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Review

Percutaneous Transcatheter Aortic Valve Implantation: A Review Focus on Outcomes and Safety

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Abstract: Aortic stenosis is highly prevalent in the elderly, when symptomatic, is associated with high mortality. Although its treatment is mainly surgical, cumulative evidence has demonstrated that transcatheter aortic valve implantation is an effective and safe treatment option for selected patients, especially for inoperable and high-risk patients. The aim of this review is to discuss the advances in current and emergent devices, with special focus on clinical and safety outcomes in randomized clinical trials and registries.

Keywords: aortic stenosis; CoreValve®; Edwards SAPIEN®; transcatheter aortic valve implantation; complications; treatment outcome

1. Introduction

Aortic stenosis (AS) is the most prevalent valvular disease, with an incidence of 5% in people older than 75 years, and it is expected to increase due to population aging [1]. In routine clinical practice is frequent that not all patients benefit from Surgical Aortic Valve Replacement (SAVR). As about a third of patients with severe AS cannot be treated with surgery because of its high mortality risk, principally driven by advanced age and comorbidities [2]. In 2002, Alain Cribier et al. conducted the first successful in human transcatheter aortic valve implantation (TAVI), providing a new treatment option for inoperable patients with symptomatic severe AS [3]. The number of TAVI procedures has increased significantly, mainly due to increasing operator experience, better clinical outcomes, safety, and improving of device technology. Since 2002, more than 120000 TAVI procedures have been performed [4].

Currently, there are two main families of transcatheter aortic prostheses:

- Self-expandable prostheses: the prototype is the CoreValve® device (Medtronic CV Luxembourg S.a.r.l., Luxembourg). The prosthesis, compressed within a sheath, is advanced and positioned at the level of the aortic valve. The removal of the sheath allows expansion of the stent and therefore of the valve;
- Balloon-expandable: the prototype is the Edwards SAPIEN XT® device (Edwards Life Sciences, Inc., CA, USA). The prosthesis, mounted and compressed over a balloon, is advanced to the level of the aortic valve. The balloon is therefore inflated, allowing prosthesis expansion and apposition.

This review analyzes the current TAVI systems, focusing on clinical outcomes and device safety.

2. Current Devices

Chronologically the first developed prostheses were Edwards SAPIEN™/Edwards SAPIEN XT™ and later Medtronic CoreValve. Both of them were studied in large clinical trials and have already obtained Conformité Européenne and US Food and Drug administration approval.

2.1. Medtronic prosthesis family

The CoreValve prosthesis is composed by three main segments with special features and functions, detailed specifications are shown on Figure 1A [5].

The Medtronic Evolut R™ provides several changes to improve anatomical fit, annular sealing, and durability, when compared with CoreValve (Figure 2A). Especially, the device was designed to enable recapturability and repositionability, to improve deployment of the prosthesis. Evolut R has a 10 mm shorter outflow portion compare to CoreValve, in order to have a better fit with the aortic root and minimize conduction disturbances. Furthermore, it has incorporated a distal skirt to produce a better sealing, reduce Aortic Regurgitation (AR) and paravalvular leak (PVL) [6]. In addition, the reduced diameter of the sheath (14 or 18 Fr) helps to prevent vascular complications [6].

The Medtronic Engager™ introduced a new stent design that consists of a main frame and a support frame sewn to a polyester sleeve (Figure 2A). The control arms of the support frame were designed to be placed into the sinus of the aortic root to achieve an anatomically correct position and to minimize the risk of coronary obstruction. Overall valve design was intended to avoid PVL. Engager valve was designed for transapical (TA) or direct aortic access site. New delivery system allows prosthesis recapturability and repositionability [15].

2.2. Edwards-Sapien prosthesis family

The Edwards SAPIEN XT prosthesis consists in a balloon-expandable valve, detailed specifications are shown on Figure 1B [5].

The Edwards SAPIEN 3 Transcatheter Heart Valve (S3 THV) incorporates a unique stent and leaflet design that allows a reduced profile and improves its delivery in smaller peripheral anatomies (Figure 2B). The inflow segment of the S3 THV is covered by an internal polyethylene terephthalate (PET) skirt and incorporates an outer PET sealing cuff intended to reduce PVL. The delivery system incorporates radiopaque valve alignment markers showing the valve position. This device is

compatible with a 14 Fr sheath that can reduce vascular complications [7].

The Edwards Centera™ is composed of short self-expanding nitinol frame that facilitates centering and fit, thus improving paravalvular sealing with minimal protrusion. It is compatible with a motorized delivery system that allows a precise and controlled deployment by the transfemoral or subclavian access site. Furthermore, prior to complete valve deployment it is able to in situ re-sheath and reposition. This device is compatible with the 14 Fr sheath resulting in a low profile [8].

