ABREVIATIONS

AS Aortic Stenosis
BAV Balloon Aortic Valvuloplasty
BMI Body Mass Index
CABG Coronary Artery Bypass Graft
CV CardioVascular
COPD Chronic Obstructive Pulmonary Disease
EuroSCORE European System for Cardiac Operative Risk Evaluation
LBBB Left Bundle Branch Block
NYHA New York Heart Association
PPI Postprocedural Pacemaker Implantation
SAVR Surgical Aortic Valvular Replacement
TAVI Transcatheter Aortic-Valve Implantation
VARC Valve Academic Research Consortium

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MISE AU POINT

Le rétrécissement aortique dégénératif

1) Epidémiologie

Le rétrécissement aortique (RA) est actuellement la plus fréquente des valvulopathies diagnostiquées; une étude parue en 2003 "The Euro Heart Survey" sur 5001 patients présentant une valvulopathie en Europe a révélé 43,1% de RA dont 81,9% d'origine dégénérative (1); proportion qui tend à augmenter avec le vieillissement de la population.
Le rétrécissement aortique serré touche quant à lui 4,6% des patients de plus de 75 ans (2).

2) Physiopathologie

La réduction de la surface de l'orifice aortique entraîne une gêne à l'éjection ventriculaire gauche avec des conséquences en aval sur la circulation systémique et en amont sur le ventricule gauche.

En amont, l'obstacle à l'éjection ventriculaire gauche augmente la post-charge et est responsable d'une surcharge systolique du ventricule gauche et donc d'une élévation de la contrainte pariétale ; celle-ci entraine une hypertrophie myocardique concentrique à l'origine d'une altération précoce de la fonction diastolique.

En aval, le ventricule gauche conserve longtemps un débit normal au repos et à l'effort grâce au mécanisme d'adaptation (l'hypertrophie ventriculaire gauche).

A long terme, en cas de détérioration secondaire de la fonction systolique ou en cas d'hypertrophie myocardique majeure, le débit cardiaque s'élève insuffisamment à l'effort entraînant une diminution du flux encéphalique et coronarien, qui peut être responsable de syncope, d'angor et de dyspnée initialement à l'effort puis au repos.

Certaines études rétrospectives ont révélé un délai moyen de survie de 5 ans après l'apparition d'un angor, de 3 ans après une première syncope et de deux ans après un premier épisode d'insuffisance cardiaque congestive (3).

Cette valvulopathie d'évolution lente reste très longtemps asymptomatique; l'apparition de symptômes signant le caractère serré constitue donc un tournant évolutif majeur et nécessite une prise en charge curative rapide.

Prise en charge thérapeutique du RA serré

1) Indications opératoires

En échographie transthoracique le caractère serré est défini selon les dernières recommandations Européennes parues en 2012 (4) par un gradient moyen trans-aortique supérieur à 40mmHg, une surface aortique inférieure à < 1cm^2 ou une surface aortique indexée à la surface corporelle inférieure à 0.6cm^2/m^2.

Actuellement le remplacement valvulaire aortique (RVA) est principalement indiqué en cas de rétrécissement aortique serré symptomatique, de rétrécissement aortique serré asymptomatique avec une FEVG inférieure à 50% non imputable à une autre cause ou lorsque l'épreuve d'effort est positive (classe I) (4).

Le RVA sous circulation extracorporelle reste le traitement de première intention avec un taux de mortalité relativement bas (<3%) et une amélioration de la survie à long terme qui rejoint celle de la population générale.
Cependant cette chirurgie peut présenter de multiples complications notamment lorsqu'il s'agit de patients âgés et fragiles présentant de nombreuses comorbidités.
Une étude parue en 2003 a révélé que 32% des patients qui avaient une indication opératoire n'étaient pas opéré de par leur risque opératoire trop important (1).
De même, dans l'European Heart Survey, 1/3 des patients de plus de 75 ans présentant un RA serré avec une indication chirurgicale n'ont pas été opéré (5).
Etant donné le pronostic extrêmement péjoratif à court et moyen terme en l'absence de prise en charge chirurgicale, de nouvelles techniques endovasculaires se sont développées ces 10 dernières années et ont actuellement une place dans les dernières recommandations (4).

2) Les techniques endovasculaires

a) Implantation d'une prothèse valvulaire aortique par voie percutanée

La première implantation d'une valve aortique par voie percutanée (TAVI) chez l'homme a été réalisée en France à Rouen par l'équipe du Dr Cribier en 2002 chez un patient de 57 ans présentant un RA serré en état de choc cardiogénique récusé pour une chirurgie conventionnelle (6). Il a par la suite publié de petites séries de 6 et 27 patients avec un succès d'implantation dans la majorité des cas et obtention d'une amélioration significative du gradient moyen trans-valvulaire et de la surface valvulaire aortique qui restaient stables à deux ans (7,8).

Avec les progrès techniques concernant les prothèses mais aussi les dispositifs d'implantation (9) et l'expérience des centres, les grands registres nationaux ont montré que la TAVI est pratiquée avec un taux de succès d'implantation très élevé. Cependant, cette technique demeure grevée d'une mortalité hospitalière de l'ordre de 8–10 % et de complications liées à la procédure, notamment des complications vasculaires, des accidents vasculaires cérébraux et des fuites aortiques paraprothétiques (10-14).

Les études PARTNER ont été les premières études randomisées ayant comparé la mortalité des patients traités par TAVI par rapport aux prises en charge conventionnelles.

La cohorte B portait sur 358 patients récusés pour une chirurgie conventionnelle; la mortalité à un an et à deux ans était significativement plus élevée chez les patients traités médicalement et/ou par dilatation aortique au ballon par rapport aux patients traités par TAVI (50.7 % vs 30.7%, $p<0.001$ à 1 an et 68.0% vs 43.3%; $p<0.001$ à 2 ans) (15,16).
L'amélioration fonctionnelle était également significative avec 25.2% des patients en classe NYHA III ou IV à 1 an dans le groupe TAVI contre 58% des patients du groupe contrôle ($p<0,0001$).
Néanmoins, à 30 jours, les complications vasculaires majeures étaient plus importantes dans le groupe TAVI (16.2% vs 1.1%, $p<0.0001$). Le taux d'accidents vasculaires cérébraux majeurs n'était pas différent dans les deux groupes (5.0% vs 1.1%, $p=0.06$). Cette étude a donc confirmé que la TAVI était une option thérapeutique qui pouvait être proposée chez les patients récusés à une prise en charge chirurgicale conventionnelle.

La 2ème cohorte (A) était cette fois ci une étude de non infériorité, qui a inclus 699 patients à haut risque opératoire mais non récusés pour un RVA; ils ont été randomisés en deux groupes : TAVI ou RVA conventionnel.

La mortalité toutes causes à un an (p=0.44) et à deux ans (p=0.78) était équivalente entre TAVI et RVA (24.2 % à un an et 33.9 % à deux ans après TAVI vs. 26.8 % à un an et 35.0 % à deux ans pour le RVA).

Il n'y avait pas de différence statistiquement significative sur le taux d'AVC majeurs à 30 jours et un an, mais plus de complications vasculaires à 30 jours dans le groupe TAVI (11.0% vs 3.2%, p<0.0001).

