Stroke following transcatheter aortic valve implantation. Is neuroprotection justified?

Maciej Dąbrowski, Adam Witkowski

Department of Interventional Cardiology and Angiology, Institute of Cardiology, Warsaw, Poland

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Abstract

Degenerative aortic stenosis (AS) is the most frequent type of valvular heart disease. In patients with symptomatic AS surgical aortic valve replacement (SAVR) is a recommended treatment strategy. Due to a high risk of perioperative mortality, up to 30% of patients with AS are considered not suitable for SAVR. In the last 10 years dynamic development of transcatheter aortic valve implantation (TAVI) has been observed as an alternative to SAVR in patients with AS and high risk for surgery. In the two randomized trials published so far and numerous registries, stroke and transient ischemic attack still remain serious periprocedural complications after TAVI. Because the majority of these episodes are driven by microembolization during the procedure, different neuroprotection devices were developed and clinically tested. Embrella and SMT are deflector devices, using a microporous membrane mounted on a nitinol frame, designed to cover the ostia of the brachiocephalic trunk and the left carotid artery. The Claret System is designed to filter cerebral blood flow within the ostia of the brachiocephalic trunk, as well as in the left common carotid artery. Randomized clinical data have demonstrated that TAVI is associated with more neurological events compared to SAVR. However, to date the efficacy of the neuroprotection systems has not been assessed in randomized trials. Before we know the results of such trials, the use of the devices should be limited to patients at high risk of neurological complications, such as patients with previous stroke, massive calcification on aortic leaflets, annulus and porcelain aorta.

Key words: transcatheter aortic valve implantation, stroke, neuroprotection.

Degenerative aortic stenosis (AS) has become the most frequent type of valvular heart disease. In patients with symptomatic AS surgical aortic valve replacement (SAVR) is a recommended treatment strategy [1–3]. However, because of many comorbidities in adults of advanced age and a high risk of perioperative mortality up to 30% of patients with symptomatic AS are considered unsuitable for SAVR [1–4]. In the last 10 years dynamic development of a new treatment modality, transcatheter aortic valve implantation (TAVI), has been observed as an alternative to SAVR in patients with AS and high risk for surgery [4–7]. From 2002 to June 2013 90 000 TAVIs were performed worldwide including 900 done in Poland from November 2008 to June 2013.

Because conservative medical therapy in patients with severe AS is ineffective and balloon valvuloplasty plays only a very limited role, TAVI emerged as feasible and clearly beneficial therapy in inoperable or high surgical risk patients. Transcatheter aortic valve reduces all-cause and cardiac mortality, improves quality of life and shortens the postprocedural rehabilitation period [8–10]. In the two randomized trials published so far and numerous registries, 30-day mortality after TAVI was 0–25% [8–10]. Nevertheless, stroke and transient ischemic attack (TIA) still remain serious periprocedural complications after TAVI [8–10].

Transcatheter aortic valve implantation versus medical treatment and surgical aortic valve replacement

Effectiveness of TAVI versus conventional pharmacotherapy in inoperable patients was proved in the randomized, multicenter PARTNER trial (cohort B). This study recruited 358 patients with severe symptomatic AS considered unsuitable for conventional surgery. Patients were randomized to transfemoral implantation of an Edwards-Sapien bioprosthesis or standard therapy supported with aortic balloon valvuloplasty in 63.7% of

Corresponding author:
Maciej Dąbrowski MD, PhD, Department of Interventional Cardiology and Angiology, Institute of Cardiology, 42 Alpejska St, 02-359 Warsaw, Poland, tel.: +48 22 343 42 72, e-mail: macidabro@yahoo.com
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cases [8]. The mean logistic EuroSCORE was 30.4 ±9.1% for all patients recruited to PARTNER B and 26.4 ±17.2% in the TAVI arm. After 1-year follow-up there was a 20% reduction of all-cause death and 24% reduction of cardiovascular mortality in favor of patients who received transfemoral aortic valve replacement [8]. The composite end point of death and major stroke was also significantly reduced in the TAVI cohort. The function of the implanted bioprosthesis was well preserved after one year. The randomized PARTNER cohort A trial compared TAVI (from transfemoral or transapical approach) with SAVR in 699 patients with high surgical (but not prohibitive) risk of conventional aortic valve surgery. Ninety-four percent of patients were in NYHA class III or IV, with predicted perioperative mortality of 29% in the logistic EuroSCORE. The rates of death from any cause were 3.4% in the transcatheter group and 6.5% in the surgical group at 30 days (p = 0.07) and 24.2% and 26.8%, respectively, at 1 year (p = 0.44), a reduction of 2.6 percentage points in the transcatheter group (p = 0.001 for non-inferiority). The rates of major stroke were 3.8% in the transcatheter group and 2.1% in the surgical group at 30 days (p = 0.20), 5.1% and 2.4%, respectively, at 1 year (p = 0.07), and 33.9% and 35% at 2 years [9–11].

