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ORIGINAL ARTICLE

Prognostic Relevance of Left Ventricular Myocardial Performance After Transcatheter Aortic Valve Replacement

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BACKGROUND: The left-ventricular myocardial performance index Tei is an echocardiographic parameter that incorporates the information of systolic and diastolic time intervals. While the prognostic value of selected systolic and diastolic parameters is well established after transcatheter aortic valve replacement, the role of Tei has not been evaluated in this setting.

METHODS AND RESULTS: Between August 2007 and December 2015, consecutive patients with symptomatic, severe aortic stenosis and transthoracic echocardiography pre- and post-transcatheter aortic valve replacement were considered eligible for this analysis. The primary end point was all-cause mortality at 1 year after transcatheter aortic valve replacement. Of 824 patients with echocardiographic images to calculate Tei, pre-Tei was normal (<0.45) in 639 and high (≥0.45) in 185, whereas post-Tei was normal in 602 and high in 120, respectively. After adjustment for confounding factors, high pre-Tei was associated with an increased risk of all-cause mortality at 30 days (adjusted hazard ratio [HR_{adj}] 3.62; 95% CI, 1.89–6.91) and 1 year (HR_{adj} 2.56; 95% CI, 1.78–3.69). Similarly, post-Tei was associated with an increased risk of mortality between 30 days and 1-year follow-up (HR_{adj} 6.70; 95% CI, 4.22–10.63). At multivariable analysis Tei emerged as an independent predictor of early (pre-Tei index per 0.1–HR_{adj} 1.40; 95% CI, 1.23–1.60) and late mortality (post-Tei index per 0.1–HR_{adj} 1.40; 95% CI, 1.31–1.50), respectively.

CONCLUSIONS: The left-ventricular myocardial performance index Tei is associated with impaired clinical outcomes during short- and longer-term follow-up after transcatheter aortic valve replacement.

VISUAL OVERVIEW: A visual overview is available for this article.

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Key Words: aortic valve stenosis ■ echocardiography ■ human ■ prognosis ■ transcatheter aortic valve replacement

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WHAT IS KNOWN

- The left-ventricular myocardial performance index Tei is an echocardiographic parameter that incorporates the information of systolic and diastolic time intervals.
- While the prognostic value of selected systolic and diastolic parameters is well established after transcatheter aortic valve replacement, the role of Tei has not been evaluated in this setting.

WHAT THE STUDY ADDS

- We found an independent association of Tei index with worse clinical outcomes at 30 days and up to 1-year follow-up after transcatheter aortic valve replacement.
- Pre-transcatheter aortic valve replacement Tei index emerged as independent predictor of all-cause mortality at 30 days follow-up, whereas post- transcatheter aortic valve replacement Tei index was strongly associated with all-cause death, cardiovascular death, and major adverse cardiovascular and cerebrovascular events between 30 days and 1 year.

Among patients with severe aortic stenosis (AS), the development of heart failure symptoms correlates with disease severity and left ventricular (LV) hypertrophy and has been attributed to LV diastolic and systolic dysfunction.[1] While diastolic dysfunction (DD) is the result of chronic pressure overload and unfavorable myocardial remodeling, owing to impairment of LV relaxation and changes in diastolic filling dynamics,[2] systolic dysfunction may develop because of an excess in afterload and changes in LV contractility related to inadequate hypertrophy of the myocardium.[3]

Transcatheter aortic valve replacement (TAVR) is the treatment of choice for inoperable and patients at increased surgical risk, and has emerged as a less-invasive therapeutic option for intermediate risk patients with symptomatic, severe AS. So far, only selected echocardiographic diastolic and systolic parameters have been evaluated after TAVR and their prognostic value is still subject to controversy.[4–6] The myocardial performance index Tei is recognized as echocardiographic parameter to determine overall cardiac performance and express global systolic and diastolic ventricular function.[7] While the prognostic value of Tei has been studied in patients with congestive heart failure and dilated cardiomyopathy,[8,9] the diagnostic and prognostic role of Tei in patients with severe AS undergoing TAVR remains to be elucidated.

METHODS

Patient Population and Procedures

Between August 2007 and December 2015, consecutive patients with symptomatic, severe AS undergoing TAVR were entered into the Bern TAVR Registry, which is part of the SwissTAVI Registry, and were considered eligible for this analysis.[10] Patients were excluded in case non-Confédération Européenne-marked device were used, and in the absence of adequate echocardiographic data to assess Tei index within 3 months before TAVR or 1 month after TAVR. Furthermore, patients with persistent atrial fibrillation and a history of permanent pacemaker implantation without showing sinus rhythm at the time point of echocardiographic assessments were excluded. TAVR was performed according to local expertise and standard techniques using a default transfemoral strategy, as described previously.[11]

The registry was approved by the local ethics committee, was conducted in accordance with the Declaration of Helsinki, and all patients provided written informed consent to participate during prospective follow-up. The present work adheres to the *AHA Journals*' implementation of the Transparency and Openness Promotion Guidelines. In accordance with this policy, the Bern TAVR publication committee decided not to make the data, methods used during the analyses, and materials used to conduct the research available to any other person. However, we would consider sharing our data for purposes of scientific collaboration on request.

