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NEW RESEARCH PAPER

Bicaval TricValve Implantation in Patients With Severe Symptomatic Tricuspid Regurgitation

One-Year Follow-Up Outcomes

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ABSTRACT

BACKGROUND Several orthotopic transcatheter strategies have been developed to treat severe tricuspid regurgitation (TR); however, many patients are deemed unsuitable. Caval valve implantation with the TricValve system addresses this unmet need.

OBJECTIVES The study sought to determine the impact of TricValve on systemic congestion and quality of life (QOL) at 1 year.

METHODS The TRICUS (Safety and Efficacy of the TricValve® Transcatheter Bicaval Valves System in the Superior and Inferior Vena Cava in Patients With Severe Tricuspid Regurgitation) and TRICUS EURO studies were prospective, non-blinded, nonrandomized, single-arm trials representing the early-in-man experience of the TricValve system in NYHA functional class III or IV severe TR patients, optimally medicated and ineligible for open heart surgery, with significant caval backflow. The primary endpoint was QOL metrics and functional status. The 1-year results of the combined cohort are described here.

RESULTS Forty-four patients were included. Mean age was 76.2 ± 7.5 years, 81.0% were women, and the TRISCORE (risk score model for isolated tricuspid valve surgery) was 5.3 ± 1.3. Clinical improvement at 1 year was achieved in 42 (95.5%) patients, measured by (at least 1 of) an increase in ≥15 points from baseline in 12-item Kansas City Cardiomyopathy Questionnaire score, improvement to NYHA functional class to I or II, or an increase ≥40 m in the 6-minute walk test. There were 3 (6.8%) deaths at 1-year follow-up (1 cardiovascular), and the heart failure rehospitalization rate was 29.5%. Stent fracture, conduction system disturbances, or clinically significant leaflet thrombosis were not detected. Abolished hepatic vein backflow was achieved and persisted in 63.8% of the patients, contributing towards a reduction in congestive symptoms, N-terminal pro-B-type natriuretic peptide levels ($P = 0.032$), and diuretic treatment.

CONCLUSIONS Caval valve implantation with the TricValve system associated with meaningful 1-year clinical improvements in terms of QOL along with relatively low mortality rates. (TRICUS Study - Safety and Efficacy of the TricValve® Device; NCT03723239). (J Am Coll Cardiol Intv 2023;■:■–■) © 2023 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

6MWT = 6-minute walking test

CAVI = caval valve implantation

CT = computed tomography

IVC = inferior vena cava

KCCQ-12 = 12-item Kansas City Cardiomyopathy Questionnaire

QOL = quality of life

SVC = superior vena cava

TAPSE = tricuspid annular plane systolic excursion

TEER = transcatheter edge-to-edge repair

TR = tricuspid regurgitation

TTVR = transcatheter tricuspid valve replacement

Severe tricuspid regurgitation (TR) is a prevalent clinical entity that has traditionally been treated with diuretic therapy alone to improve right heart failure symptoms.[1-4] A surgical approach to treating severe TR is typically undertaken at the time of concomitant left-sided heart pathology; the severity of TR and coexisting pathology invariably determines surgical risk and clinical outcomes.[4-7] Given the poor natural history of untreated severe TR, several percutaneous strategies have been developed: transcatheter edge-to-edge repair (TEER), percutaneous annuloplasty, or orthotopic transcatheter tricuspid valve replacement (TTVR).[8] However, for a variety of anatomical, functional, and imaging reasons, a relevant proportion of patients is not perfectly suitable for current percutaneous therapies that directly treat the native valve, such as TEER or TTVR.[9-11] Heterotopic caval valve implantation (CAVI) could have a role in reducing congestive symptoms associated with severe TR.[12] The relative simplicity of the procedure contrasts somewhat with the physiologic unknowns of its mechanistic effects and longer-term clinical outcomes.

The TricValve system (Products & Features) is the first CE mark-approved CAVI device consisting of 2 dedicated self-expanding nitinol stents with bovine pericardial leaflets implanted in the inferior vena cava (IVC) and superior vena cava (SVC) to abolish the backflow responsible for systemic venous congestion.[12] Thirty-day safety and 6-month efficacy in terms of right heart remodeling have already been demonstrated.[12,13] We report the prospective clinical results at 1-year follow-up of the patients enrolled in the early feasibility trial (TRICUS [Safety and Efficacy of the TricValve Transcatheter Bicaval Valves System in the Superior and Inferior Vena Cava in Patients With Severe Tricuspid Regurgitation]) and the CE mark study (TRICUS EURO).

METHODS

TRIAL DESIGN AND STUDY POPULATION. The TRICUS study (NCT03723239) was an early feasibility/first-in-human study, including 9 patients from Lithuania. The TRICUS EURO study (NCT04141137) was a CE mark trial testing the safety and efficacy of this CAVI system in patients with severe symptomatic TR with high surgical risk, enrolling patients from 12 institutions in Spain and Austria. Both studies were prospective, nonblinded, nonrandomized, single-arm trials enrolling patients with symptomatic severe TR (grade ≥3 in a 5-grade classification) despite optimal medical treatment leading to NYHA functional class III or IV, ineligible for open heart surgery, with significant backflow in the IVC and/or SVC. Even though most centers consider CAVI as an alternative for patients not suitable for other percutaneous procedures, dismissal of other therapies such as edge-to-edge repair was not required per protocol, and the decision was left to the heart team; echocardiographic parameters of the included patients suggest that they were poor candidates for TEER and, indeed, out of the 47 patients non included in the any of the trials after screening, none of them received an alternative therapy despite its availability in all participating institutions. All patients had to have a left ventricular ejection fraction ≥40% and to be able to walk ≥60 m during the 6-minute walking test (6MWT). All patients were evaluated by an independent committee that determined the clinical and anatomical suitability for CAVI. The main reasons for exclusion were severe right ventricular dysfunction (tricuspid annular plane systolic excursion [TAPSE] ≤13 mm), a systolic pulmonary artery pressure >65 mm Hg, or a significant renal disfunction defined as serum creatinine >3 mg/dL or in need of any form of dialysis

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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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4 weeks prior to screening. Complete inclusion and exclusion criteria are listed in the Supplementary Appendix (Supplemental Tables 1 and 2).

Computed tomography corelab analysis was performed by Drs Teresa Sevilla and Ana Revilla-Orodea. The second has been included as author due to her coordinating role. Echocardiography corelab analysis was performed by Dr Jose Luis Zamorano. He has been included as author due to his coordinating role.

The TRICUS study was approved by the Kaunas Regional Biomedical Research Ethics Committee, and the TRICUS EURO study was approved by the ethics committee of each recruiting institution. All patients gave informed consent prior to screening.

