INFOGRAPHIC

Neurohormonal therapies at baseline and follow-up and survival in wild-type transthyretin cardiac amyloidosis

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Background Transthyretin cardiac amyloidosis (ATTR-CA) typically manifests with heart failure. Discontinuing beta-blockers and avoiding angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB) in patients with ATTR-CA has been recommended.

Methods We investigated the prescription of neurohormonal therapies and their relationship with all-cause mortality in a multicenter cohort.

Results Patients ($n=926$) had a median age of 79 years (interquartile range 74–83), 90% were men, 17% had a left ventricular ejection fraction (LVEF) 40% or less, and 27% were in New York Heart Association (NYHA) class III/IV. At diagnosis, 60% of patients were on beta-blockers, 58% on ACEi/ARB/ARNI, and 35% on MRA. Patients on beta-blockers had more often NYHA class III/IV, a greater burden of comorbidities, and lower LVEF, and those on ACEi/ARB/ARNI had more comorbidities. Nonetheless, the survival of patients on beta-blockers or ACEi/ARB/ARNI was not significantly shorter over a 2.5-year follow-up (1.6–3.8) ($P=0.577$ and $P=0.977$, respectively), and patients on both drugs did not have a worse outcome than those not receiving any neurohormonal drug ($P=0.575$). During the entire follow-up, the number of neurohormonal drugs remained unchanged in 54%, decreased in 27%, and increased in 19%. Patients with a number of neurohormonal drugs either unchanged or increased had a lower risk of mortality (odds ratio 0.71, 95% confidence interval 0.53–0.95, $P=0.023$).

Conclusion ATTRwt-CA patients on beta-blockers or ACEi/ARB/ARNI at diagnosis did not have a shorter survival. Beta-blockers were discontinued less often than were ACEi/ARB/ARNI. There was no sign of better outcomes in patients discontinuing these therapies, or worse outcomes in those starting them.

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Background

Cardiac amyloidosis is a disorder caused by the accumulation of amyloid fibers leading to organ dysfunction. In 95% of cases of cardiac amyloidosis, the amyloid fibrils consist of either immunoglobulin light chains (AL amyloidosis) or transthyretin (ATTR amyloidosis), the latter being a transport protein for thyroid hormones and retinol-binding globulin.[1] Genetic mutations reducing transthyretin stability cause the hereditary or variant (v) form of ATTR amyloidosis. This condition may be characterized by an exclusive involvement of the heart, peripheral/autonomic nervous system, or mixed, and can manifest as early as the fifth decade.[1] The nonmutated (wild-type, wt) form typically affects elderly male individuals.[1] The accumulation of amyloid fibers causes thickening of the cardiac walls (pseudo-hypertrophy), with an increased risk of heart failure. Heart failure primarily requires therapy with loop diuretics, which is effective in controlling symptoms and usually well tolerated. Mineralocorticoid receptor antagonists (MRA) are generally well tolerated and have been recommended. Additionally, MRA counteract the elevation in aldosterone levels found in patients with cardiac amyloidosis[2] and have an antifibrotic activity that might prove useful given the significant amount of cardiac fibrosis observed in patients with cardiac amyloidosis.[3] A possible theoretical framework for beta-blockade and antagonism of the renin–angiotensin axis is provided by the evidence of an intense neurohormonal activation in cardiac amyloidosis,[2] which may promote cardiac damage over the long term. Some evidence on the prognostic benefit is available only for beta-blockers in ATTR-cardiac amyloidosis (ATTR-CA), with retrospective studies finding either no survival benefit[4] or a reduced risk of mortality.[5] For angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB), both studies did not find any evidence of improved survival.[4,5]

In 2021, a position statement by the European Society of Cardiology (ESC) recommended to discontinue beta-blockers and preferably avoid ACEi or ARB.[6] This document did not refer specifically to ATTRwt-CA, and advocated for studies assessing the efficacy of heart failure drugs, and identifying patients who may benefit from them.[6] In this analysis of a multicenter cohort from Italy, we analyzed the patterns of prescription of neurohormonal drugs at baseline and during the follow-up and their relationships with outcome. We focused mostly on beta-blockers and ACEi/ARB or angiotensin receptor neprilysin inhibitors (ARNI) because of the recommendations for discontinuing or preferably avoiding them, while the same recommendation was not provided for MRAs.[6]

Methods

Patient population and baseline characteristics

The 'DIagnostic pathways to transthyretin AMyloid cardiomyOpathy: a multicenter Network stuDy' (DIAMOND) was a retrospective study of patients diagnosed with ATTRwt-CA in 17 Italian referral centers for cardiac amyloidosis.[7] Inclusion criteria were: a definite diagnosis of ATTRwt-CA according to the Gillmore algorithm,[8] a diagnostic workup for cardiac amyloidosis started between January 2016 and December 2021, age at least 18 years at first evaluation, and written informed consent for the collection and treatment of anonymized clinical data for research purposes. The original publication provides the list of variables collected.[7] Data were collected and managed using the Research Electronic Data Capture (REDCap) tool. The Institutional Review Board of the Genova University Hospital approved the study protocol.

