UNIVERSITE DE NANTES

_____

FACULTE DE MEDECINE

_____

Année 2015 N° 072

THESE

pour le

DIPLOME D'ETAT DE DOCTEUR EN MEDECINE

DES de Médecine Interne

par

Anne Sophie Boureau
née le 28 Octobre 1984 à Brest

_____

Présentée et soutenue publiquement le 23 Mars 2015

_____

Facteurs prédictifs de l'évolution de la qualité de vie en post-interventionnel d'un remplacement valvulaire aortique par voie percutanée (TAVI) chez les patients âgés. Etude observationnelle, multicentrique, prospective.

_____

Président : Monsieur le Professeur Berrut
Directeur de thèse : Dr de Decker

REMERCIEMENTS

Au jury de thèse

Au président de jury, le Professeur Gilles Berrut,

Vous me faites l'honneur de présider ce jury de thèse. C'était un réel plaisir d'apprendre à vos cotés durant ces années d'internat tout au long desquelles vous m'avez apporté votre soutien et vos précieux conseils. Je vous en remercie.

Au directeur de thèse, le Docteur Laure de Decker,

Merci d'avoir accepté de diriger cette thèse et de m'avoir épaulée tout au long de nos travaux de recherche avec un dynamisme scientifique qui force le respect. Je suis profondément reconnaissante pour tout le temps que tu m'as accordé pour lire et relire ces travaux. C'est un réel plaisir de travailler avec toi.

Aux membres du jury,

Au Professeur Jean Noël Trochu,

C'est avec grand plaisir que je vous présente mon travail de thèse, il constitue une synthèse de la collaboration entre nos services. Je suis très sensible à la disponibilité dont vous avez fait preuve à mon égard. Je vous remercie pour votre implication dans ce projet.

Au Professeur Pierre Potier,

Vous avez si gentiment et spontanément accepté de participer au jury. Veuillez trouver l'expression de mes sincères remerciements et de ma gratitude.

Aux services de gériatrie et de cardiologie, des CHU de Nantes et d'Angers, ainsi que l'unité de recherche clinique, qui ont participé activement à la réalisation de ce travail.

A l'équipe mobile de gériatrie et à mes collègues (internes ou déjà chefs) présents au quotidien de notre formation et avec qui nous échangeons tant.

Aux maîtres d'internat et anciens chefs, pour m'avoir fait partager leurs connaissances et leur amour de la médecine, notamment le Pr Hamidou, le Pr Agard, le Dr Brisseau, le Dr Masseau, le Dr Connault, le Dr Gueffet et le Dr Cormier.

A mes amis, ces moments de bonheur et bonne humeur partagés. A mes amis parisiens pour avoir fait perdurer ici les liens qui nous unissaient là-bas.

A ma famille,

A mes grands parents, qui je l'espère, sont fiers du chemin parcouru. Merci Mutti d'être présente en ce jour si particulier pour moi.

A mes parents qui m'ont encouragé et guidé dans mes choix, merci pour l'amour que vous m'avez tant donné.

A Xavier, Valentine et Agathe, mes frères et sœurs, qui comptent tant pour moi.

A Richard, pour ton amour et tous les projets que nous avons ensemble.

A Lénaëlle, notre rayon de soleil depuis 1 an.

SOMMAIRE

CONTEXTE

La prévalence des pathologies valvulaires augmentent avec l'âge [1]. Parmi elles, le rétrécissement aortique est la plus fréquente, atteignant 5% de la population de plus de 75 ans [1]. Le remplacement de valve aortique par voie chirurgicale est le traitement de référence [2]. Toutefois, certaines études ont mis en évidence que 30% à 40% des patients de plus de 80 ans ayant un rétrécissement aortique serré symptomatique n'ont pas d'intervention chirurgicale [3]. Le remplacement valvulaire aortique par voie percutanée est une alternative pour ces patients à haut risque opératoire ou polypathologiques, récusés pour une chirurgie conventionnelle. Cette procédure permet l'implantation d'une nouvelle valve biologique au niveau de la valve aortique calcifiée, montée sur un cathéter par voie trans-fémorale ou par voie trans-apicale. Les bénéfices par rapport au traitement médical en terme de survie et de qualité de vie en postopératoire ont été prouvés à plusieurs reprises que ce soit à 6 mois, 1 an et 2 ans [4,5]. Cependant ces résultats favorables sont à nuancer car la mortalité reste de 35% à 2 ans et 25% des patients ne présentent pas d'amélioration de la qualité de vie 6 mois après l'intervention [4,5].

En 2012, lors de l'élaboration de ce projet de recherche, aucune étude publiée ne détaillait les caractéristiques des patients qui ne tiraient pas de bénéfice clinique de cette intervention. Par conséquent, le choix thérapeutique entre TAVI et traitement médical restait compliqué comme le confirmait notre précédente étude qui révélait qu'aucun facteur cardiologique ou gériatrique ne semblait orienter la décision médicale entre TAVI et le traitement médical seul [6]. Afin d'identifier ces patients à haut risque de décès ou de dégradation de leur qualité de vie, il semble donc nécessaire de décrire les paramètres gériatriques et cardiologiques qui influencent l'évolution post-interventionnelle notamment les évolutions défavorables telles que la mortalité, la perte d'autonomie, la perte de qualité de vie.

Depuis plusieurs articles en ce sens ont été publiés. En 2013, Schoenenberger et al. ont mis en évidence qu'un index de fragilité était prédictif d'une perte d'autonomie dans la vie quotidienne

à 1 an [7]. En 2014, Arnold et al. ont montré que la présence de certains facteurs cardiologiques comme une arythmie, ou un gradient moyen trans-aortique élevé étaient des facteurs prédictifs de mortalité ou de perte de qualité de vie à 6 mois [8]. Aucune étude publiée ne décrit les paramètres gériatriques qui influencent la survie ou l'évolution de la qualité de vie après un TAVI.

Notre étude, avec pour objectif principal de mettre en évidence les facteurs prédictifs d'altération de la qualité de vie, de la mortalité et de déclin fonctionnel à 6 mois d'une intervention par TAVI, reste donc totalement d'actualité.

C'est dans ce contexte que nous avons vous présentons ces résultats sous la forme d'un article en langue anglaise en vue d'une publication internationale.

