Revista da
SOCESP
Sociedade de Cardiologia do Estado de São Paulo

CRITICAL ANALYSIS OF STUDIES THAT HAVE CHANGED RECENT CLINICAL PRACTICE: VALVULAR HEART DISEASE

ANÁLISE CRÍTICA DOS ESTUDOS QUE MUDARAM A PRÁTICA CLÍNICA RECENTE: DOENÇA VALVAR

Matheus Simonato[1]
Alexandre A. C. Abizaid[1]

1. Instituto Dante Pazzanese de Cardiologia, São Paulo, Brazil.

Correspondence:
Alexandre A. C. Abizaid
Instituto Dante Pazzanese de Cardiologia. Av. Dante Pazzanese, 500. São Paulo, SP, Brazil.
aabizaid@uol.com.br

Received on 07/10/2019,
Accepted on 07/22/2019

ABSTRACT

In this short critical review, we will discuss three trials with the potential to alter clinical practice and the main international guidelines regarding valvular heart disease. The PARTNER III trial was a study of 1000 low surgical risk patients randomized between transcatheter aortic valve replacement (TAVR) and conventional surgery, showing the superiority of the transcatheter technique with a combined primary endpoint of all-cause mortality, stroke and rehospitalization over twelve months of follow-up (8.5% vs. 15.1%, p = 0.001). The Evolut Low Risk trial randomized 1468 patients between the two techniques with a primary endpoint of death or incapacitating stroke at the end of two years of follow-up, achieving non-inferiority in a Bayesian comparison (5.3% TAVR vs. 6.7% surgery). Finally, we also will discuss the COAPT study, in which 614 patients were randomized between the edge-to-edge MitraClip device and clinical treatment for secondary mitral regurgitation. Among these selected patients, the annual rate of hospitalizations for heart failure was 35.8% per patient-year in the MitraClip group, compared with 67.9% in the control group (HR 0.53, 95% CI 0.4-0.7). Under the new guidelines, we may reasonably expect a class I indication for transcatheter valvular replacement in low-risk patients and a class IIa indication for the edge-to-edge technique in patients with characteristics similar to those of the COAPT study. These procedures should be considered within the context of the Heart Team so that the best results are achieved.

Keywords: Aortic Valve Stenosis; Mitral Valve Insufficiency; Risk.

RESUMO

Nesta breve análise crítica, discutiremos três estudos com potencial de alterar a prática clínica e as principais diretrizes internacionais no que tange à doença valvar. O estudo PARTNER III foi um estudo que randomizou 1000 pacientes de baixo risco cirúrgico entre troca valvar transcateter e cirurgia convencional, com superioridade da técnica transcateter em um desfecho primário combinado de mortalidade de todas as causas, acidente vascular cerebral (AVC) e re-hospitalização em doze meses de seguimento (8,5% vs. 15,1%, p = 0,001). Já o estudo Evolut Low Risk randomizou 1468 pacientes entre as duas técnicas, com um desfecho primário de mortalidade ou AVC incapacitante ao final de dois anos de seguimento que atingiu não-inferioridade na comparação Bayesiana (5,3% transcateter vs. 6,7% cirurgia). Finalmente, discutimos também o estudo COAPT, no qual 614 pacientes foram randomizados entre o dispositivo edge-to-edge MitraClip e o tratamento clínico da insuficiência mitral secundária. Nesses pacientes selecionados, a taxa anualizada de hospitalizações por insuficiência cardíaca foi de 35,8% por paciente-ano no grupo MitraClip, comparado com 67,9% no grupo controle (HR 0,53, IC 95% 0,4-0,7).Nas novas diretrizes, pode-se razoavelmente esperar uma indicação I para a troca valvar transcateter em pacientes de baixo risco e uma indicação IIa para a técnica edge-to-edge em pacientes com características semelhantes aos do COAPT. Esses procedimentos devem ser considerados no contexto do Heart Team para que sejam atingidos os melhores resultados.

