



## Residual mitral regurgitation grade 2+ after transcatheter edge-to-edge mitral valve repair: Epic fail?

*Regurgitación mitral grado 2+ después de la reparación valvular mitral transcatóter borde a borde: ¿un gran fracaso?*

Ovidio A García-Villarreal\*

### Keywords:

functional mitral regurgitation, mitral valve, mitral valve insufficiency, mitral valve repair, transcatheter edge-to-edge mitral valve repair.

### Palabras clave:

insuficiencia mitral funcional, válvula mitral, insuficiencia valvular mitral, reparación valvular mitral, reparación valvular mitral borde a borde transcatóter.

### ABSTRACT

Cardiac surgery and interventional cardiology have been pursuing the idea of working together to build a critical process for patients, from which an appraisal is made of long-term procedural outcomes. The sole intention is to avoid therapies which fail to solve the pivotal issues of clinical significance to patient well-being. One such example is the efficacy of transcatheter edge-to-edge mitral valve repair (TEER) in treating the functional mitral regurgitation (FMR), a critical parameter being the presence of post procedural residual, or recurrent mitral regurgitation (MR). The impact that this has in relation to the patient's survival, mortality, and rehospitalization for heart failure rates, should be emphasized before making any special assumptions. Roughly half of patients after TEER experienced post procedural MR 2+ (grade 2/4 by echocardiography) within the first year. In fact, the aforementioned has been greatly ignored in the current guidelines for valvular heart disease, giving a recommendation Class IIa for TEER in FMR. Therefore, whether MR 2+ after TEER influences the patient post procedural outcome in the short and longer terms, requires careful consideration.

### RESUMEN

La cirugía cardíaca y la cardiología intervencionista han estado persiguiendo conjuntamente la idea de trabajar juntos para construir un progreso crítico destinado a nuestros pacientes, a partir de lo cual estamos obligados a rendir cuentas de nuestros resultados a largo plazo. Todo lo anterior está orientado a evitar promesas poco realistas y medidas prácticas que no logran resolver el problema principal. En este punto, surge de nuevo la misma antigua pregunta sobre la eficacia de la reparación mitral borde a borde transcatóter (TEER) en el tratamiento de la insuficiencia mitral funcional (IMF) o primaria. Un punto crítico y de inflexión es la insuficiencia mitral (IM) residual o recurrente después del procedimiento sin anuloplastia. Se debe enfatizar el impacto que ésta tiene en relación con las tasas de supervivencia, mortalidad y rehospitalización por falla cardíaca del paciente, antes de hacer algunas suposiciones especiales. Aproximadamente casi la mitad de los pacientes después de TEER tenían IM 2+ (grado 2/4 por ecocardiografía) dentro del primer año. De hecho, lo anterior ha sido ignorado en gran medida en las guías actuales para la enfermedad cardíaca valvular, dando una clase de recomendación IIa para TEER en IMF o primaria. Por lo tanto, si la IM 2+ después de TEER afecta o no el resultado del paciente debe revisarse nuevamente, así como su impacto en la clase de recomendación para TEER en las actuales guías clínicas.

### INTRODUCTION

The first objective of this paper is to provide an overview about the impact of residual or recurrent mitral regurgitation (MR) 2+ (grade 2/4 by echocardiography) after transcatheter edge-

to-edge mitral valve repair (TEER) in treating the functional mitral regurgitation (FMR). The second objective is to review the results in terms of residual or recurrent MR after TEER, which have featured in the most significant trials and reports within the literature of recent years.

\* Mexican College of Cardiovascular and Thoracic Surgery. Mexico City, Mexico.

