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par

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TITRE

Prédiction de la futilité médicale du remplacement valvulaire aortique par voie percutanée

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Tables des matières :

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
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Je donnerai mes soins gratuits à l'indigent,
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mes yeux ne verront pas ce qui s'y passe,
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et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime.

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Titre : Prédiction de la futilité médicale du remplacement valvulaire aortique par voie percutanée

Introduction: Les indications du remplacement valvulaire aortique percutané sont de plus en plus élargies. Nous proposons un score de futilité afin d'identifier les patients fragiles dont l'espérance de vie est inférieure à 1 an après la procédure.

Méthodes: Il s'agit d'une étude de cohorte longitudinale, recueillant les informations médicales de tous les patients hospitalisés en France. Après avoir identifié les comorbidités statistiquement associées à un décès précoce, nous avons créé un score de futilité pour prédire la mortalité à 1 an. Une régression logistique a été réalisée pour chaque variable, puis celles-ci ont été pondérées proportionnellement au hazard ratio.

Résultats: De janvier 2010 à septembre 2018, 42 866 patients ont bénéficié d'un remplacement valvulaire aortique percutané. 3 702 patients étaient décédés à 1 an (8.6%). Les caractéristiques statistiquement associées à un décès précoce étaient : sexe masculin, âge>87 ans, insuffisance cardiaque, œdème pulmonaire aigu, accident vasculaire cérébral, fibrillation atriale, maladie vasculaire, comorbidité hépatique, rénale ou respiratoire, cancer au cours des 5 dernières années, métastases, dépression et dénutrition. Un score ≥15 prédit une mortalité dans l'année qui suit avec une sensibilité de 18,59% et une spécificité de 93,45%.

Conclusion: Après remplacement valvulaire aortique percutané, un nombre significatif de patient sont décédés dans l'année suivant la procédure. Cette mortalité précoce était statistiquement associée à des marqueurs de fragilité et aux antécédents médicaux. Nous proposons un score de risque permettant de mieux identifier les patients avec un profil d'évolution défavorable précoce.

Mots Clés:

Remplacement Valvulaire Trans Aortique, futilité, score de risque, mortalité précoce à 1 an

Title: Prediction for medical futility of percutaneous aortic valve replacement

Introduction: Indications of Trans Aortic Valve Replacement are more and more extended. We aimed to propose a futility score for identifying frail patients whose life expectancy is shorter than one year after procedure.

Methods: We propose a French longitudinal cohort study, collecting medical information of all hospitalized patients. After having identified comorbidities responsible of early death issue, we aimed to propose a new aortic valve replacement futility score that could predict mortality risk at one year. Logistic regression was performed on each variable, and we attributed them a ponderation factor proportionally to HR.

Results: From January, 2010 to September, 2018, 42,866 patients had a trans-aortic valve replacement. Mortality at one year was 3,702 (8.6%). Characteristics statistically associated to premature death were : sex (male), age>87 years, heart failure, history of pulmonary edema, stroke, atrial fibrillation, vascular disease, renal, liver or lung disease, cancer within preceding 5 years, history of metastasis, depression, denutrition. A score ≥ 15 predicts mortality during the following year with sensibility 18.59% and specificity 93.45%.

Conclusion: After undergoing TAVR, a significant amount of patient dies during the year after procedure. Premature death was statistically associated to frail markers and usual cardiovascular comorbidities. We propose a new risk score that permits a better identification of patients who are going to present poor issues after TAVR.

Key words:

Trans Aortic Valve Replacement, risk score, futility, premature death at one year

ABBREVIATIONS :

AS = Aortic Stenosis

AVR = Aortic Valve Replacement

CABG = Coronary Artery Bypass Graft

CCAM = Classification Commune des Actes Médicaux

ESC = European Society of Cardiology

HFRS = Hospital Frailty Risk Score

HR = Hazard Ratio

IC95% = Interval of confidence 95% probability

ICD-10 = International Classification of Diseases, Tenth Revision

NYHA = New York Heart Association Functional Classification

PMSI = Programme de Médicalisation des Systèmes d'Information

SMVR = Surgical Mitral Valve Replacement

PMSI = Programme de Médicalisation des Systèmes d'Information

SAVR = Surgical Aortic Valve Replacement

TAVR = Trans Aortic Valvular Replacement

Introduction

Aortic stenosis (AS) is a slowly evolving disease that finally causes significant obstruction of left ventricular outflow, leading to heart failure and death due to its complications (poor mobility, refractory pulmonary edema, traumatic syncope, sudden death). It has become the most frequent valvular heart disease due to aging of population.[1-2] Prevalence is about 10% in octogenarians and no medical therapy can limit its progression.

Surgical aortic valve replacement (SAVR) has been historically the gold standard therapy for AS. Current epidemiological studies reported 300,000 SAVR procedures per year worldwide.[3] However, with a more than fifteen-years of experience since first implantation (Alain Cribier, France, 2002), Trans Aortic Valve Replacement (TAVR) has profoundly modified AS management.[46] Initially restricted to elderly and inoperable patients, indications have been extended, due to recent randomized trials showing results at least as good as SAVR in intermediate- and low- surgical risk patients. This has been obtained thanks to technological improvement of the device, and the decrease in the number of post-operative complications. [5-10,42,43] For instance, diabetic patients are prone to present sternal wound infections, postoperative respiratory and renal failure, need for blood transfusion and in hospital mortality. Patients considered as frail or with denutrition also present poor outcomes after cardiac surgery, and both acute and chronic renal dysfunction have an incidence on operative mortality [23-25,29-31]. All those complications are limited with a femoral vascular approach in comparison to a classical thoracic surgery.

In the 2017 ESC guidelines on valvular heart disease management, SAVR is recommended in patients at low surgical risk (STS or EuroSCORE II < 4% or logistic EuroSCORE I < 10% with no other risk factor and for patients undergoing associated CABG or surgery of the ascending aorta or of another valve.[11] On the other hand, TAVR is recommended in patients who are at increased surgical risk (STS or EuroSCORE II > 4% or logistic EuroSCORE I > 10% or other risk factors such as frailty, porcelain aorta, sequelae of chest radiation).[5,8,12-18] In August 2019, US Food and Drug Administration (FDA) approved TAVR for low-risk patients opening perspectives to extended indications in future recommendations.

Nguyen and al. recently proposed an evaluation of implementation of TAVR in France by using a national database, and showed the increased number of aortic valve replacement (AVR) performed due to adoption of TAVR which represents about one third of all interventions. Despite a worse patient's clinical profile, the immediate outcomes of TAVR compared to isolated SAVR are encouraging in patients over 75 years of age. [20]

We are still looking to assess for each patient if AVR is an individual relevant decision and how we could identify patients who would present low survival after TAVR, by proposing a futility score as Zusman et al recently did in a relatively small number of patients.[40]

The aim of our study was to compare mortality rate for SAVR and TAVR using a nationwide database, to define predictive factors of premature death after TAVR that would render the procedure futile; and to develop a simple tool to identify these frail patients.

