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

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Abstract

Background: Patients' selection for transcatheter aortic valve implantation (TAVI) remains a major concern. Indeed, despite promising results, it is still unclear which patients are the most and least likely to benefit from this procedure.

Objectives: Our objective was to identify predictors of 6-months clinical poor outcomes after TAVI.

Methods: Patients who were discharged from our institution with a transcatheter-implanted aortic valve were prospectively followed. Our population was divided into 2 groups, "good outcomes" and "poor outcomes", according to the occurrence of the primary endpoint which was a composite of all-cause mortality, all stroke and hospitalizations for valve-related symptoms or worsening heart failure from discharge to 6 months or 6-months New-York Heart Association functional class III or IV. The patients' characteristics were studied to find predictors of poor outcomes.

Results: We included 163 patients (mean age: 80±9 years, 90 male (55%)). Their mean logistic Euroscore was 18.4±11.4%. The primary endpoint occurred in 49 patients (mean age: 83±5 years, 31 male (63%)). By multivariate analysis, atrial fibrillation (odds-ratio [OR] = 3.94), systolic pulmonary artery pressure≥60 mm Hg (OR=7.56), right ventricle dysfunction (OR=3.55) were independent predictors of poor outcomes whereas baseline aortic regurgitation≥2/4 (OR=0.07) demonstrated a protective effect.

Conclusion: AF, severe baseline PH and RV dysfunction i.e. variables suggesting a more evolved AS, were predictors of 6-months poor outcomes. Conversely, baseline AR≥2/4 showed a protective effect which has to be confirmed in future studies. Our study highlights the need of a specific "TAVI Risk Score" which could lead to better selection of patients.

Key words: Transcatheter aortic valve implantation, aortic stenosis, aortic regurgitation, outcomes;

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: 163 patients consécutifs (âge moyen :80±9 ans ; 90 hommes (55%)) ont été inclus. L'Euroscore logistique moyen était de 18.4±11.4%. 49 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. A 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.

Abbreviations and Acronyms:

AF: Atrial Fibrillation;

AR: Aortic regurgitation;

AS: Aortic stenosis;

EOA: Effective orifice area;

HF: Heart failure;

LVEF: Left ventricular ejection fraction;

NYHA: New-York Heart Association;

PH: Pulmonary Hypertension;

RV: Right ventricle;

SAVR: Surgical Aortic Valve Replacement;

sPAP: Systolic pulmonary artery pressure;

TAVI: Transcatheter Aortic Valve Implantation;

TT/TE-E: Transthoracic / transesophageal-echocardiography;

TR: Tricuspid regurgitation

Introduction

Aortic stenosis (AS) is the most common valvular disease with increasing incidence in 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) so that it is now the standard of care for inoperable patients and a valid alternative to surgery for many high-risk but patients (7).

Despite these promising results, a significant proportion of patients either die or have no functional benefits within first months after TAVI (2,5,6,8). Numerous predictors of mortality were identified such as post-procedural aortic regurgitation (AR) (2,3,9,10), chronic obstructive pulmonary disease (3), chronic kidney disease , pulmonary hypertension (PH) or post-procedural complications (10).

Moreover, recently, post-procedural AR and severe mitral regurgitation (MR) were identified as independent predictors of poor treatment response (8). Nonetheless, data about predictors of functional outcomes after TAVI are scarce. Yet, given that this technique is generally intended to elderly patients, symptomatic improvement is as critical as the increase in life expectancy. A risk score to identify which patients are the 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-months poor outcomes after TAVI defined as the clinical components of “clinical efficacy” as defined in the recommendations of the Valve Academic Research Consortium (11).

