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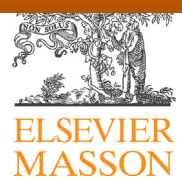

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CLINICAL RESEARCH

Predictors of 6-month poor clinical outcomes after transcatheter aortic valve implantation

Facteurs prédictifs de mauvais résultat clinique à 6 mois de l'implantation d'une valve aortique percutanée

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KEYWORDS
Transcatheter aortic valve implantation;
Aortic stenosis;
Aortic regurgitation;
Outcomes

Summary
Background. — Patient selection for transcatheter aortic valve implantation (TAVI) remains a major concern. Indeed, despite promising results, it is still unclear which patients are most and least likely to benefit from this procedure.
Aims. — To identify predictors of 6-month poor clinical outcomes after TAVI.

Abbreviations: AF, atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; CI, confidence interval; EOA, effective orifice area; HR, hazard ratio; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; OR, odds ratio; RV, right ventricular; SAVR, surgical aortic valve replacement; sPAP, systolic pulmonary artery pressure; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography; TR, tricuspid regurgitation.

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Methods. — Patients who were discharged from our institution with a transcatheter-implanted aortic valve were followed prospectively. Our population was divided into two groups ('good outcomes' and 'poor outcomes') according to occurrence of primary endpoint (composite of all-cause mortality, all stroke, hospitalizations for valve-related symptoms or worsening heart failure from discharge to 6 months or 6-month New York Heart Association functional class III or IV). Patient characteristics were studied to find predictors of poor outcomes.
Results. — We included 163 patients (mean age, 79.9 ± 8.8 years; 90 men [55%]; mean logistic EuroSCORE, 18.4 ± 11.4%). The primary endpoint occurred in 49 patients (mean age, 83 ± 5 years; 31 men [63%]). By multivariable analysis, atrial fibrillation (odds ratio [OR] 3.94), systolic pulmonary artery pressure ≥ 60 mmHg (OR 7.56) and right ventricular dysfunction (OR 3.55) were independent predictors of poor outcomes, whereas baseline aortic regurgitation ≥ 2/4 (OR 0.07) demonstrated a protective effect.
Conclusion. — Atrial fibrillation, severe baseline pulmonary hypertension and right ventricular dysfunction (i.e. variables suggesting a more evolved aortic stenosis) were predictors of 6-month poor outcomes. Conversely, baseline aortic regurgitation ≥ 2/4 showed a protective effect, which needs to be confirmed in future studies. Our study highlights the need for a specific 'TAVI risk score', which could lead to better patient selection.

MOTS CLÉS
Valve aortique percutanée ;
Sténose aortique ;
Insuffisance aortique ;
Résultat

Résumé
Contexte. — La sélection des patients pour l'implantation d'une valve aortique transcathéter (TAVI) demeure un challenge clinique. En effet, malgré des résultats prometteurs, il reste difficile de savoir quels patients sont les moins susceptibles de tirer bénéfice de cette procédure.
Objectif. — Notre objectif était d'identifier des facteurs prédictifs d'un mauvais résultat 6 mois après TAVI.
Méthodes. — Nous avons prospectivement suivi les patients sortis de l'hôpital avec une valve aortique implantée par voie transcathéter. Notre population a été divisée en 2 groupes, « bon résultat » et « mauvais résultat », en fonction de la survenue du critère primaire qui était un critère composite des décès toutes causes, des accidents vasculaires cérébraux, des hospitalisations pour insuffisance cardiaque ou symptômes en rapport avec la valve entre la sortie de l'hospitalisation et le suivi à 6 mois ou une classe fonctionnelle New York Heart Association III ou IV à 6 mois. Les caractéristiques des patients ont été étudiées afin de déterminer des facteurs prédictifs de mauvais résultat.
Résultats. — Cent soixante-trois patients consécutifs (âge moyen : 79,9 ± 8,8 ans ; 90 hommes [55 %]) ont été inclus. L'EuroSCORE logistique moyen était de 18,4 ± 11,4 %. Quarante-neuf patients ont présenté le critère primaire. En analyse multivariée, la fibrillation atriale (OR 3,94), une pression artérielle pulmonaire systolique ≥ 60 mmHg (OR 7,56), une dysfonction ventriculaire droite (OR 3,55) étaient des facteurs prédictifs indépendants de mauvais résultat alors que l'insuffisance aortique préopératoire ≥ 2/4 (OR 0,07) présentait un effet protecteur.
Conclusion. — La fibrillation atriale, une pression artérielle pulmonaire systolique ≥ 60 mmHg et une dysfonction ventriculaire droite, des variables évoquant un rétrécissement aortique plus évolué, étaient des facteurs prédictifs de mauvais résultat à 6 mois après TAVI. À l'inverse, une insuffisance aortique préopératoire ≥ 2/4 présentait un effet protecteur qui doit être confirmé dans des études futures. Notre étude souligne la nécessité de développer un score de risque spécifique du TAVI qui pourrait améliorer la sélection des patients.

Introduction

Aortic stenosis (AS) is the most common valvular disease, with an increasing incidence in the elderly population [1]. Transcatheter aortic valve implantation (TAVI) was developed as an alternative to surgical aortic valve replacement (SAVR) in patients at prohibitive surgical risk. Several registries [2—4] showed functional improvement in patients with severe symptomatic AS treated with TAVI. TAVI demonstrated a 2-year survival advantage over medical therapy in inoperable patients [5] and non-inferiority against SAVR in high-risk patients [6]; it is now the standard of care for inoperable patients and a valid alternative to surgery for many high-risk patients [7].

Despite these promising results, a significant proportion of patients either die or have no functional benefits within the first months after TAVI [2,5,6,8]. Numerous predictors of mortality have been identified, such as postprocedural aortic regurgitation (AR) [2,3,6,9], chronic obstructive pulmonary disease [3], chronic kidney disease, pulmonary hypertension and postprocedural complications [9].