Methods

Study design

This French longitudinal cohort study was based on the national database covering hospital care from entire population. Data for all patients admitted with aortic stenosis in France were collected from the national administrative hospital database, the PMSI (Programme de Médicalisation des Systèmes d'Information), inspired by the US Medicare system. Medical activity is recorded in this database, computed, and rendered anonymous. It includes more than 98% of French population (67 million persons) from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires. This process allows determination of each hospital's budget, in the 1,546 French healthcare facilities both for public and private hospitals. Each hospitalization is encoded in a standardized dataset, which includes information about the patient (age and sex), hospital stay (date of admission, date of discharge and mode of discharge), pathologies, and procedures. Routinely collected medical information includes the principal diagnosis and secondary diagnoses. In the PMSI system, diagnoses identified are coded according to the International Classification of Diseases, Tenth Revision (ICD-10).(Table 5). Also, all medical procedures are recorded according to a national procedure nomenclature named CCAM (*Classification Commune des Actes Medicaux*). They are used for the funding of hospitals and that for well inquired.

Our study population was identified with codes related to aortic stenosis and its replacement (I350, I352, I060, and I062 using ICD-10 codes). For each hospital stay, all diagnoses were obtained together at discharge. Patients undergoing a simultaneous surgical mitral valve replacement (SMVR) were identified with its correlated code (I08.0). The reliability of PMSI data has already been assessed and this database has previously been used to study patients with cardiovascular conditions, including those with aortic stenosis treated with TAVR [20,34-38]. Concerning TAVR procedure, we included all adults with a single percutaneous procedure (DBLF001 using CCAM code). Patient information (demographics, comorbid conditions, medical history, and events during follow-up or during hospitalization) were described using data collected in the hospital records.

The study was conducted retrospectively, patients were not involved in its conduct, and there was no impact on their care. Ethical approval was not required, as all data were anonymized. The French Data Protection Authority granted access to the PMSI data. Procedures for data collection and management were approved by the Commission Nationale de l'Informatique et des Libertés (CNIL), the independent National ethical committee protecting human rights in France which ensures that all information is kept confidential and anonymous, in compliance with the Helsinki Declaration (authorization number 1897139).

Study population

From January 1st, 2010 to September 1st, 2018, 487,122 patients aged over 18 were hospitalized with a diagnosis of aortic stenosis as the principal diagnosis (i.e. the health problem that justified admission to hospital), the related diagnosis (i.e. potential chronic disease or health state during hospital stay) or the significantly associated diagnosis (i.e. comorbidity or associated complication).

Comorbidities

We collected anterior medical history data that are involved in higher surgical risk by limiting functional reserve needed for post operative recovery: chronic lung disease (with or without home oxygen use), chronic renal failure, cerebral stroke, atrial fibrillation, diabetes mellitus. We also considered frailty estimated by standardized scores: the Charlson Comorbidity Index and the Clinical Frailty Scale.[19,22,47] Variables (for Charlson score: acquired immune deficiency syndrome, metastatic solid tumor, moderate or severe liver disease, malignant lymphoma, leukaemia, any non-metastatic solid tumor, diabetes with end organ damage, hemiplegia, ulcer disease, connective tissue disease, dementia, peripheral vascular disease, congestive heart failure, myocardial infarction and all previously quoted data; for Frailty Scale: Charlson score combined with scaled dependence in daily living activities, malnutrition) were identified by using related ICD-10 codes.

Outcomes

Futile aortic valve replacement was defined as premature death happening during the year following procedure. We analyzed the incidence of all-cause and cardiovascular death. Data on outcomes during follow-up was obtained by analyzing PMSI codes for each patient. Cause of death (cardiovascular or no), was identified based on the main diagnosis during hospitalization resulting in death.

Statistical analysis

Qualitative variables are described using counts and percentages and continuous quantitative variable as means ± standard deviation. Comparisons were made using chi-square tests for comparing categorical variables and the Student t test or non-parametric Kruskal Wallis test where appropriate for continuous variables. A p value <0.05 was considered statistically significant. All analyses were performed using Enterprise Guide 7.1, (SAS Institute Inc., SAS Campus Drive, Cary, North Carolina), USA and STATA version 12.0 (Stata Corp, College Station, TX).

After having identified comorbidities responsible of early death issue (<1 year), we aimed to propose a new AVR futility score that could predict mortality risk at one year. Logistic regression was performed on each variable, and we attributed them a ponderation factor proportionally to HR, using the same method as Lloyd-Jones[39,44].

Receiver operating characteristic (ROC) curves were constructed to assess the predictive ability of the new score to detect early death after AVR, and areas under the curve (c-indexes) were calculated. A c-statistic of 0.5 was taken to represent chance discrimination, and a value of 1 to correspond to perfect discrimination. The Harrell's c statistics with 95% confidence intervals were calculated as a measure of model performance and compared to other predictive scores using the DeLong test.

Internal validation was obtained by bootstrap sampling procedure, with groups of 50 patients to verify robustness of our score in several sub-groups of patients. We assessed the calibration, discrimination and accuracy of our model, using the Hosmer–Lemeshow goodness-of-fit test statistic (whether or not the observed event rates match expected event rates; a non-significant result, P-value > 0.05, for this test indicates that the model is a good fit).[63]

Results

Study population

Among the overall population (478,836 patients), 370,224 patients were treated medically, regardless severity of AS. From 108,612 benefited from an aortic valve replacement, and 65,746 patients (60.53%) had a surgical aortic valve replacement. 3,786 (3.49%) of them had an associated mitral valve surgery. During the same period, 42,866 patients (39.47%) had a TAVR procedure (16 of them with apical approach). 25,874 (60.36%) were implanted using a balloon-expandable device, and 16,992 (39.64%) with a self-expandable one (Figure 1).

The population of interest was constituted of patients with at least one year of medical-follow-up or who died during the first year following the procedure, which represents 20,443 TAVR patients. Mean duration of medical- follow-up available data was 2.08±1.36 years. (median 1.89 years). Mean medical follow-up duration for alived patients was 2.48 ±1.16 years (median 2.22 years).

Baseline patients characteristics

Our data were comparable with previously published studies[20]: 108,612 patients were included, with 42,866 in the TAVR group and 61,960 in the SAVR group. Significant differences were observed between the two groups (age, gender, hypertension, heart failure, vascular disease, ischemic cardiomyopathy, pacemaker or defibrillator implantation, prior ischemic stroke, tobacco smoking, dyslipidaemia, obesity, renal disease, inflammatory diseases, cancer within preceding 5 years, anaemia, alcohol-related diagnoses, lung disease, HIV positive serology, atrial fibrillation, hyperthyroidism and hypothyroidism).

TAVR group patients were older (82.56 ± 6.86 years vs. 72.09 ± 9.9 years). Mean Charlson score was respectively 4.23 ± 2.86 in TAVR group and 3.35± 2.88 in SAVR group. Women were proportionally more represented in TAVR group (26,938 (50.61%) vs. 27,519 (36.54%)). Considering comorbidities, the most important difference between both groups was heart failure: 40,683 (76.44%) in TAVR group vs. 46,219 (61.37%) in SAVR group. Most prevalent non cardiological comorbidity was anemia (48,785 (37.96%)).

Global practice evolution/activity

Permanent increase in the number of percutaneous aortic valve replacements was observed from 2010 to 2017 (Figure 2), with 1210 TAVR procedures in 2010 compared to 7,886 in 2017, which is 6.5 times more. We did not have complete results for 2018 when statistical analysis began, but an increasing curve is still expected. During the same period, there was an important decrease in the yearly number of SAVR (more than 10,197 in 2010 vs. 5,072 in 2017). Overall, global aortic valve replacement showed only a small progression till 2017 (11,407 in 2010, to 12,958 procedures in 2017). Over that period, median age at SAVR procedure decreased (72.9 years in 2010 vs. 70.13 years in 2017).