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet. 2006;368(9540):1005‑11.
2. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, et al. Guidelines on the management of valvular heart disease. Eur Heart J. 2012;33(19):2451‑96.
3. Bach DS. Prevalence and characteristics of unoperated patients with severe aortic stenosis. J Heart Valve Dis. 2011;20(3):284‑91.
4. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 21 2010;363(17):1597‑607.
5. Reynolds MR, Magnuson EA, Lei Y, Leon MB, Smith CR, Svensson LG, et al. Health-related quality of life after transcatheter aortic valve replacement in inoperable patients with severe aortic stenosis. Circulation. 2011;124(18):1964‑72.
6 Boureau AS, Trochu JN, Colliard C, Volteau C, Jaafar P, Manigold T, et al. Determinants in treatment decision making in older patients with symptomatic severe aortic stenosis. Plos One, under review.
7. Schoenenberger AW, Stortecky S, Neumann S, Moser A, Jüni P, Carrel T, et al. Predictors of functional decline in elderly patients undergoing transcatheter aortic valve implantation (TAVI). Eur Heart J. 2013;34(9):684‑92.
8. Arnold SV, Reynolds MR, Lei Y, Magnuson EA, Kirtane AJ, Kodali SK, et al. Predictors of poor outcomes after transcatheter aortic valve replacement: results from the PARTNER (Placement of Aortic Transcathet1er Valve) trial. Circulation. 2014;129(25):2682‑90.

ARTICLE

Predictors of health-related quality of life decline after transcatheter aortic valve replacement in older patients with severe aortic stenosis

AS. Boureau, MD, MS 1

JN. Trochu, MD, PhD 2

A. Rouaud, MD, MS 1

G. Berrut, MD, PhD 1

L. de Decker, MD, PhD 1

1: Department of Geriatrics, EA 1156-12, Nantes University Hospital, Nantes, France

2: Inserm, UMR 1087, Department of Cardiology and Vascular diseases, Institut du Thorax, CHU Nantes, France

Correspondence to:

Corresponding author: Anne Sophie Boureau, MD, Department of Geriatrics, Nantes University Hospital, boulevard Jacques Monod, 44093 Nantes Cedex 1, France; e-mail: anne-sophie.boureau@etu.univ-nantes.fr

Abstract: 260

Words count: 3092

Tables count: 5

Figure count: 3

References count: 35

ABSTRACT

Background:

Transcatheter aortic-valve implantation (TAVI) has been shown to improve survival and quality of life in patients with severe aortic stenosis. However, one-third of patients have poor outcome as death, functional decline or quality of life (QoL) decline.

The aim of this study was to determine cardiac and geriatric predictors of physical and mental QoL decline 6 months after a TAVI procedure in patients aged 75 and older.

Methods:

Between January 2013 and June 2014, we did a prospective and multicenter study including patients ≥ 75 years old referred for TAVI. .The primary outcome was the measure of QoL, assessed by the Short Form 36 survey (SF-36), before and 6 months after the intervention. Association between QoL decline and baseline characteristics including cardiac and geriatric factors was analysed by logistic regression models.

Results:

Mean age of the 150 patients studied was 83.7 years old and 56% were men. The primary end point, mean SF-36 physical summary score, significantly improved between baseline and 6-month (33.6 vs. 36.4, p=0.003) whereas mental component score significantly decreased (48.2 vs. 36.4, p-value < 0.001). The risk of depression was associated with mental QoL decline (OR 21.9 [5.1-93.7], p-value < 0.001) and no significant geriatric predictors were associated with physical QoL decline.

Conclusion:

The mental QoL significantly decreased and baseline risk of depression was identified as a predictor of this decline. This study highlights the importance of detection of the pre-operative depression. Researches are needed to determine if treatment of depression in patients treated by TAVI improves 6-month mental quality of life.

Key words: older patients, aortic valve stenosis, geriatric assessment, health-related quality of life

INTRODUCTION

Aortic stenosis is the most common heart valve disease in patients aged 75 years and older[1]. Although surgical aortic valve replacement improves survival and quality of life, at least one-third of older patients do not undergo surgery because of comorbidities or a high risk of preoperative mortality [2]. For these patients, a less alternative invasive treatment as transcatheter aortic valve implantation (TAVI) may be chosen. Indeed, numerous studies have proven that TAVI in older patients improves quality of life (QoL) and survival compared to medical treatment [3–5]. However, it is established that some patients do not improve heart failure symptoms and functional limitation [5–7]. Moreover, 15 to 25% of patients who underwent TAVI do not improve quality of life at 6 months [5]. In order to describe these patients, some studies tried to identify predictors of mortality, functional decline and worsened QoL [4,7-10]. In theses studies, the predictors of poor outcomes were NYHA III or IV, oxygen-dependent lung disease, renal dysfunction, lower mean aortic valve gradient, a frailty index and the 6-minute walk test [4,7-10]. Specific geriatric factors assessed as routinely during a comprehensive geriatric assessment (CGA), have not been independently analysed as predictors of mortality or functional decline or worsened QoL after TAVI [8]. CGA developed by geriatricians is a multidisciplinary evaluation of comorbid medical conditions, cognitive and psychological status, nutritional status, functional status and social support [11].

The aim of this prospective study was to determine cardiac and geriatric predictors of health-related quality of life decline 6 months after a TAVI procedure in patients aged 75 and older. The secondary objectives were to analyse the predictors of mortality, the predictors of functional decline and post operative complications.

METHODS

Study population

Between January 2013 and June 2014, all patients aged ≥ 75 years referred for a severe symptomatic aortic stenosis pre-operative evaluation in Nantes University Hospital or in Angers University Hospital were eligible for this prospective observational study. The inclusion criteria were 1) an age of 75 years old and over, 2) presence of a symptomatic aortic stenosis considered severe if aortic valve area is < 1 cm^2 or a mean aortic-valve gradient is ≥ 40 mmHg, and 3) presence of a comprehensive pre-operative geriatric assessment. The following patients were excluded from the present study: patients under legal protection, patients who could not have the geriatric baseline examination, patients for whom TAVI was done as an emergency procedure, patients who refused and patients with valve in valve procedure.

Patients underwent TAVI with the self-expandable Medtronic CoreValve bioprosthesis or the balloon-expandable Edwards Sapien transcatheter heart valve. The transcatheter aortic valve procedure was done under general anaesthesia, using the transfemoral approach whenever feasible.

This study was conducted in accordance with the ethical standards set forth in the declaration of Helsinki (1983). The Committee for the local Ethical Committee of Nantes (France) approved the project and the study is in compliance with the STROBE statement guidelines. All patients provided written informed consent for baseline and follow up assessment.