Echocardiography and Data Collection

All subjects underwent transthoracic echocardiography within 3 months before TAVR and at hospital discharge after TAVR. Routine echocardiographic follow-up assessment was recommended to be performed at 30 days after TAVR. For the assessment of echocardiographic measures, we selected 3 of 15 consecutive heart beats and used the average of each parameter. Images were recorded with a workstation allowing for offline analysis (Syngo Dynamics Workplace, version 9.5, Siemens Medical Solutions, Inc, PA). Before (pre-Tei) and after TAVR (post-Tei), the LV Tei index was calculated using the following equation: Tei index=(ICT+IRT)/ET, where ICT denotes isovolumic contraction time, IRT isovolumic relaxation time, and ET refers to the ejection time (Figure I in the Data Supplement). The mitral inflow velocity pattern and the LV outflow velocity pattern were recorded from the apical 4-chamber view, and the apical long-axis view using pulsed wave Doppler, respectively. The predefined cutoff for normal Tei was <0.45, as previously reported.[12] The echocardiographic evaluation was independently performed by board-certified cardiologists and experienced echocardiographers who were blinded to patient outcomes.

Clinical Follow-Up and End Point Assessment

Clinical follow-up was standardized and performed at 30 days (early) and 1-year (longer-term) follow-up after TAVR. All adverse events were systematically collected and independently adjudicated according to the updated definitions of the Valve Academic Research Consortium-2. The primary end point was all-cause mortality within 1 year after TAVR.

Statistical Analysis

Continuous data are reported as means with SD (±SD, with *P* from *t* tests), and categorical variables are reported as

number of patients (% of patients, with *P* from χ^2 tests, or in case of 2-by-2 associations Fisher exact tests), comparing pre-Tei index high versus normal, and again comparing post-Tei index high versus normal.

Events are reported as counts of first occurrence per (sub)-type of event within 30 days or 1 year of follow-up (% of from lifetable estimates), comparing high pre-Tei versus normal pre-Tei index using Cox's regressions (ie, censoring patients at death or lost to follow-up). Reported are crude hazard ratios (HR with 95% CI) with *P* from Wald χ^2 tests, or continuity correct risk ratios with *P* from Fisher exact tests in case of zero events. Reported are adjusted HR (HR_{adj}; 95% CI), with the pre-Tei high compared with pre-Tei normal. Adjusted analyses conducted in case >10 events were available overall. Post-Tei index was assessed up to 1-month follow-up, accordingly high post-Tei index event rates were compared with normal post-Tei index using events reported from 30 days to 1 year of follow-up (by setting a landmark at 30 days, which includes only patients still at risk for that particular event starting from 30 days onwards). Again, both crude and HR_{adj} (95% CI) are reported.

Predictors of 30-day clinical outcomes were evaluated separately (univariable Cox's regressions). Similarly, predictors of clinical outcomes between 30 days to 1 year after TAVR were evaluated separately (univariable Cox's regressions). These potential predictors were retained in the multivariable model, if the univariable *P* value was <0.2. The final model shows all potential predictors with *P*<0.2 in the multivariable model. Stratified analyses of the following subgroups were performed: sex (women versus men), LV ejection fraction (EF; <40% versus ≥40%), and Society of thoracic surgeon score (>8 versus 4–8 versus <4); and additionally the *P* value for the interaction between these subgroups (eg, women versus men) and Tei index are reported (high versus normal—separate tables for pre- and post-Tei index). Exploratory analyses of combinations of pre-Tei and post-Tei index on clinical end points were also conducted (Tables I through IX in the Data Supplement). All analyses were performed with Stata version 14.2 (StataCorp, College Station, TX). Two-sided *P*<0.05 were considered statistically significant.

RESULTS

Study Population

Out of 1339 consecutive patients undergoing TAVR during the study period, the evaluation of pre- and post-Tei index was performed in 824 patients (61.5%; normal pre-Tei; n=639, high pre-Tei; n=185), and 722 (53.9%) patients (normal post-Tei; n=602, high post-Tei; n=120), respectively (Figure II in the Data Supplement).

Baseline clinical characteristics of the study population are described in Table 1. Patients with normal and high pre-Tei index were comparable for most of the baseline characteristics, except for female sex (54.3% versus 38.9%; *P*<0.001), New York Heart Association functional class III or IV (64.3% versus 75.7%; *P*=0.004), and LVEF (55.2±14.7% versus 51.5±14.9%; *P*=0.004). Similarly, baseline characteristics were comparable for patients with normal and high post-Tei. Significant differences were found for paroxysmal atrial fibrillation (25.6% versus 38.3%, *P*=0.005), previous permanent pacemaker implantation (7.3% versus 15.8%, *P*=0.004), New York Heart Association functional class III or IV (63.6% versus 83.3%, *P*<0.001), Society of thoracic surgeons score (5.69±3.94% versus 6.63±4.39%, *P*=0.02), LVEF (55.4±14.5% versus 51.4±15.1%, *P*=0.008), and deceleration time (236.0±88.6 msec versus 217.6±81.6 msec, *P*=0.04).

Procedural Characteristics

Table 2 provides the information on procedural characteristics between patient groups, showing significant differences in access route, valve type selection, and aortic regurgitation post TAVR greater than or equal to moderate among pre-Tei patients, whereas length of hospital stay, access route, valve type selection, and valve in series were different comparing normal and high post-Tei patients. A total of 182 patients received permanent pacemaker during the early periprocedural period after TAVR. Among them, 45 patients (high pre-Tei; 15 patients, normal pre-Tei; 30 patients) were excluded from the measurement of post-Tei index because of permanent pacemaker rhythm. For the remaining 137 patients sufficient echocardiographic data were available to calculate Tei index (Figure II in the Data Supplement).

Clinical Outcomes According to Pre- and Post-Tei Index

Event rates with crude and HR_{adj} for clinical end points are provided in Tables 3 and 4. The primary end point of all-cause mortality at 12 months was observed in 124 (15.0%) patients (normal versus high Tei; 11.6% versus 28.0%; $HR_{adj.}$ 2.56; 95% CI, 1.78–3.69; *P*<0.001) with pre-Tei index, and occurred in 75 (12.5%) patients (6.1% versus 38.8%; $HR_{adj.}$ 6.70; 95% CI, 4.22–10.6; *P*<0.001) with post-Tei index assessment (Figure 1A and 1B).

