Journal Pre-proof

Transcatheter versus medical treatment of symptomatic severe tricuspid regurgitation

Maurizio Taramasso, MD PhD, Giovanni Benfari, MD, Pieter van der Bijl, MD, Hannes Alessandrini, MD, Adrian Attinger-Toller, MD, Luigi Biasco, MD, Philipp Lurz, MD PhD, Daniel Braun, MD, Eric Brochet, MD, Kim A. Connelly, MD, Sabine de Bruijn, MD, Paolo Denti, MD, Florian Deuschl, MD, Rodrigo Estevez-Loureiro, MD PhD, Neil Fam, MD, Christian Frerker, MD, Mara Gavazzoni, MD, Jo¨rg Hausleiter, MD, Edwin Ho, MD, Jean-Michel Juliard, MD, Ryan Kaple, MD, Christian Besler, MD, Susheel Kodali, MD, Felix Kreidel, MD, Karl-Heinz Kuck, MD, Azeem Latib, MD, Alexander Lauten, MD, Vanessa Monivas, MD, Michael Mehr, MD, Guillem Muntané-Carol, MD, Tamin Nazif, MD, Georg Nickening, MD, Giovanni Pedrazzini, MD, François Philippon, MD, Alberto Pozzoli, MD, Fabien Praz, MD, Rishi Puri, MD, Josep Rodés-Cabau, MD, Ulrich Scha¨fer, MD, Joachim Schofer, MD, Horst Sievert, MD, Gilbert H.L. Tang, MD, MSC, MBA, Holger Thiele, MD, Yan Topilsky, MD, Karl-Philipp Rommel, MD, Victoria Delgado, MD, Alec Vahanian, MD, Ralph Stephan Von Bardeleben, MD, John G. Webb, MD, Marcel Weber, MD, Stephan Windecker, MD, Mirjam Winkel, MD, Michel Zuber, MD, Martin B. Leon, MD, Rebecca T. Hahn, MD, Jeroen J. Bax, MD, Maurice Enriquez-Sarano, MD, Francesco Maisano, MD

PII: S0735-1097(19)37739-3

DOI: https://doi.org/10.1016/j.jacc.2019.09.028

Reference: JAC 26774

To appear in: *Journal of the American College of Cardiology*

Received Date: 18 August 2019

Revised Date: 20 September 2019

Accepted Date: 23 September 2019

Please cite this article as: Taramasso M, Benfari G, van der Bijl P, Alessandrini H, Attinger-Toller A, Biasco L, Lurz P, Braun D, Brochet E, Connelly KA, de Bruijn S, Denti P, Deuschl F, Estevez-Loureiro R, Fam N, Frerker C, Gavazzoni M, Hausleiter J¨r, Ho E, Juliard J-M, Kaple R, Besler C, Kodali S, Kreidel F, Kuck K-H, Latib A, Lauten A, Monivas V, Mehr M, Muntané-Carol G, Nazif T, Nickening G, Pedrazzini G, Philippon F, Pozzoli A, Praz F, Puri R, Rodés-Cabau J, Scha¨fer U, Schofer J, Sievert H, Tang GHL, Thiele H, Topilsky Y, Rommel K-P, Delgado V, Vahanian A, Von Bardeleben RS, Webb JG, Weber M, Windecker S, Winkel M, Zuber M, Leon MB, Hahn RT, Bax JJ, Enriquez-Sarano M, Maisano

F, Transcatheter versus medical treatment of symptomatic severe tricuspid regurgitation, *Journal of the American College of Cardiology* (2019), doi: https://doi.org/10.1016/j.jacc.2019.09.028.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 Published by Elsevier on behalf of the American College of Cardiology Foundation.

Journal Pre-proof

Transcatheter versus medical treatment of symptomatic severe tricuspid regurgitation

Maurizio Taramasso MD PhD*[1], Giovanni Benfari MD*[2], Pieter van der Bijl MD[3], Hannes Alessandrini, MD[4], Adrian Attinger-Toller MD[5], Luigi Biasco, MD[6], Philipp Lurz, MD PhD[7], Daniel Braun MD[8], Eric Brochet, MD[9], Kim A. Connelly, MD[10], de Bruijn Sabine MD[11], Paolo Denti, MD[12], Florian Deuschl, MD[13], Rodrigo Estevez-Loureiro MD PhD[14], Neil Fam, MD[10], Christian Frerker, MD[4,15], Mara Gavazzoni MD[1], Jörg Hausleiter MD[8], Edwin Ho, MD[10,16], Jean-Michel Juliard, MD[9], Ryan Kaple, MD[17], Christian Besler, MD[7]; Susheel Kodali MD[18], Felix Kreidel, MD[19], Karl-Heinz Kuck, MD[4], Azeem Latib, MD[16] Alexander Lauten, MD[20], Vanessa Monivas MD[14], Michael Mehr, MD[8], Guillem Muntané-Carol MD[21], Tamin Nazif, MD[18], Georg Nickening, MD[22], Giovanni Pedrazzini, MD[6], François Philippon MD[21], Alberto Pozzoli MD[1], Fabien Praz, MD[23], Rishi Puri, MD[21], Josep Rodés-Cabau, MD[21], Ulrich Schäfer, MD[13], Joachim Schofer, MD[24], Horst Sievert, MD[11], Gilbert H.L. Tang, MD, MSC, MBA[25], Holger Thiele MD[7], Yan Topilsky MD[2,26], Karl-Philipp Rommel, MD[7], Victoria Delgado MD[3], Alec Vahanian MD[9], Ralph Stephan Von Bardeleben MD[19], John G. Webb, MD[5], Marcel Weber MD[22], Stephan Windecker MD[23], Mirjam Winkel MD[23], Michel Zuber, MD[1], Martin B. Leon MD[18], Rebecca T. Hahn, MD[18], Jeroen J. Bax MD[3], Maurice Enriquez-Sarano MD[2], Francesco Maisano MD[1]

