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Review · **Open Access** ·

Transcatheter aortic valve implantation: a revolution in the therapy of elderly and high-risk patients with severe aortic stenosis

Teoman Kilic[1], Irem Yilmaz[2]

[1]*Invasive Cardiology Research and Application Unit, Department of Cardiology, Kocaeli University, Kocaeli, Turkey*
[2]*Department of Cardiology, Kocaeli University, Kocaeli, Turkey*

Abstract

Transcatheter aortic valve implantation (TAVI) represents a real revolution in the field of interventional cardiology for the treatment of elderly or high-risk surgical patients with severe symptomatic aortic valve stenosis. Today, TAVI seems to play a key and a reliable role in the treatment of intermediate and maybe low-risk patients with severe aortic stenosis. TAVI has also evolved from a complex and hazardous procedure into an effective and safe therapy by the development of new generation devices. This article aims to review the background and future of TAVI, clinical trials and registries with old and new generation TAVI devices and to focus on some open issues related to post-procedural outcomes.

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1 Introduction

Transcatheter aortic valve implantation (TAVI) has emerged as a life-saving therapy in patients with severe aortic valve stenosis who are considered to be high-risk surgical candidates. After its first implantation in 2002, TAVI has now been improved to become a standard procedure worldwide. Although TAVI was initially administered in patients at highest risk, it is now gradually being applied in intermediate and even in low-risk patients. Currently, TAVI has also evolved from a complex and hazardous procedure into an effective, safe and minimalist therapy especially by the development of new-generation devices. We aimed to review the background and future of TAVI, first and new generation TAVI devices and to focus on some open issues related to post-procedural outcomes and future perspectives of TAVI.

2 Indications of TAVI

The joint task force on the management of valvular heart disease of the European Society of Cardiology and the European Association for Cardiothoracic Surgery defined indications for TAVI in the 2012 guidelines on the management of valvular heart disease.[1] The corresponding 2014 U.S. guidelines defined similar indications.[2] Both guidelines recommended TAVI in patients with severe symptomatic aortic stenosis (AS) who are not suitable to undergo conventional surgical aortic valve replacement (SAVR) as assessed by a heart team, if they are likely to gain improvement in their quality of life (QoL) and if they have a life expectancy more than 1 year with their comorbidities [class of recommendation (COR) I, level of evidence (LOE) B]. TAVI should also be considered in high-risk patients with severe symptomatic AS who are suitable for surgery but in whom TAVI is favored by a heart team (COR IIa LOE B).[2]

Appropriate patient selection is the key for best outcomes for TAVI. Especially in the absence of an established, accurate predictive risk score, optimal patient selection is best accomplished by a Heart Team, who must consider all of the patient's comorbidities (COR Ⅰ, LOE C). A heart team, consisting of interventional cardiologists, cardiac surgeons and other specialists help to determine the most effective treatment approach. A heart team is tasked with the selection of those who would benefit most from SAVR or TAVI, and those who should not undergo intervention on the basis that they would not benefit in terms of either symptoms (minimum expected gain more than one NYHA class) or life expectancy (minimum expected survival > 1year fol-

Correspondence to: Teoman Kilic, MD, Invasive Cardiology Research and Application Unit, Department of Cardiology, Kocaeli University, Umuttepe Yerleskesi, 41380 Kocaeli, Turkey. E-mail: kilicteoman@yahoo.com
Telephone: +90-262-3037335 **Fax:** +90-262-3038483
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lowing a successful procedure). The role of the heart team is not only for pre-operative assessment and choices but also concerning valve type and access route. Furthermore, as the majority of patients referred for a TAVI procedure are beyond 80 years of age, a geriatric assessment to evaluate frailty and to judge upon QoL improvement can also be useful and helpful.[3]

Currently, operative mortality risk is mostly assessed by using the European System for Cardiac Operative Risk Evaluation (EuroSCORE) and Society of Thoracic Surgeons (STS) risk scores. According to these scores, patients with logistic EuroSCORE > 20 or STS > 10 represent patients who are "high-risk" for conventional surgery. However, these risk scores do not include some other important surgical risk factors such as frailty, chest deformities, porcelain aorta, malnutrition, liver disease or radiotherapy to chest. Recently, some new TAVI scores are developed in order to more accurately predict prognosis in comparison with surgical risk scores.[4] Nevertheless, these new scores have not been validated in large randomized clinical trials. Thus, a specific TAVI risk score implementing both geriatric and anatomical variables is mandatory. As a consequence, clinical experience and heart team decision in this new field is crucial for appropriate patient selection.

3 Overview of old and new generation transcatheter aortic valves

After the first-in-man case performed in 2002 by Cribier, *et al*.,[5] more than 120,000 TAVI procedures were done worldwide with the chronologically first CE-marked devices: balloon expandable Edwards SAPIEN™/SAPIEN XT™ (Edwards Lifesiences, Irvine, CA, USA) and self expandable Medtronic CoreValve® (Medtronic, Minneapolis, MN, USA).[6] During long-term follow-up (5 years), TAVI with these first generation devices was shown to be superior to medical treatment. Considering both high and intermediate-risk patients and all access routes, pooled randomized trials of these first generation devices show a 13% relative risk reduction of all-cause death in favor of TAVI compared with SAVR at 2-year follow-up. However, the survival benefit was only found with transfemoral TAVI and appeared more pronounced in women than in men.[7] A recent meta-analysis investigated the results of six studies with the usage of these first generation devices, 957 self-expandable valve (SEV) and 947 balloon-expandable valve (BEV, one randomized controlled trial and 5 observational studies). At 30 days follow-up, rates of death did not differ between self-expanding and balloon-expandable valves [odds ratio (OR): 0.74, 95% CI: 0.47–1.17], whereas BEV reduced rates of moderate or severe aortic regurgitation (AR; OR: 0.51, 95% CI: 0.27–0.99) and of pacemaker implantation (OR: 0.28, 95% CI: 0.17–0.47). However, rates of all-cause death did not differ between the two groups.[8]

Although favorable outcomes were observed with these first generation devices, TAVI associated complications such as paravalvular leak (PVL), device embolization, vascular and cerebral complications and conduction disturbances emerged from the experience with the first generation transcatheter aortic valves. Thus, various new devices, so-called "second generation devices" are developed to address the limitations of first generation TAVI devices (Table 1).[6,9]

