Occult Transthyretin Cardiac Amyloid in Severe Calcific Aortic Stenosis: Prevalence and Prognosis in Patients Undergoing Surgical Aortic Valve Replacement

Running title: Treibel et al.; Transthyretin Cardiac Amyloid in Severe Aortic Stenosis

Thomas A. Treibel, MBBS\textsuperscript{1,2}; Marianna Fontana, MD\textsuperscript{1,2,3}; Janet A. Gilbertson, CSci\textsuperscript{3}; Silvia Castelletti, MD\textsuperscript{1}; Steven K. White, MBChB\textsuperscript{1,2}; Paul R. Scully, MBBS\textsuperscript{1}; Neil Roberts, MD\textsuperscript{1}; David F. Hutt, BApSc\textsuperscript{3}; Dorota M. Rowczenio, PhD\textsuperscript{3}; Carol Whelan, MD\textsuperscript{3}; Michael A. Ashworth, MD\textsuperscript{4}; Julian D. Gillmore, MD, PhD\textsuperscript{3}; Philip N. Hawkins, FMedSci\textsuperscript{3}; James C. Moon, MD\textsuperscript{1,2}.

\textsuperscript{1}Barts Heart Centre, St Bartholomew’s Hospital, London, UK; 
\textsuperscript{2}Institute of Cardiovascular Science, University College London, London, UK. 
\textsuperscript{3}National Amyloidosis Centre, Royal Free Campus, University College London, London, UK. 
\textsuperscript{4}Great Ormond Street Hospital for Children, London, UK.

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Correspondence Address:

Dr Thomas Treibel
Barts Heart Centre
St Bartholomew’s Hospital
2nd Floor, King George V Block
London EC1A 7BE, United Kingdom
Tel: +442034563081 Fax: +442034563086
Thomas.Treibel.12@ucl.ac.uk
ABSTRACT

Background: Calcific aortic stenosis (cAS) affects 3% of individuals aged over 75 years, leading to heart failure and death unless the valve is replaced. Wild-type transthyretin cardiac amyloid (wtATTR) is also a disorder of ageing individuals. Prevalence and clinical significance of dual pathology are unknown. This study explored the prevalence of wtATTR in cAS by myocardial biopsy, its imaging phenotype and prognostic significance.

Methods and Results: 146 patients with severe AS requiring surgical valve replacement underwent cardiovascular magnetic resonance (CMR) and intra-operative biopsies; 112 had cAS (75±6 years; 57% male). Amyloid was sought histologically using Congo red staining, then typed using immunohistochemistry and mass spectrometry; patients with amyloid underwent clinical evaluation including genotyping and ⁹⁹ᵐTc-DPD bone scintigraphy. Amyloid was identified in 6 out of 146 patients, all with cAS and >65 years (prevalence 5.6% in cAS >65). All six patients had wtATTR amyloid (mean age 75, range 69-85, 4 males), not suspected on echocardiography. CMR findings were of definite cardiac amyloidosis in two, but could be explained solely by AS in the other four. Post-op ⁹⁹ᵐTc-DPD scans demonstrated cardiac localization in all four patients who had this investigation (two died prior). At follow-up (median 2.3 years), 50% with amyloid had died (versus 7.5% in cAS; 6.9% in age >65). In univariable analyses, the presence of ATTR amyloid had the highest hazard ratio for death (HR 9.5 [2.5-35.8], p=0.001).

Conclusion: Occult wtATTR cardiac amyloid had a prevalence of 6% among AS patients >65 undergoing sAVR and was associated with a poor outcome.

Key words: Aortic stenosis, cardiac amyloidosis, magnetic resonance imaging, transthyretin, ⁹⁹ᵐTc-DPD scintigraphy.
INTRODUCTION