Descritores: *Estenose Aórtica; Insuficiência da Valva Mitral; Risco.*

 http://dx.doi.org/10.29381/0103-8559/20192903249-54

INTRODUCTION

Management of valve disease has made great strides over the past fifteen years by the introduction of new transcatheter therapies. In this short presentation, our goal is to discuss three recently published papers that will certainly change national and international guidelines for the treatment of valvular heart disease.

GUIDELINES REVIEW

The three main guidelines in the national context are the guideline of the Brazilian Society of Cardiology (SBC), the guideline of the American Heart Association/American College of Cardiology (AHA/ACC) and finally the guideline of the European Society of Cardiology (ESC). The Brazilian guideline was published in 2011.[1] with an update in 2017.[2] The American guideline was originally published in 2014[3] with an update focused on 2017.[4] Finally, the new version of the European guideline was published in 2017.[5]

The most up-to-date guidelines recommendations and degrees of evidence vary between these guidelines. Table 1 includes the main recommendations of each guideline regarding symptomatic severe aortic stenosis and secondary mitral regurgitation.

SEVERE SYMPTOMATIC AORTIC STENOSIS IN LOW-RISK PATIENTS

Studies with SAPIEN balloon-expandable valve family (Edwards Lifesciences, Irvine, California, United States) pioneered in inoperable[6], high-risk[7] and intermediate-risk patients.[8] After a long wait, in 2019 PARTNER III[9] study was published in the New England Journal of Medicine. This trial included patients with symptomatic severe aortic stenosis considered to be of low surgical risk, defined as Society of Thoracic Surgeons (STS) score below 4% (i.e., 30-day death risk below 4%). Patients with bicuspid valves, frailty, severe aortic insufficiency, among other anatomical and clinical criteria that would render the procedure impossible were excluded.

