FERNANDO LUIZ DE MELO BERNARDI

Impacto da curva de aprendizado e evolução das práticas de implante de válvula aórtica transcateter no Brasil e na América Latina

Tese apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção do título de Doutor em Ciências

Programa de Cardiologia
Orientador: Prof. Dr. Henrique Barbosa Ribeiro

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DEDICATION

I dedicate this thesis to all my family members who supported me and were present with me during this journey. To my parents, Luiz and Jane, responsible for my education and for the person I am today. To my brother, Guilherme, my friend, partner, and professional colleague. To my loves, my wife Mariana and my son Rafael, the reason I live.

"The future belongs even more to hearts than to minds. Loving is the only thing that can occupy eternity. The inexhaustible is necessary for the infinite."

(Victor Hugo)

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“Those who pass by us don't go alone, they don't leave us alone. They leave a little of themselves, they take a little of us.”

(Antoine de Saint-Exupéry)

"This is a historic moment, and all of us here should remember it as such. We will talk to our grandchildren about this — that we were here at the time this incredible advance in the care of patients with aortic stenosis was presented."

(Eugene Braunwald)

ADOPTED STANDARDIZATION

This dissertation or thesis complies with the following standards, in force at the time of this publication:

Presentation of theses in the form of a compilation of articles, in accordance with the approved REGULATION of the CARDIOLOGY GRADUATE PROGRAM of the UNIVERSITY OF SAO PAULO on the 10th of August 2022 (*Resolução CoPGr 8300 - DOE 23/08/2022*).

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Sumário

RESUMO

Bernardi FLM. *Impacto da curva de aprendizado e evolução das práticas de implante de válvula aórtica transcateter no Brasil e na América Latina* [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2023.

INTRODUÇÃO: O implante de válvula aórtica transcateter (TAVI) foi introduzido na América Latina em 2008. Trata-se de procedimento complexo, minimamente invasivo para o tratamento da estenose aórtica importante, que requer uma curva de aprendizado (CA), estando a experiência dos centros possivelmente associada a melhores resultados. Desde 2008, inúmeras evoluções da prática do TAVI e das próteses ocorreram, trazendo melhorias nos resultados clínicos, potencialmente interferindo na CA. Os objetivos desta tese foram avaliar a evolução das práticas de TAVI no Brasil e na América Latina e o impacto da experiência e da CA nos desfechos clínicos. MÉTODOS: Realizaram-se quadro estudos. Estudo 1) estudo transversal entre 2019-2020 onde foi aplicado questionário a 46 centros da América Latina a respeito das suas práticas de TAVI. Os resultados foram comparados aos obtidos em 2015 quando o mesmo questionário foi aplicado a 250 centros do mundo, incluindo 29 da América Latina. Estudo 2) observacional multicêntrico (16 centros) que avaliou o impacto clínico da utilização da técnica de reposicionamento de válvula autoexpansíveis de nova geração (VAENG) e a associação da experiência dos centros aos desfechos clínicos. Estudo 3) observacional multicêntrico (25 centros ativos do Registro Brasileiro de TAVI entre de 2008 e 2023). A CA foi avaliada para mortalidade hospitalar. Conforme a sequência cronológica, os casos foram separados em experiência inicial (1o ao 40o), precoce (41o ao 80o), intermediária (81o ao 120o) e alta (>120o). Estudo 4) Uma comparação entre válvulas balão expansíveis de nova geração (VBENG) e VAENG para mortalidade hospitalar no registro brasileiro de TAVI. RESULTADOS: Estudo 1) Em 2015, em comparação aos centros do restante do mundo, os centros da América Latina apresentavam um volume anual significativamente menor de procedimentos e uma menor proporção de centros adotando práticas de TAVI minimalista. Em 2020, observou-se um aumento significativo de centros realizando TAVI com técnica minimalista na América Latina, porém com aumento pouco significativo do volume anual de procedimentos. Estudo 2) Nos 1.026 pacientes incluído, a necessidade de múltiplos reposicionamentos se associou a taxas menores de sucesso do procedimento (P=0,01) e aumento de mortalidade em um ano (P=0,014). Menor experiência (volume anual de procedimento < 25) foi um preditor independente de morte em um ano. Estudo 3) Em 3.194 pacientes, análise da CA demonstrou uma primeira queda de mortalidade no caso #40, seguido de estabilização da curva a partir do caso #118. Alta experiência se associou a menor mortalidade hospitalar em relação a experiência inicial após ajuste para confundidores (OR 0,57, P=0,013). Utilização de válvulas de nova geração também foi preditor de menor mortalidade. Nos centros com experiência inicial antes de 2014, tanto a experiência intermediária quanto a alta se associariam a menor mortalidade hospitalar. Nos centros com experiência inicial após 2014, a experiência acumulada não foi preditor de redução de mortalidade. Estudo 4) Em 1.703 casos, não houve diferença na mortalidade intra-hospitalar entre VBENG e VAENG (3,6% vs. 4,8%, P=0,27).

CONCLUSÃO: As práticas de TAVI evoluíram no Brasil e na América Latina com a crescente adoção de técnicas minimalistas e incorporação de dispositivos de nova geração, os quais têm se associados a melhores resultados clínicos. Também, a CA e a experiência dos centros demonstraram significativo impacto na redução da mortalidade. No entanto, o efeito da CA foi atenuado em centros que iniciaram sua experiência de TAVI mais tardiamente.

Descritores: Substituição da válvula aórtica transcateter; Estenose da valva aórtica; Curva de aprendizado; Brasil; América Latina.

SUMMARY

Bernardi FLM. *Impact of the learning curve and evolution of transcatheter aortic valve implantation practices in Brazil and Latin America* [thesis]. São Paulo: “Faculdade de Medicina, Universidade de São Paulo“; 2023.

INTRODUCTION: Transcatheter aortic valve implantation (TAVI) was introduced in Latin America in 2008. It is a complex, minimally invasive treatment for severe aortic stenosis that requires a learning curve (LC), with the experience of centers possibly being associated with improved outcomes. Since 2008, numerous evolutions in the practices of TAVI and prostheses emerged, promoting improvements in clinical results, and potentially interfering with the LC. The objectives of this thesis were to evaluate the evolution of TAVI practices in Brazil and Latin America and the impact of experience and LC on clinical outcomes. METHODS: Four studies were conducted. Study 1) cross-sectional study between 2019-2020 where a questionnaire was applied to 46 centers in Latin America on their TAVI practices. The results were compared to those obtained in 2015 when the same questionnaire was applied to 250 centers around the world, including 29 centers in Latin America. Study 2) Multicenter observational study (16 centers) that evaluated the clinical impact of using the repositioning technique for new generation self-expanding valves (NGSEV) and the association of centers' experience and outcomes. Study 3) multicenter observational (25 active centers from the Brazilian TAVI Registry between 2008 and 2023). The LC was evaluated for in-hospital mortality. According to the chronological sequence, the cases were stratified into initial (1st to 40th), early (41st to 80th), intermediate (81st to 120th), and high experience (>120th). Study 4) A comparison between new-generation balloon-expandable valves (NGBEV) and NGSEV for in-hospital mortality in the Brazilian registry. RESULTS: Study 1) In 2015, compared to centers from the rest of the world, Latin American centers had a much lower annual volume of procedures and a lower proportion of centers adopting minimalist TAVI practices. In 2020, there was a significant increase in centers performing minimalist TAVI in Latin America, but with a slight increase in the annual procedural volume. Study 2) 1,026 patients were included. The need for multiple repositioning was associated with lower procedural success rates (P=0.01) and increased one-year mortality (P=0.014). Lower experience centers (annual procedure volume < 25) were an independent predictor of death at one year. Study 2) LC analysis of 3,194 patients showed a first drop in mortality in case #40, followed by slope stabilization from case #118 onwards. High experience was associated with lower in-hospital mortality compared to initial experience after adjusting for confounders (OR 0.57, P=0.013). Utilization of new-generation valves were also predictive of lower mortality. In centers with initial experience before 2014, both intermediate and high experience were associated with lower hospital mortality. In centers with initial experience after 2014, the effect of the LC was attenuated, so that accumulated experience did not predictive in-hospital mortality reduction. Study 4) In 1,703 cases, there was no difference in in-hospital mortality between NGBEV and NGSEV (3.6% vs. 4.8%, P=0.27). CONCLUSION: TAVI practices have evolved in Brazil and Latin America with increasing adoption of minimalist techniques and incorporation of newer generation devices which have been associated with better clinical

outcomes. Also, the LC and the experience of centers had significant impact on mortality reduction. However, the LC effect was attenuated in centers that started their TAVI experience later.

Descriptors: Transcatheter aortic valve replacement; Aortic valve stenosis; Learning curve; Brazil; Latin America.

1. INTRODUCTION

Aortic stenosis (AS) is the pathological impairment of the opening of the aortic heart valve, causing pressure overload in the left ventricle. The most frequent etiology of AS stems from calcific degeneration of its valve leaflets, a process closely related to senility, with a prevalence of 4.6% being observed in individuals aged over 75 years(1). With the phenomenon of population aging observed in virtually all regions of the world, AS has become a global health and economic problem.

The disease, according to its severity, is classified according to the degree of obstruction of the left ventricular outflow tract. Severe AS is defined as an aortic valve area < 1.0cm2 or an indexed area < 0.6cm2/m2 of body surface. The severity of AS can also be assessed by the transvalvular gradient and the peak jet velocity on the echocardiogram. Severe AS presents with a mean gradient ≥ 40 mmHg and peak velocity ≥ 4 m/s. The classic symptoms of severity are dyspnea on exertion, chest pain and syncope(2). Individuals with severe symptomatic AS have a poor prognosis if not properly treated, with reduced quality of life and approximate mortality of 25% per year(3).

The most effective treatment for severe AS consists of replacing the native valve with a prosthesis, a procedure classically performed through cardiac surgery with cardiopulmonary bypass. Surgical aortic valve replacement (SAVR), when successful, is highly effective in reducing symptoms and increasing survival(4). Nonetheless, because it is a pathology commonly found in very elderly individuals with a high burden of comorbidities, up to 30-40% of cases ended up being refused to SAVR due to the high surgical risk(5). In this scenario, the transcatheter aortic valve implantation

(TAVI), or also known as transcatheter aortic valve replacement (TAVR), emerged as a less invasive alternative to the conventional surgical technique, with the first procedure in human being performed in 2002(6).

In TAVI procedure, a valve prosthesis with leaflets made of biological material, called a transcatheter heart valve (THV), is implanted over the diseased native valve, introduced percutaneously, through catheterization techniques. The main access route for TAVI is transfemoral, where the device is introduced and advanced through the common femoral artery until the heart. The transfemoral is the most studied and preferable access for TAVI because it is associated with a lower risk of complications such as major vascular complications, bleeding, and myocardial injury(7,8). In cases with unfavorable anatomy, there is the possibility of performing the procedure by other routes, such as transaortic, transsubclavian, transcarotid and even the possibility of using a transvenous or transcaval route(9). Although the original indication for TAVI was for the treatment of severe AS of a native tricuspid valve, the procedure has now been performed successfully and safely in cases of bicuspid AS, low-flow and low-gradient, pure or predominant aortic regurgitation (AR), and for cases of severe dysfunction of a surgical aortic bioprosthesis, denominated as valve-in-valve procedure(10–12).

Since its conception that can be traced back to the early 1990s when the concept of percutaneous valve replacement was first proposed(13), to the first in-human implantation by Cribier and his team in France in 2002(14,15), TAVI has undergone significant advancements and improvements. The first device approved for commercialization in the world was the Edwards Sapien balloon-expandable valve (Edwards LifeSciences, Irvine, California, USA), being considered the first generation of THV for clinical use(15). The second generation consisted of the balloon-

expandable Sapien XT device (Edwards LifeSciences, Irvine, California, USA) and the self-expandable CoreValve device (Medtronic, Minneapolis, Minnesota). These showed improvements that made it possible to increase the safety and efficacy of TAVI(16,17).

Today, a series of new devices are on the market, called new generation THVs, which, in addition to improving clinical results in relation to previous generations, (18–20), provide greater simplification of the procedure as a whole. These new devices have lower profiles which attenuates the risk of vascular and bleeding complications. Moreover, most of them have an external skirt to reduce paravalvular leakage, a main limitation of older generation devices, which is associated with poor prognosis (21–23). Specific new self-expanding prosthesis offer the possibility of resheathing and recapturing during implantation, in case there is need for repositioning the valve before final deployment. This feature allows more precise anatomical implantation of the device(24,25).

Currently, TAVI is a globally accepted procedure for the treatment of patients with severe AS. Although it was initially developed for the treatment of patients with a prohibitive risk for SAVR, with the evolution of techniques and materials, together with the positive results of clinical trials, TAVI today is already an alternative for patients with high, intermediate and even low surgical risk(16,17,26–28). Consequently, the volume of procedures has increased considerably year by year all over the world, accompanied by a growing number of centers adopting TAVI in their routine practices (29–31).

The improvement in clinical results obtained with TAVI in its brief history is expressive. In less than two decades, there has been a progressive increase in the

success rates of the procedure, with a significant reduction in mortality and various complications rates. This progress is mainly attributed to the following factors(29,32): i) evolution of materials; ii) improvement of techniques; iii) improvement of the selection process of patients to be treated; iv) improvement of operators and centers learning curve (LC); v) increased knowledge of the scientific community as a whole.

Continuous efforts are being undertaken by the scientific community so that this progress persists and is achieved globally in a homogeneous way. TAVI is a complex procedure, with a large number of fundamental steps for its success, that involves proper patient selection, pre-TAVI clinical and imaging evaluation, performance of the procedure *per se*, care during hospital recovery, to post-TAVI follow-up. This whole process involves several techniques, materials, and complementary exams, as well as a large team of different professionals. As a consequence, there are numerous variations in TAVI practices between regions and institutions – sometimes even between teams from the same institution – which can potentially impact the clinical outcomes of patients(33).

Operator experience, LC and volume of cases per center have been the subject of growing discussion and gained much emphasis in the literature. Previous studies, mostly involving institutions in European and North American countries, demonstrate an association between increased experience and better clinical outcomes, including reduced mortality(34–37). Studies with the first generations of devices estimated that up to 225 procedures would be necessary to optimize the death rates of a center, a high number and still seldomly found in institutions from developing countries, as is the case of Brazil(34,38). On the other hand, in a study derived from the North American TAVI registry, a much lower LC was observed in centers that started their experience with the third generation of balloon-expandable prostheses, demonstrating

that technological advances can positively impact this homogenization process of TAVI results and shorten the LC(35). In Brazil, a small study involving two centers from São Paulo during the early TAVI days with old-generation THVs also demonstrated a positive impact of the LC on clinical outcomes in the first 150 cases of both centers combined(39). Nevertheless, there is no large multicenter study evaluating the behavior of the LC along with the evolution of TAVI's practices in developing countries (such as Brazil and Latin-American), that present centers with a much lower procedural volume with respect to developed countries (34,38).

1.1 TAVI in Brazil and Latin America

The really first TAVI in Latin America was performed in Venezuela in 2004, with the first generation of the CoreValve made of bovine pericardium. This was followed in 2008, by the first cases with the porcine pericardium CoreValve performed in 2008 in Brazil and Colombia(40,41). In the following years, the technique quickly spread, being adopted by a growing number of hospitals across the continent. However, the number of procedures practiced in Latin American institutions, overall, is still considerably lower compared to institutions in developed countries(33). There is, therefore, a real concern about the clinical efficacy and safety outcomes of TAVI in these lower-volume centers.

Among the reasons for this lower procedural volume, the economic issue has been a key factor limiting the expansion of TAVI programs in developing countries. Even though TAVI has already surpassed cardiac surgery for aortic valve replacement in

terms of the number of procedures performed in many countries(42), its high cost has jeopardized its democratization and incorporation into public services in less developed nations. In Brazil, for instance, an estimate placed the average cost of the procedure at R$120,172.14 (43). This has been crucial for the approval of the procedure in the public health system, a fact that occurred only in June 2021, despite the fact that the country's first implant occurred 13 years earlier (41).

With the advent of less invasive contemporary techniques, the minimalist TAVI permits the realization of safe procedures with shorter hospital stays, using fewer resources, and reducing hospital costs, (44–47), becoming an increasingly interesting alternative in this context of enabling an increase in procedural volume. In this minimalist TAVI concept, the procedure is performed without the need for general anesthesia, without the need for transesophageal echocardiography, without the need for surgical dissection of the access route and. In some cases, the minimalization of the procedure can even suppress the need for balloon pre-dilation valvuloplasty and the use of a temporary pacemaker cable. However, this is a strategy that may require an additional LC for the team, but with the potential to increase TAVI access to the growing number of individuals with severe AS, especially in countries where health services are financially limited, as in Brazil.

Despite a slower phenomenon of demographic transition compared to developed nations, developing countries in Latin America have also been showing a change in their demographic pyramids, indicating a rapid and progressive rise in population aging.(48,49). Therefore, the burden of cardiovascular disease, including severe AS, is expected to be considerable in these societies within the near future. It is estimated that in 2013, there were 17 million deaths from cardiovascular diseases in the world, with approximately 80% of these occurring in countries of low and medium

socioeconomic power, including Latin American nations(50). Added to the fact that international data indicate that only 3.5% of individuals with cardiac surgical pathologies effectively have access to surgery in these countries, there is a large gap of potential candidates for TAVI in the continent(51,52).

Even though the global TAVI literature is vast, there has also been a huge gap of scientific publications from developing countries. For such a high-cost treatment that can impact on the health systems, it is essential to carry out studies to monitor the development of the procedure in the reality where they are inserted. Much of what is applied in the daily practice of Brazil and the other Latin American countries derives from scientific evidence obtained from developed nations, where high-volume TAVI centers are the norm, and with very different health system realities.

In this sense, there is a need to study the TAVI practices in Brazil and Latin America in greater depth. The implementation of protocols for the homogenization of practices, as well as understanding and improving the LC in these centers on the context of upcoming technologies are crucial factors so that this revolutionary procedure can be increasingly offered in the most effective and safe possible manner to the increasing demand of our population.

2. OBJECTIVES

2.1 Primary objetive

The objectives of this thesis were to evaluate the evolution of TAVI practices in Brazil and Latin America and the impact of experience and LC on clinical outcomes.

2.2 Secondary objectives

To compare the TAVI practices in Latin America with the rest of the world and their evolution between 2015 and 2020.

To evaluate the clinical impact of incorporation of more contemporary TAVI practices in Latin American centers.

To analyze the impact of the LC and the experience of the centers on the clinical outcomes of patients undergoing TAVI in Brazil.

3. ARTICLE 1

Title: Current Status and Evolution of Transcatheter Aortic Valve Replacement Practice in Latin America – the WRITTEN LATAM study

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Estado Atual e Evolução das Práticas de Implante Transcateter de Válvula Aórtica na América Latina – estudo WRITTEM LATAM

Current Status and Evolution of Transcatheter Aortic Valve Replacement Practice in Latin America – the WRITTEN LATAM study

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Short Title: TAVR practice: Latin America vs. World centers

Descritores: Substituição da Valva Aórtica Transcateter; Estenose da Valva Aórtica; América Latina

Descriptors: Transcatheter Aortic Valve Replacement; Aortic Valve Stenosis; Latin America

ABSTRACT

Fundaments: Transcatheter aortic valve replacement (TAVR) is a worldwide adopted procedure with rapidly evolving practices. Regional and temporal variations are expected to be found.

Objective: To compare TAVR practice in Latin American (LATAM) with that around the world and to assess its changes in Latin America from 2015 to 2020.

Methods: A survey was applied to global TAVR centers between March and September 2015, and again in LATAM between July 2019 and January 2020. The survey consisted of questions addressing: i) center's general information; ii) pre-TAVR evaluation; iii) procedural techniques; iv) post-TAVR management; v) follow-up. Answers from the 2015 survey of Latin-American centers (LATAM15) were compared with those of centers around the world (WORLD15) and with the 2020 updated Latin-American survey (LATAM20). A 5% level of significance was adopted for statistical analysis.

Results: 250 centers participated in the 2015 survey (LATAM15=29; WORLD15=221) and 46 in the LATAM20. Combined centers experience accounted for 73,707 procedures, with WORLD15 centers performing, on average, 6- and 3-fold more procedures than LATAM 15 and LATAM20 centers, respectively. LATAM centers performed less minimalistic TAVR than WORLD15, but there was a significant increase in less invasive procedures after five years at Latin-American centers. For post-procedural care, a lower period of telemetry and maintenance of temporary pacing wire, along with less utilization of dual antiplatelet therapy was observed in LATAM20 centers.

Conclusion: Despite still having a much lower volume of procedures, many aspects of TAVR practice in LATAM centers have evolved in recent years, following in the footsteps of the trend of developed country centers.

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has been adopted worldwide for severe symptomatic aortic stenosis with various risk profiles. This achievement has been built on more than a decade of advancements in technology and patient care. As a consequence, TAVR practices have been evolving rapidly, resulting in a significant improvement in clinical outcomes(16,26,27,53).

In Latin America, the first TAVR procedures were performed in 2008 in Brazil and Colombia(40,41). Although a steady growth of cases has been observed since then, there have been concerns in the adoption of the most up-to-date practices in Latin America(34,38,54). In developing countries, disparities in practice of a high-cost medical procedure can be exacerbated due to several factors, such as lower-income health systems, lower center volumes, less experienced operators, unavailability of certain devices, among others. Understanding such differences is crucial to better comprehend the contemporary practices and seek for further standardization. Moreover, it could aid in developing policies by the local regulators to achieve more widespread adoption of TAVR in such underserved populations, since published data in Latin America are limited.

Therefore, the general and secondary objectives of the study were: i) to compare TAVR practice between Latin-American centers and centers from the rest of the world based on data obtained from the 2015 WRITTEN survey; ii) to assess the changes in TAVR practice in Latin America after 5 years through reapplication of the survey in the continent.

METHODS

The WRITTEN survey was an internet-based questionnaire designed to investigate the practices in TAVR centers around the world. The survey design has been described previously(33). In summary, at least one regional TAVR expert from each country or region was contacted and invited to distribute the survey locally. The survey was promoted through general interventional cardiology mailing lists, announcements by official societies of interventional cardiology, website advertisements, and personalized emails to TAVR operators. Invitations were distributed in different geographic areas simultaneously over 6 months (March 2015 to September 2015). A second enquiry was performed from July 2019 to January 2020, with similar methods, involving only Latin- American centers without a specific cutoff on the number of procedures performed by the center (Figure 1). The survey consisted of an online platform hosted on the collaborative research website (www.cardiogroup.org/TAVI/) with 59 questions addressing five domains of TAVR (Supplemental Table 1): (i) general information about the program at each institution, (ii) patient selection, (iii) procedural techniques and imaging, (iv) postprocedural management, and (v) follow-up. It was requested that only one individual from each TAVR center completed the survey, and only one questionnaire per center was accepted.

Statistical analysis

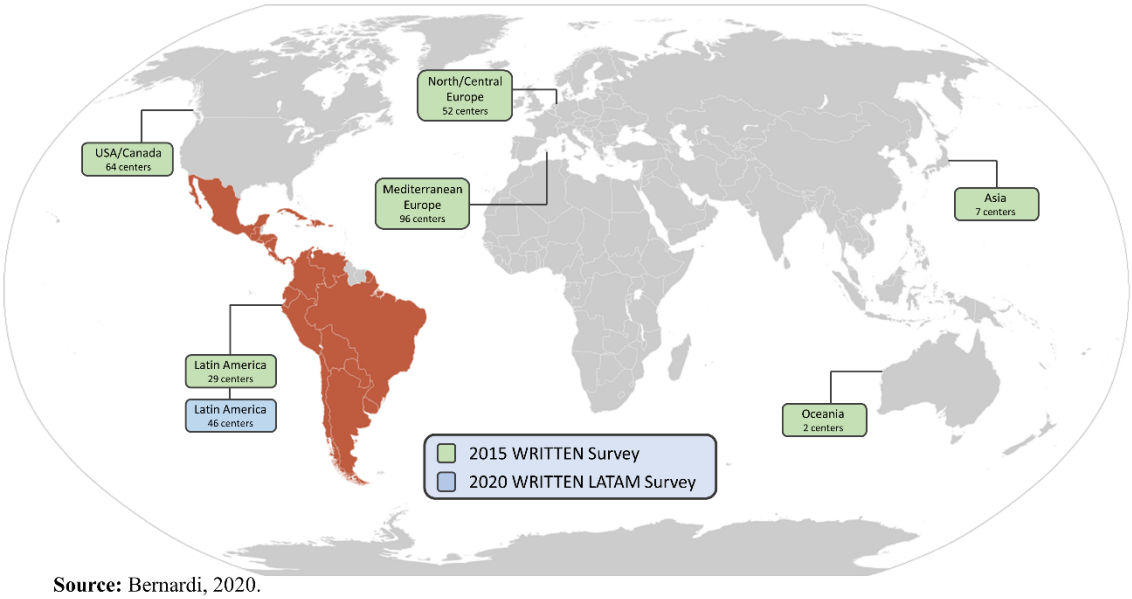
For the study analysis, the answers corresponding to the TAVR practices of the Latin-American centers in 2015 (LATAM15 centers) were used as reference. Categorical variables were expressed as absolute frequencies and percentages, and

continuous variables as median and interquartile range (IQR). For comparison of categorical variables, Fisher's exact test was used to assess the association between dependent (centers group) and independent variables (results from the questionnaire) for dichotomous answers with a two-tailed P value. For questions with more than two possible answers, the association between independent and dependent variables was tested with the chi-square test. Continuous variables were compared with the Mann-Whitney test due to the non-normal distribution of the variables, confirmed by the Shapiro-Wilk test, also with a two-tailed P value. A 5% level of significance was adopted for all statistical analyses. All analyses were performed with the software GraphPad Prism version 7.0 (GraphPad Software, USA).

RESULTS

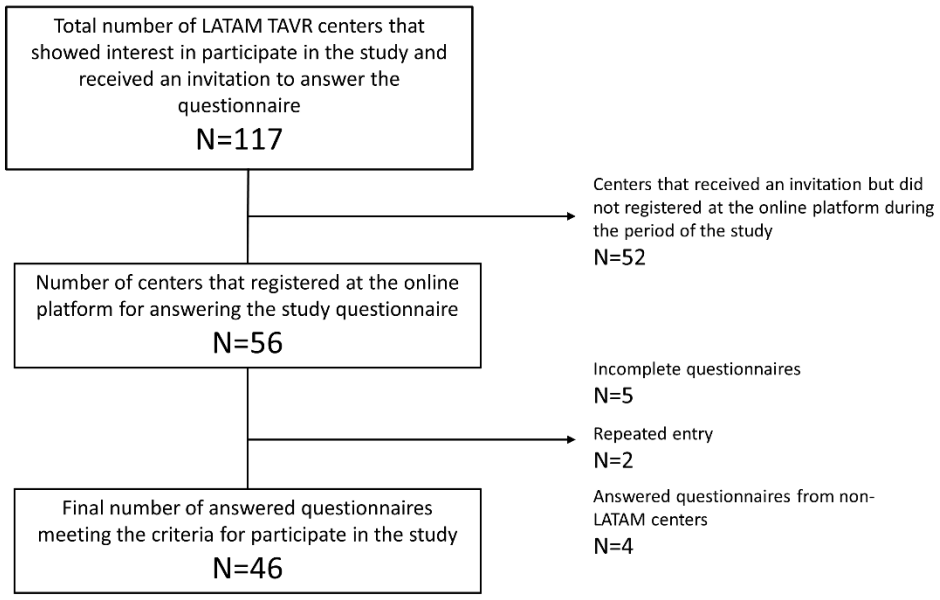
As previously published, 250 centers completed the questionnaire properly and were included in the 2015 survey.7 Of these, 29 (11.6%) were from LATAM15 centers. Figure 1 illustrates the global distribution of the centers. Figure 2 summarizes the enrollment of the 46 centers participating in the Latin-American survey in 2020 (LATAM20). Out of the 296 questionnaires, 263 (88.8%) were fully answered, while the remaining had more than 80% of their questions responded. The very few missing data were considered as completely at random, and no special treatment was made. The names of the cities and countries of all centers are listed in the Supplemental Tables 2 and 3.

Figure 1. Geographical distribution of the participating centers in the 2015 and 2020 surveys.



Source: Bernardi, 2020.

