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Futility Risk Model for Predicting Outcome After Transcatheter Aortic Valve Implantation

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Risk-benefit assessment for transcatheter aortic valve implantation (TAVI) is still a matter of debate. We aimed to identify patients with a bad outcome within 1 year after TAVI, and to develop a Futile TAVI Simple score (FTS). Based on the administrative hospital-discharge database, all consecutive patients treated with percutaneous TAVI in France between 2010 and 2018 were included. A prediction model was derived and validated for 1-year all-cause death after TAVI (considered as futility) by using split-sample validation: 20,443 patients were included in the analysis (mean age 83 ± 7 years). 7,039 deaths were recorded (yearly incidence rate 15.5%), among which 3,702 (53%) occurred in first year after TAVI procedure. In the derivation cohort (n = 10,221), the final logistic regression model included male sex, history of hospital stay with heart failure, history of pulmonary oedema, atrial fibrillation, previous stroke, vascular disease, renal disease, liver disease, pulmonary disease, anaemia, history of cancer, metastasis, depression and denutrition. The area under the curve (AUC) for the FTS was 0.674 (95%CI 0.660 to 0.687) in the derivation cohort and 0.651 (95%CI 0.637 to 0.665) in the validation cohort (n = 10,222). The Hosmer−Lemeshow test had a p-value of 0.87 suggesting an accurate calibration. The FTS score outperformed EuroSCORE II, Charlson comorbidity index and frailty index for identifying futility. Based on FTS score, 7% of these patients were categorized at high risk with a 1-year mortality at 43%. In conclusion, the FTS score, established from a large nationwide cohort of patients treated with TAVI, may provide a relevant tool for optimizing healthcare decision. © 2020 Elsevier Inc. All rights reserved. (Am J Cardiol 2020;130:100−107)

Continuous development has improved the results of transcatheter aortic valve implantation (TAVI) for severe aortic stenosis in high surgical risk patients.[1,2] Although TAVI provides tremendous survival rate and symptom benefit for most, a sizeable group of patients do not fully benefit from intervention despite a technically successful procedure. The option to consider palliative care instead of a futile invasive procedure for these patients is increasingly recognized.[3,4] Identifying them should be grounded on predicting post-TAVI outcomes. We previously developed the CAPRI score, a score of futility meant to estimate 1-year all-scause and cardiovascular mortalities after TAVI [5]; it encompasses thoracic aortic calcification (TAC) as TAC conveys some important prognostic information [6]; yet its determination from the CT scan may be cumbersome with available tools what could limit its implementation. In addition, the CAPRI score does not encompass frailty markers. We feel that there is still room for a futility score based on simple clinical variables that can be universally used. Based on the national hospitalization database, we therefore sought to identify patients with a survival <1 year following TAVI and to develop a prediction model and calculator for identification of these patients.

Methods

This longitudinal cohort study was based on the national hospitalization database covering hospital care from the entire French population. The data for all patients admitted with aortic stenosis in France from January 2008 to December 2018 were collected from the national administrative French Programme de Médicalisation des Systèmes d'Information (PMSI) database. Each hospitalisation is encoded in a standardised dataset, which includes information about the patient (age and sex), hospital, stay, pathologies, and procedures. Routinely collected medical information includes the principal diagnosis and secondary diagnoses coded according to the International Classification of Diseases, Tenth Revision

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(ICD-10). All medical procedures are recorded according to the national nomenclature, Classification Commune des Actes Medicaux (CCAM). The reliability of PMSI data has already been assessed[7] and this database has previously been used to study patients with cardiovascular conditions, including those with aortic stenosis treated with TAVI.[8-11] The study was conducted retrospectively and, as patients were not involved in its conduct, there was no impact on their care. Ethical approval was not required, as all data were anonymized. Procedures for data collection and management were approved by the Commission Nationale de l'Informatique et des Libertés, the independent National Ethical Committee protecting human rights in France, which ensures that all information is kept confidential and anonymous (authorisation number 1897139).

