Beta-Blocker Exposure and Survival in Patients With Transthyretin Amyloid Cardiomyopathy

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Abstract

Objective. To investigate a potential association between beta-blocker exposure and survival in patients with transthyretin amyloid cardiomyopathy (ATTR-CM).

Methods. In this real-world prospective registry of 128 consecutive patients with ATTR-CM recruited in 7 institutions in Galicia (Spain), survival of 65 patients who received beta blockers on registry enrollment was compared with that of 63 untreated controls by means of both unweighted Cox regression and Cox regression with inverse probability of treatment weighting. Tolerance to and adverse effects of beta blockers were recorded. Median study follow-up was 520 days.

Results. Patients with ATTR-CM who received beta blockers showed statistically significant lower all-cause mortality than untreated controls as evaluated by either unweighted Cox regression (hazard ratio, 0.31; 95% CI, 0.12 to 0.79) or Cox regression with inverse probability of treatment weighting (hazard ratio, 0.18; 95% CI, 0.08 to 0.41; $P<.001$). Several sensitivity analyses confirmed the internal validity of these results. The overall frequency of beta-blocker suspension due to adverse effects was 25% (95% CI, 15.5% to 34.5%).

Conclusion. In this real-world, prospective, multi-institutional registry, patients with ATTR-CM who received beta blockers had lower all-cause mortality than untreated controls.

Abbreviations and Acronyms: ATTR-CM, transthyretin amyloid cardiomyopathy; HF, heart failure; IPTW, inverse probability of treatment weighting; IQR, interquartile range; LVEF, left ventricular ejection fraction; NT-proBNP, Nterminal proeB-type natriuretic peptide; 99mTc-DPD, technetium Tc 99melabeled 3,3-diphosphono-1,2- propanodicarboxylic acid

Heart failure (HF) is the most frequent clinical manifestation of amyloid cardiomyopathy, and it is associated with poor outcomes.[1] In these patients, the prescription of neurohormonal blocking agents is a matter of concern as they may be poorly tolerated. Because of this, potential disease-modifying therapies are often denied to these individuals.

Current expert consensus documents advise against the routine prescription of beta blockers in patients with amyloid cardiomyopathy. [2,3] In the presence of advanced restrictive physiology, excessive bradycardia may lead to a reduced cardiac output, hypotension, fatigue, and dizziness. Neurogenic orthostatic intolerance, which is characteristic of some types of the disease, may also be aggravated.

However, a recent Italian single-center study[4] challenged this classic paradigm as it suggested that beta blockers might be initiated and up-titrated safely in a substantial proportion of patients with cardiac amyloidosis. Tolerance to beta blockers is better in patients with transthyretin amyloid cardiomyopathy (ATTR-CM) than in patients with light-chain cardiomyopathy,[4] a fact that might be explained by the lower frequency of autonomic dysfunction in patients with ATTR-CM. Almost half of patients with ATTR-CM included in contemporary real-world registries are prescribed beta blockers.[5,6]

Until now, the impact of beta blockers on the clinical outcomes of patients with cardiac amyloidosis has remained unknown. The aim of this investigation was to explore a potential association between beta-blocker exposure and survival in patients with ATTR-CM. Data were obtained from a realworld, multicenter, prospective registry conducted in 7 institutions in Galicia, a northwestern Autonomous Community of Spain.

METHODS

Description of the Study

The AMI-GAL study (Registro de AMIloidosis cardiaca de GALicia; in English, Galician Registry of Cardiac Amyloidosis) is a realworld, prospective, observational registry of patients with cardiac amyloidosis who are recruited and observed in 7 hospitals of the Servicio Gallego de Saúde (SERGAS), the public health care system of the Autonomous Community of Galicia (Spain). Study enrollment started on January 1, 2018, and is currently ongoing. The Galician Committee of Ethics in Clinical Research approved the

research protocol. Written informed consent is obtained from study participants. The research project is conducted in accordance with the Declaration of Helsinki.
According to the study protocol, the diagnosis of ATTR-CM required one of the following criteria:

- positive immunohistochemical staining for transthyretin together with negative immunohistochemical staining for immunoglobulin light chains in endomyocardial biopsy specimens that show typical amyloid deposition by red Congo staining; or
- positive immunohistochemical staining for transthyretin in extracardiac biopsy specimens that show typical amyloid deposition by red Congo staining together with typical findings suggestive of cardiac amyloidosis in cardiac imaging studies; or
- grade 2 or grade 3 cardiac uptake on nuclear scintigraphy with technetium Tc 99melabeled 3,3-diphosphono-1,2- propanodicarboxylic acid (^{99m}Tc-DPD) in a patient with typical findings suggestive of cardiac amyloidosis in cardiac imaging studies together with the absence of a detectable monoclonal protein in serum and urine immunofixation electrophoresis and serum free light-chain assay.[7]

A genetic test to identify pathogenic mutations of the transthyretin gene and to establish a differential diagnosis between the wild type and variant subtypes is recommended but not mandatory for patients with ATTR-CM.

Beta-Blocker Therapy

In this study, patients with ATTR-CM were divided in 2 groups, depending on whether they were receiving a beta blocker (ie, treatment group) or not (ie, control group) at the time of their enrollment in the AMI-GAL registry. In the treatment group, the type and daily doses of beta blockers prescribed at baseline were collected and monitored during subsequent follow-up. Adverse effects and causes of drug withdrawal or dose reduction were registered. Causes of drug withdrawal were also registered in patients of the control group who had been prescribed beta blockers in the past but who were not taking them at the time of their inclusion in the registry as well as in those who initiated beta blockers during subsequent follow-up after enrollment.

Clinical Outcomes

Patients were observed from the date of their inclusion in the AMI-GAL registry until September 30, 2020, or until the date of death, whatever occurred first. All-cause mortality was the primary end point of the study. We also explored other relevant clinical outcomes, like hospital admissions, cardiovascular admissions, HF admissions, syncope, pacemaker or defibrillator implantation, new-onset atrial fibrillation or flutter, other arrhythmic events, acute coronary syndrome, and stroke.