Figure 2. Enrollment flowchart of the participating centers in the WRITTEN LATM 2020 survey



Source: Bernardi, 2021

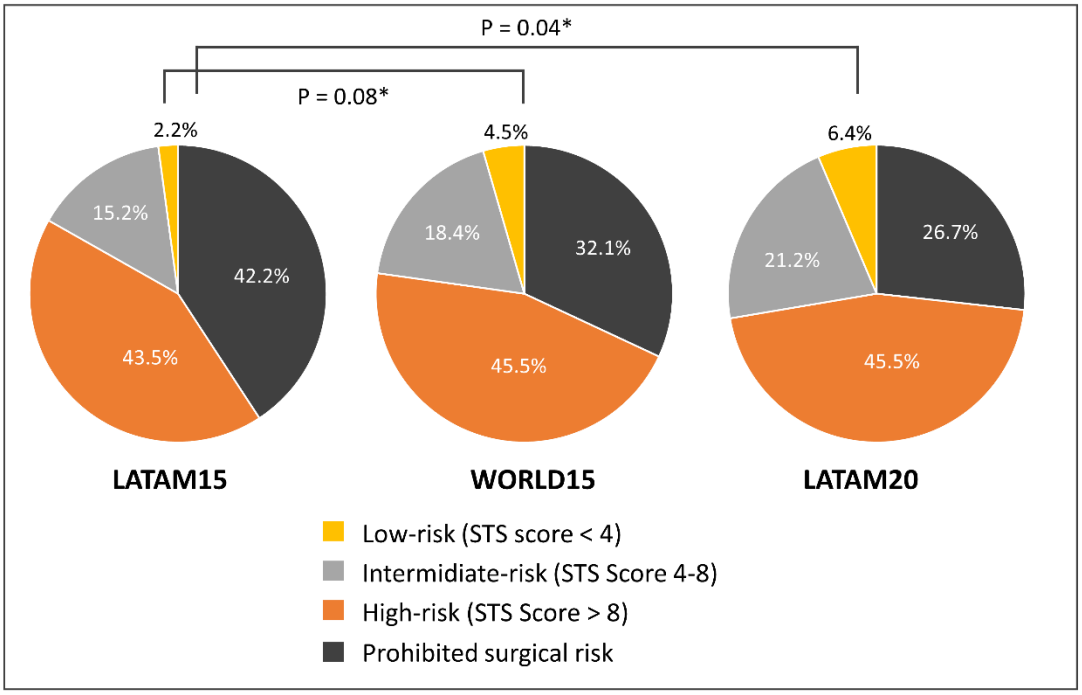
By the time of the surveys' completion, the sum of all TAVR performed by the participating centers in Latin America in 2015 and 2020 (LATAM15 and LATAM20) and worldwide (WORLD) accounted for 73 707 procedures combined. In comparison

to LATAM15, WORD15 centers had performed a much higher number of procedures in their whole experience (median of 34, IQR: 12 to 101 vs. 200, IQR: 84 to 453, p<0.001), as well as in the year before survey completion (median of 12, IQR: 5 to 23 vs. 60, IQR: 27 to 110, p<0.001). Compared to LATAM15, the LATAM20 total experience was ~2-fold larger (median of 62, IQR: 22 to 138, p=0.08), but only slightly higher in the year before the survey (median of 16, IQR: 6 to 30, p=0.29). The complete survey results are found in Supplemental Tables 4-7.

Pre-procedural evaluation

In all three groups, the majority of TAVR patients treated in their current practice were at high or prohibited surgical risk. Nonetheless, when comparing LATAM15 to LATAM20, an increase over time was observed in the proportion of intermediate and low surgical risk patients (Figure 3). WORLD15 centers had a higher median number of heart-team meetings monthly than LATAM15 centers (4, IQR: 2 to 4 vs. 1, IQR: 1 to 2, p=0.001), with a slight increase in LATAM20 centers (1.5, IQR: 1 to 4, p=0.27). The Society of Thoracic Surgeons (STS) score was the most common risk-stratification tool, used routinely by 90%, 69%, and 98% of the LATAM15, WORDL15, and LATAM20 centers, respectively. Meanwhile, only 28%, 47%, and 39% of the centers, respectively, applied frailty tests routinely. Regarding pre-TAVR imaging (Figure 4), almost all centers performed cardiac computed tomography in their practice. Transesophageal echocardiography as a routine before the procedure was performed more often by LATAM15 centers.

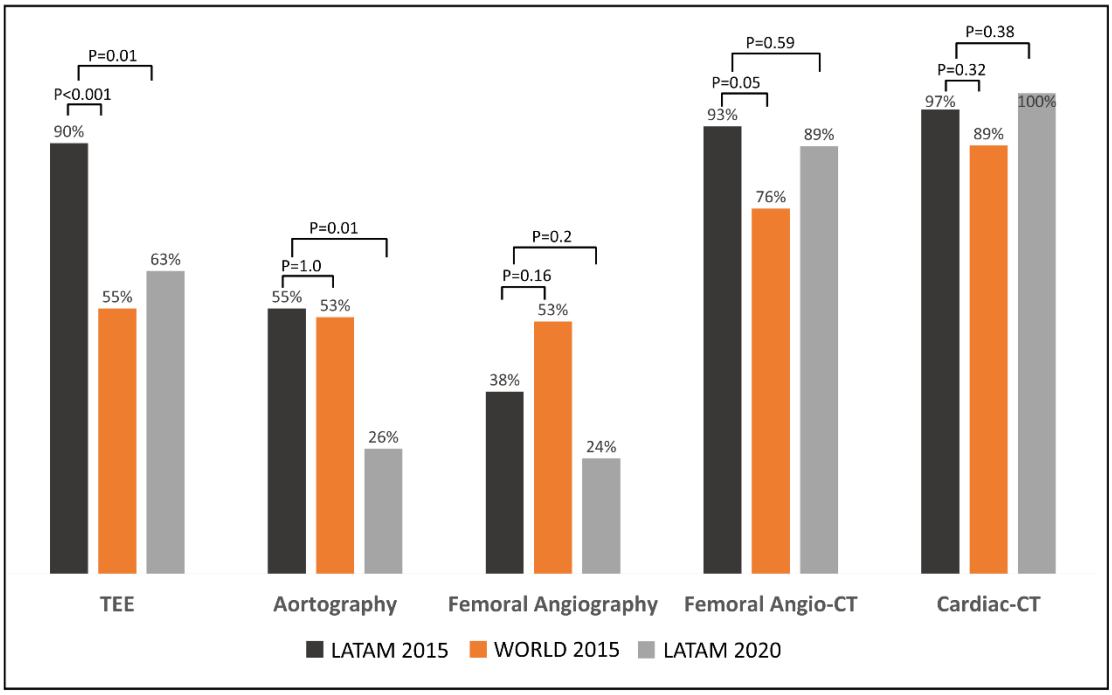
Figure 3. Proportion of treated patients by risk profile.



* P value for the comparison of the median of the proportions of low/intermediate-risk patients between the groups (Mann-Whitney test)
Source: Bernardi, 2021

A lower proportion of WORLD15 and LATAM20 centers regularly administered dual-antiplatelet therapy (DAPT) before transfemoral procedures in comparison to LATAM15 centers (45% and 56% vs. 83%, p<0.001 and p=0.02, respectively). Regarding the time of percutaneous coronary intervention (PCI) when a severe proximal coronary lesion was detected, the most common approach by the centers from all groups was to perform PCI before TAVR. In cases deemed risky for coronary obstruction, the three groups agreed the most frequent strategy was to have a PCI protection wire during TAVR (Supplemental Table 4). Regarding antibiotic prophylaxis, more than 90% of the centers administer antibiotics as a routine, with half of them administering 1 dose and the other half ≥ 2 doses.

Figure 4. Comparison of routinely performed pre-procedural imaging studies (% of centers).



Source: Bernardi, 2020

Procedural management

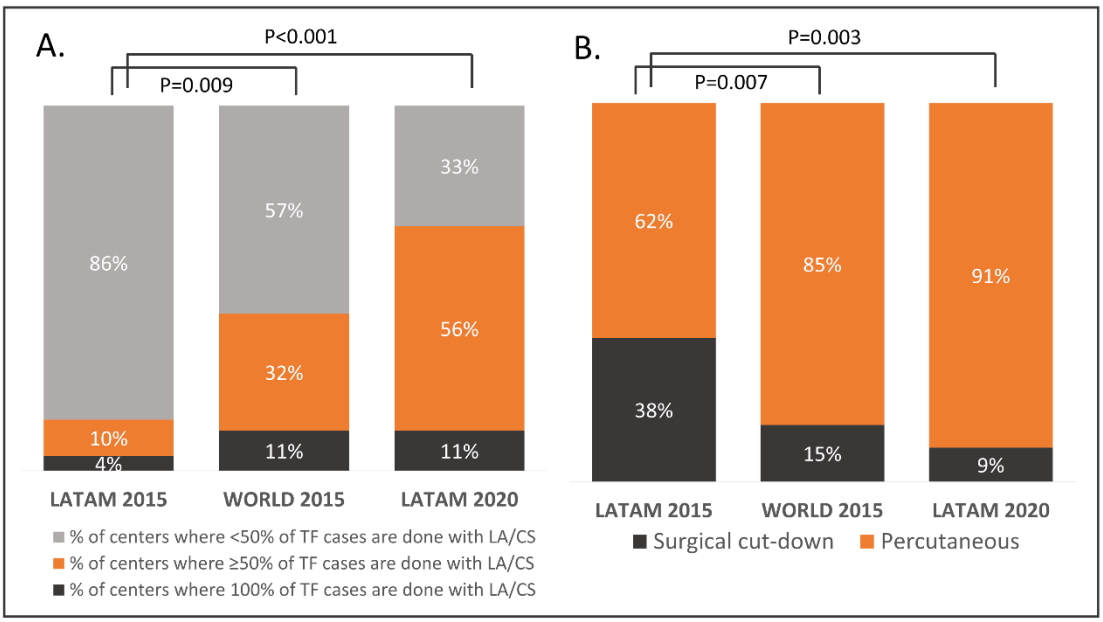
The comparison of answers to procedural management questions is summarized in Table 1. Transfemoral TAVR was the preferred approach by all centers, but a higher proportion of LATAM15 over WORLD15 centers performed ≥ 90% of their cases via the transfemoral route (72% vs. 42%, respectively, p=0.003). No significant change was noted after 5 years (LATAM20 87%, p=0.14). Almost all centers reported having an anesthesiologist to assist in transfemoral procedures, but LATAM15 centers more commonly performed these procedures under general anesthesia compared to WORLD15 and LATAM20 centers (Figure 5). Additionally, 86% of LATAM15 centers reported having a cardiac surgeon assisting transfemoral TAVR vs. 61% for WORLD15 (p=0.01) and 52% for LATAM20 (p=0.005). Meanwhile, interventional cardiologists regularly assisted transapical/transaortic procedures in most LATAM15

(88%) and WORLD15 (88%) centers, with a significant reduction after 5 years in LATAM20 centers (56%, p=0.008). Regarding procedural transesophageal echocardiography guidance, 83% of LATAM15 centers reported always relying on it, compared to 41% for WORLD15 and 15% for LATAM20 centers (Table 1).

In transfemoral cases, TAVR with a fully percutaneous approach was more frequently performed by the WORLD15 and LATAM20 centers (Figure 5). For these, the Perclose (Abbott Vascular, Abbott Park, IL) was the most utilized device in all groups (Table 1). When asked about protective strategies in percutaneous transfemoral access, the most common approach by all groups was to leave a protection guidewire from the collateral artery only in challenging iliofemoral access and use of a peripheral balloon during access closure only when a complication ensues. In the case of femoral perforation, the most common approach consisted of using self- or balloon-expandable covered stent by the operator himself (Table 1).

The Corevalve system (Medtronic, Minneapolis, MN) and Edwards valves (Edwards Lifesciences, Irvine, CA) were reported as being regularly used by most centers from all three groups. Nonetheless, in 2015 a higher proportion of Latin-American centers implanted a self-expanding valve in > 50% of their patients compared to the other centers in the world without a significant change after 5 years in Latin-American centers. Of note, in 2015, only the Corevalve and Sapien XT transcatheter heart valves were commercially available in Latin America for these families of valves. In contrast, for LATAM20, most centers used the Evolut R and the Sapien 3 systems. The WORLD15 centers more routinely employed predilatation valvuloplasty than LATAM15 and LATAM20 centers (Table 2). Neither LATAM15 nor LATAM20 centers reported using embolic protection devices as a routine as compared to 16% of the WORLD15 centers (Table 1).

Figure 5. A) Percentages of transfemoral procedures that are done with conscious sedation/local anesthesia (% of centers). TF: transfemoral; LA: local anesthesia; CS: conscious sedation. B) Type of vascular access routinely performed for transfemoral cases (% of centers).



Source: Bernardi, 2021

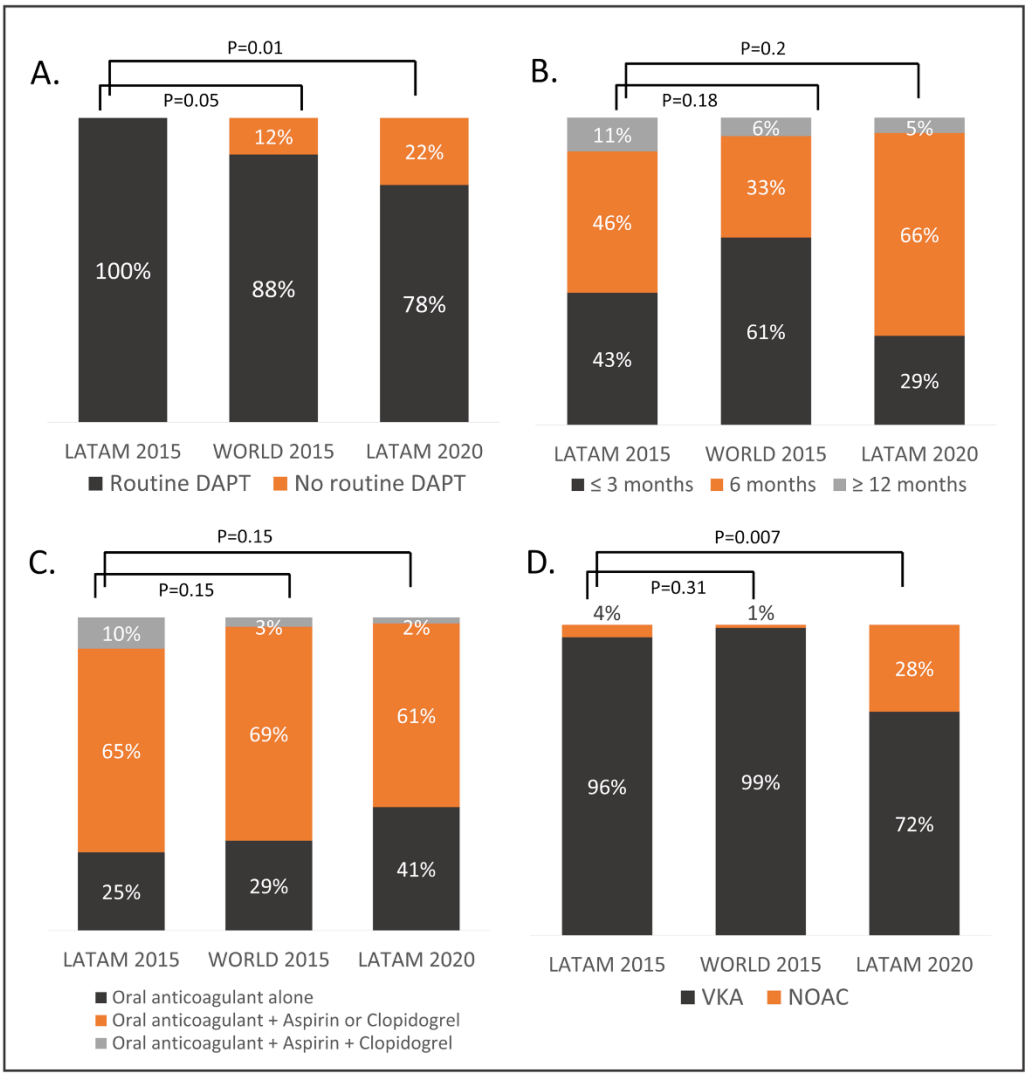
Postprocedural management and follow-up

The main findings on postprocedural care are shown in Table 3. Maintenance of telemetry after TAVR varied widely among institutions, with no difference between LATAM15 and WORLD15 centers (72% vs. 59%, during 48 hours), although a significant reduction in the period of surveillance was observed in LATAM20 centers (72% of centers maintained telemetry for just 24 hours). When a self-expandable valve was implanted, LATAM15 centers tended to remove the temporary pacemaker wire (TPW) later than WORLD15 and LATAM20 centers, whereas no difference was seen with balloon-expandable valves. The preferred initial management of transient atrioventricular block by all groups was to keep the TPW and watch, regardless of the type of valve. Centers also agreed on the management of a new left bundle branch

block, most opting to keep telemetry or TPW for a longer period while waiting for any other indication of permanent pacemaker implantation (Supplemental Table 5).

Concerning the antithrombotic therapy at discharge, when no indication for anticoagulation existed, DAPT with aspirin and clopidogrel was the strategy of choice for most institutions. However, within the past 5 years, more Latin- American centers discharged their patients with a single antiplatelet agent (Figure 6). For the duration of DAPT, there was heterogeneity in practice, but ~90% of the centers suspended one of the agents within 6 months. In patients with an indication for anticoagulants, antithrombotic therapy varied considerably, being the association of an oral anticoagulant with only one antiplatelet agent the preferred choice by most centers from all groups. In these cases, the utilization of novel oral anticoagulants (NOACs) increased significantly from 4% to 28% in Latin-American centers during the 5-year period (Figure 6).

Figure 6. Comparison of routine antithrombotic therapy after TAVR. A) Routine DAPT after TAVR when there is no other indication for anticoagulation (% of centers). DAPT – dual-antiplatelet therapy; B) Routine duration of DAPT (% of centers); C) Routine antithrombotic therapy in cases where there is an indication for anticoagulation (% of centers). D. Type of oral anticoagulant utilized when an indication for anticoagulation exists (% of centers). VKA: vitamin K antagonist; NOAC: novel oral anticoagulant.



Source: Bernardi, 2021

DISCUSSION

In the present study, the current TAVR practices in Latin- American centers and their changes between 2015 and 2020 were evaluated, having for comparison the practice status at centers from developed countries in 2015. The main findings can be

summarized as: 1) overall, Latin-American centers had a much lower cumulative experience and annual volume in comparison to centers from the rest of the world; 2) there has been an increase in the proportion of low and intermediate surgical risk patients now being treated with TAVR in Latin America; 3) the adoption of minimalistic TAVR approaches has increased in Latin-American centers from 2015 to 2020, a trend already observed in centers around the world in 2015; 4) postprocedural care varied considerably among institutions, but some significant changes in the TAVR practice have been observed in Latin-American centers over the studied period, such as a reduction in the time of telemetry and TPW after the procedure, less frequent administration of DAPT, and more frequent use of NOACs when anticoagulation was clinically recommended.

Center volume

Recent studies have highlighted the importance of center volume and experience as indicators in TAVR, linking them to improved outcomes and better practices(34,35,38,54). In the present study, we observed that the volume of procedures in Latin- American centers is still much lower than that in developed countries. Even in 2020, the median number of procedures performed in Latin-American institutions corresponded to a third of the volume performed in centers around the world 5 years earlier. Our data corroborate an estimate from 2017 on the geographical dispersion of TAVR across the world, showing that Latin-American countries implant less than 10 valves per 1,000,000 inhabitants, while the numbers for nations, such as the United States, France, and Germany, were above 100 implants per 1,000,000 people(55). When considering the proportion of centers per elderly

inhabitants, this discrepancy is even more evident. Currently, Latin America has an estimate of 200 active TAVR centers for an elderly population of ~56 million (3.6 centers/million) vs. 698 centers in the United States (according to the National Cardiovascular Data Registry(56)) for ~52 million elderly (13.4 centers/million) (57). Economic factors are most probably one of the most significant in explaining this disparity.

Over the past decades, despite economic growth and improvement in social indicators, wealth inequality is still a major issue in Latin America, directly impacting population well-being and health systems(58). Developing countries often lag behind wealthier nations in implementing high-cost technological medical procedures in their health systems, which is the case of TAVR and cardiovascular surgery in general(59). With demographic changes in Latin America towards population aging, the demand for TAVR is expected to rise accordingly. For the health systems to afford such demand, governments and local leaders will need to find ways to improve the cost-effectiveness of TAVR in the continent. Implementation of policies targeting a reduction in procedural costs will be key, primarily by lowering device prices that today represent on average ~70% of the procedure's total cost. This could be achieved by subsidizing or reducing importation taxes, stimulating more medical industries to come to Latin America, and creating incentives for manufacturing the high-cost prosthesis locally, which has been the case of Brazil recently. On the effectiveness side, the present study signals to a reduction in the disparities between Latin-American countries and the current TAVR practices compared to the rest of the world. In addition, data from the Brazilian TAVR registry from 2016 showed similar clinical outcomes as compared with the literature, even though more contemporary data is lacking(47). This development in practice can be attributed mainly to a strong support

of the local medical societies and industries, promoting scientific and hands-on training sessions, along with strong proctoring programs in Latin America over the recent years.

Periprocedural management

In addition to a volume-outcomes relationship, a volume-practice relationship exists, as centers with a higher number of TAVR change their routine practice over time. Recent analysis from the North American Transcatheter Valve Therapy (TVT) Registry on the TAVR learning curve demonstrates that, as an institution's cumulative experience progresses, TAVR procedures are more likely to be performed with conscious sedation, local anesthesia, and fully percutaneous vascular access. The so-called minimalistic approach(35,38). Although there is no definitive data in the literature showing that these less invasive techniques are directly associated with improvements in hard clinical outcomes(46,60–62), they surely represent incremental expertise of the heart teams.

The present study captured this phenomenon. In 2015, a higher proportion of centers around the world had already adopted the routine use of the minimalistic TAVR when compared to their Latin-American counterparts. But interestingly, after 5 years, even though Latin-American centers continue to have low volumes overall, with a median of only 16 cases yearly, there has been consistent incorporation of these more current techniques. The proportion of centers that performed more than half of cases with local anesthesia and conscious sedation increased ~6-fold. A similar trend has been observed in the TVT Registry during the latest years, where a steady increase in conscious sedation procedures has been reported, currently accounting for 64% of

the North American cases(63). Similarly, a fully percutaneous approach as a routine practice increased from 62% to 91% of the Latin-American centers, showing that TAVR practices are evolving in the continent despite the struggle to improve procedural volume.

Postprocedural management and follow-up

Proper postprocedural care is another fundamental, but sometimes overlooked, factor in a TAVR program. Of note, most clinical trials to date have aimed to assess intraprocedural aspects of TAVR. Consequently, there is a scarcity of definitive data on the best management of patients after the procedure. Not surprisingly, the present study showed heterogeneity in practice among centers in this domain. Yet, some significant changes in practice have been noted in Latin-American centers in the last 5 years. The routine prescription of DAPT on hospital discharge was less frequent and NOACs were more often used in patients with an indication for oral anticoagulation therapy. These changes in practice are probably attributed to data published between the two surveys showing a potential benefit of single oral antiplatelet therapy in reducing bleeding complications(64) and to a more widespread use of NOACs in general cardiology due to safety profile in elderly patients. Still, the optimal antithrombotic regimen and the utilization of NOACs after TAVR remain open to debate, particularly after the dismal results from a recent large randomized trial with rivaroxaban(65). Hence, data from future randomized trials are warranted to define the optimal postprocedural care.

Finally, the progression of Latin-American practices reveals that even centers from developing and underserved countries can follow along with the rapid ongoing

progressions in the field. This has been catalyzed thanks to a deep engagement of the medical societies in spreading the knowledge in Latin America. For instance, in Brazil, a formal TAVR certification has been adopted since 2017. Through multi-faceted and multilevel educational programs, the country has already trained more than 700 cardiologists. Likewise, similar initiatives in other countries, such as Argentina, Chile, Colombia, and Mexico, have also been adopted. All these efforts have contributed to a steady increase in new centers performing TAVR in Latin America and have played a significant role in the development of the most modern techniques and adherence to them. However, continous efforts should be implemented for diminishing the gap to developed nations. As the number of TAVR centers increases, expansion of proctoring and continuing medical education programs will be necessary. In the post-COVID-19 era, innovations, like teleproctoring, can be an invaluable asset. The creation of virtual simulation programs to soften the learning curve of lower volume centers/operators seems another attractive emerging option(66). Finally, improving publication of scientific content by Latin-American centers is urgently warranted, accompanied by the creation of nationwide databanks in all Latin-American countries to determine the actual clinical outcomes and further define the potential gaps for improvement.

Limitations

Although this study was a unique opportunity to capture variations in practice among centers and regions of the world, as well as the changes in Latin-American centers over the past 5 years, some limitations must be mentioned. First, this was a self-reported voluntary survey, which, by its nature, makes it prone to biases. Results from such studies can under- or overestimate the actual reality of the participating

centers. Reports on the differences in the baseline characteristics of the patients treated by each center, which could influence the adoption of different practices, were not available. Moreover, the study did not include information on clinical outcomes. Thus, it is impossible to draw conclusions on whether the differences in practice impacted patients' outcomes. In addition, there is big heterogeneity among Latin-American countries, regions, and institutions. It is difficult to assume that one survey can precisely represent the whole continent's reality, even though we estimate ~15% of Latin-American centers participated in the latest inquiry. Nevertheless, the results give us a notion of which direction we are moving to and the gaps that still need to be filled, in addition to serving as a guide for the less experienced centers in defining their protocols. Finally, since the WRITTEN survey was not reconducted in the rest of the world during 2019-2020, a direct comparison of the current TAVR practice in Latin America with other centers through the survey's responses was not possible.

CONCLUSION

In conclusion, differences in TAVR practice exist between the Latin America and other developed nations of the world, with an at least 5-year delay in the widespread adoption of some techniques in Latin America. Some of these differences in practice seem to be linked to a lower procedural volume in Latin-American centers, while others could be merely associated with a lack of global consensus and regional variability. Nevertheless, the gap appears to be diminishing since this volume-practice relationship has softened in the latest years due to practice development and the adoption of more refined techniques even by lower volume centers in Latin America.

Future studies in the continent are warranted to evaluate the impact of such changes in practice on patients' clinical outcomes.

Author Contributions

Conception and design of the research: Bernardi FLM, Ribeiro HB, Nombela-Franco L, Cerrato E, Nazif T, Rodes- Cabau J; Acquisition of data: Bernardi FLM, Ribeiro HB, Nombela-Franco L, Cerrato E, Maluenda G, Nazif T, Lemos PA, Sztejfman M, Lamelas P, Echeverri D, Brito Jr. FS, Mangione JA, Søndergaard L, Rodes-Cabau J; Analysis and interpretation of the data: Bernardi FLM, Ribeiro HB, Nombela-Franco L, Cerrato E; Statistical analysis, Obtaining financing and Writing of the manuscript: Bernardi FLM, Ribeiro HB; Critical revision of the manuscript for intellectual content: Bernardi FLM, Ribeiro HB, Nombela-Franco L, Cerrato E, Maluenda G, Nazif T, Lemos Neto PA, Sztejfman M, Lamelas P, Echeverri D, Lopes MACQ, Brito Jr. FS, Abizaid AA, Mangione JA, Eltchaninoff H, Søndergaard L, Rodes-Cabau J.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

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Study Association

This article is part of the thesis of doctoral submitted by Fernando Luiz de Melo Bernardi, from Instituto do Coração da Faculdade de Medicina da Universidade de São Paulo.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Table 1 - Comparison of technical procedural management between the LATAM15, WORLD15, and LATAM20 centers.

	LATAM 2015 (N=29)	WORLD 2015 (N=221)	P value	LATAM 2020 (N=46)	P value[#]
Site where TAVI is routinely performed (% centers)					
Operating room	3%	9%	0.48	0	0.38
Cath lab	83%	63%	0.04	83%	1.0
Hybrid room	24%	45%	0.04	19%	0.77
TEE during TAVI (% of centers)					
Always	83%	41%		15%	
Only in certain patients	10%	42%	<0.001	63%	<0.001
Never	7%	17%		22%	
Type of closure device routinely used in TF percutaneous access (% centers)					
1 Perclose	0	1%		9%	
2 or more Perclose	90%	59%	0.03	83%	0.17
Prostar	10%	40%		2%	
Protection guidewire from contralateral artery in femoral percutaneous cases (% of centers)					
Always	33%	35%		32%	
Never	4.8%	25.2%	0.06	4%	1.0
Only in challenging iliofemoral access	62%	40%		61%	
Peripheral balloon during access closure in percutaneous cases (% centers)					
Routinely	10%	12.9%	1.0	4%	0.6
Just in case of complication	90%	87.1%		96%	
In case of femoral perforation in percutaneous cases (% centers)					
Usually implant self-expandable or balloon-expandable covered stent	70%	78%	0.99	78%	0.54
Usually assisted by vascular surgeons or an interventional radiologist	30%	22%		22%	
Embolic protection device as a routine (% centers)	0	16%	0.02	0	1.0

Source: Bernardi, 2021

Notes:

[#] P-values for the LATAM20 are in comparison to the LATAM15 results.

TAVI: transcatheter aortic valve implantation

TEE: transesophageal echocardiography

TTE: transthoracic echocardiography

THV: transcatheter heart valve

ACT: activated coagulation time

Table 2 - Comparison of type of implanted TAVR valve between groups.

	LATAM 2015 (N=29)	**WORLD 2015 (N=221)**	**P value**	**LATAM 2020 (N=46)**	**P value[#]**
Type of THV routinely implanted (% centers)					
Corevalve system	86%	79%		91%	
Edwards valve	72%	84%		93%	
Acurate valve	10%	4%		41%	
Lotus valve	3%	26%		11%	
Portico valve	0	1%		0	
Centers where >50% of cases are done with self-expanding THV (% centers)	52%	33%	0.06	46%	0.64
Routine balloon valvuloplasty predilation (% centers)					
For self-expanding valves	44%	50%	0.68	47%	0.81
For balloon-expandable valves	52%	68%	0.13	37%	0.23
In no case	30%	14%	0.04	44%	0.32

Source: Bernardi, 2021

Notes:

[#] P-values for the LATAM20 are in comparison to the LATAM15 results.

THV: transcatheter heart valve

Table 3 - Comparison of answers regarding post-procedural care between LATAM2015, WORLD2015, and LATAM2020 centers.

