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# Prognostic Influence of Feature Tracking Multidetector Row Computed Tomography-Derived Left Ventricular Global Longitudinal Strain in Patients with Aortic Stenosis Treated With Transcatheter Aortic Valve Implantation

Tea Gegenava, MD, PhD<sup>a</sup>, Pieter van der Bijl, MBChB, MMed<sup>a</sup>, E. Mara Vollema, MD<sup>a</sup>, Frank van der Kley, MD<sup>a</sup>, Arend de Weger, MD<sup>b</sup>, David Hautemann, MSc<sup>c</sup>, Johan H.C. Reiber, PhD<sup>c</sup>, Nina Ajmone Marsan, MD, PhD<sup>a</sup>, Jeroen J. Bax, MD, PhD<sup>a</sup>, and Victoria Delgado, MD, PhD<sup>a,\*</sup>

> Computed tomography plays a central role in the evaluation of patients with severe aortic stenosis who underwent transcatheter aortic valve implantation (TAVI). Advances in left ventricular (LV) analysis with multidetector row computed tomography (MDCT) permit measurement of LV global longitudinal strain (GLS). The present study aimed at evaluating the association between feature tracking (FT) MDCT derived LV GLS and all-cause mortality in patients treated with TAVI. A total of 214 patients with severe aortic stenosis (51% male,  $80 \pm 7$  years) who underwent TAVI and with dynamic MDCT data allowing LV GLS measurement with novel FT algorithm were included. LV GLS was measured at baseline and were divided according to a previously published cut-off value of LV GLS associated with all-cause mortality (<-14% [more preserved LV systolic function] vs >-14% [more impaired LV systolic function]). Patients were followed for the occurrence of all-cause mortality. Mean FT MDCT-derived LV GLS was  $-12.5 \pm 4\%$ . During a median follow-up of 45 months (interguartile range: 29 to 62 months), 67 (31%) patients died. The cumulative rate of all-cause mortality for the patients with FT MDCT-derived LV GLS  $\leq -14\%$  was 15% versus 28% for the patients with FT MDCT-derived LV GLS > -14%, Log rank p = 0.001). FT MDCT-derived LV GLS was independently associated with all-cause mortality (hazard ratio: 0.851; 95% confidence interval: 0.772 to 0.937; p=0.001). In conclusion, impaired FT MDCTderived LV GLS is independently associated with all-cause mortality in patients treated with TAVI. Besides aortic valve area and calcification, FT MDCT-derived LV GLS is an important prognostic marker. © 2019 Elsevier Inc. All rights reserved. (Am J Cardiol 2020;125:948-955)

Transcatheter aortic valve implantation (TAVI) is a minimally invasive treatment option for patients with severe aortic stenosis (AS) regardless of the operative risk.<sup>1-4</sup> Currently, this treatment is recommended in symptomatic severe AS and

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0002-9149/© 2019 Elsevier Inc. All rights reserved. https://doi.org/10.1016/j.amjcard.2019.12.024 are at least at intermediate operative risk.<sup>5</sup> Left ventricular ejection fraction (LVEF) is one of the prognostic markers in patients with severe AS. However, LVEF may not be the ideal parameter for risk stratification of patients with severe AS since it may remain within the normal range for a long time despite changes in the myocardial structure such as hypertrophy and replacement fibrosis.<sup>6</sup> In contrast, left ventricular (LV) global longitudinal strain (GLS) has been shown to correlate better with LV remodeling induced by pressure overload and has incremental prognostic value over LVEF.7-9 Feature tracking (FT) multidetector row computed tomography (MDCT) data analysis permits assessment of LV GLS and may become an important adjuvant tool for risk stratification of patients with severe AS by adding functional data to well-known anatomical prognostic parameters such as aortic valve calcification burden.<sup>10</sup> The present study evaluated the association between FT MDCT-derived LV GLS and allcause mortality in patients with severe AS who underwent TAVI. In addition, the incremental prognostic value of FT MDCT-derived LV GLS over anatomical prognostic markers such as aortic valve area and aortic valve calcification was investigated.



