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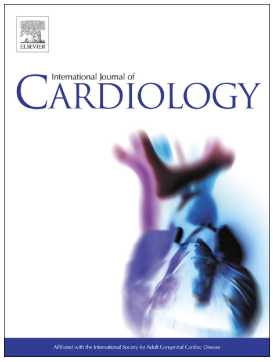

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Long-Term Outcomes In Patients With Aortic Stenosis And Transthyretin Cardiac Amyloidosis

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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ABSTRACT

Background

The coexistence of aortic stenosis (AS) and transthyretin cardiac amyloidosis (CA) is common. If treated with transcatheter aortic valve replacement (TAVR), patients with the combined phenotype (AS-CA) have a similar survival at 1 year compared to those with lone AS. This study aims to evaluate the long-term outcomes of AS-CA compared to lone AS.

Methods

Using a prospective, multicenter, observational, case-control design, we studied patients with severe AS referred for TAVR. All underwent bone scintigraphy to differentiate between AS-CA and lone AS. Outcomes were compared between the two cohorts. Mortality (all-cause and cardiovascular [CV]) and hospitalization for heart failure (HHF) were captured as clinical endpoints for long-term outcome.

Results

406 patients [84(80-88) years, 50% female, EuroSCORE-II 4.2 (3.7-5.0)] were recruited, of which 47 (11.6%) had AS-CA (all transthyretin). Over a follow-up of 5.4 (4.9-5.8) years, 244 (60.1%) patients died. AS-CA was associated with higher all-cause mortality (crude HR 1.75, 95% CI 1.24-2.46; log-rank, p=0.001), which remained significant after multivariate adjustment for clinical confounders (EuroSCORE-II, valve replacement; adjusted HR 1.72, 95% CI 1.22-2.42; p=0.002). AS-CA was not associated with CV mortality (log-rank, p=0.18) or time to first HHF (log-rank, p=0.43), but the rate of HHF was significantly higher in AS-CA compared to lone AS (129 versus 65 per 1,000 patient years, p=0.022).

Conclusion

AS-CA is associated with an increased long-term risk of all-cause mortality and rate of hospitalization for heart failure compared to patients with AS. Further studies evaluating the role of CA-specific therapies are warranted in this population.

ABBREVIATIONS

AL	light chain
AS	aortic stenosis
AS-CA	coexisting aortic stenosis and transthyretin cardiac amyloidosis
ATTR	amyloid transthyretin
AVR	aortic valve replacement
CA	Transthyretin cardiac amyloidosis
CV	cardiovascular
DPD	^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid
HHF	Hospitalization for heart failure
Hs	high sensitivity
ICD	international classification of diseases
IQR	interquartile range
LVEF	left ventricular ejection fraction
NT-proBNP	N terminal pro brain natriuretic peptide
SAVR	surgical aortic valve replacement
SD	standard deviation
(SPECT)-CT	Single photon emission computed tomography- computer tomography
TAVR	transcatheter aortic valve replacement

INTRODUCTION

Among elderly patients with severe aortic stenosis (AS) undergoing aortic valve replacement (AVR), a high prevalence (13-16%) of coexisting transthyretin cardiac amyloidosis (CA) has been reported [1–6], which significantly exceeds the estimated prevalence of CA in the general population [7,8]. Individually, both AS and CA are associated with symptoms of heart failure, cardiac remodeling and dysfunction and premature mortality [9–12]. Several non-randomized studies have demonstrated similar mortality in AS-CA compared to lone AS after transcatheter aortic valve replacement (TAVR), at a median follow-up of 1.6-2.0 years [1,4,6]. Conversely, medical therapy was associated with a higher mortality compared to TAVR in patients with AS-CA, concluding that TAVR should not be withheld because of the coexistence of CA [1]. With the advent of novel CA-specific therapies [13,14], there is now a pertinent question of whether the residual amyloid component following AVR should be treated in patients with AS-CA. In order to answer this, the clinical significance and prognostic implications of this persistent amyloid component need to be addressed. However, the longer term outcome data on all-cause, and cardiovascular (CV) mortality as well as heart failure hospitalization with AS-CA remains unknown. The aim of this study was to compare, at longer term follow-up (5 years), both mortality and heart failure hospitalizations in patients with AS-CA to those with lone AS using a multicenter, prospective, observational cohort.

METHODS

Study population

This is a prospective, observational, multicenter study, comparing outcomes in consecutively recruited patients from two prospective observational studies. The ATTRact AS study is a two-center (St Bartholomew's Hospital, London, UK and John Radcliff Hospital, Oxford, UK) study of patients 75 years or older with severe AS referred for potential transcatheter aortic

valve replacement (TAVR) recruited between October 2016 and February 2019 (NCT03029026). A study from the Medical University of Vienna recruited consecutive patients referred for potential TAVR between October 2017 and January 2019. Consenting patients underwent pre-TAVR ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) scintigraphy to identify coexisting amyloid (details below), and comprehensive echocardiographic assessment on top of usual pre-TAVR work-up. Patients were divided into two cohorts depending on the presence of coexisting amyloidosis (AS-CA) and absence of amyloidosis (lone AS). This study complied with the Declaration of Helsinki; relevant local ethics and site approvals were obtained, and all patients provided written informed consent. Patients, as part of the patient and public involvement programme for valvular heart disease, were involved in the design of this study.

