JACC: CARDIOVASCULAR INTERVENTIONS VOL. 16, NO. 8, 2023

PUBLISHED BY ELSEVIER

NEW RESEARCH PAPER

SRUCTURAL

Sex-Related Differences in Clinical Characteristics and Outcome Prediction Among Patients Undergoing Transcatheter Tricuspid Valve Intervention

Vera Fortmeier, MD,[a,*] Mark Lachmann, MD,[b,c,*] Maria I. Körber, MD,[d] Matthias Unterhuber, MD,[e] Anne R. Schöber, MD,[e] Lukas Stolz, MD,[f] Thomas J. Stocker, MD,[c,f] Mohammad Kassar, MD,[g] Muhammed Gerçek, MD,[a] Tanja K. Rudolph, MD,[a] Fabien Praz, MD,[g] Stephan Windecker, MD,[g] Roman Pfister, MD,[d] Stephan Baldus, MD,[d] Karl-Ludwig Laugwitz, MD,[b,c] Jörg Hausleiter, MD,[c,f] Philipp Lurz, MD,[e] Volker Rudolph, MD[a]

ABSTRACT

BACKGROUND Men and women differ regarding comorbidities, pathophysiology, and the progression of valvular heart diseases.

OBJECTIVES This study sought to assess sex-related differences regarding clinical characteristics and the outcome of patients with severe tricuspid regurgitation (TR) undergoing transcatheter tricuspid valve intervention (TTVI).

METHODS All 702 patients in this multicenter study underwent TTVI for severe TR. The primary outcome was 2-year all-cause mortality.

RESULTS Among 386 women and 316 men in this study, men were more often diagnosed with coronary artery disease (52.9% in men vs 35.5% in women; $P = 5.6 \times 10^{-6}$). Subsequently, the underlying etiology for TR in men was predominantly secondary ventricular (64.6% in men vs 50.0% in women; $P = 1.4 \times 10^{-4}$), whereas women more often presented with secondary atrial etiology (41.7% in women vs 24.4% in men, $P = 2.0 \times 10^{-6}$). Notably, 2-year survival after TTVI was similar in women and men (69.9% in women vs 63.7% in men; $P = 0.144$). Multivariate regression analysis identified dyspnea expressed as New York Heart Association functional class, tricuspid annulus plane systolic excursion (TAPSE), and mean pulmonary artery pressure (mPAP) as independent predictors for 2-year mortality. The prognostic significance of TAPSE and mPAP differed between sexes. Consequently, we looked at right ventricular-pulmonary arterial coupling expressed as TAPSE/mPAP and identified sex-specific thresholds to best predict survival; women with a TAPSE/mPAP ratio <0.612 mm/mm Hg displayed a 3.43-fold increased HR for 2-year mortality ($P < 0.001$), whereas men with a TAPSE/mPAP ratio <0.434 mm/mm Hg displayed a 2.05-fold increased HR for 2-year mortality ($P = 0.001$).

CONCLUSIONS Even though men and women differ in the etiology of TR, both sexes show similar survival rates after TTVI. The TAPSE/mPAP ratio can improve prognostication after TTVI, and sex-specific thresholds should be applied to guide future patient selection. (J Am Coll Cardiol Intv 2023;16:909-923) © 2023 by the American College of Cardiology Foundation.

From the [a]Department of General and Interventional Cardiology, Heart and Diabetes Center North Rhine-Westphalia, Ruhr University Bochum, Bad Oeynhausen, Germany; [b]First Department of Medicine, Klinikum Rechts der Isar, Technical University of Munich, Munich, Germany; [c]DZHK (German Center for Cardiovascular Research), Partner Site Munich Heart Alliance, Munich Germany; [d]Department of Cardiology, Heart Center, University of Cologne, Cologne, Germany; [e]Department of Cardiology, Heart

ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2023.01.378

ABBREVIATIONS AND ACRONYMS

AUC = area under the curve

dPAP = diastolic pulmonary artery pressure

mPAP = mean pulmonary artery pressure

NYHA = New York Heart Association

PVR = pulmonary vascular resistance

ROC = receiver-operating characteristic

sPAP = systolic pulmonary artery pressure

TAPSE = tricuspid annular plane systolic excursion

TR = tricuspid regurgitation

TTVI = transcatheter tricuspid valve intervention

Men and women with valvular heart disease differ regarding comorbidities, pathophysiology, and the progression of disease.[1,2] This is particularly true for a heterogeneous disease entity such as tricuspid regurgitation (TR) mainly encompassing secondary forms.[3] Moreover, the prevalence of TR and female sex are strongly associated; by the eighth decade, women with at least moderate TR outnumber their male counterparts by 4:1.[4] Because the prevalence of TR-associated cardiac comorbidities such as coronary artery disease and atrial fibrillation varies between men and women, sex-related differences regarding the etiology and subsequent prognosis in the natural course of TR have been described; men with significant TR are more often diagnosed with coronary artery disease (48% vs 28%; $P < 0.001$), they present with poorer left ventricular function (left ventricular ejection fraction = 42% ± 16% vs 47% ± 15%; $P < 0.001$), and they eventually show worse 10-year survival rates than women (39% vs 49%; $P = 0.001$).[5]

Transcatheter tricuspid valve interventions (TTVIs) have meanwhile emerged as a treatment option in inoperable patients with severe TR, fueling the hope to be superior to conservative treatment in prolonging survival and reducing rehospitalization for heart failure.[6] Although female sex is generally recognized as a risk factor for hospital mortality and is thus included in surgical risk scores used by interdisciplinary heart teams,[7] no study to date has investigated the impact of sex on survival prediction after TTVI. Do sex-related differences in the prevalence of comorbidities and the etiology of TR affect the procedural success of TTVI and hence influence survival? To address this important question, this multicenter study sought to shed light on sex-related differences in baseline characteristics and outcomes, both in terms of procedural success and survival, among patients undergoing TTVI for severe TR. Moreover, this study aimed to explore: 1) if there exist sex-related differences in the etiology and underlying pathophysiology of TR; 2) if predictors for mortality after TTVI differ between men and women; and 3) if sex-specific thresholds should be applied to improve prognostication and hence refine patient selection in the future.

METHODS

STUDY POPULATION. This is a post hoc, multicentric analysis of prospectively and systematically collected data from 702 patients undergoing TTVI for severe TR from 2016 to 2021. The key inclusion criterion was severe TR[8] with high symptomatic burden despite optimal medical treatment. Patients were further deemed inoperable because of prohibitive perioperative risk as assessed by the local heart team. Planned and conducted in conformity with the Declaration of Helsinki, the study was approved by the local ethics committee of each center, and all patients provided written informed consent.

ECHOCARDIOGRAPHIC ANALYSIS. All echocardiographic studies were performed by experienced institutional cardiologists during clinical routine. Pulmonary hypertension was routinely evaluated by preprocedural transthoracic echocardiography. Echocardiographic systolic pulmonary artery pressure (sPAP) levels were calculated by adding peak systolic pressure gradients between the right ventricle and right atrium (estimated from the continuous wave Doppler profile of the TR jet) to right atrial pressure levels. In turn, right atrial pressure was estimated by the diameter and collapsibility of the inferior vena cava as described in contemporary guidelines.[9,10] Right ventricular systolic function was estimated based on tricuspid annular plane systolic excursion (TAPSE) measurements and right ventricular fractional area change calculations.

INVASIVE PULMONARY HYPERTENSION ASSESSMENT. A 7-F Swan-Ganz catheter was routinely used for preprocedural right heart catheterization via a femoral access. Systolic and diastolic pulmonary artery pressure (dPAP) levels were directly recorded.

Center Leipzig, University of Leipzig, Leipzig, Germany; [f]Medizinische Klinik und Poliklinik I, Klinikum der Universität München, Ludwig Maximilians University of Munich, Munich, Germany; and the [g]Department of Cardiology, Inselspital Bern, Bern University Hospital, Switzerland. *Drs Fortmeier and Lachmann contributed equally to this work.

George Nickenig, MD, served as Guest Editor for this paper. Lars Søndergaard, MD, served as Guest Editor-in-Chief for this paper.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received November 13, 2022; revised manuscript received January 24, 2023, accepted January 31, 2023.

