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## **Transcatheter edge-to-edge repair following surgical valve repair with ring implantation: Results from the multicentre “Clip-in-Ring” registry**

**Abbreviated title:** Multicentre “Clip-in-Ring” registry

**Tweet:** Transcatheter edge-to-edge repair seems safe and efficient in patient with severe mitral regurgitation following surgical valve repair with ring implantation, according to the french multicenter “clip-in-ring” registry.

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## Summary

*Background.* – Management of mitral regurgitation recurrence after failed surgical valve repair with ring implantation is controversial.

*Aim.* – To describe the French experience regarding mid-term safety and efficacy of transcatheter edge-to-edge mitral valve repair (TEER) in patients with failed surgical valve repair with ring implantation.

*Methods.* – The “Clip-in-Ring” registry is a multicentre registry conducted in 11 centres in France, approved by local institutional review boards, of consecutive TEER following surgical valve repair with ring implantation. Outcomes were Mitral Valve Academic Research Consortium (MVARC) technical success, modified 30-day device and procedural success (where 10 mmHg is considered as a cut-off for significant mitral stenosis) and MVARC complications.

*Results.* – Twenty-three patients were studied: mean age,  $69 \pm 10$  years; male sex, 74%; EuroSCORE II,  $16 \pm 17$ ; left ventricular ejection fraction,  $53 \pm 12\%$ ; mitral regurgitation grade 3+/4+, 17%/78%; New York Heart Association class III/IV, 47%/22%; median surgery to TEER delay, 23 (6–94) months. Technical success was 100%. At discharge, residual mitral regurgitation grade was  $\leq 2+$  in 87% and median transmitral gradient was 4 (3–5) mmHg. Thirty-day modified MVARC device and procedural success was 82%: four patients (17%) had residual mitral regurgitation grade  $> 2+$ , including two patients who needed complementary surgery. No patient had a 30-day transmitral gradient  $> 7$  mmHg. No patient died or had a stroke or any life-threatening complications. One patient presented a vascular access complication requiring transfusion. No other MVARC-2 adverse event was reported.

*Conclusions.* – TEER in patients with failed mitral ring is feasible and safe. Further studies should delineate its exact role in the therapeutic armamentarium for this medical issue.

## Résumé

*Contexte.* – La prise en charge d'une insuffisance mitrale (IM) après échec de plastie mitrale avec implantation d'un anneau est controversée.

*Objectif.* – Décrire l'expérience française en terme d'efficacité et de sécurité à moyen terme des résultats de la réparation bord-à-bord (RBAB) après échec de plastie mitrale avec implantation d'un anneau.

*Méthodes.* – Le registre « Clip-in-Ring » est un registre multicentrique conduit dans 11 centres en France, approuvé par le comité institutionnel local, de toutes les procédures consécutives de RBAB après plastie mitrale avec implantation d'un anneau. L'évaluation portait sur le succès technique défini par le consortium académique de recherche sur la valve mitrale (MVARC), les succès modifiés du dispositif et de procédure (avec 10 mmHg comme seuil de définition d'une sténose mitrale significative) à 30 jours et les complications MVARC.

*Résultats.* – Vingt-trois patients ont été étudiés : âge,  $69 \pm 10$  ans ; sexe masculin, 74 % ; EuroSCORE II,  $16 \pm 17$  ; fraction d'éjection du ventricule gauche,  $53 \pm 12$  % ; IM grade 3+/4+, 17 %/78 % ; classe NYHA III/IV, 47 %/22 % ; délai médian chirurgie à RBAB, 23 (6–94) mois. Le succès technique des RBAB était de 100 %. A la sortie, l'IM résiduelle était  $\leq$  grade 2+ chez 87 % des patients, et le gradient médian trans-mitral gradient était 4 (3–5) mmHg. Les succès modifiés du dispositif et de procédure à 30 jours étaient de 82 % : quatre patients (17 %) avaient une IM résiduelle  $>$  grade 2+, dont deux patients qui ont nécessité une chirurgie complémentaire. Aucun patient n'a eu de gradient trans-mitral  $>$  7 mmHg. Aucun patient n'est mort ou n'a présenté de complications vitales. Un patient a présenté une complication liée à l'accès vasculaire nécessitant une transfusion. Aucune autre complication MVARC n'a été reportée.

*Conclusions.* – La RBAB après échec de plastie mitrale avec implantation d'un anneau est faisable et sûre. Sa place précise dans l'arsenal thérapeutique de ce problème médical devra être précisée par des études ultérieures.

## **KEYWORDS**

Mitral regurgitation;

Transcatheter edge-to-edge repair;

MitraClip;

Surgical valve repair;

Registry

## **MOTS CLÉS**

Insuffisance mitrale ;

Réparation bord-à-bord ;

MitraClip ;

Annuloplastie mitrale ;

Registre

*Abbreviations:* IQR, interquartile range; MR, mitral regurgitation; MV, mitral valve; MVARC, Mitral Valve Academic Research Consortium; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons; TEER, transcatheter edge-to-edge mitral valve repair.

