

Impact of Renal and Liver Function on Clinical Outcomes Following Tricuspid Valve Transcatheter Edge-to-Edge Repair

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ABSTRACT

BACKGROUND The TRILUMINATE Pivotal trial is a prospective, randomized, controlled study of patients with severe tricuspid regurgitation (TR). Venous congestion due to TR may lead to end-organ dysfunction and failure. The potential to reverse or stop further deterioration in end-organ function is an important goal of treatment.

OBJECTIVES This study sought to examine changes in end-organ function after tricuspid transcatheter edge-to-edge repair (TEER) and assess the association of baseline end-organ function with heart failure (HF) hospitalizations and mortality.

METHODS Subjects were randomized 1:1 to either the TEER group (TriClip System + medical therapy) or control group (medical therapy alone). Laboratory assessments and TR grading were performed at baseline and at all follow-up visits (discharge, 30 days, 6 months, and 12 months). An independent echocardiography core laboratory assessed TR severity and an independent clinical events committee adjudicated adverse events.

RESULTS A total of 572 subjects were enrolled and randomized (285 TEER, 287 control patients). Patients with moderate-to-severe end-organ impairment (estimated glomerular ejection fraction [eGFR] <45 mL/min/1.73 m² or Model for End-Stage Liver Disease excluding INR [MELD-XI] >15) at baseline had increased incidence of HF hospitalization and death through 12 months, regardless of treatment. There were no statistically significant differences between TEER and control patients in eGFR or MELD-XI at 12 months. In subgroup analyses examining only successful TEER patients (moderate or less TR at discharge) compared with control patients, as well as when censoring patients with normal baseline values, both eGFR (+3.55 ± 1.04 mL/min/1.73 m² vs 0.07 ± 1.10 mL/min/1.73 m²; *P* = 0.022) and MELD-XI (−0.52 ± 0.18 vs 0.34 ± 0.18; *P* = 0.0007) improved.

CONCLUSIONS Baseline end-organ function was associated with HF hospitalization and death in patients with severe TR. At 12 months, eGFR and MELD-XI scores were not statistically significantly different between the overall TEER and control groups. In patients who had successful TEER, statistically significant, yet small, favorable changes occurred for both eGFR and MELD-XI. Further investigation is needed to assess whether these changes in end-organ function after successful TEER are clinically meaningful and reduce HF hospitalization or death. (Clinical Trial to Evaluate Cardiovascular Outcomes In Patients Treated With the Tricuspid Valve Repair System Pivotal [TRILUMINATE Pivotal]; [NCT03904147](https://doi.org/10.1016/j.jacc.2024.08.044)) (JACC. 2024;■:■-■) © 2024 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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**ABBREVIATIONS
AND ACRONYMS****ALT** = alanine transaminase**ANCOVA** = analysis of covariance**AST** = aspartate transaminase**BUN** = blood urea nitrogen**eGFR** = estimated glomerular filtration rate**GGT** = gamma-glutamyl transferase**HF** = heart failure**INR** = international normalized ratio**KCCQ** = Kansas City Cardiomyopathy Questionnaire**MELD-XI** = Model for End-Stage Liver Disease excluding INR**TEER** = transcatheter edge-to-edge repair**TR** = tricuspid regurgitation

Tricuspid regurgitation (TR) is a valvular disorder characterized by the retrograde flow of blood from the right ventricle into the right atrium during systole. At least 3% of the population >65 years old in the United States (~58 million people) have significant TR, resulting in an estimated 1.7 million people.¹⁻⁶ Severe TR decreases forward cardiac output and elevates right-sided systemic venous pressures, with volume overloading that leads to further tricuspid dilatation, exacerbating regurgitation over time. This pathophysiology often results in hepatorenal congestion and dysfunction, leading to peripheral edema and ascites. Severe hepatorenal dysfunction is associated with adverse clinical events, including heart failure (HF) hospitalization and mortality.⁷⁻¹⁰

The TRILUMINATE Pivotal (Clinical Trial to Evaluate Cardiovascular Outcomes In Patients Treated With the Tricuspid Valve

Repair System Pivotal; [NCT03904147](#)) trial is the first randomized study of reducing TR with tricuspid transcatheter edge-to-edge repair (TEER) in symptomatic severe TR patients. Results from the primary analysis population have shown immediate and sustained improvements in health status following TEER with the TriClip System (Abbott).¹¹ Mortality and hospitalization rates were similar between the TEER group (TEER + medical therapy) and the control group (medical therapy alone) at 1 year. Recent publications have noted the low rates of prior HF hospitalizations and only mildly reduced end-organ function at enrollment, raising questions about the timing of therapeutic intervention.¹²

Despite the lack of significant differences in mortality or HF hospitalizations between the TEER and control groups at 1 year in the TRILUMINATE primary analysis cohort, changes in end-organ function following the reduction in TR would suggest a favorable physiologic change with potential longer-term impact. Indeed, results from bRIGHT (An Observational Real-World Study Evaluating Severe Tricuspid Regurgitation Patients Treated with the Abbott TriClip Device), the European postmarket study of TEER, demonstrated that lower baseline serum creatinine was associated with improved

survival; thus possibly making a case for early intervention.¹³ An analysis of outcomes stratified by varying levels of end-organ dysfunction may provide insight into which populations experience certain clinical benefits. Therefore, herein we examined: 1) the association of baseline liver and kidney function with HF hospitalizations and mortality; 2) changes in end-organ function through 1-year follow-up; and 3) the impact of changes in end-organ dysfunction on clinical outcomes following tricuspid TEER in the TRILUMINATE Pivotal population.

METHODS

TRIAL DESIGN. The TRILUMINATE Pivotal is a prospective, multicenter, randomized (1:1), controlled trial to assess the superiority of TriClip in addition to medical therapy (TEER group) compared with medical therapy alone (control group). The trial protocol was designed by the principal investigators (2 authors, P.S. and D.A., who were not employees of the sponsor) in collaboration with the steering committee and sponsor, Abbott Structural Heart. The protocol was approved by the U.S. Food and Drug Administration and by the Institutional Review Boards of the participating centers.