Les fuites aortiques paraprothétiques modérées ou sévères étaient plus fréquentes dans le groupe TAVI par rapport aux patients traités par chirurgie conventionnelle à 30 jours (12.2% vs. 0.9%, p<0.001), à 1 an (6.8% vs. 1.9%, P<0.001) et à 2 ans (6.9% vs. 0.9% ; P<0.001).

La survenue plus fréquente d'insuffisance aortique paraprothétique dans le groupe TAVI était associée à une surmortalité à long terme (17,18).

L'année 2012 a été marquée par la publication des nouvelles recommandations Européennes (4) sur la prise en charge des valvulopathies. Il s'agit de recommandations communes à la Société Européenne de Cardiologie (ESC) et l'Association Européenne de Chirurgie Cardiothoracique (EACTS).

La TAVI est désormais intégrée comme une technique valide de traitement du RA serré; celle-ci est recommandée chez les patients porteurs d'un RA serré, symptomatiques, récusés (classe I) ou considérés à haut risque opératoire (classe IIa) pour une chirurgie conventionnelle mais pour qui une amélioration de leur qualité de vie est attendue avec une espérance de vie supérieure à 1 an.

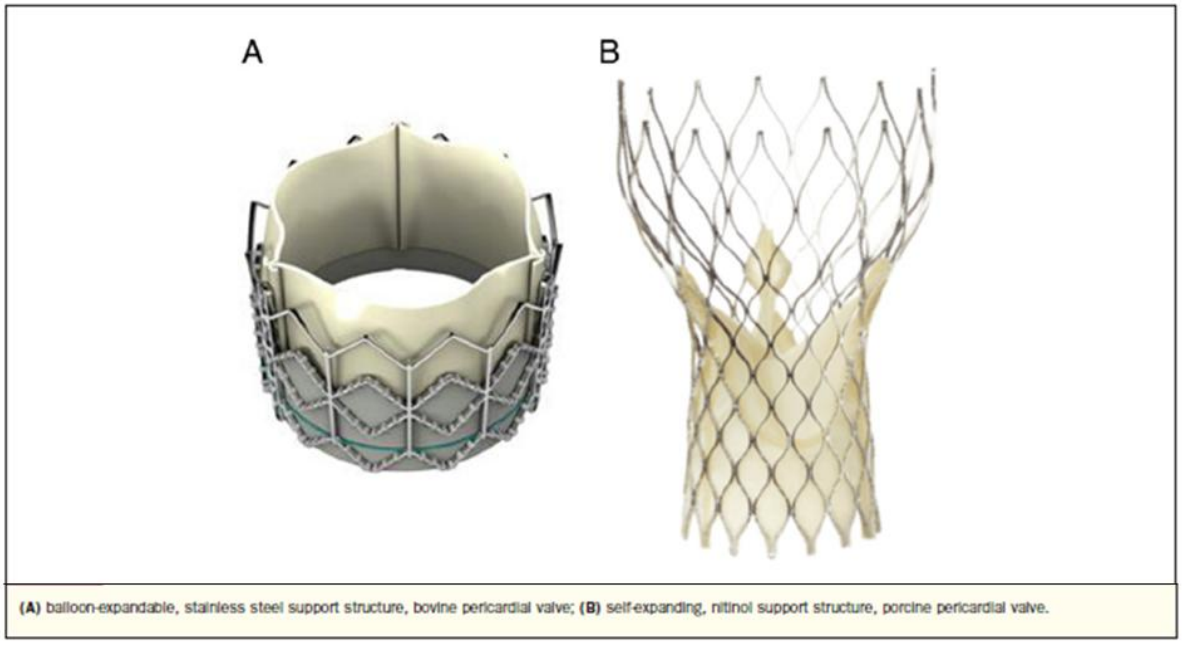
Les seuils d'EuroSCORE supérieurs ou égaux à 20 % ou de score STS supérieurs ou égaux à 10 % ont été proposés pour définir les patients à haut risque de RVA et chez qui la TAVI devrait donc être envisagée. Cependant les recommandations Européennes insistent sur les limites de ces scores et privilégient le jugement clinique d'une équipe multidisciplinaire pour l'évaluation préopératoire.

b) Les différents types de prothèses aortiques implantées

Deux types de valves sont actuellement commercialisés (Figure 1). La valve Edwards Sapien actuellement Sapien 3 (Edwards Lifescience) est une valve tricuspide en péricarde bovin cousue dans un stent en acier inoxydable. Après éventuelle prédilatation au ballon de la valve aortique native sous stimulation ventriculaire droite rapide la prothèse est déployée par gonflage d'un ballon, sous contrôle scopique. Différentes voies d'abord sont possibles : la voie artérielle fémorale rétrograde, la voie apicale par mini-thoracotomie latérale gauche, la voie trans-aortique, la voie trans-carotidienne et plus rarement la voie sous-clavière.

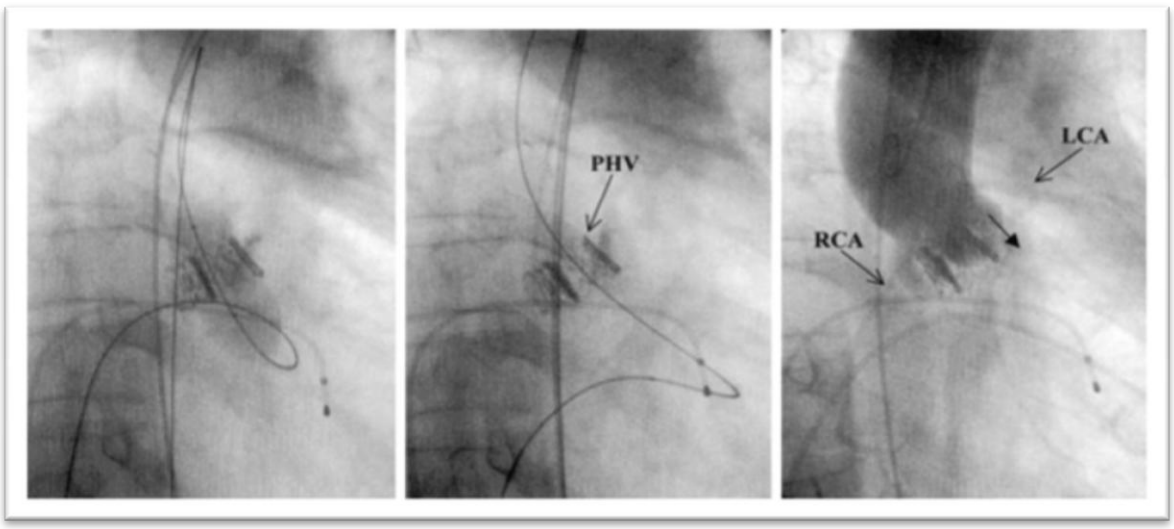
L'autre valve est auto-expansible (CoreValve, Medtronic) et se déploie au retrait de la gaine qui l'entoure. Cette valve en péricarde de porc est cousue sur un stent en nitinol. Elle nécessite occasionnellement une prédilatation. Actuellement, cette valve s'insère par voie artérielle fémorale rétrograde, sous-clavière ou trans-aortique.

