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Expert Review of Cardiovascular Therapy

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ierk20

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To cite this article: Carolina Montonati, Dario Pellegrini, Daniele Oreste d'Atri, Mariano Pellicano, Daniele Briguglia, Francesco Giannini, Giuseppe De Blasio, Giulio Guagliumi, Maurizio Tespili & Alfonso Ielasi (2024) A novel balloon-expandable transcatheter aortic valve bioprosthesis: Myval and Myval Octacor, Expert Review of Cardiovascular Therapy, 22:7, 325-337, DOI: 10.1080/14779072.2024.2375345

To link to this article: https://doi.org/10.1080/14779072.2024.2375345

Published online: 15 Jul 2024.

EXPERT REVIEW OF CARDIOVASCULAR THERAPY
2024, VOL. 22, NO. 7, 325–337
https://doi.org/10.1080/14779072.2024.2375345

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REVIEW

A novel balloon-expandable transcatheter aortic valve bioprosthesis: Myval and Myval Octacor

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ABSTRACT

Introduction: Over the past two decades, transcatheter aortic valve replacement (TAVR) has expanded its application across all surgical risk levels, including low-risk patients, where, due to longer life expectancy, reducing common pitfalls of TAVR is essential. To address these needs, many technological advancements have been developed. Myval and the new generation Myval Octacor (Meril Life Sciences Pvt. Ltd) are novel balloon-expandable (BE) transcatheter heart valve (THV) systems designed for the treatment of severe aortic stenosis.

Areas covered: This review aims to illustrate the design features of these novel THVs and the main evidence from available studies. Furthermore, we provide evidence of these THVs' performance in challenging scenarios such as extra-large aortic annuli, bicuspid aortic valves, and valve-in-valve/valve-in-ring procedures.

Expert opinion: Myval and Myval Octacor have demonstrated comparable early safety and clinical efficacy to the leading contemporary THVs, exhibiting remarkably low rates of moderate to severe paravalvular leak (PVL) and permanent pacemaker implantation (PPI). The wide range of sizes offered by the Myval family may minimize the risk of under-/oversizing, potentially explaining the lower rates of the aforementioned phenomena. Moreover, the presence of both internal skirt and external reinforced cuff may also explain the low rate of moderate to severe PVL.

ARTICLE HISTORY
Received 28 February 2024
Accepted 28 June 2024

KEYWORDS
Aortic stenosis; transcatheter aortic valve replacement; balloon-expandable valve; Myval; Octacor; paravalvular leaks; permanent pacemaker implantation

1. Introduction

Transcatheter aortic valve replacement (TAVR) has become a well-established alternative treatment to surgical aortic valve replacement (SAVR) for patients with severe aortic stenosis (AS) at intermediate surgical risk and the standard of care for AS patients at high or prohibitive surgical risk [1–3]. The noninferiority and/or superiority of TAVR, when compared with SAVR, even for patients with severe AS at low surgical risk has led to an expanded adoption of TAVR globally [4–6].

Therefore, over the past two decades, there has been a notable increase in the application of TAVR. This has been accompanied by numerous technological advancements and design enhancements aimed at addressing the challenges of complex and unconventional anatomies. Next to two commonly used transcatheter heart valves (THVs) (Sapien 3 [Edwards Lifesciences, Irvine, California] and Evolut R and Pro [Medtronic, Minneapolis, Minnesota]), newer THVs have become available in recent years to simplify, enhance safety, and improve the effectiveness of TAVR by reducing the need for permanent pacemaker implantation (PPI) and the incidence of moderate-severe paravalvular leak (PVL), which can impair clinical outcomes [7–9]. Myval and Myval Octacor (Meril Life Sciences Pvt. Ltd, Vapi, India) are novel balloon-expandable (BE) THV systems. Following the first-in-human study, Myval was approved by the Central Drugs Standard Control Organization (CDSCO) of India in October 2018 and received CE marking in April 2019 [10,11]. It is presently approved for commercial use in 60 countries. The main feature of Myval, compared to other BE THVs, is their availability in intermediate and extra-large sizes, in addition to conventional sizes. This guarantees tailored sizing, which, by reducing under- or oversizing, could potentially lower adverse events and improve long-term outcomes.

For the purpose of the review, the authors systematically searched several databases including MEDLINE, Embase, the Cochrane database, Google Scholar, ClinicalTrials.gov, and Clinical Trial Results for studies reporting outcomes on the efficacy and safety of TAVR following percutaneous Myval implantation, from the inception of each database to 22 May 2024. The search string used was: 'Myval' [All Fields] OR 'Myval transcatheter aortic valve replacement' [All Fields] OR 'Myval TAVR' [All Fields]. An initial search was independently conducted by two authors (C.M. and D.P.). Titles, abstracts, and full texts of relevant papers were reviewed to assess if the screened studies met the inclusion criteria. Any discrepancies were resolved through discussion and consensus with senior authors (A.I.). The outcomes of interest were PPI, PVL, and clinical outcomes, as well as echocardiographic measurements during follow-up. Outcomes were adjudicated according to each study's definitions. To be included in our analysis, published studies had to involve patients undergoing TAVR with Myval implantation.

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Article highlights

- Myval and the new generation Myval Octacor are novel balloon-expandable (BE) transcatheter heart valve (THV) systems designed for the treatment of severe aortic stenosis.
- Both THVs demonstrated comparable valve academic research consortium (VARC)-3 device success, early safety, and clinical efficacy compared to the primary contemporary THV systems (e.g. Sapien 3 and Evolut R/Pro).
- Low rates of moderate to severe paravalvular leak (PVL) and permanent pacemaker implantation (PPI) have been reported in non-randomized and randomized studies using these THVs.
- The intermediate and extra-large sizes of Myval present a promising option for widening the range of patients suitable for transcatheter aortic valve replacement (TAVR), of whom those with large annuli and non-calcified aortic regurgitation.

2. Myval THV system and the new generation Octacor

Myval is a trileaflet BE THV system made of bovine pericardium which underwent decellularization through Meril's proprietary anti-calcium treatment. The first Myval generation THV consists of a novel hybrid honey-comb scaffold design, made of a nickel-cobalt alloy (MP35N). The upper part of the frame (53% of the frame) is composed of a single row of tall, large, hexagonal, open cells (6 mm) that may facilitate future coronary access (Figure 1, panel A). The lower part of the frame (47% of the frame) consists of two short rows of tightly packed, hexagonal closed cells to ensure optimal radial strength (Figure 1, panel A). Internally, the lower part of the frame is covered with a sealing cuff, made of polyethylene terephthalate (PET) for minimizing PVL. An additional PET external skirt covers the lower row of closed cells to plug microchannels and further avoid PVLs. The THV is available in conventional (20, 23, 26, and 29 mm), intermediate (21.5, 24.5, and 27.5 mm), and extra-large (30.5 and 32 mm) sizes, allowing for the addressing of a broader range of annular sizes. All sizes are compatible with a 14-Fr expandable sheath (e.g. Python Sheath, Meril Life Sciences Pvt. Ltd) (Figure 2). During the TAVR procedure, the THV is manually crimped on the balloon with a mechanical crimping tool (Val-de-Crimp, Meril Life Sciences Pvt. Ltd) and delivered with a proprietary over-the-wire balloon catheter delivery system (Navigator, Meril Life Sciences Pvt. Ltd) that boasts a distinctive design. The Navigator delivery system includes a proximal flexion segment and a distal balloon equipped with two counter-opposing soft stoppers (Figure 1, panel B). These features create a superficial low-profile crimping zone, resulting in a comfortable fit that prevents dislocation of the THV during THV delivery. The Navigator enables flexion of the distal catheter system, ensuring a trauma-free negotiation across the aortic arch and a reduced risk of embolization of plaque debris. The balloon has two internal expansion ports to facilitate simultaneous expansion at extremities (similar to a dog bone), stabilizing the THV during the deployment (Figure 1, panel C). Thanks to the angiographic design of the crimped valve, characterized by alternating dense and light bands, precise positioning is achieved by aligning the mid-segment of the second distal dense band of Myval sizes ranging between 20 and 29 mm with the annular plane. For Myval extra-large sizes (e.g. 30.5 and 32 mm) focus on aligning the upper part of the second distal dense band. This leads to a post-implantation aorto-ventricular depth of 70:30 (Figure 1, panel C).