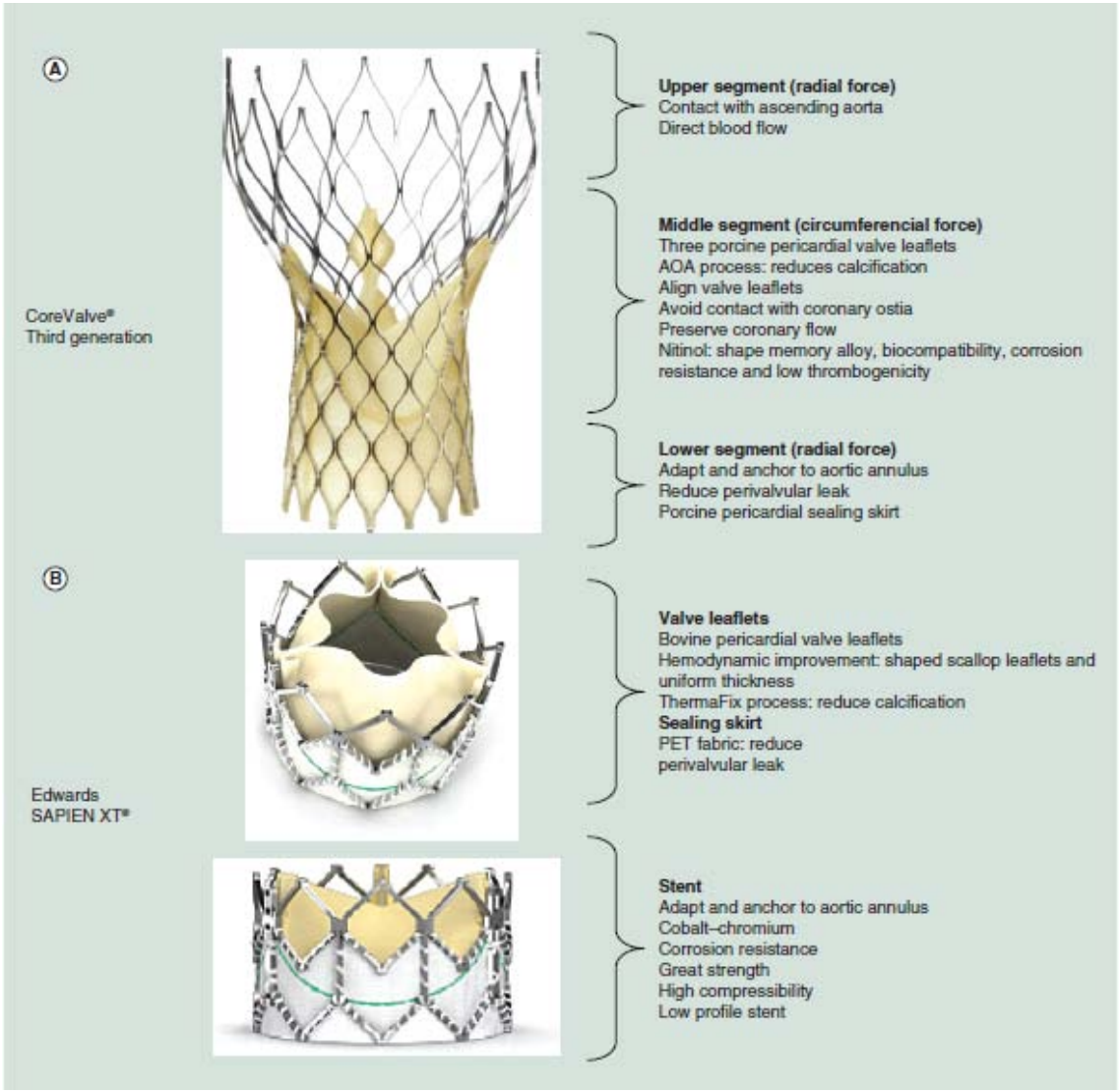

Figure 1. Comparison of (A) third-generation CoreValve® and (B) Edwards SAPIEN XT®. AOA: a-oleic acidification; PET: polyethylene terephthalate. Retrieved from: Expert Rev. Med. Devices 10(2), 185–199.

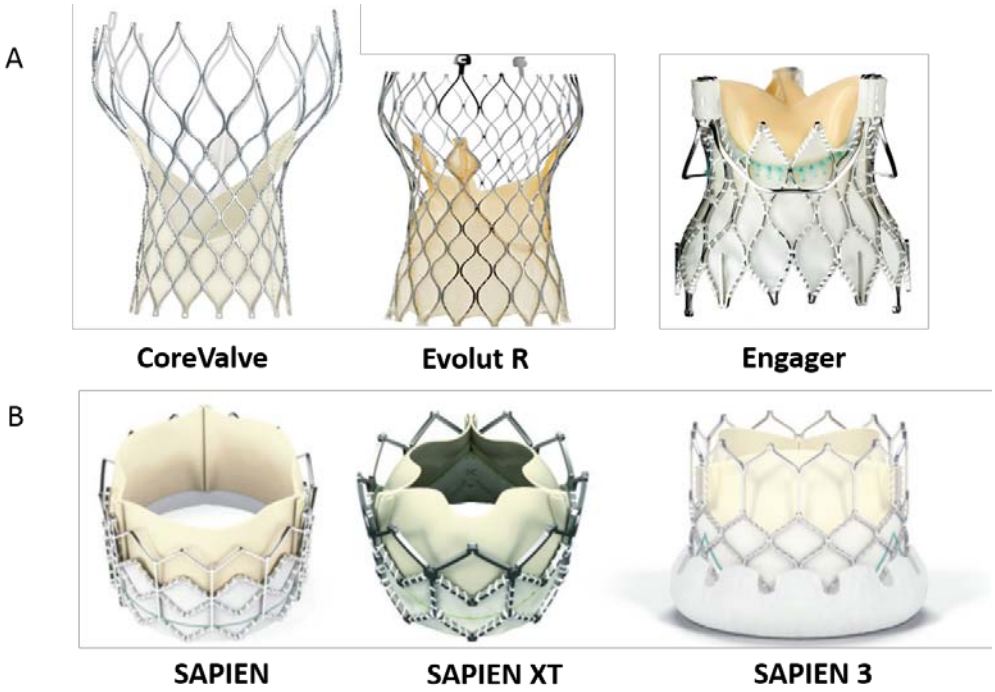

Figure 2. Evolution of (A) CoreValve and (B) SAPIEN devices.