Pour ces 2 types de prothèses, différents diamètres sont disponibles permettant de s'adapter aux différentes anatomies valvulaires et artérielles (Figure 2).
Un bilan de pré-implantation exhaustif permet de définir le type et la taille de la valve ainsi que la voie d'abord (percutanée ou chirurgicale).



(JACC 2011 ; 57 : 253-69)

Figure 1 : Les deux types de prothèses valvulaires aortiques percutanées commercialisés.



Left : Maximal balloon inflation (23 mm) for valve delivery.
Middle : The PHV (percutaneously implanted heart valve) in position at mid part of the native aortic valve, pushing aside the calcific leaflets.
Right : Supraaortic angiogram after PHV implantation showing no aortic regurgitation across the PHV and a mild paravalvular regurgitation (arrow).
Both coronary ostia are patent and removed from the valve prosthesis.
LCA indicates left coronary artery; RCA, right coronary artery.

(Circulation. 2002;106:3006-3008)

Figure 2 : Implantation d'une valve aortique par voie percutanée sous contrôle scopique

c) La valvuloplastie aortique percutanée

La valvuloplastie aortique percutanée (BAV) est une technique apparue en 1986 décrite par Cribier (19) dont le principe est de dilater l'orifice valvulaire à l'aide d'un ballonnet; celui-ci est introduit par voie rétrograde et placé au niveau de la valve aortique sous stimulation ventriculaire droite rapide.
Après un enthousiasme initial, cette procédure a rapidement été abandonnée; en effet elle présentait un fort taux de complications, une évolution inéluctable vers une resténose en quelques mois (de l'ordre de 80% à 1 an) (20) et peu d'impact sur la survie à long terme comparée à l'évolution naturelle (survie de 55.0% à 1 an et 23.0% à 3 ans) (21).

Avec le développement de la TAVI, on assiste à une véritable renaissance de cette technique depuis quelques années.
Malgré l'absence de modification majeure concernant la procédure, l'utilisation de cathéters plus petits, de systèmes de fermeture artérielle percutanée efficaces mais aussi l'expérience grandissante des différents centres ont fortement diminué l'incidence des complications vasculaires.
Actuellement le taux de complications majeures liées à cette procédure a nettement diminué (6.8%) comme décrit dans une publication récente d'Eltchaninoff *et al*. Ils rapportaient un taux de mortalité per-procédure de 2.5%, la survenue d'un AVC dans 1.8% des cas, de complications vasculaires dans 2.5% des cas, 0.3% de rupture d'anneau aortique, 1.5% d'insuffisance aortique sévère et 0.6% d'implantation de pacemaker au décours (22).
Ben Dor *et al.* ont rapporté en 2013 chez 387 patients ayant bénéficié d'une valvuloplastie aortique un taux d'AVC au décours de 2.3% et d'implantation de pace maker de 1.1% (23).
De plus la réalisation de la valvuloplastie aortique dans leur série était associée à de bons résultats hémodynamiques avec une diminution du gradient moyen trans-aortique de plus de 50% et/ou l'obtention d'une surface valvulaire aortique supérieure à 1 cm2 dans 80.8% des cas.

De nombreuses autres séries ont rapporté les mêmes résultats avec l'obtention d'une amélioration clinique et échographique immédiatement après la valvuloplastie aortique mais aussi un taux de complications per-procédures faible rendant cette technique intéressante en attendant une prise en charge curative (8,24,25).

La valvuloplastie aortique percutanée est actuellement intégrée dans les dernières recommandations Européennes sur les valvulopathies (4) : celle-ci peut être indiquée préalablement à la chirurgie ou à la TAVI chez des patients instables hémodynamiquement considérés à haut risque pour la chirurgie, ou chez des patients qui nécessitent une chirurgie non cardiaque en urgence. Cette technique peut aussi être considérée à visée palliative.

On peut aussi penser qu'elle peut avoir un intérêt en tant qu'outil diagnostique avant la réalisation d'une TAVI chez les patients pour qui la symptomatologie n'est pas forcément imputable au RA ; notamment les patients ayant des troubles cognitifs qui peuvent être secondaires au bas débit cérébral et réversibles après la valvuloplastie aortique ou encore en cas de double valvulopathie mitro-aortique.
Par ailleurs certaines publications ont rapporté une réduction significative d'une insuffisance mitrale sévère après la réalisation d'une valvuloplastie aortique (26), ou encore une diminution significative de la PAPS dans 50% des cas (27) et une amélioration de la FEVG dans 25% des cas (28).

Peu d'études ont analysé la mortalité à court et long terme chez les patients ayant eu une TAVI d'emblée comparé aux patients ayant bénéficié d'une valvuloplastie aortique préalable.

Saia *et al*. ont rapporté un taux de mortalité à 30 jours après TAVI identique chez 47 patients qui ont bénéficié d'une TAVI d'emblée comparé à 36 patients ayant bénéficié d'une valvuloplastie aortique préalable malgré un profil clinique et échographique plus sévère à l'inclusion (proportion plus importante de patient en stade IV de la NYHA ou ayant une FEVG inférieure à 30% et proportion plus importante de patients « fragiles » avec de multiples comorbidités) (29).

Dans une autre série publiée par Tissot *et al*. les patients traités par valvuloplastie aortique préalable à un traitement curatif (TAVI ou RVA) étaient plus sévères à l'admission en ce qui concerne la classe NYHA, la présence d'une insuffisance rénale mais aussi des EuroSCORE et score STS plus élevés. Pour autant la mortalité à deux ans était identique entre les deux groupes (30).

L'équipe d'Eltchaninoff *et al*. a quant à elle rapporté une mortalité à 5 ans après TAVI de 23.2% chez 54 patients ayant bénéficié d'une valuloplastie aortique préalable versus 33.4% chez 29 patients ayant eu une TAVI d'emblée (p=0.26) (22).

L'objectif de ce travail était de comparer la mortalité à 1 mois et 1 an et les évènements cardio-vasculaires chez les patients ayant eu une TAVI selon la réalisation ou non d'une valvuloplastie aortique préalable.

Notre travail s'est basé sur le registre FRANCE 2 (FRench Aortic National CoreValve and Edwards registry) (31) ayant inclus toutes les procédures TAVI en France entre Janvier 2010 et Janvier 2012.

Devenir clinique des patients ayant bénéficié de l'implantation d'une valve aortique percutanée avec ou sans valvuloplastie aortique au ballon préalable; d'après le registre FRANCE 2

RESUME

Introduction

Le remplacement valvulaire aortique est le traitement de choix en cas de rétrécissement aortique serré; cependant l'implantation d'une valve aortique par voie percutanée (TAVI) a actuellement toute sa place pour les patients contre-indiqués ou à haut risque chirurgical.
La valvuloplastie aortique percutanée (BAV) quant à elle revoit le jour depuis le développement de la TAVI, permettant d'améliorer le statut clinique du patient avant la procédure. Il existe cependant peu de données sur le suivi des patients ayant effectivement bénéficié d'une TAVI et d'une BAV préalable.

Méthode et résultats

3953 patients ayant bénéficié d'une TAVI ont été inclus dans le registre FRANCE 2.
664 patients (16.8%) ont bénéficié d'une BAV préalable; ces patients étaient significativement plus âgés et plus symptomatiques, avaient un EuroSCORE plus élevé et présentaient plus de comorbidités. La mortalité à un mois après TAVI était plus élevée chez les patients avec BAV préalable (12.5% vs 8.7%; p=0.001). Il n'y avait pas de différence significative en terme de mortalité de 1 mois à 1 an entre les 2 groupes.
La BAV ne s'est pas révélée être un facteur prédictif indépendant de mortalité à un mois et de 1 mois à 1 an.