Myval Octacor represents the new generation of bovine pericardial trileaflet BE Myval THV. The leaflets retain the same properties of the original Myval THV, but the frame, while maintaining the same nickel-cobalt alloy and height (17.35–21.14 mm), consists of two rows of interlacing geometrically identical octagonal open cells (6 mm), in contrast to the three rows of hexagonal cells of the first generation Myval THV (Figure 3, panel A). This design modification aims to reduce foreshortening (19–20% of Octacor vs. 21–24% of Myval) during expansion and enhance deployment accuracy. In addition, compared to the first generation Myval THV, the Octacor lower row (which constitutes 50% of the frame height), features a 3% larger PET internal skirt, in addition to a larger circumferential external skirt to further reduce PVL (Figure 3, panel A). The Myval Octacor comes in the same range of available sizes as the original Myval THV (from 20 mm to 32 mm). In addition to this novel structural design, Octacor can be oriented during crimping, according to the specific patient's anatomy (assessed by computed tomography [CT] scan), to lower the risk of commissural misalignment, thanks to the so-called Octalign technique [12,13]. This technique involves the following steps: a) A virtual circle is delineated on the cross-sectional image of the sinus of Valsalva; b) A clock face is overlapped onto this cross-sectional image with 12 o'clock positioned at the top; c) A line is drawn at the midpoint of the right coronary cusp (the ideal point of origin for the right coronary artery [RCA]); d) The clock angle is then determined as the distance from 12 o'clock to the drawn line. One of the posts of the Myval Octacor is aligned with this clock angle using the iris opening and the 'CrocoDial' compass of the crimper, and subsequently crimped. Given the 180° rotation of the THV across the aorta, the post of the Octacor should be positioned opposite to the ostium of the RCA, specifically at the commissure site. A 3-cusps view guides the deployment of the THV [12,13].

All sizes are compatible with a 14-Fr expandable sheath (e.g. Python) (Figure 2). The new proprietary Navigator Inception delivery system (Figure 3, panel B) has an additional landing zone marker toward the ventricular end, aiding in precise positioning at the annulus level. This leads to a post-implantation aorto-ventricular depth of 85:15 (Figure 3, panel C). The expected implantation depth ranges between 2.95 and 3.60 mm, theoretically lowering PPI [14].

3. Clinical data

Clinical data on the Myval BE-THV come from observational studies, and their main features are summarized in Table 1.

Following preclinical works, MyVal-1 study was the first-in-human, prospective, single-arm, feasibility study, enrolling 30 symptomatic AS patients, at intermediate or high surgical risk, to evaluate safety and efficacy [10]. A notable improvement in the aortic valve area and mean aortic valve gradient was observed and maintained at 1-year, with no episodes of moderate-severe PVL or PPI need [10]. Myval THV showed a good

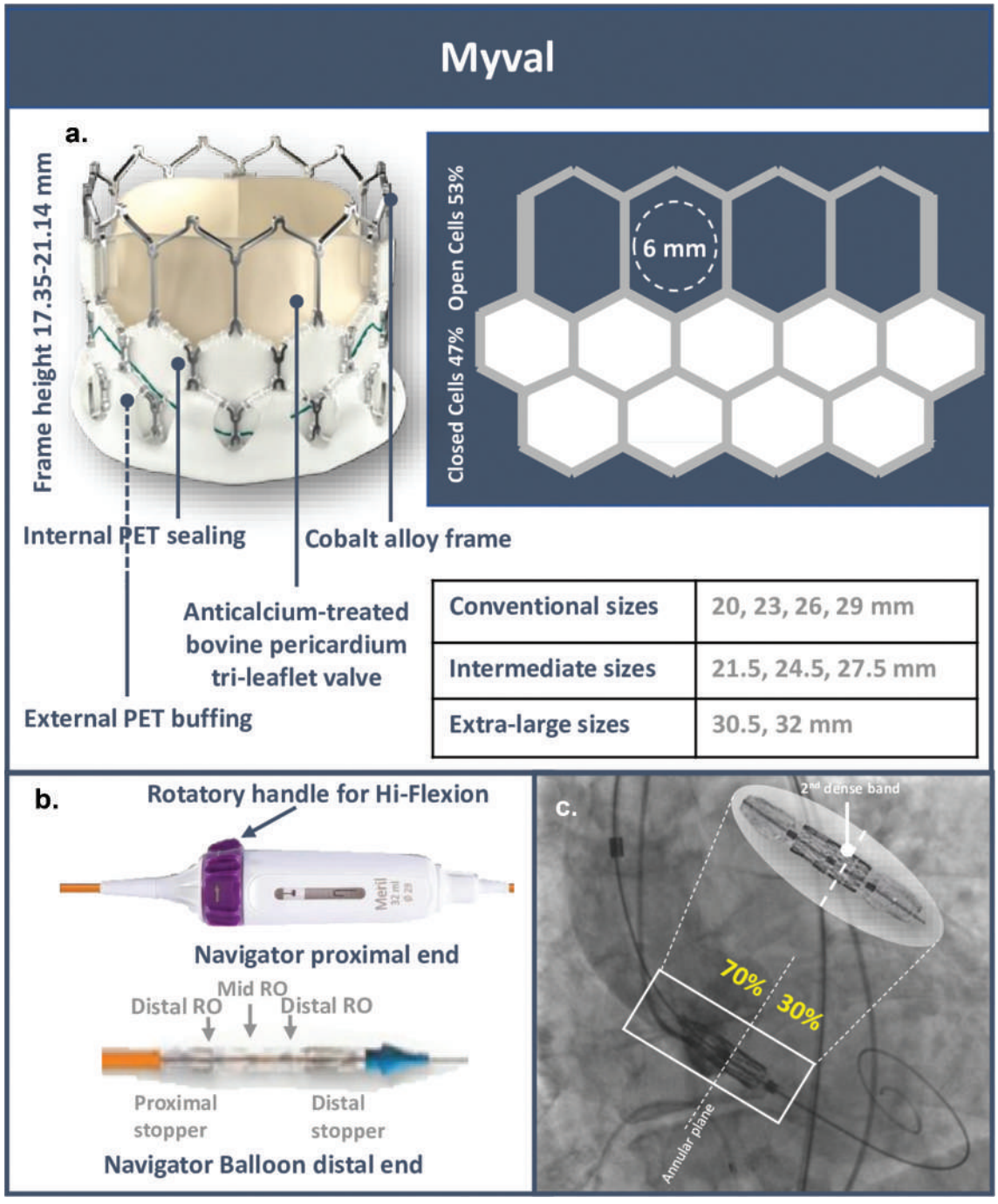

Figure 1. (a) Myval device and sizes. (b) Navigator delivery system. (c) Myval deployment. PET, polyethylene terephthalate.

safety and efficacy profile, with 100% device success and 100% of patients in NYHA functional Class I/II during follow-up [10]. Also, Magyari et al. have shown a substantial decrease between baseline and discharge mean aortic gradient (47.9±14.4 vs 10.0±4.3 mmHg, $p < 0.0001$) and no further significant change at 1-year follow-up (10.7±4.2 mmHg, $p = 0.1$) [15]. Instead, a significant increase in left ventricular ejection fraction was observed during follow-up, confirming previously published data by Akyuz et al. [15,16]. The reported rates of serious intraprocedural complications, including annulus rupture (0%) [10,15–22], device embolization (0–1.7%) [10,15–22], coronary artery obstruction (0–4%) [10,15–22], as well as major vascular complications (0–10%) [10,15–22] and bleeding (0–10%) [16–18,20,21] are low and comparable to those reported in the PARTNER trials [4,23]. In Supplementary Table S1, the main features of procedural details and procedure-related complications of single-arm studies are reported.

