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REVIEW

*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 Registry[3] and the United States Transcatheter Valve Therapy registry[4] 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]

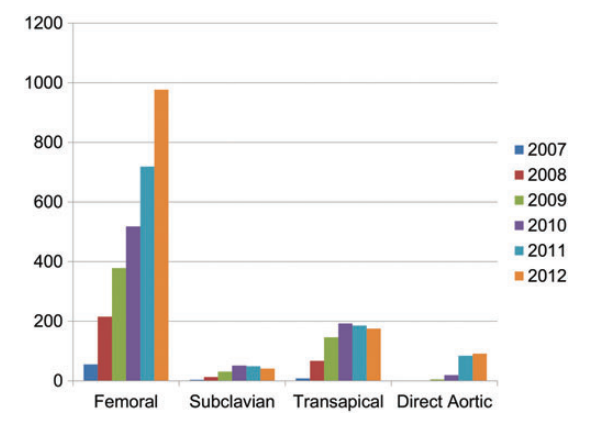


**Figure 1** Transcatheter aortic valve implantation access routes. Data from the UK TAVI Registry illustrating the change in access route choice over the years 2007–12, emphasizing the rapid rise in trans-femoral procedures (figure courtesy of Dr Peter Ludman).

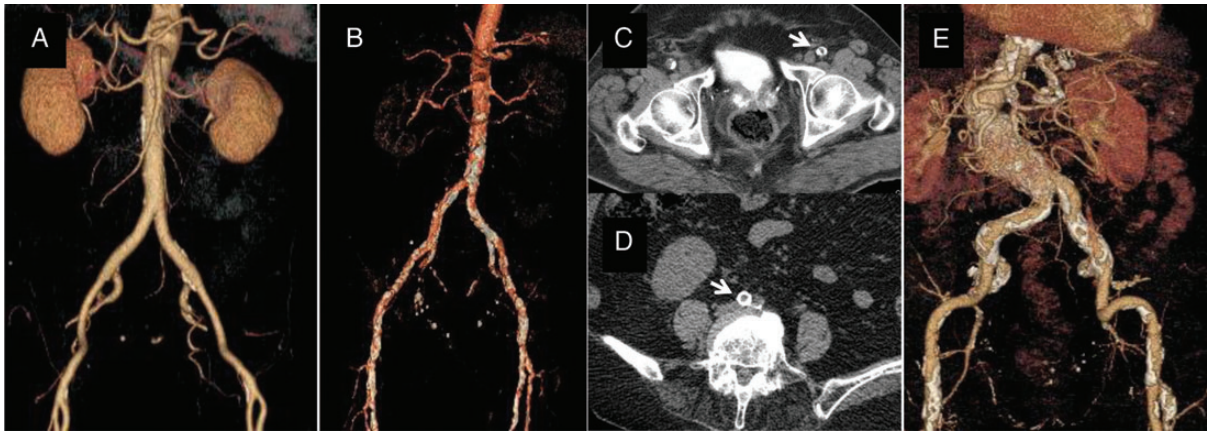


**Figure 2** Multi-detector row computed tomography for assessment of the peripheral vasculature to decide on optimal access sites for transcatheter aortic valve implantation. Aortogram of 'ideal' arterial anatomy for a TFprocedure: non-calcified iliac and femoral arteries which are of good calibre and 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 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]

