P.R.S. is supported by a British Heart Foundation Clinical Research Training Fellowship (FS/16/31/32185). All other authors have nothing to disclose with regard to commercial support.

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.

Paul R. Scully, MBBS, MRes, MRCP^{a,b}

James C. Moon, MD^{a,b}

Thomas A. Treibel, PhD^{a,b}

^aBarts Heart Centre

St Bartholomew's Hospital

London, United Kingdom

^bInstitute of Cardiovascular Sciences

University College London

London, United Kingdom

References

1. Java AP, Greason KL, Dispenzieri A, Grogan M, King KS, Maleszewski JJ, et al. Aortic valve replacement in patients with amyloidosis. *J Thorac Cardiovasc Surg*. December 19, 2017 [Epub ahead of print].
2. Çiçek S. Cardiac amyloidosis and aortic stenosis: great masquerader back again! *J Thorac Cardiovasc Surg*. February 13, 2018 [Epub ahead of print].
3. Treibel TA, Fontana M, Gilbertson JA, Castelletti S, White SK, Scully PR, et al. Occult transthyretin cardiac amyloid in severe calcific aortic stenosis: prevalence and prognosis in patients undergoing surgical aortic valve replacement. *Circ Cardiovasc Imaging*. 2016;9.
4. Scully PR, Treibel TA, Fontana M, Lloyd G, Mullen M, Pugliese F, et al. Prevalence of cardiac amyloidosis in patients referred for transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2018;71:463-4.
5. Castaño A, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J*. 2017;38:2879-87.

<https://doi.org/10.1016/j.jtcvs.2018.03.142>

V _{cardiac}	=	917 kg/m ³
V _{total}	=	1029 kg/m ³
V = volume, ρ = density		

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.

Authors have nothing to disclose with regard to commercial support.

involvement was undocumented in the 5 patients with immunoglobulin light chains-type amyloidosis, the literature would support that 50% of these patients also have such involvement.³ Our study cohort was identified retrospectively by collating 2 separate databases. We feel that this represents our best-available data.

Another criticism is that there were probably patients at our institution who were declined intervention because of “advanced amyloidosis.”¹ Given the nature of our retrospective study, there was no way for us to identify such patients. We agree that our patient cohort was a selected group (see the Discussion in our article), but we feel that declining intervention on patients with “advanced amyloidosis” represents just good surgical judgment.²

Scully and colleagues also suggest that more than 98% of our cases were either missed or excluded from intervention.¹ They base their assumption on an estimated prevalence of 6% to 16% for cardiac amyloidosis in patients with severe aortic valve stenosis. We agree that our prevalence is an underestimation (see Discussion).² We would like to point out that the authors’ estimated prevalence comes from only 3 studies, each with comparable small numbers of patients with cardiac amyloidosis (ie, 6, 14, and 24).

The final criticism from Scully and colleagues is that they advocate caution with respect to our reported outcomes.¹ We had no cases of operative stroke or dialysis and no operative or 1-year mortality in 11 patients with transthyretin/prealbumin-type amyloidosis (n = 6) and immunoglobulin light chains-type amyloidosis (n = 5).² We updated our vital status follow-up for this response, and our Kaplan–Meier estimated 2-year mortality stands now at $16.7 \pm 10.8\%$. Our estimated mortality is consistent with what was reported in the prospective, randomized, intermediate-risk aortic valve replacement Placement of Aortic Transcatheter Valves (PARTNER) 2A trial.⁴

Scully and colleagues¹ go on to report “red flags” for occult cardiac amyloidosis in elderly patients with aortic stenosis. Several of those “red flags” (eg, advanced age, male sex, and low-flow, low-gradient aortic valve stenosis) can be found in the patients in the low-flow severe aortic stenosis PARTNER trial.⁵ In that study, importantly, survival was improved with transcatheter aortic valve replacement compared with medical management and was similar with transcatheter and surgical aortic valve replacement.

Patient selection is critical when offering aortic valve replacement to patients with amyloidosis. However, based on the evidence presented, we feel that aortic valve replacement should not be denied solely on the basis of underlying amyloidosis.

Amit P. Java, MD^a

Kevin L. Greason, MD^a

Angela Dispenzieri, MD^b

Martha Grogan, MD^c

Joseph J. Maleszewski, MD^d

Richard C. Daly, MD^a

Mackram F. Eleid, MD^c

Hartzell V. Schaff, MD^a

Departments of ^aCardiovascular Surgery

^bInternal Medicine

^cCardiovascular Diseases

^dLaboratory Medicine and Pathology

Mayo Clinic

Rochester, Minn

References

1. Scully PR, Moon JC, Treibel TA. Cardiac amyloidosis in aortic stenosis: the tip of the iceberg. *J Thorac Cardiovasc Surg.* 2018;156:964-6.
2. Java AP, Greason KL, Dispenzieri A, Grogan M, King KS, Maleszewski JJ, et al. Aortic valve replacement in patients with amyloidosis. *J Thorac Cardiovasc Surg.* 2018;156:98-103.
3. UpToDate, McKenna WJ. Clinical manifestations and diagnosis of amyloid cardiomyopathy. In: Yeon SB, ed. *UpToDate.* 2017. Available at: <https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-amyloid-cardiomyopathy>. Accessed April 1, 2018.
4. Leon MB, Smith CR, Mack MH, Makkar RR, Svensson LG, Kodaly SK, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med.* 2016;374:1609-20.
5. Herrmann HC, Pibarot P, Hueter I, Gertz ZM, Stewart WJ, Kapadia S, et al. Predictors of mortality and outcomes of therapy in low-flow severe aortic stenosis. A placement of aortic transcatheter valves (PARTNER) trial analysis. *Circulation.* 2013;127:2316-26.

<https://doi.org/10.1016/j.jtcvs.2018.04.052>

ALPHA-STAT VERSUS pH STAT ACID BASE BALANCE FOR AORTIC ARCH SURGERY: THE DEBATE CONTINUES

Reply to the Editor:

In his letter to the Editor regarding the recent article by Damberg and colleagues¹ and my accompanying editorial commentary,² Jonas³ offers several criticisms and suggestions regarding the management of adult patients who require intervals of hypothermic circulatory arrest (HCA) during operations on the thoracic aorta that involve the aortic arch. His major criticism relates to use of the alpha-stat strategy for acid-base management during these procedures, and he discusses why he considers the pH-stat strategy to be preferable to the alpha-stat strategy in this setting. This recommendation is based primarily on a randomized, controlled clinical trial in infants reported by his group (du Plessis and colleagues⁴) in 1997, which showed that use of the pH-stat strategy during procedures that required deep hypothermic cardiopulmonary bypass, which included patients requiring deep HCA, was