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REVIEW ARTICLE

A European update on transcatheter aortic valve implantation (TAVI) in the COVID era

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Abstract

Minimally invasive approaches for aortic valve replacement are now at the forefront of pathological aortic valve treatment. New trials show comparability of these devices to existing therapies, not only in high-risk surgical cohorts but also in low-risk and intermediate-risk cohorts. This review provides vital clinical and anatomical background to aortic valvular disease treatment guidelines, while also providing an update on transcatheter aortic valve implantation (TAVI) devices in Europe, their interventional trials and associated complications.

KEYWORDS
aortic valve disease, aortic valve prosthesis, device clinical trials, transcatheter aortic valve implantation, transcatheter aortic valve replacment

1 | INTRODUCTION

The global burden of aortic valvular disease is increasing worldwide due to an increase in the aging population (Coffey et al., 2021). Conventional treatment of aortic valve disease typically involves surgical aortic valve replacement (SAVR), wherein the degenerated aortic valve cusps are excised completely to allow for surgical implantation of a prosthetic valve (Walther et al., 2012). Surgical cardiac intervention requires access to the thoracic cage, via a limited access incision but often it necessitates a median sternotomy. Thus, SAVR is precluded to patients at risk for surgery, such as those with prior surgical complications, chest wall anatomical defects, porcelain aorta, severe pulmonary hypertension, severe right ventricular dysfunction, frailty, radiation damage, severe liver disease, impaired renal function, diabetes mellitus, and severe lung disease (Kappetein et al., 2012). Transcatheter aortic valve implantation (TAVI) or transcatheter aortic valve replacement (TAVR) is fast emerging as an alternative intervention for this patient cohort. TAVI or TAVR is a minimally invasive, cost-effective (Mennini et al., 2022; Reynolds et al., 2012; Watt et al., 2012), a procedure wherein a prosthetic valve is implanted within the existing native aortic valve, without removal of the old damaged tissue. The new prosthetic valve is typically deployed via the transfemoral route, though other approaches include transapical, subclavian, direct aortic, and transcaval access. The first use of TAVI in humans took place in 2002 with the implantation of a balloon-expandable, stainless steel stented bovine pericardial aortic valve developed by Percutaneous Valve Technologies (later acquired by Edwards Lifesciences; Cribier et al., 2002). CoreValve (later acquired by Medtronic in 2009) followed with their self-expandable, nitinol stented bovine pericardial aortic valve prosthesis, with the first successful human implants in 2005 (Grube et al., 2005). Newer generations of these valves currently exist and other devices are entering the market currently indicated for certain populations or

Ishan Antony and Hyab Mehari Abraha equal contribution.

only for clinical trials. This review aims to give a perspective on TAVI devices in Europe, their interventional trials, and associated complications while also providing the background of aortic valvular diseases and their treatment guidelines. Articles were gathered through PubMed and clinicaltrials.gov using key terms "TAVI" and "TAVR". A list of TAVI devices in the market or on trials around the world was additionally populated through Google search. After the first round of retrieval, every TAVI device found was searched separately on PubMed to retrieve any articles missed. These devices were reviewed for the European CE mark status. All devices with a published interventional trial documenting a minimum of 30-day outcomes of participants with defined surgical risk of participants were included in the study. Devices not having any published research data, observational trials, patient registries, and first-in-human publications were excluded from the study.

2 | ANATOMY AND PATHOLOGY OF THE AORTIC VALVE

The healthy aortic valve consists of three cup-shaped leaflets or cusps (left, right, and posterior) and an annulus separating the left ventricle from the aorta (Cary & Pearce, 2013). During systole, the leaflets open due to an increase in forward pressure across the valve, allowing for the unobstructed ejection of blood from the left ventricle to the aorta. During diastole the leaflets close due to an increase in backward pressure against the valve, preventing regurgitation of blood back into the left ventricle (Cary & Pearce, 2013). The leaflets extend from their basal attachment at the myocardium of the left ventricle to their peripheral attachment at the sinotubular junction, which demarcates the aortic root from ascending aorta. At this junction, the peripheral attachments of the three aortic leaflets join to create a "crown-like" annular ring (Piazza et al., 2008). Though an "annulus" is typically defined as a single concentric ring that spans the diameter of a tubular structure, the aortic annulus is better described as the area occupied by the 'crown-like' ring within the aortic root.

While the anatomy of the aortic valve itself is particularly relevant to TAVI device design, there are also important neighboring structures that need to be considered when designing device specification and deployment. Namely, immediately adjacent to the aortic valve are the left and right coronary artery orifices, housed in the left and right aortic sinuses respectively (Piazza et al., 2008). Immediately below the aortic valve (~2–3 cm) is the left branching of the bundle of His fibers (conductive tissue). Finally, the left (or left coronary) and posterior (or noncoronary) aortic leaflets connect to the neighboring anterior leaflet of the mitral valve via the aortomitral continuity—a fibrous curtain culminating in the left fibrous trigone that is continuous with the mitral annulus (Saremi et al., 2017).

