REVIEW ARTICLE

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Transcatheter edge-to-edge mitral valve repair: a surrogate technique that imperfectly mimics. The cold hard truth from data-driven observations

Reparación de la válvula mitral borde a borde con catéter: una técnica sustitutiva que imita de forma imperfecta. La cruda y fría verdad a partir de observaciones basadas en datos

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ABSTRACT

The transcatheter edge-to-edge mitral valve repair procedure has gained prominence as a pioneering technology in structural interventional cardiology to treat degenerative mitral valve regurgitation in recent years. This innovative approach is rooted in the surgical technique of mitral valve repair, yet distinctively devoid of an annuloplasty ring, a *sine qua non* condition for surgical mitral valve repair. Therefore, the transcatheter edge-to-edge mitral valve repair shows uncertain long-term efficacy in treating mitral regurgitation. Hence, it is crucial to carefully consider the potential long-term consequences of an imperfect technique, encompassing patient survival, quality of life, and unplanned rehospitalizations for heart failure rates, as well as the likelihood of mitral regurgitation recurrence. From a theoretical perspective, integrating transcatheter edge-to-edge mitral valve repair with annuloplasty ring implantation, both percutaneous techniques, could potentially address the issue of long-term durability. Owing to the intricate nature of functional mitral regurgitation, this article will exclusively focus on degenerative mitral regurgitation.

Keywords: annuloplasty, degenerative mitral regurgitation, mitral valve repair, prosthetic annuloplasty ring, transcatheter edge-to-edge mitral valve repair.

RESUMEN

En los últimos años, el procedimiento de reparación de la válvula mitral de borde a borde mediante catéter ha ganado popularidad como una tecnología pionera en cardiología intervencionista estructural. Este enfoque innovador tiene sus raíces en la técnica quirúrgica de reparación de la válvula mitral, pero carece de un anillo de anuloplastia, una condición sine qua non para la reparación quirúrgica de la válvula mitral. Por lo tanto, la reparación de la válvula mitral de borde a borde mediante catéter muestra una eficacia incierta a largo plazo en el tratamiento de la insuficiencia mitral. De tal manera que es crucial considerar cuidadosamente las posibles consecuencias a largo plazo de una técnica imperfecta, que abarcan la supervivencia del paciente, la calidad de vida y las rehospitalizaciones no planificadas por tasas de insuficiencia cardíaca, así como la probabilidad de recurrencia de la insuficiencia mitral. Desde una perspectiva teórica, la integración de la reparación transcatéter borde a borde con la implantación percutánea de un anillo de anuloplastia podrían mitigar potencialmente el problema de la durabilidad a largo plazo. Debido a la complejidad del tema de la insuficiencia mitral funcional, este artículo se enfocará exclusivamente en la insuficiencia mitral degenerativa.

Palabras clave: *anuloplastia, insuficiencia mitral degenerativa, reparación valvular mitral, anillo protésico de anuloplastia, reparación valvular mitral transcatéter borde a borde.*

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Mitral valve (MV) repair is the technique of first choice for treating cases of degenerative mitral regurgitation (MR).[1,2] The mitral annuloplasty ring, first described by Carpentier, remains the cornerstone of this surgical technique.[3,4] This article explores the fundamentals of the surgical technique that led to the development of transcatheter edge-to-edge mitral valve repair (TEER). We also discuss the main difference between the two techniques, the omission of an annuloplasty ring in TEER, and assess the impact of this ringless approach on patient survival, quality of life, heart failure-related rehospitalization, and failure rates after procedure. Theoretically, a combined approach using both percutaneous TEER and annuloplasty ring implantation may offer a viable solution to the problem of long-term durability.

Mitral valve repair: annuloplasty ring, the essential sine qua non

A constant imperative in surgical MV repair, regardless of the underlying pathology, is the use of an annuloplasty ring, a cornerstone concept introduced by Carpentier[3-8] in the seminal French Correction[7] *(Figure 1)*. The annuloplasty ring fulfills several key functions; namely, reshapes the MV native annulus, preserving the optimal 3:4 diameter ratio between anteroposterior and transverse dimensions, fixes the annular size in systole promoting optimal leaflet coaptation and maximizing the coaptation surface area, and prevents progressive annular dilation, ensuring long-term stability[7,8] *(Figure 2)*.

