

# Current developments in the use of transcatheter aortic valve implantation in high-risk patients

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**Abstract:** Transcatheter aortic valve implantation (TAVI) has revolutionized the landscape of interventional cardiology. Since its introduction in 2002 by Cribier, this novel technology has developed remarkably over time, with new generations of devices, a reduction in profile sizes, and new access routes, allowing for safer and more efficacious procedures. Innovation brings new solutions as well as new challenges. The initial promising results have not only created high expectations but also a need to address the shortcomings of this procedure. Improved understanding of the potential complications associated with TAVI might help improve outcomes and broaden the application of this rapidly evolving, innovative therapy. This paper summarizes the current evidence, discusses the limitations of current TAVI technology, and highlights future perspectives.

**Keywords:** aortic stenosis, transcatheter aortic valve implantation

## Introduction

Aortic stenosis is the most common valvular heart disease in adults<sup>1</sup> and primarily presents as calcific aortic stenosis due to degeneration of the valve in the elderly population, with an estimated incidence of 2%–7% in those older than 65 years.<sup>2</sup> Symptomatic severe aortic stenosis has a poor prognosis when treated medically and inevitably leads to functional deterioration, heart failure, and death.<sup>3</sup> Surgical aortic valve replacement (SAVR) has long been the standard of care for symptomatic aortic stenosis, but approximately 30% of patients do not undergo SAVR due to various comorbidities and increased operative risk.<sup>1,4</sup> Cribier pioneered the first transcatheter aortic valve implantation (TAVI) in an inoperable patient in 2002 using a balloon-expandable aortic valve prosthesis via a transseptal antegrade approach.<sup>5</sup> A first-in-man retrograde implantation of a self-expanding prosthesis (CoreValve®, Medtronic CoreValve LLC, Irvine, CA, USA) was performed in 2005 with the aid of extracorporeal circulation.<sup>6</sup> Based on registry data, both the CoreValve and Edwards SAPIENT™ valve (Edwards Lifesciences, Irvine, CA, USA) obtained CE marking in 2007, which opened up sales in European countries for surgically high-risk and inoperable patients.

Following the first randomized study, ie, PARTNER I (Placement of Aortic Transcatheter Valves),<sup>7,8</sup> the US Food and Drug Administration approved the Edwards valve for use in inoperable patients with symptomatic severe aortic stenosis in 2011 and extremely high surgical risk patients in 2012. CoreValve has also recently been approved for inoperable patients since the presentation of the US CoreValve clinical study in an extreme risk population at the 2013 Transcatheter Cardiovascular Therapeutics meeting in San Francisco, CA, USA.<sup>19</sup> The growth in use of TAVI has been exponential,

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with >50,000 procedures having been performed in over 40 countries worldwide in the last 11 years. With this widespread implementation of TAVI, there is now a great need to understand and overcome the limitations of TAVI and find answers to unresolved questions, including who should receive it? What are the technological improvements that are required to reduce the complications and to optimize the outcomes following TAVI? In this paper, we review the historical data on TAVI in high-risk patients, as well as the complications and evolution of transcatheter valves, and discuss procedural and technical considerations in high-risk patients along with future perspectives.

## Historical review of TAVI

Following the first-in-man experience of TAVI in 2002 reported by Cribier, several feasibility studies were performed using both the balloon-expandable Edwards valve (Edwards Lifesciences) and the self-expandable CoreValve ReValving system (Medtronic CoreValve LLC).<sup>9–13</sup> These early studies showed that TAVI could be performed in high-risk patients via both antegrade transapical and retrograde transfemoral routes with a high procedural success rate and a 30-day mortality of approximately 10%–15%.

## Randomized controlled studies Edwards SAPIEN valve

Three randomized controlled trials have assessed the efficacy of TAVI in different populations. The landmark PARTNER study incorporated two parallel, prospective, multicenter, randomized, active-treatment controlled clinical trials. In the PARTNER I study cohort B, 358 patients with severe symptomatic aortic stenosis, whom surgeons considered not suitable for SAVR, were randomized to either standard therapy (medical therapy including balloon aortic valvuloplasty) or transfemoral TAVI using the Edwards SAPIEN valve.<sup>7</sup> At one year, the rate of death from any cause (Kaplan–Meier analysis) was 30.7% with TAVI, as compared with 50.7% with standard therapy (hazard ratio 0.55 for TAVI; 95% confidence interval [CI] 0.40–0.74;  $P<0.001$ ). TAVI was associated with fewer cardiac symptoms (New York Heart Association functional class III or IV, 25.2% versus 58.0%,  $P<0.001$ ) and lower rehospitalization rates (22.3% versus 44.1%,  $P<0.001$ ). Among patients who underwent TAVI, the mean aortic valve area increased from  $0.6\pm0.2$  cm<sup>2</sup> at baseline to  $1.5\pm0.5$  cm<sup>2</sup> at 30 days ( $P<0.001$ ), and the mean aortic valve gradient decreased from  $44.5\pm15.7$  mmHg to  $11.1\pm6.9$  mmHg ( $P<0.001$ ). At the one-year follow-up assessment, the improvement in aortic valve area and mean gradient was

maintained. The rate of death at 2 years was 43.3% in the TAVI group and 68.0% in the standard therapy group ( $P<0.001$ ), and the corresponding rates of cardiac death were 31.0% and 62.4%, respectively ( $P<0.001$ ).<sup>14</sup> At 2 years, the rate of rehospitalization was 35.0% in the TAVI group and 72.5% in the standard therapy group ( $P<0.001$ ).

In the PARTNER I study cohort A, 699 high-risk patients with severe aortic stenosis were randomized to undergo either TAVI (via a transfemoral or transapical approach) or SAVR.<sup>8</sup> The all-cause mortality at one year in the TAVI arm was noninferior to that in the SAVR arm (24.2% versus 26.8%,  $P=0.001$  for noninferiority). There was no significant difference in rehospitalization rates (18.2% versus 15.5%) or New York Heart Association functional class between the two arms at one year. At 2 years, all-cause mortality was similar in the two groups by Kaplan–Meier analysis (33.9% in the TAVI group versus 35.0% in the SAVR group,  $P=0.78$ ).<sup>15</sup> At one year, TAVI was slightly superior to SAVR with respect to the mean aortic valve gradient ( $10.1\pm3.9$  mmHg versus  $11.4\pm5.3$  mmHg,  $P=0.005$ ) and mean valve area ( $1.59\pm0.47$  cm<sup>2</sup> versus  $1.44\pm0.47$  cm<sup>2</sup>,  $P=0.002$ ), but there was no such difference between the two groups at the 2-year follow-up.<sup>16</sup> At one year, the cost analysis was similar for TAVI and SAVR.<sup>17</sup> However, access site-based stratification showed transfemoral access to be less costly and with better quality-adjusted life years compared with SAVR, indicating an economically attractive option. Transapical access proved to be substantially more costly with fewer quality-adjusted life years compared with SAVR, indicating a loss.

Makkar et al recently presented the 3-year follow-up results of the PARTNER trial at the 2013 Transcatheter Cardiovascular Therapeutics meeting (as yet not published). In cohort B (inoperable) patients, TAVI continues to be superior to medical therapy, with an all-cause mortality and cardiac mortality of 54.1% versus 80.9% and 41.4% versus 74.5%, respectively ( $P<0.0001$ ). All-cause mortality of TAVI patients in PARTNER cohort A (high-risk) was comparable with that of SAVR at the 3-year follow-up (44.2% versus 44.8%). STACCATO (A Prospective, Randomised Trial of Transapical Transcatheter Aortic Valve Implantation versus Surgical Aortic Valve Replacement in Operable Elderly Patients with Aortic Stenosis) randomized low-risk patients aged >75 years to transapical TAVI or SAVR but was prematurely terminated due to a high event rate in the TAVI arm.<sup>18</sup>

## Medtronic CoreValve

Medtronic CoreValve LLC have completed their US pivotal trial in both high-risk (against SAVR) and extreme-risk

(against a prespecified objective performance goal) cohorts. Popma et al recently published the results of the CoreValve Extreme Risk Iliofemoral Study,<sup>19</sup> which evaluated the safety and efficacy of the CoreValve System in 471 patients deemed extreme risk for surgical aortic valve replacement (predicted risk of operative mortality or serious irreversible morbidity of  $\geq 50\%$  at 30 days). At one-year follow-up, the rate of death or major stroke was 25.5% against a prespecified objective performance goal of 43% ( $P < 0.0001$ ), with an all-cause mortality and cardiovascular mortality of 24.0% and 17.9%, respectively. Adams et al recently presented the landmark US CoreValve trial results in high-risk patients (estimated risk of death within 30 days after surgery  $\geq 15\%$  and risk of death or irreversible complications within 30 days after surgery  $< 50\%$ ).<sup>20</sup> In the as-treated analysis, the rate of death from any cause at one year was significantly lower in the TAVI group than in the surgical group (14.2% versus 19.1%;  $P < 0.001$  for noninferiority;  $P = 0.04$  for superiority). The results were similar in the intention-to-treat analysis. Using a hierarchical testing procedure, TAVI was noninferior with respect to echocardiographic indices of valve stenosis, functional status, and quality of life. Exploratory analyses suggested a reduction in the rate of major adverse cardiac and cerebrovascular events (20.4% for TAVI versus 27.2% for SAVR,  $P = 0.03$ ) and no increase in the risk of stroke at one-year follow-up (8.8% in the TAVI group versus 12.6% in the SAVR group,  $P = 0.10$ ).