***MT and GB equally contributed and should be both considered as first authors**

[1]Cardiac Surgery Department, University Hospital of Zurich, Univeristy of Zurich, Switzerland; [2]Division of Cardiovascular Disease, Mayo Clinic, Rochester, Minnesota; [3]Department of Cardiology, Leiden University Medical Center; the Netherlands; [4]Asklepios Klinik St. Georg, Hamburg, Germany; [5]St. Paul Hospital, Vancouver, Canada; [6]Cardiocentro, Lugano, Switzerland; [7]Heart Center Leipzig - University Hospital, Leipzig, Germany; [8]Klinikum der Universität München, Munich, Germany; [9]Hôpital Bichat, Université Paris VI, Paris, France; [10]Toronto Heart Center, St. Michael's Hospital, Toronto, Ontario, Canada; [11]CardioVascular Center Frankfurt, Frankfurt am Main, Germany; [12]San Raffaele University Hospital. Milan, Italy; [13]University Heart Center Hamburg, Hamburg, Germany; [14]Department of Cardiology, Hospital Universitario Puerta de Hierro, Madrid, Spain; [15] University Hospital of Köln, Köln, Germany; [16] Montefiore Medical Center, New York, New York; [17]Westchester Medical Center, Valhalla, New York, New York; [18]New York-Presbyterian/Columbia University Medical Center, New York, New York; [19]Department of Cardiology, University Medical Center Mainz, Mainz, Germany; [20]Charité University Hospital, Berlin, Germany; [21]Quebec Heart and Lung Institute, Laval University, Quebec City, Canada; [22]Universitatsklinikum Bonn, Bonn, Germany; [23]Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [24]Albertinen Heart Center, Hamburg, Germany; [25]Mount Sinai Hospital, New York; [26] Department of Cardiology, Tel Aviv Medical Center, Sackler Faculty of Medicine, Israel

Running title: Transcatheter treatment of severe TR improves outcomes

Disclosures:
Dr. Taramasso is a consultant for Abbott Vascular, Boston Scientific, 4TECH, and CoreMedic; and has received speaker honoraria from Edwards Lifesciences. Dr. Latib has served on the advisory board for Medtronic and Abbott Vascular; on the Speakers Bureau for Abbott Vascular; on the scientific advisory board for Millipede; and as a consultant for 4Tech, Mitralign, and

Millipede. Dr. Braun has received speaker honoraria and travel support from Abbott Vascular. Dr. Brochet has received speaker fees from Abbott Vascular. Dr. Denti has served as a consultant for Abbott Vascular, 4Tech, Neovasc, and InnovHeart; and has received honoraria from Abbott. Dr. Deuschl has served as a proctor and consultant for Valtech/Edwards Lifesciences and Neovasc; has received speaker honoraria from Abbott; and has received unre- stricted travel grants from Boston Scientific, Abbott, Edwards Lifesciences, and Neovasc. Dr. Hausleiter has received speaker honoraria from Abbott Vascular and Edwards Lifesciences. Dr. Himbert has served as a proctor and consultant for Edwards Lifesciences. Dr. Kreidel has received speaker honoraria and consulting fees from Abbott and Edwards Lifesciences. Dr. Kuck has served as a consultant for Abbott Vascular, St. Jude Medical, Biotronik, Medtronic, Biosense Webster. Boston Scientific, Edwards Lifesciences, and Mitralign; and is cofounder of Cardiac Implants. Dr. Lauten has received research support from Abbott and Edwards Lifesciences; and has been a consultant to Abbott, Edwards Lifesciences, and TricValve. Dr. Lurz has received speaker fees from Abbott. Dr. Mehr has received a travel grant from Bristol-Myers Squibb. Dr. Nazif has been a consultant to Edwards Lifesciences, Boston Scientific, and Medtronic. Dr. Praz has been a consultant to Edwards Lifesciences. Dr. Rodés-Cabau has received institutional research grants from Edwards Lifesciences. Dr. Schäfer has received lecture fees, study honoraria, travel expenses from, and has been a member of an advisory board for Abbott. Prof. H. Sievert has received study honoraria, travel expenses, and consulting fees from 4tech Cardio, Abbott, Ablative Solutions, Ancora Heart, Bavaria Medizin Technologie GmbH, Bioventrix, Boston Scientific, Carag, Cardiac Dimensions, Celonova, Comed B.V., Contego, CVRx, Edwards, Endologix, Hemoteq, Lifetech, Maquet Getinge Group, Medtronic, Mitralign, Nuomao Medtech, Occlutech, pfm Medical, Recor, Renal Guard, Rox Medical, Terumo, Vascular Dynamics, and Vivasure Medical. Dr. Tang has served as a consultant, advisory board member, and faculty trainer for Abbott Structural Heart. Dr. Vahanian has served as a consultant for Abbott Vascular, Edwards Lifesciences, and MitralTech; and has received speakers fees from Abbott Vascular and Edwards Lifesciences. Dr. Webb has received research support from Edwards Lifesciences; and served as a consultant for Abbott Vascular, Edwards Lifesciences, and St. Jude Medical. Dr. Windecker has received institutional research grants from Abbott, Amgen, Boston Scientific, Biotronik, Edwards Lifesciences, Medtronic, St Jude, and Terumo. Dr. Maisano has served as a consultant for Abbott Vascular, Edwards Lifesciences, Cardiovalve, Valtech, and Medtronic; and is cofounder of 4Tech. Dr. Leon has served as a nonpaid member of the scientific advisory board of Edwards Lifesciences; and has been a consultant to Abbott Vascular and Boston Scientific. Dr. Hahn has served as a consultant for Abbott Vascular, NaviGate, and GE Healthcare, Dr. Kodali is conslultant for Claret Medical, Abbott Vascular, Meril Lifesciences, Admedus and has equity of Thubrikar Aortic Valve, Inc, Dura Biotech, Biotrace Medical, MID; Dr. Topilsky declares consultation fee and research grants from Edwards Liefisciences; Dr. Delgado declares speaker fees from Abbott Vascular; Dr. Bax reported speaker fees from Abbott Vascular and Boehringer Ingelheim; Dr. Sarano declared Research Grant from Edwards Lifescience; All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Correspondence to:
Maurizio Taramasso MD
University Hospital of Zürich, Cardiovascular Surgery Department
Rämistrasse 100