Transthoracic echocardiography

All patients underwent a clinical transthoracic echocardiogram prior to aortic valve replacement according to local protocols derived from international recommendations [15]. Further details regarding specific measurements can be found in a previously published study [4]. Classical low-flow, low-gradient AS was defined as an aortic valve area ≤1.0cm^2, left ventricular ejection fraction (LVEF) <50%, an indexed stroke volume <35ml/m^2, a mean gradient <40mmHg and a peak aortic velocity <4m/s^2. Paradoxical low-flow, low-gradient AS was defined as the same albeit with a LVEF ≥50%. Where equivocal, AS severity was adjudicated using low dose dobutamine stress echocardiography or computed tomography derived aortic valve calcification as appropriate [16].

DPD scintigraphy

All patients underwent DPD scintigraphy. The imaging protocol consisted of an early (5 minutes) and late (3 hours) planar whole-body image. Patients were scanned using a Phillips Brightview single-photon emission computed tomography gamma camera (Philips Healthcare, Amsterdam, the Netherlands), Siemens Symbia gamma camera (Siemens Healthcare, Erlangen, Germany), and/or Pulse CDC gamma camera (IS2, London, United Kingdom), or the General Electric Infinia Hawkeye 4/GE Discovery 670 hybrid gamma camera (Vienna, Austria) , following the administration of 700 MBq of 99mTc-DPD. Whole body images were acquired at a scan speed of 10cm/min using low energy high resolution collimators. Planar whole-body images were performed at 3 hours at all study-sites [17]. Additional SPECT/CT of the chest at 3 hours was performed routinely in London and Oxford, but not in Vienna. DPD scans were adjudicated by two readers from each institution (CN, TV, PS, LM) who were blinded to the clinical data according to the Perugini classification; with grade 0 being negative, and grades 1 to 3 increasingly positive as previously described [4,18]. Among positive patients, further assessments to identify light chain amyloid (AL) included serum free light chain ratio and monoclonal immunoglobulin in the serum and urine by immunofixation. Transthyretin cardiac amyloidosis (ATTR) genotyping identified wild-type and variant transthyretin cardiac amyloidosis according to current consensus criteria [19,20]. Clinicians managing the patients were blinded to the results of the DPD scintigraphy until after the AVR.

Aortic valve replacement

The decision to perform an AVR, whether a TAVR or surgical aortic valve replacement (SAVR), was made by a multi-disciplinary heart team composed of interventional cardiologists, imaging cardiologists, cardiothoracic surgeons and specialist nurses, who were blinded to the results of the DPD scintigraphy. Patients deemed to be too high risk were managed medically. The choice of prosthesis type was made clinically by the treating clinician.

Study outcomes

The study outcomes were time to all-cause death, time to cardiovascular (CV) death, time to first hospitalization for heart failure (HHF) and the rate of HHF. Mortality was obtained from a UK national database (NHS Digital) and the Austrian Death Registry. Cardiovascular death was defined by using international classification of diseases (ICD)-10 codes that are directly derived from the death certificate of the patient. Data on HHF was obtained via NHS Digital (UK) and from three sources, covering hospitalizations in all Austrian hospitals (Austria): patient records of the Medical University of Vienna, Vienna Health Association database, and the nationwide electronic health records. Data regarding cardiovascular death or HHF was not available for patients recruited at Oxford (n=30) due to ethical constraints, related to data transfer outside the hospital. All-cause mortality was available for all patients. This study reports long-term outcomes of a previously published cohort after the exclusion of one patient diagnosed with light-chain CA [4].

Statistical analysis

Normality was assessed using the Shapiro-Wilk test. Continuous data are expressed as mean ± standard deviation (SD) or as median and interquartile range (IQR) depending on their distribution. Categorical variables are presented as numbers and percentage. Patients with lone AS were compared to those with AS-CA. Differences between groups were analyzed using the Mann-Whitney U test or Student's t test. Chi-square tests or Fisher exact tests were used for categorical variables as appropriate. Cox proportional hazards regression analysis was used to assess the prognostic impact of dual AS-CA on time to death, time to CV death and time to first HHF, with aortic valve replacement (versus conservative care) and EuroSCORE-II as covariates. To allow better comparison between continuous parameters,

scaled hazard ratios (Z-scores) were created by subtracting the mean from individual values and dividing them by the respective SD. The proportional hazards assumption was tested with the examination of Schoenfeld residuals. Kaplan–Meier plots were used to view event-free survival from baseline. In order to identify when mortality starts to diverge between AS and AS-CA, we performed a pooled logistic regression analysis (a discrete-time hazards model) to estimate the conditional probability of survival each month based on exposure (AS vs. AS-CA), baseline covariates, and follow-up time. Time-varying hazards were incorporated by including interaction terms between exposure and time. Survival probabilities were estimated by multiplying predicted values over time for individuals with the same covariates, generating adjusted survival curves for AS and AS-CA. Individual survival estimates were then averaged across all subjects to create standardized marginal survival curves for each exposure group. Finally, the survival difference between AS and AS-CA was calculated monthly, with 95% confidence intervals obtained via non-parametric bootstrapping [21]. We utilised this pooled logistic regression, rather than the Kaplan Meier estimator and the survival curves plotted after Cox regression as the former cannot control for confounders, while with the latter relies on the proportionality assumption and hence the survival curves are forced to be proportional [22]. Pooled logistic regression successfully controls for confounders and does not assume that the two survival curves would be proportional. The rate of HHF was assessed in lone AS and dual AS-CA by dividing the total number of HHF by the follow-up time in each group and compared using Chi-Square test. A two-sided p value ≤ 0.05 was considered statistically significant. All statistical analyses were computed using SPSS 29 (IBM SPSS, USA).