This study was registered at ClinicalTrials.gov. (Number: NCT01761357)

Baseline Data

An extensive cardiac and geriatric assessment was performed for all patients during the in-hospital pre-operative evaluation. This evaluation included the patient's history, his

comorbidities, symptoms and a systematic clinical examination. The echocardiographic assessment provided information on aortic valve area (cm^2), mean aortic-valve gradient (mmHg), left ventricular ejection fraction (LVEF), and pulmonary hypertension (PH). The coronary angiography and aorto-iliofemoral computed tomography angiography completed the cardiologic assessment. The perioperative mortality risk was estimated by Logistic EuroSCORE, EuroSCORE II and the Society of Thoracic Surgeons score (STS). The geriatric assessment (CGA) performed by a geriatrician, included the following items: patients comorbidities evaluated by the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) [12], Body Mass Index (BMI) for nutritional status, Mini-Mental State Examination (MMSE) and Frontal Assessment Battery (FAB) for cognitive assessment [13,14], Instrumental activities of daily living of Lawton (IADL) for functional assessment [15], Timed Get Up and Go Test (TUG) for mobility impairment [16], mini-Geriatric Depression Scale (mini-GDS) for risk of depression [17].

For the purpose of this analysis, geriatric test's scores were dichotomized at standard cut points which were defined according to current literature: TUG at $\geq$ 20 s (mobility impairment) vs. < 20 s (normal gait function) [16], BMI $\leq$ 21 (malnutrition) vs. > 21 (normal nutrition), and mini-GDS $\geq$ 1 (risk of depression) vs. mini-GDS=0 (no depression) [17]. MMSE, FAB, CIRS-G, ADL and IADL were coded as continuous variables. CIRS-G score varies from very low (0) to high (56) burden of disease. IADL score ranges from 0 to 8. An IADL score of 8 indicates full function, and 2 or less indicates severe functional impairment.

Study end points

The main outcome was the decline of health-related quality of life decline 6 months after the TAVI procedure. The health-related quality of life (QoL) was evaluated with a standardized written questionnaire, the Medical Outcomes Study (MOS) Short Form 36 (SF-36) tool. Each

patient completed a questionnaire at baseline, by interview the day before the procedure. At 6 months, the questionnaire was completed by postal survey.

The SF-36 tool consists of 36 items self-administered questionnaire grouped in 8 dimensions of health parameters: physical functioning, role–physical, bodily pain, general health, vitality, social functioning, role–emotional, and mental health. Each dimension is scored on a 0 to 100 scale, with 0 corresponding to worst and 100 to best QoL. These 8 scales can be summarized in 2 scores: the Physical Component Score (PCS) and the Mental Component Score (MCS). They are scaled to overall population norms of 50 and SDs of 10; higher scores meaning better QoL [18]. The SF-36 has undergone extensive reliability and validity testing in various countries, in older patients and in patients with aortic stenosis [19]. The individual QoL change was calculated by the difference in the physical component score and mental component scores between baseline and and 6 months. A health-related quality of life decline was defined by a difference in the PCS or the MCS $\leq$ zero at 6 months [18].

The secondary outcomes were death at 6 months, functional decline at 6 months assessed by IADL and complications. Functional decline was defined as a decrease of $\geq$ 0.5 point in the ability to perform IADL between baseline and 6 months follow-up.

Clinical adverse events were defined according to the VARC criteria [20]. Complications of interest were stroke, vascular complications requiring unplanned endovascular or surgical intervention, implantation of pace maker or new permanent atrial fibrillation, acute renal failure defined as an absolute increase in serum creatinine $\geq$ 200%, and other TAVI-related complication as ventricular perforation or cardiac tamponade. Geriatric complications were also gathered as delirium, falls or acute failure of chronic diseases requiring hospitalisation.

Follow up

The follow up was performed 6 months after the procedure. For all patients, quality of life and functional status (IADL) were assessed. At 6 months, IADL was assessed by phone survey whereas SF-36 questionnaire was completed by postal survey. All relevant adverse event data were recorded by phone and by medical records.

Statistical analysis

The participants' baseline characteristics were summarized using means ± standard deviations for continuous variables or counts and percentages for categorical variables. Patient's characteristics were compared between 2 groups according the presence of physical or mental QoL decline, by Fisher exact test for dichotomous variables and by t test for means of continuous variables.

The following baseline predictors of quality of life decline were evaluated in the univariate analysis: age, gender, Logistic EuroSCORE, EuroSCORE 2, STS score, NYHA, LVEF, PH, MMS, FAB, BMI, CIRS-G, IADL, mini-GDS. Baseline predictors of quality of life decline that were found with a p-value less than 0.20 in univariate analysis, confounding factors and variables of the main objective (MMS, FAB, BMI, CIRS-G, IADL, mini-GDS) were included in multivariate analyses. Baseline predictors of functional decline and mortality that were found with a p-value less than 0.20 in univariate analysis, confounding factors and variables of the main objective (MMS, FAB, BMI, CIRS-G, mini-GDS) were respectively included in multivariate logistic regression or multivariate Cox model.

Odds ratio or Hazard ratio with their 95 % confidence intervals were presented. All p-value were two sided. P-values less than 0.05 were considered statistically significant. All statistics were performed using SAS(r) (version 9.3 SAS Institute Inc., Cary, NC, USA).

RESULTS

Between January 2013 and June 2014, 193 patients ≥ 75 years were referred for a TAVI procedure in Nantes University Hospital and in Angers University Hospital. Forty three patients were excluded patients (2 patients under legal protection, 24 patients with no geriatric baseline examination or emergency procedure, 13 patient's refusal, 4 with valve in valve procedures). The study population consisted of 150 patients.

Patient characteristics

The mean age of the study population was 83.7 ± 4.6 years (range 77-95) and 56% were men. A total 73 out of the patients (48.7%) were in NYHA functional class III or IV. The mean aortic-valve gradient was 51.7 ± 14.8 mmHg. The mean Logistic EuroSCORE was 17.0 ± 8.1%, and the mean STS score was 7.25 ± 3.7%. The geriatric assessment revealed that patients had many comorbidities with a high score of CIRS-G (10.8 ± 3.1), 55.3% had impaired gait function. The mean MMS was of 24.9 ± 3.5. Patients had limited ability to performed activities of daily living (mean IADL= 5.5 ± 2.2).

At baseline, the physical component score (PCS) and the mental component score (MCS) were respectively of 33.6 ± 8.4 and 55.6 ± 8.1. Baseline characteristics of patients with or without QoL decline at 6 months are shown in Table 1.

Follow up Data

During 6-month follow up, 12 patients died (8.0%) and 19 were lost to follow up (Figure 1). At 6-month follow-up, 47 patients (31.3%) had physical QoL decline and 74 (49.3%) had mental QoL decline.

Overall, the improvement of the physical component score was significant (33.6 vs. 36.4, p-value = 0.003) whereas mental component score significantly decreased (48.2 vs. 36.4, p-value < 0.001) (Figure 2). Sixty four patients (53.8%) had 6-month functional decline.

Predictors of QoL decline among survivors

There were no group differences age or gender ratios. There were no significant intergroup differences in any of the cardiac or geriatric factors (Table 1).

