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Tricuspid Regurgitation and Clinical Outcomes in Heart Failure With Reduced Ejection Fraction

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ABSTRACT

BACKGROUND Tricuspid regurgitation (TR) is common and is associated with poor outcomes in patients with heart failure (HF). However, data with adjudicated events from fully characterized patients with heart failure with reduced ejection fraction (HFrEF) are lacking.

OBJECTIVES This study sought to explore the association between mild or moderate/severe TR and clinical outcomes of patients with HFrEF.

METHODS GALACTIC-HF (Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure) was a double-blind, placebo-controlled randomized trial comparing omecamtiv mecarbil vs placebo in patients with symptomatic HFrEF.

RESULTS Among the 8,232 patients analyzed in the GALACTIC-HF trial, 8,180 (99%) had data regarding baseline TR (none: n = 6,476 [79%], mild: n = 919 [11%], and moderate/severe: n = 785 [10%]). The primary composite outcome of a first HF event or cardiovascular death occurred in 2,368 (36.6%) patients with no TR, 353 (38.4%) patients with mild TR, and 389 (49.6%) patients with moderate/severe TR. Moderate/severe TR was independently associated with a higher relative risk of the primary composite outcome compared with either no TR (adjusted HR: 1.12 [95% CI: 1.01-1.26]; $P = 0.046$) or no/mild TR (adjusted HR: 1.14 [95% CI: 1.02-1.27]; $P = 0.025$) driven predominantly by HF events. The association between moderate/severe TR and clinical outcomes was more pronounced in outpatients with worse renal function, higher left ventricular ejection fraction, and lower N-terminal pro-B-type natriuretic peptide and bilirubin levels. The beneficial treatment effect of omecamtiv mecarbil vs placebo on clinical outcomes was not modified by TR.

CONCLUSIONS In symptomatic patients with HFrEF, baseline moderate/severe TR was independently associated with cardiovascular death or HF events driven predominantly by HF events. The beneficial treatment effect of omecamtiv mecarbil on the primary outcome was not modified by TR. (J Am Coll Cardiol HF 2024;12:552–563) © 2024 by the American College of Cardiology Foundation.

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Tricuspid regurgitation (TR) is common in patients with heart failure (HF). Moderate or severe TR was observed in about 20% of patients with chronic HF in the European Society of Cardiology Heart Failure Long-Term Registry regardless of left ventricular ejection fraction (LVEF).[1] Right ventricular dysfunction caused by heart failure with reduced ejection fraction (HFrEF) is one of the most common causes of secondary TR.[2-4] Observational retrospective studies have suggested an association between greater TR severity and a higher risk of clinical outcomes, although the adjustment for other clinical and echocardiographic parameters was variable and incomplete.[5-8] Data on fully characterized patients with HFrEF from large, prospective studies with adjudicated events are lacking, and it remains unsettled whether TR is a central driving force of HF progression or rather a bystander, reflecting the severity of HFrEF.

Given the recent advances in transcatheter tricuspid valve interventions, a better understanding of the role of TR and its impact on the clinical presentation and outcomes of HF patients seems even more important.[9-12] The GALACTIC-HF (Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure) study is the largest contemporary trial of patients with HFrEF with information on baseline TR.[13] The aim of the present study was to explore the association of mild or moderate/severe TR and clinical outcomes of patients with HFrEF enrolled in the GALACTIC-HF trial.

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METHODS

STUDY POPULATION. The design, baseline characteristics, and main results of the GALACTIC-HF trial have been previously reported.[13-15] Briefly, this was a phase 3, global, double-blind, placebo-controlled randomized clinical trial comparing omecantiv mecarbil vs placebo in 8,256 patients with symptomatic HFrEF (NYHA functional class II-IV and LVEF ≤35%). Both inpatients (currently hospitalized for HF) and outpatients (urgent visit to the emergency department for HF or hospitalization for HF within 1 year) were included. All participants were required to receive optimized background HF therapy and to have elevated natriuretic peptides (N-terminal pro-B-type natriuretic peptide [NT-proBNP] level ≥400 pg/mL [1,200 pg/mL for patients in atrial fibrillation] or B-type natriuretic peptide ≥125 pg/mL [375 pg/mL for patients in atrial fibrillation]). The key exclusion criteria were hemodynamic or clinical instability requiring mechanical or intravenous therapy, systolic blood pressure (SBP) <85 or >140 mm Hg, diastolic blood pressure >90 mm Hg, estimated glomerular filtration rate (eGFR) <20 mL/min/1.73 m^2, and a recent acute coronary syndrome or cardiovascular (CV) procedure (including planned procedures). All participants provided written informed consent and the study protocol was approved by the relevant local ethics committees.

For the present analyses, only patients with data regarding baseline TR were included. Questions on the trial case report form asked about concomitant valvular heart disease; type of valve disease; and, if present, whether the severity was mild, moderate, or severe according to the previously reported classification.[16] To ensure adequate numbers for analysis, the population was stratified according to 3 baseline TR categories (none vs mild vs moderate or severe).

ABBREVIATIONS AND ACRONYMS

CRT = cardiac resynchronization therapy

CV = cardiovascular

eGFR = estimated glomerular filtration rate

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

ICD = implantable cardioverter-defibrillator

KCCQ = Kansas City Cardiomyopathy Questionnaire

LVEF = left ventricular ejection fraction

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

SBP = systolic blood pressure

TR = tricuspid regurgitation

TSS = total symptom score

STUDY OUTCOMES. The prespecified primary outcome was a composite of the time-to-first HF event or CV death. The secondary outcomes of interest included a first HF event, first HF hospitalization, CV death, and all-cause death. An HF event was defined as an urgent clinic visit, emergency department visit, or hospitalization for worsening HF leading to treatment intensification beyond a change in oral diuretic therapy. Changes in the total symptom score (TSS) on the Kansas City Cardiomyopathy Questionnaire (KCCQ) from baseline to week 24 (on a scale of 0 to 100, with higher scores indicating a lower frequency and severity of symptoms) were also considered. All events were adjudicated by an independent external clinical events committee (Duke Clinical Research Institute) using standardized definitions as reported in the publication of the primary results.

STATISTICAL ANALYSIS. Continuous variables are reported as mean ± SD or median (IQR) as appropriate. Categoric variables are reported as numbers and percentages.

Comparisons between groups were conducted using the Kruskal-Wallis and chi-square tests as appropriate. Survival analyses were conducted using unadjusted Poisson regression models to estimate incidence rates and Cox proportional hazards models to estimate HRs. Kaplan-Meier methods were used to construct cumulative incidence curves for time-to-event data. All non-CV deaths are considered as censoring.

