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Concomitant Cardiac Amyloidois in Severe Aortic Stenosis: The Trojan Horse?

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Per the *Aeneid* of Virgil, the Trojans were defeated after the Greeks left behind a huge wooden horse at the gates of Troy and pretended to sail back home after a 10-year siege. The wooden horse was filled with Greek warriors who invaded Troy after the Trojans brought the horse inside the city walls. Quite like the hidden warriors, cardiac amyloidosis (CA) is an insidious and often undetected process. Aortic stenosis (AS) and transthyretin (ATTR) amyloidosis are both more prevalent in the elderly people, and may impact functional and clinical outcomes if they co-existed (1). However, there are, hitherto, few data pertaining to the exact prevalence and severity of CA, and its impact on outcomes in patients with AS, both before and after aortic valve replacement (AVR).

In this issue of JACC, Nitsche et al. (2) report results of a multi-center international registry of the prevalence, predictors, and outcomes in 408 consecutive severe AS patients with AS evaluated for transcatheter AVR (TAVR) at 3 referral centers. Bone scintigraphy with ^{99m}Tc-DPD was performed in all and assessed by a core laboratory using the Perugini grading system (grade-0, negative and grade 1–3 for increasingly positive scans). ATTR-CA was diagnosed by a positive DPD result, and the absence of a clonal immunoglobulin and light-chain-CA (AL) by a tissue biopsy.

Prevalence, Type, and Severity of CA in Severe AS

In the present study (2), CA was detected in 48 (11.8%) patients, which is consistent with previous reports of prevalence between 9 and 16%.(1,3-6). Of these 48 patients, one third (n= 16, 3.9% of the total population) had Grade 1 and 7.9% had Grade 2 or 3 DPD uptake. In this elderly population (age, 83.4±6.5 years) with severe AS, not surprisingly, ATTR CA was verified in all patients except one light chain CA. Compared to patients with lone AS, those with AS and CA were older and had worse functional status, worse cardiac remodeling, higher circulating NT-proBNP and troponin levels, and more frequently exhibited a low-flow, low-gradient AS pattern.

Red Flags for Concomitant CA in Severe AS

The present study (2) confirms that CA is frequent (1 out of 8 patients) in patients with severe AS referred for TAVR evaluation. However, systematic screening for CA using bone scintigraphy and light chain analysis does not appear to be an optimal approach from logistic and economic standpoints. The challenge, in this context, is to differentiate a wooden horse (lone AS) from a Trojan horse (AS with CA). Hence, it is of paramount importance to develop and validate 'red flags' for identification of AS patients who are likely to carry concomitant CA and who should therefore undergo confirmatory diagnostic testing. However, CA shares several clinical, electrocardiographic, and echocardiographic features with AS phenotype, including old age, and left ventricular concentric hypertrophy, diastolic dysfunction and depressed global longitudinal strain (1). Hence, the challenge in the AS population is to identify red flags that are more specific to CA. In the present study (2), a clinical score (i.e. the RAISE score, including several clinical, electrocardiographic, echocardiographic parameters and blood biomarkers) was developed to predict the risk of CA in patients with severe AS. In this multi-parameter score, age ≥85 years (1 point); history of carpal tunnel syndrome (3 points), presence of right bundle branch block (2 points), Sokolow/Lyon index <1.9 mV (1 point), high sensitivity troponin level >20 ng/ml (1 point), and E/A ratio >1.4 (1 point); a score ≥2 showed a high sensitivity (84%) and a score ≥3 had a high specificity (94%) for the detection of CA. Among the aforesaid 6 parameters, carpal tunnel syndrome and low ECG voltage despite the presence of LV hypertrophy were more specific for co-existing CA. Old age, advanced diastolic dysfunction, and reduced longitudinal strain even if associated with apical sparing were not specific for co-existent CA and are frequently encountered in severe AS; furthermore the E/A ratio is not an optimal determinant of diastolic dysfunction. Despite limitations, this simple score provides

reasonable accuracy to raise suspicion for CA and a score ≥2 should prompt confirmatory tests including bone scintigraphy and light chain analysis. The RAISE score allows room for further improvement by inclusion of other potentially valuable red flags, such as the presence of biventricular hypertrophy, tricuspid annulus S' velocity <9 cm/s, or TAPSE <1.4 cm ***(Figure)*** (1,4). Furthermore, this score will need to be validated in a larger and independent population.

