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Incidence and causes of silent and symptomatic stroke following surgical and transcatheter aortic valve replacement: a comprehensive review

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Abstract

Stroke associated with aortic valve replacement in calcific aortic stenosis, either via transcatheter implantation (TAVR) or via surgical replacement (SAVR), is one of the most devastating complications. However, data concerning the clinical impact and incidence of clinical and silent stroke complicating SAVR and TAVR are varying. This comprehensive review of the literature explores the genuine incidence of neurological events after these procedures. Additionally, potential factors responsible for the discrepancies in stroke rates in the current literature are analysed and a lack of uniform neurological definitions and standardized neurological assessments revealed. Current stroke rates after TAVR show a decline from 7 to 1.7–4.8% in recent studies. Randomized studies comparing TAVR with SAVR yielded initially a significantly higher stroke rate after TAVR procedures as opposed to SAVR. Recently published data showed opposite results with strokes being higher following SAVR. Current data concerning stroke after surgical valve replacement report significantly higher rates of clinical strokes (17%) than previously mentioned in the literature (≤4.9%). Silent cerebral lesions were detected in 68–93% after TAVR and 38–54% after SAVR. A broader application of cerebral protection devices may help to reduce embolic cerebral events.

Keywords: Aortic stenosis • Surgical aortic valve replacement • Transcatheter aortic valve replacement • Stroke • Ischaemic infarction • Cognitive dysfunction

INTRODUCTION

Calcific aortic valve stenosis is a common valvular heart disease in the Western world, with an incidence rate of 3% in patients ≥75 years [1]. Once symptoms develop, it is associated with a dismal prognosis if patients remain untreated. Surgical aortic valve replacement (SAVR) has become the gold standard for the treatment of severe aortic stenosis [2], even in octogenarians and patients with increased surgical risk [3–5]. However, there is a growing number of patients deemed unsuitable for a conventional surgical procedure due to significant comorbidities [6, 7]. The introduction of a new minimally invasive transcatheter method [transcatheter aortic valve replacement (TAVR)] in 2002 has led to a paradigm shift in the treatment of patients at prohibitive risk for surgery [8]. A large randomized study in patients deemed inoperable for a surgical procedure showed significantly improved survival after TAVR when compared with medical therapy [9]. Another randomized study in high-risk patients compared SAVR with TAVR and showed both treatment modalities to be equally effective with regard to survival [10]. Over the past few years, TAVR has become a routine procedure for high-risk patients with aortic valve stenosis [2]. However, the promising results were dwarfed by the complication rate of new neurological events, with stroke rates after TAVR being nearly twice as high as after SAVR [10]. In more recent studies, the incidence of cerebrovascular events after TAVR decreased to rates comparable with those following SAVR [11, 12]. However, Messe *et al*. [13] recently presented a concerning stroke rate of 17% in 196 patients undergoing SAVR. Contrary to most other studies, Messe *et al*. designed a prospective cohort study focusing on a detailed neurological assessment. The present review seeks to analyse the potential reasons for the discrepant data on neurological events after SAVR and TAVR.

PROCEDURE-DEPENDENT FACTORS FOR STROKE

Most strokes associated with SAVR or TAVR are thought to be rather embolic than ischaemic or haemorrhagic [14]. During SAVR solid embolism through plaque dislocation can occur while inserting the aortic cannula, during cross-clamping the ascending aorta and after declamping at the end of cardiopulmonary bypass [15]. Embolization of solid particles after excising the calcified leaflets of the native aortic valve may cause cerebral infarction. Van der Linden and Casimir-Ahn [16] indicate that cerebral gaseous emboli in SAVR mostly develop during redistribution of blood from the heart–lung machine to the patient when the heart starts ejecting actively again.

