European Geriatric Medicine
https://doi.org/10.1007/s41999-023-00794-x

RESEARCH PAPER

# OLD-TAVR score to predict 2-year mortality in patients aged 75 years and more undergoing transcatheter aortic valve replacement

**Christophe de Terwangne[1] · Frédéric Maes[2,3] · Isabelle Gilard[1] · Joëlle Kefer[2,3] · Pascale Cornette[1,4] · Benoit Boland[1,4]**

Received: 7 January 2023 / Accepted: 26 April 2023


## Key summary points

**Aim** This study aimed to identify predictors of 2-year mortality in very old (aged 75+) after transcatheter aortic valve replacement (TAVR), with special attention to frailty, to develop a 2-year mortality risk score.

**Findings** Frailty is prevalent in older patients with severe aortic stenosis (68%) and enhanced discriminative power of a newly developed 12-point score (OLD-TAVR) to estimate 2-year mortality after TAVR.

**Message** During a pre-TAVR assessment of older patients, the use of specific risk scores of long-term mortality, encompassing a frailty measure such as the Clinical Frailty Scale, may improve the identification of older patients in which TAVR might be futile.

## Abstract

**Purpose** Decision-making on transcatheter aortic valve replacement (TAVR) in patients aged 75 years and older is complex. It could be facilitated by the identification of predictors of long-term mortality. This study aimed to identify predictors of 2-year mortality to develop a 2-year mortality risk score.

**Methods** Cohort study of consecutive patients aged ≥ 75 years who underwent TAVR after a comprehensive geriatric assessment (CGA) at our university hospital between 2012 and 2019. Predictors of 2-year mortality were determined using multivariable Cox regression. A point-based predictive model was developed based on risk factors and subsequently internally validated by fivefold cross-validation.

**Results** The 345 patients (median age 87 years, 54% women) were fit/vulnerable (32%), mildly frail (37%), or moderately/severely frail (31%). The overall 2-year mortality rate was 26%, predicted by atrial fibrillation, hemoglobin ≤ 10 g/dL, age ≥ 87 years, BMI ≤ 24, eGFR ≤ 50 ml/min, and moderate/severe frailty. The risk score (range 0–12), named OLD-TAVR score, for 2-year mortality showed good discriminative power (AUC 0.70) and remained consistent after fivefold cross-validation (cvAUC 0.69). A risk score ≥ 8 (prevalence 20%) predicted a 45% (95%CI: 34–58%) two-year mortality, with high specificity (86%) and good positive predictive power (+ LR 2.43).

**Conclusion** A 2-year mortality risk score (OLD-TAVR score) for very old patients undergoing TAVR was developed based on six bio-clinical items. A score ≥ 8 identified patients in whom 2-year mortality was very high and thereby the TAVR futile.

**Trial registration number and date of registration** Study protocol B403, 26/09/2022, retrospectively registered.

**Keywords** TAVR · Aortic stenosis · Frailty · Older adults · Risk score · CFS

✉ Christophe de Terwangne
Christophe.deterwangne@saintluc.uclouvain.be

[1] Geriatric Medicine, Cliniques Universitaires Saint-Luc – Université Catholique de Louvain, Avenue Hippocrate 10, 1200 Brussels, Belgium

[2] Division of Cardiology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain (UCLouvain), Brussels, Belgium

[3] Pôle de Recherche Cardiovasculaire, Institut de Recherche Expérimentale et Clinique (IREC), Université Catholique de Louvain (UCLouvain), Brussels, Belgium

[4] Institute of Health and Society (IRSS), Université Catholique de Louvain (UCLouvain), Brussels, Belgium

Published online: 11 May 2023

## Introduction

Severe aortic stenosis (SAS) is a prevalent disease in older patients and threatens medium-term vital prognosis in those without valve replacement strategy. Transcatheter aortic valve replacement (TAVR) has revolutionized the treatment of SAS in particular in older patients considered unfit or at high risk for surgical aortic valve replacement. Since the advent of the first TAVR 20 years ago, the safety and feasibility of TAVR in older patients have been well documented but also considerably improved [1–3]. Although older patients with severe SAS are often multi-morbid and/or frail, identifying those too unfit and thus unlikely to benefit from TAVR remains a challenge. Presently, during a pre-TAVR assessment, the use of scores able of predicting adverse outcomes and mortality in individual patients is recommended by the cardiovascular Societies [4]. Whereas traditional surgical risk scores are helpful to predict peri-interventional morbidity and mortality in surgical valve replacements, they repeatedly showed poor performance in estimating short and long-term mortality after TAVR [5–7]. Some TAVR-specific short-term (30-day) mortality scores have been developed and showed variable performance [8, 9]. Current mortality risk scores are often limited to 1-year given actual recommendations of a minimal 1-year life expectancy to decide for aortic valve replacement, thereby limiting evidence of predictors of longer-term mortality after TAVR [10]. Few long-term (≥ two years) mortality risk scores have been developed but they often lack a frailty assessment [11, 12]. However, frailty evaluation does enhance risk stratification in patients eligible for TAVR [13]. Among the large panel of frailty assessment tools that have been developed and studied in the last decade in TAVR, the Clinical Frailty Scale (CFS) has been shown to be useful in predicting 1-year mortality in older patients undergoing TAVR [14]. The CFS is a simplified phenotypic geriatric scale that has proven to be easy to use and accessible with the support of validated decision trees [15, 16]. Whether the CFS is valuable in longer-term risk stratification in older patients undergoing TAVR, as well as compared to other medical conditions, remains unclear.

In this study, we, therefore, aimed to identify risk factors of 2-year mortality with special attention to the CFS to develop a specific risk score for older patients with SAS and assess its predictive performance.

## Methods

### Study design and patient inclusion

This cohort study was conducted at Cliniques Universitaires Saint-Luc, a tertiary hospital center in Brussels, Belgium. Medical records of all patients with symptomatic SAS who benefited from a TAVR between 2012 and 2019 were examined. All patients aged 75 years and older underwent a comprehensive geriatric assessment (CGA) before TAVR. Symptomatic SAS was defined according to ESC guidelines as an aortic peak jet velocity of ≥ 4 m/s, a mean transvalvular gradient of ≥ 40 mmHg or an aortic valve area < 1 $cm^2$, and concomitant clinical symptoms compatible with SAS [4]. The Logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE II) and the Society of Thoracic Surgeons Predictive Risk of Mortality (STS) score were used to estimate peri-operative risk. Treatment decision (TAVR, SAVR, medical treatment) was made for each patient by the multidisciplinary heart team (cardiologists, anesthetists, cardiac surgeons, and geriatricians). Patients were followed-up until 2 years after TAVI for vital status.

