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Outcomes After Current Transcatheter Tricuspid Valve Intervention

Mid-Term Results From the International TriValve Registry

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ABSTRACT

OBJECTIVES A large, prospective international registry was developed to evaluate the initial clinical applications of transcatheter tricuspid valve intervention (TTVI) with different devices.

BACKGROUND TTVI for native tricuspid valve dysfunction has been emerging during the last few years as an alternative therapeutic option to serve a large high-risk population of patients with severe symptomatic tricuspid regurgitation (TR).

METHODS The TriValve Registry included 312 high-risk patients with severe TR (76.4 ± 8.5 years of age; 57% female; EuroSCORE II 9 ± 8%) at 18 centers. Interventions included repair at the level of the leaflets (MitraClip, Abbott Vascular, Santa Clara, California; PASCAL Edwards Lifesciences, Irvine, California), annulus (Cardioband, Edwards Lifesciences; TriCinch, 4tech, Galway, Ireland; Trialign, Mitraling, Tewksbury, Massachusetts), or coaptation (FORMA, Edwards Lifesciences) and replacement (Caval Implants, NaviGate, NaviGate Cardiac Structures, Lake Forest, California). Clinical outcomes were prospectively determined during mid-term follow-up.

RESULTS A total of 108 patients (34.6%) had prior left heart valve intervention (84 surgical and 24 transcatheter, respectively). TR etiology was functional in 93%, and mean annular diameter was 46.9 ± 9 mm. In 75% of patients the regurgitant jet was central (vena contracta 1.1 ± 0.5; effective regurgitant orifice area 0.78 ± 0.6 cm^2). Pre-procedural systolic pulmonary artery pressure was 41 ± 14.8 mm Hg. Implanted devices included: MitraClip in 210 cases, Trialign in 18 cases, TriCinch first generation in 14 cases, caval valve implantation in 30 cases, FORMA in 24 cases, Cardioband in 13 cases, NaviGate in 6 cases, and PASCAL in 1. In 64% of the cases, TTVI was performed as a stand-alone procedure. Procedural success (defined as the device successfully implanted and residual TR ≤2+) was 72.8%. Greater coaptation depth (odds ratio: 24.1; $p = 0.002$) was an independent predictor of reduced device success. Thirty-day mortality was 3.6% and was significantly lower among patients with procedural success (1.9% vs. 6.9%; $p = 0.04$); Actuarial survival at 1.5 years was 82.8 ± 4% and was significantly higher among patients who had procedural success achieved.

CONCLUSIONS TTVI is feasible with different technologies, has a reasonable overall procedural success rate, and is associated with low mortality and significant clinical improvement. Mid-term survival is favorable in this high-risk population. Greater coaptation depth is associated with reduced procedural success, which is an independent predictor of mortality. (J Am Coll Cardiol Intv 2019;12:155–65) © 2019 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CAVI = caval valve implantation

EROA = effective regurgitant orifice area

IQR = interquartile range

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

NYHA = New York Heart Association

RV = right ventricle/ventricular

sPAP = systolic pulmonary artery pressure

TAPSE = tricuspid annular plane systolic excursion

TR = tricuspid regurgitation

TTVI = transcatheter tricuspid valve intervention

TV = tricuspid valve

Transcatheter tricuspid valve intervention (TTVI) for native tricuspid valve (TV) dysfunction has been emerging during the last few years as an alternative therapeutic option to serve a large high-risk population of patients experiencing severe symptomatic tricuspid regurgitation (TR) (1–3).

Although only limited clinical data are available regarding the efficacy of TTVI to date, feasibility has been shown with different techniques, including annuloplasty devices (4–7), leaflet and coaptation devices (8–10), and valve replacement, both in the heterotopic (11) (caval valve implantation [CAVI] to reduce the backflow in the venous system) and the orthotropic positions (12).

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During the development of various TTVI techniques, several challenges related to the complexity of the TV have surfaced in this new field related to clinical (indication, proper timing, avoiding futile procedures, outcome assessment), anatomic (proximity of the TV to vital structures that can easily be injured during TTVI, such as the right coronary artery or the atrioventricular node), as well as technical (access, procedural guidance, pre-procedural imaging) specificities.

The international TriValve registry (Transcatheter Tricuspid Valve Therapies, NCT03416166) is the first international registry to our knowledge to collect data of patients undergoing TTVI with the currently available devices. It has been established in order to address some of these issues and to investigate the clinical profile and clinical outcomes of patients treated with the different devices. A first report of the TriValve registry showed that patients currently undergoing TTVI are mostly at high surgical risk, have a functional TR etiology, and have severe or greater central regurgitation in the setting of impaired right ventricular (RV) function. Initial results suggested that TTVI is feasible with different techniques with promising early outcomes (13). The aim of the present study is to report mid-term clinical outcomes of patients included in the TriValve registry to date.

METHODS

DESIGN OF THE STUDY. The design of the registry has been described previously (13). A total of 18 heart centers across Europe and North America had