<sup>&</sup>lt;sup>a</sup>Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands; <sup>b</sup>Department of Cardio-Thoracic surgery, Leiden University Medical Center, Leiden, The Netherlands; and <sup>c</sup>LKEB, Leiden University Medical Center, Leiden, The Netherlands. Manuscript received September 15, 2019; revised manuscript received and accepted December 17, 2019.

<sup>1.</sup> All authors have participated in the work and have reviewed and agree with the content of the article.

See page 953 for disclosure information.

<sup>\*</sup>Corresponding author: Tel: +31715262020; fax: +31715266809. *E-mail address:* v.delgado@lumc.nl (V. Delgado).

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## Methods

This retrospective analysis included a total of 214 patients with severe AS, treated with TAVI who underwent MDCT and had complete echocardiographic evaluation within 3 months of the MDCT data acquisition. Of 230 randomly selected patients of the overall population treated with TAVI between December 2007 and July 2017, 16 patients were excluded because of lack of appropriate computed tomography data for analysis. Severe AS was defined according to current recommendations: an aortic valve area

<1.0 cm<sup>2</sup> or indexed aortic valve area <0.6 cm<sup>2</sup>/m<sup>2</sup>, peak aortic jet velocity  $\geq$ 4 m/s and a mean transvalvular pressure gradient  $\geq$ 40 mm Hg.<sup>11</sup> For retrospective analysis of clinically acquired data the institutional review board waived the need for written patient informed consent.

Clinical data included demographics, cardiovascular risk factors, symptoms, medications, and operative mortality risk calculated according to the logistic European System for Cardiac Operative Risk Evaluation (euroSCORE). All clinical data were collected from the Cardiology Department Information System (EPD-Vision; Leiden University



Figure 1. Assessment of left ventricular global longitudinal strain with feature tracking multi-detector row computed tomography. MDCT feature tracking in left ventricular 2-chamber (panel A), 3-chamber (panel B) and 4-chamber (panel C) views formatted via multiplanar reconstruction and processed with the help of QMass. After analysis in QMass, strain plots (Panel D), bull's eye (panel E) and dynamic MDCT 3D images (Panel F) are derived. Abbreviations: MDCT = multi-detector row computed tomography.

Medical Centre, Leiden, The Netherlands) and retrospectively analyzed. TAVI patients were followed-up at the outpatient clinic or respective referral centers. Data on allcause mortality was gathered from medical records and the municipal civil registries.

Commercially available ultrasound systems equipped with M5S transducers (Vivid-7 or E9 systems, General Electric Vingmed, Horten, Norway) were used to acquire 2-dimensional, color, continuous, and pulsed wave Doppler data from parasternal and apical views with the patient in the left lateral decubitus position. Images were stored digitally on hard disks for offline analysis (EchoPac version 202; GE Medical Systems). LV end-diastolic and end-systolic volumes were measured on the apical 2- and 4-chamber views using the Simpson's method and the LVEF was derived.<sup>12</sup> Aortic valve peak jet velocity was estimated from continuous wave Doppler recordings obtained in the 3- or 5-chamber apical views and, if needed, on the right parasternal view using a Pedoff probe. The peak and mean transaortic pressure gradients were calculated according to the modified Bernoulli equation. The aortic valve area was calculated using the continuity equation.<sup>1</sup>