Stroke in TAVR is most likely to occur through dislodgement of atheromatous, calcific plaques [17]. In addition, scraping of aortic debris may also be caused by catheter manipulation in the ascending aorta and the aortic arch [18] or during retrograde crossing of a severely calcified aortic valve [19]. The risk of cerebral embolism following TAVR has also been shown to be increased during balloon pre-dilatation of the native valve, positioning and implantation of a balloon-mounted valve (crushing of the native calcified aortic valve) and post-procedural balloon dilatation [20]. Besides embolic lesions, ischaemic damage may also be due to severe cerebral hypoperfusion during rapid pacing for balloon valvuloplasty in the presence of a significant carotid stenosis [21]. Furthermore, it is suggested that air embolism may play a role in transapical (TA) TAVR [22]. Table 1 depicts an overview about the procedure-dependent reasons for cerebral embolism during aortic valve replacement.

CLINICAL STROKE OCCURRING WITH SURGICAL AORTIC VALVE REPLACEMENT

According to the Society of Thoracic Surgeons (STS) database, the risk for stroke within 30 days among 67.292 patients after isolated SAVR was found to be as high as 1.5% [7]. The German aortic valve registry reported an in-hospital stroke rate of 1.3% in 6523 patients undergoing SAVR [23]. In light of the TAVR technique in surgical high-risk patients, several recent studies focused on risk assessment and outcome after conventional SAVR in elderly, high-risk patients (Table 2). Besides large registry studies, current recommendations mainly refer to rather small, retrospective single-centre observational studies [30]. In 2009, Leontyev *et al*. reviewed 282 patients aged 80 years and older, undergoing isolated AVR. According to Logistic EuroSCORE (ESlog) risk stratification, patients were divided into subgroups (low risk = ESlog < 10%, moderate risk = 10% < ESlog < 20%, high risk = ESlog > 20%). The in-hospital overall stroke rate was 1.4%, with no significant differences between the study groups [26]. Another larger single-centre study reported an increased incidence rate of stroke of 4% in 249 octogenarians (STS Score 10.5%) receiving minimally invasive SAVR [27]. Stroke rates up to 4% have also been published by several others, mostly smaller single-centre series [4, 24, 25]. Thourani *et al*. sought to evaluate very high-risk patients undergoing SAVR between 2002 and 2007 based on a STS Prom of 10% or greater. In this retrospective multicentre analysis, in-hospital stroke was detected in 4.4% of patients (n = 7/159) with an in-hospital mortality rate of 16.4% (n = 26/159) [5].

Likosky *et al*. [31], reporting for the Northern New England Cardiovascular Disease Study Group, conducted a large registry study and presented a stroke rate of 2.1% (intra- and

Table 1: Procedure dependent reasons for cerebral embolism during aortic valve replacement

Transfemoral TAVR	Transapical TAVR	SAVR
Manipulation through diagnostic catheters and large valve delivery systems	Air embolism through catheter changes and final catheter retrieval	Plaque dislocation due to - Insertion of the aortic cannula - Cross-clamping - Declamping
Balloon Valvuloplasty		Solid embolism during exercising the calcified leaflets
Positioning and implantation of the balloon-mounted valve		Air embolism through insufficient deairing
Balloon post-dilatation		
Hypoperfusion due to rapid passing		

TAVR: transcatheter aortic valve replacement; SAVR: surgical aortic valve replacement.

Table 2: Clinical stroke after SAVR in octogenarians and/or moderate to high-risk patients