Methods

Patients

Patients with severe and symptomatic AS (effective orifice area [EOA]≤1cm²) who underwent TAVI at our institution were prospectively enrolled. Exclusion criteria were death during the procedure or the subsequent hospitalization, conversion to surgery or unsuccessful implantation defined as impossibility to deliver and deploy a valve into proper location for anatomical reasons. Before TAVI, these patients underwent an evaluation including physical examination, blood tests, transthoracic (TTE) and transesophageal (TEE) echocardiography and a computerized tomography. Indications, contraindications, and anatomical requirements for TAVI were described previously (7). SAVR risk for mortality was estimated using the logistic EuroSCORE (12) and the Society of Thoracic Surgeon (STS) Risk Score (13). Finally, TAVI indication was retained by a multidisciplinary "heart-team" based on the evaluation cited above. Patients were followed on-site before discharge and 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' physician. Patients gave written informed consent before participation. The study was approved by the local ethic committee.

Endpoints

The primary end-point was the clinical components of "clinical efficacy" (11) i.e. a composite of all-cause mortality, all stroke (disabling and non-disabling), hospitalizations for valve-related symptoms or worsening HF from discharge to 6 months or a 6-months NYHA class III or IV. Secondary end-points were clinical efficacy as defined in the recommendations of the Valve Academic Research Consortium (11) (clinical components or valve-related dysfunction i.e. mean aortic valve gradient ≥20 mmHg, EOA ≤0.9–1.1 cm2 and/or Doppler velocity index<0. 35 m/s and/or moderate or severe prosthetic valve regurgitation) and 6-months all-

cause mortality. The cohort was subsequently divided into 2 groups, i.e the "good outcomes" and the "poor outcomes", according to the occurrence of the primary end-point.

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 the hospitalization for the preoperative assessment or the day before TAVI. Coronary artery disease was defined as presence of lesions with ≥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 (11).

Study devices and procedures

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

Echocardiography

TTE was performed according to American Society of Echocardiography's guidelines (14) by an experienced echocardiographist using a digital ultrasound scanner (Vivid7; General Electrics or Ie33; Philips Healthcare).

In apical 5-chamber view, peak and mean pressure gradients across the aortic valve were calculated using the Bernoulli equation. EOA was calculated by means of the continuity equation.

A multiparametric approach with both semi-quantitative and quantitative parameters 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 post-procedural AR were graded in accordance with the European society of cardiology guidelines for native valves (15). However, given the frequent eccentric and irregular jet of post-procedural AR, we also gave a heavy weight to the circumferential extent of prosthetic AR in parasternal short-axis view to provide integrated assessment of post-procedural AR (11). Thresholds were as follows: none-no regurgitant color flow; mild-extent <10%; moderate-extent=10-29%; severe-extent≥30%. Before TAVI, we used TEE to measure accurately the annulus diameter and sometimes grade AR or MR when TTE was not conclusive.

PH was defined as systolic pulmonary artery pressure (sPAP), estimated using tricuspid regurgitation (TR) velocity, ≥40 mmHg at rest (16). Right atrial pressure was assessed using inferior vena cava diameter (in its long axis) and inspiratory collapse in the subcostal view (16): a diameter≤21mm and a collapse>50% with a sniff were used as cut-offs for normal right atrial pressure i.e. 3mmHg (range, 0-5mmHg) whereas diameter>21mm and collapse<50% defined high right atrial pressure (15 mmHg, range, 10-20mmHg). In indeterminate cases in which the IVC diameter and collapse did not fit these definitions, an intermediate value of 8 mm Hg (range, 5-10 mm Hg) was used. Right ventricle (RV) function was assessed in apical 4-chamber view using tricuspid annular plane systolic excursion

measured by M-mode with reference value for impaired RV systolic function of <16mm and right ventricular peak systolic velocity of the tricuspid annulus measured by tissue Doppler with a value of ≥10cm/s defining normal RV function (16). Left ventricular ejection fraction (LVEF) was measured by Simpson method from 4- and 2-chamber views (14). Left atrial end-systolic area was measured from 4-chamber apical view. LV end-diastolic, 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, 1 month and 6 months after TAVI.

