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ORIGINAL RESEARCH

SGLT2 Inhibitor Therapy in Patients With Transthyretin Amyloid Cardiomyopathy

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ABSTRACT

BACKGROUND Transthyretin cardiomyopathy (ATTR-CM) was an exclusion criterion in randomized clinical trials of sodium-glucose cotransporter 2 inhibitors (SGLT2i).

OBJECTIVES This study sought to assess the effectiveness and tolerability of SGLT2i in patients with ATTR-CM.

METHODS Data of 2,356 consecutive ATTR-CM patients (2014-2022) were analyzed: 260 (11%) received SGLT2i. After comparing the groups according to the treatment, 14 variables were significantly different—age and N-terminal pro-B-type natriuretic peptide were included in the model. A propensity score reflecting the likelihood of being treated with SGLT2i for each patient was determined using 16 variables.

RESULTS The study comprised 220 patients treated with SGLT2i (age 77 ± 2 years; 82.3% wild-type ATTR-CM; left ventricular ejection fraction 45.8% ± 11%) and 220 propensity-matched control individuals. Adequacy of matching was verified (standardized differences: <0.10 between groups). Discontinuation rate for SGLT2i was 4.5%; at 12 months, SGLT2i treatment was associated with less worsening of NYHA functional class, N-terminal pro-B-type natriuretic peptide, estimated glomerular filtration rate, and fewer new initiations of loop diuretic agent therapy. Over 28 months (Q1-Q3: 18-45 months), SGLT2i therapy was associated with lower all-cause mortality (HR: 0.57; 95% CI: 0.37-0.89; $P = 0.010$), cardiovascular mortality (HR: 0.41; 95% CI: 0.24-0.71; $P < 0.001$), heart failure (HF) hospitalization (HR: 0.57; 95% CI: 0.36-0.91; $P = 0.014$), and the composite outcome of cardiovascular mortality and HF hospitalization (HR: 0.57; 95% CI: 0.38-0.84; $P = 0.003$).

CONCLUSIONS SGLT2i treatment in ATTR-CM patients was well tolerated and associated with favorable effects on HF symptoms, renal function, and diuretic agent requirement over time. SGLT2i treatment was associated with reduced risk of HF hospitalization and cardiovascular and all-cause mortality, regardless of the ejection fraction, despite the effect size being likely overestimated. In the absence of randomized trials, these data may inform clinicians regarding the use of SGLT2i in patients with ATTR-CM. (J Am Coll Cardiol 2024;83:2411-2422) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

ARB = angiotensin receptor blocker

ATTR-CM = transthyretin amyloid cardiomyopathy

ATTRv-CM = variant transthyretin amyloid cardiomyopathy (hereditary)

ATTRwt-CM = wild-type transthyretin amyloid cardiomyopathy (acquired)

eGFR = estimated glomerular filtration rate

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

LVEF = left ventricular ejection fraction

MRA = mineralocorticoid receptor antagonists

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PS = propensity score

SBP = systolic blood pressure

SGLT2i = sodium-glucose cotransporter 2 inhibitor

TTR = transthyretin

Transthyretin amyloid cardiomyopathy (ATTR-CM), either acquired (ATTRwt-CM) or hereditary (ATTRv-CM), is caused by misfolding and aggregation of the plasma protein transthyretin into insoluble amyloid fibrils that accumulate in the myocardial extracellular space, causing progressive cardiac failure.[1] Until recently, ATTR-CM was thought to be very rare, but the creation of noninvasive diagnostic pathways[2,3] has proven otherwise and is stimulating development of several highly promising disease-modifying therapies.[4-6]

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Currently, the only drug approved for treatment of ATTR-CM is tafamidis, which is bound by and increases the stability of circulating transthyretin (TTR) in its normal soluble form, thereby reducing its propensity to misfold and form ATTR amyloid fibrils.[7,8] In a phase 3 placebo-controlled trial (ATTR-ACT [Tafamidis in Transthyretin Cardiomyopathy Clinical Trial]), tafamidis decreased cardiovascular-related hospitalizations and mortality,[9] but its high cost has prohibited its use in many countries.[10] Supportive care thus remains paramount, but the role and value of standard heart failure (HF) therapies has been long debated because HF trials have excluded patients with amyloid. However, a recent retrospective study of more than 2,000 patients with ATTR-CM indicated that all-cause mortality[11] was lower among patients treated with beta blockers (when ejection fraction was <40%) and mineralocorticoid receptor antagonists (MRA), supporting an unmet need to study the potential roles for conventional HF medications in ATTR-CM generally.

In HF, in recent years, new therapeutic pathways beyond neurohormonal modulation have recently been associated with clinical and prognostic benefits.[12,13] In phase 3 randomized clinical trials, treatment with sodium-glucose cotransporter 2 inhibitors (SGLT2i) was associated with fewer HF hospitalizations and decreased progression of kidney disease and cardiovascular mortality in patients with HF with reduced ejection fraction (HFrEF)[14-16]; more recently, these findings have been extended to patients with HF and mildly reduced or preserved ejection fraction.[17,18] However, patients with ATTR-CM were excluded from these SGLT2i clinical trials.

Because no randomized trial data are available in this area, we sought to assess, in a large, multicenter, longitudinal database of patients with ATTR-CM, the effectiveness and tolerability of treatment with SGLT2i using propensity-matched observational data and the association between treatment and mortality and HF hospitalization.

METHODS

This is a multicenter, longitudinal, observational study performed across 14 referral centers for amyloid cardiomyopathy: the National Amyloidosis Centre (London, United Kingdom), 2 U.S. centers (Portland and San Diego), Wien (Austria), and 10 Italian centers (Trieste, Brescia, Florence, Genoa, Padua, Pisa, Rome [2 centers], Bologna, and Ferrara). Local Institutional Review Board approval for the study was obtained from each of the participating centers. The study was conducted according to the

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Declaration of Helsinki, and informed consent was obtained under the Institutional Review Board policies of the relevant hospital administrations.