Severe degenerative calcific aortic stenosis (cAS) is common, affecting 3% of individuals aged over 75 years and leads to heart failure and death unless the valve is replaced.\textsuperscript{1,2} Its coexistence with cardiac amyloidosis has been reported but this has not been studied systematically and the prognostic significance is unknown.\textsuperscript{3} Cardiac amyloidosis is a progressive infiltrative cardiomyopathy in which deposits of amyloid, almost always of either immunoglobulin light-chain (AL) or transthyretin (ATTR) type,\textsuperscript{4-6} accumulate in the ventricular myocardium; ATTR amyloid is usually wild-type (wtATTR) and acquired, but it may also be hereditary and associated with mutant forms of transthyretin. Wild-type cardiac ATTR amyloid has a male preponderance and was formerly known as senile amyloid reflecting its first appearance beyond 60-70 years of age, and prevalence at autopsy of up to 25% among octogenarians.\textsuperscript{7,8} Its natural history and the prevalence of clinically significant ATTR amyloid deposition in the heart are unknown. In a recent small cohort of AS patients who underwent transcatheter aortic valve replacement (TAVR) but subsequently died, cardiac amyloid deposits were identified at autopsy in a third of cases.\textsuperscript{9} It has been suggested that occult amyloid might account for the frequent need for pacemakers among TAVR patients, and the high prevalence of cardiovascular magnetic resonance (CMR) late gadolinium enhancement (LGE),\textsuperscript{10} but this has not been studied systematically.

It has not hitherto been possible to reliably detect the presence of cardiac amyloidosis without recourse to biopsy, but this is now possible in most patients using a combination of multiparametric CMR incorporating native T1 mapping,\textsuperscript{11} estimation of the extracellular volume fraction (ECV),\textsuperscript{12} and the Phase Sensitive Inversion Recovery (PSIR) LGE technique,\textsuperscript{13} coupled with bone scintigraphy.\textsuperscript{14} This is all the more important given that several specific drug therapies for ATTR amyloidosis are now in clinical trial.\textsuperscript{15,16} We hypothesized that unrecognized ATTR amyloid deposits may act as a disease modifier in
aortic stenosis, and report here a cohort of 146 severe AS patients requiring surgery who were investigated as part of the RELIEF-AS study (NCT 02174471), in which myocardial biopsy and comprehensive multimodality imaging was performed. We aimed to: 1 – assess the prevalence of occult cardiac amyloid in AS; 2 - identify the amyloid subtype; 3 – determine the role of comprehensive imaging; and 4 - elucidate its clinical and prognostic significance.

METHODS

Research was carried out in a single center (University College London Hospital NHS Trust, London, UK) between January 2011 and March 2015. Study approval was granted by the ethical committee of UK National Research Ethics Service and conformed to the principles of the Helsinki Declaration (UK NRES 07/H0715/101). 181 patients with severe AS awaiting surgical aortic valve replacement (sAVR) underwent echocardiography and multiparametric CMR (76% of all sAVR) as part of the RELIEF-AS Study (NCT 02174471). 146 patients (81%) also underwent intra-operative myocardial biopsies. The echocardiography was performed as a clinical test and the CMR as a research study pre-operatively, whilst DPD bone scintigraphy was conducted during subsequent specialist clinical evaluation of subjects found to have amyloid on biopsy (see later). Exclusion criteria comprised contraindications to CMR including glomerular filtration rate <30 mL/min and CMR-incompatible devices. Assessment of patients with amyloid was performed at the National Amyloidosis Centre.

Diagnosis of severe aortic stenosis by echocardiography

Prior to AVR, all patient underwent a clinical transthoracic echocardiogram (TTE), primarily to assess aortic valve mean gradient, peak jet velocity and effective orifice area, i.e. assessment of AS severity, as well as systolic and diastolic function. Global longitudinal
strain was not performed routinely as and was therefore not available prior to AVR. Analysis was performed retrospectively in patients with adequate endocardial border definitions as previously described.  

**CMR scanning**

All subjects underwent CMR at 1.5 Tesla (Magnetom Avanto, Siemens Medical Solutions) using a standard clinical protocol with late gadolinium imaging (LGE) using PSIR and T1 mapping prior to and after a bolus of 0.1mmol/kg of Gadoterate meglumine, (gadolinium-DOTA, marketed as Dotarem, Guerbet S.A., Paris, France) for extracellular volume fraction (ECV) quantification. Post contrast LGE imaging was performed at 5-15 minutes. T1 mapping for ECV quantification was performed using ShMOLLI (Shortened Modified Look-Locker Inversion recovery), providing single-section T1 map in one breath-hold at fifteen minutes (bolus only, pseudo-equilibrium technique). Two amyloid specific indices, myocardial contraction fraction (the ratio of stroke to myocardial volume) and EKG-voltage/LV mass ratio, were calculated.

