CARDIAC AMYLOIDOSIS IN AORTIC STENOSIS: THE TIP OF THE ICEBERG

To the Editor:

We read with interest the article by Java and colleagues¹ reporting the Mayo Clinic experience of patients with amyloidosis who underwent aortic valve

replacement. They reported on 16 patients with systemic amyloidosis (6 light chain, 6 transthyretin, and 4 localized) undergoing valve intervention (11 surgical aortic valve replacements and 6 transcatheter aortic valve replacements) during a 17-year period in which 6437 interventions were performed. They highlight low operative morbidity and mortality, short hospital stay, and good 1-year survival for these patients.

The excellent accompanying editorial by Çiçek² highlights the limitations: only 6 of the 16 patients had confirmed cardiac involvement (5 confirmed by endomyocardial biopsy and 1 by bone scintigraphy), the degree of cardiac involvement was not commented on, and, importantly, the inclusion of only those who underwent valve intervention creates a significant selection bias. Patients with advanced amyloidosis may have been declined intervention and therefore would not be included in the study.

We wish to highlight another potential limitation of the study. Six patients identified with cardiac amyloidosis of 6437 interventions is a prevalence of 0.0009%. Recent

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FIGURE 1. Technetium-99m-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) scintigraphy in an 84-year-old woman with severe aortic stenosis referred for transcatheter aortic valve replacement. A, Whole body late (3-hour) planar image showing Perugini grade 2 cardiac uptake diagnostic of cardiac amyloidosis. B and C, Single photon emission tomographic image (B) and fused single photon emission tomographic image and computed tomographic image (C) confirming cardiac retention of tracer.

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studies looking prospectively for cardiac amyloidosis in patients with severe aortic stenosis by using either endomyocardial biopsy or bone scintigraphy have found a prevalence of between 6% (endomyocardial biopsy in patients older than 65 years undergoing surgical aortic valve replacement)³ and 13% to 16% (bone scintigraphy in older patients undergoing transcatheter aortic valve replacement).^{4,5} If these prospective cohorts (1 US cohort and 2 European cohorts; n = 359 in total) are representative, this cohort should have contained between 380 and 1030 cases of cardiac amyloidosis, suggesting that more than 98% of cases were either missed or excluded from intervention. Figure 1 shows an example of positive bone scintigraphy, diagnostic of cardiac amyloidosis, in an elderly woman referred for transcatheter aortic valve replacement.

Accordingly, we advocate caution. Cardiac amyloidosis is not benign. Conclusions based on this data alone about the safety of aortic valve intervention and its benefits in cardiac amyloidosis cannot be made. Outcome data are pending, but early results suggest higher medium-term mortality in patients referred for transcatheter aortic valve replacement with severe aortic stenosis (ATTRact-AS Study, NCT03029026). If the finding is confirmed, however, it will still not tell us the net benefit (or otherwise) of aortic valve intervention in patients with cardiac amyloidosis.

We believe that looking for occult cardiac amyloidosis in elderly patients with aortic stenosis is likely to prove important, not least because of promising new therapies that we hope will have a role in the treatment of transthyretin cardiac amyloidosis. Red flags include previous carpal tunnel syndrome; inappropriate left ventricular hypertrophy; low-flow, low-gradient aortic stenosis phenotype; advanced age; and male sex (although, interestingly, there is so far no male predominance among the patients found to have cardiac amyloidosis in the ATTRact-AS study cohort).⁴ Further work is pending to refine our understanding of the role of cardiac amyloidosis in these patients.

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V _{cardiac} =	Pit =	917 kg/m ³
V _{ventr} =	P _{ventr} =	1029 kg/m ³
V = volume, p = density		0.89

CARDIAC AMYLOIDOSIS IN AORTIC STENOSIS—ICEBERGS AND ARCHIMEDES' PRINCIPLE

Reply to the Editor:

It is our pleasure to respond to the letter by Scully and colleagues.¹ We take the “tip of the iceberg” analogy to be based on Archimedes principle, which in this instance implies to us a 90% below-the-waterline, invisible, unknown knowledge base about the role of aortic valve replacement in patients with amyloidosis. We don't agree with Scully and colleagues' ¹ implication.

The authors provide a critique of our study with respect to a lack of objective cardiac involvement, selection bias, limited number of patients, and outcomes. We reported that only 6 of our patients had documented cardiac involvement (all transthyretin/prealbumin-type amyloidosis; Figure 1; patient 13 in our series),² and although cardiac

FIGURE 1. SPECT/CT imaging shows patchy increased tracer activity in the left ventricular myocardium.