

## Conventional heart failure therapy in cardiac ATTR amyloidosis

Adam Ioannou MBBS BSc<sup>\*1</sup>, Paolo Massa MD<sup>\*1</sup>, Rishi K Patel MBBS BSc<sup>1</sup>, Yousuf Razvi MBChB BSc<sup>1</sup>, Aldostefano Porcari MD<sup>1,2</sup>, Muhammad U Rauf MBBS<sup>1</sup>, Anita Jiang MA MBBS<sup>1</sup>, Giacomo Cabras<sup>1</sup>, Stefano Filisetti<sup>3</sup>, Roos E Bolhuis BSc<sup>1</sup>, Francesco Bandera MD PhD<sup>3</sup>, Lucia Venneri MD PhD<sup>1</sup>, Ana Martinez-Naharro PhD<sup>1</sup>, Steven Law<sup>1</sup>, Tushar Kotecha PhD<sup>1</sup>, Ruta Virsinskaite MD<sup>1</sup>, Daniel S Knight MD<sup>1</sup>, Michele Emdin MD PhD<sup>4,5</sup>, Aviva Petrie MSc<sup>6</sup>, Helen Lachmann MD<sup>1</sup>, Ashutosh Wechelakar MD<sup>1</sup>, Mark Petrie<sup>7</sup>, Alun Hughes<sup>6</sup>, Nick Freemantle<sup>6</sup>, Philip N Hawkins MD PhD<sup>1</sup>, Carol Whelan MD<sup>1</sup>, John JV McMurray MD<sup>7</sup>, Julian D Gillmore MD PhD<sup>1\*\*</sup>, Marianna Fontana MD PhD<sup>1\*\*</sup>

\*Joint first authors

\*\*Joint last authors

1. National Amyloidosis Centre, University College London, Royal Free Campus, Rowland Hill Street, London, NW3 2PF, UK
2. Center for Diagnosis and Treatment of Cardiomyopathies, Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, Italy
3. Cardiology University Department, IRCCS Policlinico San Donato, Milan, Italy
4. Health Science Interdisciplinary Center, Scuola Superiore Sant'Anna, Pisa, Italy
5. Fondazione Toscana Gabriele Monasterio, Pisa, Italy
6. University College London, London, UK
7. University of Glasgow, Glasgow, UK

### Address for Correspondence

Professor Marianna Fontana MD, PhD  
National Amyloidosis Centre, University College London, Royal Free Hospital  
Rowland Hill Street  
London, NW3 2PF, UK.  
E-mail: m.fontana@ucl.ac.uk  
Phone No: +44 20 7433 2764  
Fax No: +44 20 7433 2803

## 1 Abstract

2 **Background and Aims:** The aims of this study were to assess prescription patterns, dosages,  
3 discontinuation rates and association with prognosis of conventional heart failure (HF)  
4 medications in patients with transthyretin cardiac amyloidosis (ATTR-CA).

5 **Methods:** A retrospective analysis of all consecutive patients diagnosed with ATTR-CA at the  
6 National Amyloidosis Centre between 2000-2022 identified 2371 patients with ATTR-CA.

7 **Results:** Prescription of HF medications was greater among patients with a more severe cardiac  
8 phenotype, comprising beta-blockers in 55.4%, angiotensin-converting enzyme inhibitors  
9 (ACEi)/angiotensin-II receptor blockers (ARB) in 57.4%, and mineralocorticoid receptor  
10 antagonists (MRAs) in 39.0% of cases. During a median follow-up of 27.8 months (IQR 10.6-  
11 51.3), 21.7% had beta-blockers discontinued, and 32.9% had ACEi/ARB discontinued. In  
12 contrast, only 7.5% had MRAs discontinued. Propensity score-matched analysis demonstrated  
13 that treatment with MRAs was independently associated with a reduced risk of mortality in the  
14 overall population (HR 0.77 [95% CI 0.66-0.89],  $P < 0.001$ ) and in a pre-specified subgroup of  
15 patients with a left ventricular ejection fraction (LVEF)  $> 40\%$  (HR 0.75 [95% CI 0.63-0.90],  
16  $P = 0.002$ ); and treatment with low-dose beta-blockers was independently associated with a  
17 reduced risk of mortality in a pre-specified subgroup of patients with a LVEF  $\leq 40\%$  (HR 0.61  
18 [95% CI 0.45-0.83],  $P = 0.002$ ). No convincing differences were found for treatment with  
19 ACEi/ARBs.

20 **Conclusions:** Conventional HF medications are currently not widely prescribed in ATTR-CA,  
21 and those that received medication had more severe cardiac disease. Beta-blockers and  
22 ACEi/ARBs were often discontinued, but low-dose beta-blockers were associated with reduced  
23 risk of mortality in patients with a LVEF  $\leq 40\%$ . In contrast, MRAs were rarely discontinued and

1 were associated with reduced risk of mortality in the overall population; but these findings  
2 require confirmation in prospective randomized controlled trials.

3

4 **Key words:** Cardiac ATTR amyloidosis; Heart failure; Heart failure medications; Beta-blockers;  
5 Mineralocorticoid receptor antagonists.

6

## 7 **Introduction**

8 Transthyretin cardiac amyloidosis (ATTR-CA) causes progressive, fatal, heart failure (HF), due  
9 to misfolding of transthyretin (TTR), forming insoluble amyloid fibrils, which are deposited  
10 within the myocardial extracellular space.<sup>1,2</sup> Until recently, ATTR-CA was considered a rare,  
11 untreatable disease. However, improvements in diagnostics coupled with emerging high-cost  
12 therapies, are challenging these long-held beliefs. ATTR-CA is far more common than  
13 previously suspected, and there is potential for successful therapeutic intervention.<sup>3</sup>

14 The only drug proven to be associated with prognostic benefit in ATTR-CA is tafamidis, which  
15 is a highly specific drug that targets the circulating TTR protein and stabilises the TTR tetramer  
16 to prevent dissociation into amyloidogenic monomers that deposit in the myocardium, causing an  
17 infiltrative and restrictive cardiomyopathy. Tafamidis was shown in a phase 3 placebo-controlled  
18 trial (ATTR-ACT) to reduce the combined primary endpoint of cardiovascular hospitalisations  
19 and mortality.<sup>4</sup> However, unfortunately, the high cost associated with tafamidis has resulted in  
20 restricted use, and tafamidis has not been approved for the treatment of ATTR-CA in many  
21 countries.<sup>5</sup>

22 At present, it is unknown whether conventional HF medications that have substantial benefits in  
23 patients with HF of other aetiologies may also benefit those with ATTR-CA, as patients with

1 known ATTR-CA have been excluded from previous HF trials.<sup>6-13</sup> Hence, the value of  
2 conventional HF medications in patients with ATTR-CA is still debated. Small-scale studies  
3 have yielded contrasting results, with some suggesting that low doses of conventional HF  
4 medications are well tolerated,<sup>14,15</sup> while others reported that not only are these medications  
5 poorly tolerated, but they may result in worse outcomes.<sup>16,17</sup> The lack of large-scale clinical trials  
6 has resulted in a significant knowledge gap, although a position statement from the ESC working  
7 group on myocardial and pericardial diseases regarding HF medications in ATTR-CA  
8 recommends stopping beta-blockers, and avoiding angiotensin-converting enzyme inhibitors  
9 (ACEi) and angiotensin-II receptor blockers (ARBs), and are silent about mineralocorticoid  
10 receptor antagonists (MRAs).<sup>18</sup>

11 The aims of this study were to: (i) assess the prescription pattern of conventional HF medications  
12 in patients with ATTR-CA; (ii) assess the dosages and discontinuation rates of HF medications  
13 in patients with ATTR-CA; and (iii) assess the association between treatment with HF  
14 medications and survival in patients with ATTR-CA.

## 16 **Methods**

17 Consecutive patients in whom a diagnosis of ATTR-CA was confirmed at the National  
18 Amyloidosis Centre (NAC), between January 2000 and September 2022, were included. Patients  
19 with evidence of ATTR-polyneuropathy were excluded, as many have autonomic neuropathy,  
20 and are not prescribed HF medications due to concomitant postural hypotension.

21 Between 2000-2005 the diagnosis of ATTR-CA was established based on HF symptoms together  
22 with a characteristic CA echocardiogram and either direct endomyocardial biopsy proof of  
23 ATTR-amyloid or ATTR-amyloid in an extra-cardiac biopsy. From 2006 onwards cardiac

1 magnetic resonance was added to the assessment if there was diagnostic doubt. From 2010  
2 onwards, <sup>99m</sup>Tc-labelled 3,3-diphosphono-1,2-propanodicarboxylic acid (<sup>99m</sup>Tc-DPD)  
3 scintigraphy was utilised, and diagnosis established based on ATTR-amyloid in an extra-cardiac  
4 biopsy with cardiac uptake on <sup>99m</sup>Tc-DPD scintigraphy; or grade 2-3 cardiac uptake on <sup>99m</sup>Tc-  
5 DPD scintigraphy in the absence of biochemical evidence of a plasma cell dyscrasia. All patients  
6 underwent genetic sequencing of the *TTR* gene and provided written consent for their data to be  
7 retrospectively analysed and published, in line with the Declaration of Helsinki and approval  
8 from the Royal Free Hospital ethics committee (REC 21/PR/0620).

9 All patients are enrolled into a protocolised follow-up program that consists of 6-12 monthly  
10 consultations. Data regarding whether HF medications were initiated, continued or stopped and  
11 medication dosages were all recorded. Medication classes were defined based on the ESC HF  
12 guidelines and comprised beta-blockers, ACEi/ARBs and MRAs. Target doses from the  
13 guidelines enabled comparisons by converting the daily dose to a percentage of the target dose.  
14 Medication classes were recorded regardless of whether the specific drug had been used in  
15 previous HF trials.<sup>19</sup> Management decisions utilised a combined decision-making process  
16 involving local clinicians and the NAC team. Considering the knowledge gap, decisions  
17 concerning the initiation or discontinuation of HF medications were made following each clinical  
18 assessment on a case-by-case basis.