The local Ethics Committee approved the study protocol B403 and due to the study design, the need for informed consent was waived. The study was performed following the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

### Data collection

Patients' characteristics, general and cardiovascular history, echocardiographic findings, laboratory findings, chest angioscan, coronarography, and CGA findings as well as TAVR procedural variables derived from the routine pre-TAVR assessment, which is prospectively encoded in an institutional database. The patient's pre-TAVR assessment is consistently carried out within the three months before the valve intervention.

Atrial fibrillation (AF) at the time of pre-TAVR assessment was diagnosed on a 12-lead ECG recording. Coronary artery disease (CAD) was defined as either past coronary artery bypass surgery, previous percutaneous angioplasty, past myocardial infarction, or significant coronary artery disease revealed on coronary angiography. Diagnosis of pulmonary arterial hypertension was based on echocardiography and defined as trans-tricuspid pressure gradient ≥ 40 mmHg.

Baseline patient characteristics were used to calculate traditional surgical risk scores (STS, Logistic Euroscore 2). A cardiovascular burden was assessed using the items of the $CHA_2DS_2VaSC$ score [17]. Frailty and functional status were assessed during the CGA by a trained geriatric team. The CGA addressed the place of living (at home or in a nursing home), the functional status two weeks before the assessment based on the basic Activities of Daily Living (ADL) [18] and instrumental Activities of Daily Living (iADL) [19], number of daily drugs, Minimal Mental State Examination (MMSE), a recent history of falls or syncope, and nutrition status using the MNA-SF [20]. Cognitive impairment was defined as either a previous diagnosis of dementia

or an MMSE score < 24/30 [21]. Additionally, the Clinical Frailty Scale (CFS) version 2.0 was used to determine clinical frailty [22]. The CFS was derived from the CGA by two researchers independently, who followed a validated classification tree [16]. According to their CFS level (range 1–9), patients were classified as fit (CFS 1–3), vulnerable (CFS 4), mildly frail (CFS 5), moderately frail (CFS 6), or severely frail (CFS 7). As expected, no patient at high risk of dying within 6 months (CFS 8–9) underwent a TAVR.

TAVR procedures were most often performed via transfemoral access (82%) and under conscious sedation (85%). In the absence of transfemoral access, a trans carotid (4%), transapical (11%), or transaortic (3%) approach was performed under general anesthesia. All procedures were performed with a commercially available bioprosthetic valve. The choice of the bioprosthetic valve was made based on the patient's anatomic characteristics and the experience of the treating physician. The procedures were elective in most cases.

### Statistical analysis

Statistical analysis was performed using R (version 4.2.2), R Core Team, Vienna, Austria, 2022. Categorical variables were expressed as count with percentages and continuous variables as mean (± SD) or median [25th–75th percentiles] as appropriate. Differences in characteristics between deceased patients and survivors at 2 years after TAVR were assessed using the $\chi^2$ test or Fischer Exact test for categorical variables, and the Wilcoxon Rank-sum test for continuous variables.

*Model development*: Several bivariable and multivariable Cox Proportional Hazard regression models were computed to develop the best predictive model. Variables were entered in the selection process if their p-value were < 0.1 in univariate analysis (i.e., age, BMI, ADL, NYHA, AF, coronary artery disease, history of coronary bypass, pacemaker, pulmonary hypertension, hemoglobin, Cockcroft-Gault based eGFR). CFS (p = 0.17) was included as it is clinically relevant. Scores (STS, Euroscore II, $CHA^2DS^2VASC$) were not included in the selection process due to the high risk of multi-collinearity. The Youden Index (sensitivity + specificity -1) was used to identify appropriate cut-off points of numerical variables to classify patients according to their vital status at 2 years after TAVR. The prediction model was selected by the best subset method [23]. Goodness-of-fit between Cox models was tested with the Likelihood Ratio test. Variables showing collinearity i.e., a variance inflation factor (VIF) greater than five, were excluded from the model. Patients with missing data in one of the studied variables were excluded from model analysis (total N included are reported). Only variables with less than 10% missing data were included in the analysis and model development.

*Development of the OLD-TAVR score*: A score was attributed to each variable included in the final model by dividing the beta coefficient of the variable by the lowest beta coefficient in the model. A total score was calculated for each patient. The discriminative ability of this 2-year mortality score was determined by a receiver operating characteristic (ROC) curve.

The sample was divided into 3 risk strata (low, medium, high) based on approximate quartiles: given the lack of significant difference between the middle two quartiles, they were pooled together.

The estimated probability of 2-year mortality was computed for each risk strata and the differences between the strata were computed with $\chi^2$ test with p-value adjustment by Tukey's method for multiple group comparisons. Survival analysis on different risk strata was conducted by Kaplan Meier and differences in survival curves were assessed by the Log-rank test.

*Internal validation*: A fivefold cross-validation process was used to internally validate the model. The total patient sample is partitioned randomly into 5 equal folds (parts) during this process. Four folds (training data) are used to compute the predictive model on which the 5th fold (considered as new data) is used to compute the AUC. This process is repeated for each cross-validation fold and is averaged to obtain one common performance estimate, in this case, an average AUC [24].

Throughout the analysis, a p-value below 0.05 was considered statistically significant, and a p-value between 0.05 and 0.1 was considered a trend.

## Results

### Patient's characteristics

Between 2012 and 2019, 345 patients with symptomatic SAS (median age 87 years [84–89]; 46% male) underwent a CGA followed by a TAVR at our institution. They had low dependency in basic ADL (median ADL score 7 on 24 points, IQR [6–8]), few had cognitive impairment (8,3%) and most patients lived at home (95%). According to the CFS, patients were fit (11%), vulnerable (21%), mildly frail (37%), and moderately/severely frail (31%). The most frequent cardiovascular conditions were arterial hypertension (87%), CAD (56%), AF (37%), PAD (31%), and CHF (26%). Cardiac echography showed the following median [IQR] values: LVEF 60% [50–60], aortic valve area (0.70 $cm^2$ [0.60–0.80], and peak aortic gradient 75 mmHg [62–93]. The median STS score and Euroscore2 were 5 [3.6–7.4] and 4.1 [2.4–6.6], respectively. Renal failure (estimated glomerular filtration rate < 50 ml/min) was present in 246 patients (73%) and marked anemia (hemoglobin < 10 g/dl)

in 45 patients (13%). Endovascular TAVR (transfemoral or transcarotid) was performed in 293 patients (86%), and mini-surgical TAVR in the other 48 patients (14%). Balloon-expandable valves were used in 124 patients (37%) while self-expandable valves were used in 209 patients (63%).

