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TRANSCATHETER AORTIC VALVE IMPLANT (TAVI): WHERE WE ARE IN 2018

IMPLANTE TRANSCATETER VALVAR AÓRTICO (TAVI): ONDE ESTAMOS EM 2018

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ABSTRACT

For around fifteen years, Transcatheter Aortic Valve Implant (TAVI) has undergone technological advances, acquired accumulated experience, and become an alternative to conventional surgery. The main indication is degenerative aortic stenosis in the elderly patient. Current evidence has been extended to those with intermediate risk, and has become more robust in high-risk and inoperable patients. In specific situations, such as bicuspid aortic valve, pure aortic regurgitation, low-risk patients, and degenerated surgical bioprosthesis, the results are not totally predictable, but are very promising. The types of device currently released for clinical use are divided into first generation and new generation devices, and into auto-expandable, balloon-expandable, and mechanically-expandable. The preferential access site is currently the transfermoral route. Other access alternatives have also proven viable and reliable. The main complications are vascular, neurological events, conduction disturbances, and paravalvular regurgitation. Despite their low incidence, aortic rupture and coronary occlusion have attracted greater interest due to their potential impact on morbimortality. The more recent use of the procedure in younger patients raises issues related to durability and the risk of thrombosis. Although TAVI is still a complex procedure, after gaining experience, there is a tendency to move towards a more simplified, safer approach. The patient selection should ideally be carried out by a multidisciplinary team, and a complete imaging assessment that includes angiotomography is absolutely essential.

Keywords: Heart valve prothesis implantation; Aortic valve stenosis; Mitral valve insufficiency.

RESUMO

Por cerca de 15 anos, o Implante Transcateter Valvar Aórtico (TAVI) passou por avanços tecnológicos, adquiriu experiência acumulada e tornou-se alternativa à cirurgia convencional. A principal indicação é a estenose aórtica degenerativa do idoso. Evidências atuais foram ampliadas para aqueles de risco intermediário e se tornaram mais robustas nos pacientes de alto risco e inoperáveis. Em situações específicas, como valva aórtica bicúspide, regurgitação aórtica pura, pacientes de baixo risco e bioprótese cirúrgica degenerada, os resultados ainda não são totalmente previsíveis, mas muito promissores. Os tipos de dispositivos atualmente liberados para uso clinico são divididos em: da geração inicial e os da nova geração, assim como em auto expansível, balão expansível e expansível mecanicamente. O sítio de acesso preferencial na atualidade é a via transfemoral. Outras alternativas de acessos também têm se mostrado viáveis e confiáveis. As principais complicações são vasculares, eventos neurológicos, distúrbios de condução e regurgitação paravalvar. Apesar da baixa incidência, a ruptura aórtica e a oclusão coronária são uma fonte de maior interesse, devido ao seu potencial impacto na morbimortalidade. A realização mais recente do procedimento em pacientes mais jovens faz necessária mais atenção à questões referentes à durabilidade e ao risco de trombose. Embora o TAVI ainda possa ser um procedimento complexo, após atingida experiência, existe a tendência de migração para uma abordagem mais simplificada com segurança. A seleção do paciente deve, idealmente, ser feita por uma equipe multidisciplinar e uma completa avaliação por imagem, em que a angitomogradia é imprescindível, mandatória.

Descritores: *Implante de prótese aórticas; Estenose da valva aórtica, Insuficiência da valva mitral.*

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INTRODUCTION

The first transcatheter aortic valve implantation (TAVI) procedure in the world dates back to 2002, when professor Alain Cribier demonstrated that it was possible to correct a severe aortic stenosis in a critically ill patient by implanting of a prosthesis without open-heart surgery or the need for extracorporeal circulation.[1] Since then, the technique has undergone numerous technological advances and has been simplified and routines have been established. Today, with global penetration and the large amount of accumulated experience, TAVI has become an alternative to conventional surgery. In the last 15 years, more than 350,000 procedures have been performed in about 70 countries.[2]