The trial enrolled symptomatic patients with severe TR despite being optimally treated with medical therapy for TR or other cardiac conditions and who were determined by the site's local heart team to be at intermediate or greater estimated risk for mortality with tricuspid valve surgery. An independent echocardiography core lab was used to assess TR severity and an independent clinical events committee was used to determine whether hospitalizations were HF related. Additional details regarding study protocol, patient eligibility, follow-up, and endpoints have been published previously.¹¹ The previous work published data on the primary analysis population of TRILUMINATE Pivotal (first 350 randomized patients), whereas these analyses utilized data on all randomized patients.

FOLLOW-UP VISITS. Following the baseline visit and randomization, patients were required to complete a treatment visit (within 14 days of randomization), discharge visit (TEER group only), and visits at 30 days, 6 months, and 12 months. Patients will continue to undergo follow-up visits at 18 months

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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and annually through 5 years. Follow-up visits for all patients consisted of symptom assessment using the NYHA functional classification, quality-of-life measurement with the Kansas City Cardiomyopathy Questionnaire (KCCQ), and blood sample collection for laboratory assessments.

LABORATORY ASSESSMENTS. Blood draws were required for patients at baseline and all follow-up visits. The sites analyzed the samples following site-specific protocols. The following liver- and kidney-related biomarkers were included: gamma-glutamyl transferase (GGT), blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine transaminase (ALT), total bilirubin, serum sodium, and serum creatinine. The international normalized ratio (INR) test was also assessed. Notably, there were no exclusion criteria associated with the assessments.

Liver and/or renal function was evaluated with 2 metrics. Renal function was evaluated with the estimated glomerular filtration rate (eGFR), which is a measure of how efficient the kidneys are at filtering blood and is calculated using serum creatinine, adjusting for age, sex, and race.¹⁴ Patients were stratified based on baseline eGFR into normal function (eGFR ≥ 60 mL/min/1.73 m²), mild-to-moderate impairment (eGFR ≥ 45 and < 60 mL/min/1.73 m²), and moderate-to-severe impairment (eGFR < 45 mL/min/1.73 m²). The Model for End-Stage Liver Disease excluding INR (MELD-XI) score was used for the assessment of liver (hepatic) and renal function. MELD-XI is calculated using serum creatinine and total bilirubin. MELD-XI was used since INR is affected by oral anticoagulants, which are commonly used in the TRILUMINATE Pivotal population. Patients were stratified based on baseline MELD-XI into normal function (MELD-XI = 9.44, the minimum value possible), mild-to-moderate impairment (MELD-XI between > 9.44 and ≤ 15), and moderate-to-severe impairment (MELD-XI > 15). The thresholds for eGFR and MELD-XI were adapted based on prior literature.¹⁵⁻¹⁸

STATISTICAL ANALYSIS. Results from the randomized cohort are presented in this analysis. Descriptive data are shown as mean \pm SD; categorical data are shown as percent of subjects with available data. Two-sided Student's *t*-tests were used for parametric continuous data, Mann-Whitney *U* tests were used for nonparametric continuous data, and chi-square tests were used for categorical data to assess differences between the TEER and control groups. Change in laboratory biomarker assessments was calculated as the difference between 12-month follow-up and baseline. If patients had missing values at 12-month

	TEER Group (n = 285)	Control Group (n = 287)	Total (N = 572)
Age, y	78.1 \pm 7.9 (285)	78.1 \pm 7.6 (287)	78.1 \pm 7.8 (572)
Female	168 (58.9)	169 (58.9)	337 (58.9)
NYHA functional class III or IV	160 (56.1)	155 (54.0)	315 (55.1)
KCCQ Overall Summary Score	55.6 \pm 22.9 (285)	54.6 \pm 24.0 (286)	55.1 \pm 23.3 (571)
Medical history			
Atrial fibrillation	236 (82.8)	272 (92.7)	502 (87.8)
Hypertension	231 (81.1)	234 (81.5)	465 (81.3)
Dyslipidemia	179 (62.8)	155 (54.0)	334 (58.4)
Prior mitral or aortic intervention	108 (37.9)	99 (34.5)	207 (36.2)
Renal disease	91 (31.9)	100 (34.8)	191 (33.4)
Prior RV lead placement	47 (16.5)	47 (16.4)	94 (16.4)
Chronic obstructive pulmonary disease	37 (13.0)	45 (15.7)	82 (14.3)
Liver disease	20 (7.0)	21 (7.3)	41 (7.2)
Stroke	18 (6.3)	29 (10.1)	47 (8.2)
Transient ischemic attack	16 (5.6)	20 (7.0)	36 (6.3)
Myocardial ischemia	9 (3.2)	15 (5.2)	24 (4.2)
TR severity			
Torrential	136 (48.7)	141 (51.3)	277 (50.1)
Massive	67 (24.0)	51 (18.9)	118 (21.3)
Severe	70 (25.1)	78 (28.4)	148 (26.8)
Moderate	6 (2.2)	4 (1.5)	10 (1.8)

Values are mean \pm SD (n) or n (%).
KCCQ = Kansas City Cardiomyopathy Questionnaire; RV = right ventricular; TEER = transcatheter edge-to-edge repair; TR = tricuspid regurgitation.

follow-up, values were imputed with the last observed measurement (6 months or 30 days). Bowker's test was used to assess TR reduction between baseline, 30 days, and 12 months among patients who had data at all 3 time points. To assess the treatment effect on biomarker change between 12-month follow-up and baseline, an analysis of covariance (ANCOVA) was used, adjusting for baseline biomarker measures as a covariate, and presented as mean \pm SE. ANCOVA was also used for subgroup analyses comparing successful TEER patients with control patients, as well as for subgroup analyses excluding patients with normal baseline values (eGFR ≥ 60 mL/min/1.73 m² or MELD-XI = 9.44). In the analyses presented herein, procedural success is defined as TEER patients whose TR was reduced to moderate or less at discharge.

