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Transcatheter Versus Medical Treatment of Patients With Symptomatic Severe Tricuspid Regurgitation

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ABSTRACT

BACKGROUND Tricuspid regurgitation is associated with increased rates of heart failure (HF) and mortality. Transcatheter tricuspid valve interventions (TTVI) are promising, but the clinical benefit is unknown.

OBJECTIVES The purpose of this study was to investigate the potential benefit of TTVI over medical therapy in a propensity score matched population.

METHODS The TriValve (Transcatheter Tricuspid Valve Therapies) registry collected 472 patients from 22 European and North American centers who underwent TTVI from 2016 to 2018. A control cohort formed by 2 large retrospective registries enrolling medically managed patients with ≥ moderate tricuspid regurgitation in Europe and North America (n = 1,179) were propensity score 1:1 matched (distance ± 0.2 SD) using age, EuroSCORE II, and systolic pulmonary artery pressure. Survival was tested with Cox regression analysis. Primary endpoint was 1-year mortality or HF rehospitalization or the composite.

RESULTS After matching, 268 adequately matched pairs of patients were identified. Compared with control subjects, TTVI patients had lower 1-year mortality (23 ± 3% vs. 36 ± 3%; p = 0.001), rehospitalization (26 ± 3% vs. 47 ± 3%; p < 0.0001), and composite endpoint (32 ± 4% vs. 49 ± 3%; p = 0.0003). TTVI was associated with greater survival and freedom from HF rehospitalization (hazard ratio [HR]: 0.60; 95% confidence interval [CI]: 0.46 to 0.79; p = 0.003 unadjusted), which remained significant after adjusting for sex, New York Heart Association functional class, right ventricular dysfunction, and atrial fibrillation (HR: 0.39; 95% CI: 0.26 to 0.59; p < 0.0001) and after further adjustment for mitral regurgitation and pacemaker/defibrillator (HR: 0.35; 95% CI: 0.23 to 0.54; p < 0.0001).

CONCLUSIONS In this propensity-matched case-control study, TTVI is associated with greater survival and reduced HF rehospitalization compared with medical therapy alone. Randomized trials should be performed to confirm these results. (J Am Coll Cardiol 2019;74:2998-3008) © 2019 by the American College of Cardiology Foundation.

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Tricuspid regurgitation (TR) is a condition prevalent in the general population, particularly in older subjects, those with concomitant left-side heart disease, or with chronic atrial fibrillation (1,2).

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For decades, TR has been considered a benign valve disease (3), but more recent cohorts have attracted attention to a possible poor prognosis attached to moderate or severe TR (4). However, the natural history of TR has remained in doubt, due to its association to confounding factors, particularly TR etiology (primary vs. functional) (5,6). Hence, it is not surprising that TR is undertreated in clinical practice, but the magnitude of undertreatment is quite staggering (2). Recently, large cohorts taking into account these confounders have demonstrated that TR moderate or severe in any context and accounting for any confounder, particularly comorbidity, is associated with excess mortality and poor outcomes (4,7–10), which emphasize the seriousness of the TR undertreatment issue.

ABBREVIATIONS AND ACRONYMS

MR = mitral regurgitation

NYHA = New York Heart Association

RCT = randomized controlled trial

RV = right ventricular/ventricle

TR = tricuspid regurgitation

TTVI = transcatheter tricuspid valve interventions

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Another root cause of TR undertreatment is the poor reputation of tricuspid valve (TV) surgery (11–13). Indeed, a recent propensity-matched analysis suggested that TR surgery, repair or replacement, may not provide a detectable survival benefit (14). Thus, most of the patients with relevant TR are treated conservatively, with few therapeutic alternatives.

Based on these observations of high risk attached to TR, the treatment of TR has recently been shifting from a conservative approach to a more interventional attitude and potentially towards prevention, when feasible (15). This shift has led to first-in-human attempts at transcatheter interventions, with early feasibility studies in high-risk or inoperable patients with severe TR (16–21). However, whether the transcatheter correction of TR by these interventions improves the patients' prognosis is uncertain. There are currently no randomized controlled trials (RCTs) available, which, combined with frequent persistence of significant residual TR post-intervention (21), leaves considerable uncertainty with regard to the clinical efficacy of transcatheter TR therapies.

Hence, all recommendations reported in the current guidelines based on expert opinions or limited data (22,23) do not include indications for transcatheter treatment of TR.