8091 Zurich, Switzerland.
Telephone: +41442553728
Fax: +41442551616
E-mail: Maurizio.Taramasso@usz.ch
Twitter: @m_taramasso

Journal Pre-proof

Abstract

Background: Tricuspid Regurgitation (TR) 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: 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 two large retrospective registries enrolling medically managed patients with ≥moderate TR in Europe and North America (1179 pts) 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 to controls, 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 (HR 0.60 [0.46-0.79], p=0.003 unadjusted) which remained significant after adjusting for sex, NYHA class, right ventricular dysfunction and atrial fibrillation (HR 0.39 [0.26-0.59], p<0.0001) and after further adjustment for mitral regurgitation and pacemaker/defibrillator (HR 0.35 [0.23.54], 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.

Condensed Abstract

Tricuspid Regurgitation (TR) is associated with increased rates of heart failure (HF) and mortality. Transcatheter tricuspid valve interventions (TTVI) are promising, but the clinical benefit is unknown. We investigated the potential benefit of TTVI over medical therapy in a propensity score matched population. Primary endpoint was 1-year mortality or HF rehospitalization or the composite; TTVI was associated with greater survival and reduced HF rehospitalization compared with medical therapy alone.

Key words: tricuspid valve, tricuspid regurgitation, heart valve diseases.

Abbreviation list

Tricuspid regurgitation (TR)
Mitral regurgitation (MR)
Right ventricular (RV)
transcatheter tricuspid valve interventions (TTVI)
guideline directed medical therapy (GDMT)
New York Heart Association (NYHA)
mitral regurgitation (MR)
Randomized Controlled Trials (RCTs)

Introduction

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).

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.

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, early feasibility studies in high risk or inoperable patients with severe TR. (16-19-21). 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 in 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 use of these devices in high-risk patients with symptomatic relevant TR on a larger scale. The TriValve International Registry represents so far the largest multicenter, multi-devices 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 of 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 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), TriCinch (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, 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 that had echo 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 the patients of both interventional and control group were medically treated according to guideline directed medical therapy (GDMT).

Echocardiographic examination

Journal Pre-proof

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). 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 LV in the standard apical 4-chamber view. RV dilatation 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 mmHg.

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 (HF). 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

Journal Pre-proof

Baseline characteristics are presented separately for the TTVI and control groups as mean (±SD) and compared with a 2-sided t test or Wilcoxon rank sum test. Categorical variables were described as frequencies (%) and compared with a $\chi 2$ or Fisher exact test.

Patients in the TTVI cohort were matched with controls 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 standard-deviation. Bias reduction and balance between the groups of patients with TTVI and the controls was assessed with standardized differences of covariates.

Survival rates after diagnosis were estimated using 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, the model fit was evaluated with martingale and Cox-Snell residuals. Analyses were performed with JMP 12 (SAS Institute Inc). $P<0.05$ was considered significant.

Journal Pre-proof

Results

General characteristics

A total of 472 TTVI patients and 1179 controls with moderate/severe TR formed the study population. Baseline clinical and echocardiographic characteristics are presented in Table 1. Patients undergoing TTVI and controls had similar left ventricular ejection fraction (50±13 vs. 49±17%), and age (77±8 vs 76±13 years). TR cause was mostly functional (91% in TTVI group, 96% in controls).

