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2. Update 2023
Systematic Review

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Project Team

Project leader: Gregor Goetz, MSSc MPH; AIHTA

Authors: Univ. Ass. Mag. rer. nat. Thomas Semlitsch, Mag.a (FH) Christine Loder, MPH;
Institute of General Practice and Evidence-Based Health Services Research, Medical University of Graz

Project Support

Systematic literature search: Tarquin Mittermayr, MA; AIHTA

External Review: PD Dr. med. Dr. Bernhard Wernly; Department of Internal Medicine, General Hospital Oberndorf, Teaching Hospital of the Paracelsus Medical University Salzburg, Oberndorf, Salzburg, Austria; Center for Public Health and Healthcare Research, Paracelsus Medical University of Salzburg, Salzburg, Austria.

Internal Review: Gregor Goetz, MSSc MPH; AIHTA

Correspondence: Gregor Goetz, MSSc MPH; AIHTA; Gregor.Goetz@aihta.at

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

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List of abbreviations

6MWT..... 6-minute walking test
AF..... atrial fibrillation
AV..... atrioventricular
CI..... confidence interval
COPD..... chronic obstructive pulmonary disease
CRD ..... Centre of Review and Dissemination
EQ-5D ..... European quality of life-5 dimensions
EROA..... effective regurgitant orifice area
GDMT..... guideline-directed medical therapy
GRADE..... Grading of Recommendations Assessment, Development and Evaluation
ICH-GCP..... International Conference of Harmonization – Good Clinical Practice
KCCQ ..... Kansas City cardiomyopathy questionnaire
LVEF..... left ventricular ejection fraction
LVESD..... left ventricular end-systolic diameter
MACE ..... major adverse cardiac event
MR..... mitral regurgitation
MV..... mitral valve
NYHA ..... New York Heart Association
OMT..... optimal medical therapy
OR ..... odds ratio
QoL ..... quality of life
RCT..... randomized controlled trial
RoB..... risk of bias
RR ..... risk ratio
RV..... regurgitant volume
RVEF ..... right ventricular ejection fraction
SAE..... serious adverse event
SD..... standard deviation
SF-36..... Short form 36
vs..... versus
WHO-ICTRP ..... World Health Organization – International clinical trial register platform

Executive Summary

Introduction

This report is the second update of the systematic review on "Perkutane Mitralklappenintervention mittels Mitralclip bei Mitralklappeninsuffizienz" initially prepared in 2010 and first updated in 2012.

2nd Update of 2010 and 2012 report

Health Problem

In mitral regurgitation (MR), the mitral valve (MV) can no longer close completely, which causes the back-flow of blood from the left ventricle into the left atrium during the ejection phase of the left ventricle. Because of this back-flow, pressure in the left atrium is increased, which in chronic cases leads to enlargement of the left atrium and a weakening of the performance of the left ventricle. This can subsequently lead to cardiac arrhythmias, heart failure and damage to other organs.

mitral regurgitation (MR): increased pressure in the left atrium

Based on the cause, a classification is made between primary (degenerative) and secondary (functional) MR.

degenerative and functional MR

Description of Technology

The mitral clip procedure is a percutaneous intervention to reduce MR. Guided by transesophageal echocardiography, the mitral clip device is placed in the proper position to clip the two MV leaflets together to restore the normal anatomy and function of the MV. The therapeutic goal of the procedure is to reduce MR severity and thereby relieve symptoms, increase physical function, improve quality of life, and prolong life. Currently, the MitraClip® is the only clip system available on the market.

mitral clip device: percutaneous intervention to reduce MR severity

Methods

This update report compares the efficacy and safety of a mitral clip device to MV repair or replacement surgery or optimal medical treatment in patients with moderate-to-severe or severe chronic MR.

A systematic literature search for RCTs was conducted in three bibliographic databases and three clinical trial registries. The study selection, data extraction and assessing the methodological quality of the studies were performed by two review authors independently from each other. If appropriate, pairwise meta-analyses were performed using the Cochrane Review Manager software, Review Manager 5.4. For the rating of the quality of evidence, the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system was used.

systematic literature search for RCTs

quality of evidence according to GRADE

Domain effectiveness

The following efficacy-related outcomes were used as evidence to derive a recommendation: overall mortality, the necessity of surgical (re-)interventions, hospitalization for heart failure, MR severity, quality of life (QoL), and physical function.

efficacy: overall mortality, MR severity, hospitalization, QoL, function

Domain safety

safety: complications, SAE

The following safety-related outcomes were used as evidence to derive a recommendation: device- or procedure-related complications, serious adverse events (SAE).

Results

Available evidence

mitral clip vs surgery: 1 RCT

mitral clip vs medical therapy: 3 RCTs

Since the previous report in 2012, results from four RCTs comparing percutaneous transcatheter MV repair using the MitraClip® device to MV surgery or optimal medical therapy have been published. No trials on other percutaneous MV clip systems could be identified. One RCT, including 279 patients with primary or secondary MR, compared MitraClip® to MV surgery. The length of follow-up was five years in this RCT. For the comparison of MitraClip® device to standard medical therapy, three RCTs, with a total of 952 patients with secondary MR ineligible for surgical interventions, were included. The length of follow-up ranged from one to three years.

Clinical effectiveness

Mitral clip versus MV surgery

mitral clip vs surgery: no difference in mortality and NYHA function, less re-interventions and less severe MR with surgery after 5 years

For the comparison of mitral clip versus MV surgery results after five years of follow-up were available on overall mortality, surgical interventions, MR severity, and physical function. There was no difference in overall mortality and NYHA functional class, but there were significantly more necessary re-interventions and significantly less patients with low to moderate MR severity in the mitral clip arm than in the MV surgery arm. Results on QoL were available after one year of follow-up, with no difference between the two interventions.

Mitral clip versus medical therapy

mitral clip vs medical therapy: no difference in mortality and hospitalization rate, less severe MR and less NYHA class with mitral clip after 1 and 2 years

QoL inconclusive

All three RCTs reported on overall mortality, cardiovascular mortality, hospitalization for heart failure, and NYHA functional class. Results on MR severity after intervention and quality of life were reported in two trials, while the number of surgical interventions during follow-up was reported only in one RCT. In general, the three included RCTs showed divergent results concerning the efficacy of a mitral clip device compared to optimal medical therapy alone. Meta-analyses in overall or cardiovascular mortality showed no statistically significant difference between MitraClip® and medical therapy alone after one and two years of follow-up, respectively. There was also no difference in hospitalization rate for heart failure after one and two years of follow-up. MitraClip® showed an advantage to medical therapy alone in terms of higher rates of patients with none to only moderate MR severity and higher rates of patients with NYHA functional class I or II (no or only slight limitations) after one or two years of follow-up. Results on QoL were inconclusive.

Safety

Mitral clip versus MV surgery

Overall, there were low rates of complications in both study groups, but during the first 30 days after the procedure, they were statistically significant with MitraClip® compared to MV surgery. There was no difference in overall SAE rates between the mitral valve clip device and MV surgery after five years of follow-up.

mitral clip vs surgery: more complications with mitral clip, SAE comparable

Mitral clip versus medical therapy

Procedure- or device-related complications in the MitraClip® arms were low in all three RCTs. There were no differences in serious adverse events after one to three years of follow-up between the mitral valve clip device and medical therapy alone.

mitral clip vs medical therapy: complication rates low with mitral clip, SAE comparable

Upcoming evidence

There are four RCTs listed in clinical trial registries, investigating percutaneous transcatheter MV repair using MitraClip® versus MV surgery. Primary completion dates range from 02/2024 to 01/2028. Four additional RCTs are listed for the comparison of the MitraClip® device versus medical therapy. Primary completion dates of these trials range from 08/2023 to 08/2025. No ongoing RCT could be identified for other percutaneous MV repair clipping systems.

4 ongoing RCTs for mitral clip vs surgery; 4 ongoing RCTs for mitral clip vs medical therapy

Conclusion

According to the available evidence, in patients with moderate-to-severe or severe mitral valve regurgitation, whether primary or secondary, who are suitable for surgery, the evaluated technology MitraClip® is shown to be comparably safe but less efficient than the alternative option of mitral valve repair surgery. The certainty of the evidence for this comparison is low. The current evidence is inconclusive for patients with secondary moderate-to-severe or severe mitral valve regurgitation, which are not eligible for mitral valve surgery, whether the assessed technology MitraClip® is more effective than the comparator medical therapy alone.

mitral clip vs surgery: less effective

mitral clip vs medical therapy: some advantages, but results inconclusive

Therefore, inclusion in the catalogue of benefits is currently not recommended. A re-evaluation is recommended in 2026.

Zusammenfassung

Einleitung

2. Update von 2010 und 2012 Berichten

Dieser Bericht ist das zweite Update des systematischen Reviews „Perkutane Mitralklappenintervention mittels Mitralclip bei Mitralklappeninsuffizienz", das 2010 erstellt und im Jahr 2012 erstmals aktualisiert wurde.

Indikation und therapeutisches Ziel

Mitralklappeninsuffizienz: Druckanstieg in linkem Vorhof, verminderte Leistungsfähigkeit der linken Herzkammer

Bei einer Mitralklappeninsuffizienz ist die zwischen linkem Vorhof und linker Herzkammer gelegene Herzklappe, die sog. Mitralklappe, nicht mehr in der Lage, sich vollständig zu verschließen. Dadurch kommt es während der Auswurfphase der linken Herzkammer zu einem Rückstrom von Blut aus der linken Herzkammer in den linken Vorhof; bei schwerer Mitralklappeninsuffizienz kann sich das Blut bis in die Lunge zurückstauen. Die Folge des Rückstroms ist ein starker Druckanstieg im linken Vorhof, der bei länger andauernder Mitralklappeninsuffizienz zu einer Vergrößerung des linken Vorhofs führt. Gleichzeitig wird die Leistungsfähigkeit der linken Herzkammer geschwächt. Ferner hat der Blutrückstrom eine Unterversorgung der Organe zur Folge, da zu wenig Blut durch die Aorta gepumpt wird.

Unterscheidung aufgrund der Ursache: degenerative (primäre) bzw. funktionelle (sekundäre) Form

Auf Grund der Ursache unterscheidet man zwei Formen der Mitralklappeninsuffizienz. Bei der primären (oder degenerativen) Mitralklappeninsuffizienz liegt ein Defekt an einer oder mehreren Komponenten der Mitralklappen vor, z. B. ein übermäßiges Wachstum der Mitralsegel oder ein Abriss von Sehnenfäden. Eine sekundäre (oder funktionelle) Mitralklappeninsuffizienz hingegen wird von einer Vorerkrankung des Herzens, wie z. B. einer Herzschwäche mit verringerter Pumpleistung der linken Herzkammer ausgelöst. Die Mitralklappe selbst ist bei dieser Form nicht krankhaft verändert.

4 Schweregrade

Grundsätzlich wird der Schweregrad einer Mitralklappeninsuffizienz mittels Herzkatheter Untersuchung beurteilt. Die Einteilung erfolgt dabei in vier Grade von leicht bis schwer.

Beschwerden: Atemnot, Leistungsminderung, Herzrhythmusstörung, reduzierte Lebenserwartung

Leichtere Formen der Mitralklappeninsuffizienz verursachen in der Regel keine Beschwerden. Bei Fortschreiten der Erkrankung treten typischerweise Symptome wie Atemnot und Leistungsminderung auf. Auch Herzrhythmusstörungen, Vorhofflimmern oder eine Herzschwäche können auftreten. Die Mitralklappeninsuffizienz ist eine progrediente Erkrankung mit reduzierter Lebenserwartung. Eine Mitralklappeninsuffizienz ist die zweithäufigste Herzklappenerkrankung im Erwachsenenalter.

primäre Form: chirurgische Rekonstruktion oder Ersatz

Eine primäre Mitralklappeninsuffizienz wird bei fortgeschrittenem Schweregrad in der Regel chirurgisch behandelt, wobei eine Reparatur der Mitralklappen die gemäß Leitlinien empfohlene Technik ist. Eine sekundäre Mitralklappeninsuffizienz wiederum wird, unabhängig vom Schwergrad, primär medikamentös behandelt, wobei eine leitliniengerechte Therapie für eine Herzinsuffizienz (ggf. inklusive Resynchronisationstherapie) erfolgen soll. Bestehen trotz optimaler medikamentöser Therapie weiterhin Symptome, kann auch bei Patient*innen mit sekundärer Mitralklappeninsuffizienz eine chirurgische Therapie erfolgen.

sekundäre Form: medikamentöse Therapie

Therapeutisches Ziel jeder Behandlung ist es, den Schweregrad der Mitralklappeninsuffizienz zu reduzieren und dadurch die Symptome zu lindern, die Leistungsfähigkeit zu steigern, die Lebensqualität zu verbessern und das Leben zu verlängern.

Beschreibung der Technologie

Mitralclip: perkutane Intervention

Das Mitralclip-Verfahren ist eine perkutane Intervention zur Reduzierung der Mitralklappeninsuffizienz. Das Grundprinzip des Verfahrens besteht dabei darin, mittels einer Klammer (Clip) die beiden Segel der Mitralklappe an der undichten Stelle miteinander zu verbinden, um so zwei kleinere Öffnungen zu schaffen. Dazu wird zunächst ein Katheter, an dem der Clip vormontiert ist, über die Leistenvene zum rechten Vorhof und dann durch die Vorhofscheidewand in den linken Vorhof gebracht. Von dort aus wird der Mitralclip – geführt unter transösophagealer Echokardiographie – in die richtige Position gebracht, um die beiden Segel an geeigneter Stelle zusammenzuklammern.

Mitralsegel werden geklammert

Clip als Alternative zu offen-chirurgischen Eingriffen bei operablen, aber auch Option für inoperable Patient*innen

Das Verfahren erfolgt unter Vollnarkose, kommt dabei jedoch ohne Thorakotomie und ohne den Einsatz einer Herz-Lungen-Maschine aus, d. h. sie wird am schlagenden Herzen durchgeführt.

Der Einsatz des Mitralclips wird sowohl als Alternative zur chirurgischen Mitralklappenrekonstruktion bzw. zum chirurgischen Mitralklappenersatz für operable Patient*innen als auch als Therapieoption für am offenen Herzen inoperable Patient*innen mit primärer oder sekundärer Mitralklappeninsuffizienz in Betracht gezogen.

Mitraclip®: derzeit einziges System

Derzeit ist der MitraClip® der Firma Abbott Cardiovascular das einzige am Markt befindliche Mitralclip-System. Der MitraClip® erhielt 2008 die CE-Zertifizierung für Europa. Seit 2013 ist es auch in den USA zugelassen.

Methoden

Dieses Update vergleicht die Wirksamkeit und Sicherheit einer perkutanen Mitralklappenintervention mittels Mitralclip mit einer chirurgischen Mitralklappenintervention (Rekonstruktion oder Ersatz) oder einer medikamentösen Behandlung bei Patient*innen mit mittelschwerer bis schwerer (Grad 3+) oder schwerer (Grad 4+) Mitralklappeninsuffizienz.

systematische Recherche nach RCTs

Es erfolgte eine systematische Literatursuche nach RCTs in drei bibliografischen Datenbanken (Medline, Embase, Cochrane Clinical Trials Registry) und drei Registern für klinische Studien (ClinicalTrial.gov, WHO-ICTRP und EU Clinical Trials) für den Zeitraum ab 2012. Die Selektion relevanter Studien, die Datenextraktion und die Bewertung der methodischen Qualität der Studien wurden von zwei Autor*innen unabhängig voneinander durchgeführt. Soweit sinnvoll und möglich, wurden paarweise Meta-Analysen durchgeführt. Zur Berechnung wurde die Cochrane Review Manager Software, Review Manager 5.4 herangezogen. Es wurden die Modelle mit festen oder zufälligen Effekten nach der Mantel-Haenszel-Methode (für dichotome Daten) oder die Inverse-Varianz-Methode (für kontinuierliche Daten) verwendet, wobei das Modell mit zufälligen Effekten bei erhöhter Heterogenität ($I^2 > 30$ %) zur Anwendung kam. Für die Bewertung der Vertrauenswürdigkeit der Evidenz wurde das GRADE-System (Grading of Recommendations Assessment, Development and Evaluation) verwendet.

Meta-Analysen, wenn sinnvoll

Bewertung der Evidenz nach GRADE

Klinische Wirksamkeit

Wirksamkeit: Gesamtmortalität, Hospitalisierung, Schweregrad, Lebensqualität, Leistungsfähigkeit

Für die Bewertung der klinischen Wirksamkeit wurden folgende Endpunkte herangezogen: Gesamtmortalität, Notwendigkeit von chirurgischen Interventionen, Hospitalisierung wegen Herzinsuffizienz, Schweregrad der Mitralklappeninsuffizienz, Lebensqualität, Leistungsfähigkeit.

Sicherheit

Sicherheit: Komplikationen, schwerwiegende unerwünschte Ereignisse

Für die Bewertung der Sicherheit wurden folgende Endpunkte herangezogen: Komplikationen im Zusammenhang mit dem Produkt bzw. der Intervention, schwerwiegende unerwünschte Ereignisse.

Ergebnisse

Verfügbare Evidenz

Mitralclip vs Operation: 1 RCT – 5 Jahre Follow-Up

Seit dem letzten Berichtsupdate im Jahr 2012 wurden Ergebnisse von vier RCTs veröffentlicht. Für den Vergleich des MitraClip® Systems versus einer chirurgischen Mitralklappenintervention bei operablen Patient*innen mit mittelschwerer bis schwerer primärer oder sekundärer Mitralklappeninsuffizienz liegen Publikationen mit Langzeitergebnissen (vier bzw. fünf Jahre Follow-Up) zu jenem RCT mit 279 Teilnehmer*innen vor, der bereits im Bericht 2012 inkludiert war.

