Transcatheter aortic valve implantation: 10-year anniversary. Part II: clinical implications

Philippe Généreux1,2†, Stuart J. Head3†, David A. Wood4, Susheel K. Kodali1, Mathew R. Williams1, Jean-Michel Paradis1, Marco Spaziano2, A. Pieter Kappetein3, John G. Webb4, Alain Cribier5, and Martin B. Leon1

1Columbia University Medical Center and the Cardiovascular Research Foundation, New York, NY, USA; 2Hôpital du Sacré-Cœur de Montréal, Université de Montréal, Montréal, Québec, Canada; 3Erasmus University Medical Center, Rotterdam, The Netherlands; 4Vancouver Regional Structural Heart Program, St Paul’s Hospital, University of British Columbia, Vancouver, British Columbia, Canada; and 5Department of Cardiology, University Hospital Charles Nicolle, Rouen, France

Transcatheter aortic valve implantation (TAVI) has been increasingly recognized as a curative treatment for severe aortic stenosis (AS). Despite important improvements in current device technology and implantation techniques, specific complications still remain and warrant consideration. Vascular complications and peri-procedural neurological events were the first concerns to emerge with this new technology. Recently, significant post procedural para-valvular leak has been shown to be more frequent after TAVI than after surgical aortic valve replacement (SAVR), and its potential association with worse long-term prognostic has raised concerns. In moving toward treatment of lower risk populations, structural integrity and long-term durability of heat valve prosthesis are becoming of central importance. Emerging technologies and newer generations of devices seem promising in dealing with these matters.

Keywords
Aortic stenosis • TAVI • TAVR

Introduction
First-generation devices for transcatheter aortic valve implantation (TAVI) were associated with specific complications. Although newer technologies, improved devices, and more appropriate patient selection and screening, paired with increased operators’ experience have shown to reduce the occurrence of such complications, they still deserve special attention.

Complications
Stroke
Depending on the definition used, reported incidence of stroke in the current literature varies between 1.7 and 8.4%.3,4,5,6,7 Neurological events may occur at different time-points during the procedure and may be related to several factors: manipulation of a wire and/or large-diameter catheter through the aortic arch, positioning of the device, performance of balloon aortic valvuloplasty, and inadequate blood flow to the brain during rapid pacing and device deployment.8,9 Moreover, the population currently undergoing TAVI consists of very elderly patients in whom the incidence of atrial fibrillation and atherosclerotic disease is high, increasing the risk of peri-procedural cerebrovascular events.2,10,11 Although stroke clearly manifests in clinical symptoms, recent studies have shown ‘silent’ new cerebral ischaemia on diffusion-weighted magnetic resonance imaging in up to 70% of patients.12,13,14 Although rarely associated with clinical events, the long-term consequences of these phenomena are unknown.

Initially it was anticipated that stroke associated with TAVI occurred during the procedure, but in-depth analysis of stroke demonstrated a continuous hazard extending beyond the early phase.15 This hazard was thought to be higher after TAVI in comparison with surgical aortic valve replacement (SAVR). However, recent data showed that although the difference is significant in the first 30 days, the late hazard is similar between TAVI and SAVR.16

Predictors of early neurological events with TAVI included a prior neurological event, more severe atherosclerotic burden, and
Vascular complications

Vascular complications remain an important limitation of TAVI performed via TF access. The use of large-diameter catheters and the high-risk characteristics of the current treated population explain the high incidence. Small vessel diameter, severe atherosclerotic disease, bulky calcification, and tortuosity are the main determinants of vascular complications. The incidence of major vascular complications using the Edwards SAPIEN system (introducer sheath of 23 and 26 Fr, outer diameter of 8.38 and 9.14 mm) varies between 8.3 and 23%2,5,7,20,21 and between 1.9 and 14%3,4,21,22 using the CoreValve™ system (18 Fr introducer sheath, outer diameter of 7 mm). However, the use of arbitrary definitions and difficulty in identifying and systematically reporting all vascular complications make interpretation of the current literature difficult.

