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ORIGINAL INVESTIGATIONS

Transcatheter Edge-to-Edge Repair for Treatment of Tricuspid Regurgitation

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ABSTRACT

BACKGROUND Tricuspid regurgitation (TR) is a frequent disease with a progressive increase in mortality as disease severity increases. Transcatheter therapies for treatment of TR may offer a safe and effective alternative to surgery in this high-risk population.

OBJECTIVES The purpose of this report was to study the 1-year outcomes with the TriClip transcatheter tricuspid valve repair system, including repair durability, clinical benefit and safety.

METHODS The TRILUMINATE trial (n = 85) is an international, prospective, single arm, multicenter study investigating safety and performance of the TriClip Tricuspid Valve Repair System in patients with moderate or greater TR. Echocardiographic assessment was performed by a core laboratory.

RESULTS At 1 year, TR was reduced to moderate or less in 71% of subjects compared with 8% at baseline ($p < 0.0001$). Patients experienced significant clinical improvements in New York Heart Association (NYHA) functional class I/II (31% to 83%, $p < 0.0001$), 6-minute walk test (272.3 ± 15.6 to 303.2 ± 15.6 meters, $p = 0.0023$) and Kansas City Cardiomyopathy Questionnaire (KCCQ) score (improvement of 20 ± 2.61 points, $p < 0.0001$). Significant reverse right ventricular remodeling was observed in terms of size and function. The overall major adverse event rate and all-cause mortality were both 7.1% at 1 year.

CONCLUSION Transcatheter tricuspid valve repair using the TriClip device was found to be safe and effective in patients with moderate or greater TR. The repair itself was durable at reducing TR at 1 year and was associated with a sustained and marked clinical benefit with low mortality after 1 year in a fragile population that was at high surgical risk. (TRILUMINATE Study With Abbott Transcatheter Clip Repair System in Patients With Moderate or Greater TR; NCT03227757) (J Am Coll Cardiol 2021;77:229–39) © 2021 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

6MWD = 6-min walk distance

KCCQ = Kansas City Cardiomyopathy Questionnaire

MAE = major adverse event

NYHA = New York Heart Association

SLDA = single leaflet device attachment

TR = tricuspid regurgitation

TTVR = transcatheter tricuspid valve repair

There is growing awareness of tricuspid regurgitation (TR) as a relevant and increasing public health concern. Recent evidence reveals that TR is not just a surrogate for more advanced cardiac disease in general, but a disease entity with independent prognostic implications (1–3). Irrespective of left ventricular function and pulmonary hypertension, TR is associated with increased morbidity and mortality, partly due to the development of right heart failure (4,5).

Due to unsatisfactory results of isolated tricuspid valve surgery with a peri-operative mortality rate of 8% to 10% (6,7), surgical treatment is often withheld from patients, leading to an increasingly underserved population of patients with relevant TR.

Recently, various minimally invasive transcatheter-based techniques for reducing TR have been applied (8–12). Although initially promising, most transcatheter tricuspid valve repair (TTVR) approaches are still in development and robust acute or longer follow-up data are lacking.

At present, the most widely applied technique is edge-to-edge repair of the tricuspid valve (13). Retrospective analyses suggest that edge-to-edge repair reduces TR and improves symptoms (14,15).

The TRILUMINATE trial evaluated the safety and performance of a TTVR system (TriClip [Abbott, Chicago, Illinois]), for the treatment of patients with symptomatic moderate or greater TR who were deemed to be at high risk for tricuspid valve surgery with valve anatomies that were considered appropriate for transcatheter edge-to-edge repair. Both the primary safety (composite of major adverse events at 6 months) and performance (TR reduction at 30 days) endpoints were successfully met and have been reported previously (16).

While these relatively short-term outcomes are promising, longer-term performance remains to be seen. We now report on the 1-year follow-up results assessing the durability of TR reduction, clinical benefits during follow-up and explore the implications for right heart structural and functional remodeling.

METHODS

STUDY DESIGN AND PATIENT COHORT. The TRILUMINATE trial is a prospective, single-arm, multicenter study evaluating the TriClip TTVR system. This study was conducted at 21 sites in Europe and the United States. An eligibility committee comprised of interventional cardiologists, cardiovascular surgeons, heart failure specialists, and echocardiographers evaluated each subject for enrollment according to the pre-specified inclusion and exclusion criteria (16). Briefly, symptomatic patients at high surgical risk with moderate or greater TR (by transthoracic and transesophageal echocardiography) and no indications for left-sided or pulmonary valve correction were included in this study. Patients with severe pulmonary artery pressure (>60 mm Hg, estimated by echocardiography), previous tricuspid valve procedures or coaptation gaps >10 mm were excluded from this study. This study complies with the Declaration of Helsinki and was approved by local ethics committees and the respective health authorities of the participating countries. All patients provided written informed consent. The study is registered in ClinicalTrials.gov (NCT03227757).