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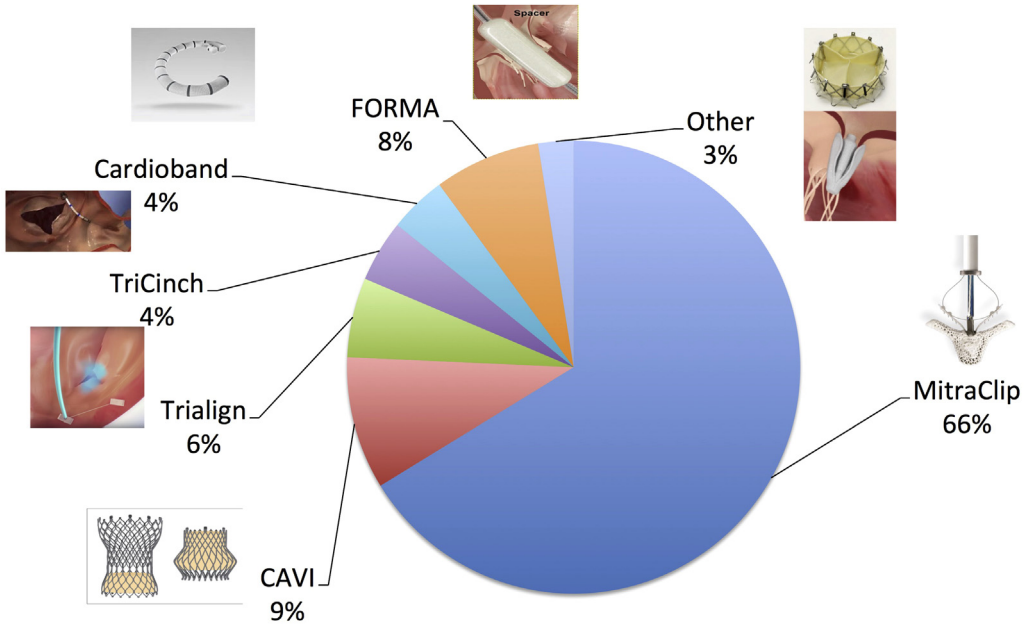
FIGURE 1 Distribution of the Devices Used in the Registry



contributed to the registry. Continued communication with involved centers (M.T.) was initiated. Data were collected with the use of a dedicated dataset. TV therapies included in the registry were: MitraClip (Abbott Vascular, Santa Clara, California), FORMA (Edwards Lifesciences, Irvine, California), Cardioband (Edwards Lifesciences), TriCinch (4tech, Galway, Ireland), Trialign (Mitraling, Tewksbury, Massachusetts), CAVI, PASCAL (Edwards Lifesciences), and NaviGate (NaviGate Cardiac Structures, Lake Forest, California) (**Figure 1**). The comprehensive descriptions of the different procedures have been reported elsewhere (4,6–12).

All inconsistencies were resolved directly with local investigators and during onsite data monitoring. Baseline and intraprocedural clinical, anatomic, and echocardiographic data were collected. Pre-discharge and follow-up events, and echocardiographic data were collected whenever available from the respective centers. The inclusion of patients in this study was approved in each center by a local ethical committee or per local practice for the collection of retrospective data.

DEFINITIONS. All the patients included in the registry had severe or greater symptomatic TR according to the European or American guidelines for the management of heart valve disease and were treated according to local multidisciplinary team decision (14,15). Grading of the severity of TR was assessed using a combination of semiquantitative and quantitative assessment, as described by the American Society of Echocardiography guidelines as well as the European Association of Echocardiography guidelines (16,17).

Procedural success was defined as patient alive at the end of the procedure, with the device successfully implanted and delivery system retrieved, with a residual TR ≤2.

Mitral Valve Academic Research Consortium criteria were used to define adverse events (18). Follow-up data were collected for patients at 1 month and then according to the time frame elapsed from the index procedure to data lock for present analysis.

STATISTICAL ANALYSIS. Statistical analysis was performed with the use of JMP version 8.0 software (SAS Institute, Cary, North Carolina). Results are presented as mean ± SD for continuous variables normally distributed (tested by the Shapiro-Wilk normality test), as median (interquartile range [IQR] IQR [25th to 75th percentiles]) for continuous variables without normal distribution, and as percentages for categorical data.

One-way analysis of variance and paired Student's *t*-test were used to compare normally distributed continuous variables, and the Kruskal-Wallis test was used for non-normally distributed data. Chi-square and Fisher exact tests were used to compare categorical variables.

Survival was reported using the Kaplan-Meier method and comparisons were performed using the log-rank test.

A p value <0.05 was considered statistically significant, and all reported p values are 2-sided. Univariate analysis of predictors of procedural success was performed with nominal logistic regression; univariate analysis of predictors of death at follow-up was performed with Cox proportional hazard regression. Variables with a p value <0.10 were then inserted in a multivariable model. The receiver-operating characteristic curve method was used to identify the best cutoff to predict procedural success.

RESULTS

STUDY POPULATION AND DEMOGRAPHIC. Between January 2014 and May 2018, 312 patients with severe or greater symptomatic TR underwent TTVI and were included in the registry across 18 centers (in Switzerland, Germany, France, Italy, United States, and Canada).

Baseline clinical and echocardiographic characteristics were available for 100% of the patients. Mean age of the treated population was 76 ± 8.5 years, with a 56% prevalence of women. Mean EuroSCORE II was 9 ± 8%. Etiology of TR was functional in 92% of the patients (n = 288); 71 patients (22.7%) had a previously implanted intracardiac device and presented with a transtricuspid RV lead. In no cases was pacemaker-induced TR due to leaflet perforation or endocarditis.

A total of 108 patients (34.6%) had a history of previous left-side valve intervention (84 surgical, 24 percutaneous, 3 both).

Prevalence of long-standing atrial fibrillation was 78%, and median N-terminal pro-B-type natriuretic peptide (NT-proBNP) at baseline was 2,759 pg/ml (IQR: 1,298 to 5,627 pg/ml).

Most of the patients were severely symptomatic at admission: 95% were in New York Heart Association (NYHA) functional class III/IV, 28% had ascites, 85% had peripheral edema; 71% of the patients had a history of previous admission for RV failure, with a median duration of severe RV failure symptoms of 15 months before the index hospitalization. **Table 1** summarizes the clinical profile of the study population.