RESULTS

Study cohort and management

In total, 406 patients were recruited in three centers. The median age was 84 (quartile 1: 80, quartile 3: 88) years and 202 (49.8%) were female. Bone scintigraphy was performed in all patients at a median of 14 (1-50) days before AVR. Of the total population screened, 9 patients (2%) had abnormal blood tests for monoclonal antibodies; 8 were diagnosed with monoclonal gammopathy of unknown significance (MGUS) and 1 had a diagnosis of kappa light chain deposition amyloidosis (not included in the present study). After heart team discussions, 331 (81.5%) patients underwent TAVR, 10 (2.5%), SAVR and 65 (16.0%) were managed medically. Management strategies did not differ significantly between lone AS and AS-CA (15.0% medical and 85.0% AVR vs 23.4% medical and 76.6% AVR; p=0.142).

Cardiac amyloidosis screening and baseline characteristics

Overall, 47 (11.6%) patients received a diagnosis of dual AS-CA (all ATTR). Among patients with AS-CA, 15 (33%) were Perugini grade 1 and 32 (67%) were Perugini grade 2/3. Genotyping revealed that all 47 patients had wild-type ATTR. The prevalence of Perugini grade 1 CA was 31% and 33% in the UK and Austrian populations (SPECT imaging was not used in the latter) respectively.

Compared to patients with lone AS, those with AS-CA were older [84 (79-88) vs 87 (83-91) years, p<0.001] and had a similar prevalence of male sex (48 vs 62%; p=0.081]. Patients with AS-CA had higher cardiac biomarkers (high sensitivity Troponin T [25 (18-34) vs 33 (25-64) ng/l; p<0.001] and NT-proBNP [1728 (647-3798) vs 3377 (1284-5936) pg/l, p=0.004). The prevalence of comorbidities was similar between both groups with the exception of a higher prevalence of atrial fibrillation among those with AS-CA (36 vs 51%; p=0.005). The prevalence of AS-related symptoms was similar between groups. Patients with AS-CA had similar LVEF [58 (44-64) vs 51 (40-63)%; p=0.184], reduced myocardial contraction fraction [0.33 (0.27- 0.42) vs 0.27 (0.21-0.33); p<0.001], worse diastolic function (E/A ratio [0.8 (0.7-

1.2) vs 1.4 (0.7-2.8); p=0.004]), reduced tricuspid annular planar systolic excursion [2.1 (1.7-2.5) vs 1.9 (1.6-2.1) cm; p=0.016], higher pulmonary artery systolic pressure [39 (27-50) vs 49 (31-59) mmHg; p=0.02] and larger indexed left ventricular mass [127 (101-150) vs 134 (113-173) g/m^2; p=0.036] (**Table 1**).

Outcomes

During a median follow-up of 5.4 (4.9-5.8) years, 244 patients died (60.1%): 204/359 patients (56.8%) with lone AS and 40/47 patients (85.1%) with AS-CA. Mortality rates at 1-, 2-, and 5-years were 17%, 28%, 70% for lone AS and 26%, 34%, 87% for AS-CA. Median survival for the lone AS and AS-CA groups was 4.0 and 3.1 years respectively. AS-CA was associated with higher all-cause mortality (crude HR 1.75, 95% CI: 1.24-2.46; log-rank, p=0.001), which remained significant after multivariate adjustment for clinical confounders (EuroSCORE-II, AVR: adjusted HR 1.72, 95% CI: 1.22-2.42; p=0.002) (**Figure 1**, **Table 2 and Supplementary Table 1 and 2**). Mortality rates diverged between lone AS and AS-CA after 4.2 years (**Supplementary Figure 1a and 1b**). Compared to lone AS, mortality was higher in patients with Perugini grade 2/3 (adjusted HR: 1.85, 95% CI: 1.25-2.74; p=0.002); this did not reach statistical significance in n=15 patients with Perugini grade 1 AS-CA (adjusted HR: 1.45, 95% CI: 0.79-2.66; p=0.232) (**Supplementary Figure 2)**.