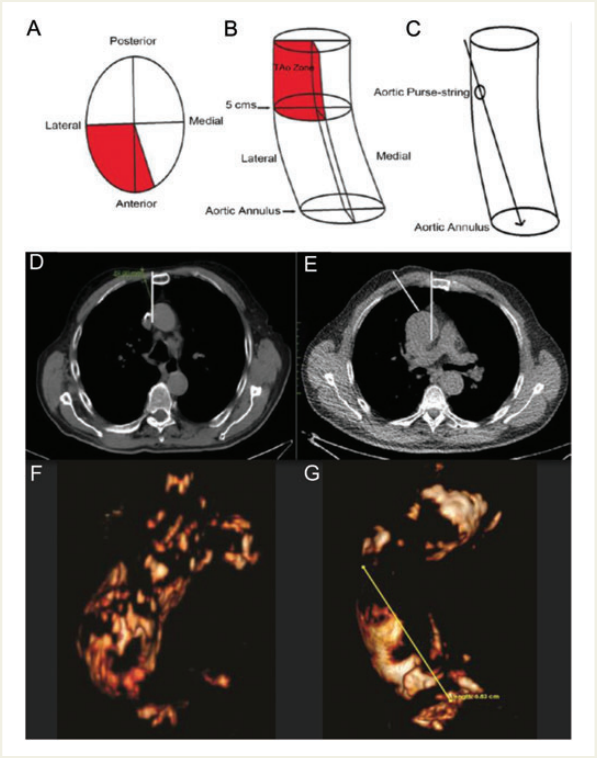


**Figure 3** Multi-detector row computed tomography for procedural planning of transaortic transcatheter aortic valve implantation. (*A* and *B*) The transaortic zone for cannulation of the aorta along the upper lateral quadrant allowing perpendicular alignment to the aortic valve (*C*). Based on the 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]

# 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.
[a]Include 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 *et al.*[31] | 74 | 100% TEE | 100% Edwards SAPIEN 62% Transfemoral | 23 | Low cover index (OR: 1.22 per 1% decrease) |
| Wilson *et al.*[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 *et al.*[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 *et al.*[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 *et al.*[40] | 358 | 86% MDCT | 100% Edwards SAPIEN 100% Transapical | 1 | Asymmetric cusp calcification and device-landing zone calcification |
| Delgado *et al.*[30] | 53 | 100% MDCT | 100% Edwards SAPIEN 57% Transfemoral | 11 | Aortic valve calcification (Agatston score) and calcification of the valve commissures |
| John *et al.*[36] | 100 | 100% MDCT | 100% CoreValve 100% Transfemoral | 10 | Calcification of the landing zone (valve and LVOT) as assessed with the Agatston score |
| Ewe *et al.*[32] | 79 | 100% MDCT | 100% Edwards SAPIEN 46% Transfemoral | 4 | Calcification of the commissures and valvular edge |
| Schultz *et al.*[151] | 56 | 100% MDCT | 100% CoreValve 100% Transfemoral | 5 | Aortic valve calcification (Agatston score) |
| Colli *et al.*[29] | 103 | 100% TEE | 100% Edwards SAPIEN 100% Transsapical | 7 | Calcification of the valve commissures |
| Haensig *et al.*[33] | 120 | 100% MDCT | 100% Edwards SAPIEN 100% Transapical | 4 | Aortic valve calcification (Agatston score) |
| Prosthesis deployment | | | | | |
| Jilaihawi *et al.*[35] | 50 | 100% Angiography | 100% CoreValve 100% Transfemoral | 4 | Deep deployment of the valve (15 mm deep from the non-coronary cusp) |
| Sherif *et al.*[39] | 50 | 100% Angiography | 100% CoreValve 100% Transfemoral | 40 | Deep (>10 mm from the non-coronary cusp) or shallow (<10 mm) implantation |
| Katsanos *et al.*[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.