## Registry data

In 2011, the SOURCE (Edwards SAPIEN Aortic Bioprosthesis European Outcome) registry reported one-year outcomes for 1,038 patients enrolled in 32 centers across Europe.<sup>21</sup> Of these patients, 575 had TAVI via a transapical approach and 463 via a transfemoral approach, with a Kaplan–Meier one-year survival of 76.1% overall (72.1% for transapical patients and 81.1% for transfemoral patients). The UK-TAVI registry data summarized the experience with 870 patients who had TAVI between 2007 and 2009 (Medtronic CoreValve,  $n = 452$  and Edwards SAPIEN,  $n = 410$ ).<sup>22</sup> Sixty-nine percent of these implants were transfemoral, with overall survival of 93%, 78.6%, and 73.7% at 30-day, one-year, and 2-year follow-up, respectively. Gilard et al reported a mortality rate of 9.7% and 24% at 30 days and one year, respectively, in FRANCE-2 (the French registry), which enrolled 3,195 patients at 34 centers in France between January 2010 and October 2011 (33% Medtronic CoreValve and 67% Edwards SAPIEN).<sup>23</sup> Di Mario et al reported the 2011–2012 European sentinel pilot registry data for 4,571 TAVI patients from 137 centers, with

an inhospital mortality of 7.4%, and this was similar in both SAPIEN-XT<sup>TM</sup> and CoreValve patients.<sup>24</sup>

## Long-term data

Owing to the earlier application of TAVI in Canada, the Canadian registry has long-term follow-up data. Rodés-Cabau et al published the Canadian multicenter experience of 339 high-risk patients who underwent TAVI with a balloon-expandable valve (Cribier-Edwards [ $n = 57$ ], Edwards SAPIEN [ $n = 275$ ], or SAPIEN XT [ $n = 7$ ]) between 2005 and 2009.<sup>25</sup> The all-cause mortality was 56% (188 patients) after a mean follow-up of  $42 \pm 15$  months (10.4% died within 30 days and 44.8% died during follow-up). Toggweiler et al recently reported their single-center, 5-year outcomes for 88 patients who underwent TAVI.<sup>26</sup> Median survival time after TAVI was 3.4 years, with one-year to 5-year survival rates of 83%, 74%, 53%, 42%, and 35%, respectively. Overall, the aortic valve area decreased on average by 0.06 cm<sup>2</sup> per year (standard error 0.01;  $P < 0.01$  for trend) and the mean gradients increased by an average of 0.27 mmHg per year (standard error 0.15;  $P = 0.06$  for trend) during 5 years of follow-up. There were no differences in gradients or aortic valve areas between the Cribier-Edwards and Edwards SAPIEN valves. The results of the ADVANCE core valve registry data, representing the real world experience of 1,015 patients from 44 international centers between March 2010 and July 2011, are very promising (albeit not as yet published).<sup>27</sup> These results show a very high procedural success rate (97.5%), with all-cause and cardiovascular mortality of 4.5% and 3.4% at 30-day follow-up and 17.9% and 11.7% at one-year follow-up, respectively. The major published data are summarized in Table 1.

## Ongoing trials

As a follow-up trial to the landmark PARTNER I trial, the PARTNER II trial is currently ongoing (ClinicalTrials.gov identifier NCT01314313). It consists of two parallel, randomized controlled trials. In an attempt to expand the indication of TAVI to lower-risk patients, the trial is designed to compare SAVR with the second-generation valve (SAPIEN XT) and delivery system (NovoFlex for transfemoral TAVI and Ascendra 2 for transapical TAVI) in intermediate-risk patients in the cohort A population. In the cohort B (inoperable) population, the PARTNER II trial is designed to study and compare the safety and effectiveness of the second-generation valve (SAPIEN XT) and delivery system (NovoFlex) with that of the first-generation valve (SAPIEN) and delivery system (RetroFlex3). It is

Table 1 Clinical outcomes after TAVI according to access site and device type: major published data

