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Research article

Myocardial analysis from routine 4D cardiac-CT to predict reverse remodeling and clinical outcomes after transcatheter aortic valve implantation

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ABSTRACT

Purpose: Our study aimed to determine whether 4D cardiac computed tomography (4DCCT) based quantitative myocardial analysis may improve risk stratification and can predict reverse remodeling (RRM) and mortality after transcatheter aortic valve implantation (TAVI).

Methods: Consecutive patients undergoing clinically indicated 4DCCT prior to TAVI were prospectively enrolled. 4DCCT-derived left- (LV) and right ventricular (RV), and left atrial (LA) dimensions, mass, ejection fraction (EF) and myocardial strain were evaluated to predict RRM and survival. RRM was defined by either relative increase in LVEF by 5% or relative decline in LV end diastolic diameter (LVEDD) by 5% assessed by transthoracic echocardiography prior TAVI, at discharge, and at 12-month follow-up compared to baseline prior to TAVI.

Results: Among 608 patients included in this study (55 % males, age 81 ± 6.6 years), RRM was observed in 279 (54 %) of 519 patients at discharge and in 218 (48 %) of 453 patients at 12-month echocardiography. While no CCT based measurements predicted RRM at discharge, CCT based LV mass index and LVEF independently predicted RRM at 12-month (OR_{adj} = 1.012; 95 %CI:1.001–1.024; p = 0.046 and OR_{adj} = 0.969; 95 % CI:0.943–0.996; p = 0.024, respectively). The most pronounced changes in LVEF and LVEDD were observed in patients with impaired LV function at baseline. In multivariable analysis age (HR_{adj} = 1.037; 95 % CI:1.005–1.070; p = 0.022) and CCT-based LVEF (HR_{adj} = 0.972; 95 %CI:0.945–0.999; p = 0.048) and LAEF (HR_{adj} = 0.982; 95 %CI:0.968–0.996; p = 0.011) independently predicted survival.

Conclusion: Comprehensive myocardial functional information derived from routine 4DCCT in patients with severe aortic stenosis undergoing TAVI could predict reverse remodeling and clinical outcomes at 12-month following TAVI.

1. Introduction

Cardiac computed tomography (CCT) acquisition protocols are a cornerstone in the evaluation and planning of transcatheter aortic valve implantation (TAVI) in patients with severe aortic stenosis (AS) [1–4]. Whereas the severity of AS is usually assessed by transthoracic

Abbreviations: **4DCCT, 4D cardiac computed tomography**; **AS, aortic stenosis**; **CI, confidence interval**; **BMI, body mass index**; **EDA /EDV, end diastolic area /volume**; **EF, ejection fraction**; **FAC, fractional area change**; **GCS/GLS/GRS, global circumferential/longitudinal/radial strain**; **HR, Hazard ratio**; **IQR, interquartile range**; **LA, left atrium**; **LV /RV, left/right ventricle**; **LVEDD, left ventricular end-diastolic diameter**; **NT-proBNP, n-terminal proB-type natriuretic peptide**; **NYHA, New York Heart Association**; **RRM, reverse remodeling**; **TAVI, transcatheter aortic valve implantation**.

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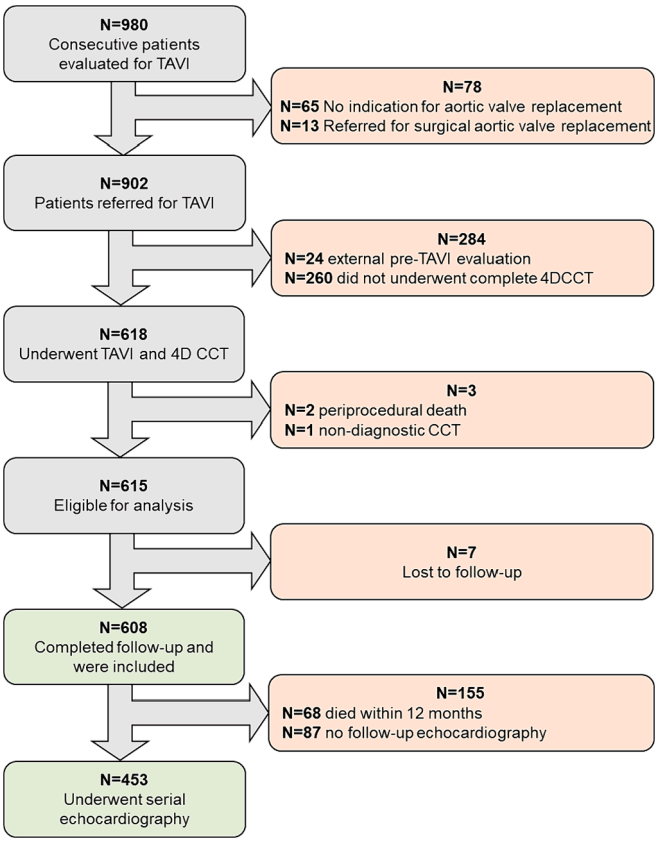

Fig. 1. Study Consort Flow. Abbreviations: 4DCCT – 4-dimensional cardiac computed tomography, TAVI – transcatheter aortic valve implantation.

echocardiography and invasive hemodynamic assessment, CCT provides incremental information related to dimensions of the aortic anulus and root, vascular access sites, coronary artery anatomy, helps to determine valve size and can reveal incidental findings such as severe calcifications or previously undetected malignant neoplasm [5–7]. The central role of CCT intrinsic to anatomic assessments can be further enhanced by incorporating a fourth dimension into the acquisition protocol, enabling cine imaging throughout the entire cardiac cycle via retrospective gating of the patient's ECG, referred to as 4-dimensional (4D) CCT. In fact, 4DCCT is clinically indicated as valve sizing needs to be performed during specific phases of the cardiac cycle (i.e. systole and diastole) [3]. Reconstructed 4DCCT enables the post-processing assessment and quantification of functional determinants of myocardial contractility and allows the acquisition of myocardial strain in various orientations with excellent reproducibility [8–10]. Several studies demonstrated 4DCCT parameters such as left ventricular (LV) global longitudinal strain (GLS) to provide independent prognostic value following TAVI [11,12]. However, data from large scale studies is scarce, and it remains unclear whether 4DCCT can predict reverse remodeling (RRM) after TAVI and whether RRM is associated with clinical outcomes. RRM describes the regression of changes induced by severe AS and chronically increased afterload such as LV hypertrophy and the subsequent improvement of cardiac mechanics following TAVI. Although RRM has been shown to be associated to improved quality of life and clinical outcomes [13], it does not occur in all patients undergoing TAVI and is difficult to be predicted by clinical characteristics alone [14]. The aim of the present study was therefore to evaluate the yield of post-processing analysis of myocardial dimension, function, and mass of clinically indicated routine 4DCCT to predict RRM at discharge and at follow-up and its association with clinical outcomes following TAVI.