Follow-up data

Neurohormonal therapies were managed at the discretion of clinicians from each center. A position statement of the ESC was published in April 2021.[6] Before that, only review articles recommending a cautious use of the same drugs were available.[9,10] The follow-up period started at the time of diagnosis, and patients were censored at the time of all-cause death or last patient contact. The prescription of beta-blockers, ACEi/ARB/ARNI and MRA was evaluated at diagnosis, and the last visit before follow-up end. Follow-up information was collected between March and September 2023.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (version 24). Normal distribution was assessed using the Shapiro–Wilk test. Continuous variables with normal distribution were expressed as mean and standard deviation, and those with nonnormal distribution as median and interquartile range. Categorical variables were reported as absolute values and percentages. Comparisons between groups were performed through the ANOVA test with the Tukey correction for multiple testing or the chi-square test, as appropriate. Predictors of mortality were searched among baseline characteristics through univariable Cox regression analysis, and predictors of drug discontinuation

through univariable logistic regression analysis. The relationship between baseline therapies and outcome was investigated through univariable Cox regression analysis. Given the finding of an association between MRA therapy and worse survival, the prognostic value of MRA therapy was investigated through multivariable Cox regression analysis, including all baseline variables in the model while avoiding multicollinearity (defined as a variance inflation factor of >5). Survival analysis was also performed through Kaplan–Meier analysis and the log-rank test. An exploratory analysis of the relationship between treatment changes and mortality was conducted through univariable logistic regression analysis. We proceeded to multivariable analysis, including all baseline variables in the model while avoiding multicollinearity, only for ACEi/ARB/ARNI discontinuation, which emerged as a univariable predictor of outcome. Two-tailed *P* values of less than 0.05 were considered significant.

Results

Baseline characteristics

Patient characteristics in the original cohort were described in a dedicated publication.[7] For the purposes of this analysis, only patients with complete data about therapies at the time of diagnosis and at follow-up end were considered ($n=926$ out of 1280, 72%). Median age was 79 years (interquartile range 74–83), 90% of the patients were men, and 27% had New York Heart Association (NYHA) class III or IV symptoms. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was 2908 ng/l (1439–4902), and 17% had left ventricular ejection fraction (LVEF) of 40% or less (Table 1).

Table 1 Patient characteristics

	Patients ($n=926$)
Age (years)	79 (74–83)
Male sex [*n* (%)]	834 (90)
NYHA III–IV [*n* (%)]	247 (27)
History of HF [*n* (%)]	456 (49)
History of hypertension [*n* (%)]	670 (72)
History of diabetes [*n* (%)]	154 (17)
History of CAD [*n* (%)]	172 (19)
History of atrial fibrillation [*n* (%)]	582 (63)
COPD [*n* (%)]	111 (12)
CKD [*n* (%)]	394 (43)
eGFR (ml/min/1.73 m^2)	57 (45–72)
NT-proBNP (ng/l)	2908 (1439–4902)
NAC score 1/2/3 [*n* (%)]	278/246/110 (44/39/17)
LVEF (%)	53 (45–60)
LVEF ≤40% [*n* (%)]	153 (17)
Maximal wall thickness (mm)	18 (16–20)
Diuretic therapy [*n* (%)]	706 (76)
Loop diuretic [*n* (%)]	665 (72)
Daily furosemide equivalent dose (mg)	50 (25–75)
PM [*n* (%)]	142 (15)
ICD [*n* (%)]	47 (5)

Percentages were calculated out of patients with available data. CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary artery disease; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PM, pacemaker.

Compared with patients with incomplete data about neurohormonal drugs at the time of diagnosis and at last evaluation ($n=354$, 28%), our cohort had less often NYHA class III or IV symptoms, fewer comorbidities, lower NT-proBNP and higher LVEF values (Supplemental Table 1, http://links.lww.com/JCM/A760). Accordingly, patients in our cohort had a better survival than patients with incomplete data (log-rank 19.3, $P<0.001$).

Neurohormonal therapies at diagnosis

At the time of diagnosis of ATTRwt-CA, 60% of patients were on beta-blockers ($n=557$), 58% on ACEi/ARB/ARNI ($n=538$), and 35% on MRA ($n=326$). The specific drugs are reported in Supplemental Table 2, http://links.lww.com/JCM/A760. Three-quarters of patients ($n=706$, 76%) were on diuretics, most often on loop diuretics ($n=643$, 69%).

We first considered patients receiving each drug class. Patients on beta-blockers or MRA had more often NYHA class III or IV symptoms, a greater burden of comorbidities, a higher National Amyloidosis Centre (NAC) score, lower LVEF and higher NT-proBNP, and were more often on loop diuretics (Table 2). Conversely, patients on ACEi/ARB/ARNI did not display any significant difference from the other patients except for having more often a history of hypertension and diabetes (Table 2).

We then evaluated patients receiving different combination therapies (Supplemental Table 3, http://links.lww.com/JCM/A760). Fourteen percent of patients ($n=129$) were on beta-blockers, ACEi/ARB/ARNI and MRA. One quarter of patients ($n=219$, 24%) were on beta-blockers and ACEi/ARB/ARNI. Conversely, 13% of patients ($n=122$) were taking none of these drugs. Patients on triple therapy (beta-blockers, ACEi/ARB/ARNI and MRA) had a much higher prevalence of severe systolic dysfunction, were more often in NYHA class III or IV, and were much more often on loop diuretics than patients who were not on neurohormonal drugs (all $P<0.001$) (Table 3). Patients on beta-blockers and ACEi/ARB/ARNI had a greater burden of comorbidities, were more often in NYHA class III or IV, and were more often on loop diuretics than patients who were not on neurohormonal drugs (Table 3).

