) II: 92 (43.2) III: 101 (47.4) IV: 6 (2.8) **MR Grade, n (%)** Severe: 213 (100) **Leaflet involvement, n (%)** PML: 193 (90.6) AML: 11 (5.2)	Retrospective registry study. February 2013 - July 2016	All enrolled people had indications for surgical MV regurgitation due to degenerative MR according to current guidelines. An additional inclusion criterion was the presence of a consistent overlap of tissue to obtain a potential postoperative coaptation length of 3mm to 5 mm. The evaluation of the potential coaptation was based on an eyeball judgement of the surgeon due to the lack of precise predefined echocardiographic measurements during the initial clinical experience. Exclusion criteria were the presence of active endocarditis and	Off-pump neochordae implantation with the NeoChord DS1000 device	1 year

Study no.	First author, date Country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		AML + PML: 9 (4.2) **Leaflet prolapse, n (%)** 74 (34.7) Leaflet flail, n (%) 139 (65.3) **Mitral valve anatomical types, n (%)** A: 82 (38.5) B: 98 (46) C: 33 (15.5)		functional MR (Carpentier's Types I and III) or mixed disease.		
2	Gerosa, 2021, Italy (1 centre)	**n=203** **Age, median (IQR)** 64 (54-74) **Male sex, n (%)** 158 (77.8) **Euroscore II, median (IQR)** 0.94 (0.61-1.75) **STS PROM MV repair score (%), median (IQR)** 0.60 (0.32-1.44) **NYHA functional class, n (%)** III or IV: 75 (37.0) **MR grade n (%)**	Retrospective registry study. November 2013-June 2019	All consecutive patients that underwent MV repair with the NeoChord procedure at University of Padua between November 2013 and June 2019 were included in the current analysis. All the included patients presented with severe symptomatic DMR due to prolapse or flail of one or both mitral leaflets. The surgical indication was based on clinical and anatomical characteristics and the	Off-pump neochordae implantation with the NeoChord DS1000 device	3 years

Study no.	First author, date Country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		Severe: 203 (100) **Leaflet involvement, n (%)** PML: 187 (92.1) AML: 8 (3.9) AML + PML: 8 (3.9) **Mitral valve anatomical types, n (%)** A: 106 (52.2) B: 68 (33.5) C: 16 (7.9) D: 13 (6.4)		patient's personal preferences regarding treatment independently from age and surgical risk profile.		
3	D'Onofrio, 2022, Italy (1 centre	**n=176** **NeoChord = 88** **Male sex, n (%)** 68 (77) Age, median (IQR): 62 (54-70) **Euroscore II, median (IQR):** 0.7 (0.5-1.0) **NYHA functional class, n (%)** I: 33 (37.8)	Retrospective propensity matched cohort	Data of people who underwent isolated mitral valve repair with NeoChord or conventional surgery from January 2010 to December 2018 were collected. The choice between Neochord and conventional surgery was primarily based on anatomical characteristics but also on surgeon's and the persons preferences. People with previous	TA: Off-pump neochordae implantation with the NeoChord DS1000 device CMVR: Conventional on-pump mitral valve repair with full sternotomy	5 years

Study no.	First author, date Country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		II: 31 (35.4) III: 24 (26.8) IV: 0 **MR grade, n (%)** 3+: 88 (100) **Mitral valve anatomical types, n (%)** A: 43 (49) B: 39 (44) C: 6 (7) **Conventional surgery = 88** **Male sex, n (%)** 64 (73) **Age, median (IQR):** 61 (52.9-71.4) **Euroscore II, median (IQR):** 0.7 (0.6-1.0) **NYHA functional class, n (%)** I: 18 (20) II: 64 (72.9) III: 6 (7.1) IV: 0		cardiac surgery, and combined operations were excluded from the analysis. People with type D mitral valve anatomy were also excluded from this analysis.		

Study no.	First author, date Country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		MR grade, n (%) 3+: 88 (100) **Mitral valve anatomical types, n (%)** A: 37 (42) B: 40 (45) C: 11 (12)				
4	Zorinas, 2019, Lithuania (1 centre)	**n=169** **Neochord = 78** **Age, mean ± SD** 59.5 ± 12.8 **Male sex, n (%)** 53 (67.9) **STS score (%), median (IQR)** 0.47 (0.24-0.74) **EuroScore II (%), median (IQR)** 0.83 (0.67-1.35) **NYHA functional class, n (%)** I: 4 (5.1) II: 45 (57.7) III: 28 (35.9)	Retrospective cohort study	All candidates had indications for surgical MV repair according to the current ACC/AHA and ESC/EACTS guidelines. MV pathology included single or bi-leaflet MV prolapse or flail, with or without chordal rupture. Patients with a restrictive mechanism of regurgitation, ischemic mitral regurgitation, MV infectious lesions and patients with a central regurgitation jet were excluded from the study. All patients with degenerative MV	TA: Off-pump neochordae implantation with the NeoChord DS1000 device CMVR: Conventional on-pump mitral valve repair with full sternotomy	30 days

Study no.	First author, date Country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		IV: 1 (1.3) **MR grade, n (%)** Severe: 78 (100) **Conventional surgery = 91** **Age, mean ± SD** 54.2 ± 11.1 **Male sex, n (%)** 52 (57.1) **STS score (%), median (IQR)** 0.43 (0.31-0.70) **EuroScore II (%), median (IQR)** 0.84 (0.67-1.13) **NYHA functional class, n (%)** I: 1 (1.1) II: 21 (23.1) III: 68 (74.7) IV: 1 (1.1) **MR grade, n (%)** Severe: 91 (100)		disease were discussed by the Heart Team for eligibility to perform either CMVR surgery or a TA procedure. Patients with a favourable MV anatomy who agreed to undergo a transapical procedure were selected for the TA.		

Study no.	First author, date Country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
5	Colli, 2018a, Italy (1 centre)	**n=112** **Age, median (IQR)** 68 (IQR 57-76) **Male sex, n (%)** 82 (73) **EuroScore II (%), median (IQR)** 1.25 (0.67-2.10) **STS score (%), median (IQR)** 0.90 (0.39-1.74) **NYHA functional class, n (%)** I: 11 (10) II: 43 (38) III: 54 (48) IV: 4 (4) **MR Grade, n (%)** Severe: 100 (100) **Leaflet involvement, n (%)** PML: 101 (90) AML: 6 (5) AML + PML: 5 (5) **Leaflet prolapse, n (%)**	Prospective case series	People presenting with severe degenerative MR with the prolapse or flail of one or both leaflets were considered candidates for the procedure. Patients with an unfavourable MV anatomy and/or the presence of active endocarditis were excluded. The surgical indication was based on a discussion between the surgeons and cardiologists considering operative risk profile, clinical and anatomical characteristics and the patient's personal preferences regarding the treatment course.	Off-pump neochordae implantation with the NeoChord DS1000 device	1 year

Study no.	First author, date Country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		48 (43) **Leaflet flail, n (%)** 64 (57) **Mitral valve anatomical types, n (%)** A: 45 (40) B: 47 (42) C: 20 (18)				
6	D'Onofrio, 2023, Italy (1 centre)	**n=100** **Age, median (IQR)** 66 (58-76) **Male sex, n (%)** 73 (73) **STS PROM MV repair, median % (IQR)** 1 (0.4-1.8) **EuroScore II** <4%: 90 (90%) 4%-8%: 6 (6%) >8%: 4 (4%) **NYHA functional class 3 or 4:** 80%	Retrospective case series	This study included all patients who underwent the NeoChord procedure at the Division of Cardiac Surgery of the University of Padua between November 2013 and March 2016. Inclusion criteria were based on a careful evaluation of MV anatomy. Exclusion criteria were severe left ventricular (LV) dysfunction (LV ejection fraction <20%), LV aneurysm, apical thrombosis, and presence of associated	Off-pump neochordae implantation with the NeoChord DS1000 device	5 years

Study no.	First author, date Country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		Anatomic type, n (%) Favourable anatomy: 81 (81) Unfavourable anatomy: 18 (19) **MR grade, n (%)** Severe: 100 (100) **Prolapse/flail, n (%)** Prolapse: 42 (42) Flail: 58 (58)		heart disease requiring surgical correction.		
7	Samalavicius, 2018, Lithuania, (1 centre)	**n=76** **Age, mean (SD)** 60 (±13) **Male sex, n (%)** 52 (68) **Euroscore II (%), mean (SD)** 1.23 (±1.16) **NYHA functional class, n (%)** I: 4 (5) II: 44 (58) III: 27 (36) IV: 1 (1) **MR Grade, n (%)**	Prospective case series	Patients with severe MR who were candidates for surgical MV repair and had a LVEF of >25% were considered. Patients with functional or ischaemic MR or severe LV dysfunction, infective endocarditis, inflammatory valve disorders, leaflet perforation, or heavily calcified valves were excluded from the study. All patients who underwent MV repair using the NeoChord	Off-pump neochordae implantation with the NeoChord DS1000 device	Procedural results

Study no.	First author, date Country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		3+: 51 (67) 4+: 25 (33) **Type of mitral pathology, n (%)** Anterior leaflet prolapse: 3 (4) Posterior leaflet prolapse: 68 (89) Bileaflet prolapse: 5 (7)		system from December 2011 to December 2016 were included in the study		
8	Colli, 2015, Italy (1 centre), Lithuania (1 centre)	**n=63** **Age, median (IQR)** 66 (IQR 52-76) **Male sex, n (%)** 42 (67) **EuroScore II (%), median (IQR)** 1 (0.7-2.3) **STS score (%), median (IQR)** 0.8 (0.4-1.7) **NYHA functional class, n (%)** I: 3 (5) II: 25 (40) III: 31 (49)	Prospective case series	All patients were candidates for conventional MV repair surgery, according to the current guidelines. Patients were considered eligible for NeoChord implantation when severe MR was due to isolated prolapse or flail of the posterior, anterior or both MV leaflets. Exclusion criteria were the presence of active endocarditis or unfavourable MV anatomy.	Off-pump neochordae implantation with the NeoChord DS1000 device	30 days