**Histological analysis**

An intra-operative septal biopsy (typically tubular, measuring 1.6x1.6x10mm) was harvested from the basal left ventricular septum under direct vision by the surgical team using a 14-gauge coaxial needle, formalin fixed and paraffin embedded (FFPE). Histological analysis was performed by Congo red staining on 6µm FFPE sections and viewed in brightfield and cross polarized light. When amyloid was confirmed by displaying apple green birefringence under cross polars, immunohistochemistry (IHC) was carried out on the Shandon Sequenza™ system using a panel of monospecific antibodies against known amyloid-forming proteins, in an attempt to identify the amyloid fibril. Antigen retrieval was not performed with the exception for TTR antibodies which uses oxidation with 1% aqueous Na-m-periodate (10 min) and 0.1% di-NA borohydride (10 min) followed by 6 M guanidine (4h). Sections were
blocked for endogenous peroxidases and with normal serum, incubated overnight at 4°C with the primary antibodies. Antibodies were detected with the appropriate species-specific IMMPRESS (Vector Laboratories) polymer detection kit and labelled using metal-enhanced 3,30-diaminobenzidine chromagen (Thermo Scientific). Interpretation was carried out initially without any clinical information by two people independently using a Leica DMLB with and without crossed polars. Diagnosis was confirmed by laser microdissection and mass spectroscopy (LDMS). 25,26

Clinical assessment of patients with amyloid on myocardial biopsy

Patients found to have amyloid were referred for full clinical assessment at the National Amyloidosis Centre, London, UK. A particular emphasis was to exclude AL amyloid, which can be treated with chemotherapy. Clinical work-up included: serum and urine immunofixation, serum free light chain analysis, comprehensive transthoracic echocardiogram, 123I-labeled serum amyloid P component scintigraphy, sequencing of the transthyretin gene, and cardiac scintigraphy using the 99mTc-labelled DPD bone tracer. This was graded on the Perugini scale: Grade 0 - no myocardial uptake; Grade 1 - minor cardiac uptake of less intensity than uptake in the bony skeleton; Grade 2 - moderate cardiac uptake with greater signal intensity than the bone; Grade 3 - strong cardiac uptake with little or no bone uptake visible. 14,27

Statistical Analysis

A statistical package (SPSS, version 22) was used for all data analysis. Continuous variables were normally distributed (Shapiro-Wilk), other than NT-proBNP which was therefore natural log transformed for bivariate testing; these are presented as mean ± standard deviation (SD) with non-transformed NT-proBNP presented as median and Q1-Q3. Comparisons between groups were performed by one-way analysis of variance with post-hoc Bonferroni correction. The chi-square test or Fisher exact test was used to compare discrete data as
appropriate. Statistical significance was defined as $p < 0.05$. Survival was evaluated using Cox proportional hazards analysis, providing estimated hazard ratios (HR) with 95% confidence intervals (CI) and Kaplan Meier curves. Due to the low number of events (deaths) multivariable Cox regression models were not tested.
RESULTS

146 patients with severe AS awaiting aortic valve replacement (AVR) were recruited. All patients had echocardiography, CMR with LGE and T1/ECV mapping as well as intra-operative myocardial biopsy. 112 patients had calcific AS (cAS) [75±6 years; 58% male]; 32 patients had bicuspid AS (bAS) [59±6 years; 66% male], one patient each rheumatic (65, female) and unicuspid AS (35, female). The treatment received was tissue or mechanical valve in 71% and 29%, respectively, with additional bypass grafting in 23%, aortic intervention in 6% (interposition graft, reduction aortoplasty, replacement of the ascending aorta) and mitral valve replacement in 1.4%. Baseline characteristics are shown in Table 1.

**Histological and Genetic Analysis**

Of the 146 biopsies, six contained amyloid (prevalence 4.1% all-comers). All six were cAS aged >65 (prevalence 5.4% for cAS and 5.6% for >65). Typing by IHC, supported by LDMS, confirmed ATTR amyloid type in all six cases (Figure 1 and 2). Genetic sequencing confirmed non-hereditary wild-type transthyretin sequence in each case.