TEER is based on the Alfieri technique

The edge-to-edge technique for repairing MR was first performed by Alfieri on April 25, 1991.[9] However, two crucial facts must be emphasized regarding this surgical technique. Firstly, despite the good results reported with this procedure, it has never been the preferred treatment for surgical MV repair. Secondly, edge-to-edge MV repair should not be the exception to the rule regarding the use of an annuloplasty ring as an integral part of this procedure.[9] In fact, the absence of an annuloplasty ring is the strongest predictor of failure after surgical MV repair.[10-14] Therefore, the complete edge-to-edge technique comprises two essential elements: the stitch that joins both MV leaflets, and the prosthetic annuloplasty ring that reinforces the repair.[15]

TEER as a ringless intervention

A pivotal distinction between surgical edge-to-edge repair and TEER is the absence of a prosthetic annuloplasty ring in the latter *(Figure 3)*. De Bonis et al. have investigated the importance of the annuloplasty ring in surgical edge-to-edge MV repair.[16-19] They found that this absence can compromise TEER outcomes, particularly in the long term.[18] Theoretically, the principles guiding MV repair remain unchanged, regardless of the approach employed; they universally apply to both surgical and percutaneous repairs. Therefore, the lack of annuloplasty ring in TEER renders this percutaneous technique only partially effective, resulting in a significant risk of MR recurrence over time.

Recurrent MR post-procedure as metric to evaluate TEER efficacy

Bearing in mind that the necessity for reoperation is subject to variability in physician clinical judgment and decision-making, as well as patient autonomy and individual preferences, recurrent MR ≥ 3+ after the procedure is the most objective and reliable metric for evaluating the efficacy of MV repair. The presence of recurrent or residual MR2+ after procedure and its inherent consequences on the patient's final outcome remains a topic of intense debate. Although it is not a definitive indicator for re-intervention, there are multiple reasons to suggest that MR2+ is a key predictor for the subsequent development of MR ≥ 3+, which may have a negative impact on the final outcome.[20-23] In turn, the incidence of recurrent MR ≥ 3+ is the most reliable indicator of the procedure's long-term effectiveness, particularly at 5 years of follow-up. Unfortunately, the vast majority of reports do not provide data on the specific incidence of MR 2+ post-procedure.

The EVEREST II trial reported a notable 50% incidence of MR ≥ 2+ at 5-year follow-up.[24] Öztürk et al. observed a significantly higher incidence in a series of 256 patients undergoing TEER, with 92.9% experiencing MR ≥ 2+ at 5 years post-procedure (MR2+: 87.5%, MR3+: 7.2%).[25]

Figure 1: Annuloplasty ring commonly used in surgical mitral valve repair.

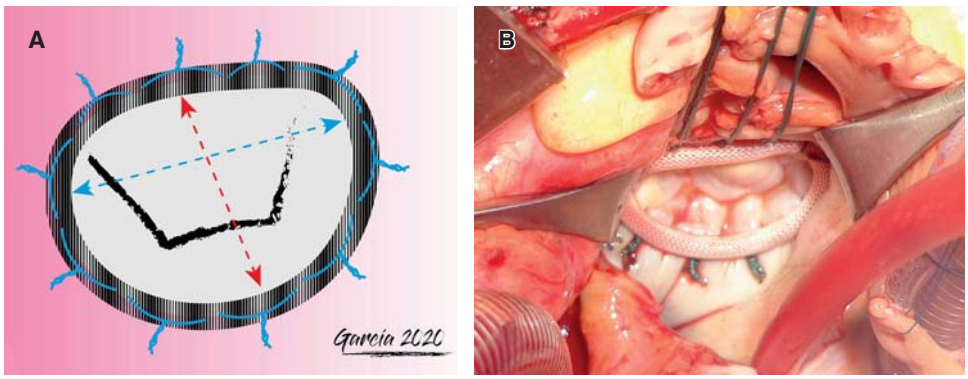

Figure 2:

A) Artistic illustration of the mitral annuloplasty ring. The blue and red arrows indicate the reshaping of the native mitral annulus by the prosthetic ring in the transverse and anteroposterior diameters (3:4 diameter ratio), respectively. **B)** Mitral valve repair using a prosthetic annuloplasty ring as a key component of the surgical approach.

