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CLINICAL RESEARCH
Valvular heart disease

Cardiac transthyretin amyloidosis treatment improves outcomes after aortic valve replacement for severe stenosis

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Abstract

Background and Aims Concomitant aortic stenosis (AS) and transthyretin-associated cardiac amyloidosis (ATTR-CA) is an increasingly recognized cause of structural heart failure. Aortic valve replacement (AVR) improves prognosis in this population, but the efficacy of ATTR-specific medication remains unclear. This study aimed to investigate the prognostic implications of ATTR-specific medication in patients with dual AS-CA.

Methods This is a multicenter, international, transatlantic registry of patients with a concomitant pathology of significant AS (moderate/severe) and ATTR-CA (ClinicalTrials.gov identifier: NCT06129331). AS severity was diagnosed by transthoracic echocardiography and ATTR-CA by myocardial uptake on bone scintigraphy and/or positive endomyocardial biopsy in the absence of monoclonal proteins. Mortality [all-cause and cardiovascular (CV)] and hospitalisation for heart failure (HHF) served as clinical endpoints. Outcomes were compared with a control cohort of confirmed lone AS receiving AVR matched for EuroSCORE II.

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Results Of 226 patients with dual pathology (85 ± 6 years, 80.4% male) identified in 16 centres across 10 countries, AS was severe in 196 (86.7%), and moderate in 30 (13.3%). Valve treatment strategies were transcatheter/surgical AVR in 71.7%/3.5%, balloon angioplasty in 1.3%, and conservative management in 23.5%. Seventy-three patients (32.3%) were prescribed, and 69 patients (30.5%) eventually received ATTR-specific medication (99% tafamidis) and were younger, with lower EuroSCORE II, a higher portion of moderate AS, but higher interventricular septum thickness and more severely impaired left ventricular function compared with patients without ATTR medication. After 3.6 ± 1.7 years, 112 (49.6%) had died [CV death: 89 (79.5%)] and 58 (25.7%) experienced HHF. ATTR-specific medication was independently associated with lower all-cause [weighted hazard ratio (HR) 0.40, 95% confidence interval (CI) 0.24–0.68] and CV mortality (weighted HR 0.47, 95% CI 0.27–0.83) but not HHF. AVR improved survival in the overall (HR 0.60, 95% CI 0.39–0.93) and severe AS cohort (HR 0.42, 95% CI 0.26–0.70). Patients who received both ATTR-specific medication and AVR had the most favourable prognosis, comparable to a control cohort with lone AS undergoing AVR.

Conclusions ATTR-specific treatment and AVR both result in significant survival benefit in dual pathology AS and ATTR-CA. Results should be interpreted in the context of the non-randomized study setting and differences in patient characteristics.

Structured Graphical Abstract

Key Question

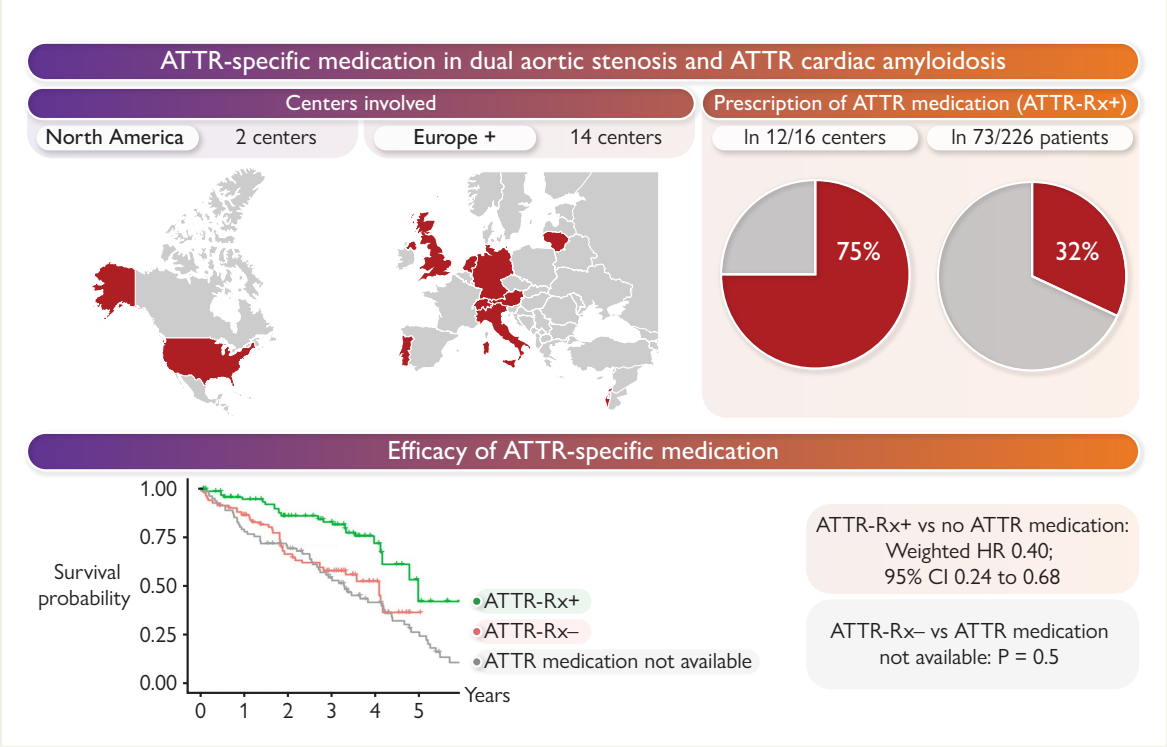
What are the prognostic implications of amyloid-specific medication in dual pathology of aortic stenosis and transthyretin (ATTR)-associated cardiac amyloidosis?

Key Finding

Patients who received both ATTR-specific medication and aortic valve replacement had the most favourable prognosis, comparable to a control cohort with lone aortic stenosis undergoing aortic valve replacement.

Take Home Message

Identification of cardiac amyloidosis in aortic stenosis is pivotal to offer optimal life-prolonging treatment options.