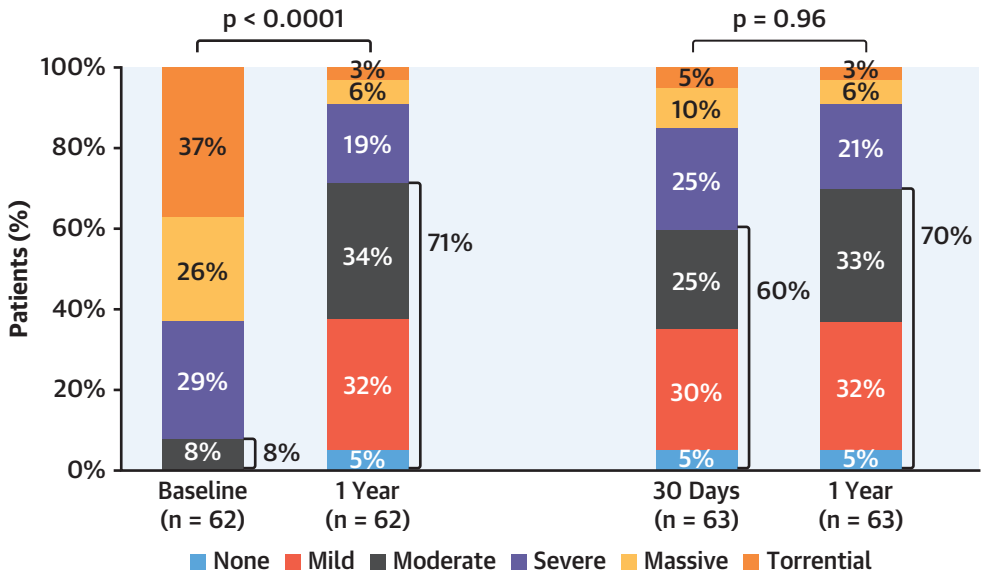
ECHOCARDIOGRAPHIC ASSESSMENT. All echocardiograms were analyzed by an independent core laboratory that followed the American Society of Echocardiography standards for echocardiography core laboratories (17). Tricuspid regurgitation was assessed using standard 2D color Doppler methods and graded using a pre-specified 5-class grading scheme: mild, moderate, severe, massive, and torrential (18). This expanded grading scheme was used to capture changes in tricuspid regurgitation even when moderate tricuspid regurgitation or less was not achieved. A number of parameters including vena contracta width, effective regurgitant orifice area and regurgitant volume were also measured. Single leaflet device attachment (SLDA) and tricuspid valve gradient were also assessed by the echocardiography core laboratory.

SEE PAGE 240

CLINICAL OUTCOMES. All major adverse events (MAE) including cardiovascular mortality, myocardial infarction, stroke, new onset renal failure, endocarditis requiring surgery, and nonelective cardiovascular surgery for tricuspid valve repair system-related adverse events were adjudicated by an independent events committee. Additional safety endpoints (major bleeding, new onset liver failure etc.) and hospitalizations were assessed at each site according to definitions provided in the clinical investigation plan. Clinical status was assessed using New York Heart Association (NYHA) functional class, Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ) and six-min walk distance (6MWD).

STATISTICAL ANALYSIS. All analyses were performed in the primary analysis population, which was

FIGURE 1 Comparison of TR Severity at Baseline, 30 Days, and 1 Year



At 1 year, TR severity was significantly reduced showing a sustained TR reduction of ≥ 1 grade in 87% of subjects, with 70% achieving moderate or less TR. Importantly, the initial TR reduction (seen at 30 days) proved durable in a majority of patients (79%) at 1-year follow-up. **Boxed labels** indicate the percentage of subjects with moderate or less TR. The p values indicate significance from Bowker's test. TR = tricuspid regurgitation.

defined as the first 85 enrolled subjects who had an attempted procedure upon femoral vein puncture. Longitudinal data for continuous variables were analyzed using a generalized linear model with unstructured correlation to account for repeated measures. Data is presented as least-squares mean ± standard error for continuous variables. Proportions are presented for categorical variables and Bowker's or McNemar's test was used to compare paired nominal data. All statistical analyses were performed with the use of SAS software, version 9.3 or higher (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS. Baseline characteristics are summarized in Supplemental Table 1. A total of 85 subjects (66% female) with significant comorbidities and at high surgical risk were included. Mean age was 77.8 ± 7.9 years with an average EuroSCORE II of 8.7 ± 10.7%. TR etiology included functional (84%), degenerative (12%), and mixed (4%). The most common comorbidities were atrial fibrillation (92%), hypertension (86%), renal disease (46%), diabetes (22%), and prior myocardial infarction (18%). Thirty-three percent of subjects had a prior mitral intervention and 75% were classified as NYHA functional class III/IV. Median follow-up time was 12 (11,13) months.

REPAIR DURABILITY. Of the 85 subjects, 63 had evaluable TR severity at 1 year. Data were missing on 22 subjects due to death (n = 7), withdrawals (n = 5), missed visits (n = 4) and lack of readable echocardiographic data to make an assessment (n = 6). One of these subjects lacked evaluable imaging at baseline, leaving 62 subjects with paired TR severities at baseline and 1-year follow-up. A comparison of baseline characteristics for those subjects with and without 1-year echocardiographic data is provided in Supplemental Table 2.