Common vascular complications include arterial dissection, closure device failure, arterial closure device-induced stenosis, and haematoma at the puncture site. Artery avulsion (‘artery on a stick’), vessel perforation leading to retroperitoneal haematoma, aortic dissection, annulus rupture, and left ventricular perforation represent more severe complications which are fatal if not rapidly recognized and treated. Although urgent surgical intervention may be necessary in the management of major vascular complications, innovative percutaneous techniques involving proximal balloon occlusion of the iliac arteries and/or endovascular stent deployment have been suggested as useful in preventing and treating some of these issues.21,24,25

An association between the occurrence of major vascular complications and survival has been demonstrated by several authors (Figure 1).2,5,20,21,26 In the light of these data, it is crucial to reduce the rate of vascular complications. Improved experience and patient selection as well as exploring alternative access routes have shown to be effective.27

Bleeding complications

Bleeding rates have been reported without much consistency in the use of definitions. Using standardized endpoint definitions, life-threatening bleeding has been reported occurring in 15.6%, whereas any minor, major, or life-threatening bleeding occurred in >40% of patients.28 At this rate, it is the most frequent complication post-TAVI, with 42.6% of patients requiring ≥1 unit of transfused blood. This, however, might be an overestimation of the true burden of TAVI; it has been reported that many patients receive blood transfusions although no obvious source of bleeding is present,29 which may be the result of the high prevalence of baseline anaemia in this elderly cohort of patients.30 In addition, no regulations exist on when to transfuse patients, and haemoglobin cut-off values as indication for transfusion may be very different between institutions.

Predictors of bleeding complications are similar to those for vascular complications, since both complications frequently occur in parallel. A recent study shows that patients who received ≥1 unit of blood had a significantly higher rate of in-hospital mortality (14.8 vs. 4.3%, P < 0.05) and a longer length of stay (17 ± 2 vs. 7 ± 1 days, P < 0.05). Those patients that received ≥3 units of blood had significantly lower 6-month survival, whereas those with 0–2 units had similar survival to patients without any transfusion.31

The use of newer generations of transcatheter heart valves and smaller delivery systems as well as increasing operator experience will likely reduce the rate of bleeding complications. The study by Gurvitch et al.32 showed that, although not statistically significant, the rate of patients who received >4 units of packed red blood cells decreased from 11.1% in the first half of their experience to 5.9% in their last patients (P = 0.13).

Acute kidney injury

Several reports have focused on acute kidney injury (AKI), and significant injury [risk, injury, failure (RIFLE) ≥2] has been reported with an incidence of ~7–8%.28 Many of these studies were consistent in identifying blood transfusions as a predictor of AKI, but other factors are associated as well: hypertension, chronic obstructive pulmonary disease, baseline renal function, previous myocardial infarction, and the logistic EuroSCORE.33,34

Bagur et al.34 reported on 213 patients who underwent TAVI. According to their definition (a decrease of >25% in eGFR at 48 h following the procedure, or the need of haemodialysis during index hospitalization), 11.7% (25 out of 213) of patients had AKI. Those patients had significantly higher in-hospital mortality (28 vs. 7.4%, P = 0.005), and AKI was, even in multivariate...
analysis, a predictor of hospital mortality (OR = 4.14, 95% CI 1.42–12.13).

Long-term survival in patients with AKI has recently been reported by Nuis et al.\(^1\) In their cohort of 118 patients, AKI as defined by the RIFLE criteria occurred in 18.6% (\(n = 22\)). At a median of 13 months of follow-up, AKI was the only independent predictor of late mortality (HR = 2.79, 95% CI 1.36–5.71).

**Conduction disturbances**

Multiple reports have been published on conduction disturbances post-TAVI.\(^{15,36,37}\) It is generally accepted that the self-expandable CoreValve\(^{\text{TM}}\) system, because of the higher and longer-lasting radial forces as well as the deeper implantation site in the left ventricle outflow tract, has a higher rate of pacemaker requirement than the Edwards SAPIEN system. A recent meta-analysis reported that \(\approx 28.9\% (23–36\%)\) of patients implanted with the CoreValve\(^{\text{TM}}\) valve and 4.9% (4–6%) of patients implanted with the Edwards SAPIEN valve will require a new permanent pacemaker.\(^2\) However, the rates reported in the literature have varied greatly. Variations in practice and threshold for pacemaker implantation among physicians may explain the discrepancy in new pacemaker insertion rates in current published series.