TABLE 1 Comparison of Clinical Characteristics Between Women and Men

	Total Population (N = 702)	Stratification According to Sex		P Value
		Women (n = 386)	Men (n = 316)	
Age, y	78.0 ± 7.86 (77.4-78.6)	78.1 ± 7.93 (77.3-78.8)	77.9 ± 7.78 (77.1-78.8)	0.683
BMI, kg/m^2	26.1 ± 4.81 (25.7-26.4)	26.1 ± 5.33 (25.5-26.6)	26.1 ± 4.10 (25.6-26.5)	0.235
Arterial hypertension	593 (84.5)	328 (85.0)	265 (83.9)	0.764
Diabetes mellitus	192 (27.4)	100 (25.9)	92 (29.1)	0.388
NYHA functional class ≤II	70 (9.97)	35 (9.07)	35 (11.1)	0.449
NYHA functional class III	533 (75.9)	309 (80.1)	224 (70.9)	0.006
NYHA functional class IV	99 (14.1)	42 (10.9)	57 (18.0)	0.009
EuroSCORE II	7.22 ± 7.16 (6.69-7.76)	7.06 ± 6.72 (6.39-7.74)	7.42 ± 7.68 (6.56-8.28)	0.670
eGFR, mL/min	50.3 ± 21.9 (48.7-51.9)	50.7 ± 21.4 (48.6-52.9)	49.8 ± 22.6 (47.3-52.3)	0.559
NT-proBNP, pg/mL	4,738 ± 8,616 (4,090-5,390)	4,204 ± 7,575 (3,430-4,980)	5,382 ± 9,699 (4,290-6,470)	0.153
CAD	304 (43.3)	137 (35.5)	167 (52.9)	5.6×10^{-6}
COPD	131 (18.7)	65 (16.8)	66 (20.9)	0.203
Atrial fibrillation	632 (90.0)	341 (88.3)	291 (92.1)	0.128
Pacemaker/defibrillator	197 (28.1)	86 (22.3)	111 (35.1)	2.0×10^{-4}

Values are mean ± SD (95% CI) or n (%) unless otherwise indicated.

BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

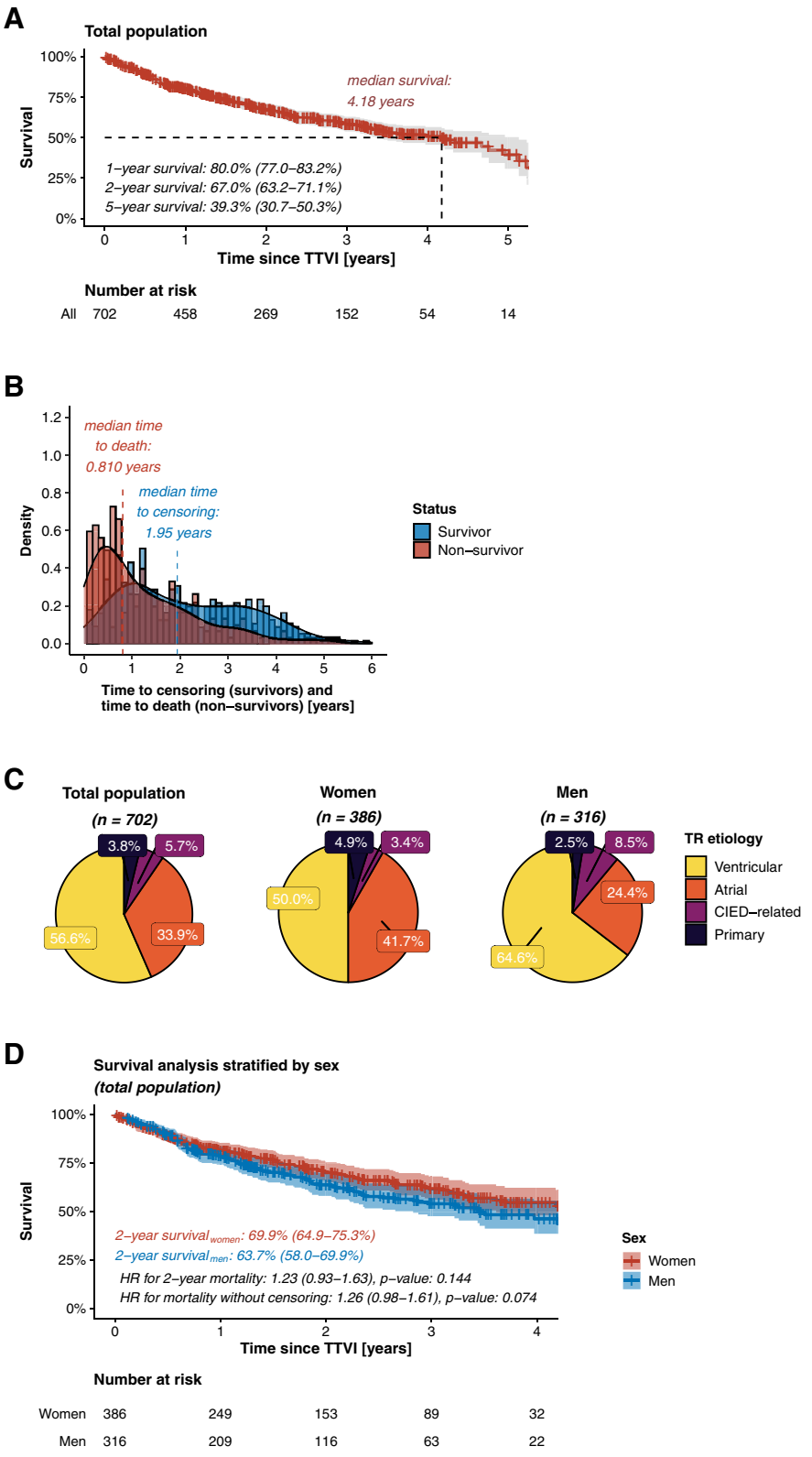
TABLE 2 Comparison of Echocardiographic and Hemodynamic Characteristics Between Women and Men

	Total Population (N = 702)	Stratification According to Sex		P Value
		Women (n = 386)	Men (n = 316)	
LVEF, %	53.6 ± 11.6 (52.7-54.5)	55.6 ± 10.6 (54.4-56.7)	51.2 ± 12.3 (49.8-52.6)	2.8×10^{-6}
LVESD, mm	39.2 ± 14.1 (38.1-40.4)	37.4 ± 14.3 (35.8-39.0)	41.2 ± 13.5 (39.6-42.8)	4.4×10^{-5}
LVEDD, mm	47.9 ± 8.24 (47.2-48.6)	45.4 ± 7.01 (44.6-46.2)	51.1 ± 8.60 (50.0-52.2)	1.3×10^{-15}
LA area, cm^2	31.4 ± 9.90 (30.6-32.1)	29.2 ± 8.91 (28.2-30.2)	33.8 ± 10.4 (32.6-35.0)	7.4×10^{-10}
$sPAP_{echo}$, mm Hg	41.1 ± 14.9 (40.0-42.2)	41.8 ± 15.1 (40.2-43.3)	40.2 ± 14.5 (38.6-41.9)	0.167
TAPSE, mm	16.6 ± 4.54 (16.3-17.0)	16.9 ± 4.58 (16.4-17.4)	16.4 ± 4.48 (15.9-16.9)	0.136
RV FAC, %	38.2 ± 11.0 (37.2-39.2)	38.5 ± 10.9 (37.2-39.9)	37.8 ± 11.2 (36.3-39.4)	0.637
Basal RV diameter, mm	47.0 ± 8.06 (46.4-47.6)	44.5 ± 7.16 (43.8-45.3)	50.1 ± 8.05 (49.2-51.0)	$< 2.2 \times 10^{-16}$
TV EROA, cm^2	0.673 ± 0.441 (0.638-0.707)	0.64 ± 0.40 (0.60-0.68)	0.71 ± 0.49 (0.65-0.77)	0.100
TR volume, mL	51.3 ± 28.0 (49.1-53.6)	50.0 ± 25.2 (47.1-52.8)	52.8 ± 30.7 (49.2-56.4)	0.152
TR vena contracta width, mm	11.2 ± 4.27 (10.9-11.5)	10.8 ± 4.11 (10.4-11.2)	11.7 ± 4.40 (11.2-12.2)	0.001
TR = III/V°	354 (50.4)	203 (52.6)	149 (47.2)	0.178
TR = IV/V°	219 (31.2)	116 (30.1)	103 (32.6)	0.514
TR = V/V°	129 (18.4)	65 (16.8)	62 (19.6)	0.389
RA area, cm^2	36.9 ± 11.6 (36.0-37.8)	33.7 ± 10.2 (32.7-34.8)	40.8 ± 12.0 (39.4-42.1)	8.5×10^{-16}
Inferior vena cava diameter, mm	25.8 ± 6.42 (25.3-26.3)	24.5 ± 6.02 (23.9-25.1)	27.4 ± 6.52 (26.7-28.2)	9.7×10^{-10}
Cardiac output, L/min	4.19 ± 1.67 (4.05-4.33)	3.68 ± 1.43 (3.51-3.85)	4.78 ± 1.74 (4.56-5.00)	$< 2.2 \times 10^{-16}$
Cardiac index, L/min/m^2	2.25 ± 0.854 (2.18-2.33)	2.09 ± 0.80 (1.99-2.18)	2.45 ± 0.87 (2.34-2.56)	5.9×10^{-9}
PVR, WU	3.00 ± 1.95 (2.82-3.18)	3.40 ± 2.17 (3.12-3.68)	2.53 ± 1.52 (2.32-2.75)	5.3×10^{-7}
mPAP, mm Hg	30.3 ± 9.38 (29.5-31.0)	29.7 ± 9.70 (28.6-30.7)	31.0 ± 8.94 (29.9-32.1)	0.055
mPCWP, mm Hg	19.5 ± 7.27 (18.8-20.1)	19.1 ± 7.31 (18.1-20.0)	20.0 ± 7.21 (19.0-21.0)	0.156

Values are mean ± SD (95% CI) or n (%) unless otherwise indicated.

