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ORIGINAL RESEARCH

Lack of Association Between Neurohormonal Blockade and Survival in Transthyretin Cardiac Amyloidosis

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BACKGROUND: Despite the belief that heart failure therapies are not effective in transthyretin cardiac amyloidosis, data are limited. We tested the association of neurohormonal blockade use with survival.

METHODS AND RESULTS: A total of 309 consecutive patients with transthyretin cardiac amyloidosis were identified. Medication inventory was obtained at baseline and subsequent visits. Exposure included a neurohormonal blockade class (β-blocker [βB], angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and mineralocorticoid antagonist) at baseline and subsequent visits. βB was modeled as baseline use, time-varying use, and in an inverse probability treatment weighted model. Primary outcome was all-cause mortality analyzed with adjusted Cox proportional hazards models. Continuing compared with stopping βB during follow-up was tested. Mean age was 73.2 years, 84.1% were men, and 17.2% had atrial fibrillation/flutter at baseline. At the time of study entry, 49.8% were on βBs, 35.0% were on angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and 23.9% were on mineralocorticoid antagonists. For the total cohort, there was a trend toward harm in the unadjusted model for baseline βB use, but this was neutral after adjustment. When βB use was analyzed as a time-varying exposure, there was no association with mortality. βB discontinuation was associated with decreased mortality for the total cohort. Findings were consistent in inverse probability treatment weighted models. For angiotensin-converting enzyme inhibitor/angiotensin receptor blocker or mineralocorticoid antagonist use, there was no association with mortality after adjustment for the total cohort.

CONCLUSIONS: There was no association of neurohormonal blockade use with survival in transthyretin cardiac amyloidosis. For the total cohort, deprescribing βB may be associated with improved survival. Additional studies are needed to confirm these findings.

Key Words: cardiac amyloidosis ■ heart failure ■ transthyretin

Recognition of transthyretin amyloid cardiomyopathy (ATTR-CM) has increased in recent years as a result of heightened clinical suspicion, acceptance of noninvasive methods to confirm ATTR-CM, and the emergence of treatment with transthyretin tetramer stabilizers.[1] To date, there have not been any clinical trials specifically designed to address the efficacy of traditional heart failure (HF) therapies for patients with ATTR-CM.

Despite the lack of data, consensus statements[2] and expert opinion reviews[1,3] have recommended against the routine use of neurohormonal blockade, including β-blockers (βBs) and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in ATTR-CM and the avoidance of high dosages. Theoretical risks include hypotension and specifically for βB, concerns that slowing heart rate may blunt the compensatory increase in heart

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CLINICAL PERSPECTIVE

What Is New?

- Although it is believed that traditional heart failure therapies may either cause harm or not be well tolerated in patients with transthyretin cardiac amyloidosis, there are limited data evaluating this.
- In the current study, we demonstrate that there does not appear to be an association of traditional heart failure neurohormonal blockade with survival (either benefit or harm) in a transthyretin cardiac amyloidosis cohort.
- However, in an exploratory analysis, deprescribing β-blockers during follow-up was associated with improved survival.

What Are the Clinical Implications?

- Our data support consensus recommendations that heart failure neurohormonal blockade should be used in selected patients with transthyretin cardiac amyloidosis rather than prescribed routinely given the lack of association with survival in our study.
- Future studies with larger cohorts, preferably randomized trials if possible, are necessary to further investigate the association of traditional heart failure therapies with outcomes in patients with transthyretin cardiac amyloidosis.
- Understanding the role of heart failure therapies will become increasingly imperative as more cases of transthyretin cardiac amyloidosis are recognized and transthyretin amyloid–specific therapies improve survival.

Nonstandard Abbreviations and Acronyms

ATTR	transthyretin amyloid
ATTR-CM	transthyretin amyloid cardiomyopathy
HFpEF	heart failure with preserved ejection fraction
IPTW	inverse probability treatment weighted
MRA	mineralocorticoid antagonist
βB	β-blocker

rate, which may be required to maintain organ perfusion in the setting of a low and fixed stroke volume resulting from low ventricular capacitance and altered ventricular–vascular coupling.[4]

Because of the assumption that neurohormonal blockade may not yield benefit in ATTR-CM but a relative scarcity in published evidence, we sought to address this gap in knowledge and evaluate the association of neurohormonal blockade with survival in ATTR-CM.

METHODS

Consecutive patients with ATTR-CM referred to a single, quaternary care center (Columbia University Irving Medical Center, New York, NY) between February 2002 and November 2018 were enrolled in a registry. All patients aged 18 years and older with either wild-type or variant ATTR-CM were included. Approval for the study was obtained from the Columbia University Irving Medical Center Institutional Review Board. Informed consent was obtained from patients except in cases where they were deceased or lost to follow-up. Demographics, clinical characteristics, and laboratory data were obtained at the baseline clinical visit. Medication data, including βB, ACEI/ARB, and mineralocorticoid antagonist (MRA; spironolactone or eplerenone) use, were available at the baseline visit and subsequent visits. Outcomes, including death and cardiac transplantation, were adjudicated manually from chart review by an amyloid specialist. The date of data lock was August 1, 2019. The data that support the findings of this study are available from the corresponding author upon reasonable request and approval from the study team.

For this study, medication inventory was reviewed, in particular for the baseline visit and the last visit before death, heart transplantation, or end of study. The medication list was obtained by a review of medical records and cross-referenced with the impression and plan of an amyloid specialist to confirm accuracy. Patients on any dose of neurohormonal blockade were coded as users at baseline. If patients stopped using βBs on follow-up visits, they were coded as discontinuing use. For βB dose conversion between βB type, previously published conversion equivalences were used to estimate carvedilol dosing.[5,6]

Statistical Analysis

Baseline characteristics were compared between βB users and nonusers. For continuous variables, distributions were visually assessed for normality with histograms, with normal distributions presented as means and comparisons with independent-sample *t* tests. For non-normally distributed variables, values are presented as medians (interquartile range) and comparisons with the Mann–Whitney *U* test. Categorical variables were compared using the χ^2 test. We had no missing data for baseline medication use for any of the drug classes. For missing data for covariates, we performed a complete case analysis for each respective model.

The association of βB, ACEI/ARB, or MRA use with outcomes were modeled with baseline exposure using Cox proportional hazards regression. In separate

Table 1. Baseline Characteristics Stratified by β-Blocker Use

	Total (n=309)	No β-blocker (n=155)	β-blocker (n=154)
Age, y*	73.2±9.8	71.8±10.8	74.6±8.4
Male sex	84.1	83.2	85.1
Race			
White	72.5	73.5	71.4
Black	23.6	23.2	24.0
Other†	3.9	3.2	4.5
ATTR type			
Wild type	66.0	61.3	70.8
Hereditary	34.0	38.7	29.2
Neuropathy*	8.4	12.3	4.5
Height, cm	172.9±8.9	172.6±8.7	173.2±9.0
Weight, kg	78.8±13.7	77.9±12.5	79.7±14.7
BMI	26.5±4.7	26.1±4.3	26.9±5.1
SBP, mm Hg	115.7±16.3	115.3±15.2	116.1±17.4
DBP, mm Hg	70.4±9.7	70.0±9.2	70.8±10.2
Heart rate, beats/min*	75.2±13.3	77.4±13.8	73.1±12.4
NYHA class*			
I	9.4	14.2	4.5
II	45.3	41.9	48.7
III	41.7	38.7	44.8
IV	3.6	5.2	1.9
Baseline AF/AFL	17.2	15.2	19.2
AF/AFL during follow-up*	51.5	40.6	62.3
Pacemaker	30.1	29.7	30.5
ICD*	15.2	8.4	22.1
Coronary artery disease	6.5	6.5	6.5
Severe aortic stenosis	3.9	2.6	5.2
Creatinine	1.3±0.5	1.3±0.6	1.4±0.5
eGFR*	60.1±22.6	63.6±24.2	56.4±20.3
BNP or NT-proBNP elevated*	40.1	33.8	46.1
Troponin I or Troponin T elevated	37.8	41.4	34.4
LVEF, %*	45.1±15.2	49.1±13.6	41.1±15.6
SHFM score*	1.0±0.8	1.2±0.8	0.7±0.6
Mayo+Loop Diuretic+NYHA Risk model	4.4±2.0	4.3±2.1	4.6±1.9
UK+Loop Diuretic+NYHA Risk model*	4.3±1.9	4.1±2.0	4.6±1.9
Carvedilol equivalent dose, mg/day	10.0 (6.3–16.7)	N/A	10.0 (6.3–16.7)
ACEI/ARB use*	35.0	29.0	40.9
MRA use	23.9	24.5	23.4
TTR stabilizer or clinical trial	17.5	15.5	19.5
RNA knockdown or clinical trial	5.8	7.7	3.9

Continuous variables are presented as mean±SD or median (25th and 75th percentiles), and categorical variables are only presented as percentages. BNP or NTpro-BNP elevated indicates BNP >600 pg/mL or NT-proBNP >3000 pg/mL. Troponin I or Troponin T elevated indicates Troponin I >0.1 ng/mL or Troponin T >0.05 ng/mL. ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AFL, atrial flutter; ARB, angiotensin receptor blocker; ATTR, transthyretin amyloid; BMI, body mass index; BNP, B-type natriuretic peptide; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; n/a, not applicable; NT-proBNP, N-terminal-pro B-type natriuretic peptide; NYHA, New York Heart Association; RNA, ribonucleic acid; SBP, systolic blood pressure; SHFM, Seattle Heart Failure Model; and TTR, transthyretin.