	LATAM 2015 (N=29)	**WORLD 2015 (N=221)**	**P value**	**LATAM 2020 (N=46)**	**P value[#]**
Maintenance of telemetry after TAVR (% center)					
24h	36%	20%		72%	
48h	36%	39%	0.13	24%	0.002
>48h	28%	41%		4%	
Maintenance of TPW after **self-expanding THV** (if no AV-block or new conduction disturbance)					
Always remove at the end of procedure	0	11%		24%	
At least 12-24h	30%	40%	0.004	59%	<0.001
At least 48h	59%	27%		4%	
No standardized protocol	11%	22%		13%	
Maintenance of TPW after **balloon-expandable THV** (if no AV-block or new conduction disturbance)					
Always remove at the end of procedure	71%	46%		70%	
At least 12-24h	10%	24%	0.08	15%	0.17
At least 48h	10%	6%		0	
No standardized protocol	10%	24%		15%	
Management of transient AV-block in **self-expanding THV** (% centers)					
Direct permanent pacemaker implantation	4%	13%		7%	
TPW and watch	81%	66%		63%	
Depends on existence of prior conduction disorders	11%	14%	0.31	28%	0.26
Other	4%	6%		2%	
Management of transient AV-block in **balloon-expandable THV** (% centers)					
Direct permanent pacemaker implantation	4.5%	7%		4%	
TPW and watch	87%	66%		63%	
Depends on existence of prior conduction disorders	0	17%	0.06	26%	0.04
Other	9%	10%		2%	

Source: Bernardi, 2021

Notes:

[#] P-values for the LATAM20 are in comparison to the LATAM15 results.

TAVR: transcatheter aortic valve implantation

THV: transcatheter heart valve

AV-block: atrioventricular block

TPW: temporary pacing wire

4. ARTICLE 2

Title: Incidence, Predictor, and Clinical Outcomes of Multiple Resheathing With Self-Expanding Valves During Transcatheter Aortic Valve Replacement

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Incidence, Predictor and Clinical Outcomes of Multiple Resheathing with Self-expanding Valves during Transcatheter Aortic Valve Replacement

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Short Title: Impact of Multiple Resheathing on TAVR

Subject Terms: Aortic Valve Replacement/Transcatheter Aortic Valve Implantation

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ABSTRACT

Background: No study has evaluated the impact of the additional manipulation demanded by multiple resheathing (MR) in patients undergoing transcatheter aortic valve replacement (TAVR) with repositionable self-expanding valves.

Methods and Results: Real-world, multi-center registry involving 16 centers from Canada, Germany, Latin America, and Spain. All consecutive patients that underwent TAVR with the Evolut R, Evolut PRO, and Portico valves were included. Patients were divided according to the number of resheathing: no resheathing (NR), single resheathing (SR), and MR. The primary endpoint was device success. Secondary outcomes included procedural complications, early safety events, and 1-year mortality. In 1,026 patients, the proportion that required SR and MR was 23.9% and 9.3%, respectively. MR was predicted by the use of Portico and moderate/severe aortic regurgitation at baseline (both with P<0.01). MR patients had less device success (NR=89.9%, SR=89.8%, MR=80%, P=0.01), driven by more need for a second prosthesis and device embolization. At 30-day, there were no differences in safety events. At 1 year, more death occurred with MR (NR=10.5%, SR=8.0%, MR=18.8%, P=0.014). After adjusting for baseline differences and center experience by annual volume, MR associated with less device success (OR=0.42, P=0.003) and increased 1-year mortality (HR=2.06, P=0.01). When including only the Evolut R/PRO cases (N=837), MR continued to have less device success (P<0.001) and a trend towards increased mortality (P=0.05).

Conclusions: Repositioning a self-expanding valve is used in a third of patients, being multiple in ~10%. MR, but not SR, was associated with more device failure and higher 1-year mortality, regardless of the type of valve implanted.

Key words: Transcatheter Aortic Valve Replacement; Aortic Valve Stenosis; Self-expanding valve; Resheathing

CLINICAL PERSPECTIVE

What is new?

- MR is required in up to 10% of cases, with independent predictors being associated with the type of valve implanted (more with Portico) and with the presence of moderate/severe aortic regurgitation at baseline
- MR, but not SR, was associated with worse device success, determined by a higher need for a second valve, more device embolization, and increased 1-year mortality, regardless of the type of valve implanted

What are the clinical implications?

- MR may not necessarily be the direct cause of the worse outcomes, but a marker of more complicated anatomies for an optimal device implantation
- It may be reasonable for the operators to consider changing the strategy/approach or type/size of the valve before final release in cases where MR is needed

INTRODUCTION

Since the beginning of the transcatheter aortic valve replacement (TAVR) era, there has been a continuous evolution of the transcatheter heart valves (THV) that led to significant improvement in clinical outcomes(16,17,26,27,53,67). Early-generation of TAVR devices had been associated with increased risk of complications and device failure, such as moderate or severe paravalvular leak, high incidence of conduction disturbances requiring new permanent pacemaker (PPM) implantation, and need for a second THV(68–70). The newer-generation devices have been designed to overcome these limitations.

Among the different self-expanding THVs, both the Evolut R/Pro (Medtronic, Minneapolis, USA) and the Portico (Abbott, Chicago, IL, USA) valves use a delivery system with a mechanism that allows for resheathing and recapturing of the THV before complete deployment, in case repositioning is required. This novel feature allows the operators to have two or even multiples attempts to position the THV, augmenting the accuracy of the valve implantation in a proper anatomical position, which has been associated with improved outcomes, including less conduction disturbances, paravalvular leak and the need for a second device(71).

Although higher success rates have been achieved with the newer generation of self-expanding THV, concerns have been raised regarding a potentially detrimental impact of the additional maneuver with resheathing and repositioning, including more debris embolization(72). Even though previous studies have shown no association of resheathing with impaired clinical outcomes, none of them has specifically evaluated the number of attempts per patient, and the potential of multiple resheathing (MR) on worse clinical outcomes. Therefore, the primary objective of the present study was to

evaluate the incidence, predictors and clinical impact of multiple resheathing (MR) in patients treated with repositionable self-expanding devices.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Population

This was a retrospective study involving all consecutive TAVR patients with severe symptomatic aortic stenosis or degenerated aortic bioprosthesis treated with the repositionable Evolut R/PRO (Medtronic, Minneapolis, USA) or Portico (Abbott, Chicago, USA) devices at 16 centers. A total of 1,030 patients were included from Canada, Germany, Latin America, and Spain, from June 2014 to May 2020. The indication of the procedure, the techniques utilized, and the decision of the THV type were defined by the local heart team. Data were collected using dedicated case report forms, and remote data monitoring was performed in all cases to search and correct missing or inconsistent information. All patients gave written informed consent to the TAVR procedures and all the local ethics committees approved the retrospective inclusion of the patients at each center. The first and last authors had full access to all the data in the study and takes responsibility for its integrity and data analysis.

To evaluate the clinical impact of resheathing, patients were divided according to the utilization and the number of resheathing for repositioning the bioprosthesis into the following groups: no resheathing (NR), single resheathing (SR), and MR. Patients

were allocated in the MR group if two or more resheathing were performed. Any partial or total recapture attempt was accounted. This information was confirmed by reviewing all angiographies and the reports of all procedures. The primary outcome was device success, defined by a combination of the absence of procedural death, implantation of a single prosthesis with a final mean transaortic gradient < 20 mmHg, and less than moderate paravalvular leak. Secondary outcomes were the 30-day and cumulative mortality, the incidence of 30-day safety events (all-cause mortality, all stroke, life-threatening bleeding, major vascular complication, stage 2 or 3 acute kidney injury, coronary artery obstruction requiring intervention, and valve-related dysfunction requiring repeat procedure), and procedural complications, that included a new permanent pacemaker implantation (PPM) at 30-day, new-onset persistent left bundle branch block (NOP-LBBB), and moderate or severe aortic regurgitation on echocardiogram at discharge. All events were assessed and reported according to the recommendation of the VARC-2 criteria(73).

Statistical Analysis

Baseline characteristics and an unadjusted comparison of the outcomes were performed between the three groups. Categorical variables were reported as total numbers of events and percentages and were compared with the Chi-Square test. Continuous variables were reported as mean ± standard deviation or as median with interquartile range, as appropriate, and analyzed with one-way ANOVA or the Kruskal-Wallis test. Anatomical and procedural variables that differed significantly between groups were tested for their capacity of predicting the need for MR in a logistic regression model. Logistic regression was also performed to ascertain the

independent effect of MR on the primary endpoint. Baseline variables that were significantly different between the groups and could theoretically impact device success were screened in a univariable model. Those with a P-value < 0.1 were selected to the multivariable. Additionally, patients were classified according to the absolute annual procedural volume of the institution using a self-expanding repositionable device (≤25 cases, 26-75 cases, or >75 cases per year) to account for the centers' experience in the regression assessment. For the 30-day and 1-year mortality, survival analysis with the Kaplan-Meier method was performed comparing the three groups with the log-rank test and pairwise method, followed by a multivariable proportional hazard regression for 1-year mortality to assess the association of MR with the outcome after accounting for other factors. Chosen independent variables were those that differed between groups and were known by the literature to be associated with mortality. For the multivariable model, variables were included if they had a P-value <0.1 in the univariable. The statistical analysis results are presented as odds ratios or hazard ratios, accordingly, with a 95% confidence interval and P values. All analyses were performed with SPSS version 24 (IBM, Armonk, New York, USA).

RESULTS

Among the 1,030 patients eligible for the study, four did not have follow-up data and were excluded. The median follow-up time was 394 days (IQR: 209 to 646). Of the studied population, 336 (32.7%) required at least one resheathing, being multiple in 95 (9.3%) cases, with a median of 2 attempts/patient (IQR 2 to 3; range of 2 to 6) (Figure 1). Baseline clinical, echocardiographic, and multidetector computed

tomography (MDCT) characteristics are shown in Table 1. Missing values were very low (< 5%) and were regarded as completely at random. Therefore, no specific analytical strategy was taken to handle them. The mean age was 81.1 ± 7.2 years, and 44% were male, with a median STS-PROM score of 4.7 (IQR of 3 to 7). Overall, clinical baseline characteristics were well-balanced between the groups, except for COPD that was more prevalent in the NR group, while atrial fibrillation and previous cerebrovascular disease were more prevalent in the MR patients. Baseline echocardiography showed that moderate/severe aortic regurgitation were more frequent in MR patients, with no difference regarding the severity of the aortic stenosis, as well as with respect to the MDCT parameters. The main procedural characteristics are shown in Table 2. Resheathing and repositioning of the THV was more frequent with the Portico valve (Figure 1), and in patients with MR more balloon pre- and post-dilation was required, as compared to NR and SR groups, in addition to significantly less conscious sedation. By multivariable analysis, the presence of moderate/severe aortic regurgitation at baseline and the utilization of the Portico valve were identified as independent predictors for the need for MR (OR=2.33, 95% CI of 1.4 to 3.87, P=0.001 and OR=2.81, 95% CI, 1.68 to 4.7, P<0.001, respectively) (Table 3).

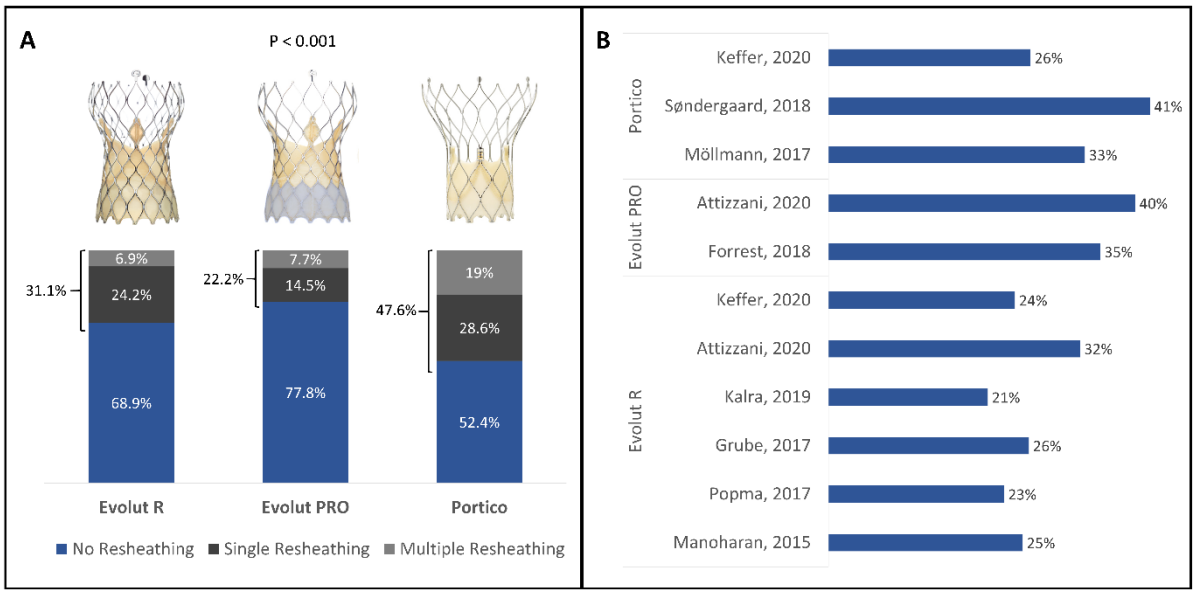

Figure 1. A) Percentage of the need for single resheathing and multiple resheathing in the study according to the type of THV implanted. B) Percentage of resheathing required reported by previous studies for the different types of THV.

Procedural and clinical outcomes

Overall, device success was achieved in 89% of cases with a lower rate in the MR patients in comparison to the other two groups (80% vs. 89.9% vs. 89.8%, P=0.01), and this was mostly driven by a higher need of a second valve and more prosthesis embolization (Table 4). No differences in procedural death or other intraprocedural complication rates were observed. The incidence of NOP-LBBB was higher in the MR patients, although the need for new permanent pacemaker (PPM) implantation was similar. On multivariable regression analysis, variables that independently impacted the device success were moderate/severe aortic regurgitation at baseline (OR: 0.47, 95% CI: 0.3 to 0.76, P=0.002) and MR (OR: 0.42, 95% CI: 0.23 to 0.74, P=0.003) (Table 5).

At 30 days, there was a similar rate of all-cause death, stroke, and other safety events among the groups (Table 3). At 1-year, MR was associated with increased mortality in comparison to NR and SR cases (18.8% vs. 10.5% vs. 8.0%, respectively, P=0.014) (Figure 2). As shown in Table 6, after adjusting for differences in baseline characteristics and center volume on a multivariable proportional hazard model, COPD (HR of 1.74, 95% CI of 1.11 to 2.73, P=0.03), the need for MR (HR of 2.06, 95% CI of 1.18 to 3.6, P=0.01), and lower center volume were independently associated with cumulative mortality (HR of 1.89, 95% CI of 1.06 to 3.36, P=0.03). Supplemental table 1 shows the rate of MR by the centers' annual volume. No interaction in the regression models was found between center volume and MR for neither device success (P=0.45 for interaction) nor for 1-year mortality (P=0.13 for interaction). In a sensitivity analysis, excluding the 187 Portico cases, MR with the Evolut R/PRO continued to be associated with less device success and with a trend towards increased mortality at 1-year (supplemental table 2 and supplemental figure 1). Supplemental tables 3-5 shows the number of cases included in each regression analysis.

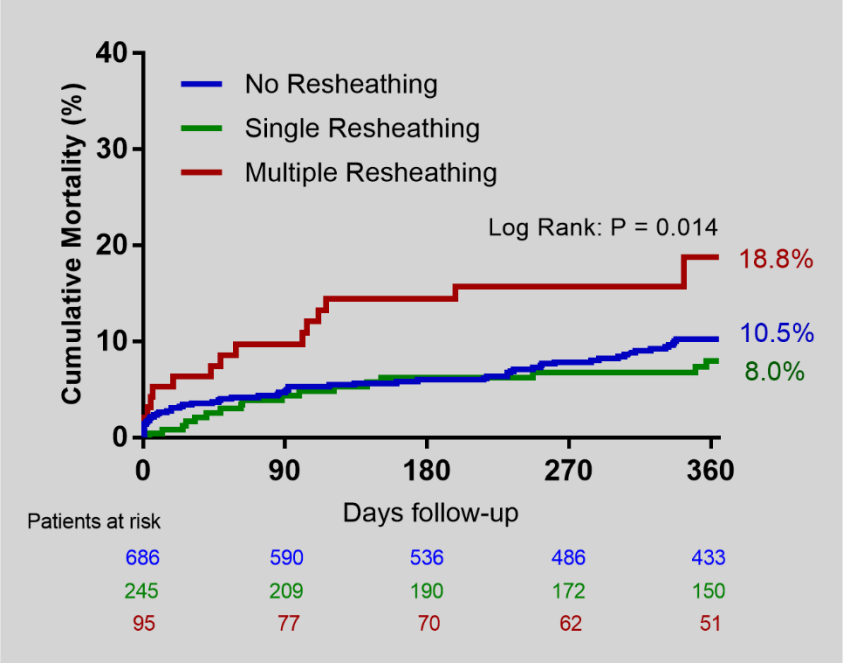

Figure 2. Comparison of the Kaplan-Meier cumulative mortality curves at 1-year among the groups. In pairwise log rank comparison, there was a significant difference between NR vs. MR (P=0.02), and between SR vs. MR (P=0.005). No difference was observed between NR vs. SR (P=0.3).

DISCUSSION

The main findings of this real-world registry of patients undergoing TAVR with repositionable self-expanding THV were: i) resheathing was required in a third of patients, being multiple in ~10% of them; ii) independent predictors of MR were moderate/severe aortic regurgitation at baseline and implantation of a Portico valve; iii) MR was associated with lower device success and a higher rate of prosthesis embolization and the need for a second valve, irrespective of the THV implanted; iv) no differences were seen with respect to the combined early safety events, although MR was an independent predictor of increased mid-term mortality.

To the best of our knowledge, this is the first study to specifically address the need for resheathing during TAVR using a self-expanding device according to the number of attempts/patients. While prior studies in the TAVR field have shown resheathing rates of ~30%, similar to our research, there has been a considerable variation among them according to valve type, ranging from 21% to 41%(24,25,74–80). Of note, MR, defined as the need for two or more partial or total recapture of the device, was required in 28% of all resheathing cases (~10% overall), somewhat lower than the 38% reported by a recent smaller study(74). Importantly, in our research, MR was more frequent with a Portico vs. Evolut R/Pro devices, and by multivariable analysis, the use of a Portico THV increased ~3-fold the chances for MR. This has also been consistent with the literature, as shown in the recent Portico-I trial, where 41% of the cases needed at least one resheathing(77). One might argue that the Portico's lower radial force might play a role in the higher resheathing rates(81). Yet, all but one of the participating centers had more experience with the Evolut P/Pro devices than with the Portico. The overall lower experience with the Portico could have also played a role in the higher need for repositioning. The first-generation delivery system could have also contributed to these findings since the new Flexnav system that showed improved outcomes in the recent Portico IDE trial is recalled for a more stable deployment(82). Nonetheless, this should be further evaluated in future studies.

Other anatomical factors that have been argued as possibly related to the need for repositioning have also been evaluated, such as the severity of aortic stenosis determined by transaortic gradient, valve orifice area, and aortic valve calcification, in addition to annulus size and eccentricity index. Yet, no significant correlation of such factors with the need for resheathing was found. Of note, a recent large study also failed to demonstrate an association of these variables with the use of the repositioning

feature with both the Evolut R and PRO devices(75), highlighting that predicting the need for recapturing and repositioning self-expanding devices might not be so evident. In this regard, however, apart from the valve type, we identified moderate or severe aortic regurgitation at baseline to be independently associated with the need for MR. Most likely, the greater pulse pressure, generally accompanied by larger stroke volumes, could translate into a less stable delivery of the valve, explaining the finding.

Although the clinical outcomes during TAVR procedures have unquestionably been improved with the current generation of devices, including lower profile delivery systems and the possibility to reposition the THV, there is controversy on whether resheathing and redeploying the valve could jeopardize clinical outcomes. Therefore, although repositioning the THV might ensure proper implants, generally, at a higher position to reduce conduction disturbances and also to improve hemodynamics, this could augment the instrumentation of the aorta, potentially increasing cerebrovascular events and device embolization. Nonetheless, recent larger studies using various repositionable devices did not show an association of this maneuver with poorer clinical outcomes, including stroke, in accordance with our findings(77,79,83,84). Notably, a recent study evaluating histological and histomorphometric data of elements captured from filters of patients undergoing TAVR using embolic protection filters showed a much higher amount of debris among those where THV was repositioned(72). The real impact of such findings is still unclear. Whether the use of embolic protection devices in patients with an anticipated higher risk for MR (e.g., patients with moderate/severe aortic regurgitation at baseline) could reduce neurologic events needs to be further evaluated in proper design studies.

Another important aspect is that prior research have not explicitly evaluated the number of resheathing and recapture during TAVR and the potential impact on clinical

outcomes. In the present study, we were able to determine that in up to 10% of the patients, MR was necessary, and it was significantly associated with less device success and increased 1-year mortality. While the overall device success in our study was ~90%, similar to what is found in most of the literature for self-expanding THV (77,79,83,84), in those patients requiring MR it went down to 80%. These results were driven by higher device embolization rates and need for a second THV in the MR group. Notably, previous studies have consistently demonstrated with the various THV that valve embolization and eventually, the need for a second device significantly increased mortality(41,85,86). It is important to mention that even though the Portico device was associated with higher MR need, the negative impact of MR was seen regardless of the type of THV implanted.

Finally, there was a trend towards more early deaths for the MR group, that on the mid-term follow-up was significant, with 2-fold greater mortality compared to NR or SR cases. It is difficult to conclude whether MR was the causative factor of the increased mortality at 1-year. One would expect a procedure-related event to rather impact early outcomes. Nevertheless, most of the Kaplan-Meier curves separation occurred during the first 120 days, a period more sensitive to the consequences of a procedural issue. Alternatively, MR could be merely a marker of more complicated anatomies for proper device implantation, leading to more prosthesis embolization, which in turn compromises the results. This was highlighted by a higher need for pre- and post-dilatation, and also less use of conscious sedation in the MR group. Therefore, we suggest that in patients where the operator has difficulties positioning the THV after more than two attempts, it may be reasonable to consider switching to a different size or even to another type of bioprosthesis before final deployment.

The present study has several limitations. Its retrospective nature makes it prone to biases related to this type of study design. Thus, although other studies in the literature support our results, they should be perceived as exploratory and confirmed by further research. Moreover, there was no central adjudication of events or a central core lab to assess pre- and post-TAVR imaging exams, even though all participating centers have well-developed TAVR programs with experienced heart teams. Nevertheless, there was some heterogeneity in experience among the centers, which was taken into account as a co-factor in the multivariable analysis according to each center's annual procedural volume with self-expanding valves. Also, we see this variation of experience among centers to better reflect the real world of TAVR practice, increasing the external validity of our findings. Another limitation was that the exact causes of the resheathing were not available, which could have also played a role in explaining the results. However, a recent study has not seen an association of the cause of resheathing with outcomes(75). Finally, most of the cases included in the study were performed before the more widespread use of current techniques using specific gantry angles for THV deployment, aiming higher implants, and more precise positioning. Thus, future studies with more contemporary techniques may be warranted to further confirm our findings.

In conclusion, repositioning a self-expanding valve during TAVR is used in a third of patients, being multiple in ~10% of them, which was predicted by the presence of moderate/severe aortic regurgitation at baseline and implantation of a Portico valve. MR, but not SR, was associated with more device failure and increased 1-year mortality, regardless of the type of transcatheter valve implanted.

SOURCE OF FUNDING

None.

CONFLICT OF INTEREST AND DISCLOSURES

Dr. Rodés-Cabau has received institutional research grants from Medtronic (significant), Edwards Lifesciences (significant), and Boston Scientific (significant). Dr. Ribeiro has served as proctor for Edwards Lifescience, Medtronic, and Boston Scientific (significant). Dr. Nombela-Franco has served as proctor for Abbott (significant) and has received speaker honoraria from Edwards Lifesciences (modest). Dr. Amat-Santos is proctor for Boston Scientific (significant) and received institutional research grants from Medtronic, Abbott, and Boston Scientific (significant). Dr. Mangione has served as proctors for Edwards Lifescience and Medtronic (modest). Dr. Pessoa de Melo has served as proctor for Medtronic (significant). Dr. Tumelero has served as proctor for Medtronic (significant). The other authors report no conflicts.

SUPPLEMENTAL MATERIAL

Supplemental tables 1-5, Supplemental figure 1.

Table 1. Baseline clinical, echocardiographic, and computed tomography characteristics of the study population.

	Overall (n=1026)	NR (n=686)	SR (n=245)	MR (n=95)	P value
Clinical variables					
Age, years	81±7	80.8±7.5	81.6±6.5	81.6±7.1	0.23
Male sex	452 (44.1)	304 (44.3)	99 (40.4)	49 (51.6)	0.17
NYHA class ≥ III	616 (60)	412 (60.1)	150 (61.2)	54 (56.8)	0.76
Hypertension	889 (86.6)	595 (86.7)	215 (87.8)	79 (83.2)	0.53
Diabetes	346 (33.7)	221 (32.2)	91 (37.1)	34 (35.8)	0.34
COPD	216 (21.1)	161 (23.5)	43 (17.6)	12 (12.6)	0.02
Coronary artery disease	495 (48.2)	342 (49.9)	114 (46.5)	39 (41.1)	0.23
Previous CABG	125 (12.2)	76 (11.1)	37 (15.1)	12 (12.6)	0.25
Previous valve surgery	128 (12.5)	77 (11.2)	37 (15.1)	14 (14.7)	0.23
Previous Afib	339 (33)	227 (33.1)	70 (28.6)	42 (44.2)	0.02
Prior Pacemaker	141 (14.1)	98 (14.6)	29 (12.3)	14 (15.4)	0.63
Prior RBBB	87 (8.8)	61 (9.1)	21 (9)	5 (5.5)	0.51
Prior LBBB	119 (12)	82 (12.2)	24 (10.3)	13 (14.3)	0.57
Cerebrovascular disease	91 (8.9)	54 (7.9)	22 (9)	15 (15.8)	0.04
Peripheral artery disease	181 (17.6)	118 (17.2)	51 (20.8)	12 (12.6)	0.18
STS-PROM score, %	4.7 (3-7)	4.7 (3.1-7.1)	4.8 (2.9-6.9)	4.8 (3.2-7)	0.9
Hemoglobin, g/dL	11.7±1.8	11.7±1.8	11.7±1.7	11.9±1.8	0.33
Creatinine, mg/dL	1.2±0.74	1.2±0.8	1.1±0.5	1.2±0.7	0.08
Echocardiographic variables*					
LVEF, %	56.1±12.4	56±12.6	56.2±12.1	55.8±12.1	0.95
Mean aortic gradient, mmHg	43.1±17.2	43.3±18.2	42.2±14.9	43.5±15.9	0.68
Aortic valve area, cm^2	0.72±0.34	0.72±0.37	0.71±0.28	0.71±0.22	0.88
Moderate/severe aortic regurgitation	151 (15.1)	91 (13.6)	35 (14.5)	25 (26.6)	0.004
Moderate/severe mitral regurgitation	180 (18)	117 (17.6)	46 (19.2)	17 (17.9)	0.86
Pulmonary hypertension	484 (57.3)	334 (59.9)	110 (53.9)	40 (48.2)	0.07
MDCT variables†					
Annulus perimeter, mm	73.8±8.9	73.9±9	73±8.4	75.5±9	0.09
Eccentricity index	0.18±0.09	0.19±0.09	0.18±0.09	0.19±0.08	0.6
Agatston calcium score ‡,§	2464±1572	2462±1593	2416±1450	2395±1555	0.9

Values are n (%) or mean ± SD. *Pre-procedural echocardiogram data was available for 98% of the patients; †Pre-procedural MDCT was available for 90% of the patients; ‡Compared the natural log transformation of the variable for normalization; §Data on Agatston calcium score was available for 592 patients overall; NR=no resheathing; SR=single resheathing; MR=multiple resheathing; NYHA=New York Heart Association; COPD=chronic obstructive pulmonary disease; CABG=coronary artery bypass graft; Afib=atrial fibrillation; RBBB=right bundle branch block; LBBB=left bundle branch block; STS-PROM=Society of Thoracic Surgeons predicted risk of mortality; eGFR=estimated glomerular filtration; LVEF=left ventricular ejection fraction; MDCT= multidetector computed tomography.

Table 2. Procedural characteristics of the study population.

