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How to reduce uncommon but severe transcatheter aortic valve implantation complications: stroke, thrombosis, endocarditis, cognitive decline?

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Transcatheter aortic valve implantation has become a valid alternative to surgical aortic valve replacement for patients with symptomatic severe aortic stenosis, regardless of baseline surgical risk. The incidence of periprocedural complications has steadily declined over the years, thanks to technical advancement of transcatheter heart valves, delivery systems, and increased operators' experience. Beyond the most common periprocedural complications, there are a few uncommon but potentially severe complications that more often occur during follow-up, although they may also arise in the periprocedural phase. Stroke, infective endocarditis, valve thrombosis, and cognitive decline are among them. In this brief review, we describe the incidence, predictive factors, and potential preventive measures for those events.

On the ground of numerous randomized clinical trials and a huge clinical experience, transcatheter aortic valve implantation (TAVI) has become a valid alternative to surgical aortic valve replacement (SAVR) for patients with symptomatic severe aortic stenosis, regardless of baseline surgical risk. The incidence of periprocedural complications has steadily declined over the years, thanks to technical advancement of transcatheter heart valves (THV), delivery systems, and increased operators' experience. Yet, vascular complications, bleedings, and need for permanent pacemaker remain the most common complications of TAVI and most of our efforts are directed towards reduction of these events. Similarly, paravalvular regurgitation, valve malposition, cardiac structural complications (e.g. wire perforation, coronary occlusion), acute kidney injury, coronary compromise, and prosthesis–patient mismatch are less frequent complications but still predominantly occurring during the procedural or in the early post-procedural phase. Importantly, there are other less common but potentially severe complications of TAVI that may also arise in the periprocedural phase but have a predominant or common occurrence during follow-up. In this short review, we will discuss some of those rare events after TAVI, namely: stroke, valve thrombosis, endocarditis, and cognitive decline.

Stroke

Stroke and its devastating consequences with increased risk of short- and long-term morbidity and mortality[1] remains a feared TAVI complication, especially with the expansion of the technique towards younger and lower risk patients. Fortunately, with the increased operator and centre experience, new iteration of the devices and inclusion of lower risk patients its incidence has decreased from 5–10% at 30 days in early trials[2] to <1% in low-risk TAVI trials.[3]

The incidence of stroke is evenly distributed between the periprocedural phase and the follow-up (*Figure 1*). In fact, around 50% of post-procedural cerebrovascular events occurs within the first 24 h.[1] The majority of

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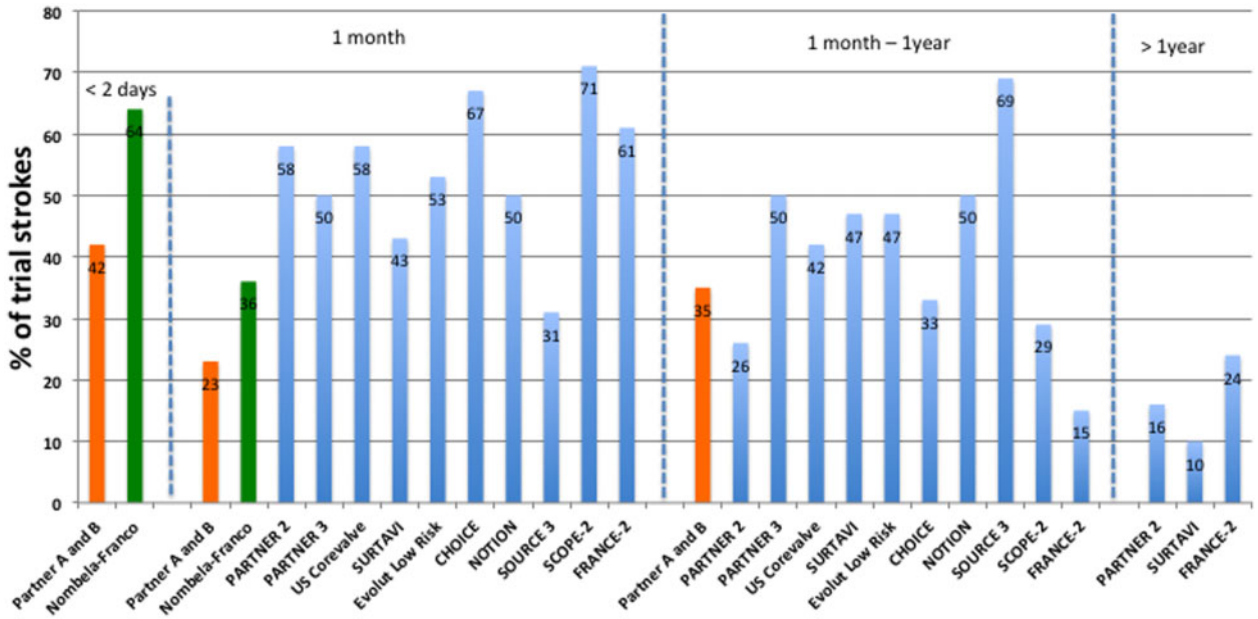