4 Newer-generation transcatheter aortic valves

4.1 CoreValve® Evolut R™

The new CoreValve® Evolut R™ (Medtronic, Minneapolis, MN, USA) made out of a trileaflet porcine pericardial valve placed in a nitinol self-expanding frame. The device uses a 14-Fr in-line sheath system, and with fully repositionable and recapturable features. This system contains the Evolut R™ valve and the EnVeo R™ Delivery Catheter System (DCS) with the InLine sheath. The trileaflet valve and sealing skirt are made out of porcine pericardial tissue, sutured in a supra-annular position on a compressible and self-expandable nitinol frame. The Enveo R™ DCS enables the valve to be fully repositionable and recapturable before full release by turning the delivery handle. The valve leaflets are in a supra-annular position to maximize the effective orifice area and the redesigned nitinol frame has a larger cell size with a smaller frame height of 45 mm. Its inflow has a more consistent radial force to achieve optimal conformation to the aortic annulus. The mid segment is narrower and the outflow segment abuts the aortic wall above the sinotubular junction for improved alignment between valve housing and the native sinus. A 12 mm porcine pericardium fabric skirt surrounds the inflow segment and is continuous with the valve leaflets to protect against PVL. Three valve sizes (23, 26 and 29 mm) are currently available covering a range of aortic annular diameters from 18 to 26 mm. And the new 34 mm valve for the annulus size over 29 mm also received the new CE mark. The Food and Drug Administration (FDA) also approved Evolut R™ 34 mm TAVI system, and clinical trials for Evolut R Pro are still ongoing. The built-in InLine sheath allows for the whole system to be inserted into a patient without the need for a separate access sheath. The InLine sheath and the EnVeo R™ delivery system have significantly reduced the overall profile and are

Table 1. Devices for transcatheter aortic valve implantation.

Device and company	Valve structure and size	Valve characteristics	Delivery system and access site	Clinical trials	CE Mark
First generation transcatheter aortic valves					
CoreValve® (Medtronic)	Porcine pericardium tissue valve Nitinol frame 26, 29, 31 mm	SEV	TF, TAo and SC	Medtronic CoreValve® US Pivotal trial ADVANCE NOTION	2007
SAPIEN™ (Edwards Lifesciences)	Bovine pericardial valve leaflets Stainless steel 23, 26, 29 mm	BEV	22 Fr TF, TA and TAo	The PARTNER I trial	2007
SAPIEN XT™ (Edwards lifesciences)	Bovine pericardial valve leaflets Cobalt chromium frame 20, 23, 26, 29 mm	BEV Partially repositionable	18 Fr TF, TA and TAo	The PARTNER II trial The SOURCE XT trial	2010
New generation transcatheter aortic valves					
Acurate® (Symetis)	Porcine native aortic leaflets Nitinol frame 23, 25, 27 mm	SEV Not retrievable Repositionable Fast pacing	Sheatless 28 Fr TA	ACURATE TA® trial ACURATE Neo and TF® trial	2011
JenaValve® (JenaValve Technology)	Porcine native aortic leaflets Nitinol frame 23, 25, 27 mm	SEV Retrievable Repositionable Not fast pacing	Sheatless 32 Fr TA	JUPITER registry	2012 for AS 2013 for AR
Portico® (St Jude)	Porcine pericardium tissue valve Nitinol frame 18, 24 mm	SEV Retrievable Repositionable Not fast pacing	18, 24 Fr TF, Tao, TA, SC	First-in-human experience	2012
DirectFlow® (Direct Flow Medical)	Bovine pericardium tissue valve Polyester cuff 25, 27 mm	Retrievable Repositionable Not fast pacing	18 Fr outer diameter TF	DISCOVER trial DISCOVER registry	2013
Engager® (Medtronic)	Bovine pericardium tissue valve Nitinol frame 23, 26 mm	SEV Not retrievable Repositionable Fast pacing	29 Fr TA and TAo	The Engager® CE pivotal trial	2013
Lotus® (Boston Scientific)	Bovine pericardium tissue valve Nitinol frame 23, 25, 27 mm	SEV Retrievable Repositionable Not fast pacing	18, 20 Fr TF	REPRISE II	2013
SAPIEN 3® (Edwards Lifesciences)	Bovine pericardium tissue valve Cobalt chromium frame 23, 26, 29 mm	BEV Not retrievable Not repositionable	14 Fr sheath TF and TA	The PARTNER II trial The SAPIEN 3 study	2014
Evolut® R (Medtronic)	Porcine pericardium tissue valve Nitinol frame 23, 26, 29, 31 mm	Recapturable Retrievable Repositionable	14, 18 Fr sheath TF and SC	The Medtronic CoreValve® Evolut CE Mark Clinical Trial Study The Medtronic CoreValve® Evolut R U.S. Clinical Study	2015
Centera® (Edwards Lifesciences)	Bovine pericardium tissue valve Nitinol frame with PET skirt 20, 23, 26 mm	SEV Not retrievable Repositionable	14 Fr sheath Motorized handle TF and SC	The ongoing Edwards CENTERA system clinical trial	Under evaluation

AR: aortic regurgitation; AS: aortic stenosis; BEV: salloon-expandable valve; CE: Conformité Européenne; Fr: French; PET: polyethylene terephthalate; SC: subclavian; SEV: self-expandable valve; TA: transapical; TAo: transaortic; TF: transfemoral.

compatible with vessel sizes 5 mm and above. This smaller profile makes a transfemoral approach possible for a wider spectrum of patients, including those with more challenging iliofemoral anatomy including small, tortuous or atherosclerotic vessels. Compared to the old generation system, the new fully repositionable and recapturable properties of

allowed important advantageous such improved stability, reduced new permanent pacemaker implantation rates and reduced significant PVL.[10] The mean gradient and effective orifice area at 30 days for the Evolut R™ were equivalent to those reported for the CoreValve® bioprosthesis in the CoreValve US Extreme Risk and High Risk studies.[11,12] There was also no annular rupture, coronary obstruction, and severe PVL and valve embolization in the CE study of Evolut R™.[13] New pacemaker implantation occurred in 16.4% of patients recruited in Evolut R IDE study and 13.3% in Evolut R US IFU trial.[14]

