Double trouble: severe aortic stenosis and cardiac amyloidosis

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Aortic stenosis (AS) as well as cardiac amyloidosis (CA) are prevalent conditions in old patients. The combination of both AS and CA has recently been identified to occur in a significant number of patients scheduled for aortic valve replacement. Age alone, however, does not fully explain the frequent overlap of the two pathologies as the prevalence of CA in individuals >80 years in the general population has been described to be <1% [1].

Although the exact pathophysiological mechanisms underlying AS-CA are incompletely understood, it has been hypothesized that increased afterload placed on the left ventricular myocardium may prime for amyloid deposition [2]. Moreover, amyloid deposits in AS were found not only in the myocardium but also the aortic valve leaflets, potentially contributing to progression of AS [3]. Such amyloid formations within calcific aortic valves have been described for apolipoprotein A1, which—in the state of chronic low-grade inflammation—may aggregate and potentially promote mineralization [3]. Conversely, amyloidogenic proteins affecting the myocardium are predominantly of transthyretin (ATTR) and immunoglobulin light chain (AL) origin. Therefore, amyloid deposition affecting aortic valve leaflets on the one hand and the myocardium on the other hand may be regarded as two different entities, with this editorial focusing on the latter.

Since Treibel et al. first described co-existing CA in tissue samples of severe AS patients undergoing surgical aortic valve replacement (AVR) [4], scientific interest in dual pathology AS-CA grew rapidly. Bone scintigraphy using tracers, such as

^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) offers a novel imaging modality for noninvasive diagnosis of ATTR-CA [5], the most common CA subtype found in severe AS [6]. ATTR-CA is diagnosed by cardiac tracer uptake on bone scan and unremarkable serum and urine free light chain assessment. This method was applied in several studies on older AS patients undergoing transcatheter AVR (TAVR) and a prevalence of AS-CA ranging from 8.4% to 16.0% was reported [2, 6–8]. AL, the other predominant amyloid protein found in the heart, is rarely detected in severe AS scheduled for TAVR [6]; however, given the immediate therapeutic implications of AL-CA, this subtype always has to be ruled out by urine and serum free light chain assessment if AS-CA is suspected [5]. In cases of suspected AL-CA, tissue biopsy (preferably endomyocardial samples) is necessary to confirm the diagnosis.

Although DPD bone scintigraphy offers a highly specific and sensitive tool to diagnose AS-CA, systematic screening of all AS patients referred for TAVR is not applicable for economic and logistic reasons. Most recently a clinical scoring system (RAISE) that can be used to screen severe AS patients for concomitant CA, has been developed (Fig. 1; [9]). This score includes parameters from 5 different domains:

- Cardiac Remodeling (left ventricular hypertrophy, diastolic dysfunction)
- Age
- Cardiac Injury (high-sensitivity troponin T)
- Systemic Disease (carpal tunnel syndrome)
- Electrical Disturbances (right bundle branch block, low voltages)

Each parameter is labelled with a distinct score if present. Scores ≥2 points should raise suspicion for concomitant CA and instigate further testing with DPD bone scan and light chain assessment. This is

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Fig. 1 Algorithm for screening, diagnosis and management of concomitant cardiac amyloidosis in severe aortic stenosis. AL light chain, AS aortic stenosis, ATTR transthyretin, AVA aortic valve area, AVR aortic valve replacement, CA cardiac amyloidosis, DPD 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid, ECV extracellular volume, GLS global longitudinal strain, HF heart failure, IVS interventricular septum,

LGE late gadolinium enhancement, LVH left ventricular hypertrophy, MG mean transvalvular gradient, MI myocardial infarction, RVW right ventricular wall, SLI Sokolow/Lyon index, SVi stroke volume index, TAPSE tricuspid plane systolic excursion, TAVR transcatheter AVR, TTE transthoracic echocardiography. With permission from [10] (License number 4954821027048)

also warranted if CA is suspected from the presence of red flags from alternative sources (e.g. extensive late gadolinium enhancement on cardiac magnetic resonance imaging consistent with CA, moderate/severe low-flow, low-gradient state on echocardiography, Fig. 1; [6, 10]).

Until recently, prognostic implications as well as effectiveness of AVR in dual AS-CA were unknown. Even futility of AVR was discussed; however, very recently several studies showed equal survival rates of AS-CA and AS alone following TAVR [2, 6, 7, 9], disproving the conception of treatment futility in AS-CA.

The introduction of novel pharmacological treatment [11–13], with promising results with respect to improved functional capacity, quality of life, disease regression and, most importantly, patient outcomes have raised hopes to even cure the disease [11, 14]. AS-CA patients, however, were so far systematically excluded from pharmacologic studies, and the effectiveness of ATTR-specific treatment in this population, therefore, remains unclear.

In conclusion, AS-CA affects about 1 in 8 patients referred for TAVR. Comprehensive screening for AS-CA in every TAVR candidate is not feasible; a clinical scoring system (RAISE) can help to identify those with a high likelihood of AS-CA, who should receive further testing by bone scintigraphy and free light chain assessment.

TAVR should not be withheld in AS-CA, as affected individuals otherwise face a dismal prognosis. Future studies will need to demonstrate whether novel ATTR-pharmacotherapies improve patient outcomes in AS-CA on top of valvular replacement compared to AVR only.

Conflict of interest C. Nitsche and J. Mascherbauer declare that they have no competing interests.

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