TTVR with the TriClip device was found to be durable, with 87% (54 of 62) of subjects having a sustained TR reduction of ≥ 1 grade at 1 year, with 70% (44 of 63) of subjects having moderate or less TR at 1 year (compared to 8% at baseline and 60% at 30 days) (**Figure 1**). In this cohort, multivariate logistic regression indicated baseline TR severity as the only significant predictor for achieving moderate or less TR at 1 year. Both torrential (OR: 10.45; p = 0.0007) and massive TR at baseline (OR: 4.34; p = 0.03) were less likely to achieve moderate or less TR at follow-up when compared to subjects with severe TR at baseline. Importantly, 56% (22 of 39) of subjects with

TABLE 1 Summary of Echocardiographic Endpoints

	Baseline	30 Days	1 Year	p Value* Baseline Versus 1 Year	p Value* 30 Days Versus 1 Year
Tricuspid regurgitation					
EROA, cm^2	0.65 ± 0.03	0.40 ± 0.03	0.32 ± 0.05	<0.0001	0.1053
Regurgitant volume, ml/beat	52.20 ± 2.35	34.83 ± 2.92	27.68 ± 3.08	<0.0001	0.0607
Regurgitation jet area, cm^2	14.28 ± 0.69	9.18 ± 0.64	7.55 ± 0.56	<0.0001	0.0007
Vena contracta width, cm	1.73 ± 0.07	1.00 ± 0.06	0.78 ± 0.05	<0.0001	<0.0001
PISA radius, cm	0.91 ± 0.03	0.68 ± 0.03	0.63 ± 0.04	<0.0001	0.2092
IVC diameter, cm	2.29 ± 0.06	2.20 ± 0.06	2.06 ± 0.06	0.0014	0.0216
Right heart remodeling					
RV end diastolic dimension, cm	5.28 ± 0.07	4.93 ± 0.08	4.79 ± 0.08	<0.0001	0.0319
Tricuspid annular diameter S-L, cm	4.34 ± 0.06	4.08 ± 0.06	4.03 ± 0.07	<0.0001	0.4640
Right atrial volume, ml	129 ± 5.84	117 ± 6.03	116 ± 6.55	0.0166	0.8536
RV fractional area change, %	36.00 ± 0.85	36.77 ± 0.74	38.19 ± 0.57	0.0057	0.0649
RV systolic pressure, mm Hg	42.7 ± 1.08	42.0 ± 1.49	43.9 ± 2.30	0.5727	0.4525
TAPSE, cm	1.44 ± 0.03	1.49 ± 0.03	1.59 ± 0.04	0.0002	0.0069
RV global longitudinal strain, %	-14.1 ± 0.64	-12.9 ± 0.86	-14.6 ± 0.86	0.5897	0.1083

*From Z-test. Data are presented as least-squares ± SE from a generalized linear model.

EROA = effective regurgitant orifice area; IVC = inferior vena cava; PISA = proximal isovelocity surface area; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion.

baseline massive or torrential TR achieved moderate or less TR at 1 year, with 90% (35 of 39) achieving at least a 1-grade reduction in TR. Significant reductions in vena contracta width (1.73 ± 0.07 to 0.78 ± 0.05 mm; p <0.0001), effective regurgitant orifice area (0.65 ± 0.03 to 0.32 ± 0.05 cm^2; p <0.0001), regurgitant jet area (14.28 ± 0.69 to 7.55 ± 0.56 cm^2; p <0.0001), regurgitant volume (52.20 ± 2.35 to 27.68 ± 3.08 ml/beat; p <0.0001) and PISA radius (0.91 ± 0.03 to 0.63 ± 0.04 cm; p <0.0001) occurred between baseline and 1-year follow-up (Table 1). Inferior vena cava (IVC) diameter also significantly decreased from 2.29 ± 0.06 cm at baseline to 2.06 ± 0.06 cm at 1 year (p = 0.0014).

Importantly, the reduction in TR achieved at 30 days was durable out to 1 year for most subjects. Comparing 30-day and 1-year TR severity, a further reduction was seen in 35% (22 of 62) of subjects, no change in 44% (27 of 62) of subjects, and a 1 grade increase in 21% (13 of 62) of subjects. Of the 13 subjects with a 1 grade increase in TR between 30 days and 1 year, 9 remained at moderate or less TR. Overall, the change in TR grade between 30 days and 1 year was not significant (p = 0.96) (Figure 1). An alluvial plot of TR severity through 1-year follow-up highlights repair durability following the initial reduction in TR (Central Illustration).

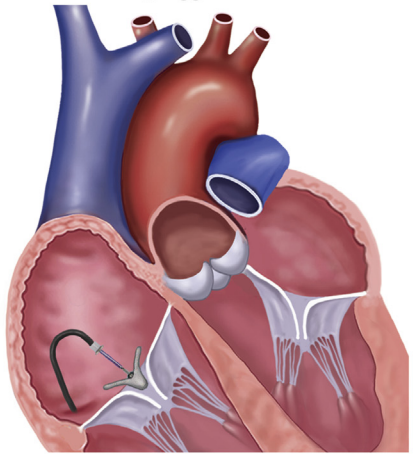
CLINICAL OUTCOMES. Significant improvements in clinical outcomes were seen in terms of clinical status, quality of life and hospitalization rates. The proportion of subjects classified as NYHA functional class I/II increased from 31% at baseline to 83% at 1 year (p <0.0001) (Figure 2). Self-assessed heart failure symptoms measured by KCCQ showed an improvement of 20 ± 2.61 points from baseline to 1 year (p <0.0001) (Figure 3), with 65% (43 of 66) of subjects experiencing ≥10 point improvement. 6MWD increased from 272 ± 15.6 meters at baseline to 303 ± 15.6 meters at 1 year, an increase of 31 ± 10.2 meters (p = 0.0023) (Figure 3B). Clinical improvements occurred mostly within the first month post-procedure, with no significant differences in NYHA functional class or 6MWD between 30-day (6-month for 6MWD) and 1-year follow-up (6MWD was assessed at 6 months per the clinical investigation protocol). KCCQ continued to increase (though less drastically) from 30-day to 1-year follow-up (6 ± 2.7 point improvement; p = 0.0290) (Figure 3A).