Pathology of the aortic valve typically presents as either aortic stenosis (AS) or aortic regurgitation (AR). AS is the narrowing of the aortic valve which prevents the valve to fully open and function normally, thereby reducing systemic blood circulation (Czarny & Resar, 2014). 43.1% of all left-sided valvular diseases in Europe were found to be AS (Iung et al., 2003) with a prevalence of 10% in the UK (Marciniak et al., 2017) and 12.4% combined across studies from Europe, USA, and Taiwan (Osnabrugge et al., 2013). AS can be caused by congenital unicuspid, bicuspid or quadricuspid aortic valve, rheumatic disease, or degenerative calcification of a normal trileaflet valve (Mrsic et al., 2018). Typically, stenosis occurs progressively, whereby increased left ventricular outflow tract obstruction from inflammation, fibrosis, and valve thickening takes place over time, leading to valvular calcification (Czarny & Resar, 2014; Mrsic et al., 2018). Left untreated, stenosis leads to long-term sequelae culminating in heart failure. To overcome the increased afterload caused by the stenotic valve and maintain adequate stroke volume/cardiac output, the left ventricle must generate higher systolic pressure, causing concentric hypertrophy of the left ventricular wall (Carabello & Paulus, 2009). This compensatory mechanism can have negative consequences such as decreased left ventricular myocardial elasticity, decreased coronary blood flow, increased myocardial workload, increased oxygen consumption, and ultimately a higher likelihood of mortality. In addition, ventricular hypertrophy increases diastolic pressure, which increases the atrial contractile force required to maintain stroke volume and cardiac output (Cary & Pearce, 2013). As a consequence of both ventricular hypertrophy and atrial hypertrophy, the left ventricular chamber decreases in size, causing decreased preload and worsened systolic function, which in turn leads to insufficient stroke volume, cardiac output, ejection fraction, and backward transmission of increased left ventricular pressure to the lungs causing secondary pulmonary hypertension (Carabello & Paulus, 2009). Due to the wide-scale cardiac impact of AS, symptoms vary depending on the stage of disease and can include fatigue, syncope, angina, dyspnea, and heart failure, typically presenting after the age of 70 in patients with degenerative calcification and earlier in patients with congenital valve malformations with manifestations (Mrsic et al., 2018).

Aortic regurgitation (AR) or aortic insufficiency is the leaking of the aortic valve causing a diastolic reversal of blood flow from the aorta into the left ventricle. The prevalence of AR was estimated as 4.9% in the Framingham study, with incidence and severity of AR seen to increase with age, peaking at 40–60 years (Maurer, 2006).

AR can be caused by a variety of factors, including morphological abnormalities, inflammation, and congenital malformations. Table 1 provides a brief summary of precursors to aortic regurgitation (Akinseye et al., 2018).

Like AS, AR results in a complex sequelae which, if left untreated, culminate in heart failure and mortality. Regurgitation of blood from the aorta to the left ventricle leads to volume overload, increased total stroke volume (sum of effective stroke volume plus regurgitant volume), and increased aortic systolic pressure (Figure 1). If the AR is acute (sudden, high volume), the heart cannot compensate for the overload, leading to sudden onset symptoms such as dyspnoea, chest pain, hypotension, tachycardia, peripheral vasoconstriction, and pulmonary congestion. If the regurgitation is chronic (low volume), the heart compensates with chamber hypertrophy and dilation, causing increased myocardial oxygen consumption and decreasing myocardial oxygen supply

due to a decrease in effective stroke volume, diastolic time, and diastolic pressure (Maurer, 2006), see Figure 1. AR in its chronic form is initially asymptomatic until the patient develops signs of heart failure, such as exertional dyspnoea, orthopnoea, and paroxysmal nocturnal dyspnoea and later angina combined with bradycardia (Akinseye et al., 2018).

TABLE 1 Factors leading to aortic regurgitation

Systemic hypertension	
Myxomatous degeneration	
Abnormalities of the aortic root and ascending aorta	• acute aortic dissection (tearing of the inner layer) • age-related aortic dilation
Inflammation	• rheumatic fever • infective endocarditis • systemic lupus erythematosus • rheumatoid arthritis • ankylosing spondylitis • Takayasu arteritis • Whipple disease • Crohn's disease • drug-induced valvulopathy • aortitis (syphilis and giant cell arteritis) • Reiter syndrome • Behcet syndrome • psoriatic arthritis • relapsing polychondritis
Congenital malformations	• congenital bicuspid valve • Ehlers-Danlos syndrome • Marfan syndrome • Turner syndrome • osteogenesis imperfecta

3 | EUROPEAN TREATMENT GUIDELINES

The European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) updated their guidelines in 2021 for the management of valvular heart disease. The guidelines highlight the importance of the Heart team in accessing patients based on key clinical (e.g. extracardiac comorbidities, risk of surgery), anatomical (e.g. presence of pathological or congenital variation, TAVI feasibility), and procedural (e.g. imaging feasibility, local procedural experience, and outcomes) factors before selecting between SAVR and TAVI in the management of aortic stenosis. The severity of AS can be categorized based on a number of parameters including but not limited to; mean pressure gradient across the valve, peak transvalvular velocity, valve area, stroke volume (volume of blood ejected from the left ventricle during systolic contraction), left ventricular ejection fraction (fraction of left ventricular blood ejected in systole relative to end-diastolic volume), left ventricular hypertrophy, and adequacy of blood pressure control. Intervention is indicated in symptomatic patients with severe, high-gradient AS (mean gradient ≥ 40 mmHg, peak velocity ≥ 4.0 m/s, and valve area ≤ 10 mm^2). The new 2021 guidelines now outline that intervention should also be considered in symptomatic patients with severe, low flow, low-gradient aortic stenosis with normal