Zu diesem Vergleich konnte kein weiterer RCTs identifiziert werden.

Mitralclip vs Medikamente: 3 RCTs – 1 bis 3 Jahre Follow-Up

Zum Vergleich des MitraClip® Systems versus medikamentöse Therapie bei inoperablen Patient*innen mit mittelschwerer bis schwerer sekundärer Mitralklappeninsuffizienz konnten drei rezente RCTs mit insgesamt 952 Teilnehmer*innen identifiziert werden. Ergebnisse wurden nach ein bis drei Jahren Follow-Up berichtet. Die eingeschlossenen RCTs sind in Bezug auf die einbezogenen Patientengruppen sehr heterogen. So schloss ein RCT nur Patient*innen ein, die nicht auf eine kardiale Resynchronisationstherapie ansprachen. Der zweite RCT (Mitra-FR) schloss Patient*innen mit einer LVEF von 15-40 % ein. Die Grenzwerte für den Einschluss hinsichtlich des Schweregrads der Mitralklappeninsuffizienz waren EROA > 20 mm^2 oder RV > 30 ml. Im Gegensatz dazu wiesen die Patient*innen in der dritten Studie (COAPT) eine LVEF von 20-50 % auf. Die Grenzwerte für den Mitralklappeninsuffizienz-Schweregrad für den Einschluss waren EROA > 30 mm^2 oder RV > 45 ml. Insgesamt hatten Patient*innen der Mitra-FR Studie eine weniger schwere Mitralklappeninsuffizienz, aber eine schwerere Herzinsuffizienz als jene in der COAPT Studie. Auch andere Parameter wie Umfang der optimalen medikamentösen Therapie, Erfahrung der Operateur*innen oder Definition der Endpunkte waren in den RCTs sehr unterschiedlich.

RCTs hinsichtlich Teilnehmer*innen, medikamentöser Therapie und Definition der Endpunkte sehr heterogen

Vertrauenswürdigkeit der Evidenz

RoB: 3 RCTs moderat, 1 RCT hoch

Von den vier eingeschlossenen RCTs wurden drei mit einem moderaten RoB und einer mit einem hohen RoB bewertet. Hauptkritikpunkt ist dabei die fehlende Verblindung von Teilnehmer*innen, Studienpersonal und Endpunkterheber*innen in allen RCTs. Insgesamt ist die Vertrauenswürdigkeit der Evidenz nach GRADE für den Vergleich Mitralclip versus chirurgische Intervention als niedrig bis sehr niedrig einzustufen. Die Vertrauenswürdigkeit der Evidenz für den Vergleich Mitralclip versus medikamentöse Therapie ist moderat bis sehr niedrig.

Klinische Wirksamkeit

Mitralclip versus chirurgischen Mitralklappenintervention

Mitralclip vs Operation: kein Unterschied bei Mortalität und Leistungsfähigkeit nach 5 Jahren

Für den Vergleich Mitralclip versus chirurgische Intervention lagen aus einem RCT zur Gesamtmortalität, zur Notwendigkeit chirurgischer Eingriffe, zum MR-Schweregrad, zur Leistungsfähigkeit und zur Lebensqualität vor. Hinsichtlich der Gesamtmortalität zeigte sich zu keinem Zeitpunkt (ein, vier oder fünf Jahre Follow-Up) ein statistisch signifikanter Unterschied zwischen Mitralclip und MV-Chirurgie (Mortalitätsrate nach fünf Jahren: 20,8 % versus 26,8 %; p=0,36).

kein Unterschied bei Lebensqualität nach 1 Jahr

Vorteil für Operation bei Schweregrad der Mitralklappeninsuffizienz und der notwendigen Re-Interventionen nach 5 Jahren

Ebenfalls kein Unterschied zwischen den Studiengruppen lag im Anteil der Personen mit eingeschränkter Leistungsfähigkeit (NYHA-Klasse ≥ III) nach fünf Jahren sowie der Lebensqualität erhoben mittels SF-36 Fragebogen nach einem Jahr vor. Statistisch signifikante Nachteile des MitraClip® gegenüber einer chirurgischen Intervention zeigten sich im Hinblick auf die Notwendigkeit einer Re-Intervention sowie den Schweregrad der Mitralklappeninsuffizienz. So lag der Anteil der Personen, bei denen eine chirurgische (Re-)Intervention notwendig war, nach fünf Jahren in der MitraClip®-Gruppe bei 27,9 %. In der Gruppe mit einer chirurgischen Mitralklappen-Rekonstruktion waren es hingegen nur 8,9 % (p>0,001). Auch der Anteil an Patient*innen mit einer weiterhin mittelschweren oder schweren Mitralklappeninsuffizienz (Grad 3+ oder 4+) war nach fünf Jahren Follow-Up in der Mitralclip-Gruppe höher als in der MV-Chirurgie-Gruppe (10 % versus 2 %).

Mitralclip versus medikamentöse Therapie

Mitralclip vs Medikamente: kein Unterschied bei Mortalität und Hospitalisierungen nach 1 und 2 Jahren

Alle drei RCTs zum Vergleich Mitralclip versus medikamentöse Therapie berichteten Ergebnisse zu Gesamtmortalität, kardiovaskulärer Mortalität, Krankenhausaufenthalte wegen Herzinsuffizienz und Leistungsfähigkeit. Ergebnisse zum Schweregrad der Mitralklappeninsuffizienz und zur Lebensqualität wurden in zwei Studien berichtet, während die Anzahl der chirurgischen Eingriffe während der Nachbeobachtung nur in einer RCT angegeben wurde. Generell waren die Ergebnisse zur Wirksamkeit eines Mitralclips im Vergleich zur optimalen medikamentösen Therapie allein in den einzelnen RCTs widersprüchlich. Meta-Analysen zur Gesamtmortalität zeigten insgesamt jedoch keinen statistisch signifikanten Unterschied zwischen MitraClip® und der alleinigen medikamentösen Therapie nach einem Jahr (RR=0,91 [95 % KI 0,72 bis 1,17]; p=0,47) bzw. zwei Jahren Nachbeobachtungszeit (RR=0,82 [95 % KI 0,56 bis 1,22]; p=0,33). Ebenso keine statistisch signifikanten Unterschiede ergaben die Metaanalysen nach ein bzw. zwei Jahren Follow-Up zur kardiovaskulären Mortalität. Die Anzahl der Hospitalisierungen wegen Herzinsuffizienz nach einem Jahr Follow-Up waren in einem RCT mit 31 Teilnehmer*innen in der Mitralclip-Gruppe geringer als in der Gruppe mit alleiniger medikamentöser Therapie (7 % versus 67 %), in einem zweiten RCT mit 307 Teilnehmer*innen zeigte sich hingegen kein Unterschied (48,7 % versus 47,4 %). Auch nach zwei Jahren waren die Hospitalisierungsraten in diesem RCT vergleichbar (55,9 % versus 62,3 %) während der dritte RCT mit 614 Patient*innen wieder einen Vorteil für die Mitralclip-Gruppe ergab (35,8 % versus 67,9 %).

Vorteil für Mitralclip bei Schweregrad und Leistungsfähigkeit

Lebensqualität nicht eindeutig

Vorteile einer perkutanen Mitralklappen-Reparatur mittels MitraClip® zeigten sich gegenüber der alleinigen medikamentösen Therapie in Bezug auf einen größeren Anteil an Patient*innen mit geringem bis mäßigem Schweregrad einer Mitralklappeninsuffizienz (Grad 0+ bis 2+) in zwei RCTs nach einem Jahr Follow-Up (85 % versus 23 % bzw. 94,8 % versus 46,9 %). Ebenso nach zwei (99,4 % versus 46,0 %) und drei Jahren (98,8 % versus 79,6 %) Nachbeobachtung, wobei Ergebnisse jedoch nur aus einem RCT vorlagen. Auch der Anteil an Patient*innen mit keiner oder nur leichter Einschränkung der Leistungsfähigkeit (NYHA-Klasse I oder II) waren in den RCTs in den Mitralclip-Gruppen insgesamt größer als in den Gruppen mit medikamentöser Therapie. Ergebnisse zur Lebensqualität lagen nach ein bzw. zwei Jahren Follow-Up vor, waren insgesamt jedoch nicht schlüssig.

Sicherheit

Mitralclip versus chirurgischen Mitralklappenintervention

Mitralclip vs Operation: mehr Komplikationen mit Mitralclip

Insgesamt war die Anzahl an schweren vaskulären Komplikationen innerhalb der ersten 30 Tage nach dem Eingriff in beiden Studiengruppen des eingeschlossenen RCTs gering, jedoch war der Anteil in der Mitralclip-Gruppe statistisch signifikant größer als in der Gruppe mit einer chirurgischen Intervention (4,9 % versus 0 %).

kein Unterschied bei SAE

Im Hinblick auf die Gesamtzahl an schwerwiegenden unerwünschten Ereignissen im Zeitraum von fünf Jahren Follow-Up zeigte sich hingegen kein Unterschied zwischen den beiden Studiengruppen (72,4 % versus 67,5 %; p=0,54).

Mitralclip versus medikamentöse Therapie

Mitralclip vs Medikamente: wenig Komplikationen im Zusammenhang mit Intervention

Komplikationen im Zusammenhang mit dem Mitralclip oder dem Eingriff waren selten. So traten in einem RCT innerhalb der ersten 30 Tage nach dem Eingriff Komplikationen im Zusammenhang mit dem Clip in 1,4 % der Teilnehmer*innen auf, im zweiten RCT lag der Anteil an periprozedural Komplikationen bei 14,6 %. In der dritten Studie wurde berichtete, dass keine schwerwiegenden unerwünschten Ereignisse im Zusammenhang mit dem Produkt auftraten.

kein Unterschied bei SAE

Die Gesamtzahl an schwerwiegenden unerwünschten Ereignissen wurde in einem RCT nach zwei und in einem zweiten nach drei Jahren Follow-Up berichtet. Dabei waren die Raten insgesamt hoch, es zeigten sich jedoch in beiden Studien keine Unterschiede zwischen Interventions- und Kontrollgruppe (84,9 % versus 82,1 % bzw. 93,1 % versus 93,3 %).

Laufende Studien

je 4 laufende RCTs zu Mitralclip vs Operation bzw. vs medikamentöse Therapie

In den Studienregistern werden aktuell vier RCTs angeführt, in denen der MitraClip® im Vergleich zu chirurgischen Interventionen untersucht wird. Die Studien werden voraussichtlich im Zeitraum von 2024 bis 2028 abgeschlossen. Vier weitere RCTs sind für den Vergleich MitraClip® mit einer medikamentösen Therapie gelistet. Das geplante Studienende dieser RCTs liegt zwischen August 2023 und 2025. Für andere perkutane Mitralclip-Systeme konnten keine laufenden RCTs identifiziert werden.

Schlussfolgerung und Empfehlung

Mitralclip vs Operation: Mitralclip weniger wirksam, Verlässlichkeit der Evidenz aber gering

Mitralclip vs Medikamente: Ergebnisse nicht eindeutig

Auf Basis der vorliegenden Evidenz ist die perkutane Mitralklappenintervention mittels Mitralclip bei Patient*innen mit mittelschwerer bis schwerer primärer oder sekundärer Mitralklappeninsuffizienz, die für einen chirurgischen Eingriff geeignet sind, vergleichbar sicher, aber weniger wirksam als die chirurgische Mitralklappenrekonstruktion. Die Verlässlichkeit der Evidenz für diesen Vergleich ist jedoch gering. Bei Patient*innen mit sekundärer mittelschwerer bis schwerer Mitralklappeninsuffizienz, die für eine Mitralklappenoperation nicht in Frage kommen, ist die derzeitige Evidenzlage nicht eindeutig, ob eine perkutane Mitralklappenintervention mittels Mitralclip wirksamer ist als eine alleinige optimale medikamentöse Therapie.

Aufnahme in den Leistungskatalog nicht empfohlen

Die Aufnahme der perkutanen Mitralklappenintervention mittels Mitralclip in den Leistungskatalog wird daher derzeit weder für operable noch für inoperable Patient*innen mit Mitralklappeninsuffizienz empfohlen. Eine neuerliche Evaluierung im Jahr 2026 wird vorgeschlagen.

Summary of previous assessment 2012 (updated background)

1. Update 2012

An initial HTA-report "*Perkutane Mitralklappenintervention mittels Mitralclip bei Mitralklappeninsuffizienz*" was prepared by the Ludwig Boltzmann Institute of Health Technology Assessments (LBI-HTA) in March 2010 [1] and updated in 2012 [2]. This chapter summarizes the results and the recommendation of this 2012 update report.

Health problem and characteristics of the technology

Overview of the disease, health condition and target population

Mitralklappeninsuffizienz: Druckanstieg in linkem Vorhof, verminderte Leistungsfähigkeit der linken Herzkammer

In mitral valve insufficiency or mitral regurgitation (MR), the heart valve located between the left atrium and the left ventricle, the so-called mitral valve, is no longer able to close completely. This "leakiness" causes the backflow of blood from the left ventricle into the left atrium during the ejection phase of the left ventricle; in severe MR, the blood can back up into the lungs. The result of the backflow is a large increase in pressure in the left atrium, which leads to enlargement of the left atrium in prolonged MR. At the same time, the performance of the left ventricle is weakened. Furthermore, the backflow of blood results in an undersupply of organs because too little blood is transported through the aorta [2].

Unterscheiden aufgrund der Ursache: degenerative (primäre) bzw. funktionelle (sekundäre) Form

Based on the cause, a classification is made between primary (degenerative) and secondary (functional) MR. Primary MR is caused by defects in the mitral valve components, such as the leaflets or the papillary muscles. Secondary MR results from pre-existing heart diseases like left ventricle dysfunction caused by ischemic heart disease or dilated cardiomyopathy, while the MV itself is structurally normal [3]. Primary MR is the most common form.

4 Schweregrade

Severity of MR is assessed by cardiac catheterization and classified into four grades ranging from mild to severe [4].

Beschwerden: Atemnot, Leistungsminderung, Herzrhythmusstörung, reduzierte Lebenserwartung

Mild forms of MR usually do not cause any symptoms. As the disease progresses, symptoms typically include dyspnea and decreased physical function. Cardiac arrhythmias and atrial fibrillation may also occur. MR is a progressive disease with reduced life expectancy [2].

Current clinical practice

primäre Form: chirurgische Rekonstruktion oder Ersatz

For patients with primary MR, valve intervention (i.e. surgery) is required to address the primary process, therefore medical therapy has a limited role. When surgery is considered, MV repair is the recommended technique [5]. The procedures usually involves opening the chest and using a cardiopulmonary bypass [2].

sekundäre Form: medikamentöse Therapie

Secondary MR, regardless of severity, is usually treated with medication. Optimal medical therapy according to the guidelines for the management of heart failure should be performed. In addition, indications for cardiac resynchronization therapy (CRT) should be evaluated. Patients with secondary MR, who remained symptomatic despite optimal medical therapy, can be treated surgically [6].

Leitlinienempfehlungen

According to current guidelines for vascular heart disease, MV surgery is recommended for all patients with severe primary MR, who are operable (strong recommendation/moderate level of evidence). For severely symptomatic patients who are not eligible for surgery or are at high surgical risk, percutaneous MV repair may be considered (moderate recommendation/moderate level of evidence) [3, 4].

For patients with secondary MR, the guidelines recommend guideline-directed medical therapy (GDMT) as primary treatment option (strong recommendation/high level of evidence). Surgical interventions are only recommended in patients who remained with severe symptomatic MR after GDMT (including CRT if indicated) (moderate recommendation/moderate level of evidence). Percutaneous MV repair should be considered in highly selected symptomatic patients, not eligible for surgery (moderate recommendation/moderate level of evidence) [3, 4].

Features of the intervention

Mitralclip: perkutane Intervention

posteriorer und anteriorer Mitralsegel werden zusammengeklammert

The mitral clip procedure is a percutaneous intervention to reduce MR. The basic principle of the procedure is to use a clamp (clip) to connect the two leaflets of the mitral valve at the leak site to create two smaller openings. The mitral clip procedure originates from a surgical method developed by Alfieri. In the so-called Alfieri operation (edge-to-edge technique), the two leaflets of the mitral valve are sawn together to reduce backflow. In the catheter intervention investigated here, in principle, only suturing is replaced by clipping [2].

The mitral clip procedure proceeds in such a way that a catheter, on which the clip is premounted, is brought via the inguinal vein to the right atrium and then through the atrial septum into the left atrium. From there, the mitral clip – guided by transesophageal echocardiography – is placed in the proper position to clip the two leaflets together at the appropriate location [2].

The mitral clip procedure does not require a thoracotomy or the use of a cardiopulmonary bypass machine, i.e., it is performed on the beating heart. The procedure is performed under general anesthesia [2].

Clip als Alternative zu offen-chirurgischen Eingriffen bei operablen, aber auch Option für inoperable Patient*innen

The use of the mitral clip is discussed both as an endovascular alternative to surgical mitral valve reconstruction or surgical mitral valve replacement for patients eligible for surgery and as a therapeutic option for patients ineligible for coronary surgery [2].

Mitraclip®: derzeit einziges System

Currently, only one such clip system is on the market. This is the MitraClip® from Abbott Laboratories (former Evalve Inc.). The MitraClip® received CE certification in 2008. In the USA, the product was FDA-approved in 2013.