**Clinical Assessment of patients with amyloid**

Clinical evaluation of the six patients with amyloid was scheduled at the National Amyloidosis Centre, UK, but two patients died prior to their appointment. Assessment revealed carpal tunnel syndrome in one patient but no other extra-cardiac manifestations, which is typically the case. AL amyloidosis was excluded in all cases. Summary findings are shown in Table 2.

**Multimodality Imaging**

Figures 3 and 4 summarize the findings of multimodality imaging.

**Echocardiography**

Pre-operative routine transthoracic echocardiography did not raise any suspicion of amyloid among the 6 patients in whom amyloid was identified histologically, and were consistent
with severe AS by indexed valve area (mean AVAi 0.41±0.17 cm²/m²) and/or transvalvular peak velocity (4.3±0.6 m/s). Clinical reporting identified significant concentric left ventricular hypertrophy (LVH) with impaired longitudinal shortening and diastolic dysfunction in 3 out of 6 patients but this was attributed to AS afterload. No suspicion of a dual pathology was raised. Retrospective analysis of global longitudinal strain (GLS; not performed routinely in our clinical AS work-up) was markedly reduced GLS in patient 1 and 2 (-6.4% and -11.6%, respectively), but could only be obtained in a minority of patients in our cohort due to poor endocardial wall definition in many patients (see Table 2).

**Cardiovascular Magnetic Resonance (CMR)**

In two patients, the pre-operative research multiparametric CMR study identified the dual pathology of AS and cardiac amyloidosis. This was based on the combination of severe LV hypertrophy out of proportion for the degree of AS, and (more definitively) tissue characterization findings of cardiac amyloid (global transmural late gadolinium enhancement with blood pool nulling after the myocardium on the TI scout, elevated native myocardial T1 (here >5SD above normal) and ECV >50%). These research findings were communicated to the surgical team but a multidisciplinary decision was made to proceed with AVR and to conduct further evaluation of amyloidosis afterwards (patients 1 and 2, table 2). The myocardial contraction fraction (MCF) was also markedly reduced in both these patients (25% and 33%, respective) despite preserved LVEF; in the other four patients, MCF fell within one SD of the overall AS cohort (53±13%; see Table 2).

**Cardiac Scintigraphy with DPD bone tracer**

DPD bone scintigraphy was performed in the four surviving patients during the post-operative amyloid evaluation and was positive in all cases, with Perugini Grade 2 uptake in both patients with features of amyloidosis on CMR, and Perugini Grade 1 uptake in the two without.
Outcome

At median follow-up of 2.3 years (0.02-4.7 years), 11 cAS patients had died whereas all of the bAS patients were alive. Three out of six cAS with wtATTR (50%; 1 cardiac death; 2 non-cardiac) died compared to 8 out of 106 (7.5%) in the remaining cAS cohort, 7 out of 101 (6.9%) in those over the age of 65, and 8 out of 140 (5.7%) in overall cohort (Figure 5). Of all variables assessed, the presence of ATTR amyloid had the highest hazard ratio for all cause mortality (HR 9.5 [2.5-35.8], \( p=0.001 \), univariable Cox regression analysis, Table 3).

DISCUSSION

In this single center study of 146 severe AS undergoing surgery, to which 70% of all patients undergoing surgery were recruited, cardiac amyloid deposits were found at biopsy in 6 cases. All had wild-type ATTR (formerly senile systemic) amyloidosis. The youngest was 69, and all had calcific AS indicating a 6% prevalence of amyloid among this latter group. Comprehensive imaging was performed which showed a diagnostic hierarchy with non-contributory echocardiography, CMR detecting a third of cases, and cardiac DPD scintigraphy positive in all four patients who had this latter investigation. Biopsy showing wtATTR amyloid deposits was prognostic and its presence was the strongest univariate predictor of adverse outcome after surgical aortic valve replacement – suggesting that the presence of cardiac amyloid is a disease modifier in AS.