Diagnosis of ATTR-CM was established on the basis of HF symptoms together with a characteristic echocardiogram or cardiac magnetic resonance study and either endomyocardial biopsy proof of ATTR amyloid or Perugini grade 2 or 3 myocardial uptake on cardiac scintigraphy in the absence of either an abnormal serum free light-chain ratio or a monoclonal immunoglobulin in the serum or urine by immunofixation.[2,3] The *TTR* gene was sequenced in all patients as previously described.[19] All echocardiographic parameters were measured according to standard international definitions.[20,21] All patients were enrolled into a protocolized follow-up program that consisted of 6 to 12 monthly consultations (or earlier according to individual clinical needs) at participating centers with clinical assessment, laboratory tests, and echocardiography. Data regarding demographics; clinical characteristics; whether medications were initiated, continued, or stopped; and medication dosages were all recorded at all attendances.

Time 0 (the time each patient entered the study) was defined as the time of ATTR-CM diagnosis.

STATISTICAL ANALYSIS. Propensity score (PS) matching was used to reduce confounding bias. The baseline characteristics of the unmatched population of 2,356 ATTR-CM patients (divided in 2 groups according to the treatment) were assessed. After comparing the groups, 14 variables were found to be significantly different: year of diagnosis, sex, diabetes mellitus, hypertension, atrial fibrillation, estimated glomerular filtration rate, wild-type or hereditary ATTR-CM, maximum wall thickness in diastole, left ventricular ejection fraction (LVEF), treatment with beta-blockers, treatment with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), treatment with MRA, treatment with loop diuretic agents, and treatment with disease-modifying drugs. Age and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were also included in the PS. A PS reflecting the likelihood of being treated with SGLT2i for each patient was determined using the set of 16 variables. The level of balance between treatment and control groups was checked by visual analysis of a density plot of the distribution of the PS in the 2 groups after defining the area of common support and graph of the PS distribution within the area of common support. When plotting the distribution of PSs for the 2 matched groups using a diagram that showed the overlap between the 2 distributions (referred to as the area of common support), any additional patients lying outside this area were excluded (ie, trimmed).

Patients were then matched on the basis of their PSs in the 2 medication groups in a 1:1 ratio using the nearest-neighbor approach without replacement and caliper width equal to 0.20 times the SD of the logit of the PSs. Adequacy of matching was verified by ensuring that the standardized differences between groups were <0.10 for all variables used to create the PS.

Descriptive statistics between the study groups were performed. All continuous variables were tested for normality (Shapiro-Wilk test) and are presented as mean $\pm$ SD if the distribution was normal or median (Q1-Q3) otherwise. Categorical variables were expressed as absolute number and frequency (percentage). The 2-sample Student's *t*-test for continuous variables was used to compare means if the data were normally distributed in each treatment group, and its nonparametric equivalent, the Mann-Whitney *U* test, was used otherwise to compare the distributions of the 2 treatment groups. The chi-square test or Fisher exact test was used for categorical variables.

The treatment effect at the 12-month assessment for each of the measured variables was estimated by performing a linear regression analysis with the outcome variable being the 12-month value and the explanatory variables being the baseline value of that variable and treatment. Baseline values were recorded upon initiation of SGLT2i therapy in the treatment group and upon diagnosis of ATTR-CM in the untreated control group. The estimated regression coefficient for the group in the regression analysis represented the differences in means (treated minus untreated) at 12 months after adjustment for the baseline value of the variable. For categorical variables, the treatment effect at the 12-month assessment was estimated by performing a logistic regression analysis after adjustment for the baseline value of the variable. Data at 12 months were missing at random because of the COVID-19 pandemic limiting clinical assessment at treating centers or, in a minority of cases, because of an overall follow-up time of <12 months among patients diagnosed with ATTR-CM after September 2022.

The primary outcome of the study was all-cause mortality. Secondary outcome measures were as follows: 1) cardiovascular mortality; 2) unplanned hospitalization for worsening HF; and 3) composite outcome of cardiovascular mortality and HF hospitalization. The mortality endpoint was defined as time to death from baseline for all deceased patients and time to censor date (October 15, 2023) from

baseline among the remainder. Cardiovascular mortality was defined as sudden cardiac death, aborted cardiac death, fatal stroke, cardiac transplantation, or end-stage HF with pump failure. Data on HF hospitalizations were obtained from scheduled follow-up evaluations at participating centers and from electronic health record systems.

For survival analysis, to avoid the "immortal time" bias, we have assessed the association between SGLT2i treatment and outcomes using 2 approaches: 1) a time-dependent Cox regression analysis with SGLT2i use as time-varying exposure; and 2) the Kaplan-Meier analysis based on "baseline treatment status." In the first approach, medication use (SGLT2i treatment) was treated as a time-varying exposure. In this analysis, each individual not treated with SGLT2i at the time of ATTR-CM diagnosis is identified as "not on treatment" from time 0 (ie, ATTR-CM diagnosis) to the day before initiation of SGLT2i therapy and then is identified as "on treatment" until the end of observation (ie, occurrence of the relevant outcome, death or censor date). Time-dependent Cox proportional hazards regression analysis, using the medication as a time-varying exposure, was performed. HRs and the associated 95% CIs were calculated using this approach. Sensitivity analysis was performed to further confirm results utilizing a time-dependent Cox regression analysis with SGLT2i treatment as a time-varying exposure where, in addition, patients were censored at the start of disease-modifying drugs or entry into a clinical trial. In the second approach (ie, baseline treatment status), patients were classified as on treatment with SGLT2i at baseline and continued to be classified as being on treatment regardless of whether or not the treatment was discontinued. Patients who were not on treatment at baseline were classed as not on treatment regardless of whether treatment was initiated during follow-up. This form of analysis meant there was no crossover between the 2 groups. This analysis was used for the Kaplan-Meier survival analysis.

Statistical significance was defined as $P < 0.05$ for all analyses. All statistical analyses were performed using IBM SPSS Statistics 24.0 package statistical software version 20 and Stata release 17 (Stata Corp).