Author and year	Study period	Age (mean ± SD)	Type of study	n	Mean EuroSCORE (%)	STS	Death in hospital (%)	Stroke in hospital (%)
Melby *et al.* 2007 [4]	1993–2005	83.6 ± 2.9	RSC	105	–	–	9.0	3.0[a]
Thourani *et al.* 2008 [28]	1996–2006	82.8 ± 2.4	RSC	88	–	–	5.7	3.4
Ferrari *et al.* 2010 [27]	1990–2005	82.0 ± 2.2	RSC	124	12.6	–	6.0	2.0
Leontyev *et al.* 2009 [25]	1995–2006	82.7 ± 2.0	RSC	282	16.2	–	10.6	1.4
Elbardissi et al. 2011 [26]	1996–2009	84.0 ± 3.0	RSC	249	11.0	10.5	3.0	4.0
Thourani *et al.* 2011 [5]	2002–2007	76.1 ± 11.2	RMS	159	–	16.3	16.4	4.4
Messe *et al.* 2014 [13]	2008–2012	75.8 ± 6.2	P	196	–	–	5.0	17.0
Saxena *et al.* 2012 [70]	2001–2009	83.4 ± 2.9	R	531	–	–	4.0	2.3
Bakeen *et al.* 2010 [69]	1991–2007	82.2 ± 2.3	R	504	–	–	5.6	2.4

RSC: retrospective single-centre study; RMS: retrospective multicentre study; P: prospective study; R: registry study; SAVR: surgical aortic valve replacement.
[a]Eight of 245 cases (105 SAVR, 140 SAVR and CABG).

postoperative) in 419 patients between 80 and 84 years, and a rate of 4.6% (intra- and postoperative) in 156 patients aged 85 years and older.

Messe *et al.* recently performed a prospective cohort study of 196 subjects (75 ± 6.2 years) undergoing isolated SAVR. Patients were examined by neurologists prior to surgery and postoperatively, followed by a magnetic resonance imaging (MRI) examination in the early postoperative course. 17% of the patients suffered from clinical strokes, 54% exhibited a silent cerebral infarction and an additional 2% a transient ischaemic attack. The total in-hospital mortality rate was 5% [13] (Table 2).

Adding coronary artery bypass grafting (CABG) or other valve procedures to SAVR usually increases the incidence of stroke significantly [32]. The STS national database reports on stroke rates after SAVR and concomitant CABG (2.7%), which are nearly twice as high as with isolated SAVR (1.5%) [33]. In case of elderly, high-risk patients, rates increase even more with strokes occurring in ∼4.9% of patients after CABG/AVR [3, 32, 34].

CLINICAL STROKE AFTER TAVR

Several large national and international registries have been published, reporting stroke rates after TAVR in surgical high-risk or inoperable patients, ranging from 1.7 to 4.8% [12, 23, 30, 35–37] (Table 3). The first public report from the US Transcatheter Valve Therapy Registry (STS/American College of Cardiology Transcatheter Valve Therapy Registry) (2011–2013) analysed in-hospital and 30-day outcomes following TAVR in 7710 patients receiving a first-generation Edwards Sapien transcatheter valve via different access pathways, such as transfemoral (TF) in 64%, TA in 29% and others in 7% [12]. This analysis found a total in-hospital stroke rate of 2.0%. In patients with completed 30-day follow-up, the incidence rate was 2.8%. Results from this US registry are comparable with those of another large, industry-sponsored European registry, the Edwards Sapien Aortic Bioprosthesis European Outcome (SOURCE) Registry [35]. Thirty-day results revealed stroke rates of 2.4 and 2.6% after TF ($n = 463$) and TA ($n = 575$) TAVR, respectively. The French Aortic National CoreValve and Edwards (FRANCE 2) Registry enrolled 3195 patients between 2010 and 2011 at 34 centres, receiving either the Edwards Sapien (66.9%) or the Medtronic CoreValve (33.1%) prosthesis [37]. The incidence rate of stroke was 3.4% at 30 days and 4.1% at 1 year, without significant differences according to access and prostheses (1-year stroke rate: Edwards Sapien valve 3.9% vs Medtronic CoreValve 4.3%). The United Kingdom Transcatheter Aortic Valve Implantation (UK TAVI) Registry analysed data of 870 patients undergoing TAVR procedures, also using both valve technologies (Medtronic CoreValve and Edwards Sapien valve) [36]. In-hospital strokes were detected in 4.1% of patients, showing no significant differences in type of valve or approach. One of the largest registries, including complete data on aortic valve interventions for aortic stenosis, either via SAVR ($n = 9984$) or via TAVR ($n = 3876$), is the German Aortic Valve Registry [23, 30]. In-hospital stroke rates after transvascular (TV) and TA interventions were 1.7 and 2.3%, respectively [23]. Strokes up to 1-year post intervention were seen in 4.8% (TV) and 3.6% (TA) of patients [30]. Beside these larger registries, there are several, smaller observational studies and also some prospective investigations (e.g. Core Valve Pivotal Trial), reporting similar 30-day stroke rates of 1.9–6.0% after TAVR [38–44].