Annualized HF hospitalization rates were calculated from total HF hospitalization up to 1 year and total patient time in the trial. The 95% CIs and *P* values are reported from Poisson regression. The Kaplan-Meier method was used to estimate the combined incidence rate of HF hospitalization and death at 1 year after index, reported with 95% CIs. Patients were censored at their last known event-free

TABLE 2 Laboratory Measures of the Patients at Baseline and Changes at 12 Months

Laboratory Assessment	Normal Range	Assessment ^a	TEER Group (n = 285)	Control Group (n = 287)	P Value
Serum creatinine, mg/dL	Male: 0.72-1.25 Female: 0.57-1.11	Baseline	1.31 ± 0.51 (274)	1.26 ± 0.49 (269)	0.23
		12 mo	1.29 ± 0.50 (277)	1.29 ± 0.49 (270)	0.98
		Difference	-0.01 ± 0.34 (266)	0.06 ± 0.27 (253)	0.0087
eGFR, mL/min/1.73 m ²	>60	Baseline	55.6 ± 21.1 (274)	57.7 ± 20.8 (269)	0.23
		12 mo	55.6 ± 20.4 (277)	56.1 ± 21.4 (270)	0.79
		Difference	0.21 ± 13.2 (266)	-2.6 ± 13.9 (253)	0.021
BUN, mg/dL	8-25	Baseline	29.7 ± 17.8 (274)	29.2 ± 15.6 (265)	0.71
		12 mo	29.3 ± 17.6 (277)	28.8 ± 15.6 (270)	0.78
		Difference	-0.15 ± 14.4 (266)	0.74 ± 14.1 (249)	0.38
Serum sodium, mmol/L	135-145	Baseline	138.6 ± 3.5 (274)	138.9 ± 3.2 (268)	0.28
		12 mo	138.9 ± 3.5 (277)	138.6 ± 3.4 (270)	0.34
		Difference	0.31 ± 3.5 (266)	-0.29 ± 3.0 (252)	0.039
INR	No atrial fibrillation: 0.8-1.1 Atrial fibrillation: 2.0-3.0	Baseline	1.6 ± 0.7 (249)	1.7 ± 1.1 (248)	0.93
		12 mo	1.7 ± 0.9 (268)	1.7 ± 0.7 (263)	0.23
		Difference	0.02 ± 0.85 (240)	-0.01 ± 1.0 (226)	0.98
Total bilirubin, mg/dL	0.2-1.2	Baseline	0.88 ± 0.60 (272)	0.90 ± 0.59 (266)	0.29
		12 mo	0.84 ± 0.57 (276)	0.88 ± 0.51 (270)	0.13
		Difference	-0.04 ± 0.39 (264)	-0.01 ± 0.44 (250)	0.29
ALT, U/L	8-45	Baseline	21.6 ± 15.9 (274)	20.8 ± 10.6 (269)	0.79
		12 mo	21.0 ± 14.0 (277)	19.9 ± 9.6 (269)	0.56
		Difference	-0.82 ± 16.48 (266)	-0.97 ± 9.7 (252)	0.35
AST, IU/L	2-40	Baseline	27.7 ± 11.6 (274)	26.3 ± 9.5 (267)	0.10
		12 mo	27.3 ± 10.2 (277)	26.5 ± 11.3 (270)	0.14
		Difference	-0.46 ± 11.1 (266)	-0.08 ± 8.1 (251)	0.99
Gamma GT, U/L	Male: 12-64 Female: 9-36	Baseline	86.9 ± 98.3 (197)	79.0 ± 75.3 (193)	0.96
		12 mo	74.2 ± 86.8 (229)	80.8 ± 99.8 (223)	0.076
		Difference	-10.6 ± 68.1 (191)	-1.93 ± 50.8 (179)	0.039
MELD-XI	9.44	Baseline	13.0 ± 3.6 (271)	12.6 ± 3.6 (266)	0.17
		12 mo	12.8 ± 3.4 (276)	12.9 ± 3.5 (270)	0.62
		Difference	-0.16 ± 2.3 (263)	0.46 ± 2.1 (250)	0.0012

Values are mean ± SD (n) unless otherwise indicated. The P values indicate significance by 2-sample t-tests for normally distributed data and by Mann-Whitney U test for non-normally distributed data. **Bold** indicates statistical significance. ^aCalculated as the change from baseline to 12 months (last observation carried forward if missing 12-month measurement).

ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; gamma GT = gamma-glutamyl transferase; INR = international normalized ratio; MELD-XI = Model for End-Stage Liver Disease excluding INR; TEER = transcatheter edge-to-edge repair.

date in the trial. The index date for patients in the control group was the baseline visit, whereas the index date for patients in the TEER group was the discharge date. Log-rank tests were used to assess differences between groups, reported with P values. Statistical significance was defined as $P < 0.05$. All analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

TRIAL POPULATION. Between August 2019 and July 2022, 572 subjects were enrolled and randomized (285 TEER, 287 control patients) from 68 centers in the United States, Europe, and Canada. Visit accountability is provided in [Supplemental Figure 1](#). Baseline characteristics are shown in [Table 1](#). The mean age was 78.1 ± 7.8 years, and 58.9% were female. Common comorbidities included atrial fibrillation (87.8%),

hypertension (81.3%), and renal disease (33.4%). Nearly one-third (36.2%) of patients had prior mitral or aortic intervention, and 16.4% previously underwent a right ventricular lead placement. Only 7.2% of patients had history of prior liver disease.