4.2 Edwards SAPIEN 3®

The third-generation Edwards SAPIEN 3® (S3) (Edwards Lifesciences, Irvine, CA, USA) has an outer skirt design against PVL and a smaller 14 French delivery system. In the transfemoral access group of global S3 trial, the rates of mortality of 2.1% and disabling stroke of 0, moderate-severe PVL of 3.5%, and vascular complication of 5.3% were all among the lowest thus far reported in the TAVI literature.[15] The PARTNER II S3 short-term outcomes with inoperable/high-risk group (STS mean 8.6%) and intermediate-risk group (STS 5.3%), showed extremely low 30-day mortality, stroke rate, and PVL in both groups, with a major vascular complication rate of 5%. New pacemaker implantation occurred in 11% of the study population.[16]

4.3 Lotus™

The Lotus™ Valve System (Boston Scientific Inc., Marlborough, Massachusetts, USA) is a fully repositionable and retrievable device. The prospective, multicenter REPRISE II (Repositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus™ Valve System: Evaluation of Safety and Performance) study displayed low 30-day mortality (4.2%) and disabling stroke (1.7%) rates in 120 high-risk patients. Paravalvular leak was moderate in 1% and severe in none, much lower than in previous studies using commercially available valves. In addition to its unique adaptive seal design, repositionability and routine multiple detector computed tomography (MDCT) sizing might also contribute to low PVL. Stroke rate did not increase in the 36 patients undergoing valve reposition and retrieval, and all attempts were successful. However, new permanent pacemaker implantation (PPI) rate was 28.6%, higher than with other newer and older transcatheter valves.[17] In a comparison of Lotus™ valve (n = 50) with CoreValve® (n = 50), device success was higher with Lotus™ (84% *vs*. 64%, P = 0.02), driven by lower rates of moderate or greater AR (4% *vs*. 17%) and higher rates of successfully implanting a single device in the correct anatomic position (100% *vs*. 86%, P = 0.06).[18] With MDCT imaging, the Lotus™ valve demonstrates nearly full device expansion and circularization of the native basal plane with low rates of eccentricity across all device segments. Reprise III is an ongoing trial that will randomize 1032 patients to the mechanically expandable Lotus™ valve (Boston Scientific, Natick, MA) versus CoreValve® (NCT02202434).

4.4 DFM™

The Direct Flow Medical (DFM™) (Direct Flow Medical, Santa Rosa, CA, USA) TAVI system includes a bovine pericardial valve mounted within a nonmetallic and inflatable cuff frame. The DFM™ prosthesis is fully repositionable and retrievable until its final delivery and is deployed in a stepwise approach. After inflating the ventricular ring and pulling the valve into an optimal intra-annular position, the aortic ring is inflated and fixed by means of polymer filling of the rings. Safety and feasibility of this prosthesis, with less than moderate PVL in 99% of patients, was demonstrated in a small patient cohort. Giustino, *et al*.,[19] retrospectively evaluated the effectiveness of DFM™ versus first generation valves in 496 patients. The DFM™ was associated with higher rates of device success (DFM™ 98% *vs*. CoreValve® 66% *vs*. XT 93%; $P < 0.001$) and a lower incidence of moderate-to-severe PVL (2.4% *vs*. 22% *vs*. 7.3%; $P < 0.001$), lower rate of valve embolization (0 *vs*. 7.3% *vs*. 0; $P = 0.041$) and need for a second valve implantation (0 *vs*. 7.3% *vs*. 0; $P = 0.041$).[19]

4.5 Acurate™

The Acurate™ TA (for transapical) and Accurate Neo™ TF (for trans-femoral) valves (Symetis SA, Ecublens, Switzerland) are made up of a nitinol self-expanding frame with three stabilisation arches at the distal/aortic edge, an upper and a lower crown. The lower inflow crown is covered by a polyethylene terephthalate sealing skirt while the upper crown segment provides supra-annular anchoring and houses three pericardial leaflets (Acurate Neo supra-annular; Acurate TA intra-annular). Transfemoral deployment follows a top-down approach. The upper crown is released first to capture the native leaflets followed by release of the stabilization arches and unsheathing of the lower crown. There is no need for rapid right ventricular pacing during deployment. During transapical deployment, the stabilization arches and upper crown are released first before pulling the system down to embrace and compress the native leaflets. The lower crown is then unsheathed and self-detaches from the delivery system. There are three available valve sizes covering annular diameters from 21 to 27 mm, and the delivery system fits within an 18 Fr transfemoral sheath.

4.6 Portico™

The Portico™ device (St. Jude Medical, St. Paul, MN, USA) is an intra-annular trileaflet bovine pericardial valve placed in a nitinol self-expanding frame with a height of 47 mm. The tubular inflow portion (9 mm height) has a porcine pericardial sealing cuff and the outflow segment (38 mm height) comprises large cells extending the frame towards the ascending aorta to provide stability. The Portico™ is fully repositionable and resheathable until approximately 85% of deployment. Implantation starts with expansion and sealing of the inflow segment, with the valve functioning early during deployment. There are four available sizes for annular diameters ranging from 19 to 27 mm. The transfemoral delivery system is a flexible 18 Fr (for smaller valve sizes) or 19 Fr catheters (for larger sizes). The valve can be implanted using dedicated sheaths or via a 19 Fr SoloPath™ sheath (Terumo Europe NV, Leuven, Belgium).

4.7 TAVI systems in clinical testing

Other new TAVI systems are in earlier phases of clinical testing as part of ongoing single-arm studies. These include the Centera® valve (Edwards Lifesciences), whose safety and performance are the object of CENTERA-EU (n = 200, NCT02458560), and the JenaValve Pericardial TAVR System (JenaValve®, Munich, Germany), which will be tested in two feasibility trials of high-risk patients with AS (n = 30, NCT02732691) or pure aortic regurgitation (n = 30, NCT02732704) in Europe and the USA.