Despite these similarities, multiple differences emerged for TTVI patients vs. controls. First of all, TTVI patients were less frequently women (55% vs. 63%), and had more chronic atrial fibrillation (85% vs 57%). Twenty-six percent in TTVI vs. 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 vs. 52±15 mmHg) as compared to the control group.

Propensity matched cohort

After matching, 268 pairs of matched patients were identified. The absolute standardized differences indicated adequate match between cases and controls. 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 vs.13±9% and pulmonary pressure level was 44±14 vs. 43±14 in TTVI vs controls. Differences persisted in the matched groups with the TTVI group having higher NYHA 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 ≥TR3+, occurred in 38/268 patients (14%). Patients with successful vs unsuccessful TTVI had similar age (75±10 vs 77±9, p=00.3), 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 vs. 43±15 mmHg, p=0.2), but 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 vs. matched controls who did not undergo tricuspid intervention (**Figure 2**) with 1-year mortality or heart failure rehospitalization occurring in 41.8% vs. 45.9% of and 1-year mortality in 27% vs. 35%.

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.

Patients who underwent combined procedures vs. isolated TTVI patients had similar age (77±7 vs. 77±9, p=0.9), proportion of women (50% vs. 60%, p=0.4), EuroScore 2 (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), primary (p=0.4) endpoint was similar in patients who received TTVI alone or a combined TTVI and mitral procedure (**Figure 3**). 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 (HR 0.28 [0.11-0.79], p=0.02 after comprehensive adjustment).

Survival for TTVI vs. controls

Median follow up time was 11 [IQR 4-28] months. Overall, death occurred in 13.8% of TTVI patients vs. 26.1% of controls at 6 months, percentages that increased to 22.6% for TTVI patients and 36.2% for controls at 1-year.

The Kaplan-Meier analysis for TTVI vs. controls 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 3**). The adopted TTVI approach did not influence the occurrence of primary endpoint as shown in **Figure 4**, comparing MitraClip are compared to other TTVI devices (p=0.8).

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 [0.46-0.79], p=0.003 unadjusted, and HR 0.39 [0.26-0.59], p<0.0001 after adjustment for sex, NYHA 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 [0.23.54], p<0.0001. Stratified for the main clinical and echocardiographic characteristics (**Figure 1**), TTVI reduced the incidence of the primary endpoint more substantially in male, in the absence of RV dysfunction, and without device-leads through the valve, independently from other factors. Furthermore, in multivariable analysis, TTVI effect was not altered by the presence of moderate/severe mitral regurgitation (MR), pulmonary hypertension or left ventricular function.

Discussion

Based on our propensity score analysis, TTVI in high-risk patients with symptomatic severe TR as compared to medical treatment alone was associated with lower rates of composite endpoint of death and re-hospitalization 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 impacting outcomes. This last observation greatly extends the recent observation of

better survival in patients with procedural success and significant TR reduction as compared to 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. To the best of our knowledge, this is the first analysis of clinical outcomes for TTVI compared with similar patients who are treated without intervention. In the absence of any RCTs results, our results suggest that interventional treatment of TR is associated with improved clinical outcomes compared to medical therapy alone.

After matching, the 2 groups were similar for age, left ventricular (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 non-severe 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 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 mostly 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 23-30% 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).

The association between procedural success and greater survival underscores the importance of patient selection for TTVI, since TR reduction should be the main target of the procedure. Current procedural success with various devices is about 75%, suggesting that there is

Journal Pre-proof

room for technical improvement in the future (better devices and better intra-procedural guidance) (20).

Limitations

Several limitations must be noted to accurately interpret the findings from this 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. Forth, all 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 Echo Core-Lab 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 HF-rehospitalization compared to medical therapy alone. In view of these very encouraging results additional studies, particularly randomized clinical trials are warranted in order to confirm our findings to ultimately adopt TTVI for the treatment of TR in routine clinical practice.

Journal Pre-proof

Journal Pre-proof

Clinical Perspectives

Competency in Patient Care and Procedural Skill: severe tricuspid regurgitation is independently associated with increased mortality and represents an undertreated disease. Different methods have been reported to reduce tricuspid regurgitation with catheter-based approached. Whether to address tricuspid regurgitation with an interventional method is associated with improved outcome is unknown.

Translational Outlook: In absence of randomized trials in the field of treatment of symptomatic severe TR, this study suggests a potential clinical benefit associated with interventional treatment in patients with symptomatic severe TR on top of medical therapy as compared to conservative treatment alone. Future studies, particularly randomized clinical trials, are warranted in order to confirm these findings to ultimately adopt TTVI for the treatment of TR in routine clinical practice.

