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OPINION

Cerebral Embolic Protection: Point–Counter Point

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Background

Transcatheter Aortic Valve Replacement (TAVR) has revolutionized the treatment of patients with severe symptomatic aortic stenosis. TAVR gained initial market approval in Europe in 2007 and 4 years later in the United States for patients considered too sick or at high-risk to undergo standard surgical valve replacement (SAVR). In 2016, the indication was expanded to patients at intermediate surgical risk. Globally, TAVR procedure volumes are expected to reach 300,000 *annually*. This rapid adoption of TAVR is spurred by the rigorous evidence of mortality benefit in inoperable patients, comparable outcomes to surgical aortic valve replacement (SAVR) in operative candidates, and clear patient preference for a less invasive alternative.

Stroke: an inconvenient reality

Early clinical trials of TAVR brought iatrogenic stroke under scrutiny: high-risk operative candidates randomized to TAVR in the original PARTNER trial had a substantially increased risk of stroke or transient ischemic attack compared with SAVR at 30 days (5.5% vs. 2.4%)[1]; the rate was 6.7% among inoperable patients. The majority of these events were disabling strokes,[2] and over 50% were directly procedure-related. [3] In the 8 years since the first PARTNER trial enrollment, TAVR has evolved significantly, and more recent comparisons generally find a similar or lower stroke risk in TAVR compared with SAVR, likely due to increased operator experience and lower-profile devices.[4,5] However, neurological events continue to affect a substantial proportion of patients, with 30-day stroke rates generally in the range of 3–6% in recent randomized trials including intermediate risk patients,[4,5] and growing evidence demonstrates that neurological events are underreported in clinical trials. When systematic neurologic evaluation by a neurologist and neuroimaging are performed, early stroke rates range from 9% up to 28% after both SAVR and TAVR.[6–8]

Routine neuroimaging studies reveal that ischemic cerebral infarction caused by showers of cerebral emboli during valve instrumentation and placement affect virtually all patients undergoing TAVR. The total volume of ischemic brain infarction quantified after TAVR in these imaging studies range from 1.5 cm^3 to 4.3 cm^3 of brain damage; equivalent to a staggering cell death of approximately 2 million neurons and 1 billion synapses.[9] These imaging findings are corroborated in the recent SENTINEL trial by the capture of embolic debris in 99% of patients, with recovery of calcium, thrombus, valve leaflet, arterial wall and even catheter material from the TAVI system, with more than 80% of debris measuring 0.15–0.5 cm and < 5% of debris > 1 cm.[10] We cannot turn a blind eye to this inconvenient reality.

Clinical relevance: patient-physician disconnect

The clinical consequences of peri-procedural stroke are devastating. Stroke not only carries a high mortality risk, but it is the severity and permanence of a life-altering disability that differentiates stroke as a fate worse than death for most patients, particularly as they get older.[11] As such, stroke cannot be equated to a peri-procedural bleeding complication or even a myocardial infarction. The facts are that not only do disabling strokes after TAVR carry a 3- to 9-fold increased risk of mortality—40% of survivors are permanently dependent and 80% face social isolation and significant financial strain.[12,13] While patients rate stroke as being 50–250% worse than death in a survey of 785 patients, cardiologists view the death of a patient as being worse than his stroke.[11] Should patient perception not prevail?

The clinical consequences of peri-procedural cerebral embolization are generally unpredictable and highly variable ranging from acutely symptomatic in 9–28% (disabling in up to 4%) to acutely subclinical in 72–91% or "covert." Large population-based evidence links acutely "subclinical" strokes to significant subsequent cognitive decline, subsequent dementia, and risk of future stroke.[14,15] Although these longer-term clinical and cognitive consequences remain largely unexplored in the context of iatrogenic cerebral embolization from cardiac procedures, they are generally considered cumulative effects and should not be dismissed.

Building evidence and expanding definitions

The true magnitude of neurologic impairment and cognitive decline after TAVR has until recently received relatively little

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attention, as the large TAVI randomized trials and registries have focused on only the most severe neurologic outcomes. In contrast to the relatively circumscribed VARC-2 stroke definition,[16] the 2017 Neurologic Endpoints in Cardiovascular Trials Consensus (NeuroARC)[17] provides a pragmatic framework for symptom-driven stroke evaluation applicable to procedures with known iatrogenic cerebral embolic risk, as well as imaging-driven stroke evaluation for devices designed to prevent cerebral embolization and stroke. To close the knowledge gap linking procedural embolization on the totality of neurologic deficits over time, more sensitive and comprehensive assessment methods of both neurologic and cognitive impairment are necessary. Improvements in our ability to fully evaluate the effectiveness of devices designed to mitigate clinically meaningful neurologic deficits are particularly critical given that TAVR indications will likely continue to broaden to lower risk patients in coming years. As TAVR indications extend to intermediate and low risk populations with greater functional capacity, in which cognitive impairment become more relevant and potentially disabling, reducing the risk of neurological events and the cumulative embolic burden to the brain become even more critical in optimizing TAVR as the uncontested procedure of choice.