Mortality

For global medical follow-up, mortality rate is significantly higher in TAVR group than in SAVR group (Table 2). Overall mortality was 15,368 (7.41% per year): 8,737 (5.46% per year) in SAVR group vs. 6,631 (14.02% per year) in TAVR group (HR 2.68, IC95% 2.59-2.77, p< 0.0001). The same trend is identified when comparing cardiovascular mortality: 6,838 deaths (3.30% per year) in the overall population; 4,080 (2.55% per year) in SAVR group vs. 2,758 (5.83% per year) in TAVR group (;HR 1.83, IC95% 1.74-1.93, p< 0.0001) (Figure 3a and 3b).

In our population of interest, 3,702 patients died during the first year following TAVR procedure, (8.60 % of all population (42,866 patients)).

Futility of aortic valve replacement

In TAVR group, 20,443 patients were followed at least for one year or died earlier. This cohort was used for futility evaluation, by comparing baseline characteristics of the 8.6% (3,702) patients who died early (<1 year) to the other patients (alived at 1 year). We then tried to propose a new user-friendly score offering sufficient ability to predict mortality occurring in the first year after TAVR procedure.

Significant differences between the two groups were: older age, sex (male), hypertension, diabetes mellitus, heart failure, vascular or coronary artery disease, pacemaker or defibrillator implantation, prior stroke, tobacco smoking, dyslipidemia, obstructive sleep apnea, renal lung or liver disease, cancer within preceding 5 years, anemia atrial fibrillation, indexed Charlson score and Frailty Index, associated mitral regurgitation, dilated cardiomyopathy, COPD, cognitive impairment, denutrition, balloon expandable device, history of metastasis, history of pulmonary edema and depression (Table 3).

A logistic regression was performed to identify predictive factors of death within the first year after TAVR (Table 4). Variables independently associated with early death were: sex (male), age over 87 years, heart failure, history of pulmonary edema, stroke, atrial fibrillation, dyslipidemia, vascular disease, abnormal renal function, liver disease, lung disease, anemia , cancer within preceding 5 years, history of metastasis, depression, denutrition. Correlated Hazard Ratios are reported in Table 4.

All these parameters were used to propose a score. Appropriated ponderation was assigned to each variable according to previously cited Hazard Ratios. Ponderations were distributed as follows: sex (male) (+1), age over 87 years (+1), heart failure (+2), history of pulmonary edema (+4), stroke (+2), atrial fibrillation (+2), vascular disease (+2), renal disease (+2); liver disease (+2) lung disease (+2), anemia (+2), cancer within preceding 5 years (+2) history of metastasis (+2), depression (+2) and denutrition (+2) (Table 6).

We compared this new tool to other existing scores to discriminate premature death issue. Indexed Charlson score showed an area under ROC curve of 0.55 (IC95% 0.54-0.56). Frailty index showed bad performances with an area under ROC curve of 0.49 (IC95% 0.48-0.50) (Figure 4a and 4b). Discrimination was significantly higher using our futility score (AUC 0.67, IC95% 0.66-0.68) (DeLong test p <0.0001) (Figure 5)). We aimed to verify internal validity of our score by making a bootstrap sampling procedure, with blocks of 50. We obtained an AUC of 0.634 (95% CI, 0.634-0.644). Hosmer-Lemeshow goodness of fit test confirmed that the model was well calibrated (p = 0.1455).

We then looked for the most interesting cut-off of our score to obtain best sensitivity and specificity. Table 7 shows correlated sensitivity and specificity percentages for each level of futility score, and the amount of patients correctly classified depending of their status (alive or death). We propose to choose a cutoff at ≥15 points, with a sensitivity of 18.59% and specificity of 93.45%, which permits a performance of 79.88% well classified patients. 1,786 patients had a score of at least 15, which represents 8.74% of the total population. Distribution is reported in Table 8.

Discussion

In the present study, we propose a simple risk score combining comorbidities and frail markers associated with premature death (<1 year after procedure) in TAVR patients, that should be considered when reffering a patient to the procedure. This score appears to have a better area under the curve than previously defined scores such as Charlson score and frailty index. It is clinically relevant to provide this kind of information regarding the fact that this percutaneous procedure is more and more performed even in very high risk patients.

Compared to previously published studies, our results present consistent data about evolution of activity in France and characteristics of patients with aortic valve replacement including TAVR.[20] French Haute Autorité de Santé reports more than 15,000 aortic valve surgery per year, which is quite three times more than our database, due to inclusion of associated surgery (ascendant aorta, mitral valve)[45]. Those patients were excluded from our data as we only considered isolated surgical aortic valve replacement, comparable to TAVR.

Figure 2 shows a clear change in medical practices as SAVR is being less and less proposed to patients, the opposite of TAVR. This is due to promising results that were confirmed in recently published prospective studies. Mack and al., Popma and al., Waksman and al. and Durko and al. realized prospective studies comparing SAVR to TAVR and found either no significant difference or significant decrease of events in TAVR group (death and/or stroke depending on each study).[32,33,42,43] Those studies are going to profoundly modify AS management. Armoiry and al. proposed a comparison of TAVR versus SAVR in high risk patients and showed this category of patients had a greater risk of mortality and morbidity after TAVR compared to SAVR (at one year 16.8% vs 12.8%, and at five years 52.4% vs 37.2%), with higher hospitalization costs (+13,896 euros)[21]. This is the only publication to our knowledge presenting contradictory results.

On the other hand, when considering TAVR intervention in patients, consequences of medical history in middle and long term evaluation on morbidity and mortality are not well described. For instance, several studies have showed that after traditional cardiothoracic surgery (not only specific aortic valve surgery), both acute and chronic renal dysfunction have an incidence on operative mortality and long term survival[25,26]; atrial fibrillation causes increased long term morbidity and mortality and is frequently associated with valvular heart disease[27,28].

This has brought us to consider a classification of patients using their medical history combined to frailty, to identify patients who should not be proposed an AVR even if TAVR offers technically a safe solution. Kundi and al. aimed at identifying prevalence and outcomes of frail individuals undergoing a transcatheter cardiac intervention in USA (mitral valve repair or aortic valve replacement), using the Hospital Frailty Risk Score (HFRS).[41] Primary outcome was all-cause mortality at one year. When classified with HFRS, patients undergoing TAVR presented 1-year mortality rate of 7.6% in low-risk patients, 17.6% in intermediate-risk patients, and 30.1% in high-risk patients. Significant results were also obtained with long term mortality, the secondary endpoint.

Scores commonly used for evaluating risk before AVR are the logistic EuroSCORE[48] and Society for Thoracic Surgery Predicted Risk for Mortality (STS score) [49, 50]. Both of those aim to predict post-operative short time mortality (<30 days), and do not include frailty evaluation whereas it concerns about half of the population.[51] Actual trends consist, as previously cited Kundi et al., also to consider frail markers associated with premature death. But their work only considered frail markers and classified patients threw the HFRS.