FOLLOW-UP. Prespecified 30-day, 3-month, 6-month, and 1-year clinical visits were performed. Yearly follow-up is also planned for all enrolled participants up to 5 years. Complete follow-up diagram including complementary studies and clinical visits is noted in the Supplemental Appendix (Supplemental Figure 1).

ENDPOINTS. The primary endpoint was clinical improvement evaluated by the composite of: change in quality of life (QOL) measured with the 12-item Kansas City Cardiomyopathy Questionnaire (KCCQ-12), with a large improvement defined as an increase of ≥15 points from baseline to 1-year follow-up; improvement in NYHA functional class to I or II at 1-year follow-up; or change in functional exercise capacity measured with the 6MWT distance, considering a significant improvement an increase in at least 40 m from baseline based on previous heart failure trials aimed to assess the effect of different pharmacological and nonpharmacological therapies that suggest a 30- to 50-m increase as associated with a significant clinical improvement.[14]

The secondary endpoints were as follows: 1) freedom from major adverse events including death, acute myocardial infarction, tricuspid valve surgery, cardiac tamponade, stroke, or major bleeding according to Valve Academic Research Consortium-3 criteria at 1-year follow-up; 2) freedom from heart failure rehospitalizations or serious adverse events related to the device at 1-year follow-up; 3) changes in right heart dimensions as measured by assorted echocardiographic parameters at baseline and 3-month, 6-month, and 1-year follow-up; 4) improvement in systemic venous congestion measured by echocardiographic and laboratory test parameters (hepatic vein backflow and N-terminal pro-B-type natriuretic peptide); and 5) changes in renal and hepatic function measured by baseline and 1-year follow-up laboratory tests (creatinine, glomerular filtration rate, alanine aminotransferase, and aspartate aminotransferase).

An independent committee evaluated and adjudicated all safety and efficacy events, and independent echocardiography and CT core laboratories assessed echocardiographic and CT parameters. All clinical events were defined according to Valve Academic Research Consortium-3 criteria. QOL was assessed using the KCCQ-12, a shorter version of the 23-item scale, designed to rate symptoms, physical and social limitations, and overall QOL in patients with heart failure, preserving the validity, reliability, prognostic relevance, and interpretability from the original questionnaire.

STATISTICAL ANALYSIS. Categorical variables are described as frequency and percentage. Continuous variables are presented as mean ± SD or median (IQR) depending on variable distribution. The normal distribution of continuous variables was verified with the Kolmogorov-Smirnov test and Q-Q plot. Differences between groups were evaluated using chi-square or Fisher exact test for categorical variables and Student *t* or Mann-Whitney tests in case of non-normal variables. Changes between basal values and 1-year follow-up were evaluated using Student's paired *t* test or the Wilcoxon test. Sensitivity analyses were carried out as well using the last-observation-carried-forward method to evaluate the effect of missing values during follow-up in the main variables of the study, only on those cases in which a 6-month value was present, showing that missing data did not influence the results. All statistical tests used a 2-sided *P* value of 0.05 as a significance threshold. Statistical analysis was performed using R software version 4.3 (R Foundation for Statistical Computing).

RESULTS

BASELINE CHARACTERISTICS. From September 2018 to February 2020, 9 patients were enrolled in the first-in-human TRICUS study from the Hospital of Lithuanian University of Health Sciences Kaunas Clinics. Likewise, between December 2019 to February 2021, a total of 35 patients were enrolled in the TRICUS EURO study across 12 institutions in Spain and Austria. The outcomes at 1 year (median 368 days [Q1-Q3: 359-371 days]) of the global 44 patients included in both studies are reported here.

Baseline characteristics are shown in **Table 1**. The mean age was 76.2 ± 7.5 years (range 50.0-89.0 years), and 82.0% were women. All patients were highly symptomatic (86.4% in NYHA functional class III and 13.6% in NYHA functional class IV), and most

TABLE 1 Baseline Characteristics (N = 44)

Age, y	76.2 ± 7.5
Male	8 (18.0)
BMI, kg/m^2	26.9 ± 5.2
NYHA functional class III	38 (86.4)
NYHA functional class IV	6 (13.6)
Hypertension	33 (75.0)
Diabetes mellitus	7 (15.9)
AF	41 (93.2)
COPD	2 (4.5)
CAD	6 (13.6)
Pacemaker	9 (20.5)
PVD	3 (6.8)
GFR <60 mL/min	29 (65.9)
GFR, mL/min/1.73 m^2	51.5 ± 18.3
Stroke	4 (9.1)
Valve surgery	
Aortic	7 (15.9)
Mitral	12 (27.3)
Tricuspid	7 (15.9)
Percutaneous valve therapy	
Aortic	2 (4.5)
Mitral	3 (6.8)
Tricuspid	1 (2.3)
EuroSCORE II, %	5.6 ± 3.6
TRISCORE	5.4 ± 1.2
AST, U/L	29.2 ± 10.0
ALT, U/L	19.3 ± 8.6
NT-proBNP, pg/mL	2,325 (1,108-2,680)
KCCQ-12 score	40.8 ± 20.9
6MWT, m	229.4 ± 91.0

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

6MWT = 6-minute walking test; AF = atrial fibrillation; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; EuroSCORE II = European System for Cardiac Operative Risk Evaluation II; GFR = glomerular filtration rate; KCCQ-12 = 12-item Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PVD = peripheral vascular disease; TRISCORE = Risk score model for isolated tricuspid valve surgery.

of them had a history of prior valve interventions (72.0%) and significant comorbidities such as atrial fibrillation (93.0%), prior pacemaker leads (20.5%), and renal dysfunction (65.9%). The overall EuroSCORE II (European System for Cardiac Operative Risk Evaluation II) was 5.6 ± 3.6%, and the overall TRISCORE was 5.4 ± 1.2. All patients presented with symptoms of right heart failure, such as lower limb edema, ascites, or pleural effusion, and the most common right heart failure signs were fatigue, shortness of breath, and exercise intolerance. The median time from diagnosis to the procedure was of 1.34 years (Q1-Q3: 0.72-4.00 years).

Baseline echocardiographic characteristics are provided in Table 2. Mean left ventricular ejection fraction was 59.8 ± 9.1% and mean TAPSE was 18.2 ± 3.4 mm with a right ventricular peak systolic free wall longitudinal strain of −17.1 ± 2.9%. Most of the patients had enlarged right heart chambers and tricuspid annular dilation. Hepatic vein backflow was present in 86.5% of the sample. Mean systolic pulmonary artery pressure estimated by echocardiography was 43 ± 9 mm Hg.

PRIMARY ENDPOINT: QOL. The primary combined endpoint of clinical improvement was achieved in 42 (95.5%) patients, including improvement in QOL as measured by an increase in at least 15 points in the KCCQ-12 score, improvement in functional class (NYHA functional class I or II at 1-year follow-up), or exercise tolerance defined as an increase in at least 40 m in the 6MWT at 1-year follow-up.