Multidetector row computed tomography scans were performed before TAVI using a 320-row computed tomography scanner (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan).<sup>13</sup> Contrast-enhanced MDCT data were acquired and data processing was performed using a remote workstation with dedicated MDCT data analysis software (Vitrea FX 1.0, Vital Images, Minnetonka, Minnesota). Additional functional reconstructions for dynamic assessment and quantification of LV GLS were created with the novel FT software (Medis Suite CT v3.1 Medis Medical Imaging Systems, Leiden, The Netherlands) (Figure 1). From the 3-dimensional multiplanar reconstructions, the 4-, 2- and 3-chamber LV views were rendered. Subsequently, the endocardial borders of the LV were traced in each view at end-diastole and end-systole and automatically interpolated to the remaining cardiac phases. LV GLS was then measured using FT, tracking of points or "features" across multiple images based on pattern-matching techniques. A point is tracked by defining a small patch around the pixel in one frame and finding the most similar patch of pixels in the next image frame allowing motion tracking through successive frames. Patients were divided according to a cut-off value of LV GLS of -14%. Patients with an FT MDCT-derived LV GLS  $\leq -14\%$  were considered to have more preserved LV systolic function whereas patients with an FT MDCT-derived LV GLS >-14% formed the group with more impaired LV systolic function. This cut-off value was based on previous literature correlating LV GLS and prognosis in patients with severe AS.<sup>14</sup>

Continuous variables are presented as mean  $\pm$  standard deviation if normally distributed or as median and interquartile range otherwise. Categorical variables are presented as frequencies and percentages. Cumulative event rates were analyzed based on Kaplan-Meier survival method for patients with FT MDCT-derived LV GLS  $\leq$ -14% and FT MDCT-derived LV GLS >-14% compared with the log-rank test. The association between FT MDCT-derived LV GLS and all-cause mortality was assessed with uni- and multivariable Cox regression analyses. In the multivariable analysis,

clinical and echocardiographic variables known to influence the outcome of patients treated with TAVI were included. The level of significance for variables to be included in the multivariable analysis was set at p <0.10. The hazard ratio and 95% confidence interval are presented. Statistical analysis was performed on SPSS for Windows version 23.0 (IBM, Armonk, New York). A 2-tailed p value <0.05 was considered statistically significant.

# Results

Clinical, echocardiographic and MDCT characteristics of the overall population are presented in Tables 1 and 2. Patients were characterized by a high prevalence of cardiovascular disease risk factors and co-morbidities. The procedural characteristics and outcomes are presented in Table 1. MDCT demonstrated a high calcification burden of the aortic valve (3134 ± 1518 Hounsfield units) and the mean FT MDCT-derived LV GLS was  $-12.5 \pm 4\%$  (Table 2). Patients were divided into 2 groups according to a prespecified cut-off value of FT MDCT LV GLS ( $\leq -14\%$  [more preserved LV systolic function] vs >-14% [more impaired LV systolic function]). Seventy-one (33%) patients had FT MDCT-derived LV GLS  $\leq -14\%$  and 143 (67%) a FT MDCT-derived LV GLS value >-14%.

Table 1

Baseline clinical and procedural characteristics of total TAVI population

Variable	Total population (n=214)
Age (years)	$80\pm7$
Men	110 (51%)
EuroSCORE $\geq 20$	83(39%)
Prior coronary artery disease	130 (61%)
Hypertension	162 (76%)
Hypercholesterolemia*	145 (68%)
Diabetes mellitus	56 (26%)
Peripheral vascular disease	62 (29%)
Current smoker	54 (25%)
NYHA class III-IV	122 (57%)
Glomerular filtration rate, (mL/min/1.73 m <sup>2</sup> )	$59 \pm 23$
Medication	
β-Blocker	126 (59%)
Angiotensin-converting enzyme inhibitor/	114 (53%)
Angiotensin receptor blocker	
Calcium channel blocker	57 (27%)
Diuretic	123 (57%)
Statin	139 (65%)
Aspirin and/or clopidogrel	123 (57%)
Vitamin K antagonist or NOAC	76 (35%)
Procedure related variables	
Moderate-severe paravalvular aortic regurgitatio	n 24 (12%)
Pacemaker implantation (after TAVI)	19 (9%)
Complication vascular $(any)^{\dagger}$	31 (15%)
Procedural approach (transfemoral)	143 (67%)

euroSCORE = European system for cardiac operative risk evaluation; NOAC = novel oral anticoagulants; NYHA = New York Heart Association; TAVI = transcatheter aortic valve implantation.