Patient outcomes, tafamidis and diuretic therapy

Patients were followed in dedicated outpatient clinics. The median follow-up duration was 2.5 years (interquartile range 1.6–3.8), with 355 deaths (38%). Among baseline characteristics, univariable predictors of all-cause mortality

Table 2 Patient characteristics according to the prescription of therapies at first evaluation

	Beta-blocker ($n = 926$)			ACEi/ARB/ARNI ($n = 926$)			MRA ($n = 926$)		
Variable	Yes ($n = 557$) (60%)	No ($n = 369$) (40%)	*P*	Yes ($n = 538$) (58%)	No ($n = 388$) (42%)	*P*	Yes ($n = 326$) (35%)	No ($n = 600$) (65%)	*P*
Age (years)	79 (74–83)	80 (74–83)	0.480	80 (74–83)	79 (74–83)	0.424	80 (74–83)	79 (74–83)	0.960
Male sex [*n* (%)]	497 (89)	337 (91)	0.304	477 (89)	357 (92)	0.094	292 (90)	543 (91)	0.705
NYHA III–IV [*n* (%)]	166 (30)	81 (22)	**0.009**	148 (28)	99 (26)	0.505	114 (35)	133 (22)	**<0.001**
History of HF [*n* (%)]	291 (51)	165 (45)	**0.029**	260 (48)	196 (51)	0.501	200 (61)	256 (43)	**<0.001**
History of hypertension [*n* (%)]	424 (76)	246 (67)	**0.002**	440 (82)	230 (59)	**<0.001**	240 (74)	431 (72)	0.535
History of diabetes [*n* (%)]	107 (19)	47 (13)	**0.010**	105 (20)	49 (13)	**0.006**	59 (18)	95 (16)	0.371
History of CAD [*n* (%)]	127 (23)	45 (12)	**<0.001**	104 (19)	68 (18)	0.448	65 (20)	108 (18)	0.463
History of atrial fibrillation [*n* (%)]	379 (68)	203 (55)	**<0.001**	343 (64)	239 (62)	0.532	225 (69)	357 (60)	**0.004**
COPD [*n* (%)]	74 (13)	37 (10)	0.140	61 (11)	50 (13)	0.470	47 (14)	64 (11)	0.092
CKD [*n* (%)]	250 (45)	144 (39)	0.086	228 (42)	166 (43)	0.891	156 (48)	238 (40)	**0.015**
eGFR (ml/min/1.73 m^2)	57 (44–72)	57 (46–72)	0.778	57 (44–71)	58 (46–73)	0.297	54 (44–69)	60 (46–75)	**0.002**
NT-proBNP (ng/l)	3320 (1871–5392)	2158 (727–4258)	**<0.001**	2,941 (1639–4954)	2,639 (1194–4757)	0.128	3559 (2010–5642)	2717 (1166–4526)	**<0.001**
NAC score 1/2/3 [*n* (%)]	152/173/73 (38/44/18)	126/73/37 (53/31/16)	**0.001**	165/152/70 (43/39/18)	114/94/40 (46/38/16)	0.643	73/104/44 (33/47/20)	206/142/66 (50/34/16)	**<0.001**
LVEF (%)	52 (45–60)	55 (47–60)	**0.002**	53 (45–60)	53 (45–60)	0.737	50 (40–57)	55 (47–60)	**<0.001**
LVEF ≤40% [*n* (%)]	103 (19)	48 (13)	**0.022**	86 (16)	65 (17)	0.749	83 (26)	68 (11)	**<0.001**
Maximal wall thickness (mm)	18 (16–20)	18 (15–19)	0.361	18 (16–20)	18 (16–19)	0.610	18 (16–20)	18 (16–19)	0.309
Diuretic therapy [*n* (%)]	449 (81)	257 (70)	**<0.001**	421 (78)	285 (74)	0.072	309 (95)	397 (66)	**<0.001**
Loop diuretic [*n* (%)]	423 (76)	242 (66)	**0.002**	388 (72)	277 (71)	0.601	307 (94)	358 (60)	**<0.001**
Daily loop diuretic equivalent dose (mg)	50 (25–75)	50 (25–75)	0.642	50 (25–66)	50 (25–75)	0.060	50 (25–75)	25 (25–50)	**<0.001**
PM [*n* (%)]	80 (14)	62 (17)	0.302	82 (15)	60 (16)	0.920	51 (16)	91 (15)	0.839
ICD [*n* (%)]	32 (6)	15 (4)	0.216	29 (5)	18 (15)	0.741	32 (10)	15 (3)	**<0.001**

Percentages were calculated out of patients with available data. Significant *P* values are reported in bold. CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary artery disease; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PM, pacemaker.

Table 3 Baseline characteristics of patients on full or partial neurohormonal antagonism versus those not on neurohormonal drugs