## 19 20 **Statistical analysis**

21 Statistical analysis was performed using Stata (StataCorp. 2021. Stata Statistical Software:  
22 Release 17. College Station, TX: StataCorp LLC). All continuous variables were tested for  
23 normality (Shapiro-Wilk test) and presented as mean±standard deviation if the distribution was

1 normal or median (interquartile range, IQR) otherwise, other than N-terminal pro-B-type  
2 natriuretic peptide (NT-proBNP) which was log-transformed for bivariate testing. The  
3 independent samples *t*-test was used to compare means if the data were normally distributed in  
4 each treatment group, or its non-parametric equivalent was used to compare the distributions of  
5 the two treatment groups. One-way analysis of variance (ANOVA) if the data were normally  
6 distributed in each treatment group was used to compare means in more than two groups; or its  
7 non-parametric equivalent was used to compare the distributions of multiple groups. A  
8 significant result was followed by post-hoc Bonferroni corrected pairwise comparisons to  
9 establish where differences lay. Categorical data are presented as absolute numbers and  
10 frequencies (%) and compared using the chi-square test.

11 All mortality data were obtained via the UK Office of National Statistics, which is the formal  
12 government registry for all deaths throughout the UK. The mortality endpoint was defined as  
13 time to death from date of diagnosis for all deceased patients and time to censor date (25<sup>th</sup>  
14 October 2022) from date of diagnosis among the remainder. Follow-up was restricted to  $\leq 60$ -  
15 months, after which patients were censored due to the majority of events occurring in the first 60  
16 months, and a low number of patients at risk after 60 months. To account for amyloid-specific  
17 disease-modifying therapy or clinical trials, patients were censored at their start date.

18 Survival was evaluated using Cox proportional hazards regression analysis, providing estimated  
19 hazard ratios (HRs) with 95% confidence intervals (CIs). The proportional hazards assumption  
20 was checked and confirmed using weighted Schoenfeld residuals. With regard to the survival  
21 analysis, patients were classed as being treated with HF medications if they were treated  
22 continuously for at least 6-months following their initial assessment, or an event occurred within  
23 the first 6 months whilst patients were continuously treated. If the medication was stopped

1 during the first 6 months, then patients were classed as not taking the medication. The initial  
2 survival analysis was performed on the whole study population using a multivariable Cox  
3 proportional hazards regression adjusting for covariates selected a priori based on clinical  
4 relevance, association with HF medication treatment and association with survival (age, sex,  
5 ischaemic heart disease [IHD], diabetes mellitus, hypertension, atrial fibrillation, NAC disease  
6 stage, wild-type or hereditary ATTR-CA, interventricular septal thickness in diastole [IVSd],  
7 longitudinal strain, beta-blocker, ACEi/ARBs and MRAs).

8 Propensity score (PS) matching is widely used to reduce confounding biases in observational  
9 studies. The PS is a score between 0 and 1 that reflects the likelihood of the patient receiving one  
10 of the HF medications of interest conditional on a set of variables, so that those with similar PSs  
11 are independent of these variables. Prior to PS matching, missing data were replaced using  
12 single imputation, whereby missing values of numerical variables were replaced by the relevant  
13 median, and missing values of categorical variables were replaced by the relevant mode, to  
14 overcome potential bias introduced by excluding patients with missing data. In order to compare  
15 two particular HF medications, a PS for each individual was determined using all the  
16 aforementioned variables, apart from the HF medications being assessed. After finding the area  
17 of common support (in which the histograms of the PSs overlapped), the patients were then  
18 matched on the basis of their PSs in the two medication groups in a 1:1 ratio using the nearest  
19 neighbour approach without replacement and calliper width equal to 0.20 times the standard  
20 deviation of the logit of the PSs. Adequacy of matching was verified by ensuring the  
21 standardised differences between groups were  $<0.10$  for all variables used to create the PS. A  
22 Cox proportional hazards regression model was then applied using the matched groups to  
23 compare the effect on survival of the two medications of interest. Additional PS-matched

1 analyses specified a priori were carried out in the subgroup of patients with a left ventricular  
2 ejection fraction (LVEF)  $\leq 40\%$  and the subgroup of patients with a LVEF  $>40\%$  (based on the  
3 guideline definition for HF with reduced ejection fraction being a LVEF  $\leq 40\%$ )<sup>19</sup>. Kaplan–Meier  
4 curves were constructed with statistical significance being assessed with a log-rank test.  
5 Significant results were followed by sensitivity analyses to assess whether these results could be  
6 replicated; firstly using an ‘intention to treat’ approach whereby patients were classed as treated,  
7 or not treated based on their treatment status at diagnosis (rather than over the first 6 months),  
8 secondly without censoring patients for the start date of clinical trials or disease-modifying  
9 therapy, and lastly analysing the medication use as a time-varying exposure. Statistical  
10 significance was defined as  $P < 0.05$ .

11

## 12 **Results**

13 We identified 2371 patients diagnosed with ATTR-CA. The population comprised 1840  
14 (77.6%) with wild-type ATTR-CA and 531 (22.4%) with hereditary ATTR-CA. The mean age of  
15 patients was  $77.5 \pm 7.3$  years and 90.0% were men. About two-thirds of patients were in New  
16 York Heart Association (NYHA) class I-II, the median NT-proBNP was 2925 ng/L and the mean  
17 LVEF was 48.2% (531 [22.4%] had a LVEF  $\leq 40\%$ ). Most patients were in NAC stages 1  
18 (45.8%) or 2 (36.0%). Approximately half of the patients had concomitant atrial  
19 fibrillation/flutter and 54.2% had an estimated glomerular filtration rate (eGFR)  $< 60$  ml/min/1.73  
20  $m^2$ . Overall, 1955 patients (82.4%) were treated with a diuretic. In most cases (76.8% patients) a  
21 loop diuretic was prescribed either alone or in combination (Table 1). A total of 467 (19.7%)  
22 patients were enrolled into clinical trials, or treated with disease-modifying therapy (clinical

1 trials, n=377; tafamidis, n=90). These patients were younger and had a milder cardiac phenotype  
2 at diagnosis than the rest of the study population (Supplementary Table S1).

3

#### 4 **Prescription pattern of heart failure medications**

5 *Beta-blockers:* A total of 1313 (55.4%) patients were treated with beta-blockers (64.4% in  
6 patients with a LVEF  $\leq$ 40%) at diagnosis. Those treated with beta-blockers had a higher  
7 prevalence of IHD, diabetes mellitus and atrial fibrillation compared to patients not receiving this  
8 type of treatment. Those treated with beta-blockers had a more severe cardiac phenotype, with a  
9 worse functional capacity evidenced by NYHA class and 6-minute walk test (6MWT), and a  
10 higher NAC disease stage (a greater proportion of patients had stage 3 [severe] disease). The  
11 median NT-proBNP among patients treated with beta-blockers was significantly higher, while  
12 median eGFR was significantly lower than patients not receiving beta-blockers. Patients treated  
13 with beta-blockers had a larger bi-atrial size, lower LVEF, lower tricuspid annular plane systolic  
14 excursion (TAPSE) and worse longitudinal strain than those not receiving this type of treatment.

15 *Renin-angiotensin system blockers:* A total of 1362 (57.4%) patients were treated with an ACEi  
16 or ARB (60.5% in patients with a LVEF  $\leq$ 40%) at diagnosis. As for beta-blockers, those treated  
17 with ACEi/ARBs had a higher prevalence of IHD, diabetes mellitus, and atrial fibrillation  
18 compared to patients not receiving this type of treatment. In addition, patients treated with an  
19 ACEi/ARB were more likely to have hypertension than patients not receiving this type of  
20 treatment. Those treated with ACEi/ARBs had a severe cardiac phenotype, with a higher NYHA  
21 class and NAC disease stage, and a higher proportion of patients having chronic kidney disease  
22 stage 3-5 than patients not receiving ACEi/ARBs. Patients treated with ACEi/ARBs had a larger

1 bi-atrial size, lower LVEF and worse longitudinal strain than those not receiving this type of  
2 treatment.

3 *Mineralocorticoid receptor antagonists:* A total of 925 (39.0%) patients were treated with an  
4 MRA (47.5% in patients with a LVEF  $\leq$ 40%) at diagnosis. Those treated with MRAs had a  
5 higher prevalence of diabetes mellitus and atrial fibrillation but, unlike beta-blocker and  
6 ACEi/ARB treatment, patients treated with an MRA did not have more IHD. Those treated with  
7 MRAs had a more severe cardiac phenotype, with a worse functional capacity evidenced by  
8 NYHA class and 6MWT, and a higher NAC disease. The median NT-proBNP among patients  
9 treated with MRAs was significantly higher, while median eGFR was significantly lower than  
10 patients not receiving MRAs. Patients treated with MRAs had a larger right atrial area, lower  
11 stroke volume, lower LVEF, lower TAPSE, higher E/e' and worse longitudinal strain than those  
12 not receiving this type of treatment (Table 2).