Keywords TAVR • SAVR • Amyloid • Tafamidis

Introduction

Degenerative aortic stenosis (AS) and cardiac amyloidosis (CA) are both conditions affecting the elderly. The dual pathology of AS and concomitant CA (AS-CA) has received great scientific and clinical interest over the recent years, and screening ascertainments of AS patients undergoing aortic valve replacement (AVR) have revealed a prevalence of ~10%.[1–6] As opposed to the initial assumption of AS treatment futility in dual AS-CA, benefit of valve replacement therapy has been demonstrated by previous work.[2,3] Valve replacement should therefore not be withheld in AS-CA. However, the question of whether and how to treat the persisting amyloidosis component remains unaddressed. Even though cases of light-chain (AL)-associated CA have been unveiled by previous screening studies,[1,2] transthyretin (ATTR)-associated CA represents the vast majority of amyloidosis patients with AS-CA. The landscape of ATTR-specific therapy development is fast evolving with three large randomized controlled trials (ATTR-ACT, ATTRibute-CM, HELIOS-B) demonstrating beneficial effects on clinical outcomes[7–9] and one drug (tafamidis) currently being approved for the treatment of patients with ATTR-associated CA. However, patients with significant AS were precluded from participation in the ATTR-ACT and HELIOS-B trial and no data on patients with concomitant AS who were recruited in the ATTRibute-CM trial are currently available. Also, the number of patients receiving ATTR-specific treatment in previous screening studies was too low to allow any analysis on the treatment effects of ATTR-specific medication in AS-CA.[1,2] Hence, it was the aim of the present large-scale transatlantic international registry to assess the effectiveness of ATTR-specific medication in patients with dual AS-CA. Owing to reimbursement issues, prescription of respective drugs varies greatly according to geographical regions. ATTR-specific medications have only become available recently which created a unique opportunity to study the impact of ATTR-targeted treatment in a cohort with AS and ATTR-CA who were allocated to receive disease-modifying therapy or not. Nevertheless, given the non-randomized setting, we expected differences in patient characteristics between groups.

Methods

Study population

This international, multicenter study enrolled adult patients with significant degenerative AS and concomitant CA at 16 specialist referral centres (September 2014 to December 2023): Vienna (Austria), Bern (Switzerland), London and Oxford (UK), New York and Charleston (US), Bologna and Trieste (Italy), Münster, Essen, Göttingen, and Frankfurt (Germany), Utrecht (Netherlands), Petah Tikva (Israel), Lisbon (Portugal), and Vilnius (Lithuania). Individual centres and respective contributions are detailed in Supplementary data online, *Table S1*. Patients were mostly identified through systematic CA screening of consecutive patients referred for potential transcatheter AVR (TAVR) therapy. Less often, CA was detected through clinical suspicion with consecutive CA assessment. Based on the current debate regarding the indication for AVR in patients with moderate AS, significant AS was defined as moderate or higher. Patients were recruited irrespective of the heart team decision regarding AS treatment. Therefore, patients were either managed medically or received balloon aortic valvuloplasty, TAVR or surgical AVR (SAVR)—as determined by an interdisciplinary heart team. Among patients undergoing intervention for AS, peri-procedural complications as defined by the Valve Academic Research Consortium-3 (VARC-3) criteria were collected.[10]

Patients with dual AS-CA were compared with a cohort of patients with proven lone AS drawn from an Austrian/UK registry of consecutive patients with severe AS referred for potential TAVR who underwent systematic CA screening with bone scintigraphy during the same period.

Study design

This is an observational cohort study. Study exposures are prescription of ATTR-specific medication and performance of AVR. ATTR medication users were compared with non-users and patients receiving AVR to those with conservative management. The day of CA diagnosis in patients with prevalent AS served as the index date. All co-variates were collected on the index date. All-cause mortality, cardiovascular (CV) mortality, and hospitalisation for heart failure (HHF) served as clinical endpoints and were 100% complete. Death and cause of death were ascertained through death queries at each centre. HHF were adjudicated by individual centres. This study complies with the Declaration of Helsinki, relevant local ethics and site approvals were obtained and all patients provided written informed consent.

Laboratory and electrocardiographic assessment

For the detection of pathological light chains underlying AL-CA, laboratory testing included serum immunoglobins and free light-chain quantification, and serum/urine immunofixation, which was performed in all patients. Additionally, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and/or B-type natriuretic peptide (BNP) was collected. Among patients who only had BNP measurements available, BNP was converted to NT-proBNP using the previously described conversion formula.[11] High-sensitivity troponin T (hs-TnT) and I (hs-TnI) were determined according to local standards. Further laboratory assessment included estimated glomerular filtration rate (eGFR) and haemoglobin levels. Electrocardiograms were recorded according to current recommendations.[12]

Echocardiography

All patients underwent clinical transthoracic echocardiography, primarily for assessment of AS severity, any concomitant valve pathology and ventricular function according to the local protocols, written in accordance with international imaging guidelines.[13–16] Left ventricular ejection fraction (LVEF) was calculated using Simpson's biplane where possible, or otherwise quantified visually. Stroke volume (SV) was quantified using the left ventricular outflow tract (LVOT) velocity time integral and the LVOT diameter and then indexed to body surface area. Left ventricular mass was calculated using the formula from Devereux *et al.*[17] Strain analysis was performed in the 4-, 3-, and 2-chamber apical views and global longitudinal strain (GLS) was calculated as the average longitudinal strain of the 17 left ventricular segments.[18] For inclusion, patients had to have at least moderate AS according to current diagnostic criteria, defined as a mean gradient >20 mmHg and/or peak velocity 3.0 m/s and/or an aortic valve area (AVA) ≤1.5 cm^2.[13] Low-flow, low-gradient AS was determined according to guidelines.[16]

Bone scintigraphy

Bone scintigraphy with amyloid-avid tracers was performed to identify ATTR-associated CA.[19] Technetium-99m pyrophosphate (PYP) was used in US centres and ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) in all other centres. Whole-body images were acquired at a scan speed of 10 cm/min using low energy high-resolution collimators.[20] Planar whole-body images were performed at 1 (PYP) to 3 h (DPD). Additional single-photon emission computed tomography/computed tomography (SPECT/CT) of the chest was performed according to local standards. Cardiac uptake was locally graded according to a semi-quantitative visual score where Grade 0 represents no cardiac uptake with normal bone uptake (i.e. negative) and Grades 1–3 represent increasing cardiac uptake with increasing bone attenuation and soft tissue uptake.[21]

