

REVIEW

# From CoreValve to Evolut PRO: Reviewing the Journey of Self-Expanding Transcatheter Aortic Valves

Dhruv Mahtta · Islam Y. Elgendy · Anthony A. Bavry

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## ABSTRACT

Transcatheter aortic valve replacement (TAVR) has become standard therapy for patients with severe aortic stenosis who are deemed at least intermediate risk for surgical valve replacement. Over the past decade, several technological advances have taken place to improve the quality and safety of these devices. The current commercially available valves are broadly grouped into balloon expandable and self-expandable valves. The latest iteration of the self-expandable valve is Medtronic's repositionable valve known as the Evolut PRO system. In this review, we highlight the evidence behind the use of TAVR, improvement in devices over previous generations, clinical evidence behind the CoreValve Evolut PRO system, and the future of TAVR.

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D. Mahtta  
Department of Medicine, University of Florida,  
Gainesville, FL, USA

I. Y. Elgendy · A. A. Bavry  
Division of Cardiology, Department of Medicine,  
University of Florida, Gainesville, FL, USA

A. A. Bavry (✉)  
North Florida/South Georgia Veterans Health  
System, Gainesville, FL, USA  
e-mail: anthony.bavry@va.gov

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## BACKGROUND

Symptomatic severe aortic stenosis (AS) when left untreated carries a dismal prognosis [1]. Although the first successful surgical aortic valve replacement (SAVR) dates back to the 1960s, advanced age and co-morbid conditions remained a significant limiting factor in performing SAVR for elderly patients with symptomatic severe AS [2]. To circumvent this limitation, percutaneous balloon aortic valvuloplasty was developed, but failed to show any significant change in long-term outcomes and is now only considered as a bridge to SAVR or transcatheter aortic valve replacement (TAVR) in hemodynamically unstable patients [3, 4]. With the evolution of percutaneous interventions, the field of interventional cardiology finally experienced a revolution in treatment of severe AS when Cribier and colleagues demonstrated the first successful TAVR [5]. Since its inception in 2002, exhaustive research and development has taken place comparing efficacy and outcomes with different approaches and various devices as it pertains to TAVR.

Today, TAVR is considered the treatment of choice for symptomatic severe AS in patients who are deemed to be at least intermediate-risk surgical candidates based on Society of Thoracic Surgeons (STS) score of  $\geq 3$ –4%. Over the years, TAVR has demonstrated excellent post-procedural results and long-term clinical outcomes in high surgical risk patients [6–9]. Furthermore, comparison between SAVR and TAVR for intermediate-risk patients has also yielded positive results. This was evidenced during the Placement of AoRTic TranNscathetER valve—PARTNER 2 trial as well as recent data from The Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial [10, 11]. SURTAVI investigators showed that TAVR with self-expandable valve (SEV) prosthesis (namely Medtronic's CoreValve) was non-inferior to SAVR in regard to primary endpoint of death and disabling strokes. On the basis of this data, TAVR is now approved for use in intermediate surgical risk patients in the USA. However, TAVR carries its own challenges including paravalvular leak, requirement of permanent pacemaker implantation, vascular access complications, and stroke [10, 12–16]. Over the past decade, progression from first- to third-generation devices has been able to mitigate many of these complications. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

## CLINICAL EVIDENCE FOR TAVR VS. MEDICAL OR SURGICAL THERAPY

Ever since its introduction, researchers have compared TAVR outcomes with standard medical therapy such as balloon valvuloplasty. In inoperable patients with severe aortic stenosis who were not candidates for surgical intervention, mortality rates after 1 year were significantly lower in the TAVR cohort compared to those who underwent medical therapy (30.7% vs. 50.7%,  $p < 0.001$ ). Among the survivors, the patients experiencing New York Heart Association (NYHA) classification III or IV symptoms were significantly lower in the TAVR group as compared to patients managed with medical

therapy (25.2% vs. 58.0%,  $p < 0.001$ ) [17]. Researchers also showed that TAVR resulted in significant reduction in mean aortic pressure gradient which further equated to improvement in patient's symptoms, their functional class, and long-term outcomes [18]. On the other hand, compared to standard medical therapy, TAVR yielded higher incidence of major strokes (5.0% vs. 1.1%,  $p = 0.06$ ) and vascular complications (16.2% vs. 1.1%,  $p < 0.001$ ) [17, 19]. Similar findings were shown by several large European registries [20–22]. The superiority of TAVR to standard medical therapy was also confirmed by 5-year results of the PARTNER 1B trial which showed significantly lower mortality rates with TAVR as compared to medical treatment (71.8% vs. 93.6%,  $p < 0.0001$ ) [23].