However, the results of PARTNER cohort A also showed an almost two-fold increase in the risk of stroke or TIA in patients who underwent TAVI in comparison to surgically treated patients: 5.5% vs. 2.4% after 30 days, 8.7% vs. 4.3% after 1 year and 11.2% vs. 6.5% after 2 years [9], TAVI vs. SAVR, respectively for all. In cohort B of the PARTNER trial TIA and stroke rates were also increased in the TAVI group [8]. Both cohort A and B of the PARTNER trial and Core Valve Expanded Evaluation Registry reported that 30% to 50% of strokes occurred between the second day and 30 days after TAVI [8–12]. However, the majority of neurological episodes occurred during the first 24 h after the procedure [13].

Pathophysiology of cerebral hypoperfusion during transcatheter aortic valve implantation

Pathophysiology of new cerebral perfusion abnormalities after TAVI is multifactorial. The predictors of TIA and stroke are advanced patient's age (> 80 years), previous stroke, atrial fibrillation, bulky aortic wall and aortic valve calcifications and left ventricular dysfunction. Also old and periprocedurally formed thrombi and air bubbles may be a source of brain embolization during TAVI. Transient cerebral hypoperfusion may also be a result of catheter manipulations, cardiac arrhythmias, rapid right ventricular pacing during balloon valvuloplasty and prosthesis implantation and periprocedural hypovolemia. However, none of these has been clinically proven yet [14–19].

Several studies with magnetic resonance imaging (MRI) suggest that subclinical cerebral perfusion abnormalities occurred much more frequently than TIA or stroke and were detected in 66–84% of patients who underwent TAVI [14–20]. This observation supports the hypothesis that TIA and strokes after TAVI are caused by embolization.

There is no correlation of the rate of cerebral defects in MRI and access site nor with clinically overt stroke. Acute stroke on the other hand is a devastating phenomenon and correlates with increased 1-year mortality and leads to cognitive impairment. The role of subclinical MRI cerebral defects remains unclear, but some surgical data suggest an association between the number of periprocedural MRI defects and cognitive impairment in late follow-up [14–24].

A study utilizing transcranial Doppler ultrasound during TAVI demonstrated the occurrence of cerebral microemboli in the majority of patients, mainly during direct manipulation of the diseased valve and crushing of the leaflets during implantation (41%), manipulations within the aortic arch and introduction of the stent-bioprosthesis assembly into the native aortic valve (37%) and balloon postdilatation (22%). The rate of embolization episodes and the number of emboli did not differ in relation to the route of TAVI access (transapical vs. transfemoral) [25, 26]. None of these patients suffered from clinical stroke or TIA [25–27].

Clinical evidence for neurologic complications during transcatheter aortic valve implantation

In a cohort of 214 patients after Core Valve implantation presented by Nuis *et al*., periprocedural stroke was diagnosed in 19 (9%) and the risk factors of acute stroke were recent onset of atrial fibrillation and significant aortic valve incompetence diagnosed before the procedure [28]. In a much larger analysis of 1061 patients the rate of cerebrovascular episodes (CVE) was 5% during the first 30 days after the procedure, with balloon postdilatation, prosthesis embolization and recent onset of atrial fibrillation as the strongest predictors of CVE. After 12 months in this group late CVE were diagnosed in 35 patients (3.3%) and the predictors were new onset atrial fibrillation and significant aortic regurgitation preceding TAVI [29]. In a metaanalysis of 53 studies with over 10 000 patients the risk of stroke or TIA during/after TAVI was 3.3% in 30-day follow-up, with the lowest rate of 2.7% after transapical access [30]. In all of these studies major stroke was associated with a higher 30-day mortality rate [28–30].