5 Open issues in TAVI

5.1 TAVI device selection: can a patient-specific approach be useful?

Majority of patients undergoing TAVI can receive either a balloon expandable or self expandable transcatheter aortic valve according to the center specific experience. However, there can be also certain patient-specific issues that might influence the choice of valve system type.[20]

Iliofemoral anatomy, aortic root anatomy and annulus size, calcium quantification and distribution, level of coronary ostiums, presence of a bicuspid valve and a valve-in valve procedure are important factors that can affect the operator's preference for the selection of the valve type. In patients with small femoral vessels such as 5.5 mm or 5 mm, SAPIEN 3® or Evolut R™ can be the choice, respectively.[20]

It is well known that annular rupture has been observed almost exclusively after use of a balloon-expandable valve and very rarely after use of a self-expandable valve. Thus, in a patient with a small highly calcified annulus, there can be a high risk of annulus rupture during implantation of a balloon-expandable valve. Thus, a self expandable repositionable and a retrievable valve may be chosen to reduce the risk of annular rupture.[21]

If there are concerns about coronary obstruction, then a valve system with recapturable technology (Evolut R™ or Portico™) may be favored. If there is an asymmetric calcification protruding into the outflow tract, then choice of a valve with external sealing skirt may be preferable. For a patient with bicuspid valve stenosis, a repositionable self expanding supra-annular valve (Evolut R™) may overcome some of the limitations by anchoring and sealing the device to the area of maximal calcification. During a valve-in-valve procedure to treat a small surgical bioprosthetic valve, a supra-annular TAVI valve (Evolut R™) might offer greater effective orifice area and less residual gradients. Thus, rather than using an only one valve type, it is generally recommended for the operators to have an experience at least two or three devices for the short and long term success of the procedure.[20]

5.2 Patient selection for TAVI: should TAVI break the low risk or nonagenarian barrier?

Recent efforts are trying to expand TAVI indications to intermediate and low-risk and even in younger patients due to its relative advantage as being a less invasive procedure and less prone to the classic surgical postoperative devastating complications.[22]

However, there are some important limitations of TAVI in intermediate and low-risk patients which can be classified as procedural, early peri-procedural and limitations during follow up. Although TAVI becomes a less invasive procedure, some of its devastating complications such as annulus rupture, coronary artery occlusion, ventricular rupture and device embolization can be important in a younger patient. Despite new generation devices reduce PVL rates, need to permanent pacemaker (PPM) implantation, vascular complications, cerebral ischemia and early valve thrombosis are still ongoing early peri-procedural problems which limits TAVI efficacy compared to surgery in a low risk patient profile. It is also well known that durability is still the Achilles' heel of all bio-prosthetic valves.[23,24] Recent reports also showed that TAVI devices can degenerate over time.[25] Although valve in valve TAVI in a failed transcatheter aortic valve can be a solution, it seems maybe early to talk about implantation of these valves to a young patient with a low risk profile but recently published and some ongoing studies are also forcing TAVI as a reasonable

therapy especially in elderly and intermediate to low risk patients.

5.2.1 TAVI in intermediate-to-low risk patients

The nonrandomized European CoreValve Prospective International Post-Market Advance (ADVANCE) study recruited intermediate-risk patients (n = 1015 median STS score 5.3%) who are selected to be treated electively with the Medtronic CoreValve® System with a high percentage of transfemoral access and conscious sedation approach from 46 highly experienced centers in Europe and Central Asia.[26] The ADVANCE study gave us important information on major adverse cardiac and cerebrovascular events; and long-term valve durability and performance in consecutive real-world patients with severe AS treated with the CoreValve®. One-year all-cause mortality and stroke were comparable to the CoreValve® US Trial based on different risk strata.

The Nordic Aortic Valve Intervention (NOTION) trial randomized 280 patients ≥ 70 years old with severe aortic valve stenosis and no significant coronary artery disease to TAVI using a self-expanding bioprosthesis (CoreValve®) (STS 2.9%) versus SAVR (STS 3.1%) in an all-comers patient cohort.[27] The primary outcome was the composite rate of death from any cause, stroke, or myocardial infarction (MI) at 1 year and no significant difference between TAVI and SAVR was found for the composite rate of death from any cause, stroke, or MI after 1 year. Although better valve hemodynamics was found in TAVI group, it had higher PPM implantation and significant PVL rate, and worse functional class compared with SAVR at 1 year.

PARTNER II trial suggested that TAVI is a reasonable alternative treatment to SAVR in intermediate-risk patients and may be superior when only using a transfemoral approach. The data are based on 2032 patients with severe symptomatic AS who underwent TAVI with the SAPIEN XT™ valve or surgery. The mean age was 81 years at the time of implantation. Patients were considered to be at intermediate risk after clinical assessment by a multidisciplinary heart team at 57 centers. The mean Society of Thoracic Surgeons score was 5.8%, with 81.3% having a score between 4% and 8%. At 2 years, the primary composite end point of all-cause death or disabling stroke occurred in 19.3% with TAVR and 21.1% with surgery in the intention-to-treat population [hazard ratio (HR): 0.89; P = 0.25].[28]

After publication of the results of NOTION and PARTNER II trials, the FDA approved an expanded indication for TAVI with the SAPIEN XT™ and SAPIEN 3® valves and new CoreValve® Evolut R making them available to patients at intermediate surgical risk. Although some of the earliest TAVI devices already have longer follow-up data than some of the newer surgical bioprostheses introduced to the market, some operators and authors still underline that the only way to get reliable long-term durability data about TAVI prosthesis is to introduce the therapy into younger, low risk patients, preferably in randomized clinical trials against SAVR. Thus, novel studies are started in young patients (> 19 years old and STS < 4) such as NCT02675114, NCT02701283 and NCT02825134.[22,29–31]

5.2.2 TAVI in nonagenerians

Thourani, *et al*.,[32] studied outcomes in nonagenerians undergoing TAVI in the PARTNER-I trial60. From April 2007 to February 2012, 531 nonagenarians, mean age 93 ± 2.1 years, underwent TAVI with a balloon-expandable prosthesis in the PARTNER-I trial: 329 through transfemoral (TF-TAVI) and 202 transapical access. Clinical events were adjudicated and echocardiographic results analyzed in a core laboratory. QoL data were obtained up to 1 year post-TAVI. Time-varying all-cause mortality was referenced to that of an age-sex-race-matched US population. For TF-TAVI, post-procedure 30-day stroke risk was 3.6%; major adverse events occurred in 35% of patients; 30-day PVL was greater than moderate in 1.4%; median post-procedure length of stay (LOS) was 5 days. Thirty-day mortality was 4.0% and 3-year mortality 48% (44% for the matched population). By six months, most QoL measures had stabilized at a level considerably better than baseline, with Kansas City Cardiomyopathy Questionnaire (KCCQ) 72 ± 21. For transapical TAVI, post-procedure 30-day stroke risk was 2.0%; major adverse events 32%; 30-day PVL was greater than moderate in 0.61%; and median post-procedure LOS was 8 days. Thirty-day mortality was 12% and 3-year mortality 54% (42% for the matched population); KCCQ was 73 ± 23. These results suggested that TAVI can be performed in nonagenarians with acceptable short- and mid-term outcomes. Although TF-TAVI and transapical TAVI outcomes are not directly comparable, transapical TAVI appears to carry a higher risk of early death without a difference in intermediate-term mortality. Thus, age alone should not preclude referral for TAVI in nonagenarians.