Reference	Type of study	Year published	Patients (n)	STS (%)	Logistic EuroSCORE (%)	Follow-up (months)	Procedural success rate (%)	30-day mortality (%)	One-year mortality (%)	Major access complications at 30 days (%)	Stroke at 30 days (%)	Need for new PPM (%)
<b>Edwards SAPIEN™ (TF)</b>												
Rodés-Cabau et al <sup>28</sup>	Registry	2009	162	9.0	–	24	90.5	9.5	25.0	13.1	3.0	3.6
Lefevre et al <sup>29</sup>	Registry	2009	61	11.3	25.7	12	95.4	8.2	21.3	16.4	3.3	1.8
Leon et al <sup>7</sup>	RCT	2010	179	11.2	26.4	12	–	5.0 <sup>c</sup>	30.7 <sup>c</sup>	16.2	6.7 <sup>d</sup>	3.4
Thomas et al <sup>21,30</sup>	Registry	2011	463	–	14.5	1	95.2	6.3	18.9	22.9	2.4	6.7
Smith et al <sup>8</sup>	RCT	2011	244	11.7	29.1	12	–	3.3 <sup>c</sup>	22.2 <sup>c</sup>	14.0	3.7 <sup>d</sup>	3.7
Bosmans et al <sup>31</sup>	Registry	2011	99	–	29.0	12	97.0	6.0	18.0	–	2.0	4.0
Elchanihoff et al <sup>32</sup>	Registry	2011	95	17.4	25.6	1	98.3 <sup>a</sup>	8.4	–	6.3	4.2	5.3
Himbert et al <sup>33</sup>	Registry	2011	51	15.0	25.0	12	90.0	8.0 <sup>b</sup>	19.0	12.0	6.0	6.0
Walters et al <sup>34</sup>	Registry	2013	67	–	26.8	12	92.4	6.0 <sup>c</sup>	13.6 <sup>c</sup>	4.5 <sup>e</sup>	3.0	4.5
Mack et al <sup>35,36</sup>	Registry	2013	3,833	7.0	–	1	92.0 <sup>f</sup>	5.0	–	–	3.2	5.8 <sup>n</sup>
Mack et al <sup>35,36</sup>	Registry	2013	1,139	7.0	–	1	92.0 <sup>f</sup>	6.7	–	–	1.6	6.9 <sup>n</sup>
<b>Edwards SAPIEN (TA)</b>												
Svensson et al <sup>36</sup>	Feasibility	2008	40	13.4	35.5	6	87.5	17.5	–	–	5.0	–
Rodés-Cabau et al <sup>28</sup>	Registry	2009	177	10.5	–	1	96.1	11.3	22.0	13.0 <sup>f</sup>	1.7	6.2
Lefevre et al <sup>29</sup>	Registry	2009	69	11.3	33.8	12	96.4	18.8	50.7	5.8 <sup>e</sup>	1.5	3.8
Walther et al <sup>11</sup>	Feasibility	2011	168	–	27.0	12	95.8	15.0	37.0	1.2	2.0	2.3
Smith et al <sup>8</sup>	RCT	2011	104	11.8	29.8	12	–	3.8 <sup>c</sup>	29.0 <sup>c</sup>	3.8	6.8	3.9
Thomas et al <sup>21,30</sup>	Registry	2011	575	–	16.3	1	95.7	10.3	27.9	4.7	2.6	7.3
D'Onofrio et al <sup>37</sup>	Registry	2011	504	11.0	26.3	24	99.0	8.3	18.8	–	3.0	5.4
Moat et al <sup>34,m</sup>	Registry	2011	410	–	18.5	24	98.1	8.5	20.6	6.3 <sup>e</sup>	4.2 <sup>n</sup>	7.4
Bosmans et al <sup>31</sup>	Registry	2011	88	–	33.0	12	97.0	14.0	37.0	–	8.0	6.0
Elchanihoff et al <sup>32</sup>	Registry	2011	71	18.4	26.8	1	98.3 <sup>a</sup>	16.9	–	5.6 <sup>f</sup>	2.8	5.6
Himbert et al <sup>33</sup>	Registry	2011	24	18.0	28.0	12	100	16.0 <sup>b</sup>	26.0	8.0	0	4.0
Walters et al <sup>34</sup>	Registry	2013	62	–	28.8	12	87.1	9.6 <sup>c</sup>	23.3 <sup>c</sup>	3.2 <sup>e</sup>	4.8	8.3
Mack et al <sup>35,36</sup>	Registry	2013	2,318	7.0	–	1	92.0 <sup>f</sup>	10.8	–	–	2.2	7.8 <sup>n</sup>
Mack et al <sup>35,36</sup>	Registry	2013	420	7.0	–	1	92.0 <sup>f</sup>	12.6	–	–	5.9	6.4 <sup>n</sup>
<b>Medtronic CoreValve (TF)</b>												
Grube et al <sup>38</sup>	Registry	2007	86	–	21.6	1	88.0	12.0	–	–	10.0	–
Piazza et al <sup>39</sup>	Registry	2008	646	–	23.1	1	97.2	8.0	–	1.9	1.9	9.3
Petronio et al <sup>40</sup>	Registry	2010	460	–	19.4	6	98.4	6.1	11.4	2.0	1.7	16.1
Tamburino et al <sup>41</sup>	Registry	2011	663	–	23.0	12	98.0	5.4	15.0	2.0	2.5 <sup>g</sup>	17.4
Moat et al <sup>22,o</sup>	Registry	2011	452	–	18.1	24	98.2	5.8	21.7	6.2 <sup>e</sup>	4.0 <sup>n</sup>	24.4
Bosmans et al <sup>31</sup>	Registry	2011	133	–	25.0	12	98.0	11.0	22.0	–	4.0	22.0
Buellesfeld et al <sup>42</sup>	Registry	2011	126 <sup>h</sup>	–	23.0	24	72.6	15.2	28.1	–	9.6	26.2
Elchanihoff et al <sup>32</sup>	Registry	2011	66	21.3	24.7	1	98.3 <sup>a</sup>	15.1	–	7.5	4.5	25.7
Meredith et al <sup>43</sup>	Registry	2012	441	5.9	17.3	24	98.2	3.7	12.0	4.1 <sup>e</sup>	3.5	28.6
Popma et al <sup>19,44</sup>	RCT	2014	489	10.3	22.6	12	77.6	8.4	24.3	8.2 <sup>e</sup>	4.0	21.6
Adams et al <sup>20,45</sup>	RCT	2014	390	7.3	17.7	12	–	3.3	14.2	5.9 <sup>e</sup>	4.9	19.8

Medtronic CoreValve (SC)		Registry		2010		2011		2012		2013		2014		2015		2016		2017		2018		2019		2020	
Petronio et al <sup>40</sup>		Registry	54	–	25.3	6	100	0	6.7	0	1.9	18.5													
Zahn et al <sup>41</sup>		Registry	697	–	20.5	1	98.4	12.4	–	19.5	2.8	39.3													
Elchaninoff et al <sup>42</sup>		Registry	12	21.0	24.6	1	98.3 <sup>a</sup>	8.3	–	8.3	0	25.0													
Bosmans et al <sup>43</sup>		Registry	8	–	25.0	12	98.0	11.0	0	–	4.0	22.0													

**Notes:** <sup>a</sup>Global procedural success rate including Edwards SAPIEN TF, Edwards SAPIEN TA and Medtronic CoreValve TF and subclavian was 98.3%; <sup>b</sup>in-hospital mortality; <sup>c</sup>intention-to-treat mortality rate; <sup>d</sup>major and minor stroke; <sup>e</sup>vascular-related complications; <sup>f</sup>apex-related complications; <sup>g</sup>one-year; <sup>h</sup>124 patients received a TF approach and two an SC approach; <sup>i</sup>outcomes reported together, ie, 566 (81.2%) Medtronic CoreValve TF, 22 (3.2%) Medtronic CoreValve SC, 106 (15.2%) Edwards SAPIEN TF; Medtronic CoreValve TF, 22% Edwards SAPIEN TA, 22% Edwards SAPIEN TF, 5.3% Medtronic CoreValve SC; Meredith, unpublished data, 2012; presented at the 2012 Transcatheter Cardiovascular Therapeutics meeting (Miami, FL, USA); <sup>j</sup>outcomes reported together: Edwards SAPIEN TA (~53%) and Edwards SAPIEN TF (~47%); <sup>k</sup>in-hospital outcome; <sup>l</sup>outcomes reported together: Medtronic CoreValve TF (~90%) and Medtronic CoreValve SC (~10%); <sup>m</sup>high-risk patients; <sup>n</sup>inoperable patients; <sup>o</sup>overall procedural success in the TVT Registry™; <sup>p</sup>includes 323 TF access and 67 non-TF access patients. Edwards SAPIEN™ (Edwards Lifesciences, Irvine, CA, USA); CoreValve® (Medtronic CoreValve LLC, Irvine, CA, USA). Copyright © 2012. Adapted from Gènéreux P, Head SJ, Wood DA, et al. Transcatheter aortic valve implantation 10-year anniversary: review of current evidence and clinical implications. *Eur Heart J*. 2012;33(19):2388–2398, by permission of Oxford University Press.<sup>38</sup>

**Abbreviations:** TAVI, transcatheter aortic valve implantation; TF, transfemoral; SC, subclavian; STS, Society of Thoracic Surgeons; EuroSCORE, European System for Cardiac Operative Risk Evaluation; RCT, randomized controlled trial; PPM, permanent pacemaker.

expected that the next-generation Edwards valve, which can be implanted using a lower profile transfemoral system (18/19 French with NovoFlex versus 22/24 French with RetroFlex 3), will further reduce vascular and access complications with TAVI, and results are expected in March 2015. Similarly, the SURTAVI trial (ClinicalTrials.gov identifier NCT01586910) is under way to evaluate the safety and efficacy of the Medtronic CoreValve system in the treatment of symptomatic severe aortic stenosis in subjects who are at intermediate risk (predicted Society of Thoracic Surgeons [STS] mortality risk score  $\geq 4\%$  and  $\leq 10\%$ ) for aortic valve surgery compared with SAVR. This international, prospective, randomized controlled study aims to recruit 2,500 patients in approximately 75 centers across the USA, Canada, Europe, and Australasia, and the results are expected in 2016.