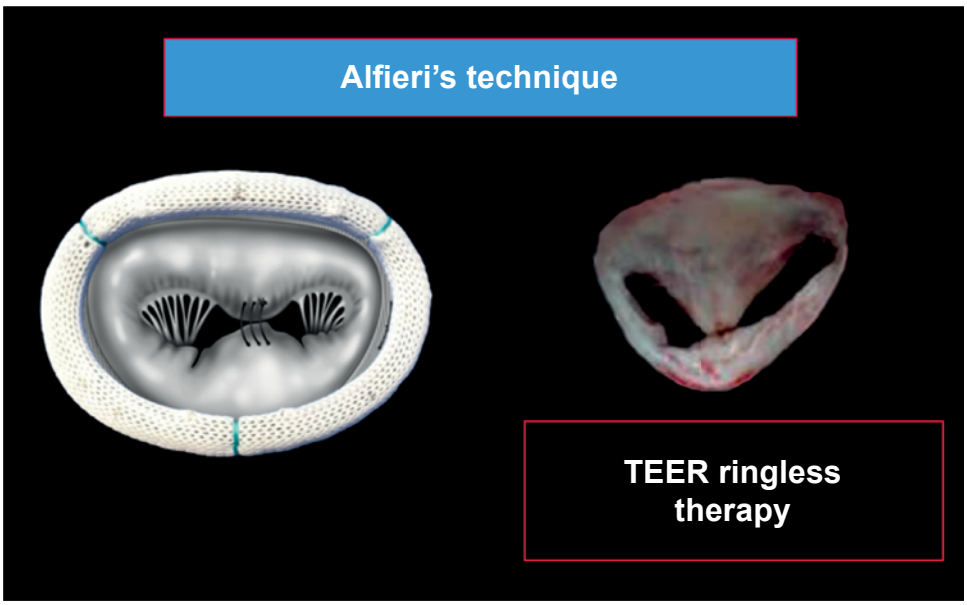

Figure 3:

Schematic illustration emphasizing the omission of an annuloplasty ring in transcatheter edge to edge repair, a key distinction between Alfieri's original edge-to-edge technique (left) and the percutaneous transcatheter edge-to-edge repair (right).
TEER = transcatheter edge to edge repair.

However, there is a scarcity of studies reporting the presence of recurrent MR ≥ 3+ after TEER at 5 years of follow-up. Feldman et al. documented **19%** of recurrent MR ≥ 3+ at 5 years of follow-up in the EVEREST II.[24] The GRASP-IT registry reported a notable **22.4%** incidence of MR ≥ 3+ at 5-year follow-up after TEER.[26] Similarly, Kar et al. observed recurrent MR ≥ 3+ in **25%** of patients at 5-years of follow-up in the EVEREST II High Risk Study.[27] The MitraSwiss registry, which included 1, 212 patients undergoing TEER, reported a higher incidence of **31.8%** with recurrent MR ≥ 3+ at 5-years.[28] The COAPT trial found a significantly lower rate of MR ≥ 3+ of 5.3% at 5-year follow-up.[29] In contrast to the aforementioned findings, the STS/ACC/TVT registry revealed a surprisingly high incidence of MR ≥ 3+ in 8.7% of 33,878 patients who underwent TEER, within just one month of follow-up.[30] This is particularly significant, as this registry reflects real-world outcomes.

To sum up, the presence of recurrent MR ≥ 3+ after TEER at 5-years of follow-up ranges between 5.3 and 31.8% (median: 22.4%, mean: 20.7 ± 9.8%) *(Table 1)*.

Adverse clinical outcomes associated with residual or recurrent MR ≥ 2+ post-TEER

TEER outcomes are compromised when residual or recurrent mitral regurgitation (MR) ≥ 2+ is present after procedure. Research by Reichart et al. revealed that patients with minimal residual MR (≤ 1+) fare better than those with moderate to severe MR (2+ or ≥ 3+) at discharge and one-year follow-up (p = 0.029).[31] Similarly, Buzzatti et al. discovered that MR 2+ post-TEER is a key driver of adverse outcomes, including increased MR ≥ 3+, poorer survival rates, and reduced quality of life, compared to patients with MR ≤ 1+ (HR: 6.71; 95% CI, 3.48-12.90, p < 0.001).[20] The GRASP-IT Registry highlights recurrent or residual MR ≥