	Triple therapy (beta-blocker + ACEi/ARB/ARNI+MRA) ($n=129$)	Dual therapy (beta-blocker + ACEi/ARB/ARNI) ($n=219$)	No drug ($n=122$)	P^a	P^b
Age (years)	80 (64–83)	79 (74–83)	79 (73–82)	0.943	0.999
Male sex [*n* (%)]	113 (88)	194 (89)	113 (93)	0.184	0.233
NYHA III–IV [*n* (%)]	48 (37)	53 (24)	18 (15)	**<0.001**	**0.039**
History of HF [*n* (%)]	84 (65)	92 (42)	50 (41)	**<0.001**	0.578
History of hypertension [*n* (%)]	103 (80)	183 (84)	61 (50)	**<0.001**	**<0.001**
History of diabetes [*n* (%)]	35 (27)	41 (19)	14 (12)	**0.002**	0.081
History of CAD [*n* (%)]	31 (24)	48 (22)	14 (12)	**0.010**	**0.017**
History of atrial fibrillation [*n* (%)]	87 (67)	143 (65)	50 (41)	**<0.001**	**<0.001**
COPD [*n* (%)]	17 (13)	23 (11)	9 (7)	0.132	0.343
CKD [*n* (%)]	63 (49)	85 (39)	43 (35)	**0.029**	0.514
eGFR (ml/min/1.73 m^2)	53 (43–70)	60 (46–74)	60 (46–77)	0.072	0.950
NT-proBNP (ng/l)	3990 (2257–5809)	2917 (1793–4778)	1670 (556–3317)	**0.002**	**0.047**
NAC score 1/2/3 [*n* (%)]	29/42/21 (32/46/23)	67/68/24 (42/43/15)	47/15/9 (66/21/13)	<0.001	0.854
LVEF (%)	50 (40–56)	55 (47–60)	54 (47–62)	<0.001	0.862
LVEF ≤40% [*n* (%)]	37 (29)	22 (10)	14 (12)	<0.001	0.733
Maximal wall thickness (mm)	17 (15–20)	18 (16–20)	18 (15–19)	0.921	0.363
Diuretic therapy [*n* (%)]	122 (95)	154 (70)	59 (48)	<0.001	<0.001
Loop diuretic [*n* (%)]	121 (94)	134 (61)	57 (47)	<0.001	0.007
Daily loop diuretic equivalent dose (mg)	50 (25–75)	25 (25–50)	50 (25–75)	0.398	0.056
PM [*n* (%)]	15 (12)	33 (15)	17 (14)	0.584	0.777
ICD [*n* (%)]	13 (10)	7 (3)	3 (3)	0.014	0.699

CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary artery disease; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PM, pacemaker. [a]Beta-blocker, ACEi/ARB/ARNI, MRA vs. no drug. [b]Beta-blocker and ACEi/ARB/ARNI.

included age, NYHA class III–IV, history of diabetes, atrial fibrillation or chronic kidney disease, NT-proBNP, NAC score and LVEF of 40% or less (Supplemental Table 4, http://links.lww.com/JCM/A760). The cause of death was adjudicated as cardiovascular in 165 patients (46%) and noncardiovascular in 36 (10%), while it was not adjudicated in 154 (43%).

During the same follow-up period, 239 patients (26%) started tafamidis treatment. In the same period, 142 (15%) started a diuretic and 380 (41%) increased the diuretic dose, while only 31 (3%) stopped a diuretic and 60 (6%) reduced the diuretic dose.

Neurohormonal therapies at diagnosis and patient outcomes

We investigated the outcomes of patients receiving single drug classes or drug combinations. Despite several indicators of a more advanced disease status (Table 2), patients on beta-blockers had no shorter survival than those not on beta-blockers, and patients on ACEi/ARB/ARNI did not have a different survival than those not taking these drugs. This was demonstrated through univariable Cox regression analysis ($P=0.577$ and $P=0.977$) and confirmed through Kaplan–Meyer analysis, both in the whole cohort (Fig. 1) and in several patient subgroups, namely: NYHA class I–II (beta-blockers, $P=0.318$; ACEi/ARB/ARNI, $P=0.645$) or III–IV ($P=0.081$ and $P=0.644$, respectively), LVEF 40% or less ($P=0.442$ and $P=0.586$, respectively) or greater than 40% ($P=0.485$ and $P=0.988$, respectively), tafamidis started during follow-up ($P=0.737$ and $P=0.230$, respectively) or never prescribed ($P=0.943$ and $P=0.730$, respectively), and diuretics started/uptitrated ($P=0.535$ and $P=0.241$, respectively) or stopped/reduced ($P=0.892$ and $P=0.056$, respectively).

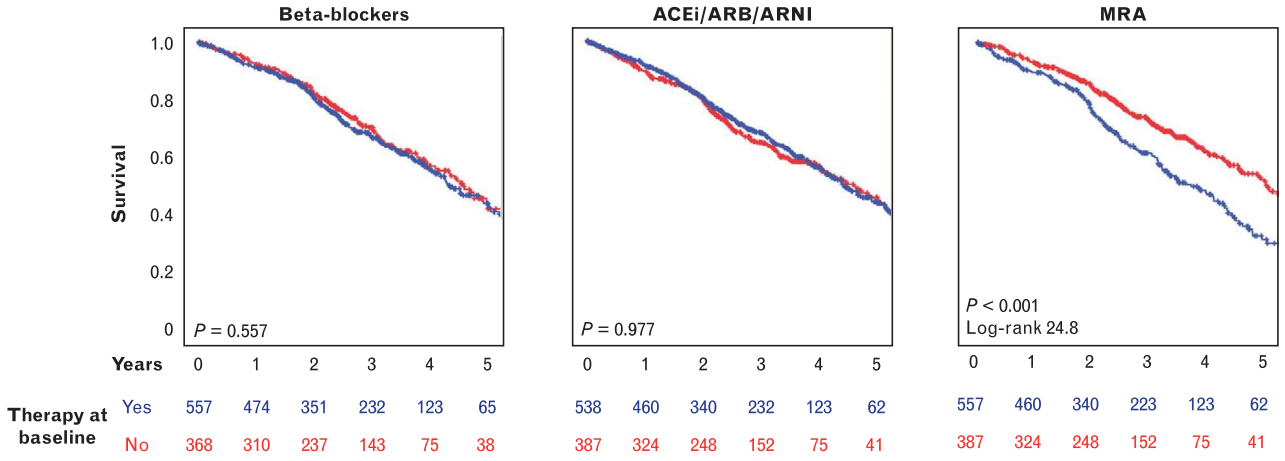
Contrary to patients on beta-blockers and ACEi/ARB/ARNI, patients on MRA at diagnosis had a shorter survival than the other patients (Fig. 1). Nonetheless, MRA therapy did not independently predict outcomes after accounting for baseline characteristics (Supplemental Table 5, http://links.lww.com/JCM/A760).

