JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 10, NO. 19, 2017

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2017.06.036

Transcatheter Tricuspid Valve Repair With a New Transcatheter Coaptation System for the Treatment of Severe Tricuspid Regurgitation

1-Year Clinical and Echocardiographic Results

Gidon Perlman, MD,[a,b] Fabien Praz, MD,[c] Rishi Puri, MBBS, PhD,[d,e,f] Hadass Ofek, MD,[a] Jian Ye, MD,[a] Francois Philippon, MD,[d] Thierry Carrel, MD,[c] Philippe Pibarot, DVM, PhD,[d] Adrian Attinger, MD,[a] Nay Min Htun, MBBS, PhD,[a] Danny Dvir, MD,[a] Robert Moss, MD,[a] Francisco Campelo-Parada, MD,[d] Elisabeth Bédard, MD,[d] David Reineke, MD,[c] Aris Moschovitis, MD,[c] Sandra Lauck, PhD,[a] Philipp Blanke, MD,[a] Jonathon Leipsic, MD,[a] Stephan Windecker, MD,[c] Josep Rodés-Cabau, MD,[d] John Webb, MD[a]

ABSTRACT

OBJECTIVES This study sought to describe the 1-year experience with the transcatheter FORMA system for severe tricuspid regurgitation (TR).

BACKGROUND Severe TR is associated with significant morbidity and mortality. Novel transcatheter therapies have been recently developed.

METHODS Eighteen patients underwent device implantation at 3 centers in Canada and Switzerland. Baseline characteristics, procedural, 30-day, and 1-year outcomes were prospectively evaluated using multimodality imaging and hemodynamic and clinical assessments.

RESULTS Procedural success was achieved in 16 (89%) patients. Unsuccessful procedures were because of right ventricular perforation requiring open surgery and device dislocation. At 1 year there were no deaths, significant arrhythmias, device infections, or dislocations. Thrombus was observed on 1 device at 4 months and there was 1 rehospitalization for heart failure. Among the 14 patients with successful device implantation and 1-year follow-up, 79% were in New York Heart Association functional class I/II ($p < 0.001$), the average 6-min walk test increased by 84 m ($p = 0.03$), and the Kansas City Cardiomyopathy Questionnaire heart failure score improved by 18 points ($p = 0.02$) compared with baseline. Echocardiography showed a reduction of TR from severe in 17 of 18 (94%) patients at baseline to moderate-severe or less in 11 of 16 patients (69%) by 30 days ($p = 0.001$) and 6 of 13 patients (46%) by 1 year ($p = 0.01$). The diameters of the tricuspid annulus and the right ventricle were reduced at 1 year (45.7 ± 4.8 mm to 42.1 ± 4.4 mm, $p = 0.004$; 54 ± 5.3 mm to 49.9 ± 4.3 mm, $p = 0.02$, respectively).

CONCLUSIONS Implantation of the FORMA system in high-risk patients with severe TR shows feasibility with a good mid-term safety profile. At 1 year, despite variable success in reducing echocardiographic TR grade, there were significant clinical improvements and reductions in right ventricular dimensions. (J Am Coll Cardiol Intv 2017;10:1994–2003) © 2017 by the American College of Cardiology Foundation.

From the [a]St. Paul's Hospital, Vancouver, British Columbia, Canada; [b]Hadassah-Hebrew University Medical Center, Jerusalem, Israel; [c]Bern University Hospital, Bern, Switzerland; [d]Québec Heart & Lung Institute, Québec City, Quebec, Canada; [e]Department of Medicine, University of Adelaide, Adelaide, Australia; and the [f]Cleveland Clinic Coordinating Center for Clinical Research, Cleveland, Ohio. Drs. Perlman, Dvir, and Leipsic are consultants for Edwards Lifesciences. Dr. Praz is a consultant for Edwards Lifesciences. Dr. Ye is a consultant for and has received a consultation fee from Edwards Lifesciences. Dr. Pibarot is a consultant for Edwards Lifesciences and Medtronic. Dr. Blanke is a consultant for Edwards Lifesciences, Circle Cardiovascular Imaging, Neovasc, and Tendyne Holdings. Dr. Windecker has received institutional research grants from Bracco, Boston Scientific, and Terumo. Dr. Rodés-Cabau is a consultant for and has received research grants from Edwards Lifesciences. Dr. Webb is a

Tricuspid regurgitation (TR) is a common valvular disease (1) most often occurring secondary to dilation of the right ventricle (RV) and of the tricuspid annulus (2,3). Moderate-to-severe TR is associated with increased mortality (4,5). TR has been observed to develop late after left-sided valve surgery in up to 10% of patients, with an adverse impact on clinical outcomes (6). Surgical repair of moderate-to-severe TR improves long-term survival when performed in conjunction with left-sided valvular surgery (7–9).

Isolated surgery for correction of TR is rarely performed and is associated with significant surgical mortality (10,11) because of comorbidities, such as RV dysfunction, pulmonary hypertension, and prior open-heart surgical procedures (12). The significant risk of isolated TR surgery and the large number of patients with uncorrected severe TR has led to the recent development of novel transcatheter approaches to treat patients who are at high surgical risk (13–17).

SEE PAGE 2004

The FORMA system (Edwards Lifesciences, Irvine, California) is a spacer device placed within the tricuspid valve over a rail that is anchored into the RV myocardium. The spacer acts as a surface for valve leaflet coaptation, with the aim to reduce the regurgitant orifice. The device concept, the details of the implantation process, and initial 30-day first-in-human clinical outcomes have been described previously (18). The aim of this study is to report the 1-year clinical and echocardiographic outcomes of the first-in-human, multicenter, compassionate use experience with the FORMA system.

