

Transcatheter-edge-to-edge for mitral valve regurgitation: *Experientia docet*

Ovidio A. García-Villarreal

Mexican College of Cardiovascular and Thoracic Surgery. México City, MÉXICO.

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In a recent article published in the JACC, Haustleiter J, et al. describe the benefits of using transcatheter edge-to-edge (TEER) to treat cases with primary mitral regurgitation (DMR) through the PASCAL IID registry. The authors reported that at 6 months, 92.4% patients had mitral regurgitation (MR) $\leq 2+$ and 56.1% did MR $\leq 1+$. Also, the probability of survival, freedom from major adverse events, and rehospitalization for heart failure (HF) were 93.7%, 85.6%, and 92.6%, respectively [1].

Although the article makes special emphasis on cases with complex anatomy, the results and conclusions in this paper should be painstakingly analyzed. The information is presented graphically as residual/recurrent MR after TEER. At a glance, this information does not differ substantially from other previously published studies [2-13].

It must be noted that the vast amount of information analyzed so far does not consider the residual/recurrent MR $2+$ after TEER as deleterious. Indeed, the impact of such a residual/recurrent MR $2+$ in the final outcome has been clearly ignored by Interventional Cardiology. No single interventional cardiological group has stringent measures aimed at pursuing the target as MR $\leq 1+$ as the only acceptable result after TEER. This is an issue that clearly needs to be sufficiently emphasized. In surgical context, the only accepted target after MV repair is MR grade 0-1+, but not greater than this [14].

There is no reason to believe that the target should be different between surgical and percutaneous approach. There-

fore, when residual/recurrent MR $\geq 2+$ is included, it is so evident that in most studies and reports, more than half of cases exhibit MR $\geq 2+$ after TEER. In this context, the PASCAL IID registry does not differ so much than previously reported information. Within the first 6 months of follow-up, up to 43.9% of the cases had MR $\geq 2+$ after TEER [1] (**Table 1**).

This issue about residual MR $2+$ after TEER has received little attention as yet. Arguments in favor of being considered as “acceptable result” after TEER endorsed by MVARC have been so feeble [15]. When this criterion is analyzed comparatively to series of patients submitted to TEER, Buzzatti et al. demonstrated by multivariate model that MR $2+$ was the only factor associated with the development of MR $>3+$ at follow-up in DMR (HR, 6.71; 95% CI, 3.48-12.90; $p < 0.001$) and FMR (HR, 7.27; 95% CI, 3.34-15.80; $P < 0.001$). In addition, the prediction for cumulative incidence function of cardiac death was higher for residual MR $2+$ when compared to MR $\leq 1+$ (HR, 5.28; 95%CI, 2.41-11.56; $p < 0.001$) [16]. In the GIOTTO registry, Bedogni et al. found that residual MR $2+$ was associated with increased risk for 1-year mortality (HR, 1.33; 95%CI, 1.02 – 1.73; $p=0.032$) [8]. In the GRASP-IT registry, procedural failure or residual MR $\geq 2+$ was associated to 3-fold increased risk of 5-year for all-cause mortality (HR, 2.17; 95%CI, 1.42-3.31; $p < 0.001$), and for all-cause mortality and rehospitalization for HF (HR, 2.20; 95%CI, 1.52-3.19; $p < 0.001$) [6]. After analyzing 685 patients underwent TEER, Sugiura et al. found that in DMR, residual MR (MR $2+$ versus $\leq 1+$, HR, 2.56; 95% CI, 1.12–5.87; $p=0.03$), and in functional MR, residual MR (HR, 2.45; 95% CI, 1.24–4.85; $p=0.01$) were independently associated with further development of recurrent MR $\geq 3+$ [17]. Five-year cumulative incidence function for MR $\geq 3+$ was associated with residual MR $2+$ in FMR (HR 4.67, CI 2.49–8.74, $p < 0.001$) and in DMR (HR 7.15, CI 2.72–18.75, $P < 0.001$) [18].