Conclusion

Dans notre étude, la mortalité à un mois après TAVI était plus élevée chez les patients ayant bénéficié d'une BAV comparativement aux patients ayant eu une TAVI d'emblée; ce surcroît de mortalité précoce ne semble pas du à la BAV en elle-même mais en lien avec un état préopératoire plus précaire; pour autant cette différence en terme de mortalité disparaît à un an ce qui laisse présager de l'intérêt de cette technique en tant que "bridge" vers un traitement définitif.

Comparison of baseline characteristics and outcomes after a Transcatheter Aortic Valve Implantation in patients with or without preceding Balloon Aortic Valvuloplasty; Insights from the FRANCE 2 Registry

ABSTRACT

Aims

This study sought to clarify the clinical course of patients that underwent Balloon Aortic Valvuloplasty (BAV) previously to Transcatheter Aortic Valve Implantation (TAVI) and were included in the FRANCE 2 registry.

Methods and results

A total of 3953 patients underwent TAVI. Patients with BAV (n=664, 16.8%) were older than primary TAVI with a higher Logistic EuroSCORE and higher rates of comorbidities and presented more symptoms.

Procedure success was similar between groups, so as moderate to severe post procedural aortic regurgitation.

The 1-month mortality from all cause was higher in patients with BAV (12.5% vs 8.7%; p=0.001) but the 1-month to 1-year mortality did not differ between groups.

BAV was not revealed to be an independent predictor of all-cause mortality at 1 month and from 1-month to 1-year.

Conclusion

The 1-month mortality was higher in patients with BAV, principally due to precarious preoperative status before TAVI. Overall the 1-month to 1-year mortality was similar in both groups supporting that bridging TAVI with previous BAV may be a reasonable option at a cost of a higher short term mortality due to individual characteristics.

INTRODUCTION

Critical aortic stenosis affects an estimated 4.6 % of individuals over 75 years of age (2). Surgical aortic valve replacement (SAVR) is the first-line therapy for symptomatic patient, improving prognosis and quality of life.

Nevertheless, about 32 % of patients do not undergo operation due to high surgical risk owing to their multiple comorbidities (1). As a consequence, percutaneous procedures such as Balloon Aortic Valvuloplasty (BAV), were introduced (19), but subsequently tempered because of high rates of complications, recurrence (20) and little impact on long term survival (21). Nowadays, Transcatheter Aortic Valve Implantation (TAVI) is an alternative treatment for high-risk or inoperable patients, as soon as it appears reasonable and their life expectancy is of more than 1 year (4).

Some patients with unstable hemodynamic conditions or presumed reversible inoperability may benefit from BAV, even if its efficacy is time-limited, as a bridge therapy toward SAVR or TAVI (4).

Data about the course of patients that endured BAV as a bridge therapy to TAVI are scarse. Previous publications of small series revealed no significant difference in survival at one month (29), two years and five years (22) between bridge BAV and primary TAVI or SAVR despite worse baseline characteristics of the bridge cohort.

This study sought to clarify the clinical course of patients that underwent BAV previously to TAVI and were included in the FRench Aortic National CoreValve and Edwards (FRANCE 2) registry (31).

METHODS

Patients

The study design, supervision, and data management have been previously described (31).
All patients who underwent TAVI in France between January 2010 and January 2012 were prospectively included into the registry. A total of 33 centers in France and one in Monaco were authorized to perform TAVI by the French Ministry of Health. Risk of cardiovascular surgery was evaluated using the logistic EuroSCORE (32).
This study complied with the Declaration of Helsinki and was approved by the institutional review board of the French Ministry of Health. In addition, the locally-appointed ethics committees approved the research protocol. All patients provided written informed consent prior to the procedure, including consent for an anonymous processing of their data.

Study devices and procedures

Some of the patients underwent BAV before TAVI. Patients who underwent TAVI first without BAV were named "primary TAVI".
The choice between femoral (73.5%), transapical (17.8%), subclavian (5.8%), or other (2.9%) approach was left to the cardiac team, based on arterial iliofemoral suitability. Each multidisciplinary team could choose to implant one of two commercially available valves: the balloon-expandable Edwards SAPIEN or SAPIEN XT prosthesis (Edwards Lifesciences) (66.5%) or the self-expandable CoreValve (Medtronic) (33.5%).
The procedural characteristics were described elsewhere (31).

Study endpoints

The primary endpoint was all-cause mortality at 1-month and from 1-month to 1-year.
Secondary endpoints comprised procedural success, post procedural aortic regurgitation, post procedural pacemaker implantation, and heart failure.
The combined safety endpoint at 1-month comprised a composite of all-cause mortality, stroke, life-threatening bleeding, acute renal failure, peri-procedural myocardial infarction, major vascular complication, and the need for repeating the procedure for valve-related

dysfunction (surgical or interventional therapy) as defined by the Valve Academic Research Consortium (VARC) (33).
Procedural success was defined by the correct deployment, positioning, and performance of one prosthetic valve. Functional status was assessed in accordance with the New York Heart Association (NYHA) classification.

Statistical analysis

All statistical tests were performed using Stata 11.0 software (Texas, USA). Quantitative variables were expressed as mean±standard deviations, and qualitative variables as numbers and percentages. Comparisons of quantitative variables were conducted by means of unpaired Student's t-test or Wilcoxon rank-sum test, where appropriate. Comparisons of qualitative variables were performed using chi-squared test or Fisher's exact test, where appropriate.
Cox regression models were applied for the purposes of explaining 1-month and 1-month to 1-year mortality, heart failure, and the combined safety endpoint. The proportional-hazard assumptions were tested by analyzing the Schoenfeld residuals. Statistical significance was set at $p<0.05$.

RESULTS

Baseline characteristics (Table I)

A total of 3953 patients underwent TAVI.
Mean age was 82.7±7.2 years and 1997 were men (50.5%).
Patients with BAV (n=664, 16.8%) were older than primary TAVI and presented with higher Logistic EuroSCORE (25.8±15.5% vs 21.0±13.7%; $p<0.001$); they presented with smaller body mass index, and higher rates of comorbidities such as diabetes mellitus, coronary artery disease, peripheral vascular disease, and renal insufficiency, but less history of hostile thorax.
Moreover, BAV patients were more symptomatic with more history of congestive heart failure in the preceding 12 months, more symptoms according to NYHA Class III or IV (83.8% vs 73.8%; $p<0.001$) and more HTAP.

The BAV patients presented smaller aortic annulus size (21.95±2.2mm vs 22.2±2.2mm; p=0.016), lower transvalvular mean gradient (44.0±16.3mmHg vs 49.0±16.5mmHg; p<0.001) and lower ejection fraction (48.9±15.1% vs 54.2±13.8%; p<0.001) than primary TAVI.

Procedure (Table II)

The procedure success was similar between groups (97.0% in primary TAVI group and 98.0% in the BAV group).

No difference was found between TAVI approach in both groups.