13 *Combination heart failure therapy:* A total of 417 (17.6%) patients were treated with all three  
14 classes of HF medications (beta-blocker, ACEi/ARB and MRA) at diagnosis, 804 (33.9%) were  
15 treated with a combination of two classes of HF medications, 741 (31.3%) were treated with one  
16 of the three classes of HF medications and 409 (17.2%) were not treated with any prognostic HF  
17 medications. The most frequent combination of two HF medications was a beta-blocker and  
18 ACEi/ARB in 454 (56.5%) patients, followed by a beta-blocker and MRA in 180(22.4%)  
19 patients, and an ACEi/ARB and MRA in 170 (21.1%) patients. Those treated with more HF  
20 medications had a higher prevalence of IHD, diabetes mellitus and atrial fibrillation. They had  
21 more severe HF, with a worse functional status, evidenced by NYHA class and 6MWT, and a  
22 higher NAC disease stage, and a higher proportion of patients having chronic kidney disease  
23 stage 3-5. Patients treated with more HF medications had a larger left ventricular wall thickness,

1 larger bi-atrial size, and worse biventricular systolic function (reflected in a lower TAPSE,  
2 LVEF and worse longitudinal strain), and there was a greater use of HF medications in patients  
3 with a LVEF  $\leq 40\%$  (Table 3).

#### 5 **Doses of heart failure medications and discontinuation rates**

6 *Beta-blockers:* Of the 1313 patients treated with beta-blockers, over half were prescribed  $\leq 25\%$   
7 of the target dose for HF (n=829, 63.1%).<sup>19</sup> The most commonly prescribed beta-blocker was  
8 bisoprolol (n=1164, 88.7%), with the majority of patients prescribed  $\leq 2.5$  mg per day (n=721,  
9 61.9%). Only 75 (5.7%) patients had the target beta-blocker dose prescribed, most of which had  
10 atrial fibrillation (n=58, 77.3%). The overwhelming majority of the study population (n=1266,  
11 96.4%) and all patients with a LVEF  $\leq 40\%$  (n=342, 100.0%) were prescribed beta-blockers  
12 approved for HF with reduced ejection fraction. During follow-up 285 (21.7%) patients had their  
13 beta-blocker discontinued (median duration to discontinuation: 14.1 [6.8-28.9] months), and 117  
14 (8.9%) had their beta-blocker dose reduced (median duration to reduction: 15.7 [7.4-34.5]  
15 months). Patients who discontinued beta-blocker treatment had a lower blood pressure and heart  
16 rate than those who continued treatment. Only 63 (4.8%) patients had their beta-blocker dose  
17 increased, of which only 8 patients eventually had the target dose prescribed. During follow-up,  
18 55 patients were initiated on beta-blockers, and the majority were prescribed  $\leq 25\%$  of the target  
19 dose (n=44, 80.0%), of which 4 (7.2%) had their beta-blocker subsequently discontinued.

20 *Renin-angiotensin system blockers:* Of the 1362 patients treated with ACEi/ARBs, over half  
21 were prescribed  $\leq 37.5\%$  of the target dose (n=728, 53.5%).<sup>19</sup> The most commonly prescribed  
22 ACEi/ARB was ramipril (n=701, 51.4%), with the majority of patients prescribed  $\leq 2.5$  mg per  
23 day (n=354, 50.5%). Only 158 (11.6%) patients were prescribed the target ACEi/ARB dose.

1 During follow-up 448 (32.9%) patients had their ACEi/ARB discontinued (median duration to  
2 discontinuation: 14.4 [6.9-26.8] months), and 77(5.7%) had their ACEi/ARB dose reduced  
3 (median duration to reduction: 14.2 [7.4-26.6] months). Patients who discontinued ACEi/ARB  
4 treatment had a lower blood pressure than those who continued treatment (Supplementary Table  
5 S2). Only 35 (2.6%) patients had their ACEi/ARB dose increased, of which only 3 patients were  
6 prescribed the target dose. During follow-up, 41 patients were initiated on ACEi/ARBs, and the  
7 majority were prescribed  $\leq 37.5\%$  of the target dose (n=26, 63.4%) of which 8 (19.5%) had their  
8 ACEi/ARB subsequently discontinued.

9 *Mineralocorticoid receptor antagonists:* Of the 925 patients treated with MRAs, 742 (80.2%)  
10 were prescribed spironolactone and 183 (19.3%) were prescribed eplerenone. The most  
11 commonly prescribed dose of both drugs was 25 mg (n=657, 71.0%), followed by 50 mg (n=79,  
12 8.5%). During follow-up 69 (7.5%) patients had their MRAs discontinued (median duration to  
13 discontinuation: 12.5 [7.9-24.9] months) and 31 (3.4%) had their MRA dose reduced (median  
14 duration to reduction: 14.1 [7.9-24.9] months). Only 77 (8.3%) patients had the dose of their  
15 MRA increased, of which 53 were prescribed 50 mg. During follow-up, 158 patients were  
16 initiated on MRAs, and the majority were prescribed  $\geq 25$  mg (n=129, 81.6%), of which only 5  
17 (3.2%) had their MRA subsequently discontinued.

18

### 19 **Association between heart failure medication classes and survival**

20 In the overall population, median follow-up was 27.8 months (IQR: 10.6-51.3), and the death  
21 rate was 14.9 deaths per 100 patient-years (95% CI 13.9-15.9). There were 1274 patients classed  
22 as being treated with beta-blockers for the survival analysis, and the death rate was 14.8 deaths  
23 per 100 patient-years (95% CI 13.5-16.2). There were 1306 patients classed as being treated with

1 ACEi/ARBs for the survival analysis, and the death rate was 15.0 deaths per 100 patient years  
2 (95% CI 13.8-16.4). There were 915 patients classed as being treated with MRAs for the survival  
3 analysis, and the death rate was 14.6 deaths per 100 patient years (95% CI 13.1-16.1).

4 *Multivariable Cox regression model:* In a multivariable Cox regression analysis with covariates  
5 age, sex, IHD, diabetes mellitus, hypertension, atrial fibrillation, NAC disease stage, wild-type or  
6 hereditary ATTR-CA, IVSd, longitudinal strain, beta-blocker, ACEi/ARB and MRA, only 4  
7 covariates (age, hATTR-CA, higher NAC disease stage, and worse longitudinal strain) were  
8 associated with a higher risk of mortality; and only one treatment (MRA: HR 0.82 [95% CI  
9 0.71-0.94], P=0.004) was convincingly associated with a lower risk of mortality (Supplementary  
10 Table S3).

11 *Propensity score-matched analyses:* To minimize the potential selection bias inherent with the  
12 baseline treatment of HF medications we also performed a PS-matched cohort analyses to assess  
13 the association between treatment with each HF medication and survival. Missing data was  
14 imputed for NAC stage in 37 patients, IVSd in 115 patients and longitudinal strain in 296  
15 patients. The remaining variables did not have any missing data. The PS-matched cohort  
16 constructed to assess the association between treatment with beta-blockers and risk of mortality  
17 comprised 1756 patients (878 treated with beta-blockers vs 878 not treated with beta-blockers)  
18 and did not provide convincing evidence for a difference in the risk of mortality between the two  
19 groups (HR 0.89 [95% CI 0.77-1.04], P=0.149), although the 95% CI of the estimate was wide  
20 and did not exclude clinically important effects (Supplementary Table S4). A second PS-  
21 matched cohort was constructed to assess the association between treatment with beta-blockers  
22 and risk of mortality in patients with a LVEF  $\leq$ 40%. This comprised 338 patients (169 treated  
23 with beta-blockers vs 169 not treated with beta-blockers), and demonstrated a 39% lower risk of

1 mortality in patients treated with beta-blockers (HR 0.61 [95% CI 0.45-0.83], P=0.002)  
2 (Supplementary Table S5). These findings were confirmed with sensitivity analysis, utilising an  
3 ‘intention to treat’ approach (HR 0.58 [95% CI 0.42-0.81], P=0.001), and whereby patients were  
4 no longer censored for the start date of clinical trials and disease modifying therapy (HR 0.63  
5 [95% CI 0.47-0.85], P=0.003), and where beta-blocker treatment was analysed as a time-varying  
6 exposure (HR 0.51 [95% CI 0.37-0.71], P<0.001). Following exclusion of patients with  
7 coexistent IHD and their corresponding pairs, repeat analysis confirmed a lower risk of mortality  
8 in patients with a LVEF  $\leq$ 40% treated with beta-blockers (HR 0.56 [95% CI 0.38-0.83],  
9 P=0.003). A third PS-matched cohort was constructed to assess the association between  
10 treatment with beta-blockers and risk of mortality in patients with a LVEF >40%. This  
11 comprised 1378 patients (689 treated with beta-blockers vs 689 not treated with beta-blockers),  
12 and did not provide convincing evidence for a difference in the risk of mortality between the two  
13 groups (HR 1.00 [95% CI 0.84-1.20], P=0.957), although the estimate was imprecise (Figure 1,  
14 Supplementary Table S6).

15 The PS-matched cohort constructed to assess the association between treatment with  
16 ACEi/ARBs and the risk of mortality comprised 1782 patients (891 treated with ACEi/ARBs vs  
17 891 not treated with ACEi/ARBs) and did not provide convincing evidence for a difference in  
18 the risk of mortality between the two groups (HR 1.09 [95% CI 0.93-1.26], P=0.283)  
19 (Supplementary Table S7). A second PS-matched analysis was constructed to assess the  
20 association between treatment with ACEi/ARBs and the risk of mortality in patients with a  
21 LVEF  $\leq$ 40%. This comprised 368 patients (184 treated with ACEi/ARBs vs 184 not treated with  
22 ACEi/ARBs) and did not provide convincing evidence for a difference in the risk of mortality  
23 between the two groups (HR 1.01 [95% CI 0.76-1.33], P=0.947), although the estimates were

1 imprecise (Supplementary Table-S8). A third PS-matched analysis was constructed to assess the  
2 association between treatment with ACEi/ARBs and the risk of mortality in patients with a  
3 LVEF >40%. This comprised 1390 patients (695 treated with ACEi/ARBs vs 695 not treated  
4 with ACEi/ARBs), and did not provide convincing evidence for a difference in the risk of  
5 mortality between the two groups (HR 1.13 [95% CI 0.94-1.35], P=0.198) (Figure 2,  
6 Supplementary Table S9).

