

# Spotlight on the SAPIEN 3 transcatheter heart valve

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**Abstract:** Transcatheter aortic valve implantation (TAVI) is increasingly performed in patients with severe aortic stenosis. The efficacy and safety have been demonstrated in large randomized trials in patients with high- or intermediate operative risk. With latest-generation transcatheter heart valve (THV) systems, growing operator experience and improved patient selection, clinical outcome has significantly improved with a decline of TAVI-related complications. In this review, the Edwards SAPIEN 3 THV is discussed in terms of technology, procedural advances and complication trends and future developments.

**Keywords:** aortic valve stenosis, transcatheter aortic valve implantation, TAVI, transcatheter heart valves, Edwards SAPIEN 3

## Introduction and current trends

Aortic stenosis is the most common valvular heart disease in the Western world.<sup>1</sup> In the last 15 years, since the first-in-human transcatheter aortic valve implantation (TAVI) performed by A Cribier in 2002, the number of TAVI procedures has increased impressively.<sup>2</sup> So far, >350,000 procedures have been performed in over 70 countries.<sup>3</sup>

Over the last decade, the indication for TAVI has gradually shifted from a challenging intervention in inoperable, high-risk patients toward a standardized straightforward procedure in intermediate to even lower-risk patients. Based on evidence from large randomized controlled trials (RCTs), current guidelines recommend TAVI in high-risk patients and also recommend to consider this treatment option for intermediate-risk patients as non-inferiority to surgical aortic valve replacement (SAVR) has been shown.<sup>4-6</sup> Currently, there are ongoing trials (ie, Placement of Aortic Transcatheter Valves [PARTNER] 3 and Low-Risk Evolut R), evaluating the safety and efficacy of TAVI even in patients with low operative risk.

## SAPIEN 3 transcatheter heart valve Technical issues

The development of current devices goes back to the first description of a transcatheter heart valve (THV) by HR Andersen et al in 1992.<sup>7</sup> Over the last decade, there has been a rapid and impressive evolution in THV, delivery systems and technical approaches. Currently, several competing THVs are available.<sup>3</sup>

The original Cribier-Edwards THV (Edwards Lifesciences, Irvine, CA, USA) consisted of a stainless-steel frame with equine pericardium valve leaflets and was subsequently modified as the Edwards SAPIEN THV, using among others a

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higher sealing cuff and bovine pericardium leaflets (Figure 1A). The SAPIEN THV was followed by the SAPIEN XT THV (Figure 1B), which consisted of cobalt chromium alloy frame and bovine pericardium leaflets.

The SAPIEN 3 (S3) THV is the latest generation of Edwards balloon-expandable valves. It features a cobalt chromium alloy frame that provides a high radial strength for circularity and optimal hemodynamics, a low frame height and an open cell geometry, allowing access to coronary vessels for future interventions and an outer polyethylene terephthalate (PET) skirt to minimize paravalvular leakage (PVL). The valve tissue consists of three leaflets manufactured from bovine pericardium (Figure 1C). Four different sizes of the S3 THV are currently available: 20 mm, 23 mm, 26 mm and 29 mm. Selection of the appropriate THV should be made according to multislice computed tomography (MSCT) annulus area-based sizing recommendations provided by the manufacturer.<sup>8</sup> The treatable range of aortic annulus diameters is wide and ranges from 18.6 mm to 29.5 mm.

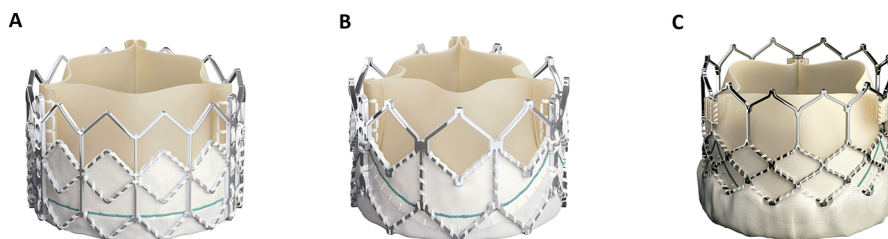
The transfemoral commander delivery catheter (Edwards Lifesciences) allows for accurate positioning of the THV within the native valve. As an aid, a central balloon marker is incorporated as a primary landmark for correct positioning during implantation. The S3 THV is compatible with a 14-French (Fr) (in the case of a 20 mm, 23 mm or 26 mm S3 THV) or 16-Fr (in the case of a 29 mm S3 THV) expandable sheath (eSheath; Edwards Lifesciences). The outer diameter of a 14-Fr sheath is 6 mm and that of a 16-Fr sheath is 6.7 mm, respectively. It should be noted that the outer sheath diameter is 18-Fr (for 20–26 mm S3 THV) and 20-Fr (for 29 mm S3 THV), which increases during THV passage up to 24-Fr (for 20–26 mm S3 THV) and 27-Fr (for 29 mm S3 THV). Taking into consideration that arteries are somewhat compliant, the recommended minimal vessel diameter for