Among patients with pre-Tei assessment, secondary end points including cardiovascular death and major adverse cardiovascular and cerebrovascular events (MACCE) at 30 days were observed in 33 (4.0%; 2.7% versus 8.8%; $HR_{adj.}$ 3.11; 95% CI, 1.55–6.22; *P*=0.001) and 55 patients (6.7%; 4.7% versus 13.6%; $HR_{adj.}$ 2.74; 95% CI, 1.60–4.71; *P*<0.001). After 1-year follow-up cardiovascular death and MACCE was observed in 82 (10.0%; 7.1% versus 21.6%; $HR_{adj.}$ 3.09; 95% CI, 1.98–4.81; *P*<0.001) and 151 patients (18.3%; 14.2% versus 33.5%; $HR_{adj.}$ 2.54; 95% CI, 1.83–3.53; *P*<0.001), respectively (Figure 1C and 1E). Moreover, life-threatening bleeding at 30 days ($HR_{adj.}$ 2.14; 95% CI, 1.28–3.59) and disabling stroke at 1-year follow-up ($HR_{adj.}$ 3.00; 95% CI, 1.44–6.27)

Table 1. Baseline Clinical Characteristics

	Pre-Tei Index				Post-Tei Index			
	All Patients	Normal	High		All Patients	Normal	High	
	N=824	N=639	N=185	*P* Value	N=722	N=602	N=120	*P* Value
Age, y	82.2±6.2	82.3±6.2	81.8±6.4	0.30	82.2±6.1	82.2±6.1	82.0±6.1	0.69
Female sex, n (%)	419 (50.8)	347 (54.3)	72 (38.9)	<0.001	368 (51.0)	316 (52.5)	52 (43.3)	0.07
Body mass index, kg/m^2	26.3±5.2	26.5±5.2	25.8±5.2	0.08	26.3±5.2	26.5±5.2	25.8±4.9	0.19
Cardiac risk factors								
Diabetes mellitus, n (%)	218 (26.5)	172 (26.9)	46 (24.9)	0.64	183 (25.3)	149 (24.8)	34 (28.3)	0.42
Hypercholesterolemia, n (%)	529 (64.2)	412 (64.5)	117 (63.2)	0.79	461 (63.9)	376 (62.5)	85 (70.8)	0.10
Hypertension, n (%)	690 (83.7)	541 (84.7)	149 (80.5)	0.21	605 (83.8)	502 (83.4)	103 (85.8)	0.59
Past medical history								
Previous myocardial infarction, n (%)	130 (15.8)	93 (14.6)	37 (20.0)	0.09	107 (14.8)	86 (14.3)	21 (17.5)	0.40
Previous PCI, n (%)	218 (26.5)	170 (26.6)	48 (25.9)	0.93	194 (26.9)	160 (26.6)	34 (28.3)	0.74
Previous CABG, n (%)	98 (12.4)	75 (12.1)	23 (13.2)	0.70	90 (12.9)	76 (13.1)	14 (12.3)	1.00
Previous stroke or TIA, n (%)	94 (11.4)	71 (11.1)	23 (12.4)	0.60	83 (11.5)	73 (12.1)	10 (8.3)	0.27
Peripheral vascular disease, n (%)	129 (15.7)	93 (14.6)	36 (19.5)	0.11	111 (15.4)	87 (14.5)	24 (20.0)	0.13
Chronic obstructive pulmonary disease, n(%)	100 (12.2)	76 (11.9)	24 (13.0)	0.70	88 (12.2)	68 (11.3)	20 (16.7)	0.13
Renal failure (eGFR<60 mL/min per 1.73 m2), n (%)	577 (70.0)	450 (70.4)	127 (68.6)	0.65	503 (69.7)	413 (68.6)	90 (75.0)	0.19
Baseline cardiac rhythm								
Paroxysmal AF,* n (%)	237 (28.8)	179 (28.0)	58 (31.4)	0.41	200 (27.7)	154 (25.6)	46 (38.3)	0.005
Permanent pacemaker, n (%)	76 (9.2)	55 (8.6)	21 (11.4)	0.25	63 (8.7)	44 (7.3)	19 (15.8)	0.004
Symptoms								
NYHA classification III or IV, n (%)	551 (66.9)	411 (64.3)	140 (75.7)	0.004	483 (66.9)	383 (63.6)	100 (83.3)	<0.001
CCS III or IV Angina, n (%)	74 (9.0)	56 (8.8)	18 (9.7)	0.66	66 (9.1)	51 (8.5)	15 (12.5)	0.17
Risk assessment								
Logistic EuroSCORE, %	20.0±13.3	19.8±13.4	20.6±13.0	0.49	19.7±13.3	19.3±13.1	21.5±14.2	0.10
STS score, %	5.90±3.97	5.90±4.12	5.90±3.42	1.00	5.84±4.03	5.69±3.94	6.63±4.39	0.02
Echocardiography								
LV ejection fraction, %	54.4±14.8	55.2±14.7	51.5±14.9	0.004	54.7±14.7	55.4±14.5	51.4±15.1	0.008
Aortic valve area, cm^2	0.67±0.25	0.66±0.25	0.68±0.25	0.30	0.67±0.25	0.66±0.25	0.71±0.26	0.11
Mean gradient, mm Hg	42.2±17.7	42.5±17.6	41.3±18.2	0.45	42.3±17.9	42.6±17.6	40.5±19.4	0.25
Deceleration time, ms	230.3±86.2	231.3±87.8	226.7±80.4	0.53	232.9±87.7	236.0±88.6	217.6±81.6	0.04
Tei index	0.37±0.17	0.31±0.08	0.61±0.17	<0.001	0.37±0.16	0.34±0.12	0.54±0.24	<0.001
LVET, ms	312.3±40.4	320.1±37.7	285.1±37.8	<0.001	312.3±40.0	316.4±37.5	292.2±46.1	<0.001
IVCT, ms	32.8±48.9	17.3±32.3	86.9±57.8	<0.001	32.1±48.6	24.4±39.9	70.8±67.2	<0.001
IVRT, ms	81.0±23.4	80.0±23.1	84.6±23.8	0.02	81.2±23.5	81.4±23.5	79.1±22.8	0.67

