Original article

Comprehensive Myocardial Assessment by Computed Tomography: Impact on Short-Term Outcomes after Transcatheter Aortic Valve Replacement

Hideki Koike, MD^a, Miho Fukui, MD, PhD^a, Thomas Treibel, MD, PhD^d, Larissa I Stanberry, PhD^a, Victor Y. Cheng, MD^b, Maurice Enriquez-Sarano, MD^{b,c}, Stephanie Schmidt, RDCS (AE, PE)^a, Erik B. Schelbert, MD^b, Cheng Wang, MD^c, Atsushi Okada, MD, PhD^c, Asa Phichaphop MD^c, Paul Sorajja, MD^{b, c}, Vinayak N. Bapat, MD^{b, c}, Jonathon Leipsic, MD^e, John R Lesser, MD^{b, c}, João L. Cavalcante, MD^{a, b, c}.

^aCardiovascular Imaging Research Center and Core Lab at Minneapolis Heart Institute Foundation, Minneapolis, MN, USA.

^bAllina Health Minneapolis Heart Institute at Abbott Northwestern Hospital, Minneapolis, MN, USA.

^cValve Science Center, Minneapolis Heart Institute Foundation, Minneapolis, MN, USA. ^dInstitute of Cardiovascular Science, University College London, and Barts Heart Centre, St Bartholomew Hospital, London.

^eDepartment of Radiology, University of British Columbia, Vancouver, BC, Canada.

Brief title: CT-ECV and GLS Pre-TAVR Relates to Outcomes

The total number of pages (words) for manuscript: 21 pages (4,886 < 5,000 words) The total number of figures and tables: 5 and 4 (including the central image)

Corresponding author:

João L. Cavalcante MD, FACC Director, Cardiac MRI and Structural CT Labs Minneapolis Heart Institute, Abbott Northwestern Hospital Director, Cardiovascular Imaging Center and Core Lab Minneapolis Heart Institute Foundation 920 E 28th Street, Suite 100 Minneapolis, MN, 55407 Phone: 412-552-8328, Fax: 612-863-3784 Email: Joao.Cavalcante@allina.com

Grant: This research work was supported unrestricted research grant by Ziosoft.

Conflict of interest:

Dr. Treibel is a shareholder of Mycardium AI Ltd.

Dr. Enriquez-Sarano has received consulting fees from Cryolife, Edwards Lifescience, Highlife, and ChemImage.

Dr. Sorajja has received consulting fees from 4C Medical, Anteris, Abbott Structural, Boston Scientific, Edwards Lifesciences, Evolution Medical, Foldax, GLG, Medtronic, Phillips, Siemens, Shifamed, WL Gore, vDyne, xDot; has Executive Committees as REPAIR MR Steering Committee, EXPAND Steering Committee, WL Gore Pipeline Executive Committee, SUMMIT Steering Committee, TRILUMINATE Steering Committee, TRILUMINATE Eligibility Committee For Anatomy, G4 Adverse Leaflet Events Committee, and Neovasc Executive Steering Committee; is a National or Global Principal Investigator as TRILUMINATE Pivotal US Trial, SUMMIT MAC Pivotal Trial, EXPAND EFS and Pivotal US Trial, HighLife (USA) EFS, VDyne EFS, SOAR EFS, and AMEND EFS.

Dr. Bapat has received consulting fees from Abbott Structural, Boston Scientific, Edwards Lifesciences, and Medtronic.

Dr. Leipsic has received consulting fees from Circle CVI; Personal CT core lab fees from MVRX; Institutional core lab fees from Boston Scientific, Abbott, Medtronic, Edwards Lifesciences, and PI Cardia.

Dr. Cavalcante has received consulting fees from 4C Medical, Abbott Structural, Anteris, AriaCV, Boston Scientific, Edwards Lifesciences, Medtronic, VDyne, WL Gore, Xylocor; has received research grant support from Abbott Northwestern Hospital Foundation.

The remaining authors have nothing to disclosure.

Abstract

Background: Quantification of myocardial changes in severe aortic stenosis (AS) is prognostically important. The potential for comprehensive myocardial assessment pre-transcatheter aortic valve replacement (TAVR) by computed tomography angiography (CTA) is unknown.

Objectives: To evaluate whether quantification of left ventricular (LV) extracellular volume (ECV) -a marker of myocardial fibrosis- and global longitudinal strain (GLS) -a marker of myocardial deformation- at baseline CTA associate with post-TAVR outcomes.

Methods: Consecutive patients with symptomatic severe AS between 01/2021 through 06/2022 who underwent pre-TAVR-CTA were included. CT-ECV was derived from septum tracing. CT-GLS used semi-automated feature-tracking analysis. The clinical endpoint was composite outcomes including all-cause mortality and heart failure hospitalization.