RESULTS

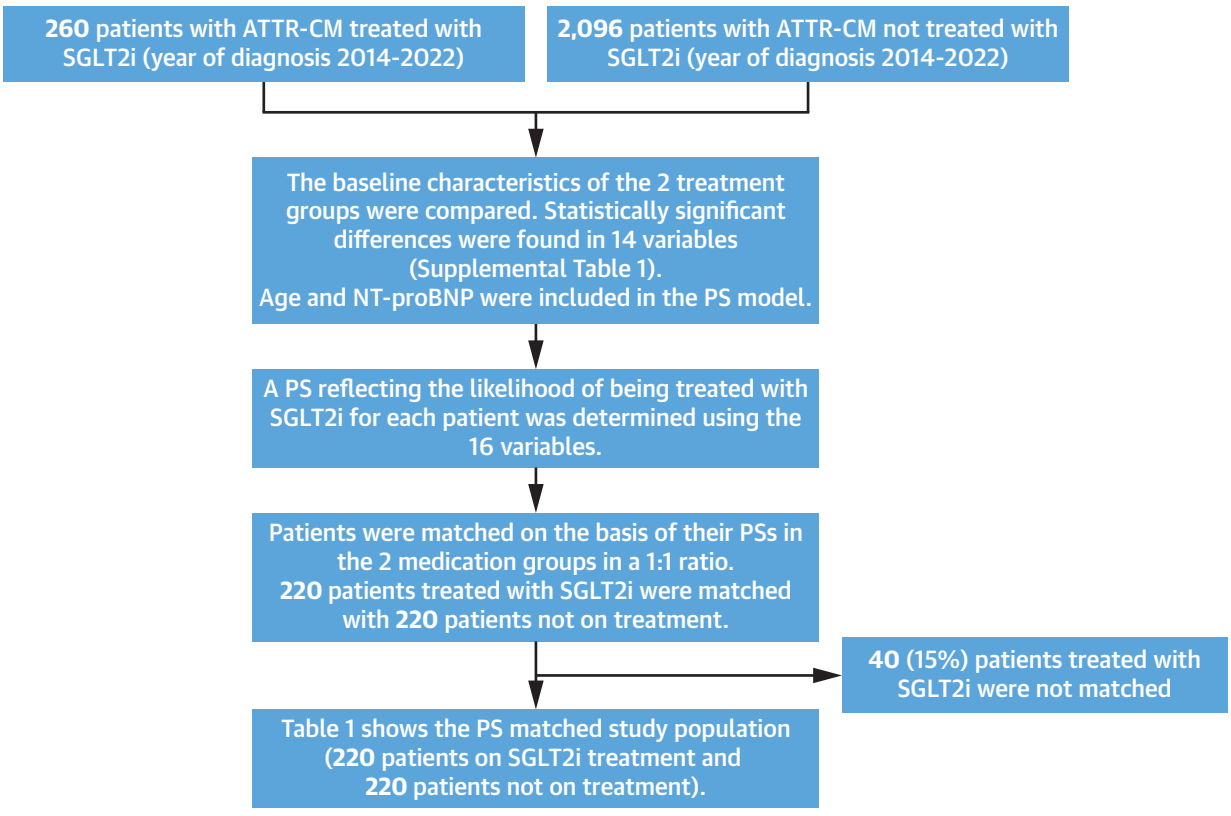
Data of 2,356 consecutive patients in whom a diagnosis of ATTR-CM was confirmed at the participating centers between January 2014 and December 2022 were analyzed (Figure 1). Among them, 260 (11%) patients received treatment with SGLT2i. Adequate matching was achieved in 85% of cases (n = 220 of 260 patients), with only 40 patients treated with SGLT2i excluded from the study population. Supplemental Table 1 shows baseline characteristics of ATTR-CM patients treated with SGLT2i and untreated patients. The study cohort comprised 440 patients with ATTR-CM: 220 who were treated with SGLT2i and 220 patients who were PS-matched control individuals not treated with SGLT2i.

Characteristics of the PS-matched study population are shown in Table 1. The population comprised 355 (80.7%) patients with ATTRwt-CM; 40 (9.0%) with p.V142I-associated ATTRv-CM; 19 (4.3%) with p.T80A-associated ATTRv-CM; and 26 (5.9%) with non-p.V142I, non-p.T80A-associated ATTRv-CM (p.Ile88Leu: 12 patients; p.Val50Met: 7 patients; and 1 patient each with p.Arg54Thy, p.Arg25His, p.Phe64Leu, p.Phe84Ile, p.Glu62Asp, p.Glu109Gln, and His128Arg).

The patients treated with SGLT2i comprised 181 (82.3%) with ATTRwt-CM and 39 (17.7%) with ATTRv-CM. The mean age was 77 ± 2 years, and 90.5% were men. About 15.5% had ischemic heart disease, 40.5% had diabetes mellitus, 58.2% had history of hypertension, and 67.3% had atrial fibrillation. The median NT-proBNP was 2,625 ng/L (Q1-Q3: 1,448-5,250 ng/L), and the mean estimated glomerular filtration (eGFR) was 56 ± 18 mL/min/1.73 m^2. The mean LVEF was 45.8% ± 11% (101 [36.8%] had an LVEF of ≤40%), and the mean E/e′ was 17.5 ± 5. Most patients were in National Amyloidosis Centre stages 1 (42.7%) or 2 (36.4%), and 20.9% were in National Amyloidosis Centre stage 3. At diagnosis, beta-blockers, ACEI/ARB, MRA, loop diuretic agents, and disease-modifying therapy were prescribed in 59.1% (n = 130), 44.5% (n = 98), 46.4% (n = 102), 84.5% (n = 186), and 20.9% (n = 46; tafamidis: n = 39 and patisiran: n = 7) of cases, respectively. There was no difference between patients with and without SGLT2i treatment when considering the mentioned parameters. During follow-up, a total of 91 (20.7%) patients of the study population were enrolled into clinical trials or treated with disease-modifying therapy (clinical trials: n = 61; tafamidis: n = 24; patisiran: n = 6).