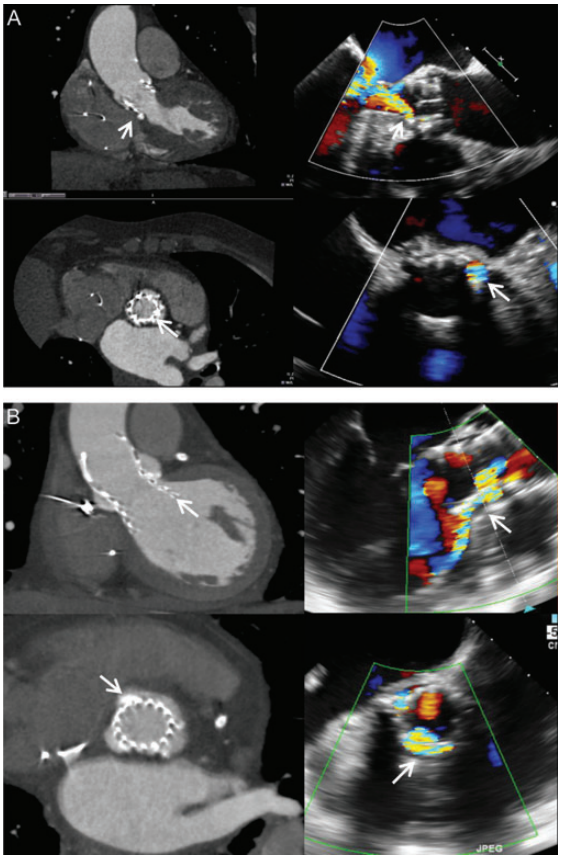


**Figure 4** Pathophysiological factors determining paravalvular aortic regurgitation. (*A*) Example of a patient with mild paravalvular aortic regurgitation at the level of the hinge point with the membranous interventricular septum (arrow). The multi-detector row computed tomography shows a bulky calcification 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 increase[2] 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.

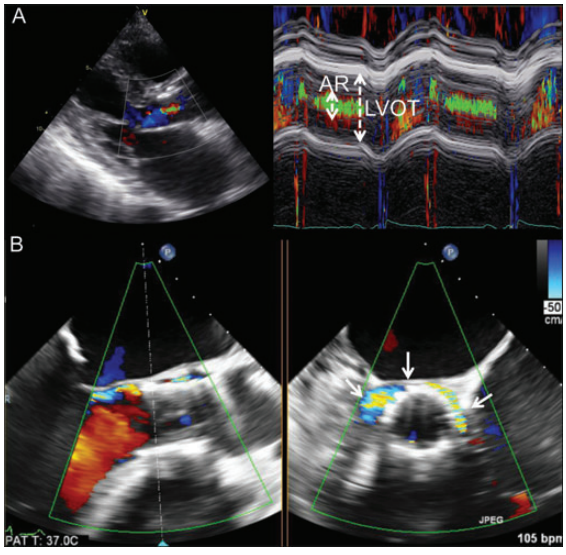


**Figure 5** Assessment of aortic regurgitation grade. (*A*) Transvalvular mild aortic regurgitation assessed with colour-Doppler M-mode from the parasternal long-axis view (left). The width of the regurgitant jet relative to the diameter of the left ventricular outflow tract is <25% (right). (*B*) Paravalvular 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 $cm^2/m^2$) in 20–70%; severe PPM, (i.e. indexed effective orifice area ≤0.65 $cm^2/m^2$) 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

