Impact of Ventricular Stroke Work Indices on Mortality in Heart Failure Patients After Percutaneous Mitral Valve Repair

Rico Osteresch, MD[a,*], Kathrin Diehl, MD[a], Patrick Dierks, MD[a], Johannes Schmucker, MD[a], Azza Ben Ammar, MD[a], Andreas Fach, MD[a], Harald Langer, MD[b,c], Ingo Eitel, MD[b,c], Rainer Hambrecht, MD[a], and Harm Wienbergen, MD[a,b]

Optimal patient selection for transcatheter mitral valve repair (TMVR) remains challenging. The aim of the study was to assess the impact of left and right ventricular stroke work index (LVSWi, RVSWi) on mortality in patients with chronic heart failure (CHF) undergoing TMVR. One hundred-forty patients (median age 74 ± 9.9 years, 67.9% male) with CHF who underwent successful TMVR were included. Primary end point was defined as all-cause mortality after 16 ± 9 months of follow-up. LVSWi was calculated as: Stroke volume index (SVi) * (mean arterial pressure − postcapillary wedge pressure) * 0.0136 = $g/m^{-1}/m^2$. RVSWi was calculated as: SVi * (mean pulmonary artery pressure − right atrial pressure) * 0.0136 = $g/m^{-1}/m^2$. Receiver operating characteristic (ROC) analysis determined an optimal threshold of 24.8 $g/m^{-1}/m^2$ for LVSWi (sensitivity 80.4%, specificity 40.2%, area under the curve (AUC) 0.71 [0.60 to 0.81]; p = 0.001) and 8.3 $g/m^{-1}/m^2$ for RVSWi (sensitivity 67.4%, specificity 57.0%, AUC 0.67 [0.56 to 0.78]; p = 0.006), respectively. Kaplan-Meier analysis showed significantly lower survival in patients with LVSWi ≤24.8 $g/m^{-1}/m^2$ (20.0% vs 39.4%; log-rank p = 0.038) and in patients with RVSWi ≤8.3 $g/m^{-1}/m^2$ (22.1% vs 43.7%; log-rank p = 0.026), respectively. LVSWi of ≤24.8 $g/m^{-1}/m^2$ and RVSWi of ≤8.3 $g/m^{-1}/m^2$ were independent predictors for all-cause mortality (hazard ratio (HR) 2.83; 95% confidence interval (CI) 1.1 to 7.6; p = 0.04; HR 2.52; 95% CI 1.04 to 6.1; p = 0.041). A risk-score incorporating LVSWi and RVSWi cut-off values from ROC analysis powerfully predicts long-term survival after successful TMVR (log-rank p = 0.02). In conclusion, LVSWi and RVSWi independently predict mortality in patients with CHF undergoing TMVR and might be useful in risk stratification of TMVR candidates. **(Am J Cardiol 2021;147:101−108)**

Transcatheter mitral valve repair (TMVR) using the MitraClip system (Abbott Vascular, Abbott Park, Illinois) has emerged as an effective treatment option for surgical high-risk patients with severe functional mitral regurgitation (MR) and chronic heart failure (CHF).[1-9] However, several predictors of worse prognosis in patients treated by TMVR have been identified, for example, high levels of NT-proBNP, New York Heart Association (NYHA) functional class IV prior to TMVR and a severely impaired left and right heart function.[5,8,10-13] Two recently published randomized controlled clinical trials investigating clinical outcome of TMVR for patients with severe functional MR and CHF yielded different results.[14,15] The COAPT trial revealed a benefit in reduction in heart failure hospitalizations and mortality whereas the MITRA-FR study found no differences between treatment groups. One reason for the presumed inconsistent findings of these 2 trials might be related to key differences in patient selection. Thus, optimal patient selection for TMVR still remains a matter of debate and there is an unmet need for identifying additional risk factors of worse prognosis. It is the purpose of the present study to evaluate if left and right ventricular stroke work index (LVSWi, RVSWi) as hemodynamic parameters of cardiac function could help identifying optimal candidates for TMVR using the MitraClip system.

Methods

From March 2015 to April 2018 all consecutive patients with NYHA functional class III or IV suffering from severe MR due to CHF who underwent successful TMVR (MR ≤2 + at discharge) at the Bremen Heart Center in Germany were included. CHF was defined as heart failure from any cause with reduced left ventricular ejection fraction (LV-EF) ≤50%. All patients received optimal medical and device treatment at least 3 months prior to the MitraClip procedure according to the current heart failure guidelines.[16] Patients undergoing TMVR were enrolled if they were judged inoperable or at unacceptable high surgical risk based on the logistic European System for Cardiac

[a]Bremer Institut für Herz- und Kreislaufforschung (BIHKF) am Klinikum Links der Weser, Bremen, Germany; [b]Lübeck University Heart Center, Medical Clinic II, Lübeck, Germany; and [c]German Center for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Lübeck, Germany. Manuscript received November 15, 2020; revised manuscript received and accepted February 19, 2021.

*Corresponding author: Tel.: 0049-421-879-1430; fax: 0049-421-879-1675

E-mail address: rico.osteresch@klinikum-bremen-ldw.de (R. Osteresch).

0002-9149/© 2021 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.amjcard.2021.02.018
www.ajconline.org

Operative Risk Evaluation (logistic EuroSCORE) and if they had a favorable anatomy suitable for the MitraClip procedure. The suitability was determined by a heart team decision. All patients included in the study were fully informed about the procedure and signed a written consent form. The study complies with the Declaration of Helsinki and the locally appointed ethics committee has approved the research protocol.