TABLE 1 Baseline Characteristics of GALACTIC-HF Patients Across TR Subgroups

	No TR (n = 6,476)	Mild TR (n = 919)	Moderate/Severe TR (n = 785)	*P* Value
Demographics				
Age, y	66 (57-73)	67 (59-73)	67 (59-74)	0.002
Female	1,359 (21.0)	188 (20.5)	184 (23.4)	0.21
Race				<0.001
Asian	577 (8.9)	84 (9.1)	39 (5.0)	
Black	467 (7.2)	49 (5.3)	45 (5.7)	
Other	454 (7.0)	72 (7.8)	36 (4.6)	
White	4.978 (76.9)	714 (77.7)	665 (84.7)	
Geographic region				<0.001
Asia	542 (8.4)	82 (8.9)	37 (4.7)	
Eastern Europe/Russia	1,801 (27.8)	414 (45.0)	451 (57.5)	
Latin America	1,435 (22.2)	85 (9.2)	52 (6.6)	
United States and Canada	1,094 (16.9)	173 (18.8)	109 (13.9)	
Western Europe/South Africa/Australasia	1,604 (24.8)	165 (18.0)	136 (17.3)	
Randomization setting: inpatient	1,580 (24.4)	239 (26.0)	252 (32.1)	<0.001
Clinical characteristics				
History of AF or AFL	1,615 (24.9)	278 (30.3)	329 (41.9)	<0.001
Hypertension	4,510 (69.6)	688 (74.9)	552 (70.3)	0.11
Type 2 diabetes mellitus	2,651 (40.9)	336 (36.6)	303 (38.6)	0.036
History of stroke	583 (9.0)	92 (10.0)	74 (9.4)	0.47
COPD	1,026 (15.8)	168 (18.3)	144 (18.3)	0.050
Ischemic heart failure etiology	3,483 (53.8)	488 (53.1)	424 (54.0)	0.96
History of myocardial infarction	2,726 (42.1)	364 (39.6)	332 (42.3)	0.64
History of CABG	1,004 (15.5)	159 (17.3)	140 (17.8)	0.043
History of PCI	1,915 (29.6)	285 (31.0)	226 (28.8)	0.96
Duration of HF history, y	2.9 (0.7-7.4)	2.7 (0.8-7.4)	4.0 (1.0-8.4)	<0.001
Prior HF hospitalization	6,217 (96.0)	875 (95.2)	764 (97.3)	0.08
LVEF, %	28 (22-32)	28 (21-32)	26 (20-32)	0.24
NYHA functional class				0.001
II	3,570 (55.1)	479 (52.1)	295 (37.6)	
III	2,707 (41.8)	423 (46.0)	460 (58.6)	
IV	199 (3.1)	17 (1.8)	30 (3.8)	
KCCQ, total symptom score	69.8 (50-87.5)	70.8 (51-87.5)	62.5 (43.8-83.3)	<0.001
Outpatient	75 (55.2-91.7)	75 (57.3-91.7)	70.3 (52.1-87.5)	<0.001
Inpatient	54.2 (31.2-71.9)	60.4 (39.6-78.1)	47.9 (29.2-64.6)	<0.001
Systolic blood pressure, mm Hg	117 (105-129)	116 (105-128)	115 (104-125)	0.003
Heart rate, beats/min	70 (64-80)	70 (63-80)	74 (66-81)	<0.001
NT-proBNP, pg/mL	1,881 (925-3,895)	2,137 (1,114-3,939)	2,974 (1,538-5,720)	<0.001
Cardiac troponin I, ng/L	26 (14-50)	27 (14-53)	30 (17-59)	<0.001
eGFR, mL/min/1.73 m^2	59.4 (44.7-74.6)	58.2 (43.1-71.9)	54.7 (41.5-71.9)	<0.001
Baseline aspartate aminotransferase, U/L	21 (17-26)	21 (17-27)	22.0 (18-28)	<0.001
Baseline alanine aminotransferase, U/L	19 (14-26)	19 (14.5-27)	20.0 (15-28)	0.038
Baseline alkaline phosphatase, U/L	81 (65-104)	79 (65-100)	89 (69-117)	<0.001
Baseline direct bilirubin, mg/dL	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.3 (0.2-0.4)	<0.001
Baseline total bilirubin, mg/dL	0.6 (0.4-0.9)	0.6 (0.4-0.9)	0.8 (0.5-1.1)	<0.001

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A Cox multivariable analysis including variables differentially distributed across TR categories was performed to evaluate the association between TR and clinical outcomes with a backward variable selection using a *P* value threshold of 0.05. Three models were used. Model 1 included age, female sex, race, region, inpatient setting, myocardial infarction, coronary artery bypass graft, percutaneous coronary revascularization, stroke, atrial fibrillation or flutter, diabetes mellitus, LVEF, NYHA functional class, ischemic HF etiology, the KCCQ, heart rate, NT-proBNP, troponin, and eGFR. Model 2 provided an extensive adjustment for the following variables: age, female sex, region, inpatient setting, atrial fibrillation or flutter, ischemic heart failure etiology, myocardial infarction, LVEF, systolic blood pressure, heart rate,

TABLE 1 Continued

	No TR (n = 6,476)	Mild TR (n = 919)	Moderate/Severe TR (n = 785)	*P* Value
Heart failure therapies				
ACE inhibitor, ARB, or ARNI	5,689 (87.8)	785 (85.4)	647 (82.4)	<0.001
ARNI	1,285 (19.8)	170 (18.5)	134 (17.1)	0.045
Beta-blocker	6,109 (94.3)	874 (95.1)	729 (92.9)	0.27
MRA	5,002 (77.2)	710 (77.3)	643 (81.9)	0.009
SGLT2 inhibitors	179 (2.8)	16 (1.7)	23 (2.9)	0.64
Furosemide	4,463 (68.9)	592 (64.4)	526 (67.0)	0.017
Torsemide	933 (14.4)	214 (23.3)	212 (27.0)	<0.001
Furosemide/Torsemide dose, mg/d	40 (20-80)	40 (20-80)	40 (20-80)	<0.001
Ivabradine	370 (5.7)	82 (8.9)	79 (10.1)	<0.001
Digitalis glycosides	1,040 (16.1)	169 (18.4)	168 (21.4)	<0.001
Cardiac resynchronization therapy	842 (13.0)	165 (18.0)	140 (17.8)	<0.001
Implantable cardioverter-defibrillator	1,990 (30.7)	325 (35.4)	281 (35.8)	<0.001

Values are median (Q1-Q3) or n (%).

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; AFL = atrial flutter; ARB = angiotensin receptor blocker; ARNI = angiotensin-converting enzyme inhibitor; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; eGFR = estimate glomerular filtration rate; GALACTIC-HF = Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PCI = percutaneous coronary intervention; SGLT2, sodium glucose co-transporter 2; TR = tricuspid regurgitation.

NT-proBNP, troponin I, eGFR, body mass index, angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, beta-blockers, mineralocorticoid receptor antagonists, sodium glucose co-transporter 2 inhibitor, ivabradine, digitalis glycosides, cardiac resynchronization therapy (CRT), implantable cardioverter-defibrillator (ICD), KCCQ TSS, baseline aspartate aminotransferase, baseline alanine aminotransferase, baseline alkaline phosphatase, baseline total bilirubin, NYHA functional class, history of hypertension, history of chronic obstructive pulmonary disease, history of stroke, history of coronary artery bypass surgery, history of percutaneous coronary revascularization, prior HF hospitalization, diabetes mellitus, duration of HF history, and furosemide dose. Model 3 was used to adjust for the Meta-Analysis Global Group in Chronic Heart Failure risk score.