INDICATIONS

The main indication for TAVI in elderly individuals is degenerative aortic stenosis. According to the guidelines of the American Heart Association (AHA), American College of Cardiology (ACC) and Society of Thoracic Surgery (STS), the TAVI is indicated for high-risk patients (Class I; Level of Evidence A), and it is also a treatment option for intermediate-risk patients (Class IIa; Level of Evidence B).[3] European directives follow the same trend, and corroborate the indication in the case of intermediate-to-high surgical risk score (STS or EuroSCORE > 4%) and especially in the elderly and inoperable patients (Class I, Level of Evidence B).[4]

The recent results from the PARTNER2[5] and SURTAVI[6] clinical trials were a determining factor for the expansion of indications for symptomatic patients at intermediate risk, both with a definition of risk based on the application of the STS score and risk of mortality within 30 days. The first trial, conducted with a sample of 2032 patients in 57 centers in Canada and the United States, indicated that TAVI was not inferior to conventional surgery with respect to death due to any cause and disabling stroke within two years of follow-up.[5] The second, published in 2017, was a multicenter study with a sample of 1746 individuals, corroborated the findings with the same primary outcome. Some of the possible complications in the TAVI group included higher rates of residual aortic regurgitation and the need for pacemaker implantation. The group with conventional surgery was associated with more frequent acute renal injury, atrial fibrillation, and the need for blood transfusion.[6]

Evidence that supports the expansion of indications for low-risk patients and younger individuals are still limited, in particular for gaps in knowledge regarding the durability of the prostheses. In these subgroups, the indication for conventional open surgery (Class I, Level of Evidence B) is still preponderant. The *PARTNER 3* and *Evolut Low Risk trial* are in progress to try to elucidate these issues. To date, the more solid evidence is based on the results of the NOTION study.[7] This trial followed 280 patients aged 70 years and older, 82% low risk, in three Nordic centers. No statistically significant differences were found in the primary endpoint (all causes of mortality, stroke or acute myocardial infarction (AMI)) between TAVI versus conventional surgery at two years of follow-up (15.8% vs. 18.8%, p = 0.43). The complications were similar to those described in the intermediate risk studies.

SPECIFIC INDICATIONS

Bicuspid aortic valve

Bicuspid aortic stenosis displays a higher incidence in young individuals. Elderly individuals aged over 80 years comprise approximately 20% of the surgical cases.[8]

A few anatomical characteristics of this pathology, such as the oval shape of the annulus, size, and uneven calcification of leaflets, confer less predictable results for use of TAVI.

In a study with a new-generation device, a higher incidence of poor positioning of the mitral valve (7.2%) and higher rates of moderate to severe paravalvular regurgitation were found, which indicated the need for new interventions.[8] Recent studies more often reported damage of the aortic annulus, need for a second valve implant, and higher rates of moderate and/or severe paravalvular leak.[9] In short, bicuspid anatomy is not an exclusion factor; however, it should be examined more carefully before the indication for the procedure.

Aortic Regurgitation

Currently, the data on the safety and efficacy in patients with pure aortic regurgitation are limited. Its application is off-label, even in those with high surgical risk. The majority of devices globally approved to date are specifically intended for the treatment of degenerated aortic stenosis. The JenaValve (JenaValve, Germany), still unavailable in Brazil and under assessment in the United States, is the only device that has a certificate of approval in the European Union (*CE mark*) for use in high-risk patients, and it is still deployed exclusively via transapical access.[10]

The absence of ring and calcified aortic valve leaflet in patients with pure regurgitation confer a higher risk for embolization and migration of the mitral valve. However, in this scenario, more recent studies have been demonstrating better outcomes with new-generation devices.[11,12]

Degenerative Surgical Bioprosthesis

Implant of a valve-in-valve transcatheter (*ViV*), a less invasive therapy for the treatment of degenerated aortic valve bioprosthesis, has emerged as a novelty.[9] The valves of the company Medtronic (CoreValve, Evolute R and Evolut Pro) and the company Edwards (Sapien XT and Sapien 3) were approved for use in high-risk patients.

The stenotic degeneration of the surgical bioprosthesis and implants in small valves lead to worse outcomes.[13] Compared to the TAVI technique in native valve, this procedure displayed a lower frequency of formation of leaks and less need for pacemaker implantation; however, there were higher rates of coronary occlusion and residual mismatch.