7 The PS-matched cohort constructed to assess the association between treatment with MRAs and  
8 the risk of mortality comprised 1788 patients (894 patients treated with MRAs vs 894 patients  
9 not treated with MRAs) and demonstrated there was a 23% lower risk of mortality in patients  
10 treated with MRAs (HR 0.77 [95% CI 0.66-0.89], P<0.001) (Supplementary Table S10). These  
11 findings were confirmed with sensitivity analysis, utilising an ‘intention to treat’ approach (HR  
12 0.81 [95% CI 0.69-0.94], P=0.006); and whereby patients were no longer censored for the start  
13 date of clinical trials and disease modifying therapy (HR 0.78 [95% CI 0.67-0.90], P<0.001), and  
14 where MRA treatment was analysed as a time-varying exposure (HR 0.81 [95% CI 0.69-0.94],  
15 P=0.004). A second PS-matched analysis was constructed to assess the association between  
16 treatment with MRAs and the risk of mortality in patients with a LVEF ≤40%. This comprised  
17 416 patients (208 patients treated with MRAs vs 208 patients not treated with MRAs), and did  
18 not provide convincing evidence for a difference in the risk of mortality between the two groups  
19 (HR 0.83 [95% CI 0.62-1.10], P=0.192), although the 95% CI of the estimate was wide and did  
20 not exclude clinically important effects (Supplementary Table S11). A third PS-matched analysis  
21 was constructed to assess the association between treatment with MRAs and the risk of mortality  
22 in patients with a LVEF >40%. This comprised 1334 patients (667 treated with MRAs vs 667 not  
23 treated with MRAs) and demonstrated there was a 25% lower risk of mortality in patients treated

1 with MRAs (HR 0.75 [95% CI 0.63-0.90], P=0.002) (Figure 3, Supplementary Table S12).  
2 These findings were confirmed with sensitivity analysis, utilising an ‘intention to treat’ approach  
3 (HR 0.78 [95% CI 0.65-0.94], P=0.008); and whereby patients were no longer censored for the  
4 start date of clinical trials and disease modifying therapy (HR 0.79 [95% CI 0.66-0.94],  
5 P=0.009), and where MRA treatment was analysed as a time-varying exposure (HR 0.77 [95%  
6 CI 0.65-0.93], P=0.005).

7 *Propensity score-matched analyses for combination therapy:* In the overall population, a PS-  
8 matched cohort was constructed to compare the association with risk of mortality, between  
9 treatment with all 3 classes of HF medications (beta-blockers, ACEi/ARBs and MRAs) and  
10 treatment with 2 classes of HF medications (beta-blockers and ACEi/ARBs). This comprised 680  
11 patients (340 treated with all 3 HF medications vs 340 treated with beta-blockers and  
12 ACEi/ARBs) and demonstrated there was a 37% lower risk of mortality in patients treated with  
13 all 3 HF medications (HR 0.63 [95% CI 0.49-0.80], P<0.001) (Supplementary Table S13). These  
14 findings were confirmed with sensitivity analysis, utilising an ‘intention to treat’ approach (HR  
15 0.64 [95% CI 0.50-0.83], P<0.001); and whereby patients were no longer censored for the start  
16 date of clinical trials and disease modifying therapy (HR 0.65 [95% CI 0.51-0.82], P<0.001), and  
17 where treatment was analysed as a time-varying exposure (HR 0.56 [95% CI 0.41-0.78],  
18 P=0.001).

19 A PS-matched cohort was used to compare the association with risk of mortality, between  
20 treatment with 2 classes of HF medications (beta-blockers and ACEi/ARBs) and treatment with  
21 just ACEi/ARBs. This comprised 558 patients (279 treated with beta-blockers and ACEi/ARBs  
22 vs 279 treated with just ACEi/ARBs) and did not provide convincing evidence for a difference in  
23 the risk of mortality between the 2 groups (HR 1.06 [95% CI 0.81-1.39], P=0.677), although the

1 estimates were imprecise (Supplementary Table S14 and Supplementary Figure S1). Data on  
2 reasons for medication discontinuation; and the association between survival and both  
3 medication dosage and medication discontinuation are presented in Appendix 1.

## 4 5 **Discussion**

6 In this study we comprehensively evaluated the prescription pattern and discontinuation rates of  
7 HF medications in >2000 patients with ATTR-CA, and assessed the association between  
8 treatment with HF medications and the risk of mortality in these individuals. Our study  
9 demonstrated that: (i) patients with ATTR-CA and a severe cardiac phenotype were more  
10 commonly treated with HF medications; (ii) beta-blockers and ACEi/ARBs were generally  
11 prescribed in low doses and often discontinued, whereas in contrast, MRAs were rarely  
12 discontinued; and (iii) MRAs were independently associated with a lower risk of mortality in the  
13 overall population, and in patients with LVEF >40%; and low-dose beta-blockers were  
14 independently associated with a lower risk of mortality in patients with a LVEF  $\leq$ 40%  
15 (Structured Graphical Abstract).

16 In the overall population of patients with ATTR-CA, a relatively low proportion were prescribed  
17 beta-blockers (55.4%), ACEi/ARBs (57.4%) and MRAs (39.0%).<sup>20</sup> Treatment with HF  
18 medications in patients with ATTR-CA appears to be driven by the presence of comorbidities  
19 and the severity of their cardiac disease. HF medications were more commonly prescribed in  
20 patients with atrial fibrillation, diabetes mellitus and chronic kidney disease. Beta-blockers and  
21 ACEi/ARBs are also more commonly prescribed in patients with IHD.<sup>15</sup> Patients prescribed  
22 conventional HF medications had more advanced cardiac disease evidenced by worse functional  
23 capacity, a more severe NAC disease stage and lower indices of systolic function. Radial systolic

1 impairment occurs in advanced ATTR-CA, and since the main evidence base for conventional  
2 HF medications is in patients with a LVEF  $\leq 40\%$ , the development of systolic impairment is  
3 likely to have contributed to greater use of HF medications in those with advanced cardiac  
4 disease.<sup>6-12</sup>

5 Beta-blockers and ACEi/ARBs were commonly discontinued, with over one-fifth of patients  
6 having their beta-blocker discontinued, and nearly one-third having their ACEi/ARB  
7 discontinued during follow-up. Beta-blocker intolerance may be exacerbated the underlying  
8 pathophysiology of ATTR-CA. In the context of a fixed stroke volume, caused by restrictive  
9 physiology, a higher heart rate is required to maintain cardiac output. The inability to augment  
10 stroke volume in response to the vasodilation may also contribute to the intolerance of  
11 ACEi/ARBs.<sup>15,21</sup> In contrast, MRAs were rarely discontinued, with less than one-tenth having  
12 their MRA discontinued. This is probably related to the limited effect on blood pressure,  
13 compared with beta-blockers and ACEi/ARB, and their possible diuretic effect. The mainstay of  
14 symptom management in ATTR-CA has long been meticulous volume control, facilitated by  
15 high-dose loop diuretics. MRAs may have a synergistic effect when utilised alongside loop  
16 diuretics and also increase potassium reabsorption, which is often needed when high doses of  
17 loop diuretics are utilised.<sup>22</sup>

18 In the current study, which represents the largest analysis of HF medications in patients with  
19 ATTR-CA to date, both regression-based and PS-matched analysis demonstrated that treatment  
20 with MRAs was independently associated with a lower risk of mortality in the overall ATTR-CA  
21 population; and PS-matched analysis demonstrated low-dose beta-blockers were associated with  
22 a lower risk of mortality in patients with a LVEF  $\leq 40\%$ . MRAs were associated with a lower risk  
23 of mortality in patients with a LVEF  $>40\%$ , but not in patients with a LVEF  $\leq 40\%$ . The point

1 estimates for these analyses were similar, hence a greater sample size may have increased power  
2 sufficiently to demonstrate a benefit in patients with a LVEF  $\leq 40\%$ . Another possibility is the  
3 benefit derived from MRAs is greater earlier in the disease process, and therefore increased  
4 survival benefit occurs in patients with a LVEF  $>40\%$ . The reduced risk of mortality associated  
5 with low-dose beta-blockers in patients with a LVEF  $\leq 40\%$ , was maintained when excluding  
6 patients with concomitant IHD, suggesting the benefit is related to treating ATTR-CA rather than  
7 treating comorbidities, and this is consistent with previous HF trials that demonstrated improved  
8 outcomes were confined to patients with a reduced ejection fraction.<sup>6,7,12</sup>

9 It has been well established that patients with ATTR-CA have a similar and possibly greater  
10 neurohormonal activation than is observed in patients with HF of different aetiologies.  
11 Furthermore, elevated neurohormone levels (specifically NT-proBNP and aldosterone) have  
12 been associated with a worse prognosis.<sup>23</sup> It is therefore plausible that patients with ATTR-CA  
13 would derive prognostic benefit from neurohormonal modulation. However, a recent position  
14 statement by the ESC on the treatment of ATTR-CA recommended the withdrawal of beta-  
15 blockers, avoiding ACEi/ARBs, and did not discuss the use of MRAs in patients with ATTR-  
16 CA, reflecting the perceived poor tolerability of these agents and lack of trial evidence to support  
17 their use (and lack of differentiation between AL and ATTR-CA, the former having greater  
18 intolerance).<sup>18</sup> Several small observational studies have contributed to these recommendations.  
19 However, differences in methodology and patient selection could explain our contrasting results.  
20 Previous studies have not matched patients and therefore the worse outcomes in patients  
21 prescribed HF medications were confounded by disease severity. Our study excluded patients  
22 with concomitant polyneuropathy, who often have autonomic disease and hypotension, resulting  
23 in a poor tolerance of HF medications.<sup>16,17</sup> Importantly, our results are supported by a