## Background

In the setting of surgical management of mitral regurgitation (MR), mitral valve (MV) repair is the preferred technique in primary MR, when the results are expected to be durable, and may be discussed in secondary MR [1]. Thus, many surgical MV repair techniques have been described in recent decades, and restrictive annuloplasty with an undersized ring implantation is considered as the cornerstone [2, 3]. However, depending on surgeon experience and centre-related volume, adopted surgical techniques and initial anatomical considerations, the rate of repair failure or recurrent MR is still a matter of concern, chiefly in secondary MR [4-6]. The management of MR recurrence following surgical valve repair with ring implantation is challenging. Insofar as it is feasible, a redo surgery may be first considered by the heart team. However, transcatheter treatments – mostly transcatheter MV replacement and transcatheter edge-to-edge MV repair (TEER) – may be appealing alternatives for the highest-risk redo surgeries. Mitral annuloplasty could be a limit for TEER [7]. An on-site ring could alter the echo-visualization of the grasping, thereby increasing the complexity of the procedure; it also reduces the preprocedural valve area, implying a greater risk of postprocedural MV stenosis. In addition, comprehension of the mechanism of MR recurrence in that setting may be challenging. Data are scarce regarding these rare procedures. Therefore, we sought to report the characteristics and outcomes of patients undergoing TEER after failed mitral annuloplasty who were included in a multicentre registry.

## Methods

The “Clip-in-Ring” registry is a multicentre retrospective registry conducted in 11 centres (eight university public hospitals and three private institutions) in France, approved by local institutional review boards, of consecutive TEER following surgical valve repair with ring implantation. Patients were eligible if they underwent TEER for recurrent symptomatic MR following surgical valve repair with ring implantation, with an available 30-day follow-up on 31 December 2020. Data were collected anonymously. The TEER was realized according to the local usual operating procedure. Importantly, TEER indications were all discussed by the local multidisciplinary heart team.

Outcomes were modified from the Mitral Valve Academic Research Consortium (MVARC) criteria [8]: Technical success was defined as successful deployment of the device with absence of

procedural mortality and freedom from emergency surgery. Significant MR reduction was defined as reduction in postprocedural MR by  $\geq 1$  grade from baseline. Device success, measured at 30 days, was defined as proper placement of the device, without procedural mortality or stroke, and freedom from emergency surgical or interventional procedures related to the device or access procedure, with a residual MR  $\leq$  grade 2+ and a MV gradient  $< 10$  mmHg. Secondary endpoints were MVARC criteria and MVARC complications (death, stroke, life-threatening bleeding, major vascular and cardiac structural complications, acute kidney injury, myocardial infarction, severe hypotension, heart failure, or respiratory failure and any valve-related dysfunction, migration, thrombosis or other complication requiring surgery or repeat intervention). Also, as an exploratory analysis, because the postprocedural trans-MV gradient seems to be the sticking point of these procedures, we studied the main patient characteristics, depending on MV gradient at discharge ( $< 5$  or  $\geq 5$  mmHg, following the MVARC recommendations). Finally, we reported the last follow-up regarding all-cause death and reintervention on the MV.

Continuous variables are expressed as mean  $\pm$  standard deviation, if they pass the Shapiro-Wilk test for normality, or median (interquartile range [IQR]). Categorical variables are expressed as frequencies and percentages. Kaplan-Meier estimates were applied for overall mortality and reintervention on the MV after TEER.

## Results

From 1473 TEER procedures performed during the inclusion period, 25 TEERS (1.69%) following surgical valve repair with ring implantation were identified. The median TEER experience of the 11 participating centres was 134 (IQR 99–179) procedures. Two patients were not included: one without 1-month follow-up; and one without a mitral ring at the time of the TEER procedure (because the ring implanted during a first surgery was subsequently removed). Therefore, 23 patients (mean age,  $69 \pm 10$  years; male sex, 74%) were studied (Fig. A.1), whose main data at the time of TEER are reported in Table 1. Initial MR aetiology, before the surgical valve repair, was primary in 19 patients (82%) (prolapse of A1, A2 and A3 in two, four and two patients, respectively; prolapse of P1, P2 and P3 in one, six and four patients, respectively; unknown in five patients [21%]), secondary in three patients (13%) (two with restriction of the posterior leaflet as the result of an ischaemic cardiomyopathy, one



with pure annular dilatation) and “mixed” (annular dilatation and anterior leaflet prolapse) in one patient (4%).

Regarding the MV surgery, coronary artery bypass graft was also performed in three patients (13%), and tricuspid annuloplasty in six patients (26%). Implanted rings were complete in 14 patients (60%), and incomplete in seven patients (40%). Ring sizes were 30–32 mm in seven patients (33%), 33–36 mm in 11 patients (52%) and 38–40 mm in three patients (14%) (data are missing for two patients). Artificial expanded polytetrafluoroethylene (ePTFE) chords were implanted in 15 patients (65%). Additional posterior and anterior leaflet resection was performed in three patients (13%) and two patients (9%), respectively, and an edge-to-edge stitch in three patients (13%).