We aimed to propose a score for predicting early death and medical futility of aortic valve replacement. On that topic, Zusman et al.[40] proposed a futility score a couple of years ago, with a better statistical performance than us (AUC 0.71 vs. 0.67). However, they considered a composite outcome (mortality, stroke, lack of functional-class improvement, and readmissions at 1 year). Variables identified and considered in their score were: diabetes mellitus, NYHA class, diastolic dysfunction, need for diuretics, mean gradient, haemoglobin level, and creatinine level. Their work analysed a far smaller mono-centric patient-cohort (435 pt), but in return, included data with more granularity (for example hemoglobin level and renal clearance) for each patient. Strong points of our analysis are the hard outcome which was considered (total mortality at one year), the amount of included patients in logistic regression (20,443) and the relatively important number of variables considered in the final score, which however still remained a simple risk tool that can be calculated in everyday-practice.

We found that validated frailty scores had no independent association with risk of early death and were not included in our score. However, individual items of these scores were relevant independent predictors (denutrition, depression, anemia). It was predictable that active cancer and/or presence of metastasis are associated to short-time mortality, so it is not surprising to recover them in our score. There is evidence that organ failure (liver/lung/renal) associated with cardiac disease is responsible for increased mortality[25,26,57,58]. Finally, usual cardiac risk factors or comorbidities (age, sex (male), heart failure, stroke, atrial fibrillation, vascular disease) also had significant association to early death. This is not surprising as they are also included in other daily-used scores (such as the euroSCORE)[48,55]. The variable most strongly associated to premature death was history of pulmonary edema (HR 3.00, IC95% 2.66-3.38 <0.0001; +4 points in our score). It is consistent with our local experience, and has been previously statistically highlighted by Tamburino and al.[59] They identified previous stroke (HR 5.47), post procedural paravalvular leak ≥ 2 (HR 3.79) and pulmonary edema (HR 2.7) as principal risk factors for mortality.

We performed a validation of our score by a bootstrap sampling procedure, with results indicating a slightly lower predictive value of our futility score, which however was still satisfying.

Strengths and limitations

We acknowledge several limitations to our work. A main limitation is inherent to the retrospective, observational nature of the study and its potential biases. 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 likely to minimize this bias. We cannot individually validate that indication of TAVR or SAVR was strictly applied following European guidelines. However, as coding is linked to reimbursement and is regularly controlled, it is expected to be of good quality, and the quality of information in the PMSI databases has improved dramatically over recent years. Patients from the present study actually showed prevalences of chronic diseases and medical history close to those reported in other observational studies. [60,61] 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.[62]

Besides, we do not have precise information about some characteristics for patients in our analysis. Even though reliability of PMSI data has been verified previously[53, 54] and used for epidemiological purposes[36], the analysis presents an inherent potential information bias. For example, we cannot know if "chronic renal failure" is reported for renal clearance at 60 ml/min or less by each center.

Concerning our database, only 20,443 patients were included in the logistic regression because we choose to include only patients who were hospitalized again, in the aim to make sure they are still alive and to avoid an information bias. Nevertheless, we still propose a robust cohort.

Finally, echography parameters, particularly left ventricular ejection fraction, were not included in our logistic regression. They might be determinant, as being independent predictors of cardiovascular events (in example after acute ischemic stroke).[52] We could not include such variables in our study as they are not reported on PMSI, which is an administrative database at a nationwide level. On the other hand, this permits our score to remain a simple tool than can be used easily in everyday life without specialized explorations.

Conclusion

After undergoing TAVR, a non-neglectable amount of patient died early after procedure. Due to costs engaged and for patients comfort when a better quality of life is not expected, a better identification of factors predicting a high risk of early death in TAVR patients is needed, which should help avoiding medical futility of the procedure. Some frailty risk factors and cardiovascular comorbidities are associated to a higher risk of early death and we propose a new risk score that allows a better identification of patients at relatively high risk of mortality in the first year after TAVR.

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Table 1: Baseline patients characteristics

Variables (n=)	Operated AVR n = 108,612	TAVR n = 42,866	SAVR n = 61,960	p_value TAVR vs. SAVR
age, years	76.38± 10.24	82.58± 6.86	72.09± 9.90	<0.0001
Age ≥75 y, n	83,636 (65.07%)	47,352 (88.97%)	36,284 (48.18%)	<0.0001
Age 65-74 y, n	28,672 (22.31%)	4,707 (8.84%)	23,965 (31.82%)	<0.0001
Sex (women)	54,457 (42.37%)	26,938 (50.61%)	27,519 (36.54%)	<0.0001
Hypertension	105,317 (81.94%)	45,337 (85.18%)	59,980 (79.64%)	<0.0001
Diabetes mellitus	40,223 (31.3%)	16,665 (31.31%)	23,568 (31.29%)	0.9494
Heart failure	86,902 (67.61%)	40,683 (76.44%)	46,219 (61.37%)	<0.0001
Vascular disease	49,442 (38.47%)	23,489 (44.13%)	25,953 (34.46%)	<0.0001
Ischemic cardiomyopathy	77,635 (60.4%)	34,060 (63.99%)	43,575 (57.86%)	<0.0001
Pacemaker or Defibrillator implantation	14,852 (11.55%)	9,918 (18.63%)	4,934 (6.55%)	<0.0001
Prior ischemic stroke	4,841 (3.77%)	2,819 (5.30%)	2,022 (2.68%)	<0.0001
Tobacco smoking	15,573 (12.12%)	4,963 (9.32%)	10,610 (14.09%)	<0.0001
Dyslipidaemia	69,593 (54.14%)	27,252 (51.20%)	42,341 (56.22%)	<0.0001
Obstructive sleep apnea	13,297 (10.34%)	5,458 (10.25%)	7,839 (10.41%)	0.3715
Obesity	39,077 (30.4%)	14,591 (27.41%)	24,486 (32.51%)	<0.0001
Renal disease	43,009 (33.46%)	21,478 (40.35%)	21,531 (28.59%)	<0.0001
Inflammatory diseases	15,495 (12.05%)	7,566 (14.22%)	7,929 (10.53%)	<0.0001
Cancer within preceding 5 years	28,931 (22.51%)	13,177 (24.76%)	15,754 (20.92%)	<0.0001
Anaemia	48,785 (37.96%)	21,563 (40.51%)	27,222 (36.15%)	<0.0001
Alcohol-related diagnoses	7,972 (6.2%)	2,778 (5.22%)	5,194 (6.90%)	<0.0001
Lung disease	34,317 (26.7%)	16,230 (30.49%)	18,087 (24.02%)	<0.0001
Liver disease	9,301 (7.24%)	3,908 (7.34%)	5,393 (7.16%)	0.2159
HIV positive	189 (0.15%)	42 (0.08%)	147 (0.20%)	<0.0001
Atrial fibrillation	71,709 (55.79%)	28,686 (53.90%)	43,023 (57.13%)	<0.0001
Charlson score	3.57± 2.87	4.23± 2.86	3.35± 2.88	<0.0001
Hyperthyroidism	3,627 (2.82%)	1,784 (3.35%)	1,843 (2.45%)	<0.0001
Hypothyroidism	15,289 (11.89%)	7,496 (14.08%)	7,793 (10.35%)	<0.0001

Table 2: Global mortality incidence

	AVR	SAVR n= 61,960	TAVR n= 42,866	HR	p value	IC 95%
All cause death *(% of patients per year)*	15,368 (*7.41%)*	8,737 *(5.46%)*	6,631 *(14.02%)*	2.68	<0.0001	2.59-2.77
CV death *(% of patients per year)*	6,838 (*3.30%)*	4,080 *(2.55%)*	2,758 *(5.83%)*	1.83	<0.0001	1.74-1.93

