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FASTTRACK - CLINICAL RESEARCH
Interventional cardiology

Tricuspid valve replacement outcomes by baseline tricuspid regurgitation severity: the TRISCEND II trial

Philipp Lurz [1,*], Rebecca T. Hahn [2], Susheel Kodali[2], Raj Makkar [3], Rahul P. Sharma[4], Charles J. Davidson [5], Brian P. O'Neill[6], Pradeep Yadav [7], Firas Zahr [8], Scott Chadderdon [8], Mackram F. Eleid [9], Molly Szerlip [10], Robert L. Smith[10], Brian Whisenant[11], Santiago Garcia[12], Tobias Kister [13], Robert M. Kipperman[14], D. Scott Lim [15], John Saxon [15], Samir Kapadia [16], James Hermiller[17], Jacob M. Mishell [18], Andrew Rassi[18], Howard C. Herrmann [19], Wilson Szeto [19], Jörg Hausleiter [20], Vasilis Babaliaros [21], Colin M. Barker [22], Brian R. Lindman [22], Azeem Latib [23], Kamran Muhammad[24], Ralph Stephan von Bardeleben [1], Matthew Summers [25], Stanley J. Chetcuti[26], Gorav Ailawadi [26], Mark Russo[27], Michael Rinaldi [28], Bassem M. Chehab [29], Georg Nickenig [30], Curtiss Stinis[31], Ignacio Inglessis-Azuaje [32], Abhijeet Dhoble [33], Adnan K. Chhatriwalla [34], George Petrossian [35], Pinak Shah [36], Cezar Staniloae [37], Mathew Williams [37], Marcos Nores[38], James M. McCabe [39], Gagan Singh [40], Stephan Baldus [41], Volker Rudolph [42], Ilie Barb[43], Charles Klodell [43], William Gray [44], Justin Strote [45], Anna Sannino [46], Paul Grayburn [10,46], Michael J. Mack [10], Martin B. Leon [2], and Vinod H. Thourani [7]; on behalf of the TRISCEND II Pivotal Trial Investigators

[1]Department of Cardiology, University Medical Centre Mainz, Langenbeckstr. 1, 55131 Mainz, Germany; [2]Division of Cardiology, Columbia University Irving Medical Center, New York, NY, USA; [3]Smidt Heart Institute for Interventional Technologies,Cedars-Sinai Medical Center, Los Angeles, CA, USA; [4]Division of Cardiovascular Medicine, Stanford University, Stanford, CA, USA; [5]Division of Cardiology, Northwestern University, Chicago, IL, USA; [6]Center for Structural Heart Disease, Henry Ford Hospital, Detroit, MI, USA; [7]Marcus Heart Valve Center, Piedmont Heart Institute, Atlanta, GA, USA; [8]Division of Cardiovascular Medicine, Oregon Health & Science University, Portland, OR, USA; [9]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, USA; [10]Department of Cardiology, Baylor Scott & White: The Heart Hospital Plano, Plano, TX, USA; [11]Division of Cardiology, Intermountain Medical Center, Murray, UT, USA; [12]Division of Cardiology, The Christ Hospital, Cincinnati, OH, USA; [13]Department of Cardiology, Heart Center Leipzig at Leipzig University, Leipzig, Germany; [14]Valve and Structural Heart Center, Atlantic Health System Morristown Medical Center, Morristown, NJ, USA; [15]Division of Cardiovascular Medicine, University of Virginia, Charlottesville, VA, USA; [16]Department of Cardiovascular Medicine, The Cleveland Clinic Foundation, Cleveland, OH, USA; [17]Division of Cardiology, Ascension St. Vincent Heart Center of Indiana, Indianapolis, IN, USA; [18]Department of Cardiology, Kaiser San Francisco Medical Center, San Francisco, CA, USA; [19]Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [20]Medizinische Klinik und Poliklinik I,Klinikum der Universität München, Munich, Germany; [21]Structural Heart and Valve Center, Emory University Atlanta, Atlanta, GA, USA; [22]Division of Cardiology, Vanderbilt University Medical Center, Nashville, TN, USA; [23]Department of Cardiology, Montefiore Medical Center, The Bronx, NY, USA; [24]Structural Heart Center, Oklahoma Heart Institute, Tulsa, OK, USA; [25]Sentara Heart Valve Center, Sentara Norfolk General Hospital, Norfolk, VA, USA; [26]Department of Interventional Cardiology, University of Michigan Hospital and Health Systems, Ann Arbor, MI, USA; [27]Division of Cardiac Surgery, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA; [28]Sanger Heart & Vascular Institute, Atrium Health, Charlotte, NC, USA; [29]Department of Medicine, Ascension Via Christi Hospital, University of Kansas, Wichita, KS, USA; [30]Department of Cardiology, University Hospital Bonn, Bonn, Germany; [31]Division of Cardiology, Scripps Memorial Hospital La Jolla, La Jolla, CA, USA; [32]Division of Cardiology, Massachusetts General Hospital, Boston, MA, USA; [33]Division of Internal Medicine, The University of Texas Health Science Center at Houston, Houston, TX, USA; [34]Division of Cardiovascular Disease, Saint Luke's Hospital of Kansas City, Kansas City, MO, USA; [35]Heart Valve Center, St. Francis Hospital, Roslyn, NY, USA; [36]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA, USA; [37]Department of Cardiothoracic Surgery, New York University Langone Medical Center, New York, NY, USA; [38]Department of Cardiothoracic Surgery, Florida Heart & Vascular Care—JFK, Atlantis, FL, USA; [39]Department of Medicine, University of Washington, Seattle, WA, USA; [40]Division of Cardiovascular Medicine, UC Davis Medical Center Sacramento, Sacramento, CA, USA; [41]Department of Cardiology, University Hospital of Cologne, Cologne, Germany; [42]General and Interventional Cardiology, University of Bad Oyenhausen, Bad Oyenhausen, Germany; [43]The Cardiac and Vascular Institute, HCA Florida, North Florida Hospital, Gainesville, FL, USA; [44]Department of Interventional Cardiology, Lankenau Medical Center, Wynnewood, PA, USA; [45]UC Health Structural Heart & Valve Clinic, Medical Center of the Rockies, Loveland, CO, USA; and [46]Cardiac Imaging Core Lab, Baylor Scott & White Research Institute Cardiac Imaging Core Laboratory, Plano, TX, USA

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* Corresponding author. Tel: +49 341 865 252022, Fax: +49 341 865 1461, Email: lurzphil@uni-mainz.de

Abstract

Background and Aims The TRISCEND II trial demonstrated superior clinical benefits for patients with ≥severe tricuspid regurgitation (TR) treated with the EVOQUE transcatheter tricuspid valve replacement (TTVR) system plus medical therapy vs medical therapy alone. This work reports 1-year and 18-month outcomes in patients stratified by baseline TR severity.

Methods The multicentre, prospective TRISCEND II trial enrolled 400 patients with symptomatic, ≥severe TR, and randomized 2:1 to TTVR ($n = 267$) or control ($n = 133$). In a post hoc analysis, patients were stratified into severe TR ($n = 172$) and massive/torrential TR ($n = 220$) cohorts. Clinical and quality-of-life outcomes were reported at 1 year, with Kaplan–Meier estimates for all-cause mortality and heart failure (HF) hospitalization assessed at 18 months. Study oversight included an independent echocardiographic core laboratory, clinical events committee, and data safety monitoring board.

Results One year after TTVR, TR was ≤mild in 95.2% of severe TR and 95.3% of massive/torrential TR patients. The primary safety and effectiveness endpoint (win ratio) favoured TTVR over control regardless of baseline TR severity: severe {1.64 [95% confidence interval (CI): 1.11, 2.43]} and massive/torrential [2.20 (1.55, 3.14)]. At 18 months, TTVR patients had similar mortality to controls [rate difference: severe 0.2% (−11.6, 11.9), massive/torrential −5.8% (−17.6, 6.0)], whereas HF hospitalization rates favoured TTVR in the massive/torrential cohort [vs control, severe 9.8% (−3.0, 22.7), massive/torrential -15.2% (−28.9, −1.5)].

Conclusions Patients with ≥severe TR benefit from TTVR, experiencing improvements in TR severity, functional capacity, and quality of life regardless of baseline TR severity, with a signal for greater benefit in patients with more advanced disease.

Structured Graphical Abstract

Key Question

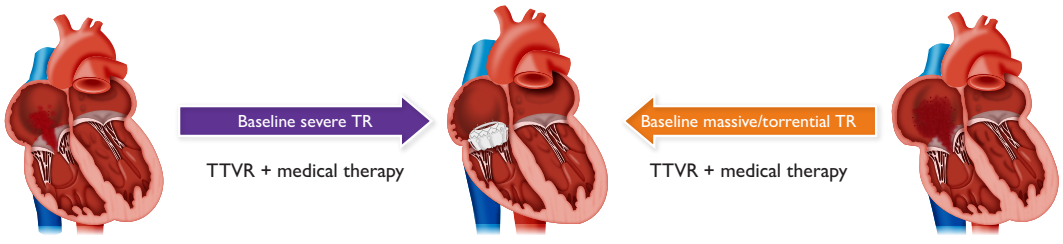
Does baseline TR severity (severe vs massive/torrential) impact clinical outcomes of TTVR compared with medical therapy alone?