PRESCRIPTION PATTERN, DOSAGES, AND DISCONTINUATION RATE OF SGLT2i. The most commonly prescribed SGLT2i was dapagliflozin (n = 148; 67.3%), followed by empagliflozin (n = 71; 32.3%) and canagliflozin (n = 1; 0.4%). The initiation of SGLT2i treatment was primarily prompted by HFrEF and diabetes. Among the 111 patients who were started on SGLT2i during follow-up, the median time duration between ATTR-CM diagnosis and SGLT2i initiation was 23 months (Q1-Q3: 12-30 months). All patients

FIGURE 1 Diagram of the Study With the Propensity Score Matching Process



The diagram provides a breakdown of the steps for selection of the study population. ATTR-CM = transthyretin amyloid cardiomyopathy; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PS = propensity score; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

(n = 220; 100%) were prescribed 100% of the target dose of SGLT2i (ie, dapagliflozin or empagliflozin 10 mg once daily). In the whole PS-matched cohort, during a median follow-up of 28 months (Q1-Q3: 18-45 months), 10 (4.5%) patients had their SGLT2i discontinued (median duration to discontinuation: 15 months [Q1-Q3: 12-18 months]). Reasons for drug discontinuation were recurrent urinary tract infections (n = 5), reduction in eGFR (n = 3), and constipation (n = 2). None of patients had their SGLT2i dose reduced during follow-up.

EFFECTS OF SGLT2i THERAPY ON NYHA FUNCTIONAL CLASS, NT-proBNP, eGFR, BLOOD PRESSURE, AND LOOP DIURETIC AGENT USE. Treatment with SGLT2i at 12 months compared to untreated patients was associated with decreased rates of worsening in HF symptoms (as assessed by NYHA functional class), reduced elevation of plasma NT-proBNP, reduced decline of eGFR, and similar blood pressure profile over 12 months (Figure 2). The odds of deteriorating NHYA functional class compared to stable or improved NYHA functional class at 12 months were reduced by 53% with SGLT2i treatment (OR: 0.47; 95% CI: 0.25-0.87; $P = 0.017$). Treatment with SGLT2i was associated with a slower rate of increase in the NT-proBNP at 12 months ($P < 0.001$) after adjustment for baseline NT-proBNP values (mean NT-proBNP of 5,032 ng/L among the 220 control individuals vs 4,148 ng/L among the 220 treated patients). Treatment with SGLT2i was associated with a slower rate of decline in eGFR at 12 months ($P < 0.001$) after adjustment for baseline eGFR values (mean eGFR of 50.4 mL/min/1.73 m^2 among the 220 control individuals vs 54.8 mL/min/1.73 m^2 among the 220 treated patients). Treatment with SGLT2i compared to untreated patients was associated with no changes in systolic blood pressure (SBP) at 12 months ($P = 0.24$) after adjustment for baseline SBP values

TABLE 1 Characteristics of the Propensity Score–Matched Study Population

	All (N = 440)	No SGLT2i (n = 220)	SGLT2i (n = 220)	MSD
Age, y	77 ± 7.6	76.7 ± 7.7	77.2 ± 7.5	-0.061
Male	89.8 (395)	89.1 (196)	90.5 (199)	0.051
Year of diagnosis ≥2018	90.5 (398)	92.3 (203)	88.6 (195)	0.123
Baseline SBP, mm Hg	126 (113-138)	129 (116-141)	122 (111-135)	0.251
wtATTR	80.7 (355)	79.1 (174)	82.3 (181)	0.075
hATTR	19.3 (85)	20.9 (46)	17.7 (39)	0.075
Atrial fibrillation	66.6 (293)	65.9 (145)	67.3 (148)	0.066
IHD	17.0 (75)	18.6 (41)	15.5 (34)	0.084
Diabetes mellitus	41.6 (183)	42.7 (94)	40.5 (89)	0.060
Hypertension	57.7 (254)	57.3 (126)	58.2 (128)	-0.012
Heart failure severity				
NYHA functional class				0.029
I	10.9 (48)	10.5 (23)	11.4 (25)	
II	66.4 (292)	66.8 (147)	65.9 (145)	
III	21.8 (96)	21.8 (48)	21.8 (48)	
IV	0.9 (4)	0.9 (2)	0.9 (2)	
Missing	0 (0)			
NAC stage				0.057
1	43.6 (192)	44.5 (98)	42.7 (94)	
2	35.0 (154)	33.6 (74)	36.4 (80)	
3	21.4 (94)	21.8 (48)	20.9 (46)	
Missing	0 (0)			
NT-proBNP, pg/L	2,693 (1,662-5,052)	2,815 (1,763-5,042)	2,625 (1,448-5,250)	0.053
eGFR, mL/min/1.73 m^2	56 ± 18	55 ± 17	56 ± 18	-0.088
Hemoglobin, mg/dL	136 (125-147)	133 (123-146)	136 (126-147)	-0.071
Echocardiographic parameters				
EDD, mm	44 (40-48)	44 (41-48)	45 (40-48)	0.083
MWT, mm	18 ± 2.9	17.9 ± 2.8	18.1 ± 3.0	0.084
LVEF, %	46.0 ± 10.6	46.0 ± 10.2	45.8 ± 11.0	0.019
LVEF ≤40%	34.1 (150)	31.8 (70)	36.4 (80)	0.096
E/e′	17.9 ± 5.8	18.3 ± 6	17.5 ± 5	0.080
TAPSE, mm	15 (12-18)	15 (12-19)	15 (12-18)	0.078
Medications				
Loop diuretic agents	84.3 (371)	84.1 (185)	84.5 (186)	0.012
ACEI/ARB	45.5 (200)	46.4 (102)	44.5 (98)	0.036
Beta-blockers	60.5 (266)	61.8 (136)	59.1 (130)	0.055
MRA	46.6 (205)	46.8 (103)	46.4 (102)	0.009
Disease-modifying therapy	21.4 (94)	21.8 (48)	20.9 (46)	0.020

Values are mean ± SD, % (n), or median (Q1-Q3).