Patients with BAV were more frequently implanted with Edwards valves with a slight over-use of smaller size prosthesis.

At discharge, patients with primary TAVI were found to have higher mean aortic gradients (10.7±5.5mmHg vs. 9.7±4.6mmHg, p<0.001) and better ejection fraction (56.1±12.3% vs. 52.7±13.5%, p <0.001).

Moderate to severe aortic regurgitation, either transvalvular or paravalvular, were similar in both groups.

Mortality outcomes (Table III and IV)

1-month mortality from all cause (12.5% vs 8.7%; p=0.001) and from cardio vascular cause (8.3% vs 5.3%; p=0.003) were higher in patients with BAV. When the cause of cardio vascular death was identified, BAV patients died of cardiac failure (27.3%), cardiac arrhythmia (14.6%) and cardiac conductance dysfunction (9.1%).

The independent predictors for 1-month mortality were as follows: LVEF<45%, post-procedural aortic regurgitation grade 2 and higher, aspirin or clopidogrel treatment.

The 1-month to 1-year mortality from all cause and from cardio vascular cause was similar in both groups (See Figure 1).

The independent predictors for 1-month to 1-year mortality were as follows: age>85 years, Euroscore>20%, post-procedural aortic regurgitation grade 2 and higher, renal failure and atrial fibrillation.

BAV was not revealed to be an independent predictor of all-cause mortality at 1-month and from 1-month to 1-year.

Safety endpoints (Table III and V)

Adverse events before 24 hours and combined safety endpoint at one month were similar between groups.

Patients with BAV presented with higher rates of hospitalization for heart failure at one year (14.0% vs 11.0%; p=0.003).

Post procedural pacemaker implantation was higher in patients with primary TAVI (11.4% vs 8.3%; p=0.022) but they had significantly less pacemaker before implantation compared to patients with BAV. New onset of post procedural left bundle branch block (LBBB) was similar between groups (11.8% vs 9.2% respectively; p=NS).

Renal failure was the only independent predictor of the composite safety endpoint.

DISCUSSION

Early outcomes

Our study was based on the largest existing multicenter prospective registry of high-risk elderly TAVI patients.

In our retrospective analysis, the 1-month mortality from all cause (12.5% vs 8.7%; p=0.001) and from cardio vascular cause (8.3% vs 5.3%; p=0.003) was higher in patients with BAV.

This is somewhat contrasting with previous report. Saia *et al*. found no difference in 30-day survival between BAV as a bridge to TAVI patients (n=36) and immediately eligible TAVI patients (n=47), despite the worse baseline characteristics of the bridge cohort (higher rates of LVEF<30%, NYHA stage IV, and frailty) (29).

In our study BAV was not revealed to be an independent predictor of all-cause mortality at 1 month so that the excess mortality at 1-month appeared to be related to more precarious preoperative status before TAVI.

BAV may not be responsible of an excess mortality in patients that effectively benefited from TAVI afterwards – indeed experienced teams now reported very low incidences of major adverse events (6.8%) after BAV (22) when former reports revealed very high rates of mortality in BAV patients with no TAVI as an issue: from 44.3% (34) to 55.2% of 1-year mortality (23).

In our study we don't know BAV indication (bridge, as a tool for diagnosis, palliation), short and long term outcomes and mean delay between BAV and TAVI.

Long term outcomes

In our study the 1-month to 1-year mortality from all-cause and from cardio vascular cause was similar in both groups despite worse baseline characteristics.
This data are similar to that found in the literature; Eltchaninoff *et al.* recently reported that long-term survival (5 years) was not significantly different in patients with (n=54) or without previous BAV use (n=29) before TAVI (23.2% vs 33.4%, p=0.26) (22) associated with similar rates of adverse events.
Tissot *et al.* reported in a cohort of 253 individuals that patients treated by previous BAV presented worse baseline characteristics in term of NYHA class, renal failure and other extra-cardiac comorbidities, which was reflected by higher logistic EuroSCORE and STS scores. Still survival rates were equal at two years between the primary TAVI/SAVR and bridge BAV groups (30).

In our study, the independent predictors for 1-month to 1-year all-cause mortality were age>85 years, Euroscore>20%, post-procedural aortic regurgitation grade 2 and higher, renal failure and atrial fibrillation.
Otherwise, BAV was not revealed to be an independent predictor of all-cause mortality from 1-month to 1-year.
We found usual predictors of long term mortality such as age, high Logistic EuroSCORE and post procedural aortic regurgitation.

Post procedural pacemaker implantation

Disturbances in atrioventricular conduction are well-recognized complications of TAVI especially with the self-expandable CoreValve (31). As recently reported by Urena *et al.*, patients with new-onset persistent left bundle-branch block (LBBB) and a QRS duration >160 ms after TAVI presented greater risk for sudden cardiac death (HR: 4.78, 95% CI: 1.56 to 14.63; p = 0.006) (35).
However, the contribution of the BAV to atrioventricular conduction disturbances has not been elucidated.

Following BAV, post procedural pacemaker implantation (PPI) rates varied from 1.1% (23) to 0.6% (22). Laynez *et al.* dedicated a report to conduction's disorders following 271 BAV patients: 8.5% presented with new conduction defects whose 1.5% required permanent pacemaker implantation and 3.3% new LBBB. The ratio of the balloon size to the left ventricular outflow tract diameter was 1.21± 1.6 in those with new conduction defects and 1.15± 0.12 ($p < 0.032$) in those without (36).
This is suggesting the role of even mild device oversizing on the new conduction defect after BAV. In our cohort BAV patients had smaller aortic annulus size and higher rate of pace maker before TAVI.

These results are strongly contrasting with older reports from before 2000, among patients who underwent BAV, 30% required need for new permanent pacemaker (37) and 38% had a new bundle branch block (38).
The improvements in equipment and operator experience during the past 20 years could well account for the reduction in post-BAV conduction disturbances.
Nevertheless, the size of the valvuloplasty balloon should be carefully selected to avoid oversizing, which may lead to the development of postprocedural conduction disturbances.

In our study, PPI was higher in patients with primary TAVI (11.4% vs 8.3%; $p=0.022$) but they had significantly less pacemaker before procedure (13.0% vs 19.7%; $p<0.001$) resulting in overall final pacemaker rates. Baseline LBBB rates were higher in BAV patients (14.3% vs 11.5%; $p=0.047$) but new-onset LBBB were similar after the procedure (see Table III).

Adverse events

We reported 5.9% of major or life threatening bleeding within 24 hours after TAVI in both group and 4.6% of major vascular events after primary TAVI versus 3.5% in the BAV group ($p=0.18$). Major vascular complications were reported in 6.3% in the UK TAVI registry (11).

Recently, Eltchaninoff *et al.* reported that BAV was associated with satisfactory hemodynamic results and the procedure could be accomplished with a low incidence of major adverse events (6.8%): mortality (2.5%), stroke (1.8%), vascular events (2.5%), postprocedural pacemaker implantation (0.6%) and post-procedural aortic regurgitation (1.5%) (22).

An other recent cohort of patients undergoing BAV between 2000 and 2009 showed a relevant improvement in complication rates and procedural success (39).