*Statistically significant, $P<0.05$.

†American Indian or Alaska Native, Asian, Native Hawaiian or Pacific Islander, or unspecified.

models, βB use was modeled as a time-varying exposure. The primary outcome was all-cause mortality, with censoring at the time of heart transplant (n=21) or at time of last clinic visit. We confirmed that the proportional hazards assumption was met using Schoenfeld residuals.

Models were adjusted for prespecified covariables known to impact survival in ATTR-CM. These included age; sex; systolic blood pressure; hereditary versus wild-type ATTR; left ventricular ejection fraction (LVEF); baseline atrial fibrillation/flutter; and our previously published ATTR-CM risk model, which incorporates NT-proBNP (N-terminal pro–brain natriuretic peptide) or BNP (B-type natriuretic peptide), troponin (either troponin I or troponin T), diuretic dose, and New York Heart Association (NYHA) class.[7] For βB analyses, heart rate was also in the multivariable model. For each of these traditional HF drug classes, analyses were stratified by a prespecified LVEF cutoff of 50% given no established benefit of these therapies in HF with preserved LVEF (HFpEF).[8] Sensitivity analysis was performed with an LVEF cutoff of 40%.

We carried out prespecified exploratory analyses for mortality stratifying medication use by ATTR-CM risk score tertiles, whether patients continued or stopped a specific medication class during follow-up, and based on an age cut-off of 75 years. Because βBs are frequently used in patients with atrial fibrillation/flutter, we further stratified βBs based on presence of atrial fibrillation/flutter at baseline.

To account for potential confounding by indication, we performed inverse probability treatment weighting (IPTW) using a propensity score for the probability of being prescribed a βB at baseline. For this, the propensity function was calculated as a logit function that incorporated prevalent atrial fibrillation/flutter, coronary artery disease, presence of conduction disease, LVEF, systolic blood pressure, and heart rate. The predicted probabilities calculated from the logit model were used as weights in the Cox proportional hazard model. This analysis was repeated with βB stoppage as the exposure using the same logit function.

Direct-adjusted survival curves were created based on the multivariable Cox proportional hazard models described previously. In short, predicted survival curves were generated for each subject based on their covariate data and then a weighted average of these curves was taken to get an overall estimate.[9]

Statistics were performed using a combination of STATA SE 15 (StataCorp LLC, College Station, TX) and R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). A 2-sided *P* value <0.05 was considered significant.

RESULTS

The cohort consisted of 309 patients with ATTR-CM. Mean age was 73.2±9.8 years, 84.1% were men, 72.5% were White patients (23.6% were Black patients), and 34.0% had hereditary ATTR-CM (Table 1). The vast majority of patients were NYHA class II (45.3%) or class III (41.7%). Mean LVEF was 45.1%±15.2%, and 17.2% had atrial fibrillation/flutter at baseline. For the total cohort, 17.5% were on a transthyretin stabilizer or transthyretin stabilizer clinical trial and 5.8% were on transthyretin knockdown therapy or a transthyretin knockdown therapy clinical trial.

Of the total cohort, 15.2% had an implantable cardioverter-defibrillator, including 8.4% for those not

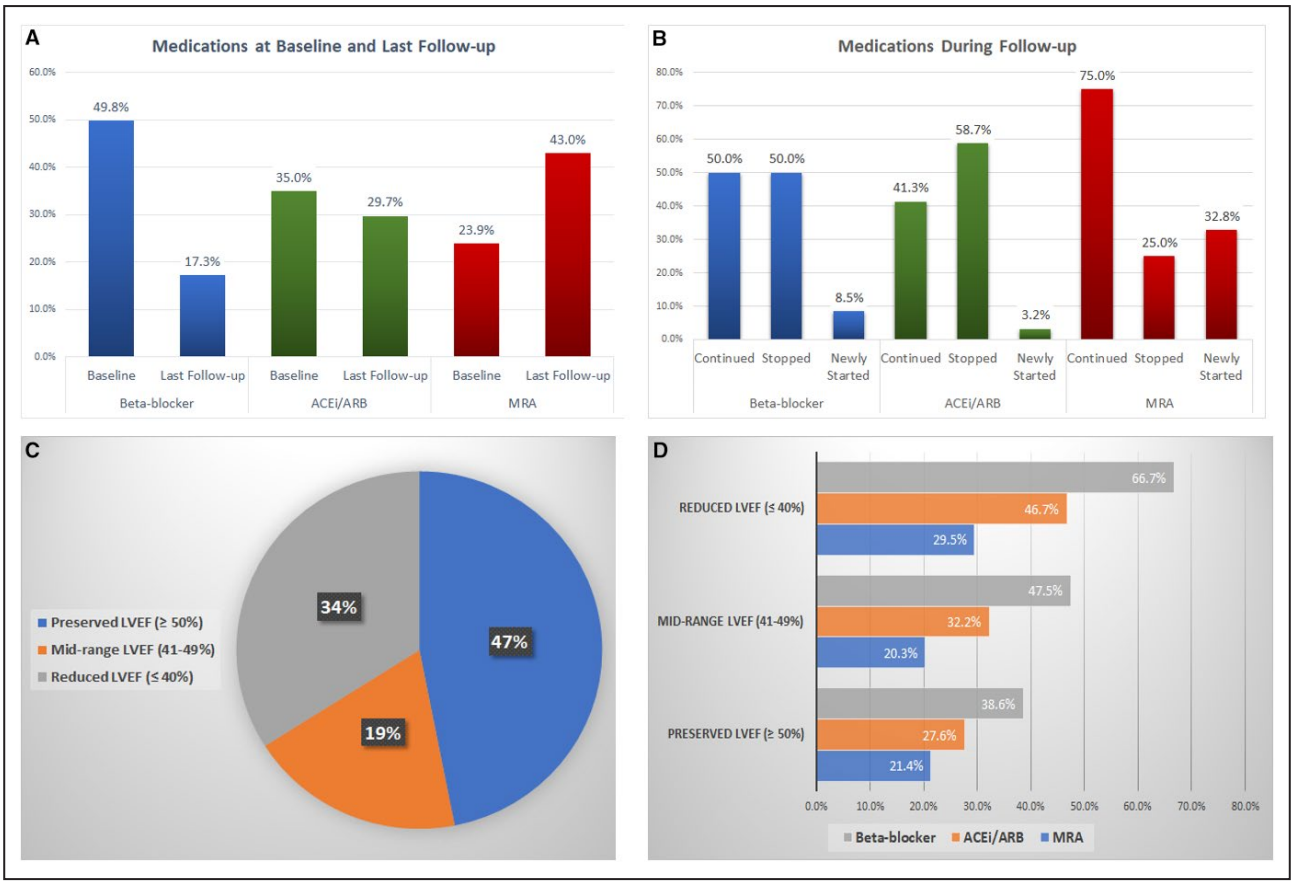

Figure 1. Medication use and distribution of LVEF.
A, Bar graph showing medication use at baseline and last clinic follow-up during the study. **B**, Bar graph showing continuation, discontinuation, and newly started medications during follow-up. **C**, Distribution of heart failure with preserved, mid-range, and reduced LVEF in our cohort. **D**, Use of β-blockers, ACEis/ARBs, and MRAs by LVEF groups at baseline. For β-blockers, approximately half of the patients discontinued use. For ACEis/ARBs, 58.7% of the patients discontinued use. For MRAs, although 25.0% discontinued use, 32.8% were newly started during study follow-up. Despite all patients having confirmed ATTR-CM, the majority of patients had LVEF<50%. Heart failure medication use was higher with lower LVEF. ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ATTR-CM, transthyretin amyloid cardiomyopathy; LVEF, left ventricular ejection fraction; and MRA, mineralocorticoid antagonist.

on βBs and 22.1% on βBs (*P*=0.002). For the total cohort, 35.3% had ECG evidence of conduction disease and 21.4% had complete heart block or were paced. This included 36.1% and 21.9% for those not on βBs and 34.4% and 20.8% for those on βBs for any conduction disease and complete heart block or pacing, respectively (*P*=0.878).

At baseline, 49.8% were on βBs, 35.0% were on ACEIs/ARBs, and 23.9% were on MRAs. At the last clinic follow-up, 17.3% were on βBs, 29.7% were on ACEIs/ARBs, and 43.0% were on MRAs. Approximately half of the patients who were on βBs at baseline were taken off them during follow-up. Of these 3 medication classes, MRA was most frequently started de novo during clinical follow-up (Figure 1A and 1B).

During the study, 66 individuals stopped βBs. Of these, 28.8% had 1 reason, 42.4% had 2 reasons, 25.8% had 3 reasons, and 3.0% had 4 reasons for stopping. The breakdown for stopping βBs is as follows: 72.7% had worsening HF, 59.1% had fatigue, 37.9% had hypotension, 22.7% stopped because of bradycardia, and 10.6% had worsening conduction disease.