Key Finding

This post hoc analysis of the TRISCEND II trial reports 1-year and 18-month outcomes in patients stratified by baseline TR severity. TTVR demonstrated greater TR reduction and superiority in the safety and effectiveness endpoints, regardless of baseline TR vs medical therapy alone. Greater improvements were observed in patients with baseline massive/torrential TR vs those with severe TR.

Take Home Message

TTVR benefits patients with severe and massive/torrential in reducing TR to ≤ mild, associated with quality-of-life and symptom improvements. Identifying patients who benefit from TTVR is important for the implementation of personalized forms of treatment.



Severe TR		Clinical outcomes	Massive/torrential TR	
TTVR	Control		TTVR	Control
1.64	-	Primary safety and effectiveness endpoint at 1 year (Win ratio)	2.20	-
95.2%	2.6%	TR grade ≤ mild at 1 year	95.3%	2.0%
13.6%	13.5%	All-cause mortality at 18 months	17.9%	23.6%
23.6%	13.7%	Heart failure hospitalization at 18 months	23.6%	38.8%
14.6 points	7.4 points	Δ KCCQ-OS score baseline to 1 year	22.2 points	-0.67 points
13.9%	4.0%	Severe bleeding at 1 year	16.8%	6.0%
19.7%	4.0%	Arrhythmia requiring new pacemaker at 1 year	16.1%	1.2%

KCCQ-OS, Kansas city cardiomyopathy questionnaire overall summary; TR, tricuspid regurgitation; TTVR, transcatheter tricuspid valve replacement

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Clinical outcomes in patients treated with transcatheter tricuspid valve replacement plus medical therapy versus medical therapy alone, stratified by baseline tricuspid regurgitation severity

Keywords Transcatheter tricuspid valve replacement • TTVR • Tricuspid regurgitation • EVOQUE • Severe TR • Massive/torrential TR

Introduction

Numerous studies have demonstrated that increasing tricuspid regurgitation (TR) severity is associated with worsening of outcomes even after adjusting for comorbidities.[1–3] Given the late presentation of patients with symptomatic disease, an extended TR grading scheme beyond severe, which includes massive [4+] and torrential [5+],[4] has been proposed to better classify disease severity in patients referred for transcatheter intervention.[5,6] Early trials of transcatheter TR therapy suggest that even a single-grade improvement in TR may be associated with short-term functional and quality-of-life improvements.[7–9] However, patients with baseline massive and torrential TR are less likely to achieve a reduction to moderate TR with tricuspid transcatheter edge-to-edge repair (T-TEER) devices.[10,11] In contrast to transcatheter repair, transcatheter tricuspid valve replacement (TTVR) studies have demonstrated that a reduction to mild or less TR can be achieved in more than 95% of patients treated, despite 40–50% of patients having massive or torrential TR at baseline.[12,13] This striking difference between T-TEER and TTVR warrants further investigation into the relationship between baseline TR severity and treatment outcomes. In this analysis, we assessed the outcomes of patients stratified by baseline TR severity in the TRISCEND II randomized controlled trial of TTVR with the EVOQUE TTVR system (Edwards Lifesciences, Irvine, CA, USA) vs optimal medical therapy

alone. We aimed to assess whether greater baseline disease severity is associated with differential treatment outcomes.

Methods

Trial design and oversight

The TRISCEND II pivotal trial (Edwards EVOQUE Transcatheter Tricuspid Valve Replacement: Pivotal Clinical Investigation of Safety and Clinical Efficacy using a Novel Device) is a prospective, global, multicentre, randomized controlled open-label clinical trial to evaluate the safety and effectiveness of TTVR with the EVOQUE system in conjunction with medical therapy compared with medical therapy alone in the treatment of patients with symptomatic ≥severe TR. Descriptions of the trial design, protocol, and 1-year results of the primary endpoint analysis have been previously published.[13,14]

All echocardiographic images were evaluated by an independent echocardiographic core laboratory (Baylor Scott & White Research Institute Cardiac Imaging Core Laboratory, Plano, TX, USA) and a clinical events committee (CEC) adjudicated prespecified adverse events; both groups were unblinded to treatment allocation. A data safety monitoring board (blinded except for a biostatistician) reviewed aggregate safety data. The TRISCEND II pivotal trial is registered at ClinicalTrials.gov (NCT04482062).

Enrolment, randomization, and follow-up

Patients were required to be at least 18 years old; have ≥severe TR as assessed by an independent echocardiographic core laboratory; have associated signs, symptoms, or prior heart failure (HF) hospitalization despite medical therapy; and be appropriate for TTVR as determined by the local heart team. Exclusions included <12-month life expectancy and anatomy precluding proper device delivery, deployment, and/or function. After patients provided informed consent, the local heart team performed the supporting computed tomography and echocardiographic imaging, which was assessed by the echocardiographic core laboratory, to assess preliminary eligibility for device feasibility and anatomical considerations. The central screening committee performed the final patient qualification based on medical history, transoesophageal echocardiography (TOE), and transthoracic echocardiography (TTE), computed tomography, and the proposed procedural approach. Baseline TR severity was rigorously confirmed first during screening and again on the day of the procedure using TOE. All TR assessments were adjudicated by an independent echocardiographic core laboratory, ensuring consistency and minimizing interobserver variability so that only patients with confirmed severe or greater TR were enrolled. For this post hoc analysis, TR severity by TTE at baseline was used to stratify patients into severe TR and massive/torrential TR cohorts using the five-grade scheme described by Hahn and Zamorano.[4]

Enrolled patients were randomized 2:1 to EVOQUE with medical therapy (TTVR group) or medical therapy alone (control group), with randomization stratified by study site. For all patients, medical treatment was managed at the investigator's discretion. Warfarin or another appropriate anticoagulant plus aspirin was recommended for at least 6 months post-TTVR. Tricuspid regurgitation severity was evaluated by TTE at baseline, discharge, and follow-up, with visits at 30 days, 6 months, 12 months, and annually through 5 years. Control patients were eligible for crossover after their 1-year follow-up visit.

Analyses of 18-month outcomes were not prespecified in the trial protocol. All-cause mortality and HF hospitalization data were collected through routine adverse event reporting by the sites, and these events were adjudicated by the CEC.

Outcomes

The 1-year primary safety and effectiveness endpoint was a hierarchical composite of death from any cause, durable implantation of a right ventricular (RV) assist device or heart transplantation, tricuspid valve surgery or percutaneous tricuspid intervention, annualized rate of hospitalization for HF, an improvement of at least 10 points in the Kansas City Cardiomyopathy Questionnaire overall summary (KCCQ-OS) score, an improvement of at least 1 New York Heart Association (NYHA) functional class, and an increase in 6-min walk distance of at least 30 m. Additional outcomes assessed at 1 year were KCCQ-OS score, NYHA class, and 6-min walk distance. To evaluate longer-term trends in safety outcomes between 1- and 2-year patient follow-up visits, Kaplan–Meier estimates for all-cause mortality and HF hospitalization were assessed up to 18 months.

Statistical analysis

Analysis was performed in the modified intent-to-treat cohort (enrolled patients who had a study procedure attempted or were randomized to medical therapy alone). The hierarchical composite outcome was tested for superiority using the Finkelstein–Schoenfeld method, and the magnitude was measured using the win ratio method.[15] The win ratio was calculated by systematically comparing all possible patient pairs, starting with the first outcome in the hierarchy, to determine wins for each trial group. In case of a tie, pairs moved to the next level in the hierarchy for comparison, with an overall win ratio calculated from the total wins for valve replacement divided by those for the control group.[16] Missing data were not imputed. Because comparisons at lower levels (e.g. KCCQ-OS score, NYHA class, and 6-min walk distance) were only made in patient pairs that tied at all higher levels, missing data at these levels affect only a subset of comparisons. To ensure fair and temporally aligned comparisons, each patient pair had a defined overlapping follow-up window, and only events within the window were considered. The 95% two-sided confidence interval (CI) was calculated by the unmatched approach. Confidence intervals are reported without adjustment for multiplicity and are not used for hypothesis testing. Continuous variables are presented as mean ± SD or median (Q1, Q3) with paired analysis using the Kruskal–Wallis test to compare baseline-to-1-year differences between groups. Statistical tests were not prespecified in the protocol, and *P*-values are shown to assist in data and clinical interpretation. Categorical variables are reported as percentages. Time-to-event variables were analysed using Kaplan–Meier survival analysis, and standard error was calculated using the Greenwood formula with the Wald *Z*-test to calculate *P*-value for intergroup comparisons at 18 months. Missing data for time-dependent outcomes were censored at the date of the last patient participation due to withdrawal or loss to follow-up. Paired analyses were limited to patients who were alive at follow-up. SAS software, version 9.4 (SAS Institute, Cary, NC, USA), was used for all statistical calculations.

Results

Out of 400 patients enrolled in the TRISCEND II trial, 392 (TTVR, $n = 259$; control, $n = 133$) were included in the analysis (eight patients exited the study before undergoing a TTVR procedure). At baseline, 172 had severe TR (TTVR, $n = 122$; control, $n = 50$) and 220 patients had massive/torrential TR (TTVR, $n = 137$; control, $n = 83$). The median (Q1, Q3) follow-up period was 2.1 years (1.7, 2.6) for the severe TR cohort and 2.1 years (1.1, 2.7) for the massive/torrential TR cohort.