Blood tests

Venous blood samples were obtained on the day before TAVI to determine levels of N-terminal pro B-type natriuretic peptide and serum creatinine. The estimated glomerular filtration rate was calculated using abbreviated Modification of Diet in Renal Disease Study Equation. Kidney disease was defined as moderate when the glomerular filtration rate was between 30 and 59ml/min/1.73m² and severe when <30ml/min/1.73m².

Statistical analysis

Numeric values are expressed as mean±SD. Normality was tested using Kolmogorov-Smirnov test. Continuous variables were compared using unpaired t-test or Mann-Whitney U-test as appropriate. $\chi 2$ analysis or Fischer's exact test were used to compare categorical variables. Patients' characteristics were evaluated for poor outcomes. All baseline variables with a p-value≤0.2 in univariate analysis were entered in an ascending stepwise multivariate logistic regression analysis to identify independent predictors of poor outcomes and in an ascending stepwise Cox multivariate 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-ratio and hazard-ratio. A p-value≤0.05 was considered significant. All probability values reported are 2-sided. Statistical analysis was performed with the use of SPSS 21.0 (SPSS, Inc., Chicago, Illinois).

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 heart-team reunions, TAVI indication was retained in 180 patients who underwent the procedure from February 2009 to July 2012. A total of 17 patients either died during the procedure (n=3), the initial hospitalization (n=6), were converted to surgery (n=4; 2 annulus rupture, 2 embolization of the prosthesis in the left ventricle) or had unsuccessful implantation (n= 6, 5 non-fatal vascular access complications, 1 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 (Figure 1). No patient was lost to follow-up.

The mean age of study patients was 79.9±8.8 years, 90 patients (55%) were male, mean logistic EuroSCORE was 18.4%±11.4% and mean STS Risk Score was 5.8±3.1%. 118 patients (72%) were NYHA functional class III or IV and 86 (53%) had history of acute HF. 44 % of patients had AF. Baseline characteristics of the study population are summarized in Table 1.

Procedural outcomes

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

Mean total procedural time was 96±31min and mean contrast agent volume was 238.8±92.7mL. Valve embolization in the aorta was observed in 2 cases and could be managed with implantation of a second prosthesis. Acute kidney injury stage 2 or 3 arose in 10 patients (6.1%) including 1 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 (8 of cardiovascular causes) between their discharge from hospital and the 6-month follow-up. Thus 6-months all-cause mortality rate was 6.7% for the study population and 11.1% for the 180 patients who underwent the procedure.

23 of 152 remaining study patients were NYHA functional class III or IV at the 6-month follow-up. Hospitalization for HF occurred in 32 patients, no stroke occurred after the initial hospitalization. Eventually, 49 patients (30%) met the criteria of "poor outcomes" group. The 114 remaining patients (70%) 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 of clinical efficacy.

Echocardiographic findings

Most patients had preserved LVEF (mean LVEF: 50.7±14.8%) and only 25 patients (16%) had LVEF≤30%. Thirty-six patients (22%) had moderate or severe (≥2/4) AR at baseline. MR≥2/4 (moderate: n=57; severe: n=8) was present in 65 patients (40%). RV dysfunction was observed in 31 patients (19%) and 38 (23%) had TR≥2/4 (moderate: n=26; severe: n=12). PH was diagnosed in 65% of patients and was moderate (40≤sPAP≤59mmHg) in 70 patients (43%) and severe (sPAP≥60mmHg) in 36 patients (22%). Overall, sPAP improved in 61 of the 106 patients (57.5%) with baseline PH.

After TAVI, AR was common as 115 patients (71%) presented a leak but AR≥2/4 was present in only 30 patients (19%). Regarding patients with postprocedural AR≥2/4, 9 out of 16 patients (56%) in the good outcomes group compared to only 1 out of 14 patients (7%) in the poor outcomes group had baseline AR≥2/4. Echocardiographic findings are summarized in table 3.