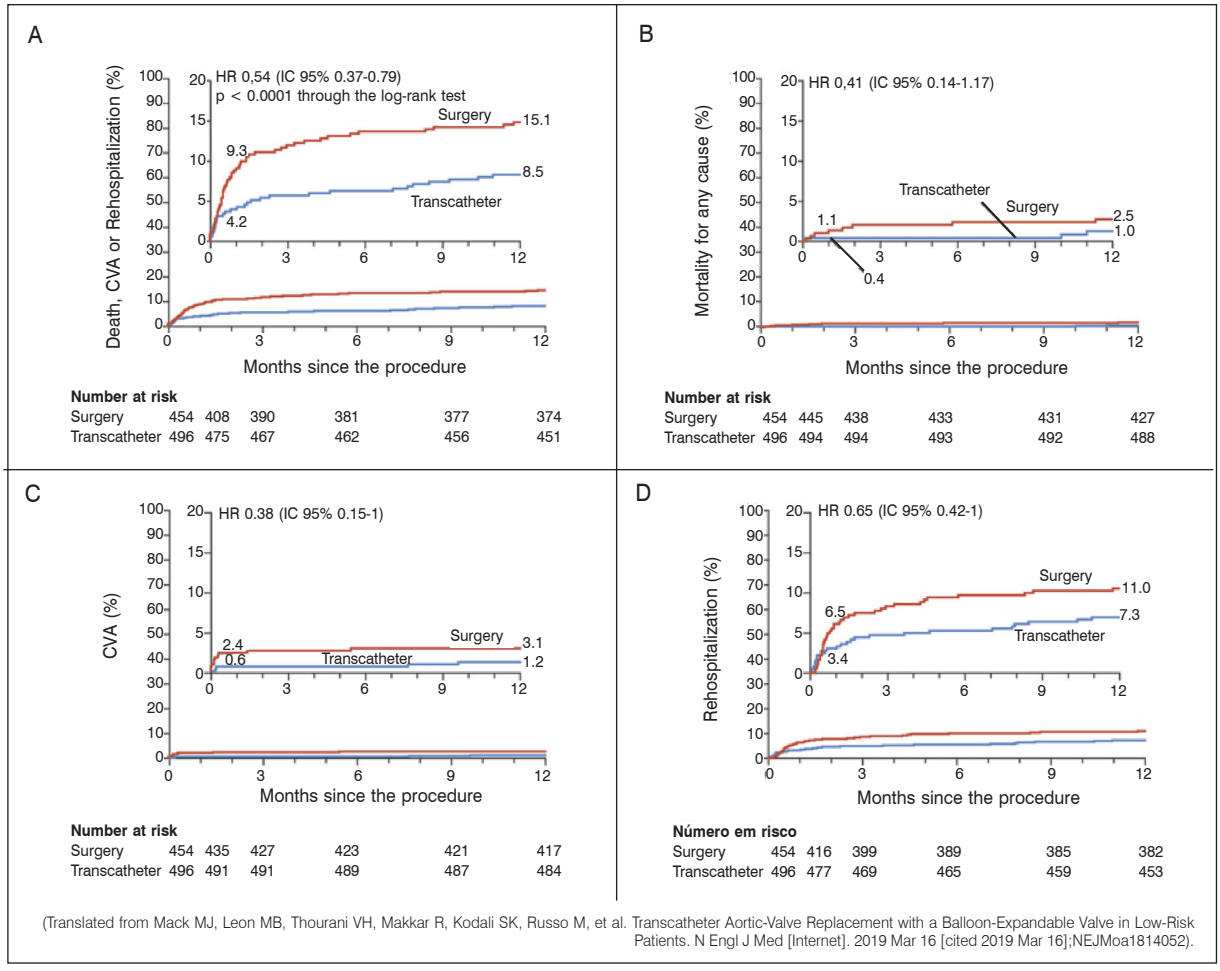
One thousand patients were randomized between conventional surgery and the SAPIEN 3 transcatheter procedure. The primary clinical endpoint was a composite of all-cause mortality, cerebrovascular accident (CVA) and rehospitalization at twelve months of follow-up. The average age of the patients was 73 years, with an average STS score of 1.9%, confirming the purpose of being a low risk study. It is noteworthy that, by low risk, it is not necessarily understood younger patients, but with a lower prevalence of comorbidity. In terms of results, the primary outcome occurred in 8.5% of patients in the transcatheter group versus 15.1% in surgical patients, thus achieving superiority ($p = 0.001$). (Figure 1) In addition, the transcatheter group had a lower incidence of CVA (0.6% vs. 2.4%, $p = 0.02$) and atrial fibrillation (5% vs. 39.5%, $p < 0.001$), and shorter hospitalization (3 days vs. 7 days, $p < 0.001$). Finally, the rate of moderate or significant paravalvular reflux between the two groups was similar at 30 days (0.8% transcatheter vs. 0% surgery) and at twelve months (0.6% transcatheter vs. 0.5% surgery).

Looking at the primary endpoint components, however, there was no significant difference in one-year mortality between the groups (1% transcatheter vs. 2.5% surgery, HR 0.41, 95% CI 0.14-1.17), CVA (1.2% transcatheter vs. 3.1% surgery, HR 0.38, 95% CI 0.15-1) and rehospitalization (7.3% transcatheter vs. 11% surgery, HR 0.65, 95% CI 0.42-1). This

Table 1. Main recommendations of each guideline regarding symptomatic severe aortic stenosis and secondary mitral insufficiency.

Severe symptomatic aortic stenosis			
	SBC Guideline	**AHA/ACC Guideline**	**ESC Guideline**
Inoperable	TAVI I A	TAVI I A	TAVI I B
High risk	TAVI I A	Surgery I A TAVI I A	Surgery I B TAVI I B
Intermediate risk	Surgery I A TAVI IIa A	Surgery I B-NR TAVI IIa B-R	Surgery I B TAVI I B
Low risk	Surgery I A	Surgery I B-NR	Surgery I B
Severe secondary mitral insufficiency			
	SBC Guideline	**AHA/ACC Guideline**	**ESC Guideline**
Myocardial revascularization	Surgery IIa B	Surgery IIa C	(EF > 30%) Surgery I C
Symptomatic	Surgery IIb B	Surgery IIb B	(EF < 30%) Surgery IIa C
			(EF > 30% low risk) Surgery IIb C
High risk surgical symptomatic	Ischemic: Percutaneous IIb B	-	(EF > 30%) Percutaneous IIb C
	Dilated: Percutaneous Ib B		