Indications for the use of the MitraClip® are patients with moderate-to-severe or severe MR (grade 3+ and 4+). The use in both patients eligible and ineligible for surgery, i.e. patients at high risk of mortality from open surgery, is considered [2].

Ziele: Verringerung des Schweregrads, Verbesserung von Lebensqualität und Leistungsfähigkeit

The therapeutic goal of the MitraClip® procedure is to reduce MR severity and thereby relieve symptoms, increase physical function, improve quality of life, and prolong life.

In Austria, a provisional XN code (XN050) has been available for the individual medical service “Implantation of a mitral valve clip transdermal” since 2011.

Scope and methods

Ziel der Untersuchung 2012

The 2012 report compared the efficacy and safety of a mitral clip procedure to medical treatment or mitral valve repair or replacement surgery in patients with moderate-to-severe or severe MR. A systematic literature search was conducted in Medline, Embase, Cochrane Library and NHS CRD databases. Two review authors independently screened and selected the literature and included eligible studies. In cases of disagreement, consensus was achieved through discussion or by involving a third person. The data were extracted by one author and checked by a second author. In the absence of (randomized) controlled trials, prospective (uncontrolled) before-after studies as best available evidence were included. The quality of evidence was assessed according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach [7].

Results

Mitralclip vs Operation: 1 RCT + 1 prospektive unkontrollierte Studie

One randomized controlled trial (RCT) and one uncontrolled before-after study were found assessing the MitraClip® system in patients suffering from MR≥3+ eligible for mitral valve surgery. The RCT, a non-inferiority study, compared the MitraClip® device to mitral-valve surgery. Since differing results for reduction of MR severity are presented, it is possible that more patients treated with this device will experience re-occurrence of MR≥3+ than surgical patients at 12 months. However, improvements in NYHA functional class were more common in the clip group, and fewer major adverse events were observed [2].

In terms of mortality, no difference between the two groups was found. After 12 months, however, 20% of patients in the percutaneous-repair group had to undergo mitral-valve surgery, in comparison to 2% in the surgery group. After 24 months, the respective rates were 22% and 4% [2].

Mitralclip vs Medikamente: kein RCT, 9 prospektive unkontrollierte Studien

MitraClip® for patients ineligible for surgery or patients at high surgical risk was evaluated in nine uncontrolled, prospective studies. Acute procedural success (defined as MR≤2+ at hospital discharge) was observed in at least 72% of all patients; corresponding numbers after six and 12 months were 73% and 78%, respectively. NYHA-Class of ≤2 was achieved in 65% after six to 12 months, and improvements in the 6-minute walking test was observed in 111 patients overall. Quality of life-related outcomes were better after one to 12 months in 192 individuals altogether. One-year mortality rates ranged from 10%-24%. Major adverse events within 30 days occurred in 3%-38% and 30-day mortality in 0%-8% [2].

Recommendation

sehr niedrige bis mittlere Verlässlichkeit der Evidenz – Aufnahme in Leistungskatalog nicht empfohlen

Due to methodological limitations of the RCT and due to the uncontrolled study design of the before-after study, the quality of evidence was low to medium for patients eligible for surgery. For patients ineligible for surgery or patients at high surgical risk the quality of evidence of the included before-after studies is very low due to their uncontrolled study design.

Overall, the available evidence in 2012 was insufficient to assess the efficacy and safety of percutaneous MR repair with the mitral clip device MitraClip® in comparison to the respective standard therapy (MV repair/replacement surgery or optimal medical therapy for heart failure) for patients with MR.

Therefore, inclusion into the hospital benefit catalogue was not recommended for patients with moderate-to-severe or severe MR eligible or ineligible for surgery [2].

UPDATE 2023

1 Objectives and Scope

1.1 PICO question

PIKO-Frage 2023

Is a percutaneous transcatheter repair of the mitral valve using a mitral clip device in comparison to surgical repair or replacement of the mitral valve, or optimal medical therapy in patients with moderate-to-severe MR more effective and safe concerning survival, MR severity, quality of life, the necessity of surgical re-intervention, and complication rates?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarized in Table 1-1.

Table 1-1: Inclusion criteria

Population	Patients with moderate-to-severe or severe mitral valve regurgitation (MR) (severity grade 3+ or 4+); both patients eligible an ineligible for surgical interventions
Intervention	Percutaneous transcatheter repair of the mitral valve using a mitral clip device
Control	■ Surgical repair of the mitral valve ■ Surgical replacement of the mitral valve ■ Optimal medical therapy (for patients not eligible for surgical interventions) ■ Other forms of percutaneous mitral valve intervention
Outcomes	
Efficacy	■ Mortality (overall/cardiovascular) ■ MR severity ■ Surgical re-intervention (for patients eligible for surgery) ■ Hospitalization for heart failure ■ Quality of life ■ Physical fitness
Safety	■ Peri- or post-procedural complications ■ Other (serious) adverse events
Study design	
Efficacy	■ Randomized controlled trials (or prospective controlled studies, if no RCTs are available)
Safety	■ Randomized controlled trials (or prospective controlled studies, if no RCTs are available)

2 Methods

Assessment elements from the European Network for Health Technology Assessment (EUnetHTA) Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customized to the specific objectives of this assessment [8].

2.1 Clinical effectiveness and safety

2.1.1 Systematic literature search

systematische Literatursuche nach RCTs in 3 Datenbanken

The systematic literature search was conducted on the 28.12. 2022 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library

insgesamt 704 Publikationen identifiziert

The systematic search was limited to the years 2012 to 2022 and in Medline and Embase to only randomized controlled trials and to articles published in English or German. After de-duplication, overall, 702 citations were included. The specific search strategy employed can be found in the Appendix.

By hand-search, two additional publications were found, resulting in overall 704 hits.

Suche nach laufenden Studien

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trial registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 25.01.2023 resulting in 96 potentially relevant hits.

2.1.2 Flow chart of study selection

Literaturauswahl

Overall, 712 hits were identified. After de-duplication, 702 references were screened by two independent researchers, and in case of disagreement, a third researcher was involved to solve the differences. The selection process is displayed in Figure 2-1.

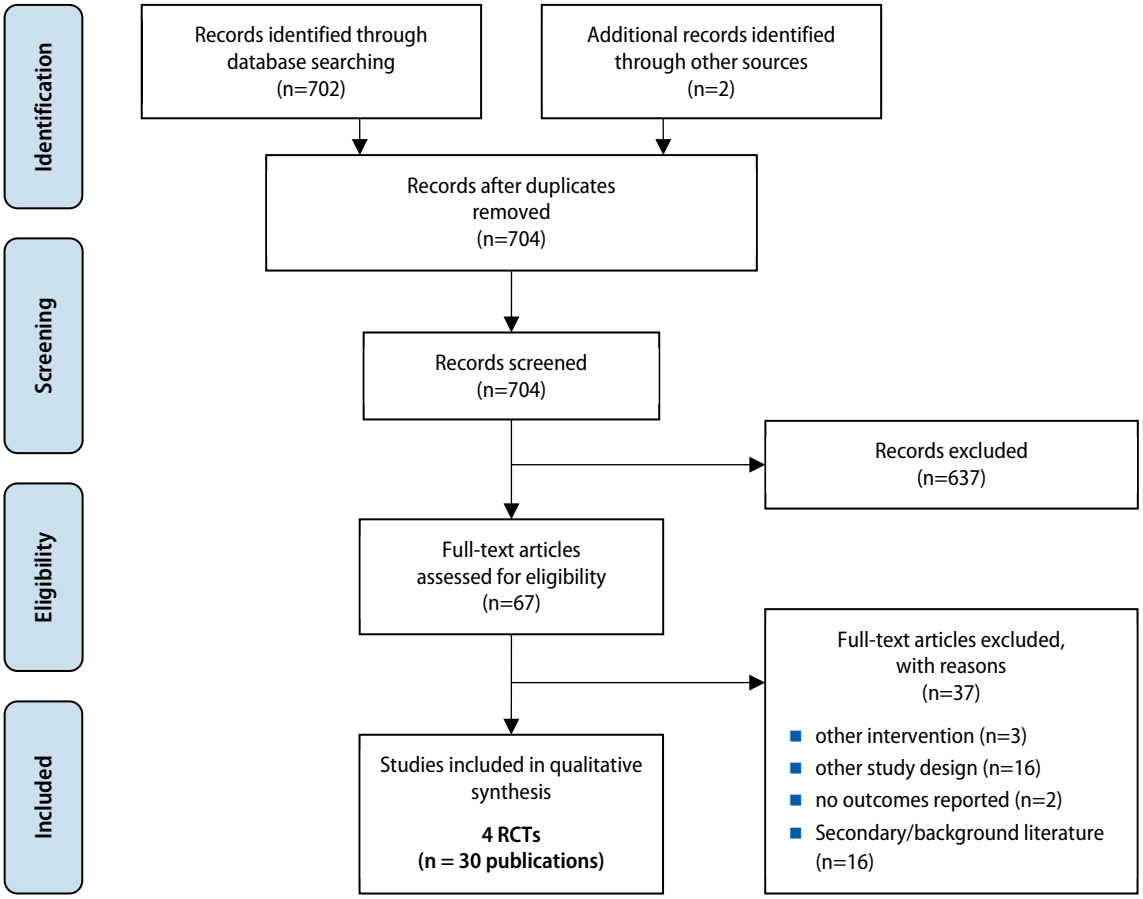

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

4 RCTs zu MitraClip® inkludiert, keine RCTs zu anderen Systemen

Finally, 30 publications [9-38] on four RCTs for effectiveness and safety outcomes could be included in this review update. All of the included RCTs investigated percutaneous transcatheter MV repair using the MitraClip® device. No trials on other percutaneous MV clip systems could be identified.

2.1.3 Analysis

Datenextraktion in Tabellen

Relevant information was retrieved from the sources identified. Data from included primary studies were extracted into data extraction tables based on the study design and research question (see Appendix Table A-1 and Table A-2). An independent second reviewer (TS) validated the data for accuracy.

Bewertung des Verzerrungspotenzials: Cochrane RoB 2

Two researchers (CL, TS) conducted risk of bias assessments independently. Differences were resolved by consensus. The risk of bias (RoB) of the included RCTs was assessed using the Cochrane RoB v.2 tool [39] (see Appendix Table A-3, Table A-4).

2.1.4 Synthesis

Meta-Analysen wenn möglich – Review Manager 5.4

Based on the data-extraction-table (see Appendix Table A-1 and Table A-2), data on each selected outcome were synthesized. If appropriate, pairwise meta-analyses were performed using the Cochrane Review Manager software, Review Manager 5.4. Dichotomous data were expressed as a risk ratio (RR) or odds ratio (OR) with 95% CIs or as the number of events and percentages. Continuous outcomes were given using the mean with standard deviation (SD). We use the fixed or random effects model to synthesise the results using the Mantel-Haenszel method (for dichotomous data) or Inverse Variance method (for continuous data). Thereby, the random effects model was used in the case of increased heterogeneity ($I^2 > 30\%$). We identified heterogeneity by visually inspecting the forest plots and by using the I^2 statistic [40]. The level of heterogeneity was taken into account as part of the assessment of the certainty of the evidence (inconsistency).

Bewertung der Vertrauenswürdigkeit der Evidenz mit GRADE

Certainty of evidence was assessed across studies for each outcome according to GRADE (Grading of Recommendations Assessment, Development and Evaluation [7]). The questions were answered in plain text format with reference to GRADE evidence tables that are included in Appendix; results were summarized in Table 4-1 and Table 4-2.

3 Results: Clinical effectiveness and Safety

3.1 Outcomes

3.1.1 Outcomes effectiveness

Wirksamkeit: entscheidungsrelevanter EP: Gesamtsterblichkeit

The following outcome was defined as *crucial* to derive a recommendation:

- Overall mortality

Mortality is considered a highly patient-relevant outcome measure when assessing the clinical effectiveness of interventions for the treatment of moderate to severe MR. Mortality was reported as overall mortality rates and as cardiovascular mortality rates in the included RCTs.

Wirksamkeit: wichtige EP: Re-Interventionen, Hospitalisierung, Schweregrad der Mitralklappeninsuffizienz, Lebensqualität, Leistungsfähigkeit

The following outcomes were defined as *important, but not crucial* to derive a recommendation:

- Surgical (re-)intervention
- Hospitalization for heart failure
- MR severity
- Quality of life (QoL)
- Function

MV repair serves the primary purpose to reduce the severity of MR and to improve function and QoL of the affected patients.

Schweregrad der Mitralklappeninsuffizienz: Unterschiedliche Definitionen in den RCTs

MR severity is reported as the percentage of patients with mild to severe MR durling follow-up. In the RCTs conducted in North America (EVEREST-II and COAPT) MR severity grading was done according to the US definition as following [41]:

- MR 1+: Regurgitant volume (RV) <30ml; right ventricular ejaction fraction (RVEF) <30%; effective regurgitant orifice area (EROA) <20mm^2
- MR 2+: RV 30-44ml; RVEF 30-39%; EROA 20-29mm^2
- MR 3+: RV 45-59ml; RVEF 40-49%; EROA 30-39mm^2
- MR 4+: RV ≥60ml; RVEF ≥50%; EROA ≥40mm^2

The French RCT Mitra-FR on the other hand used the 2012 European guidelines definition for grade of MR when recruiting patients [42]:

- severe MR: RV > 30ml; EROA > 20mm^2

Hospitalization is reported as the percentage of patients being hospitalized for heart failure during follow-up.

Surgical (re-)intervention is reported as the percentage of patients with a necessity of surgery for mitral-valve dysfunction during follow-up.

Allgemeine Lebensqualität: SF-36 und EQ-5D

Generic QoL was assessed by two different questionnaires, the Short Form 36 (SF-36) questionnaire and the European Quality of Life–5 Dimensions (EQ-D) questionnaire. The SF-36 consists of 36 questions and is a general health questionnaire yielding a profile of two health component summary measures through assessing the patient's health status using eight different dimensions (vitality, physical functioning, bodily pain, general health perceptions, role limitations due to physical health, role limitation due to emo-

tional health, social role functioning, mental health). The score ranges from 0 to 100 points, with 0 points representing the greatest possible limitation of health and 100 points representing the absence of health restrictions [43]. The EQ-5D is a five-item measure of mobility, self-care, usual activity, pain or discomfort, and anxiety or depression. Scores range from 0 to 100, with higher scores indicating fewer symptoms and better health status [44].

Erkrankungsspezifische Lebensqualität: KCCQ

Disease-specific QoL und physical function was assessed in one RCT using the Kansas City Cardiomyopathy Questionnaire (KCCQ). The KCCQ is a 23-item, self-administered instrument that quantifies physical function, symptoms, social function, self-efficacy and knowledge, and quality of life. The score ranges from 0 to 100 points, with 100 representing the least burden of symptoms. The KCCQ tool quantifies six domains (symptoms, physical function, QoL, social limitation, self-efficacy, symptom stability) and two summary scores (clinical summary score and overall summary score). Scores are summarized in 25-point ranges to represent the health status of individuals: 0 to 24: very poor to poor; 25 to 49: poor to fair; 50 to 74: fair to good; and 75 to 100: good to excellent [45].

Leistungsfähigkeit: NYHA Klassifikation

Physical function is also assessed using the New York Heart Association (NYHA) functional classification system. It classifies the patients on their extent of heart failure and their limitation during physical activity in four classes [46]:

- Class I: No symptoms and no limitation in ordinary physical activity
- Class II: Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
- Class III: Marked limitation in activity due to symptoms
- Class IV: Severe limitations.

The endpoint was reported as the percentage of patients in each NYHA functional class during follow-up.

6-Minuten Gehtest

In addition, physical function was assessed by the 6-minute walking test (6-MWT). The test measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface. The goal is to walk as far as possible in six minutes. The individual is allowed to self-pace and rest as needed [47].

kombinierte Endpunkte sehr heterogen, daher nicht relevant

A composite outcome was defined as the primary efficacy endpoint in three of the four included RCTs. This composite outcome included freedom from death, from surgery for mitral-valve dysfunction, and from grade 3+ or 4+ mitral regurgitation in the EVEREST-II trial, all-cause death and unplanned hospitalizations for heart failure in the Mitra-FR trial, and cardiovascular death, heart transplantation, and hospitalizations for heart failure in the Mitra-CRT trial, respectively. Since all of these endpoints are composed of individual outcomes of very different severity, the overall results are of little relevance compared to the results of the individual components. Therefore the composite endpoints of the included trials are judged as not relevant for this report update.

3.1.2 Outcomes safety

Sicherheit: entscheidungsrelevante EP: ...

The following outcomes were defined as *crucial* to derive a recommendation:

- Device- or procedure-related complications
- Serious adverse events

... Komplikationen im Zusammenhang mit Intervention, ...

Procedure-related complications are defined in one RCT as adverse events that are adjudicated by the studies clinical events committee as possibly, probably or definitely device and/or procedure-related, regardless of the temporal relationship to the MitraClip® device or implantation procedure [16]. The other included RCT reported peri-procedural complications such as device-implantation failure, atrial septum lesion, cardiogenic shock, tamponade, or cardiac embolism [15], or major vascular complications, defined as events such as hematoma at the access site > 6cm, retroperitoneal hematoma, AV fistulas, symptomatic peripheral ischemia/nerve injury or the clinical signs or symptoms lasting > 48 hours, vascular surgical repair at catheter access sites, pulmonary embolism, ipsilateral deep vein thrombus, access site-related infection requiring intravenous antibiotics and/or extended hospitalization within the first 30 days or before hospital discharge [9].