Predictors of 6-months poor outcomes

All variables with p-value≤0.2 on univariate analysis for poor outcomes are listed in table 4. These variables were entered in a stepwise multivariate logistic regression analysis that identified AF (OR= 3.94, 95%CI: 1.67-9.29 ,p=0.002), RV dysfunction (OR=3.55, 95%CI: 1.21-10.39,p=0.02), severe baseline PH (OR=7.56,95%CI: 2.58-22.17,p<0.001) as independent predictors of 6-months poor outcomes whereas baseline AR≥2/4 (OR=0.07, 95%CI: 0.02-0.32, p=0.001) demonstrated a protective association (Table 4).

Predictors of secondary end-points

All variables with a p-value≤0.2 on univariate analysis for secondary endpoints are listed in tables 5 and 6.

Independent predictors of clinical efficacy (table 5) were as follows: AF (OR=4.09, 95%CI: 1.99-8.39, p<0.001) and sPAP≥60 mmHg (OR=3.84, 95%CI: 1.52-9.72, p=0.004). Again, baseline AR≥2/4 (OR= 0.30, 95%CI: 0.11-0.79, p=0.015) showed a protective effect.

In a stepwise Cox multivariate model, STS risk score (HR=1.32, 95%CI: 1.11-1.57, p=0.002), prior 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-months 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 the most likely to benefit from this procedure.

Indeed, if numerous studies identified predictors of mortality (2,3,8-10), few of them focused on predictors of functional results (8,17,18). Thus, a strength of the present study is to identify predictors of "global", clinical 6-months poor outcomes after TAVI with both valves available in clinical routine and all possible accesses. One of our main findings is the significant proportion of patient showing "poor outcomes".

Moreover, this is, to the best of our knowledge, the first study to highlight the potential independent role of baseline AR on TAVI outcomes.

Atrial fibrillation

After TAVI, AF has been associated with increased all-cause mortality (19). In the work 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-months poor outcomes because of increased rates of HF events and symptoms' sustainability. Given the preserved LVEF presented by our patients, it can be hypothesized that they were more likely to suffer from HF with preserved ejection fraction. Indeed, AS, by increasing the pressure afterload and wall stress, first lead to LV hypertrophy and then to myocardial apoptosis and fibrosis, which is a key factor in the progression towards HF (20). AF, also related to myocardial fibrosis might be a marker of such evolved AS highlighting the need for rigorous echocardiographic screening before TAVI and tailored medication upon discharge for these patients.

Pulmonary hypertension

In TAVI series, prevalence of sPAP>60mmHg range from 11 to 32% (10,21). There is consistent evidence that PH is an independent predictor of mortality in AS patients (10,22). Worse functional results after TAVI have also been highlighted (23).

Diastolic dysfunction and AF are considered to be major determinants of PH in patients with severe AS (22,24). As previously discussed, these factors reflect detrimental hemodynamic effects of evolved AS leading to a vicious circle. Whether this effect can be relieved by TAVI is a major concern. Indeed, if TAVI has been shown to improve sPAP during the first year (24), Roselli et al (23) demonstrated, after this initial improvement, a progressive rise towards the pre-operative level of sPAP in about 3½ years after SAVR. Considering the large amount

of TAVI candidates with reactive PH, almost 50% of patients with sPAP>60 mm Hg (24), it suggests that patients with longstanding AS have pulmonary vasculature abnormalities able to maintain PH and worsen outcomes.

Right ventricle dysfunction

It has been shown that under the influence of various factors such as pericardiotomy, hypothermia, inflammation or prolonged cardio-pulmonary bypass, RV function decrease after SAVR which is not observed after TAVI (25).Some authors have therefore recommended that RV dysfunction should prompt to favor TAVI over SAVR (25,26). Nonetheless, there is no data supporting the fact that patients with pre-existing RV dysfunction experience functional improvement after TAVI.

We showed that RV dysfunction was an independent predictor of poor outcomes. This is in line with previous observations in the setting of SAVR (25).