2.3. Other devices

Several unsolved issues of the Edwards-SAPIEN and Medtronic prostheses have encouraged the development of emerging devices. These devices and their specifications are shown on Table 1.

3. Clinical outcomes

The use of arbitrary endpoints in early TAVI clinical trials produced serious limitations when results were compared. Introduction of Valve Academic Research Consortium (VARC) unified endpoints of clinical trials. In 2012, due to fast development of TAVI devices and techniques, VARC was updated to VARC-2. Is highly recommended to use VARC-2 endpoints for clinical trials design and analysis [23,24].

3.1. Edwards-Sapiens family trials

The PARTNER trial (NCT00530894) and PARTNER II trial (NCT01314313) are the principal clinical trials evaluating Edwards-SAPIEN prostheses [12,21].

The PARTNER trial was composed by two cohorts: cohort B composed by inoperable patients for SAVR, and cohort A composed by high-risk patients for SAVR [27–31]. In PARTNER cohort B, between 1 to 5 year follow-up, TAVI showed a marked superiority over medical treatment in terms of mortality, hospital readmission, and functional class [25]. TAVI group had a higher stroke and major vascular complication rate. Furthermore, at 5-years follow-up, all-cause mortality still lower in the TAVI group when compared to standard treatment group. There were no evidences of structural valve deterioration [25,26].

The PARTNER cohort A showed a non-inferiority efficacy of TAVI compared to SAVR in high-risk patients in terms of all-cause mortality at 1 and 2 years follow-up [27,28]. However, TAVI group had an increased stroke and major vascular complications rate, whereas surgical group had a higher major bleeding complications and atrial fibrillation rate [27]. At 5-year follow-up, there are still no differences between TAVI and SAVR in mortality risk. There was no structural valve deterioration. TAVI group had a significantly higher moderate-severe AR rate and this was associated with a higher mortality [29].

The PARTNER II trial was non-inferiority randomized trial that assessed the performance of Edwards SAPIEN, SAPIEN XT, and S3 THV [13]. The trial was composed by two cohorts, A and B.

The Cohort B was composed by inoperable patients because of high surgical risk (Surgeon Thoracic Society [STS] > 8%). They were allocated to TAVI with SAPIEN XT or with SAPIEN. At 30-day follow-up, all-cause mortality and disabling strokes rate were similar, but major vascular complications rate were lower in SAPIENT XT group. At 1-year follow-up, the composite endpoint (all-cause mortality, disabling strokes and re-hospitalizations) was similar between both groups (SAPIEN XT 33.9% vs. SAPIEN 34.7%) [30].

The PARTNER II cohort A aims to recruit 2000 operable patients with an intermediate surgical risk (STS 4–8%) and will random allocate them to TAVI with SAPIEN XT or SAVR. Trial design is shown on Figure 3.

The SAPIEN 3 study (NCT01808287) was a non-randomized trial that assessed S3 THV performance. One hundred fifty patients at high, high to intermediate, and intermediate surgical risk were enrolled. In overall, the mean logistic EuroSCORE was 21.6 ± 12.3% and TF access site was used in 64.0%. At 30 days, TF access site was associated with lower mortality (2.1%), no disabling stroke, and higher fully percutaneous access with closure rate (95.8%). Non-TF access site was associated with a higher mortality (11.6%) and stroke rate (5.6%). The moderate-or-severe PVL rate was 3.5% [14]. At 1-year follow-up, TF access site was still associated with a lower mortality (8.4% vs. 24.3%) and permanent pacemaker implantation (PPMI) rate (15.7% vs. 19.8%) when compared with non-TF. A low stroke rate at 1-year (2.1%) was found in the TF group. There were no cases of valve thrombosis, structural valve deterioration, migration, or embolization. Moderate-or-severe PVL rate remained low at 1-year (2.1%) [31].

The PARTNER II S3 was a non-randomized trial that assessed the S3 THV performance in high risk/inoperable patients (STS > 8 %) and intermediate risk (STS 4–8%). Five hundred eighty-three patients were included in the high-risk group (S3HR) and 1076 in the intermediate group (S3i). At 30 days, all-cause mortality (1.1% vs. 2.2%) and PPMI rate (10.1% vs. 13.0%) were lower in the S3i group when compared to S3HR. Also at 30 days, disabling stroke (0.86% vs. 1.02%) and PVL rate (2.9% vs. 4.2%) were lower in the S3i group when compared to S3HR [32].

Because PVL is an important predictor of mortality, improvements from SAPIEN XT to S3 THV include an outer PET skirt, which substantially decreased moderate-or-severe PVL rate (5.5% vs. 2.1%), and also a lower need of balloon postdilatation [33]. Conversely, patients treated with S3 THV have a higher PPMI rate compared with SAPIENS XT (13.3% vs. 6.4%). A single center trial hypothesizes that this higher rate can be associated with an implantation depth ≥ 8 mm [34]. Nowadays there is no accepted hypothesis to explain this increased in conductance disturbance, extensive research is needed to elucidate this relevant issue [35].

Table 1. Comparison of emerging devices for transcatheter aortic valve implantation.