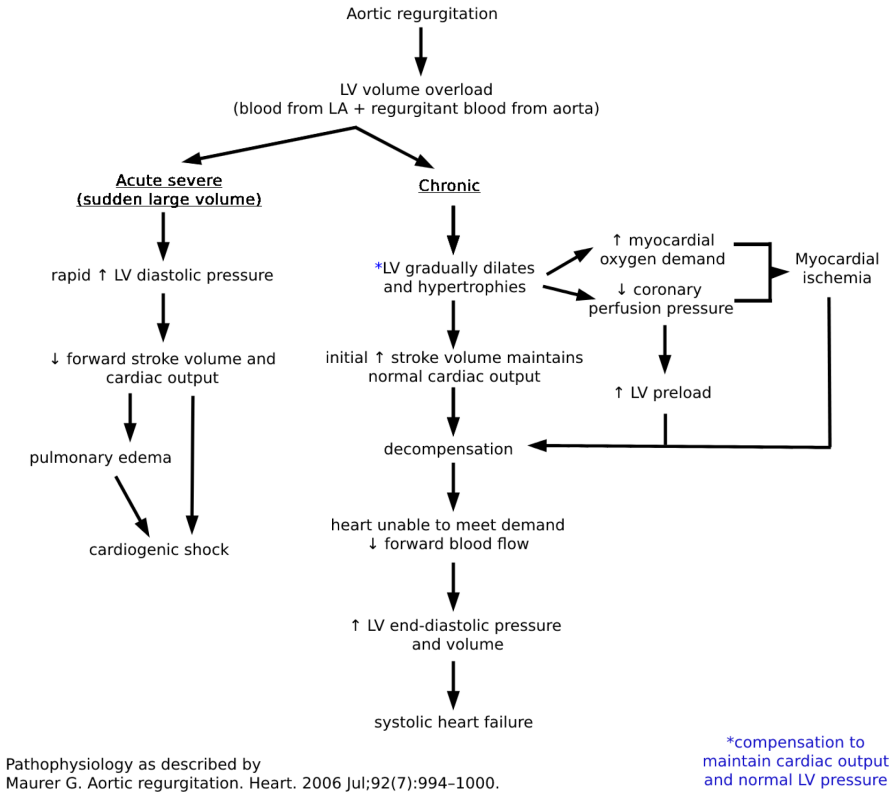

FIGURE 1 Pathophysiology of aortic regurgitation.

ejection fraction, and with reduced ejection fracture where there is evidence of no flow (contractile) reserve. However, intervention in low-flow low-gradient patients should be considered only after additional testing excludes pseudo-severe AS. Intervention is indicated in asymptomatic patients with severe stenosis and left ventricular dysfunction (ejection fraction < 50%). Patients with severe comorbidities are not recommended any intervention as it is unlikely to improve quality of life and outcome. TAVI is recommended in patients deemed unsuitable for surgery (patients aged above 75 years, history of previous cardiac surgery, porcelain aorta, reduced mobility, difficult rehabilitation, frailty, severe chest wall deformities, sequelae of chest radiation, risk of sternotomy affecting previous coronary bypass grafts, favorable transfemoral access, and expected patient-prosthetic mismatch) and at an increased surgical risk with Society of Thoracic Surgeons (STS) or European System for Cardiac Operative Risk Evaluation (EuroSCORE) II greater than 8 (Vahanian et al., 2022). EuroSCORE is a cardiac risk calculator available online used for predicting mortality after cardiac surgery based on 18 items of information about the patient, the state of the heart, and the proposed operation. EuroSCORE II, published in 2012, is an updated version of EuroSCORE I which was first published in 1999 (Nashef et al., 2012). The STS Short-Term Risk Calculator calculates a patient's risk of mortality and morbidities for the most commonly performed cardiac surgeries based on STS risk models (O'Brien et al., 2018; Shahian et al., 2018).

TAVI is suggested in patients aged >75 years, previous history of cardiac surgery, having favorable access to transfemoral TAVI, frailty, restricted mobility, and conditions that may affect the rehabilitation process. Sequelae of chest radiation, porcelain aorta, presence of intact coronary bypass grafts at risk when sternotomy is performed, expected patient-prosthesis mismatch, and severe chest deformation or scoliosis in patients requiring aortic valve replacement also favor TAVI. In AR, surgery is recommended in symptomatic patients and in asymptomatic patients with severe AR, impairment of LV function (ejection fraction ≤ 50%) and LV enlargement with an LV end-diastolic diameter (LVEDD) > 70 mm or left ventricular end-systolic diameter (LVESD) > 50 mm (Vahanian et al., 2022).

The Health Information and Quality Authority (HIQA) in Ireland has recommended that TAVI should be available for patients aged 70 years and over with severe symptomatic AS at low and intermediate surgical risk in the Irish public healthcare system (HTA of transcatheter aortic valve implantation (TAVI) | HIQA, 2019).

4 | TAVI DEVICES AND TRIALS

TAVI devices consist of an expandable stent frame (made from nitinol or cobalt-chromium alloys or stainless steel biomedical grade) that suspends animal (bovine or porcine) tissue leaflets (Rotman et al., 2018). During a TAVI procedure, the compressed prosthetic valve is passed through a hollow catheter. Once the catheter is in the correct position the frame expands—either autonomously or using a balloon in the catheter tip—to press the valve into place (Rotman et al., 2018). The primary device design considerations are crimping, stent deployment (balloon or self-expandable), leaflet mechanics, durability, calcification susceptibility, hydrodynamics, and thrombogenicity. A thorough design history of available devices and a description of how these device considerations are thought to impact biological performance is provided (Rotman et al., 2018).