One-year all-cause mortality was 7.1% (6 of 84), with only 7.1% (6 of 84) of subjects experiencing a major adverse event (MAE) through 1 year (Table 2). MAEs included cardiovascular mortality (4), myocardial infarction (1), stroke (1) and new onset renal failure (1) with no cases of endocarditis requiring surgery or nonelective cardiovascular surgery for a device-related adverse event. MAEs are reported for 84 subjects (rather than 85) due to 1 subject withdrawing from the study prior to any MAEs. Major bleeding (defined as BARC 3a) occurred in 11.9% (10 of 84) of subjects. A total of 21.4% (18 of 84) of subjects experienced either major bleeding, MAE or mortality through 1 year. SLDA occurred in 5 subjects without

CENTRAL ILLUSTRATION **1-Year Outcomes From the TRILUMINATE Trial**

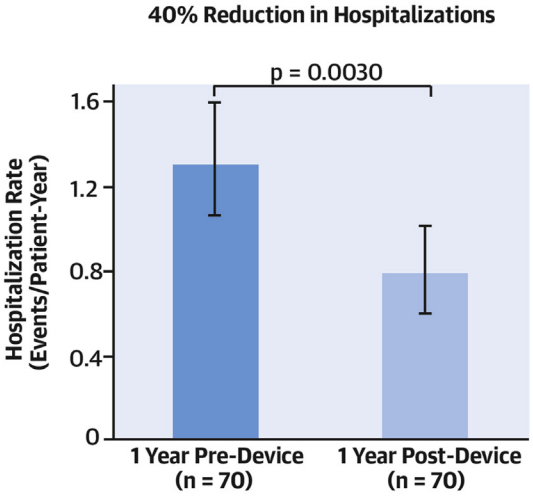
TRILUMINATE Study

n = 85

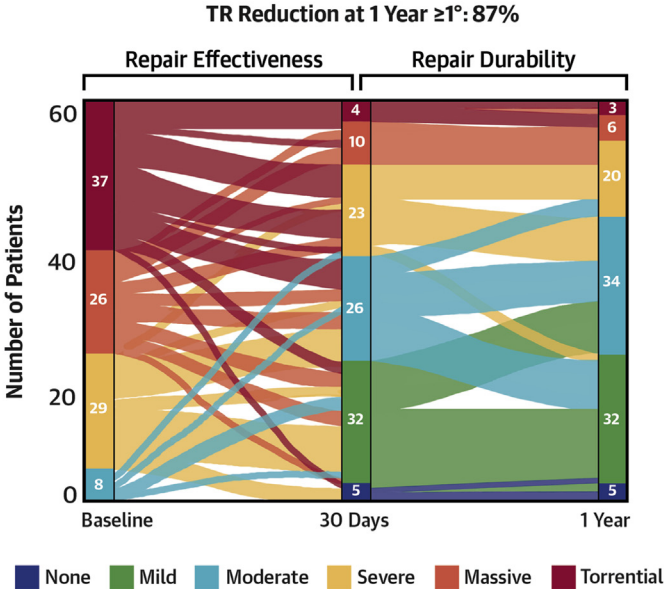


Major Adverse Events: 7.1%
Cardiovascular Mortality: 4.8%

Clinical Implications



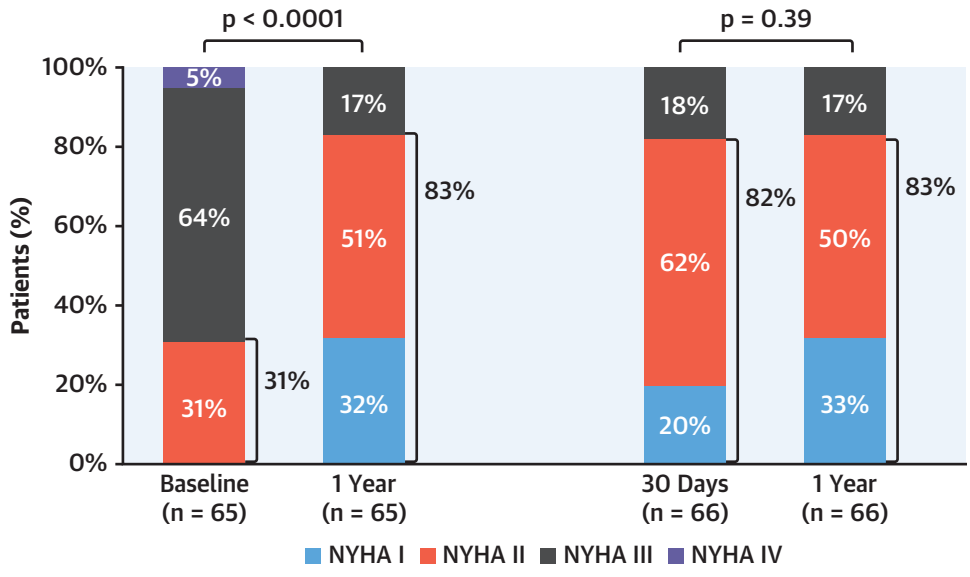
Durability of Repair



Lurz, P. et al. J Am Coll Cardiol. 2021;77(3):229-39.