Baseline characteristics

Patient demographics and comorbidities were well balanced between TTVR and control groups and between TR severity cohorts (*Table 1*). Patients with severe and massive/torrential TR, respectively, had a mean age of 80.0 and 78.6 years, 74.4% and 76.4% were female, and 69.2% and 73.6% were NYHA class III/IV, with the mean baseline KCCQ-OS scores of 53.1 and 51.2 points, and Society of Thoracic Surgeons predicted mortality scores (mitral valve replacement) of 9.8% and 9.7%. Each cohort had similar comorbidities between groups, including history of atrial fibrillation (severe TR, 96.5%; massive/

Table 1 **Baseline demographics and medical history**

	Severe TR			Massive/Torrential TR		
	TTVR (*n* = 122)	**Control (*n* = 50)**	**Total (*n* = 172)**	**TTVR (*n* = 137)**	**Control (*n* = 83)**	**Total (*n* = 220)**
Age, years	80.5 ± 6.4 (122)	78.8 ± 9.1 (50)	80.0 ± 7.3 (172)	78.2 ± 8.1 (137)	79.3 ± 7.0 (83)	78.6 ± 7.7 (220)
Female sex	70.5 (86)	84.0 (42)	74.4 (128)	78.8 (108)	72.3 (60)	76.4 (168)
Race or ethnic group, %						
American Indian or Alaskan Native	0.8 (1)	0 (0)	0.6 (1)	0.7 (1)	0 (0)	0.5 (1)
Asian	4.1 (5)	8.0 (4)	5.2 (9)	6.6 (9)	4.8 (4)	5.9 (13)
Black	1.6 (2)	6.0 (3)	2.9 (5)	7.3 (10)	2.4 (2)	5.5 (12)
Native Hawaiian or Other Pacific Islander	0 (0)	2.0 (1)	0.6 (1)	0 (0)	0 (0)	0 (0)
White	82.0 (100)	74.0 (37)	79.7 (137)	69.3 (95)	73.5 (61)	70.9 (156)
Other	4.1 (5)	6.0 (3)	4.7 (8)	5.8 (8)	8.4 (7)	6.8 (15)
Missing	7.4 (9)	4.0 (2)	6.4 (11)	10.2 (14)	10.8 (9)	10.5 (23)
STS predicted risk of mortality, %						
MV repair	6.6 ± 4.1 (122)	7.1 ± 4.5 (50)	6.8 ± 4.2 (172)	6.8 ± 5.3 (137)	6.9 ± 4.4 (83)	6.8 ± 5.0 (220)
MV replacement	9.6 ± 4.5 (122)	10.2 ± 5.8 (50)	9.8 ± 4.9 (172)	9.6 ± 5.6 (137)	9.8 ± 4.8 (83)	9.7 ± 5.3 (220)
EuroSCORE II, %	4.9 ± 3.4 (122)	5.7 ± 4.3 (50)	5.1 ± 3.7 (172)	5.9 ± 4.6 (137)	5.6 ± 4.3 (83)	5.8 ± 4.5 (220)
NYHA class III-IV	69.7 (85/122)	68.0 (34/50)	69.2 (119/172)	75.9 (104/137)	69.9 (58/83)	73.6 (162/220)
Hypertension (treated)	91.8 (112)	90.0 (45)	91.3 (157)	89.8 (123)	92.8 (77)	90.9 (200)
Renal disease	52.5 (64)	60.0 (30)	54.7 (94)	55.5 (76)	59.0 (49)	56.8 (125)
Type II diabetes	21.3 (26)	26.0 (13)	22.7 (39)	21.9 (30)	24.1 (20)	22.7 (50)
CAD ≥50% stenosis	26.2 (32)	36.0 (18)	29.1 (50)	25.5 (35)	26.5 (22)	25.9 (57)
Prior myocardial infarction	9.8 (12)	18.0 (9)	12.2 (21)	12.4 (17)	12.0 (10)	12.3 (27)
Prior stroke	16.4 (20)	14.0 (7)	15.7 (27)	13.9 (19)	6.0 (5)	10.9 (24)
Ascites	16.4 (20)	16.0 (8)	16.3 (28)	20.4 (28)	25.3 (21)	22.3 (49)
LVEF, %	55.9 ± 9.5 (122)	55.0 ± 11.8 (50)	55.7 ± 10.2 (172)	53.1 ± 10.1 (137)	53.9 ± 10.7 (83)	53.4 ± 10.3 (220)
LVEF >50%	71.3 (87)	68.0 (34)	70.3 (121)	62.8 (86)	67.5 (56)	64.5 (142)
Cardiomyopathy	11.5 (14)	16.0 (8)	12.8 (22)	14.6 (20)	14.5 (12)	14.5 (32)
Estimated PASP (mm Hg)	41.4 ± 11.4 (116)	41.2 ± 12.8 (50)	41.3 ± 11.8 (166)	36.1 ± 9.8 (133)	35.5 ± 9.6 (83)	35.9 ± 9.7 (216)
Atrial fibrillation	97.5 (119)	94.0 (47)	96.5 (166)	94.9 (130)	91.6 (76)	93.6 (206)

Continued

Table 1 *Continued*

	Severe TR			Massive/Torrential TR		
	TTVR (*n* = 122)	Control (*n* = 50)	Total (*n* = 172)	TTVR (*n* = 137)	Control (*n* = 83)	Total (*n* = 220)
Pacemaker/ICD	41.0 (50)	30.0 (15)	37.8 (65)	35.8 (49)	45.8 (38)	39.5 (87)
COPD	18.0 (22)	22.0 (11)	19.2 (33)	13.1 (18)	18.1 (15)	15.0 (33)
KCCQ-OS score, points	54.8 ± 21.3 (122)	49.2 ± 21.5 (50)	53.1 ± 21.5 (172)	51.0 ± 22.5 (136)	51.5 ± 21.4 (83)	51.2 ± 22.0 (219)
Left-sided valve surgery/intervention						
Mitral valve	21.3 (26)	14.0 (7)	19.2 (33)	25.5 (35)	21.7 (18)	24.1 (53)
Aortic valve	17.2 (21)	16.0 (8)	16.9 (29)	18.2 (25)	21.7 (18)	19.5 (43)

Values are given as mean ± standard deviation (*n*), or % (*n*).
CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire overall summary; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MV, mitral valve; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; STS, Society of Thoracic Surgeons; TR, tricuspid regurgitation.

torrential TR, 93.6%), history of pacemaker (37.8%; 39.5%), myocardial infarction (12.2%; 12.3%), and ascites (16.3%; 22.3%).

Compared with the massive/torrential TR group, patients with baseline severe TR had lower mean TR vena contracta width (severe TR, 9.1 mm vs massive/torrential TR, 12.3 mm, $P < .001$), RV size (≥ moderate enlargement: 42.6% vs 69.3%, $P < .001$), inferior vena cava diameter during expiration (22.8 mm vs 27.1 mm, $P < .001$), RV diastolic mid diameter (36.7 mm vs 41.3 mm, $P < .001$), RV end-diastolic area (25.5 cm^2 vs 30.6 cm^2, $P < .001$) and systolic area (15.7 cm^2 vs 18.4 cm^2, $P < .001$), and RV end-diastolic volume (129.3 mL vs 153.1 mL, $P = .004$) and systolic volume (69.9 mL vs 88.6 mL, $P = .005$) (*Table 2*).

Procedural outcomes

Procedural outcomes were similar between severe TR and massive/torrential TR cohorts (*Table 3*). The EVOQUE device was successfully implanted in 95.9% of severe TR patients and 94.9% of massive/torrential TR patients. The median (min, max) procedure times were 102.0 (51.0, 284.0) min for severe TR patients and 93.0 (37.0, 351.0) min for massive/torrential TR patients. Three patients required conversion to surgery for RV laceration: two in the severe TR cohort and one in the massive/torrential TR cohort. Early permanent pacemaker implantation occurred in 16.4% of TTVR patients in the severe TR cohort, comparable with 14.6% in the massive/torrential TR cohort ($P = .732$). Among patients without a pacemaker at baseline, 27.4% of severe TR patients and 22.5% of massive/torrential TR patients received new permanent pacemakers ($P = .583$). Four patients had pacemakers placed interprocedurally (one severe TR and three massive/torrential TR). Eight patients died from cardiovascular causes within the first 30 days (see Supplementary data online, *Table S1*), of whom one (massive/torrential) died within the first 7 days and three within days 8–14 (one severe and two massive/torrential).

Primary safety and effectiveness endpoint

The TRISCEND II primary safety and effectiveness endpoint at 1 year yielded a win ratio of 2.02 favouring TTVR over the control group (95% CI: 1.56, 2.62; $P < .001$), as previously reported.[13] When stratified by baseline TR severity, the win ratio consistently favoured TTVR regardless of cohort with a 1.64 win ratio for severe TR (95% CI: 1.11, 2.43) and 2.20 win ratio for massive/torrential TR (95% CI: 1.55, 3.14) (*Table 4*).