Values are mean±SD or counts (%). *P* value from χ^2 tests (Fisher test in case of 2×2 table) or *t* test (for age and BMI). AF indicates atrial fibrillation; CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; eGFR, estimated glomerular filtration rate; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; LV, left ventricle; LVET, left ventricular ejection time; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons; and TIA, transient ischemic attack.

*At the time point of echocardiographic assessments in sinus rhythm.

were more frequently observed among patients with high pre-Tei index compared with patients and normal pre-Tei values (Table 3).

Among patients with post-Tei assessment, cardiovascular death, and MACCE were observed in 42 (5.8%; 3.5% versus 24.6%; $HR_{adj.}$ 6.34; 95% CI, 3.40–11.8; *P*<0.001) and 82 patients (11.4%; 7.5% versus 41.2%; $HR_{adj.}$ 6.35; 95% CI, 4.09–9.88; *P*<0.001) between 30 days and 1 year (Figure 1D and 1F). Subgroup analyses for pre- and post-Tei indices demonstrated a consistent effect across all subgroups. (Figure 2; Figure III in the Data Supplement). During subgroup analyses, significant interaction was found between the effect of pre-Tei on all-cause death at 30 days and patients with

Table 2. Procedural Characteristics

	Pre-Tei Index				Post-Tei Index			
	All Patients N=824	Normal N=639	High N=185	*P* Value	All Patients N=722	Normal N=602	High N=120	*P* Value
Procedural characteristics								
Procedure time, min	60 (46–81.8)	60 (47–80.3)	59 (45–84.3)	0.88	59 (46–82)	59 (46–80)	61 (48–88)	0.20
Length of hospital stay, d	8 (6–10)	8 (6–10)	8 (6–11)	0.45	8 (6–10)	8 (6–10)	9 (7–12.3)	0.011
General anesthesia, n (%)	232 (28.2)	175 (27.4)	57 (30.8)	0.40	186 (25.8)	153 (25.4)	33 (27.5)	0.65
Access route				0.04				0.004
Femoral, n (%)	717 (87.0)	565 (88.4)	152 (82.2)	0.03	645 (89.3)	539 (89.5)	106 (88.3)	0.75
Apical, n (%)	96 (11.7)	67 (10.5)	29 (15.7)	0.07	66 (9.1)	57 (9.5)	9 (7.5)	0.60
Subclavian, n (%)	8 (1.0)	4 (0.6)	4 (2.2)	0.08	8 (1.1)	3 (0.5)	5 (4.2)	0.004
Other, n (%)	3 (0.4)	3 (0.5)	0 (0.0)	1.00	3 (0.4)	3 (0.5)	0 (0.0)	1.00
Valve type				0.001				0.001
Medtronic CoreValve, n (%)	264 (32.0)	194 (30.4)	70 (37.8)	0.06	239 (33.1)	182 (30.2)	57 (47.5)	<0.001
Edwards Sapien XT, n (%)	221 (26.8)	156 (24.4)	65 (35.1)	0.005	191 (26.5)	155 (25.7)	36 (30.0)	0.37
BSC/Symetis ACURATE valve, n (%)	34 (4.1)	28 (4.4)	6 (3.2)	0.67	26 (3.6)	26 (4.3)	0 (0.0)	0.01
Abbott/SJM Portico, n (%)	4 (0.5)	4 (0.6)	0 (0.0)	0.58	4 (0.6)	4 (0.7)	0 (0.0)	1.00
Edwards Sapien 3, n (%)	190 (23.1)	165 (25.8)	25 (13.5)	<0.001	166 (23.0)	147 (24.4)	19 (15.8)	0.04
BSC Lotus, n (%)	56 (6.8)	47 (7.4)	9 (4.9)	0.32	45 (6.2)	41 (6.8)	4 (3.3)	0.21
Medtronic Evolut R, n (%)	55 (6.7)	45 (7.0)	10 (5.4)	0.51	51 (7.1)	47 (7.8)	4 (3.3)	0.12
Procedural specifications								
Post-TAVR AR moderate or severe, n (%)	74 (9.0)	50 (7.8)	24 (13.0)	0.04	69 (9.6)	57 (9.5)	12 (10.0)	0.87
Valve in valve, n (%)	16 (1.9)	14 (2.2)	2 (1.1)	0.55	15 (2.1)	9 (1.5)	6 (5.0)	0.03

Values are counts (%) or medians (25%–75% interquartile range). *P* Value from χ^2 tests (Fisher test in case of 2×2 table) or *t* test (for procedure time and length of stay). AR indicates aortic regurgitation; and TAVR, transcatheter aortic valve replacement.

moderate or severe AR after TAVR and between post-Tei on all-cause death between 30 days and 1 year and reduced LVEF (<40%) after TAVR (Figure III in the Data Supplement).