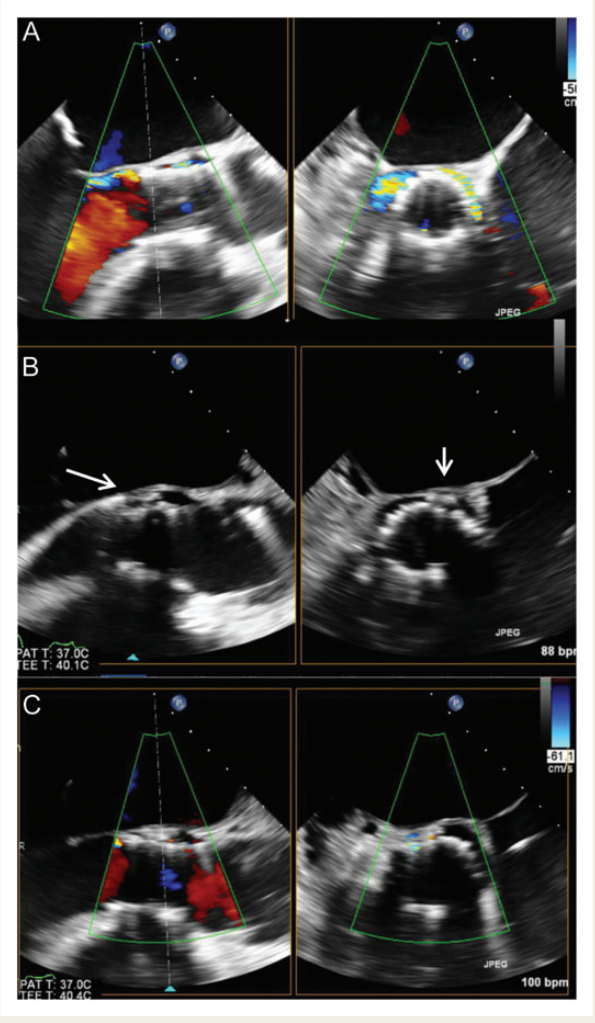


**Figure 6** Treatment of significant paravalvular aortic regurgitation after transcatheter aortic valve implantation. Implantation of an AMPLATZER® Vascular Plug III closure device to seal a severe paravalvular aortic regurgitation as observed in the parasternal short-axis view with a circumferential 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

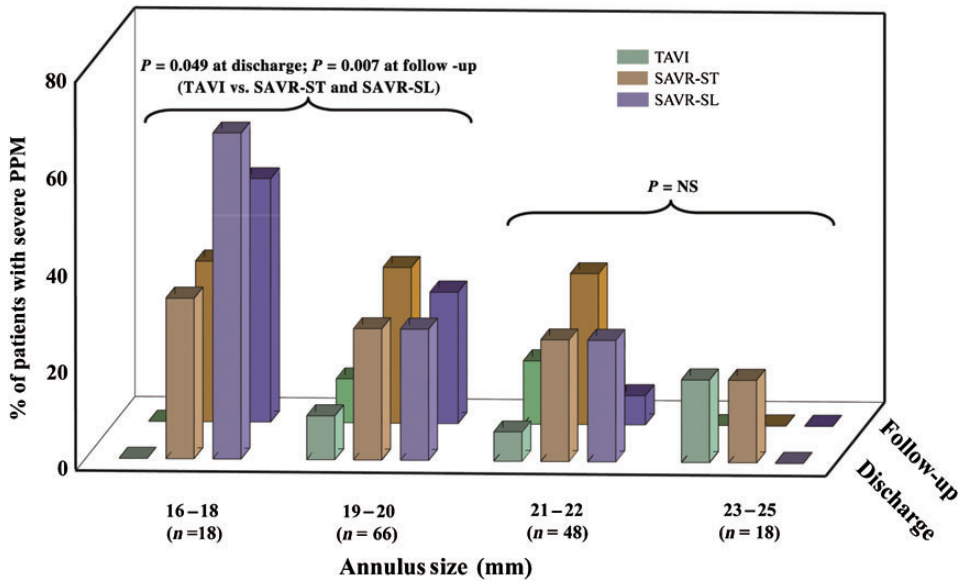


**Figure 7** Incidence of severe prosthesis–patient mismatch in transcatheter vs. surgical prosthetic valves according to aortic annulus size. For each category of aortic annulus size, the comparison of the incidence of severe prosthesis–patient mismatch at hospital discharge and at 6–12-month follow-up 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, Généreux *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 thrombogenic 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 artery[101] 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 thrombogenic origin of subacute and late neurological events calls for the evaluation of pharmacological measures like