Results: Among the 300 patients (80 ± 9 years, 45% females, median STS-PROM score 2.8%), the LV ejection fraction (LVEF) was $58\pm12\%$, median [IQR] CT-ECV was 28.5 [26.2, 32.1]%, and CT-GLS was -20.1 [-23.8, -16.3]%. Over a median follow-up of 16 [12, 22] months, 38 deaths and 70 composite outcomes occurred. Multivariable Cox proportional-hazard model, accounting for clinical and echocardiographic variables, demonstrated that CT-ECV (HR=1.09 [95% CI 1.02-1.16], p=0.008) and CT-GLS (HR=1.07 [1.01-1.13], p=0.017) associated with the composite outcome. In combination, elevated CT-ECV and CT-GLS (above median for each) showed a stronger association with the outcome (HR=7.14 [2.63-19.36], p<0.001).

Conclusions: Comprehensive myocardial quantification of CT-ECV and CT-GLS associated with post-TAVR outcomes in a contemporary low-risk cohort with mostly preserved LVEF. Whether these imaging biomarkers can be potentially used for the decision-making including timing of AS intervention and post-TAVR follow-up, will require integration into future clinical trials.

(250 < 250 words)

Key words: transcatheter aortic valve replacement, aortic stenosis, extracellular volume, global longitudinal strain.

Abbreviation List

AF=atrial fibrillation AS=aortic stenosis BMI=body mass index CMR=cardiac magnetic resonance CTA=computed tomography angiography CT-ECV=computed tomography extracellular volume CT-GLS=computed tomography global longitudinal strain ECG=electrocardiography LVEF=left ventricular ejection fraction LV=left ventricular/ left ventricle TAVR=transcatheter aortic valve replacement

Introduction

Aortic stenosis (AS) is a disease of the aortic valve and of the left ventricular (LV) myocardium. With AS progression, the chronic pressure overload eventually leads to maladaptive LV remodeling with ultimately LV dysfunction. While the myocardial alterations are generally evaluated by echocardiography, currently, the only criterion considered as an indication for surgical/transcatheter aortic valve replacement (SAVR/TAVR) is LV ejection fraction (LVEF) below 50% (1). However, such profound alteration of LV function is rare, particularly in asymptomatic patients (2) and suffers from the measurement variability of LVEF by echocardiography. Furthermore, patients with low LVEF continue to incur outcomes that are catastrophic under medical management and remain poor even after AVR (2). Thus, considerable interest has been raised around measures that could reveal incipient LV myocardial alterations, that could contribute to earlier therapy for patients with AS. Among those ventricular deformation measured by global longitudinal strain (GLS) (3,4), and reactive interstitial myocardial fibrosis quantified by myocardial extracellular volume (ECV) have been touted as potentially useful risk markers (5,6). Cardiac magnetic resonance (CMR) is generally used to identify these myocardial abnormalities. In a multicentric registry of low gradient AS patients, abnormalities in each of the domains of structure and function contributed to the outcome prediction (7). Importantly, even considering some overlap between these domains (8), their assessment remains complimentary to improve risk stratification. However, CMR is rarely used in patients with AS whereas computed tomography angiography (CTA) is the pre-requisite for symptomatic severe AS patients considered for TAVR planning. Systematic CTA analysis defines the aortic valve anatomy, quantifies calcification, determines the annular sizing and procedural access (9). Work by our group and others leveraging functional assessment by CTA in severe AS patients prior to TAVR, demonstrated a feasibility of feature-tracking CT-GLS compared to echocardiography (10-12),

along with its association with post-TAVR outcomes (13,14). More recently, other groups have evaluated the CT-ECV assessment in severe AS patients with either smaller cohorts with high surgical risk treated with either SAVR/TAVR (15–17), or in the evaluation for concomitant cardiac amyloidosis (18). However, none of these studies have to date provided a comprehensive CTA assessment, combining the analysis of both imaging biomarkers within the same cohort, particularly inclusive of low/intermediate-risk patients with normal LVEF which represents the largest group of patients treated with contemporary TAVR. Our aim was, therefore, to investigate the feasibility of a comprehensive TAVR CTA imaging protocol for systematic evaluation of CT-ECV and CT-GLS, and their association with post-TAVR outcomes, while establishing the potential value of these new imaging biomarkers through cardiac CTA.

