

CONFLICTS OF INTEREST AMONG TRANSCATHETER MITRAL VALVE REPAIR

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We have lost valuable ideas and concepts to get rid of what we just don't want. Our understanding of transcatheter edge-to-edge repair (TEER) to treat the mitral valve (MV)—of which MitraClip is the most common device used in the routine medical practice (MitraClip therapy MitraClip™; transcatheter mitral valve repair (TMVR); Abbott, 3200 Lakeside Dr, Santa Clara, CA, United States)—comes from not very reliable systems of prediction that, on many occasions, are not compatible with reality. Conflicts of interest have appeared between members of the Mitral Valve Academy Research (MVARC) and a few trials conducted to analyze TEER outcomes in mitral regurgitation (MR). This adds to the potential irregularities that have come up as we keep investigating the disparity of data available from large randomized clinical trials up to this date. More specifically, the conflicts of interest among MVARC, COAPT, and MitraClip (Abbott) is disturbing, and should be cleared out as soon as possible.

Surgical mitral valve repair as a reference framework for transcatheter therapies to treat mitral regurgitation

The comparison point for state-of-the-art technologies used for MV repair is surgical repair like the treatment of choice of mitral regurgitation. By applying specific parameters on MV repair in degenerative disease, McCarthy *et al.* demonstrated that the 10-year reintervention-free rate was 99.7%, the lack of recurrent MR $\geq 3+$ was 98.4%, and 84.4% for grade 2+ MI.⁽¹⁾

Using quadrangular resection, native annulus plication, and the use of annuloplasty ring in patients with degenerative disease of the MV, Lapenna *et al.* reported a reintervention rate of $4.3\% \pm 1.7\%$ [95% confidence interval (95%CI) 1.7% to 8.8%], and a rate of MR 3+ of $8.8\% \pm 2.8\%$ (95%CI, 4.3% a 15.5%). Regarding MR grade 2+, the rate was only 10% at 18-year follow-up.⁽²⁾ De Bonis *et al.* used a maximum 17.6-year follow-up in patients with degenerative disease of MV after MV repair due to regurgitation using Alfieri's "edge-to-edge" technique and annuloplasty ring, and reported an reintervention-free rate of $89.6 \pm 2.51\%$, with MR $\geq 3+$ in 13.6% of the patients.⁽³⁾

Working on patients with anterior valve prolapse due to degenerative disease and using Alfieri's "edge-to-edge" technique combined with the use of mitral annuloplasty, De Bonis *et al.* reported a reintervention-free rate of $89.6\% \pm 2.74\%$, and a rate of MR $\geq 3+$ of 12.5% at a maximum follow-up of 21 years.

⁽⁴⁾ In cases with degenerative disease, David *et al.* demonstrated that after MV repair, the recurrence-free ratio for MR $\geq 3+$ and $\geq 2+$ was 90.7% and 69.2%, respectively. The rate of reintervention was 5.9%. All these data come from a 20-year follow-up.⁽⁵⁾ Regarding the durability of the MV surgical repair due to degenerative etiology, the reintervention-free rate at 15 and 20 years was 84% and 80%, respectively. The reintervention-free rate was 72% and 89% for the anterior valve prolapse and posterior valve, respectively, at 15-year follow-up.⁽⁶⁾

After this analysis, we should understand that surgical repair of MV due to degenerative disease is associated with very low rates of reintervention and recurrence of MR $\geq 2+$ at almost 2-decade follow-up. Therefore, these results provide solid evidence in favor of surgical repair as the treatment of

choice. These values should come back as remain the reference foundation on which to base any comparisons between surgery and emergent technologies with catheter-based techniques such as TEER.

Alfieri's "edge-to-edge" technique supporting the TEER therapy

Before repairing the MV in the adult population, the use of a mitral annuloplasty annulus is a prerequisite. Carpentier described it phenomenally in the so-called "French Correction"^(7,8). As a matter of fact, the lack of an annuloplasty annulus is the strongest predictor of failure after the MV repair in the long run.^(5,9) This rule is universal and, therefore, applicable to all MV repair in the adult population. Alfieri's "edge-to-edge" technique that is based on the TEER principle is not an exception to this rule.^(2-4,10-14)

These days, when a comparison is drawn between TEER therapy and surgical repair important details appear we should address here. The first detail is that despite the excellent results reported with Alfieri's "edge-to-edge" technique for mitral repair,^(2-4,10-14) such technique was never the first-line therapy in the therapeutic armamentarium to repair MV regurgitation in the surgical community.