In the analysis, neither cardiac nor geriatric predictors were significantly associated with physical QoL decline at 6 months (Table 2).

Table 3 shows the results for the prediction of mental QoL decline at 6 months. The presence of risk of depression before the intervention was strongly and significantly associated with mental QoL decline (OR 21.9 [5.1-93.7], p-value < 0.001).

Secondary analyses

Predictors of mortality

The Figure 3 shows the survival curves for the whole study population. The Logistic EuroSCORE was significantly associated with death in the analysis (Table 4). No geriatric predictors were associated with mortality.

Functional Status

At baseline, mean IADL was 5.5 ± 2.2 and decreased to 4.9 ± 1.9 at 6 months. Functional status for Instrumental Activities of Daily Living significantly decreased after the procedure (p<0.001). No geriatric predictors were significantly associated with functional decline (Table 5).

Complications

The rate of strokes after TAVI was of 2% (3 patients). Permanent pace maker was the most frequent adverse effect, occurring in 25 patients (16.6%) and seven patients (4.6%) had a new permanent atrial fibrillation. Vascular complications after TAVI occurred in 13 patients (8.6%) and 8 patients (5.3%) had pericardial effusion with tamponade or ventricular perforation, only one had a conversion to surgery. The overall rate of acute renal failure was of 6%.

The incidence of delirium during hospital stay was of 12% (18 patients) and falls occurred in 11 patients (7.3%). Eleven patients had an acute failure of chronic diseases requiring hospitalisation.

DISCUSSION

This survey is the first prospective study specially designed to describe geriatric factors associated with health-related quality of life decline after TAVI procedure. Overall, patients had significant physical QoL improvement and significant mental QoL decrease 6 months after TAVI. One-third of patients had physical QoL decline at 6 months but no cardiac or geriatric predictor has been identified. Half of the population study had 6-month mental QoL decline and baseline risk of depression was identified as a predictor of this decline. No geriatric factor was associated with functional decline. Finally, Logistic EuroSCORE was the only factor associated with 6 month-mortality.

In this study, patients had significant physical QoL improvement. Our findings are consistent with previous studies. Indeed, numerous studies shown that physical QoL improves at 6 months and later [5,21] but these studies did not try to find out predictors of improvement or decline. Even though we did not found any geriatric predictors, our study is the first one to include geriatric factors gathered during a pre-operative complete geriatric assessment. Only one other study analysed predictors of poor outcomes defined by poor physical QoL and mortality after TAVI (PARTNER trial) [8]. In their survey, the geriatric factor analysed were the MMS, the Body mass index and the gait speed. Gait speed, assessed by 6-minute walk test was significantly associated with a poor outcome at 6 months [8]. Two reasons can explain our different results. First, the methods were different especially with different outcome: physical QoL alone versus an arbitrary construct endpoint combining poor physical QoL and mortality. Second, the population-based studies were slightly different. Even though the mean age, predominance of male and cardiac factors were similar; the mean MMS score was lower and the mobility impairment at baseline was more frequent in our study. In the present study, mental QoL life significantly declined 6 months after TAVI. In previous studies, results on

mental QoL evolution were contrasted. Studies using SF-36 tool found improvement or decline but did not reach statistical significance [21,22]. One study using another tool, the SF-12 tool, found a significant mental QoL improvement [5]. Our study showed that the risk of depression before the intervention was a predictor of mental QoL decline. In line with our results, previous studies found depression was an important predictor of mental health QoL after aortic valve replacement and after coronary artery bypass grafting [23,24].

The rate of mortality was of 8% in our study, which is coherent with the literature [4,10]. The 6-month mortality was associated with Logistic EuroSCORE in our study. Our results are consistent with numerous studies [4,10,25]. Indeed, cardiac predictors of mortality after TAVI are well known as NYHA class, Logistic EuroSCORE, LVEF, and access route. However, current surgical risk scores, including Logistic EuroSCORE, predict 30-day survival after conventional surgery and are used to identify high risk patients. Although these risk scores are associated with increased mortality after TAVI, they are not designed nor validated to assess mortality risk for TAVI. Few studies that have evaluated the value of conventional surgical risk scores to predict 1-year mortality after TAVI concluded that in practice TAVI should be guided by the interdisciplinary team decision [26-28].

In our survey, the functional status assessed by the ability to perform the IADL declined in 53.8% of patients. In the only previous study that assessed functional decline after TAVI, Schoenenberger and al. found that 20.8% of patients had functional decline [7]. These different results can be explained by the different endpoint. Indeed, in their study, the functional decline was defined as a decrease of ≥1 point in the ability to perform ADL between baseline and follow-up. The ADL ranks adequacy of performance in everyday tasks as bathing or eating [29]. The IADL, used in our study, has been shown to be more sensitive in detection of

early stage of functional decline, because it measures higher order functioning such as managing medications and money [15,30]. Schoenenberger and al. also found that a frailty index was associated with functional decline. In our study, we did not found any independent geriatric predictor. Methodological reasons can explain our different results. In our study, the frailty index wasn't measured because there is no clear consensual definition of frailty and a large array of criteria has been proposed to define and assess this syndrome. The pre-operative geriatric assessment was based on consensual and validated scores done routinely in geriatric evaluation. Moreover, at the beginning of our study the frailty index was not yet the confounding factors because the study of Schoenenberger and al. was not published.

The incidences of cardiac complications were similar in our study than in previous studies [31]. However this study is the first to show geriatric complications occurring in post-interventional period. About delirium, our findings are consistent with the only previous study. Tse and al. retrospectively showed that delirium occurred between 12% and 43% of patients depending on access route [32]. There is no published study on occurrence of falls or acute failure of chronic disease. Acute failure of chronic disease seemed an interesting factor and may explain why some patients had quality of life decline after TAVI procedure.

The strengths of our study include the prospective cohort study design, the multicenter study and the absence of sponsor, which minimizes the potential for selection bias. However because of the predominance of non-significant results, it seemed important to look through the methods to exclude any bias. Although numerous methods exist to evaluate health-related QoL, the SF-36 health survey questionnaire was chosen because it is a validated generic scale for cardiac patients and for older patients [33-35]. Furthermore, previous studies had proved improvement of quality of life after TAVI procedure using SF-36 scale [21]. Therefore the study

design seemed appropriate. Our consistent results as the population's study age, the significant physical QoL improvement and the incidence of cardiac complications confirm the study's strength.

This study has some limitations. The first limitation is the lack of the NYHA score evolution and echocardiography parameters between baseline and 6-month evaluation. This additional information could have helped to understand the QoL evolution especially in patients with QoL decline. However, it would not have changed results about predictors of QoL decline.
Second, the sample size was small. Further studies of larger patient populations are required to confirm our results.

