

1 **Sex-Related Characteristics and Short-Term Outcomes**
2 **of Patients Undergoing Transcatheter Tricuspid Valve Intervention**
3 **for Tricuspid Regurgitation**
4

5 Andrea Scotti, MD ^{a,b*}; Augustin Coisne, MD, PhD ^{a,b,c*}; Maurizio Taramasso, MD ^d; Juan F. Granada, MD ^b;
6 Sebastian Ludwig, MD ^{a,b,e}; Josep Rodés-Cabau, MD ^f; Philipp Lurz, MD, PhD ^g; Jörg Hausleiter, MD ^h; Neil
7 Fam, MD ⁱ; Susheel K. Kodali, MD ^j; Joel Rosiene, MD ^a; Ari Feinberg, MD ^a; Alberto Pozzoli, MD ^k; Hannes
8 Alessandrini, MD ^l; Luigi Biasco, MD ^m; Eric Brochet, MD ⁿ; Paolo Denti, MD ^o; Rodrigo Estevez-Loureiro,
9 MD ^p; Christian Frerker, MD ^q; Edwin C. Ho, MD ^a; Vanessa Monivas, MD ^r; Georg Nickenig, MD ^s; Fabien
10 Praz, MD ^t; Rishi Puri, MD, PhD ^u; Horst Sievert, MD ^v; Gilbert H.L. Tang, MD, MSC, MBA ^w; Martin
11 Andreas, MD, PhD ^x; Ralph Stephan Von Bardeleben, MD ^y; Karl-Philipp Rommel, MD ^z; Guillem Muntané-
12 Carol, MD ^f; Mara Gavazzoni, MD ^d; Daniel Braun, MD ^h; Benedikt Koell, MD ^e; Daniel Kalbacher, MD ^{e,z};
13 Kim A. Connelly, MD ⁱ; Jean-Michel Juliard, MD ⁿ; Claudia Harr, MD ^l; Giovanni Pedrazzini, MD ^{aa}; Giulio
14 Russo, MD ^{ab}; François Philippon, MD ^f; Joachim Schofer, MD ^l; Holger Thiele, MD ^g; Matthias Unterhuber,
15 MD ^g; Dominique Himbert, MD ⁿ; Marina Ureña Alcázar, MD, PhD ⁿ; Mirjam G. Wild, MD ^l; Stephan
16 Windecker, MD ^t; Ulrich Jorde, MD ^a; Francesco Maisano, MD ^o; Martin B. Leon MD ^{b,j}; Rebecca T. Hahn,
17 MD ^{b,j}; Azeem Latib, MD ^a

^a Montefiore-Einstein Center for Heart and Vascular Care, Montefiore Medical Center, Albert Einstein College of
Medicine, Bronx, New York

^b Cardiovascular Research Foundation, New York, New York

18 ^c Univ. Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011- EGID, F-59000 Lille, France

19 ^d Heart Center Hirslanden Zürich, Zürich, Switzerland

20 ^e Department of Cardiology, University Heart and Vascular Center, Hamburg, Germany

21 ^f Quebec Heart and Lung Institute, Laval University, Quebec City, Quebec, Canada

22 ^g Heart Center Leipzig at University of Leipzig and Leipzig Heart Institute, Leipzig, Germany

23 ^h Medical Clinic and Polyclinic I, University Hospital of Munich, Munich, Germany

24 ⁱ Division of Cardiology, Toronto Heart Center, St. Michael's Hospital, Toronto, Ontario, Canada

25 ^j Division of Cardiology, Columbia University Medical Center-NewYork Presbyterian Hospital, New York, NY

26 ^k Division of Cardiac Surgery, Cardiocentro Ticino Institute, Ente Ospedaliero Cantonale, Lugano, Switzerland

27 ^l Asklepios Clinic St. Georg, Medical Care Center Prof. Mathey, Prof. Schofer, Hamburg, Germany

28 ^m Azienda Sanitaria Locale Torino 4. Via Battitore 7, 10071 Ciriè, Italy; Department of Biomedical Sciences,
29 University of Italian Switzerland, Lugano, Switzerland

30 ⁿ Division of Cardiology, Bichat Hospital, Paris, France

31 ^o Division of Cardiology and Department of Cardiac Surgery, San Raffaele University Hospital, Milan Italy

32 ^p Interventional Cardiology Clinic, University Hospital Alvaro Cunqueiro, Vigo, Spain

33 ^q University Heart Center, Schleswig-Holstein University, Lübeck, Germany

34 ^r Division of Cardiology, Puerta de Hierro University Hospital, Madrid, Spain

35 ^s Division of Cardiology, Bonn University Hospital, Bonn, Germany

36 ^t Division of Cardiology, Inselspital, Bern University Hospital, Bern, Switzerland

37 ^u Department of Cardiovascular Medicine, Cleveland Clinic Foundation, Cleveland, Ohio

38 ^v Division of Cardiology, Cardiovascular Center Frankfurt, Frankfurt am Main, Germany

39 ^w Department of Cardiovascular Surgery, Mount Sinai Health System, New York, New York

© The Author(s) 2022. Published by Oxford University Press on behalf of the European Society of Cardiology. All
rights reserved. For permissions, please e-mail: journals.permissions@oup.com This article is published and
distributed under the terms of the Oxford University Press, Standard Journals Publication Model

(https://academic.oup.com/journals/pages/open_access/funder_policies/chorus/standard_publication_model) 1

1 ^x Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria

2 ^y Division of Cardiology, University Medical Center, Mainz, Germany

3 ^z German Center for Cardiovascular Research, Partner Site Hamburg/Luebeck/Kiel, Germany

4 ^{aa} Division of Cardiology, Istituto Cardiocentro Ticino, Ente Ospedaliero Cantonale, Lugano, Switzerland;

5 Department of Biomedical Sciences, University of Italian Switzerland, Lugano, Switzerland

6 ^{ab} Cardiology Unit, Policlinico Tor Vergata, University of Rome, Italy

7

8 * *Drs. Scotti and Coisne contributed equally to this work and are joint first authors*

9 **Brief title:** Impact of Sex after TTVI

10 **Total Word count:** 2822/5000

11

12 **Address for correspondence:**

13 Azeem Latib, MD

14 Interventional Cardiology

15 Montefiore Medical Center / Albert Einstein College of Medicine

16 1825 Eastchester Road, Bronx, NY 10461

17 Fax: 718-920-6798; Telephone: 718-904-3388

18 Email: alatib@gmail.com

19

20 Andrea Scotti, MD

21 Interventional Cardiology

22 Montefiore Medical Center / Albert Einstein College of Medicine

23 1825 Eastchester Road, Bronx, NY 10461

24 Fax: 718-920-6798; Telephone: 718-904-3388

25 Email: a.scotti@hotmail.com

26

ABSTRACT

Background and Aims. The impact of sex in patients with significant tricuspid regurgitation (TR) undergoing transcatheter tricuspid valve intervention (TTVI) is unknown. The aim of this study was to investigate sex-specific outcomes in patients with significant TR treated with TTVI versus medical therapy alone.

Methods. The TriValve (Transcatheter Tricuspid Valve Therapies) registry collected patients with significant TR from 24 centers who underwent TTVI from 2016 to 2021. A control cohort was formed by medically managed patients with \geq severe isolated TR diagnosed in 2015-2018. Primary endpoint was freedom from all-cause mortality. Secondary endpoints were heart failure (HF) hospitalization, New York Heart Association (NYHA) functional status, and TR severity. One-year outcomes were assessed for the TriValve cohort and compared with the control cohort with the inverse probability of treatment weighting (IPTW).

Results. A total of 556 and 2072 patients were included from the TriValve and control groups, respectively. After TTVI, there was no difference between women and men in 1-year freedom from all-cause mortality (80.9% vs. 77.9%, $p=0.56$, nor in HF hospitalization ($p=0.36$), NYHA functional class III-IV ($p=0.17$), and TR severity $>2+$ at last follow-up ($p=0.42$). Multivariable Cox-regression weighted by IPTW showed an improved 1-year survival after TTVI compared to medical therapy alone in both women (adjusted hazard ratio [HR] 0.45, 95% confidence interval [CI] 0.23-0.83, $p=0.01$) and men (adjusted HR 0.42, 95% CI 0.18-0.89, $p=0.03$).

Conclusions. After TTVI in high-risk patients, there were no sex-related differences in terms of survival, HF hospitalization, functional status, and TR reduction up to 1 year. The IPTW analysis shows a survival benefit of TTVI over medical therapy alone in both women and men.