To the best of our knowledge, there are limited data regarding durability. However, the SAPPHIRE registry reported sustained improvement in echocardiographic parameters during follow-up for up to 2 years, with a sustained low mean aortic gradient (8±6 mmHg) and without any events of

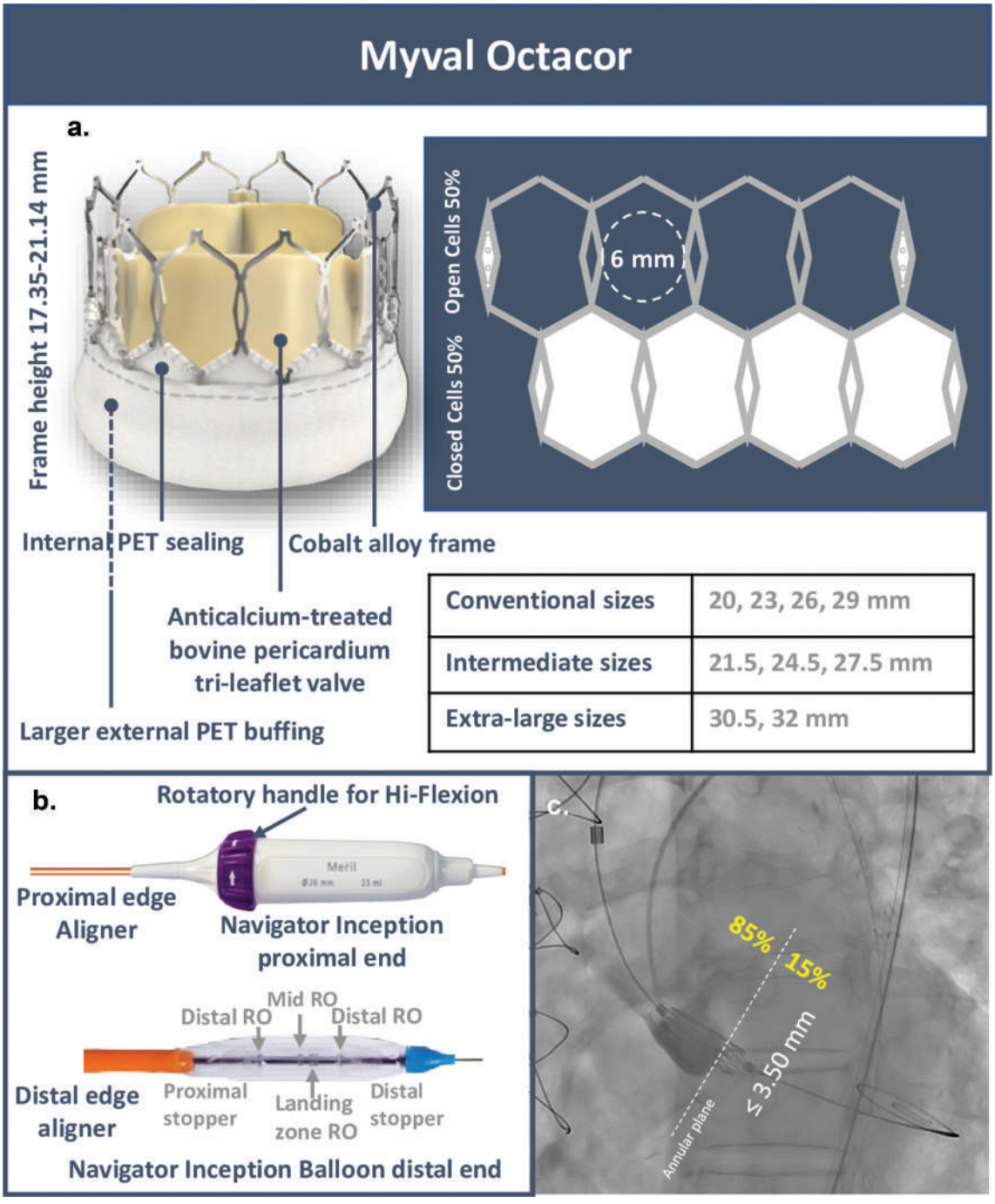

Figure 2. (a) Myval Octacor device and sizes. (b) Navigator Inception delivery system. (c) Myval Octacor deployment. PET, polyethylene terephthalate.

structural valve deterioration [20]. This result has been confirmed by a recently published study reporting a low mean aortic gradient at 2-year follow-up (7.3±4.7 mmHg) [22].

Expanding TAVR to younger and low-risk populations highlights the importance of allowing coronary re-engagement post-TAVR. Currently, no data are available regarding this aspect for the Myval THV family. However, its short frame design height, ranging from 17.3 mm to 21.1 mm, is comparable to that of the Sapien 3/Ultra 3 THV family (ranging from 15.5 mm to 22.5 mm). Precise deployment is ensured by the Myval design, featuring an alternative dark-light band-like pattern visible under fluoroscopy, and the presence of the implantation marker in the Octacor generation. Additionally, the Ocatalign technique allows commissural alignment with the Octacor Myval THV [12,13]. Therefore, due to the similar short frame design and implantation technique shared with the Sapien 3/Ultra THVs, accessing the coronary arteries post-TAVR is not expected to pose significant challenges with this THV. Nevertheless, further studies are needed to confirm this.

3.1. Paravalvular leaks

Concerning the low incidence of more than mild PVL with Myval BE assessed in MyVal-1 study, several subsequent studies have