In conclusion, this study showed that the mental QoL significantly declined and baseline risk of depression was identified as a predictor of this decline. No cardiac or geriatric predictors were associated with the physical QoL decline. This study highlights the importance of detection of pre-operative depression.
The present study has research implications. First, larger studies with complete geriatric assessment are needed to confirm geriatric characteristic of the TAVI population, and consensual geriatric scores as predictors of a health-related quality of life decline. Second, researches are needed to determine if detection and treatment of depression in patients treated by TAVI improve their quality of life.

ACKNOWLEDGMENTS

We are grateful to the participants for their cooperation.

Conflict of interest: The authors declare no conflict of interest

Sponsor's role: None.

REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;368(9540):1005-1011.

2. Iung B, Cachier A, Baron G, et al. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? *Eur Heart J*. 2005;26(24):2714-2720.

3. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363(17):1597-1607.

4. Gilard M, Eltchaninoff H, Iung B, et al. Registry of Transcatheter Aortic-Valve Implantation in High-Risk Patients. *N Engl J Med*. 2012;366(18):1705-1715.

5. Reynolds MR, Magnuson EA, Lei Y, et al. Health-related quality of life after transcatheter aortic valve replacement in inoperable patients with severe aortic stenosis. *Circulation*. 2011;124(18):1964-1972.

6. Buellesfeld L, Gerckens U, Schuler G, et al. 2-year follow-up of patients undergoing transcatheter aortic valve implantation using a self-expanding valve prosthesis. *J Am Coll Cardiol*. 2011;57(16):1650-1657.

7. Schoenenberger AW, Stortecky S, Neumann S, et al. Predictors of functional decline in elderly patients undergoing transcatheter aortic valve implantation (TAVI). *Eur Heart J*. 2013;34(9):684-692.

8. Arnold SV, Reynolds MR, Lei Y, et al. Predictors of poor outcomes after transcatheter aortic valve replacement: results from the PARTNER (Placement of Aortic Transcatheter Valve) trial. *Circulation*. 2014;129(25):2682-2690.

9. Stortecky S, Schoenenberger AW, Moser A, et al. Evaluation of multidimensional geriatric assessment as a predictor of mortality and cardiovascular events after transcatheter aortic valve implantation. *JACC Cardiovasc Interv*. 2012;5(5):489-496.

10 Ludman PF, Moat N, de Belder MA, et al. Transcatheter Aortic Valve Implantation in the UK: Temporal Trends, Predictors of Outcome and 6 Year Follow Up: A Report from the UK TAVI Registry 2007 to 2012. *Circulation*. 2015.

11 Ellis G, Whitehead MA, Robinson D, O'Neill D, Langhorne P. Comprehensive geriatric assessment for older adults admitted to hospital: meta-analysis of randomised controlled trials. *BMJ*. 2011;343:d6553.

12. Miller MD, Paradis CF, Houck PR, et al. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. *Psychiatry Res*. 1992;41(3):237-248.

13. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.

14. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. *Neurology*. 2000;55(11):1621-1626.

15. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *The Gerontologist*. 1969;9(3):179-186.

16. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*. 1991;39(2):142-148.

17. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res*. 1982;17(1):37-49.

18. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-483.

19. Ware JE Jr, Kosinski M, Gandek B, et al. The factor structure of the SF-36 Health Survey in 10 countries: results from the IQOLA Project. International Quality of Life Assessment. *J Clin Epidemiol*. 1998;51(11):1159-1165.

20. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Thorac Cardiovasc Surg*. 2013;145(1):6-23.

21. Krane M, Deutsch M-A, Piazza N, et al. One-year results of health-related quality of life among patients undergoing transcatheter aortic valve implantation. *Am J Cardiol*. 2012;109(12):1774-1781.

22. Krane M, Deutsch M-A. Quality of life among patients undergoing transcatheter aortic valve implantation. *Am Heart J*. 2010;160.

23. Middel B, El Baz N, Pedersen SS, van Dijk JP, Wynia K, Reijneveld SA. Decline in health-related quality of life 6 months after coronary artery bypass graft surgery: the influence of anxiety, depression, and personality traits. *J Cardiovasc Nurs*. 2014;29(6):544-554.

24. Oterhals K, Hanssen TA, Haaverstad R, Nordrehaug JE, Eide GE, Norekvål TM. Factors associated with poor self-reported health status after aortic valve replacement with or without concomitant bypass surgery. *Eur J Cardio-Thorac Surg*. 2014.

25. Moat NE, Ludman P, de Belder MA, et al. Long-Term Outcomes After Transcatheter Aortic Valve Implantation in High-Risk Patients With Severe Aortic Stenosis: The U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. *J Am Coll Cardiol*. 2011;58(20):2130-2138.

26. Wenaweser P, Stortecky S, Schwander S, et al. Clinical outcomes of patients with estimated low or intermediate surgical risk undergoing transcatheter aortic valve implantation. *Eur Heart J*. 2013.

27. Watanabe Y, Hayashida K, Lefèvre T, et al. Is EuroSCORE II better than EuroSCORE in predicting mortality after transcatheter aortic valve implantation? *Catheter Cardiovasc Interv*. 2013;81(6):1053-1060.

28. Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur Heart J*. 2014;35(35):2383-2431.

29. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. the index of ADL: a standardized measure of biological and psychosocial function. *Jama*. 1963;185:914-919.

30. Wolinsky FD, Bentler SE, Hockenberry J, et al. Long-term declines in ADLs, IADLs, and mobility among older Medicare beneficiaries. *BMC Geriatr*. 2011;11:43.

31. Khatri PJ, Webb JG, Rodés-Cabau J, et al. Adverse Effects Associated With Transcatheter Aortic Valve Implantation: A Meta-analysis of Contemporary Studies. *Ann Intern Med*. 2013;158(1):35-46.

32. Tse L, Bowering JB, Schwarz SKW, Moore RL, Burns KD, Barr AM. Postoperative delirium following transcatheter aortic valve implantation: a historical cohort study. *Can J Anaesth*. 2015;62(1):22-30.

33. Lyons RA, Perry HM, Littlepage BN. Evidence for the validity of the Short-form 36 Questionnaire (SF-36) in an elderly population. *Age Ageing*. 1994;23(3):182-184.

34. Vicchio M, De Feo M, Giordano S, Provenzano R, Cotrufo M, Nappi G. Coronary artery bypass grafting associated to aortic valve replacement in the elderly: survival and quality of life. *J Cardiothorac Surg*. 2012;7(1):13.

35. Geschke K, Fellgiebel A, Laux N, Schermuly I, Scheurich A. Quality of life in dementia: impact of cognition and insight on applicability of the SF-36. *Am J Geriatr Psychiatry*. 2013;21(7):646-654.