Recently, Poliacikova et al (26), reported outcomes of 155 patients. In this study, RV dysfunction was noted in about 10% of patients and was not associated with a pejorative prognosis. Still, a higher mortality was observed in patients with RV dysfunction and low mortality rates in this study might have prevent 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 patients' selection.

Aortic regurgitation

Our finding that patients with baseline AR≥2/4 have a lower risk of poor outcomes may seem counterintuitive since AR≥2/4 has been shown to lower event-free survival of medically-

managed AS (27). However there is no evidence that patients with such AR have worse outcomes after SAVR (28).

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 (29,30). There is now consistent evidence that such AR negatively impacts survival and functional results after TAVI (2,3,8,9,29,30).

A hemodynamical study by Azadani et al (31) 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 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 decreases. Furthermore, the increased LV filling pressure results in additional reduction in coronary perfusion, which is already affected due to preexisting myocardial hypertrophy. Eventually, these dramatic hemodynamic changes promote symptoms 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 remodeling. Future studies should investigate the potential independent role of preoperative AR on TAVI outcomes.

Limitations

When interpreting results of this study, some limitations need to be acknowledged. First, we report the experience of a single, tertiary-care referral center with a small population. Thus our results are first of all hypothesis-generating and deserve to be confirmed in larger studies. Second, we had no standardized evaluation of frailty which has recently be pointed out as a

predictor of functional decline and mortality after TAVI (18). 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 PH and RV dysfunction i.e. variables suggesting a more evolved AS, were predictors of 6-months poor outcomes. Conversely, baseline AR≥2/4 showed a protective effect which has to be confirmed in future studies. Our study highlights the need of a specific "TAVI Risk Score" which could lead to better selection of patients.

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Conflict of interest

None.

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Figures

Figure 1- Flowchart.

* 1 patient died during surgical aortic valve replacement after aortic annulus rupture during transcatheter aortic valve implantation.

TAVI= transcatheter aortic valve implantation.