Cardiovascular death was defined as a death caused by arrhythmia, refractory HF, cerebrovascular disease, arterial or venous thromboembolism, peripheral artery disease, or complications of a cardiovascular proced- ure. Unexplained sudden deaths were also classified as cardiovascular deaths.

Statistical Analyses

In this manuscript, categorical variables are presented as proportions, and continuous variables are presented as means ± standard deviation or medians and interquartile range (IQR), as appropriate. Group comparisons were conducted by means of the χ^2 test or the Fisher exact test for qualitative variables and by means of *t*-Student or Mann-Whitney tests for quantitative variables.

Survival curves of patients treated with beta blockers and controls were depicted by the Kaplan-Meier curve and compared by the log-rank test. The hazard ratio for all-cause mortality for patients treated with beta blockers vs controls was calculated by means of Cox regression.

Several relevant baseline clinical variables showed a disbalanced distribution between treatment and control groups. Given the limited sample size of the study and the low number of deaths that occurred during follow-up, we considered that inverse probability of treatment weighting (IPTW)[8] was a more accurate method than conventional covariate adjustment or propensity score matching to control the effect of potential confounders on survival associations. On the basis of Austin's rule,[9] a covariable was considered disbalanced between treatment and control groups if the absolute value of its standardized mean difference was more than 0.25.[10]

Multivariable logistic regression was used to construct a propensity score model that allowed us to predict the probability of a deter- mined patient to be prescribed beta blockers, according to his or her specific baseline clinical characteristics. Only for the purpose of this analysis, missing values of continuous var- iables were substituted by their mean value in the whole cohort. Missing values requiring imputation affected 3 variables: left ventricular end-diastolic diameter (4 patients), left atrium dimension (1 patient), and serum N-terminal pro-β-type natriuretic peptide (NT-proBNP; 4 patients).

Survival estimates were recalculated after giving to each patient an individual weight that represented his or her inverse probability of being prescribed a beta blocker (in case of treated participants) or of not being prescribed it (in case of controls). Individual weights were calculated as [1/(propensity score)] for treated participants and as [1/ (1 – propensity score)] for controls. To avoid a disproportionately high weight of patients with very low probability of being treated (or not treated), individual weights were truncated to a maximum value of 10.

We conducted several sensitivity analyses to evaluate the internal consistency of the results. First, given that a few patients of the control group received beta blockers during prospective follow-up, survival estimates were recalculated from Cox regression models (both unweighted and with IPTW) that considered beta-blocker exposure as a time-varying covariate. Second, unweighted survival estimates were recalculated from a multivariable Cox regression model in which propensity score was entered as an adjusting covariable, together with beta-blocker treat- ment. Finally, weighted survival estimates were recalculated from 3 different multivari- able Cox regression models in which we entered as adjusting covariables the baseline clinical characteristics or medications that remained disbalanced between treatment and control groups after IPTW, that is, those with a standardized mean difference of more than 0.25 (Supplemental Figure 3, available online at http://www.mayoclinicproceedings. org). The first model used for this doubly robust approach included beta-blocker exposure together with medication variables (anti-coagulant use, statin use); the second model included beta-blocker exposure together with clinical variables (tricuspid annulus plane systolic excursion, previous pacemaker implantation, NT-proBNP, history of atrial fibrillation or flutter); and the third model included beta-blocker exposure together with both medication and clinical variables.

Exploratory analyses of the association between beta-blocker exposure and mortality were conducted in selected clinical sub- groups according to sex, left ventricular ejection fraction (LVEF), New York Heart Association class, and United Kingdom clinical staging system[11] and by the presence or absence of prior hospitalization due to HF and atrial fibrillation or flutter.

Statistical analyses were performed with SPSS 25 (IBM) and Stata 14 (StataCorp LP). Statistical significance was set as a *P* value of less than .05.

RESULTS

Study Population

The study population comprised 128 patients with a diagnosis of ATTR-CM who were consecutively enrolled in the AMI- GAL registry until June 30, 2020. Among them, 110 (85.9%) patients represented newly diagnosed cases; 18 (14.1%) corresponded to prevalent cases that had already been diagnosed with the disease before January 1, 2018. The median (IQR) time elapsed since the first diagnosis of ATTR- CM to study enrollment was 0 days (IQR, 0 to 0 days) for newly diagnosed cases and 671 days (IQR, 394 to 1018 days) for preva- lent cases.

All patients included in this study had an abnormality detected on ^{99m}Tc-DPD scintigraphy compatible with ATTR-CM. The diagnosis of the disease was made noninvasively in 108 (84.4%) patients and invasively in 20 (15.6%). Nineteen patients (14.8%) had positive endomyocardial biopsy specimens, whereas 1 (0.8%) patient had a positive abdominal fat biopsy specimen. There were 115 (89.8%) patients who had wild-type ATTR-CM, whereas 2 (1.6%) patients had variant ATTR-CM (p.Val50Met mutation). Genetic testing was not performed in 11 (8.6%) patients, in whom the subtype of the disease could not be determined.

Beta-Blocker Therapy

On study enrollment, 65 (50.8%) patients were receiving beta blockers. The median duration of beta-blocker therapy before registry inclusion was 570 days (IQR, 130 to 1526 days).

Fifty-six patients were taking bisoprolol and 6 patients were taking carvedilol; atenolol, propranolol, and nebivolol were each prescribed to 1 patient. Median daily doses of beta blockers prescribed were 2.5 mg of bisoprolol, 12.5 mg of carvedilol, 50 mg of atenolol, 20 mg of propranolol, and 1.25 mg of nebivolol. Only 19 (29.2%) patients were receiving at least 50% of a target daily dose of beta blockers, as defined by practice guidelines.[12]

Clinical reasons for beta-blocker prescription were atrial fibrillation or flutter (n=43), reduced LVEF (n=8), concomitant ischemic heart disease (n=6), ventricular tachycardia (n=2), atrial tachy- cardia (n=1), hypertension (n=1), esopha- geal varices (n=1), and unknown (n=3). On registry enrollment, a reduced LVEF was also present in 18 patients in whom beta blockers had been started mainly for atrial fibrillation or flutter and in 4 patients with concomitant ischemic heart disease.