Cerebral protective devices

Despite the recent advances in TAVI technology, e.g. downsizing of TAVI device systems, periprocedural neurologic complications remain an important and still unresolved issue. Because the majority of these episodes are

driven by microembolization during the procedure, different neuroprotection devices were developed and clinically tested. There are published data on three emboli protection systems dedicated to TAVI: Embrella (Edwards Lifesciences, Irvine, CA, USA), Montage System (Claret Medical, Inc., Santa Rosa, CA, USA), and SMT (SMT Research and Development, Herzliya Pituach, Israel) [31–33].

Both Embrella and SMT are deflector devices, using a microporous membrane mounted on a nitinol frame, designed to cover the ostia of the brachiocephalic trunk (and its right carotid branch) and the left carotid artery originating directly from the transverse aorta, thereby deflecting emboli away from the cerebral circulation. The Claret Montage System, based on the filter concept used for carotid angioplasty, is designed to filter cerebral blood flow within the ostia of the brachiocephalic trunk and its right carotid branch, as well as in the left common carotid artery, both originating directly from the aortic arch [31–34].

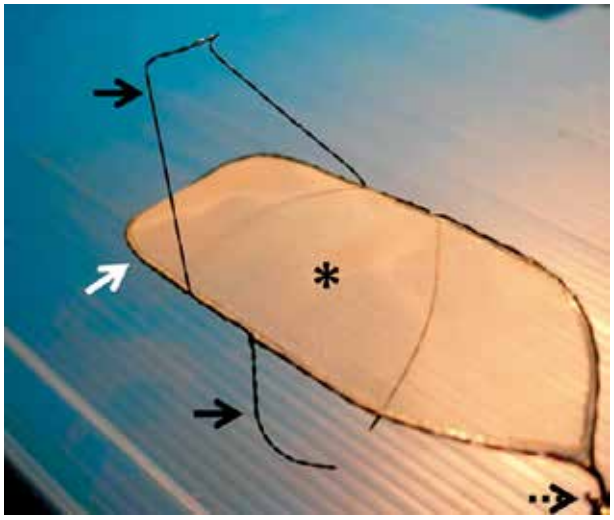

Fig. 1. SMT. The SMT device consists of 5 functional parts: a dual wire nitinol frame (white arrow), a thin nitinol mesh (asterisk), an upper and lower stabilizer (black arrows) and the tail end (dotted arrow)

Fig. 2. The Embrella device consists of a porous membrane, a nitinol frame and a nitinol shaft

The SMT device (Figure 1) is a biocompatible filter, implanted in a transcatheter procedure, through a needle puncture in either common femoral artery, and is located under fluoroscopy in the aortic arch. The SMT device consists of 5 functional parts:

1) a dual wire nitinol frame that anchors the device in the desired location in the aortic arch,
2) a thin nitinol mesh designed to allow blood flow through, while diverting clinically significant emboli towards the descending aorta,
3) and 4) two stabilizers that facilitate the positioning of the filter; they lock into position by retrograde traction and gradually release from the delivery shaft; the filter is anchored in the aortic arch by the upper stabilizer in the innominate artery ostium which prevents filter retrograde migration and by the lower stabilizer that pushes the filter in apposition with the upper wall of the aortic arch,
5) the tail end (distal from the heart) of the SMT filter is a connection by which the SMT filter remains securely attached to the plunger ("pusher") during the procedure.

While the filter does not block or decrease normal blood flow to the brain via the aortic branches and vertebral artery, it diverts emboli and particulate matter downstream, where they can be treated effectively or probably cause less harm, although the clinical impact on kidney and other end-organ function has to be further established. The SMT device is made of nitinol wires and can be crimped into an 8 Fr or 9 Fr sheath, the latter providing the possibility to use simultaneously a 6 Fr pigtail through the same sheath, hence avoiding additional groin punctures. Upon deployment the filter unfolds and regains its original shape [34].