Clinical Outcomes According to Categories of Pre- and Post-Tei Index

Patients were grouped according to the evolution of post-Tei index in relation to pre-Tei assessment. Out of 185 patients with high pre-Tei index, Tei changed to normal values after the intervention in 91 (49.2%) patients, whereas 50 (7.8%) patients with normal Tei at baseline had high Tei index after TAVR. Patients with high pre-Tei index and high post-Tei index (HH) were more often men, more often had paroxysmal atrial fibrillation, previous permanent pacemaker implantation, presented in New York Heart Association functional class III or IV, had higher surgical risk, lower LVEF, and lower deceleration time compared with patients with normal pre-Tei and normal post-Tei index (NN; Table I in the Data Supplement). Significant differences were found in terms of access route, type of valve selection, and length of hospital stay comparing HH patients with NN (Table II in the Data Supplement). Furthermore, there were higher rates of all-cause death, cardiovascular death, and MACCE between 30 days and 1-year follow-up in patients with high post-Tei index (both NH and HH groups; Tables III and IV, Figure IV in the Data Supplement). The difference between pre- and post-Tei index and its effect on clinical outcomes was evaluated. Consistent results were observed according to Tei change for all-cause death, cardiovascular death, and MACCE and are presented in Table V in the Data Supplement.

Predictors for Adverse Clinical Outcomes

Independent predictors for death from any cause are displayed in Table 5. Multivariable analyses identified pre-Tei index (per 0.1–$HR_{adj.}$ 1.40; 95% CI, 1.23–1.60) as an independent predictor of all-cause mortality during short-term follow-up. Moreover, post-Tei index (per 0.1–$HR_{adj.}$ 1.40; 95% CI, 1.31–1.50); diabetes mellitus ($HR_{adj.}$ 2.78; 95% CI, 1.72–4.50); LVEF ($HR_{adj.}$ 0.98; 95% CI, 0.96–0.99), and lower body mass index ($HR_{adj.}$ 2.70; 95% CI, 1.30–5.60) emerged as independent predictors of all-cause death between 30

Table 3. Short- and Long-Term Clinical Outcomes According to Pre-Tei Index

	Normal Pre-Tei Index Patients	High Pre-Tei Index Patients	Crude Hazard Ratio		Adjusted Hazard Ratio	
	N=639	N=185	HR (95% CI)	*P* Value	Adjusted HR (95% CI)	Adjusted *P* Value
30-D follow-up						
All-cause death, n (%)	18 (2.8)	20 (10.9)	3.99 (2.11–7.54)	<0.001	3.62 (1.89–6.91)	<0.001
Cardiovascular death, n (%)	17 (2.7)	16 (8.8)	3.37 (1.70–6.68)	<0.001	3.11 (1.55–6.22)	0.001
Myocardial infarction, n(%)	8 (1.3)	3 (1.6)	1.30 (0.34–4.90)	0.70	1.40 (0.37–5.36)	0.62
Cerebrovascular events						
Disabling stroke, n (%)	14 (2.2)	9 (5.0)	2.25 (0.98–5.21)	0.06	2.28 (0.98–5.31)	0.06
MACCE, n (%)	30 (4.7)	25 (13.6)	2.95 (1.73–5.01)	<0.001	2.74 (1.60–4.71)	<0.001
Bleeding						
Life-threatening, n (%)	39 (6.1)	24 (13.1)	2.18 (1.31–3.62)	0.003	2.14 (1.28–3.59)	0.004
Kidney injury						
Stage 3, n (%)	19 (3.0)	9 (4.9)	1.66 (0.75–3.66)	0.21	1.81 (0.81–4.03)	0.15
Access site complications						
Major, n (%)	68 (10.7)	23 (12.5)	1.18 (0.73–1.89)	0.50	1.17 (0.73–1.88)	0.51
1-Y follow-up						
All-cause death, n (%)	73 (11.6)	51 (28.0)	2.71 (1.89–3.87)	<0.001	2.56 (1.78–3.69)	<0.001
Cardiovascular death, n (%)	44 (7.1)	38 (21.6)	3.31 (2.14–5.11)	<0.001	3.09 (1.98–4.81)	<0.001
Myocardial infarction, n (%)	13 (2.1)	6 (3.7)	1.73 (0.66–4.56)	0.27	1.75 (0.66–4.66)	0.26
Cerebrovascular events						
Disabling stroke, n (%)	16 (2.6)	13 (7.7)	2.95 (1.42–6.15)	0.004	3.00 (1.44–6.27)	0.003
MACCE, n (%)	90 (14.2)	61 (33.5)	2.65 (1.92–3.67)	<0.001	2.54 (1.83–3.53)	<0.001

No. of events (% from lifetable estimate). Hazard ratios (HR; 95% CI) from Cox regressions for time-to-event data. In case of >10 event also reported: Adjusted (HRs; 95% CI) from Cox regressions adjusting for diabetes mellitus, peripheral vascular disease, paroxysmal atrial fibrillation, BMI ≤20, logistic EuroSCORE ≥40%, concomitant PCI. Fisher exact test and continuity correct Risk ratios reported in case of zero events in 1 group. MACCE indicates major adverse cardiovascular and cerebrovascular events (composite of all-cause death, stroke, and myocardial infarction).

days and 1 year after TAVR. Predictors for worsening and improving Tei index are presented in Table VI and VII in the Data Supplement.

Short- and Long-term clinical Outcomes according to pre- and post-Tei index in patients exclusively in sinus rhythm without previous history of any atrial fibrillation is provided in Table VIII and IX in the Data Supplement.

DISCUSSION

The salient findings of our study investigating the association of periprocedural Tei index and clinical outcomes after TAVR can be summarized as follows:

1. One-quarter of patients undergoing TAVR for severe AS were found to have impaired LV myocardial performance according to the Tei index.