In light of the superiority of TAVR to standard medical therapy, attention of researchers soon shifted towards comparison between TAVR and SAVR. The results of the landmark PARTNER 1A trial showed non-inferiority of TAVR to SAVR in surgical high-risk patients [7, 8]. The 1-year mortality rates were reported to be 24.2% vs. 26.8% ( $p = 0.001$ ) for TAVR and SAVR, respectively. Similar results were yielded during a 5-year follow-up which showed that mortality rates were similar in the TAVR group as compared to their SAVR counterparts (67.8% vs. 62.4%,  $p = 0.76$ ) [7]. Although survival rates were similar between the two modalities, periprocedural risks differed with statistically significant higher risk of major bleeding and new-onset atrial fibrillation with SAVR and higher incidence of vascular complications with TAVR [8]. Furthermore, these findings were reiterated by a large meta-analysis consisting of 4659 patients by Panchal and colleagues, who showed that TAVR was superior to SAVR for major bleeding outcomes and non-inferior to SAVR in terms of all-cause mortality and major adverse cardiovascular and cerebrovascular events (MACCE) [24]. With these findings in sight, the guideline committees have provided TAVR with a Class Ia and IIa recommendation for patients with severe AS with high and intermediate surgical risk, respectively [25]. According to the most recently published 2017 ESC/EACTS guidelines on valvular heart diseases, TAVR now carries a Class I indication for

patients with symptomatic AS who are considered to be unsuitable for SAVR by the heart team while it is favored over SAVR in elderly patients with suitable transfemoral access and elevated surgical risk (STS  $\geq$  4%) [26].

## TYPES OF TRANSCATHETER VALVES

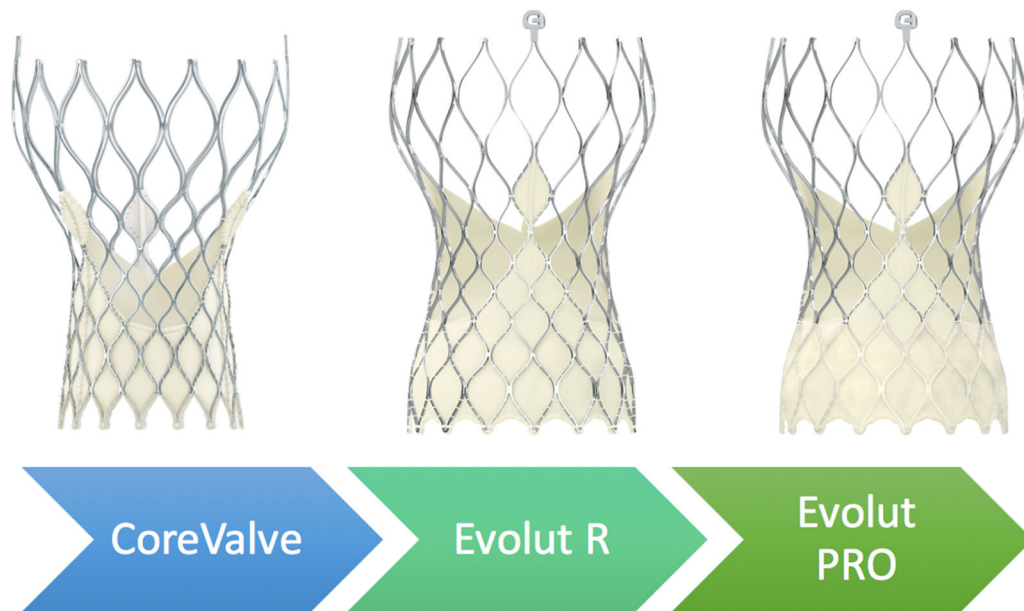
Two broad categories of devices that are currently approved by the Food and Drug Administration (FDA) include balloon-expandable valves and self-expandable valves. Edwards SAPIEN system (Edwards Lifesciences Corporation, Irvine, California) was the first-generation balloon-expandable valve which consisted of a trileaflet, bovine pericardial tissue valve attached to a stainless-steel frame. Newer generations of balloon-expandable valves consist of SAPIEN XT and SAPIEN 3 valves which can be deployed through transapical, transfemoral, transaxillary, and transaortic approaches and consist of a cobalt–chromium frame [27]. On the other hand, the self-expandable valve was first introduced by Medtronic's CoreValve system (Medtronic Inc, Minneapolis, Minnesota) which consisted of self-expanding trileaflet porcine pericardial tissue with a Nitinol frame. This initial self-expandable valve iteration was followed by Medtronic Evolut R valve and later by the newest-generation Evolut Pro valve (Fig. 1). Boston Scientific's Lotus system is another self-expanding, fully recapturable, and repositionable valve which is made up of trileaflet bovine pericardial tissue with an adaptive seal at the inflow segment. Other newer-generation devices which have not yet received FDA approval include JenaValve Technology's The JenaValve and St. Jude Medical's Portico TAVR system.