The promising initial results observed with different interventional methods have generated interest in the use of these devices in high-risk patients with symptomatic relevant TR on a larger scale. The TriValve International Registry so far represents the largest multicenter, multidevice series of patients with symptomatic severe TR who underwent transcatheter tricuspid valve interventions (TTVI) (20,24). In the context of lacking RCTs, we aimed at comparing outcomes of TTVI in high-risk patients from the TriValve registry to a control group of similar patients under conservative treatment. To achieve the goal, a control series of patients with symptomatic severe TR from 2 large tertiary centers under clinical and echocardiographic follow-up was obtained using a pre-specified propensity score analysis.

METHODS

TTVI COHORT. The interventional cohort was formed by TTVI performed at 22 heart centers across Europe and North America (The TriValve registry, NCT03416166). The details of the registry have been described elsewhere (24). In brief, it included patients with severe or greater symptomatic TR according to the European or American guidelines (22,23). The decision to perform the intervention was taken by a local multidisciplinary team following clinical and anatomical assessment. TV therapies included in the registry were: MitraClip (Abbott Vascular, Santa Clara, California), FORMA (Edwards Lifesciences, Irvine, California), Cardioband (Edwards Lifesciences), Tri-Cinch (4TECH, Galway, Ireland), Trialign (Edwards Lifesciences), caval valve implantation (using different devices), PASCAL (Edwards Lifesciences), and NaviGate (NaviGate Cardiac Structures, Lake Forest, California). Clinical and echocardiographic data were collected at baseline. Follow-up events and echocardiographic data were collected whenever available from the respective centers.

CONTROL COHORT. The control cohort of patients with severe TR was formed by consecutive patients evaluated at Mayo Clinic, Rochester, Minnesota, and Leiden University Medical Center, Leiden, the Netherlands.

Exclusion criteria were previous TV surgery or intervention and iatrogenic (pacemaker lead-related) tricuspid regurgitation.

The Mayo clinic patients were all Olmsted County residents who had echocardiography examination at age >18 years detecting > moderate TR, excluding those who previously denied research authorization in accordance with Minnesota law or those incarcerated in the federal medical center.

The Leiden Medical Center patients were retrospectively extracted from the echocardiographic database as having severe TR. None of the patients of the control group underwent TV intervention or surgery during the follow-up period.

The inclusion of patients in this study was approved in each center by a local institutional review board or per local practice for the collection of retrospective data.

All of the patients of both interventional and control groups were medically treated according to guideline-directed medical therapy.

ECHOCARDIOGRAPHIC EXAMINATION. All patients had comprehensive 2-dimensional and Doppler echocardiography. Grading of TR severity used integration of semiquantitative and quantitative (if possible) measures, as described by the American Society of Echocardiography guidelines as well as the European Association of Cardiovascular Imaging guidelines (25,26). Right ventricular (RV) function was estimated visually or by measuring tricuspid annular plane systolic excursion (TAPSE). RV was considered of normal size if it appeared to be no more than two-thirds the size of the left ventricle (LV) in the standard apical 4-chamber view. RV dilatation

TABLE 1 Clinical and Echocardiographic Characteristics Are Presented for TTVI Versus Control Patients in the Overall Study Population and in the Propensity-Matched Cohort

	Overall Population (N = 1,652)			Propensity-Matched Cohort (n = 536)		
	TTVI (n = 472)	Control Subjects (n = 1,179)	p Value	TTVI (n = 268)	Control Subjects (n = 268)	p Value
Age, yrs	77 ± 8	76 ± 13	0.07	77 ± 8	76 ± 13	0.2
Women	55	63	0.007	56	59	0.4
TR of functional etiology	90	96	0.0004	90	95	0.1
Left ventricular ejection fraction	50 ± 13	49 ± 17	0.2	49 ± 15	50 ± 15	0.2
Left ventricular ejection fraction <35%	18	26	0.0006	22	21	0.7
EuroSCORE II	10.5 ± 11.2	17.9 ± 11.7	<0.0001	12 ± 11	13 ± 9	0.6
Right ventricular dysfunction	34	20	<0.0001	37	29	<0.0001
Pulmonary pressure level, mm Hg	40 ± 15	52 ± 15	<0.0001	44 ± 14	43 ± 14	0.3
Pulmonary hypertension	27	50	<0.0001	34	29	0.2
NYHA functional class III to IV	93	39	<0.0001	93	23	<0.0001
Mitral regurgitation >2+	33	18	<0.0001	40	17	<0.0001
Atrial fibrillation	83	57	<0.0001	82	50	<0.0001
Pacemaker or defibrillator	26	5	<0.0001	29	12	<0.0001

Values are mean ± SD or %.
NYHA = New York Heart Association; TR = tricuspid regurgitation; TTVI = transcatheter tricuspid valve intervention.

was identified when RV was larger than the LV in this view, or if RV displaced LV apex. Annular diameter was considered dilated when >4 cm in the standard apical 4-chamber view.