Keywords. tricuspid regurgitation; sex; transcatheter tricuspid valve intervention.

Clinical Trial Registration:

Trial Name: International Multisite Transcatheter Tricuspid Valve Therapies Registry (TriValve)

ClinicalTrial.gov Identifier: NCT03416166

URL: <https://clinicaltrials.gov/ct2/show/NCT03416166>

ABBREVIATIONS

- 1
- 2 HF = heart failure
- 3 IPTW = inverse probability of treatment weighting
- 4 NYHA = New York Heart Association
- 5 OMT = optimal medical therapy
- 6 TEER = transcatheter edge-to-edge repair
- 7 TR = tricuspid regurgitation
- 8 TTVI = transcatheter tricuspid valve intervention
- 9 TV = tricuspid valve

ACCEPTED MANUSCRIPT

INTRODUCTION

1
2 Tricuspid regurgitation (TR) is a highly prevalent valvular heart disease and is associated with
3 increased long-term mortality and adverse clinical outcomes ¹⁻³. The majority of patients with
4 significant TR are deemed at high or prohibitive surgical risk and surgery for isolated TR is
5 seldom performed ⁴. The unmet clinical need of operative TR management led to the
6 development of transcatheter tricuspid valve intervention (TTVI), which has been shown to be a
7 safe and effective therapeutic option ^{5,6}. Several studies have shown sex-related differences in the
8 presentation and outcomes of patients with aortic stenosis or mitral regurgitation irrespective of
9 the medical or operative management ⁷⁻⁹. In particular, women have been found to be older at
10 presentation for intervention, having less clinical benefit after mitral transcatheter edge-to-edge
11 repair (TEER), and markedly higher mortality after aortic valve intervention for low-flow low-
12 gradient aortic stenosis. Natural history studies report an increased prevalence of significant TR
13 in women ¹⁰, and risk score to predict outcomes for isolated tricuspid valve surgery include
14 female sex as a risk factor ¹¹. However, the impact of sex on characteristics and outcomes of
15 patients with significant TR undergoing TTVI remains unknown.

16 Hence, we sought to perform a comprehensive analysis of sex-related differences
17 regarding clinical presentation, echocardiographic characteristics, and outcomes of patients
18 undergoing TTVI enrolled in a large real-world, international registry (TriValve Registry,
19 NCT03416166) and compare them with a control group of patients with \geq severe isolated TR
20 under optimal medical therapy (OMT).

21

22

METHODS

1
2 **TTVI cohort.** The details of the TriValve registry have been previously described¹². Briefly, the
3 TriValve registry included patients with symptomatic TR who underwent TTVI across 24 centers
4 in Europe and North America. All patients had symptomatic heart failure (HF) and significant (\geq
5 moderate) TR according to the European and American guidelines.^{13,14} Patients were referred to
6 the registry by local investigators and were deemed at prohibitive risk by the local
7 interdisciplinary heart team. The Institutional Review Board at each participating site approved
8 the study protocol, and informed, written consent for participation was provided by all patients.
9 Baseline characteristics, including clinical and echocardiographic data, were collected before
10 TTVI. Procedural success was defined as patient alive at the end of the procedure, with the
11 device successfully implanted and delivery system retrieved, with a TR reduction of at least one
12 grade, and an absolute residual TR $\leq 2+$.

13 **Medical Therapy Cohort.** The control cohort was formed by all consecutive patients with a new
14 diagnosis of severe or greater TR made with echocardiographic assessment at Montefiore-
15 Einstein Center for Heart and Vascular Care (Bronx, New York, USA) between 2015 and 2018.
16 All data were prospectively collected in an institutional registry and further examined for the
17 presence of the inclusion (severe or greater TR) and exclusion (age < 18 years, previous TV
18 intervention [whether surgical or transcatheter], heart valvular intervention during the follow-up
19 period, or patients with concomitant more than moderate mitral or aortic valve disease) criteria.
20 No transcatheter option was available for these patients in the study period. Baseline
21 characteristics, including clinical and echocardiographic data, were collected at the time of
22 echocardiographic assessment. Clinical follow-up was carried out by clinical visits and/or phone
23 consultation. The inclusion of patients in this study was approved by the local institutional review

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

3 **Echocardiographic Evaluation.** All patients underwent a comprehensive 2-dimensional and
4 Doppler echocardiography. TR severity was graded into four grades: mild (1+), moderate (2+),
5 severe (3+) and massive/torrential (4+) using a combination of semiquantitative and quantitative
6 assessment, as described by the American Society of Echocardiography guidelines as well as the
7 European Association of Echocardiography guidelines¹⁵⁻¹⁷. TR effective regurgitant orifice area
8 was quantified using the proximal isovelocity surface area method. Pacemaker-induced TR was
9 diagnosed with targeted interrogation of the tricuspid valve leaflets in presence of leads and
10 leaflet impingement, leaflet adherence, leaflet perforation, or pacing mediated TR. Chamber sizes
11 and function were quantified in accordance with the most recent European and U.S. guidelines.
12^{16,18} Specially, right ventricular (RV) function was estimated by measuring tricuspid annular
13 plane systolic excursion (TAPSE) or Doppler tissue imaging-derived tricuspid lateral annular
14 systolic velocity. Right ventricular end-diastolic diameter was defined as the maximal transversal
15 dimension in the basal one third of the RV inflow at end diastole and right atrial volume was
16 calculated using single-plane area-length or disk summation techniques. All right-side
17 measurements were performed in dedicated apical four-chamber view.

18 **Clinical Outcomes.** In the absence of specific criteria and definitions for TTVI adverse
19 outcomes, Mitral Valve Academic Research Consortium criteria were adopted to define adverse
20 events. The primary endpoint was 1-year freedom from all-cause death. Secondary endpoints
21 were HF hospitalization, functional status (assessed by the New York Heart Association [NYHA]
22 functional class), and recurrence of more than moderate TR severity. Acute kidney injury was
23 defined as stage 2 or 3 of the modified RIFLE criteria. Follow-up data were collected at

1 discharge, at 30 days, and then according to the time frame elapsed from the index procedure to
2 data lock for the present analysis. The data underlying this article will be shared on reasonable
3 request to the corresponding author.

4 **Statistical analysis.** Patients were divided into two groups according to sex in both cohorts.
5 Categorical variables were reported as numbers and corresponding proportions and compared with
6 the χ^2 test with continuity correction or the Fisher exact test, as appropriate. Continuous variables
7 were described as mean \pm SD or as median (interquartile range) and compared with two-sided
8 Student's t-test (parametric test) or the Wilcoxon rank sum test (non-parametric test), according
9 to their distribution. A propensity score methodology with inverse probability of treatment
10 weighting (IPTW) was performed to limit selection bias and balance baseline characteristics
11 between TTVI and medical therapy groups^{19,20}. Propensity scores predicting each patient's
12 probability of undergoing TTVI or not were estimated using generalized linear models including
13 variables with a difference in their distribution between the two groups or considered clinically
14 significant (age, atrial fibrillation, diabetes, and chronic kidney disease). Propensity scores were
15 used to compute stabilized weights. IPTW was used to maintain the numbers of patients in both
16 cohorts, contrary to traditional propensity matching that requires trimming of both groups in
17 order to create a balanced match. The balance of measured covariance between groups was
18 compared by generating a standardized difference and optimal balance was determined with a
19 value of 10% or less. Subsequent survival analyses including both TTVI and medical therapy
20 groups were weighted by IPTW. Overall survival and freedom from the composite endpoint of
21 death or unplanned HF hospitalization were estimated using the Kaplan-Meier method and
22 compared using the log-rank test. The incidence of HF hospitalization was estimated using the
23 cumulative incidence function accounting for death as a competing risk. Hazard ratios (HRs) and

1 95% confidence intervals (CIs) were determined using Cox proportional hazards regression.
2 Multivariable Cox proportional hazards regression models were used to explore the association of
3 TTVI and sex with primary and secondary endpoints. A two-sided p value of <0.05 was
4 considered statistically significant. Statistics were performed using R, version 4.1.3 (The R
5 Foundation for Statistical Computing, Vienna, Austria).