There was a significant improvement in overall QOL ($P < 0.001$), detecting a large improvement (≥15 points) in 56.4% of the patients (Figure 1). A significant improvement in NYHA functional class was also observed ($P < 0.001$), with 62.2% of patients in functional class I or II at 1-year follow-up (vs 0% at baseline) (Figure 2). Additionally, an improvement in the 6MWT was detected (229 ± 91 m at baseline vs 270 ± 111 m at 1-year follow-up), although it did not reach statistical significance ($P = 0.285$) (Figure 3). However, 40% of the patients achieved a large improvement in the 6MWT distance (≥40 m) 1 year after the implantation. The main factors associated with QOL improvement are reported in Table 3.

SECONDARY ENDPOINT: MAJOR EVENTS AND REHOSPITALIZATION. Major adverse events at 6-month and 1-year follow-up are shown in Table 4. There were 3 deaths during the 6-months follow-up (1 due to cardiovascular cause), with no further deaths at 1-year follow-up. No cases of myocardial infarction nor cardiac tamponade were detected, but 1 patient in the TRICUS first-in-human cohort required emergent cardiac surgery the day after the implantation due to embolization of the SVC prosthesis during deployment. Therefore, the TricValve system was not implanted. The Kaplan-Meier survival curve is presented in Figure 4A.

Major bleedings were essentially gastrointestinal hemorrhages (9.0% of the population) in the context of supratherapeutic vitamin K antagonist levels and puncture site complications (6.8%), from which only 1 needed surgical vascular repair. Also, a subdural hematoma secondary to an accidental fall and a severe epistaxis that required 1-month hospitalization occurred. Additionally, 4 (9.0%) patients experienced a stroke during follow-up.

The heart failure rehospitalization rate was 29.5% (13 readmissions in 11 [25.0%] patients) at 1-year follow-up and occurred more often in those patients with prior mitral percutaneous repair (27.3% vs 0%; $P = 0.012$) but was not related to prior mitral surgery ($P = 0.698$). Regarding other adverse events, 6 cases of right heart chamber thrombi were detected (all incidental findings in scheduled CT or echocardiography, medically managed with no clinical consequences and with neither leaflet involvement nor acute disfunction of the device). Also, 3 cases of paravalvular leak were detected, from which only 1 caused significant regurgitation and required percutaneous closure of the leak. No other complications were detected, including stent fracture, conduction system disturbances, or displacement of previously implanted pacemaker leads. The freedom from rehospitalization Kaplan-Meier curve is presented in **Figure 4B**.

One-year echocardiographic parameters are shown in **Table 2**. No significant differences on right ventricular function as assessed by TAPSE were detected, but there was a significant reduction in tricuspid annular diameter at 1-year follow-up ($P = 0.013$). Hepatic vein backflow was abolished in 63.8% of patients at hospital discharge post-CAVI and remained unchanged throughout the rest of the follow-up period, resulting in reduced congestion symptoms, a lowering of N-terminal pro-B-type natriuretic peptide levels ($P = 0.032$), and less reliance on diuretic therapy (Supplemental Figure 2). In this regard, 40% of the patients maintained a low-dose of loop diuretics at 1-year follow-up, while in 34% of the sample the loop diuretic dose was significantly lowered during this period. It is worth noting that the 23% of the patients that increased their loop diuretic intake had reduced or withdrawn other diuretic medications such as aldosterone receptor antagonists or thiazides. Regarding other laboratory test parameters (**Table 2**), no significant changes were found in any of the studied variables. Thus, renal ($P = 0.245$) and liver function (alanine aminotransferase: $P = 0.319$; aspartate aminotransferase: $P = 0.391$) stayed stable throughout the follow-up.

TABLE 2 Echocardiographic and Laboratory Parameters: Baseline and 1-Year Follow-Up

	Baseline	1-y Follow-Up	*P* Value
Echocardiographic characteristics			
RV peak systolic free wall longitudinal strain, %	−17.1 ± 2.9	−17.5 ± 5.2	0.814
TAPSE, mm	18.2 ± 3.4	17.2 ± 4.5	0.257
Basal RV diameter, mm	49.0 ± 6.9	48.0 ± 7.2	0.291
Mid-RV diameter, mm	40.0 ± 8.8	38.0 ± 8.2	0.314
RV base-to-apex diameter, mm	69.0 ± 9.4	67.0 ± 7.3	0.103
Larger RA diameter, mm	71 ± 12	73 ± 10	0.285
Smaller RA diameter, mm	59 ± 10	58 ± 8.4	0.931
Right atrial area, cm^2	37 ± 11	37 ± 10	0.602
Tricuspid annular diameter, mm	43 ± 6	41 ± 5	0.013[a]
LVEF, %	59.8 ± 9.1	59.5 ± 8.7	0.836
sPAP, mm Hg	43.9 ± 8.1[b]	43.0 ± 11.0	0.831
TR severity			
Severe (III)	24 (54.5)	26 (63.4)	
Massive (IV)	5 (11.3)	3 (7.3)	0.406
Torrential (V)	15 (34.0)	12 (29.3)	
Laboratory characteristics			
Creatinine, mg/dL	1.2 ± 0.4	1.3 ± 0.4	0.245
NT-proBNP, pg/mL	2,325 (1,108-2,680)	3,100 (1,311-3,129)	0.032[a]
ALT, U/L	20 ± 9	18 ± 8	0.319
AST, U/L	30 ± 10	29 ± 12	0.391

Values are mean ± SD, n (%), or median (Q1-Q3). [a]Statistically significant. [b]Baseline sPAP includes patients with grade 3 or 4 TR. Grade 5 tricuspid regurgitation is not included, as sPAP is underestimated.