Considering the different approaches, some studies reported a higher incidence of clinical strokes up to 6.1% after TF valve implantation, compared with TA TAVR [39, 45, 46]. In contrast, these findings could not be confirmed by other, larger studies, presenting similar risks of stroke unrelated to the chosen approach [22, 35–37]. A meta-analysis of >30 000 patients from 25 multicentre studies [2.8% (TF) vs 2.8% (TA)] and 33 single-centre studies [3.8% (TF) vs 3.4% (TA)] revealed no differences between the TF and TA approach [47]. Comparing the two most common valves, the Edwards Sapien valve and the Medtronic CoreValve, Eggebrecht *et al.* [46] reported in a pooled analysis of 5097 patients that 30-day stroke rates were higher using the Edwards Sapien valve (4.2 vs 3.1%). However, results from a recent randomized trial [48], comparing these two transcatheter heart valve technologies in 241 patients, showed no statistically significant differences in the occurrence of postoperative stroke (*P* value 0.33).

The contemporary randomized controlled Placement of Aortic Transcatheter Valves (PARTNER) trial II analyses the Edwards Sapien XT™ valve in patients deemed unsuitable for operation

Table 3: Clinical stroke after TAVR according to approach in large registry studies

Registry	N	Stroke (%)												Death (%)	
		In hospital				30 days				1 year				30 days	1 year
		All	TF	TA	O	All	TF	TA	O	All	TF	TA	O	ALL	ALL
FRANCE 2 [35]	3195	–	–	–	–	3.4	–	–	–	4.1	3.7	4.4	7.0	9.7	24.0
SOURCE [33]	1038	–	–	–	–	2.5	2.4	2.6	–	4.5	–	–	–	8.5	23.9
UK TAVI [34]	870	–	–	–	–	4.1	4.0	4.1[a]		–	–	–	–	7.1	21.4
GARY [23, 24]	3876	1.7	1.7[b]	2.2	–	–	–	–	–	4.4	4.8[b]	3.6	–	7.1	25.1
STS/ACC [12] TVT	7710	2.0	1.7[c]	1.8[c]	–	2.8	2.6[c]	2.5[c]	–	–	–	–	–	7.6	–

FRANCE 2: French Aortic National CoreValve and Edwards Registry; SOURCE: Sapien Aortic Bioprosthesis European Outcome Registry; UK TAVI: United Kingdom Transcatheter Aortic Valve Implantation Registry; GARY: German Aortic Valve Registry; STS/ACC TVT: Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry; TF: transfemoral; TA: transapical; O: other approaches (transaortic, subclavian); TAVR: transcatheter aortic valve replacement.
[a]Transapical, subclavian or transaortic.
[b]Transfemoral and other transvascular routes.
[c]TAVR in high-risk and inoperable patients.

