Université de Montréal

L'implantation valvulaire aortique par cathéter: Évolution des résultats cliniques suite aux avancées technologiques et techniques

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Mémoire présenté à la faculté de études supérieures
en vue de l'obtention du grade de Maîtrise ès Sciences
en Sciences biomédicales
option Recherche Clinique

Avril 2017

Résumé

Contexte: L'implantation valvulaire aortique par cathéter (TAVI) est une procédure relativement jeune dont l'objectif est de traiter les patients atteints de sténose aortique sévère pour qui la chirurgie cardiaque conventionnelle est considérée à haut risque ou contre-indiquée. Cette procédure a subi, au fil du temps, des améliorations sur le plan technologique (succession de différentes générations de prothèses valvulaires) ainsi que sur le plan technique (simplification des différentes étapes de la procédure).

Objectif: L'objectif de ce travail est de décrire l'impact clinique d'une avancée technologique, soit le passage de la deuxième vers la troisième génération de la prothèse Edwards, et d'une avancée technique, soit l'implantation de la prothèse sans pré-dilatation de la valve native.

Méthodes: Nous présentons d'abord, par le biais d'une revue et méta-analyse, les résultats cliniques du TAVI au début de son utilisation à plus grande échelle, en 2012. Ensuite, une étude monocentrique rétrospective dans un centre à haut volume décrit les résultats du passage de la deuxième vers la troisième génération de la valve Edwards chez 507 patients. Enfin, une étude rétrospective avec appariement a testé différentes stratégies de pré-dilatation durant la procédure: une pré-dilatation systématique, une pré-dilatation sélective chez des patients présentant des caractéristiques cliniques précises, et l'absence de pré-dilatation.

Résultats: Dans l'article présentant les résultats cliniques au début de l'expérience TAVI, le taux de mortalité à 30 jours variait entre 5 et 18%. Le taux de décès à 1 an était estimé à 23% (méta-analyse, *random effects model*). Le taux d'AVC à 30 jours était entre 0 et 6.7% et le taux de complication vasculaire majeure entre 2 et 16%. L'étude sur le passage de la SAPIEN XT vers la SAPIEN 3 a montré une diminution non significative de la mortalité à 30 jours (de 8.7 à 3.5%; p=0.21) et des AVC à 30 jours (de 2.8 à 1.4%; p=0.6), ainsi qu'une diminution significative des complications vasculaires majeures à 30 jours (de 9.9 à 2.8%; p<0.0001). Cependant, il y a eu une augmentation significative du taux de pacemaker (de 9.8 à 17.3%; p=0.03). L'étude sur la pré-dilatation versus le *direct TAVI* a montré une absence d'effet adverse du *direct TAVI* en termes de décès ou complications vasculaires à 30 jours. Nous avons trouvé une tendance à la réduction des AVC avec le *direct TAVI* (3 vs. 1%; p=0.11), en particulier chez les patients avec une valve aortique peu ou modérément calcifiée. Cependant, chez les patients avec calcification extensive de la valve, le risque de malposition de la

prothèse était numériquement plus élevé. Au cours des 3 études présentées, la mortalité à 1 an a peu évolué (entre 20 et 25%).

Conclusions: Les événements adverses à court terme ont diminué après le changement de génération de valve Edwards. Le *direct TAVI* permet de simplifier la procédure sans augmenter les taux d'effets adverses. Cependant, les deux avancées présentent des limites qui incitent à la prudence.

Mots-clés : Implantation valvulaire aortique par cathéter, TAVI, Edwards SAPIEN XT, Edwards SAPIEN 3, pré-dilatation, valvuloplastie aortique, avancée technologique, avancée technique

Abstract

Context: Transcatheter aortic valve implantation (TAVI) is a relatively young procedure intended to treat patients with severe aortic stenosis who are at high risk for conventional surgery, or inoperable. This procedure underwent multiple technological improvements (successive generations of devices) and multiple technical improvements (simplification of various steps in the procedure).

Objective: We intend to describe the clinical impact of a technological improvement (the transition from the second to the third generation of the Edwards device in a high-volume center) and that of a technical improvement (TAVI without pre-dilatation, known as direct TAVI).

Methods: We first describe, through a meta-analysis, the state of TAVI at the beginning of its widespread use, in 2012. Next, we describe, through a single-center retrospective study, the clinical impact of the transition from the second to the third generation of the Edwards device in 507 patients. Finally, in a retrospective study with matching, we tested three pre-dilatation strategies: systematic pre-dilatation, selective pre-dilatation, and direct TAVI.

Results: In the article describing the initial TAVI experience, the 30-day mortality rate was between 5 and 18%. One-year mortality was estimated at 23% by meta-analysis (random effects model). Stroke rate at 30 days was between 0 and 6.7% and major vascular complication rate was between 2 and 16%. The transition from SAPIEN XT to SAPIEN 3 resulted in a non-significant reduction in 30-day mortality (from 8.7 to 3.5%; $p=0.21$) and 30-day stroke rate (from 2.8 to 1.4%; $p=0.6$), and a significant reduction in major vascular complications (from 9.9 to 2.8%; $p<0.0001$). However, there was a significant increase in permanent pacemaker rate (from 9.8 to 17.3%; $p=0.03$). Next, we found no adverse effect of performing direct TAVI in terms of mortality or vascular complications at 30 days. We found a trend towards a reduction in stroke rate with direct TAVI (3 vs. 1%; $p=0.11$), particularly in patients with mildly or moderately calcified valves. However, in those with extensive valvular calcification, the risk of device malposition was numerically higher. In all three studies presented, there was little variation in 1-year mortality (20 to 25%).

Conclusions: Short-term adverse events were reduced by the transition towards the third-generation Edwards device. Direct TAVI is feasible and safe. However, both of these improvements have limitations and should be considered carefully.

Keywords : Transcatheter aortic valve implantation, TAVI, Edwards SAPIEN XT, Edwards SAPIEN 3, pre-dilatation, aortic valvuloplasty, technological improvement, technical improvement.

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Liste des sigles et abréviations

AVC: accident vasculaire cérébral

BAV: balloon aortic valvuloplasty

ECG: electrocardiogram

GFR: glomerular filtration rate

ICER: incremental cost-effectiveness ratio

INESSS: Institut National d'Excellence en Santé et Services Sociaux

MSCT: multislice computed tomography

NYHA: New York Heart Association

PPM: permanent pacemaker

PVR: para-valvular regurgitation

QALY: quality-adjusted life year

S3-THV: Edwards SAPIEN 3 transcatheter heart valve

STS: Society of Thoracic Surgeons

TAVI: Transcatheter aortic valve implantation

VARC-2: Valve Academic Research Consortium-2

XT-THV: Edwards SAPIEN XT transcatheter heart valve

Remerciements

Je voudrais d'abord remercier tous les professeurs qui m'ont enseigné les bases de la recherche. De Montréal à Paris, en passant par Boston, je cois que ce périple m'a non seulement appris comment on construit une étude, de l'idée jusqu'aux réponses aux *reviewers*, mais aussi l'importance d'un bon réseau, en utilisant les forces de chacun, pour mener à bien un projet. Je suis particulièrement reconnaissant envers mes directeurs. Dr. Thibault, votre support indéfectible et vos encouragements ne seront jamais oubliés. Dr. Lambert, vous m'avez fait confiance au tout début de ma carrière, et je ne serais pas là où je suis sans l'opportunité que vous m'avez accordée.

Merci aux professeurs Cook et Orav du Harvard School of Public Health qui m'ont ouvert les yeux sur la science des nombres, une science exacte et flexible à la fois. Merci aux professeurs de médecine et plus spécifiquement de cardiologie à l'Université de Montréal qui ont su aiguiser mon sens clinique tout en me permettant de réaliser mes objectifs académiques. Merci à mes collègues de Paris sans qui beaucoup de papiers n'auraient jamais pu être écrits.

Merci à Bianca et Carlo, mes parents, et Lisa, ma sœur, qui ont toujours cru en moi. Enfin, le merci le plus important, à Zineb, qui continue de me soutenir dans cette folle aventure.

Introduction

La sténose aortique est la maladie valvulaire cardiaque la plus commune. Les formes légère, modérée et sévère atteignent environ 2.8% de la population âgée de 75 ans ou plus.(1) Cette maladie représente un fardeau grandissant pour la communauté médicale car elle atteint principalement les personnes âgées, un groupe démographique dont le poids ne cessera d'augmenter dans les décennies à venir.(2)

Jusqu'au milieu des années 2000, le seul traitement efficace de la sténose aortique sévère était le remplacement valvulaire par chirurgie cardiaque, impliquant anesthésie générale, sternotomie, et circulation extra-corporelle. Depuis 2006, le remplacement valvulaire aortique percutané (TAVI: *transcatheter aortic valve implantation*) s'est imposé comme procédure alternative chez les patients jugés trop fragiles pour subir une chirurgie conventionnelle de remplacement valvulaire. En 2010, suite à la publication des premières études randomisées contrôlées démontrant un bénéfice de mortalité par rapport au traitement médical seul et des résultats cliniques équivalents par rapport à la chirurgie conventionnelle, le TAVI s'est démocratisé au Canada comme partout au monde.(3,4)

D'abord considéré comme une procédure complexe, le TAVI nécessitait l'intervention de plusieurs spécialistes pour être mené à bien: cardiologues interventionnels, anesthésiste, échocardiographiste, chirurgien cardiaque. La procédure durait plusieurs heures et était à risque de complications en raison du matériel volumineux et du manque d'expérience de l'équipe traitante. Cependant, deux facteurs ont contribué à la sécurisation et à la simplification du TAVI au fil du temps: les avancées technologiques et les avancées techniques.

Les avancées technologiques sont le résultat de l'implication des médecins et chercheurs engagés dans la procédure, avec les ingénieurs et concepteurs des dispositifs. Cette collaboration a permis de développer de nouvelles générations de dispositifs avec des propriétés rendant la procédure plus sécuritaire avec le potentiel d'améliorer les résultats cliniques à long terme. Par exemple, la deuxième génération du dispositif CoreValve, s'utilisant sans désilet, crée une ouverture plus petite dans l'artère fémorale, réduisant le risque de complication vasculaire durant la procédure. Le dispositif est aussi devenu repositionnable, ce qui améliore la précision de l'implantation, et réduit ainsi potentiellement les taux de

malposition et de fuite paravalvulaire, prédicteurs de mortalité à long terme.(5) Le dispositif Edwards de troisième génération, de son côté, est muni d'une jupe qui réduit le taux de fuite para-valvulaire.

Les avancées technologiques, combinées à l'expérience grandissante des opérateurs, ont permis l'élaboration d'avancées techniques dont le but est de simplifier la procédure tout en augmentant sa sécurité. Par exemple, avec des dispositifs plus faciles à positionner et plus étanches, la nécessité d'avoir une guidance par échographie trans-œsophagienne pendant l'implantation est devenue facultative.(6) En mettant de côté l'échographie trans-œsophagienne, l'anesthésie générale qui l'accompagnait, avec les risques qu'elle comporte, a pu aussi être écartée.

Par la présentation de 3 articles scientifiques publiés, l'objectif de ce travail est de décrire l'évolution des résultats cliniques du TAVI au fil des avancées technologiques et techniques. Pour ce faire, il convient d'abord de dresser un portrait de la situation au début de l'expérience TAVI, en 2012 (Chapitre 1). Ensuite, nous porterons notre attention sur l'évolution des résultats cliniques suite au passage de la deuxième vers la troisième génération de la prothèse Edwards (Chapitre 2). Enfin, nous décrirons les résultats du passage de l'implantation avec pré-dilatation vers le « direct TAVI » (Chapitre 3).

État des connaissances

La sténose aortique

La sténose valvulaire aortique est une maladie causée par le rétrécissement de l'orifice de la valve unidirectionnelle qui permet le passage du sang du ventricule gauche vers l'aorte. Le ventricule gauche, forcé à lutter contre une résistance plus importante, peut initialement s'adapter à cet état, mais finit par défaillir.(7) Les patients atteints de sténose aortique manifestent donc le plus fréquemment des symptômes d'insuffisance cardiaque comme la dyspnée d'effort, mais peuvent aussi avoir de l'angor ou des pertes de conscience.(8) Une fois les symptômes apparus, le pronostic de la sténose aortique est sombre, avec une survie moyenne de deux ans chez ceux avec insuffisance cardiaque.(8) Les patients symptomatiques sont aussi à risque de mort subite.(9)

L'étiologie la plus commune de la sténose aortique, dans le monde occidental, est la dégénérescence calcifiante de l'anneau et des feuillets de la valve.(7) Il s'agit d'une calcification lentement progressive des feuillets de la valve, qui deviennent plus rigides et s'opposent ainsi au passage du sang. Une autre étiologie fréquente est la bicuspidie, un défaut congénital de la valve qui possède deux feuillets plutôt que trois. Les patients atteints de bicuspidie voient leur atteinte valvulaire progresser plus rapidement que les patients atteints de dégénérescence calcifiée.(10) Alors que ces derniers deviennent symptomatiques entre 70 et 80 ans, les patients atteints de bicuspidie peuvent présenter des symptômes dans la soixantaine. Il est à noter que bien que le TAVI ait été décrit dans la bicuspidie, la technique n’a pas de recommandation formelle pour cette étiologie.

En outre, la sténose aortique est la maladie valvulaire cardiaque la plus commune et la troisième maladie la plus fréquente du système cardiovasculaire chez l'adulte, après l'hypertension artérielle et la maladie coronarienne.(11) Elle atteint 2,8 % de la population de 75 ans et plus aux États-Unis.(1) Sachant que la population du Québec, comme partout ailleurs dans le monde occidental, est vieillissante (les octogénaires représenteront près de 10% de la population en 2035), il est raisonnable de croire que la sténose aortique deviendra, au cours

des décennies à venir, un problème de santé qui mobilisera des ressources de plus en plus importantes pour les systèmes de santé.(2)

Options thérapeutiques

Jusqu'au milieu des années 2000, la seule avenue thérapeutique pour le traitement de la sténose aortique était le remplacement valvulaire chirurgical.(9) Il s'agit d'une chirurgie où la cage thoracique est ouverte (sternotomie), le cœur est arrêté et la circulation assurée par un appareil (circulation extra-corporelle). La valve peut ainsi être excisée et remplacée par une valve biologique ou mécanique. Alors que les résultats de cette chirurgie sont bons, la procédure en elle-même comporte, entre autres, des risques de décès, d'accident-vasculaire cérébral, d'insuffisance rénale ou d'infection. Par ailleurs, la population atteinte de sténose aortique sévère devant subir une telle chirurgie est souvent âgée et atteinte d'autres comorbidités (maladie pulmonaire, maladie vasculaire périphérique, atteinte motrice). Dans ce contexte, jusqu'à 30 % des patients nécessitant une chirurgie se voyaient récusés en raison d'un risque opératoire jugé prohibitif.(12)

Afin d'offrir une option thérapeutique chez des patients jugés «sans option», le Professeur Alain Cribier du Centre Hospitalier Universitaire de Rouen a mis au point un système permettant de sertir une bioprothèse sur un cathéter et de la livrer au niveau de la valve native par une approche vasculaire: le TAVI pour *transcatheter aortic valve implantation*.(13) La première procédure, réalisée en 2002, a été effectuée par voie veineuse fémorale. Plusieurs petites séries ont suivi, mais le développement de la voie transartérielle fémorale, par l'équipe de Vancouver, a permis de simplifier la procédure et d'ouvrir la voie aux premières études randomisées contrôlées.(14) Parallèlement à cette valve Cribier-Edwards, déployée par ballon, une valve auto-expansible du nom de CoreValve était mise au point.(15)

Initialement, les patients qui subissaient ces interventions étaient inclus dans des registres nationaux ou liés aux fabricants.(16-19) Les résultats des premières séries et registres étant jugés prometteurs, la table était mise pour les premières études randomisées contrôlées. La première comparait la valve Edwards SAPIEN (une deuxième itération de la valve Cribier-Edwards) avec soit la chirurgie (patients à haut risque, cohorte A) ou soit le traitement médical (patients jugés inopérables, cohorte B).(3,4) La seconde étude randomisée contrôlée comparait

la valve CoreValve à la chirurgie chez des patients à haut risque opératoire.(20) Dans la première étude, la valve SAPIEN s'est montrée supérieure au traitement médical et non-inférieure à la chirurgie en ce qui a trait à la mortalité à un an. Dans la deuxième étude, la CoreValve s'est montrée supérieure à la chirurgie pour la mortalité à un an. Ces études, publiées entre 2010 et 2014, ont permis la démocratisation du TAVI à travers le monde et la mise en place d'équipes dédiées à cette procédure. En 2016, plus de 200 000 interventions avaient été réalisées sur tous les continents.(21)

Avancées technologiques et techniques

Dans l'objectif de rendre la procédure plus sécuritaire, les fabricants ont produit des dispositifs plus performants. Par exemple, Edwards a produit deux générations subséquentes à valve SAPIEN: la SAPIEN XT et la SAPIEN 3. Ces dernières s'insèrent dans des cathéters de plus en plus petits et sont munies de jupes réduisant les fuites paravalvulaires. De son côté, Medtronic (qui a acquis la compagnie CoreValve), a mis au point la deuxième génération de la CoreValve, maintenant rétractable et repositionnable. La Figure I illustre les différentes générations des valves Edwards et CoreValve. Parallèlement, d'autres fabricants ont mis de l'avant des valves avec des propriétés techniques différentes. Certaines ont réussi à s'approprier une part de marché, comme la Lotus de Boston Scientific,(22) mais d'autres, dont les propriétés mécaniques étaient plus complexes, n'auront pas survécu.(23)

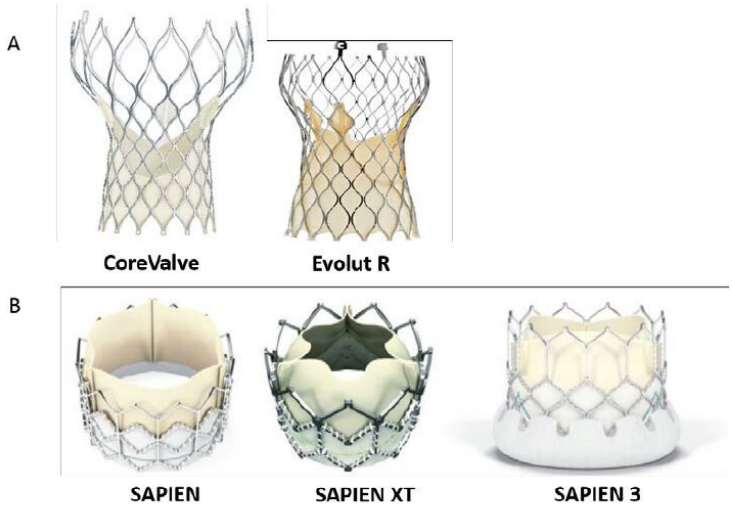

Figure I. Différentes générations des bioprothèses CoreValve (A) et Sapien (B).

Toutes ces avancées technologiques, dont le but était de simplifier et de sécuriser la procédure, combinées à l'expérience grandissante des opérateurs, ont permis à ces derniers de simplifier la procédure au point de vue technique. La première avancée technique majeure a été celle de l'équipe de Vancouver décrite précédemment.(14) Plutôt que d'insérer le cathéter dans la veine fémorale, puis de faire une ponction trans-septale, pour enfin passer la valve mitrale avant de déployer la prothèse au niveau aortique, le Dr. Webb et son équipe ont réalisé la procédure en rétrograde, par la voie artérielle fémorale. Cet exemple montre que pour simplifier la procédure par une avancée technique, une avancée technologique a été nécessaire: produire une valve sertie sur un cathéter de diamètre assez petit pour entrer dans l'artère fémorale (plus petite et moins extensible que la veine) et être en mesure de sertir cette valve « à l'envers » sur le cathéter puisqu'elle est déployée par voie rétrograde. Inversement, l'avancée technologique n'aurait pu être accomplie sans l'objectif qu'était l'avancée technique.

Plus récemment, d'autres avancées techniques ont eu lieu pour simplifier la procédure. Grâce aux cathéters de plus petits diamètres, un abord entièrement percutané est possible.(24) Ceci permettrait de réduire les risques d'infection et d'augmenter la mobilisation des patients après la procédure, comparé à un abord fémoral chirurgical.(25) Par ailleurs, comme les dispositifs sont plus faciles à positionner et les opérateurs plus expérimentés, la nécessité d'une guidance échographique par échographie trans-œsophagienne est moins nécessaire. L'anesthésie générale, dont l'utilité principale est de permettre l'échographie, est donc

superflue. Il est donc devenu possible d'effectuer la procédure chez un patient conscient, sous sédation et anesthésie locale seulement, afin d'éviter les complications liées à l'anesthésie générale.(6) Un autre exemple d'avancée technique est l'utilisation du guide ventriculaire gauche pour le pacing, plutôt que d'utiliser une sonde ventriculaire droite dédiée.(26) Ceci permet d'éviter une ponction supplémentaire ainsi que le risque de perforation ventriculaire associé à la sonde de stimulation. Enfin, l'utilisation de l'artère radiale comme abord secondaire (plutôt que la fémorale) permettrait de réduire le taux de complications vasculaires.(26)

Au final, le TAVI, initialement considéré comme une procédure complexe et nécessitant plusieurs intervenants (cardiologues interventionnels, chirurgiens, échocardiographiste, anesthésiste, personnel de bloc opératoire et de cathétérisme, perfusionniste, etc) a pu être simplifié, par l'interaction bilatérale des avancées technologiques et techniques, au point d'être faisable d'une façon « minimaliste » ou simplifiée.(26) (Figure II)

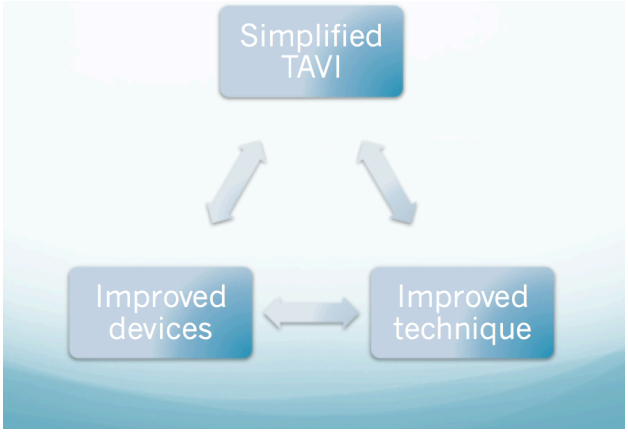

Figure II. L'interaction bilatérale des avancées technologiques et techniques permettant de simplifier la procédure TAVI.

Objectifs

Certains pourront avancer que les différentes générations de valves n'ont que peu d'impact sur les résultats cliniques du TAVI. Il est possible de croire que toutes ces itérations sont en fait des façons de justifier des prix élevés pour une technologie toujours en évolution. De même, les avancées techniques simplifient-elles à outrance la procédure, compromettant ainsi la sécurité du patient au profit de la productivité?

Dans ce contexte, l'objectif de ce travail sera, par le biais de trois articles publiés, de décrire l'impact clinique d'une avancée technologique (le passage de la deuxième vers la troisième génération de la valve Edwards), ainsi que d'une avancée technique (l'absence de pré-dilatation durant la procédure). Au préalable, il conviendra de décrire les résultats cliniques au début de l'expérience, en 2012, comme point de référence. Le chapitre 1 décrira donc les issues cliniques du TAVI à ses débuts, sous forme d'un article de revue avec méta-analyse. Les chapitres 2 et 3 seront dédiés aux avancées technologique et technique, respectivement, sous forme d'études rétrospectives avec analyses multivariées.

Puisqu'il est complexe de décrire toutes les issues cliniques, dont les définitions ont parfois évolué au fil du temps, nous nous concentrerons, dans la synthèse qui conclut ce travail, sur les issues cliniques les plus pertinentes, soit la mortalité à 30 jours et 1 an, les accidents vasculaires cérébraux (AVC), les complications vasculaires ainsi que les fuites paravalvulaires.

Chapitre 1. Résultats cliniques d'une nouvelle technologie: le TAVI en 2012.

Cet article original a été publié dans le *Canadian Journal of Cardiology*:

Boothroyd LJ, Spaziano M, Guertin JR, Lambert LJ, Rodés-Cabau J, Noiseux N, Nguyen M, Dumont É, Carrier M, de Varennes B, Ibrahim R, Martucci G, Xiao Y, Morin JE, Bogaty P. Transcatheter aortic valve implantation: recommendations for practice based on a multidisciplinary review including cost-effectiveness and ethical and organizational issues. Can J Cardiol. 2013 Jun;29(6):718-26. doi: 10.1016/j.cjca.2012.09.002. Pubmed PMID: 23218465.

Cet article est une version abrégée du rapport complet disponible sur le site de l'INESSS (www.inesss.qc.ca), dont la référence complète est la suivante:
M Spaziano, LJ Boothroyd, JR Guertin, H Chakor, Y Xiao, LJ Lambert, P Bogaty. (2012) Implantation valvulaire aortique par cathéter: Évaluation des données probantes et synthèse des considérations organisationnelles. ETMIS. Vol. 8: No 8. Available at www.inesss.qc.ca.

Contribution des auteurs

Lucy Boothroyd: Implication active au cours de chacune des étapes du processus de recherche. Conception du devis, collecte des données, interprétation des résultats et rédaction du manuscrit

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Jason Guertin: Collecte, analyse et interprétation des données en lien avec le coût-efficacité. Rédaction de la section coût-efficacité du manuscrit

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Josep Rodés-Cabau, Nicolas Noiseux, Michel Nguyen, Éric Dumont, Michel Carrier, Benoit De Varennes, Réda Ibrahim, Giuseppe Martucci, Jean Morin : Participation à la correction de l'article

Transcatheter Aortic Valve Implantation:

Recommendations For Practice Based On A Multidisciplinary Review Including Cost-Effectiveness, Ethical And Organizational Issues

Short title: Issues in transcatheter aortic valve implantation

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WORD COUNT: 5932 (title page, abstract, text, references, tables and figures legends)

1.1. Abstract

Transcatheter aortic valve implantation (TAVI) is a relatively new technology for the treatment of severe and symptomatic aortic valve stenosis. TAVI offers an alternative therapy for patients unable to be treated surgically due to contra-indications or severe comorbidities. It is being rapidly dispersed in Canada, as it is worldwide. The objective of this article is to present our recommendations for the use of TAVI, based on a multidisciplinary evaluation of recently published evidence. We systematically searched and summarized published data (2008-2011) on benefits, risks and cost-effectiveness of TAVI. We also examined ethical issues and organizational aspects of delivering the intervention. We discussed the soundness and applicability of our recommendations with clinical experts active in the field. The published TAVI results for high-risk and/or inoperable patients are promising in terms of survival, function, quality of life and cost-effectiveness, although we noted large variability in the survival rates at 1 year and in the frequency of important adverse outcomes such as stroke. Until more data from randomized controlled trials and registries become available, prudence and discernment is necessary in the choice of patients most likely to benefit. Patients need to be well-informed about gaps in the evidence base. Our recommendations support the use of TAVI in the context of strict conditions, with respect to patient eligibility, the patient selection process, organizational requirements and the tracking of patient outcomes with a mandatory registry.

1.2. Brief Summary

Transcatheter aortic valve implantation (TAVI) is an emerging technology for the treatment of aortic valve stenosis. It is being rapidly dispersed in Canada and worldwide. We performed a literature-based review that went beyond benefits and risks to include cost-effectiveness as well as organizational and ethical issues, and consulted with clinical experts. Our recommendations support the use of TAVI under strict conditions, with respect to patient eligibility, patient selection process, organizational requirements and tracking of outcomes.