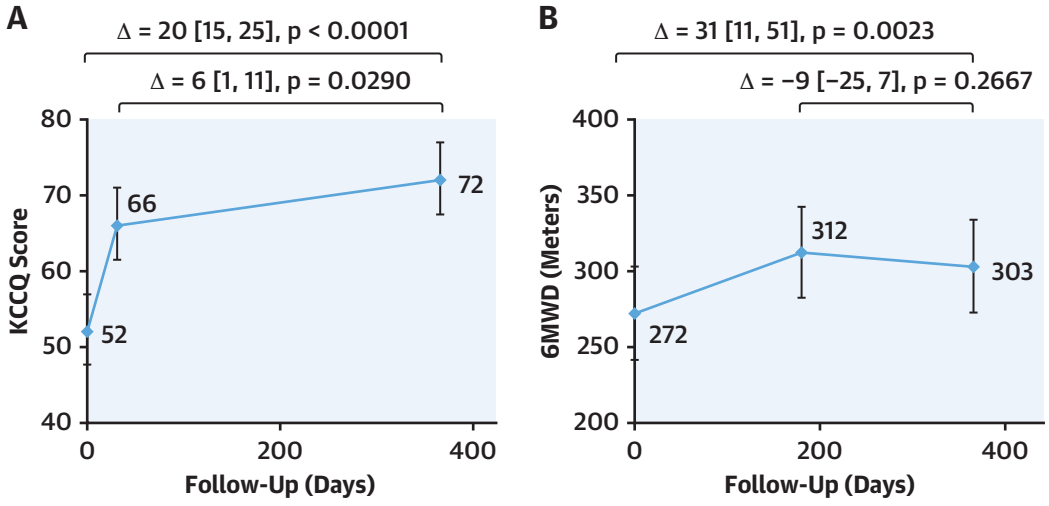
Transcatheter tricuspid valve repair using the TriClip device was found to be safe and effective. A low major adverse event rate and low mortality was observed in this fragile, high-risk population. The repair was effective. Tricuspid regurgitation (TR) was significantly reduced, with 87% of subjects achieving a ≥ 1 grade reduction at 1 year with a sustained reduction in tricuspid regurgitation; 70% achieving moderate or less TR. A significant reduction in overall hospitalization rate was also observed following treatment of tricuspid regurgitation, indicating the important clinical implications of treating this disease. In the **lower panel**, the numbers shown at baseline, 30 days, and 1 year are percentages.

FIGURE 2 NYHA Functional Class Through 1-Year Follow-Up



The proportion of subjects classified as NYHA functional class I/II increased from 31% at baseline to 83% at 1 year. Functional class improvements occurred mostly within the first month post-procedure, with no significant differences in NYHA class between 30-day and 1-year follow-up. The p values indicate significance from McNemar's test. NYHA = New York Heart Association.

FIGURE 3 Clinical Outcome Measures Over 1-Year Follow-Up



(A) Self-assessed heart failure symptoms measured by KCCQ showed a significant improvement from baseline to 1 year, with 65% of subjects experiencing ≥ 10 point improvement. While the majority of improvement was observed within the first 30 days, KCCQ continued to increase from 30-day to 1-year follow-up. **(B)** 6MWD significantly increased from baseline to 1-year follow-up. 6MWD assessed at 6 months rather than 30 days per the clinical investigation protocol. The p values indicate significance from the *z*-test. **Error bars** represent 95% confidence interval. Change over time is shown as mean [95% confidence interval]. KCCQ = Kansas City Cardiomyopathy Questionnaire overall summary score; 6MWD = six-minute walk distance.

clinical consequence or TR worsening, with no new cases occurring after 30 days. All SLDAs were subclinical and detected by routine echo core lab review. Four subjects showed mean tricuspid valve gradient ≥5 mm Hg at 1-year follow-up with no related clinical symptoms and no further intervention required. Three of these subjects had mean tricuspid gradients ≥5 mm Hg since 30-day follow-up and 1 since 6-month follow-up. There were no cases of pulmonary thromboembolism, new onset liver failure or embolization.

Among all subjects with 1-year follow-up (n = 70), hospitalization rate decreased from 1.30 to 0.78 events/patient-year 1 year prior versus one year after TriClip repair respectively, a reduction of 40% (p = 0.0030) (**Central Illustration**). Reduction to moderate or less TR was associated with reduced mortality and heart failure hospitalizations at 1 year, with nearly a 3-fold decrease in subjects with moderate or less TR (8.8% vs. 24.5%; HR: 0.31; p = 0.041) (**Figure 4**). Furthermore, a death or heart failure hospitalization did not occur until nearly 6 months post-index procedure in subjects whose TR was reduced to moderate or less.

