

Clinical update

Open issues in transcatheter aortic valve implantation. Part 2: procedural issues and outcomes after transcatheter aortic valve implantation

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This article provides an overview on procedure-related issues and uncertainties in outcomes after transcatheter aortic valve implantation (TAVI). The different access sites and how to select them in an individual patient are discussed. Also, the occurrence and potential predictors of aortic regurgitation (AR) after TAVI are addressed. The different methods to quantify AR are reviewed, and it appears that accurate and reproducible quantification is suboptimal. Complications such as prosthesis-patient mismatch and conduction abnormalities (and need for permanent pacemaker) are discussed, as well as cerebrovascular events, which emphasize the development of optimal anti-coagulative strategies. Finally, recent registries have shown the adoption of TAVI in the real world, but longer follow-up studies are needed to evaluate the outcome (but also prosthesis durability). Additionally, future studies are briefly discussed, which will address the use of TAVI in pure AR and lower-risk patients.

Keywords Transcatheter aortic valve implantation • Access site • Aortic regurgitation • Complications • Registries

Introduction

The current article is the second part of a review on the open issues in transcatheter aortic valve implantation (TAVI). In the first part, areas of controversy in patient selection were addressed,¹ while in this second part the focus is on procedural issues and outcomes. Procedure-related areas of uncertainty include the choice between different access sites,

and also the quantification and prediction of aortic regurgitation (AR) after TAVI. The prevalence of patient–prosthesis mismatch (PPM) after TAVI and its impact on the outcome will be addressed, as well as specific complications after TAVI such as development of conduction abnormalities with subsequent need for permanent pacemaker therapy, and occurrence of cerebrovascular events (CVE). Moreover, the optimal anti-coagulative strategy after TAVI is currently unclear.

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Recently, valve-in-valve procedures (TAVI in a failing bioprosthetic valve) have been introduced and preliminary data are promising. In addition, the potential role of large clinical registries to determine the position of TAVI in the current clinical practice is important. All these issues will be reviewed and the potential future indications (pure AR, low-risk populations) of TAVI will be discussed at the end of this article.

Access route

Choosing the most appropriate access route for each individual patient is key to a successful TAVI procedure. Potential vascular access sites for TAVI include: transfemoral (TF), transapical (TA), transaortic (TAo), transsubclavian, and others (retroperitoneal iliac approach, transaxillary, and transcarotid approach).

Data from European registries using the Edwards SAPIEN-XT valve (Edwards Lifesciences, Irvine, CA, USA),² the UK TAVI Registry³ and the United States Transcatheter Valve Therapy registry⁴ using both the Edwards valve and the CoreValve (Medtronic, Inc., Minneapolis, MN, USA) show that 75% of TAVI procedures in Europe are performed using the TF approach. Currently, the selection of access for TAVI is driven by practical considerations (depending on the anatomy and the patient). In a recent meta-analysis, transarterial approaches were associated with higher 30-day (18 studies, 6175 patients: 93.7 vs. 88.7%, $P < 0.001$) and 1-year (13 studies, 5263 patients: 82.9 vs. 73.3%, $P < 0.001$) survival rates compared with TA access.⁵ However, transarterial access was associated with higher vascular complications rate (12 studies, 3135 patients: 20.1 vs. 4.2%, $P < 0.001$).⁵ In general, more outcome studies comparing the different access routes are needed.

Transfemoral access

The TF approach is considered the least invasive and default approach. This is supported by the increasing dominance of the TF

approach in the European arena in recent years (Figure 1), a pattern driven by decreasing delivery system calibre enabling a complete percutaneous approach and reduction in TA TAVI procedures in extremely high-risk patients. The decision that the TF approach is appropriate is based on peripheral angiography and multi-detector row computed tomography (MDCT) (Figure 2). For currently available TAVI delivery catheters (14–20F), the minimal femoral and iliac diameter should be 6–6.5 mm. In addition, there should be limited vessel calcification and tortuosity (Figure 2). Patients not meeting these criteria should be moved to a non-TF approach to avoid vascular complications which are associated with impaired prognosis.⁶

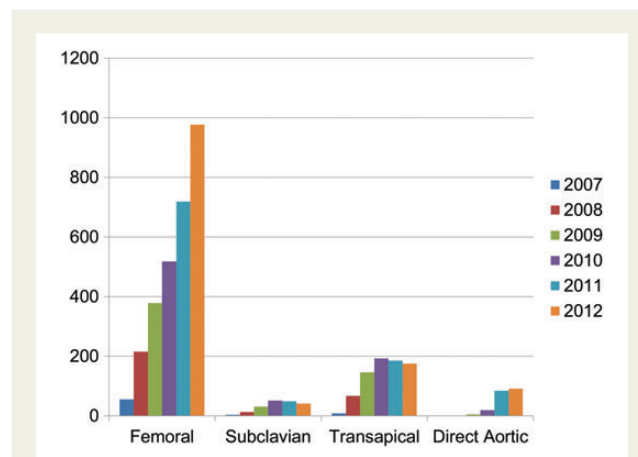


Figure 1 Transcatheter aortic valve implantation access routes. Data from the UK TAVI Registry illustrating the change in access route choice over the years 2007–12, emphasizing the rapid rise in trans-femoral procedures (figure courtesy of Dr Peter Ludman).

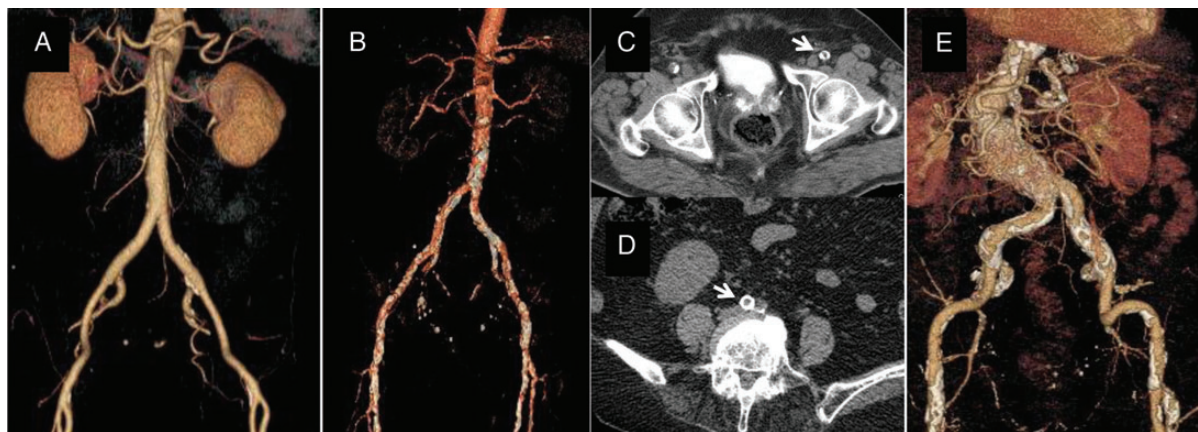


Figure 2 Multi-detector row computed tomography for assessment of the peripheral vasculature to decide on optimal access sites for transcatheter aortic valve implantation. Aortogram of 'ideal' arterial anatomy for a TF procedure: non-calcified iliac and femoral arteries which are of good calibre and not too tortuous (A). Multi-detector computed tomographic aortogram showing heavy arterial calcifications in the aorta and iliac arteries (B), non-concentric but significant calcification in the iliac artery (C, arrow), and concentric calcification in the aorta (D, arrow). Multi-detector row computed tomography aortogram showing both heavy calcification and excessive tortuosity of iliac arteries (E).

Transapical access

The TA approach evolved alongside the TF technique, but is more invasive and usually reserved when TF access is impossible. Patients selected for the TA approach are by definition at higher risk, due to the presence of heavily calcified pelvic arteries and therefore a high 'atheroma burden'.

The TA approach allows close control of the valve during deployment and is well suited to valve-in-valve procedures (on both mitral and aortic bioprostheses). Less favourable for the TA approach are patients with severe pulmonary disease, chest wall deformity, severe LV dysfunction, or intracavitary thrombus and obesity.

Transaortic access

This approach was initially utilized as an alternative when other approaches were not possible (Supplementary material online, *Movies S1–S3*).^{7,8} With increasing experience, it was used for those patients not ideal for either TF (e.g. aortic tortuosity, friable atheroma in the arch, or borderline peripheral arteries) or TA (e.g. poor lung function, very poor LV function, or high frailty index).^{9,10} However, the technique has increased in popularity which has coincided with the availability of the next generation Ascendra Plus™ system (Edwards Lifesciences, Irvine, CA, USA) with a nose-cone.¹¹

Multi-detector row computed tomography analysis of the ascending aorta is important in selecting patients for the TAO approach (*Figure 3*). Essentially, the TAO zone (where the purse-string sutures are placed) should be calcium free.¹² A true porcelain aorta (*Figure 3*) is actually quite uncommon—in the majority of patients the calcification is patchy, making the TAO procedure feasible (*Figure 3*). The minimum distance from the aortic annulus to the TAO zone is 5–7 cm for the Edwards SAPIEN-XT valve and 6–7 cm for the CoreValve to allow complete valve deployment. In re-do patients, the proximity of the innominate vein and/or aorta to the sternum should be analysed if contemplating a mini-sternotomy. If these structures are in close proximity, a right anterior thoracotomy should be considered.⁷

Advantages of TAO access include: familiarity of an aortic approach to cardiothoracic surgeons, avoidance of access site problems (apical rupture and delayed pseudoaneurysm formation); avoidance of interference with post-operative respiratory dynamics due to thoracotomy, rib retraction and pleural effusions, and avoidance of effects on LV function.

Other vascular approaches (subclavian/axillary access)

Subclavian access for TAVI is an alternative access route for patients with severe peripheral artery disease.^{13,14} In general, the left subclavian or axillary arteries are preferred over the right access site, as it provides a better implantation angle of the transcatheter valve prosthesis during device placement.¹⁵ Clinical experience shows that only a vertical orientation of the ascending aorta is suitable for the use of the right subclavian artery, whereas an extreme horizontal angulation of the ascending aorta favours a left subclavian approach. Meticulous assessment of subclavian artery diameter, tortuosity and calcification, as well as exclusion of relevant stenoses prior to the procedure is important. Among patients with previous coronary artery bypass grafting and patent left internal mammary artery graft, insertion of the intravascular delivery sheath may lead to flow

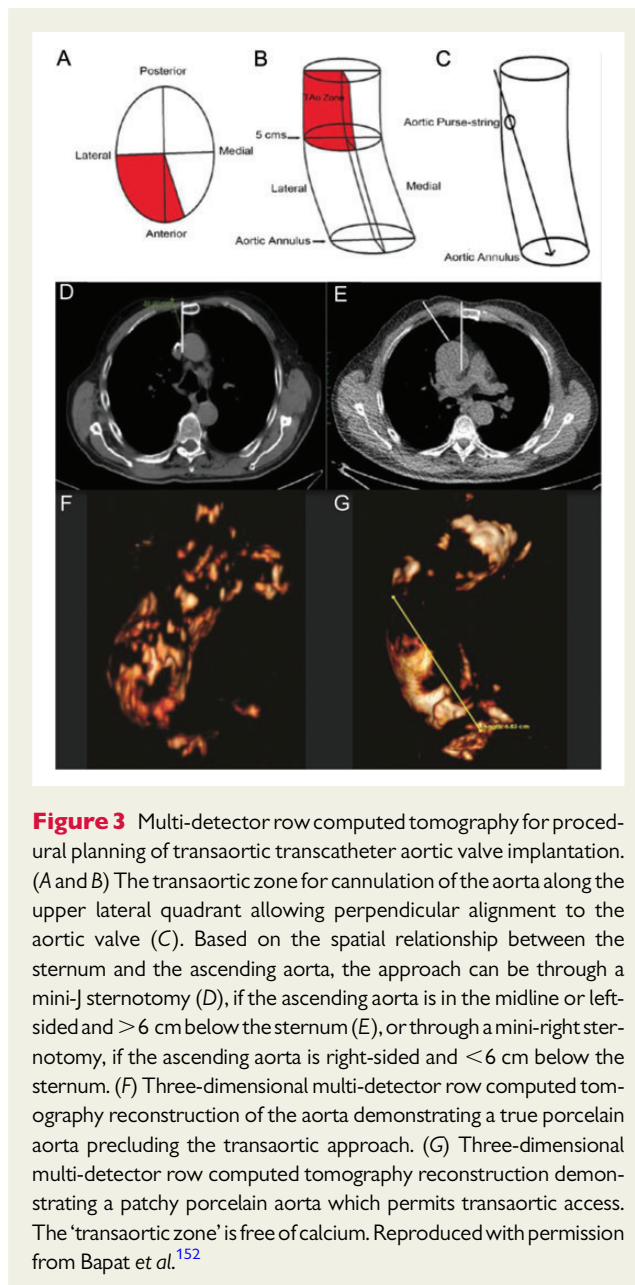


Figure 3 Multi-detector row computed tomography for procedural planning of transaortic transcatheter aortic valve implantation. (A and B) The transaortic zone for cannulation of the aorta along the upper lateral quadrant allowing perpendicular alignment to the aortic valve (C). Based on the spatial relationship between the sternum and the ascending aorta, the approach can be through a mini-J sternotomy (D), if the ascending aorta is in the midline or left-sided and > 6 cm below the sternum (E), or through a mini-right sternotomy, if the ascending aorta is right-sided and < 6 cm below the sternum. (F) Three-dimensional multi-detector row computed tomography reconstruction of the aorta demonstrating a true porcelain aorta precluding the transaortic approach. (G) Three-dimensional multi-detector row computed tomography reconstruction demonstrating a patchy porcelain aorta which permits transaortic access. The 'transaortic zone' is free of calcium. Reproduced with permission from Bapat et al.¹⁵²

obstruction and ischaemia during the procedure which needs to be carefully considered. Although no randomized comparisons between transsubclavian and TF access are available, published reports of clinical outcomes show comparable outcomes.¹⁶

Aortic regurgitation after transcatheter aortic valve implantation: incidence, determinants, and prognostic implications

Aortic regurgitation occurs relatively frequent after TAVI (*Table 1*).^{2–4,6,17–27} A recent meta-analysis including 12 926 patients

Table 1 Incidence of aortic regurgitation after transcatheter aortic valve implantation in major registries and randomized trials

Study	No patients	Type of THV	Access route	Moderate–severe AR (%)	Moderate–severe AR at follow-up (%)	
					1-year	2-year
PARTNER cohort B ²²	179	100% Edwards SAPIEN	100% Transfemoral	13.2	—	4.5
PARTNER cohort A ²¹	348	100% Edwards SAPIEN	70% Transfemoral 30% Transapical	10.6	9.2	11
SOURCE Registry ⁶	1038	100% Edwards SAPIEN	45% Transfemoral 55% Transapical	1.9	—	—
FRANCE-2 ²	3195	70% Edwards SAPIEN 30% CoreValve	74% Transfemoral 26% Non-transfemoral	16.5	20.2	—
Canadian Registry ²³	339	18% Cribier-Edwards 82% Edwards SAPIEN	48% Transfemoral 52% Transapical	10	10	10
GARY Registry ²⁰	3876	53% Edwards SAPIEN 42% CoreValve 5% Other ^a	70% Transfemoral 30% Transapical	6.2	—	—
UK-TAVI Registry ³	870	48% Edwards SAPIEN 52% CoreValve	69% Transfemoral 31% Transapical	13.6	—	—
Italian Registry of transapical TAVI ¹⁸	774	100% Edwards SAPIEN	100% Transapical	8.8	—	—
Italian Registry (self-expandable THV) ²⁴	663	100% CoreValve	90% Transfemoral 10% Transsubclavian	21	—	—
PRAGMATIC Plus Registry ¹⁷	793	43% Edwards SAPIEN 57% CoreValve	100% Transfemoral	1.9	—	—
TAVI Sentinel Pilot Registry ¹⁹	4571	57% Edwards SAPIEN 43% CoreValve	74% Transfemoral 26% Non-transfemoral	9	—	—
STS/ACC TVT registry ⁴	7710	100% Edwards SAPIEN	64% Transfemoral 36% Non-transfemoral	8.5	—	—
ADVANCE study ²⁶	1015	100% CoreValve	88% Transfemoral 12% Non-transfemoral	15.6	12.5	—
Popma et al. ²⁷	489	100% CoreValve	100% Transarterial	9.7	4.2	—
Adams et al. ²⁵	389	100% CoreValve	100% Transarterial	9.1	7.0	—
CHOICE trial ⁶⁶	241	50% Edwards SAPIEN 50% CoreValve	100% Transfemoral	3.7	—	—

ACC, American College of Cardiology; AR, aortic regurgitation; GARY, German Aortic Valve Registry; PARTNER, Placement of AoRTic TraNscathetER Valve Trial; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation; THV, transcatheter heart valve.