Moreover, recently, postprocedural AR and severe mitral regurgitation (MR) were identified as independent predictors of poor treatment response [8]. Nonetheless, data on predictors of functional outcomes after TAVI are scarce. Yet, given that this technique is generally intended for elderly patients, symptomatic improvement is as critical as the increase in life expectancy. A risk score to identify those patients who are least likely to benefit from TAVI should further improve the selection of TAVI candidates.

The goal of this prospective study was to identify predictors of 6-month poor outcomes after TAVI, defined as the clinical components of 'clinical efficacy', as outlined in the recommendations of the Valve Academic Research Consortium [10].

Methods

Patients

Patients with severe and symptomatic AS (effective orifice area [EOA] $\leq 1\,cm^2$) who underwent TAVI at our institution were prospectively enrolled. Exclusion criteria were death during the procedure or subsequent hospitalization, conversion to surgery or unsuccessful implantation (defined as impossibility to deliver and deploy a valve into the proper location for anatomical reasons). Before TAVI, these patients underwent an evaluation, which included a physical examination, blood tests, transthoracic and transoesophageal echocardiography (TTE and TEE, respectively) and computerized tomography. Indications, contraindications and anatomical requirements for TAVI have been described previously [7]. SAVR risk of mortality was estimated using the logistic EuroSCORE [11] and the Society of Thoracic Surgeons (STS) risk score [12]. Finally, TAVI indication was retained by a multidisciplinary 'Heart Team' based on the evaluation cited above. Patients were followed on-site before discharge, 1 month after implantation and either on-site or by their cardiologist 6 months after TAVI. Follow-up information was also obtained by telephone contact with deceased patients' physicians. Patients gave written informed consent before participation. The study was approved by the local ethics committee.

Endpoints

The primary endpoint was the clinical components of 'clinical efficacy' [10] (i.e. a composite of all-cause mortality, all stroke [disabling and non-disabling], hospitalizations for valve-related symptoms or worsening heart failure from discharge to 6 months or a 6-month New York Heart Association [NYHA] class III or IV). Secondary endpoints were clinical efficacy, as defined in the recommendations of the Valve Academic Research Consortium [10] (clinical components or valve-related dysfunction, i.e. mean aortic valve gradient ≥ 20 mmHg, EOA ≤ 0.9—$1.1\,cm^2$ and/or Doppler velocity index < 0.35 m/s and/or moderate or severe prosthetic valve regurgitation), and 6-month all-cause mortality. The cohort was subsequently divided into two groups: 'good outcomes' and 'poor outcomes', according to the occurrence of the primary endpoint.

Atrial fibrillation (AF) was defined as any history of AF regardless of type of arrhythmia or presence of AF on at least one electrocardiogram during hospitalization for the preoperative assessment or the day before TAVI. Coronary artery disease was defined as presence of lesions with $\geq 50\%$ diameter stenosis on pre-TAVI angiography and/or previous treatment with percutaneous coronary intervention or coronary artery bypass grafting. Complications were defined according to the recommendations of the Valve Academic Research Consortium [10].

Study devices and procedures

The two CE-approved prostheses and implantation techniques have been described previously [2,4]. The procedure was performed in a catheterization laboratory in a sterile environment by at least two interventional cardiologists, a cardiac surgeon and an anaesthesiologist. The choice of whether to use local or general anaesthesia was left at the discretion of the anaesthesiologist in charge of the patient. The type of anaesthesia used was not recorded routinely in our database, but was known for 81% ($n = 132$) of patients, 66% of whom ($n = 87$) underwent local anaesthesia. TEE was used for transapical cases, to accurately define the apical surgical access site. Fluoroscopy was used for valve positioning in all cases, with the help of TEE guidance only in transapical cases.

Echocardiography

TTE was performed according to the American Society of Echocardiography guidelines [13] by an experienced echocardiographer using a digital ultrasound scanner (Vivid7, GE Healthcare, Little Chalfont, UK; or iE33, Philips Healthcare, Andover, MA, USA).

In apical five-chamber view, peak and mean pressure gradients across the aortic valve were calculated using the Bernoulli equation. EOA was calculated using the continuity equation.

A multiparametric approach with both semiquantitative and quantitative variables was used to grade valvular regurgitation on a scale from 0 to 4, with higher grades indicating greater severity (0, no; 1, mild; 2, moderate; 3/4, severe). Baseline and postprocedural AR were graded in accordance with the European Society of Cardiology guidelines for native valves [14]. However, given the frequent eccentric and irregular jet of postprocedural AR, we also gave a heavy weighting to the circumferential extent of prosthetic AR in parasternal short-axis view, to provide an integrated assessment of postprocedural AR [10]. Thresholds were as follows: none, no regurgitant colour flow; mild extent, $< 10\%$; moderate extent, 10—29%; severe extent, $\geq 30\%$. Before TAVI, we used TEE to measure the annulus diameter accurately and sometimes to grade AR or MR when TTE was not conclusive.