Device, company name and valve size	Valve structure and characteristics	CE Mark	Delivery system and access site	Clinical trials
Lotus™ (Boston Scientific) 23,25,27mm	Bovine pericardium tissue valve. SE Nitinol frame. Retrievable, repositionable, not fast pacing.	October 2013 for AS	18, 20 Fr TF	REPRISE II (NCT01627691) [9]
Engager® (Medtronic) 23,26 mm	Bovine pericardium tissue valve. SE Nitinol frame. Not retrievable, repositionable, fast pacing.	February 2013 for AS	29 Fr TA and TAo	The Engager® CE pivotal trial (NCT01348438) [10]
Evolut® R (Medtronic) 23,26,29,31mm	Porcine pericardium tissue valve. SE Nitinol frame. Recapturable, retrievable, repositionable.	February 2015 for AS	14, 18 Fr sheath TF and SC	The Medtronic CoreValve Evolut R CE Mark Clinical Study (NCT01876420). The Medtronic CoreValve Evolut R U.S. Clinical Study (NCT02207569) [11,12].
SAPIEN 3® (EdwardsLifesciences) 23,26,29 mm	Bovine pericardium tissue valve. BE Cobalt chromium frame. Not retrievable, notrepositionable.	January 2014 for AS	14 Fr sheath TF and TA	The PARTNER II trial (NCT01314313) [13] The SAPIEN 3 study (NCT01800287) [14]
Centera® (Edwards Lifesciences) 20,23,26 mm	Bovine pericardium tissue valve. SE nitinol frame with PET skirt. Not retrievable, repositionable.	Under evaluation	14 Fr sheath and Motorized Handle TF and SC.	First in man experience was performed in 15 patients. At 30-day follow-up, 100% procedural success rate, 27% PPMI, no neurological or major vascular complications, and 92% mild or absent PVL [15]. The ongoing Edwards CENTERA system clinical trial is a non-randomized trial to evaluate safety and device success [16].

Acurate® (Symetis) 23,25,27 mm	Porcine native aortic leaflets. SE nitinol frame. Not retrievable, repositionable, fast pacing.	September 2011 for AS	Sheatless 28 Fr TA	ACCURATE TA® trial [17]. ACCURATE Neo and TF® trial [18]
JenaValve® (JenaValve Technology) 23,25,27 mm	Porcine native aortic leaflets. SE nitinol frame. Retrievable, repositionable, not fast pacing	September 2012 for AS, September 2013 for AR	Sheatless 32 Fr TA	JUPITER registry (NCT01598844) [19]
Portico® (St Jude) 18, 24 mm	Porcine pericardium tissue valve. SE nitinol frame. Retrievable, repositionable, not fast pacing	November 2012 for AS	18, 24 Fr TF, TAo, SC and TA	First in man experience was performed in 10 patients: At 30 days, there was not major stroke or PPMI. Six patients develop new LBBB. PVL was absent or mild in the 95% of the patients [20].
DirectFlow®(Direct Flow Medical) 25, 27 mm	Bovine pericardium tissue valve. Polyester cuff. Retrievable, repositionable, not fast pacing	January 2013for AS	18 Fr outer diameter TF	DISCOVER trial [21] DISCOVER registry (NCT01845285) [22]

Abbreviations: Fr: French; TF: transfemoral; TA: transapical; TAo: Transaortic; SC: subclavian; SE: self-expandable; BE: balloon-expandable; PVL: paravalvular leak; CE: Conformité Européenne; AS: aortic stenosis; PET: polyethylene terephthalate; PPMI: permanent pacemaker implantation; LBBB: left bundle branch block

Table 2. Most relevant data from large multicenter transcatheter aortic valve implantation randomized controlled trials and registries.

Study	N	Valve type (%)	Vascular access (%)	Age mean (SD)	euroSCORE mean in % (SD)	30-day mortality (%)	MVC (%)	30-day stroke (%)	Permanent pacemaker implantation at 1-year (%)	1-year survival (%)	2-year survival (%)	3-year survival (%)	≥5-year survival (%)	Ref.
PARTNER B	179	SAPIEN	TF	83.1 (8.6)	26.4 (17.2)	5	16.2	6.7	3.4	69.3	56.7	45.9	28.2	(25, 26)
PARTNER A	348	SAPIEN	TF: 70.1 TA: 29.9	83.6 (6.8)	29.3 (16.5)	TF: 3.3 TA:3.8	11.0	4.6	3.8	All: 75.8 TF: 77.8 TA: 71	66.1	55.8	32.3	(27-29)
PARTNER II B	560	SAPIEN (49.3) SAPIEN XT (50.7)	TF										-	(30)
			SAPIEN	84.6 (8.6)	11.0 (5.7)	5.1	15.5	4.1	5.9	76.3	-	-	-	
			SAPIEN XT	84.0 (8.7)	10.3 (5.4)	3.5	9.6	4.3	6.4	77.5	-	-	-	
SAPIEN 3	150	SAPIEN 3	TF: 64 NTF: 36	83.6 (5.0)	21.6 (12.3)	All: 5.3 TF: 2.1 NTF: 11.1		All: 2.7 TF:1 NTF: 5.6	All: 13.3 TF: 12.5 NTF: 14.8	All: 86.0 TF: 91.6 NTF: 75.7	-	-	-	(15, 31)
CoreValve US Pivotal Extreme risk	489	CoreValve	TF	83.2 (8.7)	22.6 (17.1)	8.4	8.4	2.3	26.2	75.7	62	-	-	(36, 37)
CoreValve US Pivotal High risk	390	CoreValve	TF	83.1 (7.1)	17.7 (13.1)	3.3	5.9	4.9	23.3	85.4	77.8	-	-	(38, 39)