^aInclude the ACCURATE TA™ device (Symetis SA, Ecublens, Switzerland) and the JenaValve™.

undergoing TAVI reported a pooled estimate incidence of moderate or severe AR of 11.7%.²⁸ Residual moderate-to-severe AR is clinically relevant and has been associated with an increased risk of all-cause mortality.²⁸

Pathophysiological determinants of aortic regurgitation after transcatheter aortic valve implantation

Aortic regurgitation can be divided into paravalvular (between the native annulus and the prosthesis frame) or transvalvular (within the prosthesis) (Supplementary material online, *Movie S4*). Paravalvular AR is more frequently observed than transvalvular AR and the underlying mechanisms differ significantly (*Table 2*).^{29–41} Accurate sizing of the aortic annulus and selection of the most appropriate prosthesis size are crucial to minimize complications such as paravalvular AR, as discussed in Part 1. Severe valvular calcification has

been also associated with paravalvular AR. The presence of bulky calcifications at the commissures may prevent complete sealing of the aortic annulus by the deployed prosthesis and lead to gaps where the regurgitant jets arise (*Figure 4*).³² Furthermore, a deep or shallow implantation of the prosthesis has been associated with significant paravalvular AR, related to inadequate sealing of the aortic annulus (*Figure 4*).^{35,37} Which of these factors contributes most to development of AR is currently unknown.

Transvalvular AR is commonly caused by the presence of guide wires or stiff catheters that restrict the movement of the prosthetic leaflets. Removal of the catheter resolves this type of transvalvular AR. Less frequently, transvalvular AR can be caused by leaflet damage (after improper crimping process or aggressive ballooning of the transcatheter valve) or an oversized prosthesis which may result in underexpansion of the prosthesis and inadequate leaflet mobility.

Table 2 Factors associated with increased risk of paravalvular aortic regurgitation after transcatheter aortic valve implantation

Author	No. patient	Assessment	Prosthesis—access	Moderate–severe paravalvular AR (%)	Correlates of paravalvular AR
Aortic annulus size					
Detaint <i>et al.</i> ³¹	74	100% TEE	100% Edwards SAPIEN 62% Transfemoral	23	Low cover index (OR: 1.22 per 1% decrease)
Wilson <i>et al.</i> ⁴¹	102	100% MDCT	100% Edwards SAPIEN 67% Transfemoral	13	Difference between nominal and mean annular diameter ≥ 1 mm Difference between nominal area and annular area $> 10\%$
Hayashida <i>et al.</i> ³⁴	175	100% MDCT	84% Edwards SAPIEN 16% CoreValve 58% Transfemoral	24	Ratio nominal diameter/mean annular diameter (OR: 0.36 per 0.1 increase)
Leber <i>et al.</i> ³⁸	107	100% MDCT	100% Edwards SAPIEN	7	Ratio nominal area/annular area (oversizing ratio $< 15\%$ higher incidence of moderate–severe AR)
Aortic valve calcification					
Unbehaun <i>et al.</i> ⁴⁰	358	86% MDCT	100% Edwards SAPIEN 100% Transapical	1	Asymmetric cusp calcification and device-landing zone calcification
Delgado <i>et al.</i> ³⁰	53	100% MDCT	100% Edwards SAPIEN 57% Transfemoral	11	Aortic valve calcification (Agatston score) and calcification of the valve commissures
John <i>et al.</i> ³⁶	100	100% MDCT	100% CoreValve 100% Transfemoral	10	Calcification of the landing zone (valve and LVOT) as assessed with the Agatston score
Ewe <i>et al.</i> ³²	79	100% MDCT	100% Edwards SAPIEN 46% Transfemoral	4	Calcification of the commissures and valvular edge
Schultz <i>et al.</i> ¹⁵¹	56	100% MDCT	100% CoreValve 100% Transfemoral	5	Aortic valve calcification (Agatston score)
Colli <i>et al.</i> ²⁹	103	100% TEE	100% Edwards SAPIEN 100% Transapical	7	Calcification of the valve commissures
Haensig <i>et al.</i> ³³	120	100% MDCT	100% Edwards SAPIEN 100% Transapical	4	Aortic valve calcification (Agatston score)
Prosthesis deployment					
Jilaihawi <i>et al.</i> ³⁵	50	100% Angiography	100% CoreValve 100% Transfemoral	4	Deep deployment of the valve (15 mm deep from the non-coronary cusp)
Sherif <i>et al.</i> ³⁹	50	100% Angiography	100% CoreValve 100% Transfemoral	40	Deep (> 10 mm from the non-coronary cusp) or shallow (< 10 mm) implantation
Katsanos <i>et al.</i> ³⁷	123	100% MDCT	100% Edwards SAPIEN 62% Transapical	20	Shallow implantation (< 2 mm from the left coronary cusp)

AR, aortic regurgitation; LVOT, left ventricular outflow tract; MDCT, multi-detector row computed tomography; OR, odds ratio; TEE, transoesophageal echocardiography.

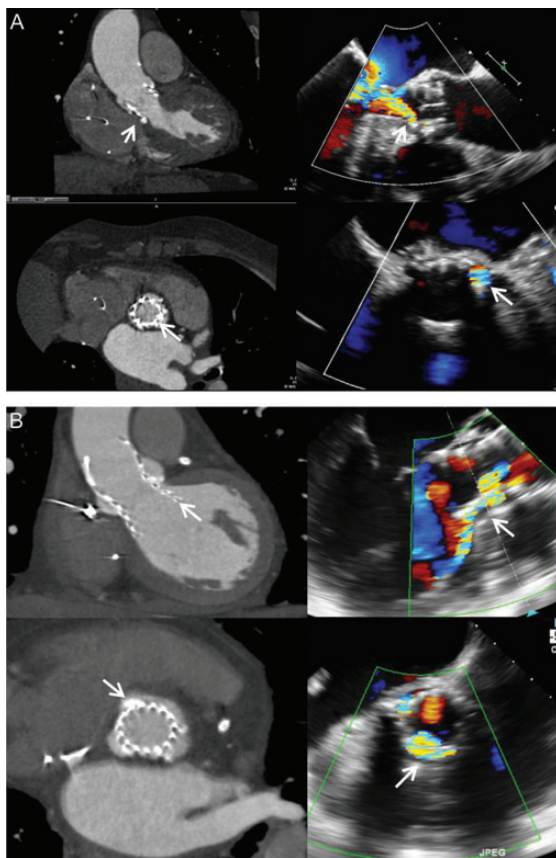


Figure 4 Pathophysiological factors determining paravalvular aortic regurgitation. (A) Example of a patient with mild paravalvular aortic regurgitation at the level of the hinge point with the membranous interventricular septum (arrow). The multi-detector row computed tomography shows a bulky calcification at this level (arrow). The short-axis view shows mild paravalvular aortic regurgitation at the level of the left coronary cusp. Please note on the multi-detector row computed tomography the presence of calcifications at this level surrounding the prosthetic frame (arrow). (B) Deep implantation of a self-expandable transcatheter aortic valve causing significant paravalvular aortic regurgitation (arrow). The multi-detector row computed tomography permits accurate assessment of the deployment of the valve. In addition, there is a paravalvular regurgitant jet originating at the level of the right coronary cusp. The multi-detector row computed tomography shows the presence of a bulky calcified right coronary cusp pushed away following valve deployment (arrow).

Quantification of aortic regurgitation after transcatheter aortic valve implantation

While the evaluation of AR immediately after TAVI is common practice, the evaluation of AR at follow-up is not systematically performed (Table 1). The quantification of AR is challenging and the most appropriate method depends on the type of regurgitation and the timing of assessment. Angiography, transthoracic echocardiography, or TEE are the most frequently used imaging techniques to assess AR immediately after transcatheter valve deployment. In addition,

haemodynamic assessment of AR using the dimensionless AR index has recently been proposed to estimate the severity of AR.⁴² An AR index <25 indicates significant AR after TAVI and has been associated with increased mortality risk at the 1-year follow-up.⁴² With supra-aortic angiography, AR can be qualitatively assessed based on an estimation of the contrast volume in the left ventricle.⁴³ However, this approach does not allow differentiation between paravalvular and transvalvular AR and is not the preferred modality for a serial follow-up. In contrast, transthoracic and TEE permit quantitative assessment of AR, differentiation between paravalvular and transvalvular AR and are well suited for subsequent surveillance of AR.

The Valve Academic Research Consortium (VARC) has proposed several criteria to standardize the assessment of AR after TAVI (Table 3).^{44,45} Some of the included parameters are more suited for transvalvular AR while others are better for paravalvular AR. For example, the ratio between the regurgitant jet width and the LV outflow tract diameter measured on the transthoracic parasternal long-axis view or the TEE 120–140° view is a valid semi-quantitative assessment of transvalvular AR (Figure 5). A regurgitant jet width relative to the LV outflow tract diameter of $\leq 25\%$, between 26 and 64% and $\geq 65\%$ define mild, moderate, or severe AR, respectively.⁴⁵ For paravalvular AR, which usually has eccentric or multiple jets, the proportion of the circumference of the prosthesis covered by the AR jet measured at the short-axis view may be a more appropriate assessment (Figure 5). Mild, moderate, and severe paravalvular AR are defined by $<10\%$, between 10 and 29% and $\geq 30\%$ extent of the circumference of the prosthesis frame.⁴⁴ However, these evaluations are semi-quantitative and are observer-dependent.

Current three-dimensional (3D) imaging techniques permit accurate quantification of AR and overcome some of the limitations inherent to two-dimensional (2D) imaging techniques. Three-dimensional TEE permits direct visualization and planimetry of the vena contracta (Supplementary material online, Movie S5), while velocity-encoded magnetic resonance imaging (MRI) allows for the measurement of blood flow velocity and volume across the valve and calculation of the regurgitant fraction.⁴⁶ A recent study demonstrated that 2D transthoracic echocardiography underestimated AR by at least 1 grade compared with MRI in 44% of patients treated with TAVI.⁴⁷

A few series have reported conflicting data on the time course of AR after TAVI (Table 1). Some studies have demonstrated that AR remains unchanged at the 1- and 2-year follow-up,^{21,23} while other studies reported a reduction^{22,26} or increase² in the prevalence of AR at the 1-year follow-up. Standardization of the methodology and timings to evaluate AR at follow-up will help to elucidate the time course of AR after TAVI and its prognostic implications.

Therapeutic strategies to reduce aortic regurgitation after transcatheter aortic valve implantation

The prognostic implications of $>$ mild AR after TAVI underscore the need for bail-out strategies that reduce at minimum the regurgitant volume. When the transcatheter valve is implanted within a very calcified aortic valve with bulky calcifications that prevent complete expansion of the frame, balloon post-dilatation may reduce paravalvular AR, ensuring full expansion of the frame, and improving the sealing of

Table 3 Echocardiographic assessment of aortic regurgitation grade after transcatheter aortic valve implantation

Parameter	Mild	Moderate	Severe
Valve structure and motion	Usually normal	Usually abnormal	Usually abnormal
Doppler parameters (qualitative or semi-quantitative)			
Colour M-mode: jet width relative to the LVOT diameter (%)	Narrow (≤ 25)	Intermediate (26–64)	Large (≥ 65)
Colour: circumferential extent of paravalvular AR (%) ^a	<10	10–29	≥ 30
Continuous wave Doppler			
Jet density	Incomplete/Faint	Dense	Dense
Jet deceleration rate (pressure half time; ms)	Slow (>500)	Variable (200–500)	Steep (<200)
Pulsed wave Doppler			
LV outflow vs. pulmonary flow	Slightly increased	Intermediate	Greatly increased
Diastolic flow reversal in the descending aorta	Absent/Early diastolic	Intermediate	Prominent/Holodiastolic
Doppler parameters (quantitative)			
Regurgitant volume (mL)	<30	30–59	≥ 60
Regurgitant fraction (%)	<30	30–49	≥ 50
Effective regurgitant orifice area (cm ²)	<0.10	0.10–0.29	≥ 0.30

AR, aortic regurgitation; LVOT, left ventricular outflow tract.

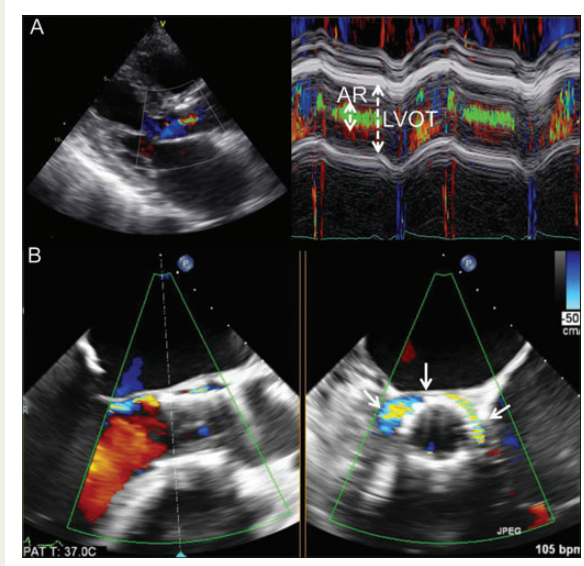


Figure 5 Assessment of aortic regurgitation grade. (A) Transvalvular mild aortic regurgitation assessed with colour-Doppler M-mode from the parasternal long-axis view (left). The width of the regurgitant jet relative to the diameter of the left ventricular outflow tract is <25% (right). (B) Paravalvular severe aortic regurgitation as shown in the short-axis plane (right) of the simultaneous transoesophageal echocardiographic biplane mode. The circumferential extent of the paravalvular regurgitant jet is almost 50%.

the aortic annulus, although risk of annulus rupture exists.⁴⁸ In patients with too shallow or too deep implantation of the transcatheter valve, transcatheter valve-in-valve may be an effective technique to reduce a significant paravalvular AR. This technique can also be used in patients with moderate-to-severe transvalvular AR. Less

frequently, the snare technique is used in patients with self-expandable prosthesis implanted too deep in the LV outflow tract, whereas the use of closure devices such as the AMPLATZER[®] Vascular Plug III (AVP III; AGA Medical Corp., Plymouth, MN, USA) has been proved safe and effective in patients with paravalvular AR after balloon-expandable prosthesis (Figure 6).⁴⁸ However, the increased peri-procedural risks are not negligible (prosthesis migration and aortic dissection) and a long-term outcome of these manoeuvres remains unexplored. Of note, the recent advent of transcatheter heart valves with dedicated sealing skirts may further reduce the risk of peri-procedural AR.

Patient–prosthesis mismatch

Prosthesis–patient mismatch occurs when the effective orifice area of a normally functioning prosthetic valve is too small in relation to the patient’s body size. In SAVR, several studies have reported that PPM is frequent [moderate PPM, (i.e. indexed effective orifice area ≤ 0.85 cm²/m²) in 20–70%; severe PPM, (i.e. indexed effective orifice area ≤ 0.65 cm²/m²) in 2–20%] and is associated with worse outcome.⁴⁹ A recent meta-analysis reported that moderate and severe PPM are associated with a 1.2- and 1.8- fold increase in the risk of all-cause mortality, respectively.⁵⁰ It thus appears important to implement preventive strategies to avoid PPM without increasing operative risk.