From January 1, 2010 to December 31, 2018, 487,085 adults (age ≥18 years) were hospitalised with a diagnosis of aortic stenosis as the principal, related or significantly associated diagnosis. We restricted the analysis to patients admitted after 2010, as this allowed us to obtain at least 2 years of past events to define comorbidities since 2008. For the analysis of TAVI procedures, we included all adults with a single percutaneous procedure (CCAM code: DBLF001). Patient information (demographics, comorbidities, medical history, procedures and events during hospitalization or follow-up) was described using data collected in the hospital records. Based on the database, we were able to estimate a proxy of the EuroSCORE II (supplemental file).[12] We also used the Charlson Comorbidity Index and the Claims-based Frailty Index to assess patients' clinical status.[13,14] Exclusion criteria were age <18 years and TAVI via a nonpercutaneous route; patients alive but with follow up <1 year were also excluded . The overall sample of 20,443 patients was randomly partitioned into derivation (n = 10,221) and validation (n = 10,222) populations (Figure 1). Patients were followed until 31 December 2018 for the occurrence of outcomes. We aimed to evaluate the incidence all-cause death, this outcome being included with the Valve Academic Research Consortium-2 consensus document.[15] The primary end point was procedural futility, defined as 1-year mortality. A prediction model was then derived and validated.

Qualitative variables were described as counts and percentages and quantitative variable as means (standard
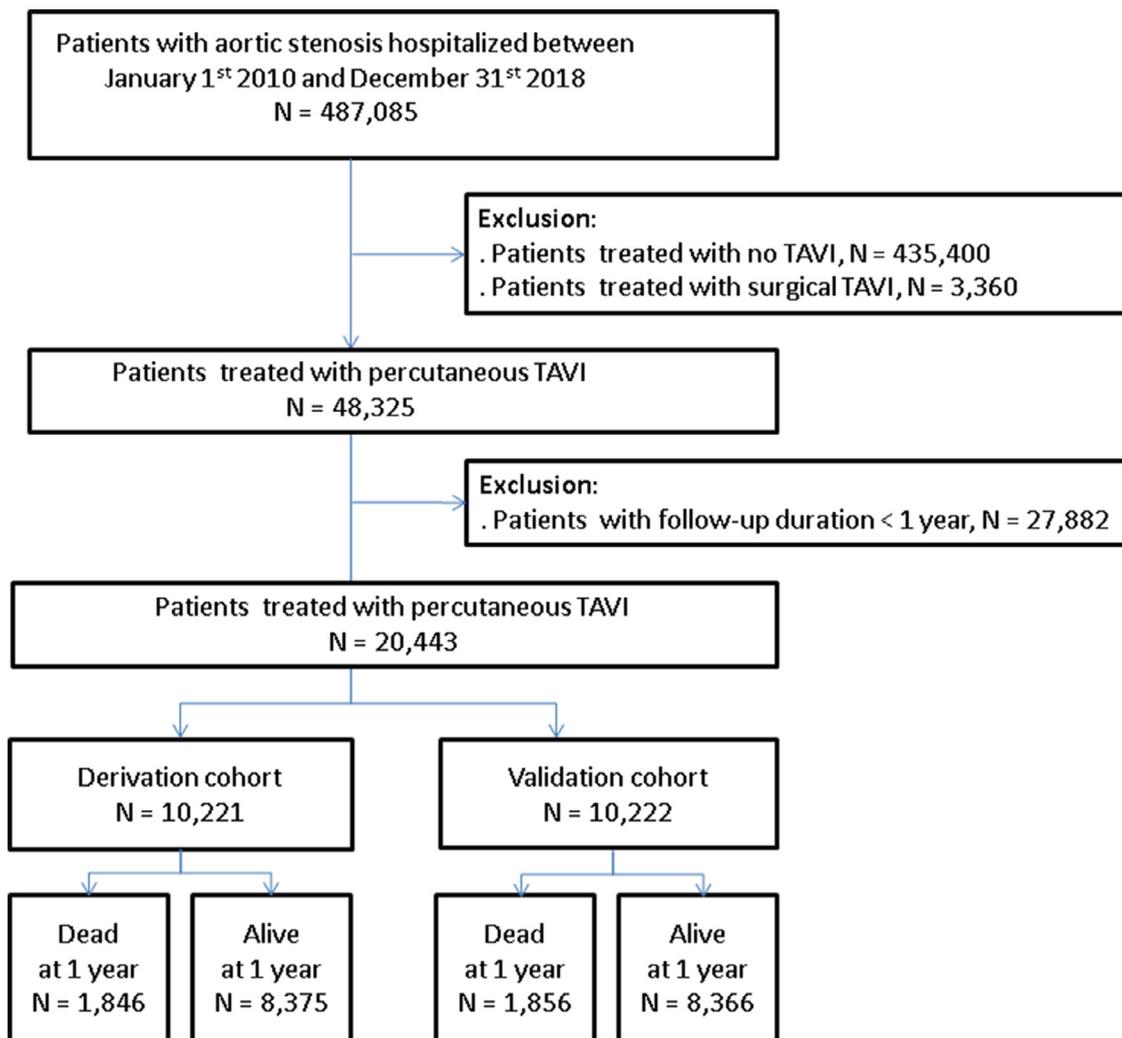