Recently, the results of the *Valve-in-Valve* PARTNER 2[5] registry and the study of Expanded Use with CoreValve were disclosed.[14,15] The first study recorded rates of mortality at 30 days and one year of 2.7% and 12.4%, respectively, while the second recorded rates of 2.2% at 30 days and 14.6% per year. Moderate or severe aortic regurgitation occurred in 3.5% of patients. The factors that were significantly associated with the highest residual gradients were size of surgical valve stenosis as modality of valve failure and previous presence of prosthesis-patient mismatch.[14,15]

Increasing experience has shown that the specific complications of *ViV* TAVI can often be prevented.[16] In particular, patients with small surgical bioprostheses represent a major challenge, as they appear to have greater residual gradients and higher late mortality than other patients submitted to *ViV* TAVI. More recently, some investigators have described a bioprosthesis valve ring fracture technique using a high-pressure balloon to facilitate *ViV* TAVI. This strategy seems to allow a greater expansion of the transcatheter valve with reduction of residual transvalvular gradients.[17]

These widely favorable results allow us to conclude that, in the near future, it is likely that the TAVI might become the preferred option in the treatment of degenerated bioprostheses, and perhaps also of bicuspid valves with compromised function.

TYPES OF DEVICES

The devices currently approved and available for clinical use are: Sapien XT and Sapien 3 (Edwards Lifesciences), CoreValve, Evolut™ and Evolut Pro (Medtronic), LOTUS™ valve (Boston Scientific), Acurate Neo™ (Symetis), PorticoTM (St. Jude Medical), and Allegra (New Valve Technology). The Lotus™ device has been temporarily withdrawn from the market and the launch of its new generation, the Lotus Edge™ is awaited. In Brazil, the Inovare (Braile Biomédica) prosthesis of national production is also available, used in South America and some Asian countries; however, it is only available for cases of transapical access. The devices of the Sapien and CoreValve family are the most extensively studied and have a larger body of clinical evidence available. Its last generations present important technological implements that allowed its assembly in catheters of low profile release, possibility of repositioning and more precise adjustments and greater sealing of the valve ring, reducing the rates of residual regurgitation. According to their development mechanism they can be divided into an expandable balloon (Sapien XT, Sapien 3 and Inovare), self-expandable (CoreValve, Evolut R, Evolut Pro, Portico, Acurate Neo and Allegra), and mechanically expandable (LOTUS).

In terms of the latest generation of devices, the Sapien 3 (Edwards Lifesciences) is manufactured with a chromium and cobalt frame and three bovine pericardium leaflets. Compared with the previous generation Sapien XT, this was designed to improve the geometry (opening of upper cells and closing lower cells) for an ultra-low profile of delivery (14F) and incorporated an outer skirt seal to reduce the possibility of residual aortic regurgitation. The Evolut R (Medtronic) is a tricuspid valve of porcine pericardial material sutured within a self-expanding nitinol frame. Compared to the previous generation of CoreValve devices, it has been redesigned to achieve optimized radial force during the release and allow its partial recapture and repositioning. This results in safer and higher release relative to the valve plane, reducing the incidence of conduction disturbances. The next-generation Evolut Pro, recently approved by the US Food and Drug Administration (FDA), consists of the same platform as Evolut R, incorporating an external porcine pericardial tissue casing to improve the seal between the prosthesis and the ring of the native aorta and minimize paravalvular leaks.

The Lotus valve system (Boston Scientific) consists of bovine pericardium mounted and sutured in a rugged braided nitinol frame. This is the only new-generation device that can be fully recaptured and repositioned even after the prosthesis has been fully implanted. Among the approved devices, this was associated with a lower rate of paravalvular leaks.[18] However, the high rate of conduction disturbance requiring definitive pacemaker implantation with this device (30%) remains one of its limitations. The latest generation Lotus™ THV (Boston Scientific) and the new releasing mechanism (Depth Guard; Boston Scientific) have been developed with the prospect of reducing the frequency of conduction disorders. However, there are as yet no robust clinical data on its efficacy.

The bioprosthesis Acurate Neo™ (Symetis) is composed of porcine pericardial leaflets sewn into a nitinol self-expandable stent, covered both externally and internally. The device includes three arches of stabilization for axial alignment with the aortic annulus, an upper crown and a lower part that is open to the total distribution in the native valve. This does not allow recapture; however, it has been demonstrated to be extremely stable during deployment.