When compared with SAVR, previous non-randomized studies suggested that TAVI could be associated with a lower incidence of PPM, particularly, in patients with a small aortic annulus (Figure 7).^{35,51} Larger body size is a risk factor for PPM in both SAVR and TAVI.^{52,53} Small aortic annulus diameter is a powerful risk factor for PPM in SAVR but has minimal impact on PPM occurrence in TAVI.^{51–53} Alternatively, in TAVI, undersizing and/or

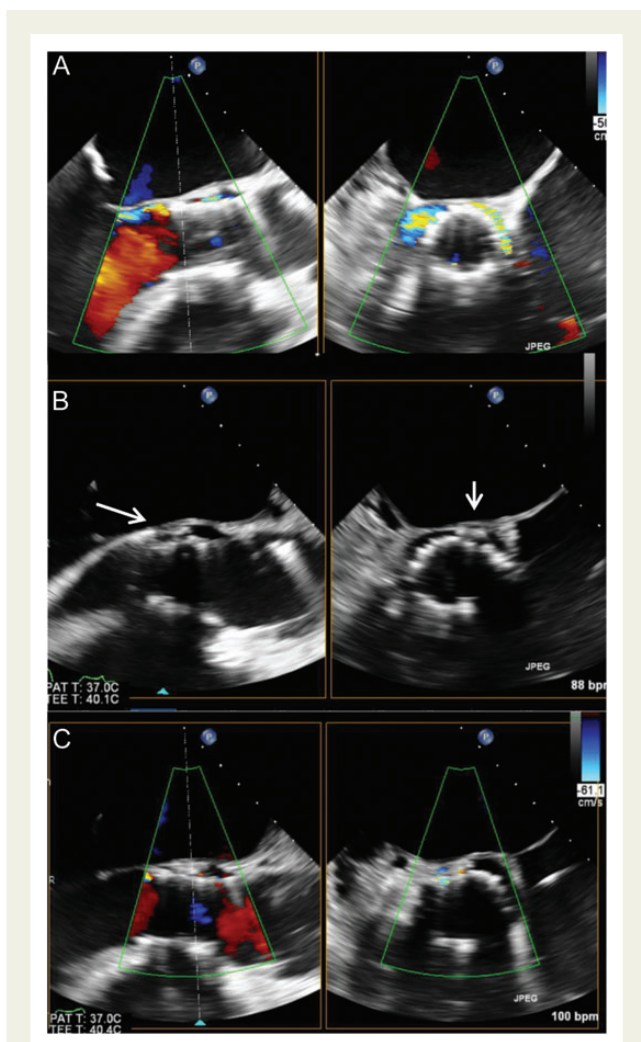


Figure 6 Treatment of significant paravalvular aortic regurgitation after transcatheter aortic valve implantation. Implantation of an AMPLATZER® Vascular Plug III closure device to seal a severe paravalvular aortic regurgitation as observed in the parasternal short-axis view with a circumferential extent >20% (A). The device is inserted between the native aortic root and the prosthetic frame (arrows) (B), resulting in significant reduction of the paravalvular regurgitant jet (C).

mal-positioning of the prosthetic valve are important risk factors for PPM.^{35,53}

A recent *post hoc* analysis of the PARTNER cohort A trial revealed that in high-risk patients with severe aortic stenosis (AS) PPM occurs more frequently following SAVR than TAVI.⁵⁴ Indeed, 28% of the patients in the SAVR arm had severe PPM vs. 20% in the TAVI arm and this difference was more pronounced in the subset of patients with a small aortic annulus diameter (<20 mm): 36 vs. 19%. Moreover, severe PPM is associated with less regression of LV hypertrophy and with a 1.8-fold increase in 2-year mortality in the SAVR arm. Likewise, severe PPM is also associated with less LV mass regression, and increased mortality after TAVI (if post-procedural AR is not present).

Hence, TAVI may offer an attractive alternative to SAVR for the prevention of PPM and its ensuing adverse impact on LV mass regression, functional capacity, and survival, particularly in patients with a small aortic annulus.^{51,54,55}

Conduction disturbances following transcatheter aortic valve implantation

The occurrence of conduction disturbances and the need for permanent pacemaker implantation remain a concern. The close proximity of the conduction system to the aortic annulus may lead to a mechanical interaction between the stent frame of the transcatheter valve prosthesis and the left bundle branch which in turn may translate into the occurrence of a left bundle branch block (LBBB) and eventually into a high grade or complete atrio-ventricular block (Figure 8).

The rate of new-onset LBBB following TAVI ranges from 4 to 57%, and is more frequent with the use of the self-expanding CoreValve system (from 38 to 57%) than with the balloon-expandable Edwards SAPIEN valve (from 16 to 28%) (Table 4).^{56–65} The first randomized trial comparing the self- and balloon-expandable systems showed a significantly higher rate of pacemaker implantation after TAVI among patients receiving a CoreValve system (37.6 vs. 17.3%; $P < 0.001$).⁶⁶ The persistence of these conduction abnormalities over time also differs between the two prostheses; whereas more than half of these conduction abnormalities disappear within a few days to months following TAVI with a balloon-expandable valve,^{56,58,63,67} most of these conduction disturbances remain at hospital discharge and at the 1-year follow-up after CoreValve implantation.⁵⁸

The rate of pacemaker implantation following TAVI has been ~6% with the use of the Edwards SAPIEN (ranging from 4 to 13%) and ~25% with the use of the CoreValve system (ranging from 11 to 39%) (Table 5).^{2,24,56,57,60,61,63,68–84} The main reason for pacemaker implantation following TAVI is the occurrence of a high grade or complete atrio-ventricular block followed by severe symptomatic bradycardia.^{56–58,68,69,73,81} However, new-onset persistent LBBB following TAVI has been considered by some centres to be an indication for prophylactic pacemaker implantation and this may partially explain the differences between centres/studies regarding the pacemaker implantation rate.^{56,58,73,81}

The predictive factors of new-onset LBBB following TAVI are summarized in Table 4. The use of the CoreValve system is one of the most important factors associated with a higher rate of conduction disturbances, probably due to the longer stent frame and a deeper implantation of the valve prosthesis in the LV outflow tract. In fact, a lower positioning of the valve prosthesis is another major predictive factor of LBBB following TAVI with both self- and balloon-expandable valves.^{56,58,60,63} Continuous electrocardiographic monitoring for at least 48 h is warranted in patients developing new LBBB following TAVI. The predictive factors for the need of pacemaker implantation following TAVI are similar to those associated with new-onset LBBB and are summarized in Table 5. In addition, a baseline right bundle branch block is one of the most important factors.^{57,68,71,73,76,85}

Various studies evaluated the outcome of patients with new-onset persistent LBBB (Table 6).^{58,59,62–64,67} Houthuizen et al.⁵⁹ reported a higher mortality rate at the 1-year follow-up in these patients

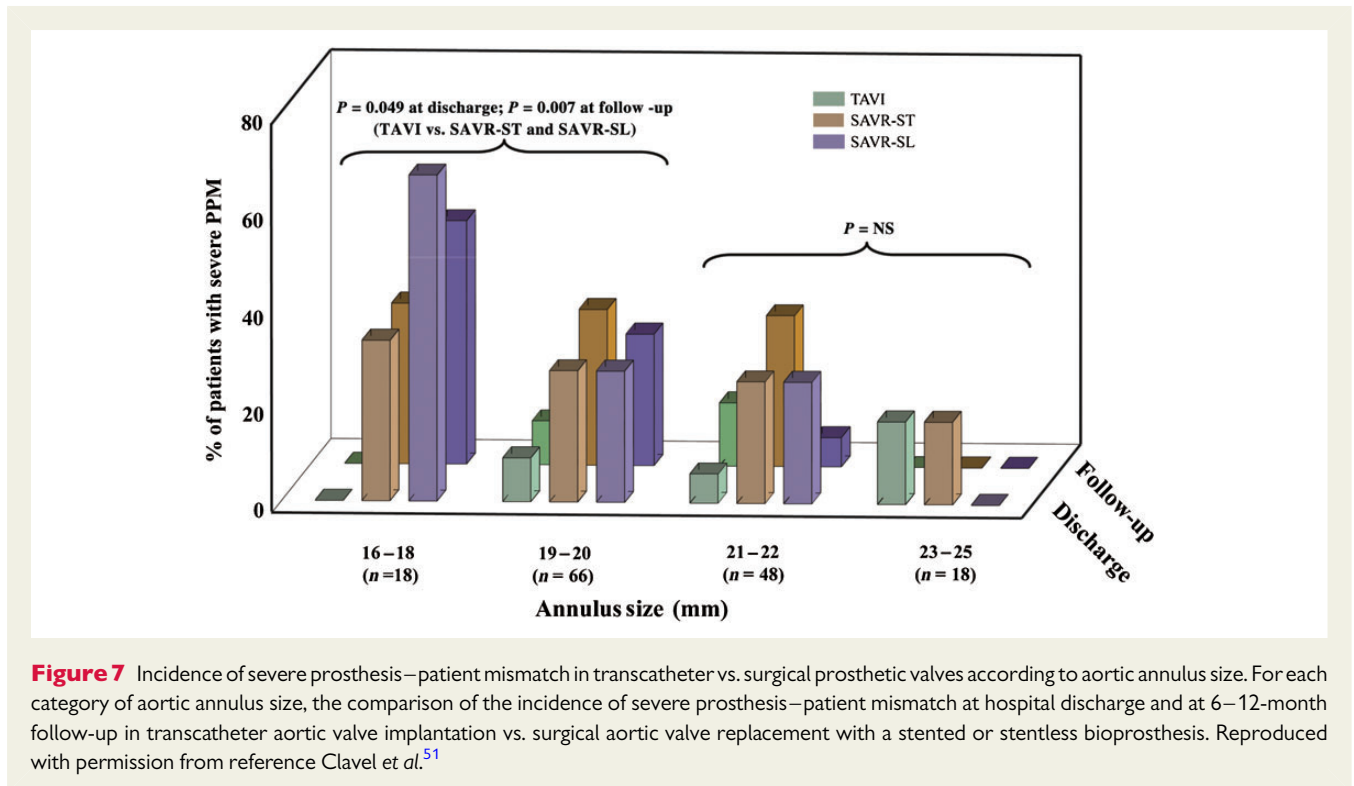


Figure 7 Incidence of severe prosthesis–patient mismatch in transcatheter vs. surgical prosthetic valves according to aortic annulus size. For each category of aortic annulus size, the comparison of the incidence of severe prosthesis–patient mismatch at hospital discharge and at 6–12-month follow-up in transcatheter aortic valve implantation vs. surgical aortic valve replacement with a stented or stentless bioprosthesis. Reproduced with permission from reference Clavel *et al.*⁵¹

($n = 679$, CoreValve in 85%), while other studies (using either balloon- or self-expandable valve systems) showed no difference.^{26,58,62–64,67} The independent predictors of the outcome in patients with new-onset LBBB (including the protective or detrimental effect of pacemaker implantation after TAVI) are currently unclear.

Stroke after transcatheter aortic valve implantation: incidence, mechanism, prevention

Stroke may complicate TAVI during or after the procedure. The PARTNER trial reported an increased CVE rate at 30 days for TAVI compared with medical therapy in inoperable patients (6.7 vs. 1.7%, $P = 0.03$) and compared with SAVR in high-risk patients (5.5 vs. 2.4%, $P = 0.04$).^{77,80} Conversely, Adams *et al.*²⁵ reported no difference in stroke rate in a more recent randomized trial comparing SAVR with CoreValve in high-risk patients. Specifically, CVE rates at 30 days were 3.9 vs. 3.1%, respectively ($P = 0.55$).²⁵ Moreover, growing experience and technical refinements may have resulted in a lower CVE rate after TAVI. A recent meta-analysis with 33 studies including 10 037 patients reported an overall CVE rate at 30 days of 3.3% with rates of 3.1% for retrograde implantation of the CoreValve prosthesis, 4.2% for TF implantation of the Edwards SAPIEN prosthesis and 2.7% for TA implantation of the latter device.⁸⁶ In another meta-analysis of 16 studies comprising 3519 patients treated with both devices, Génèreux *et al.*⁸⁷ reported estimate rates of VARC-defined major stroke, minor stroke, and transient ischaemic attack of 3.2, 1.0, and 1.2%, respectively. Very recently, two meta-analyses comparing TAVI and SAVR reported stroke incidences

of 3.5 vs. 2.8%⁸⁸ and 2.6 vs. 2.3%⁸⁹ for TAVI and SAVR, respectively, suggesting similar risks in high-risk patients regarding stroke.

Most CVE occur within the first month after TAVI with a peak in the acute peri-procedural period, but there is also a non-negligible proportion of late events after 30 days. In cohort A of the PARTNER trial, 15 (75%) of the 20 strokes observed in the first year occurred within 30 days, 10 (67%) of these even within 48 h.⁷⁷ Likewise, 11 (65%) of the 17 strokes in cohort B occurred within 30 days, 5 (45%) of them within 48 h.⁸⁰

Neuro-imaging studies have revealed a high incidence of new, albeit clinically silent cerebral lesions on post-procedural diffusion-weighted MRI (Figure 9) as a surrogate for procedural embolization,^{90,91} and procedural neuro-monitoring using transcranial Doppler has identified direct manipulation of the calcified, native valve during positioning, and implantation of the stent-valves as the main source of procedural emboli.^{92,93} In contrast, subacute and late neurological events seem to have a more thrombotic origin and reflect the background risk of the comorbid TAVI patients.^{94–97} Thrombo-emboli may arise from the implanted stent-valves^{98,99} or may be related to new-onset or chronic atrial fibrillation.¹⁰⁰

Cerebral embolization causing acute CVEs may be prevented by less-traumatic devices, avoidance of extensive manipulations, and active cerebral protection using filters deployed within the brachiocephalic trunk and the left carotid artery¹⁰¹ or porous-membrane deflectors covering the carotid artery ostia in an umbrella-like fashion.^{102,103} While debris is frequently found in these filters,¹⁰⁴ their efficacy in preventing CVEs is unclear. In addition, the deflector devices appear not to reduce the number of patients with new diffusion-weighted MRI lesions but may reduce lesion size. The thrombotic origin of subacute and late neurological events calls for the evaluation of pharmacological measures like

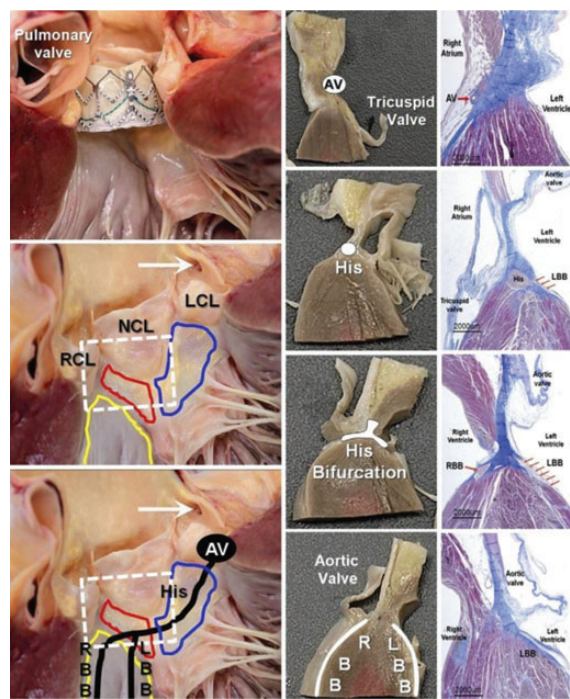


Figure 8 Macroscopic and histological view of the conduction system. A 23 mm Edwards SAPIEN-XT (Edwards Lifesciences, Irvine, CA, USA) placed into a pathological specimen showing the anatomical relationships and conduction system pathways from a macroscopic view (left panels). Blue-line area highlights the aortic-mitral curtain; red-line area highlights the membranous septum; yellow-line area highlights the muscular septum; white arrow highlights the left coronary artery ostium; dashed box represents the virtual space where the transcatheter aortic valve would be placed. The various segments of the atrio-ventricular conduction system are represented in anato-pathological sections of the atrio-ventricular septal junction (central panels). The corresponding histological samples show the fibrous bundles surrounding the several parts of the conduction system (right panels): while the atrio-ventricular node is protected by myofibres and fibrous tissue, the left and right bundle branches are more exposed and have a higher risk of damage by the deployed prosthesis. From Bagur *et al.*,⁶⁸ with permission. AV, atrio-ventricular node; His, His bundle; LBB, left bundle branch; LCL, left coronary leaflet; NCL, non-coronary leaflet; RCL, right coronary leaflet; RBB, right bundle branch.

intensified antiplatelet therapy before and during TAVI and a more aggressive anticoagulation after TAVI.

Antithrombotic treatment in patients undergoing transcatheter aortic valve implantation

Patients undergoing TAVI bear a risk of ischaemic stroke and major bleeds, which are both independent predictors of mortality.¹⁰⁵

Guidelines on antithrombotic therapy for bioprosthetic valve implantation are scarce and no randomized evaluation has been performed to demonstrate what the best strategy is during and after the procedure of TAVI (Table 7).

During TAVI, unfractionated heparin is recommended with a target activated clotting time of 300 s or more because of its ease of use and fast reversal with protamine sulphate.¹⁰⁶ However, there is no evidence showing the relevance of activated clotting time in this specific setting. Bivalirudin is under investigation in the pilot BRAVO (Bivalirudin on Aortic Valve intervention Outcomes) study,¹⁰⁷ although some concerns remain when immediate reversal is required due to life-threatening vascular and bleeding complications in a procedure using large sheaths and closure devices.