Journal Pre-proof

References

1. Singh JP, Evans JC, Levy D et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). Am J Cardiol. 1999;83:897-902.
2. Topilsky Y, Maltais S, Medina Inojosa J et al. Burden of Tricuspid Regurgitation in Patients Diagnosed in the Community Setting. JACC Cardiovasc Imaging 2019;12:433-442.
3. Braunwald NS, Ross J, Jr., Morrow AG. Conservative management of tricuspid regurgitation in patients undergoing mitral valve replacement. Circulation 1967;35:I63-9.
4. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. J Am Coll Cardiol 2004;43:405-9.
5. Prihadi EA, Delgado V, Leon MB, Enriquez-Sarano M, Topilsky Y, Bax JJ. Morphologic Types of Tricuspid Regurgitation: Characteristics and Prognostic Implications. JACC Cardiovasc Imaging 2019;12:491-499.
6. Taramasso M, Gavazzoni M, Pozzoli A et al. Tricuspid Regurgitation: Predicting the Need for Intervention, Procedural Success, and Recurrence of Disease. JACC Cardiovasc Imaging 2019;12:605-621.
7. Topilsky Y, Nkomo VT, Vatury O et al. Clinical outcome of isolated tricuspid regurgitation. JACC Cardiovasc Imaging 2014;7:1185-94.
8. Taramasso M, Vanermen H, Maisano F, Guidotti A, La Canna G, Alfieri O. The growing clinical importance of secondary tricuspid regurgitation. J Am Coll Cardiol 2012;59:703-10.

Journal Pre-proof

9. Benfari G, Antoine C, Miller WL et al. Excess Mortality Associated With Functional Tricuspid Regurgitation Complicating Heart Failure With Reduced Ejection Fraction. Circulation 2019;140:196-206.

10. Topilsky Y, Inojosa JM, Benfari G et al. Clinical presentation and outcome of tricuspid regurgitation in patients with systolic dysfunction. Eur Heart J 2018;39:3584-3592.

11. Kilic A, Saha-Chaudhuri P, Rankin JS, Conte JV. Trends and outcomes of tricuspid valve surgery in North America: an analysis of more than 50,000 patients from the Society of Thoracic Surgeons database. Ann Thorac Surg 2013;96:1546-52; discussion 1552.

12. Topilsky Y, Khanna AD, Oh JK et al. Preoperative factors associated with adverse outcome after tricuspid valve replacement. Circulation 2011;123:1929-39.

13. 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.

14. Axtell AL, Bhambhani V, Moonsamy P et al. Surgery Does Not Improve Survival in Patients With Isolated Severe Tricuspid Regurgitation. J Am Coll Cardiol 2019;74:715-725.

15. Chikwe J, Itagaki S, Anyanwu A, Adams DH. Impact of Concomitant Tricuspid Annuloplasty on Tricuspid Regurgitation, Right Ventricular Function, and Pulmonary Artery Hypertension After Repair of Mitral Valve Prolapse. J Am Coll Cardiol 2015;65:1931-8.

16. Rodes-Cabau J, Taramasso M, O'Gara PT. Diagnosis and treatment of tricuspid valve disease: current and future perspectives. Lancet 2016;388:2431-2442.

17. Taramasso M, Pozzoli A, Guidotti A et al. Percutaneous tricuspid valve therapies: the new frontier. Eur Heart J 2017;38:639-647.

Journal Pre-proof

18. Asmarats L, Puri R, Latib A, Navia JL, Rodes-Cabau J. Transcatheter Tricuspid Valve Interventions: Landscape, Challenges, and Future Directions. J Am Coll Cardiol 2018;71:2935-2956

19. Asmarats L, Taramasso M, Rodes-Cabau J. Tricuspid valve disease: diagnosis, prognosis and management of a rapidly evolving field. Nat Rev Cardiol. 2019;16:538-554

20. Taramasso M, Alessandrini H, Latib A et al. Outcomes After Current Transcatheter Tricuspid Valve Intervention: Mid-Term Results From the International TriValve Registry. JACC Cardiovasc Interv. 2019;12:155-165.

21. Nickenig G, Kowalski M, Hausleiter J et al. Transcatheter Treatment of Severe Tricuspid Regurgitation With the Edge-to-Edge MitraClip Technique. Circulation 2017;135:1802-1814.

22. 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.

23. Baumgartner H, Falk V, Bax JJ et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739-2791.

24. Taramasso M, Hahn RT, Alessandrini H et al. The International Multicenter TriValve Registry: Which Patients Are Undergoing Transcatheter Tricuspid Repair? JACC Cardiovasc Interv 2017;10:1982-1990.

25. Lancellotti P, Tribouilloy C, Hagendorff A et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary

Journal Pre-proof

from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2013;14:611-44.

26. Zoghbi WA, Adams D, Bonow RO et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 2017;30:303-371.

27. 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;66:308-321.

28. 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. JACC Cardiovasc Interv 2018;11:1119-1128.

29. Mehr M, Taramasso M, Besler C et al. 1-Year Outcomes After Edge-to-Edge Valve Repair for Symptomatic Tricuspid Regurgitation: Results From the TriValve Registry. JACC Cardiovasc Interv 2019;12:1451-1461.

30. Mullens W, Abrahams Z, Francis GS et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol 2009;53:589-596.

31. Bart BA. Treatment of congestion in congestive heart failure: ultrafiltration is the only rational initial treatment of volume overload in decompensated heart failure. Circulation Heart failure 2009;2:499-504.

Journal Pre-proof

32. Damman K, Voors AA, Navis G, van Veldhuisen DJ, Hillege HL. The cardiorenal syndrome in heart failure. Prog Cardiovasc Dis. 2011;54:144-53.