### Two-year mortality rate

Early mortality (30-day) was observed in 11 (3%) patients, whereas mid-term and long-term mortality (1-year and 2-year) were observed in 56 (16%) and 89 (26%) patients, respectively. Differences in clinical characteristics between the 256 patients alive (74.2%) and the 89 deceased patients (25.8%) at 2 years after TAVR are reported in Table 1. Deceased patients were significantly older, more dependent (higher ADL score), more often in atrial fibrillation, had lower eGFR, and were more often implanted with balloon-expandable valves ($p < 0.05$ for all comparisons). The most appropriate cut-off value (see methods) of risk factors associated ($p < 0.1$) with 2-year mortality in this univariable analysis were age ≥ 87 years, ADL ≥ 9, BMI ≤ 24 kg/m$^2$, eGFR ≤ 50 mL/min, hemoglobin ≤ 10 g/dL, atrial fibrillation, NYHA III/IV, pulmonary hypertension, previous CABG, coronary artery disease, valve type, and presence of a pacemaker before intervention.

### Risk score for two-year mortality

These twelve items were introduced, alongside moderate/severe clinical frailty (CFS 6–7), in the best subset selection process. The best multivariable Cox model to predict 2-year mortality included six risk factors, namely atrial fibrillation (HR 2.01, $p = 0.002$), hemoglobin ≤ 10 g/dL (HR 2.03, $p = 0.008$), age ≥ 87 years (HR 1.77, $p = 0.014$), eGFR ≤ 50 mL/min (HR 1.64, $p = 0.10$), BMI ≤ 24 kg/m$^2$ (HR 1.67, $p = 0.025$) and CFS 6–7 (HR 1.62, $p = 0.038$) (Table 2). No significant interactions among the selected variables were found. Points were assigned to each risk factor (Table 3) and a cumulative risk score was computed by the sum of points for each patient (range 0 to 12). The resulting risk score (median 5, interquartile range = 3) showed a good discriminative power for 2-year mortality prediction (AUC 0.70, ROC curve).

The 2-year mortality rate risk was defined as low (0–3 points), medium (4–7 points), or high (8–12 points) (Table 4), which related to 2-year mortality rates of, respectively, 10.5% (CI 5.3–19.7), 25% (CI 19.4–31.5) and 45.3% (CI 33.6–57.5) (Fig. 1). Compared to low-risk patients, medium-risk patients (HR 2.60, p-value 0.011) and high-risk patients (HR 5.45, p-value < 0.001) had a higher 2-year mortality risk (Log-rank p-value < 0.001) (Fig. 2). The cut-off of 8 points, defining high-risk patients, could discriminate patients with 2-year mortality with a specificity of 86% and a sensitivity of 34% (positive likelihood ratio: 2.43). The mean AUC computed from the internal fivefold cross-validation process was 0.69, showing that the model remained robust toward new data (Fig. 3.).

## Discussion

This study provides some important findings in very old patients undergoing a TAVR. First, 2-year mortality was associated with several baseline variables (medical, biological, and functional) readily available at the time of Heart Team TAVR decision-making. Interestingly, atrial fibrillation was the strongest predictor of mortality. Second, moderate to severe frailty (CFS 6–7) could significantly increase discrimination of those at higher risk of 2-year mortality in multivariable modeling. Third, a 2-year mortality risk score, the OLD-TAVR score, was developed based on the best-dichotomized cut-off values of six bio-clinical risk factors. At last, this simple risk score showed a fair predictive performance (AUC 0.70), robust against new data, and was able to identify patients with a poor vital prognosis after the TAVR procedure.

Decision-making regarding TAVR can be challenging in very old patients and should be oriented by the expected benefits and risks in those eligible for such an intervention. Long-term survival (two years and more) in this population is a key indicator. As traditional surgical risk scores failed to predict long-term survival, the identification of risk factors of long-term mortality is important [7, 13, 25].

In the present analysis, the overall two-year mortality (26%) was in line with the figures (16.9–38%) reported by three TAVR studies [2, 26, 27]. We paid special attention to the frailty status, as the clinical frailty score (CFS) has been shown to be associated with survival in the Japanese OCEAN-TAVI registry [14]. In our study, a non-significant trend ($p = 0.17$) was observed between moderate/severe frailty (CFS 6–7) and two-year mortality in univariable analysis. Considered along with other bio-clinical variables in multivariable analysis, frailty (CFS 6–7) did however significantly contribute to discriminating patients at high risk of 2-year mortality. The latter observation is due to the significant cumulative effect of comorbidity and frailty. Therefore, we suggest that CFS 6–7, considered by itself, should not preclude a patient from receiving a TAVR. Hence, frailty should be integrated and interpreted with patients' other morbidities.

As reported in the literature, several other bio-clinical markers contribute to the risk stratification of older patients. First, low BMI in older patients is associated with poor outcome [28–30]. Our data similarly exposed lower BMI to be predictive of 2-year mortality with a cut-off value of 24 kg/m$^2$. Second, CKD has been shown to be frequent in older