Figure 1 Incidence and timing of stroke after TAVI in the principal trials and clinical studies.

periprocedural strokes are embolic due to either atherocalcific material or non-atheromatous emboli (thrombus, air, devices) and the minority are non-embolic, e.g. prolonged hypotension. Various patient and procedural factors have been associated with the occurrence of early post-procedural stroke, including a lower aortic valve area and higher degree of valve calcifications that more frequently underwent balloon post-dilatation.[1,4] Interestingly, the presence of a porcelain aorta, a surgical stroke risk factor, is not related with early post-TAVI stroke.[5] Other procedural factors associated with periprocedural stroke are as follows: number of implantation attempts, valve embolization, and need for second valve implantation. Subacute (>1 day post-TAVI) and late (>30 days post-TAVI) strokes represent the remaining half of the stroke episodes, and are less determined by procedural factors and more related to patient-specific factors as new-onset atrial fibrillation (AF) and a history of chronic AF, peripheral vascular disease and prior cerebrovascular disease.[6]

The controversial issue of subclinical valve thrombosis and stroke will be discussed later in the article.

How can stroke risk be reduced?

First, providing an adequate procedural anticoagulation to reduce thrombus formation. Secondly, the less manipulation of the device the better, the less damage to the aortic wall, the less debris formation—'no touch' aortic arch crossing, non-traumatic co-axial valve crossing, and avoiding multiple recaptures and balloon pre- and post-dilation. Embolic protection devices (EPDs) were designed to prevent the embolic material reaching the cerebral vasculature. The currently available randomized trials, however, were not designed to detect a reduction in clinical cerebrovascular events. They included a relatively low number of patients and used surrogate endopoints, showing that EPD do reduce number and volume of new cerebral lesions identified on magnetic resonance imaging (MRI). Most of those lesions, however, are asymptomatic. Published results show that EPD reduce volume and size of periprocedural silent ischaemic brain lesions identified on MRI but not in reducing the incidence of new lesions associated with new neurological events.[7] The largest to date SENTINEL study with 365 patients showed similar volume of new brain lesions with or without EPD and no significant reduction of stroke (5.6% vs. 9.1%, $P=0.25$, respectively).[8] Similarly, the REFLECT trials used a different device that met the primary safety endpoint but did not meet the prespecified primary superiority efficacy endpoint.[9] This brings us to the point of silent brain infarcts (SBI) after TAVI, present in up to 70% of TAVI patients, an incidence higher then surgery[10] that probably represents an inherent part of the endovascular procedure. The number of SBI per patient depends on the strength of the MRI magnet used—a stronger magnet showing more small lesions.[11] The presence of SBIs is associated with prevalence of conventional stroke risk factors (diabetes and chronic kidney disease) but procedural factors such as balloon pre-dilations have been associated with more lesions per patient.[11] Although termed 'clinically silent', the consequences of SBI lesions depend on their location within brain areas—when they affect areas without primary motor, sensory or linguistic functions they remain silent. Outside TAVI setting SBIs have been associated with cognitive dysfunction.[12] Their impact on cognitive function after TAVI will be discussed later. As stated previously, EPDs do not reduce the absolute number of new SBIs but have been associated with smaller volume of lesions and smaller total SBI volume.[11] It is therefore difficult to give strong evidence-based recommendations on EPD during TAVI. The ongoing PROTECTED TAVR trial (clinicaltrials.gov NCT 04149535) will randomize 3000 patients undergoing TAVI to cerebral protection vs. no EPD with a

clinical primary endpoint (stroke at 72 h) and should provide more definitive answers.