TABLES AND FIGURES

Table 1: Baseline characteristics of patients with or without physical QoL decline at 6 months.

Characteristics	All participants n= 150	Physical QoL Decline			Mental QoL Decline		
		No n=72	Yes n=47	p-value	No n= 33	Yes n=89	p-value
Age, years, mean ± SD	83.7 ± 4.6	83.6 ± 4.4	84.0 ± 4.7	0.77	84.1 ± 4.6	82.6 ± 4.0	**0.03**
Male, n (%)	84 (56.0)	38 (52.8)	28 (59.6)	0.89	16 (48.5)	37 (41.6)	0.14
Dyspnea NHYA III or IV, n, (%)	73 (48.7)	33 (45.8)	20 (42.5)	0.21	15 (45.5)	38 (42.7)	0.84
Mean gradient aortic valve, mmHg, mean ± SD	51.7 ± 14.9	52.9 ± 14.4	51.2 ± 16.4	0.56	52.8 ± 15.4	50.6 ± 14.7	0.49
Ejection Fraction, mmHg, mean ± SD	55.9 ± 10.7	55.8 ± 11.1	54.9 ± 11.4	0.68	54.1 ± 11.5	59.4 ± 9.2	**0.05**
Pulmonary hypertension, n (%)	53 (34.7)	27 (37.5)	14 (29.8)	0.71	10 (30.3)	31 (34.8)	0.52
Logistic EuroSCORE, mean ± SD	17.0 ± 8.1	16 ± 7.2	16.9 ± 7.8	0.49	16.4 ± 7.4	16.3 ± 7.7	0.14
EuroSCORE 2, mean ± SD	5.0 ± 2.5	4.9 ± 2.4	5.1 ± 2.7	0.69	4.9 ±2.5	5.2 ± 2.6	0.66
STS risk score, mean ± SD	7.2 ± 3.7	6.6 ± 3.0	7.9 ± 4.1	0.07	6.9 ±3.2	7.6 ± 4.3	0.94
CIRS-G score, mean ± SD	10.8 ± 3.1	10.6 ± 3.3	10.8 ± 3.1	0.72	10.3 ± 3.1	11.6 ± 3.2	0.96
Body mass index ≤ 21,n (%)	18 (12.0)	11 (15.3)	5 (10.6)	0.66	6 (18.2)	10 (11.2)	0.43
Mini-Mental Status score, mean ± SD	24.9 ± 3.5	25.3 ± 3.3	24.7 ± 3.4	0.29	25.9 ± 3.3	24.4 ± 3.6	0.88
Frontal Assessment Battery score , mean ± SD	12.8 ± 3.2	13.1 ± 3.1	12.7 ± 3.1	0.47	12.9 ±2.9	12.9 ± 3.5	0.79
Risk of depression, n (%)	23 (15.3)	12 (16.7)	8 (17)	0.89	12 (36.4)	8 (8.9)	**0.02**
IADL, mean ± SD	5.5 ± 2.2	5.6 ± 2.2	5.5 ± 2.1	0.97	5.4 ± 2.2	5.9 ± 2.0	0.16
Timed Up and Go test,n (%)	83 (55.3)	38 (52.8)	24 (51.1)	0.71	14 (42.4)	48 (53.9)	0.66

STS: Society of Thoracic Surgeons; CIRS-G: Cumulative Illness Rating Scale-Geriatric;

IADL: Instrumental activities of daily living

Table 2: Association of preprocedure factors with physical QoL decline 6 months after transcatheter aortic valve implantation, in multivariate analysis.

Predictors	**Physical QoL Decline**	
	OR (95% CI)	**p-value***
Age, years, mean ± SD	1.03 (0.94-1.12)	0.55
Male, n (%)	0.99 (0.42-2.33)	0.55
Ejection fraction, mmHg, mean ± SD	0.99 (0.95-1.03)	0.52
CIRS-G score, mean ± SD	1.03 (0.89-1.19)	0.71
Body mass index, n (%)	1.89 (0.43-8.29)	0.40
Mini-Mental Status score, mean ± SD	1.71 (0.60-4.85)	0.31
Frontal Assessment Battery score, mean ± SD	0.72 (0.28-1.86)	0.5
Risk of depression, n (%)	0.78 (0.26-2.39)	0.67
IADL, mean ± SD	0.99 (0.81-1.19)	0.87
Timed Up and Go test, n (%)	1.4 (0.61-3.23)	0.43

CIRS-G: Cumulative Illness Rating Scale-Geriatric; IADL: Instrumental activities of daily living

p-value and OR significant (i.e., $P < 0.05$) indicated in bold.

* Between-group comparison based on simple *t*-test or Chi-square test, as appropriate

Table 3: Association of preprocedure factors with mental QoL decline 6 months after transcatheter aortic valve implantation, in multivariate analysis.

Predictors	**Mental QoL Decline**	
	OR (95% CI)	**p-value***
Age, years, mean ± SD	1.03 (0.92-1.16)	0.63
Male, n (%)	1.44 (0.44-4.69)	0.54
Ejection fraction , mmHg, mean ± SD	0.98 (0.93-1.03)	0.41
CIRS-G score, mean ± SD	0.97 (0.81-1.17)	0.78
Body mass index, n (%)	0.97 (0.09-10.76)	0.98
Mini-Mental Status score, mean ± SD	0.42 (0.1-1.75)	0.23
Frontal Assessment Battery score, mean ± SD	1.58 (0.41-6.16)	0.51
Risk of depression, n (%)	**21.88 (5.11-93.68)**	**<0.001**
IADL, mean ± SD	1.01 (0.78-1.31)	0.94
Timed Up and Go test, n (%)	1.4 (0.61-3.23)	0.04

CIRS-G: Cumulative Illness Rating Scale-Geriatric; IADL: Instrumental activities of daily living

p-value and OR significant (i.e., $P < 0.05$) indicated in bold.

* Between-group comparison based on simple *t*-test or Chi-square test, as appropriate

Table 4: Association of preprocedure factors with 6-month mortality after transcatheter aortic valve implantation, in multivariate analysis.