Continuous-wave Doppler-measured TR velocity and combined with right atrial pressure, estimated using inferior vena cava size and response to respiration, allowed to estimate systolic pulmonary artery pressure. Pulmonary hypertension was defined as systolic pulmonary artery pressure ≥50 mm Hg.

CLINICAL OUTCOMES. Mitral Valve Academic Research Consortium criteria were used to define adverse events (27). Primary endpoint was mortality from any cause or rehospitalization for heart failure. Secondary endpoint was overall mortality. Follow-up data were collected for patients up to 12 months.

After TTVI, procedural success was defined as patient alive at the end of the procedure, with device successfully implanted, delivery system retrieved, and residual TR <3+.

STATISTICAL ANALYSIS AND PROPENSITY MATCHING. Baseline characteristics are presented separately for the TTVI and control groups as mean ± SD and compared with a 2-sided Student's *t*-test or Wilcoxon rank sum test. Categorical variables were described as frequencies (%) and compared with a chi-square or Fisher exact test.

Patients in the TTVI cohort were matched with control subjects using propensity scores. The variable adopted to calculate propensity score were age, EuroSCORE II (ESII), and pulmonary pressure level. For each case, a control patient was randomly selected from the potential pool of candidates defined by the parameters using the nearest neighbor rule of ± 0.2 SD. Bias reduction and balance between the groups of patients with TTVI and the control subjects was assessed with standardized differences of covariates.

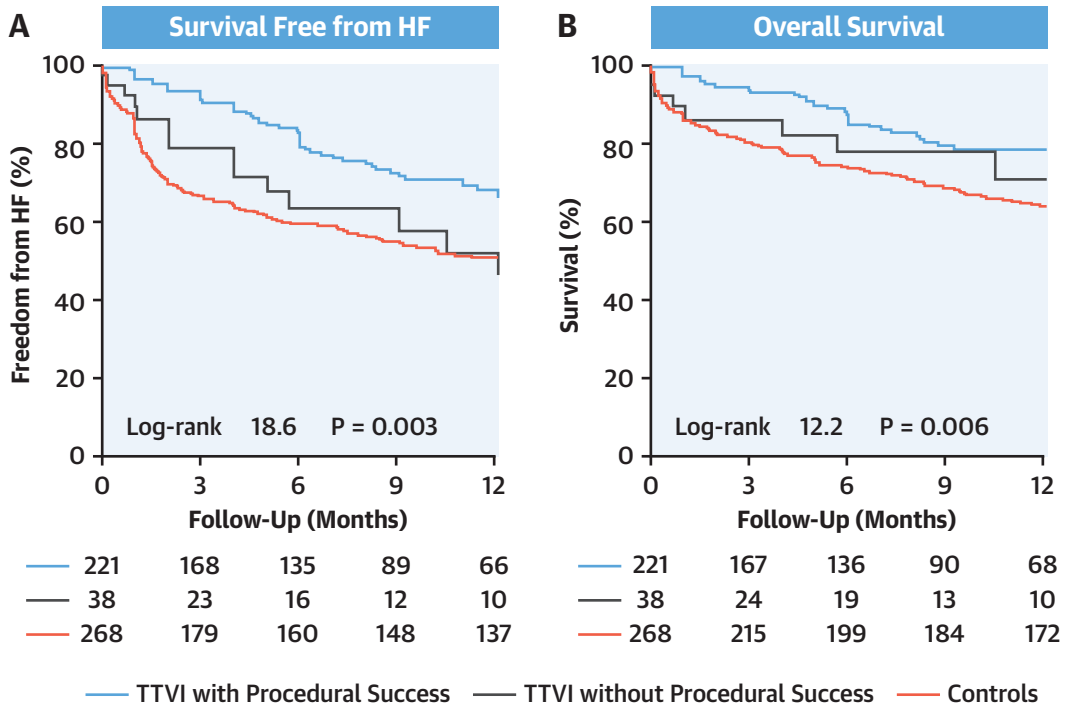
Survival rates after diagnosis were estimated using the Kaplan-Meier method and compared using log-rank test. Cox proportional hazards regression models analyzing the association of TTVI with primary and secondary endpoints. The proportional hazards assumption in the Cox models was assessed with Schoenfeld residuals, and the model fit was evaluated with martingale and Cox-Snell residuals. Analyses were performed with JMP 12 (SAS Institute, Cary, North Carolina). A value of $p < 0.05$ was considered significant.