Diagnosis of CA

ATTR-associated CA was diagnosed in patients with positive cardiac tracer uptake on bone scintigraphy and unremarkable serum and urine free light-chain assessment.[22] As previously described, Grade-1 cardiac uptake

without monoclonal gammopathy was considered to represent early ATTR amyloid infiltration, and Grade-2/3 as clinical ATTR-CA.[2,23,24] The non-biopsy diagnostic pathway of ATTR-associated CA was postulated in 2016.[22] As some patients were recruited prior to 2016, a minority were diagnosed based on an endomyocardial biopsy positive for ATTR ($n = 12$). Genetic sequencing of the transthyretin (TTR) gene was performed from whole blood samples to differentiate wild-type ATTR-CA from mutant ATTR-CA. AL-associated CA was diagnosed if light-chain assessment was positive and there was endomyocardial or extracardiac biopsy amyloid of light-chain origin. Patients with a dual pathology of significant AS and AL-associated CA ($n = 3$) were collected within this registry but excluded from the analysis presented here (see Supplementary data online, *Figure S1*).

Statistical analysis

Continuous data are expressed as mean ± standard deviation (SD) or as median and interquartile range (IQR), and categorical variables are presented as numbers and percentages. Differences between groups were analyzed with the Chi-square, Mann–Whitney *U*, and Kruskal–Wallis test as appropriate. *Post hoc* analyses were performed using Dunn-Bonferroni tests for continuous variables. To assess the prognostic implications of ATTR-specific treatment two statistical models were applied:

(1) Target trial emulation of a randomized trial by inverse probability of treatment weighting (IPTW) in patients with the possibility of receiving ATTR medication. Potential confounders of ATTR-specific treatment prescription (age, sex, EuroSCORE II, NYHA class, NT-proBNP, eGFR, AS severity, year of recruitment) were used to calculate propensity scores with consecutive performance of IPTW (stabilized weights, *Figure 1*). Standardized mean differences in the co-variates before and after IPTW were visualized using a Love plot. Hazard ratios and 95% confidence intervals were estimated using IPT weighted Cox proportional hazard regression. Patients with scheduled prescription who died before treatment initiation ($n = 4$) were included in the treatment group to simulate intention-to-treat analysis of a randomized trial. Analyses were performed for both (i) the population with the basic possibility of ATTR treatment prescription (excluding those with no availability or no reimbursement), and (ii) the overall population (where patients with no possibility of receiving ATTR-medication were included in the analysis with a weight of 1). Weighted Kaplan-Meier curves were used to visualize survival.

(2) Covariate-adjusted Cox regression. All baseline parameters were proposed for univariate analysis. Multivariate analysis was performed using a stepwise forward selection with the cut-off *P*-value to enter the multivariate model being ≤ .1 in univariate testing and the *P*-value to remove from multivariate testing being >.1. ATTR-specific medication and performance of AVR were entered as time-dependent co-variates to avoid potential immortal time bias. Dates of AVR and ATTR treatment initiation were known for all cases and ATTR treatment was continued until censoring date in all users. Cause-specific hazard analysis was performed as a competing risk analysis to assess the impact of ATTR-specific treatment on experiencing HHF. To allow better comparison between continuous parameters within the multivariate model, scaled hazard ratios (HRs) (*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.

For both models, the date of CA diagnosis served as baseline date and the date of event (in patients experiencing an event) or last follow-up (in patients without an event) served as censoring date. In the Cox models with time-dependent co-variates, the date of treatment initiation was the starting date of exposure.

Kaplan-Meier curves for time-dependent co-variates were used to visualize the time-dependent treatment effect of AVR. Additionally, to evaluate the potential additive benefit of prescription of ATTR-specific medication

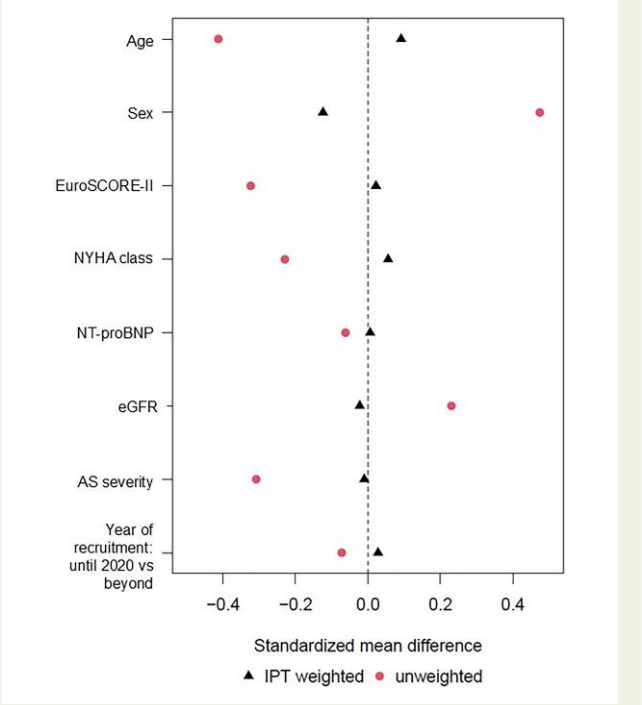


Figure 1 Love plot depicting standardized mean differences before and after inverse probability of treatment weighting. NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; AS, aortic stenosis

(ATTR-Rx+) and performance of aortic valve replacement (AVR+) the population was stratified according to three groups (ATTR-Rx−/AVR−, ATTR-Rx or AVR+, and ATTR-Rx+/AVR+) and compared using Cox regression with time-dependent co-variates. To allow outcome comparison of patients with dual AS-CA and confirmed lone AS receiving TAVR, case-control 1:1 matching (for EuroSCORE II) was performed using the 'fuzzy matching' method with a match tolerance of 0.5 for EuroSCORE II. Patients with dual severe AS and CA were matched against lone AS patients undergoing AVR ($n = 305$) which yielded matched pairs for comparison of 193 patients each.[25] A Cox model was fit with sex, age and EuroSCORE II as co-variates. Receipt of ATTR medication and AVR (whichever occurred last) was included as time-dependent covariate such that the model allowed for estimation of covariate adjusted HRs for patients receiving both treatments vs lone AS patients. A *P*-value ≤ .05 was considered statistically significant. All statistical analyses were computed using SPSS 29 (IBM SPSS, USA) and R.