6 RESULTS

7 **Baseline and procedural characteristics.** A total of 556 patients underwent TTVI and were
8 included in the Trivalve Registry. Among them, 316 (56.8%) were women. Baseline
9 characteristics according to sex are depicted in **Table 1**. Compared to men, women were less
10 likely to have ascites (20.3% vs. 32.1%, $p<0.01$) or previous hospitalization for RV failure
11 (65.1% vs. 75.7%, $p=0.02$). Conversely, there was no difference regarding the incidence of
12 NYHA class III-IV (women 93.6% vs. men 91.5%, $p=0.19$), diabetes (women 29.8% vs. men
13 24.2%, $p=0.18$), or atrial fibrillation (women 66.6% vs. men 68.5%, $p=0.70$). Although men had
14 more implanted pacemaker or intracardiac defibrillator (31.2% vs. 21.6%, $p=0.02$), TR
15 mechanism was mainly functional (88.8%) with similar proportions between men and women
16 (91.6% vs. 86.7%, $p=0.28$). Women had higher left ventricular ejection fraction ($53.8 \pm 11.5\%$
17 vs. $46.3 \pm 14.7\%$, $p<0.01$), with similar left ventricular and left atrial sizes, measured as left
18 ventricular end-diastolic diameter index ($p=0.63$) and left atrial volume index ($p=0.82$). There
19 were no statistical differences in RV size (i.e. RV end-diastolic diameter) and function (i.e.
20 TAPSE), **Table 2**.

21 **TTVI and procedural outcomes.** Procedural characteristics and outcomes are shown in **Table 3**.
22 Overall, the duration of the procedure was similar between women and men (132.4 ± 66.4 min

1 vs. 132.0 ± 60.4 min, $p=0.95$). Women were less frequently treated with TEER than men (74.4%
2 vs. 83.3%, $p<0.01$) and in case of TEER, fewer clips were implanted in women compared to men
3 ($p<0.01$). The rates of procedural success were similar between the two groups (79.5% vs. 77.1%,
4 $p=0.56$) as well as the risk of acute kidney injury (10.8% vs. 14.6%, $p=0.32$), conversion to
5 surgery (1.2% vs. 2.1%, $p=0.46$), or in-hospital death (3.5% vs. 2.1%, $p=0.57$).

6 **Sex-related outcomes following TTVI.** At 1 year after TTVI, all-cause mortality occurred in 66
7 (20.4%) patients, HF hospitalization in 81 (25.4%), and the composite endpoint of all-cause
8 mortality and HF hospitalization in 118 (35.4%). At 1 year no differences between women and
9 men were observed in the Kaplan-Meier analyses for the freedom from all-cause mortality and
10 the composite endpoint of all-cause mortality or HF hospitalization, nor in the cumulative
11 incidence function of HF hospitalization, **Figure 1**. After adjustment for left ventricular ejection
12 fraction, previous myocardial infarction, and hospitalization for RV failure on multivariable Cox
13 regression analysis, results remained consistent with the unadjusted Kaplan-Meier method:
14 freedom from all-cause mortality (adjusted HR 1.02; 95% CI 0.59-1.74; $p=0.95$), HF
15 hospitalization (adjusted HR 1.28; 95% CI 0.79-2.09; $p=0.31$), and all-cause mortality or HF
16 hospitalization (adjusted HR: 1.11; 95% CI 0.74-1.65; $p=0.62$). In addition, there were no
17 differences between women and men in NYHA functional class III-IV nor in TR severity $>2+$ at
18 30 days ($p=0.17$ and $p=0.42$, respectively), and at last follow-up ($p=0.87$ and $p=0.90$,
19 respectively), **Figure 2**.

20 **TTVI plus OMT versus OMT alone.** A total of 2072 patients formed the control group and
21 were compared with those undergoing TTVI in the TriValve registry, **Table 4**. After IPTW,
22 baseline characteristics of the weighted groups were more balanced between TTVI and OMT
23 patients, in particular with regard to age (73.9 ± 11.5 years vs. 73.4 ± 15.2 years, standardized

1 difference=3.8%), atrial fibrillation (48.6% vs. 42.8%, standardized difference=5.8%), and
2 chronic kidney disease (52.3% vs. 51.6%, standardized difference=0.7%), **Supplemental Figure**
3 **S1**. Differences persisted in the weighted groups, with the TTVI group having higher left
4 ventricular end-diastolic diameter index, left atrial volume index, and lower TAPSE. Similar
5 findings were observed comparing the two treatments groups within each sex category,
6 **Supplemental Table S1-S2**. IPTW-weighted Kaplan-Meier analyses at 1 year showed a lower
7 overall survival for women in the OMT group (women 66.1% vs. men 70.7%, log-rank $p=0.01$),
8 that was no longer evident after Cox-regression adjustment for age, body mass index, left
9 ventricular ejection fraction, and TAPSE (Adjusted HR 0.70, 95% CI 0.33-1.49, $p=0.35$, **Figure**
10 **3**). In the TTVI cohort, overall survival weighted by IPTW was not affected by sex (women
11 79.1% vs. men 78.6%, log-rank $p=0.74$; adjusted HR 0.98, 95% CI: 0.53-1.84, $p=0.96$). Finally,
12 the benefit of TTVI plus OMT over OMT alone was consistently observed in women (TTVI plus
13 OMT 79.1% vs. OMT alone 66.1%, log-rank $p<0.01$; adjusted HR: 0.45, 95% CI 0.23-0.83,
14 $p=0.01$) and men (TTVI plus OMT 78.6% vs. OMT alone 70.7%, log-rank $p<0.01$; adjusted HR
15 0.42, 95% CI 0.18-0.89, $p=0.03$, adjusted $p_{\text{interaction}}=0.74$), **Figure 3**.

16 DISCUSSION

17 In this study, we investigated the sex-related differences in characteristics and outcomes of
18 patients undergoing TTVI for TR in the large, international real-world TriValve Registry. After
19 TTVI, women and men showed similar improvements in terms of survival, HF hospitalization,
20 functional status, and sustained TR reduction up to 1 year of follow-up. Compared to a control
21 group of patients with isolated TR under OMT weighting by IPTW and adjusting with Cox-
22 regression analyses, TTVI plus OMT was associated with substantial and consistent increase in
23 1-year survival in both women and men (**Structured Graphical Abstract**).

1 Sex-related differences in valvular disease epidemiology and ventricular responses to
2 changes in loading conditions lead to differences in disease prevalence and clinical
3 manifestations⁸. Despite a predominance of males with aortic stenosis, several studies reported a
4 higher prevalence and incidence, ranging from 53% to 75%, of TR among women^{21–25}. Our
5 results are consistent with these findings with 57% of women with significant TR referred for
6 TTVI and 64% present in the OMT group. Besides, clinical manifestations of patients with
7 significant TR are different between women and men. We showed that, compared to men, women
8 were less likely to have ascites or previous hospitalization for RV failure, and less left ventricular
9 systolic dysfunction which is in line with recent findings from Dietz et al. and Gual-Capllonch et
10 al.²⁶. In their study, Dietz et al. investigated the sex-specific differences in prognosis in patients
11 with significant TR²³. In a cohort of 1569 patients (51% females), women had better 10-year
12 survival rates compared with men (49% vs. 39%, $p=0.001$). However, after propensity score
13 matching, there was no significant difference in mortality ($p=0.23$). Accordingly, our analyses
14 with IPTW and Cox-regression adjustments for baseline characteristics show that women and
15 men with TR under medical management had similar overall survival.

16 Exploring gender differences in Medicare beneficiaries undergoing mitral valve
17 operations, women were found to have higher operative mortality and lower long-term survival
18²⁷. However, these findings were largely driven by an older age, higher number of comorbidities,
19 and later presentation with more advanced disease for women. In the subgroup of patients
20 undergoing mitral valve replacement, the survival benefit over medical therapy was consistent
21 irrespective of sex. In case of TEER for mitral regurgitation, two studies from the randomized
22 COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart
23 Failure Patients with Functional Mitral Regurgitation) trial and the EuroSMR registry found that

1 women had a less pronounced reduction in HF hospitalizations compared to men, with overall
2 survival and improvement in clinical outcomes being similar in both sexes.^{28,29}

3 Few studies investigated the sex-related differences in postoperative outcomes after
4 tricuspid valve surgery. Exploring 92 patients who underwent isolated TV surgery, Pfannmueller
5 et al. did not show significant differences in postoperative mortality between women and men³⁰.
6 Using the National Inpatient Sample to identify 5005 patients who underwent isolated TV
7 surgery from 2004 to 2013, Chandrashekar et al. compared outcomes in 366 paired patients after
8 propensity-matching. They found that overall in-hospital mortality was similar for matched
9 women and men.³¹ However, no assessment was available after discharge.