Methods

Study Population and Study Design

This was a retrospective cohort study of consecutive patients with severe aortic stenosis who underwent TAVR procedure at Abbott Northwestern Hospital, Minneapolis Heart Institute (Minneapolis, MN) between January 1st 2021 and June 30th 2022. Patients underwent comprehensive clinical evaluation, transthoracic echocardiography, and pre TAVR planning CTA. In addition to our routine TAVR planning CTA protocol (pre-contrast and arterial phase), a 3minute-delayed acquisition was performed to assess CT-ECV as previously reported (19,20). Exclusion criteria were patients undergoing valve-in-valve TAVR procedures, those with inadequate CTA for analysis due to either incomplete left ventricular (LV) coverage, or lack of delayed imaging. Patients with a documented history of cardiac amyloidosis were excluded from this study. The clinical endpoints of this study were time to event of all-cause mortality and time to first event of the composite outcome of all-cause mortality or heart failure hospitalization. Patients were divided into four pre-specified groups according to the median values of CT-ECV and CT-GLS, 1) Normal: CT-ECV< median and CT-GLS< median, 2) High CT-GLS: CT-GLS≥ median and CT-ECV<median, 3) High CT-ECV: CT-ECV≥ median and CT-GLS<median, and 4) Both: CT-ECV≥ median and CT-GLS≥ median. There are no established cut-off values of CT-ECV and CT-GLS, therefore median value was used for this classification.

Coronary artery disease was defined by any history of percutaneous coronary intervention, coronary artery bypass grafting, or myocardial infarction. Myocardial infarction by CTA was defined when meeting the two criteria: 1) systolic akinesis of left ventricular segment and 2) left ventricular systolic wall thickness<5 mm. Chronic obstructive pulmonary disease (COPD) was defined according to medical history and supportive pulmonary function tests, chest x-rays and/or chest CT scans.

The study protocol was approved by the Allina Institutional Review Board and conducted in accordance with the Declaration of Helsinki. All study patients provided authorization for the use of their medical records for research.

CTA data acquisition and reconstruction

All pre-TAVR CTA was performed using a 3rd generation dual-source CT system (SOMATOM Force, Siemens Healthineers, Germany). The TAVR CTA protocol evaluation at our institution includes a topogram, pre-contrast aortic valve calcium score, retrospective gated CTA covering the entire heart and cardiac cycle with dose modulation, followed by a helical prospectively ECG triggered (high-pitch, FLASH, Siemens Healthineers, Germany) scan encompassing the neck, chest, abdomen, and pelvis. In addition to TAVR planning CTA, pre-contrast and 3-minutedelayed acquisitions were obtained encompassing the entire heart in end-systolic phase using either high-pitch mode or axial prospective-ECG-gated axial sequential acquisition mode. The timing of late acquisition for CT-ECV calculation was determined based on previous studies which demonstrated the feasibility for 3-minutes delay (19,20). In addition, this shorter delayed acquisition is logistically easier for the patient and for clinical incorporation into the daily workflow of a cardiac CT lab. Pre-contrast and 3-minute-delayed acquisitions were performed at the fixed tube voltage of 120 kV and the reference tube current of 300 mAs, determined with the assistance of the semi-automatic control system (CARE kV) algorithm. Images were reconstructed with ADMIRE iterative reconstruction 3 as a standard on the Force scanner (Siemens Healthineers, Germany) using medium smooth reconstruction kernel (Bv40), and slice thickness of 1.0 mm. For CTA, intravenous contrast (Omnipaque-350, GE Healthcare Inc., Marlborough, MA) 100 \pm 30mL bolus injection was adjusted depending on the patient's renal function, body mass index (BMI), and kV used for cardiac imaging. Scan time used the bolus tracking method in the descending thoracic aorta.

Echocardiography protocol

A comprehensive 2D transthoracic echocardiography was performed on all pre-TAVR patients using spectral and color Doppler. The echocardiographic parameters were measured as per standard guidelines, using multiple windows including parasternal long-axis and apical 2-chamber, 3-chamber, and 4-chamber views. The left ventricular ejection fraction (LVEF) was calculated by the biplane method of disks.

Assessment of CT-ECV

The methodology for CT-ECV assessment used in this study has been described previously (19), mid-septum manual region of interest (ROI) tracing (septal CT-ECV) using an automatic threedimensional non-rigid image co-registration of pre-contrast/delayed datasets with dedicated software (Ziostation2. Ver. 2.9.8, Ziosoft, Japan). CT-ECV was expressed as a percentage, and calculated using the following formula:

CT-ECV=(1-hematocrit)*($\Delta HU_{myo}/\Delta HU_{blood}$),

where ΔHU_{myo} and ΔHU_{blood} represent ($HU_{delayed} - HU_{pre-contrast}$) of the myocardium and blood pool ROI, respectively. Hematocrit measurements from the blood samples were obtained on the same CTA day.

For septal CT-ECV, after generating the 3D CT-ECV map, a free ROI was manually drawn in the axial view along the mid-wall of the interventricular septum with a minimum area of 35 mm² for septal CT-ECV measurement (**Figure 1**). This allowed for the image quality control while excluding the blood pool and avoiding identifiable myocardial infarction and/or artifacts from cardiac implantable electronic devices (CIED). For the outcomes analysis, septal CT-ECV values were used (and hereinafter referred as CT-ECV), along with CT-GLS.