## Who should we treat?

Currently, TAVI is indicated in patients with symptomatic severe aortic stenosis who are deemed either inoperable or at high-risk for conventional SAVR. Severe aortic stenosis is defined as an aortic valve area  $\leq 1.0 \text{ cm}^2$  or  $\leq 0.6 \text{ cm}^2$  per  $\text{m}^2$ . Patients are considered to be symptomatic if they have symptoms of exertional breathlessness (New York Heart Association class II–IV), angina, or syncope that are attributable to aortic stenosis. In the PARTNER I trial, high-risk patients (cohort A) were defined as those with a STS<sup>44</sup> risk score of  $\geq 10\%$  or predicted risk of operative mortality  $\geq 15\%$  at 30 days and inoperable patients (cohort B) were defined as those with a predicted risk of operative mortality or serious, irreversible morbidity  $\geq 50\%$  at 30 days. Currently, no scoring system or predicted mortality by surgeons translates to events in the real world, indicating a need for a better mortality and morbidity scoring system for these valve patients. In PARTNER, the 30-day mortality in the surgical arm in cohort A was 6%–7%. TAVI as a therapeutic option for symptomatic severe aortic stenosis is included in the recently published 2012 guidelines for management of valvular heart disease published by the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology and the European Association for CardioThoracic Surgery,<sup>45</sup> and also in the 2012 US Expert Consensus Document on Transcatheter Aortic Valve Replacement,<sup>46</sup> and the indications and contraindications are summarized in Tables 2 and 3. The definition of high-risk versus inoperable state is arbitrary, and this should be considered a continuum. As far as patients with low or intermediate risk are concerned, there is no evidence to date regarding TAVI versus SAVR. Valve durability will



**Table 2** Indications for TAVI in severe aortic stenosis

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
TAVI should only be undertaken with a multidisciplinary “heart team” including cardiologists and cardiac surgeons and other specialists if necessary.	I	C
TAVI should only be performed in hospitals with cardiac surgery on site.	I	C
TAVI is indicated in patients with severe symptomatic AS who are not suitable for AVR as assessed by a “heart team” and who are likely to gain improvement in their quality of life and to have a life expectancy of more than one year after consideration of their comorbidities.	I	B
TAVI should be considered in high-risk patients with severe symptomatic AS who may still be suitable for surgery, but in whom TAVI is favored by a “heart team” based on the individual risk profile and anatomic suitability.	Ila	B

**Notes:** <sup>a</sup>Class of recommendation; <sup>b</sup>level of evidence.

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**Abbreviations:** AS, aortic stenosis; AVR, aortic valve replacement; TAVI, transcatheter aortic valve implantation.

be an important factor when extending TAVI to this group, given that patients are likely to live longer following corrective surgery. The ongoing PARTNER II and SURTAVI trials might shed light on the question of efficacy in this risk group and durability in vivo. With the current pricing of the device, the cost-effectiveness of this program lies in treating high-risk surgical patients who are likely to live at least more than a year as determined by the heart team. However, the willingness to pay to save a life will vary based on the gross domestic product of each country.

## Complications of TAVI

Despite being less invasive than the SAVR, TAVI is associated with serious complications including stroke, vascular complications, paravalvular aortic regurgitation (AR), and conduction abnormalities. These major complications remain the “Achilles heel” of TAVI in terms of becoming a widely accepted alternative to SAVR, especially with the move towards treating intermediate-risk patients. The Valve Academic Research Consortium (VARC) has attempted to standardize the definitions of complications to encourage uniform reporting.<sup>47,48</sup>

## Cerebrovascular events

Stroke is the most dreaded complication of interventional cardiology procedures, and is associated with not only increased mortality but also increased morbidity and

**Table 3** Contraindications to transcatheter aortic valve implantation

### Absolute contraindications

Absence of a “heart team” and no cardiac surgery on site

Appropriateness of TAVI, as an alternative to AVR, not confirmed by a “heart team”

#### Clinical

Estimated life expectancy less than one year

Improvement of quality of life by TAVI unlikely because of comorbidities

Severe primary associated disease of other valves with major contribution to the patient's symptoms, that can be treated only by surgery

#### Anatomical

Inadequate annulus size (<18 mm, >29 mm<sup>3</sup>)

Thrombus in the left ventricle

Active endocarditis

Elevated risk of coronary ostium obstruction (asymmetric valve calcification, short distance between annulus and coronary ostium, small aortic sinuses)

Plaques with mobile thrombi in the ascending aorta or arch

For transfemoral/subclavian approach: inadequate vascular access (vessel size, calcification, tortuosity)

### Relative contraindications

Bicuspid or noncalcified valves

Untreated coronary artery disease requiring revascularization

Hemodynamic instability

LVEF <20%

For transapical approach: severe pulmonary disease, LV apex not accessible

**Notes:** <sup>a</sup>Contraindication when using the current devices.

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**Abbreviations:** AVR, aortic valve replacement; LV, left ventricle; LVEF, left ventricular ejection fraction; TAVI, transcatheter aortic valve implantation.

long-term disability. Not surprisingly, elderly patients who are currently referred for TAVI are often as concerned about stroke as about dying during the procedure. The overall rate of stroke after conventional isolated aortic valve replacement is approximately 1.5% according to the STS database, but may be increased to 2%–4% in older or high-risk populations.<sup>49</sup> In the PARTNER I trial, major strokes were observed more frequently in the TAVI group, both in cohort B (compared with standard therapy group) at 30 days (5.0% versus 1.1%,  $P=0.06$ ) and at one year (7.8% versus 3.9%,  $P=0.18$ )<sup>7</sup> and in cohort A (compared with the surgical group) at 30 days (3.8% versus 2.1%,  $P=0.20$ ) and at one year (5.1% versus 2.4%,  $P=0.07$ ).<sup>8</sup> This was somewhat attributed to the early iterations of large delivery systems of the Edwards valve. Using the smaller delivery system of the CoreValve, the US Extreme Risk Iliofemoral Study demonstrated a stroke rate of 2.4% and 4.1% at 30 days and one year, respectively.<sup>19</sup> Depending on the definition used, the reported incidence of

stroke is quite variable in the published data (Table 1), but in a recent meta-analysis of 10,037 patients by Eggebrecht et al, the average cerebrovascular event rates were  $3.3\% \pm 1.8\%$  at 30 days and  $5.2\% \pm 3.4\%$  at one-year follow-up.<sup>50</sup> It was also noted that the 30-day mortality was 3.5-fold higher in patients who had stroke after TAVI compared with those without stroke. Diffusion-weighted magnetic imaging studies have revealed that clinically silent cerebral embolism occurs in up to 70% patients after TAVI.<sup>51–53</sup> Even though there was no measurable deterioration of neurocognitive function during 3 months of follow-up,<sup>52</sup> the long-term effects of these silent strokes are unknown. The common underlying mechanism is embolization. Intraprocedural transcranial Doppler suggested that neurological events may occur at different time points during the procedure and relate to manipulation of the catheter through the calcified aortic arch, positioning of the device, performance of balloon aortic valvuloplasty, and inadequate blood flow to the brain during rapid pacing.<sup>54,55</sup> These periprocedural events can be viewed as the consequences of embolization of calcified material or atheromatous debris from the aorta.

Even though the stroke risk is highest in the first week post TAVI, detailed analysis of the PARTNER trial revealed that this risk continues beyond the early phase.<sup>56</sup> Predictors of early neurological events post TAVI included a prior neurological event, more severe atherosclerotic burden, and smaller valve area, while more advanced functional disability, previous stroke, and transapical access are predictors of late events. Remaining native calcified aortic valve and thrombogenicity of the stent of the prosthesis are also significant risk factors for late strokes. Recently, atrial fibrillation was also reported as a potential risk factor for stroke after TAVI, with more than one third of patients noted to have transient atrial fibrillation during their hospital stay.<sup>57</sup> Although atrial fibrillation was not associated with increased mortality, it has been shown to increase the risk of stroke by four-fold.<sup>57,58</sup>

## Paravalvular AR after TAVI

During SAVR, the heavily calcified valve is initially excised and a new prosthesis is sutured to the annulus, resulting in a better seal with a low incidence of significant ( $\geq 2+$ ) paravalvular AR (4.2%).<sup>59</sup> Paravalvular AR is a much more frequent complication after TAVI, and depending on the method of assessment, the initial reported rates for trivial to mild AR were 40%–67% and for moderate to severe AR were 7%–20%.<sup>60–62</sup> Device undersizing, aortic valve calcium, and suboptimal device implantation were the major predictors of AR after TAVI.<sup>63–68</sup> In the PARTNER trial, moderate or

severe paravalvular AR was more common after TAVI than after surgical replacement (7.0% versus 1.9% at one year and 6.9% versus 0.9% at 2 years;  $P < 0.001$ ).<sup>15</sup> Quantification of paravalvular AR has been challenging, and has been revised between the VARC 1 and 2 publications,<sup>47,48</sup> and does not conform to the American Society of Echocardiography.<sup>69</sup> All agree that paravalvular AR  $\geq 2+$  is associated with increased mortality. During the 2-year follow-up, paravalvular AR remained unchanged, improved, and worsened in 46%, 32%, and 22% respectively. In a meta-analysis of 12,926 patients (CoreValve 41%), the overall incidence of moderate to severe AR was 13.9% and trivial to mild AR was 46%, as per VARC guidelines.<sup>70</sup> While there is no direct comparison between the two valve types, this meta-analysis revealed that the CoreValve was associated with a higher rate of AR compared with the Edwards valve (16.0% versus 9.1%,  $P = 0.005$ ). This may be related to the fact that the CoreValve continues to expand over 24–48 hours to improve its sealing, hence, AR may look worse with this device if assessed immediately after TAVI. This theory was supported by the recent US CoreValve trial results,<sup>19</sup> in which the frequency of moderate or severe paravalvular AR was 10.7% at discharge and improved to 4.2% at 12 months, suggesting that there is ongoing remodeling at the annular-bioprostheses interface with the self-expanding nitinol frame. Paravalvular AR due to malposition of the CoreValve is more evident because the valve is more forgiving and will function normally without embolizing under less precise deployment. Traditionally, a slightly higher AR has been considered acceptable, if tolerated by the patient. The radial strength of the self-expanding nitinol frame (CoreValve) compared with the balloon-expandable cobalt chromium (Edwards valve) stent may be suboptimal in terms of obtaining adequate sealing.