Response to Treatment and Outcomes in Patients with AS and Concomitant CA

The risk of futility of AVR has been a widely held concern in the management of AS patients with concomitant CA. Indeed, initial reports had suggested that such patients carry higher risk of futility of AVR and have worse outcomes compared to those with lone AS (1,5,6). These previous studies, however, suffered from selection bias. The present study (2) that included a consecutive series of patients with systematic detection algorithm for CA is re-assuring that patients with AS and CA had outcomes similar to those with lone AS. However, there was a trend (p=0.05) for higher mortality at 1 year in AS-CA vs. lone AS but the former had worse risk profile at baseline and multivariable analysis demonstrated no independently adverse effect of coexisting CA on outcomes both in patients undergoing TAVR and those treated medically. Assessment of treatment utility vs. futility not only includes patient's vital status but also improvement in symptomatic and functional status and quality of life. The present study (2) only reported all-cause mortality obtained from national registries. Further studies are thus needed to assess the impact of CA on other relevant clinical outcomes, including re-hospitalization for heart failure, functional class, and quality of life. Also, this study is limited to 1-year follow-up, whereas CA may have an impact on longer-term outcomes.

Valvular Amyloidosis and the Longevity of Bioprosthesis

The Trojan Horse has come to mean any stratagem that causes a target to invite a foe into a protected location, and this analogy is not only consequential for the myocardium but also the valve ***(Figure)***. The amyloid protein may also deposit within the aortic valve leaflets and could therefore contribute to the valve leaflet thickening and the progression of AS (7,8). Aortic valve calcium scoring measured by non-contrast CT may be useful to confirm stenosis severity in the context of low-flow, low-gradient AS, which is more prevalent in patients with AS-CA ***(Figure)*** (1). However, non-contrast CT only captures mineralized tissues and would underestimate AS severity in patients, whose valve stenosis is predominantly caused by non-calcific tissues, such as fibrous tissues or even amyloid substance. New imaging methods based on contrast CT are currently being developed to quantitate the volume of both calcific and non-calcific valvular tissues. These methods could eventually become helpful to confirm severity of AS in patients with low-flow, low-gradient AS and CA. It is plausible that amyloid proteins may also infiltrate and accumulate within the bioprosthetic valve leaflets and contribute to accelerated structural deterioration of the prosthetic valve. Further studies are needed to determine whether AS-CA patients will have shorter valve durability following AVR.

Algorithm for Screening, Diagnosis and Management of CA in Severe AS

Due to a substantial prevalence of CA in severe AS, it is prudent to follow a systematic approach for the care of such patients (Figure 1). As the first step it is important to recognize red flags for CA. If present, the second step is to perform additional tests including DPD scintigraphy, monoclonal light chain analysis in blood and urine, and/or myocardial biopsy to confirm the diagnosis and type of CA. The third step should confirm the severity of AS by documenting either the echocardiographic evidence of high gradient, or severe aortic valve calcification on non-contrast CT in the case of low-flow, low-gradient AS. The last step should allow the selection of the type of treatment; patients with confirmed severe AS should

promptly undergo AVR, and TAVR should be preferred in patients with concomitant CA. Indeed, patients with AS and CA often have advanced cardiac damage (9) with frequent impairment of the right heart including RV dysfunction, tricuspid regurgitation, and/or pulmonary hypertension. In this vulnerable subset of patients, transfemoral TAVR is usually associated with better outcomes than surgical AVR (10,11). Finally, treatment with tafamidis should be considered in patients with confirmed ATTR-CA, and chemotherapy in those with light chain CA, regardless of the AS severity or the decision to perform AVR ***(Figure)*** (1).

Conclusions

CA occurs in 1 out of 8 patients with severe AS evaluated for TAVR and is associated with worse risk profile at baseline but similar prognosis following TAVR, when compared to lone AS. The RAISE score ≥2 raises the suspicion for CA and should prompt confirmatory tests. The diagnosis of CA in symptomatic patients with severe AS should not preclude or delay the consideration for TAVR. Further, it should trigger the consideration for pharmaco-therapeutic approach targeting of CA, e.g. tafamidis in case of ATTR-CA. Like the Trojan Horse, CA is more dangerous if it is not recognized and not dealt with.