Corresponding author: Dr. Ovidio A. García Villarreal
email: ovidiocardiotor@gmail.com

TABLE 1. Residual/recurrent MR $\geq 3+$ and $\geq 2+$ after TEER

STUDY/REGISTRY	YEAR	RECURRENT MR $\geq 3+$	RECURRENT MR $\geq 2+$	FOLLOW-UP
ACCESS-EU ²	2013	21.9%	69.4%	1 year
EVEREST II ³	2015	19%	50%	5 years
REALISM ¹⁰	2018	12.8%	53.8%	5 years
MITRA-FR ⁴	2018	18%	50%	1 year
GRASP-IT ⁶	2019	22.4%	22.4%	5 years
MITRASWISS ⁷	2020	31.8%	63.6%	5 years
GIOTTO ⁸	2020	3.7%	36.4%	30 days
COAPT ⁹	2021	1.2%	16.3%	3 years
MIDA (high risk tertile) ¹²	2021	Not available	59%	2 years
STS/ACC/TVT ¹¹	2022	8.7%	Not available	30 days
PASCAL IID ¹	2023	7.5%	43.9%	6 months

Better success criteria for TEER should be systematically applied in daily practice. However, there is a substantial difference in officially accepted criteria between surgery and catheter-based techniques. A far greater priority should be given to this question by interventional cardiology in order to get the best success, especially in the long-term. In summary, MR 2+ does impact the survival, quality of life, and development of recurrent MR $\geq 3+$ after MV repair, regardless of surgical or percutaneous approach [19] (Table 2).

As previous models available on the market, Pascal system used in PASCAL IID registry is also a ringless therapy, which has been one of the main concerns related to this kind of therapies. The use of annuloplasty ring plays a pivotal role in surgical MV repair. It was duly emphasized by Carpentier since the beginning in the French Correction [20-23]. Suri et al. have demonstrated that the lack of annuloplasty ring was associated to recurrent MR over time ($p < 0.0001$). In turn, the use of annuloplasty ring was associated to a lower risk for long-term mortality in univariate (HR, 0.51; 95% CI, 0.36-0.76; $p = 0.001$) and multivariate analyses (HR, 0.51; 95% CI, 0.32-0.80; $p = 0.004$), respectively. Also, the annuloplasty ring decreased the risk for recurrent MR in the univariate (HR, 0.31; 95% CI, 0.18-0.59, $p = 0.0008$) and multivariate analyses (HR, 0.33, 95% CI, 0.18-0.63; $p = 0.002$) [24].

Nardi et al. found that the only independent predictor of late progression to MR $\geq 3+$ was the lack of prosthetic ring (OR, 0.1; 95% CI, 0.025 to 0.892; $p = 0.04$). At 10-year follow-up, the freedom from MR $\geq 3+$ was $92\% \pm 3.2\%$ versus $76\% \pm 9.8\%$ in patients using and not using annuloplasty prosthetic ring, respectively [25].

Shimokawa et al. found that the no use of annuloplasty ring was an independent predictor of mortality (HR, 2.80; 95% CI, 1.48-5.27; $p < 0.001$), reoperation (HR, 2.74; 95% CI, 1.29-5.83; $p = 0.009$), and recurrent MR $> 3+$ (HR, 2.80; 95% CI, 1.48-5.27; $p < 0.001$) [26].

In a study of 3,057 patients underwent MV repair for DMR, Gillinov reported that recurrent MR was directly linked to the use of annuloplasty ring ($p = 0.0002$). Also, survival was better when an annuloplasty ring was used (84% versus 81% at 10 years, $p = 0.009$) [27].