For sub-analysis, global CT-ECV measurement was used as well as septal CT-ECV. The methodology of global CT-ECV is described in the **supplemental methods** and our previous study (19). The association of global CT-ECV and CT-GLS with post-TAVR outcomes were also assessed (**supplemental file**). CT-ECV measurements were performed by the imaging Core Lab following standard protocols. In the core lab assessment of a random sample of 30 patients, an estimated intra- and inter-rater reliabilities of CT-ECV using intraclass correlation (ICC [95% CI]) were 0.87 [0.74-0.93], and 0.84 [0.70-0.92], respectively.

Assessment of CT-GLS analysis

CT-GLS were assessed as endocardial GLS using an offline dedicated feature tracking software (Medis Suite CT ver.3.1, Medis Medical Imaging Systems, Leiden, The Netherlands). Three

long-axis views (four-, three-, and two-chamber) were manually reconstructed using the threedimensional double-oblique multiplanar reconstructions. Subsequently, an outlining of the endocardial and epicardial border was manually trace in each view at end-diastole (largest LV cavity) and end-systole (smallest LV cavity), avoiding the mitral annulus, papillary muscles, and LV outflow tract (LVOT) areas. This process was followed by automated feature-tracking propagation throughout the cardiac cycle (**Figure 1**). Individual tracings were reviewed, and if necessary, manual adjustments of the contours were performed to optimize tracking. LVEF, LV volumes, and LV mass were also obtained through the biplane method, using the same software by integrating the reconstructed four-chamber and two-chamber views from CTA datasets. Intra-(ICC,0.97 [0.93–0.99]) and inter-observer (ICC,0.88 [0.73–0.95]) reliability for CT-GLS had been previously reported (14).

Clinical Outcomes

The clinical endpoints of this study were composite outcomes of all death and heart failure hospitalization following TAVR. Cardiac death events were classified according to the standardized endpoints defined by the Valve Academic Research Consortium-3 (VARC-3) criteria (21). All death events were confirmed by examination of the Minnesota Department of Health records. For the composite outcome, time-to-event was calculated as time to the first adverse event following TAVR. The patient outcomes data were frozen on June 1st 2023.

Statistical Analysis

Continuous variables were summarized as either means±standard deviations or medians [interquartile ranges, (IQRs)], as appropriate; categorical data were summarized as counts (%). Univariable method (t-test, one-way ANOVA, Mann-Whitney U test, and Fisher's exact test) was used to compare the patient characteristics vs. CT-ECV and CT-GLS values.

The patient characteristics and outcomes among the 4 pre-specified groups were assessed according to median values of CT-ECV and CT-GLS. For evaluating the cut-off values of CT-ECV and CT-GLS, the relative hazard was estimated using a relative hazard risk curve. Survival was estimated using the Kaplan-Meier method and compared across the groups using a log-rank test. In addition, tertiles of both CT-ECV and CT-GLS were tested for their association with the clinical endpoints (Supplemental files). Finally, multivariable Cox regression models were used to estimate the association between CT-ECV and CT-GLS and the risk of adverse events, adjusted for patient's baseline complexity using Society of Thoracic Surgeons Predicted Risk of Mortality (STS PROM) score. Models were built incrementally with covariates that are considered clinically relevant outcomes to AS patients. Covariates in the first model were age, gender, STS PROM score, LVEF, AV mean gradient, and stroke volume index (SVi). Models 2 and 3 were built by sequentially adding CT-ECV and CT-GLS or the combination group of CT-ECV and CT-GLS to the first model. In addition, the other model was built using LV mass index, age, gender, STS PROM score, LVEF, AV mean gradient, and SVi, and then CT-ECV and CT-GLS were added to this model. Because presence of amyloidosis was considered, LV mass index was added to the model.

Goodness-of-fit statistics were computed using a chi-square test and Akaike information criterion (AIC). The time-varying performance of the model was estimated using the survival concordance index (c-index). As a sub-analysis, CT-ECV and CT-GLS in patients with preserved LVEF (\geq 50%), as well as in those with LV mass index \geq median value was evaluated. The statistical analyses were performed using R Commander, a graphical user interface for R (The R Foundation for Statistical Computing, version 4.2.1) with survival and rms packages. Statistical significance was determined at a p<0.05.