33. Karam N, Braun D, Mehr M et al. Impact of Transcatheter Tricuspid Valve Repair for Severe Tricuspid Regurgitation on Kidney and Liver Function. JACC Cardiovasc Interv 2019;12:1413-1420.

34. Rommel KP, Besler C, Noack T et al. Physiological and Clinical Consequences of Right Ventricular Volume Overload Reduction After Transcatheter Treatment for Tricuspid Regurgitation. JACC Cardiovasc Interv 2019;12:1423-1434.

Journal Pre-proof

FIGURE LEGENDS

Central Illustration: Transcatheter treatment of severe tricuspid regurgitation: Primary and secondary endpoints. The figure displays Kaplan-Meier curves for TTVI (red curve) vs. controls (blue curve) according to primary (A) and secondary (A) endpoint. Shadowing identifies the pointwise confidence interval (TTVI: Transcatheter Tricuspid Valve Intervention; HF: Heart Failure).

Figure 1: **Subgroup analysis.** Subgroup analysis of the TTVI impact on death or heart failure rehospitalization (primary endpoint) rehospitalization stratified by the major clinical and echocardiographic characteristics. TTVI: Transcatheter Tricuspid Valve Intervention.

Figure 2: **Impact of procedural success.** The Kaplan-Meier survival curves showing the effect of successful TTVI (green curve), unsuccessful TTVI (red curve), and controls (blue curve) on primary (A) and secondary (B) endpoint. (TTVI: Transcatheter Tricuspid Valve Intervention; HF: Heart Failure).

Figure 3A: Outcomes in isolated and concomitant TR: The Kaplan-Meier for primary endpoint in TTVI patients and controls without significant mitral regurgitation (>2+). **Figure 3B**: The Kaplan-Meier for primary endpoint in TTVI patients and controls with significant mitral regurgitation (>2+). TTVI patients who received MR intervention (green line) had similar outcome as compare to TTVI patients who received tricuspid valve intervention alone (red line).

Figure 4: **Impact of the device used.** Kaplan-Meier survival curves comparing the impact on primary endpoint of TTVI using MitraClip vs. other devices.

Journal Pre-proof

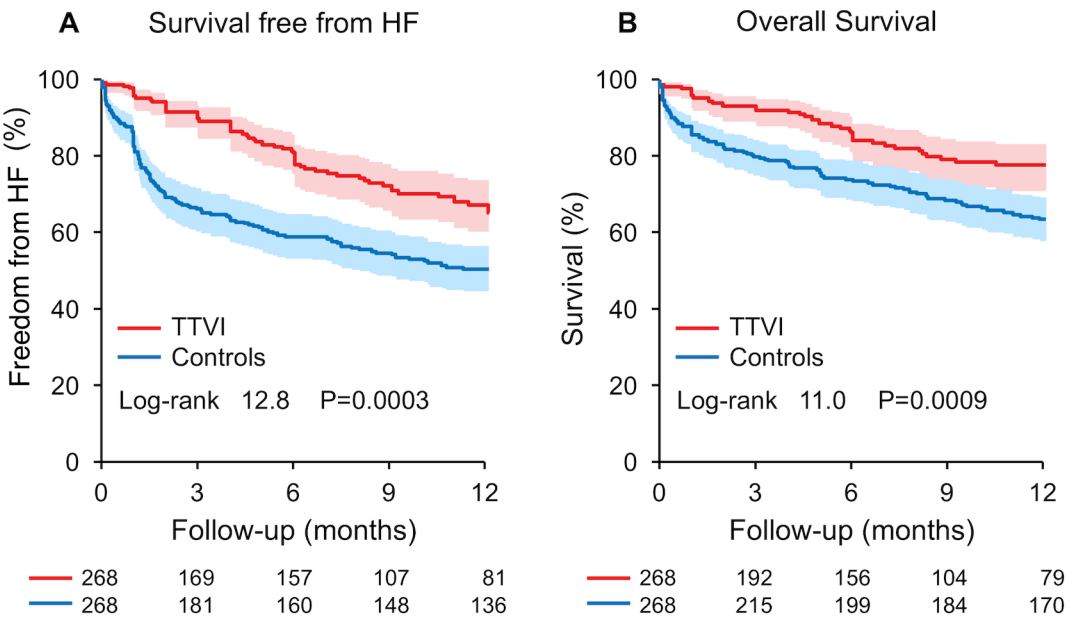
Table 1: clinical and echocardiographic characteristics are presented for TTVI vs. control patients in the overall study population and in the propensity matched cohort

	Overall population N=1652			**Propensity matched cohort N=536**		
	TTVI N=472	**Controls N=1179**	P-value	**TTVI N=268**	**Controls N=268**	P-value
Age, y±SD	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, mmHg	40±15	52±15	<0.0001	44±14	43±14	0.3
Pulmonary hypertension, %	27%	50%	<0.0001	34%	29%	0.2
NYHA III-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