Predictors	**Mortality**	
	HR (95% CI)	**p-value**
Age, years, mean ± SD	0.92 (0.79-1.08)	0.35
Male, n (%)	1.48 (0.43-5.17)	0.53
NYHA III or IV, n (%)	1.64 (0.44-6.11)	0.46
Pulmonary hypertension, n (%)	0.75 (0.20-2.77)	0.67
Ejection fraction, mmHg, mean ± SD	1.02 (0.96-1.09)	0.41
Logistic EuroSCORE, mean ± SD	**1.11 (1.03-1.19)**	**0.003**
CIRS-G score, mean ± SD	1.08 (0.84-1.39)	0.52
Body mass index, n (%)	1.03 (0.92-1.16)	0.54
Mini-Mental Status score, mean ± SD	1.02 (0.82-1.26)	0.84
Frontal Assessment Battery score, mean ± SD	1.05 (0.89-1.24)	0.54
Risk of depression, n (%)	0.18 (0.02-1.72)	0.14
IADL, mean ± SD	1.31 (0.94-1.82)	0.11
Timed Up and Go test, n (%)	2.54 (0.71-9.04)	0.15

CIRS-G: Cumulative Illness Rating Scale-Geriatric; IADL: Instrumental activities of daily living

p-value and OR significant (i.e., $P < 0.05$) indicated in bold.

* Between-group comparison based on multivariate Cox model.

Table 5: Association of preprocedure factors with 6-month functional decline after transcatheter aortic valve implantation, in multivariate analysis.

Predictors	**Functional Decline**	
	OR (95% CI)	**p-value**
Age, years, mean ± SD	1.04 (0.95-1.15)	0.38
Male, n (%)	0.44 (0.2-1.01)	0.05
Logistic EuroSCORE, mean ± SD	0.86 (0.71-1.03)	0.11
STS score, mean ± SD	1.03 (0.89-1.18)	0.71
CIRS-G score, mean ± SD	1.09 (0.92-1.31)	0.29
Body mass index, mean ± SD	0.92 (0.81-1.03)	0.15
Mini-Mental Status score, mean ± SD	0.93 (0.78-1.1)	0.38
Frontal Assessment Battery score, mean ± SD	1.18 (0.99-1.41)	0.06
Risk of depression, n (%)	0.79 (0.27-2.37)	0.68
Timed Up and Go test, n (%)	0.71 (0.31-1.65)	0.41

CIRS-G: Cumulative Illness Rating Scale-Geriatric; IADL: Instrumental activities of daily living

p-value and OR significant (i.e., $P < 0.05$) indicated in bold.

* Between-group comparison based on simple *t*-test or Chi-square test, as appropriate

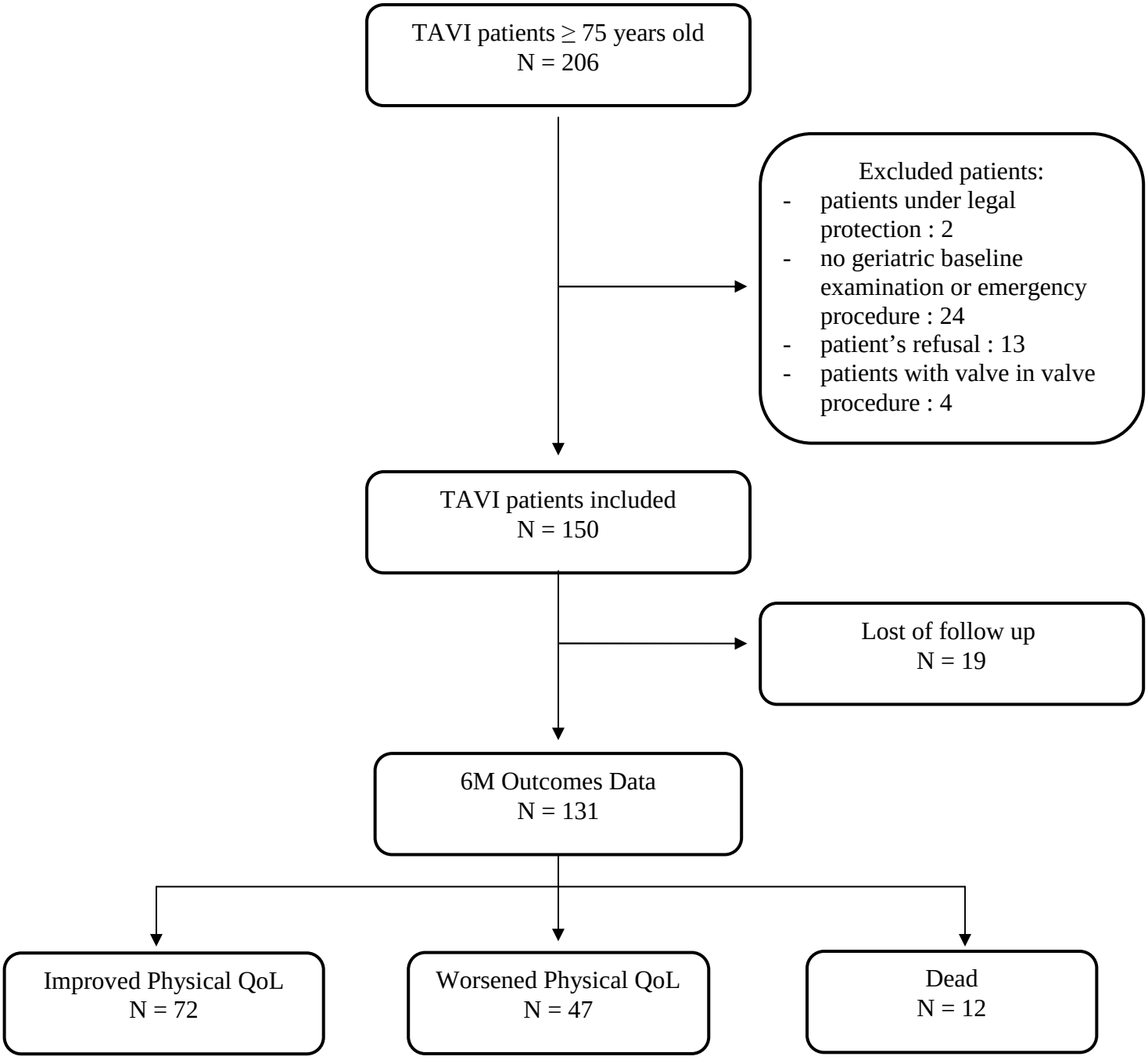

Figure 1: Patient Flow.