Cause of death and HHF was available in 376 patients. Amongst these, 230 patients died. CV death accounted for 45.7% (n=105) of mortality: 41.6% (n=15/36) in AS-CA and 46.4% (n=90/194) in lone AS patients. Non-cardiovascular death accounted for 54.3% (n=125) of mortality: 58.3% (n=21/36) in AS-CA and 54.1% (n=105/194) in lone AS patients (**Supplementary Table 3).**

AS-CA was not associated with CV mortality (adjusted HR 1.46, 95% CI: 0.85-2.53; p=0.175) (**Figure 2**). HHF occurred in 66 patients (17.6%): 9 patients (20.9%) with AS-CA

and 57 patients (17.1%) with lone AS. AS-CA was not associated with time to first HHF using either multivariable cox regression analysis (adjusted HR 1.31, 95% CI: 0.64-2.64; p=0.459) or an adjusted competing risks model (HR: 1.41, 95% CI: 0.62-3.23; p=0.414), (**Supplementary Table 4 and Supplementary Figure 3**). Nineteen patients (5% of the study population) experienced repeat HHF amounting to a total of 47 HHF for the study population. The rate of HHF was significantly higher in AS-CA compared to lone AS (129 versus 65 per 1,000 patient years, p=0.022). However, using recurrent event analysis, AS-CA was not associated with repeat HHF (HR: 2.42, 95% CI: 0.87-6.74; p=0.090).

A sensitivity analysis was performed with AS-CA only considered if patients were Perugini grade 2 or 3. Perugini grade 1 was considered as not having AS-CA. This showed that all-cause mortality remained significantly higher among patients with AS-CA (adjusted HR: 1.82, 95% CI: 1.23-2.69; p=0.002) **(Supplementary Table 5).** AS-CA was not associated with CV death (adjusted HR: 1.23, 95% CI: 0.62-2.44; p=0.554) (**Supplementary Table 6**). AS-CA was not associated with time to first HHF (HR: 1.41, 95% CI: 0.62-3.23; p=0.414) (**Supplementary Table 7**). The rate of HHF remained significantly higher among patients with AS-CA (69 versus 43 per 1,000 patient years; p=0.011). However, using recurrent event analysis for repeated HHF, AS-CA was not associated with repeated HHF (HR: 1.53, 95% CI: 0.44-5.26; p=0.500). A landmark analysis after excluding patients who died within 30 days of their AVR (n=8), demonstrated that AS-CA continues to have an adverse impact on all-cause mortality (HR: 1.692, 95% CI: 1.19-2.40; p=0.003), but not on CV mortality (HR: 1.374, 95% CI: 0.77-2.47; p=0.288) **(Supplementary Table 8 and 9).** Outcomes according to AS subtype demonstrated a very high all-cause death among patients with low flow low gradient AS (**Supplementary Table 10**).

Among patients with dual AS-CA, 7/47 (14.9%) received tafamidis, which was associated with a trend towards reduced mortality (log-rank for all-cause mortality: p=0.098).

(**Supplementary Figure 4**). However, this study was not powered to assess prognostic differences with respect to amyloid therapies.

DISCUSSION

This multi-center, prospective, cohort study demonstrates that patients with dual AS-CA have more advanced disease according to cardiac biomarkers and function. For the first time, we provide data on long-term clinical outcomes of AS-CA. Over a 5-year follow-up, AS-CA patients had a higher all-cause mortality and possibly a higher rate of hospitalization for heart failure, but similar CV mortality, compared to those with lone AS.

Thus far, short and mid-term outcome studies in patients with AS-CA detected using screening, demonstrated similar mortality to patients with lone AS. Three cohort studies showed similar mortality in dual AS-CA and lone AS at a median of 1.6 to 2.0 years after AVR (mostly TAVR) [1,4,6]. Results from these studies highlighted that the presence of CA itself should not preclude AVR. However, CA – in particular the ATTR subtype – represents a chronic disease with slow but steady progression. This is also illustrated by the fact that an improvement in prognosis through ATTR stabilization can only be achieved after 18 months of treatment [14]. Indeed, AS-CA has many phenotypic features similar to patients with lone ATTR [23] and previous studies indicated that the residual amyloid component is not insignificant in terms of morphology, functional capacity and clinical performance. At one year post-AVR, patients with dual AS-CA continued to be more symptomatic, with higher residual cardiac biomarkers and less reverse remodeling compared to patients with lone AS. The contractility pattern in dual pathology also resembled a "lone ATTR phenotype" at follow-up [24]. Another study demonstrated a higher rate of hospitalization for heart failure in AS-CA compared to lone AS within the first year of TAVR [6].

Dual AS-CA and lone AS may therefore exhibit similar mortality after TAVR in the short term, but may experience differential outcomes in the long run, potentially driven by ongoing/persistent amyloid infiltration. However, data on long-term outcomes in AS-CA compared to lone AS is currently lacking.

Our findings now show worse clinical long-term outcomes in patients with AS-CA post-AVR. This includes an increased hazard of mortality and possibly a higher rate of HHF over a median of 5-years post-AVR. With the valvular lesion treated, myocardial remodeling is known to reverse to a certain extent [25]. Therefore, by assuming a similar impact of AVR on reversing AS-mediated remodeling in both lone AS and AS-CA, it is possible that the CA component in patients with AS-CA contributes to an increase in adverse events. Grade 1 AS-CA is often considered a pre-clinical phenotype of CA [26]. When considering AS-CA defined only as Perugini grade 2 or 3, we demonstrated similar results to our main findings. AS-CA had a prognostic impact on all-cause mortality and possibly on the rate of HHF but not on cardiovascular mortality. Differences in the progression of comorbidities, frailty (not captured in this study) and older age among patients with AS-CA may account for the increased rate of non-cardiovascular death. Although this creates uncertainty whether CA-specific therapies would benefit patients with AS-CA, recent multi-centric registry data suggests that Tafamidis improves outcomes [27]. Our findings suggest that patients with AS-CA who have a HHF are at increased risk of recurrent HHF rather than having an overall increased risk of HHF. This is supported by a previous study showing similar results [28]. However, our data is limited by population size and event rate.