RIGHT HEART REMODELING. Significant improvements in both right heart size and function were observed at 1-year follow-up, indicating a positive physiologic response to TR reduction and the capacity for right heart reverse remodeling (**Table 1**). Right ventricular end diastolic diameter (RVEDD) decreased from 5.28 ± 0.07 cm at baseline to 4.79 ± 0.08 cm at 1-year follow-up (p <0.0001) (**Figure 5A**). Similarly, right atrial volume and tricuspid annular diameter decreased from 129 ± 5.84 ml to 116 ± 6.55 ml (p = 0.0166) (**Figure 5B**) and 4.34 ± 0.06 cm to 4.03 ± 0.07 cm (p <0.0001) at baseline and 1 year respectively. In terms of right ventricular function, tricuspid annular plane systolic excursion (TAPSE) increased from 1.44 ± 0.03 cm at baseline to 1.59 ± 0.04 cm at 1-year follow-up (p = 0.0002) (**Figure 5C**). RV fractional area change also showed improvements from 36.00 ± 0.85% to 38.19 ± 0.57% (p = 0.0057).

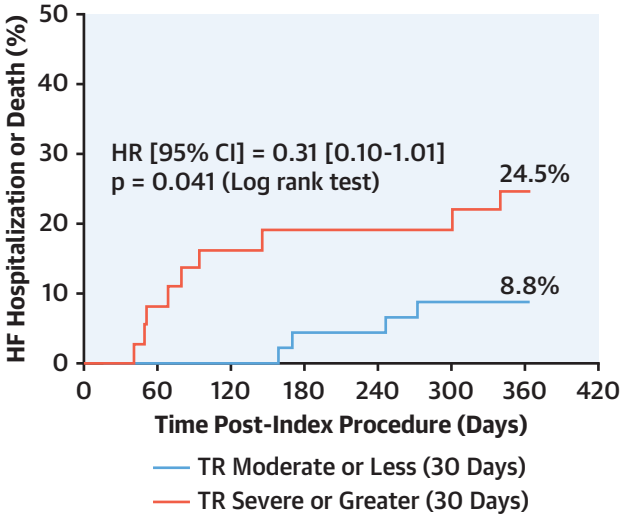
While most metrics suggest that the majority of remodeling occurs within the first 30-days post-procedure, both RVEDD and TAPSE show important signals of continued reverse remodeling through 1 year. RVEDD decreased from 4.93 ± 0.08 cm to 4.79 ± 0.08 cm from 30-day to 1-year follow-up respectively (p = 0.0319) (**Figure 5A**). TAPSE showed significant improvement between baseline and 1 year, with the majority of improvement occurring after 30-day follow-up (**Figure 5C**). RV fractional area change and RV global longitudinal strain also showed improvements between 30-day and 1-year follow-up. Diuretic usage remained the same (defined as no more than a 100% increase or a 50% decrease in dose and maintained for at least 30 days) in 77.6% (66 of

TABLE 2 Major Adverse Events and Clinical Safety Endpoints at 1-Year Follow-Up

Major adverse events through 1-yr	7.1 (6/84)
Cardiovascular mortality	4.8 (4/84)
Myocardial infarction	1.2 (1/84)
Stroke	1.2 (1/84)
New onset renal failure	1.2 (1/84)
Nonelective CV surgery, TVRS device-related AE	0
Other clinical safety endpoints	
All-cause mortality	7.1 (6/84)
Major bleeding*	11.9 (10/84)
Pulmonary thromboembolism	0
New onset liver failure	0
New onset atrial fibrillation	1.2 (1/84)
Single leaflet device attachment†	7.7 (5/65)
Embolization	0 (0/65)
Mean tricuspid gradient ≥5 mm Hg‡	6.3 (4/64)