After TAVI, the standard of care is the combination of low dose aspirin with a maintenance dose of 75 mg clopidogrel (Table 7),¹⁰⁸ Dual antiplatelet therapy is recommended without clear specifications on loading dose and duration of therapy.^{106,109} In addition, there is no robust evidence demonstrating that early thromboembolic events after TAVI are platelet-mediated. The benefit of clopidogrel may be questioned among elderly patients for several reasons. High on-clopidogrel platelet reactivity is a common finding among elderly.¹¹⁰ The risk of bleeding is increased with dual antiplatelet therapy and the risk of treatment cessation is high.^{111–113} Finally, <1/3 of TAVI patients undergo PCI prior to valve replacement,²⁴ while >1/3 display transient or permanent atrial fibrillation and would require long-term anticoagulation.¹⁰⁰ The ongoing ARTE (Aspirin vs. aspirin + clopidogrel following Transcatheter aortic valve implantation) pilot trial (NCT01559298) which tests the hypothesis of single antiplatelet therapy vs. dual antiplatelet therapy after TAVI in patients not requiring anticoagulation is awaited.¹¹⁴

Atrial fibrillation occurs in up to 40% of the TAVI patients and is associated with a >2-fold increased risk of all-cause and cardiovascular mortality.¹¹⁵ These patients should benefit from long-term anticoagulation therapy, a strategy that is underused, especially in a high CHADS₂-VASc risk score [congestive heart failure or left ventricular dysfunction; hypertension, age ≥75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74, sex category (female)]. Of importance, the benefit of oral anticoagulation with vitamin-K antagonists over dual antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control, which is usually poor in frail patients.¹¹⁶

The clinical challenge is to demonstrate whether an anticoagulation strategy is superior to dual antiplatelet therapy, the standard of care. This is mainly supported by the fact that the vast majority of post-TAVI ischaemic events is cerebrovascular of which atrial fibrillation is a major determinant. Direct oral thrombin/Xa inhibitors which have shown superiority or non-inferiority compared with vitamin-K antagonists to prevent thromboembolic events with a consistent reduction in intracranial bleeds in patients with non-valvular atrial fibrillation should be seen as key players.^{117,118} New P2Y₁₂ inhibitors may also be discussed when coronary stenting is performed in the setting of acute coronary artery disease or alone. Short duration of dual antiplatelet therapy and maintenance of prasugrel or ticagrelor without aspirin should also be investigated to further support the antiplatelet hypothesis as the best antithrombotic regimen after TAVI. Finally, in patients with contraindications for anticoagulation therapy, the use of left atrial appendage closure

Table 4 Predictors of new-onset left bundle branch block following transcatheter aortic valve implantation

Author, no. patients	Valve type	Incidence n (%)	Multivariate predictors
Urena et al., ⁶³ n = 202	Edwards SAPIEN	61 (30.2)	Longer baseline QRS duration ^a Depth of implantation
Aktug et al., ⁵⁶ n = 154	Edwards SAPIEN (n = 82) CoreValve (n = 72)	13 (16) in Edwards SAPIEN 27 (38) in CoreValve	Depth of implantation
Franzoni et al., ⁵⁸ n = 238	Edwards SAPIEN (n = 151) CoreValve (n = 87)	20 (13.5) in Edwards SAPIEN 43 (50) in CoreValve	Use of CoreValve
Khawaja et al., ⁶⁰ n = 185	CoreValve	105 (56.8)	Absence of RBBB Native valve

CABG, coronary artery bypass grafting; CAD, coronary artery disease; RBBB, right bundle branch block.
^aPredictors of a persistent new-onset LBBB.

Table 5 Predictors of permanent pacemaker implantation following transcatheter aortic valve implantation

Author, no. patients	Valve type	In-hospital/30-day incidence n (%)	Multivariate predictors
D'Ancona et al., ⁷² n = 322	Edwards SAPIEN	20 (6.2)	Age
Bagur et al., ⁶⁸ n = 411	Edwards SAPIEN	30 (7.3)	Pre-existing RBBB
Ledwoch et al., ⁷⁶ n = 1147	Edwards SAPIEN (n = 232) CoreValve (n = 912)	33 (14.2) Edwards SAPIEN 352 (38.6) CoreValve	Absence of prior valve surgery Porcelain aorta Core valve
Khawaja et al., ⁶⁰ n = 243	CoreValve	82 (33.3)	Peri-procedural complete AVB Balloon predilatation Prolonged baseline QRS duration 29-mm prosthesis
De Carlo et al., ⁷³ n = 275	CoreValve	66 (24.0)	Depth of implantation Pre-existing RBBB Pre-existing LAHB Longer PR at baseline
Chorianopoulos et al., ⁷¹ n = 130	CoreValve	46 (35.4)	Pre-existing RBBB
Munoz-Garcia et al., ⁸⁵ n = 174	CoreValve	48 (27.6)	Depth of implantation Pre-existing RBBB Use of the traditional system
Calvi et al., ⁵⁷ n = 162	CoreValve	52 (32.1)	Pre-existing RBBB
Siontis et al., ⁶⁵ n = 11 210	CoreValve and Edwards SAPIEN	Median 28% (CoreValve) Median 6% (Edwards SAPIEN)	Male gender Pre-existing first degree AV-block Pre-existing left anterior hemiblock Pre-existing right bundle branch block Intraprocedural AV-block

CAD, coronary artery disease; LAHB, left anterior hemiblock; LVOT, left ventricular outflow tract; RBBB, right bundle branch.

devices may be a feasible therapeutic option that can be performed sequentially to TAVI.

Durability of transcatheter heart valves

Durability of transcatheter heart valves is important, particularly if younger patients will eventually be considered. Durability is

determined by numerous factors including the characteristics of the tissue, tissue treatments, valve design, symmetric leaflet coaptation, and optimal geometry, transvalvular gradients, as well as multiple clinical factors, and patient age. Mechanical stress and collagen fibres disruption of the prosthetic leaflets may favour early calcification of the leaflets and valve degeneration.¹¹⁹ Anticalcification treatment of the leaflets may prevent these degenerative changes. In addition, the pre-crimping process inherent to transcatheter aortic valves may cause structural changes of the collagen and elastic

Table 6 Impact of new-onset left bundle branch block following transcatheter aortic valve implantation on mortality

Author, no. patients	Type of valve	1-year Mortality		
		LBBB (%)	No-LBBB (%)	P value
Urena et al., ⁶³ n = 202	Edwards SAPIEN	16.0	13.0	0.610
Urena et al., ⁶⁴ n = 668	Edwards SAPIEN	11.0	19.9	0.17
Houthuizen et al., ^{59a} n = 679	Edwards SAPIEN (n = 292) CoreValve (n = 387)	26.6	17.5	0.006
Testa et al., ⁶² n = 818	CoreValve	18.7	19.7	0.12
Franzoni et al., ⁵⁸ n = 238	Edwards SAPIEN (n = 151) CoreValve (n = 87)	20	15.4	0.42
Nazif et al., ⁶⁷ n = 1151	Edwards SAPIEN	17.1	18.4	0.67

LBBB, left bundle branch block.

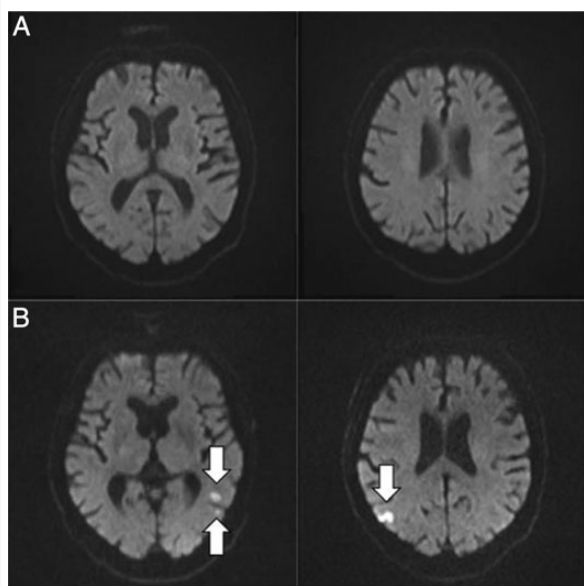
^aIncluded all new-onset LBBB, regardless persistence.

Figure 9 Magnetic resonance imaging to detect cerebral lesions as a surrogate for procedural embolization after TAVI. Pre- (A) and post-interventional (B) diffusion-weighted magnetic resonance imaging of a patient undergoing transfemoral transcatheter aortic valve implantation with new foci of restricted diffusion in the right and left posterior hemisphere (arrows). DW-MRI, diffusion-weighted magnetic resonance imaging.

fibres of the leaflets.¹²⁰ The impact of these changes on the long-term durability of the transcatheter aortic valve is unknown.

In addition, mechanical loading forces, deployed configuration, and axial alignment among other factors may influence frame fatigue and cause stent fracture, as observed with the Melody valve (Medtronic, Inc., MN, USA) implanted in degenerated pulmonary conduits.¹²¹ Stent fractures, however, have not been observed on either rotational angiography or MDCT in two studies including 108 patients with up to 2.5-year follow-up.^{122,123}

The reported mid- and long-term durability of balloon- and self-expandable valves is promising.^{21–24,124,125} In the Canadian multicentre registry (339 patients, data analysed in core laboratory) the aortic valve area (AVA), and transvalvular gradients remained stable during the 4-year follow-up and changes in valve structure or AR severity were not observed.²³ Similarly, in the PARTNER trials, significant changes in valve gradients were not observed during the 2-year follow-up.^{21,22} In 88 patients treated with the Edwards SAPIEN valve, 85 showed stable valve haemodynamics, and 3 (3.4%) patients developed moderate stenosis at the 5-year follow-up.¹²⁶ Similarly, the CoreValve system has been evaluated in several clinical registries showing stable haemodynamic function at the 1- and 2-year follow-up.^{24,124,125} Ussia et al.¹²⁵ reported stable AVA and transvalvular gradients during the 3-year follow-up in 181 patients treated with the CoreValve system and progression of AR or structural valve degeneration were not observed.

The durability of the currently available transcatheter valves appears adequate for the elderly patient with limited life expectancy. The remaining questions are: Will the durability of the transcatheter valves match that of surgical bio-prostheses? Moreover, the durability of the next generation valves needs to be determined.

Transcatheter aortic valve implantation for failing surgical bioprostheses

The number of aortic bioprostheses implanted in patients 65 years and older has tripled in the last 10 years.¹²⁷ The durability is the main concern when using a bioprosthesis. However, a recent large-scale registry (n = 307 054, 36% receiving bioprosthetic aortic valves) demonstrated a re-operation rate of 3.1% at 10 years follow-up.¹²⁷ Wear and tear, calcification, pannus formation, endocarditis, and thrombosis are the most common indications for bioprosthetic heart valve re-operation. For elective procedures and low-surgical risk patients, 30-day mortality rates are reported to range between 2 and 7%.^{128,129} In high-surgical risk patients, especially those with advanced heart failure (New York Heart Association functional class IV) or in need of urgent surgery, the mortality rate

can exceed 20%.¹³⁰ For these patients, transcatheter aortic valve-in-surgical aortic valve (TAV-in-SAV) implantation may be preferred over repeat surgery.¹³¹

A thorough understanding of stented and stentless surgical bioprosthetic valves, their physical characteristics and radiographic appearances on MDCT and fluoroscopy, is necessary for optimal patient selection and transcatheter valve selection, positioning, and deployment.^{132,133}

Several dimensions characterize stented valves but the inner base ring diameter (commonly referred to as the inner stent diameter) has received most attention as it relates to transcatheter aortic valve size selection. Importantly, the geometric orifice diameter permitting blood flow across the bioprosthetic valve, however, can be a few millimetres smaller than the inner stent diameter provided by the

manufacturer owing to the thickness of the leaflets and covering cloth of the base ring that are not taken into consideration. Furthermore, calcification and pannus may further reduce the geometric orifice area. The geometric orifice diameter can be measured on MDCT (Figure 10). It is not uncommon to obtain disparate values between the manufacturer's inner stent diameter and the geometric orifice diameter measured by MDCT; which of these measures is best for transcatheter valve size selection is currently a topic of debate. Sizing charts to help guide TAV-in-SAV procedures are available (<http://www.ubqo.com/viv>).¹³²

The Global Valve-in-Valve registry pooled the results from 202 patients with a mean age of 77 years from 38 centres.¹³¹ Procedural success was obtained in 93% of cases with a 30-day mortality rate of 8.4%. Coronary ostial obstruction was observed in 3.5% of cases.

Table 7 Recommendations for antithrombotic therapy during and after bioprosthetic valves including transcatheter aortic valve implantation

	ACC/AHA/STS ¹⁰⁶	ESC ¹⁰⁹
TAVI		
Procedural	Unfractionated heparin (ACT > 300 s)	Unfractionated heparin (ACT > 300 s)
Post-procedural	Aspirin 75–100 mg indefinitely Clopidogrel 75 mg, for 6 months If vitamin K antagonist indicated, no clopidogrel	Aspirin or clopidogrel indefinitely Aspirin and clopidogrel early after TAVI If vitamin K antagonist indicated, no antiplatelet therapy
Bioprosthetic valves		
Low risk	Aspirin 75–100 mg/day (Class IIa ^b) Vitamin K antagonist INR 2.0–3.0 (Class IIb ^b)	Low dose aspirin (Class IIa ^b) Vitamin K antagonist INR 2.0–3.0 (Class IIb ^c)
High risk	Aspirin 75–100 mg/day (Class IIa ^b) Vitamin K antagonist INR 2.0–3.0 (Class I ^a)	Vitamin K antagonist (target INR 2.5) (Class IC ^a)

ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; ESC, European Society of Cardiology; INR, international normalized ratio. AHA risk factors: atrial fibrillation, left ventricular dysfunction, previous thrombo-embolism, and hypercoagulable condition; ESC risk factors: atrial fibrillation, venous thrombo-embolism, hypercoagulable state, or with a lesser degree of evidence, severely impaired left ventricular dysfunction (ejection fraction ≤35%).

^aClass I: conditions for which there is evidence for and/or general agreement that the procedure or treatment is beneficial, useful, and effective.

^bClass IIa: weight of evidence/opinion is in favour of usefulness/efficacy.

^cClass IIb: usefulness/efficacy is less well established by evidence/opinion.

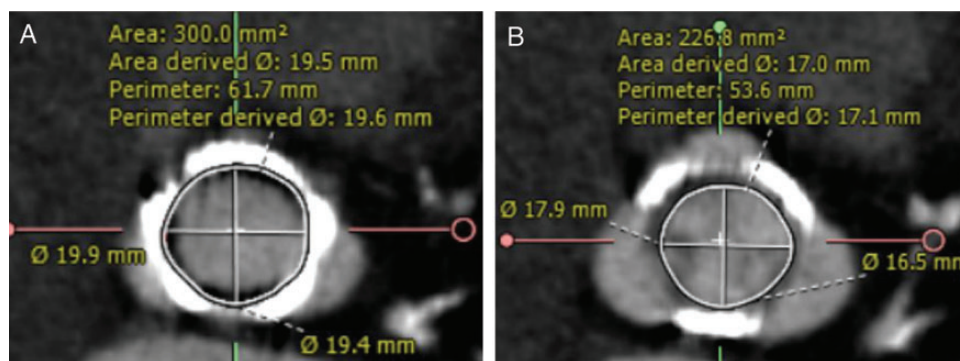


Figure 10 Transcatheter valve-in-valve implantation: multi-detector row computed tomography assessment of internal dimensions of aortic bioprosthesis. Multi-detector row computed tomography permits the measurement of the geometric orifice diameter, area or perimeter from contrast-edge to contrast-edge at the level of the basal ring. (A and B) the inner stent diameters, perimeter, and area of two bioprostheses.

Post-procedure peak and mean trans-prosthetic gradients were 28 ± 14 and 16 ± 9 mmHg, respectively. The mean trans-prosthetic gradient was 5 mmHg lower with the CoreValve system than with the Edwards SAPIEN valve. This may be explained by the supra-annular location of the CoreValve leaflets that promote space efficiency. Based on anecdotal evidence, patients with an internal stent diameter <17 mm should not undergo a TAV-in-SAV procedure due to increased residual gradients.

If these promising results are confirmed in large series, cardiothoracic surgeons may change their practice by implanting bioprostheses that can hold a transcatheter valve device in the future, avoiding a high-risk surgical redo-procedure. However, first, the durability of the transcatheter valves implanted within a bioprosthesis should be demonstrated.