TR severity was graded on a 5-grade scale.¹⁹ At baseline, TR severity was categorized as massive or torrential in 71.4% of patients. More than one-half of the cohort (55.1%) were classified as NYHA functional class III or IV, and the average KCCQ Overall Summary score was 55.1 ± 23.3 , which is on the lower end of the “Fair to Good” range (50-74).²⁰

CHANGE IN TR AT 30 DAYS. Patients with TEER had immediate and sustained reductions in TR ([Supplemental Figure 2](#)), with 92.4% being categorized as moderate or less TR at 30 days ($P < 0.0001$) with no statistically significant differences between 30 days and 12 months ($P = 0.41$). Patients in the

control group did not experience meaningful changes in TR severity ($P = 0.78$ at 30 days, $P = 0.11$ at 12 months).

LABORATORY ASSESSMENTS. Table 2 shows average laboratory values at baseline and 12 months (unpaired), as well as the respective normal ranges for each laboratory assessment. Overall, baseline values were not statistically different between the TEER and control groups, including serum creatinine (1.31 ± 0.51 mg/dL vs 1.26 ± 0.49 mg/dL; $P = 0.23$), BUN (29.7 ± 17.8 mg/dL vs 29.2 ± 15.6 mg/dL; $P = 0.71$), serum sodium (138.6 ± 3.5 mmol/L vs 138.9 ± 3.2 mmol/L; $P = 0.28$), INR (1.6 ± 0.7 vs 1.7 ± 1.1 ; $P = 0.93$) total bilirubin (0.88 ± 0.60 mg/dL vs 0.90 ± 0.59 mg/dL; $P = 0.29$), ALT (21.6 ± 15.9 U/L vs 20.8 ± 10.6 U/L; $P = 0.79$), AST (27.7 ± 11.6 IU/L vs 26.3 ± 9.5 IU/L; $P = 0.10$), and GGT (86.9 ± 98.3 U/L vs 79.0 ± 75.3 U/L; $P = 0.96$). Overall, 12-month values were not statistically different between the TEER and control groups, including serum creatinine (1.29 ± 0.50 mg/dL vs 1.29 ± 0.49 mg/dL; $P = 0.98$), BUN (29.3 ± 17.6 mg/dL vs 28.8 ± 15.6 mg/dL; $P = 0.78$), serum sodium (138.9 ± 3.5 mmol/L vs 138.6 ± 3.4 mmol/L; $P = 0.34$), INR (1.7 ± 0.9 vs 1.7 ± 0.7 ; $P = 0.23$) total bilirubin (0.84 ± 0.57 mg/dL vs 0.88 ± 0.51 mg/dL; $P = 0.13$), ALT (21.0 ± 14.0 U/L vs 19.9 ± 9.6 U/L; $P = 0.56$), AST (27.3 ± 10.2 IU/L vs 26.5 ± 11.3 IU/L; $P = 0.14$), and GGT (74.2 ± 86.8 U/L vs 80.8 ± 99.8 U/L; $P = 0.076$).

Table 2 also shows the changes in laboratory biomarker assessments through 12 months, for patients with both baseline and 12-month values. On average, changes were small in both groups, with high variability across subjects. However, statistically significant changes were observed in serum creatinine (-0.01 ± 0.34 mg/dL for TEER vs 0.06 ± 0.27 mg/dL for control patients; $P = 0.0087$), serum sodium (0.31 ± 3.54 mmol/L for TEER vs -0.29 ± 3.0 mmol/L for control patients; $P = 0.039$), and GGT (-10.6 ± 68.1 U/L for TEER vs -1.93 ± 50.8 U/L for control patients; $P = 0.039$). Paired baseline and 12-month values for these patients were also assessed (Supplemental Table 1), with no significant differences observed between TEER and control patients.

To further examine potential changes in end-organ function, eGFR and MELD-XI scores were calculated and assessed. On average, baseline eGFR was 56.7 ± 20.9 mL/min/1.73 m², and MELD-XI score was 12.8 ± 3.6 (Table 3). Patients were divided into categories based on baseline values. Figure 1A provides alluvial diagrams that illustrate the categorical changes in patients' renal function, as assessed by eGFR, between baseline and 12 months. The majority of

TABLE 3 ANCOVA for the Change in End-Organ Function at 12 Months, Adjusting for Baseline