Among 63 (49.2%) controls, 11 (17.5%) had been prescribed a beta blocker in the past, but they were not receiving the drug on registry enrollment. In these patients, the median time elapsed from beta-blocker suspension to registry enrollment was 35 days (IQR, 28 to 445 days).

Also, 4 (6.2%) controls were prescribed a beta blocker at any time during the prospec- tive follow-up period of the study. In these patients, the median time elapsed from registry enrollment to beta-blocker initiation was 150 days (IQR, 61 to 446 days).

Baseline Clinical Characteristics

Table 1 shows the baseline clinical characteristics of patients with ATTR-CM who were receiving beta blockers at the time of registry enrollment (n=65) compared with controls (n=63).

Patients treated with beta blockers showed a statistically significant ($P<.05$) higher prevalence of a previous history of atrial fibrillation or flutter, chronic obstructive pulmonary disease, and previous pacemaker implantation than controls. The frequency of prescription of loop diuretics, oral anticoagulants, and mineralocorticoid receptor antagonists was also significantly higher among treated patients ($P<.05$).

Patients treated with beta blockers showed significantly higher mean serum levels of NT-proBNP and lower mean serum levels of albumin than controls ($P<.05$). On echocardiography, patients who received beta blockers had significantly lower mean

values of tricuspid annulus plane systolic excursion and significantly higher prevalence of significant heart valve dysfunction than controls (P<.05).

According to the United Kingdom clinical staging system of ATTR-CM,[12] 24 (36.9%) patients of the treatment group were assigned to stage I, 26 (40%) patients were assigned to stage II, and 15 (23.1%) patients were assigned to stage III. In the control group, 39 (61.9%) patients were assigned to stage I, 13 (20.6%) patients were assigned to stage II, and 7 (11.1%) patients were assigned to stage III. This staging system could not be applied to 4 (6.3%) controls in whom the serum NT-proBNP level was not available.

Inverse Probability of Treatment Weighting

The statistical details of the propensity score model constructed to estimate the individual probability of each patient's being prescribed a beta blocker are presented in Supplemental Figures 1 and 2 (available online at http://www.mayoclinicproceedings.org). The model included 43 baseline clinical variables, which are detailed in Supplemental Figure 3.

On the basis of this propensity score, the use of the IPTW methodology substantially improved the quality of balance of baseline clinical characteristics between treatment and control groups as the number of disbalanced baseline variables decreased from 18 to 6 (Supplemental Figure 3).

Survival

Patients were observed during a median period of 520 (IQR, 334 to 684) days after registry enrollment. Six deaths were regis- tered in the treatment group, whereas 15 deaths were registered among controls. The cause of death was identified in 20 of 21 deceased patients, 17 of which had a cardiovascular origin (Supplemental Table, available online at http://www.mayoclinic proceedings.org).

Figure 1 shows the cumulative probability of survival in patients treated with beta blockers and in controls, estimated by means of unweighted Kaplan-Meier regression and by means of Kaplan-Meier regression with IPTW. In both analyses, patients treated with beta blockers showed statistically significant higher survival than controls (unweighted log-rank test, P=.010; log-rank test with IPTW, P<.001). Unweighted Kaplan-Meier estimates of 1-year and 2-year survival were 0.95 (standard error, 0.03) and 0.84 (standard

error, 0.06) for pa- tients treated with beta blockers and 0.89 (standard error, 0.04) and 0.66 (standard er- ror, 0.08) for controls, respectively.

The estimated hazard ratios for all-cause mortality for patients treated with beta blockers vs controls were 0.31 (95% CI, 0.12 to 0.79) as calculated by means of un- weighted Cox regression and 0.18 (95% CI, 0.08 to 0.41) as calculated by means of Cox regression with IPTW.

We performed several sensitivity analyses to confirm the internal consistency of our results. All of them showed statistically significant associations between beta-blocker exposure and lower all-cause mortality, with estimated hazard ratios that varied from 0.10 to 0.30 (Table 2).

Subgroup Analyses

The statistical association between beta-blocker exposure and all-cause mortality was explored in several relevant clinical sub- groups of patients with ATTR-CM by means of both crude (unweighted) Cox regression analysis and Cox regression analysis with IPTW (Figure 2).

No statistically significant interaction between beta blocker and the explored baseline clinical characteristics was observed with re- gard to all-cause mortality.

Other Clinical Outcomes

Figure 3 shows a comparison of the incidence rate of several adverse clinical events other than mortality in patients treated with beta blockers vs controls. No statistically significant differences between groups were observed with regard to the explored outcomes.

Adverse Effects and Drug Withdrawal

During prospective follow-up, beta blockers were withdrawn in 22 (33.8%) of 65 patients who received them at baseline. In 1 (1.5%) patient, the drug was resumed transiently and subsequently reintroduced with good clinical tolerance. Two (3%) patients treated with carvedilol and 1 (1.5%) patient treated with atenolol at baseline switched to biso- prolol during follow-up. Median time on beta-blocker therapy was 476 days (IQR, 224 to 632 days).

Adverse effects were the reason for with- drawal of beta blockers in 11 (16.9%) patients of the treated group. In the remaining 11 cases, beta blockers were deprescribed despite that patients were tolerating them well. Four (6.2%) patients developed adverse effects of beta blockers that disappeared after dose reduction, so medica- tion could be maintained. Figure 4 shows the temporal trend of the daily dose of beta blocker prescribed in the treated group. The proportion of patients who remained on therapy was 93.7%, 90.3%, 77.3%, and 66.2% at 3, 6, and 12 months of follow-up and at last follow-up, respectively. In the same time points, the proportion of patients who received a daily dose of a beta blocker of 50% or more of the guideline-recommended target dose was 26.6%, 24.2%, 24.5%, and 20%, respectively.