AVR = aortic valve replacement

CV = cardiovascular

SAVR = surgical aortic valve replacement

TAVR = trans aortic valve replacement

Table 3 : Baseline patients characteristics treated with TAVR with at least one year of follow-up or dead within the first year

Variables	Alive patients n= 16,741 (91.4%)	Dead patients n= 3,702 (8.60%)	p_value alive vs. dead at 1 year TAVR
age, years	82.6±6.88	82.92±7.26	0.01
Sex (Male , %)	8,219 (49.1)	1,975 (53.3)	<0.0001
Hypertension	13,535 (80.8)	3,093 (83.5)	0.0001
Diabetes mellitus	5,114 (30.5)	1,248 (33.7)	0.0002
Heart failure	9,967 (59.5)	2,774 (74.9)	<0.0001
Vascular disease	6,227 (37.2)	1,697 (45.8)	<0.0001
Coronary artery disease	10,509 (62.8)	2,459 (66.4)	<0.0001
Pacemaker or Defibrillator implantation	3,586 (21.4)	898 (24.3)	0.0002
Prior ischemic stroke	846 (5.1)	265 (7.2)	<0.0001
Tobacco smoking	1,562 (9.3)	388 (10.5)	0.03
Dyslipidaemia	8,978 (53.6)	1,843 (49.8)	<0.0001
Obstructive sleep apnea	1,487 (8.9)	403 (10.9)	0.0001
Obesity	4,337 (25.9)	1,003 (27.1)	0.14
Renal disease	3,131 (18.7)	999 (27)	<0.0001
Inflammatory diseases	1,685 (10)	1,700 (10.1)	0.79
Cancer within preceding 5 years	3,148 (18.8)	917 (24.8)	<0.0001
Anaemia	4,785 (28.6)	1,424 (38.5)	<0.0001
Alcohol-related diagnoses	983 (5.9)	246 (6.6)	0.07
Lung disease	4,301 (25.7)	1,213 (32.8)	<0.0001
Liver disease	853 (5.1)	337 (9.1)	<0.0001
HIV positive serology	20 (0.1)	3 (0.1)	0.53
Atrial fibrillation	7,694 (46)	2,194 (59.3)	<0.0001
Indexed Charlson score	4.89±2.88	5.32±2.85	<0.0001
Thyroid disease	2,318 (13.8)	556 (15)	0.06
Associated mitral regurgitation	3,276 (19.6)	882 (23.8)	<0.0001
Frailty index	1.75 ± 0.93	1.7 ± 0.88	0.01
Dilated cardiomyopathy	2,793 (16.7)	784 (21.2)	<0.0001
COPD	2,723 (16.3)	763 (20.6)	<0.0001
Cognitive impairement	1,109 (6.6)	296 (8)	0.003
Denutrition	1,924 (11.5)	671 (18.1)	<0.0001
Balloon expandable device	10,404 (62.1)	2,080 (56.2)	<0.0001
History of metastasis	331 (2)	129 (3.5)	<0.0001
History of pulmonary edema	791 (4.7)	607 (16.4)	<0.0001
Depression	2,769 (16.5)	777 (21)	<0.0001

Table 4: Variables logistic regression

	HR, 95%CI	p	Score Ref. Lloyd jones Points	Coefficient
Sex (male), n (%)	1.147 (1.058-1.243)	0.001	1	1.15
Age (quartile)	1.146 (1.096-1.199)	<0.0001	1	1.15
Heart failure	1.372 (1.256-1.500)	<0.0001	2	1.37
History of pulmonary edema	2.999 (2.662-3.380)	<0.0001	4	3.00
Mitral regurgitation	1.045 (0.952-1.148)	0.36		
Aortic regurgitation	0.996 (0.894-1.110)	0.95		
Tricuspid regurgitation	1.074 (0.901-1.281)	0.43		
Coronary artery disease	1.007 (0.925-1.097)	0.87		
Previous myocardial infarction	1.030 (0.917-1.158)	0.62		
Dilated cardiomyopathy	1.060 (0.963-1.165)	0.23		
Hypertension	1.003 (0.904-1.112)	0.96		
Stroke	1.301 (1.120-1.511)	0.001	2	1.30
Atrial fibrillation	1.421 (1.315-1.535)	<0.0001	2	1.42
Previous pacemaker/Defibrillator	0.954 (0.872-1.042)	0.30		
Obesity	0.982 (0.896-1.076)	0.69		
Diabetes mellitus	1.062 (0.976-1.155)	0.16		
Dyslipidemia	0.766 (0.708-0.830)	<0.0001	0	0.77
Smoker	0.975 (0.856-1.111)	0.71		
Vascular disease	1.253 (1.145-1.371)	<0.0001	2	1.25
Renal disease	1.230 (1.124-1.346)	<0.0001	2	1.23
Liver disease	1.525 (1.313-1.772)	<0.0001	2	1.53
Lung disease	1.263 (1.121-1.423)	<0.0001	2	1.26
COPD	0.930 (0.809-1.069)	0.31		
Sleep apnea syndrome	1.099 (0.965-1.252)	0.16		
Anaemia	1.212 (1.118-1.315)	<0.0001	2	1.21
Cancer within preceding 5 y	1.267 (1.153-1.392)	<0.0001	2	1.27
History of metastasis	1.610 (1.281-2.023)	<0.0001	2	1.61
Alcohol related diagnoses	0.872 (0.737-1.031)	0.11		
Thyroid diseases	0.932 (0.837-1.037)	0.20		
VIH infection	0.712 (0.200-2.533)	0.60		
Cognitive impairment	1.008 (0.874-1.162)	0.91		
Depression	1.187 (1.079-1.305)	<0.0001	2	1.19
Denutrition	1.304 (1.176-1.446)	<0.0001	2	1.30

Table 5 : International Classification of Disease 10 (ICD-10) codes and classification commune des actes médicaux (CCAM) codes

Atrial fibrillation	I48.0, I48.1, I48.2
Hypertension	I10–I15
Diabetes mellitus	E10–E14
Heart failure	I50, I11.0, I13.0, I13.2, I25.5, I42, I43, R06.0
Vascular disease	I21, I25.2, I65, I70, I71, I72, I73
Ischemic stroke	I63
Coronary artery disease	I20, I21, I22, I23, I24, I25
Cardiomyopathy	I42, I43, O99.4
Valvular disease	I05, I06, I07, I08, I34, I35, I36, I37, Q22, Q23
Aortic stenosis	I35.0, I 35.2
Simultaneous aortic and mitral valve disease	I08.0
Obesity (BMI > 30)	E65, E66
Dyslipidaemia	E78
Liver disease	K70-K77
Renal disease	N17, N18, N19, T86.1, Z49, Z94, Z99.2
Anaemia	D50-D64
Lung disease	J40-J70, J96.1
Obstructive sleep apnea	G47.3
Cancer within preceding 5 years	Entire C-series
Inflammatory diseases	M05-M14, M45, M46, K50, K51, K52
Alcohol-related diagnoses	E24.4, F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, O35.4, P04.3, Q86.0, T51, Y90, Y91, Z50.2, Z71.4, Z72.1
Tobacco smoking	Z72.0, F17.2
Thyroid disease	E00, E01, E02, E03, E05, E89.0
Trans Aortic Valve Replacement	DBLF001