Study no.	First author, date Country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		IV: 4 (6) **MR Grade, n (%)** 3+/4: 7 (11) 4+/4: 56 (89) **Prolapsing mitral leaflet, n (%)** PML: 56 (89) AML: 4 (6) AML + PML: 3 (5) **Leaflet involvement, n (%)** PML: 56 (89) AML: 4 (6) AML + PML: 3 (5) **Mitral valve anatomical types, n (%)** A: 22 (35) B: 27 (43) C: 14 (22)				
9	Colli, 2016, Italy (1 centre)	**n=49** **Age, median (IQR)** 72 (IQR 58-78) **Male sex, n (%)** 34 (69) **EuroScore II (%), median (IQR)**	Prospective case series	People selected for the NeoChord procedure presented severe degenerative MR due to posterior, anterior or both MV leaflets prolapse/flail. Exclusion criteria were the	Off-pump neochordae implantation with the NeoChord DS1000 device	12 months

Study no.	First author, date Country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		1.75 (0.73-2.75) **STS score (%), median (IQR)** 1.44 (0.73-2.75) **NYHA functional class, n (%)** II: 14 (28.6) III: 32 (65.3) IV: 3 (6.1) **MR Grade, n (%)** Severe (3 or 4+/4): 49 (100%) **Prolapsing mitral leaflet, n (%)** PML: 44 (89.8) AML: 4 (8.2) AML + PML: 1 (2)+/4): 49 (100%)		presence of active endocarditis, secondary MR and unfavourable MV anatomy.		
10	Wrobel, 2019, Poland (1 centre)	**n=37** **Age, mean (SD)** 62.3 (± 13.4) **Male sex, n (%)** 29 (78) **Euroscore II, median (range):** 0.92 (0.56-3.73)	Prospective case series	Transapical chordal implantation was considered suitable for patients if severe MR was present due to prolapse or flail of 1 leaflet and had the potential for good coaptation without	Off-pump neochordae implantation with the NeoChord DS1000 device	Procedural results

Study no.	First author, date Country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		Leaflet pathology, n (%) Posterior: 35 (95) Anterior: 2 (5) **Type of pathology, n (%)** A (Isolated central posterior leaflet prolapse): 25 (67.6) B (multiple prolapsing segments): 8 (21.6) C (commissural involvement, anterior leaflet): 4 (10.8)		requiring a prosthetic annuloplasty.		
11	Seeburger, 2014, Germany (3 centres), Italy (2 centres), Denmark (1 centre), Lithuania (1 centre)	**n=30** **Age, mean (SD)** 63.5 (± 11.9) **Male sex, n (%)** 18 (60%) **MR grade, n (%)** 3+: 3 (10) 4+ 27 (90) **NYHA functional class, n (%)** II: 13 (43.3) III: 17 (56.6)	Prospective case series	Patients with severe MR due to isolated Carpentier type II prolapse of the posterior MV leaflet and no annulus dilation, with an indication for surgery confirmed according to guidelines, were included in the trial. Key exclusion criteria included secondary MR, severe left ventricular dysfunction, anterior or bileaflet MV prolapse, permanent atrial fibrillation, and	Off-pump neochordae implantation with the NeoChord DS1000 device	30 days

Study no.	First author, date Country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
				concomitant cardiac disease with an indication for surgical treatment.		
12	Kurnicka, 2019, Poland (1 centre)	**n=21** **Age, mean (SD)** 60.7 SD ±12.7 **Male sex, n (%)** 17 (81) **NYHA functional class, n (%)** I: 6 (28.6) II: 12 (57.1) III: 3 (14.3) IV: 0 **Posterior leaflet flail, n (%)** 12 (57.1) **Posterior leaflet prolapse, n (%)** 9 (42.8) **Mitral valve anatomical types, n (%)** A: 12 (57.1) B: 8 (38.1)	Prospective case series	Severe MR, posterior leaflet prolapse or flail, single eccentric MR jet due to prolapse/flail, good potential for coaptation, a healthy long anterior leaflet, technical possibility to place chords. Exclusion criteria included severe LV enlargement, no tissue overlap, functional MR, multiple jets in different areas, endocarditis, significant leaflet and annulus calcifications, bileaflet prolapse, prolapse/flail of the commissural regions, leaflet perforation.	Off-pump neochordae implantation with the NeoChord DS1000 device	6 months

Study no.	First author, date Country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		C: 1 (4.8)				

Table 3 Study outcomes

First author, date	Efficacy outcomes	Safety outcomes
Colli, 2018b	**Early procedural success** 100% **Median procedure time, min (IQR)** 130 (117.5-150) **MR at discharge, n (%)** 0+: 32 (51) 1+: 22 (35) 2+: 7 (11) 3+: 1 (2) 4+: 1 (2) **MR at 30 days, n (%)** 0+: 29 (46) 1+: 16 (25)	**Perioperative complications, n (%)** Ventricular fibrillation: 3 (5) CPB/ECMO: 1 Bleeding requiting >2 blood units: 3 (5) **Major adverse events, n (%)** Myocardial infarction: 1 Septicaemia: 2 (3%) **Minor adverse events, n (%)** Severe pericardial effusion: 2 (3) Wound dehiscence: 1 Persistent AF: 13 (21) Permanent AF: 1 PM implantation: 2 (3)

First author, date	Efficacy outcomes	Safety outcomes
	2+: 10 (16) 3+: 7 (11) 4+: 1 (2) **NYHA class at 30 days, n (%)** 1: 55 (87) 2: 4 (6) 3: 4(6)	**Reoperation for NeoChord procedure failure at 30 days, n (%)** New Neochordae implantation: 1 Neochordae retensioning: 2 (3) Mitral valve repair: 3 (5) Mitral valve replacement: 2 (3) **Median ICU stay, hours** 24 **Median duration mechanical ventilation, hours (IQR)** 3 (2-5) **Median hospital stay, days (IQR)** 8 (6-11) **Discharge location, n (%)** Home: 9 (14) Cardiac rehabilitation centre: 54 (86)
Gerosa, 2021	**Procedural success, n (%)** 200 (99%) **KM 1 year survival** 99% ±1% **KM 3 year survival** 94% ±3% **Operative time, min (IQR)** 120 (106-150)	**Median mechanical ventilation time, hours (IQR)** 2 (1-3) **Procedural ECMO, n (%)** 4 (2) **Median hospital stay, days (IQR)** 7 (6-8) **Discharge location, n (%)** Home: 157 (77.7)

First author, date	Efficacy outcomes	Safety outcomes
	Rate of patient success 1 year: 91% ±2% 2 year: 90% ±2% 3 year: 81%±4% **Patient success by anatomy at 3 years:** Type A: 88%±5% Type B: 83±5% Type C: 73% ±12% Type D: 57%±19% p=0.001 **MR at discharge, n (%)** Absent/trivial: 83 (42) Mild: 89 (45) Moderate: 21 (10) Severe: 5 (3) **MR at 3 years, n (%)** Absent/trivial: 60 (12) Mild: 26 (52) Moderate: 15 (30) Severe: 3 (6) **Change in echocardiographic outcomes from preoperation to discharge** LVEDVi (mL/m2): 12.8±19.6, P<0.001 LVESVi (mL/m2): −0.4±10.8, P=0.960 LVEF (%): 8.0±10.2, P<0.001	Rehabilitation centre: 41 (20.3) **In-hospital death, n** 1 **TIA, n (%)** 1 **Major or extensive bleeding, n (%)** 8 (4) **Major pleural effusion, n (%)** 4 (2) **AKI stage 3, n (%)** 5 (3) **Ventricular fibrillation, n** 1 **New-onset atrial fibrillation, n** 1

First author, date	Efficacy outcomes	Safety outcomes
	LAVi (mL/m2): −11.6±17.3, P<0.001 sPAP (mmHg): 5.7±12.8, P<0.001 **Change in echocardiographic outcomes from discharge to 3 years** LVEDVi (mL/m2): 5.8±14.8, P=0.138 LVESVi (mL/m2): 5.6±14.2, P=0.150 LVEF (%): −5.1±8.0, P=0.021 LAVi (mL/m2): 3.2±11.3, P=0.260	
D'Onofrio, 2022	**Median follow-up, years** NeoChord: 3.4 Conventional: 6.6 **Median surgery duration, hours (IQR)** NeoChord: 2.0 (1.8-2.5) Conventional: 4.0 (3.5-4.0) **5 year survival** NeoChord: 92.1% (95% CI, 82.1-100) Conventional: 95.5% (95% CI, 90.6-100) p=0.94 **5 year survival (type A anatomy)** NeoChord: 100% Conventional: 92.8% (95% CI, 83.7-100) p=0.94 **NeoChord MR grade at discharge, n (%) p=0.084** 0-1+: 80 (91) 2+: 4 (5%)	**30-day mortality, %** 0% **Mean ICU stay, days** 1 **Conversion to repair, n** 1 **Mean intubation time, hours (IQR)** NeoChord: 2 (1-3) Conventional: 7.5 (5-12) **Re-exploration for bleeding, n (%)** NeoChord: 0 Conventional: 4 (5) **Atrial fibrillation, n (%)** NeoChord: 5 (6) Conventional: 30 (34) **Median in-hospital stay, days ((IQR)**