More patients had preserved (46.9%) compared with mid-range (19.1%) or reduced (34.0%) LVEF. Patients with reduced LVEF were more likely to be on an ACEI/ARB (*P*=0.007) or a βB (*P*<0.001). There was no significant difference in MRA use by LVEF (*P*=0.254), although there was a trend toward increased MRA use in those with LVEF<40% (Table S1, Figure 1C and 1D).

Baseline βB Use

Patients on βB compared with no βB at baseline were more likely to have atrial fibrillation/flutter, had a lower LVEF (41.1%±15.6% versus 49.1%±13.6%) and lower estimated glomerular filtration rate, were more likely to have elevated BNP, were higher risk by the ATTR (transthyretin amyloid) risk model, and were more frequently on an ACEI/ARB. There was a significant difference in resting heart rate (73.1±12.4 versus 77.4±13.8 beats/min) between those taking and not taking βBs (Table 1). The distribution of βB dose in carvedilol equivalence is shown in Figure S1.

For the total cohort, there was no association between βBs and mortality in the final adjusted model (hazard ratio [HR], 1.37 [95% CI, 0.81–2.33]; *P*=0.244; Table 2). The association remained nonsignificant after IPTW adjustment (HR, 1.34 [95% CI, 0.70–2.57]; *P*=0.380; Figure S2A). In addition, findings remained consistent after adding either implantable cardioverter-defibrillator or coronary artery disease into the model (data not shown). Moreover, addition of ATTR treatment–specific therapy (transthyretin stabilizers or clinical trial, transthyretin knockdown therapy or clinical trial) did not change our findings (data not shown). Interaction testing for βB and continuous LVEF was not significant with *P*=0.377 for mortality. When stratified by LVEF<50% and LVEF≥50%, there was no association in either LVEF group between βB and mortality. Similarly, there were no significant differences by any strata when using a LVEF threshold of 40% or age 75 years (Table S2). Interaction testing for βB and the ATTR risk model showed significant interaction with *P*=0.003 for mortality. There was heterogeneity in effect by baseline risk, with a trend of βB use toward increased mortality in the low-risk (1–3 points; HR, 3.84 [95% CI, 0.74–19.89]; *P*=0.108) and moderate-risk groups (4–6 points; HR, 2.27 [95% CI, 1.04–4.93]; *P*=0.039), whereas this was not seen in the highest risk group (7–9 points). βB use was not significantly different across risk groups (Table S3) and mean dose for βB users was highest in the intermediate-risk group (scores 1–3: 48.0%, carvedilol equivalent mean dose 11.8±9.2 mg/day; scores 4–6: 54.4%, mean dose 16.4±12.2 mg/day; and scores 7–9: 52.1%, mean dose 11.0±10.4 mg/day [χ^2 for use versus nonuse, *P*=0.598;

Table 2. Cox Regression Models for Baseline β-Blocker Use and All-Cause Mortality

	n	Hazard ratio (95% CI)	*P* value
β-blocker use			
Total cohort, unadjusted	309	1.41 (0.95–2.10)	0.087
Total cohort, adjusted	252	1.37 (0.81–2.33)	0.244
Model*			
Total cohort, IPTW adjusted†	252	1.34 (0.70–2.57)	0.380
LVEF<50%, adjusted model*	127	1.34 (0.69–2.70)	0.406
LVEF≥50%, adjusted model*	125	1.81 (0.77–4.29)	0.171
β-blockers—stratified by risk model into groups, adjusted‡			
1 to 3 points, low risk	90	3.84 (0.74–19.89)	0.108
4 to 6 points, moderate risk	123	2.27 (1.04–4.93)	0.039
7 to 9 points, high risk	39	0.63 (0.22–1.82)	0.393
β-blockers—stopping use			
Unadjusted model	154	1.14 (0.66–1.96)	0.638
Adjusted model*	115	0.36 (0.18–0.76)	0.007
IPTW adjusted†	115	0.44 (0.22–0.87)	0.018

Interaction for β-blocker and continuous LVEF for all-cause mortality, *P*=0.377. Interaction for β-blocker and risk model for all-cause mortality, *P*=0.003. ATTR indicates transthyretin amyloid; IPTW, inverse probability treatment weighted; and LVEF, left ventricular ejection fraction.

*Adjusted for age, sex, systolic blood pressure, hereditary vs wild type, LVEF, baseline atrial fibrillation/flutter, heart rate, and ATTR risk model.

†IPTW using a propensity score for the probability of being prescribed a β-blocker at baseline.

‡Adjusted for age, sex, systolic blood pressure, hereditary vs wild type, LVEF, baseline atrial fibrillation/flutter, and heart rate.

ANOVA for mean dose, *P*=0.025]). Given the question of whether there may be differential effect by baseline heart rate, we tested for the interaction of βB with heart rate for mortality, which was not significant (*P*=0.251). We additionally tested whether there was an association of βB dose on survival for those on βB, modeled using βB as a continuous variable. There was no association of βB dose on mortality, with an HR of 1.006 (95% CI, 0.985–1.027; *P*=0.569) for each 1-mg increase in carvedilol dose equivalent in an adjusted model.

Figure 2A and 2C depicts the adjusted survival curves for baseline βB use for the total cohort, stratified by an LVEF of 50% and stratified by ATTR risk model. Figure 3 shows the forest plot for prespecified comparisons of subgroups for the association between baseline βB use and mortality.

βB Use as a Time-Varying Exposure

βB use was further analyzed as a time-varying exposure (Table 3). There was no association with mortality in either the unadjusted or final adjusted model (HR, 1.35 [95% CI, 0.78–2.33]; *P*=0.283). There was no interaction of βB as a time-varying exposure by LVEF (*P*=0.247), with no association of βB with mortality in either those with preserved or reduced LVEF.

Baseline ACEI/ARB Use

Baseline characteristics comparing ACEI/ARB use to nonuse are shown in Table S4. For ACEI/ARB use, there was no association of ACEI/ARB and mortality after adjustment (HR, 0.74 [95% CI, 0.47–1.12]; *P*=0.192; Table 4). The interaction term between ACEI/ARB and LVEF (*P*=0.307) for mortality was not