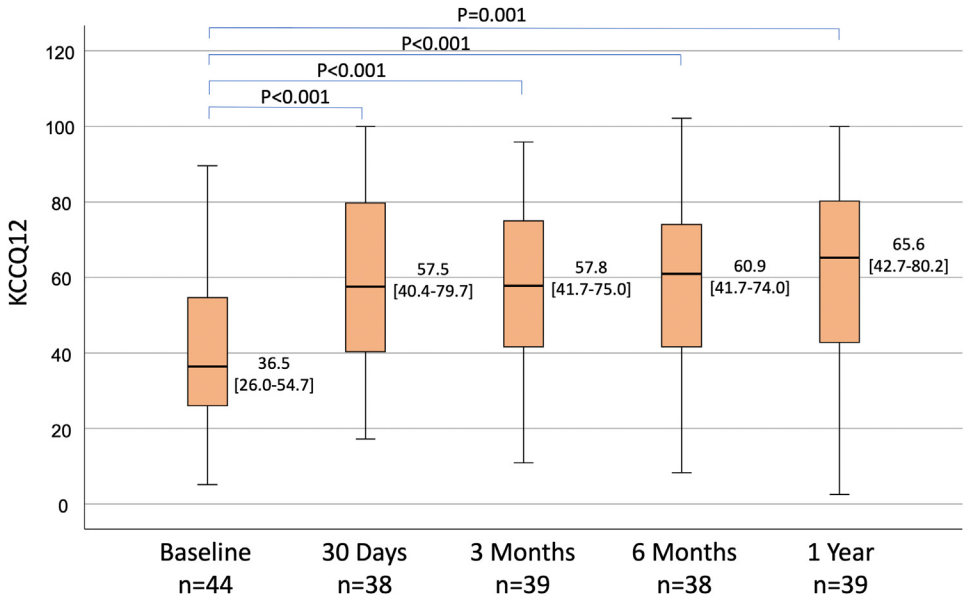
LVEF = left ventricular ejection fraction; RA = right atrial; RV = right ventricle/ventricular; sPAP = systolic pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion; other abbreviations as in **Table 1**.

DISCUSSION

CAVI with the TricValve system has been previously shown in a CE mark trial to be safe and effective in relieving congestion and significantly improving QOL metrics at 6 months in patients with NYHA functional class III or IV and severe TR with right heart failure.[9-13] Longer-term clinical and functional data involving the CAVI concept are yet to be established. The present findings confirm these beneficial effects remain stable and significant out to 1 year in the combined TRICUS/TRICUS EURO cohorts (**Central Illustration**). The vast majority (95.0%) of TricValve recipients demonstrated some objective evidence of significant functional improvement, with 56.0% demonstrating a significantly large improvement in the KCCQ-12 score of ≥15 points from baseline. The heart failure hospitalization rate at 1 year was 29.5% with an all-cause mortality rate of 6.8%. The immediate abolition of reverse hepatic vein flow on Doppler imaging post-CAVI significantly associated with a large (delta KCCQ-12 score of ≥15 points from baseline) functional improvement at 1 year. These data provide reassurance regarding the functional benefits of CAVI and underscore the value of a randomized pivotal trial of CAVI in the severely symptomatic TR/right heart failure population who currently have limited to no treatment options, although whether certain impact of CAVI on mortality exists or not merits further research.

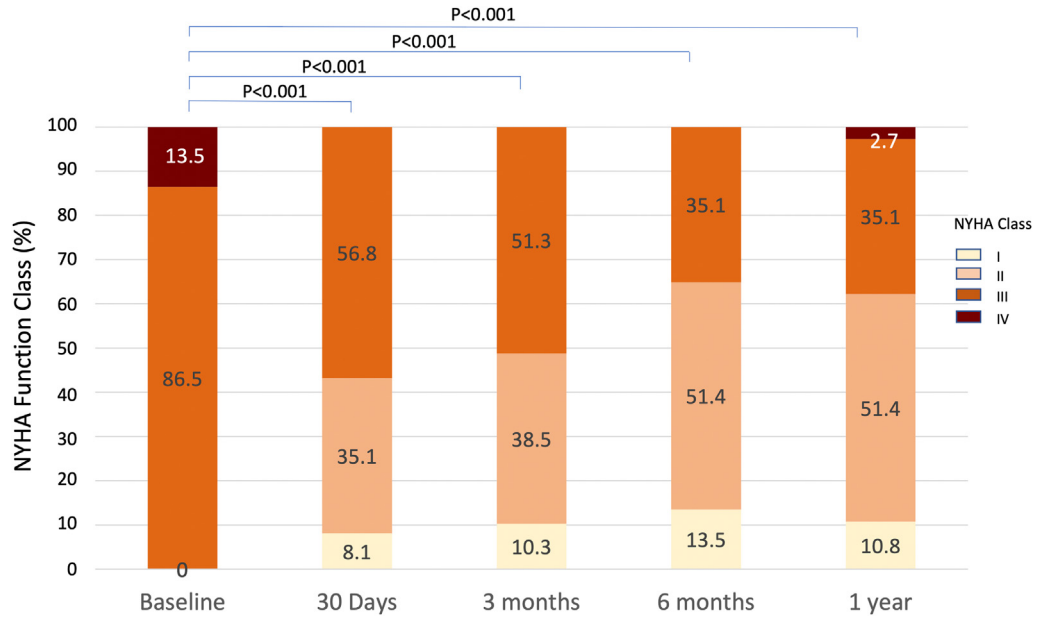
The overall mean improvement in KCCQ-12 scores in the present analysis (delta KCCQ-12 score of 19) is in line with a range of other transcatheter therapies

FIGURE 1 KCCQ-12 Score



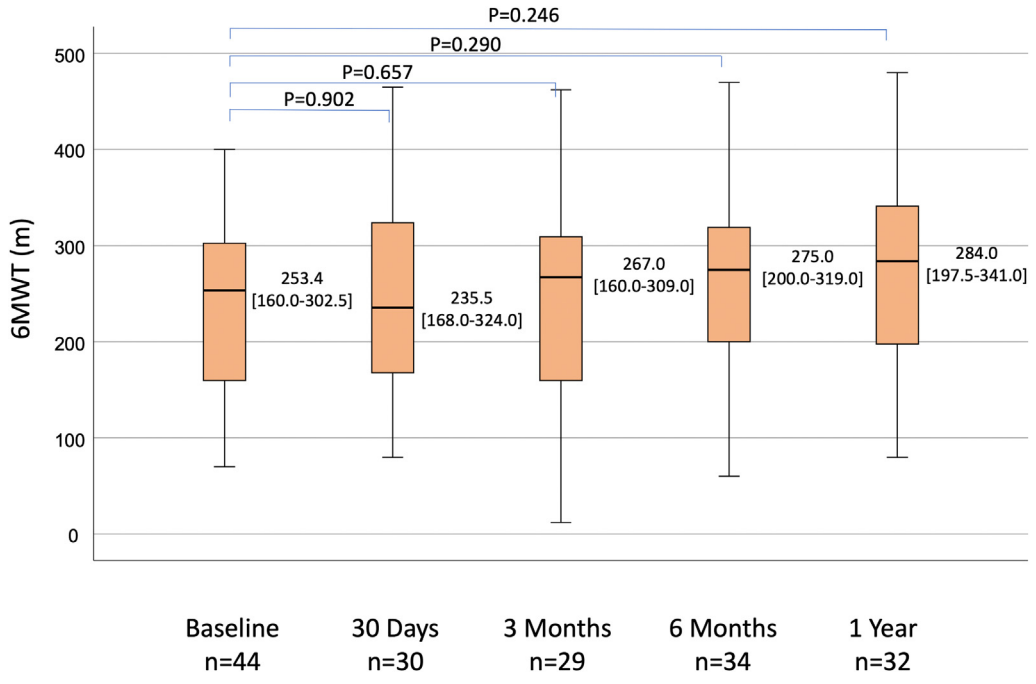
Baseline and 30-day, 3-month, 6-month, and 1-year follow-up in the 12-item Kansas City Cardiomyopathy Questionnaire (KCCQ-12) score. Values are median (Q1-Q3).