Table 1
Patient characteristics.

	Total (N = 608)	No death at follow-up (N = 513)	Death at follow-up (N = 95)	P-value
Demographic data				
Age [years], *mean ± SD*	81.1 ± 6.6	80.9 ± 6.5	82.7 ± 6.7	**0.014**
Sex [male], *n (%)*	337 (55.4 %)	281 (54.8 %)	56 (58.9 %)	0.523
BMI [kg/m^2], *median (IQR)*	26.2 (23.3–29.7)	26.4 (23.4–30.1)	25.6 (22.7–28.7)	0.078
Medical history				
Arterial hypertension *n (%)*	554 (91.1 %)	465 (90.6 %)	89 (93.7 %)	0.447
Dyslipidemia *n (%)*	424 (69.7 %)	356 (69.4 %)	68 (71.6 %)	0.761
Diabetes mellitus *n (%)*	181 (29.8 %)	143 (27.9 %)	38 (40.0 %)	**0.024**
Coronary artery disease *n (%)*	285 (46.9 %)	228 (44.4 %)	57 (60.0 %)	**0.007**
Prior myocardial infarction *n (%)*	71 (11.7 %)	53 (10.3 %)	18 (18.9 %)	**0.026**
History of atrial fibrillation *n (%)*	220 (36.2 %)	164 (32.0 %)	56 (58.9 %)	**<0.001**
Permanent pacemaker *n (%)*	49 (8.1 %)	41 (8.0 %)	8 (8.4 %)	0.999
STS calculated risk of mortality *mean ± SD*	3.2 (2.0–5.9)	3.0 (1.8–5.4)	4.7 (3.3–7.1)	**<0.001**
Symptoms at admission				
Dyspnea				
NYHA I n (%)	19 (3.1 %)	18 (3.5 %)	1 (1.1 %)	**<0.001**
NYHA II n (%)	273 (44.9 %)	247 (48.1 %)	26 (27.4 %)	
NYHA III n (%)	272 (44.7 %)	215 (41.9 %)	57 (60.0 %)	
NYHA IV n (%)	44 (7.2 %)	33 (6.4 %)	11 (11.6 %)	
Anginal chest pain *n (%)*	96 (15.8 %)	85 (16.6 %)	11 (11.6 %)	0.284
Syncope *n (%)*	62 (10.2 %)	50 (9.7 %)	12 (12.6 %)	0.284
Medication				
Single antiplatelet *n (%)*	229 (37.7 %)	201 (39.2 %)	28 (29.5 %)	0.093
Dual antiplatelet *n (%)*	74 (12.2 %)	60 (11.7 %)	14 (14.7 %)	0.508
Oral anticoagulant *n (%)*	215 (35.4 %)	170 (33.1 %)	45 (47.4 %)	**0.011**
ACE-inhibitor *n (%)*	172 (28.3 %)	146 (28.5 %)	26 (27.4 %)	0.926
Angiotensin receptor blocker *n (%)*	188 (30.9 %)	162 (31.6 %)	26 (27.4 %)	0.487
Betablocker *n (%)*	292 (48.0 %)	235 (45.8 %)	57 (60.0 %)	**0.015**
Diuretic *n (%)*	347 (57.1 %)	286 (55.8 %)	61 (64.2 %)	0.156
Laboratory markers				
Creatinine [mmol/l], *median (IQR)*	90 (72–113)	88 (72–109)	107 (82–131)	**0.003**
eGFR [ml/min], *median (IQR)*	55 (39–72)	56 (42–73)	44 (31–59)	**<0.001**
NT-proBNP [pg/ml], *median (IQR)*	1270 (564–3160)	1010 (519–2590)	3300 (1550–6440)	**0.003**
Aortic stenosis characteristics				

(*continued on next page*)

Table 1 (*continued*)

	Total (N = 608)	No death at follow-up (N = 513)	Death at follow-up (N = 95)	P-value
Mean gradient [mmHg], *mean ± SD*	36.9 ± 16.9	37.8 ± 16.7	32.0 ± 17.4	**0.003**
Peak gradient [mmHg], *mean ± SD*	55.7 ± 27.2	56.9 ± 27.0	49.6 ± 27.4	**0.019**
Aortic valve area [cm^2], *mean ± SD*	0.85 ± 0.32	0.85 ± 0.32	0.87 ± 0.32	0.467
TAVI Procedural characteristics				
Femoral access *n (%)*	593 (98.3 %)	502 (98.6 %)	91 (96.8 %)	0.999
Prosthesis type				
Balloon-expandable *n (%)*	374 (61.6 %)	314 (61.3 %)	60 (63.2 %)	0.572
Self-expandable *n (%)*	226 (37.2 %)	193 (37.7 %)	33 (34.7 %)	
Mechanically-expandable *n (%)*	7 (1.2 %)	5 (1.0 %)	2 (2.1 %)	
Mean gradient post *[mmHg], mean ± SD*	4 (2–6)	4 (2–6)	3 (2–6)	0.508
Aortic regurgitation ≥ moderate *n (%)*	15 (2.5 %)	14 (2.7 %)	1 (1.1 %)	0.539
Discharge echocardiography				
LVEF [%], *mean ± SD*	56.8 ± 12.5	57.4 ± 12.1	53.7 ± 13.9	**0.027**
LVEDD [%], *mean ± SD*	44.9 ± 9.27	44.8 ± 9.48	45.1 ± 7.98	0.776
AV mean gradient [mmHg], *mean ± SD*	10.4 ± 4.88	10.5 ± 4.89	9.57 ± 4.79	0.098
Aortic valve area [cm^2], *mean ± SD*	1.72 ± 0.52	1.74 ± 0.52	1.61 ± 0.48	**0.032**
Aortic regurgitation ≥ moderate *n (%)*	15 (2.5 %)	14 (2.8 %)	1 (1.1 %)	0.546

Abbreviations: ACE – angiotensin converting enzyme, ARNI – angiotensin neprilysin inhibitor, BMI – body mass index, CKD – chronic kidney disease, eGFR – estimated glomerular filtration rate, IQR – interquartile range, NT-proBNP – n-terminal proB-type natriuretic peptide, SD – standard deviation

2. Methods

2.1. Patients and design

Consecutive patients with symptomatic severe AS referred for evaluation of TAVI at the University Cardiovascular Center at Bern University Hospital, Bern, Switzerland were considered eligible for the present study. Inclusion criteria were the completion of a 4DCCT protocol and subsequent successful TAVI implantation without procedural death. Patients with non-diagnostic 4DCCT due to poor image quality or those who did not undergo a 4DCCT with 0–100 % RR interval acquisition were excluded. Patients were prospectively enrolled in the institutional Bern TAVI registry (NCT01368250), that was approved by the local ethics committee (KEK-BE) and was designed in accordance with the Declaration of Helsinki.