a transfemoral approach is 5.5 mm (for 14-Fr eSheath) and 6 mm (for 16-Fr eSheath), respectively. However, due to the expanding nature, some caution needs to be exerted in the case of circular vascular calcifications.

## Procedural advances and complication trends

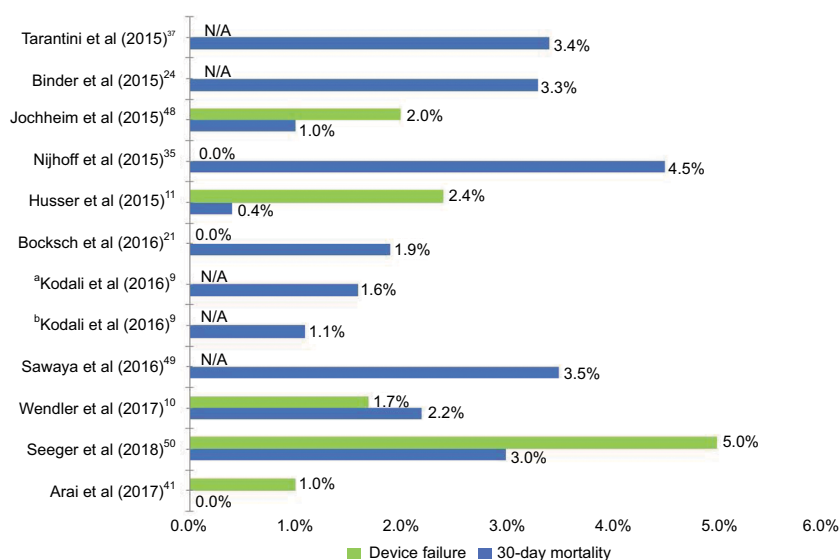
The S3 THV has received CE (Communauté européenne)-mark approval in Europe in January 2014 and US Food and Drug Administration approval in the US in June 2015. The 30-day mortality rate of 2.1% and further important adverse events were among the lowest reported at that time.<sup>8</sup> Early clinical results of the PARTNER II trial confirmed the favorable outcome of the S3 THV system with low 30-day mortality rates, which were 2.2% in high-risk or inoperable patients and 1.1% in intermediate-risk patients, respectively.<sup>9</sup> Real-world data from large registries have also been promising (Figure 2).<sup>10,11</sup> Further studies with longer follow-up confirmed these excellent results with 1-year mortality rates of 17.7% in inoperable patients and 12.7% in high-risk patients, respectively.<sup>12</sup> These results demonstrated a considerable improvement compared with 1-year mortality rates of 31% in inoperable patients and 24% in high-risk patients reported from the first PARTNER trial, which began enrollment in 2007.<sup>13,14</sup>

Despite these tremendous advances in survival with new-generation devices, increasing operator experience and improvement in patient selection, there are several TAVI-related complications requiring special attention when evaluating a novel THV. In the following, these important issues, including PVL, conduction disturbances leading to permanent pacemaker implantations (PPIs), vascular complications and cerebrovascular events (CVE), are further discussed with special focus on the S3 THV (Table 1).



**Figure 1** Overview of Edwards Lifesciences balloon-expandable valves.

**Note:** (A) Edwards SAPIEN, (B) Edwards SAPIEN XT, (C) Edwards SAPIEN 3. Copyright ©2018 Edwards Lifesciences Corporation. Reproduced from <https://www.edwards.com> [homepage on the Internet]. transcatheter heart valve. Available from: <https://www.edwards.com/gb/devices/heart-valves/transcatheter>.<sup>70</sup>



**Figure 2** Device failure and 30-day mortality rates after TAVI with SAPIEN 3

**Note:** <sup>a</sup>Inoperable/high-risk cohort, transfemoral approach, <sup>b</sup>intermediate-risk cohort, transfemoral approach. N/A, not applicable.

