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Editorial

Frailty matters. How-to predict “I'll be back“ after TAVR

Transcatheter aortic valve replacement (TAVR) has emerged as break-through technology as an alternative to surgical approaches. TAVR currently skyrocketing, with 71,000 procedures performed worldwide in 2015 with an estimated rise to 289,000 in 2025. Indications have gradually expanded, and now extend to both high as well as intermediate risk patients with severe aortic stenosis (AS), with the evaluation of low-risk patients underway. Beyond mortality benefits associated with TAVR, improvements in quality of life are similarly impressive. Patients, who didn't make it to the next grocery without shortness of breath, are able to hike up the mountains. Thus, the hype around TAVR has created more and more patients specifically requesting the procedure.

A careful selection of TAVR candidates is the key to ensure procedure success. In practice, the decision is settled by a specialized interdisciplinary „heart team“, after discussing all clinical parameters obtained from physical and laboratory exams (biomarkers, ECG) and following the calculation of risk by conventional scores such as the EuroScore or that provided by the Society of Thoracic Surgeons (STS). However, a dedicated TAVR risk score is currently lacking. EURO or STS scores are based on general populations but not offer specific insight on TAVR-specific patient profiles, which tend towards the inclusion of very old and fragile individuals.

Although the entirety of parameters predicting outcome remains not fully known, FRAILTY –despite its difficulty in defining, doubtlessly matters. Prevalence of Frailty is high in patients with severe AS, ranging from 26% up to 68%[1]

In this regard, numerous Frailty score have been proposed such as the Fried, Fried+, Rockwood, Short Physical Performance Battery, Bern, Columbia, and the Essential Frailty Toolset (EFT) have been proposed.

In 2017, a prospective multicenter study (14 centers, 3 countries) identified frailty[1] as important risk factor for outcome in 1020 subjects (82 years; 41% female) undergoing TAVR or SAVR (60% vs 40%). Among the 7 Frailty Scales, the EFT, a brief four-item scale encompassing lower-extremity weakness, cognitive impairment, anemia, and hypoalbuminemia outperformed other scores for prediction of both death at 30 days and 1 year (adjusted OR, 3.72) and worsening disability at 1 year (OR, 2.13).

In 2016, the definitions of frailty evolved towards more patient –specific and imaging-based parameters, including CT based body and muscle fat measures.[2–4] These included: *Psoas muscle area (PMA)*, and *subcutaneous (SC) and visceral body fat. Mamane et al.* firstly described (Munich-Montreal trial) in 208 patients the PMA as predictor for all-cause mortality after 1.5 years, after adjustment for STS score (HR 0.88),[2] as well as for TAVR-related bleeding. All studies to date, however[2–5] enrolled small patient cohorts of < 300 patients.[3] *Paknikar*[3] found total PMA as independent predictor for both composite adverse short-term outcome as defined by 30 day mortality, stroke, renal failure- and prolonged ventilation-defined by length of stay > 7 days, discharge to rehabilitation, or readmission within 30 days) and late 2-year survival. Males had a poorer survival and beyond, PMA predicted high-resource utilization.

Similarly, *Garg*[5] et al. reported in 152 patients, the indexed PMA as predicting early poor outcome (30 days mortality, stroke, dialysis, and prolonged ventilation) as well as high-resource utilization after TAVR.

A full body CT scan, which is routinely performed for TAVR procedure planning, indeed reflects the perfect playground to explore the full spectrum of frailty parameters. Uniquely, CT-based parameters are „personalized“ and highly specific. In this regards, they might offer more accurate assessments than conventional FRAILTY scores, the EURO or STS.

In this issue of the Journal, *Foldyna et al.*[6] enrolled 403 patients (83 ± 8 years; 52% female), and observed high associations of muscle and fat characteristics with long-term outcomes > 1 year (median, 458 days) after TAVR. Psoas muscle (PM), subcutaneous adipose (SAT), and visceral adipose tissue (VAT) area and density (Hounsfield units, HU) measurements were indexed to height, and log-transformed, in order to minimize bias. Mortality rate was quite high with 41.4% ultimately expiring. The study's key finding was that selective CT-based parameters -decreased PM, SAT, VAT area; and increased SAT density-were associated with higher long-term mortality after TAVR, which persisted after adjustment for age, sex, BMI, and STS score. Especially individuals with the lowest PMA, SAT or VAT area exhibited the highest hazard of mortality. In this regards, it seems that a greater degree of both muscle and fat are indeed beneficial to predict favorable outcome „ More fat and muscle is good for you “, but only in the scenario of the elderly and fragile TAVR setting. The data are certainly not transferrable to the general population, so don't overeat.