RESULTS

GENERAL CHARACTERISTICS. A total of 472 TTVI patients and 1,179 control subjects with moderate/severe TR formed the study population. Baseline clinical and echocardiographic characteristics are presented in Table 1. Patients undergoing TTVI and control subjects had similar LV ejection fraction (50 ± 13% vs. 49 ± 17%) and age (77 ± 8 years vs. 76 ± 13 years). TR cause was mostly functional (91% in TTVI group, 96% in control subjects).

Despite these similarities, multiple differences emerged for TTVI patients versus control subjects. First, TTVI patients were less frequently women (55% vs. 63%), and had more chronic atrial fibrillation

FIGURE 1 Impact of Procedural Success



The Kaplan-Meier survival curves showing the effect of successful TTVI **(blue curve)**, unsuccessful TTVI **(black curve)**, and control subjects **(red curve)** on the primary **(A)** and secondary **(B)** endpoint. HF = heart failure; TTVI = transcatheter tricuspid valve intervention.

(85% vs. 57%). A total of 26% of TTVI versus 5% of patients in the control group had a previously implanted pacemaker or defibrillator with a lead across the tricuspid valve. The majority of patients in the TTVI group were severely symptomatic at the time of the procedure; indeed, 93% were in New York Heart Association (NYHA) functional class III/IV. TTVI patients had lower ESII (10 ± 11% vs. 17 ± 11%), more prevalent right ventricular dysfunction (34% vs. 20%), and lower pulmonary pressure level (40 ± 15 mm Hg vs. 52 ± 15 mm Hg) compared with the control group.

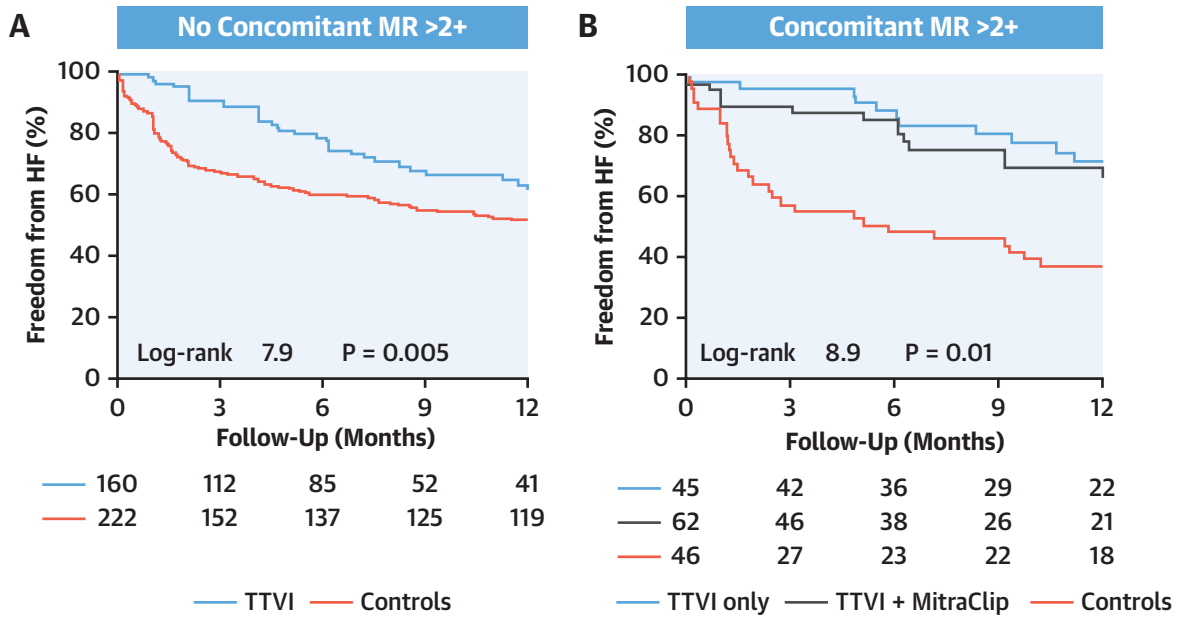
PROPENSITY-MATCHED COHORT. After matching, 268 pairs of matched patients were identified. The absolute standardized differences indicated adequate match between case and control subjects. Baseline characteristics of the matched subgroup were more balanced between TTVI and control patients, as shown in Table 1. In particular, ESII was 12 ± 11% versus 13 ± 9%, and pulmonary pressure level was 44 ± 14 vs. 43 ± 14 in TTVI versus control subjects. Differences persisted in the matched groups, with the TTVI group having higher NYHA functional class and more prevalence of atrial fibrillation, right ventricular dysfunction, mitral regurgitation, and implanted pacemaker/defibrillator (Table 1).