**Abbreviation:** TAVI, transcatheter aortic valve implantation.

## Paravalvular aortic regurgitation

Historically, PVL has been a frequent complication after TAVI, with much higher rates when compared with SAVR. In a meta-analysis of Génèreux et al,<sup>15</sup> the incidence of moderate or severe PVL has been reported to be 7.4% after TAVI using first-generation devices. Long-term data of the PARTNER A and B trial with up to 5 years follow-up showed that the presence of PVL negatively impacts prognosis.<sup>13,16,17</sup> Severe or asymmetric calcification of the native aortic annulus leading to incomplete apposition, annular eccentricity, malpositioning and undersizing of the device are probable mechanisms contributing to PVL.<sup>18–20</sup>

As PVL was initially regarded as a barrier for a widespread use of TAVI, the so-called “next”-generation devices were developed to incorporate special features, such as repositionability and retrievability, allowing for a controlled deployment as well as external sealing features to overcome this issue.

In line with this demand, one key modification of the current S3 THV is an outer skirt surrounding the valve frame to provide external sealing and to reduce the rate of PVL. As expected, the number of any kind of PVL was reduced with the S3 THV, and the rate of moderate or severe PVL has decreased from 6.9% with SAPIEN XT to 1.6% with S3.<sup>21–25</sup> Besides technical developments of the valve design, more sophisticated sizing algorithms with a routine use of pre-procedural MSCT may also have contributed to a reduction in PVL by an optimized valve deployment.<sup>8</sup>

## New-onset conduction disturbances

Based on the proximity of the cardiac conduction system to the aortic root, conduction disturbances are frequently observed after TAVI and may reach up to 40% of the cases, depending on the implanted THV type.<sup>26</sup> The most prevalent conduction disturbances are non-specific intraventricular conduction abnormalities (CA), left bundle branch block (LBBB) and complete atrioventricular block requiring PPI. Development of new-generation devices had the goal to overcome this issue, in particular because it has been shown that new-onset CA, especially new LBBB, and PPI may be negatively associated with recovery of left ventricular function after TAVI<sup>27–29</sup> and may lead to a higher rate of hospitalizations for worsening heart failure.<sup>30</sup> Regarding the impact of PPI on long-term mortality, available data are conflicting.<sup>30,31</sup> While some investigations found no effect of PPI on mortality,<sup>6,32</sup> recent analyses from the PARTNER trial identified chronic pacing as an independent predictor of 1-year mortality after TAVI.<sup>30,33</sup>

With the introduction of the new S3 THV, it was of special interest to assess how the new valve design and the outer skirt would affect the rate of new CA and PPI in comparison with its predecessor. Indeed, patients treated with the S3 had a higher rate of new CA compared with SAPIEN XT.<sup>34</sup> Nevertheless, the rate of new PPI with S3 compared with SAPIEN XT was comparable, with only a slight, non-significant trend toward a higher rate with S3.<sup>24,34,35</sup> In line with other valve types, one of the major baseline predictors for a new PPI