First author, date	Efficacy outcomes	Safety outcomes
	3+: 4 (5%) **Conventional MR grade at discharge, n (%) p=0.084** 0-1+: 87 (99) 2+: 1 3+: 0 **Freedom from moderate MR at 5 years** NeoChord: 58% (95% CI 43 - 77) Conventional: 85% (95% CI 76-95) p=0.001 **Freedom from severe MR at 5 years** NeoChord: 78.1% (95% CI 65-93) Conventional: 90% (95% CI, 82-98) p=0.032 **Freedom from reoperation** NeoChord: 79% (95% CI, 59-95) Conventional: 92% (95% CI, 85-99) **Median LVEF at discharge, % (IQR)** NeoChord: 55 (51-60) Conventional: 56 (51-61) p=0.867 **Median LVEF at follow-up, % (IQR)** NeoChord: 59 (56-63) Conventional: 60 (55-64) p=0.89 **Median iLVEDV at discharge, ml/m2 (IQR)** NeoChord: 76 (59-87) Conventional: 50 (63-72) p=0.001	NeoChord: 7 (6-8) Conventional: 8 (7-10) **CVVH, n** NeoChord: 0 Conventional: 1 **Wound infection, n** NeoChord: 0 Conventional: 1

First author, date	Efficacy outcomes	Safety outcomes
	Median iLVEDV at follow-up, ml/m2 (IQR) NeoChord: 66 (66-72) Conventional: 62 (60-65) p=0.001 **>90% of patients in both groups were in NYHA class 1 or 2 at follow-up**	
Zorinas, 2019	**Median duration of surgery, min (IQR)** NeoChord: 120 (110-146) Conventional: 312 (280-361) p<0.001 **NeoChord postoperative MR, n (%)** Absent: 43 (56) p<0.001 Mild: 28 (36) p=0.007 Moderate: 4 (5) p=0.03 Severe (failed repair): 2 (3) p=0.12 **Conventional postoperative MR, n (%)** Absent: 75 (82%) p<0.001 Mild: 16 (18) p=0.007 **NeoChord severe MR at 30-days, n (%)** 9 (12) p=0.001 **Conventional severe MR at 30-days, n** 0 p=0.001	**Mortality, n** Neochord: 1 Conventional: 0 p=0.277 **Mean postoperative blood loss, ml** NeoChord: 200ml Conventional: 300ml p=0.001 **Median time to weaning from ventilation, hours** NeoChord: 4 Conventional: 7 p<0.005 **Median length of ICU stay, hours (IQR)** NeoChord: 22 (20-24) Conventional: 67.5 (44-113) p<0.001 **Median length of hospital stay, n (IQR)** NeoChord: 8 (7-9) Conventional: 16 (14-21) p<0.001 **Conversion to full sternotomy, n** NeoChord: 1 **New atrial fibrillation, n (%)**

First author, date	Efficacy outcomes	Safety outcomes
		NeoChord: 9 (12) Conventional: 23 (25) p=0.031 **Stroke, n (%)** NeoChord: 0 Conventional: 2 (2) p=0.191 **Wound infection, n** NeoChord: 0 Conventional: 1 p=0.354 **Renal failure, n (%)** NeoChord: 2 (3) Conventional: 14 (15) p=0.007 **New PPM within 30-days post-procedure, n (%)** NeoChord: 2 (3) Conventional: 11 (12) p=0.003 **Re-exploration, n (%)** NeoChord: 3 (4) Conventional: 3 (3) p=0.577
Colli, 2018a	**Treatment success at one year, % (SD)** 89 (2.9) **Procedural success, n (%)** 110 (98) **Operative time, min (IQR)** 118 (110-155) **Survival at one year, n (%)**	**Death, n (%)** 2 (2) **TIA, n (%)** 1 **Myocardial infarction, n (%)** 1 (1) **AKI, n (%)**

First author, date	Efficacy outcomes	Safety outcomes
	104 (96) **MR at discharge, n (%)** Trivial: 30 (31) Mild: 51 (53) Moderate: 14 (15) Severe: 1 (1) **MR at one year, n (%)** Trivial: 33 (39) Mild: 36 (39) Moderate: 20 (22) Severe: 3 (3)	Stage 1: 9 (8) Stage 2: 2 (2) Stage 3: 2 (2) Need for CVVH: 2 (2) **Bleeding, n (%)** Minor: 9 (8) Major: 3 (3) Extensive: 5 (4) **Conduction disturbance, n (%)** 2 (2) **New-onset atrial fibrillation, n (%)** Paroxysmal: 25 (23) Persistent: 5 (5) **Pericardial effusion, n (%)** Minor: 7 (6) **Pleural effusion, n (%)** Minor: 68 (62) Major: 2 (2) **Wound dehiscence. n** 1 **Hospital stay, days (IQR)** 7 (6-9) **Discharge location, n (%)** Home: 72 (65)

First author, date	Efficacy outcomes	Safety outcomes
		Rehabilitation centre: 36 (33)
D'Onofrio, 2023	**Median follow-up** 5.1 years **Median operative time, min (IQR)** 123 (105-150) **Technical success, %** 98 **Procedural success, %** 94 **Device success, %** 30 days: 94 1 year: 9 5 year: 78 **Patient success at 1-year, %** 92 **5 year overall survival, %** 84 (95% CI, 76-92) No statistically significant difference (p=0.13) between FA and UA in terms of survival **MR grade at discharge, n (%)** None/trace: 30 (31) Mild: 51 (53) Moderate: 14 (15%) Severe: 1	**30-day mortality, n (%)** 2 (2) **Intraoperative complications, n (%)** ECMO: 2 (2) Conversion to conventional surgery: 2 (2) Major or extensive bleeding: 5 (5) **Early mortality, n (%)** 2 (2) **Median ICU stay, day (IQR)** 1 (1-1) **Hospital stay, days (IQR)** 7 (6-9) **Periprocedural complications, n (%)** Reoperation for severe MR: 2 (2) TIA: 1 AKI stage 2 or 3: 4 (4) Renal replacement therapy: 2 (2) New onset AF: 28 (28) **Early reintervention, n (%)** 3 (3)

First author, date	Efficacy outcomes	Safety outcomes
	MR grade at 5 years, n (%) None/trace: 5 (8) Mild: 33 (51) Moderate: 19 (30) Severe: 7 (11) **Overall cumulative incidence of severe MR recurrence, %** 1 year: 9 (95% CI, 4-15) 3 years: 12 (95% CI, 6-19) 5 years: 24 (95% CI, 15-32) **Overall cumulative incidence of reoperation, %** 1 year: 7 (95% CI, 2-12) 3 years: 10 (95% CI, 4-16) 5 years: 17 (95% CI, 9-24) Patients with FA compared with UA had a lower incidence of reintervention (5% vs 19% at 1 year; 6% vs 26% at 3 years; and 15% vs 43% at 5 years; P <.001 **NYHA functional class at 5 years, %** Class 1: 78 Class 2: 22 **Median LVEF preoperative, % (IQR)** 61 (57-67) **Median LVEF at discharge, % (IQR)**	

First author, date	Efficacy outcomes	Safety outcomes
	57 (53-60) p=0.09 **Median LVEF at 5 years, % (IQR)** 59 (56-64) p=0.09	
Samalavicius, 2018	**Median duration of surgery, min (IQR)** 120 (115-145) **MR post procedure, n (%)** Trivial: 42 (56%) Grade 1+: 27 (36) Grade 2+: 4 (5) Grade >2+: 2 (3) **Procedural success, n (%)** 75 (99)	**Postoperative, n (%)** New atrial fibrillation: 9 (12) Need to inotropic support: 20 (26) **Median duration of mechanical ventilation, hours (IQR)** 4 (2.6-6) **Median length of ICU stay, hours (IQR)** 22 (21-24) **Median length of hospital stay, days (IQR)** 8 (7-11) **Postoperative mortality, n** 0 **Sepsis, n** 1 **Renal failure, n (%)** 2 (3) **Re-exploration for bleeding, n (%)** 2 (3)
Colli, 2015	**Early procedural success**	**Perioperative complications, n (%)**

First author, date	Efficacy outcomes	Safety outcomes
	100% **Median procedure time, min (IQR)** 130 (117.5-150) **MR at discharge, n (%)** 0+: 32 (51) 1+: 22 (35) 2+: 7 (11) 3+: 1 (2) 4+: 1 (2) **MR at 30 days, n (%)** 0+: 29 (46) 1+: 16 (25) 2+: 10 (16) 3+: 7 (11) 4+: 1 (2) **NYHA class at 30 days, n (%)** 1: 55 (87) 2: 4 (6) 3: 4(6)	Ventricular fibrillation: 3 (5) CPB/ECMO: 1 Bleeding requiting >2 blood units: 3 (5) **Major adverse events, n (%)** Myocardial infarction: 1 Septicaemia: 2 (3%) **Minor adverse events, n (%)** Severe pericardial effusion: 2 (3) Wound dehiscence: 1 Persistent AF: 13 (21) Permanent AF: 1 PM implantation: 2 (3) **Reoperation for NeoChord procedure failure at 30 days, n (%)** New Neochordae implantation: 1 Neochordae retensioning: 2 (3) Mitral valve repair: 3 (5) Mitral valve replacement: 2 (3) **Median ICU stay, hours** 24 **Median duration mechanical ventilation, hours (IQR)** 3 (2-5) **Median hospital stay, days (IQR)**

First author, date	Efficacy outcomes	Safety outcomes
		8 (6-11) **Discharge location, n (%)** Home: 9 (14) Cardiac rehabilitation centre: 54 (86)
Colli, 2016	**Acute procedure success** 100% **Echocardiographic success at 3 months** 90% **Median operative time, mins (IQR)** 120 (100 - 135) **Residual MR at discharge, n (%)** 0+: 22 (44.9) 1+: 14 (28.6) 2+: 11 (22.4) 3+: 2 (4.1) **Residual MR at 3 months, n (%)** 0+: 16 (33.4) 1+: 15 (31.2) 2+: 12 (25) 3+: 5 (10.4) **NYHA class at discharge, n (%)** 1: 47 (95.9) 2: 1 3: 1	**Perioperative complications, n (%)** Ventricular fibrillation: 1 CPB/ECMO: 1 Bleeding requiting >2 blood units: 4 (8.2) **Major adverse events, n (%)** Death: 1 Myocardial infarction: 1 Septicaemia: 1 **Minor adverse events, n (%)** Severe pericardial effusion: 3 (6.1) Deep wound dehiscence: 1 ARF: 4 (8.2) ARF needing CVVH: 1 Persistent AF: 20 (40.8) Permanent AF: 3 (6.1) **Reoperation for NeoChord procedure failure at 3 months, n (%)** 4 (8.2) **Median ICU stay, hours** 24