Table 4: Clinical stroke: TAVR versus SAVR in high-risk patients

Author and year	Type of study	N		Stroke (%)		P	Death—30 days (%)	
		TAVI	SAVR	TAVI	SAVR		TAVI	SAVR
Smith *et al*. 2011 [10]	R	348	351	4.6[a]	2.4[a]	NS	3.4	6.5
Adams *et al*. 2014 [11]	R	390	357	4.9	6.2	NS	14.2[b]	19.1[b]
Tamburino *et al*. 2012 [51]	PSA	218	400	2.3	3.0	NS	6.9	4.8
Conradi *et al*. 2012 [52]	PSA	82	82	2.4	2.4	NS	7.3	8.6
Wilbring *et al*. 2013 [53]	PSA	53[c]	53	3.9	5.7	NS	9.4	5.7
Higgins *et al*. 2011 [54]	PSA	46[c]	46	0.0	4.0	NS	13.0	9.0
Stohr *et al*. 2011 [55]	PSA	175	175	1.0	0.5	NS	12.0	8.0
Walther *et al*. 2010 [56]	PSA	100[c]	100	0.0	2.0	NS	8.0	14.0

Incidence of stroke presented as 30-day results or early clinical outcomes.
NS: not significant; R: randomized trial; PSA: propensity-score analysis; TAVR: transcatheter aortic valve replacement; SAVR: surgical aortic valve replacement.
[a]Major and minor strokes [major strokes: 3.8% (TAVR) vs 2.1% (SAVR); minor strokes: 0.9% (TAVR) vs 0.3% (SAVR)].
[b]Rate of death at 1 year.
[c]TAVR using a transapical approach.

or intermediate risk (STS = 4–8%). A subset of inoperable patients ($n = 560$) were randomized to undergo TAVR with either the newer Edwards Sapien XT™ valve or the first-generation Edwards Sapien® valve. At 30 days, disabling strokes were similar in both groups (Sapien XT™ 3.2% vs Sapien® 3.0%) (Webb *et al.*, 2015 [49]). Results from the initial PARTNER I trial, which randomly assigned inoperable patients to standard therapy or TF TAVR with the first-generation Edwards Sapien® valve, revealed stroke rates of 6.7% [9, 10]. Comparing data from both trials, stroke frequencies decreased significantly over the last years from 6.7% in 2008 to 3.0% in 2013.

STROKE RATE COMPARING SAVR VERSUS TAVR

Although a lot of TAVR studies reported about favourable clinical outcomes after transcatheter valve replacement compared with SAVR in high-risk patients [35, 38, 41, 50], data from randomized studies are rare. In the PARTNER trial, high-risk patients were randomized to TAVR with the Edwards Sapien valve ($n = 348$) or SAVR ($n = 351$). This study showed comparable survival at 1 year in both groups (24.2% TAVR vs 26.8% SAVR). However, the incidence of major stroke at 30 days and 1 year was nearly twice as high after TAVR compared with SAVR (30 days: 3.8 vs 2.1%, $P = 0.20$; 1 year: 5.1 vs 2.1%, $P = 0.07$) (Table 4). Including all neurological events (minor stroke, major stroke, transient ischaemic attacks), 30-day and 1-year rates were also significantly higher in the transcatheter group compared with the surgical group (30 days: 5.5 vs 2.4%, $P = 0.04$; 1 year: 8.3 vs 4.3%, $P = 0.04$) [10]. However, at the 5-year follow-up, the event rates merged, showing no difference after SAVR (15.9%) and TAVR (14.7%) [57]. A second recently published randomized trial did not substantiate these former results [11]. Adams and colleagues reported lower stroke rates after TAVR with the self-expanding Medtronic CoreValve prosthesis ($n = 390$) compared with SAVR ($n = 357$) at 30 days with 4.9 and 6.3% ($P = 0.46$), respectively (Table 4). Additionally, all-cause mortality at 1 year was significantly lower in patients receiving TAVR [11].

Beside these two randomized trials, numerous studies used propensity-matched comparison of outcomes following TAVR and SAVR in high-risk patients [51–56]. Reported strokes (30-day or early clinical outcome) in these studies were in the range of 0–3.9% after TAVR vs 0.5–5.7% after SAVR; thus, there were no differences in the incidence of stroke (Table 4).