Table 4. Post 30-Day Clinical Outcomes According to Post-Tei Index

	Normal Post-Tei Index Patients	High Post-Tei Index Patients	Crude Hazard Ratio		Adjusted Hazard Ratio	
	n=602*	n=120*	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
30-d follow-up to 1 y*						
All-cause death, n (%)	36 (6.1)	39 (38.8)	7.60 (4.83–11.96)	<0.001	6.70 (4.22–10.63)	<0.001
Cardiovascular death, n (%)	20 (3.5)	22 (24.6)	7.82 (4.26–14.34)	<0.001	6.34 (3.40–11.80)	<0.001
Myocardial infarction, n (%)	5 (0.9)	1 (1.2)	1.55 (0.18–13.25)	0.69	1.88 (0.21–16.76)	0.57
Cerebrovascular events						
Disabling stroke, n(%)	2(0.4)	3(4.0)	12.08(2.01–72.44)	0.006	12.76(2.12–76.92)	0.005
MACCE, n(%)	43(7.5)	39(41.2)	6.81(4.41–10.51)	<0.001	6.35(4.09–9.88)	<0.001

No. of events (% from lifetable estimate). Hazard ratios (HR; 95% CI) from Cox regressions for time-to-event data. In case of >10 event also reported: Adjusted HRs (95% CI) from Cox regressions adjusting for diabetes mellitus, peripheral vascular disease, paroxysmal atrial fibrillation, BMI ≤20, logistic EuroSCORE ≥40%, concomitant PCI. Fisher exact test and continuity correct Risk ratios reported in case of zero events in 1 group. MACCE indicates major adverse cardiovascular and cerebrovascular events (composite of all-cause death, stroke, and myocardial infarction); and PCI, percutaneous coronary intervention.

*Landmark at 30 days, that is, excludes patients no longer at risk for the specified event at day 30.

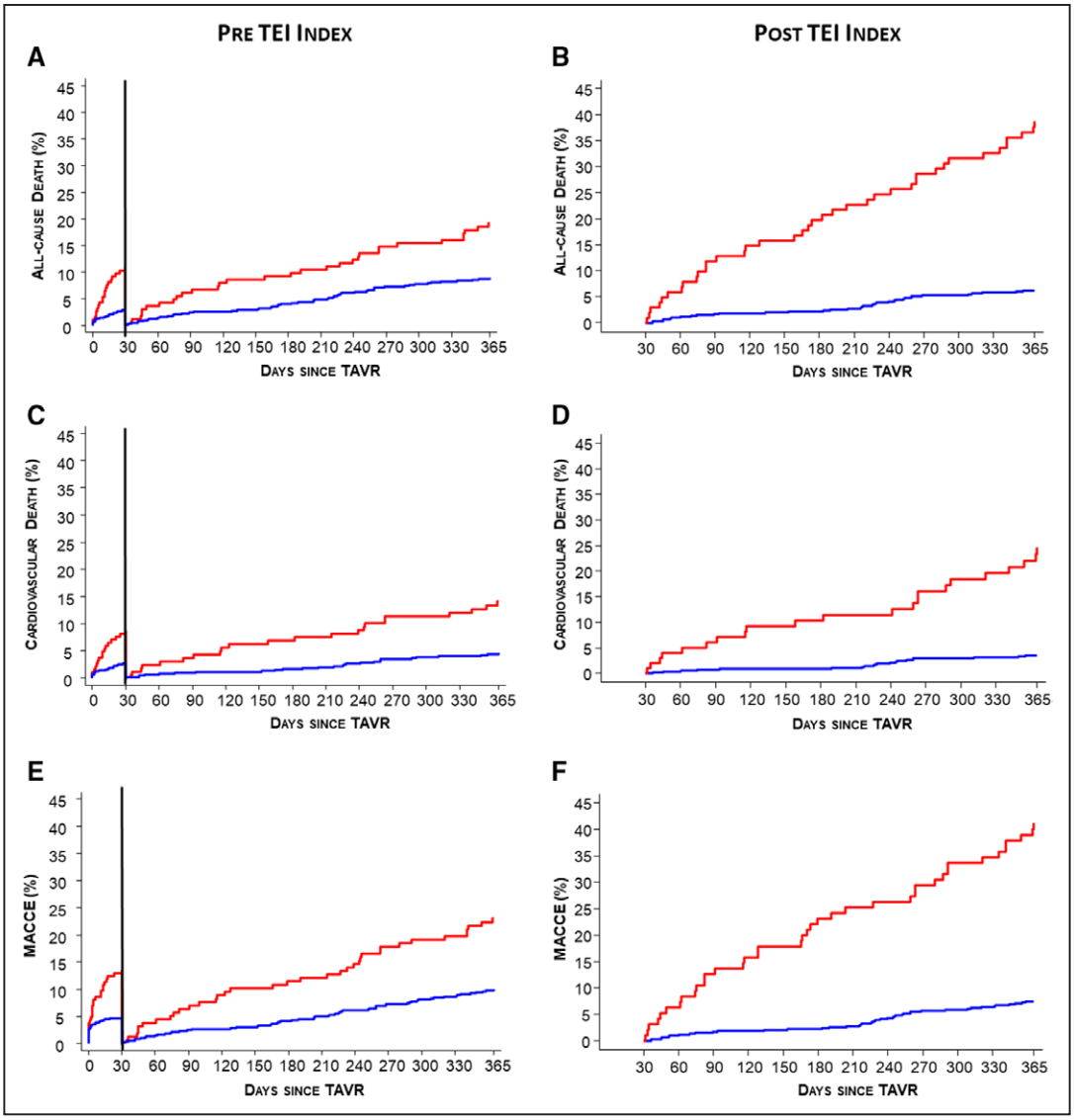

Figure 1. Kaplan-Meier analysis of end points after transcatheter aortic valve replacement (TAVR).
Landmark analysis at 30 d for cumulative incidence of all-cause death (**A**), cardiovascular death (**C**), and major adverse cardiovascular and cerebrovascular events (MACCE; **E**) according to pre-Tei index. Cumulative incidence of all-cause death (**B**), cardiovascular death (**D**), and MACCE (**F**) between 30 d and 1 y according to post-Tei index. Blue line = normal Tei index; Red line = high Tei index.