On the contrary, data from the 90's depicted very high complications rates; on 674 patients who underwent BAV, 31% experienced a significant complication before discharge included the need for transfusion (23%), vascular surgery (7%), cerebrovascular accident (3%), other systemic embolus (2%), myocardial infarction (2%), acute tubular necrosis (1%), or cardiac surgery (1%) and 3% died during the procedure (37).
The use of smaller sheath, smaller catheters and vascular closure devices for arterial haemostasis might be associated with a lower incidence of vascular and bleeding complications. Similarly, stable device positioning by rapid pacing may limit adverse events. Furthermore the new interest for BAV since the development of TAVI might have improved the operator experience and pre-operative assessment, notably with CT scan and aortic annulus sizing.

The course of BAV use

The implementation of a TAVI program was associated with a significant change in BAV usage in term of rates and indications.
A recent serie reported that stand-alone BAV use increased 145% from the pre-TAVI period to the TAVI period.
During the pre-TAVI period, BAV was performed almost entirely as palliation or as a bridge to noncardiac surgery. In contrast, during the TAVI period, there was a marked increase in the use of BAV in emergent patients or as a bridge to TAVI and a slight increase in its use for palliation (40).

In the FRANCE 2 registry, the use of BAV is relatively stable during the study and varied from 13.8% to 24.2% (see Figure 2). BAV was performed in 16.8% of the patients; this rate is not insignificant suggesting that TAVI could have been proposed in very frail patient with success and class IIa indication is frequent.
In fact, previous prospective studies reported a contraindication to primary TAVI or SAVR in 10.6% (39) and 37% (29) of patients who underwent BAV. In 2013, Saia *et al.* reported among 415 patients who underwent BAV, a use as bridge to TAVI or SAVR in 62.4% (34).
German registry of TAVI reported 13.6% of BAV previous TAVI (13).

Potential role of BAV in the TAVI era

There are currently few data concerning the potential role of BAV in the TAVI era.
BAV can often serve both on diagnostic purpose to confirm the potential benefit of TAVI as well as a therapeutic purpose to palliate symptoms while patients are screened and await definitive therapy. In particular, assessing improvement in low LVEF, severe pulmonary hypertension, mitral regurgitation but also cognitive alteration after BAV may be considered as a preliminary treatment strategy to choose the best option: TAVI or palliative treatment.

As previously reported, nearly half of patients with severe aortic stenosis and coexistent mitral regurgitation showed a reduction in the magnitude of mitral regurgitation after BAV (26); and in half, a reduction in pulmonary artery systolic pressure was observed (27). Further, in 25%, the left ventricular ejection fraction significantly improved after BAV (28).
In another study BAV is associated with LV function recover and/or reduction of mitral valve regurgitation, and recover from severe debilitation in around 75% of the cases (29).

Our study demonstrated that BAV as a bridge to TAVI was not an independent predictor of mortality after TAVI. The use of a previous BAV should not be considered during in pre TAVI assessment.

Study limitations

This new technique may be subject to the operators' learning curve in terms of procedure decisions and practice, but as mentioned previously, the use of BAV remained relatively stable during the study. Furthermore the eligibility to perform TAVI in France was conditioned with individual experience of at least 50 BAV procedures.

In the FRANCE 2 registry beginning with the TAVI procedure itself, the collection of data about previous history of BAV was not predefined. Indication for BAV, previous complication during the procedure and acute outcome after BAV were not mentioned. Only the patients that were suitable for the bridge to TAVI are regarded.

One of the reasons for TAVI not being performed was death while waiting for TAVI. In previous series, only 26.3% of the patients initially eligible for a bridge after BAV were treated by definitive therapy: TAVI (16.7%) or SAVR (31, 9.6%) after a mean delay of 5.9 ± 6.1 and 7.3 ± 9.8 months respectively (22).

In order to precise the role of BAV in AS patients, similar registry should be set up from the diagnosis of symptomatic AS. There is still a need to define the predictors of favourable course after BAV as a bridge to SAVR/TAVI.

CONCLUSION

Recently the interest toward BAV has flourished again thanks to the development of TAVI but remained only a brief temporizing procedure with a poor long term outcome without subsequent definitive therapy.

In this largest analysis of previous BAV in the TAVI era we reported higher 1-month mortality absolute rates in patients with previous BAV compared to primary TAVI. This excess of mortality appeared to be related with a precarious preoperative status before TAVI. More, the 1-month to 1-year mortality was similar in both groups suggesting that bridging TAVI with previous BAV was feasible and reasonably safe.

Moreover BAV is currently associated with a low incidence of major adverse events.

In this context predicting good responder to BAV could be very interesting.