SILENT STROKE AND NEUROCOGNITIVE DYSFUNCTION AFTER TAVR AND SAVR

Clinically silent multiple cerebral ischaemic events are frequent after SAVR in cases of severe calcific aortic valve stenosis [13]. Transcranial Doppler examination and diffusion-weighted MRI (DW-MRI), with DW-MRI more reliably, reveal these lesions [58]. Since ischaemia rapidly leads to cytotoxic oedema, inducing a decrease in the rate of water movement, new cerebral ischaemia may be detected by DW-MRI within minutes to hours after the event [59, 60].

In three independent studies, DW-MRI was used in a small number of patients ($n = 37$, $n = 15$, $n = 30$) undergoing SAVR in order to analyse the occurrence of new cerebral infarctions. Postoperative DW-MRI findings revealed new cerebral lesions in 38–47% of the patients, with only 0–13% of them suffering from a clinical stroke [61–63]. Messe *et al*. recently analysed the incidence and impact of clinical and silent infarction in 196 patients after SAVR and found new cerebral lesions in 61% of patients ($n = 79/129$). A focal neurological deficit was only discovered in 15% of them ($n = 20$) [13]. The discrepancy between the presence of new cerebral lesions and the appearance of symptomatic strokes is even greater after TAVR. Imaging studies detected new ischaemic lesions after TAVI in 68–84% of patients [20, 22, 64–68]. Despite these high incidences of new radiographic lesions, only a minority of patients developed a focal neurological deficit (0–10%). Concerning the number and location of new cerebral lesions, most studies agreed that ischaemic findings were mainly multiple and disseminated in both cerebral hemispheres and vascular territories after TAVI [20, 22, 64, 66]. Comparing the TF and TA access for TAVR, no significant differences were detected [22, 69]. Concerning cerebral lesion volume, most studies reported larger ischaemic lesions after TAVR when compared with SAVR [67, 68].

In conclusion, there is a manifest discrepancy between the incidence of new brain embolization after TAVR and SAVR and the rates of clinically manifested neurological deficits. However,

whether these 'subclinical' radiographic lesions have a potential effect on long-term cognitive function and patient's behaviour is not clear yet. To address subtle changes in cognitive function, specialized neurocognitive tests need to be performed, focusing on neurological domains, such as memory, attention, language skills and emotion.

Aiming to evaluate the relationship between new cerebral lesions after SAVR and a potential impairment in neurocognitive function, Knipp *et al.* in 2005 performed a prospectively designed study. Besides DW-MRI, patients ($n = 30$) received a comprehensive neuropsychological assessment, including 11 psychometric tests and 2 questionnaires for emotional and depressive status. Results showed a significant cognitive decline in 5 of 13 tests at 5 days postoperatively, especially in domains responsible for attention, memory and rate of information processing. A 4-month follow-up showed a recovery of cognitive function in all domains. However, a straight correlation of the occurrence of new cerebral lesions to neurocognitive function could not be found [63]. Similarly in 2013, Knipp *et al.* prospectively compared cognitive outcomes in 27 patients undergoing TA TAVR with 37 patients undergoing SAVR. Neuropsychological examination showed no statistically significant decline in cognitive function following TAVR but a marked cognitive impairment after SAVR. Patients receiving TA TAVR were significantly older, had more comorbidities and a significantly higher Logistic EuroSCORE compared with SAVR patients. But again, a relationship between postoperative DW-MRI lesions and neurocognition could not be noticed [70].

However, beside studies demonstrating no relationship to neurocognitive function [22, 61, 64, 70], there are others claiming the opposite [71]. Latest results from the multicentre, randomized, Mistral-C study, examining TAVI patients undergoing periprocedural cerebral embolic protection with the Claret Sentinel™ Device, showed a significant neurocognitive benefit for patients protected against brain embolization by using the Sentinel Device (Van Mieghem *et al.*, 2015 [72]).

