7. Aldenkortt M, Lysakowski C, Elia N, et al. Ventilation strategies in obese patients undergoing surgery. *Br J Anaesth*. 2012;109(4):493-502. doi:10.1093/bja/aes338

8. Writing Committee for the PROBESE Collaborative Group of the PROtective VEntilation Network (PROVEnet) for the Clinical Trial Network of the European Society of Anaesthesiology. Effect of intraoperative high positive end-expiratory pressure (PEEP) with recruitment maneuvers vs low PEEP on postoperative pulmonary complications in obese patients: a randomized clinical trial [published online June 3, 2019]. *JAMA*. doi:10.1001/jama.2019.7505

9. Ball L, Hemmes SNT, Serpa Neto A, et al. Intraoperative ventilation settings and their associations with postoperative pulmonary complications in obese patients. *Br J Anaesth*. 2018;121(4):899-908. doi:10.1016/j.bja.2018.04.021

10. Pereira SM, Tucci MR, Morais CCA, et al. Individual positive end-expiratory pressure settings optimize intraoperative mechanical ventilation and reduce postoperative atelectasis. *Anesthesiology*. 2018;129(6):1070-1081. doi:10.1097/ALN.0000000000002435

11. Pirrone M, Fisher D, Chipman D, et al. Recruitment maneuvers and positive end-expiratory pressure titration in morbidly obese ICU patients. *Crit Care Med*. 2016;44(2):300-307. doi:10.1097/CCM.0000000000001387

12. Neto AS, Hemmes SN, Barbas CS, et al. Association between driving pressure and development of postoperative pulmonary complications in patients undergoing mechanical ventilation for general anaesthesia. *Lancet Respir Med*. 2016;4(4):272-280. doi:10.1016/S2213-2600(16)00057-6

Stroke After Transcatheter Aortic Valve Replacement
An Important but Underreported Outcome in Clinical Practice

Steven R. Messé, MD; Gorav Ailawadi, MD

Stroke after cardiovascular procedures has been associated with substantially increased morbidity, mortality, and cost.[1] Aortic valve replacement is the most common intracardiac procedure performed in the United States and its use has been increasing over the past decade due to the aging of the population, improved survival from other conditions, and new technologies that allow for less invasive procedures. In 2010, the Placement of Aortic Transcatheter Valves (PARTNER) 1B randomized study[2] involving patients at inoperable surgical risk reported that transcatheter aortic valve replacement (TAVR) improved survival compared with the best medical care. This study reported about a 7% risk of stroke, which was not surprising given the patient population and the likelihood of particulate embolization when expanding a new valve within the annulus of the stenosed and calcified native valve. Nevertheless, even with this stroke risk, there was a clear mortality benefit and quality of life was improved as well. After the PARTNER 1A high-risk cohort demonstrated similar or improved outcomes relative to open surgical aortic valve replacement (SAVR) in patients at high (but not inoperable) surgical risk, the US Food and Drug Administration (FDA) approved TAVR in 2011 and the procedure was rapidly adopted into clinical practice.[3]

Related article page 2306

The Transcatheter Valve Therapy (TVT) Registry, introduced by the Society of Thoracic Surgeons (STS) and the American College of Cardiology (ACC), was subsequently established in 2012 to track TAVR use and outcomes in clinical practice, via an online reporting system. Importantly, the Centers for Medicare & Medicaid Services reimbursement was tied to participation in this registry, ensuring that the vast majority of these procedures performed in the United States were captured in the database. Additional TAVR randomized studies followed, incorporating lower-risk patients and using iteratively improved versions of the valve devices, which consistently demonstrated similar or improved clinical outcomes, faster recovery, and greater patient satisfaction than with the traditional SAVR. In August 2016, FDA approval expanded the indication to include intermediate-risk patients. In 2019, the PARTNER 3 trial[4] and the Evolut Low Risk trial[5] demonstrated similar or improved outcomes for TAVR compared with SAVR in low-risk patients and the expansion of the labeling for these devices is likely imminent. Nevertheless, stroke complicating TAVR remains a great concern and insight into this complication in clinical practice has been lacking.