Lessons from transcatheter aortic valve implantation registries: results in clinical practice

Although randomized clinical trials are the foundation to establish evidence-based guidance in patient management, observational studies serve an important complementary role by evaluating novel therapies in routine clinical practice, investigating more complex and diverse patient populations excluded from (or under-represented in) randomized trials (renal failure, atrial fibrillation, and peripheral vascular disease).^{115,134–137}

Both nation-wide registries and valve-specific registries have been reported.^{2–4,4,6,17,19,78,138} Data from these registries confirmed that TAVI improved survival compared with medical treatment alone in patients encountered in routine clinical practice.¹³⁹ Moreover, safety and efficacy were comparable with randomized trials with acceptable complication rates confirming that TAVI is a reasonable treatment option in high-risk patients.^{2,4,25} This was recently confirmed by a multicentre trial randomizing 390 high-risk patients to TAVI (STS-PROM $7.3 \pm 3.0\%$) and 357 to SAVR (STS-PROM $7.5 \pm 3.4\%$).²⁵ Transcatheter aortic valve implantation was associated with a lower mortality rate at 1-year follow-up when compared with SAVR (14.2 vs. 19.1%) representing an absolute risk reduction of 4.9%. Importantly, improved outcomes over time highlighted the learning curve experience as a result of improved patient selection and implantation techniques.¹⁴⁰ More recently, several registries pointed to the inclusion of lower-risk patients with a parallel decrease in peri-procedural complications, indicating a change in practice as a result of ongoing improvements in a device design.^{4,140,141} The registries also allowed to unveil important improvements in the outcome such as the decrease in vascular complications due to small-sized delivery catheters.¹²⁶ Moreover, registries were instrumental to establish TAV-in-SAV implantation as a valuable alternative to redo-operations in patients with failed surgical bioprostheses with important insights as it relates to device selection.¹³¹ Finally, TAVI implantation data from 11 countries including Germany, France, Italy, UK, Spain, the Netherlands, Switzerland, Belgium, Portugal, Denmark, and Ireland between 2007 and 2011 allowed to describe the adoption of this technology across Europe and highlighted important variations related to economic indices and healthcare reimbursement scheme.¹⁴²

To comprehensively define the therapeutic role of TAVI in clinical practice, data from conventional SAVR are desirable as a comparator. However, the patient cohorts undergoing SAVR or TAVI are so different in many critical variables that the statistical analysis of these registries reaches its limits. In the GARY registry, the measured outcome was compared with the outcome results as predicted by the German Aortic Valve (AV) Score.¹⁴³ By using this score in TAVI patients treated in 2011, the expected mortality for the highest risk quartile ($>6\%$ expected in hospital) was 18.6%, but actually amounted to only 16.8%. In parallel, in the highest risk quartile of patients undergoing SAVR, the observed mortality was 9% instead of 17%. These findings highlight that TAVI was at least as good as SAVR in high-risk patients. However, there have also been a considerable number of patients with low-estimated risk undergoing TAVI. This is not necessarily due to inappropriate indications, but may reflect the limitation of the scores (as discussed in the paragraph on risk scores, see Part 1).

Future: expanding indications for aortic regurgitation

The results of the first randomized controlled trials not only allowed us to appreciate the efficacy and the potential of TAVI treatment but also revealed the limitations of the technology demonstrating a relatively high incidence of vascular and neurological complications.^{21,144} Over the recent years, an effort has been made to develop new valves and TAVI-enabling devices that would overcome the initial limitations of TAVI technology, facilitate the procedure and reduce considerably the risk of complications.¹⁴⁵ The technological advancements and recent evidence from small-scale studies in low-risk patients have created promise that TAVI may have a value in the future for the treatment of lower-risk surgical subjects.^{140,141,146} This potential is currently being explored by two randomized clinical trials which have recently commenced and aim at comparing the efficacy of TAVI and SAVR in intermediate-risk patients: the Placement of Aortic Transcatheter Valves (PARTNER) II Cohort A¹⁴⁷ and the SURgical and Transcatheter Aortic Valve Implantation (SURTAVI) trial (Figure 1).¹⁴⁸ The PARTNER II Cohort A study is a non-inferiority study that is anticipated to recruit 2000 patients with an estimated STS risk score $\geq 4\%$ who will be randomized to TAVI with an Edward SAPIEN-XT device and SAVR at 1:1 basis and will be followed up for 2 years.¹⁴⁷ The primary endpoint of the study is the combined endpoint of all-cause mortality and stroke. The SURTAVI is also a non-inferiority study that aims to randomize 2500 patients with an STS score $\geq 4\%$ and $\leq 10\%$ to TAVI with a CoreValve or SAVR at 1:1 basis.¹⁴⁸ The patients will be followed up for 5 years and the primary endpoint is the combined endpoint of all-cause mortality and disabling stroke (modified Rankin Scale ≥ 2).

Two recently published small-scale studies have examined the efficacy of TAVI in patient with pure AR.^{149,150} The first included 43 patients who underwent TAVI with the CoreValve prosthesis and reported a relatively low VARC-success rate of 74.4% that was due to the increased incidence of post-procedural AR (nine patients had post-procedural AR grade 2–3).¹⁴⁹ The low success rate was attributed to the complexity of the anatomy of the aortic valve, the aortic dilation noted in this setting and the absence of valve calcification that could serve as a landmark and could facilitate optimal device

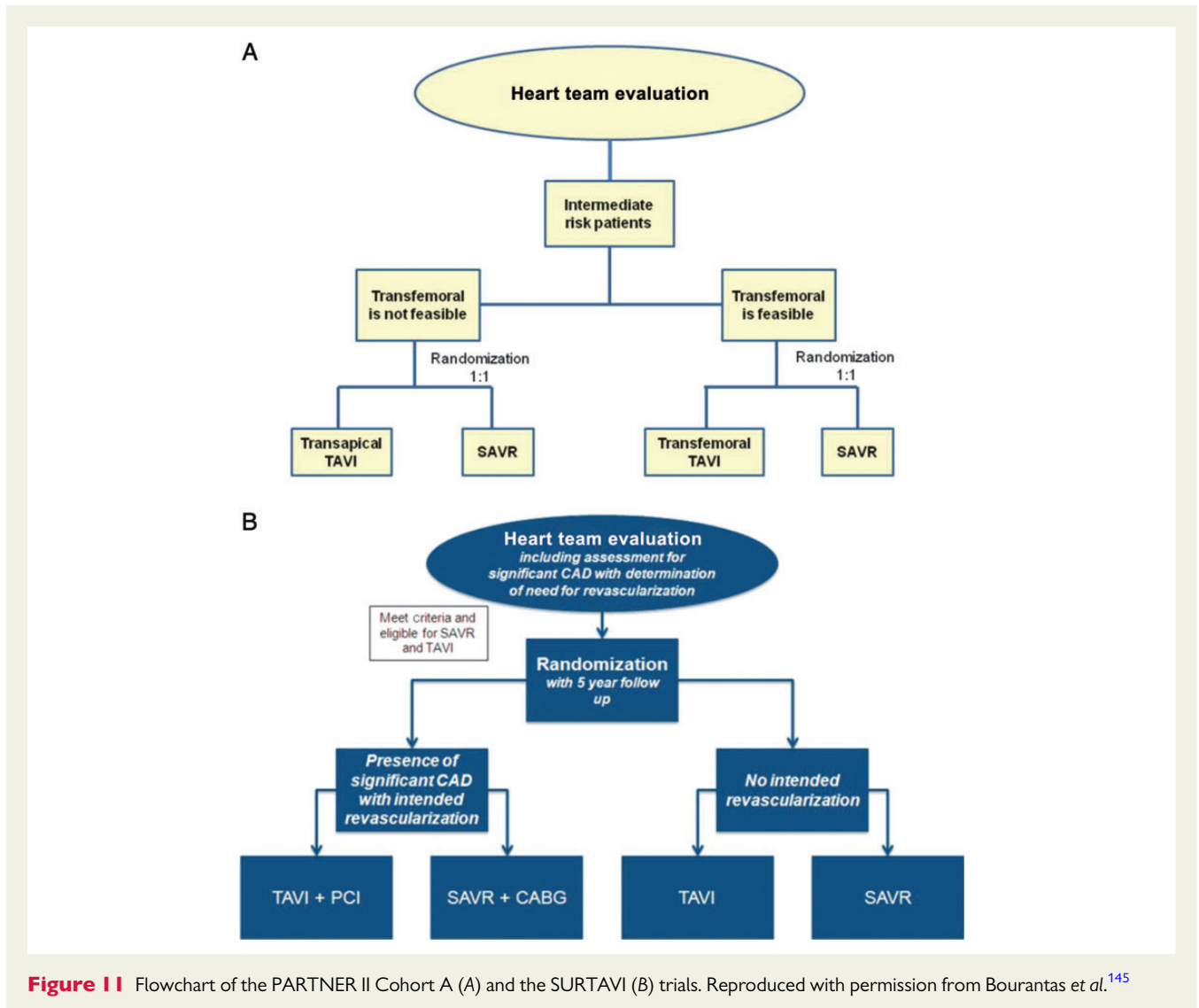


Figure 11 Flowchart of the PARTNER II Cohort A (A) and the SURTAVI (B) trials. Reproduced with permission from Bourantas *et al.*¹⁴⁵

positioning. To address these challenges, Seiffert *et al.*¹⁵⁰ proposed the use of the Jena Valve prosthesis (JenaValve Technology GmbH, Munich, Germany) which is repositionable and includes a clip-fixation mechanism for optimal positioning. More robust evidence is needed and further research is required to define the valve anatomy that is suitable for TAVI and how to perform optimal prosthesis sizing.

Conclusion

In this review, procedure-related issues and uncertainties in outcomes after TAVI were addressed. The different access sites were discussed and with the increasing possibilities, algorithms are needed to tailor the access to the individual patient. An important complication is the occurrence of AR after TAVI, and the severity appears related to the outcome. There is however no consensus on accurate and reproducible quantification of AR. The occurrence of PPM and conduction disturbances has an impact on symptoms, LV function and outcome. Early CVE after TAVI appear related to manipulation of the calcified, native valve during implantation, whereas late CVE

(>30 days) are related to atrial fibrillation, and this underscores the importance of optimal anticoagulation therapy after TAVI. Currently, dual antiplatelet therapy is the standard of care, but the safety and efficacy of alternative anti-coagulative therapies needs prospective evaluation.

The durability of current transcatheter prostheses at the 5-year follow-up has been demonstrated but longer-term follow-up data are needed. Recently, the feasibility of valve-in-valve procedures has been explored, and may become the therapy of choice in degenerative bioprosthetic valves, once the long-term outcome has been provided.

Finally, expansion of TAVI to low-risk populations and pure AR will be explored in various prospective studies.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: N.P. is proctor and consultant for Medtronic, P.M. is proctor for Edwards Lifesciences, J.W. disclosed consultant

fees from Edwards Lifesciences, V.D. disclosed consulting fees from Medtronic and St. Jude Medical, speaking fees from Abbott Vascular. A.P.K. is member of the steering committee of the SURTAVI trial, P.P. has research contract with Edwards Lifesciences and V-Wave Ltd., C.H. is advisor to Medtronic and received speaker fees from Abbott Vascular and Edwards Lifesciences, M.T. is advisor to Edwards Lifesciences, Alec Vahanian received speakers fees from Edwards Lifesciences, H.B. received speaker and consultant fees for Edwards Lifesciences, Direct Flow Medical, Abbott Vascular and Actelion, J.R.-C. received consulting fees from Edwards Lifesciences and St. Jude Medical, V.B. is consultant for Edwards, Medtronic and St. Jude Medical. J.P.C. received research grants from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, Guerbet Medical, Medtronic, Boston Scientific, Cordis, Stago, Centocor, Fondation de France, INSERM, Fédération Française de Cardiologie et Société Française de Cardiologie. The remaining authors have nothing to disclose. The Department of Cardiology of the Leiden University Medical Center received research grants from Medtronic, Boston Scientific and Biotronik. The Department of Cardiac Imaging of the University Hospital Ramon y Cajal received research grants from Philips Healthcare, Siemens and Toshiba. The Department of Cardiology of the Bern University Hospital received research grants from Biotronik and Edwards Lifesciences.