2.2. 4DCCT image acquisition and analysis

All patients enrolled in this study underwent retrospectively ECG-gated 4DCCT imaging (entire cardiac cycle) on a dual-source 128-row multi slice CT (Somaton Definition Flash; Siemens Healthcare, Erlangen, Germany). Following the recommendations outlined in professional guidelines [1,3], the applied 4DCCT protocols were clinically indicated to evaluate the eligibility for TAVI and to plan the procedure [2]. The detailed scan parameters were previously published [15,16,8], and

Table 2
4DCCT imaging characteristics.

	Total (N = 608)	No death at follow-up (N = 513)	Death at follow-up (N = 95)	P-value
Left ventricle				
EDV indexed [ml/m^2], *mean ± SD*	96.2 ± 32.2	96.2 ± 32.9	96.0 ± 28.8	0.939
Mass indexed [g/m^2], *mean ± SD*	72.0 ± 19.3	72.0 ± 19.1	72.0 ± 20.1	0.997
EF [%], *mean ± SD*	52.3 ± 15.0	53.3 ± 14.6	46.9 ± 15.9	**<0.001**
GLS [%], *mean ± SD*	−14.5 ± 4.78	−14.7 ± 4.73	−13.2 ± 4.82	**0.005**
GCS [%], *mean ± SD*	−16.9 ± 6.22	−17.2 ± 6.08	−15.3 ± 6.70	**0.009**
GRS [%], *mean ± SD*	57.6 ± 29.6	59.3 ± 29.9	48.3 ± 26.2	**<0.001**
Right ventricle				
EDA [cm^2], *mean ± SD*	26.9 ± 6.71	26.8 ± 6.43	27.3 ± 8.08	0.597
FAC [%], *mean ± SD*	35.7 ± 11.4	36.2 ± 11.4	32.9 ± 10.9	**0.009**
GLS [%], *mean ± SD*	−19.7 ± 7.27	−20.1 ± 7.32	−17.3 ± 6.50	**<0.001**
Left atrium				
ESV indexed [ml/m^2], *mean ± SD*	64.0 ± 23.2	63.1 ± 22.8	69.1 ± 24.6	**0.029**
EF [%], *mean ± SD*	29.1 ± 17.8	30.7 ± 17.7	20.6 ± 15.5	**<0.001**
GLS [%], *mean ± SD*	15.0 ± 10.2	15.8 ± 10.3	11.1 ± 8.24	**<0.001**

Abbreviations: EDA /EDV – end diastolic area /volume, EF – ejection fraction, ESV – endsystolic volume, FAC – fractional area change, GCS – global circumferential strain, GLS – global longitudinal strain, GRS – global radial strain, LV /RV – left/right ventricle, SD – standard deviation

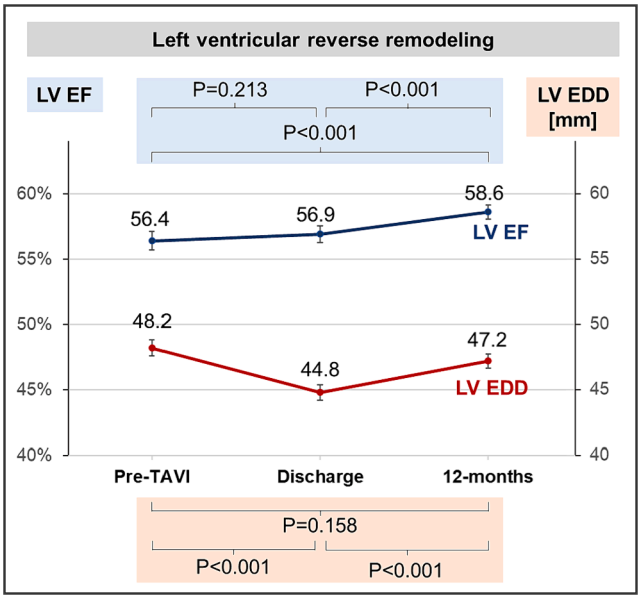

Fig. 2. Left ventricular reverse remodeling by transthoracic echocardiography. Abbreviations: LVEF – left ventricular ejection fraction, LVEDD – left ventricular end diastolic diameter, TAVI – transcatheter aortic valve implantation.