Figure 1. Flow chart of the study population.

deviations [SDs]). Comparisons were made using chi-square tests for categorical variables and the Student *t* test or nonparametric Kruskal-Wallis test, as appropriate, for continuous variables. Patients who died during the first year following the procedure were compared to patients alive at 1 year. Multivariate logistic regression was used, and results were expressed as odds ratio (OR) and 95% confidence intervals (95%CI). The Futile TAVI Simple (FTS) score was built using the multivariate logistic regression. To create the score points, the regression coefficients with p <0.05 were divided by the smallest coefficient and rounded to the nearest integer.[16,17] Receiver operating characteristic (ROC) curves were constructed and the Harrell's C-indexes (i.e., area under the curve) were calculated as a measure of model performance. ROC curves with the EuroSCORE II, Charlson Comorbidity Index and Claims-based Frailty Index were compared using the DeLong test, first in the derivation cohort and then in the validation cohort. Model calibration was considered acceptable at the Hosmer-Lemeshow goodness-of-fit test p >0.1. We then plotted observed versus predicted risks by decile of predicted risk, and the regression line was compared against the line of equality (intercept = 0, slope = 1). All comparisons with p <0.05 were considered statistically significant. Analyses were performed using Enterprise Guide 7●1, (SAS Institute Inc., SAS Campus Drive, Cary, NC) and STATA version 12.0 (Stata Corp, College Station, TX).

Results

Between January 1, 2010 and December 31, 2018, 20,443 patients with percutaneous TAVI were identified for the analysis (mean age 83 ± 7 years). The characteristics of patients in the derivation and validation cohorts are presented in Table 1. Mean follow-up was 2.09 ± 1.36 years (median 1.89, interquartile 1.18 to 2.92) and 7,039 deaths were recorded (yearly incidence rate 15.5%), among which 3,702 (53%) occurred in first year after TAVI procedure (18.1% of all patients with TAVI in our study). In the derivation cohort, patients with all-cause death during the first year of follow-up were more frequently men and had higher EuroSCORE II, Charlson comorbidity and frailty indexes. They also had higher rates for most comorbidities (Table 2). Among patients excluded of the main analysis, 77,325 had surgical aortic valve replacement (1-year death rate 7.95%) and 3,360 had surgical TAVI with apical access (1-year death rate 24.72%).

The final logistic regression model for futility included older age, history of hospital stay with heart failure, history of pulmonary oedema, atrial fibrillation, previous stroke, vascular disease, renal disease, liver disease, pulmonary disease, anaemia, history of cancer, metastasis, depression, and denutrition. The model is presented in Table 3, with corresponding points for each variable. The area under the curve (AUC) for the FTS score was 0.674 (95%CI 0.660 to 0.687). The FTS score outperformed EuroSCORE II (AUC 0.627, 95%CI 0.613 to 0.641, p <0.0001 for DeLong test), Charlson comorbidity index (AUC 0.562, 95%CI 0.548 to 0.576, p <0.0001 for DeLong test), and frailty index (AUC 0.486, 95%CI 0.472 to 0.499, p <0.0001 for DeLong test) for identifying futility (Figure 2). AUC for the FTS score

Table 1

Baseline characteristics in the derivation and validation populations treated with TAVI