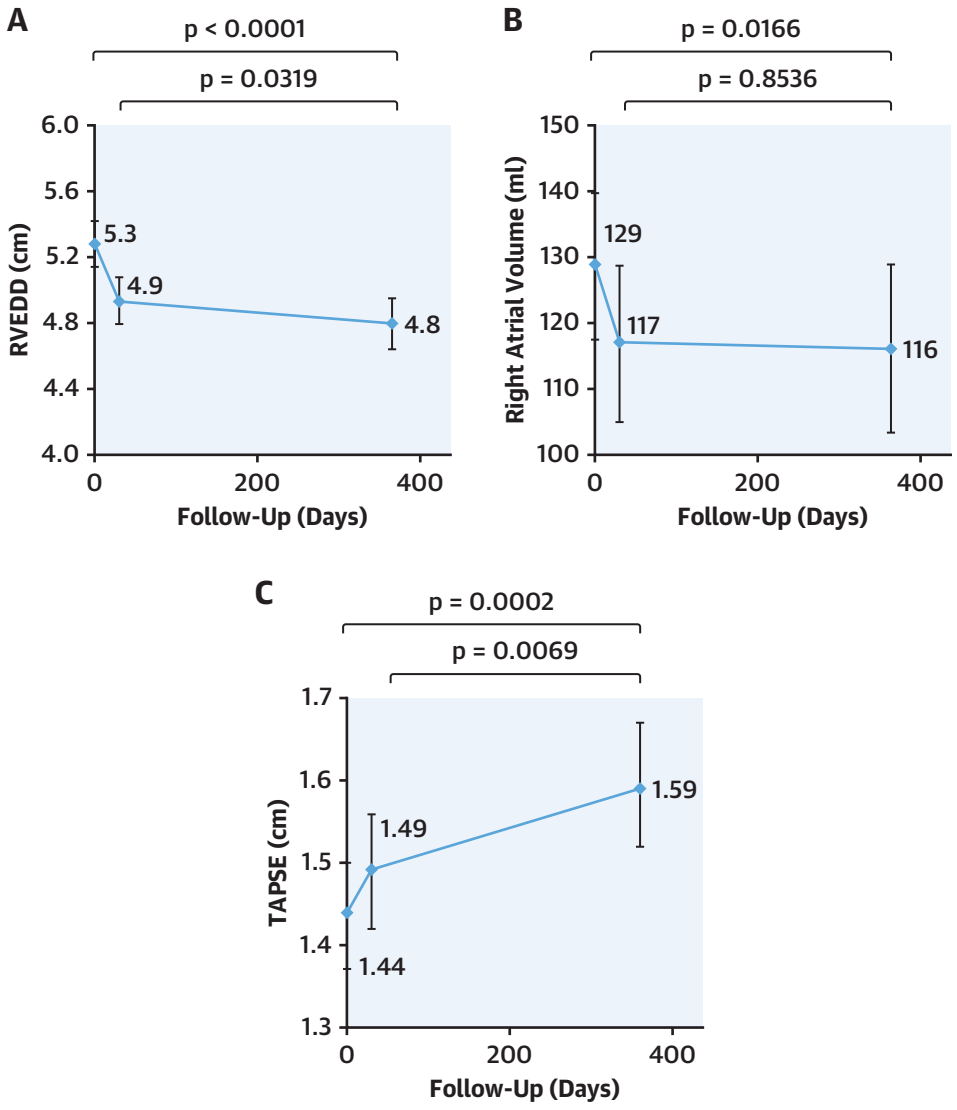
Values are % (n/N). *Subjects reported a drop in hemoglobin of 3–5 g/Dl (BARC Type 3a). †Subjects' TR severity and clinical symptoms did not worsen as compared to baseline. No additional intervention was needed. ‡Subjects did not present with clinical symptoms. No additional intervention was needed.

FIGURE 4 Effect of TR Reduction On Mortality and Heart Failure Hospitalization



Reduction to moderate or less tricuspid regurgitation (TR) was associated with reduced mortality and heart failure hospitalizations at 1 year, with nearly a 3-fold decrease in subjects with moderate or less TR. Furthermore, a death or heart failure hospitalization did not occur until nearly 6 months post-index procedure in subjects whose TR was reduced to moderate or less. CI = confidence interval; HF = heart failure.

FIGURE 5 Right Heart Remodeling Through 1 Year



Significant improvements in both right heart size and function were observed at 1-year follow-up, indicating a positive physiologic response to TR reduction and the capacity for right heart reverse remodeling. Significant decreases in right heart size were measured by **(A)** right ventricle end diastolic dimension (RVEDD) and **(B)** right atrial volume. Significant improvements in right ventricle function were seen as indicated by an increase in **(C)** tricuspid annular plane systolic excursion (TAPSE). The p values indicate significance from the *z*-test. **Error bars** represent 95% confidence interval.

85), decreased in 15.3% (13 of 85) and increased in 8.2% (7 of 85) of subjects at 1 year (Supplemental Table 3).

DISCUSSION

We present the 1-year follow-up results of the prospective, multicenter, international, single-arm TRILUMINATE study evaluating the safety and performance of TTVR system using the TriClip device (Abbott, Chicago, Illinois). The results at 1 year show: 1) a durable repair with sustained reduction in TR and device function; 2) improvements in quality of life and functional capacity; 3) reduced rates of hospitalization and low mortality in a fragile population at high risk; and 4) positive structural and functional right ventricular reverse remodeling over time.

Among the most important findings was the observation that the initial TR reduction (seen at 30 days) proved durable in a majority of patients (79%) at 1-year follow-up. Considering the progressive nature of TR, this is an important finding. Furthermore, 35% of subjects experienced further reduction in TR between 30-day and 1-year follow-up. While 13 subjects showed a 1 grade increase in TR following the 30-day follow-up, 9 of these remained moderate or less. These results are promising and support the concept of TTVR as a dedicated device for a disease that is otherwise progressive in nature (2,14). In addition, the comparison of baseline characteristics between subjects with and without echocardiographic follow-up at 1 year indicates these subjects are representative of the overall cohort.

Mortality was low in this study. The mortality rate of 7.1% at 1 year compares favorably to real-world data on transcatheter tricuspid valve interventions (23%) and the previously published TRI-REPAIR study (16.7%), which prospectively investigated the role of an indirect annuloplasty device for treatment of TR (19,20). The rate of major bleeding was found to be 11.9%. Although not included in the predefined MAEs in this study, major bleeding has been proven to be prognostically relevant in patients undergoing transcatheter heart valve interventions (21). Other studies on transcatheter repair of TR report similar rates of major bleedings underlying the need to refine strategies to avoid this complication in the future (20).