5.3 Imaging for optimal valve size

Optimal valve sizing is very important before a TAVI procedure since undersizing can result patient prosthesis mismatch, PVL and device embolization. Conversely, oversizing may cause annular rupture, risk of underexpansion and development of central regurgitation and conduction

system abnormalities due to the compression of the conduction system in the left ventricular outflow track.[9] Compared to a BEV, self expanding devices generally require more oversizing. Thus, meticulous risk-stratification and accurate procedural planning with the necessary imaging modalities are of paramount importance. Although 3D transoesophageal echocardiography, magnetic resonance imaging and other modalities such as rotational angiography were tried to be used, Multislice Computed Tomography (MSCT) has become the standard approach for the measurements of aortic annulus, valsalva sinus diameter, sinotubular junction, coronary ostium heights, LVOT diameter and calcium distribution which are the key measurements for the selection and sizing of the appropriate valve. It is also very important to find the best co-planer view from MSCT. Thus, various software packages such as 3mensio, Philips heart Navigator, Siemens syngo Aortic Valve Guide and GE Innova were developed to facilitate multi-planar reconstruction and improve sizing in special anatomies such as bicuspid aorta.[33] Despite multiple CE-marked options for TAVI exists and MSCT is now the gold standard to determine the optimal valve sizing, there is still much to know to prevent unwanted peri and post procedural issues such as PVL, PPM, cerebral events, clinical and subclinical thrombosis and vascular complications.

5.4 Procedural issues after TAVI

5.4.1 Paravalvular aortic regurgitation after TAVI

Paravalvular aortic regurgitation is an important clinical issue seen with both self-expanding and balloon expandable valve. The strongest predictor of PVL is aortic valve calcification mass for SEV, whereas under sizing of prosthesis for BEV. As compared with SAVR, calcified aortic leaflets are not removed during TAVI, so incomplete sealing between the prosthesis and the native annulus results, leading to PVL. At least mild PVL is reported be present in up to 61% of patients after TAVI. Following SAVR, even mild PVL has not traditionally been tolerated, but trace and mild PVL after TAVI is often considered to be acceptable and benign. Studies have shown that moderate and severe PVL are associated with a worse outcome, and some studies even reveal a higher mortality rate in cases of even mild PVL.[3] In 2434 patients who underwent TAVI in the PARTNER trials and registries, one-year mortality was higher in patients with mild PVL (adjusted HR: 1.4) and moderate/severe PVL (adjusted HR: 2.2) compared to patients with none/trace PVL.[33]

In cases of more than mild PVL, post-dilatation (one or more additional dilatations within valve following stent deployment) or valve-in-valve (ViV) implantation (a second TAVI valve) should be considered at the time of the procedure.[34] Another option in selected patients is percutaneous PVL closure using an Amplatzer vascular plug. Saia, *et al*.,[35] evaluated outcomes of percutaneous closure of PVL after TAVI in a pooled, international multicenter experience of 24 patients (54% ESV, 46% CoreValve®; 75% men, mean age 81 years, mean STS 6.6%). Amplatzer Vascular Plug (St. Jude Medical, St. Paul, MN) was used in 80% of the cases; 89% of the procedures were technically successful and the results assessed by echocardiography were durable. However, cumulative survival rates at 1, 6, and 12 months were 83%, 67%, and 62%, respectively. Most deaths (8 of 11) were due to noncardiac causes.[35]

Quantitative assessment of PVL after TAVI is also challenging. Although transthoracic echocardiography (TTE) is the main tool used for the assessment of PVL, it is modestly reproducible. Inadequate identification and grading of PVL interfere with the interpretation of prognosis and guidance to management. Accurate identification of severity and acuteness of PVL, location, and underlying etiology (e.g., valve malposition, inadequate sizing, calcium pattern, and central *vs*. paravalvular) are all essential points to evaluate indication, timing, and choice of corrective procedures for PVL, such as balloon post-dilation, valve-in-valve, snaring or trans-catheter closure. It has also been shown that transesophageal echocardiography based sizing is significantly undersized in relation to MDCT based sizing.[36] Perimeter-derived diameters were significantly larger than area-derived diameters, and the relative oversizing was therefore larger by area compared with perimeter.

However, the incidence of moderate and severe PVL has been decreasing in recent experience. The use of 3D computerized tomographic (CT) reconstruction for measurement of the annulus, which is more accurate than echocardiography and results in better pre-interventional choice of valve size; the knowledge that most TAVI valves should be modestly oversized relative to the annulus (when measured by MSCT); improved delivery devices that allow repositioning of the valve, leading to optimized valve deployment; and new TAVI valves that are designed to minimize the risk of PVL (e.g., with special sealing cuffs, skirts, or inflatable cuffs); and the increasing experience of the operators regarding all technical aspects of valve deployment and the choice of valves contribute definitely to better functional results with less PVLs.