Variable	Derivation (n=10221)	Validation (n=10222)	p
Age (years)	82.5±7.0	82.8±6.8	0.002
Men	5101 (50%)	5093 (50%)	0.91
Charlson comorbidity index	5.0±2.9	4.9±2.8	0.05
Frailty index	7.4±6.4	7.2±6.2	0.02
EuroSCORE II	3.9±1.0	3.9±1.0	0.87
Heart failure	6389 (63%)	6352 (62%)	0.59
History of pulmonary oedema	711 (7%)	687 (7%)	0.5
Mitral regurgitation	2093 (21%)	2065 (20%)	0.62
Aortic regurgitation	1332 (13%)	1366 (13%)	0.48
Tricuspid regurgitation	443 (4%)	416 (4%)	0.35
Coronary artery disease	6447 (63%)	6521 (64%)	0.29
Previous myocardial infarction	1550 (15%)	1591 (16%)	0.43
Dilated cardiomyopathy	1809 (18%)	1768 (17%)	0.45
Hypertension	8268 (81%)	8360 (82%)	0.1
Ischemic stroke	560 (6%)	551 (5%)	0.78
Atrial fibrillation	4897 (48%)	4991 (49%)	0.19
Previous pacemaker or Defibrillator	2214 (22%)	2270 (22%)	0.35
Obesity	2678 (26%)	2662 (26%)	0.8
Diabetes mellitus	3203 (31%)	3159 (31%)	0.5
Dyslipidaemia	4834 (47%)	4813 (47%)	0.76
Smoker	809 (8%)	799 (8%)	0.79
Vascular disease	3983 (39%)	3941 (39%)	0.54
Abnormal renal function	2116 (21%)	2014 (20%)	0.08
Liver disease	625 (6.1%)	565 (5.5%)	0.07
Lung disease	2743 (27%)	2771 (27%)	0.66
Chronic obstructive pulmonary disease	1738 (17%)	1748 (17%)	0.85
Sleep apnoea syndrome	942 (9%)	948 (9%)	0.89
Anaemia	3131 (31%)	3078 (30%)	0.42
Previous cancer	2050 (20%)	2015 (20%)	0.54
History of metastasis	242 (2%)	218 (2%)	0.26
Alcohol related diagnoses	480 (5%)	446 (4%)	0.25
Thyroid diseases	1485 (15%)	1389 (14%)	0.05
HIV infection	14 (0.1%)	9 (0.1%)	0.3
Cognitive impairment	730 (7%)	675 (7%)	0.13
Depression	1793 (18%))	1753 (17%)	0.46
Denutrition	1351 (13%)	1244 (12%)	0.02

Values are mean (SD) or n (%). SD = standard deviation; TAVI = transcatheter aortic valve replacement.

was 0.651 (95%CI 0.637 to 0.665) in the validation cohort where the FTS score similarly outperformed EuroSCORE II, Charlson comorbidity index and frailty index for identifying futility. The Hosmer−Lemeshow goodness of fit test had a p value of 0.87 suggesting that the model was accurate. The observed versus predicted risks of all-cause death during the first year post-TAVI within risk deciles are shown in Figure 3. We further divided the model arbitrarily into 3 groups with 11%, 22% and 43% futility, respectively. The low-risk group consisted of 47% of the patients and the high-risk group consisted of 7% of these patients (Table 4). Performance of the different strata of risk are in Table 4 with high specificity for the high-risk (>8 points) strata. Survival curves for these 3 groups are shown in Figure 4.

Of note, we also evaluated our new score in some patients initially excluded of the analysis: the AUC) for the FTS score was 0.664 (95%CI 0.641 to 0.685) in patients

Table 2

Baseline characteristics in the derivation population treated with TAVI

Variable	Death during follow-up		p
	No (n=8375)	Yes (n=1846)	
Age (years)	82.5±7.0	82.6±7.3	0.63
Men	4110 (49%)	991 (54%)	0.0003
Charlson comorbidity index	4.9±2.9	5.5±2.9	<0.0001
Frailty index	7.5±6.6	6.8±5.3	<0.0001
EuroSCORE II	3.8±1.0	4.2±1.1	<0.0001
Heart failure	4982 (60%)	1407 (76%)	<0.0001
History of pulmonary edema	384 (5%)	327 (18%)	<0.0001
Mitral regurgitation	1656 (20%)	437 (24%)	0.0002
Aortic regurgitation	1064 (13%)	268 (15%)	0.04
Tricuspid regurgitation	339 (4%)	104 (6%)	0.002
Coronary artery disease	5203 (62%)	1244 (67%)	<0.0001
Previous myocardial infarction	1173 (14%)	377 (20%)	<0.0001
Dilated cardiomyopathy	1402 (17%)	407 (22%)	<0.0001
Hypertension	6726 (80%)	1542 (84%)	0.001
Ischemic stroke	421 (5%)	139 (8%)	<0.0001
Atrial fibrillation	3790 (45%)	1107 (60%)	<0.0001
Previous pacemaker or Defibrillator	1770 (21%)	444 (24%)	0.01
Obesity	2149 (26%)	529 (29%)	0.01
Diabetes mellitus	2543 (30%)	660 (36%)	<0.0001
Dyslipidemia	3938 (47%)	896 (49%)	0.24
Smoker	632 (8%)	177 (10%)	0.003
Vascular disease	3125 (37%)	858 (47%)	<0.0001
Abnormal renal function	1583 (19%)	533 (29%)	<0.0001
Liver disease	445 (5%)	180 (10%)	<0.0001
Lung disease	2124 (25%)	619 (34%)	<0.0001
Chronic obstructive pulmonary disease	1347 (16%)	391 (21%)	<0.0001
Sleep apnea syndrome	731 (9%)	211 (11%)	0.0003
Anaemia	2404 (29%)	727 (39%)	<0.0001
Previous cancer	1568 (19%)	482 (26%)	<0.0001
History of metastasis	168 (2%)	74 (4%)	<0.0001
Alcohol related diagnoses	364 (4%)	116 (6%)	0.0004
Thyroid diseases	1202 (14%)	283 (15%)	0.28
HIV infection	12 (0.1)	2 (0.1)	0.71
Cognitive impairment	573 (7%)	157 (9%)	0.01
Depression	1390 (17%)	403 (22%)	<0.0001
Denutrition	1007 (12%)	344 (19%)	<0.0001