Figure 1 Flowchart

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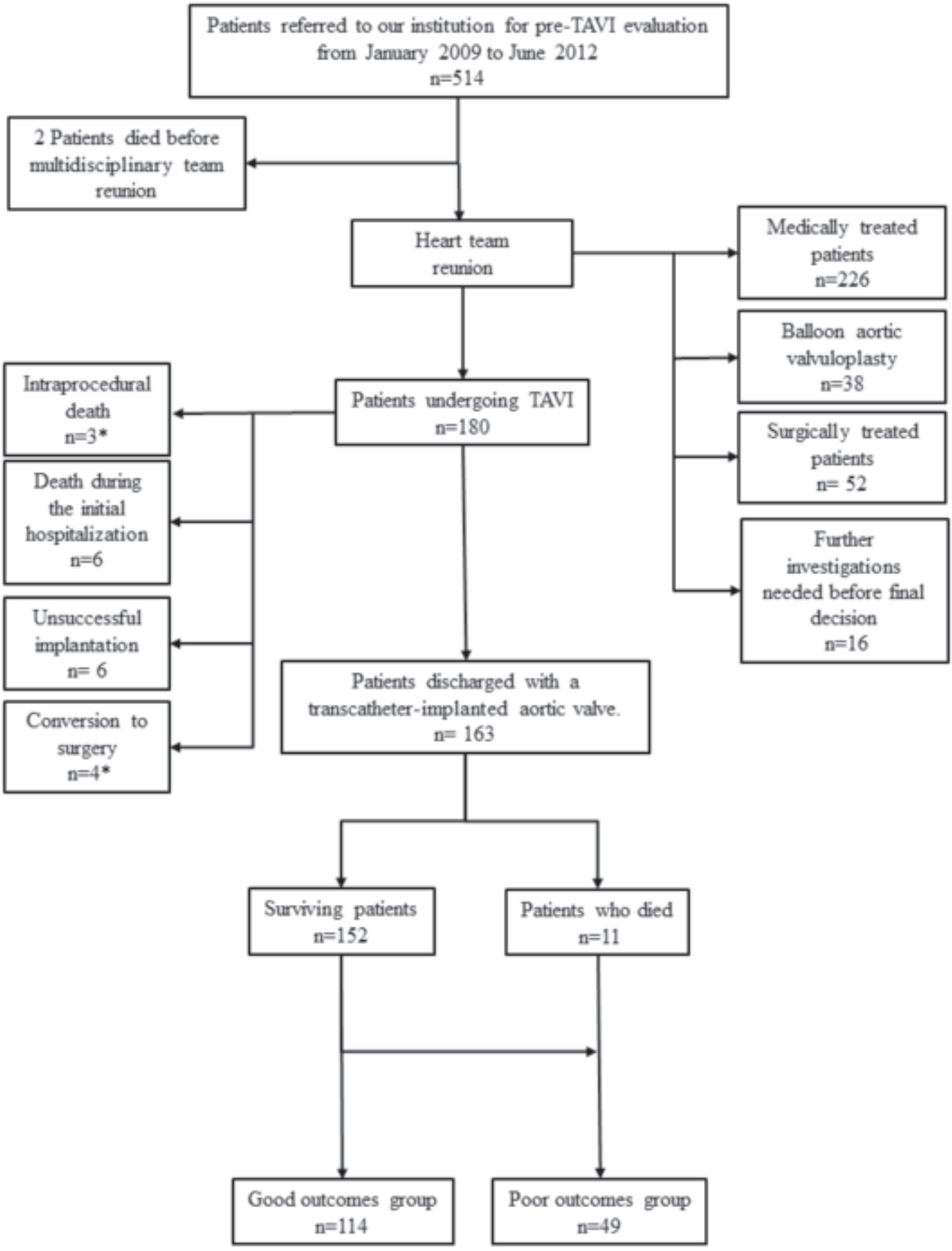

Table 1- Characteristics of the study patients at baseline

Table 1-Characteristics of the study patients at baseline.

Characteristics	All patients (n=163)	Good outcomes patients (n=114)	Poor outcomes patients (n=49)	p-value
Age - yr	79.9±8.8	78.6±9.7	82.8±5.0	0.01
Male sex -no. (%)	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
Society of Thoracic Surgeons score - %	5.8±3.1	5.4±3.0	6.0±3.0	0.002
New-York Heart Association class III or IV - no. (%)	118 (72.4)	76 (66.7)	42 (85.7)	0.02
Angina pectoris-no. (%)	32 (19.6)	25 (21.9)	7 (14.3)	0.36
Syncope-no. (%)	21 (12.9)	19 (16.7)	2 (4.1)	0.04
Previous acute heart failure-no. (%)	86 (52.8)	57 (50.0)	29 (59.2)	0.36
Clinical history -no. (%)				
Coronary artery disease	85 (52.1)	64 (56.1)	21(42.9)	0.17
Previous percutaneous coronary intervention	24 (14.7)	18 (15.8)	6 (12.2)	0.73
Previous balloon aortic valvuloplasty	29 (17.8)	16 (14.0)	13 (26.5)	0.09
Previous coronary artery bypass graft	28 (17.2)	21 (18.4)	7 (14.3)	0.68
Previous surgical aortic valve replacement	3 (1.8)	2 (1.8)	1 (2.0)	1.0
Cerebrovascular disease	24 (14.7)	17 (14.9)	7 (14.3)	1.0
Peripheral vascular disease	32(19.6)	26 (22.8)	6 (12.4)	0.18
Porcelain aorta	11 (6.7)	8 (7.0)	3 (6.1)	1.0
Atrial fibrillation	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
Chronic obstructive pulmonary disease	63 (38.9)	41 (36.3)	22 (44.9)	0.39
Chronic kidney disease-no. (%)				0.47
Moderate chronic kidney disease	66 (40.5)	43 (37.7)	23 (46.9)	
Severe chronic kidney disease	6 (3.7)	5 (4.4)	1 (2.0)	
NT pro-BNP-pg/ml	4281.3±4378.4	4329.6±4724.1	4172.1±3518.2	0.36