Eleven (17.5%) controls had been prescribed a beta blocker in the past, but they were not receiving the drug on registry enrollment. In 8 (72.7%) of these patients, adverse effects had been the reason for drug withdrawal. Also, 4 (6.2%) controls initiated a beta blocker during prospective follow-up; in 1 (25%) of these patients, the drug was stopped because of adverse effects.

A total of 80 (62.5%) patients included in this study received beta blockers at any time, either before or after registry enrollment. This therapy was withdrawn in 34 cases, adverse effects being the reason for suspen- sion in 20 cases. Therefore, the estimated overall prevalence of beta-blocker with- drawal was 42.5% (95% CI, 31.7% to 53.3%), and the overall prevalence of beta- blocker withdrawal due to adverse effects was 25% (95% CI, 15.5% to 34.5%).

Table 3 shows the specific adverse effects that motivated beta-blocker suspension or dose reduction in the study population.

DISCUSSION

To the best of our knowledge, this is the first study that explored the potential impact of beta-blocker therapy on the clinical outcomes of patients with ATTR-CM. Our analysis, based on a prospective, multicenter, real-world Spanish registry, found a significant association between beta-blocker exposure and increased survival in these individuals. Most of the deaths registered in the study had a cardiovascular origin. In most patients, beta blockers were prescribed for other concomitant indications, like arrythmias, left ventricular systolic dysfunc- tion, or coronary artery disease.

In our study, the baseline clinical characteristics of patients with ATTR-CM who were prescribed beta blockers were substan- tially different from the rest of the cohort; however, it is difficult to justify the observed results only by confusion bias. Indeed, patients who received beta blockers showed a more severe clinical profile than controls; as a result, a higher risk of death would be expected in the treatment group.[11] This appreciation is consistent with the fact that the estimated statistical effect of beta- blocker exposure on survival was even greater after weighting the analysis by the inverse probability of treatment,[8] a methodology that reduces the disparity of baseline clinical characteristics between treated and untreated patients and makes both groups more suitable for comparison. Moreover, several sensitivity analyses with varying statistical methods confirmed the internal consistency of the observed associations.

A few hypothetical reasons could explain why beta-blocker exposure might be beneficial in patients with ATTR-CM. First, it is possible that patients with ATTR-CM and HF who are able to tolerate beta blockers could gain benefit from them in a similar way to patients with other causes of HF, especially when the LVEF is reduced.[12] Second, the negative chronotropic effect of beta blockers allows longer ventricular filling periods and then optimizes the ventricular preload in patients with diastolic dysfunction.[13] However, in patients with advanced restrictive physiology, excessive bradycardia might result in a significant reduction of cardiac output; because of this, the general recommendation in the setting of HF that beta blockers be initiated at low doses and then up-titrated slowly to reduce the risk of adverse effects is of even greater importance for patients with ATTR-CM. If well tolerated, beta blockers may be a reasonable option to control the ventricular rate in patients with ATTR-CM and atrial fibrillation,[14] provided the use of other chronotropic negative drugs like calcium channel blockers or digoxin is usually not recommended because of safety concerns.[2] Third, patients with amyloid cardiomyopathy and HF are exposed to a significant risk of malignant ventricular arrythmias,[15] which might be reduced by beta-blocker therapy. Fourth, asymmetric left ventricular hypertrophy is frequent in patients with amyloid cardiomyopathy[16]; therefore, beta-blockade could prevent the development of dynamic left ventricular obstruction in some of these individuals. Finally, the antischemic and antioxidative[17] properties of beta blockers might play a role in slowing the progression of cardiac damage in patients with amyloid cardiomyopathy, which has been related to coronary microvascular

dysfunction[18] and oxidative stress induced by a toxic effect of amyloid fibrils.[19] A preliminary experimental study suggested that the administration of carvedilol might reduce the deposition of transthyretin in a mouse model of familial amyloid polyneuropathy.[20]

Clinical intolerance and adverse effects constitute the major limitations to the use of beta blockers in patients with amyloid cardiomyopathy. Expert consensus documents advise against routine use of neurohormonal antagonists in these patients[2,3]; however, recommendations are usually based on individual experience and pathophysiologic assumptions as solid scientific evidences are lacking. Clinical researchers from Bologna, Italy, have recently published the most comprehensive study on this topic.[4] The authors analyzed the clinical tolerance to and incidence of adverse effects of neurohormonal antagonists in a cohort of 99 patients with amyloid cardiomyopathy (67% ATTR- CM), among whom 87 received beta blockers. The overall frequency of beta-blocker withdrawal was 7%; moreover, the incidence of adverse events like pacemaker implantation, HF hospitalization, fatigue, syncope, bradycardia, or hypotension was similar in patients in whom beta-blocker therapy was started or up-titrated after the diagnosis of cardiac amyloidosis compared with the rest of the cohort. The risk of having problems related to beta blockers was higher among patients who presented with lower cardiac output, lower arterial blood pressure, and lower LVEF at baseline as well as among those with light-chain amyloid cardiomyopathy in comparison to those with ATTR-CM.