MR recurrence was caused by pure restriction of the posterior leaflet in three patients (13%), prolapse in 17 patients (74%) (posterior leaflet in 12 patients [52%], anterior leaflet in five patients [21%] and both leaflets in two patients [8%]) and “mixed” (combination of restriction and prolapse) in three patients (13%). Surgical valve repair techniques, results and mechanisms of MR recurrence according to the initial aetiology of MR are detailed in [Table 2](#). The number of previous cardiac surgeries was one in 18 patients (78%), two in four patients (17%) and three in nine patients (4%). Haemolysis was reported in three patients (13%).

The median delay between MV surgery and TEER was 23 (IQR 6–94) months. All the TEER procedures were performed with the MitraClip® device (second and third generations: MitraClip NT®, NTR® and XTR®; Abbott Vascular, Santa Clara, CA, USA) in 2014 (one procedure; 4%), 2016 (one procedure; 4%), 2018 (two procedures; 8%), 2019 (eight procedures; 34%) and 2019 (11 procedures; 48%). The number of implanted clips was one, two and three in 17 patients (74%), five patients (21%) and one patient (4%), respectively. The largest device (MitraClip XTR®) was used in seven patients (30%). Four clips (13% of the implanted clips) were implanted in A1/P1, 13 clips (43%) in A2/P2 and 13 clips (43%) in A3/P3. The median total length of the procedure (from vein puncture to skin closure) was 80 (IQR 60–99) minutes, and the Kerma area was 216 (IQR 91–302) mGy. The main outcomes are summarized in [Table 3](#). The technical success of the TEER was 100% (23 patients). The median length of stay was 4 (IQR 3–15) days. Significant MR reduction was achieved in 20 patients (87%): at discharge, residual MR grade was ≤ 2+ in 20 patients (87%) and the median MV gradient was 4 (IQR 3–5) mmHg. At 30 days, modified MVARC device and procedural success was 82% (19 patients). Four patients (17%) had residual MR grade > 2+, including two patients who needed complementary

MV surgery. Thirty-day MVARC device and procedural success was 65% (15 patients). The evolution of the New York Heart Association (NYHA) class is presented in [Fig. 1](#): NYHA class III or IV was reported in 16 patients (69%) before the TEER, versus three patients (12%) at 30 days. Among the 21 patients who did not require unplanned MV surgery within the first month after TEER, the transmitral gradient was < 5 mmHg in 15 patients (71%), ≤ 5 to ≤ 7 mmHg in six patients (28%) and > 7 mmHg in no patient, and the residual MR grade was none/trivial in two patients (9%), 1+ in eight patients (38%), 2+ in nine patients (43%), 3+ in two patients (9%) and 4+ in no patient ([Fig. 2](#)). No patient died or had a stroke or any life-threatening complications. One patient (4%) presented vascular access complication requiring transfusion. No other MVARC-2 adverse event was reported. An illustrative case is presented in [Fig. 3](#) and in [Videos A.1–A.5](#).

The main patient characteristics, depending on the MV gradient at discharge (< 5 or ≥ 5 mmHg), are reported in [Table A.1](#): patients with a high gradient had severe MR and early recurrence after the initial surgery, which always included implantation of artificial cords. Interestingly, initial MV gradient, the completeness and the size of the implanted ring and the number of MitraClips used did not differ between the two groups.

At a median follow-up of 23.4 ±15 months, 22 patients (95%) were alive: one patient, who required MV surgery, died 3 months after the TEER. In addition to the two previously reported patients who required surgery at days 15 and 20 after TEER, one patient was treated surgically at day 40 after TEER. All these three patients (13%) had an MV replacement. Therefore, the number living and free from reintervention at follow-up was 20 patients (86.9%) ([Fig. 4](#)).

## Discussion

Data are limited about TEER after surgical valve repair with ring implantation, whose place in the therapeutic armamentarium for this medical issue is still unclear [9-11]. The main points of this work are: (1) although uncommon, TEER in this setting is safe, with no major procedure-related complications; (2) TEER is an efficient therapeutic option for failed annuloplasty, although its results are not as good as in the general population, mostly because of higher postprocedural MV gradient; and (3) mid-term prognosis is good because, beyond the first 3 months after TEER, all of the studied patients were alive and free from reoperation on the MV ([Central Illustration](#)).

Recurrence of MR after surgical repair is not uncommon. Among 261 consecutive patients treated by restrictive mitral annuloplasty and revascularization for moderate-to-severe functional MR with excellent initial results (no residual MR in 95%, trace or grade 1 residual MR in 5% of patients), Petrus et al. reported cumulative incidences of recurrent MR  $\geq$  grade 2 of  $9.6 \pm 1.8\%$ ,  $20.3 \pm 2.5\%$  and  $27.6 \pm 2.9\%$  at 1, 5 and 10-year follow-up, respectively [6]. In addition, among 1234 consecutive patients treated with MV repair for MR caused by leaflet prolapse followed prospectively for a median of 13 (IQR 8–34) years, the probability of recurrent moderate or severe MR was 12.5% [12].