A sensitivity analysis excluding inpatients whose TR grade would be overestimated at baseline evaluation was also performed. Subgroup analyses were performed to test the interaction between TR and demographic and clinical variables on outcomes. Treatment effect modification was assessed via the introduction of interaction terms between randomized treatment assignment and baseline TR categories. All analyses were performed using STATA version 16 (StataCorp). All values of $P < 0.05$ were considered statistically significant. All *P* values were 2-sided.

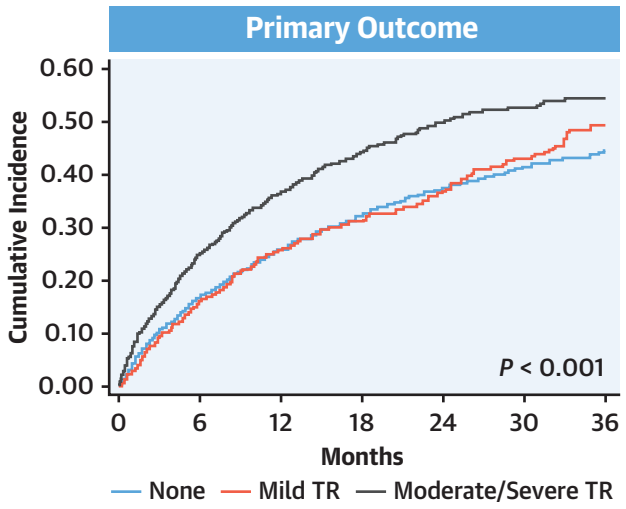
RESULTS

STUDY POPULATION. Among the 8,232 patients analyzed in the GALACTIC-HF trial, 8,180 had data regarding baseline TR. Among them, 6,476 (79%) had no TR, 919 (11%) had mild TR, and 785 (10%) had moderate or severe TR. Baseline characteristics according to TR severity are reported in Table 1. Age and the proportion randomized as an inpatient increased with increasing TR severity. Geographic regions were distributed differently across TR subgroups, with proportionately more patients from Eastern Europe or Russia in the moderate/severe TR subgroup and proportionately fewer from Latin America in this category. More advanced functional limitation (ie, NYHA functional class III or IV); lower SBP and eGFR; and higher levels of NT-proBNP, cardiac troponin I, and markers of hepatic dysfunction were observed in patients with greater TR severity compared to those with less severe TR.

With regard to evidence-based therapies, patients with moderate/severe TR were less likely to receive an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, or angiotensin receptor-neprilysin inhibitor and more likely to receive a mineralocorticoid receptor antagonist, ivabradine, digitalis, and CRT compared to the others (Table 1).

ASSOCIATION BETWEEN TR AND CLINICAL OUTCOMES. During a median follow-up of 22 months (Q1-Q3: 15-29 months), the primary composite outcome of a first HF event or CV death occurred in 2,368 (36.6%)

FIGURE 1 Cumulative Incidence of Primary Outcome According to TR Severity



Kaplan-Meier estimate incidence of heart failure events or cardiovascular death in patients with no tricuspid regurgitation (TR) vs those with mild TR vs moderate/severe TR.

patients with no TR, 353 (38.4%) patients with mild TR, and 389 (49.6%) patients with moderate/severe TR. The incidence of the primary composite endpoint was 24.3 per 100 patient-years in the no TR group, 24.4 per 100 patient-years in the mild TR group, and 35.3 per 100 patient-years in the moderate/severe TR group (mild TR [HR: 1.02; 95% CI: 0.91-1.14; $P = 0.735$] and moderate/severe TR [HR: 1.45; 95% CI: 1.31-1.62; $P < 0.001$]) (**Figure 1**, **Table 2**).

After adjustment for several covariates, moderate/severe TR was independently associated with a higher relative risk of the primary composite outcome compared to either no TR (adjusted HR: 1.12 [95% CI: 1.01-1.26]; $P = 0.046$) or no/mild TR (adjusted HR: 1.14 [95% CI: 1.02-1.27]; $P = 0.025$). Similar results were observed by using different models (**Table 2**, Supplemental Table 1, **Central Illustration**).

Regarding secondary endpoints, moderate/severe TR compared with no TR or no/mild TR remained independently associated with an increased relative risk of first HF event and HF hospitalization, whereas no significant association was observed for CV mortality or all-cause mortality, considered as individual endpoints (**Figure 2**, **Table 2**, Supplemental Table 1, **Central Illustration**). Outcome analysis performed excluding inpatients showed similar results for all the endpoints (Supplemental Table 2).

ASSOCIATION BETWEEN TR AND QUALITY OF LIFE. In the overall population and in the outpatient subgroup, moderate/severe TR was associated with a lower KCCQ TSS at both baseline and after 24 weeks of follow-up compared with no or mild TR, and similar changes between baseline and 24-week KCCQ TSS were observed across TR groups. On the other hand, among participants enrolled as an inpatient, those with moderate/severe TR had a lower KCCQ TSS at baseline and a greater improvement at 24 weeks compared to inpatients with no or mild TR (Supplemental Table 3).

SUBGROUP ANALYSIS. Moderate/severe TR was associated with a higher rate of the primary outcome across all different subgroups. This association was larger in outpatients compared with inpatients (P for interaction = 0.041), patients with eGFR ≤60 mL/min/1.73 m^2 compared to those with eGFR >60 mL/min/1.73 m^2 (P for interaction = 0.030), and those with low vs high bilirubin levels (P for interaction = 0.034) (**Figure 3**). Similar results were found for HF events and HF hospitalizations, with a greater association of moderate/severe TR in outpatients (P for interaction = 0.008 and 0.018, respectively) and patients with a higher LVEF (P for interaction = 0.036 and 0.026, respectively), lower NT-proBNP (P for interaction = 0.014 and 0.005, respectively), lower bilirubin levels (P for interaction = 0.027 and 0.052, respectively), and lower eGFR (P for interaction = 0.025 and 0.012, respectively) (**Figures 4 and 5**).

IMPACT OF TR ON THE TREATMENT EFFECT OF OMECAMTIV MECARBIL. TR severity did not modify the effects of omecamtiv mecarbil vs placebo on the primary or other outcomes (Supplemental Figures 1 and 2).

DISCUSSION

In the GALACTIC-HF population, a worse TR grade was associated with greater severity of HF. Moderate/severe TR, but not mild TR, was independently associated with a higher relative risk of the composite outcome including a worsening HF event or CV death. The independent association between moderate/severe TR and the primary outcome was mainly driven by HF events. Moderate/severe TR was associated with a higher rate of the primary outcome as well as HF hospitalizations alone across all the different subgroups examined, although this association was larger in outpatients and patients with a higher LVEF, lower NT-proBNP, lower bilirubin, and lower eGFR. Finally, the beneficial treatment effect of omecamtiv mecarbil on the primary outcome was not modified by baseline TR.