METHODS

PATIENTS AND PARTICIPATING SITES. Patients treated in 2 centers in Canada and 1 center in Switzerland were included. All patients had severe symptomatic TR and were assessed by institutional heart teams to be inoperable because of unacceptable surgical risks. The patients in Canada were treated under a special access protocol approved by Health Canada, and the patients in Switzerland were treated under the conditions of the Compassionate Use Program of the Swiss Agency for Therapeutic products (Swissmedic). All patients provided informed consent for the procedures. Important exclusions included primary TR or prior tricuspid surgery. Patients with reduced RV function severe pulmonary hypertension and dilated RV and right atrium (RA) were included. Patients with severe concomitant valvular diseases or severe left ventricular dysfunction were excluded. Patients with pacemakers or defibrillators were included after enrollment of the first 15 patients.

CARDIAC IMAGING METHODS. Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) were both performed before the procedures. The right-sided structures were assessed with a focus on tricuspid valve anatomy and TR graded according to published guidelines (19,20). During the procedure, TEE guiding served to localize the implantation site and confirm correct anchoring of the device in the myocardium of the RV apex. In addition, device placement was optimized under continuous echocardiographic appreciation of TR reduction. In the case of the presence of a RV pacemaker lead, TEE was used to exclude adhesion of the pacemaker lead to any of the valve leaflets. RV measurements were performed in end diastole from apical 4-chamber view for tricuspid annulus, basal, and mid-RV. RV function was evaluated using current indices for moderate/severe RV dysfunction including tricuspid annular plane systolic excursion (<15 mm) and tricuspid annulus systolic velocity (<11 cm/s). All studies were interpreted by a consensus of 2 echocardiographers.

All patients underwent electrocardiogram-synchronized multidetector cardiac computed tomography. The recorded images were used to measure tricuspid annular dimension, mid-ventricular diameter, and the distance from the valvular annulus to the RV apex (21). In addition, the configuration of the subvalvular apparatus including the position of the papillary muscles, the moderator band, and pacing leads were assessed. The target anchoring site was selected based on a sagittal computed tomography reconstruction perpendicular to the tricuspid annulus by drawing a perpendicular line linking the tricuspid plane with the RV septal free wall groove (**Figure 1**) (Circle Cardiovascular Imaging, Calgary, Alberta, Canada). Based on this projection, a fluoroscopic angulation allowing perpendicular representation

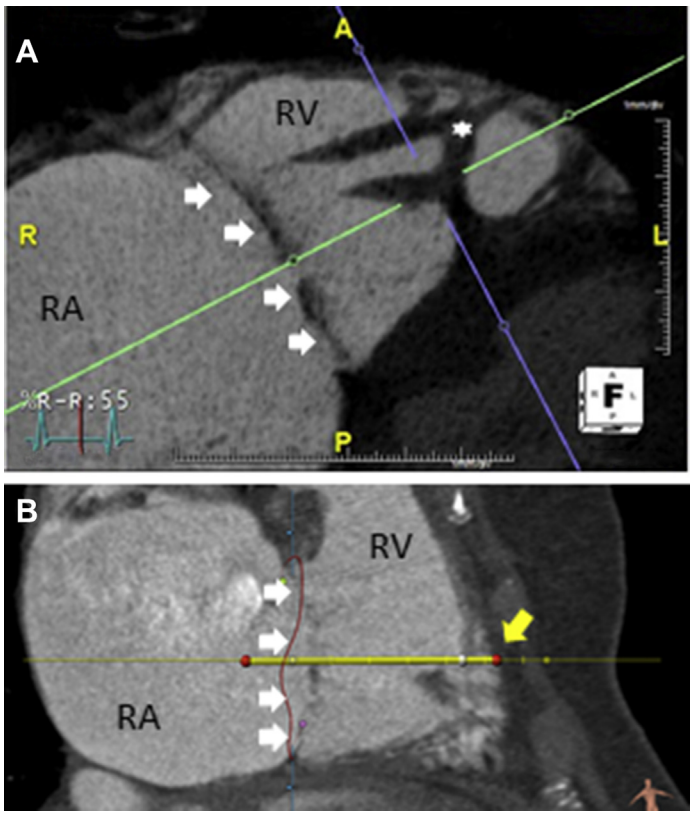
ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
EROA = effective regurgitant orifice area
RA = right atrium
RV = right ventricle
TEE = transesophageal echocardiography
TR = tricuspid regurgitation
TTE = transthoracic echocardiography
VC = vena contracta

consultant for and has received research grants from Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Perlman and Praz contributed equally to this work.

Manuscript received April 26, 2017; revised manuscript received June 11, 2017, accepted June 12, 2017.

FIGURE 1 Pre-Procedural Contrast Enhanced CT Derived 2D and 3D Images



(A) Important anatomical structures of the right heart: right atrium, right ventricle, the tricuspid valve leaflets and annular plane **(white arrows)** and a prominent moderator band **(star)**. **(B)** Sagittal reconstruction delineating the annular plane **(white arrows)** and the planned anchoring site **(yellow arrow)**. CT = Computed tomography; RA = right atrium; RV = right ventricle.

of the tricuspid annulus was defined. Finally, the information collected was computed to obtain a 3-dimensional-printed model of the right heart chambers including the access vessels (subclavian and axillary veins) enabling simulation of the device implantation process.

HEMODYNAMIC ASSESSMENT. Right heart pressure measurements for assessment of pre- and post-procedural hemodynamics were obtained in all patients. Post-procedural and 30-day measurements were obtained at 1 center (n = 6).

EDWARDS FORMA SYSTEM IMPLANTATION PROCESS. Procedures were performed under general anesthesia with TEE, fluoroscopic, and hemodynamic monitoring. Vascular access for a 24-F catheter vascular sheath was gained through the left subclavian vein by surgical cut-down or axillary vein puncture under angiography guidance. Vascular closure was achieved either surgically or with the use of a Perclose Proglide closure system (Abbott Vascular, Santa Clara, California). The 12- and 15-mm diameter FORMA spacers were available.