Results

Patient characteristics

A total of 226 patients with a diagnosis of dual AS and ATTR-associated CA (median age 84 years [IQR, 80–89], 80.4% male) were recruited in 16 centres across 10 countries (*Structured Graphical Abstract*). AS was severe in 196 (86.7%), and moderate in 30 (13.3%) patients. The vast majority had wild-type ATTR ($n = 224$, 99.1%), whereas variant ATTR was only identified in 2 patients (1.3%; both Val30Met). Expectedly, given the advanced age and concomitant AS, the prevalence of cardiovascular comorbidities was high with hypertension seen in 78.8%, atrial fibrillation in 57.3%, chronic kidney disease in 50.4%, and diabetes in 25.2% of

Table 1 Reasons why patients did not receive/were not prescribed ATTR-specific medication

	No ATTR-specific medication $n = 157$
Not yet available, %	31.2
No reimbursement, %	21.0
No data suggesting benefit in AS, %	12.7
Grade-1 cardiac uptake, %	12.7
Severe comorbidities, %	6.4
Patient age, %	5.7
Patient frailty, %	3.2
Severe symptoms, %	1.9
A-/pauci-symptomatic, %	1.3
Combined patient factors, %	1.3
Died before initiation, %	2.5

AS, aortic stenosis; ATTR, transthyretin-related cardiac amyloidosis.

patients. Pursued valve treatment decisions included TAVR in 162 (71.7%), SAVR in 8 (3.5%), urgent balloon angioplasty in 3 (1.3%), and conservative management or ongoing surveillance in 53 (23.5%) patients.

Prescription of ATTR-specific medication

Overall, one third of patients ($n = 69/226$, 30.5%) were prescribed and received ATTR-specific treatment. Another four patients were scheduled for treatment but died before initiation. Out of 16 centres, 12 prescribed ATTR-specific medication to at least one patient. Reasons why patients did not receive/were not prescribed ATTR treatment are displayed in *Table 1* and included no availability (pre-market authorisation, 31.2%), lack of local reimbursement (21.0%), lack of data suggesting benefit in AS population (12.7%), Grade-1 cardiac uptake (12.7%), severe comorbidities (6.4%), and others. ATTR-specific treatment increased over time: from 0% (2014 to 2017) to 25.5% (2018 to 2020) to 53.1% (2021 to 2023, difference between time periods: $P < .001$). The vast majority were treated with tafamidis ($n = 67$, 97.1%), one patient received tafamidis and patisiran (1.5%), another patient acoramidis (1.5%). The median time from CA diagnosis to ATTR treatment initiation was 126 (35 to 368) days, which decreased significantly over time [2014 to 2017: n.a.; 2018 to 2020: 335 days (128 to 642); 2021 to 2023: 76 days (14 to 183), $P < .001$]. Among patients undergoing AVR, the median time from AVR to CA diagnosis was 6 (−5 to 53) days, and the median time from AVR to ATTR treatment initiation was 98 (−94 to 371) days.

Patients with vs without ATTR-specific medication

Demographics, comorbidities, symptoms, bloods, ECG

Patients receiving ATTR-specific medication were younger [81 years (78 to 86) vs 86 years (82 to 90), $P < .001$] with a higher percentage of males (88.4% vs 77.1%, $P = .047$) and a lower EuroSCORE II [3.9 (3.7 to 4.4) vs 4.1 (3.8 to 4.6), $P = .010$] compared with treatment-naïve patients (*Table 2*). The prevalence of cardiovascular comorbidities was equally distributed between groups. History of carpal tunnel syndrome was more common in patients receiving ATTR-specific treatment (36.2% vs 17.8%, $P = .003$). AS-attributable symptoms (dyspnoea, angina, syncope) and presence of pitting oedema were evenly distributed between groups, whereas palpitations were slightly more common in patients with ATTR treatment ($P = .007$). Patients with ATTR medication had a numerically lower presence of ≥ moderate dyspnoea (NYHA class ≥ III), which was borderline significant (52.2% vs 65.0%, $P = .069$). Laboratory results included comparable NT-proBNP [2790 ng/dL (1151 to 6323) vs 3616 ng/dL (1599 to 5842), $P = .33$] and hs-TnT [53 ng/L (27 to 75) vs 43 ng/dL (27 to 80), $P = .73$] serum levels for patients with vs without ATTR treatment. Haemoglobin levels were higher in patients with ATTR treatment [13.3 mg/dL (12.2 to 14.2) vs 12.5 mg/dL (10.8 to 13.6), $P < .001$]. Conduction disorders were highly prevalent in both groups (>50%).

Imaging characteristics

Echocardiographic findings included a higher interventricular septum thickness [17 mm (14 to 21) vs 16 mm (13 to 18), $P = .006$] and more severely impaired GLS [−10% (−13 to −8) vs −12% (−16 to −9), $P = .012$] in patients with ATTR-specific medication (*Table 3*). Left ventricular stroke volumes were similarly impaired in both groups (34 mL/m^2 vs 31 mL/m^2 for patients with vs without ATTR medication, $P = .16$) and—accordingly—the prevalence of low-flow low-gradient AS (Stage D2 or D3) was high with >60% in both groups ($P = .42$). AS of moderate degree was more common among patients with ATTR treatment (26.1% vs 7.6%, $P < .001$) and markers denoting AS severity were therefore less pronounced in these patients (AVA, transvalvular velocity, mean pressure gradient; all $P \leq .05$).

Among patients who underwent bone scintigraphy ($n = 214$, 93.8%), high-grade cardiac uptake (Grade 2/3) was more common in those receiving ATTR treatment compared with treatment-naïve patients (96.8% vs 78.9%, $P = .001$).