2+ as the strongest predictor of all-cause mortality (HR: 2.17, 95% CI, 1.42-3.31, p < 0.001) and the composite endpoint of all-cause death and unplanned heart failure rehospitalization (HR: 2.20, 95% CI, 1.52-3.19, p < 0.001) at five-year follow-up.[26] Furthermore, Buzzatti et al. found residual MR 2+ after TEER to be the most critical predictor of all-cause mortality in both univariate (HR: 2.71; 95% CI, 1.73-4.25; p < 0.001) and multivariate (HR: 4.18; 95% CI, 1.87-9.37; p < 0.001) analyses at five-year follow-up.[21] According to an analysis from the The Italian Society of Interventional Cardiology (GIse) Registry of Transcatheter Treatment of Mitral Valve RegurgitaTiOn (GIOTTO) Registry, Adamo et al. found that patients with residual MR ≤ 1+ after TEER had significantly lower rates of all-cause and cardiac mortality (25.7 vs 40%, p < 0.001 and 16.3 vs 24.8%, p = 0.003, respectively) and heart failure hospitalizations (24 vs 30%; p = 0.035) compared to those with residual MR 2+ at 2-year follow-up.[32] An additional analysis of the same GIOTTO registry by Bedogni et al. revealed that residual MR ≤ 1+ was independently associated with a reduced risk of 1-year mortality in both multivariate (HR 0.62; 95% CI, 0.46-0.84, p = 0.002) and univariate analysis (HR 0.52, 95% CI, 0.40-0.67, p ≤ 0.001). Furthermore, at the 2-year follow-up, Kaplan-Meier estimates showed a significant correlation between all-cause mortality and the severity of residual MR. In fact, residual MR2+ was associated to 2-year all-cause mortality (HR 1.33, 95% CI, 1.02-1.73, p = 0.032).[33] De Felice et al. reported strong and independent association was found between the combination of a mean gradient > 4 mmHg after TEER and residual MR ≥ 2+ and an increased risk of adverse events (HR 1.98; 95% CI, 1.10-3.58)[34] *(Table 2)*.

Table 1: Recurrent mitral regurgitation ≥ 3+ after transcatheter edge to edge repair.

Study/Author	Year	Recurrent MR ≥ 3+ (%)	Follow-up (years)
EVEREST II[24]	2015	19.0	5
Kar[27]	2019	25.0	5
GRASP-IT[26]	2019	22.4	5
MitraSwiss[28]	2020	31.8	5
Oztürk[25]	2021	7.2	5
COAPT[29]	2023	5.3	5

Upon removing the COAPT trial data, which solely represent functional mitral regurgitation, the following results were obtained at five years of follow-up: median: 22.4%, mean: 21 ± 3%.
MR = mitral regurgitation.

Mean gradient after TEER

The application of one or multiple clips to both MV leaflets during TEER predictably reduces the MV area *(Figure 4)*. In fact, Alfieri recommends maintaining a minimum MV area of 2.5 cm² after surgical edge-to-edge repair.[9] According to the 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease, a MV area of ≤ 1.5 cm² is considered severe and typically correlates with a trans-mitral mean gradient of > 5 mmHg at a normal heart rate.[1] The Mitral Valve Repair Clinical Outcomes Committee (MVARC) defines post-procedural mitral valve stenosis as a mean gradient > 5 mmHg.[35] Post-TEER mitral valve stenosis is associated with significantly worse long-term clinical outcomes and increased mortality risk.[36] A study of 216 patients undergoing TEER for mitral regurgitation found that a post-TEER transvalvular gradient of > 4.4 mmHg (echo) or > 5.0 mmHg (invasive) predicted adverse outcomes during follow-up in both univariate (HR 2.1, 95% CI 1.3-2.4, p = 0.003) and multivariate analysis (HR 2.3, 95% CI 1.4-3.8, p = 0.002).[36] Moreover, patients with two or more clips exhibited a significantly higher mitral valve mean gradient and increased incidence of mitral valve stenosis post-procedure.[36] The STS/ACC TVT Registry reported that 26.3% of patients had a mean gradient > 5 mmHg after TEER at only one month of follow-up.[30] Additionally, the threshold for intervention in mitral valve stenosis is a MV area of ≤ 1.5 cm².[1] Of particular significance is the fact that the combination of residual MR ≥ 2+ and mean gradient > 5 mmHg was consistently linked to the worst outcomes.[36,37]

In summary, it is advisable to achieve a mean gradient ≤ 5 mmHg and residual MR ≤1+ as optimal outcomes after

Table 2: Residual or recurrent mitral regurgitation 2+ as predictor for development of mitral regurgitation MR ≥ 3+ after transcatheter edge to edge repair in degenerative mitral regurgitation.