Table 2-Procedural characteristics

Table 2- Procedural characteristics and postprocedural outcomes

Variables	All patients (n=163)	Good outcomes patients (n=114)	Poor outcomes patients (n=49)	p value
Valve type-no.(%)				0.03
Edwards (Sapiens and Sapiens XT)	99 (60.7)	76 (66.7)	23 (46.9)	
Medtronic Corevalve	64 (39.2)	38 (33.3)	26 (53.1)	
Valve Diameter- no (%)				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-no.(%)				0.88
Transfemoral	132 (80.9)	92 (80.7)	40 (81.6)	
Sub-clavian	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- min	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- no.(%)	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- no. (%)				
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- no. (%)	3 (1.8)	3 (2.6)	0 (0.0)	0.55
Stroke- no.(%)	4 (2.5)	3 (2.6)	1 (2.0)	1.0
Major vascular complication- no. (%)	16 (9.8)	10 (8.8)	6 (12.2)	0.57
Acute kidney injury Rifle stage 2 or 3- no. (%)	10 (6.1)	3 (2.6)	7 (14.3)	0.009
Need for permanent pacemaker implantation- no. (%)	16 (9.8)	6 (5.3)	10 (20.4)	0.007
Post-operative treatments- no (%)				
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 / ARB	80 (49.1)	62 (54.9)	18 (36.7)	0.05

ACE= angiotensin converting enzyme; ARB= angiotensin receptor blocker; ICU= intensive care unit.

Table 3-Echocardiographic findings

Table 3- Echocardiographic findings

Variables	All patients (n=163)	Good outcomes patients (n=114)	Poor outcomes patients (n=49)	p value
At baseline				
Left ventricle ejection fraction-%	50.7±14.8	50.2±15.1	51.9±14.0	0.48
Left ventricle end-diastolic diameter- mm	50.1±7.9	50.5±7.9	49.3±7.9	0.32
Left ventricle end-systolic diameter- mm	36.1±9.5	36.4±9.9	35.3±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- mm Hg	50.8±15.5	53.0±15.9	45.7±13.6	0.006
Moderate or severe aortic regurgitation -no. (%)	36 (22.1)	32(28.1)	4 (8.2)	0.004
Moderate or severe mitral regurgitation- no. (%)	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
Right ventricule dysfunction-no. (%)	31 (19.0)	15 (15.2)	16 (32.7)	0.007
Moderate or severe tricuspid regurgitation- no. (%)	38 (23.3)	17 (14.9)	21 (42.9)	0.0002
Pulmonary hypertension- no. (%)	106 (65.0)	69 (60.5)	37 (75.5)	0.0007
40≤ systolic pulmonary artery pressure ≤ 59 mm Hg	70 (42.9)	53 (46.5)	17 (34.7)	0.173
systolic pulmonary artery pressure ≥ 60 mm Hg	36(22.1)	16 (14.0)	20 (40.8)	<0.001
Post-operative assessment				
Aortic valve area- cm^2	1.87±0.53	1.85±0.53	1.90±0.55	0.48
Aortic mean gradient- mm Hg	10.5±4.2	10.9±3.8	9.7±4.9	0.01
Moderate or severe aortic regurgitation-no (%)	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 (8.5)	
6 month follow-up	**n=152**	**n=114**	**n=38**	
Left ventricle ejection fraction-%	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 aortic valve regurgitation- no (%)	29 (19.0)	19 (16.7)	10 (26.3)	0.21
Moderate or severe mitral regurgitation- no. (%)	25 (16.4)	15 (13.2)	10 (26.3)	0.15
Moderate or severe tricuspid regurgitation- no. (%)	21 (13.8)	7 (6.1)	14 (36.8)	<0.001
Pulmonary hypertension- no. (%)	56 (36.8)	32 (28.1)	24 (63.2)	<0.001