In this issue of *JAMA*, Huded et al[6] provide an assessment of stroke outcomes from the first 5 years of the TVT Registry, shedding light on the incidence and prognosis of stroke complicating TAVR in clinical practice. This analysis of more than 100 000 patients treated with TAVR during the first 5.5 years of the registry yielded a number of important observations reflecting routine practice rather than care delivered as part of a clinical trial. First, the authors report that during this period, the periprocedural stroke rate, occurring within 30 days of the procedure, was 2.3%. This rate is lower than what would be expected given that the clinical trials of TAVR that informed patient selection during this period all reported considerably higher stroke rates, ranging from 3.4% to 6.7%.[2,3,7-10] Patients included in this TVT analysis were predominantly in the high- or extreme-risk category, with only approximately 10% considered to be intermediate or low risk.

The authors provide potential explanations for the low event rate, noting that TVT sites are not mandated to perform neurologic assessments or neuroimaging, in contrast to the trials. There is no doubt that ascertainment methods have a direct influence on the reported incidence of stroke outcomes after procedures.[1] The data supplied to the TVT Registry are predominantly obtained via retrospective chart abstraction. Multiple studies have shown that passive retrospective chart reviews lead to significantly lower reported event rates than do active ascertainment with prospective patient assessments.[11,12] Serial assessments performed by neurologists is the most sensitive

approach to identify subtle findings of stroke, although this is difficult to accomplish.

The authors posit that low event rates in the TVT database reflect a failure to detect or document minor strokes, which may be clinically less important. The definition of stroke used by TVT requires symptoms that persist for more than 24 hours, or have neurologist or neuroimaging confirmation of stroke if the symptoms lasted less than 24 hours. Most patients who are assessed for acute neurologic change in the hospital would receive a head computed tomographic scan, which is insensitive to small infarcts, particularly compared with magnetic resonance imaging (MRI), which has found acute infarcts in between 70% and 100% of patients undergoing TAVR.[1,13,14] It remains uncertain whether minor neurologic events have important long-lasting consequences, but existing evidence suggests that they are clinically meaningful. Prospective studies with active ascertainment of stroke after surgical AVR and TAVR have found much higher rates of clinical stroke, which were strongly associated with poor outcomes including late cognitive decline.[12,14-16] Other potential reasons the stroke rate is lower in the TVT Registry than expected is that they excluded TAVR procedures that were aborted prior to completion, some of which may have resulted in stroke, and patients who died may have had a stroke that was not diagnosed. In addition, neurologic events were adjudicated by centrally unblinded cardiologists who may be less confident than a neurologist at determining what symptoms could represent an acute stroke.

In addition to being low, the stroke rate was also remarkably stable over the period being studied, ranging from 2.2% to 2.4% annually, although progressively lower-risk patients were being treated and improved devices were being used. The clinical trials of TAVR that led to the expanded indication for intermediate-risk patients also did not show large reductions in stroke rates until the most recent trials of the lowest-risk patients published this year, PARTNER 3 and EVOLUT Low Risk. Data from the TVT Registry demonstrated an association of volume and experience with most clinical outcomes, although the association with stroke did not reach statistical significance.[17] Although it would seem likely that centers gained experience over time (which would have led to reduced complications), the continual expansion of TVT with new inexperienced sites, less experienced proceduralists, or both may have offset this benefit overall.

This analysis by Huded et al also assessed factors associated with periprocedural stroke in clinical practice. Patients with stroke were older, were more likely to be women, had higher rates of prior stroke and presence of other vascular disease including aortic atherosclerosis and carotid stenosis, had more nonfemoral access, and had more often received a self-expanding valve relative to the balloon expandable valve. In addition, concordant with prior studies, patients who experienced a stroke experienced a high 30-day mortality rate, with a hazard ratio of more than 6. Studies of stroke after SAVR also demonstrated 5- to 10-fold increased mortality rate.[18] Although the TVT Registry does not capture long-term disability or cognitive decline, these outcomes also have been shown to be substantially higher in patients who had a stroke after cardiac surgery.[16,19]

In conclusion, the analysis from the TVT Registry reported by Huded et al provides important insight into stroke complicating TAVR in clinical practice, although it is likely that stroke events were underestimated. There is little doubt that TAVR is a major step forward for patient care. In another study in *JAMA*, Bevan et al[20] report that the mortality rate due to aortic stenosis has decreased since 2013, likely reflecting the rise of this intervention. Nevertheless, stroke remains a potentially devastating complication, so studies that actively ascertain strokes in clinical practice and interventions to reduce these events are needed. In addition, among patients who are carefully screened for clinical stroke symptoms, the neurologic and cognitive effects of truly silent acute cerebral infarcts after TAVR remains poorly characterized. Thus far, one embolic protection device has been approved for use in patients undergoing TAVR, primarily based on reassuring safety data and successful capture of debris, even though use of the device was not associated with significantly lower stroke rates and MRI infarct volumes.[14] The TVT Registry is a worthwhile endeavor, but there is more work to be done on neurologic outcomes following TAVR.