Results

The study workflow is shown in **Figure 2**. Among the 375 patients with severe AS enrolled, 300 patients were ultimately included in this analysis. Reasons for exclusion were 17 patients undergoing valve-in-valve TAVR procedure, one with history of cardiac amyloidosis, and 57 patients with inadequate CTA images available for CT-ECV and/or CT-GLS analysis (incomplete coverage of the LV or lack of adequate delayed imaging). The mean age was 80.0±9.4 years, 45% were females, and the median STS-PROM score was 2.80 [1.98, 4.04]%. The mean LVEF was preserved (57.6±11.6%), 111 patients (37%) had atrial fibrillation, and 41 patients (14%) had CIED.

Septal CT-ECV was measurable in all patients, whereas global CT-ECV was feasible in 279/300 (93%) mostly due to the presence of intracardiac leads causing beam-hardening artifacts (**Supplemental Figure 1**). The estimated correlation coefficient between septal and global ECV is described in the supplemental file (**Supplemental Figure 2**). CT-GLS was feasible in 97% patients with a median value of -20.1 [-23.8, -16.3] %. The correlations in each parameter are described in the supplemental file (**Supplemental Figure 3**).

Table 1 summarizes the patient characteristics according to the 4 pre-specified groups. From the imaging perspective, the group with high CT-ECV and CT-GLS had worse LV remodeling and function, worse hemodynamics (lower stroke volume index, lower AVA, higher E/e', PASP, and lower TAPSE). Presence of the other valvular disease did not differ across 4 groups (Table 2). CT-ECV values did not differ compared to the LV mass index (Supplemental Table 1).

After a median follow-up of 16 [12, 22] months, 38 deaths occurred, and composite outcome (all-cause death + HF hospitalization) happened in 70 patients. The relative hazard

thresholds estimated from relative hazard risk curve for composite outcome for CT-ECV was around 29%, similar to the median value of this cohort (**Figure 3A**). Equally, CT-GLS threshold identified by this methodology for both endpoints were around -20%, similar to the median value (**Figure 3B**).

On Kaplan-Meier survival analysis, there was an increased risk for endpoint of composite outcome according to the presence of either high CT-ECV or CT-GLS, but even more so for the group with the combination of above median CT-ECV and CT-GLS (**Figure 4**). A multivariable analysis for composite outcomes demonstrated that, as continuous variables, CT-GLS (HR=1.07 [1.01-1.13], p=0.017) and CT-ECV (HR=1.09 [1.02-1.16], p=0.008) were associated with higher risk (**Table 3**). Furthermore, the presence of either myocardial abnormality (High CT-GLS; CT-GLS≥ median, HR=3.64 [1.24-10.66], p=0.018, High CT-ECV; CT-ECV≥ median, HR=4.84 [1.74-13.52], p=0.003) and even more so when Both (CT-GLS+CT-ECV≥ median, HR=7.14 [2.63-19.36], p<0.001) was associated with increased risk. Since that patients with both severe AS and cardiac amyloidosis have increased LV Mass, the last Cox model adjusted for LV mass, results were unchanged (**Table 3**). Anodel 2). The addition of CT-GLS+CT-ECV improved the model fit and its performance (**Table 4**). A Kaplan-Meier survival analysis and a multivariable cox analysis for all-cause mortality were described in the **Supplementary Figure 4 and Table 2**.

Sensitivity analysis restricted to patients with echo LVEF≥50% (n=250/300, 83%), corroborated similar findings to the entire cohort (**Supplemental Tables 3 and 4**). When the combination of the CT-GLS and the global CT-ECV was used, similar results were obtained (**Supplementary Tables 5 and 6** and **Supplemental Figures 5**).

Discussion

Findings of our study from a contemporary low-risk cohort of patients with severe AS and mostly preserved LVEF can be summarized as the following: a) a comprehensive pre-TAVR CTA analysis of myocardial structure (CT-ECV) and function (CT-GLS) are feasible, b) abnormalities of these imaging biomarkers associated with increased risk of post-TAVR outcomes, emphasizing the synergism of these two domains going beyond echo detection of reduced LVEF, and c) this could be important not only for risk stratification, but also for the decision-making including timing of AS intervention and post-TAVR follow-up, given their association with increased vulnerability.

Aortic stenosis is a disease of the valve and the myocardium. Therefore, assessment of myocardial structure and function becomes increasingly important with the expansion of TAVR across all risk spectrum, including younger and potentially asymptomatic patients. Since majority of patients with severe AS present with normal LV systolic function, detection of more sensitive indices is necessary. While CMR allows for its detection, logistically is rarely performed in routine clinical care of patients with AS, while CTA is part of the work-up for TAVR. The CT-ECV assessment can be easily added to the standard TAVR CT planning using a prospective sequential ECG-gated acquisition pre-contrast and a 3-minutes delayed acquisition (just adding 3-4 minutes to standard CTA protocol). This is feasible from any vendor with minimal increase in effective radiation dose on average of 2 mSv with standard chest conversion factor (0.014mSv·mGy⁻¹cm⁻¹) (19). While the global CT-ECV map is useful to identify regional myocardial fibrosis and/or infarction, the presence of beam-hardening artifacts from CIED decreases its feasibility, which in this study occurred in 21 patients (7%).