Received:  
04/09/2022

Accepted:  
08/09/2022

**How to cite:** García-Villarreal OA. Residual mitral regurgitation grade 2+ after transcatheter edge-to-edge mitral valve repair: Epic fail? Cardiovasc Metab Sci. 2022; 33 (4): 181-186. <https://dx.doi.org/10.35366/109245>

Extreme caution should be exercised regarding the definition of a «good result» after TEER, in consideration of echo parameters utilized for this purpose. The definitions discussed herein are useful in considering the success or failure of MV repair, by accepted practices, irrespective of the approach being surgical or percutaneous. As such, it must be referenced in order to be adequately defined. Hence, a «standard acceptable good result» must be adopted, in order to provide a realistic outcome after TEER in the real-life scenario. However, since the reference point between surgery and TEER is completely different at present, the final outcome for TEER in terms of residual or recurrent MR needs to be revisited.

Most of the current protocols studying the efficacy of TEER consider  $MR \leq 2+$  as a «good result». Hence, the most common practice in catheter-based techniques is to omit the importance of residual or recurrent  $MR 2+$ . As a result, the big trials do not show the impact of having the above pathological condition. However, according to what has been previously published in literature related to cardiac surgery, the most effective way of defining success after MV repair procedure is the presence of  $MR \leq$  grade 1+ (grade 1/4 by echo). Moreover, the value of the outcome is highly dependent upon whether this variable is incorporated into the success definition.

#### IMPACT OF MITRAL REGURGITATION 2+ IN SURGICAL SERIES

Over the years, surgical experience has demonstrated the negative impact of residual or recurrent  $MR \geq 2+$  after MV repair. In this framework, Enriquez-Sarano et al. have highlighted how much the presence of MR affects patient survival. Special consideration must be given to the fact that  $MR \leq 1+$  is the only degree that does not negatively affect survival. All the others, including  $MR 2+$ ,  $3+$  and  $4+$  (grades 2, 3, and 4/4) negatively affect the patient survival ( $p > 0.01$ ).<sup>1</sup>

There is a general agreement that residual  $MR > 1+$  is a risk factor for moderate or severe MR at follow-up.<sup>2</sup> De Bonis et al. found that the only predictor of recurrence for  $MR \geq 3+$  was the presence of residual  $MR > 1+$  at

hospital discharge (HR: 5.7; 95% CI, 1.6-20.6;  $p = 0.007$ ).<sup>3</sup> Chang et al. figured out that, by applying logistic regression, one of the most important independent prognostic factors for recurrence of MR, was residual  $MR \geq 2+$  after hospital discharge.<sup>4</sup> Suri et al. have stressed the risk of having mild intraoperative residual  $MR 1+$  in the operating room progressing towards  $MR \geq 3+$ , is associated with adverse left ventricular remodeling, poor outcome and death (HR: 1.72).<sup>5</sup> Obata et al. found that when residual MR was more than  $2.0 \text{ cm}^2$  color Doppler flow area on intraoperative TEE, the MR increased to  $\geq 3+$  during the follow-up period.<sup>6</sup> Residual MR should be targeted to less than  $2.0 \text{ cm}^2$  color Doppler flow area during echocardiographic study.

Rizza et al. compared patients with postoperative residual  $MR \leq 1+$  vs  $MR 2+$ , and they found a higher incidence for the use of inotropics in the intensive care unit ( $p = 0.12$ ) and a longer in-hospital stay, involving patients with residual  $MR 2+$  ( $p = 0.18$ ).<sup>7</sup> In general terms, residual MR reduces the efficacy and durability of MV repair.<sup>8</sup>

At this point, it can be shown that the analysis of results backed up by surgical experience, clearly shows the negative impact of residual  $MR 2+$  on patients' survival, especially in the long-term. Consequently, the implicit hypothesis of the «acceptable» good result as  $MR \leq 2+$  after TEER, is likely to be untrue. Furthermore, there is no logic to support why the outcomes from TEER should be analyzed using different criteria to those from surgical MV repairs.