Industry and technology have worked and evolved a lot and new options of devices are already on the horizon.

ACCESS ROUTES

The first implants were performed using an anterograde transeptal approach. After a few years, this pathway was abandoned in favor of the preferential approach, that is, the transfemoral approach and other alternative routes (transapical, transaortic, trans-subclavian, transcarotid and transcaval). An accurate angiotomography-guided analysis is essential for selection of the most appropriate access route that should consider vessel anatomy and the profile and size of the device chosen to minimize the risk of vascular complications.[19] Operator preference, diameter of peripheral vascular accesses, local expertise, evaluation of imaging methods, and discussion of team cases are the main determinants in the choice of the access route.

COMPLICATIONS

Despite the technological advances in the development of implantation devices and techniques, as well as the greater number of procedures and the expansion of indications, potential complications can occur and need consideration and prevention. The first cases that emerged with TAVI were vascular complications, peri- and post-procedural neurological events, conduction disorders, and perivalvar regurgitation.[2,3] More recently, aortic rupture and coronary occlusion, despite a low incidence, were sources of greater concern owing to their potential and serious impact.[11,15] It is worth noting that other concerns have also emerged regarding the durability and risk of thrombosis since procedures are progressively being performed in younger, lower-risk patients.[20-22]

Vascular complications such as bleeding, need for blood transfusion and hemodynamic instability were already the greatest limitations. However, improvements in devices, in the selection of patients, and experience have made these

complications rarer. Currently, the major vascular complications are minor bleeding and direct injury to the vessel, such as dissection and occlusion.[23]

Cerebrovascular events are associated with high morbidity and mortality. The first studies reported event rates of 3.3% in 30 days in a meta-analysis of 64 studies involving 72,318 patients.[24] Approximately 50% of the events occurred after 24 hours of the procedure, and the others occurred during manipulation of the catheter in the aortic valve, balloon dilation, and with prosthesis release. Neurological events manifest clinically with focal signs or even silent ischemia, which is detected by brain magnetic resonance imaging.[2] Recent studies reported a favorable trend of reduction in the occurrence of events to around 2.5%, mainly with the advancement of the devices and experience gained. In addition, protective devices are being developed to filter or deflect debris always distant from the cerebral circulation.[25] The FDA approved the Sentinel™ (Claret Medical) device; however, trials have not demonstrated relevant clinical reductions in the rates of cerebral vascular accidents.

The most commonly found conduction disorders are left bundle branch block and total atrioventricular block.[26] Figure 1 shows that the rates of permanent pacemaker implants are variable depending on the device used. Efforts are made to avoid these complications, as they are associated with lower dyssynchrony and recovery of left ventricular function, a greater likelihood of needing a pacemaker, longer hospital stays, and the need for new admissions. The assessment of valve anatomy and selecting the most appropriate prosthesis does not always minimize these effects. The development of the second-generation devices (particularly Evolut R and Lotus), with their ability to recapture and reposition failed to fully resolve these problems.[18]

The emergence of paravalvular leak can be observed and is more common in TAVI than conventional surgery.[2,28] The incidence of moderate-to-severe leak in first generation devices was reported as 12 to 21% of the cases[28] and, as shown in Figure 1, it displays variable incidences between the devices. This observation deserves special attention and prevention given its relationship with high morbidity and mortality.[29] The three mechanisms involved in this are incomplete apposition to the valve ring due to severe calcification, undersizing and/or malposition of the prosthesis. In more recent series, leak rates have decreased significantly.[18] This is due to a better evaluation of the preoperative valve ring diameters with angiotomography, recapture capacity, repositioning and fine-tuning of the new prostheses and the addition of a skirt or extra outer seal layer to fill spaces between the transcatheter prosthesis and the aortic annulus.