ECHOCARDIOGRAPHIC BASELINE PROFILE. Mean left ventricular ejection fraction was 49.8 ± 13.5% and 29% (n = 149) of the patients had concomitant mitral regurgitation (MR) ≥3+. Most of the patients included in the registry had severe or greater TR (vena contracta width 1.1 ± 0.5 cm; effective regurgitant orifice area [EROA] 0.78 ± 0.6 cm^2; regurgitant volume 54 ± 34 ml/beat). The main location of the TR jet was central in 75% of the patients (n = 234). Mean tricuspid annular dimension was 46.9 ± 9 mm, with a coaptation depth of 9.4 ± 4.1 mm. RV dysfunction (defined as tricuspid annular plane systolic excursion [TAPSE] <17 mm) was observed in 57.7% of the patients (TAPSE 16.2 ± 5 mm). Mean systolic pulmonary artery pressure (sPAP) was 41 ± 14.8 mm Hg. **Table 2** illustrates the baseline echocardiographic profile of the patients.

INTRAPROCEDURAL RESULTS AND 30-DAY OUTCOMES. All but 1 procedures were performed using general anesthesia under fluoroscopic and echocardiographic guidance, in a hybrid room or in a cath-lab. One case of TriCinch was performed under conscious sedation using intracardiac echocardiography. Implanted devices included: MitraClip in 210 cases, Trialign in 18 cases, TriCinch first generation in 14 cases, CAVI in 30 cases, FORMA in 24 cases, Cardioband in 13 cases, and NaviGate and Pascal were used in 6 and 1 cases each, respectively. One patient underwent combined MitraClip and Trialign during the same procedure. Isolated TTVI was performed in 64% of the cases (n = 202), whereas in the remaining, TTVI was performed concomitantly during transcatheter mitral repair (108 cases), transcatheter aortic valve replacement (1 case) or paravalvular leak closure (1 case). Overall mean procedural time was 133 ± 66 min, whereas it was 129 ± 72 min in isolated TTVI.

MitraClip and CAVI were the techniques most frequently used in the presence of transtricuspid pacemaker lead; patients treated with MitraClip and TriCinch had greater regurgitant volume, and procedural time was significantly shorter with CAVI. **Table 3** shows the profile of the patients treated with the different devices.

Procedural and periprocedural outcomes were available for 280 patients (the remaining 32 patients were included in ongoing unpublished trials; therefore, only baseline characteristics were provided at this stage). Intraprocedural death was 0%. Procedural success (defined as patient alive at the end of the procedure with the device successfully implanted, delivery system retrieved, and a residual TR grade ≤2) was achieved in 72.8% of cases, with no differences among the different devices (p = 0.20). A device was implanted, and the

TABLE 1 Baseline Clinical Profile of the Study Population (N = 312)

Age, yrs	76 ± 8.6
Female	171 (55)
EuroSCORE II	9 ± 8
TR etiology	
Functional	288 (93)
Degenerative	8 (2)
Mixed	9 (3)
Pacemaker induced	7 (2)
Previous left side valve intervention (surgical/transcatheter/both)	84/24/3
Transvalvular tricuspid lead	71 (22)
Atrial fibrillation	245 (78)
COPD	237 (78)
eGFR, ml/min	42.6 ± 18.5
Median AST/ALT, UI/l	29/20
NT-proBNP, pg/ml	2,759 (1,298–5,627)
Ascites	87 (28)
Peripheral edema	265 (85)
NYHA functional class III–IV	297 (95)
Previous admission for RV failure	216 (69)
Median duration of severe RV failure symptoms, months	15 (9–24)
Baseline hemoglobin, g/dl	10.6 ± 2.3
Diuretic therapy	
Torsemide, mg, n = 176	30 (10–40)
Furosemide, mg, n = 118	80 (20–140)

Values are mean ± SD, n (%), or median (interquartile range).

ALT = alanine aminotransferase; AST = aspartate aminotransferase; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; RV = right ventricle; TR = tricuspid regurgitation.

TABLE 2 Baseline Echocardiographic Profile (N = 312)

Right atrial volume, ml	111 ± 82
LV ejection fraction, %	49 ± 13
LV end-diastolic diameter, mm	50 ± 9
Concomitant MR ≥3+	149 (29)
TR jet location	
Central	228 (75)
Anteroseptal	43 (14)
Anteroposterior	11 (4)
Posteroseptal	22 (7)
Tricuspid vena contracta, cm	1.1 ± 0.5
Tricuspid regurgitant volume, ml	54 ± 34
Tricuspid anteroseptal diameter, mm	46.9 ± 9
Tricuspid EROA, cm^2	0.78 ± 0.6
TAPSE, mm	16.2 ± 5
S-TDI, cm/s	10 ± 7
Coaptation depth, mm	9.5 ± 4.1
Tenting area, cm^2	2.8 ± 1.7
Systolic pulmonary artery pressure, mm Hg	41 ± 14.8
IVC diameter, cm	2.3 ± 1

Values are mean ± SD or n (%).

EROA = effective regurgitant orifice area; IVC = inferior vena cava; LV = left ventricle; MR = mitral regurgitation; S-TDI = systolic tissue Doppler imaging; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

delivery system retrieved in all cases. In all the cases, procedural failure was due to residual TR grade ≤2. Reduction of at least 1 degree of TR severity (TR reduction ≥1+) was achieved in 84% of the patients (235 patients).

Greater coaptation depth, annular diameter, and sPAP were identified as predictors of procedural failure at univariate analysis. Greater coaptation depth was confirmed as an independent predictor of procedural failure at multivariate analysis (Table 4).

A baseline coaptation depth >1 cm was identified as the best cutoff to predict the risk for procedural failure, with a sensitivity of 73.9% and a specificity of 60% (area under the curve 0.66).

Post-procedural length of stay was longer in patients in whom procedural success was not achieved (8.3 vs. 4.3 days; p = 0.004).

Thirty-day mortality was 3.6% (10 patients: 2 sepsis, 2 respiratory insufficiency, 6 progressive RV failure), and it was significantly lower among patients with procedural success (1.9% vs. 6.9%; p = 0.04).