1.3. Introduction

Transcatheter aortic valve implantation (TAVI) is an innovative treatment that allows insertion of a prosthetic device to replace a severely stenotic aortic valve without surgery. Aortic stenosis is a progressive disease that generally affects persons over 65 years of age. Once symptoms appear (dyspnea, angina, syncope) the person's condition deteriorates rapidly, accompanied by a high risk of death. With aging of the population, aortic stenosis is expected to have an increasingly greater impact on the health care system in the future.

Until recently, the only effective therapy for aortic stenosis was surgical valve replacement. Despite high success rates, this procedure involves general anesthesia, sternotomy and extracorporeal circulation. At least one-third of elderly patients are denied surgery due to anatomic or medical factors (i.e., comorbidities) that preclude the procedure or render it too risky.[1] Starting with the first successful human procedure in 2002, TAVI has emerged as an alternative to surgery and has been rapidly adopted in some countries. More than 50,000 procedures have been performed worldwide.[2] The Canadian province of Quebec has a population of 8 million dispersed over a large geographical area and served by 13 hospitals with cardiac catheterization laboratories. By 2010, 6 hospitals were performing TAVI or developing programs.

In late 2010, the Quebec Ministry of Health requested that *the Institut d'excellence en santé et en services sociaux* (INESSS) perform a literature-based evaluation of TAVI in order to make recommendations regarding use of this procedure in the province. INESSS is an

independent, publicly funded organization that assesses health technologies using a multidisciplinary perspective, considering benefits, risks, economic and organizational factors, and social and ethical issues. INESSS engaged local physician experts in the process in order to increase the clinical relevance of its recommendations and their acceptance by various stakeholders, including clinicians and hospital administrators. The objective of this article is to present the multidisciplinary review and resulting recommendations regarding patient eligibility, patient selection, and organizational requirements for performance of TAVI.

1.4. Methods

Multiple methods were used in preparing this article, including (1) systematic literature review (January 2008-January 2011) of benefits, risks and cost-effectiveness of TAVI using either of the 2 predominant types of valves (Cribier-Edwards/Edwards SAPIEN® and CoreValve®); (2) meta-analysis of survival for TAVI patients at 1 year; (3) narrative review of organizational and ethical issues; (4) consultation with clinical TAVI experts; and (5) external peer review. For detailed methods, see **Appendix S1.1 in Annex 1**.

1.5. Results

1.5.1. Benefits

Of 734 documents identified by our search, 17 met our selection criteria regarding survival of TAVI patients at 1 year (see **Supplemental Table S1.1 in Annex 1**). Thirteen were research studies, from Europe, United States, and Canada (1 randomized controlled trial; 4 non-randomized comparative studies; 8 case series). Four were registries: 2 regional ("Belgium national" and "UK-TAVI") and 2 industry-based ("SOURCE" for the Edwards SAPIEN® valve in Europe and "Italian CoreValve"). In all, there were 4218 TAVI patients of whom 63% received a SAPIEN® valve. The studies involved different generations of valves, delivery systems, and approaches (most often transfemoral or transapical).

TAVI patients were carefully selected in the studies. They can be divided into these categories: (1) "not suitable for surgery" due to multiple comorbidities,[3-5] anatomy,[4] patient's choice[4] or without further details;[6, 7] (2) inoperable (i.e., surgery contraindicated);[8-13] or (3) considered at high or prohibitive risk for surgery.[8-19] In some studies, high surgical risk was defined as a logistic EuroScore (European System for Cardiac Operative Risk Evaluation) ≥20%[9, 10, 12-14, 16] or ≥15%,[10, 16] or an STS score (Society of Thoracic Surgeons Predicted Risk of Mortality) ≥10%.[9, 12] The majority of patients were in New York Heart Association (NYHA) class III or IV before TAVI (symptoms with minimal activity or even at rest); that is, 85-100% of research patients (except 63% in one investigation[4]) and 72-79% of registry patients.

One-year survival across the 17 studies varied from 63% to 87%. In meta-analysis, the overall pooled estimate was 77% survival (95% CI: 73-80%) **(Figure 1.1)**, with registries showing a higher estimate than research studies (p=0.002). The pooled average age of the TAVI patients was equivalent across the 2 types of studies, at 82 years (p=0.6). The pooled average logistic Euroscore was slightly but not significantly higher for the research studies (28.6 [95% CI: 24.3-32.8]) than for the registries (26.2 [95% CI: 22.8.3-29.5]) (p=0.4). There was significantly greater use of the transapical method in the research studies (40% of approaches versus 30% in the registries, p<0.001) and thus greater use of Edwards valves (78% of valves versus 56% in the registries, p<0.001).

Figure 1.1

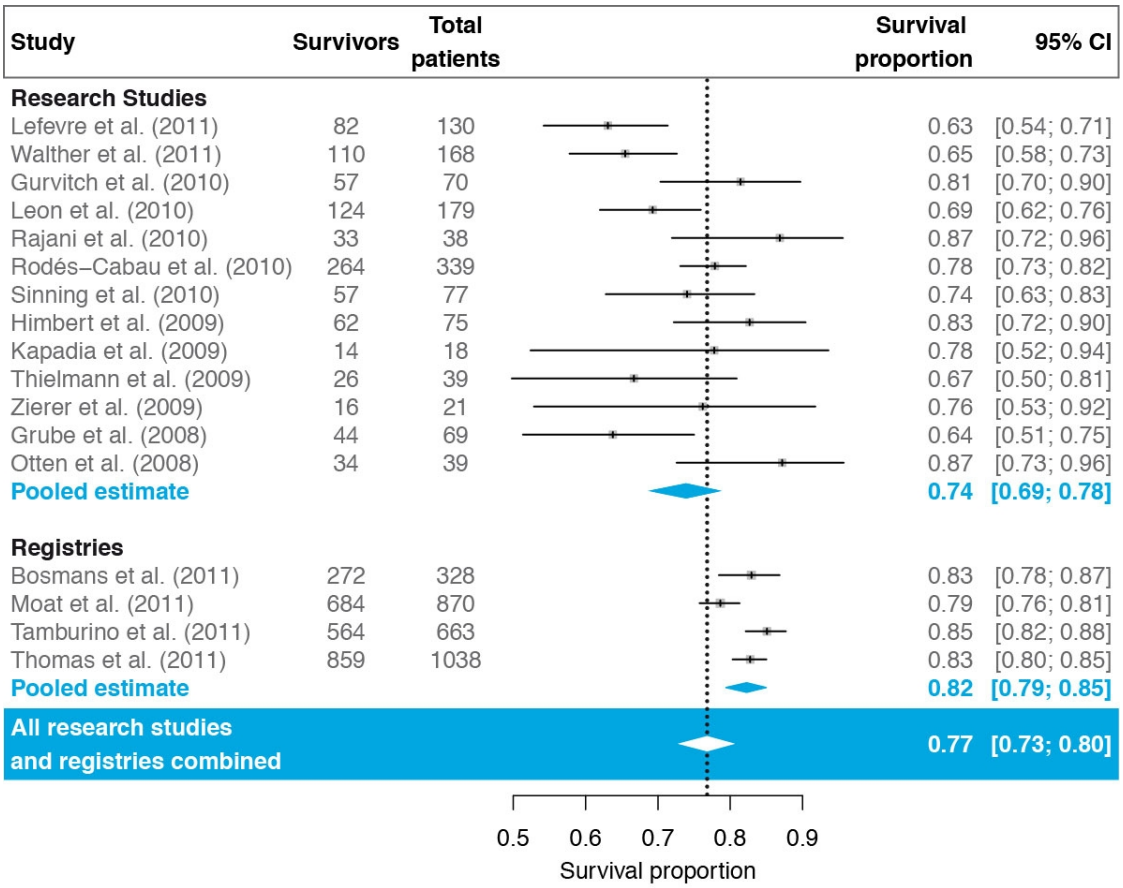

Figure 1.1. Survival of TAVI patients at 1 year: results of meta-analysis

A randomized controlled trial of TAVI involving two transcatheter cohorts has been carried out. The PARTNER-Cohort B study, published during our literature search period, randomized 179 patients to TAVI and 179 patients to "medical" treatment (which included the option of balloon aortic valvuloplasty [BAV] as part of the trial, received by 84% of this group).[3] Survival at 1 year was 19% greater for TAVI patients (69% versus 50%; intention-to-treat perspective). The hazard ratio for death for the TAVI versus medical/BAV patients at 1 year was 0.55 (95% CI: 0.40-0.74); the hazard ratio at 2 years was recently found to be 0.58 (95% CI: 0.36-0.92).[20]

Figure 1.2 presents functional status results before TAVI and at 1 year for the 6 studies reporting this outcome.[3, 9, 12, 17, 18, 21] There was an important increase (of at least 40% to more

than 80%) in the proportion of TAVI patients at follow-up who were in NYHA class I-II (no or slight limitation of physical activity). Two other studies, not in **Figure 1.2**, provided supportive results presented in other ways.[15, 16] In the PARTNER-B trial, proportion of medical/BAV patients in NYHA class I-II improved from 6.1% at baseline to 42% at 1 year, compared to nearly 75% at 1 year for TAVI patients ($p<0.001$).[3] Among evaluable PARTNER-B patients (sample sizes not reported), the TAVI group showed significant improvement in the 6-minute walking test ($p=0.002$); there was no change for medical/BAV patients ($p=0.67$).[3]

Figure 1.2

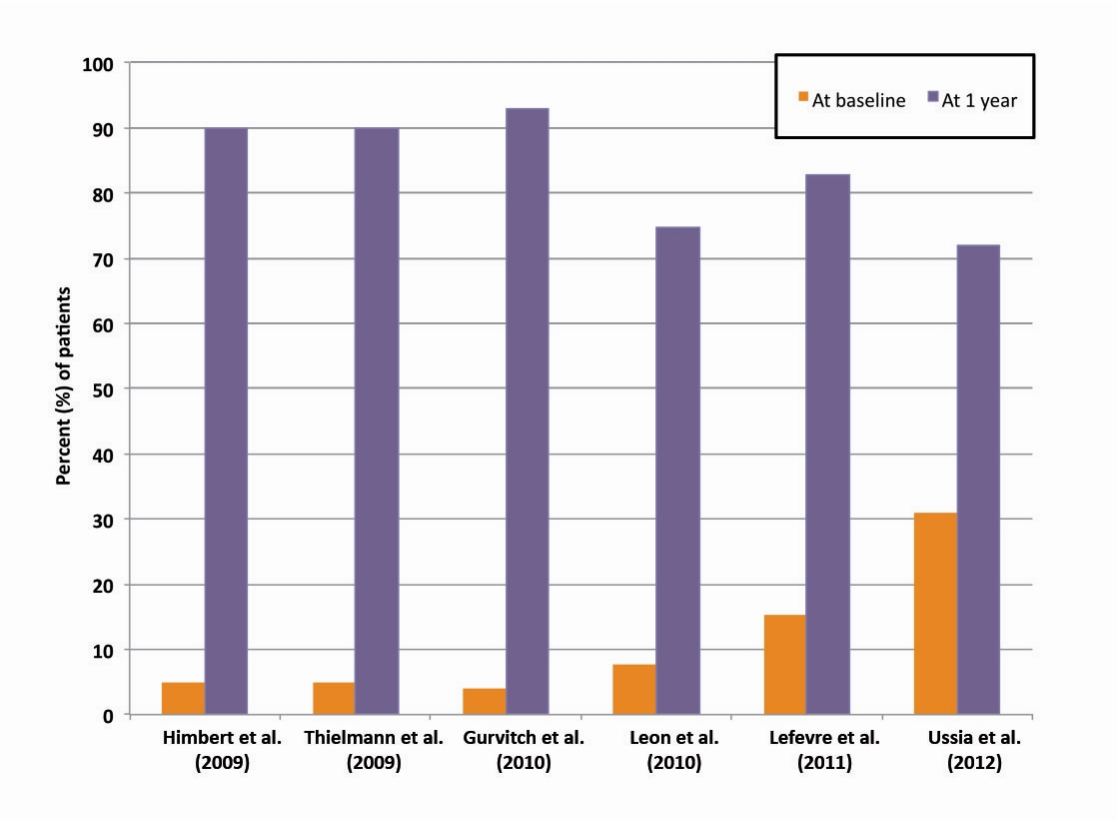

Figure 1.2. Proportion (%) of TAVI patients in NYHA Class I or II at baseline and at 1 year. NYHA: New York Heart Association.

Table 1.1 presents the quality-of-life results for the 5 studies with follow-up assessments at 5/6 months and/or at 1 year. [9, 22-25] Several different standardized measures were used. The results consistently show clinically-significant improvement. The comparison medical/BAV group in PARTNER-B presented improvement at 6 months that was not maintained at 1 year.[24]

Table 1.1. Summary of quality of life results for TAVI patients

Study	Results at 6 months* or 1 year versus baseline			
	Quality of life measure		Improvement in mean score	p value
Svensson, 2008[22]	SF-12 physical	6 months	6.5	0.002
	SF-12 mental	6 months	2.3	NR
Ussia, 2009[23]	SF-12 physical	6 months	12.8	<0.001
	SF-12 mental	6 months	10.5	<0.001
Reynolds, 2011[24] (PARTNER B)	SF-12 physical	6 months 1 year	7.7 6.6	<0.001
	SF-12 mental	6 months 1 year	5.9 7.0	<0.001
	KCCQ summary	6 months 1 year	33.5 31.8	<0.001
Lefevre, 2010[9]	KCCQ summary	1 year	27.5 (TF) 18 (TA)	<0.001
Bekeredjian, 2010[25]	SF-36 physical	6 months	18.4	<0.001
	SF-36 mental	6 months	13.3	<0.001

*with the exception of the study by Ussia et al., for which follow-up was at 5 months
KCCQ: Kansas City Cardiomyopathy Questionnaire; NR: not reported; SF-12: Medical Outcomes Study Short-Form 12; SF-36: Medical Outcomes Study Short-Form 36; TF: transfemoral; TA: transapical.

Possible scores on all measures vary from 0 to 100; higher scores indicate better quality of life. Clinically important changes in score: SF-12: 2-2.5;[24] KCCQ: 5 (small), 10 (moderate), 20 (large);[24] SF-36: 10 (small), 25 (moderate), 35 (large).[52]

1.5.2. Risks

Using the same 17 studies evaluating benefits, **Table 1.2** displays the range in proportions of TAVI patients who experienced procedural events and adverse outcomes. The Table shows large variability in risks, and the consistency of our findings with other recent reviews[26, 27] including those by other health technology assessment organizations.[28-30]

Table 1.2. Procedural events and adverse outcomes within 24 hours and 30 days of TAVI

Event or adverse outcome	This article	NICE, 2011[28]	Yan et al., 2010[26]	Coeytaux et al., 2010[27]	CADTH, 2010[29]	McGregor et al., 2009[30]
	Minimum to maximum proportion (%) of patients with event or outcome					
Conversion to surgery during TAVI procedure	0 – 10	NR	0 – 8	NR	9.5 (1 study)	NR
Use of multiple valves or "valve-in-valve", or new TAVI within 24 hours of first	1.0 – 8.3	2 – 3	2 –12	2.6 (2 registries)	NR	NR
Death, 30 days	5 – 18	5 – 25	0 – 25	0 – 50	8 – 25	8 – 10
Stroke*, 30 days	0 – 6.7	0 – 8	0 – 10	NR	3 – 10	2.3 – 2.5
1 year	4.4 – 10	10	NR	NR	NR	NR
Major access site or access-related vascular injury, 30 days	2 – 16	0 – 17†	8 – 17†	1.9 – 13	10 – 15†	7 – 13
Major bleeding, 30 days	8.5 – 17	17 (1 study)	3 – 24‡	NR	NR	NR

New permanent pacemaker, 30 days	0 – 34§	0 – 36	0 – 36	NR	NR	7 (1 registry)
Log EuroScore¶	15 – 44	NR	12 – 37	11 – 41	15 – 38	15 – 37
Period of literature search	01-01-2008 to 01-12-2011	Inception# to 11-11 2010	01-2000 to 03-2009	01-01-1990 to 15-10-2009	01-2004 to 12-2009	2007 to 2009

*major or minor stroke; transfemoral: 3.1-6.7%; transapical: 0-2.4%; †"vascular complication"; ‡blood transfusion of more than 2 units; §Edwards valves: 0-10%; CoreValve: 22-34%; ¶mean or median; #earliest date of database; NR: not reported

The definition of a "successful" TAVI procedure varied widely. When we selected the 2 research studies and the 1 registry that employed criteria that appear to meet the proposed standardized definition by the international Valve Academic Research Consortium [31], procedural success varied from 86% to 91.7%.[9, 16, 21] Surgical risk of patients and operator experience also varied across studies.

With respect to valve durability, 8 of the 17 studies reported data at 1 year: no structural degeneration was noted.[6, 7, 9, 11, 12, 15, 17, 18] The single study (70 patients) with longer follow-up (median 3.7 years) likewise did not note any structural deterioration. This study also reported no migration, thrombosis or late embolization of the valve, and no need for repeat TAVI, surgery for restenosis or regurgitation, or valvuloplasty.[17] Recently, a registry (181 patients) reported no structural valve degeneration over 3 years of follow-up.[21]

Among adverse events after TAVI, stroke is a particular concern, although small numbers and varying or unspecified definitions preclude firm conclusions. The highest 30-day stroke incidence (6.7%) was found in PARTNER-B, significantly higher than the 1.7% observed in the medical/BAV group (p=0.03).[3] Greater risk for TAVI patients persisted at 1 year, at 10% versus 4.5% (p=0.06).[3] This finding was sustained at 2 years (13.8% vs. 5.5%, p=0.01).[20]

Adverse outcomes beyond 30 days after TAVI were infrequently reported. One-year rates of re-intervention (re-TAVI or surgical aortic valve replacement) after 24 hours of the

initial TAVI varied from 0 (PARTNER-B) to 5%.[3, 9, 14, 17] Re-hospitalization was only reported in PARTNER-B and was substantial for TAVI patients at 1 year, at 22.3%.[3] Only two research studies in our systematic review provided frequencies of aortic regurgitation at 1 year: 40-46% mild and 0-4.3% moderate or severe.[17, 18] Results at 2 years in PARTNER-B showed 30% mild and 4.5% moderate regurgitation.[20]

The PARTNER-A study (published beyond our search limit date but included due to its experimental design) randomized high-risk yet operable patients to TAVI (n=348) or surgical replacement (n=351).[32] One-year survival was similar in the two groups (76% for TAVI versus 73% for surgery), consistent with the non-inferiority design of the study (hazard ratio for death: 0.93 [95% CI: 0.71-1.22]). However, TAVI patients had higher 1-year stroke incidence (6.0% versus 3.1%; p=0.07). A non-significant trend of more stroke for TAVI rather than surgery patients was recently shown at 2 years (7.7% versus 4.9%).[33] Major bleeding was less frequent among TAVI patients (15% at 1 year versus 26%; p<0.001), but a major vascular complication, such as an access site or access-related vascular injury, was more likely following TAVI (11% at 1 year versus 3.5%; p<0.001).

1.5.3. Summary of the evidence on benefits and risks

The published TAVI results for high-risk and/or inoperable patients are promising in terms of survival, functional status and quality of life. However, reported survival rates at 1 year and particularly frequency of adverse outcomes (at 30 days and 1 year) vary widely. This variability is partly explained by differences in patient selection and outcome definitions, and relatively limited numbers of patients per study. Nevertheless, uncertainty persists with respect to risks and net benefits of TAVI. The stroke risk in the PARTNER studies gives cause for concern.

Using an internationally-recognized system of appraisal,[34] we judged the overall strength of the scientific evidence on benefits and risks as moderate. The limitations of the PARTNER studies include the (unavoidable) lack of double blinding, the absence of information on other patient care received and its intensity, and, in PARTNER-B, some imbalances in baseline (risk factor) characteristics between patient groups despite randomization. Also notable with regards to generalizability of the PARTNER-B findings is

the frequent use of BAV in the medical treatment group, an intervention that is rarely performed in our region.

The non-randomized studies that we examined provide supportive but lower-quality evidence. The quality-of-life literature shows that this outcome is much less frequently studied, with great variability in both types of questionnaires used and timing of follow-up measurement. More information is needed concerning valve durability beyond 3 years. The 4 registries provide favourable "real-world" results for some clinical outcomes, but are limited in their completeness for the detection and reporting of adverse events. At the time of our evaluation, other existing registries had not reported survival at 1 year. The FRANCE 2 registry recently showed 76% 1-year survival, consistent with our meta-analysis result.[2]

1.5.4. Summary of the evidence on cost-effectiveness

Of 871 documents identified by our search, only 3 met our selection criteria, but their quality was judged to be very high. Two were health technology assessment reports, from Ontario[35] and Belgium[36], and 1 was a published article from the PARTNER investigators.[37] **Table 1.3** presents an overview of methodology and results. All studies compared TAVI to standard medical treatment in patients at prohibitive surgical risk. Two also compared TAVI to surgery in patients at high risk but still deemed operable.[35, 36] Effectiveness was based on PARTNER trial results (SAPIEN valves),[3, 32] with extrapolation of data beyond 30 months. Country-specific costs were estimated by each study. These included acquisition and implantation of the valves, and costs of the comparison treatment, as well as hospital and health care system costs (inpatient services and outpatient follow-up) up to the time of death for all patients.

The conclusions of the 3 studies were quite consistent. Both assessment reports concluded that TAVI was not cost-effective compared to surgery in operable patients, with incremental cost-effectiveness ratios (ICER) well beyond the generally accepted maximum threshold ($100,000 CAN per quality-adjusted life year [QALY][38]).[35, 36] In comparison, results for patients at prohibitively high risk for surgery were considerably more favourable, placing TAVI either inside the cost-effective zone[35] (i.e., less than $50,000 per QALY[38]) or at the low end of the "grey zone"[36, 37] ($50,000 to 100,000 per QALY[38]), compared to standard medical

treatment. Sensitivity analyses indicated that the results in non-surgical candidates were highly sensitive to several factors (e.g. patient's life expectancy, utility values used for quality-of-life adjustment, cost of the valve).

Table 1.3. Cost-effectiveness studies: methodologies and results

Study	Country	Perspective	TAVI versus	Patient population	ICER (CAN $)
Neyt, 2011[36]	Belgium	Third-party payer	standard medical treatment	At too high risk for surgery (PARTNER B)	$48,449 per LYG $56,481 per QALY
			surgery	Operable but high risk (PARTNER A)	$1,021,020 per LYG* $1,008,033 per QALY*
Reynolds et al., 2012[37]	United States	Third-party payer	standard medical treatment	At too high risk for surgery (PARTNER B)	$55,368 per LYG† $64,303 per QALY†
Sehatza-deh, 2012[35]	Ontario	Third-party payer	standard medical treatment	At too high risk for surgery (PARTNER B)	$33,141 per LYG $48,912 per QALY
			surgery	Operable but high risk (PARTNER A)	$870,143 per LYG TAVI dominated by surgery‡

Unless otherwise indicated, future costs and benefits discounted at 5%. Belgian and American results converted using the Bank of Canada rate on March 28, 2012 (http://www.banqueducanada.ca/taux/taux-de-change/convertisseur-de-devises-taux-du-jour/) and actualized to 2012 values using the American and Belgium Consumer Price Index for medical care (http://www.bls.gov/cpi and http://statbel.fgov.be, respectively).
*future costs discounted at 3%, future benefits discounted at 1.5%; †future costs and benefits discounted at 3%; ‡TAVI provided fewer benefits at a higher cost than surgery; ICER: incremental cost-effectiveness ratio; LYG: life-year gained; QALY: quality-adjusted life year.

1.5.5. Key organizational elements

The clinical practice guidelines,[39, 40] health technology assessments,[28, 41] and the expert consensus document[42] were consistent regarding the following key elements of a TAVI program:

(1) restriction of patient eligibility to those considered inoperable or at high surgical risk

(2) restriction to a small number of high volume, expert performing centres

(3) close collaboration between interventional cardiologists and cardiac surgeons

(4) quality monitoring and tracking of patient outcomes with registries

(5) standardization of clinical outcome definitions and reporting practices

The recommended characteristics of the medical team and of TAVI performing centres were presented in greater detail in 4 documents.[28, 41-43] All concluded that patient selection should involve a multidisciplinary team. The following health professionals were considered as key members: treating ("primary") cardiologists, interventional cardiologists, cardiac surgeons, specialists in anaesthesiology, cardiac imaging and heart failure, advanced care nurses, administrators, dietary and rehabilitation specialists, and social workers.[42] In its recent position statement, the Canadian Cardiovascular Society recommends a minimum of 25 TAVI cases per year for primary operators and 25-50 per year for a given institution.[43] There was a lack of consensus on whether a hybrid operating room (equipped with imaging machines), or a modified cardiac catheterization laboratory, was the optimal environment for performance of the procedure. [40, 41, 43] Nevertheless, a large amount of space is required to accommodate the medical and nursing team (at least 800 square feet[42, 43], compared to a typical cardiac catheterization laboratory of 600 square feet).[39]

The challenge of patient selection for TAVI is to identify those who are too ill to undergo conventional surgical valve replacement, but healthy enough to derive clinical benefit from the procedure. The STS score for surgical risk has shown moderately better ability to predict early mortality in TAVI compared to the logistic EuroScore.[43, 44] The literature highlights the need to consider other conditions absent from existing risk scores, such as frailty and a severely calcified or porcelain aorta,[43, 45] to use multiple methods to quantify

risk,[46] and to perform "local calibration" to identify predictors of mortality[45] (through a registry, for example), as well as the centrality of an individual, patient-specific assessment.[44, 47]

1.5.6. Key ethical considerations

The following ethical considerations were identified in the course of our literature review and discussions with the expert committee, and are grouped according to 4 guiding principles:

(1) *Benefit versus harm.* The fundamental question when considering TAVI is to what extent the patient's quality of life will be improved.[48] While there are no globally accepted, easily applicable criteria to judge the appropriateness of TAVI in persons with severe aortic stenosis, most often elderly, who may have important comorbidities as well as being frail,[48] this key question must be addressed in each individual being assessed.

(2) *Patient autonomy.* "What can be done" and "what should be done" are not equivalent. A patient's right to die with dignity must be respected.[48]

(3) *Fairness of access.* Patient selection criteria should be as objective as possible and thus reproducible across physicians and performing centres such that access to the procedure is fair and just. While it is reasonable to allow for some subjectivity of physician opinion regarding patient eligibility, selection criteria must be transparent and uniformly applied.

(4) *Informed decision-making and consent.* The patient should be provided with clear information about the expected benefits and risks of the procedure.[28] In particular, the patient should be made aware of the risk of death or serious complications such as stroke, and of the planned response of the procedure team regarding emergency open-heart surgery in the event of a life-threatening problem during the TAVI procedure. The patient should also understand the uncertainty about the long-term benefits and risks of TAVI and valve durability.[28, 48]

1.5.7. Recommendations

Our recommendations support the use of TAVI under strict conditions, with respect to patient eligibility, the patient selection process, organizational requirements and the tracking of patient outcomes using a mandatory registry. The recommendations are displayed in **Supplemental Appendix S1.2**, with the bases for each recommendation in italics. "Expert opinion" refers to the consensus view of the authors.

1.6. Discussion

This article is the result of a multidisciplinary evaluation of the scientific evidence, consultation with clinical experts in the field, and an external review process. It is unique in the range of issues that have been examined. Beyond current knowledge about the benefits and risks of TAVI, we have considered the quality of the available evidence base, organization of care, ethical issues, cost-effectiveness, and guidance from other organizations concerning the practice of TAVI. Our recommendations are particularly relevant to Canadian provinces and any jurisdiction with a universal access, public health care system.