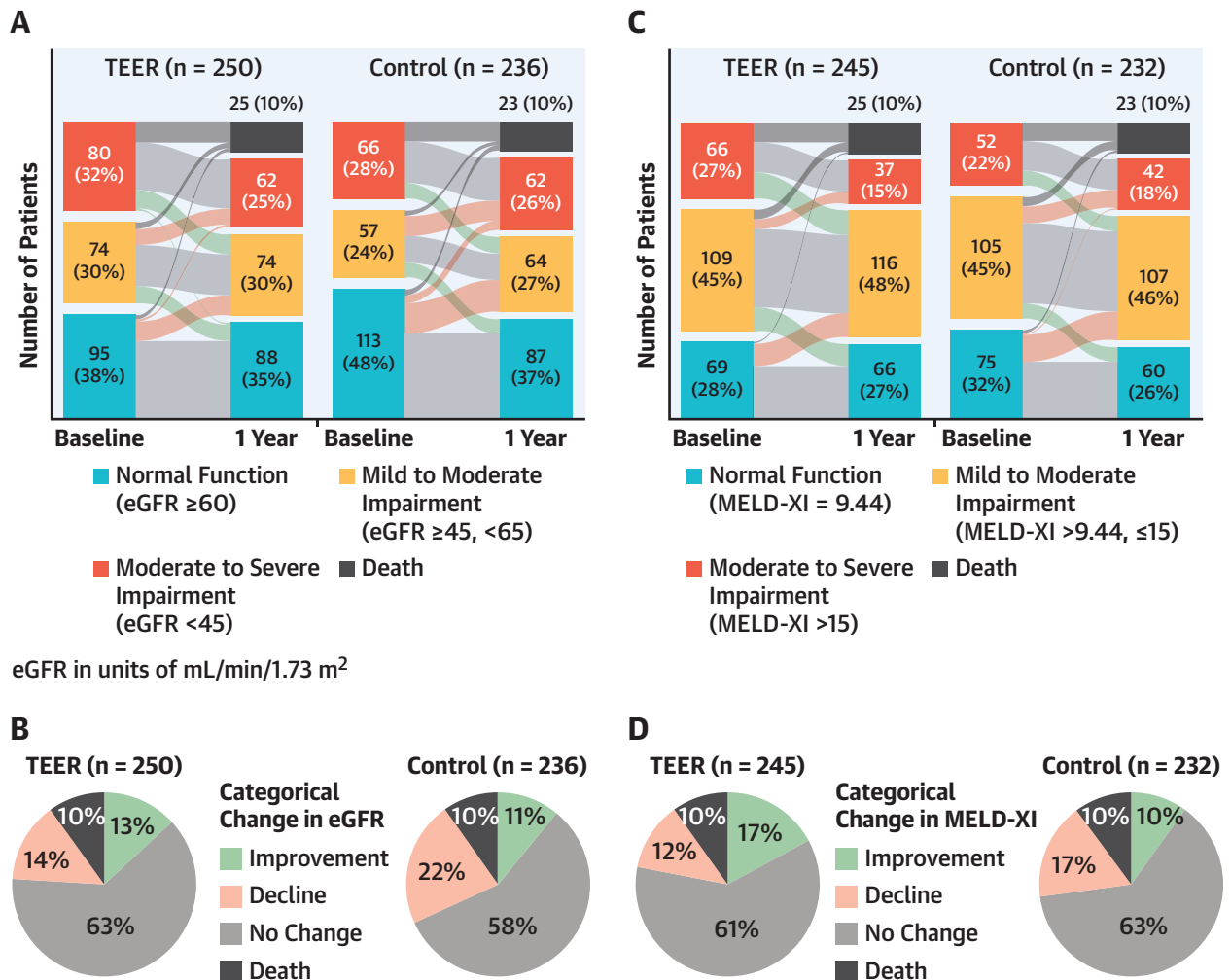
ANCOVA Results	TEER Group	Control Group	P Value
All patients			
eGFR, mL/min/1.73 m ²	-0.10 ± 0.79 (266)	-2.22 ± 0.82 (253)	0.063
MELD-XI Score	-0.11 ± 0.13 (263)	$+0.41 \pm 0.13$ (250)	0.0043
Only successful TEER patients ^a			
eGFR, mL/min/1.73 m ²	$+0.30 \pm 0.85$ (239)	-2.27 ± 0.82 (253)	0.030
MELD-XI Score	-0.19 ± 0.13 (236)	$+0.42 \pm 0.13$ (250)	0.0013
Only successful TEER patients and censoring patients with normal baseline values ^{a,b}			
eGFR, mL/min/1.73 m ²	$+3.55 \pm 1.04$ (149)	0.07 ± 1.10 (133)	0.022
MELD-XI Score	-0.52 ± 0.18 (170)	0.34 ± 0.18 (169)	0.0007

Values are mean \pm SD (n) and least square mean \pm SE (n). For baseline, P values indicate significance by 2-sample t-tests. For 12-month change, the P value indicates significance by analysis of covariance (ANCOVA). **Bold** indicates statistical significance. ^aIncludes only TriClip patients in whom TR was reduced to moderate or less at discharge. ^bCensoring patients with normal baseline values (eGFR ≥ 60 mL/min/1.73 m² and MELD-XI = 9.44). Abbreviations as in Tables 1 and 2.

subjects who died before 12-month follow-up had moderate-to-severe renal impairment at baseline (average eGFR of 41.8 ± 20.1 mL/min/1.73 m²). Figure 1B shows the percentage of subjects that experienced categorical improvement, decline, or no change, as well as those who died before 12-month follow-up. End-organ function, as assessed by the MELD-XI score, is illustrated in Figures 1C and 1D. Again, the majority of patients who died before 12-month follow-up had moderate-to-severe impairment (average MELD-XI score of 16.3 ± 4.6). Overall, categorical changes were similar between groups for eGFR and MELD-XI score, but there was variation based on patients' baseline function.

The ANCOVA model (Table 3), adjusting for baseline eGFR, showed no significant difference in eGFR change at 12 months between TEER and control patients (-0.10 ± 0.79 mL/min/1.73 m² vs -2.22 ± 0.82 mL/min/1.73 m²; $P = 0.063$). However, when examining only TEER patients with procedural success, the ANCOVA model (Table 3) showed a statistically significant difference in eGFR change at 12 months between TEER and control patients (-0.30 ± 0.85 mL/min/1.73 m² vs -2.27 ± 0.82 mL/min/1.73 m²; $P = 0.030$). This analysis was repeated, censoring all patients with normal baseline values (eGFR ≥ 60 mL/min/1.73 m²), and continued to demonstrate statistically significant differences in the change of eGFR at 12 months between TEER and control patients ($+3.55 \pm 1.04$ mL/min/1.73 m² vs $+0.07 \pm 1.10$ mL/min/1.73 m²; $P = 0.022$).