5.4.2 Pacemaker rates

Conduction disturbances are a frequent complication of TAVI and higher than in SAVR. This complication is due to the anatomical proximity of the aortic valve to the atrioven-

tricular (AV) node, bundle of His, and major conduction branches. The rate of PPI ranges from 3.4% to 17.3% for BEV and from 15.7% to 37.6% for SEV mostly as a result of complete atrioventricular block.[26] This wide range suggested that various thresholds of PPI may exist between operators. Indeed, in the CoreValve® ADVANCE II study, when the PPI was restricted to class I/II indications, the overall 30-day incidence dropped from 24.4% to 18.2%.[37] PPI was required in 8.8% of 1973 patients in the PARTNER study, but 50% of them were not pacing-dependent at 1 year.[38] Urena, *et al*.,[39] reported 1556 consecutive patients without prior PPI undergoing TAVI. In total, 15.4% required a PPI within the first 30 days (25.5% for SEV *vs.* 7.1% for BEV). At 6–12 months follow-up, paced rhythm was observed in only 72.8% of SEV versus 46.7% of BEV patients.[39]

The rate of PPI varies between studies and implanted valves. While the rate is 5%–12% after implantation of an Edwards SAPIEN™ valve,[40] it is considerably higher (24%–33%) with Medtronic CoreValve®.[41] Siontis, *et al*.,[42] published a meta-analysis that included 11,210 patients undergoing TAVI with a median PPI rate of 6% after Edwards Saphien and 28% after Medtronic CoreValve® implantation consistent with earlier reports. Some reports compare these PPI rates of the Edwards SAPIEN™ and Medtronic CoreValve® and conclude that, due to their design, self-expandable valves are associated with a higher incidence of PPI. However, several second generation self-expanding devices appear to have a PPI rate more comparable with the Edwards SAPIEN™ valve.[43]

Whether PPI is to be considered a major complication and/or significantly influences patients' functional outcomes and QoL is controversial. To date, all TAVI studies have failed demonstrate the negative impact of PPI on mid-term survival. Weber, *et al*.,[44] have reported that left ventricular conduction disturbances with permanent right ventricular pacing are associated with worse recovery of left ventricular ejection fraction and increased heart failure-related symptoms (20.4% of patients with PPI remained in NYHA III or IV after 3 months). Urena, *et al*.,[39] has showed that the new incidence of new PPM (within 30 days of TAVR) is 15.4% in a study that included both BEVs and SEVs. However, they found no difference in mortality or heart failure at mean follow-up of 22 months between the group that received PPM and the group that did not. In addition, those patients with PPM have been protected from sudden death or death of unknown cause and that effect persisted through the follow-up period. This preventive mechanism can be caused by prevention of very late bradyarrhytmias. However, at 6–12 months, there is a drop in left ventricular ejection fraction due to right ventricular pacing; but this phenomenon seems in only 20% of the TAVI patients.

In the PARTNER trial, new PPI was associated with a longer duration of hospitalization and higher rates of repeat hospitalization of any cause (18.2% *vs*. 23.9%, $P = 0.045$), and higher incidence of death at one year (20.8% *vs.* 26.3%, $P = 0.08$).[38] PARTNER 1 data showed no association of post-TAVI PPI with 1-year all-cause mortality and left ventricle dysfunction, but found a significantly higher repeat hospitalization. There was no difference in the LVEF at one year between the two groups.[38] Despite lack of certain prognostic long-term data in patients with PPM post-TAVR, there is a consensus that PPM-dependency at long term follow-up seems in less than half of the patients that indicates recovery in the conduction system. Prediction of dependency to PPM is not possible yet. Identification of patient who will recover their conduction system needs further research. With the trend of expanding TAVI to lower-risk and younger patients, the long-term adverse effect of pacing can be a concern and may require a more strict approach to PPI.

5.4.3 Cerebral complications and embolic protection devices

The risk of cerebrovascular events was one of the major concerns associated with TAVI. New ischemic lesions can be detected by magnetic resonance imaging (MRI) in 68%–84% of patients after TAVI.[45] However, in these studies, only up to 4% of the lesions by imaging were associated with clinical stroke. About half of perioperative strokes occur intra-procedurally or within the first 24 h after TAVI. The degree of device manipulation performed during the procedure, including multiple valve positioning maneuvers or post-balloon dilatation, is associated with a higher rate of early stroke. Delayed strokes may be related to post-operative atrial fibrillation or other factors. A meta-analysis, including more than 6000 patients, reports a mean 30 days clinically significant stroke rate of 3%–4%.[46] In the PARTNER trial, TAVI showed a statistically significant higher rate of stroke and transient ischemic attack at 30 days (2.4 *vs.* 5.5%, $P = 0.04$) and 1 year compared with SAVR, but no difference was appreciable after 5 years.[38] Although the rate of major stroke seems to be similar between TAVI and SAVR, new ischemic lesions are higher in TAVI patients and new embolic protection devices are developed to reduce the number of neurological events caused by intra-operative embolization of debris dyring TAVI. These devices can be categorized in two groups: filters that capture debris liberated into the cerebral circulation and devices deflecting such debris away from the cerebral circulation. Several small trials have studied their ability to reduce neu-

rological events. In the CLEAN-TAVI trial, a 100 patient single-centre study, patients were randomized to either TAVI without emboli protection or TAVI with the Claret Montage™ dual-filter Cerebral Protection System.[47] In patients for whom the device was implemented, the number and volume of cerebral lesions, as determined by MRI at 2 and 7 days, were significantly reduced. The rate of post- operative ataxia was also reduced at 2 days, but not at 7 days or 30 days. Another study found that the Edwards Embrella Embolic Deflector (EED) also reduced lesion volume compared with TAVI without embolic protection device.[48] However, a recently published study confirmed this reduced lesion volume, but an increased number of cerebral ischemic lesions after EED use were discovered. The TriGuard™ HDH Embolic Deflection Device achieved complete coverage of the cerebral vessels in 89% of the patients in an initial trial. This small study suggested a trend to less new neurologic deficits following TAVI (15.4% *vs.* 3.1%) but was unable to reach significance ($P = 0.16$).[49] Currently, all published studies employ very small cohorts, so larger studies must be completed to determine whether using an embolic protection device truly improves neurological outcomes after TAVI or not.

5.4.4 Clinical and subclinical valve thrombosis and antithrombotic therapy after TAVI

Symptomatic transcatheter valve thrombosis is reported in up to 1% of patients after TAVI. The clinical presentations include cardiopulmonary arrest, recurrent symptoms on follow-up and non ST elevation myocardial infarction.[50] Latib, *et al*.,[51] reported an incidence of 0.61% in a large study with 4266 patients undergoing TAVI. However, Leetmaa, *et al*.,[55] showed in a study employing computed tomography (CT) imaging that, within 1–3 months after TAVI valve thrombosis was more common than anticipated but was asymptomatic in the majority of cases (4% after 1–3 months).