Baseline characteristics according to ATTR and AS treatment strategies

Detailed patient characteristics stratified by ATTR and AS treatment approaches are depicted in Supplementary data online, *Tables S2* and *S3*. Differences in clinical and imaging characteristics included lower haemoglobin levels (12.0 mg/dL vs 12.7 mg/dL vs 13.3 mg/dL, $P = .019$) and a higher prevalence of moderate AS (37.9% vs 9.9% vs 8.9%, $P < .001$) among ATTR-Rx−/AVR− compared with ATTR-Rx or AVR+ and ATTR-Rx+/AVR+.

Peri-procedural complications

Among patients undergoing aortic valve intervention (AVI), major adverse events according to VARC-3 occurred at a similar rate in both groups: stroke 0% vs 2.0%, vascular complication 2.5% vs 4.0%, new pacemaker implantation 15.0% vs 19.2% for patients with vs without ATTR-specific medication (P for all > .05).

Outcome

All-cause mortality

After a median of 3.5 years (IQR, 2.3 to 4.9) following CA diagnosis, 112 patients (49.6%) had died. Patients with intention-to-receive ATTR-specific treatment had better survival compared with treatment-naïve

Table 2 Baseline clinical characteristics

	No ATTR-specific medication $n = 157$ (69.5%)	ATTR-specific medication $n = 69$ (30.5%)	*P*-value
Demographics			
Age, y	86 (82–90)	81 (78–86)	**<.001**
Sex, male, %	77.1	88.4	**.047**
Ethnicity			.51
Caucasian	99.4	100	
Black	0.6	0	
BMI, kg/m^2	25.8 (23.8–28.7)	26.2 (24.6–29.2)	.20
EuroSCORE II, %	4.1 (3.8–4.6)	3.9 (3.7–4.4)	**.010**
Comorbidities			
CAD, %	44.6	47.8	.65
Past myocardial infarction, %	14.9	9.8	.34
Coronary artery bypass graft, %	13.6	12.1	.77
Atrial fibrillation, %	57.1	58.0	.90
Diabetes, %	23.6	29.0	.39
Arterial hypertension, %	82.2	71.0	.059
Chronic kidney disease, %	51.6	47.8	.60
Hypercholesterolemia, %	54.0	54.7	.93
Carpal tunnel syndrome, %	17.8	36.2	**.003**
Lumbar spinal stenosis, %	13.0	15.2	.76
Pre-interventional cardiac device, %	17.8	24.2	.27
AV conduction defect			.10
None	46.4	46.9	
1st degree AVB, %	10.0	15.6	
2nd degree AVB, %	1.8	0	
High-grade AVB, %	1.8	1.6	
RBBB, %	15.5	6.4	
LBBB, %	3.6	7.8	
LAFB, %	3.6	4.7	
Non-specific, %	15.5	7.8	
Combination, %	1.8	9.4	
Signs and symptoms			
Asymptomatic, %	3.2	4.3	.66
Palpitations, %	2.9	16.7	**.007**
Dyspnoea, %	94.9	95.7	.81
NYHA stage			.069
I/II	35.0	47.8	
III/IV	65.0	52.2	
Angina, %	15.1	20.6	.34
(Pre-)syncope, %	11.0	9.5	.75

Continued

Table 2 ***Continued***

	No ATTR-specific medication $n = 157$ (69.5%)	ATTR-specific medication $n = 69$ (30.5%)	*P*-value
Leg oedema, %	29.8	39.0	.25
Conventional heart failure medication			
ACE inhibitor, %	26.1	29.0	.65
ARB, %	16.6	24.2	.18
ARNI, %	3.2	7.2	.17
MRA, %	27.4	39.1	.079
Betablocker, %	55.4	58.0	.72
ATTR-specific medication			
Tafamidis, %	n.a.	98.6[a]	
Patisiran, %	n.a.	1.4	
Acoramidis, %	n.a.	1.4	
Laboratory results			
Hs-TnT, ng/L ($n = 131$)	43 (27–80)	53 (27–75)	.73
Hs-TnI, ng/L ($n = 54$)	36 (11–103)	27 (14–71)	.97
NT-proBNP, ng/dL	3616 (1599–5842)	2790 (1151–6323)	.33
eGFR, mL/min/1.73 m^2	58 (43–72)	62 (44–80)	.20
Haemoglobin, mg/dL	12.5 (10.8–13.6)	13.3 (12.2–14.2)	**<.001**
Monoclonal protein, %	24.1	35.8	.093
ATTR subtype			.28
Wild-type ATTR	100	97.1	
Mutant ATTR	0	2.9	
Aortic stenosis treatment			**.016**
Ballon angioplasty	1.9	0	
SAVR	2.5	5.8	
TAVR	77.1	59.4	
Conservative management	18.5	34.8	

For parameters with missing values the number of patients with available data is mentioned. Bold values indicate $P \leq 0.05$.
ACE, angiotensin-converting-enzyme; ARB, angiotensin-II receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; ATTR, amyloid transthyretin; AVB, atrioventricular block; BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; hs-TnI, high sensitive troponin I; hs-TnT, high sensitive troponin T; LAFB, left anterior fascicular block; LBBB, left bundle branch block; MRA, mineral corticoid receptor antagonist; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; RBBB, right bundle branch block; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.
[a]Includes one patient treated with both Tafamidis and Patisiran.

patients for both the population with ATTR-treatment availability [weighted HR 0.45; 95% confidence interval (CI) 0.25 to 0.83; $P = .011$] and the overall population (weighted HR 0.40; 95% CI 0.24 to 0.68; $P = .001$, *Figure 2*). Patients not receiving ATTR-treatment despite the basic availability had similarly impaired prognosis to those who were untreated because of the lack of availability/reimbursement (HR 0.85; 95% CI 0.54 to 1.34; $P = .48$; *Graphical Abstract*). Results were comparable for the covariate adjusted model with ATTR-specific treatment conveying significant survival benefit (adjusted HR 0.45; 95% CI 0.26 to 0.77; $P = .004$; Supplementary data online, *Table S4*). Results remained unchanged when only considering patients on treatment with tafamidis (adjusted HR 0.47; 95% CI 0.28 to 0.82), and patients with severe AS (adjusted HR 0.52; 95% CI 0.29 to 0.92; Supplementary data online, *Table S5*). Among those receiving ATTR medication, the delay in initiation of ATTR-specific treatment did not significantly impact mortality hazard (≥1 year delay vs < 1 year delay: HR 1.58; 95% CI 0.60 to 4.16; log-rank, $P = .35$; Supplementary data online, *Figure S2*). However, this study was not sufficiently powered to address this issue.