... schwerwiegende unerwünschte Ereignisse

Serious adverse events (SAE) include ischemic or hemorrhagic stroke, myocardial infarction, need for renal-replacement therapy, peri-procedural complications, and bleeding events in one RCT [15]. In addition, major adverse cardiovascular events (MACE), a composite of death, stroke, myocardial infarction, or unplanned hospitalization for heart failure, were assessed as the primary safety endpoint in this trial. The primary safety endpoint in the EVEREST-II trial was the rate of major adverse events at 30 days, defined as the composite of death, myocardial infarction, reoperation for failed mitral-valve surgery, non-elective cardiovascular surgery for adverse events, stroke, renal failure, deep wound infection, mechanical ventilation for more than 48 hours, gastrointestinal complication requiring surgery, new-onset permanent atrial fibrillation, septicemia, and transfusion of two units or more of blood [9]. No specific definition of SAE was stated in the other included RCTs. According to ICH-GCP guideline an SAE is an adverse event that led to a death, to a serious deterioration in health of the subject, that either resulted in a life-threatening illness or injury, or a permanent impairment of a body structure or a body function, or in-patient hospitalization or prolongation of existing hospitalization, or in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made, or c) if circumstances had been less fortunate.

3.2 Included studies

3.2.1 Included studies effectiveness

Patient eligible for surgery

Mitralclip vs Operation: 1 RCT

Since the previous report update in 2012 [2], additional publications to one already included RCT comparing MitraClip® device to MV repair or replacement surgery were identified (EVEREST-II). These publications reported long-term results after four [13] and five years of follow-up [14], respectively. Besides, no additional RCTs comparing MitraClip® to surgical interventions could be identified for the review update.

279 Patient*innen

64 % Männer

mittleres Alter 67 Jahre

primäre und sekundäre Mitralklappeninsuffizienz

The included RCT is a two-arm parallel open-label trial conducted in 37 study centres in Canada and the USA. A total of 279 symptomatic or asymptomatic patients with primary or secondary moderate-to-severe (3+) or severe (4+) chronic MR were randomized in a 2-to-1 ratio to percutaneous MV repair using the MitraClip® implant or to MV repair surgery. Symptomatic patients had to have a left ventricular ejection fraction (LVEF) of more than 25% and a left ventricular end-systolic diameter (LVESD) of 55mm or less, while asymptomatic patients with an LVEF of 25 to 60%, with an LVESD of 40 to 55mm, with new onset of atrial fibrillation (AF), or with pulmonary hypertension were included. The included patients were predominantly male (~ 64%) with a mean age of 67 years. 27% of the included patients had functional (secondary) MR. About 34% of the participants had AF, 15% had a chronic obstructive pulmonary disease (COPD), and about ten percent had diabetes mellitus. The LVEF at baseline was 60%, and most patients had NYHA function class II or III.

5 Jahre Follow-Up

The length of follow-up was five years in this RCT. The primary efficacy end point was a composite endpoint of freedom of death from any cause, freedom from (re-)surgery for valve dysfunction, and freedom from grade 3+ or 4+ MR at 12 months follow-up. The primary safety end point was the proportion of patients with major adverse events in the first 30 days after intervention [9, 10, 13, 14].

Study characteristics and results of included studies are displayed in Table A-1 and in the evidence profile in Table A-5.

Patient ineligible for surgery

Mitralclip vs Medikamente: 3 RCTs

For the comparison of MitraClip® device to standard medical therapy in patients with secondary MR ineligible for surgical interventions, three recently published RCTs (Mitra-FR [15, 17, 21], COAPT [16, 18, 33], and Mitra-CRT [38]) were included in this report update.

952 Patient*innen mit sekundärer Mitralklappeninsuffizienz

Einschlusskriterien hinsichtlich Patient*innen sehr unterschiedlich

Two of the three RCTs comparing the percutaneous MV repair device MitraClip® to GDMT were multi-centre trials conducted in North America [16, 18, 33] and France [15, 17, 21], respectively. The third RCT was a single-centre trial comparing MitraClip® to OMT located in Spain [38]. All of them were 2-arm parallel, open-label studies. Two RCTs were funded by the MitraClip® manufacturer [16, 18, 33, 38], while one trial had an academic/governmental funding [15, 17, 21]. The three included RCTs enrolled a total of 952 patients with secondary MR, with a sample size ranging from 31 participants [38] to 614 participants [16, 18, 33]. Besides the inclusion criteria of a secondary moderate-to-severe or severe MR, the patient-groups in the three trials were

quite different. While the Mitra-FR trial included only patients with at least one hospitalization for heart failure within 12 months prior to randomization and an LVEF of 15 to 40%, recent hospitalization for heart failure was no inclusion criterion in the COAPT trial. In addition, the patients in the COAPT trail had to have an LVEF of 20 to 50% for inclusion. In the third RCT (Mitra-CRT), only non-responders to cardiac resynchronization therapy were included.

64-80 % Männer

mittleres Alter etwa 70 Jahre

In all three RCTs, the majority of the included patients were male (64 to 80%), and the mean age was about 70 years. Common comorbidities were AF (34 to 53%) and Diabetes mellitus (23 to 32%). The LVEF at baseline was 33% in the Mitra-FR, 31% in the COAPT, and 21% in the Mitra-CRT trial, respectively. Most patients had NYHA function class II or III in all three RCTs.

geplantes Follow-Up: 1-3 Jahre

All hospitalizations for heart failure within 24 months were the primary efficacy end point of the COAPT trial, while it was a composite of death from any cause or unplanned hospitalization for heart failure at 12 months in the Mitra-FR RCT. In the Mitra-CRT study, the primary efficacy end point was defined as the combined of cardiovascular death, heart transplantation, or hospitalization for heart failure at 12 months. The planned maximum length of follow-up in the three RCTs was one (Mitra-CRT), two (Mitra-FR) and five years (COAPT).

Study characteristics and results of included studies are displayed in Table A-2 and in the evidence profile in Table A-6.

3.2.2 Included studies safety

Patient eligible for surgery

Results from the only RCT included for effectiveness outcomes were also included in the safety analyses [9, 10, 13, 14]. No additional studies were included.

Study characteristics and results of included studies are displayed in Table A-1 and in the evidence profile in Table A-5.

Patient ineligible for surgery

Results from all three RCTs included for effectiveness outcomes were also included in the safety analyses [15-18, 21, 33, 38]. No additional studies were included.

Study characteristics and results of included studies are displayed in Table A-2 and in the evidence profile in Table A-6.

3.3 Results

3.3.1 Patient eligible for surgery

Mortality[1]

Mitralclip vs Operation: kein Unterschied bei Mortalität nach 5 Jahren

For the comparison of MitraClip® versus surgery, **overall mortality** rates were reported in one RCT, including 279 patients. After one year of follow-up, there were no significant differences between patients who underwent percutaneous MV repair with MitraClip® or those who underwent MV surgery (6% vs 6%; p=1.0) [10]. Also, in long-term follow-up after four and five years, respectively, the overall mortality rates where comparable between the two study groups (four-year follow-up: 17.4% vs 17.8%; p=0.914 [13]; five-year follow-up: 20.8% vs 26.8%; p=0.36 [14]).

There were no results from RCTs on **cardiovascular mortality** for the comparison of MitraClip® versus surgery.

Morbidity[2,3]

Mitralclip vs Operation: Vorteil für Operation bei Schweregrad der Mitralklappeninsuffizienz nach 5 Jahren

In the EVEREST-II trial, the number of patients with different grades of **MR severity** was reported at one-, four- and five-year follow-up. In both study arms, the percentage of patients with moderate-to-severe or severe MR (grade 3+ or 4+) were significantly lower at all three-time points compared to baseline. Nevertheless, a comparison of the two study groups showed that there were fewer participants with none, mild or moderate MR (grade 0+ to 2+) in the device arm compared to the surgery arm after one (107/153 (70%) vs 57/69 (89%)) [10], four (84/105 (79%) vs 43/48 (90%)) [13] or five years of follow-up (81/101 (80%) vs 39/40 (98%)) [14].

Mitralclip vs Operation: Vorteil für Operation bei notwendigen Re-Interventionen nach 5 Jahren

The number of patients with **surgical re-intervention** was also reported in the timeframes of one, four and five years of follow-up. The proportion of patients requiring re-operation was always significantly higher in the MitraClip® group compared to the surgery group: 21% vs 2.2%; p<0.001 (one year [10]), 24.8% vs 5.5%; p<0.001 (four years [13]) and 27.9% vs 8.9%; p<0.001 (five years [14]).

keine Ergebnisse zur Hospitalisierungsrate

The number of patients with **hospitalization for heart failure** during follow-up was not reported in the EVEREST-II trial for the comparison of percutaneous MV clip device versus MV surgery.

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[1] **D0001** – What is the expected beneficial effect of MitraClip® implantation on mortality in comparison to mitral valve surgery?

[2] **D0005** – How does MitraClip® implantation affect symptoms and findings (severity, frequency) of mitral valve regurgitation in comparison to mitral valve surgery?

[3] **D0006** – How does MitraClip® implantation affect progression (or recurrence) of mitral valve regurgitation in comparison to mitral valve surgery?

Function[4,5]

Regarding physical function assessed by **NYHA functional class**, an advantage of MitraClip® versus surgical intervention was observed after 12 months (NYHA class ≥ III: 2% vs 13%; p=0.002) [10]. After four years of follow-up no difference in the proportion of patients with limited exercise capacity was observed (NYHA class ≥ III: 7.9% vs 7.9%) [13]. After five years, a reversal of the trend was observed, with more patients classified as having NYHA functional class ≥ III in the MitraClip® group compared to the surgery group. This difference was not statistically significant (NYHA class ≥ III: 7.7% vs 2.6%) [14].

Mitralclip vs Operation: kein Unterschied bei Leistungsfähigkeit nach 5 Jahren

There were no results from a **6MWT** for the comparison of MitraClip® device versus MV surgery.

Quality of life[6,7]

Generic quality of life was assessed by the SF-36 questionnaire in the EVEREST-II trial and results were reported after one year, with no difference between the device arm and the MV surgery arm: At 12 months the mean score in the SF-36 physical summary increased by the same amount in both study groups compared to baseline (4.4 ± 9.8 vs 4.4 ± 10.4; p=0.98), while the difference to baseline in SF-36 mental summary score was 5.7 ± 9.9 points in the MitraClip® group, compared to 3.8 ± 10.3 points in the MV surgery group (p=0.24) [10].

Mitralclip vs Operation: kein Unterschied bei Lebensqualität nach 1 Jahr

There were no results concerning the **disease-specific quality** of life for the comparison of MitraClip® versus MV surgery.

Patient safety[8,9,10]

Major vascular complications during the first 30 days after intervention were generally rare but more frequent in the device group (4.9%) than with MV surgery group (0%) [10].

Mitralclip vs Operation: mehr Komplikationen mit Mitralclip

Major adverse events were reported within 30 days and after one year of follow-up. Contrary to the major vascular complications, they occurred significantly less frequently in patients of the MitraClip® group compared to those in the surgery group at both time-periods (30 days: 13/136 (9.6%) vs 45/79 (57.0%); p<0,001; one year: 39/184 (21.2%) vs 44/95 (46.3%); p<0,001) [10]. Major adverse event rates after four or five years of follow-up were not reported.

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[4] **D0011** – What is the effect of MitraClip® implantation on patients' body functions in comparison to mitral valve surgery?

[5] **D0016** – How does the MitraClip® implantation affect activities of daily living in comparison to mitral valve surgery?

[6] **D0012** – What is the effect of MitraClip® implantation on generic quality of life in comparison to mitral valve surgery?

[7] **D0013** – What is the effect of MitraClip® implantation on disease-specific quality of life in comparison to mitral valve surgery?

[8] **C0008** – How safe is MitraClip® implementaion in comparison to mitral-valve surgery?

[9] **C0004** – How does the frequency or severity of harms change over time or in different settings?

[10] **C0005** – What are the susceptible patient groups that are more likely to be harmed through the use of MitraClip®?

Mitralclip vs Operation: kein Unterschied bei SAE nach 5 Jahren

All SAE were reported in the EVEREST-II trial after five years of follow-up with no difference between MV clip device and MV surgery (127/178 (72.4%) vs 54/80 (67.5%); p=0.54). Minor AEs after five years of follow-up were reported in nearly all patients, again with no difference between the study groups (168/178 (94.4%) vs 80/80 (100%)) [48].

Results from subgroup analyses were only reported for efficacy outcomes but not for safety outcomes. Therefore, no information is available on whether there are patient groups that are more likely to be harmed through the use of the MitraClip® technology compared to surgery.

3.3.2 Patient ineligible for surgery

Mortality[11]

Mitralclip vs Medikamente: kein Unterschied bei Gesamtmortalität nach 1 bzw. 2 Jahren

For the comparison of percutaneous MV repair using MitraClip® device versus medical therapy, **overall mortality** rates were reported in three RCTs [15-18, 21, 33, 38]. The results on overall mortality were inconsistent across the RCTs. While the COAPT trial reported statistically lower mortality rates in the MitraClip® group compared to the medical control group after one, two and three years, respectively [18, 33], the other two RCTs (Mitra-FR and Mitra-CRT) showed no difference after one and two years of follow-up [17, 21, 38].

In summary, there were no significant differences in overall mortality rates between patients receiving percutaneous MV repair intervention and those treated with medical treatment alone. A meta-analysis after one-year follow-up, including results from all three RCTs with 949 patients, resulted in an RR of 0.91 [95% CI 0.72, 1.17] (p=0.47; heterogeneity: I^2=0% (Figure 3-1)). In addition, meta-analysis after a follow-up of two years, including two RCTs with 918 patients, resulted in RR 0.82 [95% CI 0.56, 1.22]; p=0.33; I^2=76% (Figure 3-2).

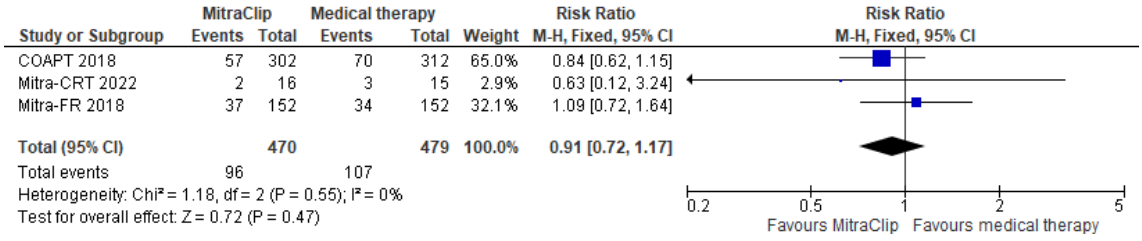

Figure 3-1: MitraClip® versus medical therapy – Overall mortality at 1 year follow-up

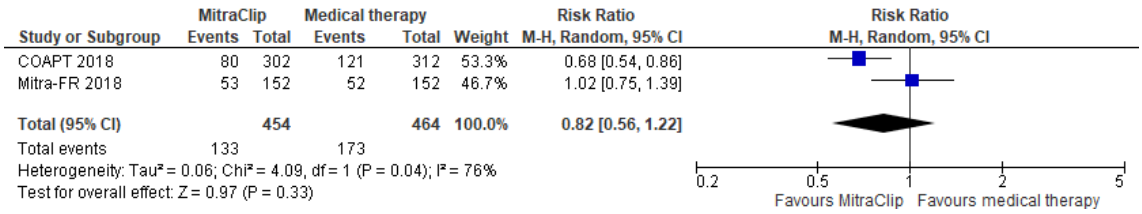

Figure 3-2: MitraClip® versus medical therapy – Overall mortality at 2 years follow-up

[11] **D0001** – What is the expected beneficial effect of MitraClip® implantation on mortality in comparison to medical therapy?

Mitralclip vs Medikamente: kein Unterschied bei kardiovaskulärer Mortalität nach 1 bzw. 2 Jahren

Cardiovascular mortality rates were also reported in all three included RCTs. Again, the COPT trial showed significant advantages for MitraClip® intervention after two and three years of follow-up [18, 33]. One-year results were not reported. In both other included studies, there was no difference in cardiovascular mortality rates after one year (Mitra-FR; Mitra-CRT) [17, 38] and two years follow-up (Mitra-FR) [21].

Combining the data from the trials at one and two years, respectively, the meta-analyses show no statistically significant benefit for the percutaneous MV repair over medical therapy alone (RR 1.03 [95% CI 0.67, 1.57]; p=0.90; I^2=0%, (Figure 3-3); RR 0.79 [95% CI 0.53, 1.18]; p=0.25; I^2=71% (Figure 3-4)).