Overall incidence of major adverse events at 30 days was 10.3% (29 events), including: 10 deaths (3.6%), 5 major bleedings (1.7%), 3 strokes (1%), 2 acute myocardial infarctions requiring right coronary artery stenting (0.7%), 4 conversions to surgery (1.4%: in 2 cases emergent conversion to surgery was required, in 2 cases tricuspid surgery was performed "elective" due to procedural failure), 2 respiratory failure (0.7%), 1 device detachment (0.3%), 1 ventricular arrhythmia (0.3%), and 1 aortic prosthetic valve thrombosis (0.3%).

Thirty-day echocardiography showed a residual TR ≤2+ in 62% of the patients (p < 0.0001 compared with baseline) (Figure 2), without any significant change in RV function (Figure 3); 61% of the patients were in NYHA functional class I to II at 30 days.

FOLLOW-UP. Clinical improvement was observed at 6 months follow-up, with 54% of the patients in NYHA functional class I to II (p = 0.04 compared with baseline) (Figure 4A), prevalence of ascites was reduced to 14% (p = 0.006 compared with baseline) and prevalence of peripheral edema to 39% (p = 0.001). The number of patients in NYHA functional class I to II at 6 months was higher among the patients with a TR reduction ≥1+ compared with baseline (64.4% vs. 35.7%; p = 0.04) (Figure 4B).

Median follow-up was 6.2 months (IQR: 0.4 to 15.5 months). Overall actuarial survival was 77.2 ± 5.9% at

TABLE 3 Profile of the Patient Treated With the Different Devices*

	MitraClip (n = 210)	Trialign (n = 18)	Cardioband (n = 13)	TriCinch (n = 14)	FORMA (n = 24)	CAVI (n = 30)	p Value
EuroSCORE II, %	9 ± 10	9.6 ± 9	5 ± 4	5.6 ± 3	12 ± 9	8 ± 4	0.50
LVEF, %	49 ± 13	53 ± 10	52 ± 5	55 ± 8	53 ± 11	52 ± 9	0.40
TAPSE, mm	16 ± 4	17 ± 3	15 ± 3	17 ± 3	15 ± 4	15 ± 3	0.90
Regurgitant volume, ml/beat	59 ± 39	49 ± 25	36 ± 22	58 ± 33	29 ± 7	50 ± 9	**0.01**
Central TR jet	73	100	81	73	100	100	0.90
Annular diameter, mm	43 ± 9	52 ± 22	44 ± 5	56 ± 6	51 ± 7	58 ± 7	**0.008**
Coaptation depth, mm	9 ± 5	5 ± 1	8 ± 6	13 ± 4	NA	10 ± 2	**0.04**
IVC diameter, cm	24 ± 8	26 ± 6	22 ± 6	27 ± 6	32 ± 5	36 ± 10	0.01
Transvalvular lead, %	34	0	7	0	10	25	**<0.0001**
Procedural time, min	131 ± 59	161 ± 93	231 ± 64	172 ± 28	155 ± 42	81 ± 53	**<0.0001**
Procedural success	70.4	69.2	57.1	62.5	100	84.1	0.20
30-day mortality	2.8	0	7.6	0	0	5	0.90

Values are mean ± SD or %. Values in **bold** are statistically significant. *Navigate and Pascal were not included, because only 6 and 1 cases were performed, respectively.
CAVI = caval valve implantation; LVEF = left ventricular ejection fraction; other abbreviations as in Table 2.

1.5 years (Figure 5). Actuarial survival at follow-up was significantly better in patients in whom acute procedural success achieved (70.3 ± 8% vs. 90.8 ± 4% at 1 year; p = 0.0002). Superior survival according to procedural success was observed also when only isolated TTVI were considered (69 ± 9% vs. 89 ± 5% at 1 year; p = 0.0037) (Figures 6A and 6B).

Actuarial survival was significantly higher also in patients who had a TR reduction ≥1+ observed in the overall population (85.2 ± 5% vs. 75.8 ± 9% at 1 year; p = 0.01), but not in the isolated TTVI patients (81.4 ± 6% vs. 79.7 ± 1% at 1 year; p = 0.26).

Procedural success and higher values of sPAP at baseline were independently associated with increased mortality at follow-up. Analysis of predictors of mortality at follow-up is shown in Table 5.

TABLE 4 Univariate and Multivariate Analysis of Predictor of Procedural Failure

	Univariate*		Multivariate*	
	OR (CI 95%)	p Value	OR (CI 95%)	p Value
Coaptation depth	31.8 (4.8–244)	**0.0002**	24.1 (3–231)	**0.002**
Annular diameter	8.07 (1.1–61.8)	0.03	7.2 (0.9–1.12)	0.06
Vena contracta	0.2 (0.1–37.9)	0.12		
Presence of PM lead	0.9 (0.5–4.5)	0.70		
MitraClip vs. other device	0.6 (0.5–5.8)	0.11		
TAPSE <17 mm	1.02 (0.2–2.9)	0.90		
LVEF, %	0.65 (0.12–2.7)	0.50		
sPAP	8.8 (1.8–77)	0.01	0.1 (0.06–1.5)	0.10

Values in **bold** are statistically significant. *Nominal logistic regression.
CI = confidence interval; OR = odds ratio; PM = pacemaker; sPAP = systolic pulmonary artery pressure; other abbreviations as in Tables 2 and 3.

DISCUSSION

The present study represents the largest worldwide series of patients treated with TTVI for TR. The most relevant results from the study are that procedural success is strongly related with survival at mid-term follow-up and that the main factor independently related to procedural success is coaptation depth, which is an index of valve tethering. Tethering of the TV leaflets is typically a consequence of RV remodeling that occurs in the late phase of this disease.