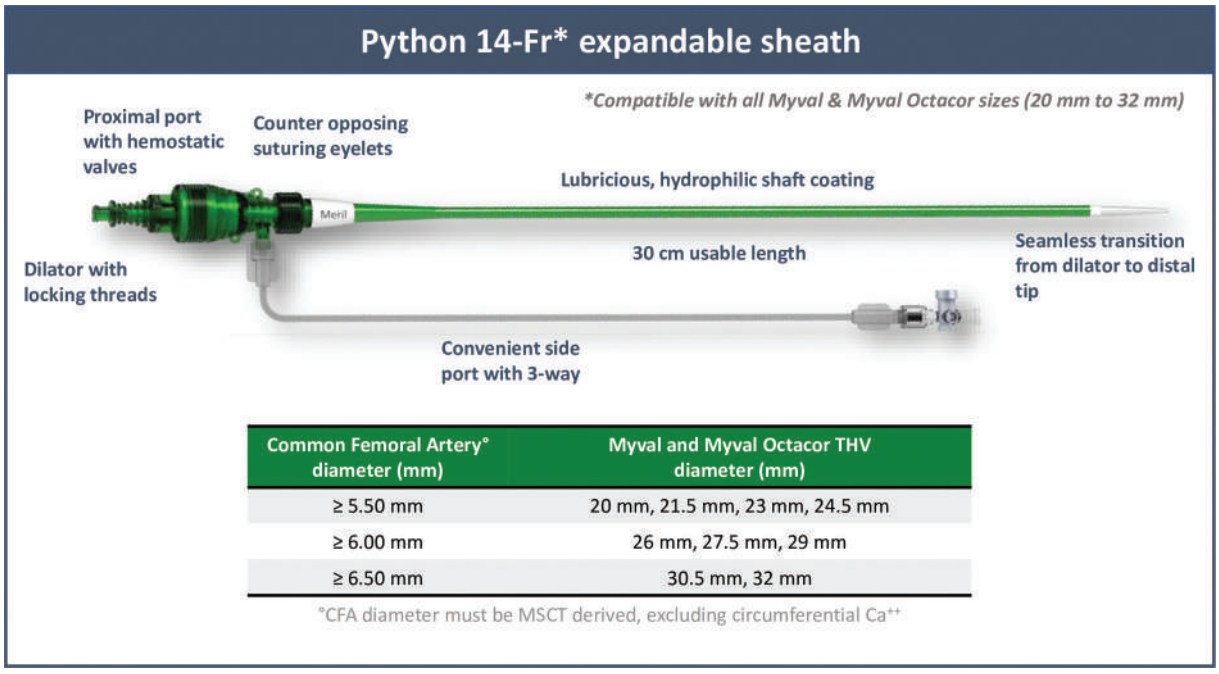

Figure 3. Python 14-Fr introducer sheath. CFA, common femoral artery; MSCT, multislice spiral computed tomography; THV, transcatheter heart valve.

confirmed this finding, with rates of moderate-severe PVL ranging between 0% and 8% [10,14–20, 22]. Furthermore, the latest generation of Myval Octacor has demonstrated promising results in decreasing the incidence of aortic regurgitation (AR) following TAVR, with a rate of 1.9% for moderate-severe AR [14], recently confirmed by Jose et al. reporting a PVL rate of 1.6% [21]. This rate is lower than the previously reported rates for Sapien 3 and Myval (8.3% and 2.8%, respectively) in a retrospective core-lab analysis of quantitative aortography assessment [24]. Moreover, a higher rate of none/trace AR with Myval Octacor has been reported compared to the previous Myval iteration (50%) [24]. It can be speculated that the new skirt design and in particular, the outer larger skirt compared to the previous generation, enables effective sealing and plugging of micro-channels, thereby reducing PVL.

3.2. Permanent pacemaker implantation

Regarding PPI, the majority of the single-arm studies reported a low incidence of events, ranging between 0% and 11% [10,16,17,19,20,22]. Multiple factors have been considered as possible determinants of these good outcomes. The availability of Myval BE intermediate sizes could reduce the risk of oversizing, leading to a decrease in the risk of conduction disturbances and PPI. Furthermore, a precise deployment preventing inadvertent deep implantation (allowed by Myval's design geometry on crimping with an alternative dark-light band-like pattern under fluoroscopy and by the presence of the implantation marker in the Octacor generation) and frame foreshortening from the ventricular end could minimize trauma of the membranous septum, reducing implantation depth. The expected implantation depth with the new Octacor design ranges between 2.95 and 3.60 mm [14]. However, there are no studies addressing implantation depth in the Myval BE family and its impact on PPI. Only two studies have reported higher PPI rates [15,18]. However, one of these studies, reporting a PPI rate of 20%, involved patients with large aortic annuli, and was biased by a low sample size [18]. Of the two patients in the study who required PPI, one had a preexisting right bundle branch block, and the other had bicuspid anatomy with a massive calcium load of 4780 mm^3. In the other study, reporting a PPI rate of 31%, there was a high calcium score (3395 mm^3) and a high prevalence of calcium in the left ventricular outflow tract (LVOT) [15]. Furthermore, the only study on Myval Octacor reported a rate of PPI of 10%, at the higher end of the range of PPI rates for Myval [21]. This could be explained by the presence of a larger external skirt, which may impact conduction disturbances.

3.3. Low-risk patients

Currently, there is growing evidence regarding the safety and efficacy of TAVR in low-surgical risk patients [4–6]. In this context, the Myval low-risk study reported favorable hemodynamic performance at 30-day, with a mean gradient of 9.0 ± 3.7 mmHg and a rate of more than mild PVL at 4%, following Myval implantation in patients with mean STS risk score of 2.4 ± 0.8 [17]. At 30-day follow-up, no adverse events were reported. Notably, no cases of severe prosthesis-to-patient mismatch were found, and the rate of PPI was only 8% [17]. However, further long-term follow-up studies are needed to confirm these findings.

4. Comparative data versus other THVs

Given the growing global utilization of the Myval BE THV, it is essential to evaluate this device alongside contemporary THV systems and identify key distinctions in terms of hemodynamic performance, clinical efficacy, and safety. In Table 2

Table 1. Single-Arm Myval and Myval Octacor Studies.

First Author *Year*	Study Design	Population	STS Score (%)	Device	Longest Clinical Follow-Up	Device Success	Post-dilatation	Major Vascular Complications	Mean Gradient at Follow-Up (mmHg)	PVL Moderate or Severe	PPI	Cerebro-Vascular Events	Outcomes
Sharma et al. [10] 2020	Prospective multicenter single-arm study	30 AS patients	6.4 ± 1.8	Myval	1 year	30 (100)	6 (20)	2 (6.7)	12.0 ± 3.3	0 (0)	0 (0)	0 (0)	1-year all-cause mortality = 13%
Garcìa-Gòmez et al. [17] 2021	Retrospective multicenter single-arm study	100 AS patients	2.4 ± 0.8	Myval (39% intermediate sizes)	30 days	99 (99)	4 (4)	3 (3)	9.0 ± 3.7	4 (4)	8 (8)	1 (1)	30-day mortality = 0%
Akyuz et al. [16] 2021	Retrospective single centre single-arm study	25 AS patients	5.4 ± 3.5	Myval (no intermediate sizes)	90 days	23 (92)	2 (8)	1 (4)	9[8-11]	2 (8)	2 (8)	0 (0)	–90-day mortality = 8% -Improvement of LVEF during follow-up
Elkoumy et al [14]. 2023	Retrospective multicenter single-arm study	103 AS patients (37% of BAV)	3.47 [2.15–7.11]	Myval Octacor (47.6% intermediate sizes)	After procedure	NA	13 (12.6)	NA	NA	2 (1.9)º	NA	NA	NA
Holzamer et al. [18] 2023	Retrospective multicenter single-arm study	10 AS patients with large annular anatomy	2.66 ± 1.37	Myval 32 mm	30 days	10 (100)	1 (10)	1 (10)	5.8 ± 2.1/P	0 (0)/P	2 (20)/P	0 (0)	At 30-days no adverse events
Magyari et al. [15] 2023	Prospective multicenter single-arm study	100 AS patients (17% of BAV)	5.6 ± 3.9	Myval (55% intermediate sizes)	1 year	99 (99)	NA	6 (6)	10.7 ± 4.2	0 (0)	31 (31)	5 (5)	–1-year all-cause mortality = 7% -Improvement of LVEF during follow-up
Halim et al. [19] 2023	Prospective single center single-arm study	120 AS patients	4.0 ± 2.8*	Myval (50% intermediate sizes)	6 months	NA	3 (2.5)	NA	7.8 ± 3.3 ‡	0 (0)‡	4 (3.3)	7 (5.8)	6-month all-cause mortality = 5.8%
Testa et al. [10] 2023	Prospective multicenter single-arm study	100 AS patients	6.3 ± 3.3	Myval (48% intermediate sizes)	2 years	99 (99)	7 (7)	0 (0)	8 ± 6	5 (5)	9 (9)	3 (3)	2-year all-cause mortality = 12%
Jose et al. [21] 2024	Retrospective multicenter single-arm study	123 AS patients (40% of BAV)	3.2[1.8 − 5.12]	Myval Octacor (45% intermediate sizes)	30 days	121 (98.4)	17 (13.8)	0 (0)	10.4 ± 4.2	2 (1.6)	13 (10.6)	0 (0)	30-day mortality = 1.6%
Kilic et al. [22] 2024	Retrospective multicenter single-arm study	207 AS patients	4.0 ± 1.9	Myval	2 years	189 (91)	13 (6.2)	3 (1.4)	7.3 ± 4.7	10 (4.8)	23 (11.1)	2 (1)	2-year all-cause mortality = 9.7%