Patients receiving both beta-blockers and ACEi/ARB/ARNI at diagnosis had a similar survival to those not receiving any neurohormonal drug ($P=0.575$). Conversely, patients on beta-blockers, ACEi/ARB/ARNI and MRA had a shorter survival driven by the worse outcome for patients on MRA (log-rank 15.0, $P<0.001$).

Treatment changes during follow-up: beta-blockers

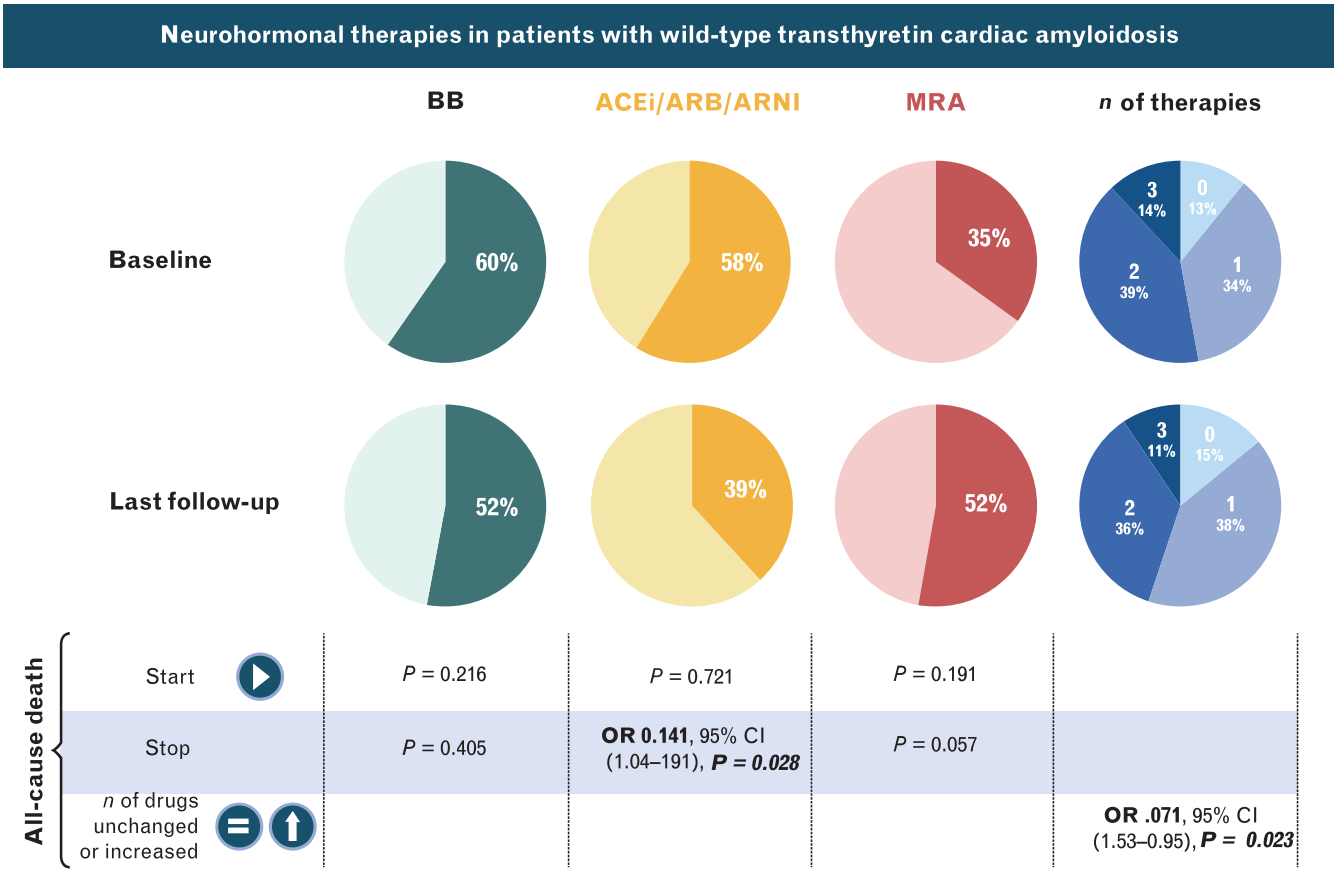
Beta-blockers were discontinued in 160 patients (17%) and started in 87 patients (9%) during follow-up (Fig. 2).

Fig. 1



Patient survival according to baseline therapy with beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor neprilysin inhibitors or mineralocorticoid receptor antagonists.

Fig. 2



Neurohormonal drugs and survival. ACEi/ARB/ARNI, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor/neprilysin inhibitor; BB, beta-blockers; CI, confidence interval; MRA, mineralocorticoid receptor antagonist; OR, odds ratio.

Reasons for discontinuation included symptomatic bradycardia in 34 (21%), symptomatic hypotension in 32 (20%) and 'new or worsening atrioventricular block' in 21 (13%). The other reasons reported for discontinuation were 'advanced diastolic dysfunction' in 13 (8%) and right heart failure in 14 (9%); the reason was not specified in 46 cases (29%). Few predictors of beta-blocker discontinuation emerged, and no predictors of discontinuation because of compelling reasons (symptomatic bradycardia or hypotension, new or worsening atrioventricular block; Supplemental Table 6, http://links.lww.com/JCM/A760).