ARTICLE INFORMATION

Author Affiliations: Division of Vascular Neurology, University of Pennsylvania, Philadelphia (Messé); Division of Cardiac Surgery, University of Virginia, Charlottesville (Ailawadi).

Corresponding Author: Steven R. Messé, MD, Division of Vascular Neurology, University of Pennsylvania, 3400 Spruce St, 3 West Gates Bldg, Philadelphia, PA 19104 (messe@pennmedicine.upenn.edu).

Conflict of Interest Disclosures: Dr Messé reported receiving personal and consulting fees from Claret Medical, personal fees from the Yale University Cardiovascular Research Group, and grant support from WL Gore and Associates. Dr Ailawadi reported receiving personal fees from Medtronic, Edwards Lifesciences, Abbott, and Admedus.

REFERENCES

1. Lansky AJ, Messé SR, Brickman AM, et al. Proposed standardized neurological endpoints for cardiovascular clinical trials: an academic research consortium initiative. *J Am Coll Cardiol*. 2017;69(6):679-691. doi:10.1016/j.jacc.2016.11.045

2. 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(17):1597-1607. doi:10.1056/NEJMoa1008232

3. 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(23):2187-2198. doi:10.1056/NEJMoa1103510

4. Mack MJ, Leon MB, Thourani VH, et al; PARTNER 3 Investigators; the PARTNER 3 Investigators. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med*. 2019;380(18):1695-1705. doi:10.1056/NEJMoa1814052

5. Popma JJ, Deeb GM, Yakubov SJ, et al; Evolut Low Risk Trial Investigators. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med*. 2019;380(18):1706-1715. doi:10.1056/NEJMoa1816885

6. Huded CP, Tuzcu EM, Krishnaswamy A, et al. Association between transcatheter aortic valve replacement and early postprocedural stroke [published June 18, 2019]. *JAMA*. doi:10.1001/jama.2019.7525

7. Popma JJ, Adams DH, Reardon MJ, et al; CoreValve United States Clinical Investigators. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with

severe aortic stenosis at extreme risk for surgery. *J Am Coll Cardiol*. 2014;63(19):1972-1981. doi:10.1016/j.jacc.2014.02.556

8. Adams DH, Popma JJ, Reardon MJ, et al; US CoreValve Clinical Investigators. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;370(19):1790-1798. doi:10.1056/NEJMoa1400590

9. Leon MB, Smith CR, Mack MJ, et al; PARTNER 2 Investigators. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374(17):1609-1620. doi:10.1056/NEJMoa1514616

10. Reardon MJ, Van Mieghem NM, Popma JJ, et al; SURTAVI Investigators. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2017;376(14):1321-1331. doi:10.1056/NEJMoa1700456

11. Wu CM, McLaughlin K, Lorenzetti DL, Hill MD, Manns BJ, Ghali WA. Early risk of stroke after transient ischemic attack: a systematic review and meta-analysis. *Arch Intern Med*. 2007;167(22):2417-2422. doi:10.1001/archinte.167.22.2417

12. Messé SR, Acker MA, Kasner SE, et al; Determining Neurologic Outcomes from Valve Operations (DeNOVO) Investigators. Stroke after aortic valve surgery: results from a prospective cohort. *Circulation*. 2014;129(22):2253-2261. doi:10.1161/CIRCULATIONAHA.113.005084

13. Cho SM, Deshpande A, Pasupuleti V, Hernandez AV, Uchino K. Radiographic and clinical brain infarcts in cardiac and diagnostic procedures: a systematic review and meta-analysis. *Stroke*. 2017;48(10):2753-2759. doi:10.1161/STROKEAHA.117.017541

14. Kapadia SR, Kodali S, Makkar R, et al; SENTINEL Trial Investigators. Protection against cerebral embolism during transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2017;69(4):367-377. doi:10.1016/j.jacc.2016.10.023