1 retrospective analysis of the TOPCAT trial, whereby an enriched cohort with echocardiographic  
2 characteristics of CA derived benefit from MRA therapy.<sup>22</sup> This analysis featured in a recent  
3 ACC consensus document that recommends MRA therapy alongside loop diuretics to augment  
4 diuresis.<sup>24</sup> Our study is the first to sub-categorise ATTR-CA patients by LVEF. The majority of  
5 HF patients with a LVEF  $\leq 40\%$  experience chronic adrenergic overstimulation, and higher  
6 serum noradrenaline levels than their counterparts with preserved systolic function. A similar  
7 pathophysiological mechanism may exist in ATTR-CA, and therefore patients with a LVEF  
8  $\leq 40\%$  could derive benefit from beta-blockade.<sup>23</sup> Lastly, the majority were prescribed bisoprolol  
9 (a cardio-selective beta-blocker), which potentially has a different haemodynamic profile to beta-  
10 blockers used in previous studies, while still providing neurohormonal modulation, and  
11 therefore, the observed benefit could potentially be confined to cardio-selective beta-blockers.  
12 While the observational analyses reported here have limitations in their ability to provide causal  
13 estimates of treatments in individuals with ATTR-CA, they do raise the question as to whether  
14 there could be benefit from some neurohumoral therapies in such patients and support testing this  
15 hypothesis in prospective randomized controlled trials.<sup>22</sup> While clinical trials are clearly needed,  
16 we believe that the data presented in this study call into question the consensus recommendations  
17 to discontinue beta-blockers and that neglect to mention MRAs.<sup>18</sup>

18  
19 *Limitations.* There is an unavoidable prescription bias, with comorbid patients with more  
20 advanced cardiac disease being prescribed more HF medications; but it is also possible that  
21 clinicians may have avoided using HF medications in some higher risk patients. Treatment  
22 decisions were made on a case-by-case basis, and therefore clinical decisions must factor in each  
23 individual's tolerance of HF medications. It is possible patients may have discontinued HF

1 medications prior to their first NAC assessment, and this could not be factored into the analysis.  
2 Although we performed multivariable adjustment and PS-matching to account for confounders  
3 known to impact mortality in ATTR-CA, we cannot exclude the possibility of residual  
4 confounding. The present study should be considered hypothesis-generating and highlights the  
5 urgent need for randomized controlled trials. Some of the estimated HRs generated following  
6 prespecified subgroup analysis were imprecise, and is likely to reflect the unavoidably small  
7 sample size. Lastly, a small minority were prescribed angiotensin receptor-neprilysin inhibitors  
8 or sodium-glucose cotransporter 2 inhibitors and had a short duration of follow-up. Therefore,  
9 they were not included in the present study, and further studies will be required to assess these  
10 medications in patients with ATTR-CA.

11

## 12 **Conclusions**

13 In summary, in this large cohort of patients with ATTR-CA, a relatively low proportion were  
14 prescribed conventional HF medications, and those that had a more severe cardiac phenotype  
15 were more commonly prescribed HF medications. Beta-blockers and ACEi/ARBs were often  
16 prescribed at a low dose, and frequently discontinued; in contrast to MRAs which were rarely  
17 discontinued. Both regression and PS-matched analyses demonstrated that treatment with an  
18 MRA was independently associated with a lower risk of mortality in the overall ATTR-CA  
19 population; and PS-matched analysis demonstrated treatment with a low-dose beta-blocker was  
20 independently associated with a lower risk of mortality in patients with a LVEF  $\leq 40\%$ , but these  
21 findings require confirmation in prospective randomized controlled trials.

22

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## 16 **Figures legends**

17  
18 **Figure 1:** Kaplan-Meier curves comparing survival in patients treated with beta-blockers to  
19 patients not treated with beta-blockers followed by a Cox proportional hazards regression  
20 analysis. (A) Treatment with beta-blockers vs no treatment with beta-blockers in the overall  
21 population. (B) Treatment with beta-blockers vs no treatment with beta-blockers in patients with  
22 a LVEF  $\leq 40\%$ . (C) Treatment with beta-blockers vs no treatment with beta-blockers in patients  
23 with a LVEF  $>40\%$ .  
24

25 **Figure 2:** Kaplan-Meier curves comparing survival in patients treated with ACEi/ARBs to  
26 patients not treated with ACEi/ARBs followed by a Cox proportional hazards regression  
27 analysis. (A) Treatment with ACEi/ARBs vs no treatment with ACEi/ARBs in the overall  
28 population. (B) Treatment with ACEi/ARBs vs no treatment with ACEi/ARBs in patients with a  
29 LVEF  $\leq 40\%$ . (C) Treatment with ACEi/ARBs vs no treatment with ACEi/ARBs in patients with  
30 a LVEF  $>40\%$ .

1  
2 **Figure 3:** Kaplan-Meier curves comparing survival in patients treated with MRAs to patients not  
3 treated with MRAs followed by a Cox proportional hazards regression analysis. (A) Treatment  
4 with MRA vs no treatment with MRA in the overall population. (B) Treatment with MRA vs no  
5 treatment with MRA in patients with a LVEF  $\leq 40\%$ . (C) Treatment with MRA vs no treatment  
6 with MRA in patients with a LVEF  $>40\%$ .

7  
8 **Graphical Abstract:** Discontinuation rates of heart failure medications in patients with cardiac  
9 ATTR amyloidosis. Kaplan-Meier curves comparing survival in patients treated with heart  
10 failure medications to propensity score matched patients not treated with heart failure  
11 medications, followed by a Cox proportional hazards regression analysis.

12 ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ATTR-  
13 CA, transthyretin cardiac amyloidosis; CI, confidence interval; HF, heart failure; HR, hazard  
14 ratio; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist.

15  
16

Baseline Characteristics	Overall study population (n=2371)	Patients with a LVEF >40% (n=1840)	Patients with a LVEF ≤40% (n=531)	P-value
Age	77.5±7.3	77.6±7.3	76.9±7.3	0.035
Sex (male)	2110 (90.0%)	1637 (89.0%)	473 (89.1%)	0.943
Ethnicity				<0.001
Caucasian	1893 (79.8%)	1525 (82.9%)*	368 (69.3%)	
Afro-Caribbean	444 (18.7%)	288 (15.7%)*	156 (29.4%)	
Asian	22 (0.9%)	18 (1.0%)	4 (0.8%)	
Other	12 (0.5%)	9 (0.5%)	3 (0.6%)	
wtATTR	1840 (77.6%)	1487 (80.8%)	353 (66.5%)	<0.001
hATTR	531 (22.4%)	353 (19.2%)	178 (33.5%)	<0.001
AF/flutter	1223 (51.6%)	937 (50.9%)	286 (53.9%)	0.233
IHD	476 (20.1%)	374 (20.3%)	102 (19.2%)	0.571
Diabetes mellitus	374 (15.8%)	273 (14.8%)	101 (19.0%)	0.020
Hypertension	828 (34.9%)	631 (34.3%)	197 (37.1%)	0.232
Stroke/TIA	109 (4.6%)	182 (9.9%)	76 (14.3%)	0.004
CKD stage 3-5	1288 (54.3%)	953 (51.8%)	335 (63.1%)	<0.001
<b>Cardiac devices</b>				
PPM	214 (9.0%)	173 (9.4%)	41 (7.7%)	0.234
ICD	46 (1.9%)	29 (1.6%)	17 (3.2%)	0.017
CRT-D	23 (1.0%)	14 (0.8%)	9 (1.7%)	0.053
CRT-P	37 (1.6%)	24 (1.3%)	13 (2.4%)	0.061
<b>Heart failure severity</b>				
NYHA class				<0.001
1	317 (13.4%)	280 (15.2%)*	37 (7.0%)	
2	1387 (58.5%)	1093 (59.4%)*	294 (55.4%)	
3	435 (18.3%)	279 (15.2%)*	156 (29.4%)	
4	30 (1.3%)	19 (1.0%)	11 (2.1%)	
Missing	202	169	33	
NAC stage				<0.001
1	1086 (45.8%)	926 (50.3%)*	160 (30.1%)	
2	853 (36.0%)	613 (33.3%)*	240 (45.2%)	
3	395 (16.7%)	266 (14.5%)*	129 (24.3%)	
Missing	37	35	2	
NT-pro-BNP (ng/L)	2925 (1530-5321)	2597 (1394-4786)	4123 (2484-7201)	<0.001
eGFR (ml/min/1.73m <sup>2</sup> )	58 (46-71)	59 (47-72)	54 (43-66)	<0.001
6-minute walk test (meters)	347 (247-430)	354 (256-436)	322 (216-407)	<0.001
6-minute walk test (% predicted)	71.2±26.5	72.9±25.7	64.7±28.3	<0.001
Systolic blood pressure (mmHg)	125.1±21.4	126.3±22.1	121.3±18.7	<0.001
Diastolic blood pressure (mmHg)	74.4±12.7	73.9±12.8	75.9±12.4	0.020
Heart rate (bpm)	72.2±13.7	71.1±13.2	75.8±14.4	<0.001
<b>Echocardiographic parameters</b>				
IVSd (mm)	16.9±2.4	16.9±2.4	17.0±2.4	0.321