The ANCOVA model also showed statistically significant differences in MELD-XI score change at 12 months between TEER and control patients

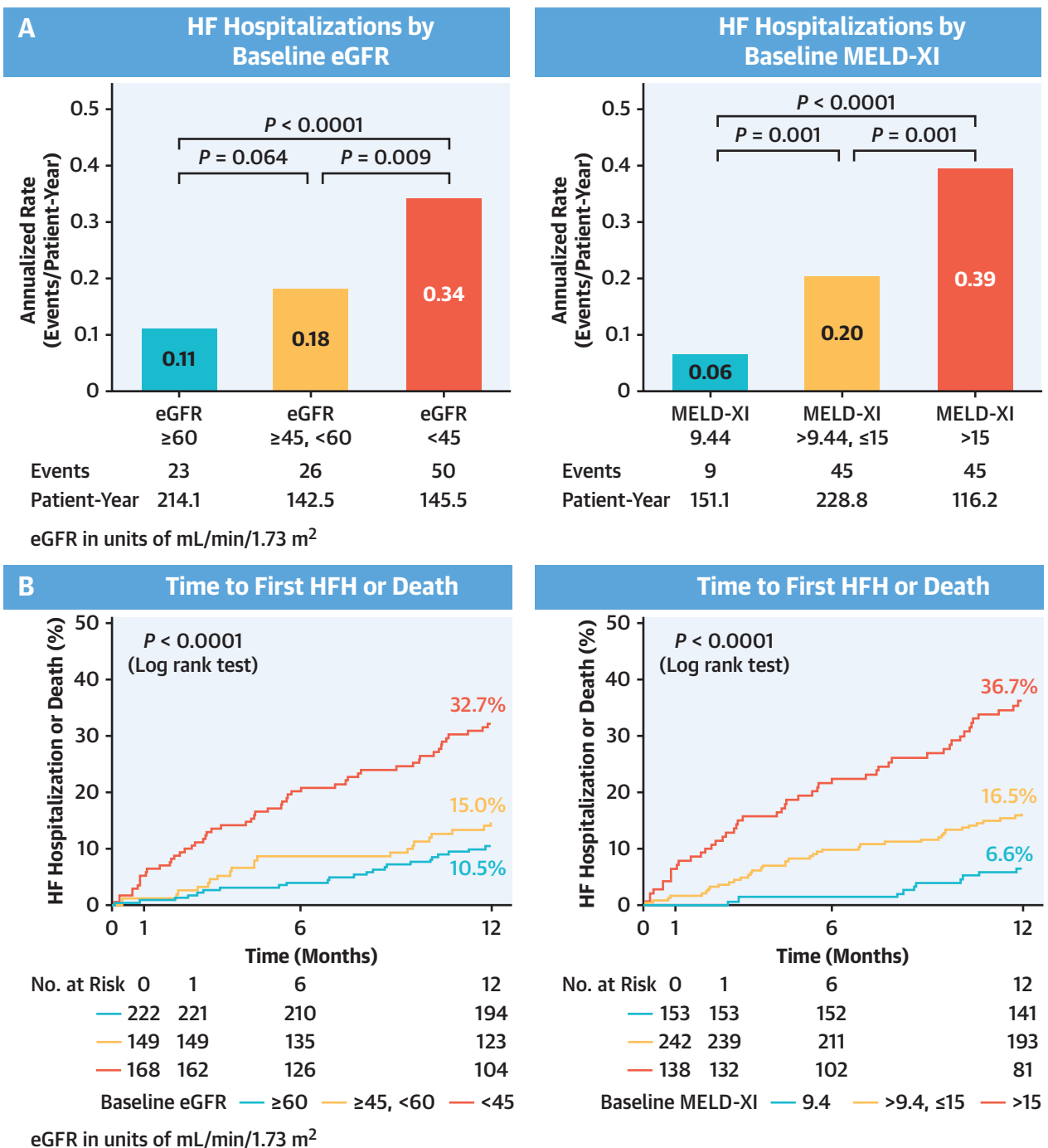
FIGURE 1 Categorical Change in End-Organ Function, Assessed by eGFR and MELD-XI

(A) Alluvial diagrams demonstrating the categorical changes in patients' end-organ status, as assessed by estimated glomerular filtration rate (eGFR), between baseline and 1 year. (B) The proportion of patients who experienced death, no categorical change, categorical improvement, or categorical decline. (C) Alluvial plots demonstrating the categorical changes in patients' end-organ status, as assessed by Model for End-Stage Liver Disease excluding INR (MELD-XI), between baseline and 1 year. (D) The proportion of patients who experienced death, no categorical change, categorical improvement, or categorical decline. TEER = transcatheter edge-to-edge repair.