PREVALENCE OF TR. The proportion of patients with reported baseline moderate/severe TR in the

TABLE 2 Clinical Outcomes by TR Grade

	No TR (n = 6,476)		Mild TR (n = 919)			Moderate/Severe TR (n = 785)			
	n (%)	Rate (per 100 pts/y)	n (%)	Rate (per 100 pts/y)	HR (95% CI); *P* Value Ref. = No TR	n (%)	Rate (per 100 pts/y)	HR (95% CI); *P* Value Ref. = No TR	HR (95% CI); *P* Value Ref. = No/Mild TR
Primary outcome	2,368 (36.6)	24.3	353 (38.4)	24.4	1.02 (0.91-1.14); 0.735 0.93 (0.83-1.04); 0.215[a] 0.96 (0.83-1.10); 0.525[b]	389 (49.6)	35.3	1.45 (1.31-1.62); <0.001 1.12 (1.01-1.26); 0.046[a] 1.14 (0.99-1.31); 0.063[b]	1.45 (1.30-1.61); <0.001 1.14 (1.02-1.27); 0.025[a] 1.15 (1.00-1.32); 0.049[b]
First HF event	1,783 (27.5)	18.3	289 (31.4)	19.9	1.11 (0.98-1.26); 0.093 0.99 (0.87-1.12); 0.878[a] 1.05 (0.90-1.23); 0.504[b]	323 (41.1)	29.3	1.61 (1.43-1.81); <0.001 1.22 (1.07-1.38); 0.002[a] 1.28 (1.10-1.49); 0.002[b]	1.58 (1.41-1.78); <0.001 1.22 (1.08-1.38); 0.002[a] 1.27 (1.09-1.48); 0.002[b]
HF hospitalization	1,719 (26.5)	17.4	272 (29.6)	18.5	1.08 (0.95-1.23); 0.235 0.95 (0.83-1.08); 0.448[a] 1.02 (0.87-1.20); 0.790[b]	313 (39.9)	28	1.61 (1.43-1.82); <0.001 1.19 (1.05-1.35); 0.008[a] 1.25 (1.07-1.47); 0.005[b]	1.59 (1.41-1.80); <0.001 1.20 (1.06-1.36); 0.005[a] 1.25 (1.07-1.46); 0.005[b]
CV death	1,233 (19)	10.7	159 (17.3)	9.2	0.86 (0.73-1.02); 0.076 0.83 (0.70-0.98); 0.032[a] 0.84 (0.69-1.03); 0.095[b]	209 (26.6)	14.8	1.39 (1.20-1.61); <0.001 1.06 (0.91-1.24); 0.452[a] 0.93 (0.76-1.13); 0.445[b]	1.41 (1.22-1.63); <0.001 1.09 (0.94-1.27); 0.258[a] 0.95 (0.78-1.15); 0.593[b]
All-cause death	1,634 (25.2)	14.1	226 (24.6)	13	0.92 (0.80-1.06); 0.242 0.90 (0.78-1.04); 0.152[a] 0.87 (0.73-1.03); 0.112[b]	264 (33.6)	18.7	1.32 (1.16-1.50); <0.001 1.04 (0.91-1.20); 0.534[a] 0.91 (0.76-1.07); 0.257[b]	1.33 (1.17-1.52); <0.001 1.06 (0.93-1.22); 0.384[a] 0.92 (0.78-1.09); 0.355[b]

[a]Model 1 adjusted for age, female sex, region, inpatient setting, myocardial infarction, coronary artery bypass graft, percutaneous coronary revascularization, stroke, atrial fibrillation or flutter, diabetes mellitus, left ventricular ejection fraction, NYHA functional class, ischemic HF etiology, Kansas City Cardiomyopathy Questionnaire total symptom score, heart rate, N-terminal pro–B-type natriuretic peptide (log transformed), troponin (log transformed), and glomerular filtration rate. [b]Model 2 adjusted for age, female sex, region, inpatient setting, atrial fibrillation or flutter, ischemic heart failure etiology, myocardial infarction, left ventricular ejection fraction, systolic blood pressure, heart rate, N-terminal pro–B-type natriuretic peptide, troponin I, estimated glomerular rate, body mass index, angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, beta blockers, mineralocorticoid receptor antagonists, sodium glucose co-transporter 2 inhibitor, ivabradine, digitalis glycosides, cardiac resynchronization therapy, implantable cardioverter-defibrillator, Kansas City Cardiomyopathy Questionnaire total symptom score, baseline aspartate aminotransferase, baseline alanine aminotransferase, baseline alkaline phosphatase, baseline total bilirubin, NYHA functional class, history of hypertension, history of chronic obstructive pulmonary disease, history of stroke, history of coronary artery bypass surgery, history of percutaneous coronary revascularization, prior HF hospitalization, diabetes mellitus, duration of HF history, and furosemide dose.

CV = cardiovascular; HF = heart failure; pts = patients; Ref. = Reference; TR = tricuspid regurgitation.

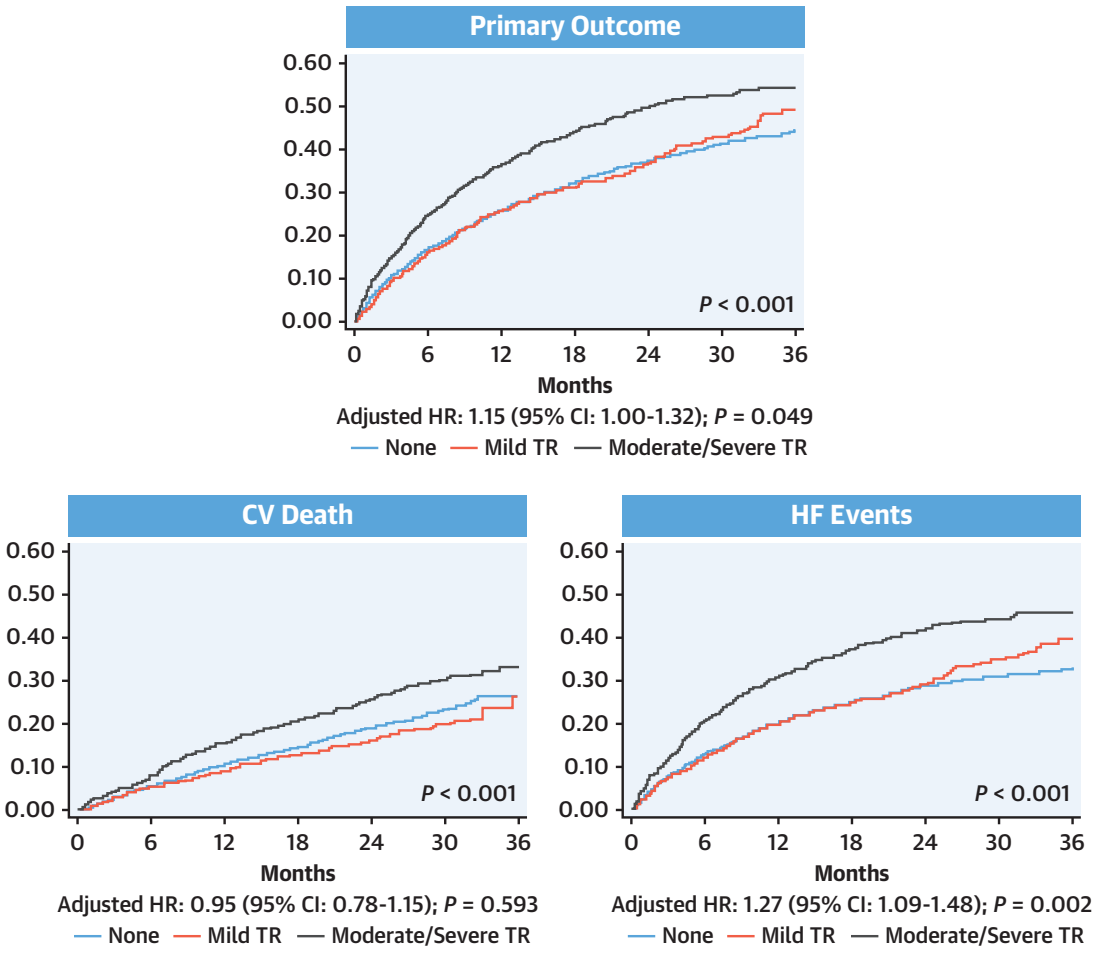
GALACTIC-HF population was 10%, which is lower compared to recent data from observational real-world studies showing a prevalence of moderate/severe TR in patients with HFrEF that ranges between 19.5% and 23%.[1,5] This may be explained by the selective exclusion criteria adopted in the GALACTIC-HF randomized controlled trial (ie, hemodynamic or clinical instability, SBP <85 or >140 mm Hg, eGFR <20 mL/min/1.73 m^2, and recent acute coronary syndrome or cardiovascular procedure) compared with observational all-comers registries.