15. Mack MJ, Acker MA, Gelijns AC, et al; Cardiothoracic Surgical Trials Network (CTSN). Effect of cerebral embolic protection devices on CNS infarction in surgical aortic valve replacement: a randomized clinical trial. *JAMA*. 2017;318(6):536-547. doi:10.1001/jama.2017.9479

16. Giovannetti T, Price CC, Fanning M, et al; DENOVO Investigators. Cognition and cerebral infarction in older adults after surgical aortic valve replacement. *Ann Thorac Surg*. 2019;107(3):787-794. doi:10.1016/j.athoracsur.2018.09.057

17. Carroll JD, Vemulapalli S, Dai D, et al. Procedural experience for transcatheter aortic valve replacement and relation to outcomes: the STS/ACC TVT Registry. *J Am Coll Cardiol*. 2017;70(1):29-41. doi:10.1016/j.jacc.2017.04.056

18. LaPar DJ, Ghanta RK, Kern JA, et al; Investigators for the Virginia Cardiac Surgery Quality Initiative. Hospital variation in mortality from cardiac arrest after cardiac surgery: an opportunity for improvement? *Ann Thorac Surg*. 2014;98(2):534-539. doi:10.1016/j.athoracsur.2014.03.030

19. Salazar JD, Wityk RJ, Grega MA, et al. Stroke after cardiac surgery: short- and long-term outcomes. *Ann Thorac Surg*. 2001;72(4):1195-1201. doi:10.1016/S0003-4975(01)02929-0

20. Bevan GH, Zidar DA, Josephson RA, Al-Kindi SG. Mortality due to aortic stenosis in the United States, 2008-2017. *JAMA*. 2019;321(22):2236-2238. doi:10.1001/jama.2019.6292

Putting the New Alzheimer Disease Amyloid, Tau, Neurodegeneration (AT[N]) Diagnostic System to the Test

David Wolk, MD; Stephen Salloway, MD, MS; Brad Dickerson, MD

The field of neurodegenerative dementias, particularly Alzheimer disease (AD), has been limited by challenges in accurate diagnosis, but has recently been potentially revolutionized by the development of imaging and cerebrospinal fluid (CSF) biomarkers. These biomarkers have influenced the diagnostic evaluation of symptomatic patients with cognitive impairment or dementia, particularly in dementia subspecialty practice. The primary biomarker modalities include magnetic resonance imaging (MRI), positron emission tomography (PET), and CSF.

Related article page 2316

MRI has widely accepted clinical utility for the evaluation of structural brain lesions of a variety of types, including evidence for cerebrovascular disease and atrophy patterns consistent with, but not specific for, neurodegenerative pathologies. PET with ^{18}fluorodeoxyglucose (FDG PET) has strong evidence and a recent practice guideline[1] supports its use as a marker of functional brain abnormalities suggestive of a variety of neurodegenerative pathologies associated with dementia.

Amyloid PET is a Food and Drug Administration–approved biomarker that is sensitive and specific for fibrillar amyloid plaques, a fundamental pathologic feature of AD; an appropriate use guideline specified how amyloid PET could be usefully deployed in subspecialty clinical practice.[2] A recent large study also provided evidence supporting the utility of amyloid PET in dementia subspecialty clinical practice.[3] In addition, several PET tracers that appear to bind to tau-based neurofibrillary tangles (NFTs), the other pathological hallmark of AD, have emerged.[4]

Alternatively, CSF can be analyzed for levels of amyloid-β, as well as tau proteins suggestive of NFTs. A recent practice guideline supports the value of CSF AD biomarkers in the subspecialist evaluation of patients with cognitive impairment or dementia.[5] Thus, these biomarkers are increasingly affecting clinical practice for the evaluation of symptomatic patients with cognitive impairment and are being used extensively in research. While it is clear that these varied tests improve diagnostic accuracy and treatment planning now, their full potential to affect patient outcomes will likely increase with the emergence of more effective therapies.

In parallel, remarkable developments have taken place demonstrating the capacity to measure these biomarkers of key pathological features of AD in cognitively normal individuals. These individuals have been classified as having preclinical AD and the assumption is that a high percentage of those with this pathology will ultimately develop symptomatic disease. Research diagnostic constructs to define preclinical AD were first established in 2011[6] and have been refined using the so-called amyloid, tau, neurodegeneration (AT[N]) system[7] with the recent proposal of a new research framework defining AD using these 3 categories of biomarkers, dichotomously classified as positive or negative, and proposing a separation between the definition of the neuropathological disease and clinical syndromes of cognitive