## Conduction abnormalities

Atrioventricular block with subsequent need for permanent pacemaker implantation is one of the major complications of aortic valve intervention. The left bundle branch exits approximately 2–3 mm below the base of the interleaflet triangle separating the noncoronary and right coronary leaflets of the aortic valve and fans along the ventricular septum to supply the left ventricle.<sup>71</sup> Because of this close anatomical relationship between the aortic valve and the branching atrioventricular bundle, aortic valve replacement may result in injury to subendocardial conduction tissue, causing the increased incidence of left bundle branch block. Rates of new permanent pacemaker implantation after TAVI in the literature vary greatly (Table 1) and this may be due to variations in practice regarding the threshold for permanent

pacemaker implantation and variable reporting among physicians. A recent meta-analysis of 8,536 patients who had aortic valve replacement including SAVR as well as TAVI using both the Medtronic CoreValve and Edwards SAPIEN valve reported that the rate of new permanent pacemaker implantation was 5.9% and 12.10% after SAVR and TAVI (overall), respectively.<sup>72</sup> There was a higher incidence of new permanent pacemaker implantation in CoreValve patients (24.50%) compared with Edwards SAPIEN valve patients (5.8% via transfemoral and 6.9% via transapical). A higher radial force and increased depth of implantation into the left ventricular outflow tract are factors potentially associated with the increased permanent pacemaker implantation after TAVI using the CoreValve.<sup>73,74</sup> Nazif et al recently reported that persistent, new-onset left bundle branch block occurred in 10.5% of patients without baseline intraventricular conduction abnormalities who underwent TAVI in the PARTNER trials.<sup>75</sup> New left bundle branch block was not associated with death, repeat hospitalization, stroke, or myocardial infarction at one year, but was associated with a higher rate of permanent pacemaker implantation at one year (4.7 versus 1.5%,  $P=0.01$ ) and failure of left ventricular ejection fraction to improve. A recent study showed that only one third of the patients implanted with a permanent pacemaker post TAVI were pacemaker-dependent at one-year follow up,<sup>76</sup> suggesting that further studies are needed to determine the predictors of long-term pacing dependency.

## Vascular complications

Major vascular complications and major bleeding are important barriers to improvement of patient outcomes after TAVI. The incidence of major vascular complications varies between 3.8% and 23% using the Edwards SAPIEN valve and between 2.0% and 14% using the CoreValve system (Table 1). Standardized definitions have been formulated for major and minor vascular complications by the VARC 2 consensus document to facilitate common clinical endpoints to increase consistency and comparability in TAVI clinical trials.<sup>48</sup> A recent analysis of 419 transfemoral TAVI patients from the two PARTNER trials revealed an incidence of major and minor vascular complications at 30-day follow-up of 15.3% and 11.9%, respectively.<sup>77</sup> Vascular dissection, perforation, and access site hematoma were the most common vascular complications. Major vascular complications were associated with significantly higher 30-day rates of major bleeding, transfusions, and renal failure requiring dialysis, and with a significantly higher rate of mortality at 30 days (14.1% versus 3.1%,  $P<0.0001$ ) and one year (39.4% versus 22.8%,  $P=0.001$ ). Sheath size  $>19$

French, female sex, a sheath-to-femoral artery ratio  $>1.05$ , and femoral artery calcification are independent predictors for major vascular complications while learning effect is associated with reduced complications.<sup>78,79</sup>

## Repositioning of the valve and embolization

An ideal transcatheter aortic prosthesis would restrain the native leaflets and relieve stenosis without having unnecessary contact with the surrounding structures. A valve extending excessively into the ventricle or the aorta might be associated with adverse events such as aortic insufficiency, conduction abnormalities, mitral valve dysfunction, coronary obstruction, or valve embolization. Repositioning of a malpositioned valve is advantageous to reduce complications; however, the first-generation valves are not repositionable. The self-expanding CoreValve can be moved towards the aorta to some degree, whereas the balloon-expanding valves (Edwards SAPIEN and SAPIEN-XT) do not have this flexibility.

Valve embolization is a rare but serious complication after TAVI, with a reported incidence of 0.3% in the SOURCE registry data<sup>21</sup> and 1.0% in the PARTNER I trials.<sup>80</sup> Valve embolization is often related to technical factors, such as timing of balloon inflation and suboptimal rapid pacing, undersizing and inaccurate valve placement, anatomical factors such as a pre-existing mitral bioprosthesis with a protruding stent frame, a large septal knuckle and native leaflet rupture, or overhanging leaflets.<sup>80</sup> Although valve embolization is mostly immediate, late embolization up to several hours has been reported. Patients with valve embolization were much more likely to require hemodynamic support and had higher rates of death (26.9% versus 5.8%,  $P<0.0001$ ; 50.5% versus 21.0%,  $P<0.0001$ ) and neurological events (13.2% versus 3.7%,  $P=0.02$ ; 13.2% versus 6.1%,  $P=0.10$ ) at 30 days and one year, respectively. Embolization to the aorta is generally well tolerated, and typically the valve can be snared or repositioned with a partially inflated valvuloplasty balloon into a more stable position in the aorta with implantation of another valve. Embolization to the left ventricle is poorly tolerated and would require surgical removal.<sup>81</sup>

## Technical advancements/considerations to reduce complications

### Cerebrovascular events

Given that the majority of strokes are due to thromboembolism and occur in the first few days after the TAVI procedure,






three mechanical cerebral embolic protection devices are being tested, ie, the Claret Pro system (Claret Medical, Santa Rosa, CA, USA), the TriGuard® (Keystone Heart Ltd, Herzliya, Israel), and the Embrella embolic deflector® (Edwards Lifesciences, Table 4). Although the initial results demonstrated safety with a high procedural success rate, there is a lack of convincing evidence with regard to reduction of new cerebral embolic lesions detected by diffusion weighted magnetic resonance imaging, and further studies are needed to determine the clinical efficacy of these devices.<sup>82–84</sup>

Grube et al evaluated the feasibility of TAVI without balloon predilation in 60 patients, and the results are encouraging, with low stroke rates (5%).<sup>85</sup> A larger randomized trial is currently recruiting 110 patients to test this hypothesis (SIMPLIFY TAVI, ClinicalTrials.gov identifier NCT01539746).