The clinical literature on TAVI is rapidly evolving, and thus any review, however systematic, is best viewed as a "snapshot" of the data available at a particular point in time. Increasing experience of performing centres and evolving delivery systems may improve clinical outcomes. The cost-effectiveness of TAVI will need to be reassessed when longer-term data become available. Emerging issues such as potential differences in both clinical outcomes and cost-effectiveness between transfemoral and transapical approaches will need to be considered.

Our recommendations share many similarities with very recent guidance from several other bodies, such as health technology assessment agencies in Ontario and Europe,[35, 36, 49] the Canadian Cardiovascular Society,[43] American professional societies,[44, 50] and a United States federal agency that administers health care programs.[51] (see **Supplemental Table S1.2**). Although we were aware of the economic analyses by 2 of these groups,[35, 36] the conclusions in these sources were not consulted during the formulation of our recommendations.

Patient-centered medicine is a desired attribute in a health care system. This concept includes ensuring that a patient considering a medical procedure is sufficiently informed. In the current case of TAVI, this requires the patient to understand the complex and uncertain evidence on potential benefits and risks. The patient needs to weigh the possibility of functional improvement afforded by TAVI against, for example, the risk of a stroke. The benefit/risk balance will also be influenced by the relative contribution of the aortic stenosis, versus other comorbidities, to the patient's disability before treatment.

The performance of TAVI has numerous implications at the organizational level, in terms of infrastructure, the development, training and support of multidisciplinary care teams, and establishment of registry-based monitoring, among other issues. The technology also raises important questions at the societal level, where limitation of resources, in a public health care system, imply the need to make choices. More money spent on cardiac interventions generally means fewer funds for other programs that may include home care services for the elderly, for example. In formulating our recommendations on TAVI, we attempted to balance the desirability of ensuring access to high-quality technology for persons in need, and of supporting innovation and continued technical improvement, with "informed diffusion" that is based on the available science. Until more data from randomized controlled trials and registries become available, prudence and discernment is necessary in the choice of patients most likely to benefit from this intervention.

1.7. Acknowledgments

The authors wish to thank the external reviewers of the Ministry report (report available in French at www.inesss.qc.ca) as well as INESSS' librarians.

1.8. Funding sources

This work was supported by public funds. The clinical experts were remunerated for meetings. The external reviewers received modest honorariums, as per standard INESSS practice.

1.9. Disclosures

Dr. Benoit de Varennes is a consultant for Medtronic, Inc.

Dr. Éric Dumont is a consultant for Edwards Lifesciences.

Dr. Reda Ibrahim has received consulting fees or honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Johnson & Johnson, Prizer, Roche and sanofi-aventis.

Dr. Josep Rodés-Cabau is a consultant for Edwards Lifesciences and St. Jude Medical.

1.10. References

1. 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;26:2714-20.
2. Gilard M, Eltchaninoff H, Iung B, et al. Registry of transcatheter aortic-valve implantation in high-risk patients. N Engl J Med 2012;366:1705-15.
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;363:1597-607.
4. Rajani R, Buxton W, Haworth P, et al. Prognostic benefit of transcatheter aortic valve implantation compared with medical therapy in patients with inoperable aortic stenosis. Catheter Cardiovasc Interv 2010;75:1121-6.
5. Sinning JM, Ghanem A, Steinhauser H, et al. Renal function as predictor of mortality in patients after percutaneous transcatheter aortic valve implantation. JACC Cardiovasc Interv 2010;3:1141-9.

6. Bosmans JM, Kefer J, De Bruyne B, et al. Procedural, 30-day and one year outcome following CoreValve or Edwards transcatheter aortic valve implantation: Results of the Belgian national registry. Interact Cardiovasc Thorac Surg 2011;12:762-7.

7. Tamburino C, Capodanno D, Ramondo A, et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. Circulation 2011;123:299-308.

8. Kapadia SR, Goel SS, Svensson L, et al. Characterization and outcome of patients with severe symptomatic aortic stenosis referred for percutaneous aortic valve replacement. J Thorac Cardiovasc Surg 2009;137:1430-5.

9. Lefevre T, Kappetein AP, Wolner E, et al. One year follow-up of the multi-centre European PARTNER transcatheter heart valve study. Eur Heart J 2011;32:148-57.

10. Otten AM, van Domburg RT, van Gameren M, et al. Population characteristics, treatment assignment and survival of patients with aortic stenosis referred for percutaneous valve replacement. EuroIntervention 2008;4:250-5.

11. Rodés-Cabau J, Webb JG, Cheung A, et al. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: Acute and late outcomes of the multicenter Canadian experience. J Am Coll Cardiol 2010;55:1080-90.

12. Himbert D, Descoutures F, Al-Attar N, et al. Results of transfemoral or transapical aortic valve implantation following a uniform assessment in high-risk patients with aortic stenosis. J Am Coll Cardiol 2009;54:303-11.

13. Thomas M, Schymik G, Walther T, et al. Thirty-day results of the SAPIEN aortic Bioprosthesis European Outcome (SOURCE) Registry: A European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. Circulation 2010;122:62-9.

14. Zierer A, Wimmer-Greinecker G, Martens S, Moritz A, Doss M. Is transapical aortic valve implantation really less invasive than minimally invasive aortic valve replacement? J Thorac Cardiovasc Surg 2009;138:1067-72.

15. Walther T, Kasimir MT, Doss M, et al. One-year interim follow-up results of the TRAVERCE trial: The initial feasibility study for trans-apical aortic-valve implantation. Eur J Cardiothorac Surg 2011;39:532-7.

16. Grube E, Buellesfeld L, Mueller R, et al. Progress and current status of percutaneous aortic valve replacement: Results of three device generations of the CoreValve Revalving system. Circ Cardiovasc Interv 2008;1:167-75.

17. Gurvitch R, Wood DA, Tay EL, et al. Transcatheter aortic valve implantation: Durability of clinical and hemodynamic outcomes beyond 3 years in a large patient cohort. Circulation 2010;122:1319-27.

18. Thielmann M, Wendt D, Eggebrecht H, et al. Transcatheter aortic valve implantation in patients with very high risk for conventional aortic valve replacement. Ann Thoracic Surg 2009;88:1468-74.

19. 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. J Am Coll Cardiol 2011;58:2130-8.

20. Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. New Engl J Med 2012;366:1696-704.

21. Ussia GP, Barbanti M, Petronio AS, et al. Transcatheter aortic valve implantation: 3-year outcomes of self-expanding CoreValve prosthesis. Eur Heart J 2012;33:969-76.

22. Svensson LG, Dewey T, Kapadia S, et al. United States feasibility study of transcatheter insertion of a stented aortic valve by the left ventricular apex. Ann Thorac Surg 2008;86:46-55.

23. Ussia GP, Mule M, Barbanti M, et al. Quality of life assessment after percutaneous aortic valve implantation. Eur Heart J 2009;30:1790-6.

24. 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;124:1964-72.

25. Bekeredjian R, Krumsdorf U, Chorianopoulos E, et al. Usefulness of percutaneous aortic valve implantation to improve quality of life in patients >80 years of age. Am J Cardiol 2010;106:1777-81.

26. Yan TD, Cao C, Martens-Nielsen J, et al. Transcatheter aortic valve implantation for high-risk patients with severe aortic stenosis: A systematic review. J Thorac Cardiovasc Surg 2010;139:1519-28.

27. Coeytaux RR, Williams JW, Jr., Gray RN, Wang A. Percutaneous heart valve replacement for aortic stenosis: State of the evidence. Ann Intern Med 2010;153:314-24.

28. National Institute for Health and Clinical Excellence (NICE). Interventional procedure overview of transcatheter aortic valve implantation for aortic stenosis. London, England: NICE; 2011. <http://www.nice.org.uk/nicemedia/live/11914/54190/54190.pdf>.

29. Canadian Agency for Drugs and Technologies in Health (CADTH). Percutaneous heart valve replacement for valvular heart disease: A review of the clinical effectiveness, cost-effectiveness, and guidelines. Health Technology Inquiry Service (HTIS). Ottawa, ON: CADTH; 2010. <http://cadth.ca/media/pdf/l0149_percutaneous_heart_valves_htis-2.pdf>.

30. McGregor M, Esfandiari S, Mines L. Transcatheter aortic valve implantation (TAVI) at the MUHC: A health technology assessment. Montreal, QC: McGill University Health Centre (MUHC); 2009. <http://www.mcgill.ca/files/tau/TAVI_REPORT.pdf>.

31. Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials. A consensus report from the Valve Academic Research Consortium. J Am Coll Cardiol 2011;57:253-69.

32. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. New Engl J Med 2011;364:2187-98.

33. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. New Engl J Med 2012; 366:1686-95.

34. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians? Bmj 2008;336:995-8.

35. Sehatzadeh S, Doble B, Xie F, et al. Transcatheter aortic valve implantation (TAVI) for treatment of aortic valve stenosis. Ontario Health Technology Assessment Series 2012;12:1-91.

36. Neyt M, Van Brabandt H, Van de Sande S, Devriese S. L'implantation percutanée de valves aortiques (TAVI) : évaluation actualisée de la technologie. KCE reports 163B. Brussels, Belgium: Centre fédéral d'expertise des soins de santé (KCE); 2011. <http://kce.fgov.be/sites/default/files/page_documents/kce_163b_tavi_actualisation.pdf >.

37. Reynolds MR, Magnuson EA, Wang K, et al. Cost-effectiveness of transcatheter aortic valve replacement compared with standard care among inoperable patients with severe aortic stenosis: Results from the Placement of Aortic Transcatheter Valves (PARTNER) Trial (Cohort B). Circulation 2012;125:1102-9.

38. Gold MR, Siegel JE, Russell L, et al. Cost-Effectiveness in Health and Medicine. New York: Oxford University Press; 1996.

39. Rosengart TK, Feldman T, Borger MA, et al. Percutaneous and minimally invasive valve procedures: A scientific statement from the American Heart Association Council on Cardiovascular Surgery and Anesthesia, Council on Clinical Cardiology, Functional Genomics and Translational Biology Interdisciplinary Working Group, and Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation 2008;117:1750-67.

40. Vahanian A, Alfieri O, Al-Attar N, et al. Transcatheter valve implantation for patients with aortic stenosis: A position statement from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2008;29:1463-70.

41. Haute Autorité de santé (HAS). Évaluation des bioprothèses valvulaires aortiques implantées par voie rétrograde transfémorale et transapicale. Saint-Denis La Plaine,

France: HAS; 2008. <http://www.has-sante.fr/portail/jcms/c_658884/evaluation-des-bioprotheses-valvulaires-aortiques-implantees-par-voie-retrograde-transfemorale-et-transapicale>.

42. Holmes DR, Jr., Mack MJ. Transcatheter valve therapy: A professional society overview from the American College of Cardiology Foundation and the Society of Thoracic Surgeons. J Am Coll Cardiol 2011;58:445-55.

43. Webb J, Rodés-Cabau J, Fremes S, et al. Transcatheter aortic valve implantation: A Canadian Cardiovascular Society position statement. Can J Cardiol 2012 Jun 14 (Epub ahead of print).

44. Holmes DR, Jr., Mack MJ, Kaul S, et al. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement. J Am Coll Cardiol 2012;59:1200-54.

45. Ranucci M, Guarracino F, Castelvecchio S, Baldassarri R, Covello RD, Landoni G. Surgical and transcatheter aortic valve procedures. The limits of risk scores. Interact Cardiovasc Thorac Surg 2010;11:138-41.

46. Dewey TM, Brown D, Ryan WH, Herbert MA, Prince SL, Mack MJ. Reliability of risk algorithms in predicting early and late operative outcomes in high-risk patients undergoing aortic valve replacement. J Thorac Cardiovasc Surg 2008;135:180-7.

47. Schenk S, Fritzsche D, Atoui R, Koertke H, Koerfer R, Eitz T. EuroSCORE-predicted mortality and surgical judgment for interventional aortic valve replacement. J Heart Valve Dis 2010;19:5-15.

48. Van Brabandt H, Neyt M. Percutaneous heart valve implantation in congenital and degenerative valve disease. A rapid Health Technology Assessment. KCE reports 95C. Brussels, Belgium: Centre fédéral d'expertise des soins de santé (KCE); 2008. <http://kce.fgov.be/sites/default/files/page_documents/d20081027381.pdf>.

49. Haute Autorité de santé (HAS). Réévaluation des bioprothèses valvulaires aortiques implantées par voie artérielle transcutanée ou par voie transapicale. Rapport d'évaluation. Saint-Denis La Plaine, France: HAS; 2011.

50. Tommaso CL, Bolman RMI, Feldman T, et al. Multisociety (AATS, ACCF, SCAI, and STS) expert consensus statement: operator & institutional requirements for transcatheter valve repair and replacement; Part 1 TAVR. J Am Coll Cardiol 2012; 59:2028-42.

51. Centers for Medicare and Medicaid Services (CMS). Proposed decision memo for transcatheter aortic valve replacement (TAVR) (CAG-00430N). Baltimore, MD: CMS, U.S. Department of Health and Human Services; 2012. <http://www.cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx?NCAId=257&ver=5&NcaName=Transcatheter+Aortic+Valve+Replacement+(TAVR)&bc=AAAAAAAAIAAA&> (Accessed on May 7, 2012).

52. Wyrwich KW, Spertus JA, Kroenke K, Tierney WN, Babu AN, Wolinsky FD. Clinically important differences in health status for patients with heart disease: An expert consensus panel report. Am Heart J 2004;147:615-22.

Chapitre 2. Résultats des avancées technologiques: l'exemple de deux générations de la valve Edwards

Cet article original a été publié dans le *World Journal of Cardiology*:
Sawaya FJ, Spaziano M, Lefèvre T, Roy A, Garot P, Hovasse T, Neylon A, Benamer H, Romano M, Unterseeh T, Morice MC, Chevalier B. Comparison between the SAPIEN S3 and the SAPIEN XT transcatheter heart valves: A single-center experience. World J Cardiol. 2016 Dec 26;8(12):735-745. doi: 10.4330/wjc.v8.i12.735. Pubmed PMID: 28070241.

Contribution des auteurs

Fadi Sawaya: Implication active au cours de chacune des étapes du processus de recherche. Conception du devis, collecte des données, interprétation des résultats et rédaction du manuscrit

Marco Spaziano: Implication active au cours de chacune des étapes du processus de recherche. Conception du devis, collecte des données, analyses statistiques, interprétation des résultats et rédaction du manuscrit

Bernard Chevalier: Conception du devis, direction générale et correction de l'article

Thierry Lefèvre: Conception du devis, direction générale et correction de l'article

Andrew Roy, Antoinette Neylon, Philippe Garot, Thomas Hovasse, Hakim Benamer, Mauro Romano, Thierry Unterseeh, Marie-Claude Morice: Participation à la correction de l'article

Comparison Between the SAPIEN S3 and The SAPIEN XT Transcatheter Heart Valves: A Single-Center Experience

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Abstract Word count : 245. Text Word Count : 4730

Conflicts of Interest:

Dr. Thierry Lefèvre is a proctor for Edwards LifeSciences. Dr. Bernard Chevalier is a proctor for Medtronic. All other authors report no conflict of interest regarding this manuscript.

2.1. Abstract

Objectives: This study sought to investigate the procedural, 30-day and one-year clinical outcomes of TAVI with the Sapien 3 transcatheter heart valve (S3-THV) versus the Sapien XT valve (XT-THV). We also explored the clinical and procedural predictors of new pacemaker implantation in the S3-THV group.

Background: Comparisons between the S3-THV and the XT-THV are scarce.

Methods: We retrospectively analyzed 507 patients that underwent TAVI with the XT-THV and 283 patients that received the S3-THV at our institution between March 2010 and December 2015.

Results: Thirty-day mortality (3.5 vs. 8.7%; OR = 0.44, p= 0.21) and 1-year mortality(25.7 vs. 20.1%, p=0.55) were similar in the S3-THV and the XT-THV groups. The rates of both major vascular complication and PVR>1 were almost 4 times lower in the S3-THV group than the XT-THV group (major vascular complication: 2.8 vs. 9.9%, p< 0.0001; PVL >1: 2.4 vs. 9.7%, p<0.0001). However, the rate of new pacemaker implantation was almost twice as high in the S3-THV group (17.3 vs. 9.8%, p= 0.03). In the S3 group, independent predictors of new permanent pacemaker were pre-procedural RBBB (OR = 4.9; p=0.001), pre-procedural PR duration (OR = 1.14, p=0.05) and device lack of coaxiality (OR = 1.13; p=0.05) during deployment.

Conclusions: The S3-THV is associated to lower rates of major vascular complications and PVR but higher rates of new pacemaker compared to the XT-THV. Sub-optimal visualization of the S3-THV in relation to the aortic valvular complex during deployment is a predictor of new PPM.

2.2. Introduction

Transcatheter aortic valve implantation (TAVI) has gained rapid acceptance for patients with severe aortic stenosis (1-4) and has recently been associated with excellent short-, mid- and long-term outcomes in patients at intermediate risk(5-7). However, TAVI is still associated with a higher incidence of para-valvular aortic regurgitation (PVR), permanent pacemaker implantation (PPM) and vascular complications(8-12) when compared to surgical aortic valve replacement. In order to justify the extension of the procedure to lower risk patients, these adverse outcomes have to be mitigated. The development of novel transcatheter heart valves (THVs) and further iterations of delivery systems and prostheses have contributed to the decrease in complications rates in TAVI(13). One of the recent developments is the balloon-expandable Sapien 3 transcatheter heart valve (S3-THV; Edwards Lifesciences, Irvine, CA). It has been designed with a lower profile to be delivered in a 14 French sheath (for sizes 23 and 26 mm), and with an external sealing cuff. The lower profile should diminish vascular complications while the sealing cuff should diminish PVR(14,15).

Despite positive procedural and short-term outcomes in small single center series and registries, large reports comparing the S3-THV to its predecessor, the Sapien XT (XT-THV), are lacking(16,17). Recent reports suggest an increased rate of new PPM implantation following TAVI with the S3-THV, compared to the XT-THV(16,17). Whether procedural characteristics such as depth of implant are related to PPM implantation with this new device remains unclear(18).

The objective of this analysis was to retrospectively compare the procedural outcomes, 30-day clinical outcomes and one-year mortality of TAVI with the S3-THV versus the XT-THV in patients with symptomatic severe aortic stenosis in a single high-volume center. We also explored clinical and procedural predictors of new PPM in the S3-THV group.

2.3. Methods

Patient population and procedure

To compare clinical outcomes of patients undergoing TAVI with the S3-THV to those undergoing TAVI with the XT-THV, we retrospectively identified all patients treated with TAVI at our institution with either device. Patients underwent TAVI by the transfemoral, transaortic or transapical approach according to previously described techniques(17).

A multidisciplinary heart team involving at least one interventional cardiologist and one cardiac surgeon discussed all cases and consensus was achieved regarding therapeutic strategy. All patients provided informed written consent for the procedure and data collection, and the local ethics committee approved the study.

Pre-procedural planning

All patients underwent TTE examination and native valve function was assessed according to the recommended guidelines(19). In addition, pre-procedural MSCT evaluation including measurements of the aortic annulus and aortic root was systematically performed. Aortic annulus dimensions were measured according to standard procedures using dedicated software (Philips Brilliance 64-slice MDCT scanner, Philips Healthcare, Best, the Netherlands). Valve prosthesis size was selected in accordance with the manufacturer's recommendations after taking into account other anatomic features such as the presence and location of calcification, eccentricity of the aortic annulus and dimensions of the sinuses of Valsalva and sino-tubular junction in case of borderline sizing ranges. In addition to dimensions, annulus orientation was assessed with MSCT. Implantation projection was selected so that the aortic valve would be seen coaxially, with the three cusps aligned. Cardiac catheterization and femoral angiography were performed prior to the procedure to assess for concomitant coronary artery disease and vessel narrowing or tortuosity.

Study devices

The SXT-THV and the S3-THV designs have been described in detail previously(15,20). Both consist of bovine pericardium sewn to a balloon-expandable cobalt-chromium tubular frame. The XT-THV was available in the 23, 26, and 29 mm sizes and was

implanted with the use of the NovaFlex catheter, which employed an 18- or 19-F introducer sheaths. The S3-THV is available in the 23, 26, and 29 mm sizes. The device's height is about 15% greater than that of the XT-THV. It was implanted with the use of the lower-profile Commander delivery catheter, which employed 14- (sizes 23 and 26 mm) or 16-F (size 29 mm) expandable sheaths (eSheath, Edwards Lifesciences, Inc.). The S3-THV stent was designed with a frame geometry that provides greater radial force. The difference in cell geometry between the inflow and the outflow causes the valve frame to foreshorten more from the ventricular side. The device also includes an outer polyethylene terephthalate fabric seal designed to minimize PVR.

Study procedure

The techniques of SAPIEN XT and SAPIEN S3 valve implantation have been described in detail elsewhere(15,20). In our center, all trans-femoral (TF) cases were performed under local anesthesia and conscious sedation in the catheterization laboratory. The selected femoral artery was “pre-closed” with two 6-Fr suture-mediated closure devices Perclose ProGlide(Abbott Laboratories, Abbot Park, Illinois). With a pigtail in the right coronary cusp, aortography was performed to correct, if necessary, the implantation projection provided by MSCT. Pre-dilatation was performed routinely in the XT-THV group, but only in cases of severe calcification in the S3-THV group. Device positioning was based on fluoroscopy using annular calcification as a landmark along with serial 12 to 15 ml supra-annular aortography to validate its position. The XT-THV was implanted by means of a 2-step inflation technique (21). The S3-THV was deployed during one-slow inflation (5–10 s). Prosthesis position and function, and patency of the coronary ostia were evaluated by angiography and transthoracic echocardiography. Significant aortic regurgitation was treated by post-dilatation adding 1 to 3 cc of contrast in the balloon delivery system or second valve implantation if the valve was positioned too high or too low. Removal of the sheath was cautiously achieved with serial contralateral angiograms to detect ilio-femoral complications. In the absence of any conduction abnormality, the pacing lead was removed at the end of the procedure. Patients were monitored in the intensive care unit for at least 24 h after valve implantation. For the transapical and transaortic cases, the SXT-THV and S3-THV were

deployed with the Ascendra and Certitude delivery systems, respectively. These cases were performed in a hybrid room.

Data collection and study endpoints

Clinical and echocardiographic data at baseline and follow-up were collected by dedicated personnel and entered in a local database and a national registry (FRANCE-TAVI) (22). Data from the ECG and MSCT prior to the intervention were retrospectively collected by the co-authors and entered into the local database. The co-authors also retrospectively collected implant depth and device coaxiality from procedure fluoroscopy.

The primary endpoint was 30-day mortality. Secondary endpoints consisted of 1-year mortality, stroke, myocardial infarction, annulus rupture, new PPM implantation, major vascular complication, PVR greater than mild, annulus rupture, acute kidney injury and post-procedural mean gradient. Endpoints were defined according to the VARC-2 criteria (23).

Implant depth and device coaxiality during implant measurement

We reviewed procedural fluoroscopy of all patients in the S3-THV group to measure valve implant depth. A post-implant aortic angiogram with the device coaxial was required for implant depth measurement. First, on a single still frame, the hinge points between the device and the sinus of Valsalva on the septal and non-septal side were identified. **(Figure 2.1)** Next, a line was drawn between both hinge points. The distances between this line and the bottom of the valve frame on both the septal and non-septal sides were then recorded as implant depth. Measurements were performed using the OsiriX sorftware, version 5.9.

In addition to depth, we also measured device lack of coaxiality during deployment. This was done on a single still frame at the end of valve deployment, while still under rapid pacing. The maximal perpendicular distance between the "front" and the "back" struts of the device was measured and recorded as device lack of coaxiality during deployment. **(Figure 2.2)**

Figure 2.1

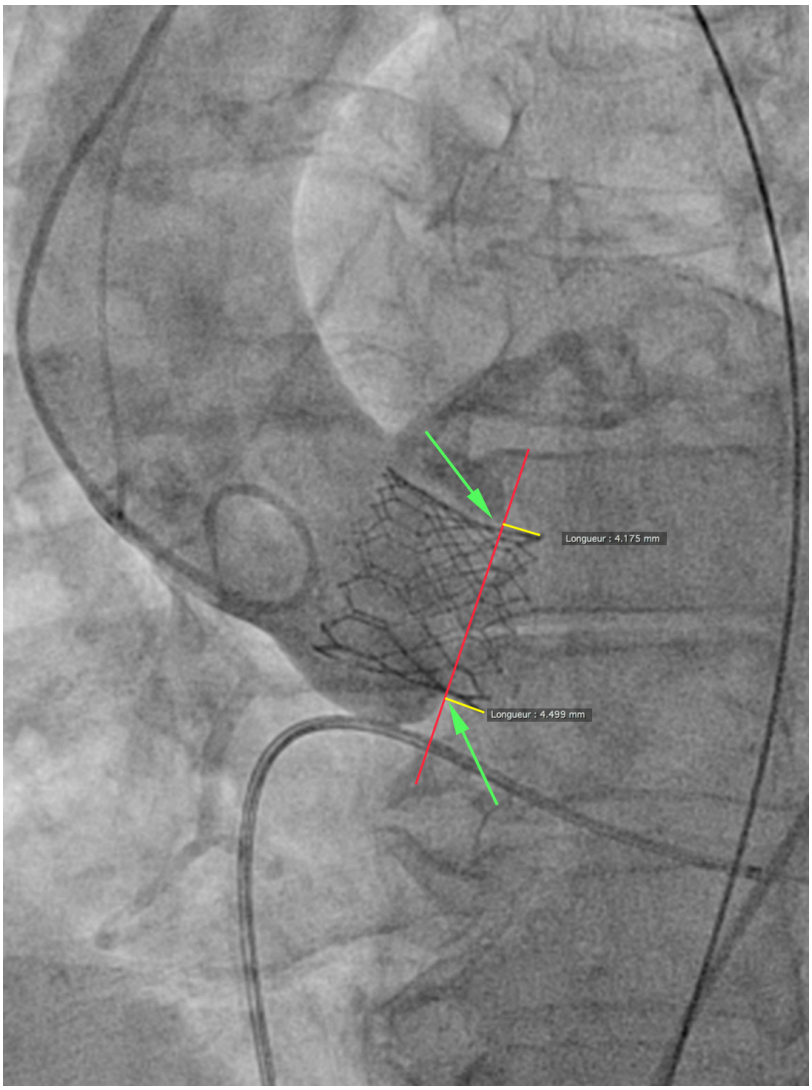

Figure 2.1. Depth of implant measurement. The arrows show the hinge points between the device and neighboring sinuses of Valsalva. Next, the red line is drawn from the septal to the non-septal hinge point. The yellow lines, drawn perpendicularly from the red line to the extremity of the device frame, represent depth on the septal side (left) and the non-septal side (right).