Values are mean (SD) or n (%). SD = standard deviation; TAVI = transcatheter aortic valve replacement.

Table 3

Logistic regression model variables for all-cause death during first year of follow-up after TAVI in the derivation cohort

	OR (95%CI)	p	Points
Gender (men)	1.106 (0.986-1.241)	0.09	
Age (quartile)	1.141 (1.071-1.216)	<0.0001	1
Heart failure	1.425 (1.254-1.620)	<0.0001	1
History of pulmonary oedema	3.288 (2.780-3.889)	<0.0001	3
Mitral regurgitation	0.993 (0.868-1.136)	0.92	
Aortic regurgitation	0.993 (0.850-1.160)	0.93	
Tricuspid regurgitation	1.144 (0.895-1.463)	0.28	
Coronary artery disease	1.020 (0.903-1.152)	0.75	
Previous myocardial infarction	1.156 (0.979-1.364)	0.09	
Dilated cardiomyopathy	1.072 (0.937-1.226)	0.31	
Hypertension	0.953 (0.822-1.105)	0.52	
Stroke	1.342 (1.088-1.655)	0.006	1
Atrial fibrillation	1.510 (1.352-1.686)	<0.0001	1
Previous pacemaker or Defibrillator	0.923 (0.813-1.049)	0.22	
Obesity	0.989 (0.869-1.126)	0.87	
Diabetes mellitus	1.101 (0.977-1.241)	0.12	
Dyslipidaemia	0.914 (0.815-1.024)	0.12	
Smoker	1.016 (0.836-1.235)	0.87	
Vascular disease	1.158 (1.017-1.318)	0.03	1
Abnormal renal function	1.310 (1.154-1.487)	<0.0001	1
Liver disease	1.409 (1.142-1.740)	0.001	1
Lung disease	1.338 (1.130-1.584)	0.001	1
Chronic obstructive pulmonary disease	0.894 (0.734-1.088)	0.26	
Sleep apnoea syndrome	1.091 (0.908-1.311)	0.35	
Anaemia	1.196 (1.066-1.343)	0.002	1
Cancer within preceding 5 y	1.308 (1.146-1.494)	<0.0001	1
History of metastasis	1.733 (1.268-2.369)	0.001	2
Alcohol related diagnoses	1.027 (0.795-1.326)	0.84	
Thyroid diseases	0.873 (0.750-1.018)	0.08	
HIV infection	0.768 (0.161-3.662)	0.74	
Cognitive impairment	1.013 (0.831-1.235)	0.90	
Depression	1.221 (1.068-1.397)	0.003	1
Denutrition	1.257 (1.087-1.454)	0.002	1

TAVI = transcatheter aortic valve replacement. * age quartile: 1 point when age >80 points, 2 points when age >84, 3 points when age >87.

with transapical TAVI and 0.768 (95%CI 0.761 to 0.775) in those with surgical aortic valve replacement for identifying the risk of 1-year death.

Discussion

The FTS score showed a relatively good performance with high specificity to predict 1-year survival. Using 3 risk categories, the FTS score assigned high risk of futility to 7% of the patients with a 1-year death rate at 43%.