In our cohort, the frequency of adverse effects leading to beta-blocker withdrawal was 16.2% among patients who were receiving them on registry enrollment and reached 25% when patients of the control group who were prescribed beta blockers at any time, before or after recruitment, were also considered. This high frequency of adverse effects leading to beta-blocker suspension was observed despite that, as in the Italian study,[4] they were prescribed at low doses in most cases. It is possible that differences in local practices have conditioned this apparent discrepancy between the studies. In the Italian cohort,[4] all patients were managed and observed closely in a single high-volume, specialized clinic. However, our analysis was based on a real-world cohort of patients recruited in 7 different in- stitutions with variable clinical experience in the management of ATTR-CM and heterogeneous follow-up protocols. One can reason- ably expect that in the second

setting, attending physicians will be more likely to suspend beta blockers when adverse effects occur, even if mild. Remarkably, about 17% of patients of our registry who received beta blockers had them deprescribed despite a good clinical tolerance, probably because of the classic assumption that these drugs may be harmful in the setting of ATTR-CM. This investigation has some relevant clinical implications. Despite that our results must be considered only as hypothesis generating and require further confirmation in larger prospective, multicenter studies, they constitute the first evidence that suggests a clinical benefit of beta-blocker therapy in patients with ATTR-CM, a population in which these drugs were traditionally considered not useful and possibly harmful. In view of this novel information, it would be reasonable to maintain beta blockers, rather than to suspend them systematically, in patients with ATTR-CM in whom they are prescribed for other concomitant indications like arrythmias, ischemic heart disease, or left ventricular systolic dysfunction, provided there is good clinical tolerance.

Our investigation has a few limitations. This is an observational, real-world study, so its results may be influenced by potential information, selection, and confusion biases. Both the number of studied patients and the number of deaths registered during follow-up were low, so our results must be considered only as hypothesis generating and require further confirmation. The use of the IPTW methodology[7] allowed us to reduce the disbalance between treated patients and controls with regard to several relevant baseline clinical characteristics and so to make these 2 groups more suitable for survival comparisons. However, this statistical technique is not able to control the potential confounding effect of nonmeasured variables. Finally, our analysis was based on a general registry of patients with ATTR-CM that was not designed specifically for the aim of this study. Therefore, diagnostic and therapeutic decisions were guided by local and individual practices rather than based on a single prespecified protocol. As discussed before, we believe that this fact could have influenced the high frequency of beta-blocker withdrawal observed in our cohort.

CONCLUSION

Our analysis based on a real-world, multi- center, prospective Spanish cohort study suggests that beta-blocker exposure is associated with reduced all-cause mortality in patients with ATTR-CM. Despite that these individuals are particularly susceptible to the

adverse effects of beta blockers, our re- sults constitute an attention call against their indiscriminate deprescription in the setting of ATTR-CM, especially when there is another indication for treatment, like arrhythmia, ischemic heart disease, or left ventricular systolic dysfunction, and the drug is tolerated properly. Further confirmation of our observation is warranted in future prospective, multicenter studies.

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TABLE 1. Baseline Clinical Characteristics of Patients With Transthyretin Amyloid Cardiomyopathy Who Received Beta Blockers Compared With Controls[a,b,c]

	Without beta blocker (n=63)	With beta blocker (n=65)	*P* value
Clinical history			
Age (y)	80.5±6.8	81.5±5	.365
Women	10 (15.9)	18 (27.7)	.106
Time elapsed since the diagnosis of cardiac amyloidosis (days)	66±196	151±399	.129
Hypertension	44 (69.8)	43 (66.2)	.655
Hypercholesterolemia	39 (61.9)	36 (55.4)	.454
Diabetes mellitus	16 (25.4)	11 (16.9)	.240
Coronary artery disease	7 (11.1)	10 (15.4)	.476
History of atrial fibrillation or flutter	24 (38.1)	48 (73.8)	<.001
Pacemaker	6 (9.5)	16 (24.6)	.024
Prior hospitalization due to heart failure	16 (25.4)	22 (33.8)	.296
Cerebrovascular disease	12 (19)	8 (12.3)	.294
Peripheral artery disease	6 (9.5)	4 (6.2)	.527
Chronic obstructive pulmonary disease	4 (6.3)	12 (18.5)	.038
Tendinopathy	20 (31.7)	26 (40)	.331
Peripheral polyneuropathy	2 (3.2)	0	.240
Clinical status			
New York Heart Association class III or IV	18 (28.6)	27 (41.5)	.114
Exploratory signs of congestion	31 (49.2)	41 (63.1)	.075
Left sided	16 (25.4)	23 (35.4)	
Right sided	26 (41.3)	38 (58.5)	
Systolic blood pressure (mm Hg)	128±19	122±15	.041
Heart rate (beats/minute)	74±11	73±10	.617
Echocardiography			
Left ventricular ejection fraction (%)	53.4±11.3	52.1±13.6	.564
Left ventricular ejection fraction categories			.084
<40%	6 (9.5)	15 (23.1)	

TABLE 1. Baseline Clinical Characteristics of Patients With Transthyretin Amyloid Cardiomyopathy Who Received Beta Blockers Compared With Controls[a,b,c]

	Without beta blocker (n=63)	With beta blocker (n=65)	*P* value
40%-49%	19 (30.2)	13 (20)	
≥50%	38 (60.3)	37 (56.9)	
Left ventricular end-diastolic diameter (mm)[d]	42.8±6	44.6±8.3	.159
Maximum left ventricular wall thickness (mm)	17.9±2.8	17.2±3.3	.218
Left atrium dimension (mm)[d]	45.9±6.3	47±6.5	.312
Tricuspid annulus plane systolic excursion (mm)	17.8±3.7	15.6±3.6	.001
Pericardial effusion	11 (17.5)	13 (20)	.713
Moderate or severe heart valve dysfunction	19 (30.2)	31 (47.7)	.042
Aortic stenosis	9 (14.3)	12 (18.5)	
Aortic regurgitation	0	4 (6.1)	
Mitral regurgitation	8 (12.7)	10 (15.4)	
Tricuspid regurgitation	10 (15.9)	19 (29.2)	
Laboratory tests			
Hemoglobin (g/dL)	13.5±1.7	13.8±1.6	.317
Creatinine (mg/dL)	1.3±1.4	1.3±0.4	.734
Bilirubin (mg/dL)	1±0.9	1.1±0.9	.440
Albumin (g/dL)	4.3±0.3	4.1±0.4	.018
NT-proBNP (ng/L)[d]	2779±3360	5123±4239	.001
Treatment			
Tafamidis[e]	33 (52.4)	35 (53.8)	.868
Angiotensin-converting enzyme inhibitor	9 (14.3)	15 (23.1)	.203
Angiotensin II receptor blocker	13 (20.6)	17 (26.2)	.461
Mineralocorticoid receptor antagonist	11 (17.5)	25 (38.5)	.008
Loop diuretic	40 (63.5)	55 (84.6)	.006
Thiazide	13 (20.6)	8 (12.3)	.203
Digoxin	2 (3.2)	4 (6.2)	.680