Bisoprolol was the most commonly prescribed drug at first and last evaluation (68 and 74%, respectively; Supplemental Table 2, http://links.lww.com/JCM/A760). When reporting the doses of other beta-blockers as the corresponding bisoprolol doses (Supplemental Table 7, http://links.lww.com/JCM/A760), the 'bisoprolol equivalent doses' were 2.5 mg (2.5–5) at diagnosis and 2.5 mg (1.3–5) at follow-up end. Beta-blockers were stopped or downtitrated in 267 (50%), and started, unchanged or uptitrated in 276 (50%).

At logistic regression analysis, beta-blocker discontinuation ($P = 0.405$), discontinuation or downtitration ($P = 0.562$), start ($P = 0.216$), or start, continuation or uptitration ($P = 0.272$) were not univariable predictors of all-cause mortality (P values of 0.405, 0.562, 0.216 and 0.272, respectively).

Treatment changes during follow-up: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor neprilysin inhibitors

ACEi/ARB/ARNI were stopped in 222 cases (24%) and started in 42 patients (5%) during follow-up (Graphical Abstract). Reasons for discontinuation included symptomatic hypotension ($n = 135$, 61%), worsening renal function ($n = 37$, 17%), or other, unspecified reasons ($n = 50$, 23%). History of heart failure, diabetes, chronic kidney disease (CKD) and maximal LV wall thickness predicted drug discontinuation (Supplemental Table 8, http://links.lww.com/JCM/A760). ACEi/ARB/ARNI discontinuation was associated with a higher risk of all-cause mortality [odds ratio (OR) 1.41, 95% confidence interval (CI) 1.04–1.91, $P = 0.028$], although this association was not confirmed when adjusting for baseline characteristics (using the same model as in Supplemental Table 5, http://links.lww.com/JCM/A760; $P = 0.788$). Conversely, ACEi/ARB/ARNI start did not predict all-cause mortality ($P = 0.721$).

Ramipril was the drug most often prescribed at diagnosis and last follow-up (45 and 41%, respectively), with a large number of other drugs that did not allow the establishment of reliable drug equivalent doses (Supplemental Table 2, http://links.lww.com/JCM/A760).

Treatment changes during follow-up: mineralocorticoid receptor antagonists

Details about the MRA prescribed are provided in Supplemental Table 2, http://links.lww.com/JCM/A760. MRA were started in 216 cases (23%) and stopped in 60 (7%) (Graphical Abstract). Neither the start ($P = 0.191$) nor the discontinuation of MRA ($P = 0.057$) was associated with all-cause mortality. When expressing eplerenone doses as equivalent canrenone doses, MRA uptitration ($P = 0.806$), start or uptitration ($P = 0.132$), reduction ($P = 0.957$), or reduction or discontinuation ($P = 0.787$) displayed no association with mortality.

Treatment changes and mortality

Details about changes in the single drug classes are provided in Supplemental Table 9, http://links.lww.com/JCM/A760. The number of neurohormonal drugs remained unchanged in 500 patients (54%), decreased in 248 (27%) and increased in 178 (19%). A number of neurohormonal drugs either unchanged or increased were associated with a lower risk of mortality (OR 0.71, 95% CI 0.53–0.95, $P = 0.023$). Patients starting the beta-blocker plus ACEi/ARB/ARNI combination ($n = 24$) had an even lower risk of death than the remaining patients (OR 0.22, 95% CI 0.07–0.75, $P = 0.016$).

Discussion

In a multicenter nationwide cohort of patients with ATTRwt-CA, those receiving beta-blockers or ACEi/ARB/ARNI at the time of diagnosis did not have a higher mortality than those not receiving neurohormonal drugs. Beta-blockers were also discontinued less often than ACEi/ARB/ARNI. The discontinuation of beta-blockers or ACEi/ARB/ARNI, currently recommended by an ESC position statement,[6] was not associated with improved outcomes. On the contrary, an unchanged or even potentiated neurohormonal heart failure treatment was associated with better survival (Graphical Abstract).

Caution regarding neurohormonal antagonists in cardiac amyloidosis arises from concerns about hypotension and conduction disease, and the reliance on heart rate to preserve cardiac output in restrictive physiology, whereby beta-blockers or ACEi/ARB/ARNI could exacerbate hemodynamic instability.[11] Nonetheless, contemporary practice demonstrates meaningful use: approximately 30% of patients in ATTR-ACT were on beta-blockers at baseline[12] and 33% in a multicenter study.[13] Moreover, in a cohort of 99 consecutive cardiac amyloidosis patients (67% ATTRwt-CA), most tolerated neurohormonal therapy (e.

g. 87% received beta-blockers) when initiated at low doses with slow up-titration and close monitoring.[14]

Dosing patterns in our study reflect this pragmatic approach. Although neurohormonal agents were generally prescribed at below the heart failure with reduced ejection fraction (HFrEF) guideline target doses,[15] their use and cautious up-titration were more liberal than recommended by the European consensus for ATTR-CA, which often advocates discontinuation or avoidance.[6] Clinicians appeared to titrate toward the highest individually tolerated dose while balancing hypotension, conduction disease and frailty, even though our retrospective design cannot confirm that the maximum tolerated doses were systematically achieved. These observations caution against directly transposing a 'treat-to-target' HFrEF strategy to ATTRwt-CA, where pathophysiology and tolerability differ and aggressive up-titration may be unsafe. Within these tolerance-limited ranges, baseline beta-blocker or ACEi/ARB/ARNI use was not associated with excess mortality. Initiation or up-titration of beta-blockers was not linked to higher rates of hypotension, fatigue, syncope, symptomatic bradycardia, pacemaker implantation or heart failure hospitalization versus no beta-blocker use.[14] Nevertheless, beta-blocker discontinuation remained common (19% in a prior cohort[13] and 17% in this cohort), frequently due to symptomatic bradycardia (21%), hypotension (20%) and atrioventricular conduction disturbances (13%).