R: Randomized; NR: Non-randomized; SBC: Brazilian Cardiology Society; AHA/ACC: American Heart Association/American College of Cardiology; ESC: European Society of Cardiology; TAVI: Transcatheter aortic valve implantation; EF: Left ventricle ejection fraction



(Translated from Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med [Internet]. 2019 Mar 16 [cited 2019 Mar 16];NEJMoa1814052).

Figure 1. Kaplan-Meier Models demonstrating superior performance in the primary endpoint of PARTNER III study.

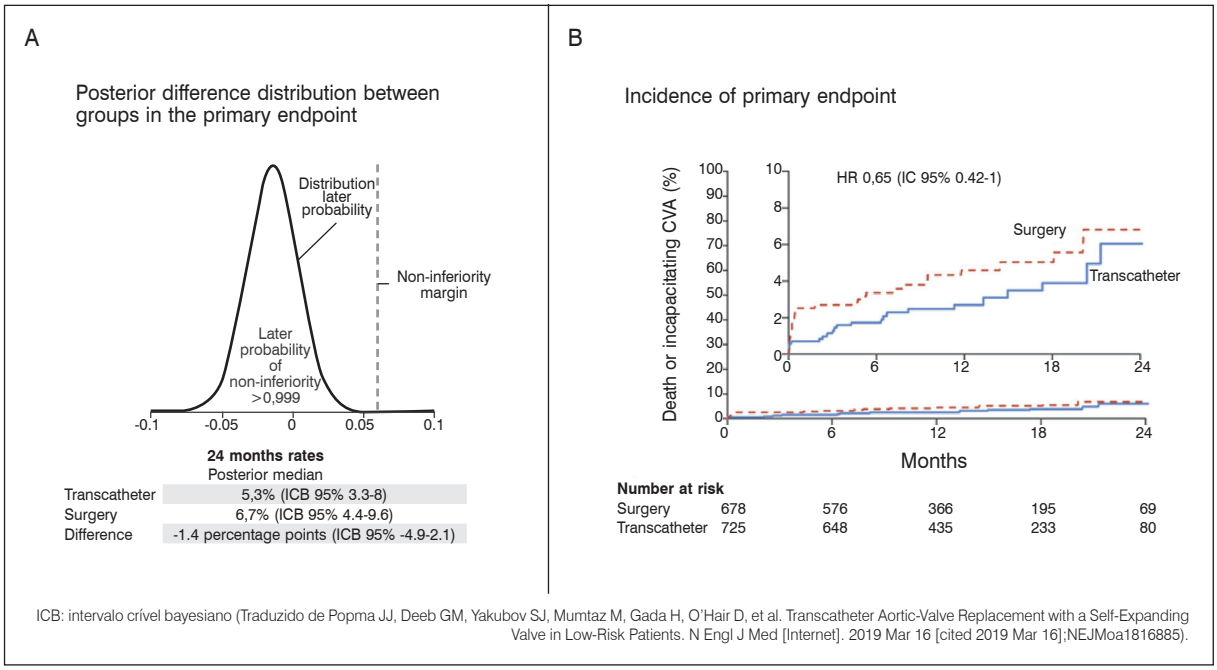
demonstrates the quality of the results obtained in surgical patients, emphasizing that the traditional technique can still be performed with a high degree of success in experienced centers. This information is important for Brazilian teams, as the availability of the transcatheter technique is still limited in the public system.

The other major trial published in 2019 was the Evolut Low Risk Trial, using the competitor self-expanding valve Evolut (Medtronic Inc., Minneapolis, Minnesota, United States). In this study, 1468 patients were randomized between transcatheter technique and conventional surgery. The primary endpoint chosen was a composite of mortality or disabling CVA within two years of follow-up. Among the secondary endpoints tested hierarchically included gradients, aortic area, symptoms, and quality of life, plus a composite of mortality, disabling CVA, bleeding, vascular complication, and acute renal injury at 30 days.