Two aspects of the coexistence of wtATTR and AS stand out: incorrect interpretation of the severity of AS, and modification of outcome. First, wtATTR amyloid in patients with moderate AS may cause severe hypertrophy and LV impairment, which can be misdiagnosed as severe AS (as low-flow-low-gradient). This was highlighted by Rapezzi et. al. in a recent communication,\(^3\) who presented data on 43 elderly cAS patient with at least 1 “red flag” on echocardiography, performed DPD on 5 patients identified in this way (all positive) and
confirmed diagnosis of wtATTR amyloid through biopsy and genotyping. Second, rather than leading to a misdiagnosis of severe AS, wtATTR amyloid may be a disease modifier, exhibiting a more severe phenotype with more heart failure and arrhythmias, and possibly amyloid involvement of other organ systems. Whether joint co-morbidities increase the prevalence or progression of AS and wtATTR is unknown but should be explored in future studies.

Implications for management of Aortic Stenosis

Identification of cardiac amyloid is important for many reasons. The presentation of amyloid (LVH and diastolic then systolic function dysfunction) has substantial overlap with the changes of AS, particularly as systemic features are limited with only carpal tunnel syndrome as a common red flag. Other traditional red flags (pericardial effusion, aortic valve thickening, concentric hypertrophy) are common in severe, symptomatic AS. Whilst it is possible that minor cardiac amyloid deposits might have no significant consequences in many individuals, the clinical syndromes caused by cardiac amyloid deposition of sufficient magnitude, i.e. overt cardiac amyloidosis of both ATTR and AL types, have a very poor prognosis from just months to a few years. Accurate typing of amyloid is essential since chemotherapy directed towards the plasma cell dyscrasias underlying AL amyloidosis can prolong life, and several specific therapies for ATTR amyloidosis are now at late stage of clinical development.15, 16 The consequences of isolated sub-clinical cardiac wtATTR amyloid deposits are unknown; in our study, those patients with wtATTR and severe AS had 50% all-cause mortality. Although only one patient with overt cardiac amyloidosis died of a cardiac cause, all-cause death is a more objective, unbiased end point that is of primary interest, and suggests that amyloid deposits are an important frailty marker.

Possible changes in clinical management could include minimizing bypass time during open valve surgery (e.g. by using rapid deployment valves), switching to TAVR and influence the
fundamental decision regarding medical management versus intervention. Interestingly, perioperative mortality was not affected by the presence of wtATTR. In addition, although there are few systematic data, clinical experience has suggested avoiding calcium channel blockers and digoxin in the presence of cardiac amyloid.

**ATTR amyloid and Heart Failure**

Wild-type ATTR amyloid is emerging as an unrecognized, important bystander and potential disease modifier not only in AS but also in Hypertrophic Cardiomyopathy (HCM) and Heart Failure with preserved Ejection Fraction (HFpEF). Historically the requirement for histology has been a major obstacle to elucidating the significance of cardiac ATTR amyloid, but the remarkable diagnostic capability of non-invasive bone scintigraphy has lately yielded much new information. A large Italian non-selective endomyocardial biopsy study (n=4221 over 28 years) found amyloid 4% of cases. More specific studies investigated autopsy specimens in a TAVR cohort in which amyloid was present in 5 out of 17 cases and thought to have contributed to progressive heart failure and the deaths of 3 patients, and examination of 95 specimens obtained at septal myectomy for LV outflow tract obstruction with congenital or acquired aortic stenosis in which 7% contained ATTR amyloid deposits. Cardiac amyloidosis is also a differential diagnosis for hypertrophic cardiomyopathy, especially in patients with predominantly basal involvement and outflow tract obstruction. Incidental deposits of amyloid have been reported in 1% of surgical septal myectomy specimens from patients with HCM. Mohammed *et. al.* reported 17% prevalence of ATTR amyloid in HFpEF patients on autopsy with a substantial (80%) male predominance. In contrast to this series and the wider clinical impression, half of the patients with amyloid in our cohort were female; this was also a finding in a recent cohort of HFpEF patients who were studied with DPD scintigraphy, suggesting that the incidence may be underestimated in females.
generally, possibly due to a lower frequency of extreme hypertrophy that serves as the main red flag.