European guidelines indicate that aortic valve replacement should be proposed to patients with a severe aortic stenosis with the exception of patients with an estimated survival of < 1 year in whom the procedure is deemed futile. [1,5] The present study shows that up to 18 % of TAVI could be considered as futile in France, that is characterized by a survival < 1 year, a percentage close to that reported by Hioki et al.[18]. While the predictable increase of TAVI procedures will mainly concern low-risk patients owing to the results of the Partner 3 trial,[19] the issue of futile interventions will remain because of population aging. The combination of simple clinical variables in the FTS score fairly predicts futility; in particular, the 7% of patients with a high-risk FTS score (>8 points) had an observed death rate of more than 40% that is very close to that of severe aortic stenosis medically treated.[20] The FTS score emphasizes the importance of comorbidities, lung and kidney disease and also of clinical presentation with an history of heart failure; it had a better predictive performance than the Charlson comorbidity index. The performance of the FTS score appeared similar to that of the CAPRI score (AUC of 0.67 vs 0.68), albeit it could not be directly compared owing to the nature of the collection of the data (the CTs were not available for analysis in this cohort). It has the advantages of encompassing important comorbidities and of being easy to use. Conversely, the relatively "rough" nature of some of the variables embedded in the FTS score
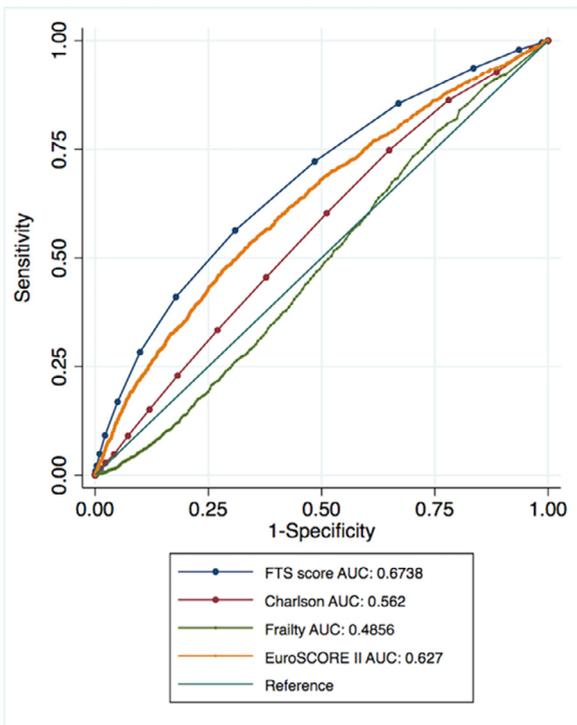
Figure 2. Receiver operating curves of the derivation model for FTS score, EuroSCORE II, Charlson comorbidity index and frailty index for identifying death at one year after TAVI in the derivation cohort.

may constitute a factor of variability. This is particularly the case for vascular disease, an important predictor of post-TAVI outcomes.[6,21] In the FTS score, vascular disease is present as a generic component while, in the CAPRI score, it is precisely assessed from the CT-scan. Whether this could make the FTS score less transposable to other populations deserves further studies. Frailty is another important issue for TAVI candidates. Using the Hospital Frailty Risk Score (HFRS), Kundi et al. showed that 1-year mortality

rate reached 30.1% in individuals undergoing TAVI categorized as high risk with HFRS.[22] The present study showed that the FTS score outperformed this frailty index. Finally, STS and EuroSCORE II are known to be poorly predictive of 1-year survival[5] what is confirmed for the Euroscore II in the present study. Albeit the FTS score surpassed the other scores in the present study, its performance appeared slightly worse than that of a futility score proposed by Zusman et al. (AUC 0.71). However, they considered a far smaller mono-centric patient-cohort and a composite outcome (mortality, stroke, lack of functional-class improvement, and readmissions at 1 year).[23] One has to realize that predicting death is difficult and that all scores, including the present one, exhibit only moderate diagnostic performance with AUC ≤ 0.7. This suggests that exceeding this threshold will probably be difficult using classical methods if one wants to stay reasonable in terms of variables included. There may be a case for artificial intelligence and machine learning.[24] In any case and although there is still room for clinical judgment within the Heart team, an imperfect score is probably better than no score at all to help the decision-making process. In this respect, no score will provide a "go-no-go" criteria; yet the FTS score could provide a more objective tool among a bunch of others to proceed to TAVI. The calculator of the FTS score and its performance are summarized in Figure 4.