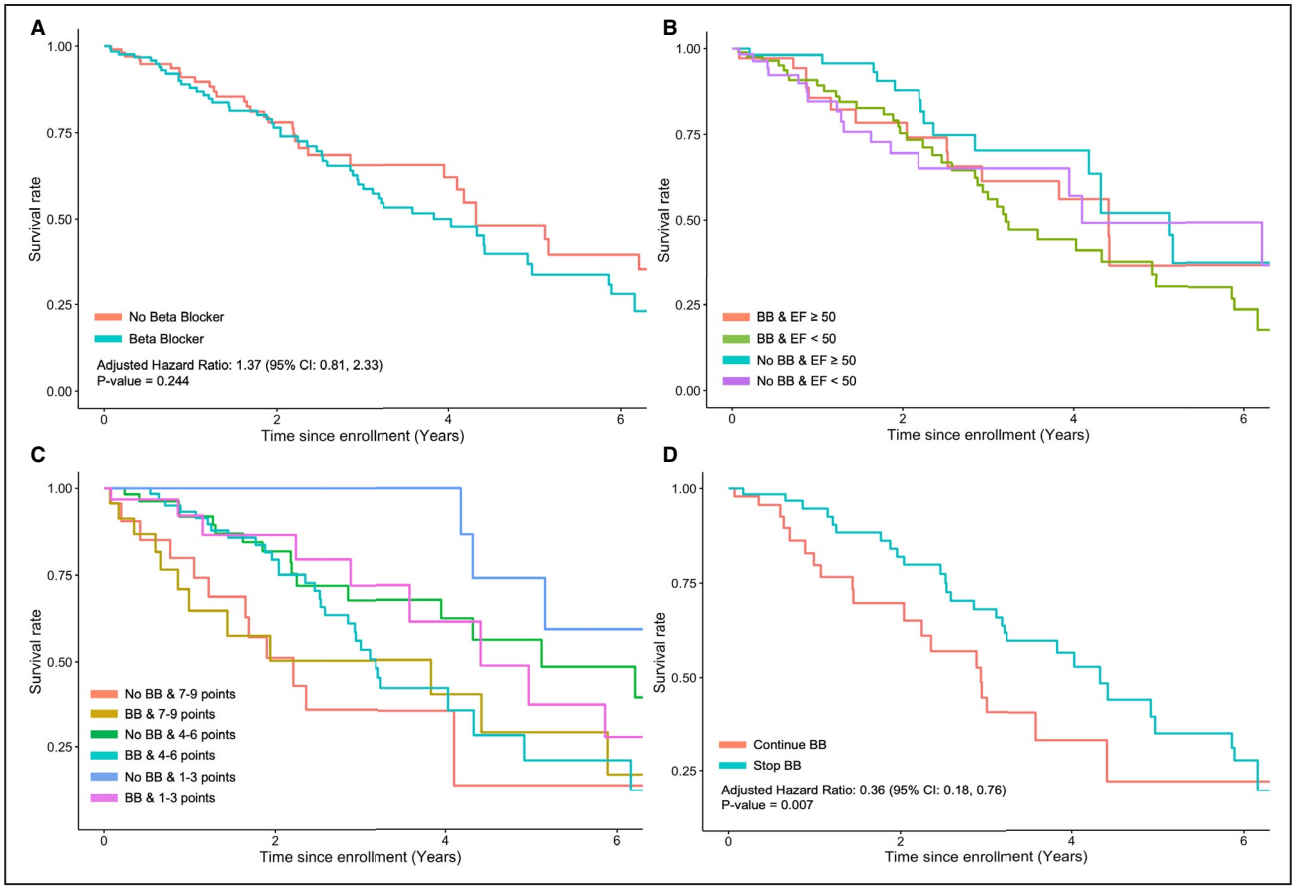

Figure 2. Adjusted survival curves for β-blocker use.
A, Adjusted survival curves for those on β-blockers compared with those not on β-blockers for all-cause mortality. **B**, Adjusted survival curves for β-blockers compared with no β-blockers, stratified by left ventricular ejection fraction, for all-cause mortality. **C**, Adjusted survival curves for β-blockers compared with no β-blockers, stratified by transthyretin cardiac amyloidosis risk model score, for all-cause mortality. **D**, Adjusted survival curves for those who continued compared with those who stopped β-blockers for all cause-mortality. There was no association with mortality for β-blocker use compared with nonuse for the total cohort or when stratified by left ventricular ejection fraction 50%. There was significant heterogeneity by transthyretin cardiac amyloidosis risk model. For patients on β-blockers at baseline, stopping them was associated with greater survival. BB indicates β-blocker; and EF, ejection fraction.

significant, whereas that for ACEI/ARB and ATTR risk model (*P*=0.054) for mortality was borderline significant. The lack of association between ACEI/ARB and mortality remained consistent when stratified by LVEF 50% or ATTR risk model score. Similarly, there was no association when stratified by LVEF 40% (Table S5). There was no significant interaction of ACEI/ARB by age for the total cohort (*P*=0.514).

Figure 4A and 4B shows the adjusted survival curves for ACEI/ARB use for the total cohort and stratified by an LVEF of 50%. For the total cohort, there was increasing separation of the survival curves over time, although comparison between curves was not statistically significant overall (*P*=0.192).

Baseline MRA Use

Baseline characteristics comparing MRA use to nonuse are shown in Table S6. For the total cohort, MRA use was associated with mortality in the unadjusted model (Table 5), likely driven by concurrent diuretic use. After adjusting only for diuretic dose, the association of MRA use with mortality was attenuated and no longer significant (HR, 1.33 [95% CI, 0.85–2.08]; *P*=0.218). Similarly, there was no association of MRA use with mortality in our final adjusted model. There was borderline effect modification for MRA by LVEF on mortality (*P*=0.088) but no interaction by risk model (*P*=0.562) or by age (*P*=0.449). When stratified by LVEF, there was a signal of harm for MRA in those with LVEF≥50%, but not in those with LVEF<50%. However, this was not seen when stratified by an LVEF threshold of 40% (Table S7), with no association of MRA with mortality in either those with LVEF<40% or LVEF≥40%.

Because of the signal of increased mortality with MRA use in those with LVEF≥50%, we compared characteristics of MRA users to nonusers for those with LVEF≥50% (Table S8). In those with LVEF≥50%, MRA users compared with nonusers had lower systolic blood pressure, more atrial fibrillation/flutter, and a large difference in diuretic dose usage (median 40.0 mg/day compared with 1.4 mg/day furosemide equivalence). However, MRA users with LVEF≥50% comprised a small proportion (n=31) of our total cohort (10.0%), decreasing the accuracy of any comparisons for this subgroup.

Figure 4C and 4D shows the adjusted survival curves for MRA use for the total cohort and stratified by an LVEF of 50%. For the total cohort, the survival curves overlapped for MRA use and nonuse.

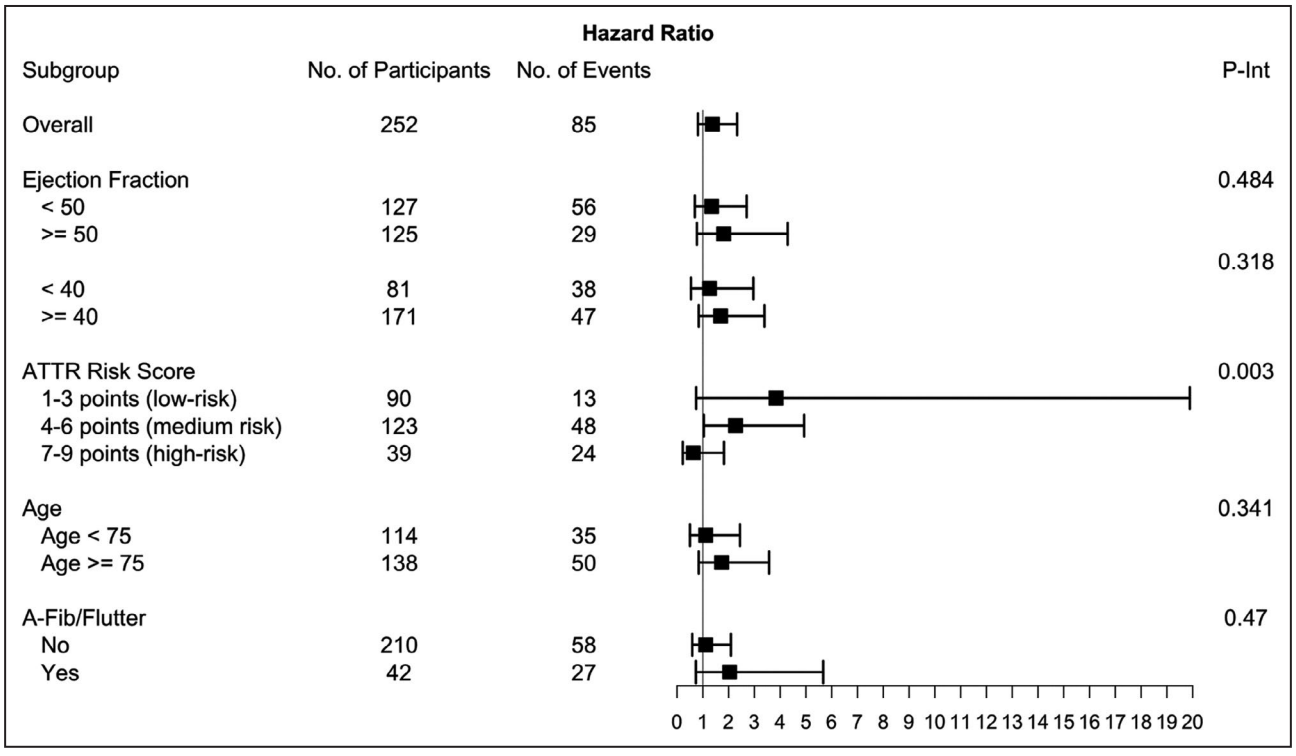

Figure 3. Forest plot for prespecified comparisons of subgroups stratified on left ventricular ejection fraction, transthyretin cardiac amyloidosis risk score, age, and presence/absence of atrial fibrillation/flutter at baseline for β-blocker use compared with no β-blocker use on all-cause mortality.

There was no effect modification by left ventricular ejection fraction cutoff at either 50% or 40%. Even in those with reduced left ventricular ejection fraction there was no association with greater survival from β-blockers. Similarly, there was no interaction by age or presence of atrial fibrillation/flutter. There was significant interaction by baseline risk stratification (with the ATTR risk model), with lower risk patients with transthyretin cardiac amyloidosis associated with increased risk from β-blockers. A-Fib indicates atrial fibrillation; and ATTR, transthyretin amyloid.

Table 3. Cox Regression Models for β-Blocker Modeled as a Time-Varying Exposure and All-Cause Mortality

	N	Hazard ratio (95% CI)	*P* value
β-blocker use			
Total cohort, unadjusted	309	0.80 (0.53–1.23)	0.315
Total cohort, adjusted model*	252	1.35 (0.78–2.33)	0.283
LVEF<50%, adjusted model*	252	1.07 (0.55–2.09)	0.836
LVEF≥50%, adjusted model*	252	1.97 (0.84–4.60)	0.117
β-blockers—stratified by risk model into groups, adjusted†			
1 to 3 points, low risk	90	1.59 (0.49–5.17)	0.443
4 to 6 points, moderate risk	123	1.05 (0.49–2.21)	0.907
7 to 9 points, high risk	39	1.10 (0.38–3.21)	0.864

Interaction for β-blocker and continuous LVEF for all-cause mortality, *P*=0.247. Interaction for β-blocker and risk model for all-cause mortality, *P*=0.550. LVEF indicates left ventricular ejection fraction.

*Adjusted for age, sex, systolic blood pressure, hereditary vs wild type, LVEF, baseline atrial fibrillation/flutter, heart rate, and transthyretin amyloid risk model.