Current recommendations regarding pharmacotherapy during and after TAVI are made on an empiric basis and

there is no randomized data. A pathological study revealed that it takes about 3 months for the valve to be completely endothelialized.<sup>86</sup> Current recommendations suggest dual antiplatelet therapy with aspirin (long-term) and clopidogrel (1–6 months),<sup>45,46</sup> but the optimal dosage and duration of treatment is unknown. A randomized trial is underway to address this (ARTE trial, ClinicalTrials.gov identifier NCT01559298). Current anticoagulation therapy during TAVI includes unfractionated heparin (activated clotting time approximately 250–350 seconds) followed by reversal with protamine at the end of procedure in some centers. Bivalirudin, a direct thrombin inhibitor, has been tested as an alternative to heparin, and following the initial encouraging results during balloon aortic valvuloplasty<sup>87</sup> and TAVI,<sup>88</sup> a larger international randomized study is currently underway (BRAVO-3 trial, [Effect of Bivalirudin on Aortic Valve Intervention Outcomes], ClinicalTrials.gov identifier NCT01651780). Similarly, with more evidence

**Table 4** Design, advantages, and disadvantages of the currently available cerebral protection devices used during transcatheter aortic valve implantation

Cerebral protection devices	Design	Advantages	Limitations
 Claret Pro	Has two filters, a proximal that consists of a nitinol frame, and a polyurethane filter with 140 µm diameter pores which is attached to a 100 cm catheter and a non-proprietary distal filter. The proximal filter is placed to the right brachiocephalic artery whereas the distal filter is placed to the left common carotid artery	Requires a small sheath (6 Fr). Is able to capture the debris delivered during the procedure	Can be implanted only through the right radial/brachial artery and not through an alternative access. The device has to be removed post procedure. Does not protect the left vertebral artery and in a small feasibility study it was possible to deploy the distal filter in only 73% of the patients studied. Small-scale studies have shown that the device can capture debris derived from the aorta and the aortic valve during TAVI; however, there is no clinical evidence in the context of a randomised control trial to support the use of the device during TAVI
 TriGuard	Consists of a nitinol mesh that is fixed onto a nitinol frame and is used to deflect the debris, 2 stabilisers that provide fixation of the device on the aortic arch, and a tail end that connects the device with the delivery system	It can be implanted through both the left and right femoral arteries. Permits full coverage of the supra-aortic trunk. Can be left in the aortic arch for days	It is a deflector device that redirects debris away from the brain towards the descending aorta. Requires a relatively large sheath (9 Fr). Although it has been tested in a small feasibility study there are no robust randomised clinical data to support its use in everyday practice
 Embella embolic deflector	Incorporates a heparin-coated polyurethane membrane that is mounted on a nitinol frame which is attached to a 110 cm catheter. The device has three radiopaque markers which facilitate the correct positioning of the device	Requires a small sheath (6 Fr)	Cannot be deployed through an alternative access point. Does not protect always the left vertebral artery. It is a deflector device that redirects emboli away from the brain towards the peripheral arteries. There is a lack of evidence to support the value of the device in a clinical setting

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**Abbreviation:** TAVI, transcatheter aortic valve implantation.

emerging about periprocedural atrial fibrillation as a cause of stroke, further studies are needed to explore the potential efficacy of prophylactic use of antiarrhythmic drugs to prevent atrial fibrillation and antithrombotic agents like warfarin to prevent strokes.

## Paravalvular AR after TAVI

Undersizing of the prosthesis relative to the patient's aortic annulus is a main reason for paravalvular AR after TAVI. As the aortic valve annulus is not circular in shape, assessment with two-dimensional echocardiography can underestimate the valve size. Several studies have shown that the annulus measurement by multidetector computed tomography is a better predictor of annulus size and is associated with reduced rates of AR after TAVI.<sup>89–91</sup> Three-dimensional transesophageal echocardiography measurements have also been shown to be superior to two-dimensional transesophageal echocardiography and correlate closely with those from multidetector computed tomography<sup>92,93</sup> but the resolution of this modality is yet to improve. Detaint et al reported that occurrence of significant AR was closely associated with a lower cover index (cover index =  $100 \times [\text{prosthesis diameter} - \text{transesophageal echocardiography annulus diameter}] / \text{prosthesis diameter}$ ) and that there was no significant AR when the measured cover index was  $>8$ .<sup>63</sup>

Paravalvular AR after TAVI is closely associated with the implantation depth,<sup>94</sup> and if the valve is positioned too low or high, the skirt of the prosthetic valve (9–13 mm height) does not provide an adequate seal around the annulus, leading to significant AR. The ideal implant height to reduce the paravalvular AR and conduction abnormality will be around 2–6 mm below the virtual annulus.<sup>95</sup> Valve position is currently based on fluoroscopy with or without intraprocedural transesophageal echocardiography guidance. The recent advances in imaging technology allow comprehensive real time visualization, which helps in optimal positioning of the prosthesis. The newer imaging systems use computer reconstruction techniques to predict the optimal angiographic views by processing either the aortogram acquired before device deployment (C-THV system, Paieon Inc., New York, NY, USA) or the computed tomography data (3mensio valve, 3mensio Medical Imaging, Bilthoven, NL, and OSIRIX, Pixmeo SARL, Switzerland). The Philips heart navigator system (Philips, Eindhoven, the Netherlands) provides three-dimensional reconstruction of the aorta and aortic valve by superimposing the computed tomography data onto the angiographic projections, while the DynaCT (Siemens AG, Erlangen, Germany) and Vitrea (Vital images [Toshiba],

Plymouth, MN, USA) use the rotational two-dimensional fluoroscopic images acquired in the catheterization laboratory to reconstruct a three dimensional aortic valve anatomy. Small studies have shown the utility of these technologies, with better positioning of the valve reducing paravalvular AR.<sup>96,97</sup>

During the procedure, careful hemodynamic monitoring helps to identify significant AR after TAVI. Loss of the dirotic notch, low diastolic pressure, and high left ventricular end-diastolic pressure (LVEDP) may indicate significant AR. Sinning et al proposed an AR index (AR index = aortic diastolic pressure – LVEDP/aortic systolic pressure) and reported that a low AR index correlates closely with significant AR after TAVI; an AR index  $<25$  was associated with significantly higher mortality (46.0% versus 16.7%,  $P=0.001$ ).<sup>98</sup>

Several interventional techniques have been suggested to treat significant AR intraprocedurally, including balloons, snares, and valve-in-valve.<sup>99</sup> If the valve position is adequate, but associated with significant AR, then postdilation with an oversized balloon may improve the sealing and reduce paravalvular AR.<sup>46</sup> This has not led to any deleterious effect on valve hemodynamics as measured by echocardiography at one-year follow-up, but caution is needed because post dilation may be associated with an increased risk of cerebrovascular events.<sup>100</sup> If the valve is implanted too low, the CoreValve can be snared towards the aorta. Although successful cases have been reported,<sup>101,102</sup> the valve may move back to the original position once the tension is released or has the potential risk of valve embolization, damage to the heavily calcified aorta or cerebral embolic events. Hence, valve-in-valve has been suggested as a preferred technique for both the Edwards and the CoreValve in this scenario.<sup>103</sup> Ussia et al reported their valve-in-valve experience in 24 of 663 patients (3.6%) undergoing TAVI using CoreValve in the Italian registry.<sup>104</sup> At 12-month follow-up, the mean gradient was  $10.5 \pm 5.2$  mmHg, which was not different from that in patients undergoing a conventional CoreValve procedure. At 12 months, the major adverse cerebrovascular and cardiac event rates in the standard procedure and valve-in-valve groups were 4.5% and 14.1%, respectively ( $P=0.158$ ), and the mortality rates were 4.5% versus 13.7%, ( $P=0.230$ ). Toggweiler et al recently reported their valve-in-valve experience in 21 of 760 patients (2.8%) undergoing TAVI using the balloon-expandable device (Edwards valve).<sup>105</sup> The mean transvalvular gradient was higher in the valve-in-valve group compared with the conventional TAVI group ( $15 \pm 4$  mmHg versus  $11 \pm 4$  mmHg, respectively,  $P=0.02$ ), but one-

year mortality rates were similar (24% versus 22%). However, a recent analysis of the PARTNER trials suggests that at one year, patients with valve-in-valve had higher all-cause mortality (33.3% versus 21.0%,  $P=0.02$ ), cardiovascular mortality (24.4% versus 9.1%,  $P=0.0005$ ), and a trend to more rehospitalization (25.5% versus 17.7%,  $P=0.12$ ).<sup>80</sup> There is also concern regarding increased risk of thrombosis, and the optimal duration of antiplatelet/anticoagulation therapy in these patients is unknown. Successful percutaneous closure of paravalvular leaks after TAVI using vascular plugs has also been described.<sup>106,107</sup> A SAVR may be a final option for patients with acute severe AR following TAVI with hemodynamic compromise, if all other interventional options are exhausted.<sup>108</sup> Several new valve designs are being developed to address this complication and are discussed below.