TABLE 1. Baseline Clinical Characteristics of Patients With Transthyretin Amyloid Cardiomyopathy Who Received Beta Blockers Compared With Controls[a,b,c]

	Without beta blocker (n=63)	With beta blocker (n=65)	*P* value
Amiodarone	2 (3.2)	3 (4.6)	.674
Calcium channel blockers	4 (6.3)	2 (3.1)	.436
Oral anticoagulant	24 (38.1)	50 (76.9)	<.001
Aspirin	9 (14.3)	6 (9.2)	.374
Statin	40 (63.5)	31 (47.7)	.072

[a] NT-proBNP, N-terminal proeB-type natriuretic peptide.

[b] To convert hemoglobin values to g/L, multiply by 10; to convert creatinine values to mmol/L, multiply by 88.4; to convert bilirubin values to mmol/L, multiply by 17.104; to convert albumin levels to g/L, multiply by 10.

[c] Categorical variables are presented as number (percentage). Continuous variables are presented as means ± standard deviation.

[d] Missing values: left ventricular end-diastolic diameter (n¼4), left atrium dimension (n=1), NT-proBNP (n=4).

[e] Patients received this drug in the course of an investigational protocol.

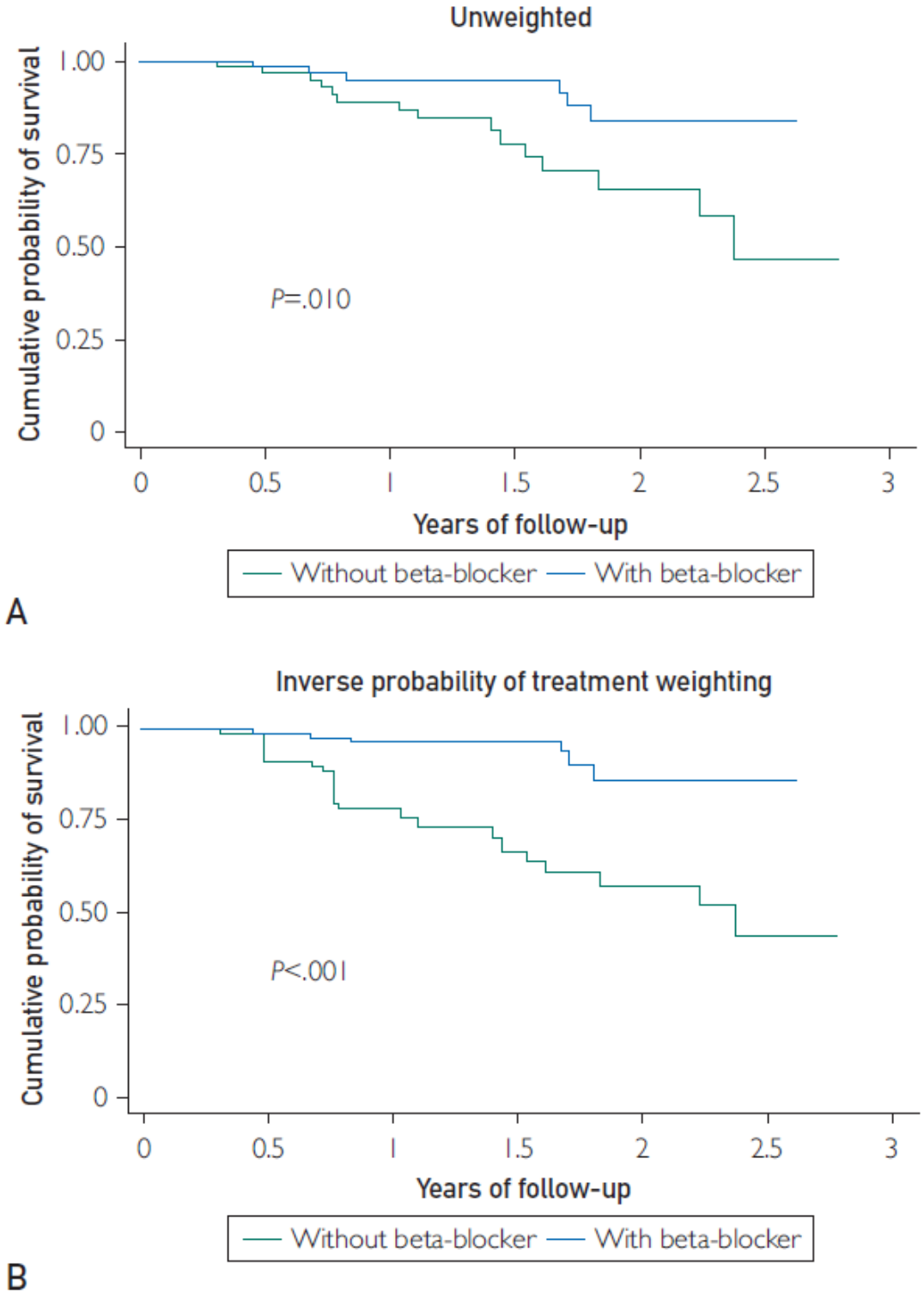

FIGURE 1. Kaplan-Meier cumulative estimates of survival in patients with transthyretin amyloid cardiomyopathy who received beta blockers compared with controls. A, Unweighted analysis. B, Inverse probability of treatment weighting analysis.