In the overall cohort, performance of AVR was associated with improved survival (HR 0.60; 95% CI 0.39 to 0.93; *Figure 3A*). This association persisted after multivariate adjustment (adjusted HR 0.41; 95% CI 0.25 to 0.65; Supplementary data online, *Table S4*). In patients with a class I treatment indication for AVR (after excluding patients with

Table 3 Baseline imaging characteristics

	No ATTR-specific medication $n = 157$ (69.5%)	ATTR-specific medication $n = 69$ (30.5%)	*P*-value
Cardiac morphology			
LVEDD, mm	46 (42–50)	45 (41–50)	.68
IVS, mm	16 (13–18)	17 (14–21)	**.006**
PWT, mm	14 (11–16)	14 (12–16)	.48
LV mass index, g/m^2	146 (117–181)	156 (130–178)	.15
Cardiac function			
LVEF, %	50 (41–60)	52 (40–60)	.94
GLS, %	−12 (−16 to −9)	−10 (−13; −8)	**.012**
SVi, mL/m^2	31 (26–39)	34 (26–42)	.16
TAPSE, mm	18 (15–20)	18 (13–23)	.88
Aortic stenosis			
AS severity			**<.001**
Moderate, %	7.6	26.1	
Severe, %	92.4	73.9	
AVA, cm^2	0.8 (0.6–0.9)	0.9 (0.7–1.0)	**.023**
AV Vmax, m/s	3.9 (3.3–4.4)	3.4 (2.7–4.0)	**<.001**
AV MPG, mmHg	34 (23–43)	28 (22–38)	**.050**
AS phenotype, %			.42
D1: High gradient	37.9	28.0	
D2: LFLG, LVEF ≥ 50%	28.6	36.0	
D3: LFLG, LVEF < 50%	33.6	36.0	
Atrioventricular valves			
MR ≥ moderate, %	25.5	27.9	.71
TR ≥ moderate, %	22.9	18.8	.49
sPAP			.15
<31 mmHg, %	45.9	33.3	
31–55 mmHg, %	38.9	52.2	
>55 mmHg, %	15.3	14.5	
Cardiac uptake on bone scintigraphy ($n = 214$)			**.002**
Grade 1, %	21.1	3.2	
Grade 2, %	46.7	46.8	
Grade 3, %	32.2	50.0	

Bold values indicate $P \leq .05$.
AS, aortic stenosis; AV, aortic valve; AVA, aortic valve area; EDD, end-diastolic diameter; EF, ejection fraction; GLS, global longitudinal strain; IVS, interventricular septum; LFLG, low-flow low-gradient; LV, left ventricular; MPG, mean pressure gradient; MR, mitral regurgitation; PWT, posterior wall thickness; sPAP, systolic pulmonary artery pressure; SVi, stroke volume index; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; Vmax, peak velocity.

moderate AS), AVI conveyed clear survival benefit (HR 0.42; 95% CI 0.26 to 0.70; *Figure 3B*).

The cohort was further stratified according to prescription of ATTR-specific medication (ATTR-Rx+) and performance of AVR+, yielding three groups: (i) ATTR-Rx−/AVR−, (ii) ATTR-Rx or AVR+, and (iii) ATTR-Rx+/AVR+. A stepwise increase in survival probability was observed: (i) ATTR-Rx or AVR+vs ATTR-Rx−/AVR− (HR 0.50; 95% CI 0.31 to 0.83), and (ii) ATTR-Rx+/AVR+ vs ATTR-Rx−/AVR− (HR 0.15; 95% CI 0.07 to 0.34). Patients with CA and severe AS receiving both ATTR-specific medication and AVR had comparable survival to a control cohort with lone AS undergoing AVR matched for operative risk (adjusted HR 1.11; 95% CI 0.81 to 1.51).