## Conduction abnormalities

Predictors of complete atrioventricular block post TAVI include presence of right bundle branch block before TAVI, low implantation of the prosthesis, and prosthesis oversizing.<sup>109,110</sup> Piazza et al reported that no patient in their study developed prosthesis-related left bundle branch block when the proximal end of the valve frame was positioned  $<6.7$  mm from the lower edge of the noncoronary cusp.<sup>73</sup> More than 90% of all atrioventricular blocks requiring implantation of a permanent pacemaker occurred immediately or within 7 days after TAVI.<sup>110</sup> Therefore, prompt recognition and appropriate management of atrioventricular block remain essential, and continuous electrocardiographic monitoring has been recommended for at least 72 hours post TAVI for all patients at increased risk of this complication.<sup>46</sup> Novel valve prostheses are being developed to reduce various complications, including conduction abnormalities after TAVI (Table 5). Some of the features of the newer valves that may minimize damage to the cardiac conduction system include low frame height (Direct Flow Medical valve, Direct Flow Medical Inc., Santa Rosa, CA, USA; SAPIEN III and Centera valves from Edwards Lifesciences) and low placement of the leaflets within the prosthesis to minimize frame protrusion into the left ventricular outflow tract (Lotus valve, Boston Scientific, Natick, MA, USA; JenaValve system, JenaValve Technology GmbH, Munich, Germany; Portico™ valve, St Jude Medical, St Paul, MN, USA; and Acurate TA™ valve, Symetis SA, Ecublens, Switzerland). Having the ability to reposition the valve (Table 5) may aid the surgeon to confidently implant the valve higher and reduce the need for a permanent pacemaker. As the practice of TAVI evolves, it remains to be seen how the next generation of

TAVI prostheses will affect the incidence, risk factors, and clinical outcomes of associated conduction disturbances.

## Vascular complications

By reducing the sheath vessel ratio, we can reduce the vascular complications.<sup>79</sup> The Edwards SAPIEN valve introducer sheath is constantly coming down, from 22 and 24 French, to 18–19 French, to the current 16, 18, and 20 French e-sheath for 23, 26, and 29 mm valves, respectively. The new SAPIEN 3 can be delivered via a 14 French e-sheath. It is important to note that the expandable sheath transiently increases by 5–6 French sizes during passage of the valve. The CoreValve started with a 25 French delivery sheath that came down to 22 French and currently uses 18 French for all valve sizes. The Evolut R™ (a new iteration of the CoreValve) will have a true 14 French inline sheath for delivery. Reducing from the 22–24 French to 18–19 French sheath has been shown to reduce major vascular complications by three-fold (11.1% versus 33.3%,  $P=0.004$ ).<sup>111</sup> In the recently presented preliminary results of the PARTNER II B trial (inoperable patients), the major vascular complication rate at 30 days were 9.6% with the SAPIEN XT valve (18/19 French) versus 15.5% with the SAPIEN valve (22/24 French).<sup>112</sup> Lately, a balloon-expandable sheath, Solopath® (Terumo Corporation, Somerset, NJ, USA), has been used to deliver the Medtronic CoreValve. This has a distal tip with a 13 French diameter that can be expanded with the use of a balloon to the nominal diameter of 19 French after being advanced into the aorta, and the initial results in a small series of patients are encouraging.<sup>113</sup>

Frequent surgical cut-down and vascular repair were commonly performed with the larger sheaths during the early years of TAVI, but with the availability of low-profile sheaths, several vascular closure devices have been tested to reduce vascular complications. Currently available closure devices include the ProStar XL (Abbott Vascular, Santa Clara, CA, USA) and the ProGlide (Abbott Vascular) for the transfemoral approach and the APICA ASC™ (APICA Cardiovascular, Galway, Ireland) for the transapical approach, while others such as the ProMed (ProMed Inc., Santa Clara, CA, USA) and the InSeal (InSeal Medical, Caesarea, Israel) for transfemoral access and the Permaseal™ (Micro Intervention Devices, Bethlehem, PA, USA) for transapical access are being developed.

Given that the predictive factors for vascular complications include peripheral vascular disease, vascular calcification, and vessel tortuosity, multimodality screening of the vascular access is of paramount significance in

**Table 5** Features of the second-generation transcatheter aortic valves that may reduce the risk of complications

Second-generation valves	Features of the second-generation valves
Direct flow medical 	Repositionable Retrievable after being fully deployed Low frame height designed to minimise conduction disturbances Bovine pericardial leaflets for increased durability
Jena 	Repositionable Anchoring system that facilitates optimal deployment Tactile feedback during deployment Low placement of the leaflets of the valve to minimise frame protrusion in the left ventricular outflow tract Large stent design to reduce the risk of coronary ostium obstruction Markers to facilitate device deployment
Engager 	Repositionable Anchoring system that facilitates optimal deployment Tactile feedback during deployment Markers to facilitate device deployment Bovine pericardial leaflets and anticalcification technology for increased durability
Portico 	Repositionable Low placement of the leaflets of the valve to minimise frame protrusion in the left ventricular outflow tract Large stent design to reduce the risk of coronary ostium obstruction Markers to facilitate device deployment Bovine pericardial leaflets and anticalcification technology for increased durability
Acurate 	Repositionable Anchoring system to facilitate optimal positioning Low placement of the leaflets of the valve to minimise frame protrusion in the left ventricular outflow tract Tactile feedback during deployment Markers to facilitate device deployment Additional cuff to reduce the risk of paravalvular leak Anticalcification technology for increased durability
CoreValve evolut R 	Repositionable Retrievable after being fully deployed Low delivery profile Large stent design to reduce the risk of coronary ostium obstruction Markers to facilitate device deployment Extended skirt and modified cell geometry to reduce the risk of paravalvular leak Anticalcification technology for increased durability
Sapien III 	Incorporates a distal flex mechanism and fine positioning control for accurate placement Low delivery profile Low frame height designed to minimise conduction disturbances Circular deployment at the annulus for optimal haemodynamics Additional cuff to reduce the risk of paravalvular leak Bovine pericardial leaflets and anticalcification technology for increased durability
Lotus 	Repositionable Retrievable after being fully deployed Tactile feedback during deployment Low placement of the leaflets of the valve to minimise frame protrusion in the left ventricular outflow tract Additional cuff to reduce the risk of paravalvular leak Markers to facilitate device deployment Bovine pericardial leaflets and anticalcification technology for increased durability
Centera 	Repositionable Low delivery profile Motorised handle with touch deployment allows precise device placement Contoured frame designed for optimal seating and sealing in the annulus Low frame height designed to minimise conduction disturbances Bovine pericardial leaflets and anticalcification technology for increased durability
Heart leaflet technology 	Repositionable Markers to facilitate device deployment Additional cuff to reduce the risk of paravalvular leak

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reducing the complications. Toggweiler et al have reported their experience with a fully percutaneous procedure using expandable sheaths, multidetector computed tomographic angiography for additional screening of the iliofemoral arteries, fluoroscopy/ultrasound-guided puncture, and preclosure using either two ProGlide devices (sutures implanted at 10 and 2 o'clock) or one Prostar.<sup>114</sup> They reported decreases in major vascular complications from 8% to 1% ( $P=0.06$ ), minor vascular complications from 24% to 8% ( $P<0.01$ ), major bleeds from 14% to 1% ( $P<0.01$ ), and unplanned surgery from 28% to 2% ( $P<0.01$ ). When the femoral vasculature is unfavorable for TAVI, several alternative routes have been explored in addition to the transapical route, ie, the transaxillary, transaortic, and transcarotid approaches.<sup>115</sup> There are no head-to-head comparisons between the various access sites for TAVI, but in general the nontransfemoral approach is associated with higher mortality when compared with transfemoral TAVI. In the recently published TVT Registry™ data, 30-day mortality was higher for nontransfemoral TAVI than for transfemoral TAVI (10.8% versus 5.0% in high-risk patients and 12.6% versus 6.7% in inoperable patients).<sup>35</sup> In a recent meta-analysis of about 6,500 patients, Li et al reported lower 30-day mortality with transfemoral TAVI when compared with transapical TAVI (7.5% versus 11.3%, respectively; odds ratio 0.63, 95% CI 0.52–0.76) and no difference in rates of postoperative stroke or heart block.<sup>116</sup> In a propensity-matched analysis, Petronio et al reported similar mortality rates at 2 years for TAVI using the subclavian approach compared with transfemoral TAVI.<sup>117</sup> It should be noted that the current patient risk scoring systems (STS score and Logistic EuroSCORE) do not take into consideration other clinical factors (eg, severe peripheral vascular disease, frailty, obesity) that might affect selection of the access site in these patients, and it will be difficult to draw any conclusions regarding superiority of one access site over another until randomized controlled trials are conducted.