\* Hypercholeterolemia is defined as total cholesterol >5.2mmol/l and/or presence of lipid lowering treatment.

 $^{\dagger}$  includes: hematoma, dissection, an eurism formation, minor and major bleeding.

Table 2

Variable	Total population (n=214)
Systolic blood pressure (mm Hg)	$138 \pm 24$
Diastolic Blood pressure (mm Hg)	$70 \pm 12$
Pulse pressure, mm Hg (SBP-DBP)	$69 \pm 21$
Pre-procedural echocardiographic findings:	
Aortic valve area $(cm^2)$	$0.8 \pm 0.2$
Mean aortic valve gradient (mm Hg)	$41 \pm 18$
Peak gradient (mm Hg)	$65 \pm 26$
Left ventricular ejection fraction (%)	$47 \pm 10$
Stroke volume index (ml/m <sup>2</sup> )	$44 \pm 16$
Left ventricular end-diastolic volume (mL)	$94 \pm 33$
Left ventricular end-systolic volume (mL)	$53 \pm 26$
Left ventricle mass (g)	$211 \pm 77$
Left ventricle mass index $(g/m^2)$	$114 \pm 43$
MDCT findings	
Aortic valve calcium burden (AU)	$3134 \pm 1518$
FT MDCT-LV GLS (%)	$-12.5 \pm 4$

FT MDCT LV GLS = feature tracking multi-detector row computed tomography derived left ventricular global longitudinal strain; GLS = left ventricular global longitudinal strain; SVi = stroke volume index; TAVI = transcatheter aortic valve implantation.

During a median follow-up of 45 months (interquartile range: 29 to 62 months), 67 (31%) patients died. The Kaplan-Meier survival analysis shows that TAVI recipients with FT MDCT-derived LV GLS >-14% (more impaired LV systolic function) experienced higher cumulative rates of all-cause mortality, compared with patients with FT MDCT-derived LV GLS  $\leq -14\%$  (Chi-square 10.615; Log rank p = 0.001) (Figure 2). At 48 months of follow-up the cumulative rate of all-cause mortality for the patients with FT MDCT-derived LV GLS  $\leq -14\%$  was 15% versus 28% for the patients with FT MDCT-derived LV GLS >-14%. On uni- and multivariate Cox-regression models, FT MDCT-derived LV GLS (as a continuous variable) demonstrated significant association with all-cause mortality (hazard ratio: 0.851; 95% confidence interval: 0.772 to 0.937; p = 0.001) (Table 3).

When investigating the incremental prognostic value of FT MDCT-derived LV GLS over clinical variables and echocardiographic findings, we observed, that after the addition of LVEF to the clinical model (age, presence of coronary artery disease, and kidney function), the predictive value of the model increased (chi-square = 16.605; p = 0.045), but the increase was more prominent when adding FT MDCT-derived



Figure 2. Kaplan-Meier survival curves for patients treated with transcatheter aortic valve implantation, divided according to the baseline FT MDCT derived LV GLS. Abbreviations: FT MDCT = feature tracking multidetector row computed tomography; LV GLS = left ventricular global longitudinal strain.

Table 3

Uni- and multivariable Cox regression analysis for all-cause mortality in total TAVI population