PWTd (mm)	16.3±2.5	16.3±2.5	16.4±2.6	0.220
MWT (mm)	17.1±2.4	17.1±2.4	17.2±2.4	0.326
Left atrial area (cm <sup>2</sup> )	26.2±5.5	26.1±5.5	26.6±6.4	0.069
Right atrial area (cm <sup>2</sup> )	24.5±6.5	23.9±6.4	26.3±6.4	<0.001
Stroke volume (ml)	37.3±13.9	39.9±13.8	29.4±10.9	<0.001
Simpson's biplane LVEF (%)	48.2±10.6	52.7±7.2	33.6±5.3	<0.001
Longitudinal strain (%)	-10.8±3.6	-11.7±3.5	-8.1±2.6	<0.001
TAPSE (mm)	15.1±4.9	15.9±4.9	12.6±3.5	<0.001
E/e'	16.8±6.4	16.5±6.2	17.8±7.0	<0.001
<b>Medications</b>				
Beta-blockers	1313 (55.4%)	971 (52.8%)	342 (64.4%)	<0.001
ACEi/ARBs	1362 (57.4%)	1041 (56.6%)	321 (60.5%)	0.112
MRAs	925 (39.0%)	673 (36.6%)	252 (47.5%)	<0.001
Loop diuretics	1808 (76.8%)	1357 (74.3%)	451 (85.3%)	<0.001

**Table 1. Baseline characteristics and echocardiographic parameters for the overall population, and for patients separated into those with a LVEF >40% and a LVEF ≤40%.**

Patients with hATTR-CA had the following variants: p.(Val142Ile)=392, p.(Thr80Ala)=93, p.(Ile127Val)=12, p.(Ile88Leu)=6, p.(Ser97Tyr)=6, p.(Glu62Asp)=4, p.(Glu109Lys)=3, p.(Gly26Ser)=3, p.(Val40Ile)=2, p.(Val50Met)=2, p.(Ala56Pro)=1, p.(Asp58Tyr)=1, p.(Asp58Val)=1, p.(Asp59Val)=1, p.(Glu74Gln)=1, p.(Glu74Gly)=1, p.(Glu74Leu)=1, p.(Phe64Leu)=1.

\* = P-value < 0.05; AF = Atrial fibrillation; IHD = Ischaemic heart disease; TIA = Transient ischaemic attack; CKD = Chronic kidney disease; PPM = Permanent pacemaker; ICD = Implantable cardioverter defibrillator; CRT-D = Cardiac resynchronisation therapy defibrillator; CRT-P = Cardiac resynchronisation therapy pacemaker; NYHA = New York Heart Association; NAC = National Amyloidosis Centre; NT-pro-BNP = N-terminal pro B-type natriuretic peptide; eGFR = Estimated glomerular filtration rate; IVSd = Interventricular septum in diastole; PWTd = Posterior wall thickness in diastole; MWT = Maximal wall thickness; LVEF = Left ventricular ejection fraction; ACEi = Angiotensin converter enzyme inhibitor; ARB = Angiotensin II receptor blocker; MRA = Mineralocorticoid receptor antagonist.

Variables	Patients with ATTR-cardiac amyloidosis split by treatment with beta-blockers			Patients with ATTR-cardiac amyloidosis split by use of ACEi/ARB			Patients with ATTR-cardiac amyloidosis split by use of MRA		
	Patients treated with beta-blockers (n=1313, 55.4%)	Patients not Treated with beta-blockers (n=1058, 44.6%)	P-value	Patients treated with ACEi/ARB (n=1362, 57.4%)	Patients not treated with ACEi/ARB (n=1009, 42.6%)	P-value	Patients treated with MRAs (n=925, 39.0%)	Patients not treated with MRAs (n=1446, 61.0%)	P-value
<b>Baseline Characteristics</b>									
Age	77.4±6.9	77.6±7.7	0.456	77.4±6.7	77.6±8.0	0.546	76.9±6.9	77.9±7.5	0.001
Sex (male)	1172 (89.3%)	938 (88.7%)	0.641	1224 (89.9%)	886 (87.8%)	0.113	824 (89.1%)	1286 (88.9%)	0.912
Ethnicity			0.016			0.040			<0.001
Caucasian	1030 (78.4%)	863 (81.6%)		1069 (78.5%)	824 (81.7%)		695 (75.1%)*	1198 (82.8%)	
Afro-Caribbean	269 (20.5%)*	175 (16.5%)		278 (20.4%)*	166 (16.5%)		215 (23.2%)*	229 (15.8%)	
Asian	11 (0.8%)	11 (1.0%)		9 (0.7%)	13 (1.3%)		9 (1.0%)	13 (0.9%)	
Other	3 (0.2%)*	9 (0.9%)		6 (0.4%)	6 (0.6%)		6 (0.6%)	6 (0.4%)	
wtATTR	1021 (77.8%)	819 (77.4%)	0.839	1067 (78.3%)	773 (76.6%)	0.318	686 (74.2%)	1154 (79.8%)	<0.001
hATTR	292 (22.2%)	239 (22.6%)	0.839	295 (21.7%)	236 (23.4%)	0.318	239 (25.8%)	292 (20.2%)	<0.001
AF/flutter	755 (57.5%)	468 (44.2%)	<0.001	728 (53.5%)	495 (49.1%)	0.034	515 (55.7%)	708 (49.0%)	0.001
IHD	300 (22.8%)	176 (16.6%)	<0.001	301 (22.1%)	175 (17.3%)	0.004	198 (21.4%)	278 (19.2%)	0.196
Diabetes mellitus	241 (18.4%)	133 (12.6%)	<0.001	249 (18.2%)	125 (12.4%)	<0.001	168 (18.2%)	206 (14.2%)	0.011
Hypertension	479 (36.5%)	349 (33.0%)	0.079	549 (40.3%)	279 (27.7%)	<0.001	335 (36.2%)	493 (34.1%)	0.290
Stroke/TIA	137 (10.4%)	121 (11.4%)	0.436	143 (10.5%)	115 (11.4%)	0.487	97 (10.5%)	161 (11.1%)	0.670
CKD stage 3-5	797 (60.7%)	491 (46.4%)	<0.001	774 (56.8%)	514 (50.9%)	0.004	573 (61.9%)	715 (49.4%)	<0.001
<b>Cardiac devices</b>									
PPM	118 (9.0%)	96 (9.1%)	0.942	138 (10.1%)	76 (7.5%)	0.029	95 (10.3%)	119 (8.2%)	0.091
ICD	32 (2.4%)	14 (1.3%)	0.051	28 (2.1%)	18 (1.8%)	0.635	22 (2.4%)	24 (1.7%)	0.216
CRT-D	15 (1.1%)	8 (0.8%)	0.340	17 (1.2%)	6 (0.6%)	0.108	13 (1.4%)	10 (0.7%)	0.084
CRT-P	21 (1.6%)	16 (1.5%)	0.865	23 (1.7%)	14 (1.4%)	0.559	21 (2.3%)	16 (1.1%)	0.026
<b>Heart failure severity</b>									
NYHA class			<0.001			<0.001			<0.001
1	135 (10.3%)*	182 (17.2%)		143 (10.5%)*	174 (17.2%)		87 (9.4%)*	230 (15.9%)	
2	755 (57.5%)	632 (59.7%)		795 (56.2%)	592 (58.7%)		555 (60.0%)	832 (57.5%)	
3	286 (21.8%)*	149 (14.1%)		275 (20.2%)*	160 (15.9%)		219 (23.7%)*	216 (14.9%)	
4	18 (1.4%)	12 (1.1%)		20 (1.5%)	10 (1.0%)		15 (1.6%)	15 (1.0%)	

Missing	119	83		129	73		49	153	
NAC stage			<0.001			0.047			<0.001
1	524 (40.0%)*	562 (52.5%)		607 (44.6%)	479 (47.4%)		379 (41.0%)*	707 (48.9%)	
2	522 (39.8%)*	331 (31.1%)		519 (38.1%)*	334 (33.1%)		369 (39.9%)*	484 (33.5%)	
3	254 (19.3%)*	141 (13.3%)		217 (15.9%)	178 (17.6%)		167 (18.1%)	228 (15.8%)	
Missing	13	24		19	18		10	27	
NT-pro-BNP (ng/L)	3369 (1886-5912)	2391 (1285-4540)	<0.001	2999 (1591-5274)	2850 (1479-5381)	0.095	3136 (1806-5420)	2732 (1433-5248)	<0.001
eGFR (ml/min/1.73m <sup>2</sup> )	56 (45-69)	62 (48-75)	<0.001	58 (46-70)	60 (46-73)	0.139	55 (45-68)	60 (47-74)	<0.001
6-minute walk test (meters)	343 (230-422)	358 (268-442)	0.001	349 (242-428)	335 (253-433)	0.985	336 (230-424)	358 (266-437)	0.004
6-minute walk test (% predicted)	68.0±26.6	75.7±25.7	<0.001	71.3±26.4	71.0±26.6	0.853	67.9±26.4	74.0±26.3	<0.001
Systolic blood pressure (mmHg)	123.7±20.2	127.0±22.9	<0.001	124.8±20.8	125.6±22.3	0.028	121.8±19.2	127.3±22.6	<0.001
Diastolic blood pressure (mmHg)	74.0±12.5	74.9±13.0	<0.001	74.0±13.3	75.0±13.5	0.004	72.8±11.5	75.5±14.1	<0.001
Heart rate (bpm)	71.2±14.0	73.5±13.1	<0.001	71.9±13.5	72.7±13.9	0.230	72.0±14.1	72.4±13.4	0.471
<b>Echocardiographic parameters</b>									
IVSd (mm)	17.00±2.4	16.9±2.5	0.672	17.0±2.5	16.8±2.4	0.051	17.1±2.4	16.8±2.5	0.015
PWTd (mm)	16.4±2.5	16.3±2.6	0.761	16.4±2.5	16.3±2.5	0.412	16.5±2.5	16.3±2.5	0.014
MWT (mm)	17.1±2.4	17.1±2.5	0.677	17.2±2.4	17.0±2.4	0.061	17.3±2.3	17.0±2.5	0.020
Left atrial area (cm <sup>2</sup> )	26.7±5.4	25.6±6.4	<0.001	26.54±5.6	25.78±5.4	0.008	26.5±5.4	26.0±5.7	0.113
Right atrial area (cm <sup>2</sup> )	25.1±6.4	23.5±6.4	<0.001	24.9±6.6	23.8±6.6	<0.001	25.1±5.4	24.0±6.4	<0.001
Stroke volume (ml)	36.6±13.9	38.3±14.0	0.023	37.7±14.5	36.6±13.0	0.126	35.9±13.0	38.5±14.6	<0.001
LVEF (%)	47.1±10.7	49.5±10.4	<0.001	47.7±10.6	48.8±10.7	0.013	46.4±10.6	49.3±10.5	<0.001
LVEF ≤40%	342 (26.0%)	189 (17.9%)	<0.001	321 (23.6%)	210 (20.8%)	0.112	252 (27.2%)	279 (19.3%)	<0.001
Longitudinal strain (%)	-10.6±3.5	-11.1±3.8	<0.001	-10.6±3.5	-11.0±3.7	0.014	-10.2±3.3	-11.2±3.8	<0.001
TAPSE (mm)	14.7±4.8	15.5±5.0	0.002	15.0±4.7	15.2±5.2	0.342	14.6±4.8	15.5±5.0	<0.001
E/e'	16.7±6.4	16.7±6.5	0.567	16.9±6.2	16.7±6.7	0.640	17.2±6.5	16.3±6.3	0.036