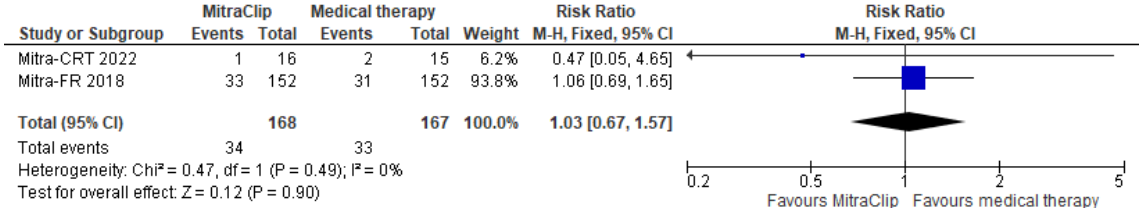

Figure 3-3: MitraClip® versus medical therapy – Cardiovascular mortality at 1 year follow-up

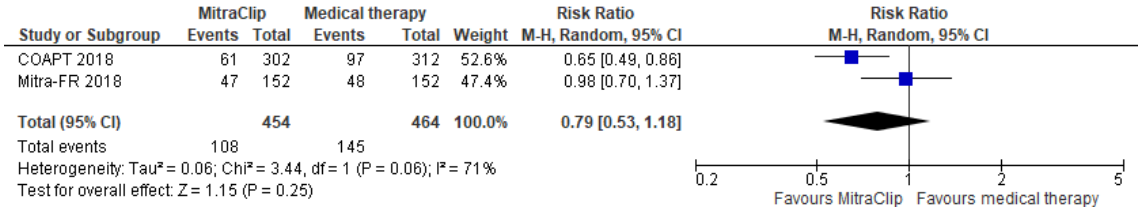

Figure 3-4: MitraClip® versus medical therapy – Cardiovascular mortality at 2 years follow-up

Morbidity[12,13]

Mitralclip vs Medikamente: mehr Patient*innen mit keiner bis mäßig-schwerer Mitralklappeninsuffizienz mit Mitralclip nach 1-3 Jahren

The number of patients with different grades of **MR severity** after intervention was reported in two RCTs (COAPT, Mitra-CRT). In both RCTs, the numbers of patients with moderate-to-severe or severe MR one or two years after intervention were lower compared to the baseline for all study groups. After one year follow-up the percentage of patients with mild (1+) or moderate (2+) MR was significantly higher in the device arm compared to the medical therapy arm in the Mitra-CRT trial (85% vs 23%; p=0.005) [38] and in the COAPT trial (94.8% vs 46.9%; p<0.001) [18]. In the latter study, this advantage was also evident after two (99.4% vs 46.0%; p<0.0001) [18] and three years of follow-up (98.8% vs 79.6%; p=0.0002) [33], respectively.

[12] **D0005** – How does MitraClip® implantation affect symptoms and findings (severity, frequency) of mitral valve regurgitation in comparison to medical therapy?

[13] **D0006** – How does MitraClip® implantation affect progression (or recurrence) of mitral valve regurgitation in comparison to medical therapy?

Mitralclip vs Medikamente: insgesamt kein Unterschied bei Hospitalisierungen nach 1 – 3 Jahren

The rates of patients with **hospitalization for heart failure** during follow-up were reported in all three included RCTs. At one year follow-up, the Mitra-CRT trial reported a significantly lower rate of re-hospitalizations for HF in the MitraClip® group compared with drug therapy (7% vs 67%; p=0.002) [38], whereas the Mitra-FR trial, which recorded the number of patients with at least one unplanned hospitalization for heart failure, showed no difference between intervention and control (48.7% vs 47.4%) [17]. Also after two years of follow-up, there was no between-group difference in this RCT (55.9% vs 62.3%; HR 0.97 [95% CI 0.72, 1.30]) [21]. In the third included RCT, all hospitalizations for heart failure during follow-up were assessed. Here, a significantly lower rate was reported with percutaneous MV repair intervention compared to medical therapy alone, both at two (35.8% vs 67.9%; p<0.001) and three years (35.5% vs 68.8%; p<0.001) [18, 33].

Function[14,15]

Mitralclip vs Medikamente: mehr Patient*innen mit guter Leistungsfähigkeit mit Mitralclip nach1-3 Jahren

Information on patients' **NYHA functional class** after the intervention was available in all three included RCTs. In the Mitra-FR trial, there was a significant improvement in NYHA class between baseline and 12 and 24 months within each study group, but no significant difference between groups at each time point [17, 21]. The Mitra-CRT trial showed significantly improved NYHA functional class in the MitraClip® arm compared to the medical therapy arm after one year [38], as did the COAPT trial after two and three years of follow-up [18, 33], respectively.

In addition, physical function was assessed by **6MWT** in all three RCTs. In the Mitra-CRT trial, patients in the device arm improved their 6MWT distance compared to patients in the medical therapy arm after one year [38]. In the Mitra-FR trial, patients in both groups improved their walking distance from baseline to 24 months follow-up, but with no difference between the two study groups [21]. In the COAPT study, on the other hand, there was a worsening of the walking distance after one and two years compared to baseline in both study arms, but it was significantly lower in the MitraClip® arm at both time points [18].

Quality of life[16,17]

Mitralclip vs Medikamente: Ergebnisse zu Lebensqualität nicht eindeutig

Generic quality of life was assessed by the EQ5D questionnaire in one RCT comparing MV repair with MitraClip® to medical therapy alone. Results after a one-year follow-up showed no difference in the global score between the two study groups (60.8 ± 20.3 vs 58.6 ± 18.2) [17].

One RCT assessed the **disease-specific quality of life** for the comparison of MitraClip® versus medical therapy using the KCCQ. After one and after two years, quality of life was significantly better in patients treated with percutaneous MV repair than those receiving medical therapy alone. Change in

[14] **D0011** – What is the effect of MitraClip® implantation on patients' body functions in comparison to medical therapy?

[15] **D0016** – How does the MitraClip® implantation affect activities of daily living in comparison to medical therapy?

[16] **D0012** – What is the effect of MitraClip® implantation on generic quality of life in comparison to medical therapy?

[17] **D0013** – What is the effect of MitraClip® implantation on disease-specific quality of life in comparison to medical therapy?

KCCQ overall score from baseline was +12.5 ± 1.8 vs -3.6 ± 1.9 (p<0.001) at one year of follow-up, and +7.8 ± 2.3 vs -12.1 ± 2.3 (p<0.0001) at two years of follow-up [18].

Patient safety[18,19,20]

Mitralclip vs Medikamente: wenig Komplikationen im Zusammenhang mit Intervention

Overall **device-related complications** were reported in one RCT within the first 30 days and after one, two, and three years of follow-up. At each time point, the percentage of complications related to the MitraClip® was low and ranged from 1.4% within the first 30 days to 8.7% during three-year follow-up [18, 33]. A second RCT reported only peri-procedural complications, with a rate of 14.6% in the MitraClip® arm [17]. The third RCT reported, that no device-related serious adverse events (SAE) occurred in the intervention group [38].

In the Mitra-FR trial, the occurrence of **MACE** was defined as the primary safety endpoint. After one year of follow-up, there was no significant difference in MACE between MV repair intervention and medical therapy (56.6% vs 51.3%) [17]. The rate of MACE was also comparable between the two study groups after two years of follow-up (66.4% vs 65.4%) [21].

Mitralclip vs Medikamente: kein Unterschied bei SAE nach 2 bzw. 3 Jahren

The number of **all SAEs** was reported in one RCT after one and after two years [21] and in a second RCT after three years of follow-up [49]. Overall, SAE rates were high in both RCTs and all study groups (about 80 to 90%), with no difference between the device group and medical therapy group. In addition, selected SAEs were separately reported in the COAPT and the Mitra-FR trials. After one, two or three years, there were no significant differences between MitraClip® and medical therapy in the rates of myocardial infarction, stroke, or heart transplantations.

As in the RCTs comparing MitraClip® to MV surgery, results from subgroup analyses in the COAPT and the Mitra-FR trial comparing MitraClip® to medical therapy alone were only reported for efficacy outcomes but not for safety outcomes. Therefore, no information is available on whether there are patient groups that are more likely to be harmed through the use of the MitraClip® technology compared to medical treatment.

[18] **C0008** – How safe is MitraClip® implementation in comparison to medical therapy?

[19] **C0004** – How does the frequency or severity of harms change over time or in different settings?

[20] **C0005** – What are the susceptible patient groups that are more likely to be harmed through the use of MitraClip®?

4 Certainty of evidence

Verzerrungspotenzial: Cochrane RoB 2

RoB for individual RCTs was assessed with the Cochrane RoB v.2 tool [39] and is presented in Table A-3 and Table A-4 in the Appendix.

RCT: geringes bis moderates RoB

Across the four included RCTs, none was ranked as having low RoB, three as having a moderate RoB [9, 10, 13-18, 21, 33] and one as having a high RoB [38]. The main reason for a moderate RoB in all three RCTs was the open-label study design, with participants, investigators, and outcome assessors being aware of the intervention during the study. In the RCT with high RoB, reasons for judgement were the sparse data on the methodology of the study (randomization process, allocation concealment, outcome assessment, statistical considerations) and the absence of blinding.

Vertrauenswürdigkeit der Evidenz nach GRADE

The certainty of the evidence was rated according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) schema for each endpoint individually [7]. Each study was rated by two independent researchers. In case of disagreement, a third researcher was involved in solving the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [7].

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

Vertrauenswürdigkeit der Evidenz insgesamt niedrig bis sehr niedrig für Mitralclip vs Operation und moderat bis sehr niedrig für Mitralclip vs Medikamente

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below and in the evidence profile in Appendix Table A-5 and Table A-6.

Overall the certainty of the evidence for the effectiveness and safety of MitraClip® in comparison to surgery in patients with MR is low to very low (see Table 4-1). For comparing MitraClip® to medical therapy in patients with MR ineligible for surgery, the overall certainty of the evidence for the effectiveness and safety is moderate to very low (see Table 4-2).

Table 4-1: Summary of findings table of percutaneous MV repair with mitral clip device versus MV surgery

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with MV surgery	Risk with MitraClip				
Overall mortality (5 years follow-up)	268 per 1000	209 per 1000	RR 0.78 (0.46 to 1.32)	210 (1 RCT)	⨁⨁◯◯ Low	Only 1 RCT
Hospitalization for heart failure	No evidence available					
Mitral regurgitation severity (patients with MR grade 0+ to 2+ at 5 years follow-up)	975 per 1000	799 per 1000	RR 0.82 (0.74 to 0.92)	141 (1 RCT)	⨁◯◯◯ Very low	Only 1 RCT
Generic quality of life (SF-36 at 1 year follow-up)	*Physical summary:* MD 0 points (3.12 lower to 3.12 higher) *Mental summary:* MD 1.9 points higher (1.2 lower to 5.0 higher)		-	192 (1 RCT)	⨁◯◯◯ Very low	Only 1 RCT
Function (patients with NYHA funcional class I or II at 5 years follow-up)	976 per 1000	917 per 1000	RR 0.94 (0.87 to 1.01)	148 (1 RCT)	⨁◯◯◯ Very low	Only 1 RCT
Complications (major vascular complications within 30 days)	*MitraClip®:* 9 (4.9%) *MV surgery:* 0 (0%)		-	279 (1 RCT)	⨁◯◯◯ Very low	Only 1 RCT
Serious adverse events (5 years follow-up)	675 per 1000	716 per 1000	RR 1.06 (0.88 to 1.26)	258 (1 RCT)	⨁⨁◯◯ Low	Only 1 RCT

Abbreviations: *CI – confidence interval; MD – mean difference; MR – mitral regurgitation; NA – not applicable; ns – statistically not significant; NYHA – New York Heart Association; RCT – randomized controlled trial; RR – risk ratio; SF-36: short form 36 questionnaire*

Table 4-2: Summary of findings table of percutaneous MV repair with mitral clip device versus optimal medical therapy in patients ineligible for surgery

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with MV surgery	Risk with MitraClip				
Overall mortality (1 year follow-up)	223 per 1000	203 per 1000	RR 0.91 (0.72 to 1.17)	949 (3 RCTs)	⨁⨁⨁◯ Moderate	
Overall mortality (2 years follow-up)	373 per 1000	306 per 1000	RR 0.82 (0.56 to 1.22)	918 (2 RCTs)	⨁⨁◯◯ Low	Increased heterogeneity
Cardiovascular mortality (1 years follow-up)	198 per 1000	204 per 1000	RR 1.03 (0.67 to 1.57)	335 (2 RCTs)	⨁⨁◯◯ Low	
Cardiovascular mortality (2 years follow-up)	313 per 1000	247 per 1000	RR 0.79 (0.53 to 1.18)	918 (2 RCTs)	⨁⨁◯◯ Low	Increased heterogeneity

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with MV surgery	Risk with MitraClip				
Hospitalization for heart failure (1 year follow-up)	491 per 1000	182 per 1000	RR 0.37 (0.03 to 4.20)	335 (2 RCTs)	⨁◯◯◯ Very low	Increased heterogeneity
Hospitalization for heart failure (2 years follow-up)	528 per 1000	401 per 1000	RR 0.76 (0.53 to 1.09)	918 (2 RCTs)	⨁⨁◯◯ Low	Increased heterogeneity
Mitral regurgitation severity (patients with MR grade 0+ to 2+ at 1 year follow-up)	447 per 1000	926 per 1000	RR 2.07 (1.76 to 2.43)	416 (2 RCTs)	⨁⨁⨁◯ Moderate	
Mitral regurgitation severity (patients with MR grade 0+ to 2+ at 2 years follow-up)	460 per 1000	993 per 1000	RR 2.16 (1.79 to 2.62)	286 (1 RCT)	⨁◯◯◯ Very low	Only 1 RCT
Generic quality of life (EQ5D at 1 year follow-up)	*Global summary:* 60.8 ± 20.3 vs 58.6 ± 18.2; ns			180 (1 RCT)	⨁◯◯◯ Very low	Only 1 RCT
Desease-specific quality of life (KCCQ at 1 and 2 years follow-up)	*Overall summary – 1 year:* MD 16.1 points higher (15.81 higher to 16.39 higher) *Overall summary – 2 years:* MD 19.9 points higher (19.54 higher to 20.26 higher)			614 (1 RCT)	⨁⨁◯◯ Low	Only 1 RCT
Function (patients with NYHA funcional class I or II at 1 year follow-up)	532 per 1000	724 per 1000	RR 1.36 (0.92 to 2.01)	726 (3 RCTs)	⨁◯◯◯ Very low	Increased heterogeneity
Function (patients with NYHA funcional class I or II at 2 years follow-up)	478 per 1000	635 per 1000	RR 1.33 (1.03 to 1.71)	589 (2 RCTs)	⨁⨁◯◯ Low	Increased heterogeneity
Complications (device-related complications within 30 days)	1 RCT: 21/144 (14.6%) peri-procedural complications; 1 RCT: 4/293 (1.4%) device-related complications			437 (2 RCTs)	⨁⨁⨁◯ Moderate	Results not pooled
Serious adverse events (2 years follow-up)	842 per 1000	851 per 1000	RR 1.01 (0.92 to 1.11)	304 (1 RCT)	⨁⨁⨁◯ Moderate	Only 1 RCT
Serious adverse events (3 years follow-up)	615 per 1000	929 per 1000	RR 1.51 (1.38 to 1.66)	614 (1 RCT)	⨁⨁⨁◯ Moderate	Only 1 RCT

Abbreviations: *CI – confidence interval; EQ5D – European quality of life 5 dimensions questionnaire; MD – mean difference; MR – mitral regurgitation; NA – not applicable; ns – statistically not significant; NYHA – New York Heart Association; RCT – randomized controlled trial; RR – risk ratio*

5 Discussion

Summary of findings

1 RCT zu Mitralclip vs Operation und 3 RCTs zu Mitralclip vs medikamentöse Therapie eingeschlossen

Since the last report update on the percutaneous repair of mitral regurgitation published in 2012 by the LBI-HTA [2], three RCTs comparing percutaneous MV repair with the MitraClip® device to medical therapy have been published [15-18, 21, 33, 38]. For the comparison of percutaneous MV repair with the MitraClip® device versus MV surgery, no additional RCT could be identified, but for the only RCT already included in the 2012 report, long-term results after four [13] and five years of follow-up [14] have been published. No RCTs investigating other percutaneous MV repair clipping systems than MitraClip® could be identified.

The only RCT investigating MitraClip® compared to MV surgery included a total of 279 participants with primary or secondary MR grade 3+ or 4+ eligible for surgery. After five years of follow-up, results on overall mortality, surgical (re-)interventions, MR severity, NYHA functional class and (serious) adverse events were reported [14]. Results on patients' quality of life were only available after one-year follow-up [10].

Mitralclip vs Operation:

Overall, the results on efficacy and safety of percutaneous repair of mitral regurgitation with MitraClip® compared with MV surgery can be summarized as follows:

- No difference in overall mortality at four and five years of follow-up

  kein Unterschied bei Mortalität und Leistungsfähigkeit
- Significant more necessary re-interventions during five years of follow-up in the device arm compared to MV surgery arm
- Significant less patients with none to moderate MR symptoms (grade 0+ to 2+) with MitraClip® compared to MV surgery after four and five years of follow-up

  Vorteil für Operation bei Schweregrad der Mitralklappeninsuffizienz und der notwendigen Re-Interventionen
- No difference in NYHA functional class at four and five years of follow-up
- No difference in QoL after one year of follow-up, but no long-term results on QoL were reported.
- Low rates of complications, but significantly more during the first 30 days with MitraClip® compared to MV surgery

  SAE vergleichbar
- No difference in serious adverse events during five years of follow-up

In summary, in patients with moderate to severe primary or secondary MR, which are eligible for MV surgery, the percutaneous MV repair with the MitraClip® device is comparably safe but less effective than MV repair or replacement surgery.

Three RCTs, including 952 participants with secondary moderate-to-severe or severe MR who were considered ineligible for MV surgery by a heart team, i.e. patients at high risk of mortality from open surgery investigated percutaneous MV repair with the MitraClip® device to optimal medical therapy for heart failure. Results were available after a one year of follow-up for all three trials [17, 18, 38], after two years of follow-up for two trials [18, 21] and after three years of follow-up for one RCT [33]. All RCTs reported on overall mortality, hospitalization for heart failure, NYHA functional class and serious adverse events. Results on MR severity, quality of life and complications were reported in two trials, while the number of surgical interventions during follow-up was reported only in one RCT. In general, the three includ-

ed RCTs showed divergent results concerning the efficacy of percutaneous MV repair with the MitraClip® device compared to medical therapy alone.