Table 4. Cox Regression Models for ACEI/ARB Use and All-Cause Mortality

	N	Hazard ratio (95% CI)	*P* value
ACEI/ARB use			
Total cohort, unadjusted	309	1.08 (0.73–1.61)	0.699
Total cohort, adjusted model*	270	0.74 (0.47–1.12)	0.192
LVEF<50%, adjusted model*	140	0.66 (0.37–1.17)	0.155
LVEF≥50%, adjusted model*	130	0.86 (0.37–1.97)	0.713
ACEI/ARB—stratified by risk model into groups, adjusted†			
1 to 3 points, low risk	86	1.22 (0.31–4.90)	0.776
4 to 6 points, moderate risk	124	1.26 (0.68–2.32)	0.461
7 to 9 points, high risk	46	0.56 (0.20–1.51)	0.250
ACEI/ARB—stopping use			
Unadjusted model	92	1.83 (0.80–4.20)	0.151
Adjusted model*	89	0.85 (0.29–2.47)	0.763

Interaction for ACEI/ARB and continuous LVEF all-cause mortality, *P*=0.307. Interaction for ACEI/ARB and risk model for all-cause mortality, *P*=0.054. ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; and LVEF, left ventricular ejection fraction.

*Adjusted for age, sex, systolic blood pressure, hereditary vs wild type, LVEF, baseline atrial fibrillation/flutter, and ATTR risk model.

†Adjusted for age, sex, systolic blood pressure, hereditary vs wild type, LVEF, and baseline atrial fibrillation/flutter.

Deprescribing Medications

When comparing patients who stopped βBs with those who continued βBs during follow-up, stopping βBs was associated with decreased mortality in the adjusted model (HR, 0.36 [95% CI, 0.18–0.76]; *P*=0.007). Findings were consistent after IPTW modeling (HR, 0.44 [95% CI, 0.22–0.87]; *P*=0.018), although optimal covariate balance was not achievable because of the restricted sample size (Figure S2B). In addition, findings remained consistent after adding either implantable cardioverter-defibrillator or coronary artery disease into the model (data not shown). Figure 2D depicts adjusted survival curves for those who discontinued βBs compared with continuing βBs; for those who stopped βB, survival appeared to improve with early separation of survival curves.

In contrast to the observed effects of stopping βBs, stopping ACEI/ARB during follow-up was not associated with mortality (adjusted model: HR, 0.85 [95% CI, 0.29–2.47]). Similarly, stopping MRAs during follow-up was not associated with mortality (adjusted model: HR, 0.85 [95% CI, 0.29–2.47]).

DISCUSSION

There were several findings in the overall study: (1) There was no association of traditional HF neurohormonal blockade medications with survival in ATTR-CM for the total cohort for βBs, ACEIs/ARBs, or MRAs. For βB use, findings remained consistent regardless of modeling usage at baseline, time-varying use, or after IPTW adjustment. (2) The association of baseline βB use with mortality may be heterogenous by patient risk at time of presentation, although this was not seen in the time-varying model. (3) Stopping βBs during follow-up was associated with improved survival. (3) For ACEIs/ARBs, there was no association with mortality, and stopping ACEIs/ARBs had no impact on survival. (4) Lastly, for MRAs, although there was a signal toward harm, this appeared to be largely driven by concurrent diuretic use, and the association was no longer significant after adjustment for diuretic use.

Medical Therapy for ATTR-CM

Historically, management of ATTR-CM was predominantly focused on maintaining euvolemia with loop diuretics. In more recent years, there has been a proliferation of studies on disease-modifying therapies for ATTR-CM. Of these, only tafamidis is approved by the US Food and Drug Administration for use in ATTR-CM[10] based on data showing reduction in HF hospitalization and mortality when compared with placebo.[11] Although there is promise for therapies that decrease transthyretin production,[12,13] studies specific to predominant cardiomyopathy phenotypes are ongoing and not currently available for this indication.

Conversely, data on traditional HF therapies with neurohormonal blockade in ATTR-CM have been

limited. Clinically, this can be challenging when encountering the patient with definitive ATTR-CM, particularly those with left ventricular systolic dysfunction. The presence of autonomic dysfunction and inability to augment stroke volume in response to vasodilation are particular concerns with neurohormonal blockade in these patients. Although ATTR-focused documents[1,2] frequently mention avoiding neurohormonal blockade in ATTR-CM, particularly βBs, systematic studies are lacking.

HF studies evaluating the benefit of traditional pharmacotherapies in HFpEF have not shown benefit with βBs,[14] ACEIs/ARBs,[15–17] or MRAs.[18] In light of these findings, current consensus does not recommend these agents for the specific treatment of HFpEF.[8] This lack of benefit has been postulated to partially be attributed to heterogeneity of the response of these agents across LVEF ranges[19,20] and disease entities classified as HFpEF, including unrecognized cardiac amyloid as one of its constituents.[21] Cardiac amyloidosis can have variable LVEF, and although the majority will have nearly preserved LVEF, a fraction will have reduced LVEF. In the present cohort, 53.1% of patients had LVEF<50% and 34.0% had LVEF<40% at their baseline visits. Hence, the traditional HFpEF paradigm may not fully encompass ATTR-CM.

In our current study, there was no association of βB with mortality for the total cohort with either baseline βB use (in either the multivariable or IPTW-adjusted models) or βB modeled as a time-varying exposure. With baseline βB use, there was effect modification depending on severity of the ATTR-CM disease phenotype

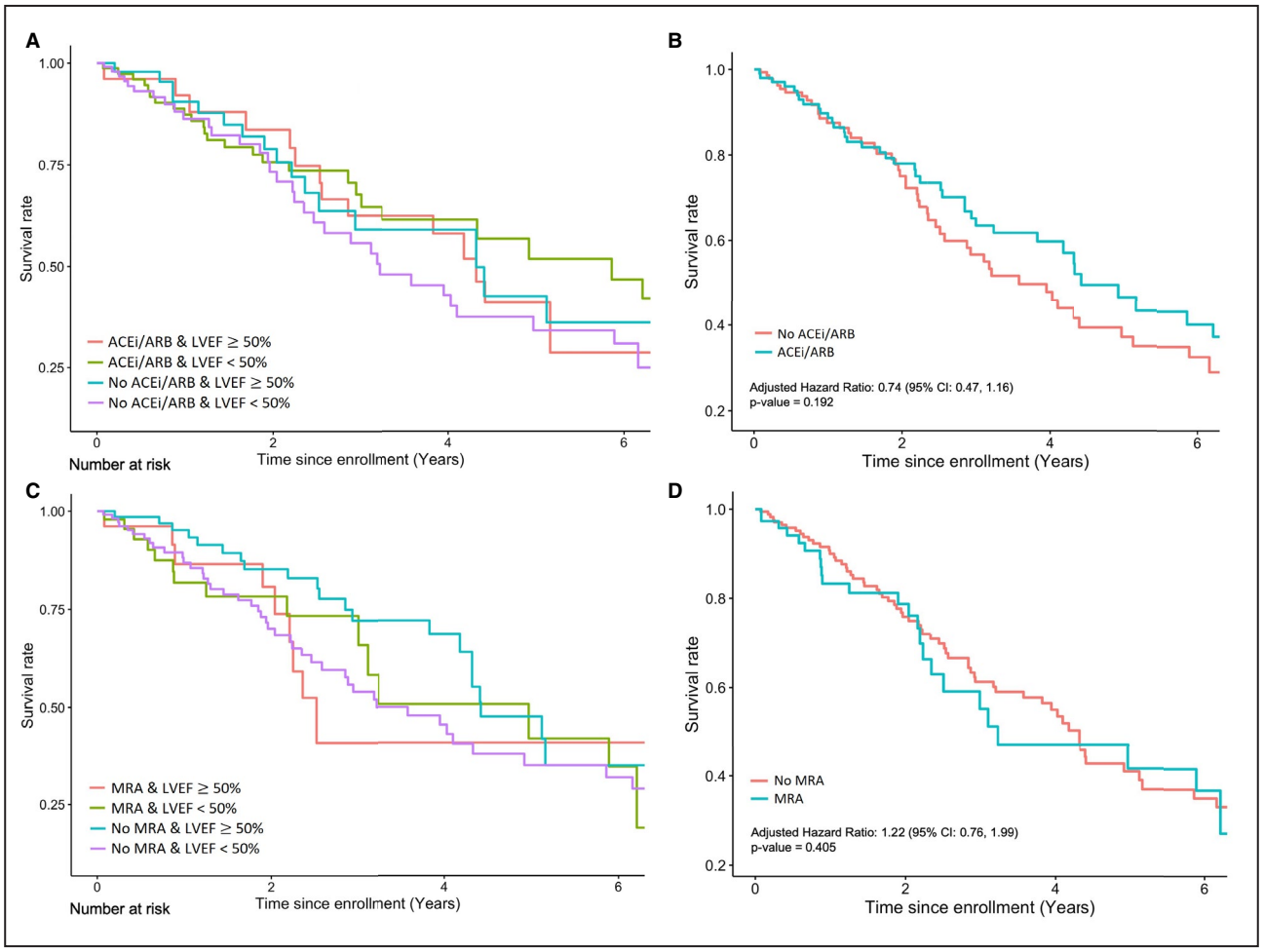

Figure 4. Adjusted survival curves for ACEi/ARB and MRA use.
A, Adjusted survival curves for those on ACEis/ARBs compared with those not on ACEis/ARBs for all-cause mortality. **B**, Adjusted survival curves for ACEi/ARB compared with no ACEi/ARB, stratified by LVEF, for all-cause mortality. **C**, Adjusted survival curves for those on MRAs compared with those not on MRAs for all-cause mortality. **D**, Adjusted survival curves for those on MRAs compared with those not on MRAs, stratified by LVEF, for all-cause mortality. For the total cohort, there was no association with mortality for ACEi/ARB use compared with nonuse. Similar findings were seen when stratified by LVEF 50%. Similarly, there was no association of MRAs use with mortality. However, when stratified by LVEF, there was an association with increased risk for MRA use compared with nonuse in those with LVEF≥50%. ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; LVEF, left ventricular ejection fraction; and MRA, mineralocorticoid antagonist.