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2 **Table 2. Baseline characteristics and echocardiographic parameters for patients treated with heart failure compared to**  
3 **patients not treated with heart failure medications.**

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5 \* = P-value < 0.05; BSA = Body surface area; AF = Atrial fibrillation; IHD = Ischaemic heart disease; TIA = Transient ischaemic  
6 attack; CKD = Chronic kidney disease; PPM = Permanent pacemaker; ICD = Implantable cardioverter defibrillator; CRT-D = Cardiac  
7 resynchronisation therapy defibrillator; CRT-P = Cardiac resynchronisation therapy pacemaker; NYHA = New York Heart  
8 Association; NAC = National Amyloidosis Centre; NT-pro-BNP = N-terminal pro B-type natriuretic peptide; eGFR = Estimated  
9 glomerular filtration rate; IVSd = Interventricular septum in diastole; PWTd = Posterior wall thickness in diastole; MWT = Maximal  
10 wall thickness; LVEF = left ventricular ejection fraction.  
11

Baseline Characteristics	Not treated with HF medications (n=409, 17.2%)	Treated with 1 HF medication (n=741, 31.3%)	Treated with 2 HF medications (n=804, 33.9%)	Treated with 3 HF medications (n=417, 17.6%)	P value
Age	76.8±9.0 <sup>α</sup>	78.5±6.9 <sup>ε</sup>	77.6±6.6 <sup>φ</sup>	76.1±6.9	<0.001
Sex (male)	359 (87.8%)	653 (88.1%)	727 (90.4%)	371 (89.0%)	0.412
Ethnicity					<0.001
Caucasian	336 (82.2%) <sup>γ</sup>	615 (83.0%) <sup>ε</sup>	647 (80.5%) <sup>φ</sup>	295 (70.7%)	
Afro-Caribbean	66 (16.1%) <sup>γ</sup>	113 (15.2%) <sup>ε</sup>	146 (18.2%) <sup>φ</sup>	119 (28.5%)	
Asian	3 (0.7%)	10 (1.3%)	8 (1.0%)	1 (0.2%)	
Other	4 (1.0%)	3 (0.4%)	3 (0.4%)	2 (0.5%)	
wtATTR	298 (72.9%) <sup>αγ</sup>	607 (81.9%) <sup>ε</sup>	638 (79.4%) <sup>φ</sup>	297 (71.2%)	<0.001
hATTR	111 (27.1%) <sup>αγ</sup>	134 (18.1%) <sup>ε</sup>	166 (20.6%) <sup>φ</sup>	120 (28.8%)	<0.001
AF/flutter	145 (35.5%) <sup>αβγ</sup>	389 (52.5%)	458 (57.0%)	231 (55.4%)	<0.001
IHD	54 (13.2%) <sup>βγ</sup>	142 (19.2%)	183 (22.8%)	97 (23.3%)	<0.001
Diabetes mellitus	41 (10.0%) <sup>βγ</sup>	104 (14.0%) <sup>ε</sup>	133 (16.5%)	96 (15.8%)	<0.001
Hypertension	92 (22.5%) <sup>αβγ</sup>	276 (37.2%)	293 (36.4%)	167 (40.0%)	<0.001
Stroke/TIA	50 (12.2%)	78 (10.5%)	91 (11.3%)	39 (9.4%)	0.568
CKD stage 3-5	151 (36.9%) <sup>αβγ</sup>	394 (53.2%) <sup>ε</sup>	479 (59.6%)	264 (63.3%)	<0.001
<b>Cardiac devices</b>					
PPM	30 (7.4%)	55 (7.4%)	91 (11.3%)	378 (9.1%)	0.031
ICD	6 (1.5%)	11 (1.5%)	16 (2.0%)	13 (3.1%)	0.227
CRT-D	1 (0.2%)	6 (0.8%)	9 (1.1%)	7 (1.7%)	0.187
CRT-P	1 (0.2%)	13 (1.8%)	17 (2.1%)	6 (1.4%)	0.092
<b>Heart failure severity</b>					
NYHA class					<0.001
1	105 (25.7%) <sup>αβγ</sup>	92 (12.4%) <sup>ε</sup>	87 (10.8%)	33 (7.9%)	
2	251 (61.4%)	412 (55.6%)	479 (59.6%) <sup>φ</sup>	245 (58.8%)	
3	50 (12.2%) <sup>γ</sup>	120 (16.2%) <sup>ε</sup>	135 (16.8%) <sup>φ</sup>	130 (31.2%)	
4	3 (0.7%)	9 (1.2%)	10 (1.2%)	8 (1.9%)	
Missing	0	108	93	1	
NAC stage					<0.001
1	214 (52.3%) <sup>αβγ</sup>	346 (46.7%)	333 (41.4%)	166 (39.8%)	
2	133 (32.5%) <sup>βγ</sup>	247 (33.3%) <sup>ε</sup>	316 (39.3%)	177 (42.4%)	
3	44 (10.8%) <sup>αβ</sup>	135 (18.2%)	145 (18.0%)	71 (17.0%)	
Missing	18	13	10	3	
NT-pro-BNP (ng/L)	2142 (1038-4224) <sup>αβγ</sup>	2899 (1517-5259) <sup>δ</sup>	3254 (1705-5785)	3201 (1958-5454)	<0.001
eGFR (ml/min/1.73m <sup>2</sup> )	66 (52-79) <sup>αβγ</sup>	59 (45-71)	56 (45-70)	55 (46-66)	<0.001
6-minute walk test (meters)	368 (276-447) <sup>γ</sup>	350 (264-437)	345 (241-431)	332 (221-414)	0.015
6-minute walk test (% predicted)	75.8±26.8 <sup>γ</sup>	74.0±26.0 <sup>ε</sup>	70.7±25.9	65.4±27.0	<0.001
Systolic blood pressure (mmHg)	127.6±25.6 <sup>βγ</sup>	128.0±20.5 <sup>δ</sup>	123.2±20.9	121.9±18.8	<0.001
Diastolic blood pressure (mmHg)	75.3±14.6 <sup>βγ</sup>	76.0±12.5 <sup>δ</sup>	73.6±12.6	72.5±11.4	<0.001
Heart rate (bpm)	73.8±13.0 <sup>β</sup>	72.7±13.3	71.5±14.2	71.3±13.6	0.008
<b>Echocardiographic</b>					

parameters					
IVSd (mm)	16.6±2.5 <sup>β</sup>	16.9±2.5	17.1±2.5	16.9±2.2	0.011
PWTd (mm)	16.0±2.6 <sup>β</sup>	16.4±2.4	16.5±2.5	16.2±2.6	0.007
MWT (mm)	16.8±2.5 <sup>β</sup>	17.1±2.4	17.3±2.5	17.1±2.2	0.008
Left atrial area (cm <sup>2</sup> )	25.1±5.5 <sup>βγ</sup>	25.9±5.7	26.6±5.4	26.8±5.4	<0.001
Right atrial area (cm <sup>2</sup> )	22.6±6.2 <sup>βγ</sup>	23.7±6.5 <sup>δε</sup>	25.3±6.1	25.4±6.7	<0.001
Stroke volume (ml)	38.4±13.8	38.2±14.2	36.8±13.8	36.3±13.8	0.158
LVEF (%)	50.4±10.2 <sup>βγ</sup>	49.0±10.5 <sup>ε</sup>	48.0±10.8 <sup>φ</sup>	45.1±10.2	<0.001
LVEF ≤40%	62 (15.2%) <sup>βγ</sup>	155 (20.9%)	182 (22.6%) <sup>φ</sup>	132 (31.7%)	<0.001
Longitudinal strain (%)	-11.6±4.0 <sup>βγ</sup>	-11.2±3.7 <sup>δ</sup>	-10.4±3.4	-10.1±3.3	<0.001
TAPSE (mm)	15.9±5.1 <sup>βγ</sup>	15.4±5.0	14.7±5.0	14.6±4.4	0.001
E/e'	16.5±6.9	16.8±6.4	16.8±6.0	17.1±6.6	0.707

**Table 3. Baseline characteristics and echocardiographic parameters for the overall population, separated by the number of heart failure medications patients were treated with.**

P-values for pairwise comparison:  $\alpha = P < 0.05$  for no HF medications vs. 1 HF medication,  $\beta = P < 0.05$  for no HF medications vs. 2 HF medications,  $\gamma = P < 0.05$  for no HF medications vs 3 HF medication,  $\delta = P < 0.05$  for 1 HF medication vs 2 HF medications,  $\epsilon = P < 0.05$  for 1 HF medication vs 3 HF medications,  $\phi = P < 0.05$  for 2 HF medications vs 3 HF medications

HF = Heart failure; AF = Atrial fibrillation; IHD = Ischaemic heart disease; TIA = Transient ischaemic attack; CKD = Chronic kidney disease; PPM = Permanent pacemaker; ICD = Implantable cardioverter defibrillator; CRT-D = Cardiac resynchronisation therapy defibrillator; CRT-P = Cardiac resynchronisation therapy pacemaker; NYHA = New York Heart Association; NAC = National Amyloidosis Centre; NT-pro-BNP = N-terminal pro B-type natriuretic peptide; eGFR = Estimated glomerular filtration rate; IVSd = Interventricular septum in diastole; PWTd = Posterior wall thickness in diastole; MWT = Maximal wall thickness; LVEF = Left ventricular ejection fraction.