PATIENT CHARACTERISTICS ACCORDING TO TR. Secondary TR can be caused by HFrEF in its advanced stage of disease when chronic congestion of pulmonary circulation and pulmonary hypertension lead to right ventricular impairment, tricuspid leaflet tethering and annular dilatation, and consequent TR. Other concomitant mechanisms can contribute to TR, such as atrial disease caused by atrial fibrillation and leading annular dilatation or ICD/CRT leads that can interfere with the tricuspid leaflet.

According to these mechanisms, an incremental correlation between TR degree and HF severity (ie, inpatient/outpatient setting, NYHA functional class, LVEF, SBP, NT-proBNP levels, and eGFR) was observed in the overall GALACTIC-HF population, and this is in line with previous findings.[5-7,17] Moreover, we noted a lower rate of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker/angiotensin receptor-neprilysin inhibitor prescriptions and a higher rate of the use of digitalis and ICD/CRT in the presence of greater TR. The former is probably caused by the low tolerance to renin-angiotensin antagonists, which is typical of TR patients because of concomitant hypotension and renal congestion or dysfunction. Regarding the latter, the higher rate of digitalis among patients with a higher TR grade may be caused by the higher proportion of patients with atrial fibrillation that may have also contributed to the development of or worsening of TR. On the other hand, the higher rate of ICD/CRT may be caused by the trend toward a lower LVEF in patients with a higher TR grade and also the possible role of leads in inducing or contributing to TR.

TR AND CLINICAL OUTCOMES. In the overall GALACTIC-HF population, the incidence of all clinical events (primary outcome, HF events, HF hospitalization, CV death, and all-cause death) was higher in patients with moderate/severe TR compared to those with no or mild TR. After adjustment for clinical

CENTRAL ILLUSTRATION **Cumulative Incidence and Adjusted HR of the Primary Outcome and Its Components According to Tricuspid Regurgitation Severity**



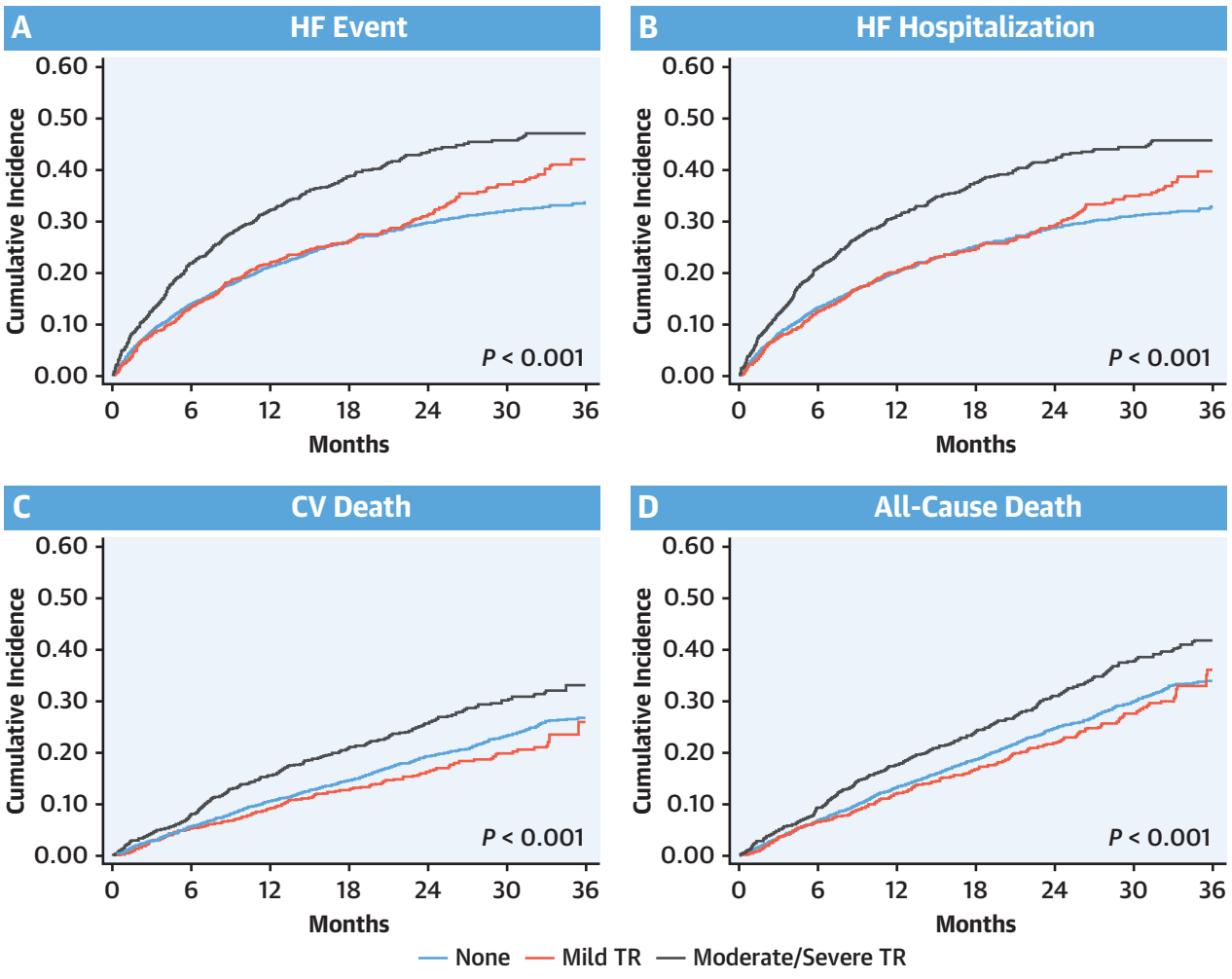
Adamo M, et al. J Am Coll Cardiol HF. 2024;12(3):552–563.