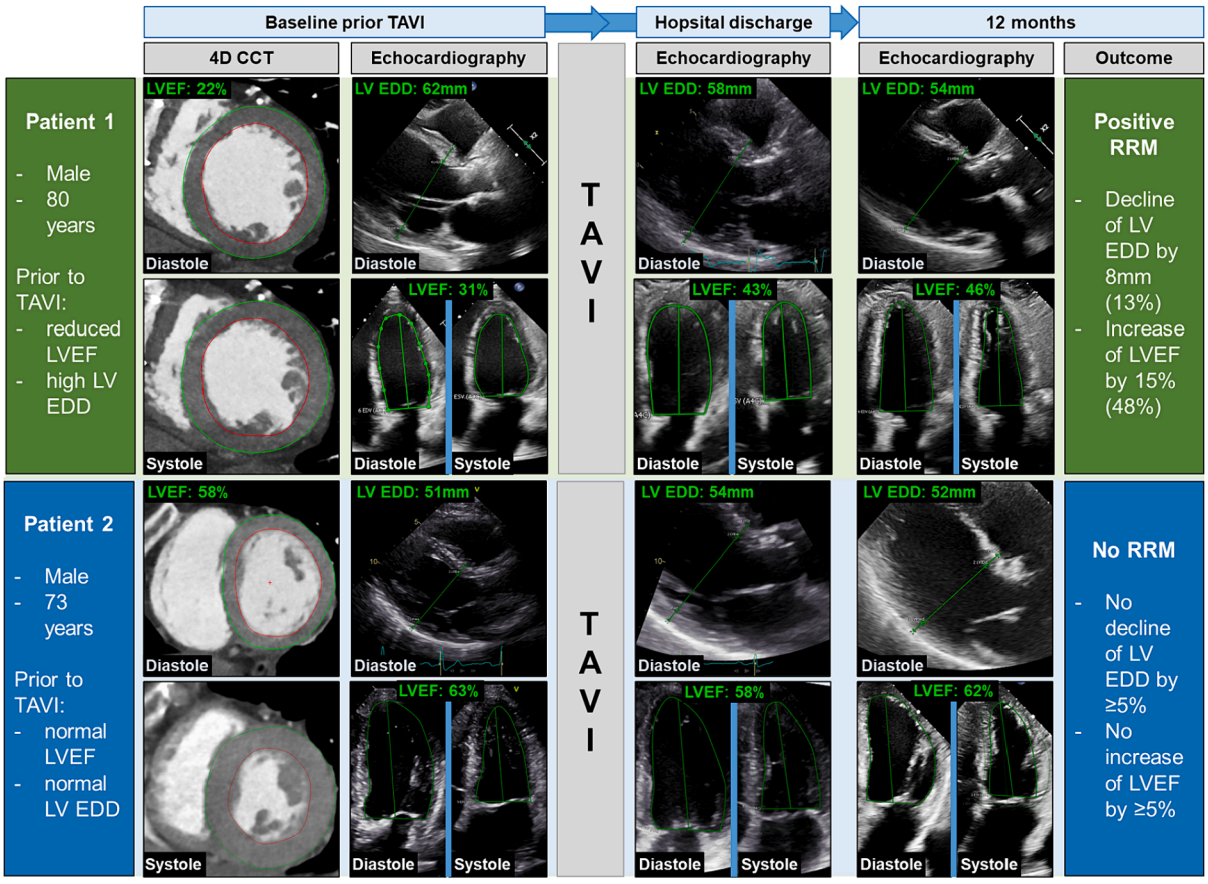

Fig. 3. 4DCCT images of a patient with normal and impaired 4DCCT based LVEF. Abbreviations: 4DCCT – 4-dimensional cardiac computed tomography, LVEDD – left ventricular end diastolic diameter, LVEF – left ventricular ejection fraction, TAVI – transcatheter aortic valve implantation.

encompassed a reference tube voltage of 100–120 kv, a reference tube-current–time product of 300 mAs_{ref} according to the body weight, a rotation time of 0.28 s, a slice collimation of 128 × 0.6 mm, and a pitch value of 0.17 for spiral acquisition 0–100 % of the RR interval. Body weight-adjusted doses of contrast agent (40–120 mL) were administered at a flow rate of 4–5 mL/s. Images were acquired during an inspiratory breath-hold in a cranio-caudal direction and reconstructed at 1 mm increments through an I30f kernel (SAFIRE, strength 3). 4DCCT datasets were reconstructed by 5 % increments to obtain a total of 20 reconstructions per cardiac cycle (0–100 %).

Image analysis was performed by an institutional core-laboratory at Bern University Hospital by investigators blinded to the clinical and echocardiographic findings. Medis Suite v.3.0 software (Medis Medical Imaging, Leiden, Netherlands) was employed for image segmentation (Medis Suite 3D Viewer), to derive LV mass and volume (Medis Suite QMass), and for feature tracking-based strain-analysis in the LV, the RV, and the left atrium (LA) (Medis Suite QStrain). Semi-automatically derived tracings of the endo- and epicardial borders were manually checked and revised at each slice in volumetrically defined end systole and end diastole. LV mass and volumes were quantified at a short-axis stack of 14–18 slices (depending on LV lengths) with a 6 mm slice thickness without any gaps between the slices. Endocardial borders were traced excluding the papillary muscles. LV global circumferential strain (GCS) and global radial strain (GRS) were evaluated in three manually selected short-axis slices at the levels of the mitral valve, papillary muscles, and the apex. LV global longitudinal strain (GLS) was computed as the average strain obtained from the 2-, 3-, and 4-chamber views. RV and LA GLS were assessed in the 4-chamber and 2-chamber views, respectively. The LA volume excluded the pulmonary veins and the left atrial appendage. LA GLS, equivalent to LA reservoir strain, was defined as the peak of the LA strain curve with ventricular end-diastole as reference value.

2.3. Study endpoints and definition of RRM

RRM was the primary endpoint of this study and was assessed by systematic evaluation of serial echocardiographic examinations at baseline, discharge, and one year, assessed in clinical practice and aligning to standardized protocols. All patients were followed clinically by standardized telephone interviews or clinic visits, documentation from referring physicians, and hospital discharge records at 30 days and one year after TAVI to assess mortality as previously described [6]. RRM was defined by the change of serial LVEF and LV end diastolic diameter (LVEDD) obtained during transthoracic echocardiography before TAVI, after TAVI before hospital discharge (2.6 ± 1.9 days after TAVI), and at 12-month (12.7 ± 2.8 months after TAVI). LVEF was assessed by Simpsons biplane method in the 2- and 4-chamber view. LVEDD was measured in parasternal long axis views. RRM was considered to be positive if a relative increase of LVEF by 5 % or a decrease of LVEDD by 5 % between two timepoints was observed.

2.4. Statistical analysis

Statistical analysis was performed using R Studio version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were presented as absolute numbers with the corresponding relative frequencies indicated in parentheses within the corresponding cohort. Continuous variables were reported as mean ± standard deviation, or if highly skewed based on the Shapiro-Wilk test, as the median and interquartile range (IQR). Chi-square tests and Fisher's exact tests

Table 3
Predictors of reverse remodeling (RRM) after TAVI.

	RRM at discharge				RRM at 12 months vs. pre-TAVI				RRM at 12 months vs. discharge			
	Odds ratio	LCI	UCI	P	Odds ratio	LCI	UCI	P	Odds ratio	LCI	UCI	P
Univariable Analysis												
Clinical data												
Age [years]	1.006	0.981	1.031	0.642	1.005	0.980	1.030	0.709	1.011	0.986	1.036	0.405
Sex [male]	0.846	0.610	1.173	0.315	0.933	0.669	1.302	0.685	0.993	0.715	1.379	0.966
Left ventricle												
EDV indexed [ml/m^2]	0.998	0.993	1.003	0.349	1.014	1.007	1.020	**<0.001**	1.014	1.008	1.021	**<0.001**
Mass indexed [g/m^2]	1.003	0.994	1.011	0.534	1.013	1.004	1.022	**0.005**	1.013	1.004	1.022	**0.005**
EF [%]	1.003	0.992	1.014	0.579	0.968	0.957	0.980	**<0.001**	0.968	0.957	0.980	**<0.001**
GLS [%]	0.989	0.956	1.023	0.532	1.086	1.047	1.126	**<0.001**	1.090	1.052	1.130	**<0.001**
GCS [%]	1.003	0.977	1.029	0.846	1.064	1.034	1.095	**<0.001**	1.058	1.029	1.087	**<0.001**
GRS [%]	1.000	0.994	1.005	0.975	0.988	0.982	0.993	**<0.001**	0.990	0.984	0.995	**<0.001**
Right ventricle												
EDA [cm^2]	0.994	0.970	1.018	0.618	1.026	1.000	1.053	**0.046**	1.018	0.993	1.044	0.150
FAC [%]	1.005	0.991	1.020	0.476	0.979	0.964	0.993	**0.005**	0.980	0.966	0.994	**0.007**
GLS [%]	1.007	0.984	1.030	0.567	1.034	1.010	1.058	**0.005**	1.038	1.014	1.062	**0.002**
Left atrium												
ESV indexed [ml/m^2]	0.994	0.987	1.001	0.075	1.007	0.999	1.014	0.069	1.013	1.005	1.021	**0.001**
EF [%]	1.009	1.000	1.019	0.052	0.983	0.973	0.992	**<0.001**	0.976	0.966	0.985	**0.000**
GLS [%]	1.013	0.996	1.030	0.129	0.975	0.960	0.991	**0.003**	0.963	0.947	0.980	**0.000**
Multivariable Model												
LV Mass indexed [g/m^2]					1.012	1.001	1.024	**0.046**	1.016	1.004	1.028	**0.008**
LV EF [%]					0.969	0.943	0.996	**0.024**	0.959	0.933	0.986	**0.003**
LV GLS [%]					0.992	0.902	1.090	0.865	0.940	0.857	1.030	0.183
RV FAC [%]					0.997	0.976	1.017	0.744	1.003	0.982	1.023	0.801
LA EF [%]					0.996	0.983	1.009	0.544	0.987	0.974	1.000	**0.046**