In this setting, a thorough analysis of the MV, according to the surgical procedure initially performed, should, above all, clearly specify the mechanisms involved in the recurrence of MR. “Procedure of repair-related factors” should be differentiated from “valve-related factors”: ring or leaflet dehiscence are typical procedure-related factors, whereas valve-related factors refer to a progression of native disease or new pathology, such as endocarditis, progression of primary disease, valvular prolapse in an area not involved by the previous repair and valvular retractions [12]. However, making this distinction may be difficult in real life. In our population, two patients (8.6%) had “unclassifiable” related factors, whereas eight (34.7%) had “valve-related factors”, and 13 (56.5%) had “procedure of repair-related factors”, encompassing four cases of ring dehiscence (17.3%).

Management of failed surgical valve repair is primarily a reoperation. Both rerepair and MV replacement should theoretically be considered, according to the mechanism of the failure. Data from real life showed, however, that MV repair is rarely attempted [13-15]. Thus, in 1627 Medicare beneficiaries who underwent MV redo surgery within a 3-year follow-up period after an initial mitral operation (repair or replacement), rerepair was performed in only 15.4%. Furthermore, the hospital mortality was 12.0% – similar to repair and replacement [13]. Recent data about specific results of rerepair surgeries are limited. A recent analysis involving 26 patients treated by surgical edge-to-edge repair for failed MV repair reported a freedom from reoperation and  $\geq$  moderate MR at 10 years of  $69.9 \pm 11.7\%$ , and a mean MV gradient of  $6.1 \pm 2.5$  mmHg [16]. A monocentric analysis encompassing 57 patients who underwent reoperation because of annuloplasty ring dehiscence reported 30-day, 1-year and 5-year mortality rates of 2%, 89% and 74%, respectively [17]. However, because redo surgery is associated with significant operative mortality [13, 18], many patients are not considered for new surgery. Thus, in the series reported by Petrus et al. regarding MV repair for functional MR, reinterventions were performed in fewer than 12% of patients with recurrent MR [6]. Similarly, in the

previously quoted work regarding MV repair for primary MR with a median follow-up of 13 years, reoperation was 4.6%, whereas the probability of recurrent moderate or severe MR was 12.5% [12].

This may explain why, in this intermediate-risk and highly selected population, the local heart team decided to favour a transcatheter approach over a surgical redo procedure. Apart from TEER, transcatheter treatment of MR consists of transcatheter valve implantation using a transcatheter aortic valve – the so-called “valve-in-ring” procedure [19]. Interesting data have recently been published on 222 valve-in-ring procedures (mean age,  $71 \pm 12$  years; Society of Thoracic Surgeons [STS] replacement score, 7.4%): authors reported a 30-day mortality of 8.6%, and device and modified-device successes (same definitions as in our work) of 32% and 63%, respectively. The postprocedural MV gradient was  $\geq 5$  and  $\geq 10$  mmHg in 67% and 12% of patients, respectively [20]. An objection may be raised that this registry started its recruitment in 2006, and more recent procedures may have better results because of the improvement in the screening process, devices and implantation technique. However, another registry encompassing 30 patients enrolled in 2016 and 2017 (mean age,  $71.5 \pm 12$  years; STS replacement score, 7.6%) reported similar results, as technical success was 66.7% (driven primarily by need for a second valve in six patients), MVARC device and procedural success were 73% and the 30-day median trans-MV gradient was 7.6 mmHg [21]. In light of these reports, the results reported in our study seem acceptable. However, these are only registries, which do not allow a head-to-head comparison. Indeed, it may be assumed that the selection of patients and the assessment of eligibility for each technique by the local multidisciplinary heart team took into account local experience and results, and mostly anatomical considerations [19], i.e. a high risk of postimplantation left ventricular outflow tract obstruction would preclude a valve-in-ring procedure. Similarly, valve-in-ring procedures in patients with open rings or bands are at risk of paravalvular leaks. Thus, one can assume that TEER would be the preferred option for these patients. Conversely, large or multisegmental prolapse, small valve area, calcification at grasping site or poor echo imaging should conceivably lead to a valve-in-ring implantation rather than a TEER. Actually, those two appealing techniques should optimally be evaluated in the setting of a prospective randomized trial. However, the small population of symptomatic patients with failed surgical rings, especially those suitable for the two strategies, and the scarce number of centres who have sufficient experience of both techniques seriously impede the feasibility of such a trial.