The introduction of an additive scoring system to assess the pretest likelihood of concomitant CA among patients with AS, substantial advancements in cardiac imaging techniques (greater use of bone scintigraphy and CMR, as well as the advent of ECV quantification by cardiac CT), and overall increased disease awareness have increasingly

facilitated the detection of CA [4,17,29,30]. With worse clinical outcomes demonstrated by the current study and accessible new treatment options, recognition and screening of CA in AS may become the mainstay of clinical care, rather than a mere scientific interest[31–33]. A suggested screening algorithm based either on clinical data [31] or extracellular volume quantification using computed tomography [32] would identify patients with a high likelihood of AS-CA. Such patients could then undergo a definitive test (nuclear scintigraphy) to confirm the diagnosis. If AS-CA is identified, current evidence suggests treating the AS according to clinical guidelines [31,33]. However, patients should concomitantly be referred to specialist services for further management of their CA [27].

Novel promising or already approved ATTR-specific treatments act at different stages of the amyloid-forming pathway including inhibition of ATTR production, protein stabilization and removal of amyloid deposits [34]. These drugs also bear potential to further improve outcomes in dual AS-CA over and above AVR. However, their effectiveness in such patients is currently unknown from the large ATTR-drug trials [35,36]. Whilst a few patients in our study did receive tafamidis, selection bias and small numbers preclude any evaluation of effectiveness. Presently, ATTR-specific therapies are expensive and not widely available. It is important to acknowledge the patient population with AS-CA, who are elderly, have multiple comorbidities and often frail. Treatment futility is an important consideration and until improvements in risk stratification and patient selection occur, such treatments should be administered using clinical judgement, preferably via a multi-disciplinary team driven decision. A multicentric registry has demonstrated that this is possible in carefully selected patients with AS-CA that derived prognostic benefit from Tafamidis [27].

Despite this being a multicentre study with a prospective design, the number of patients with AS-ATTR are small and does limit the **s**tatistical power for secondary analyses and increase uncertainty of effect estimates. Patients were recruited from tertiary referral

centres and the population were elderly with a high burden of comorbidities. As such our findings may not be applicable to a younger lower risk population. External validation would help to clarify our findings in other populations. Serial data on biomarkers, echocardiography and clinical comorbidities are lacking. This does limit our findings in terms of providing a complete evaluation of AS-CA's natural history and treatment effect. Our study lacked data on medications which can influence outcomes. Future studies need to evaluate whether non-CA-specific medications influence outcomes in patients with AS-CA. Routine assessment for monoclonal proteins in all patients (before or alongside bone scintigraphy) was not systematically performed. Consequently, there is a possibility that patients with AL amyloidosis and Perugini grade 0 uptake were included in the lone AS group and were not correctly identified. Our methodology also raises the possibility of amyloid variants with low radiotracer sensitivity (e.g., S77Y, F64L) that may have gone undetected and been incorrectly classified within the lone AS cohort. Among patients with Perugini grade 1 uptake and no detectable monoclonal proteins, a histological diagnosis was not obtained. In our elderly, multimorbid population, this was not feasible and is a limitation of our study. Our study was conducted between 2015-2020 when most disease modifying medications were not available. Medical therapy for heart failure has also advanced since then. As such our findings may not necessarily reflect contemporary practise. We still believe that our findings of worse outcomes among AS-CA patients compared to lone AS remains relevant and has important clinical implications. A proportion of our patients did not have SPECT/CT imaging (Vienna cohort) which would provide clarity regarding the location of DPD uptake and is especially important to differentiate between myocardial uptake from the blood pool in Perugini grade 1 AS-CA. However, the prevalence of Perugini grade 1 CA did not vary between the two populations. Future studies using DPD scintigraphy should incorporate SPECT/CT imaging.

CONCLUSIONS

In elderly patients with severe AS, concomitant CA is associated with a higher all-cause mortality and higher rate of hospitalization for heart failure compared to lone AS over a 5-year follow-up, despite successful AVR. Cardiac amyloid specific treatments in patients with dual pathology may normalize outcomes to what is expected in patients with lone AS but needs to be evaluated in future studies.

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Table 1. Baseline characteristics.