PATIENTS UNDERGOING TTVI: WHO AND HOW. Compared to the first report from the TriValve registry (13), patients enrolled in the ongoing phase of the study display a similar epidemiology, confirming that patients treated worldwide with TTVI are high-risk patients, mostly with a functional etiology of TR and massive or torrential regurgitation. However, the risk profile of the new cohort has changed: compared with the first 100 patients, EuroSCORE II increased from 7.6% to 9%, NT-proBNP from 2,500 pg/ml to about 2,800 pg/ml, and the prevalence of previous admission for RV failure is almost 30% higher. This is probably the consequence of 2 factors: first, the promising results of early feasibility trials and other registries have led investigators to test the clinical boundaries of the current techniques (7,19); second, more advanced disease is excluded from current trials, leading investigators to seek solutions for these extreme cases. The current TriValve registry thus represents the "real world" of disease severity currently being treated as compassionate procedures.

Despite the increased risk of the patients, the current report confirms the safety and feasibility of TTVI: intraprocedural mortality was 0%, 30-day mortality and periprocedural adverse events did not change, and procedural success improved significantly, from 62% to 72.8%. Improved procedural success is likely multifactorial and related to: the early learning curve effect in TTVI, which is common and universal for new devices and techniques; a better understanding of TV anatomy and disease pathophysiology; and improved and more standardized intraprocedural guidance (20,21).

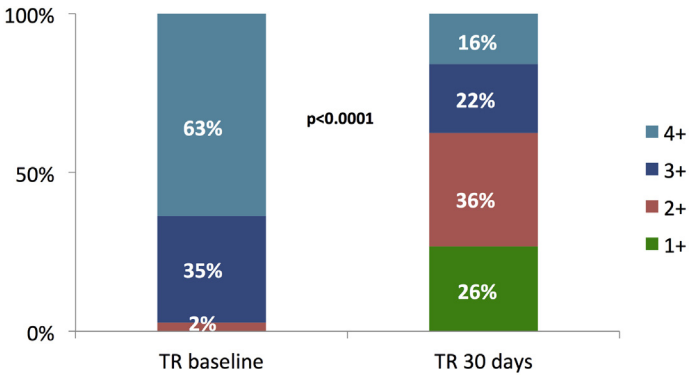
The most used device is off-label use of the MitraClip in the tricuspid position, due to the unrestricted availability and operator familiarity with the device. Moreover, the recent availability of the larger MitraClip XTR allows the operator an easier grasping of the valve leaflets, even in the presence of broader coaptation gap. However, Cardioband recently obtained CE-Mark (April 2018) for the treatment of functional TR, becoming the first device commercially available and approved in the field. Despite the relative technical complexity of the procedure, broader adoption of Cardioband is expected.

PROCEDURAL SUCCESS: THE IMPORTANCE OF PROCEDURAL TIMING AND PATIENT SELECTION. The present study clearly shows that, independent of the specific device, the main factor influencing procedural success is coaptation depth, which is a measure of leaflet tethering. Although this is a new finding in the field of percutaneous TV treatment, this is not surprising, because it is known from surgical experience that increased coaptation depth (>1 cm) is associated with increased risk of failure of surgical tricuspid repair (22).

Other factors associated with procedural success are annular diameter and pulmonary artery pressure, which are similarly determinants of surgical tricuspid repair failure (23). Increased coaptation depth, annular diameter, and pulmonary artery pressure may be indicators of late disease progression (phase 3), when RV remodeling is advanced, and the ability to affect the natural history of the disease with any treatment is limited (24). The present study suggests that TTVI should be performed earlier, in order to increase the chance of procedural success, before that advanced tethering occurs. This also supports a better patients' selection for TTVI, suggesting that patients with extreme RV remodeling should probably be excluded from the treatment.

Interestingly, it has been observed that procedural success has a clinical impact already in the early post-procedural phase after TTVI, because 30-day mortality was significantly higher in patients in whom procedural success is not achieved (6.9% vs. 1.9%; p = 0.04), with a longer hospital length of stay. This last observation may, of course, be affected by a selection bias, because patients with greater coaptation depth and reduced procedural success are patients with more advanced RV failure and more compromised clinical conditions.

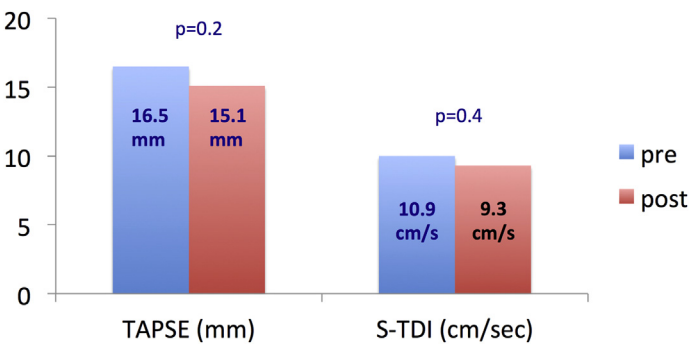
FIGURE 2 Comparison of TR Grade at Baseline and at 30 Days



TR = tricuspid regurgitation.