Values are expressed as n (%), mean ± standard deviation, or median [interquartile range].
AS, aortic stenosis; BAV, bicuspid aortic valve; NA, not available; PVL, paravalvular leak; PPI, permanent pacemaker implantation. *EuroSCORE II; ¶At discharge; ‡ At 30-day; ºAortic regurgitation.

the main features of the more relevant studies are reported. The EVAL registry was the first study analyzing the clinical efficacy and early safety of Myval BE compared to Evolut R self-expanding (SE) THV [25]. It has shown higher valve academic research consortium (VARC)-3 device success of Myval compared to Evolut R (94.8%vs 83.3%, respectively; $p = 0.048$) with no significant differences in all-cause death and mean aortic gradient at 6-month follow-up [25,26]. Up to now, other retrospective data comparing Myval BE valve and Evolut R/Pro SE valve have demonstrated equivalent clinical outcomes in terms of all-cause death at 1 year (9% vs 8%, respectively; $p = 0.79$) and similar increase in aortic valve area ($p = 0.08$) [27]. The EVAL Registry at 2 years follow-up has confirmed these data reporting no difference in all-cause of death at longer follow-up but with a lower rate of cardiovascular rehospitalization for the Myval group compared to Evolut ($p = 0.027$) [28]. Furthermore, a lower mean gradient at 2-year follow-up was found in Myval compared to Evolut (6.9 ± 2.2 vs 9.5 ± 4.3 mmHg, respectively; $p < 0.001$). The investigators attributed these outcomes to the use of intermediate sizes of Myval in nearly 45% of the patients, resulting in a potentially more optimal annular fitting. Furthermore, in this registry, the rate of small aortic annuli was low with a low rate of TAVR sizes ≤23 mm (9% in Evolut group and 28% in Myval group) [25,28]. This aspect could lose the hemodynamic advantage of supra-annular valves, predominantly seen in small annuli. However, the single center, retrospective, observational nature of the study might have played a role in this result.

Even a comparison between a matched population of 103 patients treated with Myval and 103 patients treated with Sapien 3 has demonstrated similar early safety and clinical efficacy at 30-day [29]. Additionally, there were significantly lower mean gradients observed in the Myval compared to the Sapien 3 group (8 [6–11.6] vs 12 [9–15] mmHg, respectively; $p < 0.001$), as determined by blinded echocardiographic analysis. The investigators attributed these outcomes to the use of intermediate sizes of Myval in nearly 45% of the patients [28,29], resulting in a potentially more optimal fit. This finding was confirmed by Santos-Martinez et al. reporting a lower mean gradient in the Myval group compared to Sapien 3 (9 mmHg vs 12 mm Hg, $p < 0.001$, respectively) at discharge [30].

Two included studies have reported data from propensity-matched populations: one comparing Myval to Sapien 3 and the other comparing Myval to Evolut R/Pro [27,29]. The results of these studies appear to be consistent with other data. Furthermore, the LANDMARK trial, the first randomized controlled trial comparing Myval THV to other contemporary THVs (Evolut/Sapien series THVs), demonstrated the non-inferiority of Myval for the primary endpoint (a composite of all-cause mortality, all stroke, major bleeding, acute kidney injury, major vascular complications, moderate or severe prosthetic valve regurgitation, and PPI) at 30 days [31,32]. Furthermore, initial data from LANDMARK showed a post-procedural higher effective orifice area (EOA) in the Myval group compared to the Sapien series group for all sizes and comparable or higher EOA compared to the Evolut group in ≥26 mm THV sizes.

In terms of serious intraprocedural complications, including annulus rupture, device embolization, coronary artery obstruction, as well as major vascular and bleeding complications, no significant differences were reported when comparing Myval vs. Evolut R/Pro [25,27,28] or Sapien 3 [29,32]. In Supplementary Table S2, the main features of procedural details and procedure-related complications of comparative studies are reported.

4.1. Paravalvular leaks

In the available studies, the rates of moderate-severe PVL were found to be comparable to or lower than the Evolut SE THV [25,27,28]. In the EVAL Registry, comparing the Myval BE valve with the Evolut R SE valve, overall residual PVL was lower in the Myval group [25]. This resulted in a rate of 7% for moderate-severe PVL in the Myval BE group compared to 19.8% in the Evolut R SE group at the 6-month follow-up ($p = 0.0396$), confirmed also at 2-year ($p = 0.008$) [28]. A recent study, including Evolut Pro, has shown that, at the cost of higher balloon post-dilatation (26% vs 3%, $p < 0.0001$), Evolut R/Pro achieved a comparable rate of moderate-severe PVL compared to the Myval BE group (4% vs 1%, $p = 0.17$) [27]. Furthermore, when comparing Myval with commonly used BE THVs (e.g. Sapien 3 or Sapien XT), a lower incidence of residual moderate-severe aortic regurgitation (2.8% vs. 8.3%, $p < 0.05$, and 2.8% vs. 10.9%, respectively; $p = 0.01$) was demonstrated with this novel THV [24]. However, Delgado-Arana et al., comparing Myval with Sapien 3 in a matched population, have found similar good results between the two devices (0% vs 1% of moderate-severe PVLs, respectively; $p = 0.28$) [29]. The first results from the LANDMARK trial have confirmed the low rate of post-procedural moderate-to-severe AR (2%) in Myval/Myval Octacor group, resulting to be significantly lower than Evolut/Sapien group (6%, $p = 0.03$) [32].

It can be speculated that the extensive device selection offered by the Myval BE THV may minimize the risk of relative under-/oversizing, potentially leading to a lower rate of moderate-severe PVL. Furthermore, the internal skirt of the Myval on the valve frame prevents the bioprosthesis from inadvertent damage caused by native calcium spicule, minimizing the propensity for AR [24]. Moreover, the external skirt of Myval can facilitate the plugging of micro-channels at the THV anchoring site, reducing PVL [24]. As of now, no comparative studies dedicated to Myval Octacor have been conducted, despite its promising results in reducing PVL, thanks to the larger external skirt [14].