FAC = fractional area change; LA = left atrial; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; mPAP = mean pulmonary artery pressure (as assessed by right heart catheterization); mPCWP = mean postcapillary wedge pressure (as assessed by right heart catheterization); PVR = pulmonary vascular resistance; RA = right atrial; RV = right ventricular; $sPAP_{echo}$ = systolic pulmonary artery pressure (as assessed by echocardiography); TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation; TV EROA = tricuspid valve effective regurgitant orifice area; WU = Wood unit.

FIGURE 1 General Information About the Study Population



Continued on the next page

TABLE 3 Comparison of TR Etiology Between Women and Men

	Total Population (N = 702)	Stratification According to Sex		
		Women (n = 386)	Men (n = 316)	*P* Value
Ventricular	397 (56.6)	193 (50.0)	204 (64.6)	1.4×10^{-4}
Atrial	238 (33.9)	161 (41.7)	77 (24.4)	2.0×10^{-6}
CIED-related	40 (5.70)	13 (3.37)	27 (8.54)	0.005
Primary	27 (3.85)	19 (4.92)	8 (2.53)	0.150

Values are n (%).
CIED = cardiac implantable electronic device; TR = tricuspid regurgitation.

Mean pulmonary artery pressure (mPAP) levels were calculated as mPAP = dPAP + 1/3 × (sPAP − dPAP). The mean postcapillary wedge pressure was calculated over the entire cardiac cycle. Cardiac output was determined using the indirect Fick method. Pulmonary vascular resistance (PVR) was defined as: PVR = (mPAP − mean postcapillary wedge pressure)/cardiac output.

ETIOLOGY OF TR. The etiology of TR was defined as recently proposed by Praz et al.[3] This classification scheme recognizes primary forms, secondary forms (considering functional atrial and ventricular TR as separate entities), and cardiac implantable electronic device-related forms; see Supplemental Figure 1 for the stepwise classification scheme.

PROCEDURAL SUCCESS DEFINITION. Procedural success was defined as a device successfully implanted and delivery system retrieved with TR reduction by at least one grade[11] and/or a residual TR grade ≤II/V°[12] as assessed on transthoracic echocardiography before discharge (ie, 2-5 days after the procedure).

CLINICAL ENDPOINT DEFINITION. Because an elderly patient population was studied, postprocedural 2-year all-cause mortality was defined as a clinically meaningful primary outcome measure. Survival data were regularly obtained from the German Civil Registry or from general practitioners, hospitals, and practice cardiologists for patients from foreign countries.

STATISTICAL ANALYSIS. All statistical analyses were performed using R statistical software (R version 3.6.3, R Foundation for Statistical Computing; see Supplemental Table 1 for a complete list of the R packages used).

Data are presented as numbers and frequencies (%) or mean ± SD (and 95% CI). The chi-square or Fisher exact test was used to evaluate the association between categoric variables, and the independent samples Wilcoxon test was used for the comparison of continuous variables.

Survival was illustrated using the Kaplan-Meier method, and the log-rank test was used to compare the cumulative survival rates between male and female patients. Moreover, a Cox proportional hazards model was used to estimate HRs.

To identify further factors related to all-cause mortality, Cox regression analyses were performed. Variables with a *P* value ≤0.05 in univariate testing were subsequently included in the multivariate logistic regression model. Variable importance for mortality prediction was assessed using the varImp function from the caret package (acknowledging that input variables were measured at different scales; all input variables were normalized before the assessment of feature importance, meaning that they had a mean of 0 and an SD of 1 after normalization; this normalization step is supposed to make each input variable contribute equally to the analysis). Receiver-operating characteristic (ROC) curves and the corresponding area under the curve (AUC) were calculated to assess the performance of distinct right ventricular-pulmonary arterial coupling indexes to predict 2-year mortality after TTVI. ROC curves were also used to identify optimal sex-specific thresholds (Youden index) of right ventricular-pulmonary arterial coupling to predict 2-year all-cause mortality after TTVI. A *P* value ≤0.05 was considered to indicate statistical significance.

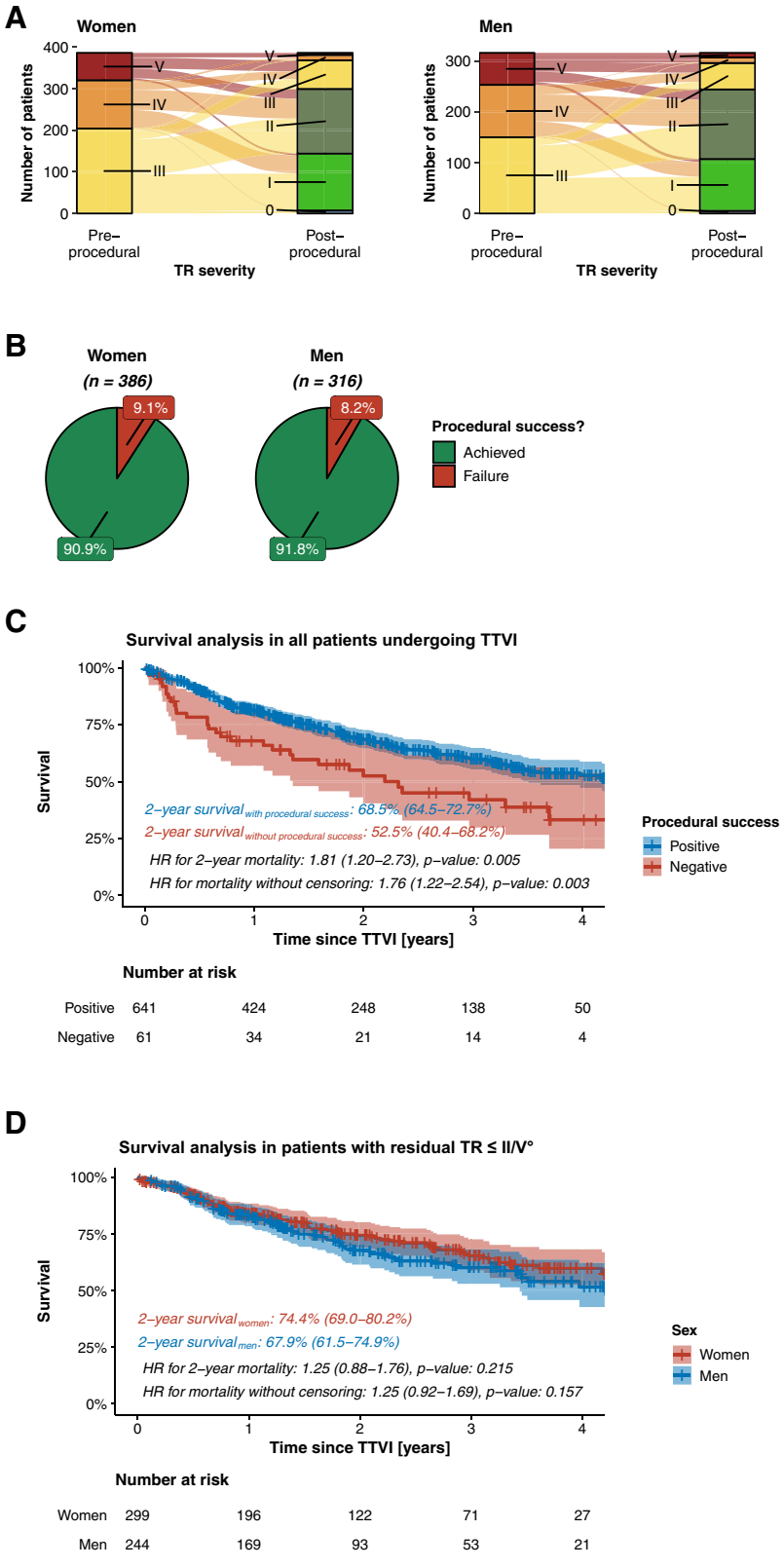
RESULTS

MEN AND WOMEN DIFFER REGARDING BASELINE CHARACTERISTICS AND THE UNDERLYING ETIOLOGY OF TR, BUT 2-YEAR SURVIVAL AFTER TTVI IS SIMILAR. Data from a total of 702 patients (mean age 78.0 ±

FIGURE 1 Continued

(A) A Kaplan-Meier survival plot for the entire study population. **(B)** A density plot showing time to censoring (survivors) and time to death (nonsurvivors) in consecutively enrolled patients. **(C)** Pie charts comparing the etiology of tricuspid regurgitation (TR) between women and men. **(D)** A Kaplan-Meier survival plot comparing survival rates between women and men. CIED = cardiac implantable electronic device; TTVI = transcatheter tricuspid valve intervention.