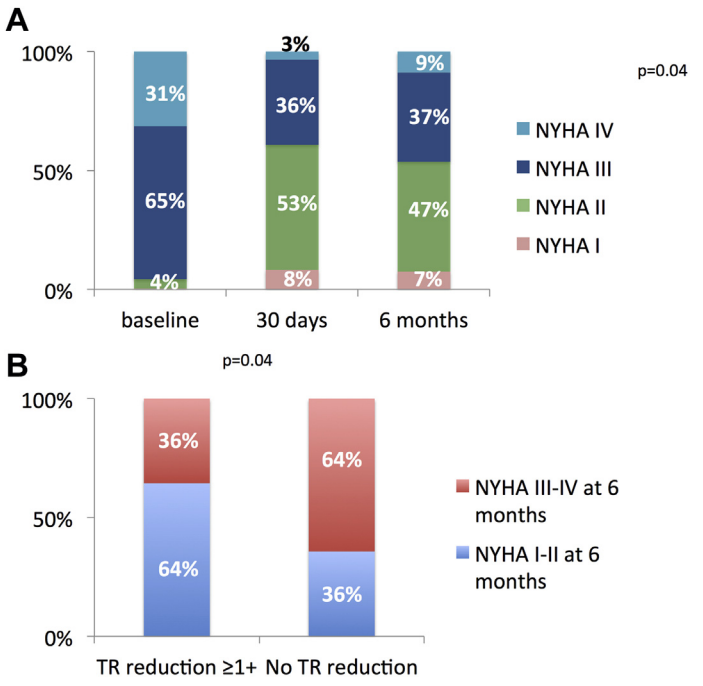
MID-TERM OUTCOMES: THE IMPORTANCE OF REDUCING TR. Because intraprocedural mortality was 0%, procedural failure in the present study was mainly driven by residual TR >2+. Most of the patients undergoing TTVI in this early phase of this new therapy present with "torrential" TR (25), as confirmed from the baseline echocardiographic

FIGURE 3 Change of RV Function Pre and 30 Days After the Procedure



RV = right ventricle; S-TDI = systolic tissue Doppler imaging; TAPSE = tricuspid annular plane systolic excursion.

FIGURE 4 NYHA Functional Class



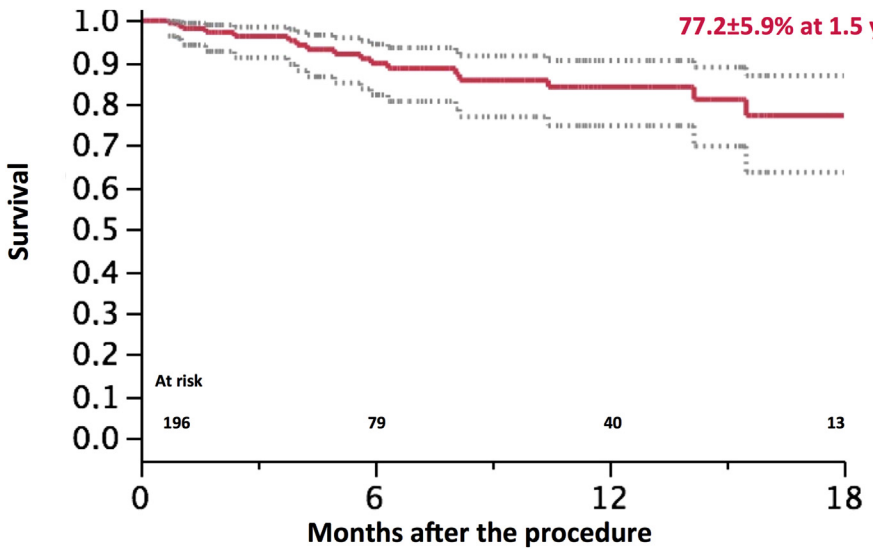
(A) NYHA functional class at baseline, 30 days, and 6 months follow-up. **(B)** NYHA functional class at 6 months according to TR reduction. NYHA = New York Heart Association.

profile of the present study (vena contracta width more than 1 cm, EROA about 0.8 cm^2, regurgitant volume 54 ml/beat). It has been shown in different feasibility trials that a mild reduction of TR severity, even if residual TR is still severe, is associated with improved symptoms and quality of life, most likely due to improved cardiac output and renal perfusion (7,8). The results of the present study show that obtaining a substantial TR reduction (≤2+) is strongly associated with improved survival at mid-term follow-up, independently from copathologies, initial symptoms, and RV function. Although observational, this is the first report of any intervention, surgical or transcatheter, showing a survival benefit associated with reducing TR. This is particularly relevant if we consider that patients included in this series are mostly high-risk and compassionate cases. Moreover, it is interesting to note that the excess mortality in patients with procedural failure and residual TR continues beyond 30 days, suggesting that residual TR has an impact on survival that is independent from the acute post-procedural phase.

The impact of procedural success on survival further emphasizes the importance of 2 elements:

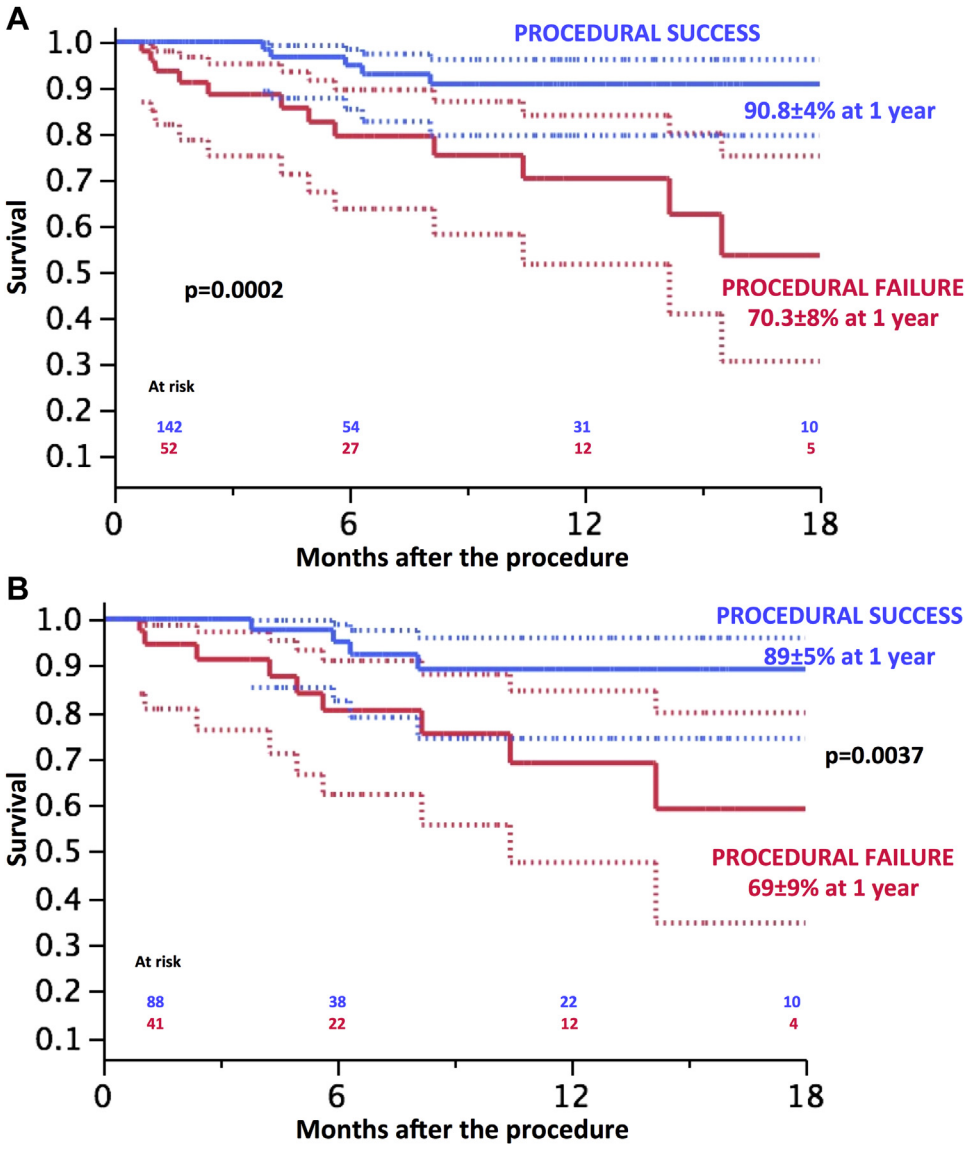
1. Clinical and anatomic patient selection: if a substantial TR reduction is the target, the patient should not be clinically too advanced in the natural history of the disease (as described earlier in the text, advanced tethering is a predictor of

FIGURE 5 Overall Actuarial Survival



Dotted lines = 95% confidence interval. Abbreviations as in Figures 2 and 4.

FIGURE 6 Actuarial Survival According to Procedural Success



Dotted lines = 95% confidence interval. Actuarial survival according to procedural success in the overall population **(A)** and in the isolated TTVI group **(B)**. TTVI = transcatheter tricuspid valve intervention.

procedural failure); moreover, careful anatomic selection should be performed in order to assess feasibility and to predict efficacy; and

2. Need for more effective devices: patients treated so far have mostly had massive/torrential TR; however, a technical improvement (including better procedural imaging) of the available devices is desirable, because greater TR reduction is associated with improved survival. Given that minimal reduction in TR severity may be associated with clinical improvement, the ideal target of a TTVI procedure in the future should be a reduction of TR to ≤2+. The second point is strongly related to the first one, because with better patient selection, better efficacy can be achieved also with the current-generation devices.

Although procedural success has been identified as an independent predictor of survival at multivariate analysis (independently from age, copathology, RV and left ventricular function, symptoms, or

TABLE 5 Univariate and Multivariate Analysis of Mortality at Follow-Up

	Univariate*		Multivariate*	
	HR (CI 95%)	p Value	HR (CI 95%)	p Value
Age, yrs	6.1 (0.4–120.0)	0.20		
Procedural success	0.2 (0.1–1.15)	**0.0001**	0.18 (0.02–2.3)	**0.01**
TR reduction ≥1+	0.4 (0.06–0.8)	0.02	0.8 (0.1–1.2)	0.80
TAPSE	3.6 (0.2–46.0)	0.30		
sPAP	5.6 (0.7–38.0)	**0.09**	17.0 (1.2–252.0)	**0.03**
Isolated TTVI	0.6 (0.3–15.0)	0.45		
LVEF	0.72 (0.12–5.1)	0.70		
Vena contracta	4.1 (0.3–39.0)	0.30		
EuroSCORE II	1.2 (0.08–7.8)	0.80		
NYHA functional class III–IV	1.5 (0.4–15.0)	0.11		
COPD	1.2 (0.5–3.0)	0.57		
Ascites	1.9 (1.1–4.0)	0.08	2.1 (0.8–15.0)	0.14
Previous RV failure	2.25 (1.02–8.0)	0.10	1.06 (0.6–9.0)	0.90
NT-proBNP	1.96 (0.06–66.0)	0.80		
eGFR	0.18 (0.01–1.6)	0.13		

Values in **bold** are statistically significant. *Cox proportional hazard regression.
HR = hazard ratio; TTVI = transcatheter tricuspid valve intervention; other abbreviations as in Tables 1 to 4.

NT-proBNP), this may be affected from selection bias, as patients in whom procedural success has been achieved are also the patients with less advanced disease, as confirmed by the impact of pulmonary hypertension on survival.

STUDY LIMITATIONS. First, it is a prospective nonrandomized study, without a control group. The number of patients with severe TR who were not treated during the same period is not available. Second, this is a real-world registry reporting the clinical practice in different centers and countries; therefore, echocardiographic and clinical outcomes have been reported by the different sites and investigators, without core lab adjudication. For the same reason, the modalities of follow-up are different within the different centers. Third, due to the different number of patients treated with the different devices, any direct comparisons among the different devices would not be appropriate.

Moreover, as specified in the Methods section, definitions of procedural success and outcomes have been established by the investigators, because they have not been standardized yet.