Transthoracic and transesophageal echocardiographic evaluations were performed at baseline. Severity grade of MR at baseline was assessed according to the current guidelines.[17,18] Transthoracic echocardiographic evaluations were performed at pre-discharge, 30 days after the procedure and, if possible, at follow-up. MR severity grade after TMVR was evaluated according to the technique reported by Foster et al.[19]

A baseline invasive hemodynamic study was conducted in all included patients during the screening phase in a conscious non-sedated state. Right heart catheterization was performed using a 6F single lumen, balloon-tipped, flow-directed Swan-Ganz catheter (Arrow International, Inc, Reading, Pennsylvania) to obtain the following variables: pulmonary capillary wedge pressure (PCWP) including v-wave analysis, pulmonary artery systolic, mean and diastolic pressure (PASP, PAP mean, PAP diast.), pulmonary artery oxygen saturation and right atrial pressure (RAP), systemic arterial systolic, mean and diastolic pressure (RR syst., RR mean, RR diast.). Systemic arterial oxygen saturation was obtained from the LV pigtail catheter. Cardiac output (CO) was calculated by the Fick method. Stroke volume (SV) was calculated as CO / heart rate. Stroke volume index (SVi) was calculated as SV / body surface area (BSA). BSA was estimated from the Du Bois formula. Pulmonary vascular resistance (PVR) was calculated as the ratio between the pressure drop along the vascular bed and the CO and converted in metric units ($dyn*s*cm^{-5}$). All values are reported at end-expiration. Pulmonary artery pulsatility index (PAPi) was calculated as (PASP − PAP diast.) / RAP. LVSWi and RVSWi were calculated as: LVSWi = SVI * (RR mean − PCWP) * 0.0136 and RVSWi = SVI * (PAP mean − RAP) * 0.0136, respectively. Transpulmonary gradient (TPG) was calculated as PAP mean − PCWP. Diastolic pulmonary gradient (DPG) was calculated as PAP diast. − PCWP. The cardiac filling pressures (CFP) as the RAP to PCWP ratio was calculated as RAP / PCWP. All MitraClip procedures were performed under general anesthesia using (3D-) transesophageal echocardiographic and fluoroscopic guidance. TMVR with the MitraClip was performed as previously described.[2,20]

Primary end point was all-cause mortality. Periprocedural and in-hospital major adverse events were reported such as death, myocardial infarction, major stroke, renal failure with the need for renal replacement therapy, pericardial tamponade with the need for pericardiocentesis and urgent or emergent cardiovascular surgery for adverse events. Bleeding complications with the need for blood transfusion and surgical re-operation for recurrent MR were documented. Follow-up was conducted at 30 days and after a mean follow-up period of 16±9 months. All follow-up evaluations were conducted by the Bremer Institut für Herz- und Kreislaufforschung (BIHKF), Germany. If a patient was not able to be present at follow-up, a telephone interview was conducted with either the patient himself, the patient‘s relatives or general practitioner. Major adverse cardiac and cerebrovascular events (MACCE) were analyzed including all-cause death, major stroke, non-fatal myocardial infarction and surgical or interventional (TMVR) re-do for recurrent severe MR according to the MVARC criteria.[21] Changes in functional capacity, categorized by the NYHA functional class, were assessed as well as a state of health self-assessment based on a standardized health-related quality of life questionnaire (EQ-5D).

Continuous data are expressed as mean ± standard deviation (SD) or median (interquartile range) where appropriate. Mann-Whitney test was used to compare continuous variables. Categorial variables are presented as numbers and proportions and were compared using chi-square or Fisher‘s exact test. Receiver operating characteristic (ROC) curves were used to assess the discriminative capacity of LVSWi and RVSWi and to determine related cut-off scores for primary end point. Parametric/nonparametric distribution of data was assumed by Kolmogorov-Smirnow-testing and distribution analysis. Pearson‘s and Spearman Rho correlation function was used to analyze the association between LVSWi and LV-EF and between RVSWi and echocardiographic parameters of RV systolic function, e.g. tricuspid annular plane systolic excursion (TAPSE) and doppler tissue imaging S‘ (DTI-S‘). The Kaplan-Meier method was used for survival analysis. Log-rank testing was used to compare event-free survival from primary end point. A multivariable Cox proportional-hazards regression analysis was performed to assess the association between LVSWi and RVSWi and all-cause mortality, adjusting for covariates reported in the literature to be associated with mortality; these included TAPSE ≤16mm, LV-EF ≤25%, severe tricuspid valve regurgitation and those variables significantly different between groups (male gender, creatinine levels ≥1.5mg/dl and NT-proBNP levels ≥10.000ng/l). A ventricular stroke work index (VSWi) risk score predicting all-cause mortality at long-term follow-up was generated from the LVSWi and RVSWi cut-off values from the aforementioned ROC curve analysis. A 2-sided p value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 22 (SPSS, Inc, Chicago, Illinois).

Results

A total of 140 consecutive patients were enrolled (Table 1). Mean age of all patients was 74 ± 9.9 years (68% male). Mean LVSWi of the study population was $22.3 \pm 10.7\ g/m^{-1}/m^2$ and $8.9 \pm 4.1\ g/m^{-1}/m^2$ for RVSWi, respectively. Clinical follow-up was obtained in all included patients. The rate of in-hospital mortality and the rate of all-cause mortality at 30 days after the procedure was 1.4% and 2.9%, respectively. No procedure related death or emergent cardiovascular surgery for adverse events occurred in the study population. Bleeding complications requiring transfusion of 2 or more units of blood occurred in 6 patients (4.2%, 3 in each group). In 4 cases, the cause of bleeding was related to vascular access site. In 2 cases, the cause of bleeding was related to gastrointestinal