DISCUSSION

Stroke is one of the most fearful complications associated with TAVR and SAVR in patients with calcific aortic stenosis. Due to an increasing life expectancy, more patients present with higher age and multiple comorbidities. In this growing population of surgical high-risk patients, therapeutic strategies for the management of severe aortic stenosis have changed during the last years, with TAVR becoming the treatment of choice in many centres. However, initial studies raised concerns due to an increased incidence of stroke associated with TAVR [9, 10]. But also recently published data concerning neurological events after SAVR aroused attention because of high rates of stroke (up to 17%) [13]. This observation is alarming, especially in comparison with previously described stroke frequencies after SAVR, ranging approximately from 1.3 to 4.9% [4, 5, 23–29, 34]. These discrepancies indicate that clinical stroke complicating SAVR might have been underreported previously. The majority of studies evaluating neurological outcomes after SAVR are designed in a retrospective fashion, collecting data from single-centre studies or from large administrative databases. In most of these cases, detailed and standardized neurological assessments by neurologists are lacking. Due to these missing analyses, events may occur unnoticed, leading to the suspicion that the real incidence of stroke is likely higher. Another reason for this discrepancy in the literature may be a lack of uniform definitions for stroke after SAVR. This becomes apparent by Messe's prospective trial: Using the studýs definition, 34 strokes were detected in 196 patients undergoing SAVR (17%), but only 13 of these 34 cases have been reported in the STS Database (6.6%) [13]. This confirms the assumption that clinical outcomes might be underestimated in self-reported quality databases [73, 74]. Therefore, it is imperative to use standardized definitions for neurological events including type and time of neurological assessment, similar to the definitions of the Valve Academic Research Consortium published in 2011 [75].

In the beginning of TAVR, 30-day stroke rates were rather high compared with conservative therapy or SAVR (TAVR versus medical therapy: 6.7 vs 1.7%) (TAVR versus SAVR: 3.8 vs 2.1%) [9, 10]. However, more recent data showed a decline in stroke rates after TAVR, with incidence rates ranging from 1.7 to 4.8% [12, 23, 30, 35–37, 76]. Over the years, improvements in valve technology have been performed, suggesting that smaller valve delivery devices and valves with a lower profile might cause fewer traumas. In 2013, Leon *et al.* first presented their results randomizing the early-generation high-profile Edwards Sapien® valve (22 or 24 delivery sheath) to the newer, low-profile Edwards Sapien XT™ valve (18 or 19 delivery sheath) in 560 surgical high-risk patients deemed unsuitable for surgery (Webb *et al.*, 2015 [49]). Thirty-day stroke rates were similar using both valves (3.0 vs 3.2%) (Webb *et al.*, 2015 [49]). The results show that, for this specific valve design, a second-generation device did not yield different results with regard to the incidence of neurological events. In contrast, comparing data from the initial PARTNER I trial with the ones from the inoperable cohort of the contemporary PARTNER II trial, stroke rates after implantation of the first-generation Edwards Sapien® valve were reduced from 6.7% in 2010 [9] to 3.0% in 2013 (Webb *et al.*, 2015 [49]). This implicates that other essential factors might be responsible for this drop in neurological events, such as growing operator's experience and improvement in high-risk patient selection over time [47].

Currently, the scientific literature contains only two randomized clinical trials, comparing SAVR versus TAVR in patients deemed high risk for a surgical procedure [10, 11]. Initial results from the PARTNER I trial showed that TAVR was associated with a higher stroke rate compared with SAVR (30 days: 3.8 vs 2.1%, $P = 0.20$) [10]. However, these findings were refuted in a more recent study from Adams and colleagues, showing similar stroke rates after both procedures [11]. Higher stroke rates in the PARTNER I trial might be related to an initial lack of expertise in TAVR procedures and possibly to a significantly higher prevalence of pre-existing cerebrovascular diseases in the TAVR cohort (29.3%) [10].