Abbreviations: EDA /EDV – end diastolic area /volume, EF – ejection fraction, ESV – endsystolic volume, FAC – fractional area change, GCS – global circumferential strain, GLS – global longitudinal strain, GRS – global radial strain, LV /RV – left/right ventricle, LCI – lower confidence interval, SD – standard deviation, UCI – upper confidence interval.

were employed to compare groups stratified by the death at follow-up for categorical variables, while independent t-tests and Mann-Whitney U tests were used for continuous variables. Repeated measure analysis of variance was used to test for significant differences in LVEF and LVEDD before TAVI, at hospital discharge and at 12-month. Uni- and multivariate linear regression models with the percentage change of continuous LVEF and LVEDD from baseline as dependent variables were established. Binary logistic regression was performed to evaluate the association between positive RRM as a binary outcome (yes/no) as described above, and odds ratios with corresponding 95 % confidence intervals (CI) were calculated. Survival analysis was performed with the Kaplan-Meier method and uni- and multivariate Cox regression models were utilized to estimate hazard ratios for the endpoint of mortality. Covariates for multivariable models were manually selected based on their significance in univariate analyses. To avoid potential collinearity with other variables in the model a maximal set of one LV volumetric variable (e.g. LVEF), one LV strain variable (e.g. LV GLS), LV mass, one RV variable, and one LA variable were selected for multivariable models. Term plots were generated to visualize the relationship between covariates, extent of RRM and survival probability, represented by restricted cubic splines with 5 knots. All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant.

3. Results

Out of 980 consecutive patients evaluated for TAVI between August 2019 and August 2021, 65 had no clinical indication for aortic valve replacement and 13 were referred for surgical aortic valve replacement. Among the remaining 902 patients, 260 did not undergo 4DCCT, most of them due to limited inclusion efforts during the peaks of the Covid-19 pandemic, while 24 underwent CCT at other centers with varying protocols. A total of 618 patients underwent complete 4DCCT followed by TAVI at our institution. After exclusion of 2 patients due to periprocedural death (fatal *peri*-procedural myocardial infarction and major stroke, respectively), one with non-diagnostic 4DCCT due to lack of contrast agent accumulation and 7 (1.1 %) patients with missing follow-up information, 608 patients were included in the final analysis of the study. Of those, 68 patients (11.2 %) died before follow-up echocardiography at 12-month and 87 patients (14.3 %) had insufficient transthoracic echocardiographic data due to lack of transfer from external institutions or missed echocardiographic follow-up, resulting in 453 patients (75 %) with serial echocardiographic data at 12-month (Fig. 1).

Mean age of included patients was 81.1 ± 6.6 years and the majority (337; 55.4 %) were male. Cardiovascular risk factors were frequently prevalent, and 285 (46.9 %) patients had concomitant coronary artery disease (Table 1). Dyspnea was the most common symptom for referral and about one third of patients received oral anticoagulation (215; 35.4 %) mostly due to atrial fibrillation (220; 36.2 %). 4DCCT demonstrated a slightly elevated mean LV mass index (72.0 ± 19.3 g/m^2) and preserved mean LVEF (52.3 ± 15.0 %) and LV GLS (-14.5 ± 4.8 %) (Table 2). LVEF was normal (≥51 %) in 350 (57.6 %) patients, while LA ESVi (>34 mL/m^2) was increased in 574 (94.4 %). All study participants met criteria for symptomatic severe AS; mean aortic valve gradient was 36.9 ± 16.9 mmHg, corresponding to a mean aortic valve area of 0.85 ± 0.32 cm^2 (Table 1). TAVI was conducted at a median of 22 (IQR 9–30) days after 4DCCT. The mean transaortic valve gradient decreased to 4.4 ± 3.9 mmHg as assessed by invasive hemodynamic measurement and to 10.4 ± 4.9 mmHg by echocardiographic assessment. Median heart rate in 4DCCT was 69.0 (59.8–77.5) bpm, resulting in a median temporal resolution of 23 (19.9–25.8) frames per second. Mean dose-length product