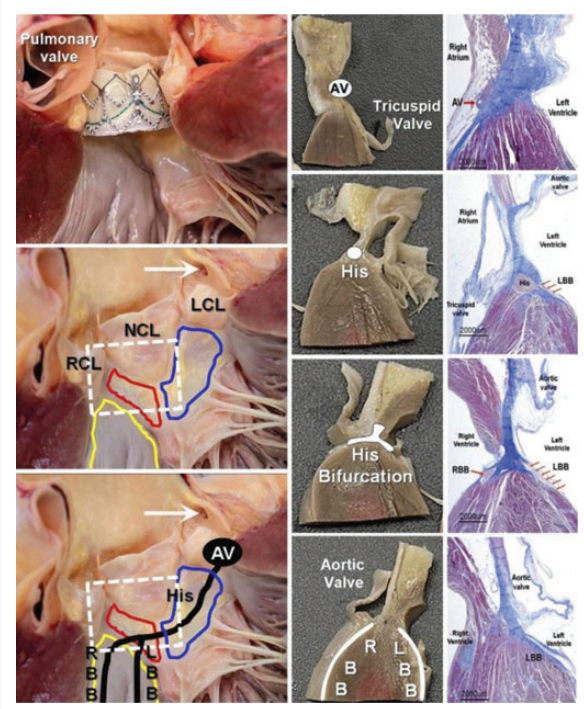


**Figure 8** Macroscopic and histological view of the conduction system. A 23 mm Edwards SAPIEN-XT (Edwards Lifesciences, Irvine, CA, USA) placed into a pathological specimen showing the anatomical relationships and conduction system pathways from a macroscopic view (left panels). Blue-line area highlights 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 anatomo-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-coronaryleaflet; 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 thrombo-embolic 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 $CHADS_2$-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 thromb-oembolic 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]<br>Depth of implantation |
| Aktug *et al.*,[56] $n = 154$ | Edwards SAPIEN ($n = 82$)<br>CoreValve ($n = 72$) | 13 (16) in Edwards SAPIEN<br>27 (38) in CoreValve | Depth of implantation |
| Franzoni *et al.*,[58] $n = 238$ | Edwards SAPIEN ($n = 151$)<br>CoreValve ($n = 87$) | 20 (13.5) in Edwards SAPIEN<br>43 (50) in CoreValve | Use of CoreValve |
| Khawaja *et al.*,[60] $n = 185$ | CoreValve | 105 (56.8) | Absence of RBBB<br>Native valve |

CABG, coronary artery bypass grafting; CAD, coronary artery disease; RBBB, right bundle branch block.
[a]Predictors 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 ($n = 232$)<br>CoreValve ($n = 912$) | 33 (14.2) Edwards SAPIEN<br>352 (38.6) CoreValve | Absence of prior valve surgery<br>Porcelain aorta<br>Core valve |
| Khawaja *et al.*,[60] $n = 243$ | CoreValve | 82 (33.3) | Peri-procedural complete AVB<br>Balloon predilatation<br>Prolonged baseline QRS duration<br>29-mm prosthesis |
| De Carlo *et al.*,[73] $n = 275$ | CoreValve | 66 (24.0) | Depth of implantation<br>Pre-existing RBBB<br>Pre-existing LAHB<br>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<br>Pre-existing RBBB<br>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)<br>Median 6% (Edwards SAPIEN) | Male gender<br>Pre-existing first degree AV-block<br>Pre-existing left anterior hemiblock<br>Pre-existing right bundle branch block<br>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.
[a]Included all new-onset LBBB, regardless persistence.