Table 1
Demographic baseline characteristics

Variable	All Patients (n=140)	Survivors (n=94)	Non-Survivors (n=46)	p-value
Age (years ± SD)	74 ± 9.9	74 ± 10.7	74 ± 8.4	0.8
Men	95 (68%)	57 (61%)	37 (80%)	**0.023**
NYHA functional class IV	24 (17%)	12 (13%)	12 (26%)	0.13
Coronary artery disease	85 (61%)	55 (59%)	29 (63%)	0.43
Chronic atrial fibrillation	67 (48%)	39 (42%)	28 (61%)	0.06
Hypertension	101 (72%)	67 (72%)	33 (72%)	0.9
Chronic obstructive pulmonary disease	21 (15%)	101 (11%)	11 (24%)	0.06
Diabetes mellitus	30 (21%)	19 (19%)	12 (26%)	0.38
Logistic EuroSCORE (mean % ± SD)	22.6 ± 15.1	20.1 ± 13.8	27.9 ± 16.6	**0.001**
NT-proBNP (mean ng/l ± SD)	8430 ± 10972	6745 ± 10820	12121 ± 10602	**0.001**
Creatinine (mean mg/dl ± SD)	1.5 ± 0.8	1.4 ± 0.8	1.8 ± 0.8	**<0.001**
Number of Clips implanted				0.13
1	69 (49%)	51 (54%)	18 (39%)	
2	69 (49%)	41 (44%)	28 (61%)	
3	2 (1%)	2 (2%)	0	

hemorrhage. One patient (0.7%) experienced pericardiac tamponade with the need for pericardiocentesis. All patients underwent a single MitraClip procedure. No patient needed an interventional re-do for recurrent MR after TMVR as a second procedure during the follow-up period. The rate of hospitalization for heart failure at 30 days after the procedure and at long-term follow-up was 9.3% and 35.0%, respectively. The primary end point of all-cause mortality at long-term follow-up occurred in 46 patients (33.1%). Patients who died presented lower LVSWi and lower RVSWi, respectively (Table 2). Nonsurvivors were more likely to have higher levels of NT-proBNP, higher levels of creatinine and a higher logistic EuroSCORE (Table 1). The proportion of male gender was significantly higher in nonsurvivors. Patients who died showed a higher proportion of atrial fibrillation and chronic obstructive lung disease (Table 1). The proportion of patients suffering from NYHA functional class IV prior to TMVR and the numbers of clips implanted were similar in both groups (Table 1).

The degree of MR severity was similar between survivors and non-survivors but nonsurvivors trend to show a higher effective regurgitant orifice area (Table 3). No differences between survivors and nonsurvivors were observed in terms of residual MR and mean mitral valve gradient after successful TMVR (Table 3).

Directly measured traditional hemodynamic values such as PASP, PAP mean, PCWP, RAP, CO, and CI were comparable between survivors and non survivors (Table 2), whereas RR syst. and RR mean were lower in non-survivors. Patients who died trend to show lower PAPi (Table 2).

Table 2
Baseline invasive hemodynamic parameters

Variable	All Patients (n=140)	Survivors (n=94)	Non Survivors (n=46)	p-value
Heart rate (mean beats/min ± SD)	77 ± 15	76 ± 15	79 ± 15	0.09
Systemic arterial systolic pressure (mean mmHg ± SD)	127 ± 15	131 ± 27	120 ± 23	**0.019**
Systemic arterial diastolic pressure (mean mmHg ± SD)	71 ± 13	72 ± 14	68 ± 11	0.24
Systemic arterial mean pressure (mean mmHg ± SD)	91± 18	94 ± 17	84 ± 17	**0.004**
Pulmonary artery systolic pressure (mean mmHg ± SD)	60 ± 16	60± 17	58 ± 15	0.64
Mean pulmonary artery pressure (mean mmHg ± SD)	39 ± 11	39 ± 11	37 ± 9	0.48
Postcapillary wedge pressure (mean mmHg ± SD)	28 ± 10	29 ± 11	27 ± 9	0.57
V-wave (mean mmHg ± SD)	42 ± 15	42 ± 16	41 ± 15	0.61
Pulmonary artery diastolic pressure (mean mmHg ± SD)	24 ± 9	25 ± 10	24 ± 8	0.97
Right atrial pressure (mean mmHg ± SD)	13 ± 7	13 ± 7	13 ± 6	0.65
Cardiac output (mean l/min ± SD)	3.7 ± 1.3	3.7 ± 1.4	3.6 ± 1.0	0.74
Cardiac index (mean l/min/m^2 ± SD)	1.9 ± 0.6	2.0 ± 0.6	1.9 ± 0.5	0.91
Pulmonary vascular resistance (mean dyn*s*cm^{-5} ± SD)	277 ± 196	295 ± 211	242 ± 159	0.25
Cardiac filling pressures (mean mmHg ± SD)	0.49 ± 0.24	0.47 ± 0.20	0.53 ± 0.29	0.31
Pulmonary artery pulsatility index (mean ± SD)	3.51 ± 2.67	3.67 ± 2.87	3.1 ± 2.21	0.07
Left ventricular stroke work index (mean g/m^{-1}/m^2 ± SD)	22.3 ± 10.7	24.1 ± 11.5	18.6 ± 7.9	**0.005**
Right ventricular stroke work index (mean g/m^{-1}/m^2 ± SD)	8.9 ± 4.1	9.4 ± 4.4	7.8 ± 3.2	**0.041**
Transpulmonary gradient (mean mmHg ± SD)	10.6 ± 7.1	10.8 ± 6.9	10.2 ± 7.5	0.38
Diastolic pulmonary gradient (mean mmHg ± SD)	3.6 ± 7.5	3.9 ± 7.3	3.0 ± 7.4	0.71
Pulmonary artery compliance (mean ml/mmHg ± SD)	1.61 ± 0.87	1.63 ± 0.92	1.55 ± 0.78	0.66
Stroke volume (mean ml/beat)	50 ± 21	51 ± 22	47 ± 17	0.22
Stroke volume index (mean ml/m^2/beat)	26.1 ± 9.7	26.8 ± 10.4	24.6 ± 8.2	0.16