Currently TAVI is being indicated for younger and lower-risk patients. This makes it mandatory to know aspects and monitor possible complications related to durability, as patients of this profile have a higher life expectancy, in addition to a calcium metabolism that accelerates the calcification of the leaflets, than do those who had the first indications of TAVI. Failures can be related to the deterioration (as a result of calcification, pannus or thrombosis) or intraprosthetic regurgitation (for example, reduction of mobility of the leaflets and/or endocarditis).[20] In the older series, no significant

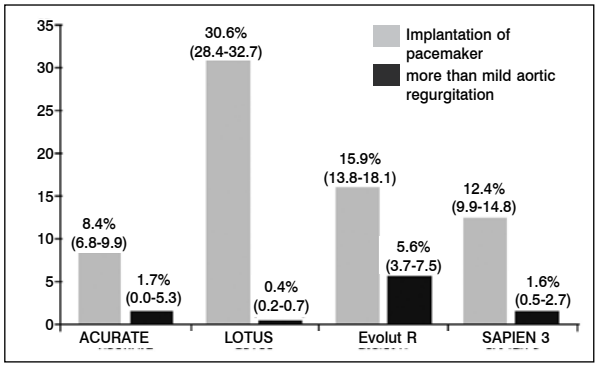


Figure 1. Comparison of the incidence of pacemaker implantation and moderate-to-severe aortic regurgitation in patients undergoing TAVI with new-generation devices.[27]

increase in the mean gradient or structural deterioration of the valves were reported during five years of follow-up in the PARTNER study.[20] Three other studies[30-32] also reported outcomes in monitoring of up to five years, two of them do not suggest important issues regarding the durability, with stable transprosthetic gradients which were maintained over time and a dysfunction rate of 3.4% and 4.2%, respectively, using different definitions.

The thrombosis, although concerning, is still a rare event, as recently stated in an observational study based on the RESOLVE and SAVORY[22] registry on the prevalence of subclinical leaflet thrombosis in patients undergoing TAVI or conventional surgery. Of a total of 890 patients who were analyzed by angiotomography, 12% had leaflet thrombosis, 4% of the 138 patients undergoing conventional surgery, and 13% of the 752 patients who underwent TAVI. It was also observed that this event was less frequent in patients who used anticoagulant therapy compared to those who used double antiplatelet therapy (4% vs. 15%, $p < 0.0001$). Both new anticoagulants and coumarins are effective in preventing leaflet thrombosis. In general, the rate of stroke was not significant among the patients; however, an association with major transient ischemic events was observed (6% vs. 1%, $p < 0.001$).[22] These results showed a new direction in the optimization of pharmacological therapy and may improve valve hemodynamics and clinical outcomes. The current recommendation under the ACC/AHA 2017 guidelines is for double antiplatelet use for three months. Two studies are under way, GALILEO and ATLANTIS. Both are evaluating the use of non-vitamin K anticoagulants (rivaroxaban and apixaban, respectively) for prevention of leaflet thrombosis, which may change recommendations in the near future.

Although uncommon (0.5% to 3.1%) [33], endocarditis may be a serious complication. In a recent multicenter registry that included 250 cases after TAVI, hospital mortality was 36% and the two-year mortality rate was 66.7%. [34] Younger age, male sex, history of diabetes mellitus, and moderate-to-severe residual aortic regurgitation were significantly associated with an increased risk of infective endocarditis.[34]

Although the possibility of a late failure in transcatheter valve replacement is perceived as a major concern, preliminary observations have demonstrated that, in contrast with the reoperation of conventional surgery, which is technically

challenging with a significant risk of morbidity and mortality, redoing TAVI seems to be safe and effective.[35]

In short, the knowledge of complications is extremely important to plan the procedure. The association of complications with the profile of patients is becoming important because as evidence unfolds, indications are being extended to patients at lower risk and those who are younger. Factors such as the accumulated experience, expertise, and technological evolution of devices, shown in Figure 2, contribute to positive changes over time in the reduction of adverse events.

MINIMALIST APPROACH

Currently, TAVI is a standardized and reproducible procedure. One of the most discussed issues is whether it should be simplified or not. As experience has grown and the learning curve has been exceeded in recent years, many groups have worked on local programs that incorporate pre-, peri, and post-procedural changes with this objective.