Despite similar age (78 vs. 78 years) and EuroSCORE II (8.7 vs. 10.5%), mortality in the TRILUMINATE trial was 16% less than in the TriValve registry. While procedural "success" may be defined in a number of ways, TR reduction to moderate or less was significantly associated with reduced mortality and heart failure hospitalizations, supporting prior findings and emphasizing the effects of TR reduction on clinical outcomes (15,19,22). Importantly, this is an observed correlation and the causal effects for lowered mortality can only be hypothesized. Therefore, randomized clinical trials comparing the effects of TTVR versus a medical control or a sham-controlled group are warranted to further investigate the role of TTVR in patients with severe TR. A pivotal trial (TRILUMINATE Pivotal; NCT03904147) comparing the clinical impact of transcatheter repair with the TriClip system to medical therapy is currently underway.

In addition to a low mortality rate, marked clinical improvements were observed after 30 days and maintained through 1-year follow-up. Significant increases in KCCQ score, 6MWD and the proportion of subjects in NYHA functional class I/II were seen through 1 year. Furthermore, a reduction in hospitalization rate by 40% following TTVR in this aging population highlights these clinical improvements. Exact interpretation remains difficult in the absence of a control group; however, it is likely that given the natural course of TR in this high-risk and fragile population, medical management alone would not yield similar benefits.

The pathophysiologic implications of TR reduction can be grouped into acute and late effects. The acute phase is mainly characterized by immediate morphological and hemodynamic modification of the RV and tricuspid valve apparatus (23). These changes are driven by an acute change in RV loading conditions. The second, longer-term phase is marked by an alleviation of the vicious cycle of TR resulting in slow but progressive RV reverse remodeling (24). We report, for the first time, an improvement in right ventricular systolic function during this second phase, as indicated by an increase in TAPSE from 30 days to 1 year (**Figure 5**). This observation is important and challenges some previous retrospective studies demonstrating stable or even borderline reduced TAPSE in the acute phase after TTVR (14,23,24).

Fundamentally, TTVR reduces RV preload at the cost of increased afterload in the acute phase. However, this appears to be compensated for by an acute and late reduction in RV size with optimized RV myocardial stretch and improved TAPSE over time. Similar to surgical correction of valve regurgitation, strain initially decreases in response to the decreased volume overload (TR reduction), and then increases as the RV remodels to a more natural, smaller state (25). However, RV size and function are inextricably linked and RVEDD reduction could also be a consequence of improved RV function. Therefore, the exact mechanisms remain speculative.

It should be noted that TAPSE has not proven to be prognostically relevant after TTVR (26). Previous work has suggested RV longitudinal strain as a prognostically more relevant marker of RV function (27). Future studies on larger cohorts incorporating measures of global RV function, which are known to be less susceptible to RV afterload, should enhance our understanding of how TTVR impacts RV function and its prognostic implications.

At present, the independent prognostic implications of relevant TR irrespective of comorbidities, pulmonary hypertension and left heart disease are widely recognized and accepted, yet only an exceedingly small minority of patients with severe TR receive treatment (28). The durable TR reduction with

few adverse events and significant clinical benefits seen in this study encourages transcatheter treatment of TR using the TriClip device. This safe and effective option may offer substantial clinical improvements in this undertreated population.

STUDY LIMITATIONS. This is not a randomized controlled study and hence the results should be interpreted with caution. Few patients with reduced LV systolic function were included and therefore these results may not be generalizable to patients with heart failure and reduced ejection fraction (29). Patients and their anatomies were evaluated by a committee upon enrollment, focusing on the morphological suitability to implant the device safely into the tricuspid valve. In addition, other factors such as imaging views, coaptation gap sizes (<10 mm), the presence of leads across the tricuspid valve and their interaction with the valve as well as jet orientation were all taken into consideration. Therefore, results of this early feasibility study may not be applicable to the total population of patients with significant TR. Furthermore, some patients did not experience a clinically relevant TR reduction, highlighting the need to refine both anatomical and clinical patient selection in the future. Nevertheless, these results should also be interpreted in light of the early stage of this therapy which certainly includes a learning curve.

While the edge-to-edge device for the mitral valve is available in multiple sizes, only the smaller (NT) device was used in this study. The version of the device that was approved for CE mark does have an additional clip size (XT), similar to the currently approved CE marked MitraClip device.

CONCLUSIONS

We show that TTVR using the TriClip device is safe and effective in patients with moderate or greater TR and is associated with excellent repair durability and a sustained and marked clinical benefit with reduced rates of hospitalization and low mortality after 1 year in a fragile population at high risk. Continued RV reverse remodeling is observed even beyond the initial phase following TTVR. These findings warrant further randomized trials investigating the effect of catheter-based reduction of TR in comparison to conservative medical therapy.

AUTHOR DISCLOSURES

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Transcatheter treatment of tricuspid regurgitation can be achieved safely and is associated with favorable right ventricle remodeling and substantial improvement in 1-year clinical outcomes.

TRANSLATIONAL OUTLOOK: Additional randomized trials are warranted to compare long-term clinical outcomes of catheter-based intervention for tricuspid regurgitation with optimum medical therapy.

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KEY WORDS transcatheter tricuspid valve repair, tricuspid regurgitation, tricuspid valve

APPENDIX For supplemental tables and a list of TRILUMINATE investigators, roles, and institutions, please see the online version of this paper.

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