Table 3
Baseline echocardiographic parameters

Variable	All Patients (n=140)	Survivors (n=94)	Non Survivors (n=46)	p-value
Vena contracta width (mean mm ± SD)	8 ± 1.3	8 ± 1.2	8 ± 1.4	0.1
Effective regurgitant orifice area (mean cm^2 ± SD)	0.36 ± 0.2	0.35 ± 0.2	0.39 ± 0.2	0.06
Regurgitant volume (mean ml ± SD)	55 ± 25	53 ± 25	58 ± 22	0.11
Left ventricular ejection fraction (mean % ± SD)	35 ± 9	36 ± 9	34 ± 9	0.36
Left ventricular enddiastolic diameter (mean mm ± SD)	59 ± 9	58 ± 9	60 ± 9	0.12
Left ventricular enddiastolic diameter index (mean mm/m^2 ± SD)	31 ± 4.8	31 ± 4.4	32 ± 5.4	0.14
Left ventricular endsystolic diameter (mean mm ± SD)	49 ± 11	48 ±11	49 ± 10	0.42
Left ventricular endsystolic diameter index (mean mm/m^2 ± SD)	26 ± 5.3	26 ± 5.0	27 ± 5.9	0.46
Right ventricular enddiastolic diameter (mean mm ± SD)	38 ± 8	38 ± 8	39 ± 9	0.30
Right ventricular enddiastolic diameter index (mean mm/m^2 ± SD)	20 ± 4.1	20 ± 4.3	21 ± 3.8	0.28
Tricuspid annular plane systolic excursion (mean mm ± SD)	17 ± 4	18 ± 4	16 ± 4	0.28
Doppler tissue imaging S‘ (mean cm/s ± SD)	10.5 ± 3.0	10.7 ± 2.8	9.9 ± 3.4	0.89
Tricuspid regurgitation severity grade III°	11 (16%)	11 (12%)	8 (17%)	0.77
Pulmonary artery systolic pressure (mean mmHg ± SD)	46 ± 12	47 ± 13	45 ± 13	0.87
Mitral valve gradient after-procedural (mean mmHg ± SD)	3.4 ± 1.5	3.3 ± 1.4	3.6 ± 1.5	0.24
Distribution of residual mitral regurgitation after-procedural				0.15
Trace	6 (4%)	3 (3%)	3 (7%)	
1	97 (70%)	71 (76%)	26 (57%)	
2	37 (26%)	20 (21%)	17 (37%)	

A weak to modest positive correlation between LVSWi and LV-EF was observed (r=.330, $p < 0.0001$). No correlation between RVSWi and echocardiographic parameters of RV function such as TAPSE or DTI-S‘ was found (TAPSE: r=.105, p = 0.24; DTI-S‘: r=.122, p = 0.37). ROC curve analysis yielded a cut-off value for LVSWi of ≤24.8 $g/m^{-1}/m^2$ as a predictive marker for primary end point (sensitivity 80.4%, specificity 40.2%, area under the curve (AUC) 0.71 [0.60 to 0.81]; p = 0.001; Figure 1) and revealed that optimal sensitivity and specificity for RVSWi were achieved using a threshold of 8.3 $g/m^{-1}/m^2$ (sensitivity 67.4%, specificity 57.0%, AUC 0.67 [0.56 to 0.78]; p = 0.006; Figure 1). Kaplan-Meier analysis for primary end point stratified according to the corresponding cut-off values revealed a significantly lower survival rate in patients with lower LVSWi (≤24.8 $g/m^{-1}/m^2$) as compared with higher LVSWi (20.0% vs 39.4%; log-rank p = 0.038; Figure 2). Patients with lower RVSWi (≤8.3 $g/m^{-1}/m^2$) showed a significantly lower

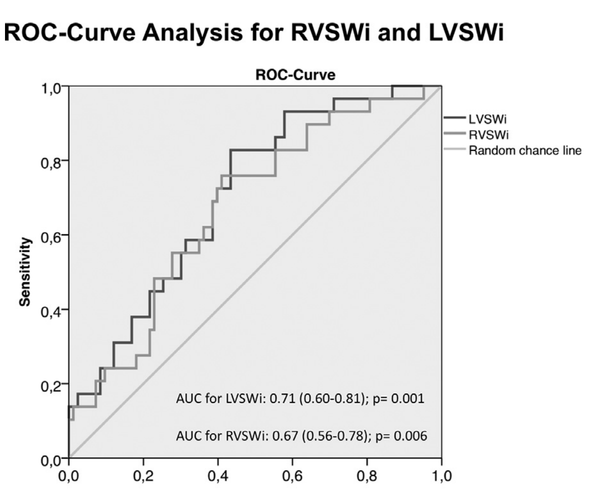

Figure 1. Receiver operating characteristic curve analysis for LVSWi and RVSWi. AUC: area under the curve; LVSWi = left ventricular stroke work index; RVSWi right ventricular stroke work index

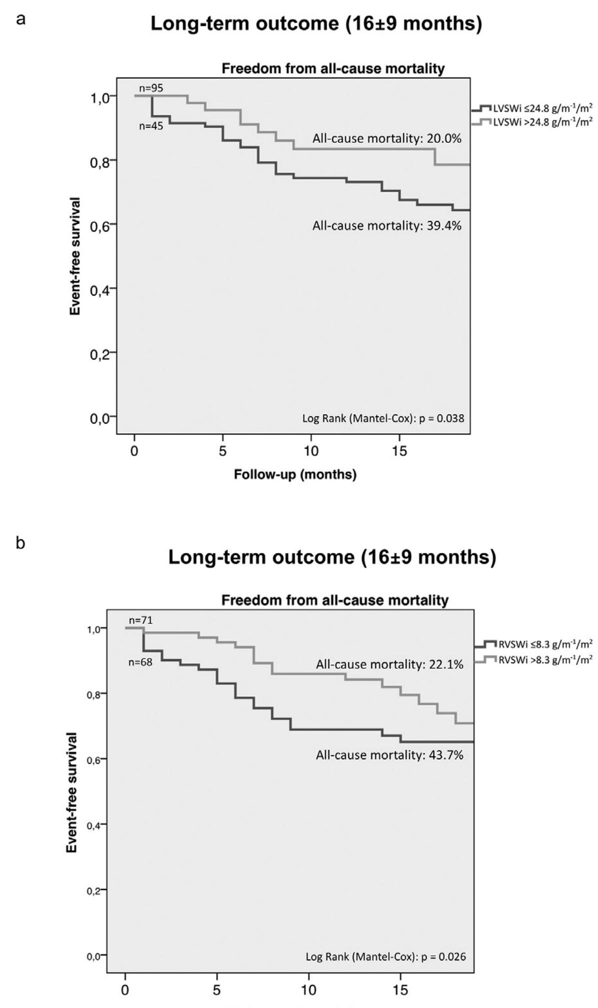

Figure 2. A, B: Kaplan-Meier estimate of primary end point (all-cause death). Kaplan-Meier analysis demonstrated a significantly lower event free survival from primary end point in the low LVSWi group (2A) and in the low RVSWi group (2B). LVSWi = left ventricular stroke work index; RVSWi = right ventricular stroke work index

survival rate as compared with higher RVSWi (22.1% vs. 43.7%; log-rank p = 0.026), as well (Figure 2).

