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EDITORIAL COMMENT

Amyloidosis and Risk of Stroke After Transcatheter Aortic Valve Replacement

It Takes Two to Tango?*

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Aortic stenosis (AS) is the most common valvular heart disease in Western countries. Patient symptoms and outcomes related to AS are largely determined by the presence of associated comorbidities, the severity of valve disease and the array of maladaptive changes of the myocardium to chronic pressure overload, such as reactive fibrosis, microvascular ischemia, and cell death with replacement fibrosis, eventually leading to irreversible myocardial dysfunction.[1] Amyloidosis is a protein-folding systemic disease sustained by the extracellular deposition of insoluble abnormal fibrils, with the pathognomonic histological property of green birefringence when viewed under polarized light after staining with Congo red.[2] Cardiac amyloidosis (CA) is an increasingly recognized cardiomyopathy, mainly derived from transthyretin—either wild-type or hereditary variants—or immunoglobulin light chain amyloid fibrils infiltration of the myocardium.[3]

AS and CA are common causes of heart failure with preserved ejection fraction in older people and both carry high morbidity and mortality, particularly when left untreated. The increased availability of advanced cardiac imaging tools has led to easier and earlier recognition of CA—mainly wild-type transthyretin—among elderly patients with degenerative AS, with an observed prevalence of coexisting diseases ranging between 6% and 25% in different cohorts.[4-6] While dual pathology portends 2-fold heightened mortality compared with each condition alone,[7,8] observational data have shown that transcatheter aortic valve replacement (TAVR) is still associated with a survival benefit in the presence of dual pathology compared with medical management alone, with similar periprocedural complications rates as for treating lone AS.[9]

In this issue of *JACC: Advances*, Elzeneini et al[10] present an interesting propensity score-weighted retrospective analysis of US hospital discharge data available from the Nationwide Readmission Database that aimed to investigate the impact of dual AS and pre-existing amyloidosis (used as a surrogate for CA) on in-hospital outcomes and 30-day readmission rate of patients undergoing TAVR. Overall, the authors retrieved 273 and 244,694 TAVR-related hospitalizations in AS patients with and without amyloidosis, respectively. Despite similar in-hospital mortality, risk of myocardial infarction, bleeding, acute kidney injury, ventricular arrhythmias, pacemaker implantation, and 30-day readmission rate, the presence of dual pathology was independently associated with a 3-fold higher risk of acute ischemic stroke during hospitalization compared with lone AS, regardless of prevalent atrial fibrillation, prior stroke, and chronic heart failure. The current analysis is inherently limited by selection and case ascertainment biases, observational