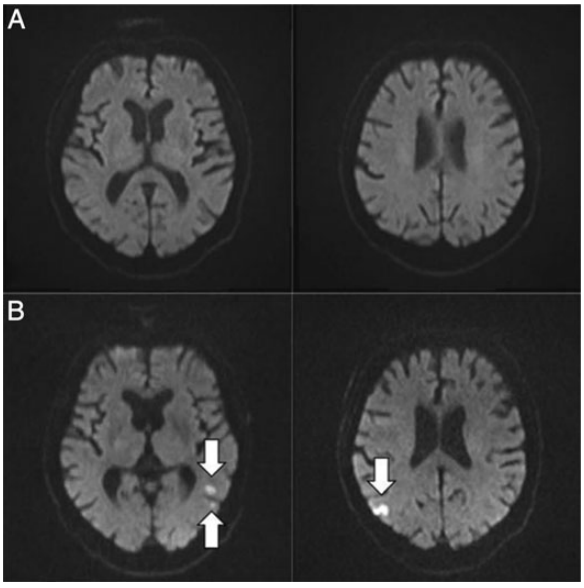


**Figure 9** Magnetic resonance imaging to detect cerebral lesions as a surrogate for procedural embolization after TAVI. Pre- (*A*) and post-interventional (*B*) diffusion-weighted magnetic resonance imaging of a patient undergoing transfemoral transcatheter aortic valve implantation with new foci of 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 | Aspirin or clopidogrel indefinitely |
| | Clopidogrel 75 mg, for 6 months | Aspirin and clopidogrel early after TAVI |
| | If vitamin K antagonist indicated, no clopidogrel | If vitamin K antagonist indicated, no antiplatelet therapy |
| | **Bioprosthetic valves** | |
| Low risk | Aspirin 75–100 mg/day (Class IIaB[a])<br>Vitamin K antagonist INR 2.0–3.0 (Class IIbB[b]) | Low dose aspirin (Class IIaC[b])<br>Vitamin K antagonist INR 2.0–3.0 (Class IIbC[c]) |
| High risk | Aspirin 75–100 mg/day (Class IIaB[a])<br>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%).
[a]Class I: conditions for which there is evidence for and/or general agreement that the procedure or treatment is beneficial, useful, and effective.
[b]Class IIa: weight of evidence/opinion is in favour of usefulness/efficacy.
[c]Class IIb: usefulness/efficacy is less well established by evidence/opinion.

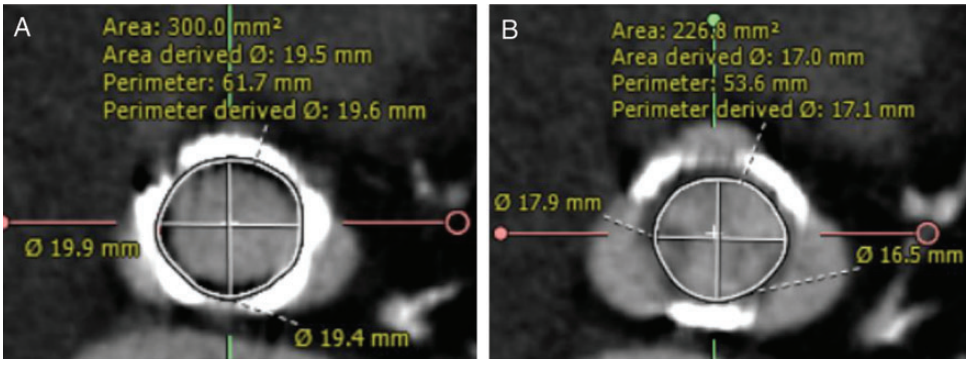


**Figure 10** Transcatheter valve-in-valve implantation: multi-detector row computed tomography assessment of internal dimensions of aortic bioprosthesis. Multi-detector row computed tomography permits the measurement of the geometric orifice diameter, area or perimeter from contrast-edge to contrast-edge 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 ± 3.0%) and 357 to SAVR (STS-PROM 7.5 ± 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 A[147] and the SURgical and Transcatheter Aortic Valve Implantation (SURTAVI) trial (*Figure 11*).[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 ≥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 ≥4% and ≤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 successs 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