#### INCIDENCE OF MITRAL REGURGITATION 2+ IN TRANSCATHETER EDGE-TO- EDGE MITRAL VALVE REPAIR SERIES

If the primary aim of treatment is to obtain a post procedural MR reduction as residual  $MR \leq 1+$ , it is highly striking that according to some European reports, half of the patients receiving TEER had a residual  $MR \geq 2+$  at 1-year follow-up.<sup>9-13</sup>

In a European multicenter registry by Adamo et al., 184 consecutive patients with FMR who underwent successful TEER procedure were analyzed. Of them, 47% showed residual or

recurrent MR 2+ at 1-year follow-up.<sup>10</sup> In the ACCESS-EU study by Maisano et al., 48.3% had MR2+ at 1-year follow-up after TEER.<sup>11</sup> The TCVT (transcatheter valve treatment sentinel pilot registry), is part of the European Society of Cardiology EuroObservational Research Programme. From this study, two reports have come to light. Nickenig et al. reported the results of 628 consecutive patients who underwent TEER. In this study, success after TEER was defined as having equal or less than moderate ( $\leq 2+$ ) after TEER. In this context, 59.1% of patients with FMR had residual MR 2+ after 12 months follow-up.<sup>12</sup> In similar conditions, Pighi et al., reported up to 61.5% of patients with post procedural MR2+ after 1-year follow-up.<sup>13</sup>

In the EVEREST-II trial, 30% of patients had residual or recurrent MR2+ after 5-year follow-up.<sup>14</sup> In the MITRA-FR trial, up to 32% had residual or recurrent MR2+ or greater, after 12 months of follow-up. More specifically, nearly 25% experienced MR 2+ in the same interval.<sup>15</sup> As the occurrence of residual or recurrent MR after TEER is neither mentioned in the original COAPT trial publication by Stone et al. nor in the supplementary material,<sup>16</sup> data coming from Stone et al. have been included in this review.<sup>17</sup> At 1-year follow-up, 25.7% of patients had recurrent MR2+. Later, at 2-years follow up, 21.9% had MR2+.<sup>17</sup> At 3 years, the only mention of residual or recurrent MR after TEER, appears cited as MR  $\leq 2+$  in 98.8% of cases.<sup>18</sup> Therefore, in the COAPT trial, there is

no clear or exact representation of the severity of MR after TEER (Table 1).

### IMPACT OF MITRAL REGURGITATION 2+ IN TRANSCATHETER EDGE-TO-EDGE MITRAL VALVE REPAIR SERIES

Regarding the impact of residual or recurrent MR after TEER, Buzzatti et al. demonstrated in a multivariate analysis, that post procedural MR 2+ was the only factor associated with a further development of MR  $\geq 3+$  (adjusted HR: 6.71; 95% CI, 3.48-12.90;  $p < 0.001$ ) and worse outcomes, including impacts on survival and quality of life, when compared to MR  $\leq 1+$ .<sup>19</sup> Reichhart et al. showed that patients with residual MR  $\leq 1+$  at discharge and 12-month follow-up after TEER, had better outcomes compared to patients with residual MR 2+ or  $\geq 3+$  ( $p = 0.029$ ).<sup>20</sup>

In the GRASP-IT registry (Getting Reduction of mitrAl inSufficiency by Percutaneous clip implantation in ITaly), a retrospective multicenter study, Adamo et al. identified the recurrence of MR as the most important predictor for all-cause mortality alone (HR: 2.17, 95% CI: 1.42-3.31,  $p < 0.001$ ) and combined with HF hospitalization (HR: 2.20, 95% CI: 1.52-3.19,  $p < 0.001$ ), at 5-year follow-up.<sup>21</sup> Buzzatti et al. analyzed 339 patients who underwent TEER, of whom 68.8% had FMR. At 5-year follow-up, residual MR2+ was identified as the most important predictor for all-cause death in univariate [ $p < 0.001$ ; HR: 2.71: 1.73-4.25] and multivariate analyses [ $p < 0.001$ ; HR: 4.18: 1.87-9.37]. In addition, residual MR2+ was also the most important factor for MR  $\geq 3+$  recurrence in univariate [ $p < 0.001$ ; HR: 5.01: 2.70-9.29] and multivariate analyses [ $p < 0.001$ ; HR: 4.67: 2.49-8.74] in patients with FMR after TEER at 5-year follow-up.<sup>22</sup>

### «MODERATE» OR «GRADE 2+» MITRAL REGURGITATION MEANS THE SAME?

Current 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease cited that the categorization of MR severity as mild, moderate, or severe is highly dependent on several factors, of which echo parameters are of paramount importance.