Table 6: TAVR Futility Score

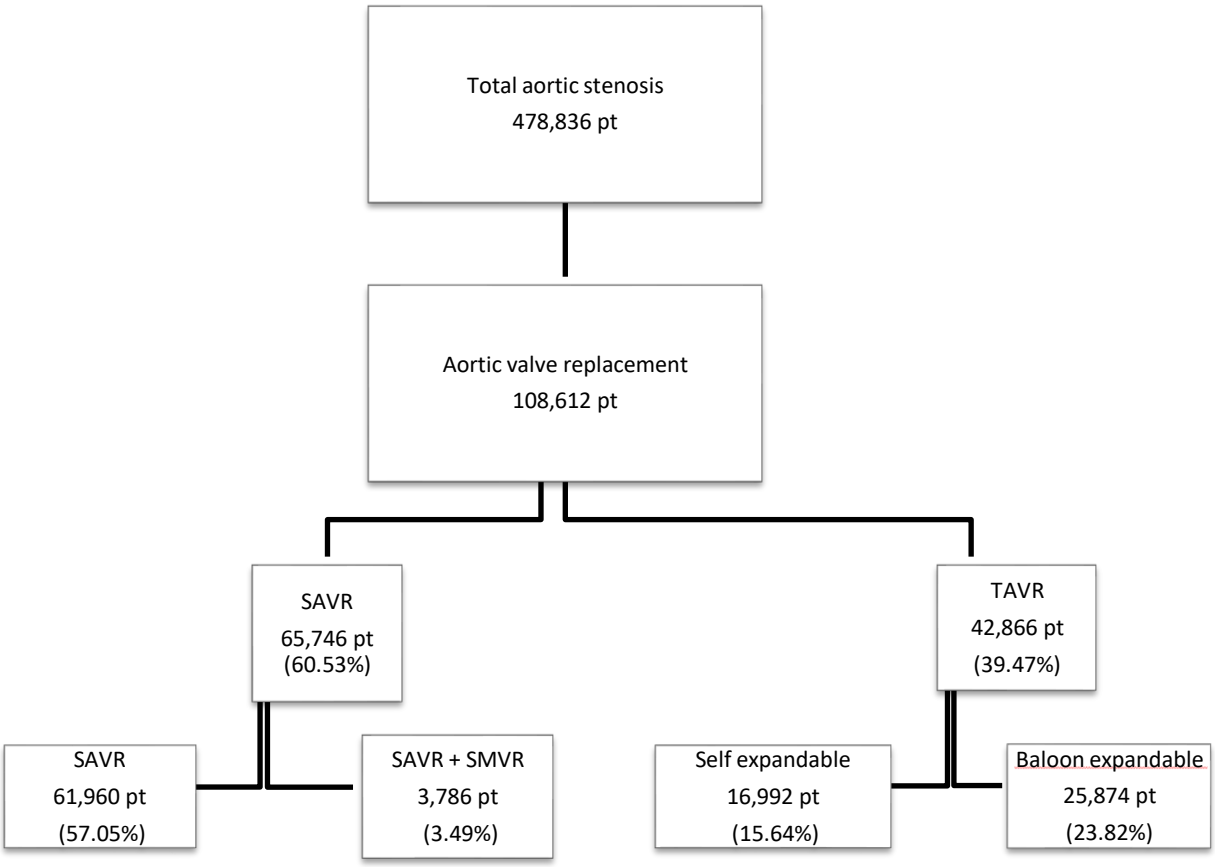
SCORE DE TOURS	
Age > 87 years	+1
Sex (male)	+1
Heart failure	+2
Pulmonary edema	+4
Stroke	+2
Atrial fibrillation	+2
Vascular disease	+2
Renal, lung or liver disease	+2/each
Anaemia	+2
Cancer within preciding 5 years	+2
History of metastasis	+2
Depression	+2
Denutrition	+2
TOTAL	30 points

Table 7: Detailed report of sensitivity and specificity

Cutpoint	Sensitivity	Specificity	Cumulated Correctly Classified patients
1	99.84%	0.20%	18.27%
2	99.51%	1.46%	19.24%
3	98.41%	4.88%	21.83%
4	96.09%	10.05%	25.65%
5	93.15%	17.00%	30.80%
6	88.37%	26.21%	37.48%
7	82.95%	35.97%	44.49%
8	75.55%	46.70%	51.93%
9	67.57%	56.69%	58.66%
10	58.04%	66.11%	64.64%
11	49.62%	74.39%	69.90%
12	41.20%	80.77%	73.60%
13	33.22%	86.40%	76.75%
14	24.80%	90.33%	78.45%
15	18.59%	93.45%	79.88%
16	13.25%	95.85%	80.87%
17	8.88%	97.44%	81.38%
18	5.72%	98.36%	81.56%
19	3.86%	99.01%	81.76%
20	2.37%	99.46%	81.86%
21	1.48%	99.70%	81.90%
22	0.89%	99.83%	81.90%
23	0.57%	99.92%	81.91%
24	0.19%	99.98%	81.91%
25	0.08%	99.99%	81.91%
>26	0.03%	99.99%	81.91%

Table 8: Number of patients in each futility score group

Futility score	Number of patient	Percentage	Cumulated percentage
0	40	0.2%	0.2%
1	223	1.09%	1.29%
2	612	2.99%	4.28%
3	952	4.66%	8.94%
4	1,272	6.22%	15.16%
5	1,719	8.41%	23.57%
6	1,835	8.98%	32.54%
7	2,070	10.13%	42.67%
8	1,967	9.62%	52.29%
9	1,929	9.44%	61.73%
10	1,699	8.31%	70.04%
11	1,380	6.75%	76.79%
12	1,237	6.05%	82.84%
13	970	4.74%	87.58%
14	752	3.68%	91.26%
15	600	2.93%	94.2%
16	428	2.09%	96.29%
17	271	1.33%	97.62%
18	179	0.88%	98.49%
19	129	0.63%	99.12%
20	74	0.36%	99.49%
21	44	0.22%	99.7%
22	26	0.13%	99.83%
23	24	0.12%	99.95%
24	6	0.03%	99.98%
25	3	0.01%	99.99%
26	2	0.01%	100%
Total	20,443	100%	100%