FIGURE 2 Comparison of Residual TR as a Confounder for Mortality After TTVI



Continued on the next page

TABLE 4 Procedural Success Rates in Accordance With Sex

	Total Population (N = 702)	Stratification According to Sex		P Value
		Women (n = 386)	Men (n = 316)	
TR reduction by at least one grade	641 (91.3)	351 (90.9)	290 (91.8)	0.796
Residual TR ≤ II/V°	543 (77.4)	299 (77.5)	244 (77.2)	1.0

Values are n (%).
TR = tricuspid regurgitation.

7.86 years) undergoing TTVI for severe TR were used for this analysis. Among them, there were 386 (55.0%) women and 316 (45.0%) men. Patients typically presented with dyspnea corresponding to New York Heart Association (NYHA) functional class III (75.9%) or IV (14.1%) (Table 1). Massive and torrential TR were diagnosed in 219 (31.2%) and 129 (18.4%) patients (Table 2). Overall, 247 deaths among the 702 enrolled patients were recorded, resulting in a 2-year survival rate of 67.0% (95% CI: 63.2%-71.1%) (Figure 1A). Notably, 50% of deaths occurred within 9.72 months after TTVI (Figure 1B). Survivors were traced on a median follow-up time of 1.95 years (IQR: 1.00-3.20 years) (Figure 1B).

There were no sex differences regarding age at TTVI (78.1 ± 7.93 years in women vs 77.9 ± 7.78 years in men; $P = 0.683$). Moreover, no differences were found regarding EuroSCORE II levels (7.06 ± 6.72 in women vs 7.42 ± 7.68 in men; $P = 0.670$). However, men presented more often than women with worse dyspnea corresponding to NYHA functional class IV (18.0% in men vs 10.9% in women; $P = 0.009$). Moreover, men were more often diagnosed with coronary artery disease (52.9% in men vs 35.5% in women; $P = 5.6 \times 10^{-6}$) and more frequently presented with a pacemaker/defibrillator implanted (35.1% in men vs 22.3% in women; $P = 2.0 \times 10^{-4}$), whereas the prevalence of chronic obstructive pulmonary disease (20.9% in men vs 16.8% in women; $P = 0.203$) and atrial fibrillation (92.1% in men vs 88.3% in women; $P = 0.128$) was similar among sexes.

Men presented with poorer left ventricular function expressed as the left ventricular ejection fraction (51.2% ± 12.3% in men vs 55.6% ± 10.6% in women; $P = 2.8 \times 10^{-6}$) and also displayed more severely enlarged right ventricles (basal right ventricular diameter = 50.1 ± 8.05 mm in men vs 44.5 ± 7.16 mm in women; $P < 2.2 \times 10^{-16}$) and atria (right atrial area = 40.8 ± 12.0 cm^2 in men vs 33.7 ± 10.2 cm^2 in women; $P = 8.5 \times 10^{-16}$) (Table 2). Importantly, most of the differences in cardiac diameters were neutralized after relating cardiac diameters to body surface area (Supplemental Table 2). Although primary TR and cardiac implantable electronic device-related TR were found in just a minority of patients (3.8% and 5.7%, respectively), a secondary ventricular etiology was described in 56.6% of patients (Table 3). Importantly, secondary ventricular TR was more often described in men (64.6% in men vs 50.0% in women; $P = 1.4 \times 10^{-4}$), whereas secondary atrial TR was more often described in women (41.7% in women vs 24.4% in men; $P = 2.0 \times 10^{-6}$) (Table 3, Figure 1C).

In the evaluation of survival outcome according to sex, Kaplan-Meier analysis showed similar 2-year survival rates among men and women (63.7% [95% CI: 58.0%-69.9%] in men vs 69.9% [95% CI: 64.9%-75.3%] in women; $P = 0.144$) (Figure 1D).

TTVI EFFECTIVELY REDUCES TR SEVERITY IN BOTH MEN AND WOMEN. Preprocedural grading of TR severity was similar among male and female patients (Table 2, Figure 2A). Moreover, equal proportions of successful TR reduction by at least one grade were observed among women (90.9%) and men (91.8%) (Table 4). Failure to ameliorate TR severity according to the aforementioned definition (ie, neither TR reduction to ≤II/V° nor any TR reduction by at least one grade) translated into a 1.8-fold increase in 2-year mortality (Figures 2B and 2C). Notably, the rate of patients with residual TR ≤II/V° was similar in women (77.5%) and men (77.2%) (Table 4). As a subset analysis, only patients with residual TR ≤II/V° were compared, finally confirming similar 2-year survival rates among women and men (74.4% [95% CI: 69.0%-

FIGURE 2 Continued

(A) Alluvial diagrams comparing pre- and postprocedural TR severity in accordance with sex. **(B)** Pie charts comparing rates of procedural success in accordance with sex (procedural success defined as a device successfully implanted and delivery system retrieved with TR reduction ≥I/V° and/ or a residual TR grade ≤II/V°). **(C)** A Kaplan-Meier survival plot comparing survival rates in accordance with procedural success. **(D)** A Kaplan-Meier survival plot comparing survival rates in accordance with residual TR and sex. Abbreviations as in Figure 1.

TABLE 5 Univariate and Multivariate Cox Regression Analysis With 2-Year Mortality as a Dependent Variable (Total Population)

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, increment per 10 years	0.94 (0.79-1.1)	0.440		
Male	1.2 (0.93-1.6)	0.140		
BMI, increment per 1 kg/m^2	0.97 (0.94-1.0)	0.089		
Arterial hypertension	0.88 (0.61-1.3)	0.490		
Diabetes mellitus	1.1 (0.84-1.6)	0.390		
CAD	1.3 (0.98-1.7)	0.065		
COPD	1 (0.73-1.5)	0.790		
Atrial fibrillation	0.76 (0.5-1.1)	0.180		
eGFR, increment per 10 mL/min	0.87 (0.81-0.93)	7.6×10^{-5}	0.95 (0.88-1.0)	0.126
NYHA functional class, increment per class	1.9 (1.4-2.5)	1.2×10^{-5}	1.5 (1.1-2.0)	0.007
NT-proBNP, increment per 2,000 pg/mL	1.0 (1.0-1.1)	8.1×10^{-5}	1.0 (0.99-1.0)	0.178
LVEF, increment per 10%	0.98 (0.97-0.99)	0.002	1.0 (0.98-1.0)	0.520
TAPSE, increment per 1 mm	0.92 (0.89-0.95)	1.2×10^{-6}	0.95 (0.92-0.98)	0.004
LVEDD, increment per 10 mm	1.2 (0.96-1.4)	0.120		
Basal RV diameter, increment per 10 mm	1.2 (1.0-1.4)	0.050	1.0 (0.83-1.2)	0.965
LA area, increment per 10 cm^2	1.1 (0.93-1.2)	0.340		
RA area, increment per 10 cm^2	1.1 (0.95-1.2)	0.260		
TV EROA, increment per 1 cm^2	1.4 (1.1-1.9)	0.018	1.0 (0.70-1.5)	0.890
Inferior vena cava diameter, increment per 10 mm	1.5 (1.2-1.8)	3.4×10^{-4}	1.2 (0.94-1.6)	0.128
$sPAP_{echo}$, increment per 10 mm Hg	1.1 (0.98-1.2)	0.120		
mPAP, increment per 10 mm Hg	1.4 (1.2-1.6)	1.8×10^{-6}	1.2 (1.1-1.5)	0.008
PVR, increment per 1 WU	1.2 (1.1-1.3)	1.9×10^{-4}	1.1 (0.99-1.2)	0.084
Preprocedural TR grade, increment per 1 grade	1.4 (1.1-1.6)	7.2×10^{-4}	1.1 (0.89-1.4)	0.321
Postprocedural TR grade, increment per 1 grade	1.3 (1.2-1.5)	1.4×10^{-5}	1.2 (0.99-1.4)	0.064