The Embrella Embolic Deflector (Figure 2) is designed to cover the ostia of the brachiocephalic trunk (and its right carotid branch) and the left carotid artery originating directly from the transverse aorta, thereby deflecting emboli away from the cerebral circulation. Deflecting petals consist of a heparin-coated polyurethane membrane with 100-µm-sized pores. This membrane is mounted on a nitinol frame, which itself is attached to a 110-cm long, 0.035-inch (0.09 cm) nitinol shaft. When deployed, the petals of the device extend over a length of 58 mm with a width of 25 mm. Three radiopaque markers help fluoroscopy-guided deployment: one at the outer point of each petal, and one on the distal shaft. The entire system can be delivered through a 6-Fr delivery sheath introduced from the right arm [32].

The Claret System (Figure 3) consists of two filters. The proximal filter consists of a nitinol frame designed to allow apposition within vessels measuring 9–15 mm in diameter and containing a polyurethane filter with 140 µm

diameter pores. The frame is radiopaque and will expand to oppose and seal against the vessel wall when unsheathed. The proximal filter is attached to a 100 cm long catheter, and following insertion, the proprietary proximal filter is deployed in the brachiocephalic artery, followed by the delivery of a second filter to the left common carotid artery (Figure 4). The entire system can be delivered through a 6 Fr sheath introduced through either the brachial or radial artery of the right arm. The system is deployed immediately prior to passage of the TAVI delivery catheter through the aortic arch and into the native valve during the TAVI procedure, and is removed after removal of the TAVI delivery catheter [33].

The stroke conundrum associated with TAVI is not trivial, especially if this technology would shift to lower risk and younger patient populations with AS and patients with degenerated aortic bioprosthesis after previous SAVR [35–39]. Also an increasing number of centers want to offer TAVI to their patients. Recently published data on TAVI emphasized the issue of clinically silent cerebral defects and their possible future influence on cognitive and motor functions [21–24].

The first human experience with embolic protection systems during transcatheter aortic valve implantation

Onse *et al*. published the first human experience with an SMT device [34]. In 15 patients with severe AS undergoing transfemoral or transapical aortic valve implantation, the SMT Embolic Deflection Device was advanced utilizing the contralateral femoral artery access using a 9 Fr delivery sheath. Brain diffusion weighted (DW)-MRI was obtained in 10 patients before and at 4 days after the procedure and retrospectively compared to 20 patients previously undergoing TAVI without a protection device. Successful placement of the embolic protection device was achieved in all patients. Additional procedural time due to the use of the device was 7 min (±2 min). There were no procedural complications. No patient developed new neurological symptoms or clinical findings of stroke except 1 patient who suffered from a transient ischemic attack (TIA) two days after the procedure. DW-MRI showed 3.2 new cerebral lesions per patient, compared to 7.2 new lesions per patient in the group without an SMT filter [34].

Naber *et al*. published first-in-man use of the Claret Filer system [33]. Patients scheduled for TAVI were prospectively enrolled at three centers. The Claret CE Pro™ (Claret Medical, Inc. Santa Rosa, CA, USA) cerebral protection device was placed via the right radial/brachial artery prior to TAVI and was removed after the procedure. The primary endpoint was technical success rate. Secondary endpoints encompassed procedural and 30-day stroke rates, as well as device-related complications. Deployment of the Claret CE Pro™ cerebral protection device was intended for use in 40 patients; 35 devices were implanted into the aortic arch. Technical success rate with delivery of the proximal and distal filter was 60% for the first generation device and 87% for the second-generation device. Delivery times for the first-generation device were 12.4 ±12.1 min and 4.4 ±2.5 min for the second-generation device ($p < 0.05$). The quantity of contrast used related to the Claret CE Pro System was 19.6 ±3.8 ml. Captured debris was documented in at least 19 of 35 implanted devices (54.3%). No procedural transient ischemic attacks, minor strokes or major strokes occurred. Thirty-day follow-up showed one minor stroke occurring 30 days after the procedure, and two major strokes both occurring well after the patient had completed TAVI [33].