PROCEDURAL RESULTS AND OUTCOMES. Procedural failure with residual TR ≥3+ occurred in 38 of 268 patients (14%). Patients with successful versus unsuccessful TTVI had similar age (75 ± 10 years vs. 77 ± 9 years; p = 0.03), proportion of women (65% vs. 57%; p = 0.3), ESII (10.4 ± 6.5% vs. 12.6 ± 11.9%; p = 0.3), and comparable systolic pulmonary pressure level (46 ± 14 mm Hg vs. 43 ± 15 mm Hg; p = 0.2), but a higher proportion of patients with RV dysfunction (65% vs. 39%; p = 0.002).

Interestingly, primary and secondary endpoints at 1 year were similar in patients with unsuccessful TTVI versus matched control subjects who did not undergo tricuspid intervention (Figure 1), with 1-year mortality or heart failure rehospitalization occurring in 41.8% versus 45.9% and 1-year mortality in 27% versus 35%, respectively.

Overall 62 (23%) patients in the TTVI group had significant mitral regurgitation (>2+) requiring concomitant mitral procedure (in all cases with MitraClip) at the time of TTVI.

FIGURE 2 Outcomes in Isolated and Concomitant TR



(A) The Kaplan-Meier curves for primary endpoint in TTVI patients and control subjects without significant mitral regurgitation (MR) (>2+). **(B)** The Kaplan-Meier curves for primary endpoint in TTVI patients and control subjects with significant MR (>2+). TTVI patients who received MR intervention **(black line)** had similar outcome as compared with TTVI patients who received tricuspid valve intervention alone **(blue line).** Abbreviations as in Figure 1.

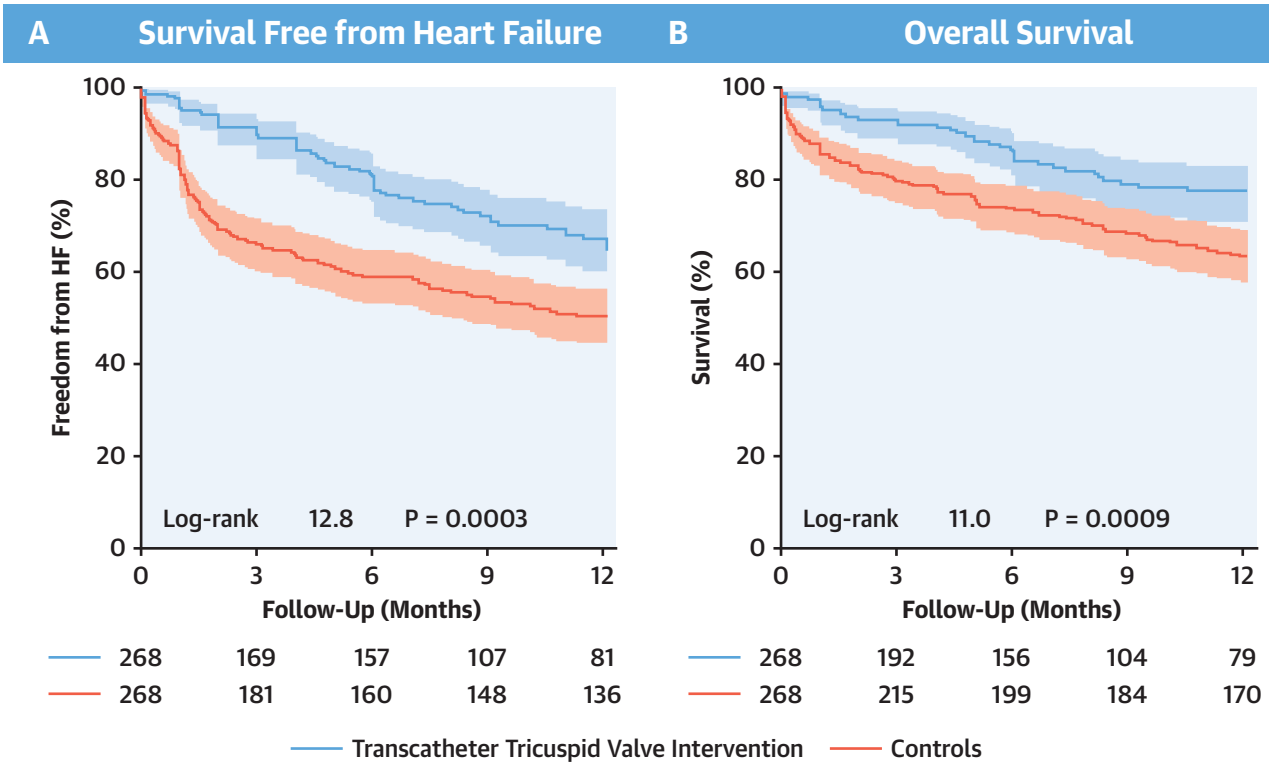
Patients who underwent combined procedures versus isolated TTVI patients had similar age (77 ± 7 years vs. 77 ± 9 years; p = 0.90), proportion of women (50% vs. 60%; p = 0.4), and ESII (10 ± 7% vs. 12 ± 12%; p = 0.4), but lower EF (45 ± 19% vs. 53 ± 11%; p = 0.01). Among TTVI patients with significant mitral regurgitation (MR), the primary (p = 0.4) endpoint was similar in patients who received TTVI alone or who had a combined TTVI and mitral procedure (Figure 2). In multivariable analysis, TTVI remained associated with greater survival free from heart failure rehospitalization, when concomitant MR treatment, by means of MitraClip, was added to the model (hazard ratio [HR]: 0.28; 95% confidence interval [CI]: 0.11 to 0.79; p = 0.02 after comprehensive adjustment).