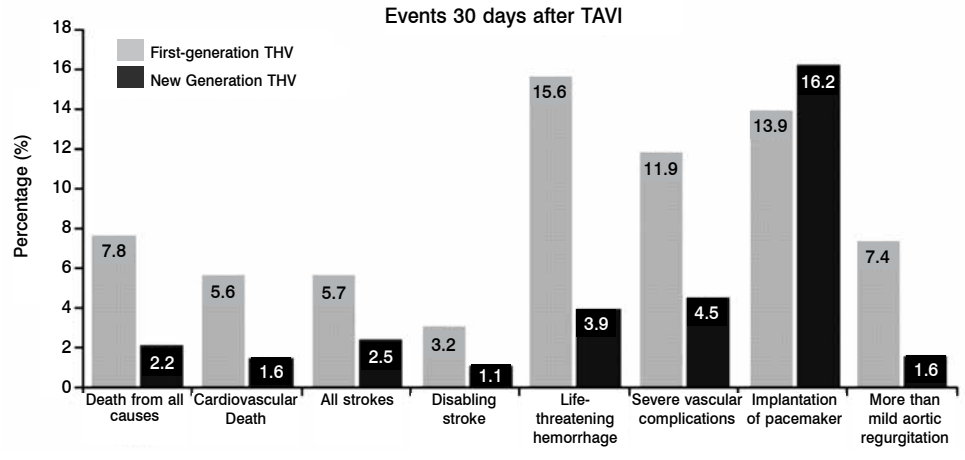
The procedure itself requires a series of preoperative evaluations as the completion of examinations aimed at clinical and anatomical confirmation of indication (echocardiogram, computed tomography). Ideally, these assessments must be performed without hospitalization of the patient. In addition, the team must assess whether it is eligible for an optimized protocol looking beyond the traditional clinical and anatomical criteria and incorporating other factors such as clinical, nonclinical and psychosocial problems. These include the involvement of the patient, the willingness to participate in the cardiac rehabilitation program, and the possible presence of associated neurological problems. One should also evaluate the family dynamics to determine whether patients have the support necessary for a successful recovery.[27]

During the periprocedure, some aspects should be considered, without which patient safety is compromised. The location may be in the hemodynamic laboratory rather than in a hybrid room. If performed by the transfemoral route, the presence of a cardiac surgeon in the room is not mandatory; however, it is fundamental that he is involved in the process and available for any intercurrences that require his action. The team should contain at least two operators, a nurse and an X-ray technician. The presence of an echocardiographer, anesthesiologist, vascular surgeon and perfusionist in the catheterization laboratory is not an absolute necessity; however, they must be involved in selected cases of greater complexity or for those personnel who are in the early stages of the learning curve.[27]

Immediately after the procedure, all patients should be monitored in the hemodynamics laboratory or hybrid surgical room for at least 10–15 minutes with special attention to the hemodynamics and cardiac rhythm. Subsequently, they should be transferred to a coronary care unit or a regular cardiology ward with telemetry, according to local protocols. The clinical status of the patient, with special attention to the procedural result, ECG, echocardiographic and laboratory results, should be carefully evaluated. The mobilization should be prescribed after a few hours, provided that there are no vascular access problems (hematoma, bleeding) and the temporary pacemaker is removed. Patients who do not present complications (or those whose complications have been resolved) can then be discharged the next day.[27]

The efforts to accelerate recovery and mobilization motivate a shorter hospitalization time and minimize unnecessary use of resources. Discharge 24–72 hours after the procedure did not prevent the safety, as has already been demonstrated in some studies. [34.35] The most common problems involved with prolonged hospitalization are conduction disturbances, bleeding and acute kidney injury. The monitoring of acute atrioventricular block is by far the most important.

The cost-effectiveness of a minimalist approach in TAVI is not yet clear. In a small American series[35] with 142



TAVI = Transcatheter Aortic Valve Implantation
THV = Transcatheter Heart Valve

Figure 2. Results comparing the rate of events in 30 days between the first-generation valves (Medtronic, CoreValve, Edwards, Sapien and Sapien XT)[28] and the new-generation devices (Sapien 3, Evolut R, Portico, Lotus, Acurate, Acurate Neo).[27]

patients (n = 70 undergoing simplified transfemoral TAVI and n = 72 standard TAVI), it was demonstrated that the simplified strategy reduces cost (estimated US $2,869) and can be used frequently to avoid expenses associated with hybrid operating rooms and anesthesia.

In conclusion, although TAVI is a complex procedure, important advances in simplifying the procedure have already been achieved. In many centers, this type of approach is already routine and proved to be as safe and effective as the traditional procedure. The results of the 3MTAVR and FAST-TAVI studies will be able to provide more information on this issue in the future.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest in conducting this study.

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