## EVOLUTION OF SELF-EXPANDABLE VALVES

Medtronic's CoreValve system was the first-generation self-expandable valve introduced to the market. The CoreValve United States Pivotal Trial compared outcomes in high surgical risk patients with severe AS who either

underwent TAVR with Medtronic's CoreValve system or underwent SAVR [12]. The authors of this study demonstrated a significant reduction in all-cause mortality with TAVR vs. SAVR at 1-year follow-up (absolute difference in mortality of 4.9%) and at 2-year follow-up (absolute difference in mortality of 6.4%). Additionally, at 2-year follow-up, the incidence of stroke was significantly lower in patients undergoing TAVR (10.9% vs. 16.6%,  $p < 0.05$ ) [28, 29]. Although the studies demonstrated positive results, these first-generation TAVR devices were far from perfect. These devices were relatively bulky and used larger diameter catheters (18-F to 24-F) which raised the incidence of intraprocedural complications and relied heavily on operator expertise. With rapid research and development in this field as well as increased operator experience, designs were modified to include smaller profile delivery systems which ensure higher safety and easier maneuverability. Numerous studies had pointed out the challenges that existed with the older-generation devices. Vascular complications, need for permanent pacing post implant, paravalvular leak (PVL), strokes, and other procedure-related complications still remained present [30–39].

The next-generation device—Medtronic's CoreValve Evolut R System—set out to mitigate these challenges. This second-generation device was tailored in such a manner as to reduce the overall height of the prosthesis while preserving the height of the pericardial skirt and extending it to allow a more secure seal against PVL. This resheathable valve had enhanced features including the EnVeo R delivery catheter system which allowed the valve to be recaptured and repositioned during deployment. This delivery system also allowed for 1:1 torque response to allow more accurate positioning of the valve. Lastly, the built-in InLine sheath enabled the operator to insert the entire system without the need of an additional access sheath, thereby reducing the overall profile of the delivery system down to 14-Fr equivalent sheath. Initial data on 30-day outcomes with this new-generation device was published by Manoharan and colleagues who reported overall device success rate of 78.6% per the VARC-2 (Valve Academic Research Consortium-2) and low rates of



**Fig. 1** Three generations of Medtronic self-expandable valves. Materials are used with permission by Medtronic© 2017

moderate (3.4%) and severe (0%) PVL, major vascular complications (8.3%), and permanent pacemaker implantation (11.7%) [40]. These promising outcomes were further confirmed during longer follow-up periods by the Evolut R United States Study as well as researchers from the UK and Ireland implanters' registry [41, 42]. This was followed by a plethora of research which showed significant reduction in PVL but similar 30-day clinical outcomes when Evolut R was compared to the CoreValve system [43–46]. Finally, in a large prospective national Italian TAVR registry, researchers included 411 propensity-matched subjects to analyze the clinical safety and efficacy outcomes of Evolut R system over its predecessor. The findings of this study were consistent with higher 30-day and 1-year overall survival along with significantly lower rates of vascular complications, bleeding events, need for permanent pacemaker implantation, and moderate to severe PVL in patients undergoing implantation with Evolut R versus CoreValve [47].