Figure 2.2

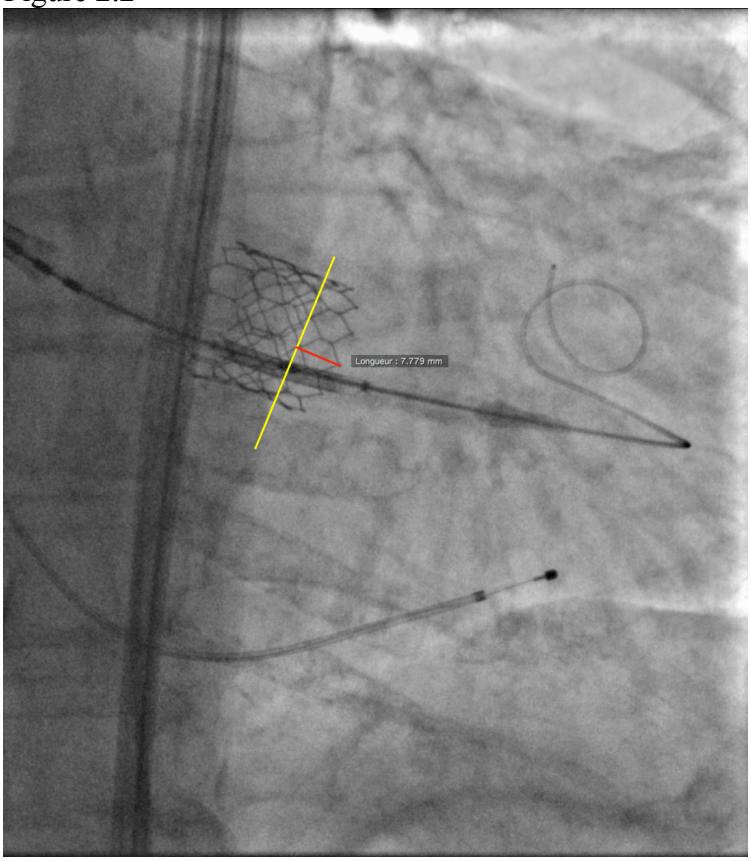

Figure 2.2. Device coaxiality measurement. On a still frame, immediately after deployment while still under rapid pacing, a line is drawn connecting neighboring valve struts on the ventricular side of the device (yellow line). Next, a perpendicular line is drawn from the yellow line to the tip of the strut that appears the deepest (red line). The length of this red line is recorded as device lack of coaxiality.

Statistical analysis

Continuous data are reported as mean ± standard deviation (SD), and categorical variables are reported as number of patients and percentages. Categorical data were compared using Fisher's exact test, and continuous data using Student's t-test or Mann-Whitney's U test, as appropriate. Event probabilities at 30 days were compared for patients treated with the XT-THV versus the S3-THV using logistic regression. Odds ratios are adjusted for procedure date (to account for a potential learning effect of time) and for baseline characteristics with a univariate p-value < 0.10 for each individual outcome. One-year survival data was fitted in a Cox proportional hazards model and the XT-THV and S3-THV groups were compared using

an adjusted hazard ratio. No adjusted analyses were performed for outcomes with less than 15 events overall. Patients with previous pacemaker implantation were excluded from analyses pertaining to the outcome of new pacemaker requirement. A p-value <0.05 was considered significant for adjusted models. Statistical analyses were performed with SPSS version 23 (IBM Corp, Armonk, NY).

2.4. Results

Between March 2010 and December 2015, 790 patients underwent TAVI with the XT-THV (n=507) or the S3-THV (n=283) in our center. The XT-THV was used from March 2010 to September 2014, after which the S3-THV was used routinely. Patients in the S3-THV group had lower STS scores than those in the XT-THV group (STS Score: 5.3 ± 3.5% vs. 6.4 ± 4.0 respectively, p<0.0001). **(Table 2.1)** Patients in the S3-THV group were also less likely to be in NYHA functional class 3 or 4 (59.1 vs. 75.8%, p<0.0001), and less likely to have peripheral vascular disease (19.8 vs. 28.4%, p=0.01) or chronic obstructive pulmonary disease (11.7 vs. 21.9%, p<0.0001). Baseline echocardiographic characteristics were similar between groups.

Table 2.1. Baseline Characteristics.

Variable	S3-THV (n=283)	XT-THV (n=507)	p-value
Age	82.8 ± 7.1	83.5 ± 7.0	0.14
Female sex	137 (48.4)	275 (54.3)	0.12
STS-PROM, %	5.3 ± 3.5	6.4 ± 4.0	< 0.0001
Logistic EuroSCORE, %	15.7 ± 10.8	18.8 ± 11.5	< 0.0001
NYHA Class 3 or 4	162 (59.1)	383 (75.8)	< 0.0001
History of syncope	1 (0.5)	10 (2.1)	0.19
Atrial arrhythmia (flutter or fibrillation)	80 (29.5)	135 (27.8)	0.67
Diabetes	71 (25.1)	124 (24.5)	0.86
Hypertension	161 (71.6)	344 (68.8)	0.49
Dyslipidemia	99 (44.0)	263 (52.6)	0.04
Active smoker	4 (1.4)	18 (3.6)	0.11
Previous PPM	35 (12.4)	60 (11.8)	0.91

Previous PCI	81 (29.3)	114 (22.9)	0.06
Previous CABG	25 (9.0)	51 (10.3)	0.62
Previous SAVR	2 (0.7)	7 (1.4)	0.50
Previous stroke	25 (8.8)	39 (7.7)	0.59
Peripheral vascular disease	56 (19.8)	143 (28.4)	0.01
eGFR, ml/min/1.73m^2	62.8 ± 24.6	61.4 ± 22.6	0.42
eGFR < 40 ml/min/1.73m^2	82 (16.2)	41 (14.5)	0.61
Dialysis	4 (1.5)	13 (2.6)	0.44
Chronic obstructive pulmonary disease	33 (11.7)	110 (21.9)	< 0.0001
Body mass index, kg/m^2	26.5 ± 5.1	26.3 ± 4.9	0.61
LVEF, %	54.9 ± 14.8	53.6 ± 14.2	0.24
LVEF < 30%	55 (11.1)	31 (11.4)	0.91
Mean aortic gradient, mmHg	46.7 ± 15.3	46.9 ± 15.3	0.92
AVA, cm^2	0.67 ± 0.17	0.65 ± 0.14	0.31
Pulmonary artery systolic pressure, mmHg	44.5 ± 13.0	46.5 ± 12.9	0.06
Pulmonary artery systolic pressure > 50 mmHg	64 (28.3)	123 (28.5)	1

Values are mean ± SD or n (%). AVA = aortic valve area; CABG = Coronary artery bypass graft; eGFR = glomerular filtration rate estimated by the MDRD formula; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association functional class; PPM = permanent pacemaker; PCI = Percutaneous coronary intervention; SAVR = surgical aortic valve replacement; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

The use of the transfemoral approach increased from 54% in XT-THV group to more than 80% in the S3-THV group (p<0.0001). **(Table 2.2)**

Predilatation was performed routinely in the XT-THV group (86.8%), which was not the case in the S3-THV group (17.7%, p<0001). **(Table 2.2)** In the S3-THV group, predilatation was reserved for patients with an extensively calcified aortic valve. The lower use of predilatation in the S3-THV group did not translate into significantly more post-dilatation (S3-THV: 15.9% vs. XT-THV: 12.0%; p=0.13). As per manufacturer recommendations, device diameter to annulus diameter (area-derived) ratio was reduced from 1.11 ± 0.05 (XT-THV) to 1.05 ± 0.05 (S3-THV; p<0.0001). As a result of this reduced oversizing, smaller device sizes were used in the S3-THV group (p<0.0001). However,

according to ROC curve analysis, a device diameter to annulus diameter ratio below the threshold of 1.03 increased the risk of post-dilatation or PVR > mild (area under the curve: 0.68; **Supplemental figure S2.1 in Annex 2**).

While fluoroscopy time was similar between groups, contrast use decreased by more than 15% in the S3-THV group compared to the XT-THV group (131.6 ± 60.9 vs. 108.2 ± 42.7 ml; p<0.0001).

Table 2.2 Procedural characteristics.

Procedural characteristic	S3-THV (n=283)	XT-THV (n=507)	p-value
Transfemoral approach	232 (82.6)	273 (53.8)	< 0.0001
Local anesthesia	232 (82.6)	271 (54.2)	< 0.0001
Predilatation	50 (17.7)	440 (86.8)	< 0.0001
Postdilatation	45 (15.9)	61 (12.0)	0.13
Implanted device size			< 0.0001
23 mm	111 (39.8)	127 (25.1)	
26 mm	101 (36.2)	270 (53.4)	
29 mm	67 (24.0)	109 (21.5)	
Valve area oversizing, %	11.5 ± 9.8	22.9 ± 11.2	< 0.0001
Device diameter / Annulus diameter (area-derived)	1.05 ± 0.05	1.11 ± 0.05	< 0.0001
Need for seconde valve implantation	7 (2.5)	8 (1.6)	0.42
Annulus rupture	0 (0)	13 (2.6)	0.01
Conversion to SAVR	2 (0.7)	14 (2.8)	0.06
Contrast use (ml)	108.2 ± 42.7	131.6 ± 60.9	< 0.0001
Fluoroscopy time (min)	17.4 ± 9.9	16.5 ± 9.8	0.28

Values are mean ± SD or n (%). SAVR = surgical aortic valve replacement.

2.4.1. Clinical outcomes

Thirty-day mortality was lower in the S3-THV group than the XT-THV group (3.5% vs 8.7%; univariate OR = 0.36; p = 0.01). **(Figure 2.3; Table 2.3)** After adjustment for baseline characteristics, this difference was no longer statistically significant (adjusted OR = 0.44, p= 0.21). One-year mortality was also similar between groups (25.7 vs. 20.1%, adjusted

p=0.55). **(Figure 2.3)** In total, 20 deaths had occurred at 1 year in the S3-THV group. These are listed in **Table 2.4** along with cause of death.

Figure 2.3

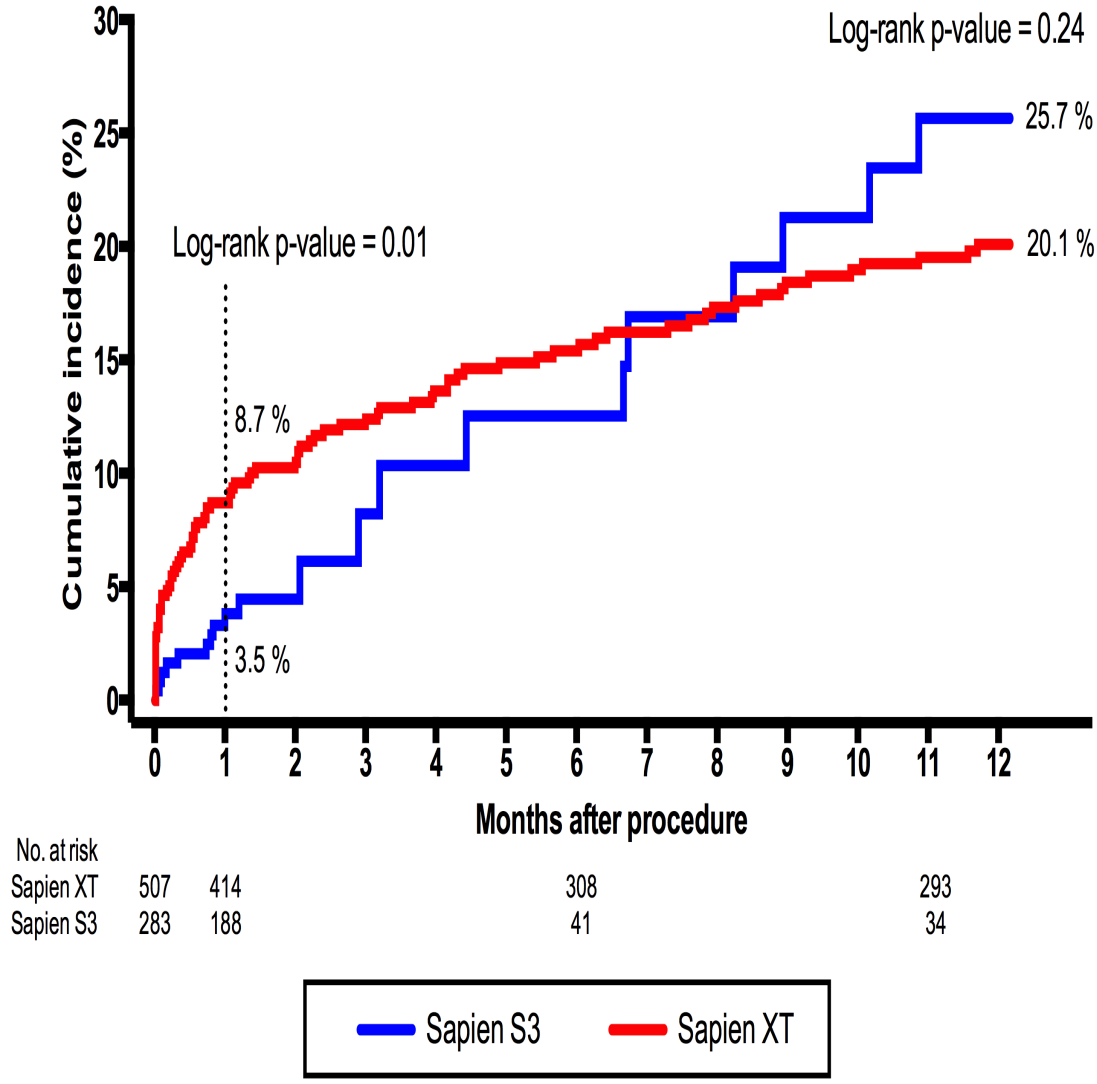

Figure 2.3. Cumulative incidence of all-cause mortality. Cumulative incidence (%) of all-cause 1-year mortality in the S3-THV group (blue line) and the XT-THV group (red line).

Table 2.3. 30-day and 1-year outcomes.

30-day outcomes	**S3-THV (n=283)**	**XT-THV (n=507)**	**Odds Ratio (95% CI)**	**p-value**	**Adjusted Odds Ratio (95% CI)**	**Adjusted p-value**
Death	8 (3.5)	42 (8.7)	0.36 (0.16 - 0.81)	0.01	0.44 (0.12 - 1.56)	0.21
Stroke	4 (1.4)	13 (2.8)	0.51 (0.16 - 1.58)	0.24	0.59 (0.08 - 4.33)	0.60
Myocardial infarction	0 (0)	2 (0.4)	0 (0 - ∞)	1		
New pacemaker implantation*	43 (17.3)	44 (9.8)	1.88 (1.19 - 2.97)	0.007	1.68 (1.05 - 2.69)	0.03
Major vascular complication	8 (2.8)	50 (9.9)	0.27 (0.13 - 0.57)	0.001	0.20 (0.09 - 0.44)	< 0.0001
Paravalvular regurgitation > mild	6 (2.4)	47 (9.7)	0.23 (0.10 - 0.55)	0.001	0.20 (0.08 - 0.47)	< 0.0001
Acute kidney injury	3 (1.1)	69 (13.6)	0.07 (0.02 - 0.22)	< 0.0001	0.12 (0.04 - 0.39)	< 0.0001
Mean gradient > 20 mmHg	7 (2.8)	6 (1.3)	2.48 (0.78 - 7.89)	0.13		
Mean gradient, mmHg	11.8 ± 5.8	10.0 ± 5.0		< 0.0001		
Total hospital length of stay, days (median [IQR])	8 [5 - 13]	9 [7 - 14]		< 0.0001		
1-year outcomes				**p-value**	**Adjusted Hazard Ratio (95% CI)**	**Adjusted p-value**
Death	20 (25.7)	87 (20.1)		0.24	0.86 (0.52 - 1.42)	0.55

Values are mean ± SD or n (%) unless specified otherwise. IQR = inter-quartile range. *Patients with previous permanent pacemaker were excluded from this analysis. No adjusted analyses were performed for outcomes with less than 15 events overall.

Table 2.4. Causes of death at 1 year in the S3-THV group.

Patient	Days to death	Cause of death
1	0	Dissection of ascending aorta
2	2	Left main compression/Cardiogenic shock
3	3	Iliac rupture
4	5	Sudden cardiac death
5	10	Cardiogenic shock
6	22	Heart failure
7	24	Subdural hematoma
8	25	Unknown
9	31	Stroke
10	36	Acute renal failure
11	62	Unknown
12	87	Heart failure
13	96	Heart failure
14	133	Unknown
15	200	Sudden cardiac death
16	202	Cancer
17	247	Myocardial infarction
18	268	Septic shock
19	305	Chronic obstructive pulmonary disease acute exacerbation
20	326	Major Stroke

The rates of major vascular complication and PVR>1 were both almost 4 times lower in the S3-THV group than the XT-THV group (major vascular complication: 2.8 vs. 9.9%, adjusted $p< 0.0001$; PVL >1: 2.4 vs. 9.7%, adjusted $p<0.0001$). **(Figure 2.4)** However, the rate of new pacemaker implantation was almost twice as high in the S3-THV group (17.3 vs. 9.8%, adjusted $p= 0.03$). **(Figure 2.4)**

Figure 2.4

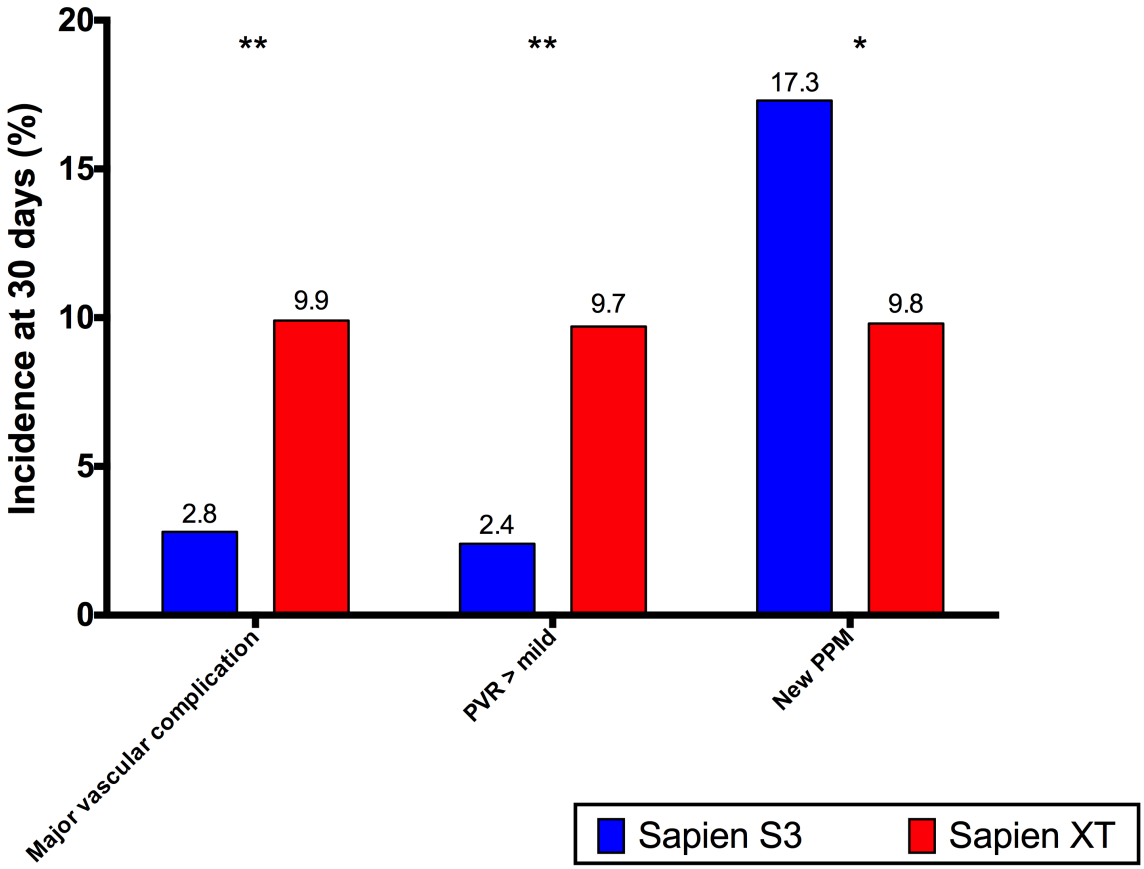

Figure 2.4. Incidence of major vascular complication, > mild PVR and new PPM. 30-day incidence (%) of major vascular complication, > mild PVR and new PPM in the S3-THV group (blue bars) and the XT-THV group (red bars). * = $p < 0.05$. ** = $p < 0.0001$.

Acute kidney injury was 10 times lower in the S3-THV group than the XT-THV group (1.1% vs. 13.6%, $p<0.0001$). There were no statistically significant differences between groups with respect to stroke, myocardial infarction and post-procedural mean gradient > 20 mmHg.

2.4.2. Predictors of new pacemaker implantation in the S3-THV group

Electrocardiographic and angiographic characteristics of patients in the S3-THV group that required a new PPM are displayed in **Tables 2.5 and 2.6**. Implantation depth in the S3-

THV group was 5.1 ± 2.5 mm on the septal side (non-coronary cusp) and 5.2 ± 2.0 mm on the non-septal side (left coronary cusp). According to multivariate analysis, independent predictors of new permanent pacemaker implantation were pre-procedural complete right bundle branch block (RBBB) (OR = 4.9; 95%CI: 1.88 - 12.95; p=0.001), PR duration (OR = 1.14 per 10 msec increment; 95%CI: 1.00 - 1.29; p=0.05) and device lack of coaxiality during deployment (OR = 1.13 per 1 mm increment; 95%CI: 1.00 - 1.29; p=0.05). Device implantation depth was not a predictor of new pacemaker implantation in our series.

Table 2.5. Electrocardiographic and angiographic characteristics according to new PPM requirement in the S3-THV group.

Variable	**New PPM (n=43)**	**No PPM (n=201)**	**p-value**
Complete RBBB	12 (32.4)	17 (9.5)	0.001
Complete LBBB	0 (0)	14 (7.8)	0.14
Fascicular block	12 (32.4)	33 (18.4)	0.07
QRS duration, ms	108 ± 26	101 ± 23	0.10
PR duration, ms	196 ± 37	183 ± 30	0.04
Implant depth (septal), mm	5.3 ± 2.4	5.0 ± 2.6	0.67
Implant depth (non-septal), mm	4.9 ± 2.4	5.2 ± 1.9	0.64
Device lack of coaxiality during deployment, mm	4.0 ± 3.6	2.9 ± 2.5	0.06

Values are mean ± SD or n (%). LBBB = left bundle branch block; RBBB = right bundle branch block.

Table 2.6. Predictors of new pacemaker implantation in the S3 group.

Variable	Univariate analysis		Multivariate analysis		
	OR	p-value	OR	95% CI	p-value
Complete RBBB	4.60	< 0.001	4.90	1.88 - 12.95	0.001
Complete LBBB	1	1	-	-	-
Fascicular block	2.12	0.06	1.88	0.71 - 5.00	0.20
QRS duration (per 10 msec increment)	1.12	0.10	0.87	0.65 - 2.72	0.345
PR duration (per 10 msec increment)	1.14	0.05	1.14	1.00 - 1.29	0.05
Implant depth (septal, per 1 mm increment)	1.05	0.66	-	-	-
Implant depth (non-septal, per 1 mm increment)	0.94	0.63	-	-	-
Device lack of coaxiality during implant (per 1 mm increment)	1.13	0.07	1.13	1.00 - 1.29	0.049

Abbreviations as per Table 2.5.

2.5. Discussion

To our knowledge, this is one of the largest observational studies to date comparing the newer balloon-expandable S3-THV to the XT-THV in an all-comer population. The major findings are as follows: 1) The S3-THV is associated with similar adjusted 30-day and one-year mortality rates compared to the XT-THV 2) The S3-THV is associated with 4-fold lower rates of both major vascular complications and PVR compared to the XT-THV; 3) The S3-THV is associated with twice the rate of new PPM implantation compared to the XT-THV; 4) Independent predictors of new pacemaker included pre-procedural complete RBBB and PR duration, and lack of device coaxiality during implant.

Mortality

In a recent study, all-cause 30-day mortality rates were reported between 0% and 17.5%, with a pooled estimate rate of 5.7% for all second-generation THVs (24). Reported 30-

day mortality rates with the S3-THV ranges from 0.5% to 4.5% (16,17,25). We report also a low 30-day mortality of 3.5% in the S3-THV cohort that was not statistically lower than the 8.7% rate of the XT-THV group after covariates adjustment. The low 30-day mortality speaks to the advancement of TAVI in regard to valve design improvement, increased operator experience, improved patient selection and procedural pre-planning, but also the lower baseline risk profile of TAVI patients.

Vascular complications

One of the shortcomings of TAVI is the association of major vascular complications with mortality (10). Sheath size, severe ilio-femoral artery calcification, sheath external diameter to minimal femoral diameter artery ratio (≥1.05), early site experience and early operator experience, have all been previously associated with major vascular complications(13,26,27). The S3-THV, with the lower profiles of its 14 and 16-F sheaths and the expanding properties of its E sheath, allows TAVI to be performed in patients with smaller arteries and for it to be safer in patients with larger arteries (28). This is reflected in our series by the significant increase in proportion of transfemoral procedures. Three studies reported rates of major vascular complications of 4.5%, 5,2% and 3.6%, reflecting increased safety compared to the XT-THV (16,17,25). We observed a similar rate of 2.9 % in our S3-THV cohort, despite seeing the number operators performing TAVI increase from 4 to 9 between 2013 and 2015.

Para-valvular regurgitation

Patients with more than mild PVR have lower short- and long-term survival than those with trivial or mild PVR, making this an important echocardiographic outcome (29,30). In the PARTNER trial, moderate or severe PVR was seen in 11.8% of patients implanted with the Edwards SAPIEN valve(31). In the France 2 Registry, it was reported in 12.2% (32). We found similar rates of PVR in the XT-THV group. In contrast, the S3-THV group had four times less PVR. Our 2.4% >mild PVR rate in the S3-THV group is comparable to other reports that showed a PVR range between 0% and 3.8%(25,33). The reduced rate of PVR can be explained by improved annular sealing by the external cuff. Whether the decreased PVR

rate with the S3 device could translate into improved long-term outcomes should be evaluated in long-term registries.

Permanent pacemaker implantation

The need for new PPM implantation following TAVI may be correlated to prognosis (34-36). As the S3-THV valve frame has greater height than the XT-THV, it may extend deeper into the LVOT after deployment(15,16). Stent frame extension in the LVOT, i.e. depth of implant, has been shown to be a predictor of PPM implantation(37).

Preliminary data on the S3-THV device from the pivotal SAPIEN 3 trial have shown an increased 30-day PPM implantation rate (13.3%), despite excluding patients with LBBB, RBBB and PR > 200 ms (38). Similarly, the Swiss registry showed an increased rate of PPM with the S3-THV of 17% compared to 11 % with the XT-THV valve(16). Our study showed similar results with a rate of 17.3% in S3-THV versus 9.8% in XT-THV. As reported by others, independent predictors of new permanent pacemaker implantation in the S3-THV group included complete right bundle branch block and PR duration(25).

However, implant depth was not a predictor of new PPM in our study. Rather, lack of coaxiality of the device during its deployment was independently associated to new PPM. These findings may be explained by flaws in the way depth is estimated before the prosthesis is deployed, and by flaws in the way depth is measured after it is deployed.

Before the prosthesis is deployed, the aortic annulus is seen in a coaxial projection, with the three cusps aligned. This projection is determined from the MSCT and confirmed during the procedure by aortography. However, the device positioned in the annulus, before deployment, is not necessarily coaxial. This may be difficult to appreciate because, unlike the Corevalve, the XT-THV and the S3-THV do not have a ring at their extremity. This lack of device coaxiality before deployment can induce flaws in the estimation of depth due to parallax error(18,39). In our experience, lack of device coaxiality induces underestimation of implant depth. In other words, the less coaxial the device, the higher it will look, and the more the operator will want to push it deeper. This increases the true depth of implant and therefore risk of conduction disturbance and new PPM.