10 To date, there are no data regarding the impact of sex in patients with advanced TR
11 undergoing transcatheter interventions. In our study, we showed that after TTVI, clinical
12 outcomes are similar in both women and men, with 1-year survival rates of 81% and 78%,
13 respectively. Similarly, the survival benefit of TTVI over medical therapy was significant
14 irrespective of sex. These findings are in line with previous reports for the transcatheter treatment
15 of mitral regurgitation^{28,29}. In the TriValve registry, there were no marked differences in baseline
16 characteristics of women versus men. This may explain the discrepancies with surgical series,
17 where women were at much higher risk compared to male candidates. Also, this stresses the
18 importance of timely referral and management of TV disease.

19 In the absence of any randomized controlled trial, our results suggest that the benefits of
20 transcatheter interventional treatment of TR are substantial and not affected by gender. With
21 increasing numbers of patients and TTVI options, further studies should explore the impact of
22 sex according to the type of procedure and the patient risk profile.

1 **Study Limitations.** The most relevant limitations of this study are inherent to its non-
2 randomized, observational design with no centralized echocardiographic core-lab or clinical
3 event adjudication committee. However, it still provides the most comprehensive information on
4 sex-related characteristics and outcomes of patients undergoing TTVI for TR. Although several
5 statistical methods, such as propensity-IPTW and multivariable Cox-regression analyses, have
6 been applied, we cannot exclude the impact on outcomes of unknown/unmeasured variables (e.g.
7 TR etiology) that could not be corrected. Right ventricular basal diameter and TAPSE may not be
8 accurate measurements of RV size and function in presence of different TR etiology (i.e. atrial
9 vs. ventricular)³² and previous cardiac surgery. Longer-term follow-up is required to determine if
10 the observed outcomes with no differences between women and men are maintained or whether
11 any new interactions may become apparent over time. Finally, our results have to be considered
12 as hypotheses generating; randomized controlled trials are needed to validate these findings and
13 define the ideal candidates and timing of transcatheter interventions for TR.

14 CONCLUSIONS

15 In the TriValve registry, after TTVI in high-risk patients with significant TR there were no sex-
16 related differences in terms of survival, HF hospitalization, functional status, and TR reduction
17 up to 1 year. The IPTW analysis suggests that TTVI may be associated with substantial and
18 consistent increase in survival in both women and men compared to medical therapy alone.
19 Future studies are needed to assess whether sex-related differences in outcomes may emerge at
20 longer-term follow-up.

21 **Funding:** none

22 **Disclosures:** Dr Scotti has served as a consultant and received consulting fees from NeoChord
23 Inc. Dr Coisne has served as a consultant for Abbott and received speaker fees from Abbott and

1 GE Healthcare. Dr Taramasso has served as a consultant for Abbott Vascular, Boston Scientific,
2 4Tech, and CoreMedic; and has received speaker honoraria from Edwards Lifesciences. Dr
3 Ludwig has received travel compensation from Edwards Lifesciences. Dr Rodés-Cabau has
4 received institutional research grants from Edwards Lifesciences. Dr Lurz has received speaker
5 fees from Abbott. Dr Hausleiter has received speaker honoraria from Abbott Vascular and
6 Edwards Lifesciences. Dr Kodali has served on the scientific advisory board for
7 Microinterventional Devices, Dura Biotech, Thubrikar Aortic Valve, and Supira; has served as a
8 consultant for Meril Lifesciences, Admedus, Medtronic, and Boston Scientific; has served on the
9 steering committee for Edwards Lifesciences and Abbott Vascular; has received honoraria from
10 Meril Lifesciences, Admedus, Abbott Vascular, and Dura Biotech; and owns equity in Dura
11 Biotech, Thubrikar Aortic Valve, Supira, and MID. Dr Alessandrini has received consulting fees
12 from Abbott and Edwards LifeSciences. Dr Brochet has received speaker fees from Abbott
13 Vascular. Dr Denti has served as a consultant for Abbott Vascular, 4Tech, Neovasc, and
14 InnovHeart; and has received honoraria from Abbott and Edwards Lifesciences. Dr Estévez-
15 Loureiro has received speaker fees from Abbott, Boston, and Edwards Lifesciences. Dr Ho has
16 served as a consultant and received consulting fees from NeoChord Inc. Dr Praz has received
17 travel expenses from Edwards Lifesciences, Abbott Vascular, and Polares Medical. Dr Sievert
18 has received study honoraria, travel expenses, and consulting fees from 4Tech Cardio, Abbott,
19 Ablative Solutions, Ancora Heart, Bavaria Medizin Technologie, Bioventrix, Boston Scientific,
20 Carag, Cardiac Dimensions, Celonova, Comed BV, Contego, CVRx, Edwards Lifesciences,
21 Endologix, Hemoteq, Lifetech, Maquet Getinge Group, Medtronic, Mitralign, Nuomao Medtech,
22 Occlutech, PFM Medical, ReCor, Renal Guard, Rox Medical, Terumo, Vascular Dynamics, and
23 Vivasure Medical. Dr Tang has served as a consultant, physician advisory board member, and
24 faculty trainer for Abbott Structural Heart; has served as a consultant for Medtronic and
25 NeoChord; and has served as a physician advisory board member for JenaValve. Dr Andreas has
26 served as a proctor/ consultant for and has received speaking fees from Abbott, Edwards
27 LifeSciences, Boston, Zoll and Medtronic; and has received institutional grants from Edwards
28 Lifesciences, Abbott, Medtronic, and LSI Solutions. Dr Gavazzoni has served as a consultant for
29 Abbott Vascular. Dr Braun has received speaker honoraria and travel support from Abbott
30 Vascular. Dr Kalbacher has received lecture fees from Abbott and Edwards Lifesciences. Dr
31 Connelly has received honoraria from Abbott. Dr Schofer has served as a consultant for Edwards

1 Lifesciences. Dr Windecker reports research, travel or educational grants to the institution from
2 Abbott, Abiomed, Amgen, Astra Zeneca, Bayer, Biotronik, Boehringer Ingelheim, Boston
3 Scientific, Bristol Myers Squibb, Cardinal Health, CardioValve, Corflow Therapeutics, CSL
4 Behring, Daiichi Sankyo, Edwards Lifesciences, Guerbet, InfraRedx, Janssen-Cilag, Johnson &
5 Johnson, Medicure, Medtronic, Merck Sharp & Dohm, Miracor Medical, Novartis, Novo
6 Nordisk, Organon, OrPha Suisse, Pfizer, Polares, Regeneron, Sanofi-Aventis, Servier, Sinomed,
7 Terumo, Vifor, V-Wave. Dr Windecker serves as unpaid advisory board member and/or unpaid
8 member of the steering/executive group of trials funded by Abbott, Abiomed, Amgen, Astra
9 Zeneca, Bayer, Boston Scientific, Biotronik, Bristol Myers Squibb, Edwards Lifesciences,
10 Janssen, MedAlliance, Medtronic, Novartis, Polares, Recardio, Sinomed, Terumo, V-Wave and
11 Xeltis, but has not received personal payments by pharmaceutical companies or device
12 manufacturers. He is also member of the steering/executive committee group of several
13 investigator-initiated trials that receive funding by industry without impact on his personal
14 remuneration. Dr Maisano has served as a consultant for and received consulting fees and
15 honoraria from Abbott Vascular, Edwards Lifesciences, Cardiovalve, SwissVortex, Perifect,
16 Xeltis, Transseptal Solutions, Magenta, Valtech, and Medtronic; has reported being a cofounder
17 of 4Tech; has received research grant support from Abbott, Medtronic, Edwards Lifesciences,
18 Biotronik, Boston Scientific, NVT, and Terumo; has received royalties and owns intellectual
19 property rights from Edwards Lifesciences (FMR surgical annuloplasty); and has reported being
20 a shareholder in Cardiovalve, Swiss Vortex, Magenta, Transseptal Solutions, Occlufit, 4Tech,
21 and Perifect. Dr Leon has received institutional clinical research grants from Abbott, Boston
22 Scientific, Edwards Lifesciences, and Medtronic. Dr Hahn has served as a consultant for Abbott
23 Vascular, Abbott Structural, NaviGate, Philips Healthcare, Medtronic, Edwards Lifesciences, and
24 GE Healthcare; has been the Chief Scientific Officer for the Echocardiography Core Laboratory
25 at the Cardiovascular Research Foundation for multiple industry-supported trials, for which she
26 receives no direct industry compensation; has received speaker fees from Boston Scientific and
27 Baylis Medical; and has received nonfinancial support from 3mensio. Dr Latib has served on the
28 advisory board for Medtronic, Abbott Vascular Boston Scientific, Edwards Lifesciences,
29 Shifamed, NeoChord Inc., V-dyne, and Philips. All other authors have reported that they have no
30 relationships relevant to the contents of this paper to disclose.