In recent years, sutureless aortic valve replacement (SU-AVR) using minimally invasive surgical techniques has been proposed in high-risk patients as an alternative to conventional SAVR. Potential advantages of SU-AVR relate to removal of the native aortic valve and shortened aortic cross clamp times; however, other surgical steps including sternotomy/ministernotomy, cardiopulmonary bypass, and aortic cross clamping, are still needed. Recent small propensity-matched studies have shown noninferiority for SU-AVR compared with transapical TAVI, with significantly better valve gradients compared with SAVR.<sup>118</sup> There was a nonsignificant

protection against pacemaker usage and AR with SAVR. Accepting the limitations of propensity-matching, SAVR appeared to be the best for survival and AR, validating the finding of the STACCATO study<sup>18</sup> and the transapical arm of the Cohort A, PARTNER study.<sup>8</sup> Given the limited data, SU-AVR may be considered in selected high-risk surgical patients as an alternative to TAVI when a transarterial approach is not available and as an alternative to SAVR to reduce patient-prosthesis mismatch. Recognizing the effect of operator and heart team experience on the outcome of TAVI, recent multisociety guidelines set minimum operator and institutional requirements for these procedures.<sup>119</sup> With careful patient and access selection using multimodality imaging tools and using advanced interventional techniques with newer-generation, low profile sheaths, vascular complications can be minimized.

## Second-generation transcatheter aortic valves

Several newer-generation devices have been developed to reduce the risk of complications associated with the first-generation transcatheter aortic valves, and Bourantas et al have summarized the features of these valves in a recent review<sup>120</sup> (Table 5). Most of these valves are repositionable and some are retrievable, even after being fully deployed (Lotus valve and Direct Flow Medical valve). To reduce the risk of paravalvular leak, valves are provided with either a special adaptive seal (Lotus valve),<sup>121</sup> an additional cuff (SAPIEN III valve,<sup>122</sup> Acurate valve,<sup>123</sup> and HLT valve [Heart Leaflet Technologies Inc., Maple Grove, MN, USA], or an extended skirt (CoreValve Evolut R). Special Thermofix technology or anticalcification measures are being used on most new-generation valves to increase prosthesis durability. However, among the huge variety of anticalcification measures applied to conventional bioprostheses during the last few years, none turned out to expand durability significantly, and we need to be cautiously optimistic regarding the results of these measures in real world practice. Schofer et al recently reported their experience using the Direct Flow Medical valve in 75 patients and the results were encouraging, with 1% mortality, 4% stroke, and 1.4% moderate AR at 30 days.<sup>124</sup> Preliminary results of the REPRISE-II trial (ClinicalTrials.gov identifier NCT01627691) using the Lotus valve presented by Meredith et al at the 2013 Transcatheter Cardiovascular Therapeutics meeting revealed 100% success in repositioning ( $n=31$ ) and retrieval ( $n=6$ ), with a 1% incidence of moderate AR at 30 days (data not published).

Larger clinical trials are needed to confirm these findings prior to rolling out these devices for routine use.

## Future indications

### Native aortic valve regurgitation

TAVI has been used to treat patients with native aortic valve regurgitation who are deemed surgically inoperable, with “off-label” use of the CoreValve prosthesis and JenaValve device. What makes aortic insufficiency different from aortic stenosis is the lack of calcium in the aortic leaflets and annulus with unrestrained expansion of the aortic annulus, making it challenging to anchor the transcatheter heart valve. With the CoreValve, secondary anchoring in the ascending aorta contributes to stabilization, while with the JenaValve, feelers assist with positioning and anchoring at the level of the native cusps. Roy et al reported their experience with the CoreValve in 43 patients, indicating limited success, with 30-day mortality and major stroke rates of 9.3% and 4.7%, respectively.<sup>125</sup> Twenty-one percent of patients had residual moderate or severe AR and 18.6% required implantation of a second valve. Seiffert et al reported their experience with the JenaValve in a small series of patients, with no major procedure-related or device-related adverse events at 3 months.<sup>126</sup> The Jena Valve is the only system that currently has a CE mark for this indication. The Helio dock (Edwards Lifesciences) is the first dedicated transcatheter device for the treatment of pure AR,<sup>127</sup> that is performed as a fully percutaneous transarterial procedure (bilateral femoral access). The dock consists of a self-expandable nitinol stent encased in polyethylene terephthalate fabric that is fixed inside the aortic root and is intended to assist in annular fixation of a standard balloon-expandable SAPIEN XT valve. A potential advantage of this system is that incorporation of the native cusps into the device not only contributes to fixation but also provides paravalvular sealing. Pasupati presented feasibility study results at the 2013 EuroPCR conference in Paris, France, using a transapical and transfemoral approach, with successful implantation of the device in four patients, all of whom were alive at one-year follow up (not published).

### Valve-in-valve for a failing bioprosthesis

Bioprostheses have limited durability, and most are expected to degenerate and eventually fail within 10–20 years.<sup>128</sup> A redo surgical valve replacement, which is the standard of care for patients with a failing bioprosthesis, is sometimes associated with high morbidity and mortality, especially in

elderly patients, because of associated comorbidities.<sup>129</sup> The valve-in-valve procedure has been proposed as an alternative to high-risk surgical valve replacement for patients with a failing bioprosthesis due to stenosis or regurgitation (transvalvular not paravalvular). Dvir et al recently summarized the global valve-in-valve registry experience in 202 patients from 38 centers (61% with the CoreValve and 39% with the Edwards valve).<sup>130</sup> Procedural success was 93.1%, with 84.1% in New York Heart Association functional class II or less at 30 days. Mortality was 8.4% and 14.2% at 30 days and one-year follow-up, respectively. However, there were concerns with regard to elevated (>20 mmHg) residual transaortic gradients in some patients (28.4%), a high rate of device malposition (15%), and a high rate of coronary obstruction (3.5%), especially in selected Sorin bioprostheses (Mitroflow® in stented valves and Freedom® in stentless valves). It has been suggested that the supra-annular leaflet position in the CoreValve may allow for a larger orifice than can be achieved with annular leaflets constrained within the bioprosthetic valve ring, resulting in a lower incidence of high-transvalvular gradients with the CoreValve than with the Edwards valve, especially when implanted in a small surgical bioprosthesis (<20–22 mm). Specific issues have been reported with regard to selection of patients and the technical aspects of this technically challenging procedure.<sup>131,132</sup> It is of paramount importance to understand the failed bioprosthetic valve (model, size, structure, position, and mode of failure) and to exclude thrombosis, endocarditis, and paravalvular regurgitation. It is also important to assess risk factors for coronary obstruction, given that a higher incidence has been reported with a valve-in-valve procedure than with TAVI in a native valve. Encouraging results of valve-in-valve as well as valve-in-ring implants at the mitral valve position have also been reported in a small series of patients.<sup>133,134</sup> Currently, both the CoreValve and the Edwards valve have the CE mark for this indication.

### Valve implantation for “nonclassic” indications

Pushing the limits further, successful cases of percutaneous valve implants have been reported for “nonclassic” indications, including bicuspid aortic valve, a failing bioprosthesis at the tricuspid valve, and valve-in-ring implantation at the tricuspid position.<sup>135–137</sup> The Edwards and Melody (Medtronic, Minneapolis, MN, USA) valves have also been implanted in right ventricular pulmonary conduits. Further, the Edwards valve has been implanted in both the superior

vena cava and the inferior vena cava to treat severe tricuspid regurgitation. Although the small number of patients included in these studies does not allow us to make any conclusions, it is likely that the indications of TAVI will broaden in the future.

## Conclusion

TAVI has emerged as a viable alternative for high-risk or inoperable patients with symptomatic severe aortic stenosis. The results from the randomized controlled trials and the real world data show that the overall efficacy and survival at short to mid-term follow-up after TAVI is comparable with or superior to that with SAVR in high-risk patients. Even though rates of paravalvular AR, strokes, and vascular complications with the first-generation devices are higher than acceptable, these are likely to decrease with improvements in TAVI technology and increasing experience with implantation techniques. However, further research is required to answer the questions regarding durability of the valve, whether to use local anesthetic or general anesthetic, and whether to expand this procedure to low-risk patients and nonclassic indications.

## Disclosure

Dr Pasupati is a proctor/consultant for the Medtronic, Edwards, and St Jude medical device companies. The authors have no other conflicts of interest in this work.

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