Mitralclip vs Medikamente:

Overall, the results on efficacy and safety of percutaneous repair of MR with MitraClip® compared with medical therapy can be summarized as follows:

kein Unterschied bei Mortalität und Hospitalisierungen

- No difference in overall or cardiovascular mortality after one and two years of follow-up
- No difference in hospitalization rate for heart failure after one and two years of follow-up

Vorteil für Mitralclip bei Schweregrad und Leistungsfähigkeit

- Less necessary interventions during two and three years of follow-up with MitraClip® compared to medical therapy
- Significant more patients with none to moderate MR symptoms (grade 0+ to 2+) with MitraClip® compared to medical therapy after one and two years of follow-up

Lebensqualität nicht eindeutig

- Significant more patients with NYHA functional class I or II (no or only slight limitations) with MitraClip® compared to medical therapy after one and two years of follow-up

SAE vergleichbar

- Results on QoL were inconclusive: no difference in generic QoL after one-year follow-up in one RCT, and significant improvement in disease-specific QoL with MitraClip® compared to medical therapy in a second RCT after one and two years of follow-up.
- Low rates of complications related to device or procedure.
- No difference in serious adverse events during one to three years of follow-up

Studienergebnisse insgesamt uneindeutig

Summarizing the results of all three RCTs, in patients with moderate to severe secondary MR, which are not eligible for MV surgery, there might be a small benefit for percutaneous MV repair with the MitraClip® device compared to optimal medical therapy alone, especially in terms of MR severity and function. But, as mentioned above, the results of the three RCTs are inconclusive; therefore, the overall evidence remains uncertain.

Interpretation of findings

Mitralclip vs Medikamente:

The included RCTs are very heterogeneous regarding their included patient groups. First, the Mitra-CRT trial included a very specific group with only patients having a dilated cardiomyopathy (LVEF 15-40%), who were non-responders to cardiac resynchronization therapy and had a secondary MR grade ≥ 3+ [38]. The Mitra-FR trial also included patients with LVEF 15-40% with no restrictions on LV dimensions. The cut-offs for inclusion concerning MR severity were EROA > 20mm^2 or RV > 30ml. Patients with severe pulmonary hypertension or moderate to severe right ventricular dysfunction were excluded. In addition, patients in the Mitra-FR trial had to have at least one hospitalization for heart failure within 12 months prior to study entry [15]. On the contrary, patients in the COAPT trial had an LVEF of 20-50% with an LVESD < 70mm. The MR-severity cut-offs for inclusion were EROA > 30mm^2 or RV > 45ml. Patients with severe pulmonary hypertension or moderate to severe right ventricular dysfunction were not excluded in the COAPT trial. Also, patients without recent hospitalization for heart failure were included if they had raised B-type natriuretic peptide levels [16]. In summary, patients in the Mitra-FR trial seem to have a less severe MR, but more advanced heart failure than those in the COAPT trial. These differences might be an explanation for the divergent study results. Therefore, two post-

Studienpopulationen sehr unterschiedlich

Mitra-CRT Studie: nur Patient*innen nach Revaskularisierung

Patient*innen in Mitra-FR Studie weniger schwere Mitralklappeninsuffizienz aber schwerere Herzinsuffizienz als in COAPT Studie

Patient*innengruppe mit Vorteil durch Mitralclip nicht eindeutig

hoc analyses have been published in 2021 to prove this hypothesis. First, a subgroup-analysis of the COAPT trial including only patients with characteristics comparable to the patients enrolled in the Mitra-FR trial were performed [32]. Contrary to the overall results of the COAPT trial, these analyses resulted in no benefit regarding overall mortality or hospitalization for heart failure for the MitraClip® intervention, while QoL or function were still improved. For the Mitra-FR trial, posthoc subgroup analyses evaluating the impact of MR severity and LV parameters on the study results were performed [35]. In these analyses, no specific subgroup of patients, also not patients comparable to the COAPT cohort, could be identified that might benefit from MitraClip® implantation in comparison to medical therapy alone. Thus, it remains unclear whether a particular group of patients with moderate to severe MR, despite medical therapy, may benefit from percutaneous repair of mitral regurgitation with MitraClip®.

optimale medikamentöse Therapie in RCTs unterschiedlich

Endpunkte unterschiedlich definiert

Erfahrung der Operateur*innen unterschiedlich

In addition to the different study populations, some other factors that differ between the Mitra-FR and COAPT trials may have led to the divergent results. First, the medical therapy was different. While in the Mitra-FR trial, drug therapy was allowed to be adjusted in both study-groups, and therefore continuous optimization of the therapy was possible, the COAPT trial only included patients who were already receiving a maximum tolerable medical treatment. There were also differences in the definition of the endpoints. For example, the Mitra-FR trial reported only unplanned heart failure hospitalizations, whereas the primary endpoint of the COAPT study was all hospitalizations for heart failure. The lack of blinding could have led to bias in the case of the COAPT study, as clinicians may have included already planned hospitalizations [50, 51]. Finally, the COAPT study was also sponsored by the manufacturer of MitraClip, which bears an additional risk of bias, whereas the Mitra-FR was an academic study. Another special feature of the MITRA-FR study is that, prior to the study, each center only had to have previously implanted five MitraClips to qualify as a center. In MITRA-FR, a significantly higher percentage of clip implantations were not possible (9.2% vs 4.9%), and the proportion of remaining severe mitral regurgitation after mitral clipping was also higher. This could possibly indicate a higher level of expertise among the interventionists in the other studies.

Internal and external validity

Limitation bei RCTs durch fehlende Verblindung

Overall, the number of published RCTs investigating percutaneous MV repair with a clip device in patients with MR is low and limited to only one device. The certainty of evidence for the comparison of percutaneous MV repair with the MitraClip® device versus MV surgery is low to very low due to the imprecision of the results and the increased risk of bias. For the comparison of percutaneous MV repair with the MitraClip® device versus optimal medical therapy the certainty of evidence ranges from moderate to very low. Limitations mainly arise from imprecision and/or inconsistency of the results. Increased RoB is mainly based on the fact that in none of the included RCTs participants, investigators or outcome assessors were blinded regarding the randomized intervention.

keine Einschränkung bei Übertragbarkeit

For external validity, there are no limitations in terms of applicability of the study results in terms of study population, intervention or setting (see Appendix Table A-7).

There are several published systematic reviews investigating MitraClip® either in comparison to surgical MV repair or to medical therapy. Overall, the results of these reviews are comparable to those of this update-report.

Mitralclip vs Operation: 2 SR mit 1 RCT und mehreren Beobachtungsstudien zeigen Vorteil für Operation

Two recent systematic reviews compared MitraClip® versus MV surgery [52, 53]. Besides the only RCT for this comparison (EVEREST-II), both included results from various non-randomized observational studies. The meta-analysis in the reviews showed significant advantages for surgery in terms of MR severity, and re-operations, with comparable mortality and adverse event rates. The length of hospital stay was significantly shorter in the MitraClip® groups than in the surgery groups. Based on these results, the authors of one review concluded, that superiority of surgical MV repair compared to MitraClip® is highlighted [53], while the author group of the second review suggests a patient-tailored approach to receive the best results [52].

Mitralclip vs Medikamente: 4 SR mit 2 RCTs und 2-7 Beobachtungsstudien zeigen Vorteil für Mitraclip, aber Ergebnisse sehr heterogen

For the comparison of MitraClip® versus medical therapy four systematic reviews were published in 2020/2021 [54-57]. They included results for two RCTs (Mitra-FR and COAPT) and two [55] to seven [57] additional non-randomized observational studies. Summarizing results from all included studies, MitraClip® leads to a reduction in overall mortality, less heart failure hospitalization rates and less severe MR compared to medical therapy alone. Thus, the review authors concluded that MitraClip® might be an option for selected patient groups, although the results showed remarkable heterogeneity.

Limitations of the report

Limitation des Berichts: nur RCTs inkludiert

This report is limited to RCTs for efficacy and safety outcomes. Therefore, non-randomized controlled studies, registries and uncontrolled single-arm studies were excluded. As a result, not the full body of evidence was considered. However, since RCTs, if conducted in a methodologically adequate manner and appropriate to the respective research question, are affected by the lowest uncertainty of results, the excluded studies would not have changed the interpretation and the drawn conclusion of the report.

Only published study data were used for this report; unpublished raw data from the included trials and individual patient data were not available.

Ongoing studies

jeweils 4 laufende Studien zu Mitralclip vs Operation bzw. vs medikamentöser Therapie

There are several ongoing RCTs on MitraClip® implantation listed in the clinical trials registries. Four RCTs comprising a total of 1360 participants investigate MitraClip® versus MV surgery. Primary completion dates range from 02/2024 to 01/2028. Four other ongoing RCTs, including 2128 patients, compare MitraClip® to medical therapy. Primary completion dates of these trials range from 08/2023 to 08/2025 (see Appendix Table A-8). For three ongoing RCTs, the study protocols have already been published [58-60]. No study registry entries for RCTs investigating other percutaneous MV repair clipping systems than MitraClip® were found.

6 Recommendation

In Table 6-1 the scheme for recommendations is displayed and the according choice is highlighted.

Empfehlung

Table 6-1: Evidence based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
X	The inclusion in the catalogue of benefits is **currently not recommended**.
	The **inclusion in** the catalogue of benefits is **not recommended**.

Reasoning:

According to the available evidence, in patients with moderate-to-severe or severe mitral valve regurgitation, whether primary or secondary, who are suitable for surgery, the evaluated technology MitraClip® is shown to be comparably safe but less effective than the alternative option of mitral valve repair surgery. The certainty of the evidence for this comparison is low. The current evidence is inconclusive for patients with secondary moderate-to-severe or severe mitral valve regurgitation, which are not eligible for mitral valve surgery, whether the assessed technology MitraClip® is more effective than the comparator medical therapy alone. New study results from eight ongoing RCTs will potentially influence the effect estimate considerably.

Mitralclip vs Operation: Mitralclip weniger wirksam, Verlässlichkeit der Evidenz aber gering

Mitralclip vs Medikamente: Ergebnisse nicht eindeutig

The re-evaluation is recommended in 2026.

Re-Evaluierung 2026

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Patients eligible for surgery: percutaneous MV repair with mitral clip device versus surgery: Results from randomized controlled trials

Name of study	**EVEREST-II**	
Study description		
Author, year	Mauri 2010 [9]; Feldmann 2011 [10]; Mauri 2013 [13]; Feldman 2015 [14]	
Country	USA + Canada	
Sponsor	Abbott Medical Devices	
Study design	Multicentre RCT, 2-arm, parallel, open-label, non-inferiority	
Intervention/Product	Percutaneous mitral valve repair using MitraClip® implant	
Comparator	Mitral valve repair or replacement surgery	
Number of pts	279 (184 vs 95)	
Follow-up (months)	60	
Loss to follow-up, n (%)	After 60 months: 30 (13) vs 39 (30)	
Main inclusion criteria	■ Moderate-severe (3+) or severe (4+) chronic mitral regurgitation (MR) and: ■ Symptomatic with N25% left ventricular ejection fraction and LVESD ≤ 55mm or, ■ Asymptomatic with one or more of the following: ■ LVEF 25-60% ■ LVESD ≥ 40mm ■ New onset of atrial fibrillation ■ Pulmonary hypertension defined as pulmonary artery systolic pressure N50 mmHg at rest or N60 mmHg with exercise ■ Candidate for mitral valve repair or replacement surgery, including cardiopulmonary bypass ■ Primary regurgitant jet originates from malcoaptation of the A2 and P2 scallops of the MV. If a secondary jet exists, it must be considered clinically insignificant	
Main inclusion criteria	■ Need of any other cardiac surgery or any emergency surgery ■ Acute myocardial infarction in prior 12 weeks ■ Any endovascular procedure in prior 30 days ■ Severe mitral annular calcification ■ Renal insufficiency	
Population characteristics		
	MitraClip® (n=184)	***Surgery (n=95)***
Age of patients [yrs], mean ± SD	67.3 ± 12.8	65.7 ± 12.9
Male, n (%)	115 (62)	63 (66)

Name of study	EVEREST-II		
Previous MI, n (%)	40 (22)	20 (21)	
Atrial fibrillation, n (%)	59 (32)	35 (37)	
Diabetes mellitus, n (%)	14 (8)	10 (11)	
COPD, n (%)	27 (15)	14 (15)	
Previous CABG, n (%)	38 (21)	18 (19)	
Previous PCI, n (%)	44 (24)	15 (16)	
NYHA function class: I/II/III/IV, %	9/40/45/7	20/33/43/4	
MR severity: 1+ to 2+/2+/3+/4+, %	0/4/71/25	1/6/71/22	
LVEF [%], mean ± SD	60.0 ± 10.1	60.6 ± 11.0	
LVEDV [ml/m^2], mean ± SD	159.03 ± 37.33	160.39 ± 46.66	
EROA [mm^2], mean ± SD	56 ± 38	59 ± 35	
Outcomes			
Efficacy			
Follow-up	***1 year***	***4 years***	***5 years***
Overall mortality, n (%)	11/184 (6) vs 5/95 (6); p=1.0	28/161 (17.4) vs 13/73 (17.8); p=0.914	32/154 (20.8) vs 15/56 (26.8); p=0.36
Cardiovascular mortality, n (%)	nr	nr	nr
Composit EP: Freedom from death, from surgery for MV dysfunction, from grade 3+ or 4+ MR	100/184 (55) vs 65/95 (73); p=0.007	64/161 (39.8) vs 39/73 (53.4); p=0.070	68/154 (44.2) vs 36/56 (64.3); p=0.01
Surgical (re)-intervention, n (%)	37/184 (21) vs 2/95 (2.2); p<0.001	40/161 (24.8) vs 4/73 (5.5); p<0.001	43/154 (27.9) vs 5/56 (8.9); p=0.003
Hospitalization for HF, n (%)	nr	nr	nr
MR severity, n (%)			
None (0)	9/153 (6) vs 13/69 (19)	6/105 (5.3) vs 5/48 (10.5)	3/101 (2.5) vs 6/40 (15)
Mild (1)	57/153 (37) vs 39/69 (57)	39/105 (36.8) vs 34/48 (71.1)	45/101 (45) vs 31/40 (77.5)
Moderate (2)	41/153 (27) vs 9/69 (13)	39/105 (36.8) vs 4/48 (7.9)	33/101 (32.5) vs 2/40 (5)
Moderate-to-severe (3)	21/153 (14) vs 3/69 (4)	22/105 (21.1) vs 4/48 (7.9)	19/101 (18.75) vs 1/40 (2.5)
Severe (4)	7/153 (5) vs 0/69	0/105 vs 1/48 (2.6)	1/101 (1.25) vs 0/40
NYHA-Class, n (%)			
I	104/151 (68.9) vs 46/66 (69.7)	70/105 (66.7) vs 35/48 (72.9)	70/106 (66.0) vs 33/42 (78.6)
II	44/151 (29.1) vs 12/66 (18.2)	29/105 (27.6) vs 10/48 (20.8)	27/106 (25.5) vs 8/42 (19.0)
III	3/151 (2.0) vs 7/66 (10.6)	6/105 (5.7) vs 3/48 (6.3)	9/106 (8.5) vs 1/42 (2.4)
IV	0/151 vs 1/66 (1.5)	0/105 vs 0/48	0/106 vs 0/42

Name of study	EVEREST-II		
Quality of life, mean ± SD			
SF-36 physical summary	Δ: 4.4 ± 9.8 vs 4.4 ± 10.4; p=0.98	nr	nr
SF-36 mental summary	Δ: 5.7 ± 9.9 vs 3.8 ± 10.3; p=0.24		
6MWT distance [metres], mean ± SD	nr	nr	nr
LVEF [%], mean ± SD	Δ: -2.8 ± 7.2 vs -6.8 ± 10.1; p=0.005	nr	Δ 1 to 5 y: -1.8 ± 0.8 vs 0.7 ± 1.2; p=nr
Safety			
Follow-up	***1 year***	***4 years***	***5 years***
Overall complications, n (%)	nr	nr	nr
Major vascular complications, n (%)	Within 30 days: 9/184 (4.9) vs 0/95	nr	nr
Peri-procedural complications, n (%)	nr	nr	nr
Post-procedural complications, n (%)	nr	nr	nr
Procedure-related mortality, n (%)	nr	nr	nr
MACE, n (%)	nr	nr	nr
All SAE, n (%)	*30 days:* 13/136 (9.6) vs 45/79 (57.0); p<0,001 [b,c] *1 year:* 39/184 (21.2) vs 44/95 (46.3); p<0.001 [b]	nr	127/178 (72.4) vs 54/80 (67.5) [d]
Stroke, n (%)	nr	nr	nr
MI, n (%)	nr	nr	nr
Infections, n (%)	nr	nr	nr
Heart transplantation or mechanical cardiac assistance, n (%)	nr	nr	nr
Heart transplantation, n (%)	nr	nr	nr
Minor AE, n (%)	nr	nr	168/178 (94.4) vs 80/80 (100) [d]

Abbreviations: 6MWT – 6-minutes walking test; AE – adverse events; CABG – coronary artery bypass graft; CAD –coronary artery disease; COPD – chronic obstructive pulmonary disease; EROA – effective regurgitant orifice area; GDMT – guideline-directed medical therapy; HF – heart failure; IQR – interquartile range; LVEDV – left ventricular enddiastolic volume; LVEF – left ventricular ejection fraction; MACE – major cardiovascular adverse event; MI – myocardial infarction; MR – mitral regurgitation; MV – mitral valve; nr – not reported; NYHA – New York Heart Association; PCI – percutaneous coronary intervention; RCT – randomized controlled trial; SAE – serious adverse events; SD – standard deviation; SF-36 – short form 36; vs – versus