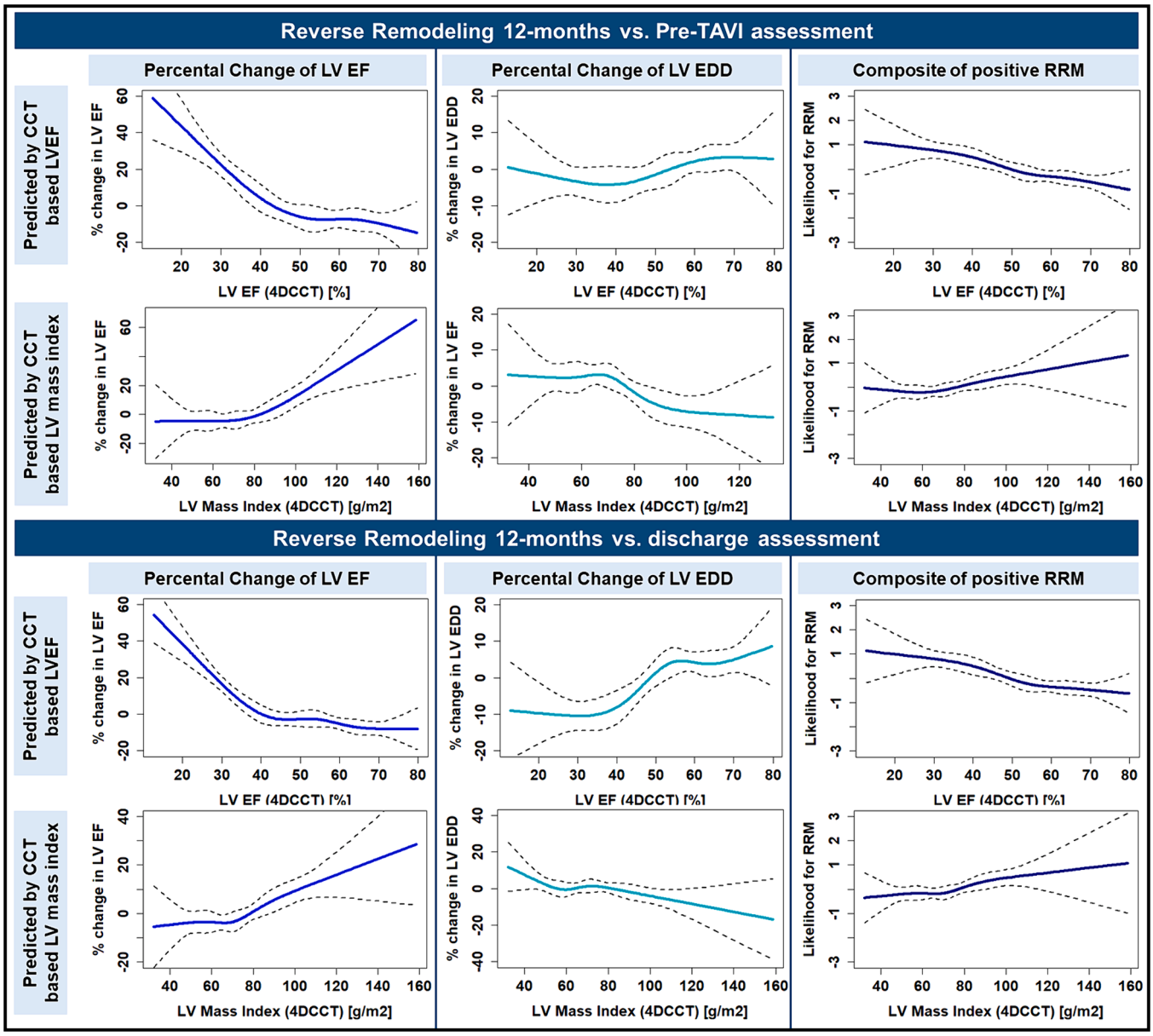

Fig. 4. 4DCCT based predictors for reverse remodeling (RRM) after TAVI. Abbreviations: 4DCCT – 4-dimensional cardiac computed tomography, EF – ejection fraction, GLS – global longitudinal strain, HR – hazard ratio, LA – left atrium, LV – left ventricle, RV – right ventricle, TAVI – transcatheter aortic valve implantation.

determined in a subsample of 269 scanned patients was 979 ± 405.8 mGycm.

Compared to pre-TAVI echocardiography, echocardiographic assessments at discharge demonstrated a decrease in mean LVEDD (48.2 ± 8.4 vs. 44.8 ± 8.4 mm; $p < 0.001$) while mean LVEF remained unchanged (56.4 ± 13.5 vs. 56.9 ± 12.7 %; $p = 0.213$) (Fig. 2). By the time of hospital discharge, the criteria for RRM were met by 279 (53.7 %) of 519 patients after TAVI. At the 12-month echocardiography follow-up, LVEF significantly increased compared to the pre-TAVI assessment (56.4 ± 13.5 % vs. 58.6 ± 10.2 %; $p < 0.001$). LVEDD increased after discharge and returned to levels comparable to those at baseline assessment (baseline: 48.2 ± 8.4 vs. discharge: 44.8 ± 8.4 vs. 12-months: 47.2 ± 7.3 mm; $p = 0.158$). Criteria for RRM at 12-month follow-up were met by 209 (48.8 %) of 428 patients compared to baseline and by 218 (48.1 %) of 453 patients compared to the echocardiographic assessment at discharge. Example cases are illustrated in Fig. 3.

RRM at discharge was not predicted by 4DCCT based measurements (Table 3). RRM at 12-month follow-up versus pre-TAVI was associated with several CCT based parameters of LV, RV and LA function of which high LV mass index (OR = 1.012; 95 %CI 1.001–1.024; $p = 0.046$) and low LVEF (OR = 0.969; 95 %CI 0.943–0.996; $p = 0.024$) were independent predictors in multivariable analysis. Accordingly, high LV mass index (OR = 1.016; 95 %CI 1.004–1.028; $p = 0.008$), low LVEF (OR = 0.959; 95 %CI 0.933–0.986; $p = 0.003$) and low LA EF (OR = 0.987; 95 %CI 0.974–1.000; $p = 0.046$) were the only independent predictors for RRM at 12-month follow-up compared to discharge echocardiography. As demonstrated in Fig. 4, RRM at 12-month versus pre-TAVI was most pronounced in patients with impaired baseline LV function and present even in patients with severely reduced LV function. Predictors by linear regression analysis for percentage changes in LVEF and LVEDD are presented in ***Supplemental Table S1 and S2***.

At median observation time of 1.0 (IQR 0.99–1.03) year, 95 patients (15.6 %) had died. Age, serum creatinine, and CCT-derived LVEF, LV GLS, LV GRS, RV GLS, LA ESVi, LA EF and LA GLS were associated with survival (Fig. 5). In multivariable analysis only age ($HR_{adj} = 1.037$; 95 %