As a matter of fact, even in the experience published by the Milan working group (Italy), the great difference seen between the total number of MV repairs and the number relative to Alfieri's "edge-to-edge" technique is obvious.⁽¹⁴⁾

The TEER therapy as an incomplete and only partially effective technique

The most significant difference between the surgical and the percutaneous technique is the lack of an annuloplasty prosthetic ring in the TEER catheter-based percutaneous technique. Therefore, this factor makes the TEER percutaneous procedure be partially effective. Therefore, we should mention that the TEER procedure as such is an incomplete procedure. However, this is a problem that has not been properly discussed by the interventional cardiology community. Consequently, we should define the potential complications that stem from such limitations especially their long-term impact.

An undisputed fact overlooked by interventional cardiology is that the rules that regulate MV repairs do not simply change just by changing the approach whether it may be surgical or percutaneous. In its condition of a ringless therapy, MitraClip is subject to repair failures due to several mechanisms. At this point a cascade of errors can be found in the clinical trials and descriptions regarding the use of MitraClip.

Incorrect and ambiguous definition of failed or successful TEER according to the Mitral Valve Academic Research Consortium

One of the greatest inconsistencies is the very definition of success or failure depending on the degree of residual MR after the procedure. Such is the case of the definition of the endpoints of success established by the Mitral Valve Academic Research Consortium. Such document includes every criterion and its values to determine when a successful outcome has been achieved after TEER therapy. Regarding residual MR after TEER, this document describes "...a reduction of MR down to optimal or acceptable levels without significant mitral stenosis (with transmitral gradient <5 mm Hg), and mild non-major paravalvular MR (1+)." However, the document ambiguously mentions in the footnote of a figure that "the reduction of MR will be considered acceptable when the MR after the procedure has been reduced in, at least, 1 functional class or degree since the beginning and does not exceed the moderate category (2+) regarding severity."⁽¹⁵⁾ This definition is totally unacceptable for the surgical or percutaneous approach used to treat MR.

It is surprising to see how easy these concepts have universally been accepted by cardiology groups worldwide without this type of deviation ever being discussed.

Impact of residual or recurrent mitral regurgitation grade 2+ after surgical mitral valve repair

The impact residual MR has after the procedure has been largely studied by different surgical groups. The presence of residual or recurrent grade 2+ MR after the MR surgical repair negatively impacts the patient's long-term survival. De Bonis *et al.* found as predictors of severe MR recurrence the presence of residual MR >1+ the moment of hospital discharge [hazard ratio (HR), 7.4; 95%CI, 2.5 to 21.2; P = .0001].⁽³⁾ In a different study, De Bonis *et al.* demonstrated that the only predictor of recurrence for MR ≥3+ was the presence of residual MR >1+ at hospital discharge (HR, 5.7; 95%CI, 1.6 to 20.6; P = .007).⁽⁴⁾ Suri *et al.* demonstrated that the presence of residual MR >1+ at the operating room had an OR of 3.99 (1.79 to 7.65), and P = .002 in the univariate analysis, and an OR of 4.23 (1.86 to 8.32), P = .001 in the multivariate analysis.⁽⁹⁾ The MR ≥ 2+ reintervention-free rate was closely associated with the degree of residual MR. In the presence of residual MR > 1+ at the operating room or at 1-year follow-up, the rate of recurrence is nearly 65% at 20 years. Therefore, the presence of MR >1+ after the procedure impacts directly the long-term results of the MR repair.⁽¹⁶⁾

Impact of residual or recurrent mitral regurgitation 2+ after transcatheter edge-to-edge repair (TEER) of the mitral valve