Table 5. Cox Regression Models for MRA Use and All-Cause Mortality

	n	Hazard ratio (95% CI)	*P* value
MRA			
Total cohort, unadjusted	309	1.82 (1.18–2.81)	0.007
Total cohort, adjusted model*	270	1.23 (0.76–1.99)	0.405
LVEF<50%, adjusted model*	140	0.98 (0.54–1.79)	0.959
LVEF≥50%, adjusted model*	130	2.70 (1.10–6.61)	0.030
MRA—stratified by risk model into groups, adjusted†			
1 to 3 points, low risk	86	0.89 (0.14–5.82)	0.905
4 to 6 points, moderate risk	124	1.16 (0.59–2.30)	0.662
7 to 9 points, high risk	46	1.08 (0.48–2.43)	0.858
MRA—stopping use			
Unadjusted model	59	0.70 (0.27–1.79)	0.455
Adjusted model*	49	1.37 (0.46–4.08)	0.568

Interaction for MRA and continuous LVEF all-cause mortality, *P*=0.088. Interaction for MRA and risk model for all-cause mortality, *P*=0.562. LVEF indicates left ventricular ejection fraction; and MRA, mineralocorticoid antagonists.

*Adjusted for age, sex, systolic blood pressure, hereditary vs wild type, LVEF, baseline atrial fibrillation/flutter, and ATTR risk model.

†Adjusted for age, sex, systolic blood pressure, hereditary vs wild type, LVEF, and baseline atrial fibrillation/flutter.

despite there being no differences in frequency of βB use across the different risk strata. However, this finding was no longer significant in our time-varying model. Regardless, these findings suggest that ATTR-CM may not be a homogenous cohort, and there may be discrete effects dependent on disease severity.

In addition, we found that deprescribing βBs in patients with ATTR-CM was associated with better outcomes. There is theoretical benefit to discontinuing βBs, particularly in advanced disease that may be dependent on heart rate because of a low stroke volume from the small left ventricular cavity. Although we did not have data on functional change over time, we found that stopping βB is associated with improved survival. Because of the relatively small sample size for our data set, we did not further stratify this subanalysis into differential risk groups or by LVEF.

Similar to βBs, there was no association of ACEIs/ARBs with mortality in the total cohort. Patients with LVEF<50% or those at high risk based on the ATTR risk model were associated with a trend toward benefit from ACEIs/ARBs for mortality. Nonetheless, these findings must be interpreted with caution because the interaction term of ACEI/ARB with LVEF with regard to mortality was not significant and for ACEI/ARB with risk model it was borderline significant. Notably, the common concerns of harm with ACEI/ARB in ATTR-CM was not seen in our total cohort or in any strata.

In unadjusted analyses, MRAs appeared to be associated with increased mortality. However, this was likely driven by concurrent use of loop diuretics. When we adjusted for loop diuretics alone, the association between MRAs and mortality was no longer significant, suggesting that loop diuretics served as the mediator for harm. We previously demonstrated that loop diuretics are an independent risk factor for mortality in ATTR-CM, supporting this finding.[7] Interestingly, when stratified by LVEF, MRA use was associated with increased risk in patients with ATTR-CM with preserved LVEF but not in those with reduced LVEF. This needs to be interpreted with caution because of the small sample size of MRA users in those with LVEF≥50% that limits accuracy of our estimates. Furthermore, MRA users were a "sicker" group, with lower blood pressure, more atrial fibrillation/flutter, and higher ATTR risk model scores; despite attempts at adjusting for confounders, there is likely residual confounding in a nonrandomized cohort.

Implications and Future Directions

Our findings lend credence to what has been commonly believed based on anecdotal experience but without previously established data. We show that there was no association of traditional HF therapy use with survival in ATTR-CM.[1,2] However, perhaps the most important finding in our study is that the deprescribing of βBs is associated with improved survival. A recent analysis of the ATTR-ACT (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial) study on causes of death demonstrated that 56% of total deaths were adjudicated because of HF and that of the cardiovascular-related deaths, HF accounted for 80% of them, whereas sudden death accounted for only 11% of total deaths.[22] In our cohort, the reason for stopping βBs during follow-up was worsening HF in 72.7% of the cases, which may partially explain our finding. Furthermore, there is some suggestion of heterogeneity of risk with βB use within the ATTR-CM cohort. Although patients with ATTR-CM are frequently classified under the uniform HFpEF designation and, more precisely, under ATTR cardiac amyloidosis, there may be a variable spectrum of disease and differential response to treatment. Our findings need to be confirmed in larger cohorts with closely adjudicated medication inventories and prospective follow-up.

Limitations

Our study has several limitations that need to be considered. First, this cohort was from a quaternary care referral center with potential for referral bias. Hence, its generalizability to patients in the community needs to be studied. Second, given that this is a retrospective analysis, there may be selection and treatment

bias in terms of which patients with ATTR-CM were on βBs, ACEIs/ARBs, or MRAs at baseline. Similarly, there may be bias regarding medication changes over time, which were up to the discretion of the providers. For example, patients who are sicker are more likely to have their βBs stopped—however, this would bias the effect of deprescribing βBs toward the null rather than the benefit that we observed. Third, although we attempted to adjust for a number of covariables known to impact mortality in ATTR-CM, there may be residual or unmeasured confounding present, as with any retrospective analysis. Hence, our results are exploratory rather than confirmatory and do not provide a direct causal link. Inference on pharmaco-epidemiology and the associations we report should be cautious. Thus, we report associations rather than casual inferences. Fourth, although we had longitudinal data on medication inventory in patients, the duration between inventories was variable, as was the duration of follow-up. Lastly, we adjusted for characteristics at the baseline visit including LVEF, which may have changed in status or severity during follow-up.

CONCLUSIONS

Use of traditional HF therapies in ATTR-CM was not associated with survival benefit. For the total cohort, stopping βBs was associated with improved survival; however, this finding was exploratory and needs to be further studied. The effects of ACEIs/ARBs and MRAs both appeared neutral for the total cohort but suggested a variable effect for MRAs depending on reduced versus preserved LVEF. Future studies with a larger patient cohort are needed to confirm and better characterize these findings.

ARTICLE INFORMATION

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Supplementary Material

Table S1–S8
Figure S1–S2

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Supplemental Material

Table S1. HF therapy use by preserved, mid-range or reduced LVEF

	Preserved LVEF (≥ 50%) (n = 145)	**Mid-range LVEF (40-49%) (n = 59)**	**Reduced LVEF (< 40%) (n = 105)**	**p-value for trend**
ACEi/ARB	40 (27.6%)	19 (32.2%)	49 (46.7%)	p = 0.007
Beta-blocker	56 (38.6%)	28 (47.5%)	70 (66.7%)	P < 0.001
MRA	31 (21.4%)	12 (20.3%)	31 (29.5%)	P = 0.254

Table S2. Cox regression models for beta-blocker use and all-cause mortality

	Hazard ratio (95% CI)	p-value
LVEF < 40%, Adjusted model*	1.26 (0.54-2.96)	0.598
LVEF ≥ 40%, Adjusted model*	1.69 (0.84-3.39)	0.140
Age ≥ 75 years, Adjusted model*	1.73 (0.84-3.57)	0.139
Age < 75 years Adjusted model*	1.10 (0.50-2.42)	0.813

(Interaction for beta-blocker and age for all-cause mortality p = 0.299)

*Adjusted for age, sex, systolic blood pressure, hereditary vs. wildtype, LVEF, and baseline atrial fibrillation/flutter, heartrate, and ATTR risk model

Table S3. Beta-blocker use across risk groups.