Tricuspid regurgitation reduction

At 1 year, 95.2% of TTVR patients with baseline severe TR and 95.3% with baseline massive/torrential TR achieved TR ≤mild, compared with 2.6% and 2.0%, respectively, for control patients (*Figure 1A*). A Sankey diagram shows the distribution of TR grades over time for the TTVR and control patients in a paired analysis for within-treatment group comparison. In the TTVR group, TR reduction to ≤mild was consistent and stable through 1-year follow-up compared with the control group. The control group had considerable fluctuations in TR grades from baseline to all follow-up periods within 1 year, with large proportions of patients remaining with severe and massive/torrential TR, although 13.9% of patients had improved to ≥moderate TR by 1 year (*Figure 1B*).

Clinical, functional, and quality-of-life outcomes

In paired analysis from baseline to 1 year, mean KCCQ-OS score for improved by 14.6 points for TTVR patients with severe TR [control,

Table 2 Baseline echocardiographic characteristics

TTE variable	Severe TR ($n = 172$)	Massive/torrential TR ($n = 220$)	*P*-value[a]
TR PISA EROA, cm^2	0.5 [0.5, 0.5] (171)	1.0 [0.9, 1.1] (214)	< .001
TR PISA regurgitant volume, mL	42.0 [40.1, 43.9] (171)	65.3 [61.9, 68.6] (214)	< .001
Mean TR vena contracta width, mm	9.1 [8.7, 9.6] (138)	12.3 [11.8, 12.9] (192)	< .001
RV size (≥ moderate enlargement)	42.6 (72/169)	69.3 (149/215)	< .001
RV end-diastolic mid diameter, mm	36.7 [35.6, 37.8] (167)	41.3 [40.2, 42.5] (214)	< .001
IVC diameter			
Inspiration, mm	14.4 [13.3, 15.4] (166)	18.9 [18.0, 19.9] (214)	< .001
Expiration, mm	22.8 [22.0, 23.7] (168)	27.1 [26.3, 28.0] (216)	< .001
RV end-diastolic area, cm^2	25.5 [24.5, 26.6] (153)	30.6 [29.4, 31.7] (203)	< .001
RV end-systolic area, cm^2	15.7 [15.0, 16.5] (153)	18.4 [17.6, 19.2] (204)	< .001
RV end-diastolic volume, mL	129.3 [115.1, 143.5] (47)	153.1 [142.5, 163.6] (82)	.004
RV end-systolic volume, mL	69.9 [62.3, 77.5] (47)	88.6 [80.4, 96.9] (82)	.005
TAPSE, mm	16.0 [15.4, 16.7] (158)	16.1 [15.4, 16.7] (190)	.728
RV fractional area change, %	38.5 [37.0, 39.9] (153)	40.0 [38.8, 41.1] (203)	.178
RVOT stroke volume, mL	62.2 [57.4, 67.0] (140)	58.6 [54.3, 62.9] (186)	.189
RVOT cardiac output, L/min	4.5 [4.2, 4.8] (140)	4.2 [3.8, 4.5] (186)	.027
LVOT stroke volume, mL	60.7 [57.0, 64.3] (168)	52.2 [49.8, 54.6] (216)	< .001
LVOT cardiac output, L/min	4.4 [4.1, 4.7] (168)	3.7 [3.5, 3.8] (216)	< .001

Values are given as mean [95% CI] (*n*), or % (*n*/*N*).
CI, confidence interval; EROA, effective regurgitant orifice area; IVC, inferior vena cava; LVOT, left ventricular outflow tract; PISA, proximal isovelocity surface area; RV, right ventricular; RVOT, right ventricular outflow tract; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TTE, transthoracic echocardiography.
[a]Kruskal–Wallis test.

7.4 points (95% CI: −0.1, 14.8), $P = .066$] and 22.2 points for those with massive/torrential TR [control, −0.67 points (95% CI: −7.3, 6.0), $P < .001$) (*Figure 2*). A higher proportion of TTVR patients achieved NYHA class I/II at 1 year compared with control: 88.6% vs 33.3% for severe TR and 93.5% vs 35.2% for massive/torrential TR (*Figure 3*). Additionally, TTVR patients exhibited greater increases in mean 6-min walk distance at 1 year compared with control: 10.6 m for severe TR [control, −27.2 m (95% CI: −54.1, −0.3), $P = .021$] and 35.2 m for massive/torrential TR [control, −5.4 m (95% CI: −34.8, 24.1), $P = .030$] (*Figure 4*).

All-cause mortality and heart failure hospitalization

Kaplan–Meier estimates for all-cause mortality at 18 months were similar in the severe TR cohort for TTVR (13.6 ± 3.2%) and control [13.5 ± 5.1%, estimated difference 0.2% (95% CI: −11.6, 11.9), $P = .980$]. In the massive/torrential TR cohort, TTVR had an 18-month mortality rate of 17.9 ± 3.3% compared with 23.6 ± 5.0% for control [−5.8% (−17.6, 6.0), $P = .338$] (*Figure 5A*). In an analysis landmarked at 30 days, 18-month mortality estimates were 12.9 ± 3.1% for TTVR vs 13.5 ± 5.1% for control [−0.6% (−12.3, 11.2), $P = .925$] in the severe TR cohort and 12.7 ± 3.0% for TTVR vs 23.6 ± 5.0% for control [−10.9% (−22.4, 0.5), $P = .061$] in the massive/torrential TR cohort (*Figure 5B*).

At 18 months, the Kaplan–Meier estimated rate for HF hospitalization was lower for TTVR compared with control in the massive/torrential TR cohort [TTVR, 23.6 ± 3.9% vs control, 38.8 ± 5.8%, estimated difference −15.2% (95% CI: −28.9, −1.5), $P = .030$; number needed to treat (NNT), 6.6], whereas HF hospitalization was lower for control in the severe TR cohort [TTVR 23.6 ± 4.0% vs control 13.7 ± 5.2%; difference 9.8% (−3.0, 22.7), $P = .134$] (*Figure 5C*). There were similar trends in the composite event rate of HF hospitalization or all-cause mortality at 18 months [massive/torrential TR: TTVR 34.2 ± 4.1% vs control 48.4 ± 5.8%; difference −14.2% (−28.0, −0.3), $P = .045$; NNT 7.1; severe TR: TTVR 30.4 ± 4.2% vs control 24.4 ± 6.4%; difference 6.0% (−9.1, 21.0), $P = .438$] (*Figure 5D*) and when crossover patients were censored (see Supplementary data online, *Figure S1*). Timing of crossovers is shown in Supplementary data online, *Figure S2*.

Discussion

In this analysis of the TRISCEND II pivotal trial, we assessed whether baseline TR severity influenced clinical outcomes following TTVR. The main findings are summarized as follows: (i) TTVR was associated with a favourable win ratio for the primary composite endpoint, regardless of baseline TR severity, and the magnitude of benefit was greater in patients with massive/torrential disease. (ii) In both TTVR cohorts, TR severity, KCCQ-OS scores, and symptoms improved compared with

Table 3 Procedural outcomes

	Severe TR (*n* = 122)	Massive/Torrential TR (*n* = 137)
General anaesthesia	100.0 (122/122)	100.0 (137/137)
Study device implanted	95.9 (117/122)	94.9 (130/137)
Total procedure time, min[a]	102.0 (51.0, 284.0)	93.0 (37.0, 351.0)
Device time, min[b]	57.5 (1.0, 189.0)	54.5 (1.0, 173.0)
Fluoroscopy duration, min	27.1 (11.8, 72.0)	26.5 (1.2, 74.1)
Conversion to surgery	1.6 (2/122)	0.7 (1/137)
Signs of valve embolization	0 (0/122)	0 (0/137)
Paravalvular leak		
Absent	70.0 (84/120)	70.6 (96/136)
Present, not clinically significant	28.3 (34/120)	27.9 (38/136)
Present, clinically significant	1.7 (2/120)	1.5 (2/136)
Closure required	0 (0/122)	0 (0/137)
Device-related valve malfunction[c]	0 (0/122)	1.5 (2/137)
Device-related valve thrombosis[c]	2.5 (3/122)	0 (0/137)

Values are given as% (*n*/*N*), or median (min, max).
[a]Procedure time is the time from first skin incision to last skin closure if the subject has multiple veins attempted.
[b]Device time is the time from delivery system insertion to delivery system removal.
[c]Site-reported adverse event occurring within 7 days after procedure.

respective control cohorts. The magnitude of improvement was consistently greater in patients with baseline massive/torrential disease. (iii) Compared with control patients, TTVR patients with massive/torrential TR had lower rates of HF hospitalization and combined all-cause mortality and first HF hospitalization, with an NNT of 6.6 and 7.1 at 18 months, respectively (*Structured Graphical Abstract*).

The TRISCEND II pivotal trial evaluated the efficacy and safety of a dedicated TTVR device, the EVOQUE system, in combination with medical therapy, compared with medical therapy alone for the treatment of symptomatic patients with at least severe TR. The primary endpoint was a hierarchical composite, tested using the Finkelstein–Schoenfeld method with the magnitude measured using a win ratio approach, and included all-cause mortality, durable implantation of a RV assist device or heart transplantation, subsequent tricuspid valve intervention, hospitalization for HF, and clinically meaningful improvements in symptoms and functional status. Although the trial met its primary endpoint, no differences were observed for individual components such as all-cause mortality or HF hospitalization.[13] While the study was not powered to detect differences in the individual components, exploratory subgroup analyses suggested that treatment benefit varied according to baseline TR severity, supporting the rationale for the present analysis.