1 REFERENCES

- 2 1. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J*
3 *Am Coll Cardiol* 2004;**43**:405–409.
- 4 2. Neuhold S, Huelsmann M, Pernicka E, Graf A, Bonderman D, Adlbrecht C, et al. Impact of
5 tricuspid regurgitation on survival in patients with chronic heart failure: unexpected findings
6 of a long-term observational study. *Eur Heart J* 2013;**34**:844–852.
- 7 3. Asmarats L, Taramasso M, Rodés-Cabau J. Tricuspid valve disease: diagnosis, prognosis and
8 management of a rapidly evolving field. *Nat Rev Cardiol* 2019;**16**:538–554.
- 9 4. Scotti A, Sturla M, Granada JF, Kodali S, Coisne A, Mangieri A, et al. Outcomes of Isolated
10 Tricuspid Valve Replacement: a systematic review and meta-analysis of 5316 patients from
11 35 studies. *EuroIntervention* 2022;**18**:840-851.
- 12 5. Taramasso M, Alessandrini H, Latib A, Asami M, Attinger-Toller A, Biasco L, et al.
13 Outcomes After Current Transcatheter Tricuspid Valve Intervention. *JACC Cardiovasc*
14 *Interv* 2019;**12**:155–165.
- 15 6. Miura M, Alessandrini H, Alkhodair A, Attinger-Toller A, Biasco L, Lurz P, et al. Impact of
16 Massive or Torrential Tricuspid Regurgitation in Patients Undergoing Transcatheter
17 Tricuspid Valve Intervention. *JACC Cardiovasc Interv* 2020;**13**:1999–2009.
- 18 7. DesJardin JT, Chikwe J, Hahn RT, Hung JW, Delling FN. Sex Differences and Similarities in
19 Valvular Heart Disease. *Circ Res* 2022;**130**:455–473.
- 20 8. Hahn RT, Clavel M-A, Mascherbauer J, Mick SL, Asgar AW, Douglas PS. Sex-Related
21 Factors in Valvular Heart Disease. *J Am Coll Cardiol* 2022;**79**:1506–1518.
- 22 9. Tribouilloy C, Bohbot Y, Rusinaru D, Belkhir K, Diouf M, Altes A, et al. Excess Mortality
23 and Undertreatment of Women With Severe Aortic Stenosis. *J Am Heart Assoc*
24 2021;**10**:e018816.
- 25 10. Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, et al. Prevalence and clinical
26 determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study).
27 *Am J Cardiol* 1999;**83**:897–902.
- 28 11. Russo M, Saitto G, Lio A, Di Mauro M, Berretta P, Taramasso M, et al. Observed versus
29 predicted mortality after isolated tricuspid valve surgery. *J Card Surg* 2022;**37**:1959–1966.
- 30 12. Taramasso M, Hahn RT, Alessandrini H, Latib A, Attinger-Toller A, Braun D, et al. The
31 International Multicenter TriValve Registry. *JACC Cardiovasc Interv* 2017;**10**:1982–1990.
- 32 13. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, Gentile F, et al. 2020
33 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease:
34 Executive Summary: A Report of the American College of Cardiology/American Heart

- 1 Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*
2 2021;**77**:450–500.
- 3 14. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021
4 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*
5 2022;**43**:561–632.
- 6 15. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, et al.
7 Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report
8 from the American Society of Echocardiography Developed in Collaboration with the
9 Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr Off Publ Am Soc*
10 *Echocardiogr* 2017;**30**:303–371.
- 11 16. Lancellotti P, Pibarot P, Chambers J, La Canna G, Pepi M, Dulgheru R, et al. Multi-modality
12 imaging assessment of native valvular regurgitation: an EACVI and ESC council of valvular
13 heart disease position paper. *Eur Heart J Cardiovasc Imaging* 2022;**23**:e171–e232.
- 14 17. Hahn RT, Zamorano JL. The need for a new tricuspid regurgitation grading scheme. *Eur*
15 *Heart J Cardiovasc Imaging* 2017;**18**:1342–1343.
- 16 18. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al.
17 Recommendations for cardiac chamber quantification by echocardiography in adults: an
18 update from the American Society of Echocardiography and the European Association of
19 Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;**28**:1-39.e14.
- 20 19. Austin PC. The performance of different propensity score methods for estimating marginal
21 odds ratios. *Stat Med* 2007;**26**:3078–3094.
- 22 20. Benedetto U, Head SJ, Angelini GD, Blackstone EH. Statistical primer: propensity score
23 matching and its alternatives. *Eur J Cardiothorac Surg* 2018;**53**:1112–1117.
- 24 21. Andell P, Li X, Martinsson A, Andersson C, Stagmo M, Zöller B, et al. Epidemiology of
25 valvular heart disease in a Swedish nationwide hospital-based register study. *Heart*
26 2017;**103**:1696–1703.
- 27 22. Bohbot Y, Chadha G, Delabre J, Landemaine T, Beyls C, Tribouilloy C. Characteristics and
28 prognosis of patients with significant tricuspid regurgitation. *Arch Cardiovasc Dis*
29 2019;**112**:604–614.
- 30 23. Dietz MF, Prihadi EA, Bijl P van der, Fortuni F, Marques AI, Ajmone Marsan N, et al. Sex-
31 Specific Differences in Etiology and Prognosis in Patients With Significant Tricuspid
32 Regurgitation. *Am J Cardiol* 2021;**147**:109–115.
- 33 24. Topilsky Y, Maltais S, Medina Inojosa J, Oguz D, Michelena H, Maalouf J, et al. Burden of
34 Tricuspid Regurgitation in Patients Diagnosed in the Community Setting. *JACC Cardiovasc*
35 *Imaging* 2019;**12**:433–442.

- 1 25. Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, et al. Prevalence and clinical
2 determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study).
3 *Am J Cardiol* 1999;**83**:897–902.
- 4 26. Gual-Capllonch F, Cediël G, Ferrer E, Teis A, Juncà G, Vallejo N, et al. Sex-Related
5 Differences in the Mechanism of Functional Tricuspid Regurgitation. *Heart Lung Circ*
6 2021;**30**:e16–e22.
- 7 27. Vassileva CM, McNeely C, Mishkel G, Boley T, Markwell S, Hazelrigg S. Gender
8 differences in long-term survival of Medicare beneficiaries undergoing mitral valve
9 operations. *Ann Thorac Surg* 2013;**96**:1367–1373.
- 10 28. Park S-D, Orban M, Karam N, Lubos E, Kalbacher D, Braun D, et al. Sex-Related Clinical
11 Characteristics and Outcomes of Patients Undergoing Transcatheter Edge-to-Edge Repair
12 for Secondary Mitral Regurgitation. *JACC Cardiovasc Interv* 2021;**14**:819–827.
- 13 29. Kosmidou I, Lindenfeld J, Abraham WT, Rinaldi MJ, Kapadia SR, Rajagopal V, et al. Sex-
14 Specific Outcomes of Transcatheter Mitral-Valve Repair and Medical Therapy for Mitral
15 Regurgitation in Heart Failure. *JACC Heart Fail* 2021;**9**:674–683.
- 16 30. Pfannmueller B, Eifert S, Seeburger J, Misfeld M, Borger M, Mende M, et al. Gender-
17 Dependent Differences in Patients Undergoing Tricuspid Valve Surgery. *Thorac*
18 *Cardiovasc Surg* 2012;**61**:37–41.
- 19 31. Chandrashekar P, Zack C, Fender E, Nishimura R. Gender differences in isolated tricuspid
20 valve surgery [abstract]. *J Am Coll Cardiol* 2017;**69**(11 Suppl):1941.
- 21 32. Florescu DR, Muraru D, Florescu C, Volpato V, Caravita S, Perger E, et al. Right heart
22 chambers geometry and function in patients with the atrial and the ventricular phenotypes of
23 functional tricuspid regurgitation. *Eur Heart J Cardiovasc Imaging* 2022;**23**:930–940.
- 24
- 25

FIGURES LEGEND

Figure 1. Kaplan-Meier Curves of Clinical Outcomes after TTVI According to Sex.