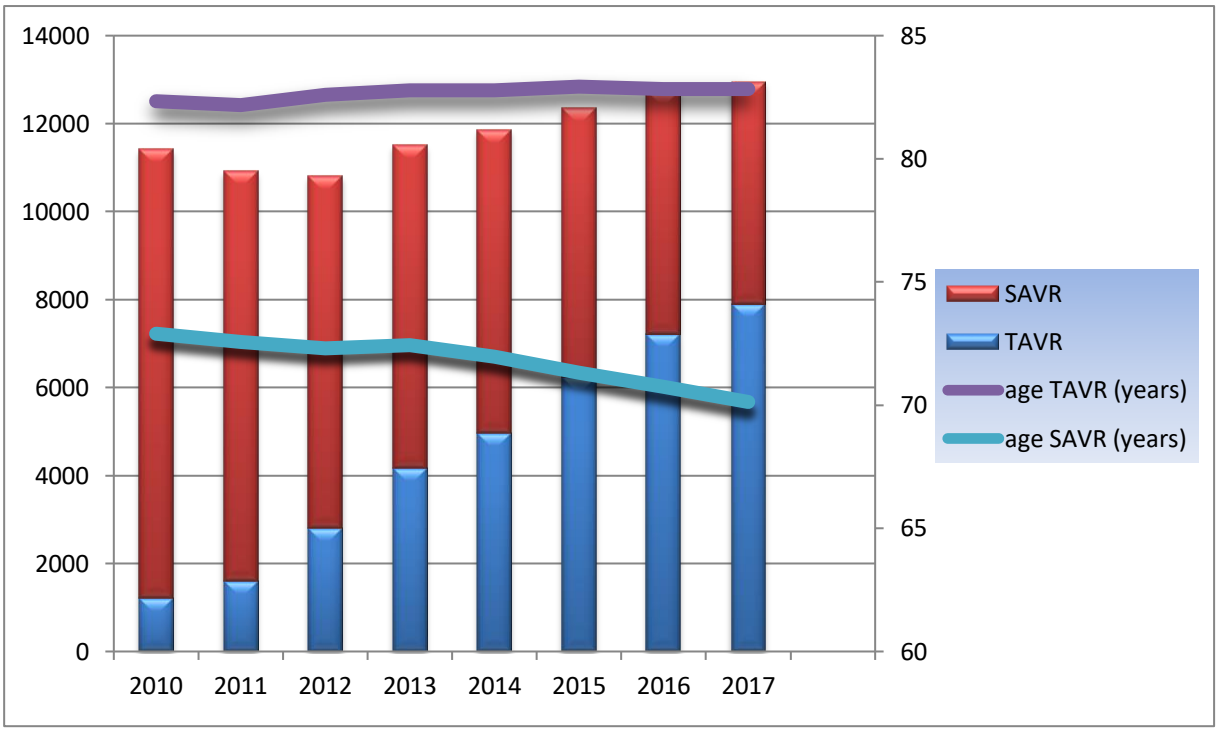
pt = patients

SAVR = Surgical aortic valve replacement

SMVR = Surgical mitral valve replacement

TAVR = Transaortic valve replacement

Figure 1: Flowchart of the study

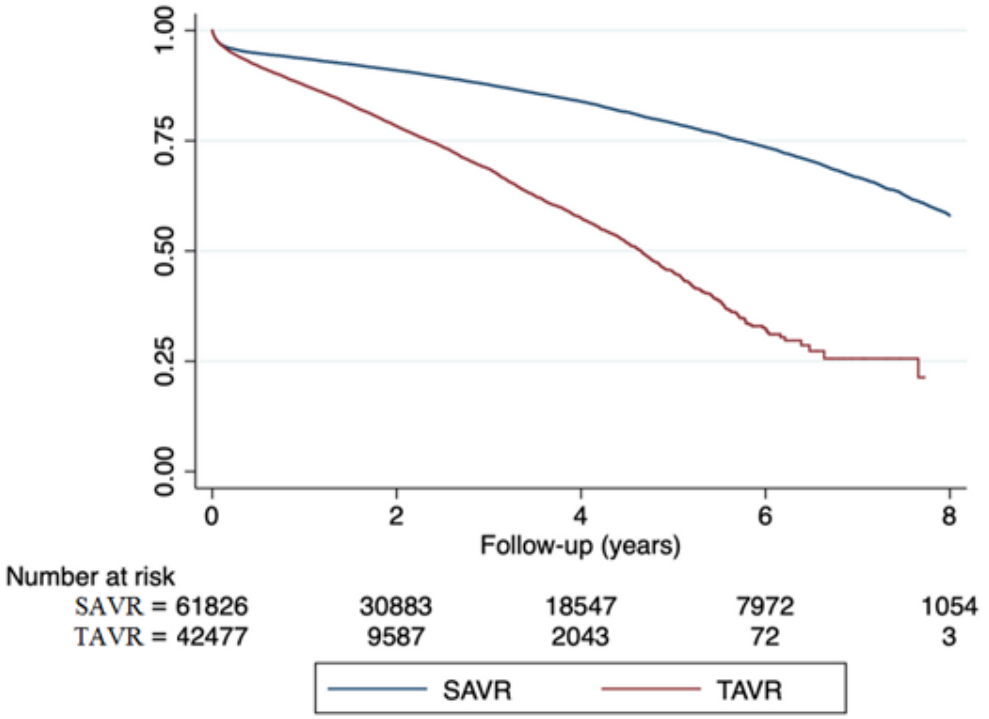


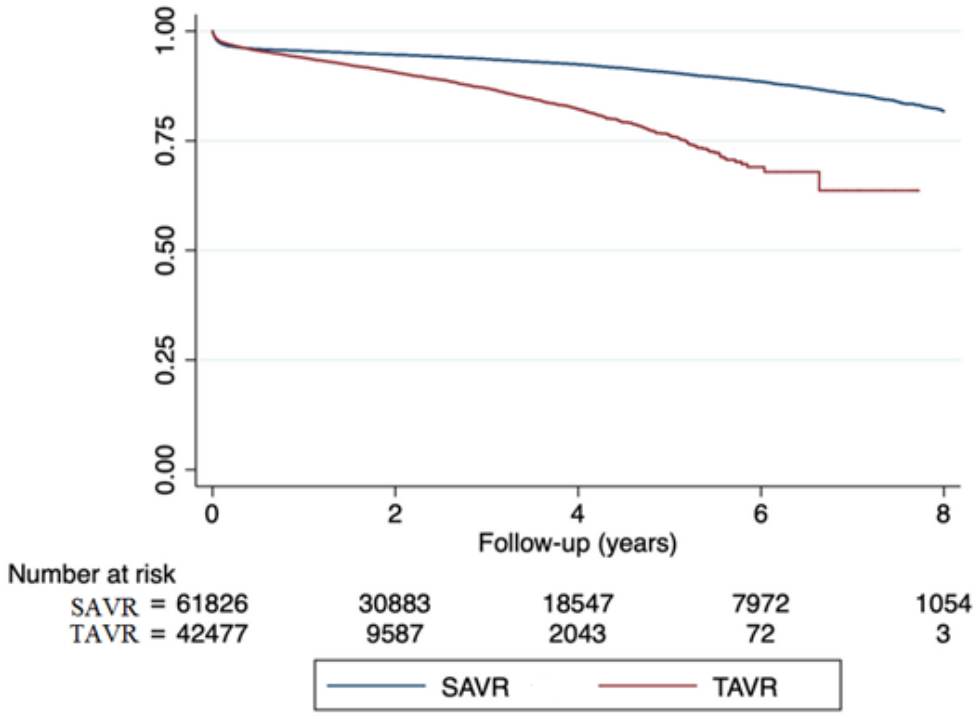
Year of inclusion	TAVR	SAVR	Total	age TAVR (years)	age SAVR (years)
2010	1,210	10,197	11,407	82.33	72.9
2011	1,607	9,307	10,914	82.18	72.56
2012	2,789	8,012	10,801	82.6	72.3
2013	4,159	7,352	11,511	82.78	72.43
2014	4,966	6,889	11,855	82.77	71.98
2015	6,248	6,099	12,347	82.93	71.32
2016	7,213	5,549	12,762	82.83	70.75
2017	7,886	5,072	12,958	82.82	70.13