2. Pre-Tei index was associated with worse clinical outcomes after TAVR and emerged as independent predictor of all-cause mortality at 30 days.
3. Moreover, post-Tei index was strongly associated with all-cause death, cardiovascular death, and MACCE between 30 days and 1 year.

The LV Tei index is an established echocardiographic parameter of advanced heart disease and a well-known predictor of worse clinical outcomes among patients with different types of cardiomyopathy, including ischemic, dilated, or hypertrophic heart disease.[8,9] Furthermore, LV Tei is effective in the early detection of subclinical ventricular dysfunction in patients with insulin resistance[13] and is used as early reference marker for hypertensive cardiomyopathy in children with essential hypertension.[14] However, it lacks precision and reproducibility in patients with atrial fibrillation, pacemaker rhythm, frequent ventricular ectopic stimuli, and disturbances of intraventricular or atrioventricular conduction.[15] Our analysis suggests that LV Tei index also provides important prognostic information for patients with symptomatic, severe AS undergoing TAVR. While an elevated Tei index at baseline was associated with a 3.5- to 2.5-fold increased risk of mortality after 30 days and 12 months after TAVR, an increased Tei index after TAVR was found to be linked to a 6-fold increased risk of mortality and MACCE up to 1-year after TAVR. The adverse effect of high Tei index was observed irrespective of sex, Society of thoracic surgeons risk, and LVEF (Figure 2), which are well-established predictors for clinical outcomes after TAVR.

Subgroup	Normal TEI index patients	High TEI index patients	High vs Normal Hazard ratio (95% CI)	p-value	interaction p-value*
Pre-TEI index: All-cause death at 30 days					
Gender					0.47
female	11/347	7/72	3.11 (1.21-8.02)	0.02	
male	7/292	13/113	5.09 (2.03-12.8)	0.001	
LVEF					0.46
<40%	4/98	3/34	2.26 (0.51-10.1)	0.29	
≥40%	14/486	16/136	4.23 (2.07-8.67)	<0.001	
STS group					0.09
>8	8/138	8/39	3.73 (1.40-9.95)	0.008	
4-8	9/251	7/89	2.24 (0.83-6.01)	0.11	
<4	1/250	5/57	22.9 (2.68-196.4)	0.004	
Post-TEI index: All-cause death from 30 days to 1 year					
Gender					0.93
female	18/316	16/52	7.58 (3.86-14.9)	<0.001	
male	18/286	23/68	7.43 (4.01-13.8)	<0.001	
LVEF					0.68
<40%	8/91	8/22	5.33 (2.00-14.2)	0.001	
≥40%	23/458	23/89	7.08 (3.97-12.6)	<0.001	
STS group					0.26
>8	13/119	10/33	4.87 (2.13-11.1)	<0.001	
4-8	13/241	17/55	6.98 (3.39-14.4)	<0.001	
<4	10/242	12/32	12.6 (5.45-29.3)	<0.001	

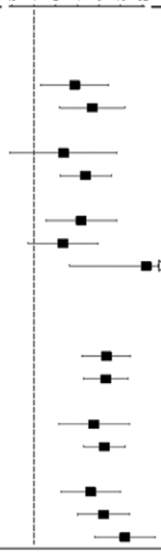

Figure 2. All-cause death after TAVR, stratified by sex, LVEF, and STS score.
All-cause death at 30 days based on pre-Tei index and all-cause death between 30 d and 1 y based on post-Tei index. Black squares represent hazard ratios (HR); horizontal black lines illustrate CI. An HR>1 (right side) is in favor of high pre-/post-Tei index patients, whereas an HR<1 (left side) is in favor of normal pre-/post-Tei index patients. Pre-Tei index up to 30 d all-cause death, post-Tei using a landmark at 30 d and all-cause death from 30 d to 1 y of follow-up. *Interaction *P* testing for an effect modification of the subgroups on the difference in all-cause death between high and normal Tei index group. LVEF indicates left ventricular ejection fraction; STS; Society of Thoracic Surgeons; and TAVR, transcatheter aortic valve replacement.

LV Tei index is considered a global myocardial performance index as it incorporates time intervals of systolic and diastolic ventricular function from Doppler echocardiographic images. It is well established, that systolic LV dysfunction is associated with increased operative mortality after surgical aortic valve replacement,[16] and considered one of the main reasons to circumvent surgery in the past. While, in the PARTNER I trial (Placement of Aortic Transcatheter Valves; cohort B+A), patients with classical low-flow, low-gradient severe AS had worse clinical outcomes after 2 years compared with normal flow patients,[17] no significant differences in outcomes were observed between surgical aortic valve replacement and TAVR patients. Both treatment options were able to restore LVEF to a similar extent and provided comparable levels of LVEF improvement in the absence of right ventricle pacing or new onset left bundle branch block during follow-up. In contrast to the PARTNER data, a meta-analysis encompassing >7600 patients from 16 studies was able to show that reduced LVEF was associated with increased mortality at 1-year follow-up. This adverse effect was consistently observed in patients with LVEF <50% (HR 1.52; 95% CI, 1.31–1.76) and LVEF <30% (HR 1.60; 95% CI, 1.19–2.16).[18]