	Overall (n=1026)	NR (n=686)	SR (n=245)	MR (n=95)	P value	SR vs. NR	MR vs. NR	MR vs. SR
Procedural Characteristic								
Transfemoral approach	918 (89.5)	608 (88.6)	223 (91)	87 (91.6)	0.45	-	-	-
Conscious sedation	584 (57)	417 (60.9)	130 (53.1)	37 (38.9)	<0.001	0.03	<0.001	0.02
Valve-in-valve	99 (9.6)	59 (8.6)	29 (11.8)	11 (11.6)	0.27	-	-	-
Pre-dilatation	466 (45.4)	296 (43.1)	116 (47.3)	54 (56.8)	0.03	0.26	0.01	0.012
Post-dilatation	277 (27)	166 (24.2)	71 (29)	40 (42.1)	0.001	0.14	<0.001	0.02
Prosthesis type								
Evolut R	720 (70.2)	496 (72.3)	174 (71)	50 (52.6)				
Evolut PRO	117 (11.4)	91 (13.3)	17 (6.9)	9 (9.5)	<0.001	0.002	<0.001	0.005
Portico	189 (18.4)	99 (14.4)	54 (22)	36 (37.9)				
Prosthesis Size*								
Small	460 (44.8)	300 (43.7)	121 (49.4)	39 (41.1)				
Medium	463 (45.1)	313 (45.6)	102 (41.6)	48 (50.5)	0.45	-	-	-
Large	103 (10)	73 (10.6)	22 (9.0)	8 (8.4)				
Number of resheathing	0 (0-1)	0	1 (1-2)	2 (2-3)	<0.001	-	-	-

Values are n (%) or mean (±SD) or median (IQR).
NR=no resheathing; SR=single resheathing; MR=multiple resheathing
*Small= Evolut R/PRO 23/26 and Portico 23/25; Medium= Evolut R/PRO 29 and Portico 27/29; Large= Evolut R/PRO 34

Table 3. Univariable and Multivariable Logistic Regression for Multiple Resheathing

Univariable			Multivariable[#]		
Variables	**OR (95% CI)**	**P value**	**Variable**	**OR (95% CI)**	**P value**
Aortic regurgitation*	2.25 (1.37-3.69)	0.001	Aortic regurgitation[a]	2.33 (1.4-3.87)	0.001
Balloon predilation	1.66 (1.08-2.54)	0.02	Balloon predilation	1.21 (0.74-2)	0.45
Evolut PRO †	1.12 (0.53-2.34)	0.77	-	-	-
Portico †	3.15 (1.98-5.01)	<0.001	Portico[b]	2.81 (1.68-4.7)	<0.001

*Moderate or severe aortic regurgitation at baseline; †Evolut R/PRO as reference; [#]1003 (97.8%) cases were included in a complete cases analysis (more details on supplemental table 3).

Table 4. Comparison of procedural and 30-day outcomes between the groups

	Overall (n=1026)	NR (n=686)	SR (n=245)	MR (n=95)	P value[#]	SR vs. NR	MR vs. NR	MR vs. SR
Procedural outcomes								
Device success	913 (89)	617 (89.9)	220 (89.8)	76 (80)	0.01	0.95	0.004	0.02
Procedural death	29 (2.8)	21 (3.1)	4 (1.6)	4 (4.2)	0.36	-	-	-
Need of a second valve	23 (2.2)	4 (0.6)	9 (3.7)	10 (10.5)	<0.001	0.001	<0.001	0.01
Prosthesis embolization	15 (1.5)	3 (0.4)	5 (2)	7 (7.4)	<0.001	0.02	<0.001	0.02
Tamponade	20 (1.9)	9 (1.3)	9 (3.7)	2 (2.1)	0.07	-	-	-
Coronary obstruction	8 (0.8)	6 (0.9)	2 (0.8)	0	0.66	-	-	-
Aortic rupture	4 (0.4)	3 (0.4)	1 (0.4)	0	0.81	-	-	-
30-day outcomes								
All-cause death*	36 (3.6)	25 (3.7)	5 (2.1)	6 (6.4)	0.15	-	-	-
Combined early safety	157 (15.3)	108 (15.7)	35 (14.3)	14 (14.7)	0.85	-	-	-
Stroke								
All stroke	24 (2.4)	18 (2.6)	5 (2)	1 (1.1)	0.6	-	-	-
Disabling stroke	15 (1.5)	10 (1.5)	4 (1.6)	1 (1.1)	0.93	-	-	-
Major vascular complication	56 (5.5)	37 (5.4)	14 (5.7)	5 (5.4)	0.98	-	-	-
Life-threatening bleeding	42 (4.1)	24 (3.5)	14 (5.7)	4 (4.3)	0.33	-	-	-
Acute kidney injury (stages 2 and 3)	61 (6)	42 (6.2)	12 (4.9)	7 (7.4)	0.65	-	-	-
New permanent pacemaker	154 (15.2)	96 (14.2)	42 (17.2)	16 (17)	0.47	-	-	-
New-onset persistent LBBB	192 (19.2)	111 (16.6)	52 (21.7)	29 (30.9)	0.002	0.08	0.001	0.08
Moderate/severe aortic regurgitation	30 (3.1)	18 (2.8)	8 (3.5)	4 (4.5)	0.65	-	-	-
Mean aortic gradient, mmHg	8.5±5.3	8.5±5.3	8.3±4.8	9.6±6.6	0.15	-	-	-

*Kaplan-Meier events probability estimates (log-rank). [#]Overall P value. LBBB= left bundle branch block; NR=no resheathing; SR=single resheathing; MR=multiple resheathing

Table 5. Univariable and Multivariable Logistic Regression for Device Success

Univariable			Multivariable[#]		
Variables	**OR (95% CI)**	**P value**	**Variable**	**OR (95% CI)**	**P value**
COPD	0.71 (0.45-1.11)	0.13	-	-	-
Aortic regurgitation*	0.44 (0.27-0.7)	<0.001	Aortic regurgitation*	0.47 (0.3-0.76)	0.002
Balloon predilation	1.01 (0.68-1.5)	0.95	-	-	-
Balloon postdilation	0.88 (0.57-1.36)	0.58	-	-	-
Evolut PRO†	0.99 (0.54-1.8)	0.96	-	-	-
Portico†	1.67 (0.93-3.02)	0.08	Portico†	1.89 (0.97-3.67)	0.06
Multiple resheathing¶	0.45 (0.26-0.78)	0.004	Multiple resheathing	0.42 (0.23-0.74)	0.003
SE-THV center annual volume <25 cases‡,¶	1.47 (0.87-2.5)	0.15	SE-THV center annual volume <25 cases‡	1.58 (0.91-2.74)	0.11
SE-THV center annual volume 26-75 cases‡,¶	1.5 (0.95-2.38)	0.08	SE-THV center annual volume 26-75 cases‡	1.28 (0.77-2.12)	0.35

COPD=Chronic obstructive pulmonary disease; SE THV=Self-expanding transcatheter heart valve; *Moderate or severe aortic regurgitation at baseline; †Evolut R as the reference; ‡SE-THV center annual volume >75 as reference; ¶Interaction between Center annual volume and Multiple Resheathing (P=0.45). [#] 1003 (97.8%) cases were included in a complete cases analysis (more details on supplemental table 4).

Table 6. Univariable and multivariable proportional hazard regression for the cumulative mortality at 1 year

Univariable			Multivariable[#]		
Variables	**HR (95% CI)**	**P value**	**Variables**	**HR (95% CI)**	**P value**
COPD	1.65 (1.07-2.55)	0.03	COPD	1.74 (1.11-2.73)	0.03
Afib*	1.44 (0.96-2.16)	0.08	Afib*	1.49 (0.98-2.73)	0.06
Cerebrovascular disease	1.19 (0.62-2.28)	0.61	-	-	-
Aortic regurgitation†	1.07 (0.62-1.86)	0.81	-	-	-
Evolut PRO‡	0.78 (0.4-1.52)	0.47	-	-	-
Portico‡	0.75 (0.43-1.31)	0.32	-	-	-
Multiple Resheathing¶	1.92 (1.11-3.32)	0.02	Multiple resheathing	2.06 (1.18-3.6)	0.01
SE-THV center annual volume <25 cases§,¶	1.72 (0.97-3.05)	0.06	SE-THV center annual volume <25 cases§	1.89 (1.06-3.36)	0.03
SE-THV center annual volume 26-75 cases§,¶	1.36 (0.8-2.33)	0.26	SE-THV center annual volume 26-75 cases§	1.33 (0.77-2.3)	0.3

COPD=Chronic obstructive pulmonary disease; SE-THV=Self-expanding transcatheter heart valve; *Afib= atrial fibrillation at baseline; †Moderate or severe aortic regurgitation at baseline; ‡Evolut R as the reference; §SE-THV center annual volume >75 as reference; ¶Interaction between Center annual volume and Multiple Resheathing (P=0.13); [#]1026 (100%) cases were included in a complete case analysis (more details on supplemental table 5).

5. ARTICLE 3

Title: Learning Curve Analysis of Transcatheter Aortic Valve Replacement for In-Hospital Mortality in Brazil

Status: in submission to the Brazilian Archives of Cardiology.

Learning Curve Analysis of Transcatheter Aortic Valve Replacement for In-Hospital Mortality in Brazil

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Short Title: TAVR learning curve in Brazil.

Descriptors: Transcatheter Aortic Valve Replacement; Aortic Valve Stenosis; Learning Curve

ABSTRACT

Introduction: In developing countries, such as Brazil, there are no robust data regarding transcatheter aortic valve replacement (TAVR) learning curve (LC) as mostly of the published data comes from high-income nations. Thus, the objective was to evaluate the TAVR LC in Brazil and how it has behaved throughout the history of the procedure in the country.

Methods: Data from centers actively participating in the Brazilian TAVR registry from February 2008 to February 2023 were used. Patients from each center were enumerated chronologically in case sequence numbers (CSNs) and a learning curve analysis was performed utilizing restricted cubic splines adjusted for EUROSCORE-II and the utilization of new-generation prostheses. Also, CSNs were grouped as: the 1st to the 40th case (initial-experience), 41st to 80th case (early-experience), 81st to 120th case (intermediate-experience) and over 121st case (high-experience). Additional analysis was performed grouping hospitals according to the number of cases treated before and after 2014: high-volume centers (≥40 procedures) and low-volume (≤40 procedures). The primary outcome was in-hospital mortality.

Results: A total of 3,194 TAVR patients from 25 centers were included. Mean age and Euroscore II were 80.7±8.1 and 7±7.1, respectively, and 51.2% were male. LC analysis demonstrated a significant drop in hospital mortality after treating 40 patients. A leveling off the curve was observed after case #118. There was a progressive improvement in in-hospital mortality through the experience groups (8.6%, 7.7%, 5.9%, and 3.7% for initial-, early-, intermediate-, and high-experience, respectively $p<0.001$). High-experience was an independent predictor of in-hospital mortality after accounting for confounders (OR 0.57, $p=0.013$ vs. initial experience). LC analysis of

low-volume center before 2014, there was no significant decrease in the likelihood of patient deaths as the centers gained experience, in contrast to the LC of high-volume centers before 2014, where a drop in mortality was evident after case #10.

Conclusion: Over the history of TAVR in Brazil, a LC phenomenon was observed for in-hospital mortality. However, this effect was much more pronounced in medical centers that had performed their first 40 cases before 2014, compared to those who reached this milestone after 2014.

INTRODUCTION

For transcatheter aortic valve replacement (TAVR), a procedure that requires high-level skills to ensure success, previous studies have demonstrated the existence of a learning curve (LC) and the significance of experience in improving the efficacy and safety of the treatment, including in reducing mortality(34,35,87,88). The LC is a concept that refers to the process of acquiring and improving skills or knowledge over time, resulting in better outcomes as experience is gained. It has been applied in many medical procedures to evaluate the performance of healthcare professionals and institutions over a certain period(89). In the case of TAVR, however, these studies revealed disparate rates of patient outcomes improve as experience is gained, indicating that there is not a universal LC for TAVR, with various potential variables playing a role, such as the period when the analysis was conducted, the types of transcatheter heart valves (THV) implanted during the period of assessment, the vascular approach utilized, among others. Moreover, the majority of this published literature evaluated data mainly from North American and European countries, and, as TAVR practices may vary among different geographical locations, limitations exist in extrapolating these data to other regions of the World(90).

Developing nations like Brazil have seen a slower rate of TAVR adoption in comparison to high-income countries(55). Yet, since its introduction in 2008, the number of TAVR procedures and center performing it have increased significantly. Also, TAVR practices have been evolving in the country, with the adoption of newer generation THV and less invasive techniques becoming the standard(90). Despite this, there has never been a nationwide multicenter study analyzing the behavior of TAVR LC throughout the history of the procedure in the country. This is crucial information for both healthcare professionals and policymakers to evaluate TAVR practices,

allocate resources appropriately, and provide valuable insights for ongoing improvement as TAVR has only recently become available in the Brazilian public health system. In addition, the findings of this study can serve as a reference for nations with socioeconomic characteristics comparable to Brazil's.

Therefore, the purpose of this study was to evaluate the behavior of the TAVR LC for in-hospital outcomes over the course of the procedure's history in Brazil.

METHODS

We utilized data from the Brazilian TAVR Registry (RIBAC-NT), an ongoing nationwide multicenter registry from Brazil organized and conducted by the Brazilian Society of Hemodynamics and Interventional Cardiology (SBHCI). The initial protocol of the registry has been previously published(41). Briefly, participating centers include all consecutive TAVR procedures from their experience through an online platform with remote central data monitoring. In 2020, an updated protocol was submitted and approved by the central ethical committee to extend the duration of the registry. Centers that entered the current study were those with a minimum of 25 consecutive included patients in the registry and those with the updated registry protocol approved by their local ethical committee, which contained a waiver of informed consent from the patients as the study posed minimal risk to them.

We included all TAVR procedures in the final analyses, irrespective of the vascular access or the type of THV implanted. We excluded cases where in-hospital information was not available. Intense efforts were made in contacting the participating centers to review cases with incomplete in-hospital information to mitigate missing data and

minimize case exclusion. We used multiple imputations (mice package in R) to handle missing values. We used a predictive mean matching model for numeric variables, and logistic regression (logreg) for binary variables (with two levels). Imputed values, residual distribution, and convergence coefficients were checked. Most variables among variables available in the dataset. We did not impute missing values for the outcomes. The imputation step resulted in 5 complete data sets, each of which contains different estimates of the missing values for all patients in the cohort. After imputation, we pooled and merged all 5 datasets to perform logistic regressions.

Learning curve assessment and statistical analysis

In a similar methodology previously described to assess the learning curve of TAVR in multiple centers(35), patients from each center were enumerated chronologically in sequence number (CS#). To define optimal cut-off points of experience and to determine if there was a learning curve termination (LCT), we used restricted cubic splines adjusted for EUROSCORE-II and the utilization of new-generation THV as shown in Figure 1. A grid search analysis was applied across a range of case sequence numbers (CS#) from 10 to 350 by increments of 1. After each case sequence cutoff, subsequent CS#s were divided into quartiles, and in-hospital mortality was compared using a logistic regression test. The optimal cut-off point was defined as number of cases necessary to observe a first significant drop in mortality curve (40 cases as show in Figure 1). Case sequence number were grouped as: 1st to 40th case (initial-experience), 41st to 80th case (early-experience), 81st to 120th case (intermediate-experience) and over 121st case (high-experience). The final LCT was

determined based on the smallest upper bound of the 95% confidence interval of the logistic regression test statistic that was below the significance level threshold.

Additional analysis was performed utilizing the year of arrival of new-generation THV in Brazil (2014) as grouping cut-point. In order to determine whether there was a difference in the pattern of the LC between early and late TAVR adopters, hospitals were divided into two groups: those that had their initial experience (≥40 procedures) prior to 2014 and those who had their initial experience after 2014.

We compared the baseline characteristics and in-hospital outcomes among the experience groups having the initial experience as control. The primary outcome was in-hospital mortality within 30 days of hospitalization. Key secondary outcomes were major vascular complication, major or life-threatening bleeding, and any stroke. All outcomes were classified according to the VARC-2 criteria(73).

Normally distributed data was presented as mean ± SD and skewed data as median [interquartile range (IQR)]. Normality of distribution and variances were checked using histograms, Kolmogorov-Smirnoff test, normal probability plots and residual scatter plots. Chi-square or Kruskal-Wallis or two tailed t-tests were used for comparison of baseline data and unadjusted outcomes. Logistic regressions were built to assess the prediction of the experience groups on in-hospital death adjusting for potential confounding factors (use of old versus new generation THV, transfemoral versus non-transfemoral approach, valve-in-valve procedures, and EUROSCORE-II). Old generation THV were those from the first line of devices commercially available in Brazil, comprising the following: Corevalve (Medtronic, Minneapolis, MN), Sapien XT (Edwards Lifescience, Irvine, CA), Lotus (Boston Scientific, Marlborough, MA), and Inovare (Braile Biomedica, São Jose do Rio Preto, Brazil). All devices are listed in the

supplemental **table S1**. P-values <0.05 were considered as statistically significant. Analyses were carried out using R [v3.5.3] language and R Studio v1.1.4.

RESULTS

A total of 3,194 TAVR patients from 25 Brazilian centers were included in this study. Ten cases were excluded for lack of sufficient in-hospital information. The first case was performed in February 2008 and the last in February 2023. Among the individuals in the database, there were 111 missing cases for the variable transfemoral approach and 63 for prosthesis generation which were handled with multiple imputation as described in the methods section.

Baseline and Procedural Characteristics

Mean age was 80.6±8.1, 51.2% were male patients, and the mean Euroscore II was 7±7.1. **Tables 1** and **2** summarize the baseline and procedural characteristics of the overall population and of each experience group levels.

When comparing the patients´ baseline data between the experience groups, the initial-, early- and intermediate- were quite balanced with similar mean ages and little difference in the rates of diabetes mellitus, coronary artery disease, peripheral arterial disease, and COPD, with a mean Euroscore-II of 7.7±8, 7.4±6.6, 8.1±8.3. In the high-experience group though, patients had less comorbidities and a Euroscore-II significantly lower of 5.4±5.7 ($p<0.001$). The median procedure date of the four groups were April 2015, May 2016, January 2017, and April 2019, respectively for the initial, early, intermediate, and high experience groups.

In terms of procedure, roughly 96% of the cases were transfemoral, with no meaningful difference between groups. However, as experience grew, a greater proportion of cases were done with a totally percutaneous approach and without general anesthesia. Valve-in-valve accounted for only 4.4% of the procedures, with an even rate among the experience levels. New generation THV steadily rose in use as the centers' experience grew, from 36.7% to 90% in the initial- and high-experience, respectively. Valve embolization, the need for a second valve, coronary obstruction, and conversion to open surgery were all less common in the high-experience stratum.

Learning Curve assessment and outcomes

Figure 1 illustrates the LC of TAVR with a spline regression for in-hospital death adjusted to log-transformed Euroscore-II and the utilization of new-generation THV, showing that it was necessary to treat 40 cases until a first drop in the adjusted probability of mortality. A change in slope was observed at CS#118, signaling a leveling off of outcomes after this experience level. The final LCT was determined to be at CS#303 based on the smallest upper bound of the 95% confidence interval of the logistic regression test statistic that was below the significance level threshold.

When comparing the groups of experience, we observed a continuous drop in the unadjusted in-hospital mortality from the initial- (8.7%), early- (8%), intermediate- (6.1%), and high-experience (4.0%) ($p< 0.001$) (**table 3**). There was also a significant difference in the incidence of major vascular complication (initial: 10.7%; early: 7.5%; intermediate: 8.1%; high: 3.1%, $p<0.001$), major or life-threatening bleeding (initial: 13.4%; early: 9.5%; intermediate: 7.9%; high: 4.8%, $p<0.001$) and stroke (initial: 3.3%; early: 2.3%; intermediate: 3.3%; high: 1.2%, $p<0.001$). After adjusting for confounders

and having the initial-experience as control, only the high-experience group was associated with a significant reduction in in-hospital mortality (OR 0.52, p=0.002). The transfemoral approach (OR 0.51, p=0.014) and the utilization of new-generation THV were also predictive of reduced hospital mortality (OR 0.69, p=0.029) along with lower Euroscore-II, as demonstrated in figure 2.

Figure 1. Spline regressions for in-hospital death (adjusted to log-transformed EUROSCORE-2 and the utilization of new generation THV) to determine a learning curve termination. To determine if there was a learning curve termination (LCT), a grid search analysis was applied across a range of case sequence numbers (CS#) from 10 to 350 by increments of 1. After each case sequence cutoff, subsequent CS#s were divided into quartiles, and in-hospital mortality was compared using a logistic regression test. It is necessary to treat 40 cases until a first drop in the learning curve. A change in slope was observed at CS#118, signaling a leveling off of outcomes after this experience level. The final LCT was determined to be at CS#303 based on the smallest upper bound of the 95% confidence interval of the logistic regression test statistic that was below the significance level threshold.

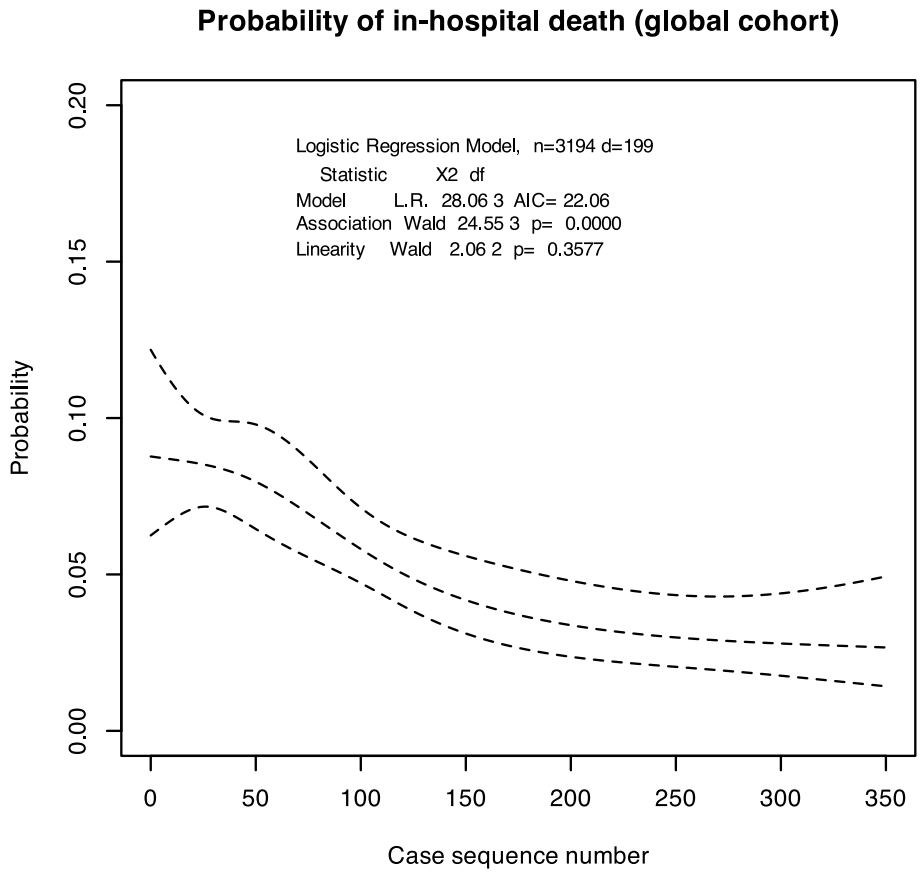
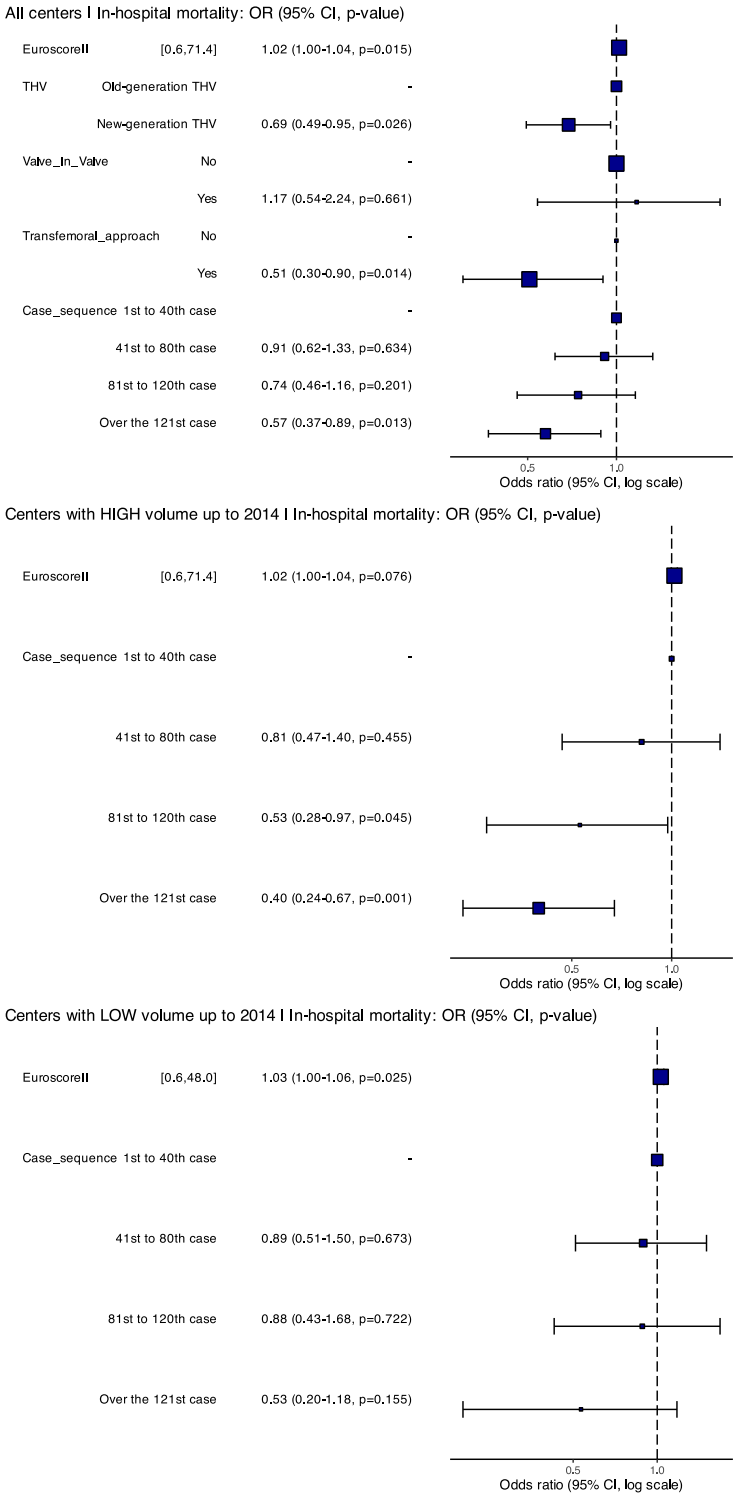


Figure 2. Forest plots for in-hospital death rate according to case sequence group and respective center TAVR volume before 2014.



Centers with initial experience before and after 2014

Eight of the 25 centers concluded their initial experience (first 40 TAVR cases) prior to 2014, accounting for a total of 1,916 patients with a median number of procedures per center of 222 (IQR 163 to 282). The remaining 17 centers completed their initial experience after 2014, accounting 1,278 patients with a median number of procedures per center of 56 (IQR 34.5 to 115). Supplemental **tables S1** and **S2** describe the baseline and procedural characteristics of patients based on groups of experience by case sequencing in centers that had their initial experience before and after 2014. Overall, patients had similar risks by Euroscore-II (mean of 7.0±7.5 and 6.9±6.8 for initial experience before and after 2014, respectively). In centers with initial experience after 2014, new-generation THV were implanted significantly more often (55.4% vs. 70.3%, $p<0.001$).

As shown in figure 3, the LC of the two cohorts differed in pattern. Center with initial experience before 2014 had a LC that resembled that of the overall centers, however, with an earlier initial drop within the first 10 cases. A change in slope was observed at CS#81, signaling a leveling off of outcomes after this experience level. Meanwhile, in centers with initial experience after 2014 (figure 4), the curve begins with a decreased likelihood of mortality and remains steady until approximately case #100. Following that, the curve drops, albeit with a steady widening of the confidence interval due to the lower number of centers with more than 100 cases in this cohort.

In the early TAVR adopter's cohort (before 2014), both intermediate- and high-experience had an odds ratio of 0.47 ($p=0.027$) and 0.44 ($p=0.003$), respectively, for in-hospital mortality in comparison to initial-experience after adjusting for Euroscore-II. We did not find a significant relationship between acquired experience and hospital

mortality among late adopters (after 2014) (figure 2). **Tables 4** and **5** shows the unadjusted event rates of the two cohorts according to the different experience levels.

Figure 3. Spline regressions for in-hospital death (adjusted to log-transformed EUROSCORE-2 and the utilization of new generation THV) to determine the learning curve termination of centers with initial experience completed before 2014.