4.2. Permanent pacemaker implantation

Compared to Evolut family, Myval BE is found to have a lower rate of PPI [27]. This finding was confirmed by the EVAL registry which demonstrated a lower rate of PPI in the Myval group compared to Evolut R (11% vs. 27.5%, respectively; $p = 0.02$) confirmed also at 2-year follow-up ($p = 0.024$) [25,28]. A significantly lower PPI rate in the Myval BE group was also found in a matched analysis ($n = 103$ in each group) versus Sapien 3 (5.8% vs 15.5%, $p = 0.02$, respectively) [29]. In this

Table 2. Comparative studies between Myval and contemporary THVs.

First Author *Year*	Study Design	Population	Devices	Longest Clinical Follow-Up	Device Success	Post-dilatation	Major Vascular Complications	Mean Gradient at Follow-Up (mmHg)	PVL Moderate or Severe	PPI	Cerebro-Vascular Events	Outcomes
Kawashima et al. [31] 2021	Retrospective corelab analysis	744 AS patients	Myval ($n = 108$) Sapien 3 ($n = 397$) Sapien XT ($n = 239$)	At discharge	NA	NA	NA	NA	3 (2.8)º 33 (8.3)º 26 (10.9)º $p < 0.05$	NA	NA	NA
Delgado-Arana et al. [29] 2022	Propensity-match of prospective multicenter study	416 AS patients (BAV excluded)	Myval ($n = 103$) Sapien 3 ($n = 103$) (45% Myval intermediate sizes)	30-day	NA	7 (6.9) 6 (5.9) $p = 0.99$	0 (0) 5 (4.9) $p = 0.99$	8 [6–11.6] 12 [9-15] $p < 0.001$	1 (1) 0 (0) $p = 0.28$	6 (5.8) 16 (15.5) $p = 0.02$	0 (0) 3 (2.9) $p = 0.24$	A 30-day no difference in mortality, clinical efficacy and early safety
Barki et al. [25] 2022	Retrospective single center study (EVAL Registry)	166 AS patients	Myval ($n = 58$) Evolut R ($n = 108$)	6-month	55 (94.8) 90 (83.3) $p < 0.05$	2 (3.4) 27 (25) $p < 0.001$	1 (1.7) 1 (0.9) $p > 0.9$	9.2 ± 3 10 ± 5 $p = 0.3$	4 (7) 21 (19.8) $p = 0.0396$	6 (11) 25 (27.5) $p = 0.02$	2 (3.4) 3 (2.8) $p > 0.99$	No difference in 6-month all-cause of death
Santoz Martinez et al. [30] 2022	Retrospective multicenter study	1131 AS patient	Myval ($n = 135$) Sapien 3 ($n = 290$) Evolut ($n = 298$) Acurate ($n = 180$) Portico ($n = 125$) Allegra ($n = 103$)	At discharge	NA	8 (5.9) 21 (7.3) 70 (24.4) 33 (19.0) 43 (35.8) 43 (41.7)	0 (0) 10 (3.4) 23 (7.9) 6 (3.4) 3 (2.5) 11 (10.7)	9.04 ± 4.59 11.88 ± 4.71 7.85 ± 4.20 9.58 ± 7.98 8.68 ± 5.38 6.92 ± 3.09	NA	10 (7.4) 39 (13.4) 53 (18.5) 16 (9.1) 36 (29.5) 22 (22)	0 (0) 4 (1.4) 7 (2.4) 5 (2.9) 4 (3.3) 6 (5.8)	NA
Halim et al. [27] 2023	Propensity-match of retrospective single center study	223 AS patients (BAV and ViV excluded)	Myval ($n = 91$) Evolut R/Pro ($n = 91$)	12-month	NA	3 (3) 24 (26) $p < 0.001$	0 (0) 0 (0)	7.8 ± 3.2‡ 7.6 ± 3.2‡ $p = 0.63$	1(1)‡ 4 (4)‡ $p = 0.17$	4 (4)‡ 14 (15)‡ $p = 0.01$	6 (7) 5(5) $p = 0.76$	No difference in 1-year all-cause of death, cardiac death, and all stroke
Moscarella et al. [28] 2023	Retrospective single center study (EVAL Registry)	166 AS patients	Myval ($n = 58$) Evolut R ($n = 108$)	2-years	55 (94.8) 90 (83.3) $p < 0.05$	2 (3.4) 27 (25) $p < 0.001$	1 (1.7) 1 (0.9) $p > 0.9$	6.9± 2.2 9.5± 4.3 $p < 0.001$	2 (4.3) 14 (21.9) $p = 0.008$	6 (10.3) 26 (24.1) $p = 0.024$	1 (1.7) 3 (2.8) $p = 0.096$	No difference in 2-year all-cause of death with a lower rate of cardiovascular hospitalization in Myval group
Baumbach et al. [32]. 2024	Randomized controlled trial (LANDMARK trial)	768 AS patients	Myval/Myval Octacor ($n = 384$) Evolut/Sapien THVs ($n = 384$) (48.1% Myval intermediate sizes)	30-day	312 (82) 320 (84) $p = 0.55$	38 (10) 81 (21.2) $p < 0.0001$	6 (1.6) 9 (2.4) $p = 0.6$	NA	8 (2)* 23 (6)* $p = 0.03$	57 (15) 65 (17.1) $p = 0.49$	12 (3.1) 12 (3.1) $p = 1$	Non-inferiority of Myval compared to contemporary THVs at 30-day

Values are expressed as n (%), mean ± standard deviation, or median [interquartile range].

AS, aortic stenosis; BAV, bicuspid aortic anatomy; NA, not available; PVL, paravalvular leak; PPI, permanent pacemaker implantation; THVs, transcatheter heart valves; ViV, valve-in-valve. ‡ At 30-day; ºAortic regurgitation; * regurgitant fraction > 17% assessed by quantitative video-densitometry at aortogram.

study, no significant differences were found regarding implantation depth or post-dilatation rates [29]. The observed disparities in conduction disturbances could be associated with lower overexpansion in the Myval group, facilitated by the availability of intermediate sizes of Myval, which were used in 45% of cases. Santos-Martinez et al. presented the findings of conduction disturbances analyzed by a core lab in an academic European registry comprising 1,131 consecutive patients undergoing TAVR with any of the six THVs: Myval, Sapien 3, Evolut, Acurate (Boston Scientific, Marlborough, Massachusetts), Portico (Abbott Vascular, Santa Clara, California), and Allegra (Biosensors, Singapore). In this analysis, the Myval exhibited the lowest rate of PPI (7.4%) [30].

The availability of Myval intermediate sizes, with only 1.5 mm difference instead of 3 mm of conventional sizes, used in 39% up to 54% of patients as reported in the studies, minimizes the risk of oversizing per se [25,27–29]. Furthermore, when comparing Myval to Evolut R/Pro, this aspect could lead to a decrease in the utilization of post-dilation, a well-known risk factor for developing conduction disturbances, and the subsequent need for a PPI [25,27,28]. Studies have shown that, in the comparison between Myval and Evolut R/Pro, the rate of post-dilatation is significantly higher in the Evolut group (25% to 26% vs. 3%) [25,27,28]. It is important to note, however, that additional risk factors, such as membranous septum length and implantation depth, were not well considered for instance. The first findings from the LANDMARK trial have shown no differences in the rate of PPI comparing Myval/Myval Octacor to Evolut/Sapien THVs (15% vs. 17.1%, respectively; $p = 0.49$) [32]. In this trial, the Myval group has shown a higher rate of PPI compared to other comparative studies. This could be explained by the use of the new generation Myval Octacor, which features a larger external skirt. This design characteristic could potentially lead to higher frequencies of conduction disturbance. However, generally, the rates of PPI were slightly higher for both groups. More data are needed to assess predictive factors within the study population and the indications for PPI used by single sites.