There have been growing concerns over the higher incidence of PVL with TAVR as compared to SAVR and its association with poor outcomes continued to linger in the interventional cardiology community [48]. To better address this

adverse event, Medtronic most recently introduced and successfully received FDA approval for its latest iteration called the Evolut Pro. Based on the prior Evolut R platform, this valve consists of an external pericardial wrap which ensures reduction in prosthetic valve regurgitation while retaining other benefits of the previous generation including a low delivery profile, self-expansion, as well as ability to recapture and reposition. The external pericardial wrap allows for increased surface contact with the native anatomy along with the added tissue volume which reduces gaps between the native anatomy and the valve. Altogether, the conforming frame with consistent radial force provides for an advanced sealing capability at multiple levels in various annulus shapes. The 1:1 response between the deployment knob and movement of the capsule provides immediate feedback to the operator and allows for positioning with enhanced accuracy. The Evolut Pro system is indicated for vessels down to 5.5 mm and its EnVeo R system with the InLine sheath allows for a delivery profile as low as 16-Fr equivalent. This latest technology is currently available in 23, 26, and 29 mm sizes. Compared to its predecessor, Evolut Pro utilizes a larger introducer sheath (16-Fr vs. 14-Fr of Evolut R) and is currently not

available in the largest (34 mm) size (Table 1). Evolut Pro's new design was tested by the investigators of the Evolut PRO clinical study. This was conducted as a non-randomized, single-arm study at eight centers in the USA which included 60 patients. These patients were prospectively followed over 30 days with a primary efficacy endpoint of none or trace aortic regurgitation. The primary safety endpoint was all-cause mortality and disabling stroke. The promising results of this study were presented at the 66th Annual American College of Cardiology meeting. The investigators showed at that 30-day follow-up, the Evolut Pro system resulted in high rates of survival (98.3%) and low rates of disabling strokes (1.7%). None to trace PVL was observed in 72.4% of patients while the remaining 27.6% experienced mild PVL. There were no patients with moderate or severe PVL. Improvement in NYHA class was seen by 87.9% of survivors within 30 days of implantation. The valve demonstrated superb hemodynamic performance with large effective orifice area ( $2.0 \pm 0.5 \text{ cm}^2$ ) and excellent mean gradients ( $6.4 \pm 2.1 \text{ mmHg}$ ) at 30 days (Figs. 2 and 3). Lastly, the investigators also showed even lower rates of permanent pacemaker implantation (10%) as compared to previous iterations of self-expandable valves [49].

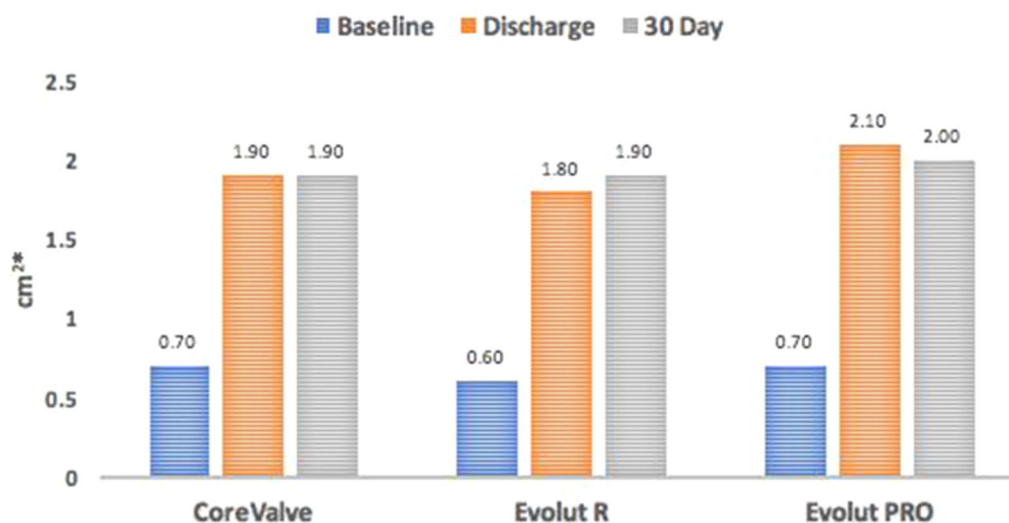
## COMPARISON OF BALLOON-EXPANDABLE VS. SELF-EXPANDABLE VALVE