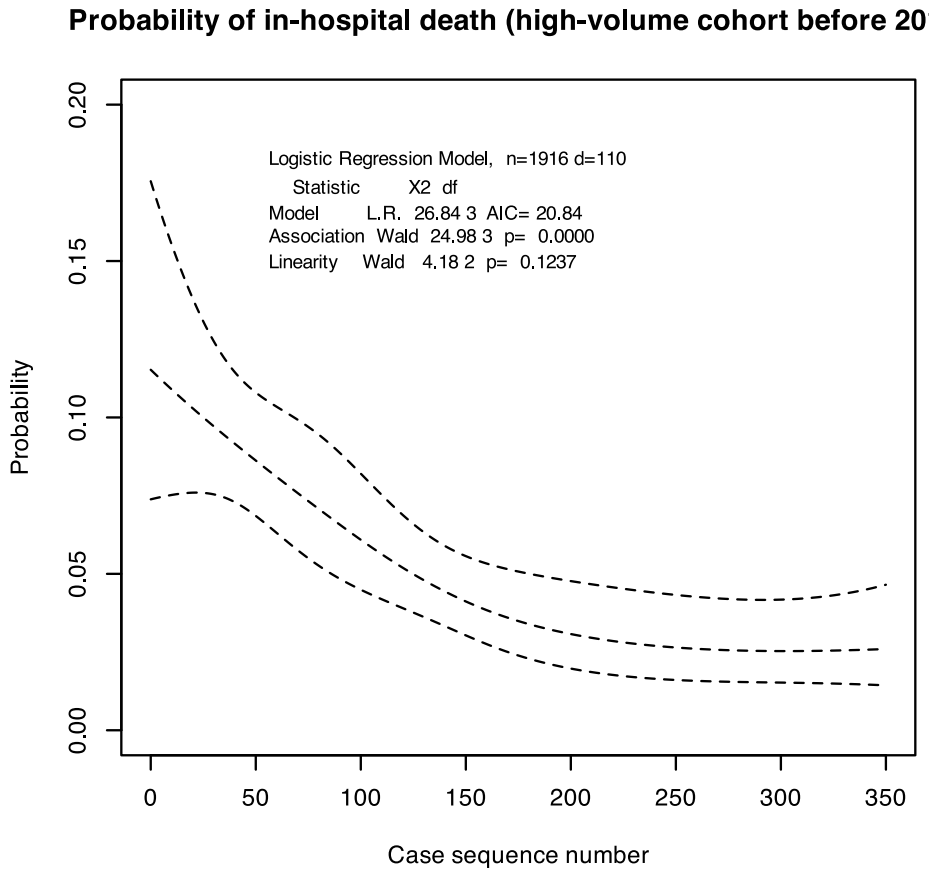
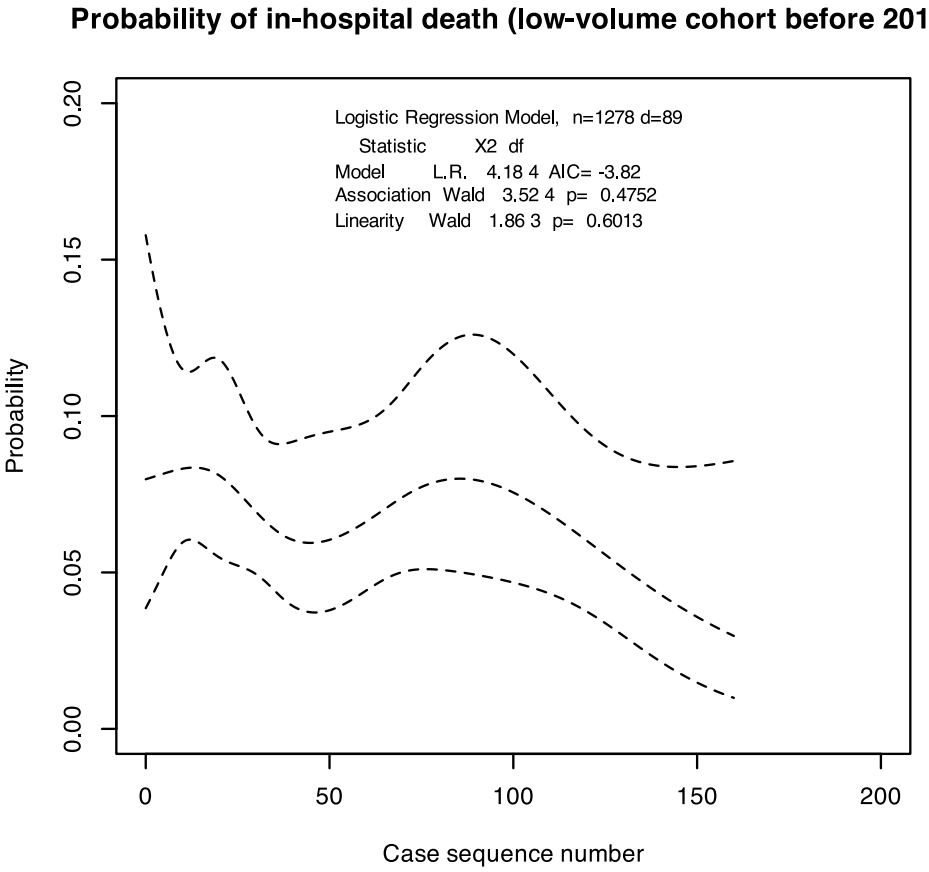


Figure 4. Spline regressions for in-hospital death (adjusted to log-transformed EUROSCORE-2 and the utilization of new generation THV) to determine the learning curve termination of centers with initial experience completed after 2014.



DISCUSSION

In this real-world study involving 25 centers and 3,194 patients, where we evaluated the LC of TAVR in Brazil through the impact of the initial accumulated experience of the centers on in-hospital mortality, we obtained the following main results: 1) the accumulated experience was associated with a reduction in in-hospital mortality, with the LC showing a first drop in mortality from case #40 until leveling off from case #118 onwards; 2) high-experience, determined by an accumulated experience of more than 120 cases, was an independent predictor of in-hospital mortality, being also associated with unadjusted lower rates of complications such as

clinically relevant bleeding, major vascular complications and stroke. 3) there was distinct pattern of LC in centers that had their initial experience before and after 2014, demonstrating a lesser impact of accumulated experience on in-hospital mortality in centers that begun their TAVR programs later; 4) besides Euroscore-II, transfemoral approach and the use of new-generation THV were other independent variables associated with lower in-hospital mortality.

The knowledge of the LC for a complex procedure such as TAVR is crucial for planning processes that aim to continuously enhance clinical practices and to optimize the allocation of future resources. Although previous studies have evaluated the LC of TAVR(34,35,39,82,87,87,88,91), ours is the first multicenter study conducted in Brazil, whose reality is vastly distinct from that of high-income countries. In Brazil and other developing nations, population access to TAVR has been significantly restricted(55,90), largely due to economic constraints and the absence of the procedure in the public health system(92,93). For instance, by 2017, less than 10 TAVR were performed per one million inhabitants in Brazil, against more than 100-150 in countries like the United States of America, France, and Germany(55). This regional variation in TAVR accessibility and volume of procedures may be a factor in determining the LC in a country's reality. Prior to that, the sole Brazilian study that sought to evaluate the impact of the LC on TAVR outcomes evaluated data from only two institutions that shared the same TAVR team in a single city, analyzing their first 150 cases during the initial phase of the procedure in the country between 2009 and 2013(39). Hence, in a continental nation such as Brazil, an updated analysis incorporating institutions from various regions of the country was required.

Our findings are consistent with international multicenter studies that demonstrate a decline in the incidence of early adverse events as institutions gained

experience(34,35,87,91). We observed a decrease in mortality beginning with centers´ case #40. In comparison, Wassef et al. found an improvement beginning with case #75(34), whereas Russo et al. found an improvement from case #38 onwards(35), both multicenter studies that analyzed the LC of institutions from high-income countries. This improvement in mortality extended beyond procedure #120 in our study, as well as beyond procedures #150 and #170 in the investigations by Wassef et al and Russo et al, respectively. Despite distinct realities, these findings demonstrate that the overall LC in Brazil was somehow comparable to that observed in countries with a higher level of socioeconomic development and where the population has had more access to the procedure.

Nevertheless, it is essential to recognize that the TAVR has evolved since its inception. In the past 15 years, numerous new devices and techniques that are more refined and less invasive have emerged. Notably, a study that assessed the development of TAVR practices in Latin American centers, the majority of which were from Brazil, revealed a significant change in practice between 2015 and 2020, with a greater incorporation of minimalist procedures and a universal adoption of the most recent versions of THV(90). In order to determine whether these temporal changes in TAVR practices affected the LC, in a sub-analysis, we separated centers whose initial experience occurred before 2014 from those whose initial experience was completed after 2014, the year in which the first new-generation THV started becoming commercially available in Brazil. As observed, the late adopter centers, did not demonstrate an expected initial LC phenomenon in terms of reduction in adjusted in-hospital mortality. Unlike the early adopter centers, where there was a clear initial LC, with a reduction in the probability of death already occurring after the first ten cases. Russo et al. analyzing data from the North American TVT registry characterized an

analogous phenomenon, where there was no evidence of a LC in centers where initial experience occurred after 2015 with the latest balloon-expandable prosthesis Sapien S3 (Edwards Lifescience, Irvine, CA). These centers did not exhibit a significant improvement in clinical outcomes with increased experience, and their initial clinical outcomes were already comparable to those of centers with greater experience. According to the authors, this result was not wholly unanticipated, as device improvements, intensive proctoring programs, and knowledge dissemination may result in a more rapid adoption of TAVR techniques in newer, lower-volume centers(35).

In fact, many elements in more modern practice have been associated with better outcomes which can contribute to this more promising start by the new TAVR centers, such as: 1) increased general knowledge of the entire scientific community associated with an impressive accumulation of scientific evidence over the course of TAVR´s history(94); 2) The beginning of experience with more modern THV, which unquestionably enhanced clinical outcomes as a result of technological advancements that made them more user-friendly and reliable, thereby allowing for safer and simpler implants(53,67,95–98); 3) The intense work of the scientific community, in collaboration with the industry, to enhance prosthesis implant techniques, accompanied by extensive knowledge dissemination efforts(99,100); 4) improvement in patient selection with greater inclusion of lower surgical-risk patients, as well as refinement of imaging techniques for better procedural planning(99,100); 5) extensive proctoring programs provided universally by the THV companies for centers that are starting their TAVR programs.

Nevertheless, despite the fact that our analysis did not identify a significant association between reduction of in-hospital deaths and the initial-experience in

centers that begun TAVR later, there was in fact a trend toward improvement, especially after 120 cases. As only 4 of the 17 institutions contributed to the high-experience group in this cohort, resulting in wide confidence intervals due to a diminished number of patients, we cannot rule out the possibility of a false negative observation. Although in a classic LC we would predict substantial gains in result early on, a so-called "diminishing-return LC," we must consider the possibility of a "increasing-return LC" for these centers whose initial experience took place after 2014. A pattern of LC in which the progression is initially sluggish and then increases, albeit on a lesser scale, until full proficiency is achieved. Even though these centers began with a lower in-hospital mortality rate (7.6% vs. 10.9% for the cohort with initial experience before 2014), there was little or no improvement until the 120th case. Despite a population with a high mean Euroscore-II (nearly 8.0), which is indicative of moderate to high-risk patients, the observed in-hospital mortality was significantly higher than that of other international publications. In the aforementioned study from the TVT registry, institutions that began their experiences with the balloon-expandable prosthesis Sapien S3 after 2015 had a stable hospital mortality rate of approximately 4% while also treating an intermediate to high-risk population(35). Hence, this lack of initial improvement as the number of cases increased in our sub-analysis suggests that these younger TAVR institutions' initial learning process may have stagnated. Furthermore, the relatively initial high rates of vascular complications also observed for this cohort, another indicator of TAVR expertise, further support this hypothesis.

Why, then, would the LC process of these centers be delayed in terms of reduced in-hospital mortality? A possible explanation could be related to the limited volume of TAVR performed at these institutions. Prior to case #120, the median annual number of procedures was only 6.4 (IQR 5 to 11) compared to 15 (IQR 12.3 to 17.1) for the

cohort of centers that had their initial experience before 2014. Numerous studies have consistently demonstrated a significant association between the volume of procedures and enhanced outcomes, including short-term mortality(34,36,37). Henceforth, within the context of Brazil's prevailing circumstances, it is reasonable to surmise that the low-volume of procedures played a significant role in the LC stagnation in these younger TAVR institutions. Given the imminent inclusion of the procedure in Brazil's public health system, this noteworthy insight ought to be duly considered for the further advancement of the field within the country. However, it remains imperative to undertake future surveillance of data derived from the Brazilian registry in order to delve more profoundly into the factors intricately associated with the learning curve process, as the practice of TAVR continues to evolve within novel institutional settings across the nation.

Study limitation

This is a retrospective observational study with data from a real-world registry with site-reported outcomes and no central adjudication. Even though standardized outcomes by the VARC-2 criteria were utilized, there could be inconsistencies in reporting endpoints. That was the reason why we chose all-cause in-hospital mortality for the primary analysis, in order to mitigate potential assessment bias. Moreover, we did not evaluate the impact of the LC for mid- and late-outcomes as we assessed only in-hospital events. There was no assessment for individual operators either. It is necessary to consider that some institutions have more than one primary TAVR interventionalist or even more than one heart team. Previous study have shown that individual operators´ experience is also is associated with improved risk-adjusted in-hospital outcomes(36). Additionally, the study englobed data from performed TAVR with all commercially available THV in Brazil. A recent publication showed distinct LC

for self- and balloon-expandable valves(101). In our case, as most centers utilized different devices even in their initial- and early-experience, and considering that experience gains are cumulative, it was impossible to asses individual LC for different types of THV. Finally, TAVR continues to evolve, with more refined techniques and even superior devices constantly appearing. Therefore, our findings may not fully represent the most up-to-date practice.

In conclusion, throughout the history of TARV in Brazil, the gain of accumulated experience by the institutions has been associated with improved in-hospital mortality indicating a true LC phenomenon. However, this relationship of experience and enhanced outcomes was much more impactful during the early days of TAVR, indicating a change in the LC behavior for newer adopters, with better initial results but a slower rate of clinical improvement as experience was gained. These findings contribute to the understanding of the LC in TAVR and provide insights for future research in this rapidly evolving field.

Table 1. Characteristics of the enrolled individuals.

	Overall	1st to 40th case	41st to 80th case	81st to 120th case	Over the 121st case	p
Sample size (n)	3194	991	616	458	1129	
Age (mean (SD))	80.7 (8.1)	80.9 (7.3)	80.9 (7.5)	81.7 (7)	79.9 (9.3)	<0.001
Female Gender (%)	1475 (48.8)	520 (52.5)	283 (45.9)	227 (49.6)	521 (46.1)	0.014
BMI (mean (SD))	26.6 (4.7)	26.3 (4.8)	26.6 (4.8)	26.6 (4.6)	26.9 (4.7)	0.138
Hypertension (%)	2157 (80.5)	777 (82)	453 (80)	348 (83.5)	581 (77.3)	0.031
Diabetes (%)	1026 (34)	344 (34.8)	210 (34.1)	150 (32.8)	360 (32.1)	0.593
NYHA (%)						
I	141 (5)	27 (2.7)	30 (4.9)	25 (5.5)	68 (7.6)	
II	687 (24.1)	174 (17.6)	144 (23.4)	124 (27.3)	285 (32)	
III	1395 (49)	512 (51.8)	302 (49)	190 (41.8)	422 (47.3)	
IV	625 (21.9)	276 (27.9)	140 (22.7)	116 (25.5)	117 (13.1)	
History AF (%)	97 (18.7)	22 (17.9)	13 (12)	20 (25)	42 (20.2)	0.133
Pacemaker (%)	81 (8.7)	17 (8.3)	15 (7.9)	14 (8.9)	35 (9.3)	0.944
Previous CAD (%)	1446 (49)	518 (53.5)	334 (56)	263 (57.5)	396 (36.2)	<0.001
Previous MI (%)	365 (13.2)	125 (13.5)	92 (16.3)	66 (15.8)	98 (9.6)	<0.001
Previous PCI (%)	772 (26.7)	285 (29.1)	169 (27.9)	143 (31.3)	213 (22)	<0.001
Previous CABG (%)	436 (15.3)	152 (5.5)	120 (19.5)	75 (16.4)	117 (12.6)	0.003
Previous Valve Surgery (%)	26 (7.4)	6 (7.2)	4 (6.4)	2 (5)	14 (8.3)	0.668
CerVascDis (%)	355 (11.9)	144 (14.8)	82 (13.6)	52 (11.4)	87 (7.8)	<0.001
Previous Stroke (%)	192 (6.4)	71 (6.3)	36 (6)	28 (6.1)	61 (5.4)	0.335
PeriphVascDis (%)	433 (14.5)	164 (16.9)	112 (18.5)	82 (17.9)	97 (8.7)	<0.001
COPD (%)	488 (16.4)	177 (18.3)	121 (20.0)	99 (21.7)	108 (9.6)	<0.001
Creatinine mg/dl (mean (SD))	1.31 (0.57)	1.31 (0.77)	1.30 (0.86)	1.37 (1.18)	1.31 (0.88)	0.461
Hemoglobin g/dL (mean (SD))	10.61 (1.82)	10.36 (2.00)	10.86 (2.09)	10.82 (2.17)	11.01 (2.12)	<0.001
Baseline Echo						
LVEF (mean (SD))	58.84 (12.49)	59.14 (13.89)	58.93 (13.98)	59.11 (12.86)	58.29 (12.95)	0.005
Max Gradient (mean (SD))	75.19 (26.75)	78.49 (26.75)	72.66 (27.52)	74.91 (26.86)	72.34 (27.25)	<0.001
Mean Gradient (mean (SD))	46.09 (16.92)	48.01 (17.61)	44.77 (18.00)	46.24 (17.38)	43.98 (17.78)	<0.001
AVA (mean (SD))	0.71 (0.20)	0.70 (0.26)	0.72 (0.33)	0.70 (0.20)	0.74 (0.61)	0.115
Bicuspid aortic valve (%)	115 (3.8)	35 (5.2)	18 (3.7)	11 (3.1)	9 (3.0)	0.160
PASP (mean (SD))	41.67 (13.05)	41.49 (14.40)	41.69 (14.94)	38.81 (12.80)	43.77 (15.91)	0.018
Surgical risk						
Euroscore II (mean (SD))	6.98 (7.14)	7.71 (8.00)	7.42 (6.64)	8.14 (8.25)	5.37 (5.75)	<0.001

BMI = body mass index; NYHA = New York Heart Association; AF = Atrial Fibrillation; CAD = Coronary Artery Disease; MI = Myocardial Infarction; PCI = Percutaneous Coronary Intervention; CABG = Coronary Artery Bypass Graft; CerVascDis = Cerebrovascular Disease; PeriphVascDis = Peripheral Vascular Disease; COPD = Chronic Obstructive Pulmonary Disease; LVEF = Left Ventricular Ejection Fraction; AVA = Aortic Valve Area; PSAP = Pulmonary Arterial Systolic Pressure.

Table 2. Procedural characteristics of the enrolled patients.

	Overall	1st to 40th case	41st to 80th case	81st to 120th case	Over the 121st case	p
Sample size (n)	3194	991	616	458	1129	
Procedure Year (median (interquartile range in months))	January/2017 (6.6)	April/2015 (3.85)	May/2016 (3.10)	January/2017 (2.49)	April/2019 (2.13)	<0.001
New-generation THV (%)	1822 (61.3)	363 (36.7)	303 (49.3)	292 (63.9)	966 (90)	<0.001
Valve In Valve (%)	134 (4.4)	43 (4.4)	18 (3.1)	23 (5.4)	50 (4.9)	0.271
General anesthesia (%)	1878 (65.1)	744 (75.8)	409 (71.9)	324 (77)	401 (43.8)	<0.001
Approach (%)						
Transfemoral	2795 (95.7)	955 (96.8)	575 (93.8)	433 (95.1)	978 (96.4)	
Transapical	61 (2.1)	12 (1.2)	25 (4.1)	8 (1.8)	19 (1.9)	
Transaortic	20 (0.7)	4 (0.4)	2 (0.3)	10 (2.2)	5 (0.5)	
Trans-subclavian	33 (1.1)	12 (1.2)	7 (1.1)	4 (0.9)	10 (1)	
Other	11 (0.4)	4 (0.4)	4 (0.7)	0 (0)	3 (0.3)	
Percutaneous Access (%)	2462 (84.4)	707 (71.6)	516 (84.2)	405 (89.2)	982 (96.9)	<0.001
Balloon Predilation (%)	1176 (41.2)	406 (42.2)	257 (43.4)	184 (40.7)	368 (37.0)	0.042
VALVE BRAND (%)						
Sapien XT	414 (13.9)	188 (19)	134 (21.8)	81 (17.7)	55 (5.1)	
CoreValve	637 (21.4)	413 (41.8)	157 (25.6)	53 (11.6)	28 (2.6)	
Lotus	60 (2)	15 (1.5)	3 (0.5)	28 (6.1)	16 (1.5)	
Sapien S3	870 (29.3)	179 (18.1)	112 (18.2)	126 (27.6)	528 (49.2)	
Evolut R/PRO	677 (22.8)	130 (13.2)	167 (27.2)	141 (30.9)	251 (23.4)	
Braile	37 (1.2)	9 (0.9)	17 (2.8)	3 (0.7)	8 (0.7)	
Portico	19 (0.6)	11 (1.1)	0 (0)	0 (0)	8 (0.7)	
Acurate Neo/Neo2	205 (6.9)	41 (4.1)	16 (2.6)	17 (3.7)	146 (13.6)	
Myval	21 (0.7)	0 (0)	3 (0.5)	6 (1.3)	12 (1.1)	
Unreported	30 (1)	2 (0.2)	5 (0.8)	2 (0.4)	21 (2)	
Balloon Post-dilation (%)	848 (29.8)	295 (30.8)	173 (31.1)	125 (29.8)	255 (28.1)	0.557
Valve Embolization (%)	55 (2.2)	25 (2.7)	13 (2.7)	8 (2.2)	10 (1.1)	0.070
Need of 2nd Valve (%)	63 (2.5)	27 (2.9)	19 (4)	9 (2.5)	11 (1.2)	0.010
Coronary artery occlusion (%)	15 (0.7)	4 (0.5)	6 (1.4)	4 (1.2)	1 (0.1)	0.015
Annulus rupture (%)	13 (0.5)	8 (0.9)	1 (0.2)	1 (0.3)	5 (0.5)	0.371
Tamponade (%)	80 (3.2)	34 (3.7)	14 (3.1)	13 (3.9)	19 (2.3)	0.345
Conversion Open Surgery (%)	66 (2.2)	34 (3.5)	12 (2.0)	10 (2.2)	11 (1.0)	0.001

THV = transcatheter heart valve.

Table 3. Post-TAVR Outcomes.

	Overall	1st to 40th case	41st to 80th case	81st to 120th case	Over the 121st case	p
Sample size (n)	3194	991	616	458	1129	
In-Hospital Mortality (%)	191 (6.6)	84 (8.6)	45 (7.7)	25 (5.9)	40 (3.7)	<0.001
Major Vasc Complication (%)	189 (6.2)	95 (10.7)	38 (7.5)	31 (8.1)	30 (3.1)	<0.001
Major or life-threatening Bleeding (%)	268 (9)	132 (13.4)	56 (9.5)	36 (7.9)	48 (4.8)	<0.001
Any stroke (%)	69 (2.4)	31 (3.3)	13 (2.3)	14 (3.3)	9 (1.2)	0.030
Myocardial infarction (%)	32 (1.1)	17 (2.7)	7 (1.9)	4 (1.6)	4 (1.0)	0.258
New Pacemaker (%)	308 (10.2)	101 (10.9)	80 (14.1)	52 (12.6)	89 (8.9)	0.038

Table 4. Post-TAVR Outcomes according to case sequence number among centers with high-volume of TAVR procedures [≥40 procedures] before 2014.

	Overall	1st to 40th case	41st to 80th case	81st to 120th case	Over the 121st case	p
Sample size (n)	1916	320	320	297	979	
In-Hospital Mortality (%)	108 (6.0)	33 (10.9)	26 (8.8)	14 (5.2)	35 (3.8)	<0.001
Major Vascular Complication (%)	101 (6.5)	34 (13.4)	16 (6.5)	22 (9.7)	29 (3.5)	<0.001
Major or life-threatening Bleeding (%)	142 (7.5)	40 (12.5)	24 (7.5)	30 (10.1)	47 (4.8)	<0.001
Any stroke (%)	36 (2.5)	12 (4.0)	8 (2.8)	8 (3.0)	8 (1.3)	0.071
Myocardial infarction (%)	17 (1.7)	8 (3.6)	3 (1.5)	2 (1.0)	4 (1.1)	0.109
New Pacemaker (%)	202 (11.8)	42 (13.6)	46 (15.2)	38 (14.8)	76 (8.9)	0.019

Table 5. Post-TAVR Outcomes according to case sequence number among centers with low-volume of TAVR procedures [<40 procedures] before 2014.

	Overall	1st to 40th case	41st to 80th case	81st to 120th case	Over the 121st case	p
Sample size (n)	1278	671	296	161	150	
In-Hospital Mortality (%)	86 (6.8)	51 (7.6)	19 (6.5)	11 (7.0)	5 (3.4)	0.327
Major Vascular Complication (%)	93 (7.8)	61 (9.6)	22 (8.6)	9 (5.8)	1 (0.7)	0.002
Major or life-threatening Bleeding (%)	126 (10.6)	86 (13.6)	32 (12.6)	6 (3.8)	2 (1.4)	<0.001
Any stroke (%)	31 (2.5)	19 (2.9)	5 (1.8)	6 (3.8)	1 (0.7)	0.256
Myocardial infarction (%)	15 (2.3)	9 (2.2)	4 (2.5)	2 (3.3)	0 (0.0)	0.767
New Pacemaker (%)	120 (10.1)	59 (9.6)	34 (12.8)	14 (8.9)	13 (8.8)	0.417

6. ARTICLE 4

Title: New-generation Balloon-expandable versus New-generation Self-expanding valves for Transcatheter Aortic Valve Replacement: an analysis of the Brazilian RIBAC-NT registry

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New-generation Balloon-expandable versus New-generation Self-expanding valves for Transcatheter Aortic Valve Replacement: an analysis of the Brazilian RIBAC-NT registry

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Short Title: New generation balloon-expandable versus self-expanding valves in TAVR

Descriptors: Transcatheter Aortic Valve Replacement; Balloon-expandable valve; Self-expanding valve; Brazil.

ABSTRACT

Introduction: There has been conflicting data regarding clinical outcomes of transcatheter aortic valve implantation (TAVR) with balloon-expandable versus self-expanding valves. The goal of this study was to compare the in-hospital outcomes of TAVR performed with new-generation balloon-expandable valves (NGBEV) and new-generation self-expanding valves (NGSEV) valves in a real-world setting of a developing country.

Methods: Retrospective study using data from centers actively participating in the Brazilian TAVR registry. Inclusion criteria: all native tricuspid TAVR procedures using new-generation valves. Main exclusion criterion: transapical procedures. The cases were separated according to the prosthesis utilized in group NGBEV and NGSEV. Primary outcome was in-hospital death. Secondary outcomes: major vascular complication, major or life-threatening bleeding, any stroke, and new pacemaker implantation.

Results: A total of 1,703 patients from 25 centers were included in the analysis, 887 in the NGBEV and 819 in the NGSEV. Mean age was 80.7±7.2 years and 48.9% were women. The NGSE group had a higher proportion of female patients (53.5% vs. 44.6%, p=<0.001) and had more comorbidities with a higher Euroscore2 score (3.4 [2 – 6.4] vs. 4.5 [2.5 – 8.2], p<0.001). The Sapien S3/S3 Ultra (Edwards Lifescience, Irvine, CA, USA) and the Evolut R/PRO (Medtronic, Minneapolis, MN, USA) accounted for 97.8% and 72.6% of NGBEV and NGSEV cases, respectively. Pre- and post-dilation was more common for NGBEV (both p<0.001). Valve embolization, the need for a second valve, and coronary occlusion were rare but more frequent for NGSE. There was no difference in unadjusted in-hospital mortality (NGBEV=3.6% vs.

NGSEV=4.8%, p=0.27). There was also no significant difference between groups in vascular complications, bleeding, stroke, and the need for a new pacemaker. Logistic regression adjusting for sex, Euroscore2, and vascular access indicated similar odds of mortality between NGBEV and NGSEV (OR 1.22, p=0.4). Sensitivity analysis including only S3 and Evolut cases showed consistent results with the primary analysis.

Conclusion: In conclusion, in real-world all-comers TAVR patients, procedures performed with NGBEV and NGSEV had comparable in-hospital outcomes.

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has emerged as an alternative to traditional surgical aortic valve replacement for treating patients with severe aortic stenosis. Since the first-generation of devices, two major types of transcatheter heart valves (THV), the balloon-expandable (BE) and self-expanding (SE) valves, have been shown to be consistently effective in treating severe aortic stenosis patients with clinical outcomes comparable to surgery(16,17,26,27,102,103). New-generation THV have emerged since then for both types of prosthesis bringing several improvements with the goal of offering more reliable and safer procedures which has culminated in better clinical outcomes(95,104).

Despite different implant mechanisms, each with its own advantages and drawbacks, in previous comparison studies(105–107), there has never been a clear superiority between the two types of devices in terms of hard clinical outcomes. Recently, however, a controversial meta-analysis demonstrated an association between BE versus SE valves and decreased short-term mortality(108). However, this meta-analysis included both old- and new-generation THV studies, some of which are obsolete and no longer available commercially. Nonetheless, this study raised concerns regarding the potential clinical superiority of one device type over the other.

Therefore, the aim of this investigation was to compare in-hospital clinical outcomes in a real-world setting, including only patients undergoing TAVR with the new-generation balloon-expandable valves (NGBEV) and the new-generation self-expanding valve (NGSEV).

METHODS

Data from the Brazilian TAVR Registry (RIBAC-NT), an ongoing multicenter registry from Brazil organized and administered by the Brazilian Society of Hemodynamics and Interventional Cardiology (SBHCI), were utilized for the current study. The initial protocol of the registry has been previously published(41). In brief, participating institutions report all subsequent TAVR procedures through an online platform with remote central data monitoring. To extend the duration of the registry, a revised protocol was submitted and endorsed by the central ethical committee in 2020. All centers participating in the current study had approval of the updated registry protocol from their local ethical committees, which waived patients' informed consent because the study posed minimal risk to them.

Population and study design

For the current study, we retrospectively included all consecutive TAVR patients that received a new generation THV. **Table 1** lists the new-generation devices included in the analysis. Major exclusion criteria were patients with bicuspid aortic valve, valve in valve procedures, and procedures performed through transapical access. The indication of TAVR as well as the type of THV utilized and the vascular access option were entirely at discretion of the local heart team.

Patients were divided into two groups, NGBEV or NGSEV, according the type of THV implanted. Primary endpoint was in-hospital mortality. Key secondary outcomes were in-hospital major vascular complication, major or life-threatening bleeding, any

stroke, and the need for new pacemaker implantation. All outcomes were reported according to the VARC-2 criteria(73).