Postprocedural mitral stenosis is major potential pitfall for TEER after surgical valve repair with ring implantation, as undersized rings reduce the preprocedural valve area. Mean MV gradient is generally the reference variable, because the accurate measurement of mitral area after clip implantation is very difficult and unreliable (especially in the setting of on-site ring annuloplasty). Thus, an MV gradient  $\geq 5$  mmHg usually defines a mitral stenosis [8]. In our study, the 30-day gradient was 2.7 (IQR 2–4) mmHg:  $\geq 5$  mmHg in six patients (28%) and  $> 7$  mmHg in none. Obviously, operators were probably concerned about the risk of postprocedural stenosis, as evidenced by the low mean number of implanted clips and the scarce use of the largest one (MitraClip XTR®), which may have affected the risk of residual MR. However, the true long-term prognostic value of moderate mitral stenosis is still unclear. Thus, in a recent analysis of the potential association between mean MV gradient and clinical outcomes among patients who underwent TEER for secondary mitral regurgitation in the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial [22], 250 patients were divided into quartiles based on discharge echocardiographic mean MV gradient. Mean gradient ranged from  $2.1 \pm 0.4$  mmHg in the first quartile to  $7.2 \pm 2.0$  mmHg in the fourth quartile. There was no difference across quartiles in the 2-year composite endpoint of all-cause mortality or heart failure hospitalization, or in functional improvement, even after adjustment for baseline clinical and echocardiographic characteristics, postprocedural MR grade and number of clips [23]. In addition, among 222 consecutive patients who underwent combined revascularization and repair for ischaemic MR between 1999 and 2006, 54% of patients (66 of 123) were found to have an MV gradient of  $\geq 5$  mmHg, with 11% demonstrating gradients of  $\geq 8$  mmHg. Interestingly, authors found no adverse effects of increasing MV gradient on survival or heart failure hospitalization [24]. Thus, these results question the relevance of MV gradient in the evaluation of MV repair results, either surgical or percutaneous (TEER), in patients with functional MR. However, in primary MR, high MV gradient may be more troublesome. Thus, in 110 patients who had MV repair for primary MR, Chan et al. reported that the 75 patients with a resting mean mitral diastolic gradient  $> 3$  mmHg had the worst intracardiac haemodynamics, higher B-type natriuretic peptide concentrations, lower exercise capacity and poorer quality of life [25] than patients with a low gradient. Literature is scarce about predictors of gradient after MV surgical repair. Considering the small number of patients in our work, looking for independent predictors of high gradient after TEER seems irrelevant. However, besides a potential statistical bias,

it may be suggested that artificial chords are mostly used in primary MR with excess of tissue (Barlow's disease). At TEER time, elevated MV gradient may be more related to this excess of tissue than to the artificial chords themselves.

Finally, apart from case reports and small series, two works regarding TEER after failed surgical MV repair should be highlighted. Braun et al. reported data on 57 patients treated from 2010 to 2016 with TEER after failed surgical MV repair. Of note, 12 patients had no ring implantation. Acute procedural success (postprocedural MR  $\leq$  2+) was achieved in 84% of all patients. In five of nine patients with procedural failure (postprocedural MR  $\geq$  3+), a clip was not placed to avoid mitral stenosis (all patients were treated for FMR with a downsized annuloplasty ring). Four patients with failed clipping procedures subsequently underwent MV replacement (surgical, three patients; transapical valve-in-ring procedure, one patient) [26]. In addition, a large registry was very recently published by Rahhab et al. regarding 104 TEER recipients after failed surgical MV repair (no mitral ring in 14 patients), reporting quite similar results to ours: technical and device successes were 90% and 89%, respectively; residual MR was moderate or less in 90% of patients; and in-hospital all-cause mortality was 2% [11]. However, this report by Rahhab et al. focused on delayed failed annuloplasty, whereas our work mostly reported early failure: the median delay between surgical valve repair and TEER was 5.3 (IQR 1–9) years vs 23 (IQR 6–94) months in our study. *De facto*, failure mechanisms are different, because degenerative causes represented 44% of patients in the report by Rahhab et al. versus 74% in our study.

## Study limitations

The short-term follow-up and the small sample size precluded the identification of potential predictors of clinical success. Thus, the hypothetical role of the initial MV surgery technique and the size of implanted clip could not be studied thoroughly. Also, the studied population represented a highly selected cohort, with suitable echocardiographic imaging, adequate anatomy for TEER and low-predicted risk of mitral stenosis. However, because of the design of this work, we were unable to provide the rate of screen failure for TEER for failed surgical valve repair. Furthermore, these results were obtained in centres with significant experience of TEER, which was taken into account by the local heart team when deciding upon the patient management strategy. Lastly, this registry only included second and third generations of the MitraClip devices, reflecting current practice in France.

## Conclusions

TEER in patients with failed mitral ring is feasible and safe, with encouraging results. The MVARC device success was lower than expected in this intermediate-risk population, because of a significant proportion of patients with moderate mitral stenosis based on a postprocedural mitral mean gradient  $\geq$  5 mmHg, the prognostic impact of which remains unclear. Further studies should delineate the exact role of TEER in the therapeutic armamentarium for this medical issue.

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## Disclosure of interest

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## Figure legends

**Central Illustration.** The “Clip-in-Ring” registry: 23 transcatheter edge-to-edge mitral valve repairs (TEERs) with ring implantation in 11 French centres. MR: mitral regurgitation; MVARC: Mitral Valve Academic Research Consortium; NYHA: New York Heart Association.