In degenerative disease, David et al. found in a follow-up at 20 years that recurrent MR $\geq 3+$ was present in 12.8%. The estimated probability of adverse events for the further development of recurrent MR was 3.3%, 4.4%, 6.3%, 8.9%, and 12.5% at 1 year, 5-years, 10-years, 15-years, and 20-years, respectively. Multivariable repeated measures models of recurrent MR $\geq 3+$ found that the no use of annuloplasty ring

TABLE 2. Residual MR 2+ as predictor for development of MR $\geq 3+$ after TEER

AUTHOR	YEAR	TYPE	PREDICTOR	HR	95% CI	p value
Buzzatti ¹⁶	2016	DMR	Residual MR 2+	6.71	3.48 - 12.9	< 0.001
Buzzatti ¹⁶	2016	FMR	Residual MR 2+	7.27	3.34 - 15.80	< 0.001
Buzzatti ¹⁸	2019	DMR	Residual MR 2+	7.15	2.72-18.75	< 0.001
Buzzatti ¹⁸	2019	FMR	Residual MR 2+	4.67	2.49-8.74	< 0.001
Sugiura ¹⁷	2022	DMR	Residual MR 2+	2.56	1.12-5.87	0.03
Sugiura ¹⁷	2022	FMR	Residual MR 2+	2.45	1.24- 4.85	0.01

All values are calculated by multivariate analysis. DMR: Primary mitral regurgitation; FMR: Functional mitral regurgitation; MR: Mitral regurgitation.

TABLE 3. Lack of annuloplasty ring as predictor for further development of MR≥3+ after surgical mitral valve repair in DMR.

AUTHOR	YEAR	PREDICTOR	HR	95% CI	p value
Shimokawa ²⁶	2011	No Ring	2.80	1.48-5.27	< 0.001
David ²⁸	2019	No Ring	2.28	1.22- 3.83	< 0.001
De Bonis ³⁰	2014	No Ring	2.80	0.9-8.7	0.06

was one of the strongest predictors for failure after MV repair (HR, 2.68; 95% CI: 1.22- 3.83; p < 0.05) [28].

Now, speaking specifically of the surgical edge-to-edge MV repair, the use of annuloplasty ring has been considered as a part of the technique [29]. De Bonis found that one of the most important predictors for recurrent MR 3 ≥+ was the lack of using a true annuloplasty prosthetic ring in a follow-up to 21 years (HR, 2.8; 95% CI, 0.9-8.7; p = 0.06) [30].

In an analysis by De Bonis et al. of 61 patients underwent surgical edge-to-edge MV repair without annuloplasty ring, freedom from reoperation was 57.8 ± 7.21% and freedom from recurrence of MR ≥3+ was 43±7.6% at 12-year follow-up. Therefore, in degenerative MR, the long-term results of the surgical edge-to-edge MV repair without annuloplasty are not satisfactory, emphasizing the need for a reliable annuloplasty to improve the long-term outcomes of TEER [31].

After analyzing 125 patients with DMR underwent paracommissural surgical edge-to-edge, De Bonis et al. found that

freedom from MR ≥3+ at 11 years was 96.3% ± 1.7%, concluding that the best results were obtained by adding annuloplasty prosthetic ring to surgical edge-to-edge technique [32].

In a series of 174 patients with DMR underwent surgical edge-to-edge MV repair in combination ring annuloplasty, De Bonis et al. found that overall freedom from MR ≥3+ at 14 years was 83.8% ± 3.39% [33].

Alferi et al. published a series of patients operated on of surgical edge-to-edge for DMR. At 5-years, freedom from reoperation was 92 ± 3.4% in whom received an annuloplasty versus 70 ± 15% in those without a ring (p = 0.02) [34]. Maisano et al. found similar conclusions without using annuloplasty ring in addition to surgical edge-to-edge MV repair [35].

Therefore, we can conclude that surgical edge-to-edge technique should always be combined with prosthetic ring annuloplasty in order to provide excellent long-term outcomes in patients with DMR. The same principle must be