FIGURE 2 NYHA Functional Class



Baseline and 30-day, 3-month, 6-month, and 1-year follow-up in NYHA functional class. Data are presented as %.

FIGURE 3 6-Minute Walking Test



Baseline and 30-day, 3-month, 6-month, and 1-year follow-up in the 6-minute walking test (6MWT). Values are median (Q1-Q3).

for treating severe TR. In the TRILUMINATE pivotal trial (Trial to Evaluate Treatment With Abbott Transcatheter Clip Rapair System in Patients with Moderate or Greater Tricuspid Regurgitation), the imputed change from baseline in the KCCQ-12 score was 16, with 50% of the TEER group achieving a delta KCCQ-12 score of ≥15 points from baseline.[15] This magnitude is also in line with transcatheter direct annuloplasty with the Cardioband system (Edwards Lifesciences).[16] Importantly, the baseline KCCQ score in the TRILUMINATE cohort ranged from 56 to 59, compared with 40.8 in the TRICUS/TRICUS EURO cohort. This highlights the much sicker and advanced nature of severe TR/right heart failure in the present CAVI cohort, who are often deemed unsuitable for TEER/TTVR therapies.

Of further note is the fact that in the TRILUMINATE trial, the change in the KCCQ score correlated with the degree of residual TR at 1-year follow-up, with a smaller increase (3.8 ± 18.4) among patients with severe residual TR. In the present analysis, owing to the nature of the CAVI procedure, all patients had severe TR at 1-year follow-up. Hence, the improvement in QOL metrics noted in the TRICUS/TRICUS EURO cohort is likely to be directly associated with a reduction in caval backflow, and furthermore, with a reduction or abolition of reverse hepatic vein flow. Although not an absolute necessity for a large functional QOL improvement, the immediate abolition of reverse hepatic vein flow on echocardiography was significantly greater in those patients who derived a large functional benefit, as measured by an increase in KCCQ-12 score of ≥15 points. This suggests that procedural and iterative device design efforts may need to focus on more optimal sizing, anchoring, sealing, and paravalvular leak mitigation to further optimize clinical outcomes.

The all-cause mortality and heart failure hospitalization rates in the present cohort are noteworthy. Considering the more advanced state of TR and right heart failure in the TRICUS/TRICUS EURO cohort, a 1-year all-cause mortality rate of 6.8% compares favorably with the TRILUMINATE trial 1-year all-cause mortality rate of 8.8% in the TEER arm.[15] However, the heart failure hospitalization rate in the TRILUMINATE trial TEER arm was 14.9%, which was comparably higher in the present cohort, at 29.5%. Interestingly, there was no significant difference in the rate of heart failure hospitalizations in those who reported a significantly large QOL/functional improvement (delta KCCQ-12 score ≥15 points

TABLE 3 Factors Associated With KCCQ-12, 6MWT Distance, and NYHA Functional Class Improvement at 1-Year Follow-Up

Baseline Characteristics	KCCQ-12 <15 (n = 17)	KCCQ-12 ≥15 (n = 22)	*P* Value	6MWT Distance <40 m (n = 22)	6MWT Distance ≥40 m (n = 15)	*P* Value	NYHA Functional Class III-IV (n = 14)[a]	NYHA Functional Class I-II (n = 23)[a]	*P* Value
Clinical characteristics									
Age, y	75.0 ± 8.9	76.0 ± 6.9	0.854	75.1 ± 6.2	78.9 ± 6.8	0.102	76.2 ± 4.7	76.2 ± 7.6	0.999
Female	14 (82.3)	17 (77.3)	0.999	18 (81.8)	9 (60)	0.221	1 (7.1)	17 (73.9)	0.217
CAD	2 (11.8)	4 (18.2)	0.999	4 (18.2)	1 (6.7)	0.624	2 (14.3)	4 (17.4)	0.999
Pacemaker	4 (23.5)	3 (13.6)	0.677	5 (22.7)	1 (6.7)	0.366	3 (21.4)	3 (13.0)	0.653
Hypertension	10 (58.8)	18 (81.8)	0.158	13 (59.1)	12 (80.0)	0.252	12 (85.7)	16 (69.6)	0.434
Diabetes mellitus	3 (17.6)	4 (18.2)	0.999	3 (13.6)	1 (6.7)	0.635	2 (14.3)	4 (17.4)	0.999
COPD	1 (5.9)	1 (4.5)	0.999	2 (9.1)	0	0.506	1 (7.1)	1 (4.3)	0.999
Chronic renal failure	6 (35.3)	6 (27.3)	0.590	1 (4.5)	6 (40)	0.010[b]	5 (35.7)	5 (21.7)	0.454
AF	15 (88.2)	21 (95.5)	0.570	21 (95.5)	13 (86.7)	0.400	12 (85.7)	23 (100)	0.137
PVD	2 (11.8)	1 (4.5)	0.570	1 (4.5)	1 (6.7)	0.999	3 (21.4)	0	0.047[b]
Stroke	4 (23.5)	0	0.029[b]	1 (4.5)	2 (13.3)	0.551	0	3 (13)	0.275
Mitral valve surgery	7 (41.2)	5 (2.7)	0.216	4 (18.2)	5 (33.3)	0.432	1 (7.1)	9 (39.1)	0.056
Aortic valve surgery	5 (29.4)	2 (9.1)	0.205	4 (18.2)	2 (13.3)	0.999	2 (14.3)	5 (21.7)	0.687
Tricuspid valve surgery	3 (17.6)	4 (18.2)	0.999	3 (13.6)	2 (13.3)	0.999	2 (14.3)	3 (13.0)	0.999
Mitral TEER	1 (5.9)	1 (4.5)	0.999	2 (9.1)	1 (6.7)	0.999	1 (7.1)	2 (8.7)	0.999
TAVR	1 (5.9)	0	0.436	1 (4.5)	1 (6.7)	0.999	2 (14.3)	0	0.137
Tricuspid TEER	1 (5.9)	0	0.436	1 (4.5)	0	0.999	0	1 (4.3)	0.999
EuroSCORE II, %	7.0 ± 4.3	5.1 ± 3.3	0.144	4.1 ± 1.9	5.0 ± 2.1	0.240	4.7 ± 3.0	4.7 ± 2.1	0.997
TRISCORE	5.7 ± 1.3	5.1 ± 1.1	0.125	5.2 ± 0.7	5.5 ± 1.4	0.958	5.3 ± 1.2	5.3 ± 1.1	0.963
Time from diagnosis, y	3.5 ± 3.7	1.9 ± 2.1	0.454	2.2 ± 1.9	3.7 ± 2.2	0.231	2.2 ± 2.0	3.4 ± 3	0.310
Echocardiographic characteristics									
RV longitudinal strain, %	−19.0 ± 7.2	−16.0 ± 6.1	0.275	−18.0 ± 7.2	−18.0 ± 6.7	0.917	−17.0 ± 3.6	−16.0 ± 7.0	0.885
TAPSE, mm	19.5 ± 5.2	18.0 ± 3.3	0.599	18.4 ± 4.8	19.2 ± 2.9	0.499	18.1 ± 3.1	19.2 ± 4.4	0.425
RV basal diameter, mm	50.0 ± 5.7	48.0 ± 7.3	0.423	49.1 ± 5.5	49.2 ± 8.2	0.920	47.2 ± 4.7	49.8 ± 6.9	0.243
RA area, cm^2	38.6 ± 9.8	35.2 ± 10.9	0.311	36.4 ± 11.0	35.8 ± 10.0	0.839	38.0 ± 6.5	35.8 ± 12.0	0.534
LVEF, %	55.9 ± 11.0	60.6 ± 9.3	0.133	61.5 ± 9.8	57.3 ± 7.6	0.166	57.8 ± 9.5	60.2 ± 9.5	0.466
Estimated sPAP, mm Hg	45.7 ± 9.1	42.3 ± 12.0	0.468	39.3 ± 10.8	46.8 ± 11.6	0.165	44.7 ± 7.0	42.8 ± 12	0.655
Baseline Doppler backflow in hepatic veins	12 (70.5)	16 (72.7)	0.999	16 (72.2)	11 (73.3)	0.999	11 (78.6)	17 (73.9)	0.999
Discharge Doppler backflow in hepatic veins	8 (47.1)	4 (18.2)	0.027[b]	4 (18.2)	7 (46.7)	0.153	4 (28.6)	7 (30.4)	0.999
Laboratory characteristics									
AST, U/L	30.3 ± 11.0	27.6 ± 10.0	0.225	31.8 ± 10.0	28.5 ± 11.0	0.312	29.2 ± 11.0	28.9 ± 9	0.951
ALT, U/L	17.6 ± 8.0	20.4 ± 10.0	0.430	21.4 ± 9.0	17.8 ± 8.6	0.221	24.1 ± 11.0	17.3 ± 6	0.050[b]
Creatinine, mg/dL	1.2 ± 0.5	1.2 ± 0.3	0.225	1.0 ± 0.26	1.2 ± 0.43	0.172	1.2 ± 0.6	1.1 ± 0.4	0.783
NT-proBNP, pg/mL	2,443 (1,838-3,346)	1,748 (1,189-3,436)	0.835	2,035 (1,310-3,208)	2,637 (1,158-3,978)	0.572	2,188 (1,904-3,436)	1,432 (1,158-3,260)	0.151