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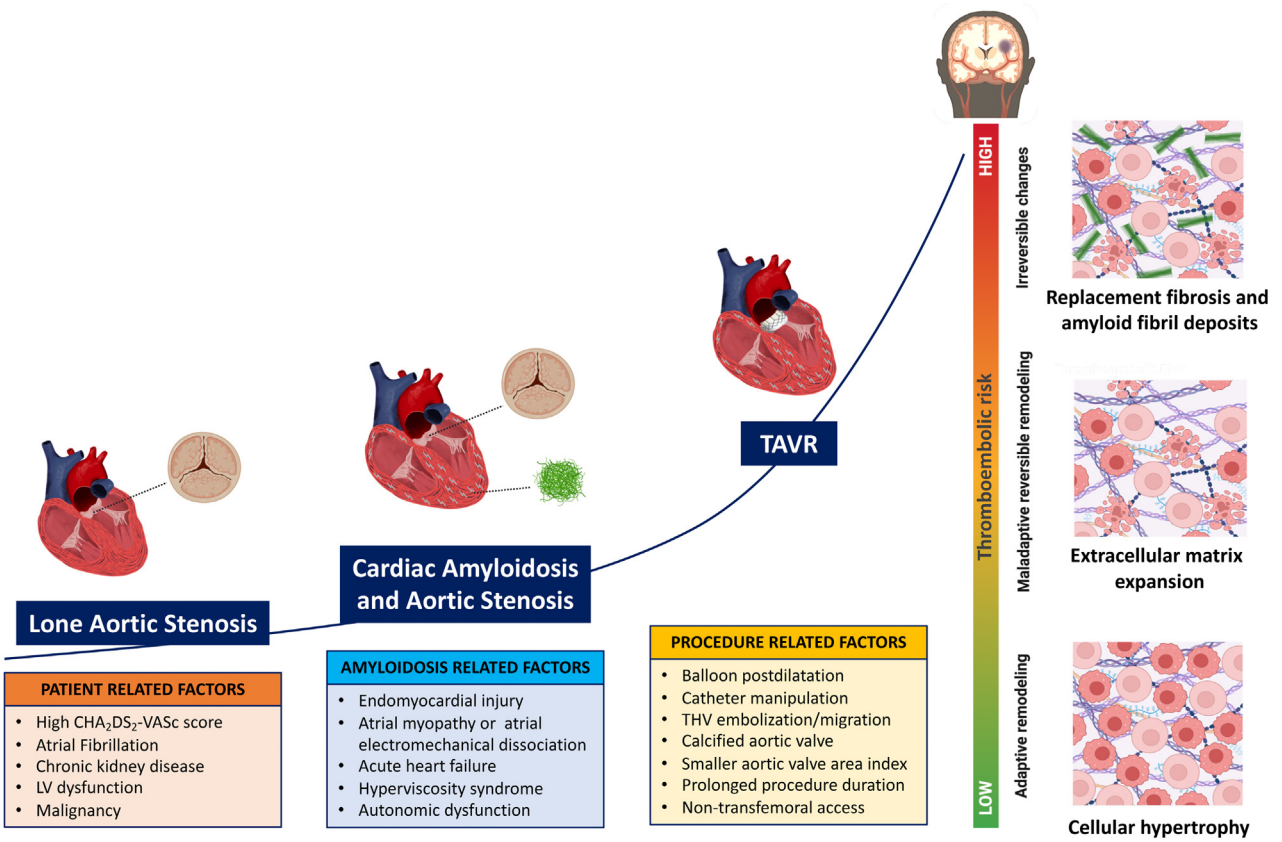
FIGURE 1 Risk Factors for Stroke in Patients Undergoing Transcatheter Aortic Valve Replacement



LV = left ventricle; TAVR = transcatheter aortic valve replacement; THV = transcatheter heart valve.

retrospective nature of the study, lack of appropriate coding, absence of relevant pieces of information about antithrombotic treatment, procedural details, and imaging data (echocardiography, cardiovascular magnetic resonance, or bone scintigraphy), and very low prevalence of CA in the cohort (0.1% of TAVR recipients), that is suggestive of a global lack of awareness and underdiagnosis. The authors have provided some hypothesis-generating data that points to greater perioperative thromboembolic risk associated with CA. However, further evidence from contemporary and deep phenotyped prospective cohort studies is required to corroborate these findings.[9,11]

Stroke prevention in patients undergoing TAVR is a complex and unsolved issue, especially while expanding the indication to younger, low-risk populations. Occurrence of cerebrovascular events remains indeed an ominous complication after TAVR, with an incidence of 2% to 3% at 30 days.[12] Risk factors for stroke after TAVI include patient-related and procedural-related factors that should guide periprocedural strategies[13] and optimal antithrombotic therapy for stroke prevention.[14] A high frequency of intracardiac thrombosis and high risk for thromboembolic events have been reported in CA patients,[15,16] with progressive amyloid deposition leading to atrial myopathy,[17] atrial electromechanical dissociation,[18] and acute decompensated AS[19] (**Figure 1**). This evidence motivated expert recommendations to anticoagulate CA patients with atrial fibrillation independently of the CHA_2DS_2-VASc score, and to perform imaging-guided cardioversion regardless of anticoagulation status.[20,21] Whether routine anticoagulation should be also considered in systemic amyloidosis, and more specifically CA patients in sinus rhythm, when the atria are enlarged and dysfunctional, and the bleeding risk is low, is yet to be determined. Randomized trials assessing

uninterrupted anticoagulation during TAVR, use of devices for cerebral embolic protection, and specific antithrombotic strategies after TAVR are awaited. In the absence of randomized data on the efficacy and safety of sequential valve- and amyloid-directed therapies in the setting of dual pathology, overall evidence calls for individualized treatment strategies that should come from Heart Team discussion with decisions based on patient life expectancy, frailty, comorbidities, and shared decision-making according to patient values and preferences.

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