There was no difference at 1 year in the Kaplan-Meier curves for death or HF hospitalization and death, nor in the cumulative incidence of HF hospitalization after TTVI between women and men. HF: heart failure; TTVI: transcatheter tricuspid valve intervention.

Figure 2. Changes in NYHA Functional Class and TR severity From Baseline to Last Follow-Up after TTVI

No significant differences in NYHA class III/IV or TR severity >2+ were observed between women and men at each time-point. * Comparison of NYHA class III/IV and TR severity >2+ between women and men. NYHA: New York Heart Association; TR: tricuspid regurgitation; TTVI: transcatheter tricuspid valve intervention.

Figure 3. Overall survival at 1 year according to treatment group and sex after IPTW.

Above: Unadjusted Kaplan-Meier analysis at 1 year. Below: forest plot from multivariable Cox regression analysis including age, body mass index, left ventricular ejection fraction, tricuspid annular plane systolic excursion, sex, and treatment. CI: confidence interval; OMT: optimal medical therapy; TTVI: transcatheter tricuspid valve intervention.

1

2 **Table 1. Baseline Characteristics According to Sex**

3

	Overall (n=556)	Women (n=316)	Men (n=240)	P-value
Age (years)	76.0 ± 9.6	76.1 ± 10.5	75.9 ± 8.2	0.82
BMI (kg/m ²)	26.0 ± 5.1	26.1 ± 5.7	25.9 ± 4.3	0.68
Diabetes	148 (27.4)	92 (29.8)	56 (24.2)	0.18
COPD	121 (22.0)	60 (19.0)	61 (25.8)	0.07
Atrial fibrillation	370 (67.4)	209 (66.6)	161 (68.5)	0.70
Prior myocardial infarction	89 (16.2)	35 (11.12)	54 (23.1)	<0.01
PM/ICD	140 (25.7)	67 (21.6)	73 (31.2)	0.02
NYHA class III-IV	509 (92.7)	294 (93.6)	215 (91.5)	0.19
Ascites	127 (25.5)	57 (20.3)	70 (32.1)	<0.01
Peripheral oedema	396 (77.3)	222 (76.3)	174 (78.7)	0.59
Previous RV failure	341 (69.6)	185 (65.1)	156 (75.7)	0.02
CKD	427 (76.8)	239 (75.6)	188 (78.3)	0.52
Previous left-side valve intervention	168 (30.4)	108 (34.2)	60 (25.3)	0.03
TR etiology				0.28
Functional	492 (88.8)	274 (86.7)	218 (91.6)	
Degenerative	27 (4.9)	17 (5.4)	10 (4.2)	
Mixed	26 (4.7)	19 (6.0)	7 (2.9)	
Other	9 (1.6)	6 (1.9)	3 (1.3)	
EuroSCORE II (%)	6.3 [3.7-12.4]	6.7 [4.1-13.2]	6.0 [3.3-11.0]	0.11
STS mortality (%)	4.1 [2.6-6.9]	4.3 [2.7-6.7]	4.0 [2.3-7.4]	0.51
Hemoglobin (g/dl)	10.7 ± 2.3	11.0 ± 2.3	10.2 ± 2.3	<0.01
eGFR (ml/min/1.73 m ²)	45.7 ± 20.5	46.6 ± 21.1	44.5 ± 19.8	0.25
NT-proBNP (pg/ml)	2656 [1309-5632]	2482 [1154-4830]	3038 [1640-6985]	<0.01
AST (U/L)	28.2 [23.0-36.0]	29.0 [22.0-37.8]	28.0 [23.9-33.0]	0.67

ALT (U/L)	19.0 [14.0-26.0]	20.0 [14.0-28.0]	18.6 [13.0-24.0]	0.05
-----------	------------------	------------------	------------------	------

1
2 Data are mean ± SD, median [interquartile range], or n (%). ALT: Alanine aminotransferase; AST: Aspartate
3 aminotransferase; BMI: Body mass index; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary
4 disease; eGFR: estimated glomerular filtration rate; ICD: implantable cardioverter defibrillator; NT-proBNP: N-
5 terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; PM: Pacemaker; RV: Right
6 ventricular; STS: Society of Thoracic Surgeons; TR: Tricuspid regurgitation
7

ACCEPTED MANUSCRIPT

1
2
3

Table 2. Baseline Echocardiographic Characteristics According to Sex

	Overall (n=556)	Women (n=316)	Men (n=240)	P-value
LVEF (%)	50.6 ± 13.5	53.8 ± 11.5	46.3 ± 14.7	<0.01
LVEDD (mm)	50.3 ± 8.9	47.9 ± 8.1	53.7 ± 8.8	<0.01
Left atrial volume (ml)	103.9 ± 52.2	99.3 ± 51.8	110.3 ± 52.3	0.04
Concomitant MR ≥3+	181 (33.2)	97 (31.2)	84 (35.9)	0.29
TR jet location				0.07
Central	362 (65.1)	205 (64.9)	157 (65.4)	
Anteroseptal	63 (11.3)	39 (12.3)	24 (10.0)	
Anteroposterior	11 (2.0)	2 (0.6)	9 (3.8)	
Posteroseptal	21 (3.8)	10 (3.2)	11 (4.6)	
Unknown	99 (17.8)	60 (19.0)	39 (16.2)	
TR vena contracta (mm)	10.5 ± 4.2	10.4 ± 4.2	10.6 ± 4.2	0.50
TR EROA (cm ²)	0.68 ± 0.53	0.70 ± 0.57	0.65 ± 0.47	0.41
TR regurgitant volume (ml)	51.5 ± 30.5	51.0 ± 32.0	52.1 ± 28.8	0.80
Tricuspid annulus diameter (mm)	47.5 ± 8.3	45.4 ± 7.9	50.2 ± 8.1	<0.01
Tricuspid coaptation gap (mm)	5.54 ± 2.96	5.33 ± 2.87	5.73 ± 3.04	0.28
Tricuspid tenting area (cm ²)	2.42 ± 1.56	2.38 ± 1.62	2.46 ± 1.51	0.67
RVEDD (mm)	39.7 ± 13.0	39.0 ± 12.4	40.3 ± 13.6	0.49
Right atrial volume (ml)	110.0 ± 69.0	107.1 ± 70.2	114.1 ± 67.3	0.41
TAPSE (mm)	16.6 ± 4.9	16.8 ± 5.2	16.3 ± 4.6	0.28
S-TDI (cm/s)	9.80 ± 3.12	9.73 ± 3.18	9.98 ± 3.02	0.66

SPAP (mmHg)	40.7 ± 15.2	42.5 ± 15.7	38.4 ± 14.2	<0.01
-------------	-------------	-------------	-------------	-------

1
2 Data are mean ± SD or n (%). EROA: Effective regurgitant orifice area; LVEDD: Left ventricular end-diastolic
3 diameter; LVEF: Left ventricular ejection fraction; MR: Mitral regurgitation; RVEDD: Right ventricular end-
4 diastolic diameter; S-TDI: S-tissue Doppler imaging; SPAP; Systolic pulmonary artery pressure; TAPSE; Tricuspid
5 annular plane systolic excursion; TR: Tricuspid regurgitation.
6

ACCEPTED MANUSCRIPT

1 **Table 3. Procedural Characteristics and Post-procedural Outcomes in the Device Group**
 2 **According to Sex**