Nietlispach *et al*. described initial human experience with a novel Embrella cerebral embolic protection device [32]. With right radial artery access, the embolic protec-

Fig. 3. The Claret System consists of two filters: proximal within a nitinol frame to be expanded into the brachiocephalic trunk, and distal to protect the left common carotid artery

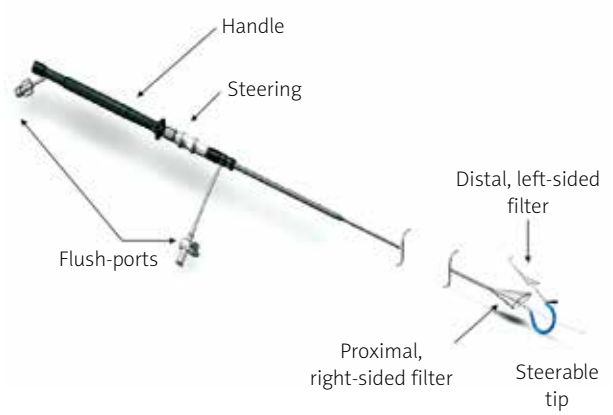

Fig. 4. The Claret CE Pro™ System consists of a proximal filter which is fixed within a flexible nitinol frame. The frame is radiopaque and will expand to oppose and seal to the vessel wall when unsheathed. Following first filter expansion, the system enables the delivery of the distal filter to the left common carotid artery

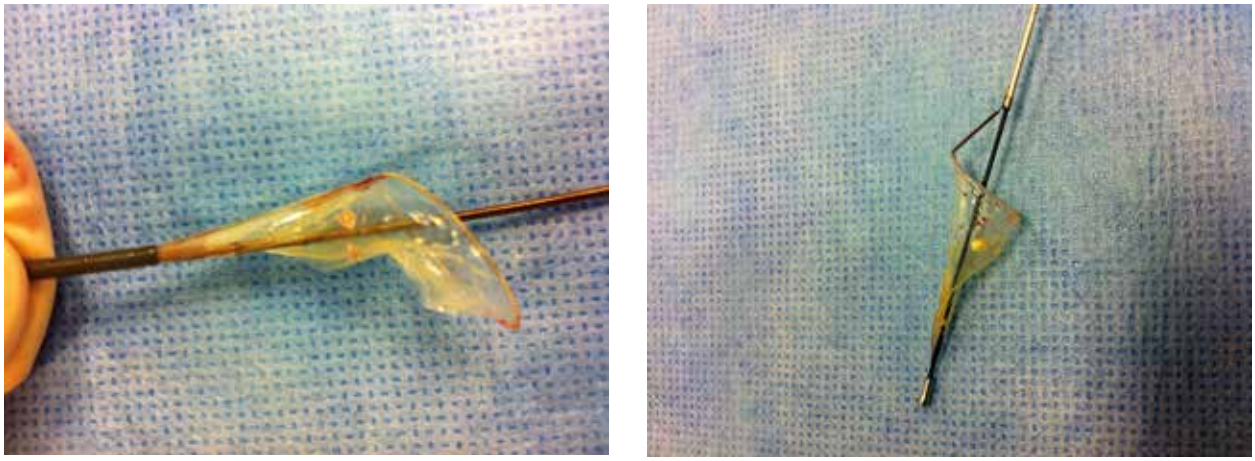

Fig. 5. Representative examples of TAVI-induced liberation of debris. Representative specimens were retrieved within the proximal (right, brachiocephalic filter) and distal filters (left, carotid filter) verifying successful bilateral reduction of embolic burden with the Claret CE Pro™ system during TAVI