First author, date	Efficacy outcomes	Safety outcomes
	NYHA class at 3 months, n (%) 1: 41 (85.4) 2: 2 (4.1) 3: 5 (10.4) **3 month freedom from MR 2+ by anatomical type (p=0.43)** Type A: 100 Type B: 89 ± 6% Type C: 83 ± 11%	**Median mechanical ventilation time, hours (IQR)** 2 (0-3) **Median hospital stay, days (IQR)** 7 (6-10)
Wrobel, 2019	**Median operative time, min (IQR)** 115 (65-175) **Post-procedure MR, n (%)** Trace to mild: 33 (90) Mild to moderate: 3 (8) Moderate 1 (2)	**Median blood loss, ml (range)** 300 (100-1280) **Median ICU stay, hours (range)** 32 (22-100) **Median hospital stay, days (range)** 7 (4-17) **Surgical complications, n** 0 **Major adverse events, n** 0 **Minor adverse events, n (%)** Atrial fibrillation: 9 (24) Pleural effusion: 2 (5)

First author, date	Efficacy outcomes	Safety outcomes
		Blood transfusion: 1
Seeburger, 2014	**Post-procedure MR ≤2+, n (%, 95% CI)** 26 (87, 69-96) **30-day MR ≤2+, n (%, 95% CI)** 17 (59, 39-77) 71% of these maintained MR grade ≤1+ **Acute procedural success, n (%)** 26 (87)	**Any major adverse event, n (%)** 8 (27) **Death, n (%)** 1 (3) **Reoperation for failed repair, n (%)** 6 (20) **Procedure-related blood transfusion >2 units of blood, n (%)** 5 (17) **Procedural ventilation >48 hours, n (%)** 1 (3) **Stroke (transient), n (%)** 1 (3)
Kurnicka, 2019	**Procedural success, %** 100 **MR grade post-procedure, %** Trivial: 43 Mild: 57 **MR grade 6 months, %** Trivial: 14 Mild: 67 Moderate: 19 **NYHA class at 6 months, %**	**Postoperative complications** 0 **Conversion to conventional surgery** 0

First author, date	Efficacy outcomes	Safety outcomes
	Class 1: 100 **Mean LAV, ml (SD)** Preoperative: 84.5±23.3 6 months: 58.5±16.6 p<0.0001 **Mean LAVi, ml/m^2 (SD)** Preoperative: 44.9±10.6 6 months: 31.1±7.5 p<0.0001 **Mean LVEDD, ml (SD)** Preoperative: 55.4±6.7 6 months: 50.2±5.6 p<0.0001 **Mean LVESD, ml (SD)** Preoperative: 37.5±6.9 6 months: 34.2±4.1 p=0.005 **Mean LVEDV, ml (SD)** Preoperative: 123.9±44.3 6 months: 91.1±25.3 p<0.0001 **Mean LVESV, ml (SD)** Preoperative: 59.8±29.7 6 months: 42.7±11.4 p=0.006	

Procedure technique

All the included studies performed the NeoChord procedure using the NeoChord DS1000 device. Technique was consistent throughout the included studies. Seeburger (2014) revised the surgical access to a posterolateral apical approach (introduced after 15 patients received implants) during the study and presented both separate and combined results.

Efficacy

Composite success endpoints

Success outcomes were reported in 10 studies with varying definitions and use of MVARC criteria.

In the prospective case series Colli (2015), early procedural success was defined as implantation of at least two neochordae with immediate reduction in MR to less than 2+ after the procedure and was achieved in 100% of people in the study. Considering the different MV anatomical types, the 30-day procedural success rate was 95% in type A, 92% in Type B, and 71% in type C.

In the prospective case series by Colli (2016), acute procedural success was defined as the successful placement of a least three neochordae with a reduction in residual MR to less than 2+ and was achieved in 100% of people in the study. Echocardiographic success was defined as freedom from residual MR of 2+ or more. At 3 month follow-up, echocardiographic success was achieved in 90% (SD=4%) of people in the study. Considering the different MV anatomy types, 3 month freedom from MR of 2+ or greater was 100% in Type A, 89% (SD= 6%) in Type B and 83% (SD=11%) in Type C. However, the difference was not statistically significant between the groups (p = 0.43).

In the prospective case series Colli (2018a), procedural success was achieved in 98% of people who had the procedure. A composite 1 year treatment success endpoint was also established based on MVARC criteria. The treatment was considered a success if the person undergoing treatment met the following criteria at the 1 year follow-up: (i) technical success including the placement of at least 2 neochordae and residual mitral regurgitation mild or less at the end of the procedure; (ii) freedom from major adverse events such as death, stroke, mitral regurgitation higher than moderate, structural or functional valvular failure and/or unplanned interventions related to the procedure or device at 1 year and (iii) freedom from a decline in baseline symptoms. This endpoint was achieved in 89% (SD=3%) of patients.

In the retrospective registry study Colli (2018b), outcome definitions were based on the MVARC guidelines. Procedural success (defined as the placement of at least 2 neochordae and mild or less MR at the end of the procedure) was achieved in 97% of people.

In the retrospective case series D'Onofrio (2023), outcome definitions for technical, device, procedural and patient success were based on MVARC guidelines. Technical and procedural success were 98% and 94%, respectively. Device success was 94%, 92%, and 78%, at 30 days, 1 year, and 5 years, respectively. Patient success at 1 year was 92%.

In the retrospective registry study Gerosa (2021), patient and procedural success were defined according to MVARC guidelines. Procedural success was defined as the placement of at least 2 neochordae and achievement of mild or less MR. The primary endpoint was patient success, a composite of procedural success, freedom from death, stroke, MR greater than moderate, unplanned interventions related to the procedure, cardiac-related rehospitalization, or worsening New York Heart Association (NYHA) functional class at each year of follow-up.

Procedural success was achieved in 99% of people who had the procedure. The rate of patients achieving the primary endpoint of patient success was 91% (SD=2%) at 1 year, 90% (SD=2%) at 2 years, and 81% (SD=4%) at 3 years. Considering the different MV anatomical types, the rate of patient success at 3 years was 88% (SD=5%) for type A, 84% (SD=5%) for type B, 73% (SD=12%) for type C, and 57% (SD=19%) for type D. The rate was statistically significantly different (P=0.001) between anatomical categorical types.

In the prospective case series Kurnicka (2019), early procedural success was defined as placement of at least 2 neochordae with a significant reduction of MR (reduction of regurgitation from severe to trace/mild). This outcome was achieved in 100% of people who had the procedure. At 6 month follow-up, MR remained trace or mild in 81% of people.

In the prospective case series Samalavicius (2018), procedural success was reported in 99% of people who had the procedure. However, this outcome was not defined.

In the prospective case series Seeburger (2014), acute procedural success was defined as the placement of at least 1 neochordae and reduction of MR to 2+ or less. 87% of people who had the procedure achieved acute procedural success.

MR reduction

MR outcomes were reported in 12 studies with varying grading scales and multiple source guidelines used.

In the prospective case series Colli (2016), MR severity was graded according to ASE guidelines. All people included in the study cohort had severe MR (3 or 4+) at baseline. At discharge, 45% had MR grade 0+, 29% had MR grade 1+, 22% had MR grade 2+, and 4% had MR grade 3+. At 3 month follow-up, 33% had MR grade 0+, 31% had MR grade 1+, 25% had MR grade 2+, and 10% had MR

grade 3+. Considering the different MV anatomical types, 3 month freedom from MR greater than 2+ was 100% in type A, 89% (SD=6%) in Type B, and 83% (SD=6%) 11% in Type C. However, this difference was not statistically significant (p=0.43).

In the prospective case series Colli (2015), MR severity was graded according to ASE guidelines. At baseline, 11% of people included in the study had MR grade 3+, and 89% had MR grade 4+. At discharge, 51% had MR grade 0+, 35% had MR grade 1+, 11% had MR grade 2+, 2% had MR grade 3+, and 2% had MR grade 4+. At 30-day follow-up, 46% had MR grade 0+, 25% had MR grade 1+, 16% had MR grade 2+, 11% had MR grade 3+, and 2% had MR grade 4+. Considering the different anatomical types at 30-day follow-up, type A anatomy was associated with the best outcomes as 95% of people in this group had MR grade of 1+ or less. 46% of people with type B anatomy had MR grade of 0+, 35% had grade 1+, 15% had grade 2+, and 4% had grade 3+. 14% of people with type C anatomy had MR grade of 0+, 7% had grade 1+, 43% had grade 2+, 29% had grade 3+, and 7% had grade 4+.

In the prospective case series Colli (2018a), residual MR was classified as absent, mild, moderate or severe. MR severity was evaluated using a combination of semi-quantitative (vena contracta width and pulmonary vein flow) and quantitative parameters (regurgitant volume) according to the ASE guidelines. At baseline, all people included in the study cohort had severe MR. At discharge, 31% had no/trivial MR, 53% had mild MR, 15% had moderate MR, and 1% had severe MR. At 1 year follow-up, 39% had no/trivial MR, 39% had mild MR, 22% had moderate MR, and 3% had severe MR.