However, if the results obtained regarding residual or recurrent MR $\geq 2+$ after TEER are thoroughly studied, we will be able to see that these are totally discouraging. Therefore, in the GRASP-IT registry, Adamo et al. identified recurrent or residual MR $\geq 2+$ as the most important predictor of mortality (HR, 2.17; IC 95%: 1.42 a 3.31; $P < .001$) and for the composite endpoint of all-cause mortality and rehospitalization due to heart failure (HR, 2.20; IC 95%: 1.52 a 3.19; $P < .001$) at 5-year follow-up.⁽¹⁷⁾ Buzzatti *et al.* found a direct correlation between the presence of residual or recurrent MR grade 2+ after TEER and the appearance of MR grade 3+, worse survival and quality of life compared to those with residual MR $\leq 1+$ (HR, 6.71; 95%CI, 3.48 a 12.90; $P < .001$)⁽¹⁸⁾. Buzzatti *et al.* identified the presence of residual or recurrent MR 2+ after TEER as a stronger predictor for all-cause mortality at 5 year follow-up in the univariate (HR, 2.71; 95%CI, 1.73 a 4.25; $P < .001$) and multivariate analyses (HR, 4.18; 95%CI, 1.87 a 9.37; $P < .001$)⁽¹⁹⁾. On this regard, Reichhart et al. demonstrated better results with residual MR $\leq 1+$ compared to cases of MR $\geq 2+$ ($P = .029$) after TEER at 1-year follow-up.⁽²⁰⁾ Similarly, it is rather obvious that the presence of residual or recurrent MR 2+ after TEER has been associated with worse general outcomes. Also, as we have been getting more and more results from the use of TEER both in the number and follow-up time, the negative impact of residual MR $\geq 2+$ (including grade 2+) after TEER has become obvious. Therefore, it seems evident that the section dedicated to describing success from the point of view of residual MR within the MVARC document⁽¹⁵⁾ is totally wrong and does not reflect reality at all. Since this could have a tremendous impact on the routine daily practice on thousands of human beings treated with TEER, the document should be reviewed once more and the recommendation downgraded from optimal down to acceptable, both as synonyms of residual MR $\leq 1+$.

The rate of MR 2+ in clinical trials and TEER reports

The lack of emphasis with which MR grade 2+ has been described in the different studies and registries is alarming. On this regard, we will briefly mention the most significant studies and reports published over the last few years on the presence of MR 2+ after TEER therapy to treat MR regurgitation.

We should mention that between one third and half of the patients show recurrent or residual MR $\geq 2+$ after TEER. In the EVEREST II trial, 50% of the

cases showed MR $\geq 2+$ at 5-year follow-up.⁽²¹⁾ In the ACCESS-EU trial, 59.4% of the patients had residual or recurrent MR $\geq 2+$ after TEER at 1-year follow-up.⁽²²⁾ In the COAPT trial up to 22.8% of the patients had MR $\geq 2+$ at 2-year follow-up.^(23,24) The MITRA-FR trial reported a rate of residual or recurrent MR $\geq 2+$ at 1-year follow-up of 32%.⁽²⁵⁾ In the GRASP-IT registry, the rate of residual or recurrent MR $\geq 3+$ at 5-year follow-up was 22.4% without reporting on the number of cases with residual or recurrent MR grade 2+.⁽¹⁷⁾ The STS/ACC TVT registry reported a rate of 8.7% for MR $\geq 3+$. However, it did not report the rate for cases with residual or recurrent MR 2+.⁽²⁶⁾

Overall, the negative impact that residual or recurrent MR 2+ after TEER has on the patient's survival, quality of life, MR $\geq 3+$ recurrence, and rate of rehospitalization due to heart failure in the mid- and long-term has been downplayed. According to the statistics shown in this document, MR $\geq 2+$ after TEER should be considered a risk factor of poor disease progression in general.