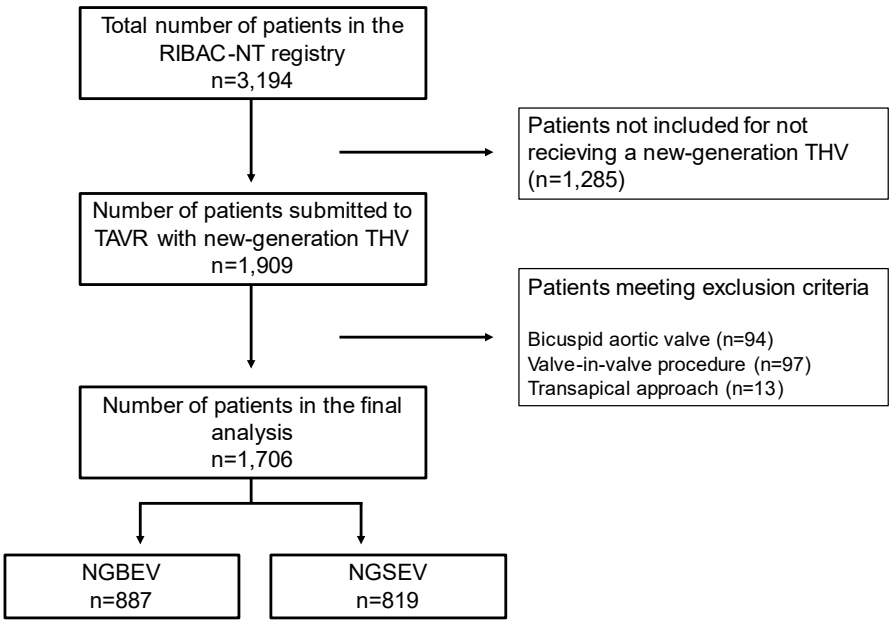
Statistical analysis

Baseline and procedural characteristics were compared between the groups, followed by unadjusted comparison of in-hospital outcomes. Categorical variables were reported as total numbers of events and percentages and compared with the Fischer´s exact test. Continuous variables were reported as mean ± standard deviation or median with interquartile range and compared with independent-samples T test or Mann-Whitney U test, as appropriate. Normality distribution of continuous variables was analyzed with Kolmogorov-Smirnov test and visually with histogram graphs. Logistic regression was then performed to assess the association of NGSEV versus NGBEV for in-hospital mortality adjusting for log transformed Euroscore 2 and vascular approach (transfemoral or non-transfemoral access). Non-normal distribution variables were transformed as appropriate for achieving near normality before inclusion in the model. A sensitivity analysis was planned to include only cases performed with the Sapien S3 and the Evolut R/PRO in the NGBEV and NGSEV, respectively, the two most commercially used TAVR devices in the world. There were less than 2% of missing data for the variables of interest and they were handed with simple imputation technique. There was no imputation of missing data for the type of THV implanted nor for in-hospital outcomes, as these cases were excluded for the final analysis. Statistical significance was considered for two-tail p values < 0.05. All analyses were performed with SPSS version 26 (IBM, Armonk, New York, USA).

RESULTS

Among all the 3,194 patients from 25 centers currently active in the Brazilian RIBAC-NT TAVR registry, 1,909 underwent TAVR with a new-generation THV between June 2014 to February 2023. After excluding patients with bicuspid aortic valve, procedures via transapical access, and valve-in-valve procedures, we ended up with 1,706 cases for the current study (figure 1). Of these, 887 underwent TAVR with a NGBEV and 819 with a NGSEV.

Figure 1. Flow-chart of patient selection for the current study.



Baseline and Procedural Characteristics

Tables 2 summarizes the baseline characteristics of the study population. Overall, the mean age was 80.7 ± 7.2 years, with no difference between the groups, and the

median Euroscore 2 was 3.8 (IQR: 2.1 to 7). In the NGSEV cases, there was a higher proportion of women (53.5% vs. 44.6%, p<0.001) and a higher prevalence of patients with peripheral artery disease and chronic obstructive pulmonary disease, culminating in higher Euroscore 2 for this group (P=0.01).

Regarding procedural characteristics, patients in the NGBEV had a higher proportion of procedures via the transfemoral route (99.4% vs. 96.8%, p<0.001) and with general anesthesia (60.4% vs. 50.1%, p<0.001). The Sapien S3 system was almost universally utilized as the NGBEV in our study, with only 2.3% of the cases employing the Myval system. For the NGSEV, the Evolut R and Pro devices was implanted in most cases (72.6%), followed by the Acurate Neo and Neo 2 (25.5%). The Portico valve was utilized in only 1.8% of the cases. Balloon pre and post dilation were considerably more frequent in cases performed with the self-expanding devices. The incidence of intraprocedural complications were overall small, but occurrence of valve embolization (0.3% vs. 0.9%, P=0.01), the need for a second valve (0.3% vs. 1.8%, p=0.003), and coronary occlusion (0.1% vs. 0.9%, P=0.03) all were significantly more frequent in the NGSEV group, albeit with small absolute differences. No difference was seen for annulus rupture, cardiac tamponade, and conversion to open surgery. Table 3 shows the detailed procedural data of the study.

Clinical Outcomes

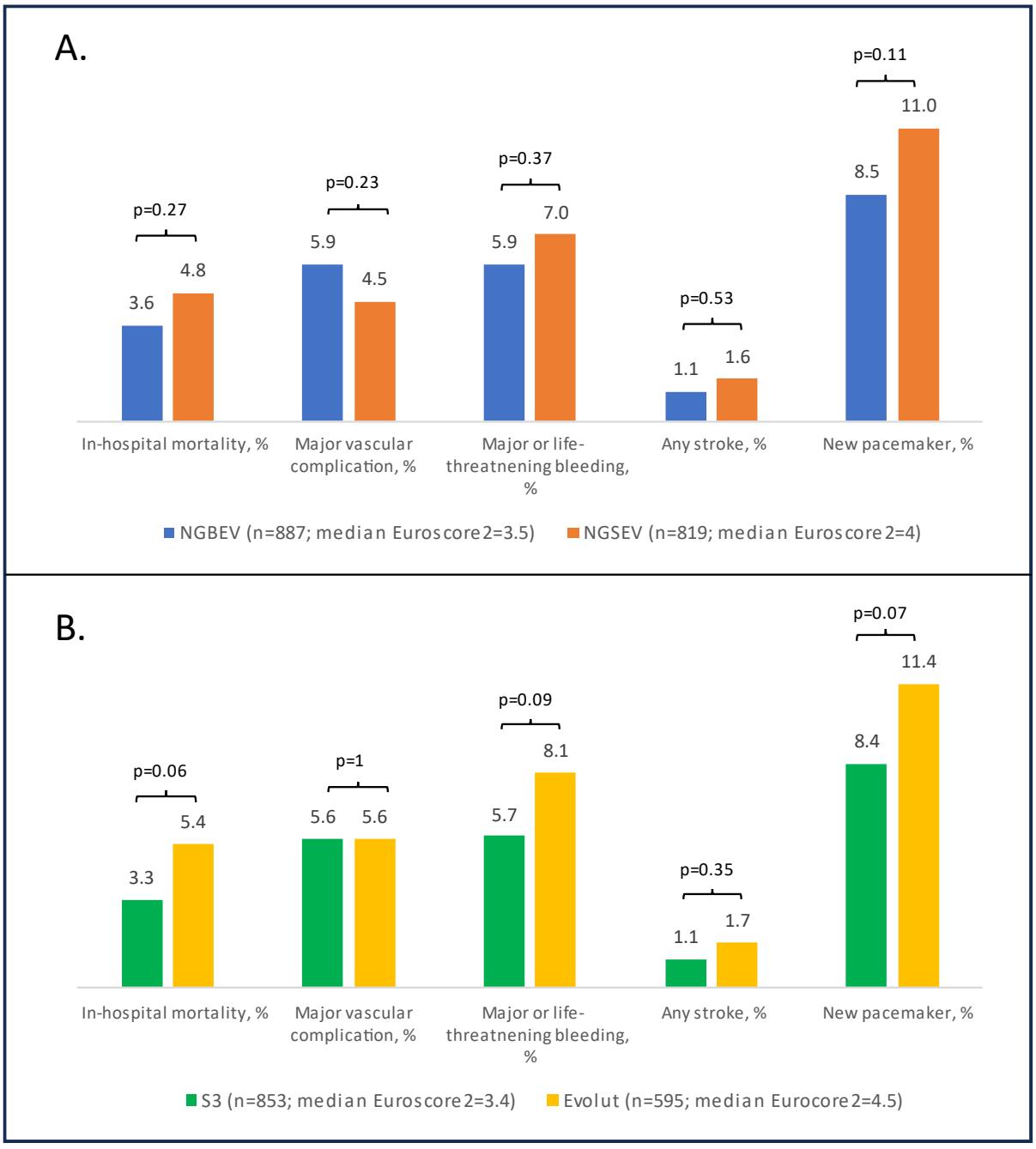
Unadjusted in-hospital mortality for the NGBEV and NGSEV were 3.6% and 4.8%, respectively, which did not meet statistical difference (p=0.27). Figure 2 depicts the comparison of the primary and secondary outcomes between groups. After adjusting for differences in log transformed Euroscore 2, gender, and vascular access, there

was no association of increased odds of mortality between patients in the NGSEV versus NGSEV (OR 1.21, 95% confidence interval, 0.75 to 1.97; p=0.43). Female sex and Euroscore 2 were independent predictors of in-hospital mortality (table 4). For the secondary outcomes, there was also no difference in the unadjusted rates of major vascular complications, clinically significant bleeding, all strokes, and the need for new pacemaker implantation.

Sensitivity analysis: S3 versus Evolut

In the sensitivity analysis, including only cases performed with the Sapien S3 (n=853) as NGBEV and the Evolut R and PRO (n=595) as NGSEV, we found consistent results with the study´s primary analysis. There were more women and higher median Euroscore 2 in the Evolut cases (supplemental table s1). No significant difference for the unadjusted in-hospital mortality was observed (3.3% vs. 5.4% for S3 and Evolut, respectively; p=0.06). After adjusting for sex, Euroscore 2, and vascular approach, there was no association of increased odd of death for the Evolut over the S3 (OR 1.5, 95% confidence interval, 0.89 to 2.5; p=0.13). We did not find either a significant difference for the secondary in-hospital outcomes as seen in figure 2. Like the primary analysis, there was more pre- and postdilation with the self-expanding system, along with a small but significant higher incidence of valve embolization, the need for a second valve, and coronary occlusion (supplemental table s2).

Figure 2. A) Unadjusted comparison of in-hospital outcomes between NGBEV and NGSEV; B) Sensitivity analysis comparing unadjusted in-hospital outcomes between Sapien S3 and Evolut devices.



DISCUSSION

In this real-world study from multiple centers in Brazil, we did not find a difference in in-hospital death between the use of NGBEV and NESEV in majority intermediate-risk patients undergoing TAVR for native tricuspid severe aortic stenosis. There was neither a difference in the incidence of major vascular complications, clinically significant bleeding, stroke, or new pacemaker implantation between the types of TAVR device.

Our study´s results discord with a recently meta-analysis showing higher short-term mortality with SE compared to BE devices(108). It is important to emphasize though, that there are several differences between the two studies. This metanalysis included patients enrolled in six randomized clinical trials mixing different generations of THV such as the Sapien XT (Edwards LifeScience, Irvine, CA, USA) and the Medtronic Corevalve (Medtronic, Minneapolis, MN, USA), two devices that are no more in clinical use and that have been upgraded to newer versions. On the other hand, our study is a retrospective analysis with data collected from a real-world national registry where only patients submitted to TAVR with new-generation valves were included. Secondly, the meta-analysis assessed 30-day all-cause mortality (2.2% for BE versus 4.5% for SE, RR: 0.51; 95% CI: 0.31–0.82; $p < 0.006$) while we assessed all-cause in-hospital mortality. Even though, 30-day and in-hospital events tend to be close, we cannot neglect the possibility of events occurring between patients discharge and the first 30 days of the procedure. Nevertheless, despite the disagreement in terms of difference in mortality, as observed in our investigation, the meta-analysis did not demonstrate a difference in early safety events such as vascular complications, bleeding, and stroke between the BE and SE valves.

Our findings go in line with other previous studies that sought to compare these two distinct mechanisms' of TAVR devices. The SOLVE-TAVI randomized clinical trial, which tested head-to-head the two most globally utilized NGBEV and NGSEV (Sapien S3 and Evolut R/PRO) enrolling 447 intermediate to high risk patients, showed that equivalence was met for short-term safety events, including 30-day mortality (2.3% vs. 3.2% for BE and SE, respectively, $p<0.0001$ for equivalence)(107). Due to the concerns highlighted by the aforementioned meta-analysis, despite the fact that a randomized trial had already been conducted on the subject, we deemed it necessary to evaluate the topic in a real-world setting by analyzing data from the Brazilian TAVR registry. Notably, the SOLVE-TAVI was a trial conducted in high-volume experience centers from Germany, which is vastly distinct to the reality of TAVR practice in Brazil, where centers perform far fewer procedures(90). This is particularly relevant because the two types of THV may have different learning curves, with the SE valves tending to take longer for centers to achieve a plateau of proficiency(101), which could have led to poorer outcomes in these lower volume and less experienced Brazilian centers.

Prior to the SOLVE-TAVI trial, the CENTER-collaboration study, mixed gathered data from 10 registries and clinical trials, in a sub-analysis comparing the new-generation valves, also showed comparable in-hospital mortality for the NGBEV and NGSEV, with rates of 2.4% and 3.1% ($p=0.14$), respectively(109). Nevertheless, in this systematic review, contrary to our findings, the authors reported higher rates of stroke and pacemaker implantation with the Evolut system, whereas the S3 had a higher incidence of major vascular complications, indicating that there are still conflicting data in the literature. Therefore, we believe our study contributes by providing additional evidence on the topic.

Despite comparable rates of in-hospital mortality and safety events, we did observe some differences in potentially catastrophic intraprocedural complications. There was an absolute small but significant higher rates of valve embolization and coronary occlusion with the NGSEV. Embolization of the device has always been a concern especially for the old generation BE valves that lacked the feature to recapture the prosthesis before final implantation. Even though most of the time an embolized valve can be handled satisfactorily by leaving it in the aorta and implanting a second device during the same procedure, studies have shown higher one-year mortality in patients where this complication ensued(85,110). Regarding coronary occlusion, contrary to our finding, SE valves have historically been associated with fewer events(111,112), with many interventionalists preferring them in unfavorable anatomy. Hence, due to the observational nature of our study, we cannot rule out a confounding bias, as it is possible that operators implanted an NGSEV rather than an NGBEV in cases considered to be of higher risk of coronary occlusion. Nonetheless, the rate of coronary occlusion was below 1% in our investigation, on par with the reported in the literature(111).

To evaluate the robustness of our results we performed a sensitivity analysis including the two most utilized valve in each group, the Sapien S3 and the Evolut R/PRO, both of which represent the prototypes of BE and SE TAVR devices. The S3 accounted for almost the totality of cases in the NGBEV group, whereas the Evolut R/PRO represented nearly three fourths of the NGSEV, while the Acurate Neo/Neo2 accounted for the other one fourth of cases. Only a fraction was made with the Portico prosthesis. Despite the fact that all of these valves are classified as SE, their implantation techniques and unique characteristics make it dubious to classify them as the same type of THV. Nevertheless, the findings of this sensitivity analysis were

consistent with the main study result, indicating that the valves had comparable in-hospital outcomes.

Our research has significant limitations. First, this is a retrospective observational study utilizing data from a real-world registry, with self-reported outcomes and no central adjudication. Even though standardized outcomes based on the VARC-2 criteria were used and all-cause in-hospital mortality was the primary endpoint, there could be inconsistencies in the reporting of events. In addition, our research was limited to hospital-based outcomes. There was also no comparison of devices' hemodynamic performance nor the assessment of paravalvular leak, both factors that may have a detectable clinical impact only in medium- to long-term follow-up.

In conclusion, in real-world all-comers TAVR patients, procedures performed with NGBEV and NGSEV had comparable in-hospital outcomes.

Table 1. New-generation transcatheter aortic valves included in the study.

NEW-GENERATION THV
Balloon-expandable
Sapien S3 and S3 Ultra (Edwards LifeScience, Irvine, CA, USA)
Myval (Meril Life Science, Gujarat, India)
Self-expanding
Evolut R and PRO (Medtronic, Minneapolis, MN, USA)
Acurate Neo and Neo 2 (Boston Scientific, Marlborough, MA, USA)
Portico (Abbott Structural Heart, St Paul, MN, USA)

THV = transcatheter aortic valve.

Table 2. Baseline characteristics of the study population.

	Overall (n=1,703)	**NGBEV** (n=887)	**NGSEV** (n=819)	**p**
Age, mean ± SD	80.7 ± 7.2	80.6 ± 7.3	80.8 ± 7.1	0.46
Female, %	48,9	44.6	53.5	<0.001
Diabetes, %	34.4	33.8	35	0.61
Atrial fibrillation, %	12.8	14.3	11.3	0.09
Previous pacemaker, %	8.3	8.5	8	0.78
Previous MI, %	12.3	10.9	13.7	0.1
Previous PCI, %	25.7	25.9	25.5	0.9
Previous CABG, %	13	12.5	13.6	0.54
Previous CerVasc, %	10.5	10	11	0.52
Previous Stroke, %	5.6	5.6	5.7	1
Previous PAD, %	13.5	11	16.2	0.002
COPD, %	14	11.5	16.8	0.002
Creatinine	1.31 ± 0.9	1.29 ± 0.9	1.32 ± 0.8	0.51
LVEF, mean % ± SD	59.8 ± 27	60.1 ± 37	60 ± 12	0.7
Euroscore 2, median (IQR)	3.8 (2.1 – 7)	3.5 (2 – 6.5)	4 (2.2 – 7.6)	0.01
Log(Euroscore 2), mean ± SD	1.8 ± 0.8	1.3 ± 0.8	1.4 ± 0.8	0.001

MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; CerVasc = cerebrovascular disease; PAD = peripheral artery disease; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; IQR = interquartile range.

Table 3. Procedural characteristics.

	Overall (n=1,703)	**NGBEV** (n=887)	**NGSEV** (n=819)	**p**
Transfemoral access, %	98.2	99.4	96.8	<0.001
General anesthesia, %	44.6	60.4	50.1	<0.001
Percutaneous access, %	94.1	98	90.1	<0.001
Valve brand				
S3, %		96.2	-	
S3 Ultra, %		1.6	-	
Myval, %		2.3	-	
Evolut R/PRO, %		-	72.6	
Acurate Neo/Neo2, %		-	25.5	
Portico, %		-	1.8	
Predilation, %	39.6	27.1	52.6	<0.001
Postdilation, %	27.9	19.4	36.7	<0.001
Valve embolization, %	0.9	0.3	1.6	0.01
Need of a 2nd valve, %	1.1	0.3	1.8	0.003
Coronary occlusion, %	0.5	0.1	0.9	0.03
Annulus rupture, %	0.5	0.7	0.2	0.29
Tamponade, %	2.4	2.6	2.1	0.52
Conversion to surgery, %	1.4	1.2	1.5	0.83

Table 4. Multivariable logistic regression for in-hospital mortality.

	OR	**IC95%**	**p**
NGSEV vs. NGBEV	1.22	0.75 – 1.97	0.43
Female vs. Male	1.87	1.14 – 3.09	0.01
Log (Euroscore 2)	1.56	1.16 – 2.08	0.003
TF vs. Non-TF approach	0.64	0.08 – 4.87	0.67

TF = transfemoral.

7. FINAL DISCUSSION

The main findings of this thesis, in light of evaluating the developments of TAVI practices and its LC in Brazil and Latin America, were as follows:

a) Relevant changes have been observed in TAVI practices within Latin American centers during the period of 2015 and 2020. Notably, a higher adoption of minimalist approaches as standard procedure has been noted, characterized by a higher prevalence of fully percutaneous vascular access techniques, an increased utilization of conscious sedation and local anesthesia as opposed to general anesthesia, and reduced use of transesophageal echocardiography in the perioperative phase. In comparison to centers from other worldwide regions, Latin American institutions exhibited a 5-fold lower annual procedure volume until 2015, with these less invasive techniques being notably less frequently employed as routine practices. This indicates a discernible progression in practices within the continent over recent years, aligning them more closely with the established standards upheld at reference centers across North America and Europe.

b) In a multicenter study with the participation of 12 centers from Latin America, where only new-generation repositionable self-expandable prostheses were evaluated, it was observed significantly elevated rates of procedural failure in cases requiring multiple repositioning, which was also associated with increased one-year mortality. In addition, an association was also identified between the annual volume of procedures and mortality. Centers characterized by a lower annual caseload involving these specific prostheses (< 25 cases per year) emerged as independent predictors of mortality.

c) Throughout the history of TAVI in Brazil, spanning the years 2008 to 2023, a notable association was observed between the accumulated experience within 25 institutions across the country and a reduction of in-hospital mortality, thus indicating the presence of a LC phenomenon. However, this LC was more pronounced in centers that initiated their TAVI programs at an earlier stage, a period when more invasive techniques and earlier-generation valve prostheses were employed. In centers that started their TAVI programs at a later stage, there was a higher proportion of employing less invasive techniques as well as a greater utilization of new-generation valve prostheses. Within these institutions, lower rates of mortality were observed during their initial experience, albeit with minimal improvement observed with the accumulation of experience, suggesting a mitigated LC that might be related to the low procedural volume at these centers.
d) In a study involving 1,703 patients from the Brazilian TAVI registry, the utilization of new-generation balloon-expandable valves (NGBEV) and new-generation self-expanding valve (NGSEV) had comparable in-hospital outcomes, including in-hospital mortality.

Implications

TAVI is a disruptive treatment that has revolutionized the management of aortic valve stenosis worldwide. This thesis makes a significant contribution to understanding the reality of TAVI in the Latin American continent, with a particular focus on Brazil. It represents the most comprehensive investigation evaluating the development of TAVI practices throughout its history in the country. The results presented in this thesis offer essential insights to inform the continuous advancement of the revolutionary treatment

for aortic valve stenosis, particularly within the current context of Brazil. This significance is further amplified as the public healthcare system has recently integrated TAVI into its roster of covered medical procedures.

In line with the existing international literature(113), our study findings offer compelling evidence that Brazilian and Latin American institutions have effectively been embracing contemporary, benchmarked TAVI practices. Specifically, our observations reveal a notable increase in the utilization of less invasive techniques and the universal adoption of new-generation transcatheter heart valves. The integration of less invasive techniques, such as fully percutaneous vascular access methods and conscious sedation coupled with local anesthesia, aligns with the global trend of minimizing the invasiveness of the TAVI procedures. By employing these approaches, institutions in Brazil and Latin America are adhering to the best practices. Furthermore, the adoption of new-generation devices implies a commitment to staying at the forefront of technological advancements in the field. By embracing these innovations, Brazilian and Latin American institutions demonstrate their readiness to provide state-of-the-art care to patients with aortic valve stenosis in line with the established standards upheld at reference centers across North America and Europe.

The significance of these findings extends beyond the clinical realm. Policymakers can find reassurance in the active engagement of the regional specialized community in the ongoing development and progression of the TAVI field. The willingness of these institutions to embrace contemporary practices reflects a commitment to staying abreast of global standards and ensuring the highest level of care for patients. By actively adopting contemporary, benchmarked practices, Brazilian and Latin American institutions are making significant strides in advancing the TAVI field within their respective healthcare systems. These efforts can contribute to the overall

improvement in patient outcomes, the advancement of clinical knowledge, and the strengthening of the region's expertise in the field.

Nonetheless, it is crucial to acknowledge the substantial disparities between our reality and that of high-income nations, making it highly improbable to achieve parity in the near future, particularly in terms of the volume of TAVI procedures performed. The present thesis (90) highlights that the annual median number of cases conducted in Latin American centers in 2015 was five times lower compared to North American and European centers (12, 5–23 vs. 60, 27–110). A subsequent reassessment of Latin American centers after a five-year period revealed an increase in the annual median to 16 (IQR 6 to 30), suggesting that the majority of TAVI-performing centers in our region operate as low-volume institutions. This thesis also incorporates a study (110) indicating that for new generation self-expanding prostheses, a low annual procedure volume, defined as fewer than 25 cases per year, emerged as an independent predictor of one-year mortality. These findings are in line with recent international literature (54) which demonstrates a negative correlation between a low number of centers and adverse clinical outcomes and mortality. Consequently, genuine concerns arise regarding the potential detrimental impact on clinical outcomes for patients undergoing TAVI in these less experienced centers.

Given the aforementioned considerations, a dilemma arises regarding whether the establishment of new TAVI centers should be encouraged and how the training and certification process should be conducted. Despite this dilemma, the reality is that there are several reasons to promote the expansion of TAVI in the country, including:

a) The number of procedures per capita remains low in Brazil and other Latin American countries, approximately 10 to 15 times lower than that observed in countries such as the United States of America, France, and Germany(55).

b) Currently, in Brazil, there is an immediate need to increase access to TAVI as many symptomatic individuals with significant aortic stenosis are ineligible for SAVR and are deprived of appropriate treatment. According to Queiroga et al., in 2019, it was estimated that Brazil had 9,300 to 12,000 patients eligible for TAVI(93).

c) Latin American countries are experiencing a significant demographic shift, with a projected doubling of the elderly population by 2050, which will inevitably lead to an increase in degenerative cardiovascular diseases, particularly aortic stenosis(57).

d) In a vast continental country like Brazil, restricting TAVI to major centers would pose difficulties in the access of treatment. It should be considered that TAVI candidates are typically elderly individuals with comorbidities that limit long-distance travel.

Additionally, TAVI is a procedure that requires not only the intervention itself but also adequate planning through multiple imaging examinations such as echocardiography, computed tomography angiography, and coronary cineangiography, as well as multidisciplinary evaluation. Pre-procedural assessment is crucial, and appropriate post-discharge follow-up is essential to identify potential complications such as paravalvular leak, conduction disturbances, arrhythmias, and prosthesis thrombosis, for instance.

Therefore, it is reasonable to think that to meet this growing demand, more professionals need to be trained, and additional TAVI centers need to be established.

This will ensure that patients receive timely and accessible care while addressing the specific challenges associated with TAVI.

The establishment of novel TAVI centers introduces a critical phase of LC which has implications for the achieved clinical outcomes. Effectively managing the impact of this LC poses a substantial challenge in the field. However, the findings from the present investigation shed light on this area of inquiry, offering significant insights where it showed that the attainment of proficiency in TAVI procedures appears to be optimized after a threshold of approximately 120 cases, with discernible enhancements in outcomes becoming apparent subsequent to the initial treatment of 40 patients.

Despite the acknowledged importance of the LC in TAVI centers over a period of almost 15 years in Brazil, which correlated with a decline of in-hospital mortality rates as the centers accumulated experience, a distinct deviation in the LC pattern emerged among centers that adopted TAVI at a later stage. Pioneering institutions that embraced TAVI before 2014 demonstrated a pronounced LC effect, marked by a notable decrease of in-hospital mortality as their initial experience grew. In contrast, centers that initiated the procedure later, specifically those performing their first 40 cases after 2014 – the year that new-generation valves started being utilized – displayed a diminished impact of cumulative case experience on in-hospital mortality. Despite initially achieving superior outcomes, these centers made limited progress in reducing in-hospital mortality, indicating a nearly negligible LC effect. Although a definitive explanation for this LC stagnation cannot be achieved by our findings, one plausible factor is the low procedural volume conducted by these centers during the analyzed period. This aligns with existing literature suggesting an association between procedural volume and improved clinical outcomes of TAVI (34,36,37,82). In our case,

it is conceivable to hypothesize that the low case volume has impeded the enhancement of outcomes during the LC phase in these centers.

These findings underscore the importance of carefully considering the implications for future TAVI planning, particularly in terms of procedure expansion and the establishment of new centers. They provide valuable insights that can inform the development of public health policies aimed at defining the minimum number of procedures an institution must perform to achieve excellence in outcomes and become a recognized TAVI reference center. Furthermore, these findings offer guidance on the minimum annual procedural volume these institutions should maintain to optimize their clinical outcomes. By taking into account these considerations, the TAVI field in the Latin America reality can progress toward more effective and standardized practices, ultimately benefiting patient care and outcomes.

Final considerations

The studies encompassed within the present thesis demonstrate notable limitations. All of these studies are characterized by an observational and retrospective nature, making them susceptible to inherent biases. Furthermore, these studies were conducted exclusively within a subset of TAVI centers located on the continent. For example, the studies involving the Brazilian TAVI registry included the participation of 25 centers, however, it is presently estimated that over 200 institutions in the country are currently performing this procedure. The same hold true for the studies that had participation of TAVI centers from other Latin American countries. Consequently, it is crucial to acknowledge that the results presented in this thesis represent merely a sample of the total hospitals conducting TAVI in the continent and the participating

centers in the are those whose operators possess a greater level of engagement with the scientific community. Therefore, it is plausible that the findings obtained may not entirely encompass the current situation of the procedure within our reality. Nevertheless, despite these limitations, this compilation of articles constitutes the most comprehensive analysis of TAVI to date, involving the largest number of patients and centers ever published in Brazil and Latin America.

Moreover, continuous monitoring of TAVI practices is of utmost importance due to its substantial cost and potential for significant impact on public health. This is particularly crucial when considering the already existing pent-up demand and the anticipated increase in demand resulting from expected population aging. Additionally, the field of transcatheter heart therapies, with TAVI being a prominent example, is constantly and rapidly evolving. Therefore, regular assessment is necessary to ensure adherence to the best practices in this rapidly advancing field. However, it is imperative to develop strategies that aim to establish universal inclusion of institutions performing TAVI in national or even multi-national registries. This can be achieved through collaborative efforts between countries and medical societies, which will ensure greater external validity of future study results. By encompassing a broader range of participating institutions, such strategies would enhance the reliability and generalizability of findings derived from subsequent researches, while concurrently fostering opportunities to enrich the scientific literature within the continental context.