<sup>a</sup>Data are on 21 patients, because the two patients who required unplanned surgery within the first month after the procedure were not taken into account.

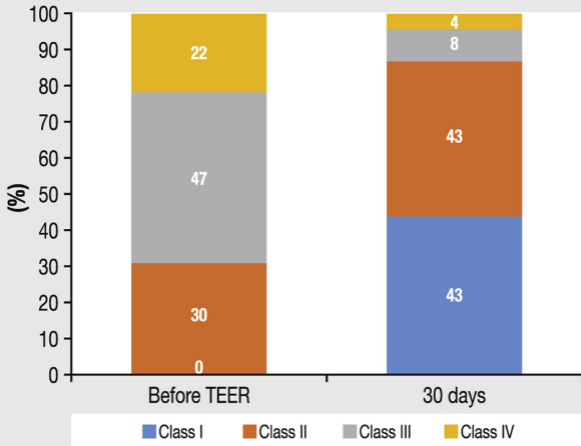
**Figure 1.** New York Heart Association (NYHA) class before and 30 days after the transcatheter edge-to-edge mitral valve repair (TEER).

**Figure 2.** Mitral regurgitation before and 30 days after the transcatheter edge-to-edge mitral valve repair (TEER). Data are on 21 patients, because the two patients who required unplanned surgery within the first month after the procedure were not taken into account.

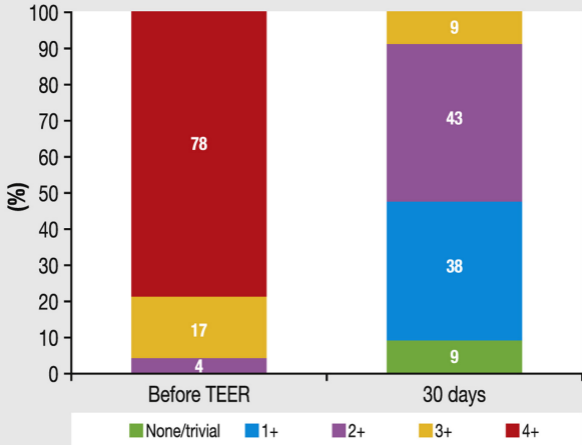
**Figure 3.** Illustrative case of a clip-in-ring procedure in a 79-year-old woman with an history of surgical valve repair (implantation of Carpentier-Edwards Physio II (40) ring and four artificial chords) 19 months earlier for primary (P2 and P3 prolapse) symptomatic mitral regurgitation (MR). A–B. The patient presented a recidive of severe MR as a result of a P2 segment prolapse related to the rupture of a posterior artificial chord release (Panel A and [Video A.1](#): transthoracic echocardiography [TTE]; Panel B, [Video A.2](#) and [Video A.3](#): transoesophageal echocardiography [TOE]), treated by transcatheter edge-to-edge mitral valve repair. C–E. One MitraClip NTR® (Abbott Vascular, Santa Clara, CA, USA) was implanted (Panel C: TOE guidance of the clip implantation), with a good initial result (Panel D and [Video A.4](#): TEE assessment of the final result; Panel E: X-ray visualization of the clip). F. The 12-month follow-up found an asymptomatic patient, with no significant MR (Panel F and [Video A.5](#)). The mitral valve gradient was 6 mmHg.

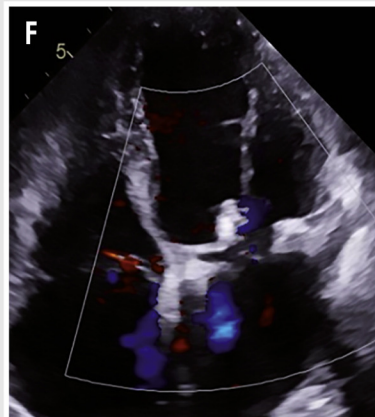
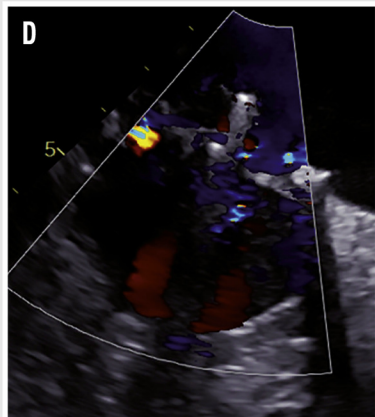
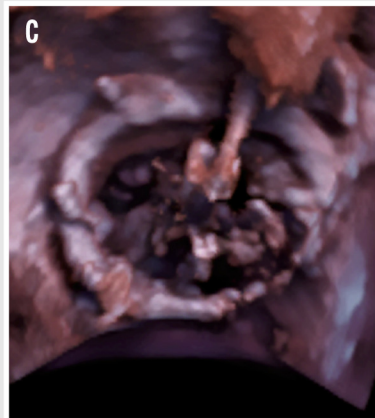
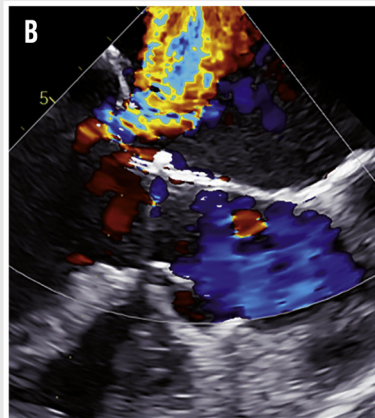
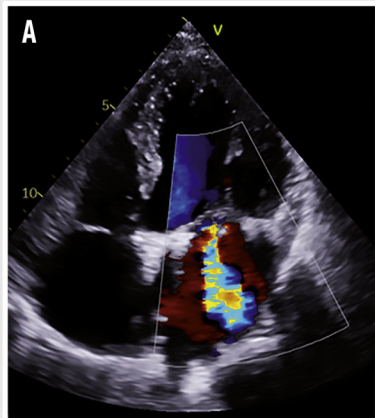
**Figure 4.** Kaplan-Meier curve depicting 24-month survival free from mitral valve reintervention.