**Table 1** Periprocedural complications and clinical outcomes with SAPIEN 3™ and SAPIEN XT

Study	Year	Cohort	Device failure	≥Moderate PVL	PPI	MVC	Bleedings <sup>a</sup>	Stroke <sup>b</sup>	MI	30-day mortality
<b>SAPIEN 3</b>										
Amat-Santos et al <sup>156</sup>	2014	27	–	0	–	0	–	0	0	–
Tarantini et al <sup>137</sup>	2015	29	–	0	6 (20.7)	–	–	0	0	1 (3.4)
Binder et al <sup>124</sup>	2015	153	–	2 (1.3)	26 (17)	5 (3.3)	6 (3.9)	2 (1.3)	2 (1.3)	5 (3.3)
Jochheim et al <sup>148</sup>	2015	100	2 (2)	2 (2)	12 (12)	7 (7)	10 (10) <sup>c</sup>	2 (2)	–	1 (1.0)
Nijhoff et al <sup>135</sup>	2015	44	0	0	4 (9.8)	2 (4.5)	1 (2.3)	0	1 (2.3)	2 (4.5)
Husser et al <sup>111</sup>	2015	250	6 (2.4)	5 (2)	35 (14)	9 (3.6)	11 (4.4)	3 (1.2)	0	1 (0.4)
Yang et al <sup>125</sup>	2015	61	–	2 (3.3)	–	–	–	–	0	0
Bocksch et al <sup>121</sup>	2016	107	0	0	13 (12.1)	10 (9.3)	–	2 (1.9)	–	2 (1.9)
Husser et al <sup>134</sup>	2016	96	0	0	12 (12.5)	2 (2)	3 (3)	2 (2)	0	–
Kodali et al <sup>9</sup>	2016	491 <sup>d</sup>	–	55 (3.4)	66 (13.5)	27 (5.5)	27 (5.5)	4 (0.8)	2 (0.4)	8 (1.6)
		953 <sup>e</sup>	–		100 (10.5)	60 (6.3)	34 (3.6)	7 (0.7)	3 (0.3)	10 (1.1)
Sawaya et al <sup>149</sup>	2016	283	–	6 (2.4)	43 (17.3)	8 (2.8)	–	4 (1.4)	0	8 (3.5)
de Torres-Alba et al <sup>157</sup>	2016	162	–	0	31 (19.1)	–	–	–	–	–
Wendler et al <sup>110</sup>	2017	1,950	33 (1.7)	60 (3.1)	233 (12)	80 (4.1)	97 (5)	28 (1.4)	5 (0.3)	43 (2.2)
Seeger et al <sup>150</sup>	2018	100	5 (5)	0	18 (18)	3 (3)	2 (2)	4 (4)	–	3 (3)
Arai et al <sup>141</sup>	2017	111	1 (1)	6 (5)	8 (7)	3 (3)	0	0	–	0
<b>SAPIEN XT</b>										
Amat-Santos et al <sup>156</sup>	2014	50	–	4 (8)	–	2 (4)	–	0	0	–
Tarantini et al <sup>137</sup>	2015	29	–	2 (6.9)	1 (3.4)	–	–	2 (6.9)	1 (3.4)	1 (3.4)
Binder et al <sup>124</sup>	2015	445	–	23 (5.2)	49 (11)	41 (9.2)	24 (5.4)	14 (3.1)	0	20 (4.5)
Jochheim et al <sup>148</sup>	2015	354	25 (7.1)	31 (8.8)	37 (10.5)	29 (8.2)	59 (16.7) <sup>c</sup>	6 (1.7)	–	15 (4.2)
Nijhoff et al <sup>135</sup>	2015	66	4 (6.1)	5 (7.7)	5 (8.8)	11 (16.7)	8 (12.1)	1 (1.5)	0	3 (4.5)
Yang et al <sup>125</sup>	2015	92	–	12 (13.0)	–	–	–	–	1 (1.1)	2 (2.2)
Bocksch et al <sup>121</sup>	2016	102	2 (2.0)	3 (2.9)	14 (13.7)	7 (6.9)	–	4 (3.9)	–	3 (2.9)
Husser et al <sup>134</sup>	2016	87	7 (8)	6 (7)	11 (12.6)	4 (5)	5 (6)	2 (2)	2 (2)	–
Sawaya et al <sup>149</sup>	2016	507	–	47 (9.7)	44 (9.8)	50 (9.9)	–	13 (2.8)	2 (0.4)	42 (8.7)
de Torres-Alba et al <sup>157</sup>	2016	287	–	8 (2.8)	35 (12.2)	–	–	–	–	–
Seeger et al <sup>150</sup>	2018	100	8 (8)	2 (2)	21 (21)	16 (16)	9 (9)	7 (7)	–	8 (8)
Arai et al <sup>141</sup>	2017	89	4 (4)	8 (9)	3 (4)	11 (12)	0	0	–	4 (5)

**Note:** <sup>a</sup>Life-threatening bleedings, <sup>b</sup>major or disabling stroke, <sup>c</sup>life-threatening or major bleedings, <sup>d</sup>inoperable/high-risk cohort, transfemoral approach and <sup>e</sup>intermediate-risk cohort, transfemoral approach.