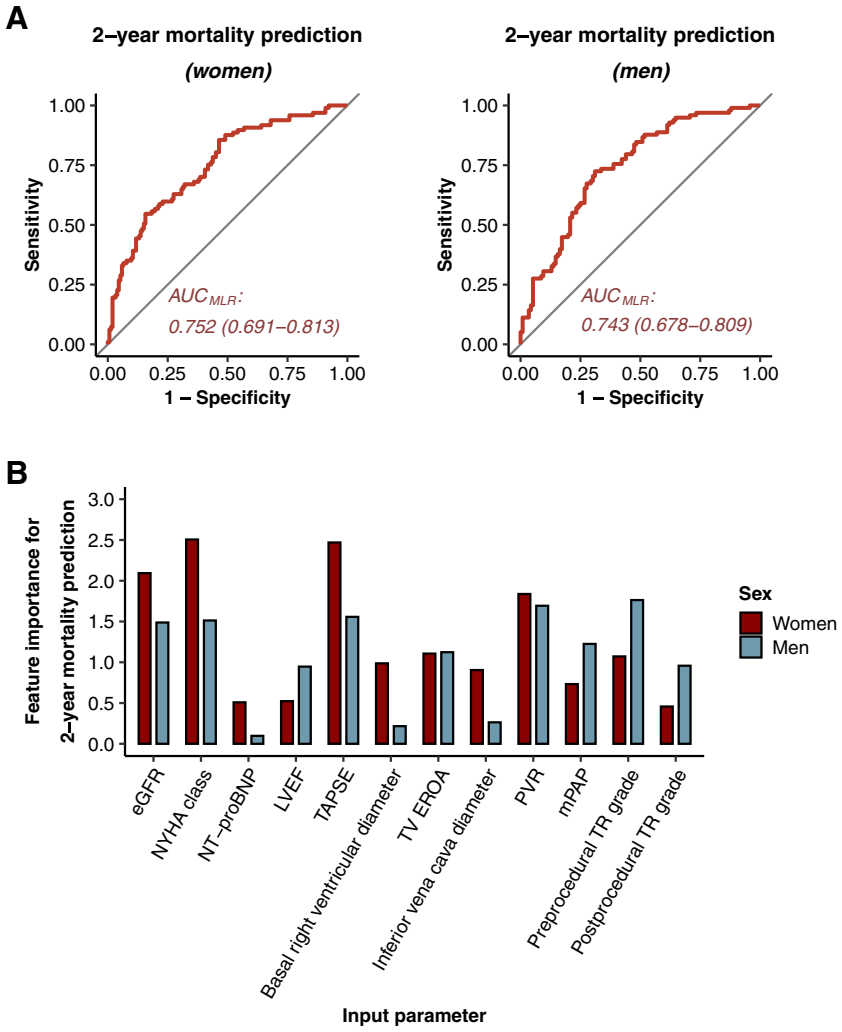
Abbreviations as in Tables 1 and 2.

80.2%] in women vs 67.9% [95% CI: 61.5%-74.9%] in men; $P = 0.215$) (Figure 2D).

MALE AND FEMALE PATIENTS DIFFER IN THE SIGNIFICANCE OF PREDICTORS FOR MORTALITY AFTER TTVI. At first, a univariate Cox regression analysis was performed to identify predictors for 2-year mortality after TTVI among clinical, echocardiographic, and hemodynamic parameters (Table 5). Parameters that were significantly associated with 2-year mortality after TTVI were hereinafter used to build a multivariate logistic regression model. In total, this model considered a set of 12 clinical, echocardiographic, and hemodynamic parameters, and it achieved an AUC of 0.752 and 0.743 to predict 2-year mortality after TTVI in female and male patients, respectively (Figure 3A). Interestingly, right ventricular function expressed as TAPSE was among the strongest predictors for death in female patients, whereas mPAP was more important for model performance in men than in women (Table 6, Figure 3B). Multivariate Cox regression analysis further revealed that only dyspnea severity expressed as NYHA functional class, TAPSE, and mPAP serve as independent predictors for mortality after TTVI (Table 5).

TAPSE/mPAP RATIO REFINES RIGHT VENTRICULAR-PULMONARY ARTERIAL COUPLING CONCEPT IN WOMEN AND MEN TO PREDICT 2-YEAR MORTALITY AFTER TTVI. Considering the significance of right ventricular function and pulmonary hypertension to predict 2-year mortality after TTVI, a novel index relating TAPSE to mPAP levels was calculated and subsequently compared with the existing concept of right ventricular-pulmonary arterial coupling expressed as the TAPSE/sPAP ratio. The TAPSE/mPAP ratio performed significantly better than the TAPSE/sPAP ratio to predict 2-year mortality ($AUC_{TAPSE/mPAP}$ vs $AUC_{TAPSE/sPAP}$: 0.672 [95% CI: 0.618-0.726] vs 0.602 [95% CI: 0.549-0.656];

FIGURE 3 Multivariate Logistic Regression Models to Predict Mortality After TTVI



(A) Receiver-operating characteristic curves comparing the performance of multivariate logistic regression models. **(B)** A feature importance plot of predictor variables from the multivariate logistic regression models to show sex-related differences in the prognostic significance of predictor variables. AUC = area under the curve; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MLR = multivariate logistic regression; mPAP = mean pulmonary artery pressure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PVR = pulmonary vascular resistance; TV EROA = tricuspid valve effective regurgitant orifice area; other abbreviations as in Figure 1.

P = 0.011) (Central Illustration). The numeric superiority of the TAPSE/mPAP ratio over the TAPSE/sPAP ratio to predict 2-year mortality was additionally confirmed in women ($AUC_{TAPSE/mPAP}$ vs $AUC_{TAPSE/sPAP}$: 0.691 [95% CI: 0.616-0.765] vs 0.625 [95% CI: 0.552-0.699]; P = 0.045) and men ($AUC_{TAPSE/mPAP}$ vs $AUC_{TAPSE/sPAP}$: 0.641 [95% CI: 0.560-0.722] vs 0.581 [95% CI: 0.501-0.660]; P = 0.235) regarded in separation (Figure 4A). Although women and men presented with similar TAPSE/sPAP levels (0.470 ± 0.259 mm/mm Hg vs 0.465 ± 0.238 mm/mm Hg; P = 0.798) (Figure 4B), TAPSE/mPAP levels were significantly higher in women than in men (0.650 ± 0.325 mm/mm Hg in women vs 0.579 ± 0.262 mm/mm Hg in men; P = 0.006) (Central Illustration). Furthermore, ROC analysis suggested sex-specific thresholds for the TAPSE/mPAP ratio to define impaired right ventricular-pulmonary arterial coupling and to ultimately predict 2-year mortality (<0.612 mm/mmHg

TABLE 6 Multivariate Logistic Regression Models to Predict 2-Year Mortality in Women and Men Separately

	Women		Men	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
eGFR, increment per 10 mL/min	0.89 (0.81-0.98)	0.019	0.91 (0.81-1.0)	0.074
NYHA functional class, increment per class	1.8 (1.1-2.9)	0.014	1.5 (1.0-2.2)	0.041
NT-proBNP, increment per 2,000 pg/mL	1.0 (0.98-1.1)	0.289	0.99 (0.95-1.0)	0.517
LVEF, increment per 10%	1.0 (0.99-1.0)	0.525	0.99 (0.97-1.0)	0.278
TAPSE, increment per 1 mm	0.94 (0.90-0.99)	0.020	0.96 (0.91-1.0)	0.085
Basal RV diameter, increment per 10 mm	1.3 (0.95-1.8)	0.099	0.91 (0.67-1.2)	0.542
TV EROA, increment per 1 cm^2	0.61 (0.30-1.3)	0.184	1.5 (1.0-2.3)	0.052
Inferior vena cava diameter, increment per 10 mm	1.1 (0.76-1.7)	0.536	1.0 (0.70-1.5)	0.985
PVR, increment per 1 WU	1.1 (0.95-1.2)	0.287	1.2 (1.0-1.5)	0.031
mPAP, increment per 10 mm Hg	1.2 (0.92-1.5)	0.205	1.1 (0.86-1.5)	0.372
Preprocedural TR grade, increment per 1 grade	1.1 (0.78-1.6)	0.570	1.4 (1.0-1.9)	0.034
Postprocedural TR grade, increment per 1 grade	1.1 (0.83-1.4)	0.579	1.1 (0.89-1.4)	0.342

Abbreviations as in Tables 1 and 2.