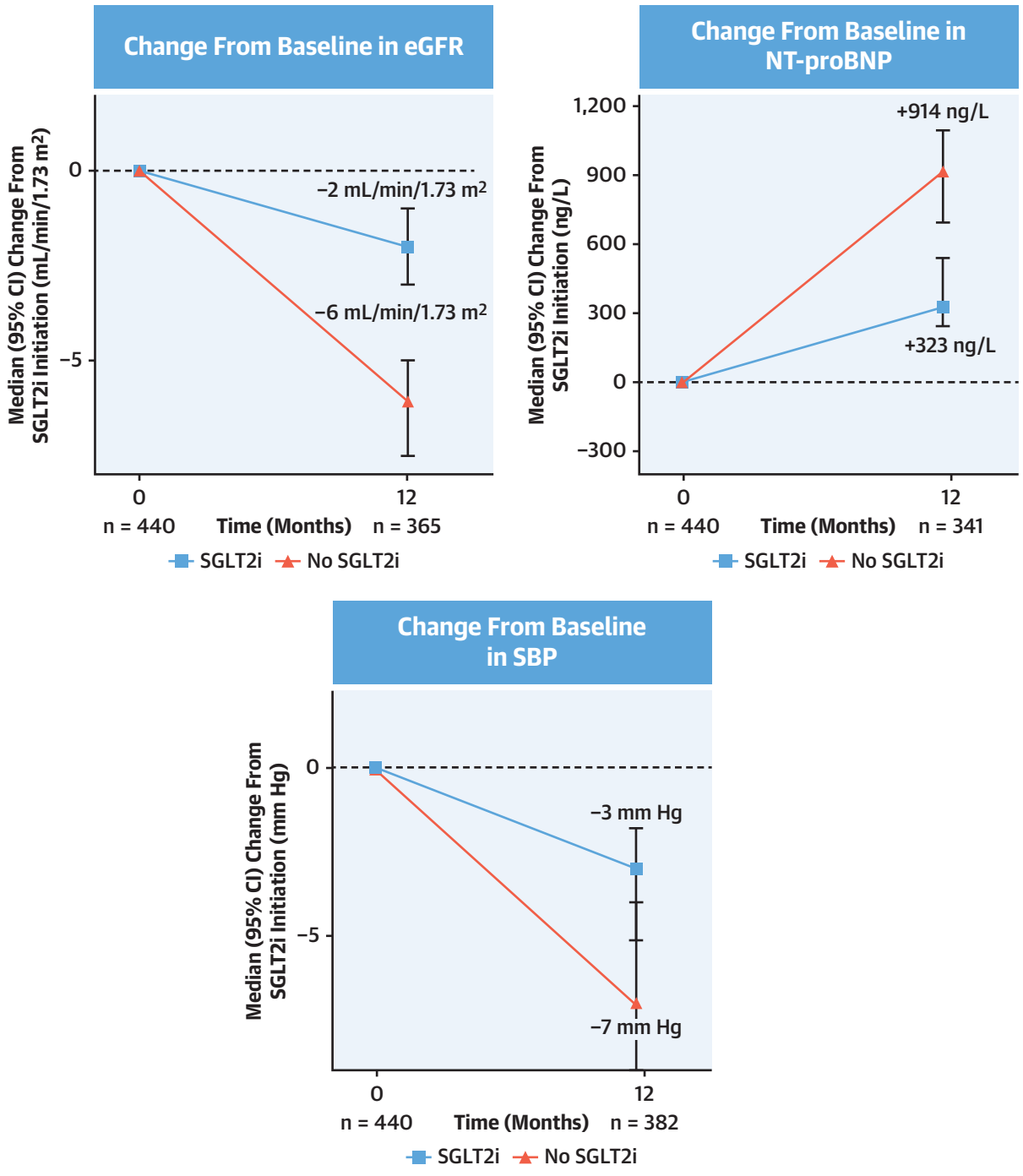
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; EDD = end-diastolic diameter; eGFR = estimated glomerular filtration rate; hATTR = hereditary transthyretin amyloidosis; IHD = ischemic heart disease; LVEF = left ventricle ejection fraction; MRA = mineralocorticoid receptor antagonist; MSD = mean standardized difference; MWT = maximal wall thickness; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal pro–B-type natriuretic peptide; SBP = systolic blood pressure; SGLT2i = sodium-glucose cotransporter 2 inhibitor; TAPSE = tricuspid annular plane systolic excursion; wtATTR = wild-type transthyretin amyloidosis.

(mean of 121 mm Hg among the 220 control individuals vs 121 mm Hg among the 220 treated patients). Among the 69 (15.7%) patients not treated with a loop diuretic agent at baseline, new initiations over 12 months occurred in 4 of 23 patients treated with SGLT2i and 17 of 46 patients not treated with SGLT2i. SGLT2i treatment reduced new initiations of loop diuretic agents over 12 months by 86% (OR: 0.14; 95% CI: 0.04-0.47; $P = 0.001$).

ASSOCIATION OF SGLT2i THERAPY WITH SURVIVAL AND HF HOSPITALIZATION. In the overall population of 440 patients with ATTR-CM, over a median follow-up of 28 months (Q1-Q3: 18-45 months), there were 111 all-cause deaths, 85 cardiovascular deaths, 100 HF hospitalizations, and 143 composite events of cardiovascular death or HF hospitalizations.

Event rates for all outcomes favored treatment with SGLT2i (Table 2).

FIGURE 2 Change From SGLT2i Initiation in eGFR, NT-proBNP, and SBP



Plots demonstrating the association between treatment with SGLT2i and changes in eGFR, NT-proBNP, and SBP at 12 months after treatment initiation. Bars describe the upper and lower 95% CIs for each measure. eGFR = estimated glomerular filtration rate; SBP = systolic blood pressure; other abbreviations as in Figure 1.

TABLE 2 Primary and Secondary Outcomes of the Study Using Time-Dependent Cox Regression Analysis

	SGLT2i (n = 220)		No SGLT2i (n = 220)			
	Values	Events/100 Patient-Years	Values	Events/100 Patient-Years	HR (95% CI)	*P* Value
All-cause mortality	29	4	82	10.8	0.57 (0.37-0.89)	0.010
Cardiovascular mortality	17	2.4	68	8.4	0.41 (0.24-0.71)	<0.001
HF hospitalization	26	3.6	74	9.2	0.57 (0.36-0.91)	0.014
Cardiovascular mortality and HF hospitalization	37	5.5	106	13.9	0.47 (0.38-0.84)	<0.001
Noncardiovascular mortality (falsification)	12	1.7	14	1.74	1.35 (0.61-3.02)	0.42

P values are measured with time-dependent Cox regression analysis.
HF = heart failure; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