Consistent with previous CMR studies which has evaluated predominantly SAVR patients (5,22), baseline CT-ECV assessment provided risk discrimination associating with post-TAVR outcomes, independent of clinical risk factors. Of note, the CT-ECV threshold of 28.5%

identified in this cohort is similar to the one from CMR literature.

Limited CMR studies have evaluated within the same cohort the relationship between ECV and GLS and their association with prognosis (7,23). In both reports, a weak correlation was seen between these parameters which were nonetheless additive to the risk stratification. CMR assessment is considered the gold standard for myocardial structure and function mostly because CTA has some limitations as worse signal to noise (for ECV) compared to CMR, and lower temporal resolution (for GLS) compared to echocardiography. Nonetheless, cardiac CTA has greater accessibility and faster acquisition time than CMR. It does not require access to T1 mapping pulse sequences, which are not commercially available for all vendors, and therefore not routinely used in clinical practice. However, to date, no study has performed a comprehensive evaluation using CTA for the evaluation of both CT-ECV and CT-GLS within the same cohort, even more so in a contemporary low-risk TAVR population with preserved LVEF.

Given the continued growth of TAVR treatment across the surgical risk spectrum and now expanding into randomized control trials for asymptomatic patients with severe AS (NCT03042104) and moderate AS (NCT04889872 and NCT05149755), further identification of objective risk markers of myocardial structure and function will be important to improving riskstratification, refining proper timing of intervention and tracking response to treatment. Thus, this approach to myocardial assessment should be advocated to evaluate patients with severe AS and assessed in large cohorts to determine whether it can contribute to alert clinicians to incipient LV myocardial alterations and to the indication of AVR in asymptomatic patients.

Study Limitations

This study has to interpreted in the context of some limitations. First, this was a single-center, single-vendor study with small number of events, albeit a high volume and clinically expert site.

Second, while one patient with clinical history of cardiac amyloidosis was excluded from this analysis, evaluation for the presence of concomitant dual pathology was not systematically performed which will have led to an underestimation of this dual pathology. Therefore, it is possible that higher CT-ECV values may reflect, in some patients, the presence of concomitant cardiac amyloidosis (CT-ECV>35%, N=27). In the multivariable Cox model, we attempted to adjust for LV mass which elevation is common in both AS and cardiac amyloidosis, leading to same results. Nonetheless, TAVR treatment remains the proper management strategy for these patients (24,25), while the residual heart failure hospitalization burden emphasizes the need for efforts in its identification, perhaps using CT-ECV (18). Third, in 29 cases, there were small differences in the number of slices obtained between pre-contrast and delayed images. While the slice thickness, field of view and voxel size were the same, the software did not allow for the creation of CT-ECV map which could be improved in future releases addressing this limitation. Fourth, despite our best intentions to exclude areas of myocardial infarction using CT-ECV map, it is possible that non-ischemic fibrosis was included in the septal ROI for CT-ECV calculation, which is an acceptable approach according to expert consensus (26). Fifth, given the novelty of this CT imaging biomarker, the follow-up was short, averaging 16 months, therefore lowering the number of events in this low-risk cohort. Nonetheless, multivariable Cox proportional-hazard analysis, suggests that CT-ECV and CT-GLS may detect incipient LV myocardial abnormalities and improve risk stratification beyond clinical and echocardiographic parameters. Lastly, the current CT-ECV methodology requires the 3-mins delayed phase acquisition, and small increased radiation. While such datasets can also be clinically leveraged for the exclusion of intracardiac and/or LAA thrombus in patients with atrial fibrillation, the interesting potential for radiomics to capture myocardial texture changes for ECV analysis is one that deserves future consideration. Initial work in this field has allowed for the detection of cardiac amyloidosis in patients with

severe AS (27). Expansion of this work, and further validation by others, could allow identification of ECV (or other radiographical marker) that would associate with superior risk stratification from just the arterial phase.

Conclusions

Myocardial assessment by CTA in patients with severe AS using CT-ECV and CT-GLS is feasible and is independently associated with one-year outcomes after TAVR, even in those with preserved LVEF. The combination of these two imaging biomarkers provides incremental information beyond echo identification of reduced LV systolic function. Future multicenter studies in emerging TAVR cohorts should explore the incremental role of these imaging biomarkers for improving risk-stratification, timing of intervention and response to treatment.

Clinical perspectives

Competencies in clinical knowledge

Baseline comprehensive cardiac CTA assessment of CT-ECV and CT-GLS is feasible and detect incipient LV myocardial abnormalities and improve risk stratification beyond clinical and echocardiographic parameters in a contemporary, and predominantly low-risk cohort.