Table 4- Univariate and multivariate predictors of poor outcomes

Variables	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value
Age*	1.09 (1.03-1.16)	0.005	-	-
Logistic Euroscore*	1.03 (0.99-1.06)	0.09	-	-
STS Risk Score*	1.16 (1.04-1.29)	0.008	-	-
Syncope†	0.21 (0.05-0.95)	0.04	-	-
CAD†	0.59 (0.30-1.15)	0.12	-	-
PVD†	0.47 (0.18-1.23)	0.13	-	-
Prior valvuloplasty†	2.21 (0.97-5.05)	0.06	-	-
AF†	4.72 (2.29-9.72)	<0.001	3.94 (1.67-9.29)	0.002
Chest-wall irradiation†	0.21 (0.05-0.95)	0.04	-	-
Hypertension†	2.54 (1.16-5.60)	0.02	-	-
Valve type†	2.26 (1.14-4.48)	0.02	-	-
Annulus diameter*	1.20 (1.02-1.42)	0.03	-	-
Aortic mean gradient*	0.97 (0.95-0.99)	0.007	-	-
Left atrial area*	1.09 (1.03-1.16)	0.003	-	-
AR≥2/4†	0.23 (0.08-0.69)	0.008	0.07 (0.02-0.32)	0.001
TR≥2/4†	4.28 (1.99-9.20)	<0.001	-	-
RV dysfunction†	3.20 (1.43-7.17)	0.005	3.55 (1.21-10.39)	0.02
sPAP ≥ 60 mm Hg†	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; RV=right ventricle; PVD=peripheral vascular disease; sPAP=systolic pulmonary artery pressure; STS= society of thoracic surgeons; TR=tricuspid regurgitation.

* Age: for each increase of 1 year; Logitic 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 1mm Hg; Left atrial area: for each increase of 1 cm^2.

† Reference values: for syncope, CAD, PVD, Prior valvuloplasty, AF, Chest-wall irradiation, hypertension and RV dysfunction: absence of the variable; for valve type: Edwards valves; for AR: AR <2/4; for TR: TR<2/4; for sPAP: sPAP<60 mm Hg.

Table 5- Univariate and multivariate predictors of clinical efficacy

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

Abbreviations, units and reference values as in table 4.

Table 6- Univariate and multivariate predictors of all-cause mortality

Variables	Univariate HR (95% CI)	p-value	Multivariate HR (95% CI)	p-value
Age*	1.08 (0.97-1.21)	0.16	-	-
STS Risk Score*	1.28 (1.09-1.50)	0.003	1.32 (1.11-1.57)	0.002
NYHA functional class>2/4†	3.91 (0.5-30.51)	0.19	-	-
Prior valvuloplasty†	4.00 (1.22-13.11)	0.02	4.31 (1.26-14.70)	0.02
AF†	2.39 (0.70-8.16)	0.17	-	-
Valve type†	2.85 (0.83-9.72)	0.10	-	-
Annulus diameter*	1.32 (1.02-1.72)	0.04	1.50 (1.12-2.00)	0.007
Left atrial area*	1.13 (1.03-1.24)	0.01	1.12 (1.01-1.25)	0.04
Permeability index*	0.82 (0.70-0.96)	0.01	-	-
MR≥2/4†	2.68 (0.78-9.15)	0.12	-	-
sPAP ≥ 60 mm Hg†	4.42 (1.35-14.47)	0.01	-	-

MR= mitral regurgitation; NYHA= New-York Heart Association. Other abbreviations as in Table 4.

* Permeability index: for each increase of 1%. Other units as in table 4

†Reference values: for MR: MR<2/4. Other reference values as in table 4.