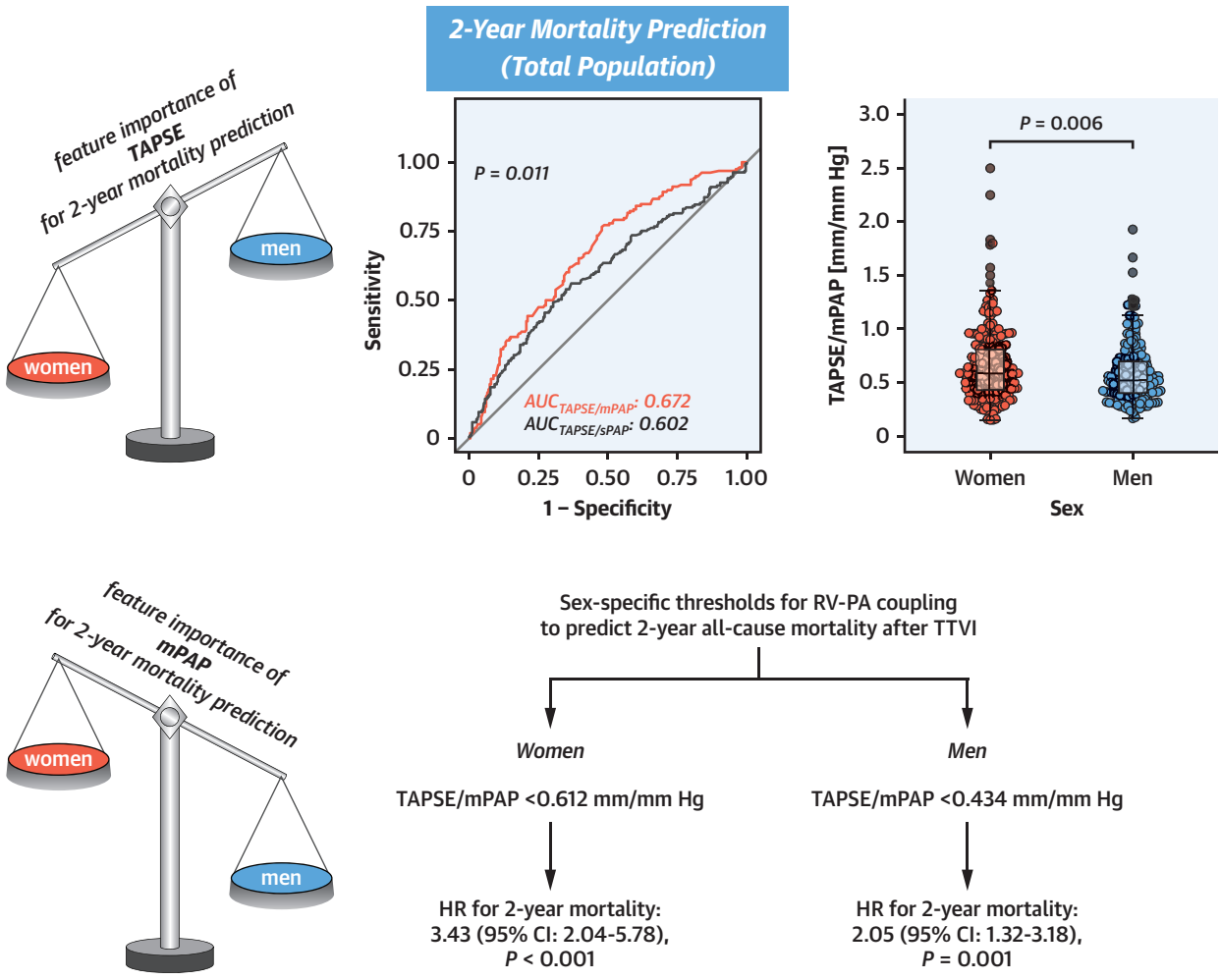
in women and <0.434 mm/mm Hg in men) (**Figure 4A, Central Illustration**). Women with a TAPSE/mPAP ratio <0.612 mm/mm Hg displayed a 3.43-fold increased HR for 2-year mortality ($P < 0.001$), whereas men with a TAPSE/mPAP ratio <0.434 mm/mm Hg displayed a 2.05-fold increased HR for 2-year mortality ($P = 0.001$) (**Figure 4C**). Importantly, TAPSE/mPAP levels remained significantly associated with 2-year all-cause mortality following TTVI after multivariate adjustment for a complementary set of clinical, laboratory, echocardiographic, and hemodynamic parameters (Supplemental Table 3). Moreover, as shown by interaction analysis, the probability of 2-year mortality after TTVI steadily increased with lower TAPSE/mPAP levels in both women and men; yet, men had higher probabilities of 2-year mortality after TTVI per TAPSE/mPAP level (Supplemental Figure 2), confirming the use of lower thresholds of TAPSE/mPAP levels in men to guide future timing of intervention and/or to optimize patient selection as calculated by ROC analyses (**Figures 4A and 4C, Central Illustration**).

DISCUSSION

FEMALE SEX PER SE IS NO RISK FACTOR FOR INCREASED MORTALITY AFTER TTVI. To calculate a patient's EuroSCORE II level is an integral part in the preparation process for heart team discussions. Female sex per se is considered as a risk factor in cardiovascular surgery risk scores, but no study to date has evaluated if female sex also represents a risk factor for increased mortality when a transcatheter approach is chosen. We hereby provide data from a large real-world registry showing that men and women undergoing TTVI for severe TR differ in comorbidities, etiology, and volumetric status; yet, procedural success rates and survival following TTVI were similar between sexes. In fact, our study reveals that male patients tend to have higher mortality rates after TTVI, which can be at least partially attributed to the higher prevalence of coronary artery disease and subsequent impairment of left ventricular systolic function and dilatation of left-sided heart chambers as similarly described in patients with secondary mitral regurgitation undergoing transcatheter edge-to-edge repair.[13]

REPLACING sPAP WITH mPAP VALUES REFINES THE RIGHT VENTRICULAR–PULMONARY ARTERIAL COUPLING CONCEPT AND ENABLES BETTER MORTALITY PREDICTION IN PATIENTS UNDERGOING TTVI FOR SEVERE TR. As tested in a multivariate Cox regression analysis to adjust for clinical, echocardiographic, and hemodynamic parameters, only dyspnea severity expressed as NYHA functional class, right ventricular function expressed as TAPSE, and pulmonary hypertension expressed as mPAP remained as independent predictors for 2-year mortality after TTVI (**Table 5**). The prognostic significance of pulmonary hypertension is well established.[14-16] Because the right ventricle is acutely forced to eject blood into the high-pressure pulmonary circulation upon ameliorating TR

CENTRAL ILLUSTRATION **Sex-Specific Thresholds for Right Ventricular–Pulmonary Arterial Coupling to Predict 2-Year All-Cause Mortality After Transcatheter Tricuspid Valve Intervention**