Kaplan-Meier estimate incidence of heart failure (HF) events and/or cardiovascular (CV) death in patients with no tricuspid regurgitation (TR) vs mild TR vs moderate/severe TR and adjusted HR and 95% CI of HF events and/or CV death in patients with no TR or mild TR vs moderate/severe TR.

characteristics and variables related to HF severity, moderate/severe TR remained independently associated with the primary outcome of CV death or HF event and with the first HF event and HF hospitalization evaluated as individual endpoints. On the other hand, moderate/severe TR did not have an independent association with CV and all-cause mortality, considered alone.

Previous observational studies reported a possible independent association between TR and long-term mortality in HFrEF patients.[5,17] Topilsky et al[17] demonstrated a strong relationship between significant TR, defined as the presence of an effective orifice area ≥0.4 cm^2, and 5-year mortality (HR: 1.8; 95% CI: 1.2-2.8) in a retrospective single-center study including 291 patients with LVEF <50%. More recently, in a larger cohort of patients with left ventricular dysfunction (N = 13,026), Benfari et al[5] showed an incremental and independent role of TR on 10-year mortality (mild TR [HR: 1.09; 95% CI: 1.01-1.17], moderate TR [HR: 1.21; 95% CI: 1.11-1.33], and severe TR [HR: 1.57; 95% CI: 1.39-1.78] with no TR as reference). In both studies, the association between TR and mortality was independent of age, sex,

FIGURE 2 Cumulative Incidence of Secondary Outcomes According to TR Severity

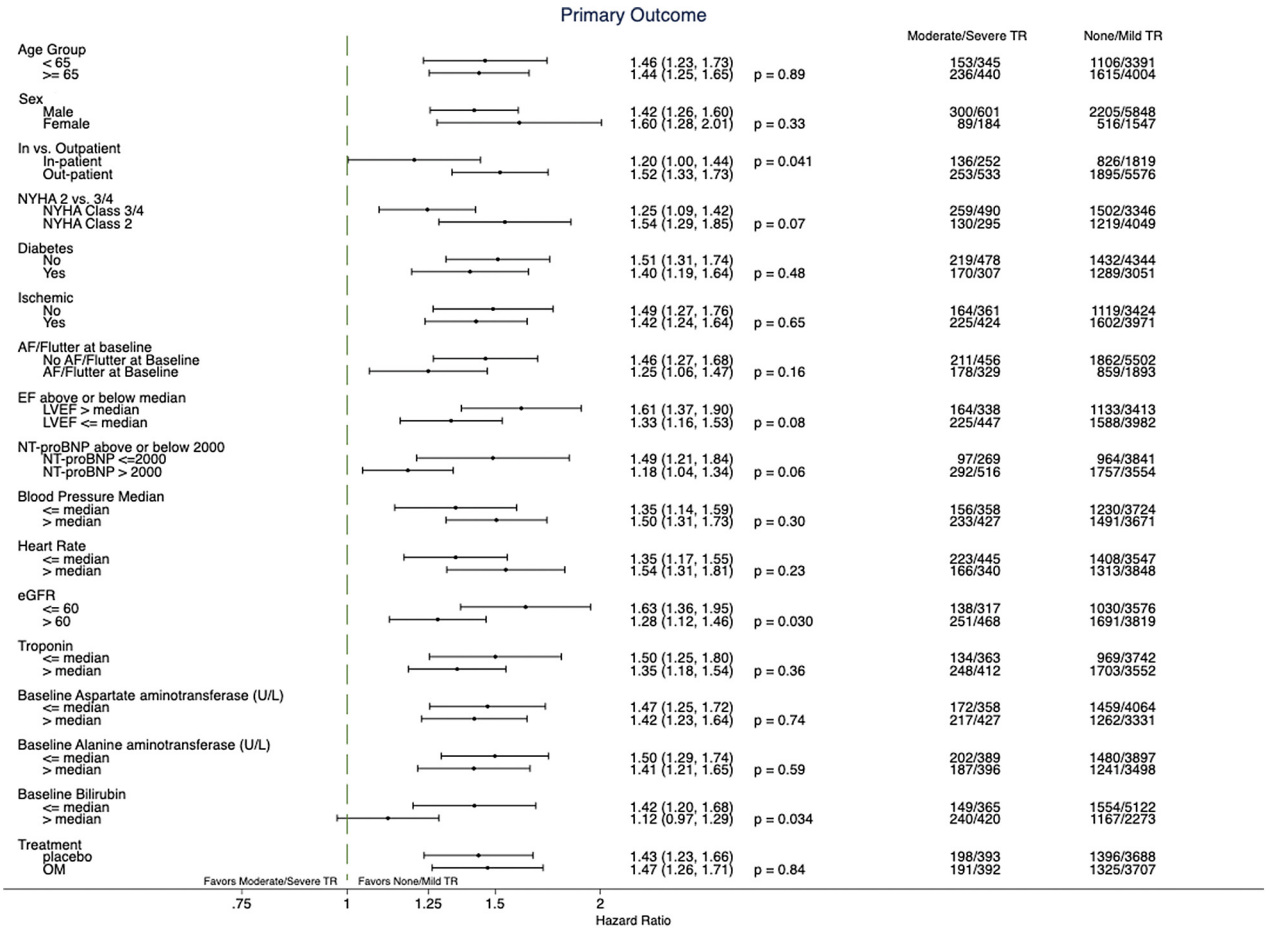


Kaplan-Meier estimate incidence of heart failure (HF) events (A), HF hospitalization (B), cardiovascular (CV) death (C), and all-cause death in patients with no tricuspid regurgitation (TR) vs those with mild TR vs moderate/severe TR (D).

comorbidities, left and right ventricular function, pulmonary hypertension, and atrial fibrillation.[5,17] The lack of a significant independent association between TR and mortality in our population could be caused by the shorter follow-up compared to previous studies as well as the low proportion of patients with moderate/severe TR compared to those with no/mild TR. Notably, a comprehensive adjustment for HF parameters, including biomarkers, was not performed in previous studies. Our findings are in line with the recent results of the TRILUMINATE Pivotal trial (The Trial to Evaluate Cardiovascular Outcomes in Patients Treated with the Tricuspid Valve Repair System Pivotal) showing a lack of survival benefit in patients with severe TR treated with TriClip (Abbott Vascular) compared to medical therapy.[18]