SOURCE	2344	SAPIEN	TA: 60.1 TF: 39.9	81.1	TF: 23.9 (14.2) TA: 27.6 (16.1)	TF: 7.4% TA: 10.8%	-	TF: 2.9% TA: 2.5%	TF: 6.7 TA: 7.1	TF: 80.1% TA: 74.2%	TF:72.2 TA: 64.7	-	-	(40)
SOURCE XT	2688	SAPIEN XT	TF:62.7 NTF: 37.3	81.5	TF: 19.8 (11.6) TA: 21.9 (13.8)	TF:4.3 TA:9.9	-	TF: 2.3 TA: 2.1	TF: 8 TA: 10.9	TF: 85 TA:72.8 TAo: 73.9	TF: 77.6 TA: 63.3	-	-	(41)
ADVANCE	1015	CoreValve		81.1 (6.4)	19.4 (12.3)	8.0	20.7	3.0	29.1	79.0	69.8	66.3	-	(42, 43)
TVT Registry	12 182	SAPIEN CoreValve	TF:56.4 NTF:43.6	84	†STS 7.1 (4.8-10.8)%	7.0	-	2.5	-	76.3	-	-	-	(44)
GARY	13 860		TV: 69.5 TA: 30.5	TV: 81.1 (6.2) TA: 80.3 (6.1)	TV: 5.2 TA: 7.7	All: 7.1 TV: 6.0 TA: 9.8	-	*TV: 2.7 *TA:1.5	TV:26.6 TA:14.1	All: 74.7 TV: 76.9 TA: 69.6	-	-	-	(45)
UK TAVI	870	SAPIEN (47) CoreValve (52.9)	TF: 68.9; Other: 31.1	81.9 (7.1)	All 18.5 TF: 17.1 Other: 21.4	7.1	6.3	4.1	16.3	78.6	73.7	-	-	(46)
		SAPIEN CoreValve	82.6 (6.7) 81.3 (7.4)	18.5 18.1	8.5 5.8	6.3 6.2	4.2 4	- -	7.4 24.4	79.4 78.3	71.7 71.7	- -	- -	
UK TAVI (Long-Term follow-up)	3980	SAPIEN (51.8) CoreValve (48.2)	TF: 71.2 Other: 28.8	81.3 (7.6)	21.9 (13.7)	6.3	3.5	2.6	20.1	81.7	72.8	63.6	‡37.3	(47)

FRANCE 2	3195	SAPIEN XT	TF: 74.6	TF: 83 (7.2)	TF: 21.2	All: 9.7	All: 4.7	All: 4.1	All: 15.6	All:	-	-	-	(48)
		(66.9)	SC: 5.8	TA: 81.5	(14.7)	TF: 8.5	TF: 5.5	TF: 3.7	TF: 15.2	76.0				
		CoreValve	Other: 1.8	(7.4)	TA: 24.8	TA: 13.9	TA: 1.9	TA: 4.4	TA: 13.6	TF: 78.3				
		(33.1)	TA: 17.8	SC: 82.2	(14.7)	SC: 10.1	SC: 4.3	SC: 7.0	SC: 25.5	TA: 67.7				
				(6.7)	SC:					SC: 74.9				
					20.3 (15.2)									
			SAPIEN	82.9 (7.2)	22.2 (14.3)	9.7	2.7	3.8	11.5	24	-	-	-	
			CoreValve	82.3 (7.2)	21.3 (14.3)	9.4	4.5	4.3	24.2	23.7	-	-	-	

*In-Hospital Mortality; †Surgical risk is assets by Society of Thoracic Surgeons risk score; ‡Six year follow-up. Abbreviations: SD: Standard Deviation; MVC: Major Vascular Complications; Ref: reference; TF: transfemoral; TA: transapical; TAo: Transaortic; SC: subclavian; NTF: Non-Transfemoral; STS: Society of Thoracic Surgeons.