As previously mentioned, around half of the stroke episodes after TAVI occur during follow-up and mostly derivate from common stroke risk factors: atrial fibrillation, aortic atherosclerosis, hypertension, and carotid disease. Post-procedural and long-term stroke prevention should therefore be personalized using guideline-recommended therapy with respect to individual risk factors.

Transcatheter valve thrombosis

Subclinical valve thrombosis (SLT) is an imaging diagnosis defined as the finding, in an asymptomatic patient, of a hypo-attenuated leaflet thickening (HALT). HALT is diagnosed by an increased thickness in typically meniscal configuration on one or more leaflets visually identified on CT (2D multiplanar reconstruction or 3D volume rendering), with or without a reduced leaflet motion (RLM). RLM is defined as a systolic leaflet excursion restriction involving the basal parts or the whole leaflets on 4-dimensional (4D) CT. At the time of detection, these lesions must be associated with absent or mild haemdynamic changes (and absent symptoms or sequela) and therefore a transthoracic echo is unsuitable for the diagnosis. Furthermore, the presence of increased gradients may not correspond with HALT and/or RLM on CT nor, vice versa, the lack of increased gradient excludes SLT.[13] SLT has been documented in all types of transcatheter valves and the prevalence of SLT after TAVI (11–40%) is higher compared with bioprosthetic surgical valve (4%).[14] It can occur at any time after TAVI peaking in the early postoperative period and most published studies performed CT within 90 days of valve implantation. Patients who are on anticoagulation have a significantly lower incidence of SLT compared to patients on single or double antiplatelet therapy.[15] The identified predictors of early leaflet thrombosis were low-flow low-gradient aortic stenosis, severe prosthesis-patient mismatch, larger prosthesis size, larger sinus of Valsalva and elevated D-dimers during follow-up.[16] SLT does not seem to be associated with clinical events with only one observational study of pooled registries hinted to an increase in stroke and TIA events in patients with SLT with the limit of very small numbers.[17] The majority of published data, however, does not confirm this finding and in fact a reduced SLT risk in patients on DOAC in GALILEO[18] or ATLANTIS[19] trials did not translate into a clinical benefit at 1 year with respect to the overall primary composite endpoint including stroke. The natural history of SLT appears to be stability or progression with spontaneous reversal being less probable and the treatment of SLT is with oral anticoagulation (OAC).[13] Although so far no clinical effect of the CT finding of HALT/RLM has been reported, whether this represent just an imaging abnormality, a physiological process or an early phase of valve thrombosis and could have a detrimental impact on valve function in longer follow-up is not known.

Currently, there is neither evidence to support routine CT for detection of post-TAVI SLT nor the evidence to support routine patient anticoagulation in the early post-TAVI phase, given the apparent lack of association with clinical outcomes but this aspect must be thoroughly investigated as it is especially relevant in low-risk patients in whom SLT may affect valve durability.

Symptomatic valve thrombosis of transcatheter aortic bioprostheses is rare (0.6–3%),[20] yet likely under-reported. It is defined as any thrombus attached to or near an implanted valve that interferes with valve function and is usually diagnosed on echocardiography. In fact, although thrombus may be not directly visualized with echocardiography, Doppler evaluation shows a significant increase of transvalvular gradients. Most patients present in the first year after implantation with progressive dyspnoea and have a poor prognosis, with death in around 30%.[15,21] Balloon-expandable valve and valve-in-valve implantation were suggested as independent predictors in a large US registry.[20] OAC appears to be effective in the prevention and treatment of valve thrombosis and TAVI thrombosis rarely requires thrombolysis.[20] However, if there are no doubts that warfarin represents the first-line treatment in the presence of THV thrombosis, prevention of this event with anticoagulation was not associated with a clinical advantage in trials evaluating the best anti-thrombotic strategy after TAVI and cannot be recommended. Clinical suspect of valve thrombosis must be raised by progressive dyspnoea and a rapid, significant increase in transvalvular gradient. Echocardiography and CT scan should confirm leaflet thickening and or thrombus.