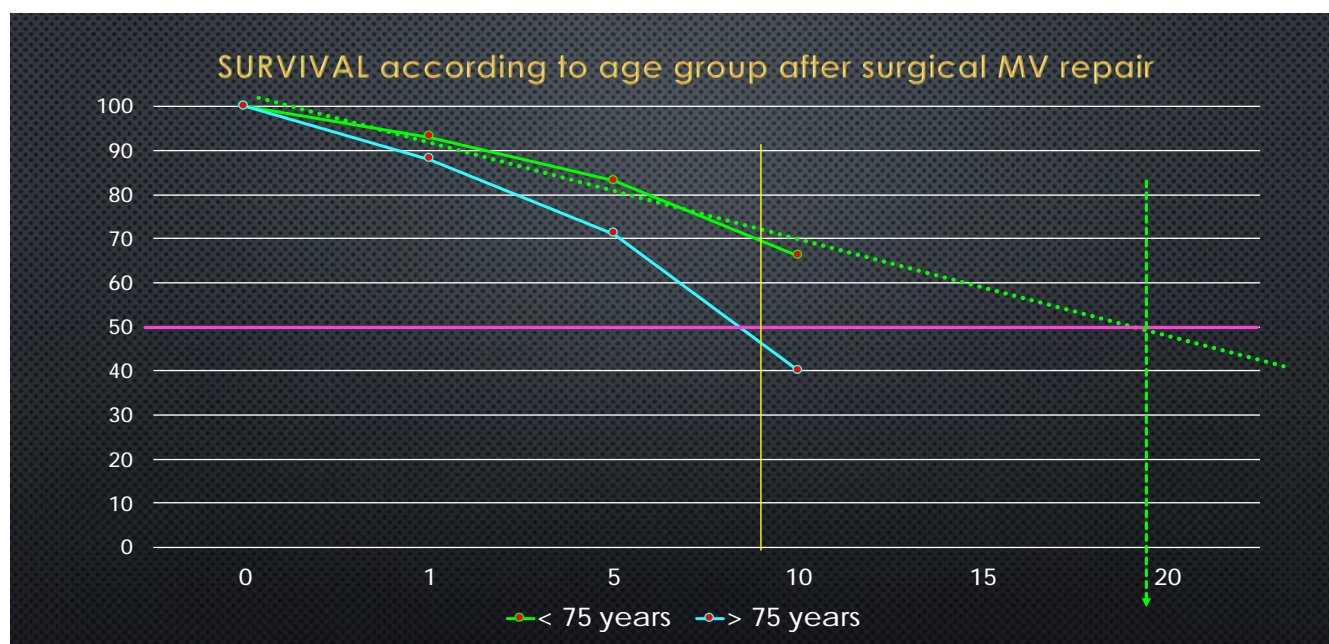


Figure 1. Kaplan-Meier survival estimates for patients undergoing surgical MV repair, according to age group. Vassileva CM et al.³⁷