The staggering evidence of near ubiquitous cerebral embolization raises a number of questions for TAVR and cardiac interventions in general. One important question that will be addressed in this point-counterpoint is: How much evidence do we have, and how much should be required, for adoption of adjunctive devices to reduce cerebral embolization, and what is the appropriate balance of pre- and post-market data collection? Is conclusive evidence of a reduction in clinically apparent neurological events required to conclude that such devices have a favorable benefit: risk profile, or are demonstrated safety and potential benefits sufficient to justify cautious adoption, accelerating patient access while generating additional data?

Disclosure statement

The author reports no conflict of interest. The author alone is responsible for the writing and content of this article.

References

1. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187–2198. doi: 10.1056/NEJMoa1103510.
2. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597–1607. doi: 10.1056/NEJMoa1008232.
3. Miller DC, Blackstone EH, Mack MJ, et al. Transcatheter (TAVR) versus surgical (AVR) aortic valve replacement: occurrence, hazard, risk factors, and consequences of neurologic events in the PARTNER trial. *J Thorac Cardiovasc Surg*. 2012;143:832–843, e13. doi: 10.1016/j.jtcvs.2012.01.055.
4. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374(17):1609–1620. doi: 10.1056/NEJMoa1514616.
5. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2017;376(14):1321–1331. doi: 10.1056/NEJMoa1700456.
6. Lansky AJ, Schofer J, Tchetche D, et al. A prospective randomized evaluation of the TriGuard HDH embolic DEFLECTion device during transcatheter aortic valve implantation: results from the DEFLECT III trial. *Eur Heart J*. 2015;36:2070–2078. doi: 10.1093/eurheartj/ehv191.
7. Sr M, Acker MA, Kasner SE, et al. Stroke after aortic valve surgery: results from a prospective cohort. *Circulation*. 2014;129:2253–2261. doi: 10.1161/CIRCULATIONAHA.113.005084.
8. Haussig S, Mangner N, Dwyer MG, et al. Effect of a cerebral protection device on brain lesions following transcatheter aortic valve implantation in patients with severe aortic stenosis: the CLEAN-TAVI randomized clinical trial. *JAMA*. 2016;316:592–601. doi: 10.1001/jama.2016.10302.
9. Insel TR, Landis SC, Collins FS. Research priorities. The NIH BRAIN Initiative. *Science* (New York, NY). 2013;340:687–688. doi: 10.1126/science.1239276.
10. Kapadia SR, Kodali S, Makkar R, et al. Protection against cerebral embolism during transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2017;69:367–377. doi: 10.1016/j.jacc.2016.10.023.
11. Stolker JM, Spertus JA, Cohen DJ, et al. Rethinking composite end points in clinical trials: insights from patients and trialists. *Circulation*. 2014;130:1254–1261. doi: 10.1161/CIRCULATIONAHA.113.006588.
12. Daniel K, Wolfe CD, Busch MA, McKevitt C. What are the social consequences of stroke for working-aged adults? A systematic review. *Stroke*. 2009;40:e431–440. doi: 10.1161/STROKEAHA.108.534487.
13. Lai SM, Studenski S, Duncan PW, Perera S. Persisting consequences of stroke measured by the stroke impact scale. *Stroke*. 2002;33:1840–1844. doi: 10.1161/01.STR.0000019289.15440.F2.
14. Miwa K, Hoshi T, Hougaku H, et al. Silent cerebral infarction is associated with incident stroke and TIA independent of carotid intima-media thickness. *Int Med*. 2010;49:817–822. doi: 10.2169/internalmedicine.49.3211.
15. Bernick C, Kuller L, Dulberg C, et al. Silent MRI infarcts and the risk of future stroke: the cardiovascular health study. *Neurology*. 2001;57:1222–1229. doi: 10.1212/WNL.57.7.1222.
16. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the valve academic research consortium-2 consensus document. *J Thorac Cardiovasc Surg*. 2013;145:6–23. doi: 10.1016/j.jtcvs.2012.09.002.
17. Lansky AJ, Messe SR, Brickman AM, et al. Proposed standardized neurological endpoints for cardiovascular clinical trials: an academic research consortium initiative. *J Am Coll Cardiol*. 2017;69:679–691. doi: 10.1016/j.jacc.2016.11.045.