Previous data regarding the association between TR and HF events in patients with chronic HFrEF are very limited. Chorin et al[6] reported the association between TR and both mortality and HF hospitalization in a large real-world population including 33,305 inpatients and outpatients without distinguishing by etiology or LVEF. A roughly 2-fold increased adjusted relative risk of mortality as well as HF hospitalization was observed at a median follow-up of 3.3 years in patients with severe TR compared to those with no TR.[6] Our findings regarding the independent association between TR and HF events in HFrEF patients

FIGURE 3 Association Between TR Severity and Primary Outcome in Different Patient Subgroups

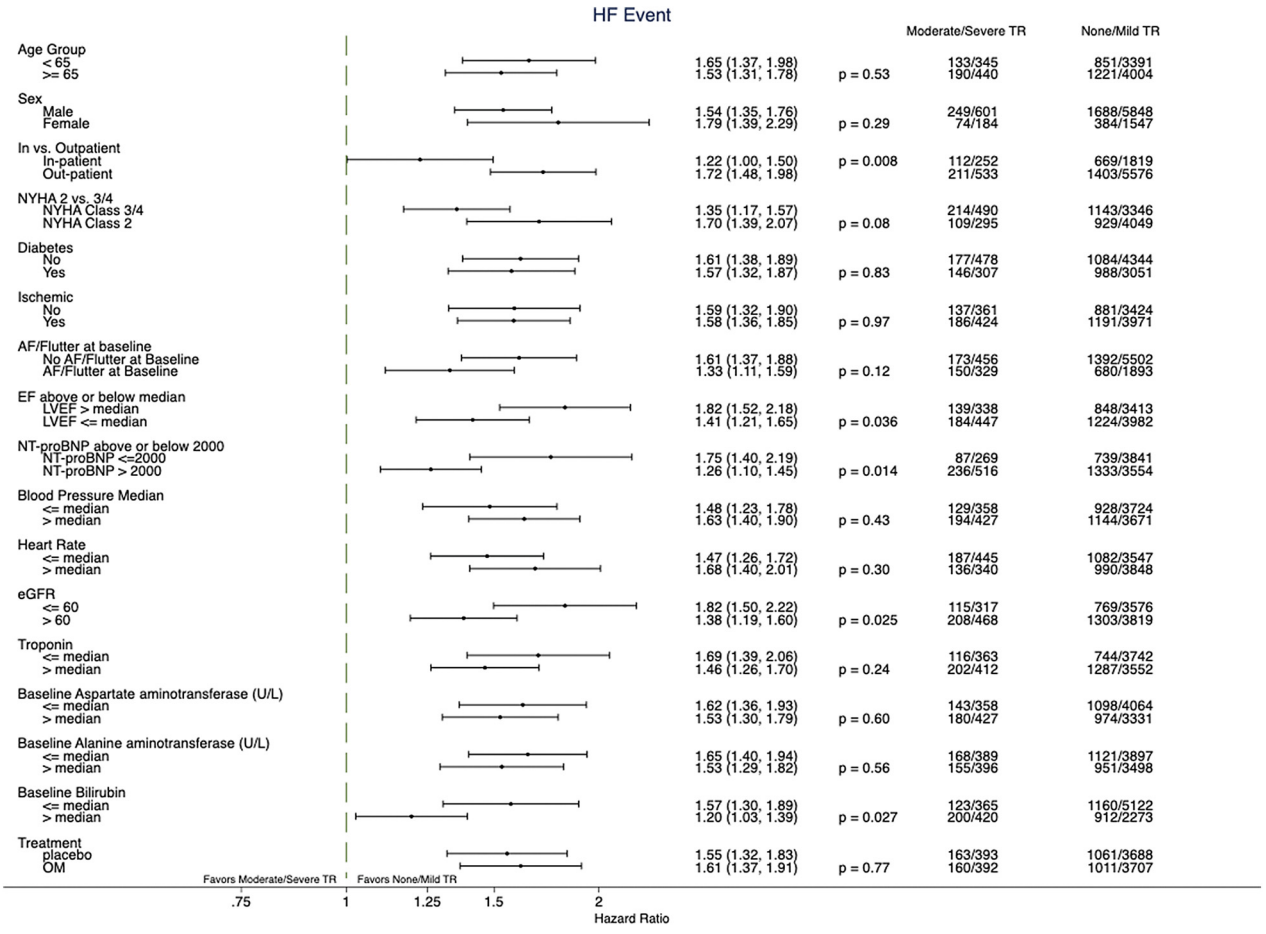


Forest plots reporting HR and 95% CI for the association between moderate/severe TR vs no/mild TR and HF events or CV death in different subgroups. AF = atrial fibrillation; EF = ejection fraction; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; OM = omecamtiv mecarbil; other abbreviations as in Figure 2.

are novel. They highlight the importance of identifying, and possibly treating, moderate/severe TR because it is a condition strongly related to an increased probability of worsening of the HF course regardless of the HF stage. They also indirectly confirm previous data showing that in patients admitted for acute HF, the presence of significant TR was an independent predictor of residual congestion at discharge,[19] which is known to be associated with poor outcomes.[20,21] Of note, TRILUMINATE did not report an advantage of TR correction in terms of HF hospitalization. On the other hand, we observed a strong and independent association between significant TR and HF events. One explanation for this difference is that compared to the TRILUMINATE cohort, the GALACTIC-HF population included patients with a reduced LVEF and a high risk of HF events. Another possibility is that although moderate to severe TR is associated with an increased risk of HF hospitalization, this risk might not be modifiable by transcatheter repair of the tricuspid valve.

TR AND CLINICAL OUTCOMES BY SUBGROUPS. Although the prognostic association of moderate/severe TR with the primary outcome and HF hospitalization and events was consistent in almost all the subgroups analyzed, we observed a more pronounced effect in outpatients as compared to inpatients. At a sensitivity analysis, the association between moderate/severe TR and poorer outcomes was confirmed in outpatients. Moreover, the association between

FIGURE 4 Association Between TR Severity and HF Events in Different Patient Subgroups



Forest plots reporting HR and 95% CI for the association between moderate/severe TR vs no/mild TR and HF events in different subgroups. Abbreviations as in Figures 2 and 3.