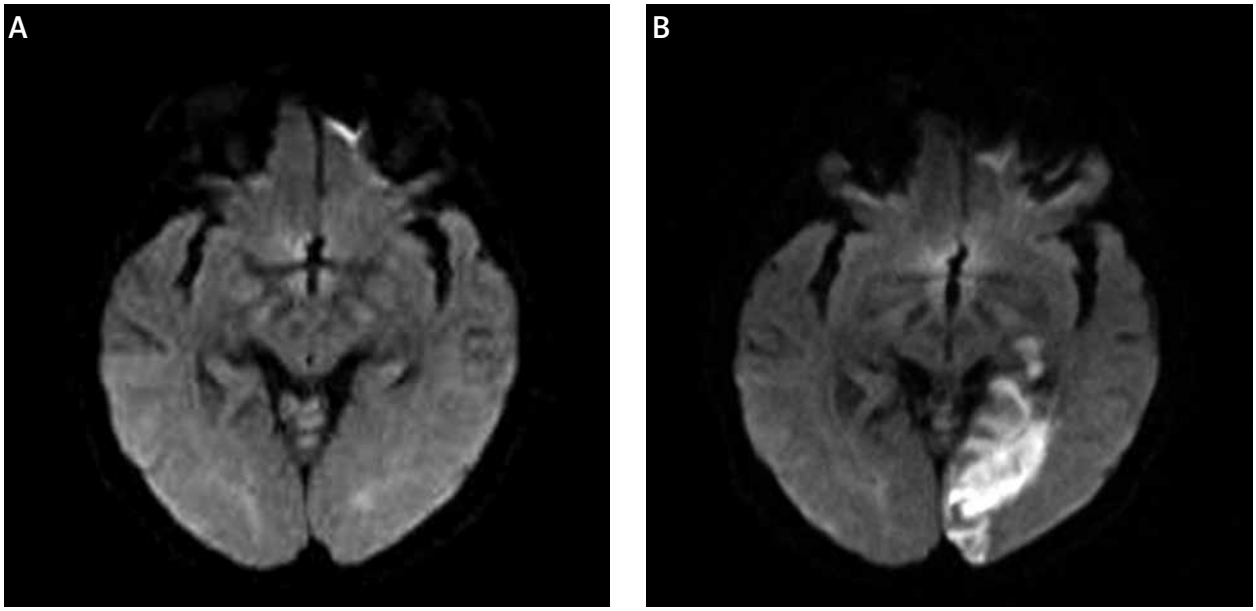

Fig. 6. Diffusion weighted MRI of the brain. Cerebral images, including the cerebellum and brainstem, before (**A**) and after (**B**) the transcatheter aortic valve implantation procedure. This patient had one, large new cerebral infarct

tion device was advanced into the aortic arch. The device was used in 4 patients (mean age 90 years) with severe aortic stenosis undergoing aortic balloon valvuloplasty (n = 1) or transcatheter aortic valve implantation (n = 3). Correct placement of the embolic protection device was achieved in all patients. Continuous brachiocephalic and aortic pressure monitoring documented equal pressures without evidence of obstruction to cerebral perfusion. Additional procedural time due to the use of the device was 13 min. There were no procedural complications. Pre-discharge cerebral MRI found no new defects in any of 3 patients undergoing TAVI and a new acute cortical infarct in 1 asymptomatic patient after balloon valvuloplasty alone. No patient developed new neurological symptoms or clinical findings of stroke [32].

The SMT Embolic Deflection Device probably provides the most complete protection of the brain, covering the ostia of all major arteries originating from the aortic arch and avoiding manipulations in the left common carotid artery and brachiocephalic trunk. However, because of the large diameter the device can be introduced to the arterial system using an 8 Fr or 9 Fr delivery sheath [34].

The Claret Filter System and Embrella can be introduced using a transradial approach and a 6 Fr delivery sheath. Stiffness of this device and the manipulations during both proximal and distal filter introduction into the brachiocephalic trunk and left common carotid artery may provoke spasm and other vascular complications and embolization. Also the left vertebral artery (originating from the left subclavian artery) is not protected with

the Claret device and may be a potential source of cerebral defects during TAVI.

The experience at the Institute of Cardiology in Warsaw

At the Institute of Cardiology in Warsaw we performed the first two Polish TAVI procedures using the Claret Filter System. In 1 patient it was not possible to fully expand the distal filter on the left common carotid artery because of unusual anatomy (bovine arch). In both filters embolic material was found after the successful completion of TAVI (Figure 5) and in DW-MRI there were no new acute cerebral defects. A second Claret device had to be used in this case to achieve full cerebral protection. In the second patient we observed minor stroke with partial amaurosis in the right eye. In DW-MRI a new acute ischemic focus was found in the territory corresponding to the left vertebral artery (Figure 6).