Differences between COAPT and MITRA-FR

After the huge differences seen with totally different results coming from the COAPT and MITRA-FR clinical trials we should take into consideration the association between the industry and the project director. The COAPT was a clinical trial sponsored by the industry (Abbott) with results favoring TEER compared to MitraClip in the management of functional MR in patients with heart failure. At 2-year follow-up, the rate of rehospitalization due to heart failure was 35.8% in the MitraClip group compared to 67.9% in the control group (HR, 0.53; 95%CI, 0.40 to 0.70; $P < .0001$). The all-cause mortality rate was 29.1% vs 46.1%, respectively (HR, 0.62; IC 95%; 0.46 to 0.82; $P < .001$).⁽²³⁾ Funding of the MITRA-FR trial was granted by the French National Institute of Health and Medical Research. No statistically significant differences between both treatment modalities were seen, in the all-cause mortality rate (24.3% vs 22.4%; HR, 1.11; 95%CI, 0.69 to 1.77) or in the rehospitalization rate due to heart failure (48.7% vs 47.4%; HR, 1.13; 95%CI, 0.81 to 1.56) at 1-year follow-up.⁽²⁵⁾ In an extension of this study at 2-year follow-up, no statistically significant differences were seen in these categories either. The all-cause mortality rate and the unscheduled rehospitalization rate due to heart failure were reported in 63.8% of the patients from the TEER group and 67.1% of the patients from the control group (HR, 1.01; 95%CI, 0.77 to 1.34).⁽²⁷⁾

Despite the huge efforts done trying to explain and reconcile the totally opposing results of both studies, to this date, it has been virtually impossible

to find a compelling explanation that can be up to the circumstances. Concepts such as proportionate/disproportionate MR^(27,28) have resulted in dilemmas that are totally out of the objective reality we are always looking for.⁽³⁰⁻³⁵⁾ Also, it has been suggested that the term proportionate/disproportionate MR is not consistent with the physical laws of conservation of both mass and energy. Such inconsistency could only be explained by contradictory and incomplete echocardiographic data like the ones found in the COAPT trial.⁽³⁴⁾

Conflicts of interest, MVARC, and COAPT

According to the Organization for Economic Cooperation and Development (OECD), “a conflict of interests is a conflict between the public duties and the private interests of an employee when this employee has personal interests that can interfere with the correct performance of his functions and official responsibilities”.⁽³⁶⁾

According to these 2 definitions, there is a flagrant conflict of interests since the lead author of the MVARC⁽¹⁵⁾ has the exact same task in the COAPT trial.⁽²³⁾ If we admit that the MVARC defines residual or recurrent MR $\leq 2+$ as an “acceptable” result after TEER, and that nearly 23% of the cases of the COAPT trial at 2 years showed MR 2+ (and, therefore, are taken as “acceptable” results), it seems rather obvious that there is a potential conflict of interests in the authorship of both authors. Therefore, there are rather important limitations that need to be responded in a clear-cut way.

Philosophical and ethical implications derived from the conflict of interests

Those involved in the development of technologies like TEER should consider the information available in this sense. They should make reassessments emphasizing the main takeaways we have considered in this study. Some of us question the convenience of taking for granted expansion programs for TEER since the best long-term results based on the current evidence available or data from the surgical field cannot be guaranteed. It is imperative that there is a paradigm and attitudinal change among the professionals involved in this type of technological proposals.

Currently, we have been seeing with an alarming frequency a philosophy based on a desire to reward all investment efforts made by the industry through biased information favorable to study devices such as MitraClip.

Therefore, the association between the industry and the project director is something that should be taken into serious consideration. Unlike the project

manager, who does not know what the final outcome will be, the industry needs a device with a guaranteed practical application. On this matter, the project or trial needs funds and, therefore, is vulnerable to pressure from the industry to achieve the results expected by the project manager. Therefore, we see, once again, strong financial reasons and, ultimately, coming from the industry to oppose to an inconvenient outcome that would otherwise be accepted as such. Conflicts of interest among MVARC, COAPT, and MitraClip (Abbott) are a pressing matter that should be dealt with and clarified as soon as possible.

Implications between residual mitral regurgitation 2+ after TEER and bias in the definition of success given by the Mitral Valve Academic Research Consortium

The study main idea is to present and explore the consequences of the real or potential conflict of interests that exist among the TEER technique, the COAPT trial, and the definitions drafted by the Mitral Valve Academic Research Consortium. To this date, this has not been taken into serious consideration. Therefore, this study can serve as a part of the stages that still need to be taken into consideration for a more prudent and realistic analysis of the current state of these technologies in our routine clinical practice. World leaders in this professional setting should come up with convincing responses to our doubts, thus avoiding any outcome distortions, and setting rules and regulations that should govern future investigations conducted in this field.