CLINICAL AND ECHOCARDIOGRAPHIC ENDPOINTS. Patients were seen at baseline, in-hospital, at 30 days, and at 1 year. Visits included a detailed clinical assessment, blood testing, and TTE evaluation. Major clinical endpoints were defined according to the updated Valve Academic Research Consortium-2 criteria (22). Peripheral edema was scored as: none = 0, ankle = 1, shin = 2, thigh = 3, anasarca = 4.

TR severity was graded as mild, moderate, moderate-to-severe, severe, and very severe. The severity of TR was determined primarily based on vena contracta (VC) width, color jet area, and in selected patients proximal flow convergence method. Systolic flow reversal in the hepatic veins and dilated RV chambers and interior vena cava were considered as weighting toward severe TR. VC width was measured in apical 4-chamber view (and in RV inflow and parasternal short axis when feasible). The largest measurement of VC width was used for TR severity grading (≥7 mm corresponding to severe). Effective regurgitant orifice area (EROA) by proximal convergence method of ≥40 mm^2 denoted severe TR. TR jet area >10 cm^2 indicated severe TR. Given that many patients in the study group had very large regurgitant orifice areas, an arbitrary category of very severe TR was created, therefore enabling the recognition of the potential for improvement within the severe TR category. VC width ≥12 mm and EROA ≥120 mm^2 were considered very severe TR. Severe pulmonary hypertension was diagnosed if 1 of the following was present at baseline: 1) the mean pulmonary arterial pressure as measured by invasive hemodynamics was >40 mm Hg; 2) peak RV systolic pressure was measured by echocardiography as >60 mm Hg; and 3) a patient was receiving specific pulmonary vasodilators for treatment of chronic pulmonary hypertension.

STATISTICAL ANALYSIS. Descriptive summaries are reported for all FORMA cases, and separately by length of follow-up. Continuous variables are presented as mean ± SD and were compared using Student *t* test, or paired t test for repeated measures. When appropriate, confidence intervals for means were reported as well. Categorical variables are presented as frequencies and percentages and were compared using the chi-square or Fisher exact test. Statistical significance was defined as $p < 0.05$. Analyses were performed using GraphPad Software (La Jolla, California).

TABLE 1 Baseline Characteristics (N = 18)

Age, yrs	76.0 ± 9.7
Female	13 (72)
Body mass index, kg/m^2	27.2 ± 5.7
Serum creatinine, μmol/l	131 ± 74
Clinical features of heart failure	
Exertional dyspnea	18 (100)
Lower extremity edema	12 (67)
Secondary tricuspid regurgitation	18 (100)
Severe pulmonary hypertension*	6 (33)
B-type natriuretic peptide, pg/ml	441 ± 432
N-terminal pro-B-type natriuretic peptide, pg/ml	2,812 ± 2,798
Daily furosemide dose, mg†	85 ± 73
NYHA functional class	
II	1 (6)
III	14 (78)
IV	3 (17)
EuroSCORE II	9.0 ± 5.7
6-min walk test	256 ± 103
Kansas City Cardiomyopathy Questionnaire	63.0 ± 20.4
Coexisting conditions	
Hypertension	16 (89)
Diabetes	2 (11)
Creatinine clearance <30 ml/min (eGFR)	3 (17)
Atrial fibrillation	16 (89)
Coronary artery disease	10 (56)
Previous open-heart surgery	13 (72)
Previous left-sided valvular surgery	9 (50)
Aortic	4 (22)
Mitral	6 (33)
Stroke/TIA	2 (11)
COPD	5 (28)
Pacemaker/defibrillator	3 (17)

Values are mean ± SD or n (%). *Mean pulmonary artery pressure >40 mm Hg or peak systolic pressure >60 mm Hg, or specific medical treatment for pulmonary arterial hypertension. †When patients received torsemide, a conversion ratio of 2:1 was used for calculating an equivalent dose of furosemide.

COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; NYHA = New York Heart Association; TIA = transient ischemic attack.

RESULTS

BASELINE CHARACTERISTICS. Eighteen patients were treated with the FORMA system between February 2015 and July 2016. To date, all patients are being followed and 15 patients have undergone 1-year follow-up. Mean age was 76 ± 9.7 years and 72% were female. As shown in Table 1, patients were high risk for surgery as estimated by a EuroSCORE II score of 9.1 ± 5.7%. Thirteen patients (72%) had a history of previous open-heart surgery, most often left-sided valvular surgery (56%). Additional comorbidities included atrial fibrillation (AF) (89%) and severe pulmonary hypertension (33%).

TABLE 2 Procedural Variables

	First 15 Patients (n = 15)	All Patients (n = 18)
Left subclavian vein access	15 (100)	17 (94)
Right subclavian vein access	0 (0)	1 (6)
Left-sided pacemaker present	0 (0)	2 (11)
Right-sided pacemaker present	0 (0)	1 (6)
FORMA spacer size implanted		
15 mm	14 (93)	16 (89)
12 mm	1 (7)	1 (6)
Retrieval attempt/success	3 (20)/1 (7)	3 (17)/1 (6)
Venous closure		
Surgical	11 (73)	13 (72)
Perclose device	4 (27)	5 (28)
Procedure time, skin-to-skin, min	131 ± 30	129 ± 31
Fluoroscopy time, min	23.9 ± 7.1	24.7 ± 7.3
Contrast media, ml	71 ± 28	65 ± 29
Successful device implantation*	14 (93)	16 (89)
Dislocation of spacer into right atrium	1 (7)	1 (6)
Conversion to surgery	0 (0)	1 (6)
Sustained ventricular arrhythmia	1 (7)	1 (6)
Mortality	0 (0)	0 (0)

Values are n (%) or mean ± SD. *A successful implantation of a FORMA spacer in the tricuspid valve resulting in an acute reduction of tricuspid regurgitation by at least 1 grade, with no need for surgical conversion or procedural death.