Conclusions

Since randomized clinical data have demonstrated that TAVI is associated with more neurological events compared to SAVR, every effort should be made to reduce such devastating complication as stroke, which dramatically impact on a patient's quality of life. The best tool we have to understand the true impact of embolic protection devices in preventing TAVI related strokes and to evaluate whether these devices would justify the additional cost as well as risk they probably add to the procedure is to perform carefully designed randomized clinical trials. Before we know the results of these trials, today the use of cerebral protection devices should be limited to patients at high risk of neurological complications, such as patients with previous stroke, massive calcification on aortic leaflets and annulus and porcelain aorta. Postprocedural atrial fibrillation is another important issue that seems to be associated with neurological events after TAVI and warrants careful documentation and appropriate therapeutic action [40].

References

1. Vahanian A, Baumgartner H, Bax J. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J 2007; 28: 230–268.
2. Schwarz F, Baumann P, Manthey J. The effect of aortic valve replacement on survival. Circulation 1982; 66: 1105–1110.
3. Ross JJ, Braunwald E. Aortic stenosis. Circulation 1968; 38 (Suppl.): 61–67.
4. Iung B, Cachier A, Baron G, et al. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? Eur Heart J 2005; 26: 2714–2720.
5. Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on valvular disease. Eur Heart J 2003; 24: 1231–1243.
6. Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation 2002; 106: 3006–3008.
7. Cribier A, Eltchaninoff H, Tron C, et al. Early experience with percutaneous transcatheter implantation of heart valve prosthesis for the treatment of end-stage inoperable patients with calcific aortic stenosis. J Am Coll Cardiol 2004; 43: 698–703.
8. Leon MB, Smith CR, Mack M, et al.; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010; 363: 1597–607.
9. Smith CR, Leon MB, Mack MJ, et al.; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011; 364: 2187–2198.
10. Grube E, Buellesfeld L, Mueller R, et al. Progress and current status of percutaneous aortic valve replacement: results of three device generations of the corevalve revalving system. Circ Cardiovasc Inter 2008; 1: 167–175.
11. Kodali SK, Williams MR, Smith CR, et al.; PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012; 366: 1686–1695.
12. Piazza N, Grube E, Gerckens U, et al. Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 Fr) corevalve revalving system: results from the multicentre, expanded evaluation registry 1-year following CE mark approval. Eurointervention 2008; 4: 242–249.
13. Tay EL, Gurvitch R, Wijesinghe N, et al. A high-risk period for cerebrovascular events exists after transcatheter aortic valve implantation. JACC Cardiovasc Interv 2011; 4: 1290–1297.
14. Astarci P, Glineur D, Kefer J, et al. Magnetic resonance imaging evaluation of cerebral embolization during percutaneous aortic valve implantation: comparison of transfemoral and trans-apical approaches using Edwards Sapiens valve. Eur J Cardiothorac Surg 2011; 40: 475–479.
15. Kahlert P, Knipp SC, Schlamann M, et al. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. Circulation 2010; 121: 870–878.
16. Ghanem A, Müller A, Nähle CP, et al. Risk and fate of cerebral embolism after transfemoral aortic valve implantation: a prospective pilot study with diffusion-weighted magnetic resonance imaging. J Am Coll Cardiol 2010; 55: 1427–1432.
17. Rodés-Cabau J, Dumont E, Boone RH, et al. Cerebral embolism following transcatheter aortic valve implantation: comparison of transfemoral and transapical approaches. J Am Coll Cardiol 2011; 57: 18–28.
18. Arnold M, Schulz-Heise S, Achenbach S, et al. Embolic cerebral insults after transapical aortic valve implantation detected by magnetic resonance imaging. JACC Cardiovasc Interv 2010; 3: 1126–1132.
19. Fairbairn TA, Mather AN, Bijsterveld P, et al. Diffusion-weighted MRI determined cerebral embolic infarction following transcatheter aortic valve implantation: assessment of predictive risk factors and the relationship to subsequent health status. Heart 2012; 98: 18–23.
20. Van Mieghem NM, Serruys PW. Embolic protection devices during TAVI – the "proof of the pudding". EuroIntervention 2012; 8: 25–29.
21. Russell D. Cerebral microemboli and cognitive impairment. J Neurol Sci 2002; 203–204: 211–214.