TABLE 2. Hazard Ratio for All-Cause Mortality in Patients Treated With Beta Blockers Compared With Controls, Estimated by Various Statistical Methods[a]

Primary analyses	Hazard ratio	95% CI
Unweighted, univariate Cox regression	0.31	0.12-0.79
IPTW, univariate Cox regression	0.18	0.08-0.41
Sensitivity analyses		
Unweighted, univariate Cox regression with beta blocker as a time-varying covariable	0.30	0.12-0.78
IPTW, univariate Cox regression with beta blocker as a timevarying covariable	0.17	0.08-0.40
Unweighted, multivariate Cox regression with propensity score as a covariable	0.10	0.02-0.48
IPTW, multivariate Cox regression		
With disbalanced clinical variables[b] as covariables	0.12	0.05-0.29
With disbalanced medication variables[c] as covariables	0.14	0.06-0.34
With disbalanced clinicalb and medication variables[c] as covariables	0.15	0.06-0.35

[a] IPTW, inverse probability of treatment weighting.

[b] Disbalanced clinical variables: serum N-terminal pro–B-type natriuretic peptide, tricuspid annulus plane systolic excursion, previous pacemaker implantation, and history of atrial fibrillation or flutter.

[c] Disbalanced medication variables: statin use, anticoagulant use.

Disbalance of a clinical or medication variable between treatment and control groups is defined by an absolute value of the standardized mean difference.

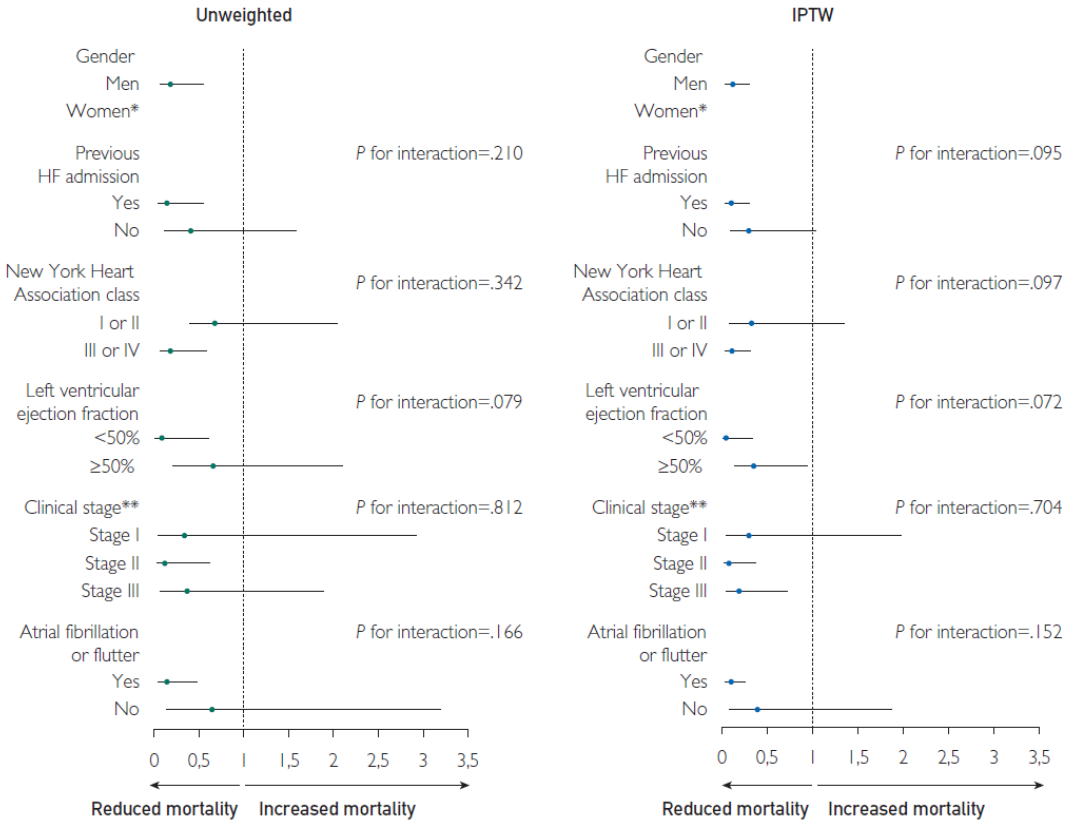

FIGURE 2. Association between beta-blocker exposure and all-cause mortality in several relevant clinical subgroups of patients with transthyretin amyloid cardiomyopathy. A, Unweighted Cox regression analysis. B, Cox regression analysis with inverse probability of treatment weighting (IPTW). HF, heart failure. *Hazard ratio was not calculated because the number of registered deaths was 0 in 1 subgroup. **Stage I: N-terminal pro–B-type natriuretic peptide (NT-proBNP) 3000 ng/L and glomerular filtration rate 45 mL/min; stage III: NT-pro P >3000 ng/L and glomerular filtration rate <45 mL/min; stage II: patients not assigned to stage I or stage III. Data from *Eur Heart J.*[11]