EROA = effective regurgitant orifice area.

CLINICAL PRESENTATION. Fatigue and exertional dyspnea were reported in all cases, and 67% of the patients had accompanying significant peripheral edema. Within the 12 months preceding the procedure, 10 patients (56%) required hospitalization for treatment of heart failure. Patients were taking an average daily dose of 85 mg of furosemide (or equivalent torasemide) for treatment of heart failure. New York Heart Association functional class was III or more in 94% of participants and the average 6-min-walk test distance was 256 ± 103 m.

PROCEDURAL AND HOSPITAL COURSE. Procedural characteristics are detailed in Table 2. Vascular access was achieved through the left subclavian or axillary veins in all cases; surgical closure was performed in 72%. Mean skin-to-skin procedure time was 129 ± 36 min. One procedure (6%) was performed with the 12-mm device, and an additional procedure was initially attempted with a 12-mm spacer that was replaced with a 15-mm spacer because of insufficient efficacy of the smaller device.

Procedural success was achieved in 16 patients (89%). One patient's device dislocated into the RA a few hours after the intervention because of inadequate anchoring. A second patient experienced a perforation of the RV during positioning of the guiding catheter at the apex, necessitating emergent

TABLE 3 30-Day and 1-Year Clinical Outcomes

	30 Day (n = 18)	1 Year (n =1 5)
Death	0 (0)	0 (0)
TIA	1 (6)	1 (7)
Myocardial infarction	0 (0)	0 (0)
Rehospitalization for heart failure	0 (0)	1 (7)
Access-related bleeding		
Life threatening*	1 (6)	NA
Major†	1 (6)	NA
Minor	2 (11)	NA
Other bleeding events, minor GI	0 (0)	1 (7)
Vascular complications		
Major	0 (0)	NA
Minor	1 (6)	NA
Hospital stay, days	4 (2-5)	NA
Acute kidney injury ≥2	0 (0)	1 (7)
Sustained ventricular arrhythmia‡	0 (0)	0 (0)
Pulmonary embolism	0 (0)	0 (0)
New pacemaker	0 (0)	0 (0)
Device thrombosis§	0 (0)	1 (7)
Infection‖	1 (6)	4 (27)

Values are n (%) or median (interquartile range). *Tamponade from right ventricle perforation that necessitated surgical repair. †Pocket hematoma with nerve compression (paresthesia). ‡Not occurring during the procedure. §Occurred in a patient with nontherapeutic international normalized ratio levels, resolved with resumption of adequate anticoagulation. ‖Three cases of pneumonia (twice in the same patient), 1 case of cholecystitis, and 1 case of leg cellulitis.

GI = gastrointestinal; IQR = interquartile range; NA = not applicable; other abbreviation as in Table 1.

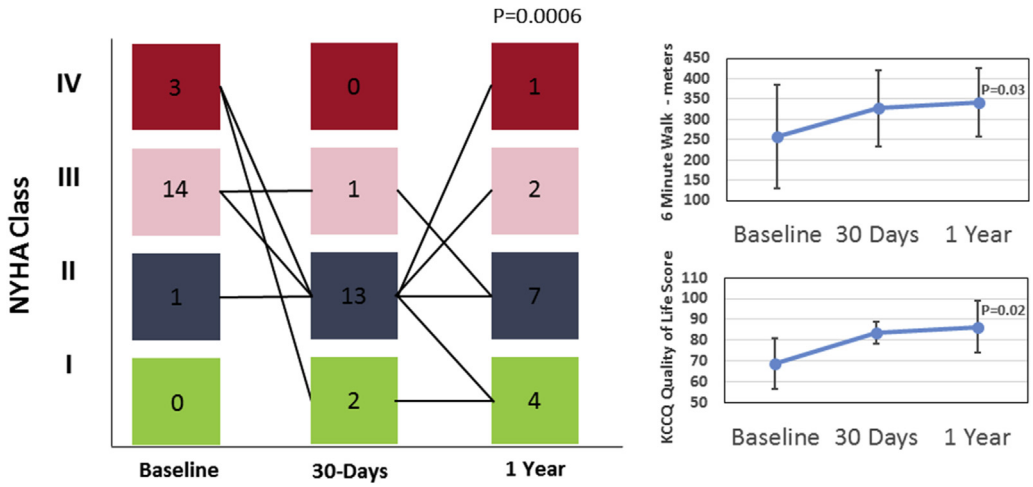
conversion to repair the perforation and to perform surgical tricuspid annuloplasty, which was done uneventfully with a good final result.

There were no procedural deaths, myocardial infarctions, or pulmonary embolisms. One patient had a prolonged hospital course because of pneumonia, transient ischemic attack, mild access site bleeding, and mild acute kidney injury. Two patients had intraprocedural sustained ventricular ectopy that resolved with repositioning of the anchoring rail. Two other patients had frequent premature ventricular beats that subsided within 24 h under medical treatment (beta-blockers). In 1 patient, paresthesia of the left hand developed as a result of an access site hematoma. Median hospital stay was 4 days (interquartile range: 2 to 5 days); it is noteworthy that at 1 center the last 3 patients were discharged within 24 h after the procedure.

ONE-YEAR CLINICAL OUTCOMES. At 1 year, there were no deaths, no surgical site or device infections, no pulmonary embolisms, and no significant arrhythmias requiring device or antiarrhythmic intervention (Table 3).

Overall, functional status improved significantly by 30 days in patients with successful implantation of the FORMA system. Clinical improvement was sustained over 1 year of follow-up; New York Heart Association

FIGURE 2 Functional Status After FORMA System Implantation



Functional status at baseline, 30 days, and 1 year was assessed by New York Heart Association functional class, 6-min walk test, and the Kansas City Cardiomyopathy Questionnaire score. The 30-day and 1-year results are not presented for 2 patients with failed procedures. The p values were calculated for the comparison between baseline and 1 year results. KCCQ = Kansas City Cardiomyopathy Questionnaire; NYHA = New York Heart Association.