After the prosthesis is deployed, measurement of depth of implant can also be flawed by parallax error. Indeed, the projection in which depth is measured is not the one in which the device was deployed. After deployment, the device is not necessarily coaxial. The projection is therefore modified to obtain device coaxiality and this is when final aortography is performed and depth is measured. In this new projection, however, the aortic annulus is no longer coaxial (18,39). An example of this is provided in **Figure 2.5**, where two cusps are seen at different levels on the septal side. Proper localization of the hinge point between the device and sinus of Valsalva, and therefore proper implant depth measurement, can be difficult in such circumstances and prone to parallax error. To adequately measure device implantation depth, future studies should rely on post-procedural MSCT. This would allow measurement of depth all around the annulus, and not only on the septal and non-septal sides. Alternatively, computer programs that allow the operator to find the unique projection where both the device and the annulus are coaxial could be used. This would be the optimal projection to deploy the device, do the final aortography and measure depth. **Figure 2.6** illustrates the coaxiality concept.

Figure 2.5

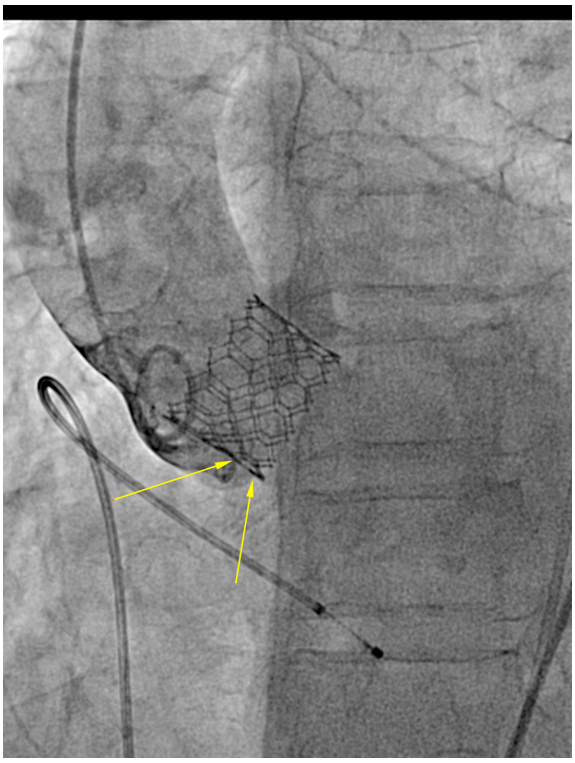

Figure 2.5. Example of difficult depth measurement. In this case, the projection has been modified after implant so the device appears coaxial. However, the annulus is no longer coaxial: two aortic cusps are seen at different levels on the septal side (arrows), making difficult the localization of the hinge point and therefore the measurement depth of implant.

Figure 2.6

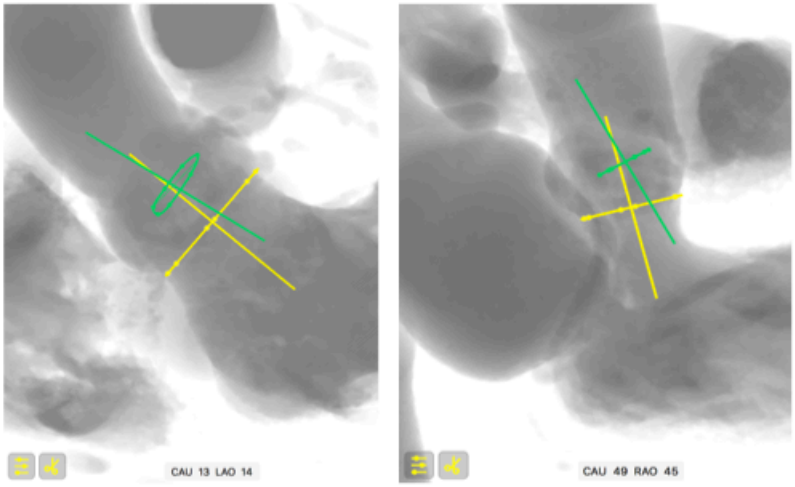

Figure 2.6. Coaxiality Concept. In this example, the aortic annulus is drawn in yellow and the device is in green. Two different C-arm angulations of the same structures are shown. If the operator selects the angulation on the left for deployment, estimation of implant depth will be more difficult as one of the structures (the device) is not coaxial. Notice that in both angulations, the annulus (yellow) is coaxial.

Limitations

This retrospective study reflects a single-center experience. Groups had significant baseline characteristics differences and adjustment for these may be incomplete or flawed by residual confounding. Although PVR was assessed by experienced echocardiographers and reported according to VARC-2 criteria, the absence of a central core lab may lead to some heterogeneity in assessment of this outcome. In addition, we did not analyze the timing of conduction disturbances. Indeed, one of the possible reasons for higher PPM in the S3-THV group may be a delayed inflammatory process caused by the skirt polymer, in addition to its immediate mechanical effect on the conduction system. To reflect contemporary practice of TAVI, we collected ECG data, depth and device coaxiality only in the S3-THV group. As it is difficult to measure device coaxiality before implant on a crimped valve, we used the device coaxiality at the end of deployment. Measurements were taken as the balloon was deflated and the patient still under rapid pacing so that measurements reflected pre-deployment status. In

addition, device coaxiality measurements were only available for procedures done in the catheterization laboratory, thereby excluding patients with non-transfemoral access.

2.6. Conclusions

The third generation Edwards S3-THV is associated to improved outcomes with lower rates of major vascular complications and PVR but higher rates of new PPM compared to its predecessor, the XT-THV.

These results are encouraging in the endeavor to take TAVI to lower risk populations. Our findings highlight the increased importance to adequately visualize the S3-THV in relation to the aortic valvular complex during deployment, in order to improve device positioning and potentially mitigate new PPM requirements.

2.7. References

1. Makkar RR, Fontana GP, Jilaihawi H et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. The New England journal of medicine 2012;366:1696-704.
2. Lefevre T, Kappetein AP, Wolner E et al. One year follow-up of the multi-centre European PARTNER transcatheter heart valve study. European heart journal 2011;32:148-57.
3. Thomas M, Schymik G, Walther T et al. One-year outcomes of cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. Circulation 2011;124:425-33.
4. Kodali SK, Williams MR, Smith CR et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. The New England journal of medicine 2012;366:1686-95.
5. Genereux P, Head SJ, Van Mieghem NM et al. Clinical outcomes after transcatheter aortic valve replacement using valve academic research consortium definitions: a

weighted meta-analysis of 3,519 patients from 16 studies. J Am Coll Cardiol 2012;59:2317-26.

6. Toggweiler S, Humphries KH, Lee M et al. 5-year outcome after transcatheter aortic valve implantation. J Am Coll Cardiol 2013;61:413-9.
7. Mack MJ, Leon MB, Smith CR et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015;385:2477-84.
8. Smith CR, Leon MB, Mack MJ et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. The New England journal of medicine 2011;364:2187-98.
9. Adams DH, Popma JJ, Reardon MJ. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;371:967-8.
10. Genereux P, Webb JG, Svensson LG et al. Vascular complications after transcatheter aortic valve replacement: insights from the PARTNER (Placement of AoRTic TraNscathetER Valve) trial. J Am Coll Cardiol 2012;60:1043-52.
11. Roten L, Wenaweser P, Delacretaz E et al. Incidence and predictors of atrioventricular conduction impairment after transcatheter aortic valve implantation. Am J Cardiol 2010;106:1473-80.
12. Kodali S, Pibarot P, Douglas PS et al. Paravalvular regurgitation after transcatheter aortic valve replacement with the Edwards sapien valve in the PARTNER trial: characterizing patients and impact on outcomes. Eur Heart J 2015;36:449-56.
13. Barbanti M, Binder RK, Freeman M et al. Impact of low-profile sheaths on vascular complications during transfemoral transcatheter aortic valve replacement. EuroIntervention 2013;9:929-35.
14. Binder RK, Schafer U, Kuck KH et al. Transcatheter aortic valve replacement with a new self-expanding transcatheter heart valve and motorized delivery system. JACC Cardiovasc Interv 2013;6:301-7.
15. Binder RK, Rodes-Cabau J, Wood DA, Webb JG. Edwards SAPIEN 3 valve. EuroIntervention 2012;8 Suppl Q:Q83-7.

16. Binder RK, Stortecky S, Heg D et al. Procedural Results and Clinical Outcomes of Transcatheter Aortic Valve Implantation in Switzerland: An Observational Cohort Study of Sapien 3 Versus Sapien XT Transcatheter Heart Valves. Circ Cardiovasc Interv 2015;8.
17. Nijhoff F, Abawi M, Agostoni P, Ramjankhan FZ, Doevendans PA, Stella PR. Transcatheter aortic valve implantation with the new balloon-expandable Sapien 3 versus Sapien XT valve system: a propensity score-matched single-center comparison. Circulation Cardiovascular interventions 2015;8:e002408.
18. Piazza N, Lauzier P, Mylotte D. Transcatheter Aortic Valve Replacement and New Conduction Abnormalities/Permanent Pacemaker: Can We Achieve the Intended Implant Depth? JACC Cardiovasc Interv 2016;9:255-8.
19. Baumgartner H, Hung J, Bermejo J et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. Eur J Echocardiogr 2009;10:1-25.
20. Webb JG, Altwegg L, Masson JB, Al Bugami S, Al Ali A, Boone RA. A new transcatheter aortic valve and percutaneous valve delivery system. J Am Coll Cardiol 2009;53:1855-8.
21. Nijhoff F, Agostoni P, Samim M et al. Optimisation of transcatheter aortic balloon-expandable valve deployment: the two-step inflation technique. EuroIntervention 2013;9:555-63.
22. Gilard M, Eltchaninoff H, Iung B et al. Registry of transcatheter aortic-valve implantation in high-risk patients. N Engl J Med 2012;366:1705-15.
23. Kappetein AP, Head SJ, Genereux 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;145:6-23.
24. Athappan G, Gajulapalli RD, Tuzcu ME, Svensson LG, Kapadia SR. A systematic review on the safety of second-generation transcatheter aortic valves. EuroIntervention 2016;11:1034-43.
25. Husser O, Pellegrini C, Kessler T et al. Outcomes After Transcatheter Aortic Valve Replacement Using a Novel Balloon-Expandable Transcatheter Heart Valve: A Single-Center Experience. JACC Cardiovasc Interv 2015;8:1809-16.

26. Hayashida K, Lefevre T, Chevalier B et al. Transfemoral aortic valve implantation new criteria to predict vascular complications. JACC Cardiovasc Interv 2011;4:851-8.
27. Gurvitch R, Toggweiler S, Willson AB et al. Outcomes and complications of transcatheter aortic valve replacement using a balloon expandable valve according to the Valve Academic Research Consortium (VARC) guidelines. EuroIntervention 2011;7:41-8.
28. Hamm CW, Mollmann H, Holzhey D et al. The German Aortic Valve Registry (GARY): in-hospital outcome. Eur Heart J 2014;35:1588-98.
29. Genereux P, Kodali S, Hahn R, Nazif T, Williams M, Leon MB. Paravalvular leak after transcatheter aortic valve replacement. Minerva Cardioangiol 2013;61:529-37.
30. Jerez-Valero M, Urena M, Webb JG et al. Clinical impact of aortic regurgitation after transcatheter aortic valve replacement: insights into the degree and acuteness of presentation. JACC Cardiovasc Interv 2014;7:1022-32.
31. Leon MB, Smith CR, Mack M et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. The New England journal of medicine 2010;363:1597-607.
32. Auffret V, Bedossa M, Boulmier D et al. [From FRANCE 2 to FRANCE TAVI: are indications, technique and results of transcatheter aortic valve replacement the same?]. Presse Med 2015;44:752-60.
33. Webb J, Gerosa G, Lefevre T et al. Multicenter evaluation of a next-generation balloon-expandable transcatheter aortic valve. J Am Coll Cardiol 2014;64:2235-43.
34. Buellesfeld L, Stortecky S, Heg D et al. Impact of permanent pacemaker implantation on clinical outcome among patients undergoing transcatheter aortic valve implantation. J Am Coll Cardiol 2012;60:493-501.
35. Urena M, Webb JG, Tamburino C et al. Permanent pacemaker implantation after transcatheter aortic valve implantation: impact on late clinical outcomes and left ventricular function. Circulation 2014;129:1233-43.
36. Tamburino C, Capodanno D, Ramondo A et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. Circulation 2011;123:299-308.

37. Binder RK, Webb JG, Toggweiler S et al. Impact of post-implant SAPIEN XT geometry and position on conduction disturbances, hemodynamic performance, and paravalvular regurgitation. JACC Cardiovasc Interv 2013;6:462-8.
38. Binder RK, Rodes-Cabau J, Wood DA et al. Transcatheter aortic valve replacement with the SAPIEN 3: a new balloon-expandable transcatheter heart valve. JACC Cardiovasc Interv 2013;6:293-300.
39. Spaziano M, Theriault-Lauzier P, Meti N et al. Optimal fluoroscopic viewing angles of left-sided heart structures in patients with aortic stenosis and mitral regurgitation based on multislice computed tomography. J Cardiovasc Comput Tomogr 2015.

Chapitre 3. Résultats des avancées techniques: l'exemple du TAVI sans prédilatation

Cet article original a été publié dans le *Canadian Journal of Cardiology*:
Spaziano M, Sawaya F, Chevalier B, Roy A, Neylon A, Garot P, Hovasse T, Benamer H, Romano M, Unterseeh T, Bouvier E, Cormier B, Morice MC, Lefèvre T. Comparison of Systematic Predilation, Selective Predilation, and Direct Transcatheter Aortic Valve Implantation With the SAPIEN S3 Valve. Can J Cardiol. 2017 Feb;33(2):260-268. doi: 10.1016/j.cjca.2016.09.007. PubMed PMID: 28034581.

Contribution des auteurs

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Bernard Chevalier: Conception du devis, direction générale et correction de l'article

Thierry Lefèvre: Conception du devis, direction générale et correction de l'article

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Comparison of Systematic Pre-dilatation, Selective Pre-dilatation and Direct TAVI with the SAPIEN S3 Valve

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Short title: Systematic or Selective Pre-dil vs. direct TAVI

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Word Count: 5616

Conflicts of Interest:

Dr. Thierry Lefèvre is a proctor for Edwards LifeSciences. Dr. Bernard Chevalier is a proctor for Medtronic. All other authors report no conflict of interest regarding this manuscript.

3.1. Abstract

Background: Despite previously described feasibility, direct TAVI with the Sapien S3 device (S3-THV) has not been compared to either a systematic or a selective pre-dilatation approach.

Methods: Patients undergoing pre-dilatation were divided in a systematic group (regardless of anatomical features) and a selective group (in the context of high valvular calcium burden). Both groups were matched in a 2:1 fashion to patients that underwent direct TAVI. Outcomes were assessed according to VARC-2 criteria.

Results: 281 patients underwent TAVI with the S3-THV in our center. Of these, 58 underwent pre-dilatation before device implantation (systematic: n=26; selective: n=32). Procedural success was achieved in all patients. Patients in the selective pre-dilatation group had severe valve calcification volume, more than double that of the systematic group (445 ± 306 vs. 970 ± 578 mm3, respectively; $p<0.0001$).

There was a trend for less post-dilatation in the systematic group compared to the selective group (4 vs. 19%, respectively; $p=0.09$). Device malposition necessitating a second device to be implanted occurred in 3 cases of the direct TAVI patients (5%) and none of the pre-dilatation patients (p=NS). 30-day and 1-year mortality rates were similar between the direct TAVI patients and their pre-dilatation counterparts.

Conclusions :In patients with moderate aortic valve calcification burden, direct TAVI appears to be feasible and safe. In those with high calcium burden, pre-dilatation should be considered, after taking into account individual risk profiles.

3.2. Brief Summary

This matched retrospective study sought to compare systematic aortic valve pre-dilatation, selective pre-dilatation and direct TAVI with the Sapien S3 device.

Mortality rates were similar between the direct TAVI and pre-dilatation patients, but direct TAVI patients had a non-significantly higher risk of device malposition.

In patients with moderate aortic valve calcification burden, direct TAVI appears to be feasible and safe. In those with high calcium burden, pre-dilatation should be considered.

3.3. Introduction

Transcatheter aortic valve implantation (TAVI) has gained rapid acceptance for patients with severe aortic stenosis (1-4) and has recently been associated with excellent short- and mid-term outcomes in patients at intermediate risk (5-9). In order to justify the extension of the procedure to lower risk patients, continuous refinement of techniques and devices should be sought to further improve outcomes (10).

Aortic valve pre-dilatation has been traditionally performed before TAVI (11). This is done to facilitate device entry and positioning in the stenotic orifice. Other potential advantages of pre-dilatation before TAVI are to optimize device expansion by reducing radial counterforces, confirm device size selection, and appreciate the risk of coronary occlusion (12). However, the risks of inappropriate device sizing and of coronary occlusion have been mitigated by the regular use of pre-procedural multi-slice computed tomography.

Aortic valve pre-dilatation has been associated with risk of stroke due to displacement of calcified debris (13,14), of conduction disturbance (15,16) and of ventricular arrthymia. It has also been associated with worse hemodynamic outcomes in patients with depressed ejection fraction because of the additional pacing run before TAVI (17). If severe aortic insufficiency develops after pre-dilatation, it may lead to hemodynamic collapse, requiring emergent rather than controlled valve implantation. Finally, it may prolong procedure duration and increase the amount of contrast used. In this context, the practice of TAVI without pre-

dilatation (direct TAVI) has emerged. The feasibility and safety of direct TAVI have been reported in small cohorts with the Sapien XT(18), the Corevalve(12) and, more recently, with the Sapien S3 transcatheter heart valve (S3-THV) (19).

In the effort to balance risks and benefits of pre-dilatation before TAVI, three strategies can be adopted: 1) systematic pre-dilatation of all TAVI patients; 2) selective pre-dilatation only in patients displaying certain anatomical features, such as high valvular calcium burden; 3) direct TAVI in all patients. These three strategies have yet to be compared in a randomized trial.

The purpose of the present study was to compare procedural and clinical outcomes of patients undergoing TAVI with systematic or selective pre-dilatation to those of matched patients who underwent direct TAVI with the S3-THV.

3.4. Methods

Patient population and procedure

To compare the clinical outcomes of patients undergoing aortic valve pre-dilatation to those undergoing direct TAVI, we first retrospectively identified all patients treated with the S3-THV at our institution. Patients who had pre-dilatation before TAVI were divided into two groups: those in whom pre-dilatation was done systematically regardless of anatomical features (either required in the context of a trial, or because of operator preference), and those in whom pre-dilatation was performed selectively because of extensive calcification of the valve leaflets. Patients in both the systematic and the selective pre-dilatation groups were then matched in a 2:1 fashion to patients that underwent direct TAVI. Both the systematic and selective pre-dilatation groups were then compared to their direct TAVI counterparts with respect to procedural, short- and long-term clinical outcomes.

A multidisciplinary heart team involving at least one clinical cardiologist, one interventional cardiologist and one cardiac surgeon discussed all cases and consensus was achieved regarding therapeutic strategy. All patients provided informed written consent for the procedure and data collection, and the local ethics committee approved the study.

Pre-procedural planning

All patients underwent pre-procedural transthoracic echocardiography and multi-slice computed tomography following recommended guidelines (20). Multi-slice computed tomography evaluation included measurements of the aortic valve complex with dedicated software (Philips Brilliance 64-slice MDCT scanner, Philips Healthcare, Best, the Netherlands). Aortic valve calcification volume was quantified and a threshold of 600 to 650 Hounsfield units was used in order to optimize signal-to-noise ratio (21-24). Valve prosthesis size was selected in accordance with the manufacturer's recommendations after taking into account other anatomic features such as the presence and location of calcification, eccentricity of the aortic annulus and dimensions of the sinuses of Valsalva and sino-tubular junction in case of borderline sizing ranges. Cardiac catheterization and femoral angiography were performed prior to the procedure to assess for concomitant coronary artery disease and femoro-iliac vessel size, calcifications, narrowing or tortuosity, respectively.

Study device

The S3-THV design has been described in detail previously (16,25). It consists of bovine pericardium sewn to a balloon-expandable cobalt-chromium tubular frame and is available in the 23, 26, and 29 mm sizes. It is implanted with the use of the low-profile Commander delivery catheter, which employs 14 French (THV sizes 23 and 26 mm) or 16 French (THV size 29 mm) expandable sheaths (eSheath, Edwards Lifesciences, Inc.). The S3-THV stent was designed with a frame geometry that provides greater radial force and larger cells towards the coronary arteries than that of its predecessor, the Sapien XT valve. The device also includes an outer polyethylene terephthalate fabric seal designed to minimize para-valvular regurgitation (PVR).

Study procedure

The technique of S3-THV valve implantation has been described in detail elsewhere(16,25). In our center, all trans-femoral cases were performed under local anesthesia and conscious sedation in the catheterization laboratory. The selected femoral artery was "pre-closed" with two 6-Fr suture-mediated closure devices Perclose ProGlide (Abbott Laboratories, Abbot Park, Illinois). After crossing the aortic valve, a 260-cm-long 0.035-inch

Amplatz Extra-Stiff J-tip guidewire (COOK, Denmark) or the dedicated Safari wire (Boston scientific, USA) was placed in the left ventricle. Aortic valve pre-dilatation, if performed, was done under rapid ventricular pacing using the balloon provided with the S3-THV. A 20 mm balloon is provided with the 23 mm valve, a 23 mm balloon with the 26 mm valve, and a 25 mm balloon with the 29 mm valve.

Device positioning was based on fluoroscopy using annular calcifications as landmarks along with serial 8 to 20 ml supra-annular aortography to validate its position. The prosthesis was delivered under rapid ventricular pacing, in one slow inflation (5–10 s). Prosthesis position and function, and patency of the coronary ostia were evaluated by transthoracic echocardiography and angiography. Significant aortic regurgitation was treated by post-dilatation adding 1 to 3 ml of contrast in the delivery system balloon or, if the valve was malpositioned, by second valve implantation. Removal of the sheath was cautiously performed with contralateral angiography to detect ilio-femoral complications. The femoral access site was then closed using the Proglide devices.

In the absence of any conduction abnormality, the pacing lead was removed at the end of the procedure. Patients were monitored in the intensive care unit for at least 24 h after valve implantation. For the transapical and transaortic cases the procedure was performed in a dedicated hybrid room using standard technique (26).

Data collection and study endpoints

The primary endpoint was 30-day mortality. Secondary endpoints consisted of 1-year mortality, post-dilatation, stroke, myocardial infarction, annulus rupture, new permanent pacemaker (PPM) implantation, major vascular complication, PVR greater than mild, acute kidney injury and post-procedural mean gradient. Endpoints were defined according to the VARC-2 criteria (27).

Clinical and echocardiographic data at baseline and follow-up were prospectively collected by dedicated personnel and entered in a local database and a national registry (FRANCE-TAVI) (28). Data from the ECGs and multi-slice computed tomography were retrospectively collected by the co-authors and added to the local database.

Statistical analysis

Continuous data are reported as mean ± standard deviation, and categorical variables are reported as number of patients and percentages. Initially, patients in the pre-dilatation group were compared to those in the direct TAVI group for baseline characteristics and outcomes. Next, patients in the pre-dilatation group were separated into a selective subgroup and a systematic subgroup. Patients in both these subgroups were matched (2:1) to patients in the direct TAVI group using the following criteria: age, sex, access site and aortic valve calcium volume. Matching was performed using a nearest neighbor matching scheme through a greedy algorithm. Random look-up was performed. No replacements were allowed. The calipers for age and calcium volume were 3 years and 300 mm3, respectively.

All comparisons between groups were done using Fisher's exact test for categorical data and Student's t-test or Mann-Whitney's U test for continuous data, as appropriate. Events are reported as counts of first occurrence per type of event. One-year survival data was estimated using the Kaplan-Meier method and comparisons were done using the log-rank test. Patients with previous pacemaker implantation were excluded from analyses pertaining to the outcome of new pacemaker requirement. P-values for this specific analysis were adjusted for baseline ECG characteristics (right bundle branch block) using logistic regression. A p-value <0.05 was considered significant. Statistical analyses were performed with SPSS version 23 (IBM Corp, Armonk, NY).

3.5. Results

Between September 2014 and December 2015, 281 patients underwent TAVI with the S3-THV in our center. Of these, 58 underwent pre-dilatation before device implantation (systematic pre-dilatation: n=26; selective pre-dilatation: n=32) **(Figure 1).** For all these patients, the decision to pre-dilate was made before the procedure (mandated by a reseach protocol: n=14; operator preference: n=12), i.e. there were no cases of ad hoc pre-dilatation in the context of impossibility to advance the device through the stenotic orifice. However, in 3 direct TAVI cases, it was necessary to inflate the distal part of the delivery system balloon by 2-3 mL to cross the valve.

Figure 3.1-A

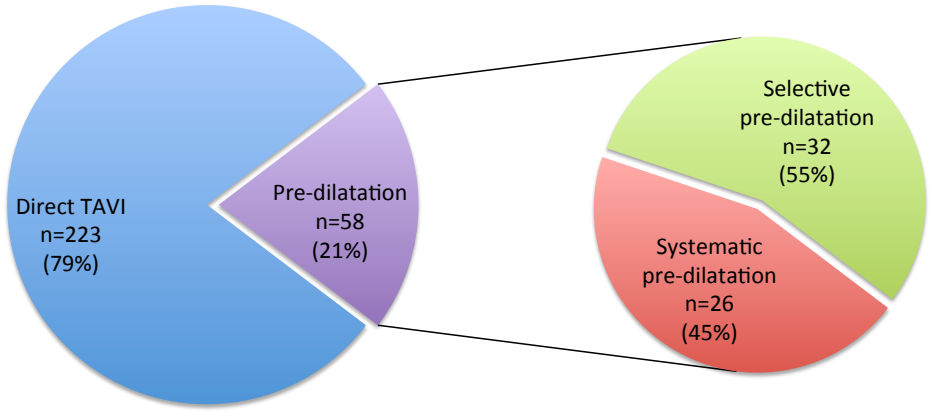


Figure 3.1-B

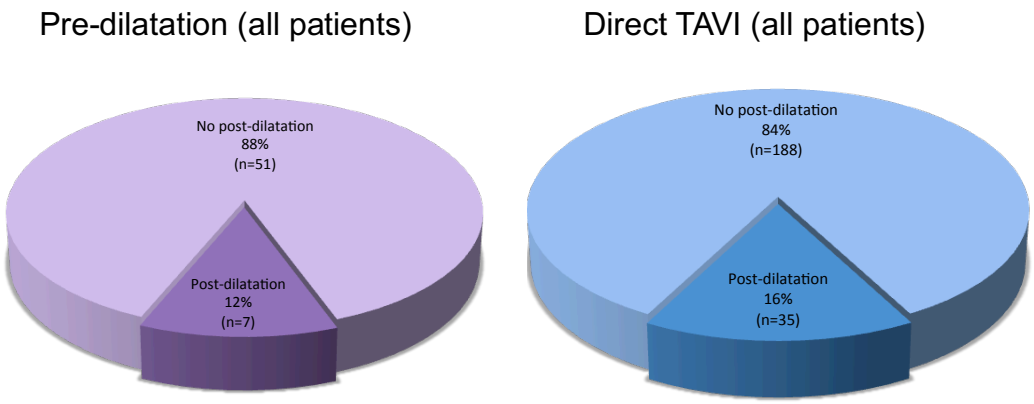


Figure 3.1-C

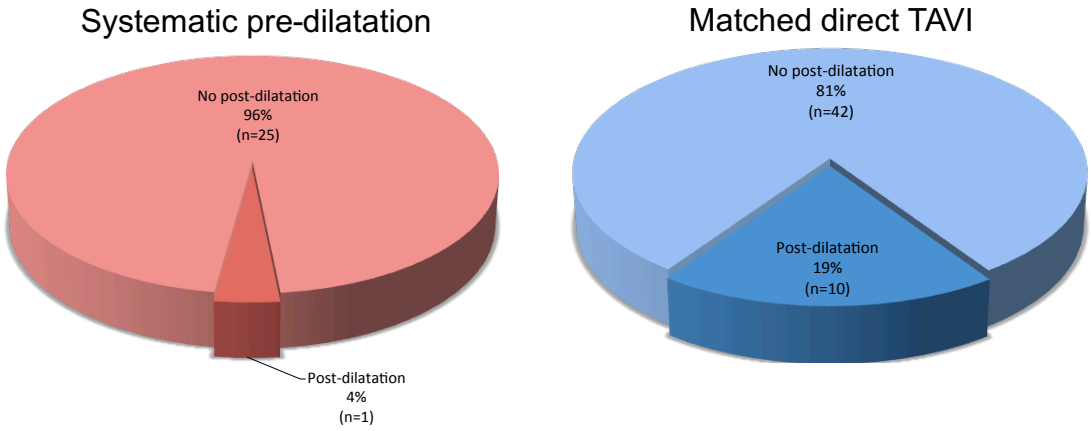


Figure 3.1-D

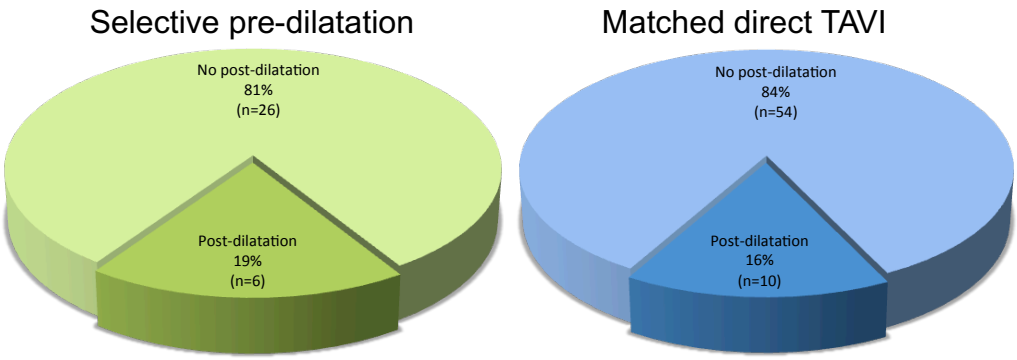


Figure 3.1. Distribution of total population between direct TAVI and pre-dilatation, either systematic or selective (Figure 3.1-A). Comparison of post-dilatation requirement between all pre-dilatation and all direct TAVI (Figure 3.1-B). Comparison of post-dilatation requirement between each pre-dilatation group and their matched direct TAVI counterparts (Figures 3.1-C and 3.1-D).