Pulmonary hypertension was defined as systolic pulmonary artery pressure (sPAP) ≥ 40 mmHg at rest, estimated using tricuspid regurgitation (TR) velocity [15]. Right atrial pressure was assessed using inferior vena cava diameter (in its long axis) and inspiratory collapse in the subcostal view [15]: a diameter ≤ 21 mm and a collapse $> 50\%$ with a sniff were used as cut-offs for normal right atrial pressure (i.e. 3 mmHg, range 0—5 mmHg), whereas a diameter > 21 mm and a collapse $< 50\%$ defined high right atrial pressure (15 mmHg, range 10—20 mmHg). In indeterminate cases,

in which the inferior vena cava diameter and collapse did not fit these definitions, an intermediate value of 8 mmHg (range 5—10 mmHg) was used. Right ventricular (RV) function was assessed in apical four-chamber view using tricuspid annular plane systolic excursion measured by M-mode, with a reference value for impaired RV systolic function of < 16 mm and an RV peak systolic velocity of the tricuspid annulus measured by tissue Doppler, with a value of ≥ 10 cm/s defining normal RV function [15]. Left ventricular ejection fraction (LVEF) was measured by Simpson's method from the four- and two-chamber views [13]. Left atrial end-systolic area was measured from the four-chamber apical view. LV end-diastolic and end-systolic diameters and end-diastolic septal thickness were measured by M-mode from parasternal views.

TTE was performed the day before TAVI, before discharge and 1 month and 6 months after TAVI.

Blood tests

Venous blood samples were obtained on the day before TAVI to determine concentrations of N-terminal pro B-type natriuretic peptide and serum creatinine. The estimated glomerular filtration rate was calculated using the abbreviated Modification of Diet in Renal Disease Study equation. Kidney disease was defined as moderate when the glomerular filtration rate was between 30 and 59 mL/min/1.73 m^2 and as severe when < 30 mL/min/1.73 m^2.

Statistical analysis

Numeric values are expressed as mean ± standard deviation. Normality was tested using the Kolmogorov-Smirnov test. Continuous variables were compared using the unpaired *t*-test or the Mann-Whitney U test, as appropriate. Chi-square analysis or Fisher's exact test was used to compare categorical variables. Patient characteristics were evaluated for poor outcomes. All baseline variables with a *P* value ≤ 0.2 in univariate analysis were entered into an ascending stepwise multivariable logistic regression analysis to identify independent predictors of poor outcomes and into an ascending stepwise Cox multivariable analysis to identify predictors of all-cause mortality. The likelihood ratio statistic was used at each step to define which variable should be included in or excluded from the model. Variables with a *P* value < 0.05 were added to or remained in the model, whereas variables with a *P* value ≥ 0.1 were removed. Results are presented as odds ratios (ORs) and hazard ratios (HRs). A *P* value ≤ 0.05 was considered significant. All probability values reported are two-sided. Statistical analysis was performed with the use of SPSS 21.0 software (SPSS, Inc., Chicago, IL, USA).

Results

Patients

From January 2009 to June 2012, 514 consecutive patients with severe and symptomatic AS were referred to our institution for pre-TAVI evaluation. After meetings of the Heart Team, TAVI indication was confirmed in 180 patients who underwent the procedure from February 2009 to July 2012. A total of 17 patients died during the procedure (*n* = 3) or the initial hospitalization (*n* = 6), were converted to surgery (*n* = 4: two annulus ruptures; two embolizations of the prosthesis in the left ventricle) or had unsuccessful implantation (*n* = 6: five non-fatal vascular access complications, one insufficient distance between valvular plane and a circumflex artery with an anomalous origin from the right sinus of Valsalva) and thus were excluded. Our study cohort included 163 surviving patients (Fig. 1). No patient was lost to follow-up.

The mean age of the study patients was 79.9 ± 8.8 years, 90 patients (55.2%) were men, the mean logistic EuroSCORE was 18.4 ± 11.4%, the mean STS risk score was 5.8 ± 3.1%, 118 patients (72.4%) were NYHA functional class III or IV, 86 patients (52.8%) had a history of acute heart failure and 71 patients (44%) had AF. The baseline characteristics of the study population are summarized in Table 1.

Procedural outcomes

The aortic valve prosthesis was inserted using the retrograde femoral artery approach (*n* = 132), the subclavian artery approach (*n* = 10), the transapical approach (*n* = 12) or the transaortic approach (*n* = 9). The implanted prosthesis was an Edwards SAPIEN (*n* = 8), an Edwards SAPIEN XT (*n* = 91) or a Medtronic CoreValve (*n* = 64). Valve size was 23 mm (*n* = 32), 26 mm (*n* = 63) or 29 mm (*n* = 4) for the Edwards devices and 26 mm (*n* = 20), 29 mm (*n* = 36) or 31 mm (*n* = 8) for the Medtronic CoreValve.

The mean total procedural time was 96 ± 31 minutes and the mean contrast agent volume was 238.8 ± 92.7 mL. Valve embolization in the aorta was observed in two cases and was managed with implantation of a second prosthesis. Acute kidney injury stage 2 or 3 arose in 10 patients (6.1%), including one who required temporary dialysis. Sixteen patients (9.8%, 15 CoreValve) received a new permanent pacemaker. Procedural outcomes are summarized in Table 2.

Mortality and poor outcomes

Eleven patients died (eight of cardiovascular causes) between discharge from hospital and 6-month follow-up. Thus, 6-month all-cause mortality rate was 6.7% for the study population and 11.1% for the 180 patients who underwent the procedure.

Twenty-three of 152 remaining study patients were NYHA functional class III or IV at 6-month follow-up. Hospitalization for heart failure occurred in 32 patients; no stroke occurred after the initial hospitalization. Eventually, 49 patients (30.1%) met the criteria for the 'poor outcomes' group. The 114 remaining patients (69.9%) formed the 'good outcomes' group.

All clinical characteristics with significant differences between groups are presented in Table 1. A total of 69 (42.3%) patients met the criteria for clinical efficacy.