TABLE 4 1 Year Functional and Laboratory Outcomes

	Baseline (n = 18)	30 Day (n = 16)*	1 Year (n = 14)*	Δ Paired (95% CI)	p Value
NYHA functional class	3.1 ± 0.5	2.0 ± 0.5	2.0 ± 0.9	−1.1 (−1.7 to −0.6)	0.0006
NYHA functional class I/II	1 (6)	15 (94)	11 (79)		0.0001
Hospitalization for heart failure†	10 (56)	0 (0)	1 (7)		0.008
6-min walk test, m	258 ± 127	327 ± 93	342 ± 85	84 (159 to 10)	0.032
Kansas City Cardiomyopathy Questionnaire score	68.7 ± 12.3	83.6 ± 5.4	86.4 ± 12.5	17.7 (32.7 to 2.6)	0.02
Edema score	1.6 ± 1.3	1.1 ± 0.9	0.5 ± 0.7	−1.1 (−1.7 to −0.6)	<0.0001
Weight, kg	73.3 ± 14.1	73.7 ± 15.5	74.1 ± 15.8	0.9 (1.9 to −3.7)	0.51
Daily furosemide dose, mg	80 ± 48	80 ± 62	72 ± 47	−8 (−22 to 39)	0.56
B-type natriuretic peptide, pg/ml	441 ± 432	482 ± 474	NA	NA	NA
N-terminal pro-B-type natriuretic peptide, pg/ml	3,264 ± 2,973	3,193 ± 2,830	2,720 ± 2,148	−543 (−1,821 to 734)	0.35
eGFR, ml/min	42.2 ± 17.0	46.6 ± 19.5	46.9 ± 20.9	4.7 (10.0 to −0.6)	0.07
Hemoglobin, g/dl	11.8 ± 2.5	11.3 ± 1.5	11.5 ± 1.8	−0.3 (−1.5 to 0.9)	0.54

Values are mean ± SD or n (%), unless otherwise indicated. The p values and change in mean values were calculated for paired data at baseline and 1 year. Edema was scored as: none = 0, ankle = 1, shin = 2, thigh = 3, anasarca = 4. *Data do not include 2 patients with failed procedures. †Baseline hospitalization events refers to the 12 months preceding the procedure.

CI = confidence interval; other abbreviations as in Table 1.

functional class improved in 12 of 14 (86%) patients with a FORMA device in place (Figure 2).

The improvement in functional status translated into significant increases in the distance walked during 6 min and in the Kansas City Cardiomyopathy Questionnaire heart failure score. Rehospitalization for heart failure occurred in only 1 patient after successful FORMA device implantation. This represents a significant reduction compared with the rate (56%) of hospitalizations during the 12 months before the procedure (Table 4).

The severity of peripheral edema significantly improved compared with baseline, with only 1 patient presenting with an edema score higher than grade 1 (ankle level) versus 13 patients (72%) at baseline (p = 0.008). Subsequently, the use of diuretics also decreased by 1 year (Table 4).

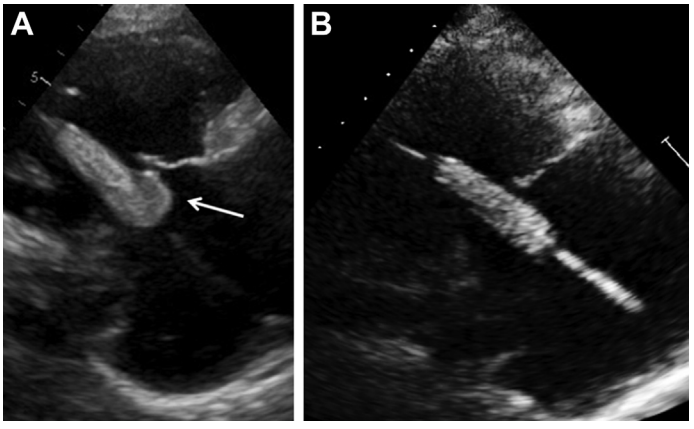
Levels of N-terminal pro-B-type natriuretic peptide decreased in most patients (3,264 ± 2,973 pg/ml at baseline vs. 2,720 ± 2,148 pg/ml at 1 year; p = 0.39). Similarly, kidney function (measured as glomerular filtration rate) improved after FORMA implantation (42.2 ± 17 ml/min at baseline vs. 46.9 ± 20.9 ml/min at 1 year; p = 0.07), although these changes did not reach statistical significance (Table 4).

One patient was diagnosed with thrombosis of a 12-mm spacer that occurred during hospitalization for treatment of pneumonia 4 months post-procedure (Figure 3). A previous TTE, 2 months earlier, had shown a normal appearance of the device. This patient had nontherapeutic international normalized ratios on warfarin most probably explained by the ongoing infection. Following antibiotic treatment and resumption of adequate anticoagulation, the thrombus resolved within 2 months. At 12 months, no recurrence was observed and the patient was feeling well (New York Heart Association functional class II).

Additional adverse events included a second transient ischemic attack 51 days after the procedure, in a patient with permanent AF who had already experienced a periprocedural event. Noncardiovascular conditions leading to hospitalization included a hip fracture in 1 patient, cholecystitis and recurrent pneumonia in a second, and severe diarrhea in a third.

ECHOCARDIOGRAPHIC FINDINGS. All patients except 1 had severe TR at baseline with a remarkably

FIGURE 3 FORMA Device Thrombosis



(A) Transthoracic echocardiography performed 4 months after FORMA implantation revealed a thrombus **(arrow)** attached to the atrial side of a 12-mm spacer. **(B)** After resumption of adequate anticoagulation the thrombus resolved and was not seen at the 1-year transthoracic echocardiography evaluation.