Variable	Univariable analysis		Multivariable analysis	
	HR (95% confidence interval)	p value	HR (95% confidence interval)	p value
Age (years)	0.966 (0.940-0.993)	0.013	0.898 (0.859-0.938)	<0.001
Men	1.296 (0.799-2.102)	0.293		
Hypertension	0.993 (0.558-1.766)	0.980		
Diabetes mellitus	1.094 (0.642-1.862)	0.742		
Prior coronary artery disease	0.978 (0.596-1.605)	0.929	0.964 (0.562-1.655)	0.896
Current smoker	1.144 (0.688-1.902)	0.603		
Glomerular filtration rate (mL/min/1.73 m <sup>2</sup> )	0.994 (0.983-1.006)	0.343	0.981 (0.967-0.995)	0.009
NYHA (class III-IV)	1.279 (0.785-2.085)	0.323		
Aortic valve area $(cm^2)$	0.971 (0.398-2.421)	0.950		
Aortic valve calcium score, (AU/1000)	0.804 (0.601-1.075)	0.141		
Mean aortic valve gradient (mm Hg)	0.994 (0.980-1.008)	0.404		
Left ventricular ejection fraction VEF (%)	1.014 (0.988-1.040)	0.298	1.060 (1.019-1.102)	0.004
Left ventricular end-diastolic volume (ml)	1.001 (0.994-1.007)	0.791		
Left ventricular end-systolic volume (ml)	0.996 (0.987-1.006)	0.459	0.987 (0.976-0.999)	0.028
Left ventricle mass index $(g/m^2)$	0.999 (0.994-1.004)	0.797		
sPAP (mm Hg)	1.012 (0.996-1.028)	0.152	1.016 (0.998-1.035)	0.083
FT MDCT LV GLS (%)	0,939 (0,884-0.996)	0.038	0.851 (0.772-0.937)	0.001
Significant paravalvular aortic regurgitation	0.895 (0.424-1.889)	0.771		
Pacemaker implantation (after TAVI)	0.754 (0.302-1.881)	0.545		
Complication, vascular (any)*	0.935 (0.463-1.889)	0.852		

FT MDCT LV GLS = feature tracking multi-detector row computed tomography derived left ventricular global longitudinal strain; LV GLS = left ventricular global longitudinal strain; NYHA = New York Heart Association; sPAP = systolic pulmonary artery pressure; TAVI = transcatheter aortic valve implantation.

\* includes: hematoma, dissection, aneurism formation, minor and major bleeding.

LV GLS to the model including clinical and echocardiographic findings (Chi-square = 29.187; p <0.001) (Figure 3).

#### Discussion

The present study demonstrates that FT MDCT-derived LV GLS is associated with all-cause mortality in patients who underwent TAVI. Patients with impaired FT MDCT-derived LV GLS showed worse survival compared with patients with more preserved FT MDCT-derived LV GLS.

MDCT is currently the imaging technique of choice to evaluate patients with severe AS who underwent TAVI. MDCT is the most reproducible and accurate method to assess the dimensions of the aortic annulus (key to select the prosthesis size) and the anatomical suitability for transfemoral access. Furthermore, MDCT provides valuable information on the severity of the AS based on calcification burden of the aortic valve (particularly in patients with discordant grading of AS based on echocardiography), anatomical relation with coronary ostia, dimensions of the aortic root and ascending aorta and information for the procedural planning such as the predicted fluoroscopic angles to safely and successfully deploy the transcatheter heart valve.<sup>15-20</sup>

With dynamic data acquired along the entire cardiac cycle, LV systolic function can be measured based on LVEF, an important parameter in the risk stratification of patients with severe AS. Currently established new MDCT technology based on detection and tracking of the endocardial border allows measurement of LV GLS. Few studies evaluating feasibility of FT MDCT-derived LV GLS are performed in AS patients with relatively small populations. Fukui et al. observed in 123 patients who underwent TAVI therapy, that FT MDCT-derived LV GLS assessment is feasible and might be helpful in patients with sinus rhythm and difficult transthoracic echocardiographic images.<sup>21</sup> Feasibility of MDCT-derived LV GLS was confirmed in smaller studies evaluating patients who underwent TAVI and showed improvement on short-term follow-up.<sup>22,23</sup>