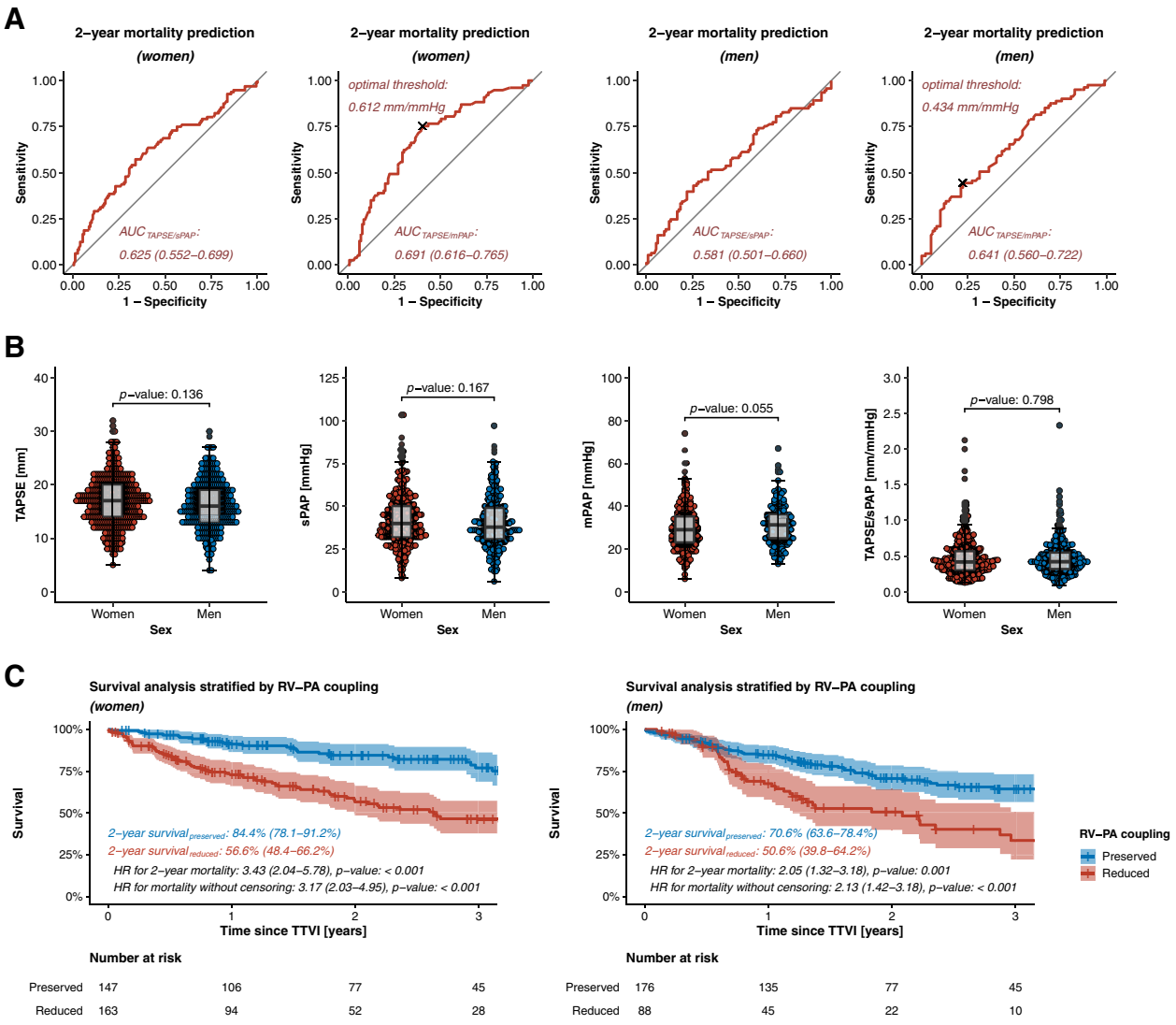


Fortmeier V, et al. J Am Coll Cardiol Intv. 2023;16(8):909-923.

In a multivariate logistic regression model to predict 2-year mortality after transcatheter tricuspid valve intervention, tricuspid annular plane systolic excursion (TAPSE) displayed a higher feature importance in women, whereas mPAP conveyed a higher feature importance in men. Given the opposing feature importance of TAPSE and mean pulmonary artery pressure (mPAP) in women and men, we looked at right ventricular–pulmonary arterial coupling. Receiver-operating characteristic analysis revealed that TAPSE/mPAP is superior to TAPSE/systolic pulmonary artery pressure (sPAP) in predicting 2-year all-cause mortality. Moreover, TAPSE/mPAP levels were significantly higher in women compared with men. Therefore, sex-specific thresholds for right ventricular–pulmonary arterial coupling (RV–PA coupling) to predict 2-year all-cause mortality after transcatheter tricuspid valve intervention should be applied to stratify women and men into low- and high-risk cohorts.
AUC = area under the curve; CIED = cardiac implantable electronic device; TR = tricuspid regurgitation; TTVI = transcatheter tricuspid valve intervention.

severity by TTVI, hence reducing the regurgitant blood flow to the low-pressure right atrium, it is of paramount importance that the right ventricle has a sufficiently preserved contractile function to compensate for an elevated afterload burden. Right ventricular–pulmonary arterial coupling expressed as the TAPSE/sPAP ratio captures right ventricular contractility related to the afterload burden imposed from the pulmonary circulation,[17,18] and higher ratios indicate a preserved afterload reserve with good prognosis after TTVI.[19] However, echocardiographic estimation of sPAP is prone to underestimation in patients with severe TR for at least 3 reasons: 1) a large coaptation defect results in rapid pressure

FIGURE 4 On the Prognostic Value of Distinct Right Ventricular-Pulmonary Arterial Coupling Models to Predict Mortality After TTVI



(A) Receiver-operating characteristic curves comparing the performance of right ventricular-pulmonary arterial coupling models to predict mortality after TTVI. The black crosses indicate the location of the Youden index-based threshold of TAPSE/mPAP level to best predict 2-year mortality after TTVI. **(B)** Beeswarm plots for comparison of right ventricular-pulmonary arterial coupling between women and men. **(C)** A Kaplan-Meier survival plot comparing survival rates in accordance with right ventricular-pulmonary arterial coupling (expressed as the TAPSE/mPAP ratio) and sex. Abbreviations as in Figures 1 and 3.

equalization between the right ventricle and right atrium with an effective loss of the right ventricular to right atrial pressure gradient, 2) the right atrial pressure might be underestimated because of a fixed upper value of 15 mm Hg, and 3) sPAP levels depend on right ventricular contractility and might therefore not sufficiently reflect the true severity of pulmonary hypertension in patients with impaired right ventricular function as commonly encountered in patients with severe TR. By replacing echocardiography-based sPAP levels with right heart catheterization-based mPAP levels, the simple and appealing nature of the right ventricular-pulmonary arterial coupling concept is preserved, whereas its

prognostic value to predict mortality after TTVI is significantly improved. Interestingly, the right ventricular-pulmonary arterial coupling has also been applied to patients undergoing transcatheter aortic valve replacement for severe aortic stenosis,[20] so future studies are needed to evaluate the predictive superiority of the TAPSE/mPAP ratio over the TAPSE/sPAP ratio in patients with intact tricuspid valve function.

DO WE NEED SEX-SPECIFIC THRESHOLDS FOR RIGHT VENTRICULAR–PULMONARY ARTERIAL COUPLING?. Differing biological factors including body size, cardiac and noncardiac comorbidities, and hormonal influences result in sex as being recognized as an important determinant of cardiac structure and function.[21] Moreover, sex dimorphism is described in the myocardial response to increased afterload as far as the left ventricle is concerned in patients with severe aortic stenosis; women seem to better tolerate a similar level of valve-related afterload.[22,23] The protective effect of estrogen as the predominant female sex hormone for better right ventricular function observed in women remains controversially debated.[24] On the one hand, idiopathic pulmonary arterial hypertension, with smooth muscle cell proliferation in the pulmonary vasculature and subsequent obliteration of pulmonary arterioles and elevation of PVR levels, affects four times as many women as men[25]; on the other hand, a pressure-volume analysis in patients with pulmonary arterial hypertension demonstrated higher right ventricular contractility and better right ventricular-pulmonary arterial coupling despite a similar afterload in female patients.[26] The molecular mechanisms underlying sex-related differences in pulmonary vascular remodeling and right ventricular adaption to afterload challenges remain elusive. Notably, female patients in this study presented at age 78.1 ± 7.93 years, meaning that they were in a postmenopausal state; moreover, we have no measurements of sex hormone levels available. Therefore, it would be speculation to assume that female sex and related higher levels of estrogen on the one hand might have caused elevated PVR levels in female patients on the other hand. Irrespective of the potential underlying mechanism, awareness of sex-specific differences in cardiac structure, function, and remodeling as well as the definition of sex-specific thresholds appear crucial to accurately tailor the timing of intervention. To the best of our knowledge, this is the first study to compare right ventricular-pulmonary arterial coupling between sexes, and, in fact, our data reveal that women preserve a better right ventricular function (expressed as TAPSE) relative to pulmonary artery pressure levels (expressed as mPAP) than men. Moreover, ROC curve analysis suggested different thresholds for the TAPSE/mPAP ratio to define right ventricular-pulmonary arterial uncoupling. Applying sex-specific thresholds promises to improve not only prognostication of survival after TTVI, but also it may guide future patient selection and/or timing of intervention.

STUDY LIMITATIONS. First, this is a registry study enrolling only patients with severe TR who underwent TTVI. Therefore, it remains elusive if our findings would also apply to patients with milder disease. The etiology of TR was assessed in the moment that patients presented with severe TR; however, it can be challenging to differentiate the initial etiology of TR in severely sick patients. For instance, in patients with initial cardiac implantable electronic device-related TR, long-standing TR will inevitably result in right atrial enlargement. However, according to our stepwise classification system, those patients would have been classified as secondary atrial TR. Moreover, a control group of patients conservatively treated with optimized guideline-directed medical therapy would have been desirable to evaluate the net benefit of TTVI among sexes. We also acknowledge that this study is based on data that were generated during clinical routine in a real-life scenario, meaning that no central core laboratory was involved. Although the TAPSE/sPAP ratio can be easily obtained from noninvasive echocardiography, calculation of the TAPSE/mPAP ratio requires invasive and potentially hazardous right heart catheterization. In our study, data to calculate the TAPSE/mPAP ratio were missing in 128 of 702 patients (18.2%). Finally, before influencing individual heart team decisions, the proposed sex-specific cutoff values for the TAPSE/mPAP ratio require external validation in separate cohorts.