Beside these randomized trials, the majority of publications commenting on the treatment alternatives are retrospective, comparing TAVR results with a matched SAVR population or historical cohorts of SAVR patients [51–56]. However, if patients are assigned to different treatment options in a non-randomized fashion, selection bias and potentially confounding variables might influence patient's outcome, possibly leading to false conclusions. This becomes apparent in a study by Higgings *et al.*, comparing TA TAVR with a propensity-matched SAVR cohort. Due to the fact that TA TAVR is mostly offered to an inoperable, very high-risk patient population, it is actually not possible to match these patients in a clinically meaningful way [54]. Concerning the incidence of stroke in different treatment strategies, these facts hinder qualitative clinical research.

Another problem is the discrepancy in definition of neurological events among the TAVR and SAVR cohorts. While the majority of neurological events after TAVR are assessed by using established

endpoint definitions (VARC criteria) from the Valve Academic Research Consortium, strokes associated with SAVR in historical trials or matched cohorts are mostly poorly defined.

Using imaging modalities like DW-MRI for the assessment of neurological events after aortic valve replacement, either via SAVR or TAVR, studies showed new ischaemic cerebral lesions with only a minority of patients suffering from apparent neurological deficits [13, 20, 22, 61–66]. Concerning a correlation between silent ischaemic infarction and a decline in neurocognitive function, data are varying. But one has to take into consideration that the study-specific examination modalities differ strongly in the extent of used neuropsychological tests [63, 64]. Therefore, results should be interpreted with regard to the specific test design [58]. Moreover, the investigator's experience, patient factors (e.g. educational background) and confounding variables (e.g. postoperative delirium) may also play a role in data acquisition and interpretation [58, 62]. Owing to the fact that early cognitive impairment in predisposed patient cohorts might be a harbinger of long-term cognitive dysfunction [77], further studies should focus on analysing the clinical significance of 'silent' cerebral infarctions complicating SAVR and TAVR in the long term. Therefore, imaging and functional standardization of endpoints for neurocognitive changes should be defined to ensure meaningful comparison of data.

Against the background of a significant high rate of ischaemic infarctions complicating TAVR procedures, cerebral embolic protection devices gained in importance over the last years. At the moment, three approved protection devices are available [TriGuard™ Embolic Deflection Device, Claret Sentinel™ Cerebral Protection System (CPS) and Embrella Embolic Deflector System (Edwards Lifesciences, Irvine, CA)], aiming to reduce brain embolism by filtering or deflecting debris. Recently published data from the Deflect III trial, randomizing 85 patients undergoing TAVR to the TriGuard™ Embolic Deflection Device vs. no protection reported an improvement in cognitive function with fewer clinical strokes in patients undergoing protection [78]. Similarly, first results from the MISTRAL-C study showed a significant cognitive benefit in patients protected by the Sentinel™ CPS (Van Mieghem *et al.*, 2015 [71]). Further studies are needed to evaluate the role of cerebral protection in this context.

CONCLUSION

Stroke associated with aortic valve replacement, either via TAVR or SAVR, in calcific aortic stenosis is one of the most fearful complications. Recent data showed a decline over implantation time in the incidence of stroke complicating TAVR procedures. The incidence of neurological events after SAVR has been reported unanimously in the past. However, new data revealed significantly higher stroke rates. Initial concerns about an inferiority of TAVR procedures to SAVR regarding clinical strokes were refuted by recently published data. Uniform post-procedural neurological assessments and definitions for neurological events after TAVR and SAVR are needed.

A high incidence of silent cerebral infarction is associated with TAVR and SAVR procedures. A broader application of cerebral protection devices may help to reduce embolic cerebral events. The long-term effects of cognitive impairment need further investigation.

Conflict of interest: Sabine Bleiziffer is Proctor for Jena Valve and Boston Scientific, as well as Proctor and Consultant for Medtronic. Rüdiger Lange is Consultant for Medtronic and LivaNova (Sorin Group).

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