The population of this study was similar to that of PARTNER III: patients had a mean age of 74 years with a STS of 1.9%. In the results, the primary endpoint was 5.3% in transcatheter patients versus 6.7% in the surgical group, reaching non-inferiority. (Figure 2) There was no superiority, however, in the comparison. The estimated two-year mortality was 4.5% in both groups. At the end of thirty days, CVA rates (0.5% transcatheter vs. 1.7% surgery), atrial fibrillation (7.7% transcatheter vs. 35.4% surgery), acute kidney injury (0.9% transcatheter vs. 2.8% surgery) and bleeding (2.4% transcatheter vs. 7.5% surgery) favored transcatheter patients. However, the pacemaker rate was worse in these compared to surgical ones (17.4% vs. 6.1%, respectively).

Regarding hemodynamic outcomes, transcatheter patients achieved non-inferiority and superiority in relation to gradients and valve area at the end of 12 months. The moderate or severe paravalvular reflux rate at 30 days was 3.5% in the TAVI group and 0.5% in the surgical group. In addition, there was a lower incidence of hospitalization for heart failure in the transcatheter group (3.2% vs. 6.5% surgery). Finally, there was no inferiority between the groups regarding symptoms and quality of life at the end of one year. However, recovery in transcatheter patients was faster, with superior quality of life after 30 days.

One criticism of this study lies in the methodological choice. Although the study had a primary endpoint of two years of follow-up, the analysis was performed when 850 patients reached 12 months of follow-up by Bayesian methods. Only 137 patients (9.3% of the total) had two years of follow-up at the time of pre-specified analysis. However, a similar methodology was used in the SURTAVI[10] study and the results were confirmed at the end of the two-year follow-up. Another criticism, which applies in reality to both PARTNER III and Evolut Low Risk, is the lack of blindness in awarding endpoints. Moreover, neither study provides information on



ICB: intervalo crível bayesiano (Traduzido de Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. N Engl J Med [Internet]. 2019 Mar 16 [cited 2019 Mar 16];NEJMoa1816885).

Figure 2. Panel A shows the subsequent probability distribution for the primary outcome in Evolut Low Risk study, confirming that the non-inferiority criterion was reached.

the long-term performance of the transcatheter technique. To remedy this issue, US FDA has mandated 10-year follow-up for all patients participating in both trials.

These two studies should change the indication for intervention in low surgical risk patients in the next update of guidelines. An indication of class I with evidence level A (due to the publication of the two high-quality randomized trials) for the transcatheter technique in low-risk surgical patients is expected.

SECONDARY MITRAL INSUFFICIENCY

In late 2018, COAPT study was published in the New England Journal of Medicine.[11] This trial used MitraClip device (Abbott Laboratories, Lake Bluff, Illinois, United States), used to attach mitral valve cusps (edge-to-edge repair, similar to Alfieri's suture) generating a reduction in reflux. The device could be used for both primary and secondary mitral regurgitation repair, but there was no evidence supporting its use in this second group.

In COAPT, 614 patients with secondary mitral regurgitation were randomized 1: 1 between MitraClip (associated with optimized drug therapy) and simple drug management (control). As an inclusion criterion, patients would have to remain symptomatic (NYHA II, III or IV able to walk) despite the use of maximum doses of drug therapy. In addition, the degree of reflux should be moderately severe or severe after core-lab evaluation. Finally, the institution's Heart Team should decide that the patient was anatomically fit to receive a MitraClip, while mitral valve surgery was inadequate.