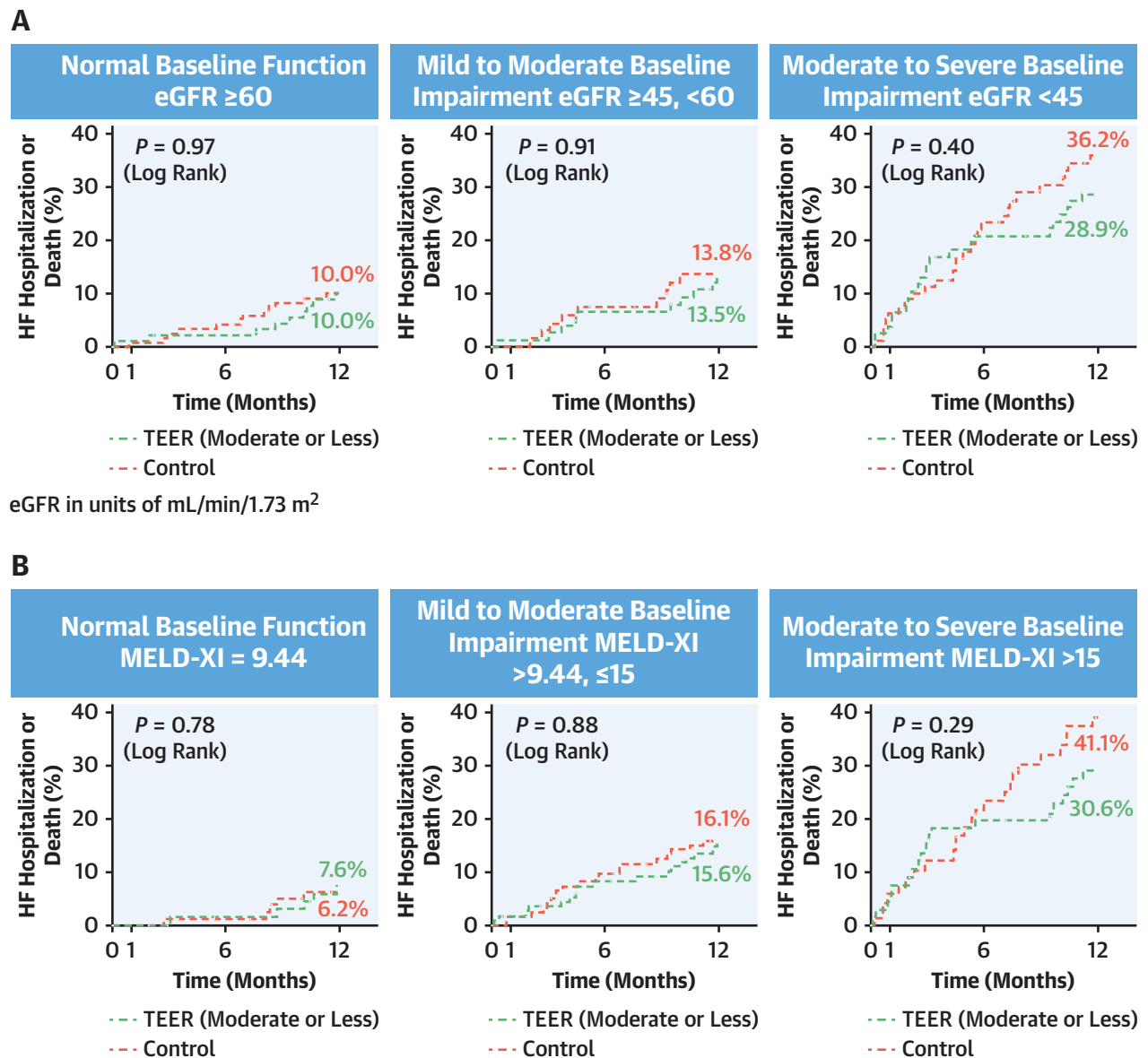
(-0.11 ± 0.13 vs $+0.41 \pm 0.13$; $P = 0.0043$) (Table 3). When examining only TEER patients with procedural success, the ANCOVA model continued to show statistically significant differences in MELD-XI score change at 12 months between TEER and control patients (-0.19 ± 0.13 vs $+0.42 \pm 0.13$; $P = 0.0013$). This analysis was repeated, censoring all patients with normal baseline values (MELD-XI = 9.44); this again demonstrated statistically significant differences in MELD-XI score change at 12 months between TEER and control patients (-0.52 ± 0.18 vs $+0.34 \pm 0.18$; $P = 0.0007$).

IMPACT OF END-ORGAN FUNCTION ON CLINICAL OUTCOMES. A statistically significant difference in clinical outcomes was observed when stratifying patients by baseline end-organ function (regardless of the treatment received). Patients with normal eGFR at baseline had significantly lower rates of annualized HF hospitalizations compared with patients with moderate-to-severe renal impairment (0.11 vs 0.34 events/patient-year; $P < 0.0001$) (Figure 2A). Similarly, patients with normal MELD-XI at baseline had significantly lower rates of annualized HF hospitalizations compared with patients with

FIGURE 2 Impact of Baseline End-Organ Function on HF Hospitalization and Death Through 12 Months (TEER and Control Groups Combined)



(A) Patients with moderate-to-severe end-organ impairment (red) have higher annualized heart failure (HF) hospitalization rates compared with patients with normal end-organ function at baseline. *P* values indicate significance by Poisson regression. (B) Baseline end-organ function impacts the composite of HF hospitalization and mortality. Moderate-to-severe end-organ impairment result in mortality/heart failure hospitalization (HFH) rates 2 times higher than rates in patients with mild-to-moderate or less impairment. *P* values indicate significance by the log-rank test. Abbreviations as in Figure 1.

FIGURE 3 Impact of Baseline Kidney and Liver Function on HF Hospitalization and Mortality Between Treatment Groups

Baseline eGFR (A) and MELD-XI (B) impact HF hospitalization and mortality, regardless of treatment. Although not statistically significant, more pronounced differences between treatment groups are observed in patients with moderate-to-severe end-organ impairment at baseline. *P* values indicate significance by the log-rank test. Abbreviations as in [Figures 1 and 2](#).

moderate-to-severe impairment (0.06 vs 0.39 events/patient-year; $P < 0.0001$). The same differences are also observed when analyzing the rate of HF hospitalization or death ([Figure 2B](#)), regardless of treatment received.

[Figure 3](#) examines the effect of baseline end-organ function and treatment on HF hospitalization and death, specifically in TEER patients whose TR was reduced to moderate or less at discharge. TEER and

control patients with normal baseline eGFR had similar rates of HF hospitalization or death through 1 year (10.0% vs 10.0%; $P = 0.97$), as did patients with mild-to-moderate impairment (13.5% vs 13.8%; $P = 0.91$). However, TEER patients with moderate to severe impairment at baseline had numerically lower rates compared to control patients (28.9% vs 36.2%; $P = 0.40$), though not statistically different. Similar findings are seen when investigating baseline

function by MELD-XI score, where no differences in the rates of HF hospitalization or death are observed in patients with normal baseline function (7.6% for TEER, 6.2% for control patients; $P = 0.78$) or patients with mild-to-moderate baseline impairment (15.6% for TEER, 16.1% for control patients; $P = 0.88$). However, TEER patients with moderate-to-severe baseline impairment had numerically lower rates of HF hospitalization or death compared with control patients (30.6% vs 41.1%; $P = 0.29$), though not statistically different.