**Table 1** General characteristics of patients according to survival status

| | Missing | Alive, N = 256[1] | Dead, N = 89[1] | p-value[2] |
|---|---|---|---|---|
| *Demographic* | | | | |
| Age, years | 0 (0%) | 86 (83, 89) | 87 (85, 90) | **0.008** |
| Female sex, % | 5 (1.4%) | 136 (54%) | 47 (53%) | 0.93 |
| Nursing home, % | 2 (0.6%) | 11 (4.3%) | 5 (5.6%) | 0.57 |
| BMI, kg/m$^2$ | 3 (0.9%) | 25.6 (23.5, 28.7) | 24.7 (22.3, 27.7) | 0.080 |
| *Scores* | | | | |
| Euroscore 2 | 70 (20%) | 4.2 (2.3, 6.7) | 3.9 (2.5, 6.4) | 0.81 |
| STS score | 37 (11%) | 4.82 (3.59, 7.05) | 6.17 (3.50, 8.00) | 0.059 |
| Charlson index | 47 (14%) | 2 (1, 3) | 2 (1, 3) | 0.79 |
| $CHA^2DS^2VASC$ | 38 (11%) | 5 (4, 6) | 5 (4, 5) | 0.29 |
| NYHA 3–4 | 1 (0.3%) | 167 (65%) | 67 (76%) | 0.059 |
| *Geriatric assessment* | | | | |
| iADL | 4 (1.2%) | 5 (3, 6) | 4 (3, 5) | 0.70 |
| ADL | 3 (0.9%) | 7 (6, 8) | 7 (6, 9) | **0.036** |
| Cognitive impairment, % | 8 (2.3%) | 22 (8.7%) | 6 (7.1%) | 0.63 |
| MNA-SF (0–14) | 17 (4.9%) | 11 (9, 13) | 11 (8, 13) | 0.40 |
| Falls, % | 20 (5.8%) | 53 (22%) | 20 (25%) | 0.58 |
| CFS, median [IQR] | 0 (0%) | 5 (4, 6) | 5 (4, 6) | 0.26 |
| CFS 6–7, % | 0 (0%) | 75 (29%) | 33 (37%) | 0.17 |
| *Cardiac echography* | | | | |
| LVEF | 22 (6.4%) | 60 (50, 61) | 60 (49, 60) | 0.17 |
| AVA | 3 (0.9%) | 0.70 (0.60, 0.80) | 0.65 (0.50, 0.80) | 0.59 |
| Peak gradient | 2 (0.6%) | 75 (63, 95) | 75 (60, 87) | 0.36 |
| Mean gradient | 7 (2.0%) | 46 (38, 58) | 44 (36, 54) | 0.24 |
| *Cardiovascular history* | | | | |
| Diabetes | 1 (0.3%) | 46 (18%) | 15 (17%) | 0.80 |
| Arterial hypertension | 1 (0.3%) | 223 (87%) | 75 (84%) | 0.45 |
| Coronary artery disease | 34 (9.9%) | 136 (58%) | 38 (49%) | 0.14 |
| Pacemaker | 34 (9.9%) | 44 (19%) | 22 (28%) | 0.081 |
| Atrial fibrillation | 0 (0%) | 86 (34%) | 43 (48%) | **0.013** |
| CHF | 0 (0%) | 65 (25%) | 25 (28%) | 0.62 |
| Stroke | 34 (9.9%) | 39 (17%) | 11 (14%) | 0.58 |
| Peripheral arterial disease | 34 (9.9%) | 76 (33%) | 21 (27%) | 0.35 |
| Previous PH | 0 (0%) | 55 (21%) | 28 (31%) | 0.058 |
| *Laboratory values* | | | | |
| Creatinine, mg/dl | 6 (1.7%) | 1.10 (0.86, 1.37) | 1.15 (0.91, 1.44) | 0.25 |
| Hemoglobin, g/dl | 6 (1.7%) | 12.10 (10.9, 13.1) | 11.80 (10.3, 12.8) | 0.093 |
| eGFR (Cockcroft-Gault), ml/min | 7 (2.0%) | 241 (31, 53) | 36 (27, 46) | **0.009** |
| *TAVR procedure* | | | | |
| *Valve type* | 12 (3.5%) | | | **0.015** |
| Balloon expandable | | 83 (33%) | 41 (48%) | |
| Self-expandable | | 165 (67%) | 44 (52%) | |
| *Valve access* | 4 (1.2%) | | | 0.35 |
| Endovascular | | 220 (87%) | 73 (83%) | |
| Mini -surgical | | 33 (13%) | 15 (17%) | |

[1]n (%); Median (IQR), ADL = Activities of Daily Living (Katz), iADL = instrumental Activities of Daily Living (Lawton), BMI = Body Mass Index, MNA-SF = Mini Nutrition Assessment Short Form, CFS = Clinical Frailty Scale, LVEF = Left Ventricul Ejection Fraction, AVA = Aortic Valve Area, CHF = Congestive Heart Failure, PH = Pulmonary Hypertension, eGFR = estimated Glomerular Filtration Rate, TAVR = Transcatheter Aortic Valve Replacement

[2]Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank sum test

**Table 2** Two-year mortality multivariable Cox regression model development

| | Univariable | | | Multivariable | | |
|---|---|---|---|---|---|---|
| | HR[1] | 95% CI[1] | p-value | HR | 95% CI | p-value |
| Atrial fibrillation | 1.65 | 1.09, 2.50 | 0.018 | 2.01 | 1.29, 3.12 | 0.002 |
| Age ≥ 87 years | 1.86 | 1.21, 2.86 | 0.005 | 1.77 | 1.12, 2.80 | 0.014 |
| BMI ≤ 24 kg/m$^2$ | 1.69 | 1.11, 2.57 | 0.015 | 1.67 | 1.07, 2.61 | 0.025 |
| Cockcroft-Gault ≤ 50 mL/min/1.73m$^2$ | 2.10 | 1.18, 3.72 | 0.011 | 1.64 | 0.91, 2.95 | 0.10 |
| Hemoglobin ≤ 10 g/dL | 2.04 | 1.23, 3.39 | 0.006 | 2.03 | 1.20, 3.43 | 0.008 |
| CFS 6–7 | 1.35 | 0.88, 2.07 | 0.17 | 1.62 | 1.03, 2.54 | 0.038 |
| NYHA | 1.58 | 0.97, 2.58 | 0.067 | Not selected | | |
| Pulmonary hypertension | 1.62 | 1.04, 2.54 | 0.034 | Not selected | | |
| Coronary artery disease | 0.62 | 0.41, 0.94 | 0.026 | Not selected | | |
| *Valve type* | | | | Not selected | | |
| Balloon expandable | – | – | | Not selected | | |
| Self-expandable | 0.59 | 0.38, 0.90 | 0.015 | Not selected | | |
| Pacemaker | 1.52 | 0.93, 2.49 | 0.10 | Not selected | | |
| ADL score > 9 | 1.66 | 1.05, 2.62 | 0.030 | Not selected | | |
| LVEF ≤ 50 | 1.19 | 0.75, 1.88 | 0.46 | Not selected | | |

HR = Hazard Ratio, CI = Confidence Interval, ADL = Activities of Daily Living, BMI = Body Mass Index, CFS = Clinical Frailty Scale, LVEF = Left Ventricul Ejection Fraction

n = 336; N events = 86

Not Selected = variables that were not selected in the multivariable model

**Table 3** Score development

| | Prevalence, N (N/Total %) | 2-year mortality, n (n/N %) | Score |
|---|---|---|---|
| Atrial fibrillation | 125 (37%) | 42 (33%) | 3 |
| CFS 6–7 | 104 (31%) | 32 (31%) | 2 |
| Age ≥ 87 year | 169 (50%) | 54 (32%) | 2 |
| BMI ≤ 24 kg/m$^2$ | 112 (33%) | 37 (33%) | 2 |
| Cockcroft-Gault < 50 ml/min | 246 (73%) | 72 (29%) | 2 |
| Hemoglobin ≤ 10 g/dL | 45 (13%) | 19 (38%) | 3 |