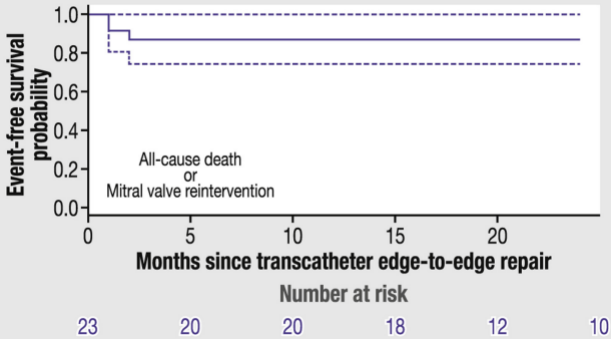
## NYHA class



## Mitral regurgitation







**Figure A.1.** Flow chart of the “Clip-in-Ring” registry. TEER: transcatheter edge-to-edge mitral valve repair.



TEER performed before the 30th of November 2020 in the 11 participating centers: 1473

TEER following surgical valve repair with ring implantation: 25 (1.69%)

Not included patients: 2

- without 1-month follow-up: 1

- without a mitral ring at the time of the TEER: 1

“Clip-in-ring” registry population: 23 (1.56%)

**Table 1** Main data at transcatheter edge-to-edge repair procedure.

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| Characteristics and medical history          |                  |
|--|------------------|
| Age (years)                                  | 69 ± 10          |
| Age ≥ 75 years                               | 8 (34)           |
| Male sex                                     | 17 (74)          |
| Diabetes                                     | 5 (21)           |
| Coronary artery disease                      | 6 (26)           |
| Atrial fibrillation                          | 13 (56)          |
| Chronic obstructive pulmonary disease        | 4 (17)           |
| Stroke                                       | 4 (17)           |
| Risk scores                                  |                  |
| STS score (%)                                | 6.5 ± 7          |
| EuroSCORE II (%)                             | 16 ± 17          |
| Biological markers                           |                  |
| NT-proBNP (ng/L) ( <i>n</i> = 13)            | 1601 (1413–4400) |
| BNP (ng/L) ( <i>n</i> = 3)                   | 116 (111–116)    |
| Glomerular filtration rate (mL/min)          | 68 ± 28          |
| Echocardiographic data                       |                  |
| Left ventricular ejection fraction (%)       | 58 ± 6           |
| Left ventricular end-diastolic diameter (mm) | 53 ± 12          |
| Mitral regurgitation grade                   |                  |
| 2+   | 1 (4)            |
| 3+   | 4 (17)           |
| 4+   | 18 (78)          |
| Regurgitant orifice area (mm <sup>2</sup> )  | 50 ± 24          |
| Regurgitant volume (mL)                      | 75 ± 38          |
| Median transmitral gradient (mmHg)           | 2.7 (2–4)        |
| Left atrial volume (mL/m <sup>2</sup> )      | 67 ± 22          |

Systolic arterial pulmonary pressure (mmHg)

49 ± 11

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Data are expressed as mean ± standard deviation, number (%) or median (interquartile range). BNP: brain natriuretic protein; NT-proBNP: N-terminal prohormone of brain natriuretic protein; STS: Society of Thoracic Surgeons.

**Table 2** Surgical valve repair techniques, immediate postsurgical valve repair results and mechanisms of valve repair failure, according to the initial aetiology of mitral regurgitation.