In multivariable Cox regression analysis, a LVSWi cut-off value of ≤24.8 $g/m^{-1}/m^2$ as well as a RVSWi cut-off value of ≤8.3 $g/m^{-1}/m^2$ remained independent predictors for all-cause mortality at long-term follow-up, even after adjustment for other known clinical, echocardiographic and hemodynamic variables (hazard ratio (HR) 2.83 for LVSWi; 95% confidence interval (CI) 1.1 to 7.6; p = 0.04; HR 2.52 for RVSWi; 95% CI 1.04 to 6.1; p = 0.041, respectively; Figure 3).

LVSWi and RVSWi were next incorporated into a simple scoring system (VSWi-risk score) to predict all-cause mortality following successful TMVR. For each index below the ROC cut-off points, 1 point was awarded (for a possible total of 2 points). Evaluating survival depending on this VSWi-risk score, patients with a VSWi-risk score of 0 points showed a survival rate of 89.7% at long-term follow-up, whilst patients with a VSWi-risk score of 2 points showed a survival rate of 54.5% (p = 0.005; Figure 4). Thus, Kaplan-Meier analysis for primary end point stratified according to the VSWi-risk score revealed a significantly lower survival rate in patients with a VSWi-risk score of 2 points as compared with a VSWi-risk score of 1 or 0 point (log-rank p = 0.02, Figure 4).

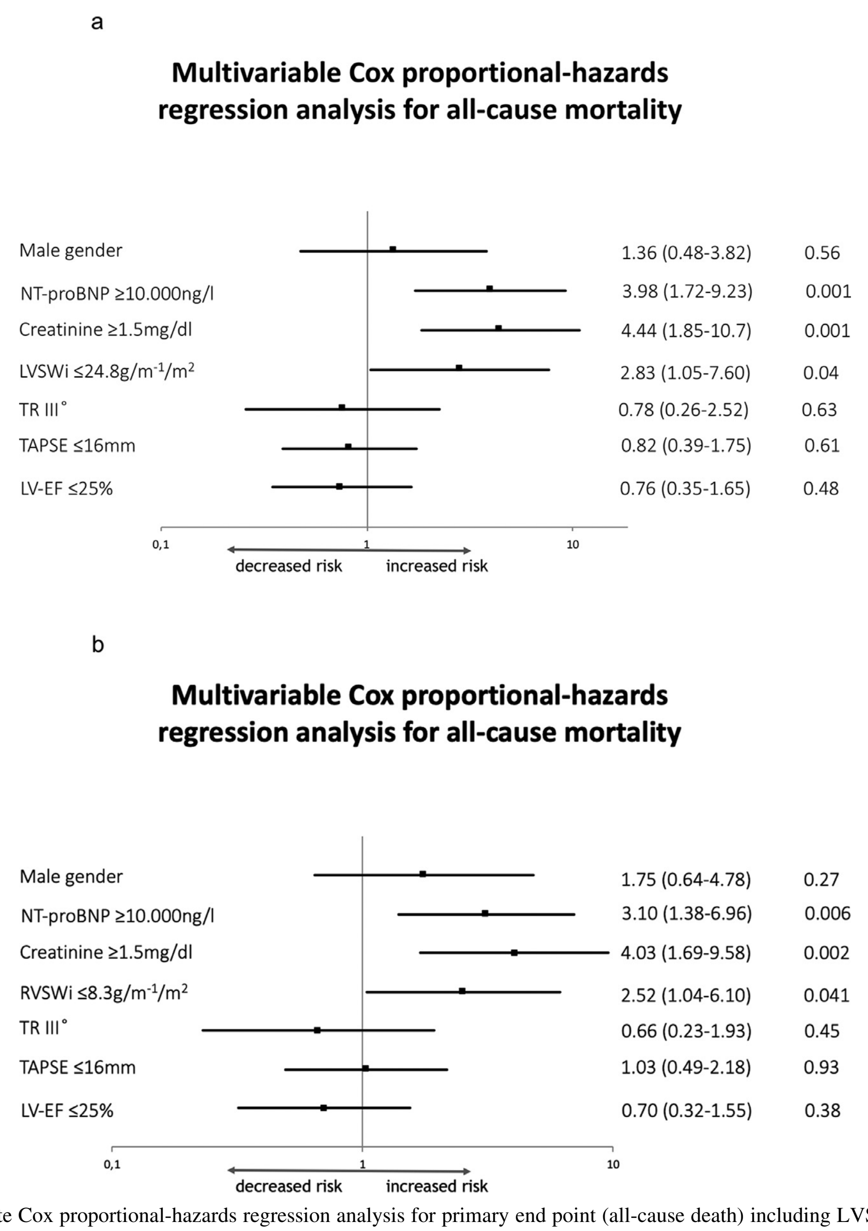

Figure 3. A, B: Multivariate Cox proportional-hazards regression analysis for primary end point (all-cause death) including LVSWi (3A) and RVSWi (3B) adjusted for TAPSE ≤16mm, LV-EF ≤25%, TR III°, male gender, creatinine levels ≥1.5 mg/dl, NT-proBNP levels ≥10.000 ng/l. LV-EF: left ventricular ejection fraction; LVSWi = left ventricular stroke work index; RVSWi = right ventricular stroke work index; TAPSE = tricuspid annular plane systolic excursion; TR III° = tricuspid valve regurgitation severity grade III°