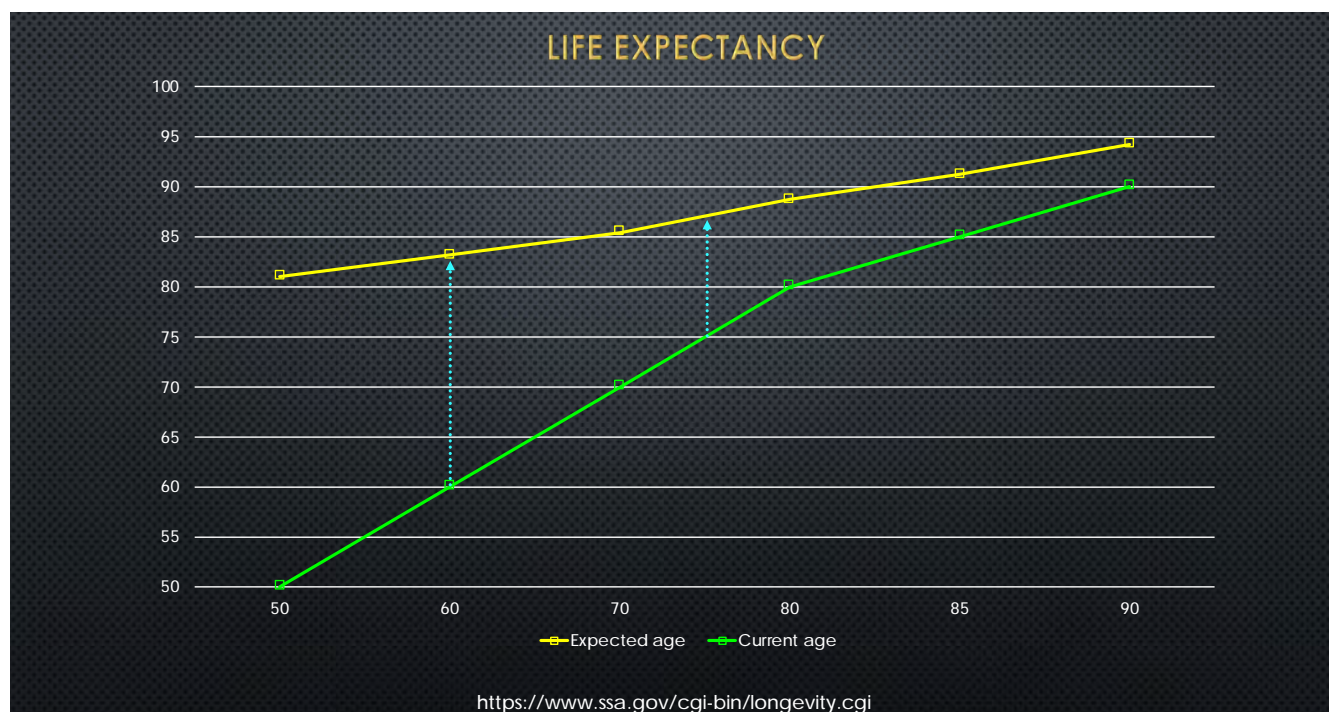


Figure 2. Life expectancy obtained by using US government calculator. Reference ³⁸

considered in TEER techniques [36]. Indeed, in the field of catheter-based therapies, all this information points to the need to implement the use of prosthetic ring annuloplasty to obtain stable long-term results. (Table 3).

We can summarize that any process for MV repair, whatever surgical or percutaneous, needs annuloplasty with a prosthetic ring to be perfect. The lack of annuloplasty has been a constant in TEER. This is one of the main concerns in terms of suboptimal efficacy and recurrence of MR. As yet, the combined use of transcatheter annuloplasty is not part of the usual armamentarium of TEER-based therapies. In this setting, the Pascal system, used in PASCAL IID registry [1], does not differ from MitraClip, entailing the same potential deleterious consequences, especially in the intermediate- and long-term.

The other point to consider is event-free survival, especially all-cause mortality. It is well known that DMR is a potentially curable disease. In fact, once MR has been successfully treated, by whatever surgical or percutaneous approach, life expectancy becomes very similar to that of the general population. In general, the Kaplan-Meier survival estimates for patients undergoing surgical MV repair were 90.9%, 77.1%, and 53.6% for 1-, 5-, and 10-year, respectively [37] (Fig. 1). Of course, as previously stated, this fact is considered provided that post-procedure result is residual/recurrent MR $\leq 1+$. In this framework, special consideration must be paid in the long-term.

Using a life expectancy calculator, the expected mean life for a 75-year-old individual is approximately 11 years, while 23.4 years for a 60-year-old [38] (Fig. 2). Thus, though this article reported survival rate of 93.7%, the follow-up at 6 months is still too short to make definite and strong results [1].

With this information, at some point, it is essential to think in the long-term after TEER. What is really concerning is the fact that no available information derived directly from TEER series is known beyond 5 years after procedure. Consequently, long-term TEER durability remains unknown. At 5-years of follow-up, recurrence MR $\geq 3+$ after TEER have been reported in 31.8% [7], 22.4% [6], and 19% [3], while only 5% after surgical MV repair [30]. Moreover, freedom from MR $\geq 3+$ was 80.2% and 87.2%, at 17 years and 20 years after surgery, respectively [28,30].

To conclude, we must recognize that after analyzing the current information available, and considering that TEER is a technique that has emerged from a surgical one, catheter-based techniques need to be improved by applying the same concepts from surgical experience in order to obtain the best and most durable results. In the end, experientia docet!

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