References

- Bax JJ, Delgado V, Bapat V, Baumgartner H, Collet JP, Erbel R, Hamm C, Kappetein AP, Leipsic J, Leon MB, MacCarthy P, Piazza N, Pibarot P, Roberts WC, Rodés-Cabau J, Serruys PW, Thomas M, Vahanian A, Webb J, Zamorano JL, Windecker S. Open issues in transcatheter aortic valve implantation. Part 1: patient selection and treatment strategy for transcatheter aortic valve implantation. *Eur Heart J* 2014; doi:10.1093/eurheartj/ehu256.
- Gilard M, Eltchaninoff H, Lung B, Donzeau-Gogue P, Chevreul K, Fajadet J, Leprince P, Leguerrier A, Lieve M, Prat A, Teiger E, Lefevre T, Himbert D, Tchetché D, Carrie D, Albat B, Cribier A, Rioufol G, Sudre A, Blanchard D, Collet F, Dos SP, Meneveau N, Tirouvanziam A, Caussin C, Guyon P, Bosch J, Le BH, Collart F, Houel R, Delpine S, Souteyrand G, Favereau X, Ohlmann P, Doisy V, Grollier G, Gommeaux A, Claudel JP, Bourlon F, Bertrand B, Van BE, Laskar M. Registry of transcatheter aortic-valve implantation in high-risk patients. *N Engl J Med* 2012;**366**:1705–1715.
- Moat NE, Ludman P, de Belder MA, Bridgewater B, Cunningham AD, Young CP, Thomas M, Kovac J, Spyt T, MacCarthy PA, Wendler O, Hildick-Smith D, Davies SW, Trivedi U, Blackman DJ, Levy RD, Brecker SJ, Baumbach A, Daniel T, Gray H, Mullen MJ. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the UK TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. *J Am Coll Cardiol* 2011;**58**:2130–2138.
- Mack MJ, Brennan JM, Brindis R, Carroll J, Edwards F, Grover F, Shahian D, Tuzcu EM, Peterson ED, Rumsfeld JS, Hewitt K, Shewan C, Michaels J, Christensen B, Christian A, O'Brien S, Holmes D. Outcomes following transcatheter aortic valve replacement in the United States. *JAMA* 2013;**310**:2069–2077.
- Khatri PJ, Webb JG, Rodes-Cabau J, Fremes SE, Ruel M, Lau K, Guo H, Wijeyesundera HC, Ko DT. Adverse effects associated with transcatheter aortic valve implantation: a meta-analysis of contemporary studies. *Ann Intern Med* 2013;**158**:35–46.
- Thomas M, Schymik G, Walther T, Himbert D, Lefevre T, Treede H, Eggebrecht H, Rubino P, Colombo A, Lange R, Schwarz RR, Wendler O. One-year outcomes of cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation* 2011;**124**:425–433.
- Bapat V, Thomas M, Hancock J, Wilson K. First successful trans-catheter aortic valve implantation through ascending aorta using Edwards SAPIEN THV system. *Eur J Cardiothorac Surg* 2010;**38**:811–813.
- Bauernschmitt R, Schreiber C, Bleiziffer S, Ruge H, Mazzitelli D, Hutter A, Tassani P, Lange R. Transcatheter aortic valve implantation through the ascending aorta: an alternative option for no-access patients. *Heart Surg Forum* 2009;**12**:E63–E64.
- Bapat V, Khawaja MZ, Attia R, Narayana A, Wilson K, Macgillivray K, Young C, Hancock J, Redwood S, Thomas M. Transaortic transcatheter aortic valve implantation using Edwards SAPIEN valve: a novel approach. *Catheter Cardiovasc Interv* 2012;**79**:733–740.
- Bruschi G, De MF, Botta L, Cannata A, Oreglia J, Colombo P, Barosi A, Colombo T, Nonini S, Paino R, Klugmann S, Martinelli L. Direct aortic access for transcatheter self-expanding aortic bioprosthetic valves implantation. *Ann Thorac Surg* 2012;**94**:497–503.
- Bapat VN, Bruschi G. Transaortic access is the key to success. *EuroIntervention* 2013;**9**(Suppl):S25–S32.
- Bapat VN, Attia RQ, Thomas M. Distribution of calcium in the ascending aorta in patients undergoing transcatheter aortic valve implantation and its relevance to the transaortic approach. *JACC Cardiovasc Interv* 2012;**5**:470–476.
- Bojara W, Mumme A, Gerckens U, Lindstaedt M, Gotzmann M, Germing A, Fritz M, Pennekamp W, Mugge A. Implantation of the CoreValve self-expanding valve prosthesis via a subclavian artery approach: a case report. *Clin Res Cardiol* 2009;**98**:201–204.
- Grube E, Laborde JC, Gerckens U, Felderhoff T, Sauren B, Buellesfeld L, Mueller R, Menichelli M, Schmidt T, Zickmann B, Iversen S, Stone GW. Percutaneous implantation of the CoreValve self-expanding valve prosthesis in high-risk patients with aortic valve disease: the Siegburg first-in-man study. *Circulation* 2006;**114**:1616–1624.
- Ruge H, Lange R, Bleiziffer S, Hutter A, Mazzitelli D, Will A, Schreiber C, Laborde JC, Bauernschmitt R. First successful aortic valve implantation with the CoreValve ReValving System via right subclavian artery access: a case report. *Heart Surg Forum* 2008;**11**:E323–E324.
- Petronio AS, De Carlo M, Bedogni F, Marzocchi A, Klugmann S, Maisano F, Ramondo A, Ussia GP, Etori F, Poli A, Brambilla N, Saia F, De Marco F, Colombo A. Safety and efficacy of the subclavian approach for transcatheter aortic valve implantation with the CoreValve revalving system. *Circ Cardiovasc Interv* 2010;**3**:359–366.
- Chieffo A, Buchanan GL, Van Mieghem NM, Tchetché D, Dumonteil N, Latib A, van der Boon RM, Vahdat O, Marcheix B, Farah B, Serruys PW, Fajadet J, Carrie D, de Jaegere PP, Colombo A. Transcatheter aortic valve implantation with the Edwards SAPIEN versus the Medtronic CoreValve Revalving system devices: a multicenter collaborative study: the PRAGMATIC Plus Initiative (Pooled-Rotterdam-Milano-Toulouse In Collaboration). *J Am Coll Cardiol* 2013;**61**:830–836.
- D'Onofrio A, Salizzoni S, Agrifoglio M, Cota L, Luzi G, Tartara PM, Cresce GD, Aiello M, Savini C, Cassese M, Cerillo A, Punta G, Cioni M, Gabbieri D, Zanchettin C, Agostinelli A, Mazzaro E, Di Gregorio O, Gatti G, Faggian G, Filippini C, Rinaldi M, Gerosa G. Medium term outcomes of transapical aortic valve implantation: results from the Italian registry of trans-apical aortic valve implantation. *Ann Thorac Surg* 2013;**96**:830–836.
- Di Mario C, Eltchaninoff H, Moat N, Goicolea J, Ussia GP, Kala P, Wenaweser P, Zembala M, Nickenig G, Alegria BE, Snow T, Lung B, Zamorano P, Schuler G, Corti R, Alfieri O, Prendergast B, Ludman P, Windecker S, Sabate M, Gilard M, Witowski A, Danenberg H, Schroeder E, Romeo F, Macaya C, Derumeaux G, Maggioni A, Tavazzi L. The 2011–12 pilot European Sentinel Registry of Transcatheter Aortic Valve Implantation: in-hospital results in 4571 patients. *EuroIntervention* 2013;**8**:1362–1371.
- Hamm CW, Mollmann H, Holzhey D, Beckmann A, Veit C, Figulla HR, Cremer J, Kuck KH, Lange R, Zahn R, Sack S, Schuler G, Walther T, Beyersdorf F, Bohm M, Heusch G, Funkat AK, Meinertz T, Neumann T, Papoutsis K, Schneider S, Welz A, Mohr FW. The German Aortic Valve Registry (GARY): in-hospital outcome. *Eur Heart J* 2014;**35**:1588–1598.
- Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, Fontana GP, Dewey TM, Thourani VH, Pichard AD, Fischbein M, Szeto WY, Lim S, Greason KL, Teirstein PS, Malaisrie SC, Douglas PS, Hahn RT, Whisenant B, Zajarias A, Wang D, Akin JJ, Anderson WN, Leon MB. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2012;**366**:1686–1695.
- Makkar RR, Fontana GP, Jilaihawi H, Kapadia S, Pichard AD, Douglas PS, Thourani VH, Babaliaros VC, Webb JG, Herrmann HC, Bavaria JE, Kodali S, Brown DL, Bowers B, Dewey TM, Svensson LG, Tuzcu M, Moses JW, Williams MR, Siegel RJ, Akin JJ, Anderson WN, Pocock S, Smith CR, Leon MB. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med* 2012;**366**:1696–1704.
- Rodes-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Osten M, Feindel CM, Natarajan MK, Velianou JL, Martucci G, Devarenes B, Chisholm R, Peterson M, Thompson CR, Wood D, Toggweiler S, Gurvitch R, Lichtenstein SV, Doyle D, Delarochelliere R, Teoh K, Chu V, Bainey K, Lachapelle K, Cheema A, Latter D, Dumesnil JG, Pibarot P, Horlick E. Long-term outcomes after transcatheter aortic valve implantation: insights on prognostic factors and valve durability from the Canadian multicenter experience. *J Am Coll Cardiol* 2012;**60**:1864–1875.
- Tamburino C, Capodanno D, Ramondo A, Petronio AS, Etori F, Santoro G, Klugmann S, Bedogni F, Maisano F, Marzocchi A, Poli A, Antonucci D, Napodano M, De CM, Fiorina C, Ussia GP. Incidence and predictors of early and

- late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. *Circulation* 2011;**123**:299–308.
25. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J Jr, Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014;**370**:1790–1798.
 26. Linke A, Wenaweser P, Gerckens U, Tamburino C, Bosmans J, Bleiziffer S, Blackman DJ, Schaefer U, Müller R, Sievert H, Sondergaard L, Klugmann S, Hoffmann R, Tchetché D, Colombo A, Legrand VM, Edogni F, Eprince P, Chuler G, Azzitelli D, Ftychiou C, Rerker C, Oekstegers P, Indecker S, Mohr FW, Woitek F, Lange R, Bauernschmitt R, Brecker S. Treatment of aortic stenosis with a self-expanding transcatheter valve: the International Multi-centre ADVANCE Study. *Eur Heart J* 2014; doi: 10.1093/eurheartj/ehu162.
 27. Popma JJ, Adams DH, Reardon MJ, Yakubov SJ, Kleiman NS, Heimansohn D, Hermiller J Jr, Hughes GC, Harrison JK, Coselli J, Diez J, Kafi A, Schreiber T, Gleason TG, Conte J, Buchbinder M, Deeb GM, Carabello B, Serruys PW, Chenoweth S, Oh J. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. *J Am Coll Cardiol* 2014;**63**:1972–1981.
 28. Athappan G, Patvardhan E, Tuzcu EM, Svensson LG, Lemos PA, Fracaro C, Tarantini G, Sinning JM, Nickenig G, Capodanno D, Tamburino C, Latib A, Colombo A, Kapadia SR. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. *J Am Coll Cardiol* 2013;**61**:1585–1595.
 29. Colli A, D'Amico R, Kempfert J, Borger MA, Mohr FW, Walther T. Transesophageal echocardiographic scoring for transcatheter aortic valve implantation: impact of aortic cusp calcification on postoperative aortic regurgitation. *J Thorac Cardiovasc Surg* 2011;**142**:1229–1235.
 30. Delgado V, Ng AC, Shanks M, van der Kley F, Schuijff JD, van de Veire NR, Kroft L, de Roos A, Schaliij MJ, Bax JJ. Transcatheter aortic valve implantation: role of multimodality cardiac imaging. *Expert Rev Cardiovasc Ther* 2010;**8**:113–123.
 31. Detaint D, Lepage L, Himbert D, Brochet E, Messika-Zeitoun D, Lung B, Vahanian A. Determinants of significant paravalvular regurgitation after transcatheter aortic valve: implantation impact of device and annulus incongruence. *JACC Cardiovasc Interv* 2009;**2**:821–827.
 32. Ewe SH, Ng AC, Schuijff JD, van der Kley F, Colli A, Palmen M, de Weger A, Marsan NA, Holman ER, de Roos A, Schaliij MJ, Bax JJ, Delgado V. Location and severity of aortic valve calcium and aortic regurgitation after transcatheter aortic valve implantation. *Am J Cardiol* 2011;**108**:1470–1477.
 33. Haensig M, Lehmkühl L, Rastan AJ, Kempfert J, Mukherjee C, Gutberlet M, Holzhey DM, Mohr FW. Aortic valve calcium scoring is a predictor of significant paravalvular aortic insufficiency in transapical-aortic valve implantation. *Eur J Cardiothorac Surg* 2012;**41**:1234–1240.
 34. Hayashida K, Bouvier E, Lefevre T, Hovasse T, Morice MC, Chevalier B, Romano M, Garot P, Mylotte D, Farge A, Donzeau-Gouge P, Cormier B. Impact of CT-guided valve sizing on post-procedural aortic regurgitation in transcatheter aortic valve implantation. *EuroIntervention* 2012;**8**:546–555.
 35. Jilaihawi H, Chin D, Spyt T, Jeilan M, Vasa-Nicotera M, Bence J, Logtens E, Kovac J. Prosthesis-patient mismatch after transcatheter aortic valve implantation with the Medtronic-Corevalve bioprosthesis. *Eur Heart J* 2010;**31**:857–864.
 36. John D, Buellesfeld L, Yuceel S, Mueller R, Latsios G, Beucher H, Gerckens U, Grube E. Correlation of device landing zone calcification and acute procedural success in patients undergoing transcatheter aortic valve implantations with the self-expanding CoreValve prosthesis. *JACC Cardiovasc Interv* 2010;**3**:233–243.
 37. Katsanos S, Ewe SH, Debonnaire P, van der Kley F, de WA, Palmen M, Scholte AJ, Schaliij MJ, Bax JJ, Marsan NA, Delgado V. Multidetector row computed tomography parameters associated with paravalvular regurgitation after transcatheter aortic valve implantation. *Am J Cardiol* 2013;**112**:1800–1806.
 38. Leber AW, Eichinger W, Rieber J, Lieber M, Schlegler S, Ebersberger U, Deichstetter M, Vogel J, Helmberger T, Antoni D, Riess G, Hoffmann E, Kasel AM. MSCT guided sizing of the Edwards Sapien XT TAVI device: impact of different degrees of oversizing on clinical outcome. *Int J Cardiol* 2013;**168**:2658–2664.
 39. Sherif MA, Abdel-Wahab M, Stocker B, Geist V, Richardt D, Tolg R, Richardt G. Anatomic and procedural predictors of paravalvular aortic regurgitation after implantation of the Medtronic CoreValve bioprosthesis. *J Am Coll Cardiol* 2010;**56**:1623–1629.
 40. Unbehaun A, Pasic M, Dreyse S, Drews T, Kukucka M, Mladenow A, Ivanitskaja-Kuhn E, Hetzer R, Buz S. Transapical aortic valve implantation incidence and predictors of paravalvular leakage and transvalvular regurgitation in a series of 358 patients. *J Am Coll Cardiol* 2012;**59**:211–221.
 41. Willson AB, Webb JG, LaBounty TM, Achenbach S, Moss R, Wheeler M, Thompson C, Min JK, Gurvitch R, Norgaard BL, Hague CJ, Toggweiler S, Binder R, Freeman M, Poulter R, Poulsen S, Wood DA, Leipzig J. 3-dimensional aortic annular assessment by multidetector computed tomography predicts moderate or severe paravalvular regurgitation after transcatheter aortic valve replacement: a multicenter retrospective analysis. *J Am Coll Cardiol* 2012;**59**:1287–1294.
 42. Sinning JM, Hammerstingl C, Vasa-Nicotera M, Adenauer V, Lema Cachiguango SJ, Scheer AC, Hausen S, Sedaghat A, Ghanem A, Müller C, Grube E, Nickenig G, Werner N. Aortic regurgitation index defines severity of peri-prosthetic regurgitation and predicts outcome in patients after transcatheter aortic valve implantation. *J Am Coll Cardiol* 2012;**59**:1134–1141.
 43. Sellers RD, Levy MJ, Amplatz K, Lillehei CW. Left retrograde cardioangiography in acquired cardiac disease: technic, indications and interpretations in 700 cases. *Am J Cardiol* 1964;**14**:437–447.
 44. Kappetein AP, Head SJ, Genereux P, Piazza N, Van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodes-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol* 2012;**60**:1438–1454.
 45. Zamorano JL, Badano LP, Bruce C, Chan KL, Goncalves A, Hahn RT, Keane MG, La CG, Monaghan MJ, Nihoyannopoulos P, Silvestry FE, Vanoverschelde JL, Gillam LD, Vahanian A, Di BV, Buck T. EAE/ASE recommendations for the use of echocardiography in new transcatheter interventions for valvular heart disease. *Eur J Echocardiogr* 2011;**12**:557–584.
 46. Goncalves A, Almeria C, Marcos-Alberca P, Feltes G, Hernandez-Antolin R, Rodriguez E, Cardoso JC, Macaya C, Zamorano JL. Three-dimensional echocardiography in paravalvular aortic regurgitation assessment after transcatheter aortic valve implantation. *J Am Soc Echocardiogr* 2012;**25**:47–55.
 47. Sherif MA, Abdel-Wahab M, Beurich HW, Stocker B, Zachow D, Geist V, Tolg R, Richardt G. Haemodynamic evaluation of aortic regurgitation after transcatheter aortic valve implantation using cardiovascular magnetic resonance. *EuroIntervention* 2011;**7**:57–63.
 48. Sinning JM, Werner N, Nickenig G, Grube E. Challenges in transcatheter valve treatment: aortic regurgitation after transcatheter aortic valve implantation. *EuroIntervention* 2013;**9**(Suppl):S72–S76.
 49. Pibarot P, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management. *Circulation* 2009;**119**:1034–1048.
 50. Head SJ, Mokhles MM, Osnabrugge RL, Pibarot P, Mack MJ, Takkenberg JJ, Bogers AJ, Kappetein AP. The impact of prosthesis-patient mismatch on long-term survival after aortic valve replacement: a systematic review and meta-analysis of 34 observational studies comprising 27 186 patients with 133 141 patient-years. *Eur Heart J* 2012;**33**:1518–1529.
 51. Clavel MA, Webb JG, Pibarot P, Altwegg L, Dumont E, Thompson C, De LR, Doyle D, Masson JB, Bergeron S, Bertrand OF, Rodes-Cabau J. Comparison of the hemodynamic performance of percutaneous and surgical bioprostheses for the treatment of severe aortic stenosis. *J Am Coll Cardiol* 2009;**53**:1883–1891.
 52. Ewe SH, Muratori M, Delgado V, Pepi M, Tamborini G, Fusini L, Klautz RJ, Gripari P, Bax JJ, Fusari M, Schaliij MJ, Marsan NA. Hemodynamic and clinical impact of prosthesis-patient mismatch after transcatheter aortic valve implantation. *J Am Coll Cardiol* 2011;**58**:1910–1918.
 53. Pibarot P, Hahn RT, Weissman NJ, Stewart WJ, Lindman BR, Svensson L, Herrmann HC, Mack M, Lim S, Thourani V, Webb J, Miller DC, McAndrew T, Kodali S, Douglas PS, Leon MB. Predictors of impact of prosthesis-patient mismatch following transcatheter aortic valve replacement: a PARTNER trial cohort A analysis. *J Am Soc Echocardiogr* 2013;**26**:B9 (abstract).
 54. Pibarot P, Weissman NJ, Stewart WJ, Hahn RT, Hueter I, Kodali S, Mack M, Thourani V, Miller DC, Svensson L, Herrmann HC, Smith C, Douglas PS, Leon MB. Reduced incidence of prosthesis-patient mismatch and its sequelae in transcatheter versus surgical valve replacement in high-risk patients with severe aortic stenosis: a PARTNER trial cohort A analysis. *J Am Coll Cardiol* 2013;**61**:E1865 (abstract).
 55. Kukucka M, Pasic M, Dreyse S, Mladenow A, Habazettl H, Hetzer R, Unbehaun A. Patient-prosthesis mismatch after transapical aortic valve implantation: incidence and impact on survival. *J Thorac Cardiovasc Surg* 2013;**145**:391–397.
 56. Aktug O, Dohmen G, Brehmer K, Koos R, Altiok E, Deserno V, Herpertz R, Autschbach R, Marx N, Hoffmann R. Incidence and predictors of left bundle branch block after transcatheter aortic valve implantation. *Int J Cardiol* 2012;**160**:26–30.
 57. Calvi V, Conti S, Pruiti GP, Capodanno D, Puzangara E, Tempio D, Di GA, Ussia GP, Tamburino C. Incidence rate and predictors of permanent pacemaker implantation after transcatheter aortic valve implantation with self-expanding CoreValve prosthesis. *J Interv Card Electrophysiol* 2012;**34**:189–195.
 58. Franzoni I, Latib A, Maisano F, Costopoulos C, Testa L, Figini F, Giannini F, Basavarajiah S, Mussardo M, Slavich M, Taramasso M, Cioni M, Longoni M, Ferrarello S, Radinovic A, Sala S, Ajello S, Sticchi A, Giglio M, Agricola E, Chieffo A, Montorfano M, Alfieri O, Colombo A. Comparison of incidence and