Parameter	AS (n=359)	AS-CA (n=47)	P value
Demographics			
Age (years)	**84 (79- 88)**	**87 (83- 91)**	**<0.001**
Male sex	173 (48%)	29 (62%)	0.081
Body mass indexed	26 (24- 30)	26 (24- 30)	0.732
EuroSCORE II	4.2 (3.7- 5.1)	4.3 (3.9- 4.7)	0.397
Hypertension	297 (83%)	38 (81%)	0.658
Hyperlipidemia	203 (57%)	23 (49%)	0.304
Diabetes	93 (26%)	9 (19%)	0.306
Coronary artery disease	164 (46%)	17 (36%)	0.206
Previous PCI	81 (23%)	6 (13%)	0.118
Atrial fibrillation	130 (36%)	24 (51%)	0.05
Chronic obstructive pulmonary disease	56 (16%)	3 (7%)	0.086
Permanent pacemaker pre-TAVR	52 (15%)	9 (19%)	0.409
Symptoms			
Dyspnea	295 (84%)	41 (89%)	0.389
NYHA I	18 (10%)	2 (5%)	0.134
NYHA II	46 (26%)	11 (26%)	
NYHA III	95 (54%)	28 (67%)	
NYHA IV	17 (10%)	1 (2%)	
Angina	89 (26%)	8 (17%)	0.226
Syncope	67 (19%)	5 (11%)	0.171
Laboratory markers			

Creatinine (mg/dl)	1.06 (0.85- 1.35)	1.11 (0.93- 1.31)	0.214
NT-proBNP (pg/ml)	**1728 (647- 3798)**	**3377 (1284- 5936)**	**0.004**
Hs-Troponin T (ng/l)	**25 (18- 34)**	**33 (25- 64)**	**<0.001**
Hemoglobin (mg/dl)	12 (11- 13)	12 (11- 13)	0.365
Albumin (g/l)	41 (37- 43)	41 (38- 42)	0.605
Echocardiography			
AS stage			
Normal flow	218 (65%)	22 (48%)	0.08
Paradoxical low flow low gradient AS	59 (18%)	12 (26%)	
Classical low flow low gradient AS	59 (18%)	12 (26%)	
Aortic valve area (cm2)	0.7 (0.6- 0.8)	0.7 (0.6- 0.8)	0.525
Aortic valve peak velocity (m/s)	**4.2 (3.9- 4.6)**	**3.9 (3.3- 4.7)**	**0.008**
Aortic valve peak gradient (mmHg)	**70 (61- 84)**	**60 (43- 86)**	**0.008**
Aortic valve mean gradient (mmHg)	**43 (36- 52)**	**37 (27- 48)**	**0.008**
Left ventricular mass index (g/m2)	**127 (101- 150)**	**134 (113- 173)**	**0.036**
End diastolic volume (ml)	91 (68- 117)	87 (64- 104)	0.242
End systolic volume (ml)	34 (23- 48)	34 (23- 46)	0.991
Stroke volume index (ml/m2)	**39 (33- 47)**	**38 (29- 40)**	**0.009**
Left ventricular ejection fraction (%)	58 (44- 64)	51 (40- 63)	0.184
Myocardial contraction fraction	**0.33 (0.27- 0.42)**	**0.27 (0.21- 0.33)**	**<0.001**
E wave deceleration time (ms)	217 (166- 281)	205 (159- 268)	0.445
E/A ratio	**0.8 (0.7- 1.2)**	**1.4 (0.7- 2.8)**	**0.004**
Left atrial diameter (mm)	53 (44- 59)	53 (46- 64)	0.279
TAPSE (cm)	**2.1 (1.7- 2.5)**	**1.9 (1.6- 2.1)**	**0.016**

sPAP (mmHg)	**39 (27- 50)**	**49 (31- 59)**	**0.02**

Continuous variables are expressed in median (interquartile range), binary variables are expressed as number (percentage). Bold values indicate statistical significance.

PCI indicates percutaneous coronary intervention; AS, aortic stenosis; AS-CA, coexisting aortic stenosis and cardiac amyloidosis; EuroSCORE II- European system for cardiac operative risk evaluation, TAVR, transcatheter aortic valve replacement; Hs, high sensitivity; NT-proBNP, N terminal pro brain natriuretic peptide; TAPSE, Tricuspid annular plane systolic excursion; sPAP, Estimated systolic pulmonary artery pressure.

Table 2. Multivariate Cox regression analysis for all-cause mortality.

Parameter	Hazard ratio	95% confidence interval	P value
Dual AS-CA	**1.72**	**1.22-2.15**	**0.002**
Aortic valve replacement	**0.46**	**0.34-0.63**	**<0.001**
EuroSCORE-II	**1.06**	**1.02-1.10**	**0.004**

AS, aortic stenosis; AS-CA, coexisting aortic stenosis and cardiac amyloidosis; EuroSCORE II-European system for cardiac operative risk evaluation,

FIGURE LEGENDS

Figure 1. All-cause mortality by Kaplan-Meier curves.

Dual pathology of aortic stenosis and cardiac amyloidosis (AS-CA) was associated with a higher all-cause mortality compared to lone AS (AS).

Figure 2. Cardiovascular death by Kaplan Meier curves.

Among patients with available cause of death (n=376), there were no significant differences observed in cardiovascular (CV) mortality between coexisting aortic stenosis and cardiac amyloidosis (AS-CA) and lone aortic stenosis (AS).

Central illustration.

Long-term outcomes of patients with lone aortic stenosis (AS) vs coexisting aortic stenosis and cardiac amyloidosis (AS-CA). Patients with lone AS (n=359) and AS-CA (n=47) were followed up for a median follow-up of 5.4 (4.9-5.8) years, having received treatment for AS. Compared to patients with lone AS, those with AS-CA had a higher rate of all-cause mortality. TAVR, transcatheter aortic valve replacement; AL, light chain amyloidosis; SAVR, surgical aortic valve replacement.