TAVI : Transcatheter Aortic Valve Implantation, QoL : Quality of Life

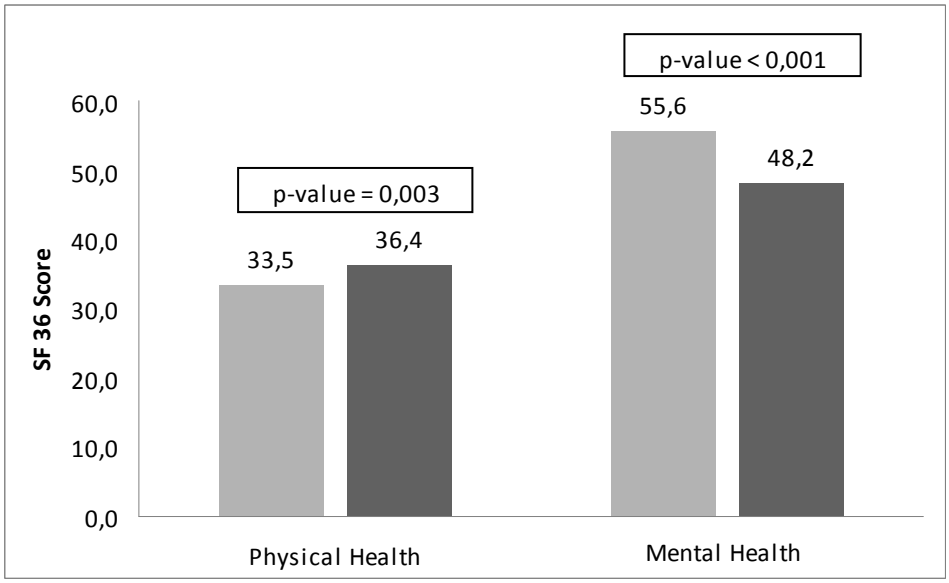

Figure 2: Results of the summarized SF-36 scores

Physical component and mental component preprocedure scores (grey bars) and 6 months after TAVI (black bars). Comparison based on Student t-test for paired data.

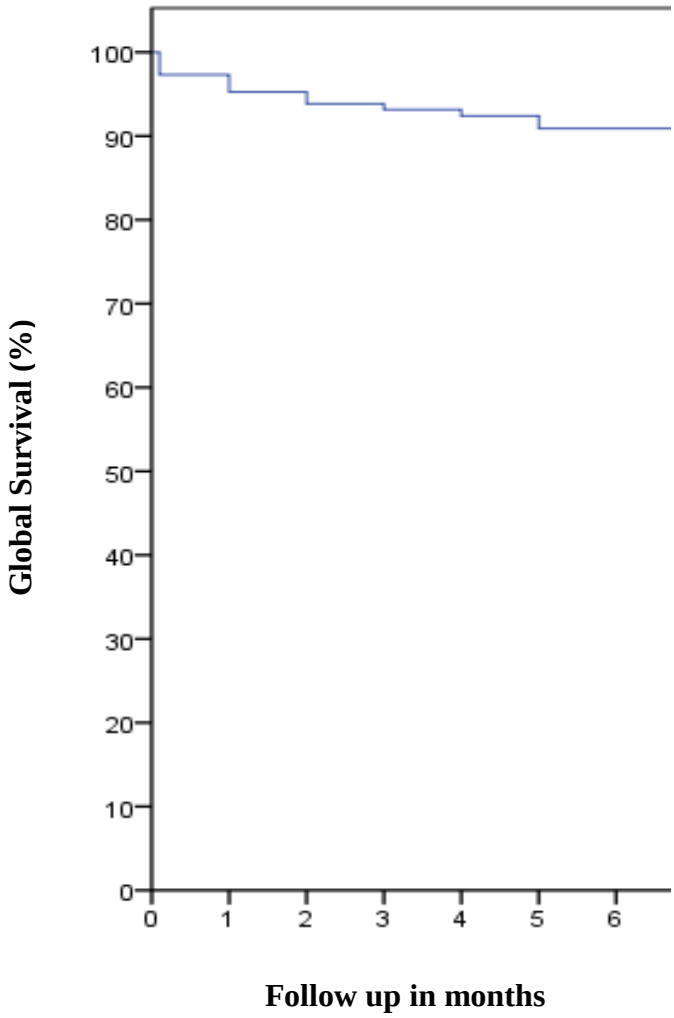

Figure 3: Survival curve for the whole population study.

PERSPECTIVES

Dans le cadre de cette thèse, nous souhaitions étudier les facteurs prédictifs de dégradation de la qualité de vie, de mortalité et de perte fonctionnelle après une intervention type TAVI chez les patients âgés de plus de 75 ans en intégrant les facteurs gériatriques tels qu'ils sont évalués en pratique courante. Les principaux résultats sont la l'amélioration de la qualité de vie physique après l'intervention, la dégradation de la qualité de vie mentale chez les patients présentant un risque de dépression, et une perte d'autonomie dans la vie quotidienne pour prés de la moitié de la population 6 mois après l'intervention.

Les principales perspectives de recherche qui apparaissent à l'issue de cette étude sont, tout d'abord, la nécessité de réaliser des études analysant l'intérêt du traitement antidépresseur sur l'évolution de la qualité de vie mentale chez les patients avec un risque de dépression avant l'intervention type TAVI.

De plus une étude avec un plus grand nombre de patients parait nécessaire pour mettre en évidence les facteurs gériatriques, évalués par les échelles utilisées en pratique courante, prédictifs d'une évolution défavorable à distance de l'intervention. En effet, il est indispensable de mettre en évidence ces facteurs prédictifs pour permettre, à terme, d'identifier ces patients à risque d'évolution défavorable. Ainsi il serait possible de mieux informer le patient et sa famille des risques de l'intervention.

NOM : BOUREAU PRENOM : Anne Sophie

Titre de Thèse :

Facteurs prédictifs de l'évolution de la qualité de vie en post-interventionnel d'un remplacement valvulaire aortique par voie percutanée (TAVI) chez les patients âgés. Etude observationnelle, multicentrique, prospective.

RESUME

L'objectif principal de cette étude prospective bicentrique était de mettre en évidence les facteurs prédictifs cardiologiques ou gériatriques d'altération de la qualité de vie, de mortalité et de déclin fonctionnel 6 mois après une intervention de remplacement valvulaire aortique par voie percutanée. Les principaux résultats sont la confirmation de l'amélioration de la qualité de vie physique après l'intervention, la dégradation de la qualité de vie mentale chez les patients présentant un risque de dépression, et une perte d'autonomie dans la vie quotidienne pour prés de la moitié de la population 6 mois après l'intervention. Aucun facteurs gériatriques prédictifs de mortalité ou de déclin fonctionnel n'a été mis en évidence. Les principales perspectives de recherche qui apparaissent à l'issue de cette étude sont, tout d'abord, la nécessité de réaliser des études analysant l'intérêt du traitement antidépresseur sur l'évolution de la qualité de vie mentale chez les patients avec un risque de dépression avant l'intervention type TAVI. De plus une étude avec un plus grand nombre de patients parait nécessaire pour mettre en évidence les facteurs gériatriques, évalués par les échelles utilisées en pratique courante, prédictifs d'une évolution défavorable à distance de l'intervention

---

MOTS-CLES

Patients âgés, rétrécissement aortique serré, qualité de vie, évaluation gériatrique