- predictors of left bundle branch block after transcatheter aortic valve implantation using the CoreValve versus the Edwards valve. *Am J Cardiol* 2013;**112**:554–559.
59. Houthuizen P, Van Garsse LA, Poels TT, deJP, van der Boon RM, Swinkels BM, Ten Berg JM, van der Kley F, Schaliij MJ, Baan J Jr, Cocchieri R, Brueren GR, van Straten AH, den HP, Bentala M, van OV, Kluijn J, Stella PR, Prins MH, Maessen JG, Prinzen FW. Left bundle-branch block induced by transcatheter aortic valve implantation increases risk of death. *Circulation* 2012;**126**:720–728.
 60. Khawaja MZ, Rajani R, Cook A, Khavandi A, Moynagh A, Chowdhary S, Spence MS, Brown S, Khan SQ, Walker N, Trivedi U, Hutchinson N, De Belder AJ, Moat N, Blackman DJ, Levy RD, Manoharan G, Roberts D, Khogali SS, Crean P, Brecker SJ, Baumbach A, Mullen M, Laborde JC, Hildick-Smith D. Permanent pacemaker insertion after CoreValve transcatheter aortic valve implantation: incidence and contributing factors (the UK CoreValve Collaborative). *Circulation* 2011;**123**:951–960.
 61. Laynez A, Ben-Dor I, Barbash IM, Hauvieu C, Sardi G, Maluenda G, Xue Z, Satler LF, Pichard AD, Lindsay J, Waksman R. Frequency of conduction disturbances after Edwards SAPIEN percutaneous valve implantation. *Am J Cardiol* 2012;**110**:1164–1168.
 62. Testa L, Latib A, De MF, De Carlo M, Agnifili M, Latini RA, Petronio AS, Ettore F, Poli A, De SS, Ramondo A, Napodano M, Klugmann S, Ussia GP, Tamburino C, Brambilla N, Colombo A, Bedogni F. Clinical impact of persistent left bundle-branch block after transcatheter aortic valve implantation with CoreValve Revalving System. *Circulation* 2013;**127**:1300–1307.
 63. Urena M, Mok M, Serra V, Dumont E, Nombela-Franco L, Delarochelliere R, Doyle D, Igual A, Larose E, Amat-Santos I, Cote M, Cuellar H, Pibarot P, de JP, Philippon F, Garcia del BB, Rodes-Cabau J. Predictive factors and long-term clinical consequences of persistent left bundle branch block following transcatheter aortic valve implantation with a balloon-expandable valve. *J Am Coll Cardiol* 2012;**60**:1743–1752.
 64. Urena M, Webb JG, Cheema A, Serra V, Toggweiler S, Barbanti M, Cheung A, Ye J, Dumont E, Delarochelliere R, Doyle D, Al Lawati HA, Peterson M, Chisholm R, Igual A, Ribeiro HB, Nombela-Franco L, Philippon F, Garcia del BB, Rodes-Cabau J. Impact of new-onset persistent left bundle branch block on late clinical outcomes in patients undergoing transcatheter aortic valve implantation with a balloon-expandable valve. *JACC Cardiovasc Interv* 2014;**7**:128–136.
 65. Siontis G, Juni P, Pilgrim T, Stortecky S, Buellesfeld L, Meier B, Wenaweser P, Windecker S. Predictors of permanent pacemaker implantation in patients with severe aortic stenosis undergoing TAVR: a meta-analysis. *J Am Coll Cardiol* 2014;**64**:129–140.
 66. Abdel-Wahab M, Mehili J, Frerker C, Neumann FJ, Kurz T, Tolg R, Zachow D, Guerra E, Massberg S, Schafer U, El-Mawardi M, Richardt G. Comparison of balloon-expandable vs self-expandable valves in patients undergoing transcatheter aortic valve replacement: the CHOICE randomized clinical trial. *JAMA* 2014;**311**:1503–1514.
 67. Nazif TM, Williams MR, Hahn RT, Kapadia S, Babaliaros V, Rodes-Cabau J, Szeto WY, Jilali H, Fearon WF, Dvir D, Dewey TM, Makkar RR, Xu K, Dizon JM, Smith CR, Leon MB, Kodali SK. Clinical implications of new-onset left bundle branch block after transcatheter aortic valve replacement: analysis of the PARTNER experience. *Eur Heart J* 2014;**35**:1599–1607.
 68. Bagur R, Rodes-Cabau J, Gurvitch R, Dumont E, Velianou JL, Manazzoni J, Toggweiler S, Cheung A, Ye J, Natarajan MK, Bainey KR, Delarochelliere R, Doyle D, Pibarot P, Voisine P, Cote M, Philippon F, Webb JG. Need for permanent pacemaker as a complication of transcatheter aortic valve implantation and surgical aortic valve replacement in elderly patients with severe aortic stenosis and similar baseline electrocardiographic findings. *JACC Cardiovasc Interv* 2012;**5**:540–551.
 69. Bleiziffer S, Ruge H, Horer J, Hutter A, Geisbusch S, Brockmann G, Mazzitelli D, Bauernschmitt R, Lange R. Predictors for new-onset complete heart block after transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 2010;**3**:524–530.
 70. Buellesfeld L, Stortecky S, Heg D, Hausen S, Mueller R, Wenaweser P, Pilgrim T, Gloekler S, Khattab AA, Huber C, Carrel T, Eberle B, Meier B, Boekstegers P, Juni P, Gerckens U, Grube E, Windecker S. Impact of permanent pacemaker implantation on clinical outcome among patients undergoing transcatheter aortic valve implantation. *J Am Coll Cardiol* 2012;**60**:493–501.
 71. Chorianopoulos E, Krumsdorf U, Pleger ST, Katus HA, Bekerjedjian R. Incidence of late occurring bradyarrhythmias after TAVI with the self-expanding CoreValve((R)) aortic bioprosthesis. *Clin Res Cardiol* 2012;**101**:349–355.
 72. D'Ancona G, Pasic M, Unbehaun A, Hetzer R. Permanent pacemaker implantation after transcatheter aortic valve implantation. *Interact Cardiovasc Thorac Surg* 2011;**13**:373–376.
 73. De Carlo M, Giannini C, Bedogni F, Klugmann S, Brambilla N, De Marco F, Zucchelli G, Testa L, Oreglia J, Petronio AS. Safety of a conservative strategy of permanent pacemaker implantation after transcatheter aortic CoreValve implantation. *Am Heart J* 2012;**163**:492–499.
 74. Dworakowski R, MacCarthy PA, Monaghan M, Redwood S, El-Gamel A, Young C, Bapat V, Hancock J, Wilson K, Brickham B, Wendler O, Thomas MR. Transcatheter aortic valve implantation for severe aortic stenosis—a new paradigm for multidisciplinary intervention: a prospective cohort study. *Am Heart J* 2010;**160**:237–243.
 75. Ewe SH, Ajmone MN, Pepi M, Delgado V, Tamborini G, Muratori M, Ng AC, van der Kley F, de Weger A, Schaliij MJ, Fusari M, Biglioli P, Bax JJ. Impact of left ventricular systolic function on clinical and echocardiographic outcomes following transcatheter aortic valve implantation for severe aortic stenosis. *Am Heart J* 2010;**160**:1113–1120.
 76. Ledwoch J, Franke J, Gerckens U, Kuck KH, Linke A, Nickenig G, Krull-Munch J, Vohringer M, Hambrecht R, Erbel R, Richardt G, Horack M, Zahn R, Senges J, Sievert H. Incidence and predictors of permanent pacemaker implantation following transcatheter aortic valve implantation: analysis from the German transcatheter aortic valve interventions registry. *Catheter Cardiovasc Interv* 2013;**82**:E569–E577.
 77. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;**363**:1597–1607.
 78. Rodes-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Feindel CM, Osten M, Natarajan MK, Velianou JL, Martucci G, Devarenes B, Chisholm R, Peterson MD, Lichtenstein SV, Nietlispach F, Doyle D, Delarochelliere R, Teoh K, Chu V, Dancea A, Lachapelle K, Cheema A, Latter D, Horlick E. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. *J Am Coll Cardiol* 2010;**55**:1080–1090.
 79. Sinhal A, Altwegg L, Pasupati S, Humphries KH, Allard M, Martin P, Cheung A, Ye J, Kerr C, Lichtenstein SV, Webb JG. Atrioventricular block after transcatheter balloon expandable aortic valve implantation. *JACC Cardiovasc Interv* 2008;**1**:305–309.
 80. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;**364**:2187–2198.
 81. Tchetché D, Modine T, Farah B, Vahdat O, Sudre A, Koussa M, Lereun C, Nejari M, Choby M, Rosencher J, Sorbets E, Fajadet J. Update on the need for a permanent pacemaker after transcatheter aortic valve implantation using the CoreValve(R) Accutrak system. *EuroIntervention* 2012;**8**:556–562.
 82. Van Mieghem NM, Chieffo A, Dumontel N, Tchetché D, van der Boon RM, Buchanan GL, Marcheix B, Vahdat O, Serruys PW, Fajadet J, Carrie D, Colombo A, de Jaegere PP. Trends in outcome after transfemoral transcatheter aortic valve implantation. *Am Heart J* 2013;**165**:183–192.
 83. Watanabe Y, Hayashida K, Yamamoto M, Mouillet G, Chevalier B, Oguri A, Dubois-Randé JL, Morice MC, Teiger E, Lefevre T. Transfemoral aortic valve implantation in patients with an annulus dimension suitable for either the Edwards valve or the CoreValve. *Am J Cardiol* 2013;**112**:707–713.
 84. Webb JG, Altwegg L, Boone RH, Cheung A, Ye J, Lichtenstein S, Lee M, Masson JB, Thompson C, Moss R, Carere R, Munt B, Nietlispach F, Humphries K. Transcatheter aortic valve implantation: impact on clinical and valve-related outcomes. *Circulation* 2009;**119**:3009–3016.
 85. Munoz-Garcia AJ, Hernandez-Garcia JM, Jimenez-Navarro MF, Alonso-Briales JH, Dominguez-Franco AJ, Fernandez-Pastor J, Pena HJ, Barrera CA, Alzueta RJ, de Teresa-Galvan E. Factors predicting and having an impact on the need for a permanent pacemaker after CoreValve prosthesis implantation using the new Accutrak delivery catheter system. *JACC Cardiovasc Interv* 2012;**5**:533–539.
 86. Eggebrecht H, Schmermund A, Voigtlander T, Kahlert P, Erbel R, Mehta RH. Risk of stroke after transcatheter aortic valve implantation (TAVI): a meta-analysis of 10 037 published patients. *EuroIntervention* 2012;**8**:129–138.
 87. Genereux P, Head SJ, Van Mieghem NM, Kodali S, Kirtane AJ, Xu K, Smith C, Serruys PW, Kappetein AP, Leon MB. Clinical outcomes after transcatheter aortic valve replacement using valve academic research consortium definitions: a weighted meta-analysis of 3,519 patients from 16 studies. *J Am Coll Cardiol* 2012;**59**:2317–2326.
 88. Panchal HB, Ladia V, Desai S, Shah T, Ramu V. A meta-analysis of mortality and major adverse cardiovascular and cerebrovascular events following transcatheter aortic valve implantation versus surgical aortic valve replacement for severe aortic stenosis. *Am J Cardiol* 2013;**112**:850–860.
 89. Cao C, Ang SC, Indraratna P, Manganas C, Bannon P, Black D, Tian D, Yan TD. Systematic review and meta-analysis of transcatheter aortic valve implantation versus surgical aortic valve replacement for severe aortic stenosis. *Ann Cardiothorac Surg* 2013;**2**:10–23.
 90. Ghanem A, Muller A, Nahle CP, Kocurek J, Werner N, Hammerstingl C, Schild HH, Schwab JO, Mellert F, Fimmers R, Nickenig G, Thomas D. Risk and fate of cerebral embolism after transfemoral aortic valve implantation: a prospective pilot study