Translational Outlook

Future multicenter studies in emerging TAVR cohorts should explore the incremental role of these imaging biomarkers for improving risk-stratification, timing of intervention and response to treatment.

References

- Otto CM., Nishimura RA., Bonow RO., et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2021;143(5):e72–227. Doi: 10.1161/CIR.00000000000923.
- Henkel DM., Malouf JF., Connolly HM., et al. Asymptomatic Left Ventricular Systolic Dysfunction in Patients With Severe Aortic Stenosis: Characteristics and Outcomes. Journal of the American College of Cardiology 2012;60(22):2325–9. Doi: 10.1016/j.jacc.2012.08.988.
- Dahl JS., Magne J., Pellikka PA., Donal E., Marwick TH. Assessment of Subclinical Left Ventricular Dysfunction in Aortic Stenosis. JACC Cardiovasc Imaging 2019;12(1):163–71. Doi: 10.1016/j.jcmg.2018.08.040.
- 4. Fukui M., Thoma F., Sultan I., et al. Baseline Global Longitudinal Strain Is Associated With All-Cause Mortality After Transcatheter Aortic Valve Replacement. JACC Cardiovasc Imaging 2020;13(4):1092–4. Doi: 10.1016/j.jcmg.2019.11.005.
- Everett RJ., Treibel TA., Fukui M., et al. Extracellular Myocardial Volume in Patients With Aortic Stenosis. Journal of the American College of Cardiology 2020;75(3):304–16. Doi: 10.1016/j.jacc.2019.11.032.
- Kwak S., Everett RJ., Treibel TA., et al. Markers of Myocardial Damage Predict Mortality in Patients With Aortic Stenosis. Journal of the American College of Cardiology 2021;78(6):545– 58. Doi: 10.1016/j.jacc.2021.05.047.
- Fukui M., Annabi M-S., Rosa VEE., et al. Comprehensive myocardial characterization using cardiac magnetic resonance associates with outcomes in low gradient severe aortic stenosis. European Heart Journal - Cardiovascular Imaging 2022:jeac089. Doi: 10.1093/ehjci/jeac089.
- Fröjdh F., Fridman Y., Bering P., et al. Extracellular Volume and Global Longitudinal Strain Both Associate With Outcomes But Correlate Minimally. JACC Cardiovasc Imaging 2020;13(11):2343–54. Doi: 10.1016/j.jcmg.2020.04.026.
- Blanke P., Weir-McCall JR., Achenbach S., et al. Computed Tomography Imaging in the Context of Transcatheter Aortic Valve Implantation (TAVI)/Transcatheter Aortic Valve Replacement (TAVR): An Expert Consensus Document of the Society of Cardiovascular Computed Tomography. JACC Cardiovasc Imaging 2019;12(1):1–24. Doi: 10.1016/j.jcmg.2018.12.003.
- Fukui M., Xu J., Abdelkarim I., et al. Global longitudinal strain assessment by computed tomography in severe aortic stenosis patients - Feasibility using feature tracking analysis. J Cardiovasc Comput Tomogr 2019;13(2):157–62. Doi: 10.1016/j.jcct.2018.10.020.
- 11. Gegenava T., van der Bijl P., Hirasawa K., et al. Feature tracking computed tomographyderived left ventricular global longitudinal strain in patients with aortic stenosis: a comparative

analysis with echocardiographic measurements. J Cardiovasc Comput Tomogr 2020;14(3):240–5. Doi: 10.1016/j.jcct.2019.11.004.