Echocardiographical findings

Most patients had preserved LVEF (mean LVEF, 50.7 ± 14.8%) and only 25 patients (16%) had an LVEF ≤ 30%. Thirty-six patients (22.1%) had moderate or severe (≥ 2/4) AR at baseline. MR ≥ 2/4 was present in 65 patients (39.9%;

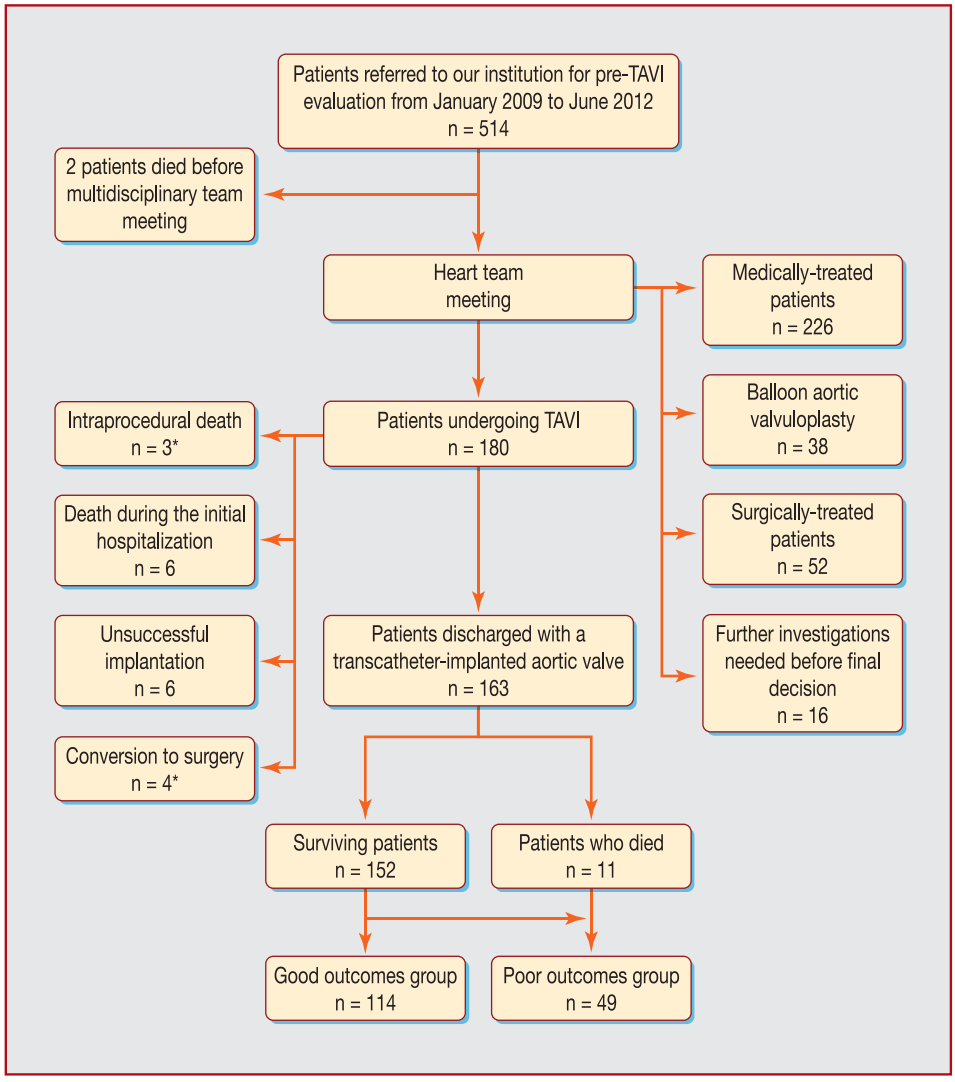

Figure 1. Flowchart. *: one patient died during surgical aortic valve replacement after aortic annulus rupture during transcatheter aortic valve implantation. †: one patient died during the initial hospitalization after conversion to surgery. TAVI: transcatheter aortic valve implantation.

moderate, $n = 57$; severe, $n = 8$). RV dysfunction was observed in 31 patients (19.0%) and 38 patients (23.3%) had TR $\geq$ 2/4 (moderate, $n = 26$; severe, $n = 12$). Pulmonary hypertension was diagnosed in 65.0% of patients; it was moderate (40 $\leq$ sPAP $\leq$ 59 mmHg) in 70 patients (42.9%) and severe (sPAP $\geq$ 60 mmHg) in 36 patients (22.1%). Overall, sPAP improved in 61 of the 106 patients (57.5%) with baseline pulmonary hypertension.

AR was common after TAVI, as 115 patients (70.6%) presented a leak, but AR $\geq$ 2/4 was present in only 30 patients (18.6%). Regarding patients with postprocedural AR $\geq$ 2/4, 9/16 patients (56.2%) in the good outcomes group compared with only 1/14 patients (7.1%) in the poor outcomes group had baseline AR $\geq$ 2/4. Echocardiographical findings are summarized in Table 3.

Predictors of 6-month poor outcomes

All variables with a P value $\leq$ 0.2 in univariate analysis for poor outcomes are listed in Table 4. These variables were entered into a stepwise multivariable logistic regression analysis that identified AF (OR 3.94, 95% confidence interval [CI] 1.67—9.29; $P = 0.002$), RV dysfunction (OR 3.55, 95% CI 1.21—10.39; $P = 0.02$) and severe baseline pulmonary hypertension (OR 7.56, 95% CI 2.58—22.17; $P < 0.001$) as independent predictors of 6-month poor outcomes, whereas baseline AR $\geq$ 2/4 (OR 0.07, 95% CI 0.02—0.32; $P = 0.001$) demonstrated a protective effect (Table 4).

Predictors of secondary endpoints

All variables with a P value $\leq$ 0.2 in univariate analysis for secondary endpoints are listed in Tables 5 and 6.

Independent predictors of clinical efficacy (Table 5) were AF (OR 4.09, 95% CI 1.99—8.39; $P < 0.001$) and sPAP $\geq$ 60 mmHg (OR 3.84, 95% CI 1.52—9.72; $P = 0.004$). Again, baseline AR $\geq$ 2/4 (OR 0.30, 95% CI 0.11—0.79; $P = 0.015$) showed a protective effect.