TABLE 5 1-Year Echocardiography Results

	Baseline (n = 18)	30 Day (n = 16)*	1 Year (n = 13)*	Δ Paired (95% CI)	p Value
Tricuspid regurgitation grade					
None/trivial	0	0	0		1.00
Mild	0	0	1		0.41
Moderate	0	9	2		0.17
Moderate-severe	1	2	3		0.28
Severe	6	4	4		1.00
Very severe†	11	1	3		0.07
Severe/very severe	17	5	7		0.01
EROA, mm^2	103 ± 61	44 ± 25	100 ± 52	NA	NA
Vena contracta width, mm	12.1 ± 3.3	7.1 ± 2.2	8.3 ± 3.9	−3.7 (−6.9 to −0.6)	0.02
Tricuspid annulus diameter, mm	45.7 ± 4.8	42.7 ± 5.2	42.1 ± 4.4	−3.6 (−5.9 to −1.4)	0.004
Tricuspid mean diastolic gradient, mm Hg	2.2 ± 0.8	2.0 ± 0.8	1.4 ± 0.4	−0.9 (−1.8 to 0.1)	0.08
RV systolic function‡					
Normal	7	4	2		0.22
Mildly reduced	7	6	3		0.44
Moderately reduced	2	4	5		0.18
Severely reduced	1	2	3		0.29
RV diameter, base, mm	54.0 ± 5.3	50.4 ± 5.4	49.9 ± 4.3	−4.2 (−7.4 to −0.9)	0.02
RV diameter, mid-ventricle, mm	42.9 ± 7.6	40.4 ± 5.5	41.8 ± 5.6	−1.1 (−3.4 to 5.7)	0.59
TAPSE, mm	14.7 ± 5.4	13.5 ± 3.1	11.3 ± 3.7	−3.4 (−8.1 to 1.2)	0.12
RV systolic pressure, mm Hg	43 ± 13	48 ± 11	47 ± 19	3.0 (9 to −3)	0.25
Inferior vena cava diameter, mm	27 ± 7	25 ± 7	25 ± 8	−2.0 (−2 to 6)	0.34
RA volume, ml^2	143 ± 59	142 ± 59	142 ± 56	−1.0 (21 to −19)	0.89
Mitral regurgitation ≥moderate	4 (22)	3 (23)	3 (28)		1.00
Left ventricle ejection fraction, %	59 ± 9	61 ± 9	60 ± 7	1.0 (3 to −2)	0.54

Values are n, mean ± SD, or n (%), unless otherwise indicated. The p values and change in mean values were calculated for paired data at baseline and 1 year. *Data do not include 2 patients with failed procedures; additionally, echocardiographic data were missing for 1 patient at 1 year. †Very severe TR was categorized as a TR consistent with severe TR but with a vena contracta >12 mm or an EROA >120 mm^2. ‡Baseline imaging not sufficient for assessment of RV function in 1 patient.

EROA = effective regurgitant orifice area; RA = right atrium; RV = right ventricle; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation; other abbreviations as in Tables 3 and 4.

high proportion (61%) presenting with a VC >12 mm or an EROA >120 mm^2, thus subclassified as very severe (or "torrential") TR (Table 5). The etiology of TR was secondary to RV annular dilatation in all patients, most often in combination with left-sided valvular heart disease or pulmonary hypertension. RV dimensions were enlarged (mean annular diameter, 46 ± 6 mm). However, systolic RV function was moderately or severely impaired in only 3 patients (17%). Pulmonary arterial pressures were moderately elevated in most patients (mean RV systolic pressure, 43 ± 13 mm Hg) and severely elevated (>60 mm Hg) in only 2 patients (11%).

The 30-day echocardiographic evaluation of TR demonstrated a reduction of TR severity in all patients with a successfully implanted device, except for 1. Residual moderate TR was observed in most cases. Five patients still had severe TR according to guidelines criteria, but there were no patients with very severe TR (Table 5). At 30 days, there was evidence of reduction of RV and RA sizes and a small increase in RV systolic pressure (3 ± 14 mm Hg on average).

After 1 year of follow-up, 3 patients had further regression of TR to mild or moderate severity. However, 7 patients still had severe TR, but of these only 3 were subclassified as recurrent very severe TR. RV diameters significantly decreased compared with baseline measurements (mean diameter measured at the base of the RV, 49.9 ± 4.3 mm vs. 54.0 ± 5.3 mm at baseline; p = 0.02).

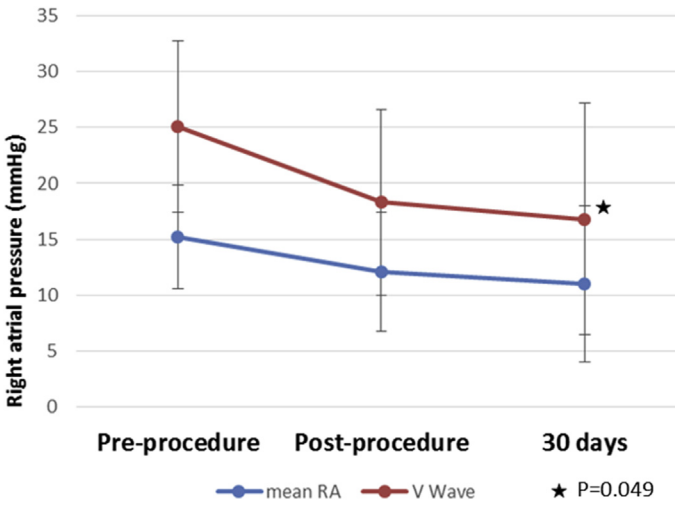
Echocardiographic evidence of reverse RV remodeling, defined as a sustained decrease in RV dimensions with concomitant evidence of significant reduction of TR, was found in 4 patients (28%). This translated into early and significant improvement of both TR and clinical status in all 4 patients. Patients with RV remodeling did not have severe pulmonary hypertension and 3 of 4 patients had good systolic RV function at baseline.