**Abbreviations:** MI, myocardial infarction; MVC, major vascular complications; PPI, permanent pacemaker implantation; PVL, paravalvular leakage.

with the S3 THV was a pre-existing right bundle branch block (RBBB).<sup>34,36</sup> Additionally, it has been postulated that a higher implantation of the THV within the virtual aortic annulus may result in lower pacemaker rates.<sup>37</sup> Oversizing has also been identified as an important predictor of PPI,<sup>38</sup> and recent data indicate a linear relationship between oversizing and PPI with no ideal sizing range to minimize PPI while maintaining device success.<sup>69</sup>

## Vascular complications

Vascular complications are another major hurdle of the TAVI procedure with initial rates of (major) vascular complications ranging from 1.9% to 17.3%.<sup>39</sup> Fortunately, life-threatening complications, such as aortic dissection, annular rupture or left ventricular perforation, have been rare with reported rates of usually <1%.<sup>40</sup> Access-site-

related vascular complications constitute the most common vascular complications in transfemoral TAVI. Apart from small vessel diameters and severe calcifications, the sheath-to-femoral artery ratio belongs to the main predictors of major vascular complications.<sup>39</sup> To address this issue, another key feature of the S3 was the reduction of the delivery system profile. To some extent, this was achieved by the feature that the THV is mounted onto the deployment balloon within the body in the descending aorta instead of an on-balloon delivery. The 14-Fr eSheath can accommodate the 20 mm, 23 mm and 26 mm S3 THV, and the 16-Fr eSheath the 29 mm S3 THV, whereas larger sheaths were necessary for SAPIEN XT, namely 16-Fr (23 mm), 18-Fr (26 mm) and 20-Fr (29 mm).

It has been shown that the modification of the delivery system led to a significant reduction in the mean sheath size

with the use of S3 (14.3-Fr) compared with SAPIEN XT (18.1-Fr).<sup>41</sup> Consequently, major vascular complications have been reduced from 8.9% using SAPIEN XT to 5.1% with S3.<sup>22</sup> This is of high clinical relevance, as vascular complications likely affect clinical outcome with higher mortality and morbidity, longer hospital stays and increased costs.<sup>42–44</sup> Accordingly, the average hospital length of stay was significantly longer for patients with major (16 days) and minor (11 days) vascular complications compared with those without (6 days).<sup>45</sup> Altogether, the reduction of vascular complications by a reduction in sheath sizes is a major driver enabling the current trend toward a simplification of the procedure.<sup>46,47</sup>

## Cerebrovascular events

CVE belong to the most dreadful complications of TAVI and have a decisive impact on mortality, morbidity and quality of life.<sup>51,52</sup> According to a large meta-analysis including >70,000 patients from 64 studies, 3.3% experienced a CVE during or after TAVI. Depending on the timing, several factors have been associated with an increased risk for CVE. The majority (54%) occurs within the first 24 hours of the TAVI procedure. Most likely, embolic mechanisms account for these acute CVE, and balloon post-dilatation and valve dislodgement/embolization belong to the major predictors in this phase. In contrast, new-onset atrial fibrillation (NOAF) seems to be the major predictor of CVE during the subacute phase after TAVI (<30 days).<sup>53</sup>

With the S3 THV, the rate of CVE has been comparatively low (1.9%).<sup>22</sup> This reduced rate of CVE with the S3 THV in line with a general decrease in CVE in TAVI in recent years, most likely reflects not only technical advances in THV technology and delivery systems but also increased operator experience. Potential differences in thrombogenicity as well as platelet activation and coagulation of current THV and different deployment mechanisms are discussed as additional contributors to CVE.<sup>54,55</sup> Therefore, due to the devastating character of CVE, optimal periprocedural pharmacotherapy and prevention and optimal medical treatment of NOAF have to be further refined. Furthermore, ongoing trials regarding the optimal medical treatment after TAVI, such as ATLANTIS (NCT02664649), ENVISAGE (NCT02943785) and GALILEO (NCT02556203), are awaited with great interest.