An ongoing trial, the COMPARE TAVI trial cohort B (ClinicalTrials.gov NCT04443023), randomizing patients to the Sapien or the Myval THV, will provide additional insights on these topics.

5. Myval in specific subgroups

5.1. Intermediate annular sizes

Optimal sizing, determined through CT assessment, is essential to mitigate the risks associated with TAVR. Undersizing can lead to PVL [33], THV embolization, and higher residual transvalvular gradients, while oversizing may cause conduction disorders and annular rupture [34]. Moreover, incorrect sizing affects THV shape, and leaflet coaptation and consequently could impact on THV durability [34]. Despite the importance of precise sizing, there are scenarios with 'grey zones,' where either of the two conventional THV sizes is suitable. These 'grey zones' occur in approximately 29–30% of TAVR cases and are associated with increased rates of residual PVL and higher post-procedural transvalvular gradients [35,36]. In such cases, the selection of THV size is left to the discretion of the operator, based on individual factors such as LVOT or annular calcification, narrow sino-tubular junction diameter, bulky leaflets, and low coronary ostia height. For commonly used BEV, the implantation of undersized but overfilled bioprosthesis has been seen to improve THV performance, decreasing mean post-procedural transvalvular gradient and incidence of PVL [35]. However, a study, based on BEV computational models in borderline annuli, has revealed that oversizing the smaller THV led to significantly higher leaflet stresses than undersizing the larger THV and this could impact the valve durability [34]. Myval THV family is available in intermediate sizes, with only a 1.5 mm difference, as opposed to the 3 mm difference in conventional sizes used in 39% to 54% of patients, as reported in the studies [25,27–29]. This highlights the operators' need for a more precisely calibrated THV choice. The availability of intermediate sizes allows for a more precise THV selection, reducing the need for over- or under-sizing. Investigators attribute the lower rates of PPI, PVL incidence, and the need for post-dilatation seen in these studies to the optimal fitting guaranteed by Myval intermediate sizes. However, to our knowledge, there are no studies comparing intermediate Myval sizes with under-/over-sizing of conventional BEVs in borderline annuli regarding post-procedural outcomes and long-term durability. In this view, more studies are needed to address this issue.

5.2. Large aortic annuli and non-calcified aortic regurgitation

The maximum dimensions specified by the manufacturer's instructions for use for the largest currently available standard devices are a 683 mm^2 annular area (Sapien 3) and a 94.2 mm annular perimeter (Evolut) [18]. To overcome the size limitations of the existing THV portfolio, Myval THV can cover larger aortic annuli sizes, being available in sizes 30.5 mm and 32 mm. Moreover, the Myval 32 mm THV covers annular areas ranging from 700 to 840 mm, being the largest aortic THV currently available [2,18]. In a studied cohort of 2219 consecutive TAVR-screened patients, a total of 1.6% of patients have an anatomy too large for conventional THVs (e.g. Sapien 3 29 mm or Evolut Pro 34 mm) [18]. It is possible to decrease this rate to 0.27% using Myval 32 mm device [18]. Recently, in a multicenter registry, Holzamer et al. have shown encouraging results regarding the performance of the Myval 32 mm in addressing aortic stenosis in extremely large annuli (average area 765.5 mm^2) [18]. The study reported a VARC-2 device success of 100% and no more than mild PVL and no transvalvular regurgitation [18,37]. However, there is not much other evidence on this topic. The first prospectively enrolled and monitored trial cohort, including patients with extra-large anatomy, in the 'Nested XL Registry' of the LANDMARK trial (ClinicalTrials.gov NCT04275726) could address this need. Furthermore, a promising application for extra-large sizes is the treatment of non-calcified aortic regurgitation (NCAR). In this challenging context, TAVR procedures are technically demanding due to large annuli and the absence of native valve calcification for bioprosthesis anchoring, necessitating a higher degree of oversizing. The availability of extra-large

sizes of Myval could effectively address this clinical need. Indeed, in cases of aortic stenosis, the recommended oversize percentage may vary according to the degree of leaflet calcification. For heavily calcified leaflets, the oversize percentage may range between 5% and 10%, while for leaflets with no calcium, as in pure aortic regurgitation cases, the oversize percentage ranges between 20% and 25%. Recently, a study involving 113 non-operable NCAR patients undergoing TAVR with Myval demonstrated encouraging results [38]. Extra-large sizes were utilized in 84% of the cases, with a mean oversizing of 17.9 ± 11.0%. The device success rate was 94.7%, and the residual moderate-severe AR rate was 9.1%. The all-cause mortality at the 1-year follow-up was 9.7%, and the PPI rate was 22.1%. Furthermore, a particular setting of NCAR is associated with left ventricular assist device (LVAD) implantation. In fact, it occurs in 25% of patients after LVAD implantation, due to changes in the aortic valve leaflet leading to cusp remodeling and fusion. Given that these patients are at extremely high risk, TAVR could offer a viable option. There is a case report that has demonstrated the safety and efficacy of Myval THV in AR linked to LVAD [39].

5.3. Bicuspid aortic valve

While TAVR is a well-established treatment for symptomatic AS at all surgical risk levels, data on TAVR in severe bicuspid AS is limited, as major RCTs excluded patients with bicuspid aortic valve (BAV). In BAV, TAVR remains a challenge due to its association with complex anatomical features such as valve-opening asymmetry, the fused raphe, differential sinuses' depth and dimensions, significant calcifications, and associated aortopathy.

A retrospective study was conducted on 68 cases of severe bicuspid AS treated with Myval BE. The mean age was 72.6 ± 9.4, and the STS risk score was 3.54 ± 2.1% [40]. The majority of treated valves was type 1 BAVs according to Sievers classification. VARC-3 device success at 30-day was achieved in 93% of cases, and the PPI rate was 8.5%. Hemodynamic results were excellent, with a mean gradient of 9.8 ± 4.5 mmHg and a moderate-severe aortic regurgitation (AR) incidence of 3% at 30 days. These results are comparable to previous data reported in a study concerning TAVR outcomes in low-surgical-risk BAV patients using contemporary BE THVs [41]. Furthermore, these findings on BAV treated with Myval have been confirmed at 1-year follow-up, showing a low rate of PPI and sustained hemodynamic performance with a mean gradient of 10 mmHg and an incidence of moderate-severe AR of 2% [42]. Comparing Myval to contemporary BE and SE THVs in a retrospective multicenter registry of 360 BAV patients, device success at 30-day was significantly higher in the Myval group with a success rate of 100% vs. 87.5% in Sapien 3 Ultra ($p = 0.002$) and 81.3% in Evolut Pro+ ($p < 0.001$) [43]. This result was mainly driven by the lower rate of moderate-severe PVL in the Myval group compared to Evolut Pro+ (1.9% vs 13%, respectively; $p = 0.005$) and the lower residual aortic mean gradient in the Myval group compared to the Sapien 3 Ultra (9.9 ± 4.4 mmHg vs 13.1 ± 4.8 mmHg, respectively; $p < 0.001$). The rate of PPI was low with no significant differences among the three devices.