In the retrospective registry study Colli (2018b), postoperative MR was assessed with transthoracic echocardiography independently by each centre's investigators according to ASE criteria. All people included in the study cohort had severe MR

at baseline. At discharge, 41% had absent/trace MR, 45% had mild MR, 12% had moderate MR, and 2% had severe MR. At 1 year follow-up, 31% had absent/trace MR, 44% had mild MR, 17% had moderate MR, 8% had severe MR. Considering the different anatomical types at discharge, type A anatomy was associated with the best outcomes as 95% of people in this group had MR grade of absent/trace or mild. 35% of people with type B anatomy had MR grade of absent/trace, 51% mild, 13% moderate, and 1% severe. 23% of people with type C anatomy had MR grade of absent/trace, 40% mild, 30% moderate, and 7% severe. At 1 year follow-up, a similar trend was observed with type A anatomy associated with improved MR grade outcomes compared to type B and C.

In the retrospective propensity-matched cohort study D'Onofrio (2022), the severity of mitral valve regurgitation was graded as mild (1+), moderate (2+) and severe (3+) according to the ASE guidelines. All people included in the study had severe MR at baseline. Patients undergoing the NeoChord procedure showed worse freedom from moderate MR (2+ or more) at 5 year follow up compared to conventional surgery: 58% (95% CI 43-77) and 84.6% (95% CI 76-95) in the NeoChord and conventional groups respectively (p=0.001). Freedom from severe MR at 5 year follow up was also lower in the NeoChord group compared to the conventional group: 78% (95% CI 65-93) and 90% (95% CI 82-98) for the NeoChord and conventional groups respectively (p=0.032).

In the retrospective case series D'Onofrio (2023), MR severity was graded as absent/trace (0), mild (1+), moderate (2+), and severe (3+) according to the ASE criteria. All people included in the study cohort had severe MR at baseline. At discharge, 31% had absent/trace MR, 53% had mild MR, 14% had moderate MR, and 1% had severe MR. At 5 year follow up, 8% had absent/trace MR, 51% had mild MR, 30% had moderate MR, and 11% had severe MR. Overall cumulative incidence of severe MR recurrence was 9% (95% CI, 4-15) at 1 year, 12% (95% CI, 6-19) at 3 years, and 24% (95% CI, 15-33) at 5 years. Patients with

favourable anatomy (type A and B) compared with unfavourable anatomy (type B and C) had a lower incidence of severe MR recurrence over the same period with 6% compared to 22% at 1 year; 8% compared to 33% at 3 years; and 15% compared to 63% at 5 years (P=0.001)

In the retrospective registry study Gerosa (2021), MR severity was graded as absent/trivial, mild, moderate and severe according to ASE and ESC guidelines. All people included in the study cohort had severe MR at baseline. At discharge, 42% had absent/trivial MR, 45% had mild MR, 10% had moderate MR, and 3% had severe MR. At 3 year follow-up, 12% had absent/trivial MR, 52% had mild MR, 30% had moderate MR, 6% had severe MR. Considering the different MV anatomical types, freedom from MR recurrence of moderate or higher was 88% (SD=5%) in type A, 8% (SD=4%) in type B, 73% (SD=12%) in type C, and 48% (SD=18%) in type D (p=0.001).

In the prospective case series Kurnicka (2019), MR severity was graded as absent, mild, moderate and severe according to ASE and ESC guidelines. Baseline MR data was not reported. Postoperatively, 43% had trace MR, and 57% had mild MR. At 6 month follow-up, 14% had trace MR, 67% had mild MR, and 19% had moderate MR.

In the prospective case series Samalavicius (2018), MR severity was graded according to AHA/ACC and ESC guidelines. At baseline, 67% of people had MR grade 3+, and 33% had MR grade 4+. After the procedure, 56% of people had trivial MR, 36% had grade 1+ MR, 5% had grade 2+ MR, and 3% had higher than grade 2+ MR.

In the prospective case series Seeburger (2014), MR severity was graded according to AHA/ACC guidelines. At baseline, 10% of people included in the study had MR grade 3+, and 90% had MR grade 4+. Post-procedure, 87% (95% CI, 70-96) had MR grade of 2+ or less. At the 30-day follow-up, 59% (95% CI,

39-77) had an MR grade of 2+ or less, with 71% of these people maintaining an MR grade of 1+ or less.

In the prospective case series Wrobel (2019), MR severity was described according to the EACVI recommendations for the assessment of native valvular regurgitation. Post-procedure, 90% of people in the study had trace/mild MR, 8% had mild/moderate MR, and 2% had moderate MR.

In the retrospective cohort study Zorinas (2019), source guidelines for the description of MR severity were not reported. All people included in the study had severe MR at baseline. Post-procedure, 100% of people in the conventional surgery group had MR grade absent or mild, compared to 92% in the NeoChord procedure group. At 30-day follow-up, zero patients in the conventional surgery had MR grade severe, compared to 8% in the NeoChord procedure group (p=0.001).

NYHA functional class

NYHA functional outcomes were reported in 5 studies. All studies showed a durable improvement from baseline after the NeoChord procedure.

In the prospective case series Colli (2016), 6% of people were NYHA class 1, 58% class 2, 36% class 3, and 1% class 4 at baseline. All successfully treated patients showed an improvement in NYHA functional class at 3 months; 85% were in NYHA class 1, 4% in class 2, and 10% in class 3. Considering NYHA functional class across the different MV anatomical types at 3 month follow-up; 100% of type A were in class 1, 96% of type B were in class 1, and 67% of type C were in class 1.

In the prospective case series Colli (2015), 5% were NYHA Class one, 40% NYHA Class 2, 49% in NYHA Class III and 6% in NYHA Class 4 at baseline. Clinical improvement was observed in all successfully treated patients. At the 30-

day follow-up, 87% were in NYHA Class one, 6% in NYHA Class 2 and 6% in NYHA Class 3. Considering NYHA functional class across the different MV anatomical types at 30-day follow-up; 100% of type A were in class 1, 88% of type B were in class 1, and 71% of type C were in class 1.

In the propensity matched study D'Onofrio (2022), significant improvement of NYHA functional class with respect to baseline was observed in both groups ($P < 0.001$) with more than 90% of patients in NYHA class I and II at follow-up.

The retrospective case series D'Onofrio (2023) reported 7% of people as NYHA class 1 at baseline, 38% in class 2, and 52% class 3. At discharge, the proportion of people in NYHA class 1 increased to 99%, decreasing to 78% at the 5 year follow-up.

The prospective case series Kurnicka (2019) reported 29% of people were NYHA class 1 at baseline, 57% in class 2, and 14% in class 3. At 6 month follow up, all people in the study were NYHA class 1.

Survival

Survival was reported in 5 studies. Length of follow-up for this outcome ranged from 3 months to 5 years.

Colli (2016) estimated overall survival using the KM method. Overall survival at 3 months was 97% (SD= 2%), no p-value was reported. In Colli (2018b), overall survival at 1 year was reported as 98%, with 4 high-risk patients dying during the study. In D'Onofrio (2022), overall all-cause mortality was similar between the NeoChord and conventional surgery groups. KM analysis showed 5 year survival of 92% (95% CI, 82 to 100) and 96% (95% CI, 91 to 100) in the NeoChord and conventional surgery groups respectively. In people with type A anatomy, survival was 100% in the NeoChord group, and 93% (95% CI, 84 to 100) in the conventional surgery group. In D'Onofrio (2023), KM analysis estimated overall

survival at 5 years of 84% (95% CI, 76% to 92%). There was no statistically significant difference in terms of survival (p=0.13) between favourable anatomy (type A and B), and unfavourable anatomy (type B and C). Gerosa (2021) reported a KM survival estimate of 99% (SD=1%) at 1 and 2 years and 94% (SD=3%) at 3 years. All deaths were cardiovascular, and all deceased patients were elderly with multiple severe comorbidities.

Reintervention

Reintervention was reported in 6 studies. Reasons for reintervention were new neochordae implantation, re-tensioning, recurrent severe MR, and failed repair.

Colli (2016) reported 4 cases (8%) of reoperation for NeoChord procedure failure at 3 months. One person underwent a further NeoChord procedure, and 3 had mitral valve replacement. Colli (2015) reported 8 cases (13%) of reoperation for NeoChord procedure failure at 30 days. One person required new neochordae implantation, 2 required neochordae re-tensioning, 3 underwent conventional mitral valve repair, and 2 underwent mitral valve replacement. Colli (2018a) reported 4 cases (4%) of reintervention due to recurrent MR at 1 year follow-up. Colli (2018b) reported 7 people (4%) with severe MR at 6 month follow up underwent conventional MV reintervention. D'Onofrio (2022) reported that 5 year freedom from reoperation in the NeoChord group was 79% (95% CI, 66 to 95), and 92% (95% CI, 85 to 99) in the conventional surgery group (p=0.022). However, in anatomical type A patients, the difference in freedom from reoperation between NeoChord and conventional surgery groups was not statistically significant. During a median follow-up of 3.4 years, 11 people in the NeoChord group had the reoperation; of these, 4 were re-repair, 6 were replacements and 1 was a further NeoChord procedure. In D'Onofrio (2023) the overall cumulative incidence of reoperation was 17% (95% CI, 9 to 24) at 5 years. People with favourable anatomy (type A and B) had a lower incidence of reintervention at 5 years compared to people with unfavourable anatomy (type B

and C); 15% compared to 43% respectively (p=0.001). Gerosa (2021) reported 13 (6%) people required reoperation for recurrent MR at 3 years. Seeburger (2014) reported 6 (20%) cases of reoperation due to failed repair.

Echocardiographic outcomes

LVEF

D'Onofrio (2022) reported a median LVEF of 55% (IQR 59 to 68) at discharge after the NeoChord procedure, a reduction from a median of 64% (IQR 59 to 68) at baseline. This increased to 59% (IQR 55.5 to 62.5) after a median follow-up of 3.4 years. D'Onofrio (2023) showed similar results, with an initial reduction at discharge from median 61% (IQR 57 to 67) to 57% (IQR 53 to 60). Median LVEF at 5 year follow-up was 59% (IQR 56 to 64) (p=0.09). Kurnicka (2019) did not report a statistically significant change between LVEF at baseline compared to 6 month follow-up.