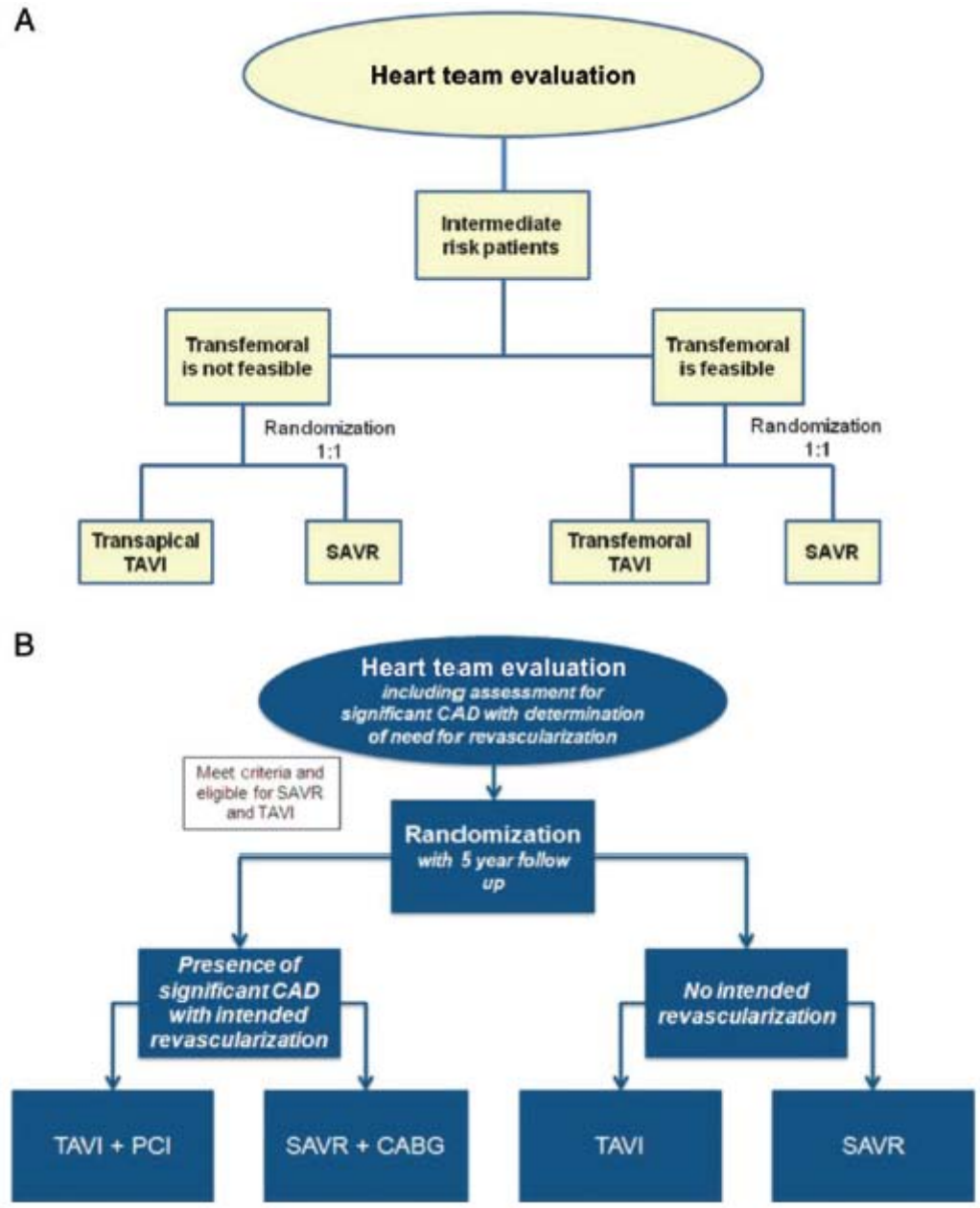

Figure 3. Trial design of the PARTNER II Cohort A (A) and the SURTAVI (B) trial.
Retrieved from Bourantas CV, et al. EuroIntervention 2013; 9(Suppl):S84–S90 [49].

3.2. Medtronic family trials

The CoreValve US trial (NCT01240902) evaluated the performance of Medtronic CoreValve in two cohorts: extremely high and high-risk patients.

The extreme-risk cohort was a non-randomized trial that evaluated TAVI in patients with a prohibitive surgical risk. Because TAVI had already shown superiority vs. medical treatment, TAVI was compared to a pre-specified objective performance goal (OPG). At 1-year follow-up, all-cause mortality and stroke rate was lower in TAVI group when compared to OPG (26.0% vs. 43.0%,). The PPMI rate was considerably high (21.6%) [36]. Two year follow-up data confirmed benefits of TAVI

compared to OPG in mortality (38% vs. 57.9%) and stroke rate [37].

The high-risk cohort was a randomized clinical trial that compared TAVI in high-risk patients vs. SAVR. At 1-year follow-up, all-cause mortality was lower in the TAVI group when compared to SAVR (14.2% vs. 19.1%). The vascular complications and PPMI rate were significantly higher in TAVI group when compared to SAVR [38]. At 2-year follow-up, mortality in TAVI group was still lower when compared to SAVR (22.2% vs. 28.6%). TAVI group had a lower stroke (10.9% vs. 16.6%) and higher PPMI rate (25.8% vs. 12.8%), when compared to SAVR [39].

The Medtronic Engager™ valve was evaluated in The Engager European Pivotal Trial (NCT01348438), a non-randomized trial that assessed the performance of the Engager System in high-risk patients. At 30-day follow-up, all-cause mortality was 8.1%, stroke was 1.7%, and PPMI rate was 27.2% [10]. The ongoing Engager Align Study (NCT02149654) will evaluate post-marketing performance [50].

Medtronic Evolut R™ valve was evaluated in the CoreValve Evolut R CE Study, a non-randomized trial that assessed the performance in extreme and high-risk patients. At 6 months follow-up, all-cause mortality was 5%, disabling stroke was 1.7%, PPMI was 13.4%, and moderate-or-severe PVL rate was 42.6% [51].

The ongoing SURTAVI trial (NCT01586910) is a randomized clinical trial that assesses safety and efficacy of TAVI vs. SAVR, in intermediate risk patients (STS 4–10%). It also assesses the concomitant need of coronary revascularization in patients with significant coronary artery disease and AS [52]. Trial design is shown on Figure 3.

3.3 Comparison between CoreValve and Edwards-Sapien

The CHOICE trial (NCT01645202) was a randomized clinical trial that compared TAVI with SAPIEN XT vs. Medtronic CoreValve in high-risk patients. The balloon-expandable group was associated with a higher device success rate when compared to self-expandable group (95.9% vs. 77.5%). Self-expandable group was significantly more associated to moderate-or-severe AR (4.1% vs. 18.3%) and PPMI rate (17.3% vs. 37.6%) when compared to balloon-expandable [53,54]. At 1-year follow-up, there were no significantly differences between balloon-expandable vs. self-expandable in all-cause mortality (17.4% vs. 12.6%), rehospitalization by heart failure (7.4% vs. 12.6%), stroke (9.1% vs. 3.3%) or valve thrombosis rate (3.4% vs. 0%). Balloon-expandable group was associated with lower moderate-or-severe AR (42.7% vs. 54.4%) and PPMI rate (23.4% vs. 38.0%) when compared to self-expandable. Thromboembolic events in the group balloon expandable need an exhaustive evaluation [55].