Risk score group	Baseline beta-blocker use	Mean dose (mg/day)
1-3	48.0%	11.8 ± 9.2
4-6	54.4%	16.4 ± 12.2
7-9	52.1%	11.0 ± 10.4
	Chi-square p = 0.598	ANOVA for mean dose trend p = 0.025; post-hoc Tukey HSD was not significant between groups

Table S4. Baseline characteristics by ACEi/ARB use

	Total (n = 309)	No ACEi/ARB (n = 201)	ACEi/ARB (n = 108)
Age (years)	73.2 ± 9.8	72.8 ± 10.7	74.0 ± 7.8
Male sex	84.1%	86.6%	79.6%
Race*			
-White	72.5%	78.1%	62.0%
-Black	23.6%	17.9%	34.3%
-Other	3.9%	4.0%	3.7%
ATTR type			
-Wildtype	66.0%	67.2%	63.9%
-Hereditary	34.0%	32.8%	36.1%
Height (cm)	172.9 ± 8.9	172.9 ± 8.4	172.9 ± 9.6
Weight (kg)	78.8 ± 13.7	77.0 ± 13.1	80.3 ± 14.6
BMI*	26.5 ± 4.7	25.9 ± 3.5	27.5 ± 6.3
SBP (mmHg)	115.7 ± 16.3	115.9 ± 15.1	115.4 ± 18.4
DBP (mmHg)	70.4 ± 9.7	70.2 ± 9.2	70.7 ± 10.6
Heartrate (bpm)	75.2 ± 13.3	75.6 ± 13.8	74.6 ± 12.4
NYHA class			
-I	9.4%	10.4%	7.4%
-II	45.3%	46.3%	43.5%
-III	41.7%	38.8%	47.2%
-IV	3.6%	4.5%	1.9%
Baseline AF/AFL	17.2%	15.7%	19.8%
AF/AFL during follow-up	51.5%	52.2%	50.0%
Creatinine	1.3 ± 0.5	1.4 ± 0.6	1.3 ± 0.5
eGFR	60.1 ± 22.6	60.4 ± 24.4	59.3 ± 18.8
BNP or NTpro-BNP elevated*	40.1%	45.2%	31.1%
Trop-I or Trop-T elevated	37.8%	34.6%	43.8%
LVEF (%)*	45.1 ± 15.2	47.0 ± 14.8	41.6 ± 15.2
-LVEF < 40%*			
-LVEF < 50%*			
SHFM score*	1.0 ± 0.8	1.0 ± 0.8	0.8 ± 0.8
Mayo + Loop Diuretic + NYHA Risk model	4.4 ± 2.0	4.4 ± 2.1	4.5 ± 1.8
UK + Loop Diuretic + NYHA Risk model	4.3 ± 1.9	4.3 ± 2.1	4.4 ± 1.7
BB use*	49.8	45.3%	58.3%
MRA use	23.9%	22.9%	25.9%

Continuous variables presented as median with 25th and 75th percentiles and Mann-Whitney test; categorical variables presented as percentages; *Statistically significant, $p < 0.05$

Abbreviations: ATTR = Transthyretin amyloid, BMI = Body Mass Index, SBP = systolic blood pressure, DBP = diastolic blood pressure, NYHA = New York Heart Class, eGFR = glomerular filtration rate, BNP = B-type

natriuretic peptide, BNP or NTpro-BNP elevated (BNP > 600 pg/ml or NT-proBNP > 3000 pg/ml), Trop = Troponin, Trop-I or Trop-T elevated (Trponin-I > 0.1 ng/ml or Troponin-T > 0.05 ng/ml), SHFM = Seattle Heart failure Model, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, MRA = mineralocorticoid receptor antagonist)

Table S5. Cox regression models for ACE/ARB use and all-cause mortality

	Hazard ratio (95% CI)	p-value
LVEF < 40%, Adjusted model*	0.67 (0.34-1.31)	0.240
LVEF ≥ 40%, Adjusted model*	0.95 (0.50-1.78)	0.866
Age ≥ 75 years, Adjusted model*	1.29 (0.69-2.41)	0.424
Age < 75 years Adjusted model*	0.39 (0.17-0.92)	0.032

(Interaction for ACEi/ARB and age for all-cause mortality p = 0.878)

*Adjusted for age, sex, systolic blood pressure, hereditary vs. wildtype, LVEF, and baseline atrial fibrillation/flutter, and ATTR risk model

Table S6. Baseline characteristics by MRA use

	Total (n = 309)	No MRA (n = 235)	MRA (n = 74)
Age (years)	73.2 ± 9.8	73.3 ± 10.0	72.9 ± 9.0
Male sex	84.1%	83.8%	85.1%
Race			
-White	72.5%	74.0%	67.6%
-Black	23.6%	22.6%	27.0%
-Other	3.9%	3.4%	5.4%
ATTR type			
-Wildtype	66.0%	65.5%	67.6%
-Hereditary	34.0%	34.5%	32.4%
Height (cm)	172.9 ± 8.9	172.7 ± 8.5	173.5 ± 9.9
Weight (kg)*	78.8 ± 13.7	77.9 ± 13.0	81.6 ± 15.5
BMI	26.5 ± 4.7	26.3 ± 4.9	26.8 ± 4.0
SBP (mmHg)*	115.7 ± 16.3	117.0 ± 16.5	111.6 ± 15.2
DBP (mmHg)	70.4 ± 9.7	71.0 ± 9.7	68.4 ± 9.5
Heartrate (bpm)	75.2 ± 13.3	75.8 ± 13.2	73.5 ± 13.6
NYHA class*			
-I	9.4%	11.9%	1.4%
-II	45.3%	46.4%	41.9%
-III	41.7%	39.6%	48.6%
-IV	3.6%	2.1%	8.1%
Baseline AF/AFL	17.2%	15.1%	24.2%
AF/AFL during follow-up	51.5%	49.4%	58.1%
Creatinine	1.3 ± 0.5	1.3 ± 0.5	1.4 ± 0.5
eGFR	60.1 ± 22.6	61.4 ± 23.5	56.0 ± 19.0
BNP or NTpro-BNP elevated	40.1%	40.8%	38.0%
Trop-I or Trop-T elevated	37.8%	35.8%	44.3%
LVEF (%)	45.1 ± 15.2	46.0 ± 14.7	42.1 ± 16.2
SHFM score	1.0 ± 0.8	1.0 ± 0.7	1.0 ± 0.9
Mayo + Loop Diuretic + NYHA Risk model*	4.4 ± 2.0	4.2 ± 2.0	5.2 ± 1.8
UK + Loop Diuretic + NYHA Risk model*	4.3 ± 1.9	4.1 ± 2.0	5.1 ± 1.7
ACEi/ARB use	35.0%	34.0%	37.8%
BB use	49.8%	50.2%	48.6%
Diuretic dose (furosemide daily equivalent)*	40.0 (0-60.0)	20.0 (0-40.0)	40.0 (20.0-80.0)

Continuous variables presented as median with 25th and 75th percentiles and Mann-Whitney test; categorical variables presented as percentages; *Statistically significant, $p < 0.05$

Abbreviations: ATTR = Transthyretin amyloid, BMI = Body Mass Index, SBP = systolic blood pressure, DBP = diastolic blood pressure, NYHA = New York Heart Class, eGFR = glomerular filtration rate, BNP = B-type natriuretic peptide, BNP or NTpro-BNP elevated (BNP > 600 pg/ml or NT-proBNP > 3000 pg/ml), Trop = Troponin, Trop-I or Trop-T elevated (Trponin-I > 0.1 ng/ml or Troponin-T > 0.05 ng/ml), SHFM = Seattle Heart failure Model, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, MRA = mineralocorticoid receptor antagonist

Table S7. Cox regression models for Mineralocorticoid antagonist (MRA) use and all-cause mortality

	Hazard ratio (95% CI)	p-value
LVEF < 40%, Adjusted model*	0.98 (0.49-1.99)	0.964
LVEF ≥ 40%, Adjusted model*	1.83 (0.90-3.70)	0.093
Age ≥ 75 years, Adjusted model*	1.23 (0.63-2.41)	0.549
Age < 75 years Adjusted model*	1.40 (0.65-3.00)	0.390

(Interaction for MRA and age for all-cause mortality p = 0.378)

*Adjusted for age, sex, systolic blood pressure, hereditary vs. wildtype, LVEF, baseline atrial fibrillation/flutter, and ATTR risk model

Table S8. Baseline characteristics by MRA use (LVEF ≥ 50% only)