This asymptomatic subclinical thrombosis is defined as hypoattennuated leaflet thickening (HALT) and reduced leaflet motion (RELM). Leetma, *et al*.,[52] investigated this finding in 140 patients with SAPIEN XT™ valves at one to three months post TAVI. Subclinical thrombosis defined as HALT was present in 5 (4%) patients, four of these patients were asymptomatic with no elevated gradients. Pache, *et al*.,[53] reported HALT as 10.3% in 156 patients undergoing TAVI with the SAPIEN 3® valve.

Different from Leetma, *et al*.,[52] and Pache, *et al*.,[53] who investigated HALT, Makkar, *et al*.,[54] evaluated the presence of RELM in Portico IDE (55 patients) study, RESOLVE and SAVORY registries (132 patients) by using 3D volume-rendered imaging in patients undergoing TAVI with Portico™, Edwards valves, CoreValve® and the Lotus™ valves. Reduced leaflet motion was noted on CT in 22 of 55 patients (40%) in the IDE trial and in 17 of 132 patients (13%) in the two registries. Although RELM was detected among patients with multiple bioprosthesis types, including transcatheter and surgical bioprostheses; it is unclear whether a difference between supra-annular or intra-annular valve type was present or not. Therapeutic anticoagulation with warfarin, as compared with dual antiplatelet therapy, was associated with a decreased incidence of reduced leaflet motion (0 and 55%, respectively, $P = 0.01$ in the IDE trial; and 0 and 29%, respectively, $P = 0.04$ in the pooled registries). In patients who were reevaluated with follow-up CT, restoration of leaflet motion was noted in all 11 patients who were receiving anticoagulation and in 1 of 10 patients who were not receiving anticoagulation ($P < 0.001$). There was no significant difference in the incidence of stroke or transient ischaemic attack between patients with RELM and those with normal leaflet motion in the IDE trial (2 of 22 patients and 0 of 33 patients, respectively; $P = 0.16$), although in the pooled registries, a significant difference was detected (3 of 17 patients and 1 of 115 patients, respectively; $P = 0.007$).[50,54]

Although the finding of increased risk of TIA associated with RELM was attributed as preliminary and inconclusive, additional studies are needed to evaluate the long term impact of this finding. Today, the fundamental reason for antithrombotic therapy in TAVI patients is to prevent cerebral ischemic events and is based on the experience of SAVR: with post-procedural sinus rhythm, dual antiplatelet therapy with clopidogrel and aspirin for 3–6 months followed by lifelong aspirin therapy is recommended (COR IIb, LOE C). Clopidogrel should not be used if a vitamin K antagonist is used. However, meta-analyses of studies comparing dual anti-platelet therapy (aspirin and clopidogrel) versus aspirin alone after TAVI, dual anti-platelet therapy was not associated with significant reductions in all-cause mortality or thrombotic events. Moreover, dual antiplatelet therapy led to higher risk of bleeding compared to single antiplatel therapy.[55] Results from the different studies which investigated HALT or RELM also triggered another indication for a real adequate antithrombotic or anticoagulant therapy in patients undergoing TAVI; however consensus about this point is also not clear. Thus, further studies are required to define optimal antithrombotic or anticoagulant therapy in patients received TAVI.

5.4.5 Vascular complications after TAVI and feasibility of percutaneous closure devices

Major and minor vascular complications (VC) after

TAVI are clearly defined by Valve Academic Research Consortium definitions.[56]

With increased experience of the operators, some specific major VC such as aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo aneurysm are clearly decreased. Currently, reported rates of major VC, range from 5.5% to 20% in the literature.[57] This wide range may be the result of studies using different definitions of VC other than the established Valve Academic Research Consortium definitions as well as the experience of the reporting centre and the availability of newer, smaller delivery systems. The size of TF-TAVI delivery sheaths has decreased significantly compared with the first generation systems. For example, the Edwards SAPIEN 3® (Edwards Lifesciences, Inc., Irvine, CA, USA) has reduced sheath size from 22 to 14 Fr for a 23 mm valve compared with the original SAPIEN valve. The new EnveoR system and integrated 14 Fr InLine™ sheath can be used in small vessel sizes as 5 mm and above. Although, together with the use of percutaneous closure devices, these technical improvements have led to a lower incidence of VC than in initial trials, recently published studies still report some VC rates up to 20%.[57] Thus, there is still a need for smaller size of delivery systems or appropriate percutanous closure devices.

Currently, two main percutaneous closure devices are generally used in TAVI procedures as Perclose ProGlide and Prostar XL devices. Both of the two devices are commonly used according to the operator's experience and preference. However, the potential contribution of the type of vascular closure device (Prostar XL *vs*. Perclose ProGlide) on the incidence of VC is still an open question. Barbash, *et al*.,[57] compared the efficacy of a Prostar XL *vs*. Perclose ProGlide-based vascular closure systems in a multicenter study (CONTROL) which included 3138 consecutive percutaneous transfemoral TAVI patients. Propensity-score matching was used to assemble a cohort of patients with similar baseline characteristics. The investigators found that Prostar XL-based vascular closure in transfemoral TAVI procedures was associated with higher major vascular complication rates when compared with ProGlide; however, in-hospital mortality was similar with both devices.

Seeger, *et al*.,[58] evaluated safety and efficacy of the two devices in 585 patients and found that TAVI with ProGlide device was associated with significantly lower rates of closure device failure, minor and major bleedings and significantly lower in-hospital mortality. In a recent metaanalysis, Maniotis, *et al*.,[59] showed that the rate of overall vascular complications did not differ between Prostar XL and ProGlide [RR: 1.35 (0.80–2.29), $P = 0.27$]. However, Prostar XL was associated with greater risk of any bleeding as well as life threatening bleeding compared to the ProGlide device. Further large randomized studies are required to confirm these results.

