Aortic stenosis (AS), a common condition affecting 3% of individuals aged >75 years, leads to heart failure and death unless the valve is replaced. Recently, patients with concomitant degenerative AS and transthyretin-related cardiac amyloidosis have been reported. One prospective study investigated the coexistence of cardiac amyloidosis in elderly patients with AS who were referred for an aortic valve replacement (surgical or transcatheter), by using echocardiography, ⁹⁹mTc-3, 3-diphosphono-1, 2-propanodicarboxylic acid scintigraphy, and endomyocardial biopsy, but no cardiac magnetic resonance; 5 of the 43 patients were diagnosed with wild-type transthyretin-related amyloidosis (wtATTR) of 2. Of the 5 patients with wtATTR, only 1 was female (median age, 79 years; 70% male). The 2-year mortality rate was not different between patients with and without AS, suggesting that the mortality in patients with both diseases may be driven by ATTR as opposed to a stenotic aortic valve or its treatment. Another retrospective study reported 16 patients (mean age, 79±6 years; 81% men) with wtATTR, on the basis of clinical presentation, in addition to endomyocardial biopsy, cardiac magnetic resonance, echocardiography with an apical sparing strain pattern, and ⁹⁹mTc-pyrophosphate scintigraphy; 27 were determined to have AS (mean age, 79 years; 70% male). The 2-year mortality rate was not different between patients with and without AS, suggesting that the mortality in patients with both diseases may be driven by ATTR as opposed to a stenotic aortic valve or its treatment. Another retrospective study reported 16 patients (mean age, 79±6 years; 81% men) with wtATTR and transthyretin cardiac amyloidosis (wtATTR, n=13; Val122I, n=1; no genetic test, n=3). After valve replacement (surgical in 63% and via transcatheter in 13%), mortality was 44% (n = 7) during the median 33-month follow-up period. These were small cohort or retrospective studies; larger prospective studies are needed to systematically know the prevalence of wtATTR in patients with severe AS and the mortality of these concomitant diseases after aortic valve replacement. Thus, the frequency of wtATTR cardiac amyloidosis and its mortality in patients with severe AS is a hot topic.
wtATTR (50%) died compared with 8 of 106 (7.5%) in the remaining calcified AS cohort. The presence of wtATTR amyloid had the highest hazard ratio for all-cause mortality (hazard ratio, 9.5 [2.5–35.8], \( P = 0.001 \), univariable Cox regression analysis). This study provides important information on the prevalence of wtATTR in patients with severe AS requiring sAVR; the frequency of wtATTR cardiac amyloidosis in patients with severe AS was 5.6%.

Furthermore, univariate analysis demonstrated that wtATTR amyloid deposit is a prognosticator in patients with AS after sAVR, and perioperative mortality was not affected by the presence of wtATTR. This finding is the first and largest prospective report in patients with severe AS after sAVR.

In previous studies, several prognostic markers were reported in patients undergoing sAVR or transcatheter aortic valve replacement (TAVR). Advanced chronic kidney disease was associated with a higher rate of early and late mortality and bleeding events after TAVR, with atrial fibrillation and dialysis therapy determining a high risk in 2075 consecutive patients.6 Severity of coexisting coronary artery disease was associated with impaired clinical outcomes at 1 year after TAVR in 445 patients with severe AS (mean age, 82.5 years; 56% female).7 Severity of coexisting coronary artery disease was associated with impaired clinical outcomes at 1 year after TAVR in 445 patients with severe AS (mean age, 82.5 years; 56% female).7

Severe AS and left ventricular ejection fraction <50% with or without aortic valve replacement,4,5 low-flow, low-gradient AS with reduced stroke volume index,10–13 and reduced global longitudinal strain by speckle-tracking echocardiography4 have increased risk of mortality after sAVR or TAVR in patients with severe AS. Midwall myocardial fibrosis that can be detected by late gadolinium enhancement,14 and prognosis—patient mismatch16,17 have also been reported as prognosticators in patients with severe AS after sAVR or TAVR.

Thus, the existence of wtATTR may be a newly recognized disease modifier in patients with AS requiring sAVR or TAVR, which may have affected patients included in previous studies.6–17 The coexistence of wtATTR and severe AS may cause severe hypertrophy and left ventricular functional impairment, which can be misdiagnosed as low-flow, low-gradient severe AS.10–13 Recent studies have suggested that patients with wtATTR are characterized by lower left ventricular ejection fraction, stroke volume index, left ventricular basal, and midradial strains compared with age and wall thickness matched mutant ATTR patients.18 These findings may be helpful in distinguishing wtATTR cardiac amyloidosis from patients with other causes of left ventricular hypertrophy. The lower 1-year mortality in women was reported in patients undergoing TAVR (mean age, 84 years for women and 82 years for men).19 This phenomenon may be accounted for by the male dominance of wtATTR (male:female = 20–50:1), which may lead the poorer prognosis in male sex in these population.20 In the study by Treibel et al,2 patients with CMR-incompatible devices were excluded from the study. Because wtATTR patients may have advanced atioventricular block requiring CMR-incompatible devices,20 some wtATTR patients with devices may have been possibly excluded from this study, may have resulted in an underestimation in the prevalence of wtATTR in patients with severe AS.

The prognostic significance of the existence of myocardial wtATTR should be considered in future studies on the prognosis of patients with severe AS. The age of patients in Treibel et al’s study is younger than that of patients who underwent TAVR (>80 years of age).19 Historically significant cardiac wtATTR occurs in 8% to 16% of people >80 years of age.20 Thus, AS patients requiring TAVR may include more wtATTR patients than AS patients requiring sAVR. The prevalence of wtATTR in patients with severe AS requiring TAVR is of interest, and further systematic prospective studies should be performed in patients with severe AS being considered for TAVR, especially in elderly patients >80 years of age.

Disclosures

None.

References


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Prognostic Significance of Occult Transthyretin Cardiac Amyloidosis in Patients With Severe Aortic Stenosis Undergoing Surgical Aortic Valve Replacement: An Unrecognized Disease Modifier
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