To date a variety of TAVI devices have been designed, with some currently approved for use in patients, others only designated for use in trials, and a few no longer in circulation. In Europe and USA Edwards' Sapien 3, Sapien 3 Ultra, and Medtronic's CoreValve Evolut R and CoreValve Evolut PRO have been approved for use in patients at low-extreme risk for SAVR while the Boston Scientific Corporation's LOTUS Edge Aortic Valve System has been approved for use in patients deemed high or greater risk for open surgical therapy. Currently available European Conformité Européenne (CE) mark devices with published trials include Portico (Linke et al., 2018; Makkar, Cheng, et al., 2020), ACURATE neo (Lanz et al., 2019; Möllmann et al., 2017), Jenavalve (Treede et al., 2012), ALLEGRA (Schäfer et al., 2019), and MyVal (Sharma et al., 2019). Other CE mark devices such as Medtronic Engager (Holzhey et al., 2013) and Edwards CENTERA (Reichenspurner et al., 2017; Tchétché et al., 2019) have been discontinued by their companies to focus on their flagship TAVI devices, while Direct Flow Medical (Lefèvre et al., 2016; Schofer et al., 2014) has shut down. Valves awaiting CE Mark approval include HLT Meridian valve (Rodés-Cabau et al., 2019) and Braile Innovare (Gaia et al., 2015). All TAVI devices with interventional trials based on surgical risk highlighting primary outcomes and key secondary outcomes have been listed with results in Table 2.

TAVI randomized control trials are usually designed to discern outcomes for specific patient populations; typically based on the risk strata of patients for surgery, such as high-risk, intermediate-risk and low-risk patients. Thus, these trials access device performance before rolling them out to the intended populations. This also helps to compare the safety and efficacy of TAVI with the conventional surgical method of replacement. TAVI was first trialed in patients who were at high risk of surgery (based per device) and investigated in the PARTNER trials looking at the SAPIEN valve (Herrmann et al., 2016; Kapadia et al., 2015; Kodali et al., 2012; Smith et al., 2011; Webb et al., 2014) followed by the CoreValve Pivotal trials (Adams et al., 2014; Deeb et al., 2016; Gleason et al., 2018; Reardon et al., 2015), Portico (Axel et al., 2018; Makkar, Cheng, et al., 2020), REPRISE II Lotus valve (Meredith et al., 2014; Meredith et al., 2016) and REPRISE III (Feldman et al., 2018; Reardon et al., 2019), CENTERA-2 (Reichenspurner et al., 2017; Tchétché et al., 2019) and SCOPE-1 ACURATE neo (Lanz et al., 2019). Other high-risk trials have compared between balloon-expandable and self-expanding transcatheter aortic valve with the CHOICE trials featuring the Medtronic CoreValve against the Edwards SAPIEN XT (Abdel-Wahab et al., 2014, 2015, 2020) while the SOLVE-TAVI trials compare the newer Medtronic Evolut R and Edwards Sapien 3 in the high-intermediate group (Thiele et al., 2020). New devices perform their feasibility and first in man trials on inoperable and high surgical risk patients before initiating their clinical trials. Major high-risk

TABLE 2 Summary of key TAVI device trials with primary outcomes

Device	Type	Trail	Approach	Surgical risk	Primary IC	Study size	Time	Morality		Moderate/severe PVL		PPMI	
Sapien	BE	PARTNER 1	TF 70.1%	High	NYHA ≥ II			TAVR	SAVR	TAVR	SAVR	TAVR	SAVR
			TT 29.9%		Severe AS	TAVR 348 /699	30 D	3.40%	6.50%	12.20%	0.90%	3.80%	3.60%
					Cardiac symptoms	SAVR 351 /699	1 Y	24.20%	26.80%	6.80%	1.90%	5.70%	5%
							2 Y	33.90%	35%	1.90%	0.90%	7.20%	6.40%
							5 Y	67.80%	62.40%	–	–	9.70%	9.10%
SAPIEN XT	BE	PARTNER 2A	TF 76.3%	Intermediate	NYHA ≥ II	TAVR 1011 /2032		TAVR	SAVR	TAVR	SAVR	TAVR	SAVR
			TT 23.7%		symptomatic senile degenerative AS	SAVR 1021 /2032	30 D	3.90%	4.10%	3.40%	0.40%	8.50%	6.90%
							1 Y	12.30%	12.90%	–	–	9.90%	8.90%
							2 Y	16.70%	18%	6.20%	0.40%	11.80%	10.30%
							5 Y	46%	42.10%	4%	4.20%	15.5	13%
SAPIEN3	BE	PARTNER 2	TF 84%	High	Severe symptomatic	583	30 D	2.60%	–	2.90%	–	0.133	
			TA 16%	Inoperable	native trileaflet severe degenerative AS		1 Y	14%	–	2.70%	–	16.80%	–
SAPIEN3	BE	PARTNER 3	TF	Low	Severe calcific AS	TAR 503 /1000		TAVR	SAVR	TAVR	SAVR	TAVR	SAVR
						SAVR 497/1000	1 Y	8.50%	15.10%	0.80%	1.10%	–	–
SAPIEN3 (cont)		SAPIEN 3 European approval trial	TF	Intermediate	NYHA ≥ II >75 y AS	101	30 D	1%	–	2.30%	–	4%	–
			TF 64% TA 36%	Intermediate/ High	NYHA ≥ II >75 y AS	150	30D	2.10%	–	3.50%	-	13.30%	-
Corevalve	SE	COREVALVE	TF 82.8%	High	NYHA ≥ II; Severe AS			TAVR	SAVR	TAVR	SAVR	TAVR	SAVR
			Non-TF 17.2%			TAVR 391 /750	30 D	3.80%	3.60%	9%	1%	3.80%	3.60%
						SAVR 359/750	1 Y	14.20%	19.10%	8%	1%	28.80%	13.30%
							2 Y	22.20%	28.60%	6%	1%	25.80%	12.80%
							3 Y	32.90%	39.10%	6%	0%	28%	14.50%
							5 Y	55.30%	55.40%	–	–	38.60%	22.30%