8. CONCLUSIONS

In Brazil and Latin America, the practices of TAVI have been progressively evolving to a higher incorporation of techniques that prioritize minimizing the invasiveness of the procedure. This evolution is accompanied by a widespread adoption of the latest generation transcatheter heart valve devices by local centers. These changes demonstrate a notable alignment with the established standards maintained by benchmark centers worldwide, emphasizing the commitment of Brazilian and Latin American institutions to deliver TAVI procedures that adhere to global best practices.

Also, the utilization of new-generation valves has been an independent factor associated with a reduction of in-hospital mortality. Importantly, no significant differences in clinical outcomes were observed between the two types of new-generation devices used, whether balloon-expandable or self-expanding. This finding underscores the significance of advancing TAVI practices in the continent, highlighting the direct impact on enhancing the clinical outcomes of patients undergoing this procedure.

Finally, throughout the history of TAVI in Brazil, a LC phenomenon was observed concerning in-hospital mortality. The optimal number of procedures required to achieve proficiency appears to be approximately 120 cases, with noticeable improvements in outcomes observed after the first 40 treated patients. However, this LC effect was less pronounced in centers that initiated their TAVI programs at a later stage. The exact reasons for this shift in the pattern of the TAVI LC cannot be definitively concluded but are likely influenced by multiple factors. These factors may include the adoption of more advanced TAVI practices by new centers, resulting in

favorable initial outcomes that reduce the magnitude of subsequent improvements as experience accumulates, which can be seen as a positive aspect. Conversely, the observed stagnation in the initial LC must be regarded as a negative factor, potentially attributable to the limited number of procedures performed in these centers. The lower procedural volume encountered in such settings may delay the achievement of proficiency and impede the progression towards improved outcomes. Although our investigation does not yield definitive conclusions regarding this matter, it underscores the intricate interplay of factors that influence the LC in TAVI programs.

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APPENDIX

SUPPLEMENTARY MATERIAL – ARTICLE 1

Table of Contents:

Supplemental Table 1: Online questionnaire (http://www.cardiogroup.org/TAVI)

Question
What is your speciality?
General cardiologist
Interventional cardiologist
Cardiac Surgeon
Imaging Cardiologist
Research Fellow
Coordinator of TAVI program
Other
When was the first transcatheter valve implanted in your institution? (year)
How many TAVI procedures have been performed in your institution to date?
How many TAVI procedures were performed in your Institution last year? (number):
Does your local or central health care system place an annual limit on the number of TAVI you can perform
yes
no
if yes, specify numbers per year
How long is your average patient waiting time to receive a TAVI? (months)
Approximately what percentage of your TAVI candidates are:
patients with a contraindication or prohibitive risk for cardiac surgery
patients at high surgical risk
patients at moderate surgical (STS score 4-8):
patients at low surgical risk (STS score < 4):

From your initial evaluation, how many patients are turned down for TAVI in your institution?

<10%

10-20%

20-30%

>30%

How many heart team meetings to discuss potential TAVI candidates are scheduled in your institution in a month? (number)

Who usually attend the heart team meeting?

General Cardiologist

Interventional Cardiologist

Cardiac surgeons

Internist/Geriatrician

Radiologist

Anesthesiologist

Other referral physician

Other

Which surgical risk score do you usually use? (choose all that apply, absolute count)

STS

Euroscore I

Logistic-Euroscore

Euroscore II

Parsonnet

None

Other: Lately Observant score

Other: Survival posT Tavi score (STT)

Do you regularly perform frailty tests?

No

Yes (overall)

Do you regularly perform quality of life tests?

No

Yes

Which examinations are routinely performed before TAVI?

TEE-2D

TEE-3D

Aortography

Femoral angiography

Femoral angio-CT

Cardiac-CT

Which method is your gold standard for aortic annulus assessment?

TTE

TEE-2D

TEE-3D

Cardiac-CT

Do you regularly perform 6-minute walk test?

yes

no

In which cases do you usually administer dual antiplatelet therapy before the procedure

Transfemoral approach

Transapical approach

Subclavian approach

Transaortic approach

In no case

In case of severe coronary artery disease (proximal lesions in main coronary arteries do you usually perform PCI and if so when:

Before the TAVI

During the index procedure

We do not usually revascularize

Sometimes before, sometimes at the index procedure

we usually perform a FFR (or iFR) guided PCI

Do you usually administer antibiotic prophylaxis before TAVI?

No

yes, 1 dose before only

Yes, 1 dose before and 2 doses after TAVI

Other protocol

In patients at risk of coronary obstruction, the TAVI procedure is generally:

Contraindicated

Done with the use of a PCI protection wire

We prefer to use self-expandable valve in these cases

Nothing, we perform the procedure as usual

<u>Part 2. Procedural management</u>

Which approaches are currently performed in your institution? (specify percentages for each approach)

Transfemoral

Transapical

Transaortic

Subclavian

Carotid

Other

Which criteria do you follow to choose a non-transfemoral approach?

If ilio-femoral access is adequate, all patients are referred for a transfemoral approach

Some TAVI candidates are referred for non-transfemoral approach even if ilio-femoral arteries are adequate

Most TAVI candidates are referred for non-transfemoral approach even if ilio-femoral arteries are adequate

In your Institution, TAVI is performed in: (choose all that apply)

Operating Room

Cath lab

Hybrid room

Is there an anaesthesiologist to assist and support with transfemoral/subclavian cases?

yes

no

Please indicate the percentage (%) of anaesthesia used for transfemoral/subclavian approach

General

Local

Do the cardiac surgeons regularly assist in transfemoral procedures in your institution?

yes

no

If the cardiac surgeon assists, who is the primary operator for transfemoral cases?

Interventional cardiologist in all cases

Interventional cardiologist in most cases

Cardiac surgeon in all cases

Cardiac surgeon in most cases

Interventional cardiologist in half of the cases and cardiac surgeon in the other half

Do the interventional cardiologist regularly assist in transapical/transaortic procedures in your institution?

yes

no

If the interventional cardiologist assists, who is the primary operator for transapical/transaortic cases?

Interventional cardiologist in all cases

Interventional cardiologist in most cases

Cardiac surgeon in all cases

Cardiac surgeon in most cases

Cardiac surgeon in half of the cases and interventional cardiologist in the other half

Do the operator/s performing TAVI, has/have previous experience with structural interventional cardiology procedures?

yes

no

Do you use transesophageal echocardiogram to guide the procedures?

Yes, we always perform TEE during the procedure

Only in certain patients

Never

What kind of arterial access do you use for aortogram injections and pressure monitoring?

Femoral access

Radial access

Femoral or radial access as appropriate depending on patient s characteristics

Other

The vascular access for the transfemoral approach is usually performed with:

Surgical cut-down

Percutaneous approach

If performed percutaneously, please specify the type closure device routinely used:

Prostar

Two Perclose

One Perclose

Two Proglide

three Proglide

If performed percutaneously, do you routinely leave a protecting guidewire in the therapeutic femoral artery from the contralateral artery?

Always

Never

Only in case of challenging ilio-femoral access

If performed percutaneously, during access closure:

I routinely use a peripheral balloon

just in case of a complication

If performed percutaneously, in case of femoral perforation:

I usually implant a Self-expandable covered-stent by yourself

I usually implant a Balloon-expandable covered-stent by yourself

I am usually assisted by vascular surgeons

I am usually assisted by an interventional radiologist

What kind of valve do you use? (indicate % of use for each valve)

Self-expandable (%)

Balloon-expandable (%)

Inflatable (%)

What kind of valve do you use? (choose all that apply)

Corevalve System

Edwards Valve

Acurate (Symetis)

Centera

Directflow

Engager

Heart Leaflet technology

Jena Valve

Lotus

Portico

Other

Do you routinely perform balloon valvuloplasty as "predilatation": (choose all that apply)

For self-expandable valve

For balloon-expandable valve

For both balloon and self-expandable valves

In no case

Do you use embolic an protection device?

No

Yes, in selected cases

Yes, in all cases

How do you assess aortic regurgitation immediately after valve implantation? (choose all that apply)

TTE

TEE

Aortography

Hemodynamic assessment

In case of discrepancy, which method is your gold standard for aortic regurgitation assessment?

TTE

TEE

Aortography

Hemodynamic assessment

What kind of anticoagulation do you administer during the procedure?

Heparin non-ACT (Activated Clotting Time) guided

Heparin ACT (Activated Clotting Time) guided

Bivalirudin

low-molecular-weight heparins

Part 3. Post-procedural

For how long is telemetry maintained after TAVI?

12 hr

24 hr

48 hr

72 hr

>72 hr

How long is the temporary pacemaker maintained after self-expandable valve implantation (if no AV-block or new conduction disturbance occurs)?

Always removed at the end of the procedure

At least 12 hr

At least 24 hr

At least 48 hr

Do not have a standardized protocol (clinical judgment patient-by-patient)

How long is the temporary pacemaker maintained after balloon-expandable valve implantation (if no AV-block or new conduction disturbance occurs)?

Always removed at the end of the procedure

At least 12 hr

At least 24 hr

At least 48 hr

Do not have a standardized protocol (clinical judgment patient-by-patient)

How do you usually manage a transient A-V block occurring during <u>self-expandable</u> valve implantation?

Direct permanent pacemaker implantation.

Temporary pacemaker and watch. Pacemaker is implanted if AV block re-appears.

The decision depends on the existence of prior conduction disorders.

None

Other

How do you usually manage a transient A-V block occurring during <u>balloon-expandable</u> valve implantation?

Direct permanent pacemaker implantation.

Temporary pacemaker and watch. Pacemaker is implanted if AV block re-appears.

The decision depends on the existence of prior conduction disorders.

None

Other

How do you usually manage a complete left bundle branch block occurring after <u>self-expandable valve implantation?</u>

Temporary transvenous pacing followed by permanent pacemaker implantations

Temporary transvenous pacing for 24-72 hours followed by permanent pacemaker implantation if LBBB persists.

Temporary transvenous pacing, watch and wait for other pacemaker indication

EKG telemetry during the period of hospitalization, and watch and wait for other pacemaker indication

Pacemaker implantation guided by EP study

Transcutaneous loop recorder before the discharge

Usual post-op management

Other

How do you usually manage a complete left bundle branch block occurring after balloon-expandable valve implantation?

Temporary transvenous pacing followed by permanent pacemaker implantations

Temporary transvenous pacing for 24-72 hours followed by permanent pacemaker implantation if LBBB persists.

Temporary transvenous pacing, watch and wait for other pacemaker indication

EKG telemetry during the period of hospitalization, and watch and wait for other pacemaker indication

Pacemaker implantation guided by EP study

Transcutaneous loop recorder before the discharge

Usual post-op management

Other

Part 4. Follow-up

Do you have a specific TAVI clinic?

Yes

No

If yes, who is responsible of it? (choose all that apply)

Interventional Cardiologist

Cardiac Surgeon

General Cardiologist

Other

If no, who is responsible for the patient's follow-up care? (choose all that apply)

Interventional Cardiologist

Cardiac Surgeon

General Cardiologist

Referral physician

First visit at 1-month with the physician who performed the procedure and referral physician afterwards

Other

What are the time points for follow-up visits?

1 month

1 month and 1 year

1 month, 1 year and yearly thereafter

1 month, 6 months, 1 year, and yearly thereafter

1 month, 3months, 6 months, 1 year, and yearly thereafter

1 month, 3months, 6 months, 9 months, 1 year, and yearly thereafter

Which is your schedule for echocardiographic follow-up?

1 month

1 month and 1 year

1 month, 1 year and yearly thereafter

1 month, 6 months, 1 year, and yearly thereafter

1 month, 3months, 6 months, 1 year, and yearly thereafter

1 month, 3months, 6 months, 9 months, 1 year, and yearly thereafter

What is your usual antithrombotic therapy at hospital discharge with no other indication for anticoagulant therapy? (choose all that apply)

Aspirin

Clopidogrel

Ticagrelor

Warfarin / Acenocoumarol

Other

In case of dual antiplatelet therapy, how long do you maintain it for:

Not applicable

1 month

3 months

6 months

12 months

Permanent

What is your usual antithrombotic therapy at hospital discharge when an other indication for anticoagulant therapy is present? (choose all that apply)

Warfarin/acenocoumarol alone

Warfarin/acenocoumarol + Aspirin

Warfarin/acenocoumarol + Clopidogrel

Warfarin/acenocoumarol + Aspirin + Clopidogrel

Other

Supplemental Table 2. List of the countries and cities from the participating centers from the 2015 WRITTEN survey

2015 Latin American Centers

Country	City	Country	City
Brazil	Curitiba	Brazil	Sao Paulo
Brazil	Rio De Janeiro	Brazil	Porto Alegre
Brazil	Joinville	Brazil	Porto Alegre
Brazil	Salvador	Colombia	Cali
Chile	Santiago	Colombia	Medellin
Brazil	Curitiba	Argentina	Buenos Aires
Venezuela	Caracas	Panama	Panama City
Brazil	Porto Alegre	Trinidad and Tobago	Port of Spain
Brazil	São Paulo	Argentina	Buenos Aires
Brazil	Salvador	Mexico	Mexico City
Brazil	São Paulo	Argentina	Buenos Aires
Mexico	Guadalajara	Chile	Santiago
Brazil	Belo Horizonte	Argentina	Cordoba
Brazil	Sao Paulo	Brazil	Porto Alegre
Mexico	Mexico City		

2015 World centers

Country	City	Country	City
United Kingdom	Middlesbrough	Netherlands	Breda
Canada	Sherbrooke	USA	Cleveland
USA	Pontiac	USA	Sacramento
Japan	Osaka	France	Paris
Spain	Tenerife	Spain	Madrid
Italy	Brescia	Switzerland	Lucerne
Canada	Edmonton	France	Annecy
USA	Kalamazoo Michigan	USA	Seattle
USA	Houston	France	Rennes
Denmark	Aalborg	France	Paris
France	Saint Etienne	Finland	Helsinki
Spain	Toledo	Denmark	Odense
Spain	Bilbao	France	Dijon
Spain	Madrid	Germany	Hamburg
Spain	Alicante	France	Toulouse
Spain	Alicante	France	Tours
Spain	Badajoz	Italy	Siena
Canada	Hamilton	Italy	Parma
Spain	Seville	USA	Springfield, IL
Italy	Cagliari	France	Bordeaux
USA	Wilkes Barre	Switzerland	Zurich
USA	Stamford	Switzerland	Zurich
Spain	Madrid	USA	New Haven

Switzerland	Aarau
USA	Peoria
Spain	Madrid
USA	Knoxville
South Africa	Somerset West
Estonia	Tartu
Spain	Barcelona
Switzerland	Bern
Belgium	Liege
Spain	Santander
Spain	Barcelona
Spain	Valencia
Germany	Muenster
Canada	Halifax
Spain	Barcelona
Spain	Badalona
USA	Augusta
Spain	Majadahonda
Netherlands	Amsterdam
USA	Little Rock
France	Rouen
United Kingdom	Oxford
Italy	Mercogliano
USA	New York
USA	Sacramento
United Kingdom	London
Finland	Oulu
USA	Portland
USA	Boston
Germany	Hamburg
FRANCE	METZ
Australia	Brisbane
USA	Lincoln
France	Besancon
Netherlands	Leiden
Italy	Bari
New Zealand	Auckland
USA	Seattle
Spain	Valencia
France	Brest
USA	Atlanta
Ireland	Dublin
USA	Chicago
USA	Plano, Texas
USA	Cape Girardeau, MO
Canada	Toronto
Norway	Oslo
France	Saint Denis
USA	New York
USA	Sacramento
Germany	Bad Krozingen
USA	Fargo
France	Grenoble
France	Lyon
Netherlands	Rotterdam
USA	Washington DC
France	Reims
United Kingdom	Leeds
Germany	Munich
USA	Chapel Hill
France	Toulouse
USA	Baltimore, MD
Netherlands	Nieuwegein
France	Villeurbanne
Sweden	Lund
Poland	Katowice
Italy	Catania
Switzerland	Zurich
Poland	Katowice
Spain	Cadiz
Israel	Petach Tikva
Italy	Turin
Spain	Leon
Singapore	Singapore
USA	Boston
USA	Houma
Canada	Montreal
USA	New York
Canada	Ottawa
Canada	Toronto
Holland	Amsterdam
France	Bois Bernard/Lens
Spain	Madrid
Germany	Bonn
Taiwan	Taipei
Switzerland	Lausanne
Netherlands	Leeuwarden
USA	Grand Rapids
USA	Boston
Spain	Valladolid
Italy	Turin
Spain	Vigo
Spain	Zaragoza
Switzerland	Geneva
Spain	Salamanca
Italy	Brescia
Spain	Oviedo
Spain	Barcelona
Italy	Monza
Spain	Malaga
Spain	Benidorm
Norway	Feiring
China	Chengdu
China	Sahnghai
Finland	Turku
Canada	Victoria BC
Netherlands	Amsterdam
Italy	Mantova

Norway	Oslo
Germany	Munchen
USA	Lansing, Michigan
Italy	Padova
France	Marseille
USA	Danbury
Latvia	Riga
USA	Stony Brook
USA	Chicago
France	Nantes
France	Massy
France	Massy
France	Lille
Canada	Montreal
USA	New York
Canada	Quebec
USA	Valhalla
Spain	Madrid
USA	San Francisco
Germany	Bad Segeberg
Italy	Bologna
USA	Tulsa
USA	Cleveland
USA	Philadelphia
France	Poitiers
Belgium	Brussels
France	Strasbourg
France	Limoges
USA	Kansas City
France	Caen
Switzerland	Basel
USA	Portland, OR
France	Amiens
Italy	Rome
USA	Norfolk
USA	Boston
Italy	Mantova
Italy	Torino
Spain	Huelva
Spain	Granada
Spain	Almeria
Iceland	Reykjavik
Spain	Albacete
Denmark	Copenhagen
Spain	Madrid
Canada	New Westminster
Czech Republic	Usti nad Labem
Spain	Oviedo
Spain	Burgos
Spain	Malaga
Belgium	Liege
France	Metz
France	Angers
Spain	Madrid
France	Mulhouse
Canada	London
Italy	MILAN
Australia	Geelong
Italy	Milan
USA	Washington, DC
Poland	Warsaw
Spain	Barcelona
Lithuania	Vilnius
Switzerland	Bern
USA	Boston
USA	Cincinnati
France	Paris
France	Toulouse
USA	Cincinnati
France	Paris
France	Toulouse

Supplemental Table 3. List of the countries and cities from the participating centers from the 2020 WRITTEN LATAM survey

Country	City	Country	City
Brazil	Concordia	Brazil	Chapecó
Brazil	São Paulo	Brazil	Salvador
Brazil	São Paulo	Brazil	Porto Alegre
Brazil	São Paulo	Brazil	Passo Fundo
Brazil	Campinas	Brazil	Rio de Janeiro
Brazil	Goiania	Brazil	Salvador
Brazil	Sao Paulo	Brazil	Teresina
Brazil	Rio de Janeiro	Argentina	Capital Federal
Brazil	Itajai	Mexico	Mexico City
Brazil	Marília	Argentina	Buenos Aires
Brazil	Recife	Chile	Santiago
Brazil	Goiania	Chile	Santiago
Brazil	Cascavel	Brazil	Goiania
Brazil	Belo Horizonte	Brazil	Porto Alegre
Brazil	Florianopolis	Mexico	San Luis Potosi
Brazil	Sao Jose	Uruguay	Montevideo
Brazil	Caxias do Sul	Puerto Rico	Cayey
Brazil	Porto Alegre	Mexico	Mexico City
Brazil	Fortaleza	Argentina	Santiago del Estero
Argentina	Rosario	Brazil	Cuiabá
Brazil	Curitiba	Brazil	São Paulo
Brazil	Londrina	Brazil	Sao Paulo
Brazil	Joinville	Brazil	Belém

Supplemental Table 4. Comparison of answers regarding pre-procedural evaluation process between LATAM and WORLD centers.

Question	LATAM 2015 (N=29)	WORLD 2015 (N=221)	P value	LATAM 2020 (N=46)	P value[#]
Number of total procedures (median, IQR)	34 (12-101)	200 (84-452)	<0.001	61.5 (22-138)	0.08
Number of procedures in the last year (median, IQR)	12 (5-23)	59.5 (27-110)	<0.001	16 (5.7-30)	0.29
Year of the first TAVI (median)	2011	2009	0.004	2013	0.03
Presence of annual limit for TAVI procedures from the local health care system (% centers)	83%	52%	0.001	15%	<0.001
Median average waiting time for TAVI (months)	2	1	0.13	1.75	0.87
Heart team meeting schedule for TAVI discussion monthly (median)	1 (1-2)	4 (2-4)	0.001	1.5 (1-4)	0.27
Participants in Heart Team meetings (% centers)					
General cardiologist	78%	61%		86%	
Interventional cardiologist	96%	99%		95%	
Cardiac surgeon	96%	98%		88%	
Internist/Geriatrician	18%	12%		16%	
Radiologist	33%	20%		28%	
Anesthesiologist	26%	40%		30%	
Median waiting time for TAVI (months)	2	1	0.13	1.75	0.87
Percentage of centers where:					
≥50% of patients are intermediate or low risk	7%	14%		24%	
20-50% of patients are intermediate or low risk	28%	34%	0.24	37%	0.05
<20% of patients are intermediate or low risk	65%	47%		39%	
Patients turned down for TAVI (% centers)					
<10%	41%	34%		54%	
10-30%	31%	54%	0.006	37%	0.09
>30	28%	8%		9%	
Surgical risk score usually used (% centers)					
STS score	90%	69%	0.03	98%	0.29
Euroscore I	65%	50%	0.13	15%	<0.001
Logistic Euroscore	55%	39%	0.11	22%	0.006
Euroscore II	45%	40%	0.69	65%	0.46
Regularly perform frailty tests (% centers)	28%	47%	0.07	39%	0.33
Regularly perform quality of life tests (% centers)	10%	31%	0.03	11%	1.0
Regularly perform 6-minute walk test (% centers)	19%	23%	0.34	11%	0.72
Exams routinely performed before TAVI (% centers)					
TEE	90%	55%	<0.001	63%	0.01
Aortography	55%	53%	1.0	26%	0.01
Femoral angiography	38%	52%	0.16	24%	0.2
Femoral angio-CT	93%	76%	0.05	89%	0.59
Cardiac CT	97%	89%	0.32	100%	0.38
Gold standard for aortic annulus assessment (% centers)					
TTE or TEE	0	10.8%	0.34	0	1.0
Cardiac-CT	100%	89.2%		100%	
DAPT before transfemoral approach (% centers)	83%	45%	<0.001	56%	0.02
DAPT before non-transfemoral approach	34%	18%	0.05	24%	0.42
Time of PCI when severe coronary disease (% centers)					
Before the TAVR	72%	81%	0.32	85%	0.24
During the index procedure	3%	3%	1.0	24%	0.02

Do not usually revascularize	7%	2%	0.19	2%	0.55
Sometimes before, sometimes at the procedure	21%	16%	0.59	22%	1.0
Usually perform a FFR (or iFR) guided PCI	10%	17%	0.43	0	0.05
In patients at risk of coronary obstruction, the TAVR procedure is generally					
Contraindicated	3%	14%	0.14	6%	0.52
Done with the use of a PCI protection wire	48%	45%		61%	
Prefer a self-expandable valve in these cases	41%	27%		28%	
Nothing, perform the procedure as usual	7%	14%		4%	
Administration of antibiotics before TAVR					
No	7%	8%	0.45	4%	0.73
Yes, 1 dose	38%	47%		46%	
Yes, 2 or more doses	55%	42%		50%	

P-values for the LATAM20 are in comparison to the LATAM15 results; TAVR = transcatheter aortic valve replacement; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography; DAPT = Dual antiplatelet therapy; PCI = percutaneous coronary intervention; FFR = fractional flow reserve; iFR = instantaneous flow reserve.

Supplemental Table 5. Comparison of answers regarding procedural management between LATAM and WORLD centers.

	LATAM 2015 (N=29)	**WORLD 2015 (N=221)**	**P value**	**LATAM 2020 (N=46)**	**P value#**
Centers where ≥ 90% of cases are transfemoral	72%	42%	**0.003**	87%	0.14
Criteria to choose non-transfemoral (% centers)					
All patients referred for TF if iliofemoral access adequate	93%	93%		100%	
Some patients referred for non-TF even if iliofemoral access adequate	7%	6%	0.82	0	0.17
Most patients referred for non-TF even if iliofemoral access adequate	0	1%		0	
Site where TAVI is routinely performed (% centers)					
Operating room	3%	9%	0.48	0	0.38
Cath lab	83%	63%	0.04	83%	1.0
Hybrid room	24%	45%	0.04	19%	0.77
Anesthesiologists routinely assist TF and TSC cases	100%	93%	0.23	100%	1.0
Centers where cardiac surgeon regularly assists in TF procedures (% center)	86%	61%	0.01	52%	0.005
If cardiac surgeon assists, who is the primary operator for TF cases? (% centers)					
Interventional cardiologist in all cases	89%	75%		79%	
Interventional cardiologist in most cases	4%	14%		10%	
Cardiac surgeon in all cases	0	1%		2%	
Cardiac surgeon in most cases	0	1%		4%	
Interventional cardiologist in half and cardiac surgeon in the other half of the cases	7%	14%		2%	
Centers where interventional cardiologist regularly assists in TA/TAO procedures (% centers)	88%	88%	1.0	56%	0.008
If interventional cardiologist assists, who is the primary operator for TA/TAO cases? (% centers)					
Interventional cardiologist in all cases	37%	17%		25%	
Interventional cardiologist in most cases	8%	8%		10%	
Cardiac surgeon in all cases	37%	55%		42%	
Cardiac surgeon in most cases	8%	10%		18%	
Interventional cardiologist in half and cardiac surgeon in the other half of the cases	8%	10%		5%	
Operators have previous experience with structural heart disease (% centers)	90%	86%	0.77	100%	1.0
Percentage of cases done with conscious sedation					
100%	3%	11%		11%	
≥ 50%	10%	32%	0.009	56%	<0.001
< 50%	86%	57%		33%	

Routine arterial access for aortogram injection (% centers)					
Femoral access	57%	60%		57%	
Radial access	7%	5%	0.95	2%	0.55
Femoral or radial depending on case	36%	36%		41%	
TEE during TAVI (% of centers)					
Always	83%	41%		15%	
Only in certain patients	10%	42%	<0.001	63%	<0.001
Never	7%	17%		22%	
Routine vascular access in TF cases (% centers)					
Surgical cut-down	38%	15%	0.007	9%	0.003
Percutaneous	62%	85%		91%	
Type of closure device routinely used in TF percutaneous access (% centers)					
1 Perclose	0	1%		9%	
2 or more Perclose	90%	59%	0.03	83%	0.17
Prostar	10%	40%		2%	
Protection guidewire from contralateral artery in femoral percutaneous cases (% of centers)					
Always	33%	35%		32%	
Never	5%	25%	0.06	4%	1.0
Only in challenging iliofemoral access	62%	40%		61%	
Peripheral balloon during access closure in percutaneous cases					
Routinely	10%	12.9%	1.0	4%	0.6
Just in case of complication	90%	87.1%		96%	
In case of femoral perforation in percutaneous cases					
Usually implant self-expandable covered stent	55%	51.5%		65%	
Usually implant balloon-expandable covered stent	15%	15.8%	0.88	13%	0.55
Usually assisted by vascular surgeons	30%	23.5%		22%	
Usually assisted by an interventional radiologist	5%	9.2%		0	
Centers where >50% of cases are done with self-expanding THV (% centers)	52%	33%	0.06	46%	0.64
Type of THV routinely implanted (% centers)					
Corevalve system	86%	79%		91%	
Edwards valve	72%	84%		93%	
Acurate valve	10%	4%		41%	
Lotus valve	3%	26%		11%	
Portico valve	0	1%		0	
Routine balloon valvuloplasty predilation (% centers)					
For self-expanding valves	44%	50%	0.68	47%	0.81
For balloon-expandable valves	52%	68%	0.13	37%	0.23
In no case	30%	14%	0.04	44%	0.32
Methods routinely used to assess aortic regurgitation immediately after THV implantation (% centers)					
TTE	17%	33%	0.13	67%	<0.001
TEE	83%	59%	0.01	30%	<0.001
Aortography	90%	83%	0.58	87%	1.0
Hemodynamic assessment	69%	62%	0.54	61%	0.62

Gold-standard for aortic regurgitation assessment in case of discrepancy (% centers)					
TTE	3%	10%		33%	
TEE	59%	45%	0.47	37%	0.01
Aortography	24%	26%		26%	
Hemodynamic assessment	14%	19%		4%	
Embolic protection device as a routine (% centers)	0	16%	0.02	0	1.0
Kind of anticoagulation during TAVI					
Heparin non-ACT guided	31%	26.7%		50%	
Heparin ACT guided	69%	72.8%	0.66	50%	0.15
Bivalirudin	0	0.5%		0	

[#] P-values for the LATAM20 are in comparison to the LATAM15 results; TAVI = transcatheter aortic valve implantation; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography; THV = transcatheter heart valve; ACT = activated coagulation time.

Supplemental Table 6. Comparison of answers regarding post-procedural care between LATAM2015, WORLD2015, and LATAM2020 centers.