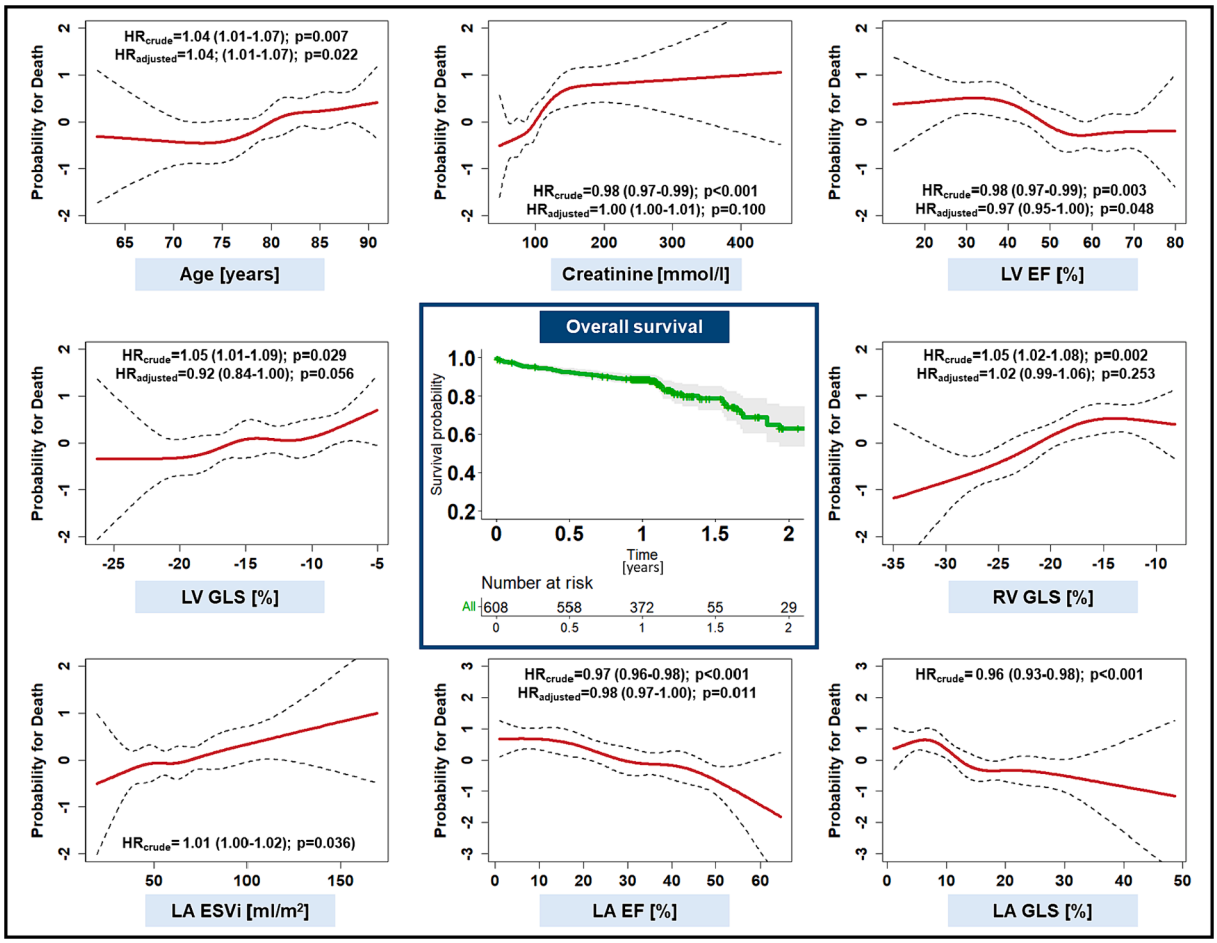

Fig. 5. Clinical and 4DCCT based predictors of survival following TAVI. Abbreviations: 4DCCT – 4-dimensional cardiac computed tomography, EF – ejection fraction, GLS – global longitudinal strain, HR – hazard ratio, LA – left atrium, LV – left ventricle, RV – right ventricle, TAVI – transcatheter aortic valve implantation.

CI:1.005–1.070; p = 0.022) and CCT-based LVEF (HR_{adj} = 0.972; 95 % CI:0.945–0.999; p = 0.048) and LA EF (HR_{adj} = 0.982; 95 % CI:0.968–0.996; p = 0.011) independently predicted mortality (Table 4). Neither RRM at discharge nor RRM at 12-month versus pre-TAVI or versus discharge translated to improved 12-month survival.

4. Discussion

In this prospective observational study, we demonstrated that post-processing myocardial analysis of 4DCCT images is able to predict both RRM and survival in patients undergoing TAVI due to severe AS. RRM occurred in about half of the TAVI patients and was best predicted by CCT-based low LVEF and high LV mass before TAVI. After adjusting for clinical variables, we found that CCT-based LVEF and LA EF showed independent associations with 12-month-survival, whereas RRM did not demonstrate a significant association. Additionally, we confirmed the feasibility of CCT-based strain analysis in the LV, RV, and LA, and although the results were associated with mortality and RRM, they did not outperform ejection fraction assessed in 4DCCT.

RRM after successful aortic valve replacement was described to encompass a reduction of LV mass, an increase in LVEF and LV GLS, a reduction in LVEDD and LVESD with consecutive improvements of diastolic function [17–24]. In our study, we investigated LVEF and LVEDD as surrogate markers for RRM and demonstrated an increase of LVEF at 12-month follow-up and a decrease of LVEDD immediately after TAVI, which however, did not persist at 12-month follow-up. RRM was most pronounced in patients with severely reduced LVEF and increased LV mass index. Our findings are in line with previous studies that demonstrated most pronounced RRM after aortic valve replacement in those with impaired LA strain [25] and impaired LVEF including in those with severely reduced LV function [6,21,26]. Rather than related to cardiac contractility, the ability for RRM to improve outcomes might be related to the extent of fibrosis and other comorbidities [27,28]. While there is strong evidence that LV remodeling (e.g. concentric LV remodeling and myocardial fibrosis) induced by severe AS is associated with poor outcomes [18,29–32], the impact of reversal of these changes is less well substantiated [13,33–35]. The absence of a significant association between RRM and survival in our study may be attributed to the fact that particularly patients with initially poor LV function showed improvement in both LVEF and LVEDD. These patients were already at a higher baseline risk of death, which might mask a survival benefit going along with RRM. Conducting larger studies with the ability to stratify results based on baseline LVEF without compromising statistical power would be valuable to further explore the potential benefits of RRM.

4DCCT strain analysis has gained increased attention to detect myocardial dysfunction and has been demonstrated to provide diagnostic and prognostic value when compared to standard anatomical and functional CCT acquisitions in several settings [11,12,16]. In our study, image quality limited the analysis of quantitative measures in only one of 618 patients (0.16 %), highlighting the potential for routine analysis of strain in various orientations by 4DCCT. Additionally, 4DCCT based strain in the LV, RV and LA was univariately associated with survival following TAVI. Severe AS is known to result in downstream structural changes that may negatively impact prognosis [36]. Consequently, there is a growing need to identify patients at an earlier stage, which may influence the decision to opt for valve replacement. While strain analysis

Table 4
Predictors of mortality after TAVI.

	Univariable analysis				Multivariable analysis			
	HR_{crude}	LCI	UCI	P-value	$HR_{adjusted}$	LCI	UCI	P-value
Clinical data								
Age [years]	**1.042**	**1.011**	**1.073**	**0.007**	**1.037**	**1.005**	**1.070**	**0.022**
Sex [male]	0.878	0.583	1.322	0.533				
BMI [kg/m^2]	0.966	0.927	1.006	0.091				
Creatinine [mmol/l]	**0.979**	**0.970**	**0.989**	**<0.001**	1.002	1.000	1.005	0.100
Left ventricle								
EDV indexed [ml/m^2]	0.998	0.991	1.005	0.526				
Mass indexed [g/m^2]	0.999	0.988	1.010	0.858				
EF [%]	**0.981**	**0.968**	**0.994**	**0.003**	**0.972**	**0.945**	**0.999**	**0.048**
GLS [%]	**1.048**	**1.005**	**1.094**	**0.029**	0.916	0.838	1.002	0.056
GCS [%]	1.030	0.999	1.061	0.059				
GRS [%]	**0.987**	**0.979**	**0.995**	**0.002**				
Right ventricle								
EDA [cm^2]	1.017	0.987	1.047	0.266				
FAC [%]	0.982	0.964	1.000	0.044				
GLS [%]	**1.047**	**1.018**	**1.078**	**0.002**	1.021	0.985	1.057	0.253
Left atrium								
ESV indexed [ml/m^2]	**1.009**	**1.001**	**1.017**	**0.036**				
EF [%]	**0.972**	**0.961**	**0.984**	**<0.001**	**0.982**	**0.968**	**0.996**	**0.011**
GLS [%]	**0.955**	**0.931**	**0.979**	**<0.001**				
Reverse Remodeling								
RRM at discharge	1.035	0.647	1.656	0.887				
RRM at 12 M vs. pre-TAVI	0.771	0.301	1.978	0.588				
RRM at 12 M vs. discharge	0.485	0.183	1.289	0.147				