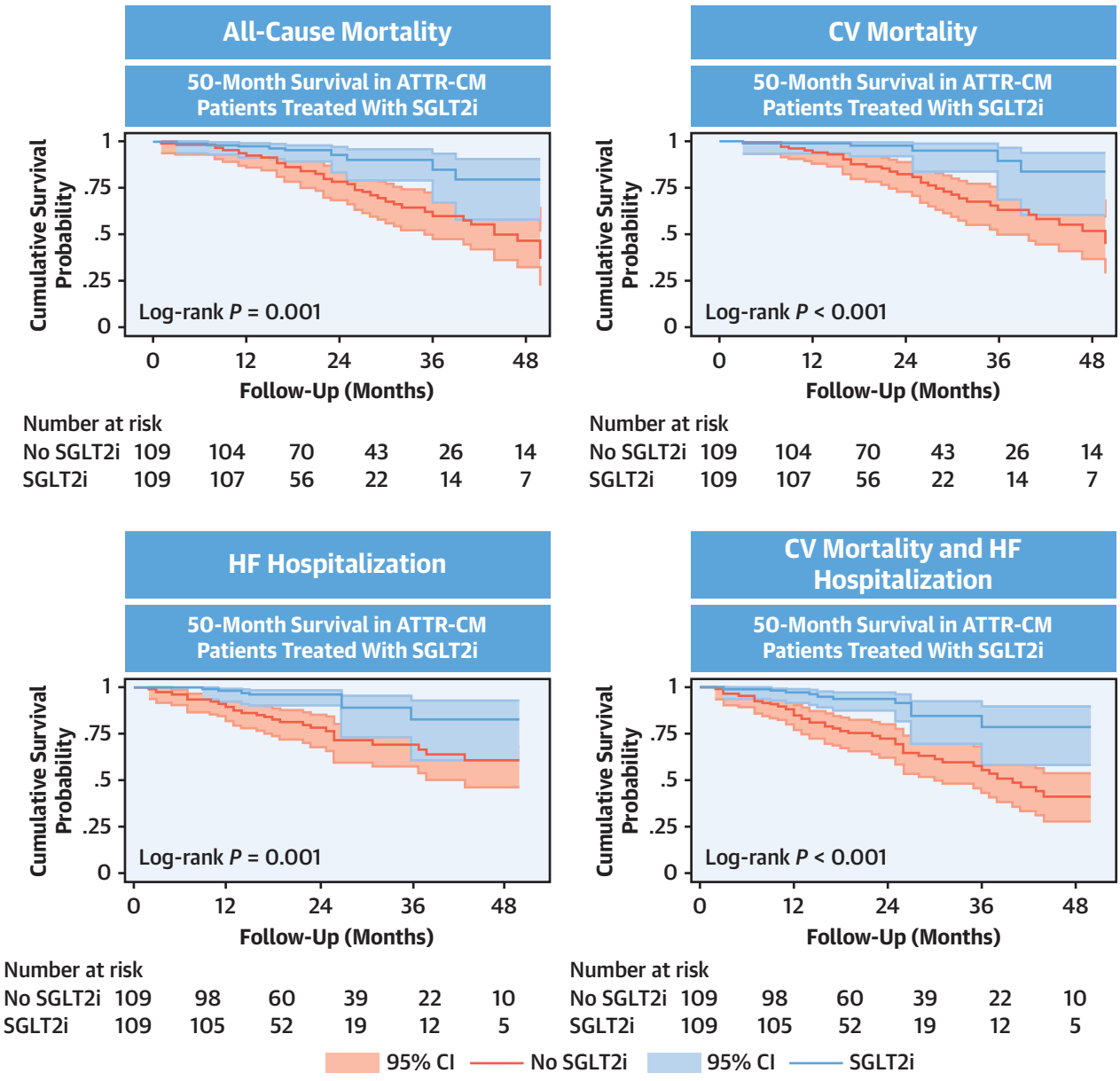
MORTALITY. Of the patients receiving SGLT2i, 29 (13.2%) died (death rate: 4 deaths/100 patient-years), compared with 82 (24.7%) patients not on SGLT2i treatment (death rate: 10.8 deaths/100 patient-years) (Table 2). Treatment with SGLT2i was associated with a reduced risk of all-cause mortality using a time-dependent analysis (HR: 0.57; 95% CI: 0.37-0.89; $P = 0.010$) (Table 2). These findings were consistent across TTR genotype (P interaction = 0.94 for ATTRwt-CM and ATTRv-CM), presence of diabetes (P interaction = 0.29 for diabetes and no diabetes), and disease-modifying treatment (P interaction = 0.46 for treated and untreated) (Supplemental Figure 1, Supplemental Tables 2 to 4). These findings were further confirmed with sensitivity analysis, using a "baseline treatment status" approach (log-rank $P = 0.001$) (Figure 3), and with a time-varying analysis censored at the start of disease-modifying drugs or entry into a clinical trial (HR: 0.55; 95% CI: 0.34-0.90; $P = 0.017$) (Supplemental Tables 5 to 7).

Cardiovascular mortality. Of the patients receiving SGLT2i, 17 (7.7%) died from cardiovascular causes (death rate: 2.4 deaths/100 patient-years), compared with 68 (20.5%) patients not on SGLT2i treatment (death rate: 8.4 deaths/100 patient-years) (Table 2). Treatment with SGLT2i was associated with reduced risk of cardiovascular mortality using a time-dependent analysis (HR: 0.41; 95% CI: 0.24-0.71; $P < 0.001$). These findings were consistent across TTR genotype (P interaction = 0.98 for ATTRwt-CM and ATTRv-CM), presence of diabetes (P interaction = 0.47 for diabetes and no diabetes), and disease-modifying treatment (P interaction = 0.51 for treated and untreated) (Supplemental Appendix). These findings were further confirmed with sensitivity analysis, using a "baseline treatment status" approach (log-rank $P < 0.001$) (Figure 3) and with a time-varying analysis censored at the start of disease-modifying drugs or entry into a clinical trial (HR: 0.40; 95% CI: 0.23-0.74; $P = 0.001$). The risk of noncardiovascular mortality (ie, falsification endpoint) was similar among patients treated with SGLT2i and PS-matched control individuals using a time-dependent analysis (HR: 1.35; 95% CI: 0.61-3.02; $P = 0.45$) (Table 2). This finding was further confirmed with sensitivity analysis, using a time-varying analysis censored at the start of disease-modifying drugs or entry into a clinical trial (HR: 1.34; 95% CI: 0.53-3.40; $P = 0.53$) (Supplemental Figure 2).