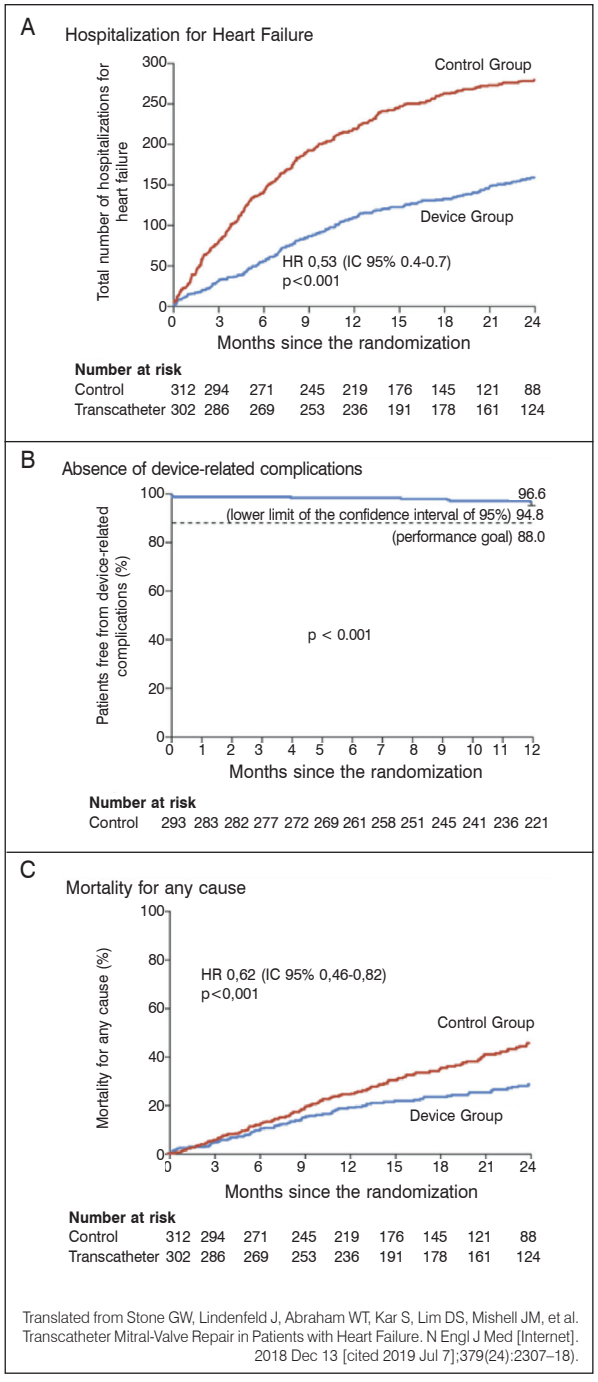
Two primary endpoints were included in the study: the primary effectiveness endpoint, 24-month hospitalization rate for heart failure (including recurrent events in the same patient), and the primary safety endpoint, no device-related complications at the end of 12 months. Since the control group would not receive the device, a pre-established rate of 88% was used for the primary safety endpoint, and patients should perform better than this for the endpoint to be achieved. Secondary endpoints would be tested hierarchically only if the primary endpoints were achieved.

The average age of the patients was 72 years. 36.5% had already received cardiac resynchronization therapy.

The average ejection fraction was 31.3%. Reflux was moderately severe in 52.2% of patients, with 47.8% with severe reflux. Device implantation was successful in 97% of patients. After using the device, 95% of patients had mild or moderate reflux. At the end of the study period, the median follow-up was 22.7 months in MitraClip group versus 16.5 months in control group.

Regarding the primary efficacy endpoint, the annualized rate of hospitalization for heart failure was 35.8% per patient year in MitraClip group, compared to 67.9% in control group (HR 0.53, 95% CI 0.4-0.7). (Figure 3) The number needed to treat (NNT) to avoid a two-year hospitalization was 3.1. As for the safety endpoint, the rate of absence of device complications at twelve months was 96.6%, far exceeding the pre-established value of 88% ($p < 0.001$). Two-year mortality also favored MitraClip group (29.1% vs. 46.1% control, HR 0.62, 95% CI 0.46-0.82), with an NNT of 5.9 to prevent one death. Other findings involved superior quality of life and functional class of MitraClip patients, as well as better left ventricular preservation in this group.