Author	Year	Predictor	Hazard Ratio	95% CI	p
Buzzatti[20]	2016	MR 2+	6.71	3.48-12.9	< 0.001
Buzzatti[21]	2019	MR 2+	7.15	2.72-18.75	< 0.001
Sugiura[22]	2022	MR 2+	2.56	1.12-5.87	0.03
Kubo[24]	2023	MR 2+	1.59	1.30-1.95	< 0.001

CI = confidence interval. MR = mitral regurgitation.

Figure 4: Mitral stenosis after placement of several clips. The red color indicates the perimeter of the functional mitral valve area after transcatheter edge to edge repair.

TEER. Of note, official statistics on the rate of reoperation for mitral stenosis subsequent to TEER are currently unavailable.

Reinterventions for failed TEER

First and foremost, it is crucial to note that, for a myriad of reasons, not all cases presenting structural failure in TEER undergo surgery. In a study published by El Shaer et al., only 31% of patients who experienced recurrent MR ≥ 3+ after TEER underwent subsequent mitral valve surgery. Furthermore, operative mortality was 4.5%. Reoperation was associated with significantly lower all-cause death (HR 0.33 [95% CI, 0.12-0.92], p = 0.001) compared with medial therapy alone.[38] In a cohort of 43 patients who underwent reoperation for failed TEER, Sugiura et al. found that reintervention was associated with significantly lower one-year mortality rates compared to medical therapy alone (10.5 vs 37.6%, p = 0.01). Additionally, reintervention conferred improved survival (HR 0.26, 95% CI 0.08-0.79, p = 0.02) and reduced the risk of the composite endpoint of mortality and heart failure rehospitalization (HR 0.34, 95% CI 0.15-0.78; p = 0.01) at one-year follow-up.[39] A data analysis conducted by Kaneko et al. on 11,396 patients who underwent TEER revealed that approximately 1 in 20 patients (4.8%) underwent repeat intervention due to TEER failure, with a mean time interval of 4.5 months between the original procedure and reoperation. Furthermore, notable rates of operative mortality (8.6%), 30-day hospital readmission (20.9%), and overall 30-day morbidity (48.2%) were observed in this patient cohort.[40] The data has been emerged piecemeal. The CUTTING-EDGE study conducted an in-depth analysis of 332 surgical cases involving MV surgery following failed TEER. The results showed a notable operative mortality rate of 16.6%, with a 1-year mortality rate of 31.1%. Additionally, the observed-to-expected mortality ratio was 3.6, indicating a higher-than-expected mortality risk. Moreover, MV replacement was deemed necessary in an overwhelming 92.5% of cases.[41,42] A retrospective study of the Society of Thoracic Surgeons database revealed outcomes for 524 patients undergoing MV surgery due to failed TEER. The analysis showed an operative mortality rate of 10.2%, with an observed-to-expected mortality ratio of 1.2, indicating a higher-than-expected mortality risk. Notably, MV replacement was necessary in 95% of patients.[43]

In summary, considering that TEER failure frequently necessitates high-risk MV replacement, the use of this ringless therapy should be call to caution, especially in patients with degenerative pathology who otherwise may have been suitable for a definitive surgical repair with a high success rate (≥ 90%), in contrast to the significantly lower success rate (6.8%) following failed TEER.[44]

Percutaneous direct annuloplasty ring complementing TEER

The similarity between percutaneous direct annuloplasty rings and surgical annuloplasty suggests that this technique may be beneficial in treating MR. It is essential to note that current studies on TEER do not include systematic use of a mitral annuloplasty ring. There are currently three percutaneous mitral annuloplasty systems available: a) Cardioband Mitral Valve Reconstruction System (Edwards Lifesciences, Irvine, California), a direct annuloplasty device that represents a partial band; b) Millipede IRIS device (Boston Scientific, Maple Grove, Minnesota), a semi-rigid, complete mitral annuloplasty ring; and c) AMEND system (Valcare, Herzliya Pituach, Herzliya, Israel), a rigid, complete mitral annuloplasty ring.[45] A comparative study between Cardioband and TEER, showed that patients with Cardioband had lower mortality and rehospitalization rates for heart failure within the first 12 months. Additionally, patients with Cardioband presented better New York Heart Association functional class, fewer hospital readmissions, and lower mortality compared to those who underwent TEER.[46] In 2018, Rogers et al. reported the outcomes in seven patients implanted with the Millipede IRIS™ with no device related death, stroke, or myocardial infarction, and ≤1+ MR at 30 days in all patients.[47] Recently, on January 27, 2021, Valcare Medical announced the first successful transseptal implantation of the AMEND™ Annuloplasty Ring for Mitral Valve Repair in a human patient.[48] None of them have been yet approved by FDA. Although promising, clinical experience with these types of devices is still in its initial stages.