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Figures

Tables

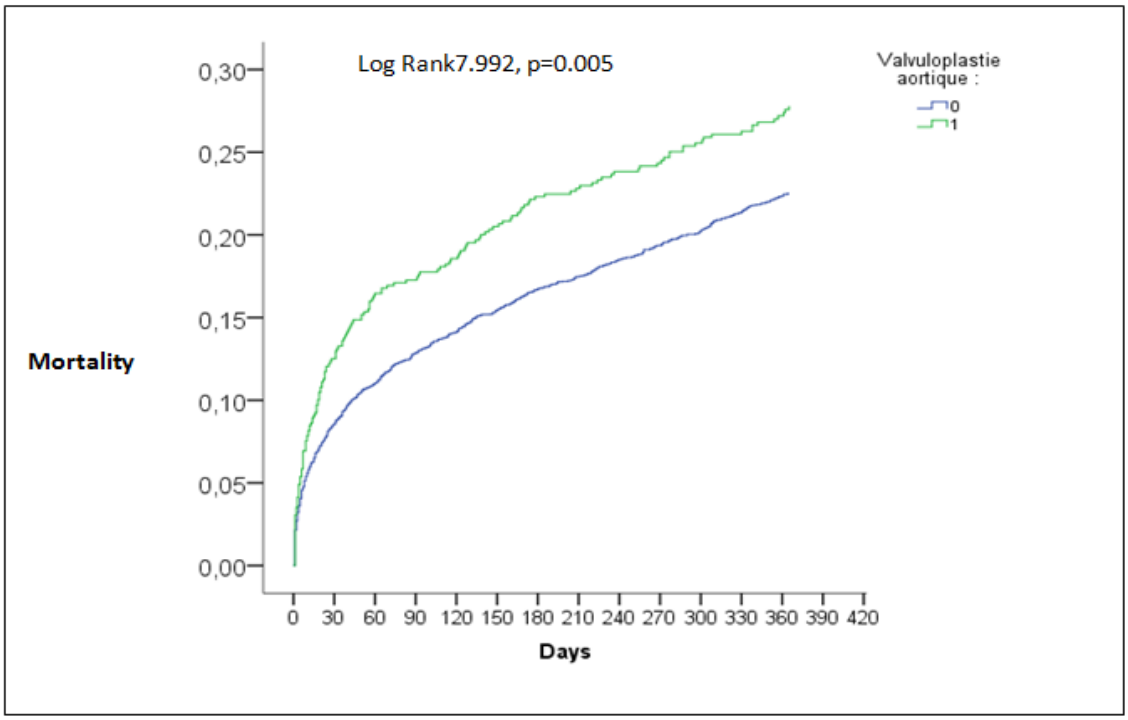
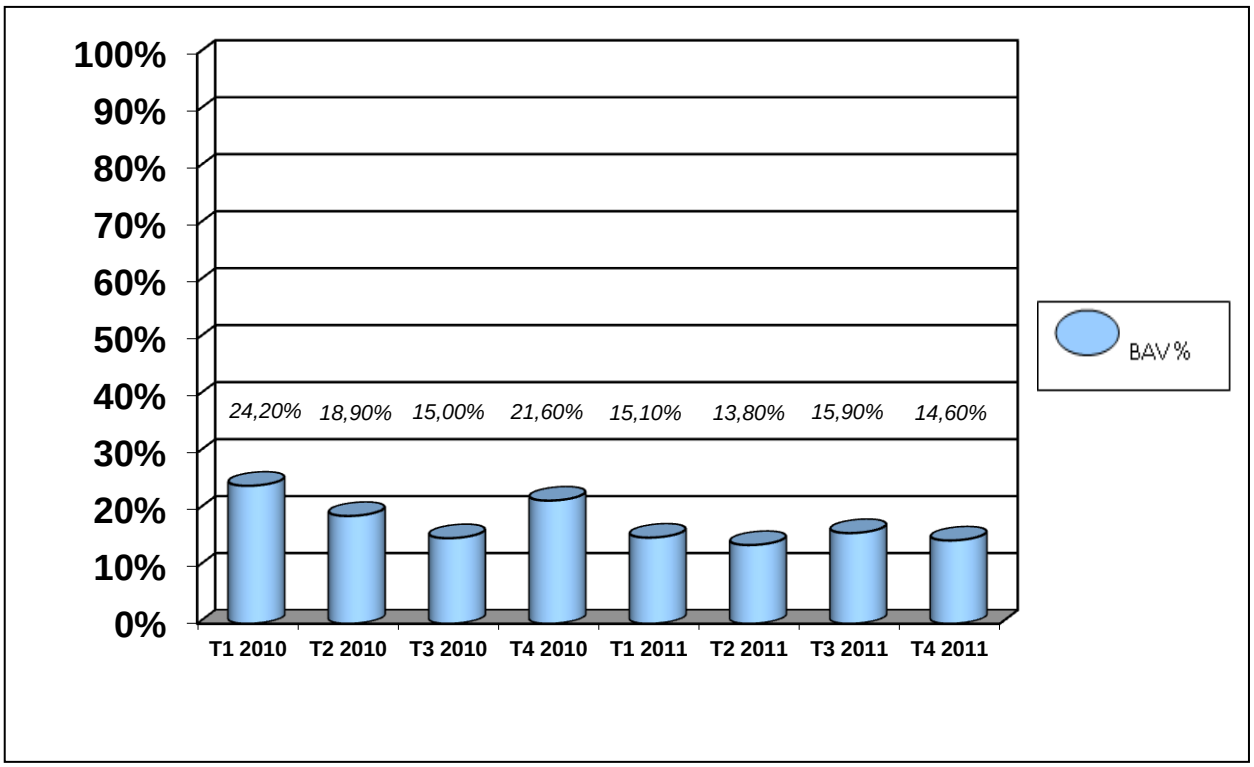


Figure 1 Time-to-event curves for mortality with regard to Balloon Aortic Valvuloplasty



T: Trimestre; BAV: Balloon Aortic Valvuloplasty

Figure 2 The course of BAV use

Table I: patient characteristics at baseline

Characteristics	**No valvuloplasty (n=3289)**	**Valvuloplasty (n=664)**	**p**
Male sexe %	1654 (50.3%)	343 (51.7%)	NS
Age, yr	82.7 ± 7.2	83.6 ± 7.0	0.002
BMI, kg/m²	26.2 ± 5.1	25.4 ± 4.4	<0.001
Logistic EuroSCORE, %	21.0 ± 13.7	25.8 ± 15.5	<0.001
Risk factors, no. (%)			
Active smoker	106 (3.2%)	24 (3.6%)	NS
Hypertension	2276 (69.2%)	446 (67.2%)	NS
Diabetes mellitus	818 (24.9%)	193 (29.1%)	0.024
Dyslipidemia	1561 (47.5%)	319 (48.0%)	NS
Symptoms, no. (%)			
NYHA class III or IV	2421 (73.8%)	555 (83.8%)	<0.001
Congestive Heart Failure < 1 year	1217 (37.1%)	426 (64.3%)	<0.001
Angina	510 (15.5%)	114 (17.2%)	NS
Syncope	255 (7.8%)	62 (9.3%)	NS
Clinical history, no. (%)			
Hostile thorax	615 (18.7%)	101 (15.2%)	0.03
Coronary artery disease	1860 (57.8%)	399 (62.1%)	0.046
Previous myocardial infarction	507 (15.4%)	118 (17.8%)	NS
Previous CABG	622 (18.9%)	81 (12.2%)	<0.001
Pulmonary artery pressure > 60mmHg	467 (18.3%)	130 (25.0%)	0,001
Chronic obstructive pulmonary disease	742 (22.6%)	155 (23.3%)	NS
Peripheral vascular disease	641 (19.5%)	158 (23.8%)	0.01
Aortic abdominal anevrysm	152 (4.6%)	31 (4.7%)	NS
Creatinine before procedure > 200 µmol/l	266 (8.1%)	72 (10.8%)	0.021
Cerebrovascular disease	327 (9.9%)	62 (9.3%)	NS
Previous surgical aortic-valve replacement	41 (1.3%)	25 (3.8%)	<0.001
Life expectancy < 1 year	72 (2.2%)	19 (2.9%)	NS
Atrial fibrillation	840 (25.9%)	171 (26.1%)	NS
Left bundle branch block	369 (11.5%)	93 (14.3%)	0.047
Permanent pacemaker	427 (13.0%)	130 (19.7%)	<0.001
Vitamin K antagonist	792 (24.1%)	165 (24.9%)	NS
Aspirin	1836 (55.8%)	440 (66.3%)	<0.001
Clopidogrel	918 (27.9%)	221 (33.3%)	0.005
Echocardiographic findings			
Aortic annulus size, mm	22.2 ± 2.2	21.95 ± 2.2	0.016
Mean gradient, mmHg	49 ± 16.5	44.0 ± 16.3	<0.001
Effective orifice area indexed, cm²/m²	0.4 ± 0.2	0.4 ± 0.2	NS
Ejection fraction, %	54.2 ± 13.8	48.9 ± 15.1	<0.001
Pulmonary artery pressure, mmHg	45 ± 13.9	47 ± 15.1	0.003
Aortic regurgitation grade 3 and 4, no. (%)	105 (3.4%)	22 (3.6%)	NS
Moderate/ severe mitral regurgitation, no. (%)	59 (1.9%)	17 (2.8%)	NS