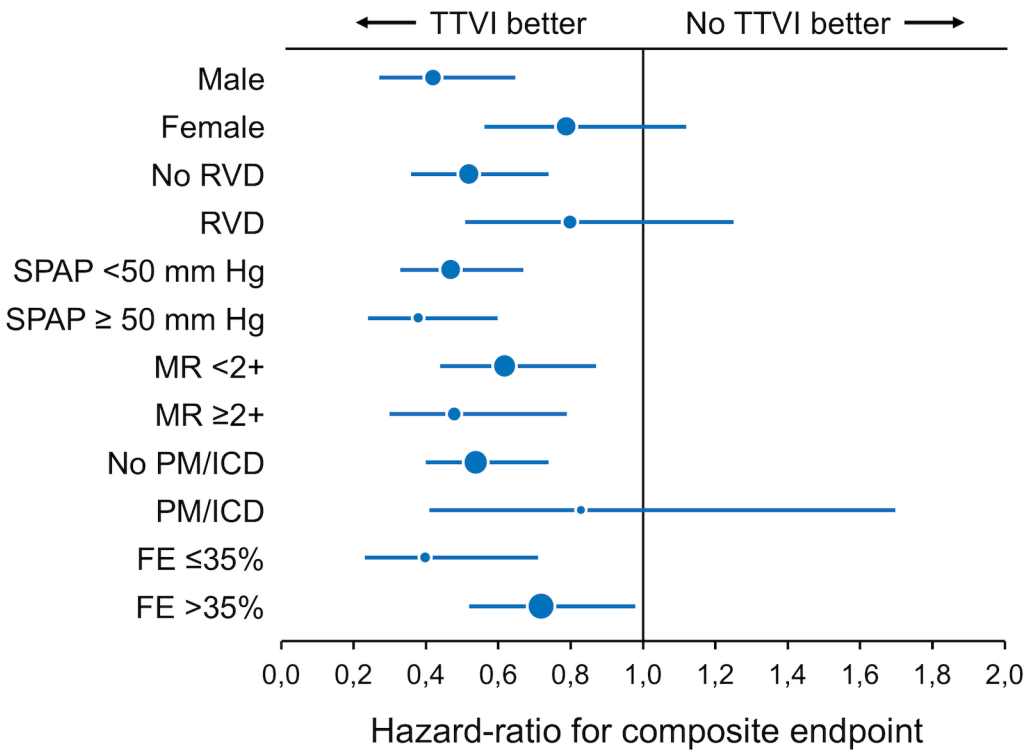
Table 2: Cox Proportional Hazard models testing the effect of TTVI in the propensity matched cohort

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
Adj. for sex and NYHA	0.46 (0.31-0.68)	0.0001	0.49 (0.31-0.79)	0.003
Adj. for sex and NYHA, Afib, and RV dysfunction	0.39 (0.26-0.59)	<0.0001	0.41 (0.26-0.67)	0.0004