SURVIVAL FOR TTVI VERSUS CONTROL SUBJECTS. Median follow-up time was 11 months (interquartile range: 4 to 28 months). Overall, death occurred in 13.8% of TTVI patients versus 26.1% of control subjects at 6 months, percentages that increased to 22.6% for TTVI patients and 36.2% for control subjects at 1 year.

The Kaplan-Meier analysis for TTVI versus control subjects showed significant separation between the curves, which persisted, with slight attenuation, at 1-year follow-up, similarly for the primary endpoint (survival without hospitalization for heart failure) (Central Illustration) and secondary endpoint (absolute survival) (Central Illustration). Survival benefit of TTVI was further confirmed in the subgroup of TR patients presenting without concomitant left side valvular disease (Figure 2). The adopted TTVI approach did not influence the occurrence of primary endpoint as shown in Figure 3, comparing MitraClip with other TTVI devices (p = 0.80).

In Cox proportional hazard models, unadjusted and adjusted for factors that were not used in propensity matching, TTVI was associated with survival or freedom from heart failure rehospitalization: HR: 0.60 (95% CI: 0.46 to 0.79); p = 0.003 unadjusted, and HR: 0.39 (95% CI: 0.26 to 0.59); p < 0.0001 after adjustment for sex, NYHA functional class, right ventricular dysfunction, and atrial fibrillation (Table 2). The beneficial TTVI impact on survival persisted after a more extensive adjustment including mitral regurgitation and pacemaker/defibrillator, HR: 0.35 (95% CI: 0.23 to 0.54; p < 0.0001). Stratified for the main clinical and echocardiographic characteristics (Figure 4), TTVI reduced the incidence of the primary endpoint more substantially in men, in the absence of RV dysfunction, and without device leads through the valve, independently from other

CENTRAL ILLUSTRATION **Transcatheter Treatment of Severe Tricuspid Regurgitation: Primary and Secondary Endpoints**



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Kaplan-Meier curves for transcatheter tricuspid valve intervention **(blue curve)** versus control subjects **(red curve)** according to primary **(A)** and secondary **(B)** endpoint. **Shading** identifies the pointwise confidence interval.

factors. Furthermore, in multivariable analysis, the TTVI effect was not altered by the presence of moderate/severe MR, pulmonary hypertension, or LV function.

DISCUSSION

Based on our propensity score analysis, TTVI in high-risk patients with symptomatic severe TR compared with medical treatment alone was associated with lower rates of composite endpoint of death and rehospitalization for heart failure as well as lower all-cause mortality at 1-year follow-up. Furthermore, in the interventional group, a significant difference was observed between patients who were treated with procedural success and those in whom procedural success was not achieved. TTVI patients without a significant reduction in TR shared similar outcomes with the control group, therefore confirming the prognostic importance of TR reduction in affecting outcomes. This last observation greatly extends the recent observation of better survival in patients with procedural success and significant TR reduction as compared with those in whom procedural success was not obtained (20,28), since the absence of procedural success is associated with an outcome identical to the natural history of TR, whereas with procedural success, survival is greater.

To the best of our knowledge, this is the only analysis of clinical outcomes for TTVI compared with similar patients who are treated with medical therapy alone, and the first analysis of clinical outcomes for TTVI compared with similar patients who are treated without intervention. In the absence of any RCT results, our results suggest that interventional treatment of TR is associated with improved clinical outcomes compared with medical therapy alone.