HEMODYNAMIC FINDINGS. Baseline mean RA pressure was elevated (15.2 ± 4.6 mm Hg) and RA systolic V-wave was 25.1 ± 7.7 mm Hg, signifying severe TR. Pulmonary pressures were mildly elevated

and pulmonary arterial systolic pressure was 39.7 ± 9.7 mm Hg.

Immediately after placement of the FORMA system a reduction in RA pressures, especially the V-wave, was observed in most patients. Mean RA pressure was reduced to 12.1 ± 5.3 mm Hg and the RA V-wave was reduced to 18.3 ± 8.3 mm Hg. Simultaneously, RV systolic pressures rose slightly by an average of 3.4 mm Hg. Cardiac output measurements pre- and post-procedure performed in 5 patients demonstrated an increase from 5.8 ± 1.9 l/min to 7.1 ± 1.9 l/min. Figure 4 describes data in 6 patients (38%) who underwent repeat hemodynamic assessment at 30 days post-procedure, with evidence of further reductions in RA pressures.

FIGURE 4 Right Atrial Pressures Before and After FORMA System Implantation



Right atrial pressures, mean **(blue line)** and V-wave **(red line)**, decreased immediately after FORMA implantation and even further by 30 days. The right atrial V-wave pressure was significantly lower than the baseline measurement by 30 days ($p = 0.049$). Abbreviation as in Figure 1.

DISCUSSION

The FORMA system was developed with the aim to address an important unmet clinical need of reducing TR in high-risk, mostly elderly patients. We report the 1-year outcomes of the first-in-human experience with the transcatheter FORMA system in a high-risk cohort of patients treated under compassionate use conditions.

The main finding of our study is the significant clinical benefit derived from the reduction of TR and improvement of RV dimensions achieved with the FORMA system at 1 year of follow-up. This favorable trend led to a reduction of the frequency of hospitalizations for heart failure and to improved functional measurements. The clinical benefit observed seems associated with the reduction in RA pressures and improvement in RV stroke volumes and forward flow. Interestingly, preliminary results with other percutaneous devices, such as the Tricinch device (4Tech Cardio Ltd., Galway, Ireland), Trialign system (Mitralign Inc., Boston, Massachusetts), and even "off-label" use of the MitraClip system (Abbott Vascular) have also shown similar clinical improvements following partial correction of TR (13-15).

Echocardiographic results of the FORMA device showed only moderate reduction of TR as assessed by TTE. This is in contrast with the significant clinical improvement observed in most of the patients. More than one-half of the patients included in this study had extreme TR (often referred to as "torrential") with unusually large EROAs and venae contracta. These patients may be refused for surgical reconstruction because of advanced disease and severely dilated right-sided heart chambers. Following successful FORMA system implantation, TR reduction was observed in most patients. Although complete coaptation may not be achieved, reductions of TR may suffice to result in significant clinical and hemodynamic improvement. Of note, the high number of patients with residual severe TR at 1 year includes patients with significant reductions in EROA and VC measurements that remain within the range of severe TR according to currently accepted guidelines.

The evaluation of TR after placement of a FORMA system is complex because splitting of the TR jet into multiple smaller noncircular jets occurs and makes quantitative and semi-quantitative assessment of TR rather challenging. In the present analysis, EROA was assessed by planimetry of 3-dimensional images of the regurgitant orifice, a technically challenging measurement. Calculating EROA based on proximal isovelocity surface area measurements is probably unreliable because the regurgitant orifices are generally multiple, slit-like, and extremely noncircular. This anatomic complexity hindered accurate calculation of EROA in several patients and made quantitative analysis of the reduction in TR volumes virtually impossible. In addition, TR severity depends on respiration, fluid (over-)load (related to the intensity of diuretics treatment), and RV function. Short-term results at 30 days seemed more favorable,

whereas some patients showed recurrence of severe TR after 1 year. This might be a result of alterations in the interaction of the FORMA device with the tricuspid leaflets because of changes in relative positioning of the spacer, or because of progressive continued dilatation of the RV annulus.

The reductions in the size of the RV and RA observed in several patients confirm the positive effect of even modest improvements in TR. Although this was not seen in all patients, 4 patients (28%) showed evidence of significant reverse remodeling of the RV geometry. These patients also experienced profound clinical improvements. However, the small number of patients in this cohort prevented the identification of baseline or procedural factors associated with this positive response and evidence of RV remodeling should be considered as hypothesis-generating at this stage.

The procedural safety of the first-in-human experience with the FORMA device seemed satisfactory. One case of RV perforation was seen, probably resulting from excessive force exerted on the RV free wall with the delivery catheter during the process of positioning before anchoring of the rail. A second unsuccessful procedure (the first ever performed in the implanting center) was caused by failure to anchor the rail securely and resulted in device dislocation. Correct rail implantation was hindered by extreme dilation of both heart chambers and trabeculation of the RV myocardium. Retrospective analysis of this case revealed in addition that the catheter length was not sufficient to make adequate contact with the landing zone. Following this case venous anatomy and the distance from the access site to the RV apex is now routinely assessed in all pre-procedural evaluations. The device settled in the RA and has been followed uneventfully for over a year. The patient continues to receive medical treatment for symptomatic TR.

The mid-term 1-year safety of the FORMA device seemed good with no deaths or severe device-related events beyond the immediate implantation process. One case of device thrombosis after 4 months was observed in a patient with uncontrolled anticoagulation treatment. The thrombus resolved uneventfully with resumption of effective anticoagulation treatment. Of note, 89% of the patients in this cohort had AF and received long-term oral anticoagulation. Indeed, AF is quite common in patients with severe TR and is linked to the dilatation of the RA and secondary TR (23,24). Current guidelines recommend oral anticoagulation for 3 months following tricuspid valve bioprosthetic valve implantation (9). It is, however, unclear at this stage if there is need for anticoagulation after FORMA system implantation and for how long this might be needed in patients who do not have other indications for anticoagulation.