Explanations:

[a] *Combined EP = CV death, HF rehospitalization, heart transplant*

[b] *Major adverse events, defined as a composite of death, myocardial infarction, reoperation for failed mitral-valve surgery, nonelective cardiovascular surgery for adverse events, stroke, renal failure, deep wound infection, mechanical ventilation for more than 48 hours, gastrointestinal complication requiring surgery, new-onset permanent atrial fibrillation, septicemia, and transfusion of 2 units or more of blood*

[c] *Per-protocol cohort*

[d] *Results from clinicaltrials.gov entry [48]*

Table A-2: Patients ineligible for surgery: percutaneous MV repair with mitral clip device versus medical therapy: Results from randomized controlled trials (Part 1)

Name of study	COAPT
Study description	
Author, year	Mack 2018 [16]; Stone 2018 [18]; Mack 2021 [33]
Country	USA
Sponsor	Abbott Medical Devices
Study design	Multicentre RCT, 2-arm, parallel, open-label, superiority
Intervention/Product	Percutaneous mitral valve repair using MitraClip® implant + maximally tolerated guideline-directed medical therapy (GDMT)
Comparator	GDMT alone
Number of pts	614 (302 vs 312)
Follow-up (months)	60
Loss to follow-up, n (%)	After 24 months: 14 (4.6) vs 29 (9.3)
Main inclusion criteria	■ Age ≥ 18 years ■ Symptomatic secondary MR (≥ 3+) due to cardiomyopathy of either ischemic or nonischemic etiology ■ NYHA Class II or above. ■ LVEF 20-50%. ■ Minimum of one hospitalization for heart failure within 12 months prior to randomization and/or a corrected brain natriuretic peptide (BNP) ≥300 pg/mL or a corrected N-terminal-proBNP ≥1500 pg/mL ■ Adequately treated per applicable standards, including for CAD, LV dysfunction, MR, and HF ■ Not eligible for a mitral surgery
Main inclusion criteria	■ Untreated clinically significant CAD requiring revascularisation ■ CABG, PCI or TAVR within 30 days prior to randomization ■ COPD requiring continous home oxigen therapy or chronic outpatient oral steroid use ■ Tricuspid valve disease requiring surgery or transcatheter intervention ■ Aortic valve disease requiring surgery ■ Cerebrovascular accident within 30 days prior to subject registration ■ Severe symptomatic carotid stenosis (> 70% by ultrasound) ■ Carotid surgery or stenting within 30 days prior to subject registration ■ Need for emergent or urgent surgery for any reason or any planned cardiac surgery within the next 12 months. ■ Prior mitral valve leaflet surgery or any currently implanted prosthetic mitral valve, or any prior transcatheter mitral valve procedure ■ Active infection requiring current antibiotic therapy ■ Terminal renal insufficiency (renal replacement therapy) ■ Severe hepatic insufficiency ■ Stroke within 3 months prior to randomization. ■ Life expectancy of less than ■ 12 months due to non-cardiac conditions

Name of study	COAPT		
Population characteristics			
	MitraClip	***GDMT***	
Age of patients [yrs], mean ± SD	71.7 ± 11.8	72.8 ± 10.5	
Male, n (%)	201 (67)	192 (62)	
Previous MI, n (%)	156 (52)	160 (51)	
Atrial fibrillation, n (%)	168 (56)	159 (51)	
Diabetes mellitus, n (%)	106 (35)	123 (39)	
COPD, n (%)	71 (24)	72 (23)	
Previous CABG, n (%)	121 (40)	126 (40)	
Previous PCI, n (%)	130 (43)	153 (49)	
NYHA function class: I/II/III/IV, %	0/43/51/6	0/35/54/11	
MR severity: 1+ to 2+/2+/3+/4+, %	0/0/49/51	0/0/55/45	
LVEF [%], mean ± SD	31.3 ± 9.1	31.3 ± 9.6	
LVEDV [ml/m^2], mean ± SD	194.4 ± 69.2	191.0 ± 72.9	
EROA [mm^2], mean ± SD	40 ± 15	41 ± 15	
Outcomes			
Efficacy			
Follow-up	***1 year***	***2 years***	***3 years***
Overall mortality, n (%)	57/302 (19.1) vs 70/312 (23.2) HR 0.81 [95% CI 0.57 to 1.15]; p=nr	80/302 (29.1) vs 121/312 (46.1) HR 0.62 [95% CI 0.46 to 0.82]; P<0.001	112/302 (42.8) vs 150/312 (55.5) HR 0.67 [95% CI 0.52 to 0.85]; p=0.001
Cardiovascular mortality, n (%)	nr	61/302 (23.5) vs 97/312 (38.2) HR 0.59 [95% CI 0.43 to 0.81]; p=0.001	88/302 (36.0) vs 121/312 (47.4) HR 0.65 [95% CI 0.49 to 0.85]; p=0.002
Composit EP: death from any cause or hospitalization for HF	nr	129/302 (45.7) vs 191/312 (67.9) HR 0.57 [95% CI 0.45 to 0.71]; p<0.001	161/302 (58.8) vs 244/312 (88.1) HR 0.48 [95% CI 0.39 to 0.59]; p<0.0001
Surgical (re)-intervention, n (%)	nr	1/302 (0.4) vs 7/312 (2.5) HR 0.14 [95% CI 0.02 to 1.17]; p=0.07	1/302 (0.4) vs 8/312 (3.3) HR 0.12 [95% CI 0.02 to 0.97]; p=0.047
Hospitalization for HF, n (%)	nr	92/302 vs 151/312 HR 0.53 [95% CI 0.40 to 0.70]; p<0.0001	HR 0.49 [95% CI 0.37 to 0.63]; p<0.0001
MR severity, n (%)			
None (0)	199/210 (94.8) vs 82/175 (46.9); p<0.001	161/162 (99.4) vs 57/124 (46.0); p<0.0001	85/89 (98.8) vs 39/49 (79.6); p=0.0002
Mild (1)			
Moderate (2)			
Moderate-to-severe (3)	9/210 (4.3) vs 60/175 (34.3)	0/162 vs 43/124 (34.7)	1/89 (1.2) vs 7/49 (14.3)
Severe (4)	2/210 (1.0) vs 33/175 (18.9)	1/162 (0.6) vs 24/124 (19.4)	0/89 vs 3/49 (6.1)

Name of study	COAPT		
NYHA-Class, n (%)			
I	40/237 (16.9) vs 18/232 (7.8)	122/206 (59.2) vs 81/206 (39.3); p<0.0001	72/147 (49.0) vs 45/149 (30.2); p=0.001
II	131/237 (55.3) vs 97/232 (41.8)		
III	42/237 (17.7) vs 65/232 (28.0)	nr	nr
IV	6/237 (2.5) vs 11/232 (4.7)	nr	nr
Quality of life, mean ± SD			
KCCQ Overall Summary	Δ: 12.5 ± 1.8 vs -3.6 ± 1.9; p<0.001	Δ: 7.8 ± 2.3 vs -12.1 ± 2.3; p<0.0001	nr
6MWT distance [metres], mean ± SD	Δ: -2.2 ± 9.1 vs -60.2 ± 9.0; P<0.001	Δ: -55.0 ± 10.8 vs -93.5 ± 10.9; p=0.01	nr
LVEF [%], mean ± SD	nr	nr	nr
Safety			
Follow-up	***1 year***	***2 years***	***3 years***
Overall complications, n (%)	30 days: 4/293 (1.4) [a] 1 year: 9/293 (3.4) [a]	13/293 (5.2) [a]	18/293 (8.7) [a]
Peri-procedural complications, n (%)	nr		
Post-procedural complications, n (%)	nr	nr	nr
Procedure-related mortality, n (%)	nr		
MACE, n (%)	nr	nr	nr
All SAE, n (%)	nr	nr	281/302 (93.1) vs 192/312 (93.3) [b]
Stroke, n (%)	nr	11/302 (4.4) vs 11/312 (5.1); p=0.93	16/302 (7.7) vs 18/312 (9.8); p=0.51
MI, n (%)	nr	12/302 (4.7) vs 14/312 (6.5); p=0.62	17/302 (7.7) vs 23/312 (13.3); p=0.19
Infections, n (%)	nr	nr	nr
Heart transplantation, n (%)	nr	3/302 (1.4) vs 8/312 (3.6); p=0.12	5/302 (2.6) vs 10/312 (4.9); p=0.14
Minor AE, n (%)	nr	nr	237/302 (78.48) vs 231/312 (74.04) [b]

Abbreviations: 6MWT – 6-minutes walking test; AE – adverse events; CABG – coronary artery bypass graft; CAD –coronary artery disease; COPD – chronic obstructive pulmonary disease; EROA – effective regurgitant orifice area; GDMT – guideline-directed medical therapy; HF – heart failure; IQR – interquartile range; KCCQ – Kansas City cardiomyopathy questionnaire; LVEDV – left ventricular enddiastolic volume; LVEF – left ventricular ejection fraction; MACE – major cardiovascular adverse event; MI – myocardial infarction; MR – mitral regurgitation; nr – not reported; NYHA – New York Heart Association; PCI – percutaneous coronary intervention; RCT – randomized controlled trial; SAE – serious adverse events; SD – standard deviation; TAVR – transcatheter aortic valve replacement; vs – versus

Explanations:

[a] *Device-related complications*

[b] *Results from clinicaltrials.gov entry [49]*

Table A-2: Patients ineligible for surgery: percutaneous MV repair with mitral clip device versus medical therapy: Results from randomized controlled trials (Part 2)

Name of study	Mitra-FR	MITRA-CRT
Study description		
Author, year	Obadia 2015 [15]; Obadia 2018 [17]; Iung 2019 [21]	Freixa 2022 [38]
Country	France	Spain
Sponsor	French Ministry of Health	Abbott Medical Devices
Study design	Multicentre RCT, 2-arm, parallel, open-label, superiority	Singlecentre RCT, 2-arm, parallel, open-label, superiority
Intervention/Product	Percutaneous mitral valve repair using MitraClip® implant + medical treatment for chronic heart failure with reduced LVEF according to the European guidelines	Percutaneous mitral valve repair using MitraClip® implant + optimal medical treatment (OMT)
Comparator	guideline-directed medical therapy (GDMT) alone	OMT alone
Number of pts	307 (152 vs 155)	31 (16 vs 15)
Follow-up (months)	24	12
Loss to follow-up, n (%)	After 24 months: 3 (2%) vs 15 (7.9%)	After 12 months: 0 vs 0
Main inclusion criteria	■ Age > 18 years ■ Severe secondary MR characterised, according to the European guidelines (regurgitation volume > 30mL/beat or a regurgitant orifice area > 20mm^2) ■ NYHA Class II or above. ■ LVEF 15-40%. ■ Minimum of one hospitalization for heart failure within 12 months prior to randomization. ■ Optimal standard of care therapy for heart failure according to investigator ■ Not eligible for a mitral surgery	■ Cardiac resynchronization therapy (CRT) implanted between 6 months and 5 years before inclusion. ■ Secondary MR (>2+) ■ Absence of clinical response to CRT defined by baseline NYHA III or NYHA II with a hospital admission for HF within the last 12 months. ■ Adequate CRT therapy (correct stimulation in >98% heart beats). ■ Correct position of the cardiac leads. ■ LVEF 15-40% ■ LVESD < 75mm
Main inclusion criteria	■ Primary mitral regurgitation ■ MI or CABG within 3 months prior to randomization ■ Cardiac resynchronisation therapy within 3 months prior to randomization ■ Need for any cardiovascular surgery ■ Coronary angioplasty within 1 month prior to randomization. ■ Previous surgical mitral valve repair ■ Active infection requiring current antibiotic therapy ■ Terminal renal insufficiency (renal replacement therapy) ■ Severe hepatic insufficiency ■ Stroke within 3 months prior to randomization. ■ Concurrent medical condition with a life expectancy of less than ■ 12 months ■ Uncontrolled systemic hypertension	■ Severe Renal Insufficiency (DFGe < 30). ■ Life expectancy < 1 year. ■ Anatomical contraindication for MitraClip® ■ Hemodynamic instability before inclusion defined by SBP < 70mmHg or the need of inotropic treatment within the previous 3 months

Name of study	Mitra-FR		MITRA-CRT	
Population characteristics				
	MitraClip	*GDMT*	*MitraClip*	*OMT*
Age of patients [yrs], mean ± SD	70.1 ± 10.1	70.6 ± 9.9	72.1 ± 7	67.2 ± 6
Male, n (%)	120 (79)	107 (70)	13 (81)	12 (80)
Previous MI, n (%)	75 (49)	52 (34)	nr	
Atrial fibrillation, n (%)	49 (35)	48 (33)	9 (56)	5 (33)
Diabetes mellitus, n (%)	50 (33)	39 (26)	2 (13)	5 (33)
COPD, n (%)	nr	nr	nr	nr
Previous CABG, n (%)	nr	nr	nr	nr
Previous PCI, n (%)	nr	nr	nr	nr
NYHA function class: I/II/III/IV, %	0/37/54/9	0/29/63/8	0/6/81/13	0/20/80/0
MR severity: 1+ to 2+/2+/3+/4+, %	nr	nr	0/6/19/75	0/0/33/67
LVEF [%], mean ± SD	33.3 ± 6.5	32.9 ± 6.7	20 (16.5-27) a	22 (19-25) a
LVEDV [ml/m2], mean ± SD	136.2 ± 37.4	134.5 ± 33.1	136.3 ± 43.1	137.4 ± 39.0
EROA [mm2], mean ± SD	31 ± 10	31 ± 11	54 ± 46	46 ± 10
Outcomes				
Efficacy				
Follow-up	***1 year***	***2 years***	***1 year***	
Overall mortality, n (%)	37/152 (24.3) vs 34/152 (22.4)	53/152 (23.1) vs 52/152 (22.8)	2/16 (13) vs 3/15 (20); p=0.65	
Cardiovascular mortality, n (%)	33/152 (21.7) vs 31/152 (20.4)	47/152 (20.5) vs 48/152 (21.1)	1/16 (7) vs 2/15 (13); p=0.60	
Composit EP	83/152 (54.6) vs 78/152 (51.3) [b]; p=0.53	97/152 (63.8) vs 102/152 (67.1) [b]	2/16 (13) vs 10/15 (67); p=0.003 [c]	
Surgical re-intervention, n (%)	nr	nr	nr	
Hospitalization for HF, n (%)	74/152 (48.7) vs 72/152 (47.4) [d]	85/152 (55.9) vs 94/152 (62.3) [d]	1/16 (7) vs 10/15 (67); p=0.002	
MR severity, n (%)			p=0.005	
None (0)	nr	nr	nr	
Mild (1)	nr	nr	5/16 (39) vs 1/15 (8)	
Moderate (2)	nr	nr	6/16 (46) vs 2/15 (17)	
Moderate-to-severe (3)	nr	nr	2/16 (15) vs 2/15 (17)	
Severe (4)	nr	nr	0/16 vs 7/15 (58)	
NYHA-Class, n (%)			p<0.001	
I	21/114 (18.5) vs 12/112 (10.5)	20/90 (22.1) vs 14/87 (15.8)	2/16 (14) vs 0/15	
II	60/114 (52.5) vs 63/112 (56.5)	52/90 (57.9) vs 45/87 (51.6)	10/16 (72) vs 1/15 (8)	

Name of study	Mitra-FR		MITRA-CRT
III	22/114 (19) vs 26/112 (23)	13/90 (14.7) vs 23/87 (26.3)	2/16 (14) vs 7/15 (54)
IV	11/114 (10) vs 11/112 (10)	6/90 (6.3) vs 5/87 (5.3)	0/16 vs 5/15 (38)
Quality of life, mean ± SD	n=93 vs 87:		
EQ5D global score	End of study: 60.8 ± 20.3 vs 58.6 ± 18.2	nr	nr
Change in 6MWT distance [metres], median (IQR)	n=73 vs 57: 25 (-40 to 71) vs 19 (-27 to 75)	n=59 vs 42: 15 (-18 to 67) vs 22 (-6 to 94)	82.5 ± 57.5 vs -31.2 ± 47.5 e; p=0.014
Change in LVEF [%], mean ± SD	nr	nr	0 ± 7.12 vs -0.58 ± 4.36; p=0.81
Safety			
Follow-up	***1 year***	***2 years***	***1 year***
Overall complications, n (%)	nr	nr	nr
Peri-procedural complications, n (%)	21/144 (14.6)		nr
Post-procedural complications, n (%)	nr	nr	nr
Procedure-related mortality, n (%)	nr	nr	nr
MACE, n (%)	86/152 (56.6) vs 78/152 (51.3)	99/152 (66.4) vs 102/152 (65.4)	nr
All SAE, n (%)	125/152 (82.2) vs 121/152 (79.6)	129/152 (84.9) vs 128/152 (82.1)	0/16 [f]
Stroke, n (%)	7/152 (4.6) vs 1/152 (0.7)	7/152 (4.6) vs 3/152 (1.9)	nr
MI, n (%)	0/152 vs 2/152 (1.3)	0/152 vs 3/152 (1.9)	nr
Infections, n (%)	28/152 (18.4) vs 27/152 (17.8)	32/152 (21.1) vs 30/152 (19.2)	nr
Heart transplantation, n (%)	6/152 (3.9) vs 9/152 (5.9) [g]	7/152 (4.6) vs 9/152 (5.8) [g]	nr
Minor AE, n (%)	nr	nr	nr