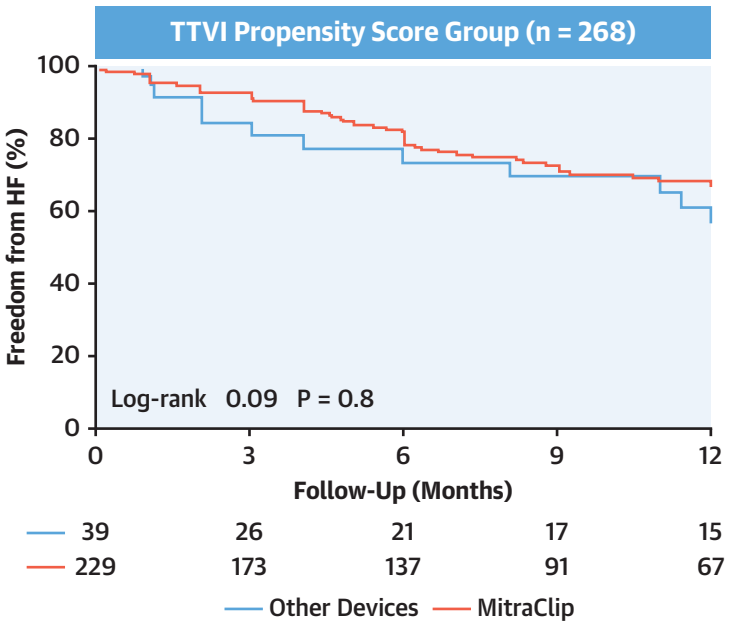
After matching, the 2 groups were similar for age, LV function, TR etiology (functional in more than 90% of the cases), operative risk, and systolic

pulmonary pressure. The interventional group, however, remains significantly different from the matched cohort, with more severe TR, worse symptoms, more severe MR, and a higher prevalence of pacemaker/defibrillator devices. Despite these additional risk factors for poor outcomes in the interventional group, TTVI was associated with superior outcomes. The benefits were consistent across numerous subgroups, including in patients who had severe and nonsevere pulmonary hypertension, in patients with and without associated MR or concomitant MR treatment, and in patients with or without RV dysfunction. Notably, the benefits were independent of the TR severity, NYHA functional class, and RV dysfunction at baseline.

Our study fills an important gap in the field of device treatment of TR, and the prognostic benefits associated with TTVI are particularly relevant if we consider that the baseline characteristics of the interventional groups were more advanced even after propensity matching. This is most likely due to the fact that at this early development stage of TTVI, more symptomatic (often end-stage) patients are referred for intervention. Initial observational studies showed feasibility and safety of TTVI with different devices, with promising clinical results (20,24,29). The most used device in the interventional group of our study was MitraClip, with similar outcomes to those observed with other devices.

The reasons why TR reduction was associated with better outcomes are not exactly known and cannot be clarified by the results of this study. It could be hypothesized that the improved outcomes with TTVI may imply a reversal of maladaptive RV remodeling caused by volume overload, with secondary worsening of annular dilatation and tricuspid tethering. The result is a vicious cycle yielding TR worsening and RV remodeling/dysfunction. Furthermore, fluid retention and chronic congestion of the venous system contribute to renal and liver impairment and further fluid retention (30). Acute and chronic passive congestion lead to diuretic resistance in up to 23% to 30% of the patients with heart failure (31,32). The ultimate consequence is refractory TR, with intractable heat failure unresponsive to medical therapy (6). In our study, TTVI and medical therapy could have synergistically interrupted this deleterious cycle before the onset of refractory end-stage TR. Hence, the prognostic benefit of TTVI may lay within the reduction of venous congestion, which may not only improve renal function per se, but also allow a better clinical response to medical therapy (33). Another potential benefit of TTVI is the reduction of chronic RV volume overload without increase in RV afterload, which results in improved RV performance, LV filling, and cardiac output (34).

FIGURE 3 Impact of the Device Used



Kaplan-Meier survival curves comparing the impact on primary endpoint of TTVI using MitraClip versus other devices. Abbreviations as in Figure 1.

The association between procedural success and greater survival underscores the importance of patient selection for TTVI, because TR reduction should be the main target of the procedure. Current procedural success with various devices is about 75%, suggesting that there is room for technical improvement in the future (better devices and better intraprocedural guidance) (20).