Persistent new left bundle branch block has been shown to be the most prevalent ECG finding post-TAVI, being present in up to 55 and 20% at 1 month after implantation of the CoreValve\(^{\text{TM}}\) or Edwards SAPIEN valve, respectively.\(^{27,38}\) However, the long-term clinical significance of this finding is unknown.

Right bundle branch block, low implantation of the prosthesis, small annulus diameter compared with implanted valve size, complete atrio-ventricular (AV) block at the time of the procedure, and CoreValve\(^{\text{TM}}\) device have been shown to be potential predictors of complete AV block post-TAVI.\(^{39,40}\) Given the variable timing of occurrence of high-degree AV block, continuous post-procedural ECG monitoring should be performed for at least 72 h in all patients at increased risk for this complication. Furthermore, recent data suggest that not only brady-arrhythmic events are important, but that the occurrence of new tachyarrhythmia, such as new-onset atrial fibrillation, also has a prognostic importance after TAVI.\(^17\)

**Paravalvular regurgitation**

Significant transvalvular regurgitation is rare after TAVI. However, paravalvular regurgitation, due to incomplete annular sealing, is common. Some degree of paravalvular aortic regurgitation is reported in 80 to 96% of cases. In most cases, the degree of regurgitation is trivial or mild. Grade \(\geq 2+\) regurgitation is found in 7–24% of patients.\(^{2,41,42,43,44}\) Although no trial has directly compared the Edwards SAPIEN and CoreValve\(^{\text{TM}}\) devices, the rates of regurgitation reported in the literature seem to be similar for the two devices.

Data from the PARTNER trial shows that significant paravalvular regurgitation \(\geq 2+\) is much more prevalent after TAVI than after SAVR (12 vs. 0.9%, \(P < 0.001\)).\(^6\) During the follow-up, regurgitation is more often reduced rather than worsening after TAVI (Figure 2A).\(^43,16,45\) Nevertheless, its clinical importance has been emphasized in several reports where grade \(\geq 2+\) regurgitation has shown to be an independent predictor of short- and long-term mortality (Figure 2B).\(^16,46,47,48\)

Therefore, correction of significant regurgitation post-implantation is needed, especially when moving to younger and lower risk patients (e.g. PARTNER II and SURTAVI). Re-dilation or implantation of a second, overlapping transcatheter valve can often correct the problem. Also, low implantation of the CoreValve\(^{\text{TM}}\) might be corrected by a snaring manoeuvre in which the valve is pulled to the correct position.\(^9\)

Predictors of \(\geq 1+\) paravalvular leakage for the Edwards SAPIEN device have been found to be larger annulus size, height, male sex, age, and cover index \(\leq 8\%\) [cover index = \(100 \times (\text{prosthesis diameter} – \text{TEE annulus size})/\text{prosthesis diameter}\)]. In a study, no aortic regurgitation (AR) of at least moderate degree was observed with a cover area \(> 8\%\).\(^11\) For the CoreValve\(^{\text{TM}}\) system, greater angle of the left ventricular outflow tract is associated with an increased risk of significant regurgitation, whereas a depth of 10 mm of the device in relation to the non-coronary cusp is associated with a decreased likelihood of AR.\(^50\)