The authors should be congratulated for evaluating these patient-specific imaging findings, as they are taking the field one step closer to a “personalized” medicine approach toward evaluation of TAVR candidacy. The lessons learned in the present study are likely applicable to other populations as well. In this regard, in 3241 women diagnosed with breast cancer[7] (mean age 54 years), 34% had sarcopenia and a 41% greater risk of death. Importantly, CT derived parameters (muscle mass and adipose tissue) were much more strongly associated with mortality than body mass index (BMI). Sarcopenia is defined as more than +2 standard deviations of muscle mass compared to a reference cohort of the same sex, according to *I. Rosenberg, 1988. This contrasts with the definitions of frailty* used in TAVR, reflecting clinical

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„vulnerability parameters“ such as cognitive impairment or walking disability. Sacropenia starts at the age of 50 with a 0.8% decline in muscle mass annually, and at 80 years of age, 50% exhibit sacropenia.

In line with the aforementioned findings, *Foldyna* et al.[6] reported greater SAT density associated with a higher mortality hazard (adjusted HR per standard deviation increase in density = 1.35, p = 0.005). These findings likely correspond to lower levels of intracellular lipid accumulation and increasing fibrous SC stroma tissue. Another potential explanation may relate to lipofuscin, a pigment originating from protein and lipid metabolism which accumulates intracellularly and limits muscular performance during aging. Thus Liposfucsin, an cellular “aging” biomarker, may explain increased PM density the “death” group. However, absolute differences in PM CT -density (HU) were rather low when comparing both cohorts. In contrast, prediction models for cardiovascular disease (CVD) link mortality with obesity. Most recently, a large metaanalysis (190, 672 patients, 10 large US cohorts),[8] found CVD outcomes including CVD deaths and non-fatal adverse events worsening along with body mass index (BMI) , with increased risk already above an > 24 BMI.[8] The metaanalysis included 3.2 million person-years of follow-ups from 1964 to 2015.

Notably, in this present study by Foldanya et al.[6] SAT/VAT density and PM area were measurable in 100% of patients, while the SAT or VAT area was not accessible in 39.7%, due to an inadequate field-of-view (FOV). Narrowing of the FOV is commonly performed during the reconstruction of an aorto-iliac full body CTA for normal TAVR planning[9,10] performed for obtaining other CT parameters, due to centering the FOV towards the great vessels. Thus, in terms of integration into structural clinical reporting, care should be taken to enlarge the FOV wider as usual, in order to encompass the entire outer body contours. In this regards, SAT and VAT area can be obtained in 100% as any object moving through the CT gantry will be imaged. The CTA study protocol can be applied to all individuals undergoing pre-TAVR assessment simply be “widening” the FOV at the time of CT image reconstruction, without adding radiation exposure.

Given the novelty of the study findings, which employed an axial CT slice (10 mm) at the level of the mid fourth lumbar vertebral body (L 4), it remains unknown whether this is the optimal measure or whether more detailed or more informative measures from CT imaging are more accurate (e.g. PM-volume). However, the author's method is simple and in their study, was rapidly done,[6] thus allowing for an easy integration into clinical reporting.

Notably, significant differences between males and females were found, warranting further dedicated analysis on gender discrepancies in future studies. Further, upcoming studies may also address whether SAT and VAT to post- TAVR outcomes are linear or whether they exhibit other relationships, such as the “J-shape” correlation with mortality as known for BMI and TAVR.[11] (like the association of Coffee-drinking, Alcohol consumption and exercise with CVD).

In conclusion, the authors should be congratulated on this first, albeit large step, towards precision medicine in the evaluation of patients being considered for TAVR. SAT and VAT rapid CT-based tissue characterization is valuable in patients referred for TAVR for predicting mortality, while decreased PM area and increased SAT density were strongest associated with long-term mortality.

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