In a stepwise Cox multivariable model, STS risk score (hazard ratio [HR] 1.32, 95% CI 1.11—1.57; $P = 0.002$), prior

Table 1 Characteristics of the study patients at baseline.

Characteristics	All patients ($n=163$)	Good outcomes ($n=114$)	Poor outcomes ($n=49$)	P
Age (years)	79.9 ± 8.8	78.6 ± 9.7	82.8 ± 5.0	0.01
Men	90 (55.2)	59 (51.8)	31 (63.3)	0.24
Body surface area (m^2)	1.78 ± 0.2	1.77 ± 0.2	1.81 ± 0.3	0.63
Logistic EuroSCORE (%)	18.4 ± 11.4	17.4 ± 10.6	20.7 ± 12.7	0.12
STS risk score (%)	5.8 ± 3.1	5.4 ± 3.0	6.0 ± 3.0	0.002
NYHA class III or IV	118 (72.4)	76 (66.7)	42 (85.7)	0.02
Angina pectoris	32 (19.6)	25 (21.9)	7 (14.3)	0.36
Syncope	21 (12.9)	19 (16.7)	2 (4.1)	0.04
Previous acute heart failure	86 (52.8)	57 (50.0)	29 (59.2)	0.36
Clinical history				
CAD	85 (52.1)	64 (56.1)	21 (42.9)	0.17
Previous PCI	24 (14.7)	18 (15.8)	6 (12.2)	0.73
Previous BAV	29 (17.8)	16 (14.0)	13 (26.5)	0.09
Previous CABG	28 (17.2)	21 (18.4)	7 (14.3)	0.68
Previous SAVR	3 (1.8)	2 (1.8)	1 (2.0)	1.0
Cerebrovascular disease	24 (14.7)	17 (14.9)	7 (14.3)	1.0
PVD	32 (19.6)	26 (22.8)	6 (12.4)	0.18
Porcelain aorta	11 (6.7)	8 (7.0)	3 (6.1)	1.0
AF	71 (43.5)	37 (32.5)	34 (69.4)	< 0.0001
Chest wall irradiation	21 (12.9)	19 (16.7)	2 (4.1)	0.04
Hypertension	108 (66.3)	69 (60.5)	39 (79.6)	0.03
Diabetes mellitus	27 (16.6)	20 (17.5)	7 (14.3)	0.78
COPD	63 (38.9)	41 (36.3)	22 (44.9)	0.39
Chronic kidney disease				0.47
Moderate	66 (40.5)	43 (37.7)	23 (46.9)	
Severe	6 (3.7)	5 (4.4)	1 (2.0)	
NT-proBNP (pg/mL)	4281.3 ± 4378.4	4329.6 ± 4724.1	4172.1 ± 3518.2	0.36

Data are mean ± standard deviation or number (%). AF: atrial fibrillation; BAV: balloon aortic valvuloplasty; CABG: coronary artery bypass graft; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; PVD: peripheral vascular disease; SAVR: surgical aortic valve replacement; STS: Society of Thoracic Surgeons.

valvuloplasty (HR 4.31, 95% CI 1.26—14.70; $P=0.02$), aortic annulus diameter (HR 1.50, 95% CI 1.12—2.00; $P=0.007$) and left atrial area (HR 1.12, 95% CI 1.01—1.25; $P=0.04$) were independent predictors of 6-month all-cause mortality (Table 6).

Discussion

TAVI is now the standard of care for 'inoperable' patients and a valid alternative to surgery for many high-risk patients [7]. Nevertheless, in recent studies [2,5], the percentage of patients who were either dead or severely symptomatic at 6 months was about 25%, highlighting that it is still unclear which patients are most likely to benefit from this procedure.

Indeed, although numerous studies have identified predictors of mortality [2,3,6,8,9], few of them have focused on predictors of functional results [8,16,17]. Thus, a strength of the present study was the identification of predictors of 'global' clinical 6-month poor outcomes after TAVI with both valves, in routine clinical practice and using all possible accesses. One of our main findings was the significant proportion of patients with 'poor outcomes'. Moreover, this is, to the best of our knowledge, the first study to highlight the potential independent effect of baseline AR on TAVI outcomes.

Atrial fibrillation

AF after TAVI has been associated with increased all-cause mortality [18]. In the study by Stortecky et al., this was mainly attributable to cardiac mortality, without differences in rates of systemic embolic events or fatal bleedings between patients with and without AF, and irrespective of the type of AF.

In our study, AF was an independent risk factor of 6-month poor outcomes because of increased rates of heart failure events and symptom sustainability. Given the preserved LVEF presented by our patients, it can be hypothesized that they were more likely to have heart failure with preserved ejection fraction. Indeed, AS, by increasing the pressure afterload and wall stress, first leads to LV hypertrophy and then to myocardial apoptosis and fibrosis, which are key factors in the progression towards heart failure [19]. AF, also related to myocardial fibrosis, might be a marker of

Table 2 Procedural characteristics and postprocedural outcomes.