A number of observational studies and meta-analyses have conducted head-to-head comparisons between self-expandable and balloon-expandable valves. In their multicenter randomized trial, the CHOICE (Randomized Comparison of Transcatheter Heart Valves in High Risk Patients With Severe Aortic Stenosis: Medtronic CoreValve Versus Edwards SAPIEN XT Trial) investigators compared the early-generation self-expandable and the balloon-expandable devices [50]. Although at 30-day follow-up, the authors showed increased device success and decreased permanent pacemaker implantation in the balloon-expandable cohort (17.3% vs. 37.6%,  $p = 0.001$ ), the 1-year outcomes between the two groups were not statistically significant [51]. More recently, comparison between the newer-generation devices (Edwards SAPIEN 3 vs. Medtronic CoreValve Evolut R) was undertaken by Rogers et al. [52]. This team of researchers showed that their 30-day outcomes were statistically significant for substantially higher rates of new complete heart block and subsequent permanent pacemaker implantation with self-expandable valves

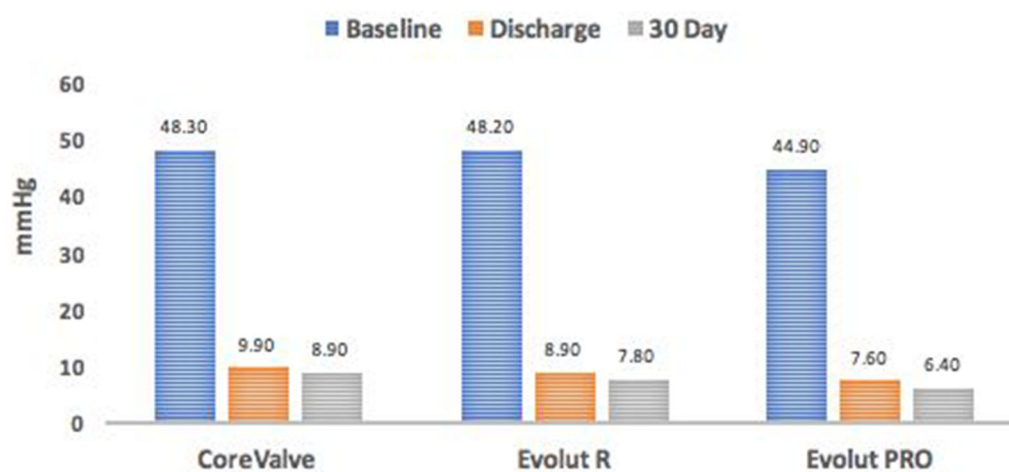
**Table 1** Characteristics of three generations of Medtronic self-expanding valve

	CoreValve	Evolut R	Evolut PRO
Available sizes (mm)	26, 29, 31	23, 26, 29, 34	23, 26, 29
Minimum vessel diameter (mm)	6.0	5.0	5.5
Introducer sheath size (Fr)	18/20	14/16	16
Approach	All except transapical	All except transapical	All except transapical
Valve material	Bovine pericardium	Porcine pericardium	Porcine pericardium
Complete recapturability	No	Yes	Yes
EnVeo R delivery system	No	Yes	Yes
Self-expanding pericardial skirt	Yes	Yes	Yes
External pericardial wrap	No	No	Yes