LVEDV

D'Onofrio (2022) reported median LVEDVi at discharge 76ml/m^2 (IQR 58.5 to 86.5), a reduction from 82ml/m^2 (IQR 67.3 to 95) at baseline. This further reduced to 66ml/m^2 (IQR 66 to 72) at median follow-up of 3.4 years. D'Onofrio (2023) reported a reduction from 82ml/m^2 (IQR 70 to 79) at baseline to 68ml/m^2 at discharge, with a further reduction of 6ml/m^2 at 5 year follow-up. Kurnicka (2019) reported a statistically significant reduction in LVEDV from 123.9ml (SD= 44.3) at baseline to 91.1ml (SD=25.3) at 6 month follow-up (p<0.0001).

LVESV

D'Onofrio (2023) reported a reduction from 33ml/m^2 (IQR 25 to 39) at baseline to 29ml/m^2 (IQR 24 to 37) at discharge, with a further reduction of 4ml/m^2 at 5 year follow-up. Kurnicka (2019) reported a statistically significant reduction in LVESV

from 59.8ml (SD=29.7) at baseline to 42.7ml (SD=11.4) at 6 month follow-up (p=0.006).

LAVi

D'Onofrio (2023) reported a reduction from 55ml/m^2 (IQR 42 to 56) at baseline to 45ml/m^2 (IQR 35 to 57) at discharge, with a further reduction of 2ml/m^2 at 5 year follow-up. Kurnicka (2019) reported a statistically significant reduction in LAVi from 44.9ml/m^2 (SD=10.6) at baseline to 31.1ml (SD= 7.5) at 6 month follow-up (p<0.0001).

sPAP

D'Onofrio (2023) reported a reduction from 33mmHg (IQR 26 to 41) at baseline to 29mmHg (IQR 24 to 39) at discharge, with a further reduction of 4mmHg at 5 year follow-up.

Operative time

Operative time was reported in 10 studies. Median operative time ranged from 115 minutes to 130 minutes across these studies for the NeoChord procedure. In D'Onofrio (2022) median operative time was 2.0 hours (IQR 1.8 to 2.5) for the NeoChord procedure, and 4.0 (IQR 3.5 to 4.0) for conventional surgery. Similar operative times were reported in Zorinas (2019), with median operative time reported as 120 minutes (IQR 110 to 146) for the NeoChord procedure, and 312 minutes (IQR 280 to 361) for conventional surgery.

Length of hospital stay

Length of hospital stay was reported in 10 studies. Median hospital stay ranged from 7 to 8 days across these studies for the NeoChord procedure. In Zorinas (2019), median hospital stay was 8 days (IQR 7 to 9) for the NeoChord procedure, and 16 days (IQR 14 to 21) for conventional surgery.

Safety

In-hospital and 30-day deaths

Early deaths occurred in 7 of the included studies. No procedural deaths occurred in any study. The primary reason for in-hospital death was cardiovascular dysfunction, other reasons included post-cardiotomy syndrome with concomitant sepsis and multi-organ failure, and bleeding-related tamponade. People who died after the procedure were considered high-surgical risk, with multiple comorbidities. In-hospital deaths ranged from 1% to 2% across all studies, and D'Onofrio (2023) reported a 30-day mortality of 2% for the NeoChord procedure.

Major adverse events

Cardiovascular or cerebrovascular

Major cardiovascular or cerebrovascular adverse events such as myocardial infarction and stroke were reported at a rate of 2% or fewer at follow-up in all 12 studies.

Septicaemia

In Colli (2015), 2 (3%) of people in the study developed septicaemia after the procedure, similar rates were reported in Colli (2016) and Samalavicius (2018). Seeburger (2014) reported 0 septicaemia occurrences. This outcome was not reported in the remaining studies.

Major or extensive bleeding

Bleeding was reported in 7 of the included studies. The proportion of people who experienced major or extensive bleeding ranged from 3% to 5% across all studies. Colli (2016) reported 8% of people had intraoperative bleeding requiring

at least 2 units of blood, however none needed surgical revision for bleeding. In Samalavicius (2018), 3% of people who underwent the procedure required re-exploration for bleeding. Zorinas (2019) reported that postoperative blood loss in the NeoChord procedure group was statistically significantly lower compared to the conventional surgery group with 200ml compared to 300ml respectively (p = 0.001).

Minor adverse events

Kidney injury

8% of people in Colli (2016) developed acute renal failure, one of these patients required CVVH. 12% of people in Colli (2018a) developed AKI, the majority of which was stage 1. However, 2 patients developed stage 3 AKI and required CVVH. Four more studies reported the rate of post-procedure kidney injury between 3 to 7%. Notably, Zorinas (2019) reported the proportion of renal failure of the NeoChord procedure compared to conventional surgery as 3% and 15% respectively (p=0.007).

Atrial fibrillation (AF)

New onset AF post-procedure was reported in 5 studies. AF can be paroxysmal (intermittent) or permanent. Proportions of people developing AF after the procedure ranged from 12% in Samalavicius (2018) to 28% in D'Onofrio (2023). In Colli (2018b), 19% of people developed paroxysmal AF, and 3% developed persistent AF. In D'Onofrio (2022), 6% of people who underwent the NeoChord procedure developed AF, and 34% of people who underwent conventional surgery developed AF. Similar results were reported in Zorinas (2019) with 12% of people who underwent the NeoChord procedure developing AF compared to 25% in the conventional surgery group (p=0.031).

Pleural or pericardial effusion

Pericardial effusion was reported in 4 studies and was categorised as minor or major. The proportion of people who experienced major pericardial effusion varied between 1% in Colli (2018b) and 6% in Colli (2016). Colli (2018a) reported that 6% of people in the study experienced minor pleural effusion.

Pleural effusion was reported in 4 studies and was also categorised as minor or major. Colli (2018a) reported 62% of people who underwent the procedure experienced minor pleural effusion, and 2% major pleural effusion. Similar results were reported in Colli (2018b) with 40% of people experiencing minor pleural effusion, and 1% major. Gerosa (2021) and Wrobel (2019) reported rates of major pleural effusion of 2% and 5% respectively.

Anecdotal and theoretical adverse events

Expert advice was sought from consultants who have been nominated or ratified by their professional society or royal college. They were asked if they knew of any other adverse events for this procedure that they had heard about (anecdotal), which were not reported in the literature. They were also asked if they thought there were other adverse events that might possibly occur, even if they had never happened (theoretical).

They listed the following anecdotal adverse events:

- Cardiac arrythmias or conduction disturbances
- Infection

They listed the following theoretical adverse events:

- Heart failure

- Emergency surgery

Five professional expert questionnaires for this procedure were submitted. Find full details of what the professional experts said about the procedure here https://www.nice.org.uk/guidance/indevelopment/gid-ipg10216/documents.

Validity and generalisability

- Sample sizes were small across all studies due to the limited use of this procedure in clinical practice and novelty of the NeoChord DS1000 device. The largest sample size was 213 in Colli (2018b), while the smallest was 21 in Kurnicka (2019). These smaller studies lack statistical power and are not generalisable.
- None of the included studies were conducted in the UK or contained UK data. Study centres were located in Italy, Lithuania, Germany, Poland and Denmark. This limits generalisability to the UK context.
- Follow-up ranged from 30 days to 5 years across all studies, providing some insight into long-term outcomes. However, more robust long-term studies are needed to assess the durability of artificial chordae implanted with the NeoChord procedure. Long-term outcomes are particularly important for this procedure.
- The potential for bias is very high as all studies are non-randomised and observational, and many are retrospective case series.
- Patient selection bias is likely across all studies because patients underwent anatomical screening before the NeoChord procedure.
- Key evidence gaps remain in long-term outcomes beyond 5 years, quality-of-life outcomes and patient-reported outcomes focusing on different subgroups. A larger number of patients and longer follow-up are needed to assess the definitive value of this therapeutic approach.

- In the comparative studies, people who underwent the NeoChord procedure were strictly followed up through clinical and echocardiographic assessment at scheduled timepoints. However, many people who underwent conventional surgery were followed up by their referral cardiologist, therefore, the possible underestimation of valve-related adverse events in the conventional surgery population cannot be excluded.
- The determination of the exact positioning, length adjustment, and neochordae tensioning depends exclusively on the ability and training of the operator and echocardiographer. Variations in experience and skill across the operators in the studies could introduce bias into the results.
- Study endpoints were not consistent across the studies and often contained composite outcomes based to varying degrees on MVARC criteria, limiting comparison of efficacy outcomes across the studies.
- Different criteria were used to grade residual MR across the studies, limiting comparison of results across the studies.
- Measurement and interpretation of MR is operator-dependant and therefore a potential source of bias
- There is likely substantial overlap in the populations of some of the included studies. There is a high potential for selection bias.
- Many authors of the included studies have potential financial conflicts of interest with the manufacturer of this device (NeoChord, Inc), including providing consulting services, receiving travel grants, and proctoring.

Ongoing trials

NCT02803957 Randomized Trial of the NeoChord DS1000 System Versus Open Surgical Repair (ReChord) is a multicentre, open-label trial to assess the safety and effectiveness of the NeoChord DS1000 device in subjects with degenerative mitral valve disease receiving a mitral valve repair without cardiopulmonary

bypass (treatment group) when compared to subjects receiving mitral valve repair using standard surgical techniques with cardiopulmonary bypass (control group). Sponsor: NeoChord, USA. Estimated completion: July 2027.