Graphical abstract

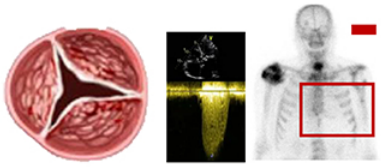
Highlights

- The coexistence of aortic stenosis (AS) and transthyretin cardiac amyloidosis (CA) is common.
- If treated with transcatheter aortic valve replacement (TAVR), patients with the combined phenotype (AS-CA) have a similar survival at 1 year compared to those with lone AS.
- AS-CA is associated with an increased long-term risk of all-cause mortality and rate of hospitalization for heart failure compared to patients with AS. Further studies evaluating the role of CA-specific therapies are warranted in this population.

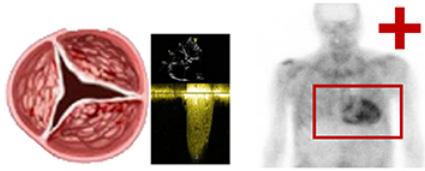
Screening TAVR patients for Cardiac Amyloidosis with Bone Scintigraphy

Multi-center international study (3 centers)
406 consecutive patients referred for TAVR
All screened by bone scintigraphy
AL amyloidosis excluded

Diagnosis of lone AS and AS-CA

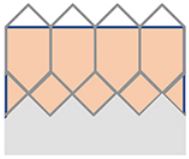


Lone Aortic Stenosis
N= 359



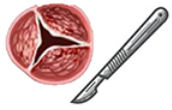
AS + Cardiac Amyloidosis
N= 47

Treatment of Aortic Stenosis



TAVR
N= 331

OR



SAVR
N= 10

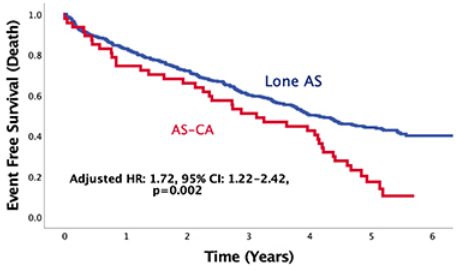
OR

Medical therapy
N= 65

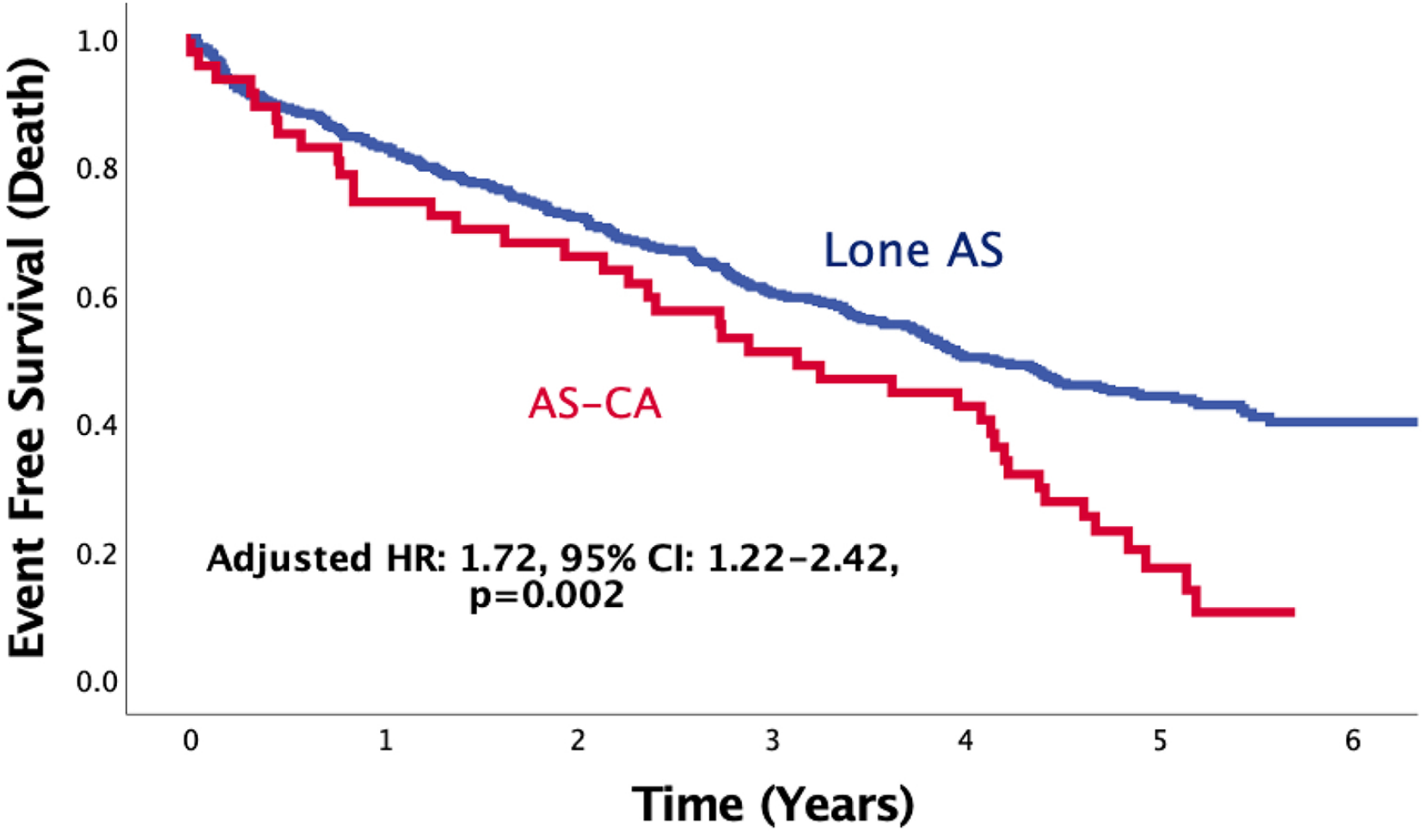
Long term outcomes

Median follow-up
5.4 (4.9-5.8) years

AS-CA: increased all-cause mortality

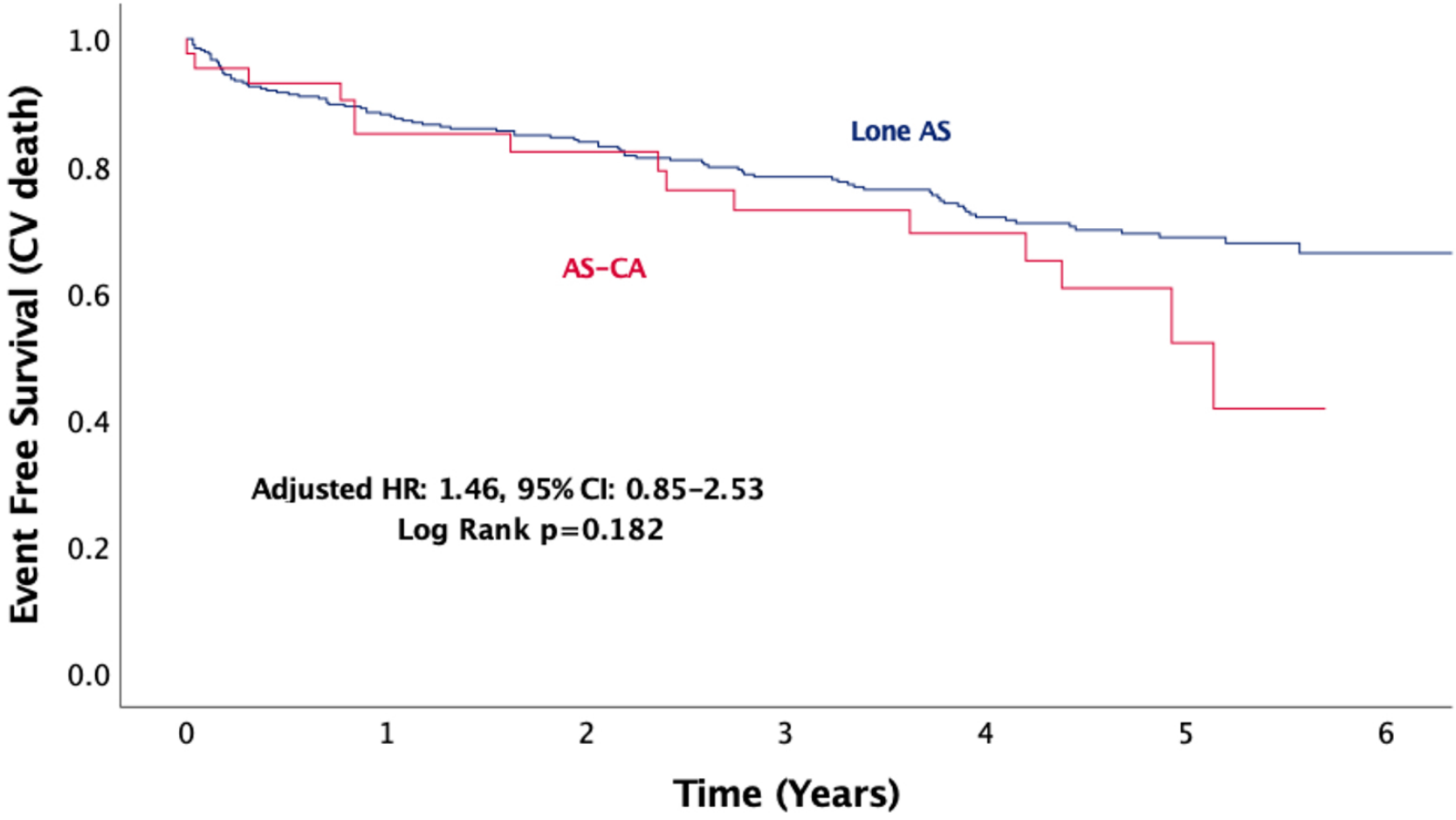


Graphics Abstract



Lone AS	359	297	258	216	175	106	13
AS-CA	47	35	31	24	20	6	0

Figure 1



Lone AS	333	274	237	198	158	90	8
AS-CA	43	32	28	22	18	6	0

Figure 2