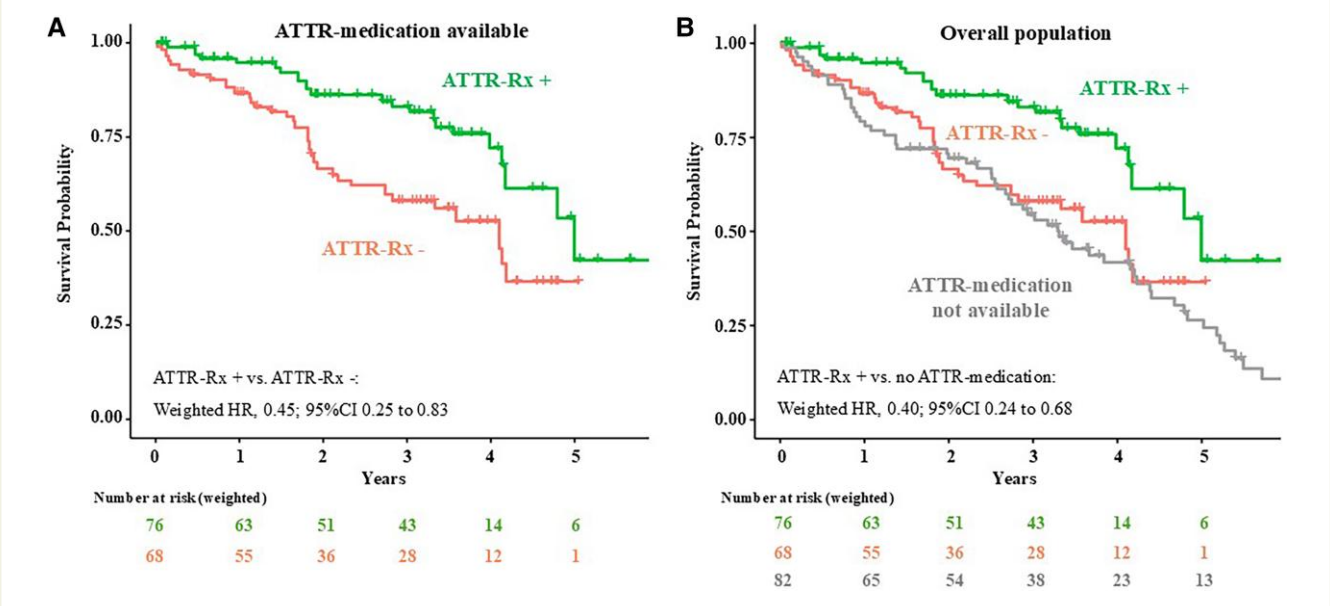


Figure 2 Weighted Kaplan-Meier curves for all-cause mortality stratified by ATTR-treatment prescription. ATTR-Rx was associated with lower mortality hazard for both the population with general availability of ATTR-medication (*A*) and the overall population (*B*)

CV mortality

Out of 112 deaths, 89 (79.5%) were of CV origin. Patients with intention-to-receive ATTR-specific treatment had a lower hazard for CV death compared with treatment-naïve patients for both the population with ATTR-treatment availability (weighted HR 0.45; 95% CI 0.24 to 0.85; $P = .014$) and the overall population (weighted HR 0.47; 95% CI 0.27 to 0.83; $P = .009$). Results were comparable for the covariate adjusted model where ATTR-specific treatment was associated with significantly lower risk for CV death (adjusted HR 0.53; 95% CI 0.29 to 0.95; $P = .032$ Supplementary data online, *Table S6*).

Hospitalisation for heart failure

During follow-up 58 patients (25.7%) experienced HHF. Intention-to-receive ATTR-specific treatment was not associated with time to first HHF in the population with ATTR-treatment availability (weighted HR 0.73; 95% CI 0.38 to 1.43) or the overall population (weighted HR 0.84; 95% CI 0.47 to 1.50). Results were comparable in a competing risk analysis of the covariate adjusted model (HR 0.85; 95% CI 0.44 to 1.67).

Discussion

Dual pathology of AS and CA is an increasingly recognized cause of combined structural heart failure. However, the largest cohort to date comprised <50 patients with AS-CA,[2] which was underpowered to evaluate the effects of ATTR-specific medication on clinical outcomes in this population. The present international, transatlantic, multicenter study of AS-CA patients demonstrates for the first time that ATTR-specific medication improves survival in AS-CA, as did AVR. Patients who received both ATTR-specific medication and AVR had the most favourable prognosis, which was non-inferior to patients with proven lone AS undergoing AVR. These data suggest that dual pathology should be targeted by AVR and ATTR-specific therapy to achieve best possible outcomes.

Previous screening ascertainments in patients with severe AS considered for AVR (mostly TAVR) have demonstrated a prevalence of 6–16%,[1–6] which is significantly higher than estimates for the general population derived from non-cardiac bone scan referrals.[26,27] Initially, AVR was considered futile in AS-CA for pathophysiological assumptions and due to frailty of the population.[28] This perception was disproven by outcome studies demonstrating survival benefit in AS-CA receiving AVR.[2,3] Nevertheless, despite multicenter efforts the numbers of AS-CA patients with ($n < 40$) and without AVR ($n \sim 10$) were relatively small and current treatment practice is therefore based on potentially underpowered reports. The current study, which includes ~5-times more patients with dual disease, now demonstrates clear survival benefit of AVR in AS-CA with significantly reduced mortality in the overall (moderate and severe AS) and severe AS cohort (*Figure 3*). These results corroborate previous findings and current clinical management strategies.

We have shown previously that despite successful AVR, patients with AS and ATTR-associated CA present with adverse features at follow-up compared with patients with lone AS including less reverse remodelling, higher residual symptomatic burden and biomarkers.[29] At one-year post-AVR, AS-CA resembled 'lone ATTR' by morphology, symptoms, and contractility pattern,[29] implicating that the residual amyloid component may warrant specific treatment.

ATTR-specific medication is a hot topic with three positive trials having demonstrated outcome benefits in patients with ATTR cardiomyopathy.[7–9] However, patients with significant AS were either excluded from participation or not reported on. Furthermore, despite increasing disease awareness structured screening efforts are still difficult to implement into daily clinical routine and AS-CA is therefore underrecognized. Conduction of sufficiently powered randomized controlled trials in a subgroup of rare diseases, such as AS-CA, has inherent challenges and the present registry therefore aimed to deliver timely results to evaluate prognostic implications of potentially life-prolonging treatment options in affected patients. The study took advantage of natural variation (temporal and geographical) to assess the