## Competing devices and procedural aspects

THV systems have usually been categorized according to the deployment mechanism, as either balloon-expandable

and self-expanding or mechanically expanding. Although direct randomized comparisons of both technologies are scarce, both have been used in large registries with good clinical outcome.<sup>58,59</sup> Historically, mainly the SAPIEN and CoreValve THV families have been compared, whereas nowadays other new THV designs and deployment systems are available, including the self-expanding ACURATE neo™ (Boston Scientific, Marlborough, MA, USA) and Portico™ (Abbott, Saint Paul, MN, USA) valves as well as the mechanically expanded Lotus valve (Boston Scientific). Until data from ongoing RCTs, such as SCOPE I, SCOPE II and SOLVE-TAVI, are available, the CHOICE trial remains the only RCT comparing two THV designs.<sup>60,61</sup> In the CHOICE trial, although device success rates were higher with the balloon-expandable SAPIEN XT valve, there was no difference in clinical outcomes after 1 year in a cohort of high-risk patients.<sup>61</sup>

Hence, with data from RCTs pending, it appears that the majority of patients can be treated safely using both types of THVs with comparable clinical outcome. The MoRENA registry, a large multicenter registry, including 1,121 patients treated with either the balloon-expandable S3 or the self-expanding ACURATE neo (NEO) THV, showed similar procedural and clinical results with both devices,<sup>11</sup> which in the case of NEO were in line with data from a large post-market registry.<sup>62</sup> Also, in another non-randomized comparison of the S3 THV with the mechanically expanding Lotus THV, comparable results regarding safety were achieved, albeit with a considerably higher PPI rate with the Lotus THV.<sup>63</sup>

Despite these comparable outcome data, there are certain putative advantages of each deployment mechanism. Compared with S3, NEO was associated with less PPI (9.9% vs 15.5%) and less elevated gradients after TAVI (3.2% vs 6.9%) but showed more moderate or severe PVL (4.8% vs 1.8%).<sup>11</sup> Whether certain anatomical features and baseline risk factors, including calcified anatomies, eccentric aortic annuli and pre-existing RBBB, may favor one over the other THV design remains to be addressed by future research.

In line with this notion, a recent study has shown that THV with higher radial force, such as the S3, may have advantages as compared to devices with lower radial force in calcified anatomies.<sup>64</sup> Being one of the most used THV in the field, several attempts have been made to simplify and to further reduce the periprocedural risk of the TAVI procedure. With regard to the S3 THV, one important factor is the possibility of direct implantation by omitting prior balloon valvuloplasty.



This approach avoids rapid ventricular pacing and may result in a reduction of adverse events, such as annular rupture and CA, and has been successfully applied in a series of patients with no apparent downside in safety.<sup>65</sup>

Pending evidence from ongoing RCT will further clarify a potential role of patient-tailored THV therapy for individual patients based on anatomical features, baseline risk factors and comorbidities and may further optimize clinical outcome and reduce adverse events after TAVI.

## Perspectives

With growing number of TAVI procedures and its widespread application, standardized pre-procedural diagnostic algorithms and intra-procedural steps have been established, resulting in a simplified procedure. With high procedural success rates and reduced complications, an expansion of TAVI to lower-risk patients as well as to specific subgroups, such as patients with degenerated bioprostheses (“valve-in-valve TAVI”) or bicuspid aortic valves, is currently underway.

As the S3 THV has only been in use in Europe for 4 years, data regarding long-term performance are limited so far. In general, long-term data with early-generation devices are encouraging with good bioprosthetic valve function up to 7 years after TAVI.<sup>16,66–68</sup> However, due to the relatively high competing risk of death with mortality rates up to 76% after 7 years,<sup>68</sup> it is difficult to determine the exact rate of structural valve degeneration. Long-term data in intermediate-risk patients and continuous follow-up of survivors are needed to clarify this issue.

Furthermore, long-term results will shed light into the uncertainty of long-term durability of the S3 THV. Currently, the S3 THV represents one of the most widely used THVs in the field, and accumulating evidence and experience show excellent clinical results. With the successor of the S3 THV, the S3 Ultra, already at the horizon (NCT03471065), we hope to further our understanding of this device in order to offer the best possible care to our patients.

## Disclosure

TR reports no conflicts of interest relevant to this work. JB has received proctor fees from Boston Scientific. HM has received proctor fees or speaker honoraria from Abbott, Biotronik, Edwards Lifesciences, Symetis SA and SJM. OH received proctor fees from Boston Scientific and minor congress support from Edwards Lifesciences. The authors report no other conflicts of interest in this work.

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