Results of COAPT study were received with great euphoria by the community. However, these were opposed to the results obtained in MITRA-FR study,[12] which was negative for differences in mortality and hospitalization between device group and control group. There are some explanations for the different findings between COAPT and MITRA-FR[13]. An important difference lies in the different severities of left ventricular disease and degree of mitral insufficiency among the studied populations. MITRA-FR



Translated from Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, et al. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. N Engl J Med [Internet]. 2018 Dec 13 [cited 2019 Jul 7];379(24):2307–18).

Figure 3. Primary endpoints of COAPT study in panels A and B. Kaplan-Meier curve for two-year mortality in panel C.

patients had larger dilated ventricles and included patients with lower ejection fraction than COAPT. In addition, due to different mitral regurgitation criteria, COAPT patients had more important reflux than MITRA-FR.[13] It is understood that mitral insufficiency was more relevant in the COAPT cohort, and its patients had a higher functional reserve, enabling better recovery if the pathophysiology driver, i.e. valve disease, was improved. Another issue is that COAPT required the optimization of drug therapy at maximally tolerated doses prior to MitraClip implantation, while this was not the case at MITRA-FR, which enabled changes throughout follow-up.

We can bring to practice then that the greatest benefit in using MitraClip is in patients with ventricular function closer to normal (i.e., earlier in the natural history of the disease) but with more severe reflux. We believe the new evidence may strengthen an indication at least IIa B-R for the use of the technique in the American guideline in well-selected patients.

FUTURE

New trials may further expand indications of transcatheter valve replacement and the mitral valve edge-to-edge procedure. For aortic valve replacement, EARLY-TAVR study will help unravel the issue of intervention in patients with so-called asymptomatic severe aortic stenosis. TAVR-UNLOAD trial will study the indication of transcatheter intervention in patients with moderate aortic stenosis and left ventricular dysfunction. In addition, long-term results from PARTNER III and Evolut Low Risk will provide insight into the durability of these devices. For the edge-to-edge technique in mitral insufficiency, Reshape-HF2 study may confirm or cast doubt on the results of COAPT.

CONCLUSION

A series of new high-quality studies have consolidated the evidence that underlies the indications of percutaneous techniques. Operators must be constantly updated so that they can offer the right interventions to their patients in the context of discussion in the Heart Team.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

AUTHORS' CONTRIBUTIONS: MS and AA wrote the text, prepared figures and tables, and conducted bibliographic research together. There are no other contributors in this text.

REFERENCES

1. Tarasoutchi F, Montera M, Grinberg M, Barbosa M, Piñeiro D, Sánchez C, et al. Diretriz Brasileira de Valvopatias - SBC 2011/ I Diretriz Interamericana de Valvopatias - SIAC 2011. Arq Bras Cardiol. Arq Bras Cardiol. 2011;97(5 Suppl 1):1-67.
2. **Tarasoutchi F, Montera M, Ramos A, Sampaio R, Rosa V, Accorsi T, et al. Atualização das Diretrizes Brasileiras de Valvopatias: Abordagem das Lesões Anatomicamente Importantes. Arq Bras Cardiol. 2017;109(6 suppl 2):1-34.**
3. **Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American**

Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(22):e57-185,

4. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease. J Am Coll Cardiol. 2017.
5. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J . 2017;38(36):2739–91.
6. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010;363(17):1597–607.
7. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011;364(23):2187–98.
8. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2016;374(17):1609–20.
9. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med. 2019; 380(18):1695-705.
10. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2017;376(14):1321–31.
11. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, et al. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. N Engl J Med. 2018;379(24):2307–18.
12. Obadia J-F, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, et al. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. N Engl J Med. 2018;379(24):2297–306.
13. Pibarot P, Delgado V, Bax JJ. MITRA-FR vs. COAPT: lessons from two trials with diametrically opposed results. Eur Hear J - Cardiovasc Imaging. 2019;20(6):620–4.