Question	LATAM 2015 (N=29)	WORLD 2015 (N=221)	P value	LATAM 2020 (N=46)	P value[#]
Maintenance of telemetry after TAVR (% center)					
24h	36%	20%		72%	
48h	36%	39%	0.13	24%	0.002
>48h	28%	41%		4%	
Maintenance of TPW after **self-expanding THV** (if no AV-block or new conduction disturbance)					
Always remove at the end of procedure	0	11%		24%	
At least 12-24h	30%	40%	0.004	59%	<0.001
At least 48h	59%	27%		4%	
No standardized protocol	11%	22%		13%	
Maintenance of TPW after **balloon-expandable THV** (if no AV-block or new conduction disturbance)					
Always remove at the end of procedure	71.5%	46%		70%	
At least 12-24h	9.5%	24%	0.08	15%	0.17
At least 48h	9.5%	6%		0	
No standardized protocol	9.5%	24%		15%	
Management of transient AV-block in **self-expanding THV** (% centers)					
Direct permanent pacemaker implantation	4%	13%		7%	
TPW and watch	81%	66%	0.31	63%	0.26
Depends on existence of prior conduction disorders	11%	14%		28%	
Other	4%	6%		2%	
Management of transient AV-block in **balloon-expandable THV** (% centers)					
Direct permanent pacemaker implantation	4.5%	7%		4%	
TPW and watch	86.5%	66%	0.06	63%	0.04
Depends on existence of prior conduction disorders	0	17%		26%	
Other	9%	10%		2%	
Management of new LBBB in **self-expanding THV** (% centers)					
Maintain telemetry or TPW and wait for another indication for permanent pacemaker	73%	73%		78%	
Electrophysiology study or implantation of a loop recorder prior to discharge	4%	4%	0.93	0	0.48
Maintain TPW until implantation of permanent pacemaker	11.5%	14%		7%	
Usual post-op or other protocol	11.5%	9%		15%	
Management of new LBBB in **balloon-expandable THV** (% centers)					
Maintain telemetry or TPW and wait for another indication for permanent pacemaker	84%	73%	0.88	79%	0.35
Electrophysiology study or implantation of a loop recorder prior to discharge	5%	5%		0	

Maintain TPW until implantation of permanent pacemaker	10%	15%		7%	
Usual post-op or other	5%	8%		14%	

[#] P-values for the LATAM20 are in comparison to the LATAM15 results; TAVR = transcatheter aortic valve implantation; THV = transcatheter heart valve; AV-block = atrioventricular block; TPW = temporary pacing wire; LBBB = left bundle branch block.

Supplemental Table 7. Comparison of answers regarding follow-up between LATAM2015, WORLD2015, and LATAM2020 centers.

Question	LATAM 2015 (N=29)	WORLD 2015 (N=221)	P value	LATAM 2020 (N=46)	P value[#]
Centers with specific TAVR clinics (% center)	45%	56%	0.31	41%	0.32
Professionals responsible for follow-up (% centers)					
Interventional cardiologist	77%	94%		65%	
Cardiac surgeon	15%	41%		13%	
General cardiologist	46%	20%		59%	
Time points for follow-up visit (% centers)					
1 month	4%	4%		4%	
1 month and 1 year	0	35%		9%	
1, 3, and 6 months and 1 year	55%	16%		45%	
1 and 6 months, and 1 year	38%	45%		41%	
Time points for follow-up echo (% centers)					
1 month	0	5%		4%	
1 month and 1 year	14%	51%		15%	
1, 3, and 6 months and 1 year	25%	8%		18%	
1 and 6 months, and 1 year	61%	36%		62%	
Antithrombotic therapy at hospital discharge with no indication for anticoagulant (% centers)					
Aspirin	100%	97%		97%	
Clopidogrel	100%	91%		83%	
Oral anticoagulant	0%	2%		0%	
Other	0%	0%		0%	
DAPT at discharge (% centers)	100%	88%	0.05	78%	0.01
Time of DAPT (% centers)					
≤ 3 months	43%	61%		29%	
6 months	46%	33%	0.18	66%	0.2
≥ 12 months	11%	6%		5%	
Antithrombotic therapy at hospital discharge with indication for anticoagulant (% centers)					
Oral anticoagulant alone	25%	29%		41%	
Oral anticoagulant + Aspirin or Clopidogrel	65%	69%	0.15	61%	0.15
Oral anticoagulant + Aspirin + Clopidogrel	10%	3%		2%	
Type of anticoagulant when required (% centers)					
VKA	96%	99%	0.31	72%	0.007
NOACs	4%	1%		28%	

[#] P-values for the LATAM20 are in comparison to the LATAM15 results; TAVR = transcatheter aortic valve implantation; DAPT = dual antiplatelet therapy; VKA = vitamin-K antagonist; NOAC = novel oral anticoagulant.

SUPPLEMENTARY MATERIAL – ARTICLE 2

Table of Contents:

Supplemental Table 1. Frequency of multiple resheathing by center´s annual volume with SE-THV.

	Annual volume	**% Multiple Resheathing**	**P value**
Centers´ annual volume with SE-THV	≤ 25 cases/year	7.2%	0.05
	25-75 cases/year	11.5%	
	> 75 cases/year	6.9%	

SE-THV = self-expanding transcatheter heart valve

Supplemental Table 2. Comparison of procedural and 30-day outcomes between the groups including only Evolut R and PRO cases.

	Overall (n=837)	NR (n=587)	SR (n=191)	MR (n=59)	P value
Procedural outcomes					
Device success	738 (88.2)	523 (89.1)	173 (90.6)	42 (71.2)	<0.001
Procedural death	26 (3.1)	20 (3.4)	3 (1.6)	3 (5.1)	0.3
Need of a second valve	19 (2.3)	3 (0.5)	6 (3.1)	10 (16.9)	<0.001
Prosthesis embolization	12 (1.4)	2 (0.3)	3 (1.6)	7 (11.9)	<0.001
Tamponade	13 (1.6)	9 (1.5)	4 (2.1)	0	0.52
Coronary obstruction	6 (0.7)	5 (0.9)	1 (0.5)	0	0.71
Aortic rupture	3 (0.4)	3 (0.5)	0	0	0.53
30-day outcomes					
All-cause death*	30 (3.7)	22 (3.8)	3 (1.7)	5 (8.6)	0.04
Early Safety	135 (16.1)	99 (16.9)	26 (13.6)	10 (16.9)	0.56
Stroke					
All stroke	21 (2.5)	17 (2.9)	3 (1.6)	1 (1.7)	0.54
Disabling Stroke	12 (1.4)	8 (1.4)	3 (1.6)	1 (1.7)	0.96
Major vascular complication	49 (5.9)	35 (6)	12 (6.3)	2 (3.5)	0.72
Life-threatening bleeding	34 (4.1)	24 (4.1)	9 (4.7)	1 (1.7)	0.6
Acute kidney injury (stages 2 and 3)	55 (6.6)	40 (6.9)	9 (4.7)	6 (10.2)	0.31
New permanent pacemaker	122 (14.8)	83 (14.4)	29 (15.3)	10 (17.2)	0.83
New-onset persistent LBBB	144 (17.7)	94 (16.5)	36 (19.4)	14 (24.1)	0.28
Moderate/severe aortic regurgitation	24 (3.1)	15 (2.8)	6 (3.4)	3 (5.6)	0.51
Mean aortic gradient, mmHg	8.8±5.6	8.7±5.5	8.3±4.8	11±8.2	0.02

*Kaplan-Meier events probability estimates (log rank). LBBB= left bundle branch block. NR=no resheathing; SR=single resheathing; MR=multiple resheathing.

Supplemental Table 3. Total number and percentage of cases included in the logistic regression analysis for multiple resheathing.

Univariable		Multivariable	
Variables	**N (%)**	**Variable**	**N (%)**
Aortic regurgitation*	1003 (97.8)	Aortic regurgitation*	1003 (97.8)
Balloon predilation	1026 (100)	Balloon predilation	1003 (97.8)
Evolut PRO†	1026 (100)	-	-
Portico†	1026 (100)	Portico†	1003 (97.8)

*Moderate or severe aortic regurgitation at baseline; †Evolut R/PRO as reference.

Supplemental Table 4. Total number and percentage of cases included in the logistic regression analysis for device success.

Univariable		Multivariable	
Variables	**N (%)**	**Variable**	**N (%)**
COPD	1026 (100)	-	-
Aortic regurgitation*	1003 (97.8)	Aortic regurgitation*	1003 (97.8)
Balloon predilation	1026 (100)	-	-
Balloon postdilation	1026 (100)	-	-
Evolut PRO†	1026 (100)	-	-
Portico†	1026 (100)	Portico†	1003 (97.8)
Multiple resheathing	1026 (100)	Multiple resheathing	1003 (97.8)
SE-THV center annual volume <25 cases‡	1026 (100)	SE-THV center annual volume <25 cases‡	1003 (97.8)
SE-THV center annual volume 26-75 cases‡	1026 (100)	SE-THV center annual volume 26-75 cases‡	1003 (97.8)

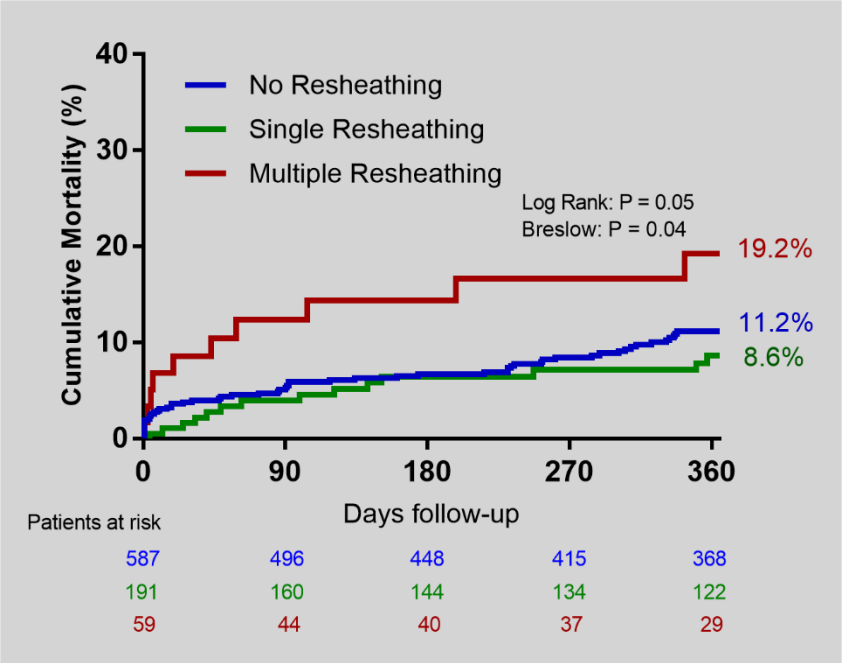
COPD=Chronic obstructive pulmonary disease; SE-THV=Self-expanding transcatheter heart valve; *Moderate or severe aortic regurgitation at baseline; †Evolut R as the reference; ‡SE-THV center annual volume >75 as reference.

Supplemental Table 5. Total number and percentage of cases included in the proportional hazard regression for the cumulative mortality at 1 year analysis for device success.

Univariable		Multivariable	
Variables	**N (%)**	**Variables**	**N (%)**
COPD	1026 (100)	COPD	1026 (100)
Afib*	1026 (100)	Afib*	1026 (100)
Cerebrovascular disease	1026 (100)	-	-
Aortic regurgitation†	1003 (97.8)	-	-
Evolut PRO‡	1026 (100)	-	-
Portico‡	1026 (100)	-	-
Multiple Resheathing	1026 (100)	Multiple resheathing	1026 (100)
SE-THV center annual volume <25 cases§	1026 (100)	SE-THV center annual volume <25 cases§	1026 (100)
SE-THV center annual volume 26-75 cases§	1026 (100)	SE-THV center annual volume 26-75 cases§	1026 (100)

COPD=Chronic obstructive pulmonary disease; SE-THV=Self-expanding transcatheter heart valve; *Afib= atrial fibrillation at baseline; †Moderate or severe aortic regurgitation at baseline; ‡Evolut R as the reference; §SE-THV center annual volume >75 as reference.

Supplemental figure 1. Comparison of Kaplan-Meier cumulative mortality curves at 1-year including only the Evolut R and PRO cases.



SUPPLEMENTARY MATERIAL – ARTICLE 3

Table of content:

Supplemental Table S1: List of old- and new-generation transcatheter heart valves.

Type of THV	**Brand**
Old-generation THV	
Corevalve	Medtronic
Sapein XT	Edwards Lifescience
Lotus	Boston Scientific
Innovare	Braile Biomédica
New-generation THV	
Evolut R and PRO	Medtronic
Sapien S3 and S3 Ultra	Edwards Lifescience
Acurate Neo and Neo 2	Boston Scientific
Portico	Abbott Vascular
Myval	Meril Life Science

THV: transcatheter heart valve.

Supplemental Table S2. Characteristics of the enrolled individuals according to case sequence number among centers with high-volume of TAVR procedures [≥40 procedures] before 2014.

		Overall	1st to 40th case	41st to 80th case	81st to 120th case	Over the 121st case	p
Sample size (n)		1916	320	320	297	979	
Demography and Past Medical History							
Age (mean (SD))		80.72 (8.48)	81.95 (7.15)	81.71 (7.21)	81.90 (6.85)	79.64 (9.51)	<0.001
Female Gender (%)		917 (47.9)	167 (52.2)	150 (46.9)	147 (49.5)	453 (46.3)	0.280
BMI (mean (SD))		26.70 (4.70)	26.40 (4.89)	26.61 (4.65)	26.75 (4.79)	26.83 (4.63)	0.545
Hypertension (%)		1101 (77.5)	215 (77.1)	206 (73.6)	207 (80.9)	473 (78.2)	0.228
Diabetes (%)		597 (31.3)	98 (30.7)	101 (31.6)	94 (31.8)	304 (31.2)	0.993
NYHABL (%)							<0.001
	I	107 (6.4)	14 (4.4)	16 (5.0)	17 (5.8)	60 (8.1)	
	II	490 (29.2)	52 (16.4)	91 (28.4)	93 (31.6)	254 (34.1)	
	III	830 (49.5)	186 (58.5)	156 (48.8)	131 (44.6)	357 (47.9)	
	IV	249 (14.8)	66 (20.8)	57 (17.8)	53 (18.0)	73 (9.8)	
History of Atrial Fibrillation (%)		87 (19.5)	17 (21.2)	8 (10.0)	20 (25.0)	42 (20.3)	0.094
Pacemaker (%)		55 (8.2)	7 (5.8)	7 (5.8)	11 (9.2)	30 (9.7)	0.413
Previous CAD (%)		833 (44.2)	172 (53.9)	173 (54.1)	171 (57.8)	317 (33.4)	<0.001
Previous MI (%)		210 (12.4)	47 (16.8)	42 (15.0)	40 (15.6)	81 (9.3)	0.001
Previous PCI (%)		446 (25.4)	87 (27.3)	82 (25.6)	90 (30.4)	187 (22.7)	0.054
Previous CABG (%)		279 (16.3)	54 (16.9)	72 (22.5)	52 (17.6)	101 (12.9)	0.001
Previous Valve Surgery (%)		130 (6.8)	21 (6.6)	21 (6.6)	27 (9.1)	61 (6.3)	0.390
CerVascDis (%)		179 (9.4)	39 (12.2)	44 (13.8)	27 (9.1)	69 (7.1)	0.001
Previous Stroke (%)		121 (6.3)	29 (9.1)	21 (6.5)	18 (6)	53 (5.4)	0.314
PeriphVascDis (%)		236 (12.4)	49 (15.4)	57 (17.8)	53 (17.9)	77 (7.9)	<0.001
COPD (%)		241 (12.6)	56 (17.7)	48 (15.0)	50 (16.9)	87 (8.9)	<0.001
Surgical risk							
Euroscore II (mean (SD))		7.03 (7.51)	9.12 (9.79)	7.95 (6.65)	8.52 (8.69)	5.27 (5.72)	<0.001

BMI = body mass index; NYHA = New York Heart Association; AF = Atrial Fibrillation; CAD = Coronary Artery Disease; MI = Myocardial Infarction; PCI = Percutaneous Coronary Intervention; CABG = Coronary Artery Bypass Graft; CerVascDis = Cerebrovascular Disease; PeriphVascDis = Peripheral Vascular Disease; COPD = Chronic Obstructive Pulmonary Disease.

Supplemental Table S3. Procedural characteristics according to case sequence number among centers with high-volume of TAVR procedures [≥40 procedures] before 2014.

	Overall	1st to 40th case	41st to 80th case	81st to 120th case	Over the 121st case	p
Sample size (n)	1916	320	320	297	979	
Procedure Year (median (interquartile range in months))	Dec/2015 (3.59)	Mar/2011 (1.73)	Jan/2014 (1.99)	July/2015 (2.00)	Dec/2018 (2.12)	<0.001
New generation THV (%)	1031 (55.4)	15 (4.7)	65 (20.3)	132 (44.4)	819 (88.4)	<0.001
Valve-In-Valve (%)	76 (4.3)	9 (2.8)	7 (2.4)	21 (8.0)	39 (4.4)	0.006
General Anesthesia (%)	1136 (63.2)	288 (90.3)	285 (89.1)	230 (78.0)	333 (38.5)	<0.001
Vascular Approach (%)						<0.001
Transfemoral	1710 (94.7)	305 (95.6)	291 (90.9)	277 (93.2)	837 (96.2)	
Transapical	59 (3.3)	8 (2.5)	24 (7.5)	8 (2.7)	19 (2.2)	
Transaortic	18 (1.0)	2 (0.6)	1 (0.3)	10 (3.4)	5 (0.6)	
Trans-subclavian	15 (0.8)	3 (0.9)	2 (0.6)	2 (0.7)	8 (0.9)	
Other	4 (0.2)	1 (0.3)	2 (0.6)	0 (0)	1 (0.1)	
Percutaneous Access (%)	1561 (86.5)	209 (65.5)	248 (77.5)	261 (87.9)	843 (97.0)	<0.001
Balloon Predilation (%)	804 (44.9)	201 (63.0)	159 (49.7)	123 (41.6)	321 (37.5)	<0.001
VALVEBRAND (%)						<0.001
Sapien XT	331 (17.8)	80 (25.1)	115 (35.9)	81 (27.3)	55 (5.9)	
CoreValve	416 (22.3)	214 (67.1)	121 (37.8)	53 (17.8)	28 (3.0)	
Lotus	49 (2.6)	3 (0.9)	2 (0.6)	28 (9.4)	16 (1.7)	
Sapien S3	553 (29.7)	6 (1.9)	17 (5.3)	69 (23.2)	461 (49.8)	
EVOLUT	292 (15.7)	7 (2.2)	35 (10.9)	50 (16.8)	200 (21.6)	
Braile Innovare	35 (1.9)	7 (2.2)	17 (5.3)	3 (1.0)	8 (0.9)	
Portico	6 (0.3)	0 (0)	0 (0)	0 (0)	6 (0.6)	
Acurate Neo	154 (8.3)	2 (0.6)	10 (3.1)	7 (2.4)	135 14.6)	
Myval	20 (1.1)	0 (0)	3 (0.9)	6 (2.0)	11 (1.2)	
Unreported	6 (0.3)	0 (0)	0 (0)	0 (0)	6 (0.6)	
Balloon Post-dilation (%)	527 (29.6)	89 (28.2)	111 (34.9)	87 (29.5)	240 (28.2)	0.144
Valve Embolization (%)	31 (1.9)	10 (3.2)	8 (2.6)	6 (2.5)	7 (0.9)	0.025
Need 2nd Valve (%)	41 (2.4)	11 (3.6)	14 (4.6)	7 (2.9)	9 (1.1)	0.003
Coronary artery occlusion (%)	4 (0.3)	2 (0.8)	1 (0.4)	0 (0)	1 (0.1)	0.222
Annulus rupture (%)	10 (0.6)	3 (1)	1 (0.3)	1 (0.4)	5 (0.6)	0.745
Tamponade (%)	47 (2.8)	12 (3.9)	7 (2.3)	10 (4.1)	18 (2.2)	0.239
Conversion Open Surgery (%)	38 (2.0)	16 (5.2)	6 (1.9)	6 (2.0)	10 (1.0)	<0.001

THV = transcatheter heart valve.

Supplemental Table S4. Characteristics of the enrolled individuals according to case sequence number among centers with low-volume of TAVR procedures [<40 procedures] before 2014.

		Overall	1st to 40th case	41st to 80th case	81st to 120th case	Over the 121st case	p
Sample size (n)		1278	671	296	161	150	
Demography and Past Medical History							
Age (mean (SD))		80.52 (7.38)	80.40 (7.30)	79.94 (7.68)	81.35 (7.27)	81.29 (7.19)	0.129
Female Gender (%)		634 (49.6)	353 (52.6)	133 (44.9)	80 (49.7)	68 (45.3)	0.107
BMI (mean (SD))		26.43 (4.74)	26.31 (4.69)	26.62 (4.90)	26.12 (4.25)	26.93 (5.12)	0.407
Hypertension (%)		1058 (83.8)	562 (84.1)	247 (86.4)	141 (87.6)	108 (73.5)	0.002
Diabetes (%)		467 (36.7)	246 (36.7)	109 (36.9)	56 (34.8)	56 (38.1)	0.943
NYHA (%)							0.030
	I	43 (3.4)	13 (1.9)	14 (4.7)	8 (5.0)	8 (5.4)	
	II	237 (18.6)	122 (18.2)	53 (17.9)	31 (19.3)	31 (21.1)	
	III	596 (46.7)	326 (48.6)	146 (49.3)	59 (36.6)	65 (44.2)	
	IV	399 (31.3)	210 (31.3)	83 (28.0)	63 (39.1)	43 (29.3)	
History Atrial Fibrillation (%)		10 (13.9)	5 (11.6)	5 (17.9)			0.021
Previous Pacemaker (%)		26 (10.1)	10 (11.9)	8 (11.4)	3 (7.9)	5 (7.6)	0.776
Previous CAD (%)		678 (55.0)	346 (53.2)	161 (58.3)	92 (57.1)	79 (54.1)	0.492
Previous MI (%)		171 (13.8)	78 (12.0)	50 (17.5)	26 (16.1)	17 (11.6)	0.091
Previous PCI (%)		364 (29.1)	198 (30.0)	87 (30.5)	53 (32.9)	26 (17.7)	0.012
Previous CABG (%)		185 (14.6)	98 (14.8)	48 (16.3)	23 (14.3)	16 (10.9)	0.508
Preval's (%)		78 (6.1)	44 (6.6)	18 (6.1)	3 (1.9)	13 (8.8)	0.065
CerVascDis (%)		186 (15.0)	105 (16.1)	38 (13.4)	25 (15.5)	18 (12.2)	0.542
Previous Stroke (%)		75 (6.0)	42 (6.4)	15 (5.3)	10 (6.2)	8 (5.4)	0.893
PeriphVascDis (%)		219 (17.6)	115 (17.7)	55 (19.4)	29 (18.0)	20 (13.6)	0.523
COPD (%)		264 (21.2)	121 (18.6)	73 (25.7)	49 (30.4)	21 (14.3)	<0.001
Surgical risk							
Euroscore II (mean (SD))		6.92 (6.79)	7.05 (6.91)	6.85 (6.59)	7.45 (7.39)	5.91 (5.89)	0.208

BMI = body mass index; NYHA = New York Heart Association; AF = Atrial Fibrillation; CAD = Coronary Artery Disease; MI = Myocardial Infarction; PCI = Percutaneous Coronary Intervention; CABG = Coronary Artery Bypass Graft; CerVascDis = Cerebrovascular Disease; PeriphVascDis = Peripheral Vascular Disease; COPD = Chronic Obstructive Pulmonary Disease.

Supplemental Table S5. Procedural characteristics of the enrolled individuals according to case sequence number among centers with low-volume of TAVR procedures [<40 procedures] before 2014.

	Overall	1st to 40th case	41st to 80th case	81st to 120th case	Over the 121st case	p
Sample size (n)	1278	671	296	161	150	
Procedure						
Procedure Year (median (interquartile range in months))	Feb/2018 (2.90)	Jan/2017 (3.16)	Aug/2018 (2.08)	May/2019 (0.92)	Feb/2021 (0.91)	<0.001
New generation THV (%)	893 (70.3)	348 (52.0)	238 (81.0)	160 (100.0)	147 (100.0)	<0.001
Valve In Valve (%)	58 (4.6)	34 (5.1)	11 (3.7)	2 (1.2)	11 (7.4)	0.051
General Anesthesia (%)	805 (64.9)	456 (68.7)	155 (55.2)	110 (69.2)	84 (61.8)	0.001
Elective Urgent (%)	444 (39.2)	342 (57.4)	36 (14.7)	17 (10.8)	49 (36.6)	<0.001
Vascular Approach (%)						0.915
Transfemoral	1231 (97.4)	650 (97.3)	284 (96.9)	156 (98.7)	141 (97.2)	
Transapical	5 (0.4)	4 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	
Transaortic	3 (0.2)	2 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	
Trans-subclavian	18 (1.4)	9 (1.3)	5 (1.7)	2 (1.3)	2 (1.4)	
Other	7 (0.6)	3 (0.4)	2 (0.7)	0 (0.0)	2 (1.4)	
Percutaneous Access (%)	1049 (83.1)	498 (74.6)	268 (91.5)	144 (91.7)	139 (96.5)	<0.001
Balloon Predilation (%)	411 (34.0)	205 (31.8)	98 (36.0)	61 (39.1)	47 (34.1)	0.301
VALVEBRAND (%)						<0.001
Sapien XT	127 (10.0)	108 (16.1)	19 (6.5)	0 (0.0)	0 (0.0)	
CoreValve	235 (18.5)	199 (29.7)	36 (12.2)	0 (0.0)	0 (0.0)	
Lotus	13 (1.0)	12 (1.8)	1 (0.3)	0 (0.0)	0 (0.0)	
Sapien S3	392 (30.9)	173 (25.9)	95 (32.3)	57 (35.6)	67 (45.6)	
EVOLUT	397 (31.3)	123 (18.4)	132 (44.9)	91 (56.9)	51 (34.7)	
Braille Innovare	2 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	
Portico	13 (1.0)	11 (1.6)	0 (0.0)	0 (0.0)	2 (1.4)	
Acurate	66 (5.2)	39 (5.8)	6 (2.0)	10 (6.2)	11 (7.5)	
Myval	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	
Unreported	24 (1.9)	2 (0.3)	5 (1.7)	2 (1.2)	15 (10.2)	
Balloon Post-dilation (%)	361 (29.8)	206 (32.0)	68 (25.1)	49 (31.2)	38 (27.3)	0.180
Valve Embolization (%)	25 (2.5)	15 (2.4)	5 (2.8)	2 (1.7)	3 (3.2)	0.894
Need2ndValve (%)	25 (2.5)	16 (2.6)	5 (2.8)	2 (1.7)	2 (2.1)	0.921
Coronary artery occlusion (%)	11 (1.2)	2 (0.4)	5 (2.8)	4 (3.3)	0 (0.0)	0.004
Annulus rupture (%)	5 (0.5)	5 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0.365
Tamponade (%)	34 (3.4)	22 (3.6)	7 (3.9)	4 (3.3)	1 (1.1)	0.618

Conversion Open Surgery (%)	29 (2.3)	18 (2.7)	6 (2.0)	4 (2.5)	1 (0.7)	0.504

THV = transcatheter heart valve.

SUPPLEMENTARY MATERIAL – ARTICLE 4

Table of content:

Supplemental table s1. Baseline characteristics of patients in the sensitivity analysis comparing Sapien S3 versus Evolut R/PRO.

	Sapien S3 (n=853)	**Evolut R/PRO** (n=595)	**p**
Age, mean ± SD			
Female, %	44.1	53.3	0.001
Diabetes, %	34.1	34.1	1
Atrial Fibrillation, %	14.7	11.3	0.08
Previous Pacemaker, %	8.5	8.2	0.9
Previous MI, %	11	14.3	0.07
Previous PCI, %	26.3	26.7	0.9
Previous CABG, %	12.6	14.4	0.37
Previous CerVasc, %	10.3	12.9	0.13
Previous Stroke, %	5.7	6.2	0.73
Previous PAD, %	11	18.2	<0.001
COPD, %	11.2	20.3	<0.001
Creatinine	1.29 ± 0.9	1.32 ± 0.8	0.51
LVEF, mean % ± SD	60.1 ± 37	60 ± 12	0.7
Euroscore 2, median (IQR)	3.4 (2 – 6.4)	4.5 (2.5 – 8.2)	<0.001
Log(Euroscore 2), mean ± SD	1.3 ± 0.8	1.4 ± 0.8	0.001

MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; CerVasc = cerebrovascular disease; PAD = peripheral artery disease; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; IQR = interquartile range.

Supplemental table s2. Procedural characteristics in the sensitivity analysis comparing Sapien S3 versus Evolut R/PRO.

	Sapien S3 (n=853)	**Evolut R/PRO** (n=595)	**p**
Transfemoral access, %	99.4	96	<0.001
General anesthesia, %	61.1	45.2	<0.001
Percutaneous access, %	98	89.5	<0.001
Predilation, %	25.7	40	<0.001
Postdilation, %	19.3	34.2	<0.001
Valve embolization, %	0.2	1.9	0.003
Need of a 2nd valve, %	0.4	2.2	0.001
Coronary occlusion, %	0.1	0.8	0.05
Annulus rupture, %	0.6	0.2	0.4
Tamponade, %	2.4	2.2	1
Conversion to surgery, %	1.1	1.5	0.48