The impact of treatment effect on annualized HF rates by baseline end-organ function is shown in [Supplemental Figure 3](#). Overall, differences in outcomes between TEER and control patients were not statistically significant; however, the rate of annualized HF hospitalizations was numerically lower in the TEER group compared with the control group (0.14 vs 0.22 events/patient-year; $P = 0.25$) in patients with mild-to-moderate renal impairment, assessed by eGFR. Similar results were seen in patients with mild-to-moderate impairment according to MELD-XI, with a numerically lower rate of annualized HF hospitalizations in the TEER group compared with the control group (0.15 vs 0.23 events/patient-year; $P = 0.19$). Smaller differences were seen between TEER and control patients for both moderate-to-severe renal impairment (0.34 vs 0.39 events/patient-year; $P = 0.61$) and moderate-to-severe impairment (0.38 vs 0.43 events/patient-year; $P = 0.69$).

Regardless of baseline end-organ function, patients in the TEER group experienced statistically significant improvements in NYHA functional class and KCCQ score compared with patients in the control group ([Supplemental Table 2](#)) except in patients with moderate-to-severe impairment, as assessed by MELD-XI. However, there remained a trend for greater KCCQ change for TEER compared to control ($P = 0.069$).

DISCUSSION

We examined the association of TR and end-organ function in 572 subjects randomized to the TEER or control group in the TRILUMINATE trial. Our principal findings are as follows: 1) baseline renal and liver function are associated with the risk of HF hospitalization or death through 12 months, regardless of treatment received; and 2) eGFR did not change in the TEER group, however, a statistically significant, yet clinically small, change in MELD-XI score was observed favoring TEER. Our findings on improved eGFR and MELD-XI in subgroup analysis of procedural success patients is hypothesis-generating;

further study is needed to validate this observation and investigate whether changes of this magnitude carry clinical significance.

Karam et al²¹ showed that TR reduction, with off-label use of MitraClip, was associated with improvement of liver function primarily in patients with liver impairment at baseline, whereas renal function remained stable. Our findings on stabilization of end-organ function with TEER in the TRILUMINATE Pivotal population are in keeping with their observations. Furthermore, when censoring patients with normal baseline function, statistically significant improvements in end-organ function were observed in TEER patients as compared with control patients ([Table 3](#)). The primary driver of the MELD-XI observation were favorable changes in serum creatinine because changes in bilirubin were negligible between the TEER and control groups; however, the latter may be attributed to baseline values being within normal range, which impacts the propensity for improvement. Changes in GGT, a hepatic function variable not included in MELD-IX, favored TEER, whereas other liver enzymes (AST, ALT, and total bilirubin) showed no statistically significant differences.

The fact that some patients experienced end-organ disease progression irrespective of TR resolution could be due to other factors, including the degree of right ventricular dysfunction, which has been shown to impact renal and liver function,^{7,9,10} and the presence of atrial fibrillation, which contributes to left ventricular dysfunction, leading to decreased cardiac output and increased venous congestion.²² Therefore, although treating TR may be beneficial to reduce venous congestion, other factors will also influence liver and/or renal disease progression.

Our data, obtained in a large randomized clinical trial, on the association of baseline end-organ function and clinical outcomes align with previous observational studies that demonstrated that severe kidney or liver impairment leads to increased rates of HF hospitalization and death.^{9,23,24} Despite this strong association, however, we are unable to conclusively demonstrate that stabilization of end-organ function will lead to reduced HF hospitalization. However, patients treated with TEER who had moderate-to-severe end-organ dysfunction at baseline did have numerically lower rates of HF hospitalization and death compared with patients in the control group, although not statistically different. The separation of the Kaplan-Meier curves at 12 months ([Figure 3](#)) may allow to speculate that the treatment of TR in a larger cohort, possibly with longer follow-up time, may influence mortality and HF hospitalization. Of note, there were no inclusion/

exclusion criteria related to baseline end-organ function, and therefore, nearly two-thirds of patients had no history of renal or liver disease, and eGFR and MELD-XI were normal at baseline in 42.8% and 30.1% of patients, respectively. It is important to note that the TRILUMINATE Pivotal trial was not specifically designed to assess the impact of renal and liver function, and therefore, these post hoc analyses are not powered to detect statistical differences in these specific subgroups. Future studies may look to target populations with moderate-to-severe end-organ dysfunction or conduct longer follow-up to find larger, significant differences in mortality or HF hospitalization following treatment of TR.

Regardless of end-organ function at baseline, patients experienced statistically significant improvements in health status, assessed by KCCQ score and NYHA functional class. Therefore, although tricuspid TEER does not appear to reduce HF hospitalization or death through 12 months in patients with normal or impaired end-organ function, symptom relief and improvements in health status are still achieved.

STUDY LIMITATIONS. This analysis was post hoc and thereby possibly subjected to selection bias. Laboratory assessments were performed by each site, and therefore, were not standardized using uniform protocols or assays. No adjustments were made for multiple comparisons, so all the *P* values are nominal. The COVID-19 pandemic occurred during enrollment and follow-up of TRILUMINATE Pivotal, which may have impacted study results. The relatively early disease state of the TRILUMINATE Pivotal population, in combination with the current follow-up limited to 12 months, may have prevented a more conclusive assessment of the effect of TEER on HF hospitalization and mortality. Future work will include observation of long-term data.

CONCLUSIONS

In the largest prospective randomized clinical trial to date examining the effect of percutaneous treatment of severe TR, baseline renal and liver function were associated with HF hospitalization and death in patients with severe TR. At 12 months, eGFR and MELD-XI scores were not statistically significantly different between the overall TEER and control groups. In subgroup analysis of patients in whom TR was successfully reduced, changes in both eGFR and MELD-IX were statistically significantly different between TEER and control patients. Further investigation is

needed to assess whether the observed favorable changes in end-organ function after successful TEER are clinically meaningful and reduce HF hospitalization or death.

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