5.4. Valve-in-valve and valve-in-ring

To date, the Myval BE system for the treatment of degenerated bioprosthesis is still off-label, and only a few data have been reported on its safety and efficacy. A multicenter prospective registry enrolled 97 patients with symptomatic, severe aortic ($n = 33$) and mitral ($n = 64$) bioprosthetic heart valves or ring failure who underwent transcatheter aortic valve-in-valve (ViV) and mitral ViV or valve-in-ring (ViR) implantation with Myval BE [44]. VARC-3 technical success was achieved in 98% of the patients with a 30-day significant reduction of trans-valvular gradients and an increase in EOA following both aortic ViV (transvalvular mean gradient 37.4 ± 15.5 mmHg at baseline vs 13.6 ± 5.4 mmHg at 30-day, $p < 0.001$; EOA 0.8 ± 0.3 cm^2 at baseline vs 1.8 ± 0.4 cm^2 at 30-day, $p < 0.001$) and mitral ViV/ViR implantations (transvalvular mean gradient 13.3 ± 9.2 mmHg at baseline vs 6.5 ± 3.2 mmHg at 30-day, $p < 0.013$; EOA 1.2 ± 0.5 cm^2 at baseline vs 2.1 ± 0.8 cm^2 at 30-day, $p < 0.018$) [26,44]. Significant improvements in the NYHA class were observed at the median follow-up of 15 months in patients who underwent both aortic ViV and mitral ViV/ViR.

6. Conclusion

Myval is a novel family of BE THVs associated with favorable, observational clinical outcomes at 2-year. Comparative studies evaluating Myval vs. contemporary THV systems have reported promising results, especially demonstrating a low aortic mean gradient at follow-up, a low rate of PVL, and a low rate of PPI. The availability of intermediate sizes of Myval could ensure a more tailored approach to aortic valve anatomy, reducing the most common pitfalls in TAVR. This is crucial, particularly with the current expansion of TAVR to a low-risk population with a longer life expectancy, where optimal results are essential. Furthermore, Myval results to be an effective option also in challenging scenarios such as extra-large aortic annuli, BAV, and ViV/ViR. However, the longest follow-up for Myval THVs is 2 years, which is significantly shorter compared to two THVs (e.g. Sapien THV and CoreValve/Evolut) that have follow-up periods reaching 8–10 years for their first generation iteration are no longer used currently. The 10-year clinical and echocardiographic follow-up of patients enrolled in the LANDMARK Trial will provide us with the answer. However, up to 2-year follow-up, no main differences were reported in terms of durability (e.g. early degeneration) versus other THVs.

7. Expert opinion

With TAVR becoming a widely adopted treatment for AS, especially being an effective option for low-risk younger AS patients, the primary goal in this field is to optimize clinical and hemodynamic outcomes. Myval and Myval Octacor aim to meet this requirement by demonstrating comparable VARC-3 device success, early safety, and clinical efficacy when compared to the leading contemporary THV systems, such as Sapien 3 and Evolut R/Pro. Notably, they have exhibited remarkably low rates of moderate to severe PVL, ranging between 0% and 8% [10,14–20,24,25,27–29,32] (Figure 4).

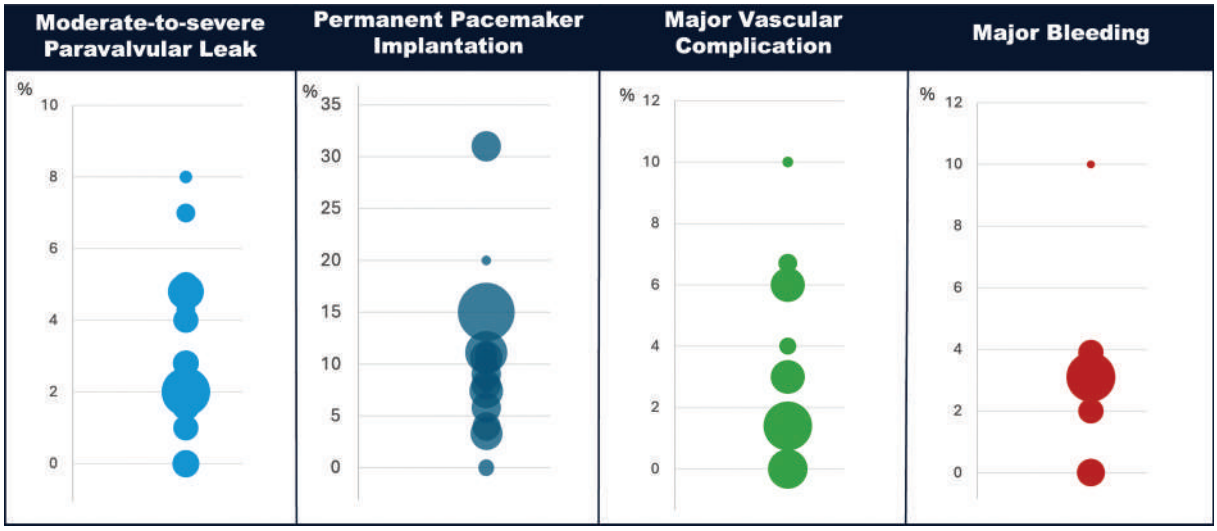

Figure 4. Distribution of the rates of moderate-to-severe PVL, PPI, major vascular complications, and major bleeding throughout the studies, both single-arm and comparative, based on the population of the study. PVL, paravalvular leak, PPI, permanent pacemaker implantation.

Additionally, PPI rates following these novel balloon-expandable valves have varied from 0% to 11% in the majority of the reported studies [10,16,17,19,20,25,27–30] (Figure 4). It can be speculated that the wide range of device sizes offered by the Myval and Myval Ocatcor BE THV may minimize the risk of relative under-/oversizing, potentially leading to a lower rate of PPI per se or lowering the need for post-dilatation, a well-established risk factor of PPI. Moreover, this optimal annulus fitting, always achieved thanks to the intermediate sizes of these novel THVs, along with the internal and external skirts, may explain the low moderate-severe PVL rate. The lower rate of post-dilatation reported in the Myval TAVR procedure could also have an impact on THV durability. However, for both single-arm and comparative studies, the longest follow-up is two years. Long-term follow-up studies are needed to confirm this data.

Furthermore, the availability of intermediate and extra-large-sized devices, along with their compatibility with a 14-Fr expandable sheath, allows for the coverage of a wide and diverse range of anatomies of aortic annuli and iliac-femoral arteries. Instead, to the best of our knowledge, the Myval 32 mm THV, covering annular areas ranging from 700 to 840 mm, is the largest aortic THV currently available and could represent an effective option for patients who have annular anatomy too large for conventional THVs.

In addition, the extra-large sizes provided by Myval could help address the challenges in treating NCAR. In this setting, the frequently large annuli, and the absence of native valve calcification for bioprosthesis anchoring necessitate a higher degree of oversizing.

Moreover, Myval has shown promising results in the treatment of bicuspid AS, demonstrating sustained hemodynamic performance up to 1 year. In this complex scenario, it has been reported to exhibit a lower residual aortic mean gradient compared to Sapien 3 and a lower rate of moderate-severe PVL compared to Evolut Pro+ [43].

Finally, the angiographic features of the crimped valve, with a dense band for Myval and a landing zone marker for Myval Octacor, facilitate precise deployment at the annular plane to minimize implantation depth and simplify the procedure, even for operators with less experience. The flexibility of the shaft allows an easier negotiation across the aortic arch, especially in tortuous anatomy, and eases the procedure.

Further studies are essential to fully comprehend the effective role of intermediate sizes in reducing PVL and PPI rates, as well as to assess the long-term performance of these two novel BE valves. Some answers will arise from the initial data of the COMPARE TAVI trial cohort B and from the long-term follow-up of the LANDMARK Trial.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

One reviewer is a proctor for Meril Life. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

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