STUDY LIMITATIONS. The first-in-human nature of this study limits the ability to generalize the results to a larger population of patients with possibly lower risk profiles. The very early experience of the centers performing the procedures may also have led to less than optimal results in patient selection and in procedural performance. The small number of patients does not permit analysis of subgroups, specifically factors predicting treatment response cannot yet be defined. Follow-up was not uniform across all centers and important data were missing from some patients (e.g., hemodynamics). Nevertheless, the significant findings in this small cohort are intriguing and should generate further investigations.

CONCLUSIONS

Initial experience with the FORMA device in high-risk patients with severe TR shows feasibility, good mid-term safety profile, and significant clinical improvements despite variable success in consistently reducing TR.

ADDRESS FOR CORRESPONDENCE: Dr. John Webb, St. Paul's Hospital, 1081 Burrard Street, Vancouver, British Columbia V6Z 1Y6, Canada. E-mail: webb@providencehealth.bc.ca.

PERSPECTIVES

WHAT IS KNOWN? Severe TR is associated with increased morbidity and mortality. Novel transcatheter devices have been developed to treat TR in high-risk patients.

WHAT IS NEW? We report the 1-year outcomes of patients treated with the FORMA system. The main findings are improved clinical outcomes at 1 year.

WHAT IS NEXT? Future developments in transcatheter treatments for TR are needed to improve efficacy and further study is necessary to identify patients more likely to respond well to these therapies.

REFERENCES

1. Stuge O, Liddicoat J. Emerging opportunities for cardiac surgeons within structural heart disease. J Thorac Cardiovasc Surg 2006;132:1258–61.

2. Rogers JH, Bolling SF. The tricuspid valve: current perspective and evolving management of tricuspid regurgitation. Circulation 2009;119:2718–25.

3. Rodés-Cabau J, Tamarasso M, O'Gara P. Diagnosis and treatment of tricuspid valve disease: current and future perspectives. Lancet 2016;388:2431–42.

4. Topilsky Y, Nkomo VT, Vatury O, et al. Clinical outcome of isolated tricuspid regurgitation. J Am Coll Cardiol Img 2014;7:1185–94.

5. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. J Am Coll Cardiol 2004;43:405–9.

6. Song H, Kim MJ, Chung CH, et al. Factors associated with development of late significant tricuspid regurgitation after successful left-sided valve surgery. Heart 2009;95:931–6.

7. Tang GHL, David TE, Singh SK, et al. Tricuspid valve repair with an annuloplasty ring results in improved long-term outcomes. Circulation 2006;114:I577–81.

8. 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 2014;63:e57–185.

9. Vahanian A, Alfieri O, Andreotti F, et al. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC); European Association for Cardio-Thoracic Surgery (EACTS), Guidelines on the management of valvular heart disease (version 2012). Euro Heart J 2012;33:2451–96.

10. Vassileva CM, Shabosky J, Boley T, et al. Tricuspid valve surgery: the past 10 years from the Nationwide Inpatient Sample (NIS) database. J Thorac Cardiovasc Surg 2012;143:1043–9.

11. Kim YJ, Kwon DA, Kim HK, et al. Determinants of surgical outcome in patients with isolated tricuspid regurgitation. Circulation 2009;120:1672–8.

12. 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.

13. Latib A, Agricola E, Pozzoli A, et al. First-in-man implantation of a tricuspid annular remodeling device for functional tricuspid regurgitation. J Am Coll Cardiol Intv 2015;8:e211–4.

14. Schofer J, Bijuklic K, Tiburtius C, Hansen L, Groothuis A, Hahn RT. First-in-human transcatheter tricuspid valve repair in a patient with severely regurgitant tricuspid valve. J Am Coll Cardiol 2015;65:1190–5.

15. Hammerstingl C, Schueler R, Malasa M, Werner N, Nickenig G. Transcatheter treatment of severe tricuspid regurgitation with the MitraClip system. Eur Heart J 2016;37:849–53.

16. Laule M, Stangl V, Sanad W, Lembcke A, Baumann G, Stangl K. Percutaneous transfemoral management of severe secondary tricuspid regurgitation with Edwards Sapien XT bioprosthesis: first-in-man experience. J Am Coll Cardiol 2013;61:1929–31.

17. Figulla HR, Kiss K, Lauten A. Transcatheter interventions for tricuspid regurgitation - heterotopic technology: TricValve. EuroIntervention 2016;12:Y116–8.

18. Campelo-Parada F, Perlman G, Philippon F, et al. First-in-man experience of a novel transcatheter repair system for treating severe tricuspid regurgitation. J Am Coll Cardiol 2015;66:2475–83.

19. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685–713.

20. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.

21. Blanke P, Dvir D, Naoum C, et al. Prediction of fluoroscopic angulation and coronary sinus location by CT in the context of transcatheter mitral valve implantation. J Cardiovasc Comput Tomogr 2015;9:183–92.

22. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol 2012;60:1438–54.

23. Topilsky Y, Khanna A, Le Tourneau T, et al. Clinical context and mechanism of functional tricuspid regurgitation in patients with and without pulmonary hypertension. Circ Cardiovasc Imaging 2012;5:314–23.

24. Utsunomiya H, Itabashi Y, Mihara H, Berdejo J, Kobayashi S, Siegel RJ, Shiota T. Functional tricuspid regurgitation caused by chronic atrial fibrillation: a real-time 3-dimensional transesophageal echocardiography study. Circ Cardiovasc Imaging 2017;10:e004897.

KEY WORDS transcatheter coaptation system, tricuspid regurgitation