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Figure Legend

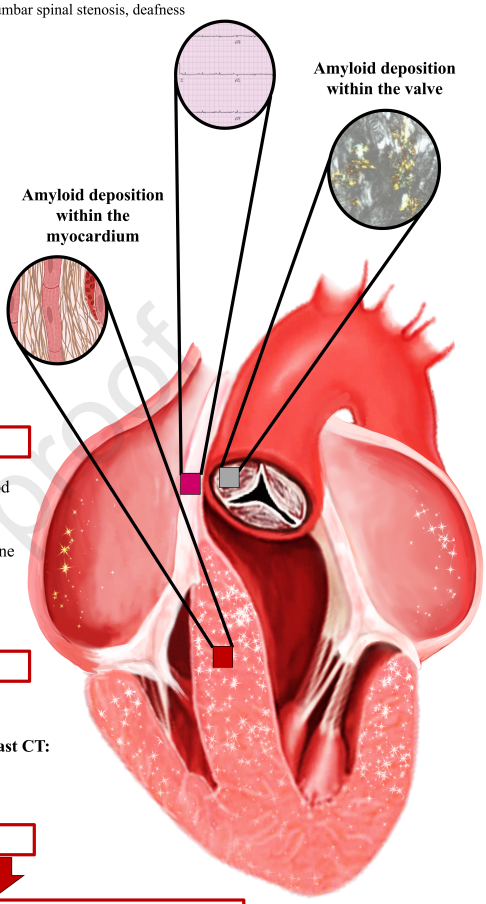
FIGURE: Screening, Diagnosis and Management of Cardiac Amyloidosis in Patients with Aortic Stenosis

Caption: AL: light chain, AS: aortic stenosis, ATTR: transthyretin, AVA: aortic valve area, AVR: aortic valve replacement, CA: cardiac amyloidosis, DPD: 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. Adapted with permission of ACC from (1).

PATIENTS WITH AORTIC STENOSIS

STEP 1: Check for Red Flags of Cardiac Amyloidosis

- **Clinical:** age ≥65 years, Male, African origins, Advanced HF but preserved LVEF, carpal tunnel syndrome, lumbar spinal stenosis, deafness
- **ECG:**
  - Low-voltage (SLI <1.9 mV) despite LVH
  - Pseudo-infarction pattern without history of MI
  - Right bundle branch block
- **Biomarkers:** Disproportionate elevation of high sensitivity troponin (>20 ng/L) and NT-proBNP/BNP
- **TTE:**
  - Disproportionate LV diastolic dysfunction (Grade ≥2, E/e'>16, E/A>1.4)
  - Severe LV longitudinal systolic dysfunction (GLS ≥-12%, Mitral S'≤ 6 cm/s) with apical sparing
  - Severe biventricular hypertrophy (IVS >18 mm, RVW ≥5mm)
  - Myocardial granular sparkling
  - Atrial septal thickening (>2mm) an biatrial dilation
  - Moderate severe RV dysfunction (Tricuspid S' <9 cm/s, TAPSE <14 mm)
  - Moderate/severe low-flow state (SVi <30 mL/m^2)
- **CMR:**
  - Extensive LV LGE
  - Elevated native T1 mapping (>1,080 ms) and ECV (>0.58)
- **RAISE Score ≥ 2**



STEP 2: Confirm Diagnosis of Cardiac Amyloidosis

- **Confirm ATTR-CA:** Grade 2 or 3 cardiac uptake on bone scintigraphy (DPD) with negative blood and urine monoclonal light chain
- **Exclude CA diagnosis:** Grade 0 cardiac uptake on bone scintigraphy with negative blood and urine monoclonal light chain
- **Prevalence of CA in AS:** 10 to 15%

STEP 3: Confirm Severity of Aortic Stenosis

- **TTE: High gradient AS** (MG≥ 40 mmHg and AVA≤ 1.0 cm^2)
- **TTE: Low Gradient AS** (MG< 40 mmHg, AVA≤ 1.0 cm^2) **with Calcium Scoring by Non-Contrast CT:**
  - ≥ 1,200 AU in women
  - ≥ 2,000 AU in men

STEP 4: Therapeutic Management

Confirmed Severe Symptomatic Aortic Stenosis

- **Evaluation by Heart Team to assess indication of AVR**
- **TAVR** may be preferred in AS-CA
- **Medical treatment** alone in patients with severe comorbidities and high risk of AVR futility

Confirmed Cardiac Amyloidosis

- **AL-CA:** Chemotherapy
- **ATTR-CA:** ATTR stabilizer in patients with HF signs
- **Heart management: CHAD-STOP**
  - **C**onduction and rhythm disorders prevention
  - **H**igh heart rate maintenance
  - **A**nticoagulation to prevent thromboembolism
  - **D**iuretics: adjusted dose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