CONCLUSIONS

Based on what we have developed in this study, the following immediate actions are advised:

- 1) The rules for mitral valve repair apply to all adult patients equally regardless of the etiology and the access route. A mitral annuloplasty ring is needed as a fundamental part of this repair. To this date, the leaders have not explained clearly how they expect TEER therapy to work properly since it does not include a mitral annuloplasty ring.
- 2) More clarity regarding the exact degree of residual MR is needed while specifying the degree of MR, including 2+, as part of poor outcomes after TEER.
- 3) It is absolutely imperative to change the definitions of “success” drafted by the MVARC on the degree of MR, including 2+, as part of failed procedures.
- 4) Conflict of interest should be avoided. The MVARC lead author cannot be, at the same, time, the lead author of one of the most controversial trials on MitraClip like the COAPT trial. Therefore, the validity of the effectiveness of the device seems

highly questionable regarding residual MR 2+ and its long-term final impact.

The central idea of this study was to express and explore the real or potential consequences of the conflict of interests among the TEER technique, the COAPT trial, and the definitions drafted by the Mitral Valve Academy Research Consortium. To this date, none of this has been taken seriously. Therefore, this study can serve as a part of the stages that still need to be taken into consideration for a more prudent and realistic analysis of the current state of these technologies in our routine clinical practice. World leaders in this professional setting should come up with convincing responses to our doubts, thus avoiding any outcome distortions, and setting rules and regulations that should govern future investigations conducted in this field.

Conflicts of interest

The authors have no disclosures to declare.