- Bernhard B., Grogg H., Zurkirchen J., et al. Reproducibility of 4D cardiac computed tomography feature tracking myocardial strain and comparison against speckle-tracking echocardiography in patients with severe aortic stenosis. J Cardiovasc Comput Tomogr 2022;16(4):309–18. Doi: 10.1016/j.jcct.2022.01.003.
- Gegenava T., van der Bijl P., Vollema EM., et al. 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. Am J Cardiol 2020;125(6):948–55. Doi: 10.1016/j.amjcard.2019.12.024.
- Fukui M., Hashimoto G., Lopes BBC., et al. Association of baseline and change in global longitudinal strain by computed tomography with post-transcatheter aortic valve replacement outcomes. European Heart Journal - Cardiovascular Imaging 2022;23(4):476–84. Doi: 10.1093/ehjci/jeab229.
- Scully PR., Patel KP., Klotz E., et al. Myocardial Fibrosis Quantified by Cardiac CT Predicts Outcome in Severe Aortic Stenosis After Transcatheter Intervention. JACC Cardiovasc Imaging 2022;15(3):542–4. Doi: 10.1016/j.jcmg.2021.10.016.
- 16. Suzuki M., Toba T., Izawa Y., et al. Prognostic Impact of Myocardial Extracellular Volume Fraction Assessment Using Dual-Energy Computed Tomography in Patients Treated With Aortic Valve Replacement for Severe Aortic Stenosis. Journal of the American Heart Association 2021;10(18):e020655. Doi: 10.1161/JAHA.120.020655.
- Vignale D., Palmisano A., Gnasso C., et al. Extracellular volume fraction (ECV) derived from pre-operative computed tomography predicts prognosis in patients undergoing transcatheter aortic valve implantation (TAVI). European Heart Journal - Cardiovascular Imaging 2023:jead040. Doi: 10.1093/ehjci/jead040.
- Scully PR., Patel KP., Saberwal B., et al. Identifying Cardiac Amyloid in Aortic Stenosis: ECV Quantification by CT in TAVR Patients. JACC: Cardiovascular Imaging 2020;13(10):2177– 89. Doi: 10.1016/j.jcmg.2020.05.029.
- Koike H., Cheng VY., Lesser A., et al. Importance of imaging-acquisition protocol and postprocessing analysis for extracellular volume fraction assessment by computed tomography. Journal of Cardiovascular Computed Tomography 2023. Doi: 10.1016/j.jcct.2023.02.007.
- Scully PR., Patel KP., Saberwal B., et al. Identifying Cardiac Amyloid in Aortic Stenosis: ECV Quantification by CT in TAVR Patients. JACC: Cardiovascular Imaging 2020;13(10):2177– 89. Doi: 10.1016/j.jcmg.2020.05.029.
- 21. VARC-3 WRITING COMMITTEE:, Généreux P., Piazza N., et al. Valve Academic Research Consortium 3: Updated Endpoint Definitions for Aortic Valve Clinical Research. J Am Coll

Cardiol 2021;77(21):2717-46. Doi: 10.1016/j.jacc.2021.02.038.

- Kwak S., Everett RJ., Treibel TA., et al. Markers of Myocardial Damage Predict Mortality in Patients With Aortic Stenosis. Journal of the American College of Cardiology 2021;78(6):545– 58. Doi: 10.1016/j.jacc.2021.05.047.
- Fröjdh F., Fridman Y., Bering P., et al. Extracellular Volume and Global Longitudinal Strain Both Associate With Outcomes But Correlate Minimally. JACC Cardiovasc Imaging 2020;13(11):2343–54. Doi: 10.1016/j.jcmg.2020.04.026.
- 24. Nitsche C., Scully PR., Patel KP., et al. Prevalence and Outcomes of Concomitant Aortic Stenosis and Cardiac Amyloidosis. Journal of the American College of Cardiology 2021;77(2):128–39. Doi: 10.1016/j.jacc.2020.11.006.
- 25. Rosenblum H., Masri A., Narotsky DL., et al. Unveiling outcomes in coexisting severe aortic stenosis and transthyretin cardiac amyloidosis. European Journal of Heart Failure 2021;23(2):250–8. Doi: 10.1002/ejhf.1974.
- 26. Moon JC., Messroghli DR., Kellman P., et al. Myocardial T1 mapping and extracellular volume quantification: a Society for Cardiovascular Magnetic Resonance (SCMR) and CMR Working Group of the European Society of Cardiology consensus statement. Journal of Cardiovascular Magnetic Resonance 2013;15(1):92. Doi: 10.1186/1532-429X-15-92.
- 27. Lo Iacono F., Maragna R., Guglielmo M., et al. Identification of subclinical cardiac amyloidosis in aortic stenosis patients undergoing transaortic valve replacement using radiomic analysis of computed tomography myocardial texture. Journal of Cardiovascular Computed Tomography 2023. Doi: 10.1016/j.jcct.2023.04.002.

Figure titles and legends

Figure 1: Methodology for CT-ECV and CT-GLS assessment

Figure 2: Study workflow diagram

Among the 375 patients with severe AS enrolled, 300 were included in this analysis.

Figure 3: Relative hazard risk curve for composite outcomes

Figure 3 shows the relationship between CT-ECV and the outcomes (A), and CT-GLS and the outcomes (B).

Figure 4: Kaplan-Meier curves for composite outcomes

Patients were divided into 4 pre-specified groups according to the median values of CT-ECV and CT-GLS, 1) Normal: CT-ECV< median and CT-GLS< median, 2) High CT-GLS: CT-GLS≥ median and CT-ECV<median, 3) High CT-ECV: CT-ECV≥ median and CT-GLS<median, and 4) Both: CT-ECV≥ median and CT-GLS≥ median.

Central Illustration:

Pre-TAVR assessment of CT-ECV and CT-GLS associate with short-term post-TAVR outcomes in a low-risk contemporary cohort of patients with mostly preserved LVEF.