Abbreviations: 6MWT – 6-minutes walking test; AE – adverse events; CABG – coronary artery bypass graft; COPD – chronic obstructive pulmonary disease; CRT – cardiac resynchronization therapy; EQ5D: European Quality of Life–5 Dimensions; EROA – effective regurgitant orifice area; GDMT – guideline-directed medical therapy; HF – heart failure; IQR – interquartile range; LVEDV – left ventricular enddiastolic volume; LVEF – left ventricular ejection fraction; MACE – major cardiovascular adverse event; MI – myocardial infarction; MR – mitral regurgitation; nr – not reported; NYHA – New York Heart Association; OMT – optimal medical therapy; PCI – percutaneous coronary intervention; RCT – randomized controlled trial; SAE – serious adverse events; SD – standard deviation; SBP – systolic blood pressure; vs – versus

Explanations:

[a] *Median (IQR)*

[b] *Primary composite endpoint = death from any cause or unplanned hospitalization for heart failure*

[c] *Composite EP = CV death, heart failure rehospitalization, heart transplant*

[d] *Unplanned hospitalizations for heart failure*

[e] *Mean ± standard deviation*

[f] *Procedure-related SAE*

[g] *Heart transplantation or mechanical cardiac assistance*

Risk of bias tables and GRADE evidence profile

Table A-3: Patients eligible for surgery: percutaneous MV repair with mitral clip device versus surgery: Risk of bias – study level (randomized studies), see [39]

Trial	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
EVEREST-II [9, 10, 13, 14]	Low	Some concern	Low	Some concern	Low	Some concern

Table A-4: Patients ineligible for surgery: percutaneous MV repair with mitral clip device versus medical therapy: Risk of bias – study level (randomized studies), see [39]

Trial	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
COAPT [16, 18, 33]	Low	Some concern	Low	Some concern	Low	Some concern
Mitra-FR [15, 17, 21]	Low	Some concern	Low	Some concern	Low	Some concern
Mitra-CRT [38]	Some concern	Some concern	Low	Some concern	Low	High

Table A-5: Evidence profile: efficacy and safety of percutaneous MV repair with mitral clip device in patients eligible for surgery

Quality assessment							Summary of findings				
							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MitraClip	Surgery	Relative (95% CI)	Absolute (95% CI)	
Overall mortality (5 years follow-up)											
1	Randomized trial	Not serious	NA	Not serious	Very serious [a]	None	154	56	RR 0.78 (0.46 to 1.32)	59 fewer per 1000 (145 fewer to 86 more)	⨁⨁◯◯ low
Recurrent heart failure (hospitalization for heart failure during follow-up)											
No evidence available											
Mitral regurgitation severity (patients with none to moderate MR (grade 0+ to 2+) at 5 years follow-up)											
1	Randomized trial	Serious [b]	NA	Not serious	Very serious [a]	None	101	40	RR 0.82 (0.74 to 0.92	176 fewer per 1000 (254 fewer to 78 fewer)	⨁◯◯◯ very low
Generic quality of life (SF-36 at 1 year follow-up)											
1	Randomized trial	Serious [b]	NA	Not serious	Very serious [c]	None	132	60	-	*Physical summary:* MD 0 points (3.12 lower to 3.12 higher) *Mental summary:* MD 1.9 points higher (1.2 lower to 5.0 higher)	⨁⨁◯◯ very low
Function (patients with no or slight limitations (NYHA funcional class I or II) at 5 years follow-up)											
1	Randomized trial	Serious [b]	NA	Not serious	Very serious [a]	None	106	42	RR 0.94 (0.87 to 1.01)	59 fewer per 1000 (127 fewer to 10 more)	⨁◯◯◯ very low
Complications (major vascular complications within 30 days)											
1	Randomized trial	Not serious	NA	Not serious	Very serious [d]	None	184	95	-	*MitraClip:* 9 (4.9%) *MV surgery:* 0 (0%)	⨁⨁◯◯ low
Serious adverse events (5 years follow-up)											
1	Randomized trial	Not serious	NA	Not serious	Very serious [a]	None	178	80	RR 1.06 (0.88 to 1.26)	41 more per 1000 (81 fewer to 176 more)	⨁⨁◯◯ low

Abbreviations: CI – confidence interval; MD – mean difference; MR – mitral regurgitation; NA – not applicable; NYHA – New York Heart Association; RR – risk ratio; SF-36 – short form 36 questionnaire

Comments:

[a] *Only 1 RCT; wide confidence interval*

[b] *High RoB because of patient reported outcome and patients aware of randomized procedure*

[c] *Only 1 RCT; low number of patients analyzed*

[d] *Only 1 RCT; very low event-rate*

Table A-6: Evidence profile: efficacy and safety of percutaneous MV repair with mitral clip device in patients ineligible for surgery

Quality assessment							Summary of findings				
							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MitraClip	Medical therapy	Relative (95% CI)	Absolute (95% CI)	
Overall mortality (1 years follow-up)											
3	Randomized trial	Not serious	Not serious	Not serious	Serious [a]	None	470	479	RR 0.91 (0.72 to 1.17)	20 fewer per 1 000 (63 fewer to 38 more)	⨁⨁⨁◯ moderate
Overall mortality (2 years follow-up)											
2	Randomized trial	Not serious	Serious [b]	Not serious	Serious [a]	None	454	464	RR 0.82 (0.56 to 1.22)	67 fewer per 1 000 (164 fewer to 82 more)	⨁⨁◯◯ low
Cardiovascular mortality (1 years follow-up)											
2	Randomized trial	Not serious	Not serious	Not serious	Serious [a]	None	168	167	RR 1.03 (0.67 to 1.57)	6 more per 1 000 (65 fewer to 113 more)	⨁⨁◯◯ low
Cardiovascular mortality (2 years follow-up)											
2	Randomized trial	Not serious	Serious [b]	Not serious	Serious [a]	None	454	464	RR 0.79 (0.53 to 1.18)	66 fewer per 1 000 (147 fewer to 56 more)	⨁⨁◯◯ low
Recurrent heart failure (hospitalization for heart failure at 1 year follow-up)											
2	Randomized trial	Not serious	Serious [b]	Not serious	Serious [a]	None	168	167	RR 0.37 (0.03 to 4.20)	309 fewer per 1 000 (467 fewer to 1 571 more)	⨁⨁◯◯ low
Recurrent heart failure (hospitalization for heart failure at 2 years follow-up)											
2	Randomized trial	Not serious	Serious [b]	Not serious	Serious [a]	None	454	464	RR 0.76 (0.53 to 1.09)	127 fewer per 1 000 (248 fewer to 48 more)	⨁⨁◯◯ low
Mitral regurgitation severity (patients with none to moderate MR (grade 0+ to 2+) at 1 year follow-up)											
2	Randomized trial	Serious [c]	Not serious	Not serious	Not serious	None	226	190	RR 2.07 (1.76 to 2.43)	479 more per 1 000 (340 more to 640 more)	⨁⨁⨁◯ moderate
Mitral regurgitation severity (patients with none to moderate MR (grade 0+ to 2+) at 2 years follow-up)											
1	Randomized trial	Serious [c]	NA	Not serious	Very serious [d]	None	162	124	RR 2.16 (1.79 to 2.62)	533 more per 1 000 (363 more to 745 more)	⨁⨁◯◯ very low
Generic quality of life uality of life (EQ5D at 1 year follow-up)											
1	Randomized trial	Serious [c]	NA	Not serious	Very serious [e]	None	93	87	-	*Global summary:* 60.8 ± 20.3 vs 58.6 ± 18.2; ns	⨁⨁◯◯ very low

Quality assessment							Summary of findings				
							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MitraClip	Medical therapy	Relative (95% CI)	Absolute (95% CI)	
Desease-specific quality of life (KCCQ at 1 and 2 years follow-up)											
1	Randomized trial	Serious [c]	NA	Not serious	Serious [f]	None	302	312	-	*Overall summary – 1 year:* MD 16.1 points higher (15.81 higher to 16.39 higher) *Overall summary – 2 years:* MD 19.9 points higher (19.54 higher to 20.26 higher)	⨁⨁◯◯ low
Function (patients with no or slight limitations (NYHA funcional class I or II) at 1 year follow-up)											
3	Randomized trial	Serious [c]	Serious [b]	Not serious	Serious [a]	None	367	359	RR 1.36 (0.92 to 2.01)	192 more per 1 000 (43 fewer to 537 more)	⨁⨁◯◯ very low
Function (patients with no or slight limitations (NYHA funcional class I or II) at 2 years follow-up)											
2	Randomized trial	Serious [c]	Serious [b]	Not serious	Not serious	None	296	293	RR 1.33 (1.03 to 1.71)	158 more per 1 000 (14 more to 339 more)	⨁⨁◯◯ low
Complications (device-related complications within 30 days)											
2	Randomized trial	Not serious	Not serious	Not serious	Serious [g]	None	437	-	1 RCT: 21/144 (14.6%) peri-procedural complications; 1 RCT: 4/293 (1.4%) device-related complications		⨁⨁⨁◯ moderate
Serious adverse events (2 years follow-up)											
1	Randomized trial	Not serious	NA	Not serious	Serious [f]	None	152	152	RR 1.01 (0.92 to 1.11)	8 more per 1 000 (67 fewer to 93 more)	⨁⨁⨁◯ moderate
Serious adverse events (3 years follow-up)											
1	Randomized trial	Not serious	NA	Not serious	Serious [f]	None	302	312	RR 1.51 (1.38 to 1.66)	314 more per 1 000 (234 more to 406 more)	⨁⨁⨁◯ moderate

Abbreviations: CI – confidence interval; EQ5D – European quality of life 5 dimensions questionnaire; MD – mean difference; MR – mitral regurgitation; NA – not applicable; ns – statistically not significant; NYHA – New York Heart Association; RCT – randomized controlled trial; RR – risk ratio

Comments:

[a] *Wide confidence interval*

[b] *Significant heterogeneity*

[c] *High RoB because of patient reported outcome and patients aware of randomized procedure*

[d] *Only 1 RCT, wide confidence interval*

[e] *Only 1 RCT; low number of patients analyzed*

[f] *Only 1 RCT*

[g] *Low number of studies with low event rate*

Applicability table

Table A-7: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	Patients enrolled in the one RCT comparing percutaneous mitral clip procedure to MV surgery had primary (73%) or secondary (27%) MR mostly with grade > 2+. Patients enrolled in the three RCTs comparing mitral clip procedure to medical therapy had secondary moderate-to-servere or severe symptomatic MR and were ineliglible for surgery or ad high surgical risk. Definition of MR severity varied between the trials.
Intervention	In all included RCTs the intervention was percutaneous mitral clip procedure using the MitraClip® device. If the MR reduction was not adaequat with one device, the device was removed or a second device could be placed. In the three RCTs including patients with secondary MR ineliglible for sugery, patients received optimal medical therapy for heart failure in addition to the percutaneous mitral clip procedure. The strength of optimal medical therapy and the adjustment during the study varied between the RCTs.
Comparators	The comparator in one RCT was conventional MV repair or replacement surgery under cardiopulmonary bypass. The comapator in three RCTs (patients ineligible for surgery) was optimal medical therapy for heart failure alone according to current guidelines. The strength of optimal medical therapy and the adjustment during the study varied between the RCTs.
Outcomes	The most frequently outcomes in the RCTs were overall mortality, NYHA functional class, MR severity and hospitalization rate for heart failure. QoL was assessed in three RCTs after short-term follow-up using different quentionaires. Primary endpoints of three RCTs were composit oucomes, composed of individual outcomes of very different severity.
Setting	In all studies, the intervention was performed in a clinical setting, corresponding to the utilisation setting in Austria. No applicability issues are expected from the geographical setting of the included studies.

List of ongoing randomised controlled trials

Table A-8: List of ongoing randomized controlled trials of percutaneous MV repair with mitral clip device

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT04009434	Patients after successful transfemoral transcatheter aortic valve implantation with concomitant, moderate to severe MR	MitraClip®	Optimal standard of care medical therapy	Composite endpoint of time to heart failure hospitalization or death from any cause	08/2023	Technische Universität Dresden
NCT04198870	Patients with severe, primary MR	MitraClip®	Mitral Valve Repair Surgery	All-cause mortality, stroke, cardiac hospitalization, or acute kidney injury requiring renal replacement therapy	02/2024	Abbott Medical Devices
NCT05292716	Patients with secondary MR and advanced heart failure on maximally tolerated standard of care therapies	MitraClip®	Optimal medical therapy	Absolute change in overall KCCQ summary score	04/2024	Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia
NCT02444338	Patients with NYHA functional class II to class IV chronic heart failure	MitraClip®	Optimal standard of care therapy	Composite rate of recurrent heart failure hospitalizations and cardiovascular death	06/2024	Institut fuer anwendungs-orientierte Forschung und klinische Studien GmbH
NCT04822675	Patients with severe ischemic MR and reversible myocardial ischemia	MitraClip®	Mitral valve surgery	All-cause mortality; rate of myocardial infarction; rate of stroke; hospitalization rate for congestive heart failure	08/2025	Ottawa Heart Institute Research Corporation
NCT05298124	Patients with cardiogenic shock and concomitant moderate or greater MR	MitraClip®	Medical therapy	Primary composite outcome: in-hospital all-cause mortality, cardiac transplantation, implantation of durable LVAD, or discharge on palliative inotropic therapy	08/2025	Ottawa Heart Institute Research Corporation
NCT03271762	Patients with severe primary MR	MitraClip®	Cardiac surgery	All-cause mortality; unplanned hospitalizations for heart failure; mitral valve reintervention	03/2026	Nantes University Hospital
NCT05051033	Patients with primary, degenerative MR	TEER with a commercially-approved edge-to-edge mitral repair device	Mitral valve repair surgery	Composite score of all-cause mortality, valve re-intervention, hospitalizations and urgent visits for heart failure, or onset of ≥ 3+ MR	01/2028	Annetine Gelijns, Icahn School of Medicine at Mount Sinai

Abbreviations: KCCQ – Kansas City cardiomyopathy questionnaire; LVAD – Left Ventricular Assist Devices; MR – mitral regurgitation; NYHA – New York Heart Association; TEER – Transcatheter Edge-to-Edge Repair

Literature search strategies

Search strategy for Cochrane

Search Name:MitraClip Update 2022	
Search date: 28/12/2022	
ID	Search
#1	MeSH descriptor: [Heart Valve Prosthesis Implantation] explode all trees
#2	MeSH descriptor: [Mitral Valve] explode all trees
#3	#1 or #2
#4	clip* (Word variations have been searched)
#5	#3 and #4 (Word variations have been searched)
#6	(mitr* NEAR clip*) (Word variations have been searched)
#7	(percutaneous or endovascular or catheter*) near clip* (Word variations have been searched)
#8	(PMVr):ti,ab,kw
#9	Mitralclip* (Word variations have been searched)
#10	MitraClip* (Word variations have been searched)
#11	(mitr* valve* NEAR repair*) (Word variations have been searched)
#12	(TMVr):ti,ab,kw
#13	evalve* (Word variations have been searched)
#14	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 with Publication Year from 2012 to 2022, in Trials
#15	(conference proceeding):pt
#16	(abstract):so
#17	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#18	#15 OR #16 OR #17
#19	#14 NOT #18
Total hits: 289	

Search strategy for Embase

Search Name: MitraClip Update 2022		
Search date: 28/12/2022		
No.	Query Results	Results
#22.	#20 NOT #21	559
#21.	#20 AND 'Conference Abstract'/it	243
#20.	(#15 OR #17) AND [2012-2023]/py AND ([english]/lim OR [german]/lim)	802
#19.	(#15 OR #17) AND [2012-2023]/py	816
#18.	#15 OR #17	1,020
#17.	#14 AND #16	994
#16.	random*:ab,ti OR placebo*:de,ab,ti OR ((double NEXT/1 blind*):ab,ti)	2,153,488
#15.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13) AND [randomized controlled trial]/lim	281
#14.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	18,898
#13.	evalve*	144
#12.	tmvr:ti,ab	768
#11.	'mitr* valve*' NEAR/1 repair*	15,322
#10.	pmvr:ti,ab	307

#9.	(percutaneous OR endovascular OR 'catheter-based') NEAR/5 clip*	1,339
#8.	mitr* NEAR/10 clip*	2,992
#7.	mitraclip*	4,221
#6.	'MitraClipsystem'/exp	18
#5.	'mitraclips'/exp	13
#4.	'MitraClip nt'/exp	17
#3.	'MitraClip ntr'/exp	19
#2.	'MitraClip xtr'/exp	40
#1.	'mitral valve clip'/exp	2,536

Search strategy for Medline via Ovid

Search Name: Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to December 27, 2022>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <2018 to December 27, 2022>	
Search date: 28.12.2022	
ID	Search
1	exp Heart Valve Prosthesis Implantation/
2	exp Mitral Valve/
3	1 or 2
4	clip*.mp.
5	3 and 4
6	(mitr* adj10 clip*).mp.
7	Mitralclip*.mp.
8	MitraClip*.mp.
9	((percutaneous or endovascular or catheter-based) adj5 clip*).mp.
10	PMVr.ti,ab.
11	mitr* valve* repair*.mp.
12	TMVr.ti,ab.
13	evalve*.mp.
14	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15	limit 14 to randomized controlled trial
16	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.)
17	14 and 16
18	15 or 17
19	limit 18 to yr="2012 - 2023"
20	limit 19 to (english or german)
21	remove duplicates from 20
Total hits: 370	

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