Values are mean ± SD, n (%), or median (Q1-Q3). [a]All patients were at NYHA functional class III or IV at baseline; therefore the rate of NYHA functional class I or II at 1-year follow-up was as clinical improvement. [b]Statistically significant.

TAVR = transcatheter aortic valve replacement; TEER = transcatheter edge-to-edge repair; other abbreviations as in Tables 1 and 2.

from baseline) vs those who reported a lesser improvement (delta KCCQ-12 score <15 points from baseline). Despite the fact that 95% of the TRICUS/TRICUS EURO population demonstrated at least 1 metric of significant functional improvement (ie, follow-up NYHA functional class I or II, improvement in 6MWT distance of ≥40 m, or delta KCCQ-12 score from baseline of ≥15 points), this did not seem to translate into significant reductions in heart failure hospitalizations. A similar phenomenon was observed at 1 year in the TRILUMINATE trial.[15] Presently, the KCCQ-12 has not yet undergone formal validation in a severe TR/right heart failure population, yet alternative heart failure QOL scores have correlated with TR reduction and subsequent reductions in heart failure hospitalizations.[17] Further research into the mechanisms underlying heart failure hospitalizations in the treated TR population who demonstrate functional improvements is needed; in particular, the presence or prior mitral TEER, despite

TABLE 4 Major and Serious Adverse Events at 1-Year Follow-Up

	6 mo	1 y	Overall 1 y (%)
Major adverse events			
All-cause death	3	0	6.8
Myocardial infarction	0	0	0
Tricuspid valve surgery	1	0	2.3
Cardiac tamponade	0	0	0
Major bleeding[a]	7	2	20.4
Stroke	3	1	9
Serious adverse events			
Heart failure rehospitalization	9	4	29.5
Right heart thrombi	4	2	13.6
Paravalvular leak	3	0	6.8

[a]Major bleeding Valve Academic Research Consortium-2 criteria: overt bleeding either associated with a drop in the hemoglobin level of at least 3 g/dL or requiring transfusion of 2 to 3 units of whole blood/red blood cells, or causing hospitalization or permanent injury, or requiring surgery and does not meet criteria of life-threatening or disabling bleeding.