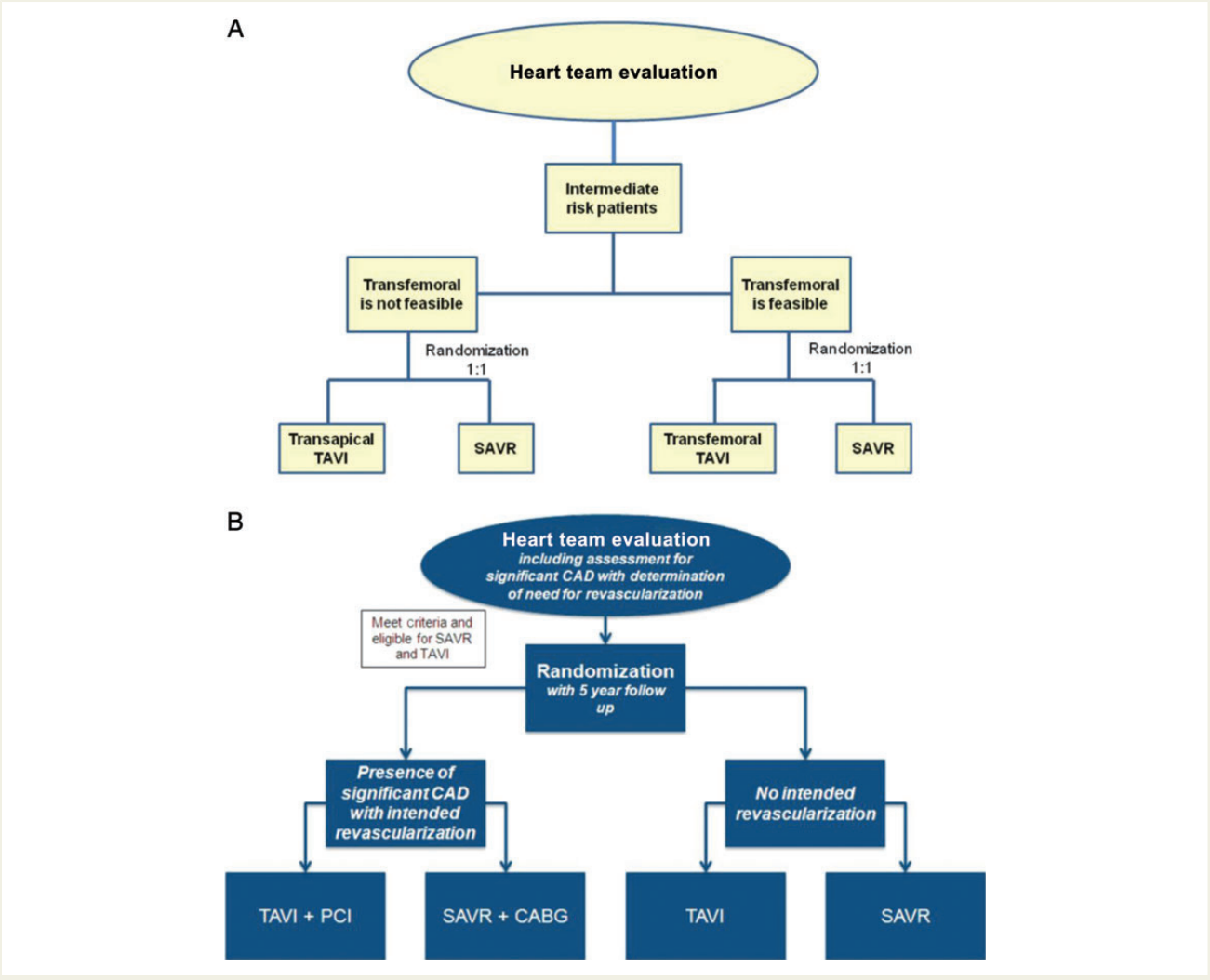


**Figure 11** Flowchart of the PARTNER II Cohort A (*A*) and the SURTAVI (*B*) trials. Reproduced with permission from Bourantas *et al.*[145]

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 Medtornic, 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.

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