3.5.1. Baseline characteristics

All patients

Baseline characteristics were similar in pre-dilatation and direct TAVI patients. **(Supplemental Table S3.1 in Annex 3)** Mean age in the total cohort was 82.7 ± 7.1 years (Pre-dilatation: 83.6 ± 6.0; Direct TAVI: 82.5 ± 7.3; p=0.28). Risk scores were also similar between patients who underwent pre-dilatation and those who did not. However, patients who underwent pre-dilatation had higher mean aortic gradient (50.7 ± 14.8 mmHg vs. 45.6 ± 15.1 mmHg; p=0.02) and were more likely to have pulmonary hypertension (54 vs. 37%; p=0.04). **(Supplemental Table S3.2)**

Systematic vs. Selective Pre-dilatation

Within the pre-dilatation group, the selective pre-dilatation subgroup was significantly younger than the systematic subgroup (82.0 ± 5.9 years vs. 85.6 ± 5.6, respectively; p=0.02). **(Table 3.1)** Patients in the selective group were also more likely to be males (56% vs. 23%; p=0.02) and had a trend for lower Logistic Euroscore (14.1 ± 8.9 vs. 19.1 ± 13.5 %; p=0.10). **(Table 3.1)** Echocardiographic parameters were comparable between the selective and the

systematic pre-dilatation groups. **(Table 3.2)** Patients in the selective group had significantly longer QRS duration than those in the systematic group (103 ± 17 vs. 94 ± 15 ms; p=0.05).

Patients in the systematic pre-dilatation group had moderate valve calcification volume, less than half of that in the selective group (445 ± 306 vs. 970 ± 578 mm^3, respectively; p<0.0001). In the total population, the lowest tertile of valvular calcium volume spanned from 77 to 435 mm^3, and the highest tertile from 803 to 2075 mm^3. **(Table 3.2) (Supplemental Figure S3.1)**

Table 3.1. Baseline clinical characteristics of matched patients.

Variable	Systematic pre-dilatation (n=26)	Direct TAVI (matched) (n=52)	p-value	Selective pre-dilatation (n=32)	Direct TAVI (matched) (n=64)	p-value	Systematic vs. Selective p-value
Age	85.6 ± 5.6	85.0 ± 5.4	0.65	82.0 ± 5.9	82.2 ± 5.7	0.91	0.02
Male sex	6 (23)	13 (25)	1	18 (56)	37 (58)	1	0.02
STS-PROM, %	6.4 ± 2.9	6.0 ± 4.3	0.68	5.4 ± 3.6	4.5 ± 2.5	0.18	0.26
Logistic EuroSCORE, %	19.1 ± 13.5	15.8 ± 9.5	0.21	14.1 ± 8.9	15.9 ± 9.1	0.38	0.10
NYHA Class 3 or 4	17 (65)	25 (49)	0.23	14 (45)	33 (58)	0.37	0.18
History of syncope	1 (4)	0 (0)	0.40	0 (0)	0 (0)	1	1
Atrial arrhythmia (flutter or fibrillation)	6 (23)	16 (31)	0.60	9 (29)	12 (21)	0.44	0.77
Diabetes	4 (15)	8 (15)	1	8 (25)	16 (25)	1	0.52
Hypertension	18 (72)	34 (76)	0.78	16 (64)	34 (72)	0.59	0.76
Dyslipidemia	10 (40)	21 (47)	0.63	11 (44)	16 (34)	0.45	1
Active smoker	0 (0)	0 (0)	1	0 (0)	1 (2)	1	1
Previous PPM	1 (4)	7 (14)	0.26	4 (13)	8 (13)	1	0.37
Previous PCI	7 (27)	18 (35)	0.61	9 (28)	17 (27)	1	1
Previous CABG	2 (8)	5 (10)	1	3 (9)	11 (18)	0.37	1
Previous SAVR	0 (0)	0 (0)	1	0 (0)	0 (0)	1	1
Previous BAV	0 (0)	0 (0)	1	0 (0)	0 (0)	1	1
Previous stroke	4 (15)	3 (6)	0.21	4 (13)	2 (3)	0.09	1
Peripheral vascular disease	6 (23)	11 (21)	1	7 (22)	20 (31)	0.47	1

eGFR, ml/min/1.73m^2	59.6 ± 31.1	69.1 ± 23.7	0.14	62.7 ± 22.0	68.7 ± 23.0	0.23	0.65
eGFR < 40 ml/min/1.73m^2	6 (23)	3 (6)	0.05	4 (13)	6 (10)	0.73	0.32
Dialysis	0 (0)	0 (0)	1	0 (0)	0 (0)	1	1
Chronic obstructive pulmonary disease	4 (15)	5 (10)	0.47	5 (16)	8 (13)	0.76	1
Body mass index, kg/m^2	25.8 ± 6.2	26.4 ± 5.3	0.66	26.6 ± 5.4	27.1 ± 5.0	0.68	0.64

Values are mean ± SD or n (%). BAV = balloon aortic valvuloplasty; CABG = Coronary artery bypass graft; eGFR = glomerular filtration rate estimated by the MDRD formula; EuroSCORE = European System for Cardiac Operative Risk Evaluation; NYHA = New York Heart Association functional class; PPM = permanent pacemaker; PCI = Percutaneous coronary intervention; SAVR = surgical aortic valve replacement; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

Table 3.2. Baseline echocardiographic, electrocardiographic and MSCT characteristics of matched patients.

Variable	Systematic pre-dilatation (n=26)	Direct TAVI (matched) (n=52)	p-value	Selective pre-dilatation (n=32)	Direct TAVI (matched) (n=64)	p-value	Systematic vs. Selective p-value
LVEF, %	59.6 ± 12.8	57.1 ± 12.8	0.43	55.2 ± 13.4	57.7 ± 12.5	0.38	0.21
LVEF ≤ 30%	1 (4)	4 (8)	0.66	3 (9)	3 (5)	0.66	0.62
Mean aortic gradient, mmHg	50.8 ± 13.2	47.0 ± 13.5	0.24	50.6 ± 16.3	49.1 ± 15.3	0.68	0.95
AVA, cm^2	0.61 ± 0.11	0.66 ± 0.17	0.13	0.64 ± 0.14	0.67 ± 0.16	0.37	0.40
Pulmonary artery systolic pressure, mmHg	44.7 ± 16.7	43.4 ± 15.0	0.74	50.9 ± 14.6	45.2 ± 13.9	0.11	0.16
Pulmonary artery systolic pressure > 50 mmHg	10 (40)	11 (25)	0.28	13 (48)	13 (30)	0.13	0.59
Complete RBBB	1/22 (5)	10/42 (24)	0.08	5/25 (20)	5/49 (10)	0.29	0.19
Complete LBBB	1/22 (5)	3/42 (7)	1	0/25 (0)	3/49 (6)	0.55	0.47
Fascicular block	4 (18)	8 (19)	1	7/25 (28)	9/49 (18)	0.34	0.73
QRS duration, ms	94 ± 15	104 ± 24	0.06	103 ± 17	98 ± 22	0.26	0.05
PR duration, ms	184 ± 24	186 ± 29	0.80	195 ± 53	180 ± 29	0.27	0.42
Aortic valve calcification volume, mm^3	445 ± 306	438 ± 281	0.93	970 ± 578	814 ± 413	0.20	<0.001

Values are mean ± SD or n (%). AVA = aortic valve area; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MSCT = multislice computed tomography; PPM = permanent pacemaker; RBBB = right bundle branch block.

Pre-dilatation vs. Direct TAVI matched comparison

Matching for age, sex, access site and aortic valve calcium volume generated direct TAVI groups comparable to each pre-dilatation group with respect to baseline characteristics. **(Tables 3.1 and 3.2)** Only chronic kidney disease with eGFR < 40 ml/min was significantly more prevalent in the systematic pre-dilatation group compared to the direct TAVI matched group (23 vs. 6%, respectively; p=0.05). There was also a trend for less complete right bundle branch block and shorter QRS duration in systematic pre-dilatation patients compared to their direct TAVI matched counterparts (right bundle branch block: 5 vs. 24%, respectively; p=0.08; QRS duration: 94 ± 15 vs. 104 ± 24 ms, respectively; p=0.06).

3.5.2. Procedural characteristics and outcomes

Patients who underwent pre-dilatation were similar to those who underwent direct TAVI with respect to procedural characteristics. **(Supplemental Table S3.3)**

Within the pre-dilatation group, the systematic and the selective pre-dilatation subgroups differed with respect to approach and device sizing. TAVI was performed via the transfemoral approach in nearly all patients of the systematic group, but in less than three-quarters of patients in the selective group (92 vs. 69%, respectively; p=0.05). **(Table 3.3)** Device size differences between the systematic and the selective groups are mainly related to the difference in sex distribution between groups. As there were significantly more females in the systematic pre-dilatation group, device sizes in that group were significantly smaller than device sizes in the selective group (p=0.03).

Table 3.3. Procedural characteristics of matched patients.

Variable	Systematic pre-dilatation (n=26)	Direct TAVI (matched) (n=52)	p-value	Selective pre-dilatation (n=32)	Direct TAVI (matched) (n=64)	p-value	Systematic vs. Selective p-value
Transfemoral approach	24 (92)	48 (92)	1	22 (69)	44 (69)	1	0.05
Local anesthesia	24 (92)	48 (92)	1	22 (69)	44 (69)	1	0.05
Pre-dilatation balloon size							
20 mm	16 (62)			8 (25)			
23 mm	6 (23)			14 (44)			
25 mm	4 (15)			10 (31)			
Implanted device size			0.88			0.82	0.03
23 mm	16 (62)	32 (62)		8 (25)	19 (30)		
26 mm	6 (23)	14 (27)		14 (44)	29 (45)		
29 mm	4 (15)	6 (12)		10 (31)	16 (25)		
Valve area oversizing, %	14.9 ± 11.7	14.0 ± 11.9	0.77	9.8 ± 8.5	12.3 ± 8.1	0.23	0.11
Device diameter / Annulus diameter (area-derived)	1.07 ± 0.06	1.07 ± 0.05	0.72	1.04 ± 0.04	1.06 ± 0.04	0.05	0.03
Post-dilatation	1 (4)	10 (19)	0.09	6 (19)	10 (16)	0.77	0.10
Need for second valve implantation	0 (0)	0 (0)	1	0 (0)	3 (5)	0.30	1
Annulus rupture	0 (0)	0 (0)	1	0 (0)	0 (0)	1	1

Conversion to SAVR	0 (0)	1 (2)	1	0 (0)	1 (2)	1	1
Contrast use (ml)	110 ± 36	106 ± 68	0.78	115 ± 38	114 ± 51	0.88	0.62
Fluoroscopy time (min)	18.1 ± 15.5	14.8 ± 5.3	0.33	17.6 ± 9.4	17.6 ± 9.3	1	0.87

Values are mean ± SD or n (%). SAVR = surgical aortic valve replacement.

Pre-dilatation vs. Direct TAVI

Again, the matched direct TAVI groups were comparable to each pre-dilatation group with respect to procedural characteristics. **(Table 3.3)**

Post-dilatation was required in 14.9% of the total cohort. **(Table 3.3)** Only 1 patient in the systematic pre-dilatation group required post-dilatation, whereas 10 patients in the matched moderate calcium direct TAVI group underwent post-dilatation (4 vs. 19%; p=0.10). **(Figure 3.1)** In the high-calcium selective pre-dilatation group, post-dilatation was performed in 19% of patients, a similar proportion to that of the direct TAVI high-calcium matched group (16%; p=0.77).

Device malposition necessitating a second device to be implanted occurred in 3 cases in the total population (1.1%). **(Table 3.3)** All 3 cases occurred in direct TAVI matched to the selective pre-dilatation group. In comparison, no cases of device malposition occurred in either pre-dilatation groups (all p-values non-significant). In addition, both cases of conversion to surgical aortic valve replacement occurred in the direct TAVI groups. No cases of annulus rupture were recorded. Both contrast use and fluoroscopy time were similar between pre-dilatation groups and their matched direct TAVI counterparts.

3.5.3. Post-procedural clinical outcomes

A total of 8 deaths occurred at 30 days in the overall population (2.8%), one in the pre-dilatation group and 7 in the direct TAVI group (2 vs. 4%; p=0.69). **(Supplemental Table S3.4)**

There were no differences in 30-day mortality rates between either the systematic or the selective pre-dilatation groups and their direct TAVI counterparts (systematic vs. direct TAVI: 0 vs. 2%; p=1; selective vs. direct TAVI: 3 vs. 0%; p=0.37). **(Table 3.4)** A total of 3 strokes occurred in the overall population (1.1%). Of those 3 events, 2 occurred in the systematic pre-dilatation group (systematic vs. direct TAVI: 8 vs. 0%; p=0.10). No strokes occurred in any of the other matched groups.

In the total population, 17.8% of patients required a new permanent pacemaker after the procedure because of persistent high-grade atrio-ventricular block.

(Supplemental Table S3.4) In the systematic pre-dilatation subgroup, this occurred in only 1 patient (4%) compared to 9 patients (27%) in the matched direct TAVI group (p=0.03). **(Table 3.4)** After adjusting for baseline complete right bundle branch duration, this difference was no longer statistically significant (p=0.16). In the selective pre-dilatation group, pacemaker implantation rate was 18%. This was similar to pacemaker implantation rate in the matched direct TAVI group (18%; adjusted p-value: 0.94).

Other clinical outcomes including major vascular complication, PVR greater than mild and mean gradient were similar between both pre-dilatation groups and their direct TAVI counterparts. **(Table 3.4)** Kaplan-Meier estimates of 1-year mortality were also similar between groups (systematic: 22.7% vs. direct TAVI: 18.6%; log-rank p=0.53; selective: 21.8% vs. direct TAVI: 25.0%; log-rank p=0.96).

Table 3.4. 30-day and 1-year outcomes of matched patients.

30-day outcome	Systematic pre-dilatation (n=26)	Direct TAVI (matched) (n=52)	p-value	Selective pre-dilatation (n=32)	Direct TAVI (matched) (n=64)	p-value
Death	0 (0)	1 (2)	1	1 (3)	0 (0)	0.37
Stroke	2 (8)	0 (0)	0.10	0 (0)	0 (0)	1
Myocardial infarction	0 (0)	0 (0)	1	0 (0)	0 (0)	1
New pacemaker implantation*	1 (4)	9 (27)	0.16	5 (18)	10 (18)	0.94
Major vascular complication	0 (0)	0 (0)	1	2 (6)	1 (2)	0.26
Paravalvular regurgitation > mild	1 (4)	1 (2)	1	1 (3)	2 (4)	1
Acute kidney injury	1 (4)	0 (0)	0.33	1 (3)	0 (0)	0.33
Mean gradient > 20 mmHg	1 (4)	0 (0)	0.33	1 (3)	0 (0)	0.33
Mean gradient, mmHg	12.7 ± 3.8	12.1 ± 4.1	0.58	11.3 ± 3.2	11.9 ± 9.5	0.73
1-year outcomes						
Any death[§]	5 (22.7)	2 (18.6)	0.53	3 (21.8)	2 (25.0)	0.96

Values are mean ± SD or n (%). * Patients with previous permanent pacemaker were excluded from this analysis; p-value adjusted for RBBB and PR duration. [§] Kaplan-Meier estimate, log-rank p-value.

3.6. Discussion

The major findings of this study are as follows: 1) Implantation of the Sapien S3 valve was successful in all but three patients from the direct TAVI group; 2) All strategies (systematic pre-dilatation, selective pre-dilatation, direct TAVI) had similar low 30-day and 1-year mortality rates; 3) In patients with moderate calcium burden, the direct TAVI approach yielded similar results as pre-dilatation; 4) In patients with heavily

calcified valves, the selective pre-dilatation strategy demonstrated numerically lower risk of valve malposition and need for second valve.

Since the initial report by Grube et al. in 2011 describing the feasibility of direct TAVI (12), multiple small non-matched retrospective studies reiterated the success rates of the procedure (19,29,30). Despite the safety and feasibility of direct TAVI described in these reports, there have been no data on whether direct TAVI with the S3-THV is associated with equivalent results in all-patient subsets. Indeed, Kim et al (19), observed that in patients with high calcium burden, there was higher risk of bailout valvuloplasty due to difficult valve crossing and higher post-implantation gradients in the patients that underwent direct TAVI. Moreover, a study by Dvir et al (31), suggested that inadequate pre-dilatation was a predictor for PVR after TAVI. These events should raise questions on proper patient selection before considering direct TAVI in all.

In our center, pre-dilatation was performed in two different contexts: either systematically in all patients, or selectively in patients with a high calcium burden. We found that baseline characteristics of these two subgroups were different. Patients in the systematic group were older, more likely to be female, had higher risk scores, but lower valve calcification than those in the selective group. Because of these disparities within the pre-dilatation group, we thought that separating both subgroups would allow more meaningful comparisons to direct TAVI. This would also provide insight towards identifying the most appropriate upstream strategy.

Of note, pre-dilatation should be strongly considered in certain clinical contexts regardless of calcium burden: bicuspid valves, annulus in the grey zone for sizing and unusual anatomy such as horizontal aorta. The case of bicuspid valves is extremely important since they are sometimes extremely difficult to cross. In addition, the leaflet opening often directs the device towards the mitral apparatus.

Procedural outcomes and mortality

In patients with moderate valvular calcium burden, systematic pre-dilatation reduced the need for post-dilatation. However, in patients with high calcium burden, selective pre-dilatation did not reduce the need for post-dilatation. Pre-dilatation did, however, numerically reduce the risk of device malpositioning, and therefore the need for

a second device. These are similar findings to those of Kim et al. that showed valve malpositioning in 2 patients with a critically calcified valve(19).

We found high device success rates in all groups with 30-day and 1-year mortality rates comparable to other studies(32,33). Contrary to other reports(19,29), our study showed that direct TAVI was not associated to decreased fluoroscopy time or contrast use. This could be explained by the experience of the operators in performing TAVI, with pre-dilatation not taking more than a few extra minutes of fluoroscopy. Moreover, contrary to other studies(12,19), direct TAVI was not associated to difficulty in device crossing the valve, even in patients with heavily calcified valves. Bailout pre-dilatation was therefore never required. These findings could be explained by the reduced crossing profile of the crimped prosthesis and the tapered nose-cone on the tip of the delivery catheter of the S3-THV(16). We also had no cases of annulus rupture in the total population. This may be due to the reduction in oversizing recommended with the S3-THV compared to previous devices.

Stroke

Nijhoff, Husser and Binder reported a stroke rate of 2.3%, 1.6% and 1.3% with the S3-THV, respectively (32-34). We report a similar risk of stroke at 30 days of 1.1% in the overall cohort. Interestingly, the strokes observed were limited to the systematic pre-dilatation group. The number of balloon inflations each patient receives could explain this. Indeed, in the systematic pre-dilatation group, all patients (100%) undergo two balloon inflations of the aortic valve: the pre-dilatation and the TAVI. One patient even received a third balloon inflation for post-dilatation. In contrast, in the direct TAVI group, two balloon inflations were performed in only 19% of patients, i.e. the patients who underwent post-dilatation. It is unclear why stroke rates were not higher in patients with high calcium burden. This may be due to our small numbers and the low stroke rate (1.1%) observed with the S3 valve. Given the small number of events, our findings may be due to chance. Nevertheless, we agree with suggestions by others to decrease balloon size or be more selective with pre-dilatation (35).

Para-valvular regurgitation

PVR is not infrequently observed after TAVI (36). In patients with more than mild PVR, it is associated with lower survival (37). In our study, moderate to severe PVR was observed in 2.4 % of TAVI cases with no differences between pre-dilatation and direct TAVI. This is comparable to other reports of S3-THV showing a PVR range between 0% and 3.8% (32,38). The low rate of PVR even in patients with high calcium burden can be explained by the improved performance of the S3-THV due to its annular sealing cuff.

Permanent pacemaker implantation

Preliminary data on the S3-THV device from the pivotal SAPIEN 3 trial have shown an increased 30-day PPM implantation rate (13.3%), despite excluding patients with bundle branch block and PR > 200 ms (39). A study by Tarantini et al, also showed an increased rate of PPM (20.7%) with the S3-THV in an all-comer population which improved after adjustments were made to positioning strategies. (40). Similarly, the Swiss registry showed an increased rate of PPM with the S3-THV of 17% (33). Our study showed similar results with a rate of 17.3% in S3-THV in the overall cohort. However, the systematic pre-dilatation group had the lowest rate of PPM implantation (4%) compared to selective (18%) and direct TAVI (18 and 27%) groups. The low rate in the systematic pre-dilatation group could be due to the low prevalence of ECG abnormalities in these patients, as many were enrolled in the initial S3-THV studies, in which right bundle branch block and long PR were exclusion criteria. These patients were also treated by the most experienced operators, which could impact procedural results. The reasons for the higher rate in the matched direct TAVI patients are unclear, as direct TAVI was shown to be protective from conduction abnormalities and PPM after TAVI (41). Nevertheless, after adjustment for baseline ECG characteristics, differences in PPM rates between both groups were no longer statistically significant.

Abramowitz et al. showed that pre-dilatation with moderate size balloons did not affect the conduction system as much as larger balloons and was not associated with increased rates of PPM (29). In our series, the balloon size in the pre-dilatation groups was undersized compared to the mean annulus diameter. This may have contributed to the low PPM rate in the systematic pre-dilatation group.

Limitations

This prospective study reflects a single-center experience with limited numbers after matching. Matching was done on a limited number of variables and residual confounding may persist. Patients in the systematic pre-dilatation group were part of initial S3 studies, which may have introduced both favorable and unfavorable biases. Favorable biases include the use of the transfemoral access in most, the low prevalence of baseline conduction defects and the procedure being performed only by the most experienced operators. Unfavorable biases in this subgroup include higher baseline risk scores and early experience with the new device. There can also be biases in the selective pre-dilatation group as calcium burden may be associated with other prognostically relevant characteristics, such as a higher rate of paravalvular regurgitation(42). All of the above are biases that matching, within small subgroups, may not easily overcome. Larger prospective trials, such as the EASE-IT study, are needed to provide more insights into the direct TAVI approach and its value compared to conventional techniques (43). We believe that our data, along with that of others, supports the use of direct TAVI in patients with low valve calcium burden. As there is still clinical equipoise in these patients, a proper randomized trial would close the debate on the subject. However, excluding these patients from such a trial, and focusing only on those with valve calcification volume in the highest tertiles (i.e. above 450 mm^3) could yield more clinically relevant answers.

In addition, although outcomes and results were assessed by experienced operators and reported according to VARC-2 criteria, the absence of a central core lab may lead to some heterogeneity in assessment. Whether the findings reported in this paper are applicable to a self-expandable TAVI technology is unknown.

3.7. Conclusions

In patients with moderate aortic valve calcification burden, direct TAVI is feasible and safe. In those with high calcium burden, pre-dilatation should be performed, after taking into account individual risk profiles.

3.8. References

1. Makkar RR, Fontana GP, Jilaihawi H et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. The New England journal of medicine 2012;366:1696-704.
2. Lefevre T, Kappetein AP, Wolner E et al. One year follow-up of the multi-centre European PARTNER transcatheter heart valve study. Eur Heart J 2011;32:148-57.
3. Thomas M, Schymik G, Walther T et al. One-year outcomes of cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. Circulation 2011;124:425-33.
4. Kodali SK, Williams MR, Smith CR et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. The New England journal of medicine 2012;366:1686-95.
5. Genereux P, Head SJ, Van Mieghem NM et al. Clinical outcomes after transcatheter aortic valve replacement using valve academic research consortium definitions: a weighted meta-analysis of 3,519 patients from 16 studies. J Am Coll Cardiol 2012;59:2317-26.
6. Toggweiler S, Humphries KH, Lee M et al. 5-year outcome after transcatheter aortic valve implantation. J Am Coll Cardiol 2013;61:413-9.
7. Mack MJ, Leon MB, Smith CR et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015;385:2477-84.
8. Thourani VH, Kodali S, Makkar RR et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. Lancet 2016.
9. Leon MB, Smith CR, Mack MJ et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med 2016.

10. Mollmann H, Kim WK, Kempfert J, Walther T, Hamm C. Complications of transcatheter aortic valve implantation (TAVI): how to avoid and treat them. Heart 2015;101:900-8.
11. 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;363:1597-607.
12. Grube E, Naber C, Abizaid A et al. Feasibility of transcatheter aortic valve implantation without balloon pre-dilation: a pilot study. JACC Cardiovascular interventions 2011;4:751-7.
13. Kahlert P, Knipp SC, Schlamann M et al. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. Circulation 2010;121:870-8.
14. Spaziano M, Francese DP, Leon MB, Genereux P. Imaging and functional testing to assess clinical and subclinical neurological events after transcatheter or surgical aortic valve replacement: a comprehensive review. J Am Coll Cardiol 2014;64:1950-63.
15. Erkapic D, Kim WK, Weber M et al. Electrocardiographic and further predictors for permanent pacemaker requirement after transcatheter aortic valve implantation. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2010;12:1188-90.
16. Binder RK, Rodes-Cabau J, Wood DA, Webb JG. Edwards SAPIEN 3 valve. EuroIntervention 2012;8 Suppl Q:Q83-7.
17. Selle A, Figulla HR, Ferrari M et al. Impact of rapid ventricular pacing during TAVI on microvascular tissue perfusion. Clin Res Cardiol 2014;103:902-11.
18. Mollmann H, Kim WK, Kempfert J et al. Transfemoral aortic valve implantation of Edwards SAPIEN XT without predilatation is feasible. Clinical cardiology 2014;37:667-71.
19. Kim WK, Praz F, Blumenstein J et al. Transfemoral aortic valve implantation of Edwards SAPIEN 3 without predilatation. Catheter Cardiovasc Interv 2016.