TABLE 2 (Continued)

Device	Type	Trail	Approach	Surgical risk	Primary IC	Study size	Time	Morality		Moderate/severe PVL		PPMI	
Corevalve/ CoreValve® Evolut R	SE	SURTAVR	TF	Intermediate	Severe AS			TAVR	SAVR	TAVR	SAVR	TAVR	SAVR
						TAVR 864/1660	30 D	2.20%	1.70%	—	—	25.90%	6.60%
						SAVR 796/166	1 Y	6.70%	6.80%	5.30%	0.60%	—	—
							2 Y	11.40%	11.60%	5.70%	1.20%	—	—
CoreValve® Evolut R	SE	EvolutR LR	TF	Low	Severe aortic-valve stenosis with suitable anatomy for TAVR or surgery	Total 1403		TAVR	SAVR	TAVR	SAVR	TAVR	SAVR
						TAVR 734/1403	30 D	0.50%	1.30%	3.50%	0.50%	17.40%	6.1%%
CoreValve® Evolut R (fcont)	SE					SAVR 734/1403	1 Y	2.40%	3.00%	3.60%	0.60%	19.40%	6.70%
Lotus	SE	REPRISE II	TF	High	NYHA ≥II, >70 y, Severe AS	120	30 D	6.70%	—	1.00%	—	3.40%	—
							1 Y	10.90%	—	0.00%	—	31.90%	—
		REPRISE III		High or extreme	Severe native AS	Lotus 607/912		Lotus	Corevalve	Lotus	Corevalve	Lotus	Corevalve
						Corevalve 305/912	30 D	2.50%	2.30%	0.20%	0%	35.50%	19.60%
							1 Y	11.90%	13.50%	0%	0%	41.40%	23%
							2 Y	21.30%	22.50%	0%	0%	41.70%	26.10%
Portico	SE	Multicenter Portico Transcatheter Aortic Valve Implantation System Study	TF	High	NYHA ≥II; Severe AS	222	30 D	3.60%	—	5%	—	13.60%	—
							1 Y	13.80%	—	7.50%	—	14.70%	—
Portico	SE	PORTICO IDE	TF	High and Extreme	NYHA ≥II; Severe AS	Portico 381/750		Portico	Control (Sapien/ Corevalve)	Portico	Control (Sapien/ Corevalve)	Portico	Control (Sapien/ Corevalve)
						Control (Sapien/ Corevalve) 369/750	30 D	3.50%	1.90%	6.10%	1.60%	27.70%	11.60%
							1 Y	14.30%	12%	7.60%	1.30%	—	—
							2 Y	22.30%	20.20%	5.20%	0.80%	—	—
Jenavalve	SE	CE mark Study 30 day	TA	High	NYHA ≥II; Severe AS	73	30 D	7.60%	—	13.60%	—	12.10%	—

TABLE 2 (Continued)

Device	Type	Trail	Approach	Surgical risk	Primary IC	Study size	Time	Morality		Moderate/severe PVL		PPMI	
ACURATE neo	SE	SCOPE I	TF	High	Severe AS, >75 y	ACURATE neo 372/739		ACURATE neo	SAPIEN 3	ACURATE neo	SAPIEN 3	ACURATE neo	SAPIEN 3
						SAPIEN 3367/739	30 days	2%	1%	9.40%	2.80%	10%	9%
		CE-approval Cohort	TF	High	Severe AS, age ≥ 75 years, NYHA >II	89							–
							30 D	3.40%	–	4.90%	–	10.30%	
							1 Y	22.50%	–	4.50%	–	11.50%	
ALLEGRA	SE	VIVALL 30 day	TF	Increased surgical risk for a "redo" operation	Symptomatic patients with a failing surgical AVR	30	30 D	0%	–	None or trace	–	0%	–
MyVal	BE	MyVal-1 Study 1 Year		Intermediate-High		30	1 Y	13.30%	–	0%	–	0%	–
HLT Meridian valve	SE	RADIANT Early Feasibility Trial	TF	High	Severe calcific aortic stenosis	25	30 D	8%	–	0%	–	14%	–
							0.5 Y	12%	–	0%	–	5%	–
Innovare	BE	–	TA	High or inoperable	NYHA ≥ II; Severe AS	90	30 D	13.30%	–	0%	–	2.20%	–
							1 Y	37.30%	–	0%	–	37.30%	–
Engager	SE	Engager European Pivotal Trial	TA	High or Extreme	NYHA ≥ II; Severe AS	61	30 D	9.90%	–	0%	–	27.60%	–
							0.5 Y	16.90%	–	0%			–
Centera	SE	CENTERA-2	TF	High	NYHA ≥II, Severe AS	203	30 D	1%	–	0%	–	5.40%	–
							1 Y	9.10%	–	0%	–	6.50%	
Direct flow medical	BE	DISCOVER	TF	High	symptomatic AS, >70 y	100	30 D	1.30%	–	1.40%	–	17%	–
							1 Y	10%	–	0%	–	21%	–

Note: Abbreviations: BE, balloon expandable; IC, inclusion criteria; PVL, paravalvular leakage; SE, self expandable; TA, transapical; TF, transfemoral.

trials are summarized in Figure 2 based on their trial start dates with device-based results in Table 2.