	Overall (n=556)	Women (n=316)	Men (n=240)	P-value
Procedure				
Duration of procedure (min)	132.2 ± 63.7	132.4 ± 66.4	132.0 ± 60.4	0.95
Concomitant mitral or aortic intervention	127 (33.0)	69 (30.3)	58 (36.9)	0.21
Type of TTVI				<0.01
TEER	435 (78.2)	235 (74.4)	200 (83.3)	
TTVR	13 (2.3)	11 (3.5)	2 (0.8)	
Annuloplasty	52 (9.4)	40 (12.7)	12 (5.0)	
Others	56 (10.1)	30 (9.5)	26 (10.8)	
Number of Clips				<0.01
1	20 (4.7)	8 (3.4)	12 (6.2)	
2	105 (24.6)	67 (28.9)	38 (19.6)	
3	199 (46.7)	115 (49.6)	84 (43.3)	
4	87 (20.4)	39 (16.8)	48 (24.7)	
5	13 (3.1)	3 (1.3)	10 (5.2)	
6	2 (0.5)	0 (0.0)	2 (1.0)	
Post-procedure Outcomes				
Procedural success	415 (78.4)	237 (79.5)	178 (77.1)	0.56
AKI	51 (12.4)	26 (10.8)	25 (14.6)	0.32
New-onset Atrial Fibrillation	6 (1.4)	5 (2.1)	1 (0.6)	0.41
Stroke	4 (0.9)	3 (1.2)	1 (0.5)	0.64
Length of stay (days)	4 [2-7]	4 [2-7]	4 [3-7]	0.59
Conversion to surgery	7 (1.6)	3 (1.2)	4 (2.1)	0.46
In-hospital death	13 (2.9)	9 (3.5)	4 (2.1)	0.57
30-day outcomes				
TAPSE (mm)	15.7 ± 4.5	15.6 ± 4.5	15.8 ± 4.7	0.79
SPAP (mmHg)	43.3 ± 14.8	44.2 ± 14.1	41.9 ± 15.8	0.22
All-cause mortality	20 (4.9)	11 (4.5)	9 (5.6)	0.82

3
 4 Data are mean ± SD, median [interquartile range], or n (%). AKI: Acute kidney injury; SPAP: Systolic pulmonary
 5 artery pressure; TAPSE: Tricuspid Annular Plane Systolic Excursion; TEER: Transcatheter edge-to-edge repair;
 6 TTVI: Transcatheter tricuspid valve intervention; TTVR: Transcatheter tricuspid valve replacement

7

8

1 **Table 4. Unweighted and Weighted Patient Characteristics by Treatment Cohort (TTVI vs. control group)**

2

	Unweighted Study Population, n (%)			Weighted Study Population, %		
	TTVI (n=556)	Control (n=2072)	Standardized Difference, %	TTVI	Control	Standardized Difference, %
Age (years)	76.8 ± 10.3	72.4 ± 15.6)	33.1	73.9 ± 11.5	73.4 ± 15.2	3.8
Women	316 (56.8)	1335 (64.4)	7.6	61.2	64.2	-1.2
BMI (kg/m ²)	26.0 ± 5.1	28.5 ± 8.6	-34.5	26.6 ± 5.7	28.3 ± 8.4	-23.9
Atrial fibrillation	370 (67.4)	752 (36.3)	31.1	48.6	42.8	5.8
COPD	121 (22.0)	468 (22.6)	-0.6	21.4	23.7	-2.3
CKD	427 (76.8)	935 (45.1)	31.7	52.3	51.6	0.7
Diabetes	148 (27.4)	724 (34.9)	-7.5	39.8	33.5	-3.0
LVEF (%)	50.6 ± 13.5	50.4 ± 18.2	1.3	50.4 ± 13.6	50.5 ± 18.1	-0.8
LVEDD (mm)	50.3 ± 8.9	46.2 ± 9.4	44.7	50.2 ± 9.4	46.2 ± 9.4	43.8
Left atrial volume (ml)	103.9 ± 52.2	82.4 ± 33.2	49.0	101.1 ± 52.1	83.1 ± 33.3	41.2
Right atrial volume (ml)	110.0 ± 69.0	93.9 ± 47.5	27.2	104.1 ± 59.0	95.1 ± 48.5	15.1
TAPSE (mm)	16.6 ± 4.9	17.6 ± 5.5	-20.5	16.5 ± 4.9	17.7 ± 5.5	-23.0

3

4 Data are mean ± SD, median [interquartile range], or n (%). BMI: Body mass index; CKD: Chronic kidney disease; COPD: Chronic Obstructive Pulmonary
5 Disease; LVEDD: Left ventricular end-diastolic diameter; LVEF: Left ventricular ejection fraction; TAPSE: Tricuspid annular plane systolic excursion; TTVI:
6 transcatheter tricuspid valve intervention.

7

8

1

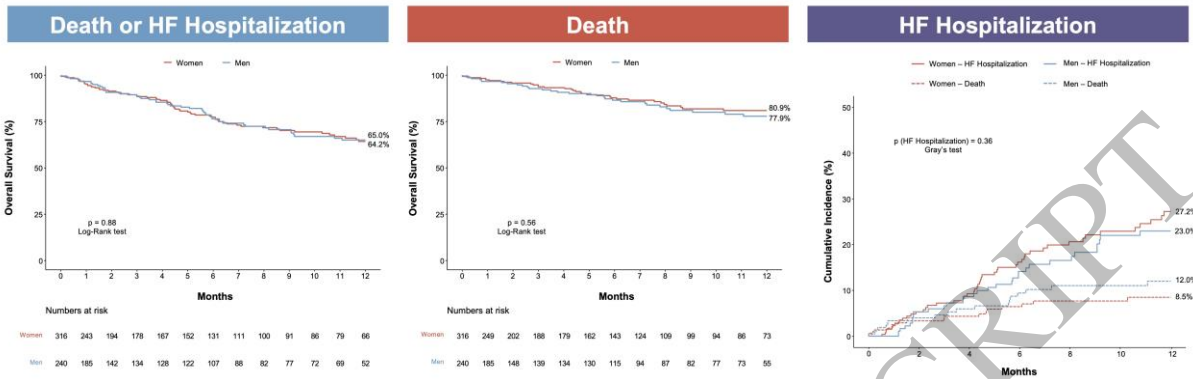


Figure 1
160x52 mm (7.0 x DPI)

2

3

4

5

ACCEPTED MANUSCRIPT

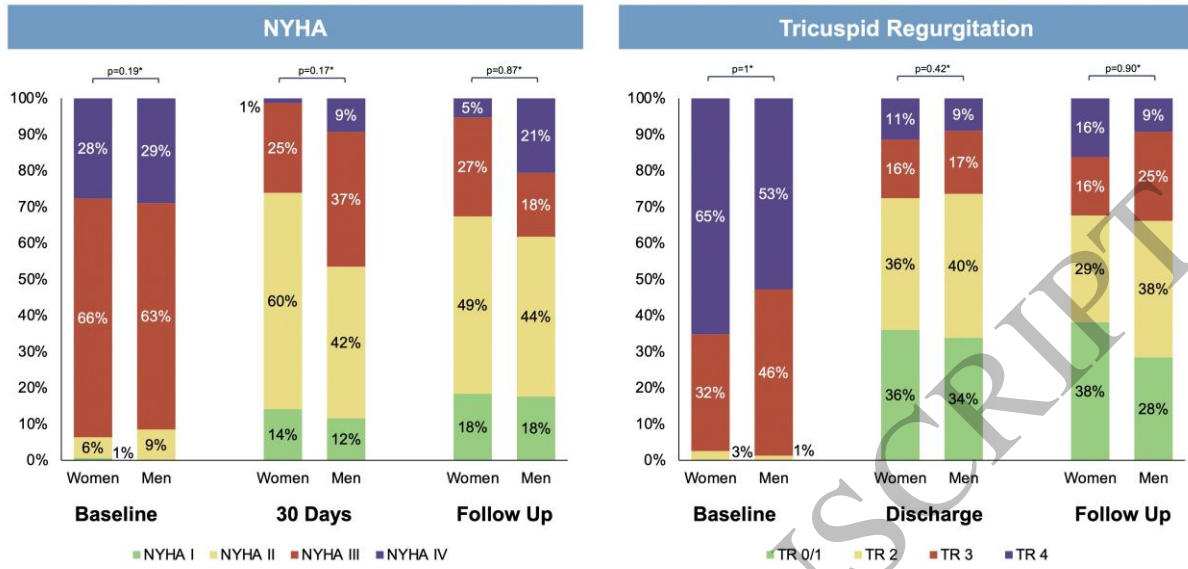
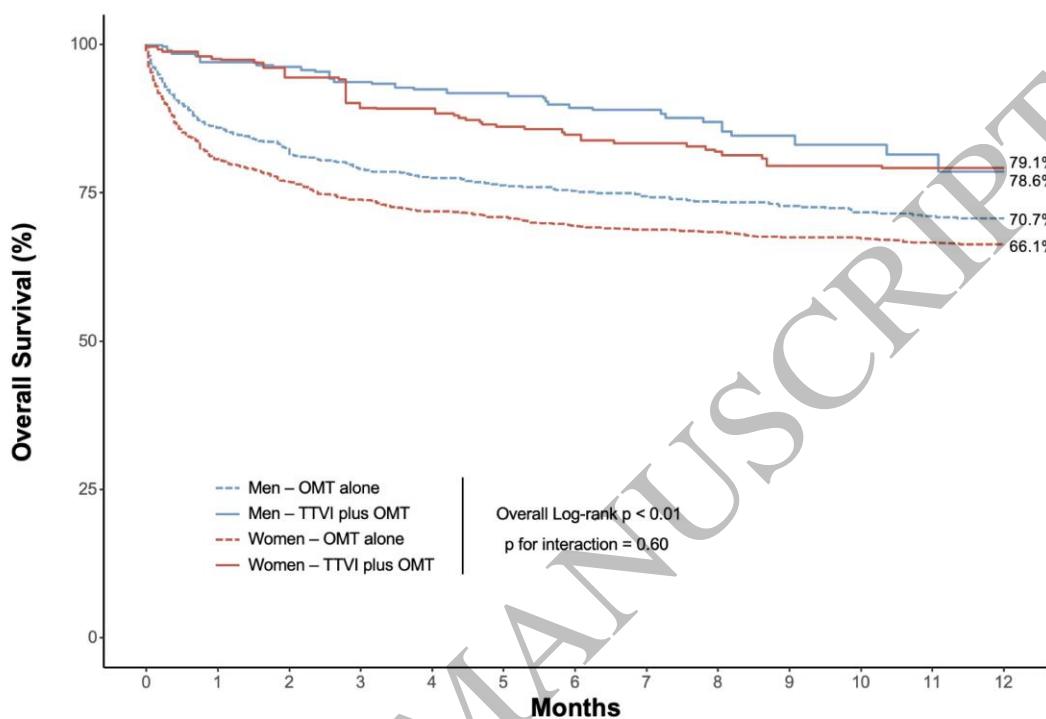