20. Baumgartner H, Hung J, Bermejo J et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. Eur J Echocardiogr 2009;10:1-25.
21. Jilaihawi H, Makkar RR, Kashif M et al. A revised methodology for aortic-valvar complex calcium quantification for transcatheter aortic valve implantation. European heart journal cardiovascular Imaging 2014;15:1324-32.
22. Schultz C, Rossi A, van Mieghem N et al. Aortic annulus dimensions and leaflet calcification from contrast MSCT predict the need for balloon post-dilatation after TAVI with the Medtronic CoreValve prosthesis. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2011;7:564-72.
23. Koos R, Mahnken AH, Dohmen G et al. Association of aortic valve calcification severity with the degree of aortic regurgitation after transcatheter aortic valve implantation. International journal of cardiology 2011;150:142-5.
24. Ewe SH, Ng AC, Schuijf JD et al. Location and severity of aortic valve calcium and implications for aortic regurgitation after transcatheter aortic valve implantation. The American journal of cardiology 2011;108:1470-7.
25. Webb JG, Altwegg L, Masson JB, Al Bugami S, Al Ali A, Boone RA. A new transcatheter aortic valve and percutaneous valve delivery system. J Am Coll Cardiol 2009;53:1855-8.
26. Bapat V, Attia R. Transaortic Transcatheter Aortic Valve Implantation: Step-by-Step Guide. Seminars in thoracic and cardiovascular surgery 2012;24:206-11.
27. Kappetein AP, Head SJ, Genereux 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;145:6-23.
28. Gilard M, Eltchaninoff H, Iung B et al. Registry of transcatheter aortic-valve implantation in high-risk patients. N Engl J Med 2012;366:1705-15.
29. Abramowitz Y, Jilaihawi H, Chakravarty T et al. Feasibility and safety of balloon-expandable transcatheter aortic valve implantation with moderate or without predilatation. EuroIntervention : journal of EuroPCR in collaboration

with the Working Group on Interventional Cardiology of the European Society of Cardiology 2016;11:1132-9.

30. Fiorina C, Maffeo D, Curello S et al. Direct transcatheter aortic valve implantation with self-expandable bioprosthesis: feasibility and safety. Cardiovascular revascularization medicine : including molecular interventions 2014;15:200-3.
31. Dvir D, Barbash IM, Ben-Dor I et al. Paravalvular regurgitation after transcatheter aortic valve replacement: diagnosis, clinical outcome, preventive and therapeutic strategies. Cardiovasc Revasc Med 2013;14:174-81.
32. Husser O, Pellegrini C, Kessler T et al. Outcomes After Transcatheter Aortic Valve Replacement Using a Novel Balloon-Expandable Transcatheter Heart Valve: A Single-Center Experience. JACC Cardiovasc Interv 2015;8:1809-16.
33. Binder RK, Stortecky S, Heg D et al. Procedural Results and Clinical Outcomes of Transcatheter Aortic Valve Implantation in Switzerland: An Observational Cohort Study of Sapien 3 Versus Sapien XT Transcatheter Heart Valves. Circ Cardiovasc Interv 2015;8.
34. Nijhoff F, Abawi M, Agostoni P, Ramjankhan FZ, Doevendans PA, Stella PR. Transcatheter aortic valve implantation with the new balloon-expandable Sapien 3 versus Sapien XT valve system: a propensity score-matched single-center comparison. Circ Cardiovasc Interv 2015;8:e002408.
35. Mastoris I, Schoos MM, Dangas GD, Mehran R. Stroke after transcatheter aortic valve replacement: incidence, risk factors, prognosis, and preventive strategies. Clin Cardiol 2014;37:756-64.
36. Genereux P, Kodali S, Hahn R, Nazif T, Williams M, Leon MB. Paravalvular leak after transcatheter aortic valve replacement. Minerva Cardioangiol 2013;61:529-37.
37. Jerez-Valero M, Urena M, Webb JG et al. Clinical impact of aortic regurgitation after transcatheter aortic valve replacement: insights into the degree and acuteness of presentation. JACC Cardiovasc Interv 2014;7:1022-32.

38. Webb J, Gerosa G, Lefevre T et al. Multicenter evaluation of a next-generation balloon-expandable transcatheter aortic valve. J Am Coll Cardiol 2014;64:2235-43.
39. Binder RK, Rodes-Cabau J, Wood DA et al. Transcatheter aortic valve replacement with the SAPIEN 3: a new balloon-expandable transcatheter heart valve. JACC Cardiovasc Interv 2013;6:293-300.
40. Tarantini G, Mojoli M, Purita P et al. Unravelling the (arte)fact of increased pacemaker rate with the Edwards SAPIEN 3 valve. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2015;11:343-50.
41. Khawaja MZ, Rajani R, Cook A et al. Permanent pacemaker insertion after CoreValve transcatheter aortic valve implantation: incidence and contributing factors (the UK CoreValve Collaborative). Circulation 2011;123:951-60.
42. Abramowitz Y, Jilaihawi H, Chakravarty T et al. Balloon-expandable transcatheter aortic valve replacement in patients with extreme aortic valve calcification. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 2016;87:1173-9.
43. Bramlage P, Strauch J, Schrofel H. Balloon expandable transcatheter aortic valve implantation with or without pre-dilation of the aortic valve - rationale and design of a multicenter registry (EASE-IT). BMC cardiovascular disorders 2014;14:160.

Synthèse des résultats

Le tableau I décrit, pour les 3 articles présentés, la synthèse des principales issues cliniques d'intérêt: décès à 30 jours et 1 an, AVC, ainsi que complications vasculaires majeures.

Tableau I. Synthèse des issues cliniques d'intérêt

Issue clinique	Référence (2012)(27)	Avancée technologique (28)			Avancée technique (29)		
		XT	S3	p-value	pré-dil.	Direct TAVI	p-value
Score STS	28.6	18.8	15.7	<0.0001	16.4	15.4	0.56
Décès 30 jours	5 -18	8.7	3.5	0.21	2	4	0.69
Décès 1 an	23	20.1	25.7	0.55	22.7	23.9	0.59
AVC 30 jours	0 - 6.7	2.8	1.4	0.60	3	1	0.11
Complication vasculaire majeure 30 jours	2 -16	9.9	2.8	<0.0001	3	3	0.67

Les valeurs sont des pourcentages. Pré-dil = pré-dilatation.

Il apparait tout d'abord qu'il y a eu une diminution des taux d'événements à 30 jours entre 2012 et 2016-2017, les années où ont été publiés l'article de référence et les articles décrivant les avancées, respectivement. En effet, même les groupes de référence de ces derniers, soit le groupe XT et le groupe pré-dilatation, respectivement, ont un taux d'événement à 30 jours dans la partie inférieure de l'intervalle de l'article de référence. Par exemple, alors que l'article de référence présente un taux de mortalité à 30 jours variant de 5 à 18 %, le groupe XT présente un taux de mortalité à 30 jours de 8.7% et le groupe pré-dilatation, de 2%. La même chose se produit en ce a trait aux AVC et aux complications vasculaires majeures. Ceci peut s'expliquer entre autres par les avancées technologiques et techniques qui se sont déjà produites entre 2012 et 2016, ainsi que par l'expérience grandissante des opérateurs, mais aussi par le profil de risque des patients qui a considérablement diminué. L'article de référence présente principalement les résultats cliniques de la valve Edwards SAPIEN (première génération) et de la première génération de la CoreValve. En ce qui concerne l'article XT vs. S3, le groupe de référence XT est déjà la

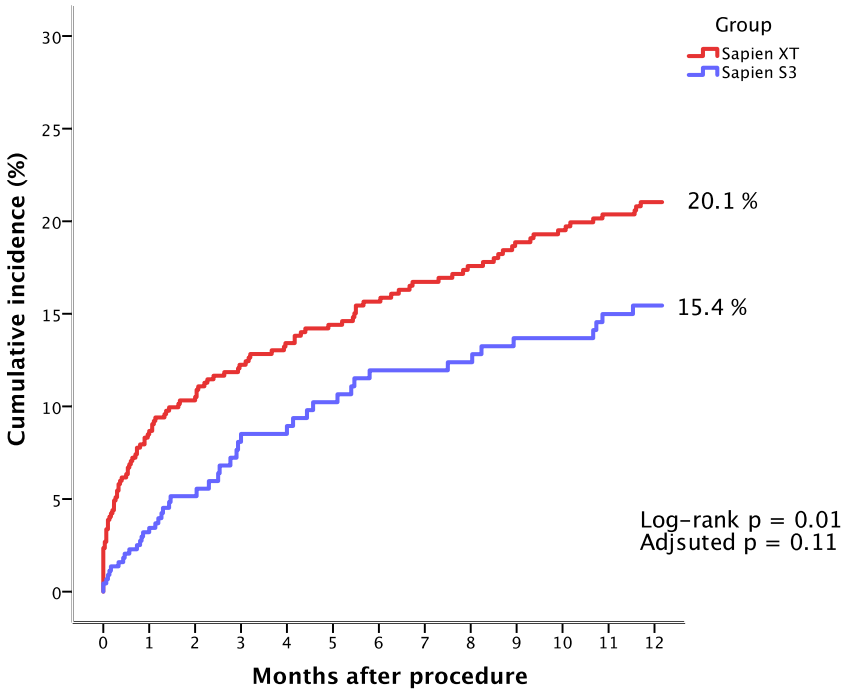
deuxième itération du dispositif SAPIEN. Dans l'autre article, le groupe de référence est la S3, donc la troisième génération.

Lorsqu'on porte notre attention plus spécifiquement sur les résultats d'une avancée technologique, le passage de la SAPIEN XT vers la SAPIEN 3, on remarque encore une fois une réduction numérique des événements cliniques à 30 jours. Puisque les procédures n'ont pas été réalisées dans la même période pour les deux groupes, et que les caractéristiques cliniques des patients ont évolué au fil du temps, il était nécessaire de faire une analyse multivariée afin de tenir compte des potentiels facteurs de confusion.

Certains constats en lien avec la mortalité à un an méritent une attention particulière : en effet, les patients du groupe S3 ont une mortalité à 1 an demeurant élevée et numériquement supérieure (25.7 vs. 20.1%; p=NS) à celle du groupe XT. Ceci paraît surprenant puisque : 1) les caractéristiques de base des patients du groupe S3 indiquent qu'ils étaient moins malades que le groupe XT; 2) la mortalité à 30 jours du groupe S3 était numériquement moindre; 3) le groupe S3 a eu moins de complications vasculaires, moins de procédures effectuées par approches alternatives, et moins de fuites paravalvulaires significatives, toutes ces issues étant associées à une mortalité plus élevée.

Les réponses à ces questions sont d'ordre méthodologique ainsi que d'ordre statistique. D'abord, le faible niveau d'expérience des opérateurs avec une nouvelle valve peut expliquer une légère augmentation de la mortalité au début de l'expérience. Ensuite, les tous premiers patients à être traités avec la S3 dans notre centre faisaient partie d'études ou de registres et devaient être « à risque très élevé ou extrême ». Alors que les caractéristiques cliniques globales du groupe S3 pointent vers des patients moins malades, le sous-groupe des premiers patients traités sont en fait très similaires, voire plus malades que les patients XT. De plus, nous nous devons d'invoquer la venue de nouveaux opérateurs moins expérimentés au sein du groupe comme possible cause de mortalité augmentée. Du point de vue statistique, le taux de mortalité est aussi influencé par le faible nombre de patients suivis à plus de 6 mois (n=41). Les « marches d'escaliers » de la courbe de Kaplan-Meier, d'autant plus hautes à chaque événement en fin d'étude, en sont la preuve. Nous avons mis à jour en janvier 2017 le suivi à un an du groupe de patients S3 (n=455) et avons obtenu un total de 45 décès pour taux de mortalité de 15.4%. Cette différence en faveur de la S3 est devenue statistiquement

significative en univarié (p=0.01), mais pas en multivarié (p=0.11). (Figure III) Ces trouvailles nous rappellent la prudence lorsqu'on interprète des différences de survie non-significatives sur de petits groupes de patients.



No. at risk				
XT	507	414	308	293
S3	454	404	203	184

Figure III. Courbes de survies mises à jour des patients S3 vs XT.

Pour ce qui est des complications vasculaires majeures, réduites par un facteur de 4 avec la S3, le bénéfice est statistiquement significatif après ajustement.

L'avancée technologique décrite semble donc présenter un bénéfice au moins en ce qui a trait aux complications vasculaires majeures, liées directement au diamètre du cathéter. Les autres complications à 30 jours présentent des réductions à tout le moins encourageantes, même si non significatives. Le seul bémol à apporter est en lien avec l'implantation de pacemakers. En effet, le passage de la XT vers la S3 s'est traduit par une multiplication par 2 du taux de pacemaker (9.8% vs. 17.3%; p=0.03), dans notre groupe comme chez

d'autres.(30,31) Ceci peut être dû aux nouvelles caractéristiques mécaniques de la valve, plus imposante en raison de sa jupe anti-fuites para-valvulaires. L'augmentation du taux de pacemaker a pu être en partie corrigée par une technique d'implantation plus haute, décrite par plusieurs auteurs.(31)

Enfin, la réduction des événements majeurs de rupture de l'anneau et de conversion en chirurgie est impressionnante, avantageant la S3 vs. XT (2 vs. 27%). La rupture d'anneau est un enjeu particulièrement important dans le TAVI en raison de la mortalité quasi universelle qui en découle. Plusieurs facteurs peuvent avoir influencé la diminution du taux de rupture d'anneau lors du passage de la XT vers la S3: certains techniques et d'autres technologiques. Au point de vue technique, il est important de mentionner l'expérience grandissante des opérateurs pour interpréter les scanners cardiaques afin de choisir le dispositif de taille approprié. En effet, durant la phase XT, les opérateurs commençaient à interpréter les scanners et n'étaient pas nécessairement autant à l'affût de particularités du scanner associé à un plus haut taux de rupture d'anneau (p.ex. calcifications extensives de la chambre de chasse et de l'anneau). Pendant la phase S3, les patients présentant ces caractéristiques recevaient soit une valve de taille inférieure à la recommandation, soit une valve de la taille recommandée mais avec moins de volume dans la seringue de déploiement, soit étaient référés vers la valve CoreValve. Cette acuité a sans doute contribué à réduire certaines complications dévastatrices. Au point de vue technologique, puisque la S3 est munie d'une jupe anti-fuite, l' « oversizing » agressif, nécessaire avec la XT pour maximiser l'apposition, n'est plus recommandé. Ceci a aussi grandement contribué à réduire les ruptures d'anneau car les dispositifs utilisés sont de taille plus similaire à l'anneau, comparé à la génération précédente. Enfin, en ce qui a trait aux conversions chirurgicales d'urgence, on peut invoquer les raisons mentionnées précédemment (les ruptures d'anneau sont souvent converties en chirurgie d'urgence), auxquelles on peut ajouter l'expérience grandissante des opérateurs à manipuler des guides rigides dans le ventricule gauche dans la phase S3. Les guides rigides peuvent en effet engendrer des perforations ventriculaires nécessitant une réparation chirurgicale urgente.

Ensuite, lorsqu'on regarde l'utilité de l'avancée technique décrite, il apparait que le TAVI sans pré-dilatation, plus simple, ne semble pas avoir d'impact sur la mortalité à 30 jours ni sur les complications vasculaires, mais pourrait réduire le taux d'AVC à 30 jours (3% vs.

1%, p=0.11). Qui plus est, lorsqu'on regarde plus spécifiquement dans le groupe de patients avec un taux de calcification valvulaire bas ou modéré, soit les patients les moins susceptibles de bénéficier de la pré-dilatation, les taux sont de 8% avec la pré-dilatation vs. 0% avec le direct TAVI (p=0.10). Les valeurs de p n'étant pas significatives, il est nécessaire de rester circonspect par rapport à ces tendances. Cependant, une valeur de p autour de 0.1 pour des taux d'événements aussi bas doit inciter à d'autres études pour confirmer ou infirmer ce signal.

Il convient donc de conclure que l'avancée technique décrite permet de simplifier la procédure TAVI sans toutefois compromettre la sécurité du patient. Encore une fois, un bémol s'impose: chez les patients avec calcification importante de la valve, le risque de malposition du dispositif est plus élevé avec le direct TAVI. Chez ces patients, la pré-dilatation demeure de mise. Une pré-dilatation sélective est donc probablement la stratégie la plus sécuritaire. Il faut donc en conclure que, probablement comme la majorité des avancées techniques, la simplification de la procédure ne doit pas être un objectif en soit et ne doit pas outrepasser le jugement clinique des opérateurs.

Seule la mortalité à 1 an ne semble pas avoir évolué au cours des trois études présentées. En effet, elle oscille toujours entre 20 et 25%. Ceci est possiblement dû aux caractéristiques de base des patients. Ceux-ci demeurent à haut risque opératoire ou inopérables dans chacun des trois articles présentés. Le score *Logistic EuroScore*, un outil de mesure pour évaluer le risque opératoire, ainsi que l'âge moyen des patients supérieur à 80 ans dans les trois papiers peuvent justifier l'absence d'amélioration de la mortalité à long terme. Dans une population à risque intermédiaire, comme dans les études PARTNER 2 et SURTAVI, récemment publiées, la mortalité à 1 an avec le TAVI était plutôt de 12.3 et 6.7%, respectivement.(32,33) Bien sûr, en plus de leurs caractéristiques cliniques intermédiaires, ces patients ont été soigneusement sélectionnés pour faire partie de l'étude, alors que les résultats présentés dans nos deux articles concernant les avancées représentent des patients à haut risque tout venant. Néanmoins, on pourrait prudemment en déduire qu'alors que les avancées technologiques et techniques ont plus d'impact sur la mortalité à péri-procédurale, ce sont plutôt les caractéristiques de base des patients qui dictent leur devenir à plus long terme. Cette conclusion, quoique biologiquement plausible, demeure à confirmer.

Une des limitations des l'analyse actuelle, en plus de celles présentées dans chacun des chapitres, est le fait de comparer plusieurs études entres elles sans ajustement. Cependant, il convient de dire qu'alors que l'article du chapitre 1 doit être considéré plutôt comme une référence afin de situer le lecteur, les articles des chapitres 2 et 3 proviennent de la même population, du même centre, des mêmes opérateurs et de la même période. On pourrait aussi mentionner que les études des chapitres 2 et 3 sont rétrospectives et donc susceptibles de présenter des biais de sélection et des facteurs de confusion résiduels (*residual confounding*), imperfections inhérentes aux études rétrospectives. Alors qu'il est clair que des études randomisées contrôlées pourraient clore le débat de l'utilité des avancées technologique et technique, celles-ci sont impossible dans le premier cas et improbable dans le deuxième. La communauté sera donc contrainte à se fier à des données rétrospectives ou des registres, comme le registre EASE-IT mis sur pied pour évaluer la pré-dilatation et le *direct TAVI*, pour conclure quant aux avantages présumés des avancées technologiques ou techniques.(34)

Conclusion et Perspectives Futures

Le TAVI est une procédure qui bénéficie, dans sa jeune existence, d'avancées technologiques et techniques perpétuelles. Dans ce contexte, les résultats cliniques de cette procédure évoluent aussi constamment. Par ce travail, nous concluons d'abord que les résultats cliniques de la procédure se sont améliorés entre les études initiales sur la procédure en 2012 et les groupes de références d'études plus récentes. Qui plus est, nous avons noté une diminution supplémentaire des événements cliniques indésirables à 30 jours mis de l'avant par le passage de la deuxième vers la troisième génération de la valve Edwards. L'absence de pré-dilatation de la valve aortique, visant à simplifier la procédure, n'augmente pas le risque d'événement adverse et pourrait même contribuer à réduire les taux d'AVC. Cependant, la mortalité globale à 1 an n'a pas été influencée par les deux innovations décrites. Enfin, les avancées technologiques et techniques présentent aussi des bémols qui rappellent l'utilité du jugement clinique ainsi que l'importance du suivi des patients pour avoir un portrait exact des résultats cliniques.

Les deux aspects fondamentaux traités dans ce mémoire (innovations technique et technologique) sont appelés à être évalués plus en profondeur dans les prochaines années. En effet, plusieurs nouvelles valves feront leur apparition sur le marché. Entre autres, la valve Symetis, récemment acquise par la compagnie Boston Scientific, fera l'objet d'une étude randomisée contrôlée à laquelle l'auteur participera. Nous travaillerons aussi sur une valve d'origine chinoise (VitaFlow de MicroPort). Du point de vue technique, nous travaillons présentement sur des études qui visent prouver l'innocuité de deux techniques allégeant la procédure : une sur l'utilisation de l'artère radiale plutôt que fémorale pour l'accès secondaire, et l'autre sur l'utilisation du guide ventriculaire gauche pour la stimulation rapide durant l'implantation. Plus avant, l'auteur sera impliqué dans l'espace mitral, beaucoup plus complexe que l'espace aortique et où beaucoup reste à faire.

Bibliographie

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;368:1005-11.
2. (INESSS) INdEeSeSS, Spaziano M, Boothroyd L et al. Implantation valvulaire aortique par cathéter. Évaluation des données probantes et synthèse des considérations organisationnelles. ETMIS 2012;8:1-84.
3. Leon MB, Smith CR, Mack M et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. The New England journal of medicine 2010;363:1597-607.
4. Smith CR, Leon MB, Mack MJ et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. The New England journal of medicine 2011;364:2187-98.
5. Piazza N, Martucci G, Lachapelle K et al. First-in-human experience with the Medtronic CoreValve Evolut R. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2014;9:1260-3.
6. Frohlich GM, Lansky AJ, Webb J et al. Local versus general anesthesia for transcatheter aortic valve implantation (TAVR)--systematic review and meta-analysis. BMC medicine 2014;12:41.
7. Freeman RV, Otto CM. Spectrum of calcific aortic valve disease: pathogenesis, disease progression, and treatment strategies. Circulation 2005;111:3316-26.
8. Ross J, Jr., Braunwald E. Aortic stenosis. Circulation 1968;38:61-7.
9. American College of C, American Heart Association Task Force on Practice G, Society of Cardiovascular A et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. Journal of the American College of Cardiology 2006;48:e1-148.
10. Philip F, Faza NN, Schoenhagen P et al. Aortic annulus and root characteristics in severe aortic stenosis due to bicuspid aortic valve and tricuspid aortic valves: implications for transcatheter aortic valve therapies. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 2015;86:E88-98.
11. Iung B, Cachier A, Baron G et al. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? European heart journal 2005;26:2714-20.
12. Bach DS, Siao D, Girard SE, Duvernoy C, McCallister BD, Jr., Gualano SK. Evaluation of patients with severe symptomatic aortic stenosis who do not undergo aortic valve replacement: the potential role of subjectively overestimated operative risk. Circulation Cardiovascular quality and outcomes 2009;2:533-9.

13. Cribier A, Eltchaninoff H, Bash A et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation 2002;106:3006-8.
14. Webb JG, Chandavimol M, Thompson CR et al. Percutaneous aortic valve implantation retrograde from the femoral artery. Circulation 2006;113:842-50.
15. Grube E, Laborde JC, Zickmann B et al. First report on a human percutaneous transluminal implantation of a self-expanding valve prosthesis for interventional treatment of aortic valve stenosis. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 2005;66:465-9.
16. Lefevre T, Kappetein AP, Wolner E et al. One year follow-up of the multi-centre European PARTNER transcatheter heart valve study. European heart journal 2011;32:148-57.
17. Piazza N, Grube E, Gerckens U et al. Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 Fr) corevalve revalving system: results from the multicentre, expanded evaluation registry 1-year following CE mark approval. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2008;4:242-9.
18. Rodes-Cabau J, Webb JG, Cheung A et al. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. Journal of the American College of Cardiology 2010;55:1080-90.
19. Tamburino C, Capodanno D, Ramondo A et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. Circulation 2011;123:299-308.
20. Adams DH, Popma JJ, Reardon MJ et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. The New England journal of medicine 2014;370:1790-8.
21. Vahl TP, Kodali SK, Leon MB. Transcatheter Aortic Valve Replacement 2016: A Modern-Day "Through the Looking-Glass" Adventure. Journal of the American College of Cardiology 2016;67:1472-87.
22. Meredith IT, Hood KL, Haratani N, Allocco DJ, Dawkins KD. Boston Scientific Lotus valve. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2012;8 Suppl Q:Q70-4.
23. Naber CK, Pyxaras SA, Ince H et al. A multicentre European registry to evaluate the Direct Flow Medical transcatheter aortic valve system for the treatment of patients with severe aortic stenosis. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2016;12:e1413-e1419.
24. Van Mieghem NM, Tchetche D, Chieffo A et al. Incidence, predictors, and implications of access site complications with transfemoral transcatheter aortic valve implantation. The American journal of cardiology 2012;110:1361-7.
25. Cockburn J, de Belder A, Lewis M, Trivedi U, Hildick-Smith D. Maintaining a minimally invasive approach-vascular closure after trans-catheter aortic valve intervention. Journal of thrombosis and thrombolysis 2013;35:494-500.

26. Sawaya FJ, Lefevre T, Spaziano M et al. Transfemoral Transcatheter Aortic Valve Implantation: How Minimalistic Can We Become? Journal of interventional cardiology 2016;29:628-631.
27. Boothroyd LJ, Spaziano M, Guertin JR et al. Transcatheter aortic valve implantation: recommendations for practice based on a multidisciplinary review including cost-effectiveness and ethical and organizational issues. The Canadian journal of cardiology 2013;29:718-26.
28. Sawaya FJ, Spaziano M, Lefevre T et al. Comparison between the SAPIEN S3 and the SAPIEN XT transcatheter heart valves: A single-center experience. World journal of cardiology 2016;8:735-745.
29. Spaziano M, Sawaya F, Chevalier B et al. Comparison of Systematic Predilation, Selective Predilation, and Direct Transcatheter Aortic Valve Implantation With the SAPIEN S3 Valve. The Canadian journal of cardiology 2017;33:260-268.
30. Nijhoff F, Abawi M, Agostoni P, Ramjankhan FZ, Doevendans PA, Stella PR. Transcatheter aortic valve implantation with the new balloon-expandable Sapien 3 versus Sapien XT valve system: a propensity score-matched single-center comparison. Circulation Cardiovascular interventions 2015;8:e002408.
31. Tarantini G, Mojoli M, Purita P et al. Unravelling the (arte)fact of increased pacemaker rate with the Edwards SAPIEN 3 valve. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2015;11:343-50.
32. Leon MB, Smith CR, Mack MJ et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. The New England journal of medicine 2016;374:1609-20.
33. Reardon MJ, Van Mieghem NM, Popma JJ et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. The New England journal of medicine 2017;376:1321-1331.
34. Bramlage P, Strauch J, Schrofel H. Balloon expandable transcatheter aortic valve implantation with or without pre-dilation of the aortic valve - rationale and design of a multicenter registry (EASE-IT). BMC cardiovascular disorders 2014;14:160.

Annexe 1. Texte et tableaux supplémentaires du Chapitre 1.