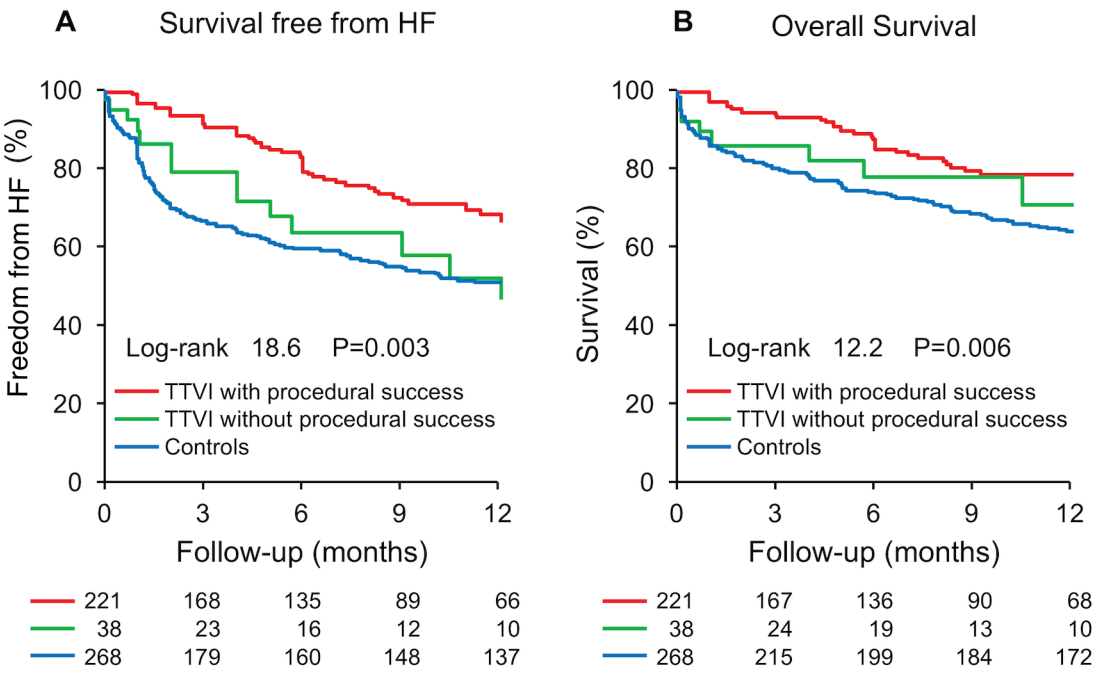
Journal Pre-proof



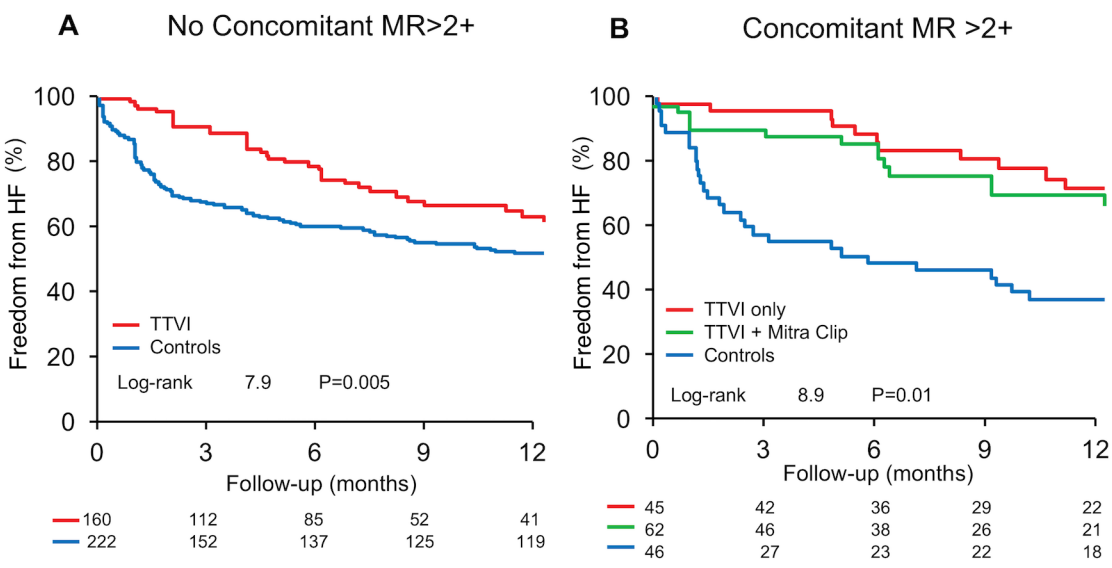
Journal Pre-proof



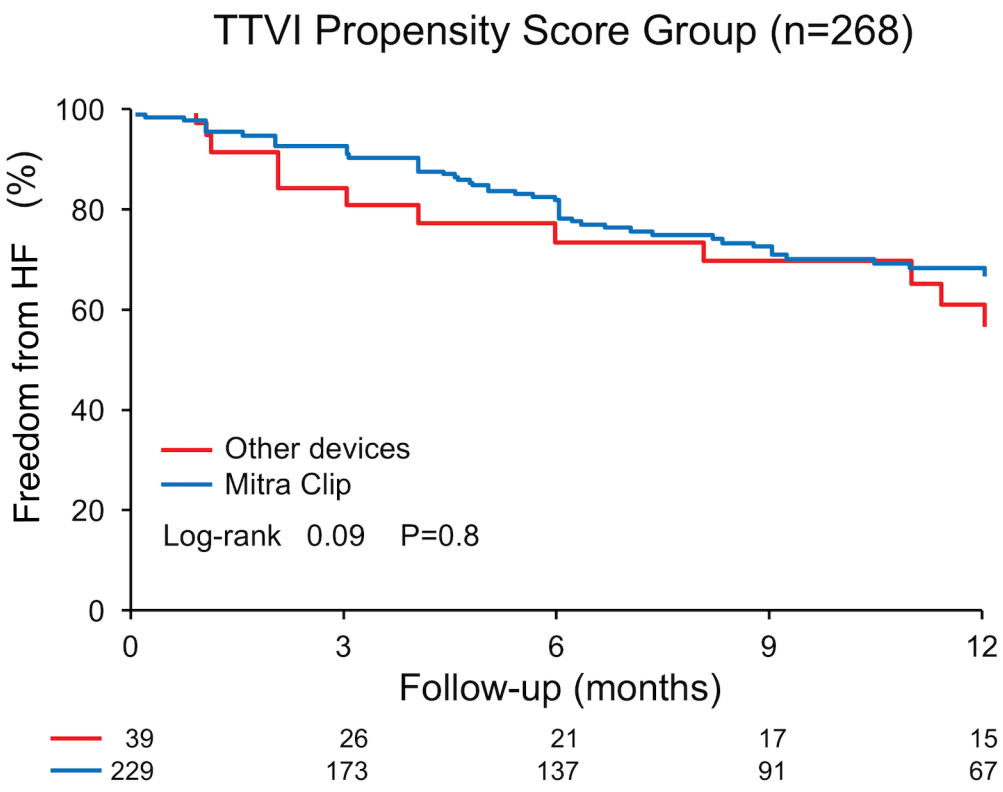
Journal Pre-proof



Journal Pre-proof



Journal Pre-proof


TTVI Propensity Score Group (n=268)
Freedom from HF (%)
100
80
60
40
20
0
Other devices
Mitra Clip
Log-rank 0.09 P=0.8
0
3
6
9
12
Follow-up (months)
39 26 21 17 15
229 173 137 91 67

Journal