**Coronary obstruction and myocardial injury**

Non-revascularized coronary artery disease is common in TAVI patients and, when severe, can increase procedural risk. In some patients, percutaneous revascularization may be desirable; however, clinical experience suggests that the majority of coronary disease in elderly patients can be managed conservatively.
Coronary obstruction of the left main or the ostium of the right coronary artery is a rare but potentially fatal event.\textsuperscript{51} It might occur if a calcified native leaflet is displaced over a coronary ostium\textsuperscript{52,53} or if the valve frame or the sealing cuff is positioned directly over a coronary origin. It could happen either at the time of balloon valvuloplasty or during the TAVI procedure. Factors that increase the risk of coronary obstruction include an unusually bulky native leaflet (adjacent to a coronary ostium), a low origin of the coronary ostium (often defined as < 12 mm from the basal leaflet insertion as assessed by multidetector computed tomography), a shallow sinus of Valsalva (offering less room for the native leaflet), an oversized prosthesis, and high implantation. Anecdotal cases have been reported in which acute coronary obstructions were successfully managed by immediate percutaneous angioplasty or bypass surgery.\textsuperscript{51,53,54,55} Careful evaluation by echocardiography or multidetector computed tomography is crucial to avoid this complication.

Myocardial injury associated with an elevation in cardiac markers following TAVI procedures could be explained by some degree of myocardial tissue compression caused by the device itself, global ischaemia instigated by short episodes of severe hypotension, and, finally, myocardial damage produced by the apical puncture and passage of the large catheter through the ventricular apex when the TA route is employed. Interestingly, transient ST-elevations, mostly in the anterior and lateral leads, have been described post- TA- TAVI immediately after the procedure in ~20% of patients and are probably related to incision and suturing of the apex.\textsuperscript{36} In fact, Rodés-Cabau et al.\textsuperscript{56} showed that TAVI is associated with some degree of cardiac troponin T rise above the upper normal limit in 97% of TF patients and in 100% of TA patients. Interestingly, after multivariate analysis, a greater elevation of cardiac troponin T was an independent predictor of mortality at 9 months as well as a factor correlated with less improvement in left ventricular ejection fraction.

Other complications

Other acute complications, less frequent but potentially lethal, have been described after TAVI: aortic rupture,\textsuperscript{57} aortic dissection,\textsuperscript{58} peri-aortic haematoma,\textsuperscript{59} ventricular or aortic embolization of the valve,\textsuperscript{60} and tamponade.\textsuperscript{61} Mitral valve apparatus damage resulting in severe acute mitral regurgitation has also been reported, especially with the TA approach.\textsuperscript{62} The wire used to deliver the device could have been malpositioned, either under or through chordae, resulting in severe distortion or irreversible damage of the mitral valve apparatus. Not unexpectedly, endocarditis has been described anecdotally.\textsuperscript{63,64} Acute structural valve failure, including prosthetic rupture or malfunctioning leaflet (‘frozen leaflet’), is a rare but possible complication after TAVI.

Conclusions

Currently, SAVR remains the standard of care for most patients with symptomatic severe aortic stenosis. However, with the publication of several real-world registries and lately, the pivotal PARTNER randomized trials, transcatheter AVR has become the standard of care for patients for whom surgical risk is prohibitive and a reasonable alternative for selected operable patients in whom the risk of either mortality or morbidity is ‘high’. Although initial reports confirmed the feasibility and safety of TAVI, observational registries and completed randomized trials have been limited by the use of older generation devices, enrolment of small numbers of patients, the initial learning curve of the TAVI operators, self-reported outcomes, and the use of non-standardized endpoints. Although bleeding and vascular complications are decreasing as TAVI technology improves and continues to miniaturize, stroke and residual paravalvular leak remain important challenges. Embolic protection devices, improved delivery systems, and restriction of the procedure to high-volume centres with a well-trained TAVI heart team offer potential solutions. Improvement of the current technology combined with adoption of standardized definitions\textsuperscript{55} for important clinical endpoints will enable meaningful comparisons and future well-conducted randomized trials.

Conflict of interest: P.G. has received consulting fees/honoraria from Edwards Lifesciences. D.W. and J.W. have received consulting fees from Edwards Lifesciences and St Jude Medical. M.R.W. and S.K. have received consulting fees from Edwards Lifesciences.

A.P.K. is a member of the steering committee for the SURTAVI trial. M.B.L. is a non-paid member of the Scientific Advisory Boards of Edwards Lifesciences and Medtronic Vascular. The other authors report no conflicts of interest.

References