REFERENCES

- McCarthy PM, Herborn J, Kruse J, Liu M, Andrei AC, Thomas JD. A multiparameter algorithm to guide repair of degenerative mitral regurgitation. *J Thorac Cardiovasc Surg.* 2020 Oct 10;S0022-5223(20)32811-7. doi: 10.1016/j.jtcvs.2020.09.129.
- Lapenna E, Del Forno B, Amore L, Ruggeri S, Iaci G, Schiavi D, Belluschi I, Bargagna M, Alfieri O, De Bonis M. Durability at 19 years of Quadrangular Resection with Annular Plication for Mitral Regurgitation. *Ann Thorac Surg.* 2018;106(3):735-741.
- De Bonis M, Lapenna E, Lorusso R, Buzzatti N, Gelsomino S, Taramasso M, Vizzardi E, Alfieri O. Very long-term results (up to 17 years) with the double-orifice mitral valve repair combined with ring annuloplasty for degenerative mitral regurgitation. *J Thorac Cardiovasc Surg.* 2012;144(5):1019-24.
- De Bonis M, Lapenna E, Taramasso M, La Canna G, Buzzatti N, Pappalardo F, Alfieri O. Very long-term durability of the edge-to-edge repair for isolated anterior mitral leaflet prolapse: up to 21 years of clinical and echocardiographic results. *J Thorac Cardiovasc Surg.* 2014 Nov;148(5):2027-32. doi: 10.1016/j.jtcvs.2014.03.041.
- David TE, Armstrong S, McCrindle BW, Manlhiot C. Late outcomes of mitral valve repair for mitral regurgitation due to degenerative disease. *Circulation.* 2013;127(14):1485-92.
- David TE. Durability of mitral valve repair for mitral regurgitation due to degenerative mitral valve disease. *Ann Cardiothorac Surg.* 2015 Sep;4(5):417-21. doi: 10.3978/j.issn.2225-319X.2015.08.07.
- Carpentier A, Deloche A, Dauptain J, Soyfer R, Blondeau P, Piwnica A, et al. A new reconstructive operation for correction of mitral and tricuspid insufficiency. *J Thorac Cardiovasc Surg.* 1971;61(1):1-13.
- Carpentier A. Cardiac valve surgery--the "French correction". *J Thorac Cardiovasc Surg.* 1983;86(3):323-337.
- Suri RM, Clavel MA, Schaff HV, Michelena HI, Huebner M, Nishimura RA, ET AL. Effect of Recurrent Mitral Regurgitation Following Degenerative Mitral Valve Repair: Long-Term Analysis of Competing Outcomes. *J Am Coll Cardiol.* 2016 Feb 9;67(5):488-498. doi: 10.1016/j.jacc.2015.10.098.
- Alfieri O, Maisano F, De Bonis M, Stefano PL, Torracca L, Oppizzi M, et al. The double-orifice technique in mitral valve repair: a simple solution for complex problems. *J Thorac Cardiovasc Surg.* 2001 Oct;122(4):674-81. doi: 10.1067/mtc.2001.117277.
- De Bonis M, Lapenna E, Maisano F, Barili F, La Canna G, Buzzatti N, et al. Long-term results (≤ 18 years) of the edge-to-edge mitral valve repair without annuloplasty in degenerative mitral regurgitation: implications for the percutaneous approach. *Circulation.* 2014;130(11 Suppl 1):S19-S24.
- De Bonis M, Lapenna E, Pozzoli A, Giacomini A, Alfieri O. Edge-to-edge surgical mitral valve repair in the era of MitraClip: what if the annuloplasty ring is missed? *Curr Opin Cardiol.* 2015 Mar;30(2):155-160. doi: 10.1097/HCO.0000000000000148.
- De Bonis M, Lapenna E, Barili F, Nisi T, Calabrese M, Pappalardo F, et al. Long-term results of mitral repair in patients with severe left ventricular dysfunction and secondary mitral regurgitation: does the technique matter? *Eur J Cardiothorac Surg.* 2016 Nov;50(5):882-889. doi: 10.1093/ejcts/ezw139.
- Alfieri O, De Bonis M, La Canna G. (Eds.). (2015). *Edge-to-Edge Mitral Repair. From a surgical to a percutaneous approach.* Springer International Publishing Switzerland 2015. Electronic version. ISBN978-3-319-19893-4 (eBook).
- Stone GW, Adams DH, Abraham WT, Kappetein AP, Génèreux P, Vranckx P, Mehran R, Kuck KH, Leon MB, Piazza N, Head SJ, Filippatos G, Vahanian AS; Mitral Valve Academic Research Consortium (MVARC). Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions: A Consensus Document from the Mitral Valve Academic Research Consortium. *J Am Coll Cardiol.* 2015 Jul 21;66(3):308-321. doi: 10.1016/j.jacc.2015.05.049.
- Gardner MA, Hossack KF, Smith IR. Long-Term Results Following Repair for Degenerative Mitral Regurgitation - Analysis of Factors Influencing Durability. *Heart Lung Circ.* 2019;28(12):1852-1865. doi: 10.1016/j.hlc.2018.10.011.
- Adamo M, Grasso C, Capodanno D, Rubbio AP, Scandura S, Giannini C, et al. Five-year clinical outcomes after percutaneous edge-to-edge mitral valve repair: Insights from the multicenter GRASP-IT registry. *Am Heart J.* 2019;217:32-41.
- Buzzatti N, Denti P, Scarfò IS, Giambuzzi I, Schiavi D, Ruggeri S, et al. Mid-term outcomes (up to 5 years) of percutaneous edge-to-edge mitral repair in the real-world according to regurgitation mechanism: A single-center experience. *Catheter Cardiovasc Interv.* 2019;94:427-435.
- Buzzatti N, De Bonis M, Denti P, Barili F, Schiavi D, Di Giannuario G, et al. What is a "good" result after transcatheter mitral repair? Impact of 2+ residual mitral regurgitation. *J Thorac Cardiovasc Surg.* 2016;151:88-96.
- Reichart D, Kalbacher D, Rübsamen N, Tigges E, Thomas C, Schirmer J, et al. The impact of residual mitral regurgitation after MitraClip therapy in functional mitral regurgitation. *Eur J Heart Fail.* 2020;22:1840-1848.
- Feldman T, Kar S, Elmariah S, Smart SC, Trento A, Siegel RJ, et al; EVEREST II Investigators. Randomized Comparison of Percutaneous