**Table 1: Incidence of mitral regurgitation 2+ in transcatheter edge-to-edge mitral valve repair.**

Author	Year	MR 2+ (%)	Follow-up (year)
Pighi <sup>13</sup>	2017	61.5	1
Nickenig <sup>12</sup>	2014	59.1	1
Maisano <sup>11</sup>	2013	48.3	1
Adamo <sup>10</sup>	2019	47.0	1
Feldman <sup>14</sup>	2015	30.0	5
Stone <sup>17</sup>	2018	25.7	1
Obadia <sup>15</sup>	2018	25.0	1

MR 2+ = mitral regurgitation grade 2/4, also called «moderate».

However, several shortcomings need to be pointed out. Firstly, there is a clear difference between FMR in Stage A (MR grade 0) and Stage B (MR grade 1+ or 2+). Secondly, however, no differences are highlighted between MR 1+ and 2+ (Stage B). Thus, the same echo parameters are applicable for both of them (ERO  $< 0.40 \text{ cm}^2$ , regurgitant volume  $< 60 \text{ mL}$ , and regurgitant fraction  $< 50\%$ ).<sup>23</sup> This is especially important, because the final outcomes with residual MR  $\leq 1+$  or MR2+ after operation are completely different, regardless surgical or percutaneous approach.

In addition, the 2019 American Society of Echocardiography guidelines score the severity of MR as only mild, moderate and severe. According to this, semiquantitative echo values are used for this purpose; namely, for mild: effective regurgitant orifice area (EROA)  $< 0.2 \text{ cm}^2$ , regurgitant volume (RVol)  $< 30 \text{ mL}$ , and regurgitant fraction  $< 30\%$ ; moderate: EROA between  $0.2$  and  $0.39 \text{ cm}^2$ , RVol between  $30$  and  $59 \text{ mL}$ , and regurgitant fraction between  $30$  and  $49\%$ ; and severe: EROA  $> 0.4 \text{ cm}^2$ , RVol  $> 60 \text{ mL}$ , and regurgitant fraction  $> 50\%$ .<sup>24</sup> Therefore, there is no reason to classify the MR as «moderate-to-severe», whatever the presentation. The foregoing indicates the nature of the conflict in measuring TEER performance. This must be resolved by selecting more correct, reliable definitions for echo parameters, since these criteria are the key point to the measurement of procedural performance and outcome.

#### **MR $\leq 2+$ IS NOT A «GOOD RESULT» AFTER TEER**

The main problem is how to classify MR2+ as a robust independent parameter. If we apply the above criteria, all cases cataloged as MR 2+ should be considered to be «moderate» MR, but not «less than moderate», mild, or any other lesser classification. Furthermore, the «moderate-to-severe» terminology of MR 3+ can be confusing and should be avoided in all definitions. Consequently, the implicit hypothesis of MR  $\leq 2+$  as an «acceptable good» result after TEER is likely to be untrue; MR2+ after TEER should be considered a risk factor of poor prognosis, especially in the

long-term. The target must be MR  $\leq 1+$  after MV repair, regardless of the approach. The same condition is equally applicable, whatever surgical or percutaneous MV repair.