NCT04190602 Multicentre Post-Market Observational Registry of the NeoChord Artificial Chordae Delivery System (AcChord) is an observational, single-arm, multicentre post-market registry. The objective of this study is to evaluate the 5 year outcomes of participants with degenerative mitral valve disease treated with the NeoChord DS1000 in a post-market setting. Sponsor: NeoChord, USA. Estimated completion: December 2027.

Related NICE guidance

Interventional procedures

Percutaneous mitral valve leaflet repair for mitral regurgitation (2019) NICE interventional procedures guidance [IPG649]. (Recommendation: standard arrangements).

Percutaneous mitral valve annuloplasty (2010) NICE interventional procedures guidance [IPG352]. (Recommendation: research only)

Thoracoscopically assisted mitral valve surgery (2007) NICE interventional procedures guidance [IPG245]. (Recommendation: standard arrangements)

NICE guidelines

Heart valve disease presenting in adults: investigation and management (2021) NICE guideline NG208.

Professional societies

- The Society for Cardiothoracic Surgery in Great Britain and Ireland

- British Cardiovascular Intervention Society
- British Society for Heart Failure
- British Cardiovascular Society
- British Society for Echocardiography
- The Royal College of Surgeons of England
- Royal College of Physicians London
- The Royal College of Physicians of Edinburgh
- The Royal College of Surgeons of Edinburgh
- The Royal College of Physicians and Surgeons of Glasgow
- NHS England
- NHS Scotland.

Company engagement

NICE asked companies who manufacture a device potentially relevant to this procedure for information on it. NICE received 1 completed submission. This was considered by the interventional procedures technical team and any relevant points have been taken into consideration when preparing this overview.

References

1. Colli A, Manzan E, Rucinskas K, Janusauskas V, Zucchetta F, Zakarkaitė D, Aidietis A, Gerosa, G. (2015) Acute safety and efficacy of the NeoChord procedure. Interactive cardiovascular and thoracic surgery. 20(5): 575-581. doi:10.1093/icvts/ivv014
2. Colli A, Manzan E, Zucchetta F, Bizzotto E, Besola L, Bagozzi L, Bellu R, Sarais C, Pittarello D, Gerosa G. (2016) Transapical off-pump mitral valve repair with Neochord implantation: early clinical results. International journal of cardiology. 204: 23-28. doi: 10.1016/j.ijcard.2015.11.131.
3. Colli A, Bagozzi L, Banchelli F, Besola L, Bizzotto E, Pradegan N, Fiocco A, Manzan E, Zucchetta F, Bellu R, Pittarello D. (2018) Learning curve analysis of transapical NeoChord mitral valve repair. European Journal of Cardio-Thoracic Surgery. 54(2):273-80. doi: 10.1093/ejcts/ezy046

4. Colli A, Manzan E, Aidietis A, Rucinskas K, Bizzotto E, Besola L, Pradegan N, Pittarello D, Janusauskas V, Zakarkaite D, Drasutiene A. (2018) An early European experience with transapical off-pump mitral valve repair with NeoChord implantation. European Journal of Cardio-Thoracic Surgery. 54(3):460-6. doi:10.1093/ejcts/ezy064

5. D'Onofrio A, Mastro F, Nadali M, Fiocco A, Pittarello D, Aruta P, Evangelista G, Lorenzoni G, Gregori D, Gerosa G. (2022) Transapical beating heart mitral valve repair versus conventional surgery: a propensity-matched study. Interactive CardioVascular and Thoracic Surgery. 35(1):ivac053. doi: doi.org/10.1093/icvts/ivac053

6. D'Onofrio A, Fiocco A, Nadali M, Mastro F, Aruta P, Lorenzoni G, Pittarello D, Gerosa G, Evangelista G, Longinotti L, Gregori D. (2023) Outcomes of transapical mitral valve repair with neochordae implantation. The Journal of Thoracic and Cardiovascular Surgery. 165(3):1036-46. doi: 10.1016/j.jtcvs.2022.02.059

7. Gerosa G, Nadali M, Longinotti L, Ponzoni M, Caraffa R, Fiocco A, Pradegan N, Besola L, D'Onofrio A, Bizzotto E, Bellu R. (2021) Transapical off-pump echo-guided mitral valve repair with neochordae implantation mid-term outcomes. Annals of Cardiothoracic Surgery. 10(1):131. doi: 10.21037/acs-2020-mv-86

8. Kurnicka K, Wróbel K, Zdończyk O, Bielecki M, Juraszyński Z, Biederman A, Pruszczyk P. (2019) Early echocardiographic results of transapical off-pump mitral valve repair with the NeoChord DS1000 device in patients with severe mitral regurgitation due to posterior leaflet prolapse: first experiences in Poland. Advances in Interventional Cardiology/Postępy w Kardiologii Interwencyjnej. 15(1):20-7. doi:10.5114/aic.2019.81438

9. Samalavicius RS, Norkiene I, Drasutiene A, Lipnevicius A, Janusauskas V, Urbonas K, Zakarkaite D, Aidietis A, Rucinskas K. (2018) Anesthetic management and procedural outcomes of patients undergoing off-pump transapical implantation of artificial chordae to correct mitral regurgitation: case series of 76 patients. Anesthesia & Analgesia. 126(3):776-84. doi: 10.1213/ANE.0000000000002767

10. Seeburger J, Rinaldi M, Nielsen SL, Salizzoni S, Lange R, Schoenburg M, Alfieri O, Borger MA, Mohr FW, Aidietis A. (2014) Off-pump transapical implantation of artificial neo-chordae to correct mitral regurgitation: the TACT Trial (Transapical Artificial Chordae Tendinae) proof of concept. Journal of the American College of Cardiology. 63(9):914-9. doi:10.1016/j.jacc.2013.07.090

11. Wróbel K, Kurnicka K, Zygier M, Zielinski D, Dyk W, Wojdyga R, Juraszynski Z, Pruszczyk P, Biederman A. (2019) Transapical beating heart

mitral valve repair with the NeoChord system: early outcomes of a single-center experience. Videosurgery and Other Miniinvasive Techniques. 14(2):320-5. doi: 10.5114/wiitm.2019.82738

12. Zorinas A, Lipnevicius A, Bleizgytė V, Janušauskas V, Liekienė D, Budra M, Samalavičius R, Drąsutienė A, Zakarkaitė D, Aidietis A, Ručinskas K. (2019) Comparison of early postoperative results between conventional and transapical mitral valve repair. Advances in Interventional Cardiology/Postępy w Kardiologii Interwencyjnej. 15(4):439-45. doi: 10.5114/aic.2019.90218

Appendix A: Methods and literature search strategy

NICE has identified studies and reviews relevant to beating heart mitral valve repair by artificial chordae insertion for mitral regurgitation from the medical literature.

Search strategy design and peer review

This search report is informed by the Preferred Reporting Items for Systematic reviews and Meta-Analyses literature search extension (PRISMA-S).

A NICE information specialist ran the literature searches on 06 May 2025. See the search strategy history for the full search strategy for each database. Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The principal search strategy was developed in MEDLINE ALL (Ovid interface). It was adapted for use in each of the databases listed in table 4a, taking into account the database's size, search functionality and subject coverage. The MEDLINE ALL strategy was quality assured by a NICE senior information specialist. All translated search strategies were peer reviewed to ensure their accuracy. The quality assurance and peer review procedures were adapted from the Peer Review of Electronic Search Strategies (PRESS) 2015 evidence-based checklist.

Review management

The search results were managed in EPPI-Reviewer version 5 (EPPI-R5). Duplicates were removed in EPPI-R5 using a 2-step process. First, automated deduplication was done using a high-value algorithm. Second, manual deduplication was used to assess low-probability matches. All decisions about inclusion, exclusion and deduplication were recorded and stored.

Limits and restrictions

The CENTRAL database search removed trial registry records and conference material. The Embase search excluded conference material.

English language limits were applied to the search when possible in the database.

The limit to remove animal studies in the searches is standard NICE practice, which has been adapted from Dickersin K, Scherer R, Lefebvre C (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. BMJ 309(6964): 1286.

Main search

Table 4a Main search results

Database	Date searched	Database platform	Database segment or version	Number of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	06/05/2025	Wiley	Issue 4 of 12, April 2025	5
Cochrane Database of Systematic Reviews (CDSR)	06/05/2025	Wiley	Issue 5 of 12, May 2025	0
Embase	06/05/2025	Ovid	1974 to 2025 May 02	413
INAHTA International HTA Database	06/05/2025	https://database.inahta.org/	-	2
MEDLINE ALL	06/05/2025	Ovid	1946 to April 23, 2025	447

Update search

Table 4b Update search results

Database	Date searched	Database platform	Database segment or version	Number of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)		Wiley		
Cochrane Database of Systematic Reviews (CDSR)		Wiley		
Embase		Ovid		
INAHTA International HTA Database		https://database.inahta.org/		
MEDLINE ALL		Ovid		

Search strategy history

MEDLINE ALL search strategy

1 mitral valve insufficiency/ 27504

2 Mitral Valve Prolapse/ 5400

3 (Mitral adj4 (prolapse* or disease* or regurgitat* or insufficien* or rupture* or incompetence or floppy or click-murmur)).tw. 34296

4 or/1-3 46050

5 (beating heart adj5 repair*).tw. 131

6 (artificial adj4 (chord* or neo-chord*)).tw. 406

7 (implant* adj4 (chord* or neo-chord*)).tw. 179

8 or/5-7 603

9 4 and 8 432

10 NeoChord.tw. 132

11 (HARPOON and (mitral or "beating heart" or "repair system")).tw. 16

12 10 or 11 142

13 9 or 12 527

14 limit 13 to english language 484

15 animals/ not humans/ 5307231

16 14 not 15 447

Embase search strategy

1 mitral valve regurgitation/ 60107

2 Mitral Valve Prolapse/ 10727

3 (Mitral adj4 (prolapse* or disease* or regurgitat* or insufficien* or rupture* or incompetence or floppy or click-murmur)).tw. 52495