Beyond tolerability, there is a pathophysiological rationale for neurohormonal antagonism in ATTRwt-CA. Activation of the sympathetic and renin–angiotensin–aldosterone systems has been reported in this population.[2] Chronic adrenergic stimulation and angiotensin-II/aldosterone signaling promote hypertrophy and fibrosis and shorten diastole, potentially worsening filling and myocardial perfusion. MRAs possess antifibrotic properties that could be particularly relevant given the myocardial fibrosis observed in CA.[3] Whether benefits demonstrated primarily in HFrEF translate to ATTRwt-CA remains uncertain and demands randomized evaluation. Observational data are mixed: a study of 309 patients (66% ATTRwt-CA) found no adjusted survival benefit of baseline beta-blocker, ACE/ARB or MRA therapy and reported lower mortality with beta-blocker discontinuation during follow-up (no LVEF stratification),[4] whereas the UK NAC analysis ($n = 2371$; 78% ATTRwt-CA) associated MRAs with lower mortality overall and in LVEF of greater than 40% and beta-blockers with lower mortality in LVEF of 40% or less.[5]

In our cohort, neurohormonal therapy was common at diagnosis (60% on beta-blockers, 58% on ACEi/ARB/ARNI and 35% on MRAs) with doses generally below the guideline targets.[15] During follow-up, ACEi/ARB/ARNI were discontinued more often than were beta-blockers, plausibly reflecting symptomatic hypotension or renal effects. Across prespecified subgroups, including LVEF of 40% or less, baseline beta-blocker or ACEi/ARB/ARNI use was not associated with shorter survival. Patients on MRA were sicker at baseline but MRA therapy was not independently harmful after adjustment, consistently with confounding by indication and external reports of potential benefit.[5] Over time, changes in beta-blocker therapy (discontinuation/downtitration or initiation/uptitration) were not associated with all-cause mortality; discontinuation of ACEi/ARB/ARNI was associated with increased mortality; and MRA initiation, discontinuation, or dose changes were not linked to mortality. Notably, maintaining or increasing the total number of neurohormonal agents correlated with better survival. While worse outcomes among patients stopping therapy may partly reflect intolerance in frailer individuals with more advanced disease, our findings do not suggest a harmful association between neurohormonal therapy and mortality. Accordingly, neurohormonal agents, including MRA, should not be considered *a priori* contraindicated in ATTRwt-CA, even as definitive efficacy remains to be established.

Patients excluded from the original cohort because therapy data were missing had more advanced disease and worse survival than those analyzed, indicating a nonrandom loss of sicker individuals. This selective availability likely introduced survivorship bias: the analytic cohort over-represents patients who survived long enough and were stable enough to have therapy recorded. Such bias can dilute between-group differences and obscure intolerance-related signals, potentially underestimating adverse associations of discontinuation or high-dose therapy and limiting generalizability to frailer patients. The observed association between maintenance/intensification of neurohormonal therapy and better survival may, therefore, partly reflect treatment selection in those who could tolerate therapy. Accordingly, our findings should be interpreted as associations in a relatively healthier, better documented subset and should not be taken to imply safety or efficacy in patients with more advanced disease or pronounced autonomic dysfunction.

During follow-up, 26% initiated tafamidis and 41% underwent diuretic intensification. Both interventions are closely linked to prognosis and to clinical decisions about maintaining or discontinuing neurohormonal drugs. Because they were not modeled as time-varying covariates, our estimates are vulnerable to confounding by indication and immortal-time bias, potentially exaggerating the apparent benefit of maintenance/intensification or the harm of discontinuation. For example, diuretic up-titration often accompanies hypotension or renal dysfunction that simultaneously prompts ACEi/ARB/ARNI withdrawal, while tafamidis initiation may cluster in patients selected for anticipated benefit or,

conversely, in those with more active disease; either pattern can distort observed associations. Future analyses should treat tafamidis initiation and diuretic changes as time-dependent variables and consider causal designs to better separate drug-related effects from signals of disease progression and co-management.

Several other limitations need to be acknowledged. First, the retrospective, nonrandomized design precludes causal inference on treatment efficacy and is susceptible to confounding by indication and selection/survivorship bias. In particular, patients excluded because of missing therapy data had more advanced disease and poorer survival than those analyzed, indicating systematic differences between the groups; therefore, all comparisons should be interpreted as associations rather than effects. Although we adjusted for available covariates and explored multiple subgroups, residual confounding is likely, some drug-defined strata were relatively small, and the limited baseline variable set constrained more robust approaches (e.g. propensity methods). Prospective, randomized studies with standardized dosing and time-updated covariates are needed to determine efficacy. Second, the timing of treatment changes was not available. To overcome this, we searched for associations between treatment at diagnosis and treatment changes during follow-up (stopped, continued until last follow-up, increased number of drugs, etc.) and survival, similarly to previous studies.[4,5] Third, the baseline variable set was limited and did not support robust propensity-based adjustment (e.g. matching or weighting). Several covariates that plausibly influence both treatment selection and outcomes (resting blood pressure and heart rate, indices of frailty and clinical surrogates of autonomic dysfunction) were not consistently collected, and time-updated vital signs were unavailable, leaving residual and unmeasured confounding. Fourth, the study population was mostly enrolled before the publication of the 2021 ESC position statement,[6] and therefore not managed according to these recommendations. On the other hand, great caution with neurohormonal therapies had already been recommended, for example, by an authoritative review paper on the management of ATTR-CA.[9] Fifth, we did not distinguish between drugs recommended by heart failure guidelines and other drugs (e.g. bisoprolol, carvedilol, metoprolol or nebivolol versus atenolol, sotalol, or propranolol or spironolactone or eplerenone versus canrenone/canrenoate).[15] Nonetheless, evaluating drugs without demonstrated prognostic benefits in heart failure is expected to potentially dilute the efficacy of neurohormonal drugs rather than enhance it. Finally, information on sodium-glucose cotransporter 2 inhibitors (SGLT2i) was not collected, although these patients were managed before the preliminary evidence about SGLT2i efficacy in ATTR-CA,[16] and in a country where SGLT2i cannot be prescribed to patients diagnosed with ATTR-CA.