Appendix S1.1. Detailed methods

Systematic literature review

We systematically searched for published scientific evidence (English or French) on benefits, risks and cost-effectiveness of TAVI, for adult patients with severe symptomatic aortic stenosis, using either of the predominant types of biological valves (Cribier-Edwards/Edwards SAPIEN® and CoreValve®). We searched PubMed, Cochrane and EMBASE bibliographic databases with key words (such as "percutaneous", "stentless", "transcatheter", "transcutaneous", "transfemoral" and "transapical", combined with "aortic valve implantation/replacement") for the period January 2008 to January 2011. We extracted data from studies that examined survival at 1 year, quality of life at 6 months or at 1 year, or cost-effectiveness. We also identified relevant presentations from conferences in 2010. In March 2012, we performed a search update to replace these presentations with peer-reviewed publications.

We also extracted data on procedural outcomes, functional status at 1 year, durability of the valve at 1 year or more, and on adverse outcomes (i.e. complications) experienced in the first 30 days after the procedure and, if available, in the first year. Adverse outcomes included major access site or access-related vascular injury, major bleeding, aortic regurgitation, implantation of a new permanent pacemaker, stroke, and transient ischemic attack, according to the study-specific definitions of these events. We compared the results obtained on procedural and adverse outcomes with other existing reviews published between 2008 and 2011.

The studies on benefits, risks and cost-effectiveness were appraised for quality using standardized assessment tools from the National Institute for Health and Clinical Excellence (www.nice.org.uk) and the Critical Appraisal Skills Programme (www.casp-uk.net). The overall strength of the evidence on benefits and risks was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE)

system.[34] Selection of studies, extraction of data and quality appraisal were carried out by 2 independent reviewers.

Meta-analysis

We performed a meta-analysis of survival at 1 year, average age and average surgical risk score (logistic Euroscore) at baseline for TAVI patients using a random effects model and pooling results at the study level. We also pooled results according to whether the data arose from an investigational *research study* or an observational *registry*.

Narrative review

We searched the bibliographic databases (listed above), as well as Internet sites of professional societies and organizations providing clinical guidance/technology assessments, for documents addressing organizational aspects of performing TAVI, methods of selecting patients, and issues related to ethics and the patient's perspective. In order to compare recommendations, we identified recent consensus and position statements from Europe and North America, including the most recent one from the Canadian Cardiovascular Society.

Consultation with clinical TAVI experts

Our expert committee of clinicians active in the TAVI domain included 4 interventional cardiologists (RI, GM, MN, JRC) and 4 cardiac surgeons (MC, ED, BdV, NN), with representatives from each of the 4 university hospital-affiliated health networks in the province. The committee's mandate was to assist the formulation of recommendations based on their knowledge and experience in the Canadian health care context. No members of the research team at INESSS had any relationships with the TAVI industry or any role in the performance of TAVI. The research team had the final responsibility for this text.

External peer review of Ministry report

Our report for the Ministry was reviewed by 6 invited, independent experts—4 from Canada and 2 from Europe— representing geriatrics, interventional cardiology, cardiac surgery, general practice, health care administration, medical ethics, and health

technology assessment. No substantive changes to recommendations were made as a result of the external review.

Table S1.1. Characteristics of included studies with 1-year survival data

Study; number of centres; region	Study design	Recruit-ment period	Number of TAVI patients; approach	Type of valve	Logistic Euroscore* (mean ± SD)
RESEARCH STUDIES					
Leon *et al.,* 2010; 21; Canada, USA, Germany	RCT (PARTNER B)	05/2007-03/2009	179; TF	ES	26 ± 17
Kapadia *et al.,* 2009; 1; USA	Controlled prospective	02/2006-03/2007	18; NR	ES	28 ± 19
Zierer *et al.,* 2009; 1; Germany	Controlled retrospective	01/2006-03/2007	21; TA	Crib-E	38 ± 14
Walther *et al.,* 2011, 3; Europe	Case series	02/2006-03/2008	168; TA	Crib-E, ES	27 ± 13
Lefevre *et al.,* 2011; 9, Europe	Case series	03/2007-01/2008	130; 61 TF, 69 TA	ES	30 ± 14
Rodés-Cabau *et al.,* 2010; 6; Canada	Case series	01/2005-06/2009	339; 162 TF, 177 TA	Crib-E, ES, SXT	NR
Gurvitch *et al.,* 2010; 1; Canada	Case series	01/2005-12/2006	70; 55 TF, 15 TA	Crib-E, ES	32 ± 16
Himbert *et al.,* 2009; 1; France	Case series	10/2006-11/2008	75; 51 TF, 24 TA	ES	26 ± 13
Thielmann *et al.,* 2009; 1; Germany	Case series	05/2005-11/2008	39; 15 TF, 24 TA	Crib-E, ES	44 ± 13
Otten *et al.,* 2008; 1; The Netherlands	Controlled prospective	09/2005-09/2007	39; TF	CV	15 ± 6
Rajani *et al.,* 2010; 1; England	Controlled retrospective	12/2007-06/2009	38; TF & TSC	CV	24 ± 15
Grube *et al.,* 2008; 1; Germany	Case series	02/2005-03/2008	136; 123 TF, 3 TSC, 10 TI	CV	23 ± 15
Sinning *et al.,* 2010; 1; Germany	Case series	NR	77; TF	CV	31 ± 18
REGISTRIES					
Bosmans *et al.,* 2011; 15; Belgium	Case series	NR-03/2010	328; 232 TF, 88 TA, 8 TSC	ES (187), CV (141)	28 ± 16
Moat *et al.,* 2011; 25; England, Wales	Case series	01/2007-12/2009	870; 599 TF, 271 other	ES (410),	18 (median)

				CV (452)	
Tamburino *et al.,* 2011; 14; Italy	Case series	06/2007-12/2009	663; 599 TF, 64 TSC	CV	23 ± 14
Thomas *et al.,* 2011; 32; Europe	Case series	11/2007-01/2009	1038; 463 TF, 575 TA	ES	28 ± 16

*rounded for consistency across studies

TAVI: transcatheter aortic valve implantation; SD: standard deviation; RCT: randomized controlled trial; TF: trans-femoral; TA: trans-apical; TSC: trans-subclavian; TI: trans-iliac; BAV: balloon aortic valvuloplasty; ES: Edwards SAPIEN; Crib-E: Cribier Edwards; SXT: Sapien XT; CV: CoreValve; NR: not reported

Appendix S1.2. Recommendations for the practice, diffusion and monitoring of TAVI

Patient selection criteria

- TAVI should only be considered for patients with symptoms attributable to severe aortic stenosis, who are considered inoperable or at a prohibitively high risk for surgery, and for whom there is reasonable probability that quality of life (related to functional capacity, autonomy and activities of daily living) would improve significantly as a result of the intervention, and be sustained for at least 1 year *(expert consensus documents, health technology assessment [HTA] reports, clinical studies, expert opinion)*. Although the 1-year criterion is necessarily arbitrary, we believe this to be a reasonable minimal length of time, given the risks of the procedure and resources required for its delivery.
- Criteria are needed to define inoperability (i.e. non-suitability for valve replacement surgery) and eligibility for TAVI that are clear, applicable and as objective as possible and which should be the same for all performing centres *(expert consensus document, clinical studies, expert opinion)*.

Process of patient selection

- A multidisciplinary team that includes interventional cardiologists and cardiac surgeons should evaluate the global state of the patient and should decide whether

the procedure is to be offered after examination of cognitive function, frailty, physical state and all other relevant dimensions *(expert consensus documents, HTA reports, clinical studies, expert opinion)*. Since the majority of patients referred for TAVI will be elderly, a geriatrician should have an active role. The evaluation team should meet in person to discuss all therapeutic options *(clinical studies, expert opinion)*, and team membership and minutes of meetings should be documented *(expert consensus documents, expert opinion)*.

- The opinion that a patient is at prohibitively high risk for surgery or that surgery is contraindicated should ideally be the consensus of 2 or more cardiac surgeons *(expert consensus document, HTA reports, clinical studies)*.
- The process of patient selection for TAVI should be transparently documented *(expert consensus document, clinical studies, expert opinion)*. The evaluation of eligibility must be documented for all patients considered for TAVI, including reasons for inoperability and for patient refusal of TAVI *(expert consensus documents, clinical studies, expert opinion)*. The workload, human resources and cost implications of the selection process must be anticipated.
- The therapeutic options judged clinically appropriate should be clearly discussed with the patient *(HTA report)*. A patient information pamphlet is recommended, in order to standardize the facts transmitted to patients across centres and to make the patient aware of the relative novelty of the procedure, anticipated benefits and possible risks (e.g. stroke, embolic events, need for a permanent pacemaker, readmissions to hospital) *(expert opinion)*.
- The fundamental importance of the patient's perspective regarding his/her needs and expectations of the therapies being offered must be recognized *(HTA reports, expert opinion)*.

<u>Conditions for the practice of TAVI</u>

- In order to maintain sufficient volume of TAVI procedures and expertise in each hospital, the number of performing centres should be limited in any given jurisdiction *(expert consensus documents, HTA reports, expert opinion)*. The

specific criteria for a TAVI program and the manner in which interventions will be distributed across the different centres will need to be developed.

- Adequate financing specific to TAVI is necessary to assure the stability and sustainability of such programs *(expert opinion)*. These funds should cover the costs of patient selection, implantation (including the cost of the valve), and long-term follow-up of patients after TAVI.

Requirements of performing centres

- Each centre should designate a multidisciplinary team that includes general cardiologists, interventional cardiologists, cardiac surgeons, anesthesiologists, geriatricians, rehabilitation specialists, and social workers, and that participates in all aspects of the TAVI program *(expert consensus document, HTA reports, clinical studies)*.
- A collaborative environment for interventional cardiologists and cardiac surgeons is essential *(expert consensus documents, HTA reports, clinical studies)*. At least 1 interventional cardiologist and at least 1 cardiac surgeon should be available for a TAVI procedure *(HTA reports, expert opinion)*.
- Adequate and appropriately-equipped space is necessary for TAVI procedures *(expert consensus document, expert opinion)*.
- Appropriate training of the multidisciplinary team is necessary regarding evaluation of eligibility and performance of the procedure according to standards recognized by professional societies and institutional accreditation bodies *(expert consensus document, HTA reports, expert opinion)*.
- Standardized definitions of outcomes should be implemented across regions *(expert consensus documents, clinical studies),* ideally consistent with the Valve Academic Research Consortium *(expert opinion)*.
- Centres should monitor TAVI patients with standardized measures of benefit in addition to survival in the short- and long-term (e.g. quality of life, functional and cognitive status, return to independent living and hospital readmissions after the initial stay) *(expert consensus documents, HTA reports)*. Follow-up testing should

include echocardiographic studies to evaluate the durability of the implanted valve *(clinical studies, expert opinion)*.

- Based on our meta-analysis, it is reasonable to expect a benchmark survival rate at 1 year of at least 75%, and a minimal standard of 65% *(clinical studies)*.

Monitoring of outcomes

- Performing centres must participate in a registry as part of quality assurance *(expert consensus documents, HTA reports, clinical studies)*. The budget for TAVI should include support for registry maintenance. The principal objective would be to collect data on the baseline characteristics of patients (ideally including those referred for but not treated by TAVI), characteristics of the procedure, adverse outcomes and other clinical results. The registry should ideally include dimensions to be used for a formal economic evaluation:

- costs of establishing and maintaining TAVI programs (e.g. construction and/or up-keep of intervention rooms, reusable equipment, overhead)
- costs related to patient selection (patient evaluation, including examinations, diagnostic tests and multidisciplinary consultation)
- costs related to patient care (medical and pharmaceutical costs, including but not limited to hospital stays, physician fees, imaging tests, dispensed medications, subsequent outpatient and emergency room visits, as well as costs to treat patients with severe aortic stenosis by means other than TAVI).
- benefits in the short- and long-term, such as survival and quality of life, for all TAVI patients as well as those not receiving TAVI.
- other factors that could influence benefits and costs such as the need for multiple interventions for the same episode of care (e.g. “valve-in-valve” procedure), valve durability, and the need for a permanent pacemaker following TAVI.

Table S1.2. Summary of recommendations concerning patient eligibility for TAVI

Jurisdiction, year of publication	Patient groups potentially eligible for TAVI			Mandatory monitoring requirement	
	Inoperable	High surgical risk	Selected patients at lower surgical risk	Via a registry	Within an "evidence development program"
Belgium, 2011[36]	X*				
France, 2011[49]	X	X		X	
USA, 2012[51]	X	X		X	
USA, 2012[44]	X	X			
Ontario, 2012[35]	X	X			X
This article (Quebec)	X	X		X	
Canada, 2012[43]	X	X	X†		

*Reimbursement for TAVI recommended only when patients are considered inoperable due to anatomic factors (by a cardiac surgeon independent of the TAVI team).
†The Canadian Cardiovascular Society appears to tentatively extend eligibility for TAVI ('conditional recommendation, low-quality evidence') to selected patients at lower surgical risk.

Annexe 2. Figure supplémentaire du Chapitre 2.

Figure S2.1

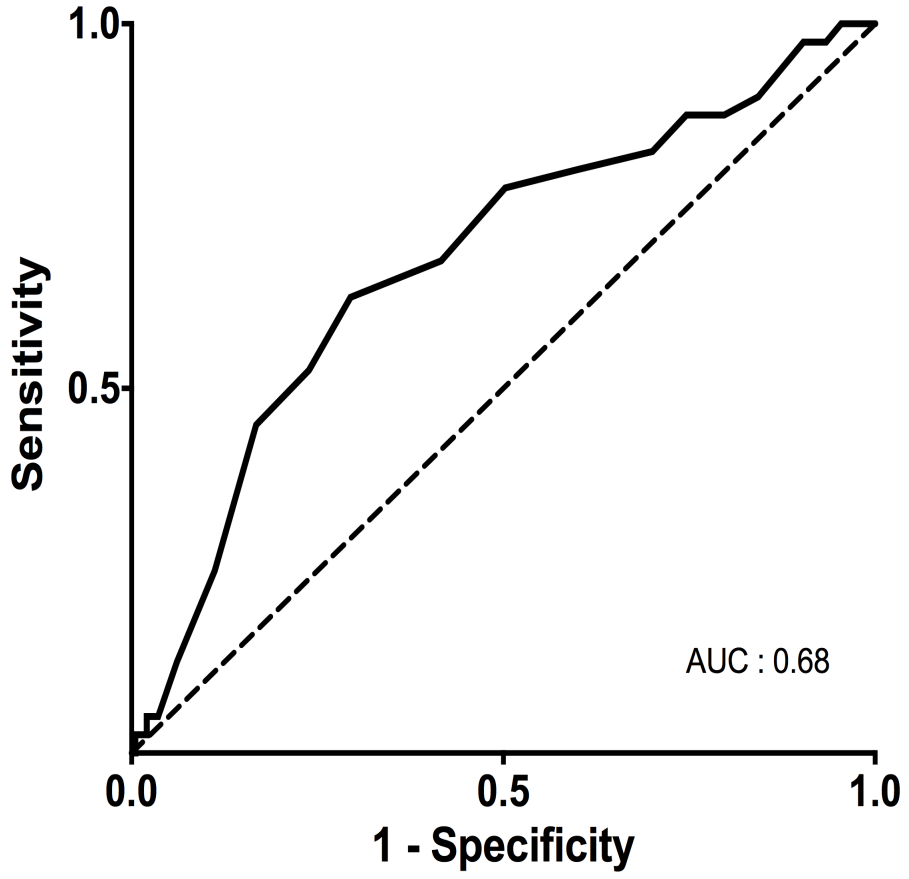


Figure S2.1. ROC curve analysis of device diameter to annulus diameter ratio. ROC curve analysis of device diameter to annulus diameter ratio below the threshold of 1.03 increased the risk of post-dilatation or PVR > mild (area under the curve: 0.68).

Annexe 3. Tableaux et figures supplémentaires du Chapitre 3.

Figure S3.1-A

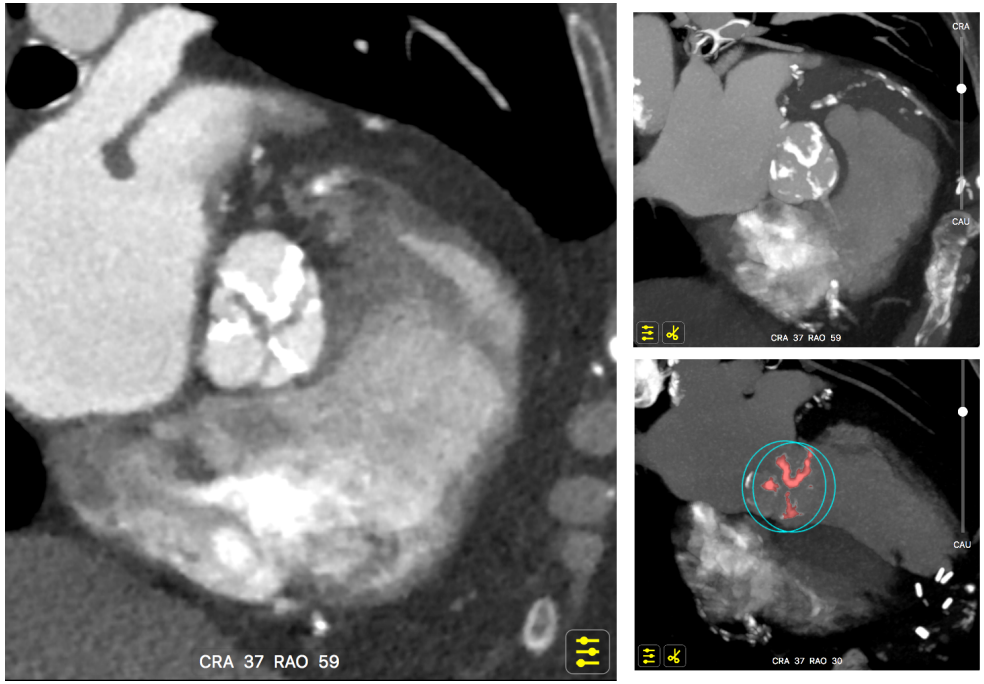


Figure S3.1-B

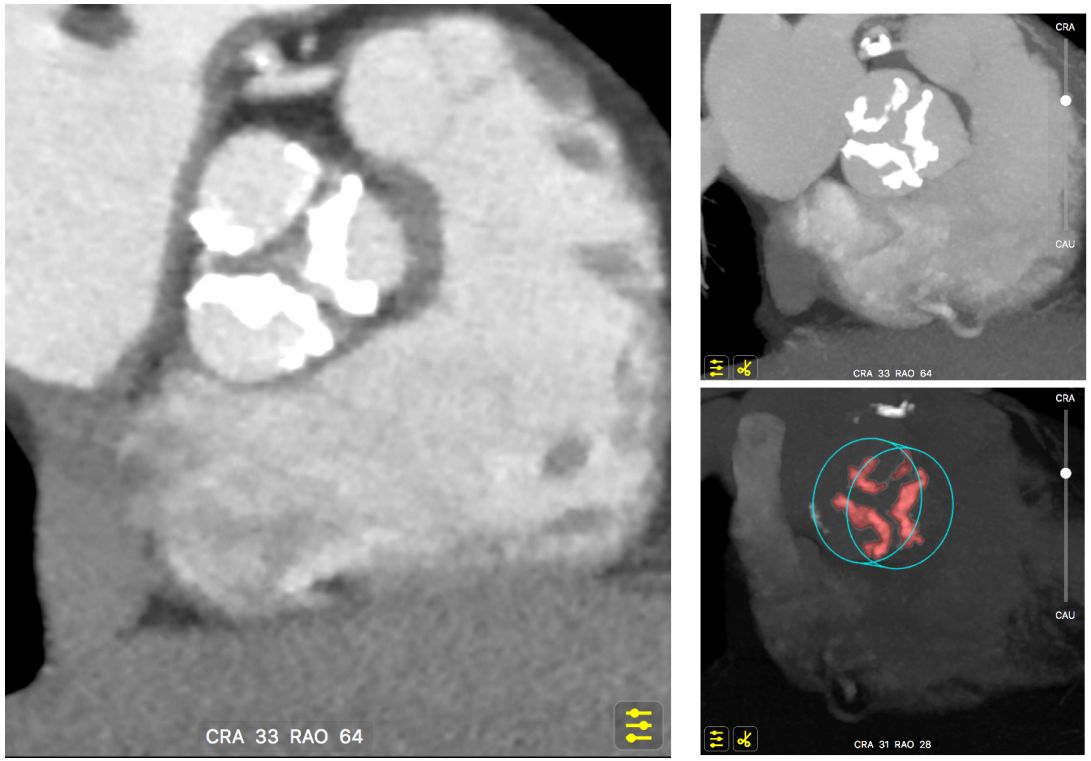


Figure S3.1. MSCT examples of a patient in the systematic pre-dilatation group (Figure S3.1-A, calcification volume = 451 mm3) and a patient in the selective pre-dilatation group (Figure S3.1-B, calcification volume = 1074 mm3). Images generated with the FluoroCT application, version 3.0.

Table S3.1. Baseline clinical characteristics of all patients.

Variable	All patients (n=281)	Pre-dilatation (n=58)	Direct TAVI (n=223)	p-value
Age	82.7 ± 7.1	83.6 ± 6.0	82.5 ± 7.3	0.28
Male sex	145 (51.6)	24 (41)	121 (54)	0.10
STS-PROM, %	5.3 ± 3.5	5.8 ± 3.3	5.1 ± 3.5	0.17
Logistic EuroSCORE, %	15.6 ± 10.7	16.4 ± 11.4	15.4 ± 10.6	0.56
NYHA Class 3 or 4	160 (56.9)	31 (54)	129 (60)	0.45
History of syncope	1 (0.4)	1 (2)	0 (0)	0.25
Atrial arrhythmia (flutter or fibrillation)	83 (29.5)	15 (26)	68 (32)	0.43
Diabetes	71 (25.3)	12 (21)	59 (27)	0.40
Hypertension	160 (71.7)	34 (68)	126 (73)	0.59
Dyslipidemia	98 (43.8)	21 (42)	77 (44)	0.87
Active smoker	4 (1.4)	0 (0)	4 (2)	0.58
Previous PPM	39 (13.9)	5 (9)	34 (15)	0.29
Previous PCI	80 (29.2)	16 (28)	64 (30)	0.87
Previous CABG	25 (9.1)	5 (9)	20 (9)	1
Previous SAVR	2 (0.7)	0 (0)	2 (1)	1
Previous BAV	0 (0)	0 (0)	0 (0)	1
Previous stroke	25 (8.9)	8 (14)	17 (8)	0.19
Peripheral vascular disease	55 (19.6)	13 (22)	42 (19)	0.58
eGFR, ml/min/1.73m^2	62.9 ± 24.6	61.3 ± 26.3	63.3 ± 24.2	0.58
eGFR < 40 ml/min/1.73m^2	41 (14.3)	10 (17)	31 (14)	0.53
Dialysis	4 (1.5)	0 (0)	4 (2)	0.59
Chronic obstructive pulmonary disease	33 (11.7)	9 (16)	24 (11)	0.36
Body mass index, kg/m^2	26.6 ± 5.1	26.3 ± 5.7	26.6 ± 4.9	0.64

Values are mean ± SD or n (%).Abbreviations as per Table 3.1.

Table S3.2. Baseline echocardiographic, electrocardiographic and MSCT characteristics of all patients.

Variable	All patients (n=281)*	Pre-dilatation (n=58)	Direct TAVI (n=223)	p-value
LVEF, %	54.9 ± 14.7	57.2 ± 13.2	54.4 ± 15.1	0.20
LVEF ≤ 30%	30 (11.2)	4 (7)	26 (12)	0.35
Mean aortic gradient, mmHg	46.7 ± 15.2	50.7 ± 14.8	45.6 ± 15.1	0.02
AVA, cm^2	0.67 ± 0.17	0.62 ± 0.13	0.68 ± 0.17	0.01
Pulmonary artery systolic pressure, mmHg	44.5 ± 13.1	47.9 ± 15.8	43.5 ± 12.0	0.03
Pulmonary artery systolic pressure > 50 mmHg	91 (40.6)	28 (54)	63 (37)	0.04
Complete RBBB	29 (13.6)	6/47 (13)	23/167 (13.8)	1
Complete LBBB	14 (6.5)	1/47 (2)	13/167 (8)	0.31
Fascicular block	44 (20.6)	11/47 (23)	33/167 (20)	0.68
QRS duration, ms	102 ± 24	99 ± 17	103 ± 25	0.27
PR duration, ms	185 ± 32	190 ± 42	184 ± 28	0.43
Aortic valve calcification volume, mm^3	692 ± 437	683 ± 517	699 ± 405	0.84

Values are mean ± SD or n (%). *Patients with previous PPM were excluded from the ECG data analysis. ECG data was also missing for 28 patients, leaving 214 patients available for analysis. AVA = aortic valve area; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MSCT = multislice computed tomography; PPM = permanent pacemaker; RBBB = right bundle branch block.

Table S3.3. Procedural characteristics of all patients.

Variable	All patients (n=281)	Pre-dilatation (n=58)	Direct TAVI (n=223)	p-value
Transfemoral approach	232 (82.6)	46 (79)	186 (83)	0.44
Local anesthesia	232 (82.6)	46 (79)	186 (83)	0.44
Pre-dilatation balloon size				
20 mm		24 (41)		
23 mm		20 (35)		
25 mm		14 (24)		
Implanted device size				0.95
23 mm	110 (39.1)	24 (41)	86 (39)	
26 mm	101 (35.9)	20 (35)	81 (37)	
29 mm	67 (23.8)	14 (24)	53 (24)	
Valve area oversizing, %	11.5 ± 9.8	12.4 ± 10.5	11.3 ± 9.7	0.52
Device diameter / Annulus diameter (area-derived)	1.05 ± 0.05	1.06 ± 0.05	1.05 ± 0.05	0.63
Post-dilatation	42 (14.9)	7 (12)	35 (16)	0.83
Need for second valve implantation	3 (1.1)	0 (0)	3 (1)	0.35
Annulus rupture	0 (0)	0 (0)	0 (0)	1
Conversion to SAVR	2 (0.7)	0 (0)	2 (2)	1
Contrast use (ml)	108 ± 43	113 ± 37	107 ± 44	0.36
Fluoroscopy time (min)	17.4 ± 9.8	17.8 ± 12.2	17.2 ± 9.2	0.69

Values are mean ± SD or n (%). SAVR = surgical aortic valve replacement.

Table S3.4. 30-day and 1-year outcomes of all patients.

30-day outcome	All patients (n=281)	Pre-dilatation (n=58)	Direct TAVI (n=223)	p-value
Death	8 (2.8)	1 (2)	7 (4)	0.69
Stroke	3 (1.1)	2 (3)	1 (1)	0.11
Myocardial infarction	0 (0)	0 (0)	0 (0)	1
New pacemaker implantation*	43 (17.8)	6 (11)	37 (20)	0.25
Major vascular complication	8 (2.8)	2 (3)	6 (3)	0.67
Paravalvular regurgitation > mild	6 (2.4)	2 (4)	4 (2)	0.61
Acute kidney injury	2 (0.7)	2 (3)	0 (0)	0.04
Mean gradient > 20 mmHg	7 (2.8)	2 (4)	5 (2)	0.63
Mean gradient, mmHg	11.8 ± 5.8	12.7 ± 3.8	12.1 ± 4.1	0.58
1-year outcomes				
Any death[§]	20 (25.7)	8 (22.7)	12 (23.9)	0.59

Values are mean ± SD or n (%). * Patients with previous permanent pacemaker were excluded from this analysis; p-value adjusted for RBBB and PR duration. [§] Kaplan-Meier estimate, log-rank p-value.