CFS = Clinical Frailty Scale, BMI = Body Mass Index

Number of observations = 336, number of events = 86

patients undergoing TAVR (eGFR < 60 mL/min in 50–70%, eGFR < 30 mL/min in 8–12%) [31, 32] and has consistently been associated with lower survival across different national registries and a large-scale meta-analysis [32–35]. In the present study, the best cut-off for eGFR was 50 ml/min/1.73m$^2$, a value comparable to those of 45 ml/min and 47 ml/min found in studies of TAVR among CKD patients [31, 36]. Thirdly, anemia is one of the most frequent comorbidities in patients with aortic stenosis and is prevalent in more than 50% of patients undergoing TAVR [37]. Pre-TAVR anemia has been shown to be associated (RR 1.43) with long-term mortality [38].

Along with those bio-clinical markers, pre-TAVR atrial fibrillation (AF) was frequent (37%) in our study, and comparable to the AF prevalence (41,5%) reported in a large observational study of TAVR patients [39]. Our analysis highlighted that atrial fibrillation (AF) was the strongest risk factor for two-year mortality in univariable and multivariable analyses. Numerous TAVR studies, including PARTNER, reported an association between AF and worse

**Table 4** Risk group stratification and Cox regression model of the final score

| | Overall, N = 336 | Survived, N = 250 | Dead, N = 86 | HR | 95% CI | p-value[a] |
|---|---|---|---|---|---|---|
| Low risk [0,3] | 76 (23%) | 68 (89%) | 8 (10.5%) | – | – | ref |
| Medium risk [4–7] | 196 (58%) | 147 (75%) | 49 (25%) | 2.60 | 1.23, 5.48 | 0.012 |
| High risk [8–12] | 64 (19%) | 35 (54%) | 29 (45.5%) | 5.45 | 2.49, 11.9 | < 0.001 |

HR = Hazard Ratio, CI = Confidence Interval, AUC = 0.70, specificity is 0.86 and sensitivity is 0.33 to detect high risk patient (score ≥ 8)

[a]Adjusted p-value by Tukey method for comparing a family of 4 estimates

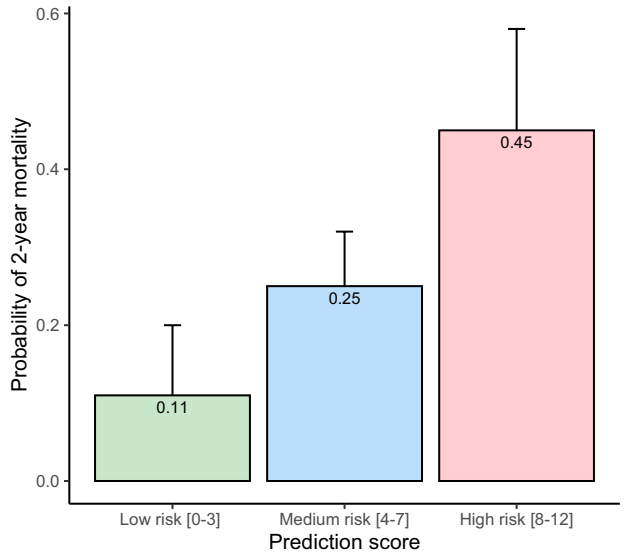


**Fig. 1** Probability of 2-year survival per risk strata. The 2-year mortality risk was defined as low (0–3 points), medium (4–7 points), or high (8–12 points), which relates to 2-year mortality rates of, respectively 10.5% (CI 5.3–19.7), 25% (CI 19.4–31.5) and 45.3% (CI 33.6–57.5)

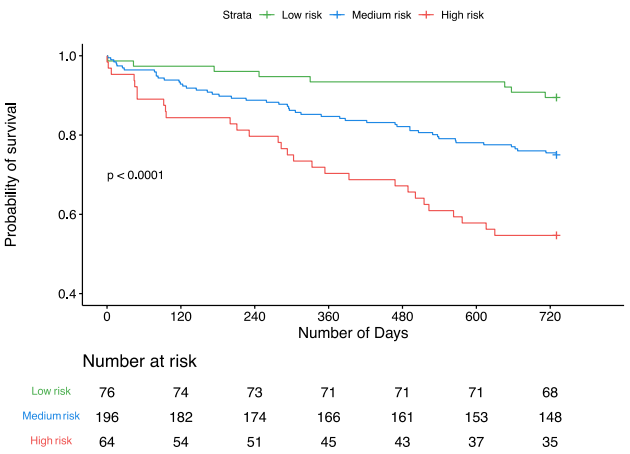


**Fig. 2** Kaplan–Meier survival plot per risk strata i.e., low (0–3 points), medium (4–7 points), or high (8–12 points) risk. Compared to low-risk patients, medium-risk patients (HR 2.60, p-value 0.011) and high-risk patients (HR 5.45, p-value < 0.001) have a higher 2-year mortality risk (Log-rank p-value < 0.001)

mid and long-term outcomes (survival, bleeding, stroke, and rehospitalization) [40–42]. It has been suggested that AF is a surrogate for a "sicker" group of patients and identifies those patients with more complicated perioperative courses [43]. In older patients, AF has indeed been associated with several geriatric syndromes, including frailty, and higher co-morbidity burden [44, 45]. These associations between AF, frailty, and poor general health are increasingly acknowledged [46, 47]. Hence, considering these data, AF in an older patient with SAS should trigger attention during pre-TAVR heart team decision-making.