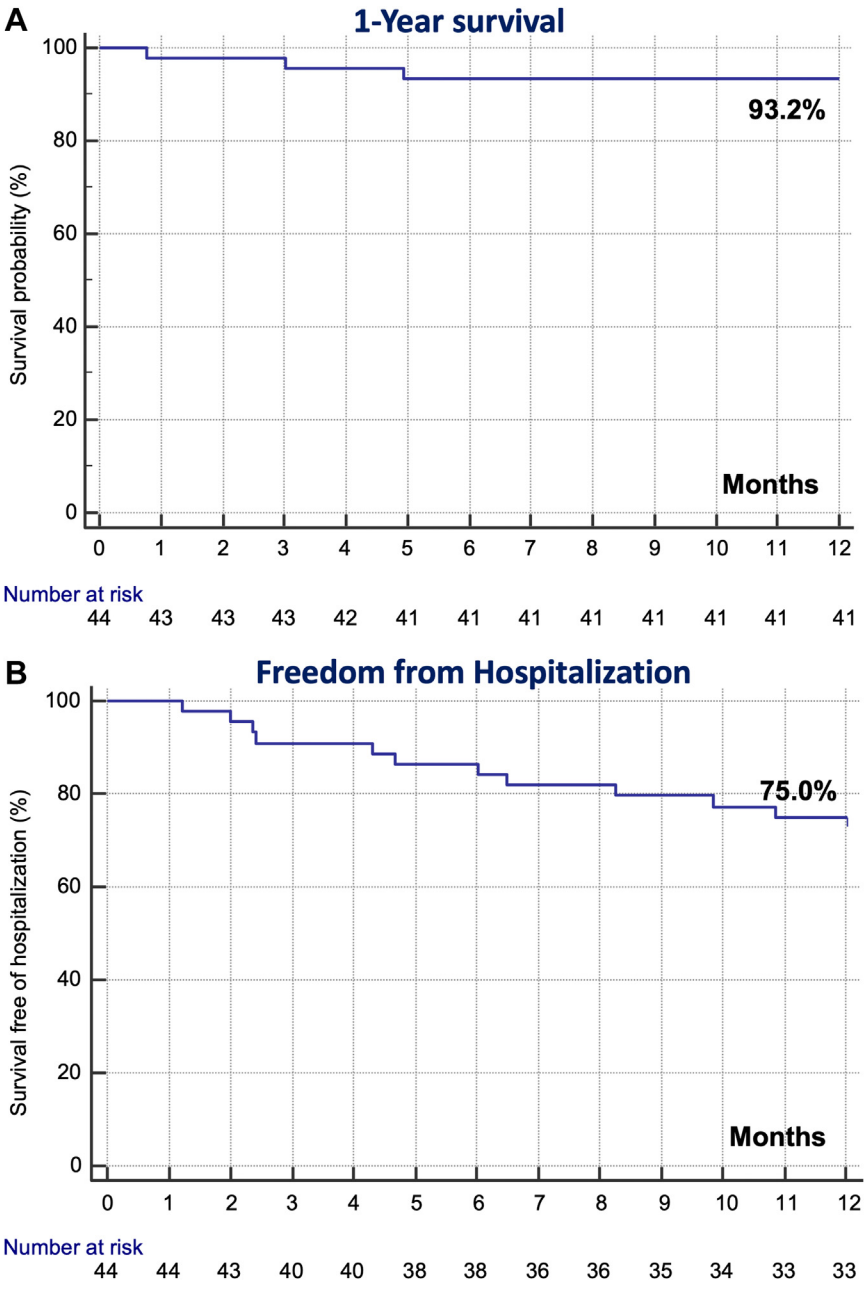
the absence of severe MR at follow-up, was associated with greater heart failure hospitalizations, which could occur through several mechanisms: 1) a certain degree of chronic impact in pulmonary circulation increasing the afterload and hindering the benefit of CAVI; 2) worse left ventricular ejection fraction; and 3) a potential persistent interatrial shunt that could eventually lead to right-to-left shunt following CAVI if not closed.

Whether the 1-year time point is too early to delineate differences in hard clinical endpoints in this (treated vs untreated) severe TR population will also require further investigation. The natural history of untreated severe TR is often dismal, with hepatic, intestinal, and renal congestion worsening in line with significant reductions in cardiac output, with resultant terminal target organ damage.[9,10,18,19] In the present study, no significant changes were noted of a range of renal and hepatic biochemical parameters. This reinforces the notion that the bicaval CAVI concept may arrest the progression of systemic congestion from ongoing right heart failure. Recent observations of significant improvements in cardiac output following TricValve (evidenced via chronic invasive hemodynamic monitoring with a pre-existing CardioMEMS [Abbott] recipient)[20] along with reverse right ventricular remodeling on serial volumetric CT analysis in the TRICUS EURO cohort[13] underscores the emerging mechanistic efficacy of bicaval CAVI.

A 6MWT distance of <300 m correlates with a poor prognosis, with death rates being fairly high in those unable to walk 200 m.[14,21,22] In our sample, the baseline 6MWT distance of 227 m reflects the fragile and comorbid nature of the TRICUS and TRICUS EURO population. Despite that, 40.0% of the patients experienced a significant improvement in their exercise tolerance, defined as an improvement in 6MWT distance of ≥40 m, although 7 (16.0%) patients were unable to walk ≥200 m. In this regard, even though most patients reached the combined endpoint of clinical improvement at 1-year follow-up, none of the 3 separate functional/QOL endpoints (ie, KCCQ-12 score, 6MWT distance, and NYHA functional class) showed a significant association with a reduced rehospitalization rate.

The most prevalent adverse event at 1 year was major bleeding (20.4%), mostly due to anticoagulation therapy (being gastrointestinal hemorrhage the most frequently detected), with only 3 (6.8%) patients presenting puncture site complications. A subdural hematoma secondary to an accidental fall was detected, leading to further death, along with 1 case of severe epistaxis that required prolonged hospitalization. On the other hand, 9.0% of the sample experienced an ischemic stroke, and right heart thrombi were observed in 6 (13.6%) patients during follow-up. The latter were all incidental findings in a scheduled CT (5 patients) or unplanned CT (1 patient, performed to rule out acute pulmonary embolism in whom a cervix uteri cancer was later detected). None of these demonstrated any adverse clinical events that were known to be related to these imaging findings and were managed conservatively with anticoagulation treatment optimization. To add more, all cases of right heart thrombus or stroke occurred in patients with either a hypercoagulable state or underdose of anti-vitamin K agents. Last, 3 cases of paravalvular leak were detected during follow-up, from which only 1 patient required percutaneous closure of the leak. In this regard, a larger IVC dimension and a marked angulation of the IVC-right atrium junction have been associated with a greater risk of periprosthetic backflow, as previously reported,[13] which will likely be solved with alternative sizes of the IVC prosthesis currently under development. To remark, the device sizes included in TRICUS EURO and TRICUS studies were 25 mm and 29 mm for the SVC and 31 mm and 35 mm for the IVC. However, a 33-mm device for the SVC and 41-mm/45-mm devices for the IVC have also been developed and might help to prevent leakage through larger degree of oversizing; however, the specific risks with them are still under investigation. Regarding the angulation of the IVC-right atrium junction, technical aspects of the procedure have been improved in the learning curve to decrease its impact, including removing the stiff wire from the SVC when the IVC device is being implanted (leaving the wire in the atrium), allowing better coaxiality of IVC and the

