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EDITORIAL

# Reduction in Afterload Reveals the Apical Sparing Phenotype

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Aortic stenosis (AS) and cardiac amyloidosis often coexist. A recent meta-analysis showed that 8% of patients with AS had concomitant cardiac amyloidosis.[1] Indeed, these two entities share the same epidemiology, both affecting the elderly population predominantly. Degenerative AS is the most common valvular heart disease in the developed countries, affecting 3% of the general population above the age of 65 years, with increasing prevalence as a function of age. Senile systemic amyloidosis is also a disease of the elderly, affecting up to 25% of individuals above the age of 80 years.[2] Among patients referred for transcatheter aortic valve replacement (TAVR), the prevalence was higher, ranging from 8% to 16%.[3–6] An autopsy study reported that approximately one-third of TAVR recipients had concomitant myocardial amyloidosis of varying severity.[7] These differences in the prevalence could be explained by patient selection, that is, higher prevalence in more elderly study population and as a result of different screening methods for cardiac amyloidosis, that is, bone scintigraphy, cardiac magnetic resonance imaging, echocardiography, or endomyocardial biopsy. Although multimodality imaging techniques are often used at various stages leading to the diagnosis of cardiac amyloidosis, they have different sensitivities and specificities, for example, cardiac magnetic resonance imaging has lower sensitivity compared with bone scintigraphy, while intraoperative myocardial septal biopsy has the lowest yield for detecting cardiac amyloidosis, ranging from 0% to 4%.[8,9]

See Article by Nitsche et al

The most common form of cardiac amyloidosis that coexists with AS is by far the TTR (transthyretin) subtype, while 2% belongs to the light-chain subtype.[1] Patients with concomitant AS and TTR cardiac amyloidosis (AS-ATTR) are often elderly (above the age of 80 years), predominantly male (at least two-thirds), more commonly have the low-flow, low-gradient AS phenotype, more prominent left ventricular (LV) hypertrophy, worse diastolic function, lower stroke volume, higher NT-proBNP (N-terminal pro-B-type natriuretic peptide) and troponin levels compared with those with lone AS.[1,4,10,11] The overall mortality rate of patients with AS-ATTR was higher compared with those with lone AS, especially if AS was managed medically.[3,5,6,9,10] Aortic valve intervention, specifically TAVR, improved survival in patients with AS-ATTR compared with those managed conservatively. Indeed, patients with AS-ATTR and lone AS had similar survival rates post-TAVR up to 3 years, supporting the argument that having concomitant cardiac amyloidosis should not preclude AS-ATTR patients from TAVR consideration.[3,5] Although the risk of periprocedural complications in patients with AS-ATTR was deemed low, occasional cases of femoral artery pseudoaneurysm, cardiac tamponade, and low output syndrome have been reported.[12] Also, AS-ATTR patients had higher heart failure rehospitalization rate at 1 year post-TAVR compared with those with lone AS.[6]

In this issue of the journal, Nitsche et al[13] presented the echocardiographic features of LV remodeling following aortic valve replacement (AVR) in patients with concomitant severe AS and TTR cardiac amyloidosis (AS-ATTR) and compared them against those with lone AS. It is a single-centered prospective study of 120 patients who underwent AVR (114 had transcatheter, whereas 6 had surgical AVR) and completed 12-month follow-up echocardiograms. Overall, AVR provided symptom relief

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in all patients, although relatively more AS-ATTR patients remained in the New York Heart Association class ≥III and had higher residual NT-proBNP levels compared with those with lone AS at 1 year post-AVR. In terms of reverse remodeling, only lone AS patients demonstrated significant LV mass reduction at 1 year post-AVR. This is consistent with a previous study that reported the lack of LV mass reduction at 3 years post-TAVR in AS-ATTR patients compared with those with lone AS.[14] Nitsche et al attributed the differential LV mass regression to the ongoing amyloid infiltration in AS-ATTR, negating the effect of afterload reduction from AVR. This study also showed improvements in global longitudinal strain post-AVR in both the lone AS and AS-ATTR groups. However, there were differential improvements in the regional strain pattern post-AVR, culminating in an apical sparing pattern in AS-ATTR patients, which was not apparent before intervention. The authors postulated that this could be due to the apical segment having relatively low amyloid burden, thus able to improve contractility most substantially post-intervention, making postoperative AS-ATTR more closely resemble the typical ATTR phenotype.