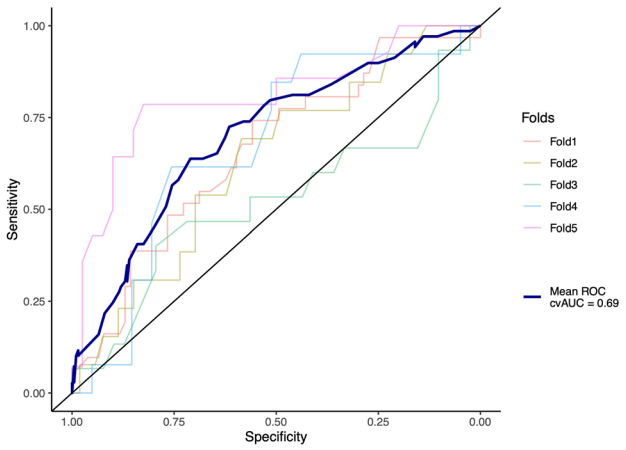


**Fig. 3** Receiver Operating Curves (ROC) of the different folds of the cross-validation process. Mean ROC is computed from ROC curves of the 5 folds. The mean cross validated Area Under the Curve (cvAUC) is 0.69

Based on those significant risk factors of two-year mortality, we developed a simple predictive risk score, named OLD-TAVR score, which showed a fair predictive yield (AUC 0.70). Only a few other 2-year mortality scores in TAVR patients have been published. The score by Skaar et al. was developed in a rather small cohort (142 patients, mean age 83.4) and based on the Charlson index and CGA items (cognition, iADL, BMI, energy level, weight loss, limb strength, and Hospital Anxiety and Depression Scale) [28]. The score by Lee et al., from a cohort of 187 patients (mean age 81 years) was based on nine variables (age ≥ 90 years, BMI < 30 kg/m$^2$, NYHA class IV, pulmonary hypertension, the critical hemodynamic state before TAVR, ≥ 2 episodes of pulmonary edema during the last year, respiratory insufficiency, dialysis, and non-transfemoral TAVR approach) and showed a rather low c-statistics (0.61) [12]. The latter score did not incorporate any geriatric variable. In contrast, our risk score has been developed in older patients and combines classical bio-clinical risk factors and frailty status. Interestingly, the main bio-clinical risk factors in our study (i.e., BMI, AF, eGFR, and CFS) are those found in the recent mid-term (one-year) mortality risk score derived from the OCEAN TAVR registry (AUC 0.76).

Patients were classified into three risk groups in our study, namely low, medium, and high risk, with significantly different survival during the 2-year follow-up. Using the OLD-TAVR score (range 0–12), the cut-off value at 8 (high risk) could identify 2-year mortality with high specificity (86%) and good predictive power (+LR 2.4). Those high-risk patients have at least a 33% and up to 58% mortality risk at

two years (lower and upper boundary of the 95% CI around the estimate). The score might therefore be helpful for Heart Teams to identify those older patients with a too-low 2-year survival expectancy and thus those in which the intervention may be futile. It must be noted that therapeutic futility has no clear definition and is rather a generic term referring to a lack of medical efficacy [48]. A published consensus paper suggested that TAVR may be futile in patients with a life expectancy < 1 year and in patients with a probability of "survival with benefit" lower than 25% at 2 years [49]. Survival with benefit, defined as improvement in functional class status, has not yet been well studied in older patients with TAVR [50].

Our study presents some limitations. First, it lacks functional outcomes, which is, unfortunately, the case in most TAVR studies conducted in very old patients. However, data on functional recovery in such patients could help better define the patients with poor expected functional benefits from TAVR besides crude survival benefits. Nevertheless, based on the CGA data, the Heart Team might initiate or intensify geriatric interventions, aiming at functionality and quality of life. Second, due to its retrospective design, our study lacks data on the cause of death, particularly cardiovascular deaths versus non-cardiovascular ones. Third, some variables of interest in older patients, e.g., serum albumin, had > 10% missing data excluding them from the multivariable analysis. Finally, even though the score has shown to be robust through internal validation, it remains to be externally validated. The main strengths of our study are the completion of a comprehensive geriatric assessment, the use of the CFS, long-term follow-up, and the development of a risk score which may help in TAVR decision-making.

## Conclusion

A risk score, named OLD-TAVR score, for 2-year mortality in very old patients undergoing TAVR was developed based on six bio-clinical items, including moderate/severe frailty (CFS 6–7). Using the score (range 0–12), a value ≥ 8 could help identify very old patients in whom TAVR might be futile. Prospective validation of the score is needed before integrating it into TAVR decision-making in very old patients with SAS.

**Author contributions:** CDT and BB conceived the study design. FM, JK and CDT were involved in data collection and CDT assured data curation. CDT performed formal analysis and statistical analysis. CDT, FM, and BB contributed to the data interpretation. CDT and BB wrote the original draft. FM, IG, JK, PC, and BB edited and reviewed the manuscript for intellectual content, BB supervised the study.

**Funding** The present study did not receive any funding.

**Data availability** The data that support the findings of this study are available from the corresponding author, [CDT], upon reasonable request.

## Declarations

**Conflict of interest** The authors have no competing interests to declare that are relevant to the content of this article.

**Ethical approval** The local Ethics Committee approved the study protocol B403 and due to the study design, the need for informed consent was waived. The study was performed following the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

**Informed consent** For this type of study, no informed consent is required.

## References

1. Yamamoto M, Mouillet G, Meguro K, Gilard M, Laskar M, Eltchaninoff H et al (2014) Clinical results of transcatheter aortic valve implantation in octogenarians and nonagenarians: insights from the FRANCE-2 registry. Ann Thorac Surg 97:29–36. https://doi.org/10.1016/j.athoracsur.2013.07.100
2. Noguchi M, Tabata M, Obunai K, Shibayama K, Ito J, Watanabe H et al (2021) Clinical outcomes of transcatheter aortic valve implantation (TAVI) in nonagenarians from the optimized catheter valvular intervention - TAVI registry. Catheter Cardiovasc Interv. https://doi.org/10.1002/ccd.28935
3. Habertheuer A, Aranda-Michel E, Schindler J, Gleason TG, Kilic A, Kliner D et al (2021) Longitudinal outcomes of nonagenarians undergoing transcatheter aortic valve replacement. Ann Thorac Surg 111:1520–1528. https://doi.org/10.1016/j.athoracsur.2020.06.140
4. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J et al (2022) 2021 ESC/EACTS Guidelines for the management of valvular heart disease: developed by the task force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Rev Esp Cardiol Engl Ed 75:524. https://doi.org/10.1016/j.rec.2022.05.006
5. Nashef SAM, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR et al (2012) EuroSCORE II. Eur J Cardiothorac Surg 41:734–745. https://doi.org/10.1093/ejcts/ezs043
6. O'Brien SM, Shahian DM, Filardo G, Ferraris VA, Haan CK, Rich JB et al (2009) The society of thoracic surgeons 2008 cardiac surgery risk models: part 2—isolated valve surgery. Ann Thorac Surg 88:S23-42. https://doi.org/10.1016/j.athoracsur.2009.05.056
7. Debonnaire P, Fusini L, Wolterbeek R, Kamperidis V, van Rosendael P, van der Kley F et al (2015) Value of the "TAVI2-SCORe" versus surgical risk scores for prediction of one year mortality in 511 patients who underwent transcatheter aortic valve implantation. Am J Cardiol 115:234–242. https://doi.org/10.1016/j.amjcard.2014.10.029
8. Al-Farra H, Abu-Hanna A, de Mol BAJM, ter Burg WJ, Houterman S, Henriques JPS et al (2020) External validation of existing prediction models of 30-day mortality after Transcatheter Aortic Valve Implantation (TAVI) in the Netherlands Heart Registration. Int J Cardiol 317:25–32. https://doi.org/10.1016/j.ijcard.2020.05.039
9. Wolff G, Shamekhi J, Al-Kassou B, Tabata N, Parco C, Klein K et al (2021) Risk modeling in transcatheter aortic valve replacement remains unsolved: an external validation study in 2946