Devices after successfully completing their high-risk trials based on non-inferiority to SAVR, move onto testing their devices in patients deemed to be in intermediate surgical risk and later in low-risk patients for surgery in order to expand their indication to these patient populations. PARTNER 2 trials looking at the Edwards Sapien XT (Leon et al., 2016; Makkar, Thourani, et al., 2020) and SURTAVI trials looking at CoreValve (Reardon et al., 2017) were trials comparing outcomes between their devices and SAVR in intermediate-risk patients with REPRISE IV trials featuring LOTUS Edge Valve (ClinicalTrials.gov number, NCT03618095) and the ACURATE IDE trial with the ACURATE neo2 (ClinicalTrials.gov number, NCT03735667) being the future trials in this cohort (Figure 2). Low-risk TAVI trials have taken place in CoreValve EvolutR (Popma et al., 2019) and PARTNER 3 trial for Sapien 3 valve (Mack et al., 2019), with currently no other devices having trials planned for this cohort (Figure 2). Low-risk TAVI (Rogers et al., 2017; Waksman et al., 2018, 2019) was another trial comparing TAVI to surgical replacement with TAVI device utilized mainly being the Sapien 3 and the rest having the CoreValve Evolut R or PRO. Future trials include the NOTION-2 trial (ClinicalTrials.gov number, NCT02825134) which aims to compare TAVI and surgical intervention in patients 75 years of age or younger and the DEDICATE trial (ClinicalTrials.gov number, NCT03112980) aims to measure 1- and 5-year all-cause mortality in low- to intermediate-operative risk patients undergoing TAVI and SAVR (Seiffert et al., 2019). The Nordic Aortic Valve Intervention Trial (NOTION) was another notable trial conducted in low, moderate, or high surgical risk profile patients with severe degenerative AS which compared the transarterial CoreValve System to SAVR (Thyregod et al., 2013) with 30-day outcomes, 1-year outcomes (Thyregod et al., 2015), and 2-year outcomes (Søndergaard Lars et al., 2016). The majority of the patients (80%) in this trial ended up being in the low-risk cohort with TAVI procedural success at 97.9%, and 5-year results for TAVI and SAVR outcomes such as all-cause mortality being 27.6% vs 28.9%, pacemaker implantation at 41.7% vs 7.8% and paravalvular leak at 47.0% vs 83.3%, respectively (Thyregod et al., 2019).

5 | COMPLICATIONS

Complications of TAVI can be classified into periprocedural and long-term complications. Periprocedural complications of TAVI can be from vascular access injury, malpositioning of valve, paravalvular leak affecting valve function, stroke, myocardial ischemia/injury, acute kidney injury, and heart block (Neragi-Miandoab & Michler, 2013). AR, stroke, myocardial infarction, prosthetic valve thrombosis, acute coronary syndrome, bleeding, permanent pacemaker implantation, and prosthetic valve endocarditis are some associated long-term complications of TAVI (Elhmidi et al., 2013; Murray et al., 2019). The most common peri-procedural complications from PARTNER I trials were major arrhythmias (17%), major vascular complications (13%), major bleeding (12%), and minor vascular complications (8%, Arnold et al., 2014). Device landing zone rupture, device embolization, coronary occlusion, and stroke are some rarer complications of the TAVI procedure (Scarsini et al., 2019). The rates of some of the major