In conclusion, patients with ATTRwt-CA on beta-blockers or ACEi/ARB/ARNI at diagnosis did not have a shorter survival. Beta-blockers were discontinued less often than were ACEi/ARB/ARNI. There was no sign of better outcomes in patients discontinuing these therapies, or worse outcomes in those starting them. These findings may raise questions about the current recommendations to discontinue or avoid these drugs. Further prospective studies and randomized trials are needed to establish clearer guidelines on neurohormonal therapy in ATTRwt-CA.

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Conflicts of interest

Outside the submitted work: P.M. received honoraria and advisory fees from Janssen-Cilag and Pfizer. A.G.C. received adviser fees from Pfizer. A.C. received a research grant from Pfizer. G.S. received fees from Biotronik, Boston Scientific, Astra Zeneca and Novartis. M.M. received fees from Pfizer, Novartis and Vifor Pharma, and an unrestricted general research grant on amyloidosis by Pfizer, without any control on intellectual contents. B.M. received adviser fees from Pfizer and Alnylam. E.B. received adviser fees from Amicus, Sanofi Genzyme and Takeda. G.P. received honoraria from Alexion, Argobio, Janssen and Protego, The Binding Site, Pfizer, Prothena, Sebia, Siemens and research fundings from Gate bioscience and The Binding Site. M.C. received speaker and adviser fees from Akcea Therapeutics, Alnylam, Astrazeneca, Boehringer Ingelheim, Boston Scientific, Novartis, Pfizer, Sanofi e Sanofi Genzyme and two investigator-initiated grants from Pfizer.

References

1 Griffin JM, Rosenblum H, Maurer MS. Pathophysiology and therapeutic approaches to cardiac amyloidosis. *Circ Res* 2021; **128**:1554–1575.
2 Vergaro G, Aimo A, Campora A, *et al.* Patients with cardiac amyloidosis have a greater neurohormonal activation than those with nonamyloidotic heart failure. *Amyloid* 2021; **28**:252–258.
3 Pucci A, Aimo A, Musetti V, *et al.* Amyloid deposits and fibrosis on left ventricular endomyocardial biopsy correlate with extracellular volume in cardiac amyloidosis. *J Am Heart Assoc* 2021; **10**:e020358.
4 Cheng RK, Vasbinder A, Levy WC, *et al.* Lack of association between neurohormonal blockade and survival in transthyretin cardiac amyloidosis. *J Am Heart Assoc* 2021; **10**:e022859.
5 Ioannou A, Massa P, Patel RK, *et al.* Conventional heart failure therapy in cardiac ATTR amyloidosis. *Eur Heart J* 2023; **44**:2893–2907.
6 Garcia-Pavia P, Rapezzi C, Adler Y, *et al.* Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2021; **42**:1554–1568.
7 Tini G, Milani P, Zampieri M, *et al.* Diagnostic pathways to wild-type transthyretin amyloid cardiomyopathy: a multicentre network study. *Eur J Heart Fail* 2023; **25**:845–853.
8 Gillmore JD, Maurer MS, Falk RH, *et al.* Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation* 2016; **133**:2404–2412.
9 Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol* 2019; **73**:2872–2891.
10 Aimo A, Rapezzi C, Vergaro G, *et al.* Management of complications of cardiac amyloidosis: 10 questions and answers. *Eur J Prev Cardiol* 2021; **28**:1000–1005.
11 Rapezzi C, Aimo A, Barison A, *et al.* Restrictive cardiomyopathy: definition and diagnosis. *Eur Heart J* 2022; **43**:4679–4693.

12 Maurer MS, Schwartz JH, Gundapaneni B, *et al.* ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 2018; **379**:1007–1016.
13 Tini G, Cappelli F, Biagini E, *et al.* Current patterns of beta-blocker prescription in cardiac amyloidosis: an Italian nationwide survey. *ESC Heart Fail* 2021; **8**:3369–3374.
14 Aimo A, Vergaro G, Castiglione V, Rapezzi C, Emdin M. Safety and tolerability of neurohormonal antagonism in cardiac amyloidosis. *Eur J Intern Med* 2020; **80**:66–72.
15 McDonagh TA, Metra M, *et al.* Authors/Task Force Members. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022; **24**:4–131.
16 Porcari A, Cappelli F, Nitsche C, *et al.* SGLT2 inhibitor therapy in patients with transthyretin amyloid cardiomyopathy. *J Am Coll Cardiol* 2024; **83**: 2411–2422.

GRAPHICAL ABSTRACT