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EDITORIAL

Echocardiography to identify cardiac amyloidosis in patients with calcific aortic stenosis

Pieter van der Bijl [1], Jan Stassen [1,2], and Jeroen J. Bax [1,3]*

[1]Department of Cardiology, Heart Lung Centre, Leiden University Medical Centre, Albinusdreef 2, 2300 RC Leiden, The Netherlands; [2]Department of Cardiology, Jessa Hospital Hasselt, Stadsomvaart 11, 3500 Hasselt, Belgium; and [3]Heart Centre, University of Turku and Turku University Hospital, Kiinamyllynkatu 4-8, FI-20520 Turku, Finland

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This editorial refers to 'Echocardiographic predictors of presence of cardiac amyloidosis in aortic stenosis', by Jaiswal *et al.*, https://doi.org/10.1093/ehjci/jeac146.

Calcific aortic stenosis (AS) is a common valve lesion, with a higher prevalence in the elderly.[1] Transthyretin cardiac amyloidosis (CA) is a frequent comorbidity in patients with severe AS and has been documented in up to 16% of transcatheter aortic valve replacement recipients.[1–3] Both the outcome implications of CA in the presence of severe AS and the optimal diagnostic approach to CA in patients with AS are still being debated. While some clinical clues may point towards the presence of CA, e.g. carpal tunnel syndrome, lumbar spinal stenosis, or premature pacemaker implantation, they are of inadequate accuracy, and the diagnosis of CA in individuals with AS is dependent on cardiac imaging.

In the current issue of the journal, Jaiswal *et al.*[4] performed a systematic review and meta-analysis of calcific AS studies, the majority comprising severe valvular stenosis. Significant differences were identified in a large number of conventional echocardiographic criteria when comparing patients with AS alone and those with AS and CA: interventricular septal thickness, relative wall thickness, posterior wall thickness, left ventricular ejection fraction, left atrial dimension, myocardial contraction fraction, mitral annular S′, E/A, tricuspid annular plane systolic excursion, tricuspid annular S′, mean transaortic gradient, and peak transaortic velocity all differed substantially between these two groups.

AS and CA cause similar cardiac morphological and functional changes in the heart, e.g. left ventricular hypertrophy, systolic and diastolic dysfunction, and left atrial enlargement, making the differentiation of these entities challenging. Even the pattern of left ventricular hypertrophy is similar between severe AS and transthyretin CA, namely disproportionate basal septal hypertrophy, thereby complicating the diagnosis of CA in AS.[5,6] The authors of the current study have addressed two very important questions in a meta-analytic fashion, namely: (i) if there is a difference in the degree of abnormality between these overlapping morphological and functional changes and (ii) if speckle tracking strain echocardiography can identify CA in the presence of AS. Analysis of data from more than 1400 patients revealed a difference in the degree of abnormality in an array of conventional echocardiographic parameters when contrasting persons with AS and those with AS and concomitant CA. While no specific thresholds for diagnosing CA in the presence of AS could be established for the echocardiographic measures that were analysed (mainly due to the heterogenous nature of the studies that were included), a fundamental principle was revealed, namely that the degree of abnormality of routine echocardiographic parameters may prove to be the key to detecting CA in the presence of AS. In patients without AS, a relative apical sparing pattern of longitudinal deformation on speckle tracking strain echocardiography has been reported to have a sensitivity of 93% and a specificity of 82% for differentiating CA from other causes of left ventricular hypertrophy.[7] In the meta-analysis by Jaiswal *et al.*,[4] however, this echocardiographic sign did not prove useful for the detection of CA in patients with AS. Interestingly, a similar conclusion has previously been drawn from a study of 151 patients who underwent transcatheter aortic valve replacement and who were screened for transthyretin CA with technetium-99 m pyrophosphate scintigraphy.[2]

The outcome implications of CA in the presence of AS are still subject to conflicting data: in a study of 191 patients with AS who underwent transcatheter valve replacement, transthyretin and light-chain CA were not associated with increased mortality.[1] Similarly, in 200 patients who underwent transcatheter valve replacement for severe AS, the presence of CA did not portend a worse outcome.[8] In contrast, outcome was worse for those with AS and CA in an analysis of 146 patients treated with surgical aortic valve replacement.[9] The latter finding is in agreement with a second study of 113 patients who underwent surgical aortic valve replacement, where increased all-cause mortality was seen in the group with CA.[10] The co-

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* Corresponding author. Tel: +3171 526 2020; Fax: +31 71 526 6809. Email: j.j.bax@lumc.nl

existence of AS and CA in a single patient may also impact on the effectiveness of treatment, (i.e. surgical or transcatheter aortic valve replacement), even in the absence of a meaningful impact on survival. The presence of amyloid fibrils in the myocardium of a patient with severe AS could conceivably impair recovery of left ventricular function after valve replacement, although this has not been thoroughly researched.

The authors of the meta-analysis investigated the utility of echocardiography only, although a variety of non-invasive approaches have been used to identify CA in patients with AS, i.e. without making use of an endomyocardial biopsy. Twelve-lead electrocardiography, cardiac magnetic resonance imaging, and computed tomography (CT) have been utilized for diagnosing CA in the presence of AS. The voltage:mass ratio, derived from electrocardiogram and echocardiography, demonstrated good discriminative power (area under the curve 0.770) for distinguishing AS and AS with CA in a population of 191 patients undergoing transcatheter aortic valve replacement. The application of cardiac magnetic resonance imaging and CT for diagnosing CA in patients with AS is predicated on expansion of the extracellular volume (ECV) by the accumulation of amyloid fibrils.[1] Cardiac magnetic resonance-derived ECV can distinguish CA from the ECV expansion caused by AS per se, while a CT-derived ECV of >33.7 has a sensitivity of 100% and a specificity of 93.8% for diagnosing CA in patients with AS.[3,11] Estimating ECV from CT data is only practical in patients who are scanned in preparation for transcatheter aortic valve replacement, while cardiac magnetic resonance imaging is not performed routinely in patients with AS at all, limiting the practical application of these modalities.

Transthyretin CA can now be successfully treated with the tetramer stabilizer tafamidis, which decreases mortality, heart failure hospitalization and improves symptoms.[12] Whether treatment directed towards transthyretin CA in patients with AS changes outcome is currently unknown. From the existing literature, transcatheter aortic valve replacement appears to be the first choice in patients with AS and CA, in preference to surgical valve replacement.[1,8] While general management principles of CA likely also apply in the context of AS, e.g., avoidance of beta-blockers and calcium channel antagonists and careful titration of diuretics, pharmacologic treatment of transthyretin CA is an attractive target. Before trials investigating drug therapy of CA in patients with AS can be performed to determine its impact on outcome, the diagnosis of CA in the presence of AS will have to be made reliably by non-invasive means. The current meta-analysis points future investigators in a clear direction, i.e. making use of routine echocardiographic measurements, taking into account the magnitude of abnormality and without overdue reliance on speckle tracking strain. Artificial intelligence and deep learning algorithms may have a role to play in identification of echocardiographic features suggestive of CA in patients with AS, precisely because they are represented by routine measurements and may be overlooked in a busy echocardiography laboratory. It is also likely that multimodality imaging will be indispensable in the diagnosis and management of CA in patients with AS. The ongoing Prevalence and Postsurgical Outcomes of CARdiac Wild-type TransthyrEtin amyloidoSIs in Elderly Patients With Aortic steNosis Referred for Valvular Replacement (NCT02260466) trial will characterize CA in AS patients referred for surgical valve replacement with histology, echocardiography, and cardiac magnetic resonance imaging, and the results are eagerly awaited by the cardiology community.

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