3.4 Self-expandable and balloon expandable in "Real-world" registries

Up to date there are many reported TAVI registries, with implementation of VARC-2, quality of registries have improved significantly and adequate comparison between them became possible [24]. Largest registries regarding number of enrolled patients and follow-up time are shown on Table 2.

3.5 Emergent devices clinical outcomes

Boston Scientific Lotus™ Valve was evaluated in the REPRISE II (NCT01627691) a

non-randomized trial that assessed performance in high-risk patients. One hundred twenty patients were enrolled, at 30-days follow-up, mortality was 4.2%, disabling stroke was 1.7%, and moderate-or-severe PVL rate was 1% [9]. At 1-year follow-up, cardiovascular mortality was 6.7%, disabling stroke rate was 3.4%, and there were no changes in valve pressure gradient or PVL. Subsequently, in the REPRISE II Extended Trial Cohort, at 30-day follow-up, all-cause mortality was 4.4%, disabling stroke was 3.2%, and PPMI rate at 30-day was 28.9% [56]. Currently the post-marketing RESPOND trial (NCT02031302) and the REPRISE III randomized clinical trial (NCT02202434) are evaluating performance in extreme or high-risk patients [56].

Direct Flow Medical® system (DFM) was evaluated in the DISCOVER CE trial that assessed performance in high-risk patients. At 30-days follow-up, freedom from all-cause mortality was 99%, freedom from event was 91%, and major stroke rate was 4%. The moderate-or-severe PVL was 1.4% and PPMI rate was 17% [57]. Later at 1-year follow-up, freedom from all-cause mortality rate was 90%, freedom from mortality and major stroke rate was 86%, without changes in PVL or PPMI rates. At 2-year follow-up, survival rate was 80% and 85% patients had none or trace AR [21,58]. The ongoing US Pivotal Trial or SALUS Trial (NCT02163850) is a non-randomized trial evaluating performance in high-risk patients [59].

The JenaValve® system is being evaluated in the ongoing JUPITER registry (NCT01598844), a non-randomized trial that assesses long-term performance in high-risk patients. In an interim analysis of 180 patients, at 30-days follow-up, all-cause mortality was 8.5%, major stroke rate was 1.1%, and no patient had severe PVL [19,60].

The Acurate® system was assessed in the ACURATE TA™ registry that enrolled high-risk patients that performed TAVI by TA access site. At 30-day follow-up, all-cause mortality was 6.8%, stroke was 2.8%, moderate-or-severe PVL was 2.3%, and PPMI rate was 10.0% [17]. Symetis ACURATE Neo™ Registry (NCT02306226) is an ongoing non-randomized trial assessing performance of the ACURATE neo™ system. In an interim analysis, the survival was 97%, stroke was 2%, freedom from VARC-2 combined safety was 84.3%, PPMI was 9%, and moderate-or-severe PVL rate was 5% [18].

Clinical outcomes of other devices are shown in Table 1.

4 Future Perspectives

4.1 Better patient selection

The candidates to TAVI and SAVR are usually high-risk patients, an adequate patient selection is crucial to improve procedural outcome. The choice between SAVR and TAVI is based on the presence of contraindications or a high-surgical risk. The STS and EuroSCORE are usually used to estimate mortality risk during cardiac surgery: when STS is > 10% or logistic EuroSCORE is ≥ 20%, patients are considered at high-risk for surgery and TAVI may be considered [61,62].

Both risk scores have some limitations, they were developed and validated in standard surgical populations, predicts only short-term mortality (up to 30-day after surgery), do not include specific risk factors (frailty, porcelain aorta, vessel tortuosity, chest wall malformation, chest radiation or access site), and cannot predict complications [63]. However, some observational studies have found that STS and logistic EuroSCORE II are strong predictors of mortality [64,65].

Investigators from the FRANCE-2 registry attempted to develop an early mortality risk score,

they defined it as in-hospital or 30-day mortality. They identify nine independent risk factors for early mortality: age ≥ 90 years, body mass index < 30 Kg/m^2, New York Heart Association class IV, pulmonary hypertension, critical hemodynamic state, ≥ 2 pulmonary edemas during the last year, respiratory insufficiency, dialysis, and others than TF access site. Using these variables, a multiparametric risk score was proposed and then validated in a subset of the FRANCE-2 registry, C-index was 0.67 for the score in the development cohort and 0.59 in the validation cohort. The concordance between predicted and observed 30-day mortality rates was good, but discrimination was modest [66].

Current guidelines recommend that discussion on individual patient management should take place in the 'Heart Team' including clinical cardiologists related to valvular disease, interventional cardiologist, imaging cardiologist, cardiothoracic surgeons, and anaesthesiologists. Since frailty has become an important risk factor, geriatricians may be included [61].

4.2 Low risk AS patients

In the 2014 AHA/ACC guidelines for management of patients with valvular heart disease, TAVI has a level of evidence and grade of recommendation of I-A in patients not suitable for SAVR and II-A in patients with high-surgical risk [62]. There has been an undeniable trend in clinical practice and clinical trials to treat lower risk patients with TAVI instead of SAVR [67]. Moreover, many reports have suggested that TAVI can have similar or even better outcomes on intermediate and low-risk patients [68–72].