The emergence of transcatheter tricuspid interventions necessitated a more granular classification of TR severity, subdividing what was previously categorized as 'severe' into the distinct grades of severe, massive, and torrential.[4] Subsequent studies have consistently demonstrated that increasing TR severity is associated with higher rates of adverse clinical events.[3,17–19] Conversely, several studies, both retrospective and prospective, reported on a dose response of the extent of TR reduction with symptomatic improvements.[20–23] In the TRILUMINATE pivotal study of patients treated with T-TEER, every 1-grade improvement in TR was associated with a 4.1-point increase in the KCCQ-OS score (95% CI: 1.8–6.5).[20] Two large retrospective registries have similarly shown more favourable outcomes in patients achieving a post-procedural TR grade of moderate or less following T-TEER.[21,22] However, these studies evaluated TEER-based therapies, which result in variable degrees of TR reduction, with only a subset of patients achieving mild or trace TR.[11] In contrast, TTVR with the EVOQUE system reliably reduces TR to mild or trace levels in nearly all treated patients.[13] Thus, while the therapeutic benefit of T-TEER depends on both baseline TR severity and the degree of procedural success, in TTVR, the degree of TR reduction is mostly uniform, making baseline severity the principal determinant of clinical outcomes.

In line with this, we observed an interaction between the baseline severity and the treatment allocation to TTVR, where patients with massive/torrential TR had lower rates of HF hospitalization and a trend for the composite rate of all-cause mortality or HF hospitalization as compared to controls (*Figure 5B*). Several mechanisms may underlie this observation. Patients with massive or torrential TR grade typically have a higher baseline risk and may therefore derive more measurable benefit, even when only a subset of the population responds favourably.[24] This concept is reinforced by the fact that patients with massive/torrential TR in the control arm had by far the highest HF hospitalization rates, while TTVR patients in both cohorts had comparable hospitalization rates at 18 months, abolishing the relationship of TR severity and outcomes (*Figure 5*). The higher baseline risk of patients with massive/torrential TR was evident in the concentration of adverse events within the first 30 days after the intervention. In the TTVR group, early cardiovascular mortality was 5.1% among patients with massive/torrential TR, compared with 0.8% in patients with severe TR. Notably, in both TR

Table 4 Primary safety and effectiveness endpoint at 1 year stratified by baseline tricuspid regurgitation severity

Win ratio analysis	Severe TR (6100 patient pairs)		Massive/Torrential TR (11 371 patient pairs)	
	TTVR ($n = 122$)	Control ($n = 50$)	TTVR ($n = 137$)	Control ($n = 83$)
Wins per treatment arm, % (patient pairs)				
All-cause mortality[a] Site reported + vital sweep	5.5% (333)	9.7% (592)	20.0% (2278)	15.1% (1712)
RVAD or heart transplant[a] CEC adjudicated	0 (0)	0 (0)	0 (0)	0 (0)
TV intervention[a] CEC adjudicated	1.8% (108)	0.7% (44)	4.0% (450)	0.6% (66)
Annualized rate of HF hospitalization[a] CEC adjudicated	7.4% (451)	13.6% (828)	10.7% (1221)	7.9% (896)
KCCQ-OS score improvement Δ Score ≥ 10 points	25.8% (1572)	8.8% (535)	21.3% (2426)	4.2% (483)
NYHA class improvement Δ ≥ 1 class	15.3% (932)	1.2% (75)	7.3% (825)	0.6% (66)
6MWD improvement Δ ≥ 30 m	1.7% (101)	0.9% (52)	0.8% (94)	0.8% (90)
Total wins	57.3% (3497)	34.9% (2126)	64.1% (7294)	29.1% (3313)
Win ratio	1.64		2.20	
95% Confidence interval	1.11, 2.43		1.55, 3.14	
Finkelstein–Schoenfeld	$P = .008$		$P < .001$	

6MWD, 6-min walk distance; CEC, Clinical Events Committee; HF, heart failure, KCCQ-OS, Kansas City Cardiomyopathy Questionnaire overall summary; NYHA, New York Heart Association; RVAD, right ventricular assist device; TR, tricuspid regurgitation; TTVR, transcatheter tricuspid valve replacement; TV, tricuspid valve.
[a]Included in the control group are 22 patients who crossed over to receive TTVR within the 1-year visit window (320 to 410 days) after completing their 1-year visit.

severity groups, the control group had no early cardiovascular deaths (see Supplementary data online, *Table S1*). Interestingly, the treatment benefit seems to be large enough in massive/torrential TR patients to make up for potential procedural risks. Kaplan–Meier curves start to separate early for HF hospitalization. A landmark analysis, which excludes the initial peri-interventional risk, indicates a potential signal for all-cause mortality with a *P*-value of .061. Despite similar demographics and medical history, massive/torrential TR patients exhibited more pronounced RV dilatation and reduced global contractility, indicating susceptibility to early adverse events and potential for long-term haemodynamic benefits. In addition, these patients might be further susceptible to changes in longitudinal function of the RV which might occur following TTVR.[25] Conversely, given that most of the included patients had a preserved left ventricular (LV) ejection fraction (*Table 1*), RV dilatation might have led those patients to develop adverse RV-to-LV interaction in line with a specific TR-HFpEF phenotype.[26] Abolishing RV overload, which has been observed following treatment with EVOQUE,[12] might restore RV-to-LV interaction, explaining improvement of symptoms but also favourable long-term outcomes which are especially reflected by a reduction in HF hospitalizations.[26,27]

Additionally, baseline KCCQ-OS scores in both cohorts were similarly poor, akin to those observed in left-sided valve diseases. However, the improvements observed at 1 year were more pronounced than those reported in other structural interventional trials.[20,28] This is further supported by the improvements in 6-min walk distance at 1 year in both cohorts.

In patients with severe TR, the treatment effect of TTVR was less pronounced compared with patients with massive/torrential TR. Kaplan–Meier curves suggested no difference in all-cause mortality between TTVR compared with medical therapy. In this cohort, there were numerical differences in HF hospitalization and the combined endpoint of all-cause mortality and HF hospitalization. In addition, there was a numerically greater KCCQ-OS improvement for TTVR patients with baseline severe TR compared with controls. Patient selection may have contributed to these observations. Among patients with baseline severe TR in the control group, 26.3% showed improvement to mild or moderate TR at 1-year follow-up, compared with only 8.1% of those with baseline massive/torrential TR. There may be multiple explanations for this regression. This pattern may represent the statistical phenomenon of regression to the mean, where patients may appear to improve over time, and may have contributed to favourable HF hospitalization outcomes in control patients in the severe TR cohort. Similar findings have been reported in other conditions. For example, in the COAPT trial, which randomized patients with severe mitral regurgitation to transcatheter edge-to-edge repair or medical therapy, ~45% of the control group had a mitral regurgitation grade of 1+ to 2+ at 1-year follow-up.[29] The finding may, however, represent true regression of TR with medical therapy, or inclusion of patients with early disease stage, in which the effects of transcatheter intervention might be less