Endocarditis

Post-TAVI infective endocarditis (IE) occurs with an incidence of 0.9–3.1% per patient-year similar to that following surgical aortic valve replacement (SAVR).[22] One-year mortality rates (40–66%), although decreasing, are significantly higher than SAVR IE.[23] In contrast to the aetiology of post-SAVR IE (*Staphylococcus spp*), a frequent causative organism after TAVI is *Enterococcus spp*, a common groin pathogen, implicating potential sources of bacteraemia.[22] Although TAVI IE is usually complicated with a surgical indication in up to 80%, the rate of surgical treatment is very low (20%).[23]

The TAVI-related higher IE risk can be due to multiple factors including groin puncture, general anaesthesia, orotracheal intubation, significant amount of exposed metal frame, the presence of paravalular leak and new-pacemaker implantation.[22] To mitigate some of the risks the TAVI procedure should be streamlined and simplified with less invasive TAVI approach using a single groin puncture, no general anaesthesia and intubation, conservative use of temporary pacemaker allowing for early patient ambulation, less unplanned urinary catheterization and shorter hospital staying and therefore reducing the risk of nosocomial infections. Initially, patients treated with TAVI were compromised high-risk patients unfit for surgery but more recently candidates for TAVI are becoming younger, with less comorbidities. They undergo fewer invasive diagnostic and therapeutic procedures thus reducing the overall risk of IE. In fact, the incidence of early IE (within 60 days) has more than halved in recent years.[23] Given that the risk of IE is not lower after TAVI in comparison with SAVR, all patients with THV should receive appropriate

antibiotic prophylaxis, as indicated in the current guidelines.[24] Routine pre-procedural antibiotic prophylaxis is recommended for all patients undergoing TAVI prior to vascular access to reduce the risk of wound infection and endocarditis[25] but enterococci exhibit a high-level resistance to most commonly used cephalosporins (cefuroxime and cefazoline).[26] Thus, appropriate aseptic conditions are mandatory and although there seems to be no difference in outcomes between TAVI performed in a catheterization laboratory or in a hybrid room,[27] it should be highlighted that asepsis for TAVI must have the same standards and characteristics of a cardiac surgical procedure.

Cognitive decline

Approximately 30% of patients undergoing TAVI have a degree of baseline cognitive impairment, usually of vascular aetiology, with its key feature of subcortical deficits (region with the highest number of microembolic lesions).[28] Cognitive function can change after TAVI and detection of changes requires appropriate tests. Many studies using mini-mental state examination (MMSE) as global cognition assessment tool showed an improvement within 3 months after the procedure. However, small improvements of MMSE may be clinically irrelevant and may be due to learning effects and MMSE may be insufficient to test executive function and subtle memory changes.[28] When assessing cognitive function more robustly approximately equivalent numbers of TAVI patients experience cognitive decline and cognitive improvement, which gives rise to the null findings (preservation of cognitive function) using a whole-group-analysis approach (cognitive decline in 14% and improvement in 19% within 6 months after TAVI).[29]

The inconsistency between results of the trials can be explained also by the fact that the direction of cognitive function change in a single patient depends on the balance between the mean number and location of SBI, the degree of improvement in cardiac output and cerebral perfusion and on functional status change that can contributes to improved cognition after TAVI. Moreover, most studies are small size, lack control groups and have a short follow-up.

Despite the limitations, it has been shown that the mean number and not just the incidence of SBI might be associated with post-procedural cognitive dysfunction after TAVI and that a threshold effect exist—a certain volume of infarcted brain is required before cognition decline becomes clinically evident.[7,11] In a meta-analysis the use of EPD, by reducing microembolic load, was found to have a significant association with lower prevalence of cognitive decline up to 1-week post-TAVI. However, this effect was no longer significant at 1 month.[29] Baseline cognitive impairment was the only factor associated with post-TAVI cognitive improvement.[29] The use of EPD and early mobilization have been also associated with reduction in post-operative delirium—a predictor of cognitive impairment and reduced long-term survival.[7,30]

Conclusions

Stroke, infective endocarditis, valve thrombosis, and cognitive decline are uncommon complications of TAVI that may occur early in the periprocedural phase or later on during follow-up. There is a valid rationale to hypothesize that a minimalist TAVI, with a streamlined procedure and early discharge, could reduce infection rates and prevent cognitive decline, especially in elderly frail patients. Embolic protection devices can reduce the number of silent cerebral micro embolizations but more evidence of clinical efficacy in preventing cerebrovascular accidents or cognitive decline is needed before recommending universal utilization. Post-TAVI pharmacologic strategies should be tailored to prevent stroke and valve thrombosis during follow-up. More studies are necessary to identify risk factors and most effective preventive measures for these untoward events.

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