Some limitations should be acknowledged. A main limitation is inherent to the retrospective, observational nature of the study. Further, the study was based on administrative data, with limitations inherent to such methodology. The PMSI database contains diagnoses coded using ICD-10, which are obtained at hospital discharge and are the physician's responsibility. Data were not systematically externally checked and this could have caused information bias. Some minor diagnoses may have been underreported in the database because of a lack of incentive for the hospital to exhaustively report every one, while others may have been misclassified. However, the large scale of the database is
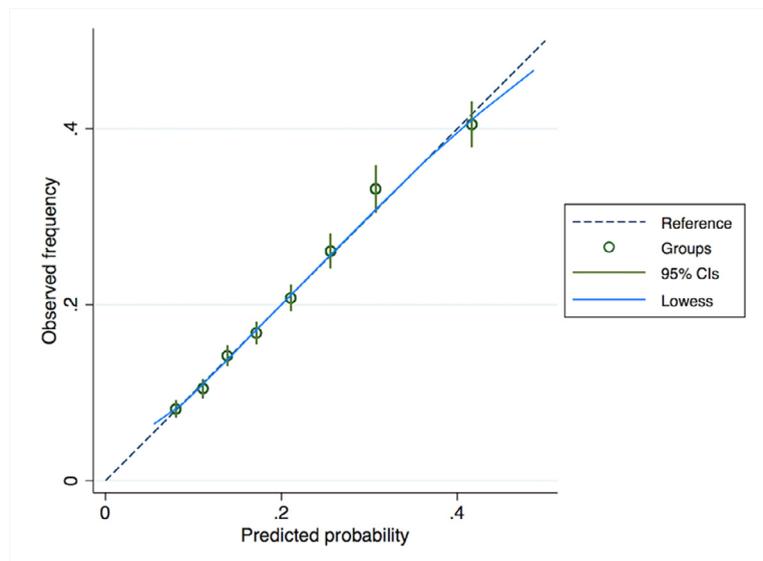

Figure 3. Calibration plots of the futility risk model in the derivation cohort. The diagonal line represents perfect calibration. Calibration of the futility prediction score is very good until a predicted in-hospital mortality rate of approximately 50%. Vertical bars represent 95% CIs.

Table 4
Rate of futility (all-cause mortality in the first year after TAVI procedure) with sensitivity and specificity by different risk strata of the TAVI futility score in the derivation cohort

TAVI futility score	Alive at 1 year N (% in the strata)	Dead at 1 year N (% in the strata)	Total N (% in the population)	Cut point	Sensitivity	Specificity	Correctly classified	LR+	LR-
Low [0-4 points]	4,314 (89.4)	514 (10.7)	4,828 (47.2)	≤4	100.00%	0.00%	18.08%	1	
Medium [5-8 points]	3,643 (78.1)	1,022 (21.9)	4,665 (45.6)	5-8	72.19%	51.52%	55.26%	1.4891	0.5398
High-risk [>8 points]	416 (57.1)	312 (42.9)	728 (7.1)	>8	16.88%	95.03%	80.90%	3.3981	0.8746
Total	8,373 (81.9)	1,848 (18.1)	10,221 (100)						