HF hospitalization. Of the patients receiving SGLT2i, 26 (11.8%) had HF hospitalization (event rate: 3.6 HF hospitalizations/100 patient-years), compared with 74 (22.3%) patients not on SGLT2i treatment (event rate: 9.2 HF hospitalizations/100 patient-years) (Table 2). Treatment with SGLT2i was associated with reduced risk of HF hospitalization using a time-dependent analysis (HR: 0.57; 95% CI: 0.36-0.91; $P = 0.014$) (Table 2). These findings were consistent across TTR genotype (P interaction = 0.86 for ATTRwt-CM and ATTRv-CM), presence of diabetes (P interaction = 0.84 for diabetes and no diabetes), and disease-modifying treatment (P interaction = 0.79 for treated and untreated) (Supplemental Appendix). These findings were further confirmed with sensitivity analysis, using a "baseline treatment status" approach (log-rank $P = 0.001$) (Figure 3).

Cardiovascular mortality and HF hospitalization. Of the patients receiving SGLT2i, 37 (16.8%) had died from cardiovascular causes or had HF hospitalization (event rate: 5.5 events/100 patient-years), compared with 106 (31.9%) patients not on SGLT2i treatment (event rate: 13.9 events/100 patient-years) (Table 2). Treatment with SGLT2i was associated with reduced risk of the composite outcome cardiovascular mortality and HF hospitalization using a time-dependent analysis (HR: 0.57; 95% CI: 0.38-0.84; $P = 0.003$) (Table 2). These findings were consistent across TTR genotype (P interaction = 0.98 for ATTRwt-CM and ATTRv-CM), presence of diabetes (P interaction = 0.75 for diabetes and no diabetes), and disease-modifying treatment

FIGURE 3 Survival and HF Hospitalizations in ATTR-CM According to SGLT2i Treatment



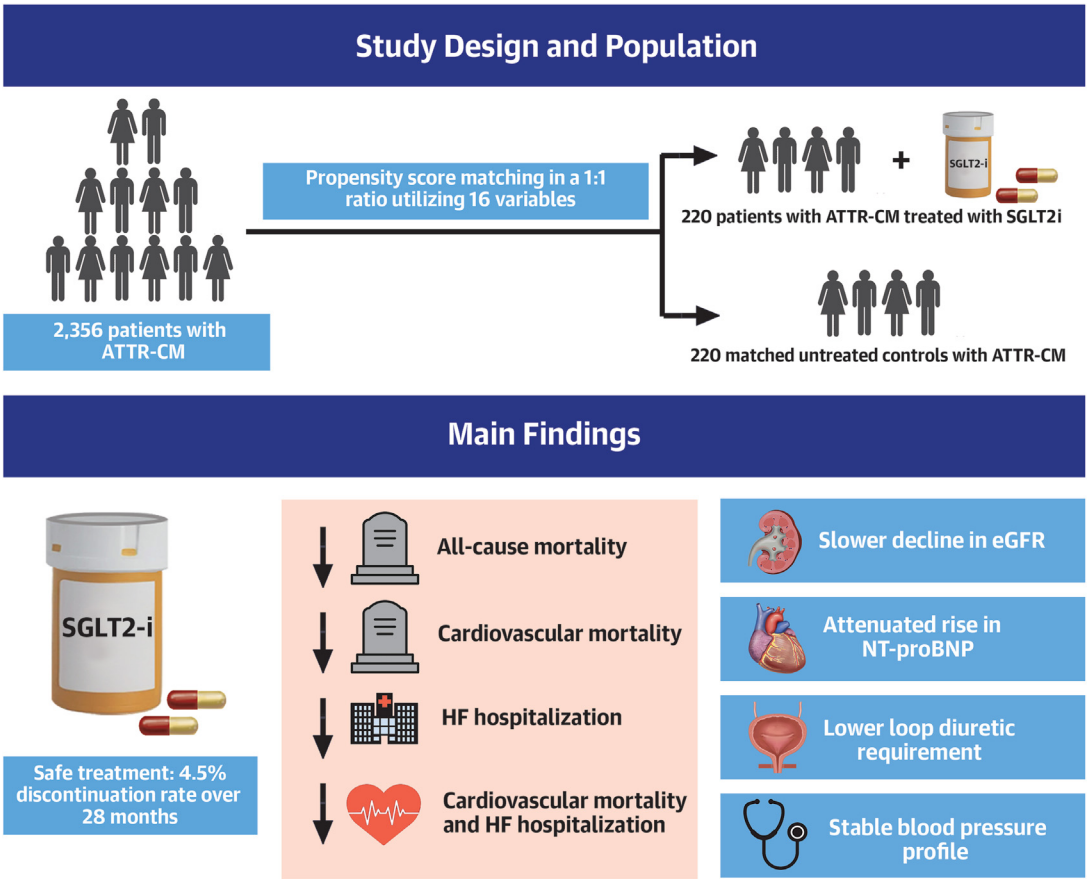
Kaplan-Meier curves demonstrating the association between treatment with SGLT2i and reduced rates of all-cause mortality, CV mortality, HF hospitalizations, and the composite of CV mortality and HF hospitalizations. This analysis was performed using a baseline treatment status approach. CV = cardiovascular; HF = heart failure; other abbreviations as in Figure 1.

(P interaction = 0.47 for treated and untreated) (Supplemental Appendix). These findings were further confirmed with sensitivity analysis, using a "baseline treatment status" approach (log-rank $P < 0.001$) (Figure 3).

DISCUSSION

In this study, we demonstrated the following in a propensity-matched comparison of patients with ATTR-CM treated with SGLT2i: 1) treatment with

CENTRAL ILLUSTRATION **Sodium-Glucose Cotransporter 2 Inhibitors in Transthyretin Amyloid Cardiomyopathy**



Porcari A, et al. J Am Coll Cardiol. 2024;83(24):2411-2422.