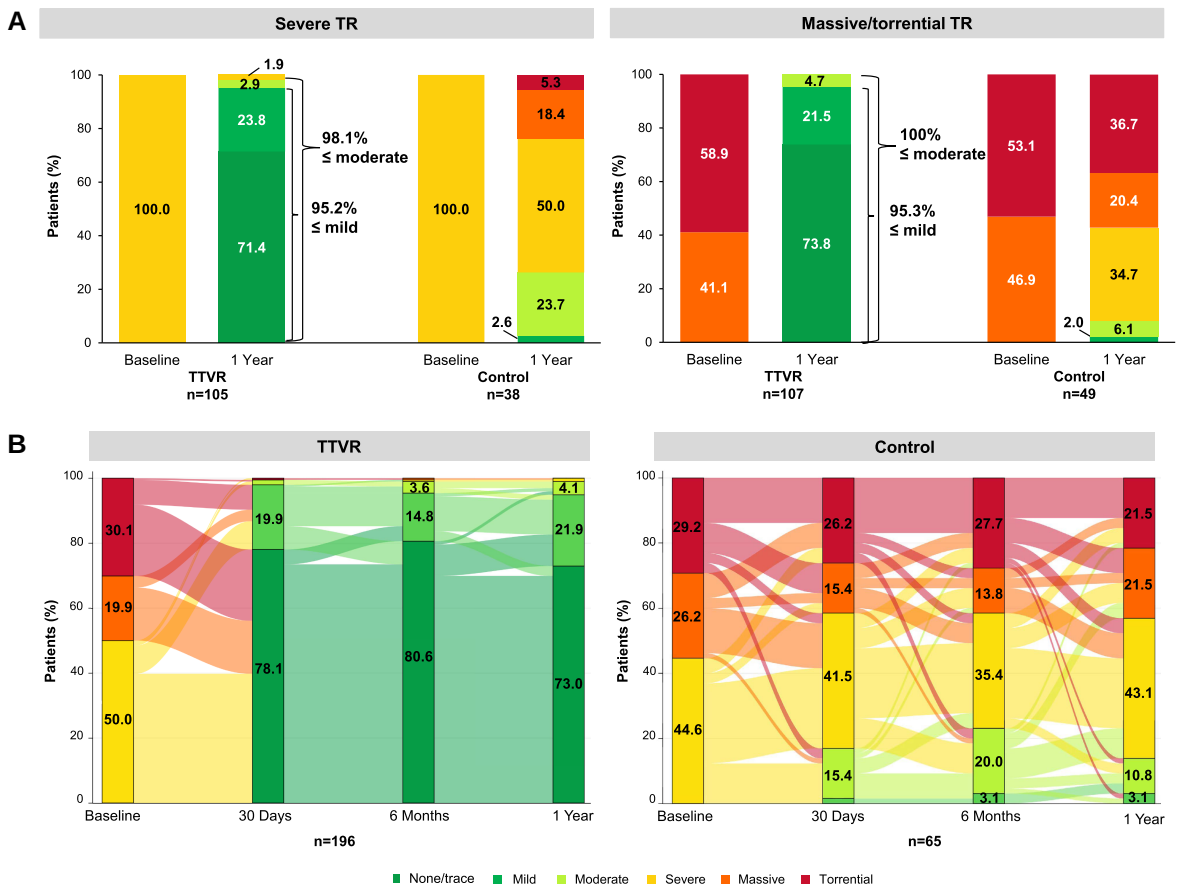

Figure 1 Changes in tricuspid regurgitation severity. (*A*) Tricuspid regurgitation at 1 year stratified by baseline tricuspid regurgitation severity. (*B*) The Sankey diagram illustrates the changes in tricuspid regurgitation severity in patients over time for transcatheter tricuspid valve replacement and control groups. The width of each band indicates the proportion of patients moving between tricuspid regurgitation grades. Echocardiographic core lab: Baylor Scott and White Research Institute Cardiac Imaging Core Laboratory, Plano, TX, USA. Graphs show paired analysis. TR, tricuspid regurgitation; TTVR, transcatheter tricuspid valve replacement

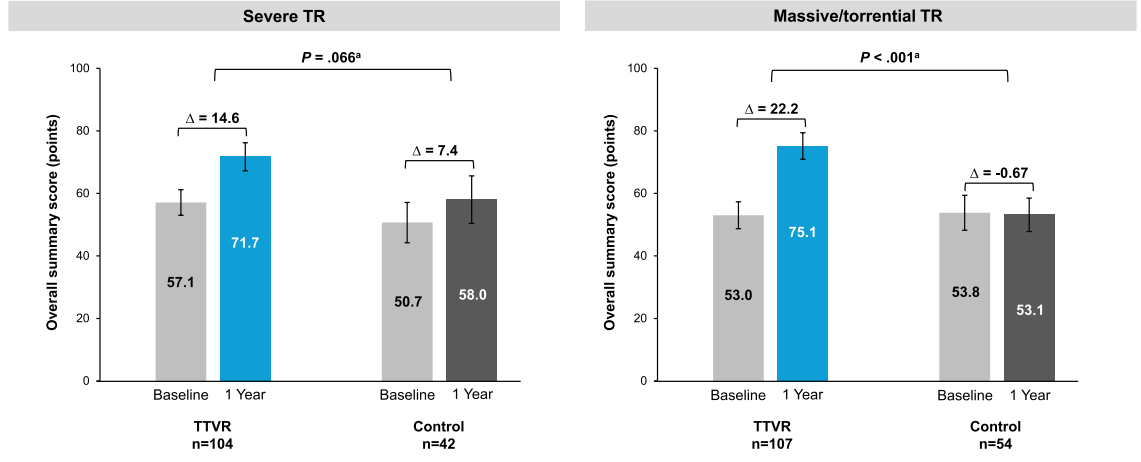

Figure 2 Kansas City Cardiomyopathy Questionnaire overall summary score at baseline and 1 year stratified by baseline TR severity. Graphs show paired analysis of mean scores, and error bars indicate 95% confidence interval. KCCQ-OS, Kansas City Cardiomyopathy Questionnaire overall summary; TR, tricuspid regurgitation; TTVR, transcatheter tricuspid valve replacement. [a]Kruskal–Wallis test

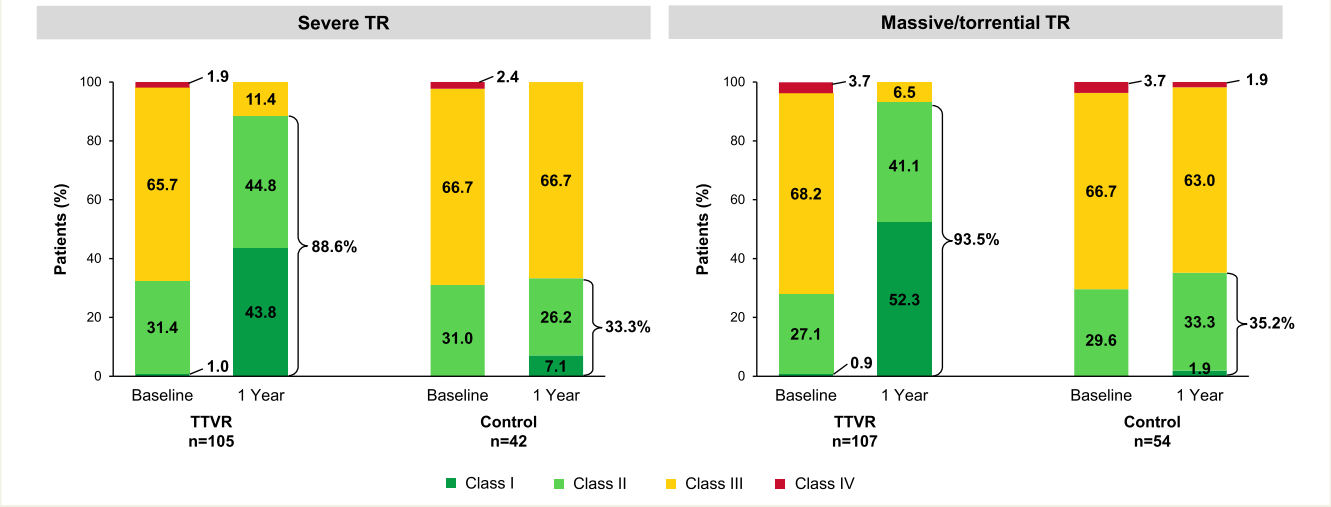

Figure 3 New York Heart Association functional class at baseline and 1 year stratified by baseline tricuspid regurgitation severity. Graphs show paired analysis. NYHA, New York Heart Association; TR, tricuspid regurgitation; TTVR, transcatheter tricuspid valve replacement

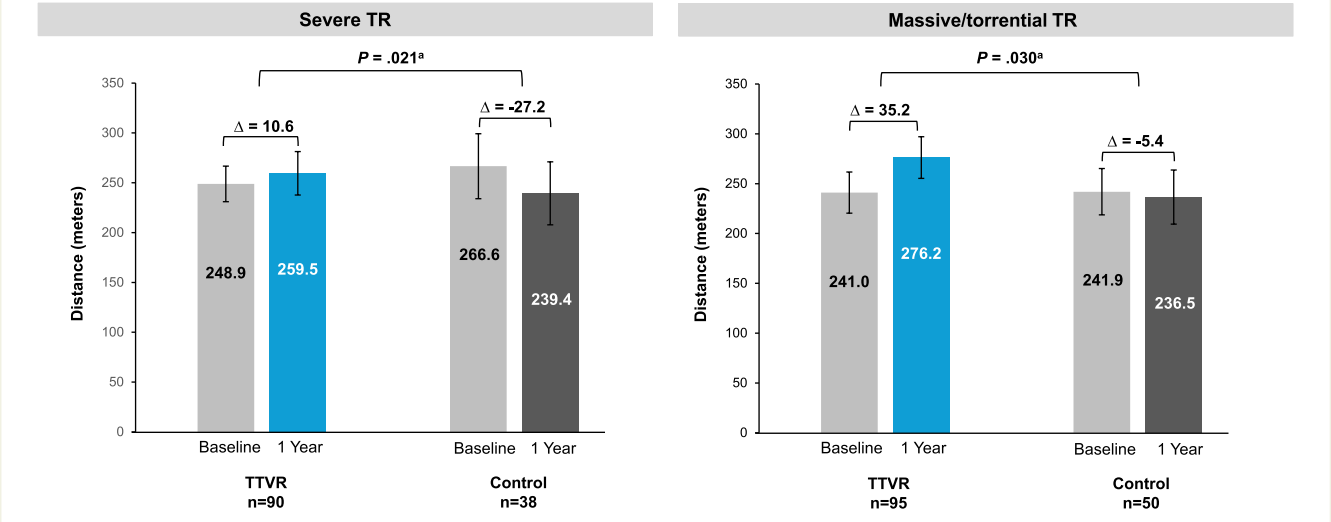

Figure 4 Six-minute walk distance at baseline and 1 year stratified by baseline tricuspid regurgitation severity. Graphs show paired analysis of mean scores, and error bars indicate 95% confidence interval. TR, tricuspid regurgitation; *TTVR*, transcatheter tricuspid valve replacement. [a]Kruskal–Wallis test

pronounced when compared with controls. In these cases, TR severity may not be the primary factor explaining symptoms and prognosis. Additionally, given the dynamic nature of TR, TR severity could regress to lower grades in a substantial number of patients.[24,30,31] Nonetheless, the 14.6-point increase in KCCQ-OS score with TTVR in the baseline severe TR patients is potentially associated with up to three-grade reduction in TR and is a clinically important improvement (*Figures 1* and *2*). Therefore, confirming the diagnosis of TR after optimization of medical therapies at multiple timepoints is crucial to identify optimal candidates for treatment of TR.