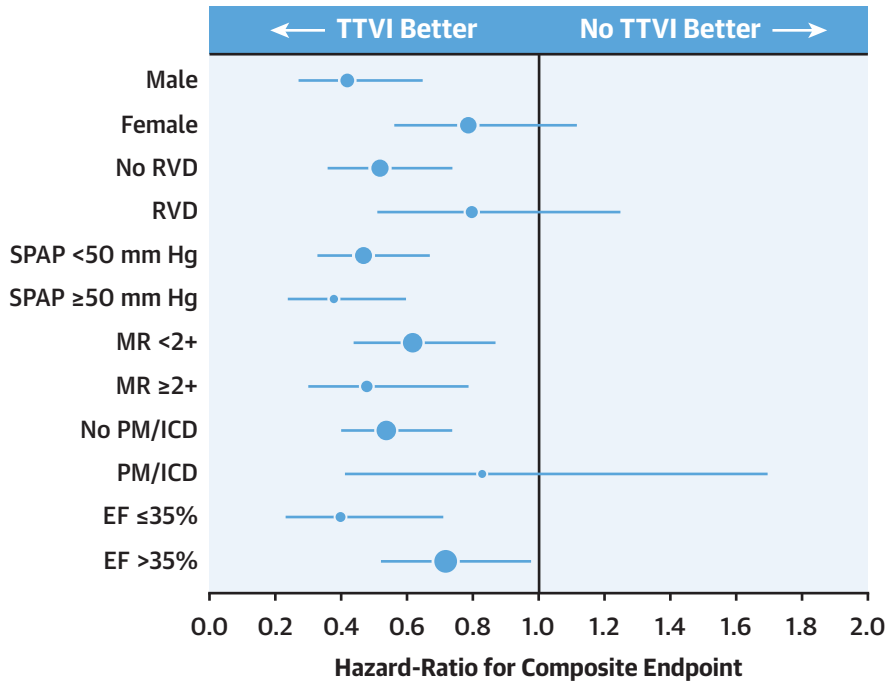
STUDY LIMITATIONS. Several limitations must be noted to accurately interpret the findings from this

TABLE 2 Cox Proportional Hazard Models Testing the Effect of TTVI in the Propensity-Matched Cohort

Model for Control Group	HR for Death or Heart Failure Hosp. (Primary Endpoint)	p Value	HR for Mortality (Secondary Endpoint)	p Value
Unadjusted	0.60 (0.46-0.79)	0.003	0.56 (0.39-0.79)	0.001
Adjusted for sex and NYHA functional class	0.46 (0.31-0.68)	0.0001	0.49 (0.31-0.79)	0.003
Adjusted for sex and NYHA functional class, atrial fibrillation, and RV dysfunction	0.39 (0.26-0.59)	<0.0001	0.41 (0.26-0.67)	0.0004

Values are HR (95% CI).
HR = hazard ratio; other abbreviations as in Table 1.

FIGURE 4 Subgroup Analysis



Subgroup analysis of TTVI's impact on death or heart failure rehospitalization (primary endpoint) stratified by the major clinical and echocardiographic characteristics. EF = ejection fraction; ICD = implantable cardioverter-defibrillator; MR = mitral regurgitation; PM = pacemaker; RVD = right ventricular dysfunction; SPAP = systolic pulmonary artery pressure; TTVI = transcatheter tricuspid valve intervention.

analysis. First, although a careful propensity score analysis justifies strong conclusions, it is not a randomized trial and relevant confounders might not be represented in the risk-adjustment process, which could have influenced the results. Nevertheless, the methodology that we selected attempts to maximize patient inclusion and the considerable magnitude of the between-group differences for major clinical endpoints in this analysis renders a false conclusion unlikely. Second, given the retrospective nature of the study, the authors were unable to standardize medical regimens for severe TR, and therefore, the medically managed group represents a heterogeneous sample of individually targeted medical therapies based on patient and provider preferences. Third, a minority of patients of the interventional group had concomitant mitral valve treatment. Although this has been addressed in the multivariable model, we cannot exclude that the concomitant treatment of MR might in part contribute to the greater survival. Fourth, all of the TTVI procedures have been performed in anatomically selected patients in highly experienced centers; therefore, the observed results may not reflect those in all-comers with TR and in all centers. Fifth, no central echocardiography core laboratory adjudication was available due to the type of the study.

CONCLUSIONS

TTVI in selected high-risk patients with symptomatic severe tricuspid regurgitation is associated with relatively low mortality and rehospitalization rates at 1 year. The propensity score-matched analysis conducted in this retrospective study suggests that TTVI might be associated with greater survival and reduced heart failure rehospitalization compared with medical therapy alone. In view of these very encouraging results, additional studies, particularly RCTs, are warranted to confirm our findings to ultimately adopt TTVI for the treatment of TR in routine clinical practice.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Observational evidence suggests that catheter-based interventions may be beneficial in selected patients with symptomatic severe tricuspid regurgitation when medication therapy alone is insufficient.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to verify the risks and benefits of catheter-based interventions to reduce the severity of tricuspid regurgitation in symptomatic patients and guide selection of optimum candidates for these procedures.

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