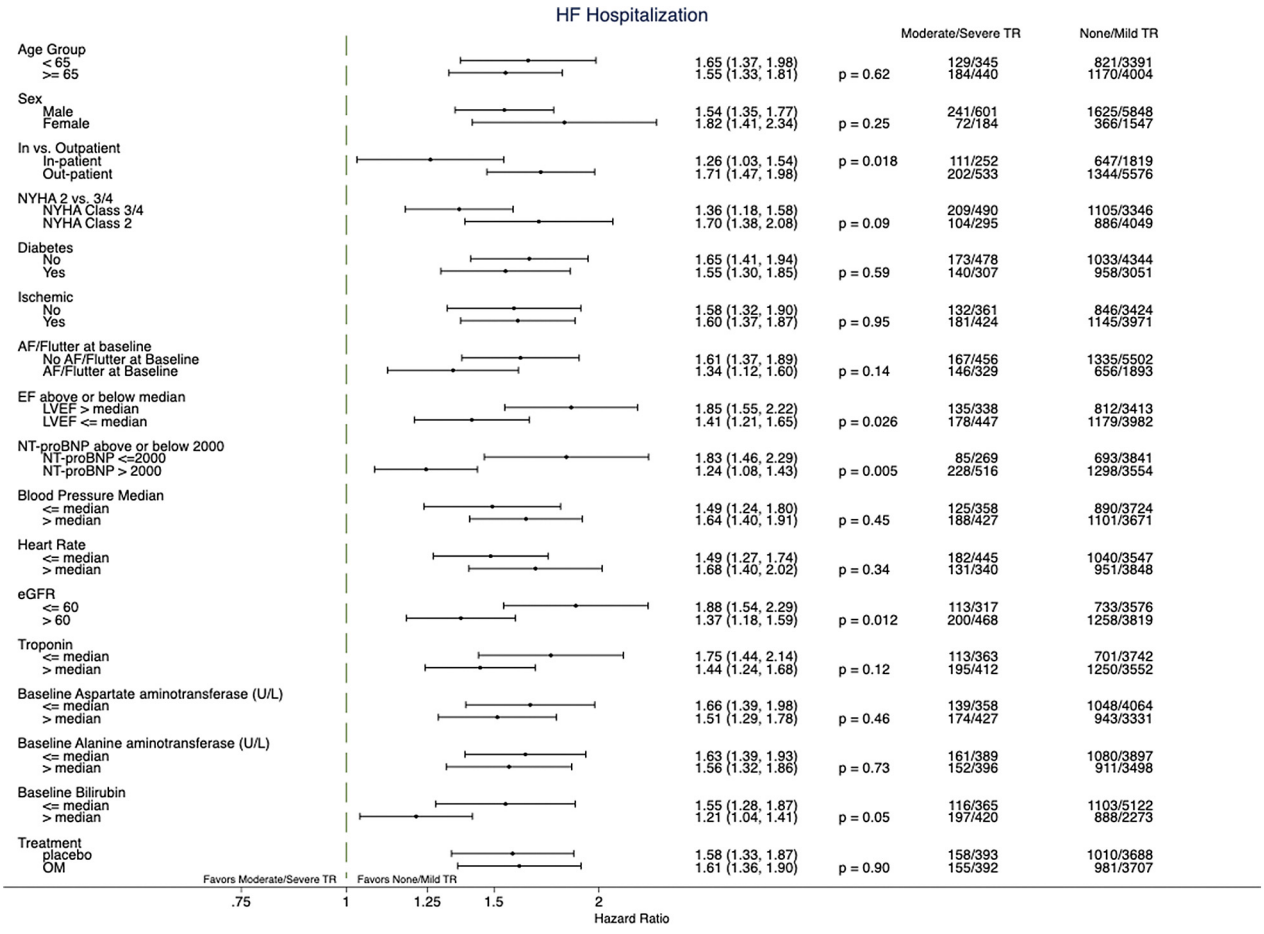
moderate/severe TR and HF hospitalization and events was higher in patients with less advanced HFrEF, namely, a higher LVEF and lower NT-proBNP and bilirubin levels. Therefore, we could speculate that early treatment of TR may have a greater benefit in reducing HF events in these patients.[22] Finally, the association between moderate/severe TR and clinical outcomes was stronger in patients with eGFR ≥ vs <60 mL/min/m^2. However, the results of this stratification could be affected by the exclusion of patients with eGFR <20 mL/min/m^2.

STUDY LIMITATIONS. Several limitations need to be acknowledged. First, the present study is a post hoc analysis of the GALACTIC-HF randomized trial because no subgroup analysis was prespecified according to the reported TR categories. Second, the TR categories were investigator reported, and there was not an echocardiographic core laboratory to assess TR severity. Third, information regarding right ventricular dimension and function and pulmonary hypertension was not collected. Fourth, subgroup analyses may have limited statistical power because of their limited sample size and small number of events. Finally, the patients in GALACTIC-HF were a highly selected population that does not entirely reflect the real-world setting; however, a proper adjudication of clinical events represents a great advantage of this study.

CONCLUSIONS

Among patients with symptomatic HFrEF enrolled in GALACTIC-HF, baseline-reported moderate/severe

FIGURE 5 Association Between TR Severity and HF Hospitalizations in Different Patient Subgroups



Forest plots reporting HR and 95% CI for the association between moderate/severe TR vs no/mild TR and HF hospitalizations in different subgroups. Abbreviations as in Figures 2 and 3.

TR was independently associated with the primary outcome of a worsening HF event or CV death driven by HF events. The beneficial effect of omecamtiv mecarbil on the primary outcome was not modified by TR.

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Dr Adamo has received specker honoraria from Abbott Vascular. Dr Metra has received consulting fees from Abbott Vascular, Actelion, Amgen, AstraZeneca, Bayer, Edwards Therapeutics, Livanova, Servier, Vifor Pharma, and WindTree Therapeutics. Dr Claggett has received consulting fees from Amgen and Myokardia. Dr Diaz has received research grants and/or consulting fees from Amgen, Cytokinetics, and Servier. Dr Felker has received grant funding to his institution from Amgen, Bayer, Cytokinetics, Merck, and Myokardia; has received consulting fees personally from Abbott, American Regent, Amgen, AstraZeneca, Becton Dickinson, Boehringer Ingelheim, Bristol Myers Squibb, Cardionomic, Cytokinetics, Medtronic, Novartis, and Sequana; and has served on the Board of Directors for the Heart Failure Society of America. Dr McMurray has received consulting fees paid to his institution from Alnylam, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardialysis, Cardurion, Dal-Cor, GlaxoSmithKline, Ionis, KBP Biosciences, Merck, Novartis, Pfizer, and Theracos. Dr Solomon has received grants from Celladon, Eidos, Ionis, Lone Star Heart, Mesoblast, National Institutes of Health/National Heart, Lung, and Blood Institute, and Sanofi Pasteur; has received grants and personal fees from Alnylam, Amgen, AstraZeneca, Bayer, Bellerophon, Bristol Myers Squibb, Cytokinetics, Gilead, GlaxoSmithKline, MyoKardia, Novartis, and Theracos; and has received personal fees from Akros, AoBiome, Arena, Cardiac Dimensions, Cardior, Cardurion, Corvia, Daiichi-Sankyo, Dinaqor, Ironwood, Janssen, Merck, Moderna, Quantum Genomics, Roche, Takeda, and Tenaya. Dr Teerlink has received research grants and/or

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with HFrEF, moderate/severe TR is associated with an increased risk of HF events (ie, unplanned visits and hospitalizations), especially in outpatients with less advanced disease (a higher LVEF and lower natriuretic peptides and bilirubin).

TRANSLATIONAL OUTLOOK: These findings suggest that an early correction of TR may prevent HF events in the setting of HFrEF. Prospective randomized controlled trials comparing invasive vs conservative management in patients with moderate/severe TR are needed to support this hypothesis.

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KEY WORDS heart failure, outcomes, tricuspid regurgitation

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