Limitations

The present analysis has several limitations. First, the 2:1 randomization ratio resulted in a smaller control group, which was further diminished by disproportionate withdrawal, missing follow-up data, and crossover to TTVR. These limitations, which were already evident in the main analysis,[13] were further amplified in this post hoc subgroup analysis and may have reduced statistical power. Thus, this analysis lacks statistical power to definitively assess significance of individual endpoints by baseline TR severity, so the results should be interpreted as hypothesis generating. This highlights the need for cautious interpretation of the magnitude and timing of benefit, particularly beyond 12 months. The true extent of the effect is difficult to assess in absence of a sham controlled trial. Crossover was permitted after the 1-year follow-up and may have introduced survival bias, complicating the interpretation of longer-term outcomes. Even with crossover, longer follow-up may be necessary to demonstrate further treatment benefits, as observed in the TRILUMINATE pivotal study at 2-year follow-up.[27]

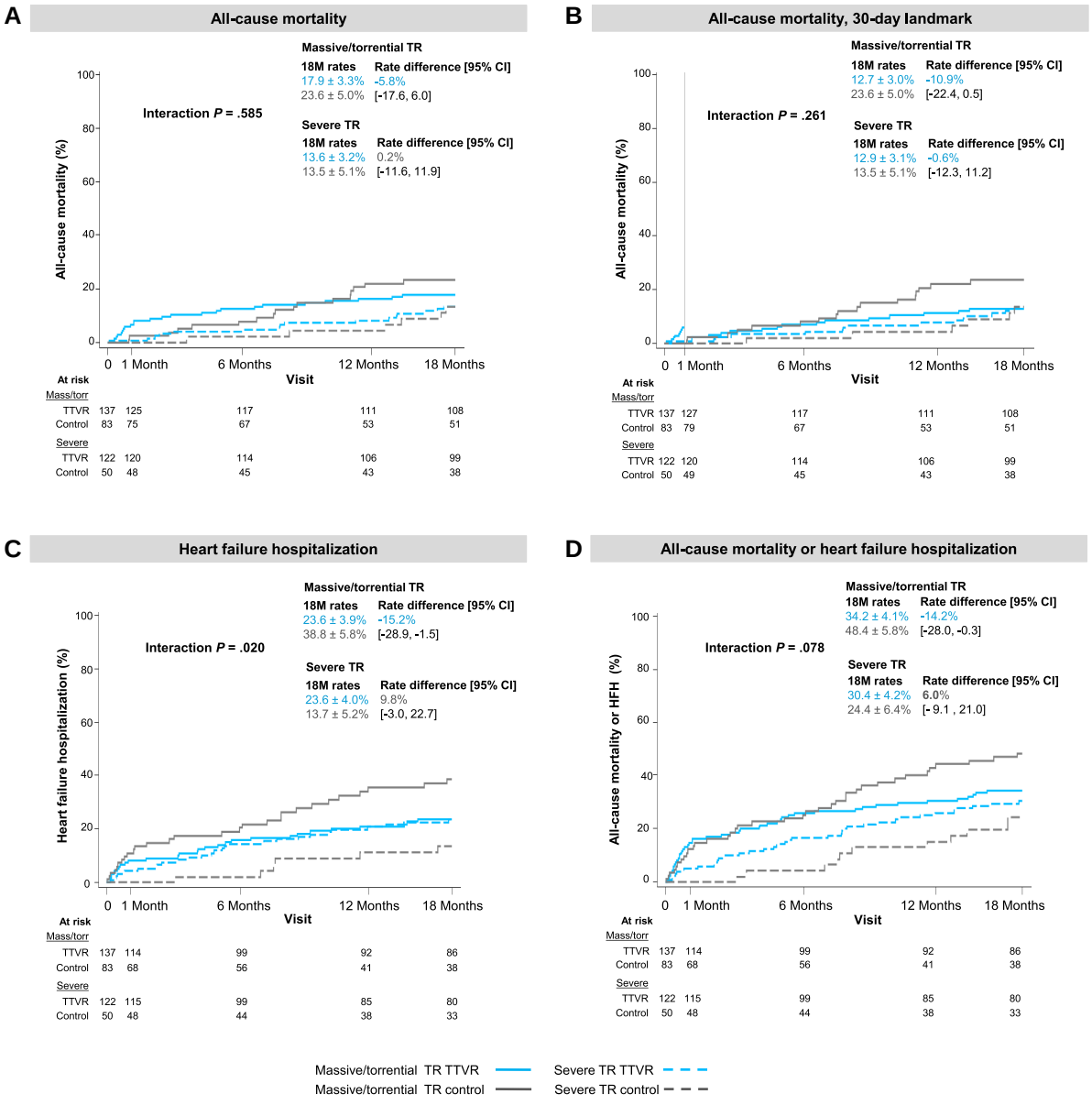

Figure 5 Kaplan–Meier estimates of clinical events committee-adjudicated clinical events at 18 months stratified by baseline tricuspid regurgitation severity. Kaplan–Meier estimates are mean ± standard error to 18 months. The curves show time-to-first events. Estimated differences between the transcatheter tricuspid valve replacement and control groups were assessed using the 95% confidence intervals, and Cox regression was used to test for interactions between baseline tricuspid regurgitation severity and treatment group. Analyses are performed in modified intent-to-treat safety population (patients with procedure attempted or treated with medical therapy). Included in the control group are 53 patients (22 severe tricuspid regurgitation, 31 massive/torrential tricuspid regurgitation) who crossed over to receive transcatheter tricuspid valve replacement after completing their 1-year visit. HFH, heart failure hospitalization; TTVR, transcatheter tricuspid valve replacement

In addition, the study population likely reflects an earlier disease stage, as indicated by the relatively low proportion of patients in NYHA class III or IV at baseline. This distribution differs from real-world registries but is consistent with prior randomized trials in this field.[11,22]

Conclusions

In patients with symptomatic TR, TTVR combined with medical therapy was superior to medical therapy alone with respect to the hierarchical composite outcome, regardless of whether patients had severe or massive/torrential TR at baseline. Both severity subgroups achieved substantial and durable reductions in TR severity, alongside improvements in functional capacity and quality of life. Patients with massive/torrential TR appeared to derive greater clinical benefit, particularly with signals of reduced HF hospitalization, despite a higher early procedural risk.

Identifying patients who benefit from this therapy will be essential to guide patient selection and to optimize benefit–risk trade-offs. These findings support a phenotype-guided, individualized treatment strategy and highlight the need to consider a patient's baseline characteristics.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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Data Availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Ethical Approval

The TRISCEND II trial was approved by Institutional Review Boards of all participating sites, and all patients provided written informed consent. Study oversight included a central screening committee, a data safety monitoring board, an independent clinical events committee, and an independent echocardiographic core laboratory.

Pre-registered Clinical Trial Number

ClinicalTrials.gov/NCT04482062

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Supplementary Material

Clinical outcomes of transcatheter tricuspid valve replacement stratified by baseline tricuspid regurgitation severity from the TRISCEND II Trial

By Philipp Lurz, et al.

Supplementary Table 1. CEC-adjudicated safety events stratified by baseline TR severity

A. Early events from 0 to 30 days

CEC-adjudicated safety event	Early events (≤ 30 days)[a]					
	TTVR			Control		
	Severe TR N=122 % (n)	Mass/torr TR N=137 % (n)	*P*-value[b]	Severe TR N=50 % (n)	Mass/torr TR N=83 % (n)	*P*-value[b]
Cardiovascular mortality	0.8 (1)	5.1 (7)	.070	0.0 (0)	0.0 (0)	1.000
Myocardial infarction	1.6 (2)	0.0 (0)	.221	0.0 (0)	0.0 (0)	1.000
Stroke	0.0 (0)	0.7 (1)	1.000	0.0 (0)	0.0 (0)	1.000
Severe bleeding[c]	7.4 (9)	13.1 (18)	.156	0.0 (0)	2.4 (2)	.527
Nonelective TV reintervention	0.8 (1)	0.7 (1)	1.000	0.0 (0)	1.2 (1)	1.000
Arrhythmia and conduction disorder requiring permanent pacing	17.2 (21)	14.6 (20)	.611	0.0 (0)	0.0 (0)	1.000
New pacemaker/CIED implantation[d]						
Implants in all patients	16.4 (20)	14.6 (20)	.732	0.0 (0)	0.0 (0)	1.000
Implants in pacemaker-naïve patients	27.4 (20/73)	22.5 (20/89)	.583	0.0 (0/35)	0.0 (0/45)	1.000