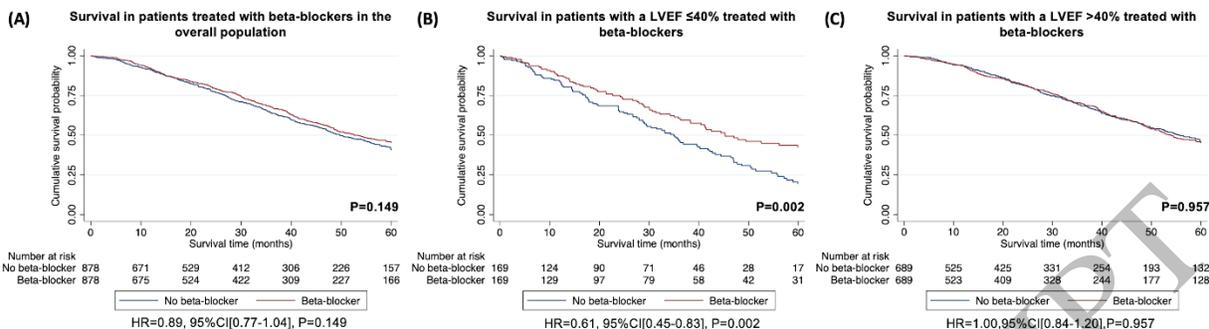


Figure 1  
452x124 mm (x DPI)

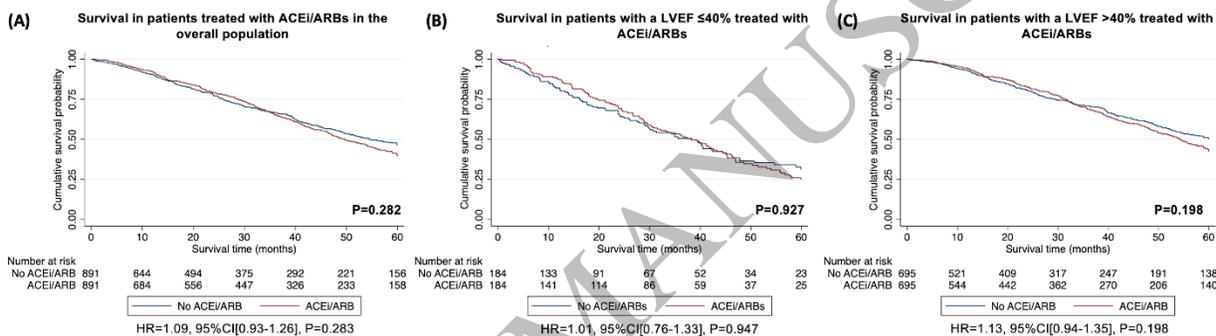


Figure 2  
447x129 mm (x DPI)

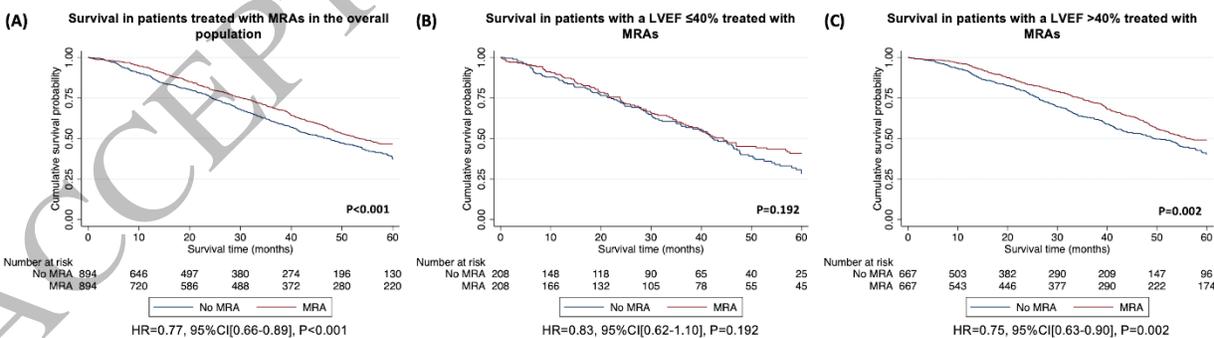


Figure 3  
450x125 mm (x DPI)

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### Key Question

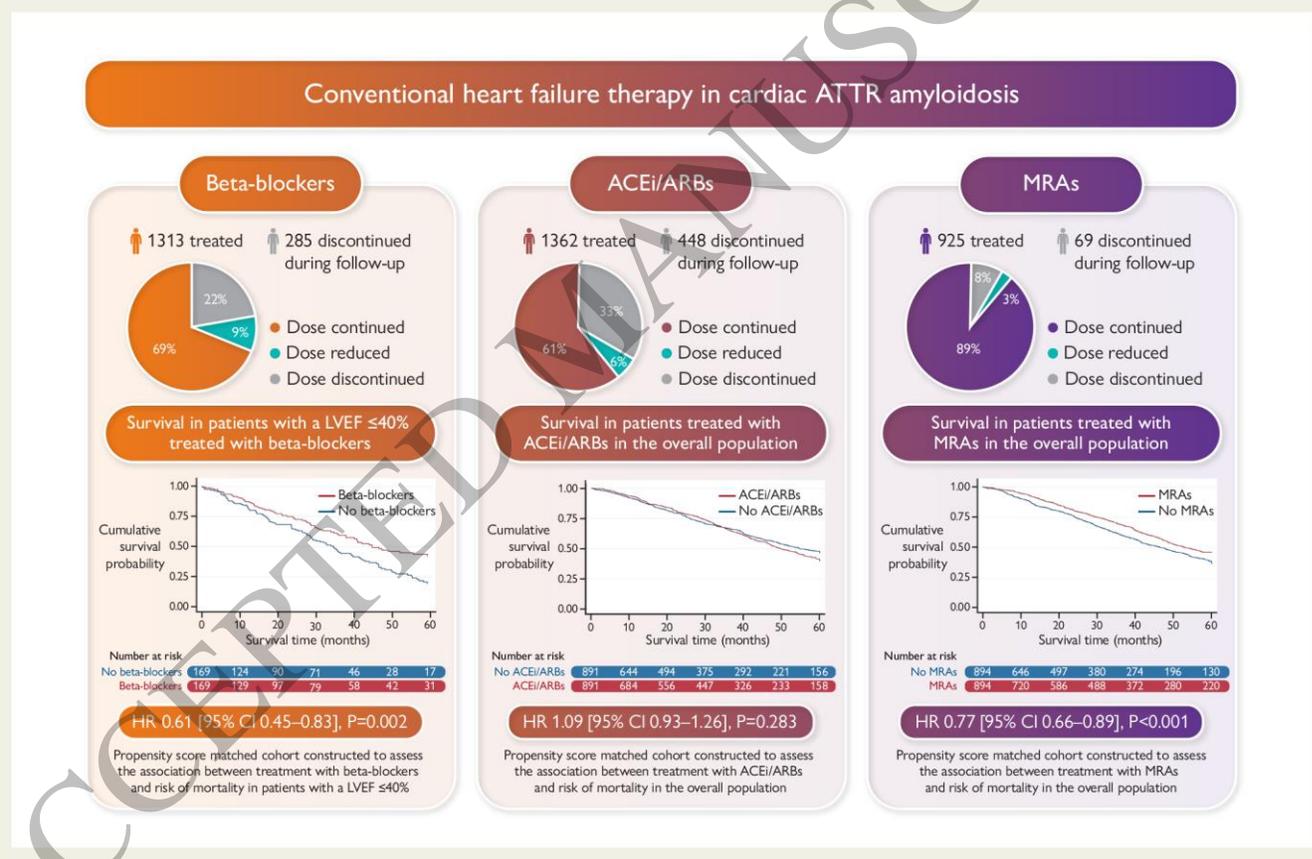
What are the prescription patterns of heart failure (HF) medications in patients with transthyretin cardiac amyloidosis (ATTR-CA)? How are HF medications tolerated in patients with ATTR-CA? Is treatment with HF medications in patients with ATTR-CA associated with survival?

### Key Finding

HF medications were given to patients with more severe cardiac disease. Beta-blockers and ACEi/ARBs were more commonly discontinued than MRAs. MRAs were associated with a reduced risk of mortality in the overall population, and low-dose beta-blockers in patients with a LVEF  $\leq$ 40%.

### Take Home Message

This study shows that MRAs are associated with a reduced risk of mortality in patients with ATTR-CA; low-dose beta-blockers exhibit a similar reduced risk of mortality in the subset with reduced ejection fraction. These findings highlight the urgent need for randomized controlled clinical trials to assess the use of HF medications in ATTR-CA.



Structured Graphical Abstract  
178x181 mm (x DPI)

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