6 Future perspectives of TAVI

6.1 Valve in valve TAVI for failing surgical and transcatheter aortic valves

The use of TAVI devices for the failing surgical aortic bioprosthesis has reduced redo SAVR rates. Although all available devices have been successfully used, the use of larger-than-necessary devices or usage of an intra-annular valve instead of a supra-annular valve especially in small surgical bio-prostheses (< 21 mm) showed high transvalvular gradients.[20,60] Dvir, *et al*.,[60] showed in VIVID registry that elevated post procedural gradients were more common with BEV than SEV especially in small and intermediate-sized surgical valves. It is therefore recommended that redo surgery be firstly considered if feasible in patients with internal surgical diameters < 21 mm. If redo surgery is not feasible, a small supra annular SEV especially a repositionable one (23 mm CoreValve® Evolut R™) can be used as a first choice. If a BEV implantation was planned, a 20 mm SAPIEN XT™ can be considered. In the VIVID registry, the implantation rate of a second transcatheter valve was 5.7%. To avoid a second valve implantation, usage of a repositionable valve can be advantageous. The option to recapture is also important when the surgical bioprosthesis presents a high risk of coronary occlusion or when control of implantation depth may be hard due to severe aortic regurgitation.[20] With the growing worldwide adoption of TAVI and its relative extension to younger and lower-risk population, some proportion of patients who develop late transcatheter valve degeneration and require repeat procedures is likely to increase in the future.[61]

Recent reports showed that it is also feasible to implant a new generation transcatheter valve for failing transcatheter aortic valves. Schaefer *et al*.,[62] successfully used S3 valve in three patients with failing SAPIEN XT™, JenaValve® and CoreValve valves and successful transfemoral implantation with significant reduction of PVL was achieved in all cases.

Shivaraju, *et al*.,[63] also used a Sapien 3® valve within a failed core valve bio-prosthesis. Although this early reports strongly suggest that valve in valve TAVI can be a useful approach for failing transcatheter valves, further studies with large number of patients are required.

6.2 Less invasive alternative therapies to TAVI for extremely frail patients

Balloon aortic valvuloplasty (BAV) can still be an option

as a bridge to TAVI especially in very frail patients. Indications for balloon aortic valvuloplasty as a bridge to AVR or TAVI can be haemodynamically unstable patients at high risk for AVR or TAVI, poor left ventricle function, cardiogenic shock, severe mitral regurgitation and malignancy. It was also used to distinguish between breathless due to AS or respiratory pathology, with patients showing improvement going on to have aortic valve surgery.[64]

Although 2014 AHA/ACC guidelines recommended BAV as a reasonable bridge to AVR or TAVI (LOEC IIb), the risk of development of severe aortic regurgitation, vascular complications and anesthesia risk limit its usage. It can be also evaluated as a risky maneuver and many centers consider this option only in much selected patients, who have been considered unacceptably high risk for TAVI.[64]

The Leaflex system (Pi-Cardia) is an early and promising percutaneous device for fracturing valve calcification using mechanical impact in order to restore leaflet mobility. Preclinical radiographic studies of *ex-vivo* human aortic valve leaflets demonstrated that 82% of leaflets had a typical "bridge" or "half-bridge" pattern. In 13 leaflets, treatment with the Leaflex system showed a reduction of more than 25% in the maximal force required to fold the leaflet was measured post treatment, with an average of 49% ± 16%. In addition, treatment with the Leaflex system demonstrated an average improvement in aortic valve area of 35% ± 12%. The initial safety and feasibility data in 12 extremely frail patients were reassuring (TCT 2015) but need further confirmation in larger patient groups.[65]

6.3 Minimalist TAVI

TAVI was performed under general anesthesia with surgical femoral cutdown and TEE monitoring in operating suites initially; but now it is commonly performed with sedation and local anesthesia with percutaneous femoral access and without TEE (minimalist TAVI). In the Sentinel European TAVI Pilot Registry, 2807 patients from 10 countries were treated via a transfemoral approach using either local (n = 1095, 39%) or general anesthesia (n = 1712, 61%).[66] Survival at one-year, compared by Kaplan–Meier analysis, was similar between groups (log-rank P = 0.1505). In 1316 consecutive patients who underwent TAVI at 7 high-volume Italian centers, the anesthetic regimen consisted of general anesthesia in 27% and local anesthesia in 73%.[67] The two groups showed similar device success, mortality, stroke and MI, but local anesthesia was associated with significantly shorter procedure time, less complications and shorter length of hospital stay (7 *vs*. 8 days; $P < 0.001$). Multiple smaller observational studies have assessed the feasibility of minimalist TAVI and generally support equivalent outcomes as traditional TAVI.[68] This minimalist approach is now becoming routinely performed in experienced TAVI centers and early discharge (24–48 h post-procedure) after TAVI has been increasingly reported. Although the effect of this approach on cost effectiveness of TAVI has not been clearly investigated, observations from randomized TAVI trials showed that procedure time, median intensive care unit stay and median total length of stay were significantly lower in TAVI group than SAVR group. It is well known that if the median lengths of hospital stay decrease, cost will automatically decrease. Thus, minimalist TAVI will be the future cost-effective treatment of patients with severe AS. Recently, Genereux, *et al*.,[69] presented the case of a patient who underwent a successful transfemoral TAVI and was safely discharged home the same day. Although it is very early to make any comment about what proportion of patients treated by TAVR in the future will be able to be safely discharged on the same day, constant improvement and miniaturization of TAVI devices, paired with the treatment of younger and lower risk patients, along with new remote biometric and ECG monitoring systems may make this type of evolution more achievable, safe, and even more cost effective for patients and health care system.

7 Conclusions

TAVI is a safe and effective treatment in elderly and high-to intermediate-risk patients with severe AS. Surgical aortic valve replacement still remains gold standard for low- and some intermediate-risk patients. The heart team is responsible for defining the optimal treatment for each patient based on risk scores, comorbidities and potential for improvement in QoL. Preventing and managing TAVI complications, advancing technology, using a minimalist approach, and particular image planning will let TAVI to become a preferred option for larger populations in the future. Newer generation TAVI devices have lower profiles, fewer vascular complications; are easier to use, retrieve, and reposition; and have less PVL. If long-term durability of TAVI valves is certainly demonstrated; the rate of PVL, stroke, and PPI is lowered to the level of SAVR; and improved use of complementary devices, that protect against embolic debris and stroke, TAVI can be also an attractive treatment modality for lower-risk patients with AS.

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