Studies have demonstrated that 2-dimensional transthoracic echocardiography derived LV GLS can detect early subtle myocardial dysfunction in AS patients while 2dimensional LVEF lacks accuracy to identify early changes in LV systolic function.<sup>8,24</sup> Ng et al. showed in 688 patients with AS that LV GLS is independently associated with allcause mortality.<sup>14</sup> Vollema et al. observed in asymptomatic patients with severe AS and preserved LVEF that impaired LV GLS at baseline is associated with an increased risk for progression to the symptomatic stage and the need for aortic valve intervention.<sup>7</sup> A recent meta-analysis by Magne et al. including 10 studies and 1067 asymptomatic patients with significant AS and preserved LVEF showed prognostic significance of LV GLS.<sup>25</sup>

Fukui and coworkers have reported on the association between MDCT-derived LV GLS and outcomes of 223 patients treated with TAVI.<sup>26</sup> The authors provided a different cut-off value of LV GLS (-20.5%) based on receiver operating characteristic curve analysis and divided the population according to the presence of preserved LVEF with or without impaired LV GLS and patients with impaired LVEF. Patients with preserved LVEF had lower all-cause mortality as compared with patients with reduced LVEF independently of the value of LV GLS. The present study provides further insight by showing the association between



Figure 3. Prognostic value of FT MDCT LV GLS, calculated with Chi-square over clinical variables and echocardiographic findings, Model 1 (including age, presence of coronary artery disease, renal function), Model 2 (added LVEF), Model 3 (added FT MDCT LV GLS). Abbreviations: FT MDCT LV GLS = feature tracking multidetector row computed tomography derived left ventricular global longitudinal strain; LVEF = left ventricular ejection fraction.

FT MDCT-derived LV GLS and all-cause mortality in severe AS patients who underwent TAVI. Patients with reduced LV longitudinal function as measured on FT MDCT showed worse survival, compared with patients with normal values of FT MDCT-derived LV GLS. The cut-off value of LV GLS was lower than that reported by Fukui et al.<sup>26</sup> since our population has lower values of LVEF (50.7  $\pm$  14.5% vs 47  $\pm$  10%, respectively).

Since MDCT acquisition is routinely used for TAVI planning and temporal resolution of newer scanners is increasing, the additional LV GLS information from MDCT datasets might be helpful in AS patients allowing a holistic evaluation of these patients.

Some limitations should be acknowledged. First, only patients with ECG-gated MDCT data acquired throughout the entire cardiac cycle were included and therefore the present results may not be applicable to patients in whom ECGgated MDCT data acquired through the entire cardiac cycle may be challenging (eg, atrial fibrillation with high heart rate). Furthermore, there may be a selection bias that resulted in a subgroup of patients with more reduced LVEF than that reported in other series. FT MDCT-derived LV GLS has not been validated against a gold standard, such as sonomicrometry or another 3-dimensional imaging technique.

#### Disclosures

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#### **Appendix.** Author contributions

Tea Gegenava	Conception and design of the study; collec- tion, analysis and interpretation of data; drafting of the manuscript; final approval of the manuscript
Pieter van der Bijl	Conception and design of the study; collec- tion, analysis and interpretation of data; final approval of the manuscript
E. Mara Vollema	Conception and design of the study; collec- tion, analysis and interpretation of data; final approval of the manuscript
Frank van der Kley	Conception and design of the study; revision of the manuscript; final approval of the manuscript
Arend de Weger	Conception and design of the study; revision of the manuscript; final approval of the manuscript

David Hautemann	Conception and design of the study; revision of the manuscript; final approval of the manuscript
Johannes HC Reiber	Conception and design of the study; revision of the manuscript; final approval of the manuscript
Nina Ajmone Marsan	Conception and design of the study; revision of the manuscript; final approval of the manuscript
Jeroen J. Bax	Conception and design of the study; revision of the manuscript; final approval of the manuscript
Victoria Delgado	Conception and design of the study; collec- tion, analysis and interpretation of data; drafting of the manuscript; final approval of the manuscript

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