CONCLUSIONS

TTVI is feasible with different technologies. Overall procedural success rate is reasonable and it is improving with the increasing of the procedures, as a consequence of learning curve process and better patient selection. Currently, TTVI is associated with low mortality and significant clinical improvement. Mid-term survival was excellent in this high-risk population. Greater coaptation depth (>1 cm) is independently associated with reduced success rate, which is a strong predictor of mortality at follow-up even in isolated tricuspid procedures. This last observation suggests the importance of proper procedural timing, in order to treat the patients before advanced RV remodeling occurs.

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PERSPECTIVES

WHAT IS KNOWN? Preliminary results of transcatheter tricuspid valve interventions are promising in term of safety and feasibility. However, several open challenges have to be addressed (clinical and technical), and mid-term outcomes are largely unknown.

WHAT IS NEW? The present multicenter study represents the largest series of patients treated with transcatheter tricuspid valve intervention with different devices so far, reporting good clinical outcomes at mid-term follow-up.

WHAT IS NEXT? Long-term outcomes and better patient selection are warranted in order to better understand the clinical role of transcatheter tricuspid valve intervention.

REFERENCES

1. Rodés-Cabau J, Taramasso M, O'Gara PT. Diagnosis and treatment of tricuspid valve disease: current and future perspectives. Lancet (London, England) 2016;388:2431–42.

2. Taramasso M, Pozzoli A, Guidotti A, et al. Percutaneous tricuspid valve therapies: the new frontier. Eur Heart J 2017;38:639–47.

3. Asmarats L, Puri R, Latib A, Navia JL, Rodés-Cabau J. Transcatheter tricuspid valve interventions: landscape, challenges, and future directions. J Am Coll Cardiol 2018;71:2935–56.

4. Kuwata S, Taramasso M, Nietlispach F, Maisano F. Transcatheter tricuspid valve repair toward a surgical standard: first-in-man report of direct annuloplasty with a Cardioband device to treat severe functional tricuspid regurgitation. Eur Heart J 2017;38:1261.

5. Schueler R, Hammerstingl C, Werner N, Nickenig G. Interventional direct annuloplasty for functional tricuspid regurgitation. J Am Coll Cardiol Intv 2017;10:415–6.

6. Rosser BA, Taramasso M, Maisano F. Transcatheter interventions for tricuspid regurgitation: TriCinch (4Tech). EuroIntervention 2016;12:Y110–2.

7. Hahn RT, Meduri CU, Davidson CJ, et al. Early feasibility study of a transcatheter tricuspid valve annuloplasty: SCOUT trial 30-day results. J Am Coll Cardiol 2017;69:1795–806.

8. Nickenig G, Kowalski M, Hausleiter J, et al. Transcatheter treatment of severe tricuspid regurgitation with the edge-to-edge MitraClip technique. Circulation 2017;135:1802–14.

9. Perlman G, Praz F, Puri R, et al. Transcatheter tricuspid valve repair with a new transcatheter coaptation system for the treatment of severe tricuspid regurgitation: 1-year clinical and echocardiographic results. J Am Coll Cardiol Intv 2017;10:1994–2003.

10. Fam NP, Ho EC, Zahrani M, Samargandy S, Connelly KA. Transcatheter tricuspid valve repair with the PASCAL system. J Am Coll Cardiol Intv 2018;11:407–8.

11. Lauten A, Figulla HR, Unbehaun A, et al. Interventional treatment of severe tricuspid regurgitation: early clinical experience in a multicenter, observational, first-in-man study. Circ Cardiovasc Interv 2018;11:e006061.

12. Navia JL, Kapadia S, Elgharably H, et al. First-in-human implantations of the navigate bioprosthesis in a severely dilated tricuspid annulus and in a failed tricuspid annuloplasty ring. Circ Cardiovasc Interv 2017;10:e005840.

13. Taramasso M, Hahn RT, Alessandrini H, et al. The international multicenter TriValve registry: which patients are undergoing transcatheter tricuspid repair? J Am Coll Cardiol Intv 2017;10:1982–90.

14. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739–91.

15. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2017;70:252–89.

16. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography. J Am Soc Echocardiogr 2017;30:303–71.

17. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2013;14:611–44.

18. Stone GW, Adams DH, Abraham WT, et al. Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 2: endpoint definitions: a consensus document from the Mitral Valve Academic Research Consortium. J Am Coll Cardiol 2015;66:308–21.

19. Besler C, Orban M, Rommel KP, et al. Predictors of procedural and clinical outcomes in patients with symptomatic tricuspid regurgitation undergoing transcatheter edge-to-edge repair. J Am Coll Cardiol Intv 2018;11:1119–28.

20. Taramasso M, Zuber M, Kuwata S, Nietlispach F, Maisano F. Clipping of the tricuspid valve: proposal of a "Rosetta Stone" nomenclature for procedural 3D transoesophageal guidance. EuroIntervention 2017;12:e1825–7.

21. Hahn RT. State-of-the-art review of echocardiographic imaging in the evaluation and treatment of functional tricuspid regurgitation. Circ Cardiovasc Imaging 2016;9:e005332.

22. Fukuda S, Gillinov AM, McCarthy PM, et al. Determinants of recurrent or residual functional tricuspid regurgitation after tricuspid annuloplasty. Circulation 2006;114 Suppl:I582–7.

23. McCarthy PM, Bhudia SK, Rajeswaran J, et al. Tricuspid valve repair: durability and risk factors for failure. J Thorac Cardiovasc Surg 2004;127:674–85.

24. Neuhold S, Huelsmann M, Pernicka E, et al. Impact of tricuspid regurgitation on survival in patients with chronic heart failure: unexpected findings of a long-term observational study. Eur Heart J 2013;34:844–52.

25. Hahn RT, Zamorano JL. The need for a new tricuspid regurgitation grading scheme. Eur Heart J Cardiovasc Imaging 2017;18:1342–3.

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