The NOTION trial (NCT01057173) was a randomized clinical trial that compared TAVI with self-expandable prosthesis versus SAVR in low-risk patients with no significant coronary artery disease. At 1-year follow-up there was no significant difference in the primary endpoint (all-cause death, stroke and MI) between TAVI and SAVR (13.1% vs. 16.3). The TAVI group (Logistic euroSCORE 1.9 ± 1.2%) had a higher PPMI and total AR rate, when compared with SAVR. The SAVR group (Logistic euroSCORE 2.0 ± 1.3%) had a higher major bleeding, cardiogenic shock, acute kidney injury, and atrial fibrillation rate [73]. The PARTNER IIA trial and SURTAVI trial will help to clarify if TAVI could be a real treatment option in lower risk patients.

4.3 ParaValvular leak

Paravalvular leak is an important predictor of 30-day and 1-year mortality in TAVI procedures. The predictors of PVL are depth implantation, valve undersizing, and a high Agatston calcium score [74]. Imaging techniques are crucial to choose optimal valve size and reduce PVL rate [75]. Some reports have also proposed postdilatation as a way of reducing PVL in patients with greater than mild PVL after a balloon-expandable TAVI [76]. The PVL rate has changed significantly due to technological improvements, in early devices mod-severe PVL rate was 11.7% (CoreValve 16% and Edwards SAPIEN 9.1%, $p < 0.005$) and in last generation devices (Lotus valve, DFM and S3 THV), moderate PVL rate was < 3.4% with no severe leaks [75].

4.4 Permanent pacemaker implantation

Because the anatomical proximity of the aortic valve to the conduction system, pacemaker

implants are a known complication of both TAVI and SAVR. The PPMI rate differs depending on valve type, being lower in balloon-expandable prosthesis than self-expandable (8.5% vs. 20%) [47,48]. Important patient and procedural variables have been related to PPMI: pre-existing conduction disorders, Right Bundle Branch Block, narrow left ventricle outflow track, septal wall thickness, balloon aortic valvuloplasty, and implantation depth (< 6 mm) [77,78]. It is highly recommended to evaluate complete atrioventricular block risk, maintaining heart rhythm monitoring, and placement of temporary pacemaker for 48–72 hours [90]. Up to date it is unclear if patients who need transitory or PPMI have a worst prognosis when compared to patients without conduction disturbances [79].

4.5 Stroke

In a meta-analysis of early devices, average 30-day stroke/transient ischemic attack rate was 3.3 ± 1.8% (range 0–6%). Most of these were major strokes and were associated to increased short-term mortality [80]. Conversely, a meta-analysis of recent trials suggested that 30-day stroke rate after TAVI was similar among different access sites and devices. There has been a decreased in the stroke risk after TAVI procedures, mainly due to improvements in valve technology, better patient selection, and experience of the operator. Although, stroke rate is still high (2.8–3.8%) [81].

Use of cerebral protection device during TAVI procedures was associated with more freedom of ischemic brain lesions, less neurological deficits, and improved in some domains discharge and 30-days cognitive function [82].

4.6 Procedural considerations

A major advance of newer devices are lower crossing profiles that helps to obtain better device success rate and decrease vascular complications. Furthermore, TF has become the most used and secure access site, being used in approximately 85% of the procedures [75].

There is a strong trend to simplify TAVI procedures, including reduced use of general anesthesia, less intra-procedural transesophageal echocardiography, and eliminating predilatation with balloon aortic valvuloplasty [83]. The Multidisciplinary, Multimodality, but Minimalist (3M) approach for TF TAVI is a recent initiative to facilitate safe next day home discharge in high-risk patients. Patients considered high risk for SAVR, but relatively low risk for TAVI procedure, were rigorously screened with functional and cognitive assessments as well as multi-modality imaging. In a cohort of 50 patients, next day home discharge was possible in all patients with a 92% survival rate at 1-year [84].

Others aspects of the procedure currently under evaluation are:

- Valvuloplasty prior TAVI: In both types of prosthesis, usually a balloon aortic valvuloplasty is performed before valve implantation. At present, there are some concerns about the role of balloon aortic valvuloplasty, because it has been related to an increased complication and conduction disturbance rate. Current trend is to use an imaging technique to adequately select patients in which valvuloplasty is beneficial [85]. The systematically use valvuloplasty is being study in the EASY-IT registry (NCT02127580) [86].
- Use of closure devices in transapical approach to reduce bleeding [87].
- Need of revascularization in significant coronary artery disease prior to TAVI procedure [88].
- Use of antiplatelet therapy: clopidogrel plus aspirin versus aspirin alone to prevent ischemic events [89].

- Security and long-term outcomes of Valve-In-Valve TAVI procedure [90].

5 Conclusions

Since first implant in 2002, TAVI has become the standard of care in inoperable patients with severe symptomatic AS and/or at high-surgical risk. In the last 15 years, there has been a dramatic change in clinical practice, supported by high quality clinical outcomes and safety profile. Emergent devices have been designed to address previous devices issues, but more scientific evidence is needed to add them to routine clinical practice. Important data will come from future trials such as PARTNER IIA and SURTAVI trials. In the following years many relevant topics such as efficacy of emergent devices, indication in lower risk patients, prior coronary revascularization, implantation in aortic regurgitation and use in others heart valves will be addressed as well.

Conflict of Interest

The authors claim no conflict of interest.

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