The present article by Nitsche et al is timely, given the increasing recognition of these dual entities in clinical practice with the use of bone scintigraphy and the emergence of novel, effective ATTR-specific therapies in recent years. The existing literature focuses mainly on the baseline clinical and echocardiographic characteristics of patients before valvular intervention. Literature on postoperative functional or structural changes, in particular, myocardial remodeling, is scarce, despite being of interest. This article has shown that the effect of ventricular afterload removal on the subsequent positive structural adaptation is not universal, and it depends on the preexisting myocardial pathology. The post-AVR remodeling unveiled the underlying phenotypic features of ATTR, placing the amyloid cardiomyopathy element at the center stage. This brings about a few questions: does AVR have an effect on the progression of ATTR cardiomyopathy? Would patients with AS-ATTR benefit from ATTR-specific therapies just like those with lone ATTR, and whether age and functional status of the patients matter? At which stage of the disease course should ATTR-specific therapies be initiated, that is, pre-AVR, post-AVR, or concurrently?

The interrelationship between AS and cardiac amyloidosis is complex. Many mechanistic pathways of one disease promoting the other have been proposed, although a consensus has yet to be reached. It is unclear whether amyloidosis has a synergistic effect in the pathogenesis of AS or conversely, whether the presence of AS incites myocardial amyloidogenesis. It has been suggested that AS might induce or accelerate myocardial amyloid deposition as a consequence of pressure overload on the LV.[11] At the valvular level, it has been postulated that the shear stress caused by flow acceleration across a stenotic aortic valve might promote valvular amyloid deposition.[8] It has also been proposed that amyloid deposits could worsen AS by promoting apoptosis and mineralization of aortic interstitial cells as shown in an in vitro study.[15] In the near horizon, the AMYLOCARTESIAN study (Prevalence and Post-surgical Outcomes of Cardiac Wild-type Transthyretin Amyloidosis in Elderly Patients With Aortic Stenosis Referred for Valvular Replacement; https://www.clinicaltrials.gov; unique identifier: NCT02260466)—a multicentered prospective study on patients referred for surgical AVR—may provide further insights into the effect of pressure overload on amyloid deposition.

The classical understanding of cardiac amyloidosis is that it is a global disease that infiltrates the entire heart, resulting in biventricular hypertrophy, atrial septal thickening, and atrioventricular valve thickening. However, this concept has been challenged by a recent study from Singhal et al[8] that reported isolated valvular amyloidosis without biopsy-proven myocardial involvement. In their study of 46 patients referred for surgical AVR, amyloid deposits were found in 72% of the explanted aortic valves, of which 58% had isolated valvular TTR amyloidosis. All patients had no amyloid deposit on basal interventricular septal biopsies. Beyond possible sampling issues, a plausible explanation could be that cardiac amyloidosis exists in a continuum, with different degrees of structural and functional involvement. On one end of the disease spectrum, valvular amyloidosis may exist in isolation without myocardial involvement or it could precede myocardial involvement early in the disease course. As this is a single-centered study with relatively small number, further study is warranted to validate these findings.

In recent years, the emerging novel ATTR-specific (disease modifying) therapies have renewed the interest in the treatment of ATTR, which was previously limited to supportive measures. These targeted therapies are directed at different stages of amyloid fibril formation, namely suppressing TTR synthesis via genetic silencers, stabilizing circulating TTR, or removing TTR deposits. In the present study, 11 of 15 patients with AS-ATTR received tafamidis—a TTR tetramer stabilizer. Tafamidis has been shown to reduce mortality and rehospitalization with a number needed to treat of 7.5 at 30 months in a randomized controlled trial.[16] Its beneficial effect is most apparent when administered early in the disease course and ideally, over an extended period of time. It is thus recommended in patients with reasonable expected survival.[17] Although the clinical outcomes of combining AVR and ATTR-specific therapies have yet to be determined, there are reasons to believe that ATTR-specific therapy could benefit this group of patients as the present study showed that patients with AS-ATTR assume a typical ATTR cardiomyopathy phenotype post-AVR and the all-cause mortality of patients with AS-ATTR was indistinguishable from those with lone AS within the first 3 years post-implant. Areas for further studies should also include the timing of initiating

tafamidis in the natural history of AS-ATTR patients. As there is evidence to suggest survival advantages of initiating therapy early in the disease course of patients with ATTR cardiomyopathy, perhaps tafamidis could be considered in younger patients with higher life expectancy and before aortic valve intervention.

In summary, the present study has further cemented the role of aortic valve intervention in patients with AS-ATTR. Building on the previous work by the same group and others that demonstrated mortality benefit of AVR in AS-ATTR patients, this study adds to the literature by showing significant functional improvement and structural changes 1 year post-AVR. Post-AVR, the underlying ATTR cardiomyopathy phenotype became more apparent, characterized by high residual NT-proBNP levels, the lack of LV mass regression, and an apical sparing regional strain pattern, thus raising the need for ATTR-specific therapies to address the underlying cardiomyopathy.

## ARTICLE INFORMATION

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### Disclosures

None.

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