TAVR : Trans-Aortic Valve Replacement

SAVR : Surgical Aortic Valve Replacement

Figure 2: Evolution of AVR activity in France





TAVR : Trans-Aortic Valve Replacement

SAVR : Surgical Aortic Valve Replacement

Figure 3: Incidence of global (a) and cardiovascular (b) mortality

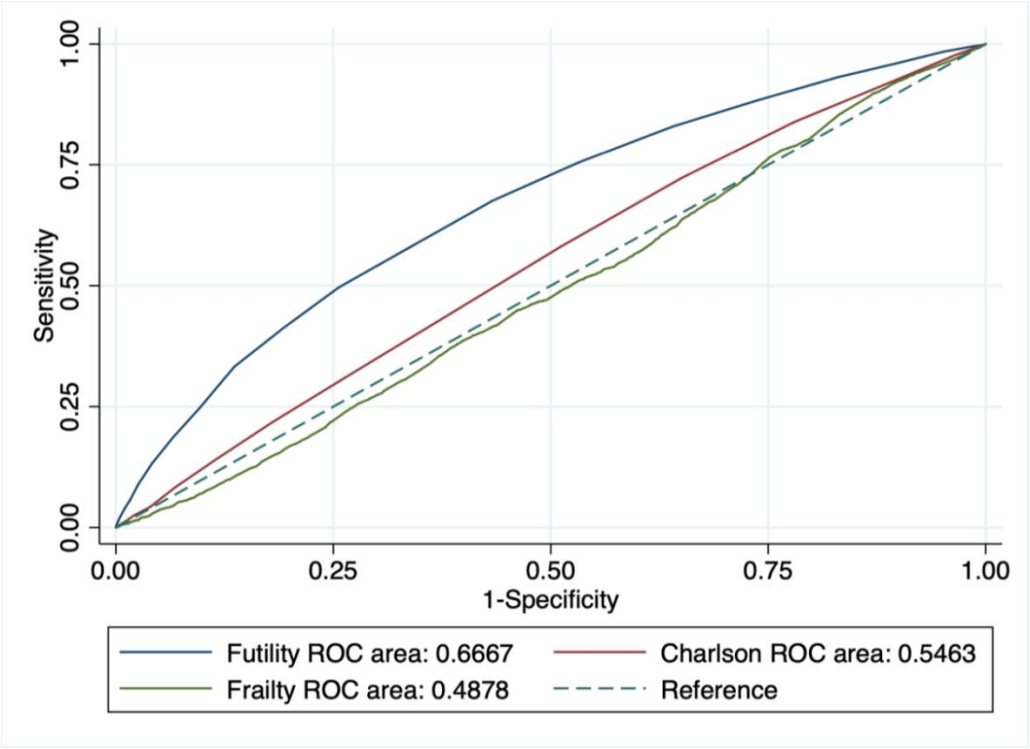


Figure 4: All cause mortality prediction at 1 year with Indexed Charlson score and Frailty score

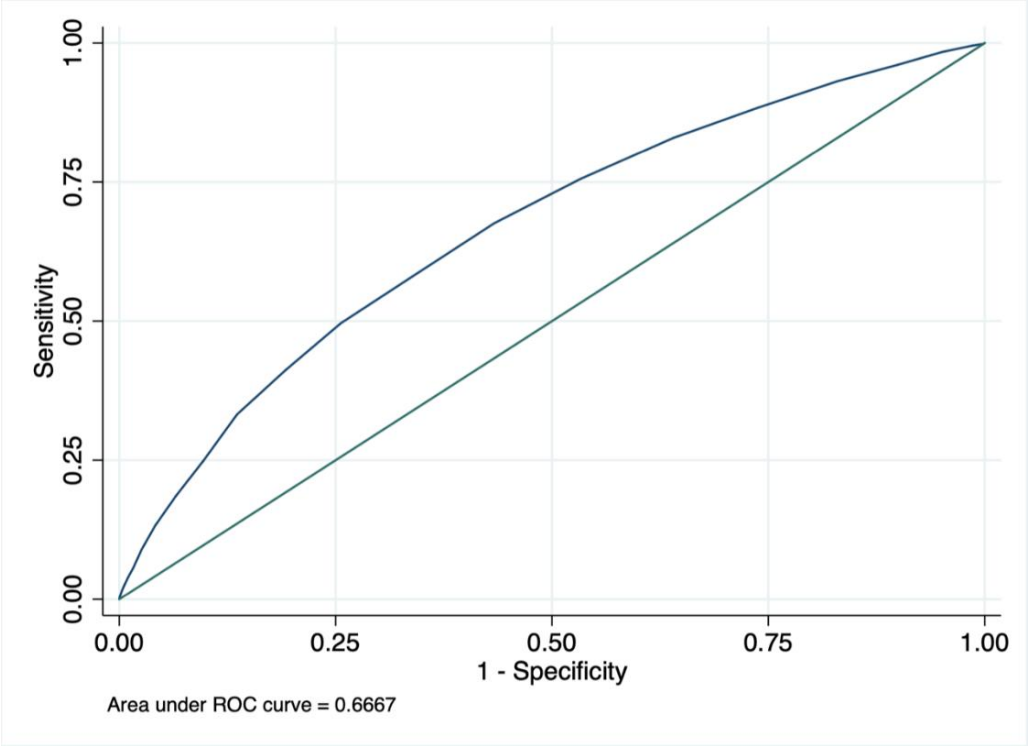


Figure 5: Receiver Operating Curves of the logistic regression model

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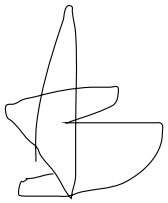

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58 pages – 8 tableaux – 5 figures

Résumé :

Introduction: Les indications du remplacement valvulaire aortique percutané sont de plus en plus élargies. Nous proposons un score de futilité afin d'identifier les patients fragiles dont l'espérance de vie est inférieure à 1 an après la procédure.

Méthodes: Il s'agit d'une étude de cohorte longitudinale, recueillant les informations médicales de tous les patients hospitalisés en France. Après avoir identifié les comorbidités statistiquement associées à un décès précoce, nous avons créé un score de futilité pour prédire la mortalité à 1 an. Une régression logistique a été réalisée pour chaque variable, puis celles-ci ont été pondérées proportionnellement au hazard ratio.

Résultats: De janvier 2010 à septembre 2018, 42 866 patients ont bénéficié d'un remplacement valvulaire aortique percutané. 3 702 patients étaient décédés à 1 an (8.6%). Les caractéristiques statistiquement associées à un décès précoce étaient : sexe masculin, âge>87 ans, insuffisance cardiaque, œdème pulmonaire aigu, accident vasculaire cérébral, fibrillation atriale, maladie vasculaire, comorbidité hépatique, rénale ou respiratoire, cancer au cours des 5 dernières années, métastases, dépression et dénutrition. Un score ≥15 prédit une mortalité dans l'année qui suit avec une sensibilité de 18,59% et une spécificité de 93,45%.

Conclusion: Après remplacement valvulaire aortique percutané, un nombre significatif de patient sont décédés dans l'année suivant la procédure. Cette mortalité précoce était statistiquement associée à des marqueurs de fragilité et aux antécédents médicaux. Nous proposons un score de risque permettant de mieux identifier les patients avec un profil d'évolution défavorable précoce.

Mots clés : Remplacement valvulaire (trans) aortique, futilité, score de risque, mortalité précoce à 1 an

Jury :

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Directeur de thèse : Professeure Anne Bernard
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Professeur Angoulvant Dominique
Docteur Fabrice Ivanès
Docteur Arnaud Bisson

Date de soutenance : 28 octobre 2019