|  | Initial aetiology of mitral regurgitation |                      |                     |
|--|---|----------------------|---------------------|
|  | Primary                                   | Secondary            | Mixed               |
|  | ( <i>n</i> = 19; 82%)                     | ( <i>n</i> = 3; 13%) | ( <i>n</i> = 1; 4%) |
| <b>Surgical valve repair technique<sup>a</sup></b>                   |   |                      |                     |
| Complete ring ( <i>n</i> = 14; 60%)                                  | 12  | 2                    | 0                   |
| Artificial ePTFE ( <i>n</i> = 15; 65%)                               | 15  | 0                    | 0                   |
| Leaflet resection ( <i>n</i> = 5; 21%)                               | 4   | 0                    | 1                   |
| Edge-to-edge stitch ( <i>n</i> = 3; 13%)                             | 2   | 0                    | 1                   |
| <b>Immediate postsurgical valve repair result</b>                    |   |                      |                     |
| Residual mitral regurgitation ≤ 2/4                                  | 19  | 3                    | 1                   |
| Transvalvular gradient < 5 mmHg                                      | 18  | 3                    | 1                   |
| <b>Mechanisms of valve repair failure</b>                            |   |                      |                     |
| Restriction of the posterior leaflet ( <i>n</i> = 3; 13%)            | 1   | 2                    | 0                   |
| Leaflet prolapse ( <i>n</i> = 17; 74%)                               | 15  | 1                    | 1                   |
| Combination of leaflet restriction and prolapse ( <i>n</i> = 3; 13%) | 3   | 0                    | 0                   |

Data are expressed as number. ePTFE: expanded polytetrafluoroethylene.

<sup>a</sup> Surgical valve repair often combines several techniques, so the total is greater than 100%.

**Table 3** Main outcomes.

|  |          |
|--|----------|
| Technical success                          | 23 (100) |
| Median length of stay (days)               | 4 (3–15) |
| Significant MR reduction (at discharge)    | 20 (87)  |
| At 30 days                                 |          |
| Device success                             | 19 (82)  |
| Procedural success                         | 19 (82)  |
| Need for unplanned surgery                 | 2 (9)    |
| MVARC adverse event                        | 1 (4)    |
| Residual mitral regurgitation <sup>a</sup> |          |
| 3+   | 2 (9)    |
| 4+   | 0 (0)    |
| Transvalvular gradient <sup>a</sup>        |          |
| < 5 mmHg                                   | 15 (71)  |
| ≤ 5 to ≤ 7 mmHg                            | 6 (28)   |
| > 7 mmHg                                   | 0 (0)    |

Data are expressed as number (%) or median (interquartile range).

<sup>a</sup> Among the 21 patients who did not require unplanned mitral valve surgery within the first month after the transcatheter edge-to-edge repair.

**Table A.1** Main data according to postpercutaneous edge-to-edge repair mean mitral valve gradient at discharge.

|   | Postprocedural mean<br>gradient < 5 mmHg<br>( <i>n</i> = 12) | Postprocedural mean<br>gradient ≥ 5 mmHg<br>( <i>n</i> = 11) |
|---|--|--|
| Patient characteristics at inclusion              |  |  |
| Age (years)                                       | 69 ± 10  | 69 ± 10  |
| Male sex  | 66   | 72   |
| STS score   | 7.2 ± 7  | 5.4 ± 8  |
| EuroSCORE II                                      | 17 ± 20  | 14 ± 12  |
| Delay since surgical mitral valve repair (months) | 92 (6–127)   | 19 (8–32)  |
| Surgical mitral valve repair data                 |  |  |
| Complete implanted rings                          | 58   | 63   |
| Ring sizes (mm) <sup>a</sup>                      |  |  |
| 30–32   | 36   | 30   |
| 33–36   | 63   | 40   |
| 38–40   | 0  | 30   |
| Artificial ePTFE cord implantation <sup>b</sup>   | 41   | 100  |
| Posterior leaflet resection <sup>b</sup>          | 16   | 0  |
| Anterior leaflet resection <sup>b</sup>           | 16   | 0  |
| Edge-to-edge stitch <sup>b</sup>                  | 16   | 10   |
| Echocardiographic data at inclusion               |  |  |
| Left ventricular ejection fraction (%)            | 50 ± 13  | 57 ± 10  |
| Left ventricular end-diastolic diameter (mm)      | 50 ± 7   | 58 ± 4   |
| Mitral regurgitation grade                        |  |  |
| 2+  | 8  | 0  |
| 3+  | 8  | 27   |
| 4+  | 83   | 72   |
| Regurgitant orifice area (mm <sup>2</sup> )       | 45 ± 18  | 63 ± 35  |
| Regurgitant volume (mL)                           | 65 ± 20  | 107 ± 71   |

|                                    |            |           |
|------------------------------------|------------|-----------|
| Median transmitral gradient (mmHg) | 3 (2–4)    | 2.3 (2–3) |
| TEER data                          |            |           |
| Number of implanted clips          | 1 (1–1.25) | 1 (1–1.5) |
| Use of MitraClip XTR®              | 25         | 36        |
| Location of clip implantation      |            |           |
| A1/P1                              | 8          | 16        |
| A2/P2                              | 58         | 54        |
| A3/P3                              | 50         | 54        |

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Data are expressed as mean  $\pm$  standard deviation, % or median (interquartile range). ePTFE: expanded polytetrafluoroethylene; STS: Society of Thoracic Surgeons; TEER: transcatheter edge-to-edge mitral valve repair.

<sup>a</sup>Data missing for two patients (one in each group).

<sup>b</sup>Data missing for one patient in the group “gradient  $\geq$  5 mmHg”.