	Total (n = 145)	No MRA (n = 114)	MRA (n = 31)
Age (years)	72.1 ± 10.8	72.0 ± 11.0	72.7 ± 10.2
Male sex	84.8%	85.1%	83.7%
Race*			
-White	82.8%	81.6%	87.1%
-Black	13.8%	16.7%	3.2%
-Other	3.4%	1.8%	9.7%
ATTR type			
-Wildtype	71.0%	67.5%	83.9%
-Hereditary	29.0%	32.5%	16.1%
Height (cm)*	173.0 ± 8.9	172.1 ± 8.9	176.4 ± 8.2
Weight (kg)	79.6 ± 14.4	78.6 ± 14.3	83.3 ± 14.5
BMI	26.6 ± 4.9	26.7 ± 5.2	26.5 ± 3.5
SBP (mmHg)*	118.4 ± 15.1	120.1 ± 14.8	112.1 ± 14.4
DBP (mmHg)	70.7 ± 9.7	71.5 ± 9.8	67.7 ± 8.7
Heartrate (bpm)	73.2 ± 13.0	74.0 ± 12.8	70.6 ± 13.8
NYHA class			
-I	14.5%	18.4%	0%
-II	49.7%	47.4%	58.1%
-III	34.5%	33.3%	38.7%
-IV	1.4%	0.9%	3.2%
Baseline AF/AFL*	12.4%	10.1%	21.4%
AF/AFL during follow-up*	52.4%	35.5%	57.0%
Creatinine	1.2 ± 0.5	1.2 ± 0.5	1.3 ± 0.3
eGFR	64.6 ± 21.9	66.3 ± 23.0	58.8 ± 16.7
BNP or NTpro-BNP elevated	28.8%	29.4%	26.7%
Trop-I or Trop-T elevated	27.7%	24.5%	38.7%
LVEF (%)	64.6 ± 21.9	58.6 ± 6.2	57.7 ± 7.8
SHFM score	0.8 ± 0.6	0.8 ± 0.6	0.8 ± 0.8
Mayo + Loop Diuretic + NYHA Risk model*	3.8 ± 2.0	3.6 ± 2.0	4.5 ± 1.7
UK + Loop Diuretic + NYHA Risk model*	3.7 ± 1.9	3.5 ± 1.9	4.5 ± 1.6
ACEi/ARB use	27.6%	27.2%	29.0%
BB use	38.6%	36.8%	45.2%
Diuretic dose (furosemide daily equivalent)*	20.0 (0.0-40.0)	1.4 (0.0-40.0)	40.0 (10.0-80.0)

Continuous variables presented as median with 25th and 75th percentiles and Mann-Whitney test; categorical variables presented as percentages; *Statistically significant, $p < 0.05$

Abbreviations: ATTR = Transthyretin amyloid, BMI = Body Mass Index, SBP = systolic blood pressure, DBP = diastolic blood pressure, NYHA = New York Heart Class, eGFR = glomerular filtration rate, BNP = B-type natriuretic peptide, BNP or NTpro-BNP elevated (BNP > 600 pg/ml or NT-proBNP > 3000 pg/ml), Trop = Troponin, Trop-I or Trop-T elevated (Trponin-I > 0.1 ng/ml or Troponin-T > 0.05 ng/ml), SHFM = Seattle Heart failure Model, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, MRA = mineralocorticoid receptor antagonist

Figure S1. Carvedilol dose equivalence in patients.

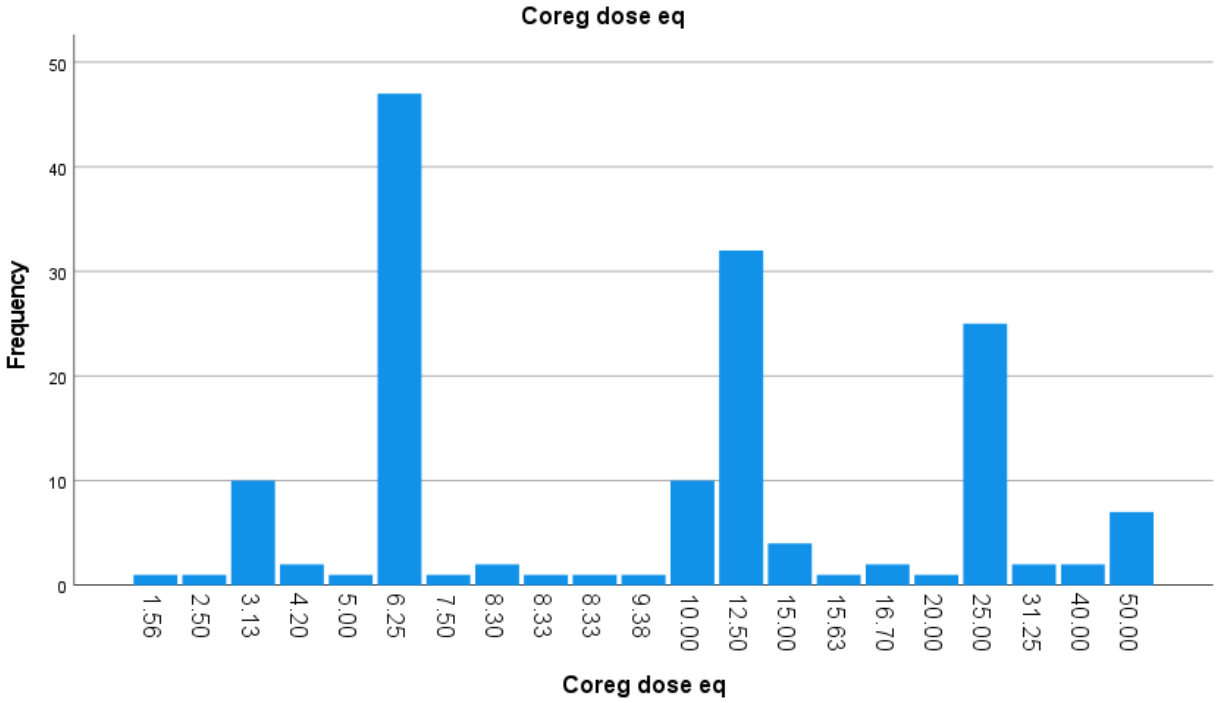

Figure S2A. IPTW adjustment for baseline beta-blocker use

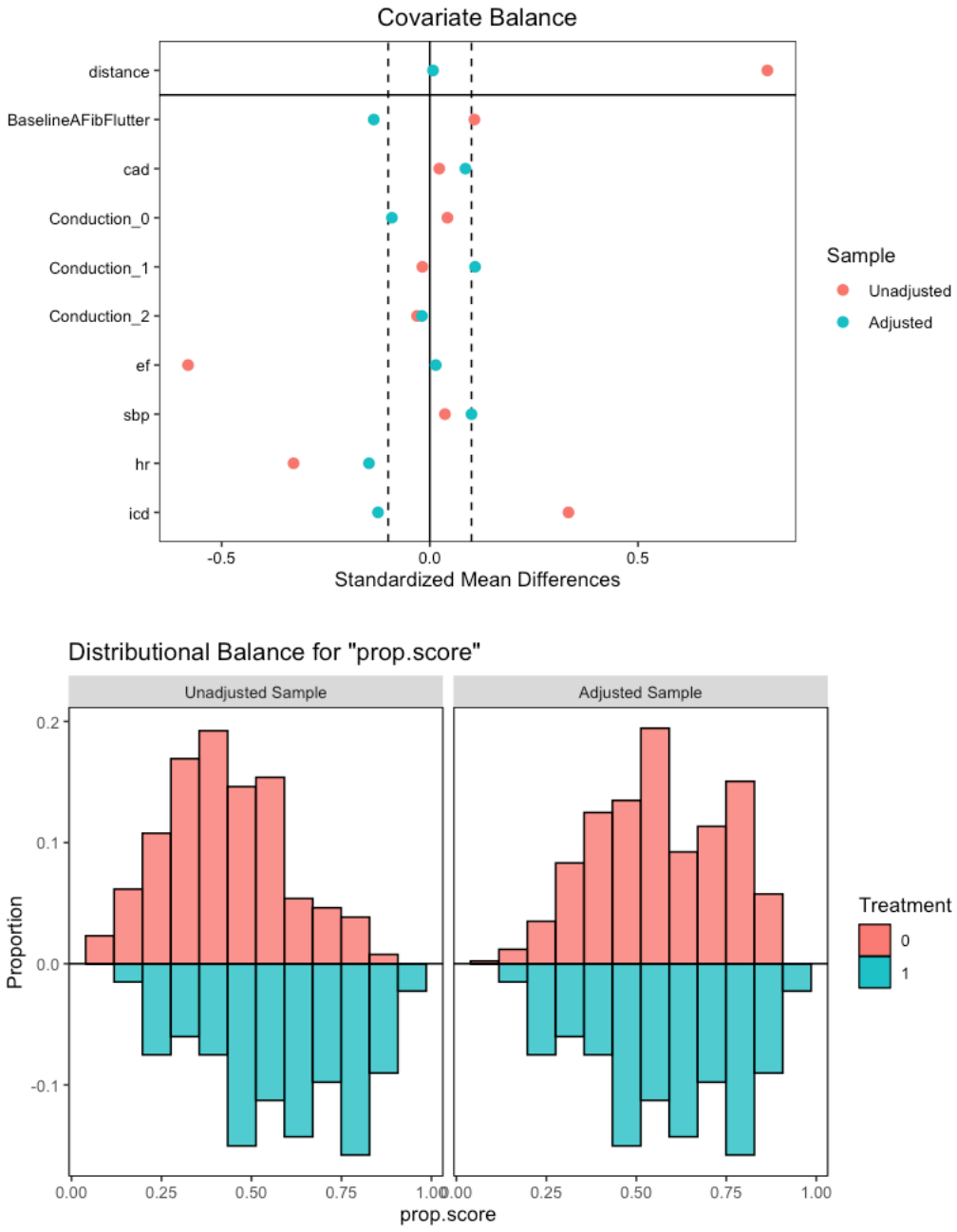

Figure S2B. IPTW adjustment for stopping beta-blocker use