#### **HOW AN UNREALISTIC «ACCEPTABLE GOOD» RESULT AFTER TEER HAS INFLUENCED THE CURRENT GUIDELINES FOR THE MANAGEMENT OF VALVULAR HEART DISEASE**

Based upon the available literature, current guidelines for the management of VHD recommend TEER for special cases of primary and FMR. For cases with primary or organic MR, with high or prohibitive surgical risk as operative mortality  $> 8\%$ , anatomy suitable for TEER and life expectancy  $> 1$  year, the recommendation for TEER is class IIa. For cases with secondary or FMR, with no requirements for coronary artery bypass grafting, as a result of heart failure, in stage D for FMR with no adequate response to guideline-directed medical treatment, with left ventricular ejection fraction  $< 50\%$ , pulmonary systolic artery pressure  $< 70 \text{ mmHg}$ , left ventricular end systolic diameter  $< 70 \text{ mm}$ , TEER appears as a class IIa recommendation.<sup>23</sup>

This being the case, current clinical guideline recommendations for the use of TEER in MR should be reviewed. It is important to realize that all these recommendations emanate from the analysis of studies and reports in which MR2+ after TEER has been taken as an optimal or acceptable result. Furthermore, given these unfavorable circumstances, these recommendations for the use of TEER should be reappraised, under the precept that MR2+ is a suboptimal result, that negatively affects the patient's survival, quality of life and hemodynamics.<sup>25,26</sup>

#### **CONCLUSIONS**

In conclusion, the key observations of this review are: 1) the classification to measure the degree of MR commonly used in daily practice should be reviewed and adapted in a clearer and more concise way than currently, especially to measure the performance after TEER; 2) echo parameters for this purpose should be uniformly utilized for all cases, regardless of the approach; 3) current echo parameters to measure the

performance of MV repair are totally different for surgery and catheter-based techniques, such as TEER; 4) MR 2+ is frequently downgraded in TEER studies; 5) MR 2+ does impact the final outcome in terms of survival, quality of life, recurrent MR  $\geq 3+$  after MV repair, regardless of the approach. In this context, TEER is no exception to this observation.

If the parameters that govern the physical laws of cardiovascular hemodynamics are the same for any individual, then the same criteria should apply for both surgery and TEER. Thus, the results of MV repair should be clearly expressed as successful, only if the residual MR is  $\leq 1+$ . That means that the final target, in terms of echo values, should always be a residual MR  $\leq 1+$  after MV repair, regardless of a surgical or transcatheter approach.