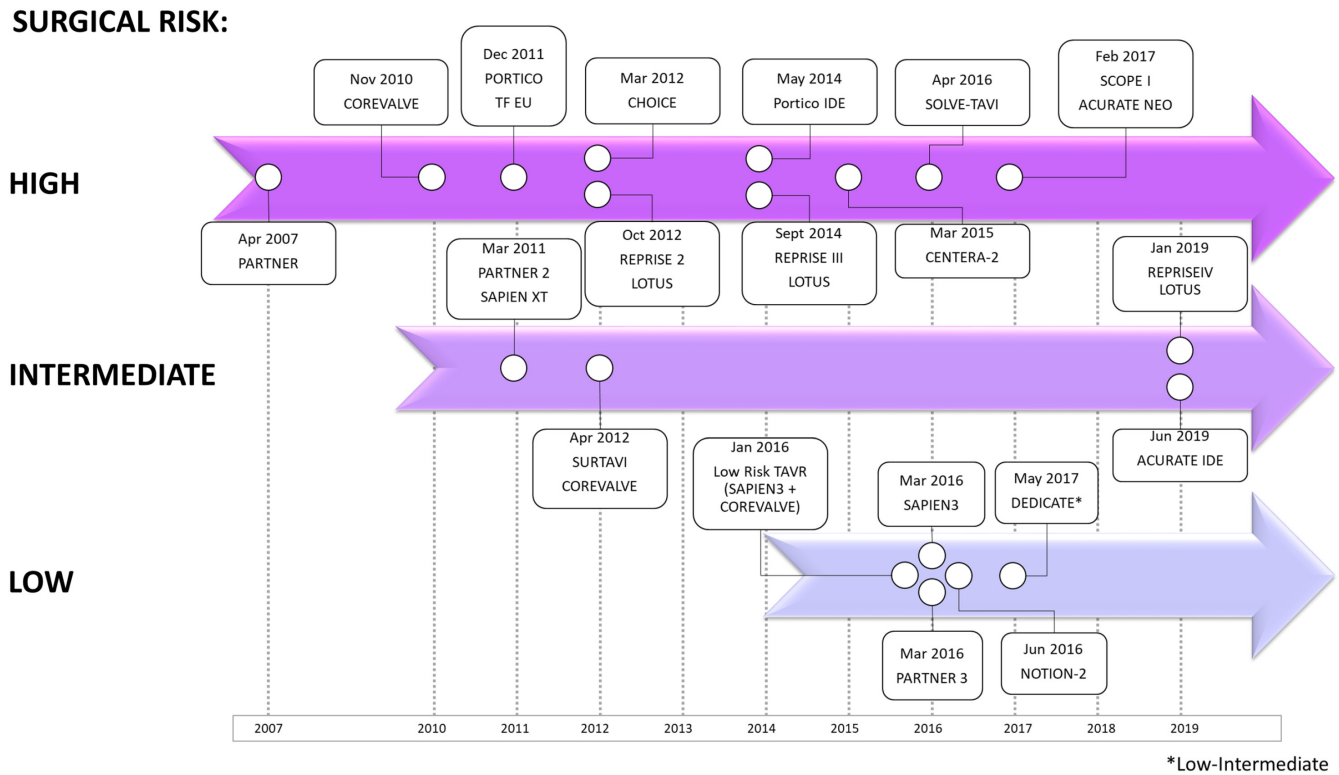

FIGURE 2 Timeline of key TAVI device trials delineated by surgical risk.

complications per device trials such as mortality, paravalvular leak, and new pacemaker implantation are listed in Table 2.

Many of the complications of TAVI arise as a consequence of variations in a patient's cardiac anatomy. For example, paravalvular leaks are caused by inadequate sealing between the device and the native valve, resulting in valve migration during or after the procedure. Failure to seal can be the result of extensive calcified aortic leaflets precluding proper frame expansion (Sturla et al., 2016) or inadequate sizing (typically under sizing) of the aortic root (Buzzatti et al., 2013). Sizing and position of the prosthetic valve can be difficult in TAVR due to the internal vascular deployment of the valve, and in fact one study has demonstrated that paravalvular leak is higher in patients who undergo TAVR than in those who undergo SAVR (Malik et al., 2020). Vascular complications can result from damage that occurs during arterial sheath insertion in transfemoral TAVI (Hamm et al., 2016), which could occur as the result of local variation in vascular morphology. Complications of cardiac conduction are also common in TAVI, with permanent pacemaker implantation required in about 17% of TAVI procedures (CoreValve, Lotus, and Portico). These conduction issues could result from damage to the left bundle branch fibers (arise from the bundle of His directly inferior to aortic root) that occurs during valve catheter deployment (from the wires, balloon valvuloplasty, position or expansion of the valve) or as a secondary result of valve migration. Finally, malpositioning of the prosthetic valve relative to the native aortic sinuses can result in partial or full occlusion of the coronary ostia and subsequent ischemia.

Previous studies have found that TAVI complications like a paravalvular leak can be minimized with the thorough characterization of cardiac anatomy using a combination of echocardiography, computed tomography (CT), and cardiac magnetic resonance (CMR) imaging (Buzzatti et al., 2013). Updates to the 2021 ESC/EACTS Guidelines provide indications for SAVR or TAVI that are largely based on aortic diameter and suggest that 3D imaging (such as cardiac CT) is an essential prerequisite for TAVI procedural planning. While this change in EU guidelines reflects a growing trend toward pre-operative patient-specific 3D imaging, it also highlights the need for a thorough understanding of the 3D anatomy and physiology of the aortic valvular complex. Thus, future studies that use recent advancements in radiographic imaging (higher resolution, faster 3D reconstruction, multi-modal image integration) to characterize aortic morphological variation in prospective TAVI patient cohorts would better inform future device design for TAVI.

6 | COVID-19 CONSIDERATIONS

As a result of COVID-19, there has been widespread deferral of nonessential procedures and operations in order to preserve PPE and prepare for a potential surge of ICU patients (Shah et al., 2020; The Task Force for the management of COVID-19 of the European Society of Cardiology, 2022). As a result, the ESC guidance for management of cardiovascular disease during the COVID-19 pandemic now recommends that patients with syncope or heart failure (New York Heart Association [NYHA] Class III/IV), high or very high transvalvular gradients, and those with reduced LV function should be prioritized, while those with minimal or no symptoms should be monitored and, if possible, wait on intervention. The change in guidelines has resulted in a heavy backlog of prospective SAVR patients, whose condition is potentially degenerating over time.