- Repair and Surgery for Mitral Regurgitation: 5-Year Results of EVEREST II. *J Am Coll Cardiol*. 2015;66:2844-2854.
22. Maisano F, Franzen O, Baldus S, Schäfer U, Hausleiter J, Butter C, et al. Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. *J Am Coll Cardiol*. 2013;62:1052-1061.
23. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, et al; COAPT Investigators. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. *N Engl J Med*. 2018;379:2307-2318.
24. COAPT. A randomized trial of transcatheter mitral valve leaflet approximation in patients with heart failure and secondary mitral regurgitation. Stone GW, on behalf of Mack M, Abraham W, Lindenfeld J, and the COAPT Investigators. TCT 2018 Presentation Slides. Available online: https://www.acc.org/-/media/Clinical/PDF-Files/Approved-PDFs/2018/09/21/TCT-2018-Slides/Sept23-Sun/115pmET_COAPT-tct-2018.pdf. Último acceso: Abr 24, 2022.
25. Obadia JF, Messika-Zeitoun D, Leurent G, lung B, Bonnet G, Piriou N, et al; MITRA-FR Investigators. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. *N Engl J Med*. 2018;379:2297-2306.
26. Mack M, Carroll JD, Thourani V, Squiers J, Manandhar P, Deeb GM, et al. Transcatheter Mitral Valve Therapy in the United States: A Report from the STS/ACC TVT Registry. *Ann Thorac Surg*. 2022;113:337-365.
27. lung B, Armoiry X, Vahanian A, Boutitie F, Mewton N, Trochu JN, Lefèvre T, Messika-Zeitoun D, Guerin P, Cormier B, Brochet E, Thibault H, Himbert D, Thivolet S, Leurent G, Bonnet G, Donal E, Piriou N, Piot C, Habib G, Rouleau F, Carrié D, Nejari M, Ohlmann P, Saint Etienne C, Leroux L, Gilard M, Samson G, Rioufol G, Maucourt-Boulch D, Obadia JF; MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation: outcomes at 2 years. *Eur J Heart Fail*. 2019;21(12):1619-1627. doi: 10.1002/ehf.1616.
28. Packer M, Grayburn PA. New Evidence Supporting a Novel Conceptual Framework for Distinguishing Proportionate and Disproportionate Functional Mitral Regurgitation. *JAMA Cardiol*. 2020;5:469-475.
29. Grayburn PA, Sannino A, Packer M. Proportionate and Disproportionate Functional Mitral Regurgitation: A New Conceptual Framework That Reconciles the Results of the MITRA-FR and COAPT Trials. *JACC Cardiovasc Imaging*. 2019;12:353-362.
30. Lindenfeld J, Abraham WT, Grayburn PA, Kar S, Asch FM, Lim DS, et al; Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) Investigators. Association of Effective Regurgitation Orifice Area to Left Ventricular End-Diastolic Volume Ratio with Transcatheter Mitral Valve Repair Outcomes: A Secondary Analysis of the COAPT Trial. *JAMA Cardiol*. 2021;6:427-436.
31. Adamo M, Cani DS, Gavazzoni M, Taramasso M, Lupi L, Fiorelli F, et al. Impact of disproportionate secondary mitral regurgitation in patients undergoing edge-to-edge percutaneous mitral valve repair. *EuroIntervention*. 2020;16:413-420.
32. Orban M, Karam N, Lubos E, Kalbacher D, Braun D, Deseive S, et al; EuroSMR Investigators. Impact of Proportionality of Secondary Mitral Regurgitation on Outcome After Transcatheter Mitral Valve Repair. *JACC Cardiovasc Imaging*. 2021;14:715-725.
33. Ooms JF, Bouwmeester S, Debonnaire P, Nasser R, Voigt JU, Schotborgh MA, et al. Transcatheter Edge-to-Edge Repair in Proportionate Versus Disproportionate Functional Mitral Regurgitation. *J Am Soc Echocardiogr*. 2022;35:105-115.e8.
34. Hagendorff A, Knebel F, Helfen A, Stöbe S, Doenst T, Falk V. Disproportionate mitral regurgitation: another myth? A critical appraisal of echocardiographic assessment of functional mitral regurgitation. *Int J Cardiovasc Imaging*. 2021;37:183-196.
35. Obadia JF, lung B, Messika-Zeitoun D. The disproportionate success of the disproportionate concept. *J Thorac Cardiovasc Surg*. 2022;163:e7-e8.
36. Organization for Economic Cooperation and Development (OECD). La gestión de los conflictos de intereses en el servicio público. Available online: https://read.oecd-ilibrary.org/governance/la-gestion-de-los-conflictos-de-intereses-en-el-servicio-publico_9788495912220-es#page1