- with diffusion-weighted magnetic resonance imaging. *J Am Coll Cardiol* 2010;**55**: 1427–1432.
91. Kahlert P, Knipp SC, Schlamann M, Thielmann M, Al-Rashid F, Weber M, Johansson U, Wendt D, Jakob HG, Forsting M, Sack S, Erbel R, Eggebrecht H. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. *Circulation* 2010;**121**:870–878.
 92. Erdoes G, Basciani R, Huber C, Stortecky S, Wenaweser P, Windecker S, Carrel T, Eberle B. Transcranial Doppler-detected cerebral embolic load during transcatheter aortic valve implantation. *Eur J Cardiothorac Surg* 2012;**41**:778–783.
 93. Kahlert P, Al-Rashid F, Dottger P, Mori K, Plicht B, Wendt D, Bergmann L, Kottenberg E, Schlamann M, Mummel P, Holle D, Thielmann M, Jakob HG, Konorza T, Heusch G, Erbel R, Eggebrecht H. Cerebral embolization during transcatheter aortic valve implantation: a transcranial Doppler study. *Circulation* 2012;**126**:1245–1255.
 94. Miller DC, Blackstone EH, Mack MJ, Svensson LG, Kodali SK, Kapadia S, Rajeswaran J, Anderson WN, Moses JW, Tuzcu EM, Webb JG, Leon MB, Smith CR. Transcatheter (TAVR) versus surgical (AVR) aortic valve replacement: occurrence, hazard, risk factors, and consequences of neurologic events in the PARTNER trial. *J Thorac Cardiovasc Surg* 2012;**143**:832–843.
 95. Nuis RJ, Van Mieghem NM, Schultz CJ, Moelker A, van der Boon RM, van Geuns RJ, van der Lugt A, Serruys PW, Rodes-Cabau J, van Domburg RT, Koudstaal PJ, de Jaegere PP. Frequency and causes of stroke during or after transcatheter aortic valve implantation. *Am J Cardiol* 2012;**109**:1637–1643.
 96. Stortecky S, Windecker S, Pilgrim T, Heg D, Buellesfeld L, Khattab AA, Huber C, Gloekler S, Nietlispach F, Mattle H, Juni P, Wenaweser P. Cerebrovascular accidents complicating transcatheter aortic valve implantation: frequency, timing and impact on outcomes. *EuroIntervention* 2012;**8**:62–70.
 97. Tay EL, Gurvitch R, Wijesinghe N, Nietlispach F, Wood D, Cheung A, Ye J, Lichtenstein SV, Carere R, Thompson C, Webb JG. A high-risk period for cerebrovascular events exists after transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 2011;**4**:1290–1297.
 98. Al-Rashid F, Konorza TF, Plicht B, Wendt D, Thielmann M, Jakob H, Erbel R, Kahlert P. Transient increase in pressure gradients after termination of dual antiplatelet therapy in a patient after transfemoral aortic valve implantation. *Circ Cardiovasc Interv* 2012;**5**:318–320.
 99. Noble S, Asgar A, Cartier R, Virmani R, Bonan R. Anatomic-pathological analysis after CoreValve Revalving system implantation. *EuroIntervention* 2009;**5**:78–85.
 100. Amat-Santos IJ, Rodes-Cabau J, Urena M, Delarochelliere R, Doyle D, Bagur R, Villeneuve J, Cote M, Nombela-Franco L, Philippon F, Pibarot P, Dumont E. Incidence, predictive factors, and prognostic value of new-onset atrial fibrillation following transcatheter aortic valve implantation. *J Am Coll Cardiol* 2012;**59**:178–188.
 101. Naber CK, Ghanem A, Abizaid AA, Wolf A, Sinning JM, Werner N, Nickenig G, Schmitz T, Grube E. First-in-man use of a novel embolic protection device for patients undergoing transcatheter aortic valve implantation. *EuroIntervention* 2012;**8**:43–50.
 102. Nietlispach F, Wijesinghe N, Gurvitch R, Tay E, Carpenter JP, Burns C, Wood DA, Webb JG. An embolic deflection device for aortic valve interventions. *JACC Cardiovasc Interv* 2010;**3**:1133–1138.
 103. Onsea K, Agostoni P, Samim M, Voskuil M, Kluin J, Budde R, Hendrikse J, Ramjankhan F, van KJ, Doesburg P, Sieswerda G, Stella P. First-in-man experience with a new embolic deflection device in transcatheter aortic valve interventions. *EuroIntervention* 2012;**8**:51–56.
 104. Van Mieghem NM, Schipper ME, Ladich E, Faqiri E, van der Boon R, Randjari A, Schultz C, Moelker A, van Geuns RJ, Otsuka F, Serruys PW, Virmani R, de Jaegere PP. Histopathology of embolic debris captured during transcatheter aortic valve replacement. *Circulation* 2013;**127**:2194–2201.
 105. Rodes-Cabau J, Dauerman HL, Cohen MG, Mehran R, Small EM, Smyth SS, Costa MA, Mega JL, O'Donoghue ML, Ohman EM, Becker RC. Antithrombotic treatment in transcatheter aortic valve implantation: insights for cerebrovascular and bleeding events. *J Am Coll Cardiol* 2013;**62**:2349–2359.
 106. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;**129**:e521–e643.
 107. Sergie Z, Lefevre T, Van BE, Kakoulides S, Baber U, Deliangyris EN, Mehran R, Grube E, Reinohl J, Dangas GD. Current periprocedural anticoagulation in transcatheter aortic valve replacement: could bivalirudin be an option? Rationale and design of the BRAVO 2/3 studies. *J Thromb Thrombolysis* 2013;**35**:483–493.
 108. Whitlock RP, Sun JC, Frenes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**:e576S–e600S.
 109. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De BM, Evangelista A, Falk V, Jung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Popescu BA, Von SL, Badano LP, Bunc M, Claeys MJ, Drinkovic N, Filippatos G, Habib G, Kappetein AP, Kassab R, Lip GY, Moat N, Nickenig G, Otto CM, Pepper J, Piazza N, Pieper PG, Rosenhek R, Shuka N, Schwammenthal E, Schwitler J, Mas PT, Trindade PT, Walther T. Guidelines on the management of valvular heart disease (version 2012): The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2012;**33**:2451–2496.
 110. Silvain J, Cayla G, Hulot JS, Finzi J, Kerneis M, O'Connor SA, Bellemain-Appaix A, Barthelemy O, Beygui F, Collet JP, Montalescot G. High on-thienopyridine platelet reactivity in elderly coronary patients: the SENIOR-PLATELET study. *Eur Heart J* 2012;**33**:1241–1249.
 111. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhilber SR, Weber MA, Brennan DM, Fabry-Ribaudo L, Booth J, Topol EJ. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;**354**:1706–1717.
 112. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, Pfeffer M, Hohnloser S, Yusuf S. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;**367**:1903–1912.
 113. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;**345**:494–502.
 114. ClinicalTrials.gov. Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation: the ARTE Trial. <http://clinicaltrials.gov/ct2/show/NCT01559298> (accessed in 2012).
 115. Stortecky S, Buellesfeld L, Wenaweser P, Heg D, Pilgrim T, Khattab AA, Gloekler S, Huber C, Nietlispach F, Meier B, Juni P, Windecker S. Atrial fibrillation and aortic stenosis: impact on clinical outcomes among patients undergoing transcatheter aortic valve implantation. *Circ Cardiovasc Interv* 2013;**6**:77–84.
 116. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, Healey JS, Yusuf S. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation* 2008;**118**:2029–2037.
 117. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012;**33**:2719–2747.
 118. Miller CS, Grandi SM, Shimony A, Filion KB, Eisenberg MJ. Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. *Am J Cardiol* 2012;**110**:453–460.
 119. Thubrikar MJ, Deck JD, Aouad J, Nolan SP. Role of mechanical stress in calcification of aortic bioprosthetic valves. *J Thorac Cardiovasc Surg* 1983;**86**:115–125.
 120. Kiefer P, Gruenewald F, Kempfert J, Aupperle H, Seeburger J, Mohr FW, Walther T. Crimping may affect the durability of transcatheter valves: an experimental analysis. *Ann Thorac Surg* 2011;**92**:155–160.
 121. McElhinney DB, Cheatham JP, Jones TK, Lock JE, Vincent JA, Zahn EM, Hellenbrand WE. Stent fracture, valve dysfunction, and right ventricular outflow tract reintervention after transcatheter pulmonary valve implantation: patient-related and procedural risk factors in the US Melody Valve Trial. *Circ Cardiovasc Interv* 2011;**4**:602–614.
 122. Piazza N, Grube E, Gerckens U, Schuler G, Linke A, den HP, Kovacs J, Spyt T, Laborde JC, Morel MA, Nuis RJ, Garcia-Garcia HM, de JP, Serruys PW. A clinical protocol for analysis of the structural integrity of the Medtronic CoreValve System frame and its application in patients with 1-year minimum follow-up. *EuroIntervention* 2010;**5**:680–686.
 123. Willson AB, Webb JG, Gurvitch R, Wood DA, Toggweiler S, Binder R, Freeman M, Madden M, Hague C, Leipsic J. Structural integrity of balloon-expandable stents after transcatheter aortic valve replacement: assessment by multidetector computed tomography. *JACC Cardiovasc Interv* 2012;**5**:525–532.
 124. Buellesfeld L, Gerckens U, Schuler G, Bonan R, Kovac J, Serruys PW, Labinaz M, den HP, Mullen M, Tymchak W, Windecker S, Mueller R, Grube E. 2-year follow-up

- of patients undergoing transcatheter aortic valve implantation using a self-expanding valve prosthesis. *J Am Coll Cardiol* 2011;**57**:1650–1657.
125. Ussia GP, Barbanti M, Petronio AS, Tarantini G, Ettori F, Colombo A, Violini R, Ramondo A, Santoro G, Klugmann S, Bedogni F, Maisano F, Marzocchi A, Poli A, De CM, Napodano M, Fiorina C, De MF, Antonucci D, de CE, Capodanno D, Tamburino C. Transcatheter aortic valve implantation: 3-year outcomes of self-expanding CoreValve prosthesis. *Eur Heart J* 2012;**33**:969–976.
 126. Toggweiler S, Humphries KH, Lee M, Binder RK, Moss RR, Freeman M, Ye J, Cheung A, Wood DA, Webb JG. 5-year outcome after transcatheter aortic valve implantation. *J Am Coll Cardiol* 2013;**61**:413–419.
 127. Schelbert EB, Vaughan-Sarrazin MS, Welke KF, Rosenthal GE. Valve type and long-term outcomes after aortic valve replacement in older patients. *Heart* 2008;**94**:1181–1188.
 128. Christiansen S, Schmid M, Autschbach R. Perioperative risk of redo aortic valve replacement. *Ann Thorac Cardiovasc Surg* 2009;**15**:105–110.
 129. Jamieson WR, Burr LH, Miyagishima RT, Janusz MT, Fradet GJ, Ling H, Lichtenstein SV. Re-operation for bioprosthetic aortic structural failure - risk assessment. *Eur J Cardiothorac Surg* 2003;**24**:873–878.
 130. Vogt PR, Brunner-LaRocca H, Sidler P, Zund G, Truniger K, Lachat M, Turina J, Turina MI. Reoperative surgery for degenerated aortic bioprostheses: predictors for emergency surgery and reoperative mortality. *Eur J Cardiothorac Surg* 2000;**17**:134–139.
 131. Dvir D, Webb J, Brecker S, Bleiziffer S, Hildick-Smith D, Colombo A, Descoutures F, Hengstenberg C, Moat NE, Bekeredjian R, Napodano M, Testa L, Lefevre T, Guetta V, Nissen H, Hernandez JM, Roy D, Teles RC, Segev A, Dumonteil N, Fiorina C, Gotzmann M, Tchetché D, Abdel-Wahab M, De MF, Baumbach A, Laborde JC, Kornowski R. Transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: results from the global valve-in-valve registry. *Circulation* 2012;**126**:2335–2344.
 132. Piazza N, Bleiziffer S, Brockmann G, Hendrick R, Deutsch MA, Opitz A, Mazzitelli D, Tassani-Prell P, Schreiber C, Lange R. Transcatheter aortic valve implantation for failing surgical aortic bioprosthetic valve: from concept to clinical application and evaluation (part 2). *JACC Cardiovasc Interv* 2011;**4**:733–742.
 133. Piazza N, Bleiziffer S, Brockmann G, Hendrick R, Deutsch MA, Opitz A, Mazzitelli D, Tassani-Prell P, Schreiber C, Lange R. Transcatheter aortic valve implantation for failing surgical aortic bioprosthetic valve: from concept to clinical application and evaluation (part 1). *JACC Cardiovasc Interv* 2011;**4**:721–732.
 134. Allende R, Webb JG, Munoz-Garcia AJ, de JP, Tamburino C, Dager AE, Cheema A, Serra V, Amat-Santos I, Velianou JL, Barbanti M, Dvir D, Alonso-Briaes JH, Nuis RJ, Faqiri E, Imme S, Benitez LM, Cucalon AM, Al LH, Garcia del BB, Lopez J, Natarajan MK, Delarochelliere R, Urena M, Ribeiro HB, Dumont E, Nombela-Franco L, Rodes-Cabau J. Advanced chronic kidney disease in patients undergoing transcatheter aortic valve implantation: insights on clinical outcomes and prognostic markers from a large cohort of patients. *Eur Heart J* 2014; doi:10.1093/eurheartj/ehu175.
 135. Chopard R, Meneveau N, Chocron S, Gilard M, Laskar M, Eltchaninoff H, lung B, Leprince P, Teiger E, Chevrel K, Prat A, Lievre M, Leguerrier A, Donzeau-Gouge P, Fajadet J, Schiele F. Impact of Chronic Obstructive Pulmonary Disease on Valve Academic Research Consortium-Defined Outcomes After Transcatheter Aortic Valve Implantation (from the FRANCE 2 Registry). *Am J Cardiol* 2014;**113**:1543–1549.
 136. Lindman BR, Pibarot P, Arnold SV, Suri RM, McAndrew TC, Maniar HS, Zajarias A, Kodali S, Kirtane AJ, Thourani VH, Tuzcu EM, Svensson LG, Waksman R, Smith CR, Leon MB. Transcatheter versus surgical aortic valve replacement in patients with diabetes and severe aortic stenosis at high risk for surgery: an analysis of the PARTNER Trial (Placement of Aortic Transcatheter Valve). *J Am Coll Cardiol* 2014;**63**:1090–1099.
 137. Sinning JM, Horack M, Grube E, Gerckens U, Erbel R, Eggebrecht H, Zahn R, Linke A, Sievert H, Figulla HR, Kuck KH, Hauptmann KE, Hoffmann E, Hambrecht R, Richardt G, Sack S, Senges J, Nickenig G, Werner N. The impact of peripheral arterial disease on early outcome after transcatheter aortic valve implantation: results from the German Transcatheter Aortic Valve Interventions Registry. *Am Heart J* 2012;**164**:102–110.
 138. Zahn R, Gerckens U, Grube E, Linke A, Sievert H, Eggebrecht H, Hambrecht R, Sack S, Hauptmann KE, Richardt G, Figulla HR, Senges J. Transcatheter aortic valve implantation: first results from a multi-centre real-world registry. *Eur Heart J* 2011;**32**:198–204.
 139. Wenaweser P, Pilgrim T, Kadner A, Huber C, Stortecky S, Buellesfeld L, Khattab AA, Meuli F, Roth N, Eberle B, Erdos G, Brinks H, Kalesan B, Meier B, Juni P, Carrel T, Windecker S. Clinical outcomes of patients with severe aortic stenosis at increased surgical risk according to treatment modality. *J Am Coll Cardiol* 2011;**58**:2151–2162.
 140. Lange R, Bleiziffer S, Mazzitelli D, Elhmidi Y, Opitz A, Krane M, Deutsch MA, Ruge H, Brockmann G, Voss B, Schreiber C, Tassani P, Piazza N. Improvements in transcatheter aortic valve implantation outcomes in lower surgical risk patients: a glimpse into the future. *J Am Coll Cardiol* 2012;**59**:280–287.
 141. Wenaweser P, Stortecky S, Schwander S, Heg D, Huber C, Pilgrim T, Gloekler S, O'Sullivan CJ, Meier B, Juni P, Carrel T, Windecker S. Clinical outcomes of patients with estimated low or intermediate surgical risk undergoing transcatheter aortic valve implantation. *Eur Heart J* 2013;**34**:1894–1905.
 142. Mylotte D, Osnabrugge RL, Windecker S, Lefevre T, de JP, Jeger R, Wenaweser P, Maisano F, Moat N, Sondergaard L, Bosmans J, Teles RC, Martucci G, Manoharan G, Garcia E, Van Mieghem NM, Kappetein AP, Serruys PW, Lange R, Piazza N. Transcatheter aortic valve replacement in Europe: adoption trends and factors influencing device utilization. *J Am Coll Cardiol* 2013;**62**:210–219.
 143. Kotting J, Schiller W, Beckmann A, Schafer E, Dobler K, Hamm C, Veit C, Welz A. German Aortic Valve Score: a new scoring system for prediction of mortality related to aortic valve procedures in adults. *Eur J Cardiothorac Surg* 2013;**43**:971–977.
 144. Nielsen HH, Klaaborg KE, Nissen H, Terp K, Mortensen PE, Kjeldsen BJ, Jakobsen CJ, Andersen HR, Egeblad H, Krusell LR, Thuesen L, Hjordtal VE. A prospective, randomised trial of transapical transcatheter aortic valve implantation vs. surgical aortic valve replacement in operable elderly patients with aortic stenosis: the STACCATO trial. *EuroIntervention* 2012;**8**:383–389.
 145. Bourantas CV, Van Mieghem NM, Soliman O, Campos CA, Iqbal J, Serruys PW. Transcatheter aortic valve update 2013. *EuroIntervention* 2013;**9**(Suppl):S84–S90.
 146. Piazza N, Kalesan B, Van MN, Head S, Wenaweser P, Carrel TP, Bleiziffer S, de Jaegere PP, Gahl B, Anderson RH, Kappetein AP, Lange R, Serruys PW, Windecker S, Juni P. A 3-center comparison of 1-year mortality outcomes between transcatheter aortic valve implantation and surgical aortic valve replacement on the basis of propensity score matching among intermediate-risk surgical patients. *JACC Cardiovasc Interv* 2013;**6**:443–451.
 147. The PARTNER II Trial: Placement of AoRTic TraNscatheterER Valves. <http://www.clinicaltrials.gov/ct2/show/NCT01314313?term=NCT01314313&rank=1> (December 2013).
 148. Safety and Efficacy Study of the Medtronic CoreValve® System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement (SURTAVI). <http://www.clinicaltrials.gov/ct2/show/NCT01586910?term=SURTAVI&rank=1> (December 2013).
 149. Roy DA, Schaefer U, Guetta V, Hildick-Smith D, Mollmann H, Dumonteil N, Modine T, Bosmans J, Petronio AS, Moat N, Linke A, Moris C, Champagnac D, Parma R, Ochala A, Medvedofsky D, Patterson T, Woitek F, Jahangiri M, Laborde JC, Brecker SJ. Transcatheter aortic valve implantation for pure severe native aortic valve regurgitation. *J Am Coll Cardiol* 2013;**61**:1577–1584.
 150. Seiffert M, Diemert P, Koschik D, Schirmer J, Conradi L, Schnabel R, Blankenberg S, Reichenspurner H, Baldus S, Treede H. Transapical implantation of a second-generation transcatheter heart valve in patients with noncalcified aortic regurgitation. *JACC Cardiovasc Interv* 2013;**6**:590–597.
 151. Schultz CJ, Tzikas A, Moelker A, Rossi A, Nuis RJ, Geleijnse MM, Van MN, Krestin GP, de FP, Serruys PW, de Jaegere PP. Correlates on MSCT of paravalvular aortic regurgitation after transcatheter aortic valve implantation using the medtronic CoreValve prosthesis. *Catheter Cardiovasc Interv* 2011;**78**:446–455.
 152. Bapat V, Attia R. Transaortic transcatheter aortic valve implantation: step-by-step guide. *Semin Thorac Cardiovasc Surg* 2012;**24**:206–211.