German patients. Clin Res Cardiol 110:368–376. https://doi.org/10.1007/s00392-020-01731-9
10. Vahanian A, Alfieri O, Al-Attar N, Antunes M, Bax J, Cormier B et al (2008) Transcatheter valve implantation for patients with aortic stenosis: a position statement from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 29:1463–1470. https://doi.org/10.1093/eurheartj/ehn183
11. Hioki H, Watanabe Y, Kozuma K, Kawashima H, Nagura F, Nakashima M et al (2019) The MAGGIC risk score predicts mortality in patients undergoing transcatheter aortic valve replacement: sub-analysis of the OCEAN-TAVI registry. Heart Vessels 34:1976–1983. https://doi.org/10.1007/s00380-019-01443-9
12. Lee ZX, Elangovan S, Anderson R, Groves P (2020) Short- and medium-term survival after TAVI: Clinical predictors and the role of the FRANCE-2 score. Int J Cardiol Heart Vasc 31:100657. https://doi.org/10.1016/j.ijcha.2020.100657
13. Stortecky S, Schoenenberger AW, Moser A, Kalesan B, Jüni P, Carrel T et al (2012) Evaluation of multidimensional geriatric assessment as a predictor of mortality and cardiovascular events after transcatheter aortic valve implantation. JACC Cardiovasc Interv 5:489–496. https://doi.org/10.1016/j.jcin.2012.02.012
14. Shimura T, Yamamoto M, Kano S, Kagase A, Kodama A, Koyama Y et al (2017) Impact of the clinical frailty scale on outcomes after transcatheter aortic valve replacement. Circulation 135:2013–2024. https://doi.org/10.1161/CIRCULATIONAHA.116.025630
15. Rockwood K, Theou O (2020) Using the clinical frailty scale in allocating scarce health care resources. Can Geriatr J 23:254–259. https://doi.org/10.5770/cgj.23.463
16. Theou O, Pérez-Zepeda MU, van der Valk AM, Searle SD, Howlett SE, Rockwood K (2021) A classification tree to assist with routine scoring of the Clinical Frailty Scale. Age Ageing 50:1406–1411. https://doi.org/10.1093/ageing/afab006
17. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM (2010) Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 137:263–272. https://doi.org/10.1378/chest.09-1584
18. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW (1963) Studies of illness in the aged: The index of ADL: a standardized measure of biological and psychosocial function. JAMA 185:914–919. https://doi.org/10.1001/jama.1963.03060120024016
19. Lawton MP, Brody EM (1969) Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 9:179–186
20. MNA-International Group, Kaiser MJ, Bauer JM, Ramsch C, Uter W, Guigoz Y et al (2009) Validation of the Mini Nutritional Assessment short-form (MNA®-SF): a practical tool for identification of nutritional status. J Nutr Health Aging 13:782–8. https://doi.org/10.1007/s12603-009-0214-7
21. Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198. https://doi.org/10.1016/0022-3956(75)90026-6
22. Rockwood K (2005) A global clinical measure of fitness and frailty in elderly people. Can Med Assoc J 173:489–495. https://doi.org/10.1503/cmaj.050051
23. Hocking RR, Leslie RN (1967) Selection of the best subset in regression analysis. Technometrics 9:531–540. https://doi.org/10.1080/00401706.1967.10490502
24. Airola A, Pahikkala T, Waegeman W, Baets BD, Salakoski T (2009) A comparison of AUC estimators in small-sample studies. Proc Third Int Workshop Mach Learn Syst Biol PMLR 3–13
25. Greason KL, Eleid MF, Nkomo VT, King KS, Williamson EE, Sandhu GS et al (2018) Predictors of 1-year mortality after transcatheter aortic valve replacement. J Card Surg 33:243–249. https://doi.org/10.1111/jocs.13574
26. Arnold SV, Petrossian G, Reardon MJ, Kleiman NS, Yakubov SJ, Wang K et al (2021) Five-year clinical and quality of life outcomes from the corevalve US pivotal extreme risk trial. Circ Cardiovasc Interv 14:e010258. https://doi.org/10.1161/CIRCINTERVENTIONS.120.010258
27. Codner P, Orvin K, Assali A, Sharony R, Vaknin-Assa H, Shapira Y et al (2015) Long-term outcomes for patients with severe symptomatic aortic stenosis treated with transcatheter aortic valve implantation. Am J Cardiol 116:1391–1398. https://doi.org/10.1016/j.amjcard.2015.08.004
28. Skaar E, Eide LSP, Norekvål TM, Ranhoff AH, Nordrehaug JE, Forman DE et al (2019) A novel geriatric assessment frailty score predicts 2-year mortality after transcatheter aortic valve implantation. Eur Heart J Qual Care Clin Outcomes 5:153–160. https://doi.org/10.1093/ehjqcco/qcy044
29. Yamamoto M, Otsuka T, Shimura T, Yamaguchi R, Adachi Y, Kagase A et al (2021) Clinical risk model for predicting 1-year mortality after transcatheter aortic valve replacement. Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv 97:E544–E551. https://doi.org/10.1002/ccd.29130
30. Seiffert M, Sinning J-M, Meyer A, Wilde S, Conradi L, Vasa-Nicotera M et al (2014) Development of a risk score for outcome after transcatheter aortic valve implantation. Clin Res Cardiol Off J Ger Card Soc 103:631–640. https://doi.org/10.1007/s00392-014-0692-4
31. Mas-Peiro S, Faerber G, Bon D, Herrmann E, Bauer T, Bleiziffer S et al (2021) Impact of chronic kidney disease in 29 893 patients undergoing transcatheter or surgical aortic valve replacement from the German aortic valve registry. Eur J Cardiothorac Surg 59:532–544. https://doi.org/10.1093/ejcts/ezaa446
32. Thourani VH, Forcillo J, Beohar N, Doshi D, Parvataneni R, Ayele GM et al (2016) Impact of preoperative chronic kidney disease in 2,531 high-risk and inoperable patients undergoing transcatheter aortic valve replacement in the PARTNER trial. Ann Thorac Surg 102:1172–1180. https://doi.org/10.1016/j.athoracsur.2016.07.001
33. Chen C, Zhao Z-G, Liao Y-B, Peng Y, Meng Q-T, Chai H et al (2015) Impact of renal dysfunction on mid-term outcome after transcatheter aortic valve implantation: a systematic review and meta-analysis. PLOS One 10:e0119817. https://doi.org/10.1371/journal.pone.0119817
34. Dumonteil N, van der Boon RMA, Tchetche D, Chieffo A, Van Mieghem NM, Marcheix B et al (2013) Impact of preoperative chronic kidney disease on short- and long-term outcomes after transcatheter aortic valve implantation: A Pooled-RotterdAm-Milano-Toulouse In Collaboration Plus (PRAGMATIC-Plus) initiative substudy. Am Heart J 165:752–760. https://doi.org/10.1016/j.ahj.2012.12.013
35. Ferro CJ, Chue CD, de Belder MA, Moat N, Wendler O, Trivedi U et al (2015) Impact of renal function on survival after transcatheter aortic valve implantation (TAVI): an analysis of the UK TAVI registry. Heart 101:546–552. https://doi.org/10.1136/heartjnl-2014-307041
36. Yamamoto M, Hayashida K, Mouillet G, Hovasse T, Chevalier B, Oguri A et al (2013) Prognostic value of chronic kidney disease after transcatheter aortic valve implantation. J Am Coll Cardiol 62:869–877. https://doi.org/10.1016/j.jacc.2013.04.057
37. Nuis R-J, Sinning J-M, Rodés-Cabau J, Gotzmann M, van Garsse L, Kefer J et al (2013) Prevalence, factors associated with, and prognostic effects of preoperative anemia on short- and long-term mortality in patients undergoing transcatheter aortic valve implantation. Circ Cardiovasc Interv 6:625–634. https://doi.org/10.1161/CIRCINTERVENTIONS.113.000409