#### REFERENCES

- Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D et al. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N Engl J Med*. 2005; 352: 875-883.
- Calafiore AM, Totaro A, Foschi M, Di Mauro M. Durability of mitral valve repair for degenerative mitral regurgitation: is it gold all that glitters? *Ann Transl Med*. 2018; 6: S10.
- De Bonis M, Lapenna E, Lorusso R et al. 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: 1019-1024.
- Chang BC, Youn YN, Ha JW, Lim SH, Hong YS, Chung N. Long-term clinical results of mitral valvuloplasty using flexible and rigid rings: a prospective and randomized study. *J Thorac Cardiovasc Surg*. 2007; 133: 995-1003.
- Suri RM, Clavel MA, Schaff HV et al. Effect of recurrent mitral regurgitation following degenerative mitral valve repair: long-term analysis of competing outcomes. *J Am Coll Cardiol*. 2016; 67: 488-498.
- Obata A, Yoshikawa J, Yoshida K et al. Residual, recurrent mitral regurgitation after mitral valve reconstruction: differences in lesion and operation method. *J Cardiol*. 1994; 24: 311-316.
- Rizza A, Sulcaj L, Glauber M et al. Predictive value of less than moderate residual mitral regurgitation as assessed by transesophageal echocardiography for the short-term outcomes of patients with mitral regurgitation treated with mitral valve repair. *Cardiovasc Ultrasound*. 2007; 5: 25.
- El-Eshmawi A, Anyanwu A, Boateng P et al. Second crossclamp to perfect degenerative mitral valve repair: Decision-making algorithm, safety, and outcomes. *J Thorac Cardiovasc Surg*. 2020; 160: 1181-1190.
- Adamo M, Metra M, Alfieri O. Percutaneous valve repair of functional mitral regurgitation: aiming at optimal and durable results. *Eur J Heart Fail*. 2020; 22: 1849-1851.
- Adamo M, Godino C, Giannini C et al. Left ventricular reverse remodelling predicts long-term outcomes in patients with functional mitral regurgitation undergoing MitraClip therapy: results from a multicentre registry. *Eur J Heart Fail*. 2019; 21: 196-204.
- Maisano F, Franzen O, Baldus S 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.
- Nickenig G, Estevez-Loureiro R, Franzen O et al. Transcatheter valve treatment sentinel registry investigators of the Euroobservational Research Programme of the European Society of Cardiology. Percutaneous mitral valve edge-to-edge repair: in-hospital results and 1-year follow-up of 628 patients of the 2011-2012 Pilot European Sentinel Registry. *J Am Coll Cardiol*. 2014; 64: 875-884.
- Pighi M, Estevez-Loureiro R, Maisano F et al. Transcatheter valve treatment sentinel registry (TCVT) Investigators of the EURObservational Research Programme (EORP) of the European Society of Cardiology. Immediate and 12-Month Outcomes of Ischemic Versus Nonischemic Functional Mitral Regurgitation in Patients Treated with MitraClip (from the 2011 to 2012 Pilot Sentinel Registry of Percutaneous Edge-To-Edge Mitral Valve Repair of the European Society of Cardiology). *Am J Cardiol*. 2017; 119: 630-637.
- Feldman T, Kar S, Elmariah S 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.
- Obadia JF, Messika-Zeitoun D, Leurent G et al; MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med*. 2018; 379: 2297-2306.
- Stone GW, Lindenfeld J, Abraham WT et al; COAPT Investigators. transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018; 379: 2307-2318.
- 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. [Last access: Mar 17, 2022] Available in: [https://www.acc.org/-/media/Clinical/PDF-Files/Approved-PDFs/2018/09/21/TCT-2018-Slides/Sept23-Sun/115pmET\\_COAPT-tct-2018.pdf](https://www.acc.org/-/media/Clinical/PDF-Files/Approved-PDFs/2018/09/21/TCT-2018-Slides/Sept23-Sun/115pmET_COAPT-tct-2018.pdf)
- Mack MJ, Lindenfeld J, Abraham WT et al; COAPT Investigators. 3-Year Outcomes of Transcatheter Mitral Valve Repair in Patients with Heart Failure. *J Am Coll Cardiol*. 2021; 77: 1029-1040.
- Buzzatti N, De Bonis M, Denti P 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.
20. Reichart D, Kalbacher D, Rübsamen N et al. The impact of residual mitral regurgitation after MitraClip therapy in functional mitral regurgitation. *Eur J Heart Fail.* 2020; 22: 1840-1848.
  21. Adamo M, Grasso C, Capodanno D 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.
  22. Buzzatti N, Denti P, Scarfò IS 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.
  23. Otto CM, Nishimura RA, Bonow RO et al. 2020 ACC/AHA Guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint. Committee on Clinical Practice Guidelines. *Circulation.* 2021; 143: e35-e71.
  24. Zoghbi WA, Asch FM, Bruce C et al. Guidelines for the evaluation of valvular regurgitation after percutaneous valve repair or replacement: a report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Angiography and Interventions, Japanese Society of Echocardiography, and Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr.* 2019; 32: 431-475.
  25. Dayan V, Garcia-Villarreal OA, Escobar A, Ferrari J, Quintana E, Marin-Cuarteras M, Almeida R. The Latin American Association of Cardiac and Endovascular Surgery statement regarding the recently released 2020 ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease. *Eur J Cardiothorac Surg.* 2021; 59: 729-731.
  26. García-Villarreal OA. Transcatheter edge-to-edge valve repair in functional mitral regurgitation. *Eur J Cardiothorac Surg.* 2021: ezab521.

**Funding/support:** no financial grant was received for this article.

**Conflict of interest:** the author has no conflict of interest.

**Correspondence:**

**Ovidio A García-Villarreal**

**E-mail:** ovidiocardiotor@gmail.com