Variables	All patients ($n = 163$)	Good outcomes ($n = 114$)	Poor outcomes ($n = 49$)	*P*
Valve type				0.03
Edwards (SAPIEN and SAPIEN XT)	99 (60.7)	76 (66.7)	23 (46.9)	
Medtronic CoreValve	64 (39.2)	38 (33.3)	26 (53.1)	
Valve diameter				0.14
23 mm	32 (19.6)	23 (20.2)	9 (18.4)	
26 mm	83 (50.9)	62 (54.4)	21 (42.9)	
29 mm	40 (24.5)	26 (22.8)	14 (28.6)	
31 mm	8 (4.9)	3 (2.6)	5 (10.2)	
Vascular access				0.88
Transfemoral	132 (80.9)	92 (80.7)	40 (81.6)	
Subclavian	10 (6.1)	6 (5.3)	4 (8.2)	
Transapical	12 (7.4)	9 (7.9)	3 (6.1)	
Transaortic	9 (5.5)	7 (6.1)	2 (4.1)	
Procedural time (minutes)	96 ± 31	97 ± 34	95 ± 24	0.90
Total amount of contrast agent (mL)	238.8 ± 92.7	233.2 ± 85.1	252.8 ± 109.0	0.25
Need for second valve	2 (1.2)	1 (0.9)	1 (2.0)	0.51
Hospital stay (days)	9.2 ± 5.5	8.4 ± 4.6	11.0 ± 6.8	0.001
ICU stay (days)	3.5 ± 2.1	3.2 ± 1.9	4.2 ± 2.6	0.03
Bleeding				
Life-threatening or disabling	4 (2.5)	2 (1.8)	2 (4.1)	0.58
Major	34 (20.9)	24 (21.1)	10 (20.4)	1.0
Myocardial infarction	3 (1.8)	3 (2.6)	0 (0.0)	0.55
Stroke	4 (2.5)	3 (2.6)	1 (2.0)	1.0
Major vascular complication	16 (9.8)	10 (8.8)	6 (12.2)	0.57
Acute kidney injury, RIFLE stage 2 or 3	10 (6.1)	3 (2.6)	7 (14.3)	0.009
Need for permanent pacemaker implantation	16 (9.8)	6 (5.3)	10 (20.4)	0.007
Postoperative treatment				
Aspirin	143 (87.7)	102 (90.3)	41 (83.7)	0.35
Clopidogrel	93 (57.1)	74 (65.5)	19 (38.8)	0.003
Vitamin K antagonists	56 (34.4)	29 (25.7)	27 (55.1)	0.0006
Diuretics	94 (57.7)	61 (53.9)	33 (67.3)	0.16
Beta-blockers	87 (53.4)	60 (53.6)	27 (55.1)	0.99
ACE inhibitors/ARBs	80 (49.1)	62 (54.9)	18 (36.7)	0.05

Data are mean $\pm$ standard deviation or number (%). ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; ICU: intensive care unit.

such evolved AS, highlighting the need for rigorous echocardiographical screening before TAVI and tailored medication upon discharge for these patients.

Pulmonary hypertension

In TAVI series, the prevalence of sPAP > 60 mmHg ranged from 11% to 32% [9,20]. There is consistent evidence that pulmonary hypertension is an independent predictor of mortality in AS patients [9,21]. Worse functional results after TAVI have also been highlighted [22].

Diastolic dysfunction and AF are considered to be major determinants of pulmonary hypertension in patients with severe AS [21,23]. As previously discussed, these factors reflect the detrimental haemodynamic effects of evolved AS, leading to a vicious circle. Whether these effects can be relieved by TAVI is a major concern. Indeed, although TAVI has been shown to improve sPAP during the first year [23], Roselli et al. [21] demonstrated that, after this initial improvement, there was a progressive rise towards the preoperative level of sPAP in about 3.5 years after SAVR. Given the large number of TAVI candidates with reactive pulmonary hypertension, almost 50% of patients with sPAP > 60 mmHg [23], it suggests that patients with longstanding AS have pulmonary vasculature abnormalities that maintain pulmonary hypertension and worsen outcomes.

Right ventricular dysfunction

It has been shown that under the influence of various factors such as pericardiotomy, hypothermia, inflammation and prolonged cardiopulmonary bypass, RV function decreases after SAVR, which is not observed after TAVI [24]. Some authors have therefore recommended that RV dysfunction should prompt TAVI to be favoured over SAVR [24,25]. Nonetheless, there are no data supporting the fact that patients with pre-existing RV dysfunction experience functional improvement after TAVI. We showed that RV dysfunction was an

Table 3 Echocardiographical findings.

Variables	All patients ($n = 163$)[a]	Good outcomes ($n = 114$)	Poor outcomes ($n = 49$)[b]	*P*
At baseline				
LVEF (%)	50.7 ± 14.8	50.2 ± 15.1	51.9 ± 14.0	0.48
LV end-diastolic diameter (mm)	50.1 ± 7.9	50.5 ± 7.9	49.3 ± 7.9	0.32
LV end-systolic diameter (mm)	36.1 ± 9.5	36.4 ± 9.9	35.5 ± 8.6	0.54
End-diastolic septal thickness (mm)	13.3 ± 2.6	13.3 ± 2.8	13.4 ± 2.4	0.96
Aortic annulus diameter (mm)	22.9 ± 2.1	22.7 ± 2.0	23.5 ± 2.1	0.05
Indexed aortic valve area (cm^2/m^2)	0.38 ± 0.10	0.38 ± 0.11	0.39 ± 0.09	0.27
Aortic mean gradient (mmHg)	50.8 ± 15.5	53.0 ± 15.9	45.7 ± 13.6	0.006
Moderate or severe AR	36 (22.1)	32 (28.1)	4 (8.2)	0.004
Moderate or severe MR	65 (39.9)	42 (36.8)	23 (46.9)	0.30
Left atrial area (cm^2)	28.0 ± 6.6	26.9 ± 6.5	30.5 ± 6.2	0.002
RV dysfunction	31 (19.0)	15 (15.2)	16 (32.7)	0.007
Moderate or severe TR	38 (23.3)	17 (14.9)	21 (42.9)	0.0002
Pulmonary hypertension	106 (65.0)	69 (60.5)	37 (75.5)	0.0007
40 mmHg ≤ sPAP ≤ 50 mmHg	70 (42.9)	53 (46.5)	17 (34.7)	0.173
sPAP ≥ 60 mmHg	36 (22.1)	16 (14.0)	20 (40.8)	< 0.001
Postoperative assessment				
Aortic valve area (cm^2)	1.87 ± 0.53	1.85 ± 0.53	1.90 ± 0.55	0.48
Aortic mean gradient (mmHg)	10.5 ± 4.2	10.9 ± 3.8	9.7 ± 4.9	0.01
Moderate or severe AR	30 (18.6)	16 (14.2)	14 (29.2)	0.04
Patient-prosthesis mismatch				0.33
Moderate	44 (27.0)	29 (26.4)	15 (31.3)	
Severe	8 (4.9)	4 (3.6)	4 (8.3)	
6-month follow-up				
LVEF (%)	55.9 ± 9.8	56.0 ± 9.6	55.6 ± 10.6	0.95
Aortic valve area (cm^2)	1.82 ± 0.6	1.77 ± 0.45	1.89 ± 0.69	0.81
Moderate or severe AR	29 (19.0)	19 (16.7)	10 (26.3)	0.21
Moderate or severe MR	25 (16.4)	15 (13.2)	10 (26.3)	0.15
Moderate or severe TR	21 (13.8)	7 (6.1)	14 (36.8)	< 0.001
Pulmonary hypertension	56 (36.8)	32 (28.1)	24 (63.2)	< 0.001