38. Kanjanahattakij N, Rattanawong P, Krishnamoorthy P, Sirinvaravong N, Chongsathidkiet P, Lapumnuaypol K et al (2019) Anaemia and mortality in patients with transcatheter aortic valve replacement: a systematic review and meta-analysis. Acta Cardiol 74:386–392. https://doi.org/10.1080/00015385.2018.1510802
39. Khan MZ, Zahid S, Khan MU, Kichloo A, Jamal S, Minhas AMK et al (2021) Outcomes of transcatheter aortic valve replacement in patients with and without atrial fibrillation: Insight from national inpatient sample. Expert Rev Cardiovasc Ther 19:939–946. https://doi.org/10.1080/14779072.2021.1988852
40. Biviano AB, Nazif T, Dizon J, Garan H, Fleitman J, Hassan D et al (2016) Atrial fibrillation is associated with increased mortality in patients undergoing transcatheter aortic valve replacement: insights from the placement of aortic transcatheter valve (PARTNER) trial. Circ Cardiovasc Interv. https://doi.org/10.1161/CIRCINTERVENTIONS.115.002766
41. Sannino A, Stoler RC, Lima B, Szerlip M, Henry AC, Vallabhan R et al (2016) Frequency of and prognostic significance of atrial fibrillation in patients undergoing transcatheter aortic valve implantation. Am J Cardiol 118:1527–1532. https://doi.org/10.1016/j.amjcard.2016.08.017
42. Tarantini G, Mojoli M, Windecker S, Wendler O, Lefèvre T, Saia F et al (2016) Prevalence and impact of atrial fibrillation in patients with severe aortic stenosis undergoing transcatheter aortic valve replacement: an analysis from the SOURCE XT prospective multicenter registry. JACC Cardiovasc Interv 9:937–946. https://doi.org/10.1016/j.jcin.2016.01.037
43. McLeod CJ, Gersh BJ (2016) Atrial fibrillation post-transcatheter aortic valve replacement: cause, consequence, or confounder?∗. JACC Cardiovasc Interv 9:947–949. https://doi.org/10.1016/j.jcin.2016.02.033
44. de Terwangne C, Lelubre C, Hanotier P, de Meester A, Descamps O, Duray C et al (2022) Prevalence and impact of atrial fibrillation on intra-hospital mortality in patients aged ≥75 years. Am J Cardiol 177:40–47. https://doi.org/10.1016/j.amjcard.2022.04.050
45. de Terwangne C, Sorgente A, Macovei S, Preumont T, Chierchia G, de Asmundis C et al (2022) Association between atrial fibrillation, frailty, and geriatric syndromes in the late elderly in a south Belgian outpatient and inpatient setting. Am Heart J Plus Cardiol Res Pract. https://doi.org/10.1016/j.ahjo.2022.100106
46. Richard G, O'Halloran AM, Doody P, Harbison J, Kenny RA, Romero-Ortuno R (2022) Atrial fibrillation and acceleration of frailty: findings from the Irish longitudinal study on ageing. Age Ageing. https://doi.org/10.1093/ageing/afab273
47. Villani ER, Tummolo AM, Palmer K, Gravina EM, Vetrano DL, Bernabei R et al (2018) Frailty and atrial fibrillation: A systematic review. Eur J Intern Med 56:33–38. https://doi.org/10.1016/j.ejim.2018.04.018
48. Puri R, Iung B, Cohen DJ, Rodés-Cabau J (2016) TAVI or No TAVI: identifying patients unlikely to benefit from transcatheter aortic valve implantation. Eur Heart J 37:2217–2225. https://doi.org/10.1093/eurheartj/ehv756
49. Minha S, Marcus G (2021) Can we truly predict futility for TAVR based on pre-procedural indices? Cardiovasc Revasc Med 23:77–78. https://doi.org/10.1016/j.carrev.2020.11.009
50. Straiton N, Jin K, Bhindi R, Gallagher R (2018) Functional capacity and health-related quality of life outcomes post transcatheter aortic valve replacement: a systematic review and meta-analysis. Age Ageing 47:478–482. https://doi.org/10.1093/ageing/afx203