TAVI in this scenario (and future similar scenarios) could be extended to intermediate and selected low-risk surgical risk patients and in hemodynamically unstable patients who are either COVID-19 positive or negative, where it is cost-effective, as deemed appropriate by the Heart Team. This may allow for optimal utilization of resources by avoiding general anesthesia and intubation, shortening ICU stay, and accelerating hospital discharge and recovery. The American College of Cardiology and Society for Cardiovascular Angiography & Interventions have set forward triage considerations for heart disease interventions. The general priorities are to minimize exposure to coronavirus to patients and the interventional team; to maintain high-quality and durable structural interventional outcomes; to minimize utilization of resources that might be needed for patients with COVID-19; and to prevent delay of intervention in patients at particularly high risk for clinical deterioration, heart failure, and death. It is understood that for any individual patient, local clinical judgment based on the impact of the COVID-19 pandemic in the region and institution should ultimately guide the evaluation and treatment pathway. TAVI should be considered for patients with severe to critical AS and class III or IV congestive heart failure symptoms or syncope due to AS while postponing consideration of TAVI for 3 months or until after hospital operations resume elective procedures for truly asymptomatic patients (Shah et al., 2020).

7 | OUTLOOKS

Various TAVI interventional trials are in the pipeline. The Evaluation of TAVR Compared to Surveillance for Patients With Asymptomatic Severe Aortic Stenosis (EARLY TAVR; ClinicalTrials.gov Identifier: NCT03042104; Edwards Lifesciences, 2021) trial is comparing the Edwards SAPIEN 3 / SAPIEN 3 Ultra THV to clinical surveillance in asymptomatic patients with severe, calcific AS. In contrast, the RHEIA trial (Randomized researcH in womEn All Comers With Aortic Stenosis) (ClinicalTrials.gov Identifier: NCT04160130; SSS International Clinical Research GmbH, 2020) looks at the safety and efficacy of Edwards SAPIEN 3 or SAPIEN 3 Ultra as compared to SAVR in exclusively female patients with severe symptomatic AS.

Devices with CE mark with future trials include; (a) the Portico NG approval study (ClinicalTrials.gov Identifier: NCT04011722; Abbott Medical Devices, 2021) in high or extreme surgical risk patient population to support CE Mark and FDA approval, (b) a trial of replacement heart valves in patients with narrowing of the heart valves (LANDMARK; ClinicalTrials.gov Identifier: NCT04275726; Meril Life Sciences Pvt. Ltd., 2020) which compares the safety and

effectiveness of the Myval THV Series with Contemporary Valves (Sapien THV Series and Evolut THV Series), and (c) the comparison of eligible TAVI-valves—Cohort B (Compare-TAVI; ClinicalTrials.gov Identifier: NCT04443023; Terkelsen, 2020) which matches between Sapien and Myval.

Other future CE mark trails include; the ALIGN-AR pivotal trial (ALIGN-AR; ClinicalTrials.gov Identifier: NCT04415047 and NCT02732704; JenaValve Technology, Inc., 2020, 2021) assessing the transfemoral JenaValve Pericardial TAVR System for treatment of high surgical risk patients with symptomatic, severe AR, and a trial of the NVT ALLEGRA TAVI System TF in failing calcified aortic heart valves in a real-world population of elevated surgical risk patients (FOLLOW; ClinicalTrials.gov Identifier: NCT03613246; NVT GmbH, 2021).

New device trials include a clinical evaluation of the Vascular Innovations Co. Ltd. HYDRA self-expanding transcatheter aortic valve (ClinicalTrials.gov Identifier: NCT02434263; Thubrikar Aortic Valve Inc., 2019), and the Colibri heart valve clinical investigation ("COL-01"), a study (ClinicalTrials.gov Identifier: NCT04029844; Colibri Heart Valve LLC, 2019) for CE marking in high surgical risk patients. Other devices still in preliminary phases or under development outside Europe include: Venus Medtech (Hangzhou) Inc Venus A-valve (Liao et al., 2017), JC Medical J-Valve (Zhu et al., 2018; Hensey et al., 2019), MicroPort VitaFlow (Zhou et al., 2020), Peijia Medical TaurusOne, Venibri Valve (Feng et al., 2018), Xeltis endogenous tissue restoration aortic valve (Miyazaki et al., 2017), Zurich tissue-engineered heart valves (TEHV; Lintas et al., 2018), SAT (Strait Access Technologies, Cape Town, South Africa) self-homing, non-occlusive balloon-expandable TAVI system for rheumatic heart disease (Scherman et al., 2019), Polynova polymeric aortic valve TAVI (Rotman et al., 2019), and Corlife oHG's decellularized human aortic valve Arise AV (Horke et al., 2020).

8 | CONCLUSION

TAVI has advanced significantly in 18 years from an intervention used for patients deemed inoperable to a procedure that can be utilized in patients deemed to be low risk for surgery. The current pandemic has shown the importance of minimalistic procedures that accommodate more patients in hospitals when required. The rise in the prevalence of global heart disease due to aging, and due to the global COVID-19 burden only increases the urgency for minimally invasive treatment options for aortic pathology. TAVI is the future of aortic valve replacement with the scope to replace surgical intervention as the conventional method. However, advancements in the field based on procedural, device updates, future expansion of indication to more patient cohorts (e.g., asymptomatic AS and AR), better characterization of implications of anatomical variation, and minimizing key complications such as stroke, paravalvular leaks, and pacemaker implantations are required to set itself apart from SAVR as the gold standard. Increased market competitors with a range of different devices, vast improvements in imaging capabilities, and increasing trials and device developments give hope for rapid advancements in this field.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable—no new data are generated.

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