FIGURE 4 Kaplan-Meier Curves

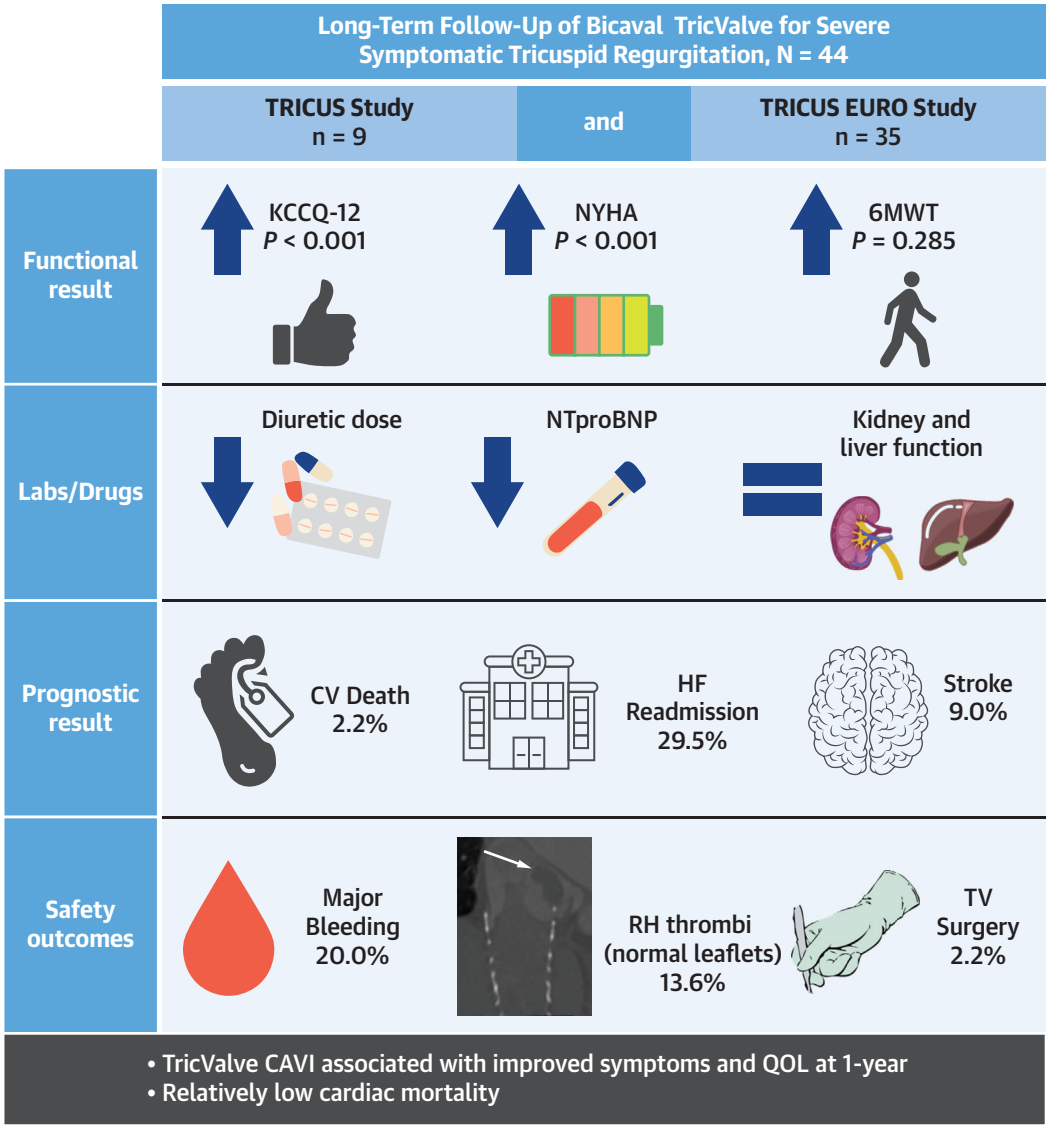


(A) Time-to-event curves for the incidence of all-cause death. (B) Time-to-event curve for the incidence of heart failure rehospitalization.

delivery system. Also, better positioning has been probably achieved as experience grew, adjusting the valve much lower during deployment to prevent leakage even if microembolization occurs after final release. On the contrary, leaflet dysfunction does not seem to be a mechanism behind persistent hepatic backflow, at least at 1-year follow-up. No mechanical complications related to the IVC/SVC stents were detected during follow-up.

STUDY LIMITATIONS. Several caveats of the present analysis require further consideration. The sample size of the TRICUS/TRICUS EURO cohort is limited and ultimately is not powered to show meaningful

CENTRAL ILLUSTRATION **Summary of Main Outcomes at 1 Year Following TricValve**



Blasco-Turrión S, et al. J Am Coll Cardiol Intv. 2023;■(■):■-■.

The 1-year follow-up primary endpoint (composite of change in quality of life [QOL] measured with the 12-item Kansas City Cardiomyopathy Questionnaire, change in NYHA functional class, or change in functional exercise capacity measured with the 6-minute walking test [MWT]) and major adverse events. CAVI = caval valve implantation; CV = cardiovascular; HF = heart failure; NTproBNP = N-terminal pro-B-type natriuretic peptide; RH = right heart; TRICUS = Safety and Efficacy of the TricValve® Transcatheter Bicaval Valves System in the Superior and Inferior Vena Cava in Patients With Severe Tricuspid Regurgitation; TV = tricuspid valve.

differences in hard clinical events or functional metrics. The present population reflects the earliest human experience with the TricValve CAVI system, reflecting the steepest part of the device and clinical learning curve. Many of the TRICUS/TRICUS EURO patients were enrolled during the COVID-19 pandemic, whose impact on functional QOL metrics cannot be underestimated. Further clinical and mechanistic insights will be gleaned from an ongoing large-scale international TRICUS registry reflective of

the current commercial experience, along with the planned U.S. Food and Drug Administration TRICAV (Tricvalve for bicaval stenting to relieve effects of severe tricuspid regurgitation) randomized pivotal trial assessing the TricValve CAVI system in NYHA functional class III or IV severe TR patients vs medical therapy.

CONCLUSIONS

The TricValve bicaval CAVI system demonstrates device safety along with stable and significant improvements in functional/QOL metrics at 1 year in NYHA functional class III or IV severe TR patients presenting with right heart failure, the magnitude of benefit appearing to be in line with other emerging transcatheter devices to directly address the tricuspid valve. The majority of patients demonstrated some form of significant functional improvement. Hard clinical event rates were commensurate with the advanced baseline state of disease. An ongoing global TricValve CAVI registry along with a planned pivotal randomized trial will yield further clinical and mechanistic insights into the longer term.

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PERSPECTIVES

WHAT IS KNOWN? Severe TR is a highly prevalent clinical entity associated with poor QOL and high mortality rate. Given the poor results of isolated TR surgery, several percutaneous therapies have been developed; however, many patients are deemed unsuitable. The TricValve bicaval valve system has shown positive clinical and structural short-term results, but long-term outcomes have not yet been established.

WHAT IS NEW? These are the first results at 1-year follow-up with the TricValve system and confirm a significant improvement in QOL, functional class, and congestive symptoms with a relatively low mortality rate despite the very advanced stage of the disease in the target population.

WHAT IS NEXT? Further prosthesis sizes along with structural improvements of the platform might help to provide better results and broaden the range of candidates for this therapy. In addition, the ongoing TricValve global registry along with a planned TRICAV pivotal randomized trial will yield further clinical and mechanistic insights into the longer term.

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