Furthermore, among patients with symptomatic, severe AS, chronic pressure overload, and unfavorable myocardial remodeling because of cardiac hypertrophy is linked to impairment of LV relaxation and changes in diastolic filling.[2] After conventional surgical aortic valve replacement, moderate-to-severe DD has been associated with relevant difficulties in perioperative weaning of cardiopulmonary bypass and was associated with worse clinical outcomes during longer-term follow-up up to 2 years after surgery.[19,20] Studies on the prognostic role of DD among patients undergoing TAVR are limited in number and patient size.[4,21] Most recently, data from a single center registry suggest that baseline DD was associated with mortality at 12 months (HR 1.163; 95% CI, 1.049–1.277; *P*=0.005) and the end point death/cardiovascular hospitalization (HR 1.174; 95% CI, 1.032–1.318; *P*=0.018) after TAVR. However, DD post-TAVR or changes in DD grade from baseline to follow-up did not emerge as predictor for worse clinical outcomes in 90 TAVR patients.[4] Conte et al[21] investigated the prognostic role of LV stiffness as expression of DD and was able to show that increased myocardial stiffness was associated with mortality at 12 months. Patients with a combination of high LV stiffness and moderate-to-severe paravalvular AR after TAVR were at particular risk for worse clinical outcomes, according to this study.

In our study, the LV Tei index was associated with worse clinical outcomes during the first year after TAVR, irrespective whether baseline or post-TAVR measures were used in multivariate analysis. By including systolic and diastolic time intervals to calculate Tei, this index might be considered a marker of global cardiac function and a reference parameter of advanced heart

Table 5. Predictive Factors for All-Cause Death

Variables	Univariate Analysis		Multivariable Analysis		Final Model	
	HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
All-cause death at 30 d						
Pre-Tei index (per 0.1)	1.42 (1.24–1.61)	<0.001	1.38 (1.21–1.58)	<0.001	1.40 (1.23–1.60)	<0.001
Logistic EuroSCORE ≥40%	3.40 (1.60–7.20)	0.001	2.71 (1.15–6.37)	0.022	2.89 (1.36–6.14)	0.006
Previous stroke or TIA	1.82 (0.80–4.13)	0.155	1.61 (0.70–3.68)	0.26		0.30*
BMI ≤20 kg/m^2	2.29 (0.95–5.48)	0.064	1.60 (0.64–4.03)	0.32		0.31*
LVEF, %	0.98 (0.96–1.00)	0.104	1.00 (0.98–1.02)	0.97		0.90*
All-cause death† 30 d to 1 y						
Post-Tei index (per 0.1)	1.40 (1.31–1.48)	<0.001	1.40 (1.30–1.50)	<0.001	1.40 (1.31–1.50)	<0.001
Diabetes mellitus	2.46 (1.59–3.80)	<0.001	2.81 (1.73–4.59)	<0.001	2.78 (1.72–4.50)	<0.001
LVEF, %	0.97 (0.95–0.98)	<0.001	0.98 (0.96–1.00)	0.012	0.98 (0.96–0.99)	0.007
BMI ≤20 kg/m^2	1.87 (0.99–3.52)	0.054	2.78 (1.32–5.87)	0.007	2.70 (1.30–5.60)	0.008
Logistic. EuroSCORE ≥40%	3.40 (2.02–5.74)	<0.001	1.51 (0.76–2.99)	0.24	1.66 (0.85–3.24)	0.14
Peripheral vascular disease	1.84 (1.11–3.05)	0.017	1.51 (0.84–2.70)	0.17		0.25*
Paroxysmal atrial fibrillation	1.68 (1.08–2.61)	0.023	1.36 (0.82–2.27)	0.24		0.37*
NYHA III or IV	1.81 (1.07–3.05)	0.026	0.86 (0.48–1.54)	0.61		0.64*
Creatinine >200µmol/L	1.61 (0.59–4.40)	0.35				
Women	0.89 (0.57–1.37)	0.59				
COPD	1.46 (0.81–2.64)	0.21				
Concomitant PCI	1.25 (0.69–2.27)	0.45				
Previous stroke or TIA	1.38 (0.75–2.55)	0.30				

Multivariable model includes variables with *P*<0.20 in the univariate analysis. Final Model after stepwise exclusion *P*<0.20, BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and TIA, transient ischemic attack.

**P* value of excluded variables if included into Final model.

†With landmark at 30 days.

disease in patients with symptomatic, severe AS undergoing TAVR. As Tei predicts worse clinical outcomes after TAVR irrespective of LVEF, future studies will show whether risk assessment using the standard surgical risk score algorithms may benefit from replacing systolic EF with LV Tei index.

Study Limitations

The findings of our study have to be interpreted in light of several limitations. First, the study population was based on the experience of a single, tertiary care center and the results might not be extrapolated to other centers with differences in patient selection and procedural experience. Second, we assessed pre- and post-Tei index in all patients irrespective of concomitant valvular heart disease (significant aortic/mitral regurgitation), coronary artery disease, or after pacemaker implantation, which might have a differential effect on Tei. Third, patients with permanent atrial fibrillation or paced cardiac rhythm at the time point of echocardiographic assessment had to be excluded because of the inability to provide a precise and reliable calculation of Tei in the absence of an A-wave. Finally, we report results from a relatively modest number of patients and not all consecutive patients had sufficient echocardiographic imaging quality to evaluate Tei pre- and post-TAVR. However, the current TAVR patient population provides the largest echo dataset evaluating the effect of Tei in the present literature, is used from a prospective registry, which adheres to high standards of data quality with rigorous data collection, standardized follow-up, and independent event adjudication at regular time intervals.

Conclusions

The LV myocardial performance index Tei is associated with impaired clinical outcomes after TAVR. Future studies will need to confirm the role of Tei as parameter for risk stratification in a patient population undergoing TAVR.

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