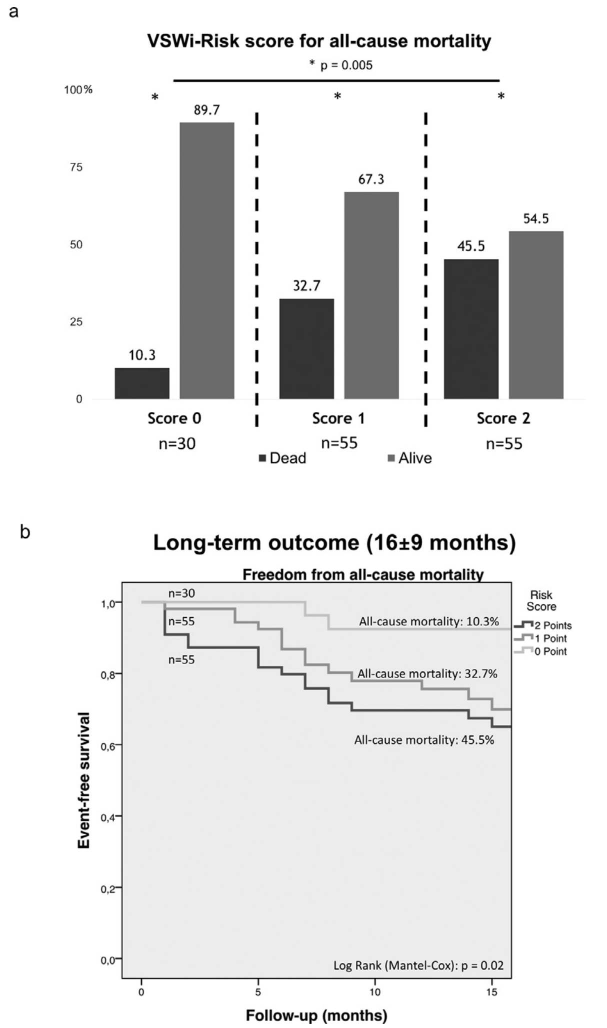

Figure 4. A, B: All-cause mortality at long-term follow-up according to VSWi-risk score (4A) and Kaplan-Meier estimate of primary end point (all-cause mortality) at long-term follow-up (4B). Group 0 = RVSWi >8.3 $g/m^{-1}/m^2$ and LVSWi >24.8 $g/m^{-1}/m^2$; Group 1 = RVSWi ≤8.3 $g/m^{-1}/m^2$ or LVSWi ≤24.8 $g/m^{-1}/m^2$; Group 2 = RVSWi ≤8.3 $g/m^{-1}/m^2$ and LVSWi ≤24.8 $g/m^{-1}/m^2$. Numbers in columns denote percentage of patients. LVSWi = left ventricular stroke work index; RVSWi = right ventricular stroke work index

Discussion

The present study shows that lower LVSWi and lower RVSWi were associated with all-cause mortality in patients with CHF undergoing TMVR. A LVSWi cut-off value of ≤24.8 $g/m^{-1}/m^2$ and a RVSWi cut-off value of ≤8.3 $g/m^{-1}/m^2$ were independent predictors of all-cause mortality even after adjustment for other known risk factors. Moreover, a novel VSWi-risk score incorporating LVSWi and RVSWi cut-off values from ROC curve analysis powerfully predicts long-term survival after successful TMVR. Both ventricular stroke work indices have shown their association with worse clinical outcome in various domains of CHF. RVSWi is a known independent risk factor for right ventricular failure after left ventricular assist device (LVAD) implantation in patients with end stage heart failure and predicts worse clinical outcome in patients with precapillary pulmonary hypertension.[22-24] LVSWi is associated with outcome after mitral valve surgery for functional MR in nonischemic dilated cardiomyopathy and predicts the need for inotropic support in CHF patients.[25,26] In this study, a weak correlation between LVSWi and LV-EF was observed, whereas no correlation between RVSWi and echocardiographic parameters of RV function such as TAPSE and DTI-S‘ was found. This is congruent with earlier findings that invasively derived indices of cardiac function are poorly correlated with echocardiographic markers of left and right ventricular function.[27] Ventricular stroke work indices are considered as more precise parameters of cardiac function compared with echocardiographic derived LV-EF or TAPSE,[17] as it takes into account the stroke volume with the influence of pre- and afterload. Thus, the ability to generate higher stroke work levels is related to a well-preserved ventricular contractility. Therefore, a well-preserved stroke work may suggest a less advanced stage of heart failure. The results of the present study support the hypothesis that hemodynamic determination of LVSWi and RVSWi could provide additional prognostic information and may be utilized when selecting optimal candidates for TMVR. Furthermore, survival estimation is increased, if both cut-off values for LVSWi and RVSWi are incorporated into a simple VSWi-risk score. Nearly half of patients with a VSWi-risk score of 2 points (both indices below the defined thresholds) died within 16 months of follow-up. On the contrary, survival rates among patients with both indices above the aforementioned cut-off values (score of 0) are excellent, reaching nearly 90% at long-term follow-up. Thus, this novel VSWi-risk score may provide an additional way to distinguish between those patients who benefit most from TMVR (score of 0), and that subgroup of patients who might show a poor prognosis despite successful TMVR (score of 2). Indeed, 2 recently published randomized controlled trials exploring outcome of MitraClip therapy in CHF patients with severe MR showed apparent opposed results and aggravate the issue of optimal patient selection.[14,15] The MITRA-FR study failed to proof any beneficial effect of TMVR on top of optimal medical therapy on the primary composite end point of all-cause death and unplanned rehospitalization for heart failure at 12 months.[15] In contrast, the COAPT trial showed that TMVR using the MitraClip in CHF patients with functional MR significantly reduced the primary end point of hospitalizations for heart failure within 24 months and also mortality at 2 years.[14] One reason for the presumed inconsistent findings of these 2 trials might be related to key differences in patient selection. Thus, identifying additional risk factors of worse prognosis could greatly facilitate selection of appropriate candidates for TMVR. The data of the present study suggest that ventricular stroke work indices, especially if incorporated into a simple VSWi-risk score, may serve as additional markers of worse clinical outcome and may help to simplify optimal patient selection. Further randomized studies are required to provide additional information regarding optimal patient selection. The ongoing RESHAPE-HF-2 (RESHAPE-HF-2, ClinicalTrials.gov Identifier: NCT01772108 Ref.) study may provide more evidence in this issue.