CONCLUSIONS

Four main conclusions can be drawn from this large multicenter analysis:

1. The underlying etiology of severe TR differs between men and women, reflecting distinct pathophysiologies.
2. Nonetheless, TTVI is equally effective in men and women as shown by similar rates of procedural success and a similar survival outcome after TTVI.

3. Irrespective of sex, the severity of dyspnea at initial presentation, pulmonary hypertension, and right ventricular dysfunction are independent predictors for mortality after TTVI.
4. The TAPSE/mPAP ratio is a better predictor for 2-year survival after TTVI than the TAPSE/sPAP ratio. Moreover, sex-specific thresholds bear the potential to improve prognostication, guide future timing of intervention, and/or optimize patient selection.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Lachmann has received funding from the Technical University of Munich (Clinician Scientist Grant) and from the Else Kröner-Fresenius Foundation (Clinician Scientist Grant). All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Volker Rudolph, Department of General and Interventional Cardiology, Heart and Diabetes Center Northrhine-Westfalia, Ruhr University Bochum, Georgstraße 11, 32545 Bad Oeynhausen, Germany. E-mail: vrudolph@hdz-nrw.de.

PERSPECTIVES

WHAT IS KNOWN? Female sex is recognized as a risk factor for mortality in surgical risk scores, but no study has ever investigated the impact of sex on procedural success and survival outcome prediction in patients with severe tricuspid regurgitation undergoing transcatheter tricuspid valve intervention.

WHAT IS NEW? Despite significant differences in cardiac volumetrics and the prevalence of comorbidities between men and women with severe tricuspid regurgitation, similar rates of procedural success and 2-year survival can be achieved by transcatheter tricuspid valve intervention. For improved prognostication after transcatheter tricuspid valve intervention, we hereby propose the TAPSE/mPAP ratio for refined right ventricular–pulmonary arterial coupling assessment.

WHAT IS NEXT? Sex-specific cutoff values for the TAPSE/mPAP ratio require external validation before influencing individual heart team decisions.

REFERENCES

1. Hahn RT, Clavel M-A, Mascherbauer J, Mick SL, Asgar AW, Douglas PS. Sex-related factors in valvular heart disease. *J Am Coll Cardiol*. 2022;79(15):1506–1518. https://doi.org/10.1016/j.jacc.2021.08.081

2. DesJardin JT, Chikwe J, Hahn RT, Hung JW, Delling FN. Sex differences and similarities in valvular heart disease. *Circ Res*. 2022;130(4):455–473. https://doi.org/10.1161/CIRCRESAHA.121.319914

3. Praz F, Muraru D, Kreidel F, et al. Transcatheter treatment for tricuspid valve disease. *EuroIntervention*. 2021;17(10):791–808. https://doi.org/10.4244/EIJ-D-21-00695

4. 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(6):897–902. https://doi.org/10.1016/s0002-9149(98)01064-9

5. Dietz MF, Prihadi EA, van der Bijl P, et al. Sex-specific differences in etiology and prognosis in patients with significant tricuspid regurgitation. *Am J Cardiol*. 2021;147:109–115. https://doi.org/10.1016/j.amjcard.2021.02.016

6. Taramasso M, Benfari G, van der Bijl P, et al. Transcatheter versus medical treatment of patients with symptomatic severe tricuspid regurgitation. *J Am Coll Cardiol*. 2019;74(24):2998–3008. https://doi.org/10.1016/j.jacc.2019.09.028

7. Nashef SAM, Roques F, Sharples LD, et al. EuroSCORE II. *Eur J Cardiothorac Surg*. 2012;41(4):734–745. https://doi.org/10.1093/ejcts/ezs043

8. Hahn RT, Zamorano JL. The need for a new tricuspid regurgitation grading scheme. *Eur Heart J Cardiovasc Imaging*. 2017;18(12):1342–1343. https://doi.org/10.1093/ehjci/jex139

9. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23(7):685–713. https://doi.org/10.1016/j.echo.2010.05.010

10. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28(1):1–39.e14. https://doi.org/10.1016/j.echo.2014.10.003

11. Besler C, Orban M, Rommel K-P, et al. Predictors of procedural and clinical outcomes in patients with symptomatic tricuspid regurgitation undergoing transcatheter edge-to-edge repair. *J Am Coll Cardiol Intv*. 2018;11(12):1119–1128. https://doi.org/10.1016/j.jcin.2018.05.002

12. Schlotter F, Miura M, Kresoja K-P, et al. Outcomes of transcatheter tricuspid valve intervention by right ventricular function: a multicentre propensity-matched analysis. *EuroIntervention*. 2021;17(4):e343–e352. https://doi.org/10.4244/EIJ-D-21-00191

13. Park S-D, Orban M, Karam N, et al. Sex-related clinical characteristics and outcomes of patients undergoing transcatheter edge-to-edge repair for secondary mitral regurgitation. *J Am Coll Cardiol Intv*. 2021;14(8):819–827. https://doi.org/10.1016/j.jcin.2020.12.042

14. Lurz P, Orban M, Besler C, et al. Clinical characteristics, diagnosis, and risk stratification of pulmonary hypertension in severe tricuspid regurgitation and implications for transcatheter tricuspid valve repair. *Eur Heart J*. 2020;41(29):2785–2795. https://doi.org/10.1093/eurheartj/ehaa138

15. Stocker TJ, Hertell H, Orban M, et al. Cardiopulmonary hemodynamic profile predicts mortality after transcatheter tricuspid valve repair in chronic heart failure. *J Am Coll Cardiol Intv*. 2021;14(1):29–38. https://doi.org/10.1016/j.jcin.2020.09.033

16. Fortmeier V, Lachmann M, Körber MI, et al. Solving the pulmonary hypertension paradox in patients with severe tricuspid regurgitation by employing artificial intelligence. *J Am Coll Cardiol Intv*. 2022;15(4):381–394. https://doi.org/10.1016/j.jcin.2021.12.043

17. Saeed S, Smith J, Grigoryan K, Lysne V, Rajani R, Chambers JB. The tricuspid annular plane systolic excursion to systolic pulmonary artery

pressure index: association with all-cause mortality in patients with moderate or severe tricuspid regurgitation. *Int J Cardiol*. 2020;317:176–180. https://doi.org/10.1016/j.ijcard.2020.05.093

18. Fortuni F, Butcher SC, Dietz MF, et al. Right ventricular-pulmonary arterial coupling in secondary tricuspid regurgitation. *Am J Cardiol*. 2021;148:138–145. https://doi.org/10.1016/j.amjcard.2021.02.037

19. Brener MI, Lurz P, Hausleiter J, et al. Right ventricular-pulmonary arterial coupling and afterload reserve in patients undergoing transcatheter tricuspid valve repair. *J Am Coll Cardiol*. 2022;79(5):448–461. https://doi.org/10.1016/j.jacc.2021.11.031

20. Cahill TJ, Pibarot P, Yu X, et al. Impact of right ventricle-pulmonary artery coupling on clinical outcomes in the PARTNER 3 trial. *J Am Coll Cardiol Intv*. 2022;15(18):1823–1833. https://doi.org/10.1016/j.jcin.2022.07.005

21. Crousillat DR, Wood MJ. Echocardiography in women: how are Mars and Venus different? *Curr Cardiol Rep*. 2021;23(10):149. https://doi.org/10.1007/s11886-021-01562-8

22. Treibel TA, Kozor R, Fontana M, et al. Sex dimorphism in the myocardial response to aortic stenosis. *J Am Coll Cardiol Img*. 2018;11(7):962–973. https://doi.org/10.1016/j.jcmg.2017.08.025

23. Ito S, Miranda WR, Nkomo VT, Lewis BR, Oh JK. Sex differences in LV remodeling and hemodynamics in aortic stenosis: sex-specific criteria for severe stenosis? *J Am Coll Cardiol Img*. 2022;15(7):1175–1189. https://doi.org/10.1016/j.jcmg.2022.02.007

24. Keen J, Prisco SZ, Prins KW. Sex differences in right ventricular dysfunction: insights from the bench to bedside. *Front Physiol*. 2021;11:623129. https://doi.org/10.3389/fphys.2020.623129

25. Beale AL, Meyer P, Marwick TH, Lam CSP, Kaye DM. Sex differences in cardiovascular pathophysiology: why women are overrepresented in heart failure with preserved ejection fraction. *Circulation*. 2018;138(2):198–205. https://doi.org/10.1161/CIRCULATIONAHA.118.034271

26. Tello K, Richter MJ, Yogeswaran A, et al. Sex differences in right ventricular-pulmonary arterial coupling in pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2020;202(7):1042–1046. https://doi.org/10.1164/rccm.202003-0807LE

KEY WORDS sex, transcatheter tricuspid valve intervention, tricuspid regurgitation

APPENDIX For supplemental figures and tables, please see the online version of this paper.