22. Mosley THJ, Knopman DS, Catellier DJ, et al. Cerebral MRI findings and cognitive functioning: the Atherosclerosis Risk in Communities study. Neurology 2005; 64: 2056–2062.
23. Vermeer SE, Longstreth WTJ, Koudstaal PJ. Silent brain infarcts: a systematic review. Lancet Neurol 2007; 6: 611–619.
24. Duffis EJ, Jones D, Tighe D, et al. Neurological complications of coronary angiographic procedures. Expert Rev Cardiovasc Ther 2007; 5: 1113–1121.
25. Drews T, Pasic M, Buz S, et al. Transcranial Doppler sound detection of cerebral microembolism during transapical aortic valve implantation. Thorac Cardiovasc Surg 2011; 59: 237–242.
26. Szeto WY, Augoustides JG, Desai ND, et al. Cerebral embolic exposure during transfemoral and transapical transcatheter aortic valve replacement. J Card Surg 2011; 26: 348–354.
27. Reinsfelt B, Westerlind A, Ioanes D, et al. Transcranial Doppler microembolic signals and serum marker evidence of brain injury during transcatheter aortic valve implantation. Acta Anaesthesiol Scand 2012; 56: 240–247.
28. Nuis RJ, Van Mieghem NM, Schultz CJ, et al. Frequency and causes of stroke during or after transcatheter aortic valve implantation. Am J Cardiol 2012; 109: 1637–1643.
29. Nombela-Franco L, Webb JG, de Jaegere PP, et al. Timing, predictive factors and prognostic value of cerebrovascular events in a large cohort of patients undergoing transcatheter aortic valve implantation. Circulation 2012; 126: 3041–3053.
30. Eggebrecht H, Schmermund A, Voigtländer T, et al. Risk of stroke after transcatheter aortic valve implantation (TAVI): a meta-analysis of 10,037 published patients. EuroIntervention 2012; 8: 129–138.
31. Etienne PY, Papadatos S, Pieters D, et al. Embol-x intraaortic filter and transaortic approach for improved cerebral protection in transcatheter aortic valve implantation. Ann Thorac Surg 2011; 92: e95–e96.
32. Nietlispach F, Wijesinghe N, Gurvitch R, et al. An embolic deflection device for aortic valve interventions. JACC Cardiovasc Interv 2010; 3: 1133–1138.
33. Naber CK, Ghanem A, Abizaid AA, et al. First-in-man use of a novel embolic protection device for patients undergoing transcatheter aortic valve implantation. EuroIntervention 2012; 8: 43–50.
34. Onsea K, Agostoni P, Samim M, et al. First-in-man experience with a new embolic deflection device in transcatheter aortic valve interventions. EuroIntervention 2012; 8: 51–56.
35. Webb JG, Wood DA, Ye J, et al. Transcatheter valve-invalve implantation for failed bioprosthetic heart valves. Circulation 2010; 121: 1848–1857.
36. Pasic M, Unbehaun A, Dreysse S, et al. Transapical aortic valve implantation after previous aortic valve replacement: clinical proof of the "valve-in-valve" concept. J Thorac Cardiovasc Surg 2011; 142: 270–277.
37. Seiffert M, Franzen O, Conradi L, et al. Series of transcatheter valve-in-valve implantations in high-risk patients with degenerated bioprostheses in aortic and mitral position. Catheter Cardiovasc Interv 2010; 76: 608–615.
38. Kempfert J, Van Linden A, Linke A, et al. Transapical off-pump valve-in-valve implantation in patients with degenerated aortic xenografts. Ann Thorac Surg 2010; 89: 1934–1941.
39. Ferrari E. Transapical aortic 'valve-in-valve' procedure for degenerated stented bioprosthesis. Eur J Cardiothorac Surg 2012; 41: 485–490.
40. Macdonald S. New embolic protection devices: a review. J Cardiovasc Surg (Torino) 2011; 52: 821–827.