Study limitations: The study is limited by its single-center, observational design with relatively small sample size. However, as a strength of the investigation the impact of ventricular stroke work indices on outcome is evaluated in a "real-world" consecutive cohort of patients undergoing TMVR without any exclusion criteria usually used in randomized studies. Furthermore, the study is limited by the lack of a conservative control group guided with optimal medical therapy alone. Therefore, it remains unclear whether patients with reduced ventricular stroke work indices might not have a better prognosis after TMVR as compared with a conservative treatment strategy alone. Thus, more studies are needed to determine whether stroke work indices might help to identify patients who do not benefit from TMVR.

Conclusions: This is the first study demonstrating a strong association between stroke work indices and all-cause mortality in patients with CHF undergoing TMVR. A LVSWi cut-off value of $\leq$24.8 $g/m^{-1}/m^2$ and a RVSWi cut-off value $\leq$8.3 $g/m^{-1}/m^2$ predict worse prognosis independent of other known risk factors. A simple VSWi-risk score based on this cut-off values might be useful in risk stratification of TMVR candidates.

Author Contributions

Rico Osteresch: Conceptualization, Methodology, Formal analysis, Writing - Original Draft; Kathrin Diehl: Investigation, Validation, Writing - Review & Editing; Azza Ben Ammar: Investigation, Writing - Review & Editing ; Patrick Dierks: Investigation, Validation, Writing - Review & Editing; Andreas Fach: Writing - Review & Editing; Johannes Schmucker: Writing - Review & Editing; Harald Langer: Writing - Review & Editing; Ingo Eitel: Writing - Review & Editing; Harm Wienbergen: Writing - Review & Editing, Supervision, Project administration; Rainer Hambrecht: Writing - Review & Editing, Supervision, Project administration.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

1. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Munoz D, Rosenhek R, Sjogren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL, Group ESCSD. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2017;38:2739–2791.
2. Franzen O, Baldus S, Rudolph V, Meyer S, Knap M, Koschyk D, Treede H, Barmeyer A, Schofer J, Costard-Jäckle A, Schlüter M, Reichenspurner H, Meinertz T. Acute outcomes of MitraClip therapy for mitral regurgitation in high-surgical-risk patients: emphasis on adverse valve morphology and severe left ventricular dysfunction. *Eur Heart J* 2010:1373–1381.
3. Whitlow PL, Feldman T, Pedersen WR, Lim DS, Kipperman R, Smalling R, Bajwa T, Herrmann HC, Lasala J, Maddux JT, Tuzcu M, Kapadia S, Trento A, Siegel RJ, Foster E, Glower D, Mauri L, Kar S. Acute and 12-month results with catheter-based mitral valve leaflet repair: the EVEREST II (Endovascular Valve Edge-to-Edge Repair) high risk study. *J Am Coll Cardiol* 2012;59:130–139.
4. Nickenig G, Estevez-Loureiro R, Franzen O, Tamburino C, Vanderheyden M, Lüscher TF, Moat N, Price S, Dall'Ara G, Winter R, Corti R, Grasso C, Snow TM, Jeger R, Blankenberg S, Settergren M, Tiroch K, Balzer J, Petronio AS, Büttner HJ, Ettori F, Sievert H, Fiorino MG, Claeys M, Ussia GP, Baumgartner H, Scandura S, Alamgir F, Keshavarzi F, Colombo A, Maisano F, Ebelt H, Aruta P, Lubos E, Plicht B, Schueler R, Pighi M, Di Mario C. Percutaneous mitral valve edge-to-edge Repair: in-hospital results and 1-year follow-up of 628 patients of the 2011-2012 pilot European sentinel registry. *J Am Coll Cardiol* 2014;64:875–884.
5. Puls M, Lubos E, Boekstegers P, Von Bardeleben RS, Ouarrak T, Butter C, Zuern CS, Bekeredjian R, Sievert H, Nickenig G, Eggebrecht H, Senges J, Schillinger W. One-year outcomes and predictors of mortality after MitraClip therapy in contemporary clinical practice: results from the German transcatheter mitral valve interventions registry. *Eur Heart J* 2016;37:703–712.
6. Tamburino C, Ussia GP, Maisano F, Capodanno D, La Canna G, Scandura S, Colombo A, Giacomini A, Michev I, Mangiafico S, Cammalleri V, Barbanti M, Alfieri O. Percutaneous mitral valve repair with the MitraClip system: acute results from a real world setting. *Eur Heart J* 2010;31:1382–1389.
7. Franzen O, Van Der Heyden J, Baldus S, Schlüter M, Schillinger W, Butter C, Hoffmann R, Corti R, Pedrazzini G, Swaans MJ, Neuss M, Rudolph V, Sürder D, Grünenfelder J, Eulenburg C, Reichenspurner H, Meinertz T, Auricchio A. MitraClip® therapy in patients with end-stage systolic heart failure. *Eur J Heart Fail* 2011;13:569–576.
8. Neuss M, Schau T, Schoepp M, Seifert M, Hölschermann F, Meyhöfer J, Butter C. Patient selection criteria and midterm clinical outcome for MitraClip therapy in patients with severe mitral regurgitation and severe congestive heart failure. *Eur J Heart Fail* 2013;15:786–795.
9. Maisano F, Franzen O, Baldus S, Schäfer U, Hausleiter J, Butter C, Ussia GP, Sievert H, Richardt G, Widder JD, Moccetti T, Schillinger W. Percutaneous mitral valve interventions in the real world: Early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the Mitraclip therapy in Europe. *J Am Coll Cardiol* 2013;62:1052–1061.
10. Rottbauer W, Muche R, Wöhrle J, Markovic S, Seeger J, Keler M. Predictors of rehospitalization after percutaneous edge-to-edge mitral valve repair by MitraClip implantation. *Eur J Heart Fail* 2019;21:182–192.
11. Kalbacher D, Schäfer U, v. Bardeleben RS, Eggebrecht H, Sievert H, Nickenig G, Butter C, May AE, Bekeredjian R, Ouarrak T, Kuck KH, Plicht B, Zahn R, Baldus S, Ince H, Schillinger W, Boekstegers P, Senges J, Lubos E. Long-term outcome, survival and predictors of mortality after MitraClip therapy: results from the German Transcatheter Mitral Valve Interventions (TRAMI) registry. *Int J Cardiol* 2019;277:41.
12. Osteresch R, Diehl K, Kühl M, Fiehn E, Schmucker J, Backhaus T, Fach A, Wienbergen H, Hambrecht R. Impact of right heart function on outcome in patients with functional mitral regurgitation and chronic heart failure undergoing percutaneous edge-to-edge-repair. *J* Interv Cardiol 2018;31:916–924.
13. Orban M, Braun D, Orban M, Grebmer C, Sibbing D, Thaler R, Tittus J, Wimbauer F, Lesevic H, Sonne C, Mehilli J, Ott I, Näbauer M, Massberg S, Boekstegers P, Hausleiter J. Long-term outcome of patients with severe biventricular heart failure and severe mitral regurgitation after percutaneous edge-to-edge mitral valve repair. *J Interv Cardiol* 2015;28:164–171.
14. Stone GW, Cohen DJ, Brieke A, Lindenfeld J, Whisenant B, Weissman NJ, Lim DS, Grayburn PA, Abraham WT, Mishell JM, Marx SO, Kar S, Sarembock IJ, Kapadia SR, Rajagopal V, Mack MJ, Rinaldi M. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. *New Engl J of Med* 2018;379:2307–2318.
15. Maucort-Boulch D, Carrié D, Guerin P, Iung B, Obadia J-F, Michel N, Teiger E, Donal E, Cormier B, Leurent G, Bonnet G, Mewton N, Nejjari M, Samson G, Barnel C, Boutitie F, Piriou N, Leroux L, Karam N, Ohlmann P, Piot C, Lefèvre T, Leclercq F, Vahanian A, Armoiry X, Saint Etienne C, Messika-Zeitoun D, Gilard M, Rouleau F, Trochu J-N. Percutaneous repair or medical treatment for secondary mitral regurgitation. *New Engl J of Med* 2018;379:2297–2306.
16. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GYH, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, ECfP

Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the heart. *Eur Heart J* 2012;14:803–869.
17. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, Hahn RT, Han Y, Hung J, Lang RM, Little SH, Shah DJ, Shernan S, Thavendiranathan P, Thomas JD, Weissman NJ. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the american society of echocardiography developed in collaboration with the society for cardiovascular magnetic resonance. *J Am Soc Echocardiogr* 2017;30:303–371.
18. Lancellotti P, Moura L, Pierard LA, Agricola E, Popescu BA, Tribouilloy C, Hagendorff A, Monin JL, Badano L, Zamorano JL, Sicari R, Vahanian A, Roelandt JRTC. European association of echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). *Eur J Echocardiogr* 2010;11:307–332.
19. Foster E, Wasserman HS, Gray W, Homma S, Di Tullio MR, Rodriguez L, Stewart WJ, Whitlow P, Block P, Martin R, Merlino J, Herrmann HC, Wiegers SE, Silvestry FE, Hamilton A, Zunamon A, Kraybill K, Gerber IL, Weeks SG, Zhang Y, Feldman T. Quantitative assessment of severity of mitral regurgitation by serial echocardiography in a multicenter clinical trial of percutaneous mitral valve repair. *Am J Cardiol* 2007;100:1577–1583.
20. Feldman T FE, Glower DD, Kar S, Rinaldi MJ, Fail PS, Smalling RW, Siegel R, Rose GA, Engeron E, Loghin C, Trento A, Skipper ER, Fudge T, Letsou GV, Massaro JM, Mauri L, EVEREST II Investigators. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 2011;364:1395–1406.
21. Stone GW, Vahanian AS, Adams DH, Abraham WT, Borer JS, Bax JJ, Schofer J, Cutlip DE, Krucoff MW, Blackstone EH, Généreux P, Mack MJ, Siegel RJ, Grayburn PA, Enriquez-Sarano M, Lancellotti P, Filippatos G, Kappetein AP. Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 1: clinical trial design principles a consensus document from the mitral valve academic research consortium. *J Am Coll Cardiol* 2015;36:1878–1891.
22. Shiga T, Kinugawa K, Imamura T, Kato N, Endo M, Inaba T, Maki H, Hatano M, Yao A, Nishimura T, Hirata Y, Kyo S, Ono M, Nagai R. Combination evaluation of preoperative risk indices predicts requirement of biventricular assist device. *Circulation* 2012;76:2785–2791.
23. Imamura T, Kinugawa K, Kinoshita O, Nawata K, Ono M. High pulmonary vascular resistance in addition to low right ventricular stroke work index effectively predicts biventricular assist device requirement. *J Artif Organs* 2016;19:44–53.
24. Ibe T, Wada H, Sakakura K, Ito M, Ugata Y, Yamamoto K, Taniguchi Y, Momomura S-i, Fujita H. Right ventricular stroke work index. *Int Heart J* 2018;59:1047–1051.
25. Kashiyama N, Toda K, Miyagawa S, Yoshikawa Y, Hata H, Yoshioka D, Sawa Y. Left ventricular stroke work index associated with outcome after mitral valve surgery for functional regurgitation in nonischemic dilated cardiomyopathy. *Semin Thorac Cardiovasc Surg* 2020;32:698–709.
26. Tanimura M, Dohi K, Takeuchi T, Sato Y, Sugiura E, Kumagai N, Nakamori S, Fujimoto N, Yamada N, Nakamura M. Novel hemodynamic subsets in predicting the need for inotropic support in heart failure. *Circulation* 2014;130. Abstract 19547.
27. Cameli M, Bernazzali S, Lisi M, Tsioulpas C, Croccia MG, Lisi G, MacCherini M, Mondillo S. Right ventricular longitudinal strain and right ventricular stroke work index in patients with severe heart failure: left ventricular assist device suitability for transplant candidates. *T*ransplant Proc 2012;44:2013–2015.