BMI: Body Mass Index, CABG: Coronary Artery Bypass Grafting

Table II: Procedural characteristics and echocardiographic findings after TAVI

	No valvuloplasty (n=3289)	**Valvuloplasty (n=664)**	**p**
TAVI approach, no. (%)			NS
Transapical	575 (17.6%)	123 (18.6%)	
Transfemoral	2412 (73.7%)	479 (72.5%)	
Subclavian	183 (5.6%)	46 (7.0%)	
Other	101 (3.1%)	13 (1.9%)	
Devices, no. (%)			
Edwards SAPIEN	2184 (66.6%)	443 (66.8%)	NS
Edwards 23mm	930 (42.7%)	193 (43.7%)	0.005
Edwards 26mm	1146 (52.6%)	243 (55.0%)	0.005
Edwards 29mm	104 (4.8%)	6 (1.4%)	0.005
Medtronic CoreValve	1096 (33.4%)	220 (33.2%)	NS
CoreValve 26mm	359 (32.8%)	81 (36.8%)	NS
CoreValve 29mm	675 (61.6%)	126 (57.3%)	NS
CoreValve 31mm	62 (5.7%)	13 (5.9%)	NS
Arterial closure, no. (%)			<0.001
Surgery	1504 (45.8%)	361 (54.4%)	
Prostar	1663 (50.7%)	278 (41.9%)	
Other	114 (3.5%)	25 (3.8%)	
Echocardiographic findings, post-procedural			
Mean gradient, mmHg	10.7 ± 5.5	9.7 ± 4.6	<0.001
Effective orifice area indexed, cm^2/m^2	1.05 ± 0.3	1.06 ± 0.3	NS
Ejection fraction, %	56.1 ± 12.3	52.7 ± 13.5	<0.001
Pulmonary artery pressure, mmHg	40.6 ± 12.5	42.2 ± 13.2	0.017
Moderate/severe AR (transvalvular), no. (%)	36 (1.3%)	7 (1.3%)	NS
Moderate/severe AR (para valvular), no. (%)	408 (14.5%)	81 (14.4%)	NS
Moderate/severe mitral regurgitation, no. (%)	420 (15.3%)	98 (18.2%)	NS

TAVI:Transcatheter Aortic Valve Implantation; AR: Aortic Regurgitation

Table III: Composite endpoints and outcomes

	No Valvuloplasty (n=3289)	Valvuloplasty (n=664)	P
Device success, no. (%)	3188 (97.0%)	648 (98.0%)	NS
Adverse events < 24h, no. (%)	931 (28.4%)	170 (25.6%)	NS
Major and life-threatening bleeding	195 (5.9%)	39 (5.8%)	NS
Major vascular event	153 (4.65%)	23 (3.46%)	NS
Post procedural LBBB, no. (%)	388 (11.8%)	61 (9.2%)	NS
PPI before one month, no. (%)			
PPI total	374 (11.4%)	55 (8.3%)	0.022
PPI in Medtronic Corevalve prosthesis	193 (17.6%)	32 (14.5%)	NS
PPI in Edwards SAPIEN prosthesis	181 (8.2%)	23 (5.2%)	0.023
Combined safety endpoint at one month, no. (%)	743 (22.6%)	167 (25.2%)	NS
Stroke	62 (8.3%)	13 (7.8%)	NS
Life-threatening bleeding	52 (7.0%)	13 (7.8%)	NS
Renal failure	350 (47.1%)	77 (46.1%)	NS
Myocardial infarction	28 (3.8%)	7 (4.2%)	NS
Major vascular events	138 (18.6%)	22 (13.2%)	NS
Conversion to conventional surgery	15 (2.0%)	0 (0%)	NS
Implantation of two valves	76 (10.2%)	15 (9.0%)	NS
Heart Failure, no. (%)			
At one month	198 (6.0%)	50 (7.5%)	NS
From one month to one year	165 (5.0%)	43 (6.5%)	NS
At one year	363 (11.0%)	93 (14.0%)	0.003
Death, no. (%)			
At one month			
From all cause	287 (8.7%)	83 (12.5%)	0.001
From cardiovascular cause	174 (5.3%)	55 (8.3%)	0.003
From one month to one year			
From all cause	398 (12.1%)	88 (13.3%)	NS
From cardiovascular cause	120 (3.6%)	30 (4.5%)	NS
Cumulative, at one year			
From all cause	685 (20.8%)	171 (25.8%)	0.007
From cardiovascular cause	294 (8.9%)	85 (12.8%)	0.002

PPI: Post procedural Pacemaker Implantation; LBBB: Left Bundle Branch Block

Table IV: All-cause mortality, multivariate analysis

	1-month all-cause mortality		**1-month to 1-year all-cause mortality**	
	HR [95% CI]	P value	HR [95% CI]	P value
Age > 85 years	1.09 [0.70-1.70]	0.71	1.36 [1.08-1.73]	**0.01**
Previous BAV	1.44 [0.90-2.34]	0.14	1.09 [0.82-1.44]	0.57
LVEF< 45%	2.31 [1.47-3.62]	**<0.001**	1.28 [0.99-1.65]	0.056
EuroSCORE > 20%	1.34 [0.82-2.20]	0.25	1.31 [1.02-1.70]	**0.04**
Pulmonary artery pressure > 60mmHg	1.07 [0.65-1.77]	0.78	1.05 [0.80-1.38]	0.71
Post procedural aortic regurgitation (grade 2 and higher)	2.24 [1.41-3.56]	**<0.001**	1.81 [1.39-2.36]	**<0.001**
Renal failure	1.35 [0.70-2.60]	0.37	1.92 [1.39-2.66]	**<0.001**
History of coronary artery disease	1.27 [0.80-2.04]	0.31	1.04 [0.82-1.33]	0.74
NYHA class III-IV	1.57 [0.84-2.92]	0.16	1.22 [0.91-1.63]	0.18
Transapical approach	1.55 [0.89-2.70]	0.13	1.26 [0.93-1.71]	0.13
Aspirin or Clopidogrel	0.60 [0.38-0.95]	**0.027**	0.86 [0.68-1.09]	0.21
BMI	0.72 [0.37-1.41]	0.34	0.91 [0.66-1.24]	0.53
Peripheral arterial disease	1.11 [0.65-1.91]	0.71	1.17 [0.87-1.55]	0.29
Atrial fibrillation	1.34 [0.86-2.08]	0.20	2.09 [1.66-2.62]	**<0.001**
Diabetes mellitus	0.84 [0.50-1.41]	0.51	1.21 [0.94-1.56]	0.14
Hostile Thorax	0.99 [0.56-1.75]	0.98	1.32 [1.00-1.75]	0.050
Chronic obstructive pulmonary disease	1.49 [0.93-2.39]	0.10	1.25 [0.96-1.62]	0.098

BAV: Balloon Aortic Valvuloplasty; BMI: Body Mass Index

Table V: Combined safety endpoint at one month, multivariate analysis

	HR [95% Conf. Interval]	p
Age > 85 years	0.96 [0.79-1.16]	0.70
Previous BAV	1.1 [0.88-1.39]	0.40
EuroSCORE >20%	0.99 [0.82-1.21]	0.97
Hostile Thorax	0.97 [0.76-1.24]	0.80
History of coronary artery disease	1.01 [0.84-1.22]	0.91
NYHA class III-IV	0.89 [0.73-1.10]	0.29
Chronic obstructive pulmonary disease	0.94 [0.75-1.18]	0 .60
Renal failure	2.66 [2.10-3.37]	< **0.001**
BMI > 30	0.89 [0.70-1.14]	0.38
Transapical approach	0.94 [0.73-1.20]	0.61
Postprocedural aortic regurgitation (moderate to severe)	1.10 [0.86-1.41]	0.44

BAV: Balloon Aortic Valvuloplasty, BMI: Body Mass Index

TABLE DES MATIERES