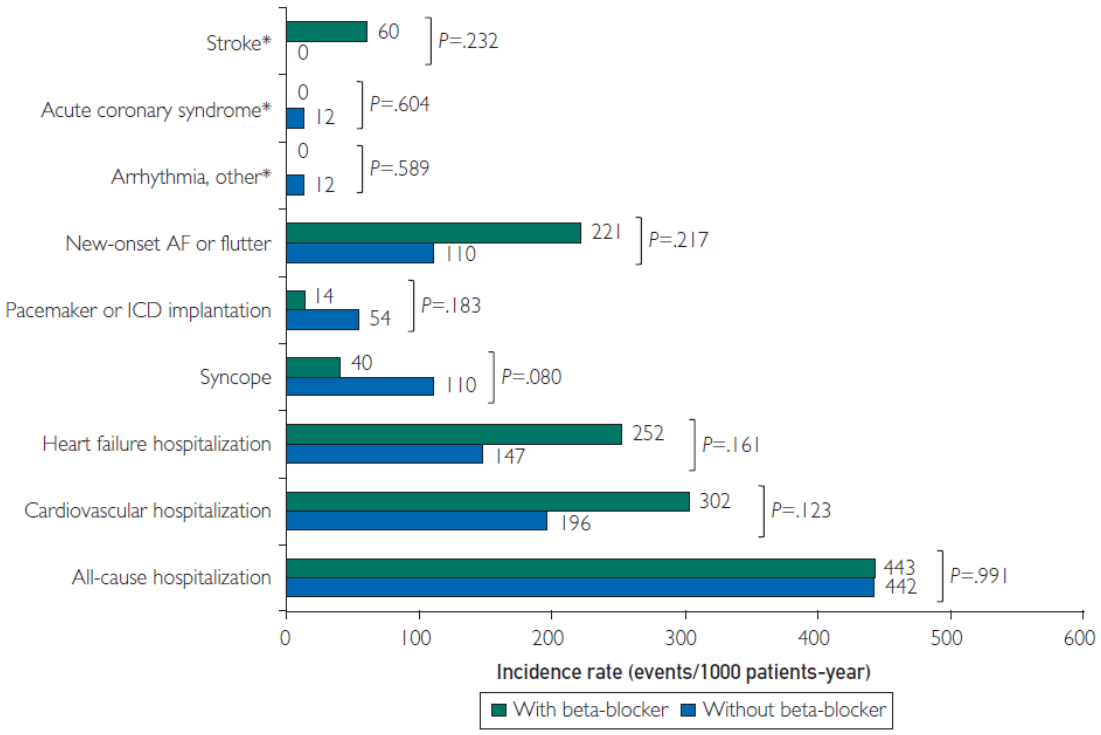

FIGURE 3. Incidence rate of several clinical outcomes other than survival in patients with transthyretin amyloid cardiomyopathy treated with beta blockers compared with controls. AF, atrial fibrillation; ICD, implantable cardioverter-defibrillator. *Given that the incidence rate of the event of interest was 0 in 1 subgroup, *P* value was calculated from univariate Cox regression.

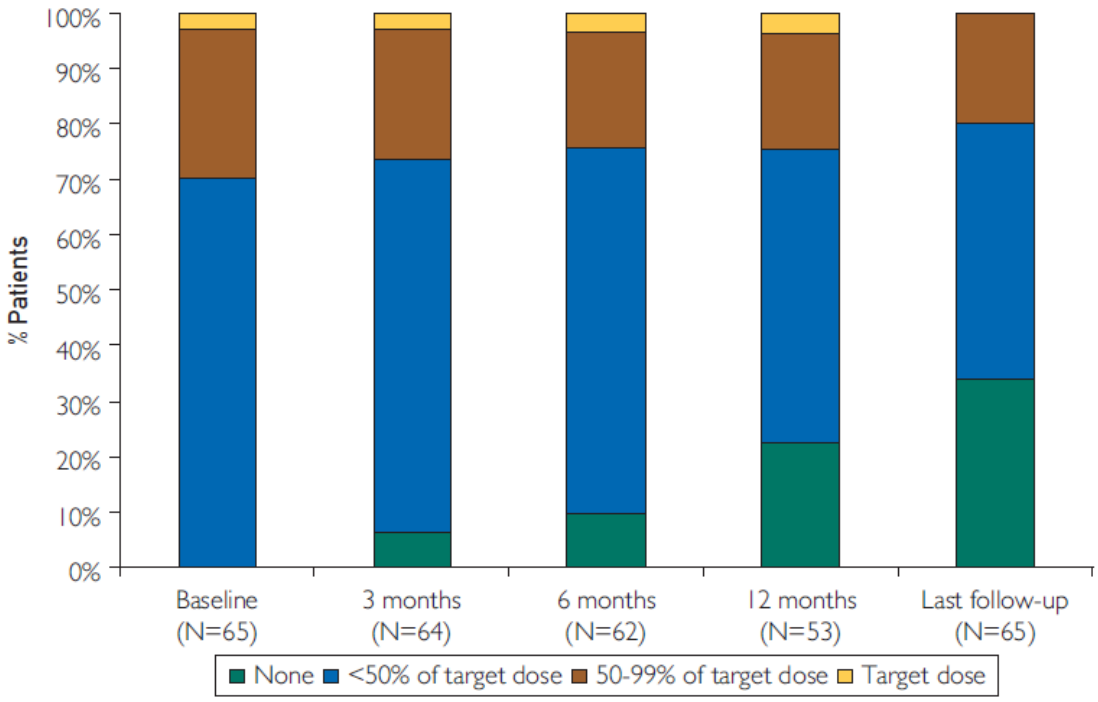

FIGURE 4. Temporal trend of the daily dose of beta blockers, expressed as percentage of the guidelinerecommended target dose, prescribed in the treated group.

TABLE 3. Adverse Effects That Led to Drug With-drawal or Dose Reduction in 80 Patients With Transthyretin Amyloid Cardiomyopathy Treated With Beta rs[a]

Adverse effects leading to drug suspensión	20 (25%)
Bradycardia	6
Hypotension, symptomatic	5
Hypotension, asymptomatic	3
Worsening of heart failure	2
Bronchial spasm	2
Peripheral vasoconstriction	1
Fatigue	1
Adverse effects leading to doce reduction	4 (5%)
Hypotension, symptomatic	1
Hypotension, asymptomatic	1
Worsening of heart failure	1
Fatigue	1

[a] This population includes 65 patients of the treatment group, 11 controls who had received beta blockers in the past, and 4 controls who were prescribed beta blockers during subsequent prospective follow-up.