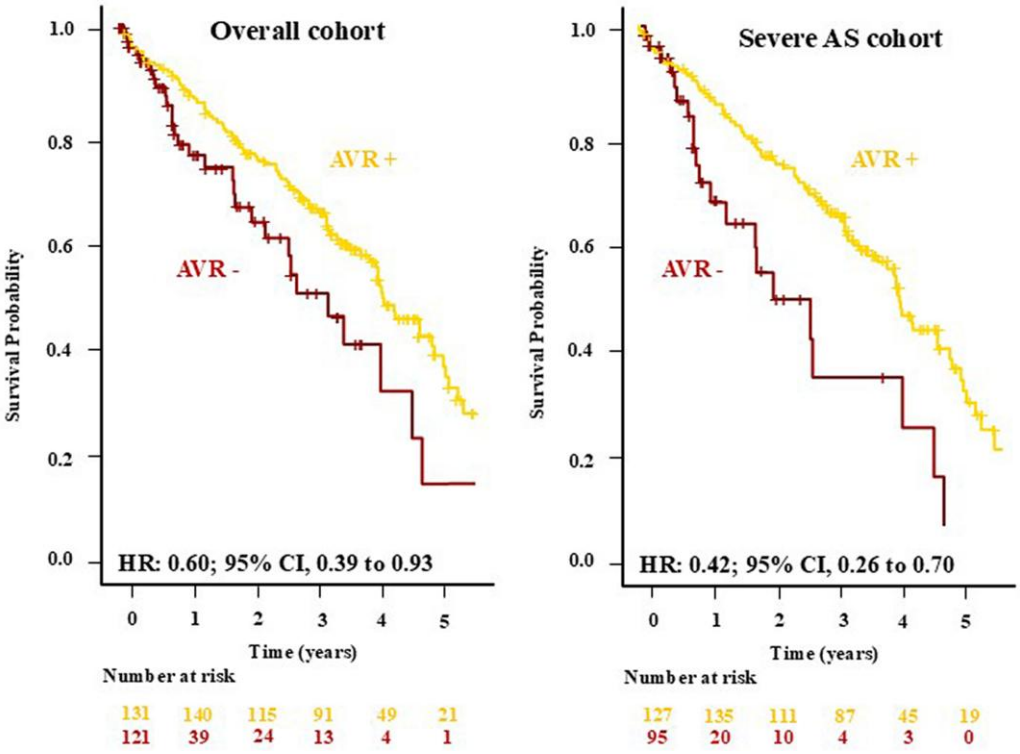


Figure 3 Kaplan-Meier curves for time-dependent co-variates stratified by performance of aortic valve replacement. Aortic valve replacement was associated with lower mortality hazard for both the overall cohort (*A*) and the severe aortic stenosis cohort (*B*)

effects of ATTR-specific medication. First, there was variation in the rollout of treatment over time, with the study considering a pre-and post-Tafamidis era. Second, there were geographical differences in the availability and reimbursement of ATTR medication, serving as an exogenous source of variation in treatment assignment. However, patient-related factors (age, frailty, comorbidities) served as the basis for not prescribing ATTR medication in ~20%. Yet, patients not receiving ATTR-treatment despite the general availability had similarly impaired prognosis to those who were untreated because of the lack of availability/reimbursement (*Structured Graphical Abstract*), which reinforces the results presented. Interestingly, the presence of severe AS or NYHA class ≥ III was commonly cited by treating physicians and insurance companies for withholding prescription/reimbursement of treatment. In AS-CA, advanced dyspnoea may indeed be related to the valvular lesion and futility of ATTR medication in patients with NYHA class ≥ III observed in previous ATTR trials may therefore not be transferable to the AS-CA population. Also, the mere presence of severe AS may not be regarded as a contraindication for ATTR medication if treated by AVR.

While the observational design is associated with the risk of selection bias and has its limitations in providing causal estimates, the presented results argue against withholding life-prolonging treatment modalities for AS-CA patients. Using target trial emulation, we demonstrate for the first time that ATTR-specific medication was significantly and independently associated with improved survival in AS-CA. These results are reassuring as patients with ATTR medication had more advanced disease than those without as highlighted by higher septum thickness, more reduced GLS, and a higher prevalence of Grade 2/3 (vs Grade 1) myocardial uptake on bone scintigraphy, and still experienced better outcome. They also had a higher prevalence of moderate AS, but results remained unchanged when adjusting for AS severity. Patients receiving both treatments, ATTR-specific medication and AVR, displayed the most beneficial clinical course with comparable survival to a matched control cohort of patients with proven lone AS (all had negative bone scintigraphy and no evidence of AL) undergoing AVR. With a median follow-up of 3.5 years these results implicate that dual treatment for dual disease may 'normalize' mid-term outcome to the level of treated lone AS. ATTR-specific medication was not associated with time to first HHF. This may be related to competing risks as patients without ATTR-specific drugs showed higher death rates—precluding the occurrence of potential future HHF.

Our results underscore the necessity to implement (logistically and economically) viable CA screening strategies into clinical practice (e.g. RAISE scoring system or extracellular volume quantification at TAVR CT)[2,30] as patients with dual disease are otherwise overlooked and undertreated with potentially life-prolonging therapies.

In summary, ATTR-specific medication and AVR both result in significant survival benefit in dual pathology of AS and ATTR-CA. Patients receiving both treatments experienced the lowest mortality comparable to patients with lone AS. These results highlight the importance of identifying CA in AS in order to provide best possible treatment options.

Limitations

Based on local standards there may have been a selection bias of prescription of ATTR-specific medication, as demonstrated by e.g. lower age in patients receiving ATTR-specific treatment. Nevertheless, ATTR-specific medication remained independently associated with

improved survival after adjusting for potential prescription confounders. Similarly, there may have been a managing clinician bias regarding the treatment allocation for AS (AVR vs conservative). Heart failure hospitalisations were recorded and adjudicated by individual centres and there may have been ascertainment bias. The variable delay between AVR and ATTR treatment initiation could have impacted the results, even though this factor was not a determinant of mortality in outcome analysis. A minority of patients (<20%) was diagnosed with ATTR-CA based on clinical suspicion, which may have introduced a selection bias. Finally, the definition of significant AS included patients with moderate AS. This was based on the ongoing debate to expand AVR indication to symptomatic patients with moderate AS [EXPAND TAVR II (NCT05149755), TAVR UNLOAD, PROGRESS (NCT04889872) trials].[31] Reassuringly, AVR significantly improved survival when considering both moderate and severe AS, and severe AS separately.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

CN: research grants (Pfizer, AstraZeneca, Austrian Society of Cardiology, European Association of Cardiovascular Imaging), speaker fees (Pfizer, Boehringer Ingelheim, Bayer), and consulting honoraria (Bayer, Prothena); MP: consultant fees (Pfizer); SD: research grants on behalf of the institution (Pfizer), speaker fees and travel grants (Boehringer Ingelheim, Alnylam, Pfizer); SG: speaker fees and travel grants (Berlin-Chemie, Servier, Novartis); SS: research grants on behalf of the institution (Edwards Lifesciences, Medtronic, Abbott, Boston Scientific), consulting fees (Inari Medical); TT: supported by the British Heart Foundation; all other authors have nothing to declare.

Data Availability

The data that support the findings of this study are available from the corresponding author, [CN], upon reasonable request.

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Ethical Approval

This study complies with the Declaration of Helsinki, relevant local ethics and site approvals were obtained and all patients provided written informed consent.

Pre-registered Clinical Trial Number

The pre-registered clinical trial number is ClinicalTrials.gov identifier: NCT06129331.

Appendix

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