Nonetheless, a remarkable fact is that the possibility of percutaneously implanting prosthetic rings is indeed a reality. Although we are still in the process of generating sufficient

data to acquire robust experience with the use of these types of rings, this development opens up the prospect of combining both therapies, TEER and percutaneous annuloplasty, akin to surgical approaches, in order to achieve optimal long-term outcomes.

TEER adherence to current clinical guidelines is not a minor issue

Despite its drawbacks and limitations, TEER has shown a steady trend of increasing adoption in recent years, driven by its less invasive approach. According to Young et al., among Medicare beneficiaries, the national trends of TEER versus surgical MV repair revealed a significant shift, with the annualized ratio of TEER to surgical repair increasing substantially from 0.05 to 1.32 between 2012 and 2019.[49] Shah et al. reported that US Medicare data from 2012 to 2019 shows a marked shift in MV therapy trends, with a 313% increase in TEER cases (1,552 per year, $p < 0.001$) and a 31.4% decrease in surgical MV repair procedures (1,446 per year, $p = 0.004$) from 2015 to 2020.[50] The STS/ACC TVT Registry revealed a total of 37,475 patients underwent mitral transcatheter procedures, including 33,878 TEER procedures, between 2014 and March 31, 2020. TEER procedure volumes have demonstrated a remarkable growth, increasing from 1,152 annual procedures in 2014 to 10,460 in 2019. This translates to a 908% increase, or a 9-fold rise in TEER utilization.[30] Kumar et al. reported that between 2015 and 2019, a total of 27,034 TEER procedures were performed on Medicare patients in the US. The national incidence rate rose from 6.2 per 100,000 patients in 2015 to 23.8 per 100,000 patients in 2019, representing a 283% increase over the study period ($p < 0.001$).[51] Chikwe et al. observed that among 53,117 Medicare beneficiaries with degenerative MR in the US from 2012 to 2019, there was a remarkable 23-fold increase in TEER procedure volume.[52]

The exponential growth in TEER adoption in the US over recent years is evident. Nevertheless, assuming the number of patients requiring MV intervention has remained relatively stable in the last years, and considering clinical guidelines clearly indicate that TEER may benefit a highly select group of patients with high-risk operative mortality,[1] a crucial question arises: what factors are contributing to this dramatic expansion in TEER adoption? Significant concerns have been raised about the degree of adherence to clinical guideline recommendations in the use of TEER. The multifaceted situation underlying the potential overutilization of TEER is influenced by various factors, including the Heart Team's practical application of the high-risk concept, advanced age as a decisive factor, the methodology employed to assess frailty, and incomplete information provided to the patient, which collectively may skew the decision-making process in favor of TEER.

Expanding TEER indications: a point of contention yet

Currently, two major randomized controlled trials are enrolling patients with degenerative (primary) MR, throughout the whole spectrum of operative risk (low-, intermediate-, or high- risk) comparing TEER with surgical MV repair. with special emphasis in intermediate and low-risk patients. The MitraClip REPAIR MR Study (NCT04198870) is actively recruiting patients aged ≥ 75 years or those < 75 years with STS-PROM score ≥ 2, anticipating a total enrollment of approximately 500 participants. In the percutaneous or surgical repair in mitral prolapse and regurgitation for ≥ 60 year-olds (PRIMARY) (NCT05051033), patients aged ≥ 60 years, spanning the entire surgical risk continuum (low, intermediate, and high risk), will be enrolled (n = 450 estimated) and randomized in a 1:1 ratio to undergo either TEER or surgical MV repair.

Notwithstanding the anticipated results of both trials, a fundamental truth remains, one that supersedes statistical evaluations, and potential biases. Failing to anticipate the long-term impact of a treatment can result in devastating effects. Expanding the indications for TEER without fully understanding its limitations may lead to catastrophic consequences, especially in young and intermediate- and low-risk patients. Therefore, we must exercise caution and carefully weigh the potential risks and benefits before proceeding.[53] Between reality and the abyss, an uncertain future awaits.

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