**Fig. 2** Effective orifice area pre and post TAVR [12, 42, 49]. \*All studies used valve size 26 mm and 29 mm, and the results were not stratified per valve size



**Fig. 3** Mean transaortic valve gradient pre and post TAVR [12, 42, 49]

(12.7% vs. 4.7%,  $p = 0.049$ ). As shown in previous studies, there was no significant difference in mortality between the two cohorts. In efforts to minimize the paravalvular leak, the latest-generation balloon-expandable valve (Edwards SAPIEN 3) and self-expandable valve (Evolut PRO) both employ a similar outer skirt or pericardial wrap design. However, there is a paucity of outcomes data regarding direct

comparison between SAPIEN 3 and Evolut PRO. In the PARTNER II SAPIEN 3 trial, moderate paravalvular leak was seen in 3.4% of patients while no patients in the US Evolut PRO Study experienced moderate paravalvular leak during the same follow-up period. Similarly, the rates of permanent pacemaker implantation for SAPIEN 3 and Evolut PRO were 13.3% and 10.0%, respectively, during the 30-day

follow-up period in the aforementioned trials [49, 53].

## BEST PRACTICE IN DETERMINING PATIENT ELIGIBILITY

Appropriate patient selection via individual risk stratification, optimal sizing based on annular dimensions, and different access routes are all factors that are carefully considered prior to TAVR. A substudy of the PARTNER trial showed that patients undergoing transapical approach experienced more adverse procedural events as compared to propensity score matched patients with transfemoral approach [54]. Device selection during TAVR has been a matter of ongoing debate. Although many of the deficiencies seen in the previous-generation devices have been overcome by the latest-generation balloon-expandable valves and self-expandable valves, individualized device selection based on patient's native aortic annulus size is still preferred. In their single-center trial, Rogers and colleagues evaluated the effect of balloon-expandable valves and self-expandable valves on post-implantation hemodynamics based on the aortic annulus size [55]. Researchers showed that self-expandable valve implantation yielded superior hemodynamics as compared to balloon-expandable valves in patients with a small aortic annulus. However, this difference was not apparent in patients with a medium or large annulus as their hemodynamics were comparable between these two valve platforms. Whether this still holds true with the latest-generation Evolut PRO remains unknown at present. Lastly, specific predictive scores such as the FRANCE 2 and OBSERVANT score have been developed and may be used to prognosticate 30-day mortality and determine patient eligibility prior to TAVR [56, 57].

## FUTURE RESEARCH

Rapid technological advances such as the recent introduction of Evolut PRO will further transform the future of TAVR. With studies showing clear benefit of TAVR in high and intermediate

surgical risk patients with severe AS, researchers are now starting to evaluate the efficacy of TAVR in low-risk patients as well. With positive data in sight from SURTAVI and the PARTNER-2 trial, the FDA has currently approved enrollment in the PARTNER 3 trial and Medtronic Low-Risk Trial to determine the safety and efficacy of TAVR in low surgical risk patients.

Despite these advancements, several limitations still exist regarding TAVR. The complication of embolic stroke still remains despite the introduction of safer devices, procedural techniques, and increased operator experience [16]. The SENTINEL trial which evaluated the efficacy of the Sentinel transcatheter cerebral embolic protection (TCEP) device showed that routine use of TCEP versus usual management did not result in reduction of strokes at 30 days post TAVR [58]. The extensive use of TAVR has also shed light on the post-procedural complication of bioprosthetic leaflet thrombosis. Observational studies have reported the incidence of subclinical thrombosis to be as high as 13% post TAVR and 4% post SAVR [59]. Several studies are underway to evaluate various antiplatelet and anticoagulation regimens to determine the optimal pharmacological regimen post TAVR. Lastly, most of the TAVR trials excluded patients with bicuspid aortic valves; however, an analysis of the Bicuspid TAVR registry had suggested that TAVR in bicuspid AS was associated with a similar prognosis, but lower device success rate, which was mainly noted with earlier devices [60]. Hence, future randomized trials are warranted to evaluate the outcomes of TAVR in patients with bicuspid aortic valve.

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**Compliance with Ethics Guidelines.** This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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