Figure 2
160x76 mm (7.0 x DPI)

1
2
3
4

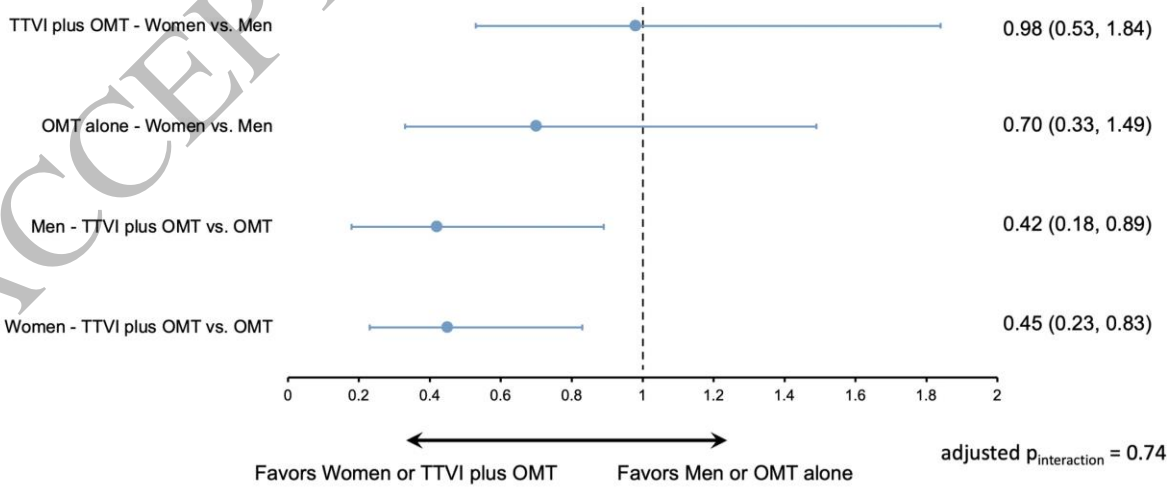
Overall Survival



Numbers at risk

Men - OMT alone	737	521	482	445	421	404	387	374	362	348	338	328	322
Men - TTVI plus OMT	240	185	148	139	134	130	115	94	87	82	77	73	55
Women - OMT alone	1335	889	805	740	705	683	658	641	631	617	610	596	590
Women - TTVI plus OMT	316	249	202	188	179	162	143	124	109	99	94	86	73

Adjusted Hazard Ratio (95% CI)



1
2
3

Figure 3
160x217 mm (7.0 x DPI)

Key Question

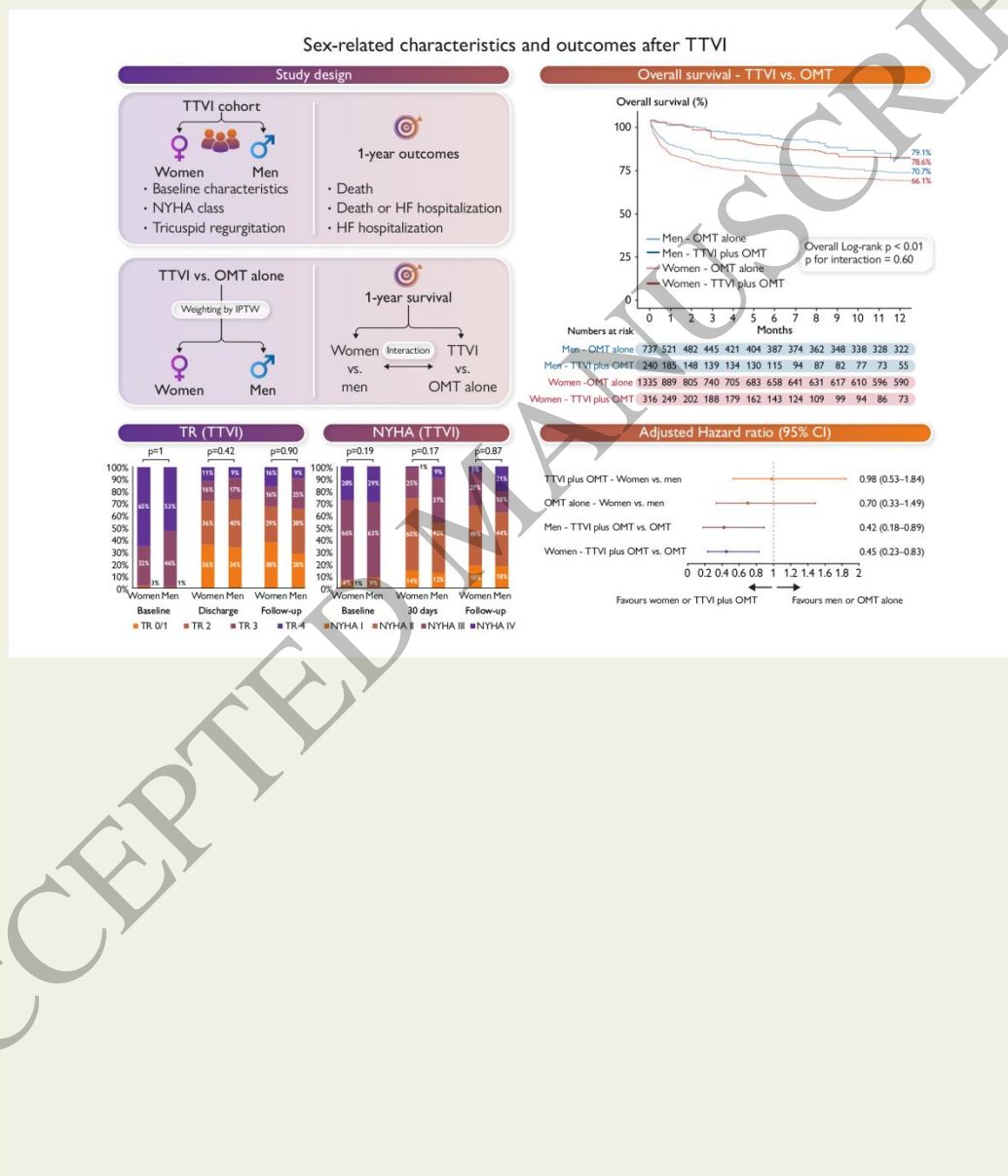
Does sex have an impact on characteristics and outcomes of patients with significant tricuspid regurgitation (TR) undergoing transcatheter tricuspid valve intervention (TTVI)?

Key Finding

TTVI was associated with similar outcomes in both women and men and increased 1-year survival over medical therapy, irrespective of sex.

Take Home Message

TTVI seems to improve 1-year survival as compared to medical therapy, irrespective of sex. This needs to be confirmed in randomized trials.



1
2

Graphical Abstract