Abbreviations: BMI – body mass index, EDA /EDV – end diastolic area /volume, EF – ejection fraction, ESV – endsystolic volume, FAC – fractional area change, GCS – global circumferential strain, GLS – global longitudinal strain, GRS – global radial strain, LV /RV – left/right ventricle, LCI – lower confidence interval, RRM – reverse remodeling, UCI – upper confidence interval.

may be helpful in this context, our study found that less time-intensive assessments of LVEF and LA EF provided superior prognostic value. These results remained significant even after adjusting for clinical variables such as age and creatinine. The unexpected findings could potentially be attributed to the pronounced effect of afterload relief achieved by TAVI, which appears to have a stronger impact on LV GLS compared to LVEF [20,37,38]. LV GLS before the intervention might therefore be less feasible as an outcome predictor when directly compared to LVEF which is also a highly reproducible parameter when assessed by 4DCCT [8].

Non-invasive analyses from CCT are essential in the Heart Team evaluation of patients with severe AS serving as indispensable tools to support the choice between TAVI and surgical valve replacement [1]. Our study demonstrated that additional information can be extracted from 4DCCT imaging without exposing patients to additional diagnostic procedures and associated risks or an increase of radiation dosage. All these aspects support the routine-analysis of 4DCCT quantitative imaging parameters such as LV and LA ejection fraction to improve risk stratification in patients evaluated for TAVI.

4.1. Limitations

The findings of this study are subject to several limitations. RRM was assessed by echocardiography, while predictors associated with RRM were derived from 4DCCT. Although measurements from both modalities correlate with each other, exact values and cutoff values are not interchangeable [8,39]. We did not apply a reference standard for LVEF or LVEDD like cardiac magnetic resonance to determine RRM and our study was limited to the investigation of only two surrogate markers of RRM. The cutoff for RRM was set at a 5 % change of LVEDD and LVEF. It is unclear if this represents a significant change with meaningful implications for patients. However, we also provided results for continuous changes of LVEF and LVEDD and results were consistent with findings from cutoff based logistic regression. Furthermore, we did not collect further endpoints such as heart failure hospitalizations that might be more strongly associated with 4DCCT based strain measurements and RRM than all-cause mortality. Finally, echocardiography image acquisition was performed in clinical practice following standardized protocols. Image acquisition by expert readers in a core laboratory could have increased reliability of findings for RRM.

5. Conclusions

In patients with severe AS referred for TAVI, comprehensive quantitative information of myocardial functional from clinically indicated routine 4D computed tomography can predict reverse remodeling and clinical outcomes following TAVI and should be implemented to improve risk stratification in this clinical setting.

CRediT authorship contribution statement

Benedikt Bernhard: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jonathan Schütze:** Writing – review & editing, Writing – original draft, Visualization, Validation, Investigation, Formal analysis, Data curation. **Zoe L. Leib:** Writing – original draft, Investigation, Formal analysis. **Giancarlo Spano:** Writing – original draft, Formal analysis. **Martina Boscolo Berto:** Writing – original draft, Investigation, Formal analysis. **Adam Bakula:** Investigation. **Daijiro Tomii:** Writing – original draft, Investigation, Data curation, Conceptualization. **Isaac Shiri:** Formal analysis. **Nicolas Brugger:** Resources. **Stefano De Marchi:** Writing – original draft, Resources. **David Reineke:** Resources. **Stephan Dobner:** Writing –

original draft, Resources, Investigation. **Dik Heg:** Methodology, Formal analysis. **Fabien Praz:** Resources, Investigation. **Jonas Lanz:** Resources, Investigation. **Stefan Stortecky:** Resources, Project administration. **Thomas Pilgrim:** Writing – original draft, Supervision, Project administration, Investigation. **Stephan Windecker:** Writing – original draft, Supervision, Resources, Investigation, Conceptualization. **Christoph Gräni:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Bernhard reports a career development grant from the Swiss National Science Foundation. Dr. Dobner reports travel grants from Pfizer and Alnylam, speaking fees from Boehringer Ingelheim. D. Heg is employed by the CTU Bern, University of Bern, which has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in design, conduct, or analysis of clinical studies funded by not-for-profit and for-profit organizations. In particular, pharmaceutical and medical device companies provide direct funding to some of these studies. Dr. Stortecky reports research grants to the institution from Edwards Lifesciences, Medtronic, Boston Scientific and Abbott, as well as personal fees from Boston Scientific, Teleflex and BTG. Dr. Pilgrim reports research grants to the institution from Biotronik, Boston Scientific and Edwards Lifesciences; speaker fees from Biotronik, Boston Scientific, Abbott, and Medtronic; Clinical event committee for study sponsored by HighLifeSAS. Stephan Windecker reports research, travel or educational grants to the institution without personal remuneration from Abbott, Abiomed, Amgen, Astra Zeneca, Bayer, Braun, Biotronik, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardinal Health, CardioValve, Cordis Medical, Corflow Therapeutics, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Farapulse Inc. Fumedica, Guerbet, Idorsia, Inari Medical, InfraRedx, Janssen-Cilag, Johnson & Johnson, Medalliance, Medicure, Medtronic, Merck Sharp & Dohm, Miracor Medical, Novartis, Novo Nordisk, Organon, OrPha Suisse, Pharming Tech. Pfizer, Polares, Regeneron, Sanofi-Aventis, Servier, Sinomed, Terumo, Vifor, V-Wave. Stephan Windecker served as advisory board member and/or member of the steering/executive group of trials funded by Abbott, Abiomed, Amgen, Astra Zeneca, Bayer, Boston Scientific, Biotronik, Bristol Myers Squibb, Edwards Lifesciences, MedAlliance, Medtronic, Novartis, Polares, Recardio, Sinomed, Terumo, and V-Wave with payments to the institution but no personal payments. He is also member of the steering/executive committee group of several investigator-initiated trials that receive funding by industry without impact on his personal remuneration. Dr. Gräni further received funding from the Swiss National Science Foundation, InnoSuisse, from the Center for Artificial Intelligence in Medicine Research Project Fund University Bern and Gambit foundation, outside of the submitted work. All other authors report no conflicts.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejrad.2024.111425.

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