4 or/1-3 79506

5 (beating heart adj5 repair*).tw. 198

6 (artificial adj4 (chord* or neo-chord*)).tw. 574

7 (implant* adj4 (chord* or neo-chord*)).tw. 309

8 or/5-7 894

9 4 and 8 605

10 NeoChord.tw. 249

11 (HARPOON and (mitral or "beating heart" or "repair system")).tw. 23

12 10 or 11 265

13 9 or 12 775

14 limit 13 to english language 735

15 Nonhuman/ not Human/ 5683074

16 14 not 15 684

17 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 6252247

18 16 not 17 413

Cochrane Library (CDSR and CENTRAL) search strategy

#1 MeSH descriptor: [Mitral Valve Insufficiency] explode all trees 605

#2 MeSH descriptor: [Mitral Valve Prolapse] explode all trees 59

#3 (Mitral near/4 (prolapse* or disease* or regurgitat* or insufficien* or rupture* or incompetence or floppy or click-murmur)) 1696

#4 {or #1-#3} 1696

#5 (beating heart near/5 repair*) 4

#6 (artificial near/4 (chord* or neo-chord*)) 5

#7 (implant* near/4 (chord* or neo-chord*)) 4

#8 {or #5-#7} 10

#9 #4 and #8 7

#10 NeoChord 5

#11 (HARPOON and (mitral or "beating heart" or "repair system")) 0

#12 #10 or #11 5

#13 #9 or #12 10

#14 "conference":pt or (clinicaltrials or trialsearch):so 824537

#15 #13 not #14 5

INAHTA HTA Database search strategy

#1. "Mitral Valve Insufficiency"[mh]

#2. "Mitral Valve prolapse"[mh]

#3. (Mitral and (prolapse* or disease* or regurgitat* or insufficien* or rupture* or incompetence or floppy or click-murmur))

#4. #1 or #2 or #3

#5. ((beating heart) and repair*)

#6. (artificial AND (chord* or neo-chord*))

#7. (implant* AND (chord* or neo-chord*))

#8. #5 or #6 or #7

#9. NeoChord

#10. (HARPOON and (mitral or "beating heart" or "repair system"))

#11. #9 or #10

#12. #4 and #8

#13. #11 or #12

Inclusion criteria

The following inclusion criteria were applied to the abstracts identified by the literature search.

- Publication type: clinical studies were included with emphasis on identifying good quality studies. Abstracts were excluded if they did not report clinical outcomes. Reviews, editorials, and laboratory or animal studies, were also excluded and so were conference abstracts, because of the difficulty of appraising study methodology, unless they reported specific adverse events not available in the published literature.
- People with mitral regurgitation
- Intervention or test: NeoChord DS1000 System.
- Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy, or both.

If selection criteria could not be determined from the abstracts the full paper was retrieved.

Potentially relevant studies not included in the main evidence summary are listed in Appendix B: Other relevant studies.

Find out more about how NICE selects the evidence for the committee.

Appendix B: Other relevant studies

Other potentially relevant studies that were not included in the main evidence summary (tables 2 and 3) are listed in table 5 below.

Table 5 additional studies identified

Study	Number of people and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Brown A, Jefferson HL, Fatehi Hassanabad A, Noss C, Webb N, Fedak PW, Kent WD, Adams C. (2023) Echocardiographic and clinical outcomes following beating heart NeoChord DS1000 mitral valve repair: a single centre case series. Frontiers in Cardiovascular Medicine.10:1160979.	Prospective case series n=10 Follow-up: 6 weeks	All patients had severe chronic MR and normal left ventricular function. At 1 month follow-up echocardiography, MR was graded from trivial to moderate and left ventricular inner diameter dimensions decreased from an average of 5.4 ± 0.4 cm to 4.6 ± 0.3 cm. The early surgical outcomes suggest this approach is feasible, safe, and effective in reducing MR.	Larger and more relevant studies included in the summary of the key evidence.
Colli A, Besola L, Bizzotto E, Fiocco A, Denas G, Bellu R, Pradegan N, Nadali M, Gregio A, Pittarello D,	Retrospective case series n=52	Possible mechanisms of recurrent MR were identified as: patient selection	Studies with more relevant outcomes included in the

Gerosa G. (2019) Mechanisms of recurrent regurgitation after transapical off-pump mitral valve repair with neochord implantation. European Journal of Cardio-Thoracic Surgery. 56(3):479-87.		(17%), technical issues (29%), progression of baseline disease (15%), left ventricle reverse remodelling (2%), excessive over-tensioning (36%) and posterior mitral leaflet curling (31%). The mechanisms of recurrent MR after the NeoChord procedure can be used to formulate prevention strategies.	summary of key evidence.
Gonçalves-Teixeira P, Costa S, Martins D, Neves P, Ribeiro J. (2021) Transapical off-pump mitral valve repair with NeoChord™ implantation: An early single-center Portuguese experience. Revista portuguesa de cardiologia. 40(12):933-41.	Prospective case series n=18 Median follow up: 194 days	Successful repair, defined by none, trace or mild mitral regurgitation, by implantation of two to four neochordae,was achieved in all 18 patients. No major complications arose intra-procedurally In selected patients, minimally invasive mitral valve repair using the NeoChord system is safe, effective and reproducible.	Larger and more relevant studies included in the summary of the key evidence.
Manzan E, Azzolina D, Gregori D, Bizzotto E, Colli A, Gerosa G.	Prospective case series	A nomogram was developed to predict the	Studies with more relevant outcomes

(2021) Combining echocardiographic and anatomic variables to predict outcomes of mitral valve repair with the NeoChord procedure. Annals of cardiothoracic surgery. 10(1):122.	n=91 Follow up: 2 years	probability of mild or less MR at follow-up. NeoChord mitral valve repair prediction tool would be helpful in clinical decision-making and in the identification of patients who may benefit from a ringless mitral valve repair using the NeoChord procedure.	included in the summary of key evidence.
Gammie JS, Bartus K, Gackowski A, D'Ambra MN, Szymanski P, Bilewska A, Kusmierczyk M, Kapelak B, Rzucidlo-Resil J, Moat N, Duncan A. (2018) Beating-heart mitral valve repair using a novel ePTFE cordal implantation device: a prospective trial. Journal of the American College of Cardiology. 71(1):25-36.	Prospective multicentre case series n=30 Follow up: 6 months	At 1 month, MR was mild or less in 89% and was moderate in 11%. At 6 months, MR was mild or less in 85 %, moderate in 8%, and severe in 8%. MVRS ePTFE cordal implantation can reduce the invasiveness and morbidity of conventional MV surgery. The device's safety profile is promising.	Harpoon system used, device has been discontinued. Studies with NeoChord DS1000 included in the summary of key evidence.
Gammie JS, Wilson P, Bartus K, Gackowski A, Hung J, D'Ambra MN, Kolsut P, Bittle GJ, Szymanski P, Sadowski J, Kapelak B. (2016) Transapical beating-heart mitral	Prospective feasibility trial n=11	Eleven patients with posterior leaflet prolapse and severe MR were treated with 100% procedural success. Immediate	Harpoon system used, device has been discontinued. Studies with NeoChord DS1000

valve repair with an expanded polytetrafluoroethylene cordal implantation device: initial clinical experience. Circulation. 134(3):189-97.	Mean follow up: 186 days	postprocedural mean MR grade was trace. At 1 month, the mean MR grade was mild with significant decreases in end-diastolic volume This MV repair technique demonstrates a significant reduction in MR with favourable left ventricular and left atrial reverse remodelling. This approach has the potential to decrease invasiveness and surgical morbidity	included in the summary of key evidence
Gammie JS, Bartus K, Gackowski A, Szymanski P, Bilewska A, Kusmierczyk M, Kapelak B, Rzucidlo-Resil J, Duncan A, Yadav R, Livesey S. (2021) Safety and performance of a novel transventricular beating heart mitral valve repair system: 1-year outcomes. European Journal of Cardio-Thoracic Surgery. 59(1):199-206.	Prospective multicentre case-series n=62 Follow up: 1 year	95% of people achieved technical success. At 1 year, 98% of the patients with HARPOON cords were in New York Heart Association class I or II, and mitral regurgitation was none/trace in 52%, mild in 23%, moderate in 23% and severe in 2%.	Harpoon system used, device has been discontinued. Studies with NeoChord DS1000 included in the summary of key evidence.
Vairo A, Gaiero L, Marro M, Russo C, Bolognesi M, Soro P, Gallone G, Fioravanti F, Desalvo P, D'Ascenzo F, Alunni G.	Retrospective case series n=72	At follow-up, MR > moderate was found in 24.6% of people. Annular dysfunction parameters were	Studies with more relevant outcomes included in the

(2023) New echocardiographic parameters predicting successful trans-ventricular beating-heart mitral valve repair with neochordae at 3 years: Monocentric retrospective study. Journal of Clinical Medicine. 12(5):1748.	Median follow up: 34 months	the best predictors of procedural success: 3D early-systolic annulus area, 3D early-systolic annulus circumference, and 3D annulus area fractional change.	summary of key evidence.
Wang S, Meng X, Hu S, Sievert H, Xie Y, Hu X, Sun Y, Luo Z, Zhou H, Zhang G, Pan X. (2022) Initial experiences of transapical beating-heart mitral valve repair with a novel artificial chordal implantation device. Journal of Cardiac Surgery. 37(5):1242-9.	Prospective feasibility trial n=10 Follow up: 1 year	MR reduced from severe to none or trace in five patients, and mild in five patients before discharge. The safety and efficacy endpoint were achieved in all patients at 1-month follow-up. At 1-year follow-up, six patients had mild MR, three patients had moderate MR, one patient had recurrence of severe MR and underwent surgical repair.	Mitralstitch system used, device not used in the UK. Studies with NeoChord DS1000 included in the summary of key evidence.