Relative strength of imaging modalities to identify amyloid

Comprehensive imaging here showed a diagnostic hierarchy comprising non-contributory echocardiography, CMR detecting a third of cases, and bone scintigraphy being diagnostic in all four patients studied. Bone scintigraphy ($^{99m}$Tc-DPD or $^{99m}$Tc-PYP)\textsuperscript{27,36} is an attractive, low cost modality with high sensitivity and specificity for cardiac ATTR amyloid. It is more practicable than cardiac biopsy for exclusion of ATTR amyloid in HCM, HFpEF and AS, and its sensitivity for occult ATTR amyloid appears to be greater than CMR. Focal myocardial uptake of these tracers may occur transiently following myocardial infarction, and diffuse uptake does occur in a small proportion of patients with cardiac amyloid of AL type.

Limitations

Our study has limitations: patients were recruited from a single cardiothoracic center. The entry criterion was surgical AVR with no CMR contraindications leading to some under-representation of older patients (undergoing TAVR instead of sAVR), renal impairment and pacemaker patients (though in reality only 18 patients were excluded due to pacemaker [n=8] or eGFR<30 [n=10]). With a recruitment rate of 76% of all sAVR performed for AS (81% had myocardial biopsy), the RELIEF-AS study was indeed representative of a surgical AVR cohort in a major UK cardiothoracic center. Due to the low number of deaths, it was not possible to adjust hazard ratio for confounders (like age, gender and comorbidities) using multivariable regression models; only univariate analysis was performed. DPD/PYP bone scintigraphy was not performed in all-comers due to limited availability at our center at the start of the study, but should be part of any future studies. It is possible that other patients with wtATTR amyloid may have died before their AS had been deemed severe enough to warrant intervention. Our echocardiographic analysis did not include strain rate imaging.
consistently (apically spared impaired longitudinal strain is characteristic of amyloid) – the markedly reduced GLS in two patients could have raised red flags at time of echocardiography. Finally, the study did not include a large proportion of Afro-Caribbean individuals, 3-4% of whom possess the transthyretin V122I variant\textsuperscript{37} that causes hereditary cardiac ATTR amyloidosis and up to 10% of hospital admissions for heart failure in this ethnic group in South London.\textsuperscript{38}

Future outlook

Myocardial wtATTR amyloid appears to be an important prognosticator in elderly individuals with AS, but more work is needed. Myocardial wtATTR should therefore be considered relevant when assess the prognosis in AS – perhaps even more so in the more elderly TAVR population, where there is greater risk, worse renal function and more heart failure (reflected by higher EuroScore II and STS score). Biopsy for amyloid is not practicable but bone tracer scintigraphy could be used. The data here suggests it could have a routine role in selected patients and influencing their management in terms of decisions surrounding intervention, procedure performance and specific amyloid therapies. Wider use of cardiac scintigraphy with bone tracers, by detecting early amyloid, is likely also to improve our understanding of conventional testing, such as echocardiography.

CONCLUSION

Six percent of patients over the age of 65 undergoing surgical AVR for cAS had wtATTR amyloid deposits on cardiac biopsy, which was associated with poor outcome. There appears to be a hierarchy of imaging diagnostic performance for identification of wtATTR amyloid, with DPD bone tracer scintigraphy superior to CMR, which was superior to echocardiography.
SOURCE OF FUNDING

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DISCLOSURES

None.

ACKNOWLEDGEMENT

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TABLE 1 – Baseline Characteristics

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<th>Calcific AS</th>
<th>Other Etiologies*</th>
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<td>N</td>
<td>112</td>
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<tr>
<td>Men</td>
<td>64 (58%)</td>
<td>21 (58%)</td>
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<td>Age, years</td>
<td>75±6</td>
<td>59±7</td>
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<tr>
<td>Hypertension (%)</td>
<td>87 (78%)</td>
<td>31(90%)</td>
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<td>Diabetes (%)</td>
<td>26 (23%)</td>
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<td>177 (8-1400)</td>
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<td>eGFR, ml/min/1.73 m²</td>
<td>72±18</td>
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<td>Surgery</td>
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<td>4 (3.6%)</td>
<td>4 (11.8%)</td>
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*Bicuspid AS n=32; unicuspid AS n=1; rheumatic AS n=1.
Values are mean +/- SD or %.
AS, aortic stenosis; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; CMR, cardiovascular magnetic resonance; EDV, end diastolic volume; ESV end systolic volume; LVEF, left ventricular ejection fraction; SV, stroke volume; LV, left ventricular; LAA left atrial area.