[a]Denominator counts patients from day 0 (procedure for TTVR, randomization for control).
[b]*P*-values calculated by Fisher's Exact test.
[c]Severe bleeding of major, extensive, life-threatening, or fatal as defined by the Mitral Valve Academic Research Consortium.
[d]Implantation may occur at a later time period than event.
CEC, clinical events committee; *CIED,* cardiac implantable electronic device; *TR,* tricuspid regurgitation; *TTVR*, transcatheter tricuspid valve replacement; *TV*, tricuspid valve

B. Late events from 31 to 365 days

CEC-adjudicated safety event	Late events (31 to 365 days)[a]					
	TTVR			Control		
	Severe TR N=120 % (n)	Mass/torr TR N=127 % (n)	*P*-value[b]	Severe TR N=49 % (n)	Mass/torr TR N=79 % (n)	*P*-value[b]
Cardiovascular mortality	1.7 (2)	9.4 (12)	.011	2.0 (1)	11.4 (9)	.088
Myocardial infarction	0.8 (1)	1.6 (2)	1.000	0.0 (0)	1.3 (1)	1.000
Stroke	1.7 (2)	0.8 (1)	.613	0.0 (0)	0.0 (0)	1.000
Severe bleeding[c]	6.7 (8)	3.9 (5)	.401	4.1 (2)	5.1 (4)	1.000
Nonelective TV reintervention	0.0 (0)	0.0 (0)	1.000	0.0 (0)	3.8 (3)	.286
Arrhythmia and conduction disorder requiring permanent pacing	2.5 (3)	1.6 (2)	.676	4.1 (2)	1.3 (1)	.558
New pacemaker/CIED implantation[d]						
Implants in all patients	3.3 (4)	0.8 (1)	.202	4.1 (2)	1.3 (1)	.558
Implants in pacemaker-naïve patients	7.7 (4/52)[e]	1.5 (1/66)[e]	.168	5.7 (2/35)[e]	2.4 (1/41)[e]	.592

[a]Patients must have at least 31 days in the study to count in the denominator.
[b]*P*-values calculated by Fisher's Exact test.
[c]Severe bleeding of major, extensive, life-threatening, or fatal as defined by the Mitral Valve Academic Research Consortium.
[d]Implantation may occur at a later time period than event.
[e]Patients who had a pacemaker implanted in the first 30 days are excluded.
CEC, clinical events committee; *CIED,* cardiac implantable electronic device; *TR,* tricuspid regurgitation; *TTVR*, transcatheter tricuspid valve replacement; *TV*, tricuspid valve

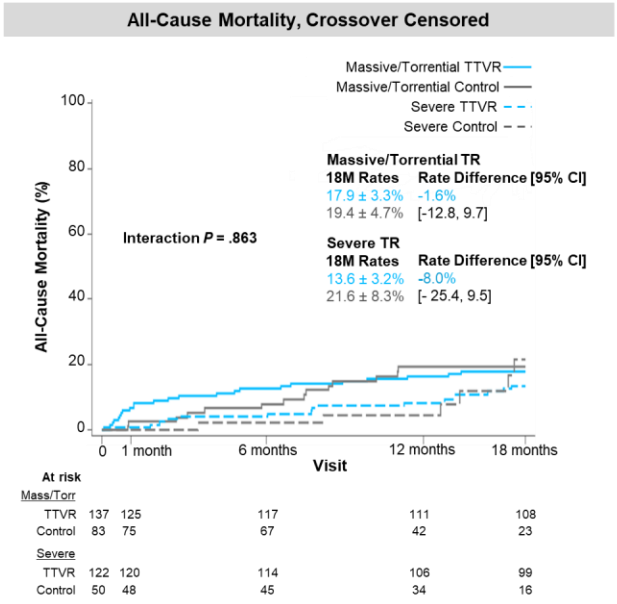
C. Cumulative events from 0 to 365 days

CEC-adjudicated safety event	Cumulative events (0 to 365 days)[a]					
	TTVR			Control		
	Severe TR N=122 % (n)	Mass/torr TR N=137 % (n)	*P*-value[b]	Severe TR N=50 % (n)	Mass/torr TR N=83 % (n)	*P*-value[b]
Cardiovascular mortality	2.5 (3)	13.9 (19)	.001	2.0 (1)	10.8 (9)	.089
Myocardial infarction	2.5 (3)	1.5 (2)	.669	0.0 (0)	1.2 (1)	1.000
Stroke	1.6 (2)	1.5 (2)	1.000	0.0 (0)	0.0 (0)	1.000
Severe bleeding[c]	13.9 (17)	16.8 (23)	.606	4.0 (2)	6.0 (5)	.711
Nonelective TV reintervention	0.8 (1)	0.7 (1)	1.000	0.0 (0)	4.8 (4)	.297
Arrhythmia and conduction disorder requiring permanent pacing	19.7 (24)	16.1 (22)	.516	4.0 (2)	1.2 (1)	.556
New pacemaker/CIED implantation[d]						
Implants in all patients	19.7 (24)	15.3 (21)	.413	4.0 (2)	1.2 (1)	.556
Implants in pacemaker-naïve patients	32.9 (24/73)	23.6 (21/89)	.219	5.7 (2/35)	2.2 (1/45)	.578

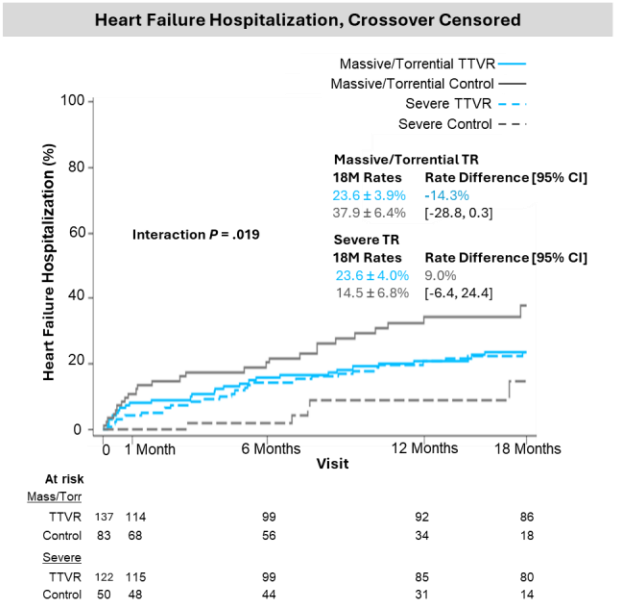
[a]Denominator counts patients from day 0 (procedure for TTVR, randomization for control).
[b]*P*-values calculated by Fisher's Exact test
[c]Severe bleeding of major, extensive, life-threatening, or fatal as defined by the Mitral Valve Academic Research Consortium.
[d]Implantation may occur at a later time period than event.
CEC, clinical events committee; *CIED,* cardiac implantable electronic device; *TR,* tricuspid regurgitation; *TTVR*, transcatheter tricuspid valve replacement; *TV*, tricuspid valve

Supplementary Figure 1. Kaplan-Meier estimates CEC-adjudicated clinical events at 18 months stratified by baseline TR severity with crossovers censored. Kaplan-Meier estimates are presented as mean ± standard error up to 18 months. The curves illustrate the time to first events. Estimated differences between the TTVR and control groups were assessed using the 95% confidence intervals, and Cox regression was used to test for interactions between baseline TR severity and treatment group. Analyses are performed in modified intent-to-treat safety population (patients with procedure attempted or treated with medical therapy). *HFH*, heart failure hospitalization; *TR*, tricuspid regurgitation; *TTVR*, transcatheter tricuspid valve replacement

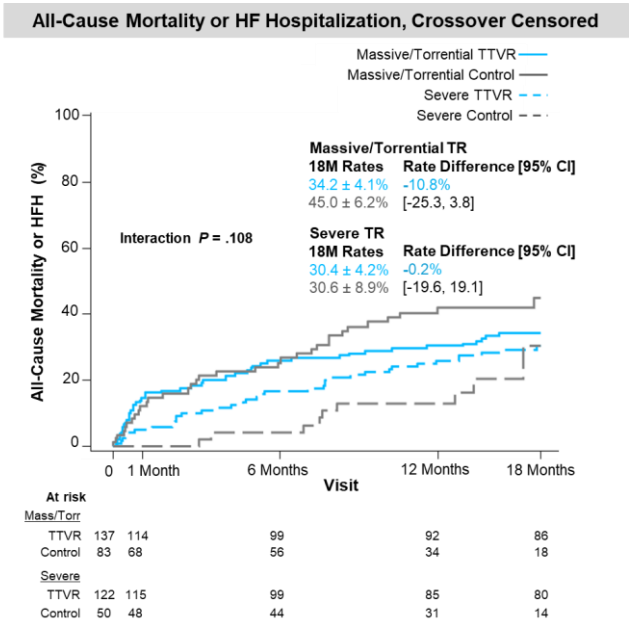
A. All-cause mortality



B. Heart failure hospitalization



C. All-cause mortality or heart failure hospitalization



Supplementary Figure 2. Timing of Crossovers. Patients were eligible for crossover to TTVR after their 1-year visits (visit window: 320-410 days). By 18 months (day 540), 53 control patients crossed over: 22 with baseline severe TR and 31 with baseline massive/torrential TR. Twenty-two patients (9 severe TR, 13 massive/torrential TR) crossed over after 1-year visits but within the visit window and were included in the win ratio calculations.