Data are mean ± standard deviation or number (%). AR, aortic regurgitation; LV: left ventricular; LVEF, left ventricular ejection fraction; MR: mitral regurgitation; RV, right ventricular; sPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation.
[a] $n = 152$ at 6-month follow-up.
[b] $n = 49$ at 6-month follow-up.

independent predictor of poor outcomes, which is in line with previous observations in the setting of SAVR [24].

Recently, Poliacikova et al. [25] reported the outcomes of 155 patients. In this study, RV dysfunction was noted in about 10% of patients and was not associated with an unfavourable prognosis. Nevertheless, a higher mortality rate was observed in patients with RV dysfunction, and low mortality rates in this study might have prevented this trend from reaching statistical significance. Besides, in our study, RV dysfunction was an independent predictor of functional outcomes, which were not assessed in the previous study. Consequently, we believe that RV function should be assessed carefully and taken into account during patient selection.

Aortic regurgitation

Our finding that patients with baseline AR ≥ 2/4 had a lower risk of poor outcomes may seem counterintuitive, as AR ≥ 2/4 has been shown to lower the event-free survival of patients with medically-managed AS [26]. However, there is no evidence that patients with such an AR have worse outcomes after SAVR [27].

AR is much more frequent after TAVI than after SAVR and a recent meta-analysis showed a pooled estimate of 12% for postprocedural AR ≥ 2/4 [28,29]. There is now consistent evidence that such an AR impacts negatively on survival and functional results after TAVI [2,3,6,8,28,29].

A haemodynamic study by Azadani et al. [30] showed substantial energy loss during diastole, even with mild AR, after implantation of a transcatheter valve resulting in higher LV workload. Indeed, postprocedural AR mimics the physiopathology of acute AR, subjecting a hypertrophied LV accustomed to pressure overload to volume overload [29]. The LV is unable to properly increase its end-diastolic volume because of impaired relaxation. Thus, the regurgitation volume precipitates an elevation in the already increased end-diastolic pressure, whereas forward stroke volume

Table 4 Univariate and multivariable predictors of poor outcomes.

Variables	Univariate OR (95% CI)	*P*	Multivariable OR (95% CI)	*P*
Age[a]	1.09 (1.03—1.16)	0.005	—	—
Logistic EuroSCORE[a]	1.03 (0.99—1.06)	0.09	—	—
STS risk score[a]	1.16 (1.04—1.29)	0.008	—	—
Syncope[b]	0.21 (0.05—0.95)	0.04	—	—
CAD[b]	0.59 (0.30—1.15)	0.12	—	—
PVD[b]	0.47 (0.18—1.23)	0.13	—	—
Prior valvuloplasty[b]	2.21 (0.97—5.05)	0.06	—	—
AF[b]	4.72 (2.29—9.72)	< 0.001	3.94 (1.67—9.29)	0.002
Chest wall irradiation[b]	0.21 (0.05—0.95)	0.04	—	—
Hypertension[b]	2.54 (1.16—5.60)	0.02	—	—
Valve type[b]	2.26 (1.14—4.48)	0.02	—	—
Annulus diameter[a]	1.20 (1.02—1.42)	0.03	—	—
Aortic mean gradient[a]	0.97 (0.95—0.99)	0.007	—	—
Left atrial area[a]	1.09 (1.03—1.16)	0.003	—	—
AR ≥ 2/4[b]	0.23 (0.08—0.69)	0.008	0.07 (0.02—0.32)	0.001
TR ≥ 2/4[b]	4.28 (1.99—9.20)	< 0.001	—	—
RV dysfunction[b]	3.20 (1.43—7.17)	0.005	3.55 (1.21—10.39)	0.02
sPAP ≥ 60 mmHg[b]	4.22 (1.94—9.19)	< 0.001	7.56 (2.58—22.17)	< 0.001

AF: atrial fibrillation; AR: aortic regurgitation; CAD: coronary artery disease; CI: confidence interval; OR: odds ratio; PVD: peripheral vascular disease; RV: right ventricular; sPAP: systolic pulmonary artery pressure; STS: Society of Thoracic Surgeons; TR: tricuspid regurgitation.

[a] Age: for each increase of 1 year; logistic EuroSCORE and STS risk score: for each increase of 1%; annulus diameter: for each increase of 1 mm; aortic mean gradient: for each increase of 1 mm Hg; left atrial area: for each increase of 1 cm^2.