The study population comprised 440 patients with ATTR-CM, 220 patients who were treated with SGLT2i and 220 patients who were propensity score-matched control individuals not treated with SGLT2i. Treatment with SGLT2i was well tolerated and was associated with favorable effects on renal function, diuretic agent requirements, and natriuretic peptides and with a reduced risk of HF hospitalization and mortality. ↓ = reduction; ATTR-CM = transthyretin amyloid cardiomyopathy; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

SGLT2i was well tolerated, with only 4.5% of patients discontinuing therapy, and was not associated with significant changes in SBP; 2) at 12 months, SGLT2i treatment was associated with decreased rate of worsening in HF symptoms, attenuated rise in NT-proBNP, slower decline in renal function, and reduced new loop diuretic agent dose initiation among diuretic agent-naive patients; and 3) during a median follow-up of 28 months (Q1-Q3: 18-45 months), treatment with SGLT2i was associated with a reduced risk of all-cause mortality, cardiovascular mortality, HF hospitalization, and the composite outcome of cardiovascular mortality and HF hospitalization.

SGLT2i were prescribed at the standard target HF dose[12] in all patients with ATTR-CM, and discontinuation was rare. This likely reflects the well-known tolerability of SGLT2i, a finding that is well established in patients with HF with preserved ejection fraction and those with HFrEF because of a limited effect on blood pressure compared with beta blockers and ACEI/ARB/angiotensin receptor-neprilysin

inhibitors, which was also confirmed in our population.[12,13] The lack of a significant blood pressure-lowering effect of SGLT2i in this population is clinically meaningful because of the heightened concern for development of symptomatic hypotension in advanced stages of the disease, which often limits the use of neurohormonal antagonists.

Treatment with SGLT2i was associated with less deterioration of HF symptoms, with treated patients having 53% less probability of worsening NYHA functional class at 12 months. Beyond stabilization in the NYHA functional class, SGLT2i treatment was also associated with a slower rate of increase in the NT-proBNP levels, slower rate of decline in eGFR, and fewer new loop diuretic agent initiations.

PS-matched analysis using either a time-dependent approach or a "baseline treatment status" approach demonstrated that treatment with SGLT2i was associated with a reduced risk of all-cause mortality, cardiovascular mortality, HF hospitalization, and the composite outcome of cardiovascular mortality or HF hospitalization among ATTR-CM patients (**Central Illustration**). For survival analysis, to avoid the "immortal time" bias, the association between SGLT2i treatment and outcomes was assessed not only using the Kaplan-Meier curves based on "baseline treatment status" but also with a time-dependent Cox regression analysis with SGLT2i use as the time-varying exposure. This allowed us to fully exploit the available data and, at the same time, avoid the immortal time bias. Notably, the effect sizes are likely representing an overestimate of the true treatment effect, which is not uncommon in PS-matched analysis approaches, especially when the number of events is relatively low. Nonetheless, the results strongly support a benefit across the different endpoints. Clinical benefit was evident early after initiation of SGLT2i, with a separation of the curves within 8 to 10 months, in line with the early benefit demonstrated in randomized controlled trials testing SGLT2i in patients with HF of nonamyloid aetiology.[13] Treatment effect on all outcomes was consistent across the spectrum of ejection fraction, TTR genotype, presence of diabetes, and treatment with disease-modifying treatment, also similar to what has been observed in randomized trials.[14,17] These results are consistent with previous HF trials demonstrating that treatment with SGLT2i improved outcomes across all values of ejection fraction and among diabetic and nondiabetic patients.[14-18]

STUDY LIMITATIONS. The use of PS matching is known not to yield results that are reproduced by randomized controlled trials. The effect sizes are far larger than those reported in clinical trials in patients without amyloidosis, likely representing an overestimate of the true effect size. This is the case especially when the number of events is relatively small, as is the case in the current analysis (Supplemental Tables 8 to 12). Although our findings remained significant after PS matching, we cannot exclude the possibility of other unmeasured confounders because PS matching cannot adequately adjust for all confounders. Although indication bias may play a role in which patients receive or do not receive SGLT2i, it is possible that some clinicians might be more likely to treat patients with more advanced disease with SGLT2i, whereas others might avoid the use of SGLT2i in patients with advanced disease because SGLT2i have never been tested in patients with ATTR-CM. Changes in covariates between baseline and follow-up timepoints may have been related to the provider decision regarding initiation of SGLT2i during follow-up, but this aspect could not be further investigated in this analysis. Data on changes in serum troponin concentration over time were not available. Adequate matching was not found for 40 patients on SGLT2i (15% of all patients treated with SGLT2i). Our study was underpowered for subgroup analysis, leading to wide CIs reflective of the small sample size of some of these analyses. Immortal time bias is frequent in studies of this type. To avoid "immortal time bias," patients entered the study from the date of diagnosis rather than the date of starting treatment, and therefore immortal time bias does not apply to our study. Finally, the findings from the present study should be considered hypothesis generating and ideally should be confirmed with prospective randomized, placebo-controlled clinical trials of SGLT2i in contemporary cohorts of patients with ATTR-CM treated with disease-modifying drugs.

CONCLUSIONS

In this large cohort of patients with ATTR-CM, SGLT2i treatment was well tolerated, with only 4.5% of patients discontinuing therapy, and was associated with a decreased rate of worsening in symptoms, less increase in NT-proBNP, slower decline in renal function,

and reduced new loop diuretic agent dose initiation. During follow-up, treatment with SGLT2i was associated with a reduced risk of all-cause mortality, cardiovascular mortality, HF hospitalization, and the composite of cardiovascular mortality and HF hospitalization. In the absence of randomized trials, these data may inform clinicians regarding the use of SGLT2i in patients with ATTR-CM.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with ATTR-CM, SGLT2i are generally well tolerated, with favorable effects on renal function, diuretic agent requirements, and risks of heart failure hospitalization and mortality, irrespective of left ventricular ejection fraction.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to determine the optimum dose and timing of SGLT2i therapy for patients with ATTR-CM with or without diabetes mellitus and to identify factors associated with treatment interruption.

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KEY WORDS heart failure hospitalization, heart failure therapy, sodium-glucose cotransporter 2 inhibitors, survival, transthyretin amyloid cardiomyopathy

APPENDIX For supplemental tables and figures, please see the online version of this paper.