Different risk strata of the TAVI futility score are as follows: Low [0-4 points], Medium [5-8 points], High-risk [>8 points]). LR + = positive likelihood ratio; LR − = negative likelihood ratio.
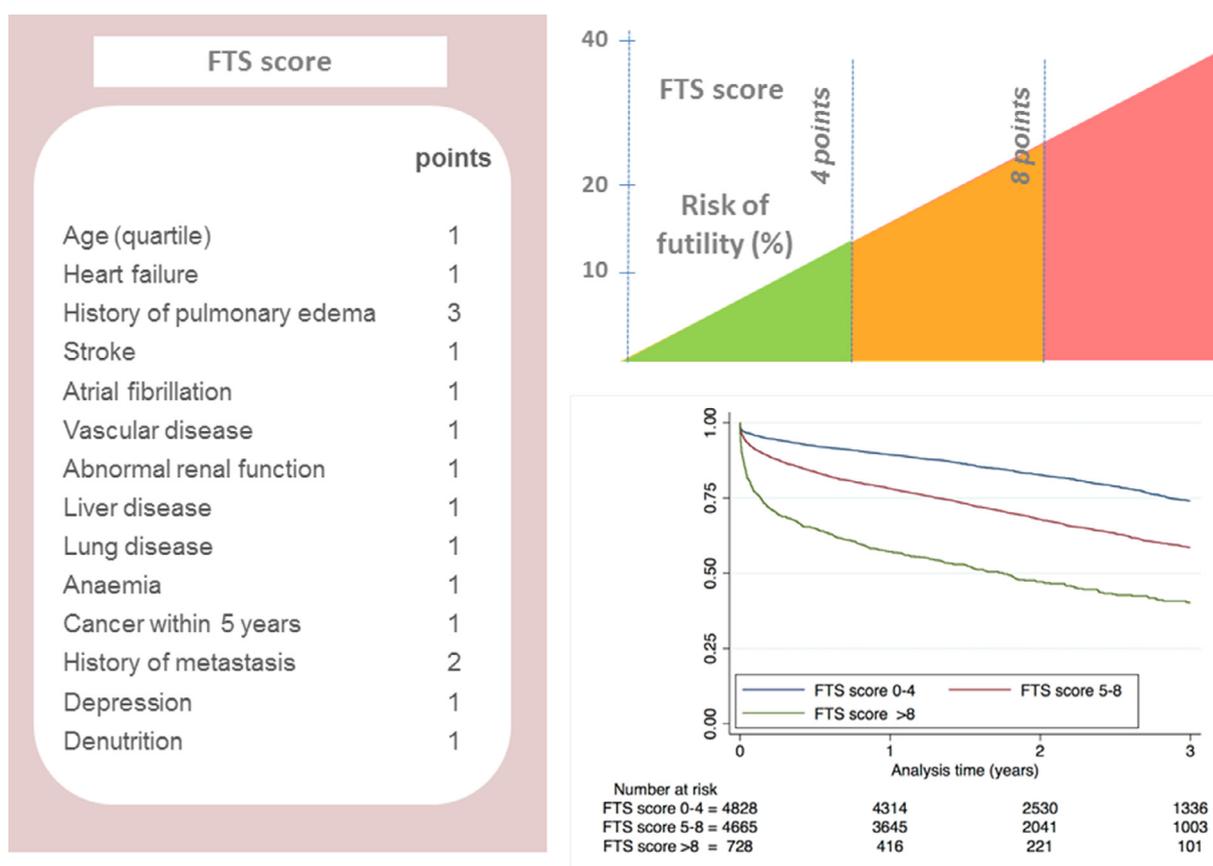

Figure 4. Kaplan-Meier Curves of total mortality during follow-up regarding 3 risk strata (Low [0-4 point], Medium [5-8 points], High-risk [>8 points]). For FTS score calculation, age quartiles are as follows: 1 point when age >80 points, 2 points when age >84, 3 points when age >87.

likely to compensate this bias and, as coding of complications is linked to reimbursement and is regularly controlled, it is expected to be of good quality. Patients from the present study actually showed prevalences of chronic diseases close to those reported in other observational studies.[25,26] The analysis was limited to deaths that occurred during hospitalization. However, French data show that hospital deaths account for a majority of all deaths in patients similar to the mean age of our population.[27] Our large population of patients admitted for a TAVI procedure likely represents a heterogeneous group of patients admitted with various kinds of illnesses and severities, which may have affected prognosis. Our analysis was restricted to the variables present in the database, which meant that characteristics such as mean gradient, valve area and calcification were not available for analysis. Another limitation is the lack of information on antithrombotic drug use, as drug therapies were not available in the database. This bias is possibly controlled by a systematic use of similar antithrombotic strategies after TAVI based on current guidelines.[1,2]

In conclusion, the FTS is a simple and efficient score that may facilitate identification of patients who, despite an

apparently successful procedure, have a risk of death that may outweigh the benefit anticipated with TAVI.

Declaration of Interests

Authors' Contribution

Pierre Lantelme: planning, writing, original draft, guarantor; *Thibaut Lacour:* ressources, database management; *Arnaud Bisson:* ressources, database management, statistical analysis; *Julien Herbert:* ressources; *Fabrice Ivanes:* ressources, drafting the manuscript; *Thierry Bourguignon:* critical reading of the manuscript; *Laurent Quilliet:* planning, critical reading of the manuscript; *Denis Angoulvant:* critical reading of the manuscript; *Brahim Harbaoui:* ressources, data management; *Dominique Babuty:* ressources, final reading of the manuscript; *Christophe Saint Etienne:* critical reading of the manuscript; *Pierre Deharo:* planning, critical reading of manuscript; *Anne Bernard:* writing, critical reading, final reading; *Laurent Fauchier:* planning, statistical analysis, writing, guarantor.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.05.043.

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