[b] Reference values: for syncope, CAD, PVD, prior valvuloplasty, AF, chest wall irradiation, hypertension and RV dysfunction: absence of the variable; for valve type: Edwards valve; for AR: AR < 2/4; for TR: TR < 2/4; for sPAP: sPAP < 60 mmHg.

decreases. Furthermore, the increased LV filling pressure results in an additional reduction in coronary perfusion, which is already affected due to pre-existing myocardial hypertrophy. Eventually, these dramatic haemodynamic changes promote symptom sustainability.

We assume that patients with significant baseline AR may be 'tolerant' to postprocedural AR. This might be the result of less-altered myocardial compliance and LV remodelling. Future studies should investigate the potential independent effect of preoperative AR on TAVI outcomes.

Table 5 Univariate and multivariable predictors of clinical efficacy.

Variables	Univariate OR (95% CI)	*P*	Multivariable OR (95% CI)	*P*
Age[a]	1.07 (1.02—1.12)	0.01	—	—
Logistic EuroSCORE[a]	1.02 (0.99—1.05)	0.11	—	—
STS risk score[a]	1.12 (1.01—1.24)	0.04	—	—
Syncope[b]	0.38 (0.13—1.10)	0.07	—	—
PVD[b]	0.56 (0.24—1.26)	0.16	—	—
Prior valvuloplasty[b]	2.23 (0.99—5.06)	0.05	—	—
AF[b]	4.37 (2.25—8.48)	< 0.001	4.09 (1.99—8.39)	< 0.001
Chest wall irradiation[b]	0.50 (0.18—1.37)	0.18	—	—
Hypertension[b]	1.63 (0.83—3.20)	0.15	—	—
Annulus diameter[a]	1.20 (1.03—1.41)	0.02	—	—
Aortic mean gradient[a]	0.98 (0.96—0.99)	0.04	—	—
Left atrial area[a]	1.05 (0.99—1.10)	0.07	—	—
AR ≥ 2/4[b]	0.23 (0.08—0.69)	0.008	0.30 (0.11—0.79)	0.015
TR ≥ 2/4[b]	2.28 (1.09—4.78)	0.03	—	—
sPAP ≥ 60 mmHg[b]	3.12 (1.44—6.73)	0.004	3.84 (1.52—9.72)	0.004

AF: atrial fibrillation; AR: aortic regurgitation; CI: confidence interval; OR: odds ratio; PVD: peripheral vascular disease; sPAP: systolic pulmonary artery pressure; STS: Society of Thoracic Surgeons; TR: tricuspid regurgitation.

[a] Age: for each increase of 1 year; logistic EuroSCORE and STS risk score: for each increase of 1%; annulus diameter: for each increase of 1 mm; aortic mean gradient: for each increase of 1 mmHg; left atrial area: for each increase of 1 cm^2.

[b] Reference values: for syncope, PVD, prior valvuloplasty, AF, chest wall irradiation and hypertension: absence of the variable; for AR: AR < 2/4; for TR: TR < 2/4; for sPAP: sPAP < 60 mmHg.

Table 6 Univariate and multivariable predictors of all-cause mortality.

Variables	Univariate HR (95% CI)	*P*	Multivariable HR (95% CI)	*P*
Age[a]	1.08 (0.97—1.21)	0.16	—	—
STS risk score[a]	1.28 (1.09—1.50)	0.003	1.32 (1.11—1.57)	0.002
NYHA functional class III or IV[b]	3.91 (0.5—30.51)	0.19	—	—
Prior valvuloplasty[b]	4.00 (1.22—13.11)	0.02	4.31 (1.26—14.70)	0.02
AF[b]	2.39 (0.70—8.16)	0.17	—	—
Valve type[b]	2.85 (0.83—9.72)	0.10	—	—
Annulus diameter[a]	1.32 (1.02—1.72)	0.04	1.50 (1.12—2.00)	0.007
Left atrial area[a]	1.13 (1.03—1.24)	0.01	1.12 (1.01—1.25)	0.04
Permeability index[a]	0.82 (0.70—0.96)	0.01	—	—
MR $\geq$ 2/4[b]	2.68 (0.78—9.15)	0.12	—	—
sPAP $\geq$ 60 mmHg[b]	4.42 (1.35—14.47)	0.01	—	—

AF: atrial fibrillation; CI: confidence interval; OR: odds ratio; MT: mitral regurgitation; NYHA: New York Heart Association; sPAP: systolic pulmonary artery pressure; STS: Society of Thoracic Surgeons.

[a] Age: for each increase of 1 year; STS risk score: for each increase of 1%; annulus diameter: for each increase of 1 mm; left atrial area: for each increase of 1 cm^2; permeability index: for each increase of 1%.

[b] Reference values: for NYHA functional class: NYHA functional class I or II; for prior valvuloplasty and AF: absence of the variable; for valve type: Edwards valve; for MR: MR < 2/4; for sPAP: sPAP < 60 mmHg.

Limitations

When interpreting results of this study, some limitations need to be acknowledged. First, we have reported on the experience of a single tertiary-care referral centre with a small population. Thus, our results are primarily hypothesis-generating and ought to be confirmed in larger studies. Second, we had no standardized evaluation of frailty, which has recently been pointed out as a predictor of functional decline and mortality after TAVI [17]. Lastly, despite rigorous prospective follow-up, there was no external adjudication of events.

Conclusion

About one-third of patients in the present study had poor outcomes after TAVI. AF, severe baseline pulmonary hypertension and RV dysfunction (i.e. variables suggesting a more evolved AS) were predictors of 6-month poor outcomes. Conversely, baseline AR $\geq$ 2/4 showed a protective effect, which needs to be confirmed in future studies. Our study highlights the need for a specific 'TAVI risk score', which could lead to better selection of patients.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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